# Indole Alkaloids, Macrocycles and Heterocycles: Interplay between Methodological Development and Total Synthesis 

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PAR

Cyril PIEMONTESI
acceptée sur proposition du jury:
Prof. N. Cramer, président du jury
Prof. J. Zhu, directeur de thèse
Prof. A. Fürstner, rapporteur Prof. E. Carreira, rapporteur Prof. J. Waser, rapporteur

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"I find your lack of faith disturbing."
Darth Vader
"The synthesis of substances occurring in Nature, perhaps in greater measure than activities in any other area of organic chemistry, provides a measure of the conditions and powers of science."

Robert Burns Woodward
"Alle Dinge sind Gift, und nichts ist ohne Gift; allein die Dosis macht, daß ein Ding kein Gift ist."

Theophrastus von Hohenheim (Paracelsus)
"Too much is not enough..."

Anonymous author - BCH, EPFL. Switzerland

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## Abstract

The total syntheses of three different indole alkaloids, as well as the development of a new macrocyclization reaction and of a novel methodology for the synthesis of proline amide derivatives serve as the basis of this thesis. Through its eight chapters, the present work intends to picture the nice interplay which exists between total synthesis and methodological development.

An enantioselective total synthesis of (-)-terengganensine A, a heptacyclic monoterpene indole alkaloid, was performed. A short sequence allowed to obtain the enantio-enriched target in good overall yield. The synthesis featured a key asymmetric transfer hydrogenation of iminium as well as a complex domino dihydroxylation, oxidative cleavage, triple cyclization, hydrolysis sequence as the last step. An excellent stereocontrol was achieved thanks to a strategy based on an in-depth conformational analysis of the substrates. The absolute configuration of the natural product was determined with the aid of our total synthesis.

A divergent synthesis of (-)-vallesamidine and of (+)-1,2-dehydroaspidospermidine was also reported. These two pentacyclic indole alkaloids are structurally similar but vallesamidine features a rearranged skeleton compared to the aspidosperma alkaloids. A key macrocyclic intermediate was obtained in enantio-enriched form as a single diastereoisomer. An enantioselective 1,4-addition on a 3-substituted cyclopent-2-en-1-one, a chiral prolinol-catalyzed aldol reaction as well as a stereoinvertive nucleophilic substitution of a benzylic mesylate with a vinylic boronic acid derivative were responsible for the obtained excellent stereocontrol. From a common intermediate, a complex domino sequence, featuring the construction of $2 \mathrm{C}-\mathrm{N}$ bonds and one C-C bond, allowed the formal diamination of a cyclopentene and therefore the synthesis of (-)-vallesamidine. Using the same intermediate, a two-step sequence, including a novel $\mathrm{TiCl}_{3}$-promoted reductive cyclization/rearrangement cascade afforded (+)-1,2-dehydroaspidospermidine. Both targets were obtained in 9 to 11 steps and good overall yield with an excellent stereocontrol.

Another target, (+)-peganumine A, was synthesized in 7 steps and excellent overall yield with a good enantioselectivity. After different unsuccessful strategies, an innovative approach was developed for the synthesis of (+)-peganumine A, a structurally uncommon octacyclic carboline dimer. The first key intermediate was accessed through Liebeskind-Srogl coupling. Consequently, a novel macrocyclization method relying on the use of a $\omega$-isocyanoaldehyde followed by transannular cyclization furnished a tetracyclic $\alpha$-ketoamide in a single step and good yield. This step featured an unprecedented intramolecular oxidative Ugi reaction. As last step, a chiral thioureacatalyzed enantioselective Pictet-Spengler reaction/transannular cyclization/deprotection domino sequence afforded (+)-peganumine A in excellent enantioselectivity. Overall, the targeted molecule was obtained in a short 7-step sequence and in excellent yields. Relying on the same strategy, analogues of (+)-peganumine A were obtained and tested for their bioactivity.

Inspired by the macrocyclization strategy developed for the synthesis of peganumine A, we then extended its scope. Macrocycles with different ring sizes (9- to 22-membered ring) and ring topologies were synthesized in moderate to good yields. Different isonitrile-based multicomponent reactions were successfully exploited including the 2-component 3-center Passerini, the 3component 4-center Ugi and the 3-component 4-center oxidative Ugi reactions. This new methodology was then successfully applied to the total synthesis of (-)-eurystatin B, a 13-membered cyclic peptides containing an $\alpha$-ketoamide function. A short synthetic sequence allowed the synthesis of a tripeptide analogue. The latter was then cyclized using a 2-component 3-center Passerini reaction to the 13 -membered core ring in excellent yield. A subsequent 3 -step strategy afforded the targeted molecule in excellent overall yield. Our total synthesis allowed the determination of the absolute configuration of (-)-eurystatin B.

The last part of this thesis focused on the development of a novel silver-catalyzed 1,1aminoacylation of homopropargylamine for the synthesis of proline amide derivatives. Mechanistic studies revealed a silver-catalyzed 5-endo-dig cyclization of homopropargylamines to 2,3-dihydro- 1 H -pyrrole derivatives followed by an unprecedented on-column 3-component addition of isonitrile and water onto the latter. Wide range of proline amide derivatives was obtained in good yields. Moreover, with the introduction of a C-3 alkyl or hydroxyl group, excellent diastereocontrol was achieved. The reaction was then extended to primary homopropargylamines. Similarly, a silver-catalyzed 5-endo-dig cyclization afforded a 3,4-dihydro-2H-pyrrole intermediate. Addition of a carboxylic acid and an isonitrile reaction partner initialized an Ugi-Joullié reaction in the reaction flask to afford the desired products in good to excellent yields.

Keywords: domino reaction, total synthesis, natural product, terengganensine A, vallesamidine, 1,2-dehydroaspidospermidine, peganumine A, macrocyclization, eurystatin B, proline amide.

## Résumé


#### Abstract

La synthèse totale de trois différents alcaloïdes indoliques et le développement d'une nouvelle réaction de macrocyclisation ainsi que d'une nouvelle méthodologie pour la synthèse de dérivés d'amides proliniques servent comme base à ce travail. A travers ses huit chapitres, cette thèse a l'intention d'imager les élégantes interactions qu'il existe entre la synthèse totale et le développement de nouvelles méthodologies.

Une synthèse enantioselective de (-)-terengganensine A, un alcaloïde indolo-monoterpénique heptacyclique, a été effectuée. Une courte séquence a permis d'obtenir la cible enantio-enrichie avec un excellent rendement global. Cette synthèse a comme caractéristiques une réaction clé de transfert asymétrique d'hydrogène sur un iminium et une séquence domino complexe de dihydroxylation, coupure oxydante, triple cyclisation, hydrolyse comme dernière étape. Un excellent stéréo-contrôle a été obtenu grâce à une stratégie basée sur une analyse en profondeur de la conformation des substrats de départ. La configuration absolue du produit naturel a été determinée grâce à cette synthèse.


Une synthèse divergente de (-)-vallesamidine et de (+)-1,2-dehydroaspidospermidine est aussi rapportée dans cette thèse. Ces deux alcaloïdes indolo-monoterpéniques pentacycliques sont structurellement similaires mais la vallesamidine est caractérisée par un squelette réarrangé comparé aux alcaloïdes de la famille aspidosperma. Un unique diastereoisomère du macrocycle clé a été obtenu dans une forme enantio-enrichie. L'utilisation d'une addition de Michael sur un cyclopentene substitué en position 3 , une réaction d'aldol catalysée par une prolinol chirale et une substitution nucléophilique avec inversion de la stéréochimie sur un mesylate benzylique avec un dérivé vinylique d'acide boronique sont responsables de l'excellent stéréo-contrôle obtenu. D'un intermédiaire commun, une séquence domino complexe, caractérisée par la formation de deux liaisons C-N et d'une liaison C-C, a permis la diamination formelle d'un cyclopentene et donc la synthèse de (-)-vallesamidine. A l'aide ce même intermédiaire, une séquence, formée de deux étapes incluant une réaction en cascade de cyclisation réductrice promue par $\mathrm{TiCl}_{3}$ suivie d'un réarrangement a permis la synthèse de (+)-1,2-dehydroaspidospermidine. Les deux cibles ont été obtenues en 9 et 11 étapes respectivement avec un bon rendement global et un excellent stéréocontrôle.

Une autre cible, (+)-peganumine $A$, a été synthétisée en sept étapes avec un excellent rendement global et une bonne enantiosélectivité. Après plusieurs stratégies infructueuses, une approche innovante a été développée pour la synthèse de ce dimère de carboline cyclique structurellement unique. Le premier intermédiaire clé a été obtenu grâce à un couplage de Liebeskind-Srogl. Puis, une nouvelle méthode de macrocyclisation basée sur l'usage d'un $\omega$-isocyanoaldehyde suivie d'une cyclisation trans-annulaire a permis la synthèse d'une $\alpha$-céto amide tetracyclique avec un
bon rendement. Cette étape est caractérisée par une utilisation sans précédent d'une réaction d'Ugi oxydante. Comme dernière étape, une séquence domino consistant en une réaction de Pic-tet-Spengler asymétrique catalysée par une thiourée chirale suivit d'une cyclisation transannulaire et d'une deprotection a permis la synthèse de (+)-peganumine A avec un excellent sté-réo-contrôle. Globalement, la molécule ciblée a été obtenue grâce à une courte séquence de sept étapes et avec une excellente enantiosélectivité. En se basant sur la même stratégie, des analogues de (+)-peganumine A ont été obtenus et testés pour leur possible activité biologique.

Inspiré par la stratégie de macrocyclisation développée pendant la synthèse de peganumine A, nous avons étendu son champ d’application. Des macrocycles de différentes tailles et de topologies variées ont été synthétisés avec des rendements moyens à bons. Différentes réactions multicomposant basée sur les isonitriles ont été exploitée avec succès, notamment celles de Passerini, d'Ugi et d'Ugi oxydante. Cette nouvelle méthodologie a ensuite été appliquée à la synthèse totale de (-)-eurystatin B, un peptide cyclique contenant une fonction $\alpha$-céto amide. Une courte séquence a permis la synthèse d'un tripeptide. Ce dernier a ensuite été cyclisé en utilisant une réaction de Passerini pour générer un cycle à 13 avec un excellent rendement. Après trois autres étapes, la molécule ciblée a finalement été obtenue avec un excellent rendement global. Notre synthèse a permis la détermination de la configuration absolue de (-)-eurystatin B.

La dernière partie de cette thèse est axée sur le développement d'une nouvelle réaction d'1,1aminoacylation d'amines homopropargyliques catalysées avec de l'argent pour accéder à des dérivés d'amides proliniques. Une étude mécanistique a révélé une cyclisation 5-endo-dig de l'amine homopropargylique catalysée par de l'argent pour générer un intermédiaire 2,3-dihydro-1Hpyrrole. Cette dernière est ensuite engagée dans une réaction unique de trois réactifs, dont un isonitrile, sur une colonne de chromatographie. Un large panel d'amides proliniques a été obtenu avec de bons rendements. De plus, l'introduction d'un substituant alkyl ou hydroxyle à la position 3 a permis d'obtenir un excellent diastéréo-contrôle. La réaction a ensuite été étendue à des amines homopropargyliques primaires. De façon similaire, une cyclisation 5-endo-dig catalysée à l'argent a fourni une 3,4-dihydro-2H-pyrrole comme intermédiaire. L'addition d'un acide carboxylique et d'un isonitrile sur ce dernier a ensuite permis à une réaction de Ugi-Joullié de se produire dans le ballon pour former les produits désirés avec d'excellent rendements.

Mots-clés: réaction domino, synthèse totale, produit naturel, terengganensine $A$, vallesamidine, 1,2-dehydroaspidospermidine, peganumine A, macrocyclisation, eurystatin B, amide prolinique.

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## List of Abbreviations

Ac Acetyl

| Adams | $\mathrm{PtO}_{2}$ |
| :--- | :--- |
| aq | Aqueous |
| Ala | L-Alanine |
| Ar | Aryl |

B3LYP Becke, 3-parameter, Lee-Yang-

BINAP (2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)

Bn Benzyl
Boc tert-Butyloxycarbonyl
bpy 2,2'-Bipyridine
BrettPhos 2-(Dicyclohexylphosphino)3,6-dimethoxy-2', 4', $6^{\prime}$-triisopropyl-

1,1'-biphenyl
brsm Based on recovered starting material

BTAF Benzyltrimethylammonium fluoride
$\mathrm{Bu} \quad$ Butyl
Burgess 1-methoxy- $N$ -triethylammoniosulfonylmethanimidate

Bz Benzoyl
${ }^{\circ} \mathbf{C} \quad$ Degree Celsius
c Concentration (in $\mathrm{g} / \mathrm{mL}$ )
calcd Calculated
CAN Ceric ammonium nitrate
cat Catalyst
Cbz Carboxybenzyl
CDI Carbonyldiimidazole

| CMBP | (Cyanomethylene) tributylphosphorane |
| :---: | :---: |
| CMMP | (Cyanomethylene) trimethylphosphorane |
| COD | 1,5-Cyclooctadiene |
| Comins | $N, N$-Bis(trifluoromethylsulfonyl)- <br> 5-chloro-2-pyridylamine |
| Conc | Concentrated |
| Cp | Cyclopentadienyl |
| CPME | Cyclopentyl methyl ether |
| CR | Component rection |
| CSA | Camphorsulfonic acid |
| CTAB | Cetrimonium bromide |
| Cy | Cyclohexyl |
| CyJohnPhos | (2- |
|  | Biphenyl)dicyclohexylphosphine |
| Cymene | 1-Methyl-4-(propan-2yl)benzene |
| d | Days |
| D or ( + ) | Dextrorotary |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| dan | 1,8-Diaminonaphthalene |
| DavePhos | 2-Dicyclohexylphosphino-2'( $\mathrm{N}, \mathrm{N}$-dimethylamino)biphenyl |
| dba | Dibenzylideneacetone |
| DBAD | Di-tert-butyl azodicarboxylate |
| DBU | 1,8-Diazabicyclo(5.4.0)undec-7ene |
| DCAD | Di-(4- <br> chlorobenzyl)azodicarboxylate |
| DCC | $N, N$--Dicyclohexylcarbodiimide |




| NHC | N-Heterocyclic carbene | $\boldsymbol{R}$ | rectus |
| :--- | :--- | :--- | :--- |
| NIS | N-lodosuccinimide | RCM | Ring-closing metathesis |
| NMO | 4-Methylmorpholine N-oxide | Red-Al | Sodium bis(2- <br> NMR |
| Nuclear magnetic resonnance |  | methoxyeth- <br> NOE | Nuclear Overhauser effect |



## EDCH Requirements

## EDCH Course Credits:

| Course Name | Credits <br> Earned |
| :---: | :---: |
| Synergism between Art of Total Synthesis and High Level Strategic Design | 2 |
| Perspectives in Modern Organic Chemistry 1 | 2 |
| Efficient Synthetic Route Towards Bioactive Molecules | 2 |
| Swiss Summer School 2015 - Rxn Design \& Synthesis | 2 |
| Swiss Summer School 2017 - Trends in Organic Synthesis | 2 |
| Frontiers in Organic Synthesis - Part II : Synthesis of carbo- and hetero- cycles | 2 |
| Frontiers in Organic Synthesis - Part III : Stereochemistry | 2 |
| Total | $14 / 12$ |

EDCH Teaching Hours:

| Course Name | Hours <br> Earned |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Atomes, Ions, Molécules et Fonctions I | 15 |  |  |  |
| Organic Chemistry Practical Work + Reports corrections | 140 |  |  |  |
| Master Project (2014-2015) | 56 |  |  |  |
| Master Project (2015-2016) | 56 |  |  |  |
| Project in Molecular Sciences | 56 |  |  |  |
| Chemical Studies Advertisement | 3 |  |  |  |
| Total Synthesis of Natural Products + Correction Exam (2014-2015) | 103 |  |  |  |
| Total Synthesis of Natural Products + Correction Exam (2015-2016) | 104 |  |  |  |
| Total Synthesis of Natural Products + Correction Exam (2016-2017) | 104 |  |  |  |
| Total |  |  |  | $637 / 630$ |

## Chapter 1 General Introduction

As stated by the World Scientists' Warning to Humanity: "Human beings and the natural world are on a collision course" ${ }^{1}$ Despite the very pessimistic vision of our actual world, it is indeed true that nowadays, mankind and more generally the whole planet Earth is facing new challenges. Among them, global warming, population growth and drug/biocide resistances are three major issues. And chemists have the power and the responsibility to be majors actors in solving them. There is, in fact, an important need for complex molecules in order to, for instance, find new and more potent drugs, less invasive agrochemicals and innovative smart materials and dyes.

Among these complex molecules, natural products, nitrogen-containing heterocycles and macrocycles play and will play important role in drug and agrochemical discovery processes and in isolation and structural identification of biological macromolecules. With the progress achieved in the field of functional genomics and proteomics, more information about the structures and functions of biologically active macromolecules is becoming available. To match such a formidable advance in biological research, the synthesis, identification and optimization of new small molecular chemical substances that can specifically interact with therapeutic targets is of utmost importance and constitute actually the bottleneck in medicinal and agrochemical chemistry.

A traditional way for the synthesis of organic compounds has been a stepwise construction of individual chemical bonds found in target molecules. The increase of molecular complexity per step with such a strategy is incremental leading to a lengthy synthesis. Searching for multiple-bond forming reactions and minimizing non-constructive transformations became therefore of increasing importance in designing synthetic strategies/tactics and methodologies. It is expected that ready access to diverse sets of natural products/heterocycles/macrocycles would not only help improving the known biological and pharmacokinetic properties of drugs/biocides, but also help discovering molecules that exhibit biological effects beyond those associated with the previous known macromolecules.

With this idea in mind, our lab is tackling natural products synthesis and methodologies development to not only access interesting chemical structures but also to develop new innovative strategies. In this thesis, the total syntheses of three different indole alkaloids as well as the development of two new annulation methods will be discussed. In this first chapter, a general overview of the targets of interest: monoterpene indole alkaloids, 5-membered nitrogen-containing heterocycles and macrocycles will be given. In this chapter, we will also explore the existing general strate-

[^0]gies and methods for the rapid construction of complexity, such as: divergent syntheses, multicomponent reactions and cascade sequences.

### 1.1 Targets of Interest

Medicinal chemists have always been inspired by natural products for the development of new drug candidates. Among them, monoterpene indole alkaloids (MIA) play a crucial role.

### 1.1.1 Monoterpene Indole Alkaloids

Alkaloids are a group of organic natural products that mostly contain basic nitrogen atom. They can be extracted from the alkaline aqueous phase resulting from treatment of the corresponding biomass. They are produced by a large variety of organisms including fungi, plants, animals and bacteria. These alkaloids are classified in many different families which are based on their structural diversity. ${ }^{2}$ Among these alkaloids, monoterpene indole ones represent a very fascinating class. As stated by the name, they contain one or more indole rings as well as two isoprene units. ${ }^{3}$

Strychnine (1.1), isolated by Pelletier and Caventou in 1819, was the first members of the monoterpene indole alkaloids. ${ }^{4}$ Since then, more than 2000 monoterpene indole alkaloids have already been discovered and isolations of new compound are continuously reported.


Strychnine (1.1) strychnos


Yohimbine (1.5) corynanthe


Ajmalicine (1.2) corynanthe


Ajmaline (1.6) ajmalan


Tabersonine (1.3) aspidosperma



Catharanthine (1.4)
iboga


Figure 1 - Examples of monoterpene indole alkaloids
Despite being restricted to indole scaffold, the structural diversity of MIA is almost infinite. For this reason, they have been divided into sub-groups according to the connectivity of their main carbon skeleton. Figure 1 shows some selected examples of MIA. They represent the main families of MIA which are indicated in italic.

Most of the indole alkaloids were discovered by extracting plants or fungi, which were known to have some beneficial effect in traditional medicine. For example, they have been used for the

[^1]treatment of hypertension, addiction, malaria, etc. and are known neuromuscular blocking agents. They have been a major source of drugs and of inspiration for the development of new drugs (Figure 2). ${ }^{5}$ Some of them, such as vincristine (1.10), reserpine (1.11) and vincamine (1.12) are currently used directly as drug for the treatment of cancer and hypertension as well as vasodilator respectively. ${ }^{6}$


Alcuronium chloride (1.9) inspired from C-toxiferine 1 neuromuscular blocking agent



Reserpine (1.11)
natura
antihypertensive


Vincamine (1.12 natural vasodilatator

Figure 2 - Examples of MIA and MIA-inspired marketed drugs
Due to their elegant polycyclic molecular architectures, their structural diversity and their biological activities, extraction, structure identification and synthesis of these alkaloids have been investigated by organic chemists and biologists over the last century.

### 1.1.1.1 Biosynthesis

It is to note that, in this chapter as well as in the rest of this thesis, the biogenetic numbering system developed by Taylor and Le Men will be used. ${ }^{7}$ In 1961, Wenkert suggested that the biosynthesis of monoterpenoid indole alkaloids ${ }^{8,9}$ (Scheme 1) uses two building blocks, secologanine (1.14) which could be synthesized from 1-deoxy-D-glucose 5-phosphate (1.13) and tryptamine (1.16) which could arise from tryptophan (1.15) by a simple decarboxylation. The proposed biosynthesis begins with the Pictet-Spengler reaction between tryptamine (1.16) and secologanine (1.14) to afford strictosidine (1.17), the key common precursor of almost all monoterpene indole alkaloids. From strictosidine (1.17), the quinoline alkaloids could be accessed. Reductive amination of the in situ generated aldehyde with the secondary amine leads to geissoschizine (1.18). The latter could then be transformed into preakuammicine (1.19) via an oxidative coupling between C 2 and C-16 and a migration of C-21 from C-2 to C-7. A C-7/C-21 bond scission (1.20) followed by double bond isomerization (1.21) and elimination of water affords the achiral secodine (1.22). Vincadifformine (1.23), an aspidosperma alkaloids, could then be generated through intramolecular Diels-Alder reaction. A different cycloaddition gives access to the iboga alkaloids. Vincadifformine

[^2](1.23) could then be rearranged to vincamine (1.12), a vincane alkaloids, probably via 1.24, and decarboxylated to form eburnamine (1.25) (eburnane alkaloids).


Scheme 1 - Proposed biosynthetic sequence to the main alkaloid families
As illustrated in Scheme 1, the biosynthesis of indole alkaloids is highly divergent (see 1.2.1-Divergent Syntheses) and contains many cascade reactions (see 1.2.3 - Cas-cade/Domino/Tandem/Sequential/One-pot Sequences). Indole alkaloids are generally polycyclic structures and 5-membered nitrogen-containing rings are highly present in their structure.

### 1.1.2 5-Membered Nitrogen-containing Heterocycles

5-membered ring heterocycles containing one or more nitrogens are among the most common scaffolds in drugs and natural products as exemplified on Figure 3.


Figure 3 - Examples of natural products and drugs containing a 5-membered nitrogen-containing heterocycle

Because the amino acid proline is composed of a pyrrolidine ring, this type of 5-membered ring plays an important role in biology, being for instance responsible for the structural disruption of $\alpha$ helices and $\beta$-sheets and being the main inducer of $\beta$-turns in the secondary structure of proteins.

5-membered nitrogen-containing heterocycles are also important in organic synthesis. They can serve as bases in organic chemistry, as pyrrolidine for instance. They can also act as organocatalysts, especially in the form of proline derivatives (Figure 4). Such catalysts are known to promote a wide array of enantioselective transformations and their development is still of high interest nowadays. ${ }^{10}$


Figure 4 - Examples of organocatalyst containing a 5-membered nitrogen-containing heterocycle

### 1.1.3 Macrocycles

A macrocycle, as defined by the International Union of Pure and Applied Chemistry (IUPAC), is a cyclic macromolecule. ${ }^{11}$ There is no defined minimum ring size to call a cyclic molecule a macrocycle but most people agreed that it must contain minimum 12 atoms. In general, molecules featuring a 7 to 11-membered ring are generally called medium-sized rings. Over the years, many different classes of macrocycle have been designed or isolated from natural sources as depicted on Figure $5 .{ }^{12}$ Among them, amphotericin B (1.38), an antifungal medication from Streptomyces nodosus and vancomycin (1.39), an antibiotic from Amycolatopsis orientalis, are both currently sold drugs

[^3]and are on the World Health Organization (WHO) Model List of Essential Medicines. ${ }^{13}$ This illustrates nicely the importance of macrocycles.




Figure 5 - Examples of synthetic and natural macrocycles
Macrocycles, such as crown-ether 1.40, have found many different uses in various areas, such as organic, analytical, medicinal and polymer chemistry. Moreover, macrocycles have also attracted a special interest from their bioactivity point of view. Opposite to the small-molecules, macrocycles have the advantage to be structurally pre-organized, avoiding a major entropy loss during the binding with the biological targets. This structural pre-organization can also be very useful for membrane penetration for instance, decreasing the apparent polarity of the macrocycle via intramolecular hydrogen-bonding. Nevertheless, despite this pre-organization, macrocycles are not rigid and it allows a good shaping to the target surfaces/pockets. Moreover, their key functional groups can interact across extended binding sites in proteins.

Cyclosporine (1.41), an immunosuppressant from Tolypocladium inflatum, adopts conformation A (Figure 6) to pass through the biological membranes. Once reached the inside of the cell, its conformation changes in order to interact strongly with the target, cyclophilin $D(B)$. This illustrates the power of the flexible pre-organization of macrocycles. Drug-like physicochemical and pharmacokinetic properties such as good solubility, metabolic stability, bioavailability and lipophilicity can surprisingly be demonstrated by macrocycles even though they do not follow the famous Lipinski's rule of $5 .{ }^{14}$ Among the macrocycles, cyclic peptides and peptidomimetics have received particular attention, especially in drug development. ${ }^{15}$

[^4]
(A)

(B)

Figure 6 - Conformations of cyclosporine $A^{16}$
The formation of a macrocycle on a linear bioactive compound can significantly enhance its bioactivity (Figure 7).


Figure 7 - Effect of macrocyclization on the biological activity of linear molecules
Because of the high interest in macrocycles, development of new methods for macrocyclization is a major highly active field of organic chemistry. The efficiency of a macrocyclization depends on the structure, the size and the structural pre-organization of the linear substrates. Figure 8 illustrates this statement with three examples. In the synthesis of riccardin C (1.48) (A), a Pd-catalyzed cross-coupling for the Ar-Ar bond formation was for instance much less efficient than a Wittig reaction. Moreover, formation of one of the two $\mathrm{CH}_{2}-\mathrm{CH}_{2}$ bonds was higher yielding than the other

[^5]one while using the same reaction. ${ }^{17}$ Similar observation could be made on 1.49 (B). $\mathrm{S}_{N} \mathrm{Ar}$ reaction proved to be much more efficient than simple macrolactamization. ${ }^{18}$ For the formation of cyclo-[Pro-Ala-Ala-Phe-Leu] (1.50) (C) using the pentafluorophenyl ester activation method, different closing sites afforded very different outcomes and yields depending on which peptide bond was formed during the macrocyclization. ${ }^{19}$




Figure 8 - Influence of the ring-closing reactions/methods/sites on the yield
These syntheses exemplify well the importance of structural pre-organization for the closing of macrocycles. Conformation-directed macrocyclization has been investigated extensively. ${ }^{20}$

Among the most used methods for macrocyclization are lactonization and lactamization reactions. This is probably associated with the prevalence of lactone and lactam groups in many macrocyclic structures, either natural or synthetic. Intramolecular nucleophilic substitution reactions and in particular aromatic substitutions also represent one of the simplest, yet effective macrocyclization methods. C-C bond forming reactions can also be used. This is nicely illustrated by the use of reactions such as ring-closing metatheses and Pd-catalyzed coupling reactions. Interestingly, DielsAlder reaction, the archetypical 6-membered ring forming process was also exploited, as in the synthesis of abyssomicin C for instance (Scheme 2, A). Another alternative method, not relying on one long linear precursor as starting material, is the use of multicomponent reactions (see 1.2.2Multicomponent Reaction) (Scheme 2, B). The concept of the Multiple Multicomponent Macrocyclizations features the integration of two or more multicomponent reactions in a one-pot fashion. ${ }^{21}$

[^6]

Scheme 2 - Examples of unusual ring-closing reactions for the synthesis of macrocycles
As already highlighted on Figure 8, the structural pre-organization of the linear precursors plays a crucial role in the closing of the macrocycles. For instance, hydrogen-bonding (Figure 9, A) ${ }^{22}$ as well as geometrical restriction $(B)^{23}$ and template effect $(C)^{24}$ can dramatically influence the outcome of the reactions.

[^7]


(A)
(B)
(C)

Figure 9 - Examples of structural pre-organization of the open-chain precursor

### 1.2 Methods to Improve Synthesis Efficiency

In order to be able to synthesize complex molecular structures, such as the ones presented below, clever strategies and efficient methods had to be developed. Nowadays, additional constrains have emerged such as time restriction and use of environmentally-friendly processes among many others. People have already identified the need for more ideal syntheses ${ }^{25}$ and have developed concepts to reach this goal such as function-oriented ${ }^{26}$ and protecting-group free ${ }^{27}$ synthesis as well as redox ${ }^{28}$ and atom ${ }^{29}$ economy. Another strategy for accessing complex molecules in a more efficient way is the use of a divergent synthesis.

### 1.2.1 Divergent Syntheses

The aim of a strategy based on a divergent synthesis is mainly to improve efficiency. From an advanced common intermediate, different targets can be reached. Strategy must therefore be

[^8]planned in accordance. Nature is extensively using divergence as exemplified by the biosynthesis of monoterpene indole alkaloids (Scheme 1). This concept revealed very powerful for the total synthesis of various natural products. ${ }^{30}$ MacMillan and coworkers were for instance able to access three different families of alkaloids, aspidosperma (1.71 and 1.23), strychnos (1.1) and kopsia (1.74 and 1.75), from a single common precursor 1.69 easily accessible from 1.68 (Scheme 3). ${ }^{31}$


Scheme 3 - MacMillan's divergent total synthesis of kopsia, strychnos and aspidosperma alkaloids
In this case, the divergence was planned in order to access well defined targets. On the opposite, access to a "random" library of compounds can also be valuable.

### 1.2.1.1 Diversity-oriented Syntheses

Among the divergent syntheses, the concept of Diversity-Oriented Synthesis (DOS) has particularly attracted the attentions of chemists. ${ }^{32}$ Natural products as well as commercial compound collections have been the primary sources for initial lead finding in medicinal chemistry. Since 2000 and the first appearance of the DOS term in a paper from Schreiber and coworkers, ${ }^{33}$ DOS approach has completed these libraries. DOS was defined by Spring and coworkers as such: "diversityoriented synthesis involves the deliberate, simultaneous and efficient synthesis of more than one

[^9]target compound in a diversity-driven approach to answer a complex problem". ${ }^{34}$ It is therefore the opposite of convergent Target-Oriented Synthesis (TOS). As shown on Figure 10, DOS allows the synthesis of a library of compounds (A) whereas TOC focuses on a single target (B).


TOS (B) :


Figure 10 - Diversity-Oriented Synthesis vs convergent Target-Oriented Synthesis
With this strategy, synthesis of combinatorial library of diverse small molecules can be done rapidly in a few steps. It allows a rapid coverage of a larger chemical space. ${ }^{35}$ DOS can therefore be not only useful for drug discovery but also for the search of new probes to investigate biological mechanisms as well as serving as a new driving force for the development of organic chemistry. Multicomponent reactions are of special importance in this field as they allow rapid building of the complexity and as they generally tolerate a broad range of starting materials and can be performed without particular precaution. ${ }^{36}$

### 1.2.2 Multicomponent Reactions

Multicomponent reactions (MCR) are chemical reactions where three or more compounds react together to afford a single molecule where all, or almost all the atoms contribute to the newly formed product. The first reported MCR was the Strecker reaction in 1850, which converted an aldehyde, KCN and ammonium chloride into an $\alpha$-aminonitrile. ${ }^{37}$ Since then, a myriad of MCR have been developed. ${ }^{38}$ Advantages of MCR included higher productivity, easy increase in complexity and rapid access to diversity. MCR are nowadays extensively used in medicinal chemistry and in total synthesis as pictured on Scheme 4.

[^10]

Scheme 4 - Examples of total syntheses featuring a MCR in their key step
Tietze and coworkers developed a 3-CR for the synthesis of hirsutine (1.76) (A). ${ }^{39}$ Knoevenagel condensation between aldehyde 1.77 and Meldrum's acid (1.78) afforded 1.80 which was directly engaged in a hetero Diels-Alder reaction with alkene 1.79 to afford 1.81. The latter spontaneously lost $\mathrm{CO}_{2}$ to afford ketene 1.82. After addition of water, the resulting acid decarboxylated immediately to furnish 1.84. The latter could easily be transformed into hirsutine (1.76). In this case, a Knoevenagel reaction/hetero Diels-Alder sequence using aldehyde 1.77, 1,3-diester 1.78 and alkene $\mathbf{1 . 7 9}$ allowed the rapid increase in complexity.

The synthesis of sialic acid (1.85) by Wong and coworkers featured a Petasis reaction (B). ${ }^{40}$ Larabinose (1.86) was condensed with amine 1.87 and the resulting imine 1.89 reacted with vinyl boronic ester 1.88, via borate 1.90 , to afford amine 1.91. The latter was then easily converted to

[^11]sialic acid (1.85). In this example, hemiacetal 1.86, amine 1.87 and boronic ester 1.88 are the three reagents engaged in the MCR.

The last example features the total synthesis of motuporin (1.93) (C). ${ }^{41}$ Ugi 4-CR of an acid 1.94, an aldehyde 1.95, methylamine (1.96) and an isonitrile 1.97 afforded 1.98. The latter was further elaborated to motuporin (1.93).

As exemplified by the last total synthesis in Scheme $4(C)$, isonitriles are partners of choice and are present in numerous MCR such as the Passerini and the Ugi reactions.

### 1.2.2.1 Isonitriles and the Passerini and Ugi Reactions

Isonitriles, also known as isocyanides are very useful building block in organic synthesis. ${ }^{42}$ Concerning their structure (Scheme 5, A), the C-N distance is very short ( $1.158 \AA$ in methylisocyanide) and the R-N-C angle is close to $180^{\circ}$. Nef initially described the isonitriles using the carbene resonance form 1.99a ${ }^{43}$ whereas Lindemann and Wiegrebe proposed a zwitterionic structure 1.99b in analogy to carbon monoxide. ${ }^{44}$ Recent investigations have shown that isonitriles have generally around $50 \%$ of their structural weight in the form of a carbene whereas the zwitterionic form accounts for around $25 \% .{ }^{45}$ The linear structure observed in spite of the $50 \%$ carbene form arises from the participation of the lone pair of the nitrogen. The proposed best representation of isonitriles is therefore 1.99c.


Scheme 5 - Structure of isonitriles and their synthesis
Concerning their synthesis (Scheme 5, B), the first synthetic isocyanide 1.101 was obtained by nucleophilic substitution of allyl iodide (1.100) with $\mathrm{AgCN} .{ }^{46}$ It is now well known that AgCN affords isonitriles instead of nitriles. The strong binding between the silver and the carbon of the CN function drastically diminished the nucleophilicity of the latter but the nitrogen can still attack and promote the substitution probably via intermediate 1.102. Nowadays, isonitriles are preferably formed by dehydration of formamides 1.103. $\mathrm{POCl}_{3}$, phosgene and Burgess' reagent are well

[^12]known suitable reagents for this purpose. They allow the conversion of $\mathbf{1 . 1 0 3}$ into the imidoyl chloride 1.104. $\alpha$-Elimination with a base furnishes the desired isonitriles 1.99.

One of the first reactions developed using isonitrile is the Nef-isonitrile reaction. It was discovered in 1892 by John Ulric Nef. ${ }^{43 a}$ As depicted in Scheme 6, it consists in the insertion of an isonitrile 1.99 into an acyl chloride 1.105 to form an $\alpha$-keto imidoyl chlorides 1.107. The formed products can then easily be converted into $\alpha$-ketoamide, $\alpha$-ketotetrazole or trapped in an intramolecular fashion for instance (1.108). ${ }^{47}$


Scheme 6 - Nef-isocyanide reaction mechanism
Concerning the mechanism, recent investigations have shown that most of the time the reaction proceeds in a single concerted step via transition state 1.106. ${ }^{48}$

Another old reaction involving carbonyl and isonitrile is the Passerini reaction. It is a threecomponent reaction between an aldehyde 1.109, a carboxylic acid 1.110 and an isonitrile 1.99 to afford an acylated $\alpha$-hydroxy amide 1.114. It was initially reported in 1921 by Mario Passerini and his colleagues. ${ }^{49}$ Different mechanisms are now commonly accepted (Scheme 7). ${ }^{50}$

The carbonyl 1.109 could first be activated by the carboxylic acid 1.110 and could then be attacked by the isonitrile 1.99 to form a nitrilium intermediate 1.112. The carboxylate salt could then react with the latter to form alcohol 1.113. A Mumm rearrangement, ${ }^{51}$ i.e. a migration of the acyl to the alcohol, can then occur to afford an acylated $\alpha$-hydroxy amide 1.114 (Scheme 7, A).

The second proposed mechanism involves the simultaneous reaction of all three partners (Scheme 7, B). This mechanism is in agreement with the fact that the reaction rate depends on all three components and that the reaction is faster in non-polar solvents (no charge generated). Two different transition states have been proposed via a 5-(1.115) or a 7-membered ring (1.116). Nevertheless, simultaneous union of three molecules is a very rare process in organic chemistry.

The third proposed possibility is a two-step process, which involves the reaction of the isocyanide 1.99 with a loosely bound adduct 1.117, formed via hydrogen-bonding between carboxylic acid

[^13]1.110 and the carbonyl compound 1.109 (Scheme 7, C). This mechanism could also explain the fact that the reaction is faster in non-polar solvents.

(A)
(B)
(C)

Scheme 7 - Commonly accepted mechanisms for the Passerini reaction

Recently, investigations have shown that the Passerini reaction goes through a slightly different mechanism (Scheme 8). ${ }^{52}$


Scheme 8 - Most recently proposed mechanism for the Passerini reaction
Two molecules of acids 1.110 could activate the aldehyde 1.109 first. Isonitrile 1.99 could then attack on the latter and the resulting nitrilium 1.119 could then be stabilized by two carboxylic acids via hydrogen bonding and C-O interaction. Addition of the carboxylate to the nitrilium could afford 1.120 which uses a second carboxylic acid to stabilize the intermediate and help for the subsequent acyl migration. The latter could occur in two steps. The alcohol $\mathbf{1 . 1 2 0}$ could first cyclize onto the ester to afford the orthoester 1.121. The latter could then fragment to the final product 1.114 with the help of a molecule of carboxylic acid.

[^14]Similar to the Passerini reaction is the Ugi one. This four-component reaction involves a carboxylic acid 1.110, a carbonyl 1.109, an amine 1.122 and an isonitrile $1.99 .{ }^{53}$ The resulting product is an $\alpha-$ amido amide 1.127. The initial mechanism proposed by Ugi and coworkers is presented in Scheme 9 (A).



Scheme 9 - Proposed mechanisms for the Ugi reaction
Condensation of the amine 1.122 with the carbonyl 1.109 could afford imine 1.123. Activation with the carboxylic acid 1.110, followed by the attack of isonitrile 1.99 on $\mathbf{1 . 1 2 4}$ could furnish nitrilium 1.125. The carboxylate could then attack back onto the nitrilium to afford the acetoxy imidate 1.126. Mumm rearrangement from oxygen to the nitrogen could promote the formation of the desired product $\mathbf{1 . 1 2 7}$ (Scheme 9, A).

Later, Ugi proposed an alternative mechanism (Scheme 9, B) where the activated iminium 1.124 could first be trapped by the carboxylate, forming aminal 1.129. ${ }^{54}$ Insertion of the isonitrile into the $\mathrm{C}-\mathrm{O}$ bond could lead to the formation of the same acetoxy imidate 1.126. Recent investigations (high resolution mass ${ }^{55}$ and computation ${ }^{56}$ ) have shown that the initial mechanism (A) is generally the one occurring.

A variation of the Ugi reaction was recently developed in our lab which allowed the formation of an $\alpha$-ketoamide 1.138 from an aldehyde 1.109 and an isonitrile 1.99 with the help of acetic acid (1.133) and $N$-methylhydroxylamine (1.130). ${ }^{57}$

[^15]

Scheme 10 - Proposed mechanism for the oxidative Ugi reaction
Scheme 10 depicts the proposed mechanism. Condensation of the $N$-methylhydroxylamine (1.130) with the aldehyde 1.109 could afford nitrone 1.131 . Isonitrile 1.99 trapping of the latter could provide the nitrilium 1.132. Acetic acid (1.133) could then trap the nitrilium to afford the $\alpha$ hydroxylamino imidoyl acetate 1.134 which is very similar to intermediate $\mathbf{1 . 1 2 6}$ in the standard Ugi reaction (Scheme 9). Acyl migration to the hydroxylamine could then occur. The difference with the Ugi reaction is the migration of the acyl from oxygen to another oxygen. Elimination of acetic acid from 1.135 could allow the formation of the unstable $N$-methylimine 1.136 which after hydrolysis could be converted to the desired $\alpha$-ketoamide 1.138. This represents a formal oxidative Ugi reaction which concomitant reduction of the $N$-methylhydroxylamine (1.130) to methylamine (1.137).

As illustrated in the different mechanisms of the Passerini/Ugi reactions, a sequence of domino processes occurs to form the desired product in MCR. Such domino-event sequences are of high importance in synthesis.

### 1.2.3 Cascade/Domino/Tandem/Sequential/One-pot Sequences

A domino reaction was initially defined by Tietze and coworkers as "a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step". ${ }^{58}$ Such processes are very often also called cascade reactions. On the other hand, tandem reactions involve two or more bond-forming transformations but are not limited to the same reactive centers. One-pot sequences, only require that more than one-step occur in the same flask but do not preclude the need for one single reaction conditions all along the process. Despite these clear definitions, people have strong tendency to mix all these terms to described multiple-bond forming processes, whatever the conditions changes and the reactive centers involved. ${ }^{59}$

[^16]Using domino reactions has numerous advantages in organic synthesis such as less work-up and purification steps, i.e. cheaper and faster reaction sequences. Even though the term was defined in 2000, domino processes are not new. Many classical chemical transformations, such as the Mannich reaction, fall into this category. The first reported cascade reaction, which is also a threecomponent reaction, was the synthesis of tropinone by Robinson back in 1917 (Scheme 11). ${ }^{60}$


Scheme 11 - Synthesis of tropinone by Robinson
Since then, evolution of cascade reactions was very impressive. The same cascade reaction can for instance efficiently be used in the synthesis of structurally very diverse natural products as exemplified by the aza-Cope/Mannich sequence initially developed by Overman and coworkers for the synthesis of didehydrostemofoline (1.143). ${ }^{61}$ Scheme 12 highlights the original aza-Cope/Mannich sequences and some natural products obtained using the same sequence.


Scheme 12 - The aza-Cope/Mannich reaction in the synthesis of structurally diverse alkaloids
There is actually a tremendous amount of examples of domino reactions reported in the literature. The fascination of chemists for these elegant and almost artistic chemical transformations will probably never fade away.

Scheme 13 to Scheme 16 show selected examples of cascade reactions in the total synthesis of monoterpene indole alkaloids.

[^17]

Scheme 13 - Danishefsky's total synthesis of phalarine
In 2010, Danishefsky and coworkers reported the total synthesis of phalarine (1.145) (Scheme 13). ${ }^{62}$ Their strategy was based on a diastereoselective Pictet-Spengler reaction/carbocation trapping. They initially condensed 1.146 with formalin (1.53) to afford iminium 1.147 , which spontaneously underwent a Pictet-Spengler reaction in acidic conditions probably via intermediate 1.148 to afford the carbocation $\mathbf{1 . 1 4 9}$ after Wagner-Meerwein rearrangement. The latter was then intramolecularly trapped by the phenol to afford 1.150. The latter was then converted into phalarine (1.145).



Scheme 14 - Boger's synthesis of vindorosine
Boger and coworkers reported in 2006 the total synthesis of vindorosine (1.151) (Scheme 14). ${ }^{63}$ Intermediate 1.152 underwent a thermal Diels-Alder reaction to afford the bridged tetrahydrofuran 1.153. After retro Diels-Alder reaction followed by a [3+2] dipolar cycloaddition of the resulting dipole 1.154, intermediate $\mathbf{1 . 1 5 5}$ was obtained. The latter was converted into the desired natural product 1.151.

[^18]

Scheme 15 - Total synthesis of aspidophytine by Corey and coworkers
In 1999, Corey and coworkers used double imine formation, aza-Mannich reaction followed by Hosomi-Sakurai reaction and reduction of enamine for the synthesis of aspidophytine (1.156) (Scheme 15). ${ }^{64} \mathbf{1 . 1 5 7}$ and $\mathbf{1 . 1 5 8}$ were initially mixed together in the presence of acid. Double imine formations afforded iminium 1.159. The latter underwent an aza-Mannich reaction and the resulting iminium 1.160 was intramolecularly trapped by the allyl TMS to afford 1.161. $\mathrm{NaBH}_{3} \mathrm{CN}$ was added in the reaction flask to reduce the enamine (via iminium), affording 1.162. The latter was converted into aspidophytine (1.156).


Scheme 16 - Qin's total synthesis of minfiensine
The last example is the total synthesis of minfiensine (1.163) by Qin and coworkers (Scheme 16). ${ }^{65}$ 1.164 was submitted to a copper-promoted cyclopropanation to afford the strained compound 1.165. The latter spontaneously opened to enol 1.166. Finally, the iminium 1.166 was intramolecularly trapped to afford 1.167. Few steps allowed its conversion to minfiensine (1.163).

As exemplified by the previous examples, various reactions can sequentially occur in domino reactions. A special sequence involving oxidation/reduction and cyclization was developed in our lab.

### 1.2.3.1 Integrated Oxidation/Reduction/Cyclization Sequences

We have recently developed an integrated Oxidation/Reduction/Cyclization (iORC) sequence. Oxidation of a cyclic alkene to a dicarbonyl compound, reduction of a nitroaryl (and azide) followed by cyclizations afforded various indole alkaloids in a single operation.

[^19]

Scheme 17 - First example of iORC developed during the synthesis of goniomitine
The iORC concept was initially developed during the synthesis of goniomitine (1.168) (Scheme 17). ${ }^{66}$ Ozonolysis of $\mathbf{1 . 1 6 9}$ afforded the dicarbonyl compound $\mathbf{1 . 1 7 0}$. Addition of Zn and $\mathrm{CaCl}_{2}$ promoted the reduction of the nitro and of the azide functions to afford aniline 1.171. The latter spontaneously cyclized onto the ketone to afford indole $\mathbf{1 . 1 7 2}$ after aromatization. Condensation of the primary amine onto the aldehyde followed by in situ trapping of the formed iminium 1.173 by the indole nitrogen afforded $\mathbf{1 . 1 7 4}$ in a single operation in $80 \%$ yield. Deprotection of the benzyl group furnished goniomitine (1.168) in a very short and efficient sequence.


Scheme 18 - iORC process in the synthesis of kopsihainanine A
The same process was later applied to the total synthesis of kopsihainanine A (1.175) (Scheme 18). ${ }^{67}$ Ozonolysis of lactam $\mathbf{1 . 1 7 6}$ afforded the dicarbonyl compound $\mathbf{1 . 1 7 7}$ which cyclized via an aldol reaction to form the cyclohexanone 1.178. Addition of $\mathrm{PtO}_{2}$ under hydrogen atmosphere promoted the reduction of the nitroaryl 1.178 to the aniline 1.179. Condensation of the latter with the cyclohexanone afforded indole $\mathbf{1 . 1 8 0}$ after aromatization. The elimination of alcohol 1.180 to iminium 1.181 was promoted by the addition of HCl in MeOH . The extended iminium was then intramolecularly trapped by the amide nitrogen to afford $\mathbf{1 . 1 8 2}$ in $63 \%$ yield. $\alpha$-Hydroxylation furnished the desired kopsihainanine A (1.175).

[^20]

Scheme 19 - iORC process in the synthesis of aspidospermidine, 1,2-dehydroaspidospermidine and vincadifformine

The last example of application of an iORC sequence can be illustrated by the total synthesis of aspidospermidine (rac-3.2), 1,2-dehydroaspidospermidine (rac-3.2) and vincadifformine (rac-1.23) (Scheme 19). ${ }^{67}$ The key intermediate rac-1.184 was submitted to ozonolysis to promote the oxidative cleavage to the dicarbonyl compound $\mathbf{1 . 1 8 5}$, which was probably in equilibrium with the cyclized form 1.186. Nosyl deprotection using thiophenol and $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ promoted the formation of the secondary amine $\mathbf{1 . 1 8 7}$ or $\mathbf{1 . 1 8 8}$. $\mathrm{TICl}_{3}$-promoted reduction of the nitro group afforded anilines 1.189. Cyclization of the latter onto the ketone followed by aromatization of the indole ring via retro aldol reaction afforded iminium 1.191. Intramolecular trapping of the latter converted it to 1,2-dehydroaspidospermidine (rac-3.2) in $51 \%$ yield. Addition of $\mathrm{NaBH}_{4}$ at the end of the cascade process allowed the reduction of rac-1.183 into aspidospermidine (rac-1.71) in $50 \%$ from rac1.184. Acylation of rac-1.183 afforded vincadifformine (rac-1.23).

With similar strategies in mind, two others reports from our group dealt with the synthesis of mersicarpine (1.192) (Scheme 20), scholarisine G(1.193) (Scheme 21) and related alkaloids. ${ }^{68}$ The main difference is the isolation of the oxidized products before the reduction/cyclization sequences.

[^21]

Scheme 20 - Total synthesis of mersicarpine from our lab
Cyclohexanone 1.194 was submitted to ozonolysis (non-reductive quench) to afford the ketoester 1.195 which was isolated in $96 \%$ yield. The latter was submitted to hydrogenation conditions to afford the aniline $\mathbf{1 . 1 9 6}$ which spontaneously cyclized to form the imine 1.197. Additional cyclization of the primary amine onto the ketone afforded diimine 1.198 which, under the reaction conditions, was reduced to the indole 1.199. Addition of KOH promoted the lactamization and furnished tetracycle 1.200. Bubbling of $\mathrm{O}_{2}$ through the reaction mixture followed by DMS quench afforded mersicarpine (1.192) in 75\% yield from 1.195.


Scheme 21 - Total synthesis of scholarisine G from our lab
Using the same diketone intermediate 1.195 , scholarisine $G$ (1.193) was also obtained (A). Reduction of the nitro and of the azide in the presence of acetic anhydride afforded aniline 1.201 which spontaneously cyclized and get reduced to afford 3-oxindole 1.202. Bubbling of $\mathrm{O}_{2}$ through the reaction mixture refurnished imine $\mathbf{1 . 2 0 3}$ which was cyclized onto the ester with the addition of KOH to afford aminal 1.204. TFA-promoted iminium 1.205 formation followed by intramolecular cyclization of the $N$-acyl amine afforded aminal 1.206 in $50 \%$ yield. The latter was transformed in one step into scholarisine $G(1.193)$ by an aldol reaction. Using this strategy, and starting from
scholarisine G (1.193), melodinine E (1.207), leuconoxine (1.208), leuconolam (1.209) and leuconodine $A(1.210), C(1.211)$ and $F(1.212)$ were also synthesized (B).

Even though the combination of an oxidant and a reductant in the same flask might sound counterintuitive, the use of iORC process proved to be a very efficient strategy to access various natural products. It allowed divergence to access diverse targets from a simple common precursor.

### 1.3 Goals of the Thesis

This thesis encompasses our contribution to the field in five chapters, which correspond to the five developed research projects we worked on.

In Chapter 2, we disclose our synthesis of (-)-terengganensine A (2.1) (Figure 11). The synthesis of the heptacyclic indole alkaloid was achieved in a short and efficient sequence featuring a diastereoselective cascade reaction based on advanced conformational analysis. The absolute configuration of terengganensine A was determined for the first time after our successful total synthesis.


Figure 11 - (-)-Terengganensine A (Chapter 2)
In Chapter 3, we focus on our synthetic endeavor towards (-)-vallesamidine (3.1) and (+)-1,2dehydroaspidospermidine (3.2) (Scheme 22). A divergent synthetic strategy allowed us to synthesize both natural products in a diastereo- and enantioselective fashion. Complex domino processes were incorporated into both total syntheses.


Scheme 22 - (-)-Vallesamidine and (+)-1,2-dehydroaspidospermidine (Chapter 3)
In Chapter 4, the total synthesis of (+)-peganumine A (4.1) is discussed (Figure 12). The octacyclic indole alkaloid was shown to have very interesting bioactivity against various cancer cell lines. The developed short and scalable synthetic strategy allowed us to access gram quantities of (+)peganumine A. Furthermore, the employed strategy allowed us to synthesize a great number of analogues.


Figure 12 - (+)-Peganumine A (Chapter 4)

As a continuation of our newly developed method during the synthesis of (+)-peganumine A (4.1), in Chapter 5 the development of a novel macrocyclization method based on the use of $\omega$ isocyanoaldehydes is discussed (Scheme 23). Various ring sizes and topologies were accessed in moderate to good yields. Eventually, we successfully applied our methodology to the total synthesis of (-)-eurystatin B (5.1) and its absolute configuration was determined.


## Scheme 23 - Macrocyclization of $\omega$-isocyanoaldehydes (Chapter 5)

Finally, the development of a novel three-component synthesis of proline amide derivatives will be presented in Chapter 6 (Scheme 24). Homopropargylamines were cyclized in the presence of isonitriles in good to excellent yields. With the aid of advanced mechanistic studies, we were able to extend the originally explored substrates scope. Moreover, we gained insight of an unprecedented on-column 3-component reaction.


Scheme 24-1,1-aminoacylation of homopropargylamines (Chapter 6)
After a general conclusion in Chapter 7, Chapter 8 is a comprehensive experimental part.

## Chapter 2 Enantioselective Total Synthesis of (-)-Terengganensine A

### 2.1 Introduction

Among the monoterpene indole alkaloids is the Hunteria-Eburnamine family and among the latter are found the eburnane alkaloids.

### 2.1.1 The Eburnane Alkaloids

### 2.1.1.1 History and Structure

This family is mainly composed of the vincane, eburnane and schizozygine skeleton types. ${ }^{69}$
The eburnane group was first described in 1959 by Bartlett, Taylor and Hamet. ${ }^{70}$ They isolated the first four members of this group from the plant Hunteria eburnean. Two of them, eburnamine (2.6) and isoeburnamine (2.9), were described as " $N$-alkyl type" (2.2). Eburnamonine (2.5) was also isolated and described as " $N$-acyl type" (2.3). Finally, eburnamenine (2.12) was reported as " $N$-vinyl" type alkaloid (2.4) (Figure 13 and Figure 14). ${ }^{71}$

$N$-alky


N -acyl
2.3


N -vinyl
N -vinyl
2.4

Figure 13 - Classification of the first four isolated eburnane alkaloids
Since the isolation of the first members, more than 25 alkaloids of the eburnane group have been isolated and characterized (Figure 14). ${ }^{72}$

[^22]
(2.5) (+)-Eburnamonine $\mathbf{R}^{1}, \mathbf{R}^{2}=\mathbf{O}(-)$-Eburnamonine (ent-2.5) (2.6) (-)-Eburnamine $\mathbf{R}^{1}=\mathrm{OH}, \mathrm{R}^{2}=\mathrm{H}(-)$-Eburnamine (ent-2.6) (2.7) (-)-O-Ethyleburnamine $\mathrm{R}^{1}=\mathrm{OEt}, \mathrm{R}^{2}=\mathrm{H}(+)$-O-Ethyleburnamine (ent-2.7) (2.8) (-)-O-Mehyleburnamine $\mathrm{R}^{1}=\mathrm{OMe}, \mathrm{R}^{2}=\mathrm{H}(+)-\mathrm{O}$-Mehyleburnamine (ent-2.8)
(2.5) (+)-Isoeburnamine $\mathrm{R}^{1}=\mathrm{H}, \mathrm{R}^{2}=\mathrm{OH}(-)$-Isoeburnamine (ent-2.9) (2.9) (+)-O-Ethylisoeburnamine $\mathbf{R}^{1}=H, R^{2}=O E t(-)-O-E t h y l i s o e b u r n a m i n e ~(e n t-2.10)$ (2.10) (+)-O-Methylisoeburnamine $\mathbf{R}^{1}=H, R^{2}=O M e(-)-O-M e t h y l i s o e b u r n a m i n e ~(e n t-2.11) ~$ (2.12) (+)-Eburnamenine $\mathbf{R}^{1}=H, R^{2}=$ nil, $\Delta^{16,17}(-)$-Eburnamenine (ent-2.12)


$\mathbf{R}^{1}=\mathrm{H}, \mathbf{R}^{\mathbf{2}}=\mathrm{OH}(-)-19(\mathrm{R})$-Hydroxyeburnamine (2.13) $\mathrm{R}^{1}=\mathrm{OH}, \mathrm{R}^{2}=\mathrm{H}(+)-19(R)$-Hydroxyisoeburnamine (2.14)

(2.15)



Figure 14 - Examples of naturally occurring eburnane alkaloids
The eburnane alkaloids are mainly found in the Apocynaceae plant family and especially in the genus Hunteria, Melodinus and Kopsia but also in Amsonia, Aspidosperma, Catharanthus, Comularia, Craspidospermum, Crioceras, Cyclocotyla, Haplophyton, Leuconotis, Pandaca, Pleiocarpa, Rhazya, Strempeliopsis, Tabernaemontana, and Voacanga. ${ }^{72 b}$

Structurally, they are pentacyclic rearranged skeletons from the vincadifformine ring system (see 1.1.1.1 - Biosynthesis) involving a migration of $\mathrm{C}-21$ from $\mathrm{C}-7$ to $\mathrm{C}-2$, a $\mathrm{C}-2 / \mathrm{C}-16$ bond fission and N -1/C-16 junction which creates an additional E ring (Figure 15).


Figure 15 - General structure and conformation of eburnane alkaloids and their numbering system
All of them embed a cis-fused D/E ring system, i.e. $\mathrm{H}-21$ is in a cis relationship with the C-18/C-19 chain. It is interesting to note that Malaysian Kopsia species were long time thought to elaborate exclusively eburnane alkaloids of one enantiomeric group (21R) while the Chinese species appeared to elaborate eburnane alkaloids of the opposite enantiomeric group (21S). ${ }^{72 a}$ Recent investigations have demonstrated exceptions to this "rule". ${ }^{73}$ It is also noteworthy that for almost every eburnane natural products, both enantiomers can be found in Nature. Even more surprising, some species such as Kopsia pauciflora are able to produce racemic or scalemic mixtures, i.e. enantioenriched but not enantiopure mixtures. ${ }^{73,74}$ Until recently, determination of the absolute configuration of newly isolated molecules based on the ones of co-isolated known compounds or based on their isolation plant was a common practice. In light of these recent new discoveries such hypotheses will probably be considered as less and less solid arguments.

[^23]The cis-fused D/E ring system in addition with the $N-1 / C-16$ connectivity forces the $C / D$ ring junction to be cis-fused as exemplified by various crystal structures found in the literature. This conformation is usually not favored in simple indoloquinolizidine (2.19) systems because of the unfavorable $\mathbf{1 , 4} 4$ steric clash it generates (Figure 15). A notable exception is larutensine (2.17) which embed a trans-fused C/D ring junction as computed by Kam and coworkers. ${ }^{73}$

Concerning their bioactivity, many eburnane alkaloids are pharmacologically active and exert diverse effects in the living body the range expanding from antitumor activity through circulatory effects to cerebroprotection for instance. ${ }^{72 b}$

### 2.1.1.2 Biosynthesis

As shown in Scheme 1, aspidosperma group of alkaloids is closely related to the eburnane one. In addition, by looking at the same scheme, achiral secodine (1.22) could explain the enantiodivergence in the aspidosperma and eburnane alkaloids biosynthesis. The key step in the eburnane alkaloids biosynthesis is the rearrangement of the aspidosperma skeleton of vincadifformine (1.23) into the eburnane (or vincane) one. This transformation was already successfully mimicked in the laboratory (Scheme 25 and Scheme 26).


Scheme 25 - Rearrangement of the aspidosperma to the vincane skeleton via oxidation with $p-\mathrm{NO}_{2^{-}}$ perbenzoic acid

When (-)-vincadifformine (ent-1.23) was treated with para-nitroperbenzoic acid in benzene at low temperature followed by reduction with $\mathrm{PPh}_{3},(+)$-vincamine (ent-1.12) and (-)-16-isovincamine (2.24) were obtained. The first step involved the oxidation of the enamine and of the tertiary amine to afford the 16 -hydroxyindolenine $N$-oxide derivative $\mathbf{2 . 2 0}$. This product spontaneously rearranged when the N -oxide was reduced under acidic conditions with $\mathrm{PPh}_{3}$ presumably via iminium 2.21 followed by re-aromatization of the indole ring by cleavage of the C-16/C-2 bond. The $\alpha-$ ketoester $\mathbf{2 . 2 3}$ cyclized then immediately on the indole nitrogen to form the two observed aminal ent-1.12 and $\mathbf{2 . 2 4}$ as a mixture of diastereoisomers. ${ }^{75}$

[^24]

Scheme 26 - Rearrangement of the aspidosperma to the vincane skeleton via photooxidation and thermal rearrangement

Other reaction conditions allowed the conversion of aspidosperma alkaloids to vincane (or eburnane) alkaloids. Photooxidation of (-)-vincadifformine (ent-1.23) using Rose Bengal as photosensitizer followed by reductive conditions allowed the isolation of the hydroxyindolenine ent1.24. ${ }^{76}$ The latter was then easily converted to the vincane alkaloids ent-1.12 and $\mathbf{2 . 2 4}$ using either heat ${ }^{77}$ or acidic conditions ${ }^{76}$ following the same reaction pathway as depicted in Scheme 25.

The interconversion between the different eburnane alkaloids was also successfully explored in the laboratory.


Scheme 27 - Biomimetic interconversion between (-)-eburnamine, ( + )-isoeburnamine and ( + )-
eburnamenine
Dissolving either (-)-eburnamine (2.6) or (+)-isoeburnamine (2.9) under slightly acidic conditions led to isomerization to afford $90 \%$ of the former and $10 \%$ of the latter (thermodynamic equilibrium) (Scheme 27, A). When the same solution was briefly warmed, elimination occurred and (+)eburnamenine (2.12) was obtained (B). ${ }^{71}$ Similarly, overnight treatment of (-)-eburnaminol (2.15) with $5 \% \mathrm{HCl}$ at room temperature leaded to (+)-larutensine (2.17) (Scheme 28). ${ }^{72 \mathrm{a}}$


Scheme 28 - Biomimetic conversion of eburnaminol into larutensine

### 2.1.1.3 Previous Syntheses

Drastic efforts have been invested in the synthesis of eburnamine alkaloids. Most of these syntheses are based on the same few strategies and disconnections (Scheme 29).

[^25]

Scheme 29 - General retrosynthetic scheme for the reported syntheses of eburnane alkaloids
Almost all syntheses disconnected first the $N-1 / \mathrm{C}-16$ bond of $\mathbf{2 . 1 8}$ to the tetracyclic system $\mathbf{2 . 2 6}$ (A). The formation of this bond was generally achieved via peptide coupling or hemiaminal formation via attack of the indole nitrogen onto an aldehyde. The tetracyclic system 2.26 was then generally formed via a Pictet-Spengler (B) or a Bischler-Napieralski reaction (C). The former generally led to lower yields except if an acyl iminium (2.27) was involved as intermediate. The BischlerNapieralski precursor $\mathbf{2 . 2 8}$ was generally obtained via peptide coupling and $\mathrm{S}_{\mathrm{N}} 2$ reaction between tryptamine (1.16) and $\mathbf{2 . 3 0}$ (D). The Pictet-Spengler precursor $\mathbf{2 . 2 7}$ was mainly obtained by condensation with aldehyde 2.31 and either amide coupling (for $N$-acyl iminium) (E) or $\mathrm{S}_{\mathrm{N}} 2$ reaction with $\mathbf{2 . 3 2}$ (for iminium) (F). Another used strategy to generate the Pictet-Spengler precursor $\mathbf{2 . 2 7}$ was the $\alpha$-alkylation of cyclic $\alpha$-substituted enamine $2.41(\mathrm{G})$. This alkylation method was also used once the tetracyclic system formed but required the reduction of the generated iminium ion (H). The monoalkylated tetracyclic system $\mathbf{2 . 2 9}$ could in turn be disconnected in different ways. The first one involved the alkylation of a non-alkylated tetracyclic enamine $\mathbf{2 . 3 5}$ (G). The second method involved the Bischler-Napieralski reaction with 2.37 (C). Finally, the last method was the oxidation of the tetracyclic amine 2.38 (I) which could be obtained by a Pictet-Spengler reaction with the in situ generated iminium from simple cyclic amine 2.39 ( $J$ ).


Scheme 30 - Challenge of the diastereocontrol in eburnane alkaloids synthesis
Control of the diastereoselectivity following these general strategies has always been a challenge (Scheme 30). The main problem arose from the relatively low diastereocontrol of C-20 towards C21. The low diastereoselectivity could easily be explained by the relatively similar steric influence of the ethyl substituent and the $\mathrm{CH}_{2} \mathrm{X}$ side chains. For instance the $A$ value for ethyl group is -1.8 $\mathrm{kcal} / \mathrm{mol}$ whereas the one of $\mathrm{CH}_{2} \mathrm{CO}_{2} \mathrm{Et}$ is $-1.3 \mathrm{kcal} / \mathrm{mol} .^{78}$ Moreover, as the $\mathrm{H}-21$ has to be cis with the ethyl group, no reaction using the X as directing group could be involved. ${ }^{79}$ The slight preference generally observed for the desired cis isomer was proposed to arise from a neighboring group effect of the ester at $\mathrm{C}-20 .{ }^{.80}$

In order to illustrate these different approaches, selected examples of total synthesis of eburnamonine (2.5) will be summarized below (Scheme 31 to Scheme 40).


Scheme 31 - Taylor's synthesis of ( $\pm$ )-eburnamonine
The first synthesis of an eburnane alkaloid was realized by Taylor and coworkers ${ }^{71}$ (Scheme 31) via a Pictet-Spengler reaction between tryptamine (1.16) and a latent aldehyde-diacid $\mathbf{2 . 4 2}$ followed by reduction of the bisamide $\mathbf{2 . 4 3}$ and reoxidation of the obtained diastereomeric mixture of hemiaminals 2.6 and 2.9 to afford ( $\pm$ )-eburnamonine (rac-2.5).

[^26]

## Scheme 32 - Wenkert's synthesis of ( $\pm$ )-eburnamonine

Wenkert and coworkers also synthesized ( $\pm$-eburnamonine (rac-2.5) (Scheme 32). ${ }^{81}$ Their synthesis involved the formation of lactam 2.37 from tryptamine (1.16) and 5-bromo ester derivative $\mathbf{2 . 4 4}$ followed by a Bischler-Napieralski reaction to afford iminium 2.45. After enamine formation, the latter was then alkylated. Iminium $\mathbf{2 . 4 6}$ was subsequently reduced and finally the $N-1 / \mathrm{C}-16$ amide bond was formed under basic conditions. In this case, a surprising 8:1 diastereoisomeric ratio was obtained using $\mathrm{Pd} / \mathrm{C}$ whereas a 1:1 mixture was obtained with sodium borohydride.


Scheme 33 - Wenkert's $2^{\text {nd }}$ synthesis of ( $\pm$ )-eburnamonine
10 years later, the same group reported a second synthesis of ( $\pm$ )-eburnamonine (rac-2.5) (Scheme 33). ${ }^{82}$ It consisted of the nucleophilic substitution of tryptophil bromide (2.49) with the cyclic amine 2.48. The latent iminium 2.50 was then cyclized twice under acidic conditions (PictetSpengler reaction followed by amide bond formation). A 1.3:1 mixture of diastereoisomers was obtained in favored of the desired one. It is interesting to note the reported surprisingly perfect diastereocontrol when submitting 2.50 to thermolysis at $250^{\circ} \mathrm{C}(0.01 \mathrm{Torr}) .^{83}$

[^27]

Scheme 34 - Lévy's synthesis of ( $\pm$ )-eburnamonine
Scheme 34 pictured the synthesis from Lévy and coworkers. ${ }^{84}$ It featured the formation of a cyclic enamine $\mathbf{2 . 2 9}$ by reaction of tryptamine (1.16) with methyl-5-formylheptanoate (2.51). The lactam 2.29 was then reduced and the resulting enamine $\mathbf{2 . 4 1}$ was alkylated to form iminium $\mathbf{2 . 4 6}$. The latter was directly engaged in a Pictet-Spengler reaction/amide bond formation sequence to afford ( $\pm$-eburnamonine (rac-2.5) in a 1:1 mixture of diastereoisomers.


Scheme 35 - Grieco's synthesis of ( $\pm$ )-eburnamonine
Not all the racemic synthesis of eburnamonine (rac-2.5) relied on the general strategies presented in Scheme 29. One alternative example is the Grieco's synthesis (Scheme 35 ). ${ }^{85}$ Combining aldehyde $\mathbf{2 . 5 2}$ and cyclopropane $\mathbf{2 . 5 3}$ afforded the precursor $\mathbf{2 . 5 4}$ after 4 steps. When submitting $\mathbf{2 . 5 4}$ under TFA-promoted [4+2] cycloaddition conditions, rac-2.5 was obtained as a sole diastereoisomer.

Concerning the enantioselective syntheses of eburnane alkaloids, almost all reported examples relied again on the use of $\mathrm{C}-20$ to control the stereochemistry at $\mathrm{C}-21$. Therefore the main challenge was the construction of the chiral C-20 quaternary center.

Selected enantioselective examples are represented below (Scheme 36 to Scheme 40).

[^28]

## Scheme 36 - Enantioselective synthesis of (-)-eburnamonine by Fuji and coworkers

(-)-Eburnamonine (ent-2.5) was synthesized by Fuji and coworkers in 1987 (Scheme 36). ${ }^{86}$ Their synthesis started with a stereoselective 1,4-addition/elimination sequence to afford chiral lactone 2.57 with the help of a chiral auxiliary derived from $(S)$-proline. The lactone $\mathbf{2 . 5 7}$ was converted in 6 steps to acetal 2.58 which, after reaction with tryptamine (1.16) and some functional group manipulations, afforded the desired product ent-2.5. This synthesis also relied on the use of C-20 to control the C-21 stereocenter and they obtained a 1:1 ratio between both diastereoisomers. To diminish the impact of this drawback, the authors described the interconversion between the two diastereoisomers of 2.59. Treatment of the trans isomers with $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$ afforded again a 1:1 mixture.


Scheme 37 - Schultz's enantioselective synthesis of (-)-eburnamonine
The Pictet-Spengler reaction for the construction of the ring $C$ was successfully used by Schultz and coworkers (Scheme 37, A). ${ }^{87}$ This synthesis also featured the use of a chiral auxiliary. Amide 2.60, easily obtained from (S)-proline was converted in 5 steps to the lactone 2.61. Reaction with tryptamine (1.16) and further functionalization afforded aldehyde 2.62. Pictet-Spengler reaction at -55

[^29]${ }^{\circ} \mathrm{C}$ in the presence of TFA afforded the desired tetracyclic system 2.63 in an excellent 18:1 dr . The same reaction at room temperature lowered down the $d r$ to 7:1. A two-step sequence converted 2.63 into (-)-eburnamonine (ent-2.5).

Compared to previous strategy based on Pictet-Spengler reaction (Scheme 31, Scheme 33 and Scheme 36), the diastereocontrol was highly superior in this case. Similar to ethyl and $\mathrm{CO}_{2} \mathrm{Et}$, steric difference between ethyl and vinyl is negligible. $A$ values are -1.8 and $-1.7 \mathrm{kcal} / \mathrm{mol}$ respectively. ${ }^{88}$ Similar remarkable diastereoselectivity was already observed previously by Barton and coworkers (Scheme 37, B). ${ }^{89}$ Instead of a vinyl, they relied on the use of an allyl group attached to the C-20. These two results did provide some support for the suggestion that electronic effects were responsible for the good diastereoselectivity in the cyclization of $\mathbf{2 . 6 2}$ and $\mathbf{2 . 6 4}$. Interactions between $\pi$-bonds of the vinyl/allyl substituent, the indole ring, and the acyl iminium ion in the presumed intermediate for the cyclization may contribute to a selection for the desired cis diastereoisomer. This kind of interaction was previously suggested by Cook and coworkers. ${ }^{90}$

An example by Takano and coworkers exemplified the introduction of the chirality element using another building block from the chiral pool, L-glutamic acid (2.66) (Scheme 38). ${ }^{91}$


Scheme 38 - Enantioselective synthesis of (-)-eburnamonine by Takano and coworkers
L-glutamic acid (2.66) was first converted to the enantiopure mono-substituted lactone 2.67. Double diastereoselective alkylation afforded $\gamma$-lactone 2.68. The latter was then converted to the doubly substituted $\delta$-lactone 2.69 in a 3 -step sequence. After merging tryptamine (1.16) and 2.69, LAH reduction of $\mathbf{2 . 7 0}$ afforded $\mathbf{2 . 7 1}$. The desired (-)-eburnamonine (ent-2.5) was obtained after functional group manipulations. Again this synthesis relied on the use of C-20 to control the C-21 stereocenter but again a poor diastereoselectivity was observed (<6:4 dr).

[^30]

## Scheme 39 - Enantioselective synthesis of (-)-eburnamonine by Argade and coworkers

A notable exception among the reported synthesis of eburnamonine is the work of Argade and coworkers (Scheme 39, A)..$^{92}$ Borrowing the chirality from chiral pool again, their synthesis relied on a C-21 to C-20 diastereocontrol. While submitting the hemiaminal $\mathbf{2 . 7 4}$ to Pictet-Spengler conditions, lactam 2.75 was obtained in 20:1 dr. ${ }^{93}$ After functional group manipulation, a 1,4-addition of ethyl cuprate on the $\alpha, \beta$-unsaturated ester 2.77 afforded ent-2.5 as a single diastereoisomer. This diastereospecific 1,4-addition was initially reported by Martel and coworkers ${ }^{94}$ and used by two other groups, the one of Santamaria ${ }^{95}$ and the one of Ghosh albeit in racemic syntheses. ${ }^{96}$ While Martel performed the reaction on a trans quinolizidine ring system (trans-rac-2.77), Santamaria performed the reaction on a 55:45 mixture cis/trans and on the pure cis rac-2.77 and Ghosh on the trans rac-2.77. ${ }^{97}$ Whatever the conformation of the starting 2.77 was, they all observed a preference for the formation of the desired cis product. Santamaria reported a $>7: 1 \mathrm{dr}$ starting from the mixture and $a>19: 1 d r$ starting from pure cis rac-2.77. The good diastereocontrol can easily be explained by looking at the concave structure of $\mathbf{2 . 7 7}$ (Scheme 39, B).


Scheme 40 - Qin's synthesis of (+)-eburnamonine

[^31]Finally, one of the most recent, and probably one of the most original syntheses of (+)eburnamonine (2.5) was published in 2017 by Qin and coworkers (Scheme 40). ${ }^{98}$ Radical cascade cyclization of enantio-enriched $\mathbf{2 . 7 8}$ afforded $\mathbf{2 . 7 9}$ in a $\mathbf{1 : 1 . 5}$ mixture of diastereoisomers in favored of the trans one. A 7-steps sequence converted it to (+)-eburnamonine (2.5).

As exemplified above, the conformation plays a major role in the synthesis of eburnane alkaloids. Among the eburnane group, terengganensine $A(2.1)$ and $B(2.81)$ are two examples of recently isolated members with very intriguing conformations and structures.

### 2.1.2 (-)-Terengganensine $A$ and $B$

### 2.1.2.1 History and Structure

Five known alkaloids, (+)-quebrachamine (2.82), (-)-eburnamine (2.6), (+)-isoeburnamine (2.9), (-)eburnaminol (2.15), and (+)-larutensine (2.17) were isolated in 1997 from a Malaysian species, Kopsia terengganensis, ${ }^{99}$ by Païs and coworkers. ${ }^{100}$

In addition to these known alkaloids, isolated from the bark and the leaves of the same plant, two unprecedented compounds, namely (-)-terengganensine A (2.1) and (-)-terengganensine B (2.81), were also identified (Figure 16).

The isolation yield of (-)-terengganensine A(2.1) from the bark was $4 * 10^{-4} \%$ and the one of (-)terengganensine $B$ (2.81) was $10^{*} 10^{-4} \%$. From the leaves, the isolation yields were similar with $3.9 * 10^{-4}$ and $18.5 * 10^{-4} \%$ respectively.


Figure 16 - Structure of (-)-terengganensine $A$ and $B$ and (+)-quebrachamine
As depicted on Figure 17, (-)-terengganensine A (2.1) is a heptacyclic indole alkaloid. It contains a dihydroindole chromophore, also named indoline. It features an aza-adamantly-like structure involving the indoline nitrogen and the C-2 of the indoline. This cage-like structure is composed of one acetal ( $\mathrm{C}-18$ ) and two aminal carbons ( $\mathrm{C}-2$ and $\mathrm{C}-16$ ). The $\mathrm{C}-7$ position of the indoline is a quaternary carbon bearing a hydroxyl group.

The observation of Bohlmann bands ${ }^{101}$ in the IR spectrum (2832, 2812, $2785 \mathrm{~cm}^{-1}$ ), arising from three $\mathrm{n}(\mathrm{N})$ to $\sigma^{*}\left(\mathrm{C}-\mathrm{H}_{\text {axial }}\right)$, interactions and the observed NOE between $\mathrm{H}-19 \beta$ and $\mathrm{H}-21$ indicated

[^32]trans-fused C/D and cis-fused D/E ring junctions, as in larutensine (2.17). Similar to all the other eburnane alkaloids, The $\mathrm{H}-21$ and the $\mathrm{C}-18 / \mathrm{C}-19$ side chain have a cis relationship. Furthermore, the formation of the ether bridges required the $\mathrm{O}-\mathrm{C}-16$ and the $\mathrm{O}-\mathrm{C}-2$ bonds to lie on the same side. Finally, a cis-fused $B / C$ junction was assigned in analogy to all other aspidosperma alkaloids and to allow ring C to be in a chair conformation.

Based on these characteristic spectroscopic data, a 3-D conformation of terengganensine A (2.1) where all five saturated 6 -membered rings are in a chair conformation could be deduced (Figure 17).


Figure 17 - Conformation of (-)-terengganensine $A$
Those spectral data did not give insight about the absolute configuration. Since the co-isolated (-)eburnamine (2.6), (+)-isoeburnamine (2.9), (-)-eburnaminol (2.15) and (+)-larutensine (2.17) all had the same absolute configurations at $\mathrm{C}-21$ and $\mathrm{C}-20$, it was assumed that (-)-terengganensine A (2.1) and $B(2.81)$ shared identical configurations. Additional clue came from the fact that, at that time, it was believed that all compounds isolated from Malaysian Kopsia species had the same $21(R)$ absolute configurations. Nevertheless, in light of recent findings (see 2.1.1.1 - History and Structure), and as no crystal structure of either terengganensine $A(\mathbf{2 . 1})$ or $B(\mathbf{2 . 8 1})$ had been obtained, great care had to be taken with this assumption.

As pictured on Figure 18, the structure of (-)-terengganensine $B(\mathbf{2 . 8 1})$ is closely related to that of terengganensine $A$ (2.1). The only difference is the lack of the oxygen forming the second aminal and the acetal. The cage-like structure is therefore replaced by an enamine in ring $E$ and a simple cyclic ether in ring F. The same conformational analysis as for terengganensine A was performed based on spectroscopic data leading to the 3-D conformation shown on Figure 18.


Figure 18 - Conformation of (-)-terengganensine B

[^33]
### 2.1.2.2 Biosynthesis and Biological Activity

Concerning the biosynthesis of (-)-terengganensine $A(2.1)$ and $B(2.81)$ the following sequence was proposed (Scheme 41). ${ }^{102}(-)$-Eburnamine (2.6) could lose water to afford (+)-eburnamenine (2.12). C-7 and C-18 oxidations followed by cyclization could then afford (-)-terengganensine B (2.81). In another route, (-)-eburnamine (2.6) could be oxidized at the $\mathrm{C}-18$ position leading to eburnaminol (2.15) which in turn could be converted to larutensine (2.17). Finally, C-7 and C-18 oxidations and cyclization could afford (-)-terengganensine A (2.1).


## Scheme 41 - Proposed biosynthetic sequence to (-)-terengganensine A and B

Concerning the bioactivity of (-)-terengganensine $A(\mathbf{2 . 1})$ and $B(\mathbf{2 . 8 1})$, no data are yet available but it would not be surprising to find interesting bioactivity as most of the eburnane alkaloids. ${ }^{72 b}$

Because of its very intriguing molecular structure and as no total synthesis of terengganensine $A$ or B was reported, we decided to tackle this challenge. If successful, this would also provide the opportunity to confirm their absolute configuration. In addition, the obtained (-)-terengganensine $A(2.1)$ and $B(2.81)$ could be submitted for bioactivity evaluation.

### 2.2 Retrosynthetic Pathway and Background

Among the total syntheses of eburnane alkaloids, we were interested in Ho's racemic synthesis of $( \pm)$-eburnamine (rac-2.6), ( $\pm$ )-isoeburnamine (rac-2.9) and ( $\pm$ )-eburnamonine (rac-2.5) (Scheme 42). ${ }^{103}$

[^34]

## Scheme 42 - Ho's synthesis of various eburnane alkaloids

They initially synthesized indole rac-2.88 in a 4 steps sequence from the commercially available methyl cyclopent-3-ene-1-carboxylate (2.83). Alkylation of 2.83 by 1-bromo-3-chloropropane (2.84) followed by ester reduction afforded alcohol 2.86. After reoxidation of the alcohol to the aldehyde 2.87, a subsequent Pictet-Spengler reaction with tryptamine (1.16) afforded indole rac2.88. Despite this short sequence, the overall yield was only $15 \%$ due to the very problematic Pic-tet-Spengler reaction. The low yield was probably due to the big steric hindrance induced by the spirocyclopentene. We, in fact, repeated Ho's synthesis in order to better understand the reason for the low yield of the Pictet-Spengler step. Mixing tryptamine (1.16) and aldehyde 2.87 for 2 hours as described in the literature did not lead to any reaction. Adding an excess of TFA and heating to reflux overnight afforded only a trace amount of the desired product rac-2.88 as well as some starting aldehyde 2.87 and a lot of tryptamine (1.16) plus a consequent amount of unidentified products. Addition of the large excess of TFA (4.2 equiv) as well as strong heating probably fully protonated the tryptamine nitrogen, rendering it unreactive to any condensation/nucleophilic substitution. It also probably promoted the decomposition of the sensitive aldehyde 2.87. A longer reaction time before the addition of TFA or a more efficient condensation method could probably afford a better yield.

In the same paper, they also attempted the cleavage of the cyclopentene moiety. Dihydroxylation of rac-2.88 followed by oxidative cleavage of the resulting diol $\mathbf{2 . 8 9}$ afforded dialdehyde $\mathbf{2 . 9 1}$ (Scheme 43) which underwent spontaneous cyclization to afford the undesired trans diastereoisomer 2.90 exclusively (as a 2.5:1 mixture of epimers at $\mathrm{C}-18$ ) and therefore three or four more steps where required to obtain the desired natural products.

While no explanation was given in Ho's paper, we hypothesized that this wrong diastereoselectivity would be a logical outcome if the C/D rings of indole rac- 2.88 were trans-fused (Scheme 43). The equatorial aldehyde ( $\mathrm{C}-18$ ) could be the only accessible one by the indole nitrogen which could explain the very good selectivity for the wrong diastereoisomer.


## Scheme 43 - Our working hypothesis for the wrong diastereoselectivity observed in Ho's synthesis of eburnane alkaloids

On the basis of this assumption and having in mind the synthesis of (-)-terengganensine $A(2.1)$, we hypothesized that oxidation at the C-7 position and in situ inter- or intramolecular cis trapping of the generated imine 2.92 could allow the complete reversal of the diastereoselectivity in the cyclization (Scheme 44, pathway A). As depicted on Scheme 44, the two newly generated $\mathrm{sp}^{3}$ centers (instead of the two $\mathrm{sp}^{2}$ in 2.92 ) could direct the cyclization of the indoline nitrogen with the axial aldehyde in 2.93 (C-16), giving rise to the formation of the correct diastereoisomer of the hemiaminal 2.94.


Scheme 44 - Conformational analysis for the final triple cyclization cascade sequence
The latter could then cyclize with the other aldehyde generating ( $\mathrm{C}-18$ ) the hemiacetal 2.95. The newly generated alcohol could then attack the indolenine carbon generating the desired diastereoisomer of 2.96. Same reaction without intra-/intermolecular trapping (Scheme 44, pathway B) could also afford the desired diastereoisomer of 2.97 but the selectivity might be less obvious than in pathway A. Possible intermolecular trapping could arise from the solvent ( $\mathrm{H}_{2} \mathrm{O}, \mathrm{MeOH}$, etc.). Possible intramolecular trapping could be performed using $X=C l, B r, O H, O C(O) R$.

With this conformational analysis in mind, we developed a retrosynthetic plan for (-)terengganensine A (2.1) which is depicted in Scheme 45.


## Scheme 45 - General retrosynthetic scheme from (-)-terengganensine A to the known indole skeleton 2.88

Because of the easy intramolecular formation of imines, aminals and acetals, we decided to disconnect the targeted molecule (2.1) to the prochiral dialdehyde 2.93. The latter was traced back to the 1,2-diol 2.99. In the forward direction, oxidative cleavage followed by cascade cyclizations could afford (-)-terengganensine A (2.1). Diol 2.99 was traced back to cyclopentene 2.100. Finally, the latter was disconnected to indole 2.88. In the forward direction, diastereoselective C-7 oxidation could furnish 2.100.

Even though it might look to be easy textbook reactions, many potential pitfalls existed (Scheme 46).


Scheme 46 - Potential issues during the oxidation of the indole skeleton 2.88
First of all, the indole 2.88 oxidation had to be selective. Indeed, the double bond as well as the tertiary amine could easily be oxidized. It also had to be diastereoselective in order for the newly introduced X group to be cis with the $\mathrm{H}-21$. It was also well known that $\mathrm{C}-3$ oxidation of indole could afford rearranged products such as 2 - and 3 -oxindole $\mathbf{2 . 1 0 2}$ and $\mathbf{2 . 1 0 1}{ }^{104}$ and these side reactions had to be avoided in our case. Concerning the relative stereochemistry between $\mathrm{H}-21$ and X-7, we thought that the center 21 could direct the oxidation of the indole. Almost all reported oxidations of tetrahydrocarboline to 3-bromo or 3-chloroindolenine afforded a cis relationship between the $\mathrm{X}-7$ and the $\mathrm{H}-21$ proton.

Direct construction of a chiral C-21 stereocenter and its subsequent use to control the formation of C-20 was, up to now, only reported once (Scheme 39). In our case, C-7 was planned to be used

[^35]as relay of stereochemistry to control the configuration of C-20 by way of a group-selective aminal formation (Scheme 47). ${ }^{105}$

4.1

Scheme 47 - General strategy for the diastereocontrol of C-20 in our synthesis of (-)-terengganensine A
For the synthesis of the indole skeleton 2.88, a different, enantioselective and more efficient route than the one reported by Ho and coworkers was envisioned (Scheme 48). There were several main issues associated with the Pictet-Spengler reaction. First of all, Pictet-Spengler reaction is known to be highly sensitive to steric hindrance, especially in all the described cases with similar skeletons (Scheme 48, A). ${ }^{72 \mathrm{~b}}$ A possible alternative to improve its efficiency could have been to perform the condensation with an amide instead of a simple amine in order to generate the more reactive $N$-acyl iminium intermediate $\mathbf{2 . 1 0 5}$. This would then require the need for the reduction of the amide $\mathbf{2 . 1 0 4}$ which could involve quite harsh conditions and additional steps (Scheme 48, B). Another common disadvantage of Pictet-Spengler reaction (of iminium or $N$-acyl iminium) is that only limited amount of enantioselective methods are currently available. For an overview of the existing methods, see: 4.2 - Initial Retrosynthetic Pathway and Background. ${ }^{106}$ Therefore, a sequence consisting in the generation of iminium salt 2.106 by a Bischler-Napieralski reaction followed by an enantioselective reduction of the iminium was chosen for the synthesis of the enantio-enriched compound 2.88 (Scheme 48, C).


Scheme 48 - General retrosynthetic scheme for the formation of the indole skeleton 2.88

[^36]The main advantage to rely on a Bischler-Napieralski reaction for the C-2/C-21 bond formation was that harsher conditions could be applied to overcome the steric hindrance of the spirocyclopentene as no stereocenter would be generated in this step. After successfully obtaining the iminium 2.106, enantioselective reduction would then be required. Up to now, this strategy has not been used in the syntheses of eburnane alkaloids. Nevertheless six different publications already described the enantioselective reduction of tetrasubstituted iminium in isoquinolinium and indoloquinolizinium scaffolds. All of them are based on asymmetric transfer hydrogenation ${ }^{107}$ using Noyori catalysts.

### 2.2.1 Asymmetric Transfer Hydrogenation

In 1987, Noyori and coworkers reported for the first time a very efficient enantioselective hydrogenation of $\beta$-keto ester using a BINAP-coordinated $\mathrm{Ru}(I I)$ catalyst. ${ }^{108}$ Since then, several ruthenium based catalysts were developed by the group of Prof. Noyori, especially for the reduction of ketone/aldehyde and one in particular including Ru-diamine complex for transfer hydrogenation. In 1996, their Ru-diamine complex was applied to the reduction of imine. ${ }^{109}$

The scope was then extended to tetrasubstituted iminium for the first time by Norton and coworkers. ${ }^{110}$ Iminium behave very differently than other reducible polar double bonds such as ketones as they lack the required lone pair for protonation/hydrogen bonding in order to form the postulated 6-membered ring transition state pictured on Figure 19. This is even more important for reaction in water. ${ }^{111}$ Inner-sphere mechanism as well as outer-sphere mechanism assisted by an ancillary ligand cannot occur anymore in this case. Norton and coworkers have shown that an ionic mechanism occurred when using $\mathrm{CpRu}(\mathrm{P}-\mathrm{P})$ catalyst. ${ }^{112}$ Morris and coworkers described the hydride transfer, the rate and enantiodetermining step, as a pure outer-sphere mechanism. ${ }^{113}$ To the best of our knowledge no mechanistic investigation has been made on $\mathrm{CpRu}(\mathrm{N}-\mathrm{N})$ catalysts.


Figure 19-6-membered ring transition state for the reduction of aldehyde/ketone

[^37]Figure 19 shows the 6-membered ring transition state (2.108) responsible for the high enantioinduction during the reduction of aldehyde/ketone. Hydrogen-bonding between the carbonyl oxygen and a hydrogen of the diamine ligand in addition to a $\mathrm{C}-\mathrm{H} / \pi$ interaction allows to fix the conformation and to deliver the hydride in a pseudo-intramolecular fashion.

Concerning the reduction of scaffolds close to $\mathbf{2 . 1 0 6}$, such as isoquinolinium and $\beta$-carbolinium, conditions were recently developed by Wills', ${ }^{114}$ Zhu's and Deng's, ${ }^{115}$ Pihko's ${ }^{116}$ and Drabowicz's ${ }^{117}$ groups.

Wills and coworkers reported the deprotection/cyclization/reduction cascade of 2.109 using asymmetric transfer hydrogenation (Scheme 49). Formic acid was used for the Boc deprotection and as hydride source. Using diamine ligand, they in situ formed the active catalyst in MeCN and they were able to isolate $\mathbf{2 . 1 1 0}$ in moderate yield and enantioselective. It is to note that they did not probe the mechanism of the reaction.


Scheme 49 - Wills' methodology for the $N$-Boc deprotection/cyclization/reduction cascade reaction of 2.109

Zhu, Deng and coworkers have performed the reduction of iminium 2.112 in water using CTAB as surfactant and sodium formate as hydride source (Scheme 50). They were able to obtain 2.113 in $88 \%$ yield and $90 \%$ ee. Here also the catalyst was formed in situ. It features two anionic groups to increase the solubility in water.


Scheme 50 - Zhu's and Deng's enantioselective reduction of isoquinolinium

[^38]The two previous examples dealt with the reduction of isoquinolinium. The two next ones focused on $\beta$-carbolinium.

Drabowicz and coworkers in situ generated Noyori's catalyst and were able to reduce iminium chloride 2.115 using the standard formic acid/triethylamine mixture in MeCN at $0{ }^{\circ} \mathrm{C}$ in good yield and with excellent enantioselectivity (Scheme 51).


Scheme 51 - Asymmetric transfer hydrogenation of iminium developed by Drabowicz and coworkers
Finally, in their paper, the Pihko's group also described an enantioselective reduction of iminium salt 2.115 and $\mathbf{2 . 1 1 7}$ based on Noyori's Ru-diamine complex 2.118. However, a different approach was used. It consisted of conducting the reaction in aqueous media using the original Noyori's catalyst 2.118, similar to the work of Zhu and Deng (Scheme 50). In this case, the mixture of formic acid and triethylamine was replaced by a mixture of sodium formate and catalytic $\mathrm{AgSbF}_{6}$. The presence of silver salt was essential for the reaction because it promoted the formation of the active catalytic species $\mathbf{2 . 1 1 9}$ (Scheme 52).


Scheme 52 - Importance of the silver salt to promote the formation of the active catalyst specie
Two different conditions were developed; one using only water as solvent (Scheme 53, A) and one using a 2:1 water/methanol mixture $(B)$ for the reduction of iminium salts $\mathbf{2 . 1 1 5}$ and 2.117. In the first case, cetrimonium bromide (CTAB) was added as cationic surfactant. CTAB allowed solubilizing the catalyst in water by encapsulating it in micelles. ${ }^{118}$ The desired tetracyclic systems $\mathbf{2 . 1 2 0}$ and $\mathbf{2 . 1 1 6}$ were obtained in good to excellent yields and high enantioselectivities.

[^39]

Scheme 53 - Enantioselective reduction of iminium developed by Pihko and coworkers
To the best of our knowledge, no model has been proposed for the induction of enantioselectivity in asymmetric transfer hydrogenation of tetra-alkylated iminium species. Interestingly, reduction of protonated imines (iminiums) and aldehydes/ketones afforded the opposite enantiomers with the same catalyst. Proposed model based on the Wills' ionic "anti" model for imine ${ }^{119}$ is represented on Figure 20.


Figure 20 - Proposed models for the enantiodetermining step in the asymmetric transfer hydrogenation of iminium salt

Importance of non-covalent interactions such as $\mathrm{C}-\mathrm{H} / \pi$ in catalysis has already been demonstrated. ${ }^{120}$ But in order to fix the conformation, a second interaction is generally required. A possible hypothesis, even though only poorly supported by experimental results, could be the involvement of an anion binding mechanism (Figure 20, B). ${ }^{121}$ Indeed, in iminium reduction, the counter-anion should not be omitted. As in Jacobsen's thioureas or related scaffolds, the two hydrogens on the amine of the ligand could for instance bind the counteranion fixing therefore the conformation. Initial experimental results led us to this hypothesis because when mixing $\mathbf{2 . 1 1 8}$ with TBAC, a shift of most of the peaks in ${ }^{1} \mathrm{H}$ NMR was observed.

[^40]Having those reported examples in mind, relying on a similar asymmetric transfer hydrogenation step seemed highly appealing to us and could potentially be an original and novel alternative for the enantioselective synthesis of eburnane alkaloids.

Different approaches were envisioned for the synthesis of the spirolactam 2.107 (Scheme 54). The first strategy relied on lactone $\mathbf{2 . 2 2 4}$ opening by tryptamine (1.16), followed by a nucleophilic displacement of the resulting alcohol $\mathbf{2 . 2 2 3}$ by the resulting amide (Scheme 54, A). This reaction was thought to be possible in a single step as it was already reported on similar substrates. ${ }^{122}$ Another alternative pathway could trace back $\mathbf{2 . 1 0 7}$ to 5-chloro-propanoic acid derivative $\mathbf{2 . 2 2 5}$ (B). In the forward direction, amide bond formation using tryptamine (1.16) follow by nucleophilic displacement of the chloride by the resulting amide could afford spirolactam 2.107.


Scheme 54 - General retrosynthetic scheme for the formation of lactam 2.107

### 2.3 Synthesis of ( - --Terengganensine A

### 2.3.1 Synthesis of the Indole Skeleton

We decided to start using the lactone $\mathbf{2 . 2 2 4}$ opening pathway (Scheme 54, A). Different approaches were attempted for the synthesis of $\mathbf{2 . 2 2 4}$ (Scheme 55, Scheme 56 and Scheme 57).


Scheme 55 -Synthesis of spirolactone 2.224 by a one-pot double allylation
Double Appel reaction ${ }^{123}$ on (Z)-butendiol afforded the dibromo compounds $\mathbf{2 . 2 2 6}$ in $80 \%$ yield (Scheme 55). ${ }^{124,125}$ Different conditions were then screened for the one-pot double allylation of $\delta$ valerolactone (2.227). ${ }^{126}$ The best result was obtained using KHMDS and HMPA but $\mathbf{2 . 2 2 4}$ was iso-

[^41]lated in $10 \%$ yield only. Competition between $S_{N} 2$ and $S_{N} 2^{\prime}$ could be troublesome in this case (some terminal alkene containing products were observed in crude NMR).


Scheme 56 - Synthesis of the spirolactone precursor 2.231 via simple alkylation
Another approach involving lactone formation was therefore envisioned (Scheme 56). It begun with the monoprotection of propanediol (2.228), leading to 2.229 in quantitative yield. ${ }^{127}$ Appel reaction converted the resulting alcohol $\mathbf{2 . 2 2 9}$ into the bromide derivative $\mathbf{2 . 2 3 0}$ in $81 \%$ yield. ${ }^{128} \mathrm{C}$ Alkylation of methyl cyclopent-3-ene-1-carboxylate (2.83) afforded the alkylated product $\mathbf{2 . 2 3 1}$ in $91 \%$ yield. Removal of the O-TBDPS group followed by lactonization was envisioned to convert $\mathbf{2 . 2 3 1}$ into spirolactone 2.224. Unfortunately, only partial cyclization occurred under all the attempted conditions. Similarly, only partial cyclization occurred when starting from the purified deprotected alcohol 2.232. Neutral (Table 1, Entry 1) and basic conditions (entry 2) did not succeed to promote full cyclization. Acidic conditions (entry 3) did not even give rise to the deprotected product, probably because of the stability of TBDPS towards Brønsted acid. Basic conditions (entry 4) as well as acidic ones (entry 5) were not effective to promote the cyclization of the alcohol 2.232. A possible explanation for the low conversion towards the lactone $\mathbf{2 . 2 2 4}$ could be found in the high steric hindrance induced by the $\alpha$-spirocyclopentene blocking both faces of the ester.

|  |  |  |  |
| :---: | :---: | :---: | :---: |
| Entry | Starting material | Conditions | Ratio ${ }^{\text {a }}$ lactone 2.224: alcohol 2.232 |
| 1 | 2.231 | HF.Py, THF, rt | 0.16:1 |
| 2 | 2.231 | TBAF, THF, $0^{\circ} \mathrm{C}$ to rt | 1:1.14 |
| 3 | 2.231 | TFA, THF, $0^{\circ} \mathrm{C}$ to rt | No reaction |
| 4 | 2.232 | $\mathrm{K}_{2} \mathrm{CO}_{3}, \mathrm{MeOH}, 40^{\circ} \mathrm{C}$ | 0.68: 1 |
| 5 | 2.232 | $\mathrm{HCl} 2 \mathrm{M}, \mathrm{DCM}, \mathrm{rt}$ | 1:1 |

(a: Determined by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture)
Table 1 - Examples of attempted conditions for the deprotection/cyclization of 2.231 to the spirolactone 2.224

[^42]An alternative synthetic route towards the desired lactone 2.224 was then pursued (Scheme 57). ${ }^{129,130}$


Scheme 57 - Synthesis of spirolactone 2.224 using RCM
$\delta$-valerolactone (2.227) was sequentially doubly allylated in $80 \%$ and $50 \%$ yield respectively. Onepot double allylation was attempted without promising yield. Ring-closing metathesis (RCM) of $\mathbf{2 . 2 3 5}$ using Grubbs $3^{\text {rd }}$ generation catalyst afforded the desired spirolactone $\mathbf{2 . 2 2 4}$ in quantitative yield. The main disadvantage of this strategy was the need to use the highly expensive Grubbs $3^{\text {rd }}$ generation catalyst (>500 $\$ / \mathrm{g}$ ) at a quite high catalyst loading.

Heating a mixture of lactone $\mathbf{2 . 2 2 4}$ and tryptamine (1.16) to $160^{\circ} \mathrm{C}$ afforded the amide $\mathbf{2 . 2 2 3}$ and the spirolactam 2.107 in $60 \%$ and $5 \%$ yield respectively (Scheme 58). As the nucleophilic substitution of an alcohol by a chloride could occur in Bischler-Napieralski conditions, alcohol 2.223 was envisioned as a direct precursor for the synthesis of iminium 2.106a. Under optimized conditions, the latter could indeed be obtained in 60\% yield. One the other hand, lactam 2.107 was converted to 2.106a in an excellent 98\% yield. An alternative pathway for the conversion of the alcohol 2.223 to the lactam 2.107 was envisioned. Appel reaction to the bromide $\mathbf{2 . 2 3 6}$ followed by lactamization under basic condition afforded the desired compound $\mathbf{2 . 1 0 7}$ in good yields but in a lengthy 3step sequence from the spirolactone $\mathbf{2 . 2 2 4}$. The use of $18-\mathrm{C}-6$ proved to be crucial for a decent reaction rate.

The moderate efficiency of the aforementioned routes prompted us to envisage an alternative synthetic strategy (Scheme 54, B).

[^43]

Scheme 58 - Lactone 2.224 opening and its subsequent to iminium 2.106a
Alkylation of $\mathbf{2 . 8 3}$ with 3-bromo-1-chloropropane (2.84) afforded $\mathbf{2 . 8 5}$ in $\mathbf{7 8 \%}$ yield (Scheme 59, A). Direct transamidation of the latter with tryptamine (1.16) (B) afforded the desired product 2.237 albeit in low yield ( $25 \%$ ). Hydrolysis of $\mathbf{2 . 8 5}$ afforded the previously desired $\delta$-lactone $\mathbf{2 . 2 2 4}$ and its corresponding dimer 2.238 in $23 \%$ and $68 \%$ yield respectively (C). The presence of the dimer 2.238, even in highly diluted conditions ( 0.01 M ), probably indicated a non-negligible ring strain in the desired lactone 2.224. Therefore, the commercially available methyl ester (2.83) was first hydrolyzed in quantitative yield (D). ${ }^{131}$ Treatment of acid $\mathbf{2 . 2 3 9}$ with an excess of LDA followed by addition of 3-bromo-1-chloropropane (2.84) afforded the acid $\mathbf{2 . 2 4 0}$ cleanly without trace amount of $O$-alkylation product. ${ }^{132}$ Substitution of the chloride was not observed either. Direct peptide coupling between $\mathbf{2 . 2 4 0}$ and $\mathbf{1 . 1 6}$ did not prove efficient in our hands (E). It afforded $\mathbf{2 . 2 3 7}$ in a moderate yield (53\%). Therefore, the acid 2.240 was first converted into an acyl chloride using oxalyl chloride and a catalytic amount of DMF. ${ }^{133}$ The resulting acyl chloride was then in situ treated with $\mathrm{NEt}_{3}$ and tryptamine (1.16) to afford amide $\mathbf{2 . 2 3 7}$ in $92 \%$ yield ( F ). ${ }^{134} \mathbf{2 . 2 3 7}$ was then cyclized to afford lactam 2.107 under the action of a strong base. ${ }^{135}$ As opposed to the bromide 2.236, LiHMDS without crown ether proved to be superior in the case of the cyclization of 2.237. Bischler-Napieralski reaction proceeded smoothly with freshly distilled $\mathrm{POCl}_{3}$ in MeCN . For this step the work-up proved to be crucial for the yield and the purity of the product. Because of the surprisingly high solubility of the chloride salt $\mathbf{2 . 1 0 6 b}$ in water, we transformed it into the perchlo-

[^44]rate one before any aqueous work-up to obtain 2.106a in $98 \%$ yield. Without this counteranion exchange, the chloride salt 2.106b was obtained in only $85 \%$ yield after $5-8$ extractions. The final step of the sequence involved the reduction of the iminium perchlorate salt 2.106a with sodium borohydride in EtOH to afford racemic rac-2.88 in good yield. ${ }^{136}$





Scheme 59 - Synthesis of the indole skeleton rac-2.88
This 5-step sequence afforded the targeted indole skeleton rac-2.88 in $56 \%$ yield from the commercially available acid $\mathbf{2 . 2 3 9}$ with only one final flash column chromatography. Having a robust and scalable sequence for the synthesis of iminium $\mathbf{2 . 1 0 6}$ in hands, the enantioselective reduction was next examined.

### 2.3.1.1 Enantioselective Reduction

The $R$ enantiomer of the reduced product was the targeted one and required, according to the previous reports and to the proposed model on Figure 20, the ( $S, S$ ) catalyst 2.118. We nevertheless made several attempts with the opposite enantiomer of the catalyst ( $R, R$-diamine ent-2.118) as it was cheaper and readily available. The temperature, the iminium salt counter-anion and the reaction time were first varied using $\mathrm{H}_{2} \mathrm{O} / \mathrm{MeOH}$ 2:1 mixture as reaction media (Table 2).

[^45]
( $1.3 \mathrm{~mol} \%$ )


| Entry | Time [hours] | Salt | $\mathrm{T}\left[{ }^{\circ} \mathrm{C}\right]$ | Yield $[\%]^{\mathrm{a}}$ | er $[S: R]^{\mathrm{b}}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 48 | $\mathbf{2 . 1 0 6 b}$ | 40 | 67 | $87: 13$ |
| 2 | 72 | $\mathbf{2 . 1 0 6 b}$ | 40 | 64 | $89: 11$ |
| 3 | 48 | $\mathbf{2 . 1 0 6 a}$ | 40 | 47 | $90: 10$ |
| 4 | 48 | $\mathbf{2 . 1 0 6 b}$ | 60 | 57 | $88: 12$ |

(a: Isolated yield; b: determined by SFC)
Table 2 - Screened conditions for the enantioselective reduction of iminium salt 2.106 in water/methanol 2:1 mixture

In all cases the conversion was not complete even after 3 days of stirring. The strong steric hindrance induced by the bulky and rigid $\alpha$-spirocyclopentene could explain this very slow conversion.

From entry 1 and 4 we concluded that the temperature has no big influence in the enantiomeric ratio as well as on the yield. Additional reaction time did not improve the yield at all (entry 2 ). Slow decomposition or inhibition of the catalyst could explain this phenomenon. The perchlorate salt 2.106a was also reduced to ent-2.88 with high ee but with much reduced yield (entry 3 vs entry 1)

Not satisfied with those results, we decided to try the phase transfer conditions in pure water described by Pinko and coworkers. The temperature, the reaction time and the catalyst and silver salt loadings were varied (Table 3).

The reaction proceeded significantly faster compared with the previous conditions. We observed that, by increasing the catalyst loading, a slightly better enantioselectivity was obtained (Table 3, entry 1 and 2). It also gave rise to a significant increase of the reaction rate. Perchlorate salt 2.106a was not effective in water (entry 3). It could be explained by the higher solubility in water of the chloride salt $\mathbf{2 . 1 0 6 b}$ compared to the perchlorate one 2.106a. Finally, we noticed that the temperature played no important role in the enantiomeric ratio and in the reaction rate (entry 4) as already observed in Table 2. Increasing the catalyst loading to $5 \mathrm{~mol} \%$ did not influence significantly the yield and the ee (entry 5 and 6).


| Entry | Catalyst | Cat. loading <br> $[$ mol\%] | Time <br> $[$ hours $]$ | Salt | T <br> $\left[{ }^{\circ} \mathrm{C}\right]$ | Yield $^{\mathrm{b}}$ <br> [Conv) $^{\mathrm{a}}[\%]$ | $e r$ <br> $[\mathrm{~S}: \mathrm{R}] \mathrm{c}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | ent-2.118 | 1.3 | 48 | $\mathbf{2 . 1 0 6 b}$ | 40 | $72(90)$ | $91: 9$ |
| 2 | ent-2.118 | 2.6 | 36 | $\mathbf{2 . 1 0 6 b}$ | 40 | $73(94)$ | $94: 6$ |
| 3 | ent-2.118 | 2.6 | 36 | $\mathbf{2 . 1 0 6 a}$ | 40 | $57(90)$ | $90: 10$ |
| 4 | ent-2.118 | 2.6 | 36 | $\mathbf{2 . 1 0 6 b}$ | 60 | $69(93)$ | $93: 7$ |
| 5 | $\mathbf{2 . 1 1 8}$ | 5 | 69 | $\mathbf{2 . 1 0 6 b}$ | 40 | $63(89)$ | $7: 93$ |
| 6 | $\mathbf{2 . 1 1 8}$ | 5 | 69 | $\mathbf{2 . 1 0 6 b}$ | 60 | $66(89)$ | $8: 92$ |

(a: Determined by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture; b : isolated yield; c : determined by SFC)
Table 3 - Screened conditions for the enantioselective reduction of iminium salt 2.106 in water
With those results in mind, we slightly modified the conditions in order to increase the conversion and get better yields (Table 4). Our hypothesis, which correlates with the results in Table 3, was the loss of catalytic activity after a certain time. To prevent a rapid catalyst inhibition/decomposition, we performed the reaction at $40^{\circ} \mathrm{C}$ with portionwise addition of catalyst 2.118 .

( $a$ : Determined by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture; b : isolated yield; c: determined by SFC)
Table 4 - Fine-tuning of the conditions for the enantioselective reduction of iminium salt 2.106 in water

The reaction in entry 1 was initiated with 2.5 mol\% catalyst loading. After 24 hours at $40^{\circ} \mathrm{C}$, an additional 2.5 mol\% of catalyst 2.118 was added and the reaction was almost complete after 6 days. Compound $\mathbf{2 . 8 8}$ was isolated in $82 \%$ yield and with $88 \%$ ee. Entry 2 used similar conditions except that 5 mol\% of catalyst 2.118 were added after the first 24 hours. No improvement of the reaction efficiency was observed. Initiating the reaction with $5 \mathrm{~mol} \%$ catalyst followed by a subsequent addition of 2.5 mol\% catalyst after 2 days afforded the desired compound $\mathbf{2 . 8 8}$ in $\mathbf{7 0 \%}$ yield and $90 \%$ ee (entry 3). In this case, a total of 4 days was required. The same conditions using the perchlorate salt 2.106a provided lower yield and ee (entry 4). This was probably due to the same solubility reason as previously mentioned. The much lower ee (80\%) using the perchlorate salt 2.106a compared to the chloride one 2.106b gave an additional clue for the proposed anionbinding mechanism (Figure 20, B).

Using the conditions of entry 3, the desired indole skeleton 2.88 was therefore obtained in $70 \%$ yield and $90 \%$ ee. Because of the steric hindrance generated by the cyclopentene, the reaction occurred slowly. Nevertheless, the portionwise addition of catalyst $\mathbf{2 . 1 1 8}$ allowed overcoming the catalyst inhibition occurring during the four required days.

Compared to the previous synthesis of rac-2.88 by Ho and coworkers, ours was one step longer but the overall yield was twice higher. Moreover, we were able to obtain gram quantity of $\mathbf{2 . 8 8}$ in 42\% overall yield and with 95:5 er.

### 2.3.2 Oxidation of the Indole and of the Cyclopentene

With a very efficient route to the indole skeleton 2.88 in hands, we turned our attention towards the oxidation of the indole C-7 position and of the double bond of the cyclopentene moiety.

The first idea was to go through a cis-2,3-dialkoxyindoline intermediate $\mathbf{2 . 2 4 4}$ and we therefore attempted the C-7 oxidation of indole (PIFA, ammonium chloride) followed by trapping of the formed indolenine 2.245 by ethylene glycol as reported by Takayama and coworkers (Scheme 60). ${ }^{137}$ Major attractive features of their methodology were the cis relationship of the newly formed ring compare to the $\mathrm{H}-21$ as well as the cis $\mathrm{B} / \mathrm{C}$ ring fusion which was required for the subsequent group-selective cyclization.


Scheme 60 - Reported dialkoxylation of indole and our targeted intermediate

[^46]Applying the Takayama's conditions to our indole skeleton $\mathbf{2 . 8 8}$ only afforded the hypothesized intermediate, the 7-chloroindolenine $\mathbf{2 . 2 4 5}$ in 58\% yield as a single diastereoisomer (Table 5, entry 1). Switching ethylene glycol to water did not furnish the desired compound, or the chloroindolenine intermediate 2.245 (entry 2). Using MeOH as smaller alcohol afforded the same chloroindolenine $\mathbf{2 . 2 4 5}$ in 50\% yield (entry 3). Finally, harsher conditions did not improve the yield (entry 4 and 5). Possible explanation for the lack of ethylene glycol attack could be the steric hindrance generated by the adjacent spirocyclopentene.


| Entry | Conditions | Yield [\%] |
| :---: | :---: | :---: |
| 1 | PIFA, $\mathrm{NH}_{4} \mathrm{Cl}, \mathrm{MeCN} / \mathrm{EG}, \mathrm{rt}$ | 58 |
| 2 | PIFA, $\mathrm{NH}_{4} \mathrm{Cl}, \mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}, \mathrm{rt}$ | Messy |
| 3 | PIFA, $\mathrm{NH}_{4} \mathrm{Cl}, \mathrm{MeCN} / \mathrm{MeOH}, \mathrm{rt}$ | 50 |
| 4 | PIFA, $\mathrm{NH}_{4} \mathrm{Cl}, \mathrm{MeCN} / \mathrm{MeOH}$, reflux | 48 |
| 5 | PIFA, $\mathrm{NH}_{4} \mathrm{Cl}, \mathrm{MeCN} / \mathrm{EG}$, reflux | 55 |

(a: Isolated yield)
Table 5 - Examples of attempted conditions for the oxidation of rac-2.88 to the cis-2,3-dialkoxy indoline adduct

Similar strategy was envisioned using $\mathrm{OsO}_{4}$ and pyridine as reported by Behrman and coworkers in $1980^{138}$ and applied successfully by Danishefsky ${ }^{139}$ and by Jimenez ${ }^{140}$ in total syntheses. Reaction of Os(VIII) and pyridine with indoles could afford the unusual bis(pyridine)oxoosmium (VI) ester 2.246 (Scheme 61). As demonstrated by Criegee and coworkers, ${ }^{141}$ amines could greatly increase the rate of reaction of osmium with double bond. It is to note that this discovery set the way to the famous asymmetric Sharpless epoxidation. ${ }^{142}$ The forced cis relationship would have been highly valuable in our case. Unfortunately, all attempted conditions afforded very messy mixture of $\mathbf{2 . 2 4 6}$ which after reduction of the potential $\mathrm{Os}-\mathrm{O}$ bonds using various methods $\left(\mathrm{Me}_{2} \mathrm{~S}, \mathrm{NaBH}_{4}\right.$, $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{4}$, etc.) did not provide any trace amount of the expected diol 2.247. Subsequent rearrangement of 2.247 to oxindoles as well as competitive reaction of the $\mathrm{OsO}_{4}$ with the cyclopentene moiety could explain these results.

[^47]

## Scheme 61 - Bis(pyridine)oxoosmium (VI) ester formation and subsequent Os-O bond reductions

Despite the absence of the desired product $\mathbf{2 . 2 4 4}$ in Table 5, we realized that the 7-Cl indolenine derivative $\mathbf{2 . 2 4 5}$ could also present the required conformation for the diastereoselective polycyclization. Indeed, as mentioned in Scheme 44, intra- (Scheme 62, A) or intermolecular trapping (Scheme 62, B) of the indolenine $\mathbf{2 . 2 4 8}$ during the cleavage of the alkene could also provide a viable alternative to the desired diastereoisomer.


Scheme 62 - Intra-/intermolecular trapping of the indolenine 2.248
We therefore decided to move forward with the chloroindolenine product $\mathbf{2 . 2 4 5}$ obtained. The Takayama conditions did provide the desired product but alternative procedures were well reported for the oxidation of indoles to chloroindolenine. Among the attempted methods, ${ }^{\mathrm{t}} \mathrm{BuOCl}, \mathrm{a}$ well-known oxidant, provided the desired compound $\mathbf{2 . 2 4 5}$ in $95 \%$ yield as a single diastereoisomer (Scheme 63). ${ }^{143}$ 1-chlorobenzotriazole was also able to promote the desired oxidation albeit in slightly lower yield (87\%). ${ }^{144}$ Using ${ }^{\text {t }} \mathrm{BuOCl}$, no traces of oxidized amine or of oxidized cyclopentene were detected only if 1.05 equivalents were used and were added slowly. Fast addition or excess of the reagent afforded a very complex mixture of products. Concerning the mechanism, initial $\mathrm{N}-\mathrm{Cl}$ indole formation such as $\mathbf{2 . 2 5 1}$ was proposed as intermediate towards the chlorination of indole derivatives using ${ }^{\text {t BuOCl. }}{ }^{145}$


Scheme 63 - Diastereoselective C-7 chlorination of indole skeleton rac-2.88
Two possibilities could explain the excellent diastereoselectivity ( $>19: 1 \mathrm{dr}$ ). Final products are both represented in Scheme 64. A cis relationship between the $\mathrm{H}-21$ and the newly introduced $\mathrm{Cl}-7$ group would lead to a pseudo equatorial indolenine 2.245. On the opposite, a trans relationship

[^48]would afford a pseudo axial lying indolenine 2.252 having strong unfavorable 1,3-diaxial interactions. A possible trans to cis flip of the C/D ring junction would allow a conformation where the indolenine is in pseudo-equatorial position but would create other steric clashes. We therefore hypothesized that the desired product 2.245 was probably the thermodynamically more stable one. The second reason to explain the observed diastereoselectivity could be the steric hindrance generated by the spirocyclopentene. Attack from the bottom face could be unfavored because of the steric clash between the axial $\mathrm{CH}_{2}$ of the cyclopentene and the oxidant. Nevertheless, literature examples ${ }^{146}$ lacking such steric hindrance were also oxidized in excellent $d r$. This could indicate that the thermodynamic of the reaction could be sufficient to favor a good diastereoselectivity.


Scheme 64 - Explanation for the observed cis diastereoselective in the oxidation of rac-2.88
With some efficient conditions for the synthesis of the desired chloroindolenine $\mathbf{2 . 2 4 5}$ in hands, we turned our attention towards the oxidation of the cyclopentene moiety (Scheme 65).


Scheme 65 - Oxidation of the indole skeleton rac-2.88 to the 7-chloro terengganensine A
The indole rac-2.88 was first converted to the chloroindolenine $\mathbf{2 . 2 4 5}$ as reported above (Scheme 65 , pathway A). We then attempted several conditions for the ozonolysis of the latter but they all led to full decomposition of the starting indolenine. Possible explanation could be the relative sen-

[^49]sitivity of the indolenine function to oxidative conditions. Instead, a one-pot sequence developed by Nicolaou and coworkers ${ }^{147}$ (Upjohn dihydroxylation/oxidative cleavage) afforded the desired fully cyclized product $\mathbf{2 . 2 5 3}$ in $89 \%$ yield as a single diastereoisomer. Catalytic amount of the toxic $\mathrm{OsO}_{4}$ easily regenerated by NMO and using 2,6-lutidine as non-nucleophilic base and accelerator of the dihydroxylation promoted the dihydroxylation of the alkene $\mathbf{2 . 2 4 5}$. The role of lutidine is not perfectly understood but studies have shown an increased reaction rate as well as a decrease in the hydroxy ketone by-product in the presence of pyridine-like bases. ${ }^{148}$ Increased reaction rate could be explained by the faster formation of osmium(VI) ester in the presence of a tertiary amine such as pyridine as already mentioned earlier. ${ }^{141,149}$ In our case, omission of the lutidine still produced the desired product $\mathbf{2 . 2 5 3}$ albeit in less clean and rapid manner.

Another sequence of reactions was also performed (Scheme 65, B). The indole skeleton rac-2.88 was first dihydroxylated with catalytic amount of $\mathrm{OsO}_{4}$ and NMO as co-oxidant to afford the diol 2.89 in $68 \%$ yield as a single diastereoisomer. ${ }^{103}$ The excellent observed diastereoselectivity could be explained by the bulky indole completely shielding one of the two faces of the cyclopentene. With the diol 2.89 in hands, the oxidation of the indole surprisingly best performed with PIFA and ammonium chloride to afford chloroindolenine $\mathbf{2 . 2 5 4}$ in $91 \%$ yield as a single diastereoisomer probably because of the same thermodynamic reason as stated before. The oxidized product $\mathbf{2 . 2 5 4}$ was finally cleaved under the action of sodium metaperiodate to afford the chloro derivative of terengganensine A $\mathbf{2 . 2 5 3}$ in $86 \%$ yield as a single diastereoisomer.

Obtaining 2.253 as a single diastereoisomer confirmed our initial hypothesis that oxidation of the indole to create an additional (or two with the indolenine trapping) $\mathrm{sp}^{3}$ center could tilt the indoline nitrogen down enough to make it react with the desired axial aldehyde only.

With the chloro derivative of terengganensine A 2.253 in hands, we then directed our effort towards its conversion into ( $\pm$ )-terengganensine A (2.1) via nucleophilic substitution. Silver(I) has high affinity with halide. Moreover, a $\mathrm{S}_{N} 1$ mechanism was required in order to retain the configuration at C-7. Therefore different silver salts were tested in order to either obtain the alcohol 2.1, the nitrate ${ }^{150} \mathbf{2 . 2 5 5}$ or the acetate $\mathbf{2 . 2 5 6}$ but all attempts failed to give the desired products (Scheme 66). The starting material was always almost fully recovered.

The benzylic cation was probably not generated. Particular focus was put on solvents screening as this parameter was reported to be crucial for this kind of substitution without positive results. ${ }^{152}$

[^50]

## Scheme 66 - Different approaches for the conversion of 2.253 to ( $\pm$ )-terengganensine A

In order to facilitate the nucleophilic substitution and knowing that bromide is a better leaving group than chloride, the 7 -bromo indolenine 2.257 was synthesized in $78 \%$ yield (Scheme 67) again as a single diastereoisomer using simply NBS in acetone. ${ }^{151}$ Iodo indolenine was also targeted (using NIS, DCM, rt) but no desired product was observed probably because of its low stability as described by Tokuyama and coworkers. ${ }^{152}$


Scheme 67 - Bromination of the indole skeleton rac-2.88
We reasoned that the $\alpha$-bromo and $\alpha$-chloro carbonyl substrates $\mathbf{2 . 2 5 7}$ and $\mathbf{2 . 2 4 5}$ could be much more reactive towards nucleophilic substitution. Moreover, the benzylic position of these substrates could probably be less hindered than the adamantanyl 2.253. We therefore reattempted the nucleophilic substitution on these two substrates (Table 6).

All the attempts for a $\mathrm{Ag}(\mathrm{I})$-promoted nucleophilic substitution mainly afforded the indole skeleton rac-2.88 (Table 6, entry 1-5). A different outcome was observed when using silver cyanide. It only produced very messy mixture without full conversion (entry 6) probably because AgCN was barely soluble in the tested solvents. The use of NaOAc afforded a similar result (entry 7). A solution of $\mathbf{2 . 2 4 5}$ or $\mathbf{2 . 2 5 7}$ in MeOH in the presence of TFA generated a complex mixture of products (entry 8). The indole rac-2.88 was again the major compound. Finally, basic conditions using NaOH in $\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}$ (entry 9) afforded similar mixture of compounds.

[^51]| Entry | Conditions | SM | Results ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: |
| 1 | AgOTf, MeCN/ $\mathrm{H}_{2} \mathrm{O}$ | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |
| 2 | $\mathrm{AgNO}_{3}, \mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}$ | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |
| 3 | $\mathrm{AgBF}_{4}, \mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}$ | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |
| 4 | AgTFA, MeCN/ $\mathrm{H}_{2} \mathrm{O}$ | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |
| 5 | $\mathrm{AgOAc}, \mathrm{AcOH}$ | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |
| 6 | AgCN, MeCN/ $\mathrm{H}_{2} \mathrm{O}$ | 2.245 | Complex mixture containing the SM 2.245 |
|  |  | 2.257 | Complex mixture containing the SM 2.257 |
| 7 | NaOAc , AcOH | 2.245 | Complex mixture containing the SM 2.245 |
|  |  | 2.257 | Complex mixture containing the SM 2.257 |
| 8 | MeOH, TFA, DCM | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |
| 9 | $\mathrm{NaOH}, \mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}$ | 2.245 | Complex mixture containing indole rac-2.88 |
|  |  | 2.257 | Complex mixture containing indole rac-2.88 |

(a: Detected by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture)
Table 6 - Examples of attempted conditions for the nucleophilic substitution on indolenine 2.245 and 2.257

The synthesis of indole derivatives from their 3-chloroindolenine counterpart was a known process. ${ }^{153}$ Indeed, direct attack of the nucleophile on the chloride could give back the starting indole rac-2.88. Moreover, in our case, many other side reactions could easily occur. Among them, formation of 2 - and 3-oxindoles (Scheme 68, A), C-21 functionalization (B) and dimerization (C) were reported in the literature. ${ }^{145 a, 153,154}$ The 3-oxindole $\mathbf{2 . 1 0 1}$ was the only compounded cleanly isolated and characterized.


Scheme 68 - Reported side reactions occurring during the nucleophilic substitution of indolenine at the C-3 position

[^52]Because of the impossibility to perform the desired nucleophilic substitution, we decided to come back to the initial oxidation step and to oxidize the indole rac-2.88 directly to C-7 hydroxylated indolenine. More than 50 different conditions were attempted without any success. The major products obtained were the corresponding 2 - and 3 -oxindoles and some $N$-oxide side products. Table 7 shows some selected oxidants attempted and the main oxindole by-products 2.101 and 2.102 obtained.

| Attempted oxidants |  | Main products ${ }^{\mathrm{a}}$ |
| :---: | :---: | :---: |
| DMDO | TFDO |  |
| $\mathrm{Br}_{2} / \mathrm{ROH}$ | mCPBA |  |
| $\mathrm{NBS} / \mathrm{ROH}$ | Oxaziridines | $\mathrm{Pb}(\mathrm{OAc})_{4}$ |
| $\mathrm{MoO}_{5} \cdot \mathrm{HMPT}$ | $\mathrm{PIDA} / \mathrm{ROH}$ |  |
| $\mathrm{PIFA} / \mathrm{NH}_{4} \mathrm{OR}$ | $\mathrm{CrO}_{3} / \mathrm{Ac}_{2} \mathrm{O}$ |  |
| $\mathrm{O}_{2} / \mathrm{Rose}^{\mathrm{Bengal} / \mathrm{h} v}$ | $\mathrm{Shi} / \mathrm{Bu}_{4} \mathrm{NHSO}_{4} / \mathrm{Oxone}$ |  |
| $\mathrm{Na}_{4} \mathrm{XeO}_{6} \cdot 6 \mathrm{H}_{2} \mathrm{O} / \mathrm{ROH}$ |  |  |
| $\mathrm{H}_{2} \mathrm{O}_{2} / \mathrm{DIC} / \mathrm{DMAP}$ | $\mathrm{C}_{6} \mathrm{Cl}_{6} \mathrm{O} / \mathrm{ROH}$ |  |

(a: No detailed analysis of the relative stereochemistry of the oxindoles was performed)
Table 7 - Selected conditions attempted for the oxidation of the indole skeleton and structure of the obtained oxindoles

Dimethyldioxirane and methyl(trifluoromethyl)dioxirane were both tested by either generation of the dioxiranes in situ or by using them directly after their synthesis but only messy reactions were obtained. $\mathrm{Br}_{2}$ or NBS in combination with nucleophiles and especially water is known to oxidize indole to 3-bromoindolenine which can then in situ be converted to the 3-hydroxyindolenine but it failed in our case. mCPBA also did not provided any trace amount of the desired product. Various oxaziridines were then used. Chiral Davis' oxaziridine and simplest achiral ones were tried without any observed desired reactivity. $\mathrm{MoO}_{5} \cdot \mathrm{HMPT}$ was synthesized and used directly without success. ${ }^{155}$ As PIFA/ $/ \mathrm{NH}_{4} \mathrm{Cl}$ conditions were able to give the 3 -chloroindolenine (see Table 5) we thought to use PIFA in combination with either $\mathrm{NH}_{4} \mathrm{OAc}$ to give the 3-acetoxyindolenine or with $\mathrm{NH}_{4} \mathrm{OH}$ to give the 3-hydroxyindolenine. Both of them failed and only gave the recovered starting material. PIDA, similar to PIFA, but this time in combination with alcohols promoted the decomposition of the starting material. Interestingly, lead tetraacetate was able to give the desired acetyl protected alcohol but only in very low yield ( $<10 \%$ ) and in a very messy reaction even after extensive optimization. ${ }^{156}$ Photooxidation using $\mathrm{O}_{2}$ and sensitizers led to a messy mixture of products. ${ }^{157}$ $\mathrm{Cr}(\mathrm{VI})$ in combination with acetic anhydride was known to promote the oxidation of indole. ${ }^{158}$ In our case, complex mixture was observed. The relatively uncommon $\mathrm{Na}_{4} \mathrm{XeO}_{6}$ combined with alco-

[^53]hol was also reported as efficient oxidant for indole. ${ }^{159}$ In our hands, a myriad of compounds were obtained. Hexachlorophenol $\left(\mathrm{C}_{6} \mathrm{Cl}_{6} \mathrm{O}\right)$ was reported to oxidize indole at the $\mathrm{C}-3$ position. In combination with alcohol, this oxidant is known to afford the C-3 alkoxy indolenine. ${ }^{160}$ In our hands, only the rearranged and the $N$-oxide products were observed. Finally, hydrogen peroxide in combination with DMAP and DIC was tested. ${ }^{161}$ Various peptide catalysts were screened but none of them led to the desired compound.

As already reported, a possible way to avoid $N$-oxidation with $m$ CPBA was to use TFA in order to in situ protect the nitrogen in the form of an ammonium salt before adding the oxidant. ${ }^{162}$ Repeating the previous $m$ CPBA oxidation in combination with TFA at $-78^{\circ} \mathrm{C}$ afforded the $\mathrm{C}-7$ oxidized product $\mathbf{2} 264$ in quantitative yield. NMR did not allow easy determination of the configuration of the newly created center. Submitting $\mathbf{2 . 2 6 4}$ to the one-pot dihydroxylation/oxidative cleavage/cyclization conditions afforded cleanly a new compound whose spectroscopic data did not correspond to terengganensine A (2.1) (Scheme 69, A).


Scheme 69 - mCPBA oxidation of the indole skeleton rac-2.88 giving rise to the undesired diastereoisomer 2.264

Careful NMR analysis of the obtained product $\mathbf{2 . 2 6 5}$ revealed that the indole oxidation occurred from the wrong face affording the wrong stereochemistry at C-7. With this trans relationship between the alcohol and the $\mathrm{H}-21$, the final cyclization occurred with the equatorial aldehyde ( $\mathrm{C}-18$ ) affording compound $\mathbf{2 . 2 6 7}$ exclusively (Scheme 69, B).

Based on the literature precedents, ${ }^{162}$ the observed stereoselectivity could be accounted for by invoking the intermediate $\mathbf{2 . 2 6 8}$ in which a hydrogen-bonding interaction between the ammonium

[^54]salt and mCPBA directed the hydroxylation from the bottom face (Scheme 69, C). Attempts to use polar solvents such as THF in order to overcome this interaction failed to give the desired product.

Encouraged by this promising result, we screened other oxidants. From Table 7, the only promising result was obtained with $\mathrm{Pb}(\mathrm{OAc})_{4}$ to afford the $\mathrm{C}-7-\mathrm{OAc}$ indolenine. Reasoning that the electronwithdrawing character of the $C(O)$ Me prevented further rearrangement to oxindoles, we decided to explore this hypothesis. Dibenzoyl peroxide was a potential candidate. ${ }^{163}$ To our delight, oxidation using this reagent afforded the desired compounds $\mathbf{2 . 2 6 9}$ in $68 \%$ yield as a single diastereoisomer (Scheme 70, A).


## Scheme 70 - Successful C-7 oxidation of the indole skeleton 2.88 using dibenzoyl peroxide at room temperature

The mechanism of this reaction remained unclear. Control experiment performed in the absence of light and oxygen afforded 2.269 in exact same yields. Knowing that the half-life of dibenzoylperoxide is 100 hour at $60{ }^{\circ} \mathrm{C}^{164}$ and that in our case the reaction proceeded in few hours at room temperature, the existence of a radical mechanism was questioned. Hariya and coworkers reported a similar transformation but at elevated temperature and reported a possible radical mechanism. ${ }^{165}$ Poloni and coworkers proposed ${ }^{166}$ that the homolytic cleavage could be induced by the indole nitrogen which might happen in our case (Scheme 70, B). It is also well known that tertiary amine could catalyze the same decomposition ${ }^{167}$ but this would not give rise to the desired product. In light of these proposed decomposition pathway, radical mechanism could not be ruled out. Nevertheless, an ionic mechanism could also be involved. Indeed, hydrogen bonding with the NH of the indole could potentially induce a big enough dipole moment for the ionic reaction to proceed (Scheme 70, C).

With the oxidized indole 2.269 in hands, we then submitted this compound to the one-pot dihydroxylation/oxidative cleavage/cyclization procedure. Gratefully, compound $\mathbf{2 . 2 7 2}$ was obtained in

[^55]$76 \%$ yield as a single diastereoisomer. Simple hydrolysis under basic methanolic conditions afforded (-)-terengganensine A (2.1) in 95\% yield (Scheme 71, A). ${ }^{168}$


Scheme 71 - Completion of the synthesis via a dihydroxylation/oxidative cleavage/triple cyclization/hydrolysis cascade

Combination of the last two steps (B) allowed us to obtain 2.1 from 2.269 in a single operation and in $80 \%$ yield. No erosion of the enantiomeric ratio was observed during the dihydroxylation/oxidative cleavage/triple cyclization/hydrolysis cascade sequence. This therefore represented the first enantioselective total synthesis of (-)-terengganensine A (2.1). It is to note that we did not use any protecting group during its synthesis. ${ }^{27}$

### 2.3.3 Summary of the Synthesis

Scheme 72 summarizes the synthesis of (-)-terengganensine A (2.1) from the commercially available carboxylic acid 2.239.
(-)-Terengganensine A (2.1) was obtained in 16.3\% overall yield with 95:5 enantiomeric ratio in 7 steps from the commercially available cyclopent-3-ene-1-carboxylic acid (2.239).

[^56]

Scheme 72 - Summary of the enantioselective total synthesis of (-)-terengganensine A
Table 8 shows the comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of both natural and synthetic (-)terengganensine A (2.1).

The carbon and proton chemical shifts correlated well with the isolated natural product. The main differences were the observation of the OH proton at 2.68 ppm which was possible in our case because of the cleaner spectra and the reassignment of the C-6 and C-15 carbons probably for the same reason.

(-)-Terengganensine $\mathbf{A ( 2 . 1 )}$

| Natural |  |  |  | Synthesized |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{N}^{\circ}$ | $\begin{aligned} & { }^{13} \mathrm{C}[\mathrm{ppm}]^{\mathrm{a}} \\ & (100 \mathrm{MHz}) \end{aligned}$ | $\begin{aligned} & { }^{1} \mathrm{H}[\mathrm{ppm}] \mathrm{a} \\ & (400 \mathrm{MHz}) \end{aligned}$ |  | $\mathrm{N}^{\circ}$ | $\begin{aligned} & { }^{13} \mathrm{C}[\mathrm{ppm}]{ }^{\mathrm{a}} \\ & (100 \mathrm{MHz}) \end{aligned}$ |  | $\begin{aligned} & \mathrm{om}]^{\mathrm{a}} \\ & \mathrm{MHz}) \end{aligned}$ |
| 14 | 20.6 | 1.90 | 1.62 | 14 | 20.5 | 1.95 | 1.56 |
| 20 | 31.4 | - | - | 20 | 31.4 | - | - |
| 17 | 34.3 | 2.70 | 1.85 | 17 | 34.3 | 2.71 | 1.82 |
| 15 | 35.2 | 1.90 | 1.35 | 6 | 35.1 | 2.05 | 1.75 |
| 6 | 36.5 | 2.00 | 1.75 | 15 | 36.4 | 1.59 | 1.30 |
| 19 | 43.1 | 1.95 | 1.80 | 19 | 43.1 | 1.97 | 1.80 |
| 5 | 51.0 | 2.57 | 2.30 | 5 | 51.0 | 2.64 | 2.32 |
| 3 | 55.6 | 2.95 | 2.10 | 3 | 55.5 | 2.98 | 2.16 |
| 21 | 65.7 | 2.30 | - | 21 | 65.6 | 2.35 | - |
| 7 | 77.2 | - | - | 7 | 77.0 | - | - |
| 16 | 77.6 | 5.45 | - | 16 | 77.7 | 5.48 | - |
| 2 | 92.5 | - | - | 2 | 92.5 | - | - |
| 18 | 95.6 | 5.20 | - | 18 | 95.6 | 5.22 | - |
| 12 | 110.1 | 6.85 | - | 12 | 110.1 | 6.81 | - |
| 10 | 121.2 | 6.92 | - | 10 | 121.2 | 6.91 | - |
| 9 | 122.4 | 7.30 | - | 9 | 122.4 | 7.28 | - |
| 11 | 128.8 | 7.20 | - | 11 | 128.8 | 7.20 | - |
| 8 | 135.8 | - | - | 8 | 135.8 | - | - |
| 13 | 145.2 | - | - | 13 | 145.2 | - | - |
| 22 | - | - | - | 22 | - | 2.68 | - |

(a: $\ln \mathrm{CDCl}_{3}$ )
Table 8 - Comparison of NMR data between the isolated and the synthetic (-)-terengganensine $A$
Both natural and synthetic (-)-terengganensine $A(2.1)$ were levorotary with $[\alpha]_{D}{ }^{20}$ values of $-25^{\circ}(c$ $=$ unspecified, $\mathrm{CHCl}_{3}$ ) and $-49.3^{\circ}\left(c=0.1, \mathrm{CHCl}_{3}\right)$ respectively. Therefore they were the same enantiomer. From previous reports and from model of Figure 20, we knew the absolute configuration of center 21. One could therefore confirm the absolute configuration of the natural product; the postulated one was the correct one.

The specific optical rotation value for the synthetic (-)-terengganensine A (2.1) was higher than that of the natural product. However, it has to be noted that the concentration for measuring the $[\alpha]_{D}$ of the natural product was not specified in the isolation paper. Moreover, the isolated natural product was not very pure according to ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra. This could therefore explain the difference of $[\alpha]_{\mathrm{D}}$.

### 2.3.4 Mechanistic and Conformational Studies

In order to better understand the reaction mechanism and the excellent diastereoselectivity for the final cyclization, we decided to perform some mechanistic studies based on computational and conformational analysis. ${ }^{169}$

Concerning the indole skeleton 2.88, it showed the presence of strong Bohlmann bands (2748 and $2811 \mathrm{~cm}^{-1}$ ) indicating a trans $\mathrm{C} / \mathrm{D}$ ring junction, a fact that accounted for the observed $\beta$-selectivity in the C7-chlorination step. With this conformation, it was also clear why only the equatorial aldehyde ( $\mathrm{C}-18$ ) resulting from the oxidative cleavage of the cyclopentene $\mathbf{2 . 8 9}$ could cyclized as observed by Chen and coworkers. ${ }^{103}$

Concerning the indolenine compounds, ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectrum showed clear differences between 7-hydroxyindolenine $\mathbf{2 . 2 6 4}$ and 7-chloro 2.245, 7-bromo indolenine $\mathbf{2 . 2 5 7}$ and 7-benzoyl indolenine 2.269 (Figure 21).

Spectra of 2.245, $\mathbf{2 . 2 5 7}$ and $\mathbf{2 . 2 6 9}$ looked broad and missing (or very broad) carbons were observed. On the other hand, spectra of $\mathbf{2 . 2 6 4}$ looked sharp and well resolved. Broadening in NMR typically occurs when slow (in the order of magnitude of the relaxation time) interconversion between different conformers exists.

[^57]

Figure 21 - Comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of various indolenine


Figure 22 - Comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of various indolenine at room temperature and at $-40^{\circ} \mathrm{C}$

To freeze the interconverting conformers and to better analyze those spectra, low temperature NMR was performed on $\mathbf{2 . 2 4 5}$ and $\mathbf{2 . 2 6 9}$ (Figure 22). ${ }^{170}{ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra with much higher resolution were obtained at $-40^{\circ} \mathrm{C}$. The estimated ratio of the two conformers was $5: 2$ for both 2.245 and 2.269.

| Entry | Compound | $\begin{gathered} \mathrm{T} \\ {\left[{ }^{\circ} \mathrm{C}\right]} \end{gathered}$ | $\mathrm{H}-21^{1} \mathrm{H}$ chemical shift [ppm] ${ }^{\text {a }}$ | $\mathrm{C}-21{ }^{13} \mathrm{C}$ chemical shift [ppm] ${ }^{\text {a }}$ | Bohlmann band [ $\left.\mathrm{cm}^{-1}\right]^{\mathrm{c}}$ (strength) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 2.88 | rt | 3.36 | 69.4 | $\begin{gathered} 2800,2748 \\ \text { (strong) } \end{gathered}$ |
| 2 | $\begin{aligned} & 2.245 \\ & \text { major } \end{aligned}$ | -40 | 4.13 | 63.8 | $\begin{gathered} 2811,2753 \\ \text { (weak) } \end{gathered}$ |
| 2' | 2.245 <br> minor |  | 3.43 | 65.7 |  |
| 3 | $\begin{aligned} & 2.269 \\ & \text { major } \end{aligned}$ | -40 | 3.72 | 64.4 | $\begin{gathered} 2820,2753 \\ \text { (weak) } \end{gathered}$ |
| 3' | $\begin{aligned} & 2.269 \\ & \text { minor } \end{aligned}$ |  | 2.94 | 67.0 |  |
| 4 | 2.257 | rt | ND | ND | $\begin{gathered} 2818,2756 \\ \text { (weak) } \end{gathered}$ |
| 5 | 2.264 | rt | 3.21 | 72.4 | $\begin{gathered} 2813,2755 \\ \text { (strong) } \\ \hline \end{gathered}$ |

(a: in $\mathrm{CDCl}_{3} ; \mathrm{b}$ : in the pure product)
Table 9-Comparison of key spectral features between indolenine compounds
Interestingly, the chemical shift of the H-21 in the major conformation was always higher than the one of the minor one ((a: in $\mathrm{CDCl}_{3} ; \mathrm{b}$ : in the pure product)
Table 9, entry 2 vs $2^{\prime}$ and 3 vs $3^{\prime}$ ). According to previous literature reports, ${ }^{171}$ higher chemical shifts for this proton in indoloquinolizidine scaffold is found for cis $\mathrm{C} / \mathrm{D}$ ring junctions whereas lower chemical shift arise in trans C/D ring junction. The higher chemical shift in the cis conformation could be explained by the induction generated by the nitrogen lone pair. Moreover, IR spectra of $\mathbf{2 . 2 4 5}$ and $\mathbf{2 . 2 6 9}$ at room temperature displayed very weak Bohlmann bands ${ }^{101 b}$ accounting for the low population of the trans isomer.

The slow interconversion between the two conformations of $\mathbf{2 . 1 0 0}$ could be explained by the relatively big steric hindrance created by the spirocyclopentene. Moreover, the favored equilibrium towards the usually less stable cis-isomer cis-2.100 could be explained by the minimization of the steric clash between the indoline and the cyclopentene found in the trans conformation trans2.100 (Scheme 73).

[^58]

## Scheme 73 - Reason for the preferred cis conformation of $\mathbf{2 . 1 0 0}$

Assuming that the dialdehyde $\mathbf{2 . 2 7 3}$ shared the same conformation as $\mathbf{2 . 1 0 0}$, it could only cyclized with the equatorial aldehyde but it seems highly improbable to get a full cyclization in this conformation. Nevertheless, as both conformations were in equilibrium at room temperature, the minor one trans- $\mathbf{2 . 2 7 3}$ could also cyclized with the required aldehyde (the axial one this time) and this conformation could lead to the fully cyclized product 2.274. Thanks to the Curtin-Hammett principle, ${ }^{172}$ and as the non-productive cyclization of cis-2.273 was reversible, the equilibrium could be displaced to the formation of the stable fully cyclized product $\mathbf{2 . 2 7 4}$ (Scheme 74).


Scheme 74 - Slow interconversion between cis and trans quinolizidine ring system and the conversion to the final product
$\mathbf{2 . 2 6 4}$ exhibited spectral features, strong Bohlmann bands as well as sharp NMR signals, indicating again a trans C/D junction which was the same at $-40^{\circ} \mathrm{C}$. In this conformation the cyclization after oxidative cleavage (2.266) could only occur with the equatorial aldehyde giving rise to the ( $\pm$ )-21-epi-terengganensine $A(\mathbf{2} \mathbf{2 6 5})$ as shown on Scheme 75.


## Scheme 75 - Trans conformation of 2.266 and its conversion to the final product

Compounds 2.245 and $\mathbf{2 . 2 5 7}$ were not very stable and slowly decomposed into the 3-oxindole derivative 2.101 (among other unidentified side products). Hydrolysis of the benzoate 2.269 was also performed giving rise to a clean conversion to the same 3 -oxindole 2.101. Perfect alignment (antiperiplanar) of the $\sigma^{*}(\mathrm{C}-\mathrm{X})$ at the $\mathrm{C}-2$ position and the $\sigma$ of the migrating $\mathrm{C}-7 / \mathrm{C}-6$ bond occurred after trapping of the imine with external nucleophile ( NaOMe ) (Scheme 76, A).

[^59]

Scheme 76 - Explanation of the stability of the different indolenines based on their relative conformation
On the other hand, alcohol 2.264 was very stable. Its aminal form did not feature the required alignment for the formation of 3-oxindole, except if the trans C/D ring system trans-2.276 could flip to the cis one cis-2.276 or if the chair C ring could flip in the boat conformation (Scheme 76, B). Both of these flips are energetically demanding and are not favored at all which could explain the relative stability of $\mathbf{2 . 2 6 4}$ compared to $\mathbf{2 . 2 4 5}$ and $\mathbf{2 . 2 5 7}$. We noted that the direct rearrangement of 3 -hydroxy-indolenine $\mathbf{2 . 2 6 4}$ to 3 -oxidinole $\mathbf{2 . 2 7 8}$ could also occur. Nevertheless, this reaction was never observed.

After considering the influence of the conformation of the precursors on the diastereoselectivity of the last cascade sequence, efforts were directed towards the elucidation of the mechanism of this triple cyclization. To the best of our knowledge no report existed concerning the nucleophilic attack of imine onto aldehyde in order to form iminium (except in the special case of pyridine) (Scheme 77, A). Therefore, we first postulated that during the oxidative cleavage of the diol, water (used as co-solvent) could first attack into the imine 2.92 to form the hemiaminal 2.93 (Scheme 77, B). The latter could then easily attack the aldehyde to form hemiacetal 2.94. The diastereoselectivity was not an issue since only the axial OH could continue the reaction sequence. 2.93 and 2.94 being in equilibrium, full conversion to the desired product could be achieved thanks to the Curtin-Hammett principle. The formed hemiacetal 2.94 could then attack on the second aldehyde. Finally, cyclization could occur from the alcohol coming from the water onto the hemiacetal or from the hemiacetal onto the hemiaminal. This mechanism would explain: 1) the high diastereoselectivity during the final cyclization as water attack onto the imine $\mathbf{2 . 9 2}$ could push even more down the indoline nitrogen 2.93 to cyclized only with the axial aldehyde as described before; and 2) the reason for the rapid cyclization as the low nucleophilic imine $\mathbf{2 . 9 2}$ would be converted into the more reactive hemiaminal 2.93.


## Scheme 77 - Possible mechanism for the final cyclization with a hypothesized attack of water as the triggering step

In order to obtain clues about our hypothesis, we ran the oxidative cleavage with $\mathrm{NaIO}_{4}$ in a 1:1 $\mathrm{THF} / \mathrm{H}_{2}{ }^{18} \mathrm{O}$ solution (Scheme 78). Reaction worked as usual but no shift on ${ }^{13} \mathrm{C}$ NMR indicating the presence of oxygen-18 in the isolated product 2.272 was observed. ${ }^{173}$ Submission of the product to high resolution mass spectroscopy revealed no presence of the labeled oxygen. Nevertheless, as expulsion of labeled water in the last cyclization could be possible, no conclusion could be drawn.


Scheme 78 - Labeled-water experiment for the oxidative cleavage/cyclization step
We then performed computational studies on the dialdehyde $\mathbf{2 . 2 8 0}$ (Figure 23). Optimized (DFT, 6$31 \mathrm{G}+(\mathrm{d})$, B3LYP) structure of the dialdehyde showed interaction of the carbonyl of the benzoyl moiety with the imine. An angle of $107.2^{\circ}$ was found for the "attack" of the carbonyl oxygen to the imine, which is almost the perfect Bürgi-Dunitz angle. ${ }^{174}$ Moreover, the distance between the same oxygen and the carbon of the imine was only $2.44 \AA$.

[^60]

Figure 23 - Computed geometry of the dialdehyde 2.280 featuring a potential neighboring group effect
We therefore hypothesized that, as planned, the OBz group could play a neighboring group effect, ${ }^{175}$ also known as anchimeric assistance to activate the imine carbon in order to render the nitrogen more nucleophilic and to improve the diastereoselectivity. Scheme 79 shows the two extreme cases: without neighboring group effect (A) and with complete attack of the OBz carbonyl onto the imine (B). Reality was probably located in between. Note that benzoyl group was already hypothesized as a potential neighboring group in reactions involving indolenine. ${ }^{162}$

Note that the final cyclization worked also with Cl instead of OBz but chloride was also known to participate in neighboring group effect in indolenine skeleton. ${ }^{154 a}$ The same was true for the wrong OH diastereoisomer 2.264. The alcohol function could also be a good directing group.

[^61]

Scheme 79 - Possible neighboring group effect of the OBz group

### 2.3.5 Towards the Synthesis of Terengganensine B, Larutensine and Eburnaminol

With (-)-terengganensine $A(2.1)$ in hands, we decided turned our attention towards the synthesis of related molecules, namely (+)-larutensine (2.17), (-)-eburnaminol (2.15) and (-)terengganensine $\mathrm{B}(\mathbf{2 . 8 1})$.


Scheme 80 - Strategy to access larutensine, eburnaminol and (-)-terengganensine B from a common intermediate

Starting from the indole skeleton $\mathbf{2 . 8 8}$, we demonstrated that we could access (-)-terengganensine A (2.1) as well as the chloro derivative $\mathbf{2 . 2 5 3}$ by different oxidation steps. It was also shown previ-
ously that the direct oxidative cleavage of the indole $\mathbf{2 . 8 8}$ afforded the partially cyclized hemiaminal $\mathbf{2 . 9 0}$ but this cyclization occurred with the equatorial aldehyde (Scheme 42). ${ }^{103}$

In order to overcome this issue, the idea was to oxidize the indole 2.88 at the C-7 position in order to force the cyclization with the desired aldehyde as in the case of terengganensine $A(2.1)$ (Scheme 80, A). Once the cyclization occurred, reformation of the indole $\mathbf{2 . 2 8 6}$ could afford the indole cyclized with the desired aldehyde. It was unknown if $\mathbf{2 . 2 8 6}$ would be stable enough to not reopen spontaneously to the dialdehyde and recyclized with the equatorial aldehyde. Selective reduction of the hemiacetal $\mathbf{2 . 2 8 6}$ could afford eburnaminol (2.15) which upon acidic treatment could give larutensine (2.17).

Concerning the strategy to access (-)-terengganensine B(2.81) (Scheme 80, B), the idea was to start from $\mathbf{2 . 2 7 2}$ or from (-)-terengganensine A(2.1) directly and to selectively reduce the acetal in order to give the corresponding hemiaminal $\mathbf{2 . 2 8 7}$ which could easily eliminate water to afford (-)terengganensine B (2.81).

Concerning the formation of indole $\mathbf{2 . 2 8 6}$ starting from 7-chloro-terengganensine A $\mathbf{2 . 2 5 3}$, sodium iodide was known to convert 3-chloroindolenine into the indole. ${ }^{153}$ We tried using stoichiometric or large excess of it under acidic conditions ( AcOH , reflux) but no reaction occurred. Other reagents such as the one in Table 6 were also attempted but no reaction occurred showing the high stability of 7-chloro-terengganensine A (2.253).

We then tested various reductive conditions to obtained (-)-terengganensine $B$ (2.81) starting from (-)-terengganensine A (2.1) or its OBz derivative $\mathbf{2 . 2 7 2}$ (Table 10).


| Entry | Substrate | Conditions | Result (yield) [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: |
| 1 | $\mathbf{2 . 2 7 2}$ | $\mathrm{NaBH}_{4} / \mathrm{EtOH} /$ rt to reflux | $\mathbf{2 . 1}(78)$ |
| 2 | $\mathbf{2 . 2 7 2}$ | $\mathrm{LiBH}_{4} / \mathrm{EtOH} / 60^{\circ} \mathrm{C}$ to reflux | $\mathbf{2 . 1}(67)$ |
| 3 | $\mathbf{2 . 1}$ | $\mathrm{NaBH}_{4} / \mathrm{THF} /$ reflux | No reaction |
| 4 | $\mathbf{2 . 1}$ | $\mathrm{NaBH}_{4} / \mathrm{LA} / \mathrm{EtOH} /-78^{\circ} \mathrm{C}$ | Decomposition |
| 5 | $\mathbf{2 . 1}$ | $\mathrm{DIBAL} / \mathrm{Toluene} /-78^{\circ} \mathrm{C}$ | Decomposition |
| 6 | $\mathbf{2 . 1}$ | $\mathrm{LiAlH} / \mathrm{THF} /-78^{\circ} \mathrm{C}$ | Decomposition |
| 7 | $\mathbf{2 . 1}$ | $\mathrm{Red}-\mathrm{Al} / \mathrm{Toluene} /-78^{\circ} \mathrm{C}$ | Decomposition |
| 8 | $\mathbf{2 . 1}$ | $\mathrm{Et}_{3} \mathrm{SiH} / \mathrm{LA} / \mathrm{DCM} /-78^{\circ} \mathrm{C}$ | Decomposition |
| (a: Isolated yield) |  |  |  |

Table 10 - Conditions attempted for the reductive opening of (-)-terengganensine $A$
$\mathrm{NaBH}_{4}$ and $\mathrm{LiBH}_{4}$ were only strong enough to deprotect 2.272 to furnish (-)-terengganensine A (2.1) but no reduction of the aminal/acetal was observed even at reflux (Table 10, entry 1 to 3). DIBAL, $\mathrm{LiAlH}_{4}$ and Red-Al were too strong, even at low temperature, and only gave full decomposi-
tion of (-)-terengganensine $\mathrm{A}(\mathbf{2} \mathbf{1})$ (entry 5 to 7). Using either $\mathrm{NaBH}_{4}$ or $\mathrm{Et}_{3} \mathrm{SiH}$ in combination with Lewis acids $\left(\ln (\mathrm{OTf})_{3}\right.$ or $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$ ) also promoted the full decomposition (entry 4 and 8 ). These results could be explained by the conformation of the expected product and its structure. First of all, selective reduction of acetal in the presence of aminal was not well reported. Overreduction could therefore easily occur. Moreover, the expected product 2.288 could be highly prone to rearrangement as the $\mathrm{C}-6 / \mathrm{C}-7$ bond is perfectly aligned with the good alkoxy leaving group as already mentioned in Scheme 75.

### 2.4 Conclusion and Outlook

In conclusion, we succeeded in the first conformation-driven enantioselective synthesis of (-)terengganensine $A$ (2.1). Combination of factors allowed a quick and efficient synthesis of the target.

- An in-depth conformational analysis of the tetracyclic precursor supported by previous published data
- A key uncommon asymmetric transfer hydrogenation on a highly hindered tetra-alkyl iminium ions using Noyori catalyst under phase-transfer conditions in water leading to excellent enantiomeric excess
- An unprecedented diastereoselective C-3 benzoyl oxidation of indole at room temperature probably following a unprecedented ionic mechanism
- A newly developed dihydroxylation/oxidative cleavage/triple cyclizations/hydrolysis cascade for the rapid construction of the aza-adamantly-like cage structure
- Perfect control of the C-7 diastereoselectivity as well as full control on the four newly generated centers in the triple cyclization cascade thanks to a neighboring group effect of the C-7 benzoyl group supported by computational studies


Scheme 81 - Summary of the total synthesis of (-)-terengganensine A
Using the combination of this key features, (-)-terengganensine A was obtained in only 7 steps and an excellent $23 \%$ overall yield with $90 \%$ ee starting from simple starting materials without any protecting group and using simple textbook reactions (Scheme 81). ${ }^{176}$

[^62]Application of this strategy in the total synthesis of other natural products is ongoing in our laboratory.

# Chapter 3 Enantioselective Total Synthesis of (-)-Vallesamidine and (+)-1,2Dehydroaspidospermidine 

### 3.1 Introduction

Terengganensine $A(\mathbf{2} .1)$ is a 2,3-disubstituted indole alkaloids. Another very important substitution patterns of indole ring found in MIA are the 2,3,3-trisubstituted indoline/indolenine and the 2,2,3-trisubstituted indoline.

Many reports have been published concerning the synthesis of 2,3,3-trisubstituted indoline alkaloids. Two methods are generally used. A 2,3-disubstituted indole can, for instance, be easily functionalized at the C-3 position by nucleophilic attack on electrophiles such as imines and alkyl halides. The 2,3,3-trisubstituted indoline skeleton can also be construct de novo using, for instance, the very well-known Fischer indole synthesis method.

On the other hand, only few reports concerned the synthesis of 2,2,3-trisubstituted indole alkaloids.

$(-)$-Vallesamidine

$(-)$-Strempeliopine
(3.3)

(+)-Schizozygine
(3.4)

Figure 24 - Examples of melonine and schizozygine alkaloid
This kind of skeleton is found in melonine and schizozygine alkaloids such as for instance in schizozygine (3.4) ${ }^{177}$ and strempeliopine (3.3). ${ }^{178}$ Among the schizozygine alkaloids is also found the structurally unusual (-)-vallesamidine (3.1) (Figure 24).

### 3.1.1 (-)-Vallesamidine

### 3.1.1.1 History and Structure

(-)-Vallesamidine (3.1) was isolated in 1965 from Vallesia dichotoma (Ruiz et Pav) ${ }^{179}$ and later from the roots of Strempeliopsis strempelioides. ${ }^{180}$ The structure, as well as the relative and absolute

[^63]configuration, was disclosed in 1968 by Djerassi and coworkers. ${ }^{181}$ They were determined by X-ray diffraction on the $N$-methyl ammonium iodide salt of vallesamidine. It is to note that this represented the first absolute configuration determination of an alkaloid related to aspidospermine (3.5).


Figure 25 - Structure of (-)-vallesamidine and the structurally related andrangine
Concerning its structure (Figure 25), (-)-vallesamidine (3.1) is a pentacyclic 2,2,3-indoline alkaloids. This unique structure does not exactly belong to any particular class of alkaloids as it is missing the $\mathrm{C}-18 / \mathrm{N}-1$ bond of schizozygine skeleton. The indoline nitrogen is methylated. Similar to eburnane alkaloids, the $\mathrm{C}-19 / \mathrm{C}-18$ ethyl substituent is cis with the $\mathrm{H}-21$, i.e. the $\mathrm{D} / \mathrm{E}$ ring junction is cis. Moreover, the $\mathrm{B} / \mathrm{C}$ ring junction is also cis, as in aspidospermidine (1.71). The only known compound closely related to it is andrangine (3.6) which contains an epoxide at $\mathrm{C}-14$ and $\mathrm{C}-15$. Surprisingly, the absolute configuration at C-2, C-7, C-20 and C-21 is opposed to vallesamidine (3.1), indicating a different biosynthetic pathway.

### 3.1.1.2 Biosynthesis

No real support for the biosynthesis of vallesamidine (3.1) has been reported. Nevertheless, it has been proposed that (-)-vallesamidine (3.1) is biogenetically derived from aspidosperma alkaloids or aspidosperma precursors. An oxidized version 3.9 of quebrachamine (2.82) could be a possible intermediate. This hypothesis was supported by the known interconversion between aspidosper$m a$ alkaloids and desmethyl-vallesamidine (3.7) which was believed to proceed via intermediate 3.8 (Scheme 82). ${ }^{182}$


Scheme 82 - Interconversion between aspidosperma alkaloids and the vallesamidine skeleton

[^64]
### 3.1.1.3 Previous Syntheses ${ }^{183}$

The very first biomimetic synthesis of (+)-vallesamidine (ent-3.1) was performed starting from tabersonine (3.10), an aspidosperma alkaloid (Scheme 83). ${ }^{182}$ The latter was first hydrolyzed and decarboxylated to 3.11. This new indolenine compound 3.11 was then heated in acetic acid at 110 ${ }^{\circ} \mathrm{C}$ in the presence of Zn powder and $\mathrm{CuSO}_{4}$. The resulting product 3.13 arose from the rearrangement of C-21 from C-7 to C-2 followed by reduction of the ammonium intermediate 3.12. The rearranged skeleton $\mathbf{3 . 1 3}$ was then formylated using a mixture of $\mathrm{Ac}_{2} \mathrm{O}$ and formic acid. This formamide was later reduced with LAH and the double bond was hydrogenated with Adam's catalyst to afford ( + )-vallesamidine (ent-3.1). It is to note that in this strategy, the C-20 stereocenter was sufficient to control all the three other generated chiral centers. This synthesis again highlighted the relationship between vallesamidine (3.1) and aspidosperma alkaloids.


Scheme 83 - Le Men's synthesis of (+)-vallesamidine from tabersonine
The second total synthesis of rac-3.1 was reported by Heathcock and coworkers (Scheme 84). ${ }^{184}$ Starting from 2-ethylcyclopentanone (3.14) they performed an alkylation of the thermodynamically more stable enolate using acrylonitrile. Reduction of the obtained product using Raney Ni in the presence of KOH afforded the bicyclic imine rac-3.15. One-pot Michel-addition/lactamization afforded the desired tricyclic product $\mathbf{3 . 1 7}$ in excellent diastereoselectivity. This selectivity was explained by the attack of the enamine from the opposite side of the ethyl side chain. Minimization of the steric interaction, i.e. orienting the Ar group and the alkene away from the bicyclic system, resulted in the observed diastereoselectivity. After nitro reduction of 3.17, NBS-mediated cyclization afforded a mixture of diastereoisomers which was directly converted to the hemiaminal 3.18 using silver nitrate in aqueous methanol. One-pot reduction of the hemiaminal and $N$-methylation cascade followed by LAH reduction of the amide afforded ( $\pm$ )-vallesamidine (rac-3.1) in 7 steps and 19\% (brsm) overall yield.

[^65]

Scheme 84 - Heathcock's first total synthesis of ( $\pm$ )-vallesamidine
An enantioselective formal synthesis based on Heathcock's one was later reported by Costa and coworkers (Scheme 85). ${ }^{185}$ Condensation of ethylcyclopentanone (3.14) with enantiopure 1phenylethylamine (3.19) followed by diastereoselective 1,4-addition to methyl acrylate (3.21) and acid hydrolysis of the imine afforded 3.22. Acetal protection of the ketone 3.22 followed by conversion of the ester into amine and deprotection afforded the enantio-enriched 3.15 in $90 \%$ ee.


Scheme 85 - Formal enantioselective synthesis of (-)-vallesamidine from Costa and coworkers
Heathcock's work inspired another racemic formal synthesis. It was reported by Padwa and coworkers in 1998 (Scheme 86). ${ }^{186}$ Double alkylation of $\delta$-lactam (3.23) followed by a 2 -step conversion of the alkene $\mathbf{3 . 2 4}$ into alkyne by bromination/elimination afforded a terminal alkyne. The latter was submitted to Sonogashira coupling with 2-bromonitrobenzene. The product was hydrogenated to a (Z)-alkene using the Trost-Braslau method ${ }^{187}\left(\mathrm{Pd}_{2} \mathrm{dba}_{3} \cdot \mathrm{CHCl}_{3}\right.$, TMDHS, $(o-\mathrm{Tol})_{3} \mathrm{P}$, AcOH , benzene, rt ). Amide bond formation using malonyl ester chloride, followed by a modified Regitz-diazotransfer reaction afforded the diazo compound 3.25. Rhodium-catalyzed reaction promoted the formation of the 1,3-dipole 3.26 which spontaneously underwent an intramolecular [3+2] cycloaddition with the alkene to form the tetrahydrofuran derivative 3.27. This cycloaddition performed with excellent diastereocontrol. TMSOTf-promoted elimination/ring opening afforded ester 3.28. Barton-McCombie deoxygenation followed by hydrolysis and decarboxylation of the ester intercepted Heathcock's intermediate 3.17.

[^66]

Scheme 86 - Padwa's formal synthesis of ( $\pm$ )-vallesamidine
The first enantioselective total synthesis of (-)-vallesamidine (3.1) was reported by Okada and coworkers in 2002 (Scheme 87). ${ }^{188}$ They first performed the synthesis of enantio-enriched 2.68 as reported in Scheme 38. A 10-step sequence converted it to the acetal ent-2.58. Pictet-Spengler reaction using tryptamine (1.16) in acetic acid afforded a 1:1 diastereoisomeric mixture of $\mathbf{3 . 3 0}$. Acetyl deprotection, mesylation and substitution afforded the selenide 3.30. The latter was submitted to radical cyclization conditions ( $\mathrm{AIBN}, \mathrm{Bu}_{3} \mathrm{SnH}$ ) to afford the product 3.32 probably via intermediate 3.31. A two-step conversion of 3.32 via reductive $N$-methylation and amide reduction afforded (-)-vallesamidine (3.1). It is interesting to note that the same intermediate 3.29 also served as precursor for the synthesis of (-)-aspidospermidine (1.71) as it will be presented in Scheme 95.


Scheme 87 - Enantioselective synthesis of (-)-vallesamidine from Okada and coworkers
A racemic formal synthesis following the one of Okada's lab was reported by Ho, Chen and coworkers (Scheme 88). ${ }^{189}$ Ester 3.33 was alkylated and then converted in a two-step process to aldehyde 3.34. Pictet-Spengler reaction with 1.16 followed by Boc protections of the resulting indole and of the secondary amine afforded 3.35 . Oxidative cleavage of the cycloheptene afforded a

[^67]diacid. Acid-catalyzed esterification and secondary amine deprotection followed by spontaneous cyclization with either of the two esters afforded 3.36 in a $3: 2$ ratio of diastereoisomers. Boc deprotection on trans- $\mathbf{3 . 3 6}$ followed by ester hydrolysis afforded an acid as well as its diastereoisomer. Esterification with $\mathrm{BnOH}, \mathrm{Boc}$ reprotection and hydrogenolysis furnished the N -Boc acid. Boc deprotection could not be avoided during the ester hydrolysis. Barton-McCombie decarboxylation in the presence of diphenyl diselenide followed by Boc deprotection intercepted Okada's intermediate rac-3.30. Epimerization was also observed during the Barton procedure to afford a mixture of diastereoisomers.


## Scheme 88 - Racemic formal synthesis of ( $\pm$ )-vallesamidine from Ho, Chen and coworkers

Qin and coworkers adopted the similar radical cyclization for the synthesis of (-)-vallesamidine (3.1) (Scheme 89). ${ }^{98} \mathrm{~N}$-methylation of enantio-enriched tetracycle $\mathbf{2 . 8 0}$, used in their synthesis of eburnamonine (Scheme 40), followed by hydrolysis of the 1,3-dioxane afforded the aldehyde 3.37. Sml2-mediated cyclization afforded alcohol 3.38 in a $5: 1$ diastereoisomeric mixture. BartonMcCombie deoxygenation followed by reduction of the lactam afforded (-)-vallesamidine (3.1).


Scheme 89 - Qin's total synthesis of (-)-vallesamidine
Other compounds related to vallesamidine (3.1) are strempeliopine (3.3) and schizozygine (3.4). Padwa reported the racemic synthesis of the former (Scheme 90). ${ }^{190}$ Reaction of thiolactam 3.39 with carbon suboxide (3.40) afforded the isolable 1,4-dipole 3.41 which upon thermolysis at 200 ${ }^{\circ} \mathrm{C}$ gave, after fragmentation of the [4+2] product 3.42, the lactam 3.43. Again, the cycloaddition was highly diastereoselective. 3.43 was converted to 3.44 following the sequence developed by Heathcock, i.e. reduction, brominative cyclization, hemiacetal formation and reduction of the latter (Scheme 84). Oxidations of the alcohol 3.44 afforded the desired product rac-3.3 after cyclization.

[^68]

## Scheme 90 - Padwa's synthesis of ( $\pm$ )-strempeliopine

Hájíček and coworkers developed a synthesis of 15-hydroxy-strempeliopine (3.45) (Scheme 91). ${ }^{191}$ Reaction of ketone 3.45 with azepine 3.46 afforded 3.47. [4+2] cycloaddition in toluene at reflux followed by hydrolysis and decarboxylation afforded a pentacyclic product 3.48 as a single diastereoisomer. Treatment of the latter with $\mathrm{Zn} / \mathrm{CuSO}_{4}$ in AcOH according to Le Men and coworkers (Scheme 83) afforded 3.51 probably via intermediates 3.49 and $\mathbf{3 . 5 0}{ }^{178,192}$ Functional-group manipulation on the allyl 3.51 afforded the desired product 3.45. The authors were not able to promote the final dehydration of $\mathbf{3 . 4 5}$ to afford $\mathbf{3 . 5 2}$.


Scheme 91 - Hájíček's synthesis of ( $\pm$ )-15-hydroxy-strempeliopine
Finally, a very similar sequence was employed in their strategy towards schizozygine (rac-3.4) (Scheme 92). 3.53 or $\mathbf{3 . 5 4}$ were submitted to various oxidation conditions but all failed. AD-mix as well as $\mathrm{OsO}_{4} / \mathrm{NaIO}_{4}$ oxidations afforded rearranged products 3.55 and 3.56 respectively. Simple dihydroxylation of 3.54 afforded the hemiacetal 3.57. Nosyl-protection of the indole nitrogen to deactivate the electron-rich indole ring was also unsuccessful. Assisted elimination of the nosyl 3.58 followed by rearrangement of $\mathbf{3 . 6 0}$ afforded compound $\mathbf{3 . 5 5}$ in excellent yield.

[^69]

Scheme 92 - Hájíček's synthetic studies towards schizozygine alkaloids

### 3.1.2 (+)-Aspidospermidine and (+)-1,2-Dehydroaspidospermidine

The aspidosperma alkaloids represent the largest family of monoterpenoid indole alkaloids, with more than 250 members isolated from various plants. Among them, very often affiliated to (-)vallesamidine (3.1) because of their known interconversion, are (+)-aspidospermidine (1.71) and the related (+)-1,2-dehydroaspdiospermidine (3.2).

### 3.1.2.1 History, Structure and Biosynthesis

(+)-Aspidospermidine (1.71) and (+)-1,2-dehydroaspidospermidine also known as eburenine (3.2), were isolated in 1961 from Aspidosperma quebracho-blanco (Schlecht) (Figure 26). ${ }^{193}$ Their structure was initially identified by UV and mass spectrometry only. They are pentacyclic 2,3,3trisubstituted indoline/indolenine alkaloids. $\mathbf{3 . 2}$ is in the form of an indolenine and $\mathbf{1 . 7 1}$ is its reduced form. The relative stereochemistry for aspidospermidine is the following: B/C, C/D as well as $C / E$ rings have a cis ring fusion whereas $D$ and $E$ ring have a trans ring fusion. This is also true for $(+)$-1,2-dehydroaspidospermidine (3.2) except the B/C ring junction as it is in an indolenine form. Concerning their absolute configuration, surprisingly aspidospermidine (1.71) was up to now only isolated in the (+) form, whereas eburenine (3.2) was isolated in the (+) and in the (-) form. ${ }^{194}$

[^70]

Figure 26 - Structure of (+-aspidospermidine and (+)-1,2-dehydroaspidospermidine
Concerning their biosynthesis, they are believed to arise from a simple decarboxylation of vincadifformine (1.23) (Scheme 1).

### 3.1.2.2 Previous Syntheses

More than 40 total syntheses of aspidospermidine (1.71) have been reported and at least the same amount of formal ones. Most of these syntheses passed by 1,2-dehydroaspidospermidine (3.2) and used a final reduction step. Few synthesis oxidized aspidospermidine (1.71) to obtain 3.2. Five main different strategies have been extensively used:

- Fischer indole synthesis from a tricyclic ketone
- Harley-Mason's rearrangement from indoloquinolizidine
- Magnus' construction of the E ring on the ABCD core
- Kuehne's intramolecular Diels-Alder reaction of indole derivatives.
- One-pot construction of the pentacyclic core (developed in our lab)

Selected examples are summarized in Scheme 93 to Scheme 103 to illustrate the relevant strategies towards aspidospermidine (1.71).

Probably the most common strategy towards aspidospermidine (1.71) is the Fischer indole synthesis starting from tricyclic intermediate rac-3.62. Stork initially developed this strategy for the synthesis of ( $\pm$ )-aspidospermine (rac-3.61) (Scheme 93, A). ${ }^{195}$ Condensation of rac-3.62 with omethoxyphenylhydrazine (3.63) followed by acidic treatment of the resulting hydrazone afforded the indolenine 3.64. Reduction of the latter and acetylation furnished ( $\pm$ )-aspidospermine (rac3.61).

Later, Aubé and coworkers applied this strategy to the synthesis of 1.71 (B). ${ }^{196}$ Starting from 2-ethyl-cyclopentanone (3.14), a 4-step sequence similar to the one used by Costa and coworkers (Scheme 85) afforded bicycle enone 3.65. Functional group manipulations afforded the azide 3.66 which was submitted to a regioselective Schmidt reaction to afford 3.67. After amide reduction, the key intermediate 3.62 was obtained. The latter was then transformed into 1,2-

[^71]dehydroaspidospermidine (3.2) via a Fischer-indole reaction. Reduction of the indolenine afforded $(+)$-aspidospermidine (1.71). Since then, many groups have targeted intermediate 3.62. ${ }^{197}$


Scheme 93 - Aubé's synthesis of (+)-aspidospermidine based on Stork's Fischer-indole strategy


Scheme 94 - Harley-Manson synthesis of ( $\pm$ )-aspidospermidine based on a rearrangement
Harley-Manson and coworkers' strategy relied on a Pictet-Spengler reaction using the masked aldehyde 3.68 (Scheme 94). ${ }^{198}$ The product of the Pictet-Spengler reaction with 1.16, rac-2.59, obtained in a $1: 1 \mathrm{dr}$ was then submitted to strongly acidic conditions (or using $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$ ) and rearranged following Scheme 82 after C-2 alkylation to afford 3.69. It is to note that the diastereoselectivity of rac-2.59 did not matter as center C-21 epimerized during the rearrangement. Center C20 was sufficient to afford full diastereocontrol on all the other ones. As last step, the indolenine and lactam reduction afforded ( $\pm$ )-aspidospermidine (rac-1.71).

[^72]

Scheme 95 - Enantioselective strategies based on the rearrangement developed by Harley-Manson and coworkers

Enantioselective formal syntheses based on this strategy were later developed for instance by Fu$j i^{86,199}(A)$ and Tomioka (B) (Scheme 95). ${ }^{200}$ Alcohol 2.59 was for instance obtained from enantioenriched 3.70 via similar Pictet-Spengler reaction. In this case, TfOH was used to catalyze the rearrangement. A slightly different strategy was reported by Tomioka and coworkers. Enantioenriched lactone 3.72 was reacted with tryptamine (1.16) to afford hemiacetal 3.73. Sulfuric acid catalyzed the one-pot acetal opening, Pictet-Spengler reaction and rearrangement to afford 3.71 directly from 3.73.


Scheme 96 - Magnus' synthesis of $( \pm)$-aspidospermidine based on the late-stage construction of the $E$ ring

Magnus' and coworkers' strategy relied on a late-stage construction of the E ring (Scheme 96). ${ }^{201}$ Diels-Alder reaction of imine 3.74 with dienophile 3.75 afforded the tetracyclic system 3.76 as a single diastereoisomer. Oxidation of the sulfide 3.76 with mCPBA followed by TFAA-promoted Pummerer rearrangement/cyclization afforded enamine 3.77. A two-step sequence allowed the reduction of the sulfide and of the enamine to furnish the desired product rac-1.71. Kuehne and coworkers developed an alternative intramolecular Diels-Alder reaction for the synthesis of ( $\pm$ )vincadifformine (rac-1.23) (Scheme 97). ${ }^{202} 3.46$ was condensed with aldehyde 3.78 and retroMichael reaction afforded 3.79 which spontaneously underwent a Diels-Alder reaction to afford

[^73]3.80 in a $5: 2$ diastereomeric mixture. A 2-step sequence converted it to ( $\pm$ )-vincadifformine (rac1.23).


Scheme 97 - Kuehne's synthesis of ( $\pm$ )-vincadifformine
An enantioselective version was later developed with the use of a chiral auxiliary by Andrade and coworkers (Scheme 98). ${ }^{203}$


Scheme 98 - Enantioselective strategy towards (+)-aspidospermidine based on a Diels-Alder reaction
Sulfinamide 3.81 was reacted with 3.82 in the presence of base and the resulting Diels-Alder product was then in situ trapped with allyl bromide (2.223) to afford 3.83. E ring formation relied this time on a simple nucleophilic substitution of alcohol 3.84.

Many other strategies featuring a double intramolecular Mannich reaction for the construction of ring C (and E) have been developed (Scheme 99).

Ishibashi and coworkers were able to generate the $N$-acyl iminium salt 3.86 by treatment of butanone 3.85 with TMSOTf. The resulting highly reactive intermediate underwent the double intramolecular Mannich reactions to afford pentacycle 3.87 which was converted to ( $\pm$ )aspidospermidine (rac-1.71) by a three-step sequence (A). ${ }^{204}$ Wenkert's lab developed a $\mathrm{BF}_{3}$ mediated formal Diels-Alder reaction from enamine 3.88 to access pentacyclic system 3.89 (B). ${ }^{205}$ This Diels-Alder strategy was also performed in an enantioselective way using McMillan's catalyst (C). ${ }^{31}$ Indole 3.91 was reacted with propiolaldehyde (3.93) in the presence of catalyst 3.92 to afford tetracyclic compound 3.94. In this case, the D ring was formed by an intramolecular Heck reaction in a later stage.

[^74]

Scheme 99 - Diels-Alder strategies for the construction of rings C and E
An alternative strategy relied on the late-stage closing of ring C. This is illustrated by the synthesis of Wenkert ${ }^{206}$ and by the formal synthesis of Waser and coworkers ${ }^{207}$ (Scheme 100).


Scheme 100 - Syntheses of aspidospermidine via ring C closing
Reaction of indole (3.96) with the enantio-enriched aminal ent-2.48 under acidic conditions afforded 3.97 as a $2: 1$ mixture of diastereoisomers. Acid-catalyzed Friedel-Craft reaction of 3.97 afforded 3.98 which was converted to aspidospermidine (1.71) in a 3-step sequence (Scheme 100,

[^75]A). Waser and coworkers targeted 3.100 via a Cu-catalyzed homo-Nazarov reaction from cyclopropane 3.99. Deprotection of the Cbz group intercepted Wenkert's intermediate rac-3.98 (B).

Other strategies were based on the construction of the indole ring. Apart from the Fischer-indole strategy discussed earlier, other methods have been developed (Scheme 101).


Scheme 101 - Syntheses of aspidospermidine featuring a de novo synthesis of the indole ring

The indole ring was constructed by a late-stage 1,4-addition on intermediate 3.103 which was synthesized using another 1,4-addition starting from intermediate $\mathbf{3 . 1 0 1}(\mathrm{A}) .{ }^{208}$ The indole ring was also synthesized using intermediate 3.106 via the reduction of the nitroaryl group followed by intramolecular condensation on a ketone (B). ${ }^{209}$ Ring B was constructed starting from diazonium salt 3.108 using TTF as oxidant (C). ${ }^{210}$ Simple $\mathrm{Cu}(\mathrm{I})$-catalyzed arylation was also used to convert oiodoaniline derivative 3.111 into tricyclic ring system 3.112 (D). ${ }^{211}$ Finally, $A / B / C$ ring system was constructed using a Pd-catalyzed cascade cyclization reaction to access 3.117 (E). ${ }^{212}$

Vallesamidine (3.1) and aspidospermidine (1.71) were shown to be synthetically related. Moreover, Gaunt and coworkers developed a divergent synthesis of ( $\pm$ )-aspidospermidine (rac-1.71) and ( $\pm$ )-rhazinilam (rac-3.120), a plumeran alkaloid.


Scheme 102 - Synthesis of ( $\pm$ )-rhazinilam and ( $\pm$ )-aspidospermidine by Gaunt and coworkers
They initially synthesized ( $\pm$ )-rhazinilam (3.120) from precursor 3.119. $N$-Boc protection of rac3.120 followed by and a superhydride-mediated reduction and acetylation of the resulting hemiaminal afforded 3.122. The latter was converted to the iminium $\mathbf{3 . 1 2 3}$ in the presence of TFA. The iminium 3.123 was then intramolecularly trapped by the C-7 position of pyrrole which, after reduction and deprotection, afforded ( $\pm$ )-aspidospermidine (rac-1.71). ${ }^{213}$

Finally, a strategy relying on cyclic alkene opening followed by cascade reaction was also developed, notably by the group of Heathcock. ${ }^{214}$

Ozonolysis of cyclopentene $\mathbf{3 . 1 2 6}$ afforded the aldehyde 3.127. TFA-promoted cascade cyclization afforded tetracyclic intermediate 3.107, known to be easily converted to aspidospermidine (1.71).

[^76]

Scheme 103 - Cascade synthesis of ( $\pm$ )-aspidospermidine by Heathcock and coworkers

### 3.2 Retrosynthetic Pathway and Background

One of the most recent syntheses of rac-1.71 was developed by our group. This strategy relied on the iORC process (1.2.3.1 - Integrated Oxidation/Reduction/Cyclization Sequence) and was presented in Scheme 19. ${ }^{67}$

It appeared to us that intermediate $\mathbf{1 . 1 8 4}$ could be exploited for the synthesis of $(-)$-vallesamidine (3.1), by way of an intramolecular diamination of alkene or by related reactions.


Scheme 104 - Initial disconnection of (-)-vallesamidine
We designed two different pathways (Scheme 104). Disconnection of the two C-N bonds traced back (-)-vallesamidine (3.1) to the macrocycle 3.128 (A). Functional group manipulation traced back the latter to the known intermediate 1.184. On the other side, (-)-vallesamidine (3.1) could also be synthesized from tetracycle 3.129 via simple $N$-alkylation (B). The latter was disconnected to the cyclopentene 3.130, which was structurally similar to another intermediate in our previous synthesis of ( $\pm$ )-aspidospermidine (rac-1.71). In the forward direction diamination process could provide 3.1.

### 3.2.1 Intramolecular Diamination of Alkene

Many reports have been published on the intramolecular diamination of alkenes. ${ }^{215}$ They can be classified in different categories (Figure 27).

- The two nitrogens are tethered together by a CO or $\mathrm{SO}_{2}$ group in the form of a urea ( $\mathrm{X}=$ CO ) or a sulfamide ( $\mathrm{X}=\mathrm{SO}_{2}$ ) giving rise to two intramolecular reactions (A)
- The two nitrogens are tethered to the alkene (B)

[^77]- One nitrogen coming from an external source giving rise to one intra- and one intermolecular reaction (C)




Figure 27 - Categories of intramolecular diamination
For intramolecular diaminations, metal-catalyzed as well as halonium-promoted reactions are reported. Moreover, substitution on the nitrogens ( $R=$ aryl, alkyl or EWG) can dramatically influence the reactions outcome. Depending on the type of nitrogen use and the conditions, various mechanisms could occur leading to different diastereoisomers (Scheme 105). ${ }^{216}$


Scheme 105 - Different mechanisms and their outcomes for the intramolecular diamination of alkenes

[^78]Metal-free conditions can have different outcome depending on the electronic of the nitrogen source. If electron-poor nitrogens are used (A), activation of the double bond via halonium 3.137 followed by trans-opening of the latter could afford 3.138. Substitution could afford the cisdiamine cis-3.136. On the other side, if electron-rich nitrogens are used (B), oxidation to 3.139 followed by trans-addition could afford the trans-diamine trans-3.136. Using copper(II) (C), synamino cupration could furnish 3.141. Radical 3.142 generation by expulsion of $\mathrm{Cu}(\mathrm{I})$ followed by trapping of the radical with $\mathrm{Cu}(I I)$ and ligand exchange could provide 3.143 with unspecified stereochemistry. Reductive elimination could deliver diamine 3.136. Finally, with palladium (II), two possible mechanisms could exist depending on the linkage between the two nitrogens. For tethered amines (D), syn-aminopalladation to cis-3.145 followed by oxidation could promote the formation of cis-3.146. Detachment of the nitrogen from the palladium (3.147) followed by $\mathrm{S}_{N} 2$-type substitution could deliver trans-diamine 3.132. An alternative mechanism (E) was proposed ${ }^{217}$ via anti-aminopalladation, oxidation and reductive amination. Finally (F), anti-aminopalladation of 3.149 could afford $\mathbf{3 . 1 5 0}$. Oxidation of the palladium (II) to $\mathrm{Pd}(\mathrm{IV})$ followed by $\mathrm{S}_{\mathrm{N}} 2$-type mechanism could afford cis-diamine cis-3.136.

Scheme 106 to Scheme 110 summarized specific examples to illustrate the different types of diamination processes and their diastereoselectivity.

By far the most common method for the diamination of alkene is the use of urea (Scheme 106). It uses $\mathrm{Pd}(\mathrm{A}),{ }^{218} \mathrm{Cu}(\mathrm{B}),{ }^{219} \mathrm{Ni}$ or Au catalysis as well as some metal-free conditions using NIS for instance (C). ${ }^{220}$ In our strategy, cleavage of the tether could allow further functionalization to the desired product. For this type of reaction the nitrogens are generally acylated or sulfonylated.


Scheme 106 - Diamination of alkenes with urea
On the other hand, diamination using secondary amines is relatively rare (Scheme 107). One fully intramolecular example was developed by Hennecke and coworkers and used NIS (A) as an activa-

[^79]tor. ${ }^{221}$ Another one involving on intra- and one inter-molecular reaction was developed by Wang and coworkers (B). ${ }^{222}$ According to the diastereochemistry of the products, the latter reaction probably occurred via initial oxidation of the benzyl amine whereas the former probably occurred via iodonium intermediate.


## Scheme 107 - Diamination of alkenes relying on the use of secondary amines

Diamination involving one electron-rich amine and one electron-poor amide has also been developed (Scheme 108), as demonstrated for instance by the work of Johnston and coworkers using KI and PIDA for the in situ generation of " $I^{+\cdots 223}(B)$ or by the work of Chemler and coworkers using Cu-catalysis (A). ${ }^{224}$


Scheme 108 - Diamination of alkenes using a combination of tosyl amides and primary amines
Diamination involving two electron-deficient amide/sulfonamide nitrogens has also been developed (Scheme 109). ${ }^{225,226,227}$

[^80]

Scheme 109 - Diamination of alkenes using two electron-poor nitrogens
Finally, the use of untethered electron-deficient nitrogens for fully intramolecular diamination was also extensively reported (Scheme 110). Pd (A), ${ }^{228} \mathrm{Cu}$ and metal-free conditions (B) ${ }^{229}$ were known.


## Scheme 110 - Fully intramolecular diamination of alkenes using electron-deficient nitrogens

When looking at our retrosynthetic pathways, the question of the diastereoselectivity could arise. As illustrated by Scheme 105, the diastereoselectivity outcome of the reaction can be very different depending on the conditions and even on the substrates. Scheme 111 illustrated a reasonable pathway involving iodonium intermediate.


Scheme 111 - Hypothesized diastereoselectivity during the diamination of 3.128
We hypothesized that activation of the alkene 3.128 could occur from the top face, as the macrocycle would block the bottom face. Transannular trans opening of the halonium 1.75 by the more nucleophilic secondary amine could afford 3.176. Formation of an aziridinium 3.177 followed by its ring opening could then afford (-)-vallesamidine (3.1) with appropriate stereochemistry (A).

[^81]On the other hand, if the oxidation occurred on the most electron-rich group, similar geometrical considerations could lead to the formation of the described diastereoisomer (B).

### 3.2.2 Previous Synthesis of Macrocycle and Its Main Drawbacks

Macrocycle rac-1.184 was previously synthesized following the strategy represented in Scheme $112 .{ }^{67}$


## Scheme 112 - Originally designed retrosynthesis of macrocycle rac-1.184

Intramolecular Mitsunobu reaction on the amino alcohol rac-3.179 afforded the desired product rac-1.184. The amino alcohol rac- $\mathbf{3 . 1 7 9}$ was obtained from the alcohol rac-3.180 by another Mitsunobu reaction with $\mathrm{NsNH}_{2}$. The alcohol rac-3.180 was obtained by a Pd-catalyzed decarboxylative cross-coupling between carboxylate $\mathbf{3 . 1 8 1}$ and vinyl triflate rac-3.182. The carboxylate $\mathbf{3 . 1 8 1}$ was synthesized from 3.183 and the vinyl triflate was prepared from enone 3.184.

In the forward direction, esterification of the acid 3.185 followed by alkylation with the alkyl iodide 3.186 afforded 3.187. The resulting compound 3.187 was hydrolysis to acid 3.188. Reaction of the acid 3.188 with an equimolar amount of KOtBu afforded the desired potassium carboxylate salt 3.181 in excellent yields (Scheme 113, A).

On the other side, enol ether formation starting from the commercially available cyclopentanedione (3.189) furnished 3.190. Reaction of 3.190 with the in situ made Grignard reagent of 3.191 followed by acid hydrolysis afforded enone 3.192. 1,2-addition followed by hydrolysis of the enol ether explained the formation of the obtained product 3.192. The alcohol $\mathbf{3 . 1 9 2}$ was then easily protected with TES. With 3.184 in hands, 1,4 addition of cuprate followed by trapping of the resulting enolate with Comins' reagent delivered the vinyl triflate rac-3.182 in $82 \%$ yield (B).


Scheme 113 - Reported racemic synthesis of macrocycle rac-1.184

Pd-catalyzed decarboxylative cross-coupling of 3.181 with rac-3.184 afforded alcohol rac-3.180 in a 1:1 mixture of diastereoisomers after TBAF-mediated selective deprotection of the more sensitive TES group. This coupling, developed in our lab, ${ }^{230}$ was known to proceed in a nonstereoretentive way, probably because of the equilibrium between 3.197 and 3.198 via 3.198a (Scheme 114). Previous attempts to render it enantioselective, i.e. to favor the reductive elimination of one of the two enantiomers of 3.199, did not give any promising results.

[^82]

## Scheme 114 - Mechanism of the decarboxylative cross-coupling and explanation for the loss of stereoselectivity

After separation of both diastereoisomer of rac-3.180, Mitsunobu reaction with $\mathrm{NsNH}_{2}$ and subsequent deprotection of the TBS group afforded the desired alcohol rac-3.179. Intramolecular Mitsunobu reaction allowed the closing of the macrocycle rac-3.184 (C). Many efforts have been put into the one-pot double amination without any good promising results. Moreover, the two Mitsunobu reactions proved to be very hard to optimize.

### 3.2.2.1 Mitsunobu Reaction

This reaction, discovered in 1961 by Oyo Mitsunobu, ${ }^{231}$ converts an alcohol into various functional groups, using a phosphine and an azodicarboxylate, with inversion of the stereocenter. ${ }^{232}$ The mechanism for the substitution of an alcohol with a carboxylic acid is represented in Scheme 115.


Scheme 115 - Mechanism of the Mitsunobu reaction as well as the most common side reactions Irreversible addition of triphenylphosphine (3.201) on the azodicarboxylate 3.202 formed the Morrison-Brunn-Huisgen (MBH) betaine 3.203. Deprotonation of the carboxylic acid by the latter

[^83]could afford the phosphonium carboxylate ion pair 3.205 (A). Side reaction from the latter could form imide 3.206 and triphenylphosphine oxide (3.207) (B). The same intermediate $\mathbf{3 . 2 0 5}$ could react with the alcohol $\mathbf{3 . 2 0 8}$ to afford alkoxyphosphonium salt $\mathbf{3 . 2 1 0}$ (C). Attack of the carboxylate in a stereoinvertive way could generate the Mitsunobu product 3.211 (D). On the other hand, from the MBH betaine 3.203, addition of two equivalents of alcohol $\mathbf{3 . 2 0 8}$ could generate phosphorane 3.212 which could be in equilibrium with $\mathbf{3 . 2 1 0}$ (E). In order to increase the yield of Mitsunobu reactions, excess of alcohol 3.208 is often used in order to shift the equilibria away from 3.203 (E) and $\mathbf{3 . 2 0 5}$ (C). An alternative to this is the use of neopentyl alcohol (3.209) which could be used for the same purpose. ${ }^{233}$ Neopentyl alcohol (3.209) is very slow to undergo Mitsunobu reaction and therefore does not compete with the real alcohol 3.208.

One of the major drawbacks of Mitsunobu reaction is known as the so-called "restriction of pKa ". If the nucleophile is not acidic enough to be deprotonated to afford intermediate 3.205, the MBH betaine $\mathbf{3 . 2 0 3}$ can directly react with alkoxyphosphonium $\mathbf{3 . 2 1 0}$ to afford the alkylated hydrazine 3.214 (F). Another side reaction of MBH betaine 3.203, related to this pKa issue, is the irreversible reaction with sulfonamide $\mathbf{3 . 2 1 5}$ (if used instead of carboxylic acid) to form the iminophosphorane $3.216(\mathrm{G}) .{ }^{234}$ In order to be able to use weaker acidic nucleophiles, different azodicarboxylates have been developed (Figure 28) such as ADDP (3.222), ${ }^{235}$ where the conjugated base is more basic.


Figure 28 - Structure and abbreviation of the most common azodicarboxylates derivatives and related phosphorus ylides

Another major drawback of Mitsunobu reactions is the purification of the reaction mixture. Stoichiometric amount of triphenylphosphine oxide (3.207) and of the hydrazine by-product $\mathbf{3 . 2 1 3}$ are generated. Different strategies have been used in order to facilitate the purification. Use of DCAD (3.221) offered the advantage to furnish almost insoluble hydrazide by-product in DCM. ${ }^{236}$ DMEAD (3.219) and its byproduct are soluble in water. ${ }^{237}$ Finally, DBAD (3.220) ${ }^{238}$ and its byproduct decomposed easily to isobutene, $\mathrm{CO}_{2}$ and $\mathrm{N}_{2}$ or $\mathrm{H}_{2} \mathrm{NNH}_{2}$ respectively upon treatment with acid. ${ }^{239}$

[^84]Alternatively, phosphorane reagents such as cyanomethylene trimethylphosphorane (CMMP) or cyanomethylene tributylphosphorane (CMBP) have been developed for the Mitsunobu reaction ( 3.223 and 3.224 ). The advantage is the generated by-products. Acetonitrile is volatile and trialkylphosphine oxide is soluble in water or very polar and easily removable by column chromatography.

Despite these troublesome Mitsunobu reactions, strategy in Scheme 112 proved successful for the construction of macrocycle rac-1.184. Nevertheless, this strategy suffered from two main drawbacks. First of all, the vinyl triflate $\mathbf{3 . 1 8 4}$ was synthetized in a racemic form. Secondly, the decarboxylative cross-coupling afforded a $1: 1$ mixture of diastereoisomers. In the case of $( \pm)$ aspidospermidine (rac-1.71), this was not a problem as the C-7 stereocenter disappeared later in the synthesis. In our case, this stereocenter, once set, would remain until the end and a 1:1 diastereoisomeric mixture was therefore not suitable.

We quickly performed preliminary experiments for the interconversion between rac-trans-1.184 and rac-cis-1.184 (Scheme 116) to see if it would be possible to convert the undesired diastereoisomer to the desired one in a single step. As proton at the C-7 position was relatively acidic, being benzylic to o-nitrophenyl and allylic, we thought that its deprotonation followed by reprotonation under kinetic or thermodynamic conditions could allow the desired interconversion between trans-1.184 and cis-1.184.


Scheme 116 - Attempts for the kinetic and thermodynamic C-7 epimerization of macrocycle rac-1.184
Kinetic conditions (A) using NaH , BuLi or LDA in THF at $-78{ }^{\circ} \mathrm{C}$ did not promote any epimerization even after briefly warming-up the reaction mixture to room temperature to facilitate the deprotonation. Thermodynamic conditions (DBU, DMSO, reflux) (B) afforded similar negative results.

Keeping in mind this stereoselectivity issue, we revised the original strategy in order to access en-antio- and diastereo-merically pure macrocycle 1.184 (Scheme 117).

On pathway A, we thought about an intramolecular decarboxylative coupling from $\mathbf{3 . 2 2 5}$ in order to potentially control the diastereoselectivity using C-20. This product 3.225 was planned to be formed via Mitsunobu reaction between alcohol 3.226 and amine 3.227. The latter was envisioned to be obtained by enantioselective 1,4-addition from enone 3.184. On pathway B, alcohol $\mathbf{3 . 1 8 0}$ was planned to be obtained from a stereoretentive/invertive coupling between benzyl borane derivative $\mathbf{3 . 2 2 8}$ and vinyl triflate 3.182. The latter was also planned to be obtained via enantioselective 1,4-addition. The benzyl borane 3.228 was planned to be obtained via an enantioselective hydroboration of styrene $\mathbf{3 . 2 2 9}$. On pathway C, alcohol $\mathbf{3 . 1 8 0}$ was planned to be obtained by stereoinvertive/retentive coupling between allyl borane derivative $\mathbf{3 . 2 3 0}$ and o-nitro phenyl deriva-
tive 3.231. The former was imagined to be accessed by either enantioselective desymmetrization of 3.232 or stereoinvertive/retentive coupling of 3.234 which could in its turn be accessed by enantioselective hydroboration on $\mathbf{2 . 2 3 5}$. Finally, on pathway D, alcohol $\mathbf{3 . 1 8 0}$ was traced back to boronic acid $\mathbf{3 . 2 3 6}$ and benzylic mesylate 2.237. In the forward sense, the stereoinvertive nucleophilic substitution of the enantio-enriched mesylate 3.237 by the vinyl boronic acid 3.236 could afford the desired product $\mathbf{3 . 1 8 0}$. The boronic acid 3.236 could be easily derived of the vinyl triflate 3.182. The enantio-enriched mesylate 3.237 was planned to be obtained via diarylprolinolcatalyzed crossed-aldol reaction followed by reduction of the resulting aldehyde and protections.


Scheme 117 - Retrosynthesis of macrocycle 1.184 in an enantio- and diastereoselective way

### 3.2.3 Enantioselective 1,4-Addition

All these possible strategies relied on an initial installation of C-20 via enantioselective 1,4addition. Enantioselective 1,4-additions onto enones were already reported in the literature. Nevertheless, most of the examples relied on the use of linear or unstrained cyclic enones. The challenging 3 -substituted cyclopentenones had rarely been used in such transformations.

Some conditions were developed by Minnaard and coworkers relying on the use of boronic acids and palladium catalysis (Scheme 118). ${ }^{240}$ Nevertheless, the scope was limited to aryl boronic acids.


## Scheme 118 - Enantioselective Pd-catalyzed 1,4-addition of arylboronic acid

The use of NHC-ligands and copper in combination with Grignard reagents was reported by Alexakis and coworkers even though generally moderate ee were obtained compare to cyclohexanone (A). ${ }^{241}$ Preliminary results on our substrate using this methodology proved to be unsuccessful with only $5-10 \%$ ee depending on the starting substrates. ${ }^{242}$ Alexakis also reported the use of trialkyl aluminum reagents in combination with diphosphite (2.246) and phosphoramidite ligands (3.244). ${ }^{243}$ It is to note that addition of $\mathrm{AlMe}_{3}$ on 3.245 afforded only $33 \%$ ee (Scheme 119).


Scheme 119 - Alexakis' enantioselective Cu-catalyzed 1,4-addition of organometallic reagents

[^85]Finally, Hoveyda and coworkers reported a chiral NHC-Ag complex-catalyzed 1,4-addition of trialkyl aluminum reagents to 3 -substituted cyclopent-2-en-1-ones leading to 3,3-disubstituted cyclopentanones in excellent yields and enantioselectivity (Scheme 120, A). ${ }^{244}$ They later extended the scope to allyl dialkyl aluminum reagents (B). ${ }^{245}$


Scheme 120 - Hoveyda's enantioselective Cu-NHC-catalyzed 1,4-addition of aluminum reagents


Scheme 121 - Proposed mechanism of the enantioselective 1,4-addition using chiral NHC-Ag complex
Concerning the mechanism of this reaction (Scheme 121), ${ }^{246}$ as most of the copper-catalyzed conjugated addition, ${ }^{247}$ a $\mathrm{Cu}(\mathrm{I}) / \mathrm{Cu}(\mathrm{III})$ process was proposed. Moreover, it was proposed that the active catalyst is a $\mathrm{Cu}-\mathrm{NHC}$ monomer. It has been shown that the $\mathrm{SO}_{3}$ moiety lied on the same side as the phenyl ring on the NHC carbene. After metal exchange, $\mathrm{AlEt}_{3}$ could add onto the copper to form the $\mathrm{Cu}(\mathrm{I})$ anion monomer having $\mathrm{AlEt}_{2}{ }^{+}$as counterion. The 3 different aryl rings shielding completely the other faces, the enone could only come from the bottom face having the ketone moiety oriented towards the $\mathrm{AlEt}_{2}{ }^{+}$. Indeed, the latter could activate the ketone and served as a relay in between the substrate and the catalyst through binding with the $\mathrm{SO}_{3}$ moiety. 1,4-addition

[^86]followed by reductive elimination could regenerate the active catalyst and delivered the aluminum enolate which after workup can generate the expected 1,4-product.

Disconnection A (Scheme 117) relied on an intramolecular decarboxylative cross-coupling. This kind of coupling has already been reported but never to form 10-membered macrocycle, and especially not for bridged ring system. Nevertheless, we expected that, if successful, this reaction could provide possible control of the diastereoselectivity. Indeed, thermodynamics could favor the closing of the macrocycle having the nitroaryl group in a more favored pseudo-equatorial position.

### 3.2.4 Enantioselective Hydroboration/Stereospecific Coupling of Benzylborane Derivatives

Concerning the other disconnection pathways they all relied, at some point of the strategy, on enantioselective hydroboration of alkenes and their subsequent coupling. Many reports dealing with the hydroboration of the styrene derivatives have been published. Hydroboration of styrenes, using copper(I) and DTBM-Segphos (3.252) or tangphos (3.253) ligands afforded pinacol boronic esters with excellent ee on a wide range of substrates (Scheme 122, A). ${ }^{248}$ Initial hydro-cupration to afford the more stable benzylic cuprate 3.255, followed by the transmetalation with HBpin accounted for the observed regioselectivity.


## Scheme 122 - Enantioselective hydroboration of styrene derivatives

[^87]Similar reactions on cinnamate derivatives were also achieved with DPEPhos (3.258) (racemic) $(A)^{249}$ or JosiPhos (enantioselective) (3.259) ligands (B). ${ }^{250}$ Reaction of amide derivatives of cinnamate was also reported. ${ }^{251}$ Direct access to the boronic acids instead of pinacol boronic ester was achieved similarly on amide, ester and ketone derivatives (C). ${ }^{252}$ In these cases, the explanation of the regioselectivity relied on the initial 1,4-addition of the $\mathrm{Cu}(1)$-Bpin complex $\mathbf{3 . 2 6 4}$ formed by transmetalation of the $\mathrm{Cu}(\mathrm{I})$ with $\mathrm{B}_{2} \mathrm{Pin}_{2}$ (Scheme 123) (D).


## Scheme 123 - Enantioselective hydroboration of cinnamate derivatives

Concerning the coupling of the obtained benzylic boronic esters/acids, very different outcome were obtained. Stereoretentive coupling on aliphatic benzylic pinacol boronic ester with various aryl halides was achieved using palladium catalysis (Scheme 124). ${ }^{253}$ Both transmetalation and reductive elimination in Suzuki coupling were thought to be stereoselective.


Scheme 124 - Coupling of aliphatic benzylic pinacol boronic ester
On the other side, coupling of $\beta$-boryl substituted- $\beta$-phenyl propanoic acid derivatives did not afford any coupling product (Scheme 125, A). The lack of reactivity was compensated by using the trifluoroborate salts as coupling partner. Moreover, Hall and coworkers showed that amide was

[^88]required for the coupling (B). ${ }^{254}$ Ester $\mathbf{3 . 2 6 9}$ did not lead the formation of the desired product (Scheme 125, A). Reasons for the unique reactivity of the $\beta$-trifluoroborato amide could be the following:

- Strong coordination of the carbonyl of the amide with the boron could facilitate the transmetalation. The strength of this interaction could explain the superiority of amides compare to esters.
- This complexation may restrict the conformation of the diorganopalladium intermediate, inhibiting therefore a syn-coplanar arrangement of the palladium and the $\beta$-hydrogen, required for the $\beta$-H elimination.
- The coordination with the palladium could prevent any agostic interaction with the $\beta$ hydrogen required for the $\beta$-hydride elimination.

Interestingly, in this case inversion of the configuration was observed. ${ }^{251 b, 252}$ This kind of inversion of the configuration has already been observed previously ${ }^{255}$ and was hypothesized to be the results of $\mathbf{3 . 2 7 4}$ as the possible transition state. In this case, a $S_{N} 2$ mechanism was proposed to be involved (C).


Scheme 125 - Coupling of $\beta$-boryl substituted- $\beta$-phenyl propanoic acid derivatives
Compound $\mathbf{3 . 1 8 0}$ could also be synthesized by two sequential stereoselective couplings from the diboron compound $\mathbf{3 . 2 3 4}$ or by desymmetrization of $\mathbf{3 . 2 3 2}$ followed by stereoselective coupling (Scheme 117, C). Achiral compound $\mathbf{3 . 2 3 2}$ could easily be prepared by simple alkylation of the dipinacolboron methane (3.233). Its desymmetrization could be achieved by TADDOL-based phosphoramidite $\mathbf{3 . 2 7 8}$ or ferrocene bidentate $\mathbf{3 . 2 8 1}$ phosphine ligands as reported by Morken and coworkers. Both aryl (A) and vinyl bromide (B) showed promising results. ${ }^{256}$ On the other hand, preparation of enantio-enriched $\mathbf{3 . 2 8 3}$ was also reported by hydroboration of vinyl borane $\mathbf{3 . 2 8 2}$ (C). ${ }^{254,257}$ Subsequent coupling was reported using the trifluoroborate salt $\mathbf{3 . 2 8 5}$ which occurred with inversion of the configuration using amide and ester (D). Coupling directly from the pinacol

[^89]boronic ester was reported to work only with amide $\mathbf{3 . 2 8 7}$ and not with ester $\mathbf{3 . 2 8 6}(\mathrm{E})$, again with inversion of the configuration. ${ }^{258}$ The increased reactivity of the gem-diborons $\mathbf{3 . 2 8 5}$ and 3.287 compared to Scheme 125 could be explained by the empty orbitals of the second boronyl unit which could not only facilitate the borate formation but also help the transmetalation step by stabilization of the $\alpha$-boronyl-Pd(II) intermediate (F) (Scheme 126). ${ }^{259}$


Scheme 126 - Desymmetrization of gem-diboron 3.275, synthesis of chiral gem-diboron 3.283 and their subsequent coupling reactions

Concerning disconnection D (Scheme 117), Tang and coworkers reported in 2016 a stereoinvertive nucleophilic substitution of benzylic bromides and mesylates by various boronic acids (Scheme $127, A) .{ }^{260}$ They proposed a simple $S_{N} 2$-type mechanism via C-B $\sigma$-bond attack (B). Another possible alternative would be via C-C $\pi$-bond attack followed by reformation of the alkene (C).

[^90]

Scheme 127 - Stereoinvertive nucleophilic substitution of benzylic mesylates with boronic acid derivatives

### 3.3 Synthesis of ( - )-Vallesamidine

We initially focused on the enantioselective 1,4-addition for the synthesis of enantio-enriched vinyl triflate 3.182.

### 3.3.1 Enantioselective 1,4-Addition/Enolate Trapping

Because of the disappointing preliminary results using Alexakis' Cu-NHC catalysis, we decided to focus on the use of Hoveyda's NHC ligands. We first synthesized the best described one $\mathbf{3 . 2 4 7}$ (Scheme 128). ${ }^{244 a}$


Scheme 128 - Synthesis of the chiral NHC-Ag ligand 3.247
$N$-Boc protection of (R)-phenylglycinol (3.293) afforded 3.294 which was converted to 1,2,3-oxathiazolidine-2-oxide 3.295. The latter was oxidized to the 1,2,3-oxathiazolidine-2,2-dioxide 3.296 in $75 \%$ yield. Subsequent ring-opening with $N$-Boc aniline derivative $3.297^{244 a}$ afforded 3.299. Treatment of $\mathbf{3 . 2 9 9}$ with concentrated sulfuric acid promoted the full deprotection of the
nitrogens to afford the diamine $\mathbf{3 . 3 0 0}$. Palladium-catalyzed cross-coupling between $\mathbf{3 . 3 0 0}$ and the freshly prepared aryl bromide derivative $\mathbf{3 . 3 0 2}{ }^{244 \mathrm{c}}$ furnished $\mathbf{3 . 3 0 1}$ in $95 \%$ yield. Reaction of $\mathbf{3 . 3 0 1}$ with Eschenmoser's salt afforded the zwitterionic dihydroimidazolium salt 3.304. The latter was finally reacted with silver oxide to eliminate water and to deliver the desired catalyst $\mathbf{3 . 2 4 7}$ in $95 \%$ yield.


Scheme 129 - Enantioselective 1,4-addition of $\mathrm{AlEt}_{3}$ and the determination of the enantiomeric excess
We then focused on the enantioselective 1,4 -addition of an ethyl group. Because the detection of the enantiomeric excess required an UV active molecule and because we were first interested simply in the 1,4 addition, we planned to convert the ketone product $\mathbf{3 . 3 0 5}$ into the TBDPS derivative 3.307 via deprotection of the TES group (3.306) and reprotection with the UV active TBDPS.

Treatment of our enone $\mathbf{3 . 1 8 4}$ (previously synthesized following Scheme 113) with catalytic amount of copper triflate, the synthesized chiral catalyst $\mathbf{3 . 2 4 7}$ and an excess of triethyl aluminum in THF at $-78^{\circ} \mathrm{C}$ afforded the desired compound $\mathbf{3 . 3 0 5}$ in $95 \%$ yield. ${ }^{244 \mathrm{a}}$ After conversion into the TBDPS compound $\mathbf{3 . 3 0 7}$ the enantiomeric excess was determined to be $91 \%$ (Scheme 129). Encouraged by this success, we then attempted to repeat the reaction with subsequent trapping of the generated enolate with an electrophile to directly obtain the desired vinyl triflate $\mathbf{3 . 1 8 2}$ (Table 11). Indeed, conversion of the ketone $\mathbf{3 . 3 0 5}$ to the vinyl triflate $\mathbf{3 . 1 8 2}$ would afford a mixture of regioisomers.
$\mathrm{Tf}_{2} \mathrm{O}$, Comins' reagent and $\mathrm{PhNTf}_{2}$ all failed to afford the desired product. While Comins' reagent and $\mathrm{PhNTf}_{2}$ afforded only the ketone $\mathbf{3 . 3 0 5}$ even after warming to room temperature (Table 11, entry $2-3$ ), $\mathrm{Tf}_{2} \mathrm{O}$ induced a very messy reaction (entry 1 ). These results were not surprising as reports on the low reactivity of aluminum enolates already existed. ${ }^{2433,261}$ Addition of TBAT, known to activate the aluminum enolate $\mathbf{3 . 3 1 0}$ via formation of an ate complex, did not improve the result (entry 4-5). ${ }^{262}$ Use of Cul to activate the enolate afforded ketone $\mathbf{3 . 3 0 5}$ as the only product

[^91](entry 6-7). ${ }^{263}$ We therefore decided to try a two-step protocol by initial isolation of silyl enol ether $\mathbf{3 . 3 0 9}$ or acetyl enol ester 3.308, followed by regeneration of enolate and trapping with a triflating agent.

We first decided to try the acetyl derivative 3.308, as the direct trapping of aluminum enolate with $\mathrm{Ac}_{2} \mathrm{O}$ was reported to be very effective. Indeed, quenching the reaction with $\mathrm{Ac}_{2} \mathrm{O}$ and warming up to room temperature afforded the desired product 3.308 in $87 \%$ yield (entry 8 ).

Concerning the TMS enol ether 3.309, after optimization (entry 9-10) we found that quenching of the reaction with TMSOTf and triethylamine followed by warming up the reaction to room temperature afforded the desired silyl enol ether 3.309. The latter revealed to be highly unstable. Following the modified work-up and purification procedures reported by Alexakis and coworkers ${ }^{243 a}$ (see experimental procedure) allowed us to obtain $\mathbf{3 . 3 0 9}$ in an almost pure form with only around $4 \%$ of the ketone.


| Entry | Trapping agent | Additive | Yield [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: |
| 1 | $\mathrm{Tf}_{2} \mathrm{O}$ | - | Messy |
| 2 | Comins' | - | Ketone 3.305 only |
| 3 | $\mathrm{PhNTf}_{2}$ | - | Ketone $\mathbf{3 . 3 0 5}$ only |
| 4 | Comins' | TBAT | Ketone $\mathbf{3 . 3 0 5}$ only |
| 5 | $\mathrm{PhNTf}_{2}$ | TBAT | Ketone $\mathbf{3 . 3 0 5}$ only |
| 6 | Comins ${ }^{\text {' }}$ | CuI | Ketone 3.305 only |
| 7 | $\mathrm{PhNTf}_{2}$ | CuI | Ketone 3.305 only |
| 8 | $\mathrm{Ac}_{2} \mathrm{O}$ | - | 87\% 3.308 |
| 9 | TMSCl | TBAT, $\mathrm{NEt}_{3}$ | 52:38:10 SM/enol 3.309/ketone 3.305, clean |
| 10 | TMSOTf | $\mathrm{NEt}_{3}$ | 96:4 enol 3.309/ketone 3.305, clean |

(a: Isolated yield)
Table 11 - Enantioselective 1,4-addition/trapping of the resulting enolate
There were different methods to access vinyl triflate from silyl or Ac enol ether. MeLi-promoted lithium enolate formation from $\mathbf{3 . 3 0 9}$ followed by trapping with $\mathrm{PhNTf}_{2}{ }^{264}$ or $\mathrm{Tf}_{2} \mathrm{O}^{265}$ as well as with Comins' reagent only afforded the ketone $\mathbf{3 . 3 0 5}$ (Table 12, entry 1-3). Corey's procedure ${ }^{266}$ using a mixture of CsF and $\mathrm{PhNTf}_{2}$ to generate gaseous $\mathrm{CF}_{3} \mathrm{SO}_{2} \mathrm{~F}$ in a sealed tube (entry 4) or a

[^92]modified procedure involving BTAF and $\mathrm{PhNTf}_{2}{ }^{267}$ (entry 5) also furnished only the ketone 3.305. Potassium ethoxide was also reported to be able to generate the potassium enolate from silyl enol ether which could then be trapped by $\mathrm{PhNTf}_{2}{ }^{268}$ In our case, after optimization, only a 3:1 mixture ketone $3.305 /$ vinyl triflate 3.182 was obtained (entry 6-8). Finally, treatment of the enol ester 3.308 with MeLi followed by addition of $\mathrm{PhNTf}_{2}$ or Comins' reagent afforded the ketone 3.305 as only product (entry 9-10). ${ }^{269}$


| Entry | SM | Trapping agent | Additive | Ratio ${ }^{\text {a }}$ ketone 3.305/enol 3.182 |
| :---: | :---: | :---: | :---: | :---: |
| 1 | 3.309 | $\mathrm{PhNTf}_{2}$ | MeLi | Ketone only |
| 2 | 3.309 | $\mathrm{Tf}_{2} \mathrm{O}$ | MeLi | Ketone only |
| 3 | 3.309 | Comins' | MeLi | Ketone only |
| 4 | 3.309 | $\mathrm{PhNTf}_{2}$ | CsF | Ketone only (with the free alcohol) |
| 5 | 3.309 | $\mathrm{PhNTf}_{2}$ | BTAF | Ketone only |
| 6 | 3.309 | $\mathrm{PhNTf}_{2}$ | KOEt | 2.5:1 |
| 7 | 3.309 | Comins ${ }^{\prime}$ | KOEt | 3:1 |
| 8 | 3.309 | $\mathrm{PhNTf}_{2}$ | KOtBu | 9:1 |
| 9 | 3.308 | Comins' | MeLi | Ketone only |
| 10 | 3.308 | $\mathrm{PhNTf}_{2}$ | MeLi | Ketone only |

(a: Determined by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture)
Table 12 - Conversion to the TMS or Ac enol ether to the desired vinyl triflate 3.182
Finally, a key report attracted our attention (Scheme 130). Saegusa and coworkers reported a 1,4reduction of enones and enals using DIBAL ( 1.1 equiv) and Cul ( $5 \mathrm{~mol} \%$ ). In order to further functionalized the aluminum enolate 3.312, addition of HMPA (1.5 equiv) and MeLi (1.15 equiv) allowed the alkylation of the aluminum enolate. MeLi was added to promote the formation of an ate complex 3.312, much more prone to react. ${ }^{270}$ Addition of HMPA, a highly polar solvent, further enhanced the reactivity of the latter. Cramer and coworkers later extended this procedure to the 1,4-addition, $\alpha$-alkylation of 2-methyl cyclohex-2-en-1-one. ${ }^{271}$


Scheme 130 - Saegusa's procedure for the $\alpha$-alkylation of aluminum enolate using MeLi and HMPA

[^93]Inspired by these results, we explored the use of MeLi and HMPA in order to activate the aluminum enolate formed after the enantioselective 1,4-addition and the subsequent trapping of the latter with a triflate group (Table 13).


| Entry | MeLi [equiv] | Additive | Trapping agent | Yield [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | 1.1 | - | Comins' | $<5$ |
| 2 | 1.1 | HMPA | Comins' | $<5$ |
| 3 | 2.5 | - | Comins' $^{\prime}$ | $<5$ |
| 4 | 2.5 | HMPA | Comins' $^{\prime}$ | 32 |
| 5 | 5 | HMPA | Comins' $^{\prime}$ | 86 |
| 6 | 5 | HMPA | PhNTf $_{2}$ | 54 |
| 7 | 5 | DMPU | Comins' $^{\prime}$ | 12 |
| (a: Isolated yield) |  |  |  |  |

Table 13 - Enantioselective 1,4-addition/trapping of the resulting enolate with MeLi and HMPA as additives

Addition of 1.1 equivalents of MeLi and excess of Comins' reagent after the 1,4-addition did not promote the formation of the desired product $\mathbf{3 . 1 8 2}$ (entry 1). The use of HMPA as additive in these conditions did not improve the result (entry 2). Increasing the amount of MeLi to 2.5 equivalents without HMPA also did not produce any trace amount of $\mathbf{3 . 1 8 2}$ (entry 3). On the other hand, addition of HMPA to these conditions afforded the vinyl triflate $\mathbf{3 . 1 8 2}$ in $32 \%$ yield (entry 4). The use of 5 equivalents of MeLi in combination with HMPA afforded the desired product in $86 \%$ yield (entry 5). Trapping of the activated enolate with $\mathrm{PhNTf}_{2}$ gave the desired product albeit in lower yield (entry 6). Finally, the use of DMPU instead of HMPA proved much less effective (entry 7).

Therefore, addition of 5 equivalents of MeLi in combination with Comins' reagent after the enantioselective 1,4-addition on 3.184 afforded the desired compound 3.182 in $86 \%$ yield with $91 \%$ ee (Scheme 131).


Scheme 131 - Enantioselective 1,4-addition of $\mathrm{AlEt}_{3}$ followed by trapping of the enolate with Comins' reagent

### 3.3.2 Intramolecular Decarboxylative Coupling

Having found a way to access enantio-enriched vinyl triflate 3.182, we then turned our attention towards the intramolecular decarboxylative cross-coupling (pathway A). The vinyl triflate rac-
3.182 was initially deprotected using in situ generated HCl and the resulting alcohol 3.315 was then submitted to Mitsunobu conditions with $\mathrm{H}_{2} \mathrm{NNs}$ to access the $N$-nosyl amide $\mathbf{3 . 2 2 7}$ (Scheme 132, A). Deprotection of the O-TBS ether from 3.187 turned out to be tricky due to the facile lactonization (3.316). Gratefully, it was found that treatment of a MeOH/DCM 1:1 solution of 3.187 with CSA afforded cleanly the desired $\gamma$-hydroxy ester 3.226 (B).


Scheme 132 - Synthesis of 3.227 and 3.226
Mitsunobu reaction between 3.226 and 3.227 was quite challenging (Scheme 133, A). Indeed, formation of cyclopropane 3.318 was a strong competing reaction. Its formation could be understood because of the high acidity of the benzylic proton ( $\mathrm{pKa} \approx 16$ ) which could therefore compete with the deprotonation of nosyl amine. Nevertheless, after optimization, compound 3.317 was isolated in $81 \%$ yield in a $1: 1 \mathrm{dr}$. It is to note that performing the first Mitsunobu reaction on alcohol 3.226 with $\mathrm{H}_{2} \mathrm{NNs}$ also proved to be troublesome because of the same side product 3.318 formation (B). Moreover, purification proved to be even harder in this case.


Scheme 133 - Mitsunobu reaction between alcohol 3.226 and amine 3.227
With ester 3.317 in hands, we then needed to perform the formation of the potassium salt rac3.325 (Scheme 134). Basic hydrolysis, even at lower temperature and with 1.00 equivalent of base promoted the hydrolysis of the triflate to afford a complex mixture of products. On the other hand, acidic hydrolysis of 3.317 with concentrated HCl in acetic acid afforded cleanly the desired carboxylic acid 3.320 in $92 \%$ yield. Stability test of the latter revealed no decarboxylation up to 150 ${ }^{\circ} \mathrm{C}$. Conversion of the acid $\mathbf{3 . 3 2 0}$ to the potassium salt using KO ${ }^{\mathrm{t}} \mathrm{Bu}$ in EtOH afforded rac-3.225 as a very unstable compound. Attempt for EtOH removal by either co-evaporation with toluene or high
vacuum promoted the facile decarboxylation very easily. KOH and KH in methanol afforded a partially hydrolyzed triflate mixture. Finally, $\mathrm{KO}^{\mathrm{t}} \mathrm{Bu}$ in MeOH , followed by careful co-evaporation of MeOH using chloroform at room temperature afforded cleanly the desired potassium salt rac3.225. For unknown reason, the salt rac-3.225 was far less stable than the previously synthesized ones.


## Scheme 134 - Preparation of the potassium carboxylate salt rac-3.225 and its intramolecular decarboxylative cross-coupling

Various solvents, temperatures, stoichiometries and ligands were then screened for the challenging intramolecular decarboxylative cross-coupling but none of them afforded the desired product rac-1.184 and the decarboxylated product was always the major side product. After extensive screening, we found that DIOP (3.321) furnished a trace amount of the desired product rac-1.184. Nevertheless, the obtained $d r$ was 1:1. Both enantiomers of DIOP were tested in order to make sure we were not in a mismatched case. Very similar $d r$ were obtained indicating that the diastereocontrol from C-20 was inexistent and that the chiral ligand exerted no asymmetric induction on the chiral benzylic center. Because of this, we decided to turn our attention towards the pathway B (Scheme 117).

### 3.3.3 Stereo-retentive/-invertive Coupling

We initially planned to synthesize benzylic boronic ester derivatives 3.329 and 3.331 (Scheme 135).
$\mathrm{Ba}(\mathrm{OH})_{2}$-promoted aldol condensation of o-nitrobenzaldehyde (3.322) with vinyl acetate (3.323) followed by reduction of the enal 3.324 afforded the allyl alcohol 3.325. ${ }^{272}$ TBS protection of the primary alcohol furnished the desired product $\mathbf{3 . 3 2 6}(\mathrm{A}) .{ }^{273}$

Simple esterification of the o-nitrocinnamic acid (3.327) afforded the desired ester 3.328 (B). ${ }^{274}$ Treatment of these two compounds under a variety of enantioselective hydroboration conditions afforded only the reduced products 3.330 and 3.332 , respectively (C). The formation of these products could possibly be explained by the relative instability of the desired products. Once

[^94]formed, 3.228 could be activated in the form of borate 3.333 by simple attack of nucleophile $\left(\mathrm{H}_{2} \mathrm{O}\right.$, ${ }^{-}{ }^{t} \mathrm{Bu}, \mathrm{MeOH}$, etc.) on the boronic ester. It could then form intermediate 3.334 thanks to the strong electron-withdrawing nitro group. Reprotonation of 3.334 afforded the observed products 3.335 (D).


## Scheme 135 - Synthesis of styrene derivative 3.326 and cinnamate derivative 3.328 as well as their enantioselective hydroboration

In order to avoid the undesired protodeborylation reactions and because anyway the reduction of the nitro group was planned at a later stage of the synthesis, we decided to target 3.337 and 3.339 (Scheme 136).

Reduction of 3.326 using iron sulfate and ammonium hydroxide in MeOH at reflux afforded aniline 3.336 which was directly protected using methyl chloroformate to furnish $\mathbf{3 . 3 3 7}$ (A). Similar sequence on 3.328 using Zn and ammonium chloride for the reduction step afforded, after N protection, the carbamate 3.338 (B). ${ }^{275}$ Because we were worried that the presence of a free NH group on the substrate could interfere with the hydroboration and coupling steps, $N$-methylated compound 3.340 and 3.341 were prepared from 3.337 and 3.339 , respectively ( $C$ and D).

[^95]

Scheme 136 - Preparation of 3.337 and 3.339


## Scheme 137 - Enantioselective hydroboration of 3.339

With the methylcarbamates 3.337 and 3.339 and the fully protected products 3.340 and 3.341 in hands, we turned our attention towards their hydroboration (Scheme 137). Reactions using 3.340 or $\mathbf{3 . 3 4 1}$ failed to afford the desired products under a variety of conditions. Steric hindrance could explain the absence of reactivity. On the other hand, 3.339 was converted to the relatively stable enantio-enriched pinacol boronic ester derivative 3.342 (A). In order to determine the enantiomeric excess, rac-3.342 was synthesized in a racemic way using DPEPhos as ligand (B). Both boranes were oxidized to the corresponding alcohols 3.343 using $\mathrm{NaBO}_{3}$ and good ee was observed.


Scheme 138 - Hypothesized intermediate and the possible reason the facile deborylation of 3.342

Even though reports on the coupling of methyl $\beta$-boryl- $\beta$-phenyl propionate compounds did not exist, we hypothesized that the ortho methyl carbamate could potential serve for the same purposes as amide (Scheme 138, A). We attempted the coupling between $\mathbf{3 . 3 4 2}$ and vinyl triflate 3.182. Various palladium sources, bases and ligands were screened. None of them led to the desired product and only the deborylated product 3.347 was obtained. Various activators such as water, phenol and silver salts were reported to help the formation of the desired product but none of them proved effective in our transformation. A possible explanation for the protodeborylation could come from an internal proton transfer after activation of 3.345 (B). We hypothesized that the lack of reactivity could arise from the boronic ester part as described in Scheme 125. We therefore converted the latter into the more reactive trifluoroborate salt 3.348 (Scheme 139).


Scheme 139 - Preparation of the trifluoroborate salt 3.348
Treatment of 3.342 with aqueous $\mathrm{KHF}_{2}$ followed by appropriate work-up and purification (see experimental procedure) afforded the trifluoroborate salt 3.348 in $69 \%$ yield. The latter was submitted to coupling conditions but all of them led to the same protodeborylated product $\mathbf{3 . 3 4 7}$ probably because of the same previously mentioned reason.

As mentioned in the literature, these kinds of couplings are reported to only work with either $\beta$ trifluoroborate substituted- $\beta$-phenyl propanoic amide derivatives or with $\alpha$-pinacol boronic ester $\alpha$-phenyl aliphatic chain. We therefore decided to synthesize 3.355 and 3.362 (Scheme 140 and Scheme 141).

Heck reaction of o-aminoiodobenzene (3.349) with acrylonitrile (3.350) afforded aniline 3.351. ${ }^{276}$ The latter was then protected with methyl chloroformate to furnish $\mathbf{3 . 3 5 2}$ (A). Hydroboration using DPEPhos as ligand followed by oxidation afforded the racemic alcohol rac-3.354 (B). In an enantioselective way, JosiPhos proved to be the best ligand and afforded 3.353 in $91 \%$ yield with $94 \%$ ee (C). The boronic ester 3.353 was finally converted into the trifluoroborate salt $\mathbf{3 . 3 5 5}$ (D).

[^96]

Scheme 141 - Synthesis and enantioselective hydroboration of 3.359

For the synthesis of 3.362, o-nitro cinnamic acid (3.327) was first converted into the acyl chloride 3.356 and then reacted with pyrrolidine to afford amide 3.357 in $91 \%$ yield. ${ }^{277}$ The nitro group was then reduced using Zn in acetic acid and the aniline 3.358 was protected in the form of a methyl carbamate (A). Racemic and enantioselective hydroboration/oxidation afforded rac-3.361 in good yields and ee ( B and C). The boronic ester 3.360 was finally converted into the trifluoroborate salt 3.362 (D).

Pd-catalyzed cross-coupling of boronic esters 3.353 and 3.360 with vinyl triflate 3.182 failed to produce even a trace amount of the coupled products. Deborylated products were observed under a variety of conditions. Some $\beta$-hydride elimination product was observed on 3.353. On the other hand, after extensive optimization, trifluoroborate salts 3.355 and $\mathbf{3 . 3 6 2}$ afforded the desired products as well as deborylated product and some $\beta$-hydride elimination for $\mathbf{3 . 3 5 5}$ (Table 14 and Table 15).

| Entry | $\begin{gathered} \mathrm{Pd} \\ \text { [equiv] } \end{gathered}$ | Ligand [equiv] | Base | $\begin{gathered} \hline 3.362 \\ \text { [equiv] } \\ \hline \end{gathered}$ | $\begin{gathered} \hline \mathrm{T} \\ {\left[{ }^{\circ} \mathrm{C}\right]} \\ \hline \end{gathered}$ | Yield $[\%]^{\text {a }}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.1$ | XPhos 0.2 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 1 | 95 | Trace DP |
| 2 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.5$ | XPhos 1 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 1 | 95 | 10 |
| 3 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 1 | 95 | 12 |
| 4 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 1.5 | 95 | 15 |
| 5 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 25 |
| 6 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | BrettPhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 12 |
| 7 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 29 |
| 8 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ |  | 80 | Trace DP |
| 9 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 90 | 18 |
| 10 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 100 | 12 |
| 11 | $\mathrm{PdCl}_{2} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 13 |
| 12 | $\mathrm{Pd}_{2} \mathrm{dba}_{3} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 22 |
| 13 | $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4} 0.3$ | DavePhos 0.6 | $\mathrm{K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 21 |
| 14 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | DavePhos 0.6 | $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ | 3 | 95 | Trace DP |

(a: Isolated yield, $d r$ was $>19: 1$ in all entries)
Table 14 - Optimization of the coupling between amide 3.362 and vinyl triflate 3.182
Increasing the palladium and the ligand loading to 50 and 100 mol\%, respectively, afforded the coupled product 3.363 in $10 \%$ yield (Table 14, entry 2 ). Increase to $30 \%$ palladium and $60 \%$ ligand

[^97]afforded 3.363 in $12 \%$ yield (entry 3 ). In order to compensate the fast protodeborylation, increasing the amount of trifluoroborate salt to 1.5 (entry 4) and then 3 equivalents (entry 5) improved the yield to 15 and $25 \%$ yield respectively. Using BrettPhos as ligand instead of XPhos led to a decreased yield (entry 6). Changing to DavePhos improved the yield up to 29\% (entry 7). Temperature screening reveled that lower temperature only afforded trace amount of the desired product 3.363 (entry 8-9) whereas higher temperature led to a slightly reduced yield (entry 10). Palladium source was then screened and $\mathrm{PdCl}_{2}$ as well as $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ and $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}$ afforded a reduced yield (entry 11-13). Finally, using $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ as a base afforded only a trace amount of the desired compound 3.363 (entry 14).

The second substrate, trifluoroborate salt 3.355, also afforded the desired product albeit in much lower yield.


| Entry | Pd <br> [equiv] | Ligand <br> [equiv] | Base | 3.355 <br> [equiv] | T <br> $\left[{ }^{\circ} \mathrm{C}\right]$ | Yield <br> $[\%]$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.1$ | XPhos 0.2 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 1 | 95 | Trace DP |
| 2 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.5$ | XPhos 1 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 1 | 95 | $<5$ |
| 3 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 1 | 95 | Trace DP |
| 4 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 1.5 | 95 | 7 |
| 5 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | 9 |
| 6 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | BrettPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | Trace DP |
| 7 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | DavePhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 95 | Trace DP |
| 8 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 80 | Trace DP |
| 9 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 90 | 12 |
| 10 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 100 | Trace DP |
| 11 | $\mathrm{PdCl} 0_{2} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 90 | Trace DP |
| 12 | $\mathrm{Pd} d_{2} \mathrm{dba}_{3} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 90 | Trace DP |
| 13 | $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4} 0.3$ | XPhos 0.6 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | 3 | 90 | Trace DP |
| 14 | $\mathrm{Pd}(\mathrm{OAc})_{2} 0.3$ | XPhos 0.6 | $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ | 3 | 90 | Trace DP |

(a: Isolated yield, $d r$ was $>19: 1$ in all entries)
Table 15 - Optimization of the coupling between nitrile 3.355 and vinyl triflate 3.182
Similar conclusion as for the amide 3.362 could be drawn. Increasing the amount of the trifluoroborate salt 3.355 and of the palladium and ligand improved the yield (Table 15, entry 1-5). For this substrate, XPhos proved to be the best ligand (entry 6-7). Running the reaction at $90^{\circ} \mathrm{C}$ afforded the product with slightly higher yield than that at $95{ }^{\circ} \mathrm{C}$ (entry 8-10). Finally, reactions performed
with other sources of palladium and other bases afforded only a trace amount of the desired product 3.364 (entry 11-14).

Control experiments (Scheme 142) revealed that the compounds 3.355 and 3.362 were stable in the chosen solvent mixture, even at high temperature (A). Nevertheless, addition of the base promoted a fast protodeborylation to afford 3.365 and 3.366 in less than 2 hours (B). Coupling with PhBr , which normally gave high yields in the literature, afforded the coupling product 3.367 in only $23 \%$ yield (C). All these results indicated that the proposed mechanism for the protodeborylation (Scheme 138) might be correct.



Scheme 142 - Control experiments to probe the stability of 3.355 and 3.362
We next targeted the cyclic substrate $\mathbf{3 . 3 7 0}$ (Scheme 143). Reduction of the nitro group of onitrobenzaldehyde (3.238) afforded aniline 3.368, which was acetylated using acyl chloride and pyridine. One-pot methylation/intramolecular aldol condensation afforded the desired compound 3.370 in $55 \%$ yield. ${ }^{278}$ Unfortunately, the latter proved to be resistant to any kind of enantioselective hydroboration conditions. Possible explanation could lie in the pseudo-aromatic character of 3.370.


## Scheme 143 - Synthesis of cyclic enone 3.370

We therefore turned our attention towards pathway C (Scheme 117). We first synthesized the trifluoroborate salt $\mathbf{3 . 2 8 5}$ (Scheme 144).

[^98]

Scheme 144 - Preparation of the enantio-enriched gem-diboron compound 3.285
The alkyne 3.371 was converted into the vinyl boronic acid 3.372 via hydroboration using in situ formed diisopinocamopheylborane, oxidative dealkylation and hydrolysis of the diethyl boronic ester. ${ }^{279} 3.372$ was then protected to the diaminonaphtalene derivative 3.282. Enantioselective hydroboration afforded 3.283, which after treatment with $\mathrm{KHF}_{2}$ was converted into the desired trifluoroborate salt $\mathbf{3 . 2 8 5}$. ${ }^{254,279,280}$ Unfortunately, all attempts on the cross-coupling between 3.285 and vinyl triflate $\mathbf{3 . 1 8 2}$ failed to produce the desired coupling product.

On the other hand, achiral diboron compound 3.375 was synthesized (Scheme 145).


Scheme 145 - Synthesis of the achiral gem-diboron compound 3.375
Benzyl protection of propargyl alcohol (3.373) followed by one-pot double hydroboration afforded the desired compound $3.375 .{ }^{281}$ All attempts on its cross-coupling with vinyl triflate $\mathbf{3 . 1 8 2}$ also afforded messy mixture of compounds.

These results prompted us to hypothesize that the vinyl triflate $\mathbf{3 . 1 8 2}$ might be the real reason for the failure of the couplings. No report of the use of vinyl triflate could be found in the literature for such kind of cross-coupling. Moreover secondary alkyl/benzyl potassium trifluoroborate salts were described to react poorly with aryl/alkenyl triflate opposite to the primary ones. ${ }^{282}$ The only

[^99]exceptions in the literature are cyclopropyl boronic acids. ${ }^{283}$ But they are known to have a reactivity similar to vinyl boronic acids. ${ }^{284}$

### 3.3.4 Metal-free Stereoinvertive Substitution of Benzylic Mesylate with Vinyl Boronic Acid

We finally turned our attention towards disconnection $D$ (Scheme 117). We first synthesized the vinyl boronic acid 3.236 (Scheme 146).


Scheme 146 - Conversion of the vinyl triflate 3.182 into the boronic acid 3.236
Coupling between triflate 3.182 and $\mathrm{B}_{2} \mathrm{Pin}_{2}$ afforded the vinyl pinacol borane 3.376 in $80 \%$ yield (A). Oxidative cleavage of the latter led to the desired boronic acid 3.236 with concomitant deprotection of the TES group. Other deprotection methods such as hydrolysis with NaOH or $\mathrm{BCl}_{3}$ also worked to provide product 3.236 albeit in lower yield. Coupling with bis(neopentanediolato)diboron afforded the desired compound 3.377 in $79 \%$ yield (B). Unfortunately its conversion to the boronic acid $\mathbf{3 . 2 3 6}$ proved to be lower yielding.

Synthesis of the mesylate rac-3.237 is summarized in Scheme 147. Aldol reaction of onitrobenzaldehyde (3.238) with ethyl acetate (LDA, THF) afforded $\beta$-hydroxy ester 3.378 in $87 \%$ yield. Reduction of the latter with LAH afforded the diol rac-3.379. ${ }^{285}$ The primary alcohol was then selectively protected with $\mathrm{TBS}^{286}$ and the secondary one was converted into the mesylate rac-3.237.


Scheme 147 - Synthesis of the racemic benzylic mesylate rac-3.237

[^100]For the enantioselective version, diaryl prolinol catalyst 3.384 was first synthesized (Scheme 148). Treatment of ( $R$ )-proline (ent-1.132) with triphosgen in the presence of $\mathrm{NEt}_{3}$ afforded the crude cyclic mixed anhydride 3.382. Direct treatment of the latter with Grignard reagent $\mathbf{3 . 3 8 3}$ afforded the prolinol 3.384 in $37 \%$ yield over 2 steps. ${ }^{287}$


## Scheme 148 - Synthesis of the enantiopure diarylprolinol catalyst 3.384 from ( $R$ )-proline

Enantioselective synthesis of $\mathbf{3 . 2 3 7}$ is depicted in Scheme 149 (A). Prolinol 3.384-catalyzed aldol reaction between o-nitrobenzaldehyde (3.238) and acetaldehyde (3.385) followed by in situ reduction of the resulting $\beta$-hydroxy aldehyde afforded diol 3.379. The transition state 3.386 (B) has been proposed to account for the observed enantioselectivity. ${ }^{288}$ Similar protection/mesylation sequence as described in Scheme 147 afforded 3.237 in 93\% yield with 96\% ee.


Scheme 149 - Enantioselective synthesis of benzylic mesylate 3.237
With both reaction partners in hands, we then performed the coupling reaction (Table 16).
Use of exact same conditions as reported by Tang and coworkers ${ }^{260}$ did not lead to any reaction (Table 16, entry 1). Increasing the temperature to $80{ }^{\circ} \mathrm{C}$ failed to promote the formation of the desired product $\mathbf{3 . 1 8 0}$ too (entry 2). Reasoning that the lack of reaction could come from the very low solubility of the boronic acid $\mathbf{3 . 2 3 6}$ in toluene, methanol was added as co-solvent without any success (entry 3). On the opposite, addition of water afforded the desired product in $25 \%$ yield (entry 4). In order to better increase the solubility of the reaction partners, toluene was exchanged for DCE and the yield increased to $39 \%$ (entry 5). A decrease in temperature inhibited slightly the reaction (entry 6). Performing the reaction at $100{ }^{\circ} \mathrm{C}$ mainly produced decomposition products (entry 7). We then explored the ratio DCE/ $\mathrm{H}_{2} \mathrm{O}$. Increasing the ratio to 100:1 decreased the yield (entry 8). A 50:1 ratio was found to be optimal and the compound $\mathbf{3 . 1 8 0}$ was obtained in $55 \%$ yield

[^101](entry 9). Exchange of $\mathrm{K}_{3} \mathrm{PO}_{4}$ for $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ or KOH reduced the yield of the product (entry 10-11). In all these entries, $\mathbf{3 . 1 8 0}$ was obtained as a single diastereoisomer.

|  |  <br> 3.237 |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Entry | Solvent | Temperature $\left[{ }^{\circ} \mathrm{C}\right]$ | Base | Yield [\%] ${ }^{\text {a }}$ |
| 1 | Toluene | 50 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | No reaction |
| 2 | Toluene | 80 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | No reaction |
| 3 | Toluene/MeOH 5:1 | 80 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | No reaction |
| 4 | Toluene/ $\mathrm{H}_{2} \mathrm{O}$ 10:1 | 80 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | 25 |
| 5 | DCE/ $\mathrm{H}_{2} \mathrm{O}$ 10:1 | 80 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | 39 |
| 6 | DCE/ $\mathrm{H}_{2} \mathrm{O}$ 10:1 | 50 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | 26 |
| 7 | DCE/ $\mathrm{H}_{2} \mathrm{O} 10: 1$ | 100 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | 26 |
| 8 | DCE/ $\mathrm{H}_{2} \mathrm{O}$ 100:1 | 80 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | 19 |
| 9 | DCE/ $\mathrm{H}_{2} \mathrm{O} 50: 1$ | 80 | $\mathrm{K}_{3} \mathrm{PO}_{4}$ | 55 |
| 10 | DCE/ $\mathrm{H}_{2} \mathrm{O} 50: 1$ | 80 | $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ | 42 |
| 11 | DCE/ $\mathrm{H}_{2} \mathrm{O} 50: 1$ | 80 | KOH | 39 |

(a: Isolated yield, $d r$ was $>19: 1$ in all entries)
Table 16 - Optimization of the substitution of the benzylic mesylate 3.237 by the vinyl boronic acid 3.236
It is to note that racemic rac-cis-3.180 has already been synthesized previously (Scheme 113). Moreover, its diastereoisomer was converted to macrocycle 1.184 and an X-ray structure unambiguously confirmed its relative stereochemistry (Figure 29). By comparing the spectroscopic data of $\mathbf{3 . 1 8 0}$ with the ones of racemic rac-cis-3.180 and rac-trans-3.180, the relative configuration of 3.180 was unambiguously attributed. The coupling reaction proceeded therefore via $\mathrm{S}_{\mathrm{N}} 2$-type mechanism with inversion of the stereochemistry.

We then reasoned that vinyl boronic acid 3.236 could be intramolecularly activated by the free alcohol (Scheme 150, A). In order to favor the reaction and increase the yield, we hypothesized that the same reaction with a free alcohol on the mesylate partner could activate the boronic acid to promote a pseudo-intramolecular reaction (B).


Scheme 150 - Deprotection of alcohol 3.237 and protection of boronic acid 3.236

We deprotected the TBS 3.237 using TBAF and obtained the alcohol 3.388 (Scheme 150, C). On the other hand, we reprotected alcohol 3.236 with TBS in other to obtain the vinyl boronic acid 3.389 (D). We then examined the substitution reaction between both substrates (Table 17).


| Entry | Solvent | Temperature $\left[{ }^{\circ} \mathrm{C}\right]$ | Base | Yield [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | DCE $/ \mathrm{H}_{2} \mathrm{O} 50: 1$ | 80 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | 46 |
| 2 | Toluene | 80 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | 25 |
| 3 | Toluene $/ \mathrm{H}_{2} \mathrm{O} 50: 1$ | 80 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | 35 |
| 4 | DCE $/ \mathrm{H}_{2} \mathrm{O} 50: 1$ | 50 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | Trace DP |
| 5 | $\mathrm{DCE} / \mathrm{H}_{2} \mathrm{O} 50: 1$ | 100 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | 31 |
| 6 | $\mathrm{DCE} / \mathrm{H}_{2} \mathrm{O} 10: 1$ | 80 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | 12 |
| 7 | $\mathrm{DCE} / \mathrm{H}_{2} \mathrm{O} 100: 1$ | 80 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | 44 |
| 8 | DCE $/ \mathrm{H}_{2} \mathrm{O} \mathrm{50:1}$ | 80 | $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ | 18 |

(a: Isolated yield, dr was >19:1 in all entries)
Table 17 - Optimization of the substitution of the benzylic mesylate 3.388 by the vinyl boronic acid 3.389
Reaction under previously optimized conditions afforded the desired product in $46 \%$ yield (Table 17, entry 1). Using toluene only as solvent, only $25 \%$ of the desired product 3.390 was obtained (entry 2). It is to note that in this case there was no more solubility issue. Using toluene/ $\mathrm{H}_{2} \mathrm{O} 50: 1$ as solvent slightly improved the yield (entry 3). We then performed the reaction in a DCE/ $\mathrm{H}_{2} \mathrm{O}$ 50:1 mixture at $50^{\circ} \mathrm{C}$ but only a trace amount of the desired product was observed (entry 4). Increasing the temperature to $100^{\circ} \mathrm{C}$ afforded 3.390 in $31 \%$ yield but the reaction crude was very messy (entry 5). The influence of the DCE/water ratio was then analyzed. Increasing or decreasing this ratio afforded 3.390 in lower yields compared to entry 1 (entry 6-7). Finally, the use of $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ as a base did not improve the result (entry 8).

Comparing the results of Table 16 with the ones of Table 17 prompted us to rely on the coupling of 3.236 with $\mathbf{3 . 2 3 7}$ for the continuation of the synthesis. Indeed, higher yield was obtained for the coupling and fewer steps were required for the synthesis of the two coupling partners.

This strategy provided access to the coupled product $\mathbf{3 . 1 8 0}$ in 6 steps. Compared to the previous reported synthesis, an additional step was required but it allowed us to obtain $\mathbf{3 . 1 8 0}$ in enantioenriched form and as a single diastereoisomer. Both enantioselective steps worked efficiently giving the desired products in high yields with excellent ee. Moreover, the coupling reaction afforded the desired compound in good yield and in a complete stereoinvertive manner.

### 3.3.5 Diamination on the 1,3,3-Trisubstituted Cyclopentene

Having succeeded to synthesize the desired enantio-enriched diastereoisomer 3.180, we turned our attention to the key diamination of the alkene.


## Scheme 151 - Synthesis of the bis tosylamide 3.396

The synthesis of bis- $N$-sulfonylated alkene is shown in Scheme 151. Initial attempts on the Mitsunobu reaction between alcohol rac-3.180 and $\mathrm{TsNH}_{2}$ failed. We therefore prepared TsNHFmoc (3.393) by addition of 9-fluorenylmethanol (3.392) to tosyl isocyanate (3.391) (A). ${ }^{289}$ Mitsunobu reaction between $\mathbf{3 . 3 9 3}$ and alcohol rac-3.180 afforded, after work-up, the deprotected desired product 3.394 in $71 \%$ yield (B). Zinc reduction of the nitro group followed by tosylation of the resulting aniline 3.395 afforded the desired bis $N$-tosylated product 3.396. We then turned our attention towards the diamination itself.


Scheme 152 - Attempts for the diamination of alkene 3.396
Intramolecular diamination of 3.396 was then examined (Scheme 152). Copper, metal-free and palladium-catalyzed conditions all led to a very messy mixture of compounds. Different reasons could explain these disappointing results. First of all, trace amount of free alcohol were detected indicating the possible deprotection of 3.396 which could then interfere with the reaction (alkoxyamination for instance). Secondly, the benzylic allylic position of 3.396 could probably be sensitive to oxidation and all of these conditions were oxidative ones. Oxidation of the latter could then generate many side products. Finally, regioselectivity of the cyclization of the aniline could also

[^102]play a role. Indeed, 5-exo-trig and 6-endo-trig cyclizations could both be possible. Because of these failures, another class of substrate was envisioned.


(B)


Scheme 153 - Synthesis of the sulfamide 3.404 and of the urea 3.403
We next turned our attention to urea $\mathbf{3 . 4 0 3}$ and sulfonamide $\mathbf{3 . 4 0 4}$ (Scheme 153). Benzyl isocyanate (3.398) was first converted into the sulfamic acid derivative 3.399. The latter was then converted into the benzyl sulfamoyl chloride (3.400) (A)..$^{290}$ On the other hand, alcohol rac- $\mathbf{3 . 1 8 0}$ was first protected with TBS (3.401) and the nitro group was reduced to aniline 3.402 (B). The latter was then reacted with either the tosyl isocyanate (3.391) (C) or the sulfamoyl chloride $\mathbf{3 . 4 0 0}$ (D) to afford the urea $\mathbf{3 . 4 0 3}$ or the sulfamide $\mathbf{3 . 4 0 4}$ respectively.


## Scheme 154 - Attempts for the intramolecular diamination of alkenes 3.403 and 3.404

With both substrates in hands, palladium-catalyzed as well as copper- and halonium-mediated reactions were tested but all led to very messy mixtures (Scheme 154). Similar hypotheses as stated above could be drawn to explain these results.

[^103]In light of these failures, another strategy was envisioned: Cyclization of the aniline 3.407 in an intramolecular fashion and trapping the intermediate using an external nitrogen source.


Scheme 155 - Conversion of 3.402 into the tosylamide 3.407
The aniline 3.402 was $N$-tosylated under standard conditions (Scheme 155).


## Scheme 156 - Attempts for the diamination of 3.407 using an external nitrogen source

Various external nucleophiles such as $\mathrm{TsNH}_{2}, \mathrm{Tf}_{2} \mathrm{NH}, \mathrm{NaN}_{3}$ and $\mathrm{Bn}_{2} \mathrm{NH}$ were tested under various oxidation conditions. All of them led again to very messy mixture of compounds (Scheme 156).

We then investigated a stepwise diamination strategy. Aminohydroxylation or aminobromination as first step could provide suitable intermediates for further functionalization to the desired product. ${ }^{291}$ Unfortunately, conditions for the aminobromination of 3.407 using either NBS or Pd and Cu did not afford the desired product. On the other side, oxygen-based oxidants afforded isolable products (Scheme 157).

Oxone with or without $p$ TsOH afforded the cyclized product 3.409 as a $3: 1$ mixture of diastereoisomers (A). These results indicated that the epoxidation of the alkene 3.407 occurred but that the TBS groups were also cleaved under the reaction conditions. This resulted in the epoxide opening in a 5-exo-tet fashion. Reasoning that Oxone was too acidic for the TBS group, we switched oxidant to the milder mCPBA. Treatment of 3.407 with $m$ CPBA in DCM at room temperature afforded the epoxide 3.410 in a $3: 1$ mixture of diastereoisomers (B). We hypothesized that $\mathbf{3 . 4 1 0}$ could be a viable intermediate towards our targeted compound. Various conditions were screened for the opening of the epoxide by the aniline moiety of $\mathbf{3 . 4 1 0}$ (Scheme 158). While basic conditions did not afford any observable conversion (A), treatment of 3.410 with $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$ afforded the undesired compound 3.411 in a $3: 1 \mathrm{dr}$ mixture resulting from a 6-exo-tet cyclization (B). ${ }^{292}$

[^104]

Scheme 157 - Oxidation of the alkene 3.407 with Oxone and with mCPBA


Scheme 158 - $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$-promoted opening of the epoxide 3.410
We hypothesized that similar sequence on 3.396 could give more chance of success as cyclization of the more nucleophilic tosyl amide would result in a 6 vs 7-membered ring regioselectivity which is in general easier to control.



Scheme 159 - Epoxidation of both diastereoisomers of the alkene 3.396 using mCPBA
Epoxidation of the cyclopentene cis-3.396 afforded the desired epoxide cis-3.412 in an excellent 10:1 diastereomeric ratio (Scheme 159, A). As a comparison, same reaction conditions on trans3.396 furnished trans-3.412 but only in a 1:1 ratio (B).


Scheme 160 - Epoxide 3.412 opening under basic conditions or with $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$
Base-mediated epoxide cis-3.412 opening afforded the undesired product 3.413 (Scheme 160, A). On the other side, $\mathrm{BF}_{3}$-mediated cyclization of cis-3.412 afforded a mixture of compounds ( B ). Among them 3.413 and 3.414 could be identified, indicating again a low stability of the TBS group towards the conditions and the preferred 6 -endo-tet cyclization mode.

Reasoning that similar diamination or epoxidation/opening sequence on the macrocycle $\mathbf{1 . 1 8 4}$ could provide a much better control on the diastereoselectivity and on the regioselectivity of the cyclization, we turned our attention towards this direction.

### 3.3.6 Macrocyclization

Following the previously developed conditions for the two consecutive Mitsunobu reactions indeed afforded the desired macrocycle 1.184 . ${ }^{67}$ Unfortunately, reproducibility issues in both steps prevented us to scale up this reaction to a decent extend. Yields started to dramatically drop above 100 mg . Reoptimization of the reaction conditions using various addition sequences, temperatures and stoichiometries did not solve the issue. Careful TLC analysis revealed a very surprising behavior of the desired products $\mathbf{3 . 1 7 9}$ and $\mathbf{1 . 1 8 4}$. It appeared that there were very strong interactions between triphenylphosphine oxide and the DEAD hydrazine by-product with our desired products. These strong interactions prevented us to easily obtain the products in pure form and induced a significant product loss on column chromatography. Changing the eluent system as well as adding additive did not induce any change. We therefore decided to explore other reagents for the Mitsunobu reactions.

Initial screening (Table 18) revealed that neopentyl alcohol was not necessary for the first Mitsunobu reaction. It also disclosed that DBAD (3.220) was the most promising azodicarboxylate reagent compared to the others. Nevertheless, on big scale, yield dropped dramatically probably because of interaction with $\mathrm{O}=\mathrm{PPh}_{3}$ (as observed by TLC). We therefore decided to try the combination DBAD/PPyPh ${ }_{2}$, where the phosphine and the phosphine oxide could be easily removed by aqueous workup. ${ }^{239}$

Using 2 equivalents of $\mathrm{H}_{2} \mathrm{NNs}, \mathrm{PPyPh}_{2}$ and DBAD for the Mitsunobu reaction and quenching with 1.5 M HCl in MeOH afforded the desired product $\mathbf{3 . 1 7 9}$ in $82 \%$ yield (Table 19, entry 1). Decreasing the amounts to 1 equivalent each in order to facilitate the purification afforded a reduced yield (entry 2). Finally, a combination of 1.2 equivalents of $\mathrm{H}_{2} \mathrm{NNs}$ and 2 equivalents of phosphine and azodicarboxylate afforded the desired product $\mathbf{3 . 1 7 9}$ in $83 \%$ (entry 3) with a much simpler purification than in entry 1 . Different quenching methods were then examined. TFA and 2 M HCl in $\mathrm{Et}_{2} \mathrm{O}$
afforded very similar yield (entry 4 and 7). 4 M HCl in dioxane afforded a slightly reduced yield (entry 5). Finally, 2 M HCl in MeOH with a slightly different work-up (see experimental procedure) afforded 3.179 in $93 \%$ yield (entry 6). Half-gram (entry 8) and gram-scale (entry 9) reaction afforded the product 3.179 in virtually the same yield without any problem.

|  |  | $\begin{gathered} \mathrm{H}_{2} \mathrm{NNs},[\mathrm{~N}=\mathrm{N}] \text {, PF } \\ \hline \text { THF, } 0^{\circ} \mathrm{C} \text { to } \\ \text { then TBAF } \end{gathered}$ |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Entry | [ $\mathrm{N}=\mathrm{N}$ ] | $\begin{gathered} \hline \text { Yield with } \\ 3.209 \\ {[\%]^{a}} \\ \hline \end{gathered}$ | Yield without <br> 3.209 <br> $[\%]^{\text {a }}$ | $\begin{gathered} \hline \text { Yield with } \\ 3.209 \\ {\left[^{2}\right]^{\mathrm{b}}} \\ \hline \end{gathered}$ |
| 1 | DIAD | 68 | 70 | 39 |
| 2 | DEAD on polystyrene | 29 | 15 | 24 |
| 3 | ADDP/TBP | 32 | 19 | - |
| 4 | DBAD ${ }^{\text {c }}$ | 70 | 81 | 53 |
| 5 | DMEAD | 69 | 73 | - |
| 6 | DCAD | 72 | 70 | - |

(a: Isolated yield using 50 mg of rac-3.180 as starting material; b: isolated yield using 200 mg of rac-3.180 as starting material; c: then TFA instead of TBAF)

Table 18 - Initial screening of azodicarboxylates for the $1^{\text {st }}$ Mitsunobu reaction


| Entry | Conditions | Quench | Yield [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: |
| $1{ }^{\text {b }}$ | 2 equiv $\mathrm{H}_{2} \mathrm{NNs} / \mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 1.5 M HCl in MeOH | 82 |
| $2^{\text {b }}$ | 1 equiv $\mathrm{H}_{2} \mathrm{NNs} / \mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 1.5 M HCl in MeOH | 54 |
| $3^{\text {b }}$ | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 1.5 M HCl in MeOH | 83 |
| $4{ }^{\text {b }}$ | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | TFA | 81 |
| $5^{\text {b }}$ | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 4 M HCl in dioxane | 69 |
| $6^{\text {b }}$ | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 2 M HCl in MeOH | 93 |
| $7{ }^{\text {b }}$ | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | $2 \mathrm{M} \mathrm{HCl} \mathrm{in} \mathrm{Et}_{2} \mathrm{O}$ | 78 |
| $8{ }^{\text {c }}$ | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 2 M HCl in MeOH | 93 |
| 9 d | 1.2 equiv $\mathrm{H}_{2} \mathrm{NNs}$, 2 equiv $\mathrm{PPyPh}_{2} / \mathrm{DBAD}$ | 2 M HCl in MeOH | 94 |

(a: Isolated yield; b: on 50 mg of 3.180 ; c: on 500 mg of $\mathbf{3 . 1 8 0}$; d: on 1000 mg of 3.180 )
Table 19 - Fine-tuning of the conditions and quench for the $1^{\text {st }}$ Mitsunobu reaction
We then turned our attention to the $2^{\text {nd }}$ Mitsunobu reaction.

|  |  DBAD, PF $\text { THF, } 0^{\circ} \mathrm{C}$ |  |  |
| :---: | :---: | :---: | :---: |
| Entry | Change from ideal conditions from Table 19, entry 6 | Concentration [M] | Yield [\%] ${ }^{\text {a }}$ |
| $1{ }^{\text {b }}$ | None | 0.03 | 45 |
| $2^{\text {b }}$ | Neopentyl alcohol 0.5 equiv | 0.03 | 75 |
| $3{ }^{\text {b }}$ | Neopentyl alcohol 0.25 equiv | 0.03 | 79 |
| 4b | Neopentyl alcohol 0.1 equiv | 0.03 | 50 |
| $5{ }^{\text {b }}$ | Neopentyl alcohol 0.25 equiv | 0.01 | 83 |
| $6{ }^{\text {b }}$ | Neopentyl alcohol 0.25 equiv DBAD/PPyPh 2.5 equiv | 0.01 | 95 |
| 7c | Neopentyl alcohol 0.25 equiv DBAD/PPyPh 2.5 equiv | 0.01 | 93 |
| $8^{\text {d }}$ | Neopentyl alcohol 0.25 equiv DBAD/PPyPh 2.5 equiv | 0.01 | 94 |

(a: Isolated yield; b: on 50 mg of 3.179; c: on 500 mg of 3.179 ; d: on 1000 mg of 3.179)
Table 20 - Optimization of the $2^{\text {nd }}$ intramolecular Mitsunobu reaction
Using conditions optimized for the intermolecular Mitsunobu reaction, cyclization of $\mathbf{3 . 1 7 9}$ afforded the desired macrocycle 1.184 in $45 \%$ yield (Table 20, entry 1). Addition of 0.5 equivalents of the sacrificial neopentyl alcohol improved the yield to $75 \%$ (entry 2 ). Reducing the loading of neopentyl alcohol to 0.25 equivalents improved slightly the yield (entry 3) whereas with 0.1 equivalents of 3.209, the yield dropped to $50 \%$ yield (entry 4). We then explored the concentration of the reaction and decreasing it to 0.01 M improved the yield to $83 \%$ (entry 5). Finally, increasing the amount of phosphine and of azodicarboxylate afforded $\mathbf{1 . 1 8 4}$ in an excellent $95 \%$ yield (entry 6). Half-gram (entry 7) and gram-scale (entry 8) reactions afforded similar yields.

### 3.3.7 Diamination on the Macrocycle

Having a scalable synthesis of macrocycle 1.184 in hands, we first attempted its direct diamination (Scheme 161).

Nosyl deprotection on rac-1.184 using thiophenol and potassium carbonate followed by zinc reduction of the nitroaryl 3.415 afforded aniline 3.416 (A). Different conditions using mainly NIS, NBS, NCS and $I_{2}$ afforded only either the starting material back or very messy mixture of compounds. Reasoning that the aniline may not be nucleophilic enough, we synthesized the $N$-methyl version rac-3.128 in 74\% yield (B). Similar conditions were attempted again with a very messy outcome. Addition of TFA, in order to in situ prevent the secondary amine to be oxidized, did not improve the result.


Scheme 161 - Synthesis of the diamine 3.416 and rac-3.128
We then turned our attention towards the epoxidation/intramolecular opening sequence (Scheme 162). Epoxidation of rac-cis-1.184 with mCPBA afforded the desired product rac-cis-3.417 in about $80 \%$ yield with an excellent diastereoselectivity (A). Submitting the opposite diastereoisomer rac-trans-1.184 to the same conditions afforded rac-trans-3.417 as one single diastereoisomer too (B). Different conditions were then screened for the epoxidation of rac-cis-1.184. DMDO proved also to be an efficient oxidant, especially when used in combination with phosphate buffer and 18-C-6 crown ether but the yield was still inferior to the one of $m$ CPBA. Finally we observed that using the latter in combination with $\mathrm{NaHCO}_{3}$ afforded the desired product rac-cis-3.417 as a single diastereoisomer in a slightly improved $82 \%$ yield.
(A)


rac-cis-3.417 $81 \%,>19: 1 d r$
(B)


Scheme 162 - Epoxidation of macrocycles rac-1.184
Figure 29 showed the X-ray structure of alkene rac-trans-1.184. ${ }^{293}$ The double bond was clearly only accessible from the top face as the NNs group pointed perfectly below it. This explained nicely the observed diastereoselectivity.

[^105]

Figure 29 - X-ray structure of the key macrocycle rac-trans-1.184 explaining the diastereoselectivity of the epoxidation

With epoxide rac-cis-3.417 in hands, we deprotected the nosyl amine using thiophenol and a base (Scheme 163, A). After reaction, the only observed compound was alcohol rac-cis-3.418 as a single diastereoisomer. A small screening of conditions was performed. In general, DCM proved to be a better solvent than MeCN and DMF. Similarly, $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ proved to be a superior base than $\mathrm{K}_{2} \mathrm{CO}_{3}$. Different thiols such as 2-hydroxyethan-1-thiol and thioethanoic acid afforded the desired compound in much lower yield. We noted that the stoichiometry of PhSH and base was crucial and slight excess promoted rapid decomposition of rac-cis-3.418 probably because of subsequent reaction of the thiophenol with our nitro aryl.

The secondary amine 3.419 generated apparently spontaneously cyclized onto the epoxide affording the tertiary alcohol 3.417 (C). This was not very surprising as the epoxide and the $10-$ membered macrocycle were located in a trans fashion, allowing a simple $\mathrm{S}_{N} 2$ mechanism to occur with inversion of the configuration at position C-21. Similar reaction could be performed on the other diastereoisomer (B) and similar deprotection/transannular cyclization cascade was observed. It is to note that similar nosyl deprotection/transannular epoxide opening was already reported previously. ${ }^{294}$


Scheme 163 - Nosyl deprotection/transannular cyclization cascade

[^106]We decided to combine both steps in a single pot as they both could be run in DCM as solvent (Scheme 164). Gratefully, treatment of a DCM solution of macrocycle 1.184 with mCPBA and Na$\mathrm{HCO}_{3}$ followed by the addition of PhSH and $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ afforded directly the tricyclic amino alcohol cis3.418 in 74\% yield.


Scheme 164 - One-pot epoxidation/deprotection/cyclization cascade
With compound cis-3.418 in hands, a sequence of nitro group reduction followed by nucleophilic substitution of the alcohol was expected to afford the vallesamidine skeleton.


Scheme 165 - Reduction of nitroaryl rac-cis-3.418
Reduction of rac-cis-3.418 using zinc and ammonium chloride afforded the desired aniline rac3.420 in quantitative yield without any trace amount of cyclized product (Scheme 165). We then screened various reduction conditions and focused on the use of DCM and THF as solvent in order to be able to combine this step with the previous epoxidation/deprotection/transannular cyclization cascade. Even though hydrogenation in the presence of Pd/C afforded the desired compounds, higher yield were observed using metals. Iron in combination with strong acids such as AcOH or HCl afforded the desired product rac-3.420 but in lower yield than Zn . Indeed, Zn , in combination with ammonium chloride, at reflux afforded the desired product in $95 \%$ yield. Coupling of these conditions with the previous sequence proved to be efficient and promoted the formation of $\mathbf{3 . 4 2 0}$ starting from 1.184 in 69\% yield (Scheme 166).


Scheme 166 - One-pot epoxidation/deprotection/cyclization/reduction cascade
In order to promote the cyclization of the aniline onto the desired tertiary alcohol and in order to obtain the correct diastereoisomer, either carbocation 3.421 of aziridinium $\mathbf{3 . 4 2 2}$ had to be
formed (Scheme 167, A). In order to include this step in the previous sequence, we focused on a DCM/THF mixture as solvent.

A


Scheme 167 - TAPC-mediated nucleophilic substitution of rac-3.420
Simple use of acid such as TFA or HCl afforded only a trace amount of the desired product rac-3.7. Montmorillonite K10, an acidic inorganic heterogeneous catalyst in association with microwave irradiation afforded the desired product in $75 \%$ yield. Strong Lewis acids promoted in general degradation of the material. HMPT, known to stabilize cation indeed afforded the desired product in $63 \%$ yield. Finally, TAPC (B), a strong dehydrating agent was found to efficiently promote the reaction to afford pentacyclic product rac-3.7 in $89 \%$ yield (C). ${ }^{295}$ One single diastereoisomer was isolated.

A one-pot procedure was then attempted and afforded the desired pentacyclic structure 3.7 in 52\% yield from 1.184 (Scheme 168).


Scheme 168 - One-pot sequence from macrocycle 1.184 to pentacyclic structure 3.7
With rac-3.7 in hands, simple reductive N -methylation (formalin, $\mathrm{NaBH}_{3} \mathrm{CN}, \mathrm{AcOH} / \mathrm{H}_{2} \mathrm{O}$ ) afforded ( $\pm$ )-vallesamidine (rac-3.1) in 95\% yield (Scheme 169).


## Scheme 169 - Reductive amination of rac-3.7 to afford ( $\pm$ )-vallesamidine

We then explored the possibility to include this alkylation step in our cascade sequence (Table 21).

[^107]
rac-1.184
then conditions 1
( $\pm$ )-Vallesamidine (rac-3.1)

| Entry | Conditions 1 | Conditions 2 | Yield [\%]a |
| :---: | :---: | :---: | :---: |
| 1 | TAPC (5 equiv), reflux | Formalin, $\mathrm{NaBH}_{3} \mathrm{CN}, \mathrm{AcOH}, \mathrm{rt}$ | 35 |
| 2 | TAPC (3 equiv), reflux | Formalin, $\mathrm{NaBH}_{3} \mathrm{CN}, \mathrm{AcOH}, \mathrm{rt}$ | 45 |
| 3 | TAPC (1 equiv), reflux | Formalin, $\mathrm{NaBH}_{3} \mathrm{CN}, \mathrm{AcOH}, \mathrm{rt}$ | 19 |
| 4 | HMPT, reflux | Formalin, $\mathrm{NaBH}_{3} \mathrm{CN}, \mathrm{AcOH}, \mathrm{rt}$ | 21 |
| 5 | HMPT, reflux | Formalin, $\mathrm{Na}(\mathrm{OAc})_{3} \mathrm{BH}, \mathrm{DCM}, \mathrm{rt}$ | 17 |
| 6 | K10, MW irradiation | Formalin, $\mathrm{NaBH} 3 \mathrm{CN}, \mathrm{AcOH}, \mathrm{rt}$ | 18 |
| 7 | K10, MW irradiation | Formalin, $\mathrm{Na}(\mathrm{OAc})_{3} \mathrm{BH}, \mathrm{DCM}, \mathrm{rt}$ | 26 |

(a: Isolated yield)
Table 21 - Optimization of the one-pot epoxida-
tion/deprotection/cyclization/reduction/cyclization/alkylation sequence
Using the previously developed conditions for the alkylation in combination with the optimized conditions for the cyclization afforded rac-3.1 in $35 \%$ yield (Table 21, entry 1). Reducing the amount of TAPC to 3 equivalents improved the yield up to $45 \%$ (entry 2) but further reduction of TAPC furnished rac-3.1 in a reduced yield (entry 2). Switching the cyclization conditions for HMPT using two different reductive amination conditions afforded ( $\pm$ )-vallesamidine (rac-3.1) in around $20 \%$ yield (entry 3-4). K10 and microwave irradiation delivered rac-3.1 in a very similar yield (entry 6). Switching the conditions 2 for $\mathrm{Na}(\mathrm{OAc})_{3} \mathrm{BH}$ and DCM improved the yield but only up to $26 \%$ (entry 7).

In conclusion, using this formal diamination cascade, (-)-vallesamidine (3.1) was obtained in 45\% yield and as a single diastereoisomer from the macrocycle 1.184 in a single step (Scheme 170).


Scheme 170 - One-pot sequence from macrocycle 1.184 to (-)-vallesamidine

### 3.4 Synthesis of (+)-1,2-Dehydroaspidospermidine

### 3.4.1 Retrosynthesis and Background

In 2015, our group developed a reductive cyclization of o-nitrostyrene derivatives such as $\mathbf{3 . 4 2 4}$ using $\mathrm{TiCl}_{3}$ as reductant. ${ }^{296}$ Similar to the Cadogan-Sunberg indole synthesis ${ }^{297}$ but using much

[^108]milder conditions ( $160{ }^{\circ} \mathrm{C}$ vs rt ), a broad scope of indoles such as 3.428 were synthesized. A domino process was also developed starting from 1,2,2-trisubstituted o-nitrostyrene derivatives to afford 2,3-disubstituted indoles, with the more electron rich group migrating from the 2 to the 3 position of the indole.


Scheme 171 - Proposed mechanisms for the $\mathrm{TiCl}_{3}$-promoted reductive cyclizations
The following mechanism was proposed (Scheme 171). $\mathrm{TiCl}_{3}$-mediated reduction of the nitro 3.424 to the nitroso $\mathbf{3 . 4 2 5}$ followed by a $4 \pi+2 \omega$ electrocyclization ${ }^{298}$ could afford 3.426. In pathway $A$, if $\mathrm{R}^{3}=\mathrm{H}$, simple aromatization could afford N -hydroxy indole 3.427 which, after a second $\mathrm{TiCl}_{3}-$ promoted reduction, could furnish the desired indole 3.428. In pathway $B$, if $R^{1}=H$, migration of the more electron rich group ( $\mathrm{R}^{3}$ ) to the $\mathrm{C}-3$ position could provide zwitterion 3.429. Aromatization and subsequent reduction could deliver indole 3.431.

Application of this reaction allowed us to develop a formal total synthesis of $( \pm)$-aspidospermidine (rac-1.71) (Scheme 172).


Scheme 172 - Formal synthesis of aspidospermidine using a $\mathrm{TiCl}_{3}$-promoted reductive cyclization.
Even though it was not attempted, we hypothesized that if none of $R^{1}, R^{2}$ and $R^{3}$ group was a hydrogen (Scheme 171, C), migration of the more electron-rich group could afford zwitterion 3.432 which could be in resonance with $\mathbf{3 . 4 3 3}$. $\mathrm{TiCl}_{3}$-promoted reduction could then afford indolenine 3.434. We therefore quickly identified 3.438 as a versatile intermediate to access aspidosperma alkaloids and especially (+)-1,2-dehydroaspidospermidine (3.2).

[^109]

Scheme 173 - Retrosynthesis of (+)-1,2-dehydroaspidospermidine
Disconnection of the C-7/C-21 bond of (+)-1,2-dehydroaspidospermidine (3.2) to 3.436 and reconnection of the C-21 with the C-2 traced it back to the intermediate 3.437, which was very similar to intermediate 3.426 in Scheme 171. In the forward direction, migration of the C-21 from C-2 to C-7 could afford (+)-1,2-dehydroaspidospermidine (3.2). The selectivity of the migration could arise from the intermediate 3.436. 3.437 was then traced back to alkene 3.438. Therefore if we control the dehydration of 3.418 towards the formation of the conjugated alkene 3.438 instead of enamine 3.439 we could then apply our hypothesized $\mathrm{TiCl}_{3}$-based methodology to convert 3.438 in one step to 3.2.

### 3.4.2 Synthesis

From alcohol 3.418, we therefore explored the possibility to access (+)-1,2dehydroaspidospermidine (3.2). Various elimination conditions were tested. We mainly explored anti-elimination conditions in order to avoid the formation of enamine 3.439. Alkene 3.438 proved to be highly unstable and could not be isolated even on deactivated silica gel or alumina oxide. We therefore directly submitted the crude mixture to the $\mathrm{TiCl}_{3}$-promoted reductive cyclization step (Table 22).


| Entry | Elimination | Reductive cyclization | Yield [\%] |
| :---: | :---: | :---: | :---: |
| 1 | $\mathrm{MsCl}^{\mathrm{a}}, \mathrm{DCM}, \mathrm{rt}$ to reflux | MeCN, rt | 11 |
| 2 | $\mathrm{SOCl}_{2}, \mathrm{DBU}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ to rt | MeCN, rt | 26 |
| 3 | $\mathrm{SOCl}_{2}, \mathrm{DBU}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ | MeCN, rt | 39 |
| 4 | $\mathrm{SOCl}_{2}, \mathrm{DBU}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ | Acetone, rt | 12 |
| 5 | $\mathrm{SOCl}_{2}, \mathrm{DBU}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ | MeCN, $\mathrm{NH}_{4} \mathrm{OAc}, \mathrm{rt}$ | 69 |
| 6 | $\mathrm{SOCl}_{2}, \mathrm{DBU}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ | Acetone, $\mathrm{NH}_{4} \mathrm{OAc}, \mathrm{rt}$ | 28 |
| 7 | $\mathrm{TFAA}, \mathrm{H}_{2} \mathrm{SO}_{4}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ | Acetone, $\mathrm{NH}_{4} \mathrm{OAc}, \mathrm{rt}$ | 21 |
| 8 | $\mathrm{TFAA}, \mathrm{H}_{2} \mathrm{SO}_{4}, \mathrm{DCM}, 0^{\circ} \mathrm{C}$ | MeCN, $\mathrm{NH}_{4} \mathrm{OAc}, \mathrm{rt}$ | 45 |

(a: Isolated yield)
Table 22 - Optimization of the elimination/reductive cyclization/rearrangement sequence
Treatment of 3.418 with $\mathrm{MsCl} / \mathrm{NEt}_{3}$ followed by $\mathrm{TiCl}_{3}(2 \mathrm{M}$ in HCl ) in MeCN afforded 3.2 in $11 \%$ (Table 22, entry 1). The use of $\mathrm{SOCl}_{2}$ in combination with DBU at room temperature for the elimina-
tion step improved the yield up to $26 \%$ (entry 2). Similar conditions at $0^{\circ} \mathrm{C}$ afforded the desired product 3.2 in $39 \%$ (entry 3). The use of acetone for the cyclization step afforded 3.2 in much lower yield (entry 4). We then focused on the addition of $\mathrm{NH}_{4} \mathrm{OAc}$ as buffer during the cyclization step. The use of the buffer in combination with acetonitrile allowed the formation of 3.2 in $69 \%$ yield (entry 5). On the other side, acetone as solvent again decreased the yield (entry 6). Finally, elimination using TFAA and sulfuric acid followed by the buffered $\mathrm{TiCl}_{3}$-promoted cyclization in either MeCN or acetone gave 3.2 in lower yields (entry 7-8).

From the same macrocycle 1.184, we therefore were able to synthesize (+)-1,2dehydroaspidospermidine (3.2) in three steps using our previously developed $\mathrm{TiCl}_{3}$-promoted reductive cyclization. In our case, an additional rearrangement took place to convert the vallesamidine skeleton to the aspidosperma one.

### 3.5 Summary of the Syntheses

Scheme 174 summarized the synthesis of (-)-vallesamidine (3.1) and (+)-1,2-
dehydroaspidospermidine (3.2) from the commercially available enone 3.190.






Scheme 174 - Summary of the enantioselective total synthesis of (-)-vallesamidine and (+)-1,2dehydroaspidospermidine
(-)-Vallesamidine (3.12) was obtained in $6.3 \%$ overall yield in 9 steps (longest linear sequence) from the commercially available enone $\mathbf{3 . 1 9 0}$ with $99 \%$ enantiomeric excess.

Table 23 shows the comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of both isolated and synthetic (-)vallesamidine (3.1).

(-)-Vallesamidine
(3.1)

|  | Isolated |  |  | Synthesized |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{N}^{\circ}$ | ${ }^{13} \mathrm{C}[\mathrm{ppm}]^{\mathrm{a}}$ | ${ }^{1} \mathrm{H}[\mathrm{ppm}]{ }^{\mathrm{a}}$ | ${ }^{13 \mathrm{C}[\mathrm{ppm}]^{\mathrm{a}}}$${ }^{1} \mathrm{H}[\mathrm{ppm}]^{\mathrm{a}}$ <br> $(100 \mathrm{MHz})$ | $(400 \mathrm{MHz})$ | $(100 \mathrm{MHz})$ | $(400 \mathrm{MHz})$ |
| 2 | 73.0 | - | - | 73.0 | - | - |
| 3 | 50.4 | 2.90 | 2.92 | 50.4 | 2.89 | 2.48 |
| 5 | 50.0 | 2.97 | 2.80 | 49.9 | 2.98 | 2.82 |
| 6 | 26.5 | 2.04 | 1.91 | 26.5 | 2.05 | 1.89 |
| 7 | 44.3 | 2.42 | - | 44.3 | 2.40 | - |
| 8 | 134.8 | - | - | 134.8 | - | - |
| 9 | 117.6 | 7.07 | - | 117.5 | 7.07 | - |
| 10 | 122.9 | 6.67 | - | 122.8 | 6.67 | - |
| 11 | 127.1 | 7.03 | - | 127.1 | 7.03 | - |
| 12 | 107.5 | 6.44 | - | 107.5 | 6.44 | - |
| 13 | 151.3 | - | - | 151.4 | - | - |
| 14 | 18.4 | 1.70 | 1.64 | 18.4 | 1.72 | 1.61 |
| 15 | 31.2 | 1.56 | 1.52 | 31.2 | 1.56 | 1.52 |
| 16 | 30.3 | 2.11 | 1.78 | 30.3 | 2.10 | 1.78 |
| 17 | 35.4 | 2.01 | 1.55 | 35.4 | 2.00 | 1.68 |
| 18 | 9.1 | 0.90 | - | 9.1 | 0.90 | - |
| 19 | 27.4 | 1.45 | 1.42 | 27.5 | 1.45 | 1.40 |
| 20 | 44.4 | - | - | 44.4 | - | - |
| 21 | 78.9 | 2.27 | - | 78.9 | 2.28 | - |
| 22 | 31.0 | 2.76 | - | 31.1 | 2.73 | - |

(a: $\ln \mathrm{CDCl}_{3}$ )
Table 23 - Comparison of NMR data between the isolated and the synthesized (-)-vallesamidine A
The carbon and proton chemical shifts correlated well with the isolated natural product.
The optical rotation of synthetic (-)-vallesamidine (3.1) was similar to the value reported for the isolated one (synthesized: $[\alpha]_{D}^{20}=-71.4^{\circ}\left(c=0.25, \mathrm{CHCl}_{3}\right)$, isolated: $[\alpha]_{D}{ }^{20}=-76.6^{\circ}(c=0.25$, $\left.\left.\mathrm{CHCl}_{3}\right)^{188 \mathrm{~b}} /[\alpha]_{\mathrm{D}}{ }^{20}=-55^{\circ}\left(c=\text { unspecified, } \mathrm{CHCl}_{3}\right)^{179}\right)$. We therefore obtained the correct enantiomer.
(+)-1,2-dehydroaspidospermidine (3.2) was obtained in $7.1 \%$ overall yield in 11 steps (longest linear sequence) from the commercially available enone $\mathbf{3 . 1 9 0}$ with $99 \%$ enantiomeric excess.

Table 24 shows the comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of both isolated and synthetic (+)-1,2-dehydroaspidospermidine (3.2).

(+)-1,2-dehydroaspidospermidine
(3.2)

|  | Isolated |  |  | Synthesized |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{N}^{\circ}$ | ${ }^{13} \mathrm{C}[\mathrm{ppm}]^{\mathrm{a}}$ | ${ }^{1} \mathrm{H}[\mathrm{ppm}]^{\mathrm{a}}$ | ${ }^{13} \mathrm{C}[\mathrm{ppm}]^{\mathrm{a}}$ | ${ }^{1} \mathrm{H}[\mathrm{ppm}]^{\mathrm{a}}$ |  |  |
|  | $(100 \mathrm{MHz})$ | $(400 \mathrm{MHz})$ | $(100 \mathrm{MHz})$ | $(400 \mathrm{MHz})$ |  |  |
| 2 | 192.4 | - | - | 192.5 | - | - |
| 3 | 52.1 | 2.46 | 3.19 | 52.2 | 2.45 | 3.18 |
| 5 | 54.7 | 2.60 | 3.20 | 54.7 | 2.59 | 3.19 |
| 6 | 35.2 | 1.64 | 2.14 | 35.3 | 1.65 | 2.16 |
| 7 | 61.3 | - | - | 61.5 | - | - |
| 8 | 147.2 | - | - | 147.3 | - | - |
| 9 | 121.1 | 7.33 | - | 121.1 | 7.33 | - |
| 10 | 125.2 | 7.16 | - | 125.3 | 7.16 | - |
| 11 | 127.6 | 7.29 | - | 127.6 | 7.29 | - |
| 12 | 120.2 | 7.51 | - | 120.3 | 7.51 | - |
| 13 | 154.6 | - | - | 154.7 | - | - |
| 14 | 22.1 | 2.11 | 1.85 | 22.2 | 2.11 | 1.85 |
| 15 | 33.3 | 1.01 | 1.56 | 33.4 | 1.00 | 1.57 |
| 16 | 23.8 | 2.76 | 3.10 | 23.9 | 2.76 | 3.11 |
| 17 | 27.3 | 1.54 | 1.48 | 27.4 | 1.55 | 1.49 |
| 18 | 7.4 | 0.50 | - | 7.4 | 0.49 | - |
| 19 | 29.8 | 0.64 | 0.69 | 29.9 | 0.64 | 0.70 |
| 20 | 36.6 | - | - | 36.7 | - | - |
| 21 | 79.1 | 2.41 | - | 79.2 | 2.40 | - |

(a: $\ln \mathrm{CDCl}_{3}$ )
Table 24 - Comparison of NMR data between the isolated and the synthesized (+)-1,2dehydroaspidospermidine

The carbon and proton chemical shifts correlated well with the isolated natural product.
The optical rotation of synthetic (+)-1,2-dehydroaspidospermidine (3.2) was similar to the value reported for the isolated one (synthesized: $[\alpha]_{D}{ }^{20}=+215^{\circ}\left(c=0.60\right.$, EtOH ), isolated: $[\alpha]_{D}{ }^{20}=+237^{\circ}$ $\left.(c=0.636, \mathrm{EtOH})^{194}\right)$. We therefore obtained the correct enantiomer.

### 3.6 Conclusion and Outlook

In conclusion, we succeeded in the development of a divergent enantioselective synthesis of (-)vallesamidine (3.1) and (+)-1,2-dehydroaspidospermidine (3.2). Combination of factors allowed a quick and efficient synthesis of the targets.

- A challenging Ag-NHC-catalyzed enantioselective 1,4-addition on 3-substituted cyclopentenone with subsequent trapping of the enolate in excellent enantiomeric excess and yield
- A diarylprolinol-catalyzed enantioselective aldol reaction. It afforded the desired compounds in excellent enantiomeric ratio
- An unprecedented stereoinvertive nucleophilic substitution of an enantio-enriched benzylic mesylate with a vinyl boronic acid to give a key diastereomerically pure enantioenriched 1,3,3-trisubstituted cyclopentene.
- A domino process involving a sequence of epoxidation/nosyl deprotection/transannular cyclization/reduction/cyclization/reductive alkylation converted cyclopentene 1.184 to (-)vallesamidine (3.1) in one single operation
- An unprecedented $\mathrm{TiCl}_{3}$-mediated reductive cyclization/rearrangement cascade, allowing the conversion of the vallesamidine skeleton into the aspidosperma one


Scheme 175 - Summary of the total synthesis of (-)-vallesamidine and (+)-1,2-dehydroaspidospermidine
Overall, (-)-vallesamidine (3.1) was obtained in only 9 steps with $6.3 \%$ overall yield and $99 \%$ ee starting from simple starting materials. From the same common macrocycle 1.184, (+)-1,2dehydroaspidospermidine (3.2) was also obtained. Overall, 3.2 was obtained in 11 steps and $7.1 \%$ overall yield. ${ }^{299}$

[^110]
# Chapter 4 Enantioselective Total Synthesis of (+)-Peganumine A 

### 4.1 Introduction

The $A / B / C-$ ring system of (-)-terengganensine $A(2.1),(-)$-vallesamidine (3.1) and (+)-1,2dehydroaspidospermidine (3.2), also called $\beta$-carboline, is in fact featured in many natural products.

### 4.1.1 The $\beta$-Carboline Alkaloids

### 4.1.1.1 History and Structure

$\beta$-Carboline alkaloids all share the same fused tricyclic skeleton formed of an indole and a pyridine ring (Figure 30). Different levels of insaturation are possible in the pyridine ring. Unsaturated members are described as fully aromatic $\beta$-carbolines ( $\beta C s$ ) (4.2), whereas the partially or completely saturated ones are known as dihydro- $\beta$-carbolines (DH $\beta C s$ ) (4.3) and tetrahydro- $\beta$ carbolines ( $\mathrm{TH} \beta \mathrm{Cs}$ ) (4.4) respectively. ${ }^{300}$

4.2

4.3

4.4

Figure 30 - Possible oxidation states of $\beta$-carboline alkaloids
These scaffolds are found in a large variety of natural products, from very simple to very complex ones (Figure 31). ${ }^{300}$

The first $\beta$-carbolines were isolated in 1841 from the seeds of Peganum harmala, a small, bushy herb known as Syrian Rue which grows along the Mediterranean and throughout Central Asia. They have been used as a traditional herbal drug in the Middle East and North Africa. In the Amazon basin, plants containing $\beta$-carbolines were widely used as hallucinogenic drinks or snuffs. Besides, the extracts of the seeds of Peganum harmala have been traditionally used for hundreds of years to treat the alimentary tract cancers and malaria in Northwest China. ${ }^{300}$

[^111]
Noharman
(4.2)

Harmalan

8-Hydroxymanzamine A
(4.7)

Figure 31 - Examples of $\beta$-carboline alkaloids
Several $\beta$-carboline alkaloids are biologically active with diverse effects such as antitumoral, antimicrobial, antimalarial, antioxidant, anti-inflammatory, analgesic effects and many more. ${ }^{300}$

At least 64 different kinds of $\beta$-carboline alkaloids are present in eight plant families. One of these being Peganum harmala of which the seeds are known to contain, by dry weight, up to $5.9 \%$ of $\beta$ carboline alkaloids. Some $\beta$-carboline alkaloids can also be found in scorpions' cuticle, in ascidians (marine tunicates) and freshwater cyanobacterium. ${ }^{300}$

### 4.1.1.2 Previous Syntheses

A tremendous amount of synthetic methods of very different $\beta$-carboline alkaloids were reported. ${ }^{301}$ As the $\beta$-carboline alkaloids group is so diversified, only the most common procedures to form the general tricyclic structures are pictured below (Scheme 176).

[^112]

Scheme 176 - General retrosynthetic scheme of $\beta$-carboline derivatives
The tetrahydro- $\beta$-carboline alkaloid 4.4 with one unsaturation on the pyridine ring can be easily formed by a simple Pictet-Spengler reaction (A) starting from tryptamine (1.16). It can also be formed by more complex reactions like for instance reductive $N$-heteroannulation (B) ${ }^{302}$ using the Cadogan-Sunberg reaction or the $\mathrm{TiCl}_{3}$-promoted reductive cyclization developed in our lab. ${ }^{296}$ The dihydro- $\beta$-carboline alkaloids with two unsaturations on the pyridine ring 4.3 can be formed by a Bischler-Napieralski reaction (C). It is of course possible to go from the tetrahydrocarboline 4.4 to the dihydrocarboline 4.3 by simple oxidation (D) using IBX for instance. ${ }^{303}$ The opposite reaction by simple reduction of the imine 4.3 is also well known. The $\beta$-carboline alkaloids with three unsaturations 4.2 can be formed from both less oxidized compounds. The tetrahydrocarboline 4.4 has to undergo a double oxidation (E). This can be done, for instance, by a palladium mediated oxidation. ${ }^{304}$ The dihydrocarboline 4.3 can be oxidized once to form the fully unsaturated product 4.2. ${ }^{305}$ The latter can also be formed by simultaneous decarboxylation and oxidation (G) using, for instance, selenium dioxide in acetic acid. ${ }^{306}$

Among all the $\beta$-carboline alkaloids, many bisindole compounds are found (Figure 32). ${ }^{307}$ Either one or both indole parts are in the form of a $\beta$-carboline. Emplacements of the linkage between

[^113]the two monomers vary extensively. Some compounds are dimers such as dispergatrine (4.14). As depicted on Figure 32, most of the bisindole natural products are the combination of two monoterpene indole alkaloids. Concerning their synthesis, most of these bisindole alkaloids are constructed by a late stage jointure of the two monomers, which are generally natural product themselves.


R = H, Villalsonine (4.11) $\mathrm{R}=\mathrm{OMe}$, Methoxyvillalstonine (4.12)


Macralstonidine (4.13)


Dispergatrine (4.14)

Figure 32 - Examples of bis $\beta$-carboline alkaloids

### 4.1.2 (+)-Peganumine A

One of the rare known examples of dimeric tetrahydro- $\beta$-carboline alkaloids, ( + )-peganumine A (4.1), was recently isolated and attracted our attention.

### 4.1.2.1 History and Structure

Hua and coworkers isolated in 2014 a new dimeric $\beta$-carboline alkaloid characterized by a unique 3,9-diazatetracyclo-[6.5.2.0 $0^{1,9} .0^{3,8}$ ]pentadec-2-one scaffold from the seeds of the Iranian Peganum harmala L. ${ }^{308}$


Figure 33 - Structure of (+)-peganumine A
(+)-Peganumine A (4.1) is an octacyclic dimeric $\beta$-carboline alkaloid formed by two tricyclic monomers which are connected together by two five-membered heterocycles. One of them is a pyrrolidine and the other one is a $\delta$-lactam. Both formed a 2,7-diazabicyclo[2.2.1]heptan-3-one bridged

[^114]ring system. The 3,9-diazatetracyclo-[6.5.2.0 $0^{1,9} .0^{3,8}$ ] pentadec-2-one was completely unique and no other known compounds exhibited such kind of ring system.

Both indole rings have a methoxy substituent on carbon 9 and $9^{\prime}$ and the pyrrolidine ring has gemdimethyl substituents at position C -16. It is to note that the gem-dimethyl substituents have a great importance in medicinal chemistry. ${ }^{309}$

The relative configuration was elucidated by analysis of the NOESY spectrum. Moreover a singlecrystal X-ray diffraction study unambiguously confirmed the planar structure and the relative configuration of (+)-peganumine $A(4.1)$ (Figure 34). The absolute configuration of the latter was established by a CD exciton chirality method. ${ }^{310}$ The UV spectrum of (+)-peganumine A (4.1) exhibited a strong absorption at 229 nm and the ECD spectrum showed a positive Cotton effect at 226 nm . These absorptions were attributed to the two identical indole chromophores and their transition dipole moments. They were therefore able to determine the clockwise orientation of the indole and thus the $S$ absolute configurations at $\mathrm{C}-1$ and $\mathrm{C}-1^{\prime}$. Additionally, a comparison between the experimental and a calculated ECD spectrum allowed them to unambiguously assign the $(S)$ configuration for both the $\mathrm{C}-1$ and $\mathrm{C}-1$ ' stereocenters.


Figure 34 - X-ray crystallographic structure of (+)-peganumine A
Another important feature of (+)-peganumine A (4.1) was its very low isolation yield. Indeed, only 3.5 mg out of 15.4 kg of seeds were isolated. Comparison of the isolation yield to other wellknown bioactive scarce natural products is listed in Table 25.

| Entry | Natural Product | Isolation yield [*10-5\%] | Source |
| :---: | :---: | :---: | :---: |
| 1 | Taxol | 696 | T. brevifolia |
| 2 | Vincristine | 20 | C. roseus |
| 3 | (+)-Peganumine A | 2.27 | P. harmala |

Table 25 - Isolation yield of (+)-peganumine A compared to other scarce natural products

[^115]
### 4.1.2.2 Biosynthesis

A hypothetical biosynthesis pathway for (+)-peganumine A (4.1) was postulated by Hua and coworkers ${ }^{308}$ and is shown in Scheme 177.


## Scheme 177 - Proposed biosynthetic pathway of (+)-peganumine A

Tryptamine (1.16) could react with pyruvic acid (4.15) in a Pictet-Spengler reaction to afford the tetrahydro- $\beta$-carboline structure 4.16. Demethylation followed by oxidation of the indole C-6 position (C-9) could afford the first key intermediate 4.17. On the other side, tryptamine (1.16) could react with a $\mathrm{C}_{5}$-carbonyl unit (4.19) to afford another tetrahydro- $\beta$-carboline unit $\mathbf{4 . 2 0}$. The latter could then be oxidized at position 6 of the indole ring ( $\mathrm{C}-9^{\prime}$ ) and the amine could also be oxidized to form the second key dihydro- $\beta$-carboline intermediate 4.21. The latter could then react with the first key intermediate 4.18 in a heteroannulation reaction via formation of C-1/C-16 and N-2/C-1' bonds. Subsequent intramolecular amide bond formation could furnish (+)-peganumine A (4.1).

### 4.1.2.3 Bioactivity

(+)-Peganumine A (4.1) was evaluated for its cytotoxicity against various cancer cell lines with the trypan blue and the MTT methods using 5-fluorouracil as positive control. Table 26 shows the obtained $\mathrm{IC}_{50}$ values. Low to moderate $\mu \mathrm{M}$ activity was obtained and selectivity effect for $\mathrm{HL}-60$ was observed.

| Cell line | HL-60 <br> (leukemia) | MCF-7 <br> (brest) | PC-3 <br> (prostate) | HepG2 <br> (liver) |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{IC}_{50}[\mu \mathrm{M}]$ | 5.8 | 38.5 | 40.2 | 55.4 |

Table 26 - Cytotoxicity of (+)-peganumine A against various cancer cell lines
These numbers showed that the molecule exhibited significant cytotoxic effects and may be a potential anticancer lead compound. ${ }^{308}$

The intriguing molecular architecture in conjunction with the significant bioactivity and extremely low isolation yield prompted us to undertake the total synthesis of (+)-peganumine A (4.1).

### 4.2 Initial Retrosynthetic Pathway and Background

Our initial retrosynthetic pathway is represented in Scheme 178.




Scheme 178 - Initial retrosynthesis of ( + )-peganumine A
(+)-Peganumine A (4.1) was planned to be obtained by a late-stage Bischler-Napieralski/iminium trapping cascade reaction. Initial selective activation of the tertiary versus the secondary amide 4.24 followed by indole attack could afford intermediate 4.23. Transannular cyclization of the secondary amide to trap the reactive iminium intermediate would afford (+)-peganumine A (4.1). The bisamide compound 4.24 was planned to be accessed via a Pictet-Spengler reaction starting from the linear bisamide 4.26. Initial intramolecular condensation of the amide on the reactive $\alpha$ ketoamide could afford iminium 4.25 which, after Pictet-Spengler reaction could deliver intermediate 4.24. The quasi-dimer linear intermediate 4.26 was planned to be obtained by double amidebond formation from the commercially available 6-MeO-tryptamine (4.27) and $\alpha$-ketodiacid 4.28.

An enantioselective Pictet-Spengler reaction could allow the synthesis of optically enriched 4.24. The second stereocenter generated by the trapping of iminium II would be stereospecific due to the nature of the 1,3-bridged ring system.

Our initial idea was based on two key textbook reactions for the synthesis of $\beta$-carboline namely the Pictet-Spengler and the Bischler-Napieralski reaction.

### 4.2.1 Pictet-Spengler Reaction

The Pictet-Spengler reaction was discovered in 1911 in Geneva, Switzerland. It was initially based on the reaction of phenylethylamine and aldehydes catalyzed by HCl for the synthesis of tetrahydroisoquinoline derivatives. ${ }^{311}$ In 1928, Tatsui extended the scope to tryptamine (1.16) for the synthesis of tetrahydro $\beta$-carboline derivatives 4.32. ${ }^{312}$


Scheme 179 - Two different proposed mechanisms of the Pictet-Spengler reaction
Acid-catalyzed condensation of tryptamine (1.16) with an aldehyde 4.29 could afford iminium 4.30 (Scheme 179). From here, two different mechanisms are commonly accepted. C-3 attack of the indole ring could provide spirocyclic intermediate 4.31 (A). Suprafacial Wagner-Meerwein rearrangement ${ }^{313}$ could afford 4.32 which after fast rearomatization could give product 4.33 . The second possible mechanism involved a direct C-2 attack to give 4.34 (B). Rearomatization afforded the same product 4.33. Evidence for the involvement of the spirocyclic intermediate 4.31 was obtained by employing isotopic labeling studies. It was demonstrated that the formation of the spiroindolenine is fast and reversible, and that the formation of the pentahydro- $\beta$-carboline carbonium ion 4.32 is the rate-limiting step of the reaction. However, it is still unclear whether, in general, the carbonium ion 4.34 is formed by rearrangement of the spiroindolenine 4.31 or by direct attack from the position 2 of the indole 4.30. ${ }^{90,106 \mathrm{c}}$

Our strategy relied on the use of an enantioselective version of the Pictet-Spengler reaction to induce the chirality in the molecule. Different methods have been reported for this transformation such as the use of stoichiometric chiral Lewis acid, catalytic chiral Brønsted acid and catalytic chiral thiourea. ${ }^{106}$

Seminal work using catalytic chiral Brønsted acid was reported in 2006 by List and coworkers (Scheme 180, A). ${ }^{314}$ The limitation lied in the required use of the gem-diester substituents. The

[^116]role of the latter was to accelerate the cyclization via the Thorpe-Ingold effect ${ }^{315}$ and to prevent imine to enamine tautomerism followed by addition onto another aldehyde partner.

Since then, BINOL- or SPINOL-based chiral phosphoric acid-catalyzed Pictet-Spengler reaction using $N$-STrityl, $N$-Bn and unmodified tryptamines were reported. ${ }^{316}$


Scheme 180 - Seminal reports for the catalytic enantioselective Pictet-Spengler reaction
Initial report for the use of chiral thiourea as anion-binding catalyst in the enantioselective PictetSpengler reactions was reported in 2004 by Jacobsen and coworkers (Scheme 180, B). ${ }^{317}$ Acylation of the formed imine generated a more reactive $N$-acyl iminium intermediate and could, at the same time, prevent catalyst inhibition by the final products. Nevertheless, only aromatic aldehydes were tolerated in this reaction because for the aliphatic ones, a higher temperature was required $\left(-30^{\circ} \mathrm{C}\right)$ and at that temperature, $S$-acylation of the catalyst occurred. The scope was later extended to other substrates. ${ }^{318}$

Most of the reported works dealt with aldehydes as carbonyl reaction partners. In our case, reaction had to occur on an $\alpha$-ketoamide (4.26). Use of stoichiometric chiral silane 4.42 was reported on similar substrates 4.41 (Scheme 181, A). ${ }^{319}$ A limitation was the use of a specific aromatic substituent on the nitrogen of the $\alpha$-ketoamide. Chiral thiourea 4.47 was also reported to work for the formation of quaternary centers but the reaction started from $N$-acyl hemiaminal 4.45 instead of ketone and tryptamine (Scheme 181, B). ${ }^{320}$ The only reaction between tryptamine and ketone was reported in 2011 for the synthesis of $\gamma$-tetrahydrocarboline 4.51 via iso-Pictet-Spengler reac-

[^117]tion (Scheme 181, C). ${ }^{321}$ The use of chiral phosphoric acids in combination with ketones, in the form of enol lactones, ${ }^{322} \alpha$-ketoacids, ${ }^{323}$ isatins ${ }^{324}$ and trifluoromethyl ketones ${ }^{325}$ was also reported.


Scheme 181 - Examples of enantioselective Pictet-Spengler reactions for the formation of quaternary centers

Among all the published works on enantioselective Pictet-Spengler reactions, one particular report attracted our attention (Scheme 182, A). ${ }^{318 a}$ Pictet-Spengler reaction of unprotected tryptamine 4.52 with various aliphatic and aromatic aldehydes using chiral thiourea 4.53 and benzoic acid as co-catalyst provided the desired products 4.54 in good yields and ee. Very surprisingly, subsequent mechanistic studies revealed that the rate and enantiodetermining step was the deprotonation of the pentahydro- $\beta$-carbolinium intermediate, i.e. the rearomatization (Scheme 182, B). ${ }^{326}$ Jacobsen and coworkers have suggested that the thiourea played multiple roles in the course of the reac-

[^118]tion. It initially could facilitate the protonation of the imine by increasing the acidity of BzOH via hydrogen bonding. On a second hand, it could stabilize the transition state of the C-2 attack on the imine. Thanks to hydrogen-bonding, it could allow the stabilization of the cationic intermediate. It also could play a significant role in the rate determining step by a complex network of hydrogenbonding (green) and of $\pi-\pi$ and $\mathrm{CH}-\pi$ interactions (red). The NH of the indole revealed to be crucial as it engaged in a hydrogen bonding with the amide (blue). Finally, the benzoate acted as base to abstract the $\mathrm{H}-2$ proton during the rearomatization (pink).


Scheme 182 - Chiral thiourea-catalyzed enantioselective Pictet-Spengler reaction of unmodified tryptamines

### 4.2.2 Bischler-Napieralski Reaction

The second key reaction in our retrosynthesis (Scheme 178) was the Bischler-Napieralski reaction. It starts from an amide instead of an imine (or amine and carbonyl), i.e. with one more degree of oxidation compared to the Pictet-Spengler reaction. Bischler and Napieralski were the firsts to develop such kind of reaction using $\mathrm{POCl}_{3} .{ }^{327}$ Two different mechanisms are commonly accepted among the community (Scheme 183). ${ }^{328}$ Activation of the secondary amide 4.56 could afford intermediate 4.57. The latter is then known to follow two different mechanisms. If its trapping is slow enough (Scheme 183, A), elimination of HCl and $\mathrm{PO}_{2} \mathrm{Cl}$ could afford the nitrilium 4.58. ${ }^{329}$ Its trapping by the aromatic ring from the C-3 position could afford 4.59 , which after WagnerMeerwein rearrangement and rearomatization could be transformed into the desired product 4.61. In the case of fast trapping of 4.57 (Scheme 183, B), no nitrilium formation occurred and direct trapping, rearrangement and rearomatization of 4.57 could afford the desired BischlerNapieralski dihydro- $\beta$-carboline product 4.61 . The reaction conditions as well as the substrates are

[^119]known to influence which of the two mechanisms occurred. ${ }^{330}$ Moreover, it was demonstrated that C-3 attack followed by rearrangement instead of direct C-2 attack is, in general, the occurring mechanism. ${ }^{331}$ Alternatively, similar mechanisms could occur from 4.64, which resulted from substitution on 4.57 (C).


## Scheme 183 - Proposed mechanisms for the Bischler-Napieralski reaction

Beside the initial method developed by Bischler and Napieralski, many other procedures have later been disclosed. Prof. Charette, Prof. Movassaghi and their collaborators have worked extensively on the activation of amides using a combination of $\mathrm{Tf}_{2} \mathrm{O}$ and base, especially pyridine derivatives. Generally, only low temperature or mild heating were enough to promote both the activation of the amides and the subsequent reactions of the activated species whereas $\mathrm{POCl}_{3}$ methods required generally much harsher temperatures. Various nucleophiles have been added intermolecularly to the activate amides as for instance hydrides, ${ }^{332}$ thiols, ${ }^{333}$ alcohols, ${ }^{334}$ amines ${ }^{335}$ and thioamines ${ }^{336}$ by Charette and coworkers. Movassaghi and coworkers also studied reaction between enamide and alkynes ${ }^{337}$ or nitriles ${ }^{338}$ to form pyridine or pyrimidine derivatives respectively.

Intramolecular reactions were also extensively studied by Movassaghi and coworkers. Indoles ${ }^{339}$ (Scheme 184, A) and activated alkenes ${ }^{340}$ (B) were added to amide to form spiroindoline or pyridine derivatives respectively.

[^120]

## Scheme 184 - Intramolecular reactions of triflic anhydride-activated amides developed by Movassaghi and coworkers

Both groups have studied the amides 4.69 and 4.70 activation mechanism by $I R$, and ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$ and ${ }^{19}$ F NMR spectroscopy. ${ }^{338,341,331 b}$ They all proposed the same following mechanism (Scheme 185).


Scheme 185 - Proposed mechanisms for the activation of amides using pyridine and triflic anhydride
Charette and coworkers observed by ${ }^{1} \mathrm{H}$ and ${ }^{19} \mathrm{~F}$ NMR that the triflating agent was the triflylpyridinium triflate 4.70. Movassaghi observed by ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR as well as by IR that no such reagent was formed when $2-\mathrm{Cl}$ pyridine was mixed with triflic anhydride. The nature of the triflating agent is therefore base-dependent.

With non-enolisable tertiary amide 4.69 (Scheme 185, A), triflation of the amide oxygen occurred with the help of the nitrogen lone-pair to form $O$-triflyliminium triflate 4.71. Pyridine addition

[^121]could occur very fast to give the double cationic substrate 4.72. Various nucleophiles could then attack the highly electrophilic carbon and expulse pyridinium salt.

With enolisable tertiary amide 4.74 (Scheme 185, B), the same mechanism could occur. The main differences were that the $O$-triflyliminium triflate 4.75 could eliminate triflic acid to yield the keteniminium triflate 4.78 and that the $N$-pyridyliminium triflate 4.76 could tautomerize to the enamine pyridinium triflate 4.79.

Both Charette's and Movassaghi's group reported that, because of equilibrium, excess of pyridine could sometimes slow down or inhibit the attack of the nucleophile into the activated intermediate 4.72 or 4.76 . Nevertheless, pyridine was generally required to prevent decomposition of the substrates under the highly acidic conditions due to the in situ formed triflic acid. Movassaghi also reported that on sterically hindered lactam, attack on the sulfur instead of the carbon could lead to deactivation of 4.71 to give back 4.69 and triflylpyridinium triflate 4.70 instead of 4.72 (C). His group also showed that pyridine derivatives were sometimes required to avoid formation of the less reactive diiminium ether dimer 4.80 (D).

Finally, in Prof. Charette's NMR experiments, secondary amides reacted much faster than tertiary ones, but no example was reported with a quaternary center $\alpha$ to the carbonyl group probably because the steric hindrance would prevent any reaction of the carbonyl.

In order to test the feasibility of our proposed retrosynthesis (Scheme 178), the diacid 4.28 had first to be synthesized.

### 4.3 Synthesis of ( + )-Peganumine A

### 4.3.1 Strategy Based on a Bischler-Napieralski Reaction

### 4.3.1.1 Synthesis of the $\alpha$-Ketoester

This apparently simple diacid 4.28 proved to be extremely difficult to obtain. Many different routes were attempted as shown on Scheme 186.


Scheme 186 - Summary of the attempted routes towards the desired $\alpha$-ketoester
Initially, double methylation was attempted on the very cheap and commercially available $\alpha$-keto glutaric acid (4.81) (or its diester form). Extensive screening of bases, solvents and methylating agents proved to be fruitless as messy reactions were always observed. The main issue was probably the steric bulk created by the insertion of the first methyl group. Moreover, ketones of $\alpha$ ketoacids are highly reactive and autocondensation could therefore occur. It is also known that $\alpha$ ketoacids are sometimes in their hydrated (hemiacetal) form which would prevent any deprotonation $\alpha$ to it.

Nucleophilic substitution on $\alpha$-bromoacetate derivative 4.82 using the ketoester 4.83 proved also to be ineffective probably again due to the high reactivity of the ketoester towards selfcondensation or the presence of its hydrated form.

It was then planned to access the desired substrate 4.28 using the corresponding alcohol 4.83 which in turn was planned to be obtained by $\alpha$-hydroxylation of the symmetric 3,3-dimethylpentan-1,5-dioic acid or ester 4.85 or its corresponding anhydride 4.87. However, all these experiments failed to produce the desired product. Interestingly, no report of $\alpha$ hydroxylation on anhydride was available. The reason was probably the high reactivity of the anhydride functionality which could easily be opened in an intermolecular fashion. The same alcohol 4.83 was then traced back to the bromide derivative 4.88 and we planned to access this compound by mono-bromination via the Hell-Volhardt-Zelinski reaction. ${ }^{342}$ Unfortunately, no desired product was observed during the latter.

The ozonolysis of enone 4.89 was another attempted approach. The synthesis of the enone 4.89 was previously reported via hydrolysis of 4.90 which was itself obtained by autocondensation of

[^122]acyl cyanide 4.91. ${ }^{343}$ Unfortunately, even after extensive re-optimization of the reported conditions, only trace amount of the lactone 4.90 was observed and this route was therefore stopped.

The 1,4-addition of $\alpha$-nitroacetate 4.93 on enone 4.94 was attempted as the desired product 4.92 could then undergo Nef reaction ${ }^{344}$ to afford the desired compound 4.28. Unfortunately, no reaction was observed during the 1,4-addition probably because of the high steric hindrance of the enone 4.94 and the low electrophilicity of $\alpha, \beta$-unsaturated acids/esters compared to more reactive $\alpha, \beta$-unsaturated aldehydes or ketones.

The next plan was to perform an ozonolysis of the Wasserman elongation ${ }^{345}$ product 4.95 but the latter was never obtained.

We finally turned our attention toward the oxidation of cyclopentenone 4.97. After multiple attempts, only overoxidized products were obtained probably because of the possibility to cleave $\alpha$ ketoacid under the reaction conditions (probably via the hydrated form). Various oxidative conditions were tested such as $\mathrm{RuCl}_{3} / \mathrm{NaIO}_{4}, \mathrm{KMnO}_{4}, \mathrm{O}_{3} / \mathrm{NaOH} / \mathrm{MeOH}$, etc. but none of them led to the desired product.

Nevertheless, encouraged by the simplicity of this strategy we finally came out with the following solution (Scheme 187).


Scheme 187 - Final retrosynthesis for the $\alpha$-ketoester building block
Protection of the $\alpha$-ketoester 2.28 in the form of an acetal 4.98 could prevent the overoxidation during the cyclopentene cleavage. The protected cyclopentenone 4.99 was planned to be obtained by protection/bromination followed by elimination on the commercially available 2,2dimethylcyclopentanone (4.97).

[^123]

## Scheme 188 - Synthesis of the $\alpha$-ketoacid/ester

One pot bromination/protection of 4.97 afforded the desired bromoacetal 4.101 which was directly submitted to elimination conditions using $K^{t}{ }^{t} \mathrm{Bu}$ in DMSO to afford the cyclopentene 4.102 in $50 \%$ yield over 2 steps (Scheme 188). ${ }^{346}$ The generated HBr probably catalyzed the bromination and the protection. Ozonolysis of $\mathbf{4 . 1 0 2}$ using NaOH in $\mathrm{MeOH}^{347}$ afforded an easily separable mixture of bis- and mono- methyl ester 4.103 and 4.104 in almost quantitative combined yield. In these conditions, the primary ozonide 4.109 probably decomposed into a carbonyl 4.110 and a carbonyl oxide 4.111 as proposed for the Criegee mechanism. ${ }^{348}$ The latter could then be trapped by MeOH in basic condition to afford a hemiacetal 4.113 and a hydroperoxide 4.112 respectively. The latter could then be deprotonated to eliminate water and to afford the methyl ester 4.114. The hemiacetal 4.113 could be oxidized by a second equivalent of ozone to afford the second methyl ester 4.115 (Scheme 189). In the reaction conditions, partial hydrolysis occurred which explained the mixture of ester 4.103 and acid 4.104.


Scheme 189 - Mechanism for the ozonolysis of alkene leading to the formation of dimethyl ester
The mixture of both compounds (or each of them separately) was then hydrolyzed to afford the protected $\alpha$-ketoacid 4.105. Alternatively, it could be submitted to methylation using TMS diazomethane to afford the protected $\alpha$-ketoester 4.103 in quantitative yield. Acetal deprotection of

[^124]4.103 or of 4.105 afforded the desired diester 4.108 or diacid 4.106 in 69 and $86 \%$ yield respectively.

### 4.3.1.2 Synthesis of 6-OMe Tryptamine

Our second starting material, 6-OMe tryptamine (4.27), was a commercially available but very expensive ( $1170 \$ /$ gram ) compound. ${ }^{349}$ We therefore decided to synthesize it by ourselves as big quantity was required. We first attempted to use previously reported conditions ${ }^{350}$ for its synthesis via the Japp-Klingmann reaction without success. One-pot ligand-controlled C-H boryla-tion/Chan-Lam coupling on various tryptamine derivatives (different protecting group on the indole nitrogen and on the primary amine) as reported by Baran and coworkers were not effective neither. ${ }^{351}$ We then tried another reported synthesis developed in our lab and extended by others via a Pd-catalyzed Heck reaction between an aldehyde 4.122 and an o-iodoaniline (4.118) (Scheme 190). ${ }^{352}$ These reports were probably all inspired from similar chemistry developed at Merck. ${ }^{353}$




Scheme 190 - Synthesis of 6-OMe tryptamine

[^125]Sandmeyer reaction on o-nitro-p-anisidine (4.116) followed by reduction of the nitro group of 4.117 afforded the desired iodoaryl 4.118 in good yields. ${ }^{354}$ On the other hand, protection of 4aminobutanol (4.119) with phthalic anhydride (4.120) followed by Swern oxidation afforded the desired aldehyde $\mathbf{4 . 1 2 2}$ in $95 \%$ yield. ${ }^{355}$ Both partners were then coupled together in a very sensitive Pd-catalyzed reaction to give the protected tryptamine 4.123 in $48 \%$ yield. The latter was then deprotected using hydrazine hydrate to furnish the desired product 4.27. ${ }^{352}$ The yield of the cyclization was low probably because of the electronic of the iodoaryl ring. The methoxy substituent rendered the oxidative insertion into the C-I bond harder.

### 4.3.1.3 Model Studies for the Cyclizations

With both building blocks in hands, we were then ready to try the cyclizations step. As 6-MeOtryptamine (4.27) was very expensive and not so easily made and as our 3,3-dimethyl- $\alpha$ ketoglutaric acid (4.106) also required a quite lengthy sequence, we first examined the cyclization using simple $\alpha$-ketoglutaric acid (4.124) and unsubstituted tryptamine (1.16) as model substrates.

We first attempted to perform the double amide-bond formation between our simple starting materials. Gratefully, the bond formation occurred easily and additional condensation/PictetSpengler cyclizations to the tetracyclic compound 4.125 spontaneously took place presumably via intermediate 4.126 (Scheme 191). We supposed the amide bond formation was followed by the Pictet-Spengler reaction to afford the tetracyclic compound 4.125 .


Scheme 191 - Formation of the hexacyclic structure 4.125 via Pictet-Spengler reaction
Temperatures and solvents screening as well as trials with tryptamine hydrochloric salt showed that reaction at room temperature with neutral tryptamine in DCM were the best conditions. The acyl iminium formation as well as the Pictet-Spengler reaction easily occurred probably because of the high reactivity of $\alpha$-ketoacids towards condensation/addition. No trace amount of the 7membered ring produced by the attack of the other indole into the $N$-acyl iminium was detected.

With this tetracyclic structure 4.125 in hands, we then turned our attention towards the final Bis-chler-Napieralski/iminium trapping cascade cyclization. Standard conditions for the BischlerNapieralski reaction were attempted $\left(\mathrm{POCl}_{3}\right.$, neat/ MeCN or toluene, reflux) but all led to highly

[^126]water soluble compounds and poor mass balances. As Bischler-Napieralski reactions conditions are generally quite harsh, possible activation of both amides could occur. We therefore turned our attention towards milder conditions such as the ones reported by Movassaghi and coworkers.

We quickly observed the triflation of the indole nitrogen (4.127) under the reaction conditions (Scheme 192, A). Only protection of the monosubstituted indole moiety was observed probably because of the steric hindrance close to the second indole ring. As the triflic protecting group could decrease the nucleophilicity of the indole, we decided to protect both of the indole nitrogens of 4.125 under phase transfer conditions (B). ${ }^{356} \mathrm{~N}$-Benzyl protecting group was chosen because of its easy removal and because it did not affect much the reactivity of the indole ring. We were able to protect both indoles at the same time to obtain 4.128 in $75 \%$ yield.


## Scheme 192 - Protection of both indoles nitrogen under phase-transfer conditions

With the protected indole 4.128 in hands, many different temperatures, bases (mainly pyridine derivatives but not only) and stoichiometries of base/triflic anhydride/substrate were screened. All our conditions led to the recovery of most of the starting material 4.128, probably due to the hydrolysis of the activated amide during the workup. The only observed interesting case is depicted in Scheme 193.


Scheme 193 - Isolation of the pyridinium triflate derivative 4.129
Activation of the substrate 4.128 with 3 equivalents of pyridine and 1.3 equivalents of triflic anhydride at $-40^{\circ} \mathrm{C}$ followed by warming to room temperature afforded after quick work-up and rapid flash column chromatography the unstable enamine pyridinium triflate intermediate 4.129. Interestingly, no reaction was observed with the secondary amide probably because the steric hindrance was bigger than for the tertiary one. This was a good news for us. Product 4.129 was probably formed through $O$-triflyliminium $4.75 \rightarrow N$-pyridyliminium triflate $4.76 \rightarrow$ enamine pyridinium triflate 4.79 as the pathway through the keteniminium 4.78 was probably impossible in our 5membered ring (Scheme 185). Prolong contact of 4.129 with wet solvent or with air afforded the starting material 4.128 back and some decomposition products.

[^127]We also tried some other reaction conditions involving triflic anhydride and triphenylphosphine oxide to form bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate also known as Hendrickson reagent, which is known for its strong dehydrating properties. ${ }^{357}$ As with $\mathrm{Tf}_{2} \mathrm{O} /$ pyridine derivatives, only starting material 4.128 was observed after work-up. With the same protected substrate 4.128, we again attempted the standard Bischler-Napieralski reaction conditions with $\mathrm{POCl}_{3}$ but again the reaction afforded a very low mass balance and mainly messy mixture of insoluble materials.


Scheme 194 - Possible reaction pathways after the activation of the amide 4.128
The idea was to form first the 9 -membered ring (4.132), probably via the 8 -membered spirocycle 4.131, and then to trap the iminium 4.133 with the amide (Scheme 194, A). In this way, the formed bridgehead double bond intermediate would be incorporated in a 9-membered ring ([6.2.1]-bridged ring system), ${ }^{358}$ reducing therefore the produced ring-strain. Anti-Bredt systems are relatively common especially with a $S \geq 7 .{ }^{359}$ Unfortunately, this pathway probably did not occur in our hands.

Our hypothesis was the following: Activation of the tertiary amide probably occurred, as shown by 4.129 but the formation of the [2.2.1] fused ring system 4.135 was presumably more favorable and faster than the attack of the indole as formation of 8 - or 9 -membered ring is known to be less favorable and slower than 5 -membered ring. The cyclized product 4.135 could then prevent any further cyclization from the indole as it would require going through an anti-Bredt alkene interme-

[^128]diate 4.136 which is prohibited in such small ring system (Scheme 194, B). As pathway B was in an equilibrium, aqueous work-up could afford the starting amide 4.128 back (C).

Another possible explanation for the recovery of amide 4.128 could come from the steric hindrance, forcing the pyridine additive to attack on the less hindered sulfur than on the carbon leading back to the amide $\mathbf{4 . 1 2 8}$ as already observed by Movassaghi and coworkers in some cases. The last possible explanation could be that the iminium 4.130 to enamine tautomerism was much faster than the indole attack, affording the less reactive 4.137 (Scheme 194, D).

In order to prevent the possible side cyclization with the amide, protection of the secondary amides 4.128 with Boc was performed in $86 \%$ yield (Scheme 195). ${ }^{360}$ The resulting substrate 4.138 was resubmitted to $\mathrm{Tf}_{2} \mathrm{O}$ activation in various conditions but the starting material or sometime the Boc-deprotected compound 4.128 were always recovered. We never observed any kind of pyridinium intermediate as in 4.128 but this did not mean that the activation did not occur as we knew such kind of compounds were unstable.


Scheme 195 - Protection of the secondary amide 4.128
We identified slightly different strategies which could allow more flexibility (Scheme 196). In order to better differentiate between the tertiary and the secondary amide, we envisioned to synthesize the tertiary amide or thioamide derivative 4.139 or 4.140 respectively.


Scheme 196 - Alternative strategies for the formation of the key C-C bond
Amide bond formation of 4.140 with tryptamine (1.16) could afford 4.141 which could provide an alternative substrate to attempt the previous Bischler-Napieralski type reaction with completely different reaction conditions (Scheme 196, A). The same thioamide $\mathbf{4 . 1 4 0}$ could also be the oppor-

[^129]tunity to attempt intermolecular amidine formation (B). The amidine 4.142 could then be cyclized to form the desired tetrahydro- $\beta$-carboline 4.143. The activation of amidines requires alternative conditions compare to amides or thioamides. Moreover, 6-membered ring formation would be required in this case which could be easier compare to the $8 / 9$-membered one of the previous strategy. Concerning the diastereoselectivity, we hypothesized that the steric hindrance generated by the methyl ester group in 4.142 could promote the attack of the indole from the opposite side. Finally, derivatives 4.139 and 4.140 could also be trapped by indole in an intermolecular way to afford 4.144 (C). Formation of the 9-membered ring via lactamization could provide an interesting alternative.


Scheme 197 - Synthesis of the tetracyclic thioamide 4.140
We first needed to synthesize 4.139 and 4.140. $\alpha$-Ketoglutaric acid (4.124) was initially doubly esterified to form the corresponding diester 4.145 in quantitative yield. ${ }^{361}$ Cyclization was then triggered under acidic conditions in the presence of tryptamine (1.16) to afford the desired tetracyclic structure 4.139 in $72 \%$ yield. ${ }^{362}$ On the opposite of the cyclization observed in Scheme 191, PictetSpengler reaction followed by lactamization probably occurred. Lawesson's reagent and especially its dithiophosphine ylide monomer converted the amide 4.139 into the desired thioamide 4.140. ${ }^{363}$

Based on pathway A (Scheme 196), we first hydrolyzed the ester 4.140 using $\mathrm{LiOH}^{364}$ and performed a peptide coupling with tryptamine (1.16) to afford 4.141 in 80 and $60 \%$ yield respectively (Scheme 198).

[^130]

Scheme 198 - Hydrolysis of the ester 4.140 and its subsequent peptide coupling with tryptamine
With 4.141 in hands, we attempted different conditions to promote its cyclization. All of them followed the same activation principle: alkylation of the thiol to form the activated thioalkyl iminium salt 4.147. ${ }^{365}$ Under all our reaction conditions we recovered in high yield the amide 4.125 indicating that the activation of the thioamide occurred but that no further desired cyclization took place. During work-up, intermediate 4.146 was probably hydrolyzed and the amide 4.125 was isolated (Scheme 199). The same rationalization as in Scheme 194 could explain the lack of cyclization. By comparing results from amide activation to these ones, the most probable explanation could be the difficulty to form the strained 8-/9-membered ring.


Scheme 199 - Attempts for the cyclization of 4.141
We therefore turned our attention towards the second strategy (Scheme 196, B), the intermolecular amidine formation followed by its cyclization to form a 6-membered ring.


Scheme 200 - Synthesis of the amidine substrate 4.142
We first activated the thioamide 4.140 with methyl triflate followed by a treatment of the resulting crude iminium salt with tryptamine in pyridine to afford the amidinium triflate 4.149. ${ }^{366}$ The latter was then neutralized by simple basic work-up to afford the free amidine base 4.142 in quantitative yield (Scheme 200). This again highlighted the fact that activation of 4.141 in Scheme 199 probably occurred in Scheme 199.

We then attempted the activation of the amidinium 4.149 using Brønsted acids as previously reported (Scheme 201).

[^131]

Scheme 201 - Brønsted-acid activation of 4.149 for the cyclization onto amidine
No reaction took place using non-aqueous Brønsted acids even at elevated temperature for a prolonged period of time (A). ${ }^{367}$ When switching to aqueous conditions (concentrated $\mathrm{AcOH} /$ concentrated HCl at reflux) only the decarboxylation of the ester without any cyclization was observed (B). After literature screening, we observed that these conditions were the exact same as described for the decarboxylation of similar structure (amide instead of amidine). ${ }^{368}$ The probable mechanism of the decarboxylation is depicted in Scheme 202. It could also occur via a reported ring-opening mechanism. ${ }^{369}$


Scheme 202 - Possible mechanism of the observed decarboxylation of 4.149 in acidic aqueous conditions
As Brønsted acids seemed ineffective for the cyclization, we turned our attention toward activation using acylating/alkylating agents (Scheme 203). Acylation of 4.142 using $\mathrm{AcCl}^{2} \mathrm{Ac}_{2} \mathrm{O}$ or TFAA and alkylation with MeOTf in various reaction conditions led to very complex mixture of products with most of the time formation of the amidinium salt 4.149 if no base was used or recovery of the amide 4.139 in the presence of DIPEA. These results indicated that activation of the amidine 4.142 occurred. Side product 4.156 with $\alpha$-acetylation was also sometimes observed. As a base was required to avoid protonation of the amidine 4.142, it was hypothesized that the iminium to enamine tautomerism was faster than the trapping by the indole ring. In light of these results and the ones from Scheme 193, enamine formation appeared to be highly favorable in our system which could be a reason for the observed absence of cyclization.


Scheme 203 - Attempts for the cyclization of 4.142 using acylation or methylation

[^132]In light of all these failures, it was clear that formation of the C-C bond between the C-2 position of indole (probably via the C-3) and the tertiary amide ( $\mathrm{C}-1$ ') was difficult to achieve. We therefore attempted to form this C-C bond before the C-N bond starting from thioamide 4.140 or amide 4.139 following pathway C (Scheme 196).

Again, activation of the amide 4.139 using $\mathrm{POCl}_{3}$ or $\mathrm{Tf}_{2} \mathrm{O}$ and reaction with various protected tryptamines did not lead to the desired products and only messy mixture of products was obtained (A). Using MeOTf for the activation of the thioamide 4.140 only afforded the amide 4.139, meaning again that activation occurred but no further reaction took place (B). It is to note that there was no report of intermolecular attack of indole derivatives onto activated amides in the literature.


Scheme 204 - Attempts for the intermolecular C-C bond formation

### 4.3.2 Strategy Based on a Liebeskind-Srogl Coupling

Because of the apparent complexity to form the C-C bond between C-2 of indole and the tertiary amide ( $\mathrm{C}-1^{\prime}$ ), we planned another strategy based on a robust reaction to form this crucial bond but still starting from the two same starting materials (Scheme 205).



Scheme 205 - Alternative strategy based on a Liebeskind-Srogl coupling
Late-stage amide bond formation and cyclizations traced back (+)-peganumine $A(4.1)$ to the intermediate 4.157. The latter was disconnected to the functionalized tryptamine 4.159 and the tetrahydro- $\beta$-carboline 4.158 which could be synthesized from 6 -OMe tryptamine (4.27) and the $\alpha$-ketodiacid 4.106 respectively. Formation of the key C-C bond was planned to be realized via a Liebeskind-Srogl coupling between a thioester 4.158 and a C-2 stannyl- or boronic acid-substituted tryptamine 4.159.

The coupling between a thioester and an organoboron was first reported in 2000 by Lanny S. Liebeskind and Jiri Srogl. ${ }^{370}$ The proposed mechanism of this reaction is reported in Scheme 206, A.


Scheme 206 - Mechanism of the Liebeskind-Srogl coupling
Coordination of the thioester 4.161 to the copper(I) weakens the carbonyl sulfur bond (4.162). Oxidative insertion of the palladium (0) to the latter (4.163) followed by transmetalation with 4.164 could afford the palladium (II) species 4.165 . It could then undergo reductive elimination to afford the desired coupled product 4.166 as well as regeneration of the $\mathrm{Pd}(0)$ catalyst. Scheme 206, B shows the proposed transition state for the transmetalation. Hydrogen-bonding between the boronic acid and the TC ligand could help for the activation of the boronic acid and allow a pseudo-intramolecular reaction.

Initially, this reaction was described with catalytic amount of $\operatorname{Pd}(0)$, stoichiometric amount of CuTC and TFP as ligand. Since this initial report, other conditions have been developed including the use of organotin ${ }^{371}$ instead of organoboron as well as palladium-free reactions. ${ }^{372}$ A palladium-free copper-catalyzed reaction ${ }^{373}$ and a one-pot hydroboration/intramolecular Liebeskind-Srogl coupling ${ }^{374}$ have also been reported recently.

[^133]Since the initial discovery, scientists have observed a noticeable change when using CuDPP instead of $\mathrm{CuTC}^{371}$ as well as when using other ligands such as $\mathrm{P}(\mathrm{OEt})_{3} .{ }^{375}$ People have also observed a sol-vent-effect when using organotin coupling partner. ${ }^{371}$ The latter have a strong tendency to be protodestannylated during the reaction. Increasing the amount of hexane as co-solvent slowed down this side reaction. This was attributed to the decrease of the solubility of the copper reagent. Indeed, copper have a strong tendency to perform directly transmetalation with organotin to afford organocopper species ${ }^{376} 4.170$ which cannot react with the thioester giving rise to the formal protodestannylated product 4.171 after workup.

With the idea to use this reaction for the key C-C bond formation we started to explore the route.


Scheme 207 - Pictet-Spengler reaction between tryptamine and the $\alpha$-ketodiacid 4.124
Pictet-Spengler reaction between tryptamine (1.16) and $\alpha$-ketodiacid 4.124 in methanol at room temperature worked perfectly well (Scheme 207) and afforded diacid 4.172 in $95 \%$ yield. ${ }^{377}$ Diacid 4.172 probably acted as the Brønsted acid required for such a transformation. No further amidation/lactamization occurred on the acid 4.172.

Methylation of the diacid 4.172 required the use of $\mathrm{TMSCHN}_{2}$ or $\mathrm{CH}_{2} \mathrm{~N}_{2}{ }^{361}$ because $\mathrm{HCl} / \mathrm{MeOH}$ or $\mathrm{SOCl}_{2} / \mathrm{MeOH}$ gave rise to very slow reactions or to undesired products such as lactamization (Scheme 208). It is to note that trace amount of the triply methylated product 4.174 was observed when using $\mathrm{TMSCHN}_{2}$ in a bit too large excess and too long reaction time. This was quite unusual as normally diazomethane do not react with amines.


## Scheme 208 - Esterification of 4.172 using diazomethane

With the dimethyl ester 4.173 in hands, we turned our attention toward the protection of the secondary amine. Simple treatment of the amine 4.173 with Hünig's base and CbzCl (Scheme 209, A)

[^134]or $\mathrm{BzCl}(\mathrm{B})$ in DCM at $0^{\circ} \mathrm{C}$ followed by heating to $30^{\circ} \mathrm{C}$ afforded the protected amines 4.175 and 4.176 respectively. It is to note that no reaction below $30^{\circ} \mathrm{C}$ was observed probably indicating a steric bulk generated by the two ester side chains around the amine. As the Cbz-protected compound $\mathbf{4 . 1 7 5}$ exhibited some rotamers, which render more complex the NMR spectra analysis, we decided to move forward with the Bz protecting compound 4.176.


Scheme 209 - Protection of the secondary amine 4.173
In order to install the thioester function, mono hydrolysis of the primary ester 4.176 was required. Various bases, solvents, temperatures and times were examined. Hydrolysis of the tertiary ester also occurred very fast and most of the conditions afforded both the mono 4.177 and the diacid 4.179. Finally, heating a solution of the diester 4.176 and NaOH in $\mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O} 1: 1$ to $65{ }^{\circ} \mathrm{C}$ for 5 minutes precisely followed by fast cooling and quenching afforded the mono acid 4.177 in excellent yield (Scheme 210, A). Possible explanation for the fast generation of the diacid 4.179 could arise from the monohydrolysis of the primary ester (4.177), followed by intramolecular anhydride 4.178 formation and subsequent opening of the latter (with attack on the primary carbonyl group) (Scheme 210, B). Coupling of 4.177 with thiophenol in the presence of TBTU and Hünig's base afforded thioester 4.180 in 98\% yield.


Scheme 210 - Monohydrolysis of the primary methyl ester 4.176 and the subsequent thioester 4.180 formation

We then turned our attention towards the synthesis of the second coupling partner. We initially decided to synthesize the boronic acid derivative of protected tryptamine 4.185 (Scheme 211). It was well known that Boc-protected indole derivatives could undergo directed C-2 deprotonation which could then be quenched by a variety of electrophiles.


## Scheme 211 - Attempts for the C-2 directed deprotonation/borylation/hydrolysis sequence of tryptamine derivatives

Use of various bases, temperatures and solvents followed by quench with trimethyl-, ${ }^{378}$ triisopro-pyl- ${ }^{379}$ or isopropylpinacol-borate ${ }^{380}$ did not afford any borylated products 4.185 but led to full recovery of the starting materials. One hypothesis was that the reaction occurred but fast protodeborylation took place afterward leading back to the starting materials.

We then turned our attention towards a reported iridium-catalyzed C-2 borylation reaction (Scheme 212). ${ }^{160,381}$


## Scheme 212 - Iridium-catalyzed C-H borylation

In general, a mixture of many compounds very hard to separate was obtained when submitting 4.186 to the reaction conditions. Among the products, the desired one 4.187 was obtained together with the phthalimide borylated products 4.188 and 4.189. Attempt to slightly modify the reaction conditions using other temperatures and boron source (HBpin) ${ }^{382}$ did not avoid the formation of the side products 4.188 and 4.189. The use of succinimide instead of phthalimide group in order to prevent regioselectivity issue led to the complete absence of reaction which was also

[^135]quite surprising as we did not expect such a drastic change in reactivity by performing this simple change of protecting group.

In parallel to the iridium-catalyzed borylation, we envisioned an alternative palladium-catalyzed borylation of 2-bromoindole derivative 4.190 (Scheme 213).


Scheme 213 - Synthesis of the 2-boronic acid tryptamine derivative 4.193
C-2 bromination ${ }^{383}$ of the phthalimide protected tryptamine 4.186 followed by a Pd-catalyzed Miyaura coupling afforded the desired pinacol boronic ester 4.191 in good yield. ${ }^{384}$ Many conditions were then tested for the hydrolysis of 4.191 which mostly led to side reactions such as protodeborylation. Finally, transformation of the ester 4.191 to the trifluoroborate salt 4.192 followed by its hydrolysis afforded the desired boronic acid 4.193 albeit in low yield.


Scheme 214 - Model study for the Liebeskind-Srogl coupling of 4.180
As there were only two reports using 2-stannyl or boronic acid indole derivatives for LiebeskindSrogl couplings, we decided to perform some initial studies. Coupling between our thioester 4.180 and the commercially available 5-methoxy- $N$-Boc-2-boronic acid indole (4.194) pleasingly afforded the desired product 4.195 under reported conditions (Scheme 214, A). ${ }^{370}$

[^136]We then performed the Liebeskind-Srogl reaction using our real coupling partners 4.180 and 4.193 (Scheme 214, B). The pinacol boronic ester 4.191 and the boronic acid 4.193 were tested. At $60^{\circ} \mathrm{C}$ no reaction of the boronic ester 4.193 was observed. At $90^{\circ} \mathrm{C}$, protodeborylation was the main product observed. At both temperatures, cyclization of the indole nitrogen on the thioester occurred to form lactam 4.196. Similar behavior was observed with the boronic acid 4.193. It is interesting to note that almost no cyclization was observed with the model substrate 4.194. Steric hindrance induced by the C-3 side chain of 4.193 probably slowed down the transmetalation and thus favored the cyclization. It is still unclear whereas the observed product 4.196 arose from simple lactamization on the activated substrate or from a Pd-catalyzed amidation process.

In order to probe the reactivity difference, the tin coupling partner 4.198 was synthesized starting from tryptamine (1.16) (Scheme 215). Mono Boc protection (4.197) followed by second Boc protection afforded the tryptamine derivative 4.181 in good yield. C-2 directed deprotonation followed by quenching with $\mathrm{Bu}_{3} \mathrm{SnCl}$ afforded the very sensitive 4.198 in $89 \%$ yield after careful purification. ${ }^{385}$


Scheme 215 - Synthesis of the stannyl coupling partner 4.198
Because of the low catalytic amount of Pd used in Liebeskind-Srogl reaction conditions, the stannyl indole compound 4.198 has to be very pure and free of other tin impurities. It was well known that tin impurities could sometimes be painful and difficult to remove. Many methods were attempted to purify the product 4.198. A lot of them led to only partial removal of tin by-products or degradation of the desired product. The final solution involved stirring of the crude reaction mixture with some silica gel in ethyl acetate containing $10 \%$ triethylamine followed by flash column chromatography with $3 \%$ triethylamine on neutralized silica gel using a solid deposit of the treated crude mixture.

With both coupling partners in hands, we were then able to try again the Liebeskind-Srogl coupling reaction (Scheme 216).

[^137]

Scheme 216 - Liebeskind-Srogl coupling of the unprotected indole 4.180
Initial attempts with standard conditions did not afford the desired product but important conclusions were drawn from the results. First of all, with the unprotected indole 4.180, cyclization to afford the lactam 4.196 occurred very rapidly and easily only in conditions A. Conditions B afforded only trace amount of the lactam 4.196 with much of the starting material 4.180 left. Secondly, protodestannylation (4.181) was very fast in conditions A but was drastically slowed down if one decreased the solubility of the copper, i.e. using hexane as co-solvent as reported previously (conditions B). ${ }^{371}$ Different sources of copper (CuTC and CuDPP) and of $\mathrm{Pd}(0)\left(\mathrm{Pd}_{2} \mathrm{dba}_{3}, \mathrm{Pd}_{2} \mathrm{dba}_{3} \cdot \mathrm{CHCl}_{3}\right.$ and $\left.\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}\right)$ as well as different ligands (TFP and $\mathrm{P}(\mathrm{OEt})_{3}$ ) all led to the same observations. It is to note that CuDPP was easily synthesized in one step from copper oxide and diphenylphosphinic acid. ${ }^{375}$ One possible explanation for the undesired cyclization in the conditions $B$ was that palladium after the oxidative insertion in the C-S bond could coordinate to the indole nitrogen which could favor the intramolecular cyclization. In conditions A, copper directly underwent the transmetalation with tin, and therefore was not able to coordinate anymore to the thioester, avoiding the formation of the lactam 4.196.

In light of these results, we envisioned protecting the indole nitrogen to avoid this side cyclization (Scheme 217).



Scheme 217 - Synthesis of the protected thioester 4.201
As protection of compound 4.180 only afforded the cyclized product 4.196, we had to perform the protection at an earlier stage. Benzylation of the indole nitrogen on the diester compound 4.176 with NaH and BnBr followed by mono hydrolysis and thioester formation according to the previously developed conditions afforded the protected substrate 4.201 in good yields. It is interesting
to note that double hydrolysis was not observed at all this time even with prolonged reaction time. Increased steric bulk around the ester group after indole protection could explain this result.

Coupling using CuDPP, $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ and $\mathrm{P}(\mathrm{OEt})_{3}$ as ligand in a $5: 1$ or $3: 1$ hexane/THF mixture afforded the desired product 4.202 but only if heated higher than $40^{\circ} \mathrm{C}$ (entry 1-4). Even though the yield was very low, blocking the indole nitrogen and increasing the hexane proportion solved the previously encountered issues. It is to note that the reaction was easier to purify when CuDPP was used. ${ }^{371}$

|  |  |  |  <br> CuDPP, $\mathrm{Pd}_{2} \mathrm{dba}_{3}$, L <br> Hexane/THF 3:1, T |  |
| :---: | :---: | :---: | :---: | :---: |
| Entry | L | Ratio Pd:L | Temperature [ ${ }^{\circ} \mathrm{C}$ ] | Yield [\%] ${ }^{\text {a }}$ |
| 1 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:8 | rt | 0 |
| 2 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:8 | 40 | 0 |
| 3 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:8 | 50 | 21 |
| 4 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:8 | 45 | 18 |
| 5 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:4 | 45 | 35 |
| 6 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:2 | 45 | 56 |
| 7 | $\mathrm{P}(\mathrm{OEt})_{3}$ | 1:1 | 45 | 84 |
| 8 | TFP | 1:8 | 45 | Messy and low conversion |
| 9 | - | - | 45 | 18 (low conversion) |
| 10 | $\mathrm{AsPh}_{3}$ | 1:8 | 45 | Very clean but slow conversion |
| 11 | $\mathrm{AsPh}_{3}$ | 1:1 | 45 | 93 |

(a: Isolated yield)
Table 27 - Optimization of the coupling conditions
We then quickly screened various ligands and Pd:L ratio (Table 27). Decreasing this ratio always led to higher yields (entry 4-7) as already observed in some cases. ${ }^{375,386}$ Moreover, switching P(OEt) ${ }_{3}$ for weaker coordinating ligands was favorable for the reaction (entry 10-11). ${ }^{387}$ In fact no ligand was required for the reaction to proceed, but because of the sensitivity of the "naked" $\operatorname{Pd}(I I)$, the conversion was limited (entry 9). A good balance was found when using $\mathrm{AsPh}_{3}{ }^{388}$ in a 1:1 ratio with $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ to afford the desired product 4.202 in $93 \%$ yield. By limiting its amount and using weaker binding ligands, the rate of the desired reaction was highly enhanced, thus competing with the rate of the undesired protodestannylation process which was slowed down by limiting the solubility of the CuDPP by addition of hexane as co-solvent.

[^138]As the desired product 4.202 and the destannylated indole 4.181 were very hard to separate on column chromatography, further optimization was performed in order to reduce the amount of destannylated indole 4.181 (Table 28).


| Entry | $\mathrm{T}\left[{ }^{\circ} \mathrm{C}\right]$ | $\mathbf{4 . 1 9 8}[$ equiv] | $\mathbf{4 . 2 0 1}[$ equiv] | Yield [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | 45 | 1.5 | 0.25 | 93 |
| 2 | 30 | 1.5 | 0.25 | 94 |
| 3 | rt | 1.5 | 0.25 | 94 |
| 4 | rt | 1.2 | 0.1 | 94 |
| 5 | rt | 1.1 | 0.1 | $89+$ trace of the thioester |

(a: Isolated yield)

Table 28 - Final optimization to avoid the formation of the destannylated product
Decreasing the temperature (entry 1-3) and the amount of stannyl 4.198 (entry 4-5) mainly allowed us to avoid the formation of the destannylated byproduct without decreasing the yield of the desired product thus allowing an easier purification. We were also able to reduce the amount of the Pd catalyst down to $10 \mathrm{~mol} \%$ (entry 4-5). It is interesting to note that, in the optimized conditions, the reaction proceeded even at room temperature, showing the increased reactivity when using weaker binding ligands.

With the coupled product in hands, we then turned our attention toward the deprotection of the tryptamine side chain.


Scheme 218 - N-Boc-deprotection/cyclization sequence
TFA-mediated removal of the Boc protecting groups afforded cleanly a primary amine which, as expected, spontaneously cyclized on the ketone to give the dihydrocarboline product 4.203 (Scheme 218).

The next plan was to perform the hydrolysis of the methyl ester 4.203 in order to form the required amide bond. Many conditions were attempted leading most of the time to a very messy
mixture. No desired product was observed. One of the main side product observed was the oxidation of the dihydrocarboline to the fully aromatic system 4.204 with concomitant hydrolysis of the ester (Scheme 219). Similar oxidation processes were known to occur under high temperature conditions. ${ }^{389}$ Careful degassing of the solvents and using glovebox conditions did not solved the issue.


Scheme 219 - Main side reaction observed during the hydrolysis of the hindered methyl ester 4.203
Such oxidation process was highly favored due to the formation of the fully aromatic system, adding an extra ${ }^{\sim} 25 \mathrm{kcal} / \mathrm{mol}$ of stability to the product.

In order to avoid the oxidation of the $\beta$-carboline, we attempted the hydrolysis of the ester on the uncyclized system 4.202 (Scheme 220, A). Again, very messy reactions were observed without detection of the desired product. Pushing the conditions often led to the removal of the Boc group on the indole, as expected.


Scheme 220 - Hydrolysis and reduction of 4.202
One hypothesis for the resistance of 4.202 to hydrolysis was that the Bn group on the indole could create a steric hindrance big enough to shield completely the neighboring ester function. The Bz protecting group could also increase significantly the steric bulk around it as already observed on Scheme 209. We also tried other deprotection methods such as Ohfune's conditions as the attack could occurred on the less hindered methyl group instead of on the carbonyl itself but these conditions led to very complex mixture of products. Boc protecting group was known to be easily cleaved under these conditions.

To limit the steric hindrance and allow an easier hydrolysis of the ester, we attempted to remove the benzyl group (Scheme 220, B). Various conditions were screened such as hydrogenation in the presence of various catalyst or reduction using metallic Na , but most of them led to the recovery of the starting material or full degradation when heated too much.

[^139]Being unable to hydrolysis the ester 4.202 and 4.203, we then tried to promote the cyclization of the imine 4.203 directly onto the methyl ester by either strong heating or in basic conditions ${ }^{390}$ to form the enamine 4.207 (Scheme 221, A) or in acidic or reductive conditions ${ }^{391}$ to remove the Bz group and promote the full cyclization (Scheme 221, B).


Scheme 221 - Attempts for the direct cyclization of imine 4.203
Treatment of the dihydrocarboline 4.203 with LDA or BuLi at low temperature followed by heating at reflux in THF for an extended period of time did not promote any cyclization and the starting material 4.203 was recovered. Heating the same compound with HCl in MeOH gave back the starting material whereas using HBr in AcOH afforded a very complex mixture of products. Decarboxylation could occur in these last conditions as observed on Scheme 201. Finally, heating the compound 4.203 in diphenyl ether at $200^{\circ} \mathrm{C}$ under microwave irradiation promoted full decomposition of the starting material.

Because of the impossibility to remove the protecting groups, we revised again slightly our strategy. We decided to use more labile protecting groups on both nitrogens of 4.212 like Boc or Moz. This could allow an easier deprotection and therefore facilitate the hydrolysis of the methyl ester 4.211 or the cyclization of the tetrahydrocarboline nitrogen directly onto the dihydrocarboline imine (4.211 to 4.210) (Scheme 222).


Scheme 222 - Refinement of the strategy relying on the use of a more labile protecting group
We therefore attempted the double Boc protection of the secondary amine 4.173.

[^140]

Scheme 223 －Attempts for the double Boc－protection of 4.173
Treatment of the diester compound 4.173 with $\mathrm{Boc}_{2} \mathrm{O}$ and DMAP（with or without base）afforded the indole－protected compound 4．214．Slight heating，acidic work－up or attempt for any kind of purification afforded the $\gamma$－lactam 4.215 cleanly（Scheme 223）．The easier cyclization of 4.214 compared to 4.173 again confirmed the steric hindrance induce by the protection of the indole， pushing the esters toward the amine．We attempted other conditions to force the Boc protection of the secondary amine without success and the lactam 4.215 was always obtained．As already described in Scheme 209，without protection of the indole ring，a temperature above $30^{\circ} \mathrm{C}$ was required to protect the secondary amine．Because of the increased steric bulk，higher temperature could be required but in these conditions，the intramolecular cyclization was faster．Because $\mathrm{Boc}_{2} \mathrm{O}$ was thought to be not reactive enough，we synthesized other uncommon Boc precursors like $\mathrm{BocCl}, \mathrm{BocF}$ and $\mathrm{BocN}_{3}$ which were all known to be much more reactive but also less stable （Scheme 224）．

BocCl（4．217）was synthesized from triphosgen（4．218）and used without purification（known to decompose already at room temperature）（Scheme 224，A）．${ }^{392}$ Boc azide（4．219）was synthesized using hydrazine $4.218^{393}$（B）and BocF（4．221）starting from the carbamate 4.220 （C）．${ }^{394}$ Both of them were purified before use．


Scheme 224 －Synthesis of various Boc precursors

[^141]Heating was still required with all three reagents and no reaction was observed apart indole Boc protection (4.214) and lactamization (4.215) probably because of the degradation of the highly unstable BocX at these "high" temperatures (about $40^{\circ} \mathrm{C}$ ). The indole nitrogen was probably protected first, increasing the steric bulk around the amine and thus rendering its protection harder.

Direct protection of the secondary amine 4.173 with Fmoc, $\mathrm{Moz}^{395}$ and Teoc ${ }^{396}$ did not afforded the desired doubly protected products or in very low yield ( $<5 \%$ ) probably because the reagents were unstable at the temperature required for the reaction ( $\mathrm{FmocCl}, \mathrm{TeocCl}, \mathrm{MozCl}$ ) or because of too low reactivity (Teoc-succinimide).

In order to be more flexible on the protecting group one could introduce on the secondary amine, we decided first to synthesize the acyl chloride derivative 4.222 and to make it react with various oxygen-based nucleophiles (Scheme 225). We thought that introduction of $\mathrm{C}(\mathrm{O}) \mathrm{Cl}$ could be more easy because of the small steric hindrance of phosgene compare to $\mathrm{Boc}_{2} \mathrm{O}$ for instance. We were indeed able to functionalize the secondary amine 4.173. The synthesized carbamoyl chloride 4.222 proved to be stable to aqueous work-up and even to flash column chromatography on silica gel. It was in fact so stable that all attempts to make it react with tert-butanol, methanol or Moz alcohol failed.


## Scheme 225 - Synthesis of the acyl chloride 4.222 followed by the undesired intramolecular cyclization under basic conditions

When harsher conditions were used, i.e. using strong bases such as NaOMe or $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$, no direct attack of these nucleophiles onto the acyl chloride was observed. Instead, deprotonation $\alpha$ to the ester 4.222 followed by Dieckmann condensation was observed (4.223).

Because of the issue of the methyl ester hydrolysis, we planned to form the amide bond earlier in the synthesis and we therefore revised our strategy (Scheme 226).

[^142]

Scheme 226 - Refinement of the strategy based on an intramolecular Liebeskind-Srogl coupling
The idea was to perform the Liebeskind-Srogl coupling in an intramolecular fashion. We knew from our previous strategies that the indole nitrogen and the secondary amine had to be protected in order to avoid undesired cyclizations. We therefore attempted to push the hydrolysis of the two methyl esters on the fully protected system 4.199 (Scheme 226, A). As expected, only mono hydrolysis was observed even when harshening the reaction conditions indicating again the steric effect induced by the benzyl group (Scheme 227, A).


Scheme 227 - Difference of reactivity between the protected and the free indole during hydrolysis
We previously had issue for the mono-hydrolysis of the methyl ester when using unprotected 4.176 and we had to use a very short reaction time in order to be selective ( $<5$ minutes) (Scheme 227, B). With the protected substrate 4.199, even 5 days reaction time did not afford the double hydrolyzed product (Scheme 227, A). It was therefore clear that we had to hydrolyze the two esters before protecting the indole nitrogen (Scheme 226, B).

The diacid 4.179 was submitted to many different reaction conditions in order to protect the indole nitrogen (Scheme 228). Most of the conditions afforded cleanly the cyclized product 4.227 probably via formation of a mixed anhydride followed by nucleophilic attack of the indole nitrogen (Scheme 228, A). Biphasic mixture was known to normally prevent this kind of reaction as initially reported by Schotten and Baumann. ${ }^{397}$ Nevertheless, even with the use of such conditions, the undesired cyclization was observed. Use of strong bases to form the tri-anion followed by quench with various protecting group precursors did not lead to any reaction probably because of the insolubility of the latter (Scheme 228, B).


Scheme 228 - Attempts for the indole protection on the diacid 4.179

[^143]Lactam 4.229 was also the major product obtained when the fully unprotected starting material 4.172 was used (Scheme 229). Interestingly, lactam formation occurred exclusively with the indole nitrogen and not with the secondary amine in spite of the fact that secondary amines are normally more nucleophilic than indole nitrogen. This could indicate that initial protection of the secondary amine occurred before the lactamization took place.


Scheme 229 - Attempts for the indole protection on the diacid 4.172
We also attempted the protection of the indole nitrogen on the mono-thioester 4.179 (Scheme 231).


Scheme 230 - Synthesis of the mono-thioester 4.230
Selective formation of the thioester on the diacid 4.179 afforded compound 4.230 (Scheme 230) without trace amount of the dithioester or lactam 4.227.

We then attempted to protection of 4.230. Using biphasic mixture always led to very fast hydrolysis of the thioester in this case (Scheme 231, A). DMAP could be responsible for the activation of the thioester to facilitate the hydrolysis. Another alternative mechanism could be the direct attack of the acid onto the thioester to form the cyclic mixed anhydride followed by hydrolysis of the latter. Using strictly anhydrous conditions afforded the clean formation of the lactam 4.227 (B).


Scheme 231 - Attempts for the indole protection on the mono-thioester 4.230
Comparing the use of a strong base in the presence of 4.230 with the one in the presence of 4.176 (Scheme 217), one can clearly see the higher reactivity of the thioester 4.230. Indeed in the case of the methyl ester 4.176, no lactam formation was observed.

Playing extensively on protecting groups did not lead to any advance in the synthesis and we therefore decided to change radically the retrosynthetic pathway.

### 4.3.3 Strategy Based on an Liebeskind-Srogl Coupling/Passerini Reaction

From the previous unsuccessful strategies, the following conclusions were drawn:

- The bond between the $\mathrm{C}-2$ position of indole ( $\mathrm{C}-13^{\prime}$ ) and the aminal carbon $\mathrm{C}-1^{\prime}$ was difficult to construct except when using the Liebeskind-Srogl coupling conditions.
- The steric hindrance was big around C-1. Moreover, in the real substrate, the gemdimethyl substituents at $\mathrm{C}-16$ could even add more steric bulk around this center.
- Competitive lactamizations were very hard to avoid and protecting group strategy was difficult to put into practice.

We therefore revised our strategy. We planned the late-stage formation of the second $\beta$-carboline on the left of the molecule (Scheme 232, A). Previous strategies focused on the construction of the the right $\beta$-carboline as last step (Scheme 232, B).


Scheme 232 - Complete change of strategy

### 4.3.3.1 Intramolecular Liebeskind-Srogl Coupling

Initial disconnection (Scheme 233) was planned around the C-1 via an enantioselective PictetSpengler reaction (4.233) followed by a transannular cyclization. It traced back (+)-peganumine A (4.1) to the tetracyclic lactam 4.234 and $6-O M e$ tryptamine (4.27). Despite the fact that PictetSpengler reactions were known to be very sensitive to steric hindrance, we hypothesized that the electron-rich tryptamine derivative (4.27) could be much more reactive in this kind of reaction, as already described. Moreover, $\alpha$-ketoamides were known to be highly reactive towards nucleophilic additions. Combination of both factors could compensate the high steric hindrance induced by the gem-dimethyl substituents. For the construction of 4.234, we imagined an intramolecular Liebeskind-Srogl coupling on 4.236, followed by a transannular cyclization of the product 4.235. Only few reports dealt with ring closing using the Liebeskind-Srogl coupling. ${ }^{374,398}$ Nevertheless, broad functional group tolerance and promising existing reports about medium-sized ring construction prompted us to examine this route. The $\alpha$-ketoamide 4.236 was disconnected to the isonitrile 4.237 and to the aldehyde 4.238. In the forward direction, a Passerini reaction followed by functional groups manipulation could afford 4.236. Both partners were planned to be accessed from 6 -OMe tryptamine (4.27) and the simple ester 4.239 via simple functional group manipulation.

[^144]


Scheme 233 - Retrosynthetic pathway featuring a key intramolecular Liebeskind-Srogl coupling
Having already experienced similar chemistry in our previous strategies, we first synthesized the stannyl moiety 4.243 (Scheme 234).


Scheme 234 - Synthesis of the stannyl building block 4.243
Starting from tryptamine (1.16), we performed a formylation using methyl formate at $55^{\circ} \mathrm{C}$ followed by a Boc protection of the indole to afford the protected tryptamine 4.241 in $72 \%$ yield overall yield. We then used a directed deprotonation using the Boc functional group to install the $\mathrm{SnBu}_{3}$ at the position 2 of indole. ${ }^{385}$ Here again, the triethylamine trick for the purification afforded a clean product 4.242 without tin impurities. We then submitted this compound 4.242 to dehydration conditions in the presence of a large excess of base ( $\mathrm{NEt}_{3}$ ) to avoid the destannylation. It converted the formamide ${ }^{399} 4.242$ to the desired isocyanide 4.243 in $73 \%$ yield.

The thioester fragment 4.238 had then to be synthesized. Formation of the orthoacetate 4.245 starting from prenol (4.244) followed by an Ireland-Claisen rearrangement afforded the ester $4.246^{400}$ in good yields. It was subsequently hydrolyzed to its acid derivative 4.247 using simply NaOH (Scheme 235, A). ${ }^{400 \mathrm{a}}$

[^145]

Scheme 235 - Synthesis of the thioester-aldehyde 4.238
Ozonolysis of the alkene 4.247 followed by reductive quench of the ozonoide with DMS afforded the 1,4-dicarbonyl compound $4.248{ }^{401}$ which spontaneously cyclized to the hydroxylactone 4.249 during its purification or during every attempt to form the thioester on the crude mixture (Scheme $235, B)$. Similar compounds were indeed known to be in equilibrium with their cyclized form. ${ }^{402}$ Even though it could have been possible to convert the lactone 4.249 to the desired thioester 4.238 by in situ lactone opening, we preferred the option to reverse the two steps in order to avoid this issue (C). Thioester $\mathbf{4 . 2 5 0}$ formation using TFAA and thiophenol ${ }^{403}$ followed by ozonolysis with triphenylphosphine as reductant ${ }^{404}$ afforded the desired coupling partner 4.238 in excellent overall yield. Great care had to be taken during the ozonolysis step in order to avoid as much as possible the oxidation of the sulfur. Moreover, purification of 4.238 proved to be challenging as this compound was unstable probably because of easy hemiacetal formation and subsequent lactonization to afford 4.249 and thiophenol.

With both coupling partners in hands, we attempted the intermolecular Passerini reaction. ${ }^{405}$ Stirring a diethyl ether solution of 4.243, 4.238 and benzoic acid at room temperature afforded 70\% of the desired product 4.251 and $15 \%$ of the destannylated one 4.252 (Scheme 236, A). Submitting the former to the previously developed reaction conditions for the Liebeskind-Srogl coupling afforded only the destannylated product 4.251 among other side products (B). Rescreening of the reaction conditions did not lead to any trace amount of desired product 4.253. 10-membered rings are known to generally be very difficult to make because of their ring strains. As the intramolecular reaction had to be favored in comparison to the intermolecular one, relatively high dilutions were used. This could result in a slower reaction rate as both the palladium and the copper needed to interact with the thioester $\mathbf{4 . 2 5 2}$ before any cyclization could occur. On the other hand, copper alone could perform the transmetalation directly on the stannyl 4.252 without the need for

[^146]palladium and this side reaction could occur at a faster rate than the desired one. Activation of the thioester with the copper could also favor the 6-membered imide formation with the amide.


Scheme 236 - Intermolecular Passerini reaction and the attempts for the intramolecular Liebeskind-Srogl coupling

Being confident about our Pictet-Spengler/transannular cyclization cascade strategy, we identified another pathway for the construction of $\mathbf{4 . 2 3 4}$.

### 4.3.3.2 Intramolecular Passerini/Ugi Reaction



Scheme 237 - Retrosynthetic pathway featuring a key intramolecular Passerini macrocyclization
The lactam 4.235 could be disconnected into two different ways. Disconnection of the C-N bond could be imagined and its formation would rely on a traditional macrolactamization (A). On the other hand, disconnection of the 1,2-dicarbonyl unit 4.235 traced it back to the $\omega$-isocyano carbonyl compound 4.255 (B). The presence of the $\alpha$-ketoamide function allowed us to hypothesize a
completely novel method for the synthesis of this cyclic lactam. In the forward synthesis, this bond could be made via intramolecular Passerini ${ }^{49}$ or Nef-isonitrile ${ }^{43 a}$ reaction for instance. The formed 10-membered ring could then spontaneously cyclized in a transannular fashion to afford the tetracyclic system 4.234. The $\omega$-isocyanocarbonyl 4.255 was then traced back to the thioester $\mathbf{4 . 2 5 6}$ and the 2 -stannyl tryptamine derivative $\mathbf{4 . 2 4 2}$. As previously described, this bond was planned to be formed via a Liebeskind-Srogl coupling. This reaction was proved to be very efficient for the construct of this crucial bond in the previous strategy.

This new strategy involved the tethering of the isonitrile and the carbonyl moieties, making of the Passerini 3-component a simple 2-component three-center reaction. The tethering of functional groups in Passerini/Ugi reactions was known and has already been exploited extensively (see 5.1.2 - Reported Macrocyclization Methods Based on Isonitriles). ${ }^{21}$ Nevertheless, no reports existed on the tethering of the isonitrile with the carbonyl. In his comprehensive review, ${ }^{50}$ Banfi mentioned (unpublished results) that 4-isocyanobutanal has been employed in a Passerini 2-component 3center reaction. However, no desired product was obtained. Despite the lack of literature precedent, we hypothesized that this novel macrocyclization method, if successfully achieved, would allow the development of this methodology beyond the scope of this total synthesis (see Chapter 5 - Macrocyclization of $\omega$-Isocyanoaldehydes).

We initially envisioned a one-pot Nef-isonitrile reaction starting from a tethered formamide - carboxylic acid. Indeed, $\mathrm{PCl}_{5}$ was known to convert carboxylic acid into acyl chloride. ${ }^{406}$ Moreover, $\mathrm{PCl}_{5}$ in the presence of triethylamine was also known to promote the dehydration of formamide into isonitrile. ${ }^{407}$ This could allow us to obtain $\mathbf{2 . 2 3 4}$ from $\mathbf{2 . 2 5 5}$ (via $\mathbf{4 . 2 3 5}$ ) in a single step.


Scheme 238 - Synthesis of the thioester coupling partner 4.260
Allylation of the ester 4.257 with LDA as base ${ }^{408}$ followed by Lemieux-von Rudloff oxidation ${ }^{409}$ of 4.258 afforded the acid 4.259. The latter was converted to the required thioester 4.260 using the previously developed conditions (TFAA, PhSH, DCM, rt) (Scheme 238).

[^147]

Scheme 239 - Coupling between 4.242 and 4.260 followed by hydrolysis
Coupling between 4.260 and the tryptamine derivative 4.242 under the previously developed conditions afforded very cleanly the desired product 4.261 in $96 \%$ yield. Saponification of the ester 4.261 afforded the desired acid 4.262 as well as a 6-membered lactam 4.263 (Scheme 239). ${ }^{410}$ The latter was formed by the N -Boc deprotection followed by lactamization. It is interesting to note the relatively low stability of the Boc protecting group under basic conditions. This could be explained by the presence of the C-2 carbonyl substituent. The ratio of the two products 4.262 and 4.263 varied depending on the reaction conditions and scale.

Treatment of 4.262 with $\mathrm{POCl}_{3}$ and a base failed to produce the desired tetracycle 4.264 (Scheme 240, A). Other dehydrating agents did not produce any better results. The messy mixtures obtained were probably due to: 1) the unstability of the generated isonitrile at the temperatures required to convert the highly hindered acid to the acyl chloride; Indeed, carboxylic acid and isonitrile were known to react together at relatively high temperature ${ }^{411} 2$ ) the possible uncontrolled reaction between the isonitrile and the acyl chloride at high temperature and 3) the possible side reactions arising from the reaction of the imidoyl chloride intermediate with the acid.


Scheme 240 - Attempts for the one pot acyl chloride formation/dehydration/Nef-isonitrile reaction In light of these results, a stepwise sequence was pursued. Conversion of the formamide 4.261 to the isonitrile 4.265 with $\mathrm{PCl}_{5}$ and triethylamine worked efficiently when the ester derivative was

[^148]used as starting material (Scheme 240, B). Subsequent ester hydrolysis revealed very troublesome in our hands. Different conditions were attempted for this reaction but none of them proved to be efficient. The reasons could be the relative unstability of isonitriles, the undesired reactions between the acid and the isonitrile as previously mentioned or the low stability of the $N$-Boc group as already observed.

Because of the impossibility to access the tethered isocyano-carboxylic acid, we moved forwards our second idea; the use of an intramolecular Passerini/Ugi reaction, i.e. having an isonitrile and an aldehyde on the same molecule (Scheme 241).


Scheme 241 - Coupling between 4.242 and 4.238 followed by dehydration and intramolecular Passerini reaction

Coupling between the tryptamine derivative 4.242 and the thioester-aldehyde 4.238 worked again very well under the optimized conditions. We were then able to promote the dehydration of the formamide 4.267 to the isonitrile 4.268 in the presence of the aldehyde in $89 \%$ yield. Low temperature as well as careful purification on alumina was required in order to avoid any decomposition. With this unstable compound 4.268 in hands we then submitted it to Passerini conditions using benzoic acid in DCM and, to our delight, we obtained directly the transannular cyclized product 4.253 as initially planned. We then had to convert the OBz group of 4.253 into the ketone 4.264 via the free alcohol 4.269. We therefore attempted the deprotection of the benzoyl group. ${ }^{412} \mathrm{Re}$ sults were not really reproducible and deprotection of the Boc (4.270) sometimes occurred during the process especially on larger scale. Again the C-2 carbonyl group could be responsible for this facile deprotection.

In order to facilitate the deprotection step, we performed the Passerini reaction using acetic acid instead of benzoic acid and we were then able to remove it much cleanly without observed deprotection of the indole (Scheme 242, A). A much shorter reaction time was required to obtain complete conversion of 4.271 to 4.269 compared to 4.253 . In order to avoid this non-constructive deprotection step, we performed the Passerini reaction using TFA (buffered with pyridine) which readily afforded $\mathbf{4 . 2 6 9}$ after the work-up (Scheme 242, B and Scheme 243, A) as previously report-

[^149]ed. ${ }^{413}$ We were therefore able to obtain the alcohol 4.269 in one single step from 4.268. Omission of pyridine as well as the use of other bases such as triethylamine proved to be messier as previously reported. The reason why pyridine was a much better base is still unclear. Two hypotheses were given in the literature. The pyrridinium 4.274 was proposed as weaker acid for the activation of aldehyde 1.109. Moreover, possible reversible trapping of the protonated isonitrile 1.99 (Scheme 243, B) could prevent imide 4.279 formation (C) with the highly acidic TFA. ${ }^{414}$ In our case, it also probably prevented the TFA-catalyzed Boc deprotection.


Scheme 242 - Alternative Passerini reaction to the $\alpha$-hydroxyamide 4.269


Scheme 243 - TFA/Py combination for Passerini reaction
With the alcohol 4.269 in hands, we then turned our attention towards its oxidation to the ketone 4.264 which turned out to be a surprisingly tricky task. Indeed, indole and enamine were also prone to oxidation (Scheme 244, B). ${ }^{415}$ After extensive screening, we finally found that the

[^150]Swern ${ }^{416}$ or the Corey-Kim ${ }^{417}$ oxidation conditions at $-78^{\circ} \mathrm{C}$ only afforded the desired product 4.264 (Scheme 244, A). Warming the reaction mixture to $-40^{\circ} \mathrm{C}$ after the addition of the base caused the reaction to become very messy. Both of these methods are based on the same mechanism and only the way of generating the key chlorodimethylsulfonium ion $\mathbf{4 . 2 8 0}$ differs. By comparing the two oxidation methods, the Corey-Kim procedure ${ }^{418}$ proved to be the cleanest and the one which gave a higher yield.


Scheme 244 - Oxidation of the alcohol 4.269 to the $\alpha$-ketoamide 4.264
We then decided to move towards to the more challenging task of obtaining the $\alpha$-ketoamide in a single step from 4.268 using our previously described procedure presented in Scheme 10 (Scheme 245).


## Scheme 245 - Oxidative Ugi cyclization for the synthesis of the $\alpha$-ketoamide 4.264

The use of the original reported conditions led mainly to polymerization (Table 29, entry 1) and we therefore started to optimize the conditions.

| Entry | Concentration [M] | MeNHOH $\cdot \mathrm{HCl}$ [equiv] | Yield of 4.264 [\%] ${ }^{\text {a }}$ |
| :---: | :---: | :---: | :---: |
| $1^{\mathrm{b}}$ | 0.1 | 1.1 | Polymerization |
| $2^{\mathrm{b}}$ | 0.01 | 1.1 | $35+50$ of $\mathbf{4 . 2 7 1}$ |
| $3^{\mathrm{b}}$ | 0.01 | 2 | $60+10$ of $\mathbf{4 . 2 7 1}$ |
| $4^{\mathrm{b}}$ | 0.01 | 3 | $75+3$ of $\mathbf{4 . 2 7 1}$ |
| $5^{\mathrm{b}}$ | 0.01 | 5 | 74 |
| $6^{\mathrm{c}}$ | 0.01 | 3 | 73 |

(a: Isolated yield; b: 30 min before adding $\mathrm{AcOH} ; \mathrm{c}: 2 \mathrm{~h}$ before adding AcOH )
Table 29 - Optimization of the oxidative Ugi cyclization of 4.268

[^151]Decreasing the concentration to 0.01 M , a more standard condition for intramolecular reaction, furnished the desired product 4.264 in $35 \%$ yield. In addition, $50 \%$ of the Passerini adduct 4.271 was observed (entry 2). We hypothesized that the formation of the oxime was too slow to prevent the Passerini reaction to occur. We therefore increased the amount of $\mathrm{MeNHOH} \cdot \mathrm{HCl}$ to 2 (entry 3) and then 3 equivalents (entry 4). We observed an increase in the yield of the product 4.264 and a decrease of the Passerini adduct 4.271. Increasing further the amount of hydroxylamine (entry 5) or waiting a longer time for the formation of the oxime before adding the acetic acid (entry 6) did not give better results.

We were really surprised about the relative ease of the transannular cyclization given the low nucleophilicity of the amide and the relatively low electrophilicity of the ketone. Computational studies offered us a very simple answer.


Figure 35 - DFT computation of the $\alpha$-ketoamide macrocycle before the transannular cyclization
The hypothesized intermediate of the macrocyclization/transannular cyclization, for instance ketone 4.235 in the case of the oxidative Ugi reaction, was computed (DFT, 6-31G+(d), B3LYP). The observed structure revealed a very important feature. The angle between the nitrogen of the amide and the reactive ketone was found to be $105^{\circ}$ which represented the almost perfect BürgiDunitz angle ${ }^{174}$ and the C-N distance was $3.228 \AA$. In fact, this famous angle was initially determined by analysis of the X-ray structure of various natural products, some of them very similar to 4.235 (Figure 36). ${ }^{419}$

[^152]


$110.2^{\circ}$

Figure 36 - Compounds used for the initial determination of the Bürgi-Dunitz angle
Having found an efficient way to access the $\alpha$-ketoamide 4.264, the last Pictet-Spengler/cyclization cascade could be attempted. We first refluxed the $\alpha$-ketoamide 4.264 with tryptamine (1.16) in the presence of $4 \AA$ molecular sieves in order to form an imine. After 24 hours, we then added various amount of TFA and heated at different temperatures to promote the cyclization (Table 30).


Table 30 - Optimization of the last cascade sequence
Heating at $65^{\circ} \mathrm{C}$ with excess (entry 1 ) or catalytic amount (entry 2) of TFA only afforded the intermediates 4.289 and 4.290 , meaning that the Pictet-Spengler reaction occurred but that the resulting intermediates did not undergo fully the subsequent cyclization/deprotection. We therefore attempted to heat to higher temperature. At $110{ }^{\circ} \mathrm{C}$ the desired product 4.291 was obtained in $45 \%$ yield but the intermediates 4.289 and 4.290 were still present (entry 3 ). Lowering the amount of TFA to 0.2 equivalents afforded $89 \%$ of the desired product 4.291 with no trace amount of the starting material 4.264 or of the intermediates 4.289 and 4.290 . We hypothesized that excess of TFA could fully protonate the formed basic secondary amine 4.289 preventing further attack of the latter into the $N$-acyl iminium. We also observed that all the isolated intermediates 4.289 and 4.290 still contained the Boc group.

Encouraged by these results, we envisioned to perform this reaction in an enantioselective way. Because it was well known that 6 -OMe tryptamine (4.27) and tryptamine (1.16) reacted at very different rates and with very different ee outcomes, ${ }^{318 a}$ we decided to use directly 6-OMe tryptamine (4.27) for the optimization.


Scheme 246 - Racemic Pictet-Spengler reaction of 4.264 and 6-OMe tryptamine
Racemic reaction between the $\alpha$-ketoamide 4.264 and 6 -OMe tryptamine (4.27) in the same previously developed conditions indeed afforded the desired $9^{\prime}$-desmethoxy peganumine A rac-4.293 and its $N$-Boc derivative rac-4.292 in a 5:1 mixture (Scheme 246). As expected, this reaction was slightly faster than the one with unsubstituted tryptamine (1.17) probably because of the electrondonating properties of the MeO substituent.

We then quickly screened the conditions for the enantioselective induction using the chiral phosphoric acid ent-4.36 (Table 31). ${ }^{314}$ In our case, we hypothesized that the gem-dimethyl substituents would prevent any side condensation as observed by List and coworkers (Scheme 180, A).

(a: Isolated yield; b: determined by SFC)
Table 31 - Optimization of the enantioselective Pictet-Spengler reaction of 4.264 and 4.27 catalyzed by the chiral phosphoric acid ent-4.36

Heating to $40^{\circ} \mathrm{C}$ after imine formation only afforded a trace amount of the intermediates 4.294 and 4.292 with extremely poor conversion even after a long reaction time (entry 1-2). Heating to $65^{\circ} \mathrm{C}$ for 5 days afforded the desired product 4.293 in a low $7 \%$ yield together with a small amount of intermediates 4.292 and 4.294 and a lot of starting material 4.264 (entry 3). Despite the low quantity obtained, we were able to determine the enantio-enrichment of the desired product 4.293 but only $30 \%$ ee was detected. In the List's original report, the required temperature to obtain good ee was $-10^{\circ} \mathrm{C}$. In our case, in order to keep a decent conversion, higher temperature
needed to be used. The steric hindrance as well as the lack of Thorpe-Ingold effect could explain the lower reactivity of our substrate $\mathbf{4 . 2 6 4}$ compared to List's ones.

We decided to move forward the use of another chiral catalyst: the Jacobsen's thiourea 4.53.


Scheme 247 - Synthesis of the thiourea catalyst 4.53
Synthesis of the best catalyst reported by Jacobsen ${ }^{318 a}$ (Scheme 247) started with the amidation of Boc-L-valine (4.295) followed by Boc deprotection in acidic conditions to afford the ammonium salt 4.297 in $95 \%$ yield. Reaction of 4.297 with the isothiocyanate 4.298 in the presence of $\mathrm{NEt}_{3}$ afforded the desired thiourea 4.53 in $87 \%$ yield.

With the catalyst 4.53 in hands, we then optimized the enantioselective reaction (Table 32).


| Entry | Temperature $\left[{ }^{\circ} \mathrm{C}\right]$ | Co-Solvent | Yield [\%] ${ }^{\text {a }}$ | $e r^{\mathrm{b}}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | rt for 5 days | - | Trace of DP + <br> intermediates + SM | ND |
| 2 | 35 for 7 days | - | DP + intermediates <br> + SM (ratio 1:5:15) | $96: 4$ |
| 3 | 60 for 5 days | - | $54+12$ intermediates | $93: 7$ |
| 3 | 60 for 10 days | - | 85 SM | 93 |


| $(0.2$ equiv)/reflux for 2 days |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| 9 c | Same as entry 8 | $10 \%$ DCM | 66 | $95: 5$ |
| $10^{\mathrm{d}}$ | Same as entry 8 | $10 \%$ DCM | 54 | $94: 6$ |
| $11^{\mathrm{e}}$ | Same as entry 8 | $10 \%$ DCM | 34 | $95: 5$ |

(a: Isolated yield; b: determined by SFC; c: with $3 \AA$ MS; d: with $5 \AA$ MS; e: without preformation of the imine)
Table 32 - Optimization of the enantioselective Pictet-Spengler reaction of 4.264 and 4.27 catalyzed by the chiral thiourea 4.53

Reaction of 4.264 with 4.27 catalyzed by 20 mol\% 4.53 and 20 mol\% benzoic acid at room temperature did not promote the reaction to a sufficient extend (entry 1). Heating to $35^{\circ} \mathrm{C}$ for 7 days afforded the desired product 4.293 with an excellent ee (92\%) albeit with very low yield (entry 2 ). The same reaction at $60^{\circ} \mathrm{C}$ afforded the desired product 4.293 in $54 \%$ yield as well as some intermediates 4.292 and 4.294 and some starting material 4.264 (entry 3). The measured ee was $86 \%$. Prolonged reaction time ( 10 days) afforded the desired product in $80 \%$ yield with $86 \%$ ee (entry 4 ). We observed that the reaction became heterogeneous after 24 hours. We hypothesized that the reaction intermediates could be relatively insoluble in toluene. We therefore decided to add 20\% DCM as co-solvent in order to solubilize them. 6 days of reaction at $40{ }^{\circ} \mathrm{C}$ afforded the desired compound in $65 \%$ with $87: 13$ er (entry 5). Reaction performed with only $10 \%$ DCM at $35^{\circ} \mathrm{C}$ delivered 4.293 in $69 \%$ yield with $90 \%$ ee (entry 6). The same reaction at $40^{\circ} \mathrm{C}$ gave 4.293 with a better ee (90\%) but in a slightly lower yield (entry 7).

We then hypothesized that only the initial step (the Pictet-Spengler) required the use of the chiral catalyst and of the weak Brønsted acid. We also reasoned that the isomerization of the enamine to the iminium as well as the Boc deprotection may require stronger acid. We therefore decided to add $20 \mathrm{~mol} \%$ TFA and to heat the reaction mixture at reflux once the full conversion of the imine to intermediate 4.294 as observed by TLC. Performing the Pictet-Spengler reaction at $35{ }^{\circ} \mathrm{C}$ for 4 days followed by the addition of TFA and 2 days at reflux afforded 4.293 in $69 \%$ yield with $92 \%$ ee (entry 8).

We then investigated the influence of the molecular sieves. The use of 3 or $5 \AA$ molecular sieves afforded the desired product 4.293 albeit in lower yield but with similar ee (entry 9-10) than that with $4 \AA$ Å ones. Finally, submitting directly the mixture of 4.264 and 4.27 without preformation of the imine to the reaction conditions promoted the formation of 4.293 in a lower yield but with a similar enantioselectivity (entry 11).


| Entry | HA | Equiv [mol\%] | Yield [\%] ${ }^{\text {a }}$ | $e r^{\text {b }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | BzOH | 20 | 69 | $96: 4$ |
| 2 | AcOH | 20 | 44 | $88: 12$ |
| 3 | $4-0 M e ~ B z O H$ | 20 | 59 | $95: 5$ |
| 4 | 4-CN BzOH | 20 | 34 | $74: 26$ |
| 5 | None | 20 | ND | ND |
| 6 | BzOH | 10 | 57 | $90: 10$ |

(a: Isolated yield; b: determined by SFC)
Table 33 - Influence of the co-catalyst on the enantioselective Pictet-Spengler reaction
We finally decided to test the influence of the co-catalyst (Table 33). Use of acetic acid afforded the product 4.293 in much lower yield and also with reduced ee (entry 2). More electron rich benzoic acid derivative also afforded 4.293 in lower yield but with similar ee (entry 3). Electron-poor benzoic acid derivative promoted a drastic reduction of the yield and of the ee (entry 4). The reaction without any co-catalyst did not promote any formation of 4.293 (entry 5). Finally, reducing the amount of benzoic acid to $10 \%$ decreased the yield but not the ee (entry 6).

Having performed the total synthesis of $9^{\prime}$-desmethoxypeganumine A (4.293), we undertook the total synthesis of (+)-peganumine A. $N$-Formylation and Boc protection of 6 -OMe tryptamine (4.27) afforded 4.300 in $87 \%$ yield. $N$-Boc-directed deprotonation followed by quenching with $\mathrm{Bu}_{3} \mathrm{SnCl}$ afforded the C-2 stannylated tryptamine derivative 4.301. The Liebeskind-Srogl coupling of 4.301 with the thioester 4.238 worked as previously to afford ketone 4.302 in $95 \%$ yield. Isonitrile 4.303 was obtained after dehydration in $92 \%$ yield (Scheme 248, A). The very sensitive product 4.303 was first submitted to the two-step procedure. Passerini reaction of 4.303 with TFA and pyridine in DCM provided the alcohol 4.304 in $85 \%$ yield. The latter was then oxidized using CoreyKim conditions and afforded the desired tetracyclic $\alpha$-ketoamide 4.234 in $96 \%$ yield (Scheme 248, B). Alternatively, the $\omega$-isocyanoaldehyde 4.303 was also submitted to the one-pot oxidative Ugi reaction conditions and the tetracyclic structure 4.234 was isolated in $75 \%$ yield (Scheme 248, C). The last Pictet-Spengler/transannular cyclization/deprotection cascade was first performed using the racemic conditions. ( $\pm$ )-peganumine A (rac-4.1) was isolated in $72 \%$ yield. Finally, the enantioselective transformation delivered the enantio-enriched ( + )-peganumine A (4.1) in $69 \%$ yield and with $92 \%$ ee (Scheme 248, D).







## Scheme 248 - Enantioselective synthesis of (+)-peganumine A

Scheme 249 shows the proposed mechanism for the Pictet-Spengler reaction/transannular cyclization/deprotection cascade. Condensation of the $\alpha$-ketoamide 4.234 with tryptamine 4.27 in the presence of molecular sieves or under Dean-Stark conditions in toluene at reflux afforded imine 4.304 which was identified by NMR. Decreasing the temperature to $35{ }^{\circ} \mathrm{C}$ and adding the chiral thiourea 4.53 and BzOH promoted the enantioselective Pictet-Spengler reaction to afford enamine 4.233. This stable intermediate 4.233 was also fully characterized. Once the chiral quaternary stereocenter was created, addition of a catalytic amount of TFA and warming up the reaction to reflux allowed a fast isomerization of enamine 4.233 to iminium 4.305. Transannular cyclization via nucleophilic addition of the secondary amine to the $N$-acyl iminium afforded 4.306. Additional time was required to observe the deprotection of the Boc group to furnish the desired (+)peganumine $A$ (4.1).


Scheme 249 - Proposed mechanism for the Pictet-Spengler reaction/transannular cyclization/deprotection cascade

### 4.3.4 Summary of the Synthesis

Scheme 250 summarizes the synthesis of (+)-peganumine A (4.1) from the commercially available 6 -OMe tryptamine (4.27) and acid 4.247.




Scheme 250 - Summary of the enantioselective total synthesis of ( + )-peganumine A
(+)-Peganumine A (4.1) was synthesized in 7 steps (longest linear sequence) in $33 \%$ overall yield from the commercially available acid 4.247 and with $96: 4$ enantiomeric ratio. The sequence highlighted in Scheme 250 was performed on large scale leading to more than one gram of the natural product in one single pass. Our strategy could therefore provide a viable route for the access to large quantity of peganumine $\mathrm{A}(4.1)$. As a comparison, only 3.5 mg of this product were initially isolated from the plant.

Table 34 shows the comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of both natural and synthetic $(+)$ peganumine $A$ (4.1).

The carbon and proton chemical shifts correlated well with the isolated natural product.

|  | Natural |  |  | Synthesized |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\mathrm{N}^{\circ}$ | $\begin{aligned} & { }^{13} \mathrm{C}[\mathrm{ppm}]^{\mathrm{a}} \\ & (151 \mathrm{MHz}) \\ & \hline \end{aligned}$ | $\begin{aligned} & { }^{1} \mathrm{H}[\mathrm{p} \\ & (600 \\ & \hline \end{aligned}$ |  | $\begin{aligned} & { }^{13 \mathrm{C}}[\mathrm{ppm}]^{\mathrm{a}} \\ & (151 \mathrm{MHz}) \\ & \hline \end{aligned}$ | $1{ }^{1} \mathrm{H}$ [p <br> 1600 |  |
| 1 | 77.4 |  | - | 77.4 | d |  |
| 3 | 40.0 | 2.34 | 2.45 | 40.0 | 2.34 | 2.45 |
| 4 | 21.0 | 2.63 | 2.64 | 21.1 | 2.63 | 2.65 |
| 5 | 109.5 | - | - | 109.5 | - | - |
| 6 | 120.5 | - | - | 120.5 | - | - |
| 7 | 118.2 | 7.24 | - | 118.2 | 7.24 | - |
| 8 | 108.3 | 6.63 | - | 108.3 | 6.63 | - |
| 9 | 155.4 | - | - | 155.4 | - | - |
| 10 | 94.9 | 6.93 | - | 94.9 | 6.92 | - |
| 11 | 137.6 | - | - | 137.6 | - | - |
| 13 | 127.3 | - | - | 127.3 | - | - |
| 14 | 171.4 | - | - | 171.4 | - | - |
| 15 | 50.4 | 1.88 | 2.30 | 50.4 | 1.88 | 2.30 |
| 16 | 40.0 | - | - | 40.0 | - | - |
| 17 | 26.8 | 1.15 | - | 26.9 | 1.14 | - |
| 18 | 26.0 | 1.38 | - | 26.1 | 1.38 | - |
| 1 | 78.8 | - | - | 78.8 | - | - |
| $3 '$ | 35.6 | 4.00 | 3.09 | 35.6 | 4.00 | 3.09 |
| 4 | 20.9 | 2.70 | 2.90 | 21.0 | 2.71 | 2.90 |
| 5' | 111.3 | - | - | 111.3 | - | - |
| 6 | 120.4 | - | - | 120.4 | - | - |
| 7 | 119.0 | 7.38 | - | 119.1 | 7.38 | - |
| 8 | 109.1 | 6.70 | - | 109.1 | 6.69 | - |
| $9 \times$ | 156.1 | - | - | 156.1 | - | - |
| $10^{\prime}$ | 94.7 | 6.87 | - | 94.7 | 6.87 | - |
| $11^{\prime}$ | 137.5 | - | - | 137.5 | - | - |
| $13^{\prime}$ | 125.7 | - | - | 125.7 | - | - |
| 12-NH | - | 11.25 | - | - | 11.27 | - |
| 12'-NH | - | 10.77 | - | - | 10.80 | - |
| 9-OMe | 55.2 | 3.78 | - | 55.2 | 3.77 | - |
| $9{ }^{\prime}$-OMe | 55.2 | 3.77 | - | 55.2 | 3.76 | - |

Table 34 - Comparison of NMR data between the natural and the synthesized ( + )-peganumine A
Being aware of the so called, self-induced diastereomeric anisochronism (SIDA) phenomenon and having experienced it on natural products exhibiting nitrogen and amides scaffold, we were won-
dering if ( + )-peganumine A (4.1) could also feature such effect. The SIDA phenomenon refers to the fact that, in some cases, racemic mixtures and enantiomers show different NMR spectra. In these cases, distinct signals of each enantiomer could be obtained. The extent of spectroscopic difference is concentration dependent indicating an autoassociation phenomenon. Only a few natural products were reported to show SIDA phenomenon. ${ }^{420}$ Having synthesized both racemic and enantio-enriched peganumine A (4.1), we could easily compare their NMR spectra. The careful comparison of the data showed no difference.

The optical rotation of synthetic $(+)$-peganumine $A(4.1)$ was similar to the value reported for the natural one (synthesized: $[\alpha]_{\mathrm{D}}{ }^{20}=+6.2^{\circ}(c=0.1, \mathrm{MeOH})$, isolated: $[\alpha]_{\mathrm{D}}{ }^{20}=+5.6^{\circ}(c=0.15, \mathrm{MeOH})$ ). We therefore obtained the correct enantiomer using the chiral thiourea 4.53 derived from $L$ valine. It is to note that ( + )-peganumine A (4.1) was really poorly soluble in organic solvents, including DMSO and DMF.

### 4.4 Analogues

Interested in the fact that this compound presented some interesting biological activities, we planned to synthesize a small library of analogues for structure-activity relationship (SAR) studies. Thanks to the two previously synthesized tetracyclic compounds 4.234 and 4.264 , and because most of the complexity was built in the last step, we were able to synthesize analogues by the same late-stage cascade reaction (Scheme 251).

Reaction of $\alpha$-ketoamides 4.264 or 4.234 with 6 -methoxytryptamine (4.27), afforded the desired analogue 4.293 and ( + )-peganumine $A(4.1)$ in moderate yields but with excellent ee. Similar reactions using 5-methoxytryptamine (4.307) gave 4.308 and 4.309 , in similar yields and with similar ee. Finally, the use of unsubstituted tryptamine delivered analogues 4.310 and 4.291 (Scheme 251).

[^153]
MS $4 \AA$, toluene, reflux then
4.53







Scheme 251 - Analogues of (+)-peganumine A using derivatives of tryptamine
We also investigated the possible enantioinduction from the use of L-tryptophan methyl ester (4.311) (Scheme 252). Reaction of 4.264 or 4.234 in the previously developed racemic reaction conditions (TFA, toluene, reflux) afforded compound 4.312 and 4.313 respectively in moderate yield as a 1:1 mixture of diastereoisomers. The poor diastereoselectivity observed could be explained in two ways: 1) A poor diastereoinduction from the tryptophan derivative or; 2) a racemization/epimerization of the starting material/final products in the harsh reaction conditions. As we could not separate both diastereoisomers, no conclusion could be drawn.


Scheme 252 - Analogues of peganumine A using of L-tryptophan methyl ester
All these analogues are currently under investigation concerning their biological activities.

### 4.5 Conclusion and Outlook

In conclusion, we developed the first enantioselective synthesis of (+)-peganumine A (4.1) featuring:

- A Liebeskind-Srogl coupling to merge our two key building blocks using a very low L:Pd ratio and a elaborated mixture of solvents to prevent the direct Sn to Cu transmetalation
- A novel isocyanide-based macrocyclization method
- A domino sequence involving an enantioselective Pictet-Spengler reaction and a transannular cyclization to afford (+)-peganumine A (4.1) in a single step and excellent enantiomeric excess


Scheme 253 - Summary of the total synthesis of (+)-peganumine A
(+)-Peganumine A (4.1) was synthesized in only 7 steps in an excellent $33 \%$ overall yield and with $92 \%$ ee starting from simple starting materials using textbook reactions (Scheme 253). ${ }^{421}$

We also developed a simple access to analogues using different starting tryptamines. They were isolated in moderate yields but with excellent enantiomeric ratio. The synthesized analogues will provide an initial structure-activity relationship of (+)-peganumine A. Access to other analogues could easily be imagined (Figure 37) using other tryptamine derivatives. Repeating the synthesis without the gem-dimethyl substituents could also provide another set of interesting derivative. Substitution on the indole nitrogens and reduction to the lactam (via the thioamide) could provide useful information for the SAR.





Figure 37 - Possible accessible analogues of (+)-peganumine A

[^154]
## Chapter 5 Macrocyclization of $\omega$ Isocyanoaldehydes

This work was realized in collaboration with Teerawat Songsichan.

### 5.1 Introduction

We realized that the macrocyclization method developed during the total synthesis of (+)peganumine A (4.1) could be valuably applied to other substrates. Indeed, macrocycles and $\alpha$ ketoamides are found in numerous natural products and bioactive molecules.

### 5.1.1 $\alpha$-Ketoamides

The $\alpha$-ketoamide moiety represents the key framework in many natural and non-natural bioactive products (Figure 38 and Figure 39).

$\operatorname{CtA}(5.2):(S), \mathrm{R}^{1}=\mathrm{CHO}, \mathrm{R}^{2}=\mathrm{Bn}$ CtB (5.3): (S), $\mathrm{R}^{1}=\mathrm{MeCO}, \mathrm{R}^{2}=\mathrm{Bn}$ CtC (5.4): $\Delta, \mathrm{R}^{1}=\mathrm{CHO}, \mathrm{R}^{2}=\mathrm{Bn}$ CtD (5.6): (S), $\mathrm{R}^{1}=\mathrm{CHO}, \mathrm{R}^{2}={ }^{i} \mathrm{Pr}$
CtE (5.7): ( $\left(\right.$ ) , $\mathrm{R}^{1}=$ BnCO-Ala, $\mathrm{R}^{2}=(S)$-sec-Bu
$\mathrm{CtE}_{2}$ (5.8): (S), $\mathrm{R}^{1}=\mathrm{Bz}-\mathrm{Ala}, \mathrm{R}^{2}=(S)$-sec-Bu $\mathrm{CtE}_{3}$ (5.9): (S), $\mathrm{R}^{1}=\mathrm{i}$ PrCO-Ala, $\mathrm{R}^{2}=(S)$-sec-Bu $\mathrm{CtE}_{4}$ (5.10): (S), $\mathrm{R}^{1}=$ 'BuCO-Ala, $\mathrm{R}^{2}=(S)$-sec-Bu

Figure 38 - Examples of natural products bearing an $\alpha$-ketoamide function
Cyclotheonamides $A-E_{4}(5.2$ to 5.10$)$ features a ketohomoarginine moiety. They have been shown to be potent inhibitors of serine proteases. It has been demonstrated that the $\alpha$-ketoamide function was responsible for the unique mode of action of cyclotheonamides: a reversible formation of a tetrahedral adduct with a hydroxyl group of the enzyme's active site. Others compounds, such as FK-506 (also known as tacrolimus) (5.11), are used as T-cell proliferation blockers to prevent organ transplant rejection or as anti-HIV agents such as chloropeptin I (5.12) and II (5.13) for instance. They probably used similar tetrahedral intermediates formation to inhibit enzymes.


5.15: Histone deacetylase inhibitor

5.16: Expoxide hydrolase inhibitor

Figure 39 - Examples of non-natural bioactive products bearing an $\alpha$-ketoamide function
Non-natural $\alpha$-ketoamides are also widely used for their biological activities (Figure 39). They can either be small peptidomimetics such as $\mathbf{5 . 1 4}$ or contain long aliphatic chain as $\mathbf{5 . 1 5}$ for instance.

Because of the high importance of the $\alpha$-ketoamide moiety, many different methodologies have been reported for its synthesis. ${ }^{422}$ Five main strategies are schematically presented in Scheme 254.


Scheme 254 - General retrosynthetic scheme for the synthesis of $\alpha$-ketoamide derivatives Isonitriles play an important role in most of these processes.

Many reports dealt with the oxidation at the C-2 position (Scheme 254, A). The starting materials were easily obtained by Ugi or Ugi-Smile reactions.


Scheme 255 - Ugi-4CR followed by oxidation for the synthesis of $\alpha$-ketoamide derivatives

[^155]Nakamura reported a two-step synthesis of $N$-pyruvoyl amino acid derivatives (A). ${ }^{423}$ The Ugireaction using 2 -hydroxypropanoic acid (5.28) led, for instance, to the formation of the desired alcohol 5.31 in $62 \%$ yield. The latter was submitted to simple PDC oxidation to furnish the $\alpha$ ketoamide 5.32 in $61 \%$ yield. The sequence was also performed in a one-pot process (in THF) and 5.32 was obtained in $81 \%$ purity.

On the other side, El Kaïm, Gamez-Montano, Grimaud and coworkers developed a two-step process for the synthesis of $\alpha$-ketoamide derivatives using an Ugi-Smile reaction followed by a Pdcatalyzed oxidation of the resulting $\alpha$-aminoamide (B). ${ }^{424}$ For instance, Ugi-Smile reaction between phenol 5.33, benzaldehyde (5.34), isonitrile 5.35 and amine 5.36 afforded the desired product 5.37 in $87 \%$ yield. The latter was submitted to the oxidation conditions leading to 5.38 in $69 \%$ yield.

Concerning the amidation at C-1 strategy (Scheme 254, B), Ugi reaction also proved useful as demonstrated by the work of Andreana and coworkers (Scheme 256). ${ }^{425}$


Scheme 256 - Ugi-4C reaction using $\alpha$-ketoacid for the synthesis of $\alpha$-ketoamide derivatives
Ugi reaction between aldehyde 5.39, methylamine (5.40), methylisocyanide (5.41) and $\alpha$-ketoacid 5.42 afforded the desired compound 5.43 in $37 \%$ yield. The latter was used for the synthesis of thaxtomin A.


Scheme 257 - Nef- isonitriles reaction for the direct access to $\alpha$-ketoamides via C-C bond formation

[^156]Isonitriles also proved competent for the C-1/C-2 bond formation (Scheme 254, C). The Nefisonitrile reaction (see 1.2.2 - Multicomponent Reactions) is one example among others (Scheme 257).

Chen and coworkers developed a microwave-assisted Nef-isonitrile reaction (A). ${ }^{426}$ Reaction of benzoyl chloride (5.44) with cyclohexyl isocyanide (5.35) afforded the intermediate 5.45 which was then hydrolyzed in a one-pot manner to the corresponding $\alpha$-ketoamide 5.46 in $74 \%$ yield.

On the other hand, El Kaïm, Abderrahim and coworkers developed a non-oxidative Passerini pathway to $\alpha$-ketoamides (B). ${ }^{427}$ Their methodology relied on the use of cinnamaldehyde derivatives. 5.47 was for instance reacted with isonitrile 5.35 and acetic acid and the resulting Passerini product 5.48 was in situ converted to the $\alpha$-ketoamide 5.49 in good yield via acetyl deprotec-tion/double-bond migration and enol-ketone tautomerism.

Finally Zhu and coworkers, as already described in 1.2.2.1 (Isonitriles and the Passerini and Ugi Reactions), developed an oxidative Ugi reaction for the direct access to $\alpha$-ketoamides. ${ }^{57 a}$ Reaction of aldehyde 5.50 with isonitrile 5.51 in the presence of acetic acid and ( $N$ methyl)methylhydroxylamine delivered the desired compound 5.52 in $75 \%$ yield. The methodology was later extended to the use of aromatic aldehydes using $\mathrm{ZnCl}_{2}$ as additive. ${ }^{57 \mathrm{~b}}$

On the other hand, the use of isonitriles was, to the best of our knowledge, not reported for the C$2 / R^{3}$ bond formation (Scheme 254, D) as well as for the Pd-catalyzed double carbonylative amination strategy (Scheme 254, E).

### 5.1.2 Reported Macrocyclization Methods Based on Isonitriles

As previously illustrated, multicomponent reactions (MCR) are very powerful for the rapid construction of complexity. By tethering two of the different components, ring and especially macrocycles can be constructed.

The tethering of different functional group can lead to different ring sizes and topologies of macrocycles. Scheme 258 represents the possibilities using the Ugi 3-component 4-center reaction.

[^157]

(B)



 (E)

(F)

Scheme 258 - All six possibilities of tethering two out of the four components involved in the Ugi reaction

Six different tethering are possible. They all lead to different connectivity. Because the Ugi and the Passerini reaction occur via a Mumm rearrangement, the ring size of the final product does not always correlate with the initial ring size of the macrocyclization. Table 35 shows the difference between the ring size of the final ring observed after the rearrangement and the one of the initial macrocyclization step.

(a: Letters refer to Scheme 258)
Table 35 - Ring size difference between the final product and the intermediate before the Mumm rearrangement

As depicted on Table 35, the ring can be enlarged by one atom, keep the same size or be reduced by one or three atoms. The Mumm rearrangement step has a high importance as the ring size, the conformation and the flexibility of $\mathbf{1 . 1 2 6}$ can drastically influence the rate of this rearrangement. For instance, tethering the amine ( $R^{3}$ ) and the carboxylic acid $\left(R^{4}\right)$ would require a transannular attack of the nitrogen on the carbonyl group. On the other hand, using an isocyanoaldehyde ( $R^{1}$ tethered with $R^{2}$ ) would require a fully exocyclic Mumm rearrangement. All the other tethering possibilities would involve a reaction between an exocyclic functionality with an endocyclic one.

Another interesting feature of the macrocyclization using the Ugi or the Passerini reaction is the influence of the concentration. It is well known that, in order to favor the intramolecular reaction, high dilutions are supposed to be used. But it is also well known that Passerini and especially Ugi reactions require low dilution in order to favor the multicomponent reaction. There is therefore a mismatch. For this reason the concentration of the following reactions will be indicated in order to analyze the differences between each case.

Out of the six combinations in Scheme 258, the most widely explored one is the tethering of the amine (1.122) with the carboxylic acid (1.110) in a $\omega$-amino acid. This was mainly illustrated with peptides. The first example reported in the literature was disclosed in 1979 by Failli and coworkers (Scheme 259, A). ${ }^{428}$

(A)
(B)

Scheme 259 - Initial reports on the macrocyclization of peptides based on Ugi reaction
They were able to cyclized various peptides such as 5.65 in the presence of benzaldehyde (5.34) and cyclohexylisonitrile (5.35) to afford cyclic peptides like 5.66. They noticed that high concentration was not an issue and they were able to synthesize various ring sizes and topologies. Nevertheless they observed that, for smaller ring such as 9-membered ones, low yields and only the dimers were observed. It is to note that 9 -membered ring formation involved an initial 12 -membered macrocycle formation. The development of this new macrocyclization method was inactive for 30 years until the work of Wessjohann and coworkers (B). ${ }^{429}$ They reinvestigated the cyclization of peptides this time using pseudo-high dilution technique, i.e. slow addition of the bifunctional partners. For instance, 5.67 was slowly added to a solution of formaldehyde and ${ }^{t}$ BuNC (5.68) in MeOH and the product 5.69 was obtained in $21 \%$ yield after deprotection.

As presented in Scheme 259, the use of high concentration was compatible with the macrocyclization of peptides. In order to better understand the reason why polymerization was not occurring, a closer look to the interactions is required. In short peptides, an electrostatic interaction between the C - and the N - termini may favor a circular conformation. When using these peptides in macrocyclization using Ugi reaction, the interaction between the ion pairs (carboxylate and iminium)

[^158]probably do not interfere with this pre-conformation (Figure 40). This is the main reason why Ugibased macrocyclization of peptides could generally be run under much lower dilution than in other conventional peptide macrocyclization methods.


Peptide


Ugi-based
macrocyclization


Figure 40 - Electrostatic interaction favoring a circular conformation of short peptides
Since the initial reports, many reports have been disclosed in this field. For instance, instead of the head to tail cyclization presented in Scheme 259, Wessjohann, Rivera and coworkers have explored in 2015 the side chain to head and side chain to tail macrocyclization. ${ }^{430}$ This obviously required the presence of Glu/Asp or Lys/Orn amino acids along the peptide sequences.

Beside the standard Ugi reaction, other variations have been reported such as the use of Ugi-Smile and Ugi-Split reaction, as well as the use of uncommon isonitriles such as ( $N$ isocyanimino) phosphorane (Scheme 260).


(A)

(B)



(C)

Scheme 260 - Variation of the Ugi-macrocyclization of peptides
Wessjohann, Rivera and coworkers developed in 2016 an Ugi-Smile macrocyclization of peptides for the synthesis of $p$-cyclophane (A). ${ }^{431}$ Reaction of 5.73 with formaldehyde and linear alkyl isoni-

[^159]trile 5.74 afforded the desired product 5.75 in $67 \%$ yield. The proposed intermediate 5.76 could furnish the observed product after Smile rearrangement.

Another variation of the Ugi reaction was used for the macrocyclization of peptides (B). This methodology, developed in 2010 by Yudin and coworker, involved the use of aziridine carboxaldehydes such as 5.78 (in a dimeric form). ${ }^{432}$ The intermediate before the Mumm rearrangement was proposed to be 5.80 . Because this methodology relied on the use of a secondary amine, such as proline, the Mumm rearrangement did not occur as in standard Ugi transformation. Instead, the secondary amine of the aziridine could trap the ester to afford 5.79. The fact that the aziridine was located outside of the ring facilitated the rearrangement.

Finally, Yudin and coworker developed a macrocyclization method for the incorporation of oxadiazole scaffold (C). ${ }^{433}$ Ugi reaction of peptide 5.81 with propanal (5.883) and ( N isocyanimino)phosphorane (5.82) afforded 5.84 in $68 \%$ yield. The proposed intermediate 5.85 could undergo an aza-Wittig reaction to deliver the observed oxadiazole product 5.84.

Beside the formation of peptide-like macrocycles, medium-sized rings were also constructed using $\omega$-amino acids (Scheme 261).


Scheme 261 - Construction of medium-sized rings relying on the use of $\omega$-amino acids
Dömling and coworkers developed in 2017 the application of Ugi reaction for the synthesis of me-dium-sized rings and macrocycles using the Ugi reaction (A). ${ }^{434} 8$ - to 19-membered rings were synthesized in low to moderate yields. In 2017, they developed a similar strategy for the construction of 8 to 11-membered rings (B). ${ }^{435}$

[^160]Besides the tethering of the amine with the carboxylic acid, other functions have been tethered such as the isonitrile and the carboxylic acid (Scheme 262).


Scheme 262 - Synthesis of macrocycles from $\omega$-isocyanocarboxylate salts
Dömling and coworkers developed in 2015 a macrocyclization method based on the Ugi reaction using carboxylate salt such as 5.93 (A)..$^{436}$ It was previously known that carboxylic acid-isonitrile bifunctional building blocks afforded only trace amount of the desired products, probably because of their low stability (see 1.2.2.1 - Isonitriles and the Passerini and Ugi Reactions). Replacing the carboxylic acid by a carboxylate salt and using ammonium chloride as additive allowed, for the first time, this macrocyclization to occur, albeit in moderate yields. Based on this methodology, 12- to 22-membered rings were synthesized in low to moderate yields.

The same group later extended the use of $\omega$-isocyanocarboxylate salt to the Passerini macrocyclization (B). ${ }^{437} 5.96$ was for instance reacted with formaldehyde and ammonium chloride and the product 5.97 was obtained in $36 \%$ yield. Thanks to this methodology, 15 - to 20 -membered rings were synthesized in low to moderate yields.

Dömling and coworker reported in 2017 the use of tethered amine and isonitrile for macrocyclization reactions (Scheme 263). ${ }^{438}$

[^161]

## Scheme 263 - Synthesis of macrocycles using TMSN ${ }_{3}$ from $\omega$-isocyano amines

In their paper, they did not rely on the use of Ugi reaction but they instead used TMSN 3 (5.99) as trapping agent of the intermediate 5.102. They proposed that the addition of $\mathrm{TMSN}_{3}$ in methanol could generate $\mathrm{HN}_{3}$ which could promote the activation of the aldehydes/ketones. The $\mathrm{N}_{3}{ }^{-}$anion could trap the nitrilium intermediate 5.102 in a [3+2] cycloaddition step to afford the desired products. 11- to 19-membered rings were synthesized in low to moderate yields.

They very recently extended the use of tethered amine and isonitrile to an Ugi-macrocyclization (Scheme 264). ${ }^{439}$ Based on this methodology, 12- to 17-membered rings were synthesized in moderate yields.


Scheme 264 - Synthesis of macrocycles based on Ugi reaction using $\omega$-isocyano amines
Another reported tethering was developed in 2012 by Saxena and coworkers (Scheme 265). ${ }^{440}$


Scheme 265 - Oxidation/dehydration/Ugi cyclization cascade of $\omega$-hydroxy formamides
They reported the in situ oxidation of primary alcohol, dehydration of formamide followed by Ugicyclization. Very surprisingly they were able to synthesized 5 - to 8 -membered rings in moderate to good yields. The oxidation of the alcohol 5.106 was based on the Parikh-Doering method using

[^162]$\mathrm{Py} \cdot \mathrm{SO}_{3}$ complex and DMSO. The resulting alkoxysulfonium intermediate 5.107 was transformed to the aldehyde 5.108 using pyridine as base. Once the full conversion of the alcohol to the aldehyde achieved, pyridine and $\mathrm{POCl}_{3}$ were added for the dehydration of the formamide 5.108 to the isonitrile 5.110 probably via $\mathbf{5 . 1 0 9}$. They reported the use of high temperature for this step. This is surprising as the expected compounds are not very stable. Moreover, for unhindered formamides, $78{ }^{\circ} \mathrm{C}$ is generally enough to obtain full conversion in few hours. Once the formation of the isonitrile $\mathbf{5 . 1 1 0}$ observed, they neutralized the basic solution using aqueous HCl up to pH 6.6 . This step looked particularly unusual in our eyes as the presence of water with isonitrile in acidic conditions is well known to promote fast hydrolysis of the latter. After the neutralization, the authors added the amine 1.122 and the carboxylic acid 1.110 and were able to obtain the desired product 5.113. The Ugi step also attracted our attention, especially for the formation of 5-and 6-membered rings. Indeed, $\omega$-isocyanoaldehydes with 2 or 3 bridging atoms looked not very suitable for such cyclization. The presence of three sp atom and one $\mathrm{sp}^{2}$ atom should prevent any attack of the isonitrile on the aldehyde.

Another alternative method, not relying on one long linear precursor as starting material, is the use of Multiple Multicomponent Macrocyclizations including Bifunctional Building Blocks $\left(\mathrm{M}^{3} \mathrm{iB}^{3}\right) .{ }^{21}$ It features the use of two or more multicomponent reactions using difunctionalized starting materials. Zhu and coworkers were the first to synthesize macrocycles using a plan multiple multicomponent reaction. ${ }^{441}$

Three previous combinations of functional groups (acid-amine, acid-isonitrile, amine-isonitrile) have been reported in such strategy. Moreover, the use of a diamine and a dialdehyde has been reported by Wessjohann and coworkers (Scheme 266). ${ }^{442}$ Aldehyde 5.114 was reacted with amine 5.115 in an Ugi 4-component reaction. 5.116 was obtained in $69 \%$ yield after an in situ macrocyclization of the tethered amine/aldehyde 5.117. It is to note that the addition of $\mathrm{Mg}(\mathrm{II})$, acting as a template, was crucial for the yield.


## Scheme 266 - Macrocyclizations of bifunctional aldehydes and amines

Among all the possible combinations, the acid-aldehyde and the isonitrile-aldehyde have not been reported yet. Nevertheless, in situ oxidation/Ugi reaction of diol 5.118 with either diacid 5.119 or

[^163]diisonitrile 5.121 has been reported by Wessjohann and coworkers (Scheme 267). ${ }^{443}$ They both relied on the work of Zhu and coworker on oxidative Passerini/Ugi reaction using IBX. ${ }^{444}$ The combination of IBX in THF at $40^{\circ} \mathrm{C}$ allowed the in situ oxidation of alcohol to aldehydes which were directly engaged in an Ugi reaction.


Scheme 267 - Macrocyclizations of in situ generated bifunctional aldehyde
Diol 5.118, was reacted with diacid 5.119 and ${ }^{t}$ BuNC (5.68) in THF at $40^{\circ} \mathrm{C}$ in the presence of IBX. 5.120 was obtained in $59 \%$ yield. On the other hand, the same diol 5.118 was engaged in a double Ugi reaction using $N$-Boc glycine (5.121) and diisonitrile 5.122. The macrocyclization occurred on $\omega$-isocyanoaldehyde 5.124.

Despite these interesting reports there was, to the best of our knowledge, no report of macrocyclization relying on Ugi or Passerini reaction using isolated $\omega$-isocyanoaldehydes.

### 5.2 Macrocyclization using $\omega$-Isocyanoaldehydes

We synthesized different cyclization precursors with different topologies and chain lengths.

### 5.2.1 Starting Material Synthesis

We first focused on the synthesis of substrates similar to the one used in the total synthesis of (+)peganumine A (4.1) (Scheme 268). We envisioned the use of a similar strategy via Liebeskind-Srogl coupling.

We first synthesized carboxylic acids containing various chain lengths (A and B). Bromides 5.125 were substituted with diethylmalonate. ${ }^{445}$ The resulting diesters 5.126 were hydrolyzed and the acids 5.127 were decarboxylated at high temperature. ${ }^{446}$ The monoacids 5.128 were obtained in high yields (A). For the synthesis of hept-6-enoic acid (5.128c), bromide 5.125 d was initially substi-

[^164]tuted with potassium cyanide. ${ }^{447}$ The nitrile 5.129 was then hydrolyzed to afforded 5.128 c in quantitative yield (B). ${ }^{448}$

The acids were then converted to the thioesters $\mathbf{5 . 1 3 0}$ following our previously developed method (C). ${ }^{403}$


Scheme 268 - Synthesis of the 10- to 13-membered ring precursors containing an indole ring
The different thioesters 5.130 were then coupled with the stannyl 4.242 (D). The previously developed conditions using hexane/THF as solvents mixture afforded the desired products 5.131 cleanly in good yields. ${ }^{421}$ We then relied on a two-step procedure for the conversion of alkenes 5.131 into aldehydes 5.132 as ozonolysis proved troublesome. Dihydroxylation using catalytic amount of potassium osmate $(\mathrm{VI})$ dihydrate and NMO followed by oxidative cleavage of the resulting diols using $\mathrm{NaIO}_{4}$ afforded 5.132 in good yields. ${ }^{449}$ In the last step, dehydration of the formamides $\mathbf{5 . 1 3 2}$ fur-

[^165]nished the desired $\omega$-isocyanoaldehydes 5.133 . 10 - to 13 -membered ring could be targeted using these precursors.


Scheme 269 - Synthesis of the 9- and 15-membered ring precursors containing an indole ring
In order to see the influence of the C-2 acyl group, derivatives lacking this functionality were then targeted (Scheme 269). Indole 4.241 was first submitted to Pd-catalyzed C-H activation/Heck coupling with propenal (5.134). ${ }^{450}$ The desired product 5.135 was obtained in $56 \%$ yield. The double bond was then reduced under hydrogenation conditions. ${ }^{450} \mathrm{~A}$ mixture of the aldehyde 5.136 and the alcohol 5.137 was obtained in an approximate $1: 2$ ratio (A). The aldehyde $\mathbf{5 . 1 3 6}$ was simply dehydrated in order to obtain 5.138, the precursor for 9 -membered ring formation (B). On the other hand, alcohol 5.137 was alkylated with alkyl bromide $\mathbf{5 . 1 2 5 d}$. The obtained product 5.139 was submitted to a dihydroxylation/oxidative cleavage sequence and aldehyde 5.140 was delivered in 66\% over 2 steps. The latter was submitted to dehydration conditions and the formamide 5.140 was converted to isonitrile 5.141 (C). 15 -membered rings could be obtained using the latter as starting material.

[^166]We then envisioned the synthesis of substrates containing other scaffolds than the indole ring (Scheme 270 and Scheme 271).

Ester 5.142 was converted to amide 5.144 in 1,3-propane diamine (5.143) at reflux. ${ }^{451}$ Formylation of the primary amine 5.144 was achieved in high yield (Scheme 270, A). On the other hand, the alkyl bromide 5.148 was synthesized from 5.146 and 5.147 by a nucleophilic substitution (B). ${ }^{452}$ Alkylation of phenol derivative 5.145 with the synthesized alkyl bromide 5.148 afforded the product 5.149b in $89 \%$ yield. ${ }^{453}$ Similar alkylation using 1-bromo-hex-5-ene (5.125d) furnished 5.149a in $94 \%$ yield. Both alkenes 5.149 were submitted to the previously developed dihydroxylation/oxidative cleavages conditions. The resulting aldehydes 5.150 were then converted to the isonitriles 5.151 using our standard dehydration procedure (C).


Scheme 270 - Synthesis of the 15- and 22-membered ring precursors containing a phenol moiety
5.158 was obtained using a similar strategy (Scheme 271). Aniline 5.152 was acylated with pent-4enoic acid (5.128a) in $67 \%$ yield. ${ }^{454}$ The obtained amide 5.154 was then alkylated with BnBr and 5.155 was obtained in moderate yield. ${ }^{455}$ The resulting ester 5.155 ester was converted into the amide and the primary amine was formylated to furnish 5.156. Conversion of the alkene $\mathbf{5 . 1 4 6}$ into the aldehyde 5.157 and of the formamide 5.157 into the isonitrile afforded 5.158 in good

[^167]yields. 14-membered rings containing an aniline moiety were expected to be obtained using this substrate.


## Scheme 271 - Synthesis of the 14-membered ring precursor containing an aniline moiety

Having in mind the potential formation of $m$ - and $p$-cyclophane using our methodology, 5.163 and 5.170 were targeted.

Ester 5.159 was converted in a 2-step procedure to the formamide 5.160 (Scheme 272). Alkylation of the phenol 5.160 with 5.125 d delivered 5.161 in $56 \%$ yield over 3 steps. Conversion of the alkene into aldehyde $\mathbf{5 . 1 6 2}$ followed by dehydration of the formamide $\mathbf{5 . 1 6 2}$ allowed the synthesis of the $m$-cyclophane precursor $\mathbf{5 . 1 6 3}$.


Scheme 272 - Synthesis of the m-cyclophane precursor
p-Cyclophane precursor 5.170 was then prepared (Scheme 273). 1,3-Propane diamine (5.143) was monoformylated to afford 5.164 (A). ${ }^{456}$ Alkylation of phenol 5.165 with 5.125 d followed by hydrolysis of the ester $\mathbf{5 . 1 6 6}$ furnished acid $\mathbf{5 . 1 6 7}$ in good yields. ${ }^{457,458}$ Peptide coupling with the synthe-

[^168]sized amine 5.164 afforded 5.168 in $87 \%$ yield. Standard dihydroxylation/oxidative cleavage sequence followed by dehydration of formamide 5.169 furnished the desired product 5.170 (B).

(B)

Scheme 273 - Synthesis of the p-cyclophane precursor
Finally, in order to compare our method with the one developed by Saxena and coworkers, ${ }^{440}$ linear alkyl substrates 5.174 and 5.177 were targeted (Scheme 274). They would provide access to 6 to 8-membered rings.


Scheme 274 - Synthesis of the aliphatic precursors
Amino alcohols 5.171 were formylated using acetyl formyl mixed anhydride. The alcohols 5.172 were then supposed to be converted to aldehydes. Unfortunately, only $\mathbf{5 . 1 7 3}$ was obtained using DMP. The other substrates could not be oxidized cleanly, probably because of hemiacetal formation, overoxidation, etc. Formamide 5.173 was finally dehydrated to obtain 5.174 (A)

With the idea to promote the in situ oxidation of $\omega$-isocyanoalcohol to aldehyde and engaged them directly to a Passerini/Ugi reaction, we synthesized 5.177 . The alcohols 5.172 were first protected using TBSCl and the resulting products 5.175 were dehydrated to afford isonitriles $\mathbf{5 . 1 7 6}$ in good yield. TBAF-promoted deprotection furnished the alcohols 5.177.

### 5.2.2 Scope

Having a bunch of starting materials available, different cyclizations were then explored (Scheme 275).


Scheme 275 - Various reactions explored for the macrocyclization of $\omega$-isocyanoaldehydes
A Passerini 2-component 3-center reaction with acetic acid or $N$-Boc glycine could convert the isocyanoaldehyde 5.57 in esters 5.178 and 5.179 respectively. Similarly, reaction of $\mathbf{5 . 5 7}$ with TFA and pyridine could afford the desired $\alpha$-hydroxylactames 5.180. An Ugi 3-component 4-center reaction of 5.57 could allow having access to $\alpha$-aminolactames 5.181 . The use of our previously developed oxidative Ugi reaction could deliver the corresponding $\alpha$-ketoamides 5.182. ${ }^{421}$ Finally, reaction of 5.57 with $\mathrm{TMSN}_{3}$ could give the tetrazole derivatives 5.183. ${ }^{438}$

We initiated our scope by the cyclization of the 9-membered ring precursor $\mathbf{5 . 1 3 8}$ (Figure 41).


$50 \%$

$55 \%$

5.184
$43 \%$


35\%

Figure 41 - Synthesis of 9-membered medium-sized rings
Passerini reaction with TFA/pyridine afforded the alcohol 5.181 in $44 \%$ yield. Similar reaction with acetic acid or $N$-Boc glycine also furnished the desired products $\mathbf{5 . 1 8 2}$ and $\mathbf{5 . 1 8 3}$ respectively in more than $50 \%$ yields. Ugi reaction using benzylamine and acetic acid promoted the formation of 5.184 in $43 \%$ yield. Finally, modified Ugi reaction using $\mathrm{TMSN}_{3}$ and 4-CN-aniline afforded tetrazole 5.185 in $35 \%$ yield. With these examples, we concluded that, as expected, the C-2 ketone functional group was not required for the cyclization.

We then turned our attention towards the formation of 6-6 fused ring systems, involving an initial 10-membered ring formation (Figure 42).


Figure 42 - Synthesis of 10-membered ring formation followed by transannular cyclization
Passerini reaction using TFA and pyridine provided the desired alcohol 5.186 in $59 \%$ yield. Acetic acid and benzoic acid afforded the corresponding esters 5.187 and 5.188 in similar yields. Ugi reaction with benzylamine and acetic acid furnished the $\alpha$-amidoamide 5.189 in $89 \%$ yield. We then turned our attention towards the previously developed oxidative Ugi reaction. Different work-up procedures allowed the synthesis of the $\alpha$-ketoamide 5.191 or the enamine 5.190 (Table 36).
$\left.\begin{array}{ccccc}\hline \text { Entry } & \text { Work-up } & \text { Purification } & \begin{array}{c}\text { Yield of } \\ \mathbf{5 . 1 9 0}[\%]^{\text {a }}\end{array} & \begin{array}{c}\text { Yield of } \\ \mathbf{5 . 1 9 1}\end{array} \\ \hline 1 & \text { Filtration }]^{\text {a }}\end{array}\right]$
(a: Isolated yield)
Table 36 - Different work-up procedures leading to enamine 5.190 or ketone 5.191
Filtration of the reaction mixture on Celite followed by flash column chromatography afforded the enamine 5.190 in $38 \%$ and the $\alpha$-ketoamide 5.191 in $22 \%$ yield (entry 1 ). Simple aqueous basic workup after the filtration did not influence drastically the yields and both products were still obtained (entry 2). If the purification was performed on neutralized silica gel, only the enamine $\mathbf{5 . 1 9 0}$ was isolated in $89 \%$ yield (entry 3). Finally, acidic work-up with 2 M HCl followed by flash column chromatography furnished the $\alpha$-ketoamide 5.191 in 79\% yield (entry 4).

The reason for the enamine $\mathbf{5 . 1 9 0}$ formation as well as for its relative stability probably relied on the conjugation with the second double bond. The obtained product showed some aromaticity character. Nevertheless, acid conditions (silica gel for instance) could easily tautomerize the enamine to the imine which was then highly prone to hydrolysis to afford $\mathbf{5 . 1 9 1}$. The enamine formation prevented us to install any stereocenter at the $\alpha$-position of the aldehyde.

It is to note that the transannular cyclization of the 10 -membered ring products proved slower than for 4.235 as the macrocyclic intermediate could be observed by TLC and ${ }^{1} \mathrm{H}$ NMR.

We then moved towards the formation of 11-membered rings (Figure 43).





Figure 43 - Synthesis of 11-membered medium-sized rings
Passerini reaction with TFA/Py, acetic acid or $N$-Boc glycine afforded the desired products 5.192, 5.193 or 5.194 in 68 to $78 \%$ yields. The Ugi reaction of 5.133b afforded amide 5.195 in $61 \%$ yield. No transannular cyclization was observed in these cases.


Figure 44 - Difference between the 10 - and 11-membered $\alpha$-ketoamide
Figure 44 shows the two computed (DFT, 6-31G(+)d, B3LYP) structures of the intermediate of 5.191 and 5.192. Dihedral angles of the attack of the nitrogen amide onto the carbonyl as well as N -C distances are highlighted in Table 37. As observed, the cyclization rate correlated well with the computed dihedral angle. The closer to the Bürgi-Dunitz the angle was, the faster the cyclization occurred. Moreover, the distance between the amide nitrogen and the carbonyl also correlated well with the experimental observations. The distance was shorter for the substrates cyclizing easily.

| Entry | Product | Dihedral angle | $\mathrm{N}-\mathrm{C}$ distance $[\AA \AA]$ | Cyclization $^{\text {a }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathbf{4 . 2 3 5}$ | $104.5^{\circ}$ | 3.228 | Instantaneous |
| 2 | $\mathbf{5 . 1 9 1}$ | $102.5^{\circ}$ | 3.465 | Slow |
| 3 | $\mathbf{5 . 1 9 2}$ | $96.7^{\circ}$ | 3.702 | None |

( $\mathrm{a}:$ Instantaneous = no observation of the intermediate, slow $=$ observation of the intermediate, none $=$ no cyclization observed)
Table 37 - Dihedral angles and distance for the amide transannular attack onto the ketone in various structures

12-membered rings were also obtained in excellent yields (Figure 45). The Passerini reaction proved again very powerful and the alcohol 5.196 was obtained in $92 \%$ yield. 5.197 and 5.198 were delivered in $85 \%$ each. Ugi 3-component 4-center reaction afforded 5.199 in good yield.





Figure 45 - Synthesis of 12-membered macrocycles
Similar results were obtained for the formation of 13-membered rings (Figure 46). It is to note that in this case the $\alpha$-ketoamide 5.204 was obtained in $60 \%$ yield.






Figure 46 - Synthesis of 13-membered macrocycles
We then continued to increase the ring size but we also moved towards another ring topology. Aniline derivative 5.158 was cyclized to form 14-membered macrocycles (Figure 47).

5.205

66\%





Figure 47 - Synthesis of 14-membered macrocycles
Passerini reaction with TFA afforded the desired product 5.205 in $66 \%$ yield. On the other hand, reaction of 5.158 with acetic acid or $N$-Boc glycine afforded the corresponding ester 5.206 and 5.207 in 77 and $93 \%$ yield respectively. Ugi reaction also proved compatible with this skeleton and the amide 5.208 was obtained in moderate yield. Finally, tetrazole formation with $\mathrm{TMSN}_{3}$ and either aniline or 4-CN-aniline afforded the desired compounds $\mathbf{5 . 2 0 9}$ and $\mathbf{5 . 2 1 0}$ respectively in $28 \%$ and $24 \%$ yield each.


Figure 48 - Synthesis of 15-membered macrocycles containing a phenol moiety
Phenol-containing 15 -membered rings were also synthesized (Figure 48). Passerini reactions afforded the alcohol 5.211 and the esters 5.212 and 5.213 in excellent yields. The $\alpha$-ketoamide 5.214 was obtained in $71 \%$ yield using the oxidative Ugi procedure. In this case, no trace amount of enamine was observed even without acidic workup. This was probably due to the fact that, in this case, no conjugation could favor and stabilize the enamine as in 5.190. Ugi reaction with benzylamine and acetic acid provided access to 5.215 in $97 \%$ yield. Reaction of 5.151a with TMSN $_{3}$ and aniline afforded tetrazole 5.216 in $43 \%$ yield. Finally, an interesting new MCR involving N hydroxy succinimide and benzylamine catalyzed by $\mathbf{Z n C l}_{2}$ furnished compound $\mathbf{5 . 2 1 7}$ albeit in low yield. ${ }^{459}$






Figure 49 - Synthesis of 15-membered macrocycles containing an indole moiety
The indole skeleton was also compatible with 15 -membered ring formation (Figure 49). The yields obtained were significantly lower than the ones on Figure 48. Pre-organization in the substrate 5.151a could explain the higher yields. For instance, hydrogen-bonding of the amide NH with the phenol oxygen could lower the conformational freedom of the side chains. High chemical shift of the amide proton ( $>8.00 \mathrm{ppm}$ ) as well as broad signal in infrared at $\sim 3400 \mathrm{~cm}^{-1}$ indicated that such hydrogen bonding exist in both the starting material 5.151a and in the final products 5.211-5.217. This kind of interaction did not exist in 5.141 (B).

[^169]



## Scheme 276 - Possible conformational pre-organization for the phenol based substrates

We then turned our attention towards the formation of bigger ring sizes such as 22 -membered macrocycles (Figure 50). Alcohol 5.225 and esters 5.226 and 5.227 were obtained in good yields. Oxidative Ugi reaction provided $\alpha$-ketoamide 5.228 in $68 \%$ yield. The Ugi reaction with benzylamine and acetic acid afforded 5.229 in $78 \%$ yield. Finally, we were able to obtained tetrazole $\mathbf{5 . 2 3 0}$ in 53\% yield.







Figure 50 - Synthesis of 22-membered macrocycles
Again, pre-organization of 5.151b could explain the high yields observed. Additional hydrogenbond could occur with the NH of the amide and the ether oxygen (Scheme 276, C). Again ${ }^{1} \mathrm{H}$ NMR and infrared confirmed the presence of such interactions in the starting material 5.151b and in the products 5.225-5.230.

Finally, m-cyclophane 5.231 was obtained in $9 \%$ yield (Figure 51, A). The dimer 5.232, in the form of two diastereoisomers was obtained in $26 \%$ yield. Lowering the concentration of the reaction to 0.002 M (instead of 0.01 M ) slightly improve the result ( $20 \%$ for the desired product). On the other hand, the corresponding $p$-cyclophane 5.233 was obtained in $61 \%$ yield (B) No trace amount of the dimer was observed in this case.
(A)

5.231
a: $9 \%$ at 0.01 M
b: $20 \%$ at 0.002 M

5.232
a: $26 \%, 1: 1 \mathrm{dr}$ at 0.01 M

Figure 51 - Synthesis of $m$ - and $p$-cyclophanes
The higher yield obtained for $\mathbf{5 . 2 3 3}$ compare to the apparently less strained $m$-cyclophane $\mathbf{5 . 2 3 1}$ could be attributed to the steric interaction between the ortho proton $(\mathrm{H}-\mathrm{a})$ with the macrocycle ring (Figure 52). Such steric clash did not exist in the $p$-cyclophane 5.233.


Figure 52 - Optimized (DFT, 6-31G(1)d, B3LYP) geometry of the obtained $m$ - and $p$-cyclophanes
We then focused on the linear aliphatic $\omega$-isocyanoaldehydes (Scheme 277). In order to better understand the reactivity and the possibility offered by $\omega$-isocyanoaldehydes, we attempted to repeat two of the best reported examples by Saxena and coworkers for the synthesis of 6- to 8membered rings (A). The reactions of $\mathbf{5 . 1 7 2}$ proved very messy and no desired products were observed. The isolated isocyanoaldehyde 5.174 was also submitted to Ugi and Passerini reactions conditions without any success (B). Finally, in situ oxidation of the $\omega$-isocyanoalcohols 5.177 failed to afford any desired compounds (C). We reasoned that the isonitrile attack onto the aldehyde/imine could not occur because of geometrical constrains.


Scheme 277 - Attempts for the cyclization of aliphatic $\omega$-isocyanoaldehydes
Table 38 summarizes the obtained results. Passerini reactions were in general higher yielding than the Ugi ones. The use of $N$-Boc glycine was in general better than TFA or acetic acid. Formation of tetrazole proved in general less efficient than other ring-closing methods. Comparing all the indole tethered entries, the yields mostly followed the ring strain of cycloalkanes.

| Entry $^{\mathrm{a}}$ | Ring size | Tether | OH <br> $[\%]$ | OAc <br> $[\%]$ | OGly <br> $[\%]$ | $=0$ <br> $[\%]$ | NBnAc <br> $[\%]$ | $\mathrm{N}_{3}$ <br> $[\%]$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 9 | Indole | 44 | 50 | 55 | - | 43 | 35 |
| 2 | 10 | Indole | 59 | 62 | - | 79 | 89 | - |
| 3 | 11 | Indole | 68 | 72 | 78 | - | 61 | - |
| 4 | 12 | Indole | 92 | 85 | 85 | - | 57 | - |
| 5 | 13 | Indole | 83 | 62 | 73 | 60 | 54 | - |
| 6 | 14 | Aniline | 66 | 77 | 93 | - | 56 | 24 |
| 7 | 15 | Indole | 51 | 57 | 58 | - | 30 | 23 |
| 8 | 15 | Phenol | 84 | 91 | 95 | 71 | 97 | 43 |
| 9 | 16 | m-cyclophane | - | 20 | - | - | - | - |
| 10 | 17 | p-cyclophane | - | 61 | - | - | - | - |
| 11 | 22 | Phenol | 71 | 85 | 80 | 68 | 78 | 53 |

(a: Refer to Scheme 275: OH = 5.180, OAc = 5.178, OGly =5.179, $=\mathrm{O}=5.182, \mathrm{NBnAc}=5.181, \mathrm{~N}_{3}=5.183$ )
Table 38 - Comparison of the yields for the macrocyclization
We aimed to implement our newly developed methodology to the synthesis of (-)-eurystatin B (5.1). We planned to determine its absolute configuration as well as to probe our methodology in a much more complex scaffold.

## 5.3 (-)-Eurystatin A and B

### 5.3.1 History, Structures and Production of Analogues

(-)-Eurystatin A (5.236) and B(5.1) (Figure 53) were isolated in 1991 from the bacteria Streptomyces eurythermus R353-21. ${ }^{460}$ They were originally called BU-4165E A and B respectively. ${ }^{461}$ The strain R353-21 was isolated from a soil sample collected in India.


Figure 53 - Structure of the naturally occurring (-)-eurystatin A and B as well as the biosynthetic C-F
They are 13-membered macrocycles containing an $\alpha$-ketoamide function. They are both composed of three different amino acids, a L-leucine (Leu), a L-ornithine (Orn) and a (S)-3-amino-2-oxobutyric acid (AOB) (derived from L-alanine). (-)-Eurystatin A (5.236) contains a (E)-6-methyl-hept-2-en-oic acid moiety whereas (-)-eurystatin $B(5.1)$ features a $(E)$-6-methyl-oct-2-en-oic acid $\left(F A_{2}\right)$ moiety. Therefore, the only difference between these two natural products is only their side chain.

Interestingly, to the best of our knowledge, nobody had reported the absolute configuration of the side chain of (-)-eurystatin $B(\mathbf{5 . 1})$ at position $\mathrm{FA}_{2}-6$. On the other side, the absolute conformation of each amino acids composing (-)-eurystatin B was determined by acid degradation, purification and chiral HPLC analysis.
(-)-Eurystatin A (5.236) and B (5.1) could be produced by fermentation. 220 L of fermentation broth afforded 85 mg of 5.236 and 45 mg of $\mathbf{5 . 1}$. Analogues were synthesized by controlled biosynthesis using supplementation of valine and isoleucine. Eurystatin C-F ( 5.237 to 5.240 ) were obtained featuring a valine or an isoleucine instead of the leucine amino acid. ${ }^{462}$

### 5.3.2 Biological Activity

(-)-Eurystatin A (5.236) and B(5.1) were both described as potent prolyl endopeptidase (PED) inhibitors (Figure 54). PED, a serine protease, is known to catalyze the hydrolysis of various biologically active peptides such as oxytocin, bradykinin, neurotensin, substance P , angiotensin I and II

[^170]and vasopressin at the carboxyl side of their proline residue. This enzyme is considered to play a key role in the biological regulation of these peptides.


Figure 54 - X-ray structure of the human $\operatorname{PED}^{463}$ and the structure of other known serine protease inhibitors

As shown in Table 39, (-)-eurystatin B (5.1) is much more potent than (-)-eurystatin A (5.236). Compared to Cbz-Val-prolinal, a synthetic inhibitor, and poststatin, another natural product also known to be a good PED inhibitor, (-)-eurystatin B (5.1) has similar activity. Eurystatins proved highly selective. ${ }^{464}$ Other peptidase such as trypsin (Try) and elastase (Ela) were not inhibited at all.

| Entry | Compound | $\mathrm{IC}_{50}[\mathrm{ng} / \mathrm{mL}]$ |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | PED <br> (Flavobacterium) | PED <br> (Rabbit) | Try $^{\text {a }}$ | Ela $^{\text {b }}$ |
| 1 | Eurystatin A (5.236) | 3.7 | 85 | $>100000$ | $>100000$ |
| 2 | Eurystatin B (5.1) | 2.1 | 31 | $>100000$ | $>100000$ |
| 3 | Poststatin (5.241) | 3.0 | - | $>100000$ | $>100000$ |
| 4 | Cbz-Val-prolinal | 3.6 | 16 | $>100000$ | $>100000$ |
| 5 | Leupeptin (5.243) | $>100000$ | - | 1400 | $>100000$ |
| 6 | Antipain (5.242) | $>100000$ | - | 700 | $>100000$ |
| 7 | Elastatinal (5.244) | 75000 | - | $>100000$ | 700 |

( $\mathrm{a}:$ Try = trypsin; b: Ela = elastase)
Table 39 - IC $\mathrm{IC}_{50}$ of (-)-eurystatin $A$ and $B$ as well as other naturally occurring protease inhibitors
Poststatin (5.241), a linear $\alpha$-ketoamide, showed similar features. This natural compound was isolated in 1991 from Streptomyces viridochromogenes MH534-30F3. ${ }^{465}$ Studies revealed that its ac-

[^171]tivity was in majority due to the $\alpha$-ketoamide function. This is probably also valid for (-)-eurystatin $A(5.236)$ and $B(5.1)$.

On the other hand, other natural products such as leupeptin (5.243), antipain (5.242) and elastatinal (5.244) feature an aldehyde moiety which is also thought to be responsible for the inhibitory activities. Nevertheless, they proved much less active than eurystatins.

Neither (-)-eurystatin A (5.236) nor B (5.1) showed antimicrobial activities at $100 \mathrm{~g} / \mathrm{mL}$ against the bacteria and fungi tested. Moreover, no behavioral effect or lethal toxicity was observed on 25 g male mice treated with $200 \mathrm{mg} / \mathrm{kg}$ of these two compounds over a period of 10 days. Therefore, eurystatins were patented, in combination with other enzyme inhibitors, for the treatment of arteriosclerosis for instance. ${ }^{466}$

### 5.3.3 Previous Syntheses

No chemical synthesis of (-)-eurystatin B (5.1) has been reported. On the other hand, (-)-eurystatin A (5.236) was synthesized three times. The first synthesis was reported in 1994 by Schmidt and coworkers (Scheme 278). ${ }^{467}$


Scheme 278 - Schmidt's synthesis of (-)-eurystatin A
Their synthesis featured a Passerini reaction between an isonitrile derived from L-leucine 5.245, an aldehyde derived from L-alanine 5.246 and benzoic acid. The product 5.247 was obtained in $85 \%$ yield as a mixture of diastereoisomers (1:1 dr). A four-step sequence converted the latter into 5.248 with the introduction of the L-ornithine amino acid. Another three-step sequence converted

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${ }^{467}$ Schmidt, U.; Weinbrenner, S. J. Chem. Soc., Chem. Commun. 1994, 1003-1004.
5.248 to the macrocyclization precursor 5.249. 5.249 was cyclized using $\mathrm{NaHCO}_{3}$ and delivered macrocycle 5.250. One diastereoisomer of 5.249 cyclized in $72 \%$ yields whereas the other one afforded the desired product $\mathbf{5 . 2 5 0}$ in $63 \%$. This represented again the importance of substrate conformation on the cyclization outcome. Both diastereoisomers 5.250 were then oxidized to deliver the $\alpha$-ketoamide 5.251 in $75 \%$ and $30 \%$ yield. Cbz-removal and coupling of the primary amine with the side chain afforded (-)-eurystatin A (5.236). This synthesis featured a macrolactamization at the ornithine/alanine junction. The benzoic was used for the Passerini reaction but was subsequently cleaved and discarded.

Wasserman and coworker disclosed in 1997 the second synthesis of (-)-eurystatin A (5.236) (Scheme 279). ${ }^{468}$ They targeted intermediate $\mathbf{5 . 2 5 7}$ and proposed two different ways for its access.


Scheme 279 - Synthesis of (-)-eurystatin A by Wasserman and coworkers
In the first sequence (A), L-alanine derivative $\mathbf{2 . 2 5 2}$ was initially condensed with cyanophosphorane $\mathbf{2 . 2 5 3}$ to afford the acyl cyano ylide $\mathbf{2 . 2 5 4}$ in good yield. Ozonolysis followed by addition of $L$ leucine derived amine $\mathbf{5 . 2 5 5}$ and treatment with $\mathrm{AgNO}_{3}$ allowed the conversion of $\mathbf{2 . 2 5 4}$ into $\mathbf{2 . 2 5 6}$ in $67 \%$ yield. A 2 -step sequence converted the latter into the tripeptide $\mathbf{2 . 2 5 7}$.

In the second sequence (B), Fmoc-Ala-OH (5.258) was condensed with 2.253 in a similar manner to afford 2.259. A 2 -step sequence allowed the introduction of the $L$-ornithine amino acid. $\mathbf{2 . 2 6 0}$ was then submitted to the same conditions for the conversion of the acyl cyano ylide to the $\alpha$ ketoamide 5.257 in $76 \%$ yield.

[^172]For the completion of the synthesis (C), $\mathbf{5 . 2 5 7}$ was deprotected using TFA and the ammonium salt 5.261 was then cyclized using DPPA at low temperature to afford 5.262 in $89 \%$ yield over 2 steps. A two-step sequence allowed the formation of (-)-eurystatin A (5.236). In this strategy, the macrolactamization occurred at the ornithine/leucine junction. Great care had to be taken during all the synthesis because of the labile $\alpha$-ketoamide function and the easy epimerization its $\alpha$ stereocenter. ${ }^{469}$

The last synthesis was reported in 2001 by Semple and coworkers (Scheme 280). ${ }^{470}$ They planned a macrocyclization between the leucine and the ornithine via peptide coupling.


## Scheme 280 - Semple's synthesis of (-)-eurystatin A

Their synthesis started with a Passerini reaction using an aldehyde $\mathbf{5 . 2 6 3}$ derived from $L$-alanine, an isonitrile 5.264 derived from L-leucine and the carboxylic acid $\mathbf{5 . 2 6 5}$ derived from L-ornithine. 5.266 was obtained in $80 \%$ yield as a mixture of diastereoisomers (1:1.2 dr). Treatment of the latter with diethylamine promoted the Fmoc deprotection and the acyl migration to furnish $\mathbf{5 . 2 6 7}$ in 75\% yield. This Passerini Reaction-Amine Deprotection-Acyl Migration was also sometimes referred as PADAM. The benzyl and Cbz group were hydrogenated and the resulting amino acid 5.268 was cyclized in $85 \%$ yield using DPPA at low temperature. A three-step sequence consisting of deprotection, acylation and oxidation afforded (-)-eurystatin A (5.236). The late-stage formation of the $\alpha$-ketoamide moiety avoided all possibility for its epimerization. Moreover, the use of the acyl migration strategy avoided the use of a dummy acid for the Passerini reaction and was therefore much more atom-economical.

[^173]
### 5.3.4 Synthesis of (-)-Eurystatin B

### 5.3.4.1 Retrosynthesis




Scheme 281 - Retrosynthesis of (-)-eurystatin B
Our retrosynthesis started by the disconnection of the side chain $\mathbf{5 . 2 7 0}$ from the macrocycles 5.269. This disconnection could allow an easy divergent synthesis of both diastereoisomers at the $\mathrm{FA}_{2}-6$ position of $(-)$-eurystatin $\mathrm{B}(5.1)$ in order to determine the absolute configuration of the side chain. The macrocycle 5.269 was planned to be synthesized using our developed macrocyclization methods using the $\omega$-isocyanoaldehyde 5.271. The latter was disconnected to $\mathbf{5 . 2 7 2}$ in order to protect the sensitive isonitrile and the aldehyde moieties. The tripeptide derivative 5.272 was disconnected between the leucine and the ornithine amino acids. The resulting dipeptide 5.274 was planned to be accessed by peptide coupling between alanine and ornithine derivatives 5.265 and 5.275 .

### 5.3.4.2 Synthesis

We started our synthesis with the formation of the 3 different amino acid derivatives (Scheme 282).

L-Alanine (5.276) was first Boc-protected to afford 5.277 in good yield. The latter was then converted to the Weinreb amide 5.278. A final Boc deprotection afforded the ammonium salt $\mathbf{5 . 2 7 5}$ in $99 \%$ yield (A). ${ }^{471}$ On the other side, $L$-ornithine hydrochloride (5.279) was protected at the terminal nitrogen of the side chain using a two-step procedure. Treatment of 5.279 with $\mathrm{CuSO}_{4}$ and NaOH allowed the formation of a Cu dimer. Addition of CbzCl and $\mathrm{K}_{2} \mathrm{CO}_{3}$ protected the terminal nitrogen to afford 5.280. The dimer $\mathbf{5 . 2 8 0}$ was decomposed using EDTA and NaOH leading to 5.281 in $85 \%$ yield over 2 steps. $N$-Boc protection of 5.281 furnished the desired ornithine derivative

[^174]5.265 (B). ${ }^{472}$ Finally, L-leucine (5.282) was protected with CbzCl to afford the desired compound 5.273 in quantitative yield (C). ${ }^{473}$


Scheme 282 - Synthesis of the starting amino acid derivatives
With the amino acid derivatives in hands, we turned our attention to the synthesis of the cyclization precursor 5.272 (Scheme 283).


Scheme 283 - Synthesis of the cyclization precursor 5.286
The ornithine derivative 5.265 was coupled with the Weinreb amide $\mathbf{5 . 2 7 5}$ under standard peptide coupling conditions to afford 5.283 in $91 \%$. Hydrogenolysis of the Cbz group allowed the formation of the primary amine 5.274 in $94 \%$ yield. ${ }^{474}$ Peptide coupling between $\mathbf{5 . 2 7 4}$ and leucine derivative 5.273 under similar conditions afforded the tripeptide 5.284 in $82 \%$ yield. Removal of $N$-Cbz group $\left(\mathrm{Pd}(\mathrm{OH})_{2}, \mathrm{H}_{2}, \mathrm{EtOAc}\right)$ from 5.284 furnished 5.285. The primary amine was formylated using the in

[^175]situ formed acetyl formyl mixed anhydride. The resulting compound 5.272 was reduced using $\mathrm{LiAlH}_{4}$ and the desired aldehyde 5.286 was obtained in $92 \%$ yield.

With the precursor 5.286 in hands, we then explored the macrocyclization reaction (Scheme 284). Because we noticed a high instability of the $\omega$-isocyanoaldehyde 5.271 , the latter was never evaporated in vacuo and was used as a DCM solution.


Scheme 284 - Macrocyclization of the $\omega$-isocyanoaldehyde 5.271
Reaction of 5.271 with TFA in DCM in the presence of pyridine at room temperature afforded the macrocycle 5.269 in $83 \%$ yield as a mixture of diastereoisomers (1:1.2 dr) (A). Similar Passerini reaction using acetic acid allowed the formation of 5.287 in similar yield and with the same $d r$ (B). Finally, we attempted the modified oxidative-Ugi reaction and we were indeed able to obtain directly the $\alpha$-ketoamide $\mathbf{5 . 2 8 8}$ in good yield. Unfortunately the $\alpha$-center epimerized leading to a 1:1 mixture of diastereoisomers (C). All attempts to refine the conditions to avoid the epimerization failed. The reason probably relied on the imine-enamine tautomerism as observed previously with the formation of the 6-6 fused ring system. With the alcohol 5.269 in hands, we then simply performed the Boc deprotection and 5.289 was obtained.

We then needed to synthesize the two enantiomers of the acid side chain $\mathbf{5 . 2 7 0}$ (Scheme 285).


Scheme 285 - Synthesis of the two enantiomers of the fatty acid side chain $\mathbf{5 . 2 7 0}$

The less expensive (S)- $\beta$-citronellol (5.290a) was tosylated. The resulting compound 5.291a was reduced using $\mathrm{LiAlH}_{4}$ and 5.292a was obtained in 74\% yield. Ozonolysis of the alkene delivered the aldehyde 5.293a in good yield. ${ }^{475}$ Wittig reaction between 5.293a and the ylide 5.294 afforded the $(E)$-enoate which was in situ deprotected to deliver the acid 5.270 a in $85 \%$ yield. ${ }^{468}$ The sequence was repeated from (R)- $\beta$-citronellol (5.290b) and 5 .270b was obtained in similar yields.


Scheme 286 - Synthesis of the two diastereoisomers of (-)-eurystatin B from macrocycle 5.289
Using the primary amine 5.289, we then attempted the synthesis of the two diastereoisomers of (-)-eurystatin B at the $\mathrm{FA}_{2}-6$ position (Scheme 286). Peptide coupling between 5.289 and 5.270a afforded 5.296a in 91\% yield (1:1.2 dr). The Parikh-Doering oxidation of the alcohol 5.296a afforded 5.297 a in $75 \%$ yield (A). ${ }^{470}$ Using 5.70 b as coupling partner, cyclopeptide 5.289 was converted to 5.297 b in a similar overall yield (B).
${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra as well as the optical rotation of 5.297 a correlated well with the data of the natural (-)-eurystatin B (3.1). We therefore unambiguously attributed the absolute configuration at position $\mathrm{FA}_{2}-6$ as $(R)$ (see: 5.3.4.5 - Structure Determination of (-)-Eurystatin B).

### 5.3.4.3 Other Approaches

Two similar approaches have been explored in parallel.
We first hypothesized that performing the Passerini reaction of 5.271 using 5.270a could allow a subsequent acyl migration (PADAM) to incorporate the side chain directly (Scheme 287).

Passerini reaction of 5.271 with 5.270a afforded the desired product 5.298 in good yield (1:1.2 dr). We then performed the deprotection of the Boc group and the primary amine 5.299 was obtained in quantitative yield. Unfortunately, transamidation of 5.299 failed to produce the desired product

[^176]5.296a. ${ }^{476}$ Hydrolysis of ester 5.299 to alcohol 5.289 was the side reaction often observed. It is to note that, in our case, O - to N -acyl migration probably should occur in an intermolecular way. Indeed, formation of an 8-membered transition state in structure $\mathbf{5 . 2 9 9}$ looked unlikely to occur.


Scheme 287 - Alternative strategy using an acyl migration step



Scheme 288 - Alternative strategy relying on the use of $N$-formyl L-leucine
We also envisioned an alternative pathway for the formation of 5.286 in a shorter sequence (Scheme 288).

[^177]L-Leucine (5.282) was formylated to formamide 5.300 (A). ${ }^{472}$ Peptide coupling between the latter and amine 5.274 afforded the desired tripeptide 5.272 in $85 \%$ yield. Despite the shorter route (1 step vs 3 step), $\mathbf{5 . 2 7 2}$ was isolated as a 19:1 mixture of separable diastereoisomers. The major stereoisomer was identified as the desired product. The reason for the formation of the other diastereoisomer arose probably from the use of the partially racemized formamide 5.300. Indeed, epimerization could occur during the formylation of L-leucine (5.282) (Scheme 289, A).


Scheme 289 - Partial racemization during the synthesis and peptide coupling of 5.300
Formylation of 5.282 could occur with concomitant activation of the carboxylic acid in the form of a mixed anhydride $5.301(X=O C(O) R)$. 5.301 could simple be hydrolyzed to afford the unepimerized formamide 5.300 . On the other hand, 5.301 could also cyclized to form oxazol-5(4H)one 5.302. The latter could then easily tautomerize to the achiral oxazol-5-ol 5.303. Reformation of the racemic lactone rac-5.302 followed by hydrolysis could afford racemic rac-5.300.

During the peptide coupling of 5.300 with 5.274 , epimerization could also occur following two different pathways ( $\mathrm{X}=$ activating agent such as HOBt, $\mathrm{Y}=$ dipeptide). Similar oxazol-5-ol intermediate 5.303 could account for partial epimerization (B). On the other hand, a base-promoted tautomerism pathway could also occur (C).

### 5.3.4.4 Summary of the Synthesis

(-)-Eurystatin B (5.1) was obtained in 9 steps (longest linear sequence) and $38 \%$ overall yield from the commercially available amino acids derivatives 5.265, 5.275 and 5.300 and in an enantiomeric pure form (Scheme 290). This synthesis featured a key C-C bond forming macrocyclization using a 2-component 3-center Passerini reaction to form the core 13-membered ring.


Scheme 290 - Summary of our total synthesis of (-)-eurystatin B

### 5.3.4.5 Structure Determination of (-)-Eurystatin B

With both diastereoisomers in hands, we then carefully compared the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra as well as the optical rotation between the (-)-natural eurystatin B (5.1) and the two synthesized diastereoisomers 5.297a and 5.297b in order to determine the absolute configuration at $\mathrm{FA}_{2}-6$.

Table 40 shows the comparison of the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of both natural and synthetic (-)eurystatin $B$ (5.1) as well as its diastereoisomer.

The carbon and proton chemical shifts of 5.297 a correlated well with the isolated natural product. The carbon and proton chemical shifts of 5.297 b also correlated well but main differences could be found around the $\mathrm{FA}_{2}-6$ stereocenter.

( $\mathrm{a}: \mathrm{In}$ DMSO- $\mathrm{d}_{6} / \mathrm{CDCl}_{3} 1: 2$ )
Table 40 - Comparison of NMR data between the isolated and the synthesized (-)-eurystatin B and its diastereoisomer

| Entry | Compound | $[\alpha]_{D^{26}}$ |
| :---: | :---: | :---: |
| 1 | Natural $(-)$-eurystatin B (5.1) | $-96^{\circ 461}$ |
| 2 | $5.297 \mathbf{a}\left(\mathrm{FA}_{2}-6=R\right)$ | $-92^{\circ}$ |
| 3 | $5.297 \mathrm{~b}\left(\mathrm{FA}_{2}-6=S\right)$ | $-12^{\circ}$ |

(a: $c=0.25$ in DMSO)
Table 41 - Comparison of the optical rotation of the isolated and the synthesized (-)-eurystatin B and its diastereoisomer

The optical rotation of synthetic (-)-eurystatin B (5.1) correlated well with the one of 5.297a (Table 41). This observation, in combination with the one of the NMR data prompted us to unambiguously assign the stereochemistry of $\mathrm{FA}_{2}-6$ of (-)-eurystatin $\mathrm{B}(5.1)$ as $(R)$.

### 5.4 Conclusion and Outlook

In conclusion, we extended the scope of our newly developed macrocyclization method using $\omega$ isocyanoaldehyde that was originally discovered during the total synthesis of (+)-peganumine A (4.1). ${ }^{477}$

9- to 22-membered rings were obtained in moderate to good yields (Figure 55). In addition to the Passerini and oxidative Ugi reaction, we probed the use of Ugi and modified Ugi reaction with TMSN ${ }_{3}$ for the ring closing step and they all proved to work efficiently.





$\alpha$-Amido amide




Figure 55 - Examples of synthesized macrocycles
Besides having access to macrocycles fused with indole and phenyl rings, we were also able to obtain $m$ - and $p$-cyclophanes (Figure 56).

[^178]
5.231
$20 \%$


Figure 56 - $p$ - and $m$-cyclophane synthesized using a 2-component 3-center Passerini reaction
Finally, in order to highlight the power of this new macrocyclization method, we applied it to the total synthesis of (-)-eurystatin B(5.1) (Scheme 291). The latter was obtained in 9 steps with $38 \%$ overall yield. This synthesis featured a key C-C bond forming macrocyclization using a 2component 3-center Passerini reaction to form the core 13-membered ring. We were also able to unambiguously determine the absolute configuration of $(-)$-eurystatin $\mathrm{B}\left(\mathrm{FA}_{2}-6=(R)\right)$.


Scheme 291 - Total synthesis of (-)-eurystatin B and determination of its absolute configuration at $\mathrm{FA}_{2}-6$

# Chapter 6 Silver-catalyzed Three-component 1,1-Aminoacylation of Homopropargylamines 

This work was realized in collaboration with Dr. Shuo Tong.

### 6.1 Introduction

Among the multicomponent reaction substrates, alkynes and isonitriles are both popular partners. ${ }^{38}$ However, the combination of terminal alkynes and isonitriles, two active triple bond containing reagents, has not been fully exploited. This was probably due to the relatively easy homocoupling of terminal alkynes and oligo-/polymerization of isonitriles in the presence of transition metal catalysts. It is to note that, opposite to terminal alkynes, dimethyl acetylene dicarboxylate (DMAD) has been extensively used as reaction partner in isonitrile-based MCR. ${ }^{42 a, 42 b, 478}$

### 6.1.1 Aim of the Project

Concerning the cross-coupling reaction between terminal alkynes and isonitriles, Fukumoto and coworkers developed a rhodium-catalyzed three-component coupling of alkynes 6.1, isocyanides 1.99, and silanes 6.2 for the synthesis of 4-silyl-1-azadienes 6.3 (Scheme 292, A). ${ }^{479}$ On the other hand, Odom and coworkers reported a titanium-catalyzed three-component reaction of terminal alkynes 6.1, isocyanides 1.99, and amines 1.122 for the synthesis of $\alpha, \beta$-unsaturated $\beta$ iminoamines 6.4 (B). ${ }^{480}$ Since Odom's seminal report, many one-pot transformations initiated by the same first 3-component reaction, followed by subsequent modifications of 6.4 have been reported. ${ }^{481}$


Scheme 292 - Previously developed multicomponent reactions using terminal alkynes and isonitriles

[^179]In both cases, an isocyanide and another nucleophile (amine or silane) added across the triple bond of a terminal alkyne to afford 1,2-difunctionalized products.


Scheme 293 - Previous reports about the use of propargylamines and isonitriles from our group
Our lab has a long term interest in the chemistry of isonitriles. Recently, we developed an efficient synthesis of imidazole 6.6 and imidazolium 6.7 from isonitriles and propargylamine 6.5 in the presence of multiple catalysts (Scheme 293, A). ${ }^{482}$ The reaction was initiated by an $\mathrm{Yb}(\mathrm{OTf})_{3^{-}}$ promoted isonitriles insertion into the $N-H$ bond of propargylamine 6.5, followed by a AgOTf catalyzed 5-exo-dig cyclization (C). Similar reaction was observed using primary propargylamine 6.8. A catalyst-loading dependent regioselective cyclization afforded 6.9 or 6.10 (B), respectively. ${ }^{483}$


## Scheme 294 - Aim of the project

Although the oxidative functionalization of terminal alkynes via metal vinylidene intermediates is well developed, ${ }^{484}$ the transformation involving cyclizative 1,1-aminoacylation of terminal alkynes was, to the best of our knowledge, unknown. ${ }^{485}$

[^180]Homopropargylamines 6.15, which contained one amino group and one terminal alkyne motif, are easily available bifunctional reagents. As a continuation of our research interest in the development of isonitrile-based novel transformations, and transition-metal-catalyzed domino reactions, we decided to promote the conversion of homopropargylamines 6.15 to proline amide derivatives 6.18 via 5-endo-dig cyclization and trapping of the resulting iminiums 6.17 with isonitriles 1.99 (Scheme 294). From our previous experience with propargylamines, isonitriles and various silver catalysts, we observed that $\mathrm{Ag}(\mathrm{I})$ alone was not able to promote the formation of the undesired amidines 6.16. ${ }^{486}$


(+)-RP 66803 (6.20)

Figure 57 - Importance of proline amide derivatives in medicinal chemistry
The resulting proline amides derivatives 6.18 could be valuable building blocks in pharmaceuticals and small molecule organocatalysts (Figure 57). They can for instance be useful for the synthesis of constrained peptidomimetics. ${ }^{487}$ They are also a key structural unit of a number of pharmaceutical such as (+)-RP 66803 (6.20). ${ }^{488}$ Moreover, substituted proline derivatives are known to induce a dramatic conformational change in peptides. ${ }^{489}$

### 6.1.2 Cyclization of Homopropargylamines

The 5-endo-dig cyclization of homopropargylamines has been reported extensively using various metals such as $\mathrm{Au},{ }^{490} \mathrm{Cu},{ }^{491} \mathrm{Pd},{ }^{492} \mathrm{Zn},{ }^{493} \mathrm{Ir}$ and $\mathrm{Rh}^{494}$. Because the reason mentioned above about the undesired isonitrile insertion into $\mathrm{N}-\mathrm{H}$ bond, we focused on the use of silver.

[^181]
### 6.1.2.1 Ag-catalyzed Cyclization of Homopropargylamines to Pyrrole Derivatives

Cyclization of homopropargylamines followed by in situ oxidation of the resulting dihydropyrrole intermediates was reported by Knölker and coworker in 2004 (Scheme 295). ${ }^{495}$
(A)



(B)


Scheme 295 - Cyclization of homopropargylamines followed by in situ oxidation to pyrrole derivatives
Treatment of 6.21 with 1.1 equivalents of AgOAc in DCM at room temperature afforded the pyrrole derivative 6.22 in $71 \%$ yield (A). Acyclic substrates also worked efficiently. For instance, they were able to synthesize 6.24 in $85 \%$ yield from $6.23(A)$. The mechanism they proposed is depicted in Scheme 295, B. Silver(I)-promoted 5-endo-dig cyclization of 6.15 could afford 6.25. Intermolecular proton transfer could promote the formation of iminium 6.26. $\beta$-hydride elimination could generate 6.27 which after tautomerism could furnish the observed product $\mathbf{6 . 2 8}$. It is to note that they applied this novel methodology to the synthesis of crispine A. ${ }^{496}$

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### 6.1.2.1 Ag-catalyzed Cyclization of Homopropargylamines to 2,3-Dihydro-1H-pyrrole Derivatives

Similar cyclization could occur without the subsequent oxidation step as demonstrated by Knölker and coworkers (Scheme 296). ${ }^{497}$


Scheme 296 - Cyclization of homopropargylamines to 2,3-dihydro-1H-pyrrole derivatives
Tosylamines 6.29 or 6.31 were cyclized to the 2,3 -dihydropyrrole derivatives 6.30 and 6.32 respectively in good yields using 10 mol\% $\operatorname{AgOAc}(\mathrm{A})$. They noticed that using a stoichiometric amount of the latter was not harmful for the reaction and that no overoxidized products were observed, even after extended reaction time. The proposed mechanism was similar to the one in Scheme 295 (B). They hypothesized that the intermediate 6.35 could undergo fast tautomerisme instead of the previously described $\beta$-hydride elimination. This could be due to the effect of the strong electronwithdrawing tosyl group. This methodology was recently extended to the use of microwave conditions with similar results. ${ }^{498}$

### 6.1.2.2 Ag-catalyzed Cyclization of Homopropargylamines to 3,4-Dihydro-2H-pyrrole Derivatives

The direct access to imines from primary homopropargylamines was also developed (Scheme 297). The initial report was published by Gleiter and coworkers (A). ${ }^{499}$

A DCM solution of the diamine 6.37 was treated with AgOTf and the silver complex 6.38 was obtained in quantitative yield (A). The methodology was later developed by Rutjes and coworkers to access 5-substituted proline derivatives via 6.40 (B). ${ }^{500}$ AgOTf-catalyzed cyclization of 6.39 afforded the desired product without trace amount of the oxidized product. Later, Osipov and coworkers

[^182]extended the scope to the $\mathrm{C}-2 \mathrm{CF}_{3}$-substituted derivatives. ${ }^{501}$ Interestingly, the use of N -hydroxy homopropargylamines was also possible. ${ }^{502}$ Treatment of a DCE solution of 6.41 with catalytic amount of silver triflate afforded the nitrone 6.42 in $95 \%$ yield (C). On the other hand, similar cyclization using gold(I) catalysis furnished the oxidized product 6.43.


Scheme 297 - Cyclization of homopropargylamines to imines and nitrones

### 6.1.2.1 Ag-catalyzed Cyclization of Homopropargylamines and In situ Trapping

Finally, the cyclization of homopropargylamines followed by in situ trapping of the resulting iminiums was also reported (Scheme 298).


Scheme 298 - In situ trapping of iminiums resulting from the homopropargylamines cyclization
Hammond and coworkers treated a dioxane solution of 6.44 with AgF in order to promote the formation of iminium 6.45. The latter was subsequently trapped by $\mathrm{TMSCF}_{3}$ to afford 6.46 in $90 \%$ yield (A). ${ }^{503}$ On the other hand, an enantioselective dimerization reaction was developed using catalyst 6.48 (B). ${ }^{504}$ Silver(I)-catalyzed cyclization of 6.47 afforded 6.53 in excellent yield and diastereoselectivity. The proposed mechanism implied the initial formation of $\mathbf{6 . 4 9}$ after the cyclization. Enamine 6.49 to iminium 6.50 tautomerism followed by dimerization could furnish iminium 6.51. Aza-Friedel-Craft cyclization and rearomatization could deliver 6.53.

[^183]Among the reports dealing with the trapping of 5-membered cyclic iminium, the ones using isonitriles as nucleophile have been extensively studied.

### 6.1.3 The Ugi-Joullié and Related Reactions

The Ugi-Joullié reaction is an Ugi-3CR with the preformed cyclic imine instead of an amine and an aldehyde. It was initially developed in 1982 by Madelaine Joullié and coworkers (Scheme 299). ${ }^{505}$
(A)

(B)


Scheme 299 - Discovery of the Ugi-Joullié reaction
From the pyrrolidine derivative 6.54, TFA-deprotection/neutralization followed by the oxidation of the resulting pyrrolidine with ${ }^{\mathrm{t}} \mathrm{BuOCl}$ and elimination with NaOMe afforded the imine 6.55. The latter was reacted with ${ }^{\mathrm{t}} \mathrm{BuNC}(5.68)$ and benzoic acid to deliver the proline amide derivative 6.56 in $58 \%$ as a mixture of diastereoisomers ( $55: 45 \mathrm{dr}$ ) from pyrrolidine 6.54 (A). They noticed similar slight preference for the cis addition on other similar substrates (B). ${ }^{506}$

### 6.1.3.1 Diastereoselectivity

Based on these observations, an explanation involving two competitive mechanisms were disclosed (Scheme 300). ${ }^{507}$ Direct attack of the isonitrile 1.99 on the protonated imine 6.61 from the less hindered face could account for the formation of the trans product trans-6.63 (A). On the other hand, attack of the carboxylate from the less hindered side of the protonated imine 6.61 followed by $\mathrm{S}_{\mathrm{N}} 2$ type mechanism on the aminal 6.64 carbon could afford the cis compounds cis6.63 (B).

[^184]

Scheme 300 - Joullié's model for the observed diastereoselectivity
They also noted a solvent-effect on the diastereoselectivity. The ratio changed depending on the solvent used. They attributed these changes to the different ability of the solvents to stabilize the charge of the protonated iminium. In toluene, a solvent with a low dielectric constent $\varepsilon$, the charge could not be stabilized and therefore the mechanism B was favored (3:1 dr observed for 6.59). On the opposite, in methanol, a solvent with a high $\varepsilon$, the charge could be stabilized and therefore the pathway $A$ became more important (1.5:1 dr observed for 6.59).

Woerpel and coworkers proposed a stereoelectronic model to explain the diastereoselective addition of nucleophiles on five-membered oxocarbenium ions (Scheme 301). ${ }^{508}$ Their model was based on the fact that the five-membered oxocarbenium ions 6.65 undergo "inside" attack to form the more stable staggered conformation 6.66a (A). "Outside" attack would lead to the destabilized eclipsed product 6.66b.

Using the model reaction of oxocarbenium ions with allyl TMS they were able to conclude about the importance of the alkyl and alkoxy substituents at various positions of the ring ( $B-E$ ).

They noticed that C-3 alkyl substituents had a big influence on the diastereoselectivity (B). The 1,3trans products trans-6.68 and trans-6.70 were always obtained, whatever the substitution at C-4 was. With the 3,4-trans starting material 6.67 , the conformation 6.67 b where both groups lied in pseudo-axial positions would afford the unfavored product cis- 6.68 where a steric clash occurred between the C-3 alkyl group and the introduced nucleophile. The conformation 6.67 a was therefore faster to react to afford trans-6.68 preferentially. Similarly, the 3,4-cis starting material 6.69 afforded mainly trans-6.70 because of the steric clash generated in product cis-6.70. The C-4 alkyl group did not have any influence in this case.

With a C-3 alkoxy substituent, things were very different (C). The 1,3-cis products cis-6.72 and cis6.74 were always preferred when using 3,4-disubstituted starting materials. With substrate 6.71 having a 3,4-trans starting material, the conformation orienting both substituents in pseudo-axial positions was preferred. Even though the obtained product cis-6.72 exhibited a steric clash, the stabilization of the oxonium group with the partially negative alkoxy substituent in 6.71b favored

[^185]the formation of this product. A similar analysis could be made for the 3,4-cis starting material 6.73. Stabilization of the oxonium in 6.73b afforded preferentially cis-6.74.

The authors then investigated the influence of a C-2 alkoxy substituent (D). They notice that the 1,2-cis product cis-6.76 was obtained when using 6.75 as starting material. The explanation for this preferences could lie in the partial stabilization of the carbonyl group via $\sigma_{C-H}$ to $\pi^{*}{ }_{C-O}$ delocalization in 6.75b. Therefore, the preferred conformation of 6.75 was the one orienting the $\mathrm{H}-2$ substituent in a pseudo-axial position (6.75b).


(B)



(E)


Scheme 301 - Stereoelectronic model for the diastereoselective addition of nucleophiles onto fivemembered oxocarbenium ions

Finally, as the C-2 and C-3 alkoxy substituents proved to have a strong influence on the diastereoselectivity, the authors decided to analyze the 2,3-cis and 2,3-trans dialkoxy substrates 6.77 and 6.79 (E). For the 2,3-cis substrate 6.77 the conformation where the $C-3$ substituent lied in pseudoaxial position and the $\mathrm{C}-2$ in a pseudo-equatorial position (6.77a) was favored because of the stabilization of the oxonium group by the partial negative charge of the C-3 alkoxy substituent and by the $\sigma-\pi^{*}$ stabilization from $\mathrm{H}-2$. This led to the preferred formation of the all-cis product cis-6.78. On the opposite, for the 2,3-trans substrate 6.79, an almost 1:1 dr was observed. The slight preference for the 1,3-cis product indicated the bigger influence of the $\mathrm{C}-3$ substituent compare to the C-2 one.

The same behavior was observed for 5-membered iminium ions. The influence of the substitution pattern on the diastereoselectivity of isonitrile attack was for instance analyzed by Furman, Stecko and coworkers. ${ }^{509}$ Computational studies have been later realized by Codée, van der Marel and coworkers on similar systems (Scheme 302). ${ }^{510}$


Scheme 302 - Diastereoselectivity of the addition of isonitriles on substituted 5-membered iminium ions
The diastereoselectivity outcome was in agreement with the model proposed by Woerpel and coworkers. Their computation also revealed an interesting interaction between the C-4 alkoxy substituent and the incoming isonitrile in 6.81a (Scheme 303). They postulated that the O-4 could partially stabilize the positive charge developing on the nitrogen of the isonitrile during the addition. The difference in energy between the two conformations 6.81a and 6.81b in the ground state and the one in the transition states 6.89 a and 6.89 b increased by $0.7 \mathrm{kcal} / \mathrm{mol}$ despite the steric clash occurring during the attack of the isonitrile in 6.89a.

[^186]

Scheme 303 - Interaction between the incoming isonitrile and the C-4 alkoxy substituent
It is interesting to note that various tricks were developed to influence the diastereoselectivity of these reactions.


Scheme 304 - Change in diastereoselectivity when using an additional Lewis acid
Addition of Lewis acids was for instance responsible for a drastic change of the diastereoselectivity as demonstrated by Overkleeft and coworkers (Scheme 304). ${ }^{511}$ The reaction of imine 6.81 with isonitrile 6.90 and carboxylic acid 5.128b afforded, in MeOH the all-cis product 6.91 in $72 \%$ yield with more than 90:10 dr. Addition of 1 equivalent of LiBr resulted in a decrease of the diastereoselectivity ( $74: 26 d r$ ). $\mathrm{ZnCl}_{2}$ addition promoted the formation of 6.91 in good yield but the $d r$ decreased to 1:1. Finally, the use of $\mathrm{HgBr}_{2}$ furnished mainly the trans 1,2-product with 29:71 dr and in good yield (A).

The authors did not give any solid explanation for the change in diastereoselectivity observed when adding Lewis acids. They hypothesized 2 possibilities. Using the stereoelectronic model, the authors suggested a "disturbance" of the electronic effects by the Lewis acids, leading to a different conformational preference of the iminiums. They additionally proposed a possible coordination of the Lewis acids with the ether substituents. Their second hypothesis involved the model initially proposed by Joullié and coworkers (B). The coordination of the Lewis acids with the imine could interfere with the carboxylate adduct formation and therefore favoring the direct attack of the isonitrile (6.92).

[^187]

Scheme 305 - Solvent-dependent diastereoselective addition of isonitriles on iminiums
A similar hypothesis was proposed by Ichikawa and coworkers. ${ }^{512}$ They noticed a drastic change in diastereoselectivity when switching the solvent for the isonitrile addition onto $\mathrm{C}-2$ alkoxy substituted iminium ions (Scheme 305). Addition of ${ }^{t}$ BuNC (5.98) and benzoic acid on imine 6.93 using toluene as solvent afforded mainly the 1,2-cis compound cis-6.94. On the other hand, the same reaction in HFIP afforded the reverse diastereoselectivity with the formation of the 1,2-trans compound trans-6.94 preferentially (A).

Interestingly, they also observed an isonitrile-dependent diastereoselectivity in HFIP but not in toluene. 6.93 was reacted with acid 6.95 and isonitrile 5.68 in toluene and in HFIP and the corresponding major cis- and trans-products 6.96 respectively were obtained. On the other hand, the use of 6.94 afforded in both cases the cis-product 6.97 mainly (B).

Their proposed explanation for these observations was based on the initial model of Joullié and coworkers. In apolar solvents such as toluene (C), the contact oriented ion-pair 6.98 (with carboxylate attack from the less hindered face) was favored resulting in a $\mathrm{S}_{\mathrm{N}} 2$-type mechanism with the isonitrile attacking from the same side as the C-2 substituent. In polar solvents such as HFIP (D), the solvent-separated ion pair $\mathbf{6 . 1 0 0}$ could be preferred as a result of the solvation effect. The isonitrile could then play a role in the diastereoselectivity. Electron-rich isonitriles, such as 5.98 could prefer the more electron-positive intermediate 6.100 therefore leading to the favored transisomer trans-6.99. On the opposite, electron-poor isonitriles, such as 6.94 could prefer to react via the less positively charged intermediate 6.98, leading to the cis isomer cis-6.99 preferentially. It is

[^188]to note that they used this interesting solvent-dependence to obtain 1,2-trans derivatives in the presence of a $\mathrm{C}-2$ alkoxy substituent in the total synthesis of plusbacin $\mathrm{A}_{3} .{ }^{513}$

### 6.1.3.2 One-pot Imine Formation/Ugi-Joullié Reaction

Among all the existing reports on Ugi-Joullié reaction on 5-membered imines, a few dealt with the in situ generation of the imine itself.

One convenient in situ synthesis of the imine was the Staudinger/aza-Wittig combination (Scheme 306). ${ }^{514}$


## Scheme 306 - Staudinger/aza-Wittig/Ugi-Joullié reaction cascade

Overkleeft and coworkers developed this cascade reaction starting from azide 6.101. Treatment of the latter with $\mathrm{PMe}_{3}$ promoted the formation of the iminophosphorane 6.102. It then underwent an intramolecular aza-Wittig reaction to furnish imine 6.81. Addition of acid $\mathbf{5 . 1 2 8 b}$ and isonitrile 6.102 in the reaction mixture promoted the Ugi-Joullié reaction to deliver $\mathbf{6 . 1 0 3}$ in good yield and $d r$. Interestingly, if $\mathrm{InCl}_{3}$ was added during the last step, a reverse diastereoselectivity was observed to mainly afford the 1,2-trans product.

The imine was also in situ generated via lactam reduction as developed by Furman and coworkers (Scheme 307). ${ }^{509}$


Scheme 307 - Lactam reduction/Ugi-Joullié reaction cascade
A THF solution of lactam 6.104 was treated with $\mathrm{Cp}_{2} \mathrm{Zr}(\mathrm{H}) \mathrm{Cl}$ and the formation of imine 6.105 occurred in few hours. Addition of TFA and ${ }^{\text {t BuNC }}(6.68)$ promoted the Ugi-Joullié reaction to afford 6.106 in good yield. Interestingly, the observed $d r$ was lower than for similar described reactions.

[^189]Our hypothesis is that the zirconium could act as Lewis acid and therefore modify the diastereoselectivity.

Opposite to the work of Furman and coworkers, the imine was also successfully generated in situ via pyrrolidine oxidation using IBX (Scheme 308). ${ }^{515}$


Scheme 308 - IBX-mediated pyrrolidine oxidation/Ugi-Joullié reaction cascade
Orru and coworkers were able to oxidize pyrrolidine 6.107 using IBX in DCM at $60^{\circ} \mathrm{C}$. The imine 6.108 was directly trapped by acid 6.109 and isonitrile 6.110 to afford the proline amide derivative 6.111 in good yield and $d r(A)$. Interestingly the tethering of the C-2 and C-3 hydroxyl groups promoted the formation of the trans product almost exclusively. Absence of any additional ring was known to afford the all-cis products with excellent dr. Conformation 6.112a could be preferred over 6.112b because of the stereoelectronic effects. In this case, attack of the isonitrile probably occurred from the convex face affording mainly the observed diastereoisomer 6.113 (B).

Beside the standard Ugi-Joullié reaction, variations also exist. They rely on the addition of isonitriles on 5-membered $N$-alkyl iminium ions. The iminium was for instance generated by decarboxylation from $L$-proline (1.62) (Scheme 309). ${ }^{516}$


Scheme 309 - Decarboxylative Ugi reaction
Condensation of 1.62 with aldehyde 6.114 afforded the oxazolidin-5-one 6.115. Decarboxylation followed by protonation of the resulting 1,3-dipole 6.116 could promote the formation of iminium

[^190]6.117. ${ }^{517}$ The latter was reacted in situ with ${ }^{\text {t }}$ BuNC (5.68) to deliver proline amide derivative 6.118 in 90\% yield.

The iminiums were also formed via 1,3- and 1,5-hydride shift (Scheme 310).


Scheme 310 - Hydride shift-mediated Ugi reaction
Seidel and coworkers developed a 1,3-hydride shift/iminium trapping cascade reaction (A). ${ }^{518}$ Pyrrolidine ( 6.119 ) was condensed with aldehyde 6.120 to afford iminium 6.121. 1,3-hydride shift converted the latter to iminium 6.122. Addition of CyNC (5.35) on it furnished the proline amide derivative 6.123 in 60\% yield.

On the other hand, Wang and coworkers (B) promoted the dehydration of alcohol 6.124 with TFA to deliver oxonium 6.125. ${ }^{519} 1,5$-hydride shift allowed the conversion of the pyrrolidine 6.125 to iminium 6.126. Subsequent isonitrile $\mathbf{5 . 3 5}$ addition afforded the product $\mathbf{6 . 1 2 7}$ in $88 \%$ yield.

It is to note that other methods, such as the interrupted Ugi/Ugi-Joullié cascade reaction, ${ }^{520}$ also existed. Moreover, the Ugi-Joullié was not limited to C-1 unsubstituted imine. ${ }^{521}$

The Ugi-Joullié reaction has found many applications for instance in total synthesis ${ }^{522}$ and in medicinal chemistry. ${ }^{523}$

[^191]
### 6.2 1,1-Aminoacylation of Secondary Homopropargylamines

### 6.2.1 Initial Studies and Optimization

Our study initiated by using homopropargylamine 6.128 and tert-butyl isocyanide (5.68) as test substrates. As silver salts were known to avoid the homocoupling of terminal alkynes ${ }^{524}$ and the insertion of amine onto isonitrile, a variety of silver salts were examined. To our delight, proline amide 6.129 was isolated in several cases but the ratio between the two diastereoisomers was always nearly 1:1. It seemed that the counteranion of the silver salt influenced the results of the reaction dramatically. Although some oxidative processes took place since silver mirror were observed in all the cases of our initial entries (Table 42, entry 1-5), AgOAc turned out to be the most efficient catalyst for the formation of the desired proline amide 6.129 (entry 5). Toluene was found to be by far the best solvents among our screening (entry 5-9). Gratefully, further decreasing the amount of AgOAc until 10 mol\% increased significantly the yield of 6.129 (entry 10-15). Reducing or increasing the temperature decreased the reaction efficiency (entry 16-17). The stoichiometry of the isonitrile 5.68 was then varied (entry 18-20). 2,3 and 1.5 equivalents revealed to be similarly efficient. Finally, the effect of the concentration on the reaction was examined. More concentrated as well as more diluted reactions mixtures furnished 6.129 albeit in lower yield (entry 21-22).

Best results were observed by using AgOAc (10 mol\%) as catalyst and 5.68 (2 equiv) in toluene at $40^{\circ} \mathrm{C}$. Under these conditions, side reactions were avoided at the most extent and 6.129 was isolated in $82 \%$ yield (entry 14). Using other Lewis acids such as $\mathrm{Zn}(\mathrm{II}), \mathrm{Y}(\mathrm{III}), \mathrm{Cu}(\mathrm{I}), \mathrm{Cu}(\mathrm{II}), \mathrm{Pd}(\mathrm{II})$ and $\mathrm{Rh}(\mathrm{I})$, polymers of 6.128 and trace amount of amine insertion product were observed.

It is to note that all these reactions were directly submitted to flash column chromatography on silica gel without work-up or any kind of evaporation.

[^192]|  |  | $\text { Bunc } \xrightarrow[\mathrm{T}, \text { solvent, } \mathrm{N}_{2}]{[\text { Cat] }}$ | $\underbrace{\text { pho }}$ <br> is-6.129 |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Entry | $\begin{aligned} & \hline \text { Catalyst } \\ & \text { [mol\%] } \\ & \hline \end{aligned}$ | Solvent [M] | $\begin{gathered} 5.68 \\ \text { [equiv] } \end{gathered}$ | $\begin{gathered} \mathrm{T} \\ {\left[{ }^{\circ} \mathrm{C}\right]} \end{gathered}$ | Time <br> [h] | Yield <br> [\%] ${ }^{\text {a }}$ |
| 1 | $\mathrm{AgNO}_{3}(50)$ | Toluene (0.1) | 2 | 40 | 2 | 32 |
| 2 | AgOTf (50) | Toluene (0.1) | 2 | 40 | 2 | 16 |
| 3 | $\mathrm{AgSbF}_{6}(50)$ | Toluene (0.1) | 2 | 40 | 2 | Trace |
| 4 | $\mathrm{Ag}_{2} \mathrm{O}$ (50) | Toluene (0.1) | 2 | 40 | 2 | 27 |
| 5 | AgOAc (50) | Toluene (0.1) | 2 | 40 | 2 | 47 |
| 6 | AgOAc (50) | MeCN (0.1) | 2 | 40 | 12 | Trace |
| 7 | AgOAc (50) | DCE (0.1) | 2 | 40 | 5 | 18 |
| 8 | AgOAc (50) | THF (0.1) | 2 | 40 | 12 | Trace |
| 9 | AgOAc (50) | DMF (0.1) | 2 | 40 | 12 | Trace |
| 10 | AgOAc (40) | Toluene (0.1) | 2 | 40 | 4 | 60 |
| 11 | AgOAc (30) | Toluene (0.1) | 2 | 40 | 6 | 73 |
| 12 | AgOAc (20) | Toluene (0.1) | 2 | 40 | 10 | 74 |
| 13 | AgOAc (15) | Toluene (0.1) | 2 | 40 | 18 | 77 |
| 14 | AgOAc (10) | Toluene (0.1) | 2 | 40 | 30 | 82 |
| 15 | AgOAc (5) | Toluene (0.1) | 2 | 40 | 48 | 23 |
| 16 | AgOAc (10) | Toluene (0.1) | 2 | 50 | 18 | 77 |
| 17 | AgOAc (10) | Toluene (0.1) | 2 | rt | 48 | 43 |
| 18 | AgOAc (10) | Toluene (0.1) | 3 | 40 | 30 | 81 |
| 19 | AgOAc (10) | Toluene (0.1) | 1.5 | 40 | 48 | 78 |
| 20 | AgOAc (10) | Toluene (0.1) | 1 | 40 | 48 | 55 |
| 21 | AgOAc (10) | Toluene (0.2) | 2 | 40 | 12 | 55 |
| 22 | AgOAc (10) | Toluene (0.05) | 2 | 40 | 48 | 68 |

(a: Isolated yield, 1:1 dr in every entry)
Table 42 - Optimization of the 1,1-aminoacylation of secondary homopropargylamines

### 6.2.2 Scope of the Reaction

In order to probe the scope of the reaction, different starting materials were first synthesized.

### 6.2.2.1 Starting Material Synthesis

Most of the starting homopropargylamines were synthesized using the same synthetic route: Condensation of a primary aniline derivative with an aldehyde followed by addition of propargyl zinc bromide to the resulting imine (Scheme 311). ${ }^{525}$

[^193]

Scheme 311 - Synthesis of homopropargylamines 6.134 via propargyl zinc bromide addition on imines.
Various secondary homopropargylamines 6.134 were synthesized bearing electron-rich and -poor aromatic ring as well as a benzyl substituent on the nitrogen. Different substitution patterns, from electron-rich to electron-poor groups, were also introduced on $R^{1}$. In addition, an amide (6.134j) was also synthesized. In order to test the compatibility of internal alkynes in our reaction, 6.134a was converted to 6.135 via Sonogashira coupling ${ }^{526}$ with PhI in $89 \%$ yield.

It is to note that careful monitoring of the reaction temperature was required in order to avoid the formation of the allenic side products. Indeed, synthesis of the propargyl zinc bromide was extremely exothermic and had to be performed at high concentration (> 3 M ). It therefore easily formed the allenic products if the temperature was not monitor properly using very slow addition. Moreover, controlled formation of the propargyl zinc bromide required proper activation of the zinc dust. Acid washes as well as activation following Knoechel procedure ${ }^{527}$ using TMSCl and dibromoethane was required.

Fully unsubstituted $N$-phenyl-homopropargylamine (6.47) was synthesized (Scheme 312) by initial tosylation of the commercially available alcohol 6.136 followed by nucleophilic substitution of the resulting tosylate 6.137 by aniline (Scheme 312). ${ }^{528}$


Scheme 312 - Synthesis of the unsubstituted $N$-phenyl-homopropargylamine 6.47
We then focused on the substitution of the carbon backbone. Three different gem-dimethylsubstituted homopropargylamines $6.142,6.148$ and 6.152 were therefore synthesized.

[^194]6.142 was obtained following a similar procedure as the one reported in Scheme 311 (Scheme 313). Condensation of aniline (6.138) on enol ether 6.139 afforded imine $6.140,{ }^{529}$ which was then reacted with propargyl magnesium bromide (6.141) to afford 6.142 in $44 \%$ yield. ${ }^{530}$ Similar to propargyl zinc bromide, extreme care had to be taken for the preparation of the propargyl magnesium bromide (6.141) and its subsequent reaction in order to avoid the allenic side product.


Scheme 313 - Synthesis of C-4 gem-dimethyl-substituted homopropargylamine 6.142
On the other hand, 6.148 was obtained following a completely different strategy (Scheme 314). Commercially available alcohol 6.143 was first converted to the bromide $\mathbf{6 . 1 4 4}$. Formation of the propargyl aluminum bromide derivative followed by addition of paraformaldehyde afforded alcohol 6.145 in $59 \%$ yield. ${ }^{531}$ The latter was then tosylated $(6.146)^{532}$ and finally substituted using benzyl amine (6.147) at high temperature to afford the desired compound 6.148 in $48 \%$ yield.


Scheme 314 - Synthesis of C-3 gem-dimethyl-substituted homopropargylamine 6.148
The same bromide 6.144 was used for the synthesis of the trisubstituted homopropargylamine 6.152 (Scheme 315). It was first reduced to obtain allene 6.149. ${ }^{533}$ Deprotonation of the latter to form the propargyl anion followed by addition of phenyl methyl ketone (6.150) furnished the tertiary alcohol 6.151. ${ }^{534}$ Copper-catalysis allowed the formation of the propargyl cuprate via C-C bond cleavage and the latter was then in situ reacted with imine 6.132a to afford the desired compound 6.152 in $89 \%$ yield. ${ }^{535}$

[^195]

Scheme 315 - Synthesis of 3,3,4-trisubstituted homopropargylamine 6.152
In order to access polycyclic structures, 6.21 and 6.154 were then targeted (Scheme 316). $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$-mediated addition of allenyl potassium trifluoroborate salt (6.153) to indole (3.96) afforded 6.154 (A). ${ }^{536}$ On the other hand, tetrahydroisoquinoline (6.155) was first oxidized to $6.156^{537}$ before being reacted with freshly prepared propargyl magnesium bromide (6.141) and $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$ to afford 6.21 in $87 \%$ yield (B). ${ }^{538}$


## Scheme 316 - Synthesis of cyclic homopropargylamines

Other $N$-alkyl substrates were synthesized (Scheme 317). Benzaldehyde (5.54) was converted to the aldimine 6.157 by treatment with $\mathrm{HN}(\mathrm{TMS})_{2}$ and BuLi. The imine 6.157 was then in situ reacted with propargyl zinc bromide (6.133) and the primary amine 6.158 was obtained in $59 \%$ yield. ${ }^{539}$ The latter was subsequently reacted with different ketones and aldehydes (6.159) under reductive amination conditions. The secondary homopropargylamines 6.160 were obtained in good yields.


## Scheme 317 - Synthesis of $N$-alkyl homopropargylamines 6.160

All the previously synthesized homopropargylamines carried an electron-rich substituents on the nitrogen. We then targeted other derivatives bearing electron-withdrawing groups on the nitrogen

[^196](Scheme 318). They all would allow a simple deprotection of the final products to access N unsubstituted proline amide derivatives.


Scheme 318 - Synthesis of homopropargylamines carrying electron-withdrawing groups on the nitrogen
The primary amine 6.156 was treated with $\mathrm{Boc}_{2} \mathrm{O}$ and DMAP to afford 6.161 in $89 \%$ (A). ${ }^{540}$ On the other hand, reaction of 6.158 with various sulfonyl and acyl chlorides afforded 6.162 in moderate to good yields (B). ${ }^{541,542}$ Finally, 6.164 was obtained by nucleophilic aromatic substitution of $\mathbf{6 . 1 5 8}$ on the electron poor 2,4-dinitrofluorobenzene (6.163) (C). ${ }^{543}$

In order to influence the diastereoselectivity of the reaction, 3-methyl and 3-hydroxy homopropargylamine derivatives 6.173 and 6.180 were synthesized.


Scheme 319 - Synthesis of 3-hydroxy homopropargylamine derivatives
2-aminoethanol (6.165) was first cross-coupled with different aryl iodides 6.166. The resulting products 6.167 were then Boc-protected to afford 6.168 in good yields. ${ }^{544}$ Swern oxidation of the

[^197]latter ${ }^{545}$ followed by addition of ethynyl magnesium bromide (6.170) on the resulting aldehydes 6.169 furnished alcohols 6.171 in excellent yields. Removal of $N$-Boc group followed by $O$-silylation provided 4 different substrates 6.173 (Scheme 319).

For the synthesis of the 3-alkyl substituted homopropargylamine 6.180, a different route was used (Scheme 320). Ene-yne 6.174 was initially protected with TBSCI. mCPBA oxidation of the alkene 6.175 afforded epoxide 6.176. The latter was then reduced to deliver alcohol 6.177 in $82 \%$ yield. ${ }^{546}$ It was subsequently tosylated to deliver 6.178. The latter was substituted with aniline (6.138) at high temperature to obtain 6.179. Finally, TBAF-mediated TBS deprotection afforded the desired compound 6.180 in quantitative yield.


## Scheme 320 - Synthesis of the 3-methyl homopropargylamine derivative 6.180

We also decided to synthesize convertible as well as more elaborated isonitriles. They were easily prepared in few steps as shown on Scheme 321.




Scheme 321 - Synthesis of convertible and more elaborated isonitriles
The Linderman's isonitrile 6.184 was obtained in a three-step sequence (A). ${ }^{547}$ Benzyl alcohol 6.181 was first protected and the aniline was subsequently formylated. Dehydration of 6.183 using $\mathrm{POCl}_{3}$ afforded the desired compound 6.184 in good yield. The Ugi's isonitrile was synthesized by deprotonation/ring opening of oxazoline 6.185 and the resulting lithium alcoholate was trapped

[^198]with ethyl chloroformate to afford 6.186 in $90 \%{ }^{548}$ Finally, 6.189 was prepared in 2 steps (C). ${ }^{549}$ Acetone (6.159a), 6.187 and ammonium formate were submitted to Ugi conditions to afford 6.188 in $55 \%$ yield. Dehydration of the latter afforded 6.189 in good yield.

### 6.2.2.2 Scope

With the different starting materials in hands, we submitted them to the previously optimized reaction conditions (Figure 58).


Figure 58 - Scope of the 1,1-aminoacylation of secondary homopropargylamines
Varying the substitution pattern around the aryl group at position C-4 did not drastically influenced the yield. 6.18 a-e were obtained in 77 to $90 \%$ yield. Electron-rich as well as electron-poor substituents were therefore well tolerated. A small preference for the trans products was obtained with $2-\mathrm{Br}$ - and $3-\mathrm{Br}-\mathrm{Ph}$ substituents (6.18d-e) but in a negligible extend.

On the other hand, substituents on the nitrogen had a strong influence on the yields. $6.18 \mathrm{f}-\mathrm{I}$ were obtained in 55 to $93 \%$ yields. Electron-donating substituents on the aryl ring ( 6.18 f and 6.18 i ) induced a decrease in the yield. On the other hand, electron-withdrawing substituents ( $6.18 \mathrm{~g}-\mathrm{h}$ ) slightly increased the yield compare to unsubstituted phenyl (6.18a). It is to note that only the cis isomer was isolated in the reaction affording 6.18i. Finally, switching the aryl group for a benzyl substituent on the nitrogen afforded the desired compound 6.18j albeit in lower yield. This was in accordance with the observation that electron-rich substituents on the nitrogen afforded the products in reduced yields.

[^199]We then focused on the influence of the substitution pattern at C-4. Absence of substituent at this position promoted the formation of the desired compound 6.18 k in $47 \%$ yield. On the other hand, gem-dimethyl substituents delivered the corresponding product $\mathbf{6 . 1 8 1}$ in an improved $65 \%$ yield. It is to note that for both of these substrates $50^{\circ} \mathrm{C}$ had to be used in order to promote the reaction. By comparing these two entries, the Thorpe-Ingold effect appeared to play a significant role by facilitating the reaction when the two methyl groups were present. Nevertheless, these two reactions were less fast and effective than with the one with a Ph substituent (6.18a). This was probably due to electronic effects.

Having an amide substituent on C-4 delivered the product 6.18 m in $69 \%$ yield. A small preference for the cis product was observed but again in a very small extend.

The influence of gem-dimethyl substituents at C-3 was then analyzed. 6.18n was obtained in $78 \%$ yield. In this case, the two geminal methyl substituents at C-3 improved the cyclization yield compare to 6.18a probably again because of the Thorpe-Ingold effect. Nevertheless, in this case, $50^{\circ} \mathrm{C}$ was also required to promote the reaction. The trisubstituted substrates also proved to be competent in our methodology. Indeed, 6.18d was obtained in $72 \%$ yield. In both cases, the observed diastereoselectivity was again 1:1.

The substituents at C-4 and on the nitrogen were then tethered. The tricyclic structure 6.18p was obtained in a good $78 \%$ yield.

We finally explored the scope of the isonitriles. A secondary isonitrile, cyclohexylisocyanide, proved efficient and delivered 6.18 q in $80 \%$ yield. Aryl isonitriles were also successful. Electronrich as well as sterically hindered phenyl isocyanide derivatives afforded the desired products 6.18r-t in good yields. Finally, primary isonitriles in the form of benzylisocyanide furnished the desired product 6.18 u in $78 \%$ yield.


Figure 59 - X-ray structure of cis-6.18d

The diastereoselectivity of the reaction was assessed thanks to similar NMR patterns found in all obtained products as well as NOE experiments. We were also able to obtain an X-ray structure of cis-6.18d, confirming our stereochemical assignment (Figure 59). ${ }^{550}$

Even though the yields for most of these transformations were good, the diastereocontrol was really poor in most of the cases (Scheme 322).


Scheme 322 - Diastereoselectivity of the isonitrile addition onto the C-4 substituted N -aryl iminiums
The low diastereoselectivity of the isonitrile addition on 6.190 could be explained by the two conformers 6.190a and 6.190b. No steric clashes were generated in both the cis-6.191 and the trans6.191 products. Moreover, no major stereoelectronic or steric preference for any of the two conformers 6.190a and $\mathbf{b}$ could favor one of the two products. The aryl ring on the nitrogen did not interfere with the geometry of the conformers even though $\pi$-stacking in 6.190 a could have been hypothesized.

We were then interested in the influence of a single substituent at C-3 on the stereocontrol of the reaction (Figure 60).

>19:1 $d r$ (cis/trans) when nothing is specified
Figure 60 - Scope of the 1,1-aminoacylation of C-3 monosubstituted homopropargylamines
A hydroxyl substituent at this specific position allowed an excellent diastereocontrol as only one single diastereoisomer (cis-6.18v) was observed. Nevertheless, the yield proved quite low in this case. Protection of the free OH with a TBS group allowed the product cis-6.18w to be obtained in much greater yield. The diastereocontrol was unaffected by the silyl group. The reaction also per-

[^200]formed well when the phenyl ring on the nitrogen was substituted with an electron-rich substituent (cis-6.18x). The yield slightly decreased as previously observed. Electron-poor substituent on the phenyl ring, on the other hand, afforded the desired product cis-6.18y in an excellent 90\% yield. Finally, the TBS was exchanged for the more bulky TIPS with only a slight decreased in the yield but no influence on the $d r$ (cis-6.18z).

We took the opportunity of the excellent diastereoselectivities observed to test other more elaborated isonitriles. cis-6.18aa was obtained in $80 \%$ yield using 6.186. The isonitrile 6.186 , developed by Ugi and coworkers, ${ }^{548}$ was what is called a convertible isonitriles (see 6.2.2.3 - Postmodifications). The same statement was true for 6.184. Using the isonitrile 6.184 developed by Linderman and coworkers ${ }^{547}$ cis-6.18ab was obtained in $85 \%$ yield.

Finally, a methyl substituent at C-3 afforded the desired product 6.18ac with a moderate diastereocontrol. The selectivity was reversed compared to the use of an oxygen-based substituent at the same position. A 2.5:1 $d r$ was obtained in favor of the trans product trans-6.18ac.


Figure 61 - X-ray structure of cis-6.18y
The diastereoselectivity was assessed thanks to similar NMR patterns found in all obtained products as well as NOE experiments. We were also able to obtain an X-ray of cis-6.18y, confirming therefore our stereochemical assignment (Figure 61). ${ }^{551}$

[^201]

Scheme 323 - Diastereoselectivity of the addition of isonitriles on the C-3 substituted N -aryl iminiums
To explain the diastereoselectivity observed, the Woerpel stereoelectronic model could be used (Scheme 323). In the case of a C-3 alkoxy substituent, the stabilization of the iminium 6.192a with the partial negative charge on the oxygen could explain the preferred formation of cis-6.193 compare to trans-6.193 (A). In the case of the C-3 alkyl substituted $N$-aryl iminium 6.194, the steric clash generated in the cis product cis-6.195 favored the formation of the trans product trans6.195 where no such steric interaction existed (B).

Beside these positive results, other substrates failed to afford the desired products (Figure 62). The primary $\left(\mathrm{NH}_{2}\right)$ homopropargylamine ( 6.158 ) and the internal alkyne 6.135 were almost fully recovered. Identically, electron-poor homopropargylamines 6.162, 6.161 and 6.164 did not show any reactivity. On the other hand, $N$-alkyl homopropargylamines 6.21 afforded very messy mixtures of compounds.


Figure 62 - Unsuccessful examples of 1,1-aminoacylation of secondary homopropargylamines

### 6.2.2.3 Post-modifications

In order to access various derivatives of our products, we explored their post-modification.


## Scheme 324 - Post-modification of proline amide derivatives

6.18n was simply deprotected using hydrogenolysis to afford 6.196 in $89 \%$ yield (Scheme 324, A). On the other hand, when 6.18j was submitted to similar conditions, a mixture of 6.197 and 6.198 was obtained. The fact that the benzylic position embedded in the ring was also hydrogenated was not surprising. It is to note that we observed by TLC the slow conversion of 6.197 into 6.198.

The 4-MeO-Ph substituent of $6.18 x$ was easily removed using CAN oxidation in acetonitrile/water and the reaction furnished 6.199 in $98 \%$ yield (B). ${ }^{552}$

Alcohol 6.18 v was oxidized to the ketone 6.200 in excellent yield (C). The latter could then be reduced again and a 2:1 mixture of diastereoisomers 6.18 was obtained in favor of the cis product. Nevertheless, the trans product was isolated in $33 \%$ yield. This strategy represented a valuable access to trans 4-hydroxy proline amide derivatives.

Finally, the alcohol group at C-3 was also easily deprotected on various substrates. Notably, 6.18aa was treated with TBAF leading to the free alcohol 6.201a in 99\% yield. Treatment of the latter with $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}$ afforded the primary amide 6.202 in $98 \%$.

[^202]

Scheme 325 - Post-modification of the proline amides obtained using convertible isonitriles
The product 6.18ab, obtained using the Linderman's convertible isonitrile 6.184, was easily transformed into the ester 6.203 in $50 \%$ yield (Scheme $325, A$ ). Treatment of $6.18 a b$ with HCl in methanol at room temperature allowed the selective deprotection of the benzylic TBS alcohol and the resulting free alcohol 6.204 could then undergo an intramolecular transesterification on the amide to furnish the desired product 6.203. ${ }^{547}$ Such ester could then potentially be hydrolyzed to a carboxylic acid for further functionalization. On the other hand, an ethyl ester 6.205 was directly obtained from 6.18aa (B). Treatment of the product 6.18aa, formed using Ugi's convertible isonitrile 6.186, with $K O^{t}{ }^{\mathrm{B}} \mathrm{Bu}$ initially promoted the cyclization of the amide on the carbamate to afford imide 6.206. ${ }^{548}$ The generated ethanol could then attack the imide carbonyl to deliver the desired product 6.205. No epimerization was observed under these conditions.

### 6.2.3 Mechanistic Studies

### 6.2.3.1 In situ NMR-monitoring

To obtain insight on the evolution of the reaction, we first monitored the reaction by NMR (Scheme 326).


Scheme 326 - In situ monitoring of the reaction of 6.134a
The reaction between 6.134 a and 6.207 in toluene- $d_{8}$ was monitored by ${ }^{1} \mathrm{H}$ NMR spectroscopy (Figure 63).


Figure 63 - In situ monitoring of the reaction of 6.134a revealing the involvement of a dihydropyrrole intermediate

Addition of AgOAc to the solution of 6.134a did not produce any noticeable change. Addition of the isonitrile 6.207 also did not promoted any change. After 3 hours of reaction at $40{ }^{\circ} \mathrm{C}$, a new compound partially formed whereas the starting material was partially consumed (around 50\%). After 18 hours, the starting material 6.134a was fully consumed and transformed cleanly into one new product. To our surprise, the observed new product was not the desired expected product 6.18s. We were able to observe that the unknown newly formed product was stable in the reaction conditions for more than 4 days. Without evaporation of the solvent and any workup procedure, the reaction mixture was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to afford, to our surprise, the desired compound 6.18s in excellent yield.

Careful NMR $\left({ }^{1} \mathrm{H}\right.$ and $\left.{ }^{13} \mathrm{C}\right)$ analysis revealed that the unknown product observed was the dihydropyrrole 6.208 (Scheme 326). We therefore concluded that the reaction proceeded, as expected, via intermediate 6.208 but that, surprisingly, the attack of the isonitrile 6.207 occurred only on flash column chromatography. Even more surprising, TLC analysis never showed any trace amount of the intermediate 6.208. Simple deposit of a drop of the reaction mixture on the TLC-plate followed by elusion was sufficient to convert the intermediate 6.208 into the desired product 6.18 s cleanly.


Scheme 327 - Effect of the isonitrile on the cyclization of secondary homopropargylamines
With this hypothesis in mind, we reasoned that the isonitrile was therefore only required for the second half of the reaction. In order to test our idea, we performed two parallel experiments (Scheme 327). The isonitrile 6.207 was added at the beginning of the reaction (A) or just before the purification (B).


Figure 64 - In situ monitoring of the cyclization of secondary homopropargylamines with and without the presence of isonitrile

Monitoring of the reactions by ${ }^{1} \mathrm{H}$ NMR (Figure 64) indicated that the cyclization in the absence of isonitrile $\mathbf{6 . 2 0 7}$ proceeded slightly faster than the reaction containing the isonitrile. Moreover, these parallel experiments showed that the cyclization in the presence of isonitrile 6.207 was cleaner than the one without. After column chromatography both reactions afforded the desired
product 6.18 s in similar yields. The addition of the isonitrile in reaction $B$ was performed in the flask just before running the column and the desired compound 6.18 s was obtained after FCC. If the reaction mixture was first added on the column and the isonitrile 6.207 was then added, a slightly reduced yield (60\%) was obtained. Moreover, spotting a toluene solution of the isonitrile 6.207 followed by the reaction mixture showed clean conversion to the final product. Reversing the order of addition on the TLC showed similar results albeit in an apparently less clean way. All attempt to purify 6.208 in the absence of isonitrile failed. It was indeed reported in the literature that 6.208 was fairly unstable. ${ }^{504}$ These results indicated that the isonitrile acted as ligand on the silver and promoted a cleaner but slower cyclization. They also indicated that intermediate 6.208 alone was unstable on silica gel.

### 6.2.3.1 Structure of the Silver-catalyst

From these control experiments, we concluded that the isonitrile played a minor role in the cyclization. Moreover, we also observed that $\mathrm{Ag}(\mathrm{I})$ salts such as $\mathrm{AgNO}_{3}$ was able to promote the fast oligomerization of 6.134a in the absence of the isonitrile. We therefore hypothesized that the latter could act as ligand of the silver. In order to have a better picture of the structure of the active catalyst, we mixed silver acetate and excess of tert-butyl isonitrile (5.68) in toluene. We obtained crystals of 6.209. Additionally, the ratio $\mathrm{AgOAc} /{ }^{\mathrm{t}} \mathrm{BuNC}$ was determined to be $1: 1$ by ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR. In order to see if $\mathbf{6 . 2 0 9}$ was a potent catalyst, we performed the control experiment pictured in Scheme 328.


Scheme 328 - Reaction of 6.134a using the hypothesized active catalyst
6.134a was treated with the silver-isonitrile complex 6.209. After full cyclization as observed by TLC, additional ${ }^{\text {t BuNC }}$ (5.68) was added and after FCC the desired product 6.18 a was obtained in $81 \%$ yield. 6.209 was therefore a potent catalyst for the cyclization and was probably the active one in our methodology.

As shown on Table 42, the counteranion of silver played a crucial role on the yield of the reaction. In order to better understand why, we analyzed different complexes obtained when mixing various silver salts and excess of ${ }^{\text {t }}$ BuNC (5.68) (Table 43).

We first mixed excess of isonitrile 5.68 in the presence of various silver salts in DCM at room temperature and we then analyzed the frequency of the $\mathrm{C} \equiv \mathrm{N}$ stretching by infrared and the chemical shift of the isonitrile carbon by ${ }^{13} \mathrm{C}$ NMR. An increase of the stretching frequency indicated a de-
crease in the $\pi$-back-bonding ability from the metal to the RNC. ${ }^{553}$ It therefore indicated a more positive charge on the metal. As depicted on Table 43, the $\mathrm{N} \equiv \mathrm{C}$ vibrational frequency increased when the isonitrile coordinated the silver salts. ${ }^{13} \mathrm{C}$ NMR spectroscopy also showed that the chemical shift of $\mathrm{N} \equiv \mathrm{C}$ moved to higher field in isonitrile- $\mathrm{Ag}(\mathrm{I})$ complexes.

(a: Yield for the reaction of 6.134a leading to 6.18a)
Table 43 - Spectroscopic characteristics of various silver(I)-isonitrile complexes 6.210
Without ligand, one could expect a higher positive charge on the more dissociative AgOTf compared to AgOAc. In the presence of the isonitrile, this trend was reversed. These spectroscopic data therefore indicated that the counteranion affected the coordinating capability of $\mathrm{Ag}^{+}$. The complex formed with AgOAc was very different from the ones with $\mathrm{AgNO}_{3}$ and AgOTf. Stronger binding counteranion like -OAc could form tight ion-pair with $\mathrm{Ag}^{+}$. Therefore, when isonitriles were added to the silver salt, the coordinating number $n$ was small due to both electronic and steric hindrance effects.

On the other hand, with more "naked" silver salts, i.e. the ones with weaker binding counteranions, more than one isonitrile molecules probably coordinated on them and therefore rendered the silver metal less electrophile. The catalytic reactivity of $A g O T f\left({ }^{t} B u N C\right)_{n}$ was therefore reduced.

The catalytic reactivity of the obtained silver acetate-isonitrile complex 6.209 was therefore probably higher compared to the ones with weaker coordinating counteranions like silver triflate. This hypothesis was in accordance with the observed results from Table 42.

### 6.2.3.2 Deuterium-labelling Experiments

In order to get more insights about the mechanism of the 5-endo-dig cyclization, we wanted to performed deuterium-labeling experiments. We first synthesized various labelled starting materials (Scheme 329).

[^203]

Scheme 329 - Synthesis of deuterated starting materials 6.134
6.134a was initially deuterated at the terminal position of the alkyne. Deprotonation with $\mathrm{K}_{2} \mathrm{CO}_{3}$ followed by quenching of the reaction mixture with $\mathrm{D}_{2} \mathrm{O}$ then with $\mathrm{H}_{2} \mathrm{O}$ afforded 6.134-d1 (A). ${ }^{554}$ $100 \%$ of the terminal positions of the alkyne were deuterated as observed by NMR. In order to see the influence of the labile proton on the nitrogen, the same sequence was repeated with omission of the $\mathrm{H}_{2} \mathrm{O}$ work-up and 6.134 -d2 was obtained with $100 \%$ deuterium at the terminal positions of the alkyne and $50 \%$ on the nitrogen (B).


Scheme 330 - Deuterium-labeling experiments
The deuterated compounds $6.134-\mathrm{d} 1$ and $6.134-\mathrm{d} 2$ were then submitted to the reactions conditions (Scheme 330, A). They both provided the desired product 6.18a-d in good yields. We also set up an alternative experiment using undeuterated 6.134a as starting material but with addition of 3 equivalents of deuterated water in the reaction mixture (B). 6.18a-d was also obtained in good yield. Careful NMR analysis allowed the determination of the incorporation of the deuterium at various positions (Table 44).

| Entry | Starting material | D-incorporation at C-1 <br> $[\%]^{\text {a }}$ | D-incorporation at C-2 <br> $[\%]^{\text {a }}$ | Yield <br> $[\%]^{\text {b }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathbf{6 . 1 3 4 - d 1}$ | 33 | 11 | 81 |
| 2 | $\mathbf{6 . 1 3 4 - d 2}$ | 45 | 20 | 80 |
| 3 | $\mathbf{6 . 1 3 4}$ | 23 | 5 | 82 |

(a: Determined by ${ }^{1} \mathrm{H}$ NMR on the isolated product; b : isolated yield)
Table 44 - Percentages of incorporation of deuterium at C-1 and C-2
Incorporation of deuterium occurred at position C-1 and C-2 in all three experiments. Moreover, the incorporation at $\mathrm{C}-1$ was in all cases higher than at the $\mathrm{C}-2$ position.

From entry 1 (Table 44), one concluded that part of the deuterium at $\mathrm{C}-1$ in $\mathbf{6 . 1 3 4 - \mathrm { d } 1 \text { was trans- }}$ ferred to the $\mathrm{C}-2$ of 6.18a-d. Moreover, part of it was lost and replaced by hydrogen. Comparing entry 1 and 2 indicated that the part of the deuterium on the nitrogen ended at $\mathrm{C}-1$ and at $\mathrm{C}-2$. Finally, from entry 3 we concluded that a transfer of deuterium occurred from the water to the product 6.18a-d.

[^204]With these observations in mind, we hypothesized the mechanism depicted in Scheme 331 for the cyclization of $6.15-\mathrm{d}$.


Scheme 331 - Proposed mechanism for the cyclization step of 6.15
From the previous chapter, we concluded that $\operatorname{AgOAc}(C N R)$ (6.210) was the active catalyst. The latter could coordinate to the alkyne 6.15-d and promote the 5-endo-dig cyclization to 6.212. Intermolecular proton transfer from the ammonium $\mathbf{6 . 2 1 2}$ could then afford $\mathbf{6 . 2 1 3}$. The latter could be in equilibrium with enamine 6.214 which in turn could be in equilibrium with iminium 6.215. Irreversible conversion of $\mathbf{6 . 2 1 5}$ to 6.17-d could then occur with regeneration of the catalyst 6.210. Flash column chromatography could then allow the conversion of 6.17 -d to the desired product 6.18-d.

### 6.2.3.1 Role of the Silica Gel Flash Column Chromatography

During the optimization process and the above control experiments we were able to isolate one main side product (Scheme 332). 6.218 was often isolated albeit in very low yield. This side product was never detected by NMR in the in situ monitoring. It therefore only formed during flash column chromatography.


Scheme 332 - Major side product observed during the reaction of 6.134a and the proposed mechanism for its formation

Its formation could be explained by the mechanism highlighted in Scheme 332. Silver-catalyzed cyclization of the homopropargylamine 6.134 a could afford the dihydropyrrole 6.208. A second molecule of 6.208 could, on silica gel, tautomerize to iminium 6.216. 6.208 and 6.216 could then react together to afford iminium 6.217. The latter could then be trapped by tert-butyl isonitrile (5.68) to afford the observed side product 6.218.

Being convinced that the acidity of the silica gel was responsible for the required enamine to iminium tautomerism, we attempted to promote the entire reaction in the flask. Addition of various Br ønsted acids in the reaction mixture was first tested (Table 45). We quickly observed that the
addition of the additives at the beginning of the reaction completely inhibited the cyclization, probably via simple protonation of the secondary amine 6.134a. The addition of the additives was therefore performed once the full conversion to the cyclized product $\mathbf{6 . 2 0 8}$ observed by ${ }^{1} \mathrm{H}$ NMR.

(a: Determined by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture)
Table 45 - Addition of Brønsted acids to promote the addition of the isonitriles in the reaction flask
All attempts led to very messy mixtures of compounds without any trace amount of the desired product. We then hypothesized that the adsorption on the silica gel was playing a crucial role. We therefore investigated the addition of heterogeneous acid supports (Table 46).

|  |  |  |
| :---: | :---: | :---: |
| Entry | Additive | Results ${ }^{\text {a }}$ |
| 1 | $\mathrm{SiO}_{2}$ (powder) | Messy |
| 2 | $\mathrm{SiO}_{2}$ (solvated) | Messy |
| 3 | Amberlyst 15 (powder) | Messy |
| 4 | $\mathrm{AgNO}_{3}$ on $\mathrm{SiO}_{2}$ (powder) | Messy |
| 5 | AgOAc on $\mathrm{SiO}_{2}$ (powder) | Messy |
| 6 | $44 \% \mathrm{H}_{2} \mathrm{SO}_{4}$ on $\mathrm{SiO}_{2}$ (powder) | Messy |
| 7 | $22 \% \mathrm{H}_{2} \mathrm{SO}_{4}$ on $\mathrm{SiO}_{2}$ (powder) | Messy |
| 8 | Sulfonic acid on $\mathrm{SiO}_{2}$ (powder) | Messy |

(a: Determined by ${ }^{1} \mathrm{H}$ NMR on the crude reaction mixture)
Table 46 - Addition of heterogeneous acid supports to promote the addition of the isonitriles in the reaction flask

Addition of silica gel, either in the form of a powder (entry 1) or already solvated with various organic solvents (entry 2) afforded a complex mixture of compounds. The desired compound 6.18a was observed in trace amount. Adsorption on silica gel followed by flash column chromatography afforded similar results. Amberlyst 15 provided similar outcomes (entry 3). We then hypothesized that a combination of silver and silica was responsible for the clean conversion of 6.208 to 6.18a. We therefore prepared adsorbed AgOAc or $\mathrm{AgNO}_{3}$ on silica gel. Unfortunately messy mixtures were always observed (entry 4-5). More acidic silica gel such as the ones containing 44\% (entry 6) or $22 \%$ (entry 7) $\mathrm{H}_{2} \mathrm{SO}_{4}$ did not afforded the desired product. Finally, addition of sulfonic acid treat-
ed silica gel only furnished messy reaction mixtures. It is to note that the side product 6.218 was often isolated in substantial amount (10-20\% yield).


## Scheme 333 - Dual role of the $\mathrm{SiO}_{2}$ column chromatography

In light of these results, the flash column chromatography appeared to be the only way to promote the clean conversion of 6.17 to $\mathbf{6 . 1 8}$. A possible explanation could rely on the dual role of the silica gel (column) (Scheme 333). The acidity of the $\mathrm{SiO}_{2}$ could promote the required enamine 6.17 to iminium 6.219 tautomerism (A). It could then allow a physical separation of enamine 6.17 and its iminium form 6.219 (B). This could prevent any dimerization/polymerization and therefore favored the formation of the desired product 6.18 (C). ${ }^{555}$

Being worried about the reproducibility of our results, various silica gel brands were compared (Table 47). All of them (entry 1-4) led to similar yields for the formation of 6.18a and 6.18s.

|  |  |  |  |
| :---: | :---: | :---: | :---: |
| Entry | Brands | Yield for 6.18a $[\%]^{\mathrm{a}}$ | Yield for 6.18s $[\%]^{a}$ |
| 1 | Silicycle | 70 | 82 |
| 2 | Aldrich | 72 | 82 |
| 3 | Fluka | 69 | 80 |
| 4 | Roth | 67 | 83 |
| 5 | Neutralized Silicycle (3\% NEt ${ }_{3}$ ) | 0 | 0 |

(a: Isolated yield, 1:1 dr in every entry)
Table 47 - Comparison of various silica gel brands for the reaction
We also performed the reaction using neutralized silica gel (entry 5). As expected, no desired products were observed. This again indicated the need for the acidic silica gel, probably for the interconversion of $\mathbf{6 . 1 7}$ to $\mathbf{6 . 1 8}$.

[^205]The use of columns packed with silica gel supported reagent/catalyst has been developed into useful synthetic technologies. ${ }^{556}$ However, an on-column multicomponent reaction was, to the best of our knowledge, unprecedented.

### 6.2.3.2 ${ }^{18}$ O-Water Experiments

Finally, in order to understand the source of the oxygen of the amide, we performed a control experiment adding 3 equivalents of $\mathrm{H}_{2}{ }^{18} \mathrm{O}$ (Scheme 334). The reaction proceeded well and, after column chromatography, we were able to isolate the desired compound ${ }^{18} \mathrm{O}-6.18 \mathrm{a}$ in $79 \%$ yield.


Scheme 334 - Labeled-water experiment
High resolution mass spectrometry as well as ${ }^{13} \mathrm{CNMR}^{173}$ indicated an incorporation of the labeled oxygen up to $95 \%$. We therefore proposed the following mechanism for the conversion of intermediate 6.17 to the final product 6.18 (Scheme 335).


Scheme 335 - Proposed mechanism for the formation of the amide (Ugi-Joullié step)
Knowing that the addition of the isonitrile 1.99 to the iminium 6.219 and that the trapping of the nitrilium 6.221 by water occurred on flash column chromatography, which was run without any precaution (wet solvents, no inert atmosphere, etc.), such a high incorporation rate was really surprising. This probably indicated that the reaction proceeded during the very first millimeters of the column.

### 6.2.3.3 Proposed Mechanism

With all these mechanistic studies in hands, we were then able to propose a detailed mechanism (Scheme 336).

[^206]

Scheme 336 - Complete proposed mechanism for the 1,1-aminoacylation of secondary homopropargylamines

This two-step process with a three-component reaction occurring during the flash column chromatography was, to the best of our knowledge, unique.

Compared to Knölker's work on the synthesis of pyrrole derivative (see 6.1.2.1 - Ag-catalyzed Cyclization of Homopropargylamines to Pyrrole Derivatives), no $\beta$-hydride elimination to form 6.223 occurred in our case, despite the use of very similar conditions. The coordination of the isonitrile onto the silver could be responsible for this different behavior.

### 6.2.3.4 Unsuccessful Examples

In order to understand the reason for the failures of some substrates, we also decided to monitor these reactions by NMR. $N$-alkyl homopropargylamines produced very messy mixtures of products. We therefore followed by ${ }^{1} \mathrm{H}$ NMR the reaction of 6.21 and $\mathbf{6 . 2 2 0}$ (Scheme 337 and Figure 65).


Scheme 337 - Cyclization of N -alkyl homopropargylamines


Figure 65 - In situ monitoring of the reaction of $N$-alkyl homopropargylamines
Cyclization of 6.21 occurred very rapidly to intermediate $\mathbf{6 . 2 2 4}$. Unfortunately, the latter proved highly unstable and quickly degraded in the reaction conditions. Similar degradation occurred on flash column chromatography. Our hypothesis was that the electron-rich enamine 6.224 more easily tautomerized to the iminium which could then undergo various side reactions such as polymerization etc.


## Scheme 338 - Cyclization of N -Ts homopropargylamines

On the opposite, 6.162a with an electron-withdrawing group on the nitrogen proved to be highly stable in the reaction conditions. Indeed, when monitoring the reaction, no cyclization took place (Scheme 338, A). Being aware that the active catalyst, $\operatorname{AgOAc}(C N R)$ (6.210) was less active than AgOAc alone, we repeated the cyclization in the absence of the latter (B). To our delight, formation of 6.226 was observed cleanly. Surprisingly, we were then able to isolate it after flash column chromatography. Resubmitting the intermediate 6.226 to the reaction with tert-butyl isonitrile in toluene did not afforded any desired compound and the intermediate 6.226 was almost fully recovered. Our hypothesis was that 6.226 was highly stable and that no tautomerism to the iminium specie 6.227 occurred, inhibiting therefore the addition of the isonitrile.


Scheme 339 - Cyclization of primary homopropargylamines


Figure 66 - In situ monitoring of the cyclization of primary homopropargylamines in the presence of isonitrile

A similar observation was made with the primary amine 6.158 (Scheme 339, A and Figure 66). Very slow cyclization occurred in the presence of silver acetate and isonitrile 6.220 (A). We rarely observed full conversion as silver acetate slowly became $\mathrm{Ag}(0)$. Nevertheless, we submitted the reaction mixture to flash column chromatography but only the intermediate 6.229 was isolated. Our hypothesis for the lack of reaction between 6.229 and the isonitrile 6.207 was that the silica gel was not acidic enough to activate the imine in the form of the iminium 6.230.

Relying on the fact that silver acetate in the absence of isonitrile was a competent catalyst for the cyclization of electron poor nitrogen and that the imine 6.229 needed a strong activation, we therefore decided to explore the cyclization using AgOAc, a more active catalyst, in the absence of isonitrile. It was expected that once dihydropyrrole 6.229 was formed, addition of an isonitrile and a carboxylic acid could promote the Ugi-Joullié reaction to afford the multicomponent adduct 6.232 (B).

### 6.3 1,1-Aminoacylation of Primary Homopropargylamine

### 6.3.1 Initial Studies and Optimization

Our study initiated by using homopropargylamine $\mathbf{6 . 1 5 8}$ and 1.2 equivalents of tert-butyl isocyanide (5.68) as test substrates (Table 48).


| Entry | Solvent | TFA <br> [equiv] $]$ | $\mathbf{5 . 6 8}$ <br> $[$ equiv $]$ | Temperature 1 <br> $\left[{ }^{\circ} \mathrm{C}\right]$ | Temperature 2 <br> $\left[{ }^{\circ} \mathrm{C}\right]$ | Yield <br> $[\%]^{\mathrm{a}}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | Toluene | 1.2 | 1.2 | 60 | 60 | 68 |
| 2 | Acetone | 1.2 | 1.2 | 60 | 60 | 50 |
| 3 | DCM | 1.2 | 1.2 | 60 | 60 | 42 |
| 4 | Toluene | 1.2 | 1.2 | rt | 60 | 12 |
| 5 | Toluene | 1.2 | 1.2 | 30 | 60 | 54 |
| 6 | Toluene | 1.2 | 1.2 | 40 | 60 | 79 |
| 7 | Toluene | 1.2 | 1.2 | 50 | 60 | 75 |
| 8 | Toluene | 1.2 | 1.2 | 40 | rt | 97 |
| 9 | Toluene | 2.0 | 1.2 | 40 | rt | 96 |
| 10 | Toluene | 1.2 | 2.0 | 40 | rt | 96 |
| 11 | Toluene | 2.0 | 2.0 | 40 | rt | 92 |
| 12 | Toluene | 1.0 | 1.0 | 40 | rt | 87 |

(a: Isolated yield, 1:1 dr in every entry)
Table 48 - Optimization of the 1,1-aminoacylation of primary homopropargylamines
As silver acetate proved efficient in our previous optimization and mechanistic studies, we focused on the use of it in a $10 \mathrm{~mol} \%$ amount. We started with a solvent screening using 1.2 equivalents of TFA. We decided to focus on the use of TFA as carboxylic acid in order to easily deprotect the obtained products and as Ugi-Joullié reactions with TFA are generally lower yielding than with weaker carboxylic acids. Using $60^{\circ} \mathrm{C}$ for the cyclization and for the Ugi-Joullié reaction, $68 \%$ yield of 6.232 c was obtained in toluene (entry 1). Switching the solvent for acetone or DCM still afforded the desired product 6.232 c albeit in lower yields (entry 2 and 3 ).

We then focused on the temperatures screening. Performing the reaction at room temperature afforded the product 6.232c in low yield (entry 4). Increasing the temperature to 30 and then 40 ${ }^{\circ} \mathrm{C}$ improved the yield up to $79 \%$ yield (entry 5 and 6 ). $50^{\circ} \mathrm{C}$ proved to be a bit too high and a reduced yield was obtained (entry 7). The reaction temperature for the Ugi-Joullié reaction has great impact on the overall yield of this one-pot process and room temperature was found optimum, leading to the desired product 6.232c in 97\% yield (entry 8).

Finally, we explored the stoichiometries of isonitrile and of acid. Increasing the amount of acid or of isonitrile did not produce any improvement (entry 9-10). Increasing the amount of both the acid and the isonitrile afforded 6.232 c in a slightly reduced yield (entry 11 ). Finally, using exactly 1
equivalent of each afforded $\mathbf{6 . 2 3 2}$ c in $87 \%$ yield (entry 12 ). It is to note that in all the entries the desired product was obtained in a 1:1 mixture of diastereoisomers.

Overall, optimum conditions consisted of performing the AgOAc-catalyzed ( $10 \mathrm{~mol} \%$ ) cyclization of homopropargylamine 6.158 in toluene at $40{ }^{\circ} \mathrm{C}$ followed by addition of 1.2 equivalents each of 5.68 and TFA at room temperature. Under these conditions, the polyfunctionalized proline amide 6.232c was isolated in 97\% yield (entry 8).

### 6.3.2 Scope of the Reaction

### 6.3.2.1 Starting Material Synthesis



Scheme 340 - Synthesis of 3-methyl substituted primary homopropargylamine 6.238
The synthesis of 6.238 is depicted Scheme 340. Treatment of isobutenol (6.233) with DPPA followed by Staudinger reduction of the resulting acid and $N$-Boc protection provided the allylamide 6.234 in $55 \%$ yield. ${ }^{557}$ The double bond was then submitted to hydroboration/oxidation to furnish the alcohol 6.235. ${ }^{558}$ Parikh-Doering oxidation afforded the desired aldehyde 6.236 in $98 \%$ yield. The latter was then converted to alkyne 6.237 using the Seyferth-Gilbert homologation reaction with the Ohira-Bestmann reagent. Finally, N -Boc deprotection afforded the desired compound 6.238 in $98 \%$ yield (Scheme 340).


Scheme 341 - Synthesis of 3-hydroxy substituted primary homopropargylamine 6.244

[^207]The synthesis of 3-hydroxy homopropargylamine 6.244 is shown in Scheme 341. N-Boc protection of glycine (6.239) afforded 5.121, which was then converted to the Weinreb amide 6.240 using under standard conditions. ${ }^{559} 6.240$ was reacted with ethynyl magnesium bromide (6.170) to afford 6.241 in $87 \% .{ }^{560}$ It is to note that careful work-up had to be performed in order to avoid the 1,4 -addition of the generated $N$-methyl-methylhydroxylamine on the final product. 6.241 was then reduced to the unstable alcohol 6.242. ${ }^{561}$ Deprotection of the latter using phenol and TMSCl delivered amine 6.243. ${ }^{562}$ It is to note that standard Boc-deprotection conditions all promoted full decomposition. Finally, alcohol 6.243 was protected to afford 6.244 in good yield.


Scheme 342 - Synthesis of cis 3,4-doubly substituted primary homopropargylamines 6.251
In order to synthesize the enantio-enriched cis-3,4-disubstituted primary homopropargylamines 6.251a and b, we first synthesized imine 6.246 in a two-step sequence (A). Formation of 6.245 from tert-butyl carbamate, benzaldehyde (5.34) and $\mathrm{NaSO}_{2} \mathrm{Ph}^{563}$ followed by elimination using $\mathrm{K}_{2} \mathrm{CO}_{3}$ afforded the desired imine 6.246. ${ }^{564}$ The latter was then reacted with various aldehydes in a proline-catalyzed Mannich reaction. ${ }^{565}$ Excellent enantio- and diastereoselectivities were obtained. We then attempted the conversion of the aldehydes 6.248 to the terminal alkynes 6.249. Unfortunately, Ohira-Bestmann conditions afforded the desired product 6.249 but partial epimerization occurred at C-3 probably because of the deprotonation of the acidic $\alpha$-proton on aldehyde 6.248 (B). We therefore relied on a two-step sequence for the conversion of the aldehydes 6.248 to the alkynes 6.249. Corey-Fuchs conditions allowed the transformation of the aldehydes 6.248 into the

[^208]1,1-dibromo alkenes 6.250 without noticeable epimerization. We then converted the latter into the desired compounds using ${ }^{n} \mathrm{BuLi}$ at low temperature. Lithium-halogen exchange and either $\beta$ elimination or $\alpha$-elimination and 1,2-hydride shift allowed the formation of 6.249. With the latter in hands, TFA promoted the deprotection of the amine and afforded 6.251 (C).

Finally, the enantio-enriched trans-3,4-disubstituted homopropargylamine 6.258 was synthesized as shown in Scheme 343.


Scheme 343 - Synthesis of trans 3,4-doubly substituted primary homopropargylamine 6.258
Ethyl glyoxylate (6.252) was first converted to the imine precursor 6.253. ${ }^{566}$ TMS-prolinol 6.254catalyzed anti-aldol reaction afforded 6.255 in $89 \%$ yield with excellent diastereocontrol. ${ }^{567}$ We then submitted this compound in our previously developed two-step sequence for its conversion into alkyne 6.257. Wittig reaction followed by Corey-Fuchs alkyne synthesis afforded the desired compound 6.257 in good yields without any loss of diastereoselectivity. It is to note that the presence of the ester at C-4 could have been responsible for an easy epimerization at this center but apparently lithium-halogen exchange was faster than the deprotonation at this low temperature. Final deprotection of the $N$-Boc group afforded the desired primary amine 6.258 albeit in low yield.

### 6.3.2.2 Scope

Having various starting primary homopropargylamines in hands, we then explored the scope of the reaction.

[^209]

1:1 $d r$ when nothing is specified

## Scheme 344 - Scope of the C-4 mono substituted primary homopropargylamine 6.158 using various carboxylic acids

6.158 was submitted to the previously optimized reaction conditions using ${ }^{\text {t }}$ BuNC (5.68) and various carboxylic acids 1.110 (Scheme 344). All the products 6.232 were obtained in excellent yields but with poor diastereoselectivity. Acetic acid, benzoic acid and TFA performed equally well. More elaborated carboxylic acid, such as the one derived from the amino acid glycine afforded the desired product 6.232 d in $97 \%$ yield. The low diastereoselectivity could easily be explained by the Woerpel model (Scheme 322). We also noted no influence of the carboxylic acid on the diastereoselectivity.

We then focused on the use of the previously synthesized 3,4-doubly substituted primary homopropargylamines 6.251 (Scheme 345).


Scheme 345 - Scope of the 3,4-doubly primary substituted homopropargylamines 6.251
6.259a was obtained in $86 \%$ yield with $4: 1$ enantiomeric ratio. The similar compound 6.259 b, bearing an isopropyl group instead of a methyl afforded a slightly better yield but similar diastereocontrol. Use of other carboxylic acids such as acetic and benzoic acid promoted the reaction in almost quantitative yield (10:1 dr).

We then explored different isonitriles focusing on the use of the carboxylic acid derived from glycine. Methyl substituent at C-3 in combination with tert-butyl isonitrile (5.68) furnished the de-
sired compound $\mathbf{6 . 2 5 9}$ e in $91 \%$ yield with $5: 1 \mathrm{dr}$. When comparing this result to $\mathbf{6 . 2 5 9 a}$, one concluded that the carboxylic acid played a role in the diastereoselectivity. Isopropyl substituent at C3 in association with an isonitrile derived from a quaternary amino acid afforded 6.259f in 90\% and with excellent diastereoselectivity. This represented an example of tri-peptide derivative synthesis.

The same isonitrile was used in combination with acetic acid on 6.251a. The resulting product 6.259 g was delivered in good yield and $d r$. This represented an example of di-peptide derivative synthesis.

Finally, acetic acid was also combined with homopropargylamine 6.251b. Benzyl isonitrile performed well and afforded 6.259 h in $95 \%$ yield ( $7: 1 \mathrm{dr}$ ). On the other hand, both convertible isonitriles also proved efficient in this reaction. Product derived from the use of Ugi's isonitrile afforded 6.259i in $92 \%$ yield with $5: 1 \mathrm{dr}$. Similarly, Linderman's isonitrile furnished $\mathbf{6 . 2 5 9 j}$ in $95 \%$ yield (3:1 $d r)$.

Again the Woerpel model could be used to explain the diastereoselectivity of the addition of isonitrile onto the iminium $\mathbf{6 . 2 6 0}$ (Scheme 346). Steric clash in the all cis product cis-6.259 could explain the favored formation of trans-6.259 (A).


## Scheme 346 - Diastereoselectivity of the isonitrile addition onto N -H iminium

Nevertheless, a big influence of the isonitrile and of the carboxylic acid on the diastereoselectivity could be noted. The Woerpel model did not include the carboxylic acid part. Looking at 6.259b-d, one could see an increase in $d r$ with an increase in pKa of the carboxylic acid. This could be rationalized by the higher binding affinity of weaker acids, favoring the formation of the carboxylate adducts 6.261 (B). The isonitrile then also played an important role. As seen in 6.259 and 6.259 i, the more electron-poor was the isonitrile, the higher was the diastereoselectivity. The combination of these factors could probably favor 6.261a and/or 6.261d. It is to note that the carboxylate model was never proposed for $\mathrm{C}-3$ substituted iminium. The inside attack of the carboxylate on the more
bulky side could potentially be preferred as the steric clash would be reduced compare to a similar situation with a $\mathrm{C}-2$ substituted iminium.


Figure 67 - Unsuccessful examples of 1,1-aminoacylation of primary homopropargylamines
Beside the previous working substrates, few others proved unsuccessful. 3-Methyl $\mathbf{6 . 2 3 8}$ as well as 3-hydroxy 6.243 and 6.244 homopropargylamines failed to afford any trace amount of the desired compounds. Similarly, the same behavior was observed for the trans 6.258. In situ NMR monitoring showed that the cyclizations occurred cleanly on all these substrates.

### 6.3.2.3 Post-modifications

Because the initial goal was to easily access to $N$-unsubstituted proline amide derivatives, we explored the deprotection of various products (Scheme 347).


Scheme 347 - Deprotection of the acyl to afford NH-proline amide derivatives
6.232c was submitted to various deprotection conditions (A). ${ }^{568}$ Among them, NaOH in $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$ proved to be the more efficient one. Heating this compound 6.232 c to $40^{\circ} \mathrm{C}$ for few hours afforded full conversion of one of the diastereoisomer while the opposite one remained mainly untouched. We therefore were able to obtain cis-6.262 as a single diastereoisomer as well as trans6.232c in a diastereoisomerically pure form. This method proved highly valuable as separation of the mixture of 6.232 c proved highly difficult whereas cis-6.262 and 6.232 c were easy to purify. In order to push the conversion of the trans-6.232c, $80^{\circ} \mathrm{C}$ was required and afforded 6.262 in $94 \%$ yield with 1:1 dr from 6.232c.

[^210]This deprotection method proved valuable as others substrates such as 6.259a and 6.259b were easily deprotected (B). Good yields were obtained and the diastereoselectivity stayed untouched. Finally, benzoyl group in $\mathbf{6 . 2 3 2}$ b was also easily deprotected under these conditions to afford 6.262 in $80 \%$ yield (C). It is to note that in all these experiments no epimerization occurred.

We rationalized the dramatic difference of reactivity between both diastereoisomers mainly because of the steric hindrance (Scheme 348).


Scheme 348 - Conformational analysis for the diastereoselective hydrolysis of TFA-amides 6.259
The all-cis diastereoisomer probably existed in conformation cis-6.259 (A). Attack of the hydroxide from the less hindered bottom face could easily occurred affording the hydrolyzed product cis6.265. One the other side, the trans conformer in conformation trans- 6.259 suffered from steric hindrance from both face (B). The bottom face was shielded by the amide whereas the top face was shielded by the phenyl group and the tip of the envelope.

### 6.3.3 Mechanistic Studies

In order to prove the reaction indeed proceeded via imine 6.229, we submitted 6.158 to the silvercatalyzed cyclization, monitored the reaction by ${ }^{1} \mathrm{H}$ NMR, and isolated the intermediate (Scheme 349). High resolution mass spectrometry as well as NMR indicated indeed the clean formation of 6.229. The latter was even purified on column chromatography without any sign of degradation.


Scheme 349-3,4-Dihydro-2H-pyrrole as an intermediate of the reaction
The purified 6.229 was resubmitted to the standard the reaction conditions using tert-butyl isonitrile (5.68) and TFA as reaction partner and we obtained the desired product 6.232c in good yield. In situ monitoring of the second reaction also showed that the reaction in this case occurred in the flask and not on flash column chromatography.

In order to better understand the effect of the order of addition of the isonitrile and of the carboxylic acid, we performed four different control experiments (Scheme 350 and Figure 68).


Scheme 350 - Cyclization of primary homopropargylamine varying the order of addition of the carboxylic acid and of the isonitrile

$\begin{array}{lllllllllllllllllllllllllllllllllllllll}14.0 & 13.5 & 13.0 & 12.5 & 12.0 & 11.5 & 11.0 & 10.5 & 10.0 & 9.5 & 9.0 & 8.5 & 8.0 & 7.5 & 7.0 & 6.5 & 6.0 & 5.5 & 5.0 & 4.5 & 4.0 & 3.5 & 3.0 & 2.5 & 2.0 & 1.5 & 1.0 & 0.5 & 0.0\end{array}$
Figure 68 - Monitoring of the cyclization of primary homopropargylamines varying the order of addition of the carboxylic acid and of the isonitrile

Cyclization of $\mathbf{6 . 2 5 1 b}$ in the presence of the sole AgOAc was completed after 12 hours (A). On the other hand, in the presence of the isonitrile $\mathbf{6 . 2 0 7}$, only around $50 \%$ conversion was observed after 3 days of reaction (B). This was probably due to the formation of the less active silver-isonitrile
complex 6.210. In the presence of acetic acid, similar low conversion was observed after 3 days (C). The protonation of the primary amine was probably responsible for this slow cyclization. Finally, the presence of both the isonitrile $\mathbf{6 . 2 0 7}$ and the carboxylic acid completely inhibited the reaction as expected (D).

With the results of these control experiments and with the information obtained in the first part of the project, the proposed mechanism is outlined in Scheme 351.


Scheme 351 - Proposed mechanism for 1,1-aminoacylation of primary homopropargylamines
In this case, competitive reactions such as protonation and/or acylation of amine, ${ }^{483}$ the Lewis acid catalyzed condensation of the acid with isonitrile, ${ }^{569}$ etc., could not hamper the occurrence of the desired reaction pathway. The reason why in this case the oxidized product was not observed was unclear. Absence of the isonitrile during the 5-endo-dig cyclization step could promote the oxidation of 6.271 but this was not observed.

### 6.4 Conclusion and Outlook

In conclusion, we developed a 1,1-aminoacylation of homopropargylamine. ${ }^{570}$


Scheme 352-1,1-aminoacylation of secondary homopropargylamines
For the reaction of secondary homopropargylamine 6.15 (Scheme 352), mechanistic studies revealed a 2 step process. During the first part, a 5-endo-dig cyclization of 6.15 afforded dihydropyrrole 6.17. The $1: 1 \mathrm{Ag} /$ RNC complex allowed to avoid most of the side reactions such as overoxidation. In the second part of the reaction, an isonitrile addition on iminium occurred only on column chromatography. This represented the first on-column three-component reaction.

[^211]The methodology afforded various examples in good to excellent yields. C-3 substitution allowed an excellent control of the diastereoselectivity which was explained using the Woerpel stereoelectronic model. Post-modification of the obtained products allowed the formation of NH proline amide as well as proline ester derivatives (Figure 69).


Figure 69 - Examples of obtained compounds using the 1,1-aminoacylation of secondary
We then extended the methodology to primary homopropargylamines 6.251 (Scheme 353). The previous mechanistic studies prompted us to revise the order of additions as well as to add an external carboxylic acid to perform a 5-endo-dig cyclization followed by an Ugi-Joullié reaction. In this case, AgOAc was the active catalyst to promote the cyclization and the Ugi-Joullié reaction occurred in the flask after addition of the isonitrile and of the carboxylic acid.


Scheme 353 -1,1-aminoacylation of primary homopropargylamines
Various examples were presented. Many acids as well as isonitriles were compatible leading to the corresponding three-component adducts in excellent yields. Again a C-3 substituent allowed a good control of the diastereoselectivity. Simple hydrolysis of the obtained amide afforded NHproline amide derivatives (Figure 70).


$6.259 f$
$90 \%, 10: 1 d r$

6.262

Figure 70 - Examples of obtained compounds using the 1,1-aminoacylation of primary homopropargylamine

The proline amides obtained could potentially be used to construct constrained peptidomimetics and as potential new proline-based organocatalysts.

## Chapter 7 General Conclusion

Interested in the interplay between the total synthesis of natural products and the methodological development in organic chemistry, this thesis featured natural product total syntheses together with methodology-oriented projects.

Initial focus was directed towards the total synthesis of indole alkaloids. To tackle these challenging tasks, each of these syntheses was performed with a different motivation in mind.

## 7.1 (-)-Terengganensine A

(-)-Terengganensine $A(\mathbf{2} \mathbf{1})$ is discussed in Chapter 2. Careful conformational analyses provided the basis of our synthesis. The heptacyclic structure $\mathbf{2 . 1}$ indeed represented a challenge in view of its complexity and unusual, beautiful conformation.


Scheme 354 - 5-step enantioselective synthesis of the key indole skeleton 2.88
Starting from the commercially available acid 2.239, the indole skeleton 2.88 was accessed in 5 steps and $78 \%$ overall yield with $90 \%$ ee. The absolute configuration of 2.88 was controlled by an unusual catalytic enantioselective transfer hydrogenation of iminium 2.206b in the presence of Noyori's catalyst 2.118 (Scheme 354).


Scheme 355 - End-game of the synthesis of (-)-terengganensine A featuring a C-7 oxidation and a highly diastereoselective cascade reaction

During the second phase of the synthesis (Scheme 355), the indole $\mathbf{2 . 8 8}$ was first oxidized at the C7 position using dibenzoyl peroxide which proved to be the crucial oxidant for this step. The reaction proceeded at room temperature, probably via unprecedented ionic mechanism and afforded $\mathbf{2 . 2 6 9}$ as one single diastereoisomer. A key dihydroxylation/oxidative cleavage/cyclization/hydrolysis cascade was then developed to convert $\mathbf{2 . 2 6 9}$ to (-)-terengganensine A (3.1) in excellent yield as a single diastereoisomer.


Scheme 356 - Conformational analysis of the key dialdehydes
Our working hypothesis, that C-7 oxidation of indole could dramatically modify the conformation of the indole 2.88 in order to induce the cyclization with the desired axial aldehyde C-16 (2.283 to 2.281), was confirmed (Scheme 356). Moreover, this geometrical change was probably caused by the neighboring group effect of the C-7 benzoate. Indeed, computational studies revealed that the possible direction of attack of the carbonyl oxygen on iminyl carbon felt very close to the BürgiDunitz angle. The calculations had also indicated a close proximity between the two centers.

A short and effective enantioselective synthesis of (-)-terengganensine A (2.1) was therefore developed for the first time. The synthesis was completed in 7 steps, $16 \%$ overall yield with $95: 5$ enantiomeric ratio. ${ }^{176}$ Thanks to our synthesis, the absolute configuration of the isolated natural product 2.1 was confirmed.

Our approach demonstrated the power of conformational analysis in the synthesis of complex molecules. Our strategy and the gathered intelligence on the conformation of similar compounds could lead to the synthesis of other natural products. This work is currently ongoing.

## 7.2 (-)-Vallesamidine and (+)-1,2-Dehydroaspidospermidine

Chapter 3 was devoted to the synthesis of (-)-vallesamidine (3.1) and (+)-1,2dehydroaspidospermidine (3.2). A divergent total synthesis of these two targets was envisioned. Indeed, even though they might look different, they are biosynthetically interconnected.

Our strategy was based on the use of the known macrocycle 1.184. Being unable to obtain it in an enantioselective and diastereoselective way following similar strategies than the reported one, its synthesis was completely redesigned. The two stereocenters were first constructed in two separate enantioselective steps (Scheme 357).

On one side, an enantioselective 1,4-addition of $\mathrm{AlEt}_{3}$ on 3.184 followed by trapping of the poorly reactive enolate afforded the vinyl triflate 3.182 in $86 \%$ yield with $91 \% e e$. The conjugatedaddition on 3-substituted cyclopentenone was challenging but the use of Hoveyda Ag-NHC catalyst 3.247 afforded very good results in our case. On the other side, a prolinol 3.338-catalyzed aldol reaction allowed the synthesis of the other coupling partner 3.237 in good yield and enantiomeric excess.




## Scheme 357 - Synthesis of the two enantio-enriched partners via 1,4-addition and aldol reaction



Scheme 358 - Assembly of the two enantio-enriched partners and the Mitsunobu-based macrocyclization
Both partners were then coupled in an unusual stereoselective $S_{N} 2$-type reaction affording $\mathbf{3 . 1 8 0}$ in $56 \%$ yield as a single diastereoisomer. The reaction proceeded in a complete stereoinvertive way. With 3.180 in hands, modified double Mitsunobu reactions afforded the desired 10membrered bridged macrocycle 1.184 in high yields (Scheme 358). This represented therefore the first access to diastereomerically pure and enantiomerically enriched macrocycle 1.184.


Scheme 359 - End-game cascade reactions for the synthesis of (-)-vallesamidine and (+)-1,2dehydroaspidospermidine

The macrocycle 1.184 served as a common intermediate for the two targeted molecules (Scheme 359). Towards (+)-1,2-dehydroaspidospermidine (3.2), a highly diastereoselective epoxidation followed by nosyl deprotection/transannular cyclization afforded the amino alcohol 3.418 as a single diastereoisomer. A regioselective trans elimination allowed the formation of the very sensitive alkene 3.438 which was directly submitted to the next step. A $\mathrm{TiCl}_{3}$-promoted reductive cyclization followed by a novel rearrangement cascade allowed the synthesis of 3.2 in good yield and excellent diastereoselectivity. This biomimetic rearrangement allowed the conversion of the vallesamidine backbone to the aspidosperma skeleton.

To access (-)-vallesamidine (3.1), the epoxidation/deprotection/transannular cyclization sequence was extended to synthesize 3.1. In situ reduction of the nitro group in $\mathbf{3 . 4 1 8}$, substitution of the alcohol by the generated aniline and alkylation of the secondary amine furnished 3.1 in $45 \%$ yield.

On the one hand, (-)-vallesamidine (3.1) was obtained in 9 steps, $6.3 \%$ overall yield and with excellent control of the diastereoselectivity. On the other hand, (+)-1,2-dehydroaspidospermidine (3.2) was synthesized in 11 steps and $7.1 \%$ overall yield. Again, almost perfect control of the diastereoselectivity was achieved. ${ }^{299}$

This project highlighted the power of cascade reactions in divergent synthesis. A structurally simple common intermediate allowed rapid access to very complex polycyclic molecules.

## $7.3 \quad(+)$-Peganumine A

In Chapter 4, (+)-Peganumine A (4.1) attracted our attention because of its complex molecular architecture and its biological activity. The possibility to use the Pictet-Spengler and/or BischlerNapieralski reactions for its constructions was immediately recognized. After unsuccessful strategies, the use of a Liebeskind-Srogl coupling (Scheme 360) for the construction of the crucial C-C bond finally proved fruitful.


Scheme 360 - Key Liebeskind-Srogl coupling during the synthesis of (+)-peganumine A
Both coupling partners were synthesized in few steps. Their coupling afforded $\mathbf{4 . 3 0 2}$ in $95 \%$ yield. The high tendency of 4.301 to undergo protodestannylation prompted us to use a combination of solvent as well as relatively uncommon reaction conditions to solve this issue.

The possibility to develop a new cyclization method relying on the use of $\omega$-isocyanoaldehyde 4.303 for $\mathrm{C}-\mathrm{C}$ bond formation instead of the traditional lactamization approach (C-N bond formation) was then explored (Scheme 361).


Scheme 361 - Novel macrocyclization method using $\omega$-isocyanoaldehyde 4.303
4.303 was converted to 4.234 in a single step. Unprecedented oxidative Ugi macrocyclization followed by transannular cyclization of the 10-membered ring 4.235 afforded 4.234 in $75 \%$ yield. Starting from $\omega$-isocyanoaldehyde 4.303 and using acetic acid and $N$-methylhydroxylamine (the oxidant) as reaction partners allowed the efficient synthesis of $\alpha$-ketolactam 4.234.


Scheme 362 - Enantioselective Pictet-Spengler reaction/transannular cyclization/deprotection cascade for the synthesis of (+)-peganumine A

As for the end-game of the synthesis, an enantioselective Pictet-Spengler reaction was developed (Scheme 362). Reaction between 4.234 and 4.27 under our optimized conditions afforded 4.1 in a single step and good yield with excellent enantiomeric excess. A cascade sequence consisting of a chiral thiourea 4.53-catalyzed enantioselective Pictet-Spengler reaction followed by a transannular cyclization allowed the rapid construction of the complexity with excellent control of the stereoselectivity. This represented one of the very few reported cases of enantioselective Pictet-Spengler reaction on a ketone to access quaternary stereocenters.
$(+)$-Peganumine A (4.1) was synthesized in 7 steps, $33 \%$ overall yield and with $92 \% e e .{ }^{421}$ More than one-gram of it was synthesized in a single batch.

Our newly developed cascade reactions allowed us to access a small library of (+)-peganumine A (4.1). Good yields and enantiomeric ratios were obtained. Biological activity evaluation of these compounds is currently ongoing.

### 7.4 Macrocyclization of $\omega$-Isocyanoaldehydes

Taking advantage of our previously developed macrocyclization method, the potential of such transformation was further exploited in Chapter 5. Macrocycles are valuable targets, known for their bioactivities, and are found in many different natural products. The possibility to synthesize such large rings with the introduction of an $\alpha$-ketoamide moiety or related functional groups was highly appealing.

5.183
$\alpha$-Acetoxy amide

5.185
$\alpha$-Amino tetrazole

$\alpha$-Amido amide

$\alpha$-Hydrazo amide


$\alpha$-Hydroxy amide



Figure 71 - Examples of macrocycles synthesized from $\omega$-isocyanoaldehydes
Macrocycles with different ring sizes and topologies were synthesized in good yields (Figure 71). Beside the previously developed oxidative-Ugi reaction, standard Ugi and Passerini reactions were also successfully applied. Other isocyanide-based multicomponent reactions afforded valuable products with the introduction of other appealing functional groups such as tetrazoles. Access to $p$ - and $m$-cyclophanes was also possible.

In order to reveal the power of our methodology, (-)-eurystatin B (5.1) was targeted (Scheme 363). This 13-membered cyclic peptide revealed to be a highly potent prolyl endopeptidase (PED) inhibitor. Its $\alpha$-ketoamide function attracted our attention and we planned its synthesis around this functionality. Tripeptide 5.286 was accessed in a few steps. Dehydration followed by a Passerini 2component 3-center reaction provided access to the 13-membered macrocycle 5.269 in $83 \%$ yield. The latter was converted to the targeted compound 5.1 in a short sequence. (-)-Eurystatin B (5.1) was synthesized in 9 steps and $38 \%$ overall yield from commercially available amino acid deriva-
tives. ${ }^{477}$ Our total synthesis also allowed the determination of the absolute configuration of (-)eurystatin B (5.1).


## Scheme 363 - Passerini 2-component 3-center macrocyclization in the synthesis of (-)-eurystatin B

### 7.5 Silver-catalyzed 1,1-Aminoacylation of Homopropargylamines

In Chapter 6, the 1,1-aminoacylation of homopropargylamines was explored. Terminal alkynes and isonitriles both offered an amazing playground for the development of multicomponent reaction.


3-component 1,1-aminoacylation
of homopropargylamines

Figure 72 - Dual $\alpha$-additions of the isonitrile and of the alkyne
The 5-endo-dig cyclization of homopropargylamines and the subsequent trapping of the generated iminium by isonitrile was explored. This offered a new method for the 1,1-difunctionalization of alkynes. This provided access to proline amide derivatives which are known as useful organocatalysts and found in numerous peptidomimetics. Unusually, $\alpha$-additions occurred for both the isonitrile and the alkyne (Figure 72).



Scheme 364-1,1-aminoacylation of secondary homopropargylamines

Secondary homopropargylamines 6.15 were converted to the proline amide derivatives 6.18 in moderate to good yields (Scheme 364). Substitution pattern on the starting material 6.15 was varied without significant influence on the reaction yields. High diastereoselectivity using C-3 substituted homopropargylamines was successfully obtained. C-3 alkoxy substituents afforded the 1,3cis products whereas C-3 alkyl substituents furnished the 1,3-trans products. The Woerpel stereoelectronic model was used to explain these outcomes.

Mechanistic studies revealed the occurrence of an unusual on-column 3-component reaction. On the other hand, the 5 -endo-dig cyclization occurred cleanly in the flask. No overoxidation was observed and this observation was attributed to the active catalyst, the silver-isonitrile complex 6.210 (Scheme 365).


Scheme 365 - Unusual on-column multicomponent reaction
Primary homopropargylamines 6.251 were also converted to the proline amide derivatives $\mathbf{6 . 2 7 7}$ (Scheme 366). Because the stability of the imine 6.273, carboxylic acids were added in the reaction mixture to afford the classic Ugi-Joullié three-component adducts.


6.259d
$99 \%, 10: 1 d r$
Diastereoselective

$6.259 f$
90\%, 10:1 dr
Access to tripeptides


Scheme 366-1,1-aminoacylation of primary homopropargylamines
Under the developed conditions, broad arrays of substrates were explorer. To our delight, excellent yield were obtained. High diastereoselectivities were observed using C-3 substituted homopropargylamines. Mechanistic studies helped us to correctly design the reaction conditions. 5 -endo-dig cyclization in the absence of isonitrile allowed the rapid formation of the imine intermediate. Addition of the isonitrile and of the carboxylic acid after the 5 -endo-dig cyclization proved crucial. It promoted, in this case, the Ugi-Joullié reaction in the flask. The obtained products were easily deprotected and allowed an access to $N$-unsubstituted proline amide derivatives. ${ }^{570}$

## Chapter 8 Experimental Section

The following chapter includes the general information, the procedures for all the reactions and the control experiments as well as the full characterization of all the products unknown in the literature.

### 8.1 General Information

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka and VWR international) and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) unless otherwise noted. When needed, glassware was dried overnight in an oven $\left(\mathrm{T}>100^{\circ} \mathrm{C}\right)$ or in vacuo with a heat gun ( $\mathrm{T}>200^{\circ} \mathrm{C}$ ).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb's design.

Flash column chromatographies were performed using Silicycle P60 silica: 230-400 mesh (40-63 $\mu \mathrm{m})$ silica.

Reactions were monitored using Merck Kieselgel $60 \mathrm{~F}_{254}$ aluminum or glass backed plates. TLC's were visualized by UV fluorescence ( 254 nm ) then one of the following: $\mathrm{KMnO}_{4}$, molybdenate, ninhydrine, pancaldi, $p$-anisaldehyde or vanillin.

NMR spectra were recorded on a Brüker Avancelll HD-600, Brüker AvancellI-400, Brüker Avance400 or Brüker DRX-400 spectrometer at room temperature, ${ }^{1} \mathrm{H}$ frequency is at $400.13 \mathrm{MHz},{ }^{13} \mathrm{C}$ frequency is at 100.62 MHz . Chemical shifts ( $\delta$ ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 ppm for proton and 0.1 ppm for carbon (ref : Acetone $\left[{ }^{1} \mathrm{H}: 2.05 \mathrm{ppm},{ }^{13} \mathrm{C}: 29.84 \mathrm{ppm}\right], \mathrm{CH}_{2} \mathrm{Cl}_{2}\left[{ }^{1} \mathrm{H}: 5.32 \mathrm{ppm},{ }^{13} \mathrm{C}: 53.84 \mathrm{ppm}\right], \mathrm{CHCl}_{3}\left[{ }^{1} \mathrm{H}: 7.26\right.$ ppm, $\left.{ }^{13} \mathrm{C}: 77.2 \mathrm{ppm}\right]$, DMSO $\left[{ }^{1} \mathrm{H}: 2.50 \mathrm{ppm},{ }^{13} \mathrm{C}: 39.5 \mathrm{ppm}\right], \mathrm{MeOH}\left[{ }^{1} \mathrm{H}: 3.31 \mathrm{ppm},{ }^{13} \mathrm{C}: 49.0 \mathrm{ppm}\right.$ ], Toluene [ $\left.{ }^{1} \mathrm{H}: 2.08 \mathrm{ppm},{ }^{13} \mathrm{C}: 20.43 \mathrm{ppm}\right]$ ). Coupling constants $(J)$ were reported in Hz to the nearest 0.1 Hz . Peak multiplicity was indicated as follows $s$ (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, a COSY, HSQC and HMBC experiments were used to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra are reported in $\mathrm{cm}^{-1}$. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were obtained by using a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (El positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Specific optical rotations $[\alpha]_{D}$ were obtained with a Jasco P-2000 polarimeter ( 589 nm ).

Melting points are uncorrected and were recorded on a Stuart SMP30 melting point apparatus.
For all general procedures the order of addition of reagents has to be respected.

## 8.2 (-)-Terengganensine A

### 8.2.1 Synthesis of the Indole Skeleton

(Z)-1,4-dibromobut-2-ene (2.226)


It was prepared according to a literature procedure. ${ }^{125}$
7-oxaspiro[4.5]dec-2-en-6-one (2.224)


Following a reported procedure, ${ }^{126}$ to a solution of the lactone $\mathbf{2 . 2 2 7}(455 \mu \mathrm{~L}, 4.99 \mathrm{mmol}, 1.00$ equiv) in dry THF ( $11 \mathrm{~mL}, 0.45 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added KHMDS ( 0.5 M in toluene, $12.0 \mathrm{~mL}, 6.00$ mmol, 1.20 equiv) dropwise over 10 minutes. The reaction mixture was stirred 1 h 30 at this temperature. A mixture of dibromobutene $2.226(2.67 \mathrm{~g}, 12.5 \mathrm{mmol}, 2.50$ equiv) and HMPA ( 3.48 mL , 20.0 mmol, 4.00 equiv) in dry THF ( 5 mL ) was added dropwise over 15 minutes. The reaction mixture was slowly warmed to room temperature and stirred for 3 hours. The reaction mixture was again cooled down to $-78^{\circ} \mathrm{C}$ and KHMDS ( 0.5 M in toluene, $12 \mathrm{~mL}, 6.00 \mathrm{mmol}, 1.20$ equiv) was added dropwise over 10 minutes. The reaction mixture was warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, diluted with water and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column
chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1\right)$ to yield the pure compound 2.224 ( $76 \mathrm{mg}, 10 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.61(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 2 \mathrm{H}), 4.38(\mathrm{dd}, J=6.9,4.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.03(\mathrm{~d}, \mathrm{~J}=16.5$ $\mathrm{Hz}, 2 \mathrm{H}), 2.37(\mathrm{~d}, \mathrm{~J}=16.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.02-1.74(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.2,132.1,70.0,45.6,44.0,35.8,17.1$.
IR: v (cm ${ }^{-1}$ ) 2914 (w), 2854 (w), 1666 (s), 1416 (w), 1409 (w), 1243 (w), 954 (w), 657 (w).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 153.0910; found: 153.0905.
(3-bromopropoxy)(tert-butyl)diphenylsilane (2.230)


It was prepared according to literature procedures. ${ }^{127,128}$
methyl 1-(3-((tert-butyldiphenylsilyl)oxy)propyl)cyclopent-3-ene-1-carboxylate (2.231)


Following a reported procedure, ${ }^{103}$ to a stirred solution of lithium diisopropylamine ( 7.13 mmol , 1.20 equiv; prepared from BuLi and ${ }^{\prime} \mathrm{Pr}_{2} \mathrm{NH}$ in anhydrous THF ( 5 ml )) at $-78^{\circ} \mathrm{C}$ was added a solution of the ester 2.83 ( $750 \mathrm{mg}, 5.95 \mathrm{mmol}, 1.00$ equiv) in dry THF ( 11.5 mL ) dropwise over 5 min . After 30 min , a solution of the bromide $2.230(2.29 \mathrm{~g}, 6.06 \mathrm{mmol}, 1.02$ equiv) in dry THF ( 1.5 mL ) was added dropwise. After being stirred for an additional hour, the reaction mixture was allowed to gradually warm up to room temperature. After being stirred for 12 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 10: 1\right)$ to yield the pure product 2.231 ( $2.29 \mathrm{~g}, 91 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\left.\mathrm{CDCl}_{3}\right): \delta 7.71-7.60(\mathrm{~m}, 6 \mathrm{H}), 7.46-7.32(\mathrm{~m}, 4 \mathrm{H}), 5.60(\mathrm{~s}, 2 \mathrm{H}), 3.67(\mathrm{~s}, 3 \mathrm{H}), 3.63$ (t, J = 6.3 Hz, 2H), 2.88 (d, J = $14.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.28(\mathrm{~d}, J=14.6 \mathrm{~Hz}, 2 \mathrm{H}), 1.77-1.69(\mathrm{~m}, 2 \mathrm{H}), 1.47(\mathrm{dq}, J$ $=10.9,6.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.04(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 175.4,134.8,132.1,130.0,129.8,129.5,64.8,52.6,44.7,43.1,35.2$, 32.8, 28.5, 26.9.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{26} \mathrm{H}_{35} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 423.2350; found: 423.2355.

IR: v ( $\mathrm{cm}^{-1}$ ) 2923 (w), 2845 (w), 1712 (s), 1456 (w), 1419 (w), 1306 (w), 1217 (w), 954 (w), 676 (w).
7-oxaspiro[4.5]dec-2-en-6-one (2.224) and methyl 1-(3-hydroxypropyl)cyclopent-3-ene-1carboxylate (2.232)


The different attempts described in Table 1 afforded the lactone $\mathbf{2 . 2 2 4}$ and the alcohol $\mathbf{2 . 2 3 2}$ in different ratios.

Alcohol 2.232:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.71-5.47(\mathrm{~m}, 2 \mathrm{H}), 3.70(\mathrm{~s}, 3 \mathrm{H}), 3.60(\mathrm{~m}, 2 \mathrm{H}), 2.88(\mathrm{~d}, \mathrm{~J}=16.8 \mathrm{~Hz}$, $2 \mathrm{H}), 2.29(\mathrm{~d}, \mathrm{~J}=16.9 \mathrm{~Hz}, 2 \mathrm{H}), 1.73(\mathrm{dt}, \mathrm{J}=11.6,3.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.49$ (ddd, $J=12.0,6.8,4.0 \mathrm{~Hz}, 2 \mathrm{H}$ ).
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 175.4,132.1,64.8,52.6,44.7,43.1,35.2,28.5$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 185.1172 ; found: 185.1170 .
IR: v ( $\mathrm{cm}^{-1}$ ) 3201 (w), 2919 (w), 2845 (w), 1690 (s), 1446 (w), 1421 (w), 1243 (w), 1219 (w), 940 (w), 675 (w).

## 7-oxaspiro[4.5]dec-2-en-6-one (2.224)



It was prepared according to literature procedures. ${ }^{129,130}$

## N-(2-(1H-indol-3-yl)ethyl)-1-(3-hydroxypropyl)cyclopent-3-ene-1-carboxamide (2.223) and 7-(2-

 (1H-indol-3-yl)ethyl)-7-azaspiro[4.5]dec-2-en-6-one (2.107)

Following a reported procedure, ${ }^{91}$ a mixture of the lactone $\mathbf{2 . 2 2 4 ( 1 . 0 4 \mathrm { g } , 6 . 8 5 \mathrm { mmol } , 1 . 0 0 \text { equiv) }}$ and tryptamine ( 1.16 ) ( $1.32 \mathrm{~g}, 8.22 \mathrm{mmol}, 1.20$ equiv) was heated neat to $160{ }^{\circ} \mathrm{C}$. After being stirred for 12 hours, the reaction mixture was cooled to room temperature. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right.$ to $\left.1: 4\right)$ to yield the pure amide 2.223 ( $1.25 \mathrm{~g}, 60 \%$ ) as a brownish amorphous solid and the lactam 2.107 ( $70 \mathrm{mg}, 5 \%$ ) as an amorphous orange solid.

## Alcohol 2.223:

${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.46(\mathrm{~s}, 1 \mathrm{H}), 7.60(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.20(\mathrm{t}, \mathrm{J}=$ $7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.12(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.01(\mathrm{~s}, 1 \mathrm{H}), 5.80(\mathrm{~s}, 1 \mathrm{H}), 5.57(\mathrm{~s}, 2 \mathrm{H}), 3.60(\mathrm{~m}, 2 \mathrm{H}), 3.48(\mathrm{t}, \mathrm{J}=$ $6.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.97(\mathrm{t}, \mathrm{J}=6.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.68(\mathrm{~d}, \mathrm{~J}=15.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.25(\mathrm{~d}, \mathrm{~J}=15.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, $1.71-1.54(\mathrm{~m}, 4 \mathrm{H}), 1.51-1.35(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 178.9,136.5,132.5,127.8,123.3,121.7,119.7,118.4,113.0,111.5$, 62.7, 46.3, 44.0, 42.3, 35.8, 26.0, 25.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 313.1911; found: 313.1910.
IR: v (cm ${ }^{-1}$ ) 3400 (w), 3310 (w), 2915 (w), 2835 (w), 1767 (w), 1641 ( ), 1510 ( s$), 1438$ (m), 1235 (m), 1098 (w), 1035 (w), 741 (s), 679 (w).

## N -(2-(1H-indol-3-yl)ethyl)-1-(3-bromopropyl)cyclopent-3-ene-1-carboxamide (2.236)



To a solution of the alcohol 2.223 ( $630 \mathrm{mg}, 2.02 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{CBr}_{4}(2.01 \mathrm{~g}, 6.05 \mathrm{mmol}$, 3.00 equiv) in dry DCM ( 19 mL ) at room temperature was added a solution of $\mathrm{PPh}_{3}(793 \mathrm{mg}, 3.03$ $\mathrm{mmol}, 1.50$ equiv) in DCM ( 12 mL ) dropwise. The reaction mixture was stirred for 1 h 30 then the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) to yield the pure bromide $\mathbf{2 . 2 3 6}(454 \mathrm{mg}, 60 \%)$ as a brownish amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.18(\mathrm{~s}, 1 \mathrm{H}), 7.62(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.44-7.33(\mathrm{~m}, 1 \mathrm{H}), 7.25-7.17$ $(\mathrm{m}, 1 \mathrm{H}), 7.13$ (ddd, $J=8.0,7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.03(\mathrm{~d}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.67(\mathrm{~s}, 1 \mathrm{H}), 5.56-5.52(\mathrm{~m}, 2 \mathrm{H})$, $3.60(\mathrm{dd}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.30(\mathrm{t}, J=6.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.98(\mathrm{t}, \mathrm{J}=6.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.77-2.59(\mathrm{~m}, 2 \mathrm{H}), 2.32-$ $2.15(\mathrm{~m}, 2 \mathrm{H}), 1.80-1.63(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 177.4,136.2,129.1,127.3,122.3,122.1,119.2,118.6,112.6,111.5$, 52.1, 42.8, 40.0, 37.1, 34.2, 28.5, 25.3.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{BrN}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 375.1067 ; found: 375.1068
IR: v ( $\mathrm{cm}^{-1}$ ) 3414 ( w ), 3276 (br), 3055 (w), 2922 (m), 2851 ( w ), 1641 ( s$), 1516$ (s), 1455 (m), 1437 (s), 1342 (m), 1308 (w), 1270 (w), 1227 (m), 1098 (w), 1011 (w), 946 (w), 909 (m), 740 (s), 671 (m).

## 7-(2-(1H-indol-3-yl)ethyl)-7-azaspiro[4.5]dec-2-en-6-one (2.107)



To a solution of $\mathrm{KH}(244 \mathrm{mg}, 1.83 \mathrm{mmol}, 1.50$ equiv) and $18-\mathrm{C}-6$ ( $193 \mathrm{mg}, 0.731 \mathrm{mmol}, 0.60$ equiv) in dry THF ( 22 mL ) at room temperature was added dropwise a solution of the bromide 2.236 (457 $\mathrm{mg}, 1.22 \mathrm{mmol}, 1.00$ equiv) in dry THF ( 87 mL ). After being stirred for 15 min , the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to obtain the lactam 2.107 ( $298 \mathrm{mg}, 87 \%$ ) which was used directly in the next step without further purification. For analysis, the crude product can be purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1) to yield the pure product $\mathbf{2 . 1 0 7}$ ( $290 \mathrm{mg}, 81 \%$ ) as a yellowish oil.

## $2^{\prime}, 3^{\prime}, 4^{\prime}, 6^{\prime}, 7^{\prime}, 12^{\prime}$-hexahydro-5' $\lambda^{4}$-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-ene perchlorate (2.106a)



A solution of alcohol 2.223 ( $175 \mathrm{mg}, 0.503 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{POCl}_{3}(1.14 \mathrm{~mL}, 0.44 \mathrm{M}$ ) was stirred at reflux for 12 hours. The reaction mixture was cooled down to room temperature and evaporated in vacuo to remove completely excess of $\mathrm{POCl}_{3}$. The residue was dissolved in DCM (5 mL ) and treated with aqueous $1 \mathrm{M} \mathrm{LiClO} 4(5 \mathrm{~mL})$. After being stirred for 20 minutes, the reaction mixture was extracted with DCM . The combined organic extracts were washed with $1 \mathrm{M} \mathrm{LiClO}{ }_{4}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the iminium salt 2.106a ( $114 \mathrm{mg}, 60 \%$ ) as an amorphous yellow solid which was used directly in the next step without further purification.
methyl 1-(3-chloropropyl)cyclopent-3-ene-1-carboxylate (2.85)


It was prepared according to a literature procedure. ${ }^{103}$
7-oxaspiro[4.5]dec-2-en-6-one (2.224) and 7,17-dioxadispiro[4.5.4 ${ }^{11} \cdot 5^{5}$ ]icosa-2,13-diene-6,16dione (2.238)


To a solution of ester 2.85 ( $500 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv) in dry $\mathrm{MeOH}(120 \mathrm{~mL}, 0.05 \mathrm{M}$ ) at room temperature was added aqueous $10 \% \mathrm{NaOH}$ solution ( $24.7 \mathrm{mmol}, 10.0$ equiv). After being stirred at $50^{\circ} \mathrm{C}$ for 24 hours, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, PE/EtOAc 9:1) to yield the pure products $\mathbf{2 . 2 2 4}(86 \mathrm{mg}, 23 \%)$ as a brownish oil and $\mathbf{2 . 2 3 8 ( 5 1 2 ~ m g , ~}$ 68\%) as a yellow oil.

## Dimer 2.238:

${ }^{1} \mathrm{H}$ NMR (400 MHz, $\left.\mathrm{CDCl}_{3}\right): \delta 5.77-5.37(\mathrm{~m}, 4 \mathrm{H}), 4.38(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, 4 \mathrm{H}), 3.19-2.77(\mathrm{~m}, 4 \mathrm{H}), 2.49-$ $2.26(\mathrm{~m}, 4 \mathrm{H}), 2.05-1.72(\mathrm{~m}, 8 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 177.5,127.8,70.1,47.9,46.6,34.2,21.0$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 305.1747$; found: 305.1749
IR: v $\left(\mathrm{cm}^{-1}\right)$ 3064, 2940, 2883, 2843, 1734, 1381, 1068.
cyclopent-3-ene-1-carboxylic acid (2.239)


It was prepared according to a literature procedure. ${ }^{131}$
1-(3-chloropropyl)cyclopent-3-ene-1-carboxylic acid (2.240)


Following a reported procedure, ${ }^{132}$ to a solution of diisopropylamine ( $15.0 \mathrm{~mL}, 105 \mathrm{mmol}, 2.25$ equiv) in dry THF ( $44 \mathrm{~mL}, 1.1 \mathrm{M}$ ) at $-10^{\circ} \mathrm{C}$ was added dropwise ${ }^{\mathrm{n}} \mathrm{BuLi}(2.5 \mathrm{M}$ in hexane, 41.0 mL , $103 \mathrm{mmol}, 2.20$ equiv) over 1 hour. The reaction mixture was stirred at $-10^{\circ} \mathrm{C}$ for 15 minutes. The acid 2.239 ( $5.24 \mathrm{~g}, 46.8 \mathrm{mmol}, 1.00$ equiv) was then added dropwise over 15 minutes, and then the temperature was raised to room temperature. After being stirred for 2 hours, the reaction mixture was cooled to $-10^{\circ} \mathrm{C}$ and 1-chloro-3-iodopropane ( $\mathbf{2 . 8 4}$ ) ( $6.54 \mathrm{~mL}, 60.8 \mathrm{mmol}, 1.30$ equiv)
was added dropwise over 30 minutes. The reaction mixture was stirred at room temperature overnight. After the completion of the reaction, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 9: 1\right)$ to yield the pure product $\mathbf{2 . 2 4 0}(7.86 \mathrm{~g}, 89 \%)$ as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 11.66(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.65-5.59(\mathrm{~m}, 2 \mathrm{H}), 3.52(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.00-$ $2.90(\mathrm{~m}, 2 \mathrm{H}), 2.38-2.29(\mathrm{~m}, 2 \mathrm{H}), 1.90-1.73(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right): \delta 184.3,128.5,52.0,45.2,42.5,36.5,28.7$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{9} \mathrm{H}_{12} \mathrm{ClO}_{2}\left([\mathrm{M}-\mathrm{H}]^{-}\right): 187.0531$; found: 187.0530 .
IR: v (cm ${ }^{-1}$ ) 3059 (w), 2923 (w), 2857 (w), 2616 (w), 1695 (s), 1445 (w), 1408 (w), 1271 (w), 1228 (w), 1207 (w), 942 (w), 775 (w), 673 (m).

## N-(2-(1H-indol-3-yl)ethyl)-1-(3-chloropropyl)cyclopent-3-ene-1-carboxamide (2.237)



To a solution of 2.85 ( $500 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv) in dry $\mathrm{MeCN}(24 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added tryptamine (1.16) ( $395 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( $370 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv) at room temperature. After being stirred at reflux for 24 hours, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ) to yield the pure product 2.237 (204 $\mathrm{mg}, 25 \%$ ) as a brownish oil.

## $N$-(2-(1H-indol-3-yl)ethyl)-1-(3-chloropropyl)cyclopent-3-ene-1-carboxamide (2.237)



To a solution of 2.240 ( $500 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv) in dry DMF ( $24 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at room temperature was added tryptamine (1.16) ( $395 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv), DIPEA ( $612 \mu \mathrm{~L}, 3.71 \mathrm{mmol}$, 1.50 equiv), DCC ( $510 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv) and HOBt ( $334 \mathrm{mg}, 2.47 \mathrm{mmol}, 1.00$ equiv). After being stirred for 24 hours, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1) to yield the pure product 2.237 ( $433 \mathrm{mg}, 53 \%$ ) as a brownish oil.

## $N$-(2-(1H-indol-3-yl)ethyl)-1-(3-chloropropyl)cyclopent-3-ene-1-carboxamide (2.237)


 1.00 equiv) in dry chloroform ( $108 \mathrm{~mL}, 0.27 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added dry DMF (catalytic amount, 36 drops) followed by addition of oxalyl chloride ( $2.70 \mathrm{~mL}, 30.7 \mathrm{mmol}, 1.05$ equiv) dropwise. After being stirred at room temperature for 1 hour, the reaction mixture was cannulated into a solution of tryptamine ( 1.16 ) ( $4.69 \mathrm{~g}, 29.3 \mathrm{mmol}, 1.00$ equiv) and triethylamine ( $4.47 \mathrm{~mL}, 32.2 \mathrm{mmol}, 1.10$ equiv) in dry chloroform ( $108 \mathrm{~mL}, 0.27 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$. After being stirred at room temperature for 2 hours, the reaction mixture was quenched with 2 M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to obtain the amide 2.237 ( $8.9 \mathrm{~g}, 92 \%$ ) which was used directly in the next step without further purification. For analysis, the crude product can be purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1) to yield the pure product 2.237 as a brownish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.70(\mathrm{~s}, 1 \mathrm{H}), 7.62(\mathrm{dd}, \mathrm{J}=8.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.38(\mathrm{dt}, \mathrm{J}=8.4,1.1 \mathrm{~Hz}, 1 \mathrm{H})$, $7.21(\mathrm{td}, J=8.1,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.13(\mathrm{td}, J=7.7,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.99(\mathrm{~d}, J=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.81(\mathrm{t}, J=5.7 \mathrm{~Hz}$, $1 \mathrm{H}), 5.62-5.56(\mathrm{~m}, 2 \mathrm{H}), 3.62(\mathrm{td}, J=6.7,5.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.42(\mathrm{t}, J=5.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.98(\mathrm{t}, J=6.7 \mathrm{~Hz}, 2 \mathrm{H})$, $2.77-2.68(\mathrm{~m}, 2 \mathrm{H}), 2.31-2.21(\mathrm{~m}, 2 \mathrm{H}), 1.75-1.62(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 177.3,136.5,129.0,127.3,122.3,122.0,119.3,118.6,112.6,111.5$, 52.1, 45.4, 42.8, 40.0, 37.1, 28.5, 25.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{ClN}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 331.1572; found: 331.1577.
IR: v ( $\mathrm{cm}^{-1}$ ) 3414 (w), 3276 (br), 3055 (w), 2923 (m), 2851 (w), 1641 (s), 1516 (s), 1455 (m), 1437 (s), 1342 (m), 1308 (w), 1270 (w), 1227 (m), 1097 (w), 1011 (w), 946 (w), 909 (m), 741 (s), 672 (m).

## 7-(2-(1H-indol-3-yl)ethyl)-7-azaspiro[4.5]dec-2-en-6-one (2.107)



Following a reported procedure, ${ }^{135}$ to a solution of the amide $\mathbf{2 . 2 3 7}$ ( $29.3 \mathrm{mmol}, 1.00$ equiv) in dry THF ( $292 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added LiHMDS ( 1 M in THF, $32.2 \mathrm{~mL}, 32.2 \mathrm{mmol}, 1.10$ equiv) dropwise. The reaction mixture was stirred for 15 minutes then warmed to room temperature and stirred for another 30 minutes. The reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to obtain the lactam 2.107 ( $7.5 \mathrm{~g}, 87 \%$ ) which was used directly in the next step without further purification. For analysis, the crude product can be
purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1\right)$ to yield the pure product 2.107 as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.49(\mathrm{~s}, 1 \mathrm{H}), 7.67(\mathrm{dd}, J=7.8,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.35(\mathrm{dt}, J=8.1,1.0 \mathrm{~Hz}, 1 \mathrm{H})$, 7.17 (ddd, J = 8.1, $7.0,1.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.11 (ddd, J = 8.0, $7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.01(\mathrm{~d}, J=1.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.67-$ $5.60(\mathrm{~m}, 2 \mathrm{H}), 3.70-3.61(\mathrm{~m}, 2 \mathrm{H}), 3.27-3.17(\mathrm{~m}, 2 \mathrm{H}), 3.09-2.95(\mathrm{~m}, 4 \mathrm{H}), 2.30-2.18(\mathrm{~m}, 2 \mathrm{H}), 1.78$ $-1.67(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 175.9, 136.4, 128.3, 127.7, 122.3, 121.9, 119.2, 118.9, 113.2, 111.3, 49.2, 49.1, 48.0, 46.5, 35.5, 23.1, 20.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{ONa}\left([\mathrm{M}+\mathrm{Na}]^{+}\right.$): 317.1624; found: 317.1630.
IR: v ( $\mathrm{cm}^{-1}$ ) 3409 (w), 3255 (br), 3054 (w), 2931 (w), 2853 (w), 1608 (s), 1493 (m), 1434 (m), 1430 (m), 1355 (m), 1303 (w), 1229 (w), 1194 (w), 1101 (w), 1012 (w), 953 (w), 909 (w), 874 (w), 809 (w), 740 (s), 670 (m).

## $2^{\prime}, 3^{\prime}, 4^{\prime}, 6^{\prime}, 7^{\prime}, 12^{\prime}-h e x a h y d r o s p i r o\left[c y c l o p e n t a n e-1,1^{\prime}-\right.$-indolo[2,3-a]quinolizin]-3-en-5'-ium perchlorate (2.106a)



A solution of lactam 2.107 ( 29.3 mmol, 1.00 equiv) and freshly distilled $\mathrm{POCl}_{3}$ ( $82 \mathrm{~mL}, 30$ equiv) in dry acetonitrile ( $35 \mathrm{~mL}, 0.85 \mathrm{M}$ ) was heated at $100^{\circ} \mathrm{C}$ for 4 hours. The reaction mixture was cooled down to room temperature and evaporated in vacuo to remove completely excess of $\mathrm{POCl}_{3}$. The residue was dissolved in $\mathrm{DCM}(138 \mathrm{~mL})$ and treated with aqueous $1 \mathrm{M} \mathrm{LiClO} 4(90 \mathrm{~mL})$ for 20 minutes. The reaction mixture was extracted with DCM. The combined organic extracts were washed with $1 \mathrm{M} \mathrm{LiClO}_{4}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to obtain the iminium salt 2.106a ( $10.8 \mathrm{~g}, 98 \%$ ) as an amorphous yellow solid which was directly used directly in the next step without further purification.
 7.20 (ddd, $J=7.9,6.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.02(\mathrm{~s}, 2 \mathrm{H}), 4.16(\mathrm{t}, \mathrm{J}=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 4.05-4.02(\mathrm{~m}, 2 \mathrm{H}), 3.31(\mathrm{t}, J$ $=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.28-3.24(\mathrm{~m}, 1 \mathrm{H}), 3.24-3.15(\mathrm{~m}, 1 \mathrm{H}), 2.82-2.75(\mathrm{~m}, 1 \mathrm{H}), 2.75-2.66(\mathrm{~m}, 1 \mathrm{H})$, 2.09-2.03(m,4H).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{2}\left(\left[\mathrm{M}-\mathrm{ClO}_{4}{ }^{-}\right]^{+}\right)$: 277.1699; found: 277.1702.
IR: v ( $\mathrm{cm}^{-1}$ ) 3616 (w), 3250 (m), 3054 (m), 2925 (s), 2859 (m), 2751 (w), 2358 (s), 1629 (s), 1458 (m), 1437 (m), 1329 (m), 1301 (w), 1255 (w), 1197 (w), 1160 (w), 1009 (w), 946 (w), 744 (m), 670 (m).

## 2',3',4',6', $\mathbf{7}^{\prime}, 12^{\prime}$-hexahydrospiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-en-5'-ium chloride (2.106b)



To the amide 2.107 ( $202 \mathrm{mg}, 0.69 \mathrm{mmol}, 1.00$ equiv) in dry acetonitrile ( $0.80 \mathrm{ml}, 0.86 \mathrm{M}$ ) was added freshly distilled phosphoryl chloride ( $2.00 \mathrm{ml}, 20.7 \mathrm{mmol}, 30.0$ equiv) in one portion and the reaction mixture was stirred under reflux for 4 hours. The reaction mixture was cooled down to room temperature and evaporated in vacuo to remove completely excess of $\mathrm{POCl}_{3}$. The reaction mixture was redissolved in DCM and brine was added. The reaction mixture was basified with $10 \%$ aqueous ammonia. The aqueous layer was saturated with NaCl and extracted 5-10 times with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the desired product 2.106b (184 mg, 85\%) as an amorphous red solid which was directly used directly in the next step without further purification.
${ }^{1} \mathrm{H}$ NMR (400 MHz, DCM- $\left.\mathrm{d}_{2} / \mathrm{CDCl}_{3} 1: 4\right): \delta 9.24(\mathrm{~s}, 1 \mathrm{H}), 7.58(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{~d}, \mathrm{~J}=8.5 \mathrm{~Hz}$, $1 \mathrm{H}), 7.42(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.19(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.00(\mathrm{~s}, 2 \mathrm{H}), 4.23(\mathrm{t}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 4.11(\mathrm{t}, J=$ $4.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.31-3.24(\mathrm{~m}, 4 \mathrm{H}), 2.77-2.71(\mathrm{~m}, 1 \mathrm{H}), 2.71-2.64(\mathrm{~m}, 1 \mathrm{H}), 2.09-2.02(\mathrm{~m}, 4 \mathrm{H})$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{2}\left(\left[\mathrm{M}-\mathrm{Cl}^{-}\right]^{+}\right)$: 277.1699; found: 277.1702.
IR: v ( $\mathrm{cm}^{-1}$ ) 3616 (w), 3250 (m), 3054 (m), 2925 (s), 2859 (m), 2751 (w), 2358 (s), 1629 (s), 1458 (m), 1437 (m), 1329 (m), 1301 (w), 1255 (w), 1197 (w), 1160 (w), 1009 (w), 946 (w), 744 (m), 670 (m).

## 3',4',6',7',12',12b'-hexahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-ene (rac-

 2.88)

Following a reported procedure, ${ }^{136}$ the perchlorate salt 2.106 a ( $29.3 \mathrm{mmol}, 1.00$ equiv) was added portionwise to a solution of $\mathrm{NaBH}_{4}\left(13.3 \mathrm{~g}, 351 \mathrm{mmol}, 12.0\right.$ equiv) in $\mathrm{EtOH}(1.46 \mathrm{~L}, 0.02 \mathrm{M})$ at $0^{\circ} \mathrm{C}$. After being stirred at $0{ }^{\circ} \mathrm{C}$ for 4 h 30 , the reaction mixture was quenched with 2 M HCl and evaporated in vacuo. The crude product was redissolved in DCM and saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 9: 1$ ) to yield the pure product rac-2.88 (4568 mg, 56\% from 2.239) as a brown amorphous solid.
(R)-3',4',6',7',12',12b'-hexahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-ene (2.88)


Following a reported procedure, ${ }^{116}$ a dry round bottom flask under argon was charged with Noyori's catalyst 2.118 ( $116 \mathrm{mg}, 0.182 \mathrm{mmol}, 5.00 \mathrm{~mol} \%$ ), silver hexafluoroantimonate $(\mathrm{V})(375 \mathrm{mg}$, $1.09 \mathrm{mmol}, 30.0 \mathrm{~mol} \%$ ), CTAB ( $1.33 \mathrm{~g}, 3.64 \mathrm{mmol}, 1.00$ equiv) and sodium formate ( $3.71 \mathrm{~g}, 54.6$ $\mathrm{mmol}, 15.0$ equiv) in degassed water $(21.8 \mathrm{ml}, 0.170 \mathrm{M})$. The reaction mixture was stirred at $40^{\circ} \mathrm{C}$ for 30 minutes. The iminium salt $2.106 \mathrm{~b}(1.14 \mathrm{~g}, 3.64 \mathrm{mmol}, 1.00$ equiv) was then added in one portion under argon. The reaction mixture was stirred at $40^{\circ} \mathrm{C}$ for 2 days. Additional Noyori's catalyst ( $58.0 \mathrm{mg}, 0.091 \mathrm{mmol}, 2.50 \mathrm{~mol} \%$ ) and silver hexafluoroantimonate( V ) ( $188 \mathrm{mg}, 0.546 \mathrm{mmol}$, 15.0 mol\%) were added in one portion under argon and the reaction mixture was stirred at $40^{\circ} \mathrm{C}$ for 2 days. The reaction mixture was cooled down to room temperature and the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 15: 1\right)$ to yield the desired product 2.88 ( $701 \mathrm{mg}, 70 \%$ ( $48 \%$ from 2.239)) as a brown amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.90(\mathrm{~s}, 1 \mathrm{H}), 7.47(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.25(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.14(\mathrm{t}, J=$ $7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.08(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.89-5.79(\mathrm{~m}, 1 \mathrm{H}), 5.79-5.70(\mathrm{~m}, 1 \mathrm{H}), 3.36(\mathrm{~s}, 1 \mathrm{H}), 3.15-$ $2.96(\mathrm{~m}, 4 \mathrm{H}), 2.76-2.62(\mathrm{~m}, 2 \mathrm{H}), 2.50-2.17(\mathrm{~m}, 4 \mathrm{H}), 1.95-1.77(\mathrm{~m}, 2 \mathrm{H}), 1.67-1.49(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 136.3,134.8,134.3,127.1,126.9,121.5,119.3,117.9,111.0,110.9$, $69.4,56.4,54.8,48.2,43.4,41.1,40.3,22.9,21.6$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 279.1856; found: 279.1861 .
IR: v ( $\mathrm{cm}^{-1}$ ) 3439 (w), 3051 (w), 2921 (w), 2849 (w), 2748 (w), 2748 (w), 1620 (w), 1462 (m), 1440 (w), 1349 (m), 1318 (m), 1269 (m), 1207 (w), 1157 (w), 1123 (w), 933 (w), 910 (w), 737 (s), 696 (m).
$[\alpha]_{D}{ }^{20}-22.4^{\circ}\left(c 0.77, \mathrm{CHCl}_{3}\right)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, 1\% $\mathrm{NEt}_{3}$ in MeOH (10\%), 230 $n m) t_{R}($ minor $)=5.6 \mathrm{~min}, t_{\mathrm{R}}($ major $)=6.7 \mathrm{~min}: 95.5: 4.5 \mathrm{er}$.

### 8.2.2 Oxidation of the Indole Skeleton

## 2',3',6',7'-tetrahydro-5'H,8a'H-dispiro[cyclopentane-1,8'-indolizine-1',2'-indolin]-3-en-3'-one (2.101)



This product was often observed and isolated during the various attempts for the oxidation of indole rac-2.88.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.69-7.51(\mathrm{~m}, 1 \mathrm{H}), 7.38(\mathrm{ddd}, J=8.4,7.0,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.75(\mathrm{t}, \mathrm{J}=7.4$ $\mathrm{Hz}, 1 \mathrm{H}), 6.71(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.49(\mathrm{dt}, J=5.9,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.24(\mathrm{dq}, J=6.8,2.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.43-$ $3.23(\mathrm{~m}, 2 \mathrm{H}), 2.97(\mathrm{dt}, J=17.6,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.58(\mathrm{~s}, 1 \mathrm{H}), 2.54(\mathrm{td}, \mathrm{J}=10.0,7.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.36-2.10$ $(\mathrm{m}, 3 \mathrm{H}), 1.97(\mathrm{ddd}, J=13.1,10.4,7.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.88-1.71(\mathrm{~m}, 3 \mathrm{H}), 1.63(\mathrm{dt}, J=12.6,3.0 \mathrm{~Hz}, 2 \mathrm{H})$, 1.32 (dt, J = 13.5, $6.6 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 204.2, 160.8, 137.4, 129.0, 128.9, 124.7, 118.6, 112.0, 78.4, 73.6, 54.2, 53.5, 44.5, 44.0, 41.3, 40.6, 37.2, 22.4.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$295.1805; found: 295.1808.
IR: v ( $\mathrm{cm}^{-1}$ ) 2919 (w), 2857 (w), 2363 (w), 1725 (s), 1579 (w), 1454 (w), 1252 (s), 1093 (m), 921 (w), 730 (s).
$3^{\prime}, 4^{\prime}, 6^{\prime}, 7{ }^{\prime}, 12$ ',12b'-hexahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizine]-3,4-diol (2.89)


Following a reported procedure, ${ }^{103}$ to a solution of the indole skeleton rac-2.88 ( $100 \mathrm{mg}, 0.359$ mmol, 1.00 equiv) and NMO ( $122 \mathrm{mg}, 1.04 \mathrm{mmol}, 2.90$ equiv) in $\mathrm{THF} /{ }^{\mathrm{t}} \mathrm{BuOH} / \mathrm{H}_{2} \mathrm{O}$ (10:0.5:1, 2.4/0.12/0.24 mL, 0.13 M ) was added $\mathrm{OsO}_{4}$ in ${ }^{\mathrm{t}} \mathrm{BuOH}(2.5 \%, 2$ drops). After being stirred at room temperature for 5 hours, the reaction mixture was diluted with $\mathrm{H}_{2} \mathrm{O}$ and DCM and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM/MeOH 9:1) to yield the pure product 2.89 ( $76 \mathrm{mg}, 68 \%$ ) as a single diastereoisomer and as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 8.09(\mathrm{br}, 1 \mathrm{H}), 7.47(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.14$ (ddd, $J=8.5,7.2,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.09$ (ddd, $J=8.6,7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.18$ (ddd, $J=9.3,7.5,4.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.83(\mathrm{~s}, 1 \mathrm{H}), 3.35(\mathrm{~s}, 1 \mathrm{H}), 3.04-2.85(\mathrm{~m}, 3 \mathrm{H}), 2.75-2.48(\mathrm{~m}, 3 \mathrm{H}), 2.49-2.35(\mathrm{~m}, 2 \mathrm{H}), 1.96-1.50$ ( $\mathrm{m}, 6 \mathrm{H}$ ).
${ }^{13}{ }^{3}$ NMR (101 MHz, CDCl $_{3}$ ): $\delta 136.3,133.3,127.0,121.9,119.7,118.1,111.1,74.2,73.8,69.0,53.2$, 53.2, 44.7, 44.5, 41.6, 36.9, 23.0, 22.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 313.1911, found: 313.1916.
IR: v (cm ${ }^{-1}$ ) 3346 (m), 2935 (m), 2353 (w), 2337 (w), 1463 (w), 1346 (w), 1319 (w), 1069 (w), 909 (w), 739 (s), 670 (w).

## 7a'-chloro-3',4',6',7',7a',12b'-hexahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizine]-3,4-diol (2.254)



Following a reported procedure, ${ }^{137 \mathrm{a}}$ to a solution of the diol $2.89(25.0 \mathrm{mg}, 0.080 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{NH}_{4} \mathrm{Cl}(9.00 \mathrm{mg}, 0.160 \mathrm{mmol}, 2.00$ equiv) in dry $\mathrm{MeCN} /$ ethylene glycol ( $1: 1,1.2 / 1.2 \mathrm{~mL}$, 0.034 M ) at $0^{\circ} \mathrm{C}$ was added PIFA ( $45.0 \mathrm{mg}, 0.104 \mathrm{mmol}, 1.30$ equiv) portionwise over 30 minutes. After being stirred overnight at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with chloroform. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, pure EA$)$ to yield the pure product $\mathbf{2 . 2 5 4}(25 \mathrm{mg}$, 91\%) as a single diastereoisomer and as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.59(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{dd}, \mathrm{J}=7.3,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{td}, \mathrm{J}=7.6$, $1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.31-7.25(\mathrm{~m}, 1 \mathrm{H}), 4.42(\mathrm{br}$ s, 2H), $3.62-3.36$ (br s, 1H), 3.11 (br s, 1H), $2.91-2.75$ (m, 2H), 2.48-2.43(m, 2H), 2.42-2.25(m,5H), 1.62-1.35 (m, 4H).
${ }^{13}$ C NMR (101 MHz, CDCl 3 ): $\delta 173.5,153.0,141.2,130.2,127.5,122.9,121.0,77.2,70.2,70.0,53.9$, $52.3,41.9,41.6,38.6,34.4,28.9,25.0,21.3$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{ClN}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 347.1521 ; found: 347.1518.
IR: v ( $\mathrm{cm}^{-1}$ ) 2919 ( w ), 2857 ( w ), 2363 ( w ), 1725 ( s$), 1579$ ( w$), 1454$ ( w ), 1252 ( s$), 1093$ (m), 921 ( w$)$, 730 (s).

## 16b-chloro-1,5,6,16b-tetrahydro-2H,4H,7aH,11H-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizine (2.253)



Following a reported procedure, ${ }^{103}$ to a solution of the indolenine $\mathbf{2 . 2 5 4}(10.0 \mathrm{mg}, 0.029 \mathrm{mmol}$, 1.00 equiv) in $\mathrm{THF} / \mathrm{H}_{2} \mathrm{O}(1: 1,0.25 / 0.25 \mathrm{~mL}, 0.06 \mathrm{M})$ at room temperature was added $\mathrm{NaIO} \mathrm{O}_{4}(37.0$ $\mathrm{mg}, 0.170 \mathrm{mmol}, 6.00$ equiv). After being stirred at room temperature for 2 hours, the reaction
mixture was diluted with water and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$ to yield the pure product 2.253 (9 $\mathrm{mg}, 86 \%$ ) as a single diastereoisomer and as a yellow amorphous solid.

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7a'-chloro-3',4',6',7',7a',12b'-hexahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-
ene (2.254)
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Following a reported procedure, ${ }^{143}$ to a solution of indole rac-2.88 ( $20.0 \mathrm{mg}, 0.020 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $0.72 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-20^{\circ} \mathrm{C}$ was added dropwise a solution of ${ }^{\mathrm{t}} \mathrm{BuOCl}(1 \mathrm{M}$ in DCM, $0.079 \mathrm{~mL}, 0.079 \mathrm{mmol}, 1.10$ equiv) over 15 minutes and the resulting solution was stirred at room temperature for an additional 30 minutes. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by
 a single diastereoisomer and as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ at room temperature): $\delta 7.64(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.46 (dd, $J=7.4,1.3 \mathrm{~Hz}$, $1 \mathrm{H}), 7.40(\mathrm{td}, J=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{td}, J=7.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.68(\mathrm{~s}, 2 \mathrm{H}), 4.15-3.74(\mathrm{~m}, 1 \mathrm{H}), 3.56$ - $3.10(\mathrm{~m}, 1 \mathrm{H}), 2.97-2.81(\mathrm{~m}, 1 \mathrm{H}), 2.73-2.68(\mathrm{~m}, 2 \mathrm{H}), 2.57-2.19(\mathrm{~m}, 5 \mathrm{H}), 2.10-1.92(\mathrm{~m}, 2 \mathrm{H})$, $1.66-1.57(\mathrm{~m}, 2 \mathrm{H}), 1.53-1.36(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ at room temperature): ${ }^{571} \delta 177.9,152.8,140.2,129.9,129.5,128.4$, $126.5,122.4,121.8,71.1,64.5,50.4,45.7,43.1,38.5,22.5$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ at $-40^{\circ} \mathrm{C}$ ): 1:0.4 mixture of conformers $\delta 7.68(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.58(\mathrm{~d}, \mathrm{~J}$ $=7.7 \mathrm{~Hz}, 0.4 \mathrm{H}), 7.53-7.35(\mathrm{~m}, 2.8 \mathrm{H}), 7.34-7.26(\mathrm{~m}, 1.4 \mathrm{H}), 5.72(\mathrm{~s}, 0.8 \mathrm{H}), 5.66(\mathrm{~s}, 2 \mathrm{H}), 4.13(\mathrm{~s}, 1 \mathrm{H})$, $3.54-3.39(\mathrm{~m}, 1.4 \mathrm{H}), 3.07(\mathrm{~d}, \mathrm{~J}=11.6 \mathrm{~Hz}, 0.4 \mathrm{H}), 3.02-2.75(\mathrm{~m}, 2.8 \mathrm{H}), 2.63-2.03(\mathrm{~m}, 9.8 \mathrm{H}), 2.02-$ $1.65(\mathrm{~m}, 2.4 \mathrm{H}), 1.65-1.44(\mathrm{~m}, 2.4 \mathrm{H}), 1.36-1.15(\mathrm{~m}, 0.8 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ at $-40{ }^{\circ} \mathrm{C}$ ): $\delta 178.1,177.7,152.5,152.3,139.8,139.3,129.9,129.8$, $129.5,129.4,128.5,128.1,126.6,126.5,122.6,122.2,121.9,121.3,71.2,70.2,65.6,63.6,57.0$, 51.2, 49.5, 45.7, 45.2, 45.1, 45.0, 42.6, 42.4, 38.9, 38.7, 38.5, 36.3, 30.4, 22.6, 21.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{ClN}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 313.1466$; found: 313.1468.

[^212]IR: $v\left(\mathrm{~cm}^{-1}\right) 2940$ (w), 2811 (w), 2332 (w), 1621 (s), 1564 (w), 1454 (w), 1261 (s), 1069 (m), 1110 (w), 711 (s).

## 16b-chloro-1,5,6,16b-tetrahydro-2H,4H,7aH,11H-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizine (2.253)



Following a reported procedure, ${ }^{147}$ to a solution of the chloroindolenine 2.245 ( $11.0 \mathrm{mg}, 0.035$ mmol, 1.00 equiv) in acetone $/ \mathrm{H}_{2} \mathrm{O}(10: 1,0.32 / 0.032 \mathrm{~mL}, 0.1 \mathrm{M})$ at room temperature were added sequentially 2,6 -lutidine ( $8.20 \mu \mathrm{~L}, 0.070 \mathrm{mmol}, 2.00$ equiv), NMO ( $6.20 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.50$ equiv) and finally $\mathrm{OsO}_{4}$ ( $0.180 \mathrm{mg}, 0.001 \mathrm{mmol}, 0.020$ equiv). The reaction mixture was stirred at room temperature for 1 h 30 . PIDA ( $17.0 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.50$ equiv) was then added and the reaction mixture was stirred at room temperature for 2 h 20 . The reaction mixture was quenched with saturated aqueous $\mathrm{NaHSO}_{3}$ and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$ to yield the pure product 2.253 (11 $\mathrm{mg}, 89 \%$ ) as a single diastereoisomer and as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.36(\mathrm{dd}, J=7.4,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.25(\mathrm{td}, J=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.96(\mathrm{td}, J=$ $7.5,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.85(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.51(\mathrm{dd}, \mathrm{J}=3.4,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.25(\mathrm{t}, \mathrm{J}=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.99$ (br s, 1H), 2.81-2.61 (m, 2H), 2.56-2.38(m, 2H), 2.35-1.81 (m, 7H), 1.66-1.54 (m, 2H), $1.41-$ 1.28 ( $\mathrm{m}, 1 \mathrm{H}$ ).
${ }^{13}{ }^{1}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 144.7,133.9,129.3,123.1,121.4,110.3,95.5,93.2,77.7,70.7,65.1$, 55.6, 50.3, 42.5, 39.6, 36.4, 34.1, 31.5, 20.5.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{ClN}_{2} \mathrm{O}_{2}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 345.1364; found: 345.1360.
IR: v ( $\mathrm{cm}^{-1}$ ) 2919 (s), 2820 (w), 2348 (w), 1612 (w), 1454 (m), 1360 (w), 1193 (m), 1119 (w), 1089 (s), 992 (m), 900 (w), 736 (m), 612 (m).

## 7a'-bromo-3',4',6',7',7a',12b'-hexahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3ene (2.257)



Following a reported procedure, ${ }^{151}$ to a solution of indole rac-2.88 (100 mg, $0.359 \mathrm{mmol}, 1.00$ equiv) in dry acetone ( $0.95 \mathrm{~mL}, 0.38 \mathrm{M}$ ) at room temperature was added NBS ( $64.0 \mathrm{mg}, 0.360$ mmol, 1.00 equiv). After being stirred for 1 hour, the reaction mixture was evaporated in vacuo.

The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 5: 1$ ) to yield the pure product $\mathbf{2 . 2 5 7}$ ( $100 \mathrm{mg}, 78 \%$ ) as a single diastereoisomer and as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, Acetone- $d_{6}$ ): $\delta 7.64-7.55(\mathrm{~m}, 2 \mathrm{H}), 7.43(\mathrm{td}, J=7.6,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{td}, \mathrm{J}=$ $7.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.65(\mathrm{~s}, 2 \mathrm{H}), 4.08(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.20(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.00-2.88(\mathrm{~m}, 1 \mathrm{H}), 2.87-2.60(\mathrm{~m}$, $5 \mathrm{H}), 2.60-2.51(\mathrm{~m}, 1 \mathrm{H}), 2.46-2.22(\mathrm{~m}, 2 \mathrm{H}), 2.16-1.94(\mathrm{~m}, 1 \mathrm{H}), 1.83-1.49(\mathrm{~m}, 2 \mathrm{H}), 1.49-1.36$ ( $\mathrm{m}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, Acetone- $\left.d_{6}\right) \cdot{ }^{571} \delta 179.2,153.0,141.8,130.6,129.9,129.1,127.4,123.9,122.1$, 65.2, 65.0, 51.4, 46.2, 43.9, 39.1, 23.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{BrN}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 357.0961$; found: 357.0960 .
IR: v ( $\mathrm{cm}^{-1}$ ) 3051 (w), 2937 (s), 2846 (m), 2822 (w), 2757 (w), 1621 (w), 1581 (m), 1454 (m), 1344 (w), 1295 (w), 1177 (w), 1115 (m), 985 (w), 931 (w), 875 (m), 831 (w), 767 (s), 748 (s), 669 (m).

## 3',4',6',7'-tetrahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-en-7a'(12b'H)-ol (2.264)



Following a reported procedure, ${ }^{162}$ to a solution of the indole skeleton rac-2.88 (100 mg, 0.359 mmol, 1.00 equiv) in dry DCM ( $14 \mathrm{~mL}, 0.026 \mathrm{M}$ ) at $-78^{\circ} \mathrm{C}$ was added TFA ( $454 \mu \mathrm{~L}, 6.11 \mathrm{mmol}, 17.0$ equiv) and the reaction mixture was stirred for 5 minutes. Purified $m C P B A(62.0 \mathrm{mg}, 0.360 \mathrm{mmol}$, 1.00 equiv) in dry DCM ( $0.14 \mathrm{~mL}, 0.3 \mathrm{M}$ ) was added dropwise and the reaction mixture was stirred at $-78{ }^{\circ} \mathrm{C}$ for 3 h . The reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{OH}$ and extracted with DCM. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the pure product 2.264 ( 106 mg , quantitative yield) as a single diastereoisomer and as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.45(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.41(\mathrm{dd}, J=7.3,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.29(\mathrm{td}, \mathrm{J}=7.6$, $1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.16(\mathrm{td}, J=7.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.61(\mathrm{dt}, J=6.1,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.42(\mathrm{dt}, J=6.0,2.3 \mathrm{~Hz}, 1 \mathrm{H})$, $4.63(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.67-3.58(\mathrm{~m}, 1 \mathrm{H}), 3.21(\mathrm{~s}, 1 \mathrm{H}), 3.05-2.93(\mathrm{~m}, 2 \mathrm{H}), 2.67-2.56(\mathrm{~m}, 2 \mathrm{H}), 2.31$ (ddd, $J=12.0,9.9,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.27-2.19(\mathrm{~m}, 1 \mathrm{H}), 2.16-2.01(\mathrm{~m}, 2 \mathrm{H}), 1.95-1.81(\mathrm{~m}, 2 \mathrm{H}), 1.62-1.54$ (m, 1H), 1.50 (ddd, $J=14.3,9.9,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.39-1.28(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 184.9, 154.2, 139.1, 129.1, 128.8, 128.6, 125.9, 122.1, 120.7, 82.6, 72.4, 55.0, 50.5, 45.5, 44.9, 39.1, 37.9, 32.4, 22.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 295.1805; found: 295.1800.

IR: v $\left(\mathrm{cm}^{-1}\right) 3382$ (w), 3052 (w), 2927 (w), 2852 (w), 2813 (w), 2755 (w), 1587 (w), 1456 (w), 1439 (w), 1399 (w), 1349 (w), 1317 (w), 1272 (w), 1176 (w), 1116 (w), 1080 (w), 999 (w), 910 (m), 841 (w), 753 (s), 732 (s), 669 (s).

## 1,2,5,6-tetrahydro-4H,7aH,11H,16bH-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizin-16b-ol (2.265)



Following a reported procedure, ${ }^{147}$ to a solution of the indolenine $\mathbf{2 . 2 6 4}$ ( $10.0 \mathrm{mg}, 0.035 \mathrm{mmol}$, 1.00 equiv) in acetone $/ \mathrm{H}_{2} \mathrm{O}(10: 1,0.32 / 0.032 \mathrm{~mL}, 0.1 \mathrm{M}$ ) were added sequentially 2,6 -lutidine ( $8.20 \mu \mathrm{~L}, 0.070 \mathrm{mmol}, 2.00$ equiv), $\mathrm{NMO}\left(6.20 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.5\right.$ equiv) and finally $\mathrm{OsO}_{4}(0.18$ $\mathrm{mg}, 0.001 \mathrm{mmol}, 0.020$ equiv). The reaction mixture was stirred at room temperature for 1 h 30 . PIDA ( $17.0 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.50$ equiv) was then added and the reaction mixture was stirred for 2h20. The reaction was quenched with saturated aqueous $\mathrm{NaHSO}_{3}$, and the reaction mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 2$ ) to yield the pure product $\mathbf{2 . 2 6 5}$ ( $9 \mathrm{mg}, 75 \%$ ) as a single diastereoisomer and as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.30(\mathrm{dd}, J=7.3,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.22(\mathrm{td}, J=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.83(\mathrm{td}, J=$ $7.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.46(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.63(\mathrm{t}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.53(\mathrm{t}, \mathrm{J}=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.06-2.92$ $(\mathrm{m}, 2 \mathrm{H}), 2.88(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.69-2.59(\mathrm{~m}, 1 \mathrm{H}), 2.42(\mathrm{dt}, J=14.1,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.22(\mathrm{td}, J=13.4,5.1 \mathrm{~Hz}$, $1 \mathrm{H}), 2.04(\mathrm{dd}, J=13.0,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.00-1.80(\mathrm{~m}, 4 \mathrm{H}), 1.68(\mathrm{dt}, J=13.0,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.57(\mathrm{dt}, J=$ $12.8,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.50-1.38(\mathrm{~m}, 2 \mathrm{H}), 1.08-0.98(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 145.9,130.3,129.5,124.3,119.4,107.0,95.1,89.8,79.8,75.5,65.1$, 56.1, 53.8, 40.3, 36.3, 33.3, 31.7, 29.3, 19.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 327.1703; found: 327.1705.
IR: v ( $\mathrm{cm}^{-1}$ ) 3398 (w), 3052 (w), 2927 (w), 2853 (w), 2813 (w), 2755 (w), 1587 (w), 1456 (w), 1439 (w), 1399 (w), 1349 (w), 1343 (w), 1317 (w), 1272 (w), 1176 (w), 1116 (w), 1080 (w), 1001 (w), 910 (m), 841 (w), 753 (s), 732 (s), 669 (s).
(7a'R,12b'R)-3',4',6',7'-tetrahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-3-en-7a'(12b'H)-yl benzoate (2.269)


Following a reported procedure, ${ }^{162}$ to a solution of indole $\mathbf{2 . 8 8 ( 5 0 0 ~ m g , ~} 1.80 \mathrm{mmol}, 1.00$ equiv) in dry chloroform ( $33 \mathrm{~mL}, 0.05 \mathrm{M}$ ) at room temperature was added purified dibenzoyl peroxide ( 440 $\mathrm{mg}, 1.80 \mathrm{mmol}, 1.00$ equiv). The reaction mixture was stirred for 1 h 30 . A mixture of triethylamine and diethylamine ( 2.0 and 3.0 mL ) was added and the reaction was stirred for one more hour. The solution was quenched with water and extracted with chloroform. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1\right)$ to yield the pure product 2.269 (490 $\mathrm{mg}, 68 \%$ ) as a single diastereoisomer and as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Acetone $-d_{6}$ at room temperature): $\delta 8.08-7.98(\mathrm{~m}, 2 \mathrm{H}), 7.70-7.62(\mathrm{~m}, 1 \mathrm{H})$, $7.58(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{t}, J=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.45(\mathrm{dd}, J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{td}, J=7.6,1.3 \mathrm{~Hz}$, $1 \mathrm{H}), 7.20(\mathrm{td}, J=7.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.67-5.58(\mathrm{~m}, 1 \mathrm{H}), 5.58-5.51(\mathrm{~m}, 1 \mathrm{H}), 3.49(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.23(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}), 3.05-2.46(\mathrm{~m}, 4 \mathrm{H}), 2.43-2.01(\mathrm{~m}, 4 \mathrm{H}), 1.95-1.71(\mathrm{~m}, 1 \mathrm{H}), 1.71-1.51(\mathrm{~m}, 2 \mathrm{H}), 1.49-1.23$ ( $\mathrm{m}, 2 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( 101 MHz , Acetone $-\boldsymbol{d}_{6}$ at room temperature): ${ }^{571} \delta 179.4,164.7,155.4,138.5,134.4$, $130.5,130.4,130.3,130.1,129.6,128.9,126.5,122.3,122.0,88.0,65.9,50.9,46.1,43.7,38.7$, 23.2.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , Acetone $-\boldsymbol{d}_{6}$ at $-40^{\circ} \mathrm{C}$ ): 2:1 mixture of conformers $\delta 8.09-7.97(\mathrm{~m}, \mathrm{3H})$, $7.76-7.61(\mathrm{~m}, 2.5 \mathrm{H}), 7.61-7.37(\mathrm{~m}, 6.5 \mathrm{H}), 7.29-7.17(\mathrm{~m}, 1.5 \mathrm{H}), 5.65(\mathrm{br} \mathrm{s}, 0.5 \mathrm{H}), 5.61(\mathrm{br} \mathrm{s}$, $0.5 \mathrm{H}), 5.56(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.51(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.72(\mathrm{~s}, 1 \mathrm{H}), 3.44-3.16(\mathrm{~m}, 1 \mathrm{H}), 3.06-2.69(\mathrm{~m}, 5 \mathrm{H}), 2.65-$ $2.28(\mathrm{~m}, 7 \mathrm{H}), 2.29-1.88(\mathrm{~m}, 3 \mathrm{H}), 1.87-1.58(\mathrm{~m}, 2.5 \mathrm{H}), 1.56-1.33(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz , Acetone- $d_{6}$ at $-40{ }^{\circ} \mathrm{C}$ ): $\delta 179.5,179.4,164.4,164.2,154.9,154.8,138.2,137.7$, 134.5, 134.4, 130.3, 130.1, 129.7, 129.7, 129.5, 129.4, 129.1, 129.1, 128.3, 126.7, 126.2, 122.1, $122.0,121.9,121.7,87.8,86.3,67.3,64.5,57.0,51.2,50.0,45.7,45.6,45.1,44.9,43.2,43.0,39.7$, 39.6, 39.2, 36.4, 31.4, 23.0, 22.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 399.2067; found: 399.2066.
IR: v ( $\mathrm{cm}^{-1}$ ) 3053 (w), 2924 (w), 2855 (w), 1727 (s), 1585 (w), 1453 (w), 1318 (w), 1276 (s), 1179 (w), 1103 (m), 1072 (w), 1026 (w), 875 (w), 771 (w), 713 (m).
$[\alpha]_{\mathrm{D}}{ }^{20}-79.3^{\circ}\left(c 0.62, \mathrm{CHCl}_{3}\right)$.

## (7a'R,12b'R)-3,4-dihydroxy-3',4',6',7'-tetrahydro-2'H-spiro[cyclopentane-1,1'-indolo[2,3-a]quinolizin]-7a'(12b'H)-yl benzoate (2.279)



Following a reported procedure, ${ }^{103}$ to a solution of the indole skeleton 2.269 ( $60.0 \mathrm{mg}, 0.150$ mmol, 1.00 equiv) and $\mathrm{NMO}\left(51.0 \mathrm{mg}, 0.440 \mathrm{mmol}, 2.90\right.$ equiv) in $\mathrm{THF} /{ }^{\dagger} \mathrm{BuOH} / \mathrm{H}_{2} \mathrm{O}$ (10:0.5:1, $0.1 / 0.005 / 0.01 \mathrm{~mL}, 0.13 \mathrm{M}$ ) was added $\mathrm{OsO}_{4}$ in ${ }^{\mathrm{t}} \mathrm{BuOH}(2.5 \%, 1$ drops). After being stirred at room temperature for 5 hours, the reaction mixture was diluted with $\mathrm{H}_{2} \mathrm{O}$ and DCM and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM/MeOH 9:1) to yield the pure product 2.279 ( $16 \mathrm{mg}, 18 \%$ ) as a single diastereoisomer and as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.02(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.68-7.57(\mathrm{~m}, 2 \mathrm{H}), 7.46(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 2 \mathrm{H})$, $7.44-7.32(\mathrm{~m}, 2 \mathrm{H}), 7.19(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.43(\mathrm{br}, 1 \mathrm{H}), 3.23-1.45(\mathrm{~m}, 16 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 164.2,154.0,136.7,133.7,130.0,129.4,128.9,128.8,126.3,122.0$, 121.6, 86.9, 74.4, 62.8, 51.1, 50.9, 43.4, 36.6, 29.8, 27.4, 22.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 433.2122; found: 433.2127.
IR: v (cm ${ }^{-1}$ ) 3339 (w), 2931 (w), 2857 (w), 2366 (w), 1725 (s), 1586 (w), 1454 (w), 1276 (s), 1093 (m), 1028 (w), 910 (w), 734 (s).
$[\alpha]_{\mathrm{D}}{ }^{20}-312.6^{\circ}\left(c=0.64, \mathrm{CHCl}_{3}\right)$.
(7R,7aR,7bR,9R,11R,16bR)-1,2,5,6-tetrahydro-4H,7aH,11H,16bH-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizin-16b-yl benzoate (2.272)


To a solution of the indolenine $2.279\left(10.0 \mathrm{mg}, 0.023 \mathrm{mmol}, 1.00\right.$ equiv) in THF/ $\mathrm{H}_{2}{ }^{18} \mathrm{O}(1: 1,0.2 / 0.2$ $\mathrm{mL}, 0.06 \mathrm{M}$ ) at room temperature was added $\mathrm{NaIO}_{4}(30.0 \mathrm{mg}, 0.139 \mathrm{mmol}, 6.00$ equiv). After being stirred at room temperature for 2 hours, the reaction mixture was diluted with water and extracted with DCM. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{EA} / \mathrm{MeOH}$ 15:1) to yield the pure product 2.272 ( $10 \mathrm{mg}, 85 \%$ ) as a single diastereoisomer and as an amorphous yellow solid. HRMS indicated no incorporation of ${ }^{18} \mathrm{O}$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 431.1965 ; found: 431.1971 .
(7R,7aR,7bR,9R,11R,16bR)-1,2,5,6-tetrahydro-4H,7aH,11H,16bH-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizin-16b-yl benzoate (2.272)


Following a reported procedure, ${ }^{147}$ to a solution of the indolenine $2.269(14.0 \mathrm{mg}, 0.035 \mathrm{mmol}$, 1.00 equiv) in acetone $/ \mathrm{H}_{2} \mathrm{O}(10: 1,0.32 / 0.032 \mathrm{~mL}, 0.1 \mathrm{M})$ were added sequentially 2,6 -lutidine ( $8.20 \mu \mathrm{~L}, 0.070 \mathrm{mmol}, 2.00$ equiv), $\mathrm{NMO}\left(6.20 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.50\right.$ equiv) and finally $\mathrm{OsO}_{4}(0.18$ $\mathrm{mg}, 0.00070 \mathrm{mmol}, 0.020$ equiv). The reaction mixture was stirred at room temperature for 1 h 30 . PIDA ( $17.0 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.50$ equiv) was then added and the reaction mixture was stirred for 2 h 20 . The reaction was quenched with saturated aqueous $\mathrm{NaHSO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, $\mathrm{EA} / \mathrm{MeOH} 15: 1$ ) to yield the pure product $\mathbf{2 . 2 7 2}(12 \mathrm{mg}, 76 \%)$ as a single diastereoisomer and as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.16-8.08(\mathrm{~m}, 2 \mathrm{H}), 7.78(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.62-7.54(\mathrm{~m}, 1 \mathrm{H}), 7.51$ $-7.43(\mathrm{~m}, 2 \mathrm{H}), 7.29-7.20(\mathrm{~m}, 1 \mathrm{H}), 6.94-6.84(\mathrm{~m}, 2 \mathrm{H}), 5.54(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.30(\mathrm{t}, \mathrm{J}=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.70$ $-3.53(\mathrm{~m}, 1 \mathrm{H}), 3.26(\mathrm{~d}, \mathrm{~J}=15.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.97(\mathrm{~d}, \mathrm{~J}=10.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.77(\mathrm{~d}, \mathrm{~J}=12.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.64(\mathrm{~d}, \mathrm{~J}$ $=11.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.57(\mathrm{~s}, 1 \mathrm{H}), 2.37-2.11(\mathrm{~m}, 2 \mathrm{H}), 2.09-1.85(\mathrm{~m}, 4 \mathrm{H}), 1.65-1.53(\mathrm{~m}, 2 \mathrm{H}), 1.44-$ 1.29 ( $\mathrm{m}, 1 \mathrm{H}$ ).
${ }^{13}$ C NMR (101 MHz, CDCl $_{3}$ ): $\delta 165.7,146.2,133.3,132.4,131.0,130.1,129.3,128.5,126.6,121.4$, $110.4,95.4,93.2,85.5,77.6,66.2,55.6,50.5,43.0,36.5,34.2,31.6,31.5,20.6$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 431.1965$; found: 431.1971.
IR: $\mathrm{v}\left(\mathrm{cm}^{-1}\right) 2935$ ( w ), 2803 ( w ), 2755 ( w$), 2358$ ( w$), 2329$ ( w$), 1722$ ( s$), 1608$ ( w$), 1466$ ( m$), 1384$ (w), 1360 (w), 1268 (s), 1165 (m), 1128 (m), 1097 (w), 1029 (w), 984 (w), 920 (w), 800 (w), 760 (w), 740 (w), 714 (s).
$[\alpha]_{D}{ }^{20}-53.02^{\circ}\left(c 0.1, \mathrm{CHCl}_{3}\right)$.
(7R,7aR,7bR,9R,11R,16bR)-1,2,5,6-tetrahydro-4H,7aH,11H,16bH-7,9:7,11-dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizin-16b-ol (2.1)


Following a reported procedure, ${ }^{168}$ to a solution of $\mathbf{2 . 2 7 2}$ ( $5.4 \mathrm{mg}, 0.013 \mathrm{mmol}, 1.00$ equiv) in dry methanol ( $0.5 \mathrm{ml}, 0.26 \mathrm{M}$ ) was added sodium hydroxide ( $3.0 \mathrm{mg}, 0.075 \mathrm{mmol}, 6.00$ equiv) in one portion. The reaction mixture was stirred at $40^{\circ} \mathrm{C}$ overnight. The methanol was removed in vacuo and the reaction mixture was redissolved in water. The aqueous phase was extracted with ethyl
acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{EA} / \mathrm{MeOH} 15: 1$ ) to yield terengganensine A ( $\mathbf{2 . 1}$ ) ( $4.0 \mathrm{mg}, 95 \%$ ) as a single diastereoisomer and as an amorphous light yellow solid.
$(7 R, 7 \mathrm{a} R, 7 \mathrm{~b} R, 9 R, 11 R, 16 \mathrm{~b} R)-1,2,5,6$-tetrahydro-4H,7aH,11H,16bH-7,9:7,11-
dimethano[1,3,5]dioxazino[5',4':1,2]indolo[2,3-a]quinolizin-16b-ol (2.1)


To a solution of the indolenine 2.269 ( $311 \mathrm{mg}, 0.778 \mathrm{mmol}, 1.00$ equiv) in acetone ( 7.1 mL )/ $\mathrm{H}_{2} \mathrm{O}$ $(0.71 \mathrm{~mL})(10: 1,0.1 \mathrm{M})$ were added sequentially 2,6 -lutidine ( $82 \mu \mathrm{~L}, 1.56 \mathrm{mmol}, 2.00$ equiv), NMO ( $138 \mathrm{mg}, 1.18 \mathrm{mmol}, 1.50$ equiv) and finally $\mathrm{OsO}_{4}(4.0 \mathrm{mg}, 0.016 \mathrm{mmol}, 0.02$ equiv). The reaction mixture was stirred at room temperature for 1 h 30 . PIDA ( $378 \mathrm{mg}, 1.18 \mathrm{mmol}, 1.50$ equiv) was then added and the reaction mixture was stirred for 2 h 20 . Methanol ( 11 mL ) was added followed by NaOH ( $378 \mathrm{mg}, 9.33 \mathrm{mmol}, 12.0$ equiv) and the reaction mixture was stirred at $40{ }^{\circ} \mathrm{C}$ overnight. The reaction was quenched with saturated aqueous $\mathrm{NaHSO}_{3}$ and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{EA} / \mathrm{MeOH} 15: 1$ ) to yield the pure product $\mathbf{2 . 1}$ ( $200 \mathrm{mg}, 80 \%$ ) as a single diastereoisomer and as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.30(\mathrm{dd}, J=7.3,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.21(\mathrm{td}, \mathrm{J}=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.92(\mathrm{t}, \mathrm{J}=$ $7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.82(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.49(\mathrm{dd}, J=3.3,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.24(\mathrm{t}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.99(\mathrm{~d}, J=$ $10.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.72(\mathrm{dt}, J=12.8,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.69-2.60(\mathrm{~m}, 2 \mathrm{H}), 2.36(\mathrm{~s}, 1 \mathrm{H}), 2.36-2.28(\mathrm{~m}, 1 \mathrm{H})$, 2.17 (ddd, $J=13.3,11.1,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.05(\mathrm{dt}, J=14.7,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.02-1.92(\mathrm{~m}, 2 \mathrm{H}), 1.90-1.80$ (m, 2H), 1.75 (td, J = 14.0, 4.6 Hz, 1H), 1.61-1.54 (m, 2H), 1.31 (td, J=14.0, 4.7 Hz, 1H).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $\left.-d_{4}\right): \delta 7.23(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.18(\mathrm{td}, J=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.89(\mathrm{~d}, J=$ $7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.54(\mathrm{t}, \mathrm{J}=2.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.14(\mathrm{~s}, 1 \mathrm{H}), 2.92(\mathrm{dd}, J=11.5,3.3 \mathrm{~Hz}$, $1 \mathrm{H}), 2.68(\mathrm{dt}, \mathrm{J}=12.7,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.60(\mathrm{ddd}, J=11.7,4.6,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.45(\mathrm{~s}, 1 \mathrm{H}), 2.37$ (ddd, $J=$ $14.0,11.7,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.27-2.17(\mathrm{~m}, 1 \mathrm{H}), 1.99-1.89(\mathrm{~m}, 3 \mathrm{H}), 1.89-1.79(\mathrm{~m}, 2 \mathrm{H}), 1.69(\mathrm{td}, \mathrm{J}=$ $14.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.64-1.52(\mathrm{~m}, 2 \mathrm{H}), 1.35(\mathrm{td}, \mathrm{J}=13.6,4.7 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 145.3,135.8,128.8,122.4,121.2,110.1,95.6,92.5,77.7,77.0,65.7$, 55.6, 51.0, 43.1, 36.4, 35.1, 34.3, 31.4, 20.5.
${ }^{13}$ C NMR (101 MHz, Methanol-d 4 ): $\delta$ 146.8, 137.5, 129.4, 123.0, 121.7, 111.1, 96.5, 93.7, 78.7, $77.8,66.8,56.5,51.7,44.0,37.2,35.1,32.4,21.3$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 327.1703; found: 327.1709.

IR: v (cm ${ }^{-1}$ ) 3414 (w), 2927 (m), 2847 (w), 2803 (w), 2759 (w), 1721 (s), 1667 (m), 1611 (w), 1471 (s), 1362 (s), 1320 (m), 1259 (w), 1193 (s), 1161 (m), 1121 (w), 1089 (s), 994 (m), 917 (w), 880 (w), 821 (w), 739 (s), 697 (w), 664 (w), 622 (s).
$[\alpha]_{D}{ }^{20}-49.3^{\circ}\left(c 0.1, \mathrm{CHCl}_{3}\right)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, $1 \% \mathrm{Et}_{3} \mathrm{~N}$ in MeOH (10\%), 230 $\mathrm{nm}) t_{\mathrm{R}}($ minor $)=8.1 \mathrm{~min}, t_{\mathrm{R}}($ major $)=8.6 \mathrm{~min}: 94.8: 5.2 \mathrm{er}$.

## 8.3 (-)-Vallesamidine and (+)-1,2-Dehydroaspidospermidine

### 8.3.1 Racemic Macrocycle

potassium 4-((tert-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoate (3.181)


It was prepared according to a literature procedure. ${ }^{67}$
3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate (rac-3.182)


It was prepared according to a literature procedure. ${ }^{67}$
3-(3-(3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propan-1-ol (rac-cis-3.180) and 3-(3-(3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-

1-ethylcyclopent-2-en-1-yl)propan-1-ol (rac-trans-3.180)


It was prepared according to a literature procedure. ${ }^{67}$
(E)-1-ethyl-8-(2-nitrophenyl)-5-((4-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene (rac-cis-1.184)


It was prepared according to a literature procedure. ${ }^{67}$
(E)-1-ethyl-8-(2-nitrophenyl)-5-((4-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene (rac-trans-1.184)


It was prepared according to a literature procedure. ${ }^{67}$

### 8.3.2 Enantioselective 1,4-Addition

tert-butyl (2,6-diethylphenyl)carbamate (3.297)


It was prepared according to a literature procedure. ${ }^{244 a}$
isobutyl 2-bromobenzenesulfonate (3.302)


It was prepared according to a literature procedure. ${ }^{244 c}$

## Catalyst 3.247



It was prepared according to a literature procedure. ${ }^{244 a}$
3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopentan-1-one (rac-3.305)


To a suspension of $\mathrm{CuBr} \cdot \mathrm{Me}_{2} \mathrm{~S}\left(5.7 \mathrm{~g}, 28 \mathrm{mmol}, 2.0\right.$ equiv) in $\mathrm{THF}(85 \mathrm{~mL})$ at $-78{ }^{\circ} \mathrm{C}$ was added dropwise EtMgBr ( 3 M in THF, 18 mL , $55 \mathrm{mmol}, 4.0$ equiv). The reaction mixture was stirred at -78 ${ }^{\circ} \mathrm{C}$ for 1 h and then warmed to $-40^{\circ} \mathrm{C}$. To the above prepared cuprate solution was added dropwise a solution of the ketone $\mathbf{3 . 1 8 4}(3.5 \mathrm{~g}, 14 \mathrm{mmol})$ in THF ( 30 mL ) while keeping the solution below $-40^{\circ} \mathrm{C}$. After 3 hours at $-40^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, $\mathrm{PE} / \mathrm{EtOAc} 18: 1$ ) to yield compound rac-3.305 (3.70 g, $93 \%$ ) as a colorless oil.

## 3-ethyl-3-(3-hydroxypropyl)cyclopentan-1-one (rac-3.306)



To a solution of the ketone rac-3.305 ( $284 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeOH}(10 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at 0 ${ }^{\circ} \mathrm{C}$ was added acetyl chloride ( $14 \mu \mathrm{~L}, 0.2 \mathrm{mmol}, 0.2$ equiv). After being stirred at room temperature for 2 h , the reaction mixture was evaporated in vacuo. The crude alcohol rac-3.306 thus obtained was used for the next step without further purification.

## 3-(3-((tert-butyldiphenylsilyl)oxy)propyl)-3-ethylcyclopentan-1-one (rac-3.307)



To a solution of the crude alcohol rac-3.306 ( 1.0 mmol , 1.0 equiv) in DMF ( $10 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added imidazole ( $75 \mathrm{mg}, 1.1 \mathrm{mmol}, 1.1$ equiv) and TBDPSCI ( $289 \mathrm{mg}, 1.05 \mathrm{mmol}, 1.05$ equiv). After being stirred for 8 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 25: 1\right)$ to yield compound rac-3.307 (388 mg, 95\% over 2 steps) as a colorless oil.
(R)-3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopentan-1-one (3.305)


To a solution of enone 3.184 ( 0.132 mmol , 1.0 equiv) in dry THF ( $1.3 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-78^{\circ} \mathrm{C}$ was added $\mathrm{Cu}(\mathrm{OTf})_{2}\left(2.4 \mathrm{mg}, 0.0066 \mathrm{mmol}, 0.05\right.$ equiv), 3.247 ( $3.6 \mathrm{mg}, 0.0033 \mathrm{mmol}, 0.025$ equiv) and $\mathrm{AlEt}_{3}$ (1.3 M in heptane, $305 \mu \mathrm{~L}, 0.396 \mathrm{mmol}, 3.0$ equiv). After 12 hours at $-78^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous Rochelle's salt and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 18: 1$ ) to yield compound 3.305 ( $36 \mathrm{mg}, 95 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 3.54(\mathrm{td}, \mathrm{J}=7.0,1.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.60-2.40(\mathrm{~m}, 2 \mathrm{H}), 2.04-1.80(\mathrm{~m}, 3 \mathrm{H})$, $1.77-1.70(\mathrm{~m}, 1 \mathrm{H}), 1.66-1.58(\mathrm{~m}, 1 \mathrm{H}), 1.56-1.25(\mathrm{~m}, 5 \mathrm{H}), 0.90-0.82(\mathrm{~m}, 9 \mathrm{H}), 0.78(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}$, $3 \mathrm{H}), 0.67-0.42(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 216.8,67.4,49.4,47.0,37.6,35.8,33.3,30.1,25.9,7.5,5.1,3.0$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 2959$ (w), 2875 (w), 1432 (w), 1211 (m), 1136 (w), 1089 (w), 907 (s), 732 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{O}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$285.2244; found: 285.2246.
$[\alpha]_{D}{ }^{20}+36.6^{\circ}\left(c 0.13, \mathrm{CHCl}_{3}\right)$.
(R)-3-ethyl-3-(3-hydroxypropyl)cyclopentan-1-one (3.306)


To a solution of the ketone 3.305 ( $28.4 \mathrm{mg}, 0.1 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeOH}\left(1.0 \mathrm{~mL}, 0.1 \mathrm{M}\right.$ ) at $0^{\circ} \mathrm{C}$ was added acetyl chloride ( $1.4 \mu \mathrm{~L}, 0.02 \mathrm{mmol}, 0.2$ equiv). After being stirred at room temperature for 2 h , the reaction mixture was evaporated in vacuo. The crude alcohol $\mathbf{3 . 3 0 6}$ thus obtained was used for the next step without further purification.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 3.63$ (dtd, $J=12.4,7.1,6.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.51 (dtd, $J=12.5,7.1,6.0 \mathrm{~Hz}$, $1 \mathrm{H}), 3.09(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.61-2.36(\mathrm{~m}, 2 \mathrm{H}), 2.02-1.80(\mathrm{~m}, 3 \mathrm{H}), 1.78-1.69(\mathrm{~m}, 1 \mathrm{H}), 1.70-$ $1.59(\mathrm{~m}, 1 \mathrm{H}), 1.56-1.43(\mathrm{~m}, 2 \mathrm{H}), 1.43-1.20(\mathrm{~m}, 3 \mathrm{H}), 0.78(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 216.8,62.7,49.4,47.0,37.6,35.8,33.3,30.1,27.4,7.5$.
IR: $\mathrm{u}\left(\mathrm{cm}^{-1}\right) 2961$ (w), 2876 (w), 1429 (m), 1207 (m), 1125 (w), 1092 (m), 907 (s), $730(\mathrm{~s})$.
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{O}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 171.1380 ; found: 171.1384.
$[\alpha]_{\mathrm{D}}{ }^{20}-12.0^{\circ}$ ( $c 0.1, \mathrm{MeOH}$ ).
(R)-3-(3-((tert-butyldiphenylsilyl)oxy)propyl)-3-ethylcyclopentan-1-one (3.307)


To a solution of the crude alcohol 3.306 ( $0.1 \mathrm{mmol}, 1.0$ equiv) in DMF ( $1.0 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added imidazole ( $7.5 \mathrm{mg}, 0.11 \mathrm{mmol}, 1.1$ equiv) and TBDPSCl ( $28.9 \mathrm{mg}, 0.105 \mathrm{mmol}, 1.05$ equiv). After being stirred 8 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 25: 1$ ) to yield compound $\mathbf{3 . 3 0 7}$ ( 40 mg , $97 \%$ over 2 steps) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.71-7.61(\mathrm{~m}, 4 \mathrm{H}), 7.50-7.33(\mathrm{~m}, 6 \mathrm{H}), 3.65(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.23$ $(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.03(\mathrm{~d}, \mathrm{~J}=2.4 \mathrm{~Hz}, 2 \mathrm{H}), 1.76(\mathrm{td}, \mathrm{J}=8.2,4.9 \mathrm{~Hz}, 2 \mathrm{H}), 1.59-1.33(\mathrm{~m}, 6 \mathrm{H}), 1.05(\mathrm{~s}$, $9 \mathrm{H}), 0.83(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 206.4,135.7,134.1,129.8,127.8,64.3,50.9,42.4,36.7,33.3,32.9$, 30.0, 27.6, 27.0, 19.3, 8.7.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2965$ (w), 2876 (w), 1434 (w), 1211 (m), 1136 (w), 907 (s), 736 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{37} \mathrm{O}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 409.2557; found: 409.2559.
$[\alpha]_{\mathrm{D}}{ }^{20}+21.3^{\circ}\left(\mathrm{c} 0.1, \mathrm{CHCl}_{3}\right)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, MeOH (2.5\%), 230 nm ) $t_{\mathrm{R}}$ (minor) $=9.2 \mathrm{~min}, t_{\mathrm{R}}$ (major) $=9.6 \mathrm{~min}: 95.5: 4.5 \mathrm{er}$.
(R)-triethyl(3-(1-ethyl-3-((trimethylsilyl)oxy)cyclopent-2-en-1-yl)propoxy)silane (3.309)


To a solution of 3.184 ( $300 \mathrm{mg}, 0.792 \mathrm{mmol}, 1.0$ equiv) in dry THF ( $8 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added $\mathrm{Cu}(\mathrm{OTf})_{2}$ ( $22 \mathrm{mg}, 0.0594 \mathrm{mmol}, 0.05$ equiv), 3.247 ( $32 \mathrm{mg}, 0.0297 \mathrm{mmol}, 0.025$ equiv) and $\mathrm{AlEt}_{3}$ ( 1.3 M in heptane, $1.83 \mathrm{~mL}, 2.377 \mathrm{mmol}, 3.0$ equiv). After 12 hours at $-78{ }^{\circ} \mathrm{C}, \mathrm{NEt}_{3}(661 \mu \mathrm{~L}, 4.755$ mmol, 6.0 equiv) and TMSOTf ( $575 \mu \mathrm{~L}, 3.17 \mathrm{mmol}, 4.0$ equiv) were added. After 6 hours at room temperature, the reaction was cooled to $0{ }^{\circ} \mathrm{C}$ before been poured in $\mathrm{Et}_{3} \mathrm{~N}(2.0 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$. A saturated aqueous solution of $\mathrm{NaHCO}_{3}(5.0 \mathrm{~mL})$ was quickly added, and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic fractions were quickly dried over $\mathrm{K}_{2} \mathrm{CO}_{3}$, filtered and evaporated in vacuo. The oily residue was purified by filtration over a mixture of dry $\mathrm{NaHCO}_{3}$ and silica gel $\left(\mathrm{NaHCO}_{3} / \mathrm{SiO}_{2} 1: 4, \mathrm{PE} / E t O A c 15: 1\right)$ to yield the pure product $3.309(259 \mathrm{mg}, 92 \%)$ as a colorless oil.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 5.18(\mathrm{~s}, 1 \mathrm{H}), 3.55(\mathrm{ddt}, \mathrm{J}=6.7,6.0,1.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.85-2.68(\mathrm{~m}, 2 \mathrm{H})$, $1.62(\mathrm{dt}, J=12.8,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.54-1.31(\mathrm{~m}, 7 \mathrm{H}), 0.90-0.82(\mathrm{~m}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.66$ - 0.47 (m, 6H), 0.16 (s, 9H).
${ }^{13}{ }^{1}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 155.0,118.1,67.3,50.5,35.4,35.1,33.2,28.9,25.6,8.6,5.1,3.0$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{41} \mathrm{O}_{2} \mathrm{Si}_{2}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 357.2640; found: 357.2641.
$[\alpha]_{\mathrm{D}}{ }^{20}+18.1^{\circ}\left(\mathrm{c} 0.2, \mathrm{CHCl}_{3}\right)$.
(R)-3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl acetate (3.308)


To a solution of 3.184 ( $40 \mathrm{mg}, 0.106 \mathrm{mmol}, 1.0$ equiv) in dry THF ( $1.05 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added $\mathrm{Cu}(\mathrm{OTf})_{2}(1.9 \mathrm{mg}, 0.0050 \mathrm{mmol}, 0.05$ equiv), 3.247 ( $2.9 \mathrm{mg}, 0.0025 \mathrm{mmol}, 4.0$ equiv) and $\mathrm{AlEt}_{3}\left(1.3 \mathrm{M}\right.$ in heptane, $243 \mu \mathrm{~L}, 0.317 \mathrm{mmol}, 3.0$ equiv). After 12 hours at $-78{ }^{\circ} \mathrm{C}, \mathrm{Ac}_{2} \mathrm{O}(40 \mu \mathrm{~L}$, $0.423 \mathrm{mmol}, 6.0$ equiv) was added. After being stirred 6 hours at room temperature, the reaction mixture was quenched with saturated aqueous Rochelle's salt and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 12: 1$ ) to yield compound $\mathbf{3 . 3 0 8}$ ( $30 \mathrm{mg}, 87 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.01(\mathrm{~s}, 1 \mathrm{H}), 3.55(\mathrm{ddt}, J=6.7,6.0,1.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.02-2.80(\mathrm{~m}, 2 \mathrm{H})$, $2.14(\mathrm{~s}, 3 \mathrm{H}), 1.65(\mathrm{ddd}, \mathrm{J}=12.2,7.4,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.56-1.29(\mathrm{~m}, 7 \mathrm{H}), 0.92-0.82(\mathrm{~m}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=$ $8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.65-0.48(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 168.1,153.8,120.7,67.3,50.8,35.1,33.3,33.2,28.9,25.6,20.7,8.6$, 5.1, 3.0.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{18} \mathrm{H}_{35} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 327.2350; found: 327.2351.
$[\alpha]_{\mathrm{D}}{ }^{20}-21.2^{\circ}\left(\mathrm{c} 0.1, \mathrm{CHCl}_{3}\right)$
(R)-3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate (3.182)


To a solution of enone 3.184 ( $10.6 \mathrm{mmol}, 1.0$ equiv), $\mathrm{Cu}(\mathrm{OTf})_{2}$ ( $191 \mathrm{mg}, 0.5 \mathrm{mmol}, 0.05$ equiv) and 3.247 ( $290 \mathrm{mg}, 0.26 \mathrm{mmol}, 0.025$ equiv) in dry THF ( $100 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-78^{\circ} \mathrm{C}$ was added dropwise AlEt $_{3}$ ( $1.3 \mathrm{M}, 24.4 \mathrm{~mL}, 31.7 \mathrm{mmol}, 3.0$ equiv). After being stirred for 8 hours at $-78{ }^{\circ} \mathrm{C}$, $\mathrm{HMPA}(100$ $\mathrm{mL})$, MeLi ( $1.6 \mathrm{M}, 33 \mathrm{~mL}, 52.8 \mathrm{mmol}, 5.0$ equiv) and Comins' reagent ( $24.9 \mathrm{~g}, 63.4 \mathrm{mmol}, 6.0$ equiv) were added and the reaction mixture was warmed to room temperature. After 24 hours, the reaction mixture was quenched with saturated aqueous Rochelle's salt and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 12:1) to yield compound 3.182 ( $3.79 \mathrm{~g}, 86 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.4(\mathrm{t}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.6(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}), 2.6(\mathrm{ddd}, J=9.3,6.2,2.0$ $\mathrm{Hz}, 2 \mathrm{H}), 1.8(\mathrm{dd}, \mathrm{J}=8.3,6.8 \mathrm{~Hz}, 2 \mathrm{H}), 1.5-1.4(\mathrm{~m}, 6 \mathrm{H}), 1.0(\mathrm{t}, \mathrm{J}=7.9 \mathrm{~Hz}, 9 \mathrm{H}), 0.8(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H})$, $0.6(q, J=7.9 \mathrm{~Hz}, 6 \mathrm{H}$ ).
${ }^{13}{ }^{1}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 148.0,124.7,118.7(\mathrm{q}, \mathrm{J}=320.6 \mathrm{~Hz}), 63.3,48.9,35.6,32.4,31.5$, 31.1, 28.1, 8.8, 6.9, 4.6.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2957$ (w), 2878 (w), 1421 (w), 1214 (w), 1141 (w), 1089 (w), 906 (s), 729 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{32} \mathrm{~F}_{3} \mathrm{O}_{4} \mathrm{SSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 417.1737; found: 417.1740.
$[\alpha]_{\mathrm{D}}{ }^{20}+54.9^{\circ}\left(c \quad 0.23, \mathrm{CHCl}_{3}\right)$.
8.3.3 Intramolecular Decarboxylative Cross-coupling

## 3-ethyl-3-(3-hydroxypropyl)cyclopent-1-en-1-yl trifluoromethanesulfonate (3.315)



It was prepared according to a literature procedure. ${ }^{242}$
3-ethyl-3-(3-((4-nitrophenyl)sulfonamido)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate (3.327)


To a solution of alcohol 3.315 ( $1.69 \mathrm{~g}, 5.60 \mathrm{mmol}, 1.0$ equiv) in dry toluene ( $56 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NsNH}_{2}\left(2.72 \mathrm{~g}, 13.43 \mathrm{mmol}, 2.4\right.$ equiv), $\mathrm{PPh}_{3}(1.76 \mathrm{~g}, 6.72 \mathrm{mmol}, 1.2$ equiv), neopentyl alcohol ( $247 \mathrm{mg}, 2.80 \mathrm{mmol}, 0.5$ equiv) and DEAD ( 2.2 M in toluene, $2.49 \mathrm{~mL}, 6.72 \mathrm{mmol}, 1.2$ equiv). After being stirred 9 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 96: 4$ ) to yield compound 3.327 (2.23 g, $82 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.19-8.03(\mathrm{~m}, 1 \mathrm{H}), 7.87-7.78(\mathrm{~m}, 1 \mathrm{H}), 7.78-7.67(\mathrm{~m}, 2 \mathrm{H}), 5.35(\mathrm{t}, \mathrm{J}$ $=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.30(\mathrm{~d}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.09(\mathrm{q}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 2.62-2.40(\mathrm{~m}, 2 \mathrm{H}), 1.76(\mathrm{ddd}, J=$ $13.3,9.1,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.66$ (ddd, $J=13.4,9.1,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.54-1.31(\mathrm{~m}, 6 \mathrm{H}), 0.78(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}$, $3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 148.2,133.9,133.8,132.9,131.1,125.5,124.6,124.1,118.63$ (q, $J=$ $320.7 \mathrm{~Hz}), 48.8,44.4,36.3,32.4,31.2,31.0,25.0,8.7$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{22} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{7} \mathrm{~S}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 487.0815 ; found: 487.0819.
methyl 4-hydroxy-2-(2-nitrophenyl)butanoate (3.226)


To a solution of TBS 3.187 ( $3.97 \mathrm{~g}, 11.19 \mathrm{mmol}, 1.0$ equiv) in dry DCM/MeOH (1:1, $110 / 110 \mathrm{~mL}$, 0.05 M ) at $0^{\circ} \mathrm{C}$ was added $\operatorname{CSA}\left(2.89 \mathrm{~g}, 12.42 \mathrm{mmol}, 1.11\right.$ equiv). After being stirred 1 hour at $0^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM/MeOH 95:5) to yield compound 3.316 ( 2.67 g , quantitative yield) as a colorless oil.

## Alcohol 3.226:

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.91(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, 7.44 (dd, J = 8.4, 7.0 Hz, 1H), $4.39(\mathrm{t}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.73(\mathrm{dt}, J=11.2,5.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.67(\mathrm{~s}, 3 \mathrm{H}), 3.60$ (ddd, J = 11.6, 7.8, 5.0 Hz, 1H), 2.57-2.35 (m, 1H), 2.14-1.98(m, 1H), $1.68(\mathrm{~s}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.4,149.4,133.3,132.2,130.5,128.4,125.0,60.5,52.6,43.6,35.7$. HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{NO}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$240.0866; found: 240.0865 .

## Lactone 3.316:

The analytical data were in accordance with those reported in the literature. ${ }^{572}$
methyl 4-((N-(3-(1-ethyl-3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)propyl)-4-nitrophenyl)sulfonamido)-2-(2-nitrophenyl)butanoate (3.317) and methyl 1-(2-nitrophenyl)cyclopropane-1-carboxylate (3.318)

[^213]

To a solution of alcohol 3.226 （ $1.16 \mathrm{~g}, 4.76 \mathrm{mmol}$ ， 1.5 equiv）in dry toluene（ $32 \mathrm{~mL}, 0.1 \mathrm{M}$ ）at $0^{\circ} \mathrm{C}$ was added amine 3.227 （ $1.55 \mathrm{~g}, 3.18 \mathrm{mmol}, 1.0$ equiv）， $\mathrm{PPh}_{3}$（ $833 \mathrm{mg}, 3.18 \mathrm{mmol}, 1.0$ equiv）and DEAD（ 2.2 M in toluene， $1.44 \mathrm{~mL}, 3.18 \mathrm{mmol}, 1.0$ equiv）．After being stirred 9 hours at room tem－ perature，the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with EtOAc．The combined organic extracts were washed with brine，dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ ，filtered and evaporated in vacuo．The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM／MeOH 95：5）to yield compound 3.317 （ $2.73 \mathrm{~g}, 81 \%$ ）as a colorless oil as a 1：1 mixture of dia－ stereoisomers and compound 3.318 （ $179 \mathrm{mg}, 17 \%$ ）as a colorless oil．

## Amine 3．317：

${ }^{1} \mathrm{H}$ NMR（ $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ）：$\delta 8.09-7.93(\mathrm{~m}, 2 \mathrm{H}), 7.77-7.65(\mathrm{~m}, 1 \mathrm{H}), 7.59$（ddd，J＝9．4，7．1， 3.3 Hz ， $2 \mathrm{H}), 7.54-7.39(\mathrm{~m}, 3 \mathrm{H}), 5.32(\mathrm{~s}, 1 \mathrm{H}), 3.69-3.62(\mathrm{~m}, 4 \mathrm{H}), 3.39-3.15(\mathrm{~m}, 2 \mathrm{H}), 2.62-2.38(\mathrm{~m}, 2 \mathrm{H})$ ， $1.83-1.62(\mathrm{~m}, 5 \mathrm{H}), 1.51-1.34(\mathrm{~m}, 3 \mathrm{H}), 1.34-1.22(\mathrm{~m}, 2 \mathrm{H}), 1.21-1.09(\mathrm{~m}, 2 \mathrm{H}), 0.80(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}$ ， $3 \mathrm{H})$ ．
${ }^{13} \mathrm{C}$ NMR（ $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ）：$\delta 173.6,150.4,148.1,134.9,133.9,133.6,133.2,133.1,131.7,130.9$ ， $128.6,125.0,124.2,118.67$（ $q, J=320.6 \mathrm{~Hz}$ ）， $52.7,48.9,47.3,36.3,32.6,32.5,31.2,31.1,27.7$ ， 23．1，17．3，8．8．

HRMS（ESI）：$m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{33} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{11} \mathrm{~S}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$：708．1503；found：708．1505．

## Cyclopropane 3．318：

The analytical data were in accordance with those reported in the literature．${ }^{573}$

> methyl 2-(2-nitrophenyl)-4-((4-nitrophenyl)sulfonamido)butanoate (3.319) and methyl 1-(2nitrophenyl)cyclopropane-1-carboxylate (3.318)

[^214]

To a solution of alcohol 3.226 ( $50 \mathrm{mg}, 0.21 \mathrm{mmol}, 1.0$ equiv) in dry toluene ( $2.1 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NsNH}_{2}$ ( $42 \mathrm{mg}, 0.23 \mathrm{mmol}, 1.1$ equiv), $\mathrm{PPh}_{3}$ ( $61 \mathrm{mg}, 0.23 \mathrm{mmol}, 1.1$ equiv) and DEAD ( 2.2 M in toluene, $95 \mu \mathrm{~L}, 0.230 \mathrm{mmol}, 1.1$ equiv). After being stirred 9 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM/MeOH 95:5) to yield compound 3.319 ( $44 \mathrm{mg}, 54 \%$ ) as a colorless oil and compound 3.318 (13.4 mg 29\%) as a brown oil.

## Amine 3.319:

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.09(\mathrm{dd}, J=5.9,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.94(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.86(\mathrm{dd}, J=6.0$, $3.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.81-7.69(\mathrm{~m}, 2 \mathrm{H}), 7.60(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 5.49(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}$, $1 \mathrm{H}), 4.24(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.65(\mathrm{~s}, 3 \mathrm{H}), 3.26-3.11(\mathrm{~m}, 2 \mathrm{H}), 2.56-2.40(\mathrm{~m}, 1 \mathrm{H}), 2.17-1.93(\mathrm{~m}$, 1 H ).
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 174.0, 148.9, 146.8, 133.6, 133.3, 132.9, 132.1, 131.8, 130.0, 129.8, 128.0, 124.9, 124.9, 52.3, 45.4, 42.1, 31.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{3} \mathrm{O}_{8} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 424.0809; found: 424.0812.

## 4-((N-(3-(1-ethyl-3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)propyl)-4-nitrophenyl)sulfonamido)-2-(2-nitrophenyl)butanoic acid (3.320)



To a solution of ester 3.317 ( 963 mg , 1.36 mmol , 1.0 equiv) in $\mathrm{AcOH}(13.6 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $37 \% \mathrm{HCl}(440 \mu \mathrm{~L})$. After 2 hours at reflux, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to afforded compound 3.320 ( 867 mg , 92\%) as a 1:1 mixture of diastereoisomers as a brown solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.06-7.89(\mathrm{~m}, 2 \mathrm{H}), 7.73-7.54(\mathrm{~m}, 4 \mathrm{H}), 7.48$ (ddd, J = 7.1, 4.1, 2.5 Hz , $2 \mathrm{H}), 5.32(\mathrm{dt}, J=3.9,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.17$ (ddd, $J=8.1,5.8,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.46-3.35(\mathrm{~m}, 1 \mathrm{H}), 3.31(\mathrm{q}, J=$ $6.6,6.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), $2.60-2.39(\mathrm{~m}, 3 \mathrm{H}), 2.13-1.97(\mathrm{~m}, 1 \mathrm{H}), 1.72$ (dddd, J = 28.4, 13.3, 8.9, $6.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), $1.54-1.14(\mathrm{~m}, 7 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 175.8,148.7,148.2,133.9,133.8,133.3,132.8,131.8,131.0,130.7$, $129.0,125.5,124.3,124.3,48.9,48.0,47.9,44.4,36.3,32.5,31.2,31.0,30.9,23.2,8.8$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{29} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{11} \mathrm{~S}_{2}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 692.1201; found: 692.1200.
potassium 4-((N-(3-(1-ethyl-3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)propyl)-4-nitrophenyl)sulfonamido)-2-(2-nitrophenyl)butanoate (rac-3.225)


To a solution of acid 3.320 ( 65 mg , 0.093 mmol , 1.0 equiv) in MeOH ( $2.6 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $\mathrm{KO}^{\mathrm{t}} \mathrm{Bu}$ ( $10.5 \mathrm{mg}, 0.093 \mathrm{mmol}, 1.0$ equiv). After 2 hours at room temperature, the reaction mixture was evaporated in vacuo to afforded compound rac-3.225 ( 68 mg , quantitative yield) as a 1:1 mixture of diastereoisomers as a brown solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl $)_{3}$ : $\delta 7.94(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.73-7.59(\mathrm{~m}, 2 \mathrm{H}), 7.55(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H})$, $7.42(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.17(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.22(\mathrm{~s}, 1 \mathrm{H}), 3.69(\mathrm{t}, J=6.7$ $\mathrm{Hz}, 1 \mathrm{H}), 3.44(\mathrm{~d}, J=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.17(\mathrm{q}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.91(\mathrm{t}, J=15.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.44(\mathrm{dq}, J=16.7$, $8.2,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.28(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.85(\mathrm{dd}, J=16.1,8.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.67(\mathrm{p}, J=7.6,6.1 \mathrm{~Hz}, 1 \mathrm{H})$, $1.56(\mathrm{td}, J=14.0,11.6,6.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.22(\mathrm{dq}, J=26.1,8.5,7.9 \mathrm{~Hz}, 7 \mathrm{H}), 0.71(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 174.9,150.5,149.4,135.3,135.2,134.6,134.6,133.9,133.8,133.1$, $131.6,131.5,129.7,126.0,125.4,121.71(d, J=318.3 \mathrm{~Hz}), 51.4,46.9,45.5,43.3,37.2,34.6,33.4$, 32.0, 30.6, 24.0, 20.9, 14.4, 8.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{29} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{11} \mathrm{~S}_{2}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 692.1201; found: 692.1197.
(E)-1-ethyl-8-(2-nitrophenyl)-5-((4-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene (rac1.184)


To a solution of salt rac-3.225 ( $16 \mathrm{mg}, 0.022 \mathrm{mmol}, 1.0$ equiv) in dry diglyme ( $0.44 \mathrm{~mL}, 0.05 \mathrm{M}$ ) was added $[\mathrm{Pd}(\mathrm{allyl}) \mathrm{Cl}]_{2}(1.6 \mathrm{mg}, 0.004 \mathrm{mmol}, 0.2$ equiv) and DIOP ( $0.013 \mathrm{mmol}, 0.6$ equiv). After being stirred 9 hours at reflux, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography
( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5$ ) to yield compound rac-1.184 ( $0.8 \mathrm{mg}, 7 \%$ ) as a $1: 1$ mixture of diastereoisomers as a colorless oil.

### 8.3.4 Enantioselective Hydroboration/Cross-coupling

## (E)-3-(2-nitrophenyl)prop-2-en-1-ol (3.325)



It was prepared according to a literature procedure. ${ }^{272,273}$
(E)-tert-butyldimethyl((3-(2-nitrophenyl)allyl)oxy)silane (3.326)


To a solution of alcohol 3.325 ( $5.06 \mathrm{~g}, 28.22 \mathrm{mmol}$, 1.0 equiv) in dry DMF ( $100 \mathrm{~mL}, 0.3 \mathrm{M}$ ) was added imidazole ( $2.88 \mathrm{~g}, 42.34 \mathrm{mmol}, 1.5$ equiv) and $\mathrm{TBSCl}(6.38 \mathrm{~g}, 42.34 \mathrm{mmol}, 1.5$ equiv). After being stirred 6 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$ to yield compound 3.326 ( $7.86 \mathrm{~g}, 95 \%$ ) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.91(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.65-7.49(\mathrm{~m}, 2 \mathrm{H}), 7.37(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 1 \mathrm{H})$, 7.10 ( $\mathrm{dt}, \mathrm{J}=15.6,2.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), $6.28(\mathrm{dt}, J=15.7,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.39(\mathrm{dd}, J=4.6,2.0 \mathrm{~Hz}, 2 \mathrm{H}), 0.95(\mathrm{~s}$, $9 H), 0.12(s, 6 H)$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 146.6,132.2,131.7,131.5,129.0,127.4,127.3,123.9,64.5,25.8$, 18.1, -5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{24} \mathrm{NO}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 294.1520; found: 294.1521.
(methyl (E)-3-(2-nitrophenyl)acrylate (3.328)


It was prepared according to a literature procedure. ${ }^{274}$


To a mixture of $\mathrm{CuCl}(1.5 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv), DTBM-Segphos ( $17.7 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}(3.0 \mathrm{mg}, 0.03 \mathrm{mmol}, 0.06$ equiv) was added dry toluene ( 0.2 mL ). After 10 minutes at room temperature, HBPin ( $90 \mu \mathrm{~L}, 0.6 \mathrm{mmol}, 1.2$ equiv) was added. After 10 minutes at room temperature, alkene 3.326 ( $147 \mathrm{mg}, 0.5 \mathrm{mmol}, 1.0$ equiv) was added. After being stirred 24 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with toluene) and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 9: 1$ ) to yield compound 3.330 ( $117 \mathrm{mg}, 79 \%$ ) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.88(\mathrm{dd}, J=8.1,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{td}, J=7.5,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.29$ $(\mathrm{m}, 2 \mathrm{H}), 3.67(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.03-2.80(\mathrm{~m}, 2 \mathrm{H}), 1.96-1.78(\mathrm{~m}, 2 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.06(\mathrm{~d}, J=1.3$ $\mathrm{Hz}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 148.7,137.1,131.5,130.5,127.1,124.9,63.9,31.1,29.9,25.9,18.3$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{26} \mathrm{NO}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 296.1676; found: 296.1680.

## methyl 3-(2-nitrophenyl)propanoate (3.332)



To a mixture of $\mathrm{CuCl}(1.0 \mathrm{mg}, 0.01 \mathrm{mmol}, 0.02$ equiv), DTBM-Segphos ( $24 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.04$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $1.4 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv) was added dry THF ( 0.3 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}(140 \mathrm{mg}, 0.55 \mathrm{mmol}, 1.1$ equiv) in THF ( 0.2 mL ) was added. After 10 minutes at room temperature, a solution of alkene $3.328(104 \mathrm{mg}, 0.5 \mathrm{mmol}, 1.0$ equiv) in THF ( 0.1 mL ) and $\mathrm{MeOH}(41 \mu \mathrm{~L}, 1.00 \mathrm{mmol}, 2.0$ equiv) were added. After being stirred 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 4: 1\right)$ to yield compound 3.332 ( $91 \mathrm{mg}, 87 \%$ ) as a white solid.

The analytical data were in accordance with those reported in the literature. ${ }^{574}$
(E)-2-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)aniline (3.336)


[^215]A solution of nitro 3.336 ( $500 \mathrm{mg}, 1.7 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{FeSO}_{4} \cdot 7 \mathrm{H}_{2} \mathrm{O}(3.68 \mathrm{~g}, 13.24 \mathrm{mmol}, 7.77$ equiv) in $\mathrm{MeOH} / \mathrm{NH}_{4} \mathrm{OH}(6: 5,16 / 14 \mathrm{~mL}, 0.05 \mathrm{mmol})$ was heated to $80^{\circ} \mathrm{C}$ for 5 hours. After cooling down to room temperature, the reaction mixture was filtered over Celite (rinsed with MeOH ) and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 9:1) to yield compound 3.336 ( $326 \mathrm{mg}, 73 \%$ ) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.85(\mathrm{~d}, \mathrm{~J}=15.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.35(\mathrm{dd}, J=7.8,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.19-7.04(\mathrm{~m}$, $1 \mathrm{H}), 6.72(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.34(\mathrm{~d}, \mathrm{~J}=15.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.94(\mathrm{~s}, 2 \mathrm{H}), 3.77(\mathrm{~s}$, $3 H)$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 148.7,137.1,131.5,130.5,127.1,124.9,63.9,31.1,29.9,25.9,18.3,-$ 5.2.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{15} \mathrm{H}_{26} \mathrm{NOSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 264.1778; found: 264.1780.
methyl (E)-(2-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)carbamate (3.337)


To a solution of amine 3.336 ( $447 \mathrm{mg}, 1.7 \mathrm{mmol}$, 1.0 equiv) in dry acetone ( $3.4 \mathrm{~mL}, 0.5 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaHCO}_{3}(286 \mathrm{mg}, 3.41 \mathrm{mmol}, 2.0$ equiv) and methyl chloroformate ( $158 \mu \mathrm{~L}, 2.05 \mathrm{mmol}$, 1.2 equiv). After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 15: 1$ ) to yield compound 3.337 (453 mg, 83\%) as a brown solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.74(\mathrm{~s}, 1 \mathrm{H}), 7.31(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.26-7.15(\mathrm{~m}, 1 \mathrm{H}), 7.04(\mathrm{t}, \mathrm{J}=$ $7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.64(\mathrm{~d}, J=15.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.49(\mathrm{~s}, 1 \mathrm{H}), 6.14(\mathrm{dt}, J=15.7,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.32(\mathrm{dd}, J=4.7,2.0$ $\mathrm{Hz}, 2 \mathrm{H}), 3.73$ (s, 3H), $0.91(\mathrm{~s}, 9 \mathrm{H}), 0.08(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 155.4,139.4,130.4,129.3,128.3,128.0,127.9,123.5,120.2,64.9$, 52.2, 25.8, 18.1, -5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{28} \mathrm{NO}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 322.1833$; found: 322.1839.
methyl (E)-3-(2-((methoxycarbonyl)amino)phenyl)acrylate (3.339)


It was prepared according to a literature procedure. ${ }^{275}$

## methyl $(E)$-(2-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)(methyl)carbamate (3.340)



To a solution of carbamate 3.337 ( $250 \mathrm{mg}, 0.778 \mathrm{mmol}, 1.0$ equiv) in dry DMF ( $3.9 \mathrm{~mL}, 0.2 \mathrm{M}$ ) at 0 ${ }^{\circ} \mathrm{C}$ was added NaH ( $60 \%$ in mineral oil, $62 \mathrm{mg}, 1.56 \mathrm{mmol}, 2.0$ equiv). After 15 minutes at $0^{\circ} \mathrm{C}$, Mel ( $99 \mu \mathrm{~L}, 1.556 \mathrm{mmol}, 2.0$ equiv) was added dropwise. After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ 19:1) to yield compound 3.340 ( $253 \mathrm{mg}, 97 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.61-7.46(\mathrm{~m}, 1 \mathrm{H}), 7.23(\mathrm{q}, \mathrm{J}=3.5,2.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.08(\mathrm{~d}, J=7.2 \mathrm{~Hz}$, $1 \mathrm{H}), 6.57(\mathrm{~d}, \mathrm{~J}=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.26(\mathrm{dt}, J=15.9,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.32(\mathrm{~d}, \mathrm{~J}=4.7 \mathrm{~Hz}, 2 \mathrm{H}), 3.57(\mathrm{~s}, 3 \mathrm{H})$, $3.16(s, 3 H), 0.91(s, 9 H), 0.07(s, 6 H)$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 154.9, 143.0, 131.1, 129.6, 129.2, 127.4, 124.8, 123.8, 122.2, 64.4, 53.8, 32.1, 25.8, 18.1, -5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{18} \mathrm{H}_{30} \mathrm{NO}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 336.1989$; found: 336.1991.
methyl (E)-3-(2-((methoxycarbonyl)(methyl)amino)phenyl)acrylate (3.341)


To a solution of carbamate 3.339 ( $100 \mathrm{mg}, 0.56 \mathrm{mmol}, 1.0$ equiv) in dry acetone ( $11 \mathrm{~mL}, 0.05 \mathrm{M}$ ) were added $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( $78 \mathrm{mg}, 0.56 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{Mel}(70 \mu \mathrm{~L}, 1.13 \mathrm{mmol}, 2.0$ equiv) dropwise. After being stirred 8 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / E t O A c 17: 1$ ) to yield compound 3.341 ( $120 \mathrm{mg}, 86 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.80-7.60(\mathrm{~m}, 2 \mathrm{H}), 7.41(\mathrm{td}, J=7.6,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}$, $1 \mathrm{H}), 7.19(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.42(\mathrm{~d}, \mathrm{~J}=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.80(\mathrm{~s}, 3 \mathrm{H}), 3.61(\mathrm{~s}, 3 \mathrm{H}), 3.23(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 167.4,154.9,143.4,141.4,129.8,129.4,129.4,124.0,122.9,113.1$, 53.8, 51.7, 32.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{16} \mathrm{NO}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$250.1074; found: 250.1075.

## methyl (S)-3-(2-((methoxycarbonyl)amino)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)propanoate (3.342)



To a mixture of $\mathrm{CuCl}(0.42 \mathrm{mg}, 0.004 \mathrm{mmol}, 0.02$ equiv), JosiPhos ( $6.2 \mathrm{mg}, 0.009 \mathrm{mmol}, 0.04$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $0.6 \mathrm{mg}, 0.006 \mathrm{mmol}, 0.03$ equiv) was added dry THF ( 0.3 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}(60 \mathrm{mg}, 0.234 \mathrm{mmol}, 1.1$ equiv) in THF ( 0.2 mL ) was added. After 10 minutes at room temperature, a solution of alkene $\mathbf{3 . 3 3 9}$ ( $50 \mathrm{mg}, 0.21 \mathrm{mmol}, 1.0$ equiv) in THF ( 0.1 mL ) and $\mathrm{MeOH}(18 \mu \mathrm{~L}, 0.42 \mathrm{mmol}, 2.0$ equiv) were added. After being stirred 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 17:1) to yield compound 3.342 ( $72 \mathrm{mg}, 95 \%$ ) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.98-7.78(\mathrm{~m}, 1 \mathrm{H}), 7.68(\mathrm{~s}, 1 \mathrm{H}), 7.22-7.12(\mathrm{~m}, 1 \mathrm{H}), 7.13-6.98(\mathrm{~m}$, 2 H ), 3.76 (s, 3H), $3.65(\mathrm{~s}, 3 \mathrm{H}), 3.03(\mathrm{dd}, J=16.9,9.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.88(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.62$ (dd, J = $17.0,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.20(\mathrm{~s}, 6 \mathrm{H}), 1.16(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{\mathbf{C}}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 174.4,155.1,135.7,129.8,128.0,126.5,124.9,123.6,84.2,52.3$, 52.0, 35.2, 24.7, 24.4, 22.77.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{18} \mathrm{H}_{27} \mathrm{BNO}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 364.1926 ; found: 364.1928.
$[\alpha]_{D^{20}}-66.8^{\circ}(c 0.12, E A)$.
methyl (S)-3-hydroxy-3-(2-((methoxycarbonyl)amino)phenyl)propanoate (3.343)


To a solution of borane 3.342 ( $20 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.0$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}(1: 1,0.75 / 0.75 \mathrm{~mL}, 0.04$ M) was added $\mathrm{NaBO}_{3} \cdot 4 \mathrm{H}_{2} \mathrm{O}(42 \mathrm{mg}, 0.275 \mathrm{mmol}, 5.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, PE/EtOAc 6:1) to yield compound $\mathbf{3 . 3 4 3}$ ( $11 \mathrm{mg}, 78 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.47(\mathrm{~s}, 1 \mathrm{H}), 7.97(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.30(\mathrm{td}, J=7.8,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.11$ (dd, $J=7.7,1.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.03(\mathrm{td}, J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.21(\mathrm{dd}, J=10.0,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H})$, 3.75 (s, 3H), 3.03 (dd, J = 17.1, $10.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.70 (dd, $J=17.1,3.5 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.4,154.5,137.2,129.4,129.1,127.3,123.6,121.7,70.8,52.4$, 52.3, 40.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{NO}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 254.1023; found: 254.1025.
$[\alpha]_{\mathrm{D}}{ }^{20}-89.6^{\circ}\left(c \quad 0.3, \mathrm{CHCl}_{3}\right)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, MeOH (5.5\%), 230 nm ) $t_{\mathrm{R}}$ (minor $)=4.2 \mathrm{~min}, t_{\mathrm{R}}($ major $)=5.4 \mathrm{~min}: 92.5: 7.5 \mathrm{er}$.
methyl 3-(2-((methoxycarbonyl)amino)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)propanoate (rac-3.342)


To a mixture of $\mathrm{CuCl}(1.26 \mathrm{mg}, 0.0128 \mathrm{mmol}, 0.03$ equiv), DPEPhos ( $6.9 \mathrm{mg}, 0.0128 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}(3.7 \mathrm{mg}, 0.0383 \mathrm{mmol}, 0.09$ equiv) was added dry THF ( 0.3 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}$ ( $119 \mathrm{mg}, 0.468 \mathrm{mmol}$, 1.1 equiv) in THF ( 0.3 mL ) was added. After 10 minutes at room temperature, a solution of alkene 3.339 ( $100 \mathrm{mg}, 0.425$ mmol, 1.0 equiv) in THF ( 0.3 mL ) and $\mathrm{MeOH}(35 \mu \mathrm{~L}, 0.850 \mathrm{mmol}, 2.0$ equiv) were added. After being stirred 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / E t \mathrm{OAc} 17: 1$ ) to yield compound rac-3.342 (142 $\left.\mathrm{mg}, 92 \%\right)$ as a white solid.
methyl 3-hydroxy-3-(2-((methoxycarbonyl)amino)phenyl)propanoate (rac-3.343)


To a solution of borane rac-3.342 ( $20 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.0$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}$ (1:1, $0.75 / 0.75 \mathrm{~mL}$, 0.04 M ) was added $\mathrm{NaBO}_{3} \cdot 4 \mathrm{H}_{2} \mathrm{O}$ ( $42 \mathrm{mg}, 0.275 \mathrm{mmol}, 5.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ) to yield compound rac-3.343 (11 mg, 78\%) as a brown oil.
methyl (S)-3-(2-((methoxycarbonyl)amino)phenyl)-3-(trifluoro-l4-boraneyl)propanoate, potassium salt (3.348)


To a solution of borane 3.342 ( $50 \mathrm{mg}, 0.138 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeCN}(1.6 \mathrm{~mL}, 0.0875 \mathrm{M}$ ) was added a solution of $\mathrm{KHF}_{2}\left(43 \mathrm{mg}, 0.550 \mathrm{mmol}, 4.0\right.$ equiv) in $\mathrm{H}_{2} \mathrm{O}(0.13 \mathrm{~mL})$. After being stirred 3 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. Recrystallization in $\mathrm{Et}_{2} \mathrm{O}$ afforded compound 3.348 ( $33 \mathrm{mg}, 69 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Acetone- $d_{6}$ ): $\delta 8.21(\mathrm{~s}, 1 \mathrm{H}), 7.59(\mathrm{~s}, 1 \mathrm{H}), 7.09$ (dd, $\left.J=7.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.90$ (dtd, $J=21.8,7.4,1.7 \mathrm{~Hz}, 2 \mathrm{H}$ ), $3.67(\mathrm{~s}, 3 \mathrm{H}), 3.44(\mathrm{~s}, 3 \mathrm{H}), 2.73(\mathrm{dd}, J=15.8,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.61(\mathrm{dd}, J=15.8$, $10.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.46-2.33(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, Acetone- $\boldsymbol{d}_{6}$ ): $\delta$ 172.2, 155.6, 139.9, 127.2, 125.4, 124.7, 122.9, 118.5, 52.2 , 51.8, 48.3, 36.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H}_{14} \mathrm{BF}_{3} \mathrm{NO}_{4}\left([\mathrm{M}-\mathrm{K}]^{-}\right)$: 304.0968 ; found: 304.0965.
$[\alpha]_{\mathrm{D}}{ }^{20}+12.3^{\circ}\left(\mathrm{c} 0.4, \mathrm{CHCl}_{3}\right)$.
(E)-3-(2-aminophenyl)acrylonitrile (3.351)


It was prepared according to a literature procedure. ${ }^{276}$
methyl (E)-(2-(2-cyanovinyl)phenyl)carbamate (3.352)


To a solution of amine 3.351 ( $3.69 \mathrm{~g}, 25.59 \mathrm{mmol}$, 1.0 equiv) in dry acetone ( $51 \mathrm{~mL}, 0.5 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaHCO}_{3}(4.30 \mathrm{~g}, 51.19 \mathrm{mmol}, 2.0$ equiv) and methyl chloroformate ( $2.37 \mathrm{~mL}, 30.71$ mmol, 1.2 equiv). ). After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 18: 1\right)$ to yield compound 3.352 ( $4.60 \mathrm{~g}, 89 \%$ ) as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.90(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 0.2 \mathrm{H}), 7.77-7.53(\mathrm{~m}, 3.4 \mathrm{H}), 77.53-7.36(\mathrm{~m}$, $3.2 \mathrm{H}), 7.36-7.11(\mathrm{~m}, 3.2 \mathrm{H}), 6.48(\mathrm{~s}, 1 \mathrm{H}), 6.39(\mathrm{~s}, 0.2 \mathrm{H}), 5.86(\mathrm{~d}, \mathrm{~J}=16.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.59(\mathrm{~d}, \mathrm{~J}=11.8$ $\mathrm{Hz}, 0.2 \mathrm{H}), 3.81(\mathrm{~s}, 3 \mathrm{H}), 3.79(\mathrm{~s}, 0.6 \mathrm{H})$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{11} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 203.0815; found: 203.0819 .

## methyl (2-(2-cyano-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)carbamate (rac3.353)



To a mixture of $\mathrm{CuCl}(1.5 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv), DPEPhos ( $8.1 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $4.3 \mathrm{mg}, 0.045 \mathrm{mmol}, 0.09$ equiv) was added dry THF ( 0.4 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}(140 \mathrm{mg}, 0.55 \mathrm{mmol}, 1.1$ equiv) in THF ( 0.3 mL ) was added. After 10 minutes at room temperature, a solution of alkene 3.352 ( $100 \mathrm{mg}, 0.5 \mathrm{mmol}, 1.0$ equiv) in THF ( 0.3 mL ) and $\mathrm{MeOH}(41 \mu \mathrm{~L}, 1.0 \mathrm{mmol}, 2.0$ equiv) were added. After being stirred 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 25:1) to yield compound rac-3.353 (152 mg, 92\%) as a white solid.
methyl (2-(2-cyano-1-hydroxyethyl)phenyl)carbamate (rac-3.354)


To a solution of borane rac- $3.353\left(18 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.0\right.$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}(1: 1,0.75 / 0.75 \mathrm{~mL}$, 0.04 M ) was added $\mathrm{NaBO}_{3} \cdot 4 \mathrm{H}_{2} \mathrm{O}$ ( $42 \mathrm{mg}, 0.275 \mathrm{mmol}, 5.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ) to yield compound rac-3.354 (11 mg, 95\%) as a brown oil.
methyl (S)-(2-(2-cyano-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)carbamate
(3.353)


To a mixture of $\mathrm{CuCl}(7.4 \mathrm{mg}, 0.074 \mathrm{mmol}, 0.03$ equiv), JosiPhos ( $46 \mathrm{mg}, 0.074 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $22 \mathrm{mg}, 0.223 \mathrm{mmol}, 0.09$ equiv) was added dry THF ( 2 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}$ ( $691 \mathrm{mg}, 2.72 \mathrm{mmol}, 1.1$ equiv) in THF ( 1.5 mL ) was added. After 10 minutes at room temperature, a solution of alkene 3.352 ( $500 \mathrm{mg}, 2.473 \mathrm{mmol}, 1.0$ equiv) in THF ( 1.5 mL ) and $\mathrm{MeOH}(200 \mu \mathrm{~L}, 4.945 \mathrm{mmol}, 2.0$ equiv) were added. After being stirred 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and
evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 25:1) afforded compound 3.353 ( $743 \mathrm{mg}, 91 \%$ ) as a white solid.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.65-7.38(\mathrm{~m}, 1 \mathrm{H}), 7.35-7.01(\mathrm{~m}, 5 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 2.97-2.82(\mathrm{~m}$, $2 \mathrm{H}), 2.71-2.57(\mathrm{~m}, 1 \mathrm{H}), 1.31-1.07(\mathrm{~m}, 12 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 155.2, 135.4, 129.7, 128.4, 127.5, 127.4, 125.9, 119.6, 85.1, 75.2, $60.5,52.6,27.4,24.9,24.8,24.7,24.5,21.2,18.4,18.1,14.3$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{BN}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 331.1824; found: 331.1825.
$[\alpha]_{\mathrm{D}}{ }^{20}-55.5^{\circ}\left(\mathrm{c} 0.11, \mathrm{CHCl}_{3}\right)$.
methyl (S)-(2-(2-cyano-1-hydroxyethyl)phenyl)carbamate (3.354)


To a solution of borane 3.353 ( $18 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{THF} / \mathrm{H}_{2} \mathrm{O}(1: 1,0.75 / 0.75 \mathrm{~mL}, 0.04$ M) was added $\mathrm{NaBO}_{3} \cdot 4 \mathrm{H}_{2} \mathrm{O}$ ( $42 \mathrm{mg}, 0.275 \mathrm{mmol}, 5.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 6:1) to yield compound 3.354 ( $11 \mathrm{mg}, 95 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.87$ (dd, $J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.57-7.46(\mathrm{~m}, 1 \mathrm{H}), 7.38$ (td, $\mathrm{J}=7.5,1.5$ $\mathrm{Hz}, 1 \mathrm{H}), 7.15(\mathrm{td}, \mathrm{J}=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.84(\mathrm{~s}, 1 \mathrm{H}), 5.05-4.91(\mathrm{~m}, 1 \mathrm{H}), 4.39(\mathrm{~d}, \mathrm{~J}=6.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.64$ (s, 3H), 2.87 (dd, $J=12.5,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.80(\mathrm{dd}, J=12.4,7.0 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 155.6,137.5,131.0,128.5,126.8,123.6,120.1,116.8,68.0,52.2$, 26.7.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 221.0921; found: 221.0926 .
$[\alpha]_{\mathrm{D}}{ }^{20}-123.6^{\circ}\left(c 0.15, \mathrm{CHCl}_{3}\right)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, MeOH ( $2 \%$ ), 230 nm ) $t_{\mathrm{R}}$ (minor) $=$ $10.9 \mathrm{~min}, t_{\mathrm{R}}$ (major) $=12.1 \mathrm{~min}: 97.0: 3.0$ er.
methyl (S)-(2-(2-cyano-1-(trifluoro-I4-boraneyl)ethyl)phenyl)carbamate, potassium salt (3.355)


To a solution of borane 3.353 ( 300 mg , $0.909 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeOH}(275 \mathrm{~mL}, 0.33 \mathrm{M}$ ) was added a solution of $\mathrm{KHF}_{2}\left(487 \mathrm{mg}, 6.23 \mathrm{mmol}, 6.86\right.$ equiv) in $\mathrm{H}_{2} \mathrm{O}(1.4 \mathrm{~mL})$. After being stirred 3 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. Recrystallization in $\mathrm{Et}_{2} \mathrm{O}$ afforded compound 3.355 (195 $\mathrm{mg}, 69 \%$ ) as a brown solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , Acetone- $\mathrm{d}_{6}$ ): $\delta 7.95$ (dd, $\left.J=7.3,1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.40-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.03(\mathrm{td}, \mathrm{J}=$ $7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.52(\mathrm{~s}, 1 \mathrm{H}), 3.85-3.78(\mathrm{~m}, 1 \mathrm{H}), 3.64(\mathrm{~s}, 3 \mathrm{H}), 2.86(\mathrm{dd}, \mathrm{J}=12.3,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.78$ (dd, J = 12.4, 7.0 Hz, 1H).
${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 0} \mathrm{MHz}$, Acetone $-d_{6}$ ): $\delta$ 155.6, 139.8, 127.2, 125.1, 124.9, 122.9, 118.5, 115.6, 52.2, 35.5, 15.5.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{11} \mathrm{BF}_{3} \mathrm{~N}_{2} \mathrm{O}_{2}$ ([M-K]): 271.0866; found: 271.0860.
$[\alpha]_{\mathrm{D}}{ }^{20}+87.8^{\circ}(c 0.22, \mathrm{MeOH})$.
(E)-3-(2-nitrophenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3.357)


It was prepared according to a literature procedure. ${ }^{277}$
(E)-3-(2-aminophenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (3.358)


A solution of nitro 3.357 ( $5.40 \mathrm{~g}, 22 \mathrm{mmol}, 1.0$ equiv), Zn powder ( $7.48 \mathrm{~g}, 114.4 \mathrm{mmol}, 5.2$ equiv) and $\mathrm{AcOH}\left(25 \mathrm{~mL}, 440 \mathrm{mmol}, 20\right.$ equiv) in EtOH ( $220 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was heated to $60^{\circ} \mathrm{C}$ for 7 hours. After cooling down to room temperature, the reaction mixture was filtered over Celite (rinsed with EtOH ) and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1\right)$ to yield compound $3.358(4.04 \mathrm{~g}, 85 \%)$ as a white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.61(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{~d}, \mathrm{~J}=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.32(\mathrm{dd}, \mathrm{J}=8.3,7.0$ $\mathrm{Hz}, 1 \mathrm{H}), 7.10(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.78(\mathrm{~s}, 1 \mathrm{H}), 3.98-3.82(\mathrm{~m}, 2 \mathrm{H}), 3.82-3.60(\mathrm{~m}, 2 \mathrm{H}), 2.23-2.06$ $(\mathrm{m}, 3 \mathrm{H}), 2.10(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 2.06-1.90(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13}{ }^{\text {C NMR ( }} \mathbf{1 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 166.3,145.9,138.5,130.7,128.5,123.2,121.4,120.8,116.0,46.4$, 25.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 217.1335; found: 217.1336 .
methyl (E)-(2-(3-oxo-3-(pyrrolidin-1-yl)prop-1-en-1-yl)phenyl)carbamate (3.359)


To a solution of amine $3.358\left(1.93 \mathrm{~g}, 8.93 \mathrm{mmol}\right.$, 1.0 equiv) in dry acetone ( $18 \mathrm{~mL}, 0.5 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaHCO}_{3}(1.50 \mathrm{~g}, 17.86 \mathrm{mmol}, 2.0$ equiv) and methyl chloroformate ( $828 \mu \mathrm{~L}, 10.72$ mmol, 1.2 equiv). ). After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1\right)$ to yield compound 3.359 (2.25 g, 92\%) as an orange solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.93-7.75(\mathrm{~m}, 2 \mathrm{H}), 7.48(\mathrm{dd}, \mathrm{J}=7.8,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.30(\mathrm{~m}, 1 \mathrm{H})$, $7.11(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.92(\mathrm{~s}, 1 \mathrm{H}), 6.66(\mathrm{~d}, \mathrm{~J}=15.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 3.70-3.51(\mathrm{~m}, 4 \mathrm{H}), 2.11-$ $1.95(\mathrm{~m}, 2 \mathrm{H}), 1.95-1.79(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 166.3,155.4,140.0,139.3,129.6,128.8,128.4,123.8,120.9,120.7$, 52.2, 46.4, 25.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 275.1390; found: 275.1394.
methyl (2-(3-oxo-3-(pyrrolidin-1-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
yl)propyl)phenyl)carbamate (rac-3.360)


To a mixture of $\mathrm{CuCl}(1.5 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv), DPEPhos ( $8.1 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $4.3 \mathrm{mg}, 0.045 \mathrm{mmol}, 0.09$ equiv) was added dry THF ( 0.4 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}(140 \mathrm{mg}, 0.55 \mathrm{mmol}, 1.1$ equiv) in THF ( 0.3 mL ) was added. After 10 minutes at room temperature, a solution of alkene 3.359 ( $137 \mathrm{mg}, 0.5 \mathrm{mmol}, 1.0$ equiv) in THF ( 0.3 mL ) and $\mathrm{MeOH}(41 \mu \mathrm{~L}, 1.0 \mathrm{mmol}, 2.0$ equiv) were added. After 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 25: 1$ ) to yield compound rac-3.360 ( $370 \mathrm{mg}, 92 \%$ ) as a white solid.
methyl (2-(1-hydroxy-3-oxo-3-(pyrrolidin-1-yl)propyl)phenyl)carbamate (rac-3.361)


To a solution of borane rac-3.360 ( $22 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.0$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}(1: 1,0.75 / 0.75 \mathrm{~mL}$, 0.04 M ) was added $\mathrm{NaBO}_{3} \cdot 4 \mathrm{H}_{2} \mathrm{O}(42 \mathrm{mg}, 0.275 \mathrm{mmol}, 5.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ) afforded compound rac-3.361 (13 mg, 82\%) as a brown oil

# methyl (S)-(2-(3-oxo-3-(pyrrolidin-1-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2$\mathrm{yl})$ propyl)phenyl)carbamate (3.360) 



To a mixture of $\mathrm{CuCl}(7.4 \mathrm{mg}, 0.074 \mathrm{mmol}, 0.03$ equiv), JosiPhos ( $46 \mathrm{mg}, 0.074 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $22 \mathrm{mg}, 0.223 \mathrm{mmol}, 0.09$ equiv) was added dry THF ( 2 mL ). After 30 minutes at room temperature, a solution of $\mathrm{B}_{2} \mathrm{Pin}_{2}(691 \mathrm{mg}, 2.72 \mathrm{mmol}, 1.1$ equiv) in THF ( 1.5 mL ) was added. After 10 minutes at room temperature, a solution of alkene 3.359 ( $678 \mathrm{mg}, 2.473 \mathrm{mmol}, 1.0$ equiv) in THF ( 1.5 mL ) and MeOH ( $200 \mu \mathrm{~L}, 4.945 \mathrm{mmol}, 2.0$ equiv) were added. After being stirred 8 hours at room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with THF) and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 12:1) afforded compound $\mathbf{3 . 3 6 0 ( 9 7 4 ~ m g , ~ 9 8 \% ) ~ a s ~ a ~ w h i t e ~ s o l i d . ~}$
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.46(\mathrm{~s}, 1 \mathrm{H}), 7.68(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.17-7.02(\mathrm{~m}, 2 \mathrm{H}), 6.96(\mathrm{td}, \mathrm{J}=$ $7.5,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{~s}, 3 \mathrm{H}), 3.67-3.52(\mathrm{~m}, 2 \mathrm{H}), 3.52-3.38(\mathrm{~m}, 2 \mathrm{H}), 3.08(\mathrm{dd}, \mathrm{J}=16.5,10.6 \mathrm{~Hz}$, $1 \mathrm{H}), 2.71-2.51(\mathrm{~m}, 2 \mathrm{H}), 2.00-1.83(\mathrm{~m}, 3 \mathrm{H}), 1.29-1.19(\mathrm{~m}, 1 \mathrm{H}), 1.11(\mathrm{~s}, 6 \mathrm{H}), 1.00(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 176.7,155.5,136.3,134.1,128.0,125.4,123.8,122.8,81.0,51.9$, $47.5,47.3,35.5,30.5,25.5,25.1,24.7,24.4$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{32} \mathrm{BN}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 403.2399; found: 403.2401.
$[\alpha]_{D}{ }^{20}+77.0^{\circ}$ (c 0.1, EtOH).
methyl (S)-(2-(1-hydroxy-3-oxo-3-(pyrrolidin-1-yl)propyl)phenyl)carbamate (3.361)


To a solution of borane 3.360 ( $22 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.0$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}$ (1:1, $0.75 / 0.75 \mathrm{~mL}, 0.04$ M) was added $\mathrm{NaBO}_{3} \cdot 4 \mathrm{H}_{2} \mathrm{O}$ ( $42 \mathrm{mg}, 0.275 \mathrm{mmol}, 5.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 6:1) to yield compound 3.361 ( $13 \mathrm{mg}, 83 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.87(\mathrm{dd}, J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{ddd}, J=7.5,1.5,0.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.38$ (td, J = 7.5, 1.5 Hz, 1H), $7.15(\mathrm{td}, J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.84(\mathrm{~s}, 1 \mathrm{H}), 5.44(\mathrm{dtd}, J=7.8,7.1,0.7 \mathrm{~Hz}, 1 \mathrm{H})$, $4.26(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.64(\mathrm{~s}, 3 \mathrm{H}), 3.47-3.34(\mathrm{~m}, 4 \mathrm{H}), 2.77(\mathrm{dd}, J=12.4,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.66(\mathrm{dd}, J=$ $12.4,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.88-1.75(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.3,155.6,137.6,131.7,128.5,126.7,123.6,120.1,68.4,52.2$, 46.5, 44.6, 24.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 293.1496; found: 293.1490 .
$[\alpha]_{\mathrm{D}}{ }^{20}+58.8^{\circ}(c 0.22, \mathrm{MeOH})$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, MeOH (4.5\%), 230 nm ) $t_{\mathrm{R}}$ (minor) $=4.5 \mathrm{~min}, t_{\mathrm{R}}$ (major) $=6.2 \mathrm{~min}: 95.5: 4.5 \mathrm{er}$.
methyl (S)-(2-(3-oxo-3-(pyrrolidin-1-yl)-1-(trifluoro-l4-boraneyl)propyl)phenyl)carbamate, potassium salt (3.362)


To a solution of borane 3.360 ( $300 \mathrm{mg}, 0.746 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeCN}(1.24 \mathrm{~mL}, 0.6 \mathrm{M}$ ) was added a solution of $\mathrm{KHF}_{2}$ ( 233 mg , $2.983 \mathrm{mmol}, 4.0$ equiv) in $\mathrm{H}_{2} \mathrm{O}(0.66 \mathrm{~mL})$. After being stirred 3 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. Recrystallization from $\mathrm{Et}_{2} \mathrm{O}$ afforded compound 3.362 ( 148 mg , 52\%) as a brown solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.95(\mathrm{dd}, \mathrm{J}=7.4,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.47-7.25(\mathrm{~m}, 2 \mathrm{H}), 7.03(\mathrm{td}, \mathrm{J}=7.5,1.5$ $\mathrm{Hz}, 1 \mathrm{H}), 6.52(\mathrm{~s}, 1 \mathrm{H}), 4.24-3.79(\mathrm{~m}, 1 \mathrm{H}), 3.64(\mathrm{~s}, 3 \mathrm{H}), 3.47-3.38(\mathrm{~m}, 4 \mathrm{H}), 2.76(\mathrm{dd}, \mathrm{J}=12.3,7.0 \mathrm{~Hz}$, $1 \mathrm{H}), 2.67(\mathrm{dd}, \mathrm{J}=12.4,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.96-1.72(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}{ }^{\mathbf{C}}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 170.6,155.6,139.9,127.2,125.9,124.7,122.9,118.5,58.8,52.2$, 46.5, 37.1, 24.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{BF}_{3} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}-\mathrm{K}]^{-}\right)$: 343.1441 ; found: 343.1449.
$[\alpha]_{D}{ }^{20}-32.3^{\circ}(c 0.22, D C M)$.
methyl (2-((S)-1-((S)-3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl)-3-oxo-3-(pyrrolidin-1-yl)propyl)phenyl)carbamate (3.363)


To a mixture of vinyl triflate 3.182 ( $10 \mathrm{mg}, 0.024 \mathrm{mmol}$, 1.0 equiv), borate 3.362 ( $28 \mathrm{mg}, 0.072$ mmol, 3.0 equiv), $\mathrm{Pd}(\mathrm{OAc})_{2}\left(1.6 \mathrm{mg}, 0.0072 \mathrm{mmol}, 0.3\right.$ equiv), $\mathrm{K}_{2} \mathrm{CO}_{3}(10 \mathrm{mg}, 0.072 \mathrm{mmol}, 3.0$ equiv) and DavePhos ( $5.7 \mathrm{mg}, 0.0144 \mathrm{mmol}, 0.6$ equiv) was added degassed CPME/ $\mathrm{H}_{2} \mathrm{O}$ (1:0.15, $0.21 / 0.03 \mathrm{~mL}, 0.1 \mathrm{M}$ ) and the reaction mixture was stirred overnight at $95^{\circ} \mathrm{C}$. After being cooled down to room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / E t O A c 1: 1$ ) to yield compound 3.363 ( $3.8 \mathrm{mg}, 29 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.00(\mathrm{dd}, J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{td}, J=7.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.23(\mathrm{dt}, J=$ $7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.88(\mathrm{td}, J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{~s}, 1 \mathrm{H}), 5.28(\mathrm{~s}, 1 \mathrm{H}), 3.99-3.83(\mathrm{~m}, 1 \mathrm{H}), 3.64(\mathrm{~s}$, 3 H ), 3.54 (ddt, J = 6.9, 5.7, 1.1 Hz, 2H), 3.48-3.35 (m, 4H), 2.83-2.57 (m, 4H), $1.92-1.77(\mathrm{~m}, 4 \mathrm{H})$, $1.61(\mathrm{dt}, \mathrm{J}=12.2,6.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.53-1.30(\mathrm{~m}, 8 \mathrm{H}), 0.90-0.83(\mathrm{~m}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.67$ - 0.46 (m, 6H).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{31} \mathrm{H}_{51} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 543.3613 ; found: 543.3610.
$[\alpha]_{D}{ }^{20}+45.9^{\circ}(c 0.35, E A)$.

## methyl (2-((S)-2-cyano-1-((S)-3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1- <br> yl)ethyl)phenyl)carbamate (3.364)



To a mixture of vinyl triflate $\mathbf{3 . 1 8 2}$ ( $10 \mathrm{mg}, 0.024 \mathrm{mmol}, 1.0$ equiv), borate $\mathbf{3 . 3 5 5}$ ( $28 \mathrm{mg}, 0.072$ mmol, 3.0 equiv), $\mathrm{Pd}(\mathrm{OAc})_{2}\left(1.6 \mathrm{mg}, 0.0072 \mathrm{mmol}, 0.3\right.$ equiv), $\mathrm{K}_{2} \mathrm{CO}_{3}(10 \mathrm{mg}, 0.072 \mathrm{mmol}, 3.0$ equiv) and XPhos ( $6.9 \mathrm{mg}, 0.0144 \mathrm{mmol}, 0.6$ equiv) was added degassed CPME/ $\mathrm{H}_{2} \mathrm{O}$ (1:0.15, $0.21 / 0.03 \mathrm{~mL}, 0.1 \mathrm{M}$ ) and the reaction mixture was stirred overnight at $90^{\circ} \mathrm{C}$. After being cooled down to room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) afforded compound $\mathbf{3 . 3 6 4}$ ( $1.4 \mathrm{mg}, 12 \%$ ) as a brown oil.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.00(\mathrm{dd}, J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{td}, J=7.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.24(\mathrm{dt}, J=$ $7.5,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.88(\mathrm{td}, J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{~s}, 1 \mathrm{H}), 5.29(\mathrm{~d}, \mathrm{~J}=1.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.67(\mathrm{tt}, J=7.0$, $0.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.64(\mathrm{~s}, 3 \mathrm{H}), 3.61-3.40(\mathrm{~m}, 2 \mathrm{H}), 2.86-2.56(\mathrm{~m}, 4 \mathrm{H}), 1.61(\mathrm{dt}, J=12.2,6.8 \mathrm{~Hz}, 1 \mathrm{H})$, $1.52-1.31(\mathrm{~m}, 8 \mathrm{H}), 0.90-0.83(\mathrm{~m}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.67-0.48(\mathrm{~m}, 6 \mathrm{H})$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{43} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 471.3037; found: 471.3039.
$[\alpha]_{\mathrm{D}}{ }^{20}+79.8^{\circ}$ (c 0.1, DCM).

## 1-methylquinolin-2(1H)-one (3.370)



It was prepared according to a literature procedure. ${ }^{278}$

> methyl $(S)$-3-(1H-naphtho $[1,8-d e][1,3,2]$ diazaborinin- $2(3 H)$-yl)-3-(trifluoro-I4boraneyl)propanoate, potassium salt (3.285)


It was prepared according to a literature procedure. ${ }^{254,279,280}$
2,2'-(3-(benzyloxy)propane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.375)


It was prepared according to a literature procedure. ${ }^{281}$

### 8.3.5 Stereoinvertive Substitution

(S)-triethyl(3-(1-ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1yl)propoxy)silane (3.376)


Triflate 3.182 ( $500 \mathrm{mg}, 1.20 \mathrm{mmol}, 1.0$ equiv), $\mathrm{KOAc}\left(294 \mathrm{mg}, 3.00 \mathrm{mmol}, 2.5\right.$ equiv), $\mathrm{PdCl}_{2}$ (dppf) ( $26 \mathrm{mg}, 0.036 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{B}_{2} \operatorname{pin}_{2}(335 \mathrm{mg}, 1.32 \mathrm{mmol}, 1.1$ equiv) where weighted in a sealed tube and the atmosphere was purged with argon. Dioxane ( $7.5 \mathrm{~mL}, 0.16 \mathrm{M}$ ) was added and the reaction mixture was heated to $70^{\circ} \mathrm{C}$ for 6 hours. After cooling down to room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ ) to yield compound 3.376 as a colorless oil ( 378 mg , 80\% yield).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 6.24(\mathrm{t}, \mathrm{J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.55(\mathrm{t}, \mathrm{J}=6.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.46-2.34(\mathrm{~m}, 2 \mathrm{H})$, $1.63(\mathrm{dd}, \mathrm{J}=7.8,6.7 \mathrm{~Hz}, 2 \mathrm{H}), 1.54-1.30(\mathrm{~m}, 6 \mathrm{H}), 1.27(\mathrm{~s}, 12 \mathrm{H}), 0.95(\mathrm{t}, \mathrm{J}=7.8 \mathrm{~Hz}, 9 \mathrm{H}), 0.81(\mathrm{t}, \mathrm{J}=$ $7.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.58(\mathrm{q}, J=7.8 \mathrm{~Hz}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 154.9,83.2,63.9,54.3,34.7,34.4,34.2,31.4,28.4,25.0,24.9,9.2$, 7.0, 4.6.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2958$ (w), 2881 (w), 1221 (w), 1141 (w), 1096 (w), 899 (s), 729 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{44} \mathrm{BO}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 395.3147; found: 395.3149.
$[\alpha]_{\mathrm{D}}{ }^{20}+99.0^{\circ}(c 0.1, \mathrm{MeOH})$.
(S)-(3-ethyl-3-(3-hydroxypropyl)cyclopent-1-en-1-yl)boronic acid (3.236)


Boronic ester 3.376 ( 363 mg , $0.92 \mathrm{mmol}, 1.0$ equiv), and $\mathrm{NH}_{4} \mathrm{OAc}(213 \mathrm{mg}, 2.76 \mathrm{mmol}, 3.0$ equiv) were dissolved in acetone $/ \mathrm{H}_{2} \mathrm{O}(1: 1,9 / 9 \mathrm{~mL} \mathrm{~mL}, 0.05 \mathrm{M}) . \mathrm{NaIO}_{4}(590 \mathrm{mg}, 2.76 \mathrm{mmol}, 3.0$ equiv) was added portionwise over 30 min . After being stirred 48 hours at room temperature, the reaction mixture was quenched with 1 M HCl , diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ ) to yield compound 3.236 as a colorless oil ( 126 mg , 69\% yield).
${ }^{1} \mathrm{H}$ NMR (400 MHz, DMSO- $d_{6}$ ): $\delta 7.5(\mathrm{~s}, 2 \mathrm{H}), 6.1(\mathrm{t}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.3(\mathrm{t}, J=5.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.3$ (ddd, J $=8.1,6.6,2.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.0(\mathrm{~s}, 1 \mathrm{H}), 1.5(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.4-1.2(\mathrm{~m}, 6 \mathrm{H}), 0.7(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, DMSO- $\boldsymbol{d}_{6}$ ): $\delta 151.3,138.5,61.9,53.7,34.8,34.5,34.4,31.4,28.2,9.3$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 2949$ (w), 2878 (w), 1426 (w), 1214 (w), 1146 (w), 1087 (m), 906 (s), 721 (s).
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{10} \mathrm{H}_{18} \mathrm{BO}_{3}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 197.1354; found: 197.1350 .
$[\alpha]_{\mathrm{D}}{ }^{20}+42.9^{\circ}\left(c 0.33, \mathrm{CHCl}_{3}\right)$.

## (S)-(3-(3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-ethylcyclopent-2-en-1yl)propoxy)triethylsilane (3.377)



Triflate 3.182 ( $100 \mathrm{mg}, 0.24 \mathrm{mmol}, 1.0$ equiv), $\mathrm{KOAc}\left(59 \mathrm{mg}, 0.60 \mathrm{mmol}, 2.5\right.$ equiv), $\mathrm{PdCl}_{2}$ (dppf) ( $5.3 \mathrm{mg}, 0.0072 \mathrm{mmol}, 0.03$ equiv) and $\mathrm{B}_{2} \mathrm{pin}_{2}(67 \mathrm{mg}, 0.264 \mathrm{mmol}, 1.1$ equiv) were weighted in a sealed tube and the atmosphere was purged with argon. Dioxane ( $1.5 \mathrm{~mL}, 0.16 \mathrm{M}$ ) was added and the reaction mixture was heated to $70^{\circ} \mathrm{C}$ for 6 hours. After cooling down to room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ ) to yield compound 3.377 as a colorless oil ( 72 mg , 79\% yield).
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ): $\delta 5.46(\mathrm{~s}, 1 \mathrm{H}), 3.68(\mathrm{~s}, 4 \mathrm{H}), 3.60-3.45(\mathrm{~m}, 2 \mathrm{H}), 2.48(\mathrm{td}, \mathrm{J}=7.0,2.7 \mathrm{~Hz}$, $2 \mathrm{H}), 1.60(\mathrm{dt}, \mathrm{J}=12.0,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.53-1.28(\mathrm{~m}, 7 \mathrm{H}), 1.04(\mathrm{~s}, 6 \mathrm{H}), 0.92-0.82(\mathrm{~m}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=$ $8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.67-0.46(\mathrm{~m}, 6 \mathrm{H})$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{42} \mathrm{BO}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 381.2991; found: 381.2995.
$[\alpha]_{\mathrm{D}}{ }^{20}+78.6^{\circ}\left(c 0.17, \mathrm{CHCl}_{3}\right)$.

## 1-(2-nitrophenyl)propane-1,3-diol (rac-3.379)



It was prepared according to a literature procedure. ${ }^{285}$

## 3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propan-1-ol (rac-3.380)



It was prepared according to a literature procedure. ${ }^{286}$
3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl methanesulfonate (rac-3.237)


To a solution of alcohol rac-3.380 ( $500 \mathrm{mg}, 1.605 \mathrm{mmol}, 1.0$ equiv) in DCM ( $5 \mathrm{~mL}, 0.33 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ were added $\mathrm{NEt}_{3}(268 \mu \mathrm{~L}, 1.926 \mathrm{mmol}, 1.2$ equiv) and $\mathrm{MsCl}(137 \mu \mathrm{~L}, 1.766 \mathrm{mmol}, 1.1$ equiv). After being stirred at room temperature for 8 h , the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ ) to yield compound rac-3.237 as a yellow oil (581 mg, 93 \% yield).
(R)-bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol (3.384)


It was prepared according to a literature procedure. ${ }^{287}$
(S)-1-(2-nitrophenyl)propane-1,3-diol (3.379)


It was prepared according to a literature procedure. ${ }^{288}$

## (S)-3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propan-1-ol (3.380)



The analytical data were in accordance with those reported in the literature. ${ }^{286}$
(S)-3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl methanesulfonate (3.237)


To a solution of alcohol $\mathbf{3 . 3 8 0}$ ( $500 \mathrm{mg}, 1.605 \mathrm{mmol}, 1.0$ equiv) in DCM $(5 \mathrm{~mL}, 0.33 \mathrm{M})$ at $0{ }^{\circ} \mathrm{C}$ were added $\mathrm{NEt}_{3}(268 \mu \mathrm{~L}, 1.926 \mathrm{mmol}, 1.2$ equiv) and $\mathrm{MsCl}(137 \mu \mathrm{~L}, 1.766 \mathrm{mmol}, 1.1$ equiv). After being stirred at room temperature for 8 h , the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ ) to yield compound 3.237 as a yellow oil ( $581 \mathrm{mg}, 93 \%$ yield).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.02(\mathrm{dd}, J=8.3,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.80(\mathrm{dd}, J=7.9,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.75-7.61$ (m, 1H), 7.49 (ddd, $J=8.6,7.3,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 6.42 (dd, $J=9.8,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.88$ (ddd, $J=10.7,9.7,4.3$ $\mathrm{Hz}, 1 \mathrm{H}), 3.80(\mathrm{ddd}, \mathrm{J}=10.7,6.1,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.23(\mathrm{dddd}, J=14.4,9.5,6.1,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.12-1.95$ $(\mathrm{m}, 1 \mathrm{H}), 0.92(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 3 \mathrm{H}), 0.08(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}{ }^{3}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 147.1,136.0,134.0,129.3,128.5,124.9,76.2,58.5,39.9,38.1,26.0$, 18.4, -5.2, -5.3.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2946$ ( w ), 2857 ( w ), 1654 ( m$), 1647$ ( w$), 1636$ ( w$), 1594$ (m), 1566 (m), 1560 ( w$), 1491$ (w), 1455 (s), 1437 (w), 1399 (m), 1376 (w), 1313 (m), 1282 (w).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{16} \mathrm{H}_{28} \mathrm{NO}_{6} \mathrm{SSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 390.1401; found: 390.1406.
$[\alpha]_{D}{ }^{20}+45.0^{\circ}(c 0.19$, EtOH $)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, MeOH (4\%), 230 nm ) $t_{\mathrm{R}}$ (minor) $=$ $12.5 \mathrm{~min}, t_{\mathrm{R}}$ (major) $=14.6 \mathrm{~min}: 99.0: 1.0 \mathrm{er}$.

## 3-((S)-3-((S)-3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propan-1-ol (3.180)



To a solution of mesylate 3.237 ( $390 \mathrm{mg}, 1 \mathrm{mmol}, 1.0$ equiv) and boronic acid 3.236 ( $300 \mathrm{mg}, 1.5$ mmol, 1.5 equiv) in DCE/ $\mathrm{H}_{2} \mathrm{O}(50: 1,430 / 10 \mathrm{~mL}, 0.1 \mathrm{M})$ at room temperature was added $\mathrm{K}_{3} \mathrm{PO}_{4}(430$ $\mathrm{mg}, 2 \mathrm{mmol}, 2.0$ equiv). After being stirred at $80^{\circ} \mathrm{C}$ for 8 h , the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ ) to yield compound $\mathbf{3 . 1 8 0}$ as a yellow oil (249 mg, 55\% yield).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.7(\mathrm{dd}, J=8.0,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.5(\mathrm{td}, J=7.7,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.4(\mathrm{dd}, J=$ $7.9,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.3$ (ddd, J = 8.1, 7.3, 1.4 Hz, 1H), $5.3-5.2(\mathrm{~m}, 1 \mathrm{H}), 4.1(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.6(\mathrm{t}, \mathrm{J}=$ $6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.5(\mathrm{t}, \mathrm{J}=6.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.2-1.9(\mathrm{~m}, 4 \mathrm{H}), 1.6(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 1.5-1.3(\mathrm{~m}, 6 \mathrm{H}), 0.8(\mathrm{~s}$, $9 \mathrm{H}), 0.8(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}),-0.0(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 150.7, 143.9, 137.7, 133.2, 132.2, 129.1, 127.0, 124.0, 63.7, 61.1, $51.8,37.3,36.9,35.3,33.4,33.3,32.1,28.3,26.0,18.4,9.2,-5.3$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3362$ (br w), 2934 (w), 2856 (w), 1527 (s), 1463 (w), 1356 (m), 1254 (m), 1099 (s), 1062 (m), 834 (s), 778 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{42} \mathrm{NO}_{4} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 448.2878; found: 448.2880.
$[\alpha]_{D}{ }^{20}-50.0^{\circ}(c 0.1, \mathrm{EtOH})$.

## (S)-3-hydroxy-1-(2-nitrophenyl)propyl methanesulfonate (3.388)



To a solution of TBS 3.237 ( $400 \mathrm{mg}, 1.03 \mathrm{mmol}$, 1.0 equiv) in THF ( $10 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added dropwise TBAF ( 1 M in THF, $3.08 \mathrm{mmol}, 3.0$ equiv). After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, PE/EtOAc) to yield compound 3.388 as a yellow oil ( $246 \mathrm{mg}, 87 \%$ yield).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.03(\mathrm{dd}, J=8.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.81(\mathrm{dd}, J=8.0,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.72(\mathrm{td}, \mathrm{J}=$ $7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.52 (ddd, $J=8.6,7.3,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.43$ (dd, J = 9.8, $3.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.96-3.81$ (m, $2 \mathrm{H}), 3.00(\mathrm{~s}, 3 \mathrm{H}), 2.42(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.27$ (dddd, $J=14.9,9.0,6.2,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.20-2.03(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 147.9,135.8,131.8,130.1,127.8,124.6,77.8,58.9,38.6,36.3$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{NO}_{6} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 276.0536; found: 276.0539.
$[\alpha]_{D}{ }^{20}-74.6^{\circ}\left(c 0.17, \mathrm{CHCl}_{3}\right)$.
(S)-(3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethylcyclopent-1-en-1-yl)boronic acid (3.389)


To a solution of alcohol 3.236 ( $198 \mathrm{mg}, 1.0 \mathrm{mmol}$, 1.0 equiv) in dry DMF ( $3.3 \mathrm{~mL}, 0.3 \mathrm{M}$ ) was added imidazole ( $102 \mathrm{mg}, 1.5 \mathrm{mmol}, 1.5$ equiv) and TBSCl ( $226 \mathrm{mg}, 1.5 \mathrm{mmol}, 1.5$ equiv). After being stirred 6 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ) to yield compound 3.389 ( $281 \mathrm{mg}, \mathrm{mg}, 90 \%$ ) as a white solid.
${ }^{1}{ }^{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.49(\mathrm{~s}, 1 \mathrm{H}), 3.60-3.54(\mathrm{~m}, 2 \mathrm{H}), 2.53(\mathrm{td}, \mathrm{J}=7.1,2.7 \mathrm{~Hz}, 2 \mathrm{H}), 1.66-$ $1.55(\mathrm{~m}, 1 \mathrm{H}), 1.54-1.32(\mathrm{~m}, 8 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.03(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 145.8,124.7,64.4,51.9,37.3,35.0,31.9,28.9,25.9,25.5,18.3,8.6,-$ 5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{BO}_{3} \mathrm{Si}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 311.2219; found: 311.2211 .
(S)-3-((S)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethylcyclopent-1-en-1-yl)-3-(2-nitrophenyl)propan-1-ol (3.390)


To a solution of mesylate 3.388 ( $39 \mathrm{mg}, 0.1 \mathrm{mmol}, 1.0$ equiv) and boronic acid 3.389 ( $30 \mathrm{mg}, 0.15$ mmol, 1.5 equiv) in DCE/ $\mathrm{H}_{2} \mathrm{O}\left(50: 1,43 / 1 \mathrm{~mL}, 0.1 \mathrm{M}\right.$ ) at room temperature was added $\mathrm{K}_{3} \mathrm{PO}_{4}$ (43 $\mathrm{mg}, 0.2 \mathrm{mmol}, 2.0$ equiv). After being stirred at $80^{\circ} \mathrm{C}$ for 8 h , the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were
washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}\right)$ to yield compound $\mathbf{3 . 3 9 0}$ as a yellow oil ( $20 \mathrm{mg}, 44 \%$ yield).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.03(\mathrm{dd}, J=7.3,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{td}, J=7.4,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{td}, J=$ $7.5,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.50-7.46(\mathrm{~m}, 1 \mathrm{H}), 5.27(\mathrm{~s}, 1 \mathrm{H}), 3.76-3.62(\mathrm{~m}, 3 \mathrm{H}), 3.61-3.49(\mathrm{~m}, 3 \mathrm{H}), 2.66$ (tdd, J = 7.1, 2.7, 1.0 Hz, 2H), 2.07-1.88 (m, 2H), 1.61 (dt, J=12.3, 6.9 Hz, 1H), 1.52-1.30(m, 7H), $0.91(\mathrm{~s}, 9 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.03(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 150.5,142.1,141.8,138.9,131.7,129.6,128.0,124.9,64.4,60.8$, $52.4,44.7,35.6,33.2,29.0,25.9,25.5,18.3,8.6,-5.2$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{25} \mathrm{H}_{42} \mathrm{NO}_{4} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 448.2878$; found: 448.2884 .
$[\alpha]_{D}{ }^{20}+12.6^{\circ}(c 0.1, \mathrm{MeOH})$.
8.3.6 Diamination of the 1,1,2-Trisubstituted Alkene
(9H-fluoren-9-yl)methyl tosylcarbamate (3.393)


It was prepared according to a literature procedure. ${ }^{289}$

## N-(3-(3-(3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propyl)-4-methylbenzenesulfonamide (3.394)



To a solution of rac-3.180 ( $297 \mathrm{mg}, 0.663 \mathrm{mmol}, 1.0$ equiv) in dry THF ( $8.7 \mathrm{~mL}, 0.077 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ were added TsNHFmoc ( $\mathbf{3 . 3 9 3 \text { ) ( } 3 9 2 \mathrm { mg } , 0 . 9 9 5 \mathrm { mmol } , 1 . 5 \text { equiv), } \mathrm { PPh } _ { 3 } ( 5 2 2 \mathrm { mg } , 1 . 9 9 \mathrm { mmol } , 3 . 0}$ equiv) and DEAD ( $754 \mu \mathrm{~L}, 1.659 \mathrm{mmol}, 2.5$ equiv). After being stirred 12 hours at room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 5: 1$ ) to yield the pure product $\mathbf{3 . 3 9 4}(282 \mathrm{mg}, 71 \%)$ as an amorphous orange solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.76-7.71(\mathrm{~m}, 2 \mathrm{H}), 7.68(\mathrm{dd}, \mathrm{J}=8.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{ddd}, \mathrm{J}=8.5$, $7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.35-7.27(\mathrm{~m}, 4 \mathrm{H}), 5.13(\mathrm{~d}, \mathrm{~J}=1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.63(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.04(\mathrm{t}, \mathrm{J}=7.4$ $\mathrm{Hz}, 1 \mathrm{H}), 3.57-3.44(\mathrm{~m}, 2 \mathrm{H}), 2.88(\mathrm{q}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 2.41(\mathrm{~s}, 3 \mathrm{H}), 2.18-2.04(\mathrm{~m}, 2 \mathrm{H}), 2.04-1.84$ $(\mathrm{m}, 2 \mathrm{H}), 1.61-1.48(\mathrm{~m}, 1 \mathrm{H}), 1.48-1.16(\mathrm{~m}, 6 \mathrm{H}), 0.84(\mathrm{~s}, 9 \mathrm{H}), 0.72(\mathrm{t}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}),-0.03(\mathrm{~s}, 3 \mathrm{H}),-$ 0.03 ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 150.7, 144.6, 143.4, 137.6, 137.2, 132.4, 132.3, 129.8, 129.2, 127.2, $127.1,124.1,61.1,51.8,44.1,37.4,37.1,36.2,33.8,33.4,32.2,26.0,26.0,25.2,21.6,18.4,9.1,-$ 5.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{32} \mathrm{H}_{49} \mathrm{~N}_{2} \mathrm{O}_{5} \mathrm{SSi}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 601.3126; found: 601.3130.

## N-(3-(3-(1-(2-aminophenyl)-3-((tert-butyldimethylsilyl)oxy)propyl)-1-ethylcyclopent-2-en-1-yl)propyl)-4-methylbenzenesulfonamide (3.395)



A solution of 3.394 ( $25 \mathrm{mg}, 0.042 \mathrm{mmol}, 1.0$ equiv), $\mathrm{NH}_{4} \mathrm{Cl}(22.3 \mathrm{mg}, 0.416 \mathrm{mmol}, 10$ equiv) and Zn powder ( $27.2 \mathrm{mg}, 0.416 \mathrm{mmol}, 10$ equiv) in $\mathrm{MeOH}(0.42 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was heated to reflux for 5 hours. After cooling down to room temperature, the reaction mixture was filtered and evaporated in vacuo to afford 3.395 ( $21 \mathrm{mg}, 88 \%$ ) as a mixture of diastereoisomers as a white powder.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.83-7.68(\mathrm{~m}, 2 \mathrm{H}), 7.35-7.17(\mathrm{~m}, 2 \mathrm{H}), 7.07-6.96(\mathrm{~m}, 1.25 \mathrm{H}), 6.96$ $-6.89(\mathrm{~m}, 0.75 \mathrm{H}), 6.76-6.67(\mathrm{~m}, 1 \mathrm{H}), 6.67-6.60(\mathrm{~m}, 1 \mathrm{H}), 5.26-5.22(\mathrm{~m}, 0.25 \mathrm{H}), 5.21(\mathrm{~s}, 0.75 \mathrm{H})$, $4.67-4.46(\mathrm{~m}, 1 \mathrm{H}), 3.69-3.45(\mathrm{~m}, 5 \mathrm{H}), 2.99-2.84(\mathrm{~m}, 2 \mathrm{H}), 2.47-2.37(\mathrm{~m}, 3 \mathrm{H}), 2.13-2.01(\mathrm{~m}$, $2 H), 1.91-1.81(\mathrm{~m}, 1 \mathrm{H}), 1.64-1.52(\mathrm{~m}, 1 \mathrm{H}), 1.52-1.20(\mathrm{~m}, 6 \mathrm{H}), 0.95-0.84(\mathrm{~m}, 9 \mathrm{H}), 0.83-0.67$ (m, 3H), 0.09--0.07 (m, 6H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 145.7,145.4,145.2,143.6,143.5,137.2,132.2,131.8,129.8,129.8$, $128.1,127.9,127.5,127.5,127.2,127.1,118.7,116.2,61.3,61.2,51.9,46.6,44.2,44.1,37.8,36.4$, $36.3,36.3,35.8,35.6,33.9,33.6,33.5,33.2,32.1,29.8,26.1,25.4,25.2,21.6,18.4,9.3,9.2,8.8,-$ 5.2,-5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{32} \mathrm{H}_{51} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{SSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 571.3384 ; found: 571.3384.
N-(2-(3-((tert-butyldimethylsilyl)oxy)-1-(3-ethyl-3-(3-((4-methylphenyl)sulfonamido)propyl)cyclopent-1-en-1-yl)propyl)phenyl)-4methylbenzenesulfonamide (3.396)


To a solution of 3.395 ( $185 \mathrm{mg}, 0.324 \mathrm{mmol}, 1.0$ equiv) in pyridine ( $3.3 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added TsCl ( $93 \mathrm{mg}, 0.486 \mathrm{mmol}, 1.5$ equiv). After being stirred 3 hours at room temperature, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the pure product 3.396 ( $203 \mathrm{mg}, 95 \%$ ) as a mixture of diastereoisomers as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.90(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{dq}, J=8.7,2.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.51-7.43(\mathrm{~m}$, $2 \mathrm{H}), 7.40(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.22-7.09(\mathrm{~m}, 3 \mathrm{H}), 7.04(\mathrm{dt}, J=9.8,4.9 \mathrm{~Hz}, 3 \mathrm{H}), 6.94(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H})$, $6.86-6.81(\mathrm{~m}, 1 \mathrm{H}), 6.78(\mathrm{dd}, J=7.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.06(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.42-4.23(\mathrm{~m}, 1 \mathrm{H}), 3.98$ ( $q d, J=7.2,1.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.40(\mathrm{t}, J=14.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.20(\mathrm{dd}, J=11.0,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.04-2.96(\mathrm{~m}, 1 \mathrm{H})$, $2.90(\mathrm{td}, J=10.8,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.83-2.70(\mathrm{~m}, 2 \mathrm{H}), 2.28(\mathrm{~s}, 1 \mathrm{H}), 2.25(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.21(\mathrm{~s}, 3 \mathrm{H})$, $1.97-1.78(\mathrm{~m}, 2 \mathrm{H}), 1.59-1.03(\mathrm{~m}, 11 \mathrm{H}), 0.79(\mathrm{t}, \mathrm{J}=2.6 \mathrm{~Hz}, 8 \mathrm{H}), 0.62(\mathrm{dtd}, J=14.4,7.5,2.0 \mathrm{~Hz}$, $3 \mathrm{H}), 0.05-0.13(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 148.2,146.0,145.7,143.5,143.4,137.8,137.2,137.1,136.0,135.1$, $134.8,132.4,131.8,129.9,129.8,129.7,128.6,127.9,127.4,127.3,127.3,126.2,124.7,124.6$, $124.2,60.5,51.9,51.8,44.2,37.0,36.1,36.0,33.7,33.5,32.1,31.9,29.8,26.3,26.3,25.4,25.3$, $21.6,21.6,18.8,18.8,14.3,9.3,9.1,8.8,1.2,-4.8,-4.9,-5.3$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{39} \mathrm{H}_{57} \mathrm{~N}_{2} \mathrm{O}_{5} \mathrm{~S}_{2} \mathrm{Si}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 725.3473 ; found: 725.3478 .

## benzylsulfamoyl chloride (3.400)



It was prepared according to a literature procedure. ${ }^{290}$

## tert-butyl(3-(3-(3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propoxy)dimethylsilane (3.401)



To a solution of alcohol rac-3.180 ( $336 \mathrm{mg}, 0.751 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $10 \mathrm{~mL}, 0.076 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added imidazole ( $77 \mathrm{mg}, 1.126 \mathrm{mmol}, 1.5$ equiv) and TBSCI ( $136 \mathrm{mg}, 0.901 \mathrm{mmol}, 1.2$ equiv). After being stirred 4 hours at $0^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 9: 1$ ) to yield the pure product 3.401 ( $396 \mathrm{mg}, 94 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.69(\mathrm{dd}, J=8.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.49(\mathrm{td}, J=7.6,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.39(\mathrm{dd}, J=$ $7.9,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.30$ (ddd, $J=8.4,7.3,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.28(\mathrm{~s}, 1 \mathrm{H}), 4.07(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.64-3.47$ $(\mathrm{m}, 4 \mathrm{H}), 2.27-2.08(\mathrm{~m}, 2 \mathrm{H}), 2.08-1.85(\mathrm{~m}, 2 \mathrm{H}), 1.68-1.53(\mathrm{~m}, 2 \mathrm{H}), 1.48-1.29(\mathrm{~m}, 6 \mathrm{H}), 0.89(\mathrm{~s}$, $9 \mathrm{H}), 0.86(\mathrm{~s}, 9 \mathrm{H}), 0.78(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 0.04(\mathrm{~s}, 6 \mathrm{H}),-0.01(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 150.7,143.9,137.9,133.3,132.3,129.2,127.0,124.0,64.1,61.2$, $51.8,37.4,37.3,35.4,33.6,32.1,28.5,26.1,26.1,26.0,18.5,18.4,9.2,-5.1,-5.3$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{31} \mathrm{H}_{56} \mathrm{NO}_{4} \mathrm{Si}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 562.3742 ; found: 562.3743.

## 2-(3-((tert-butyldimethylsilyl)oxy)-1-(3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethylcyclopent-

 1-en-1-yl)propyl)aniline (3.402)

A solution of nitro 3.401 ( $369 \mathrm{mg}, 0.657 \mathrm{mmol}, 1.0$ equiv), $\mathrm{NH}_{4} \mathrm{Cl}$ ( $351 \mathrm{mg}, 6.57 \mathrm{mmol}, 10$ equiv) and Zn powder ( $429 \mathrm{mg}, 6.57 \mathrm{mmol}, 10$ equiv) in $\mathrm{MeOH}(6.5 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was heated to reflux for 5 hours. After cooling down to room temperature, the reaction mixture was filtered and evaporated in vacuo to afford $3.402(279 \mathrm{mg}, 80 \%)$ as a brown powder.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.06-6.95(\mathrm{~m}, 2 \mathrm{H}), 6.72(\mathrm{td}, J=7.4,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.64(\mathrm{dd}, \mathrm{J}=8.2,1.3$ $\mathrm{Hz}, 1 \mathrm{H}), 5.36(\mathrm{~s}, 1 \mathrm{H}), 3.92(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 3.73-3.53(\mathrm{~m}, 5 \mathrm{H}), 2.22-1.99(\mathrm{~m}, 3 \mathrm{H}), 1.99-1.84(\mathrm{~m}, 1 \mathrm{H})$, $1.68-1.59(\mathrm{~m}, 2 \mathrm{H}), 1.57-1.32(\mathrm{~m}, 6 \mathrm{H}), 1.00-0.88(\mathrm{~m}, 18 \mathrm{H}), 0.87(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.07(\mathrm{~s}, 6 \mathrm{H})$, $0.06(\mathrm{~s}, 3 \mathrm{H}), 0.05(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 145.3,144.9,132.7,128.1,127.7,127.0,118.6,116.1,64.2,61.3$, $51.9,37.9,35.8,35.3,33.8,33.6,32.2,28.5,26.1,26.1,26.1,18.5,18.4,9.4,-5.1,-5.2,-5.2$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{31} \mathrm{H}_{58} \mathrm{NO}_{2} \mathrm{Si}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 532.4001$; found: 532.4006.
N-((2-(3-((tert-butyldimethylsilyl)oxy)-1-(3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethylcyclopent-1-en-1-yl)propyl)phenyl)carbamoyl)-4-methylbenzenesulfonamide (3.403)


To a solution of amine 3.402 ( $100 \mathrm{mg}, 0.188 \mathrm{mmol}$, 1.0 equiv) in dry DCM ( $1.88 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added TsNCO ( $44 \mu \mathrm{~L}, 0.282 \mathrm{mmol}, 1.5$ equiv). After being stirred 8 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc $12: 1$ ) to yield the pure product $\mathbf{3 . 4 0 3}$ ( $122 \mathrm{mg}, 89 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.21(\mathrm{~s}, 1 \mathrm{H}), 7.87(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.50(\mathrm{dd}, J=7.0,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.32$ (d, J = 8.0 Hz, 2H), $7.25-7.09(\mathrm{~m}, 3 \mathrm{H}), 5.29(\mathrm{~s}, 1 \mathrm{H}), 3.71-3.47(\mathrm{~m}, 5 \mathrm{H}), 2.44(\mathrm{~s}, 3 \mathrm{H}), 2.23-1.97(\mathrm{~m}$, $3 \mathrm{H}), 1.97-1.84(\mathrm{~m}, 1 \mathrm{H}), 1.66-1.52(\mathrm{~m}, 2 \mathrm{H}), 1.52-1.20(\mathrm{~m}, 6 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.88(\mathrm{~s}, 9 \mathrm{H}), 0.81(\mathrm{t}, \mathrm{J}$ $=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 0.06(\mathrm{~s}, 6 \mathrm{H}), 0.04(\mathrm{~s}, 3 \mathrm{H}), 0.03(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, CDCl 3 ): $\delta$ 150.1, 144.8, 144.2, 136.8, 134.4, 133.2, 129.9, 129.7, 127.7, 127.3, $126.9,126.4,64.2,61.5,51.7,37.7,36.2,35.1,33.9,33.0,31.8,28.3,26.1,26.1,21.7,18.5,9.2,-$ 5.1, -5.2, -5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{39} \mathrm{H}_{65} \mathrm{~N}_{2} \mathrm{O}_{5} \mathrm{SSi}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 729.4147; found: 729.4150.

### 3.404



To a solution of amine 3.402 ( $70 \mathrm{mg}, 0.132 \mathrm{mmol}, 1.0$ equiv) in dry benzene ( $1.4 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added $\mathrm{NEt}_{3}\left(37 \mu \mathrm{~L}, 0.263 \mathrm{mmol}, 2.0\right.$ equiv) and $\mathrm{BnNHSO}_{2} \mathrm{Cl}$ ( $41 \mathrm{mg}, 0.197 \mathrm{mmol}, 1.5$ equiv). After being stirred 6 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 12: 1$ ) to yield the pure product 3.404 ( $68 \mathrm{mg}, 74 \%$ ) as a brown oil.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{38} \mathrm{H}_{65} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{SSi}_{2}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 701.4198; found: 701.4200.

## N-(2-(3-((tert-butyldimethylsilyl)oxy)-1-(3-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-ethylcyclopent-1-en-1-yl)propyl)phenyl)-4-methylbenzenesulfonamide (3.407)



To a solution of 3.402 ( $100 \mathrm{mg}, 0.188 \mathrm{mmol}, 1.0$ equiv) in dry pyridine ( $1.88 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added TsCl ( $54 \mathrm{mg}, 0.282 \mathrm{mmol}, 1.5$ equiv). After being stirred 3 hours at room temperature, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 7: 1$ ) to yield the pure product 3.407 ( 122 mg , 95\%) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.24(\mathrm{~s}, 1 \mathrm{H}), 7.63-7.57(\mathrm{~m}, 3 \mathrm{H}), 7.21-7.15(\mathrm{~m}, 3 \mathrm{H}), 7.08(\mathrm{td}, \mathrm{J}=7.5$, $1.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.97(\mathrm{dd}, \mathrm{J}=7.8,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.25(\mathrm{~s}, 1 \mathrm{H}), 3.65-3.55(\mathrm{~m}, 3 \mathrm{H}), 3.31(\mathrm{dd}, \mathrm{J}=11.0,4.2 \mathrm{~Hz}$, $1 \mathrm{H}), 3.13(\mathrm{td}, \mathrm{J}=11.2,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.35(\mathrm{~s}, 3 \mathrm{H}), 2.12-1.94(\mathrm{~m}, 1 \mathrm{H}), 1.52-1.19(\mathrm{~m}, 10 \mathrm{H}), 1.20-$ $1.03(\mathrm{~m}, 1 \mathrm{H}), 0.95(\mathrm{~s}, 9 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.82(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.20(\mathrm{~s}, 3 \mathrm{H}), 0.16(\mathrm{~s}, 3 \mathrm{H}), 0.07(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 145.2,143.3,138.0,136.0,135.6,132.4,129.7,128.0,127.2,127.2$, $126.3,125.2,64.2,60.7,51.9,37.5,36.7,35.1,33.6,33.5,32.1,28.5,26.3,26.2,21.5,18.9,18.5$, 9.3, -4.8, -5.0, -5.2, -5.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{38} \mathrm{H}_{64} \mathrm{NO}_{4} \mathrm{SSi}_{2}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 686.4089; found: 686.4093.

## N-(2-(7-ethyl-6-hydroxy-7-(3-hydroxypropyl)-1-oxaspiro[4.4]nonan-4-yl)phenyl)-4methylbenzenesulfonamide (3.409)



To a solution of 3.407 ( $20 \mathrm{mg}, 0.029 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}(2: 1,0.2 / 0.1 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added Oxone ( $36 \mathrm{mg}, 0.058 \mathrm{mmol}, 4$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ 6:1) to yield the pure product 3.409 ( $13 \mathrm{mg}, 97 \%$ ) as a brown oil and as a 3:1 mixture of diastereoisomers.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.37(\mathrm{~s}, 1 \mathrm{H}), 7.62-7.45(\mathrm{~m}, 2 \mathrm{H}), 7.45-7.33(\mathrm{~m}, 1 \mathrm{H}), 7.12-6.95(\mathrm{~m}$, $6 \mathrm{H}), 3.86-3.68(\mathrm{~m}, 1 \mathrm{H}), 3.59-3.54(\mathrm{~m}, 1 \mathrm{H}), 3.54-3.36(\mathrm{~m}, 4 \mathrm{H}), 3.28-3.14(\mathrm{~m}, 1 \mathrm{H}), 2.35-2.21$ $(\mathrm{m}, 4 \mathrm{H}), 1.87-1.70(\mathrm{~m}, 1 \mathrm{H}), 1.57-1.43(\mathrm{~m}, 1 \mathrm{H}), 1.43-1.23(\mathrm{~m}, 6 \mathrm{H}), 1.13-0.95(\mathrm{~m}, 2 \mathrm{H}), 0.74-$ 0.58 (m, 6H).
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 143.3,137.3,135.6,135.1,129.6,129.5,128.4,127.3,127.2,127.2$, $125.7,97.3,96.1,83.9,65.8,65.2,63.7,63.2,60.6,48.6,48.4,41.4,34.9,34.6,34.0,32.7,29.8$, 29.3, 27.6, 27.2, 24.9, 21.6, 14.3, 9.4, 8.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{36} \mathrm{NO}_{5} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 474.2309; found: 474.2311.

## N-(2-(7-ethyl-6-hydroxy-7-(3-hydroxypropyl)-1-oxaspiro[4.4]nonan-4-yl)phenyl)-4methylbenzenesulfonamide (3.409)



To a solution of 3.407 ( $20 \mathrm{mg}, 0.029 \mathrm{mmol}, 1.0$ equiv) in $\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}(2: 1,0.2 / 0.1 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $p \mathrm{TsOH} \cdot \mathrm{H}_{2} \mathrm{O}$ ( $0.56 \mathrm{mg}, 0.003 \mathrm{mmol}, 0.1$ equiv) and Oxone ( $36 \mathrm{mg}, 0.058 \mathrm{mmol}, 4$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ) to yield the pure product 3.409 ( $12 \mathrm{mg}, 90 \%$ ) as a brown oil and as a 3:1 mixture of diastereoisomers.

## N-(2-(-3-((tert-butyldimethylsilyl)oxy)-1-(4-(3-((tert-butyldimethylsilyl)oxy)propyl)-4-ethyl-6-oxabicyclo[3.1.0]hexan-1-yl)propyl)phenyl)-4-methylbenzenesulfonamide (3.410)



To a solution of 3.407 ( $22 \mathrm{mg}, 0.032 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $1.3 \mathrm{~mL}, 0.025 \mathrm{M}$ ) was added $m C P B A$ ( $8.6 \mathrm{mg}, 0.038 \mathrm{mmol}, 1.2$ equiv). After being stirred 2 hours at room temperature, the reaction mixture was quenched with the addition of saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$,

PE/EtOAc 12:1) to yield the pure product $\mathbf{3 . 4 1 0}(22 \mathrm{mg}, 99 \%)$ as a brown oil and as a $3: 1$ mixture of diastereoisomers.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.46(\mathrm{~d}, J=36.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.66(\mathrm{dd}, J=8.3,3.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.60(\mathrm{dd}, J=8.1$, $1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.30(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.23-7.15(\mathrm{~m}, 3 \mathrm{H}), 7.11(\mathrm{~d}, J=4.4 \mathrm{~Hz}$, $2 \mathrm{H}), 3.68-3.47(\mathrm{~m}, 2 \mathrm{H}), 3.34(\mathrm{ddd}, J=11.3,7.8,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.23(\mathrm{dd}, J=11.4,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.13(\mathrm{~d}$, $J=5.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.10-2.96(\mathrm{~m}, 1 \mathrm{H}), 2.90(\mathrm{dd}, J=10.1,5.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.36(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 3 \mathrm{H}), 2.06-$ $1.87(\mathrm{~m}, 1 \mathrm{H}), 1.69$ (dddd, $J=13.5,10.7,6.7,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.57-1.08(\mathrm{~m}, 9 \mathrm{H}), 0.98-0.79(\mathrm{~m}, 24 \mathrm{H})$, $0.17-0.03(\mathrm{~m}, 12 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 143.4,143.3,138.1,136.4,136.3,135.8,133.4,129.7,127.7,127.6$, $127.4,127.2,125.7,125.6,124.8,71.5,70.7,69.0,63.9,60.8,60.5,45.2,45.1,44.9,33.7,31.0$, 30.4, 29.8, 29.6, 29.4, 28.1, 27.5, 26.2, 26.1, 26.1, 25.3, 22.8, 21.6, 21.6, 18.7, 18.5, 9.1, 8.1, -4.9, 5.1, -5.1, -5.2, -5.2.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{38} \mathrm{H}_{64} \mathrm{NO}_{5} \mathrm{SSi}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 702.4038$; found: 702.4040.

## 3-ethyl-9-(2-hydroxyethyl)-3-(3-hydroxypropyl)-4-tosyl-1,2,3,3a,4,9-hexahydro-9aH-cyclopenta[b]quinolin-9a-ol (3.411)



To a solution of $3.410\left(13 \mathrm{mg}, 0.019 \mathrm{mmol}, 1.0\right.$ equiv) in dry DCM $(0.38 \mathrm{~mL}, 0.05 \mathrm{M})$ at $-78^{\circ} \mathrm{C}$ was added $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}\left(3.2 \mu \mathrm{~L}, 0.025 \mathrm{mmol}, 1.3\right.$ equiv). After being stirred 3 hours at $0{ }^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ) to yield the pure product $\mathbf{3 . 4 1 1}(7 \mathrm{mg}, 78 \%)$ as a brown oil and as a 3:1 mixture of diastereoisomers.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.83(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.76-7.66(\mathrm{~m}, 1 \mathrm{H}), 7.29(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 2 \mathrm{H})$, 7.21 (ddd, $J=7.3,4.3,2.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.99(\mathrm{td}, J=7.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.64(\mathrm{~s}, 1 \mathrm{H}), 3.75-3.64(\mathrm{~m}, 3 \mathrm{H})$, $3.64-3.47(\mathrm{~m}, 1 \mathrm{H}), 3.28(\mathrm{dd}, J=11.7,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.95(\mathrm{ddt}, J=17.0,11.7,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.42(\mathrm{~s}, 3 \mathrm{H})$, $2.00-1.58(\mathrm{~m}, 2 \mathrm{H}), 1.58-1.15(\mathrm{~m}, 9 \mathrm{H}), 1.02(\mathrm{td}, \mathrm{J}=12.1,8.9 \mathrm{~Hz}, 1 \mathrm{H}), 0.84(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}{ }^{3}$ CNMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 144.3,141.7,139.0,135.4,130.0,127.6,126.8,125.9,123.1,115.7$, 83.4, 79.8, 63.6, 59.6, 45.5, 42.7, 32.4, 32.2, 31.4, 31.1, 30.7, 26.9, 21.7, 8.8.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{26} \mathrm{H}_{36} \mathrm{NO}_{5} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 474.2309$; found: 474.2310 .

## N-(2-(3-((tert-butyldimethylsilyl)oxy)-1-(4-ethyl-4-(3-((4-methylphenyl)sulfonamido)propyl)-6-oxabicyclo[3.1.0]hexan-1-yl)propyl)phenyl)-4-methylbenzenesulfonamide (trans-3.412)



To a solution of trans- 3.396 ( $20 \mathrm{mg}, 0.0276 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $1.1 \mathrm{~mL}, 0.025 \mathrm{M}$ ) was added mCPBA ( $7.5 \mathrm{mg}, 0.033 \mathrm{mmol}, 1.2$ equiv). After being stirred 2 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 12:1) to yield the pure product trans-3.412 (19 mg, 95\%) as a brown oil and as a 1:1 mixture of diastereoisomers.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, CDCl $_{3}$ ): $\delta 8.37(\mathrm{~s}, 1 \mathrm{H}), 8.18(\mathrm{~s}, 1 \mathrm{H}), 7.77-7.69(\mathrm{~m}, 7 \mathrm{H}), 7.66(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 3 \mathrm{H})$, $7.57(\mathrm{dd}, \mathrm{J}=8.1,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 3 \mathrm{H}), 7.21-7.03(\mathrm{~m}, 7 \mathrm{H}), 4.63(\mathrm{t}, \mathrm{J}=6.3 \mathrm{~Hz}, 1 \mathrm{H})$, $4.33(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.50(\mathrm{~d}, J=12.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.44(\mathrm{ddd}, J=10.4,6.7,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.24(\mathrm{ddd}, J=$ $11.6,7.4,4.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.43(\mathrm{~s}, 3 \mathrm{H}), 2.40(\mathrm{~s}, 7 \mathrm{H}), 2.36(\mathrm{~s}, 3 \mathrm{H}), 2.00(\mathrm{ddt}, J=11.0,6.8,3.4 \mathrm{~Hz}, 1 \mathrm{H})$, $1.75-1.64(\mathrm{~m}, 1 \mathrm{H}), 0.93(\mathrm{~s}, 10 \mathrm{H}), 0.89(\mathrm{~s}, 11 \mathrm{H}), 0.79(\mathrm{dt}, J=11.9,7.5 \mathrm{~Hz}, 7 \mathrm{H}), 0.13(\mathrm{~d}, \mathrm{~J}=3.1 \mathrm{~Hz}$, $6 \mathrm{H}), 0.06(\mathrm{~s}, 4 \mathrm{H}), 0.04(\mathrm{~s}, 4 \mathrm{H})$.
${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 143.6,143.4,138.3,137.2,137.0,136.0,135.7,129.9,129.8,129.7$, $127.7,127.4,127.3,127.3,127.3,126.2,68.0,60.8,60.4,45.0,44.9,44.1,34.0,31.6,31.0,30.4$, 30.1, 29.8, 29.0, 27.2, 27.0, 26.2, 26.1, 25.3, 24.4, 21.7, 18.7, 18.6, 9.2, 8.4, -5.0, -5.1, -5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{39} \mathrm{H}_{57} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{~S}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 741.3422; found: 741.3423.
N-(2-(3-((tert-butyldimethylsilyl)oxy)-1-(4-ethyl-4-(3-((4-methylphenyl)sulfonamido)propyl)-6-oxabicyclo[3.1.0]hexan-1-yl)propyl)phenyl)-4-methylbenzenesulfonamide (cis-3.412)


To a solution of cis-3.396 ( $200 \mathrm{mg}, 0.276 \mathrm{mmol}$, 1.0 equiv) in dry DCM ( $11 \mathrm{~mL}, 0.025 \mathrm{M}$ ) was added $m C P B A$ ( $93 \mathrm{mg}, 0.414 \mathrm{mmol}, 1.5$ equiv). After being stirred 2 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 12: 1$ ) to
yield the pure product cis-3.412 (202 mg, 99\%) as a brown oil and as a 10:1 mixture of diastereoisomers.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.45(\mathrm{~s}, 1 \mathrm{H}), 7.75(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.65(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.48(\mathrm{~d}, \mathrm{~J}=$ $7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.35-7.28(\mathrm{~m}, 2 \mathrm{H}), 7.25-7.15(\mathrm{~m}, 3 \mathrm{H}), 7.15-7.03(\mathrm{~m}, 2 \mathrm{H}), 4.51(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 1 \mathrm{H})$, 3.31 (ddd, $J=11.5,7.7,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.07(\mathrm{~s}, 1 \mathrm{H}), 3.06-2.97(\mathrm{~m}, 1 \mathrm{H}), 2.97-2.84(\mathrm{~m}, 4 \mathrm{H}), 2.42(\mathrm{~s}$, $3 \mathrm{H}), 2.37(\mathrm{~s}, 3 \mathrm{H}), 1.94(\mathrm{dtd}, J=13.3,7.9,5.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.78-1.57(\mathrm{~m}, 3 \mathrm{H}), 1.55-1.06(\mathrm{~m}, 7 \mathrm{H}), 0.88$ ( $\mathrm{s}, 9 \mathrm{H}), 0.80(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 0.03(\mathrm{~s}, 3 \mathrm{H}), 0.02(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}{ }^{\text {C NMR ( }} \mathbf{1 0 0} \mathbf{~ M H z}, \mathrm{CDCl}_{3}$ ): $\delta 143.5,143.5,138.0,137.0,136.2,133.3,129.9,129.7,127.8,127.4$, $127.3,127.2,125.8,124.9,71.6,68.8,60.7,45.1,44.0,33.6,30.7,30.0,26.2,26.1,25.5,25.1,21.7$, 21.6, 18.5, 8.1, -5.1, -5.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{39} \mathrm{H}_{57} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{~S}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 741.3422; found: 741.3424.

## N-(3-(7-ethyl-6-hydroxy-4-(2-((4-methylphenyl)sulfonamido)phenyl)-1-oxaspiro[4.4]nonan-7- <br> yl)propyl)-4-methylbenzenesulfonamide (3.414) and $N$-(3-(3-ethyl-9a-hydroxy-9-(2-hydroxyethyl)-4-tosyl-2,3,3a,4,9,9a-hexahydro-1H-cyclopenta[b]quinolin-3-yl)propyl)-4methylbenzenesulfonamide (3.413)



To a solution of cis-3.412 ( $20 \mathrm{mg}, 0.027 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $2.7 \mathrm{~mL}, 0.01 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}\left(4.5 \mu \mathrm{~L}, 0.035 \mathrm{mmol}, 1.3\right.$ equiv). After being stirred 3 hours at $0{ }^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ) to yield the pure product $\mathbf{3 . 4 1 4}$ ( $5 \mathrm{mg}, 28 \%$ ) as a brown oil and as a 10:1 mixture of diastereoisomers and 3.413 ( $7 \mathrm{mg}, 40 \%$ ) as a brown oil and as a $10: 1$ mixture of diastereoisomers.

## Spiro 3.414:

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.09(\mathrm{~s}, 1 \mathrm{H}), 7.69$ (ddd, $\left.J=28.1,15.8,8.1 \mathrm{~Hz}, 8 \mathrm{H}\right), 7.55(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}$, $3 \mathrm{H}), 7.30(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.26(\mathrm{~s}, 1 \mathrm{H}), 7.17-7.00(\mathrm{~m}, 9 \mathrm{H}), 6.95(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.99-5.65(\mathrm{~m}$, $1 \mathrm{H}), 4.93(\mathrm{t}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.53(\mathrm{~s}, 1 \mathrm{H}), 3.81(\mathrm{~s}, 2 \mathrm{H}), 3.64(\mathrm{~d}, J=21.0 \mathrm{~Hz}, 3 \mathrm{H}), 3.47(\mathrm{q}, J=8.3 \mathrm{~Hz}$, $2 \mathrm{H}), 3.32-3.12(\mathrm{~m}, 4 \mathrm{H}), 2.99-2.83(\mathrm{~m}, 1 \mathrm{H}), 2.72(\mathrm{~h}, \mathrm{~J}=7.0 \mathrm{~Hz}, 4 \mathrm{H}), 2.34(\mathrm{~d}, \mathrm{~J}=2.9 \mathrm{~Hz}, 8 \mathrm{H}), 2.30$ $(\mathrm{d}, \mathrm{J}=3.0 \mathrm{~Hz}, 8 \mathrm{H}), 1.82(\mathrm{dt}, J=17.6,8.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.75-1.51(\mathrm{~m}, 3 \mathrm{H}), 1.51-1.07(\mathrm{~m}, 22 \mathrm{H}), 1.06-$ 0.75 (m, 5H), 0.69 (dt, J = 15.5, 7.4 Hz, 7H).
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 144.3,143.6,143.5,143.3,141.6,138.9,137.8,137.2,137.0,135.5$, $130.0,129.9,129.8,129.6,127.6,127.4,127.3,127.2,127.2,126.8,126.2,125.9,123.2,115.7$, $95.7,84.3,83.2,65.6,59.3,47.4,45.2,44.0,43.7,42.5,34.6,33.6,32.1,31.5,31.1,30.1,30.0$, 28.2, 24.9, 23.3, 21.7, 21.6, 21.6, 9.0, 8.8.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{33} \mathrm{H}_{43} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{~S}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$627.2557; found: 627.2560.

## N-(3-(3-ethyl-9a-hydroxy-9-(2-hydroxyethyl)-4-tosyl-2,3,3a,4,9,9a-hexahydro-1H-cyclopenta[b]quinolin-3-yl)propyl)-4-methylbenzenesulfonamide (3.413)



To a solution of cis-3.412 (10 mg, 0.0135 mmol , 1.0 equiv) in dry THF ( $0.27 \mathrm{~mL}, 0.05 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added LiHMDS (1 M in THF, $30 \mu \mathrm{~L}, 0.0297 \mathrm{mmol}, 2.2$ equiv). After being stirred 5 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1\right)$ to yield the pure product 3.413 ( $6 \mathrm{mg}, 67 \%$ ) as a brown solid and as a 10:1 mixture of diastereoisomers.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.93(\mathrm{dd}, \mathrm{J}=8.2,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.86-7.76(\mathrm{~m}, 2 \mathrm{H}), 7.48(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}$, $2 \mathrm{H}), 7.32(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.28-7.23(\mathrm{~m}, 3 \mathrm{H}), 7.13(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.11-7.06(\mathrm{~m}, 1 \mathrm{H}), 6.97$ (dd, J = 7.5, 1.6 Hz, 1H), 4.86 (t, J = 5.8 Hz, 1H), $4.25(\mathrm{~s}, 1 \mathrm{H}), 3.02$ (dddd, J = 31.1, 21.4, 10.1, 3.4 Hz , $4 \mathrm{H}), 2.73(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.43(\mathrm{~s}, 3 \mathrm{H}), 2.32(\mathrm{~s}, 3 \mathrm{H}), 1.81-1.20(\mathrm{~m}, 20 \mathrm{H}), 1.07(\mathrm{dd}, \mathrm{J}=14.3,7.4$ $\mathrm{Hz}, 1 \mathrm{H}), 0.95(\mathrm{td}, J=6.9,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 0.89(\mathrm{~s}, 9 \mathrm{H}), 0.68(\mathrm{t}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 0.02(\mathrm{~d}, J=1.8 \mathrm{~Hz}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 143.5,143.3,137.2,137.0,135.9,129.9,129.8,129.4,127.8,127.5$, $127.4,126.4,126.2,126.0,86.1,72.2,62.0,50.9,47.8,44.0,40.3,33.2,32.5,31.8,29.8,26.6,26.1$, 25.9, 23.9, 21.7, 21.6, 18.4, 9.0, -5.3, -5.4.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{33} \mathrm{H}_{43} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{~S}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 627.2557 ; found: 627.2558 .
8.3.7 Macrocyclization

N-(3-((S)-1-ethyl-3-((S)-3-hydroxy-1-(2-nitrophenyl)propyl)cyclopent-2-en-1-yl)propyl)-4nitrobenzenesulfonamide (3.179)


To a solution of the alcohol $3.180(2.00 \mathrm{~g}, 4.47 \mathrm{mmol}, 1.0$ equiv), o-nitrophenylsulfonamide ( 1.08 $\mathrm{g}, 5.36 \mathrm{mmol}, 1.2$ equiv) and $\mathrm{PPyPh}_{2}(2.35 \mathrm{~g}, 8.94 \mathrm{mmol}, 2.0$ equiv) in dry THF ( $45 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at room temperature was added dropwise DBAD ( $2.06 \mathrm{~g}, 8.94 \mathrm{mmol}, 2.0$ equiv). After being stirred for 3 h at room temperature, 2 M HCl in $\mathrm{MeOH}(10 \mathrm{~mL})$ was added. After being stirred 1 hour, the reaction mixture was evaporated in vacuo. The crude residue was redissolved in $\mathrm{Et}_{2} \mathrm{O}$, cooled to 0 ${ }^{\circ} \mathrm{C}$ and filtered. The filtrate was stirred 30 min with 4 M HCl and extracted with DCM. The combined organic extracts were washed twice with 4 M HCl and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude alcohol $\mathbf{3 . 1 7 9}$ thus obtained was used for the next step without further purification.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.2-8.1(\mathrm{~m}, 1 \mathrm{H}), 8.0-7.8(\mathrm{~m}, 1 \mathrm{H}), 7.8-7.7(\mathrm{~m}, 2 \mathrm{H}), 7.7(\mathrm{dd}, \mathrm{J}=8.1$, $1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.6-7.5(\mathrm{~m}, 1 \mathrm{H}), 7.4-7.3(\mathrm{~m}, 2 \mathrm{H}), 5.3(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.2(\mathrm{~d}, \mathrm{~J}=1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.1(\mathrm{t}, \mathrm{J}$ $=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.6(\mathrm{dt}, J=11.7,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.6-3.5(\mathrm{~m}, 1 \mathrm{H}), 3.1(\mathrm{q}, J=6.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.2-2.1(\mathrm{~m}$, $1 \mathrm{H}), 2.0-1.9(\mathrm{~m}, 3 \mathrm{H}), 1.6-1.2(\mathrm{~m}, 8 \mathrm{H}), 0.7(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 150.9,148.2,144.5,137.1,134.1,133.7,132.9,132.7,132.6,131.2$, 129.1, 127.4, 125.5, 124.1, 60.8, 51.8, 44.8, 37.5, 36.8, 36.2, 33.4, 33.2, 32.3, 25.2, 9.2.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3565$ (br w), 3354 (br w), 2937 (w), 2852 (w), 1525 (m), 1352 (m), 1165 (m), 1051 (w), $909(\mathrm{~m}), 730$ ( s ).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{32} \mathrm{~N}_{3} \mathrm{O}_{7} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 518.1955$; found: 518.1954.
$[\alpha]_{D}{ }^{20}-93.3^{\circ}\left(c 0.3, \mathrm{CHCl}_{3}\right)$.
(1S,8S,E)-1-ethyl-8-(2-nitrophenyl)-5-((4-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)ene (1.184)


To a solution of the crude alcohol $\mathbf{3 . 1 7 9}$ ( $4.47 \mathrm{mmol}, 1.0$ equiv), neopentyl alcohol ( $98 \mathrm{mg}, 1.12$ mmol, 0.25 equiv) and $\mathrm{PPyPh}_{2}(2.94 \mathrm{~g}, 11.17 \mathrm{mmol}, 2.5$ equiv) in THF ( 447 mL ) at room temperature was added dropwise DBAD ( $2.57 \mathrm{~g}, 11.17 \mathrm{mmol}, 2.5$ equiv). After being stirred for 3 h at room temperature, 2 M HCl in $\mathrm{MeOH}(10 \mathrm{~mL})$ was added. After being stirred 1 hour, the reaction mix-
ture was evaporated in vacuo. The crude residue was redissolved in $\mathrm{Et}_{2} \mathrm{O}$, cooled to $0^{\circ} \mathrm{C}$ and filtered. The filtrate was stirred 30 min with 4 M HCl and extracted with DCM. The combined organic extracts were washed twice with 4 M HCl and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ) to yield the pure product 1.184 ( $1.98 \mathrm{~g}, 89 \%$ over 2 steps) as a yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.9(\mathrm{dd}, J=7.5,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.8(\mathrm{dd}, J=8.0,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.7-7.6(\mathrm{~m}$, $2 \mathrm{H}), 7.6-7.5(\mathrm{~m}, 3 \mathrm{H}), 7.4-7.3(\mathrm{~m}, 1 \mathrm{H}), 5.6(\mathrm{~d}, J=1.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.8(\mathrm{dd}, J=11.5,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.5$ (ddd, $J=15.5,7.6,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.3-3.2(\mathrm{~m}, 1 \mathrm{H}), 3.1(\mathrm{dt}, J=14.6,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.9$ (ddd, $J=15.4,7.1$, $2.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.5 (dddd, $J=15.1,11.5,7.3,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.5-2.3(\mathrm{~m}, 2 \mathrm{H}), 2.2$ (ddt, J = 15.1, 7.6, 2.9 $\mathrm{Hz}, 1 \mathrm{H}), 1.8-1.2(\mathrm{~m}, 8 \mathrm{H}), 0.9(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 149.7,149.0,140.7,137.6,137.4,133.7,132.9,131.4,131.2,131.0$, $129.6,127.4,124.5,124.0,54.5,52.5,48.7,42.1,39.2,38.3,35.6,33.3,32.1,22.3,9.8$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2958$ (w), 2932 (w), 2850 (w), 1545 ( s$), 1526$ (s), 1462 (w), 1354 (s), 1165 (m), 782 (m), 734 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{30} \mathrm{~N}_{3} \mathrm{O}_{6} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 500.1850$; found: 500.1853.
$[\alpha]_{\mathrm{D}}{ }^{20}+109.0^{\circ}(c 0.4, \mathrm{MeOH})$.

### 8.3.8 Domino Sequence

9-ethyl-2-(2-nitrophenyl)-5-((4-nitrophenyl)sulfonyl)-11-oxa-5-azatricyclo[7.2.2.0 ${ }^{1,10}$ ]tridecane (rac-cis-3.417)


To a solution of rac-cis-1.184 ( $36 \mathrm{mg}, 0.072 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $0.72 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added mCPBA ( $24 \mathrm{mg}, 0.108 \mathrm{mmol}, 1.5$ equiv). After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 3:1) to yield the pure product rac-cis-3.417 (30 mg, 81\%) as a brown oil and as a single diastereoisomer.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.89(\mathrm{dd}, J=7.7,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.76-7.63(\mathrm{~m}, 4 \mathrm{H}), 7.57$ (ddd, J=16.3, $7.9,1.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.35(\mathrm{ddd}, J=8.6,7.4,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.32(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.95(\mathrm{~s}, 1 \mathrm{H}), 3.93-3.84$ (m, 1H), 3.82 (dd, $J=11.5,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.72$ (ddd, $J=13.9,10.3,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.99-2.79(\mathrm{~m}, 2 \mathrm{H})$,
2.40 (dddd, $J=15.6,10.8,8.9,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.98 (ddd, $J=14.6,9.3,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.87-1.64(\mathrm{~m}, 4 \mathrm{H})$, $1.58-1.44(\mathrm{~m}, 2 \mathrm{H}), 1.44-1.33(\mathrm{~m}, 2 \mathrm{H}), 0.92(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 149.3,149.2,136.2,134.0,132.9,131.5,131.2,130.8,130.6,127.6$, $124.2,123.9,71.4,69.4,64.4,54.7,52.4,44.9,42.3,33.7,33.4,33.1,22.4,14.3,9.4$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2749$ (m), 2489 (w), 2222 (w), 1610 (w), 1491 (m), 1107 (s), 735 (m).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{30} \mathrm{~N}_{3} \mathrm{O}_{7} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 516.1799; found: 516.1801.

## 9a-ethyl-7-(2-nitrophenyl)octahydro-1H-cyclopenta[ij]quinolizin-7a(5H)-ol (rac-cis-3.418)



To a solution of epoxide rac-cis-3.417 ( $24 \mathrm{mg}, 0.047 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $1.0 \mathrm{~mL}, 0.05 \mathrm{M}$ ) were added $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( $13 \mathrm{mg}, 0.0931 \mathrm{mmol}, 2.0$ equiv) and PhSH ( $10 \mu \mathrm{~L}, 0.0931 \mathrm{mmol}, 2.0$ equiv). After being stirred 1 hour at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) to yield the pure product rac-cis-3.418 (82\%) as a colorless oil and as a single diastereoisomer.
(41R,7R,7aS,9aR)-9a-ethyl-7-(2-nitrophenyl)octahydro-1H-cyclopenta[ij]quinolizin-7a(5H)-ol (cis3.418)


To a solution of the alkene 1.184 ( $100 \mathrm{mg}, 0.20 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{NaHCO}_{3}(26 \mathrm{mg}, 0.30 \mathrm{mmol}$, 1.5 equiv) in DCM ( 2.0 mL ) at room temperature was added purified $m C P B A(412 \mathrm{mg}, 0.24 \mathrm{mmol}$, 1.2 equiv). After stirring for 2 h at room temperature, $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ ( $130 \mathrm{mg}, 0.40 \mathrm{mmol}, 2.0$ equiv) and $\mathrm{PhSH}(41 \mu \mathrm{~L}, 0.40 \mathrm{mmol}, 2.0$ equiv) were added sequentially. After stirring for 3 h at room temperature, the reaction mixture quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) to yield cis-3.418 (49 mg, 74\% yield) as colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.6(\mathrm{td}, J=8.2,1.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.5(\mathrm{td}, J=7.6,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.3(\mathrm{ddd}, J=$ $8.0,7.4,1.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.8(\mathrm{dd}, J=12.6,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.0(\mathrm{q}, J=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.7(\mathrm{t}, \mathrm{J}=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.4-$ $2.2(\mathrm{~m}, 1 \mathrm{H}), 2.2-2.1(\mathrm{~m}, 1 \mathrm{H}), 2.0-1.9(\mathrm{~m}, 1 \mathrm{H}), 1.9-1.2(\mathrm{~m}, 12 \mathrm{H}), 0.8(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 151.7,135.0,131.5,131.4,127.3,123.8,83.7,78.6,52.0,51.1,44.6$, $39.5,38.4,33.5,32.3,27.5,24.6,19.8,8.6$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3240$ (w), 2747 (m), 2489 (w), 1611 (w), 1486 (s), 1109 (w), 733 (m) 635 (m).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 331.2016; found: 331.2020.
$[\alpha]_{D}{ }^{20}+118.6^{\circ}(c 0.43, \mathrm{MeOH})$.

## 7-(2-aminophenyl)-9a-ethyloctahydro-1H-cyclopenta[ij]quinolizin-7a(5H)-ol (rac-3.420)



To a solution of the nitro rac-cis- $\mathbf{3 . 4 1 8}(66 \mathrm{mg}, 0.20 \mathrm{mmol}, 1.0$ equiv), $\mathrm{Zn}(65 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv) and $\mathrm{NH}_{4} \mathrm{Cl}(60 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv) in THF ( $20 \mathrm{~mL}, 0.01 \mathrm{M}$ ) was stirring for 6 h at reflux. The reaction mixture was cooled to room temperature quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 2$ ) to yield $\mathbf{3 . 4 2 0}$ ( 60 mg , quantitative yield) as colorless oil.
(41R,7R,7aS,9aR)-7-(2-aminophenyl)-9a-ethyloctahydro-1H-cyclopenta[ij]quinolizin-7a(5H)-ol (3.420)


To a solution of the alkene 1.184 ( $100 \mathrm{mg}, 0.20 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{NaHCO}_{3}(26 \mathrm{mg}, 0.30 \mathrm{mmol}$, 1.5 equiv) in DCM ( 2.0 mL ) at room temperature was added purified $m$ CPBA ( $412 \mathrm{mg}, 0.24 \mathrm{mmol}$, 1.2 equiv). After stirring for 2 h at room temperature, $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ ( $130 \mathrm{mg}, 0.40 \mathrm{mmol}, 2.0$ equiv) and $\mathrm{PhSH}(41 \mu \mathrm{~L}, 0.40 \mathrm{mmol}, 2.0$ equiv) were added sequentially. After stirring for 3 h at room temperature, $\mathrm{Zn}\left(65 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0\right.$ equiv), $\mathrm{NH}_{4} \mathrm{Cl}(60 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv) and THF ( 18 mL ) were added. After stirring for 6 h at reflux, the reaction mixture was cooled to room temperature quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was puri-
fied by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 2$ ) to yield 3.420 ( $41 \mathrm{mg}, 69 \%$ yield) as colorless oil.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3240$ (w), 2755 (m), 2489 (w), 1613 (w), 1486 (s), 1110 (w), 733 (m).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 301.2274; found: 301.2278.
$[\alpha]_{D}^{20}+75^{\circ}(c 0.25, \mathrm{EtOH})$.

## 13a-ethyl-2,3,41,5,6,6a,11,12,13,13a-decahydro-1H-cyclopenta[ij]indolo[2,3-a]quinolizine (rac-

 3.7)

To a solution of the alcohol rac-3.420 ( $60 \mathrm{mg}, 0.20 \mathrm{mmol}, 1.0$ equiv) in DCM/THF (1:9, $2 / 18 \mathrm{~mL}$, 0.01 M ) was added TAPC ( $348 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv). After stirring for 12 h at reflux, the reaction mixture was cooled to room temperature, quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1) to yield 3.7 ( $50 \mathrm{mg}, 89 \%$ yield) as colorless oil.
(41R,6aR,11aS,13aR)-13a-ethyl-2,3,41,5,6,6a,11,12,13,13a-decahydro-1H-cyclopenta[ij]indolo[2,3-a]quinolizine (3.7)


To a solution of the alkene 1.184 ( $100 \mathrm{mg}, 0.20 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{NaHCO}_{3}(26 \mathrm{mg}, 0.30 \mathrm{mmol}$, 1.5 equiv) in DCM ( 2.0 mL ) at room temperature was added purified $m$ CPBA ( $412 \mathrm{mg}, 0.24 \mathrm{mmol}$, 1.2 equiv). After stirring for 2 h at room temperature, $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ ( $130 \mathrm{mg}, 0.40 \mathrm{mmol}, 2.0$ equiv) and $\mathrm{PhSH}(41 \mu \mathrm{~L}, 0.40 \mathrm{mmol}, 2.0$ equiv) were added sequentially. After stirring for 3 h at room temperature, Zn ( $65 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv), $\mathrm{NH}_{4} \mathrm{Cl}(60 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv) and THF ( 18 mL ) were added. After stirring for 6 h at reflux, the reaction mixture was cooled to room temperature and TAPC ( $348 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv) was added. After stirring for 12 h at reflux, the reaction mixture was cooled to room temperature, quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ 2:1) to yield 3.7 ( $29 \mathrm{mg}, 52 \%$ yield) as colorless oil.

The analytical data were in accordance with those reported in the literature. ${ }^{192 a}$
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{27} \mathrm{~N}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 283.2169; found: 283.2171 .
$[\alpha]_{\mathrm{D}}{ }^{20}-85.6^{\circ}\left(c \quad 0.2, \mathrm{CHCl}_{3}\right)$.
rac-Vallesamidine (rac-3.1)


It was prepared according to a literature procedure. ${ }^{192 a}$

## (-)-Vallesamidine (3.1)



To a solution of the alkene 1.184 ( $100 \mathrm{mg}, 0.20 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{NaHCO}_{3}(26 \mathrm{mg}, 0.30 \mathrm{mmol}$, 1.5 equiv) in DCM ( 2.0 mL ) at room temperature was added purified mCPBA ( $412 \mathrm{mg}, 0.24 \mathrm{mmol}$, 1.2 equiv). After stirring for 2 h at room temperature, $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ ( $130 \mathrm{mg}, 0.40 \mathrm{mmol}, 2.0$ equiv) and PhSH ( $41 \mu \mathrm{~L}, 0.40 \mathrm{mmol}, 2.0$ equiv) were added sequentially. After stirring for 3 h at room temperature, Zn ( $65 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv), $\mathrm{NH}_{4} \mathrm{Cl}(60 \mathrm{mg}, 1.00 \mathrm{mmol}, 5.0$ equiv) and THF ( 18 mL ) were added. After stirring for 6 h at reflux, the reaction mixture was cooled to room temperature and TAPC ( $209 \mathrm{mg}, 0.60 \mathrm{mmol}, 3.0$ equiv) was added. After stirring for 12 h at reflux, the reaction mixture was cooled to room temperature and formalin ( 2 mL ), $\mathrm{NaBH}_{3} \mathrm{CN}(126 \mathrm{mg}, 2.00 \mathrm{mmol}, 10$ equiv) and $\mathrm{AcOH}(2 \mathrm{~mL})$ were added. After being stirred for 12 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield 3.1 ( $27 \mathrm{mg}, 45 \%$ yield) as colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.07(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.03(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H})$, $6.44(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.00-2.80(\mathrm{~m}, 3 \mathrm{H}), 2.73(\mathrm{~s}, 3 \mathrm{H}), 2.50-2.25(\mathrm{~m}, 3 \mathrm{H}), 2.12-1.35(\mathrm{~m}, 12 \mathrm{H})$, $0.90(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 3 \mathrm{H})$
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 151.3,134,8,127.1,122.9,117.51,107.6,78.9,73.0,50.4,50.0,44.4$, $44.2,35.4,31.2,31.0,30.3,27.4,26.5,18.4,9.1$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2751$ (m), 1608 (w), 1487 (s), 1112 (w), 734 (m).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{20} \mathrm{H}_{29} \mathrm{~N}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 297.2325; found: 297.2322.
$[\alpha]_{D}^{20}-71.4^{\circ}\left(c 0.25, \mathrm{CHCl}_{3}\right)$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, $3 \% \mathrm{NEt}_{3}$ in $\mathrm{MeOH}(3 \%), 230 \mathrm{~nm}$ ) $t_{\mathrm{R}}($ minor $)=7.8 \mathrm{~min}, t_{\mathrm{R}}($ major $)=9.1 \mathrm{~min}: 99.5: 0.5 \mathrm{er}$.

## (+)-1,2-dehydroaspidospermidine (3.2)



To a solution of alcohol 1.184 ( $50 \mathrm{mg}, 0.15 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $15 \mathrm{~mL}, 0.01 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added DBU ( $45 \mu \mathrm{~L}, 0.30 \mathrm{mmol}, 2.0$ equiv) and $\mathrm{SOCl}_{2}(17 \mu \mathrm{~L}, 0.23 \mathrm{mmol}, 1.5$ equiv). After stirring for 5 hours at $0{ }^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo (Temperature of the bath $=25^{\circ} \mathrm{C}$ !). The resulting crude was immediately dissolved in dry MeCN and $\mathrm{NH}_{4} \mathrm{OAc}\left(2.5 \mathrm{M}, 1.51 \mathrm{~mL}, 3.78 \mathrm{mmol}, 25.0\right.$ equiv) and $\mathrm{TiCl}_{3}$ ( $20 \mathrm{wt} \%$ in 2 $\mathrm{M} \mathrm{HCl}, 1.2 \mathrm{mmol}, 8.0$ equiv) were added. After being stirred for 12 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield $\mathbf{3 . 2}$ ( $29 \mathrm{mg}, 69 \%$ yield over 2 steps) as colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.51(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{~d}, \mathrm{~J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.24(\mathrm{~m}, 1 \mathrm{H})$, $7.16(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.23-3.14(\mathrm{~m}, 2 \mathrm{H}), 3.11$ (ddd, $J=14.1,12.0,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.76$ (ddd, $J=14.1$, $10.4,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.59$ (ddd, $J=11.4,8.4,5.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.46(\mathrm{td}, J=12.7,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.40(\mathrm{~s}, 1 \mathrm{H})$, $2.23-2.11(\mathrm{~m}, 2 \mathrm{H}), 1.85(\mathrm{qt}, J=13.0,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.65(\mathrm{dd}, J=12.3,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.62-1.52(\mathrm{~m}$, 2 H ), 1.47 (dt, J = 14.7, 3.2 Hz, 1H), $1.00(\mathrm{td}, \mathrm{J}=13.5,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 0.75-0.55(\mathrm{~m}, 2 \mathrm{H}), 0.49(\mathrm{t}, \mathrm{J}=7.3$ $\mathrm{Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 192.5, 154.7, 147.3, 127.6, 125.2, 121.1, 120.3, 61.4, 54.7, 52.2, 36.6, 35.3, 33.4, 29.9, 27.4, 23.9, 22.2, 7.4.

IR: $u\left(\mathrm{~cm}^{-1}\right) 2934$ (m), 2773 (m), 1575 (m), 1454 (m), 1324 (w), 1251 (w), 1195 (w), 1123 (w), 1014 (w), 752 (w), 616 (s).

HRMS (ESI) calcd for $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$281.2012; found 281.2013.
$[\alpha]_{\mathrm{D}}{ }^{20}+215^{\circ}(c 0.6, \mathrm{EtOH})$.

The enantiomeric purity was determined by SFC (Chiralcel, OD-H, 3\% NEt ${ }_{3}$ in $\mathrm{MeOH}(2 \%), 230 \mathrm{~nm}$ ) $t_{\mathrm{R}}($ minor $)=8.2 \mathrm{~min}, t_{\mathrm{R}}($ major $)=8.9 \mathrm{~min}: 99.5: 0.5 \mathrm{er}$.

## 8.4 (+)-Peganumine A

### 8.4.1 Strategy Based on a Bischler-Napieralski Reaction

9,9-dimethyl-1,4-dioxaspiro[4.4]non-6-ene (4.102)


Following a reported procedure, ${ }^{346}$ to a solution of $4.97(2.00 \mathrm{~g}, 23.78 \mathrm{mmol}, 1.00$ equiv) in ethylene glycol ( $30 \mathrm{~mL}, 0.8 \mathrm{M}$ ) was added dropwise $\mathrm{Br}_{2}(2.22 \mathrm{~mL}, 23.78 \mathrm{mmol}, 1.00$ equiv). After being stirred 24 hours at room temperature, the reaction mixture was quenched with the addition of water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the acetal 4.101 as a colorless oil which was directly used directly in the next step without further purification.

To a solution of acetal 4.101 ( 23.78 mmol, 1.00 equiv) in DMSO ( $48 \mathrm{~mL}, 0.5 \mathrm{M}$ ) was added portionwise $\mathrm{KO}^{\mathrm{t}} \mathrm{Bu}$ ( $6.67 \mathrm{~g}, 59.45 \mathrm{mmol}, 2.50$ equiv). After being stirred 4 days at room temperature, the reaction mixture was quenched with the addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 19: 1$ ) to yield the pure product 4.102 ( $1.83 \mathrm{~g}, 50 \%$ over 2 steps) as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.79-5.43(\mathrm{~m}, 2 \mathrm{H}), 4.01-3.65(\mathrm{~m}, 4 \mathrm{H}), 2.37(\mathrm{~d}, \mathrm{~J}=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 0.98$ ( $s, 6 H$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 138.7,128.4,122.0,65.7,45.6,44.7,24.2$.
HRMS (ESI): $m / z$ calcd $\mathrm{C}_{9} \mathrm{H}_{15} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 155.1067; found: 155.1069.
methyl 2-(4-methoxy-2-methyl-4-oxobutan-2-yl)-1,3-dioxolane-2-carboxylate (4.103) and 2-(4-methoxy-2-methyl-4-oxobutan-2-yl)-1,3-dioxolane-2-carboxylic acid (4.104)


Following a reported procedure, ${ }^{347}$ to a solution of the cyclopentene 4.102 ( $122 \mathrm{mg}, 0.796 \mathrm{mmol}$, 1.00 equiv) in dry $\mathrm{MeOH} / \mathrm{DCM}(1: 4,1.7 / 6.8 \mathrm{~mL}, 0.094 \mathrm{M}$ ) at room temperature was added NaOH ( $170 \mathrm{mg}, 3.98 \mathrm{mmol}, 5.00$ equiv). The reaction mixture was cooled to $-78^{\circ} \mathrm{C}$ and ozone was bubbled through the solution. The reaction mixture became yellow, then blue, then colorless then
finally blue again. Oxygen was bubbled through the solution until the blue color disappeared and water was added to quench the reaction. The solution was warm to room temperature and extracted with ether. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the dimethylester 4.103 a colorless oil. The aqueous layer was acidified to $\mathrm{pH}=1$ with the addition of 6 M HCl and extracted again with ether. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the acid 4.104 as a colorless oil ( $97 \%$ combined yield).

## Diester 4.103:

${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}$, Methanol- $\boldsymbol{d}_{4}$ ): $\delta 4.04-3.91(\mathrm{~m}, 4 \mathrm{H}), 3.84(\mathrm{~s}, 3 \mathrm{H}), 3.59(\mathrm{~s}, 3 \mathrm{H}), 2.52(\mathrm{~s}, 2 \mathrm{H}), 1.05$ ( $s, 6 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 172.2,169.4,111.5,65.9,52.9,52.8,42.8,38.6,23.2$.
IR: v $\left(\mathrm{cm}^{-1}\right) 1770$ (s), 1741 (s), 1540 (m), 932 (m), 771 (m).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{19} \mathrm{O}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 247.1176; found: 247.1179 .

## Monoester acid 4.104:

${ }^{1} \mathrm{H}$ NMR (400 MHz, Methanol- $d_{4}$ ): $\delta 4.14-3.89(\mathrm{~m}, 4 \mathrm{H}), 3.59(\mathrm{~s}, 3 \mathrm{H}), 2.52(\mathrm{~s}, 2 \mathrm{H}), 1.05(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 172.2,170.8,109.6,66.0,52.9,42.9,38.5,23.2$.
IR: v ( $\mathrm{cm}^{-1}$ ) 3220 (br), 3207 (br), 1771 (s), 1746 (s), 1549 (m), 956 (m), 729 (m).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{O}_{6}\left([\mathrm{M}-\mathrm{H}]^{-}\right):$233.1020; found: 233.1022.

## 2-(1-carboxy-2-methylpropan-2-yl)-1,3-dioxolane-2-carboxylic acid (4.105)



To a solution of the diester 4.103 or the monoester 4.104 or a mixture of both ( $0.049 \mathrm{mmol}, 1.00$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}$ (1:1, $0.2 / 0.2 \mathrm{~mL}, 0.13 \mathrm{M}$ ) was added NaOH ( $8.0 \mathrm{mg}, 0.2$ mmol, 4.00 equiv). The reaction mixture was stirred overnight at room temperature and then evaporated in vacuo. The crude was redissolved in saturated aqueous $\mathrm{NaHCO}_{3}$ and washed with DCM. The aqueous layer was acidified to $\mathrm{pH}=1$ with the addition of 6 M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the diacid 4.105 ( $9.1 \mathrm{mg}, 98 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, Methanol-d $\mathrm{d}_{4}$ ): $\delta 4.13-3.72(\mathrm{~m}, 4 \mathrm{H}), 2.51(\mathrm{~s}, 2 \mathrm{H}), 1.05(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, Methanol- $d_{4}$ ): $\delta$ 175.5, 170.8, 109.6, 66.0, 42.2, 38.9, 23.1.
IR: v(cm $\left.{ }^{-1}\right) 3200$ (br), 3150 (br), 1741 (s), 1701 (s), 1540 (m), 952 (m), 748 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{O}_{6}$ ([M] $]^{-}$): 217.0718; found: 217.0720.

## 3,3-dimethyl-2-oxopentanedioic acid (4.106)



To a solution of acid 4.105 ( $44 \mathrm{mg}, 0.2 \mathrm{mmol}, 1.00$ equiv) in dry THF ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $5 \%$ $\mathrm{HCl}(2 \mathrm{~mL})$. After 12 hours at room temperature, the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the pure product $\mathbf{4 . 1 0 6}(30 \mathrm{mg}, 86 \%)$ as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 11.92(\mathrm{~s}, 1 \mathrm{H}), 8.54(\mathrm{~s}, 1 \mathrm{H}), 2.73(\mathrm{~s}, 2 \mathrm{H}), 1.38(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 191.7,174.5,161.4,41.8,39.7,25.5$.
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{7} \mathrm{H}_{9} \mathrm{O}_{5}([\mathrm{M}-\mathrm{H}])$ : 173.0455 ; found: 173.0451 .
methyl 2-(4-methoxy-2-methyl-4-oxobutan-2-yl)-1,3-dioxolane-2-carboxylate (4.107)


To a solution of acid 4.104 or a mixture of acid 4.104 and ester 4.103 ( $6.85 \mathrm{mmol}, 1.00$ equiv) in benzene/ $\mathrm{MeOH}\left(7: 2,50 / 14 \mathrm{~mL}, 0.11 \mathrm{M}\right.$ ) at $0^{\circ} \mathrm{C}$ was added dropwise TMS diazomethane ( 0.6 M in hexane, $15.06 \mathrm{mmol}, 2.20$ equiv). After being stirred 4 hours at room temperature, concentrated acetic acid was added to quench the reaction and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the pure product $\mathbf{4 . 1 0 7}$ ( 1382 mg , quantitative yield) as a yellowish amorphous solid.
dimethyl 3,3-dimethyl-2-oxopentanedioate (4.108)


To a solution of ester 4.107 ( $46 \mathrm{mg}, 0.2 \mathrm{mmol}, 1.00$ equiv) in dry THF ( $2.0 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $5 \% \mathrm{HCl}(2 \mathrm{~mL})$. After 6 hours at room temperature, the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the pure product $\mathbf{4 . 1 0 8}(28 \mathrm{mg}, 69 \%)$ as a yellowish amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 3.79(\mathrm{~s}, 1 \mathrm{H}), 3.59(\mathrm{~s}, 1 \mathrm{H}), 2.74(\mathrm{~s}, 1 \mathrm{H}), 1.37(\mathrm{~s}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 199.4, 170.6, 165.0, 53.2, 51.7, 43.2, 42.7, 25.5 .

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{9} \mathrm{H}_{15} \mathrm{O}_{5}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 203.0914; found: 203.0914.

## N -(2-(1H-indol-3-yl)ethyl)-3-oxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)carboxamide (4.125)



To a solution of $\alpha$-ketoglutaric acid (4.124) ( $2.00 \mathrm{~g}, 13.7 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( 228 mL , 0.06 M ) was added tryptamine (1.16) ( $4.40 \mathrm{~g}, 27.4 \mathrm{mmol}, 2.00$ equiv), HOBt ( $3.72 \mathrm{~g}, 27.4 \mathrm{mmol}$, 2.00 equiv) and EDC•HCl ( $5.28 \mathrm{~g}, 27.4 \mathrm{mmol}, 2.00$ equiv) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM and saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} /\right.$ Acetone $\left.4: 1+2 \% \mathrm{NEt}_{3}\right)$ to yield the pure product 4.125 ( 4408 mg , 78\%) as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.66(\mathrm{~s}, 1 \mathrm{H}), 7.91(\mathrm{~s}, 1 \mathrm{H}), 7.48-7.34(\mathrm{~m}, 2 \mathrm{H}), 7.27(\mathrm{~m}, 2 \mathrm{H}), 7.12(\mathrm{~m}$, $2 H$ ), 7.05 (ddd, $J=8.0,7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.94$ (ddd, $J=8.0,7.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.78(\mathrm{~d}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H})$, $6.28(\mathrm{t}, J=5.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.27(\mathrm{ddd}, J=12.8,5.6,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.65-3.50(\mathrm{~m}, 1 \mathrm{H}), 3.50-3.37(\mathrm{~m}, 1 \mathrm{H})$, $3.02-2.80(\mathrm{~m}, 2 \mathrm{H}), 2.66$ (dddd, $J=15.7,11.6,5.8,3.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.57(\mathrm{dd}, J=4.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.56-$ $2.42(\mathrm{~m}, 1 \mathrm{H}), 2.42-2.22(\mathrm{~m}, 2 \mathrm{H}), 2.19-2.03(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 175.4,171.7,136.8,136.4,132.1,127.3,126.3,122.7,122.5,122.2$, $119.9,119.8,118.6,118.6,112.3,111.6,111.5,108.3,65.8,40.2,37.5,33.5,30.6,24.8,21.2$.

IR: v (cm ${ }^{-1}$ ) 3490 (br), 3350 (s), 1706 (s), 1602 (m), 1304 (s), 800 (w), 775 (w), 500 (w).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{25} \mathrm{~N}_{4} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 413.1972; found: 413.1970.

## 3-oxo-N-(2-(1-((trifluoromethyl)sulfonyl)-1H-indol-3-yl)ethyl)-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)-carboxamide (4.127)



To a solution of indole 4.125 ( $20 \mathrm{mg}, 0.048 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $1.0 \mathrm{~mL}, 0.05 \mathrm{M}$ ) at -40 ${ }^{\circ} \mathrm{C}$ was added dropwise pyridine ( $28 \mu \mathrm{~L}, 0.339 \mathrm{mmol}, 7.00$ equiv) and $\mathrm{Tf}_{2} \mathrm{O}(21 \mu \mathrm{~L}, 0.126 \mathrm{mmol}$, 2.60 equiv). After being stirred 2 hours at room temperature, the reaction mixture was quenched with the addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined
organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, $\mathrm{DCM} /$ Acetone $6: 1+2 \% \mathrm{NEt}_{3}$ ) to yield the pure product $\mathbf{4 . 1 2 7}(23 \mathrm{mg}, 87 \%)$ as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.80(\mathrm{~s}, 1 \mathrm{H}), 7.85(\mathrm{dd}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.48(\mathrm{dq}, J=7.9,1.0 \mathrm{~Hz}, 2 \mathrm{H})$, $7.41-7.32(\mathrm{~m}, 2 \mathrm{H}), 7.24-7.16(\mathrm{~m}, 3 \mathrm{H}), 7.13(\mathrm{ddd}, J=8.0,7.1,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.88(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 1 \mathrm{H})$, $4.53-4.41(\mathrm{~m}, 1 \mathrm{H}), 3.74(\mathrm{ddt}, J=13.4,7.2,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.53$ (dtd, $J=13.3,7.4,5.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.03-$ $2.91(\mathrm{~m}, 2 \mathrm{H}), 2.84-2.67(\mathrm{~m}, 4 \mathrm{H}), 2.54-2.37(\mathrm{~m}, 2 \mathrm{H}), 2.34-2.20(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 175.6,172.2,136.9,135.7,131.9,130.9,126.3,126.3,125.0,124.5$, $123.1,122.8,122.1,120.0,119.9,119.68$ (q, J = 323.9 Hz ), 118.7, 115.2, 115.1, 115.1, 115.0, 114.8, $114.8,114.7,114.5,114.2,114.1,111.7,108.4,65.9,39.4,37.9,33.8,30.7,24.8,21.3$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{26} \mathrm{H}_{24} \mathrm{~F}_{3} \mathrm{~N}_{4} \mathrm{O}_{4} \mathrm{~S}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 545.1465 ; found: 545.1666.
11-benzyl-N-(2-(1-benzyl-1H-indol-3-yl)ethyl)-3-oxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)-carboxamide (4.128)


Following a reported procedure, ${ }^{356}$ the amide 4.125 ( $860 \mathrm{mg}, 2.08 \mathrm{mmol}, 1.00$ equiv), $\mathrm{NaOH}(500$ $\mathrm{mg}, 12.5 \mathrm{mmol}, 6.00$ equiv), and the ammonium salt ( $71 \mathrm{mg}, 0.21 \mathrm{mmol}, 0.10$ equiv) were dissolved in dry DCM ( $11 \mathrm{~mL}, 0.20 \mathrm{M}$ ) and stirred at room temperature for 10 minutes. Benzyl bromide ( $549 \mu \mathrm{~L}, 4.57 \mathrm{mmol}, 2.20$ equiv) was added and the reaction was stirred for 20 hours. Water was added and the reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} /\right.$ Acetone $\left.9: 1\right)$ to yield the desired product 4.128 ( $924 \mathrm{mg}, 75 \%$ ) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.50(\mathrm{~m}, 2 \mathrm{H}), 7.33-7.13(\mathrm{~m}, 8 \mathrm{H}), 7.12-6.93(\mathrm{~m}, 5 \mathrm{H}), 6.83-6.69(\mathrm{~m}$, $2 \mathrm{H}), 6.63(\mathrm{~s}, 1 \mathrm{H}), 5.73(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.29(\mathrm{~d}, J=17.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.05(\mathrm{~d}, \mathrm{~J}=17.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.02-4.91(\mathrm{~m}$, $2 \mathrm{H}), 4.34(\mathrm{dd}, \mathrm{J}=12.9,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.47(\mathrm{q}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.88(\mathrm{t}, J=6.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.83-2.57(\mathrm{~m}$, $5 \mathrm{H}), 2.34-2.22(\mathrm{~m}, 1 \mathrm{H}), 1.88(\mathrm{dt}, J=12.3,9.9 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 176.2,176.1,138.2,137.6,136.7,134.6,128.9,128.8,128.4,127.7$, $127.3,126.9,126.9,126.2,125.8,122.6,121.8,119.6,119.5,118.9,118.7,111.2,110.3,109.9$, 109.3, 69.5, 49.8, 49.5, 42.1, 37.0, 30.1, 28.1, 27.4, 25.1, 20.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{39} \mathrm{H}_{37} \mathrm{~N}_{4} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 593.2911; found: 593.2910.
IR: v (cm ${ }^{-1}$ ) 3348 (s), 1708 (s), 1600 (m), 1309 (s), 809 (w), 769 (w), 540 (w).
tert-butyl (2-(1-benzyl-1H-indol-3-yl)ethyl)(11-benzyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-11b-carbonyl)carbamate (4.138)


Following a reported procedure, ${ }^{360}$ to a solution of the amide $4.128(100 \mathrm{mg}, 0.169 \mathrm{mmol}, 1.00$ equiv) in dry THF ( $0.5 \mathrm{~mL}, 0.25 \mathrm{M}$ ) at $-78^{\circ} \mathrm{C}$ was added LiHMDS ( 1 M in THF, $0.194 \mathrm{~mL}, 0.194 \mathrm{mmol}$, 1.15 equiv) dropwise. After 5 minutes, $\mathrm{Boc}_{2} \mathrm{O}(74 \mathrm{mg}, 0.34 \mathrm{mmol}, 2.00$ equiv) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$ to yield the pure product 4.138 ( $101 \mathrm{mg}, 86 \%$ ) as an amorphous white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.51(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.44-7.33(\mathrm{~m}, 1 \mathrm{H}), 7.24-6.99(\mathrm{~m}, 13 \mathrm{H}), 6.98$ $-6.90(\mathrm{~m}, 3 \mathrm{H}), 6.89-6.81(\mathrm{~m}, 2 \mathrm{H}), 6.75(\mathrm{~s}, 1 \mathrm{H}), 5.74(\mathrm{~d}, \mathrm{~J}=18.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.52(\mathrm{~d}, \mathrm{~J}=18.1 \mathrm{~Hz}, 1 \mathrm{H})$, $4.92(\mathrm{~d}, J=3.5 \mathrm{~Hz}, 2 \mathrm{H}), 4.29(\mathrm{dd}, J=13.2,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.99(\mathrm{ddd}, J=13.5,8.9,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.61$ (ddd, J = 13.9, 9.1, $5.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.06-2.90(\mathrm{~m}, 3 \mathrm{H}), 2.84$ (ddd, $J=15.6,12.0,6.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.71 (ddd, $J=12.5,11.1,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.57$ (ddd, $J=16.0,11.1,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.33$ (ddd, $J=16.9,13.9,4.6 \mathrm{~Hz}$, $2 H$ ), 2.11 (ddd, $J=17.0,11.0,6.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.36 (s, 9 H ).
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 176.8,176.6,153.8,138.2,137.6,136.7,134.9,128.9,128.8,128.1$, 127.7, 127.2, 126.9, 126.7, 126.2, 125.7, 122.7, 121.9, 119.6, 119.3, 118.9, 118.8, 111.2, 110.8, 109.9, 109.3, 84.2, 69.5, 49.8, 49.5, 48.1, 37.0, 30.1, 28.4, 28.0, 27.1, 25.0, 20.3.

IR: v(cm $\left.{ }^{-1}\right) 3340$ (s), 1703 (s), 1680 (m), 1301 (s), 825 (w), 792 (w), 598 (w).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{39} \mathrm{H}_{37} \mathrm{~N}_{4} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 593.2911; found: 593.2906.
methyl 3-oxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)-carboxylate (4.139)


It was prepared according to a literature procedure. ${ }^{368}$
methyl 3-thioxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)-carboxylate (4.140)


It was prepared according to a literature procedure. ${ }^{363}$

## 3-thioxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)-carboxylic acid (4.146)



Following a reported procedure, ${ }^{364}$ to a solution of the thioamide 4.140 ( $48 \mathrm{mg}, 0.16 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{MeOH} / \mathrm{THF} / \mathrm{H}_{2} \mathrm{O}(0.21 \mathrm{~mL} / 0.12 \mathrm{~mL} / 0.1 \mathrm{~mL}, 1 \mathrm{M})$ was added $\mathrm{LiOH}(10 \mathrm{mg}, 0.40 \mathrm{mmol}, 2.50$ equiv) at $0^{\circ} \mathrm{C}$. After being stirred 3 hours at room temperature, the reaction mixture was diluted with water and washed with ether. The aqueous layer was acidified to $\mathrm{pH}=1$ with the addition of 6 M HCl and extracted with ether. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the pure product $4.146(37 \mathrm{mg}, 80 \%)$ as an amorphous yellow solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $-d_{4}$ ): $\delta 7.32(\mathrm{dt}, \mathrm{J}=8.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.28-7.21(\mathrm{~m}, 1 \mathrm{H}), 7.01$ (ddd, J = $8.2,7.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.90$ (ddd, $J=8.0,7.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.12$ (ddd, $J=13.0,5.9,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.36$ (ddd, J = 13.0, 11.6, 5.4 Hz, 1H), 3.01-2.90 (m, 2H), 2.86-2.62 (m, 3H), 2.16-2.01 (m, 1H).
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta$ 202.2, 172.6, 138.6, 131.7, 127.1, 123.2, 120.2, 119.3, 112.4, 108.8, 74.1, 44.6, 42.8, 34.1, 21.2.

IR: v ( $\mathrm{cm}^{-1}$ ) 3498 (br), 3330 (br), 1666 (m), 1145 (s), 849 (w), 703 (w), 565 (w).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{~S}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 285.0703; found: 285.0706 .

## $N$-(2-(1H-indol-3-yl)ethyl)-3-thioxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-11b(5H)carboxamide (4.141)



Following a reported procedure,Error! Bookmark not defined. to a solution of the thioamide $.146(42 \mathrm{mg}, 0.176 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $0.3 \mathrm{~mL}, 0.5 \mathrm{M}$ ) were added tryptamine (1.16) ( $32 \mathrm{mg}, 0.16 \mathrm{mmol}, 1.10$ equiv), $\mathrm{HOBt}(24 \mathrm{mg}, 0.18 \mathrm{mmol}, 1.20$ equiv), $\mathrm{EDC} \cdot \mathrm{HCl}(31 \mathrm{mg}, 0.16 \mathrm{mmol}$, 1.10 equiv) and triethylamine ( $43 \mu \mathrm{~L}, 0.31 \mathrm{mmol}, 2.10$ equiv). After being stirred overnight at room
temperature, the reaction mixture was diluted with DCM and saturated aqueous $\mathrm{NaHCO}_{3}$, and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$ to yield the pure product $4.141(38 \mathrm{mg}, 60 \%)$ as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.59(\mathrm{~s}, 1 \mathrm{H}), 8.07(\mathrm{~s}, 1 \mathrm{H}), 7.50(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.38(\mathrm{ddd}, \mathrm{J}=16.8$, $10.9,8.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.31-7.11(\mathrm{~m}, 4 \mathrm{H}), 7.06$ (ddd, J = 7.9, 6.9, $1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.91(\mathrm{~d}, \mathrm{~J}=2.3 \mathrm{~Hz}, 1 \mathrm{H})$, $5.92(\mathrm{t}, \mathrm{J}=5.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.45-5.28(\mathrm{~m}, 1 \mathrm{H}), 5.24-5.07(\mathrm{~m}, 1 \mathrm{H}), 3.69-3.42(\mathrm{~m}, 2 \mathrm{H}), 3.29-2.66(\mathrm{~m}$, $8 \mathrm{H}), 2.31(\mathrm{td}, \mathrm{J}=12.3,9.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.16(\mathrm{td}, \mathrm{J}=11.9,9.1 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 203.1, 169.8, 138.4, 136.8, 136.4, 131.0, 128.6, 127.8, 126.8, 126.0, $122.8,122.4,120.0,119.7,118.4,115.8,112.1,111.5,73.0,43.7,42.2,40.1,34.9,24.4,20.7$.

IR: v (cm ${ }^{-1}$ ) 3501 (br), 3345 (s), 1660 (m), 1145 (s), 812 (w), 780 (w), 598 (w).
HRMS (ESI): $m / z$ calcd $\mathrm{C}_{25} \mathrm{H}_{25} \mathrm{~N}_{4} \mathrm{OS}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 429.1744; found: 429.1740 .
(E)-2-(1H-indol-3-yl)-N-(11b-(methoxycarbonyl)-1,2,5,6,11,11b-hexahydro-3H-indolizino[8,7-b]indol-3-ylidene)ethan-1-aminium trifluoromethanesulfonate (4.142)


Following a reported procedure, ${ }^{366}$ to a solution of the thioamide 4.146 ( $200 \mathrm{mg}, 0.67 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $3.3 \mathrm{~mL}, 0.20 \mathrm{M}$ ) was added dropwise MeOTf ( $133 \mu \mathrm{~L}, 1.17 \mathrm{mmol}, 1.76$ equiv). After 30 minutes at room temperature, the reaction mixture was evaporated in vacuo. Tryptamine (1.16) ( $213 \mathrm{mg}, 1.33 \mathrm{mmol}, 2.00$ equiv) and pyridine ( $3.3 \mathrm{~mL}, 0.2 \mathrm{M}$ ) were added to the residue. After being stirred overnight at room temperature, the reaction mixture was evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, 9: 1 \mathrm{DCM} / \mathrm{MeOH}$ ) to yield the pure compounds 4.149 ( 380 mg , quantitative yield) as an amorphous yellow solid. The free base could easily be obtained by basic extraction ( $\mathrm{NaOH} 6 \mathrm{M} / E t O A c$ ) to yield the amidine 4.142 ( 284 mg , quantitative yield) as a yellowish amorphous solid.

## Amidinium 4.149:

${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $d_{4}$ ): $\delta 7.51(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.48(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{~d}, J=8.1$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 7.26 (d, $J=7.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.17 (ddd, $J=8.2,7.1,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.11(\mathrm{~s}, 1 \mathrm{H}), 7.07$ (ddd, $J=8.0$, $7.1,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.88$ (ddd, $J=8.1,6.9,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.83(\mathrm{td}, J=7.4,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.34(\mathrm{dt}, \mathrm{J}=13.7$, $3.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.76(\mathrm{~s}, 3 \mathrm{H}), 3.67-3.50(\mathrm{~m}, 2 \mathrm{H}), 3.15-3.07(\mathrm{~m}, 2 \mathrm{H}), 2.98-2.88(\mathrm{~m}, 2 \mathrm{H}), 2.66-2.47$ (m, 2H), 2.32 (dd, J = 17.0, 8.5 Hz, 1H), 1.55 (ddd, $J=12.2,10.8,9.1 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 170.7,168.9,138.5,138.0,129.7,128.4,126.8,124.5,123.7$, $122.6,120.5,120.3,119.4,118.8,112.5,111.9,108.3,72.4,54.1,41.2,32.2,29.8,26.5,21.3$.

IR: $v\left(\mathrm{~cm}^{-1}\right) 3504$ (br), 1600 (m), 1742 (s), 1672 (m), 1520(m), 865 (w), 749 (w), 599 (w).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{~N}_{4} \mathrm{O}_{2}\left([\mathrm{M}-\mathrm{OTf}]^{+}\right): 427.2129$; found: 427.2125.

## Amidine 4.142:

${ }^{1} \mathrm{H}$ NMR (400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 8.24(\mathrm{~s}, 1 \mathrm{H}), 7.92(\mathrm{~s}, 1 \mathrm{H}), 7.61(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{~d}, J=$ $7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.34-7.20(\mathrm{~m}, 3 \mathrm{H}), 7.12(\mathrm{dt}, J=11.7,7.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.04(\mathrm{t}, J=$ $7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.98(\mathrm{~d}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.65(\mathrm{dd}, J=13.6,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.84-3.66(\mathrm{~m}, 4 \mathrm{H}), 3.60(\mathrm{dt}, J=$ $13.4,6.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.55-3.44(\mathrm{~m}, 1 \mathrm{H}), 3.38-3.26(\mathrm{~m}, 1 \mathrm{H}), 3.05(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.98$ (ddd, $\mathrm{J}=$ $17.3,11.7,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.73(\mathrm{dd}, J=15.6,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.58-2.45(\mathrm{~m}, 1 \mathrm{H}), 2.23(\mathrm{dd}, J=9.3,6.1 \mathrm{~Hz}$, $2 H$ ).

IR: v(cm $\left.{ }^{-1}\right) 3302$ (br), 1612 (m), 1726 (s), 1679 (m), 1523(m), 866 (w), 751 (w), 612 (w).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{~N}_{4} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 427.2129; found: 427.2125.

### 8.4.2 Strategy Based on a Liebeskind-Srogl Coupling

## 1-(2-carboxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylic acid (4.172)



It was prepared according to a literature procedure. ${ }^{377}$
methyl 1-(3-methoxy-3-oxopropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (4.173)


To a solution of acid 4.172 ( $400 \mathrm{mg}, 1.387 \mathrm{mmol}, 1.00$ equiv) in toluene/ MeOH ( $2: 1,10 / 5 \mathrm{~mL}, 0.1$ M ) was added diazomethane ( 2 M in $\mathrm{Et}_{2} \mathrm{O}, 1.53 \mathrm{~mL}, 3.05 \mathrm{mmol}, 2.20$ equiv). After being stirred 2 hours at room temperature, concentrated acetic acid was added to quench the reaction and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the pure product 4.173 ( 441 mg , quantitative yield) as a brown amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 7.84(\mathrm{~s}, 1 \mathrm{H}), 7.42(\mathrm{dt}, J=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.22(\mathrm{~m}, 1 \mathrm{H})$, 7.07 (ddd, $J=8.2,7.0,1.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 6.99 (ddd, $J=8.1,7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.67(\mathrm{~s}, 3 \mathrm{H}), 3.52(\mathrm{~s}, 3 \mathrm{H}), 3.37$

- $3.22(\mathrm{~m}, 1 \mathrm{H}), 2.93-2.76(\mathrm{~m}, 2 \mathrm{H}), 2.73-2.55(\mathrm{~m}, 2 \mathrm{H}), 2.48-2.36(\mathrm{~m}, 1 \mathrm{H}), 2.18(\mathrm{ddd}, \mathrm{J}=15.7$, $8.5,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.85$ (ddd, J = 16.1, 8.7, $5.7 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13}$ C NMR (101 MHz, Methanol- $\boldsymbol{d}_{4}$ ): $\delta$ 176.0, 174.0, 138.4, 132.4, 127.8, 122.6, 119.8, 118.9, 112.0, 111.9, 67.0, 52.0, 51.9, 38.6, 29.9, 29.6, 22.2.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$317.1496; found: 319.1498.

## 2-benzyl 1-methyl 1-(3-methoxy-3-oxopropyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-1,2dicarboxylate (4.175)



To a solution of amine 4.173 ( $50 \mathrm{mg}, 0.158 \mathrm{mmol}, 1.00$ equiv) and DIPEA ( $31 \mu \mathrm{~L}, 0.174 \mathrm{mmol}, 1.10$ equiv) in dry $\operatorname{DCM}(1.58 \mathrm{~mL}, 0.1 \mathrm{M})$ at $0^{\circ} \mathrm{C}$ was added $\mathrm{CbzCl}(25 \mu \mathrm{~L}, 1.74 \mathrm{mmol}, 1.10$ equiv). After being stirred 24 hours at $30^{\circ} \mathrm{C}$, the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1\right)$ to yield the pure product 4.175 ( $61 \mathrm{mg}, 86 \%$ ) as a mixture of rotamers and as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ): $\delta 8.26(\mathrm{~s}, 1 \mathrm{H}), 7.42(\mathrm{dd}, \mathrm{J}=7.8,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.38-7.19(\mathrm{~m}, 6 \mathrm{H}), 7.12$ (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.04 (ddd, J = 8.0, $7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $5.40-4.84(\mathrm{~m}, 2 \mathrm{H}), 4.09-3.76$ $(\mathrm{m}, 2 \mathrm{H}), 3.65-3.49(\mathrm{~m}, 2 \mathrm{H}), 3.39(\mathrm{~d}, J=11.7 \mathrm{~Hz}, 3 \mathrm{H}), 3.31-2.91(\mathrm{~m}, 2 \mathrm{H}), 2.80(\mathrm{dt}, J=5.9,2.8 \mathrm{~Hz}$, $2 H$ ), 2.66 (ddd, $J=15.0,10.0,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.16$ (ddd, $J=16.2,10.0,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.02-1.85(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.3,172.5,171.3,156.2,136.6,129.2,128.7,128.3,128.0,127.7$, $127.1,126.1,122.9,120.0,118.6,111.8,111.5,67.7,65.4,64.4,60.5,53.0,51.7,43.1,32.4,31.3$, 29.0, 24.0, 21.2, 20.7, 14.3.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{25} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 451.1865; found: 451.1865.

## methyl 2-benzoyl-1-(3-methoxy-3-oxopropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1caboxylate (4.176)



To a solution of amine 4.173 ( $2.00 \mathrm{~g}, 6.32 \mathrm{mmol}, 1.00$ equiv) and DIPEA ( $1.35 \mathrm{~mL}, 7.59 \mathrm{mmol}, 1.20$ equiv) in dry $\mathrm{DCM}\left(65 \mathrm{~mL}, 0.1 \mathrm{M}\right.$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{BzCl}(881 \mu \mathrm{~L}, 7.59 \mathrm{mmol}, 1.20$ equiv). After
being stirred 24 hours at $30^{\circ} \mathrm{C}$ the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1\right)$ to yield the pure product 4.176 ( $2363 \mathrm{mg}, 89 \%$ ) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.17(\mathrm{~s}, 1 \mathrm{H}), 7.58-7.42(\mathrm{~m}, 6 \mathrm{H}), 7.38(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.22(\mathrm{dd}, J=$ 8.1, 1.2 Hz, 1H), $7.19-7.06(\mathrm{~m}, 1 \mathrm{H}), 3.84(\mathrm{t}, \mathrm{J}=5.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.74(\mathrm{~s}, 3 \mathrm{H}), 3.47(\mathrm{~s}, 3 \mathrm{H}), 3.34$ (ddd, J = $15.4,10.0,6.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.97-2.72$ (m, 3H), 2.36 (ddd, J = 16.0, 9.9, $6.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.17 (ddd, $J=15.9$, $10.0,5.9 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.3,173.3,168.8,136.5,136.2,133.9,131.3,128.4,127.8,126.9$, $120.9,119.2,118.6,111.4,104.7,66.3,52.9,51.5,41.3,29.7,28.2,19.2$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{24} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 421.1758; found: 421.1760.

## 3-(2-benzoyl-1-(methoxycarbonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propanoic acid (4.177)



To a solution of ester $4.176\left(1.00 \mathrm{~g}, 2.27 \mathrm{mmol}, 1.00\right.$ equiv) in $\mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O}(1: 1,11 / 11 \mathrm{~mL}, 0.1 \mathrm{M})$ was added NaOH ( $200 \mathrm{mg}, 5.00 \mathrm{mmol}, 2.20$ equiv). After being stirred 5 minutes at reflux, the reaction was immediately cooled to $-78{ }^{\circ} \mathrm{C}$, acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) to yield the pure product 4.177 ( 921 mg , quantitative yield) as a brown amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 7.58-7.49(\mathrm{~m}, 5 \mathrm{H}), 7.46(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}$, $1 \mathrm{H}), 7.13$ (ddd, $J=8.3,7.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.03(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.99(\mathrm{dt}, J=13.3,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.67$ (s, 3H), $3.66-3.56(\mathrm{~m}, 1 \mathrm{H}), 3.21$ (ddd, $J=15.4,9.1,6.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.87(\mathrm{tdt}, J=8.8,6.4,2.9 \mathrm{~Hz}, 3 \mathrm{H}$ ), $2.44-2.16(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 176.7,174.5,172.9,138.7,137.8,131.3,131.0,129.9,127.8$, $127.4,123.3,120.4,119.1,112.5,112.0,66.2,53.2,48.1,30.5,30.3,22.1$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{23} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 405.1456; found: 405.1458 .
methyl 2-benzoyl-1-(3-oxo-3-(phenylthio)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1carboxylate (4.180)


To a solution of acid 4.177 ( $25 \mathrm{mg}, 0.06 \mathrm{mmol}, 1.00$ equiv) and DIPEA ( $16 \mu \mathrm{~L}, 0.09 \mathrm{mmol}, 1.50$ equiv) in dry EtOAc ( $2 \mathrm{~mL}, 0.03 \mathrm{M}$ ) was added TBTU ( $22 \mathrm{mg}, 0.068$, 1.10 equiv) and PhSH ( $7 \mathrm{\mu L}$, $0.06 \mathrm{mmol}, 1.00$ equiv). After being stirred 12 hours at room temperature, the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 9: 1$ ) to yield the pure product 4.180 ( $30 \mathrm{mg}, 98 \%$ ) as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.29(\mathrm{~s}, 1 \mathrm{H}), 7.61-7.41(\mathrm{~m}, 6 \mathrm{H}), 7.41-7.20(\mathrm{~m}, 5 \mathrm{H}), 7.16(\mathrm{t}, \mathrm{J}=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 7.13-7.03(\mathrm{~m}, 2 \mathrm{H}), 3.86(\mathrm{t}, \mathrm{J}=5.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.73(\mathrm{~s}, 3 \mathrm{H}), 3.38$ (ddd, J = 14.8, 8.4, 6.4 Hz, 1 H ), $2.98-2.89(\mathrm{~m}, 3 \mathrm{H}), 2.70$ (ddd, $J=15.0,8.3,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.59$ (ddd, $J=15.7,8.3,6.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 196.0, 173.3, 168.8, 136.5, 136.2, 133.9, 132.6, 131.3, 129.9, 129.2, $128.4,127.8,127.4,126.8,120.8,119.2,118.6,111.3,104.7,66.6,52.9,41.3,35.8,30.4,19.2$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{29} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 499.1686 ; found: 499.1687.
methyl 2-benzoyl-1-(3-(1-(tert-butoxycarbonyl)-5-methoxy-1H-indol-2-yl)-3-oxopropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (4.195)



To a mixture of boronic acid 4.194 ( $15.4 \mathrm{mg}, 0.053 \mathrm{mmol}, 1.10$ equiv), thioester 4.180 ( 24 mg , $0.048 \mathrm{mmol}, 1.00$ equiv), TFP ( $0.14 \mathrm{mg}, 0.0006 \mathrm{mmol}, 0.012$ equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}(0.30 \mathrm{mg}, 0.0003$ mmol, 0.006 equiv) and CuTC ( $14 \mathrm{mg}, 0.072 \mathrm{mmol}, 1.5$ equiv) was added dry and degassed THF $(0.58 \mathrm{~mL}, 0.082 \mathrm{M})$. After being stirred 5 hours at $50^{\circ} \mathrm{C}$, the reaction mixture was quenched with the addition of water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 20: 1$ ) to yield the pure product 4.195 (31 $\mathrm{mg}, 91 \%$ ) as a black amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.10(\mathrm{~s}, 1 \mathrm{H}), 7.89(\mathrm{~d}, J=9.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.58-7.40(\mathrm{~m}, 5 \mathrm{H}), 7.35(\mathrm{~d}, \mathrm{~J}=$ $8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.29-7.21(\mathrm{~m}, 1 \mathrm{H}), 7.16(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.05-6.91(\mathrm{~m}, 1 \mathrm{H}), 6.86(\mathrm{~d}, \mathrm{~J}=2.7 \mathrm{~Hz}, 1 \mathrm{H})$,
$6.63(\mathrm{~s}, 1 \mathrm{H}), 3.95-3.79(\mathrm{~m}, 5 \mathrm{H}), 3.73(\mathrm{~s}, 3 \mathrm{H}), 3.37(\mathrm{~d}, \mathrm{~J}=14.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.99-2.84(\mathrm{~m}, 4 \mathrm{H}), 2.84-$ $2.69(\mathrm{~m}, 1 \mathrm{H}), 1.47(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 193.4,172.8,171.7,156.4,149.7,138.8,136.6,136.6,133.1,130.5$, $130.4,128.9,128.4,127.2,126.4,123.1,120.2,118.7,116.8,115.9,114.0,111.7,104.1,84.8,64.6$, $55.8,53.2,46.6,37.1,30.7,27.8,21.6$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{37} \mathrm{H}_{38} \mathrm{~N}_{3} \mathrm{O}_{7}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$636.2704; found: 636.2704.

## 2-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)isoindoline-1,3-dione

 (4.187)

It was prepared according to a literature procedure. ${ }^{161}$
2-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)isoindoline-1,3-dione (4.191)


It was prepared according to literature procedures. ${ }^{161,383}$
(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-indol-2-yl)boronic acid (4.193)


To a solution of trifluoroborate salt 4.192 ( $10 \mathrm{mg}, 0.025 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{MeCN}(0.3 \mathrm{~mL}, 0.1$ M) was added water ( $1.5 \mu \mathrm{~L}, 0.076 \mathrm{mmol}, 3.00$ equiv) and TMSCI ( $4 \mu \mathrm{~L}, 0.076 \mathrm{mmol}, 3.00$ equiv). After being stirred for 2 hours, the reaction mixture was evaporated in vacuo. The residue was redissolved in ethyl acetate, acidified to $\mathrm{pH}=1$ with the addition of 3 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered
and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM/MeOH 9:1) to yield the pure product 4.193 ( $17 \%$ over 2 steps) as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.30(\mathrm{~s}, 1 \mathrm{H}), 7.72(\mathrm{dd}, J=5.4,3.1 \mathrm{~Hz}, 2 \mathrm{H}), 7.63(\mathrm{dd}, J=5.5,3.1 \mathrm{~Hz}, 2 \mathrm{H})$, $7.30(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.84(\mathrm{dt}, J=7.5,3.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.86(\mathrm{dt}, J=14.6,7.4$ $\mathrm{Hz}, 1 \mathrm{H}), 3.71(\mathrm{dt}, J=13.7,6.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.88(\mathrm{dt}, J=14.6,7.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.72(\mathrm{dt}, J=13.6,6.2 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 168.8,142.7,140.8,133.2,132.6,130.0,126.3,125.3,123.1,120.3$, 119.6, 112.2, 39.1, 28.6.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{18} \mathrm{H}_{14} \mathrm{BN}_{2} \mathrm{O}_{4}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 333.1052; found: 333.1057 .
methyl 3-benzoyl-6-oxo-2,3,5,6-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-3a(4H)carboxylate (4.196)


To a mixture of CuTC ( $12 \mathrm{mg}, 0.060 \mathrm{mmol}, 1.20$ equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}(1.15 \mathrm{mg}, 0.001 \mathrm{mmol}, 0.025$ equiv), TFP ( $0.14 \mathrm{mg}, 0.0006$ equiv, 0.012 equiv), thioester 4.180 ( $25 \mathrm{mg}, 0.050 \mathrm{mmol}, 1.00$ equiv) and stannyl 4.198 ( $36 \mathrm{mg}, 0.055 \mathrm{mmol}, 1.1$ equiv) was added dry and degassed THF ( 0.25 mL ) and dry and degassed hexane ( 0.5 mL ). After being stirred 5 hours at $40^{\circ} \mathrm{C}$, the reaction mixture was filtered over Celite (rinsed with THF), quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 20: 1$ ) to yield the pure product 4.196 ( $18 \mathrm{mg}, 93 \%$ ) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.49(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.54-7.43(\mathrm{~m}, 6 \mathrm{H}), 7.44-7.38(\mathrm{~m}, 1 \mathrm{H}), 7.33$ (td, $J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.10-3.99(\mathrm{~m}, 1 \mathrm{H}), 3.93-3.78(\mathrm{~m}, 1 \mathrm{H}), 3.72(\mathrm{~s}, 3 \mathrm{H}), 3.59$ (ddd, $J=13.3$, $6.8,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.41$ (ddd, $J=12.5,10.5,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.99$ (ddd, $J=15.1,10.5,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.94-$ $2.77(\mathrm{~m}, 2 \mathrm{H}), 2.13(\mathrm{td}, \mathrm{J}=13.1,6.4 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 172.3,170.9,168.2,136.5,135.6,131.0,130.5,128.8,128.1,127.2$, $125.8,124.4,118.6,117.5,117.0,60.1,53.1,47.0,31.8,29.1,21.8$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{23} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 389.1496$; found: 389.1498 .
2-benzoyl-1-(2-carboxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylic acid (4.178)


To a solution of ester 4.176 ( $1000 \mathrm{mg}, 2.378 \mathrm{mmol}, 1.0$ equiv) in EtOH/ $\mathrm{H}_{2} \mathrm{O}(1: 1,12 / 12 \mathrm{~mL}, 0.1 \mathrm{M})$ was added NaOH ( $285 \mathrm{mg}, 7.135 \mathrm{mmol}, 3.0$ equiv). After 30 minutes at reflux, the reaction was cooled to room temperature, acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, DCM/MeOH 9:1) to yield the pure product 4.178 ( 932 mg , quantitative yield) as a brown solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 10.59(\mathrm{~s}, 1 \mathrm{H}), 7.52(\mathrm{~d}, \mathrm{~J}=2.4 \mathrm{~Hz}, 5 \mathrm{H}), 7.46(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H})$, $7.38(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.12(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.03(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.96(\mathrm{dt}, J=13.3,4.7 \mathrm{~Hz}, 1 \mathrm{H})$, 3.65 (ddd, $J=13.0,7.5,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.26(\mathrm{dd}, \mathrm{J}=9.1,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.87-2.82(\mathrm{~m}, 3 \mathrm{H}), 2.42-2.12$ ( $\mathrm{m}, 2 \mathrm{H}$ ).
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta$ 177.1, 174.8, 169.0, 136.5, 136.2, 135.2, 131.3, 128.4, 127.8, 126.9, 120.8, 119.2, 118.7, 111.4, 106.5, 66.5, 41.4, 29.7, 29.0, 19.2.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{22} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 391.1299; found: 391.1301.

# methyl 2-benzoyl-9-benzyl-1-(3-methoxy-3-oxopropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4- <br> b]indole-1-carboxylate (4.199) 



To a solution of indole 4.180 ( $4808 \mathrm{mg}, 11.44 \mathrm{mmol}, 1.0$ equiv) in dry DMF ( $100 \mathrm{~mL}, 0.12 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added portionwise washed NaH ( $357 \mathrm{mg}, 14.87 \mathrm{mmol}, 1.3$ equiv). After 1 hour at $0^{\circ} \mathrm{C}, \mathrm{BnBr}$ ( $4103 \mu \mathrm{~L}, 34.31 \mathrm{mmol}, 3.0$ equiv) was added dropwise. After 5 hours at room temperature, the reaction mixture was quenched with the addition of water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 25: 1$ ) to yield the pure product 4.199 ( $4376 \mathrm{mg}, 75 \%$ ) as a white amorphous solid.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.69-7.43(\mathrm{~m}, 5 \mathrm{H}), 7.43-7.08(\mathrm{~m}, 7 \mathrm{H}), 6.83(\mathrm{~d}, \mathrm{~J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 5.67$ $(\mathrm{d}, J=17.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.59(\mathrm{~d}, J=17.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.00(\mathrm{dt}, J=13.3,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.91-3.79(\mathrm{~m}, 1 \mathrm{H}), 3.45$ (s, 3H), 3.35 (s, 3H), 3.21 (td, J = 10.3, 9.9, $4.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.03$ (dtd, J = 23.4, 10.1, 9.6, $4.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), 2.75 (ddd, $J=15.3,9.6,6.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.47 (ddd, $J=15.9,9.5,6.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.24 (ddd, $J=16.1,9.6,6.0$ $\mathrm{Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.4,173.2,168.8,137.6,137.2,136.2,135.1,131.3,128.6,128.4$, $127.5,127.3,127.3,127.2,127.1,126.9,120.8,120.1,111.0,105.3,68.0,52.9,51.5,46.1,41.0$, 29.9, 27.4, 19.8.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{31} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 511.2227$; found: 511.2230.

## 3-(2-benzoyl-9-benzyl-1-(methoxycarbonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1$\mathrm{yl})$ propanoic acid (4.200)



To a solution of ester 4.199 ( $100 \mathrm{mg}, 0.196 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O}(1: 1,2 / 2 \mathrm{~mL}, 0.05 \mathrm{M})$ was added NaOH ( $18 \mathrm{mg}, 0.431 \mathrm{mmol}, 2.20$ equiv). After being stirred 30 minutes at reflux, the reaction was cooled to room temperature, acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1\right)$ to yield the pure product $4.200(49 \mathrm{mg}, 50 \%)$ as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.60-7.53(\mathrm{~m}, 1 \mathrm{H}), 7.50(\mathrm{~s}, 5 \mathrm{H}), 7.26-7.00(\mathrm{~m}, 6 \mathrm{H}), 6.72(\mathrm{~d}, \mathrm{~J}=7.1$ $\mathrm{Hz}, 2 \mathrm{H}), 5.63(\mathrm{~d}, J=18.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.57(\mathrm{~d}, J=18.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.93(\mathrm{dt}, J=13.5,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.74$ (ddd, J $=13.1,8.2,4.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.29(\mathrm{~s}, 3 \mathrm{H}), 3.12$ (ddd, $J=15.2,8.5,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.97(\mathrm{dt}, J=9.4,4.8 \mathrm{~Hz}$, 2 H ), 2.69 (ddd, $J=15.2,8.5,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.42-2.28(\mathrm{~m}, 1 \mathrm{H}), 2.18$ (ddd, $J=16.1,8.5,6.4 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 177.1,173.4,168.8,137.6,137.2,136.2,135.1,131.3,128.6,128.4$, $127.5,127.3,127.3,127.1,126.9,120.8,120.0,111.0,105.3,68.0,52.9,46.1,41.0,29.0,28.3$, 19.8.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{30} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 495.1925; found: 495.1921.
methyl (S)-2-benzoyl-9-benzyl-1-(3-oxo-3-(phenylthio)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (4.201)


To a solution of acid 4.200 ( $68 \mathrm{mg}, 0.137 \mathrm{mmol}, 1.00$ equiv) and DIPEA ( $34 \mu \mathrm{~L}, 0.205 \mathrm{mmol}, 1.50$ equiv) in dry EtOAc ( $4.6 \mathrm{~mL}, 0.03 \mathrm{M}$ ) was added TBTU ( $49 \mathrm{mg}, 0.151 \mathrm{mmol}, 1.10$ equiv) and PhSH ( $14 \mu \mathrm{~L}, 0.137 \mathrm{mmol}, 1.00$ equiv). After being stirred 12 hours at room temperature, the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The
crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 15: 1\right)$ to yield the pure product $4.201(73 \mathrm{mg}, 90 \%)$ as a white amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.73-7.60(\mathrm{~m}, 1 \mathrm{H}), 7.59-7.45(\mathrm{~m}, 5 \mathrm{H}), 7.45-7.30(\mathrm{~m}, 3 \mathrm{H}), 7.30-$ $7.18(\mathrm{~m}, 5 \mathrm{H}), 7.18-7.03(\mathrm{~m}, 3 \mathrm{H}), 6.83(\mathrm{~d}, \mathrm{~J}=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 5.68(\mathrm{~d}, \mathrm{~J}=17.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.57(\mathrm{~d}, \mathrm{~J}=17.8$ $\mathrm{Hz}, 1 \mathrm{H}), 3.99(\mathrm{dt}, J=13.5,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.86(\mathrm{ddd}, J=13.3,7.3,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.33(\mathrm{~s}, 3 \mathrm{H}), 3.23(\mathrm{tt}, J=$ $10.0,5.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.15-2.98(\mathrm{~m}, 2 \mathrm{H}), 2.88$ (ddd, J = 19.7, 15.6, 6.9 Hz, 2H), $2.81-2.62(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 196.0,173.4,168.8,137.6,137.2,136.2,135.1,132.6,131.3,129.9$, $129.2,128.6,128.4,127.4,127.4,127.3,127.2,127.1,126.9,120.8,120.0,111.0,105.3,68.3,52.9$, 46.1, 41.0, 35.4, 30.3, 19.8 .

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{36} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 589.2156; found: 589.2159.
methyl 2-benzoyl-9-benzyl-1-(3-(1-(tert-butoxycarbonyl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indol-2-yl)-3-oxopropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (4.202)


To a mixture of thioester 4.201 ( $200 \mathrm{mg}, 0.339 \mathrm{mmol}, 1.00$ equiv), stannyl 4.198 ( $331 \mathrm{mg}, 0.509$ mmol, 4.50 equiv), CuDPP ( $115 \mathrm{mg}, 0.408 \mathrm{mmol}, 1.20$ equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ ( $78 \mathrm{mg}, 0.085 \mathrm{mmol}, 0.25$ equiv) and $\mathrm{AsPh}_{3}$ ( $104 \mathrm{mg}, 0.85 \mathrm{mmol}, 0.25$ equiv) was added dry and degassed THF ( 1.25 mL ) and dry and degassed hexane ( 3.75 mL ). After being stirred 5 hours at $40^{\circ} \mathrm{C}$, the reaction mixture was filtered over Celite (rinsed with THF), quenched with the addition of water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 17:1) to yield the pure product 4.202 ( $264 \mathrm{mg}, 93 \%$ ) as a black amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.90(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.51-7.44(\mathrm{~m}, 1 \mathrm{H})$, $7.44-7.29(\mathrm{~m}, 6 \mathrm{H}), 7.22(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.14-7.01(\mathrm{~m}, 5 \mathrm{H}), 7.00-6.93(\mathrm{~m}, 1 \mathrm{H}), 6.62(\mathrm{~d}, \mathrm{~J}=7.3$ $\mathrm{Hz}, 2 \mathrm{H}), 5.52(\mathrm{~d}, \mathrm{~J}=17.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.31(\mathrm{~d}, J=17.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.02(\mathrm{t}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{dt}, J=13.4$, $5.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.69$ (ddd, $J=13.3,8.5,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.23-3.16(\mathrm{~m}, 3 \mathrm{H}), 3.13(\mathrm{~s}, 3 \mathrm{H}), 3.10-2.90(\mathrm{~m}$, $2 \mathrm{H}), 2.90-2.74(\mathrm{~m}, 1 \mathrm{H}), 2.74-2.44(\mathrm{~m}, 3 \mathrm{H}), 1.39(\mathrm{~s}, 9 \mathrm{H}), 1.34(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 196.9, 172.6, 170.8, 156.2, 149.9, 138.2, 137.5, 136.5, 136.1, 135.5, $131.7,130.5,129.5,128.8,128.6,127.1,127.0,126.9,125.8,125.6,123.6,123.1,122.6,120.8$, $120.1,118.6,115.6,111.4,110.9,85.3,79.0,65.0,52.5,47.6,39.2,30.1,29.8,28.6,28.0,21.9$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{50} \mathrm{H}_{55} \mathrm{~N}_{4} \mathrm{O}_{8}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 839.4014; found: 839.4015.

# methyl 2-benzoyl-9-benzyl-1-(2-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylate (4.203) 



Indole 4.202 ( $200 \mathrm{mg}, 0.267 \mathrm{mmol}, 1.00$ equiv) was dissolved in DCM/TFA (1:1, 2.7/2.7 mL, 0.05 $\mathrm{M})$ at $0^{\circ} \mathrm{C}$. After being stirred 5 hours at $0^{\circ} \mathrm{C}$, the reaction mixture was evaporated in vacuo. The residue was dissolved in ethyl acetate and neutralized with saturated aqueous $\mathrm{NaHCO}_{3}$. The reaction mixture was extracted with EtOAc. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the desired product 4.203 (149 mg, 90\%) as a black gum.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.92(\mathrm{~s}, 1 \mathrm{H}), 7.62(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.60-7.52(\mathrm{~m}, 2 \mathrm{H}), 7.52-7.42$ $(\mathrm{m}, 5 \mathrm{H}), 7.38(\mathrm{ddd}, J=8.2,6.9,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.24-7.13(\mathrm{~m}, 3 \mathrm{H}), 7.10(\mathrm{dd}, J=7.7,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.03$ $(\mathrm{t}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.93(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 6.65-6.50(\mathrm{~m}, 2 \mathrm{H}), 5.45(\mathrm{~d}, J=17.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.31(\mathrm{~d}, J=$ $17.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.05 (ddd, $J=13.8,5.0,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.85-3.76$ (m, 1H), 3.69 (ddd, J = 14.1, 10.5, 3.9 $\mathrm{Hz}, 1 \mathrm{H}), 3.48(\mathrm{t}, J=12.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.37(\mathrm{~s}, 3 \mathrm{H}), 3.12(\mathrm{tt}, J=10.6,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.98-2.63(\mathrm{~m}, 3 \mathrm{H}), 2.41$ (ddd, $J=14.5,11.7,6.8 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 172.4,172.0,161.7,138.2,137.5,137.0,136.1,132.3,130.3,128.9$, $128.4,127.8,126.8,126.6,125.6,125.4,125.3,123.1,120.4,120.2,120.1,118.7,112.5,110.4$, $110.3,64.8,53.0,47.1,44.5,33.9,22.0,19.3$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{40} \mathrm{H}_{37} \mathrm{~N}_{4} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 621.2860; found: 621.2864 .
1-(2-(9H-pyrido[3,4-b]indol-1-yl)ethyl)-2-benzoyl-9-benzyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylic acid (4.204)


To a solution of imine $4.203\left(16 \mathrm{mg}, 0.0258 \mathrm{mmol}, 1.00\right.$ equiv) in $\mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O}(4: 1,0.4 / 0.1 \mathrm{~mL}, 0.05$ $\mathrm{M})$ was added KOH ( $100 \mathrm{mg}, 0.258 \mathrm{mmol}, 10$ equiv) at room temperature. After being stirred 5 hours at $70{ }^{\circ} \mathrm{C}$, the reaction mixture was cooled to room temperature, acidified to $\mathrm{pH}=1$ with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash col-
umn chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1\right)$ to yield the pure product $4.204(11 \mathrm{mg}, 67 \%)$ as an orange oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.23(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.07-7.97(\mathrm{~m}, 2 \mathrm{H}), 7.77(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H})$, 7.69 (ddd, $J=8.2,7.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{dd}, J=7.6,1.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.52-7.40(\mathrm{~m}, 4 \mathrm{H}), 7.37$ (ddd, $J=$ 8.0, 7.0, 1.0 Hz, 1H), $7.08-6.96(\mathrm{~m}, 3 \mathrm{H}), 6.61-6.53(\mathrm{~m}, 2 \mathrm{H}), 6.51-6.33(\mathrm{~m}, 3 \mathrm{H}), 5.94(\mathrm{~d}, \mathrm{~J}=17.7$ $\mathrm{Hz}, 1 \mathrm{H}), 5.51(\mathrm{~d}, J=18.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.03(\mathrm{dt}, J=13.5,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.95(\mathrm{t}, \mathrm{J}=10.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.70(\mathrm{td}, J=$ $10.2,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.23-2.94(\mathrm{~m}, 3 \mathrm{H}), 2.83(\mathrm{dt}, J=15.0,3.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.53-2.39(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 174.2,174.1,145.1,143.7,139.8,139.6,139.0,136.4,135.4,133.5$, $131.7,130.9,129.7,128.6,127.8,127.4,127.0,126.4,123.2,123.1,122.3,121.6,120.5,119.1$, $114.9,113.6,111.3,111.0,71.2,47.8,46.5,35.7,29.3,22.7$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{39} \mathrm{H}_{33} \mathrm{~N}_{4} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 605.2547; found: 605.2550 .

## 11-(tert-butyl) 11b-methyl 3-oxo-2,3,5,6-tetrahydro-1H-indolizino[8,7-b]indole-11,11bdicarboxylate (4.215)



To a solution of amine 4.173 ( $50 \mathrm{mg}, 0.158 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $2.26 \mathrm{~mL}, 0.07 \mathrm{M}$ ) at room temperature was added $\mathrm{Boc}_{2} \mathrm{O}(121 \mathrm{mg}, 0.553 \mathrm{mmol}, 3.50$ equiv) and DMAP ( $12 \mathrm{mg}, 0.095$ mmol, 0.60 equiv) portionwise. After being stirred 2 hours at $50^{\circ} \mathrm{C}$, the reaction mixture was quenched with the addition of water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 25: 1\right)$ to yield the pure product 4.215 ( $55 \mathrm{mg}, 90 \%$ ) as an orange amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.96(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H})$, $7.30-7.15(\mathrm{~m}, 1 \mathrm{H}), 4.48(\mathrm{dt}, J=12.0,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.70(\mathrm{~s}, 3 \mathrm{H}), 3.32(\mathrm{dd}, J=13.3,9.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.17-$ $3.05(\mathrm{~m}, 1 \mathrm{H}), 2.95(\mathrm{dt}, J=16.9,10.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.85-2.73(\mathrm{~m}, 2 \mathrm{H}), 2.42(\mathrm{dd}, J=16.8,10.0 \mathrm{~Hz}, 1 \mathrm{H})$, 2.03 ( $\mathrm{dt}, \mathrm{J}=13.1,10.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), $1.67(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 174.4,171.0,150.2,135.4,133.9,128.8,125.1,123.1,118.9,116.5$, 115.9, 84.9, 67.2, 52.7, 35.3, 31.1, 30.5, 28.2, 21.5.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{21} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 385.1758; found: 385.1761.
methyl 2-(chlorocarbonyl)-1-(3-methoxy-3-oxopropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-
b]indole-1-carboxylate (4.222)


To a solution of amine 4.173 ( $50 \mathrm{mg}, 0.158 \mathrm{mmol}, 1.00$ equiv) and DIPEA ( $32 \mu \mathrm{~L}, 0.190 \mathrm{mmol}, 1.20$ equiv) in dry DCM ( $1.6 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added triphosgen ( $19 \mathrm{mg}, 0.063 \mathrm{mmol}, 0.40$ equiv) portionwise. After being stirred 5 hours at room temperature, the reaction mixture was quenched with the addition of water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 19: 1$ ) to yield the pure product 4.222 (59 $\mathrm{mg}, 98 \%$ ) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.27(\mathrm{~s}, 1 \mathrm{H}), 7.60-7.47(\mathrm{~m}, 1 \mathrm{H}), 7.36(\mathrm{dt}, J=8.3,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-$ 7.20 (m, 1H), 7.15 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 4.23 (ddd, J = 13.0, 6.4, 4.9 Hz, 1H), $4.17-4.05$ (m, 1 H ), $3.71(\mathrm{~s}, 3 \mathrm{H}), 3.50(\mathrm{~s}, 3 \mathrm{H}), 3.16$ (ddd, $J=15.5,9.6,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.96$ (ddd, $J=6.4,4.9,3.3 \mathrm{~Hz}$, 2 H ), 2.76 (ddd, $J=15.2,9.7,5.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.25 (ddd, $J=16.1,9.7,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.16-2.07(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 173.3,173.3,146.9,136.5,133.2,127.8,120.9,119.3,118.7,111.3$, 104.7, 63.1, 52.9, 51.5, 42.8, 29.7, 28.2, 19.2.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{18} \mathrm{H}_{20} \mathrm{ClN}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 379.1055; found: 379.1056.

## dimethyl 3-oxo-2,3,6,11-tetrahydro-1H-indolizino[8,7-b]indole-2,11b(5H)-dicarboxylate (4.223)





To a solution of indole 4.222 ( $38 \mathrm{mg}, 0.1 \mathrm{mmol}, 1.00$ equiv) in dry $\mathrm{THF}(1 \mathrm{~mL}, 0.1 \mathrm{M})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaO}^{\mathrm{t}} \mathrm{Bu}$ ( $21 \mathrm{mg}, 0.21 \mathrm{mmol}, 2.10$ equiv). After being stirred 3 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, PE/EtOAc 18:1) to yield the pure product 4.223 ( $30 \mathrm{mg}, 87 \%$ ) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 8.26(\mathrm{~s}, 1 \mathrm{H}), 7.50(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, $7.23-7.14(\mathrm{~m}, 1 \mathrm{H}), 7.10(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.95-3.84(\mathrm{~m}, 2 \mathrm{H}), 3.76(\mathrm{~s}, 3 \mathrm{H}), 3.67(\mathrm{~s}, 3 \mathrm{H}), 2.94-$ $2.80(\mathrm{~m}, 2 \mathrm{H}), 2.68$ (ddd, $J=14.8,9.7,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.38-2.12(\mathrm{~m}, 1 \mathrm{H}), 2.12-1.88(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 177.8,172.6,156.9,136.6,129.3,129.1,126.2,123.0,120.1$, 118.7, 111.6, 64.3, 53.2, 53.2, 43.2, 43.1, 29.8, 28.8.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 343.1288 ; found: 343.1291.

## 3-((benzyloxy)carbonyl)-6-oxo-2,3,5,6-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-3a(4H)carboxylic acid (4.229)



To a solution of acid 4.179 ( $20 \mathrm{mg}, 0.0413 \mathrm{mmol}, 1.00$ equiv) in dry $\mathrm{MeCN}(0.4 \mathrm{~mL}, 0.1 \mathrm{M})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NEt}_{3}\left(12 \mu \mathrm{~L}, 0.0825 \mathrm{mmol}, 2.00\right.$ equiv), $\mathrm{Boc}_{2} \mathrm{O}(18 \mathrm{mg}, 0.0825 \mathrm{mg}, 2.00$ equiv) and DMAP ( $1 \mathrm{mg}, 0.0083 \mathrm{mmol}, 0.20$ equiv). After being stirred 3 hours at room temperature, the reaction mixture was acidified to $\mathrm{pH}=1$ with the addition of 1 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 4:1) to yield the pure product 4.229 ( $15 \mathrm{mg}, 95 \%$ ) as a yellow amorphous solid.
${ }^{1}{ }^{\mathbf{H}}$ NMR (400 MHz, CDCl $)_{3}$ ): $\delta 8.45-8.13(\mathrm{~m}, 1 \mathrm{H}), 7.58-7.39(\mathrm{~m}, 6 \mathrm{H}), 7.29(\mathrm{tt}, \mathrm{J}=7.4,5.7 \mathrm{~Hz}, 2 \mathrm{H})$, $3.83(\mathrm{dt}, \mathrm{J}=13.2,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.68(\mathrm{ddd}, \mathrm{J}=18.4,12.3,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.63-3.45(\mathrm{~m}, 2 \mathrm{H}), 2.95-2.66$ $(\mathrm{m}, 3 \mathrm{H}), 2.22(\mathrm{td}, \mathrm{J}=12.6,5.8 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 176.6,174.6,171.0,138.7,136.6,135.3,131.3,130.0,129.7,128.0$, $125.8,125.2,119.5,117.1,116.5,64.6,48.2,33.2,30.3,22.2$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{22} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 373.1194; found: 373.1190.

## 3-((benzyloxy)carbonyl)-6-oxo-2,3,5,6-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-3a(4H)carboxylic acid (4.229)



To a solution of amine 4.172 ( $50 \mathrm{mg}, 0.173 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{NaOH}(21 \mathrm{mg}, 0.520 \mathrm{mmol}, 3.00$ equiv) in THF/ $\mathrm{H}_{2} \mathrm{O}(1: 1,0.9 / 0.9 \mathrm{~mL}, 0.1 \mathrm{M})$ at $0^{\circ} \mathrm{C}$ was added dropwise $\mathrm{CbzCl}(27 \mu \mathrm{~L}, 0.191 \mathrm{mmol}$, 1.10 equiv). After being stirred 4 hours at $0^{\circ} \mathrm{C}$, the reaction mixture was acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1\right)$ to yield the pure product 4.229 (64 $\mathrm{mg}, 91 \%)$ as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 8.60-8.17(\mathrm{~m}, 1 \mathrm{H}), 7.53-7.45(\mathrm{~m}, 1 \mathrm{H}), 7.45-7.24(\mathrm{~m}, 7 \mathrm{H}), 5.21(\mathrm{~d}, \mathrm{~J}$ $=12.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.15(\mathrm{~d}, \mathrm{~J}=12.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.28-4.09(\mathrm{~m}, 1 \mathrm{H}), 3.65-3.47(\mathrm{~m}, 2 \mathrm{H}), 3.34-3.11(\mathrm{~m}$, 1H), $2.95-2.68(\mathrm{~m}, 3 \mathrm{H}), 2.26-2.07(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 170.6,157.4,137.8,136.6,129.9,129.6,129.3,129.2,129.0,128.0$, 126.0, 125.2, 119.6, 117.1, 68.6, 43.9, 33.0, 30.8, 21.9.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{23} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 403.1299; found: 403.1297.

## 2-benzoyl-1-(3-oxo-3-(phenylthio)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1carboxylic acid (4.230)



To a solution of acid 4.179 ( $320 \mathrm{mg}, 0.815 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $8.2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added EDC ( $196 \mathrm{mg}, 1.019 \mathrm{mmol}, 1.25$ equiv), DMAP ( $10 \mathrm{mg}, 0.082 \mathrm{mmol}, 0.10$ equiv) and PhSH (92 $\mu \mathrm{L}, 0.897 \mathrm{mmol}, 1.10$ equiv). After being stirred 12 hours at room temperature, the reaction mixture was acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the pure product 4.230 ( $351 \mathrm{mg}, 89 \%$ ) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.52-7.41(\mathrm{~m}, 7 \mathrm{H}), 7.34(\mathrm{t}, \mathrm{J}=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.32-7.24(\mathrm{~m}, 2 \mathrm{H}), 7.18-$ $7.08(\mathrm{~m}, 3 \mathrm{H}), 7.04(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{dt}, J=13.1,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.77-3.64(\mathrm{~m}, 1 \mathrm{H}), 3.42-3.33$ $(\mathrm{m}, 1 \mathrm{H}), 2.99-2.89(\mathrm{~m}, 1 \mathrm{H}), 2.85(\mathrm{t}, \mathrm{J}=4.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.68-2.47(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 198.3,175.1,174.7,138.3,138.3,135.7,132.0,131.2,130.4,130.1$, 129.8, 129.1, 127.9, 127.4, 123.1, 120.3, 119.1, 112.6, 111.8, 66.8, 39.9, 31.2, 30.8, 22.1.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{28} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}\left([\mathrm{M}-\mathrm{H}]^{-}\right)$: 483.1384; found: 483.1380 .
3-benzoyl-6-oxo-2,3,5,6-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-3a(4H)-carboxylic acid (4.227)


To a solution of amine 4.230 ( $20 \mathrm{mg}, 0.0413 \mathrm{mmol}, 1.00$ equiv) in THF ( $0.2 \mathrm{~mL}, 0.2 \mathrm{M}$ ) at $-78^{\circ} \mathrm{C}$ was added dropwise LiHMDS ( 1 M in THF, $91 \mu \mathrm{~L}, 0.091 \mathrm{mmol}, 2.20$ equiv). After 30 minutes at $-78^{\circ} \mathrm{C}$, $\mathrm{CbzCl}\left(6.5 \mu \mathrm{~L}, 0.045 \mathrm{mmol}, 1.10\right.$ equiv). After the addition of 1 hours at $-78^{\circ} \mathrm{C}$, the reaction mixture was acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ) to yield the pure product 4.227 ( 15 mg , quantitative yield) as a yellow amorphous solid.

## 2-benzoyl-1-(2-carboxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylic acid (4.179)



To a solution of amine 4.230 ( $20 \mathrm{mg}, 0.0413 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{MeCN} / \mathrm{THF} / \mathrm{H}_{2} \mathrm{O}$ (25:1:1, $0.2 / 0.01 / 0.01 \mathrm{~mL}, 0.2 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NEt}_{3}\left(12 \mu \mathrm{~L}, 0.0825 \mathrm{mmol}, 2.00\right.$ equiv), $\mathrm{Boc}_{2} \mathrm{O}(18 \mathrm{mg}$, $0.0825 \mathrm{mmol}, ~ 2.00$ equiv) and DMAP ( $1 \mathrm{mg}, 0.0083 \mathrm{mmol}, 0.20$ equiv). After being stirred 6 hours at room temperature, the reaction mixture was acidified to $\mathrm{pH}=1$ with the addition of 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$ to yield the pure product 4.179 ( 16 mg , quantitative yield) as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 10.59(\mathrm{~s}, 1 \mathrm{H}), 7.52(\mathrm{~d}, \mathrm{~J}=2.4 \mathrm{~Hz}, 5 \mathrm{H}), 7.46(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.38(\mathrm{~d}, \mathrm{~J}$ $=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.12(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.03(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.96(\mathrm{dt}, J=13.3,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.65$ (ddd, J = 13.0, 7.5, 5.3 Hz, 1H), 3.26 (dd, J = 9.1, $6.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.96-2.72$ (m, 3H), $2.39-2.13$ (m, 2 H ).
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 177.1,174.8,169.0,136.5,136.2,135.2,131.3,128.4,127.8,126.9$, $120.8,119.2,118.6,111.4,106.5,66.5,41.4,29.7,29.0,19.2$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{22} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}-\mathrm{H}]^{-}\right):$391.1299; found: 391.1302.

### 8.4.3 Strategy Based on an Liebeskind-Srogl Coupling/Passerini Reaction

## 5-hydroxy-4,4-dimethyldihydrofuran-2(3H)-one (4.249)



The acid 4.247 ( $200 \mathrm{mg}, 1.56 \mathrm{mmol}, 1.00$ equiv) was dissolved in dry DCM ( $10 \mathrm{~mL}, 0.15 \mathrm{M}$ ) and cooled to $-78{ }^{\circ} \mathrm{C}$. Ozone was bubbled in the reaction mixture until blue then $\mathrm{O}_{2}$ until colorless again. DMS ( $346 \mu \mathrm{~L}, 4.68 \mathrm{mmol}, 3.00$ equiv) was added. After being stirred for 4 hours at room temperature, the reaction mixture was evaporated in vacuo to give the crude aldehyde 4.248. This crude was dissolved in DCM and saturated aqueous $\mathrm{NaHCO}_{3}$, washed with DCM, acidified with the addition of 1 M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to give the lactone 4.249 ( $183 \mathrm{mg}, 90 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.39(\mathrm{~s}, 1 \mathrm{H}), 5.15(\mathrm{~s}, 1 \mathrm{H}), 2.54(\mathrm{~d}, \mathrm{~J}=16.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.23(\mathrm{~d}, \mathrm{~J}=17.8 \mathrm{~Hz}$, 1H), 1.12 (s, 6H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 177.6,105.3,41.8,40.3,25.7$, 21.0.
HRMS (ESI): $m / z$ calcd $\mathrm{C}_{6} \mathrm{H}_{11} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 131.0703; found: 131.0707 .

## 4-ethoxy-3,3-dimethyl-4-oxobutanoic acid (4.259)



It was prepared according to a literature procedure. ${ }^{408,409 a}$
ethyl 2,2-dimethyl-4-oxo-4-(phenylthio)butanoate (4.260)


Following a reported procedure, ${ }^{403}$ to a solution of the acid 4.259 ( $20 \mathrm{mg}, 0.115 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $0.4 \mathrm{~mL}, 0.3 \mathrm{M}$ ) at room temperature was added dropwise TFAA ( $16 \mu \mathrm{~L}, 0.115 \mathrm{mmol}$, 1.00 equiv). The reaction mixture was stirred for 10 minutes and thiophenol ( $12 \mu \mathrm{~L}, 0.115 \mathrm{mmol}$, 1.00 equiv) was added. After being stirred at $45^{\circ} \mathrm{C}$ overnight, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 9: 1 \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O}\right)$ to yield the pure product 4.260 (27 $\mathrm{mg}, 88 \%$ ) as a white solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl $)_{3}$ : $\delta 7.39-7.37(\mathrm{~m}, 5 \mathrm{H}), 4.14(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.96(\mathrm{~s}, 2 \mathrm{H}), 1.29(\mathrm{~s}, 6 \mathrm{H})$, $1.24(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 195.2,176.4,134.6,129.5,129.3,127.8,61.0,52.7,41.5,25.4,14.2$.
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{O}_{3} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 267.1049; found: 267.1050 .
tert-butyl 3-(2-isocyanoethyl)-2-(tributylstannyl)-1H-indole-1-carboxylate (4.243)


Following a reported procedure, ${ }^{399}$ the formamide 4.242 ( $50 \mathrm{mg}, 0.098 \mathrm{mmol}, 1.00$ equiv) was dissolved in dry DCM ( $0.26 \mathrm{~mL}, 0.34 \mathrm{M}$ ). Triethylamine ( $60 \mu \mathrm{~L}, 0.433 \mathrm{mmol}, 5.00$ equiv) was added at $-78{ }^{\circ} \mathrm{C}$ followed by $\mathrm{POCl}_{3}(12 \mu \mathrm{~L}, 0.13 \mathrm{mmol}, 1.50$ equiv). After being stirred 4 hours at room temperature, the reaction mixture was quenched with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ and extracted
with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 95: 5 \mathrm{PE} / E t O A c+2 \% \mathrm{NEt}_{3}\right)$ to yield the pure product $4.243(40 \mathrm{mg}, 73 \%)$ as an orange solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.06-7.84(\mathrm{~m}, 1 \mathrm{H}), 7.52(\mathrm{dt}, J=7.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.14(\mathrm{~m}, 2 \mathrm{H})$, $3.68(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.23-3.07(\mathrm{~m}, 2 \mathrm{H}), 1.71(\mathrm{~s}, 9 \mathrm{H}), 1.64-1.49(\mathrm{~m}, 6 \mathrm{H}), 1.40-1.29(\mathrm{~m}, 6 \mathrm{H})$, $1.18-1.08(\mathrm{~m}, 6 \mathrm{H}), 0.89(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 9 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 156.5,153.8,141.4,138.8,132.8,128.6,125.2,123.5,119.0,116.5$, 85.7, 43.3, 30.4, 28.5, 28.4, 27.0, 14.4, 14.0.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{28} \mathrm{H}_{45} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{Sn}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 561.2498; found: 561.2501.
((diphenylphosphoryl)oxy)copper


It was prepared according to a literature procedure. ${ }^{375}$
tert-butyl 2-(4-ethoxy-3,3-dimethyl-4-oxobutanoyl)-3-(2-formamidoethyl)-1H-indole-1-
carboxylate (4.261)


The thioester 4.242 ( $50 \mathrm{mg}, 0.188 \mathrm{mmol}, 1.00$ equiv), the stannyl 4.260 ( $131 \mathrm{mg}, 0.225 \mathrm{mmol}, 1.20$ equiv), CuDPP ( $64 \mathrm{mg}, 0.225 \mathrm{mmol}, 1.20$ equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}(43 \mathrm{mg}, 0.047 \mathrm{mmol}, 0.25$ equiv), and $\mathrm{AsPh}_{3}(15 \mathrm{mg}, 0.047 \mathrm{mmol}, 0.25$ equiv) were dissolved in dry and degassed THF/Hexane (1:3, 2.8 $\mathrm{mL}, 0.067 \mathrm{M}$ ). The reaction mixture was warm to $40^{\circ} \mathrm{C}$ and stirred overnight. The reaction mixture was filtrated through Celite (rinsed with THF), washed with $1 \mathrm{M} \mathrm{HCl}, 10 \% \mathrm{NH}_{4} \mathrm{OH}$, and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 95: 5\right.$ to $\left.1: 1 \mathrm{PE} / \mathrm{EtOAc}+3 \% \mathrm{NEt}_{3}\right)$ to yield the pure product $4.261(80 \mathrm{mg}$, 96\%) as a red solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.10(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.97(\mathrm{dt}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{dt}, J=7.8$, $1.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.42 (ddd, $J=8.5,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.29$ (ddd, $J=8.1,7.2,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.04(\mathrm{~s}, 1 \mathrm{H}), 4.06$ ( $\mathrm{q}, \mathrm{J}=7.2 \mathrm{~Hz}, 2 \mathrm{H}$ ), $3.61-3.51(\mathrm{~m}, 2 \mathrm{H}), 3.08(\mathrm{~s}, 2 \mathrm{H}), 2.89(\mathrm{dd}, J=7.3,5.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H}), 1.26$ ( $\mathrm{s}, 6 \mathrm{H}$ ) , $1.21(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 196.0, 177.2, 161.8, 150.1, 136.5, 136.1, 128.9, 127.3, 123.8, 122.9, $120.5,115.7,85.7,60.8,52.8,41.2,38.2,28.2,25.6,22.9,14.1$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 445.2333$; found: 445.2339.
4-(1-(tert-butoxycarbonyl)-3-(2-formamidoethyl)-1H-indol-2-yl)-2,2-dimethyl-4-oxobutanoic acid


Following a reported procedure, ${ }^{410}$ to a solution of the ester $4.261(25 \mathrm{mg}, 0.056 \mathrm{mmol}, 1.00$ equiv) in $\mathrm{MeOH}\left(0.84 \mathrm{~mL}, 0.067 \mathrm{M}\right.$ ) at $0^{\circ} \mathrm{C}$ was added dropwise $\mathrm{NaOH}\left(2 \mathrm{M}\right.$ in $\mathrm{H}_{2} \mathrm{O}, 0.11 \mathrm{~mL}, 4.00$ equiv). After being stirred overnight at room temperature, the solution was evaporated in vacuo. To the residue was added $10 \% \mathrm{NaOH}$ and the solution was washed with ethyl acetate. The aqueous solution was acidified with concentrated HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ to 1:3) to yield the pure product 4.262 as a solid ( $10.5 \mathrm{mg}, 45 \%$ ) and $4.263(6.5 \mathrm{mg}, 39 \%)$ as a solid.

## tert-butyl 2-(4-ethoxy-3,3-dimethyl-4-oxobutanoyl)-3-(2-isocyanoethyl)-1H-indole-1-carboxylate

(4.265)


To a solution of the ester $4.261(10 \mathrm{mg}, 0.023 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $0.25 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $78{ }^{\circ} \mathrm{C}$ were added triethylamine ( $16 \mu \mathrm{~L}, 0.113 \mathrm{mmol}, 5.00$ equiv) and $\mathrm{PCl}_{5}(7 \mathrm{mg}, 0.034 \mathrm{mmol}, 1.50$ equiv). After being stirred at room temperature for 8 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 9: 1\right.$ to $\left.8: 2 \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O}\right)$ to yield the pure product 4.265 ( $8.6 \mathrm{mg}, 88 \%$ ) as a solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.99(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.41$ (ddd, $J=8.4,7.1$, $1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.29(\mathrm{t}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.09(\mathrm{q}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.78(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.10(\mathrm{~s}, 2 \mathrm{H}), 3.03$ ( $\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $1.68(\mathrm{~s}, 9 \mathrm{H}), 1.28(\mathrm{~s}, 6 \mathrm{H}), 1.22(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 193.3,177.0,157.5,150.0,139.5,136.6,128.9,128.1,125.8,122.6$, $120.4,115.4,82.5,62.6,50.2,43.6,40.7,28.1,22.4,21.5,13.9$.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{24} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 427.2227; found: 427.2230 .
tert-butyl 3-(2-(2-(benzoyloxy)-3,3-dimethyl-5-oxo-5-(phenylthio)pentanamido)ethyl)-2-(tributylstannyl)-1H-indole-1-carboxylate (4.252)


Following a reported procedure, ${ }^{405}$ to a solution of the isonitrile 4.243 ( $56 \mathrm{mg}, 0.10 \mathrm{mmol}, 1.10$ equiv) in dry $\mathrm{Et}_{2} \mathrm{O}$ ( $0.45 \mathrm{~mL}, 0.2 \mathrm{M}$ ) was added the aldehyde 4.238 ( $20 \mathrm{mg}, 0.09 \mathrm{mmol}, 1.00$ equiv) and benzoic acid ( $11 \mathrm{mg}, 0.09 \mathrm{mmol}, 1.00$ equiv). After being stirred overnight at room temperature, the reaction mixture was evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 95: 5\right.$ to $\left.4: 1 \mathrm{PE} / E t O A c+3 \% \mathrm{NEt}_{3}\right)$ to yield the pure product 4.252 (57 $\mathrm{mg}, 70 \%$ ) as a white solid and the pure 4.251 ( $8 \mathrm{mg}, 15 \%$ ) as a white solid.

## Indole 4.251:

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.12-7.97(\mathrm{~m}, 4 \mathrm{H}), 7.70-7.52(\mathrm{~m}, 2 \mathrm{H}), 7.55-7.45(\mathrm{~m}, 3 \mathrm{H}), 7.41-$ $7.33(\mathrm{~m}, 2 \mathrm{H}), 7.32-7.15(\mathrm{~m}, 5 \mathrm{H}), 5.05(\mathrm{~s}, 1 \mathrm{H}), 3.67-3.51(\mathrm{~m}, 2 \mathrm{H}), 3.01-2.91(\mathrm{~m}, 2 \mathrm{H}), 2.87(\mathrm{~d}, \mathrm{~J}=$ $14.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.70(\mathrm{~d}, \mathrm{~J}=14.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.65(\mathrm{~s}, 9 \mathrm{H}), 1.18(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 196.8,170.5,167.0,151.0,135.5,134.6,131.8,130.9,130.7,130.5$, $130.2,130.2,129.7,129.3,125.4,124.5,123.6,120.0,119.1,116.1,84.6,80.8,52.3,39.8,38.5$, 28.4, 25.6, 24.8, 24.4.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd $\mathrm{C}_{36} \mathrm{H}_{39} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 615.2523; found: 615.2525.

## Stannyl 4.252:

${ }^{1}{ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $d_{4}$ ): $\delta 8.18-8.02(\mathrm{~m}, 2 \mathrm{H}), 7.91(\mathrm{dd}, J=7.6,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.74-7.56$ $(\mathrm{m}, 2 \mathrm{H}), 7.49(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.41-7.33(\mathrm{~m}, 3 \mathrm{H}), 7.33-7.25(\mathrm{~m}, 2 \mathrm{H}), 7.25-7.09(\mathrm{~m}, 2 \mathrm{H}), 5.12$ $(\mathrm{s}, 1 \mathrm{H}), 3.48-3.35(\mathrm{~m}, 2 \mathrm{H}), 3.04-2.88(\mathrm{~m}, 3 \mathrm{H}), 2.78(\mathrm{~d}, \mathrm{~J}=14.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H}), 1.52(\mathrm{ddd}, J=$ $15.8,8.6,6.2 \mathrm{~Hz}, 6 \mathrm{H}), 1.39-1.28(\mathrm{~m}, 6 \mathrm{H}), 1.27(\mathrm{~s}, 3 \mathrm{H}), 1.26(\mathrm{~s}, 3 \mathrm{H}), 1.18-1.07(\mathrm{~m}, 6 \mathrm{H}), 0.85(\mathrm{t}, \mathrm{J}=$ $7.3 \mathrm{~Hz}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 196.8,170.2,167.0,153.8,140.0,138.7,135.5,134.6,133.5$, $130.9,130.8,130.6,130.5,130.2,129.7,129.3,124.9,123.4,119.5,116.4,85.3,80.8,52.4,42.0$, 38.7, 28.5, 28.4, 27.0, 25.0, 24.6, 14.1, 14.0.

HRMS (ESI): $m / z$ calcd $\mathrm{C}_{27} \mathrm{H}_{65} \mathrm{~N}_{2} \mathrm{O}_{6} \mathrm{SSn}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 905.3580; found: 905.3585.
tert-butyl 3-(benzoyloxy)-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)carboxylate (4.253)


To a solution of the isonitrile $4.268(27 \mathrm{mg}, 0.071 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $7 \mathrm{~mL}, 0.01 \mathrm{M}$ ) was added benzoic acid ( $9 \mathrm{mg}, 0.071 \mathrm{mmol}, 1.00$ equiv). After being stirred at room temperature for 3 days, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 4:1) to yield the pure product $4.253(34 \mathrm{mg}, 98 \%)$ as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.21-8.09(\mathrm{~m}, 2 \mathrm{H}), 8.00(\mathrm{dt}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.63-7.54(\mathrm{~m}, 1 \mathrm{H})$, $7.52-7.42(\mathrm{~m}, 3 \mathrm{H}), 7.36(\mathrm{ddd}, J=8.4,7.2,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.55(\mathrm{~s}, 1 \mathrm{H}), 5.43(\mathrm{~s}$, $1 \mathrm{H}), 4.39(\mathrm{dt}, J=12.6,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.83(\mathrm{ddd}, J=12.8,8.1,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.01-2.79(\mathrm{~m}, 2 \mathrm{H}), 1.68(\mathrm{~s}$, 9H), 1.31 (s, 3H), 1.28 (s, 3H).
${ }^{13}{ }^{2}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 166.3,166.2,150.7,139.5,133.3,130.1,130.0,129.1,128.5,127.6$, $127.4,126.2,123.4,122.5,119.2,115.0,113.9,76.4,39.0,34.8,28.2,26.6,21.4,21.2$.

IR: v $\left(\mathrm{cm}^{-1}\right) 3467$ (w), 2975 (w), 1737 (m), 1660 (m), 1610 (w), 1569 (w), 1501 (w), 1471 (w), 1426 (w), 1352 (m), 1311 (m), 1277 (m), 1205 (m), 1151 (s), 1108 (s), 1055 (m), 911 (m), 845 (w), 812 (w).

HRMS: (ESI) $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 487.2227; found: 487.2229.
tert-butyl 3-hydroxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)carboxylate (4.269)


Following a reported procedure, ${ }^{412}$ to a solution of the ester 4.253 ( $141 \mathrm{mg}, 0.289 \mathrm{mmol}, 1.00$ equiv) in dry $\mathrm{MeOH}\left(3 \mathrm{~mL}, 0.1 \mathrm{M}\right.$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( $60 \mathrm{mg}, 0.433 \mathrm{mmol}, 1.50$ equiv). After being stirred at room temperature for 24 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1\right.$ to $\left.\mathrm{PE} / \mathrm{EtOAc} 3: 1\right)$ to yield the pure products 4.269 ( $94 \mathrm{mg}, 85 \%$ ) as a yellowish solid and 4.270 ( $11 \mathrm{mg}, 13 \%$ ) as a yellowish solid.

## Alcohol 4.270:

${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 8.01$ (br s, 1H), $7.51(\mathrm{dd}, J=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{dt}, J=8.2,0.9 \mathrm{~Hz}$, $1 \mathrm{H}), 7.26-7.21(\mathrm{~m}, 1 \mathrm{H}), 7.13$ (ddd, $J=8.0,7.1,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.35(\mathrm{~s}, 1 \mathrm{H}), 4.88(\mathrm{ddd}, J=12.7,5.2,2.1$
$\mathrm{Hz}, 1 \mathrm{H}), 4.08(\mathrm{~s}, 1 \mathrm{H}), 3.85(\mathrm{~s}, 1 \mathrm{H}), 3.30(\mathrm{dddd}, J=12.7,11.6,5.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.08-2.80(\mathrm{~m}, 2 \mathrm{H})$, $1.32(\mathrm{~s}, 3 \mathrm{H}), 1.00(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.6,137.3,127.7,127.2,126.8,124.0,120.4,119.2,112.4,111.2$, 110.5, 74.9, 40.7, 35.3, 26.5, 20.6, 19.9.

IR: v ( $\mathrm{cm}^{-1}$ ) 3459 (w), 2974 (w), 1731 (m), 1664 (m), 1613 (w), 1555 (w), 1493 (w), 1464 (w), 1352 (m), 1311 (m), 1279 (m), 1248 (m), 1209 (m), 1152 ( s$), 1113$ ( s$), 1048$ (m), 911 (m), 852 (m), 800 (w), 729 (s), 684 (w).

HRMS: (ESI) $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 283.1441; found: 283.1442.

## (S)-N-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,3-dimethylbutanamide (4.53)





It was prepared according to a literature procedure. ${ }^{318 a}$

## 2-iodo-5-methoxyaniline (4.118)



It was prepared according to a literature procedure. ${ }^{354}$
4-(1,3-dioxoisoindolin-2-yl)butanal (4.122)


It was prepared according to a literature procedure. ${ }^{355}$

2-(6-methoxy-1H-indol-3-yl)ethan-1-amine (4.27)


It was prepared according to a literature procedure. ${ }^{352 d}$

## $N$-(2-(1H-indol-3-yl)ethyl)formamide (4.240)



According to a reported procedure, ${ }^{399}$ a solution of tryptamine (1.16) ( $16.0 \mathrm{~g}, 100 \mathrm{mmol}, 1.00$ equiv) in dry ethyl formate ( $60 \mathrm{~mL}, 1.67 \mathrm{M}$ ) was refluxed for 5 h . The reaction mixture was cooled to room temperature and evaporated in vacuo to obtain the formamide $4.240(18.8 \mathrm{~g})$ which was used directly in the next step without further purification. For analysis, the crude product can be purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 95: 5 \mathrm{DCM} / \mathrm{MeOH}\right)$ to yield the pure product 4.299 as a yellowish oil.

The spectral data were in accordance with those reported in the literature. ${ }^{399}$

## N -(2-(6-methoxy-1H-indol-3-yl)ethyl)formamide (4.299)



According to a reported procedure, ${ }^{399}$ a solution of 6-methoxytryptamine (4.27) (3.10 g, 16.3 mmol, 1.00 equiv) in dry ethyl formate ( $50 \mathrm{~mL}, 0.33 \mathrm{M}$ ) was refluxed for 12 h . The reaction mixture was cooled to room temperature and evaporated in vacuo to obtain the formamide 4.299 ( 3.45 g ) which was used directly in the next step without further purification. For analysis, the crude product can be purified by flash column chromatography $\left(\mathrm{SiO}_{2}, 95: 5 \mathrm{DCM} / \mathrm{MeOH}\right)$ to yield the pure product 4.299 as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.34$ (br s, 0.2 H ), $8.30(\mathrm{br} \mathrm{s}, 0.8 \mathrm{H}), 8.06(\mathrm{~s}, 0.8 \mathrm{H}), 7.85(\mathrm{~d}, \mathrm{~J}=12.2 \mathrm{~Hz}$, $0.2 \mathrm{H}), 7.43(\mathrm{~d}, \mathrm{~J}=8.6 \mathrm{~Hz}, 0.8 \mathrm{H}), 7.39(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 0.2 \mathrm{H}), 6.89(\mathrm{~s}, 0.8 \mathrm{H}), 6.83(\mathrm{~s}, 1.2 \mathrm{H}), 6.78(\mathrm{~d}, \mathrm{~J}=$
$8.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.79(\mathrm{~s}, 1 \mathrm{H}), 3.82(\mathrm{~s}, 3 \mathrm{H}), 3.60(\mathrm{q}, \mathrm{J}=6.5 \mathrm{~Hz}, 1.6 \mathrm{H}), 3.46(\mathrm{q}, \mathrm{J}=6.3 \mathrm{~Hz}, 0.4 \mathrm{H}), 2.98-2.85$ ( $\mathrm{m}, 2 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $\mathbf{1 0 1} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Major rotamer: 161.4, 156.7, 137.3, 121.7, 121.1, 119.3, 112.4, 109.6, 94.9, 55.8, 38.4, 25.3. Minor rotamer: 164.8, 156.7, 137.4, 121.6, 121.3, 119.0, 111.4, 109.7, 95.0, 55.8, 42.1, 27.5.

IR: v ( $\mathrm{cm}^{-1}$ ) 3297 (w), 2937 (w), 2818 (w), 1660 (s), 1626 (m), 1552 (w), 1504 (m), 1457 (m), 1385 (w), 1342 (w), 1306 (w), 1259 (m), 1199 (m), 1160 (s), 1093 (w), 1027 (m), 943 (w), 804 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 219.1128; found: 219.1131 .
tert-butyl 3-(2-formamidoethyl)-1H-indole-1-carboxylate (4.241)


According to a reported procedure, ${ }^{399}$ the above-obtained formamide 4.240 ( $18.8 \mathrm{~g}, 1.00$ equiv) and DMAP ( $305 \mathrm{mg}, 2.5 \mathrm{mmol}, 0.025$ equiv) were dissolved in dry DMF ( $333 \mathrm{~mL}, 0.3 \mathrm{M}$ ). $\mathrm{Boc}_{2} \mathrm{O}$ ( $21.8 \mathrm{~g}, 100 \mathrm{mmol}, 1.00$ equiv) in DMF ( 60 mL ) was added dropwise. After being stirred at room temperature for 24 hours, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\left.\mathrm{SiO}_{2}, 98: 2 \mathrm{DCM} / \mathrm{MeOH}\right)$ to yield the pure product 4.241 ( $20.8 \mathrm{~g}, 72 \%$ over 2 steps) as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.12(\mathrm{brs}, 1.7 \mathrm{H}), 7.96-7.93(\mathrm{~m}, 0.3 \mathrm{H}), 7.53(\mathrm{dt}, J=7.8,0.9 \mathrm{~Hz}, 0.85 \mathrm{H})$, 7.47 (dt, J = 7.8, $1.0 \mathrm{~Hz}, 0.15 \mathrm{H}$ ), $7.42(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.36-7.28(\mathrm{~m}, 1 \mathrm{H}), 7.29-7.19(\mathrm{~m}, 1 \mathrm{H}), 5.92(\mathrm{~s}$, $1 \mathrm{H}), 3.62(\mathrm{q}, J=6.6 \mathrm{~Hz}, 1.7 \mathrm{H}), 3.53(\mathrm{q}, J=6.7 \mathrm{~Hz}, 0.3 \mathrm{H}), 2.96-2.87(\mathrm{~m}, 2 \mathrm{H}), 1.66(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Major rotamer: $161.4,149.7,135.6,130.3,124.7,123.4,122.7$, $118.9,117.4,115.4,83.8,37.8,28.3,25.1$. Minor rotamer: 164.5, 149.6, 135.7, 129.9, 124.8, 123.7, 122.7, 118.6, 116.4, 115.6, 83.9, 41.4, 28.3, 27.3.

IR: v (cm ${ }^{-1}$ ) 3282 (w), 3052 (w), 2978 (w), 2934 (w), 2865 (w), 1735 (m), 1728 (s), 1662 (s), 1537 (w), 1453 (m), 1375 (s), 1308 (w), 1254 (m), 1224 (w), 1156 (s), 1090 (s), 1050 (w), 1019 (w), 857 (w), 766 (m), 746 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 289.1547; found: 289.1550.


According to a reported procedure, ${ }^{385}$ the above-obtained formamide 4.299 ( $3.45 \mathrm{mg}, 1.00$ equiv) and DMAP ( $50 \mathrm{mg}, 0.41 \mathrm{mmol}, 0.025$ equiv) were dissolved in dry DMF ( $50 \mathrm{~mL}, 0.3 \mathrm{M}$ ). $\mathrm{Boc}_{2} \mathrm{O}$ ( 3.56 $\mathrm{g}, 16.30 \mathrm{mmol}, 1.00$ equiv) in DMF ( 10 mL ) was added dropwise. After being stirred at room temperature for 24 hours, the reaction was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, 98: 2$ $\mathrm{DCM} / \mathrm{MeOH})$ to yield the pure product $4.300(4.52 \mathrm{~g}, 87 \%$ over 2 steps) as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.10(\mathrm{~d}, J=1.6 \mathrm{~Hz}, 0.85 \mathrm{H}), 7.92(\mathrm{~d}, J=11.9 \mathrm{~Hz}, 0.15 \mathrm{H}), 7.71(\mathrm{~s}, 1 \mathrm{H})$, $7.36(\mathrm{~d}, \mathrm{~J}=8.6 \mathrm{~Hz}, 0.85 \mathrm{H}), 7.33-7.27(\mathrm{~m}, 1.15 \mathrm{H}), 6.87-6.84(\mathrm{~m}, 1 \mathrm{H}), 5.99(\mathrm{~s}, 1 \mathrm{H}), 3.85(\mathrm{~s}, 0.45 \mathrm{H})$, $3.80(\mathrm{~s}, 2.55 \mathrm{H}), 3.59(\mathrm{q}, J=6.6 \mathrm{~Hz}, 1.70 \mathrm{H}), 3.50(\mathrm{q}, J=6.6 \mathrm{~Hz}, 0.3 \mathrm{H}), 2.92-2.80(\mathrm{~m}, 2 \mathrm{H}), 1.65(\mathrm{~s}$, $9 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Major rotamer: 161.3, 158.0, 149.8, 136.6, 124.0, 121.9, 119.4, 117.4, 111.9, 99.6, 83.6, 55.7, 37.7, 28.2, 25.2. Minor rotamer: 164.5, 158.1, 149.7, 136.6, 123.6, 122.3, 119.1, 116.4, 112.1, 99.6, 83.7, 55.7, 41.4, 28.2, 27.3.

IR: v (cm ${ }^{-1}$ ) 3291 (w), 2977 (w), 2936 (w), 1726 (s), 1663 (m), 1619 (w), 1572 (w), 1533 (w), 1487 (m), 1442 (m), 1380 (s), 1325 (w), 1253 (m), 1226 (s), 1156 (s), 1091 (s), 1037 (m), 905 (m), 851 (w), 808 (w), 767 (w), 732 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 319.1652; found: 319.1657.
tert-butyl 3-(2-formamidoethyl)-2-(tributylstannyl)-1H-indole-1-carboxylate (4.242)


According to a reported procedure, ${ }^{385}$ to a solution of tetramethylpiperidine ( $19.6 \mathrm{~mL}, 115 \mathrm{mmol}$, 2.30 equiv) in dry THF ( 170 mL ) was added ${ }^{\text {n }}$ BuLi ( $2.35 \mathrm{M}, 53.2 \mathrm{~mL}, 125 \mathrm{mmol}, 2.50$ equiv) dropwise at $-78^{\circ} \mathrm{C}$. After stirring at $-78^{\circ} \mathrm{C}$ for 10 minutes, the formamide $4.241(14.4 \mathrm{~g}, 50 \mathrm{mmol}, 1.00$ equiv) in THF ( 80 mL ) was added dropwise at $-78^{\circ} \mathrm{C}$. After stirring at $-78^{\circ} \mathrm{C}$ for 40 minutes, Bu 3 SnCl $\left(40.7 \mathrm{~mL}, 150 \mathrm{mmol}, 3.00\right.$ equiv) was added and the reaction mixture was stirred at $-78{ }^{\circ} \mathrm{C}$ for another 20 min . The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evapo-
rated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}$ $95: 5+3 \% \mathrm{NEt}_{3}$ to $\mathrm{PE} / E t \mathrm{OAc} 2: 1+3 \% \mathrm{NEt}_{3}$ ) to yield the pure product $4.242(23.1 \mathrm{~g}, 80 \%)$ as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , Methanol- $\boldsymbol{d}_{4}$ ): $\delta 8.04(\mathrm{~s}, 1 \mathrm{H}), 7.97-7.91(\mathrm{~m}, 1 \mathrm{H}), 7.63-7.57(\mathrm{~m}, 1 \mathrm{H}), 7.26$ $7.18(\mathrm{~m}, 2 \mathrm{H}), 3.48-3.38(\mathrm{~m}, 2 \mathrm{H}), 3.00-2.92(\mathrm{~m}, 2 \mathrm{H}), 1.70(\mathrm{~s}, 9 \mathrm{H}), 1.62-1.49(\mathrm{~m}, 6 \mathrm{H}), 1.42-1.29$ $(\mathrm{m}, 6 \mathrm{H}), 1.18-1.07(\mathrm{~m}, 6 \mathrm{H}), 0.88(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $\boldsymbol{d}_{4}$ ): $\delta$ 163.6, 153.8, 140.1, 138.8, 133.5, 130.6, 124.9, 123.4, 119.4, 116.4, 85.4, 40.4, 30.4, 28.5, 28.4, 27.2, 14.1, 14.0.

IR: v ( $\mathrm{cm}^{-1}$ ) 3475 (w), 2950 (w), 2922 (w), 2851 (w), 1713 (s), 1660 (m), 1613 (w), 1488 (w), 1441 (w), 1369 (s), 1333 (m), 1292 (w), 1218 (m), 1158 (s), 1103 (m), 1065 (w), 1038 (w), 960 (w), 915 (w), 812 (w), 769 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{47} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Sn}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 579.2603 ; found: 579.2607.
tert-butyl 3-(2-formamidoethyl)-6-methoxy-2-(tributylstannyl)-1H-indole-1-carboxylate (4.301)


According to a reported procedure, ${ }^{385}$ to a solution of tetramethylpiperidine ( $5.61 \mathrm{~mL}, 32.93$ mmol, 2.30 equiv) in dry THF ( 47 mL ) was added ${ }^{\mathrm{n}}$ BuLi ( $2.35 \mathrm{M}, 15.23 \mathrm{~mL}, 35.79 \mathrm{mmol}, 2.50$ equiv) dropwise at $-78^{\circ} \mathrm{C}$. After stirring at $-78^{\circ} \mathrm{C}$ for 10 minutes, the formamide $4.300(4558 \mathrm{mg}, 14.32$ mmol, 1.00 equiv) in THF ( 24 mL ) was added dropwise at $-78^{\circ} \mathrm{C}$. After stirring at $-78^{\circ} \mathrm{C}$ for 40 min , $\mathrm{Bu}_{3} \mathrm{SnCl}(11.65 \mathrm{~mL}, 42.95 \mathrm{mmol}, 3.00$ equiv) was added and the reaction mixture was stirred at -78 ${ }^{\circ} \mathrm{C}$ for another 20 min . The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, $\mathrm{PE} / \mathrm{EtOAc} 95: 5+3 \% \mathrm{NEt}_{3}$ to $\mathrm{PE} / E t O A c 2: 1+3 \% \mathrm{NEt}_{3}$ ) to yield the pure product 4.301 ( $6.79 \mathrm{~g}, 78 \%$ ) as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 8.04(\mathrm{~s}, 0.9 \mathrm{H}), 7.77(\mathrm{~s}, 0.1 \mathrm{H}), 7.52(\mathrm{~d}, \mathrm{~J}=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{~d}, \mathrm{~J}$ $=8.5 \mathrm{~Hz}, 0.9 \mathrm{H}$ ), $7.35(\mathrm{~d}, \mathrm{~J}=8.6 \mathrm{~Hz}, 0.1 \mathrm{H}), 6.83(\mathrm{dd}, J=8.6,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.80(\mathrm{~s}, 3 \mathrm{H}), 3.44-3.34(\mathrm{~m}$, $2 \mathrm{H}), 2.96-2.85(\mathrm{~m}, 2 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H}), 1.64-1.42(\mathrm{~m}, 6 \mathrm{H}), 1.39-1.25(\mathrm{~m}, 6 \mathrm{H}), 1.20-0.98(\mathrm{~m}, 6 \mathrm{H})$, $0.87(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 163.6,159.0,153.7,139.7,138.1,130.6,127.5,119.8,112.1$, 101.1, 85.1, 55.9, 40.4, 30.4, 28.5, 28.4, 27.2, 14.1, 14.0.

IR: v $\left(\mathrm{cm}^{-1}\right) 3476$ (w), 2954 (w), 2923 (w), 2852 (w), 1709 (s), 1660 (m), 1613 (w), 1485 (w), 1438 (w), 1369 (s), 1327 (m), 1291 (w), 1240 (w), 1218 (m), 1158 (s), 1103 (m), 1065 (w), 1038 (w), 960 (w), 915 (w), 855 (w), 812 (w), 769 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{49} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{Sn}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 609.2709; found: 609.2712.
ethyl 3,3-dimethylpent-4-enoate (4.246)


According to a reported procedure, ${ }^{350 \mathrm{a}}$ a solution of prenol 4.244 ( $10.0 \mathrm{~g}, 116 \mathrm{mmol}, 1.00$ equiv) and phenol ( $1.00 \mathrm{~g}, 12 \mathrm{mmol}, 0.10$ equiv) in trimethyl orthoacetate ( $45 \mathrm{~mL}, 244 \mathrm{mmol}, 2.10$ equiv) was heated to $130{ }^{\circ} \mathrm{C}$ for 12 h with continuous distillation of the ethanol produced then to $160{ }^{\circ} \mathrm{C}$ for 4 h . The reaction mixture was cooled to room temperature, partitioned between $\mathrm{Et}_{2} \mathrm{O}$ and 4 M HCl and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to obtain the pure ester 4.246 ( 18.1 g , quantitative) which was used directly in the next step without further purification.

The spectral data were in accordance with those reported in the literature. ${ }^{350 a}$

## 3,3-dimethylpent-4-enoic acid (4.247)



According to a reported procedure, ${ }^{400 \mathrm{a}}$ to a solution of $50 \% \mathrm{NaOH}(1.02 \mathrm{~g}$ in $1 \mathrm{~mL} \mathrm{H} 2 \mathrm{O}, 25.6 \mathrm{mmol}$, 2.00 equiv) in $\mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O}(1: 1,6.4 / 6.4 \mathrm{~mL}, 1 \mathrm{M})$ at $0^{\circ} \mathrm{C}$ was added dropwise ester 4.246 ( 2.00 g , $12.8 \mathrm{mmol}, 1.00$ equiv) over 1 h . After being stirred at room temperature for 5 hours, the reaction mixture was partitioned between $\mathrm{Et}_{2} \mathrm{O}$ and $\mathrm{H}_{2} \mathrm{O}$. The organic phase was extracted with $5 \% \mathrm{KOH}$, and the combined aqueous phases were cooled in an ice bath, acidified with concentrated HCl , and extracted with DCM. The combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The residue was distilled at reduced pressure through a Vigreux column (bp $87^{\circ} \mathrm{C}$ at 4 mm Hg ) to yield 4.247 ( $1.21 \mathrm{~g}, 74 \%$ ) as a colorless liquid.

The spectral data were in accordance with those reported in the literature. ${ }^{400 a}$
S-phenyl 3,3-dimethylpent-4-enethioate (4.250)


According to a reported procedure, ${ }^{403}$ to a solution of the acid $4.247(2.91 \mathrm{~g}, 22.7 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $76 \mathrm{~mL}, 0.3 \mathrm{M}$ ) was added dropwise TFAA ( $3.16 \mathrm{~mL}, 22.7 \mathrm{mmol}, 1.00$ equiv) at room temperature. The reaction mixture was stirred for 10 minutes and thiophenol ( $2.32 \mathrm{~mL}, 22.7$
mmol, 1.00 equiv) was added. After being stirred at $45^{\circ} \mathrm{C}$ for 24 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, pure PE to $\left.\mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 9: 1\right)$ to yield the pure product 4.250 ( $4.25 \mathrm{~g}, 85 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.48-7.32(\mathrm{~m}, 5 \mathrm{H}), 5.93(\mathrm{dd}, J=17.4,10.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.00(\mathrm{dd}, J=17.4$, $1.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.98(\mathrm{dd}, J=10.7,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.65(\mathrm{~s}, 2 \mathrm{H}), 1.18(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 195.5, 146.6, 134.5, 129.5, 129.3, 128.3, 111.4, 55.1, 37.3, 27.0.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{OS}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 221.0995; found: 221.0998
IR: v ( $\mathrm{cm}^{-1}$ ) 3082 (w), 2963 (m), 2874 (w), 1708 (s), 1642 (w), 1586 (w), 1476 (w), 1441 (w), 1417 (w), 1328 (w), 1192 (w), 1111 (w), 1001 (s), 915 (m), 746 (s), 714 (m), 690 (m).

## $S$-phenyl 3,3-dimethyl-4-oxobutanethioate (4.238)



According to a reported procedure, ${ }^{404}$ the thioester 4.250 ( $4.00 \mathrm{~g}, 18.2 \mathrm{mmol}, 1.00$ equiv) was dissolved in dry DCM ( $180 \mathrm{~mL}, 0.1 \mathrm{M}$ ) and cooled to $-78^{\circ} \mathrm{C}$. Ozone was bubbled through the reaction mixture until a blue color persisted. $\mathrm{N}_{2}$ was then bubbled through the reaction mixture until the blue color disappeared. $\mathrm{PPh}_{3}(9.52 \mathrm{~g}, 36.3 \mathrm{mmol}, 1.05$ equiv) was added. After being stirred at room temperature for 5 hours, the reaction mixture was evaporated in vacuo. The residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 9: 1\right.$ to $\left.8: 1\right)$ to yield the pure product 4.238 ( $3.35 \mathrm{~g}, 83 \%$ ) as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl 3 ): $\delta 9.55(\mathrm{~s}, 1 \mathrm{H}), 7.65-7.26(\mathrm{~m}, 5 \mathrm{H}), 2.91(\mathrm{~s}, 2 \mathrm{H}), 1.19(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 203.6,195.4,134.5,129.7,129.4,127.4,50.6,45.3,21.9$.
IR: v ( $\mathrm{cm}^{-1}$ ) 2967 (w), 2928 (w), 2711 (w), 1725 (s), 1700 (s), 1583 (w), 1474 (w), 1442 (w), 1397 (w), 1327 (w), 1194 (w), 1004 (s), 908 (m), 878 (w), 785 (w), 745 (s), 689 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H1}_{5} \mathrm{O}_{2} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 223.0787; found: 223.0790.
tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-formamidoethyl)-1H-indole-1-carboxylate (4.267)


The aldehyde 4.238 ( $321 \mathrm{mg}, 1.44 \mathrm{mmol}, 1.00$ equiv), compound 4.242 ( $600 \mathrm{mg}, 1.59 \mathrm{mmol}, 1.10$ equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}\left(132 \mathrm{mg}, 0.14 \mathrm{mmol}, 0.10\right.$ equiv), $\mathrm{AsPh}_{3}(44 \mathrm{mg}, 0.14 \mathrm{mmol}, 0.10$ equiv), and CuDPP ( $500 \mathrm{mg}, 1.73 \mathrm{mmol}, 1.20$ equiv) were dissolved in dry and degassed THF/Hexane (1:3, $5.4 / 16.2 \mathrm{~mL}, 0.067 \mathrm{M})$. After being stirred at room temperature for 6 h , the reaction mixture was filtered through Celite (rinsed with THF). The filtrate was washed with $1 \mathrm{M} \mathrm{HCl}, 10 \% \mathrm{NH}_{4} \mathrm{OH}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 2$ ) to yield the pure product 4.267 (544 mg, 94\%) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.63(\mathrm{~s}, 1 \mathrm{H}), 8.09(\mathrm{~s}, 1 \mathrm{H}), 7.95(\mathrm{dt}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.64-7.56(\mathrm{~m}$, 1 H ), 7.43 (ddd, $J=8.4,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.30$ (ddd, $J=8.1,7.2,1.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 6.97 (br s, 1H), $3.58-$ $3.50(\mathrm{~m}, 2 \mathrm{H}), 3.07(\mathrm{~s}, 2 \mathrm{H}), 2.94-2.83(\mathrm{~m}, 2 \mathrm{H}), 1.69(\mathrm{~s}, 9 \mathrm{H}), 1.14(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 204.7, 195.8, 161.9, 150.2, 136.2, 136.1, 128.9, 127.6, 123.9, 123.6, $120.7,115.8,85.8,51.0,45.3,38.3,28.2,23.1,22.1$.

IR: v (cm ${ }^{-1}$ ) 3335 (w), 2979 (w), 2935 (w), 2362 (w), 2338 (w), 1726 (s), 1673 (s), 1617 (w), 1560 (w), 1492 (w), 1440 (w), 1370 (s), 1324 (m), 1291 (m), 1213 (m), 1149 (s), 1084 (w), 1035 (m), 922 (w), 841 (w), 811 (w), 717 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 401.2071; found: 401.2070.
tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-formamidoethyl)-6-methoxy-1H-indole-1carboxylate (4.302)


The aldehyde 4.238 ( $1.44 \mathrm{~g}, 6.49 \mathrm{mmol}, 1.00$ equiv), compound 4.301 ( $4.34 \mathrm{~g}, 7.14 \mathrm{mmol}, 1.10$ equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}\left(594 \mathrm{mg}, 0.65 \mathrm{mmol}, 0.10\right.$ equiv), $\mathrm{AsPh}_{3}$ ( $199 \mathrm{mg}, 0.65 \mathrm{mmol}, 0.10$ equiv), and CuDPP ( $2.19 \mathrm{~g}, 7.79 \mathrm{mmol}, 1.20$ equiv) were dissolved in dry and degassed THF/Hexane (1:3, 24/96 $\mathrm{mL}, 0.067 \mathrm{M})$. After being stirred at room temperature for 6 h , the reaction mixture was filtered through Celite (rinsed with THF). The filtrate was washed with $1 \mathrm{M} \mathrm{HCl}, 10 \% \mathrm{NH}_{4} \mathrm{OH}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 2$ ) to yield the pure product 4.302 ( $2.65 \mathrm{~g}, 95 \%$ ) as a yellow amorphous solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ): $\delta 9.63(\mathrm{~s}, 1 \mathrm{H}), 8.11(\mathrm{~s}, 1 \mathrm{H}), 7.52(\mathrm{~d}, \mathrm{~J}=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.48(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}$, $1 \mathrm{H}), 7.00(\mathrm{~s}, 1 \mathrm{H}), 6.93(\mathrm{dd}, J=8.7,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.59-3.49(\mathrm{~m}, 2 \mathrm{H}), 3.05(\mathrm{~s}, 2 \mathrm{H}), 2.88-$ 2.85 (m, 2H), 1.70 (s, 9H), 1.13 (s, 6H).
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 204.6, 195.1, 161.8, 160.5, 150.3, 137.9, 135.5, 125.1, 122.6, 121.5, $113.2,100.0,85.7,55.7,50.9,45.5,38.4,28.3,23.2,22.1$.

IR: v ( $\mathrm{cm}^{-1}$ ) 3330 (w), 2976 (w), 2936 (w), 2361 (w), 2338 (w), 1726 (s), 1673 (s), 1616 (w), 1554 (w), 1490 (w), 1441 (w), 1368 (s), 1322 (m), 1289 (w), 1213 (m), 1149 (s), 1084 (w), 1035 (m), 922 (w), 841 (w), 811 (w), 766 (w), 717 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 431.2177; found: 431.2178 .
tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-isocyanoethyl)-1H-indole-1-carboxylate (4.268)


To a solution of the formamide $4.267\left(204 \mathrm{mg}, 0.51 \mathrm{mmol}, 1.00\right.$ equiv) and $\mathrm{NEt}_{3}(354 \mu \mathrm{~L}, 2.55$ mmol, 5.00 equiv) in dry DCM ( $1.7 \mathrm{~mL}, 0.3 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added $\mathrm{POCl}_{3}(71 \mu \mathrm{~L}, 0.76 \mathrm{mmol}, 1.50$ equiv) dropwise over 30 min . After being stirred at $-78^{\circ} \mathrm{C}$ for 3 hours, the reaction mixture was poured into a cold saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ solution and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{Al}_{2} \mathrm{O}_{3}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 2: 1+3 \% \mathrm{NEt}_{3}\right.$ to $\left.\mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 1: 1+3 \% \mathrm{NEt}_{3}\right)$ to yield the pure product $4.268(174 \mathrm{mg}, 89 \%)$ as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ): $\delta 9.65(\mathrm{~s}, 1 \mathrm{H}), 7.98(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.66(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.45$ (ddd, $J=8.3,7.2,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.73(\mathrm{t}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.13-3.02(\mathrm{~m}, 4 \mathrm{H}), 1.70(\mathrm{~s}$, 9H), 1.16 (s, 6H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 204.7, 194.7, 157.1, 150.1, 136.4, 136.0, 129.1, 127.6, 123.9, 121.9, $120.6,115.8,86.0,51.2,45.2,42.5,28.3,24.9,22.3$.

IR: v ( $\mathrm{cm}^{-1}$ ) 2976 (w), 2934 (w), 2148 (w), 1728 (s), 1676 (w), 1617 (w), 1557 (w), 1499 (w), 1371 (m), 1323 (m), 1287 (w), 1239 (w), 1211 (m), 1153 (s), 1079 (w), 1031 (w), 839 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 383.1965 ; found: 383.1968.

## tert-butyl 2-(3,3-dimethyl-4-oxobutanoyl)-3-(2-isocyanoethyl)-6-methoxy-1H-indole-1- <br> carboxylate (4.303)



To a solution of the formamide $4.302\left(1.96 \mathrm{~g}, 4.56 \mathrm{mmol}, 1.00\right.$ equiv) and $\mathrm{NEt}_{3}(3.17 \mathrm{~mL}, 22.81$ mmol, 5.00 equiv) in dry DCM ( $15 \mathrm{~mL}, 0.3 \mathrm{M}$ ) was added $\mathrm{POCl}_{3}(638 \mu \mathrm{~L}, 6.84 \mathrm{mmol}, 1.50$ equiv) dropwise at $-78^{\circ} \mathrm{C}$ over 30 min . After being stirred at $-78^{\circ} \mathrm{C}$ for 3 hours, the reaction mixture was
poured into a cold saturated aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ solution and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{Al}_{2} \mathrm{O}_{3}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 2: 1+3 \% \mathrm{NEt}_{3}\right.$ to $\mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 1: 1+3 \% \mathrm{NEt}_{3}$ ) to yield the pure product $4.303(1.73 \mathrm{~g}, 92 \%)$ as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.64(\mathrm{~s}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.96(\mathrm{dd}, J$ $=8.8,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.89(\mathrm{~s}, 3 \mathrm{H}), 3.73(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.05(\mathrm{~s}, 2 \mathrm{H}), 3.02(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 1.70(\mathrm{~s}$, $9 H), 1.13(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 204.6,193.9,160.4,157.0,150.2,137.7,135.4,123.6,122.8,121.5$, 113.3, 99.8, 85.8, 55.8, 51.0, 45.3, 42.7, 28.3, 25.1, 22.2.

IR: v (cm ${ }^{-1}$ ) 2974 (w), 2934 (w), 2148 (w), 1728 (s), 1676 (w), 1617 (w), 1555 (w), 1494 (w), 1368 (m), 1322 (m), 1290 (w), 1238 (m), 1211 (m), 1150 (s), 1076 (w), 1032 (w), 840 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 413.2071; found: 413.2075.

## tert-butyl 3-acetoxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)carboxylate (4.271)



To a solution of the isonitrile 4.268 ( $20 \mathrm{mg}, 0.052 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $5.3 \mathrm{~mL}, 0.01 \mathrm{M}$ ) was added acetic acid ( $3 \mu \mathrm{~L}, 0.052 \mathrm{mmol}, 1.00$ equiv). After being stirred at room temperature for 1.5 days, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 4:1) to yield the pure product 4.271 ( $19 \mathrm{mg}, 85 \%$ ) as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.99(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.35(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.30-7.22(\mathrm{~m}, 1 \mathrm{H}), 5.37(\mathrm{~s}, 1 \mathrm{H}), 5.30(\mathrm{~s}, 1 \mathrm{H}), 4.36(\mathrm{dt}, J=12.9,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.79$ (ddd, J = 12.9, 8.1, $4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.97-2.78(\mathrm{~m}, 2 \mathrm{H}), 2.25(\mathrm{~s}, 3 \mathrm{H}), 1.66(\mathrm{~s}, 9 \mathrm{H}), 1.20(\mathrm{~s}, 3 \mathrm{H}), 1.15(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 170.8,166.3,150.6,139.5,129.1,127.6,127.3,126.2,123.4,122.4$, 119.2, 115.0, 114.0, 84.5, 75.9, 38.9, 34.5, 28.2, 26.4, 21.4, 21.0.

IR: v $\left(\mathrm{cm}^{-1}\right) 3469$ (w), 2982 (m), 1736 (m), 1665 (m), 1610 (w), 1568 (w), 1497 (w), 1461 (w), 1428 (w), 1354 (m), 1312 (m), 1276 (m), 1250 (m), 1207 (m), 1150 (s), 1049 (m), 917 (m), 851 (m), 808 (w), 731 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 425.2071; found: 425.2075.


To a solution of the ester 4.271 ( $8 \mathrm{mg}, 0.019 \mathrm{mmol}, 1.00$ equiv) in dry $\mathrm{MeOH}(0.19 \mathrm{~mL}, 0.1 \mathrm{M})$ at 0 ${ }^{\circ} \mathrm{C}$ was added $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( $5.2 \mathrm{mg}, 0.038 \mathrm{mmol}, 1.50$ equiv). After being stirred at room temperature for 2 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 4:1) to yield the pure product 4.269 ( $7 \mathrm{mg}, 98 \%$ ) as a yellowish solid.
tert-butyl 3-hydroxy-2,2-dimethyl-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)carboxylate (4.269)


According to a reported procedure, ${ }^{413 \mathrm{~b}}$ to a solution of the isonitrile $4.268(1.50 \mathrm{~g}, 3.85 \mathrm{mmol}, 1.00$ equiv) and pyridine ( $1.87 \mathrm{~mL}, 23.1 \mathrm{mmol}, 6.00$ equiv) in dry DCM ( $385 \mathrm{~mL}, 0.01 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added TFA ( $857 \mu \mathrm{~L}, 11.5 \mathrm{mmol}, 3.00$ equiv) and the reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 2 hours. After being stirred at room temperature for 7 days, the reaction mixture was evaporated in vacuo. The residue was dissolved in ethyl acetate and stirred with saturated aqueous $\mathrm{NaHCO}_{3}$ for $1 h$. The organic phase was separated and washed with 1 M HCl , aqueous saturated $\mathrm{NaHCO}_{3}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ) to yield the pure product $4.269(1.25 \mathrm{~g}, 85 \%)$ as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.99(\mathrm{dt}, J=8.3,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.50-7.40(\mathrm{~m}, 1 \mathrm{H}), 7.35(\mathrm{ddd}, \mathrm{J}=8.4$, $7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.25(\mathrm{td}, J=7.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.40(\mathrm{~s}, 1 \mathrm{H}), 4.35(\mathrm{dt}, J=12.8,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.04(\mathrm{~d}, J=$ $1.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.85(\mathrm{ddd}, \mathrm{J}=12.8,7.9,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.81(\mathrm{~d}, \mathrm{~J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.99-2.79(\mathrm{~m}, 2 \mathrm{H}), 1.66(\mathrm{~s}$, $9 \mathrm{H}), 1.31(\mathrm{~s}, 3 \mathrm{H}), 1.02(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.5,150.6,139.4,129.1,127.5,126.5,126.1,123.3,121.7,119.1$, 116.3, 115.0, 84.6, 74.7, 39.4, 35.4, 28.2, 26.5, 21.3, 19.4.

IR: $v\left(\mathrm{~cm}^{-1}\right) 3467$ (w), 2975 (w), 1736 (m), 1660 (m), 1610 (w), 1568 (w), 1497 (w), 1465 (w), 1422 (w), 1351 (m), 1313 (m), 1281 (m), 1246 (m), 1207 (m), 1150 (s), 1110 (s), 1049 (m), 913 (m), 851 (m), 808 (w), 731 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 383.1965; found: 383.1970.


According to a reported procedure, ${ }^{413 \mathrm{~b}}$ to a solution of the isonitrile $4.303(1.25 \mathrm{~g}, 3.04 \mathrm{mmol}, 1.00$ equiv) and pyridine ( $984 \mu \mathrm{~L}, 12.2 \mathrm{mmol}, 6.00$ equiv) in dry DCM ( $304 \mathrm{~mL}, 0.01 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added TFA ( $452 \mu \mathrm{~L}, 6.08 \mathrm{mmol}, 3.00$ equiv) and the reaction mixture was stirred at $0^{\circ} \mathrm{C}$ for 2 hours. After being stirred at room temperature for 5 days, the reaction mixture was evaporated in vacuo. The residue was dissolved in ethyl acetate and stirred with saturated aqueous $\mathrm{NaHCO}_{3}$ for 1 h . The organic phase was separated and washed with 1 M HCl , aqueous saturated $\mathrm{NaHCO}_{3}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ) to yield the pure product $4.304(1.07 \mathrm{~g}, 85 \%)$ as a yellowish solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.58(\mathrm{~d}, \mathrm{~J}=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{dd}, J=8.5,0.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{dd}, J=8.6$, $2.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.30(\mathrm{~s}, 1 \mathrm{H}), 4.34(\mathrm{dt}, J=12.8,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.02(\mathrm{~s}, 1 \mathrm{H}), 3.87(\mathrm{~s}, 3 \mathrm{H}), 3.86-3.77(\mathrm{~m}$, $2 \mathrm{H}), 2.93-2.73(\mathrm{~m}, 2 \mathrm{H}), 1.65(\mathrm{~s}, 9 \mathrm{H}), 1.30(\mathrm{~s}, 3 \mathrm{H}), 1.01(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 171.4, 159.2, 150.6, 140.7, 127.8, 126.6, 121.9, 121.4, 119.6, 114.9, 112.2, 99.5, 84.4, 74.7, 55.7, 39.3, 35.2, 28.1, 26.6, 21.3, 19.5.

IR: v $\left(\mathrm{cm}^{-1}\right) 3459$ ( w ), 2974 ( w ), 1731 ( m$), 1665$ ( m$), 1613$ ( w$), 1560$ ( w$), 1493$ ( w$), 1464$ ( w$), 1420$ ( w ), 1352 (m), 1311 (m), 1278 (m), 1244 (m), 1206 (m), 1152 ( s$), 1113$ ( s$), 1047$ (m), 911 (m), 852 (m), 805 (w), 730 (s), 683 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 413.2071 ; found: 413.2073 .

## tert-butyl 2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate

(4.264)


According to a reported procedure, ${ }^{418}$ to a solution of NCS ( $1.49 \mathrm{~g}, 11.1$ mmol, 5.00 equiv) in dry DCM ( 56 mL ) at $0^{\circ} \mathrm{C}$ was added dropwise DMS ( $4.12 \mathrm{~mL}, 55.7 \mathrm{mmol}, 25$ equiv) and the reaction mixture was stirred at $-78^{\circ} \mathrm{C}$ for 1 h . The alcohol 4.269 ( $852 \mathrm{mg}, 2.23 \mathrm{mmol}, 1.00$ equiv) in DCM $(10 \mathrm{~mL})$ was added dropwise and then the reaction mixture was stirred at $-78^{\circ} \mathrm{C}$ for two hours. Triethylamine ( $5.17 \mathrm{~mL}, 37.2 \mathrm{mmol}$, 17 equiv) in DCM ( 4 mL ) was added and the reaction mixture was stirred at $-78{ }^{\circ} \mathrm{C}$ for 2 hours. The reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the pure product $4.264(805 \mathrm{mg}, 95 \%)$ as a yellow solid.

# tert-butyl 10-methoxy-2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (4.234) 



According to a reported procedure, ${ }^{418}$ to a solution of NCS ( $1.16 \mathrm{~g}, 8.69 \mathrm{mmol}, 5.00$ equiv) in dry DCM ( 44 mL ) at $0^{\circ} \mathrm{C}$ was added dropwise DMS ( $3.21 \mathrm{~mL}, 43.4 \mathrm{mmol}, 25$ equiv) and the reaction mixture was stirred at $-78^{\circ} \mathrm{C}$ for 1 h . The alcohol 4.304 ( $716 \mathrm{mg}, 1.74 \mathrm{mmol}, 1$ equiv) in DCM (9 mL ) was added dropwise and the reaction mixture was stirred at $-78{ }^{\circ} \mathrm{C}$ for two hours. Triethylamine ( $4.03 \mathrm{~mL}, 29.0 \mathrm{mmol}, 17$ equiv) in DCM ( 2.3 mL ) was added and the reaction mixture was stirred at $-78^{\circ} \mathrm{C}$ for 2 hours. The reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1\right)$ to yield the pure product 4.234 ( $685 \mathrm{mg}, 96 \%$ ) as a yellow solid.
tert-butyl 2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (4.264)


According to a reported procedure, ${ }^{57 \mathrm{a}}$ a mixture of the isonitrile 4.268 ( $200 \mathrm{mg}, 0.52 \mathrm{mmol}, 1.00$ equiv), $\mathrm{MeNHOH} \cdot \mathrm{HCl}\left(48.2 \mathrm{mg}, 0.58 \mathrm{mmol}, 3\right.$ equiv), $\mathrm{NaHCO}_{3}(9.21 \mathrm{mg}, 1.05 \mathrm{mmol}, 6.00$ equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol}$ isonitrile) in $\mathrm{MeOH}(5.3 \mathrm{~mL}, 0.01 \mathrm{M}$ ) was stirred for 30 min . $\mathrm{AcOH}(274 \mu \mathrm{~L}, 4.71 \mathrm{mmol}, 27$ equiv) was added and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was then filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the pure product $4.264(150 \mathrm{mg}, 75 \%)$ as a yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.98(\mathrm{dt}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.49(\mathrm{ddd}, J=7.6,1.4,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.37$ (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), $7.32-7.25(\mathrm{~m}, 1 \mathrm{H}), 5.34(\mathrm{~s}, 1 \mathrm{H}), 4.21(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.95(\mathrm{t}, \mathrm{J}=$ $5.8 \mathrm{~Hz}, 2 \mathrm{H}), 1.65(\mathrm{~s}, 9 \mathrm{H}), 1.39(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 195.7,156.6,150.5,139.6,129.1,127.4,126.5,125.6,123.6,122.8$, 119.3, 115.2, 113.0, 84.8, 45.3, 39.7, 28.2, 25.1, 21.2.

IR: v (cm ${ }^{-1}$ ) 2979 (w), 2938 (w), 2932 (w), 1731 (s), 1681 (s), 1612 (w), 1567 (w), 1491 (w), 1465 (w), 1421 (w), 1395 (w), 1355 (m), 1307 (m), 1283 (m), 1256 (m), 1166 (m), 1157 (s), 1138 (s), 1036 (m), 911 (w), 843 (w), 728 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 381.1809$; found: 381.1812.
tert-butyl 10-methoxy-2,2-dimethyl-3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (4.234)


According to a reported procedure, ${ }^{57 \mathrm{a}}$ a mixture of the isonitrile 4.303 ( $2.00 \mathrm{~g}, 4.85 \mathrm{mmol}, 1.00$ equiv), $\mathrm{MeNHOH} \cdot \mathrm{HCl}\left(1.22 \mathrm{~g}, 14.6 \mathrm{mmol}, 3.00\right.$ equiv), $\mathrm{NaHCO}_{3}(2.44 \mathrm{~g}, 29.1 \mathrm{mmol}, 6.00$ equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol}$ isonitrile) in $\mathrm{MeOH}(485 \mathrm{~mL}, 0.01 \mathrm{M}$ ) was stirred for 30 min . AcOH ( $7.50 \mathrm{~mL}, 131 \mathrm{mmol}, 27$ equiv) was added and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was then filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the pure product 4.234 ( $1.49 \mathrm{~g}, 75 \%$ ) as a yellow solid.
${ }^{1}{ }^{\mathbf{H}}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.54(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{~d}, J=8.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.86(\mathrm{dd}, J=8.6,2.3$ $\mathrm{Hz}, 1 \mathrm{H}), 5.23(\mathrm{~s}, 1 \mathrm{H}), 4.15(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.84(\mathrm{~s}, 3 \mathrm{H}), 2.87(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}), 1.63(\mathrm{~s}, 9 \mathrm{H}), 1.35(\mathrm{~s}$, 6 H ).
${ }^{13}$ C NMR (101 MHz, CDCl $_{3}$ ): $\delta 195.7,159.3,156.5,150.4,140.8,127.7,125.6,122.9,121.1,119.8$, 112.3, 111.5, 99.6, 84.5, 55.6, 45.1, 39.4, 28.1, 25.0, 21.1.

IR: v ( $\mathrm{cm}^{-1}$ ) 2977 (w), 2936 (w), 2930 (w), 1732 (s), 1678 (s), 1614 (w), 1565 (w), 1493 (w), 1462 (w), 1421 (w), 1391 (w), 1353 (m), 1304 (m), 1280 (m), 1252 (m), 1168 (m), 1156 (s), 1133 (s), 1040 (m), 909 (m), 843 (m), 729 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 411.1914; found: 411.1910.


A mixture of $\alpha$-ketoamide 4.264 ( $185 \mathrm{mg}, 0.487 \mathrm{mmol}, 1.00$ equiv), 6 -methoxytryptamine (4.27) ( $102 \mathrm{mg}, 0.536 \mathrm{mmol} 1.1$ equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol} \alpha$-ketoamide) in toluene $(4.9 \mathrm{~mL}, 0.1 \mathrm{M})$ was heated to reflux for 24 h . The reaction mixture was cooled to room temperature and toluene ( 4.9 mL ) and TFA ( $7.2 \mu \mathrm{~L}, 0.097 \mathrm{mmol}, 0.2$ equiv) were added. The reaction mixture was heated to reflux for 6 days. The solvent was evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} /\right.$ Acetone $\left.98: 2\right)$ to yield the pure product rac-
$4.293(201 \mathrm{mg}, 91 \%)$ as a white solid. rac-4.293 is poorly soluble in most of the common organic solvents including methanol and DMSO. rac-Peganumine A (rac-4.1)


A mixture of $\alpha$-ketoamide 4.234 ( $200 \mathrm{mg}, 0.487 \mathrm{mmol}, 1.00$ equiv), 6-methoxytryptamine (4.27) ( $102 \mathrm{mg}, 0.536 \mathrm{mmol} 1.10$ equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol} \alpha$-ketoamide) in toluene $(4.9 \mathrm{~mL}, 0.1 \mathrm{M})$ was heated to reflux for 24 h . The reaction mixture was cooled to room temperature and toluene ( 4.9 mL ) and TFA ( $7.2 \mu \mathrm{~L}, 0.097 \mathrm{mmol}, 0.20$ equiv) were added. The reaction mixture was heated to reflux for 6 days. The solvent was evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} /$ Acetone $98: 2$ ) to yield the pure product rac$4.1(170 \mathrm{mg}, 72 \%)$ as a white solid. rac-4.1 is poorly soluble in most of the common organic solvents including methanol and DMSO.

### 4.293



A mixture of $\alpha$-ketoamide 4.264 ( $200 \mathrm{mg}, 0.53 \mathrm{mmol}, 1.00$ equiv), 6 -methoxytryptamine (4.27) ( $113 \mathrm{mg}, 0.58 \mathrm{mmol} 1.10$ equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol} \alpha$-ketoamide) in toluene $(0.5 \mathrm{~mL}, 0.1 \mathrm{M})$ was heated to reflux for 24 h . The reaction mixture was cooled to room temperature and toluene/DCM were added ( $0.5 / 0.1 \mathrm{~mL}, 0.05 \mathrm{M}$ ). The thiourea $4.53(52 \mathrm{mg}, 0.11 \mathrm{mmol}$, 0.20 equiv) and benzoic acid ( $13 \mathrm{mg}, 0.11 \mathrm{mmol}, 0.20$ equiv) were added and the reaction mixture was stirred at $35^{\circ} \mathrm{C}$ for 5 days. The reaction mixture was cooled to room temperature, TFA ( $8 \mu \mathrm{~L}$, $0.11 \mathrm{mmol}, 0.20$ equiv) was added and the reaction mixture was heated to reflux for 2 days. The solvent was evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} /$ Acetone 98:2) to yield the pure product 4.293 ( $161 \mathrm{mg}, 67 \%, 96: 4 \mathrm{er}$ ) as a white solid. 4.293 is poorly soluble in most of the common organic solvents including methanol and DMSO.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $d_{4}$ ): $\delta 7.47-7.35(\mathrm{~m}, 2 \mathrm{H}), 7.09(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.99(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}$, $1 \mathrm{H}), 6.93(\mathrm{~d}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.73(\mathrm{dd}, J=8.6,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.14(\mathrm{dd}, J=13.1,5.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{~s}$, $3 \mathrm{H}), 3.19(\mathrm{td}, J=12.4,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.99(\mathrm{dd}, J=15.3,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.89-2.81(\mathrm{~m}, 2 \mathrm{H}), 2.79-2.70$ $(\mathrm{m}, 1 \mathrm{H}), 2.61(\mathrm{dd}, \mathrm{J}=11.0,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.51-2.40(\mathrm{~m}, 1 \mathrm{H}), 2.41(\mathrm{~d}, \mathrm{~J}=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.96(\mathrm{~d}, \mathrm{~J}=$ $11.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.46(\mathrm{~s}, 3 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta$ 175.0, 158.4, 139.6, 138.7, 129.1, 127.7, 126.4, 122.4, 122.2, $120.0,119.8,118.7,112.9,112.4,112.3,110.5,95.7,81.3,79.7,56.0,51.9,41.8,41.6,37.3,27.3$, 26.3, 22.5, 22.1.

IR: v ( $\mathrm{cm}^{-1}$ ) 2979 (w), 2937 (w), 2931 (w), 1734 (s), 1676 (s), 1612 (w), 1498 (w), 1467 (w), 1425 (w), 1387 (w), 1359 (m), 1308 (m), 1254 (m), 1169 (m), 1156 (s), 1133 (s), 1041 (m), 913 (m), 843 (m), 732 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{29} \mathrm{~N}_{4} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 453.2285; found: 453.2288.
$[\alpha]_{\mathrm{D}}{ }^{20}+9.6^{\circ}(c 0.10, \mathrm{MeOH})$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, $15 \% \mathrm{MeOH}, 270 \mathrm{~nm}$ ) $t_{\mathrm{R}}$ (minor) $=$ $36 \mathrm{~min}, t_{R}$ (major) $=39 \mathrm{~min}: 96.3: 3.7 \mathrm{er}$.
(+)-Peganumine A (4.1)


A mixture of $\alpha$-ketoamide 4.234 ( $1.50 \mathrm{~g}, 3.65 \mathrm{mmol}, 1.00$ equiv), 6-methoxytryptamine (4.53) (765 $\mathrm{mg}, 4.02 \mathrm{mmol} 1.10$ equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol} \alpha$-ketoamide) in toluene (38 $\mathrm{mL}, 0.1 \mathrm{M}$ ) was heated to reflux for 24 h . The reaction mixture was cooled to room temperature and toluene/DCM were added ( $38 / 9 \mathrm{~mL}, 0.05 \mathrm{M}$ ). The thiourea 4.53 ( $359 \mathrm{mg}, 0.73 \mathrm{mmol}, 0.20$ equiv) and benzoic acid ( $90 \mathrm{mg}, 0.73 \mathrm{mmol}, 0.20$ equiv) were added and the reaction mixture was stirred at $35^{\circ} \mathrm{C}$ for 5 days. The reaction mixture was cooled to room temperature, TFA ( $54 \mu \mathrm{~L}, 0.73$ $\mathrm{mmol}, 0.20$ equiv) was added and the reaction mixture was heated to reflux for 2 days. The solvent was evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} /$ Acetone 98:2) to yield the pure product 4.1 ( $1.22 \mathrm{~g}, 69 \%, 96: 4 \mathrm{er}$ ) as a white solid. 4.1 is poorly soluble in most of the common organic solvents including methanol and DMSO.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( 600 MHz, DMSO- $_{6}$ ): $11.27(\mathrm{~s}, 1 \mathrm{H}), 10.80(\mathrm{~s}, 1 \mathrm{H}), 7.38(\mathrm{~d}, \mathrm{~J}=8.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.24(\mathrm{~d}, \mathrm{~J}=8.5$ $\mathrm{Hz}, 1 \mathrm{H}), 6.92(\mathrm{~d}, \mathrm{~J}=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{~d}, J=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.69(\mathrm{dd}, J=8.6,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.63(\mathrm{dd}, J=$ $8.5,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.00(\mathrm{dd}, \mathrm{J}=12.9,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 3.76(\mathrm{~s}, 3 \mathrm{H}), 3.09(\mathrm{td}, \mathrm{J}=12.5,4.4 \mathrm{~Hz}$, $1 \mathrm{H}), 2.90$ (dd, $J=15.4,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.77-2.60(\mathrm{~m}, 3 \mathrm{H}), 2.45(\mathrm{dd}, \mathrm{J}=10.6,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.34(\mathrm{dd}, J=$ $11.0,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.30(\mathrm{~d}, \mathrm{~J}=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.88(\mathrm{~d}, J=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.38(\mathrm{~s}, 3 \mathrm{H}), 1.14(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 151 MHz, DMSO- $d_{6}$ ): $\delta$ 171.4, 156.1, 155.4, 137.6, 137.5, 127.3, 125.7, 120.5, 120.4, $119.1,118.2,111.3,109.5,109.1,108.3,94.9,94.7,78.8,77.4,55.2,55.2,50.4,40.1,40.0,35.6$, 26.9, 26.1, 21.1, 21.0.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}$, Methanol $-d_{4}$ ): $\delta 7.38(\mathrm{~d}, J=8.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.26(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.99(\mathrm{~d}, J=2.3$ $\mathrm{Hz}, 1 \mathrm{H}$ ), $6.93(\mathrm{~d}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.73$ (dd, $J=8.6,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{dd}, J=8.6,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.14$ (dd, $J=13.0,5.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.83(\mathrm{~s}, 3 \mathrm{H}), 3.82(\mathrm{~s}, 3 \mathrm{H}), 3.18(\mathrm{td}, \mathrm{J}=12.3,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.98(\mathrm{dd}, \mathrm{J}=15.4,4.5$ $\mathrm{Hz}, 1 \mathrm{H}), 2.90-2.74(\mathrm{~m}, 2 \mathrm{H}), 2.69(\mathrm{dd}, J=15.2,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.59(\mathrm{dd}, J=10.8,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.44(\mathrm{dd}$, $J=11.2,4.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.39(\mathrm{~d}, J=11.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.94(\mathrm{~d}, J=11.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.44(\mathrm{~s}, 3 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13}$ C NMR ( 101 MHz, Methanol $-d_{4}$ ): $\delta$ 175.2, 158.4, $157.6,139.5,139.4,127.8,126.5,122.3,122.2$, $120.0,119.2,112.9,112.2,110.5,109.8,96.0,95.7,81.3,79.7,56.0,56.0,51.9,41.7,41.6,37.3$, 27.3, 26.3, 22.5, 22.1.

IR: v (cm ${ }^{-1}$ ) 2981 (w), 2938 (w), 1734 (s), 1676 (s), 1612 (w), 1499 (w), 1467 (w), 1430 (w), 1387 (w), 1359 (m), 1308 (m), 1254 (m), 1168 (m), 1153 (s), 1137 (s), 1040 (m), 914 (m), 842 (m), 731 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{31} \mathrm{~N}_{4} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 483.2391; found: 483.2392 .
$[\alpha]_{D}{ }^{20}+6.2^{\circ}(c 0.10, \mathrm{MeOH})$.
The enantiomeric purity was determined by SFC (Chiralcel, OD-H, 18\% MeOH, 270 nm ) $t_{\mathrm{R}}($ minor $)=$ $22 \mathrm{~min}, t_{\mathrm{R}}($ major $)=24 \mathrm{~min}: 96.1: 3.9 \mathrm{er}$.

### 8.5 Macrocyclization of $\omega$-Isocyanoaldehydes

8.5.1 Starting Material
hex-5-enoic acid (5.128b) and oct-7-enoic acid (5.128d)


They were prepared according to literature procedures. ${ }^{445,446}$
hept-6-enoic acid (5.128c)


It was prepared according to literature procedures. ${ }^{447,448}$
GP 5-1:


According to a reported procedure, ${ }^{403}$ to a solution of the acid 5.128 (1.00 equiv) in dry DCM ( 0.3 M) was added dropwise TFAA (1.00 equiv) at room temperature. The reaction mixture was stirred for 10 minutes and thiophenol ( 1.00 equiv) was added. After being stirred at $45^{\circ} \mathrm{C}$ overnight, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired compound 5.130.

## $S$-phenyl pent-4-enethioate (5.130a)



The analytical data were in accordance with those reported in the literature. ${ }^{575}$

## $S$-phenyl hex-5-enethioate (5.130b)



Procedure: GP 5-1 starting from acid 5.128b
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 98: 2\right)$. Yield: $80 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.53-7.34(\mathrm{~m}, 5 \mathrm{H}), 5.79(\mathrm{ddt}, J=16.9,10.2,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.14-4.96$ $(\mathrm{m}, 2 \mathrm{H}), 2.67(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 2.14(\mathrm{q}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.82(\mathrm{p}, \mathrm{J}=7.4 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 197.5,137.6,134.6,129.5,129.3,128.0,115.8,43.0,33.0,24.7$.
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{OS}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 207.0838; found: 207.0841 .

[^216]
## S-phenyl hept-6-enethioate (5.130c)



Procedure: GP 5-1 starting from acid 5.128c

Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 98: 2\right)$. Yield: $74 \%$, isolated as a yellow oil.
${ }^{1}{ }^{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.53-7.34(\mathrm{~m}, 5 \mathrm{H}), 5.80(\mathrm{ddt}, \mathrm{J}=16.9,10.0,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.08-4.89$ $(\mathrm{m}, 2 \mathrm{H}), 2.67(\mathrm{t}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 2.08(\mathrm{q}, J=7.5,7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.73(\mathrm{p}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 1.47(\mathrm{p}, J=7.7$ $\mathrm{Hz}, 2 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 197.6,138.4,134.6,129.5,129.3,128.0,115.0,43.6,33.5,28.3,25.2$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{OS}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 221.0995; found: 221.0999.

## S-phenyl oct-7-enethioate (5.130d)



Procedure: GP 5-1 starting from acid 5.128d

Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{Et}_{2} \mathrm{O} 98: 2\right)$. Yield: Quantitative, isolated as a yellow oil.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.50-7.33(\mathrm{~m}, 5 \mathrm{H}), 5.81$ (ddt, $\left.J=16.9,10.2,6.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.08-4.90$ $(\mathrm{m}, 2 \mathrm{H}), 2.66(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 2.06(\mathrm{q}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 1.73(\mathrm{p}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.49-1.30(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 197.6,138.9,134.6,129.4,129.3,128.0,114.6,43.8,33.6,28.6,28.5$, 25.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{OS}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 235.1151; found: 235.1150.
GP 5-2:


Following a reported procedure, ${ }^{421}$ a mixture of stannyl 4.242 ( 1.10 equiv), thioester 5.130 (1.00 equiv), $\mathrm{Pd}_{2} \mathrm{dba}_{3}\left(0.1\right.$ equiv), $\mathrm{AsPh}_{3}(0.10$ equiv) and CuDPP ( 2.00 equiv) in dry degassed hexanes/THF (3:1, 0.067 M ) was stirred at room temperature for 6 h . After completion of reaction, the
reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with $2 \mathrm{M} \mathrm{HCl}, 10 \% \mathrm{NH}_{4} \mathrm{OH}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired compound 5.131.

## tert-butyl 3-(2-formamidoethyl)-2-(pent-4-enoyl)-1H-indole-1-carboxylate (5.131a)



Procedure: GP 5-2 starting from thioester 5.130a
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$. Yield: $71 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.15(\mathrm{~s}, 1 \mathrm{H}), 8.02(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{dt}, J=7.9,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.50$ $-7.40(\mathrm{~m}, 1 \mathrm{H}), 7.32$ (ddd, $J=8.0,7.2,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.13(\mathrm{~s}, 1 \mathrm{H}), 5.80(\mathrm{ddt}, J=16.8,10.2,6.5 \mathrm{~Hz}, 1 \mathrm{H})$, $5.11-4.80(\mathrm{~m}, 2 \mathrm{H}), 3.66-3.44(\mathrm{~m}, 2 \mathrm{H}), 2.95-2.78(\mathrm{~m}, 4 \mathrm{H}), 2.51-2.38(\mathrm{~m}, 2 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 198.2, 161.9, 150.1, 136.8, 136.4, 136.2, 128.9, 127.4, 123.9, 122.5, $120.4,115.8,115.7,85.8,42.8,38.4,29.2,28.2,23.1$.

IR: v ( $\mathrm{cm}^{-1}$ ) 2984 (br), 1741 (s), 1596 (w), 1459 (m), 1370 (m), 1251 (s), 1172 (s), 1144 (m), 1124 (s), 1090 (m), 994 (m), 969 (m), 874 (w), 813 (m), 791 (m), 767 (w), 726 (m), 704 (m), 676 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 371.1965 ; found: 371.1962.

## tert-butyl 3-(2-formamidoethyl)-2-(hex-5-enoyl)-1H-indole-1-carboxylate (5.131b)



Procedure: GP 5-2 starting from thioester 5.130b
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$. Yield: $66 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.15(\mathrm{~s}, 1 \mathrm{H}), 8.02(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.44$ (ddd, $J=8.3,7.4,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.32(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.11(\mathrm{~s}, 1 \mathrm{H}), 5.76(\mathrm{ddt}, J=17.0,10.1,6.7 \mathrm{~Hz}, 1 \mathrm{H})$, $5.08-4.93(\mathrm{~m}, 2 \mathrm{H}), 3.67-3.45(\mathrm{~m}, 2 \mathrm{H}), 2.88(\mathrm{t}, 2 \mathrm{H}), 2.74(\mathrm{t}, 2 \mathrm{H}), 2.14-2.06(\mathrm{~m}, 2 \mathrm{H}), 1.83-1.73$ $(\mathrm{m}, 2 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 198.9,161.9,150.1,137.8,136.5,136.2,128.9,127.3,123.9,122.2$, 120.4, 115.9, 115.6, 85.8, 43.1, 38.3, 33.3, 28.3, 24.1, 23.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 407.1941; found: 407.1936.
tert-butyl 3-(2-formamidoethyl)-2-(hept-6-enoyl)-1H-indole-1-carboxylate (5.131c)

5.131c

Procedure: GP 5-2 starting from thioester 5.130c
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / E t O A c 2: 1\right)$. Yield: $68 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.15(\mathrm{~s}, 1 \mathrm{H}), 8.02(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, \mathrm{J}=$ $7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.12(\mathrm{~s}, 1 \mathrm{H}), 5.76(\mathrm{ddd}, J=16.6,10.7,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.01-4.91$ $(\mathrm{m}, 2 \mathrm{H}), 3.56(\mathrm{q}, J=5.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.88(\mathrm{t}, J=5.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.74(\mathrm{t}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.05(\mathrm{q}, J=7.0 \mathrm{~Hz}$, 2H), 1.67 ( $\mathrm{s}, 9 \mathrm{H}$ ), $1.48-1.36$ (m, 2H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right): \delta 198.9,161.8,150.0,138.4,136.4,136.1,128.9,127.2,123.8,122.1$, $120.3,115.8,114.9,85.7,43.6,38.3,33.5,28.5,28.2,24.5,23.1$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 421.2098; found: 421.2090.
tert-butyl 3-(2-formamidoethyl)-2-(oct-7-enoyl)-1H-indole-1-carboxylate (5.131d)

5.131d

Procedure: GP 5-2 starting from thioester 5.130d
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$. Yield: $63 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.15(\mathrm{~s}, 1 \mathrm{H}), 8.02(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, \mathrm{J}=$ $7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.16(\mathrm{~s}, 1 \mathrm{H}), 5.76(\mathrm{ddt}, J=16.9,10.1,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.04-4.77(\mathrm{~m}$, $2 \mathrm{H}), 3.62-3.42(\mathrm{~m}, 2 \mathrm{H}), 2.92-2.84(\mathrm{~m}, 2 \mathrm{H}), 2.78-2.69(\mathrm{~m}, 2 \mathrm{H}), 2.03(\mathrm{q}, J=6.9 \mathrm{~Hz}, 2 \mathrm{H}), 1.67(\mathrm{~s}$, $9 H), 1.69-1.60(m, 2 H), 1.43-1.28(m, 4 H)$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 199.1, 161.9, 150.1, $138.8,136.5,136.1,128.9,127.3,123.8,122.1$, $120.4,115.8,114.6,85.7,43.7,38.3,33.6,28.8,28.7,28.2,24.9,23.1$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 435.2254; found: 435.2245.

## GP 5-3:



Following a reported procedure, ${ }^{449}$ to a solution of alkene 5.131 (1.0 equiv) in acetone/ $\mathrm{H}_{2} \mathrm{O}(3: 1$, 0.13 M ) was added $\mathrm{K}_{2} \mathrm{OsO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ ( 0.05 equiv) and NMO ( 2.0 equiv). After being stirred at room temperature for 5 h , the acetone was evaporated in vacuo and the resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to give the crude diol. To a solution of the crude diol in THF/ $\mathrm{H}_{2} \mathrm{O}(4: 1,0.13 \mathrm{M})$ was added $\mathrm{NaIO}_{4}$ ( 2.0 equiv). After being stirred at room temperature for 1 h , the resulting mixture was filtered through a pad of Celite (rinsed with DCM) and the filtrate was washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired compound 5.132.
tert-butyl 3-(2-formamidoethyl)-2-(4-oxobutanoyl)-1H-indole-1-carboxylate (5.132a)

5.132a

Procedure: GP 5-3 starting from alkene 5.131a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 97: 3$ ). Yield: 93\%, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.87(\mathrm{~s}, 1 \mathrm{H}), 8.13(\mathrm{~s}, 1 \mathrm{H}), 7.98(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}$, 1 H ), 7.44 (ddd, $J=8.4,7.2,1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.32(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{~s}, 1 \mathrm{H}), 3.63-3.54(\mathrm{~m}, 2 \mathrm{H})$, $3.09(\mathrm{t}, \mathrm{J}=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.02-2.88(\mathrm{~m}, 4 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 200.6, 196.7, 161.8, 150.3, 136.1, 136.0, 129.1, 127.4, 123.9, 122.8, 120.6, 115.9, 85.9, 38.7, 38.2, 35.7, 28.3, 23.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 373.1758 ; found: 373.1754 .
tert-butyl 3-(2-formamidoethyl)-2-(5-oxopentanoyl)-1H-indole-1-carboxylate (5.132b)

5.132b

Procedure: GP 5-3 starting from alkene 5.131b
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right.$ to $\left.95: 5\right)$. Yield: $95 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.79(\mathrm{t}, J=1.3 \mathrm{~Hz}, 1 \mathrm{H}), 8.14(\mathrm{~s}, 1 \mathrm{H}), 7.98(\mathrm{dt}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.59$ (dt, $J=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.43 (ddd, $J=8.4,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{ddd}, J=8.0,7.3,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.98$ $(\mathrm{s}, 1 \mathrm{H}), 3.56(\mathrm{q}, J=5.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.92-2.84(\mathrm{~m}, 2 \mathrm{H}), 2.79(\mathrm{t}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.59(\mathrm{td}, J=7.0,1.3 \mathrm{~Hz}$, $2 \mathrm{H}), 2.05$ ( $\mathrm{p}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), 1.68 ( $s, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 201.9, 197.9, 161.8, 150.2, 136.3, 136.0, 128.9, 127.3, 123.9, 122.2, 120.4, 115.9, 85.9, 42.8, 42.4, 38.3, 28.3, 23.2, 17.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 409.1734; found: 409.1727.
tert-butyl 3-(2-formamidoethyl)-2-(6-oxohexanoyl)-1H-indole-1-carboxylate (5.132c)

5.132c

Procedure: GP 5-3 starting from alkene 5.131c
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right.$ to $\left.95: 5\right)$. Yield: $83 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.76(\mathrm{t}, \mathrm{J}=1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.14(\mathrm{~s}, 1 \mathrm{H}), 8.00(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, \mathrm{~J}=$ $7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.07(\mathrm{~s}, 1 \mathrm{H}), 3.56(\mathrm{q}, J=5.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.88$ (t, 2H), 2.76 (t, J = 7.0 Hz, 2H), 2.47 (t, J = 6.3 Hz, 2H), $1.75-1.64(\mathrm{~m}, 4 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 202.2, 198.3, 161.9, 150.1, 136.3, 136.1, 128.9, 127.3, 123.9, 122.3, 120.4, 115.8, 85.8, 43.7, 43.3, 38.3, 28.2, 24.4, 23.1, 21.7.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 423.1890; found: 423.1881.
tert-butyl 3-(2-formamidoethyl)-2-(7-oxoheptanoyl)-1H-indole-1-carboxylate (5.132d)


Procedure: GP 5-3 starting from alkene 5.131d
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5\right)$. Yield: $82 \%$, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.74(\mathrm{t}, \mathrm{J}=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.14(\mathrm{~s}, 1 \mathrm{H}), 8.00(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, \mathrm{~J}=$ $7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.43(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.04(\mathrm{~s}, 1 \mathrm{H}), 3.55(\mathrm{q}, 2 \mathrm{H}), 2.87(\mathrm{t}, 2 \mathrm{H})$, $2.74(\mathrm{t}, 2 \mathrm{H}), 2.43(\mathrm{td}, \mathrm{J}=7.2,1.6 \mathrm{~Hz}, 2 \mathrm{H}), 1.67(\mathrm{~s}, 9 \mathrm{H}), 1.77-1.55(\mathrm{~m}, 4 \mathrm{H}), 1.42-1.32(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 202.5,198.7,161.9,150.1,136.4,136.1,128.9,127.3,123.8,122.2$, $120.4,115.8,85.8,43.7,43.4,38.3,28.7,28.2,24.7,23.1,21.8$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 437.2047; found: 437.2038.

## GP 5-4:



To a solution of formamide 5.132 (1.0 equiv) in dry DCM ( 0.3 M ) at $-78{ }^{\circ} \mathrm{C}$ was added $\mathrm{NEt}_{3}(5.0$ equiv) and $\mathrm{POCl}_{3}$ ( 1.5 equiv) dropwise. After being stirred at $-78{ }^{\circ} \mathrm{C}$ for 3 h , the reaction mixture was quenched with saturated $\mathrm{Na}_{2} \mathrm{CO}_{3}$ at $-78^{\circ} \mathrm{C}$, allowed to warm to room temperature and extracted with $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the $\omega$-isocyanoaldehyde 5.133 which was used for the next step without further purification.

## tert-butyl 3-(2-isocyanoethyl)-2-(4-oxobutanoyl)-1H-indole-1-carboxylate (5.133a)


5.133a

Procedure: GP 5-4 starting from formamide 5.132a
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.86(\mathrm{t}, \mathrm{J}=0.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.01(\mathrm{dt}, \mathrm{J}=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.64(\mathrm{dt}, \mathrm{J}=7.9$, $1.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.45 (ddd, $J=8.4,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.45 (ddd, $J=8.4,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.72(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}$, $2 \mathrm{H}), 3.12-3.08(\mathrm{~m}, 4 \mathrm{H}), 2.95(\mathrm{t}, \mathrm{J}=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 1.67(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 200.6,195.6,157.2,150.1,136.2,135.9,129.1,127.3,123.9,120.8$, 120.3, 115.9, 85.9, 38.6, 35.9, 29.8, 28.2, 24.7.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 355.1652 ; found: 355.1649.
tert-butyl 3-(2-isocyanoethyl)-2-(5-oxopentanoyl)-1H-indole-1-carboxylate (5.133b)

5.133b

Procedure: GP 5-4 starting from formamide 5.132b
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.79(\mathrm{t}, J=1.3 \mathrm{~Hz}, 1 \mathrm{H}), 8.00(\mathrm{dt}, J=8.5,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{dt}, J=7.9$, $1.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.44(\mathrm{ddd}, J=8.5,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{ddd}, J=8.0,7.2,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{t}, J=7.1 \mathrm{~Hz}$, $2 H), 3.07(\mathrm{t}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.81(\mathrm{t}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.59(\mathrm{td}, J=7.0,1.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.06(\mathrm{p}, J=7.1 \mathrm{~Hz}$, 2H), 1.67 ( $s, 9 H$ ).
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 202.0, 196.7, 157.2, 150.1, 136.6, 135.8, 128.9, 127.2, 123.9, 120.1, 120.0, 115.9, 85.9, 42.8, 42.6, 42.3, 28.2, 24.8, 16.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 391.1628; found: 391.1629.
tert-butyl 3-(2-isocyanoethyl)-2-(6-oxohexanoyl)-1H-indole-1-carboxylate (5.133c)


Procedure: GP 5-4 starting from formamide 5.132c
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.77(\mathrm{~s}, 1 \mathrm{H}), 8.03(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, \mathrm{J}=$ $7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.07(\mathrm{t}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.78(\mathrm{t}, J=6.9 \mathrm{~Hz}$, $2 \mathrm{H}), 2.48(\mathrm{t}, \mathrm{J}=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 1.81-1.57(\mathrm{~m}, 2 \mathrm{H}), 1.67(\mathrm{~s}, 9 \mathrm{H}), 1.20(\mathrm{t}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 202.2,197.1,157.2,150.0,136.6,135.9,128.9,127.2,123.8,120.2$, 120.1, 115.9, 85.8, 46.1, 43.8, 43.6, 28.2, 24.9, 24.2, 21.7.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 405.1790; found: 405.1790.
tert-butyl 3-(2-isocyanoethyl)-2-(7-oxoheptanoyl)-1H-indole-1-carboxylate (5.133d)

5.133d

Procedure: GP 5-4 starting from formamide 5.132d
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.75(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.03(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H})$, 7.44 (ddd, $J=8.4,7.1,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.32(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{t}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.07(\mathrm{t}, J=7.4 \mathrm{~Hz}$, $2 \mathrm{H}), 2.75(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.44(\mathrm{td}, J=7.3,1.7 \mathrm{~Hz}, 2 \mathrm{H}), 1.77-1.55(\mathrm{~m}, 4 \mathrm{H}), 1.66(\mathrm{~s}, 9 \mathrm{H}), 1.47-$ $1.30(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 202.6,197.5,157.0,150.0,136.6,135.9,128.9,127.2,123.8,120.2$, 120.1, 115.8, 85.8, 45.9, 43.8, 43.6, 28.8, 28.2, 24.9, 24.5, 21.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 419.1941; found: 419.1933.
tert-butyl (E)-3-(2-formamidoethyl)-2-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylate (5.135)


According to a reported procedure, ${ }^{450}$ acrolein ( 5.134 ) ( $2.1 \mathrm{~mL}, 32.0 \mathrm{mmol}, 4.0$ equiv), $t-\mathrm{BuO}_{2} \mathrm{Bz}$ ( $2.1 \mathrm{~mL}, 11.2 \mathrm{mmol}, 1.4$ equiv) and $\mathrm{Pd}(\mathrm{OAc})_{2}(179.6 \mathrm{mg}, 0.8 \mathrm{mmol}, 0.10$ equiv) were added to a solution of 4.241 in dioxane ( 12 mL ) and $\mathrm{AcOH}(4 \mathrm{~mL})$. After being stirred at $70{ }^{\circ} \mathrm{C}$ for 24 h , the reaction mixture was allowed to cool to room temperature, neutralized with saturated $\mathrm{NaHCO}_{3}$ and filtered through a pad of Celite (rinsed with EtOAc). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 99: 1$ to $98: 2$ ) to yield compound 5.135 ( $1.53 \mathrm{~g}, 56 \%$ ) as yellow solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.71(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.18(\mathrm{~s}, 1 \mathrm{H}), 8.09(\mathrm{~d}, \mathrm{~J}=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.99(\mathrm{~d}, \mathrm{~J}=$ $16.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.73(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.39(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.30(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.46(\mathrm{dd}, J=$ $16.2,7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.20(\mathrm{~s}, 1 \mathrm{H}), 3.56(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.08(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 194.2,162.0,150.7,144.1,137.1,132.1,130.2,130.0,127.2,124.0$, 123.1, 120.4, 116.2, 85.6, 38.6, 28.6, 25.7.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 365.1472; found: 365.1470.

## tert-butyl 3-(2-formamidoethyl)-2-(3-oxopropyl)-1H-indole-1-carboxylate (5.136) and tert-butyl 3-(2-formamidoethyl)-2-(3-hydroxypropyl)-1H-indole-1-carboxylate (5.137)



According to a reported procedure, ${ }^{450}$ to a solution of unsaturated aldehyde $5.135(685 \mathrm{mg}, 2.0$ $\mathrm{mmol}, 1.0$ equiv) in dry DCM ( 20 mL 0.1 M ) was added $10 \% \mathrm{Pd} / \mathrm{C}(94 \mathrm{mg})$. The resulting mixture was stirred under $\mathrm{H}_{2}$ atmosphere ( 1 atm ) at room temperature for 6 h . The reaction mixture was filtered through a pad of Celite (rinsed with DCM) and the filtrate was evaporated in vacuo. The crude mixture was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to $97: 3$ ) to
 yellowish oil.

## Aldehyde 5.136:

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.83(\mathrm{t}, \mathrm{J}=1.1 \mathrm{~Hz}, 1 \mathrm{H}), 8.15(\mathrm{~s}, 1 \mathrm{H}), 8.05(\mathrm{dd}, \mathrm{J}=7.3,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.60$ $-7.48(\mathrm{~m}, 1 \mathrm{H}), 7.32-7.21(\mathrm{~m}, 2 \mathrm{H}), 5.71(\mathrm{~s}, 1 \mathrm{H}), 3.54(\mathrm{q}, \mathrm{J}=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.33(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.96$ $(\mathrm{t}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.84(\mathrm{td}, J=7.3,1.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 201.5,161.4,150.5,136.5,136.0,129.6,128.7,127.8,127.1,124.3$, 123.0, 118.4, 115.9, 84.4, 44.4, 38.3, 28.4, 24.3, 19.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 367.1628; found: 367.1629.

## Alcohol 5.137:

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.15(\mathrm{~d}, 1 \mathrm{H}), 8.10-8.04(\mathrm{~m}, 1 \mathrm{H}), 7.53-7.45(\mathrm{~m}, 1 \mathrm{H}), 7.29-7.20(\mathrm{~m}$, $1 \mathrm{H}), 5.81(\mathrm{~s}, 1 \mathrm{H}), 3.69(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.61-3.50(\mathrm{~m}, 3 \mathrm{H}), 3.17(\mathrm{t}, 2 \mathrm{H}), 2.96(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H})$, $2.02-1.82(\mathrm{~m}, 2 \mathrm{H}), 1.69(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{\text {C NMR (101 MHz, }} \mathrm{CDCl}_{3}$ ): $\delta 161.5,150.7,138.3,136.0,129.7,123.9,122.9,118.1,115.9,115.5$, 84.2, 61.8, 38.4, 33.2, 28.4, 24.4, 22.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 369.1785 ; found: 369.1784.
tert-butyl 3-(2-isocyanoethyl)-2-(3-oxopropyl)-1H-indole-1-carboxylate (5.138)


Procedure: GP 5-4 starting from of formamide $\mathbf{5 . 1 3 6}$ ( $219 \mathrm{mg}, 0.64 \mathrm{mmol}$ )
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.84(\mathrm{~s}, 1 \mathrm{H}), 8.07(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.41(\mathrm{dd}, J=6.8,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.29$ ( td, J = 7.3, 1.4 Hz, 1H), $7.26-7.24(\mathrm{~m}, 1 \mathrm{H}), 3.63(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.36(\mathrm{t}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.15(\mathrm{t}, \mathrm{J}$ $=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.91(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.69(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 201.1,156.9,150.3,137.4,135.9,128.8,124.3,123.0,117.7,116.1$, 114.2, 84.5, 45.8, 44.6, 28.3, 24.7, 19.4.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 327.1703; found: 327.1700.
tert-butyl 3-(2-formamidoethyl)-2-(3-(hex-5-en-1-yloxy)propyl)-1H-indole-1-carboxylate (5.139)


According to a reported procedure, ${ }^{450}$ to a solution of primary alcohol 5.137 ( $1.00 \mathrm{~g}, 2.90 \mathrm{mmol}$, 1.0 equiv) in dry DMF ( 10 mL ) at $0^{\circ} \mathrm{C}$ was added $\mathrm{NaH}(60 \%$ dispersion in mineral oil, $127.6 \mathrm{mg}, 3.19$ mmol, 1.1 equiv). After stirring at the same temperature for 30 min , a solution of 6-bromo-1hexene ( 5.125 d ) ( $520.2 \mathrm{mg}, 3.19 \mathrm{mmol}, 1.1$ equiv) in dry DMF ( 4.5 mL ) was added dropwise at 0 ${ }^{\circ} \mathrm{C}$. After being stirred at room temperature for 15 h , the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude mixture was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$ to afford compound 5.139 ( $438 \mathrm{mg}, 35 \%$ ) as yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.12(\mathrm{~d}, J=1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.55(\mathrm{dt}, J=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.32-7.23(\mathrm{~m}$, $1 \mathrm{H}), 7.18$ (ddd, $J=8.2,6.9,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.09$ (ddd, $J=8.0,7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.78$ (ddtd, $J=16.9,10.2$, $6.7,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.59(\mathrm{~s}, 1 \mathrm{H}), 5.08-4.91(\mathrm{~m}, 2 \mathrm{H}), 4.11(\mathrm{t}, \mathrm{J}=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 4.09-4.02(\mathrm{~m}, 2 \mathrm{H}), 3.58$ $(\mathrm{q}, J=6.6 \mathrm{~Hz}, 2 \mathrm{H}), 2.96(\mathrm{t}, J=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.90-2.78(\mathrm{~m}, 2 \mathrm{H}), 2.10(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.99-1.87$ (m, 2H), $1.82-1.70(\mathrm{~m}, 2 \mathrm{H}), 1.49(\mathrm{~s}, 9 \mathrm{H}), 1.55-1.41(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 161.2, 153.6, 138.2, 136.3, 136.2, 127.9, 121.3, 119.4, 118.4, 115.3, 109.5, 108.1, 82.4, 66.1, 53.6, 43.5, 38.9, 33.5, 29.6, 27.9, 26.4, 24.7, 21.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 451.2567; found: 451.2576.
tert-butyl 3-(2-formamidoethyl)-2-(3-((5-oxopentyl)oxy)propyl)-1H-indole-1-carboxylate (5.140)


Procedure: GP 5-3 starting from alkene 5.139 ( $362 \mathrm{mg}, 0.85 \mathrm{mmol})$

Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: 243 mg , 66\%, white solid.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.74(\mathrm{t}, \mathrm{J}=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.15-8.12(\mathrm{~m}, 1 \mathrm{H}), 7.55(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, 7.27 (d, $J=8.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.18 (td, 1H), 7.09 (ddd, $J=7.9,7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.68(\mathrm{~s}, 1 \mathrm{H}), 4.16-4.02$ $(\mathrm{m}, 4 \mathrm{H}), 3.58(\mathrm{q}, J=6.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.96(\mathrm{t}, J=6.9 \mathrm{~Hz}, 2 \mathrm{H}), 2.85(\mathrm{t}, 2 \mathrm{H}), 2.46(\mathrm{td}, J=7.1,1.4 \mathrm{~Hz}, 2 \mathrm{H})$, $1.98-1.89(m, 2 H), 1.83-1.73(m, 2 H), 1.70-1.61(m, 2 H), 1.49(s, 9 H)$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 201.7,161.3,153.6,136.3,136.2,127.9,121.4,119.5,118.5,109.4$, 108.5, 82.4, 66.1, 43.5, 43.2, 38.8, 29.9, 29.6, 27.9, 24.6, 21.0, 19.5.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{35} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 431.2540; found: 431.2531 .
tert-butyl 3-(2-isocyanoethyl)-2-(3-((5-oxopentyl)oxy)propyl)-1H-indole-1-carboxylate (5.141)


Procedure: GP 5-4 starting from formamide 5.140 ( $246 \mathrm{mg}, 0.56 \mathrm{mmol}$ )
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.75(\mathrm{t}, J=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{dt}, J=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.31-7.24(\mathrm{~m}$, $1 \mathrm{H}), 7.19$ (ddd, $J=8.2,7.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.11$ (ddd, $J=7.9,7.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.16-4.02(\mathrm{~m}, 4 \mathrm{H}), 3.59$ $(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.14(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.90(\mathrm{t}, 2 \mathrm{H}), 2.47(\mathrm{td}, J=7.0,1.4 \mathrm{~Hz}, 2 \mathrm{H}), 2.01-1.90(\mathrm{~m}$, $2 \mathrm{H}), 1.85-1.73$ (m, 2H), $1.73-1.63$ (m, 2H), $1.50(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 201.7, 156.3, 153.6, 136.8, 136.2, 127.3, 121.6, 119.6, 117.9, 109.6, 106.9, 82.4, 65.9, 53.6, 43.5, 43.3, 29.8, 29.6, 27.9, 25.4, 21.0, 19.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 435.2254; found: 435.2247.
N -(3-formamidopropyl)-2-hydroxybenzamide (5.145)


A mixture of methyl salicylate ( 5.142 ) ( $3.04 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0$ equiv) in 1,3-diaminopropane (1.67 $\mathrm{mL}, 20.0 \mathrm{mmol}, 1.0$ equiv) was stirred vigorously at $110{ }^{\circ} \mathrm{C}$ for 3 h . After being cooled to room temperature, the reaction mixture was evaporate in vacuo to yield the adduct 5.144 which was used for the next step without further purification.

The analytical data were in accordance with those reported in the literature. ${ }^{576}$
The latter was dissolved in ethyl formate ( $12.0 \mathrm{~mL}, 1.67 \mathrm{M}$ ). After being stirred at $75{ }^{\circ} \mathrm{C}$ for 21 h , the reaction mixture was cooled down to room temperature and evaporated in vacuo. The crude mixture was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 95:5) to afford compound 5.145 ( 2.31 g , 52\% over 2 steps) as yellowish viscous oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.28(\mathrm{~s}, 1 \mathrm{H}), 7.72(\mathrm{~s}, 1 \mathrm{H}), 7.57(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.38(\mathrm{t}, \mathrm{J}=7.8 \mathrm{~Hz}$, $1 \mathrm{H}), 6.96(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.24(\mathrm{~s}, 1 \mathrm{H}), 3.49(\mathrm{q}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.42(\mathrm{q}, J=$ $6.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.76(\mathrm{p}, J=6.1 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 170.4,162.7,161.6,134.3,126.0,119.0,118.5,114.4,35.5,35.0$, 29.5

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{NaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 245.0897 ; found: 245.0892 .
6-((6-bromohexyl)oxy)hex-1-ene (5.148)


According to a reported procedure, ${ }^{452}$ to a suspension of $\mathrm{NaH}(60 \%$ dispersion in mineral oil, 1.60 $\mathrm{g}, 40.0 \mathrm{mmol}, 2.0$ equiv) in dry THF ( 110 mL ) at $0^{\circ} \mathrm{C}$ was added dropwise a solution of 5-hexen-1-ol ( 5.147 ) $\left(2.00 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0\right.$ equiv) in dry THF ( 20 mL ). After stirring the reaction mixture at $0{ }^{\circ} \mathrm{C}$ for $30 \mathrm{~min}, 1,6$-dibromohexane ( 5.146 ) ( $3.03 \mathrm{~mL}, 20.0 \mathrm{mmol}, 1.0$ equiv) was added dropwise at 0 ${ }^{\circ} \mathrm{C}$. After stirring at reflux for 22 h , the resulting mixture was allowed to cool to room temperature, quenched at $0{ }^{\circ} \mathrm{C}$ with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude mixture was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{DCM} 4: 1$ ) to afford compound 5.148 ( 728 mg , $14 \%)$ as colorless liquid.
${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.81(\mathrm{ddt}, J=16.9,10.2,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.06-4.90(\mathrm{~m}, 2 \mathrm{H}), 3.47-3.32$ (m, 6H), $2.07(q, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.87(\mathrm{p}, J=6.9 \mathrm{~Hz}, 2 \mathrm{H}), 1.64-1.51(\mathrm{~m}, 5 \mathrm{H}), 1.51-1.30(\mathrm{~m}, 5 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 139.0,114.6,70.9,70.8,34.1,33.7,32.9,29.7,29.4,28.2,25.7,25.6$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H}_{24} \mathrm{BrO}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 263.1005; found: 263.1000.
GP 5-5:

[^217]

According to a reported procedure, ${ }^{453}$ to a solution of phenol 5.145 (1.0 equiv) in acetone ( 0.2 M ) were added $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( 2.0 equiv) and bromo alkene 5.125 d or 5.148 ( 1.1 equiv). After being stirred at reflux for 14 h , the reaction mixture was allowed to cool to room temperature and evaporated in vacuo. Water was added to the residue and the reaction mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude mixture was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield compound 5.149.

## $N$-(3-formamidopropyl)-2-(hex-5-en-1-yloxy)benzamide (5.149a)



Procedure: GP 5-4 starting from phenol 5.145 ( $881 \mathrm{mg}, 4.0 \mathrm{mmol}$ ) and alkyl bromide 5.125d
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: $1.15 \mathrm{~g}, 94 \%$, colorless viscous oil.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.21(\mathrm{~s}, 1 \mathrm{H}), 8.20-8.11(\mathrm{~m}, 2 \mathrm{H}), 7.49-7.39(\mathrm{~m}, 1 \mathrm{H}), 7.08(\mathrm{t}, \mathrm{J}=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 6.97(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.93(\mathrm{~s}, 1 \mathrm{H}), 5.81(\mathrm{ddt}, J=16.9,10.0,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.11-4.93(\mathrm{~m}$, $2 \mathrm{H}), 4.15(\mathrm{t}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.55(\mathrm{q}, J=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.35(\mathrm{q}, J=6.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.21-2.10(\mathrm{~m}, 2 \mathrm{H}), 1.94$ - 1.85 (m, 2H), $1.82-1.69(m, 2 H), 1.59(p, J=7.5 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 166.8,161.6,157.1,138.0,133.2,132.3,121.4,121.2,115.5,112.4$, 69.0, 36.2, 34.4, 33.4, 30.1, 28.7, 25.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 305.1860; found: 305.1866.
$N$-(3-formamidopropyl)-2-((6-(hex-5-en-1-yloxy)hexyl)oxy)benzamide (5.149b)


Procedure: GP 5-4 starting from phenol $5.145(507 \mathrm{mg}, 2.3 \mathrm{mmol})$ and alkyl bromide 5.148
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5$ ). Yield: $825 \mathrm{mg}, 89 \%$, colorless viscous oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.21(\mathrm{~s}, 1 \mathrm{H}), 8.17(\mathrm{~s}, 1 \mathrm{H}), 8.15(\mathrm{dd}, \mathrm{J}=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.44$ (ddd, $\mathrm{J}=$ $8.3,7.3,1.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.07(\mathrm{td}, J=7.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.00(\mathrm{~s}, 1 \mathrm{H}), 6.96(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.80(\mathrm{ddt}, J=$
$16.9,10.2,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.07-4.89(\mathrm{~m}, 2 \mathrm{H}), 4.14(\mathrm{t}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.55(\mathrm{q}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.45-$ $3.38(\mathrm{~m}, 4 \mathrm{H}), 3.35(\mathrm{q}, \mathrm{J}=6.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.10-2.02(\mathrm{~m}, 2 \mathrm{H}), 1.97-1.85(\mathrm{~m}, 4 \mathrm{H}), 1.75(\mathrm{p}, \mathrm{J}=6.2 \mathrm{~Hz}$, $2 H), 1.65-1.55(m, 4 H), 1.52-1.42(m, 4 H)$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 166.8,161.6,157.1,138.9,133.1,132.3,121.4,121.2,114.7,112.4$, 71.0, $70.7,69.1,36.3,34.5,33.7,30.2,29.9,29.3,29.3,26.3,26.1,25.6$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 427.2567; found: 427.2563.


## N -(3-formamidopropyl)-2-((5-oxopentyl)oxy)benzamide (5.150a)



Procedure: GP 5-3 starting from alkene 5.149a ( $761 \mathrm{mg}, 2.50 \mathrm{mmol}$ )
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 97: 3$ to 95:5). Yield: $243 \mathrm{mg}, 66 \%$, brown oil.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.83(\mathrm{~s}, 1 \mathrm{H}), 8.21(\mathrm{~s}, 1 \mathrm{H}), 8.19-8.10(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.16(\mathrm{dd}, \mathrm{J}=7.8,1.9$ $\mathrm{Hz}, 1 \mathrm{H}), 7.44(\mathrm{ddd}, J=8.7,7.4,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.08(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.00-6.90(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 6.95(\mathrm{~d}, J=$ $8.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.15(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 2 \mathrm{H}), 3.58(\mathrm{q}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.36(\mathrm{q}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.61(\mathrm{t}, \mathrm{J}=6.5$ $\mathrm{Hz}, 2 \mathrm{H}), 1.98-1.87(\mathrm{~m}, 2 \mathrm{H}), 1.87-1.70(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 201.7, 166.6, 161.7, 156.9, 133.1, 132.4, 121.5, 121.4, 112.3, 68.7, $43.4,36.4,34.7,30.1,28.7,18.8$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 307.1652$; found: 307.1647.

## $N$-(3-formamidopropyl)-2-((6-((5-oxopentyl)oxy)hexyl)oxy)benzamide (5.150b)



Procedure: GP 5-3 starting from alkene 5.149b ( $769 \mathrm{mg}, 1.9 \mathrm{mmol}$ )
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 97: 3$ to 95:5). Yield: $532 \mathrm{mg}, 69 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.76(\mathrm{t}, J=1.9 \mathrm{~Hz}, 1 \mathrm{H}), 8.21(\mathrm{~s}, 1 \mathrm{H}), 8.18(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.15(\mathrm{dd}, J=7.8$, $1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.47-7.39(\mathrm{~m}, 1 \mathrm{H}), 7.07(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.00-6.90(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 6.96(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}$, $1 \mathrm{H}), 4.14(\mathrm{t}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.55(\mathrm{q}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.45-3.38(\mathrm{~m}, 4 \mathrm{H}), 3.35(\mathrm{q}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.46$ (td, J = 7.2, 1.6 Hz, 2H), 1.89 (p,J=6.8 Hz, 2H), 1.80-1.66 (m, 4H), 1.59 (p, J = 6.7 Hz, 4H), $1.54-$ $1.38(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}{ }^{3}$ CNMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 202.7, 166.8, 161.6, 157.1, 133.1, 132.2, 121.4, 121.2, 112.4, 70.8, 70.5, 69.1, 43.8, 36.3, 34.5, 30.1, 29.8, 29.3, 29.2, 26.2, 26.1, 19.1.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{22} \mathrm{H}_{34} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 429.2360$; found: 429.2353 .

$N$-(3-isocyanopropyl)-2-((5-oxopentyl)oxy)benzamide (5.151a)


Procedure: GP 5-4 starting from formamide 5.150a ( $460 \mathrm{mg}, 1.5 \mathrm{mmol}$ )
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.84(\mathrm{~s}, 1 \mathrm{H}), 8.19(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 8.16(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.44(\mathrm{t}, \mathrm{J}=8.1 \mathrm{~Hz}$, $1 \mathrm{H}), 7.08(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.95(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.15(\mathrm{t}, J=5.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.64(\mathrm{q}, J=5.5,5.0 \mathrm{~Hz}$, $2 \mathrm{H}), 3.50(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.63(\mathrm{t}, \mathrm{J}=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.08-2.02(\mathrm{~m}, 2 \mathrm{H}), 1.97-1.89(\mathrm{~m}, 2 \mathrm{H}), 1.89-$ $1.79(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 201.6, 166.0, 157.0, 156.7, 133.1, 132.5, 121.5, 121.3, 112.2, 68.7, 43.4, 39.5, 36.7, 29.0, 28.8, 18.8.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 289.1547; found: 289.1540.

## N -(3-isocyanopropyl)-2-((6-((5-oxopentyl)oxy)hexyl)oxy)benzamide (5.151b)



Procedure: GP 5-4 starting from formamide 5.150b ( $488 \mathrm{mg}, 1.2 \mathrm{mmol}$ )
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.76(\mathrm{t}, \mathrm{J}=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.18(\mathrm{dd}, \mathrm{J}=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 8.15(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 7.43 (ddd, $J=8.4,7.3,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.13-7.03(\mathrm{~m}, 1 \mathrm{H}), 6.96(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.14(\mathrm{t}, J=6.6 \mathrm{~Hz}$, $2 \mathrm{H}), 3.60(\mathrm{q}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.51(\mathrm{tt}, J=6.6,1.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.47-3.37(\mathrm{~m}, 4 \mathrm{H}), 2.46(\mathrm{td}, J=7.2,1.7$ $\mathrm{Hz}, 2 \mathrm{H}), 2.09-1.98(\mathrm{~m}, 2 \mathrm{H}), 1.96-1.87(\mathrm{~m}, 2 \mathrm{H}), 1.74-1.57(\mathrm{~m}, 6 \mathrm{H}), 1.55-1.44(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 202.7, 166.0, 157.1, 133.1, 132.3, 121.4, 121.1, 112.3, $70.8,70.4$, 69.0, 43.7, 36.6, 29.8, 29.3, 29.2, 29.1, 26.2, 26.1, 19.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 389.2435$; found: 389.2433.
methyl 2-( N -benzylpent-4-enamido)benzoate (5.155)


Following a reported procedure, ${ }^{454}$ to a solution of 4-pentenoic acid ( 5.128 a ) ( $4.00 \mathrm{~g}, 40.0 \mathrm{mmol}$, 2.0 equiv) in dry THF ( 10 mL ) was added 1,1'-carbonyldiimidazole ( $6.49 \mathrm{~g}, 40.0 \mathrm{mmol}, 2.0$ equiv) portionwise. The solution was stirred at room temperature for 30 min . A solution of methyl anthranilate ( 5.152 ) ( $3.02 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0$ equiv) in dry THF ( 10 mL ) was added. After being stirred at reflux for 24 h , the reaction mixture was allowed to cool to room temperature, quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield methyl 2-(pent-4-enamido)benzoate (5.154) which was used for the next step without further purification.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 11.09(\mathrm{~s}, 1 \mathrm{H}), 8.73(\mathrm{dd}, J=8.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 8.02(\mathrm{dd}, J=8.0,1.7 \mathrm{~Hz}$, 1 H ), 7.54 (ddd, $J=8.7,7.3,1.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.07 (ddd, $J=8.3,7.3,1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $5.95-5.82(\mathrm{~m}, 1 \mathrm{H}), 5.11$ (dq, J = 17.2, 1.5 Hz, 1H), $5.02(\mathrm{dq}, J=10.3,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.93(\mathrm{~s}, 3 \mathrm{H}), 2.60-2.47(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 171.5, 168.9, 141.7, 136.8, 134.8, 130.9, 122.5, 120.5, 115.8, 114.9, 52.5, 37.9, 29.5.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{15} \mathrm{NNaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 256.0944; found: 256.0945 .
To a suspension of NaH ( $60 \%$ dispersion in mineral oil, $880 \mathrm{mg}, 22.0 \mathrm{mmol}, 1.1$ equiv) in dry DMF $(100 \mathrm{~mL})$ was added a solution of crude 5.154 in dry DMF $(100 \mathrm{~mL})$ dropwise at $0^{\circ} \mathrm{C}$. After stirring at $0^{\circ} \mathrm{C}$ for 30 min , benzyl bromide ( $4.73 \mathrm{~mL}, 40.0 \mathrm{mmol}, 2.0$ equiv) was added. After being stirred at room temperature for 17 h , the reaction mixture was quenched at $0^{\circ} \mathrm{C}$ with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude mixture was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 9:1 to 4:1) to yield compound 5.155 ( $2.17 \mathrm{~g}, 34 \%$ over two steps) as yellowish oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 7.99-7.92(\mathrm{~m}, 1 \mathrm{H}), 7.49-7.37(\mathrm{~m}, 2 \mathrm{H}), 7.25-7.20(\mathrm{~m}, 3 \mathrm{H}), 7.15$ (dd, $J=6.7,2.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.91-6.84(\mathrm{~m}, 1 \mathrm{H}), 5.73(\mathrm{ddt}, J=16.9,10.2,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.29(\mathrm{~d}, J=14.3 \mathrm{~Hz}$, $1 \mathrm{H}), 4.99-4.83(\mathrm{~m}, 2 \mathrm{H}), 4.31(\mathrm{~d}, \mathrm{~J}=14.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 2.41-2.33(\mathrm{~m}, 2 \mathrm{H}), 2.14-2.00(\mathrm{~m}$, $2 H$ ).
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 172.1,166.1,141.8,137.8,137.3,133.3,132.0,131.3,129.5,129.5$, 128.5, 128.4, 127.5, 115.0, 53.1, 52.7, 34.0, 29.4.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{20} \mathrm{H}_{21} \mathrm{NNaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 346.1414 ; found: 346.1417 .

## 2-(N-benzylpent-4-enamido)-N-(3-formamidopropyl)benzamide (5.156)



A mixture of methyl benzoate 5.155 ( $2.13 \mathrm{~g}, 6.6 \mathrm{mmol}, 1.0$ equiv) in 1,3-diaminopropane (5.143) ( $0.55 \mathrm{~mL}, 6.6 \mathrm{mmol}, 1.0$ equiv) was stirred vigorously at $110^{\circ} \mathrm{C}$ for 3 h . The reaction mixture was allowed to cool to room temperature and evaporate in vacuo to give the adduct which was used for the next step without further purification.

The latter was dissolved in ethyl formate ( $4.0 \mathrm{~mL}, 1.67 \mathrm{M}$ ). After being stirred at $75^{\circ} \mathrm{C}$ for 16 h , the reaction mixture was allowed to cool down to room temperature and evaporated in vacuo. The crude mixture was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to $97: 3$ ) to yield compound $\mathbf{5 . 1 5 6}$ ( $1.89 \mathrm{~g}, 73 \%$ over 2 steps) as yellowish viscous oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.21(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.63(\mathrm{dd}, J=5.9,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{dd}, J=5.8$, $3.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.32-7.23(\mathrm{~m}, 3 \mathrm{H}), 7.24-7.13(\mathrm{~m}, 2 \mathrm{H}), 6.93(\mathrm{dd}, \mathrm{J}=5.7,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.34(\mathrm{~s}, 1 \mathrm{H}), 6.15$ $(\mathrm{s}, 1 \mathrm{H}), 5.73(\mathrm{ddt}, J=16.9,10.2,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.15(\mathrm{~d}, \mathrm{~J}=14.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.06-4.80(\mathrm{~m}, 2 \mathrm{H}), 4.65(\mathrm{~d}, \mathrm{~J}$ $=14.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.47-3.28(\mathrm{~m}, 2 \mathrm{H}), 3.19$ (dddd, $J=25.3,13.6,7.0,5.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.35(\mathrm{tdd}, \mathrm{J}=7.8$, $6.6,1.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), 2.23 (ddd, $J=15.9,8.0,6.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.09(\mathrm{dt}, J=15.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.78-1.39(\mathrm{~m}$, 2 H ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 172.7,167.6,162.0,139.5,137.6,137.2,135.0,131.6,130.4,129.7$, 129.5, 128.7, 127.9, 115.3, 53.4, 36.4, 34.7, 34.1, 29.7, 29.4.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{27} \mathrm{~N}_{3} \mathrm{NaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 416.1945 ; found: 416.1943.
2-(N-benzyl-4-oxobutanamido)-N-(3-formamidopropyl)benzamide (5.157)


Procedure: GP 5-3 starting from alkene 5.156 ( $1.89 \mathrm{~g}, 4.81 \mathrm{mmol}$ )
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5\right)$. Yield: $1.17 \mathrm{~g}, 61 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.78(\mathrm{~s}, 1 \mathrm{H}), 8.21(\mathrm{~d}, \mathrm{~J}=1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.75(\mathrm{dd}, \mathrm{J}=7.6,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.41$ (td, J = 7.5, 1.3 Hz, 1H), 7.34 (td, J = 7.7, $1.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.24-7.20(\mathrm{~m}, 3 \mathrm{H}), 7.16-7.08(\mathrm{~m}, 2 \mathrm{H}), 6.81$ (dd, J = 7.8, 1.3 Hz, 1H), $6.56(\mathrm{~s}, 1 \mathrm{H}), 5.40(\mathrm{~d}, \mathrm{~J}=14.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.21(\mathrm{~d}, \mathrm{~J}=14.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.48(\mathrm{q}, \mathrm{J}=$
$6.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), $3.42-3.31(\mathrm{~m}, 2 \mathrm{H}), 3.15$ (ddd, $J=19.3,9.9,4.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.67$ (ddd, $J=19.3,5.9,3.7 \mathrm{~Hz}$, 1 H ), 2.41 (ddd, $J=16.8,9.9,3.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.24 (ddd, $J=16.8,5.9,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.78(\mathrm{p}, \mathrm{J}=6.2 \mathrm{~Hz}$, 2 H ).
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 202.6,171.1,167.8,161.7,138.3,136.5,134.5,131.3,130.6,130.5$, 129.4, 129.0, 128.6, 127.8, 53.1, 39.3, 36.9, 34.8, 29.6, 27.8.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{~N}_{3} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 418.1737; found: 418.1738.

## 2-(N-benzyl-4-oxobutanamido)-N-(3-isocyanopropyl)benzamide (5.158)



Procedure: GP 5-4 starting from formamide 5.157 ( $593 \mathrm{mg}, 1.5 \mathrm{mmol})$
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.78(\mathrm{~s}, 1 \mathrm{H}), 7.77(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.41(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{t}, \mathrm{J}=$ $7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.24-7.17(\mathrm{~m}, 4 \mathrm{H}), 7.16-7.09(\mathrm{~m}, 2 \mathrm{H}), 6.79(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.36(\mathrm{~d}, \mathrm{~J}=13.9 \mathrm{~Hz}$, $1 \mathrm{H}), 4.22(\mathrm{~d}, J=13.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.66-3.50(\mathrm{~m}, 2 \mathrm{H}), 3.48(\mathrm{t}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.24(\mathrm{ddd}, J=19.3,10.6$, $2.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.64(\mathrm{ddd}, J=19.5,5.8,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.40(\mathrm{ddd}, J=17.0,10.5,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.20(\mathrm{dt}, J=$ $16.9,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.03(\mathrm{p}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 202.6, 171.0, 167.3, 156.7, 138.1, 136.4, 134.5, 131.3, 131.1, 130.3, $129.5,129.0,128.6,127.9,53.0,39.6,39.4,37.5,29.2,27.8$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{~N}_{3} \mathrm{NaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 400.1632; found: 400.1631.

## $N$-(3-formamidopropyl)-3-(hex-5-en-1-yloxy)benzamide (5.161)



A mixture of phenol 5.159 ( $3.04 \mathrm{~g}, 20.0 \mathrm{mmol}, 1.0$ equiv) in 1,3-diaminopropane ( 5.143 ) ( 1.67 mL , $20.0 \mathrm{mmol}, 1.0$ equiv) was stirred vigorously at $110^{\circ} \mathrm{C}$ for 3 h . After being cooled to room temperature, the reaction mixture was evaporate in vacuo to yield an adduct which was used for the next step without further purification.

The latter was dissolved in ethyl formate ( $12.0 \mathrm{~mL}, 1.67 \mathrm{M}$ ). After being stirred at $75{ }^{\circ} \mathrm{C}$ for 21 h , the reaction mixture was cooled down to room temperature and evaporated in vacuo to afford compound 5.160 which was used for the next step without further purification.

Compound 5.160 was then alkylated.

Procedure: GP 5-5 starting from phenol 5.160 ( $791 \mathrm{mg}, 2.6 \mathrm{mmol}$ )
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 99: 1$ to 97:3). Yield: 56\% over 3 steps, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.14(\mathrm{~s}, 1 \mathrm{H}), 7.40-7.15(\mathrm{~m}, 4 \mathrm{H}), 6.94(\mathrm{dd}, \mathrm{J}=8.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.72(\mathrm{br}$ s, 1H), 5.74 (ddt, $J=17.0,10.3,6.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $4.95(\mathrm{~d}, \mathrm{~J}=17.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.89(\mathrm{~d}, J=10.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.92$ $(\mathrm{t}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.41(\mathrm{q}, J=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.29(\mathrm{q}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.04(\mathrm{q}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.79-$ $1.58(\mathrm{~m}, 4 \mathrm{H}), 1.48(\mathrm{p}, \mathrm{J}=7.5 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 168.1, 162.2, 159.4, 138.5, 135.7, 129.7, 118.8, 118.3, 114.9, 113.0, 68.0, 36.2, 34.7, 33.5, 29.6, 28.7, 25.4.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{NaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 327.1679; found: 327.1680.
N -(3-formamidopropyl)-3-((5-oxopentyl)oxy)benzamide (5.162)


Procedure: GP 5-3 starting from alkene 5.161 (791 mg, 2.6 mmol$)$
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5\right.$ to 9:1). Yield: $608 \mathrm{mg}, 76 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 9.79(\mathrm{~s}, 1 \mathrm{H}), 8.23(\mathrm{~s}, 1 \mathrm{H}), 7.39-7.28(\mathrm{~m}, 3 \mathrm{H}), 7.18(\mathrm{br} \mathrm{t}, \mathrm{J}=6.4 \mathrm{~Hz}$, $1 \mathrm{H}), 7.01(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.59(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.02(\mathrm{brt}, J=4.7 \mathrm{~Hz}, 2 \mathrm{H}), 3.50(\mathrm{q}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.38$ (q, J = 6.4 Hz, 2H), 2.52 (brt, J = 6.2 Hz, 2H), $1.85-1.80(m, 4 H), 1.75(p, J=6.4 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 202.4,168.0,162.2,159.3,135.7,129.8,119.0,118.4,112.9,67.7$, 43.6, 36.2, 34.7, 29.7, 28.7, 18.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 329.1472; found: 329.1469.
N -(3-isocyanopropyl)-3-((5-oxopentyl)oxy)benzamide (5.163)


Procedure: GP 5-4 starting from formamide 5.162
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl $)_{3}$ ): $\delta 9.73(\mathrm{t}, \mathrm{J}=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.28-7.19(\mathrm{~m}, 3 \mathrm{H}), 6.96(\mathrm{dd}, \mathrm{J}=7.7,2.6 \mathrm{~Hz}$, 1 H ), 6.39 (br t, J = 5.9 Hz, 1H), 3.96 (q, J = 5.0, 3.5 Hz, 2H), $3.54(q, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.45(\mathrm{t}, J=6.4 \mathrm{~Hz}$, $2 \mathrm{H}), 2.52-2.40(\mathrm{~m}, 2 \mathrm{H}), 2.01-1.94(\mathrm{~m}, 2 \mathrm{H}), 1.79-1.72(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR (101 MHz, CDCl $_{3}$ ): $\delta 202.4,167.9,159.3,156.9,135.6,129.8,118.9,118.5,113.0,67.7$, 43.6, 39.6, 37.3, 29.2, 28.6, 18.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 289.1547; found: 289.1542.
$N$-(3-aminopropyl)formamide (5.164)


It was prepared according to a literature procedure. ${ }^{456}$
4-(hex-5-en-1-yloxy)benzoic acid (5.167)


It was prepared according to a literature procedure. ${ }^{458}$
$N$-(3-formamidopropyl)-4-(hex-5-en-1-yloxy)benzamide (5.168)


To a solution of acid 5.167 ( $1.08 \mathrm{~g}, 4.88 \mathrm{mmol}, 1.0$ equiv) in dry DMF ( $23 \mathrm{~mL}, 0.215 \mathrm{M}$ ) at room temperature were added amine 5.164 ( $850 \mathrm{mg}, 4.88 \mathrm{mmol}, 1.0$ equiv), DIPEA ( $4.03 \mathrm{~mL}, 24.39$ mmol, 5.0 equiv), EDC•HCl ( $1.08 \mathrm{~g}, 5.61 \mathrm{mmol}, 1.15$ equiv) and HOBt ( $725 \mathrm{mg}, 5.37 \mathrm{mmol}, 1.1$ equiv). After being stirred at room temperature for 12 hours, the reaction mixture was quenched with HCl 1 M and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The residue was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ) to yield the desired product 5.168 (87\%) as a yellow oil.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.23(\mathrm{~s}, 1 \mathrm{H}), 7.78(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.11(\mathrm{~s}, 1 \mathrm{H}), 6.90(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}$, $2 \mathrm{H}), 6.73(\mathrm{~s}, 1 \mathrm{H}), 5.82(\mathrm{ddt}, \mathrm{J}=16.9,10.2,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.10-4.92(\mathrm{~m}, 2 \mathrm{H}), 3.99(\mathrm{t}, \mathrm{J}=6.5 \mathrm{~Hz}, 2 \mathrm{H})$, $3.50(\mathrm{q}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.38(\mathrm{q}, J=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.12(\mathrm{q}, J=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 1.89-1.68(\mathrm{~m}, 4 \mathrm{H}), 1.57(\mathrm{q}$, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}$ ).
${ }^{13}{ }^{3} \mathrm{CNR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 168.7,162.8,162.2,138.2,132.6,126.4,115.1,114.8,68.1,38.5$, 37.6, 33.2, 28.7, 25.5.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 305.1860 ; found: 305.1854.

## N -(3-formamidopropyl)-4-((5-oxopentyl)oxy)benzamide (5.169)



Procedure: GP 5-3 starting from alkene 5.168
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5\right.$ to 9:1). Yield: 78\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.79(\mathrm{t}, \mathrm{J}=1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.23(\mathrm{~d}, J=1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.78(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H})$, $7.12(\mathrm{~s}, 1 \mathrm{H}), 6.90(\mathrm{~d}, \mathrm{~J}=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.69(\mathrm{~s}, 1 \mathrm{H}), 4.05-3.91(\mathrm{~m}, 2 \mathrm{H}), 3.56-3.43(\mathrm{~m}, 2 \mathrm{H}), 3.37(\mathrm{q}, \mathrm{J}$ $=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 2.53(\mathrm{ddt}, \mathrm{J}=6.9,4.9,1.7 \mathrm{~Hz}, 2 \mathrm{H}), 1.91-1.79(\mathrm{~m}, 4 \mathrm{H}), 1.73(\mathrm{t}, \mathrm{J}=6.1 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 202.3,167.8,162.2,161.7,128.9,126.4,114.4,67.7,43.6,36.1,34.7$, 29.8, 28.6, 18.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 307.1652 ; found: 307.1648.
N -(3-isocyanopropyl)-4-((5-oxopentyl)oxy)benzamide (5.170)


Procedure: GP 5-4 starting from formamide 5.169
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.81(\mathrm{t}, J=1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.72(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.91(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H})$, $4.01(\mathrm{q}, J=2.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.60(\mathrm{q}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.51(\mathrm{tt}, J=6.6,1.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.55(\mathrm{td}, J=5.2,2.5 \mathrm{~Hz}$, 2 H ), 2.04 (qd, J = 4.7, 2.2 Hz, 2H), $1.88-1.81(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 202.2,167.5,161.9,157.0,128.8,126.4,114.4,67.7,43.6,39.7,37.3$, 29.3, 28.7, 18.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 289.1547; found: 289.1551 .

### 8.5.2 Scope

GP 5-6:


To a solution of $\omega$-isocyanoaldehyde 5.57 ( 1.0 equiv) in dry $\mathrm{DCM}\left(0.01 \mathrm{M}\right.$ ) at $0{ }^{\circ} \mathrm{C}$, were added dropwise pyridine ( 6.0 equiv) and TFA ( 3.0 equiv). The reaction mixture was allowed to warm to
room temperature and stirred until completion of the reaction (1-5 days). The reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and the reaction mixture was stirred at room temperature for 1 h . The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with 2 M HCl , saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the product 5.180.

GP 5-7:


To a solution of $\omega$-isocyanoaldehyde 5.57 ( 1.0 equiv) in dry $\mathrm{DCM}\left(0.01 \mathrm{M}\right.$ ) at $0{ }^{\circ} \mathrm{C}$ was added dropwise AcOH or N -Boc glycine or BzOH (1.3 equiv). The reaction mixture was allowed to warm to room temperature and stirred until completion of the reaction (1-5 days). The reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The combined organic extracts were washed with 2 M HCl , saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the product $\mathbf{5 . 1 7 8}$.

## GP 5-8:



According to a reported procedure, ${ }^{57 a}$ a mixture of the $\omega$-isocyanoaldehyde 5.57 (1 equiv), MeN$\mathrm{HOH} \cdot \mathrm{HCl}$ (3 equiv), $\mathrm{NaHCO}_{3}$ ( 6 equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol}$ isonitrile) in dry $\mathrm{MeOH}(0.01 \mathrm{M})$ was stirred for 30 min . AcOH ( 27 equiv) was added and the reaction mixture was stirred at room temperature until completion of the reaction (1-5 days). The reaction mixture was then filtered, washed with 2 M HCl , brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the product 5.182.

## GP 5-9:



To a solution of $\omega$-isocyanoaldehyde 5.57 (1.0 equiv) and amine ( 1.2 equiv) in dry MeOH ( 0.01 M ) at $0^{\circ} \mathrm{C}$ was added dropwise AcOH ( 1.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred until completion of the reaction (1-5 days). The reaction mixture was evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the product 5.181.

## GP 5-10:


$\operatorname{TMSN}_{3}$ (1.1 equiv) was added dropwise to a solution of $\omega$-isocyanoaldehyde 5.57 (1.0 equiv) and amine ( 1.1 equiv) in dry $\mathrm{MeOH}\left(0.01 \mathrm{M}\right.$ ) at $0^{\circ} \mathrm{C}$. The reaction mixture was allowed to warm to room temperature and stirred until the completion of reaction (1-5 days). The reaction mixture was evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the product 5.183.
tert-butyl 5-hydroxy-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)-carboxylate (5.181)


Procedure: GP 5-6 starting from 5.138
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: 44\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 367.1634 ; found: 367.1631.
tert-butyl 5-acetoxy-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)-carboxylate (5.182)


Procedure: GP 5-7 starting from 5.138
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: 50\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 409.1734; found: 409.1731.
tert-butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole$8(1 H)$-carboxylate (5.183)


Procedure: GP 5-7 starting from 5.138
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 55\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{25} \mathrm{~N}_{3} \mathrm{NaO}_{7}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 524.2367 ; found: 524.2369.
tert-butyl 5-(N-benzylacetamido)-4-oxo-2,3,4,5,6,7-hexahydroazonino[5,4-b]indole-8(1H)carboxylate (5.184)


Procedure: GP 5-9 starting from 5.138
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 99: 1$ to 98:2). Yield: 43\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{34} \mathrm{~N}_{3} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 476.2544$; found: 476.2543 .
tert-butyl 14-((4-cyanophenyl)amino)-6,12,13,14-tetrahydrotetrazolo[1',5':1,9]azonino[5,4-b]indole-11(5H)-carboxylate (5.185)


Procedure: GP 5-10 starting from 5.138
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 99: 1$ ). Yield: 35\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathbf{~ M H z}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{27} \mathrm{~N}_{7} \mathrm{NaO}_{2}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 492.2118$; found: 492.2118 .
tert-butyl 3-hydroxy-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (5.186)


Procedure: GP 5-6 starting from 5.133a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: 59\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.99(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.47(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.35$ (ddd, $J=8.4,7.2$, $1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.31-7.23(\mathrm{~m}, 1 \mathrm{H}), 5.58(\mathrm{dd}, J=7.5,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{dt}, J=12.7,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.23$ (dd, J = 14.6, 7.7 Hz, 1H), 3.81 (ddd, J = 12.9, 7.4, 5.6 Hz, 1H), 2.94-2.85 (m, 2H), 2.78 (dt, J = 16.4, $7.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.57-2.45(\mathrm{~m}, 1 \mathrm{H}), 1.66(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.8,150.6,139.3,129.5,129.4,127.6,126.2,123.4,121.8,119.2$, 115.3, 103.1, 84.6, 66.4, 39.4, 28.3, 27.7, 21.4.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 377.1472 ; found: 377.1470.
tert-butyl 3-acetoxy-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (5.187)

5.187

Procedure: GP 5-7 starting from 5.133a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: $62 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.98(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.47$ (ddd, $\left.J=7.7,1.3,0.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.35$ (ddd, J $=8.5,7.3,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.30-7.22(\mathrm{~m}, 1 \mathrm{H}), 5.54(\mathrm{dd}, J=6.9,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.45(\mathrm{dd}, J=13.3,7.7 \mathrm{~Hz}$, $1 \mathrm{H}), 4.40(\mathrm{dt}, J=12.8,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.79$ (ddd, $J=12.8,7.6,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.91-2.83(\mathrm{~m}, 2 \mathrm{H}), 2.79-$ $2.62(\mathrm{~m}, 2 \mathrm{H}), 2.21(\mathrm{~s}, 3 \mathrm{H}), 1.67(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 170.4,166.6,150.6,139.3,129.8,129.4,127.7,126.2,123.4,122.4$, $119.3,115.3,101.4,84.6,67.9,39.0,28.3,25.6,21.4,21.1$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 419.1577; found: 419.1579.
tert-butyl 3-(benzoyloxy)-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (5.188)


Procedure: GP 5-7 starting from 5.133a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1$ ). Yield: 55\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.14(\mathrm{dd}, J=8.4,1.4 \mathrm{~Hz}, 2 \mathrm{H}), 8.00(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.58(\mathrm{t}, 1 \mathrm{H}), 7.50$ $-7.43(\mathrm{~m}, 3 \mathrm{H}), 7.36$ (ddd, $J=8.5,7.2,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{td}, J=7.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.71(\mathrm{dd}, \mathrm{J}=13.5$, $7.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.60(\mathrm{dd}, J=7.0,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.43(\mathrm{dt}, J=12.7,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.83$ (ddd, $J=12.8,7.8,5.0$ $\mathrm{Hz}, 1 \mathrm{H}), 3.02-2.73(\mathrm{~m}, 4 \mathrm{H}), 1.68(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 166.6,166.0,150.7,139.4,133.4,130.1,129.9,129.9,129.5,128.5$, $127.7,126.3,123.4,122.4,119.3,115.3,101.3,84.6,68.3,39.1,28.3,25.8,21.4$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 481.1734; found: 481.1730.
tert-butyl 3-(N-benzylacetamido)-4-oxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)carboxylate (5.189)


Procedure: GP 5-9 starting from 5.133a
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: 89\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.95(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.45(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.32(\mathrm{~m}, 3 \mathrm{H})$, $7.32-7.21(\mathrm{~m}, 4 \mathrm{H}), 5.43(\mathrm{dd}, \mathrm{J}=7.5,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.24-5.11(\mathrm{~m}, 1 \mathrm{H}), 4.80(\mathrm{~d}, \mathrm{~J}=17.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.50$ (d, J = 17.9 Hz, 1H), $4.40(\mathrm{dt}, J=12.8,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.79$ (ddd, $J=12.7,7.5,5.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.91-2.69$ (m, 3H), 2.35 (dt, J = 16.3, 7.2 Hz, 1H), 2.18 (s, 3H), $1.61(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 172.6,167.8,150.6,139.3,137.9,129.7,129.3,129.0,127.7,127.6$, $126.2,126.0,123.3,122.1,119.2,115.2,103.0,84.4,55.2,51.6,39.2,28.3,24.8,22.2,21.4$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{32} \mathrm{~N}_{3} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 486.2387; found: 486.2390.
tert-butyl 3-(methylamino)-4-oxo-6,7-dihydroindolo[2,3-a]quinolizine-12(4H)-carboxylate (5.190)

5.190

According to a reported procedure, ${ }^{57 a}$ a mixture of the $\omega$-isocyanoaldehyde 5.133a (1 equiv), $\mathrm{MeNHOH} \cdot \mathrm{HCl}$ (3 equiv), $\mathrm{NaHCO}_{3}$ ( 6 equiv) and $4 \AA$ molecular sieves ( $750 \mathrm{mg} / \mathrm{mmol}$ isonitrile) in dry $\mathrm{MeOH}(0.01 \mathrm{M})$ was stirred for 30 min . AcOH ( 27 equiv) was added and the reaction mixture was stirred at room temperature until completion of the reaction (1-5 days). The reaction mixture was then filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right.$ to $\left.95: 5+3 \% \mathrm{NEt}_{3}\right)$ to yield the product 5.190 ( $89 \%$ ) as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $\mathrm{d}_{4}$ ): $\delta 8.01(\mathrm{dt}, J=8.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.49(\mathrm{dt}, J=7.5,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.30$ (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.23 (td, J = 7.4, 1.0 Hz, 1H), 6.45 (d, J = 7.9 Hz, 1H), 6.37 (d, J = 8.0 $\mathrm{Hz}, 1 \mathrm{H}), 4.43(\mathrm{t}, \mathrm{J}=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.89(\mathrm{t}, \mathrm{J}=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 2.86(\mathrm{~s}, 3 \mathrm{H}), 1.61(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta 158.2,151.8,140.6,140.0,131.7,128.8,126.6,124.5,124.4$, 121.4, 119.8, 116.1, 109.3, 106.8, 85.6, 41.5, 29.9, 28.3, 21.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{24} \mathrm{~N}_{3} \mathrm{O}_{3}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 366.1812$; found: 366.1813.
tert-butyl 3,4-dioxo-3,4,6,7-tetrahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (5.191)

5.191

Procedure: GP 5-8 starting from 5.133a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5$ to 9:1). Yield: 79\%, yellowish oil.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 375.1315$; found: 375.1311 .

## tert-butyl 5-hydroxy-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-b]indole-10(1H)-carboxylate (5.192)



Procedure: GP 5-6 starting from 5.133b
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: 68\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.05(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.41(\mathrm{t}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.29(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.23-4.14(\mathrm{~m}, 1 \mathrm{H}), 3.71-3.59(\mathrm{~m}, 1 \mathrm{H}), 3.45-3.31(\mathrm{~m}, 1 \mathrm{H}), 3.16$ (ddd, J = 15.0, 10.0, 2.8 Hz, 1H), 3.08-2.90(m, 2H), 2.90-2.73(m, 2H), 2.13-1.93(m, 4H), $1.58(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 199.3,174.2,149.7,136.9,135.5,128.6,127.2,123.5,122.0,119.8$, 115.4, 85.1, 70.1, 41.8, 39.7, 30.8, 28.0, 23.0, 16.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 409.1734; found: 409.1736.
tert-butyl 5-acetoxy-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4-b]indole-10(1H)-carboxylate (5.193)


Procedure: GP 5-7 starting from 5.133b
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 72\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.05(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.42$ (ddd, $J=8.4,7.2$, $1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.30(\mathrm{ddd}, J=8.0,7.2,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.23(\mathrm{t}, \mathrm{J}=6.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.13(\mathrm{t}, \mathrm{J}=4.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.79$ (dtd, $J=13.5,6.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.45-3.33(\mathrm{~m}, 1 \mathrm{H}), 3.17$ (ddd, $J=14.9,9.5,3.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.03 (ddd, J $=14.9,6.4,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.92-2.85(\mathrm{~m}, 2 \mathrm{H}), 2.10(\mathrm{~s}, 3 \mathrm{H}), 2.08-2.01(\mathrm{~m}, 2 \mathrm{H}), 1.88-1.75(\mathrm{~m}, 2 \mathrm{H})$, $1.60(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 197.3,169.6,169.5,149.7,136.9,135.8,128.6,127.0,123.4,121.5$, 119.9, 115.4, 85.2, 72.9, 42.9, 39.3, 29.3, 28.1, 23.3, 21.1, 17.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{NaO}_{6}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 451.1840; found: 451.1841.
tert-butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-
[1]azacycloundecino[5,4-b]indole-10(1H)-carboxylate (5.194)


Procedure: GP 5-7 starting from 5.133b
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 95:5). Yield: 78\%, yellowish oil.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.03(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.40$ (ddd, $J=8.4,7.2$, $1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.28(\mathrm{~d}, \mathrm{~J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.63(\mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.24-5.08(\mathrm{~m}, 2 \mathrm{H}), 3.97-3.72(\mathrm{~m}, 3 \mathrm{H})$, $3.41-3.26(\mathrm{~m}, 1 \mathrm{H}), 3.26-3.15(\mathrm{~m}, 1 \mathrm{H}), 2.99(\mathrm{dd}, J=14.2,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.87(\mathrm{t}, J=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 2.13$ - $1.78(\mathrm{~m}, 4 \mathrm{H}), 1.60(\mathrm{~s}, 9 \mathrm{H}), 1.28(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathbf{C D C l}_{3}$ ): $\delta$ 197.2, 169.3, 169.2, 156.2, 149.8, 136.9, 135.6, 128.7, 127.0, 123.4, $121.7,119.9,115.4,85.1,80.4,73.7,42.9,42.8,39.5,28.9,28.2,28.1,23.1,17.7$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{37} \mathrm{~N}_{3} \mathrm{NaO}_{8}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 566.2473$; found: 566.2472.
tert-butyl 5-( $N$-benzylacetamido)-4,9-dioxo-2,3,4,5,6,7,8,9-octahydro-[1]azacycloundecino[5,4b] indole-10(1H)-carboxylate (5.195)


Procedure: GP 5-9 starting from 5.133b
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.02(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.53(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.30(\mathrm{~m}, 3 \mathrm{H})$, $7.29-7.22(\mathrm{~m}, 2 \mathrm{H}), 7.14(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 6.92(\mathrm{~s}, 1 \mathrm{H}), 4.91(\mathrm{~d}, \mathrm{~J}=18.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.70(\mathrm{~d}, J=11.2$ $\mathrm{Hz}, 1 \mathrm{H}), 4.58(\mathrm{~d}, \mathrm{~J}=18.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.93-3.77(\mathrm{~m}, 1 \mathrm{H}), 3.22-3.06(\mathrm{~m}, 2 \mathrm{H}), 3.06-2.94(\mathrm{~m}, 1 \mathrm{H}), 2.85$ ( $\mathrm{t}, \mathrm{J}=6.6 \mathrm{~Hz}, 2 \mathrm{H}$ ), 2.16-1.98(m,1H), $1.88-1.76(\mathrm{~m}, 4 \mathrm{H}), 1.72-1.60(\mathrm{~m}, 2 \mathrm{H}), 1.58(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 197.9, 172.7, 171.2, 149.8, 138.2, 136.5, 135.6, 128.9, 128.7, 127.2, $126.9,125.7,123.4,121.7,119.8,115.6,85.1,58.5,50.0,42.0,39.0,28.1,28.0,23.3,22.1,20.4$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{30} \mathrm{H}_{35} \mathrm{~N}_{3} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 540.2469$; found: 540.2472.
tert-butyl 5-hydroxy-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]azacyclododecino[5,4-b]indole-11-carboxylate (5.196)


Procedure: GP 5-6 starting from 5.133c
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: $92 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $-\mathrm{d}_{4} / \mathrm{CDCl}_{3}$ ) : $\delta 8.06(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{t}, J$ $=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.58(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.08(\mathrm{t}, \mathrm{J}=4.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.83-3.77(\mathrm{~m}, 1 \mathrm{H})$, $3.66-3.58(\mathrm{~m}, 1 \mathrm{H}), 3.10-2.89(\mathrm{~m}, 3 \mathrm{H}), 2.65(\mathrm{ddd}, \mathrm{J}=14.4,10.9,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.57-2.41(\mathrm{~m}, 2 \mathrm{H})$, $1.87-1.73(\mathrm{~m}, 3 \mathrm{H}), 1.59(\mathrm{~s}, 9 \mathrm{H}), 1.41-1.33(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR ( 101 MHz, Methanol $-d_{4} / \mathrm{CDCl}_{3}$ ): $\delta$ 198.1, 173.7, 149.9, 136.6, 136.6, 128.7, 127.0, 123.6, 122.1, 120.6, 115.8, 85.6, 71.3, 42.8, 37.1, 32.2, 28.0, 24.8, 24.4, 22.4.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 423.1890$; found: 423.1893 .

## tert-butyl 5-acetoxy-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]azacyclododecino[5,4-

 b]indole-11-carboxylate (5.197)

Procedure: GP 5-7 starting from 5.133c
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: $85 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.11(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.31(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.04(\mathrm{t}, \mathrm{J}=6.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.01(\mathrm{t}, \mathrm{J}=5.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.92-3.81(\mathrm{~m}, 1 \mathrm{H}), 3.70-$ $3.60(\mathrm{~m}, 1 \mathrm{H}), 3.17-3.01(\mathrm{~m}, 2 \mathrm{H}), 2.88-2.71(\mathrm{~m}, 2 \mathrm{H}), 2.00(\mathrm{~s}, 3 \mathrm{H}), 1.95-1.86(\mathrm{~m}, 1 \mathrm{H}), 1.78-1.68$ $(\mathrm{m}, 2 \mathrm{H}), 1.61(\mathrm{~s}, 9 \mathrm{H}), 1.51-1.26(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 197.7,169.6,168.9,149.9,136.7,136.3,128.8,127.2,123.7,122.5$, 120.7, 115.9, 85.7, 73.9, 43.4, 37.4, 29.6, 28.1, 24.7, 24.6, 23.0, 21.1.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{30} \mathrm{~N}_{2} \mathrm{NaO}_{6}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 465.1966; found: 465.1961.
tert-butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-
[1]azacyclododecino[5,4-b]indole-11-carboxylate (5.198)


Procedure: GP 5-7 starting from 5.133c
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 85\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.08(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.41(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.27(\mathrm{t}, \mathrm{J}=9.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.49(\mathrm{~s}, 1 \mathrm{H}), 5.19-5.08(\mathrm{~m}, 1 \mathrm{H}), 5.06(\mathrm{t}, \mathrm{J}=5.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.95-3.81(\mathrm{~m}, 1 \mathrm{H})$, $3.84-3.65(\mathrm{~m}, 2 \mathrm{H}), 3.67-3.45(\mathrm{~m}, 1 \mathrm{H}), 3.18-2.96(\mathrm{~m}, 2 \mathrm{H}), 2.87-2.69(\mathrm{~m}, 2 \mathrm{H}), 2.02-1.82(\mathrm{~m}$, $2 \mathrm{H}), 1.74(\mathrm{t}, \mathrm{J}=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 1.61(\mathrm{~s}, 9 \mathrm{H}), 1.49-1.41(\mathrm{~m}, 2 \mathrm{H}), 1.32(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\left.\mathrm{CDCl}_{3}\right): \delta 197.9,169.3,168.8,156.1,149.9,136.6,136.2,128.8,127.0,123.6$, 122.5, 120.6, 115.9, 85.6, 80.3, 74.6, 43.1, 42.8, 37.7, 29.4, 28.3, 28.1, 24.7, 24.4, 22.8.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{39} \mathrm{~N}_{3} \mathrm{NaO}_{8}\left(\left[\mathrm{M}+\mathrm{Na}^{+}\right)\right.$: 580.2629; found: 580.2632.
tert-butyl 5-( $N$-benzylacetamido)-4,10-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-11H-[1]azacyclododecino[5,4-b]indole-11-carboxylate (5.199)


Procedure: GP 5-9 starting from 5.133c
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: 57\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.09(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.58(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42$ (ddd, $J=8.5,7.2$, $1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.34-7.27(\mathrm{~m}, 3 \mathrm{H}), 7.23(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.19-7.06(\mathrm{~m}, 2 \mathrm{H}), 6.58(\mathrm{~s}, 1 \mathrm{H}), 4.96(\mathrm{~d}, \mathrm{~J}=$ $18.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.83(\mathrm{dd}, J=12.6,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.59(\mathrm{~d}, J=18.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.16-3.94(\mathrm{~m}, 1 \mathrm{H}), 3.35(\mathrm{ddt}$, $J=13.7,10.1,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.11$ (ddd, $J=13.8,10.1,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.06-2.95(\mathrm{~m}, 2 \mathrm{H}), 2.66-2.50(\mathrm{~m}$, $1 \mathrm{H}), 2.01-1.89(\mathrm{~m}, 1 \mathrm{H}), 1.86(\mathrm{~s}, 3 \mathrm{H}), 1.79-1.68(\mathrm{~m}, 1 \mathrm{H}), 1.60(\mathrm{~s}, 9 \mathrm{H}), 1.56-1.45(\mathrm{~m}, 1 \mathrm{H}), 1.39(\mathrm{~d}$, $J=240.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.34-1.17(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 197.4,172.8,170.3,149.9,138.3,136.8,136.2,128.8,127.2,127.1$, $125.6,123.7,123.0,120.6,116.0,85.6,56.3,49.2,43.6,37.3,28.1,24.6,24.0,23.9,22.2$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{31} \mathrm{H}_{37} \mathrm{~N}_{3} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 554.2625 ; found: 554.2616.
tert-butyl 5-hydroxy-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4b] indole-12(1H)-carboxylate (5.200)


Procedure: GP 5-6 starting from 5.133d
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: 83\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 437.2047; found: 437.2050.
tert-butyl 5-acetoxy-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4b] indole-12(1H)-carboxylate (5.201)


Procedure: GP 5-7 starting from 5.133d
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ to 1:2). Yield: 62\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.08(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.63(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.31(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.11(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.05(\mathrm{dd}, J=6.5,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.13-3.96(\mathrm{~m}, 1 \mathrm{H})$, $3.61-3.49(\mathrm{~m}, 1 \mathrm{H}), 3.24-3.15(\mathrm{~m}, 1 \mathrm{H}), 3.10(\mathrm{ddd}, J=15.9,6.3,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.88(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 2 \mathrm{H})$, $1.95(\mathrm{~s}, 3 \mathrm{H}), 1.91-1.76(\mathrm{~m}, 3 \mathrm{H}), 1.72-1.65(\mathrm{~m}, 1 \mathrm{H}), 1.62(\mathrm{~s}, 9 \mathrm{H}), 1.41-1.23(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR (101 MHz, $\mathbf{C D C l}_{3}$ ): $\delta 197.8,169.7,169.3,149.9,136.9,136.8,128.8,127.2,123.6,122.4$, 120.7, 115.7, 85.4, 73.7, 41.6, 37.6, 29.6, 28.1, 27.2, 25.1, 23.9, 22.7, 21.0.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{32} \mathrm{~N}_{2} \mathrm{NaO}_{6}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 479.2153; found: 479.2147.
tert-butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (5.202)


Procedure: GP 5-7 starting from 5.133d
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 95: 5\right)$. Yield: 73\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 197.8, 169.7, 169.1, 156.2, 149.9, 136.8, 136.6, 128.9, 127.0, 123.5, $122.7,120.8,115.6,85.3,80.3,74.4,42.8,41.8,38.1,29.5,28.3,28.1,27.3,25.1,23.8,22.6$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{30} \mathrm{H}_{41} \mathrm{~N}_{3} \mathrm{NaO}_{8}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 594.2786; found: 594.2776.
tert-butyl 5-(N-benzylacetamido)-4,11-dioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (5.203)


Procedure: GP 5-9 starting from 5.133d
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 2$ to 1:3). Yield: 54\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.06(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.58(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.42(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.35-7.27(\mathrm{~m}, 3 \mathrm{H}), 7.23(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.11(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 6.38(\mathrm{dd}, J=8.6,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, $4.92-4.72(\mathrm{~m}, 2 \mathrm{H}), 4.56(\mathrm{~d}, J=18.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.20-4.04(\mathrm{~m}, 1 \mathrm{H}), 3.28(\mathrm{ddt}, J=13.1,8.5,4.1 \mathrm{~Hz}$, $1 \mathrm{H}), 3.18-3.04(\mathrm{~m}, 2 \mathrm{H}), 2.98$ (ddd, $J=17.1,8.5,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.78$ (ddd, $J=17.1,7.1,4.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $1.94(\mathrm{~s}, 3 \mathrm{H}), 1.80-1.73(\mathrm{~m}, 2 \mathrm{H}), 1.62(\mathrm{~s}, 9 \mathrm{H}), 1.41-1.18(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 197.4,172.7,170.8,150.0,138.3,136.9,136.8,128.8,128.8,127.2$, $127.1,125.7,123.6,122.7,120.6,115.7,85.2,57.0,48.9,41.7,38.0,28.1,26.5,25.2,24.8,23.3$, 22.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{~N}_{3} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 568.2782; found: 568.2773.

## tert-butyl 4,5,11-trioxo-2,3,4,5,6,7,8,9,10,11-decahydro-[1]azacyclotridecino[5,4-b]indole-12(1H)-carboxylate (5.204)



Procedure: GP 5-8 starting from 5.133d
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1\right)$. Yield: 60\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.07(\mathrm{dt}, J=8.8,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{dt}, J=7.8,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.44$ (ddd, J $=8.5,7.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.31 (ddd, $J=8.0,7.2,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{t}, \mathrm{J}=6.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.82-3.72(\mathrm{~m}$, $2 H), 3.15-3.05(\mathrm{~m}, 2 \mathrm{H}), 2.79-2.72(\mathrm{~m}, 2 \mathrm{H}), 2.72-2.63(\mathrm{~m}, 2 \mathrm{H}), 1.84(\mathrm{p}, \mathrm{J}=6.6 \mathrm{~Hz}, 2 \mathrm{H}), 1.62(\mathrm{~s}$, $9 \mathrm{H}), 1.57-1.48(\mathrm{~m}, 2 \mathrm{H}), 1.48-1.40(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 202.4, 197.9, 161.4, 149.8, 136.5, 136.4, 128.7, 127.0, 123.6, 120.7, $120.3,115.9,85.5,42.5,38.0,36.9,28.2,27.3,24.6,24.2,23.6$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{23} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 435.1890; found: 435.1887.
1-benzyl-5-hydroxy-4,5,8,9,10,11-hexahydrobenzo[b][1,5,9]triazacyclotetradecine-2,6,12(1H,3H,7H)-trione (5.205)


Procedure: GP 5-6 starting from 5.158
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: 66\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.48(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.45(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.36(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.29-$ $7.23(\mathrm{~m}, 4 \mathrm{H}), 7.23-7.17(\mathrm{~m}, 2 \mathrm{H}), 6.75(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 6.57(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.67(\mathrm{~d}, J=14.4 \mathrm{~Hz}, 1 \mathrm{H})$, $4.18(\mathrm{~d}, \mathrm{~J}=14.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.99-3.88(\mathrm{~m}, 1 \mathrm{H}), 3.68(\mathrm{dt}, J=15.5,8.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.18(\mathrm{t}, \mathrm{J}=12.1 \mathrm{~Hz}, 1 \mathrm{H})$, $3.12-3.02(\mathrm{~m}, 1 \mathrm{H}), 2.21-2.07(\mathrm{~m}, 3 \mathrm{H}), 2.01-1.82(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 174.9,174.4,167.8,138.2,136.9,136.1,131.0,130.3,129.5,129.3$, 129.1, 128.6, 127.8, 71.6, 53.6, 40.7, 38.9, 32.5, 29.0, 26.9.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{~N}_{3} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 418.1737; found: 418.1744 .
1-benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-
dodecahydrobenzo[b][1,5,9]triazacyclotetradecin-5-yl acetate (5.206)


Procedure: GP 5-7 starting from 5.158

Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: 77\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{27} \mathrm{~N}_{3} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 460.1843; found: 460.1840.
1-benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-
dodecahydrobenzo[b][1,5,9]triazacyclotetradecin-5-yl (tert-butoxycarbonyl)glycinate (5.207)


Procedure: GP 5-7 starting from 5.158
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: 93\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathbf{~ M H z}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{36} \mathrm{~N}_{4} \mathrm{NaO}_{7}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 575.2476 ; found: 575.2485.

N-benzyl-N-(1-benzyl-2,6,12-trioxo-1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrobenzo[b][1,5,9]triazacyclotetradecin-5-yl)acetamide (5.208)


Procedure: GP 5-9 starting from 5.158

Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: 56\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathbf{~ M H z}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{31} \mathrm{H}_{35} \mathrm{~N}_{4} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 527.2653; found: 527.2644.
14-benzyl-18-(phenylamino)-5,6,7,8,17,18-hexahydrobenzo[b]tetrazolo[1,5-i][1,5,9]triazacyclotetradecine-9,15(14H,16H)-dione (5.209)


Procedure: GP 5-10 starting from 5.158
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 99: 1$ to 97:3). Yield: 28\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{30} \mathrm{~N}_{7} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 496.2455; found: 496.2462.

## 4-((14-benzyl-9,15-dioxo-5,6,7,8,9,14,15,16,17,18-decahydrobenzo[b]tetrazolo[1,5-i][1,5,9]triazacyclotetradecin-18-yl)amino)benzonitrile (5.210)



Procedure: GP 5-10 starting from 5.158
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}$, $\mathrm{DCM} / \mathrm{MeOH} 99: 1$ to 95:5). Yield: 24\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{29} \mathrm{~N}_{8} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 521.2408; found: 521.2422.
tert-butyl 5-hydroxy-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-
[1]oxa[8]azacyclopentadecino[12,11-b]indole-14-carboxylate (5.218)


Procedure: GP 5-6 starting from 5.141

Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 51\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{34} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 453.260; found: 453.2354.
tert-butyl 5-acetoxy-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-
[1]oxa[8]azacyclopentadecino[12,11-b]indole-14-carboxylate (5.219)


Procedure: GP 5-7 starting from 5.141

Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 52\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{NaO}_{6}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 495.2466; found: 495.2458.
tert-butyl 5-(((tert-butoxycarbonyl)glycyl)oxy)-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-[1]oxa[8]azacyclopentadecino[12,11-b]indole-14-carboxylate (5.220)


Procedure: GP 5-7 starting from 5.141
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 58\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{31} \mathrm{H}_{45} \mathrm{~N}_{3} \mathrm{NaO}_{8}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 610.3099; found: 610.3089.
tert-butyl 5-(N-benzylacetamido)-4-oxo-1,2,3,4,5,6,7,8,9,11,12,13-dodecahydro-14H-
[1] oxa[8]azacyclopentadecino[12,11-b]indole-14-carboxylate (5.221)


Procedure: GP 5-9 starting from 5.141
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: 30\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right):$; found:.
tert-butyl 4-(phenylamino)-5,6,7,8,11,12,18,19-octahydro-4H-
tetrazolo[5',1':7,8][1]oxa[8]azacyclopentadecino[12,11-b]indole-13(10H)-carboxylate (5.222)


Procedure: GP 5-10 starting from 5.141
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: $23 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right):$; found:.

## 6-hydroxy-3,4,5,6,9,10,11,12-octahydrobenzo[b][1]oxa[5,9]diazacyclopentadecine-7,13(2H,8H)-

 dione (5.211)

Procedure: GP 5-6 starting from 5.151a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 97: 3$ to 95:5). Yield: 84\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, Methanol- $d_{4}$ ): $\delta 8.25(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.14 \mathrm{br}(\mathrm{s}, 1 \mathrm{H}), 7.82(\mathrm{dd}, J=7.7,1.8 \mathrm{~Hz}, 1 \mathrm{H})$, 7.45 (ddd, $J=8.9,7.3,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.10(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.03(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.26-4.09(\mathrm{~m}$, $3 H), 3.65-3.55(\mathrm{~m}, 2 \mathrm{H}), 3.51-3.44(\mathrm{~m}, 1 \mathrm{H}), 3.18-3.07(\mathrm{~m}, 1 \mathrm{H}), 2.00-1.84(\mathrm{~m}, 4 \mathrm{H}), 1.83-1.71$ $(\mathrm{m}, 2 \mathrm{H}), 1.69-1.58(\mathrm{~m}, 1 \mathrm{H}), 1.52-1.43(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, Methanol- $d_{4}$ ): $\delta$ 176.93, 168.73, 158.21, 133.84, 131.56, 123.72, 121.80, 113.71, 72.53, 68.61, 37.84, 37.73, 33.63, 29.54, 29.35, 21.00.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 329.1472; found: 329.1469.
7,13-dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[b][1]oxa[5,9]diazacyclopentadecin-6yl acetate (5.212)


Procedure: GP 5-7 starting from 5.151a

Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: $91 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.04$ (dd, $J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.87 (brt, $\mathrm{J}=6.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.38(\mathrm{ddd}, \mathrm{J}=$ $8.3,7.3,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.02(\mathrm{td}, J=7.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.94(\mathrm{dd}, J=8.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.73(\mathrm{br} \mathrm{t}, \mathrm{J}=6.2 \mathrm{~Hz}$, $1 \mathrm{H}), 5.19(\mathrm{dd}, J=5.8,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.16(\mathrm{t}, \mathrm{J}=5.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.67$ (dddt, $J=15.4,10.1,9.0,3.6 \mathrm{~Hz}, 2 \mathrm{H}$ ), 3.53 (dtd, $J=14.1,6.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.18$ (dddd, $J=13.9,7.6,4.7,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.06(\mathrm{dtd}, J=14.8$, $7.5,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.99(\mathrm{~s}, 3 \mathrm{H}), 1.91$ (dddd, $J=12.5,9.0,7.5,3.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.86-1.68(\mathrm{~m}, 4 \mathrm{H}), 1.55(\mathrm{p}$, $J=7.7 \mathrm{~Hz}, 2 \mathrm{H}$ ).
${ }^{13}{ }^{3} \mathrm{CNMR}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $\delta 169.78,169.53,166.33,156.33,132.63,131.69,122.58,121.26$, 112.63, 73.90, 67.67, 38.02, 37.80, 29.80, 29.16, 28.22, 20.93, 20.47.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{NaO}_{5}$ ([ $\left.\mathrm{M}+\mathrm{Na}\right]^{+}$): 371.1577; found: 371.1574.

## 7,13-dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[b][1]oxa[5,9]diazacyclopentadecin-6yl (tert-butoxycarbonyl)glycinate (5.213)



Procedure: GP 5-7 starting from 5.151a
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to $97: 3$ ). Yield: $95 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.98$ (dd, $J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.86(\mathrm{brt}, J=6.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.36$ (ddd, $J=$ $8.8,7.4,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.99(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.90(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.53(\mathrm{brt} \mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.28$ (dd, $J=5.4,2.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.14 (ddd, $J=10.4,7.4,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.06(\mathrm{dt}, J=9.4,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.80(\mathrm{~d}, J=$ $5.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.74-3.62(\mathrm{~m}, 1 \mathrm{H}), 3.57(\mathrm{q}, J=6.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.06(\mathrm{ddd}, J=14.3,9.0,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.16-$ $2.06(\mathrm{~m}, 1 \mathrm{H}), 2.00-1.69(\mathrm{~m}, 6 \mathrm{H}), 1.64-1.50(\mathrm{~m}, 2 \mathrm{H}), 1.35(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 169.74,169.27,166.28,156.56,156.43,132.57,131.53,122.50$, $121.17,112.23,80.44,74.61,67.35,43.01,37.75,37.23,29.63,29.13,28.33,28.28,20.48$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{33} \mathrm{~N}_{3} \mathrm{NaO}_{7}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 486.2211 ; found: 486.2205 .
N-benzyl- $N$-(7,13-dioxo-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo[b][1]oxa[5,9]diazacyclopentadecin-6-yl)acetamide (5.215)


## Procedure: GP 5-9 starting from 5.151a

Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: 97\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.00(\mathrm{dd}, J=7.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.81(\mathrm{brt}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.38-7.28(\mathrm{~m}$, $3 \mathrm{H}), 7.25(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.14(\mathrm{br} \mathrm{d}, \mathrm{J}=6.8 \mathrm{~Hz}, 3 \mathrm{H}), 6.98(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{~d}, J=8.3 \mathrm{~Hz}$, $1 \mathrm{H}), 4.92(\mathrm{dd}, J=12.4,2.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.80(\mathrm{~d}, J=18.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.61(\mathrm{~d}, \mathrm{~J}=18.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.10-4.00$ $(\mathrm{m}, 2 \mathrm{H}), 3.80-3.64(\mathrm{~m}, 2 \mathrm{H}), 3.40(\mathrm{ddt}, J=14.0,9.1,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.98(\mathrm{dq}, J=13.8,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.23$ - $2.11(\mathrm{~m}, 1 \mathrm{H}), 2.02(\mathrm{~s}, 3 \mathrm{H}), 1.99-1.88(\mathrm{~m}, 2 \mathrm{H}), 1.82-1.71(\mathrm{~m}, 1 \mathrm{H}), 1.63-1.35(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 172.96, 171.14, 166.13, 156.44, 137.79, 132.34, 131.71, 128.87, $127.30,125.63,122.55,120.96,111.80,66.50,57.62,49.28,37.26,36.67,28.58,28.08,27.26$, 22.39, 22.34.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{31} \mathrm{~N}_{3} \mathrm{NaO}_{4}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 460.2207; found: 460.2203.

## 19-(phenylamino)-5,6,7,8,16,17,18,19-octahydro-9H,15H-benzo[b]tetrazolo[1,5i][1] oxa[5,9]diazacyclopentadecin-9-one (5.216)



Procedure: GP 5-10 starting from 5.151a
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: 43\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.18(\mathrm{dd}, J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.78(\mathrm{t}, J=5.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.52-7.39(\mathrm{~m}$, $1 \mathrm{H}), 7.10(\mathrm{t}, \mathrm{J}=7.8 \mathrm{~Hz}, 3 \mathrm{H}), 6.99(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.74(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.55(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H})$, $4.93(\mathrm{t}, J=6.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.49(\mathrm{dt}, J=13.4,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.28(\mathrm{tt}, J=13.9,6.4 \mathrm{~Hz}, 2 \mathrm{H}), 4.19(\mathrm{td}, J=9.4$, $3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.55(\mathrm{ddd}, J=13.5,10.4,6.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.46(\mathrm{dq}, J=14.3,6.4,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.61-2.49(\mathrm{~m}$, $2 \mathrm{H}), 2.27-2.09(\mathrm{~m}, 2 \mathrm{H}), 2.05-1.96(\mathrm{~m}, 1 \mathrm{H}), 1.92-1.83(\mathrm{~m}, 1 \mathrm{H}), 1.68-1.48(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 166.25,156.53,145.67,133.20,132.31,129.64,121.76,121.59$, $119.56,113.90,112.36,68.48,49.91,44.64,35.88,34.49,27.62,27.57,23.67$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{6} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 429.2009; found: 429.2008.

## 6-(benzyl(2,5-dioxopyrrolidin-1-yl)amino)-3,4,5,6,9,10,11,12-octahydrobenzo[b][1]oxa[5,9]diazacyclopentadecine-7,13(2H,8H)-dione (5.217)



A mixture of benzylamine ( $1 \mathrm{mmol}, 1.0$ equiv), 5.151 a ( $1 \mathrm{mmol}, 1.0$ equiv), $N$-hydroxamic acid ( 1.5 $\mathrm{mmol}, 1.5$ equiv) and $\mathrm{ZnCl}_{2}(0.3 \mathrm{mmol}, 0.3$ equiv) in dry toluene $(0.01 \mathrm{M})$ were stirred for overnight at room temperature. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ) to yield 5.217 (22\%) as a yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.14$ (dd, $J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.71(\mathrm{dd}, \mathrm{J}=8.2,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.44-7.36$ $(\mathrm{m}, 3 \mathrm{H}), 7.32(\mathrm{t}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.28-7.21(\mathrm{~m}, 2 \mathrm{H}), 7.04(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.91(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H})$, $4.18-4.09(\mathrm{~m}, 2 \mathrm{H}), 4.06(\mathrm{~d}, J=12.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.00-3.90(\mathrm{~m}, 1 \mathrm{H}), 3.80(\mathrm{dd}, J=11.5,3.5 \mathrm{~Hz}, 1 \mathrm{H})$, $3.76(\mathrm{~d}, \mathrm{~J}=12.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.29(\mathrm{td}, J=13.3,11.7,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.20(\mathrm{dt}, J=14.8,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.96$ (dddd, $J=13.8,11.6,4.4,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.89-2.75(\mathrm{~m}, 4 \mathrm{H}), 2.19-2.10(\mathrm{~m}, 1 \mathrm{H}), 2.03-1.95(\mathrm{~m}, 2 \mathrm{H})$, $1.92-1.85(\mathrm{~m}, 2 \mathrm{H}), 1.76-1.61(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 170.55, 165.65, 156.92, 156.41, 139.11, 132.67, 132.29, 128.70, $128.64,127.46,121.82,121.25,111.84,68.97,54.56,51.58,42.81,35.50,32.83,29.90,29.46$, 25.77, 23.48 .

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{33} \mathrm{~N}_{4} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 493.2445; found: 493.2439.
13-hydroxy-2,3,4,5,6,7,10,11,12,13,16,17,18,19-
tetradecahydrobenzo[b][1,16]dioxa[5,9]diazacyclodocosine-14,20(9H,15H)-dione (5.225)


Procedure: GP 5-6 starting from 5.151b
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 97: 3$ to 95:5). Yield: 71\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ Complex mixture of conformers
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{34} \mathrm{~N}_{2} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 429.2360; found: 429.2356.
14,20-dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-
octadecahydrobenzo[b][1,16]dioxa[5,9]diazacyclodocosin-13-yl acetate (5.226)

5.226

Procedure: GP 5-7 starting from 5.151b
Purification: Flash column chromatography ( $\left.\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2\right)$. Yield: $85 \%$, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.22(\mathrm{t}, J=5.8 \mathrm{~Hz}, 1 \mathrm{H}), 8.11(\mathrm{dd}, J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.37$ (ddd, $J=8.6$, $7.5,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.00(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.92(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.50(\mathrm{t}, J=6.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.15(\mathrm{t}, \mathrm{J}=$ $5.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.12(\mathrm{ddt}, J=26.8,9.0,6.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.53-3.35(\mathrm{~m}, 7 \mathrm{H}), 3.29(\mathrm{p}, J=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.12(\mathrm{~s}$, $3 \mathrm{H}), 1.98-1.84(\mathrm{~m}, 4 \mathrm{H}), 1.77(\mathrm{p}, \mathrm{J}=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 1.58-1.42(\mathrm{~m}, 10 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 170.14, 169.76, 165.81, 157.08, 132.63, 132.01, 121.77, 120.97, 112.31, 74.22, 70.19, 70.03, 69.17, 37.04, 36.73, 31.39, 30.08, 29.52, 29.21, 28.91, 26.35, 26.09, 21.79, 21.12.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{NaO}_{6}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 471.2466; found: 471.2460.
14,20-dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-
octadecahydrobenzo[b][1,16]dioxa[5,9]diazacyclodocosin-13-yl (tert-butoxycarbonyl)glycinate (5.227)


Procedure: GP 5-7 starting from 5.151b
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 95:5). Yield: 80\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.28(\mathrm{t}, J=5.8 \mathrm{~Hz}, 1 \mathrm{H}), 8.12(\mathrm{dd}, J=7.9,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{ddd}, J=8.3$, $7.3,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.06(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.00(\mathrm{td}, J=7.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.92(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.46(\mathrm{t}$, $J=5.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.22(\mathrm{t}, J=5.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{dt}, J=9.5,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.08(\mathrm{dt}, J=9.2,6.8 \mathrm{~Hz}, 1 \mathrm{H})$, $3.88(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, 2 \mathrm{H}), 3.51-3.32(\mathrm{~m}, 7 \mathrm{H}), 3.28(\mathrm{p}, \mathrm{J}=6.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.03-1.84(\mathrm{~m}, 4 \mathrm{H}), 1.76(\mathrm{p}, J=$ $6.4 \mathrm{~Hz}, 2 \mathrm{H}), 1.60-1.42(\mathrm{~m}, 10 \mathrm{H}), 1.41(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 169.98, 169.38, 165.81, 157.12, 156.72, 132.60, 132.05, 121.79, $120.91,112.27,80.50,74.91,70.20,69.97,69.16,43.11,36.98,36.63,31.29,29.84,29.50,29.18$, 28.87, 28.38, 26.41, 25.99, 21.90.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{45} \mathrm{~N}_{3} \mathrm{NaO}_{8}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 586.3099 ; found: 586.3091.

## 2,3,4,5,6,7,9,10,11,12,16,17,18,19-tetradecahydrobenzo[b][1,16]dioxa[5,9]diazacyclodocosine-

 13,14,20(15H)-trione (5.228)

Procedure: GP 5-8 starting from 5.151b
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ ). Yield: 68\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.38(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.21(\mathrm{dd}, J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.41$ (ddd, $J=8.2$, $7.3,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.10(\mathrm{t}, J=6.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.04(\mathrm{ddd}, J=8.1,7.3,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.95(\mathrm{dd}, J=8.4,1.1 \mathrm{~Hz}$, $1 \mathrm{H}), 4.16(\mathrm{t}, \mathrm{J}=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.55-3.28(\mathrm{~m}, 8 \mathrm{H}), 3.10(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.03-1.91(\mathrm{~m}, 2 \mathrm{H}), 1.89-$ $1.73(\mathrm{~m}, 5 \mathrm{H}), 1.72-1.59(\mathrm{~m}, 2 \mathrm{H}), 1.58-1.38(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 199.2, 165.8, 161.0, 157.3, 132.8, 132.4, 121.4, 121.1, 112.2, 71.3, $70.8,69.2,37.0,36.7,36.5,29.8,29.7,29.3,27.9,26.8,26.3,21.6$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{27} \mathrm{H}_{33} \mathrm{~N}_{4} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$:; found:.
N-benzyl-N-(14,20-dioxo-2,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,20-octadecahydrobenzo[b][1,16]dioxa[5,9]diazacyclodocosin-13-yl)acetamide (5.229)


Procedure: GP 5-9 starting from 5.151b
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 98: 2$ to 97:3). Yield: 78\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.20(\mathrm{t}, J=5.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.16(\mathrm{dd}, J=7.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{td}, J=8.0$, $1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.23(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.15(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.01(\mathrm{t}, J=7.6 \mathrm{~Hz}$, $1 \mathrm{H}), 6.91(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.74(\mathrm{t}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.91(\mathrm{dd}, J=10.3,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.70(\mathrm{~d}, J=17.4$ $\mathrm{Hz}, 1 \mathrm{H}), 4.59(\mathrm{~d}, J=18.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.18-4.03(\mathrm{~m}, 2 \mathrm{H}), 3.54-3.31(\mathrm{~m}, 7 \mathrm{H}), 3.14(\mathrm{p}, J=6.7 \mathrm{~Hz}, 1 \mathrm{H})$, $2.09(\mathrm{~d}, J=9.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.04(\mathrm{~s}, 3 \mathrm{H}), 1.90(\mathrm{p}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 1.76(\mathrm{p}, J=6.9 \mathrm{~Hz}, 2 \mathrm{H}), 1.60-1.36(\mathrm{~m}$, 10H), $1.33-1.24(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, CDCl $_{3}$ ): $\delta 172.98,170.91,165.54,157.09,137.73,132.65,132.62,132.19$, $128.79,127.30,125.86,121.55,121.00,112.18,70.05,69.98,69.11,57.84,49.15,37.25,37.03$, 29.91, 29.55, 29.36, 29.12, 28.39, 26.45, 26.07, 23.79, 22.42.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{31} \mathrm{H}_{43} \mathrm{~N}_{3} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 560.3095$; found: 560.3084.
4-((21-oxo-5,6,7,8,10,11,12,13,14,15,22,23,24,25-tetradecahydro-4H,21H-benzo[b]tetrazolo[1,5-i][1,16]dioxa[5,9]diazacyclodocosin-4-yl)amino)benzonitrile (5.230)


Procedure: GP 5-10 starting from 5.151b

Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 99: 1$ to 97:3). Yield: 53\%, yellowish oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.18(\mathrm{t}, J=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.10(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.43(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.36(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.05(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.97(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.62(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 4.95$ $(\mathrm{t}, J=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.52(\mathrm{t}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.16(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 2 \mathrm{H}), 3.49(\mathrm{~m}, 2 \mathrm{H}), 3.35(\mathrm{dt}, J=14.9,5.5$ Hz, 4H), $2.14(\mathrm{~m}, 4 \mathrm{H}), 1.87(\mathrm{p}, \mathrm{J}=6.5 \mathrm{~Hz}, 2 \mathrm{H}), 1.71$ - 1.31 (m, 10H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 166.19, 157.02, 155.39, 149.49, 134.02, 133.13, 132.05, 121.38, $119.89,112.98,112.44,100.82,70.51,70.23,69.12,49.11,45.46,36.70,33.67,30.07,29.87$, 29.31, 28.40, 26.60, 26.27, 23.48.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{37} \mathrm{~N}_{7} \mathrm{NaO}_{3}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 554.2850; found: 554.2853.
8.5.3 Total Synthesis of ( - )-Eurystatin B
(S)-1-(methoxy(methyl)amino)-1-oxopropan-2-aminium chloride (5.275)


It was prepared according to a literature procedure. ${ }^{471}$
(S)-5-(((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)pentanoic acid (5.265)


It was prepared according to a literature procedure. ${ }^{472}$
((benzyloxy)carbonyl)-L-leucine (5.273)


It was prepared according to a literature procedure. ${ }^{473}$
benzyl tert-butyl ((S)-5-(((S)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)amino)-5-oxopentane-
1,4-diyl)dicarbamate (5.283)


To a solution of ammonium salt $\mathbf{5 . 2 7 5}$ ( $1000 \mathrm{mg}, 5.97 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $12 \mathrm{~mL}, 0.5 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added DIPEA ( $990 \mu \mathrm{~L}, 5.97 \mathrm{mmol}, 1.0$ equiv), acid $5.265(2190 \mathrm{mg}, 5.97 \mathrm{mmol}, 1.0$ equiv) and DCC ( $1360 \mathrm{mg}, 0.656 \mathrm{mmol}, 1.1$ equiv). A solution of $\mathrm{HOBt}(810 \mathrm{mg}, 5.97 \mathrm{mmol}, 1.0$ equiv) in a minimal amount of DMF was added dropwise. After being stirred overnight at room temperature, the solution was filtered over Celite (rinsed with DCM). The organic filtrate was washed with 2 M HCl , saturated aqueous $\mathrm{NaHCO}_{3}$ and with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$ ) to yield 5.283 ( $91 \%$ ) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{4} \mathrm{NaO}_{7}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 503.2476$; found: 503.2477.
$[\alpha]_{D}{ }^{20}+64.2^{\circ}(c 0.12$, EtOH $)$.
tert-butyl ((S)-5-amino-1-(((S)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)amino)-1-oxopentan-2-yl)carbamate (5.274)


To a solution of5.283 ( $753 \mathrm{mg}, 1.60 \mathrm{mmol}, 1.00$ equiv) in dry EtOAc ( $100 \mathrm{~mL}, 0.015 \mathrm{M}$ ) was added $\mathrm{Pd}(\mathrm{OH})_{2}(400 \mathrm{mg}, 250 \mathrm{mg} / \mathrm{mmol}) . \mathrm{H}_{2}$ was bubbled through the solution during 15 minutes. After being stirred 12 hours at room temperature under a hydrogen atmosphere, the reaction mixture
was filtered through Celite (rinsed with EtOAc) and evaporated in vacuo to yield 5.274 (94\%) as a colorless oil. The crude product was directly used for the next step without further purification.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{31} \mathrm{~N}_{5} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 347.2289; found: 347.2287.
$[\alpha]_{\mathrm{D}}{ }^{20}-18.7^{\circ}(c 0.20, \mathrm{DCM})$.
benzyl tert-butyl ((5S,8S,14R)-3,5,16-trimethyl-4,7,13-trioxo-2-oxa-3,6,12-triazaheptadecane-8,14-diyl)dicarbamate (5.284)


To a solution of amine 5.274 ( $560 \mathrm{mg}, 1.62 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $16 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added DIPEA ( $270 \mu \mathrm{~L}, 1.62 \mathrm{mmol}, 1.0$ equiv), acid 5.273 ( $430 \mathrm{mg}, 1.62 \mathrm{mmol}, 1.0$ equiv) and DCC ( $370 \mathrm{mg}, 1.78 \mathrm{mmol}, 1.1$ equiv). A solution of $\mathrm{HOBt}(220 \mathrm{mg}, 1.62 \mathrm{mmol}, 1.0$ equiv) in a minimal amount of DMF was added dropwise. After being stirred overnight at room temperature, the solution was filtered over Celite (rinsed with DCM). The organic filtrate was washed with HCl 2 M , saturated $\mathrm{NaHCO}_{3}$ and with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield 5.284 ( $82 \%$ ) as a white solid as a mixture of rotamers.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.57(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.29$ (tdd, $\left.J=9.0,5.5,3.2 \mathrm{~Hz}, 5 \mathrm{H}\right), 7.19-6.99$ $(\mathrm{m}, 1 \mathrm{H}), 6.41(\mathrm{~s}, 1 \mathrm{H}), 6.24(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.54(\mathrm{~d}, J=5.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.34(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.04(\mathrm{~d}$, $J=2.6 \mathrm{~Hz}, 2 \mathrm{H}), 4.96-4.76(\mathrm{~m}, 1 \mathrm{H}), 4.46(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.15(\mathrm{q}, J=8.1,7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.02(\mathrm{~d}, J=$ $9.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.75(\mathrm{~s}, 3 \mathrm{H}), 3.29(\mathrm{td}, J=6.4,5.6,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.10(\mathrm{~s}, 3 \mathrm{H}), 3.01-2.85(\mathrm{~m}, 1 \mathrm{H}), 1.87(\mathrm{qp}$, $J=7.7,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.73-1.48(\mathrm{~m}, 3 \mathrm{H}), 1.41(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 12 \mathrm{H}), 1.27(\mathrm{dd}, J=21.8,5.3 \mathrm{~Hz}, 4 \mathrm{H}), 0.89$ (dd, J = 11.5, 5.9 Hz, 6H).
${ }^{13}{ }^{3}$ CNMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 173.6,173.5,172.2,156.9,156.0,155.7,136.6,128.5,128.1,127.9$, 79.7, 79.4, 66.9, 61.6, 53.7, 53.5, 52.4, 45.6, 41.8, 40.6, 37.4, 32.1, 29.8, 29.6, 28.4, 28.0, 24.7, 24.7, 22.8, 22.3, 21.2, 17.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{49} \mathrm{~N}_{5} \mathrm{NaO}_{8}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 616.3317; found: 616.3318.
$[\alpha]_{D}{ }^{20}-109.8^{\circ}(c \quad 0.25, \mathrm{MeOH})$.
tert-butyl ((5S,8S,14R)-14-amino-3,5,16-trimethyl-4,7,13-trioxo-2-oxa-3,6,12-triazaheptadecan-8-yl)carbamate (5.285)


To a solution of 5.284 ( $740 \mathrm{mg}, 1.25 \mathrm{mmol}, 1.00$ equiv) in dry EtOAc ( $80 \mathrm{~mL}, 0.015 \mathrm{M}$ ) was added $\mathrm{Pd}(\mathrm{OH})_{2}(300 \mathrm{mg}, 250 \mathrm{mg} / \mathrm{mmol}) . \mathrm{H}_{2}$ was bubbled through the solution during 15 minutes. After being stirred 12 hours at room temperature under a hydrogen atmosphere, the reaction mixture was filtered through Celite (rinsed with EtOAc) and evaporated in vacuo to yield 5.285 (92\%) as a colorless oil. The crude product was directly used for the next step without further purification.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{42} \mathrm{~N}_{5} \mathrm{O}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 460.3130$; found: 460.3128 .
$[\alpha]_{D}{ }^{20}-85.5^{\circ}(c 0.1, E t O H)$.
tert-butyl ((5S,8S,14R)-14-isobutyl-3,5-dimethyl-4,7,13,16-tetraoxo-2-oxa-3,6,12,15-tetraazahexadecan-8-yl)carbamate (5.272)


To a solution of amine 5.285 ( $2300 \mathrm{mg}, 5 \mathrm{mmol}, 1.0$ equiv) in DCM ( $50 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added dropwise formic acetic mixed anhydride (formed by heating to $60^{\circ} \mathrm{C}$ for 1 hour $705 \mu \mathrm{~L}, 7.51 \mathrm{mmol}$, 1.5 equiv of acetic anhydride and $283 \mu \mathrm{~L}, 7.51 \mathrm{mmol}, 1.5$ equiv $\mathrm{HCO}_{2} \mathrm{H}$ ). After being stirred for 3 hours the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$ ) to yield 5.272 (94\%) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.11(\mathrm{~d}, J=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.78(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.64(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H})$, $7.13(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.30(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.95(\mathrm{p}, J=7.5,6.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.55(\mathrm{p}, J=7.2,6.8 \mathrm{~Hz}$, $2 \mathrm{H}), 3.96-3.68(\mathrm{~m}, 1 \mathrm{H}), 3.82(\mathrm{~s}, 3 \mathrm{H}), 3.17(\mathrm{~s}, 3 \mathrm{H}), 2.93(\mathrm{dq}, \mathrm{J}=14.0,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.76-1.45(\mathrm{~m}$, $7 \mathrm{H}), 1.40(\mathrm{~s}, 9 \mathrm{H}), 1.35(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}), 0.92(\mathrm{~d}, J=6.3 \mathrm{~Hz}, 3 \mathrm{H}), 0.89(\mathrm{~d}, J=6.3 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 173.9,173.1,172.6,161.8,155.8,79.4,61.7,51.8,50.5,45.3,40.3$, $36.9,32.2,30.1,28.5,25.4,24.8,22.8,22.5,17.5$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{41} \mathrm{~N}_{5} \mathrm{NaO}_{7}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 510.2898$; found: 510.2300.
$[\alpha]_{\mathrm{D}}{ }^{20}-55.5^{\circ}(c 0.23, \mathrm{DCM})$.
tert-butyl ((S)-5-((R)-2-formamido-4-methylpentanamido)-1-oxo-1-(((S)-1-oxopropan-2-yl)amino)pentan-2-yl)carbamate (5.266)


To a solution of amide 5.272 ( 1.22 g , 2.5 mmol , 1.0 equiv) in dry THF ( $63 \mathrm{~mL}, 0.04 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ was added portionwise LAH ( $1.56 \mathrm{~g}, 3.75 \mathrm{mmol}, 1.5$ equiv). After being stirred at $-78^{\circ} \mathrm{C}$ for 4 hours, the reaction mixture was carefully quenched with 1 M HCl and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield 5.286 ( $984 \mathrm{mg}, 92 \%$ ). The crude product was directly used for the next step without further purification.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{36} \mathrm{~N}_{4} \mathrm{NaO}_{6}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 451.2527; found: 451.2524.
$[\alpha]_{D}{ }^{20}-42.9^{\circ}(c 0.30, E t O H)$.

## tert-butyl ((3S,7S,10S)-6-hydroxy-3-isobutyl-7-methyl-2,5,9-trioxo-1,4,8-triazacyclotridecan-10yl)carbamate (5.269)



To a solution of isonitrile 5.266 ( 428 mg , $1 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $10 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $-78^{\circ} \mathrm{C}$ was added $\mathrm{NEt}_{3}\left(417 \mu \mathrm{~L}, 3.0 \mathrm{mmol}, 3.0\right.$ equiv) and $\mathrm{POCl}_{3}(112 \mu \mathrm{~L}, 1.2 \mathrm{mmol}, 1.2$ equiv). After being stirred at $-78{ }^{\circ} \mathrm{C}$ for 5 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo (temperature of the bath $=25^{\circ} \mathrm{C}$ !) to approximatively 50 mL . To this solution at room temperature was added a solution of Py ( $402 \mu \mathrm{~L}, 5.0 \mathrm{mmol}, 5.0$ equiv) and TFA (191 $\mu \mathrm{L}, 2.5 \mathrm{mmol}, 2.5$ equiv) in dry DCM ( 50 mL ). After being stirred 2 days at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO 3 and extracted with DCM. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield 5.269 ( $83 \%$ over 2 steps) as a colorless oil.

The analytical data were in accordance with those reported in the literature. ${ }^{470}$
(3S,7S,10S)-10-amino-6-hydroxy-3-isobutyl-7-methyl-1,4,8-triazacyclotridecane-2,5,9-trione (5.289)


It was prepared according to a literature procedure. ${ }^{470}$

## 4-methylhexanal (5.293)



They were prepared according to a literature procedure. ${ }^{475}$

## (E)-6-methyloct-2-enoic acid (5.270)



To a solution of aldehyde 5.293 ( $2.6 \mathrm{~g}, 18.54 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $94 \mathrm{~mL}, 0.2 \mathrm{M}$ ) was added ylide 5.294 ( $6.98 \mathrm{~g}, 18.54 \mathrm{mmol}, 1.0$ equiv) portionwise. After being stirred at room temperature for 6 hours, the reaction mixture was cooled to $0^{\circ} \mathrm{C}$ and TFA ( 50 mL ) was added dropwise. After being stirred at room temperature for 3 hours, the reaction mixture was evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the acid 5.270 as a colorless liquid.

### 5.270a:

Yield: 85\%, yellow oil.
${ }^{1} \mathrm{H}^{\mathrm{H}}$ NMR (400 MHz, CDCl $)_{3}$ : $\delta 10.44(\mathrm{~s}, 1 \mathrm{H}), 7.10(\mathrm{dt}, J=15.7,6.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.83(\mathrm{dt}, J=15.7,1.6 \mathrm{~Hz}$, $1 \mathrm{H}), 2.38-2.10(\mathrm{~m}, 2 \mathrm{H}), 1.54-1.40(\mathrm{~m}, 1 \mathrm{H}), 1.41-1.22(\mathrm{~m}, 4 \mathrm{H}), 1.16(\mathrm{dtd}, \mathrm{J}=14.8,7.4,1.6 \mathrm{~Hz}$, 1H), $0.91-0.83(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right): \delta 170.5,147.0,120.9,36.0,35.0,30.6,30.2,18.7,11.9$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{9} \mathrm{H}_{15} \mathrm{O}_{2}\left([\mathrm{M}-\mathrm{H}]^{-}\right):$155.1078; found: 155.1080.
$[\alpha]_{\mathrm{D}}{ }^{20}+105.3^{\circ}(c 0.1, \mathrm{EtOH})$.

### 5.270b:

Yield: 84\%, yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 10.45(\mathrm{~s}, 1 \mathrm{H}), 7.10(\mathrm{dt}, J=15.7,6.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.84(\mathrm{dt}, J=15.7,1.6 \mathrm{~Hz}$, $1 \mathrm{H}), 2.38-2.10(\mathrm{~m}, 2 \mathrm{H}), 1.56-1.39(\mathrm{~m}, 1 \mathrm{H}), 1.41-1.21(\mathrm{~m}, 4 \mathrm{H}), 1.15$ (dtd, $\mathrm{J}=14.8,7.4,1.6 \mathrm{~Hz}$, 1 H ), $0.90-0.83(\mathrm{~m}, 6 \mathrm{H})$.
${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 170.6,147.0,121.0,36.0,35.0,30.5,30.2,18.7,12.0$.
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{9} \mathrm{H}_{15} \mathrm{O}_{2}$ ([M - H] ${ }^{\top}$ ): 155.1078; found: 155.1081.
$[\alpha]_{D}^{20}-103.5^{\circ}$ ( $c 0.1$, EtOH).
(E)-N-((3S,7S,10S)-6-hydroxy-3-isobutyl-7-methyl-2,5,9-trioxo-1,4,8-triazacyclotridecan-10-yl)-6-methyloct-2-enamide (5.296)


To a solution of amine 5.289 ( 33 mg , $0.1 \mathrm{mmol}, 1.0$ equiv) in dry DMF ( $1 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added acid 5.270 ( 16 mg , $0.1 \mathrm{mmol}, 1.0$ equiv), EDC ( $16 \mathrm{mg}, 0.1 \mathrm{mmol}, 1.0$ equiv) and HOAt ( $14 \mathrm{mg}, 0.1$ $\mathrm{mmol}, 1.0$ equiv). After being stirred 12 hours at room temperature, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield the pure 5.296. The crude products were used directly used for the next step without further purification.

### 5.296a:

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{24} \mathrm{H}_{42} \mathrm{~N}_{4} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right): 489.3047$; found: 489.3048.
$[\alpha]_{\mathrm{D}}{ }^{20}-97.2^{\circ}$ (c 0.2, DCM).

### 5.296b:

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{24} \mathrm{H}_{42} \mathrm{~N}_{4} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 489.3047; found: 489.3048.
$[\alpha]_{\mathrm{D}}{ }^{20}+95.9^{\circ}$ (c 0.2, DCM).
(E)-N-((3S,7S,10S)-3-isobutyl-7-methyl-2,5,6,9-tetraoxo-1,4,8-triazacyclotridecan-10-yl)-6-methyloct-2-enamide (5.297)

$\mathrm{Py} \cdot \mathrm{SO}_{3}(24 \mathrm{mg}, 0.15 \mathrm{mmol}, 1.5$ equiv) was added portionwise in dry DCM/DMSO ( $2: 1,0.7 / 0.3 \mathrm{~mL}$, 0.1 M ) at $0^{\circ} \mathrm{C}$. After stirring 1 hour at $0^{\circ} \mathrm{C}$, the alcohol $5.296(47 \mathrm{mg}, 0.1 \mathrm{mmol}, 1.0$ equiv) was added. After being stirred 4 hours at $0^{\circ} \mathrm{C}, \mathrm{NEt}_{3}(28 \mu \mathrm{~L}, 0.2 \mathrm{mmol}, 2.0$ equiv) was added. Once warmed to room temperature, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the acid 5.297 as a colorless crystal.

### 5.297a:

${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $\boldsymbol{d}_{6} / \mathrm{CDCl}_{3}$ 1:2): See Table 41
${ }^{13} \mathrm{C}$ NMR ( 100 MHz, DMSO- $d_{6} / \mathrm{CDCl}_{3}$ 1:2): See Table 41
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3342$ (br), 2956 (w), 1666 (m), 1641 (w), 1621 (w), 1541 (m), 1517 (m), 1455 (w), 1391 (m), 1369 (s), 1348 (m), 1152 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{40} \mathrm{~N}_{4} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 487.2891; found: 487.2887.
$[\alpha]_{\mathrm{D}}{ }^{26}-92^{\circ}(c 0.25, \mathrm{DMSO})$.

### 5.297b:

${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $_{6} / \mathrm{CDCl}_{3}$ 1:2): See Table 41
${ }^{13} \mathrm{C}$ NMR ( 100 MHz, DMSO- $d_{6} / \mathrm{CDCl}_{3}$ 1:2): See Table 41
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3343$ (br), 2956 (w), 1666 (m), 1640 (w), 1621 (w), 1540 (m), 1515 (w), 1455 (w), 1389 (m), 1374 (s), 1152 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{40} \mathrm{~N}_{4} \mathrm{NaO}_{5}\left([\mathrm{M}+\mathrm{Na}]^{+}\right)$: 487.2891; found: 487.2888.
$[\alpha]_{\mathrm{D}}{ }^{20}-12^{\circ}(c \quad 0.25, \mathrm{DMSO})$.

## $N$-Formylleucine (5.300)



It was prepared according to a literature procedure. ${ }^{472}$

## tert-butyl ((5S,8S)-14-isobutyl-3,5-dimethyl-4,7,13,16-tetraoxo-2-oxa-3,6,12,15-tetraazahexadecan-8-yl)carbamate (5.272)



To a solution of amine 5.274 ( $560 \mathrm{mg}, 1.62 \mathrm{mmol}, 1.0$ equiv) in dry DCM ( $16 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added DIPEA ( $270 \mu \mathrm{~L}, 1.62 \mathrm{mmol}, 1.0$ equiv), acid 5.300 ( $258 \mathrm{mg}, 1.62 \mathrm{mmol}, 1.0$ equiv) and DCC ( $370 \mathrm{mg}, 1.78 \mathrm{mmol}, 1.1$ equiv). A solution of HOBt ( $220 \mathrm{mg}, 1.62 \mathrm{mmol}, 1.0$ equiv) in a minimal amount of DMF was added dropwise. After being stirred overnight at room temperature, the solution was filtered over Celite (rinsed with DCM). The organic filtrate was washed with HCl 2 M , saturated $\mathrm{NaHCO}_{3}$ and with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield 5.272 ( $85 \%$ ) as a 19:1 mixture of diastereoisomers and as a white solid.

### 8.6 1,1-Aminoacylation of Homopropargylamine

### 8.6.1 Imine Synthesis

GP 6-1:


Unless otherwise indicated, imines were prepared by mixing the corresponding aldehydes 6.130 (1.00 equiv), anilines 6.131 (or benzylamine) ( 1.00 equiv) and $\mathrm{Na}_{2} \mathrm{SO}_{4}(0.5 \mathrm{~g} / \mathrm{mmol}$ ) in toluene $(0.25 \mathrm{M})$ and the reaction mixture was refluxed for $12-48 \mathrm{~h}$ until the starting materials have disappeared (monitored by taking ${ }^{1} \mathrm{H}$ NMR spectra of aliquots from the reaction). Solvent was removed in vacuo to yield the imines 6.132 which was recrystallized from EtOH or used directly for the next reaction.

## $N$-(propan-2-ylidene)aniline (6.140)



It was prepared according to a literature procedure. ${ }^{529}$
tert-butyl (Z)-benzylidenecarbamate (6.246)


It was prepared according to literature procedures. ${ }^{563,564}$
3,4-dihydroisoquinoline (6.156)


It was prepared according to a literature procedure. ${ }^{537}$
tert-butyl (1-phenylbut-3-yn-1-yl)carbamate (6.161)


It was prepared according to a literature procedure. ${ }^{540}$
4-methyl-N-(1-phenylbut-3-yn-1-yl)benzenesulfonamide (6.162a)


It was prepared according to a literature procedure. ${ }^{540}$
$N$-(1-phenylbut-3-yn-1-yl)acetamide (6.162b)


It was prepared according to a literature procedure. ${ }^{541}$
4-nitro-N-(1-phenylbut-3-yn-1-yl)benzenesulfonamide (6.162c)


To a solution of 6.158 ( $100 \mathrm{mg}, 0.669 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{NEt}_{3}(240 \mu \mathrm{~L}, 1.72 \mathrm{mmol}, 2.50$ equiv $)$ in dry DCM ( $1.9 \mathrm{~mL}, 0.36 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added portionwise NsCl ( $183 \mathrm{mg}, 0.826 \mathrm{mmol}, 1.20$ equiv). After being stirred at room temperature overnight, the reaction mixture was carefully quenched with 2 M HCl and extracted with DCM. The combined organic extracts were washed with brine,
dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 25: 1$ ) to yield the desired product $6.162 \mathrm{c}(172 \mathrm{mg}, 78 \%)$ as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.75(\mathrm{dd}, J=8.0,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.68(\mathrm{dd}, J=7.9,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{td}, J=$ $7.7,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.41(\mathrm{td}, J=7.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.24-7.15(\mathrm{~m}, 2 \mathrm{H}), 7.10(\mathrm{dd}, J=5.1,1.9 \mathrm{~Hz}, 3 \mathrm{H}), 6.23$ (d, $J=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.75(\mathrm{dt}, J=8.8,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.82(\mathrm{ddd}, J=16.8,6.3,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.67$ (ddd, $J=$ $16.9,5.4,2.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.04(\mathrm{~d}, \mathrm{~J}=2.8 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR ( $\mathbf{1 0 0} \mathbf{M H z}$, CDCl $_{3}$ ) $\delta 147.5,138.7,134.6,133.2,132.6,130.8,128.5,128.3,126.7,125.1$, 78.6, 72.7, 56.9, 27.5.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3341$ (w), 1608 (s), 1505 (s), 1491 (m), 731 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{15} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 331.0747; found: 331.0748.
methyl (1-phenylbut-3-yn-1-yl)carbamate (6.162d)


To a solution of 6.158 ( $100 \mathrm{mg}, 0.669 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{NEt}_{3}(144 \mu \mathrm{~L}, 1.033 \mathrm{mmol}, 1.50$ equiv) in dry DCM ( $2.0 \mathrm{~mL}, 0.33 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$ was added dropwise $\mathrm{MeOC}(\mathrm{O}) \mathrm{Cl}(64 \mu \mathrm{~L}, 0.826 \mathrm{mmol}, 1.20$ equiv). After being stirred at room temperature overnight, the reaction mixture was carefully quenched with 2 M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 28: 1$ ) to yield the desired product 6.162 d ( 88 mg , 65\%) as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.30-7.10(\mathrm{~m}, 5 \mathrm{H}), 5.24(\mathrm{~s}, 1 \mathrm{H}), 4.98-4.59(\mathrm{~m}, 1 \mathrm{H}), 3.60(\mathrm{~s}, 3 \mathrm{H}), 2.75$ $-2.66(\mathrm{~m}, 1 \mathrm{H}), 2.66-2.51(\mathrm{~m}, 1 \mathrm{H}), 1.93(\mathrm{t}, \mathrm{J}=2.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 156.4,140.8,128.7,127.9,126.5,79.9,71.7,53.0,52.4,26.4$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3289$ (w), 1597 (s), 1503 (s), 1488 (m), 729 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{12} \mathrm{H}_{14} \mathrm{NO}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 204.1019; found: 204.1021.

## 2,4-dinitro-N-(1-phenylbut-3-yn-1-yl)aniline (6.164)



To a solution of $6.158(100 \mathrm{mg}, 0.669 \mathrm{mmol}, 1.00$ equiv $)$ and ${ }^{\mathrm{i}} \mathrm{Pr}_{2} \mathrm{NEt}(342 \mu \mathrm{~L}, 2.066 \mathrm{mmol}, 3.00$ equiv) in dry DMF ( $6.9 \mathrm{~mL}, 0.10 \mathrm{M}$ ) was added portionwise 6.163 ( $130 \mu \mathrm{~L}, 1.033 \mathrm{mmol}, 1.50$ equiv). After being stirred at room temperature overnight, the reaction mixture was carefully quenched with 2 M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 40: 1$ ) to yield the desired product 6.164 (198 $\mathrm{mg}, 95 \%$ ) as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 9.28(\mathrm{~d}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 9.15(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.11(\mathrm{dd}, J=9.5,2.7 \mathrm{~Hz}$, $1 \mathrm{H}), 7.53-7.29(\mathrm{~m}, 5 \mathrm{H}), 6.71(\mathrm{~d}, J=9.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.85(\mathrm{q}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.98$ (ddd, J=17.0, 5.4, 2.7 $\mathrm{Hz}, 1 \mathrm{H}), 2.82$ (ddd, $J=17.0,6.5,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.21(\mathrm{t}, \mathrm{J}=2.7 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 147.5,139.2,136.8,131.2,130.3,129.4,128.8,126.2,124.2,115.3$, 78.2, 73.3, 56.6, 28.3.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3301$ (w), 1600 (s), 1502 (s), 1495 (m), 738 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{~N}_{3} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 312.0979; found: 312.0981.

### 8.6.2 Synthesis of Secondary Homopropargylamines

GP 6-2:


Unless otherwise indicated, homopropargyl amines 6.134 were synthesized following reported procedures. ${ }^{525}$ In a flame-dried three-necked round-bottom flask fitted with a magnetic bar was placed zinc powder ( $0.39 \mathrm{~g}, 6.00 \mathrm{mmol}$ ) and the flask was purged three times with dry nitrogen. The zinc powder was heated to $60-70{ }^{\circ} \mathrm{C}$. 1,2-Dibromoethane ( 0.1 mL ) in dry THF ( 0.5 mL ) was added dropwise for 10 min while maintaining the temperature at $60-70{ }^{\circ} \mathrm{C}$. The flask was then cooled to room temperature and trimethyl chlorosilane ( 0.1 mL in 0.5 mL of dry THF) was added. After stirring at room temperature for 15 min , the solvent was evaporated under reduced pressure. The freshly prepared activated zinc was used immediately for the reaction.

To the flask containing activated zinc was added imine $6.132(4.00 \mathrm{mmol})$ and the flask was purged three times with dry nitrogen. Dry toluene ( 0.5 mL ) was added to the flask followed by careful addition of propargyl bromide ( 5.00 mmol ) while maintaining the temperature below $40{ }^{\circ} \mathrm{C}$. After addition of the propargyl bromide (6.133), the reaction mixture was stirred at room temperature for another 2 h . The reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the homopropargyl amine 6.134.

## N-(1-phenylbut-3-yn-1-yl)aniline (6.134a)



## Procedure: GP 6-2

The analytical data were in accordance with those reported in the literature. ${ }^{527}$

## N-(1-(4-chlorophenyl)but-3-yn-1-yl)aniline (6.134b)



Procedure: GP 6-2

Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h. Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 84\% ( 857 mg ), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.41-7.36(\mathrm{~m}, 4 \mathrm{H}), 7.19(\mathrm{dd}, J=8.5,7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.78(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H})$, $6.60(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 4.58(\mathrm{t}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.45(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.80(\mathrm{ddd}, J=16.9,5.4,2.6 \mathrm{~Hz}, 1 \mathrm{H})$, 2.68 (ddd, J = 16.9, 6.7, 2.6 Hz, 1H), 2.15 (t, J = 2.6 Hz, 1H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 146.6,140.5,133.0,129.1,128.7,127.7,118.0,113.6,79.8,71.7$, 55.6, 27.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3299$ (w), 1601 (s), 1504 (s), 1489 (m), 730 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{ClH}_{15} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$256.0888; found: 256.0889.
$N$-(1-(4-methoxyphenyl)but-3-yn-1-yl)aniline (6.134c)


Procedure: GP 6-2

Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h. Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 81\% (813 mg), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.39(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.21-7.18(\mathrm{~m}, 2 \mathrm{H}), 6.95(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.77$ $(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.64(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 4.58(\mathrm{t}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.44(\mathrm{br} s, 1 \mathrm{H}), 3.84(\mathrm{~s}, 3 \mathrm{H}), 2.80$ (ddd, $J=16.8,5.6,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.71$ (ddd, $J=16.9,6.8,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{t}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 158.8,146.9,134.0,129.0,127.3,117.6,113.9,113.6,80.4,71.3$, 55.7, 55.1, 28.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3287$ (w), 1602 (s), 1504 (s), 1244 (s), 748 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{NO}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 252.1383; found: 252.1383.

## $N$-(1-(2-bromophenyl)but-3-yn-1-yl)aniline (6.134d)



## Procedure: GP 6-2

Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 72\% ( 864 mg ), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.68(\mathrm{dd}, \mathrm{J}=7.9,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{dd}, \mathrm{J}=7.8,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.33(\mathrm{t}, \mathrm{J}=$ $7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.25-7.18(\mathrm{~m}, 3 \mathrm{H}), 6.81(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.61(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 5.09-5.07(\mathrm{~m}, 1 \mathrm{H})$, $4.71(\mathrm{~s}, 1 \mathrm{H}), 3.00(\mathrm{ddd}, \mathrm{J}=17.0,4.6,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.76$ (ddd, $J=17.0,6.7,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.20(\mathrm{t}, \mathrm{J}=2.6$ $\mathrm{Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 146.3,139.9,132.9,129.1,128.9,127.9,127.6,122.8,117.9,113.4$, 79.6, 71.8, 54.7, 25.7.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3294$ (w), 1601 (m), 1503 (s), 747 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16}{ }^{79} \mathrm{BrH}_{15} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 300.0382$; found: 300.0375 and calcd for $\mathrm{C}_{16}{ }^{81} \mathrm{BrH}_{15} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 302.0362$; found: 302.0360.
$N$-(1-(3-bromophenyl)but-3-yn-1-yl)aniline (6.134e)


Procedure: GP 6-2
Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 91\% ( 1.09 g ), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.67(\mathrm{~s}, 1 \mathrm{H}), 7.49(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.43(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.30-7.21$ $(\mathrm{m}, 3 \mathrm{H}), 6.82(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.64(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 4.58(\mathrm{t}, \mathrm{J}=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.48(\mathrm{~s}, 1 \mathrm{H}), 2.83$ (ddd, $J=16.9,5.3,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.71$ (ddd, $J=16.9,6.9,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{t}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 146.5,144.6,130.6,130.2,129.4,129.1,125.0,122.7,118.0,113.6$, 79.6, 71.8, 55.8, 27.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3294$ (w), 1601 (s), 1504 (s), 748 (s), 691 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16}{ }^{79} \mathrm{BrH}_{15} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 300.0382; found: 300.0380 and calcd for $\mathrm{C}_{16}{ }^{81} \mathrm{BrH}_{15} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 302.0362; found: 302.0359.

4-Methoxy-N-(1-phenylbut-3-yn-1-yl)aniline (6.134f)


Procedure: GP 6-2
Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 94\% ( 944 mg ), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.50(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.43(\mathrm{t}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.35(\mathrm{t}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H})$, $6.81(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.63(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.58-4.55(\mathrm{~m}, 1 \mathrm{H}), 4.26(\mathrm{~s}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 2.83$ (ddd, $J=16.8,5.4,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.72$ (ddd, $J=16.9,7.1,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.17(\mathrm{t}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 152.1,142.2,141.0,128.4,127.3,126.3,114.9,114.6,80.4,71.3$, 57.1, 55.4, 27.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3289$ (w), 1509 ( s$), 1235$ (s), 700 (m).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{NO}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 252.1383; found: 252.1385.
4-chloro-N-(1-phenylbut-3-yn-1-yl)aniline ( 6.134 g )


Procedure: GP 6-2
The analytical data were in accordance with those reported in the literature. ${ }^{527}$
3-chloro-N-(1-phenylbut-3-yn-1-yl)aniline (6.134h)


Procedure: GP 6-2
Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h. Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 55\% ( 561 mg ), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.46-7.40(\mathrm{~m}, 4 \mathrm{H}), 7.35(\mathrm{t}, \mathrm{J}=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.07(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.76-$ $6.74(\mathrm{~m}, 1 \mathrm{H}), 6.65(\mathrm{t}, \mathrm{J}=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.49(\mathrm{dd}, J=8.2,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.61-4.58(\mathrm{~m}, 2 \mathrm{H}), 2.84(\mathrm{ddd}, \mathrm{J}=$ $16.9,5.2,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.71$ (ddd, $J=16.9,6.8,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.16(\mathrm{t}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 148.0,141.3,134.7,130.0,128.6,127.6,126.1,117.6,113.4,111.7$, 79.9, 71.7, 56.0, 27.8.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3293$ ( w ), 1595 ( s$), 1498(\mathrm{~m}), 1481(\mathrm{~m}), 760(\mathrm{~m}), 700(\mathrm{~s}), 681(\mathrm{~m})$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{ClH}_{15} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right): ~ 256.0888$; found: 256.0888 .

## 2-Methyl-N-(1-phenylbut-3-yn-1-yl)aniline (6.134i)



Procedure: GP 6-2
Conditions: $22^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: $66 \%$ $(620 \mathrm{mg})$, yellow oil.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.48(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.41(\mathrm{t}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.34(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.16(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.04(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.72(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.44(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.68-$ $4.65(\mathrm{~m}, 1 \mathrm{H}), 4.44(\mathrm{~s}, 1 \mathrm{H}), 2.88(\mathrm{ddd}, J=16.9,5.2,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.77(\mathrm{ddd}, J=16.9,7.3,2.6 \mathrm{~Hz}, 1 \mathrm{H})$, $2.36(\mathrm{~s}, 3 \mathrm{H}), 2.16(\mathrm{t}, \mathrm{J}=2.6 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta$ 144.9, 142.2, 130.0, 128.6, 127.4, 126.9, 126.2, 122.4, 117.4, 111.3, 80.3, 71.4, 56.3, 28.3, 17.5.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3295(\mathrm{w}), 1510(\mathrm{~m}), 1314$ (m), 908 (m), 746 ( s$), 731(\mathrm{~s}), 699(\mathrm{~s})$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$236.1434; found: 236.1428 .
$N$-benzyl-1-phenylbut-3-yn-1-amine (6.134k)


Procedure: GP 6-2
The analytical data were in accordance with those reported in the literature. ${ }^{577}$

[^218]
## N-phenyl-2-(phenylamino)pent-4-ynamide (6.134j)


6.134j

Procedure: GP 6-2

Conditions: $22{ }^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography (PE/EtOAc 40:1). Yield: 46\% (486 mg), yellow oil.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.80(\mathrm{~s}, 1 \mathrm{H}), 7.57(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.35(\mathrm{t}, \mathrm{J}=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.28(\mathrm{t}, \mathrm{J}=$ $7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.15(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.92(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.77(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.47(\mathrm{~s}, 1 \mathrm{H}), 4.01$ ( $\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.95(\mathrm{~m}, 2 \mathrm{H}), 2.18(\mathrm{t}, \mathrm{J}=2.5 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 169.7,146.2,137.1,129.6,129.0,124.6,120.1,119.9,114.4,79.0$, 72.4, 58.6, 22.8.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3373$ (m), 3257 (m), 1667 (m), 1597 (s), 1497 (s), 1314 (s), 748 (s), 692 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$265.1335; found: 265.1336 .

## N-(but-3-yn-1-yl)aniline (6.47)



It was prepared according to literature procedures. ${ }^{528,530 a}$

## $N$-(2-methylpent-4-yn-2-yl)aniline (6.142)



It was prepared by Grignard reaction according to literature procedures. ${ }^{528,530 \mathrm{~b}}$

## N-benzyl-2,2-dimethylbut-3-yn-1-amine (6.148)



To a solution of the known tosylate ${ }^{532} 6.149$ ( $700 \mathrm{mg}, 2.774 \mathrm{mmol}, 1.00$ equiv) in dry acetonitrile ( $5.6 \mathrm{~mL}, 0.5 \mathrm{M}$ ) in a sealed tube was added $\mathrm{K}_{2} \mathrm{CO}_{3}(767 \mathrm{mg}, 5.548 \mathrm{mmol}, 2.00$ equiv) followed by benzylamine 6.147 ( $304 \mu \mathrm{~L}, 2.774 \mathrm{mmol}, 1.00$ equiv). The resulting mixture was stirred at $150^{\circ} \mathrm{C}$ for 2 days. After completion of the reaction, the reaction was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 9: 1$ ) to yield homopropargyl amine 6.148 as a yellow oil ( $249 \mathrm{mg}, 48 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.42-7.34(\mathrm{~m}, 2 \mathrm{H}), 7.34-7.28(\mathrm{~m}, 2 \mathrm{H}), 7.29-7.20(\mathrm{~m}, 1 \mathrm{H}), 3.70(\mathrm{~s}$, $2 \mathrm{H}), 2.40(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 2 \mathrm{H}), 2.06(\mathrm{t}, \mathrm{J}=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.24(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13}{ }^{13}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 141.1,128.5,128.5,127.0,81.8,70.9,52.8,47.1,30.9,27.0$.
IR: $\mathrm{u}\left(\mathrm{cm}^{-1}\right) 3321(\mathrm{w}), 2134(\mathrm{w}), 1462(\mathrm{~m}), 1378(\mathrm{w})$.
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 188.1434; found: 188.1436.
N -(2,2-dimethyl-1-phenylbut-3-yn-1-yl)aniline (6.152)


It was prepared according to literature procedures. ${ }^{531,533,534,535}$
2-(prop-2-yn-1-yl)indoline (6.154)


It was prepared according to a literature procedure. ${ }^{536}$
GP 6-3:

6.173 were synthesized from the known 2-(arylamino)ethanol 6.167 according to the following 4 step procedures:

Boc protection was undertaken according to a literature procedure. ${ }^{544}$ To a solution of 6.167 (10 mmol ) in $\mathrm{EtOH}(10 \mathrm{~mL}, 1 \mathrm{M})$ at $30^{\circ} \mathrm{C}$ was added $\mathrm{Boc}_{2} \mathrm{O}$ ( $15 \mathrm{mmol}, 1.5$ equiv). After being stirred at $30{ }^{\circ} \mathrm{C}$ overnight, the reaction mixture was evaporated in vacuo. The residue was dissolved in EtOAc, washed with saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield 6.168 in $92 \%$ to $99 \%$ yield.

Swern oxidation was undertaken according to a literature procedure. ${ }^{545}$ To a solution of oxalyl chloride ( $12 \mathrm{mmol}, 1 \mathrm{~mL}, 1.50$ equiv) in DCM ( 60 mL ) at $-78^{\circ} \mathrm{C}$ was added dropwise DMSO (24 mmol, $1.7 \mathrm{~mL}, 3.00$ equiv). After 5 min at this temperature, the reaction mixture was allowed to warm to $-60{ }^{\circ} \mathrm{C}$ over 30 min , whereupon a solution of a $6.168(8.00 \mathrm{mmol})$ in DCM ( 10 mL ) was added slowly. The solution was warmed to $-45^{\circ} \mathrm{C}$ over 30 min and stirred at this temperature for 5 $\mathrm{min} . \mathrm{NEt}_{3}(6.8 \mathrm{~mL})$ was added slowly. After 5 min at this temperature, the cooling bath was removed and the reaction mixture was allowed to warm to $0{ }^{\circ} \mathrm{C}$ and quenched with 1 M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield 6.169 in $91 \%$ to $99 \%$ yield.

To a solution of $6.169(5.00 \mathrm{mmol})$ in THF ( $10 \mathrm{~mL}, 0.5 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added ethynylmagnesium bromide ( 6.170 ) ( 0.5 M in THF, $10.0 \mathrm{mmol}, 20 \mathrm{~mL}$ ). After being stirred at $0{ }^{\circ} \mathrm{C}$ for 2 h , the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield $\mathbf{6 . 1 7 1}$ in $88 \%$ to $99 \%$ yield.

To a solution of $6.171(2.00 \mathrm{mmol})$ in DCM $(10 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added slowly TFA ( 5 mL ). After being stirred at $0{ }^{\circ} \mathrm{C}$ for 2 h , the reaction mixture was carefully quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The combined organic extracts were washed with brine, dried
 used for the next step without further purification.

To a solution of 6.172 ( $1.00 \mathrm{mmol}, 1.00$ equiv) and imidazole ( $136 \mathrm{mg}, 2.00 \mathrm{mmol}, 2.00$ equiv) in DCM ( $5 \mathrm{~mL}, 0.2 \mathrm{M}$ ) at room temperature was added TBSCI ( $158 \mathrm{mg}, 1.05 \mathrm{mmol}, 1.05$ equiv) or TIP$\mathrm{SCl}(202 \mathrm{mg}, 1.05 \mathrm{mmol}, 1.05$ equiv). After being stirred overnight, the resulting mixture was quenched with MeOH , diluted with $\mathrm{H}_{2} \mathrm{O}$ and extracted with DCM. The combined organic extracts were washed with 1 M HCl , saturated aqueous $\mathrm{NaHCO}_{3}$, brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.173 in 69 to $99 \%$ yield.

## 1-(phenylamino)but-3-yn-2-ol (6.173a)



Procedure: GP 6-3
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 5: 1$ ) Yield: $96 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.21(\mathrm{dd}, J=8.6,7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.78(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.70(\mathrm{dd}, J=8.6$, $1.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), 4.57 (ddd, $J=7.2,4.3,2.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.49 (dd, $J=13.3,4.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.35 (dd, $J=13.3,7.2$ $\mathrm{Hz}, 1 \mathrm{H}), 3.27(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 2.53(\mathrm{~d}, \mathrm{~J}=2.1 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 147.3,129.3,118.5,113.6,82.7,74.2,60.8,50.0$.
IR: $0\left(\mathrm{~cm}^{-1}\right) 3287(\mathrm{w}), 2922(\mathrm{w}), 1738(\mathrm{w}), 1601(\mathrm{~m}), 1506(\mathrm{~m}), 1325(\mathrm{~m}), 1071(\mathrm{~m}), 757(\mathrm{~m}), 720(\mathrm{~s})$, $690(\mathrm{~m})$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{NO}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 162.0913 ; found: 162.0911 .

## $N$-(2-((tert-butyldimethylsilyl)oxy)but-3-yn-1-yl)aniline (6.173b)



Procedure: GP 6-3
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 40: 1\right)$ Yield: $69 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.21(\mathrm{dd}, J=8.5,7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.76(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{dd}, J=8.6$, $1.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), 4.57 (ddd, $J=6.9,4.7,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.12(\mathrm{brs}, 1 \mathrm{H}), 3.44(\mathrm{dd}, \mathrm{J}=13.1,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.34$ (dd, $J=13.1,7.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.48(\mathrm{~d}, \mathrm{~J}=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 0.95(\mathrm{~s}, 9 \mathrm{H}), 0.17(\mathrm{~s}, 3 \mathrm{H}), 0.12(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 147.4,129.3,117.9,113.3,83.6,73.4,61.3,50.4,25.7,18.1,-4.7,-5.1$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3307$ (w), 2953 (w), 2930 (w), 2856 (w), 1738 (m), 1603 (m), 1506 (m), 1363 (m), 1253 (m), 1095 (s), 938 (m), 836 (s), 779 (s), 691 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{26} \mathrm{NOSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 276.1778; found: 276.1781.
$N$-(2-((tert-butyldimethylsilyl)oxy)but-3-yn-1-yl)-4-methoxyaniline (6.173c)


Procedure: GP 6-3
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 40: 1\right)$ Yield: $88 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 6.79(\mathrm{~d}, \mathrm{~J}=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.62(\mathrm{~d}, \mathrm{~J}=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.53$ (ddd, $J=6.9,4.6$, $2.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.75(\mathrm{~s}, 3 \mathrm{H}), 3.36(\mathrm{dd}, J=12.9,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.27(\mathrm{dd}, J=12.9,7.7 \mathrm{~Hz}$, $1 \mathrm{H}), 2.46(\mathrm{~d}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 0.92(\mathrm{~s}, 9 \mathrm{H}), 0.14(\mathrm{~s}, 3 \mathrm{H}), 0.09(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 152.5,141.4,114.9,114.8,83.7,73.4,61.2,55.7,51.5,25.7,18.1,-$ 4.6, -5.1.

IR: $v\left(\mathrm{~cm}^{-1}\right) 3289$ (w), 2951 (w), 2930 (w), 2856 (w), 1738 (m), 1512 (s), 1363 (m), 1234 (s), 1092 (s), 1039 (m), 938 (m), 836 (s), 819 (s), 779 (s), 667 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{28} \mathrm{NO}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 306.1884$; found: 306.1880.
$N$-(2-((tert-butyldimethylsilyl)oxy)but-3-yn-1-yl)-4-chloroaniline (6.173d)


Procedure: GP 6-3

Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 40: 1\right)$ Yield: $82 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.13(\mathrm{~d}, \mathrm{~J}=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.56(\mathrm{~d}, \mathrm{~J}=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.53$ (ddd, $J=7.4,4.6$, $2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.11(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.38(\mathrm{dd}, J=13.1,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.29(\mathrm{dd}, J=13.1,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.46(\mathrm{~d}, J=$ $2.1 \mathrm{~Hz}, 1 \mathrm{H}), 0.92(\mathrm{~s}, 9 \mathrm{H}), 0.14(\mathrm{~s}, 3 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 146.0,129.1,122.4,114.4,83.3,73.6,61.2,50.5,25.7,18.1,-4.6,-5.1$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3303(\mathrm{w}), 2961(\mathrm{w}), 2952(\mathrm{w}), 2930(\mathrm{w}), 2856(\mathrm{w}), 1738(\mathrm{~m}), 1600(\mathrm{w}), 1500(\mathrm{~s}), 1364$ (m), 1253 (m), 1090 (s), 938 (m), 837 ( s$), 814$ (s), 779 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{CINOSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 310.1388$; found: 310.1385.

## $N$-(2-((triisopropylsilyl)oxy)but-3-yn-1-yl)aniline (6.173e)



Procedure: GP 6-3
Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 40: 1\right)$ Yield: $99 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.20(\mathrm{dd}, \mathrm{J}=8.6,7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.75(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.67(\mathrm{dd}, J=8.6$, $1.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.69(\mathrm{ddd}, \mathrm{J}=6.0,5.6,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.20(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.43(\mathrm{dd}, \mathrm{J}=12.8,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.38$ (dd, $J=12.8,5.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.47(\mathrm{~d}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.23-1.10(\mathrm{~m}, 21 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 147.5,129.3,117.9,113.3,83.8,73.461 .6,50.7,17.95,17.97,12.2$.
IR: $0\left(\mathrm{~cm}^{-1}\right) 3308(\mathrm{w}), 2943(\mathrm{w}), 2866(\mathrm{w}), 1739(\mathrm{~m}), 1603(\mathrm{~m}), 1506(\mathrm{~m}), 1366(\mathrm{~m}), 1230(\mathrm{~m}), 1218$ (m), 1102 (s), 1069 (m), 882 (s), 748 (s), 688 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{32} \mathrm{NOSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 318.2248$; found: 318.2247.

## N -(2-methylbut-3-yn-1-yl)aniline (6.180)


6.177 was synthesized from 2-methylbut-1-en-3-yne (6.174) according to a literature procedure. ${ }^{546}$

To a solution of $6.177(1.0 \mathrm{~g}, 5.00 \mathrm{mmol})$ in $\mathrm{DCM}(10 \mathrm{~mL}, 0.5 \mathrm{M})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{Et}_{3} \mathrm{~N}(834 \mu \mathrm{~L}$, 6.00 mmol ) and $\mathrm{TsCl}(1.0 \mathrm{~g}, 5.25 \mathrm{mmol})$. After being stirred at room temperature overnight, the reaction mixture was quenched with $\mathrm{H}_{2} \mathrm{O}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 50: 1$ ) to yield the desired product $6.178(60 \%)$ as a yellow oil.

To a solution of 6.179 ( $821 \mathrm{mg}, 3.00 \mathrm{mmol}$ ) in THF ( $3 \mathrm{~mL}, 1 \mathrm{M}$ ) at room temperature was added TBAF ( 1 M in THF, 4.5 mL , 1.50 equiv). After being stirred for another 2 h at room temperature, the
reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}\right.$ $50: 1$ ) to yield the desired product 6.180 ( 477 mg , quantitative yield) as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 7.22-7.18 (m, 2H), 6.67-6.65 (m, 1H), $6.66(\mathrm{~m}, 2 \mathrm{H}), 4.11(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.23$ (dd, J = 12.4, 6.0 Hz, 1H), 3.16 (dd, J = 12.4, 7.8 Hz, 1H), 2.85-2.76 (m, 1H), 2.14 (d, J = 2.4 Hz, 1H), 1.27 (d, J = 7.0 Hz, 3H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta$ 147.7, 129.3, 117.8, 113.2, 86.6, 69.8, 49.3, 25.9, 18.4.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3413$ (w), 3291 (w), 2970 (w), 1738 (m), 1602 (s), 1506 (s), 1377 (m), 1314 (m), 1255 (m), 1229 (m), 749 (s), 692 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 160.1121; found: 160.1119.

## 1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (6.21)



It was prepared according to a literature procedure. ${ }^{538}$
$N$-isopropyl-1-phenylbut-3-yn-1-amine (6.160a), $N$-(1-phenylbut-3-yn-1-yl)cyclohexanamine (6.160b) and N -butyl-1-phenylbut-3-yn-1-amine (6.160c)


They were prepared according to a literature procedure. ${ }^{529}$

## $N$-(1,4-diphenylbut-3-yn-1-yl)aniline (6.135)



To a mixture of alkyne 6.134 a ( $200 \mathrm{mg}, 0.904 \mathrm{mmol}, 1.20$ equiv), $\mathrm{Phl}(85 \mu \mathrm{~L}, 0.753 \mathrm{mmol}, 1.00$ equiv), Cul ( $2.9 \mathrm{mg}, 0.015 \mathrm{mmol}, 0.02$ equiv) and $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}(5.3 \mathrm{mg}, 0.0075 \mathrm{mmol}, 0.01$ equiv) in a sealed tube was added degassed $\mathrm{Et}_{2} \mathrm{NH}(5.5 \mathrm{~mL}$ ) and dry DMF ( 4.5 mL ). After being stirred at 50 ${ }^{\circ} \mathrm{C}$ for 12 h , the reaction mixture was quenched by the addition of 2 M HCl and extracted with
ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 40:1) to yield the desired product 6.135 ( $239 \mathrm{mg}, 89 \%$ ).
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 7.49-7.43(\mathrm{~m}, 2 \mathrm{H}), 7.38-7.32(\mathrm{~m}, 4 \mathrm{H}), 7.32-7.27(\mathrm{~m}, 4 \mathrm{H}), 7.15-$ $7.06(\mathrm{~m}, 2 \mathrm{H}), 6.68(\mathrm{tt}, J=7.2,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.63-6.51(\mathrm{~m}, 2 \mathrm{H}), 4.62(\mathrm{dd}, J=6.9,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.51(\mathrm{~s}$, 1H), 2.99 (dd, J = 16.9, 5.5 Hz, 1H), 2.88 (dd, J = 16.9, $6.9 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 147.3,142.6,131.8,129.3,128.8,128.4,128.2,127.6,126.6,123.3$, 117.9, 113.9, 85.9, 83.7, 57.1, 29.4.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 1510$ (m), 1314 (m), 909 (m), 748 (s), 730 (s), 701 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 298.1590; found: 298.1595.

### 8.6.3 Synthesis of Primary Homopropargylamines

## 1-phenylbut-3-yn-1-amine (6.158)



It was synthesized according to a literature procedure. ${ }^{539}$

## GP 6-4:


6.248 was synthesized according to a literature procedure. ${ }^{565}$

To a suspension of Zn ( 2.00 equiv) and $\mathrm{PPh}_{3}\left(4.00\right.$ equiv) in DCM $\left(0.025 \mathrm{M}\right.$ ) at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{CBr}_{4}$ ( 2.00 equiv) and the reaction mixture was stirred for 30 min at $0^{\circ} \mathrm{C}$ and for 1 h at room temperature. Aldehyde 6.248 (1.00 equiv) was then added and the reaction mixture was stirred at room temperature until full conversion (as indicated by TLC). The reaction mixture was quenched by addition of hexane (twice the volume of DCM) and filtered over Celite (rinsed with DCM). The sol-
vent was evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.250.

To a stirred solution of 6.250 ( 1.00 equiv) in THF ( 0.02 M ) at $-78{ }^{\circ} \mathrm{C}$ was added ${ }^{\mathrm{n}} \mathrm{BuLi}(2.2 \mathrm{M}$ in hexane, 3 equiv) dropwise and the reaction mixture was stirred for 5 hours. After warming up to $50{ }^{\circ} \mathrm{C}$, the reaction mixture was quenched by the addition of a saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.249.
6.249 ( 1.00 equiv) was added to a mixture of DCM/TFA ( $4: 1,0.05 \mathrm{M}$ ) at $-78{ }^{\circ} \mathrm{C}$ and the reaction mixture was warm to room temperature. After full conversion (as indicated by TLC) the reaction mixture was evaporated in vacuo. The residue was dissolved in ethyl acetate and neutralized with saturated aqueous $\mathrm{NaHCO}_{3}$. The reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.251.
(1S,2R)-2-methyl-1-phenylbut-3-yn-1-amine (6.251a)


Procedure: GP 6-4
Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) Yield: 97\%, isolated as a brown oil as a mixture of diastereoisomers of cis/trans in a ratio of >19:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.43-7.20(\mathrm{~m}, 5 \mathrm{H}), 4.01(\mathrm{~d}, J=5.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.86(\mathrm{qdd}, J=7.0,5.3,2.5$ $\mathrm{Hz}, 1 \mathrm{H}), 2.11(\mathrm{~d}, \mathrm{~J}=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.92(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 1.08(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 142.9,128.2,127.5,127.3,86.5,70.8,59.1,33.9,16.4$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 2554$ (w), 2363 (s), 2342 (s), 2018 (s), 1976 (s), 1700 (m), 1653 (m), 1541 (m), 1082 (w), 669 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 160.1121$; found: 160.1123.
$[\alpha]_{\mathrm{D}}{ }^{20}-19.6^{\circ}\left(c 0.5, \mathrm{CHCl}_{3}\right)$.
(1S,2R)-2-isopropyl-1-phenylbut-3-yn-1-amine (6.251b)


Procedure: GP 6-4

Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1\right)$ Yield: $99 \%$, isolated as a brown oil as a mixture of diastereoisomers of cis/trans in a ratio of $>19: 1$.
${ }^{1}{ }^{\mathbf{H}}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.52-7.38(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.22(\mathrm{~m}, 3 \mathrm{H}), 3.97(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.60$ (ddd, J = 8.0, 5.5, 2.4 Hz, 1H), $2.03(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.98-1.78(\mathrm{~m}, 3 \mathrm{H}), 1.05(\mathrm{~d}, \mathrm{~J}=6.7 \mathrm{~Hz}, 3 \mathrm{H})$, 1.01 (d, J = $6.7 \mathrm{~Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $\left.100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 144.2,128.3,127.5,127.5,83.1,73.1,56.8,47.3,27.7,21.9,18.2$.
IR: v (cm ${ }^{-1}$ ) 3301 (w), 2961 (m), 2930 (w), 2872 (w), 1683 (w), 1455 (w), 757 (w), 701 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 188.1434; found: 188.1435.
$[\alpha]_{\mathrm{D}}{ }^{20}-54.2^{\circ}\left(c 0.4, \mathrm{CHCl}_{3}\right)$.
2-methylbut-3-yn-1-amine (6.238)

6.235 was synthesized according to literature procedures. ${ }^{557,558}$
$\mathrm{Py} \cdot \mathrm{SO}_{3}(1.20 \mathrm{~g}, 7.53 \mathrm{mmol}, 1.50$ equiv) was added portionwise in DCM/DMSO (2:1, $12 / 6 \mathrm{~mL}, 0.28$ $\mathrm{M})$ at $0{ }^{\circ} \mathrm{C}$. After 20 minutes, 6.235 ( $950 \mathrm{mg}, 5.02 \mathrm{mmol}, 1.00$ equiv) was added portionwise. After 2 hours, $\mathrm{NEt}_{3}(1.40 \mathrm{~mL}, 10.03 \mathrm{mmol}, 2.00$ equiv) was added and the reaction mixture was warmed to room temperature. After stirring for 1 hour, saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ was added and the resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield 6.236. The residue was used directly in the next step without further purification.

In a solution of 6.236 ( $939 \mathrm{mg}, 5.02 \mathrm{mmol}, 1.00$ equiv), Ohira-Bestman reagent ( $1.45 \mathrm{~g}, 7.53 \mathrm{mmol}$, 1.50 equiv) in dry $\mathrm{MeOH}\left(63 \mathrm{~mL}, 0.08 \mathrm{M}\right.$ ) was added portionwise $\mathrm{K}_{2} \mathrm{CO}_{3}(1.39 \mathrm{~g}, 10.04 \mathrm{mmol}, 2.00$ equiv). After being stirred 6 hours, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.237 ( $795 \mathrm{mg}, 86 \%$ ).
${ }^{1}{ }^{\mathbf{H}} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.86(\mathrm{~s}, 1 \mathrm{H}), 3.28(\mathrm{dt}, J=12.6,5.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.05(\mathrm{ddd}, J=13.0,7.8,4.8$ $\mathrm{Hz}, 1 \mathrm{H}), 2.64(\mathrm{qd}, J=8.3,7.6,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.08(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.44(\mathrm{~s}, 11 \mathrm{H}), 1.17(\mathrm{~d}, J=7.0 \mathrm{~Hz}$, 4H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 156.0,86.7,79.6,69.7,45.8,28.5,27.1,18.1$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3413$ (w), 3291 (w), 2971 (w), 1738 (m), 1602 (s), 1506 (s), 1377 (m), 1334 (m), 1256 (m), 1229 (m), 749 (s), 692 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{10} \mathrm{H}_{18} \mathrm{NO}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 184.1332 ; found: 184.1335.
6.237 ( $920 \mathrm{mg}, 5.02 \mathrm{mmol}, 1.00$ equiv) was added dropwise in dry TFA ( $30 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0^{\circ} \mathrm{C}$. After being stirred 2 hour at room temperature, the reaction mixture was evaporated in vacuo. The residue was redissolved in DCM and saturated aqueous $\mathrm{NaHCO}_{3}$ was added slowly. The resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.238 ( $408 \mathrm{mg}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol- $\mathrm{d}_{4}$ ) $\delta 3.03(\mathrm{dd}, J=12.0,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.96-2.80(\mathrm{~m}, 2 \mathrm{H}), 2.67(\mathrm{~d}, J=$ $2.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.26(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 100 MHz, Methanol $-d_{4}$ ) $\delta 84.2,73.4,45.4,26.0,18.5$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3413$ (w), 3291 (w), 2970 (w), 1738 (m), 1606 (s), 1506 (s), 1377 (m), 1314 (m), 1255 (m), 1231 (m), 752 (s), 693 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{5} \mathrm{H}_{10} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 84.0808; found: 84.0813.
2-((tert-butyldimethylsilyl)oxy)but-3-yn-1-amine (6.244)

6.241 was synthesized according to a literature procedure. ${ }^{560}$

To a solution of ketone $6.241\left(1.33 \mathrm{~g}, 7.26 \mathrm{mmol}, 1.00\right.$ equiv) and $\mathrm{CeCl}_{3}(537 \mathrm{mg}, 2.18 \mathrm{mmol}, 0.3$ equiv) in $\mathrm{MeOH}\left(165 \mathrm{~mL}, 0.044 \mathrm{M}\right.$ ) at $0^{\circ} \mathrm{C}$ was added $\mathrm{NaBH}_{4}$ ( $330 \mathrm{mg}, 8.711 \mathrm{mmol}, 1.20$ equiv). After being stirred 6 hours at $0{ }^{\circ} \mathrm{C}$, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield 6.242. The residue was used directly in the next step without further purification.

To a solution of 6.242 ( $940 \mathrm{mg}, 5.08 \mathrm{mmol}, 1.00$ equiv) in dry DCM ( $102 \mathrm{~mL}, 0.05 \mathrm{M}$ ) was added TMSCl ( $11 \mathrm{~mL}, 86.39 \mathrm{mmol}, 17$ equiv) and phenol ( $8.13 \mathrm{~g}, 86.4 \mathrm{mmol}, 17$ equiv). After being stirred 2 hours at room temperature, the reaction mixture was quenched with 2 M HCl and extracted
with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.243 ( $389 \mathrm{mg}, 90 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $-d_{4}$ ) $\delta 4.54$ (ddd, $J=7.8,4.1,2.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.11(\mathrm{dd}, J=12.9,4.1 \mathrm{~Hz}$, 1H), $3.04-2.96(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 100 MHz, Methanol- $\boldsymbol{d}_{4}$ ) $\delta$ 82.4, 75.9, 59.7, 46.4.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3413$ (w), 3284 (w), 2970 (w), 1741 (m), 1602 (s), 1506 (s), 1377 (m), 1317 (m), 1256 (m), 1229 (m), 749 (s), 696 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{4} \mathrm{H}_{8} \mathrm{NO}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 86.0600$; found: 86.0603.
To a solution of 6.243 ( $100 \mathrm{mg}, 1.18 \mathrm{mmol}, 1.00$ equiv) and $\mathrm{NEt}_{3}(327 \mu \mathrm{~L}, 2.35 \mathrm{mmol}, 2.00$ equiv) in dry DCM ( $12 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $\operatorname{TBSCI}(213 \mu \mathrm{~L}, 1.41 \mathrm{mmol}, 1.20$ equiv). After being stirred 12 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.244 ( $204 \mathrm{mg}, 87 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $-d_{4}$ ): $\delta 4.39(\mathrm{td}, J=5.8,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.89(\mathrm{~d}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.74(\mathrm{~d}, \mathrm{~J}=$ $5.8 \mathrm{~Hz}, 2 \mathrm{H}), 0.93(\mathrm{~s}, 6 \mathrm{H}), 0.17(\mathrm{~s}, 3 \mathrm{H}), 0.15(\mathrm{~s}, 3 \mathrm{H})$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3415$ (w), 3291 (w), 2973 (w), 1738 (m), 1608 (s), 1506 (s), 1387 (m), 1316 (m), 1255 (m), 1225 (m), 749 (s), 690 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{10} \mathrm{H}_{22} \mathrm{NOSi}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 200.1465; found: 200.1467.
ethyl ( $2 R, 3 R$ )-2-amino-3-methylpent-4-ynoate (6.258)

6.255 was synthesized according to a literature procedure. ${ }^{567}$

To a solution of $\mathrm{Zn}\left(1.59 \mathrm{~g}, 24.26 \mathrm{mmol}, 2.00\right.$ equiv) and $\mathrm{PPh}_{3}(12.73 \mathrm{~g}, 48.52 \mathrm{mmol}, 4.00$ equiv) in dry DCM ( 120 mL ) was added $\mathrm{CBr}_{4}(8.05 \mathrm{~g}, 24.26 \mathrm{mmol}, 2.00$ equiv) portionwise. After 30 min at 0 ${ }^{\circ} \mathrm{C}$, 6.255 ( $3.15 \mathrm{~g}, 12.13 \mathrm{mmol}, 1.00$ equiv) in DCM ( 24 mL ) was added dropwise. After being stirred
at room temperature for 12 hours, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ was added and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.256 (54\%).
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 6.27(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.10(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.32(\mathrm{dd}, J=9.0,5.4$ $\mathrm{Hz}, 1 \mathrm{H}), 4.21(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.99(\mathrm{dt}, \mathrm{J}=13.0,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.45(\mathrm{~s}, 9 \mathrm{H}), 1.30(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$, 1.08 (d, J = $6.9 \mathrm{~Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.5,155.9,140.2,92.1,79.5,63.4,61.3,28.8,24.4,14.4,14.1$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3291$ (w), 2973 (w), 1738 (m), 1612 (s), 1506 (s), 1387 (m), 1319 (m), 1255 (m), 1220 (m), 749 (s), 691 ( s$)$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{13} \mathrm{H}_{22} \mathrm{Br}_{2} \mathrm{NO}_{4}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 413.9910 ; found: 413.9912.
To a solution of 6.256 ( $1.04 \mathrm{~g}, 2.50 \mathrm{mmol}, 1.00$ equiv) in dry THF ( $25 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added ${ }^{\mathrm{n}} \mathrm{BuLi}$ ( 2.2 M in hexane, $3.8 \mathrm{~mL}, 7.51 \mathrm{mmol}, 3.00$ equiv) dropwise at $-78^{\circ} \mathrm{C}$. After being stirred 5 hours at $-78{ }^{\circ} \mathrm{C}$, the reaction mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo to yield 6.257 (72\%). The residue was used directly in the next step without further purification.
6.257 ( $164 \mathrm{mg}, 0.64 \mathrm{mmol}, 1.00$ equiv) was added in dry DCM/TFA (4:1, 10/2.5 mL, 0.05 M ) at room temperature. After being stirred 2 hours at room temperature, the resulting mixture was evaporated in vacuo. The residue was redissolved in DCM and saturated aqueous $\mathrm{NaHCO}_{3}$ was added slowly. The resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.258 (24\%).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $-d_{4}$ ): $\delta 4.31(\mathrm{dq}, J=12.4,8.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.16(\mathrm{dq}, J=12.5,8.1 \mathrm{~Hz}, 1 \mathrm{H})$, $3.85(\mathrm{~d}, \mathrm{~J}=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.58(\mathrm{td}, J=8.5,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.04(\mathrm{pd}, J=6.8,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.24(\mathrm{~d}, J=2.9 \mathrm{~Hz}$, $1 \mathrm{H}), 1.26(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 3 \mathrm{H}), 1.13(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, Methanol- $d_{4}$ ): $\delta 171.5,87.3,70.2,61.3,61.1,27.0,15.0,14.1$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3419$ (w), 3291 (w), 2973 (w), 1741 (m), 1608 (s), 1506 (s), 1401 (m), 1316 (m), 1250 (m), 1225 (m), 759 (s), 690 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{8} \mathrm{H}_{14} \mathrm{NO}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 156.1019 ; found: 156.1022.

### 8.6.4 Synthesis of Isonitriles

tert-butyl((2-isocyanobenzyl)oxy)dimethylsilane (6.184)


It was prepared according to a literature procedure. ${ }^{547}$

> ethyl (2-isocyano-2-methylpropyl) carbonate (6.186)


It was prepared according to a literature procedure. ${ }^{548}$
methyl (2-isocyano-2-methylpropanoyl)glycinate (6.189)


It was prepared according to a literature procedure. ${ }^{549}$

### 8.6.5 AgOAc-catalyzed Cyclization of Secondary Homopropargylamines

GP 6-5:


To a suspension of $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol})$ in toluene ( 1 mL ) was added a solution of isocyanide $1.99(0.4 \mathrm{mmol})$ and homopropargylamine $6.15(0.2 \mathrm{mmol})$ in toluene ( 1 mL ). The resulting mixture was stirred at the indicated temperature for the indicated time. After completion of the reaction, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 $\mathrm{cm} \mathrm{SiO}_{2}$ packed with $\mathrm{PE} / \mathrm{EtOAc} 95: 5$, solvents system: $25 \mathrm{mLPE} / \mathrm{EtOAc} 95: 5$ then the indicated solvent system) and purified to yield proline amide 6.18.

## N -(tert-butyl)-1,5-diphenylpyrrolidine-2-carboxamide (cis-6.18a)



Procedure: GP 6-5 from homopropargylamine 6.134a

Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 41\% (26 mg), white solid.

MP: 89-91 ${ }^{\circ} \mathrm{C}$.
${ }^{1}{ }^{\mathbf{H}} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.30-7.18(\mathrm{~m}, 5 \mathrm{H}), 7.10(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.86(\mathrm{~s}, 1 \mathrm{H}), 6.74(\mathrm{t}, \mathrm{J}=7.3$ $\mathrm{Hz}, 1 \mathrm{H}), 6.54(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 4.63(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.98(\mathrm{dd}, J=8.4,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.38-2.17(\mathrm{~m}$, $3 \mathrm{H}), 1.85(\mathrm{~m}, 1 \mathrm{H}), 1.29(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{1}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.9,148.0,143.3,129.0,128.9,127.1,125.6,118.9,114.7,68.8$, 66.1, 51.0, 35.5, 30.0, 28.6.

IR: u ( $\mathrm{cm}^{-1}$ ) 3308 (w), 2976 (w), 1654 (s), 1545 (s), 1504 (s), 1344 (s), 1222 (s), 745 (s), 689 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 323.2118$; found: 323.2120.

## N-(tert-butyl)-1,5-diphenylpyrrolidine-2-carboxamide (trans-6.18a)



Procedure: GP 6-5 from homopropargylamine 6.134a
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc}, 8: 1$ ). Yield: $41 \%$ ( 26 mg ), white solid.

MP: $138-140^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.20-7.17(\mathrm{~m}, 2 \mathrm{H}), 7.11(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.06-7.02(\mathrm{~m}, 2 \mathrm{H}), 6.95(\mathrm{~d}, \mathrm{~J}$ $=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.61(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.39(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 5.90(\mathrm{~s}, 1 \mathrm{H}), 5.07(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H})$, $4.24(\mathrm{~d}, \mathrm{~J}=9.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.43-2.27(\mathrm{~m}, 2 \mathrm{H}), 2.07-2.03(\mathrm{~m}, 1 \mathrm{H}), 1.84-1.81(\mathrm{~m}, 1 \mathrm{H}), 1.20(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.5,144.3,142.2,129.0,128.5,126.8,126.0,117.4,113.7,64.5$, 62.7, 50.9, 33.5, 28.5, 28.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2972$ (w), 1667 (m), 1598 (m), 1520 (m), 1499 (s), 1451 (m), 1357 (m), 1335 (m), 748 (s), 696 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 323.2118; found: 323.2120.

## N -(tert-butyl)-5-(4-chlorophenyl)-1-phenylpyrrolidine-2-carboxamide (cis-6.18b)



Procedure: GP 6-5 from homopropargylamine 6.134b
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 42\% (30 mg), white solid.

MP: $134-136{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.33(\mathrm{~d}, J=8.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.28(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.19(\mathrm{dd}, J=8.8,7.4 \mathrm{~Hz}$, $2 \mathrm{H}), 6.83(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.81(\mathrm{~s}, 1 \mathrm{H}), 6.57(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.67(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.05(\mathrm{dd}, J=$ $8.5,4.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.41 (dtd, $J=12.3,6.4,4.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.33-2.22 (m, 2H), 1.88 (dddd, J = 12.1, 10.0, 8.4, 6.7 Hz, 1H), 1.36 (s, 9H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.7,147.7,141.9,132.8,129.1,129.0,127.0,119.2,114.6,68.7$, 65.6, 51.0, 35.5, 30.0, 28.7.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3301$ (w), 3058 (w), 2970 (w), 2868 (w), 1655 (s), 1599 (m), 1542 (m), 1502 (s), 1342 (s), 1218 (m), 836 (m), 748 (s), 691 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{ClH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 357.1728; found: 357.1728.

## N-(tert-butyl)-5-(4-chlorophenyl)-1-phenylpyrrolidine-2-carboxamide (trans-6.18b)



Procedure: GP 6-5 from homopropargylamine 6.134b
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 42\% (30 mg), white solid.

MP: $140-142{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.23(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.14-7.10(\mathrm{~m}, 2 \mathrm{H}), 6.96(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 6.70$ $(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.44(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 5.93(\mathrm{~s}, 1 \mathrm{H}), 5.12(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.30(\mathrm{~d}, J=8.3 \mathrm{~Hz}$, 1H), 2.51-2.29 (m, 2H), 2.13 (m, 1H), 1.86 (m, 1H), $1.26(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.3,144.0,140.8,132.5,129.1,128.7,127.4,117.6,113.7,64.3$, 62.2, 50.9, 33.5, 28.5, 28.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3309$ (w), 2977 (w), 1655 (s), 1549 (m), 1504 (s), 1358 (s), 1256 (m), 906 (m), 746 (s), $690(\mathrm{~m})$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{ClH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 357.1728; found: 357.1729.
N-(tert-butyl)-5-(4-methoxyphenyl)-1-phenylpyrrolidine-2-carboxamide (6.18c)


Procedure: GP 6-5 from homopropargylamine 6.134c
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $77 \%$ ( 54 mg ) as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.18(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.10(\mathrm{dd}, J=8.7,7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.04(\mathrm{dd}, J=8.6$, $7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.87-6.71(\mathrm{~m}, 8 \mathrm{H}), 6.61(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.54(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.39(\mathrm{~d}, J=7.9 \mathrm{~Hz}$, $2 \mathrm{H}), 5.90(\mathrm{~s}, 1 \mathrm{H}), 5.04(\mathrm{~d}, J=6.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.60-4.56(\mathrm{~m}, 1 \mathrm{H}), 4.21(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.96(\mathrm{dd}, J=8.3$, $4.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.73(\mathrm{~s}, 3 \mathrm{H}), 3.67(\mathrm{~s}, 3 \mathrm{H}), 2.34-1.77(\mathrm{~m}, 8 \mathrm{H}), 1.29(\mathrm{~s}, 9 \mathrm{H}), 1.19(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.0,172.6,158.6,158.4,148.1,144.3,135.3,134.1,128.98,128.95$, $127.1,126.7,118.9,117.3,114.7,114.2,113.9,113.8,68.7,65.6,64.4,62.2,55.3,55.2,50.9,50.8$, 35.6, 33.7, 30.0, 28.7, 28.5, 28.1.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3382$ (w), 3330 (w), 2966 (w), 1661 (m), 1598 (m), 1504 (s), 1343 (m), 1246 (s), 1173 (m), 1035 (m), 731 (s), 693 ( s$)$.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 353.2224; found: 353.2226.

## 5-(2-Bromophenyl)-N-(tert-butyl)-1-phenylpyrrolidine-2-carboxamide (cis-6.18d)



Procedure: GP 6-5 from homopropargylamine 6.134d
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 26\% (21 mg), white solid.

MP: $142-144{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.64(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.42(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.28-7.13(\mathrm{~m}, 4 \mathrm{H}), 6.82$ $(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.76(\mathrm{~s}, 1 \mathrm{H}), 6.50(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.98(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.06(\mathrm{dd}, J=8.7,4.3$ $\mathrm{Hz}, 1 \mathrm{H}), 2.68-2.61(\mathrm{~m}, 1 \mathrm{H}), 2.35(\mathrm{ddt}, J=18.7,9.5,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.28-2.21(\mathrm{~m}, 1 \mathrm{H}), 1.76(\mathrm{ddt}, J=$ $12.6,9.7,7.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.40(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.7,147.6,141.9,133.6,129.1,128.7,127.9,126.4,122.5,119.2$, 114.8, 68.5, 66.3, 51.1, 33.2, 29.9, 28.7.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3286$ (w), 2974 (w), 1652 (s), 1601 (m), 1552 (m), 1504 (s), 1338 (m), 1218 (m), 907 (w), 736 (s), 689 ( s ).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21}{ }^{79} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 401.1223; found: 401.1230 and calcd for $\mathrm{C}_{21}{ }^{81} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 403.1203; found: 403.1201.

5-(2-Bromophenyl)-N-(tert-butyl)-1-phenylpyrrolidine-2-carboxamide (trans-6.18d)


Procedure: GP 6-5 from homopropargylamine 6.134d
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $62 \%$ ( 50 mg ), white solid.

MP: $190-192{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.59(\mathrm{dd}, \mathrm{J}=7.4,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.15-7.06(\mathrm{~m}, 4 \mathrm{H}), 6.72-6.68(\mathrm{~m}, 2 \mathrm{H}), 6.39$ (d, J = $8.0 \mathrm{~Hz}, 2 \mathrm{H}), 5.95(\mathrm{~s}, 1 \mathrm{H}), 5.39(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.36(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.51-2.28(\mathrm{~m}, 2 \mathrm{H})$, 2.16 (dd, $J=12.9,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.98(\mathrm{dd}, J=12.1,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.28(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.3,143.7,140.0,133.3,129.2,128.6,127.6,127.3,122.4,117.7$, 113.6, 64.7, 62.5, 51.0, 31.5, 28.6, 28.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3322$ (w), 2962 (w), 1656 (s), 1597 (m), 1538 (m), 1505 (s), 1366 (m), 1260 (m), 1021 (m), 747 (s), 690 (m).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{21}{ }^{79} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 401.1223; found: 401.1226 and calcd for $\mathrm{C}_{21}{ }^{81} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 403.1203; found: 403.1200.

## 5-(3-Bromophenyl)-N-(tert-butyl)-1-phenylpyrrolidine-2-carboxamide (cis-6.18e)



Procedure: GP 6-5 from homopropargylamine 6.134e
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $36 \%$ ( 29 mg ), light yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.41(\mathrm{~s}, 1 \mathrm{H}), 7.34(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.23-7.10(\mathrm{~m}, 4 \mathrm{H}), 6.79-6.75(\mathrm{~m}$, $2 \mathrm{H}), 6.52(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.58(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.99(\mathrm{dd}, J=8.0,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.37-2.17(\mathrm{~m}, 3 \mathrm{H})$, 1.82 (ddd, $J=17.3,12.2,7.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.31 (s, 9H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.6,147.7,146.1,130.5,130.4,129.1,128.6,124.5,123.2,119.3$, 114.6, 68.6, 66.0, 51.1, 35.5, 29.9, 28.7.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3385$ (w), 2967 (w), 1673 (m), 1598 (m), 1499 (s), 909 (m), 752 (s), 731 (s), 693 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21}{ }^{79} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 401.1223$; found: 401.1227 and calcd for $\mathrm{C}_{21}{ }^{81} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 403.1203; found: 403.1199.

5-(3-Bromophenyl)-N-(tert-butyl)-1-phenylpyrrolidine-2-carboxamide (trans-6.18e)


Procedure: GP 6-5 from homopropargylamine 6.134e
Conditions: $40{ }^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $54 \%$ ( 43 mg ), white solid.

MP: $155-157^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.26(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.19(\mathrm{~m}, 1 \mathrm{H}), 7.08-7.01(\mathrm{~m}, 3 \mathrm{H}), 6.81(\mathrm{~d}, J=7.7$ $\mathrm{Hz}, 1 \mathrm{H}), 6.64(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.38(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 5.82(\mathrm{~s}, 1 \mathrm{H}), 5.02(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.25(\mathrm{~d}$, $J=9.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.44-2.25(\mathrm{~m}, 2 \mathrm{H}), 2.10-2.04(\mathrm{~m}, 1 \mathrm{H}), 1.84-1.79(\mathrm{~m}, 1 \mathrm{H}), 1.19(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 172.2,145.0,143.9,130.10,130.07,129.1,124.6,122.8,117.7,113.7$, 64.3, 62.3, 50.9, 33.4, 28.5, 28.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3293$ (w), 2971 (w), 1652 ( s$), 1598$ (m), 1556 (m), 1504 (s), 1355 (s), 1260 (m), 1205 (m), 748 (s), 697 ( $s$ ).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21}{ }^{79} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 401.1223; found: 401.1225 and calcd for $\mathrm{C}_{21}{ }^{81} \mathrm{BrH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 403.1203$; found: 403.1202.

## $N$-(tert-butyl)-1-(4-methoxyphenyl)-5-phenylpyrrolidine-2-carboxamide (cis-6.18f)



Procedure: GP 6-5 from homopropargylamine 6.134f

Conditions: 50 mol\% catalyst loading, $22{ }^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $24 \%$ ( 17 mg ), yellow oil.
${ }^{1}{ }^{\mathbf{H}}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.31-7.19(\mathrm{~m}, 5 \mathrm{H}), 7.01(\mathrm{~s}, 1 \mathrm{H}), 6.68(\mathrm{~d}, \mathrm{~J}=9.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.48(\mathrm{~d}, \mathrm{~J}=9.1$ $\mathrm{Hz}, 2 \mathrm{H}$ ), 4.56 (dd, $J=8.3,6.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{dd}, J=8.8,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.65(\mathrm{~s}, 3 \mathrm{H}), 2.33$ (dtd, $J=12.0$, $6.4,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.23$ (ddd, $J=10.2,6.4,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.16(\mathrm{ddt}, J=12.6,7.2,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.86-1.79$ (m, 1H), $1.30(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 173.2,152.9,143.5,142.2,128.9,127.1,125.6,115.7,114.4,69.2$, $66.5,55.6,50.9,35.7,30.1,28.7$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3372$ (w), 2965 (w), 1674 (m), 1509 (s), 1244 (s), 1036 (m), 822 (m), 731 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{2}[\mathrm{M}+\mathrm{Na}]^{+}$375.2043; found: 375.2040.

## N-(tert-butyl)-1-(4-methoxyphenyl)-5-phenylpyrrolidine-2-carboxamide (trans-6.18f)



Procedure: GP 6-5 from homopropargylamine 6.134f
Conditions: 50 mol\% catalyst loading, $22{ }^{\circ} \mathrm{C}$ for 2 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $24 \%$ ( 17 mg ), yellow oil.
${ }^{1} \mathbf{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.20-7.16(\mathrm{~m}, 2 \mathrm{H}), 7.11(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.93(\mathrm{~d}, \mathrm{~J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.63$ $(\mathrm{d}, J=9.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.33(\mathrm{~d}, J=9.1 \mathrm{~Hz}, 2 \mathrm{H}), 5.99(\mathrm{~s}, 1 \mathrm{H}), 5.04(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.19(\mathrm{~d}, J=9.1 \mathrm{~Hz}$, $1 \mathrm{H}), 3.62(\mathrm{~s}, 3 \mathrm{H}), 2.42-2.27(\mathrm{~m}, 2 \mathrm{H}), 2.05-2.00(\mathrm{~m}, 1 \mathrm{H}), 1.83-1.79(\mathrm{~m}, 1 \mathrm{H}), 1.20(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.9,151.6,142.5,138.6,128.5,126.7,126.1,114.6,114.4,64.7$, 63.0, 55.5, 50.8, 33.6, 28.6, 28.2.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3370$ (w), 1674 (m), 1511 (s), 1244 (s), 1036 (m), 732 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 353.2224; found: 353.2223.
N -(tert-butyl)-1-(4-chlorophenyl)-5-phenylpyrrolidine-2-carboxamide ( 6.18 g )


Procedure: GP 6-5 from homopropargylamine 6.134g

Conditions: $50^{\circ} \mathrm{C}$ for 18 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $93 \%(66 \mathrm{mg})$ as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.29(\mathrm{t}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.24-7.17(\mathrm{~m}, 5 \mathrm{H}), 7.12(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.03$ (d, J = $9.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), $6.97(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.91(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.76(\mathrm{~s}, 1 \mathrm{H}), 6.43(\mathrm{~d}, J=9.1 \mathrm{~Hz}$, $2 \mathrm{H}), 6.30(\mathrm{~d}, J=9.1 \mathrm{~Hz}, 2 \mathrm{H}), 5.85(\mathrm{~s}, 1 \mathrm{H}), 5.04(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.58(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.19(\mathrm{~d}, \mathrm{~J}=$ $9.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.93(\mathrm{dd}, J=8.6,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.44-1.81(\mathrm{~m}, 8 \mathrm{H}), 1.28(\mathrm{~s}, 9 \mathrm{H}), 1.21(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{\text {C NMR ( }}$ ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.5,172.1,146.4,143.0,142.8,141.6,129.0,128.9,128.8,128.6$, $127.3,127.0,125.9,125.5,124.0,122.3,115.7,114.7,68.7,66.2,64.6,63.0,51.02,50.95,35.5$, 33.6, 30.0, 28.6, 28.5, 28.1.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3290(\mathrm{w}), 2969(\mathrm{w}), 2872(\mathrm{w}), 1656(\mathrm{~m}), 1597(\mathrm{~m}), 1547(\mathrm{~m}), 1494(\mathrm{~s}), 1345(\mathrm{~m}), 1259$ (m), 811 (s), 702 (s).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{21} \mathrm{ClH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 357.1728; found: 357.1728.

## N-(tert-butyl)-1-(3-chlorophenyl)-5-phenylpyrrolidine-2-carboxamide (6.18h)



Procedure: GP 6-5 from homopropargylamine 6.134h
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $86 \%(61 \mathrm{mg})$, as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.32-7.18(\mathrm{~m}, 7 \mathrm{H}), 7.13(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.99(\mathrm{t}, \mathrm{J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.95-$ $6.91(\mathrm{~m}, 3 \mathrm{H}), 6.71-6.69(\mathrm{~m}, 2 \mathrm{H}), 6.57(\mathrm{dd}, J=7.9,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.52(\mathrm{t}, \mathrm{J}=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.40-6.38(\mathrm{~m}$, $2 \mathrm{H}), 6.25(\mathrm{dd}, J=8.3,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.80(\mathrm{~s}, 1 \mathrm{H}), 5.04(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.61(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.22$ (d, J = 9.2 Hz, 1H), 3.96 (dd, J=8.4, 4.3 Hz, 1H), 2.44-2.15 (m, 5H), 2.05 (dd, J = 12.1, 5.9 Hz, 1H), 1.91-1.81 (m, 2H), 1.29 (s, 9H), 1.21 (s, 9H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.3,171.8,149.0,145.5,142.7,141.6,134.83,134.81,130.0,129.9$, $129.0,128.6,127.4,127.0,125.9,125.5,118.9,117.4,114.6,113.5,112.7,112.0,68.5,66.2,64.4$, 62.9, 51.11, 51.05, 35.4, 33.5, 30.0, 28.6, 28.5, 28.0.

IR: $u\left(\mathrm{~cm}^{-1}\right) 3291$ (w), 2975 (w), 1656 ( s$), 1594$ ( s$), 1558$ ( s$), 1487$ ( s$), 1357$ (m), 1226 (m), 1005 (w), 827 (w), 750 (m), 700 (s), 679 (s).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{21} \mathrm{ClH}_{26} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 357.1728; found: 357.1720.

## N-(tert-butyl)-5-phenyl-1-(o-tolyl)pyrrolidine-2-carboxamide (cis-6.18i)



Procedure: GP 6-5 from homopropargylamine 6.134i
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $55 \%$ ( 37 mg ), yellow oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 7.16-7.07(\mathrm{~m}, 5 \mathrm{H}), 6.98(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 6.94(\mathrm{~d}, \mathrm{~J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.88$ (d, J = 7.4 Hz, 1H), 6.77 (t, J=7.7 Hz, 1H), 5.77 (s, 1H), 5.02 (t, J = 6.7 Hz, 1H), 4.50 (t, J=7.1 Hz, 1H), $2.53(\mathrm{~m}, 2 \mathrm{H}), 2.31(\mathrm{~s}, 3 \mathrm{H}), 2.16-1.92(\mathrm{~m}, 2 \mathrm{H}), 1.06(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.6,144.2,143.0,131.1,130.4,128.1,126.9,126.8,126.3,122.4$, 121.0, 65.8, 65.1, 50.4, 35.4, 30.0, 28.3, 19.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2965$ (w), 1662 (m), 1516 (m), 1491 (m), 1453 (m), 1262 (w), 910 (w), 734 (s), 700 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 337.2274$; found: 337.2268 .

## 1-Benzyl-N-(tert-butyl)-5-phenylpyrrolidine-2-carboxamide (cis-6.18j)



Procedure: GP 6-5 from homopropargylamine 6.134k
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 21\% (14 mg), colorless oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 7.35-7.01(\mathrm{~m}, 11 \mathrm{H}), 3.79-3.75(\mathrm{~m}, 1 \mathrm{H}), 3.74(\mathrm{~d}, \mathrm{~J}=12.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.35$ (d, $J=12.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.29(\mathrm{dd}, J=10.6,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.25-2.14(\mathrm{~m}, 1 \mathrm{H}), 2.01-1.95(\mathrm{~m}, 2 \mathrm{H}), 1.67-1.56$ (m, 1H), 1.04 (s, 9H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 173.7,142.7,137.9,129.6,128.7,128.5,127.5,127.4,127.3,71.0$, 67.3, 58.2, 49.9, 34.7, 30.3, 28.4.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3338$ (w), 2964 (w), 1672 (m), 1510 (m), 1454 (m), 1229 (m), 760 (m), 700 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 337.2274; found: 337.2279.
1-Benzyl-N-(tert-butyl)-5-phenylpyrrolidine-2-carboxamide (trans-6.18j)

trans-6.18j
Procedure: GP 6-5 from homopropargylamine 6.134k
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 21\% (14 mg), colorless oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 7.28-7.08(\mathrm{~m}, 10 \mathrm{H}), 6.38(\mathrm{~s}, 1 \mathrm{H}), 4.27(\mathrm{dd}, J=7.5,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.62-$ $3.46(\mathrm{~m}, 3 \mathrm{H}), 2.47-2.22(\mathrm{~m}, 2 \mathrm{H}), 1.88(\mathrm{ddt}, J=12.5,8.8,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.73(\mathrm{ddt}, J=12.4,8.9,3.4 \mathrm{~Hz}$, 1H), 1.22 ( $\mathrm{s}, 9 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 174.0,142.7,139.5,128.43,128.36,128.3,127.7,127.0,126.9,66.6$, 66.2, 53.0, 50.5, 32.8, 28.9, 28.7.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3328$ (w), 2962 (w), 1662 (m), 1513 (m), 1453 (m), 1363 (w), 1224 (m), 756 (m), 700 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 337.2274; found: 337.2268.

## $N^{2}$-(tert-butyl)- $N^{5}$,1-diphenylpyrrolidine-2,5-dicarboxamide (6.18m)



Procedure: GP 6-5 from homopropargylamine 6.134j
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $69 \%(50 \mathrm{mg})$, as a mixture of diastereoisomers of cis/trans in a ratio of 2.2:1.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 10.89(\mathrm{~s}, 2.2 \mathrm{H}), 7.77-6.92(\mathrm{~m}, 23.8 \mathrm{H}), 6.85(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.78(\mathrm{t}, \mathrm{J}=$ $7.3 \mathrm{~Hz}, 2.2 \mathrm{H}), 6.66(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.54(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 4 \mathrm{H}), 6.12(\mathrm{~s}, 2.2 \mathrm{H}), 5.51(\mathrm{~s}, 1 \mathrm{H}), 4.47(\mathrm{~d}, J=$ $8.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.32-4.29(\mathrm{~m}, 2.2 \mathrm{H}), 4.12-4.08(\mathrm{~m}, 2.2 \mathrm{H}), 2.53-2.11(\mathrm{~m}, 12.8 \mathrm{H})$, $1.44(\mathrm{~s}, 19.8 \mathrm{H}), 1.24(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.6,172.7,171.3,171.0,144.9,143.8,138.7,136.9,129.8,129.4$, $129.0,128.7,124.8,123.8,120.2,119.7,119.3,118.1,113.4,112.1,65.4,64.02,63.99,63.8,52.0$, 51.3, 30.79, 30.75, 29.6, 29.4, 28.7, 28.5.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3281$ (w), 2972 (w), 1655 (m), 1598 (s), 1501 (s), 1444 (m), 1343 (m), 908 (m), 729 (s), 691 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{~N}_{3} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 366.2176$; found: 366.2176.


Procedure: GP 6-5 from homopropargylamine 6.47
Conditions: $50^{\circ} \mathrm{C}$ for 96 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 47\% (23 mg), white solid.

MP: $97-99^{\circ} \mathrm{C}$.
${ }^{1} \mathbf{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.28-7.24(\mathrm{~m}, 2 \mathrm{H}), 6.81(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.63(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.35$ $(\mathrm{s}, 1 \mathrm{H}), 3.86-3.83(\mathrm{~m}, 1 \mathrm{H}), 3.64-3.60(\mathrm{~m}, 1 \mathrm{H}), 3.20(\mathrm{td}, J=9.6,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.22(\mathrm{~m}, 2 \mathrm{H}), 2.05-1.90$ ( $\mathrm{m}, 2 \mathrm{H}$ ), $1.29(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $\left.100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 173.0,147.6,129.2,118.1,113.1,65.3,50.7,49.7,31.4,28.6,24.2$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3266$ (w), 3074 (w), 2963 (w), 1645 (s), 1599 (m), 1554 (s), 1506 (s), 1358 (s), 1262 (m), 995 (w), 746 (s), 691 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$247.1805; found: 247.1804.
$N$-(tert-butyl)-5,5-dimethyl-1-phenylpyrrolidine-2-carboxamide (6.18l)


Procedure: GP 6-5 from homopropargylamine 6.142
Conditions: $50^{\circ} \mathrm{C}$ for 48 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $65 \%$ ( 35 mg ), yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.22(\mathrm{t}, \mathrm{J}=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.81-6.79(\mathrm{~m}, 3 \mathrm{H}), 6.40(\mathrm{~s}, 1 \mathrm{H}), 4.00(\mathrm{dd}, \mathrm{J}=8.7$, $3.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.33(\mathrm{~m}, 1 \mathrm{H}), 2.05-1.82(\mathrm{~m}, 3 \mathrm{H}), 1.60(\mathrm{~s}, 3 \mathrm{H}), 1.30(\mathrm{~s}, 3 \mathrm{H}), 1.22(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.3,145.2,128.9,118.7,116.9,66.8,62.8,50.4,42.2,29.7,28.5$, 27.9, 23.6.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3293$ (w), 2967 (w), 1657 (s), 1543 (m), 1504 (s), 1342 (s), 1186 (m), 741 (s), 690 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$275.2118; found: 275.2114 .
N-cyclohexyl-1,5-diphenylpyrrolidine-2-carboxamide (6.18q)


Procedure: GP 6-5 from homopropargylamine 6.134a
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $80 \%$ ( 56 mg ), as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 7.29-7.07(\mathrm{~m}, 10 \mathrm{H}), 7.03(\mathrm{t}, \mathrm{J}=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 6.95(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.86$ ( $\mathrm{d}, \mathrm{J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), $6.73(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.60(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.54(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.38(\mathrm{~d}, J=$ $7.9 \mathrm{~Hz}, 2 \mathrm{H}), 5.99(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.08(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.64-4.61(\mathrm{~m}, 1 \mathrm{H}), 4.36(\mathrm{~d}, J=8.2 \mathrm{~Hz}$, $1 \mathrm{H}), 4.10(\mathrm{dd}, J=7.5,4.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.84-3.67(\mathrm{~m}, 2 \mathrm{H}), 2.38-2.21(\mathrm{~m}, 5 \mathrm{H}), 2.09-2.06(\mathrm{~m}, 1 \mathrm{H}), 1.86-$ $1.75(\mathrm{~m}, 5 \mathrm{H}), 1.68-1.64(\mathrm{~m}, 1 \mathrm{H}), 1.57-1.45(\mathrm{~m}, 6 \mathrm{H}), 1.31-1.20(\mathrm{~m}, 4 \mathrm{H}), 1.12-0.99(\mathrm{~m}, 5 \mathrm{H}), 0.88-0.79$ ( $\mathrm{m}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.5,172.1,148.0,144.2,143.4,142.1,129.01,128.96,128.9,128.5$, $127.2,126.8,126.0,125.6,118.9,117.4,114.6,113.7,68.1,66.3,63.8,62.7,47.8$ (2C), 35.6, 33.5, $33.0,32.88,32.85,32.6,30.0,28.1,25.4,25.3,24.7,24.6,24.48,24.46$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3389$ (w), 3303 (w), 2931 (w), 2853 (w), 1651 (m), 1597 (m), 1501 (s), 1343 (m), 909 (m), 730 (s), 700 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 349.2274; found: 349.2281.

## N -(4-methoxyphenyl)-1,5-diphenylpyrrolidine-2-carboxamide (6.18r)



Procedure: GP 6-5 from homopropargylamine 6.134a
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $72 \%(53 \mathrm{mg})$, as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.72(\mathrm{~s}, 1 \mathrm{H}), 7.85(\mathrm{~s}, 1 \mathrm{H}), 7.40-7.04(\mathrm{~m}, 16 \mathrm{H}), 6.96(\mathrm{~d}, \mathrm{~J}=7.1 \mathrm{~Hz}, 2 \mathrm{H})$, 6.80-6.74 (m, 5H), 6.65-6.62 (m, 3H), $6.47(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 5.20(\mathrm{~d}, \mathrm{~J}=6.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.72-4.69(\mathrm{~m}$, $1 \mathrm{H}), 4.46(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.22(\mathrm{t}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.71(\mathrm{~s}, 3 \mathrm{H}), 3.69(\mathrm{~s}, 3 \mathrm{H}), 2.46-1.89(\mathrm{~m}, 8 \mathrm{H})$.
${ }^{13}{ }^{2}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.62,171.59,156.7,156.5,148.0,144.2,143.1,141.8,130.6,130.2$, $129.3,129.2,129.1,128.6,127.4,126.9,126.1,125.6,122.2,121.2,119.5,117.9,114.9,114.2$, 114.1, 113.9, 68.7, 66.5, 64.2, 63.0, 55.48, 55.46, 35.5, 33.6, 30.1, 28.3.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3306$ (w), 2951 (w), 1667 (m), 1597 (m), 1510 (s), 1245 (s), 1170 (m), 909 (m), 828 (m), 730 ( s ), 693 ( s ).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 373.1911$; found: 373.1915 .

## N -mesityl-1,5-diphenylpyrrolidine-2-carboxamide (6.18s)



Procedure: GP 6-5 from homopropargylamine 6.134a
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $72 \%$ ( 55 mg ), colorless oil, as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $8.20(\mathrm{~s}, 1 \mathrm{H}), 7.46(\mathrm{~s}, 1 \mathrm{H}), 7.35-7.25(\mathrm{~m}, 4 \mathrm{H}), 7.25-7.18(\mathrm{~m}, 3 \mathrm{H}), 7.17-$ $7.11(\mathrm{~m}, 3 \mathrm{H}), 7.08(\mathrm{dd}, J=8.5,7.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.02-6.96(\mathrm{~m}, 2 \mathrm{H}), 6.82(\mathrm{~s}, 2 \mathrm{H}), 6.81-6.75(\mathrm{~m}, 3 \mathrm{H})$, $6.69(\mathrm{dt}, J=7.8,1.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.65(\mathrm{tt}, J=7.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.55(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 5.21(\mathrm{~d}, J=7.5 \mathrm{~Hz}$, $1 \mathrm{H}), 4.73(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.58(\mathrm{dd}, J=9.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.31(\mathrm{dd}, J=8.4,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.67-2.55$ $(\mathrm{m}, 1 \mathrm{H}), 2.55-2.41(\mathrm{~m}, 2 \mathrm{H}), 2.41-2.29(\mathrm{~m}, 2 \mathrm{H}), 2.28-2.20(\mathrm{~m}, 1 \mathrm{H}), 2.19(\mathrm{~s}, 3 \mathrm{H}), 2.16(\mathrm{~s}, 3 \mathrm{H}), 2.07$ $(\mathrm{s}, 6 \mathrm{H}), 2.05-1.99(\mathrm{~m}, 1 \mathrm{H}), 1.97(\mathrm{~s}, 6 \mathrm{H}), 1.96-1.91(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.3,171.9,148.1,144.2,143.3,142.0,137.1,135.1,135.0,130.7$, $130.5,129.3,129.1,129.0,128.6,127.3,127.0,126.1,125.5,119.4,117.9,115.1,114.2,68.2,67.0$, $63.9,62.8,35.8,33.7,30.4,28.4,20.9,18.6,18.4$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3247$ (w), 2921 (w), 1662 (m), 1599 (m), 1504 (s), 1452 (w), 1341 (m), 849 (w), 749 (s), 703 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 385.2274; found: 385.2291.

## $N$-(2,6-dimethylphenyl)-1,5-diphenylpyrrolidine-2-carboxamide (6.18t)



Procedure: GP 6-5 from homopropargylamine 6.134a
Conditions: $40{ }^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $72 \%$ ( 53 mg ), colorless oil, as a mixture of diastereoisomers of cis/trans in a ratio of 0.6:1.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathbf{~ M H z}, \mathrm{CDCl}_{3}$ ) $8.35(\mathrm{~s}, 0.6 \mathrm{H}), 7.62(\mathrm{~s}, 1 \mathrm{H}), 7.44-7.33(\mathrm{~m}, 2.6 \mathrm{H}), 7.33-7.26(\mathrm{~m}, 2.6 \mathrm{H})$, $7.25-7.19(\mathrm{~m}, 2 \mathrm{H}), 7.16(\mathrm{dd}, \mathrm{J}=8.5,7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.12-6.99(\mathrm{~m}, 7.4 \mathrm{H}), 6.86(\mathrm{tt}, \mathrm{J}=7.3,1.0 \mathrm{~Hz}$,
$0.6 \mathrm{H}), 6.77(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 0.6 \mathrm{H}), 6.72(\mathrm{tt}, J=7.3,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.63(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 5.29(\mathrm{~d}, J=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 4.81(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 0.6 \mathrm{H}), 4.67(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.39(\mathrm{dd}, J=8.4,4.3 \mathrm{~Hz}, 0.6 \mathrm{H}), 2.78-2.62$ $(\mathrm{m}, 1 \mathrm{H}), 2.61-2.47(\mathrm{~m}, 1.2 \mathrm{H}), 2.47-2.39(\mathrm{~m}, 1.2 \mathrm{H}), 2.32(\mathrm{dd}, \mathrm{J}=13.1,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{~s}, 3.6 \mathrm{H})$, $2.15-1.99(m, 2 H), 2.09(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.3,172.0,148.3,144.3,143.4,142.1,135.6,135.5,133.3,129.5$, $129.3,129.2,128.8,128.5,128.5,127.6,127.5,127.4,127.1,126.3,125.6,119.6,118.1,115.3$, $114.3,68.4,67.1,64.0,63.0,35.9,33.9,30.5,28.5,25.0,18.9,18.7$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3249$ (w), 2919 (w), 1661 (m), 1602 (m), 1501 (s), 1456 (w), 1348 (m), 854 (w), 743 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 371.2118; found: 371.2120.

## 1-benzyl- $N$-(tert-butyl)-4,4-dimethylpyrrolidine-2-carboxamide (6.18n)



Procedure: GP 6-5 from homopropargylamine 6.148
Conditions: $50{ }^{\circ} \mathrm{C}$ for 48 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $78 \%$ (50 mg), yellow oil.
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 7.38(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.37-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.30-7.24(\mathrm{~m}, 3 \mathrm{H}), 3.84(\mathrm{~d}, \mathrm{~J}=$ $13.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.43(\mathrm{~d}, J=13.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.17(\mathrm{dd}, J=10.3,5.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.76(\mathrm{dd}, J=9.1,1.1 \mathrm{~Hz}, 1 \mathrm{H})$, $2.24(\mathrm{~d}, J=9.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.08(\mathrm{dd}, J=13.1,10.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.67(\mathrm{ddd}, J=13.1,5.8,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.30(\mathrm{~s}$, $9 \mathrm{H}), 1.06(\mathrm{~s}, 3 \mathrm{H}), 1.02(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.7,139.1,128.7,128.6,127.4,68.9,67.5,60.4,50.2,45.1,37.7$, 28.8, 28.7, 27.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3331$ (w), 2960 (w), 1667 (m), 1519 (m), 1450 (m), 1228 (m), 761 (m), 708 (s).
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{18} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 289.2274; found: 289.2276.
N -(tert-butyl)-4,4-dimethyl-1,5-diphenylpyrrolidine-2-carboxamide (6.180)


Procedure: GP 6-5 from homopropargylamine 6.152

Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $72 \%(50 \mathrm{mg})$, as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.40-7.27(\mathrm{~m}, 7 \mathrm{H}), 7.19-7.11(\mathrm{~m}, 4 \mathrm{H}), 7.09-7.03(\mathrm{~m}, 2 \mathrm{H}), 6.78(\mathrm{tt}, \mathrm{J}$ $=7.3,1.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.63(\mathrm{tt}, J=7.4,1.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.58(\mathrm{dt}, J=7.8,1.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.47(\mathrm{dt}, J=7.4,1.1 \mathrm{~Hz}$, $2 \mathrm{H}), 6.15(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.67(\mathrm{~s}, 1 \mathrm{H}), 4.42(\mathrm{dd}, J=10.8,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.27(\mathrm{~s}, 1 \mathrm{H}), 4.07(\mathrm{dd}, J=8.0,6.9 \mathrm{~Hz}$, 1 H ), 2.41 (dd, $J=13.4,10.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.24(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.23(\mathrm{~d}, J=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.10(\mathrm{dd}, J=$ $13.4,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.37(\mathrm{~s}, 9 \mathrm{H}), 1.35(\mathrm{~s}, 3 \mathrm{H}), 1.25(\mathrm{~s}, 9 \mathrm{H}), 1.15(\mathrm{~s}, 3 \mathrm{H}), 0.64(\mathrm{~s}, 3 \mathrm{H}), 0.62(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.8,172.3,148.5,145.2,141.8,140.6,129.1,128.8,128.7,127.5$, $127.0,126.9,119.0,117.7,115.1,114.5,77.6,74.8,66.0,64.3,51.1,51.0,43.6,42.3,42.2,41.8$, 30.1, 28.8, 28.6, 26.3, 24.4.

IR: $\mathrm{u}\left(\mathrm{cm}^{-1}\right) 3309$ (w), 2979 (w), 1650 (s), 1541 (s), 1508 (s), 1345 (s), 1221 (s), 749 (s).
HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{23} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right]^{+}\right.$: 351.5431; found: 351.5434.

## $N$-(tert-butyl)-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole-3-carboxamide (6.18p)



Procedure: GP 6-5 from homopropargylamine 6.154
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $78 \%(40 \mathrm{mg})$, as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.

The analytical data were in accordance with those reported in the literature. ${ }^{578}$
cis-N-(tert-butyl)-4-hydroxy-1-phenylpyrrolidine-2-carboxamide (6.18v)


Procedure: GP 6-5 from homopropargylamine 6.172a
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash chromatography (pure EtOAc). Yield: $34 \%$ ( 17 mg ), isolated as a white solid.

MP: $162-164{ }^{\circ} \mathrm{C}$.

[^219]${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.27-7.23(\mathrm{~m}, 2 \mathrm{H}), 6.80(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.62(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.59$ (br s, 1H), $4.56(\mathrm{t}, \mathrm{J}=4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{dd}, J=10.3,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.65(\mathrm{dd}, J=10.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.37$ (dd, J = 10.2, 3.9 Hz, 1H), 3.25 (br s, 1H), 2.41 (ddd, J = 14.5, 10.3, 4.4 Hz, 1H), 2.27-2.23 (m, 1H), $1.32(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 173.7,147.3,129.2,117.9,112.8,70.4,64.2,57.8,50.9,39.6,28.5$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3307$ (w), 2970 (w), 1738 (w), 1647 (m), 1599 (m), 1503 (m), 1363 (s), 1218 (s), 1089 (m), 746 (s), 693 (m), 690 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 263.1754; found: 263.1758 .

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cis-N-(tert-butyl)-4-((tert-butyldimethylsilyl)oxy)-1-phenylpyrrolidine-2-carboxamide (6.18w)
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Procedure: GP 6-5 from homopropargylamine 6.173a
Conditions: $40^{\circ} \mathrm{C}$ for 24 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $80 \%$ (only one diastereoisomer cis), isolated as a white solid.

MP: $146-147{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.28-7.24(\mathrm{~m}, 2 \mathrm{H}), 6.82(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.63(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.54$ (br s, 1H), $4.50(\mathrm{t}, \mathrm{J}=4.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{dd}, J=10.8,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.53(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.32(\mathrm{dd}, J=$ $9.9,4.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.44 (ddd, J = 13.9, 10.8, $4.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.24-2.20 (m, 1H), $1.29(\mathrm{~s}, 9 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H})$, $0.11(\mathrm{~s}, 3 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.9,147.7,129.1,118.2,113.2,71.1,64.8,58.8,50.5,39.7,28.4$, 25.9, 18.3, -4.7, -4.8.

IR: $v\left(\mathrm{~cm}^{-1}\right) 3388$ (w), 2954 (m), 2930 (m), 2856 (w), 2360 (s), 2343 (m), 1676 (s), 1600 (s), 1519 (m), 1503 (s), 1025 (m), 837 (s), 752 (m), 692 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{37} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{Si}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 377.2619 ; found: 377.2620.
cis-N-(tert-butyl)-4-((tert-butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)pyrrolidine-2-
carboxamide (6.18x)


Procedure: GP 6-5 from homopropargylamine 6.173b
Conditions: $30^{\circ} \mathrm{C}$ for 48 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ). Yield: $62 \%$ (only one diastereoisomer cis), isolated as a yellow oil.
${ }^{1} \mathbf{H}^{\text {NMR }}\left(\mathbf{4 0 0} \mathbf{~ M H z}\right.$, CDCl $\left._{3}\right) \delta 6.84(\mathrm{~d}, \mathrm{~J}=9.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.66(\mathrm{br} \mathrm{s}, 1 \mathrm{H}) 6.59(\mathrm{~d}, \mathrm{~J}=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 4.49(\mathrm{t}, \mathrm{J}$ $=4.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.77-3.76(\mathrm{~m}, 4 \mathrm{H}), 3.50(\mathrm{~d}, \mathrm{~J}=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.27(\mathrm{dd}, J=9.8,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.45$ (ddd, J = $15.3,10.9,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{~d}, \mathrm{~J}=14.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.29(\mathrm{~s}, 9 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 3 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.0,152.6,142.2,114.7,114.3,71.2,65.4,59.3,55.8,50.5,39.8$, 28.5, 25.9, 18.3, -4.7, -4.8.

IR: ט ( $\mathrm{cm}^{-1}$ ) 3392 (w), 2955 (w), 2929 (w), 2856 (w), 1674 (m), 1516 (m), 1495 (s), 1352 (m), 1226 (m), 1094 (s), 1023 (s), 839 (s), 811 (s), 779 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{39} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 407.2724$; found: 407.2718.
cis-N-(tert-butyl)-4-((tert-butyldimethylsilyl)oxy)-1-(4-chlorophenyl)pyrrolidine-2-carboxamide (6.18y)


Procedure: GP 6-5 from homopropargylamine 6.173c
Conditions: $40{ }^{\circ} \mathrm{C}$ for 48 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: 90\% (only one diastereoisomer cis), isolated as a white solid.

MP: $150-152^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.19(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.53(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.44(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.51(\mathrm{t}, \mathrm{J}$ $=4.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.80(\mathrm{dd}, J=10.8,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.50(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.30(\mathrm{dd}, J=9.9,4.0 \mathrm{~Hz}, 1 \mathrm{H})$, 2.45 (ddd, J = 13.9, 10.8, 4.7 Hz, 1H), 2.21 (dq, J = 13.9, 1.7 Hz, 1H), 1.28 (s, 9H), $0.91(\mathrm{~s}, 9 \mathrm{H}), 0.11$ (s, 3H), $0.10(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.5,146.2,129.0,123.2,114.3,71.2,64.9,58.9,50.6,39.8,28.5$, 25.9, 18.3, -4.7, -4.8.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3392$ (w), 2955 (w), 2929 (w), 2856 (w), 1674 (m), 1516 (m), 1495 (s), 1352 (m), 1226 (m), 1094 (s), 1023 (s), 839 (s), 811 (s), 779 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{36} \mathrm{ClN}_{2} \mathrm{O}_{2} \mathrm{Si}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 411.2229; found: 411.2217.


Procedure: GP 6-5 from homopropargylamine 6.173d
Conditions: $40^{\circ} \mathrm{C}$ for 36 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 8: 1$ ). Yield: $71 \%$ (only one diastereoisomer cis), isolated as a white solid.

MP: $184-186{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.26(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.83(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.64(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 2 \mathrm{H})$, $6.52(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.57(\mathrm{t}, J=4.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.86(\mathrm{dd}, J=10.8,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.60(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.36$ (dd, J = 9.9, $4.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.48 (ddd, $J=14.0,10.8,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.29(\mathrm{~d}, J=13.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.28(\mathrm{~s}, 9 \mathrm{H})$, 1.13-1.07 (m, 21H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.8,147.8,129.1,118.2,113.3,71.0,64.8,59.0,50.5,39.9,28.4$, 18.0, 11.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3273$ (w), 2959 (m), 2943 (m), 2866 (m), 1656 (s), 1505 (m), 1363 (m), 1119 (m), 747 (m), 688 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{42} \mathrm{~N}_{2} \mathrm{NaO}_{2} \mathrm{Si}[\mathrm{M}+\mathrm{Na}]^{+} 441.2908$; found: 441.2905.

## 2-(cis-4-((tert-butyldimethylsilyl)oxy)-1-(4-chlorophenyl)pyrrolidine-2-carboxamido)-2methylpropyl ethyl carbonate (6.18aa)



Procedure: GP 6-5 from homopropargylamine 6.173c
Conditions: $40^{\circ} \mathrm{C}$ for 24 h. Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 5: 1$ ). Yield: $80 \%$ (only one diastereoisomer cis), isolated as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.20-7.17(\mathrm{~m}, 2 \mathrm{H}), 6.62(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 6.57-6.53(\mathrm{~m}, 2 \mathrm{H}), 4.52-4.49(\mathrm{~m}$, $1 \mathrm{H}), 4.38(\mathrm{~d}, J=10.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.14-4.01(\mathrm{~m}, 3 \mathrm{H}), 3.82(\mathrm{dd}, J=10.7,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.49(\mathrm{~d}, J=9.9 \mathrm{~Hz}$, 1 H ), 3.30 (dd, $J=9.9,4.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.44 (ddd, $J=13.8,10.7,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.25-2.21(\mathrm{~m}, 1 \mathrm{H}), 1.37$ (s, $3 \mathrm{H}), 1.27(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H}), 0.91(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 3 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 173.0, 155.1, 146.2, 129.0, 123.2, 114.4, 71.6, 71.1, 64.8, 64.2, 58.9, $52.8,39.8,25.9,24.4,23.2,18.4,14.2,-4.7,-4.8$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2954$ (w), 2931 (w), 2855 (w), 1747 (m), 1676 (m), 1496 (m), 1375 (w), 1256 (s), 1094 (m), 1018 (m), 837 (m), 812 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{39} \mathrm{ClN}_{2} \mathrm{NaO}_{5} \mathrm{Si}[\mathrm{M}+\mathrm{Na}]^{+} 521.2209$; found: 521.2198.
cis-4-((tert-butyldimethylsilyl)oxy)-N-(2-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-1-(4-chlorophenyl)pyrrolidine-2-carboxamide (6.18ab)


Procedure: GP 6-5 from homopropargylamine 6.173c
Conditions: $40^{\circ} \mathrm{C}$ for 12 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 6: 1$ ). Yield: $85 \%$ (only one diastereoisomer cis), isolated as a colorless oil.
${ }^{1}{ }^{\mathbf{H}} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 9.24(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.05(\mathrm{dd}, J=8.0,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.29(\mathrm{td}, J=8.0,1.7 \mathrm{~Hz}$, $1 \mathrm{H}), 7.22-7.18(\mathrm{~m}, 2 \mathrm{H}), 7.11(\mathrm{dd}, \mathrm{J}=7.5,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.04(\mathrm{td}, J=7.4,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.65-6.62(\mathrm{~m}, 2 \mathrm{H})$, 4.57-4.55 (m, 1H), 4.36 (d, J = $12.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.32(\mathrm{~d}, \mathrm{~J}=12.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.17-7.10(\mathrm{~m}, 1 \mathrm{H}), 3.56(\mathrm{~d}, \mathrm{~J}=$ $9.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.42(\mathrm{dd}, J=9.8,4.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.48-2.46(\mathrm{~m}, 2 \mathrm{H}), 0.78(\mathrm{~s}, 9 \mathrm{H}), 0.75(\mathrm{~s}, 9 \mathrm{H}), 0.04(\mathrm{~s}, 3 \mathrm{H})$, $0.01(\mathrm{~s}, 3 \mathrm{H}),-0.15(\mathrm{~s}, 3 \mathrm{H}),-0.18(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.7,146.4,136.2,130.9,129.1,128.1,127.9,124.2,123.5,122.8$, 114.3, 70.9, 64.6, 63.6, 58.8, 40.4, 25.9, 25.7, 18.4, 18.0, -4.8, -5.0, -5.2, -5.4.

IR: $v\left(\mathrm{~cm}^{-1}\right) 3345$ (w), 2954 (w), 2929 (m), 2856 (w), 1686 (m), 1519 (m), 1496 (s), 1454 (m), 1256 (m), 1092 (m), 1058 (m), 1024 (m), 836 (s), 813 (m), 779 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{30} \mathrm{H}_{47} \mathrm{ClN}_{2} \mathrm{NaO}_{3} \mathrm{Si}_{2}[\mathrm{M}+\mathrm{Na}]^{+}$597.2706; found: 597.2702.
trans- N -(tert-butyl)-4-methyl-1-phenylpyrrolidine-2-carboxamide (trans-6.18ac)

trans-6.18ac
Procedure: GP 6-5 from homopropargylamine $\mathbf{6 . 1 8 0}$
Conditions: $40^{\circ} \mathrm{C}$ for 24 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ). Yield: $44 \%$, isolated as a white solid.

MP: $120-122{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.25(\mathrm{dd}, J=8.7,7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.81(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.60(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}$, $2 \mathrm{H}), 6.40(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.86(\mathrm{dd}, \mathrm{J}=9.9,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.67-3.64(\mathrm{~m}, 1 \mathrm{H}), 2.82-2.77(\mathrm{~m}, 1 \mathrm{H}), 2.42-2.35$ $(\mathrm{m}, 1 \mathrm{H}), 2.31-2.27(\mathrm{~m}, 1 \mathrm{H}), 1.85(\mathrm{td}, \mathrm{J}=12.0,10.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.30(\mathrm{~s}, 9 \mathrm{H}), 1.12(\mathrm{~d}, \mathrm{~J}=6.4 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 173.0,147.7,129.2,118.0,112.9,66.0,56.7,50.7,39.2,32.0,28.6$, 16.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 373$ (w), 3312 (w), 2968 (w), 2929 (w), 1738 (m), 1675 (s), 1599 (s), 1500 (s), 1364 (s), 1227 (s), 749 ( s$), 692$ (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 261.1961; found: 261.1963.
cis-N-(tert-butyl)-4-methyl-1-phenylpyrrolidine-2-carboxamide (cis-6.18ac)


Procedure: GP 6-5 from homopropargylamine $\mathbf{6 . 1 8 0}$
Conditions: $40{ }^{\circ} \mathrm{C}$ for 24 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ). Yield: $18 \%$, isolated as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.26-7.22(\mathrm{~m}, 2 \mathrm{H}), 6.80(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.61(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.26$ (br s, 1H), 3.86 (dd, $J=8.5,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.50(\mathrm{dd}, J=9.3,7.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.28$ (dd, J = 9.3, 5.7 Hz, 1H), 2.54 (ddd, $J=12.7,8.5,6.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.36(\mathrm{dq}, J=13.8,6.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.80(\mathrm{dt}, J=13.0,6.6 \mathrm{~Hz}, 1 \mathrm{H})$, $1.27(\mathrm{~s}, 9 \mathrm{H}), 1.15(\mathrm{~d}, \mathrm{~J}=6.9 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.9,147.8,129.1,118.0,113.3,65.4,57.9,50.5,39.2,32.1,28.5$, 19.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3283$ (w), 2962 (w), 2930 (w), 1737 (m), 1655 (s), 1597 (m), 1505 (s), 1363 (s), 1226 (s), 744 (s), 690 ( s ).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 261.1961; found: 261.1963.
8.6.6 AgOAc-catalyzed Cyclization of Primary Homopropargylamines GP 6-6:


To a solution of homopropargylamine 6.251 ( $0.2 \mathrm{mmol}, 1.00$ equiv) in toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.10$ equiv) at room temperature. The resulting mixture was
stirred at $40^{\circ} \mathrm{C}$. After completion of the cyclization (as indicated by TLC, usually around 12 hours), the reaction mixture was cooled to room temperature and isocyanide 1.99 ( $0.24 \mathrm{mmol}, 1.20$ equiv) and carboxylic acid $\mathbf{1 . 1 1 0 ( 0 . 2 4 ~ m m o l , ~} 1.20$ equiv) were added sequentially. The reaction mixture was stirred at room temperature until complete conversion of the intermediate (as indicated by TLC). Saturated aqueous $\mathrm{NaHCO}_{3}$ solution was added and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.259.

## N-(tert-butyl)-5-phenyl-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (6.232c)



Procedure: GP 6-6 from homopropargylamine 6.158
Conditions: room temperature for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}$, PE/EtOAc 1:1). Yield: $97 \%$ ( 69 mg ), brown oil as a mixture of 4 isomers (diastereoisomers and rotamers). The determination of the $d r$ was difficult based on the ${ }^{1} \mathrm{H}$ NMR and the ${ }^{13} \mathrm{C}$ NMR spectra due to the presence of the diastereoisomers and the rotamers. Removal of the $N$-trifluoroacetyl group afforded compound $\mathbf{6 . 2 6 2}$ as a mixture of two diastereoisomers in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.45-6.95(\mathrm{~m}, 5 \mathrm{H}), 6.62,5.72,5.50$ and $5.38(4 \mathrm{~s}, 1 \mathrm{H}), 5.38-5.34$ and 5.15-5.12 (m, 1H), 4.61-4.47 (m, 1H,), 2.74-2.66, 2.41-2.24 and 2.15-1.68 (m, 4H), 1.32, 1.28, 1.27 and $1.17(4 \mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 170.0,169.5,169.2,168.4,158.6(\mathrm{q}, \mathrm{J}=37.4 \mathrm{~Hz}), 158.0(\mathrm{q}, \mathrm{J}=37.8$ Hz ), 157.4 ( $q, J=38.1 \mathrm{~Hz}$ ), $156.2(q, J=36.7 \mathrm{~Hz}$ ), 142.9, 141.5, 141.3, 139.9, 129.0, 128.9, 128.7, $128.1,127.7,127.6,127.5,127.3,126.1,125.2,124.9,116.2(q, J=287.2 \mathrm{~Hz}), 116.1(q, J=287.6$ $\mathrm{Hz}), 64.8,64.3,63.8,63.7,63.7,62.9,62.9,62.4,52.0,51.8,51.7,36.5,35.2,31.6,31.1,31.1,30.3$, 28.8, 28.8, 28.7, 28.6, 25.5, 25.5.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3299$ (w), 2967 (w), 1681 (m), 1633 (s), 1546 (m), 1409 (s), 1361 (m), 1255 (w), 1226 (w), 758 (w), 702 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{22} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 343.3697 ; found: 343.3699 .

## 1-acetyl-N-(tert-butyl)-5-phenylpyrrolidine-2-carboxamide (6.232a)



Procedure: GP 6-6 from homopropargylamine 6.158

Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1). Yield: $94 \%$ ( 58 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.42(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.39-7.16(\mathrm{~m}, 8 \mathrm{H}), 7.12-7.02(\mathrm{~m}, 2 \mathrm{H}), 6.61(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, $5.03(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.75-4.67(\mathrm{~m}, 2 \mathrm{H}), 4.61(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.79-2.62(\mathrm{~m}, 1 \mathrm{H}), 2.59-2.45$ $(\mathrm{m}, 1 \mathrm{H}), 2.45-2.33(\mathrm{~m}, 1 \mathrm{H}), 2.23-1.87(\mathrm{~m}, 3 \mathrm{H}), 1.80(\mathrm{~s}, 3 \mathrm{H}), 1.77(\mathrm{~s}, 3 \mathrm{H}), 1.75-1.66(\mathrm{~m}, 2 \mathrm{H}), 1.37$ (s, 9H), $1.33(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.6,171.6,170.6,170.1,143.3,143.0,129.0,129.0,127.6,127.4$, $126.0,125.3,64.6,63.3,62.1,61.8,51.2,51.1,37.3,35.1,28.9,28.8,25.9,25.1,23.2,22.9$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3299$ (w), 2967 (w), 1681 (m), 1633 (s), 1546 (m), 1409 (s), 1361 (m), 1255 (w), 1226 (w), 758 (w), 702 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 289.3985$; found: 289.3987 .

## 1-benzoyl-N-(tert-butyl)-5-phenylpyrrolidine-2-carboxamide (6.232b)



Procedure: GP 6-6 from homopropargylamine 6.158
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1). Yield: $98 \%$ ( 70 mg ), brown oil as a mixture of 4 isomers (diastereoisomers and rotamers). The determination of the $d r$ was difficult based on the ${ }^{1} \mathrm{H}$ NMR and the ${ }^{13} \mathrm{C}$ NMR spectra due to the presence of the diastereoisomers and the rotamers. Removal of the $N$-benzoyl group afforded compound $\mathbf{6 . 2 6 2}$ as a mixture of two diastereoisomers in a ratio of 1:1. For the two major isomers:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.72(\mathrm{br} \mathrm{s}, 0.5 \mathrm{H}), 7.48-6.78(\mathrm{~m}, 10 \mathrm{H}), 6.66(\mathrm{br} \mathrm{s}, 0.5 \mathrm{H}), 5.02(\mathrm{~d}, \mathrm{~J}=7.9$ $\mathrm{Hz}, 0.5 \mathrm{H}), 4.91(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 0.5 \mathrm{H}), 4.86-4.81(\mathrm{~m}, 1 \mathrm{H}), 2.74-1.76(\mathrm{~m} 4 \mathrm{H}), 1.41$ and 1.36 (two s, 9H).
${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 173.2,172.8,170.3,169.8,143.8,142.7,137.2,136.3,129.9,129.5$, 128.6, 128.5, 128.2, 128.1, 127.2, 127.1, 126.6, 126.4, 126.3, 125.7, 65.7, 64.6, 62.2, 61.9, 51.4, 51.3, 35.7, 35.2, 28.9, 25.3, 25.1.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3299$ (w), 2967 (w), 1681 (m), 1633 (s), 1546 (m), 1409 (s), 1361 (m), 1255 (w), 1226 (w), 758 (w), 702 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 351.4695 ; found: 351.4698.
(2S,4R,5S)-N-(tert-butyl)-4-methyl-5-phenyl-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide (6.259a)


Procedure: GP 6-6 from homopropargylamine 6.251a
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1). Yield: $86 \%$ ( 71 mg ), brown oil as a mixture of 3 major isomers (diastereoisomers and rotamers, 3:1:1). The determination of the $d r$ was difficult based on the ${ }^{1} \mathrm{H}$ NMR and the ${ }^{13} \mathrm{C}$ NMR spectra due to the presence of the diastereoisomers and the rotamers. Removal of the N trifluoroacetyl group afforded a mixture of two diastereoisomers in a ratio of 4:1.
${ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.45(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 0.4 \mathrm{H}), 7-34-7-22(\mathrm{~m}, 3 \mathrm{H}), 7.01(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 0.4 \mathrm{H})$, $6.94(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 1.2 \mathrm{H}) ; 6.32(\mathrm{~s}, 0.2 \mathrm{H}), 5.87(\mathrm{~s}, 0.6 \mathrm{H}), 5.51(\mathrm{~s}, 0.2 \mathrm{H}), 5.26(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 0.2 \mathrm{H}), 5.21$ (d, J = $7.8 \mathrm{~Hz}, 0.6 \mathrm{H}$ ), $5.09(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 0.2 \mathrm{H}), 4.68(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 0.2 \mathrm{H}), 4.59(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 0.6 \mathrm{H})$, 4.32 (dd, J = 9.8, 8.0 Hz, 0.2H), 3.11-2.99 (m, 0.6H), 2.78-2.69 (m, 0.2H), 2.57-2.48 (m, 0.2H), 2.20$1.99(\mathrm{~m}, 1.4 \mathrm{H}), 1.82(\mathrm{td}, \mathrm{J}=9.0,13.0 \mathrm{~Hz}, 0.6 \mathrm{H}), 1.38,1.35,1.34(3 \mathrm{~s}, 9 \mathrm{H}), 0.66,(\mathrm{~d}, \mathrm{~J}=6.7 \mathrm{~Hz}, 0.6 \mathrm{H})$, 0.60 ( $d, J=6.7 \mathrm{~Hz}, 1.8 \mathrm{H}$ ), 0.56 ( $d, J=6.7 \mathrm{~Hz}, 0.6 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 170.3,169.5,168.7,158.2(\mathrm{q}, \mathrm{J}=37.8 \mathrm{~Hz}), 157.4(\mathrm{q}, \mathrm{J}=37.8 \mathrm{~Hz})$, $139.0,138.1,137.8,128.6,128.5,128.4,127.9,127.7,127.6,126.6,126.5,116.2(q, J=287.2 \mathrm{~Hz})$, $116.0(q, J=287.2 \mathrm{~Hz}), 67.3,67.0,66.6,64.0,63.4,62.1,52.0,51.8,51.8,38.8,37.9,37.7,33.7$, 33.0, 28.8, 28.7, 15.2, 15.0, 14.6. Only two sets of signals of $\mathrm{CF}_{3}$ and $\mathrm{COCF}_{3}$ were observed probably because of overlaps or too low signal intensities for the minor isomer due to C-F coupling.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3425$ (w), 3342 (w), 2970 (w), 2935 (w), 2879 (w), 1665 (s), 1545 (w), 1456 (m), 1365 (w), 1223 (s), 1200 (s), 1150 (s), 911 (w), 731 (s), 703 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 357.3967 ; found: 357.3969.

## (2S,4S,5S)-N-(tert-butyl)-4-isopropyl-5-phenyl-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxamide

 (6.259b)

Procedure: GP 6-6 from homopropargylamine 6.251b
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 4:1). Yield: $98 \%(77 \mathrm{mg})$, brown oil as mixture of 2 diastereoisomers in a ratio of 4:1, which was confirmed by the ${ }^{1} \mathrm{H}$ NMR and the ${ }^{13} \mathrm{C}$ NMR spectra of the product after removal of the $N$-trifluoroacetyl group. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.32-7.24(\mathrm{~m}, 3 \mathrm{H}), 7.05-7.03(\mathrm{~m}, 2 \mathrm{H}), 5.84(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.32(\mathrm{~d}, \mathrm{~J}=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 4.58(\mathrm{~d}, \mathrm{~J}=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.71-1.96(\mathrm{~m}, 4 \mathrm{H}), 1.36(\mathrm{~s}, 9 \mathrm{H}), 0.97(\mathrm{~d}, \mathrm{~J}=6.3 \mathrm{~Hz}, 3 \mathrm{H}), 0.75(\mathrm{~d}, \mathrm{~J}=$ $6.5 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 169.2,157.3(\mathrm{q}, \mathrm{J}=37.8 \mathrm{~Hz}), 139.3,128.4,127.9,127.0,115.8(\mathrm{q}, \mathrm{J}=$ $287.5 \mathrm{~Hz}), 65.4,63.1,51.5,47.5,29.8,28.7,27.5,22.0,21.0$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3341$ (w), 2969 (w), 2959 (w), 2879 (w), 1668 (s), 1545 (w), 1456 (w), 1369 (w), 1219 (s), 1200 (s), 1153 (s), 810 (w), 757 (w), 704 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{28} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 385.4507; found: 385.4510.

$$
[\alpha]_{\mathrm{D}}^{20}+39.5^{\circ}\left(\mathrm{c} 0.6, \mathrm{CHCl}_{3}\right) .
$$

(2S,4S,5S)-1-acetyl-N-(tert-butyl)-4-isopropyl-5-phenylpyrrolidine-2-carboxamide (6.259c)


Procedure: GP 6-6 from homopropargylamine 6.251b
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 4: 1$ ). Yield: $99 \%$ ( 66 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:10. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.39-7.22(\mathrm{~m}, 3 \mathrm{H}), 7.24-7.02(\mathrm{~m}, 2 \mathrm{H}), 6.80(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.95(\mathrm{~d}, \mathrm{~J}=7.6$ $\mathrm{Hz}, 1 \mathrm{H}), 4.66(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.67-2.48(\mathrm{~m}, 1 \mathrm{H}), 2.28(\mathrm{dd}, J=12.7,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.98-1.82(\mathrm{~m}$, $1 \mathrm{H}), 1.74(\mathrm{~s}, 3 \mathrm{H}), 1.35(\mathrm{~s}, 9 \mathrm{H}), 0.94(\mathrm{~d}, J=5.9 \mathrm{~Hz}, 3 \mathrm{H}), 0.78(\mathrm{~d}, \mathrm{~J}=6.1 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.7,170.6,140.1,128.7,127.7,127.5,66.3,61.1,51.5,51.1,29.8$, 28.8, 27.7, 23.2, 22.1, 21.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3316$ (w), 2965 (w), 2933 (w), 2872 (w), 1631 (s), 1547 (m), 1412 (s), 1365 (m), 1259 (m), 1224 (m), 923 (w), 910 (w), 731 (s), 706 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{20} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 331.4795; found: 331.4798.
$[\boldsymbol{\alpha}]_{\mathrm{D}}{ }^{20}+29.2^{\circ}\left(\mathrm{c} 0.1, \mathrm{CHCl}_{3}\right)$.
(2S,4S,5S)-1-benzoyl-N-(tert-butyl)-4-isopropyl-5-phenylpyrrolidine-2-carboxamide (6.259d)


Procedure: GP 6-6 from homopropargylamine 6.251b
Conditions: $40^{\circ} \mathrm{C}$ for 30 h . Purification: Flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 2: 1$ ). Yield: $99 \%$ ( 79 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:10. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.25-7.04(\mathrm{~m}, 6 \mathrm{H}), 7.01(\mathrm{~s}, 1 \mathrm{H}), 6.94(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.74-6.58$ $(\mathrm{m}, 2 \mathrm{H}), 5.02(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.93(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.61(\mathrm{dq}, J=13.7,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.50(\mathrm{dd}, J=$ $12.6,6.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), $1.96(\mathrm{td}, \mathrm{J}=12.9,8.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.47-1.33(\mathrm{~m}, 1 \mathrm{H}), 1.40(\mathrm{~s}, 9 \mathrm{H}), 0.88-0.78(\mathrm{~m}$, 6 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.4,170.2,140.4,137.4,129.3,128.1,128.0,127.7,127.1,125.9$, 67.7, 60.9, 51.8, 51.3, 29.5, 28.9, 28.1, 21.8, 21.2.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3320$ (w), 2964 (w), 2931 (w), 2872 (w), 1677 (m), 1623 (m), 1547 (m), 1403 (m), 1366 (m), 1260 (w), 1224 (w), 1029 (w), 910 (w), 730 (s), 700 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 393.5505 ; found: 393.5510.
$[\alpha]_{\mathrm{D}}{ }^{20}+19.2^{\circ}\left(\mathrm{c} 0.1, \mathrm{CHCl}_{3}\right)$.
(2S,4S,5S)-1-acetyl-N-benzyl-4-isopropyl-5-phenylpyrrolidine-2-carboxamide (6.259h)


Procedure: GP 6-6 from homopropargylamine 6.251b
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 1:2). Yield: $95 \%$ ( 69 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:7. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.44-7.19(\mathrm{~m}, 8 \mathrm{H}), 7.16-7.04(\mathrm{~m}, 2 \mathrm{H}), 4.95(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.79$ (d, J = $8.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $4.49(\mathrm{dd}, J=15.0,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.39(\mathrm{dd}, J=15.0,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.63-2.42(\mathrm{~m}, 1 \mathrm{H})$, $2.33(\mathrm{dd}, \mathrm{J}=12.8,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.07-1.83(\mathrm{~m}, 1 \mathrm{H}), 1.73(\mathrm{~s}, 3 \mathrm{H}), 1.41-1.16(\mathrm{~m}, 1 \mathrm{H}), 0.93(\mathrm{~d}, \mathrm{~J}=5.6$ $\mathrm{Hz}, 3 \mathrm{H}), 0.76(\mathrm{~d}, \mathrm{~J}=6.2 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.9,171.6,139.9,138.5,128.8,128.7,127.9,127.6,127.5,127.4$, $66.3,60.5,51.5,43.6,29.9,27.6,23.2,22.2,21.1$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3282$ (w), 2960 (w), 2932 (w), 2871 (w), 1646 (s), 1541 (m), 1454 (m), 1408 (m), 1246 (m), 1030 (w), 910 (w), 730 (s), 704 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 365.2224$; found: 365.2229.
$[\alpha]_{D}{ }^{20}+74.2^{\circ}\left(c 0.2, \mathrm{CHCl}_{3}\right)$.

## methyl 2-((2S,4R,5S)-1-acetyl-4-methyl-5-phenylpyrrolidine-2-carboxamido)-2-benzyl-3phenylpropanoate $(6.259 \mathrm{~g})$



Procedure: GP 6-6 from homopropargylamine 6.251a
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1). Yield: $94 \%$ ( 100 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:10. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $\left.400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.33-7.13(\mathrm{~m}, 11 \mathrm{H}), 7.08(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.97(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H})$, $6.94(\mathrm{~s}, 1 \mathrm{H}), 4.80(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.69(\mathrm{dd}, J=7.2,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.95(\mathrm{~d}, J=14.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.91(\mathrm{~d}, J$ $=14.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 3.32(\mathrm{~d}, J=13.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.22(\mathrm{~d}, J=13.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.70-2.41(\mathrm{~m}, 1 \mathrm{H})$, $1.75-1.58(\mathrm{~m}, 5 \mathrm{H}), 0.51(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.1,171.1,170.7,139.6,136.5,136.2,130.1,129.9,128.6,128.3$, $128.2,127.7,127.0,127.0,126.8,67.0,66.8,60.9,52.6,41.4,41.2,37.2,33.3,22.9,15.1$.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3399$ (w), 3030 (w), 2935 (w), 1737 (w), 1654 (m), 1496 (m), 1455 (w), 1405 (m), 1347 (w), 1222 (m), 1091 (w), 909 (m), 746 (m), 702 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{31} \mathrm{H}_{35} \mathrm{~N}_{2} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 499.6305; found: 499.6306.
$[\alpha]_{D}{ }^{20}-25.7^{\circ}\left(c \quad 0.2, \mathrm{CHCl}_{3}\right)$.
tert-butyl (2-((2S,3R,5S)-5-(tert-butylcarbamoyl)-3-methyl-2-phenylpyrrolidin-1-yl)-2-
oxoethyl)carbamate (6.259e)


Procedure: GP 6-6 from homopropargylamine 6.251a
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 1:1). Yield: $91 \%$ ( 76 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:5. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.39-7.24(\mathrm{~m}, 3 \mathrm{H}), 7.02(\mathrm{~d}, \mathrm{~J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 6.48(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.22(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}), 4.92(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.67(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.94(\mathrm{dd}, J=17.3,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.09(\mathrm{dd}, J=$ $17.3,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.04-2.81(\mathrm{~m}, 1 \mathrm{H}), 2.19(\mathrm{dd}, J=12.9,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.79(\mathrm{td}, J=12.9,8.7 \mathrm{~Hz}, 1 \mathrm{H})$, $1.38(\mathrm{~s}, 9 \mathrm{H}), 1.36(\mathrm{~s}, 9 \mathrm{H}), 0.59(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 170.4,169.6,155.7,138.6,128.9,128.0,126.7,79.6,65.7,61.9,51.4$, 43.7, 37.5, 33.0, 28.8, 28.4, 15.0.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3335$ (w), 2970 (w), 2932 (w), 2876 (w), 1647 (m), 1498 (w), 1455 (m), 1430 (m), 1365 (m), 1254 (m), 1168 (m), 1053 (w), 910 (m), 862 (w), 730 (s), 703 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{3} \mathrm{O}_{4}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 418.2700$; found: 418.2705.
$[\alpha]_{\mathrm{D}}{ }^{20}+42.9^{\circ}\left(\mathrm{co.6}, \mathrm{CHCl}_{3}\right)$.
methyl 2-benzyl-2-((2S,4S,5S)-1-((tert-butoxycarbonyl)glycyl)-4-isopropyl-5-phenylpyrrolidine-2-carboxamido)-3-phenylpropanoate (6.259f)


Procedure: GP 6-6 from homopropargylamine 6.251b
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1). Yield: $90 \%$ ( 129 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:10. For the major isomer:
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl ${ }_{3}$ ) $\delta 7.37-7.13(\mathrm{~m}, 10 \mathrm{H}), 7.12-7.01(\mathrm{~m}, 5 \mathrm{H}), 6.88(\mathrm{~s}, 1 \mathrm{H}), 5.19(\mathrm{~s}, 1 \mathrm{H})$, $4.90(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.67(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.96(\mathrm{~d}, \mathrm{~J}=13.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.90-3.78(\mathrm{~m}, 2 \mathrm{H}), 3.76(\mathrm{~s}$, $3 \mathrm{H}), 3.31(\mathrm{~d}, J=13.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.22(\mathrm{~d}, J=13.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.09(\mathrm{dd}, J=17.4,3.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.47-2.23$ $(\mathrm{m}, 1 \mathrm{H}), 2.05-1.84(\mathrm{~m}, 2 \mathrm{H}), 1.45-1.27(\mathrm{~m}, 10 \mathrm{H}), 0.92(\mathrm{~d}, \mathrm{~J}=6.1 \mathrm{~Hz}, 3 \mathrm{H}), 0.74(\mathrm{~d}, \mathrm{~J}=6.4 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.8,170.1,168.6,155.3,138.9,136.4,136.0,130.2,129.7,128.9$, $128.3,128.2,128.1,127.4,127.1,127.1,79.3,67.2,64.4,61.2,52.5,51.0,43.6,41.5,41.1,30.2$, 28.4, 27.5, 22.1, 21.2.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3423$ (w), 2971 (w), 2945 (w), 2871 (w), 1711 (m), 1657 (m), 1497 (m), 1430 (w), 1367 (w), 1226 (w), 1167 (m), 1053 (w), 909 (m), 730 (s).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{38} \mathrm{H}_{48} \mathrm{~N}_{3} \mathrm{O}_{6}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 642.8165; found: 642.8170.
$[\alpha]_{\mathrm{D}}{ }^{20}-89.6^{\circ}\left(c 0.3, \mathrm{CHCl}_{3}\right)$.
2-((2S,4S,5S)-1-acetyl-4-isopropyl-5-phenylpyrrolidine-2-carboxamido)-2-methylpropyl ethyl carbonate (6.259i)


Procedure: GP 6-6 from homopropargylamine 6.251b
Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 1:1). Yield: 92\% (84 mg), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:5. For the major isomer:
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.40-7.21(\mathrm{~m}, 3 \mathrm{H}), 7.16-7.02(\mathrm{~m}, 2 \mathrm{H}), 6.95(\mathrm{~s}, 1 \mathrm{H}), 4.92(\mathrm{~d}, \mathrm{~J}=7.6$ $\mathrm{Hz}, 1 \mathrm{H}), 4.67(\mathrm{~d}, \mathrm{~J}=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.29(\mathrm{~d}, \mathrm{~J}=10.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.23-4.14(\mathrm{~m}, 3 \mathrm{H}), 2.57-2.38(\mathrm{~m}, 1 \mathrm{H})$, 2.25 (dd, J = 12.7, $6.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $2.00-1.78(\mathrm{~m}, 1 \mathrm{H}), 1.72(\mathrm{~s}, 3 \mathrm{H}), 1.41-1.37(\mathrm{~m}, 1 \mathrm{H}), 1.36(\mathrm{~s}, 3 \mathrm{H})$, $1.35(\mathrm{~s}, 3 \mathrm{H}), 1.29(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 0.92(\mathrm{~d}, \mathrm{~J}=5.9 \mathrm{~Hz}, 3 \mathrm{H}), 0.75(\mathrm{~d}, \mathrm{~J}=6.3 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 171.9,171.2,155.4,140.1,128.7,127.8,127.5,72.0,66.3,64.2,61.0$, 53.3, 51.5, 29.7, 27.7, 24.1, 24.1, 23.2, 22.2, 21.1, 14.4.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3300$ (w), 2963 (w), 2934 (w), 2873 (w), 1747 (m), 1631 (m), 1547 (w), 1409 (m), 1375 (m), 1250 (s), 1013 (m), 920 (w), 878 (w), 792 (w), 734 (m), 707 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{35} \mathrm{~N}_{2} \mathrm{O}_{5}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 419.5415; found: 419.5418.
$[\alpha]_{D}{ }^{20}+102.9^{\circ}\left(c \quad 0.2, \mathrm{CHCl}_{3}\right)$
(2S,4S,5S)-1-acetyl-N-(2-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-4-isopropyl-5-phenylpyrrolidine-2-carboxamide (6.259j)


Procedure: GP 6-6 from homopropargylamine 6.251b

Conditions: room temperature for 30 h . Purification: Flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, PE/EtOAc 2:1). Yield: $95 \%$ ( 99 mg ), brown oil as a mixture of diastereoisomers of cis/trans in a ratio of 1:3. For the major isomer:
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 9.17(\mathrm{~s}, 1 \mathrm{H}), 8.16(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.43-7.26(\mathrm{~m}, 4 \mathrm{H}), 7.24-7.14$ (m, 3H), $7.13-7.01(m, 1 H), 5.09(d, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.87(\mathrm{~d}, J=9.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.81(\mathrm{~d}, \mathrm{~J}=12.9 \mathrm{~Hz}$, $1 \mathrm{H}), 4.76(\mathrm{~d}, \mathrm{~J}=13.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.66-2.50(\mathrm{~m}, 1 \mathrm{H}), 2.31(\mathrm{dd}, \mathrm{J}=13.0,6.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.17(\mathrm{td}, \mathrm{J}=13.3$, $9.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.85(\mathrm{~s}, 3 \mathrm{H}), 0.98(\mathrm{~d}, \mathrm{~J}=5.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.95(\mathrm{~s}, 9 \mathrm{H}), 0.80(\mathrm{~d}, J=5.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.14(\mathrm{~s}, 3 \mathrm{H})$, 0.12 (s, 3H).
${ }^{13}$ C NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.3,170.1,139.8,137.1,130.2,128.8,128.5,127.9,127.9,127.6$, 124.1, 122.4, 66.1, 64.8, 61.8, 51.2, 31.1, 27.7, 26.0, 23.0, 22.2, 21.1, 18.4, -4.9, -4.9.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3274$ (w), 2957 (m), 2930 (m), 2864 (w), 2856 (w), 1654 ( s$), 1525$ (m), 1455 (m), 1398 (m), 1256 (m), 1118 (m), 1079 (m), 838 (s), 779 (m), 734 (m), 706 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{43} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 495.7585; found: 495.7587.
$[\alpha]_{D}{ }^{20}-112.0^{\circ}\left(\mathrm{c} 0.5, \mathrm{CHCl}_{3}\right)$.

### 8.6.7 Post-modifications

## N-(tert-butyl)-4-oxo-1-phenylpyrrolidine-2-carboxamide (2.200)



To a stirred solution of $\mathrm{Py} \cdot \mathrm{SO}_{3}\left(1.99 \mathrm{~g}, 1.2 \mathrm{mmol}, 6.00\right.$ equiv) in $\mathrm{DCM}(1 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ was slowly added DMSO ( 0.5 mL ). The resulting mixture was stirred for another 30 min then $6.18 \mathrm{v}(52 \mathrm{mg}, 0.2$ mmol, 1.00 equiv) was added. After 2 hours at $0{ }^{\circ} \mathrm{C}, \mathrm{NEt}_{3}(140 \mu \mathrm{~L}, 1.0 \mathrm{mmol}, 5.00$ equiv) was added dropwise and the reaction mixture was warmed to room temperature. Saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ solution was added to quench the reaction. The resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 1: 1$ ) to yield the desired deprotected product $\mathbf{2 . 2 0 0}$ ( $50 \mathrm{mg}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.29-7.21(\mathrm{~m}, 2 \mathrm{H}), 6.85(\mathrm{tt}, J=7.4,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.65-6.58(\mathrm{~m}, 2 \mathrm{H})$, $6.08(\mathrm{~s}, 1 \mathrm{H}), 4.24(\mathrm{dd}, J=9.8,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.98(\mathrm{~d}, J=17.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.70(\mathrm{dt}, J=17.9,1.1 \mathrm{~Hz}, 1 \mathrm{H})$, 3.06 (ddt, J = 19.3, 9.8, $0.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.63 (ddt, J = 19.3, 5.6, 1.0 Hz, 1H), 1.20 (s, 10H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 209.3,171.3,146.5,129.7,120.0,113.7,61.7,56.8,51.3,42.2,28.6$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3309$ (w), 2971 (w), 1738 (w), 1648 (m), 1599 (m), 1503 (m), 1364 (s), 1218 (s), 1089 (m), 745 (s), 690 (m), 689 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 261.1598; found: 261.1599 .
$N$-(tert-butyl)-4-hydroxy-1-phenylpyrrolidine-2-carboxamide (6.18v)


To a stirred solution of 6.200 ( $26 \mathrm{mg}, 0.1 \mathrm{mmol}, 1.0$ equiv) in dry $\mathrm{MeOH}(500 \mu \mathrm{~L}, 0.2 \mathrm{M})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaBH}_{4}$ ( $11.3 \mathrm{mg}, 0.3 \mathrm{mmol}, 3.0$ equiv). After 2 hours at $0^{\circ} \mathrm{C}$, water was added to quench the reaction. The resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, pure EA) to yield the desired product 6.18 v ( 26 mg , quantitative yield) as a white solid as a mixture of diastereoisomers of cis/trans in a ratio of 2:1.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.32-7.14$ (m, 8H (cis+trans)), $6.90-6.73$ (m, 3H (cis+trans)), $6.69-$ 6.57 ( $\mathrm{m}, 6 \mathrm{H}$ (cis+trans)), $6.52(\mathrm{~s}, 2 \mathrm{H}$ (cis)), 6.26 ( $\mathrm{s}, 1 \mathrm{H}$ (trans)), $4.63-4.51$ (m, 3H (cis+trans)), 4.04 (dd, J = 8.4, 6.0 Hz, 1H (trans)), $3.94-3.84(\mathrm{~m}, 3 \mathrm{H}$ (cis+trans)), $3.65(\mathrm{dd}, J=10.2,1.8 \mathrm{~Hz}, 2 \mathrm{H}(c i s))$, $3.38(\mathrm{dd}, \mathrm{J}=10.3,3.9 \mathrm{~Hz}, 2 \mathrm{H}(c i s)), 3.28(\mathrm{dd}, J=9.8,4.9 \mathrm{~Hz}, 1 \mathrm{H}($ trans $)), 2.49-2.33(\mathrm{~m}, 3 \mathrm{H}$ (cis+trans)), $2.33-2.19$ (m, 3H (cis+trans)), 1.32 (s, 18H (cis)), 1.26 (s, 9H (trans)).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.8,172.6,147.4,129.4,129.4,118.8,118.2,113.5,113.0,70.7$, $69.8,64.3,64.0,58.0,51.1,51.0,40.2,39.8,28.6$.

IR: $v\left(\mathrm{~cm}^{-1}\right) 3309$ (w), 2971 (w), 1738 (w), 1648 (m), 1599 (m), 1503 (m), 1364 (s), 1218 (s), 1089 (m), 745 (s), 690 (m), 689 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 263.1754; found: 263.1759.
GP 6-7:


To a stirred solution of $6.18(0.5 \mathrm{mmol})$ in THF ( $5 \mathrm{~mL}, 0.1 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was slowly added TBAF ( 1.0 M in THF, $0.75 \mathrm{mmol}, 750 \mu \mathrm{~L}, 1.5$ equiv). The resulting mixture was stirred for another 30 min then saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ was added to quench the reaction. The resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, pure $E A$ ) to yield the desired deprotected product 6.201.
cis- $N$-(tert-butyl)-4-hydroxy-1-phenylpyrrolidine-2-carboxamide (6.201a)


Procedure: GP 6-7
Yield: 98\% for OTBS deprotection; quantitative yield for OTIPS deprotection. Isolated as a white solid.

MP: $162-164{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.27-7.23(\mathrm{~m}, 2 \mathrm{H}), 6.80(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.62(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.59$ (br s, 1H), 4.56 (t, J = 4.0 Hz, 1H), 3.88 (dd, J=10.3, 1.6 Hz, 1H), 3.65 (dd, J=10.2, 1.3 Hz, 1H), 3.37
(dd, $J=10.2,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.25(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.41$ (ddd, $J=14.5,10.3,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.27-2.23(\mathrm{~m}, 1 \mathrm{H})$, 1.32 (s, 9H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 173.7,147.3,129.2,117.9,112.8,70.4,64.2,57.8,50.9,39.6,28.5$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3307$ (w), 2970 (w), 1738 (w), 1647 (m), 1599 (m), 1503 (m), 1363 (s), 1218 (s), 1089 (m), 746 (s), 693 (m), 690 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 263.1754; found: 263.1758 .
cis- $N$-(tert-butyl)-1-(4-chlorophenyl)-4-hydroxypyrrolidine-2-carboxamide (6.201b)


Procedure: GP 6-7
Yield: 99\%, isolated as a white solid.
MP: $181-183^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.19-7.17(\mathrm{~m}, 2 \mathrm{H}), 6.53-6.50(\mathrm{~m}, 3 \mathrm{H}), 4.55(\mathrm{t}, \mathrm{J}=4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{dd}, \mathrm{J}$ $=10.2,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.61(\mathrm{dd}, J=10.2,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.35(\mathrm{dd}, J=10.2,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.17(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 2.42 (ddd, $J=14.5,10.3,4.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.23 (d, J = $14.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.31 (s, 9H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 173.3,145.7,129.1,122.9,113.8,70.4,64.1,57.9,51.1,39.6,28.5$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3404$ (w), 3362 (w), 2965 (w), 2913 (w), 1651 (s), 1601 (w), 1532 (m), 1495 (s), 1356 (m), 1341 (m), 1223 (m), 1173 (m), 1093 (w), 972 (w), 811 (m), 710 (w)..

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{CIN}_{2} \mathrm{O}_{2}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 297.1364; found: 297.1362.
ethyl (cis-4-((tert-butyldimethylsilyl)oxy)-1-(4-chlorophenyl)pyrrolidine-2-carboxylate (6.205)


Following a reported procedure, ${ }^{548}$ to a stirred solution of 6.18 aa ( $50 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in dry THF ( 0.5 $\mathrm{mL}, 0.2 \mathrm{M}$ ) at $0{ }^{\circ} \mathrm{C}$ was added potassium tert-butoxide ( $13 \mathrm{mg}, 0.12 \mathrm{mmol}, 1.2$ equiv). After 1 h , saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ was added and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in
vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 10: 1$ ) to yield the desired product 6.205 (72\%) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.16-7.13(\mathrm{~m}, 2 \mathrm{H}), 6.44-6.41(\mathrm{~m}, 2 \mathrm{H}), 4.52-4.48(\mathrm{~m}, 1 \mathrm{H}), 4.25(\mathrm{dd}, \mathrm{J}=$ $9.8,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.21-4.02(\mathrm{~m}, 2 \mathrm{H}), 3.51(\mathrm{dd}, J=9.6,5.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.35(\mathrm{dd}, J=9.6,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.40$ (ddd, J = 13.8, 8.9, 5.0 Hz, 1H), $2.29(\mathrm{dt}, J=12.8,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.21(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 0.86(\mathrm{~s}, 9 \mathrm{H})$, 0.072 (s, 3H), 0.068 (s, 3H).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 172.9,145.3,128.9,121.4,113.0,70.4,61.0,59.7,56.9,39.8,25.7$, 18.0, 14.2, -4.86, -4.92.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 2954$ (w), 2930 (w), 2856 (w), 1751 (w), 1600 (w), 1500 (s), 1364 (m), 1256 (w), 1183 (s), 1096 (s), 1025 (m), 838 (m), 806 (m), 777 (m), 617 (w).

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{19} \mathrm{H}_{30} \mathrm{ClNNaO}{ }_{3} \mathrm{Si}[\mathrm{M}+\mathrm{Na}]^{+} 406.1576$; found: 406.1577.
cis-2-aminobenzyl-1-(4-chlorophenyl)-4-hydroxypyrrolidine-2-carboxylate (6.203)


Following a reported procedure, ${ }^{547}$ a mixture of compound 6.18ab ( $57 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) and 1 M HCl in $\mathrm{MeOH}(5 \mathrm{~mL})$ was stirred at room temperature for 5 h . Solvent was evaporated in vacuo and the residue was taken up in water. The solution was neutralized with saturated aqueous $\mathrm{K}_{2} \mathrm{CO}_{3}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{PE} / \mathrm{EtOAc} 3: 1\right)$ to yield the desired product 6.203 (50\%) as a colorless oil.
${ }^{1} \mathrm{H}$ NMR ( $\mathbf{4 0 0} \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.25-7.21(\mathrm{~m}, 1 \mathrm{H}), 7.18-7.14(\mathrm{~m}, 3 \mathrm{H}), 7.05(\mathrm{dd}, \mathrm{J}=7.7,1.0 \mathrm{~Hz}, 1 \mathrm{H})$, 6.94-6.92 (m, 1H), 6.62-6.60 (m, 2H), 6.06 (br s, 1H), $5.38(\mathrm{~d}, \mathrm{~J}=13.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.33(\mathrm{~d}, \mathrm{~J}=13.2 \mathrm{~Hz}$, $1 \mathrm{H}), 4.55(\mathrm{br} s 1 \mathrm{H}), 4.23(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.70-3.67(\mathrm{~m}, 1 \mathrm{H}), 3.53(\mathrm{dd}, J=10.1,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.49$ (ddd, $J=14.3,9.4,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.35(\mathrm{~d}, J=13.9 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 165.9,145.2,137.2,129.2,129.1,127.1,124.1,123.7,121.9,120.7$, 113.3, 71.1, 67.0, 61.2, 58.9, 39.4.

IR: $\cup\left(\mathrm{cm}^{-1}\right) 3374$ (w), 2927 (w), 2855 (w), 1730 (w), 1599 (m), 1499 (s), 1369 (w), 1178 (m), 1088 (w), 810 (w), 755 (w), 634 (m), 611 (m).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{18} \mathrm{H}_{20} \mathrm{CIN}_{2} \mathrm{O}_{3}\left(\left[\mathrm{M}+\mathrm{H}^{+}\right)\right.$: 347.1157 ; found: 347.1157.
cis- $N$-(tert-butyl)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-2-carboxamide (6.199)


Following a reported procedure, ${ }^{552}$ to a stirred solution of $6.18 \mathbf{x}$ ( $40 \mathrm{mg}, 0.1 \mathrm{mmol}$ ) in $\mathrm{MeCN}(1.6$ mL ) and $\mathrm{H}_{2} \mathrm{O}(400 \mu \mathrm{~L})$ at $0^{\circ} \mathrm{C}$ was added CAN ( $121 \mathrm{mg}, 0.22 \mathrm{mmol}, 2.2$ equiv). After 15 min , saturated aqueous $\mathrm{NaHCO}_{3}$ and saturated aqueous $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ were added and the resulting mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}, \mathrm{DCM} / \mathrm{MeOH} 10: 1$ ) to yield the desired deprotected product 6.199 ( $50 \mathrm{mg}, 95 \%$ ) as a yellow oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.40(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.28(\mathrm{~m}, 1 \mathrm{H}), 3.65(\mathrm{dd}, J=9.6,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.10(\mathrm{dd}, J=$ $10.7,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.82(\mathrm{dd}, J=10.5,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.45(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.33(\mathrm{ddd}, J=13.4,9.6,5.8 \mathrm{~Hz}, 1 \mathrm{H})$, 1.86 (dt, J = 13.3, 5.3 Hz, 1H), 1.34 ( 9 H$), 0.87$ (s, 9H), $0.04(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 173.6,72.7,59.8,54.9,50.2,39.6,28.7,25.8,18.1,-4.81,-4.83$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3319$ (w), 2957 (m), 2929 (m), 2857 (m), 1660 ( s$), 1520$ (m), 1363 (m), 1254 (m), 1228 (m), 1118 (m), 836 (s), 777 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{Si}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 301.2306$; found: 301.2307.

## cis-1-(4-chlorophenyl)-4-hydroxypyrrolidine-2-carboxamide (6.202)


$\mathrm{BF}_{3} \cdot \mathrm{Et}_{2} \mathrm{O}$ (10 equiv) was slowly added to a solution of 6.201 b (1 equiv) in DCE ( 0.05 M ) at room temperature. After the addition was completed, the solution was allowed to reflux overnight. The reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO}_{3}$ and extracted with DCM. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The residue was washed with $\mathrm{CHCl}_{3}$ to give the desired product 6.202 ( $95 \%$ ) as a white solid without further purification.

MP: $200-202{ }^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, Methanol $-d_{4}$ ) $\delta 7.18(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.58(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.50(\mathrm{t}, J=4.4$ $\mathrm{Hz}, 1 \mathrm{H}), 3.95(\mathrm{dd}, \mathrm{J}=10.3,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.59(\mathrm{~d}, J=10.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.40(\mathrm{dd}, J=10.1,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.52$ (ddd, $J=13.9,10.3,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{dq}, J=13.9,1.7 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13}$ C NMR (100 MHz, Methanol- $d_{4}$ ) $\delta$ 180.1, 147.7, 130.0, 123.6, 115.2, 71.3, 64.2, 58.8, 40.5.

IR: $v\left(\mathrm{~cm}^{-1}\right) 2568$ (w), 1672 (m), 1596 (w), 1496 (s), 1359 (m), 1349 (m), 1326 (w), 1181 (w), 1088 (w), 807 (m), 714 (w), 622 (w).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{ClN}_{2} \mathrm{NaO}_{2}[\mathrm{M}+\mathrm{Na}]^{+}$263.0558; found: 263.0558.

## GP 6-8:



To a stirred solution of 6.232 ( 0.2 mmol, 1.0 equiv) in $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(2: 1,4 \mathrm{~mL}, 0.05 \mathrm{M})$ at room temperature was added NaOH ( $40 \mathrm{mg}, 1.0 \mathrm{mmol}, 5.0$ equiv). The resulting mixture was stirred at $80{ }^{\circ} \mathrm{C}$ overnight then saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, pure EA ) to yield the desired deprotected products cis-6.262 and trans6.262. Control experiments have shown that no epimerization occurred under these conditions.
trans- N -(tert-butyl)-5-phenylpyrrolidine-2-carboxamide (trans-6.262)


Procedure: GP 6-8
Yield: 48\% (24 mg) for TFA deprotection, $40 \%(20 \mathrm{mg})$ for Bn deprotection. Isolated as a white solid.

MP: $167-188^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.48(\mathrm{~s}, 1 \mathrm{H}), 7.43-7.11(\mathrm{~m}, 5 \mathrm{H}), 4.39-4.13(\mathrm{~m}, 1 \mathrm{H}), 4.02-3.80(\mathrm{~m}$, $1 \mathrm{H}), 2.60-2.30(\mathrm{~m}, 1 \mathrm{H}), 2.30-2.11(\mathrm{~m}, 1 \mathrm{H}), 2.05-1.86(\mathrm{~m}, 1 \mathrm{H}), 1.87-1.64(\mathrm{~m}, 1 \mathrm{H}), 1.36(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 173.9,143.3,128.8,127.6,126.5,63.4,61.8,50.5,35.1,30.8,28.9$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3456$ (w), 3339 (w), 2970 (w), 2935 (w), 2879 (w), 1665 (s), 1545 (w), 1456 (m), 1365 (w), 1223 (s), 1150 (s), 911 (w), 731 (s), 703 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{1}\left([\mathrm{M}+\mathrm{H}]^{+}\right):$247.3615; found: 247.2618 .
cis-N-(tert-butyl)-5-phenylpyrrolidine-2-carboxamide (cis-6.262)


Procedure: GP 6-8

Yield: 48\% (24 mg) for TFA deprotection, $40 \%(20 \mathrm{mg})$ for Bn deprotection. Isolated as a white solid.

MP: $185-187^{\circ} \mathrm{C}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.71(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.43-7.32(\mathrm{~m}, 4 \mathrm{H}), 7.32-7.23(\mathrm{~m}, 1 \mathrm{H}), 4.36(\mathrm{dd}, \mathrm{J}=$ $10.1,5.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.83 (dd, J = 9.6, 3.5 Hz, 1H), 2.34-2.08 (m, 3H), 1.72-1.58 (m, 1H), 1.37 ( $\mathrm{s}, 9 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 174.2,143.7,128.7,127.4,126.6,63.2,60.8,50.6,33.8,31.4,28.9$.
IR: $v\left(\mathrm{~cm}^{-1}\right) 3425$ (w), 3342 (w), 2970 (w), 2937 (w), 2882 (w), 1665 (s), 1456 (m), 1368 (w), 1223 (s), 1200 (s), 1150 (s), 911 (w), 739 (s), 703 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}_{1}\left([\mathrm{M}+\mathrm{H}]^{+}\right)$: 247.3615; found: 247.2617.

### 8.6.8 Mechanistic Studies

## Characterization of the intermediate 6.208:



To a solution of isocyanide 6.207 ( 0.4 mmol , 2 equiv) in deuterated toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) in an NMR tube was added $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.10$ equiv) and 6.134a ( $0.2 \mathrm{mmol}, 1$ equiv). The resulting mixture was heated at $40^{\circ} \mathrm{C}$ and monitored by ${ }^{1} \mathrm{H}$ NMR. After completion of the reaction, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with PE/EtOAc 95:5, eluent: 25 mL PE/EtOAc $95: 5$ then $8: 1$ ) and purified to yield 6.18 s . The $5-e n d o-d i g$ cyclization was finished in around 20 h . The intermediate formed can be stored for 3 days without noticeable degradation.

## Characteristic ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ chemical shifts (in ppm) of 1,2-diphenyl-2,3-dihydro-1H-pyrrole (6.208) in toluene- $d_{8}$



The other signals are not easily assigned due to the presence of isocyanide and solvent signals.

## Characterization of the intermediate 6.229:



To a solution of homopropargylamine $6.158(0.2 \mathrm{mmol})$ in toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) was added AgOAc ( $3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv) at room temperature. The resulting mixture was stirred at $40{ }^{\circ} \mathrm{C}$. After completion of the cyclization (as indicated by TLC, usually around 12 hours), saturated aqueous $\mathrm{NaHCO}_{3}$ solution was added and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield intermediate 6.229. The analytical data were in accordance with those reported in the literature. ${ }^{579}$

## 2-phenyl-3,4-dihydro-2H-pyrrole (6.229)



Yield: $97 \%$ isolated as a brown oil.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.81(\mathrm{~s}, 1 \mathrm{H}), 7.40-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.30-7.15(\mathrm{~m}, 3 \mathrm{H}), 5.25-5.03(\mathrm{~m}$, $1 \mathrm{H}), 2.84-2.69(\mathrm{~m}, 1 \mathrm{H}), 2.68-2.53(\mathrm{~m}, 1 \mathrm{H}), 2.47-2.31(\mathrm{~m}, 1 \mathrm{H}), 1.78-1.61(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 167.6,144.2,128.5,126.9,126.5,76.0,37.6,30.4$.
IR: $\cup\left(\mathrm{cm}^{-1}\right) 3425$ (w), 3342 (w), 2970 (w), 2935 (w), 2879 (w), 1665 (s), 1545 (w), 1456 (m), 1365 (w), 1223 (s), 1200 (s), 1150 (s), 911 (w), 731 (s), 703 (s).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}\left([\mathrm{M}+\mathrm{H}]^{+}\right): 146.0964$; found: 146.0967 .
The intermediate 6.229 was dissolved in toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) and tert-butyl isocyanide 5.68 (0.24 mmol, 1.2 equiv) and TFA ( $0.24 \mathrm{mmol}, 1.2$ equiv) were added sequentially. The reaction mixture was stirred at room temperature until complete conversion of the intermediate (as indicated by TLC). Saturated aqueous $\mathrm{NaHCO}_{3}$ solution was added and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right)$ to yield the desired product 6.232 c .

5-endo-dig cyclization of 6.134a in the presence or in the absence of isocyanide:

[^220]

In one NMR tube (A): To a solution of isocyanide 6.207 ( $0.4 \mathrm{mmol}, 2$ equiv) in deuterated toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) in an NMR tube was added AgOAc ( $3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv) and 6.134 a ( 0.2 mmol, 1 equiv). The resulting mixture was heated at $40{ }^{\circ} \mathrm{C}$ and followed by ${ }^{1} \mathrm{H}$ NMR. After completion of the cyclization, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with $\mathrm{PE} / E t O A c$ 95:5, eluent: $25 \mathrm{~mL} \mathrm{PE} / E t O A c 95: 5$ then 8:1) and purified to yield 6.18s.

In another NMR tube (B): To a solution of 6.134a ( $0.2 \mathrm{mmol}, 1$ equiv) in deuterated toluene ( 2 mL , 0.1 M ) in an NMR tube was added $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv). The resulting mixture was heated at $40^{\circ} \mathrm{C}$ and followed by ${ }^{1} \mathrm{H}$ NMR. After completion of the cyclization, isocyanide 6.207 ( $0.4 \mathrm{mmol}, 2$ equiv) was added and the reaction mixture was immediately loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with $\mathrm{PE} / E t O A c 95: 5$, eluent: $25 \mathrm{~mL} \mathrm{PE} / \mathrm{EtOAc}$ $95: 5$ then $8: 1$ ) and purified to yield 6.18 s in similar yield.

The ${ }^{1} \mathrm{H}$ NMR spectra showed that the reaction in the presence of isocyanide was cleaner than the reaction without isocyanide. After full conversion, the reaction mixture in the NMR tube containing the isocyanide looked clear. However, in the NMR tube without the isocyanide, a silver mirror and some precipitates were formed.

5-endo-dig cyclization of 6 e in the presence or in the absence of isocyanide and/or of acid:


In one NMR tube (A): To a solution of 6.251 b ( 0.2 mmol , 1 equiv) in deuterated toluene ( $2 \mathrm{~mL}, 0.1$ M ) in an NMR tube was added $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv). The resulting mixture was heated at $40^{\circ} \mathrm{C}$ and followed by ${ }^{1} \mathrm{H}$ NMR. Full conversion to 6.266 was observed after 12 h .

In another NMR tube (B): To a solution of isocyanide 6.207 ( $0.24 \mathrm{mmol}, 1.2$ equiv) in deuterated toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) in an NMR tube was added $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv) and 6.251 b ( $0.2 \mathrm{mmol}, 1$ equiv). The resulting mixture was heated at $40{ }^{\circ} \mathrm{C}$ and followed by ${ }^{1} \mathrm{H}$ NMR. Full conversion to 6.266 was observed after 3 days.

In another NMR tube (C): To a solution of 6.251b ( $0.2 \mathrm{mmol}, 1$ equiv) in deuterated toluene ( 2 mL , 0.1 M ) in an NMR tube was added $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv) and acetic acid ( 0.24 mmol, 1.2 equiv) The resulting mixture was heated at $40{ }^{\circ} \mathrm{C}$ and followed by ${ }^{1} \mathrm{H}$ NMR. Only $50 \%$ conversion to 6.266 was observed after 3 days.

In another NMR tube (D): To a solution of isocyanide 6.207 ( $0.24 \mathrm{mmol}, 1.2$ equiv) in deuterated toluene ( $2 \mathrm{~mL}, 0.1 \mathrm{M}$ ) in an NMR tube was added AgOAc ( $3.3 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv), 6.251b ( $0.2 \mathrm{mmol}, 1$ equiv) and acetic acid ( $0.24 \mathrm{mmol}, 1.2$ equiv). The resulting mixture was heated at 40 ${ }^{\circ} \mathrm{C}$ and followed by ${ }^{1} \mathrm{H}$ NMR. Almost no conversion to 6.266 was observed after 3 days and the reaction mixture became messy.

## Characterization of the side product 6.218:



In a glove box, to a suspension of $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol})$ in toluene ( 2 mL ) was added a solution of isocyanide 5.68 ( 0.4 mmol ) and homopropargylamine 6.134a ( 0.2 mmol ) in toluene ( 2 mL ). The resulting mixture was stirred at $40^{\circ} \mathrm{C}$ for 15 h . After completion of the reaction, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with PE/EtOAc 95:5, solvents system: 25 mL PE/EtOAc 95:5 then 8:1) and purified to yield proline amide 6.18a and the side product 6.218.

## N-(tert-butyl)-1,1',5,5'-tetraphenyl-[2,3'-bipyrrolidine]-2'-carboxamide (6.218)


${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 7.37-7.28(\mathrm{~m}, 4 \mathrm{H}), 7.25-7.15(\mathrm{~m}, 5 \mathrm{H}), 7.15-7.09(\mathrm{~m}, 1 \mathrm{H}), 7.01(\mathrm{~d}, \mathrm{~J}$ $=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.93(\mathrm{dd}, J=8.6,7.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.84(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 6.76(\mathrm{~s}, 1 \mathrm{H}), 6.61(\mathrm{~d}, J=7.8 \mathrm{~Hz}$, $2 \mathrm{H}), 6.53-6.44(\mathrm{~m}, 3 \mathrm{H}), 5.08(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.90-4.86(\mathrm{~m}, 2 \mathrm{H}), 3.77(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.18-$ $3.11(\mathrm{~m}, 1 \mathrm{H}), 2.51(\mathrm{tt}, J=12.8,7.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.39(\mathrm{dt}, J=12.2,9.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.27(\mathrm{tt}, J=13.1,7.9 \mathrm{~Hz}$, $1 \mathrm{H}), 2.07$ (ddd, J = 12.4, 6.8, $3.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), $1.88-1.82(\mathrm{~m}, 2 \mathrm{H}), 1.38(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{1} \mathrm{CNMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 172.7,147.7,145.1,144.2,144.1,129.3,129.1,128.9,128.5,127.4$, $126.5,126.4,126.0,119.0,115.8,114.6,114.1,69.4,65.7,62.7,58.0,51.1,43.3,35.0,34.7,28.6$, 24.0.

## Comparison of the silica gel brands:



To a suspension of $\operatorname{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol})$ in toluene ( 2 mL ) was added a solution of isocyanide 5.58 or 6.207 ( 0.4 mmol ) and homopropargylamine $\mathbf{6 . 1 3 4 a}$ ( $45 \mathrm{mg}, 0.2 \mathrm{mmol}$ ) in toluene (2 mL ). The resulting mixture was stirred at $40^{\circ} \mathrm{C}$ for 30 h . After completion of the reaction, the reaction mixture was loaded onto a column of silica gel of different brands ( 1 cm diameter column, 12 $\mathrm{cm} \mathrm{SiO}_{2}$ packed with $\mathrm{PE} / E t O A c$ 95:5, eluent: 25 mL PE/EtOAc 95:5 then 8:1) and purified to yield proline amide 6.18a or 6.18s.

## Synthesis of deuterated compound 6.134-d:

6.134-d1 and 6.134-d2 were prepared according to a modified literature procedure. ${ }^{554}$


A flame dried 10 mL round-bottom flask was charged with alkyne 6.134a ( $221 \mathrm{mg}, 1 \mathrm{mmol}$ ) and $\mathrm{K}_{2} \mathrm{CO}_{3}$ (206 mg, 1.5 mmol ) in dry $\mathrm{CH}_{3} \mathrm{CN}(2 \mathrm{~mL})$. The reaction mixture was stirred under a $\mathrm{N}_{2}$ atmosphere for 1 h , then $\mathrm{D}_{2} \mathrm{O}$ ( $\sim 50$ equiv) was added. After stirring overnight, the reaction mixture was diluted with DCM ( 5 mL ). The combined organic extracts were washed with 2 M HCl , saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. Subsequent NMR analysis showed only alkyne had been fully deuterated, no N-H had been deuterated.


A flame dried 10 mL round-bottom flask was charged with alkyne 6.134 ( $221 \mathrm{mg}, 1 \mathrm{mmol}$ ) and $\mathrm{K}_{2} \mathrm{CO}_{3}(206 \mathrm{mg}, 1.5 \mathrm{mmol})$ in dry $\mathrm{CH}_{3} \mathrm{CN}(2 \mathrm{~mL})$. The reaction mixture was stirred under a $\mathrm{N}_{2}$ atmosphere for 1 h , then $\mathrm{D}_{2} \mathrm{O}$ ( $\sim 50$ equiv) was added. After stirring overnight, the reaction mixture was diluted with DCM ( 5 mL ). The combined organic extracts were washed with 2 M HCl , saturated aqueous $\mathrm{NaHCO}_{3}$ and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated in vacuo. Subsequent NMR analysis showed the alkyne had been fully deuterated and an estimated round $50 \%$ of $\mathrm{N}-\mathrm{H}$ had been deuterated.

## Isotope-labeling experiments:



A: To a suspension of $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol})$ in toluene $(2 \mathrm{~mL})$ was added a solution of isocyanide 5.68 ( 0.4 mmol ) and deuterated homopropargylamine $6.134-\mathrm{d}$ ( 0.2 mmol ) in toluene ( 2 mL ). The resulting mixture was stirred at $40^{\circ} \mathrm{C}$ for 30 h . After completion of the reaction, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with PE/EtOAc 95:5, eluent: 25 mL PE/EtOAc 95:5 then 8:1) and purified to yield proline amide 6.18a-d. Deuterium incorporation was calculated based on the ${ }^{1} \mathrm{H}$ NMR spectra.

B: To a suspension of $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol})$ and $\mathrm{D}_{2} \mathrm{O}(0.6 \mathrm{mmol}, 3$ equiv) in toluene ( 2 mL ) was added a solution of isocyanide 5.68 ( 0.4 mmol ) and deuterated homopropargylamine 6.134a $(0.2 \mathrm{mmol})$ in toluene ( 2 mL ). The resulting mixture was stirred at $40^{\circ} \mathrm{C}$ for 30 h . After completion of the reaction, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with $\mathrm{PE} / E t O A c$ 95:5, eluent: 25 mL PE/EtOAc 95:5 then 8:1) and purified to yield proline amide 6.18a-d.


In an argon-filled glove box, to a suspension of $\mathrm{AgOAc}(3.3 \mathrm{mg}, 0.02 \mathrm{mmol}), \mathrm{H}_{2}{ }^{18} \mathrm{O}$ (3 equiv) in toluene ( 2 mL ) was added a solution of tert-butyl isocyanide $5.68(33 \mathrm{mg}, 45 \mu \mathrm{~L}, 0.4 \mathrm{mmol})$ and 6.134a $(44 \mathrm{mg}, 0.2 \mathrm{mmol})$ in toluene ( 2 mL ). The resulting mixture was stirred at $35{ }^{\circ} \mathrm{C}$ for 48 h . After completion of the reaction, the reaction mixture was loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with $\mathrm{PE} / E t O A c$ 95:5, eluent: 25 mL PE/EtOAc 95:5 then 8:1) and purified to yield ${ }^{18} \mathrm{O}$-labeled proline amide ${ }^{18} \mathrm{O}-6.18 \mathrm{a}$.

## Silver-isocyanide complexes:



A solution of $\mathrm{AgOAc}(17 \mathrm{mg}, 0.1 \mathrm{mmol}, 1$ equiv) and isocyanide 5.68 ( $17 \mathrm{mg}, 23 \mu \mathrm{~L}, 0.2 \mathrm{mmol}, 2.0$ equiv) in toluene ( 1 mL ) was stirred at room temperature for 1 h . The resulting colorless solution was evaporated in vacuo to yield the silver-isocyanide complex 6.209 in a quantitative yield as a white solid. Subsequent NMR analysis showed the ratio of silver salt and isocyanide was 1:1.


To a suspension of $\operatorname{AgOAc}(\mathrm{RNC})(10 \mathrm{mg}, 0.02 \mathrm{mmol})$ in toluene $(1 \mathrm{~mL})$ was added a solution of homopropargylamine 6.134 a ( $44 \mathrm{mg}, 0.2 \mathrm{mmol}$ ) in toluene ( 1 mL ). The resulting mixture was stirred at $40^{\circ} \mathrm{C}$. After completion of the reaction, isocyanide $5.68(46 \mu \mathrm{~L}, 0.4 \mathrm{mmol})$ was added in the reaction mixture. The reaction mixture was directly loaded onto a column of silica gel ( 1 cm diameter column, 12 cm SiO 2 packed with $\mathrm{PE} / E t O A c$ 95:5, solvents system: 25 mL PE/EtOAc 95:5 then $8: 1$ ) and purified to yield proline amide 6.18a ( $81 \%, 26 \mathrm{mg}$ ).


A solution of AgX ( $0.1 \mathrm{mmol}, 1$ equiv) and isocyanide $5.68(17 \mathrm{mg}, 23 \mu \mathrm{~L}, 0.2 \mathrm{mmol}, 2.0$ equiv) in DCM ( 1 mL ) was stirred at room temperature for 1 h . The resulting colorless solution was evaporated in vacuo to yield the silver-isocyanide complex 6.210 in a quantitative yield as a white solid. Subsequent NMR and IR analysis was performed.

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## Curriculum Vitae

| Cyril PIEMONTESI | Email:cyril.piemontesi@epfl.ch |
| :--- | :--- |
| Rue de l'Ale 31 | Born: 24.02 .1989 |
| 1003 Lausanne - Switzerland | Single |
| T: 0041 21/693.94.80 | Google Scholar: Cyril Piemontesi |
| M: $004179 / 584.27 .69$ | ORCID: 0000-0001-6062-7137 |

## EDUCATION

## 2014-2018: PhD in Organic Chemistry (EPFL)

- Thesis title: "Indole Alkaloids, Macrocycles and Heterocycles: Interplay between Methodological Development and Total Synthesis".

2012-2014: Master of Science (EPFL)

- Master Thesis title: "Studies Towards the Total Synthesis of Strictamine". Grade: 6/6
- Average grade: 5.89/6

2008-2011: Bachelor of Science (EPFL)

- Average grade: 5.59/6 - Ranking 2/50


## RESEARCH EXPERIENCES

PhD (4 years, EPFL, Professor Jieping Zhu):

- Total synthesis of complex natural products, asymmetric organo- and transition metal catalysis, novel domino reactions
- 1,1-Aminoacylation of homopropargylamines, proline amides synthesis, novel multicomponent reactions
- Macrocyclization of $\omega$-isocyanoaldehyde, multicomponent reactions, natural product synthesis


## Master Thesis (6 months, EPFL, Professor Jieping Zhu):

- $\alpha$-Arylation of ketones, alkyne synthesis, $\alpha$-vinylation of oxindoles


## Semester Project in Organic Chemistry (6 months, EPFL, Professor Jieping Zhu):

- Heteroannulation reaction, benzyne chemistry, unsymmetrical 2,3-disubstituted indoles synthesis
Semester Project in Computational Chemistry (5 months, EPFL, Professor Clémence Corminboeuf):
- DFT computation of charge-transfer complexes

Volunteer Internship in Organic Chemistry (8 months, EPFL, Professor Jieping Zhu):

- Nucleophilic substitution on 3-hydroxy-oxindole synthesis, Brønsted-acid catalysis
- Computational analysis for reactivity and regio-/chemoselectivity

Volunteer Internship in Drug Discovery (6 months, F. Hoffmann-La Roche Ltd):

- Multistep organic syntheses of drug candidates for in vivo \& in vitro biological tests
- Structure - activity relationship analysis


## Volunteer Internship in Organic Chemistry (2 months, EPFL, Professor Jérôme Waser):

- Palladium-catalyzed aminoalkynylation, hypervalent iodine chemistry


## MANAGEMENT AND TEACHING EXPERIENCES

- Mentoring of 3 master students during 6 months each
- Teaching assistant for undergraduate practical organic chemistry courses and M.Sc. lectures on total synthesis
- Lab management including group meeting organization, machines and website maintenance


## PUBLICATIONS

1. Nicolai, S.; Piemontesi, C.; Waser, J., A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of ( $\pm$ )-Trachelanthamidine. Angew. Chem., Int. Ed. 2011, 50, 4680-4683. DOI: 10.1002/anie. 201100718
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## AWARDS AND FELLOWSHIPS

1. Excellence scholarship at Master level from EPFL for the Master in Molecular Chemistry
2. Best Poster presentation for the Master Project Day at EPFL, Switzerland
3. Prix BASF Monthey SA for the Best Master Thesis in Chemistry
4. Teaching assistant prize 2015 from EPFL
5. Runner-Up Prize for the Best Oral presentation at the Fall Meeting 2015 of the Swiss Chemical Society at EPFL, Switzerland
6. Best team prize at the Syngenta Workshop 2016 for Talented Young Chemists in Stein, Switzerland
7. Chemistry Travel Award 2017 from the sc|nat and the Swiss Chemical Society
8. Runner-Up Prize for the Best Oral presentation at the Fall Meeting 2017 of the Swiss Chemical Society in Bern, Switzerland
9. Best Oral presentation at the Swiss Summer School 2017 in Villars, Switzerland
10. 2017 Albert Hofmann PhD Award for Excellence in Research
11. Swiss National Science Foundation Early Postdoc.Mobility fellowship

## RESEARCH PRESENTATIONS

1. Poster presentation at the Fall Meeting 2012 of the Swiss Chemical Society at ETH, Switzerland
2. Oral presentation at the CUSO Science Days 2012 at the University of Geneva, Switzerland
3. Poster presentation at the Swiss Summer School 2013 in Villars, Switzerland
4. Poster presentation for the Master Project Day at EPFL, Switzerland
5. Oral presentation at the Fall Meeting 2015 of the Swiss Chemical Society at EPFL, Switzerland
6. Oral/Poster presentation at the Swiss Summer School 2015 in Villars, Switzerland
7. Poster presentation at the COST action CM1407 2016 in Madrid, Spain
8. Poster presentation at the Syngenta Workshop 2016 for Talented Young Chemists in Stein, Switzerland
9. Poster presentation at the $18^{\text {th }}$ Tetrahedron Symposium in Budapest, Hungary
10. Oral presentation at the Fall Meeting 2017 of the Swiss Chemical Society at Bern, Switzerland
11. Oral presentation at the Swiss Summer School 2017 in Villars, Switzerland
12. Oral presentation at the 2017 Albert Hofmann Symposium in Zürich, Switzerland

## LANGUAGES

| English: | Professional working proficiency |
| :--- | :--- |
| German: | Limited working proficiency |
| French: | Mother tongue |

## REFERENCES

- Professor Dr. Jieping Zhu - jieping.zhu@epfl.ch - +41 (0)21 6939742
- Professor Dr. Jérôme Waser - jerome.waser@epfl.ch - +41 (0)21 6939782
- Professor Dr. Eric M. Carreira - erickm.carreira@org.chem.ethz.ch - +41 (0) 446322830
- Dr. Bernhard Fasching - bernhard.fasching@gmail.com - +41 (0)78 8652916


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