"Divergent Total Synthesis of (-)-Rhazinilam, (-)-Leucomidine B and (+)-Leuconodine F" and "Synthetic Studies Towards Sarpagine-Related Indoles"

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ÉCOLE POLYTECHNIQUE
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À mon père.

‘’Il n'y a pas de problèmes ; il n'y a que des solutions.
L'esprit de l'homme invente ensuite le problème.
Il voit des problèmes partout.’’

André GIDE

Acknowledgement

First of all, I would like to thank all the members of the jury; Prof. Cramer, Prof. Clark, Dr. Ratovelomanana-Vidal and Prof. Waser; for accepting and taking the time to review the manuscript of my thesis and also for being present at my private defense.

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Abstract

The work presented in this thesis focuses on the synthesis of monoterpene indole alkaloids.

The first part describes the divergent total synthesis of (-)-rhazinilam, (-)-leucomidine B and (+)-leuconodine F, three structurally distinct natural products of the *Aspidosperma* family. The key step involves the heteroannulation of an advanced tetrahydropyridine with bromoacetaldehyde or oxalyl chloride in order to afford the corresponding tetrahydroindolizine and 2,3-dioxopyrrole moieties, respectively. By fine tuning of the reaction conditions, the former was converted into rhazinilam while the latter led to the syntheses of leucomidine B and leuconodine F. In the case of leucomidine B, the development of a substrate-directed diastereoselective reduction of a sterically unbiased double bond is also discussed.

The second part details the synthetic studies towards various members of the *Sarpagan* family. After the exploration of several strategies and indoles alkaloids, the enantioselective total synthesis of *N*(1)-demethyl-3,5-diepi-alstolactone was accomplished. This synthesis features three key points: 1) the incorporation of a vinyl ketone function in the C-2 position of indole by using the Liebeskind-Srogl coupling in order to afford, after ring-closing metathesis, an advanced eight-membered cyclic enone, 2) a highly diastereoselective intramolecular Michael addition and 3) the formation of an azabicyclo[3.3.1]nonane bridged system from the corresponding eight-membered ring *via* a dehydration / transannular cyclization process.

Keywords:

Total synthesis, asymmetric synthesis, indole alkaloids, rhazinilam, leucomidine B, leuconodine F, alstolactone, affinine, amerovolficine, vobasidine, alstonerine, heteroannulation, diastereoselective reduction, transannular cyclization, 8-membered ring, 1,4-addition.

Résumé

Ce travail de thèse porte sur la synthèse d'alcaloïdes indoliques monoterpéniques.

La première partie décrit la synthèse totale divergente de la (-)-rhazinilam, de la (-)-leucomidine B et de la (+)-leuconodine F, trois produits naturels de la famille des *Aspidosperma* possédant des structures bien distinctes. L'étape clé implique l'hétéroannulation d'une tétrahydropyridine avancée avec du bromoacétaldéhyde ou du chlorure d'oxalyle afin d'obtenir respectivement les motifs tétrahydroindolizine et 2,3-dioxopyrrole correspondants. Par l'ajustement des conditions de réaction, le premier intermédiaire a été convertit en rhazinilam alors que le second a mené aux synthèses de la leucomidine B et de la leuconodine F. Dans le cas de la leucomidine B, le développement d'une réduction diastéréosélective, dirigée par le substrat, d'une double liaison stériquement impartiale est aussi discuté.

La seconde partie détaille les études synthétiques envers différents membres de la famille des *Sarpagan*. Après l'exploration de plusieurs stratégies et d'alcaloïdes indoliques, la synthèse totale énantiosélective de la *N*(1)-déméthyl-3,5-diépi-alstolactone a été accomplie. Cette séquence réactionnelle comporte trois points clés: 1) l'incorporation d'une fonction vinyle cétone en position C-2 d'indole en utilisant le couplage de Liebeskind-Srogl afin de former, après une métathèse cyclisante, une énone cyclique à huit chainons avancée, 2) une addition de Michael intramoléculaire hautement diastéréosélective et 3) la formation d'un système ponté, de type azabicyclo[3.3.1]nonane, à partir du cycle à huit correspondant *via* une séquence de déshydratation et de cyclisation transannulaire.

Mots-Clés:

Synthèse totale, synthèse asymétrique, alcaloïdes indoliques, rhazinilam, leucomidine B, leuconodine F, alstolactone, affinine, amerovolficine, vobasidine, alstonerine, hétéroannulation, réduction diastéréosélective, cyclisation transannulaire, cycle à huit chainons, addition-1,4.

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Abbreviations

°C	Degree Celsius
9-BBN	9-Borabicyclo(3.3.1)nonane
Å	Ångström
Ac	Acetyl
Aq.	Aqueous
Ar	Aromatic
atm	Atmosphere
BHT	Butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
BIPHEP	2,2'-bis(diphenylphosphanyl)-1,1'-biphenyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
brsm	Based on recovered starting material
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cat*	Chiral catalyst
Cbz	Carboxybenzyl
CDI	Carbonyldiimidazole
cf.	Confer
COD	Cyclooctadiene
Conv.	Conversion
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Day
DABCO	1,4-diazabicyclo[2.2.2]octane
DAVEPHOS	2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminium hydride
DIAD	Diisopropyl azadicarboxylate
DIPEA (Hünig's base)	*N,N*-Diisopropylethylamine
dig	Digonal
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Demethylformamide
DMP	Dess-Martin periodinane - 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
DPEPHOS	Bis[(2-diphenylphosphino)phenyl] ether
DPP	Diphenylphosphoryl
DPPA	Diphenylphosphoryl azide

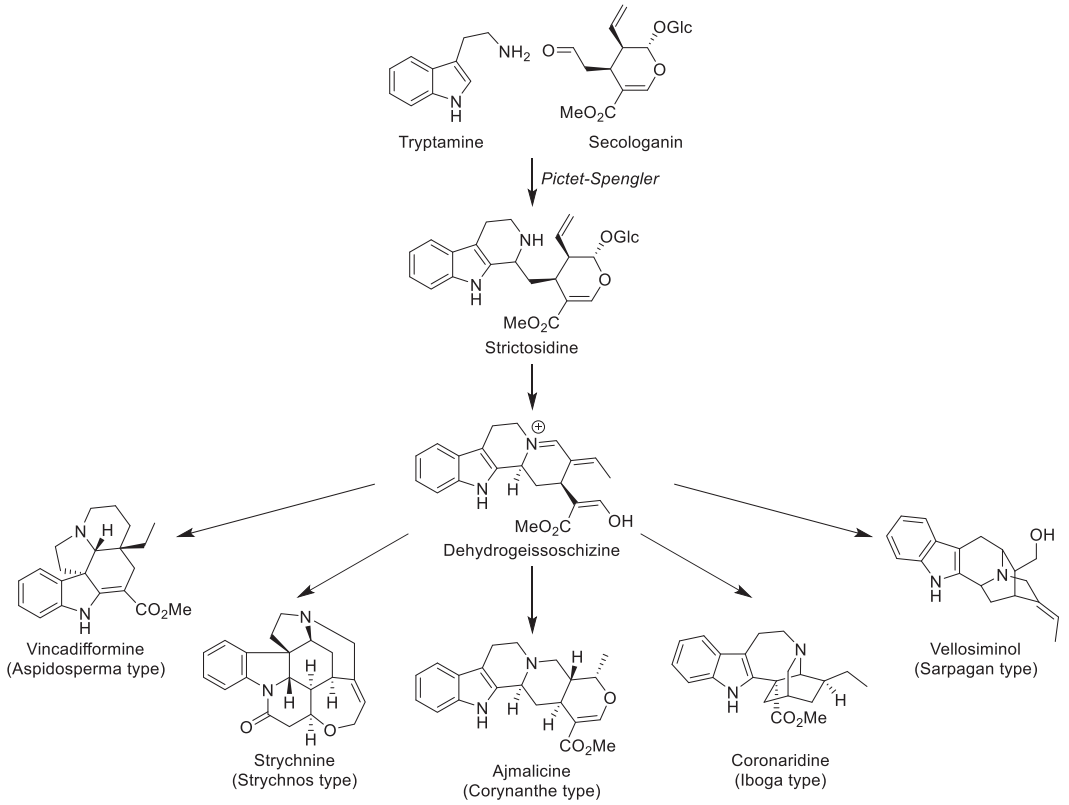
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
E	Electrophile
E	Entgegen
EDCI	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	Enantiomeric excess
eq.	Equation
equiv	Equivalent
er	Enantiomeric ratio
Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
FGI	Functional group interconversion
g	Gram
h	Hour
Hantzsch ester	Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
HFIP	Hexafluoro-2-propanol
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
hυ	Light
Hz	Hertz
IBX	2-Iodoxybenzoic acid
***i*-Pr or *i*Pr**	*iso*-Propyl
JOSIPHOS	1-[(1R)-1-[Bis(1,1-dimethylethyl)phosphino]ethyl]-2-(diphenylphosphino)ferrocene
L	Litre
LA	Lewis Acid
LDA	Lithium diisopropylamide
ligand*	Chiral ligand
LiTMP	Lithium tetramethylpiperidide
m	Milli
m	Meta
M	Molar
***m*CPBA**	*meta*-Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
mol	Mole
MOM	Methoxymethyl ether
Ms	Mesyl
MS	Molecular sieves or Mass spectroscopy
MW	Microwave
N	Normal

NBS	*N*-Bromosuccinimide
***n*-Bu or *n*Bu**	*normal*-butyl
NHC	*N*-Heterocyclic carbene
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic resonance
nr	No reaction
Nu	Nucleophile
o	Ortho
p	Para
PCC	Pyridinium chlorochromate
PE	Petroleum ether
PG	Protecting group
Ph	Phenyl
PhD	Doctor of Philosophy
Phth	Phthalimide
Pin	Pinacol - 2,3-dimethyl-2,3-butanediol
PMB	*para*-Methoxybenzyl
PPA	Polyphosphoric acid
PPTS	Pyridinium para-toluenesulfonate
Pr	Propyl
PTSA	*para*-Toluenesulfonic acid
Pyr	Pyridine
quant.	Quantitative
R	Rectus
rt	Room temperature
S	Sinister
SEGPHOS	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, [4(R)-(4,4'-bi-1,3-benzodioxole)-5,5'-diyl]bis[diphenylphosphine]
SFC	Supercritical Fluid Chromatography
S_N (1 or 2)	Nucleophilic substitution
S_NAr	Nucleophilic Aromatic Substitution
S_Ni	Nucleophilic Substitution Internal
T°	Temperature
TBAAz	Tetrabutylammonium azide
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TBAI	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
***t*-Bu or *t*Bu**	*tert*-Butyl
***t*BuPHOX**	4-*tert*-Butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline
TES	Triethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

TFE	Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Tr	Trityl - Triphenylmethyl
trig	Trigonal
Ts	Tosyl
UPLC	Ultra performance liquid chromatography
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Z	Zusammen

General Introduction

For ages plants and fungi were used to treat and cure diverse diseases. It was found that most of the active natural products isolated from these sources belong to the class of monoterpene indole alkaloids. For example reserpine, which is extracted from the roots of *Rauvolfia Serpentina*, was used in India to treat fever, snake bites and insanity since 1000 B.C. Due to its antihypertensive property, tea based on this root was also made by Mahatma Gandhi to help him relax after an overstimulating day.[1] On the contrary, other alkaloids can be toxic for human beings. For instance fungus *Claviceps Purpurea*, which can contaminate rye and related cereals, produces ergotamine. The latter and close alkaloids can provoke ergotism which manifests itself either by convulsive symptoms or by dry gangrene.[2] As the majority of the monoterpene indole alkaloids exhibited biological activity, this family of natural products was, and still is, largely studied. Until now, more than two thousand members of this class were isolated and identified.[3]



Scheme 1 Common biosynthesis of monoterpene indole alkaloids

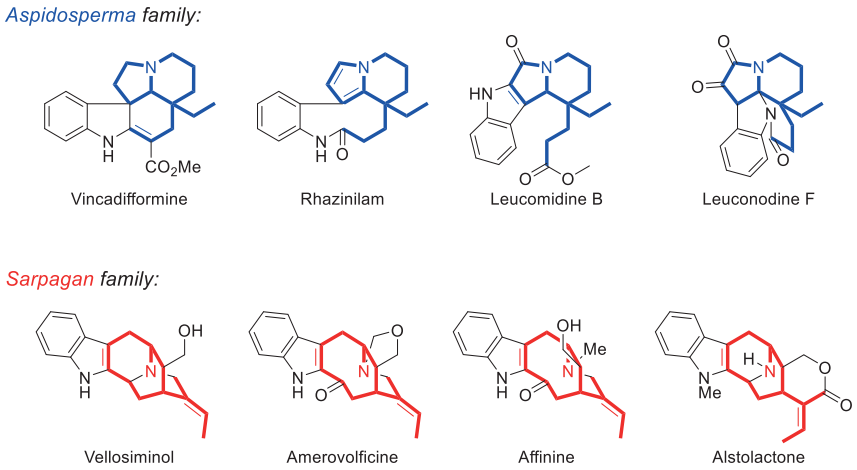
As depicted in Scheme 1, monoterpene indole alkaloids are all biosynthesized from the same starting point: a Pictet-Spengler reaction between tryptamine and secologanin to give

[1] Lobay, D. *Integrative Medicine* **2015**, *14*, 40–46.
[2] Piquemal, R.; Emmerich, J.; Guilmot, J. L.; Fiessinger, J. N. *Angiology* **1998**, *49*, 493–497.
[3] (a) Hájíček, J. *Collect. Czech. Chem. Comm.* **2011**, *76*, 2023−2083. (b) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2015**, *32*, 1389−1471 and references cited herein.

strictosidine. Hydrolysis of the acetal and next condensation of the amine onto the resulting aldehyde gave the corresponding iminium, dehydrogeissoschizine. Reactions involved in the further steps give the skeletal diversification of this class of natural products.[4]

Unfortunately, some of the most potent active alkaloids were revealed to be present in insignificant amounts in the biomass. Based on the isolation papers, the extraction of only a few milligrams of desired alkaloids from tens, even hundreds, kilograms of plants is indeed common. In order to avoid destruction of the nature and its ecosystem, the synthesis of these natural products, from easily available materials, appears to be the best alternative. In addition, the chemist would have the opportunity to bring substrate modifications to even further modulate the activity of the compounds.

Interest in the total synthesis of monoterpenoid indoles by the scientific community is not only due to their biological activities. This class of compounds possesses interesting polycyclic structures of various sizes and arrangements which gives multiple challenges to synthetic chemists. Furthermore, with the perpetual discovery and development of new reactivities, more elegant, step-economic and higher yielding syntheses are always targeted.



Scheme 2 Selected examples of monoterpenoid indoles

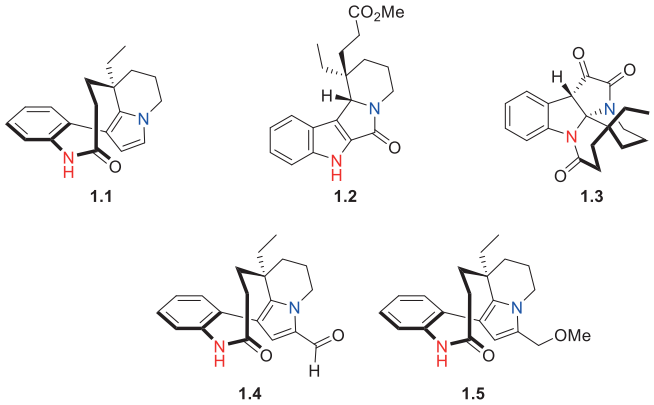
The total synthesis of monoterpene indole alkaloids is one of the main topics of our group. This work was focused particularly on two families as shown in Scheme 2. More precisely, we will see in the first part of the thesis the synthesis of three *Aspidosperma*-related indoles named rhazinilam, leucomidine B and leuconodine F. The second part is centered on the synthetic studies towards the *Sarpagan* family. Several natural products were considered such as amerovolficine, affinine or alstolactone.

[4] O'Connor, S. E.; Maresh J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

PART I :
Divergent Total Synthesis of (-)-Rhazinilam, (-)-Leucomidine B and (+)-Leuconodine F

Introduction

The first part of the thesis will cover the very first research project investigated during my PhD. The initial objective was to develop a new strategy, involving a domino process, in order to accomplish the total synthesis of (-)-rhazinilam (**1.1**). The next step was to extend this new approach to the synthesis of an additional two natural products: (-)-leucomidine B (**1.2**) and (+)-leuconodine F (**1.3**). Synthetic studies of other members of the rhazinilam family, (-)-rhazinal (**1.4**) and (-)-kopsiyunnanine C1 (**1.5**), were also explored (Scheme 3).



Scheme 3 Targets explored during the first project

In the first chapter, we will pay our attention to literature reports that described the isolation and synthesis of the natural products **1.1**, **1.2** and **1.3**. In this chapter, the work previously accomplished by our laboratory in the field of monoterpene indole alkaloid total synthesis will also be discussed. The total synthesis of (-)-rhazinilam (**1.1**), (-)-leucomidine B (**1.2**) and (+)-leuconodine F (**1.3**) will be described in detail in chapters two, three and four, respectively. Finally, we will see a conclusion covering this first part of the thesis.

Chapter 1. State of the Art

1.1. (-)-Rhazinilam

1.1.1. Generality

(-)-Rhazinilam (**1.1**) is a macrocyclic natural product, first isolated by Linde from *Melodinus Australis* in 1965 and named as "Ld 82".[5] Five years later, (-)-rhazinilam (**1**) was also extracted from *Rhazya Stricta* which gave it its final name.[6] The structure was elucidated in 1972 by X-Ray analysis which confirmed the unsual 9-membered lactam of this monoterpenoid indole.[7]

(-)-Rhazinilam (**1.1**) possesses anti-mitotic properties due to its interference with tubulin polymerization and dynamics. This particular tubulin-binding characteristic of (-)-rhazinilam (**1.1**) was evidenced by its *in-vitro* activity againts various cancer cell lines. However, no cytotoxicity was found *in-vivo*, potentially due to the fast hydrolysis of the 9-membered lactam. Baudoin and coworkers synthesized some analogues of (-)-rhazinilam (**1.1**) by varying the size of the lactam ring and demonstrated that the rigidity of the 9-membered cyclic amide was critical for the activity of the molecule.[8]

1.1.2. Biosynthesis and Semi Synthesis

The biosynthesis of (-)-rhazinilam (**1.1**) was hypothesized to start from (+)-vincadifformine (**1.7**). Hydrolysis of the ester and subsequent decarboxylation should give (+)-1,2-didehydroaspidospermidine (**1.8**) which, after oxidation, would lead to 5,21-dihydrorhazinilam (**1.6**). Due to the known sensitivity of the dihydropyrrole moiety towards oxygen, exposure of **1.6** to air would trigger the aromatization to the pyrrole and therefore furnish **1.1**. In 2006, this route was experimentally tested and confirmed by Guénard and coworkers (Scheme 4).[9] It was postulated that **1.6** is the actual natural product and that (-)-rhazinilam (**1.1**), due to the presence of air, is just an artifact of the plant extraction procedure.

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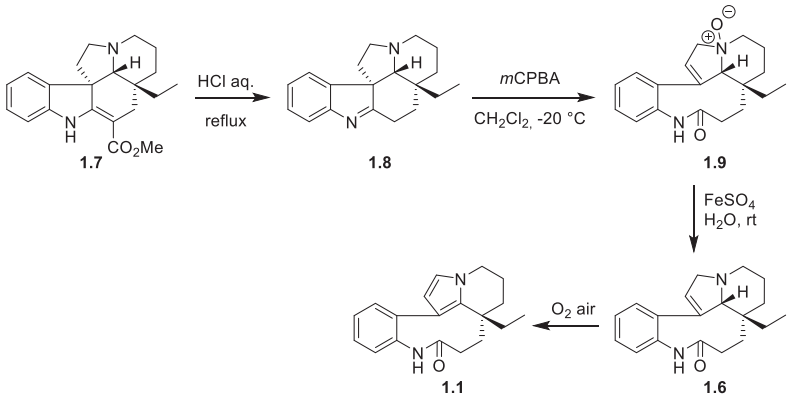
[5] Linde, H. H. A. *Helv. Chim. Acta*, **1965**, *48*, 1822–1842.
[6] Banerji, A.; Majumder, P. L.; Chatterjee, A. *Phytochemistry*, **1970**, *9*, 1491–1493.
[7] Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *10*, 909–912.
[8] Décor, A.; Monse, B.; Martin, M.-T.; Chiaroni, A.; Thoret, S.; Guénard, D.; Guéritte F.; Baudoin, O. *Bioorganic & Medicinal Chemistry* **2006**, *14*, 2314–2332.
[9] (a) David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155–2158. (b) Dupont, C.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Bioorg. Med. Chem.* **1999**, *7*, 2961–2969.



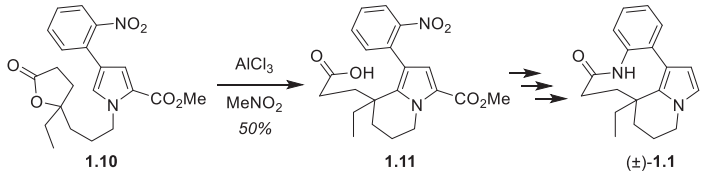
Scheme 4 Semi synthesis of rhazinilam

1.1.3. Total Synthesis

Due to its unusual skeleton, (-)-rhazinilam (**1.1**) was, and still is, a privileged target for many groups. Over the years, **1.1** has been synthesized several times with in mind the challenge of increasing the efficiency and the elegancy of the route but also, to demonstrate the potential of newly developed methodologies. In the literature, 16 total syntheses have been reported already; 8 of which are enantioselective.[10]

Smith's Synthesis

The first total synthesis of **1.1** in racemic form was reported by Smith in 1973.[11] The key step involved an intramolecular Friedel-Crafts cyclization of pyrrole **1.10** *via* lactone opening (Scheme 5). The desired transformation was achieved using aluminium trichloride in nitromethane which afforded tetrahydroindolizine **1.11** in 50% yield. After reduction of the nitro group to give an aniline, macrolactamization and deprotection of the pyrrole by decarboxylation, (±)-rhazinilam (**1.1**) was obtained in 10 steps in 3.6% overall yield.

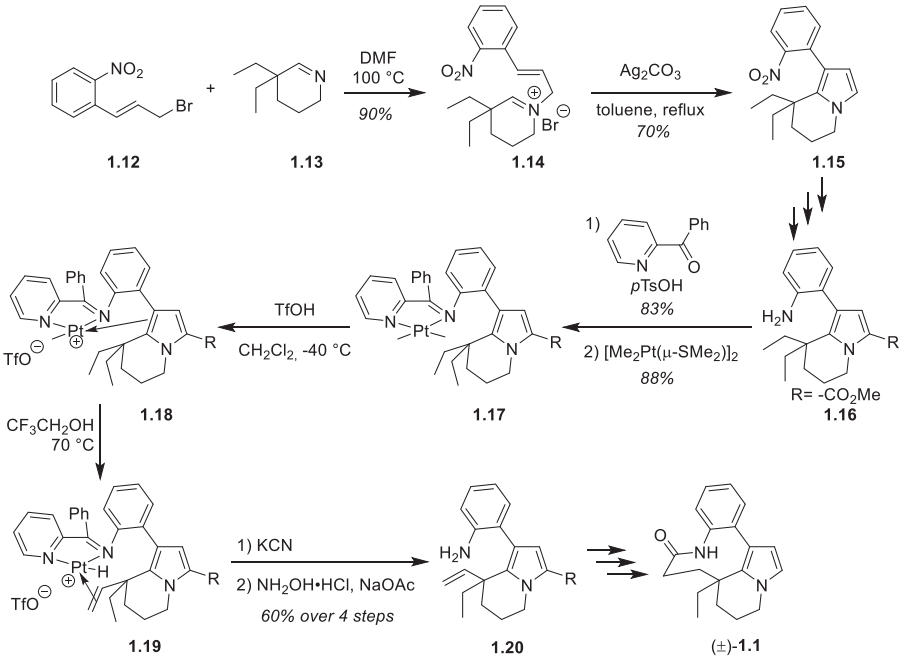


Scheme 5 Smith's synthesis

[10] For reviews on the total synthesis of rhazinilam see: (a) Kholod, I.; Vallat, O; Buciumas, A.-M.; Neier, R. *Hetereocycles* **2011**, *82*, 917–948. (b) Crossley, S. W. M.; Shenvi, R. A. *Chem. Rev.* **2015**, *115*, 9465−9531.
[11] Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179–5184.

Sames' Synthesis

Almost thirty years later, a second total synthesis of (±)-rhazinilam (**1.1**) was reported by Sames and coworkers in 2000 (Scheme 6).[12] The first key step was the pyrrole formation *via* a Grigg-type 1,5-electrocyclization reaction of iminium **1.14** catalyzed by silver carbonate. Pyrrole **1.15**, isolated in 70% yield over 2 steps, was then protected and after reduction of the nitro group, aniline **1.16** was obtained. Then, platinum-catalyzed C-H activation of the ethyl group was accomplished to obtain the corresponding ethylene group. To this end, a Schiff base was first introduced followed by complexation to form the platinum complex **1.17** which can be isolated in 73% yield over 2 steps. Treatment of the latter with triflic acid to generate cationic platinium *via* loss of methane and subsequent thermolysis in trifluoroethanol then yielded the desired ethylene moiety. After metal decomplexation with potassium cyanide and removal of the Schiff base, desired intermediate **1.20** was isolated in 60% yield over 4 steps. After functionalization of the vinyl group and macrocyclization, (±)-rhazinilam (**1.1**) was obtained in 20 steps and 3.5% overall yield. In spite of the additional steps, a similar overall yield to that of the Smith synthesis was obtained.



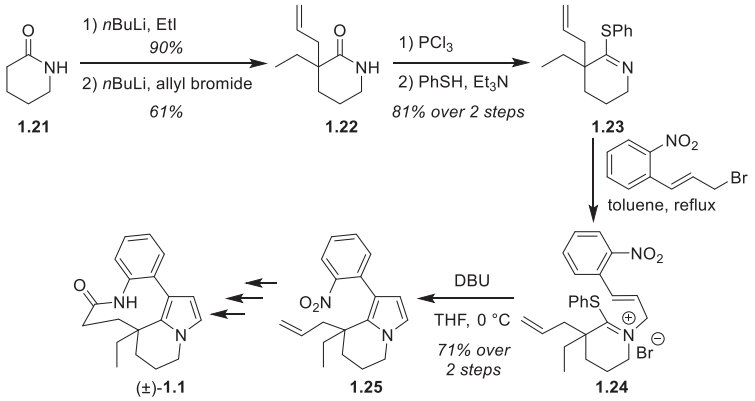
Scheme 6 Sames' synthesis

[12] Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321–6322.

Magnus's Synthesis

In 2001, Magnus reported the third total synthesis of racemic rhazinilam (**1.1**).[13] The synthesis was similar to the Sames' synthesis regarding the pyrrole formation. Indeed, lactam **1.22** was converted to the corresponding thiophenyl imino ether **1.23** which, after allylation, afforded iminium **1.24**. Upon treatment with DBU, a Grigg-type 1,5-electrocyclization / thiophenol elimination sequence occurred to afford pyrrole **1.25** in 71% yield from **1.23**. The main difference in this synthesis, compared to the previous one, resided in the differentiation of the two aliphatic chains in *alpha* position of the pyrrole at an early-stage (Scheme 7). This saved multiple steps and (±)-rhazinilam (**1.1**) was synthesized in 11 steps and in a remarkable 7.6% overall yield. It was also the first synthesis completed without protection of the pyrrole moiety.

It should be noted that, in 2012, intermediate **1.22** was synthesized enantioselectively by Stoltz and coworkers in their formal synthesis of the unnatural (+)-rhazinilam (**1**).[14] The group employed their enantioselective Pd-catalyzed decarboxylative allylation reaction in order to reach **1.22** with 99% ee using (*S*)-$(CF_3)_3$-*t*-BuPHOX as ligand.

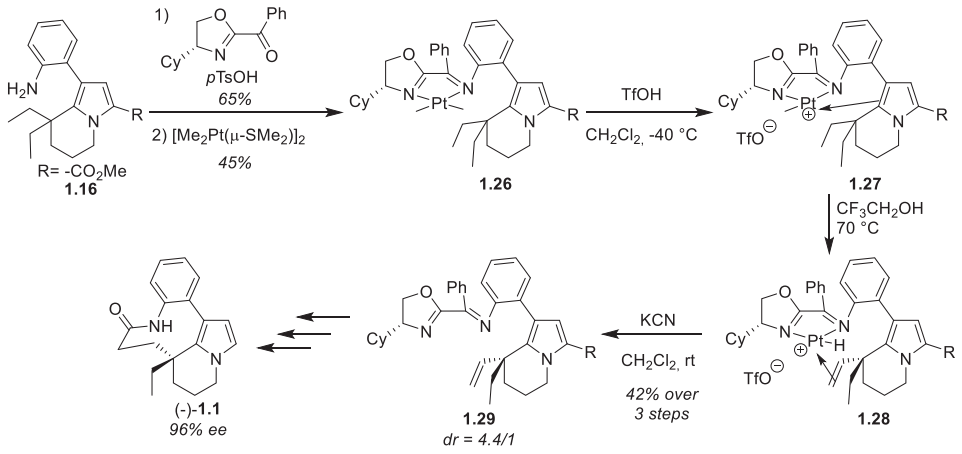


Scheme 7 Magnus's synthesis

Sames' Second Synthesis

The first enantioselective total synthesis of rhazinilam (**1.1**) was reported by Sames and coworkers in 2002.[15] This novel synthesis was an adaptation of the racemic one. The key step involved the desymmetrization of the two ethyl groups *via* a similar C-H activation utilizing a chiral Schiff base (Scheme 8). The obtained 4.4/1 diastereomeric mixture of **1.29** was separated by preparative HPLC before removal of the chiral auxiliary. Following the original pathway onwards, (-)-rhazinilam (**1.1**) was synthesized in 16 steps and in 1.6% overall yield with 96% ee.

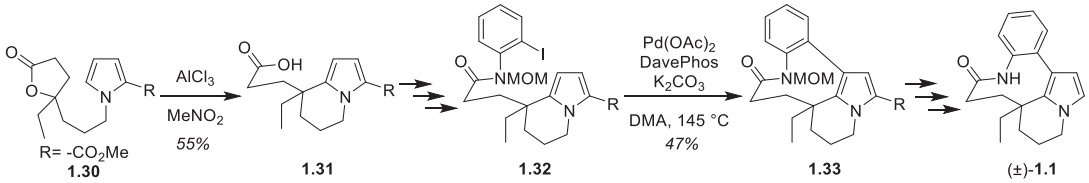
[13] Magnus P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647–8651.
[14] Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133.
[15] Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900–6903.



Scheme 8 Sames' second synthesis

Trauner's Synthesis

In 2005 Trauner reported the fourth total synthesis of rhazinilam (**1.1**) in racemic form.[16] Tetrahydroindolizine **1.31** was obtained in a similar manner as for the Smith synthesis *via* a Friedel-Crafts reaction. While all previous syntheses were accomplished *via* a final macrolactamization between the aniline and the aliphatic acid, Trauner pursued a different strategy. Intramolecular Pd-catalyzed C-H activation between the pyrrole moiety and the iodobenzene **1.32** afforded protected lactam **1.33** in a moderate yield of 47% (Scheme 9). Protection of the amide proved crucial for the success of this coupling reaction as only deiodination was observed using the free amide substrate. After deprotection of the amide and pyrrole, (±)-rhazinilam (**1.1**) was obtained in 13 steps in 1.7% overall yield.



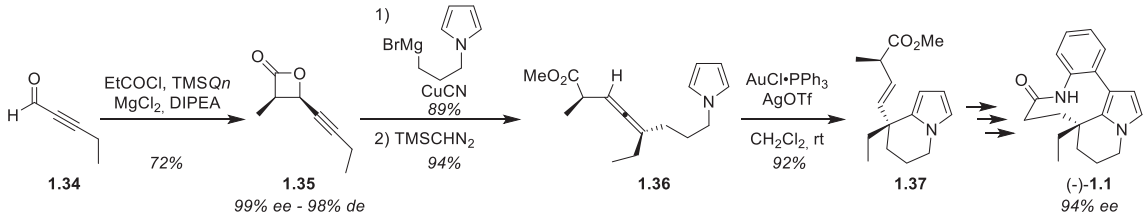
Scheme 9 Trauner's synthesis

Nelson's Synthesis

In 2006, a novel enantioselective total synthesis of rhazinilam (**1.1**) was reported by Nelson (Scheme 10).[17] The chiral center was installed at the very beginning of the synthesis *via* an asymmetric cyclocondensation between pent-2-ynal **1.34** and propionyl chloride, a method

[16] Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207–5209.
[17] Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352–10353.

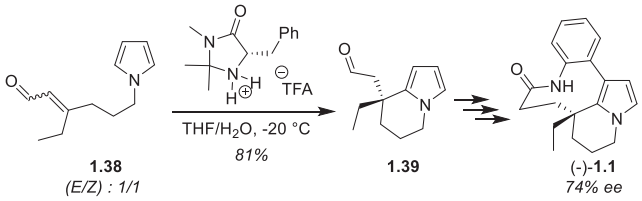
previously developed by his group utilizing a quinine derivative as a chiral organocatalyst. The *beta*-lactone **1.35**, obtained in 72% yield, was opened by addition of an *in-situ* generated cuprate reagent onto the alkyne followed by methylation of the liberated carboxylic acid to form enantioenriched allene **1.36** in 84% yield over 2 steps. Tetrahydroindolizine **1.37** was obtained by intramolecular gold-catalyzed annulation with transfer of the allene chirality in an excellent yield of 92%. The need for a silver salt suggested that the reaction occurred through a cationic gold catalyst *via* abstraction of the chloride by the silver. It should be noted that other metals such as palladium gave poor chirality transfer. After functional group manipulations of the side chain, pyrrole iodination, subsequent Suzuki coupling and final macrolactamization, (-)-rhazinilam (**1**) was synthesized in 11 steps and in a high overall yield of 19.8% with 94% ee.



Scheme 10 Nelson's synthesis

Banwell's Synthesis

The same year, Banwell reported another enantioselective synthesis of rhazinilam (**1.1**).[18] The key step in this case consisted of an intramolecular asymmetric 1,4-addition of the pyrrole moiety onto the enal in **1.38**, assisted by a MacMillan imidazolidinone organocatalyst (Scheme 11). Unstable aldehyde **1.39** was obtained in a good yield of 81%. Further steps were similar to the previous synthesis: transformation of the side chain, pyrrole iodination, Suzuki coupling and lactamization to afford (-)-rhazinilam (**1.1**) in 18 steps and in 4.4% overall yield with 74% ee.

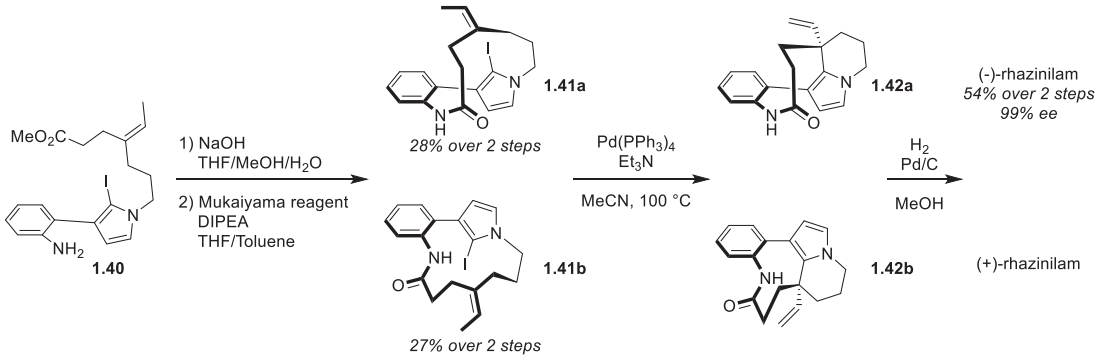


Scheme 11 Banwell's synthesis

[18] Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, (iii), 163–174.

Zakarian's Synthesis

The next total synthesis was reported in 2010 by Zakarian.[19] His strategy was to first synthesize the 13-membered macrolactam starting from aminoester **1.40** and to form the 6-membered ring of the tetrahydroindolizine core at the late-stage *via* an intramolecular Heck coupling (Scheme 12). After hydrolysis of ester **1.40**, the macrolactamization was successfully carried out using the Mukaiyama reagent. It should be noted that other coupling reagents such as DCC, EDCI, BOP or HATU failed to give the desire macrocycle product. Due to the steric hindrance of the iodine substituent, desired product **1.41** was obtained as a 1/1 mixture of two stable atropisomers which were separated by chiral HPLC. The group demonstrated that each atropisomer furnished, after Pd-catalyzed transannulation and reduction of the resulting vinyl, the corresponding enantiomer (+) or (-). With this approach, natural (-)-rhazinilam (**1.1**) was obtained in 13 steps and in 4.0% overall yield with 99% ee.

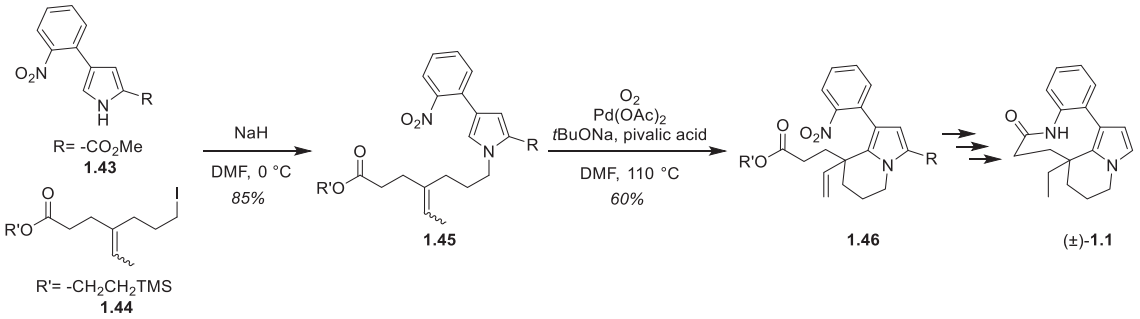


Scheme 12 Zakarian's synthesis

Gaunt's Synthesis

The ninth total synthesis was reported by Gaunt and coworkers in 2012.[20] Their work represents the fifth synthesis of rhazinilam (**1.1**) in racemic form. Intermediate **1.45** was obtained from the alkylation of corresponding pyrrole **1.43** with advanced iodoalkyl **1.44**, a building block already used in their total synthesis of rhazinicine.[21] The key step in this case was the Pd(II)-catalyzed C-H bond alkenylation in C-5 of pyrrole **1.45**. This transformation, carried out under oxygen atmosphere to provide a terminal oxidant, afforded desired tetrahydroindolizine core **1.46** in 60% yield (Scheme 13). After functional group interconversions of the latter, (±)-rhazinilam (**1.1**) was obtained in 9.5% overall yield over 11 steps.

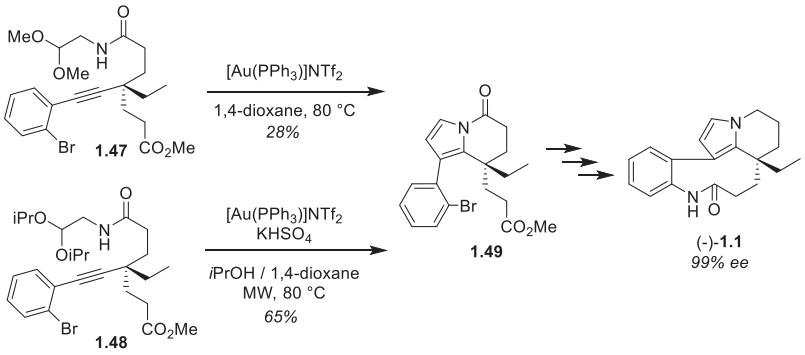
[19] Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224–4227.
[20] McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 9288–9291.
[21] Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008**, *120*, 3046–3049.



Scheme 13 Gaunt's synthesis

Tokuyama's synthesis

In 2013, Tokuyama reported the fifth enantioselective total synthesis of (-)-rhazinilam (**1.1**) as an application of a novel methodology: intramolecular gold-catalyzed cascade cyclization to form, in one operation, the tetrahydroindolizine moiety.[22] This method involves the intramolecular addition of an amide on an alkyne in a *6-exo-dig* manner to form a 6-membered lactam. The resulting enamide further reacts with an acetal to form a 5-membered ring and then aromatization by alcohol elimination affords the pyrrole. This novel methodology, when applied to the synthesis of rhazinilam (**1.1**), gave first only 28% yield when starting from linear intermediate **1.47** (Scheme 14). When a bulkier acetal **1.48** was used and intermittent microwave irradiation was employed, desired tetrahydroindolizine **1.49** was obtained in 65% yield. The use of the isopropyl acetal, instead of the methyl one, avoids the gold-catalyzed alcoholysis of the alkyne as a side reaction. The chirality of intermediates **1.47** and **1.45** was installed at the very beginning of the synthesis by chiral enamine chemistry as described by d'Angelo et al. After additional transformations of **1.49**, (-)-rhazinilam (**1.1**) was synthesized in a total of 16 steps and in 7.6% overall yield with 99% ee.

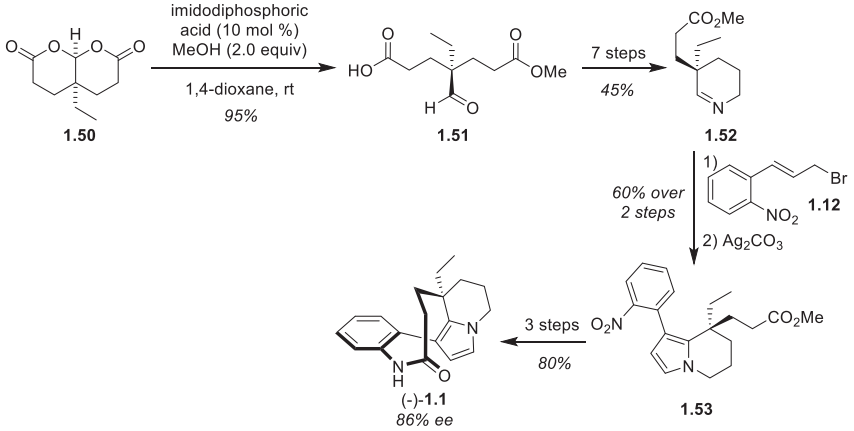


Scheme 14 Tokuyama's synthesis

[22] Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7168–7171.

Zhu's Synthesis

The next synthesis was reported in 2014 by our group, also as an application of a novel methodology.[23] Desymmetrization of bicyclic bislactone **1.50** by ring opening with methanol in the presence of a chiral imidodiphosphoric acid afforded enantioenriched Kuehne's aldehyde **1.51** in an excellent yield of 95% and with 84% ee (Scheme 15). Further functional group interconversion afforded key imine **1.52** which, following a similar path to Sames' strategy *via* alkylation of **1.52** with allylic bromide **1.12** and Grigg's 1,5-electrocyclization of the resulting iminium ion, then gave tetrahydroindolizine **1.53**. After nitroaryl reduction, ester hydrolysis and macrolactamization, (-)-rhazinilam (**1.1**) was obtained in 15 steps in a high overall yield of 19.5% with 86% ee.



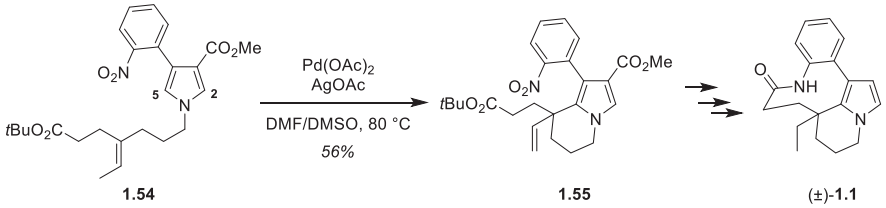
Scheme 15 Zhu's synthesis

Lin and Yao's Synthesis

Lin and Yao reported the same year an additional total synthesis of racemic rhazinilam (**1.1**).[24] Similarly to the strategy of Gaunt, the tetrahydroindolizine core was formed by intramolecular Pd(II)-catalyzed C-H bond alkenylation in C-5 of pyrrole **1.54**. Unlike in the case of Gaunt's intermediate **1.45**, bearing an ester group in C-2 of the pyrrole, the coupling reaction of **1.54** can deliver two regioisomers (Scheme 16). The regioselectivity was controlled by the solvent system used for this transformation. When a non-coordinating solvent is used, such as toluene, mesitylene or 1,2-DCE, C-2 functionalization is obtained. It was proposed that coordination of the Pd catalyst with the ester in the C-3 position of the pyrrole could occur thereby explaining this regioselectivity. In contrast, the use of a coordinating solvent, for instance DMF or DMSO, prevents this metal coordination with the ester therefore favouring the electrophilic palladation

[23] Gualtierotti, J.-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9926–9930.
[24] Su, Y.; Zhou, H.; Chen, J.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Org. Lett.* **2014**, *16*, 4884–4487.

at the more electron rich C-5 carbon. Overall, when using $Pd(OAc)_2$ in a mixture of DMF/DMSO with a silver salt as terminal oxidant, desired coupling product **1.55** can be obtained in 56% yield with a high C-5/C-2 regioselectivity of 12/1. After vinyl reduction, hydrolysis of the esters, with concomitant deprotection of the pyrrole *via* decarboxylation, nitro reduction and lactamization, (±)-rhazinilam (**1.1**) was obtained in 8.1% yield over 13 steps.

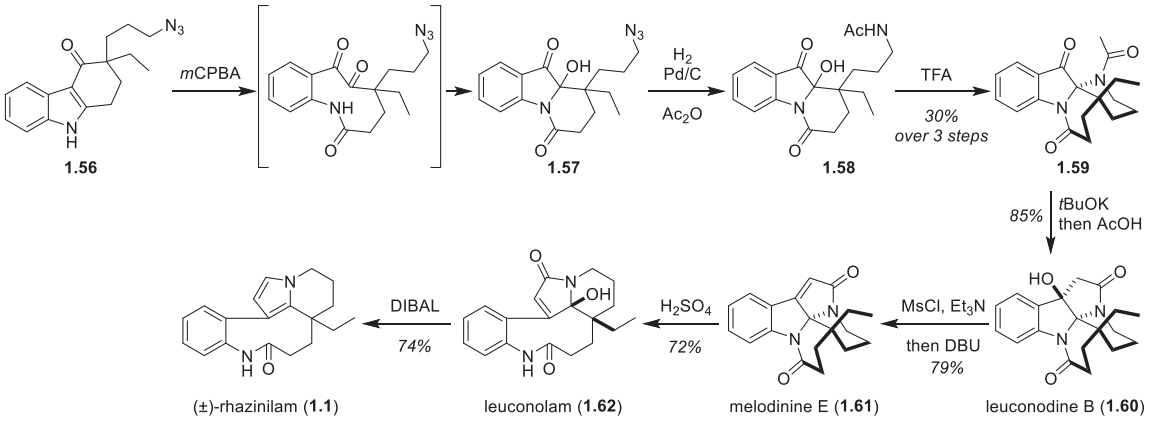


Scheme 16 Lin and Yao's synthesis

Dai's Synthesis

In 2014, Dai reported a bio-inspired total synthesis of (±)-rhazinilam (**1.1**).[25] The key step was the formation the 9-membered lactam *via* a Witkop-Winterfeldt oxidative indole cleavage. This transformation was successfully carried on advanced substrate **1.56** using freshly purified *m*CPBA as the oxidant. The macrocycle intermediate was not isolated due to spontaneous transannulation of the amide into the diketone in order to afford hemiaminal **1.57** (Scheme 17). The azide group was reduced to the corresponding amine which was acetylated directly in the presence of acetic anhydride. Dehydration of the hemiaminal **1.58** in the presence of TFA allowed the formation of an iminium species which was subsequently trapped by the acetamide to afford aminal **1.59** in 30% yield over 3 steps. Deprotonation of the acetamide **1.59** with *t*-BuOK formed the natural product leuconodine B (**1.60**) by intramolecular aldol addition. Mesylation and elimination of the alcohol **1.60** afforded conjugated lactam **1.61**, melodinine E. Treatment of the latter with sulfuric acid promoted the fragmentation of the aminal to reform hemiaminal **1.62** known as leuconolam. Mono-reduction of the conjugated lactam **1.62** in a 1,2-fashion and further aromatization to give the pyrrole *via* elimination of two equivalents of water afforded desired (±)-rhazinilam (**1.1**) in 3.7% yield over a total of 14 steps.

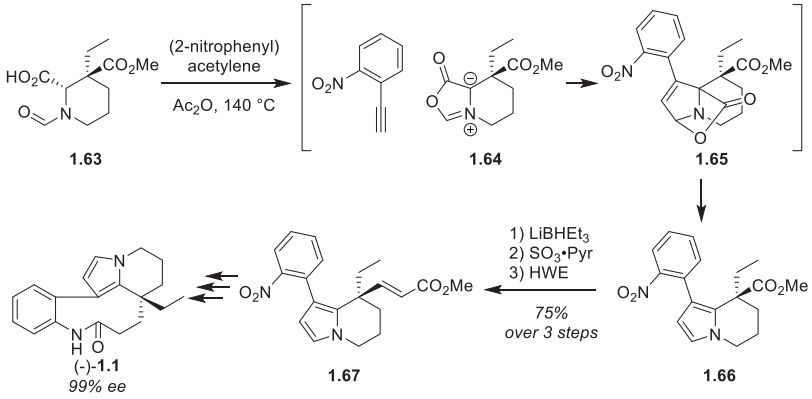
[25] Yang, Y.; Bai, Y.; Sun, S.; Dai, M. *Org. Lett.* **2014**, *16*, 6216–6219.



Scheme 17 Dai's synthesis

Tokuyama's Second Synthesis

In 2015, Tokuyama and coworkers reported a second enantioselective total synthesis of rhazinilam (**1.1**) which was based on a completely different strategy compared to their first synthesis.[26] Elaborated intermediate **1.63**, synthesized in 7 steps from D-aspartic acid, was refluxed in acetic anhydride to form 1,3-dipole **1.64**. In the presence of (2-nitrophenyl)acetylene, **1.64** undergoes a [3+2] cycloaddition reaction in a regioselective manner to afford **1.65** which spontaneously decarboxylates under the harsh reaction conditions to give pyrrole **1.66** with an impressive yield of 94% (Scheme 18). The ester group was then converted by a reduction / oxidation sequence to an aldehyde which was subjected directly to a two-carbon homologation using the HWE reaction. After three additional steps, **1.67** was converted to (-)-rhazinilam (**1.1**) in a total of 14 steps and in 7.1% overall yield with 99% ee.

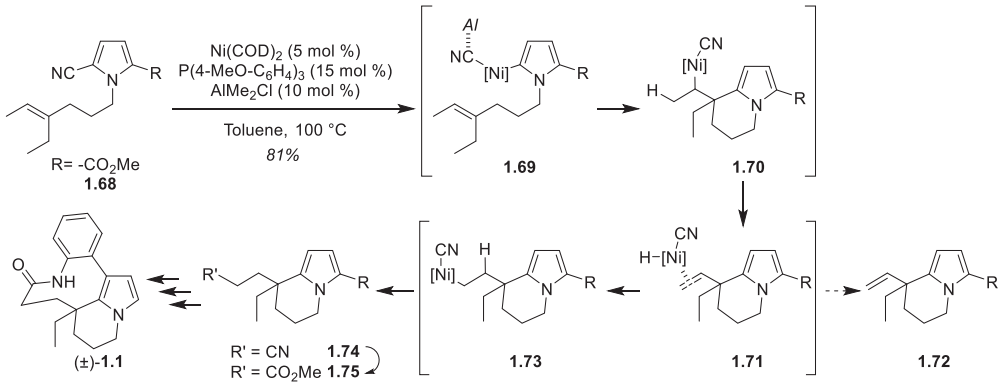


Scheme 18 Tokuyama's second synthesis

[26] Sugimoto, K.; Miyakawa, Y.; Tokuyama, H. *Tetrahedron* **2015**, *71*, 3619−3624.

Nakao's Synthesis

To the best of our knowledge, Nakao's group reported in 2015 the last total synthesis of rhazinilam (**1.1**) in racemic form. The key step in their synthesis involved an intramolecular arylcyanation of an alkene catalyzed by a bimetallic nickel/aluminium system.[27] Under the optimized conditions of 5 mol % $Ni(COD)_2$ with P(4-OMe-$C_6H_4)_3$ as ligand in the presence of 10 mol % of $AlMe_2Cl$ in hot toluene, desired compound **1.74** was obtained in 81% yield from **1.68** (Scheme 19). Mechanistically, the authors proposed that the Lewis acid first activated the nitrile, thus allowing the oxidative addition of the Ni(0) catalyst into the pyrrole − cyanide bond. Coordination of the resulting Ni(II) species with the trisubstituted olefin followed by migratory insertion would give secondary alkylnickel **1.70**. *Beta*-hydride elimination would form alkene/Ni complex **1.71** which after decoordination would deliver the minor, but isolable, side product **1.72**. Nickel complex **1.71** could, however, reinsert into the vinyl group in order to give primary alkylnickel species **1.73** which could result in product **1.74** after reductive elimination together with the regeneration of the Ni(0) catalyst. Nitrile **1.74** was hydrolyzed to the corresponding acid and after esterification with methanol, Nelson type intermediate **1.75** was obtained. The endgame was accomplished following a slightly modified Nelson procedure to afford (±)-rhazinilam (**1.1**) in 3.5% yield over 14 steps.



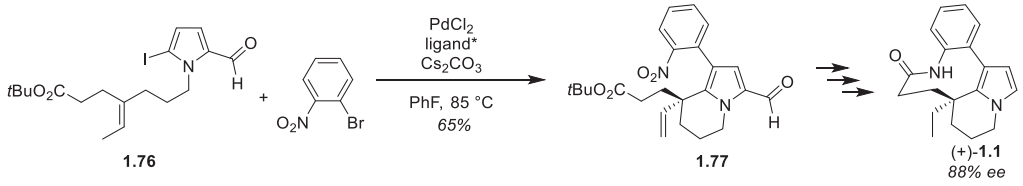
Scheme 19 Nakao's synthesis

Gu's synthesis

In 2016, Gu and coworkers reported the last enantioselective total synthesis of popular rhazinilam (**1.1**), but this time of the (+)-enantiomer.[28] The key step involved a Catellani-type reaction in order to install in one operation the tetrahydroindolizine moiety and, regioselectively, a nitrobenzene in the C-4 position of the pyrrole. Gu's group studied this transformation starting from iodopyrrole **1.76** in the presence of an excess of 1-bromo-2-nitrobenzene using various

[27] Yamada, Y.; Ebata, S.; Hiyama, T.; Nakao, Y. *Tetrahedron* **2015**, *71*, 4413−4417.
[28] Zhao, K.; Xu, S.; Pan, C.; Sui, X.; Gu, Z. *Org. Lett.* **2016**, *18*, 3782−3785.

chiral Pd(0) catalysts. After screening several ligands, a phosphoramidite based on (*S*)-BINOL and a chiral tetrahydroquinoline derivative proved to be the most efficient. The solvent was revealed to be also critical for the reaction outcome and when fluorobenzene was used, adduct **1.77** could be obtained with up to 88% ee and in 65% yield (Scheme 20). Compound **1.77** was then converted to (+)-rhazinilam (**1.1**) by deformylation with Wilkinson's catalyst in refluxing xylene followed by the typical nitro reduction / ester hydrolysis / lactam coupling sequence.



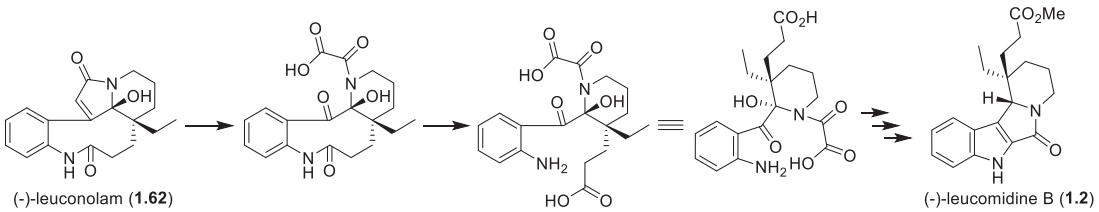
Scheme 20 Gu's synthesis

It should be noted that intermediate **1.77** was also converted to other members of the rhazinilam family including rhazinal (**1.4**) and kopsiyunnanine C1 (**1.5**).

1.2. (-)-Leucomidine B

1.2.1. Generality

(-)-Leucomidine B (**1.2**) is a natural indole alkaloid, isolated in 2012 by Morita, from the bark of *Leuconotis Griffithii*.[29] A plausible biosynthetic pathway was proposed by Morita in his isolation paper starting from the natural compound leuconolam. It was assumed that initially an oxidative ring opening of (-)-leuconolam (**1.62**) followed by lactam hydrolysis occurred. Subsequent cyclization to an indole, esterification of the acid group and reduction of the hemiaminal carbon could lead to (-)-leucomidine B (**1.2**) (Scheme 21).

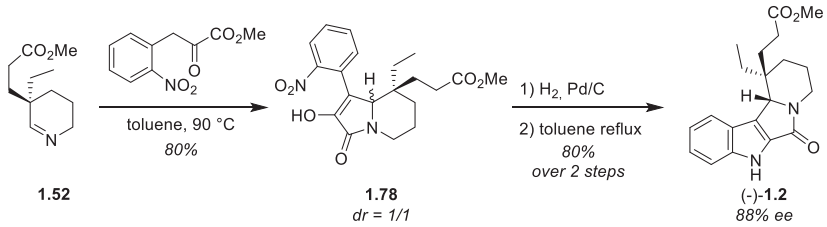


Scheme 21 Plausible biosynthetic pathway towards leucomidine B

[29] Motegi, M.; Nugroho, A. E.; Hirasawa, Y.; Arai, T.; Hadi, A. H. A.; Morita, H. *Tetrahedron Lett.* **2012**, *53*, 1227–1230.

1.2.2. Total Synthesis

Only one total synthesis of (-)-leucomidine B (**1.2**) had, to the best of our knowledge, previously been reported. This first total synthesis was accomplished in our group as an application of the desymmetrization of bicyclic bislactones mentioned previously (cf. 1.1.3.).[23] Using the same enantioenriched imine **1.52** and methyl 3-(2-nitrophenyl)-2-oxopropanoate, an intermolecular Mannich reaction followed by transamidation afforded intermediate **1.78** in 80% yield. Due to a lack of steric differentiation between the ethyl and ester side chains on **1.52**, a 1/1 diastereomeric mixture was obtained for **1.78**. Final nitroaryl reduction followed by cyclization to the indole gave (-)-leucomidine B (**1.2**) and its epimer in 80% yield (Scheme 22). It should be noted that the ketone in **1.78** being in the enol form slows down the condensation of the aniline intermediate and higher temperatures were thus required to form the desired indole fully. After separation of the two diastereoisomers, pure (-)-leucomidine B (**1.2**) was obtained in 12 steps from Kuehne's aldehyde with an overall yield of 13.0% and with 88% ee.



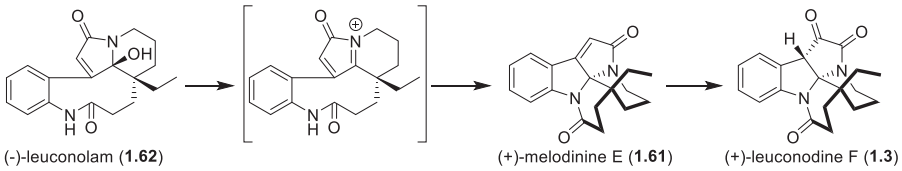
Scheme 22 First total synthesis of leucomidine B

1.3. (+)-Leuconodine F

1.3.1. Generality

(+)-Leuconodine F (**1.3**) (also named 6-oxoleuconoxine) was isolated in 2007 by Kam and coworkers from the leaf of *Kopsia Griffithii*. [30] (+)-Leuconodine F (**1.3**) has a very interesting skeleton with four fused rings linked to the same quaternary carbon center. The biosynthetic pathway was proposed to also start from (-)-leuconolam (**1.62**).[31] Dehydration of **1.62** would lead to an iminium intermediate which then can undergo a transannular cyclization to give melodinine E (**1.81**). Further oxidation of **1.81** would afford (+)-leuconodine F (**1.3**) (Scheme 23).

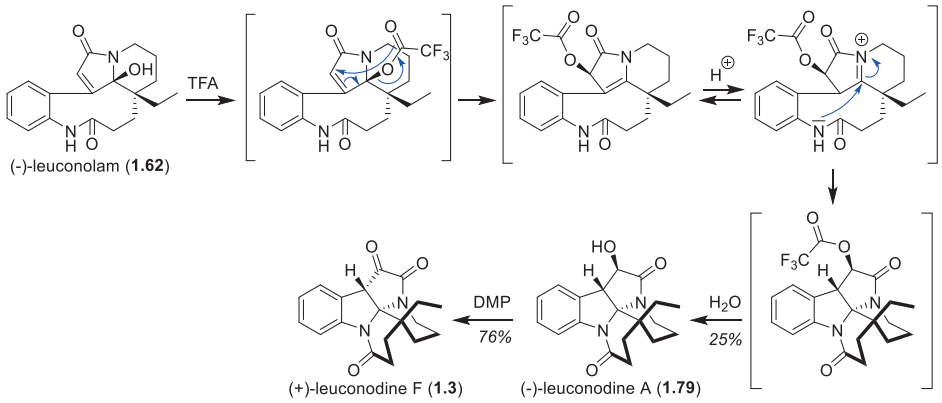
[30] Lim, S.-H.; Sim, K.-M.; Abdullah, Z.; Hiraku, O.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1380–1383.
[31] Low, Y.-Y.; Hong, F.-J.; Lim, K.-H.; Thomas, N. F.; Kam, T.-S. *J. Nat. Prod.* **2014**, *77*, 327–338.



Scheme 23 Plausible biosynthetic pathway towards leuconodine F

1.3.2. Semi Synthesis

Kam reported, in 2014, the semi synthesis of (+)-leuconodine F (**1.3**) from (-)-leuconolam (**1.62**). [22] Leuconolam was treated with an excess of trifluoroacetic acid to afford as expected the transannular product (+)-melodinine E (**1.61**) in 30% yield. Interestingly, the natural product (-)-leuconodine A (**1.79**) was also isolated in 25% yield. The generation of **1.79** under these conditions was rationalized by first trifluoroacetate formation followed by a [3,3] sigmatropic rearrangement as depicted in Scheme 24. Oxidation of (-)-leuconodine A (**1.79**) with Dess-Martin periodinane afforded the desired (+)-leuconodine F (**1.3**) in 76% yield.



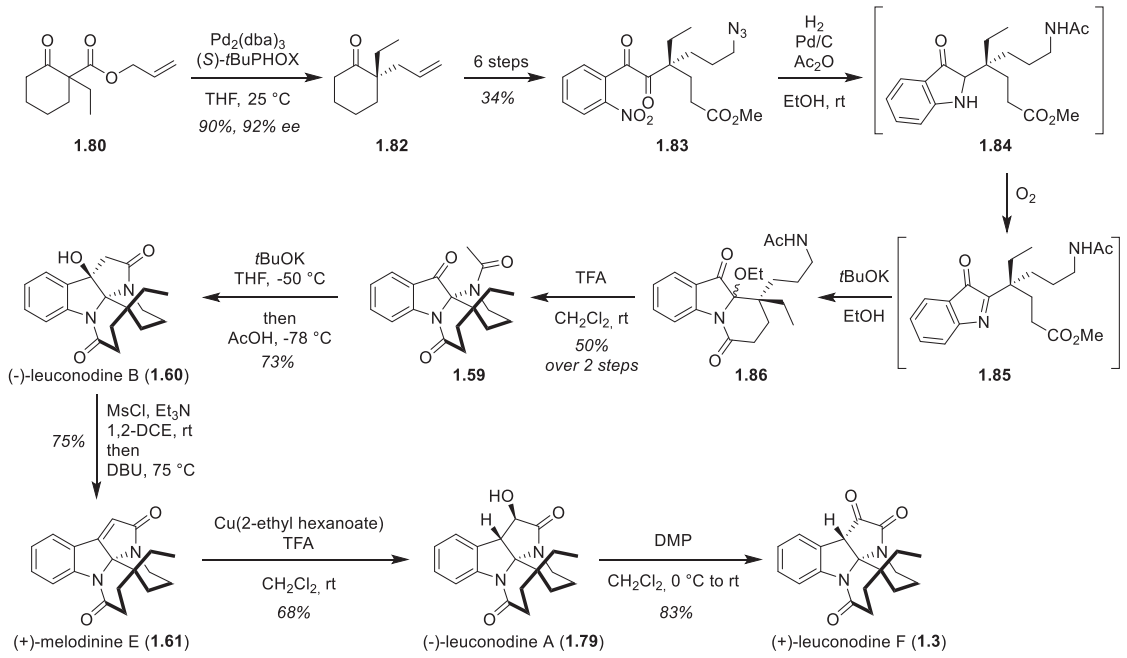
Scheme 24 Semi synthesis of leuconodine F

1.3.3. Total Synthesis

In 2015, the first and only total synthesis of (+)-leuconodine F (**1.3**) was also accomplished by our laboratory.[32] The configuration was determined at the very beginning of the synthesis using the enantioselective decarboxylative allylation reaction developed by Stoltz.[33] When 1,3-keto allylester **1.80** was treated with the $Pd_2(dba)_3$ / (*S*)-*t*BuPHOX catalytic system, enantioenriched

[32] Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712−6724.
[33] Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223.

compound **1.82** was obtained in 90% yield with 92% ee. After 6 additional steps, key diketone **1.83** was synthesized in 34% overall yield from **1.82** (Scheme 25). Pd-catalyzed reduction of both the nitroaryl and azide moieties under hydrogen atmosphere in the presence of acetic anhydride afforded indolin-3-one **1.84** with selective mono-acylation of the primary amine, therefore avoiding any unwanted cyclization onto the aryl ketone. Purging the reaction mixture with oxygen readily oxidized **1.84** to unstable 3*H*-indol-3-one **1.85** which upon the addition of base smoothly underwent the formation of the corresponding ethoxy hemiaminal and 6-membered lactam. Treatment of crude **1.86** with TFA triggered the elimination of ethanol and the corresponding iminium was intramolecularly trapped by the secondary amide to afford **1.59** as a single diastereoisomer in 50% yield from **1.83**. Deprotonation of acetamide **1.59** with *t*-BuOK triggered the formation of the last 5-membered ring of (−)-leuconodine B (**1.60**) in 73% yield *via* aldol addition on the indolin-3-one moiety. Mesylation of the tertiary alcohol followed by one-pot elimination of the mesylate with DBU afforded (+)-melodinine E (**1.61**) in 75% yield. Hydroxylation of **1.61** in the presence of a catalytic amount of a copper complex and TFA gave in 68% yield (-)-leuconodine A (**1.79**). Further oxidation of **1.79** with DMP gave (+)-leuconodine F (**1.3**) in a total of 13 steps with an overall yield of 4.7% and with 92% ee.



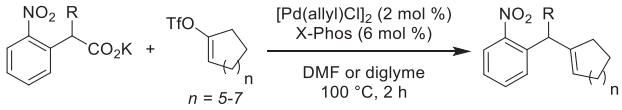
Scheme 25 First total synthesis of leuconodine F

By fine tuning the reaction conditions, (-)-leuconolam (**1.62**), (-)-mersicarpine (**1.87**), (-)-leuconoxine (**1.88**) and (-)-leuconodine C (**1.89**) were also synthesized starting from diketone **1.83** or (+)-melodinine E (**1.61**).

1.4. Previous Work

Our group is interested in the development of new methodologies and their application to the total synthesis of indole alkaloids.[23,34] We are also interested in the design of new strategies focusing on late-stage formation of the indole core.[32,35] Several methods had already been developed towards these goals within our group. Of these, two are relevant in the context of this thesis.

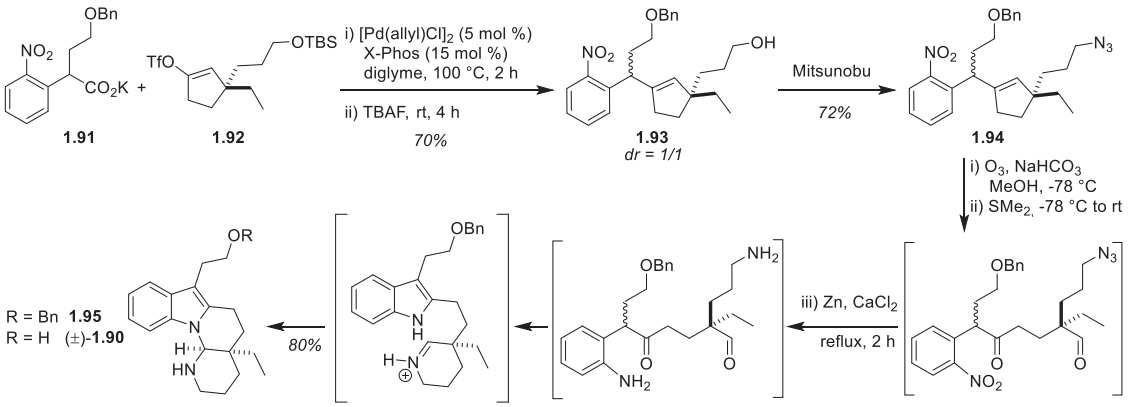
The first involves a palladium-catalyzed decarboxylative coupling between potassium nitrophenyl acetates and cyclic vinyl triflates (Scheme 26).[36] The efficiency of this reaction was demonstrated over a wide range of substrates and showed good yields overall.



Scheme 26 General scheme of decarboxylative coupling

This new methodology was then applied in the total synthesis of racemic goniomitine (**1.90**) (Scheme 27). The decarboxylative coupling between easily accessible vinyl triflate **1.91** and potassium carboxylate **1.92** afforded cleanly the desired coupling product. Subsequent one-pot deprotection of the alcohol with TBAF gave key intermediate **1.93** in 70% yield. The alcohol was then converted to an azide *via* a Mitsunobu reaction. Resulting intermediate **1.94** was then submitted to a second of our recently developed methodology: the integrated Oxidation / Reduction / Cyclization (iORC) sequence. This gave in one operation the desired tetracyclic compound **1.95** in 80% yield. From a stepwise point of view, this domino process begins with the ozonolysis of cyclopentene **1.94** generating the corresponding ketoaldehyde. Then the reduction of the nitroaryl and azide moieties with zinc triggers the spontaneous cyclization of the aniline onto the ketone in order to form the aromatic indole core. In parallel, the primary amine reacts with the aldehyde to form the 6-membered cyclic iminium ion which is further trapped by the nitrogen of the indole to give **1.95**. Deprotection of the primary alcohol results in the formation of desired (±)-goniomitine (**1.90**).

[34] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.
[35] Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127–19130.
[36] Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3272–3276.

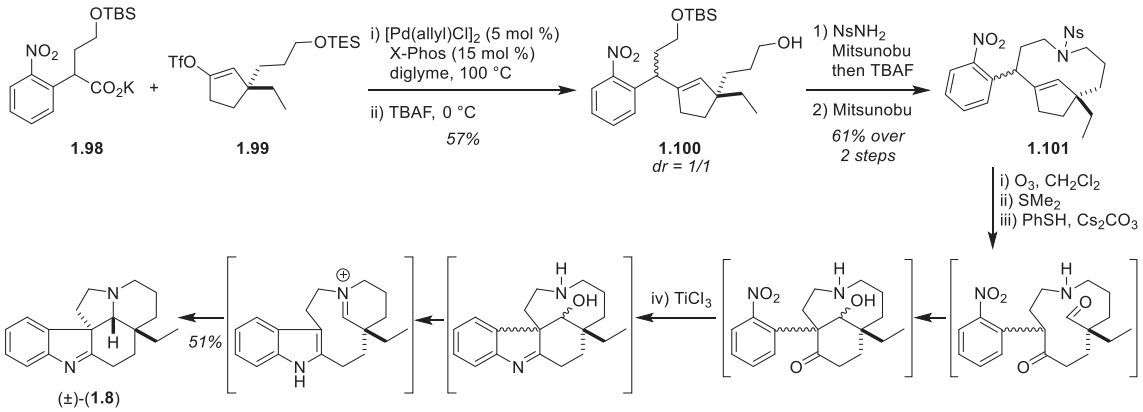


Scheme 27 Total synthesis of (±)-goniomitine

This efficient strategy was further adapted to the synthesis of (±)-vincadifformine (**1.7**), (±)-1,2-dehydroaspidospermidine (**1.8**), (±)-aspidospermidine (**1.96**), and (±)-kopsihainanine A (**1.97**).[37] This was achieved by inverting the chemoselectivity of the attack onto the final iminium intermediate from indolic N-H position to an attack by the nucleophilic C-3 position.

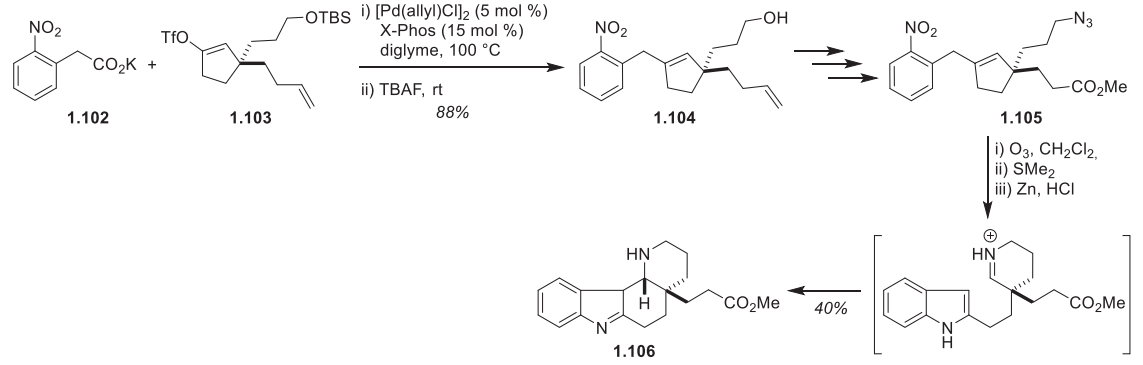
This was done by first performing the decarboxylative coupling between **1.98** and **1.99**, followed by the one-pot removal of the TES group to furnish adduct **1.100**. A Mitsunobu / deprotection / Mitsunobu three-step sequence gave 10-membered ring **1.101** in high yield (Scheme 28). Application of the iORC process on this particular intermediate afforded, in 51% yield, (±)-1,2-dehydroaspidospermidine (**1.8**) with complete diastereoselective control. Specifically, cleavage of cyclopentene **1.101** to the corresponding ketoaldehyde and subsequent removal of the nosyl group were performed using ozone and thiophenol respectively. NMR analysis of the crude revealed that at this stage, partial aldol addition of the 1,3-ketonitroaromatic onto the aldehyde had occurred to form the corresponding 6-membered ring. Reduction of the nitroaryl and azide moieties with $TiCl_3$, buffered by ammonium acetate, triggered the formation of both the indole and iminium ion. At this point, due to the geometric constraint of the intermediate, only a C-3 attack of indole to form the last ring was possible.

[37] Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102−15108.



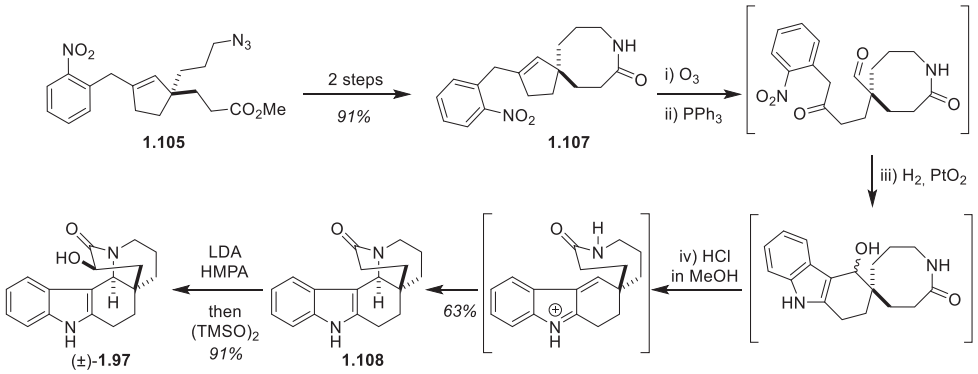
Scheme 28 Total synthesis of (±)-1,2-dehydroaspidospermidine

The synthesis of (±)-kopsihainanine A (**1.97**) from substrate **1.105** gave intriguing results. During the iORC, the iminium intermediate should be easily formed and the indole should be able to attack from either the NH or the C-3 carbon positions (Scheme 29). No substituent was present on the C-3 position of the indole, in contrast to the (±)-goniomitine (**1.90**) case, and thus the carbon attack to form tetracycle **1.106** should be favoured. However, while the desired product was obtained in 40% yield, the relative stereochemistry did not match the *trans*-fused rings system observed on the natural product.



Scheme 29 Synthetic studies towards (±)-kopsihainanine A

To overcome this issue, spiro 8-membered lactam ring **1.107** was synthesized from **1.105**. As shown in Scheme 30, the iORC domino process followed by addition of methanolic HCl resulted in the formation of conjugated iminium ion. The geometric constraint imposed by the 8-membered ring forced the lactam to attack with the desired diastereoselectivity in order to give the *trans*-fused rings in **1.108** in 63% yield. Finally, *alpha*-hydroxylation of the amide delivered the natural product (±)-kopsihainanine A (**1.97**).

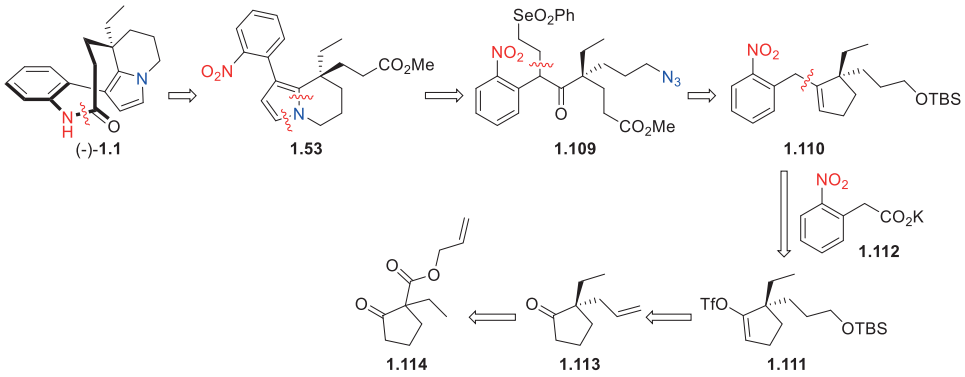


Scheme 30 Total synthesis of (±)-kopsihainanine A

Chapter 2. Enantioselective Total Synthesis of (-)-Rhazinilam

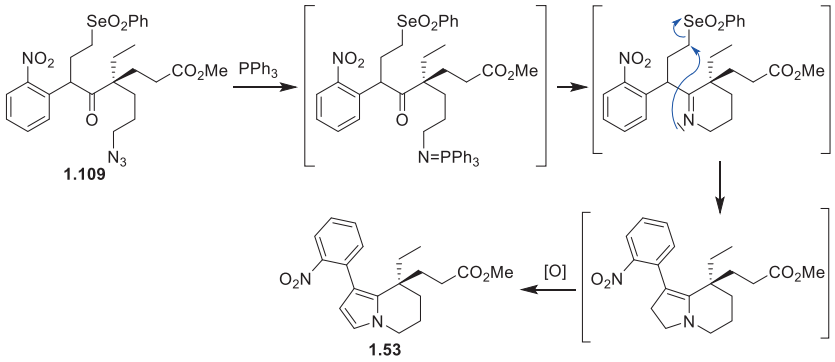
2.1. Retrosynthesis

As described in the introduction, our aim was to synthesize (-)-rhazinilam (**1.1**) *via* a novel strategy and, more precisely, using a domino process. Retrosynthetic analysis suggested the synthesis of tetrahydroindolizine core **1.53** could be achieved in a single operation from the linear compound **1.109** (Scheme 31). Key intermediate **1.109** could be obtained from cyclopentene **1.110** in 3 steps *via* subsequent azidation, ozonolysis and Michael addition to phenyl vinyl selenone. Required intermediate **1.110** could be obtained *via* the decarboxylative coupling between the corresponding vinyl triflate **1.111** and potassium carboxylate **1.112** in a similar fashion to what had been described previously. Triflate **1.111** could be synthesized from ketone **1.113** *via* hydroboration / oxidation and triflation. Finally, **1.113** can be obtained using a reported asymmetric decarboxylative allylation reaction from the known 1,3-ketoallylester **1.114**.



*Scheme 31 Retrosynthesis of (-)-rhazinilam (**1.1**)*

The planned domino reaction for the formation of **1.53** from **1.109** is inspired by the iORC protocol and consists of, first, a tandem Staudinger / aza-Wittig sequence to afford a cyclic imine (Scheme 32). Second, an intramolecular substitution of the phenyl selenone group by the imine would result in the formation of the 5-membered ring. Finally, after tautomerization of the resulting iminium ion to enamine, spontaneous oxidation to the pyrrole, as often seen for this class of substrates, was expected.



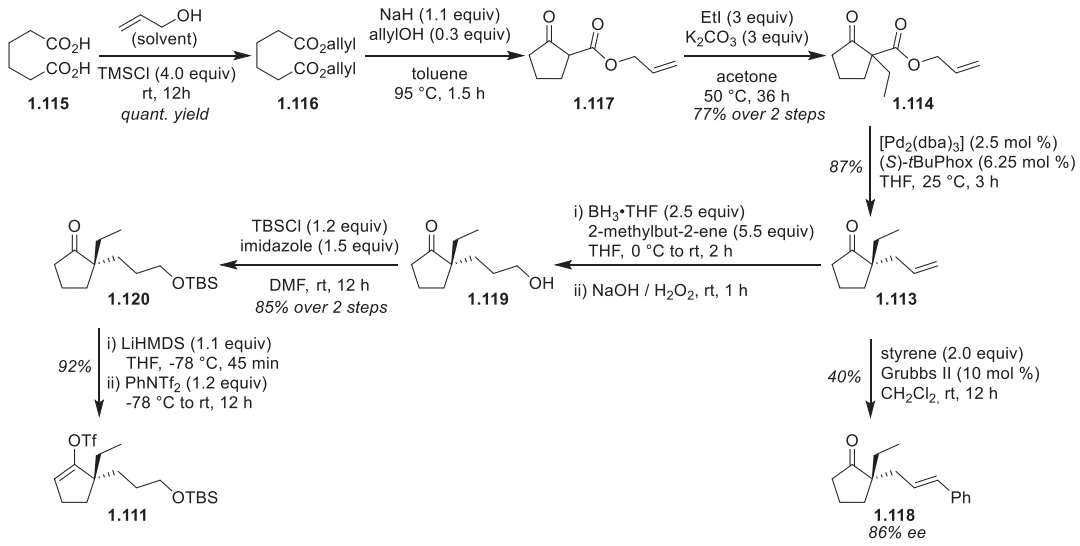
Scheme 32 Key domino process envisaged

2.2. Synthesis of the Starting Materials

The synthesis of ketoallylester **1.114** is known in the literature[38] and it can be performed on a multigram scale from commercially available adipic acid (**1.115**) in 77% yield over 3 steps. These steps involve a diesterification of **1.155** with allyl alcohol to form diallyl adipate (**1.116**) followed by a Dieckmann condensation using sodium hydride and finally alkylation of the resulting 1,3-ketoester with ethyl iodide.

With ketoallylester **1.114** in hand, the asymmetric decarboxylative allylation was performed under the conditions developed by Stoltz and coworkers using Pfaltz's ligand, (*S*)-*t*BuPHOX.[33] This ligand can be easily prepared in 4 steps from L-*tert*-leucine in 56% overall yield following known literature procedures.[39] Desired intermediate **1.113** was isolated with a high yield of 87% on a 5 g scale. Measuring the enantiomeric excess obtained during this reaction proved challenging as **1.113** presented nearly no UV activity and therefore had to be derived. An intermolecular metathesis reaction with styrene was chosen to reach, in one step, a more U.V active compound. Using Grubbs 2nd generation catalyst, desired styrene derivative **1.118** was obtained with a moderate yield of 40%. The enantiomeric excess was then determined by SFC and proved to be 86% which was in accordance with the results reported by the Stoltz group (Scheme 33). Racemic **1.113** was simply obtained using palladium(II) acetate and triphenylphosphine as ligand with a similar yield of 77%.[40]

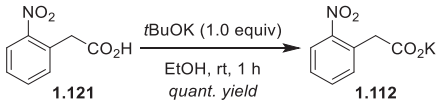
[38] (a) Tsuji, J.; Nisar, M.; Shimizu, I.; Minami, I. *Synthesis* **1984**, *16*, 1009. (b) Gilchrist, T. L.; Sanchez Romero, O. A.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 353–359.
[39] Krout, M. R.; Mohr, J. T.; Stoltz, B. M.; Schumacher, A.; Pfaltz, A. *Org. Synth.* **2009**, *86*, 181–193.
[40] Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, 52, 2988–2995.



*Scheme 33 Synthesis of vinyl triflate **1.111***

Enantioenriched intermediate **1.113** was then submitted to hydroboration / oxidation conditions to afford crude alcohol **1.119**. To avoid any unwanted reduction of the ketone, the hindered disiamylborane was chosen as reductant for this reaction and was generated *in-situ* from BH_3**.**THF and 2-methylbut-2-ene. The alcohol was then protected directly with *tert*-butyldimethylsilyl chloride to afford **1.120** in 85% over 2 steps. The *alpha* proton of ketone **1.120** was next deprotonated with lithium bis(trimethylsilyl)amide and the corresponding enolate was then trapped with *N*-phenyl-bis(trifluoromethanesulfonimide) to afford desired vinyl triflate **1.111** in 92% yield.

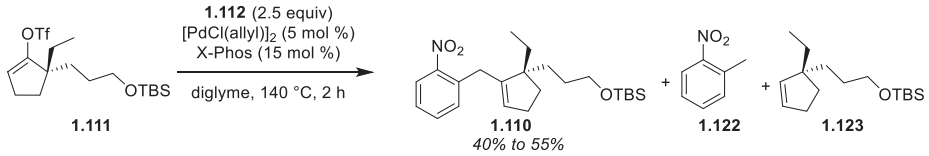
Potassium carboxylate **1.112** was obtained quantitatively by simple deprotonation of the commercially available 2-nitrophenylacetic acid (**1.121**) with potassium *tert*-butoxide (Scheme 34).



*Scheme 34 Synthesis of potassium carboxylate **1.112***

2.3. Decarboxylative Coupling

The decarboxylative coupling of vinyl triflate **1.111** with potassium carboxylate **1.112** under our reported optimized conditions gave desired coupling product **1.110** in low yield together with reduced products **1.122** and **1.123**. In order to obtain satisfactory yields, 2.5 equivalents of potassium carboxylate, instead of 1.5, and a higher temperature (140 °C instead of 100 °C) had to be used. Coupling product **1.110** was then isolated as an inseparable mixture with 2-nitrotoluene **1.122** in yields ranging from 40% to 55% (Scheme 35). This lower yield, when compared to the initial reported examples, can be explained by the steric hindrance in *alpha* position of the triflate which favours the formation of side products **1.122** and **1.123**. It was also observed that quality of both the hydroscopic diglyme and potassium carboxylate **1.112** had a significant influence on the yield. Supposedly, water could either hydrolyze the triflate or deprotect the silyl ether at such a high temperature.

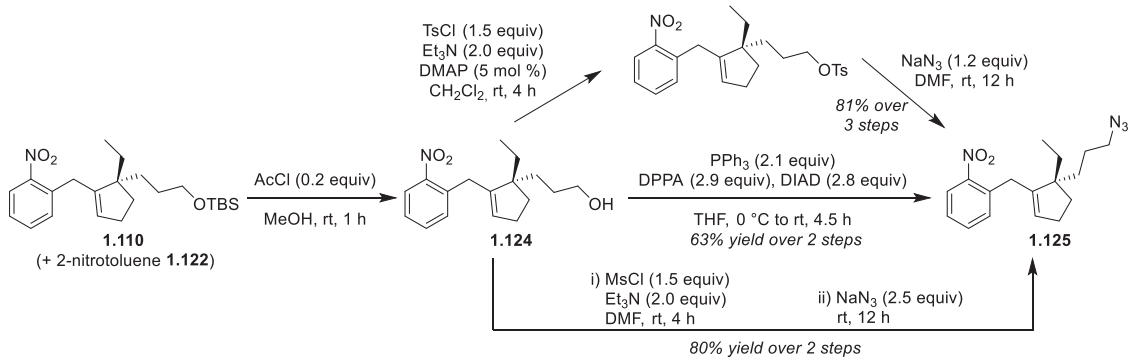


*Scheme 35 Decarboxylative coupling between **1.111** and **1.112***

A one-pot decarboxylative coupling and deprotection of the alcohol with tetra-*n*-butylammonium fluoride was attempted. Unfortunately, corresponding alcohol **1.124** was obtained in only 20% yield and was contaminated by oxidized X-Phos. As a consequence, it was chosen to perform the deprotection separately after purification of the coupling product. Protected alcohol **1.110** was simply dissolved in methanol and a catalytic amount of acetyl chloride was added to generate hydrochloric acid *in-situ*.[41] Clean crude alcohol **1.124** was obtained directly after evaporation of the volatiles.

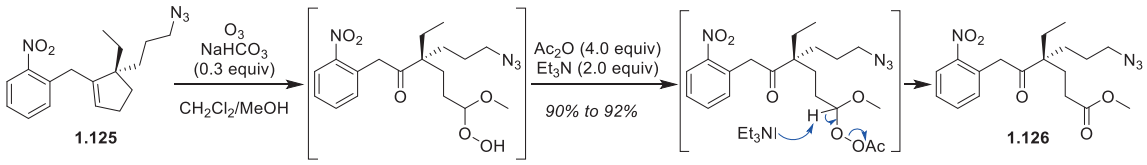
Three different routes were then explored to prepare corresponding azide **1.125** from alcohol **1.124** (Scheme 36). Firstly, a robust two-step sequence *via* tosylation and azidation with sodium azide was run to afford **1.125** in 81% yield over 3 steps (from protected alcohol **1.110**). To save one step in the synthesis, direct conversion of alcohol **1.124** to azide **1.125** *via* a Mitsunobu reaction was attempted but a lower yield of 63% over 2 steps was obtained. Besides, all side products from the reagents used (PPh_3, DIAD and DPPA) made the purification of the mixture tedious. Finally, the best result was obtained by mesylation of **1.124** followed by a one-pot substitution with sodium azide to give desired azide **1.125** in 80% yield over 2 steps.

[41] Khan, A. T.; Mondal, E. *Synlett* **2003**, *14*, 694–698.



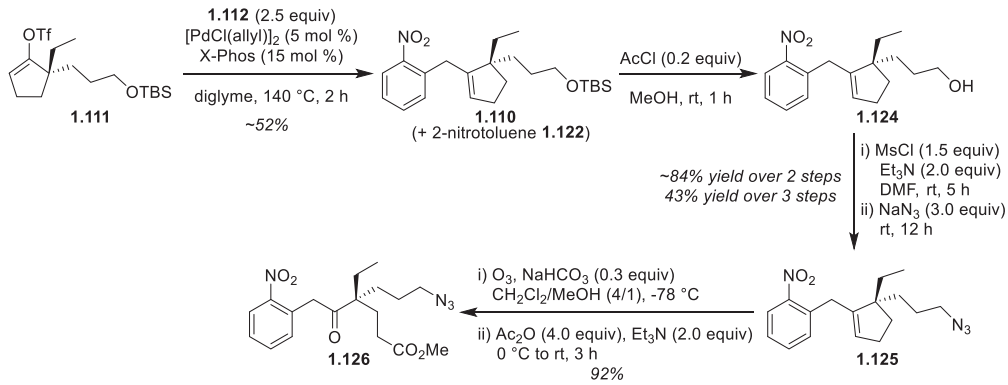
*Scheme 36 Different routes explored towards the synthesis of azide **1.125***

Cyclopentene **1.125** was then submitted to ozone in the presence of methanol and sodium bicarbonate as buffer to form the peroxide intermediate as depicted in Scheme 37.[42] After acetylation and elimination, ketoester **1.126** could be isolated in high and reproducible yields (90–92%).



*Scheme 37 Ring cleavage of cyclopentene **1.125** by ozonolysis*

The optimized route to obtain ketoester **1.126** from vinyl triflate **1.111** on a 3 g scale is summarized in Scheme 38. Compound **1.126** was synthesized in 4 steps from **1.111** in 40% overall yield with 86% ee.



*Scheme 38 Optimized synthetic route towards **1.126***

[42] Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867–3870.

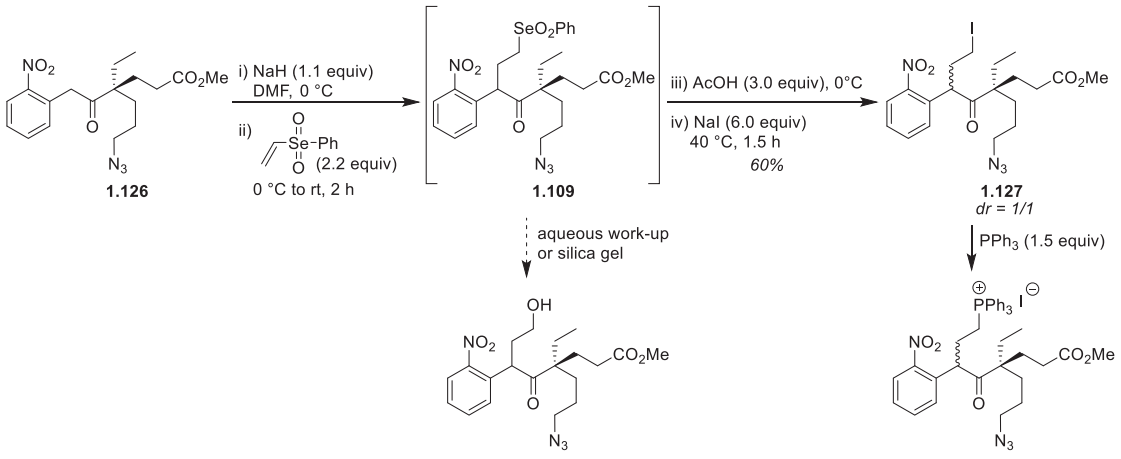
2.4. Key Step

2.4.1. Synthesis of the Key Intermediate

The last step before the domino process, involving the Michael addition of **1.126** to phenyl vinyl selenone, proved more challenging than expected. After a screening of different conditions, 2.0 equivalents of phenyl vinyl selenone and 1.1 equivalents of sodium hydride or caesium carbonate as base in dimethylformamide gave the cleanest reactions based on TLC. Unfortunately, desired Michael product **1.109** exhibits high instability and could never be isolated. The phenyl selenone was labile enough to be totally replaced by a hydroxyl group when purified on silica gel or even when simple aqueous work-up was performed. (Scheme 39).

It was decided in consequence to try one-pot the substitution of phenyl selenone by sodium iodide to avoid hydrolysis, however a complex mixture was obtained at first. This problem was solved by adding a few equivalents of acetic acid, to quench excess of base, prior to the addition of sodium iodide. This resulted in a cleaner reaction and alkyliodide **1.127** was isolated in 60% yield as a 1/1 diastereomeric mixture.

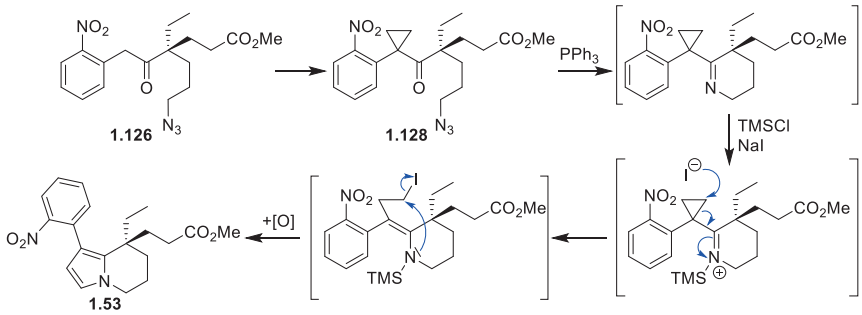
With iodide **1.127** in hand, the key step was attempted with triphenylphosphine at room temperature to initiate the azide reduction to the corresponding iminophosphorane. However, as we feared, the phosphonium salt resulting of the substitution of the iodide appeared to be preferentially formed and inhibited the reaction. No imine formation was even detected in presence of a slight excess of PPh_3 (1.5 equivalents) and when the mixture was heated, only decomposition could be observed.



*Scheme 39 Michael addition of **1.126** to phenyl vinyl selenone*

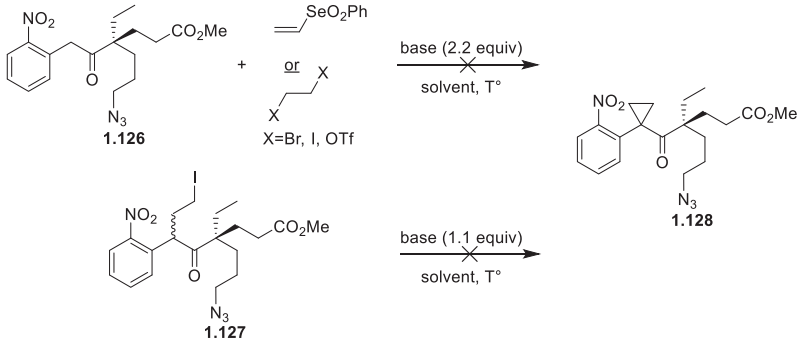
2.4.2. First Alternative: Cyclopropyl Iminium Ion Rearrangement

As an alternative strategy, shown in Scheme 40, we decided to attempt the formation of **1.53** *via* an elegant cyclopropyl iminium ion rearrangement similar to that used in the Rawal's total synthesis of (±)-dehydrotubifoline.[43]



Scheme 40 Domino process via cyclopropyl iminium ion rearrangement

In order to obtain desired cyclopropane **1.128**, we investigated the dialkylation of intermediate **1.126** using various "$^{+}CH_2$-CH_2^{+}" synthons such as 1,2-dihalogenoethane, 1,2-ditriflatethane or phenyl vinyl selenone. Unfortunately, either no reaction or complex mixtures were observed under the different conditions that we employed. The synthesis of **1.128** was also explored from iodide **1.127** but again mostly degradation was observed (Scheme 41).

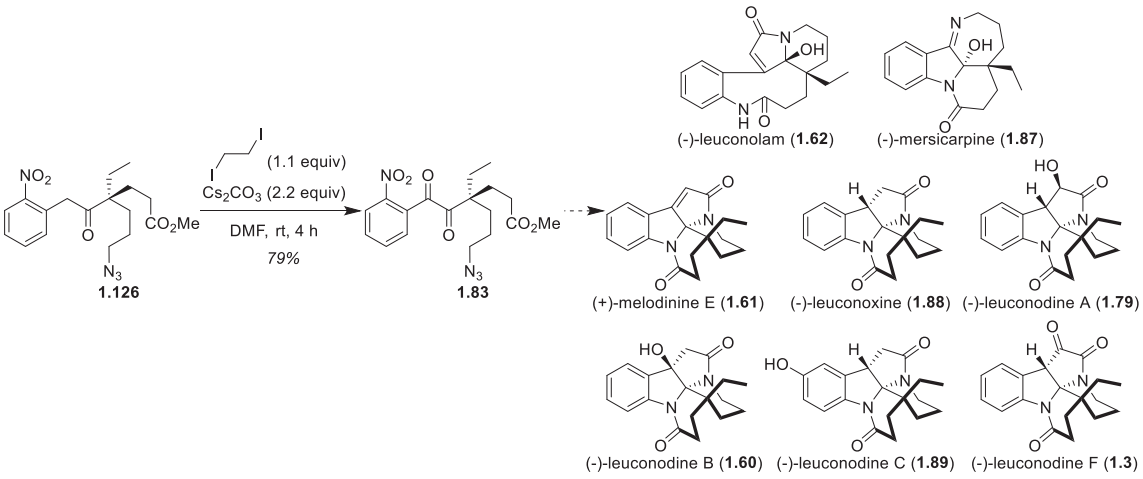


Scheme 41 Cyclopropanation failure

However, during this investigation, an unexpected benzylic oxidation of intermediate **1.126** to diketone **1.83** was observed when using 1,2-diiodoethane and caesium carbonate in dimethylformamide (Scheme 42). The reaction worked smoothly and **1.83** was isolated with a

[43] Rawal, V. H.; Michoud, C.; Monestel R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030–3031.

good yield of 79%. Diketone **1.83**, previously synthesized by our group *via* a different route, was already mentioned in the previous chapter (1.3.3) and was the key intermediate in the total synthesis of eight natural products: (−)-leuconolam, (−)-mersicarpine, (+)-melodinine E, (−)-leuconoxine, (-)-leuconodine A, (-)-leuconodine B, (-)-leuconodine C and (+)-leuconodine F.[32] Therefore, this work represented a formal synthesis of these natural products.



*Scheme 42 Unexpected benzylic oxidation of **1.126***

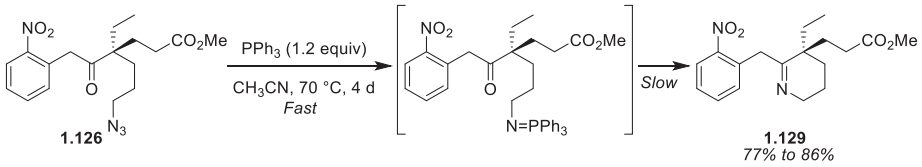
This oxidation reaction seemed to occur by *in-situ* molecular iodine generation as diiodoethane is a white solid and the reaction mixture turned to orange very rapidly. As a control experiment, the same reaction was performed except that diiodoethane was replaced with 1.1 equivalents of molecular iodine. After 4 h at room temperature, diketone **1.83** was isolated with a similar yield of 72%. This experiment supported the initial hypothesis of *in-situ* molecular iodine generation or showed that, at least, the unclear mechanistic pathway of this oxidation is similar when using either diiodoethane or iodine.

2.4.3. Second Alternative: Dialkylation of Imine/Enamine

In view of the difficulties encountered when attempting to obtain either **1.109** or **1.128**, the domino process and cyclopropyl iminium ion rearrangement approaches were put on standby and it was decided to find alternate strategies to form the pyrrole moiety from the imine **1.129**.

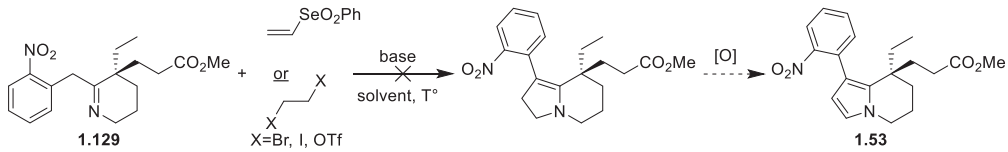
The first of these, the tandem Staudinger / aza-Wittig reaction using triphenylphosphine on substrate **1.126**, was quickly investigated. The Staudinger step was fairly fast but it was observed that the aza-Wittig reaction was very slow. This observation can be attributed to the steric hindrance generated by the quaternary carbon center in *alpha* position of the ketone. Harsher conditions were, in consequence, required. After screening, the optimal temperature was found

to be 70 °C to obtain cyclization without any decomposition. It was also found that the polarity of the solvent had an influence on the cyclization rate: the more polar was the solvent, the faster was the cyclization reaction. Under the optimized conditions, using acetonitrile at 70 °C, complete conversion was obtained in 3 or 4 days (Scheme 43). Imine **1.129** is relatively stable and can be purified on neutralized silica gel in high yields ranging from 77% to 86%. It should be noted that enamine isomerization was not observed in spite of the possible conjugation with the nitroaryl substituent. It appears that, in our case, the endocyclic double bond of the imine is more favourable than the exocyclic olefin of the enamine.



*Scheme 43 Tandem Staudinger / aza-Wittig reaction of **1.126***

With imine **1.129** in hand, the formation of the 5-membered ring was investigated with various "$^{+}CH_2$-CH_2^{+}" synthons. Once again, either no reaction or degradation was observed under all attempted conditions (Scheme 44).



Scheme 44 Dialkylation failure

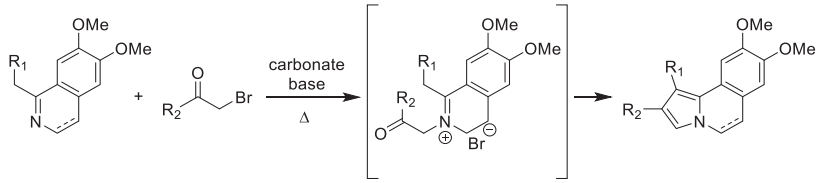
2.4.4. Third Alternative: Tschitschibabin-Like Reaction

In 1968, Casagrande reported an extension of the Tschitschibabin indolizine synthesis[44] to form pyrrolo[2,1-α]isoquinolines from isoquinolines and phenacyl bromide.[45] More recently in 2001, Ruchirawat reported the total synthesis of lamellarin alkaloids using this method to form tetrasubstituted pyrroles (Scheme 45).[46]

Based on the substitution pattern observed in the final compound, the first step of the mechanism was proposed to be alkylation of the imine with the alkyl bromide. The resulting iminium salt under basic conditions then tautomerizes to the corresponding enamine which then

[44] Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1607–1617.
[45] Casagrande, C.; Invernizzi, A.; Ferrini, R.; Ferrari, G. G. *J. Med. Chem.* **1968**, *11*, 765–770.
[46] (a) Ruchirawat, S.; Mutarapat, T. *Tetrahedron Lett.* **2001**, *42*, 1205–1208. (b) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363–1366.

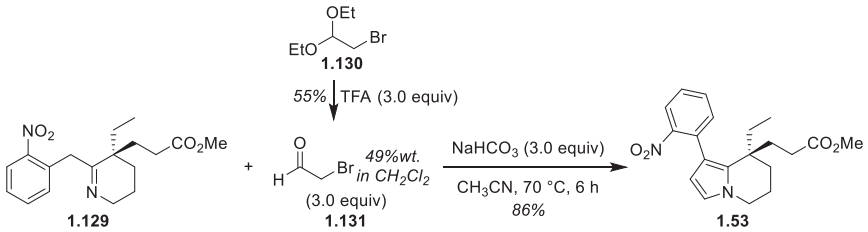
attacks the carbonyl group. The final elimination of the hydroxyl group gives the aromatized pyrrole.



Scheme 45 General scheme of Tschitschibabin-like reaction

We believed this strategy could be adapted to our purposes. While the R_2 group was an aryl moiety in most cases, there were some examples with alkyl groups. However, in our case R_2 should be a simple proton which corresponds, as starting materials, to 2-bromoacetaldehyde (**1.131**). This small and lachrymal molecule was synthesized in one step by acetal hydrolysis of commercially available 2-bromo-1,1-diethoxyethane (**1.130**) and isolated by distillation.[47,48] Due to its instability, **1.131** was kept in dichloromethane solution.

The first reaction attempt with imine **1.129** and 3 equivalents of 2-bromoacetaldehyde (**1.131**) in the presence of sodium bicarbonate at 80 °C for 12 h afforded desired pyrrole **1.53** in 55% yield. Heating was necessary for the reaction to proceed, but pyrrole **1.53** exhibited instability at high temperatures. As a consequence, the temperature was decreased to 70 °C and the reaction time to 6 h which resulted in an 86% yield of tetrahydroindolizine **1.53** (Scheme 46).



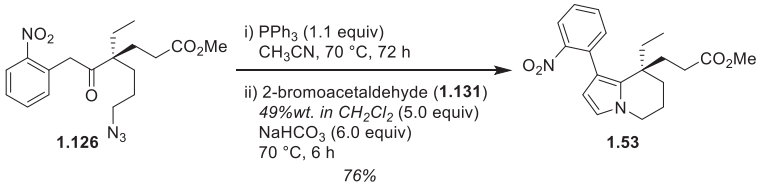
*Scheme 46 Formation of **1.53** via Tschitschibabin-like reaction*

As the solvent and the temperature for this reaction were the same as the ones used in the tandem Staudinger / aza-Wittig sequence, a one-pot synthesis could be easily set up from the ketoester **1.126**. Initially, the same conditions were kept with 3 equivalents of 2-bromoacetaldehyde (**1.131**) and 6 h at 70 °C. However, incomplete conversion of the *in-situ* formed imine **1.129** was observed and pyrrole **1.53** was isolated in 62% yield. The remaining triphenylphosphine or triphenylphosphine oxide appeared to consume some of **1.131**. Full

[47] Li, W.; Li, J.; Wu, Y.; Fuller, N.; Markus M. A. *J. Org. Chem.* **2010**, *75*, 1077–1086.
[48] Kraus, G. A.; Gottschalk, P. *J. Org. Chem.* **1983**, *48*, 2111–2112.

conversion of imine **1.129** was thus obtained by increasing the amount of **1.131** added to the reaction to 5 equivalents as traces of **1.129** was still observed when 4 were used.

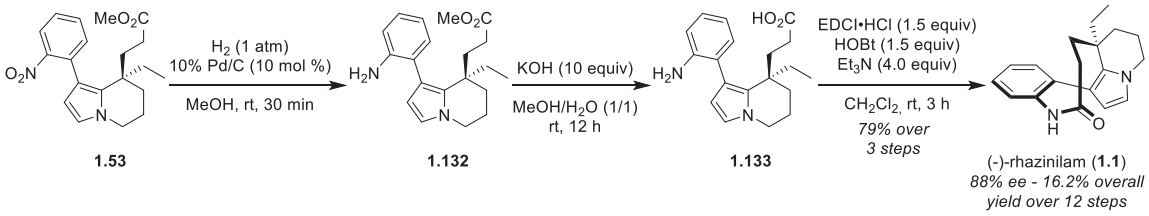
Finally, we were able to obtain desired tetrahydroindolizine moiety **1.53** in one operation from the linear intermediate **1.126** in a high yield of 76% on a 100 mg scale (Scheme 47).



*Scheme 47 One-pot synthesis of **1.53** from **1.126***

2.5. Endgame of the Synthesis

Like several previous strategies, the synthesis was completed by a reduction / hydrolysis / lactamization sequence. Nitroaryl reduction to aniline was carried out under hydrogen atmosphere in the presence of Pd/C followed by ester hydrolysis with KOH to afford, after acidic work up, aminoacid **1.133**. Final macrolactamization of crude **1.133** was accomplished using EDCI / HOBt as coupling reagents to afford the desired (-)-rhazinilam (**1.1**) in 79% yield over 3 steps (Scheme 48).

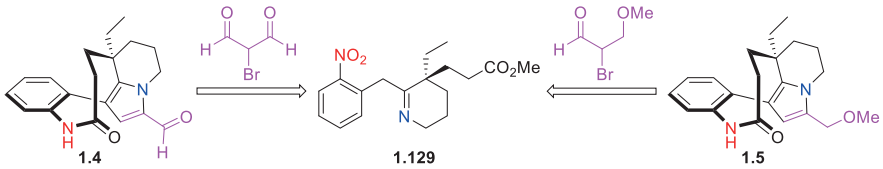


*Scheme 48 Final steps of the (-)-rhazinilam (**1**) synthesis*

With this novel strategy, (-)-rhazinilam (**1.1**) was successfully synthesized in 12 steps from known ketoallylester **1.114** in 16.2% overall yield with 88% ee.

2.6. Synthetic Studies Towards (-)-Rhazinal and (-)-Kopsiyunnanine C1

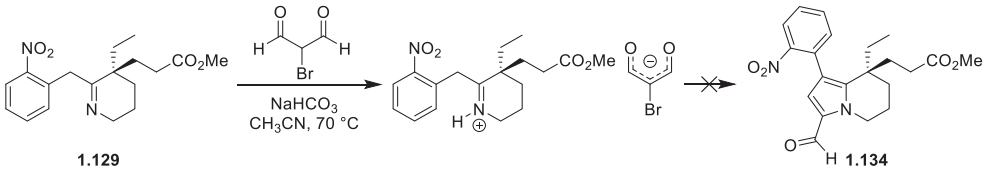
Our facile access to enantioenriched imine **1.129** opened a new avenue for the synthesis of other natural products. Indeed, if we were able to utilize different *alpha*-haloaldehydes in this process, we could obtain various pyrroles starting from **1.129** which in turn would lead to different natural compounds of the rhazinilam family. We first targeted (-)-rhazinal (**1.4**) using 2-bromomalonaldehyde and (-)-kopsiyunnanine C1 (**1.5**) using 2-bromo-3-methoxypropanal (Scheme 49).



*Scheme 49 Retrosynthesis of **1.4** and **1.5** from **1.129***

2.6.1. (-)-Rhazinal

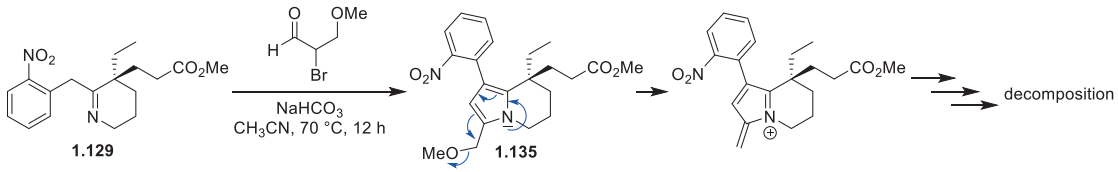
Imine **1.129** and commercial 2-bromomalonaldehyde were submitted to our optimized conditions. By TLC, **1.129** was consumed relatively fast and a new, very polar, compound was formed. However, after aqueous work-up, **1.129** was recovered as the only product. As 2-bromomalonaldehyde has a very acidic proton, it was supposed that protonation of the imine occurred, inhibiting therefore the desired transformation (Scheme 50). This hypothesis was supported by NMR studies in deuterated acetonitrile. Indeed, after adding 2-bromomalonaldehyde to **1.129**, the chemical shifts of the protons of the benzylic methylene and methylene *alpha* to the nitrogen moved to the lower field. Additions of additives and harsher conditions were attempted but only decomposition was obtained and desired 2-formylpyrrole **1.134** was never observed.



Scheme 50 Tschitschibabin-like reaction failure with 2-bromomalonaldehyde

2.6.2. (-)-Kopsiyunnanine C1

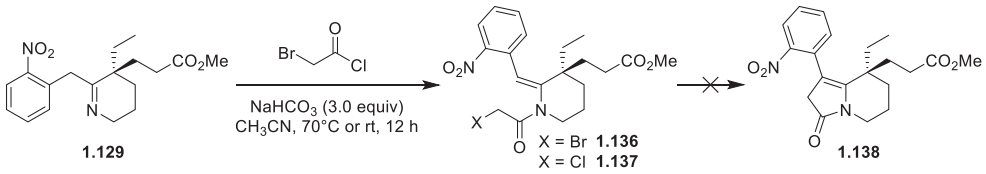
We turned our attention towards (-)-Kopsiyunnanine C1. The required 2-bromo-3-methoxypropanal was obtained by acetal hydrolysis of commercially available 2-bromo-1,1,3-trimethoxypropane in a similar manner as 2-bromoacetaldehyde (**1.131**). Under optimized conditions, significant amounts of starting imine **1.129** were still observed after 6 h at 70 °C. After an additional 6 h, full conversion was observed but a complex mixture was obtained, potentially due to the instability of desired product **1.135** under these conditions. Indeed, as shown in Scheme 51, the 2-hydroxymethyl pyrrole moiety is known to easily form azafulvenium cations which can lead, by different pathways, to decomposition.[49]



Scheme 51 Tschitschibabin-like reaction failure with 2-bromo-3-methoxypropanal

2.6.3. Reactivity Tests with *Alpha*-Haloacyl Chloride

Out of curiosity, imine **1.129** was reacted with commercially available 2-bromoacetyl chloride in the hope of obtaining **1.138**. After 12 h at 70 °C or at room temperature, a 1/1 mixture of enamides **1.136** and **1.137** was formed based on NMR and MS analyses of the crude reaction mixture (Scheme 52). Enamide **1.137** came from enamide **1.136** by simple halogen exchange. This occurred even if no brine was used during work-up, confirming that the chloride involved in the halogen exchange came from the initial acyl chloride. Both enamides were put under harsher conditions in an attempt to push the cyclization towards intermediate **1.138**, but without success.



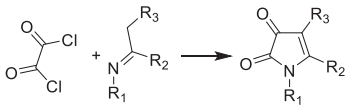
*Scheme 52 Cyclization failure of enamides **1.136** and **1.137***

[49] Dinsmore, A.; Mandy, K.; Michael J. P. *Org. Biomol. Chem.* **2006**, 1032–1037.

Chapter 3. Enantioselective Total Synthesis of (-)-Leucomidine B

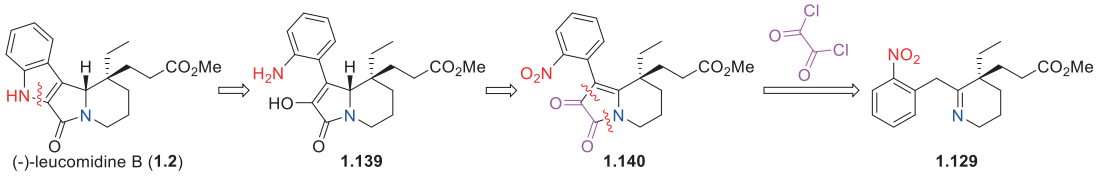
3.1. Retrosynthesis

We next turned our attention towards another indole alkaloid we believed we could obtain using one of our intermediate, leucomidine B (**1.2**). In 1966, Zielger et al. reported the first synthesis of the 2,3-dioxopyrrole moiety (also named pyrrole-2,3-dione) from the reaction between an imine and oxalyl chloride *via* a double addition / elimination process (Scheme 53).[50] The reaction was some years later studied in detail by Sano and Tsuda utilizing an imine or an enaminoester.[51] Since the 1990's, Mikhailovskii group has investigated this reaction with focus on isoquinoline substrates.[52]



Scheme 53 General scheme of 2,3-dioxopyrrole formation

If this reaction is applicable to our imine **1.129**, the resulting hypothetic 2,3-dioxopyrrole **1.140** should be a perfect intermediate to reach in few steps (-)-leucomidine B (**1.2**) (Scheme 54). Indeed, only three additional steps, which would involve the reduction of both the olefin and nitroaryl groups as well as the condensation of the resulting aniline to form the indole core, would be required. The main challenge in this case would be to find the right selective double bond reduction protocol to control the second stereocenter. This diastereoselective control unfortunately failed during our first total synthesis.[23]



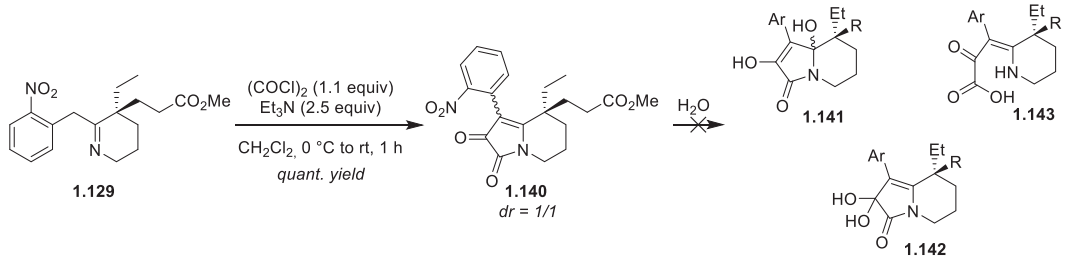
*Scheme 54 Retrosynthesis of (-)-leucomidine B (**1.2**) from imine **1.129***

[50] Ziegler, E.; Hradetzky, F.; Eder, M. *Monatsh. Chem.* **1966**, *97*, 1391–1393.
[51] Sano, T.; Horiguchi, Y.; Toda, J.; Imafuku, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1984**, *32*, 497–503.
[52] (a) Mikhailovskii, A. G. *Chemistry of Heterocyclic Compounds* **1996**, *32,* 590–595 and references cited herein. (b) Polygalova, N. N.; Mikhailovskii, A. G.; Vikhareva, E. V.; Vakhrin M. I. *Chemistry of Heterocyclic Compounds* **2007**, *43*, 900–905.

3.2. Synthesis of the 2,3-Dioxopyrrole

Our first attempt to synthesize 2,3-dioxopyrrole **1.140** was performed by adding to **1.129** a slight excess of oxalyl chloride in the presence of triethylamine. After 1 h of reaction time and acid aqueous work-up, the desired product was obtained cleanly and in quantitative yield. The reaction was scaled-up from 5 mg to 100 mg scale and the exact same results were obtained. By NMR, a mixture of two diastereoisomers in a 1/1 ratio was observed. The second chirality element was the result of the formation of atropisomers between the nitroaryl and the 2,3-dioxopyrrole core (Scheme 55). A one-pot reaction from linear intermediate **1.126** to dioxopyrrole **1.140** was not possible due to the side reaction between triphenylphosphine oxide and oxalyl chloride which generates triphenylphosphine dichloride[53], therefore leading to the formation of various side products.

Sano and Tsuda in 1985[54] and also Kappe in 1995[55] reported that 2,3-dioxopyrroles are sensitive to nucleophiles such as methanol and water. Depending on the nature of the substituents on the heterocycle, the addition of water can occur in a 1,4- or a 1,2-manner. It was observed that water can also add onto the amide moiety which results in the opening of the 5-membered ring. However, in our case, none of the three possible hydrate forms (**1.141**, **1.142** or **1.143**) were observed after acidic work-up (Scheme 55). Despite this, the further use of alcoholic solvents was avoided to limit possible side reactions and these were replaced mainly by tetrahydrofuran.



*Scheme 55 Synthesis of 2,3-dioxopyrrole **1.140***

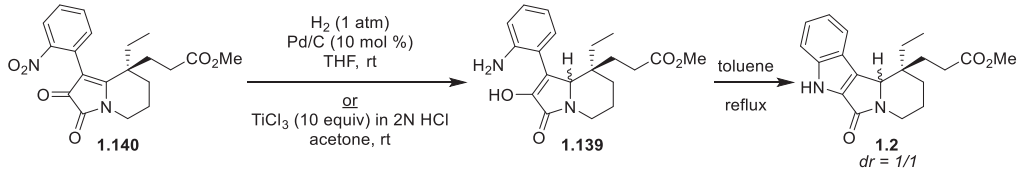
[53] Yano, T.; Hoshino, M.; Kuroboshi, M.; Tanaka, H. *Synlett* **2010**, *21*, 801–803.
[54] Sano, T.; Horiguchi, Y.; Tsuda, Y. *Chem. Pharm. Bull.* **1985**, *33*, 110–120.
[55] Kappe, C. O.; Terpetschnig, E.; Penn, G.; Kollenz, G.; Peters, K.; Peters, E.-M.; Schnering H. G. *Liebigs Ann.* **1995**, 537–543.

3.3. Asymmetric Reduction and Endgame

3.3.1. First Attempts of Reduction

Initially, 2,3-dioxopyrrole **1.140** was submitted to typical hydrogenation conditions using a catalytic amount of Pd/C under hydrogen atmosphere in tetrahydrofuran. As the 2,3-dioxopyrrole moiety has a strong red colour, the double bond reduction was easily observed with the reaction mixture turning to yellow. When the nitroaryl and the double bond were both reduced, the final solution was colourless. From these physical observations and NMR monitoring, it appears that the double bond was reduced fairly fast and longer reaction times were needed to obtain complete nitroaryl reduction. Surprisingly, the same result was obtained using an excess of titanium(III) chloride as reducing reagent, despite the fact that normally double bonds are less prone to reduction under these conditions (Scheme 56). After reduction of both the double bond and nitroaryl, resulting aniline **1.139** exhibited no atropisomeric character.

Compound **1.139** corresponds to the final intermediate of the first total synthesis of leucomidine B (**1.2**) and the same conditions were used to finalize the synthetic pathway. Complete cyclization can be obtained by refluxing aniline **1.139** in toluene for several hours. When either Pd/C under hydrogen or $TiCl_3$ was used, a 1/1 diastereomeric mixture of (-)-leucomidine B (**1.2**) was unfortunately obtained.



*Scheme 56 Reduction of **1.140***

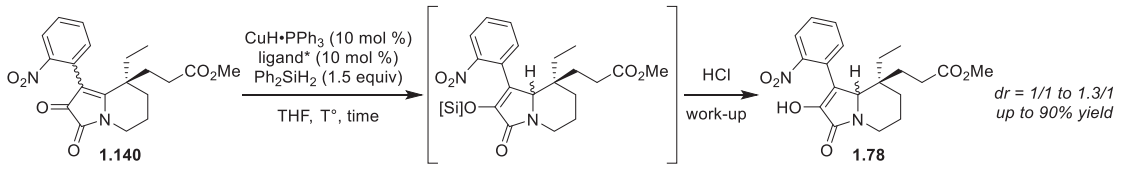
3.3.2. CuH-Catalyzed Pseudo-Enantioselective Reduction

With a reliable pathway toward (-)-leucomidine B (**1.2**) in hand, the asymmetric double bond reduction was then investigated. Because of the observations made during the first total synthesis, where the steric differentiation between the ethyl group and the ester side chain was too weak to induce substrate control, a pseudo-enantioselective approach was firstly studied. In the literature, many examples of asymmetric 1,4-reduction of enones with chiral copper-hydride are reported.[56] The copper-hydride catalyst, due to its high sensitivity towards oxygen, is often

[56] (a) Review on asymmetric CuH catalyzed reduction: Deutsch C.; Krause N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927. (b) Recent application in total synthesis: Williams, D. R.; Shah, A. A. *J. Am. Chem. Soc.* **2014**, *136*, 8829–8836.

generated *in-situ* typically from copper(I) chloride, sodium *tert*-butoxide and hydrogen. The commercially available stabilized hexamer $[(PPh_3)CuH]_6$, also known as Stryker's reagent, is also used as a reliable copper-hydride source. Originally used in a stoichiometric amount,[57] the copper-hydride can be used catalytically with a silane as hydride source. Good to excellent enantioselectivities were reported using various bisphosphine chiral ligands such as SEGPHOS, BIPHEP or BINAP families for cyclic enones and the JOSIPHOS family for acyclic enones.

For our screening, Stryker's reagent was chosen as copper catalyst and diphenylsilane as hydride source. Most of the reported procedures use toluene as solvent but the substrate **1.140** proved insoluble in this. As some literature examples demonstrated that tetrahydrofuran could be used as solvent without changing significantly the enantioselectivity or the yield of the reaction[58], we selected it as an alternative. After testing various chiral ligands, the best result were obtained using (*R*)-Tol-BINAP. Under these conditions, **1.78** was isolated with an excellent yield of 90% but with poor diastereoselectivity (up to 1.3/1) (Scheme 57). It was rationalized that the atropisomeric character of compound **1.140** might inhibit the chiral induction of the ligand.



*Scheme 57 Attempts towards the pseudo-enantioselective reduction of **1.140***

3.3.3. Substrate-Directed Reduction

After the failure to obtain any pseudo-enantioselective reduction, we moved to a diastereoselective approach. We noted that in the natural product, the H-21 proton and the ester group are in a *cis*-conformation. We believed we might be able to take advantage of this as examples of diastereoselective double bond reduction directed by different functional groups, such as esters and acids, had been reported.[59] This diastereoselectivity was mainly observed with homogeneous metal but some examples with heterogeneous catalysts, for instance Pd/C, exist.

First, acid derivative **1.144**, synthesized from ester **1.140**, was investigated under the previously described conditions as the acid possesses a higher coordinating ability. Surprisingly, when copper hydride was used, even in excess, no reaction was observed. Under hydrogen atmosphere with Pd/C or $Pd(OH)_2/C$, the reaction occurred at 0 °C, but no selectivity was obtained. Finally, when using titanium(III) chloride, most of the formed amino acid **1.145** was lost

[57] Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293.
[58] Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover A. A. *Org. Lett.* **2004**, 6, 1273–1275.
[59] Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26,* 190–203.

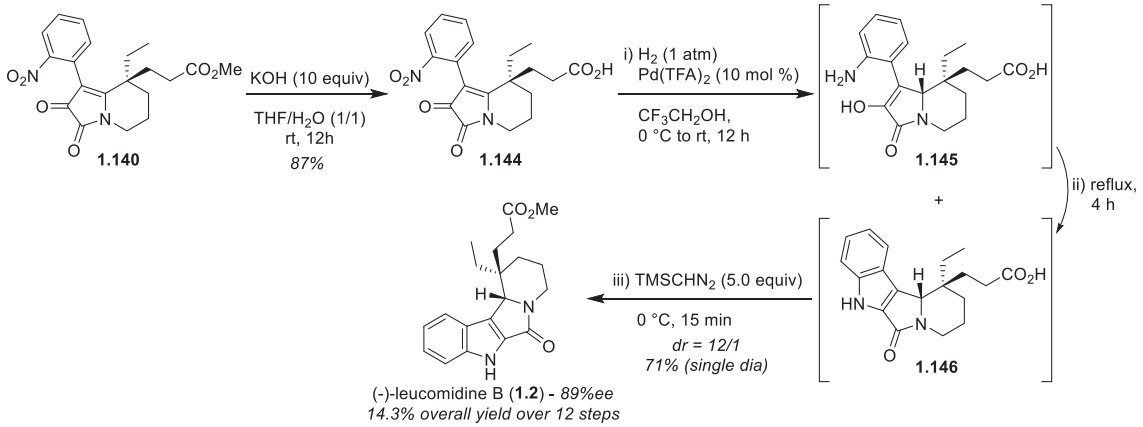
in the aqueous phase during the work-up. Ester **1.140** and acid **1.144** were then submitted to hydrogenation conditions in the presence of the well-known Crabtree catalyst which is a homogeneous iridium-based catalyst. However, absolutely no conversion was observed, even after several hours.

While palladium itself gave a good reactivity, the heterogeneous support appeared to completely inhibit the complexation of the metal with the substrate, therefore giving no diastereoselectivity. As a consequence, we moved to the use of homogeneous palladium catalyst in order to favour this complexation. Many examples of diastereoselective homogeneous hydrogenation with an iridium, rhodium or ruthenium catalyst have been reported[60] but, to the best of our knowledge, no example was found for a homogeneous palladium catalyst, only enantioselective version.[61]

In 2011, Zhou and coworkers reported the homogeneous palladium-catalyzed enantioselective hydrogenation of acyclic enones under hydrogen atmosphere.[62] Using the same reaction conditions without the chiral ligand [H_2, $Pd(OTf)_2$ in TFE], the reduction of ester **1.140** and acid **1.144** was attempted. After 12 h at room temperature, the reduction of **1.140** into intermediate **1.139** occurred smoothly, but unfortunately no selectivity was observed. However, with acid derivative **1.144**, reduced compound **1.145** was obtained with a high diastereoselectivity (10/1). When performing the reaction at 0 °C, the ratio was slightly improved reaching 14/1 on a 5 mg scale. In order to obtain complete cyclization to indole from amino acid **1.145**, the reaction mixture was heated to reflux. This can be done without degradation, even in the presence of the palladium complex. The final esterification of **1.146** to reach (-)-leucomidine B (**1.2**) was performed in a one-pot fashion by addition of an excess of trimethylsilyldiazomethane (Scheme 58). Interestingly, the unreacted diazomethane was *in-situ* quenched by the slightly acidic solvent, 2,2,2-trifluoroethanol. Usually, remaining diazomethane is quenched by addition of acetic acid which generates intense gas evolution. This was not observable in our case, even after short reaction time (addition of AcOH after 15 min at 0 °C). The solvent is believed to have also other functions during the reaction. Firstly, TFE was suggested to play the role of a stabilizer for the active palladium catalyst through weak coordination.[63] Secondly, as shown above, 2,3-dioxopyrrole moieties are sensitive to protic solvent but TFE is less nucleophilic compared to ethanol limiting therefore possible side reactions.

[60] de Vries, J. G.; Elsevier, C. J. *The Handbook of Homogeneous Hydrogenation,* Wiley-VCH, Weinheim, **2007**.
[61] Chen, Q.-A.; Ye, Z.-S.; Duan Y.; Zhou Y.-G. *Chem. Soc. Rev.* **2013**, *42*, 497–511.
[62] Wang, D. S.; Wang, D. W.; Zhou, Y. G. *Synlett* **2011**, *22*, 947–950.
[63] (a) Abe, H.; Amii H.; Uneyama, K. *Org. Lett.* **2001***, 3*, 313-315. (b) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis*, **2007**, *39*, 2925–2941.

When the reaction was performed on a 100 mg scale, a similar diastereomeric ratio of 12/1 was obtained. After separation of the remaining wrong diastereoisomer by flash chromatography, the desired (-)-leucomidine B (**1.2**) was isolated in 71% yield from acid **1.144**.



*Scheme 58 Synthesis of (-)-leucomidine B (**1.2**) via substrate-controlled reduction of **1.144***

Overall, applying our novel strategy, (-)-leucomidine B (**1.2**) was successfully synthesized in 12 steps from known ketoallylester **1.114** in 14.3% overall yield with 89% ee.

3.4. Self-Induced Diastereomeric Anisochronism

It is a common belief that, under the same analytical conditions in an achiral solvent, the NMR spectra of a compound will be the same whether it is racemic or enantiopure. However, there are some literature reports that refute this postulate. In 1969, Uskokovic and coworkers reported the first observation of this phenomenon in deuterated chloroform.[64] It was observed that racemic and enatiopure samples of some dihydroquinine derivatives showed major differences in their proton NMR chemical shifts. Besides, if the ratio of (-)- and (+)-dihydroquinine in a mixture differed from 1/1, two sets of peaks appeared for some protons. The integration of these peaks was proportional to the relative amount of each enantiomer. However, if a highly diluted sample was used, the exact same spectra was observed for the racemate and the enantioenriched compound. The phenomenon also disappeared when the analysis was performed in a polar and, especially, in a protic solvent.

In 1976, Harger rationalized this phenomenon by hypothesizing the formation of different dimers by hydrogen bonding.[65] The racemic mixture would form heterodimers between the two enantiomers while the enantiopure mixture would only form homodimers. As a consequence, for an enantioenriched compound, a mixture of hetero- and homodimers should be obtained, proportionally to the enantiomeric excess. This hypothesis also explained why the phenomenon disappeared with high dilution or with protic solvents: the formation of dimers was inhibited under these conditions.

The term of Self-Induced Diastereomeric Anisochronism (or SIDA) was introduced only in 1995 by Fedin and Okruszek[66] and this denomination is still used nowadays.[67]

In our laboratory this phenomenon had already been observed with (-)-leuconodine A (**1.79**), (-)-leuconodine B (**1.60**) and (-)-leuconodine C (**1.89**).[32] In the case of enantioenriched (-)-leucomidine B (**2**), SIDA was also observable but it was less pronounced than for the leuconodine family. Indeed, the indole proton and the proton on C-21 only split if the sample was sufficiently concentrated. A titration was performed to highlight this effect. This titration consists of doing NMR analysis of a compound at the same concentration but at different enantiomeric purities. The titration starts by using a racemic sample which is then incrementally enriched with the enantiopure form (Figure 1).

---

[64] Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871–1872.
[65] (a) Harger, M. J. P. *J. C. S. Chem. Comm.* **1976**, 555–556. (b) Harger, M. J. P. *J. C. S. Perkin Trans.* **1977**, 1882–1887. (c) Harger, M. J. P. *J. C. S. Perkin Trans.* **1978**, 326–331.
[66] Ouryupin, A. B.; Kadyko, M. I.; Petrovskii, P. V.; Fedin, E. I.; Okruszek, A.; Kinas, R.; Stec, W. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1813–1824.
[67] (a) Nieminen, V.; Murzin, D. Y.; Klika, K. D. *Org. Biomol. Chem.* **2009**, 537-542. (b) Klika, K. D.; Budovská, M.; Kutschy, P. *J. Fluorine Chem.* **2010**, *131*, 467–476.

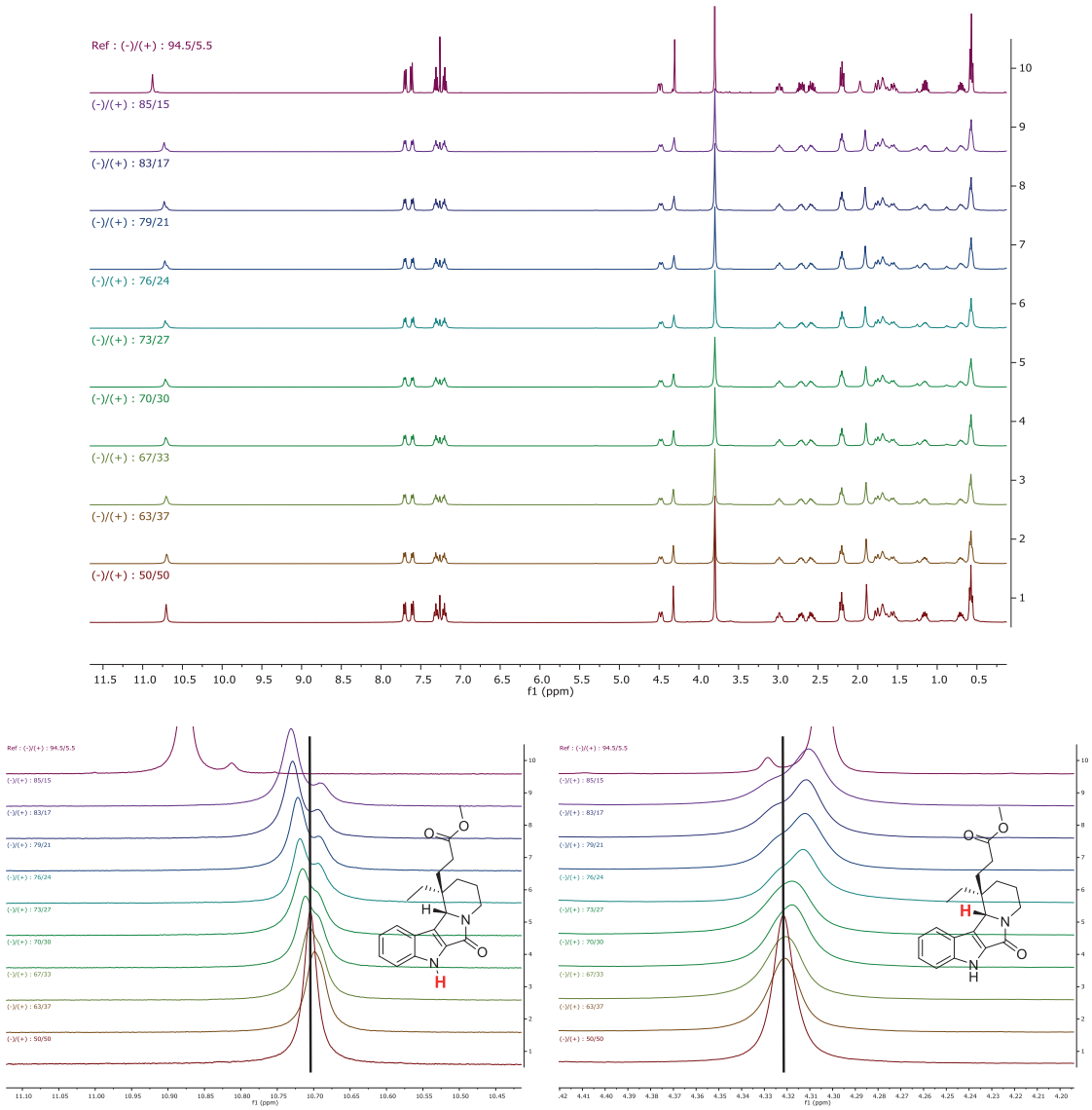


Figure 1 Titration of leucomidine B

In Figure 1, we can clearly see the splitting of these two protons proportionally to the enantiomeric excess. As expected, when the two peaks are sufficiently separated for an integration of their relative areas, these correspond to their relative ratio (-)/(+).

A concentration study was also performed by simple dilution of the sample (Figure 2).

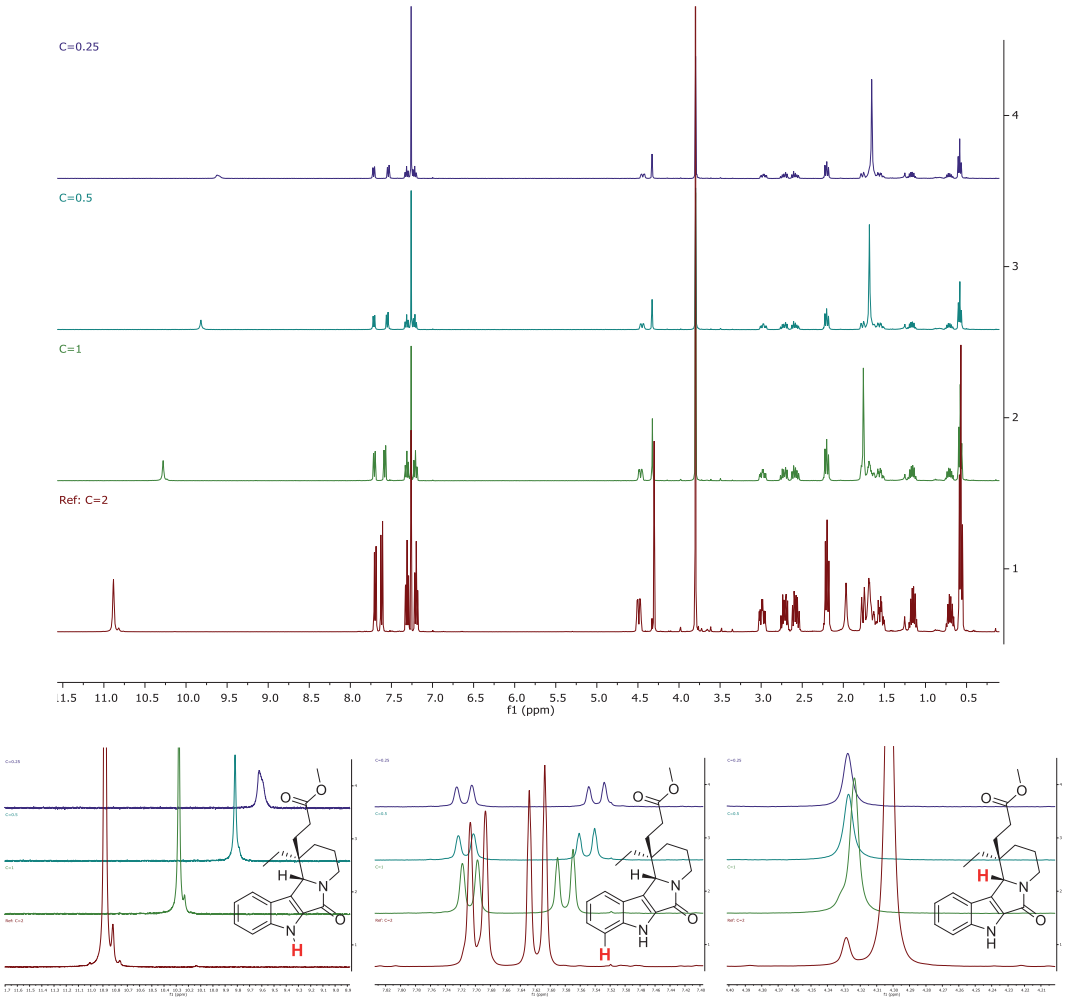


Figure 2 Concentration effect on (-)-leucomidine B spectra

In Figure 2, we can easily see with the N-H proton of indole and the proton on C-21 the loss of the SIDA phenomenon when the dilution increases. A shift of these protons can also be observed. With dilution other protons shifted as well, such as the aromatic proton in ortho position of the indole nitrogen.

The NMR behaviour of these three protons suggested that intermolecular hydrogen bonds could be formed between the indole proton and the carbonyl oxygen of the lactam. To confirm the structure of the dimer, a monocrystal of racemic leucomidine B was grown. As expected, the X-Ray structure indeed shows the formation of a heterodimer by hydrogen bonding (Figure 3).

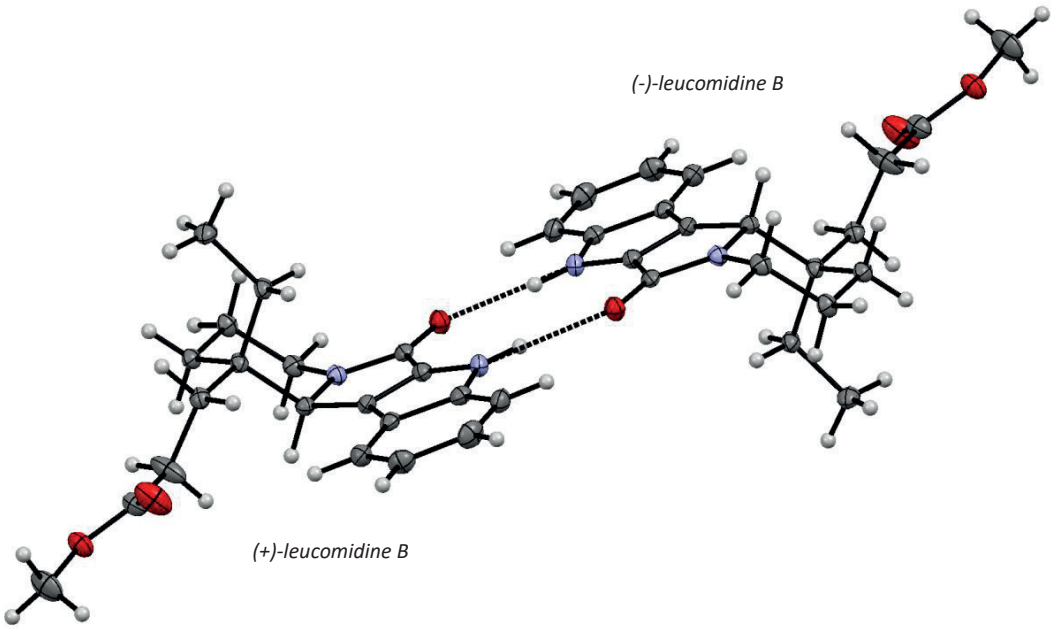


Figure 3 Heterodimer X-Ray structure of leucomidine B

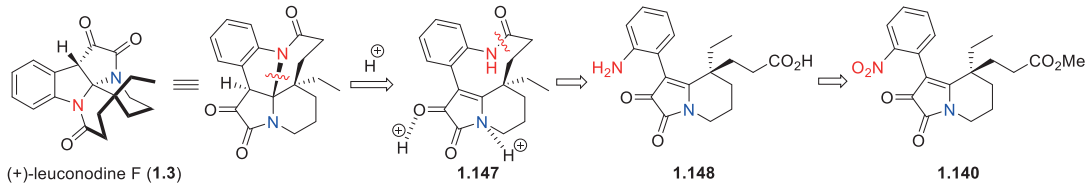
The X-Ray analysis did not exhibit any other hydrogen bonds and the stacking study revealed no *pi*-stacking with the indole moiety. The growing of enantioenriched leucomidine B monocrystals failed when using the same conditions as for the racemate. This led us to believe that the packing of the homodimers is different from that of the heterodimers. Other solvent systems were investigated but all failed to give crystals of sufficient quality. Consequently, we cannot confirm completely the formation of homodimers in the case of enantioenriched leucomidine B

Due to the formation of these dimers, the specific rotation of (-)-leucomidine B (**1.2**) was concentration dependent. For instance at concentration 1, a specific rotation of -21 was obtained, whereas at concentration 0.3, -29 was observed.

Chapter 4. Enantioselective Total Synthesis of (+)-Leuconodine F

4.1. Retrosynthesis

With the 2,3-dioxopyrrole **1.140** in hand, we asked ourselves if it would be possible to selectively reduce the nitroaryl to an aniline without reduction of the double bond. If this was possible and if we could find the right conditions that favour the macrolactamization of **1.148** over the condensation of the aniline onto the 2,3-dioxopyrrole moiety, it should be possible to synthesize (+)-leuconodine F (**1.3**). Under acidic conditions, a transannulation of **1.147** to form the natural product is expected, amide **1.147** being able to cyclize either *via* either a 1,4-addition pathway or an iminium pathway. (Scheme 59).



*Scheme 59 Retrosynthesis of (+)-leuconodine F (**1.3**) from dioxopyrrole **1.140***

4.2. Monoprotected 2,3-Dioxopyrrole

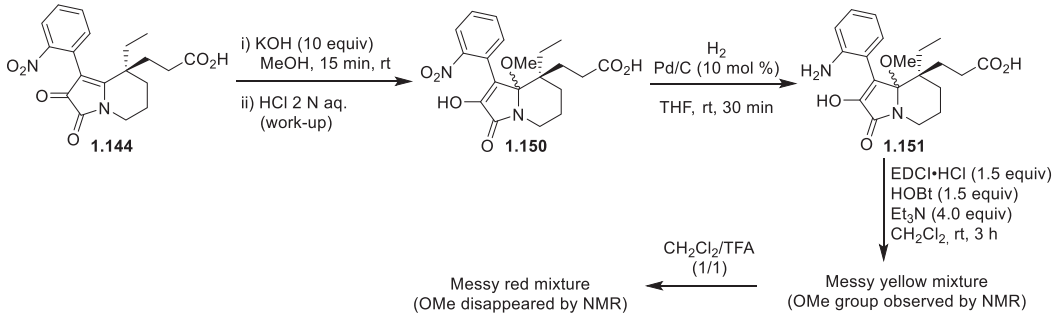
In view of our past experience and initial experiments on the selective reduction of **1.140** (cf. 3.3.), we quickly realized that we would not be able to reduce the nitroaryl group selectively. The olefin proved to be more reactive in all cases. As a consequence, we needed to first find a way to protect the double bond. As we saw previously, 2,3-dioxopyrroles are sensitive to protic solvents. We believed we could use this property to protect the double bond temporarily. Indeed, the 1,4-addition of any nucleophile onto the 2,3-dioxopyrrole core would mask the double bond. In addition, the ketone should be in its enol tautomeric form, as observed before, therefore slowing down the aniline condensation for the desired macrolactamization reaction.

To this end, the 2,3-dioxopyrrole **1.140** was dissolved in methanol in the presence of potassium hydroxide. After a few minutes, all 2,3-dioxopyrrole was consumed and, upon adding aqueous hydrochloric acid, the red solution turned yellow rapidly. The crude NMR confirmed

total conversion of **1.140** to hemiaminal **1.149** with addition of methanol in a 1,4-manner as desired (Scheme 60). Variable diastereomeric ratios were obtained without evident correlation. The addition of methanol was also attempted using one molar hydrochloric acid in methanol but the reaction was much slower compared to the initial basic conditions.

*Scheme 60 Methanol addition onto **1.140***

Monoprotected intermediate **1.149** showed high instability, particularly in solution, undergoing retro 1,4-addition spontaneously. Significant amount of starting 2,3-dioxopyrrole **1.140** could be observed by NMR analysis after a few hours in deuterated chloroform (neutralized or not). In consequence, the hydrolysis of the ester was performed before the methanol addition and, after preparation of the 1,4-adduct **1.150**, the reduction of the nitroaryl to aniline was done immediately. With crude amino acid **1.151** in hand, the macrolactamization was attempted. Unfortunately, a complex mixture was obtained (Scheme 61). In an attempt to confirm that the olefin protection worked, the mixture was treated with TFA. The yellow mixture turned to the characteristic red of the free double bond and the disappearance of methoxyl group could be observed by crude NMR. Unfortunately, the natural product was not detected.

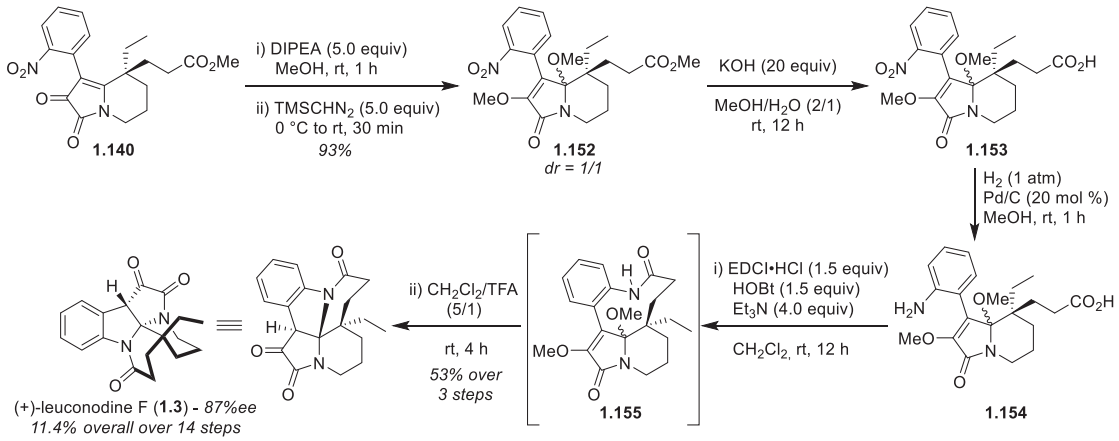


*Scheme 61 Synthetic route failure from monoprotected 2,3-dioxopyrrole **1.150***

The problem encountered during the macrocyclization step could be due to the enol functionality. Indeed, condensation of the aniline onto the enol could still proceed. In addition, competitive macrolactonization between the enolate and the acid could also occur under these reaction conditions. In consequence, the protection of the enol was apparently required.

4.3. Bisprotected 2,3-Dioxopyrrole and Endgame

Methoxy protection of the enol functionality of compound **1.149** was chosen, as it was judged sufficiently robust and it could probably be removed under acidic conditions. After a screening of conditions, which showed complete unreactivity of methyl iodide, a one-pot procedure involving methanol addition and enol methylation by trimethylsilyldiazomethane was optimized. The desired bisprotected intermediate **1.152** exhibited higher stability and could be purified on silica gel. High to excellent yields were always obtained, these ranging from 84% to 93%. After ester hydrolysis and nitroaryl reduction, macrolactamization was attempted on amino acid **1.154**. TLC analysis showed a fairly clean reaction but the NMR spectrum of the crude mixture was complex. The presence of a third chiral element like a rotamer or an atropisomer may have complicated the spectra. Thus, assuming that we had indeed formed macrocycle **1.155**, a strong acid such as trifluoroacetic acid was added to the crude mixture. After a few hours at room temperature, the crude NMR spectra showed only one major product, the desired (+)-leuconodine F (**1.3**) (Scheme 62). After optimization of a one-pot macrolactamization / transannulation and a scale-up to 100 mg, the desired natural product **1.3** was isolated in 53% yield over 3 steps (from bisprotected intermediate **1.152**).

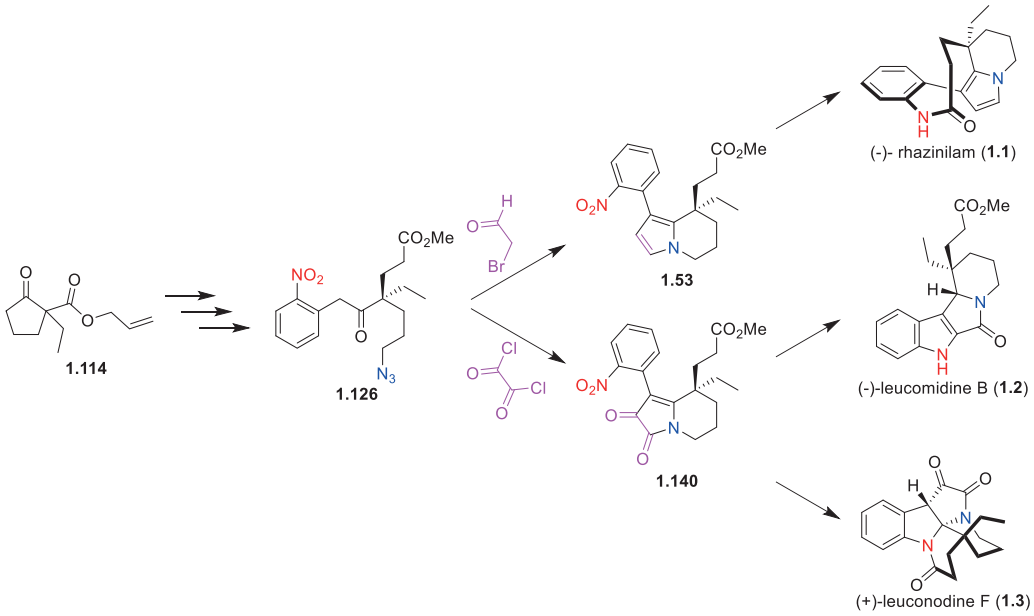


*Scheme 62 Synthesis of (+)-leuconodine F (**1.3**) from bisprotected dioxopyrrole **1.152***

Via the application of our novel strategy, (+)-leuconodine F (**1.3**) was successfully synthesized in 14 steps from known ketoallylester **1.114** in 11.4% overall yield with 87% ee.

Conclusion

In this first part was presented our work towards the development of a novel strategy in order to accomplish the divergent total synthesis of three natural compounds: (-)-rhazinilam (**1.1**), (-)-leucomidine B (**1.2**) and (+)-leuconodine F (**1.3**). These products, despite possessing three distinctly different skeletons, were all obtained from the same advanced intermediate **1.126** *via* the fine tuning of reaction conditions (Scheme 63).



Scheme 63 Overview of the three total synthesis accomplished in the first part

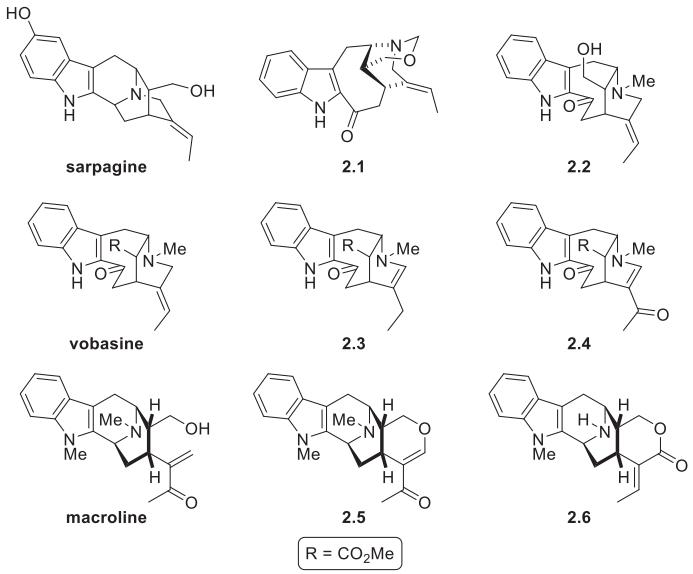
Our initial strategy towards the enantioselective total synthesis of (-)-rhazinilam (**1.1**) *via* a domino Staudinger / aza-Wittig / cyclization process failed. However, a suitable alternative was found using intermediate **1.126**. Our novel route *via* a one-pot Staudinger / aza-Wittig / formal [3+2] cycloaddition sequence using 2-bromoacetaldehyde allowed us to reach desired tetrahydroindolizine moiety **1.53** in high yield. After further functionalizations, enantioenriched (-)-rhazinilam (**1.1**) was obtained in 12 steps and in 16.2% overall yield. Using the same strategy, a formal [3+2] cycloaddition between imine **1.129** and oxalyl chloride afforded quantitatively 2,3-dioxopyrrole **1.140**. This versatile heterocycle furnished quickly two other skeletons of natural products. Firstly, (-)-leucomidine B (**1.2**) was synthesized in 14.3% overall yield over 12 steps. The configuration of the second stereogenic center of this natural compound was controlled diastereoselectively *via* a palladium-hydride reduction taking advantage of a complexation with the carboxylic acid function. Secondly, (+)-leuconodine F (**1.3**) was obtained

in 14 steps with an overall yield of 11.4%. In this last case, the sensitivity of 2,3-dioxopyrrole **1.140** towards protic solvent was used to mask the double bond against reductive conditions. These three novel total synthesis demonstrated once again the utility of the decarboxylative coupling between vinyl triflate and potassium carboxylate to access key building blocks in a few steps.

PART II :
Synthetic Studies Towards Sarpagine-Related Indoles

Introduction

After the successful completion of the previous project, we will see in this second part of the thesis our synthetic studies towards various sarpagine-type natural products. Two sub-families derived of sarpagine, vobasine and macroline, piqued particularly our interest. More precisely, we focused our initial effort on the synthesis of amerovolficine (**2.1**) with in mind the use of the iORC domino process described in the previous part. After exploring additional unfruitful strategies, we moved to the study of affinine (**2.2**) which is basically a diastereoisomer of **2.1**. The key step envisaged in this case was a late-stage cyclization *via* intramolecular 1,4-addition. Related natural products, vobasidine B (**2.3**) and vobasidine D (**2.4**), were also investigated following this approach. At last, we attempted to convert one of our advanced intermediates into stereoisomers of alstonerine (**2.5**) and alstolactone (**2.6**), two macroline-related indoles.



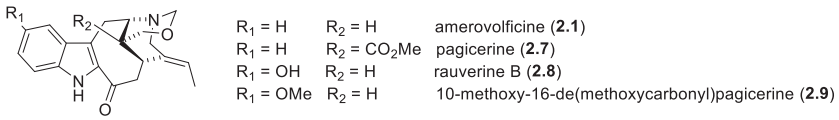
Scheme 64 Targets investigated during the second project

In a similar fashion to the previous part, the first chapter will highlight literature reports concerning the isolation and synthesis of natural products **2.1** to **2.6**. We will also see additional work accomplished by our group on the 1,4-addition of vinyl iodide to conjugated carbonyl group. The various strategies attempted for the synthesis of amerovolficine (**2.1**) will be depicted in the second chapter while the application of one of these strategies towards the synthesis of affinine (**2.2**) will be discussed in the third chapter. Next, the synthetic studies towards vobasidines (**2.3**) and (**2.4**) will be described in the fourth chapter, whereas the approaches to alstonerine (**2.5**) and alstolactone (**2.6**) will be detailed in chapters five and six, respectively. Finally, there will be a conclusion covering this second part.

Chapter 1. State of the Art

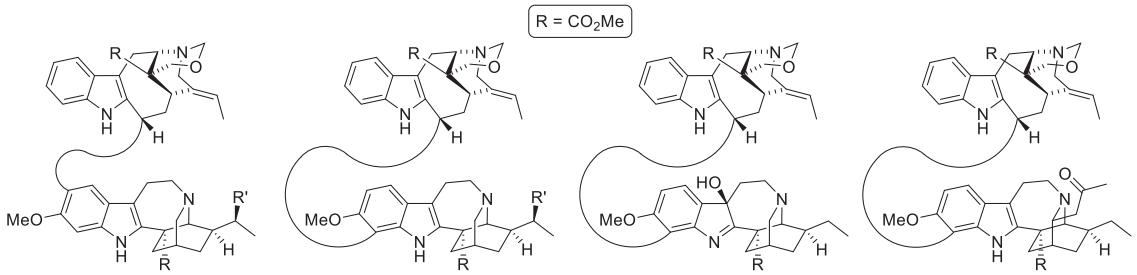
1.1. Amerovolficine

Amerovolficine (**2.1**), isolated from the stem bark of *Rauwolfia Cubana* in 1989 by Martinez and coworkers, possesses an unusual tetrahydro-1,3-oxazine ring based on a vobasine skeleton.[68] Koch et al. were the first to identify this particular heterocycle in 1985 with the isolation of pagicerine (**2.7**) from the stem bark of *Pagiantha Cerifera*.[69] As depicted in Scheme 65, only two other derivatives with a similar structure have been reported to the best of our knowledge: rauverine B (**2.8**) and 10-methoxy-16-de(methoxycarbonyl)pagicerine (**2.9**).[70]



Scheme 65 Amerovolficine and its derivatives

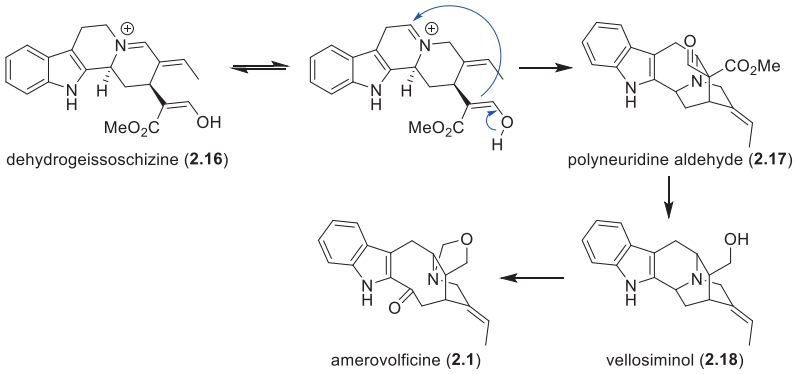
In 2003, Kam and coworkers isolated from the plant *Tabernaemontana Corymbosa* the first pagicerine-iboga based bisindoles: conodirinine A and conodirinine B.[71] During the last decade, four additional bisindoles have been isolated from the same genus by Hao and Cai & Luo groups (Scheme 66).[72]



Scheme 66 Pagicerine-based bisindoles

[68] Martinez, J. A.; Gomez, C.; Santana, T.; Velez, H. *Planta Medica* **1989**, *55*, 283–285.
[69] G. Baudouin, F. Tillequin, M. Koch, *Heterocycles* **1985**, *23*, 2505–2508.
[70] (a) Hu, X. J.; He, H. P.; Zhou, H.; Di, Y. T.; Yang, X. W.; Hao, X. J.; Kong, L. Y. *Helv. Chim. Acta* **2006**, *89*, 1344–1350. (b) Zhang, B.-J.; Peng, L.; Wu, Z.-K.; Bao, M.-F.; Liu, Y.-P.; Cheng, G.-G.; Luo, X.-D.; Cai, X.-H. *J. Asian Nat. Prod. Res.* **2013**, *15*, 1221–1229.
[71] Kam, T.-S.; Sim, K.-M. *Helv. Chim. Acta* **2003**, *86*, 122–126.
[72] (a) Bao, M.-F.; Yan, J.-M.; Cheng, G.-G.; Li, X.-Y.; Liu, Y.-P.; Li, Yan, Cai, X.-H.; Luo, X.-D. *J. Nat. Prod.* **2013**, *76*, 1406−1412. (b) Zhang, Y.; Guo, L.; Yang, G.; Guo, F.; Di, Y.; Li, S.; Chen, D.; Hao, X. *Fitoterapia* **2015**, *100*, 150−155.

Similarly to most of monoterpene indole alkaloids, the biosynthesis of amerovolficine (**2.1**) started with dehydrogeissoschizine (**2.16**). Presumably, after the isomerization of the iminium followed by the intramolecular attack of the 1,3-dicarbonyl group as depicted in Scheme 67, polyneuridine aldehyde (**2.17**) should be formed. Further enzymatic decarboxylation and reduction of the aldehyde to the corresponding alcohol should afford vellosiminol (**2.18**) (also named 10-deoxysarpagine).[73] The oxidative carbon – nitrogen bond cleavage followed by the hemiaminal formation should lead to amerovolficine (**2.1**).



Scheme 67 Plausible biosynthetic pathway towards amerovolficine

To the best of our knowledge, no total synthesis of **2.1** has been reported.

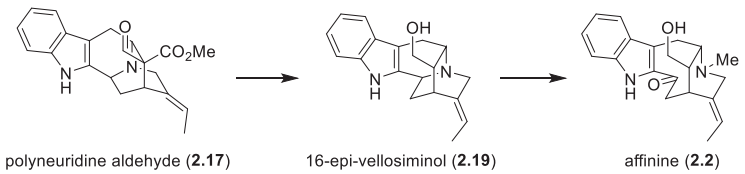
1.2. Affinine

1.2.1. Generality

Affinine (**2.2**) was firstly isolated from the *Peschiera Affinis* in 1963 by Weisbach and coworkers.[74] This monoterpenoid indole was also found in the plants of the *Tabernaemontana* genus in 1971 by Burnell & Medina and more recently, in 2005, by Vieira et al.[75] Limited pharmacological testing has indicated that affinine (**2.2**) may be an effective inhibitor of both acetylcholinesterase and butyrylcholinesterase.[76]

[73] Namjoshi, O. A.; Cook, J. M. "Sarpagine and related alkaloids" *Alkaloids Chem Biol.* **2016**; *76*: 63–169.
[74] Weisbach, J. A.; Raffauf, R. F.; Ribeiro, O.; Macko, E.; Douglas, B. *Journal of Pharmaceutical Sciences* **1963**, *52*, 350–353.
[75] (a) Burnell, R. H.; Medina, J. D. *Can. J. Chem.* **1971**, *49*, 307–316. (b) Monnerat, C. S.; Souza, J. J. de; Mathias, L.; Braz-Filho, R.; Vieira, I. J. C. *J. Braz. Chem. Soc.* **2005**, *16*, 1331–1335.
[76] Vieira, I. J. C.; Medeiros, W. L. B.; Monnerat, C. S.; Souza, J. J. de; Mathias, L.; Braz-Filho, R.; Pinto, A. C.; Sousa, P. M.; Rezende, C. M.; Epifanio, R. de A. *Anais da Academia Brasileira de Ciencias*.**2008**, *80*, 419–426.

For a biosynthetic point of view, a similar route as shown previously for amerovolficine (**2.1**) could be proposed. Decarboxylation, isomerization and reduction of polyneuridine aldehyde (**2.17**) could afford 16-epi-vellosiminol (**2.19**). Further oxidation and methylation should give affinine (**2.2**) (Scheme 68).



Scheme 68 Plausible biosynthetic pathway towards affinine

It should be noted that 16-epi-affinine is also a natural product which came certainly from oxidation / methylation of vellosiminol (**2.18**).

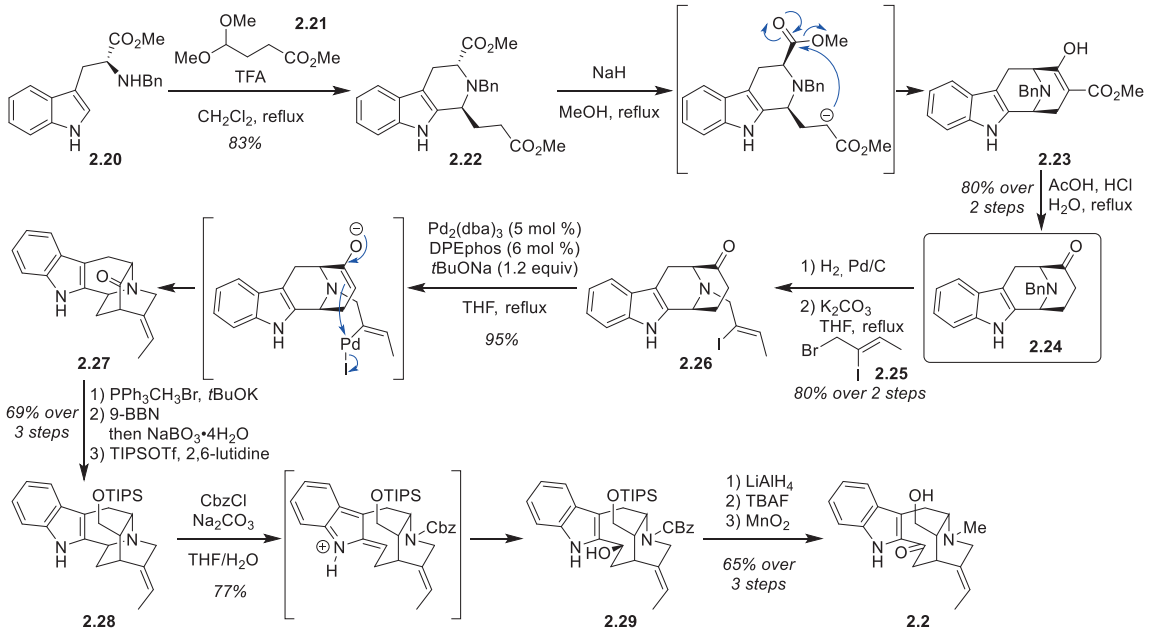
1.2.2. Total Synthesis

Only one total synthesis has currently been reported. Cook is well-known in the community for the general approach he and his coworkers developed over the years in order to synthesize a library of sarpagine-related natural products. Affinine (**2.2**) was one of their targets and the Cook group accomplished the synthesis of it in 2010.[77]

As depicted in Scheme 69, starting with unnatural protected *D*-tryptophan **2.20**, a Pictet-Spengler reaction with acetal **2.21** in the presence of TFA afforded diastereoselectively tetrahydrocarboline **2.22**. Refluxing the latter in sodium methoxide triggered the epimerization of the aminoacid center and allowed the Dieckmann condensation which afforded bridged system **2.23**. By refluxing **2.23** in acidic aqueous media, decarboxylation of the 1,3-ketoester moiety occurred to furnish compound **2.24**, which is the Cook key intermediate for the synthesis of several sarpagine-type indoles. Deprotection of the benzyl group under hydrogenation conditions and then alkylation of the resulting amine with allylic bromide **2.25** afforded allylic amine **2.26**. The second bridged system of the sarpagine skeleton was installed by an intramolecular Pd-catalyzed cross coupling. From a detailed point of view, treatment of ketone **2.26** with sodium *tert*-butoxide generates the formation of the corresponding sodium enolate. After oxidative addition of the palladium(0) catalyst into the carbon – iodine bond, the enolate attacks the palladium(II) complex by displacement of the iodide. Finally, after reductive elimination, desired compound **2.27** was obtained in 95% yield. Olefination of the ketone *via* Wittig reaction, followed by diastereoselective hydroboration / oxidation of the resulting double

[77] Yang, J.; Rallapalli, S. K.; Cook, J. M. *Tetrahedron Lett.* **2010**, *51*, 815–817.

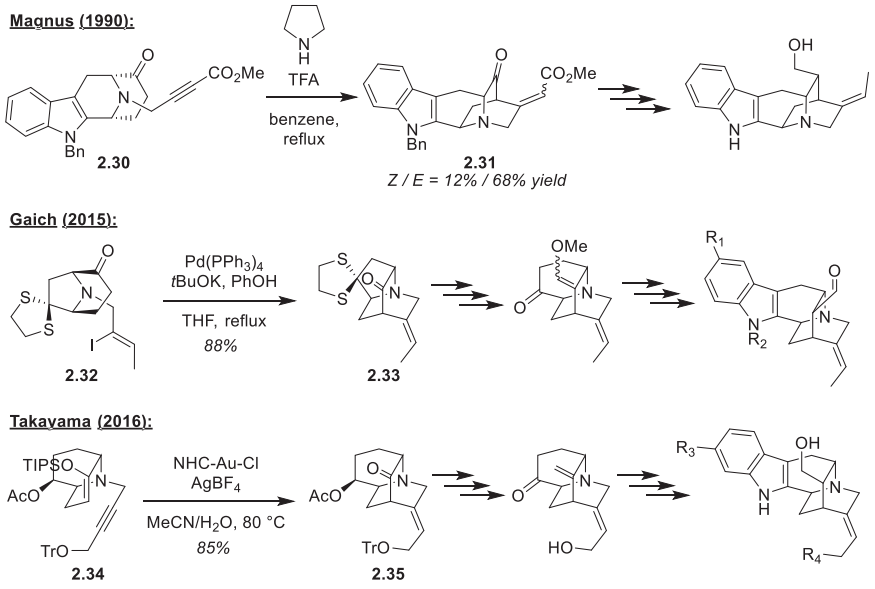
bond using 9-BBN and subsequent protection of the alcohol with TIPSCl gave intermediate **2.28**. Cleavage of the carbon – nitrogen bond of the latter to afford **2.29** was performed using CbzCl in an aqueous media. It is proposed that the amine first reacts with CbzCl and the resulting ammonium ion is next eliminated by the indole *via* dearomatization. The attack of water on the reactive azafulvenium cation rearomatizes the indole and delivers desired compound **2.29**. Next, reduction of the carbamate to the corresponding methylamine followed by deprotection of the alcohol with TBAF and oxidation of the allylic alcohol to ketone using MnO_2 afforded the desired affinine (**2.2**). The synthesis was accomplished from *D*-tryptophan in 15 steps and in 15.8% overall yield with 98% ee.



Scheme 69 Cook's synthesis

The formation of the sarpagine skeleton was also accomplished by other groups using similar approaches to Cook which are shown in Scheme 70. Starting from a close intermediate of **2.24**, possessing a azabicyclo[3.3.1]nonane moiety, Magnus et al. accomplished in 1990 the intramolecular 1,4-addition of ketone **2.30** onto the methyl pent-2-ynoate moiety *via* enamine chemistry.[78] In 2015, Gaich showed that the Pd-catalyzed intramolecular *alpha*-vinylation of ketones, used in the Cook synthesis, is also viable in the case of azabicyclo[3.2.1]octane substrate **2.32**.[79] In 2016, Takayama and coworkers used bicycle **2.34** to demonstrate the efficiency of the gold catalysis for the *6-exo-dig* cyclization of alkynyl silyl enol ethers.[80]

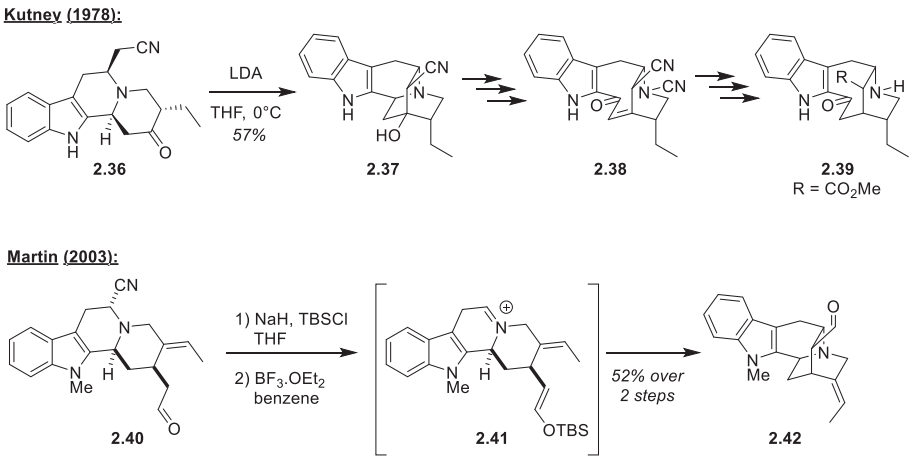
[78] Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220–5230.
[79] Krüger, S.; Gaich, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 315 –317.
[80] Kitajima, M.; Watanabe, K.; Maeda, H.; Kogure, N.; Takayama, H. *Org. Lett.* **2016**, *18*, 1912−1915.



Scheme 70 Sarpagine-related indoles synthesis following similar strategies to Cook

In the literature, there are additional examples of total synthesis of sarpagine-type natural products, but following a different approach. In 2003, Martin reported a biomimetic synthesis of *N*-methylvellosimine (**2.42**).[81] The key step involved the intramolecular trapping of iminium intermediate **2.41**, generated *in-situ via* cyanide elimination, by a silyl enol ether. Earlier, in 1978, Kutney et al. already demonstrated the feasibility of this cyclization reaction on a similar fused rings substrate.[82] As we can observed on Scheme 71, the nucleophilic and electrophilic sites on intermediate **2.36** are reversed compared to the biosynthetic approach. With the correct relative stereochemistry on **2.36**, addition of deprotonated alkyl cyanide onto ketone occurred with good yield to afford the bridged system **2.37**. Kutney showed that any other diastereoisomer of **2.36** failed to cyclize. This observation was rationalized to be due either to an unfavourable conformation of the substrate if one of the two stereocenters *alpha* to the nitrogen is reversed or to the steric hindrance if the ethyl *alpha* to ketone is epimerized. Advanced enone **2.38** was then synthesized in 3 steps involving first, oxidative carbon – nitrogen bond cleavage of **2.37** with cyanogen bromide, followed by oxidation of the resulting allylic alcohol to ketone with MnO_2 and finally by further elimination of the tertiary alcohol using $SOCl_2$. After a few additional steps, dihydroperivine (**2.39**), a natural product closely related to affinine (**2.2**), was obtained.

[81] Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550.
[82] Kutney, J. P.; Eigendorf, G. K.; Matsue, H.; Murai, A.; Tanaka, K.; Sung, W. L.; Wada, K.; Worth, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 938–943.

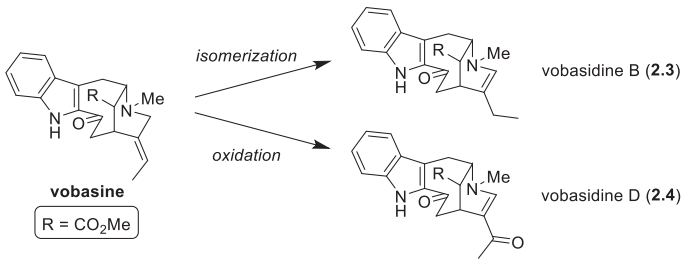


Scheme 71 Sarpagine-related indoles synthesis following other strategies

1.3. Vobasidine B and Vobasidine D

In contrast to amerovolficine (**2.1**) and affinine (**2.2**) which have been known for many years, vobasidines B (**2.3**) and D (**2.4**) were isolated recently, in 2014, by Kam and coworkers.[83] These two natural products were extracted from the stem-bark of a Malayan plant also belonging to the *Tabernaemontana* genus. Preliminary bioassays revealed that vobasidine B (**2.3**) showed slight cytotoxicity towards KB cells, whereas vobasidine D (**2.4**) was inactive. Vobasidines B and D are rare examples of sarpagine-related natural products containing an enamine or enaminone functionality.

No biosynthesis was proposed in the isolation paper but we supposed that **2.3** and **2.4** came from vobasine, as shown in Scheme 72. Vobasidine B (**2.3**) could be obtained by simple isomerization of the allylic amine to the enamine, whereas vobasidine D (**2.4**) could be biosynthesized *via* oxidation to the corresponding enaminone.



Scheme 72 Plausible biosynthetic pathway towards vobasidines

[83] Sim, D. S.-Y.; Chong, K.-W.; Nge, C.-E.; Low, Y.-Y.; Sim, K.-S., Kam T.-S. *J. Nat. Prod.* **2014**, *77*, 2504−2512.

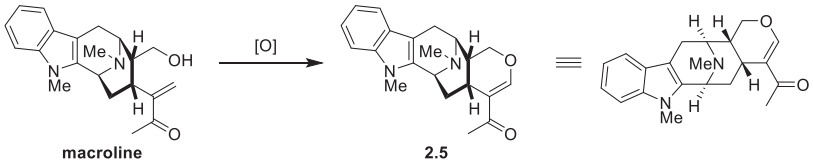
Unlike affinine (**2.2**), no total synthesis of **2.4** or **2.5** has been reported.

1.4. Alstonerine

1.4.1. Generality

Alstonerine (**2.5**) is a macroline-type natural product, first isolated in 1959 from the bark of *Alstonia Muelleriana* by Gilman and Elderfield.[84] The structure was elucidated 10 years later by Le Quesne and coworkers and was confirmed by the same group in 1976 by semi synthesis.[85] In 2014, Kam reported that **2.5** showed no particular cytotoxicity against KB cells but exhibited a strong activity in reversing multidrug resistance in vincristine-resistant KB/VJ300 cells.[86]

Alstonerine (**2.5**) was proposed to be biosynthesized from macroline *via* intramolecular Michael addition followed by oxidation of the resulting ketone to enone (Scheme 73).



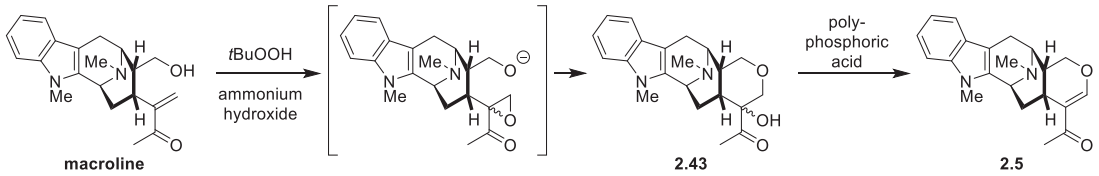
Scheme 73 Plausible biosynthetic pathway towards alstonerine

1.4.2. Semi Synthesis

Le Quesne's Semi Synthesis

In 1976, 7 years after the structural elucidation of **2.5**, Le Quesne reported the first semi synthesis.[87] Starting from macroline, epoxidation of the enone in the presence of base afforded the *alpha*-ketoepoxide intermediate which was subsequently opened intramolecularly by the alkoxide to give **2.43** (Scheme 74). Treatment of the latter with polyphosphoric acid triggered the dehydration to afford directly alstonerine (**2.5**).

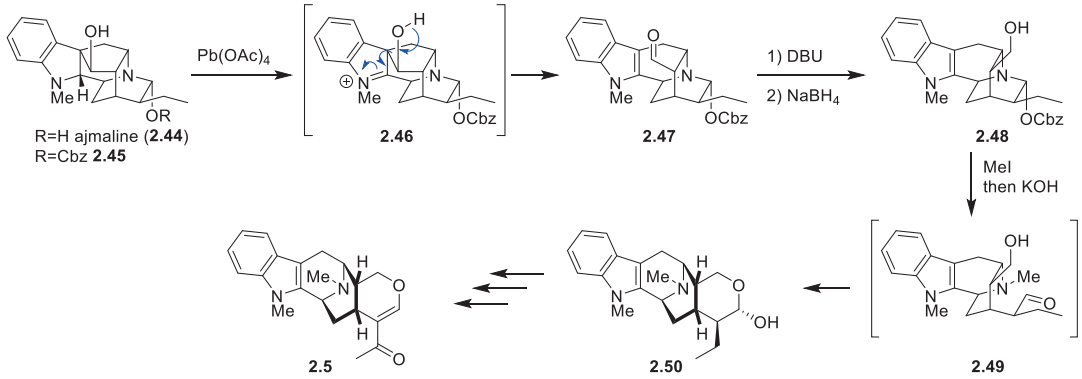
[84] (a) Gilman, R. E. *Diss. Abs.* **1959**, *20*, 1578. (b) Elderfield, R. C. *Amer. Scientist* **1960**, *48*, 193.
[85] Cook, J. M.; Le Quesne, P. W.; Elderfield, R. C. *J. C. S. D Chem. Comm.* **1969**, 1306−1307.
[86] Tan, S.-J.; Lim, J.-L.; Low, Y.-Y.; Sim, K.-S.; Lim, S.-H.; Kam, T.-S. *J. Nat. Prod.* **2014**, *77*, 2068−2080.
[87] Garnick, R. L.; Le Quesne, P. W. *Tetrahedron Lett*. **1976**, 17, 3249−3252.



Scheme 74 Le Quesne's semi synthesis

Sakai's Semi Synthesis

In 1991, Sakai and coworkers accomplished the second semi synthesis of **2.5** starting from ajmaline (**2.44**).[88] Oxidation of Cbz-protected ajmaline **2.45** with lead(IV) acetate generated iminium intermediate **2.46** which then fragmented to afford methylindole **2.47** (Scheme 75). After epimerization and reduction of aldehyde **2.47**, sarpagine derivative **2.48** was treated with methyl iodide. The corresponding ammonium salt, in the presence of KOH, fragmented upon hydrolysis of the carbonate to form aldehyde **2.49**. Spontaneous intramolecular trapping of the aldehyde with the primary alcohol furnished hemiacetal **2.50**. After several functional group interchanges, the desired alstonerine (**2.5**) was obtained.



Scheme 75 Sakai's Semi Synthesis

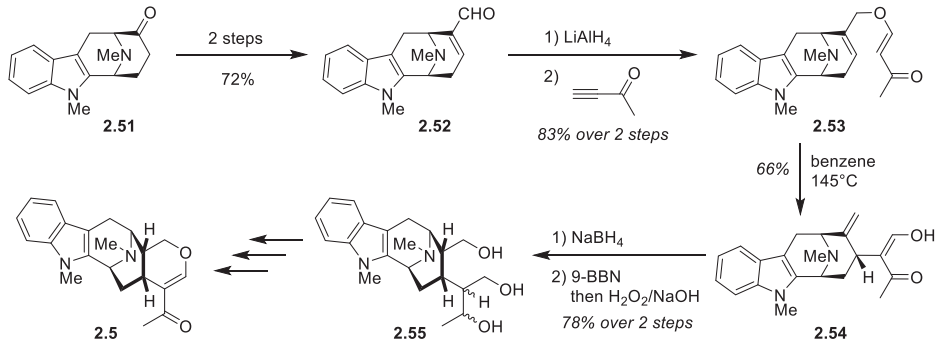
1.4.3. Total Synthesis

The total synthesis of alstonerine (**2.5**) interested particularly Cook starting from the 90s. Between 1990 and 2006, the Cook group reported three different enantioselective approaches to this natural product. Martin and Craig groups also accomplished the synthesis of **2.5** in 2007 and 2013, respectively.

[88] Takayama, H.; Phisalaphong, C.; Kitajima, M.; Aimi, N.; Sakai, S.-I. *Tetrahedron* **1991**, *47*, 1383−1392.

Cook's first synthesis

Cook reported the first total synthesis of alstonerine (**2.5**) in 1990.[89] As depicted in Scheme 76, oxidative one carbon homologation of enantioenriched ketone **2.51**, obtained in a similar manner as for **2.24**, afforded enal **2.52**. 1,2-reduction of the latter with lithium aluminium hydride, followed by 1,4-addition of the corresponding allylic alcohol onto 3-butyn-2-one, afforded key intermediate **2.53**. Next, Claisen rearrangement under thermal conditions afforded desired adduct **2.54** in 66% yield with good diastereoselectivity thanks to the concave / convex conformation of the bridged system. Reduction of the 1,3-ketoaldehyde moiety to the diol and subsequent diastereoselective hydroboration / oxidation sequence using 9-BBN gave **2.55** in high yield. After treatment of triol **2.55** with tosyl chloride to form the ether ring and oxidation to the enone, alstonerine (**2.5**) was obtained in a total of 18 steps from *D*-tryptophan and in 3.7% overall yield with 98% ee.



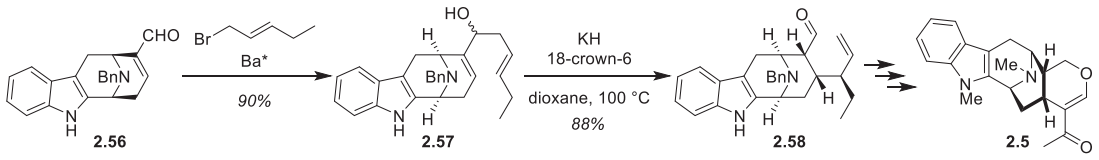
Scheme 76 Cook's first synthesis

Cook's second synthesis

In 2000, Cook et al. reported their second synthesis of **2.5** involving also a sigmatropic rearrangement.[90] Mixing active barium metal, obtained from reduction of barium iodide with lithium biphenylide,[91] with 1-bromo-2-pentene gave the corresponding allylic barium reagent. Reacting this freshly prepared barium species with enal **2.56** allowed a selective 1,2-addition without any allylic rearrangement (Scheme 77). When potassium hydride was used in the presence of crown ether in refluxing dioxane, an anionic oxy-Cope rearrangement of **2.57** occurred to furnish desired adduct **2.58** in 88% yield and with excellent diastereoselectivity. Further transformations of the aldehyde and vinyl moieties gave the desired alstonerine (**2.5**). In

[89] (a) Zhang, L.-H.; Cook, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 4088−4090. (b) Bi, Y.; Zhang, L.-H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027−9041.
[90] Yu, P.; Wang, T.; Li, J.; Cook, J. M. *J. Org. Chem.* **2000**, *65*, 3173−3191.
[91] Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130−6141.

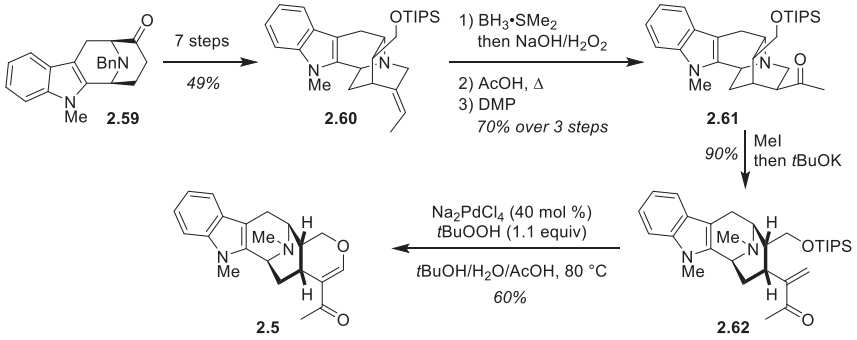
spite of the 19 steps required from *D*-tryptophan, the natural product was obtained in an impressive 13.1% overall yield with 98% ee.



Scheme 77 Cook's second synthesis

Cook's third synthesis

In 2005, Cook and coworkers reported their last total synthesis of **2.5** following a biomimetic approach.[92] Starting with TIPS-protected affinisine **2.60**, diastereoselective hydroboration / oxidation with BH_3 gave the corresponding alcohol. Due to complexation of the tertiary amine with borane, treatment of this intermediate with acetic acid was necessary to free the nitrogen. Further oxidation of the alcohol to ketone using Dess-Martin periodinane gave compound **2.61** in high yield (Scheme 78). Inspired by the Sakai semi synthesis, methylation of **2.61** and subsequent treatment with base triggered the elimination of the resulting ammonium ion to form corresponding enone **2.62**, which was revealed to be the TIPS-protected macroline. The key step of this synthesis was the direct conversion of **2.62** to alstonerine (**2.5**) *via* a domino alcohol deprotection / intramolecular Wacker-type oxidation process. This reaction was accomplished in 60% yield using Na_2PdCl_4 as palladium catalyst, *t*-BuOOH as oxidant and an acidic solvent system. Alstonerine (**2.5**) was obtained in 18 steps from *D*-tryptophan with 98% ee, which is similar to the previous synthesis but in a lower, still very good, overall yield of 11.2%.

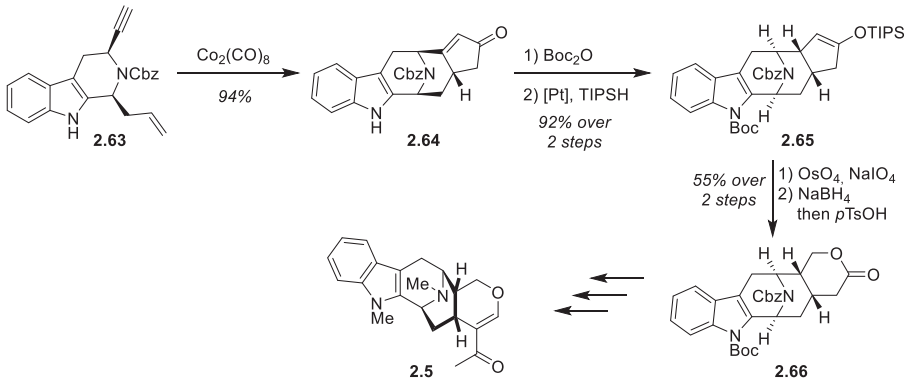


Scheme 78 Cook's third synthesis

[92] (a) Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J. M. *Org. Lett.* **2005**, *7*, 3501−3504. (b) Liao, X.; Zhou, H.; Yu, J.; Cook, J. M. *J. Org. Chem.* **2006**, *71*, 8884−8890.

Martin's synthesis

Martin accomplished the fourth enantioselective total synthesis of alstonerine (**2.5**) in 2007.[93] The first key step of his strategy was the formation of the bridged and fused rings system in a single operation using the Pauson-Khand reaction. Treatment of enantioenriched compound **2.63** with the cobalt complex $Co_2(CO)_8$ triggered the desired transformation and pentacycle **2.64** was obtained in 94% yield (Scheme 79). After protection of the indole, diastereoselective Pt-catalyzed 1,4-reduction of the enone moiety, using TIPSH as reductant, furnished silyl enol ether **2.65** in high yield. Ring expansion of the latter to required 6-membered ring **2.66** was accomplished in 3 steps. First, alkene cleavage of the silyl enol ether under Lemieux-Johnson conditions furnished the corresponding acyclic aldehyde / acid. After reduction of the latter with sodium borohydride, the resulting alcohol / acid was then treated with sulfonic acid to form targeted lactone **2.66**. After functional group interconversions of the 6-membered lactone, the natural product **2.5** was obtained in 3.7% yield over 15 steps from *L*-tryptophan with 99% ee.



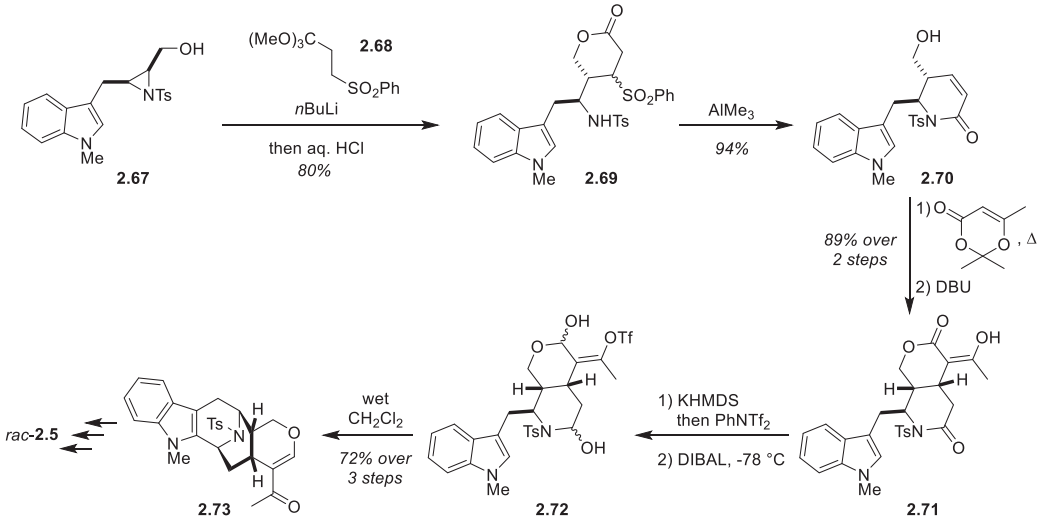
Scheme 79 Martin's synthesis

Craig's synthesis

In 2013, Craig reported the last total synthesis of **2.5** which was the first one of a racemate.[94] As described in Scheme 80, regioselective aziridine opening of **2.67** with the deprotonated sulfone **2.68**, followed by hydrolysis of the orthoester moiety and spontaneous lactonization afforded **2.69** in 80% yield. Treatment of lactone **2.69** with trimethylaluminium triggered both the lactamisation and the sulfone elimination to give conjugated amide **2.70**. Microwave assisted esterification of alcohol **2.70** with 2,2,6-trimethyl-1,3-dioxin-4-one furnished the corresponding 1,3-ketoester which next underwent intramolecular 1,4-addition upon treatment with DBU. Triflation of resulting 1,3-ketolactone **2.71** followed by DIBAL reduction of both the lactone and amide groups afforded the corresponding lactol / hemiaminal intermediate **2.72**. Submitting the

[93] Miller, K. A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113−1116.
[94] Craig, D.; Goldberg, F. W.; Pett, R. W.; Tholen, N. T. H.; White, A. J. P. *Chem. Comm.* **2013**, *49*, 9275−9277.

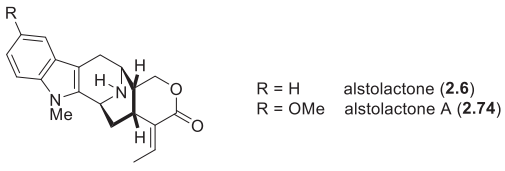
latter to wet dichloromethane initiated the triflate hydrolysis, generating therefore triflic acid in the mixture. The presence of strong acid with **2.72** catalyzed both the dehydration to enone and the Pictet-Spengler reaction to furnish pentacycle **2.73**. After removal of the tosyl group and methylation of the free secondary amine, alstonerine (**2.5**) was obtained in an excellent 19.8% yield over 15 steps from *Z*-but-2-ene- 1,4-diol.



Scheme 80 Craig's synthesis

1.5. Alstolactone

Alstolactone (**2.6**) is a monoterpene indole alkaloid based on a macroline skeleton like **2.5**. This natural product was isolated for the first time in 2004 by Kam et al. from extracts of the leaf of *Alstonia Angustifolia*.[95] An oxygenated derivative of **2.6**, alstolactone A (**2.74**), was also isolated by Kam in 2014 from the bark and leaf of the same plant.[86] These two compounds are the only examples of macroline-related indoles which incorporate a conjugated lactone functionality (Scheme 81).

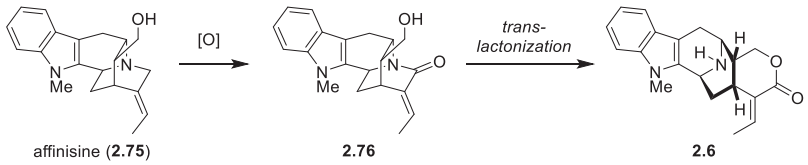


Scheme 81 Alstolactone and its derivative

[95] Kam, T. S.; Choo, Y. M. *Phytochemistry* **2004**, *65*, 603−608.

Like **2.5**, alstolactone (**2.6**) was found to be inactive against KB cells but it showed moderate activity in reversing multidrug resistance in vincristine-resistant KB/VJ300 cells.[86]

In contrast to the case of alstonerine (**2.5**), the biosynthetic pathway probably does not start from macroline. Indeed, no methylamine is present on **2.6** and a demethylation process would not be favourable. As shown in Scheme 82, the biosynthesis can be proposed to start from affinisine (**2.75**). After oxidation of the allylic amine group to the corresponding conjugated lactam **2.76**, a translactonization could occur to release the ring strain and therefore forming alstolactone (**2.6**).

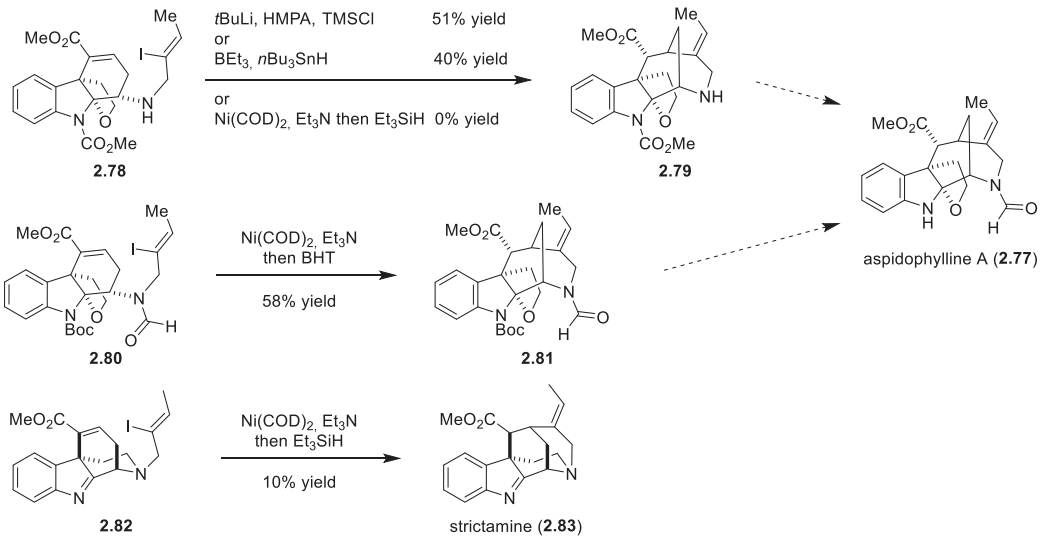


Scheme 82 Plausible biosynthetic pathway towards alstolactone

1.6. Previous Work

The intramolecular conjugate addition of vinyl iodide, in order to construct bridged systems in natural product synthesis, is an important reaction in our group. With this strategy, we successfully reached, in 2014, aspidophylline A (**2.77**) from intermediate **2.78** either *via* a lithium / halogen exchange or *via* a radical pathway.[96] This transformation could be in theory performed under other conditions. Indeed, with the possible insertion of palladium into the carbon – iodine bond, a reductive Heck reaction should give the desired cyclization. Some examples with nickel chemistry had also been reported. In our case, both of these metals failed to give the natural product. However, it should be noted that with a very close substrate **2.80**, Ma and coworkers accomplished the cyclization using $Ni(COD)_2$.[97] Thus, this type of transformation appears to be very substrate sensitive.

[96] Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1818–1821.
[97] Teng, M.; Zi, W.; Ma, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 1814–1817.



Scheme 83 1,4-addition of vinyl iodide in total synthesis

Our group also experienced the limitation of the conjugate addition reactions of vinyl iodides. In 2016, in the case of the strictamine (**2.83**) synthesis, difficulties were encountered.[98] After a screening of various reaction conditions and substrates, including vinyl bromide and vinyl boronate derivatives, the desired cyclization occurred in only one case. When vinyl iodide intermediate **2.82** was treated with $Ni(COD)_2$ and triethylamine, and after reduction of the Ni(II) intermediate with triethylsilane, the desired natural product **2.83** was obtained in 10% yield. Unfortunately, other groups have reported similar issues in literature.[99,100]

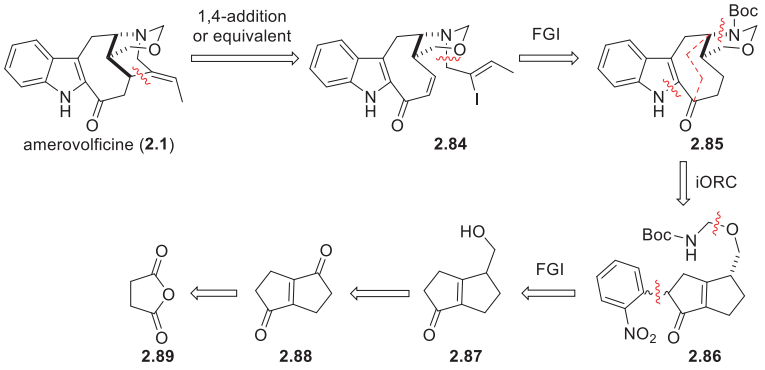
[98] Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 3500–3503.
[99] (a) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057–2059. (b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565–7581.
[100] (a) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649–651. (b) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17–46.

Chapter 2. Synthetic Studies Towards Amerovolficine

2.1. First Strategy

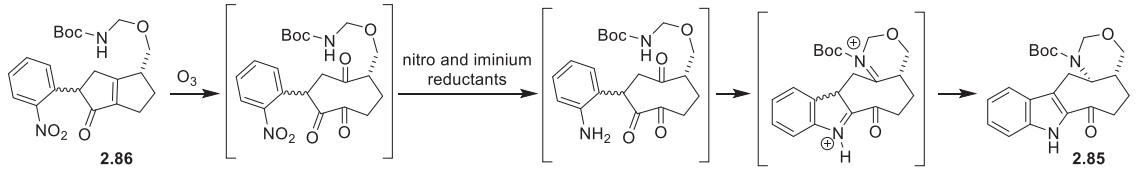
2.1.1. Retrosynthesis

The particular motif of amerovolficine (**2.1**) attracted our attention and was chosen as the primary candidate to explore the synthesis of vobasine-related indole. As we saw in the first chapter, most of the strategies towards the synthesis of sarpinge-type natural products involve the skeleton construction around either the bridged bicyclo[3.3.1]nonane or the fused bicyclo[4.4.0]decane systems (cf. 1.2.2.). We were interested in investigating a novel approach and in constructing the skeleton around an 8-membered ring intermediate. With this idea and the iORC process in mind, the following retrosynthesis of the racemate, depicted in Scheme 84, was considered. Amerovolficine (**2.1**) could be obtained from **2.84** by a final intramolecular 1,4-addition, or an equivalent reaction, of vinyl iodide onto enone. The latter could be synthesized from **2.85** by oxidation of the ketone to the corresponding enone, followed by Boc-deprotection and subsequent allylation of the resulting free amine. The 8-membered ring in **2.85** was expected to be formed from bicyclo[3.3.0]octane **2.86** *via* an iORC process. Key intermediate **2.86** could be obtained from **2.87** *via* hemiaminal formation and *alpha* ketone arylation. Mono-Wittig olefination and subsequent hydroboration / oxidation sequence of diketone **2.88** should lead to **2.87**. Finally, the synthesis of intermediate **2.88** is reported in literature from succinic anhydride (**2.89**).



Scheme 84 First retrosynthesis

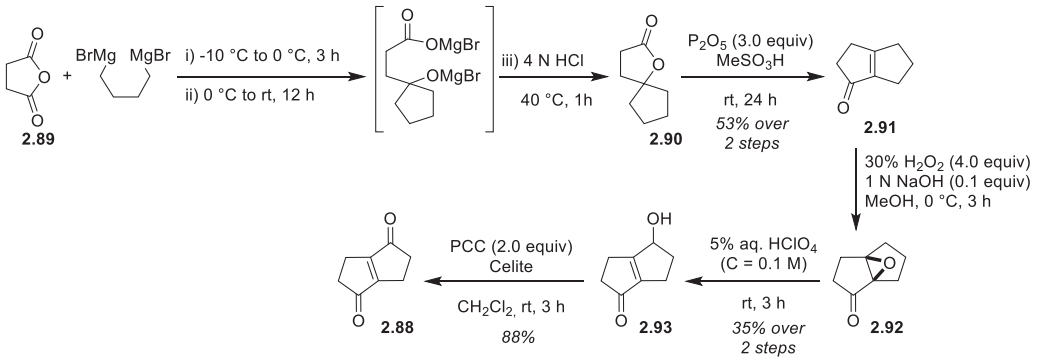
From a stepwise point of view of the iORC process, we believed that ozonolysis of the bicyclic enone **2.86** should form the corresponding 8-membered cyclic triketone intermediate. After nitroaryl reduction, followed by the condensation onto ketones of both the resulting aniline and Boc-protected amine, we expected that the Boc-iminium intermediate could be trapped diastereoselectively with a suitable reductant (Scheme 85). The undesired reduction of the iminium of the indole moiety should not occur due to rapid aromatization.



Scheme 85 Key iORC process

2.1.2. Towards the Synthesis of the Key Intermediate

As reported in the literature and depicted in Scheme 86, double Grignard addition of 1,4-dibromobutane onto succinic anhydride (**2.89**) afforded, after acidic work-up, spiro lactone **2.90**.[101] Skeletal rearrangement of the latter to ketone **2.91** proceeded upon treatment of the crude material with P_2O_5 in methanesulfonic acid in 53% yield over 2 steps. Epoxidation of enone **2.91**, followed by treatment with a 5% aqueous solution of perchloric acid, afforded compound **2.93** in 35% yield over 2 steps. Careful optimization of the acid concentration was necessary to obtain reproducible results, particularly on a large scale. Finally, oxidation of alcohol **2.93** with PCC afforded enedione **2.88** in 88% yield.

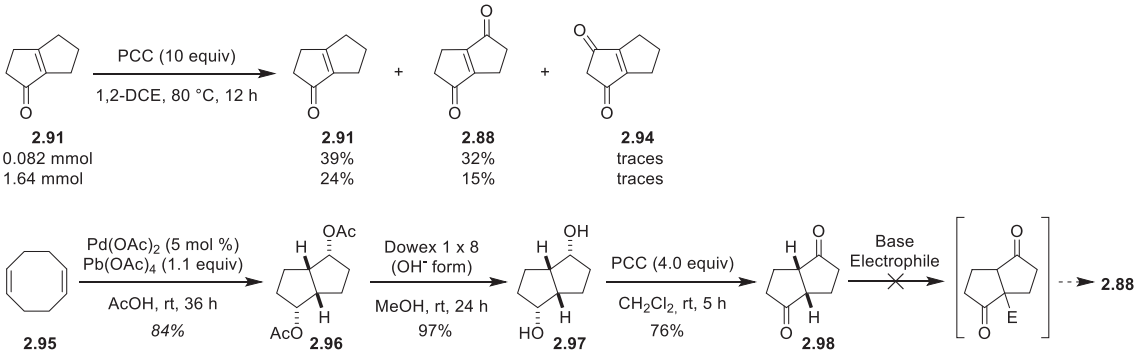


*Scheme 86 Synthesis of enedione **2.88***

[101] Spirolactone: (a) Canonne, P.; Bélanger, D. *J. C. S. Chem. Comm.* **1980**, 125−126. (b) Canonne, P.; Foscolos, G. B.; Bélanger, D. *J. Org. Chem.* **1980**, *45,* 1828−1835. (c) Canonne, P.; Bélanger, D.; Lemay, G.; Foscolos, G. B. *J.* Org. *Chem.* **1981**, 46, 3091-3097. (d) Canonne, P.; Bélanger, D.; Bernatchez, M. *Tetrahedron* **1989**, *45*, 2525−2540. Enone from spirolactone: (e) Narayana Murthy, Y. V. S.; Narayana Pillai, C. *Tetrahedron Lett.* **1990**, *31*, 6067−6074. (f) Narayana Murthy, Y. V. S.; Narayana Pillai, C. *Tetrahedron* **1992**, *48*, 5331−5346. Enone to enedione: (g) Winkler, J. D.; Hong, B.-C.; Bahador, A.; Kazanietz, M. G.; Blumberg, P. M. *J. Org. Chem.* **1995**, *60*, 1381−1390.

Due to the rather poor yield obtained to access enedione **2.88** (16% over 5 steps), other routes were also attempted in parallel. First, direct allylic oxidation of enone **2.91** to **2.88** was investigated using different chromium sources.[102] When PCC was used in refluxing 1,2-DCE, encouraging results were obtained, on a small scale, with 32% isolated yield of the desired product and 39% of the starting materials recovered. However, on a larger scale, both yields decreased dramatically to 15% and 24%, respectively (Scheme 87).

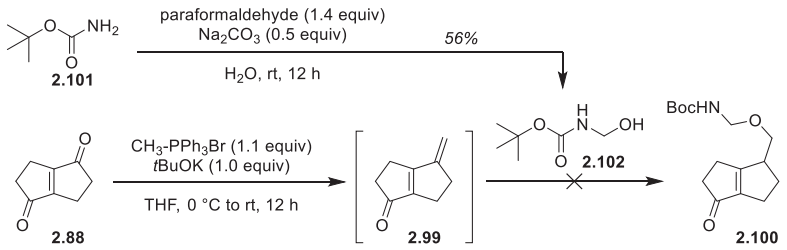
The second approach attempted involved the oxidation of diketone **2.98**, synthesized in high yield over 3 steps from 1,5-cyclooctadiene (**2.95**).[103] Introduction of an electrophile, typically a halide, in *alpha* position of the ketone, followed by its direct elimination to furnish **2.88**, was explored but gave complex mixtures and only a trace of the desired product was observed.



*Scheme 87 Additional routes explored towards enedione **2.88***

Next, selective mono-Wittig olefination of enedione **2.88** was explored. However, low conversion was observed using 1 equivalent of the ylide. Besides, difficulties in isolating desired product **2.99** was encountered due to both its volatility and the isomerization of the exocyclic double bond on silica gel. If more than 1 equivalent of Wittig reagent was used, better conversion was obtained but several side products were formed in the process. Reaction with the Petasis reagent at 60 °C was also tried but gave similar results. 1,6-Addition of hemiaminal **2.102**[104] onto crude **2.99** was also attempted, but desired 1,6-adduct **24** was never observed (Scheme 88).

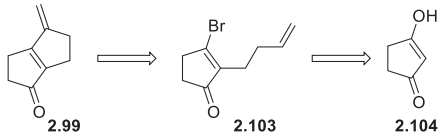
[102] Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2003**, *5*, 2295−2298.
[103] (a) Henry, P. M.; Davies, M.; Ferguson, G.; Phillips S.; Restivo, R. *J. C. S. Chem. Comm.* **1974**, 112−113. (b) Mehta, G.; Srinivas, K. *Synlett* **1999**, *10*, 555. (c) Cramer, N.; Buchweitz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem. Eur. J.* **2006**, *12,* 2488−2503.
[104] Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; Pozo, C. *Org. Lett.* **2007**, *9*, 5283−5286.



*Scheme 88 Synthesis attemps of hemiaminal **2.100** from enedione **2.88***

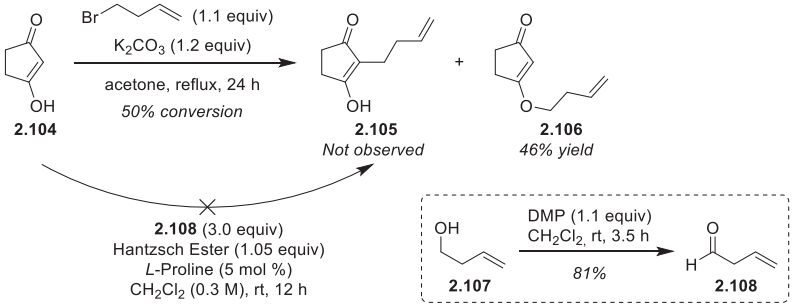
2.1.3. Alternative Routes Towards the Key Intermediate

It was necessary to find a more efficient route to generate diene **2.99** in order to attempt additional conditions for the following steps. As shown in Scheme 89, **2.99** could be synthesized from vinyl bromide **2.103** *via* intramolecular Heck coupling. The latter should be obtained by C-alkylation of 1,3-cyclopentandione (**2.104**) followed by bromination of the 1,3-diketone moiety.



*Scheme 89 Alternative route envisaged towards diene **2.99***

C-alkylation of **2.104** with 4-bromobut-1-ene unfortunately failed and only the O-alkylated product **2.106** was isolated. The best route described in literature to obtain selective C-alkylation of 1,3-cyclopentandione is *via* the proline-catalyzed condensation with an aldehyde followed by a one-pot 1,4-reduction of the resulting Knoevenagel adduct with Hantzsch ester.[105] This procedure was attempted with but-3-enal (**2.108**), obtained by oxidation of but-3-en-1-ol (**2.107**) with DMP, but led only to decomposition of **2.108** and its isomerization to enal (Scheme 90).

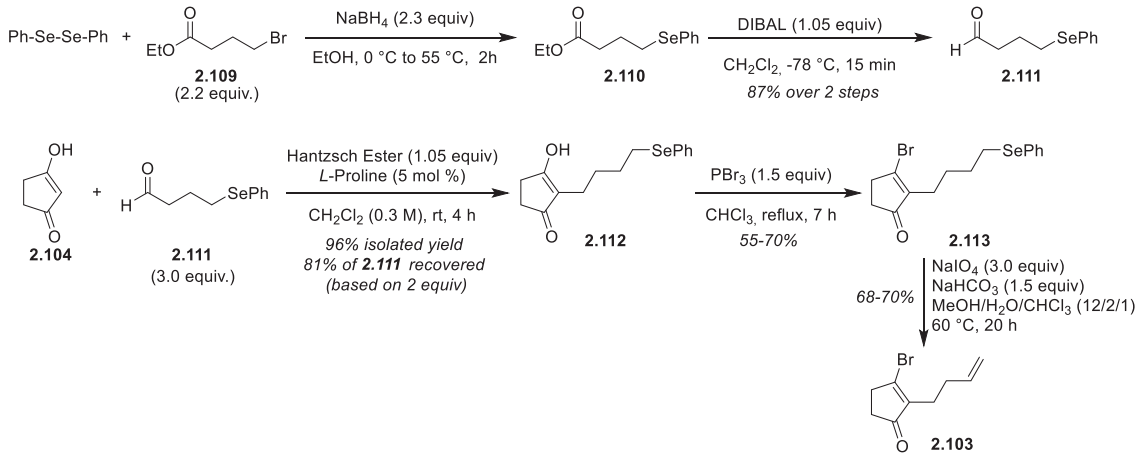


*Scheme 90 Selective C-alkylation failure of cyclopentandione (**2.104**)*

[105] Ramachary, D. B.; Kishor, M. *Org. Biomol. Chem.* **2008**, *6,* 4176−4187.

As the double bond appeared to be an issue, we believed we could introduce it later using the Grieco elimination procedure. Required aldehyde **2.111** was synthesized in 87% yield over 2 steps *via* substitution of the bromide of ethyl 4-bromobutanoate (**2.109**) with the *in-situ* formed sodium phenyl selenolate and subsequent mono-reduction of the ester group with DIBAL (Scheme 91).[106]

Reaction of diketone **2.104** with 3 equivalents of aldehyde **2.111**, in the presence of Hantzsch ester and a catalytic amount of proline, furnished in 96% yield desired C-alkylated product **2.112** and 81% of excess of **2.111** was recovered. Bromination of 1,3-diketone **2.113** with PBr_3 afforded the vinyl bromide **2.113** in a yield ranging from 55% to 70%. Subsequent selenide oxidation / elimination sequence gave desired **2.113** in a reproducible yield of 70%.[107]



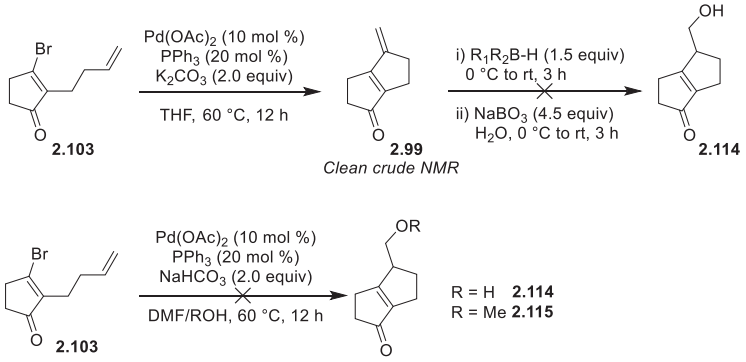
*Scheme 91 Synthesis of starting bromovinyl **2.103***

The intramolecular Heck coupling of **2.113** was then performed under the typical reaction conditions [$Pd(OAc)_2$, PPh_3, K_2CO_3] and gave a complete and clean conversion to desired cyclized product **2.99**.[108] The hydroboration / oxidation sequence of **2.99** was next explored with various borane sources, either in a one-pot manner or on the crude product. However, only complex mixtures were obtained (Scheme 92). We supposed that the tetrasubstituted double bond also reacted under these conditions, even with hindered borane such as 9-BBN, as no more UV active compound was observed on TLC after the hydroboration step.

The Heck coupling was also attempted in the presence of water or methanol in order to perform *in-situ* a 1,6-addition onto **2.99**. In these cases, with K_2CO_3 as base, replacement of the

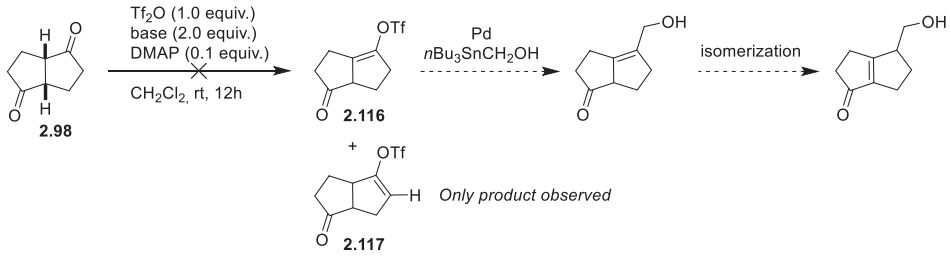
[106] SN2 with PhSeNa: Bhalla, A.; Sharma, S.; Bhasin, K. K.; Bari S. S. *Synthetic Communications* **2007**, *37*, 783−793. DIBAL reduction: Clive, d. L. J.; Bergstra, R. J. *J. Org. Chem.* **1990**, *55*, 1786−1792.
[107] Bromination: Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210−223. Grieco elimination: Kim, K. S.; Choi, S. O.; Park, J. M.; Lee, Y. J.; Kim, J. H. *Tetrahedron: Asymmetry* **2001**, *12*, 2649−2655.
[108] Heck, R. F. *Org. React.* **1982**, *27*, 345−390.

bromide with either water or methanol was observed as major product. By using the weaker base $NaHCO_3$, hydrolysis of the vinyl bromide was inhibited and, once again, a clean formation of Heck adduct **2.99** was observed. However, desired 1,6-products **2.114** or **2.115** were not detected. When longer reaction times and higher temperatures were attempted, both the isomerization of the exocyclic olefin and the decomposition of **2.99** were observed.



*Scheme 92 Cylization of **2.103** via intramolecular Heck coupling*

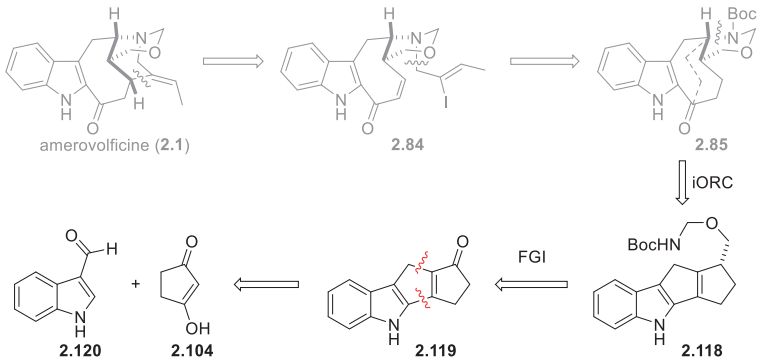
Mono-triflation of diketone **2.98**, to furnish corresponding vinyl triflate **2.116**, was also explored in order to perform a subsequent Pd-catalyzed homologation, as shown in Scheme 93. Unfortunately, only the formation of regioisomer **2.117** was observed based on crude ^1H NMR.



*Scheme 93 Mono-triflation of diketone **2.98***

2.1.4. Partial Modification of the Strategy

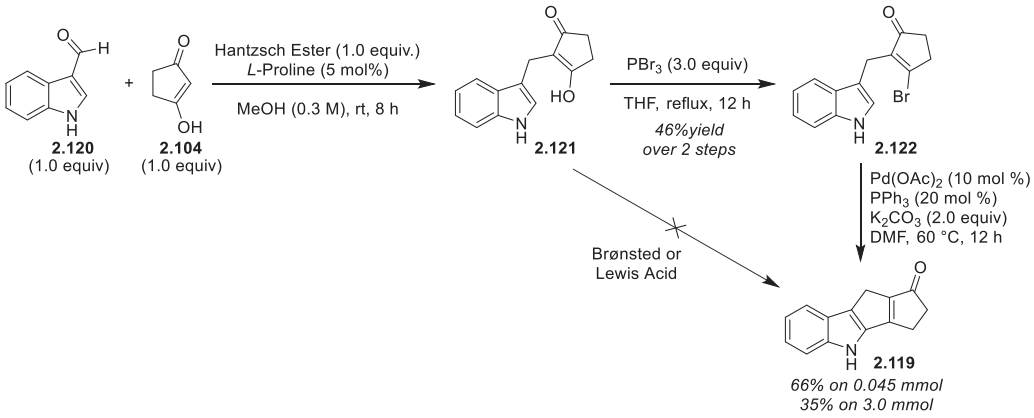
We decided to modify the early-stage of the synthesis and to incorporate the indole core in order to functionalize one of the carbonyl group of enedione **2.88**. We believed that, with indole **2.119**, we could have a better control of the selectivity compared to **2.88** during the Wittig and hydroboration steps (Scheme 94). The potential issue with this new route would be the chemoselectivity of the oxidative cleavage reaction between the tetrasubstituted olefin of the enone and the indole double bond on key intermediate **2.118**.



Scheme 94 Partial modification of the retrosynthesis

2.1.5. Towards the Modified Key Intermediate

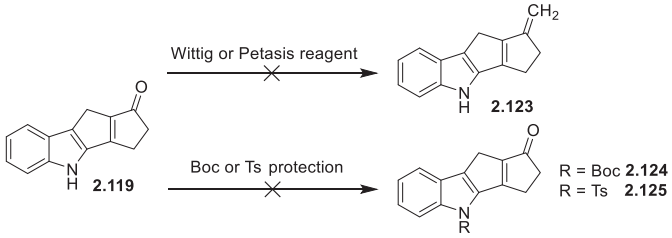
Following the condensation / 1,4-reduction sequence described previously, C-alkylation of 1,3-cyclopentandione (**2.104**) with indole-3-carboxaldehyde (**2.120**) afforded intermediate **2.121** cleanly. Subsequent bromination of the crude product gave vinyl bromide **2.122** in a reproducible 46% yield over 2 steps. Intramolecular Heck coupling afforded desired tetracyclic compound **2.119** in 66% yield on a small scale (Scheme 95). Unfortunately, a rather poor yield on a larger scale was obtained due to purification issues with the product. Intramolecular condensation of indole **2.121** onto the diketone moiety was also investigated to furnish directly compound **2.119**. However, mainly decomposition of the starting materials was observed upon treatment with a variety of Brønsted and Lewis acids.



*Scheme 95 Synthesis of enone **2.119***

Olefination of enone **2.119** to diene **2.123** was then attempted with the Wittig reagent but no reaction was surprisingly observed at rt, even with an excess of reactant. However, when the reaction was heated to 50 °C, the reaction turned to black and only decomposition was observed.

Reaction with the Petasis reagent was also tried but, once again, a complex mixture was obtained. Compound **2.119** appeared to be rather unstable as simple indole protection to **2.124** or **2.125**, with either Boc_2O or TsCl respectively, led also to a complex mixture (Scheme 96). It should be noted that intramolecular Heck coupling with the *N*-tosyl indole derivative of **2.119** failed to give the desired coupling adduct, and mainly decomposition was observed in this case. This instability could be explained by the presence of a cylopentadiene core on **2.119**. The deprotonation of the benzylic position, especially in the presence of both the indole and ketone groups, to form the corresponding aromatic cyclopentadienyl should be facile and therefore could lead to the formation of side products.



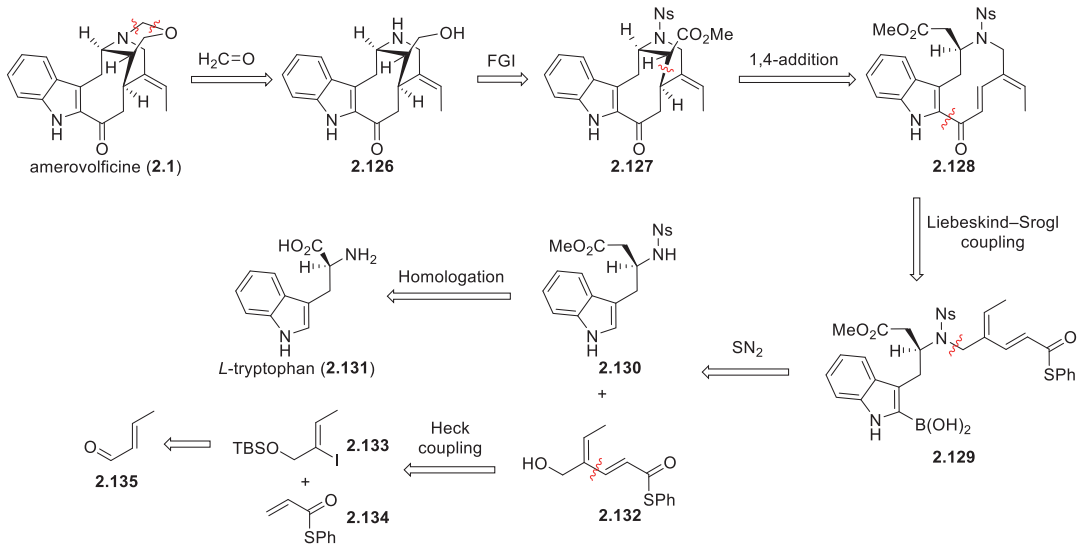
*Scheme 96 Functionalization attempts of tetracycle **2.119***

2.2. Second Strategy

2.2.1. Retrosynthesis

Due to the instability of **2.119** and the difficulties when attempting to functionalize both enones **2.88** and **2.119**, another strategy was designed.

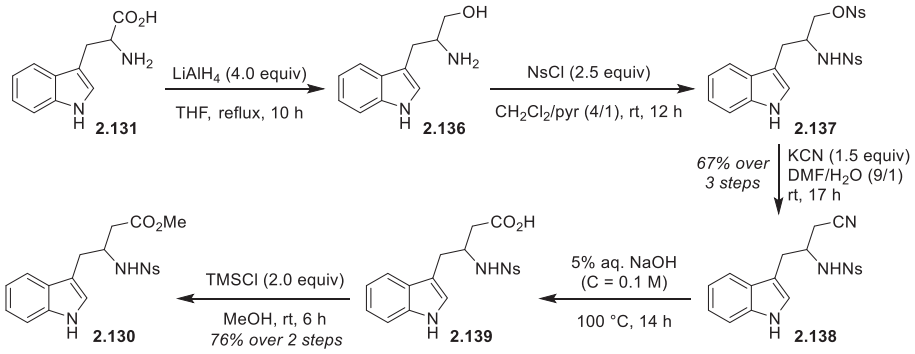
As described in Scheme 97, amerovolficine (**2.1**) could be synthesized by the late-stage formation of the 6-membered cyclic hemiaminal of aminoalcohol **2.126** with formaldehyde. The second 6-membered ring in **2.127** could be obtained *via* intramolecular Michael addition by deprotonation at the *alpha* position of ester **2.128**. The required 10-membered macrocycle should be formed by intramolecular Liebeskind-Srogl coupling between the thioester and the indole-2-boronic acid in **2.129**. Nucleophilic substitution of activated allylic alcohol **2.132** by homologated tryptophan **2.130** should give desired advanced intermediate **2.129**. Building blocks **2.130** and **2.132** should be synthesized from *L*-tryptophan (**2.131**) and (*E*)-but-2-enal (**2.135**), respectively. Compared to the previous strategy, this new approach had the advantages of being both convergent and enantioselective. The non-asymmetric version of the strategy, by starting from *DL*-tryptophan, was explored at first.



Scheme 97 Second retrosynthesis

2.2.2. Synthesis of the Indole Block

Homologation of *DL*-tryptophan (**2.131**) to give compound **2.130** was performed following literature procedures.[109] Reduction of aminoacid to aminoalcohol **2.136** by lithium aluminium hydride and subsequent protection of both the amine and alcohol with nosyl chloride furnished **2.137**. Nucleophilic substitution of the ONs group of crude **2.137** by potassium cyanide afforded compound **2.138** in 67% yield over 3 steps. Next, hydrolysis of the nitrile group was carried out in a refluxing aqueous solution of sodium hydroxide which gave, after esterification of the resulting acid **2.139**, adduct **2.130** in 76% over 2 steps (Scheme 98).[110] Careful optimization of the NaOH concentration was necessary in order to obtain good conversion without significant degradation. Also, the use of degassed water was required to avoid oxidation of the indole.

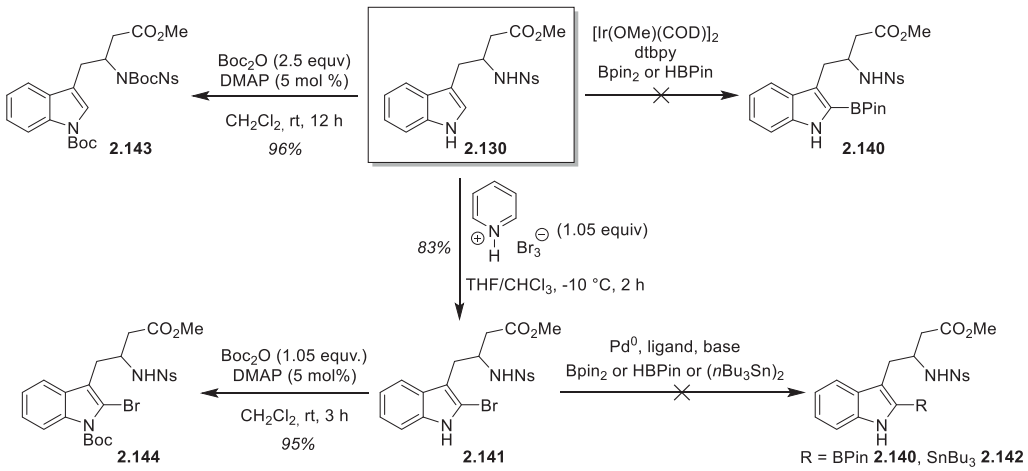


*Scheme 98 Synthesis of homolagated tryptophan **2.130***

[109] Li, X.-G.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2005,** *16,* 1709−1714.
[110] (a) Winkler, M.; Martínková, L.; Knall, A. C.; Krahulec, S.; Klempier, N. Tetrahedron **2005**, *61,* 4249−4260. (b) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48,* 2471−2475.

In the literature, a one-step borylation of the C-2 position of indole was reported with either $BPin_2$ or HBPin *via* a C-H activation using the iridium catalyst $[Ir(OMe)(COD)]_2$ and the ligand 4,4-di-*tert*-butyl bipyridine.[111] However, when homologated tryptophan **2.130** was submitted to these conditions, no reaction was observed. In order to test additional borylation conditions, using the palladium chemistry, the halogenation of **2.130** was then explored. The C-2 bromination of indole **2.130** with pyridinium tribromide at -10 °C afforded desired compound **2.141** in 83% yield (Scheme 99). When the more commonly used *N*-bromosuccinimide was employed, a dirtier reaction was obtained. Various conditions to convert **2.141** to desired borylated product **2.140** were screened, including the palladium sources, ligands, bases, boron sources, solvents and temperatures.[112] However, only traces of **2.140** were observed and unreacted starting materials together with debrominated product **2.130** were often isolated as the major products. A Pd-catalyzed stannylation reaction of **2.141** was also attempted, but it failed to give the desired product.

Next, we decided to protect the N-H of indole in order to stannylate the C-2 position with tributyltin chloride either *via* deprotonation in the case of **2.143** or *via* lithium / halogen exchange in the case of bromoindole **2.144**. Mono-protection of **2.130** with 1.05 equivalent of Boc_2O failed and a mixture of starting materials, monoprotected and bisprotected products were observed. When 2.5 equivalents of reagent were used, total conversion of **2.130** to bisprotected product **2.143** was obtained. In the case of **2.141**, reaction with 1.05 equivalent of Boc_2O gave exclusively monoprotected adduct **2.144** in 95% yield.



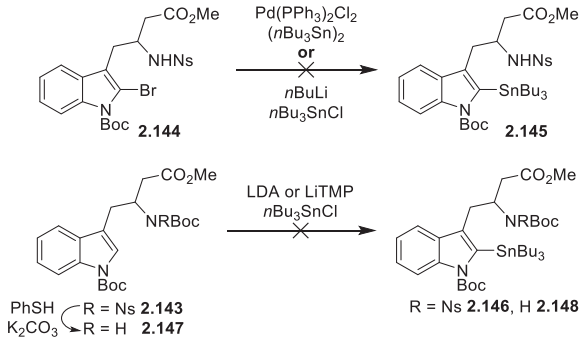
*Scheme 99 C-2 functionalization and protection of the indole **2.130***

[111] (a) Kolundzic, F.; Noshi, M. N.; Tjandra, M.; Movassaghi, M.; Miller, S. J. *J. Am. Chem. Soc*. **2011**, *133*, 9104−9111. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056−3058.

[112] (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510. (b) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271. (c) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164-168. (d) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc*. **2002**, *124*, 8001−8006.

Lithium / halogen exchange of **2.144** with *n*-BuLi gave a complex mixture in the presence or absence of tributyltin chloride, even at very low temperature (from -100 °C to -78 °C).[113] Stannylation using the palladium chemistry was also attempted on substrate **2.144** but the reaction failed to give desired product **2.145** once again (Scheme 100).[114]

Deprotonation in C-2 position of indole **2.143** at -78 °C with either LDA or TMPLi followed by addition of tributyltin chloride resulted in no reaction at low temperature.[115] When the reaction mixture was warmed, up to 0 °C, decomposition of the starting materials was observed. Similar results were obtained with substrate **2.147**, synthesized quantitatively from **2.143** by removal of the nosyl group with thiophenol, under the same reaction conditions. In all these cases, we supposed that competitive *alpha* stannylation of ester could be occuring,[116] therefore complicating the outcome of this reaction.

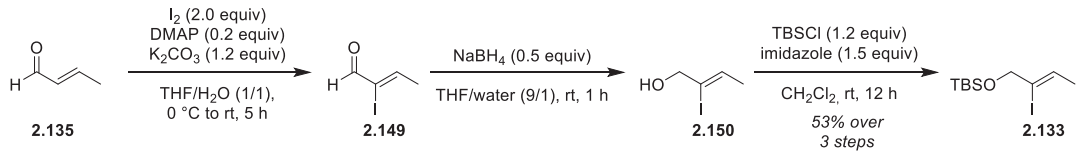


Scheme 100 Additional attempts for the C-2 functionalization of indole

2.2.3. Synthesis of the Diene Block

While we explored the synthesis of the indole block, synthetic studies towards the diene were also carried out. Synthesis of the first Heck partner **2.133** was accomplished in 3 steps, as shown in Scheme 101, by following a literature procedure.[117] Iodination of (*E*)-but-2-enal (**2.135**) with molecular iodine in the presence of potassium carbonate and DMAP afforded vinyl iodide **2.149**. Subsequent reduction of the aldehyde with sodium borohydride and protection of the resulting alcohol with TBSCl gave desired product **2.133** in 53% yield over 3 steps.

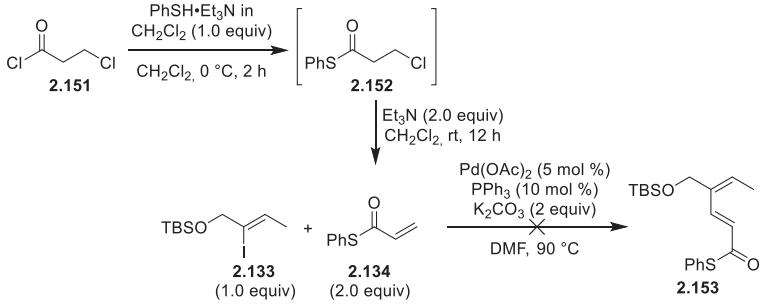
[113] Beaulieu, P. L.; Gillard, J.; Bykowski, D.; Brochu, C.; Dansereau, N.; Duceppe, J.-S.; Hache, B.; Jakalian, A.; Lagace, L.; LaPlante, S.; McKercher, G.; Moreau, E.; Perreault, S.; Stammers, T.; Thauvette, L.; Warrington, J.; Kukolj, G. *Bioorg. & Med. Chem. Let*., **2006**, *16*, 4987–4993.
[114] Rhoennstad, P.; Kallin, E.; Apelqvist, T.; Wennerstaal, M.; Cheng, A. *Patent WO 2009127686 A1,* 2009-10-22.
[115] Qi, X.; Bao, H.; Tambar, U. K *J. Am. Chem. Soc.*, **2011**, *133*, 10050–10053.
[116] Zapata, A.; Acuñia A., C. *Synthetic Communications* **1984**, *14,* 27–32.
[117] Yin, W.; Kabir, M. S.; Wang, Z.; Rallapalli, S. K.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2010,** *75*, 3339–3349.



*Scheme 101 Synthesis of Heck partner **2.133***

The second Heck partner **2.134** was prepared freshly by reacting 3-chloropropanoyl chloride (**2.151**) with a premixed mixture of thiophenol and triethylamine to afford intermediate **2.152**. Addition of 2 equivalents of triethylamine to the above mixture afforded cleanly, after acidic work-up, *S*-phenyl thioacrylate (**2.134**) (Scheme 102).

Unfortunately, Heck coupling between **2.133** and **2.134** only led to decomposition of both substrates. The generation *in-situ* of **2.134** from thioester **2.152** was also attempted but this reaction gave a similar complex mixture. These observations could be explained by both the known insertion of the palladium into the carbon − sulfur bond and the facile polymerization of **2.134**, particularly at such high temperature, therefore leading to the formation of various side products.

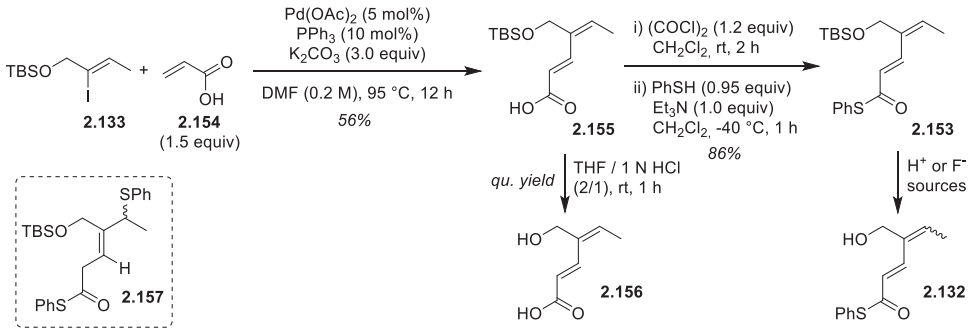


*Scheme 102 Heck coupling trial between **2.133** and S-phenyl thioacrylate (**2.134**)*

However, the Heck reaction between vinyl iodide **2.151** and acrylic acid (**2.154**) gave desired coupling product **2.155** in 56% yield (Scheme 103).[118] The conversion of the acid to corresponding thioester **2.153** was revealed to be more challenging than expected. Indeed, if a slight excess of thiophenol was used, isomerization of the double bond was observed certainly *via* reversible 1,6-addition as adduct **2.157** was observed by crude ^{1}H NMR. Consequently, a substoichiometric amount of thiophenol (0.95 equivalent) was employed at low temperature (-40 °C) and desired product **2.153** was obtained in 86% yield. In spite of the clean TBS-deprotection of **2.153** to give alcohol **2.132** with various proton or fluoride sources, in most cases isomerization of the double

[118] Kitajima, M.; Murakami, Y.; Takahashi, N.; Wu, Y.; Kogure, N.; Zhang, R.-P.; Takayama, H. *Org. Lett.* **2014**, *16*, 5000−5003.

bond was once again observed. When HF.pyridine was used, limited isomerization was noted but this reaction was not reproducible. It should be noted that the TBS-deprotection of acid derivative **2.155** with dilute HCl afforded **2.156** without noticeable isomerization.

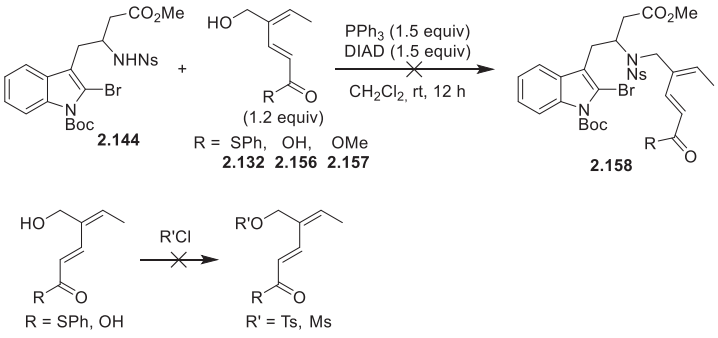


*Scheme 103 Synthesis of Heck adduct **2.155** and further functionalizations*

2.2.4. Attempts of Coupling both Building Blocks

The coupling of the homologated tryptophan with the diene building block was also examined. The Mitsunobu reaction between sulfonamide **2.144** and alcohol **2.132** led only to decomposition of the diene and the indole block was completely recovered (Scheme 104). Similar results were observed when either acid **2.156** or methyl ester derivative **2.157**, synthesized quantitatively from **2.156** with trimethylsilyldiazomethane, was used as partner.

The conversion of alcohols **2.132** and **2.156** into the corresponding mesylate or tosylate derivatives gave in all cases a complex mixture.



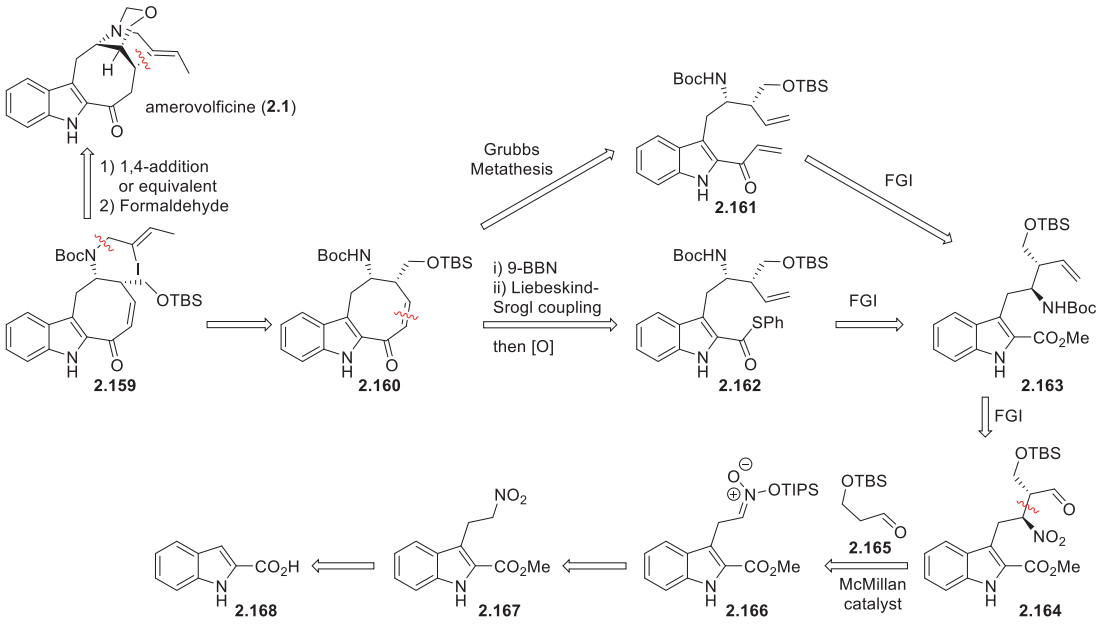
Scheme 104 Coupling attempts of both building blocks

2.3. Third Strategy

2.3.1. Retrosynthesis

Due to the difficulties encountered when attempting to insert a boron or a tin functionality in C-2 position of the indole block and the instability of the diene, therefore giving issues for the coupling of the two blocks; a third strategy was designed as shown in Scheme 105.

Amerovolficine (**2.1**) should be obtained from **2.159** *via* a similar 1,4-addition of vinyl iodide envisaged in the first approach, followed by the hemiaminal formation with formaldehyde. 8-membered ring **2.160** could be synthesized either from **2.161** by intramolecular Grubbs metathesis or from **2.162** by intramolecular Liebeskind-Srogl coupling[119] followed by oxidation of the ketone to enone. Both intermediates should be obtained by functional group interconversion of the common intermediate **2.163**. The latter could be synthesized from silyl nitronate **2.166** and aldehyde **2.165** using an enantioselective aldehyde *alpha*-nitroalkylation reaction developed by MacMillan *via* oxidative organocatalysis. The required silyl nitronate should be easily accessible from indole-2-carboxylic acid (**2.168**). As with the second stategy, the non-asymmetric version was first explored.

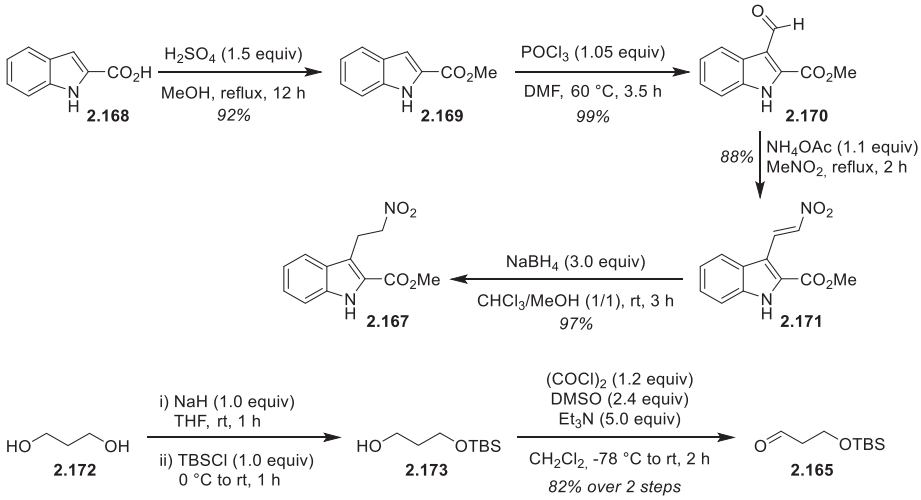


Scheme 105 Third retrosynthesis

[119] Tsuna, K.; Noguchi, N.; Nakada, M. *Tetrahedron Lett.* **2011**, *52*, 7202–7205.

2.3.2. Towards the Synthesis of the 8-Membered Ring

The synthesis of the two starting materials required for the aldehyde *alpha*-nitroalkylation step is described in Scheme 106. First, esterification of indole-2-carboxylic acid (**2.168**) followed by Vilsmeier-Haack formylation at the C-3 position[120] gave dicarbonyl intermediate **2.170**. Nitromethane condensation onto the aldehyde group[121] and subsequent 1,4-reduction of the resulting nitrovinyl moiety with sodium borohydride[122] afforded desired nitroalkane **2.167** in 78% yield from **2.168**. Next, aldehyde **2.165** was synthesized in 82% yield from propane-1,3-diol (**2.172**) by sequential mono TBS-protection of the diol[123] and Swern oxidation.



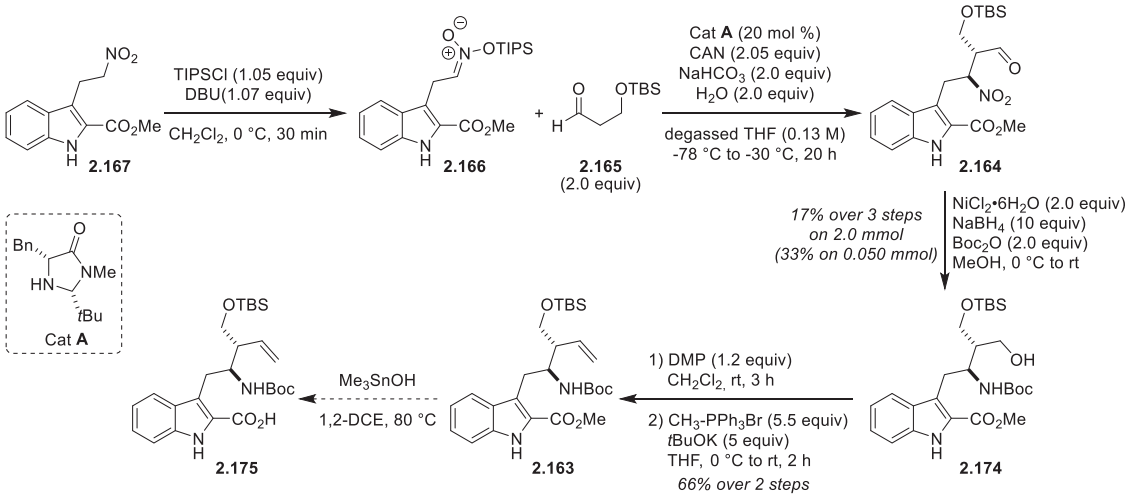
Scheme 106 Starting materials synthesis

Due to the instability of the silyl nitronate function, compound **2.166** was prepared freshly from nitro **2.167** using a slight excess of TIPSCl and DBU.[124] After a quick aqueous work-up, the crude product with 95% purity based on ^{1}H NMR (5% of starting **2.167**) was used directly in the following step with aldehyde **2.165**. Under the optimized conditions developed by the MacMillan group,[125] desired nitroaldehyde **2.164** was observed by crude NMR but was not isolated due to its poor stability on silica gel or alumina. Indeed, elimination of the nitro group to form the corresponding enal was obtained. Consequently, crude **2.164** was reduced directly and *in-situ* protected to *N*-Boc aminoalcohol **2.174** in a moderate yield of 31% (from **2.167**) on a 0.15 mmol

[120] Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem.* **2005**, *70*, 9077−9080.
[121] Sofiyev, V.; Lumb, J.-P.; Volgraf, M.; Trauner, D. *Chem. Eur. J.* **2012**, *18*, 4999−5005.
[122] Di Giacomo, B.; Bedini, A.; Spadoni, G.; Tarzia, G.; Fraschini, F.; Pannacci, M.; Lucini, V. *Bioorg. & Med. Chem.*, **2007**, *15*, 4643−4650.
[123] McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388−3390.
[124] (a) Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697–710. (b) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrehedron Lett.* **1987**, *28*, 5361–5364.
[125] Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332–11334.

scale (Scheme 107).[126] Unfortunately, when the reaction was scaled-up to 2.0 mmol, only 17% of **2.174** was isolated. Despite the poor yield, this reaction was reproducible on the same scale.

It should be noted that the major part of the mass balance was lost during the aldehyde *alpha*-nitroalkylation step. A significant amount of dimerization of **2.167** and deprotection of the silyl nitronate moiety to nitro **2.167** were observed. Potentially, oxidation of the indole moiety with CAN could be an explanation for the formation of the additional side products. Increasing the amount of catalyst and/or aldehyde **2.165** led to even dirtier mixtures. When the reaction was performed in a more diluted system, the generation of the dimer was indeed retarded but a lack of reactivity was also observed, leading to the formation of deprotected nitronate **2.167** as the major product. The Boc and tosyl indole derivatives of **2.166** were also examined but the desired product was not isolated in these cases.



Scheme 107 Aldehyde alpha-nitroalkylation step and further functionalizations

With small amounts of material in hand, the following steps were explored. Oxidation of alcohol **2.174** to aldehyde with freshly prepared DMP,[127] followed by Wittig olefination, afforded advanced intermediate **2.163** in 66% yield over 2 steps. The hydrolysis of the ester to corresponding acid **2.175** was revealed to be more challenging than expected. Indeed, poor conversion was observed using 10 equivalents of potassium hydroxide at rt. If more equivalents and/or higher temperatures were employed, the reaction produced complex mixtures. Worse results were obtained if sodium hydroxide was used. The mild hydrolysis of methyl ester with trimethyltin hydroxide was also investigated.[128] A cleaner reaction was observed but the conversion was still low in spite of the use of a large excess of reagents.

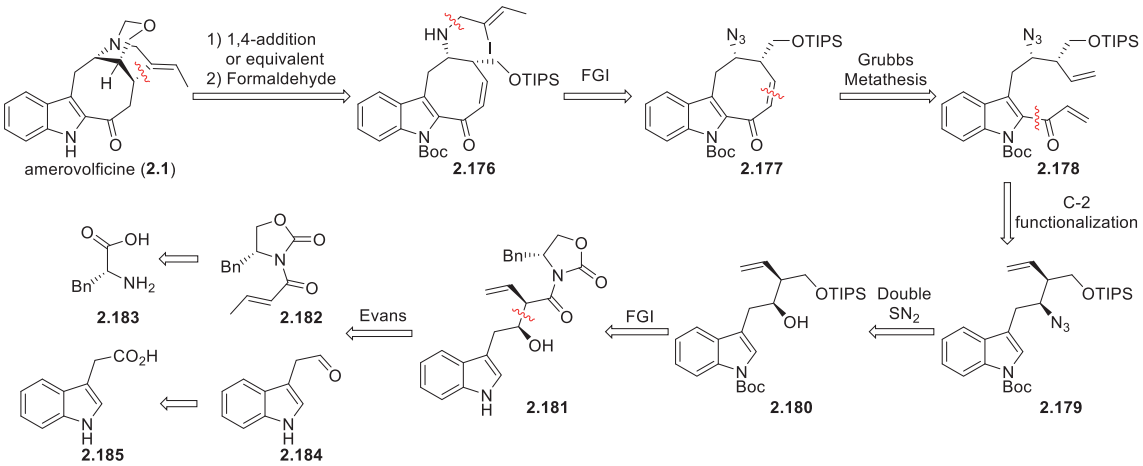
[126] Nonn, M.; Kiss, L.; Sillanpää, R.; Fülop, F. *Tetrehedron* **2012**, *68*, 9942–9948.
[127] (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
[128] Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Hyup Lee, S.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378–1382.

2.4. Fourth Strategy

2.4.1. Retrosynthesis

The poor yield obtained for the aldehyde *alpha*-nitroalkylation step and the issues encountered when scaling-up this transformation resulted in difficulties in cumulating material for the rest of the synthesis and forced us to halt this approach. Consequently, a fourth strategy was elaborated. As described in Scheme 108, the later steps of the envisaged synthesis are basically the same as in the third strategy. The main difference resides in the synthesis of the starting materials.

Thus, amerovolficine (**2.1**) should be obtained from key compound **2.176** *via* intramolecular 1,4-addition, or equivalent transformations, of vinyl iodide onto enone followed by hemiaminal formation. The 8-membered ring **2.177** could be synthesized from **2.178** by Grubbs metathesis and this required diene could be obtained by C-2 functionalization of Boc-Indole **2.179** with a suitable electrophile. The latter could be synthesized from **2.180** by functional group interchanges including a double S_N2 displacement of the secondary alcohol in order to obtain retention of configuration for the corresponding azide. The incorporation of the two chiral centers was planned *via* diastereoselective aldol reaction of imide **2.182**, containing the Evans auxiliary, with aldehyde **2.184**. The syntheses of both compounds are literature known and start with aminoacid phenylalanine (**2.183**) and commercially available indole-3-acetic acid (**2.185**), respectively. Unlike the second and third strategies, the enantioselective version of this fourth approach was explored directly.



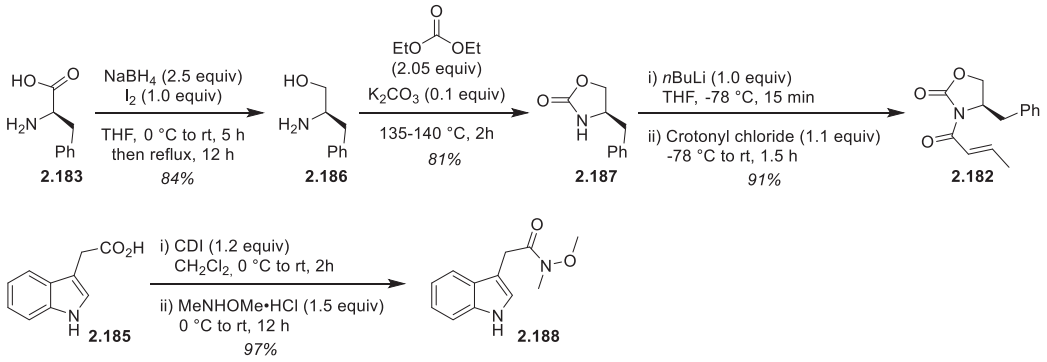
Scheme 108 : Fourth retrosynthesis

2.4.2. Towards the Synthesis of the 8-Membered Ring

As reported in the literature and depicted in Scheme 109, reduction of *D*-phenylalanine (**2.183**) with sodium borohydride in the presence of iodine afforded desired aminoalcohol **2.186** without any racemization.[129] Refluxing the latter in diethylcarbonate furnished corresponding oxazolidinone **2.187** in high yield.[130] The deprotonation of cyclic carbamate **2.187** with *n*-BuLi, followed by trapping with crotonyl chloride,[131] afforded desired imide **2.182** in 62% overall yield on a 0.2 mol scale.

The cleanest way to generate unstable aldehyde **2.184** was by mono-reduction of corresponding Weinreb amide **2.188** with DIBAL at -78 °C, followed by acidic work-up. Lithium aluminium hydride showed promising results, but more of over-reduction to the alcohol was observed by crude NMR and the work-up was more tedious. Aldehyde **2.184** could be obtained also by oxidation of tryptophol. The mild Swern conditions gave a complex mixture, whereas IBX showed a rather clean conversion. However, column chromatography was still necessary in this case to remove all side products and, due to partial decomposition of **2.184** on silica gel, a poor mass balance was obtained.

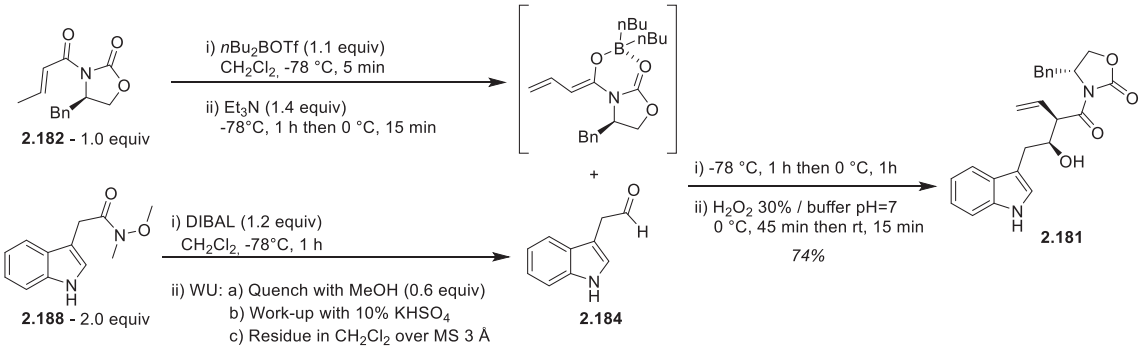
The required Weinreb amide **2.188** can be synthesized on a 0.3 mol scale from indole-3-acetic acid (**2.185**) by amide coupling with N,O-dimethylhydroxylamine.[132] In order to avoid large scale column chromatography and the use of a large amount of solvent, it was found that **2.188** can be purified easily by recrystallization in ethyl acetate in 97% yield.



Scheme 109 : Starting materials synthesis

[129] (a) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964–5965. (b) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *8*, 3568–3571.
[130] Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.
[131] Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
[132] Lacrampe, J. F. A.; Meyer, C.; Schoentjes, B.; Poncelet, A. P.; Wermuth, C. G.; Giethlen, B.; Contreras, J.-M.; Joubert, M.; Van Hijfte, L. *Patent WO 2007107545 A1* – 2007-09-27 – page 33.

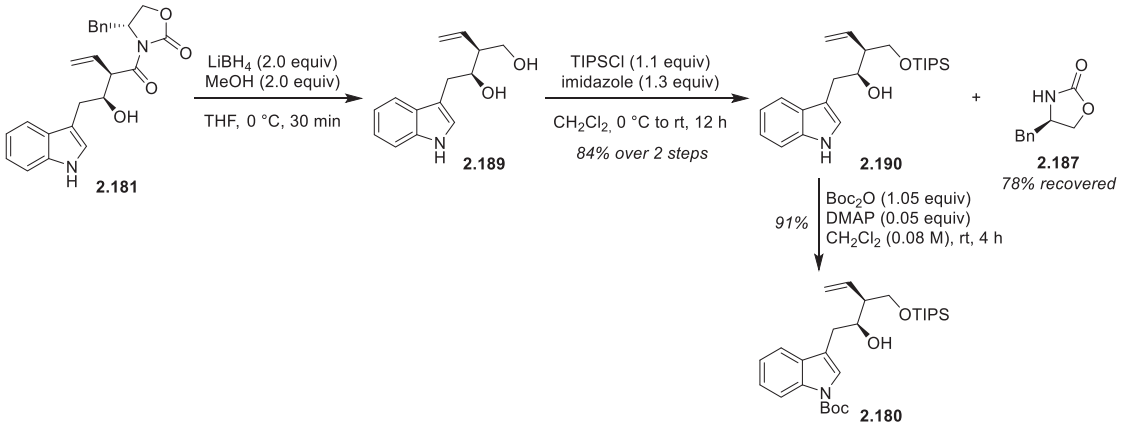
Due to the instability of aldehyde **2.184**, it was always prepared freshly and then submitted directly to the Evans aldolisation reaction. It was found that higher yields of the aldol adduct **2.181** can be obtained if crude **2.184**, in a CH_2Cl_2 solution, was stirred over molecular sieves prior to use. We supposed that residual water from the work-up partially quenched the boron enolate of imide **2.182** during the reaction. Finally, using the standard conditions developed by Evans,[133] combined with the little tricks described above, a reproducible yield of 74% of the aldol adduct **2.181** was obtained on a 20.0 mmol scale (Scheme 110). The oxidative work-up was also an important step in order to decomplex all boron species attached to the final product. It should be noted that the presence of a pH buffer was necessary to avoid the unwanted retro aldol reaction during the work-up.



Scheme 110 : Evans aldolisation reaction

As shown in Scheme 111, the Evans auxiliary was next removed by reduction of imide **2.187** to corresponding diol **2.189** and oxazolidinone **2.187** with lithium borohydride in the presence of methanol.[134] The work-up procedure was important to obtain good mass balance of the desired diol. Indeed, if acidic conditions were used, almost half of the product was lost in the aqueous phase, certainly due to strong complexation of the diol with boron. It was necessary to use an aqueous solution of 10% NaOH to break up these complexes and extract all of product **2.189**. Next, the crude material was submitted directly to the following step which was the mono-protection of the primary alcohol with TIPSCl. Desired product **2.190** was obtained in 84% yield over 2 steps and 78% of Evans auxiliary **2.187** was recovered. The indole was then protected selectively with Boc_2O in the presence of a catalytic amount of DMAP to afford **2.180** in 91% yield.

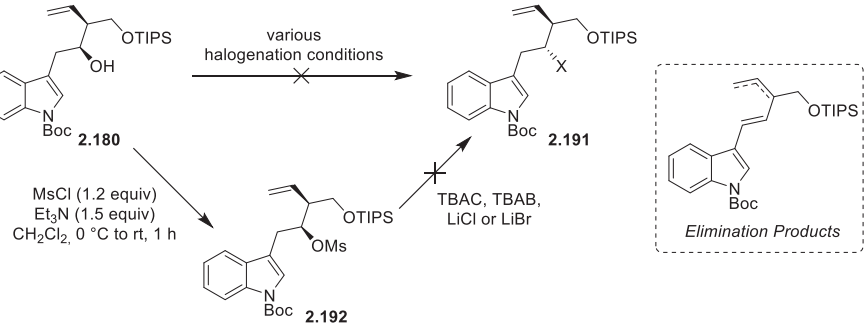
[133] Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957–4960.
[134] Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000–4005.



*Scheme 111 : Functionalization of Evans adduct **2.181***

Compound **2.180** was then submitted to several conditions in order to perform the desired double S_N2 of the secondary alcohol. The first substitution was planned *via* halogenation and the second by displacement of the resulting halide with an azide source. Unfortunately, the first S_N2 reaction was problematic. Indeed, depending of the reaction conditions, either decomposition (PBr_3/DIPEA, $POCl_3$/pyridine or PCl_3/pyridine system) or a mixture of elimination products (Appel conditions CX_4/PPh_3 or X_2/PPh_3/imidazole system) was observed (Scheme 112).[135] When NH-indole **2.190** was exposed to these conditions, only its decomposition occured.

A two-step sequence for the first S_N2 reaction was also explored. Mesylation of the secondary alcohol **2.180** at rt gave desired product **2.192** cleanly. The latter was then submitted to various conditions to substitute the mesylate with a halide. Unfortunately, a mixture of elimination products was mainly obtained using TBAC, TBAB, LiCl or LiBr.[136]



*Scheme 112 : S_N2 attempts of alcohol **2.180***

[135] (a) Appel, R. *Angew. Chem. Int. Ed.* **1975**, 14, 801–811. (b) Garegg, P. J. *Pure Appl. Chem.* **1984**, *56*, 845–858. (c) Garegg, P. J.; Regberg, T.; Stawinski, J.; Strömberg, R. *J. Chem. Soc. Perkin Trans. II* **1987**, *11*, 271–274. (d) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *J. Org. Chem.* **2011**, *76*, 6749–6767.

[136] (a) Cahiez, G.; Gager, O.; Moyeux, A.; Delacroix, T. *Adv. Synth. Catal.* **2012**, *354*, 1519–1528. (b) Cahiez, G.; Lefèvre, N.; Poizat, M.; Moyeux, A. *Synthesis* **2013**, *45*, 231–236.

Finally, halogenation of **2.180** was accomplished using 5.0 equivalents of $SOCl_2$ in the presence of pyridine. The order of addition of the reagents proved crucial. When thionyl chloride was added to a mixture of **2.180** and pyridine, dimerization was observed by crude NMR and MS analyses. This can be rationalized by the reaction of two equivalents of alcohol **2.180** with one $SOCl_2$ to give the corresponding sulfite. Chlorination occurred when substrate **2.180** was added to an excess of $SOCl_2$ and pyridine. The amount of pyridine was revealed to be an important factor in order to deliver clean conversion. When pyridine was used as cosolvent with CH_2Cl_2, as often reported, a dirty reaction was obtained. However, when the amount of pyridine was reduced to 11 equivalents, an 81% yield of chlorinated product **2.193** was obtained. An even higher and more reproducible yield, up to 89% on a large scale, was obtained by replacing the pyridine and CH_2Cl_2 by 2,6-lutidine and 1,2-DCE, respectively.

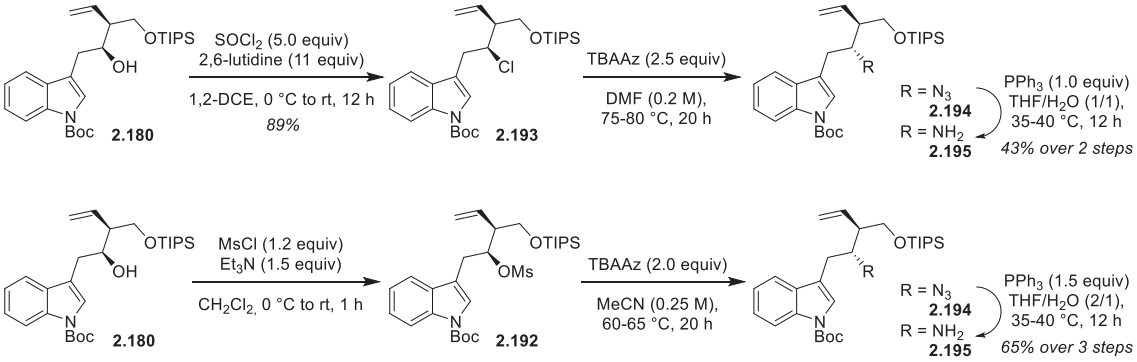
The second substitution with azide to displace the chloride was then examined. Once again, the main issue encountered was the competition with the elimination of the leaving group. In order to limit this side reaction, several azide sources was tested including NaN_3, LiN_3, $TMSN_3$ and TBAAz. The latter showed the best results with the generation of less, but still in a significant amount, of elimination products. After further optimization of the solvent, concentration and temperature parameters, desired azide **2.179** was obtained in 48% yield by using 2.5 equivalents of TBAAz and after 20 h at 80 °C in DMF. The purification of the azide adduct proved difficult due to a very similar polarity with respect to the unwanted elimination products. However, when the crude azide was reduced under the Staudinger conditions, prior to the purification step, the corresponding amine could be easily isolated in 43% yield from chloride **2.193**.

Unfortunately, we discovered later on, after obtaining an incomplete X-ray structure, that the relative stereochemistry was not that required. In consequence, azide **2.194** was obtained and not **2.179** as expected. As a control experiment, mesylate **2.192** was resynthesized and the crude was submitted directly in the previously optimized conditions of azidation. In this case, the same azide adduct **2.194** was obtained which confirmed that chlorination with $SOCl_2$ occurred with retention of configuration, as depicted in Scheme 113. The observed retention can be explained by a competitive S_Ni mechanism instead of the required S_N2 which had already been reported in the literature with thionyl chloride.[137] Another explanation would be first intramolecular attack of indole to displace the alkyl chlorosulfite intermediate followed by attack of chloride to rearomatize the indole, therefore giving a double S_N2.

However, the azidation from the mesylate intermediate was by far cleaner, compared to chloride **2.193**, with only small amounts of elimination products being observed by crude NMR. After reoptimization, the best conditions for the azidation were obtained by using 2.0 equivalents

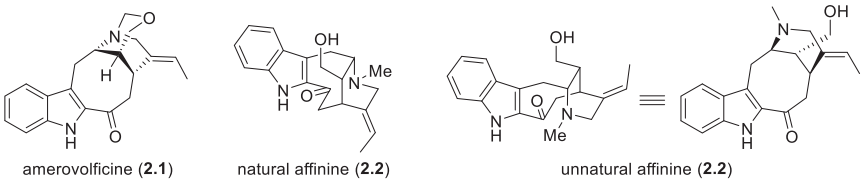
[137] (a) Lewis, E. S.; Boozer, C. E. *J. Am. Chem. Soc.* **1952**, *74*, 308-311. (b) Cram, D. J. *J. Am. Chem. Soc.* **1953**, *75*, 332–338.

of TBAAz in acetonitrile after 20 h at 60-65 °C. Corresponding amine **2.195**, resulting from the Staudinger reduction of **2.194**, was obtained in 65% yield from alcohol **2.180**.



*Scheme 113 : Azidation sequences from **2.180***

With wrong diastereoisomer **1.194**, the targeted amerovolficine (**2.1**) could not be synthesized but the natural product affinine (**2.2**) could be obtained (Scheme 114). We decided to move on to this target in order to test the strategy further. It should be noted that the enantiomer of Evans auxiliary **1.182**, used for the approach towards amerovolficine (**2.1**), would give the antipode of the natural affinine (**2.2**). In addition, due to the relative configuration of the amine and the alcohol chain, the formation of the 1,3-oxazine ring observed in **2.1** would not be possible in the case of **2.2**.

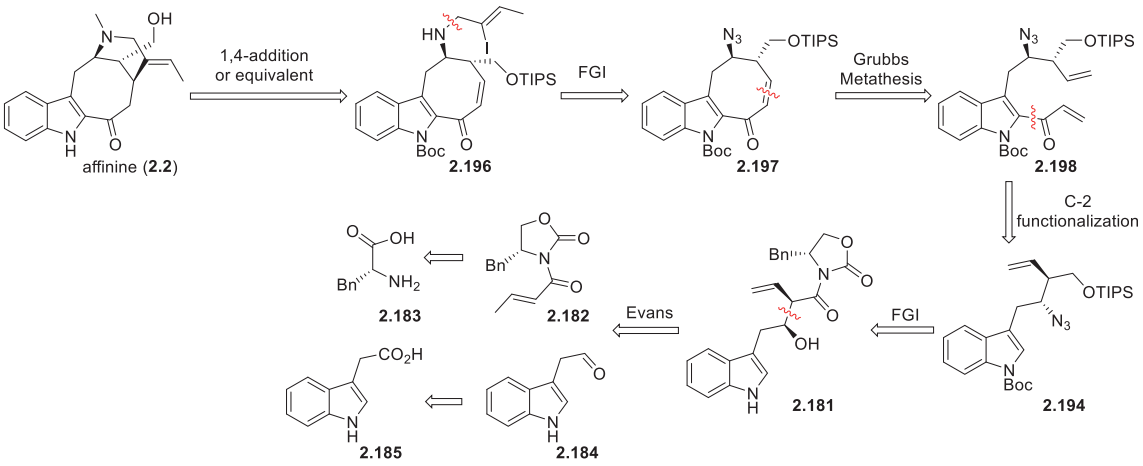


Scheme 114 : Change of the target

Chapter 3. Synthetic Studies Towards Affinine

3.1. Retrosynthesis

The retrosynthetic analysis towards the unnatural affinine (**2.2**) was based on the fourth strategy for the synthesis of amerovolficine (**2.1**) which was discussed in the previous chapter (cf. 2.4.1.) (Scheme 115).

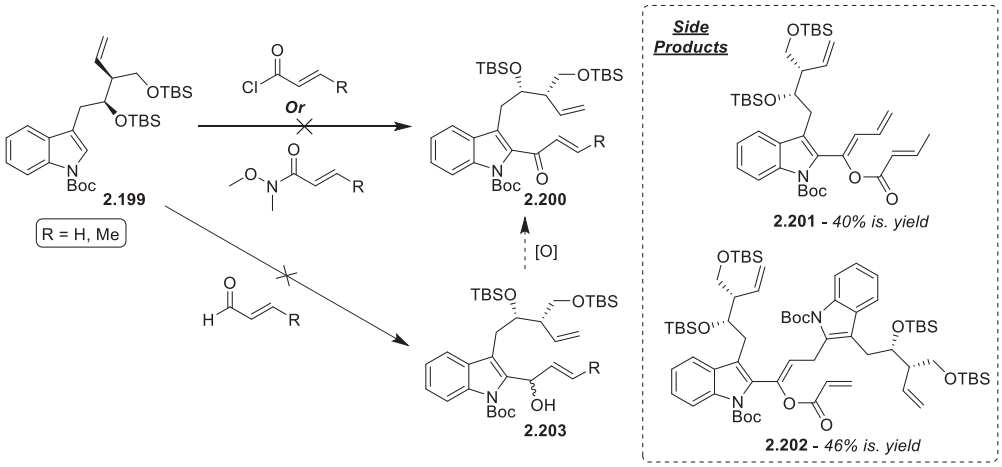


Scheme 115 Retrosynthetic analysis towards unnatural affinine

3.2. Synthesis of the Key 8-Membered Ring and Vinyl Iodide Intermediates

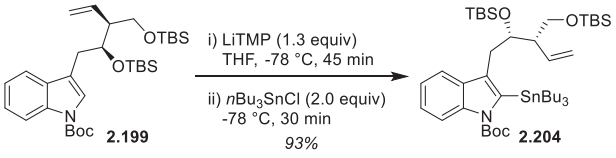
During the optimization of the azidation step, which was described previously (cf. 2.4.2.), the C-2 functionalization of Boc-indole using model substrate **2.199** was investigated in order to incorporate the vinyl ketone moiety required for the metathesis step. Various strong bases were first explored to perform the desired deprotonation of the C-2 position of the indole moiety at -78 °C. LiHMDS was not sufficiently basic to abstract the proton and when *n*-BuLi was used, partial deprotection of the Boc-indole was observed, certainly due to competitive nucleophilic addition of the organolithium. LDA and LiTMP proved to be the best bases and trapping of the lithium

intermediate with several electrophiles was next attempted to obtain diene **2.200**. As described in Scheme 116, reaction of **2.199** with acryloyl chloride or crotonyl chloride at -78 °C gave, after warming up to 0 °C, side products **2.201** and **2.202**, respectively. When their corresponding Weinreb amide was used, no reaction was noted. Reactions with aldehydes, such as acrolein and crotonaldehyde, were then attempted to afford allylic alcohol **2.203** but a complex mixture and no reaction were observed, respectively. Finally, incorporation of a formyl group in the C-2 position of indole was explored with ethyl formate and DMF as electrophiles but, once again, a complex mixture was observed in the first case and no reaction in the second.



*Scheme 116 : Attempts for direct C-2 functionalization of **2.199***

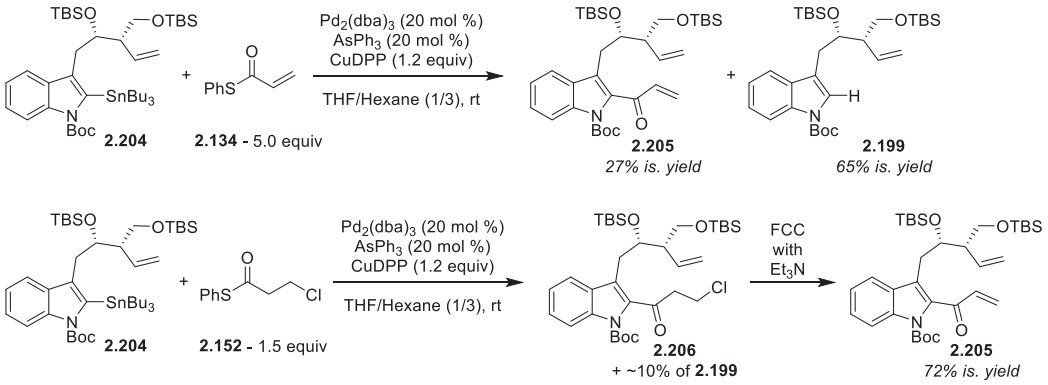
Inspired by another total synthesis completed at the same time in our group, we attempted a two-step procedure *via* a Liebeskind-Srogl coupling.[138] The synthesis of required tin partner **2.204** was accomplished by C-2 deprotonation of Boc-indole **2.199** with LiTMP followed by anion trapping with *n*-Bu_3SnCl (Scheme 117). Stannylated product **2.204** was very sensitive to acid and thus, the purification on silica gel required a minimum of 3% of triethylamine in the solvent system to avoid any protodestannylation.



*Scheme 117 : Synthesis of tin partner **2.204***

[138] Piemontesi, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2016**, *138*, 11148–11151.

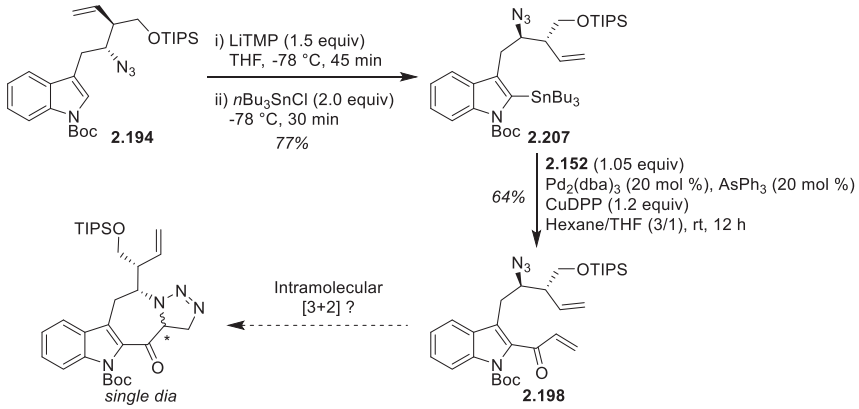
With **2.204** in hand, the Liebeskind-Srogl coupling was first investigated with the thioester **2.134** under the optimized conditions [Pd_2dba_3, $AsPh_3$, CuDPP, hexane/THF: 3/1][138,139] and desired diene **2.205** was obtained in 27% yield together with 65% of the destannylated product **2.199**. Reproducibility problems were encountered due to the instability of thioester **2.134** which polymerizes easily. As a consequence, precursor **2.152** of thioester **2.134**, synthesized in 85% yield from thiophenol and 3-chloropropanoyl chloride, was submitted to the Liebeskind-Srogl conditions with tin partner **2.204**. Clean conversion to coupling adduct **2.206** was obtained with only 10% of destannylated product **2.199** based on crude ^{1}H NMR. As depicted in Scheme 118, when crude **2.206** was purified on silica gel in the presence of triethylamine, complete elimination of the chloride occurred to directly afford desired diene **2.205** in 72% yield.



*Scheme 118 : Synthesis of diene **2.205***

As shown in Scheme 119, the same sequence was next applied to azide substrate **2.194**. Stannylation of **2.194** was performed with a good yield of 77% and the resulting tin partner **2.207** was then submitted to the Liebeskind-Srogl conditions to furnish, after purification, desired coupling adduct **2.198** in 64% yield. However, during the period of time required for NMR characterization, compound **2.198** converted to another major product which unfortunately decomposed on silica gel. We suspected that an intramolecular [3+2] cycloaddition occurred between the azide and the vinyl ketone, as the signals corresponding to the vinylic protons disappeared in the ^{1}H NMR spectrum.

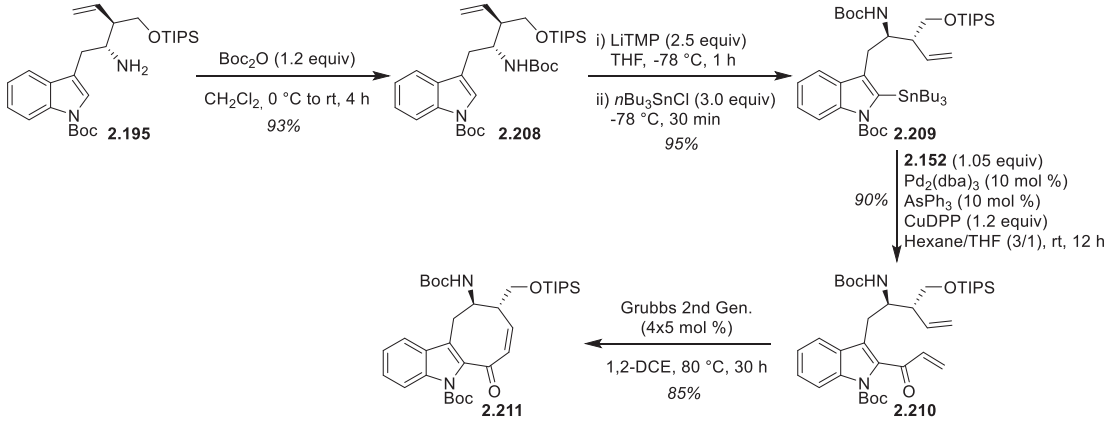
[139] (a) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033–3035. (b) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375–4378. (c) Li, H.; He, A.; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682–3685.



*Scheme 119 : Attempts to synthesize diene **2.198***

To avoid this problem, we decided to use Boc-protected amine **2.208** which was synthesized from amine **2.195** in 93% yield. Stannylation of substrate **2.195** gave required tin partner **2.209** in 95% yield and the latter was submitted directly to the Liebeskind-Srogl coupling with thioester **2.152** to afford stable diene **2.210** in 90% yield on a multigram scale (Scheme 120). It should be noted that the same route was attempted with the tosyl-protected amine instead of Boc **2.208**. Under the Liebeskind-Srogl conditions, the desired coupling adduct was formed but during the elimination step of the chloride on silica gel, complete dimerization occurred. Indeed, 1,4-addition of one sulfonamide onto a second vinyl ketone was observed.

Diene **2.210** was then submitted to several ring-closing metathesis (RCM) conditions.[140] After careful optimization, the best results were obtained using Grubbs 2nd generation catalyst (20 mol %) at 80 °C in 1,2-DCE. It proved important to add the catalyst in 4 portions over 30 h in order to observe a complete and clean conversion, particularly on a larger scale. Desired 8-membered cyclic enone **2.211** was synthesized in 85% yield on a 500 mg scale.

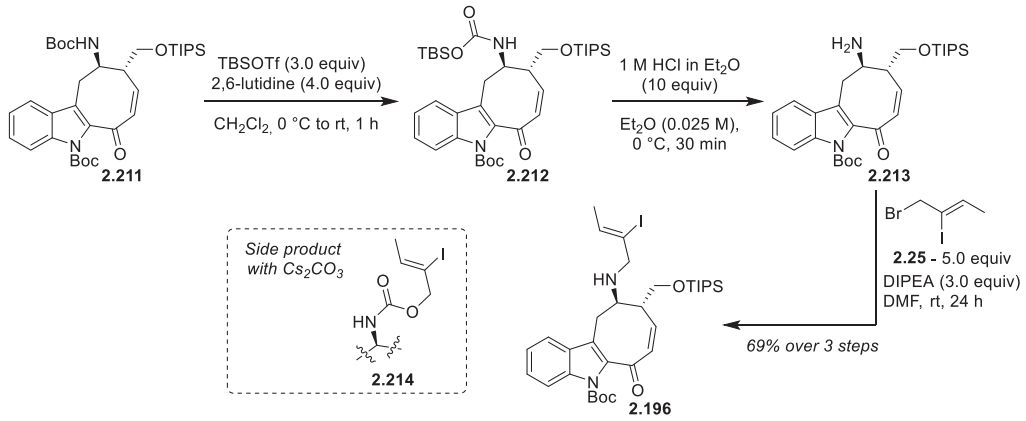


*Scheme 120 : Synthesis of the 8-membered cyclic enone **2.211** via stable diene **2.210***

[140] (a) Bennasar, M.-L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett.* **2004**, 45, 6283–6285. (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, 63, 861–866.

The next step of the synthesis was the incorporation of the vinyl iodide functionality. Direct allylation of **2.211** with allylic bromide **2.25** failed. Indeed, a strong base is needed to deprotonate the carbamate but **2.25** decomposed under these conditions. The deprotection of the Boc-amine was then explored but treatment of **2.211** with a standard acid such as TFA afforded a complex reaction mixture. Other methods were investigated and finally, the Ohfune conditions [TBSOTf, 2,6-lutidine][141] provided the mono silyl-carbamate **2.212**. Simply by dissolving the latter in a HCl solution (1 M in Et_2O) furnished, after 30 min at 0 °C, desired primary amine **2.213**. Unfortunately, **2.213** showed particular instability on silica gel, probably due to dimerization *via* addition of the amine to the enone moiety, and thus was not purified.

Reaction of crude amine **2.213** with allylic bromide **2.25** in the presence of caesium carbonate[96,98] afforded desired *N*-allyl amine **2.196** together with allylic carbamate **2.214**. The latter appeared to be formed by carbonylation of the amine with *in-situ* formed CO_2, from the carbonate base, and then by allylation of the resulting carbamate.[142] In order to avoid the formation of **2.214**, other bases, particularly organic bases, were screened and DIPEA was found to give the cleanest reaction. Finally, with the optimized sequence described in Scheme 121, key vinyl iodide **2.196** was obtained in 69% yield over 3 steps.



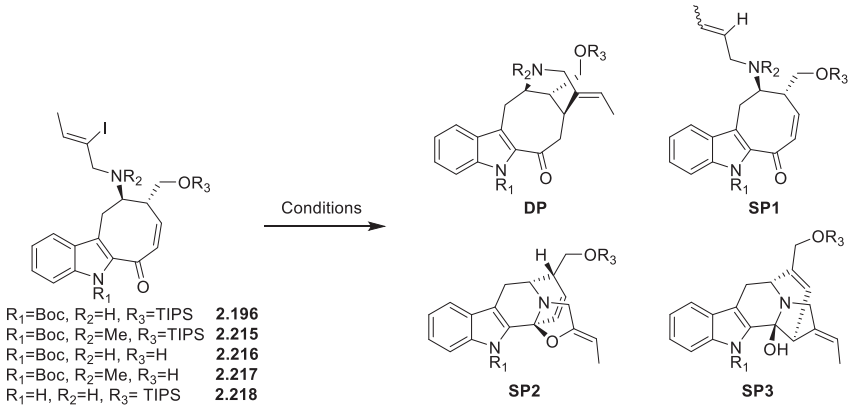
*Scheme 121 : Optimized synthetic sequence towards vinyl iodide **2.196** from **2.211***

[141] Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150–1158.
[142] (a) Butcher, K. J. *Synlett* **1994**, *5*, 825–826. (b) Chaturvedi, D. *Current Organic Chemistry* **2011**, *15*, 1593–1624.

3.3. Last Cyclization Attempts

With vinyl iodide **2.196** in hand, the final cyclization reaction could be investigated (Table 1).

Table 1 Pertinent results of the 1,4-addition investigation



Entry	R_1	R_2	R_3	Conditions	Results[(a)]
1	Boc	H	TIPS	*t*-BuLi, HMPA, TMSCl, THF, -78 °C	Decomposition
2	Boc	H	TIPS	AIBN, *n*-Bu_3SnH, benzene, 70 °C	**SP1** (38%) + decomposition
3	Boc	H	TIPS	BEt_3, *n*-Bu_3SnH, toluene, rt	**SP1** major (73%)
4	Boc	H	TIPS	$Ni(COD)_2$, Et_3N, MeCN, rt then Et_3SiH	**SP2** [42%] + unknown product (40%)
5	Boc	H	TIPS	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 60 °C	**SP3** major [63%] + **SP1** minor (16%)
6	Boc	Me	TIPS	*t*-BuLi, HMPA, TMSCl, THF, -78 °C	Decomposition
7	Boc	Me	TIPS	Mg*, THF, reflux	No reaction
8	Boc	Me	TIPS	AIBN, *n*-Bu_3SnH, benzene, 70 °C	**SP1** (49%) + decomposition
9	Boc	Me	TIPS	BEt_3, *n*-Bu_3SnH, toluene, rt	**SP1** major (81%)
10	Boc	Me	TIPS	$Ni(COD)_2$, Et_3N, MeCN, rt then Et_3SiH	**SP1** (29%) + unknown product (64%)
11	Boc	Me	TIPS	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 60 °C	**SP1** major (76%)
12	Boc	H	H	BEt_3, *n*-Bu_3SnH, toluene, rt	**SP1** major (69%)
13	Boc	H	H	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 60 °C	**SP3** major (56%) + **SP1** minor (27%)
14	Boc	Me	H	BEt_3, *n*-Bu_3SnH, toluene, rt	**SP1** major (75%)
15	Boc	Me	H	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 60 °C	**SP1** major (79%)
16	H	H	TIPS	AIBN, *n*-Bu_3SnH, benzene, 70 °C	**SP1** (32%) + decomposition
17	H	H	TIPS	$Ni(COD)_2$, Et_3N, MeCN, rt then Et_3SiH	No reaction
18	H	H	TIPS	$Pd(OAc)_2$, PPh_3, HCO_2Na, DMF, 60 °C	**SP1** major (46%) + deallylation (38%)

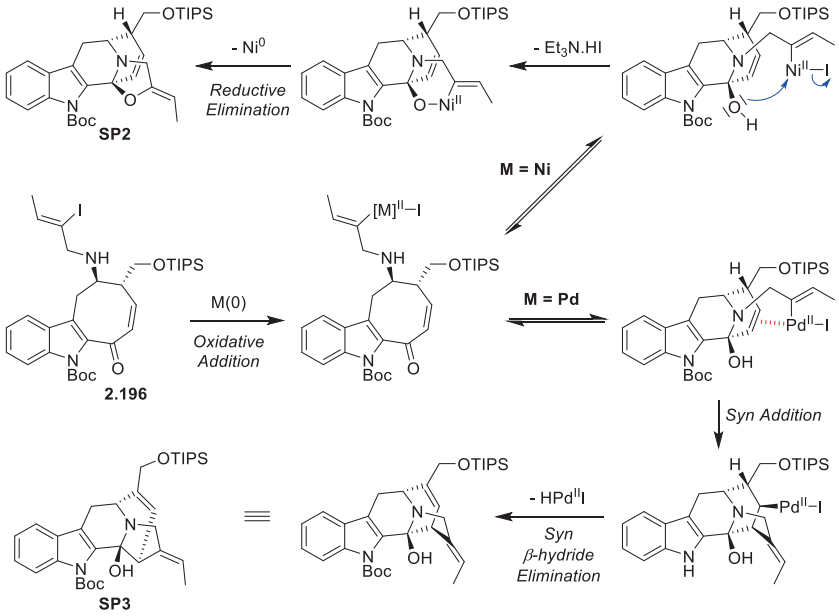
(a) Isolated yields are indicated in square brackets and NMR yields in parentheses.

The best conditions developed in the case of aspidophylline A (**2.77**) were attempted first on our substrate (entries 1 to 3).[96] Using the lithium / halogen exchange strategy with *t*-BuLi, only decomposition of the starting materials and a poor mass balance were obtained. Under the radical conditions, either with AIBN[99] or BEt_3 in the presence of oxygen[143] as initiators, a rather clean reaction was observed. However, deiodinated side product **SP1** was the major adduct and desired compound **DP** was not detected. The alternative approach using a stoichiometric amount, or an excess, of nickel(0) complex, followed by reduction of the resulting Ni(II) intermediate with triethylsilane, was then attempted with substrate **2.196**.[97,144] Under these conditions, the formation of two new major products was observed at rt or at 40 °C (entry 4). One was identified as **SP2**, involving the formation an oxygen – carbon bond in the process, and the second decomposed on silica gel and therefore its structure was not determined. We suspected for the latter that a nickel complex with the substrate was formed because black materials were observed on TLC where this side product was. The reductive Heck reaction was next examined (entry 5).[145] Using the $Pd(OAc)_2$ / PPh_3 catalytic system with either sodium formate or Hünig's base as a hydride source, a new major product together with some deiodinated product **SP1** were obtained. This new compound was identified as the Heck adduct **SP3** which involved the 1,2-insertion of the double bond into the palladium complex with the undesired regioselectivity. When **2.196** was submitted to the classical Heck conditions [$Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 60 °C] in order to confirm the structure, same side compound **SP3** was obtained as the major product. Other Pd sources, ligands and temperatures were screened for the reductive variant but similar results were also obtained.

Possible reaction pathways leading to products **SP2** and **SP3** are depicted in Scheme 122. Oxidative addition of vinyl iodide to Ni(0) would generate the Ni(II) species which may undergo transannular cyclization to hemiaminal. Ligand exchange followed by reductive elimination would provide **SP2**. For the formation of this side product, a catalytic amount of $Ni(COD)_2$ should be sufficient and no reduction step with silane should be necessary because the Ni(0) should be regenerated in the mixture, in contrast to the formation of the desired product. In the case of **SP3**, oxidative addition of the vinyl iodide to the Pd(0) catalyst and subsequent transannulation to the hemiaminal form should first occur in a similar manner as the nickel chemistry. Next, if the *syn* migratory insertion of the olefin onto the Pd(II) species occurs with the desired regioselectivity, the resulting palladium complex would have to wait the ligand exchange step

[143] Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307–5310.
[144] (a) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230–7240. (b) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827–7828.
[145] (a) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655–665. (b) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187. (c) Gao, P.; Cook, S. P. *Org. Lett.* **2012**, *14*, 3340–3343. (d) Jana, G. K.; Sinha, S. *Tetrahedron Lett.* **2012**, *48,* 1671−1674. (e) Mannathan, S.; Raoufmoghaddam, S.; Reek, J. N. H.; de Vries, J. G.; Minnaard, A. J. *ChemCatChem* **2015**, *7*, 3923–3927. (f) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253–9258.

with the hydride source in order to perform afterwards the reductive elimination step. In contrast, if the *syn* addition step occurs with the undesired regioselectivity, the resulting Pd intermediate would be in a perfect position with the hydrogen in *beta* to undergo a spontaneous *syn beta*-hydride elimination and therefore generate **SP3**. We believed that this last step was the driving force for the formation of **SP3** instead of the desired product. The reductant, formate or Hünig's base, actually plays the role of base in this case by deprotonating the resulting Pd(II)HI complex and thus, regenerating the Pd(0) active species.



*Scheme 122 Proposed mechanism towards the formation of **SP2** and **SP3***

On the assumption that formation of hemiaminal intermediate was responsible for the formation of **SP2** and **SP3**, it was decided to methylate the amine. In addition, the final natural product affinine (**2.2**) required this methyl group. Submitting **2.196** to an excess of formaldehyde and $NaBH_3CN$ in methanol at rt gave desired methyl amine **2.215** in 89% yield. Submitting the latter to lithium / halogen exchange reaction, using *t*-BuLi, led once again to decomposition (entry 6). Insertion of activated magnesium metal into the carbon – iodine bond was also attempted (entry 7). Surprisingly, no reaction was observed in refluxing THF using Mg^0 freshly activated with acid or in the presence of a catalytic amount of activator, such as iodine or diiodoethane. Using the freshly prepared and very reactive Riecke magnesium,[146] decomposition was observed between 0 °C and rt. Under radical conditions (entries 8 to 9), deiodinated adduct **SP1** was the only isolable product. When $Ni(COD)_2$ was used with substrate **2.215**, **SP1** together

[146] (a) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925–1956. (b) Rieke, R. D.; Bales, S. E.; Hudnall, P. M., Burns, T. P.; Poindexter, G. S. *Org. Synth.* **1979**, *59*, 85. (c*)* Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4324–4326.

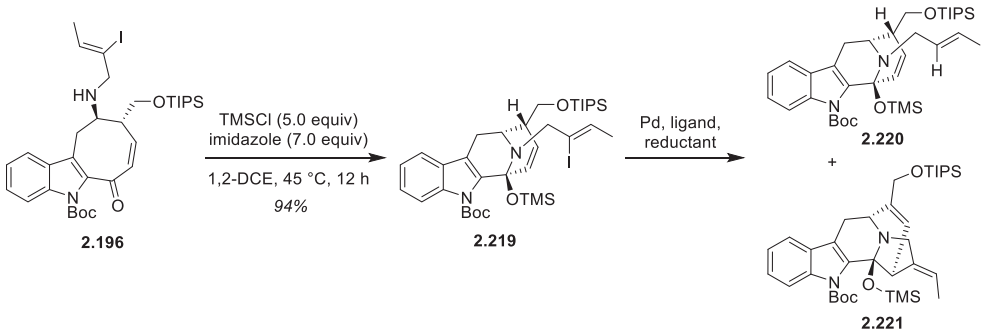
with another product, which decomposed on silica gel, were obtained (entry 10). It should be noted that the use of either slightly higher temperature (40 °C) or BHT as reductant, a complex mixture was obtained. Submitting methyl amine **2.215** to reductive Heck conditions with sodium formate gave mainly deiodinated compound **SP1** (entry 11). Using a higher temperature (80 °C) or Hünig's base as hydride source, partial deallylation of the starting material was also observed.

Deiodination of **2.215** being a main reaction pathway, we asked ourselves if the hindered TIPS group prevented the vinyl iodide from approaching sufficiently close to the enone moiety. To explore this, substrates **2.196** and **2.215** were both cleanly deprotected using TBAF in the presence of AcOH. Without acetic acid, the formation of minor side products were observed. With a limited amount of alcohols **2.216** and **2.217** in hand, the radical conditions and reductive Heck reaction were then investigated. The preliminary results showed that with or without the TIPS group, the formation of the same type of products were observed (entries 3 with 12, 5 with 13, 9 with 14 and 11 with 15). When tributyltin hydride and triethylborane were used, only deiodination was observed with both substrates. Under reductive Heck conditions, the same Heck adduct **SP3** was formed with **2.216**, whereas with **2.217**, **SP1** was the major product. As observed previously, when the Hünig's base or a higher temperature was employed, partial deallylation of **2.217** was obtained.

The TIPS group did not impact the reaction outcome significantly, and so we decided to examine next the influence of the Boc-indole and to attempt a few conditions on the free NH derivative. The deprotection of **2.196** was performed using an excess of TFA and, after a basic work-up, clean crude product **2.218** was submitted directly to the 1,4-addition reactions. Under the radical conditions, significant deiodination was once again observed (entry 16). However, using the nickel chemistry, conversion was not observed in acetonitrile either at rt or at 40 °C (entry 17). A partial insolubility issue was noticed in this case and when a mixture MeCN/DMF was used, NH-indole **2.218** was completely soluble but still no reaction occurred at rt. When the reaction mixture was heated to 40 °C in the latter solvent system, decomposition was unfortunately observed. Submitting **2.218** to the reductive Heck conditions led to deiodinated product **SP1** together with deallylation (entry 18). To our surprise, Heck adduct **SP3** was not detected. As formation of **SP2** and **SP3** side products was not observed, the formation of the hemiaminal in the case of free NH-indole **2.218** appeared to be limited. We concluded that the Boc-indole exacerbated the electrophilicity of the ketone to allow the formation of the hemiaminal. If we pay sufficient attention to the ^{1}H NMR spectra, several peaks of the hemiaminal form of **2.196** (<5%) can be observed, whereas none of those peaks are detected with substrate **2.218**.

3.4. Alternatives Investigated

In all the reactions described above, formation of desired bridged system **DP** was never observed. We considered as a first alternative forcing the formation of **2.196** into its hemiaminal form by trapping it with a silyl electrophile. We expected that under reductive Heck conditions, the silyl group would slow down the formation of the Heck adduct **SP3** by providing steric hindrance around the undesired position of the double bond. Treatment of **2.196** with TMSCl in the presence of imidazole, as base and activator, at 45 °C in 1,2-DCE afforded hemiaminal **2.219** in 94% yield (Scheme 123). It should be noted that the TMS group showed surprising stability towards aqueous work up and **2.219** can even be purified on neutralized silica gel. After a screening of various Pd sources and ligands, only deiodinated product **2.220** and Heck adduct **2.221** were observed with various ratios. The formation of the more hindered hemiaminal, with TBS group instead of TMS, was attempted but without success.

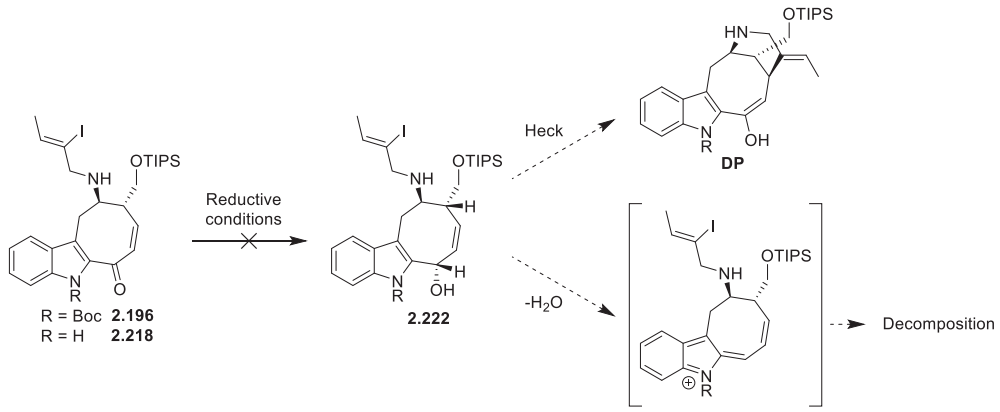


*Scheme 123 Attempts of cylization from hemiaminal **2.219***

Afterwards, we designed another alternative. If enone **2.196** could be reduced regio- and diastereoselectively to the corresponding allylic alcohol **2.222**, a classical Heck reaction could be performed. If the *syn* addition of the palladium occurred with the desired regioselectivity, the following *beta*-hydride elimination would reformed the desired ketone in the process (Scheme 124). In addition, in this case, the palladium intermediate would not require to wait a hydride source for the reaction to proceed. However, when substrate **2.196** was treated with sodium borohydride, only the formation of the 1,4-reduction adduct was observed. Under the Luche conditions [$CeCl_3$ / $NaBH_4$],[147] the reaction rate was slowed down but again only 1,4-reduction occurred. The same selectivity was observed with the $LiBH_4$ / MeOH system.[134] Aluminium-based reductants, which are known to deliver 1,2-selectivity, were also attempted. $LiAlH_4$ gave a complex mixture, whereas DIBAL gave to our surprise poor conversion, even at rt.

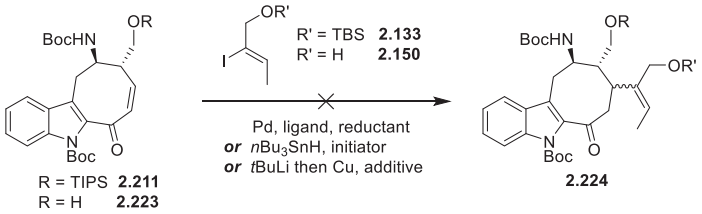
[147] (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

With all these observations, we assumed that the Boc group on the indole hindered the ketone and thus we decided to remove it. With substrate **2.218**, Luche conditions gave a complex mixture, whereas DIBAL gave a rather clean conversion at -78 °C and a promising major product was obtained. However, the latter decomposed rapidly in the NMR tube and the structure was not confirmed. We supposed that if desired compound **2.222** was obtained, dehydration to give the conjugated azafulvenium intermediate should be facile and therefore lead to the formation of side products.



*Scheme 124 Attempts of cylization from allylic alcohol **2.222***

Finally, we explored as a last alternative an intermolecular approach using vinyl iodide **2.133** and **2.150** on substrate **2.211** or the corresponding TIPS-deprotected **2.223**. Under various variants of the reductive Heck reaction, the vinyl iodide was always consumed, whereas the enone block did not react (Scheme 125). At high temperature (above 100 °C), deprotection of Boc-indole was observed as the only reaction. Using the radical chemistry, similar results were noted. Converting the vinyl iodide to the corresponding reactive cuprate was also explored. First, lithium / halogen exchange with *t*-BuLi gave *in-situ* the corresponding vinyl lithium which was followed by addition of a variety of copper source in a catalytic or stoichiometric amount to afford the desired cuprate.[148] After addition of the enone substrate, all the conditions gave the same result: up to 0 °C, no reaction was observed but decomposition of the enone occurred when rt was reached.



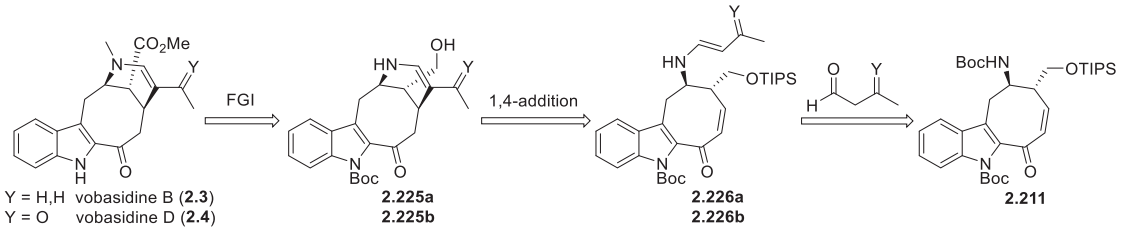
Scheme 125 Intermolecular approach failure

[148] Fevig, J. M.; Marquis, R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085–5086.

Chapter 4. Synthetic Studies Towards Vobasidines B and D

4.1. Retrosynthesis

After the failure to perform the last cyclization reaction in the previous chapter, we moved to the studies of the antipode of vobasidines B (**2.3**) and D (**2.4**). The retrosynthetic analysis was very similar to that of affinine, as shown in Scheme 126. The synthesis of these two targets was planned by final functional group manipulations of the advanced intermediate **2.225**, including *N*-methylation of the enamin(on)e, oxidation of the alcohol to ester and deprotection of the indole. The formation of the bridged system in **2.225** was envisaged once again by an intramolecular 1,4-addition of the corresponding enamine /enaminone **2.226** onto the enone moiety. We believed that this chemistry would allow us to use of a wider range of temperatures, compared to the vinyl iodide substrate, in order to favour the formation of an 8-membered ring conformer suitable for this cyclization. Key intermediate **2.226** should be obtained from 8-membered cyclic enone **2.211**, which had been synthesized previously (cf. 3.2), *via* the condensation of the amine with the required aldehydes.



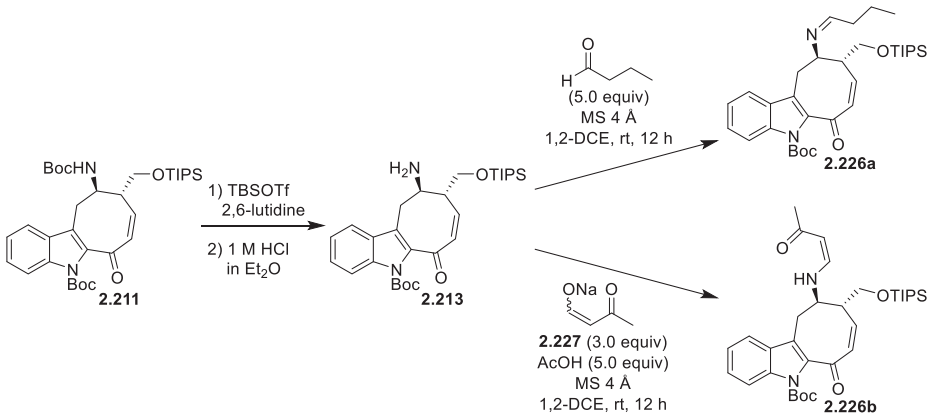
Scheme 126 Retrosynthetic analysis towards vobasidines

4.2. Synthesis of the Key Intermediates and Cyclization Attempts

Following the sequence optimized previously for the selective deprotection of Boc-amine (cf. 3.2), amine **2.213** was next treated with an excess of butanal in the presence of molecular sieves to provide **2.226a** exclusively in its imine form (Scheme 127). Due to the sensitivity of imine

towards water, neither aqueous work-up nor silica gel purification was performed. Simple filtration of molecular sieves and then concentration of the filtrate to dryness, for the removal of excess of aldehyde, gave cleanly crude **2.226a**.

A similar approach was used to synthesize enaminone **2.226b**. The required acetoacetaldehyde is very unstable, due to a facile trimerization to 1,3,5-triacetylbenzene,[149] and so it was generated *in-situ* from the corresponding sodium salt **2.227** and acetic acid.[150] Using this method, amine **2.213** was converted cleanly to the desired enaminone with exclusively (*Z*)-configuration, due to intramolecular hydrogen bonding. **2.226b** exhibited higher stability than imine **2.226a** but it was still sensitive towards water. Dilution of the crude mixture with Et_2O facilitated the precipitation of all sodium acetate salts and after filtration and concentration, clean **2.226b** was also obtained.



*Scheme 127 Synthesis of key enamin(on)e **2.226***

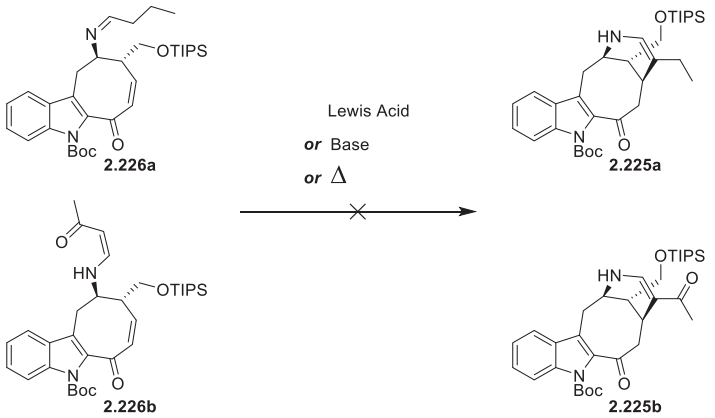
The 1,4-addition of **2.226** to form desired bridged system **2.225** was attempted mainly in the presence of a Lewis acid but also with strong base and by thermolysis of the substrate (Scheme 128).[151]

In the case of imine **2.226a**, using $MgBr_2$ or $ZnCl_2$ at rt only led to the deprotection of the Boc-indole moiety. Gentle heating of the reaction mixture with either Lewis acid gave decomposition. The deprotonation of **2.226a** with LiHMDS failed and gave only recovery of the starting materials. Treatment with a stronger base such as LiTMP gave in contrast a complex mixture. Slow decomposition (~48 h) was observed when the imine was heated in refluxing

[149] Royals, E. E.; Brannock, K. C. *J. Am. Chem. Soc.* **1953**, *75*, 2050–2053.
[150] Qi, H.; Zhang, J.; Xu, J. *Synthesis* **2011**, *43*, 887−894.
[151] (a) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guigant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505. (b) Li, Y.; Xu, H.; Xing, M.; Huang, F.; Jia, J.; Gao, J. *Org. Lett.* **2015**, *17*, 3690−3693.

1,2-DCE in the presence or absence of molecular sieves. In refluxing toluene, complete decomposition was obtained in less than 6 h.

Regarding enaminone **2.226b**, the use of a wide range of Lewis acids was explored. At rt, in the presence of CuCl, $CuCl_2$ or AgOAc, there was no reaction. With either $MgBr_2$ or $ZnCl_2$, only deprotection of Boc-indole was observed, whereas with $FeCl_3$, $AlCl_3$, $BF_3.Et_2O$, TBSOTf or TIPSOTf, both the indole and alcohol were deprotected. It should be noted that, in these last cases, crude NMR analysis showed that partial cyclization of the alcohol onto the enaminone had occured *via* 1,4-addition. When the reaction was heated to 50 °C in the presence of those Lewis acids, similar results were obtained, whereas decomposition was observed when the temperature reached 75 °C. As with imine **2.226a**, exposure to LiHMDS and carbonates gave no reaction, whereas LiTMP decomposed the starting material. However, enaminone **2.226b** exhibited a high stability towards thermolysis: no reaction was observed when **2.226b** was refluxed either in 1,2-DCE or in toluene. In refluxing xylene, deprotection of the indole occurred and, below 180 °C, it was the only reaction observed. Decomposition started when the 200 °C barrier was reached.



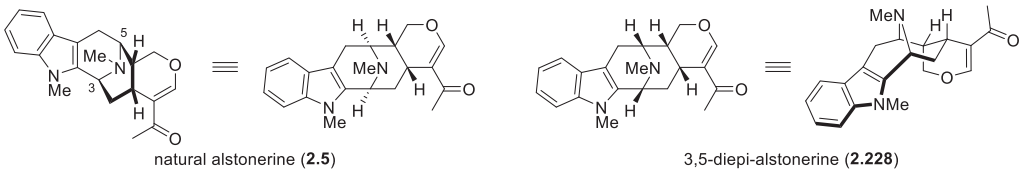
*Scheme 128 Cyclization failure from **2.226***

In all cases, desired bridged compounds **2.225a/b** were again not observed. An intermolecular approach was also investigated by attempting the 1,4-addition of an enamine or an enaminone onto the 8-membered cyclic enone **2.211**, but without success. Only decomposition of the enamin(on)e partner occurred together with partial deprotection of **2.211.**

Chapter 5. Synthetic Studies Towards a Stereoisomer of Alstonerine

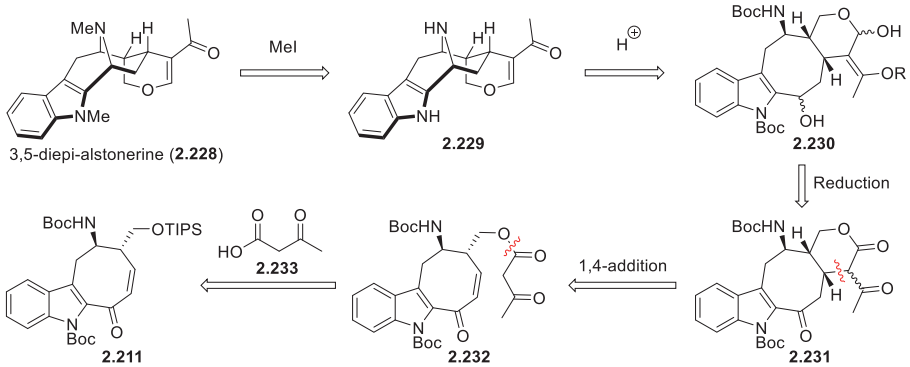
5.1. Retrosynthesis

As the syntheses of all the investigated vobasine-based natural products failed, we decided to design a strategy to convert our advanced intermediate **2.211** into the macroline-type skeleton. The first target chosen was alstonerine (**2.5**). However, due to the relative stereochemistry between the alcohol chain and the amine in **2.211**, only a diastereoisomer of alstonerine, isomer **2.228**, could be reached (Scheme 129).



*Scheme 129 Alstonerine and its targeted stereoisomer **2.228***

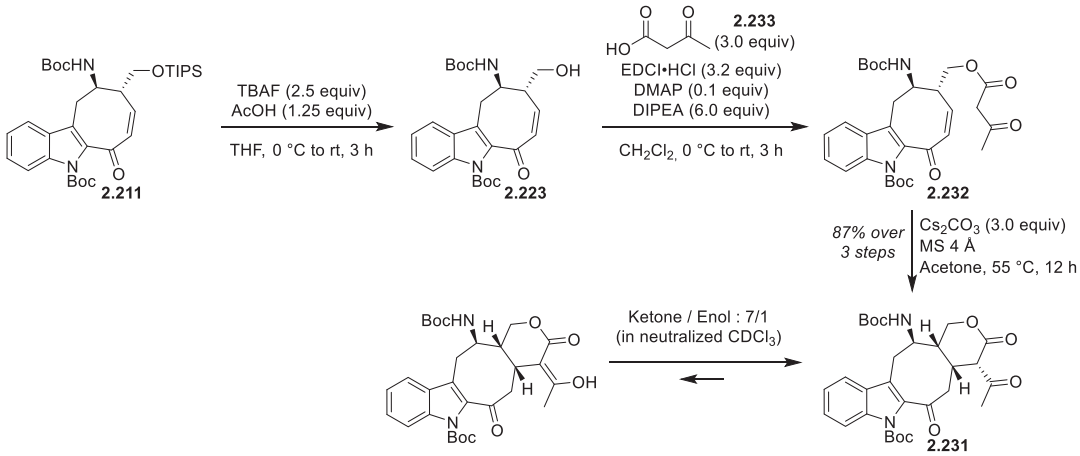
As depicted in Scheme 130, we planned to synthesize 3,5-diepi-alstonerine (**2.228**) by final methylation of both the indole and amine of pentacycle **2.229**. The formation of the latter was envisaged by double dehydration of **2.230** followed by the transannulation of the amine to form the desired bridged system. Intermediate **2.230** should be obtained from **2.231** by the reduction of both the ketone to alcohol and the lactone to lactol. The second ketone, of the 1,3-ketolactone moiety, should be protected in this case in order to avoid over-reduction. The formation of 6-membered lactone ring **2.231** was planned by an intramolecular 1,4-addition of 1,3-ketoester **2.232** onto the enone. Compound **2.232** would be synthesized by a simple esterification of our previously synthesized intermediate **2.211**.



Scheme 130 Retrosynthetic analysis towards 3,5-diepi-alstonerine

5.2. Synthesis of the Key Intermediate and Cyclization

Deprotection of TIPS-protected alcohol **2.211** was performed using TBAF. However, under this condition, partial Boc-deprotection of the indole core was also observed. When the same reaction was performed in the presence of acetic acid, to protonate the *in-situ* formed alkoxide, the unwanted deprotection of the indole was avoided. Subsequent esterification with acetoacetic acid **2.233** using EDCI as coupling reagent and a catalytic amount of DMAP afforded cleanly desired ester **2.232** (Scheme 131). Due to the slight instability of **2.233**, *via* facile decarboxylation, it was prepared freshly by treatment of *tert*-butyl acetoacetate with TFA.[152] The synthesis of **2.233** was also attempted by classical transesterification, in refluxing toluene, of either tert-butyl 3-oxobutanoate or 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one with alcohol **2.223**.[153] In these two cases, the formation of desired ester **2.233** occurred with good conversion but the reaction was less clean and required a longer reaction time (~24 h) compared to the ester coupling.



*Scheme 131 Synthesis of ester **2.232** and further key 1,4-addition*

The intramolecular 1,4-addition was next investigated. Strong bases such as *t*-BuOK or NaH led only to decomposition at rt.[154] With the weaker base DBU, no reaction was observed at rt, and slow decomposition occurred at 45 °C to give only a small amount of desired 1,4-adduct **2.231**.[155] Carbonates, which are even weaker bases but sufficiently strong to deprotonate a

[152] Ling, T.; Danishefsky, S. *Patent US 20090234137 A1* – 2009-09-17 – page 45.
[153] Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713−1718.
[154] (a) Kwan, E. E.; Scheerer, J. R.; Evans, D. A. *J. Org. Chem.* **2013**, *78*, 175−203. (b) Elliott, M. C.; El Sayed, N. N. E.; Ooi, L.-L. *Tetrahedron Lett.* **2007**, *48*, 4561–4564.
[155] Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2011**, *17*, 2048–2051.

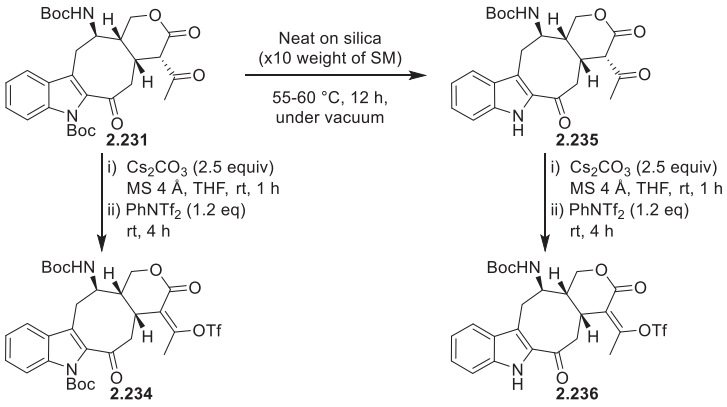
1,3-ketoester, were then attempted. With potassium carbonate at rt, no reaction was observed, whereas after 16 h in refluxing acetone, ~90% conversion to desired tetracycle **2.231** was obtained based on ^{1}H crude NMR. It should be noted that a longer reaction time did not improve the conversion. Switching to sodium carbonate, the reaction stopped at ~70% conversion. Finally, using caesium carbonate in refluxing acetone for 12 h, complete conversion of the starting material was obtained and desired 1,4-adduct **2.231** was isolated in 87% yield over 3 steps on a 200 mg scale. ^{1}H NMR analysis in neutralized deuterated chloroform showed an equilibrium of the 1,3-ketoester with its tautomeric enol form in a ratio of 7 / 1 (ketone / enol). The *cis*-fused configuration at the ring junction was determined by a ROESY analysis, as well as the orientation of the ketone in the pseudo-equatorial position.

5.3. Towards the Synthesis of the Pentacycle

The successful synthesis of tetracycle **2.231** allowed the exploration of the following steps. As shown in Scheme 132, the ketoester group was monotriflated *via* deprotonation with caesium carbonate and trapping of the resulting enolate with $PhNTf_2$. The use of other bases, such as DIPEA, gave a complex mixture of products. Partial hydrolysis of the triflate, to regenerate the starting materials, was observed during the aqueous work-up or after purification on silica gel. Consequently, the crude solution was concentrated and the residue was dissolved in chloroform. The resulting suspension was filtered to give clean triflate **2.234** together with unreacted $PhNTf_2$. Usually, the side product PhNHTf can be tedious to remove, even by column chromatography. In our case, we believed that the corresponding PhNCsTf salt was insoluble, therefore facilitating its removal by simple filtration.

In previous attempts to reduce the ketone in the C-2 position of indole, we encountered some difficulties with the Boc-indole substrates that we rationalized by involving steric hindrance (cf. 3.4.). We decided to synthesize the Boc-deprotected triflate **2.236** in parallel. The selective deprotection of Boc-indole **2.231** was attempted using TFA at low temperature but always a small amount of free amine was obtained. Boc-indoles are known to be also sensitive to nucleophilic attack. Treatment of **2.231** with potassium carbonate in methanol gave a complex mixture with complete disappearance of the methylketone. This result was unexpected and a retro-Dieckmann condensation probably occurred under these reaction conditions. Finally, we found that simple solid deposition of substrate **2.231** on silica gel followed by heating to 55 °C

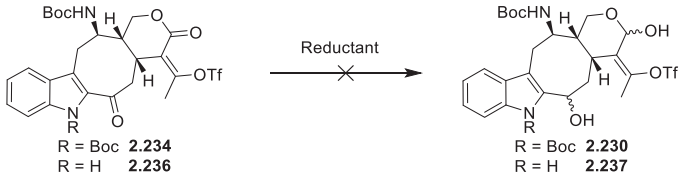
under vacuum gave a clean mono-deprotection of the indole.[156] Compound **2.235** was then triflated to **2.236** using the same conditions optimized previously.



*Scheme 132 Synthesis of vinyl triflates **2.234** and **2.236***

When NH-substrate **2.236** was treated with DIBAL in CH_2Cl_2 at -78 °C, a complex reaction mixture formed rapidly but the desired secondary alcohol and lactol peaks were observed by crude ^{1}H NMR. Switching to THF as solvent resulted in a far cleaner reaction and a major product, which seemed to be desired **2.237**, was obtained. However, the latter proved to be highly unstable. Indeed, the attempted purification or treatment of the crude with acid, base or heating led only to complete decomposition. The same observation was noted when the crude was simply allowed to stand in a neutralized $CDCl_3$ solution. L-Selectride, which is also known for the reduction of lactones to lactols,[157] led only to the mono-reduction of the ketone at -78 °C. With a higher reaction temperature, a complex mixture was obained and in contrast to DIBAL, the solvent system was not crucial for the reaction outcome (Scheme 133).

With Boc-substrate **2.234**, only a complex mixture of products was observed with either reductant, whatever the temperature and solvent system.



Scheme 133 Double reduction failure

It should be noted that similar substrates possessing a TBS enol ether instead of an enol triflate as protecting group were also investigated, but these gave no better results.

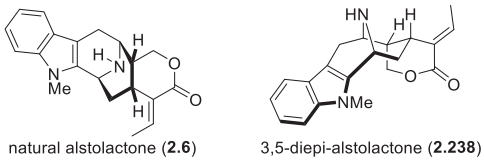
[156] Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1472–1472.
[157] Burkhardt, E. R.; Matos, K. *Chem. Rev.* **2006**, *106*, 2617−2650.

Chapter 6. Total Synthesis of *N*(1)-demethyl-3,5-diepi-alstolactone

6.1. First Approach

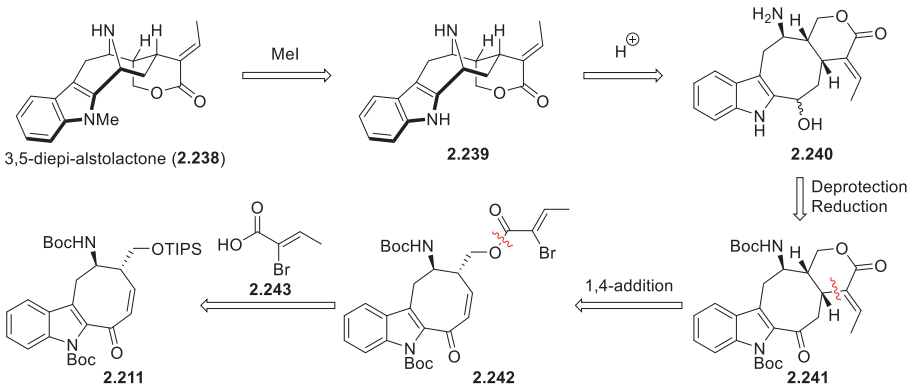
6.1.1. Retrosynthesis

The last natural product to be investigated was the macroline-type alstolactone (**2.6**). For the reasons discussed in the previous chapter with respect to alstonerine (**2.5**)(cf. 5.1.), only the diastereoisomer **2.238** could be prepared from the advanced 8-membered cyclic enone **2.211**.



*Scheme 134 Alstolactone and its targeted stereoisomer **2.238***

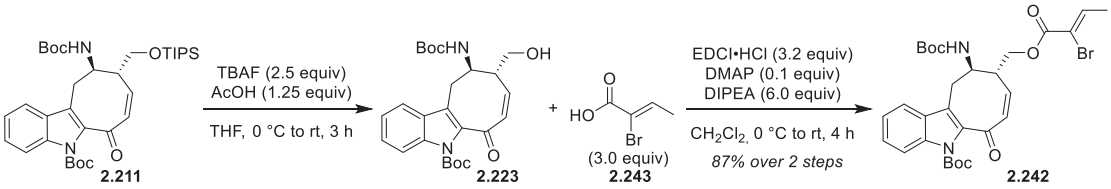
Targeted stereoisomer **2.238** could be synthesized from **2.239** by a selective methylation of the indole. Preparation of required pentacycle **2.239** was planned from 8-membered ring **2.240** *via* dehydration followed by transannular cyclization. The latter could be obtained from **2.241** by removal of *N*-protecting groups and chemoselective reduction of the ketone. Formation of the fused rings system in **2.241** was envisaged once again by an intramolecular 1,4-addition of vinyl bromide **2.242** onto enone. Esterification of **2.211** should afford key intermediate **2.242**.



Scheme 135 Retrosynthetic analysis towards 3,5-diepi-alstolactone

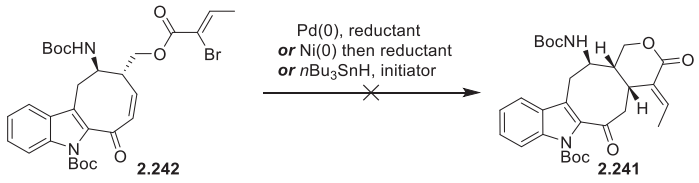
6.1.2. Synthesis of the Key Intermediate and Cyclization Attempts

Following the same approach used in the synthesis of ester **2.232**, TIPS-deprotection using the TBAF / AcOH system followed by esterification of the resulting alcohol with acid **2.243**, in the presence of EDCI and DMAP, afforded key intermediate **2.242** in 87% yield over 2 steps. (*Z*)-2-Bromobut-2-enoic acid **2.243** was synthesized from methyl crotonate in 64% yield over 3 steps *via* dibromination followed by selective elimination of HBr, under thermal condition in wet DMSO, into the desired (*Z*)-isomer and by subsequent hydrolysis of the ester group.[158] It was found that crude (*Z*)-acid **2.243**, which was contaminated with 10% of the (*E*)-isomer, could be purified by simply washing the crude solids twice with petroleum ether.



*Scheme 136 Synthesis of ester **2.242***

With vinyl bromide **2.242** in hand, the 1,4-addition reaction was then investigated. First, with the reductive Heck approach,[159] no reaction was observed at 60 °C even though oxidative addition of palladium into vinyl iodide **2.196** had occurred previously at this temperature. Conversion was observed when the reaction was heated to 80 °C, but a mixture of products containing the enone functionality was obtained. The use of higher temperatures gave an even dirtier reaction. Using the Ni(0) chemistry, a complex mixture was obtained at rt. Treatment of **2.242** with tributyltin hydride[160] and triethylborane as initiator at rt gave also decomposition of the starting materials. However, with AIBN as initiator, no reaction was observed in refluxing benzene. Decomposition was only noted when the 100 °C barrier was reached.



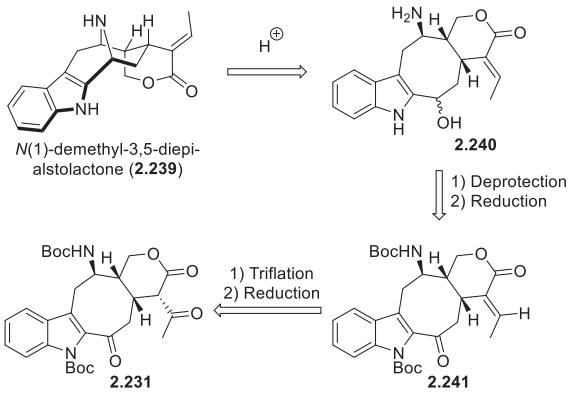
*Scheme 137 Cyclization failure from **2.242***

[158] (a) Li, W.; Li, J.; Wan, Z.-K.; Wu, J.; Massefski, W. *Org. Lett.* **2007**, *9*, 4607–4610. (b) Holstein, P. M.; Dailler, D.; Vantourout, J.; Shaya, J.; Millet, A.; Baudoin, O. *Angew. Chem. Int. Ed.* **2016**, *55*, 2805–2809.
[159] Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146–9147.
[160] Kawaguchi, M.; Satoh, S.; Mori, M.; Shibasaki, M. *Chemistry Letters* **1992**, *21*, 395–398.

6.2. Second Approach and Endgame

6.2.1. Retrosynthesis

We focused our final efforts on the synthesis of the pentacyclic core of *N*(1)-demethyl-3,5-diepi-alstolactone **2.239**. We were mainly interested in the feasibility of forming the bridged system from the corresponding 8-membered ring **2.240** *via* a dehydration / transannular cyclization process. We envisaged that required conjugated lactone **2.241** could be actually obtained from the previously synthesized 1,3-ketoester **2.231** (cf. 5.2.) *via* triflation and subsequent reduction of the resulting vinyl triflate.

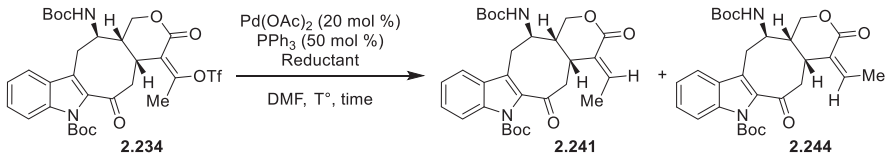


Scheme 138 Retrosynthetic analysis towards N(1)-demethyl-3,5-diepi-alstolactone

6.2.2. Synthesis of the Conjugated Lactone and Last Cyclization

The triflation of 1,3-ketolactone **2.231** was performed under the previously optimized conditions [Cs_2CO_3, $PhNTf_2$, MS 4 Å; cf. 5.3.] to furnish vinyl triflate **2.234** as a single (*Z*)-isomer. Pd-Catalyzed reduction, using the catalytic system $Pd(OAc)_2$ / PPh_3, was next investigated as described in Table 2. It should be noted that complete consumption of the starting materials was obtained in each case and that anhydrous DMF has to be used in order to avoid the hydrolysis of the triflate moiety back to the 1,3-ketolactone.

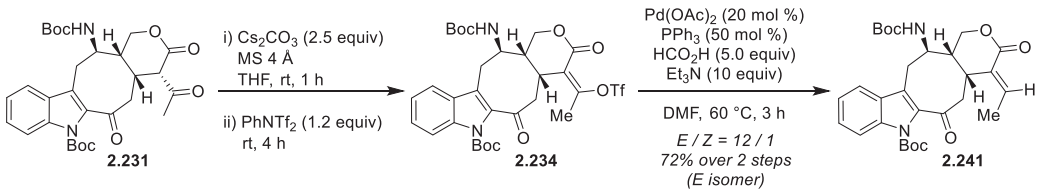
Table 2 Optimization of the vinyl triflate reduction



Entry	Reductant	T°, time	Ratio E / Z (crude ^{1}H NMR)
1	Et_3SiH (5.0 equiv)	60 °C, 4.5 h	2 / 1
2	HCO_2Na (5.0 equiv)	60 °C, 4.5 h	2.5 / 1
3	HCO_2H (5.0 equiv), Et_3N (5.0 equiv)	60 °C, 4.5 h	4 / 1
4	HCO_2H (10 equiv), Et_3N (5.0 equiv)	60 °C, 4.5 h	3 / 1
5	HCO_2H (5.0 equiv), Et_3N (10 equiv)	60 °C, 4.5 h	7.5 / 1
6	HCO_2H (5.0 equiv), Et_3N (10 equiv)	60 °C, 6.5 h	4.5 / 1
7	HCO_2H (5.0 equiv), Et_3N (10 equiv)	60 °C, 3 h	12 / 1

When triethylsilane was used as reductant and after 4.5 h at 60 °C,[161] the desired product was formed cleanly, but as a 2/1 mixture of isomers E/Z (**2.241**/**2.244**) (entry 1). Similar results were noted by switching the reductant to the sodium formate salt (entry 2). More promising results for the generation of the desired (*E*)-isomer were obtained using triethylammonium formate as hydride source.[162] With an equimolar amount of formic acid and triethylamine, a 4/1 mixture (E/Z) was obtained (entry 3). When an excess of formic acid was employed, the ratio decreased to 3/1, whereas with an excess of triethylamine, a good E/Z ratio of 7.5/1 was obtained (entries 4 and 5). As shown in entry 6, isomerization of the double bond was observed under the reaction conditions when longer reaction times were used. After monitoring the reaction carefully, 3 h was found to be sufficient to obtain complete conversion and in this case, an excellent E/Z ratio of 12/1 was obtained.

Under the optimized conditions for the triflation / reduction sequence, conjugated lactone **2.241** was synthesized in 72% yield over 2 steps on a 40 mg scale (Scheme 139).



Scheme 139 Optimized triflation / reduction sequence

[161] Garvey, D. S. *Patent WO 2012174064 A1* – 2012-12-20 – page 102.

[162] (a) Ramachandran, S. A.; Kharul, R. K.; Marque, S.; Soucy, P.; Jacques, F.; Chenevert, R.; Deslongchamps, P. *J. Org. Chem.* **2006**, *71*, 6149–6156. (b) McGowan, C. A.; Schmieder, A.-K.; Roberts, L.; Greaney, M. F. *Org. Biomol. Chem.* **2007**, *5*, 1522–1524.

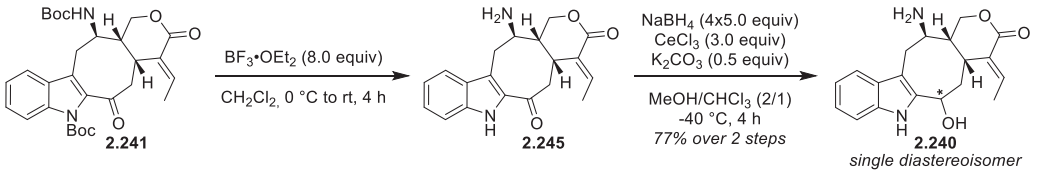
The Boc-deprotection of both the indole and amine was then attempted on substrate **2.241**. Classically, with an excess of TFA, the desired product was observed but the reaction was not sufficiently clean, and so other methods were investigated. With HCl in methanol, isomerization of double bond was observed, whereas with HCl in dioxane, 1,4-addition of chloride onto the conjugated lactone was observed based on crude NMR and MS analyses. Thermolysis of **2.241** in water (150 °C), TFE (150 °C) or HFIP (100 °C) gave the desired bisdeprotection but in an even less clean manner than TFA.[163] Finally, using an excess of the Lewis acid BF_3**.**Et_2O and after a basic aqueous work-up, desired bisdeprotected product **2.245** was obtained cleanly.

The chemoselective reduction of ketone was then explored. DIBAL was not attempted because it would have reduced the lactone group to lactol. However, we saw previously with L-Selectride that the lactone was not reduced at -78 °C. Unfortunately using this reductant, a complex reaction mixture was obtained and 1,4-reduction of the conjugated lactone moiety was also observed. With sodium borohydride in methanol at 0 °C, the desired ketone reduction occurred together with significant amount of 1,4-reduction. When the same reaction was performed at -78 °C, no conversion was detected, even with a large excess of reductant.[164] At -40 °C, chemoselective reduction of the ketone was observed but with a slow reaction rate. It was noted that substrate **2.245** was not completely soluble in methanol at this temperature. Using the solvent system MeOH / $CHCl_3$ (2/1), complete solubility was observed and better conversion was obtained while difficulties were still encountered to reach full conversion. When the Lewis acid $CeCl_3$ was added into the reaction mixture, a total consumption of the starting materials was obtained after 4 h at -40 °C. However, we faced reproducibility issues under these conditions. We could obtain either a very clean conversion to desired product **2.240** or a completely dirty reaction involving a significant amount of 1,4-reduction of the conjugated lactone. We found that the addition of a substoichiometric amount of potassium carbonate, in order to regulate the pH of the reaction, gave a clean and reproducible mono-reduction of the ketone without noticeable undesired 1,4-reduction.

Under these optimized conditions, desired secondary alcohol **2.240** was synthesized in 77% yield over 2 steps (Scheme 140). It should be noted that the reduction reaction occurred diastereoselectively as only one isomer was isolated. However, the exact stereochemistry was of no consequence since the following transannular cyclization step was expected to proceed *via* a S_N1 mechanism.

[163] (a) Choy, J.; Jaime-Figueroa, S.; Jiang, L.; Wagner, P. *Synthetic Communications* **2008**, *38*, 3840–3853. (b) Wang, G.; Li, C.; Li, J.; Jia, X. *Tetrahedron Lett.* **2009**, *50*, 1438–1440. (c) Wang, J.; Liang, Y.-L.; Qu, J. *Chem. Comm.* **2009**, *45*, 5144–5146.

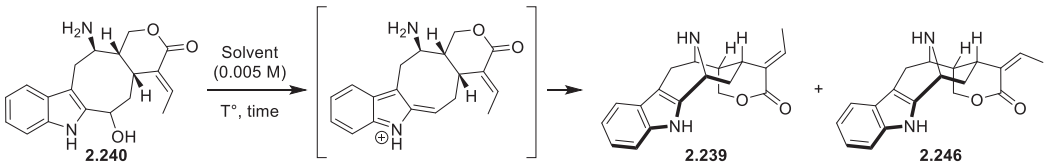
[164] Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206–1211.



Scheme 140 Optimized deprotection / mono-reduction sequence

In order to accomplish the final cyclization, it was required to dehydrate alcohol **2.240** to form the azafulvenium species. We believed we could trap this intermediate intramolecularly with the amine *via* transannulation. We saw, in the first chapter, the opening of azabicyclo[3.3.1]nonane system *via* the formation of an ammonium intermediate followed by its elimination by an indole and then trapping of the azafulvenium cation with water (cf. 1.2.2.). To our surprise, the desired reverse reaction is relatively unexplored. To the best of our knowledge, there is only one example in the literature.[165] Büchi and coworkers reported in 1964 that the desired cyclization could proceed by simple thermolysis of the substrate in refluxing xylene for 8 h. They noted that no transannular cyclization occurred upon treatment with acids such as methanolic HCl or PTSA. They rationalized that the amine was no longer available due to its protonation under acidic conditions.

Table 3 Optimization of the dehydration / transannulation process



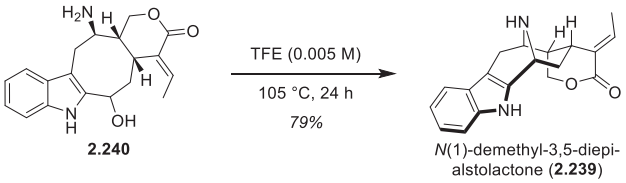
Entry	Solvent	T°, time	Results (crude ^{1}H NMR)
1	Xylene	140 °C, 12 h	70% conversion with ~10% of **2.239**. Messy.
2	Toluene	110 °C, 12 h	No reaction
3	HFIP	80 °C, 24 h	Full conversion with ~50% of **2.239**. Not clean.
4	TFE	80 °C, 12 h	No reaction
5	TFE	105 °C, 12 h	60% conversion (~60% of **2.239** + traces of **2.246**)
6	TFE	105 °C, 24 h	90% conversion (85% of **2.239** + 5% of **2.246**)
7	TFE	105 °C, 36 h	95% conversion (80% of **2.239** + 15% of **2.246**)

[165] Büchi, G.; Manning, R. E.; Monti, S. A. *J. Am. Chem. Soc.* **1964**, *86*, 4631–4641.

Submitting our substrate **2.240** in refluxing xylene gave, after 12 h, 70% consumption of the starting materials (Table 3, entry 1). A complex mixture of products was obtained but the formation of the desired carbon – nitrogen bond was observed in ~10% based on crude ^{1}H NMR analysis. When a lower reaction temperature was employed, no conversion was observed, even in the presence of molecular sieves to trap the generated water (entry 2).

Based on the previous report, the use of a strong acid is not advisable for the reaction. However, we decided to try slightly acidic conditions to help the dehydration step while avoiding the protonation of the amine. Fluorinated solvents such as HFIP and TFE, with a pka of 9.3 and 12.4 respectively, were the best candidates for our desired transformation.[166] When **2.240** was heated in HFIP to only 80 °C, complete conversion was observed after 24 h (entry 3). Under these conditions, even though the reaction was not clean, the desired product was the major one. Unfortunately, the conversion was not reproducible as the second time the reaction was attempted, only 60% of the starting material was consumed after 36 h. With TFE, no reaction was however observed at 80 °C (entry 4). Due to its lower acidity compared to HFIP, a higher temperature was thus necessary. Finally, when a solution of **2.240** in TFE was heated to 105 °C, good conversion into desired product **2.239** was obtained and the reaction was by far cleaner than in previous experiments (entries 5 to 7). However, under these conditions, isomerization of the conjugated lactone moiety in desired pentacycle **2.239** was also observed. Thus, a balance between the consumption of alcohol **2.240** and the unwanted isomerization to side product **2.246** was required. After 12 h of reaction, 60% conversion was observed with traces of the isomer, whereas after 24 h, 90% conversion with 5% of unwanted **2.246** was obtained. After 36 h, only 5% more conversion was noted but a significant amount of isomer **2.246** was formed (15%). As a consequence, we decided that a reaction time of 24 h was the best compromise.

Some purification issues were then encountered on silica gel, neutralized or not, involving the partial decomposition of the product. This problem was solved by using alumina instead and the desired *N*(1)-demethyl-3,5-diepi-alstolactone (**2.239**) was isolated in 79% yield (Scheme 141).

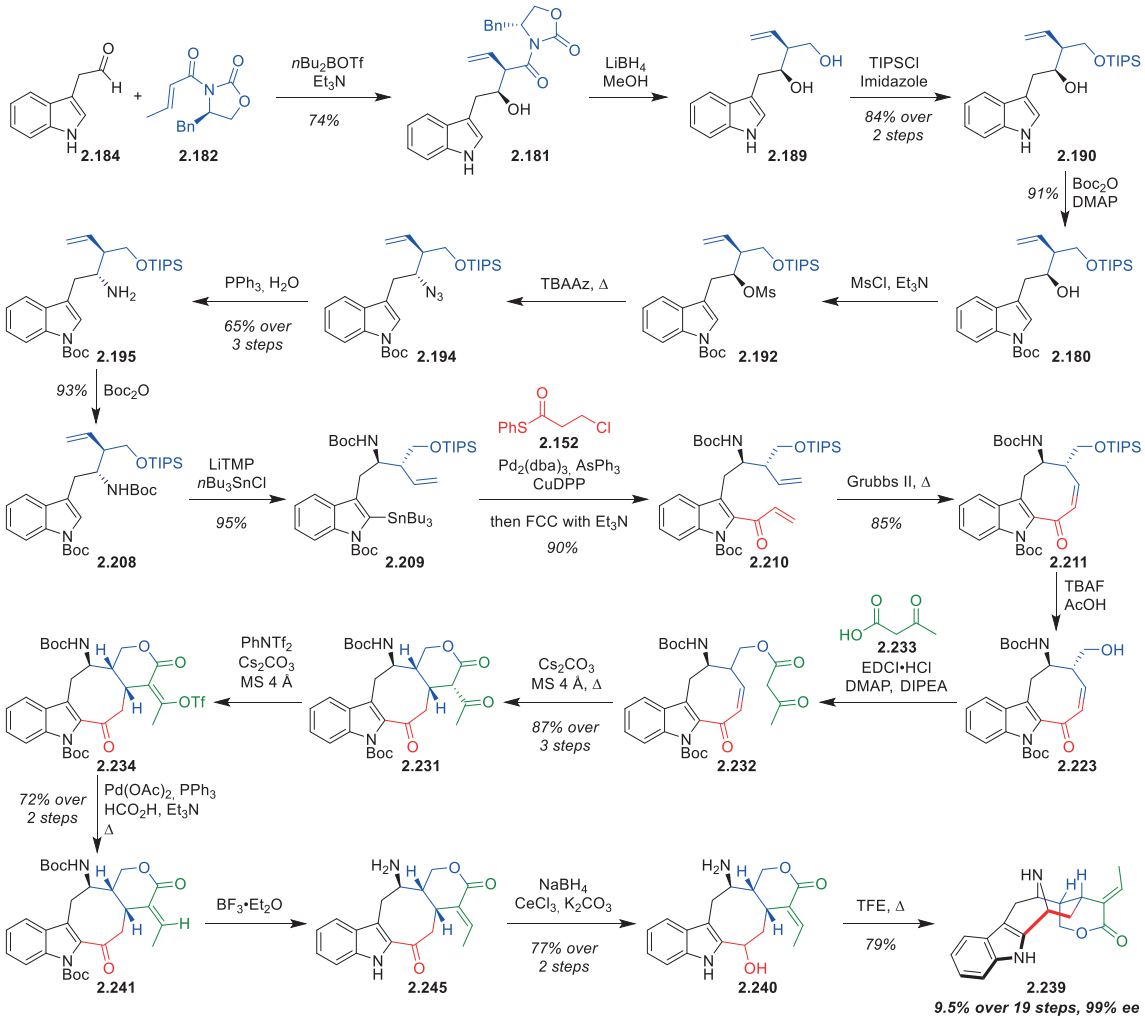


*Scheme 141 Synthesis of targeted N(1)-demethyl-3,5-diepi-alstolactone (**2.239**)*

[166] Filler, R.; Schure, R. M. *J. Org. Chem.* **1967**, *32*, 1217–1219.

6.3. Overview of the Total Synthesis of *N*(1)-demethyl-3,5-diepi-alstolactone

To develop the enantioselective total synthesis of *N*(1)-demethyl-3,5-diepi-alstolactone (**2.239**), a long journey was necessary. As the different parts of the synthesis were dispatched between chapters, the Scheme 142 regroups all the transformations leading to **2.239**. In spite of the 19 steps that were required, the product was obtained in a remarkable overall yield of 9.5% with 99% ee.



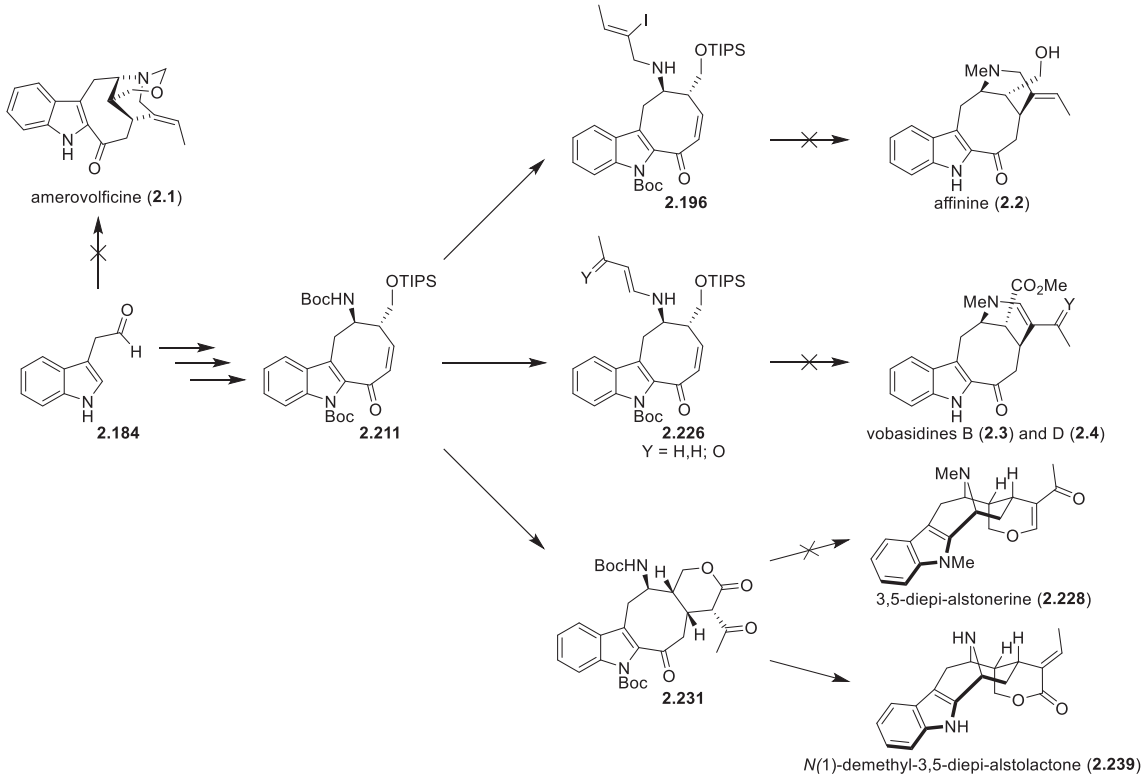
*Scheme 142 Enantioselective total synthesis of N(1)-demethyl-3,5-diepi-alstolactone (**2.239**)*

Conclusion

Our synthetic studies towards sarpagine-related indoles started with amerovolficine (**2.1**) as a target. Four strategies in total were explored to reach this vobasine-based natural product. In the first three, difficulties were encountered during the synthesis of the key intermediates. With the more promising fourth approach, issues relating to the control of the desired relative stereochemistry forced us to pause the synthesis of **2.1**.

However, this last route provided the diastereoselectivity for the synthetic studies concerning the antipode of affinine (**2.2**). From aldehyde **2.184** and imide **2.182**, the advanced 8-membered cyclic enone **2.211** was synthesized in 25% yield over 11 steps. Selective deprotection of the Boc-amine in the presence of sensitive Boc-indole followed by subsequent allylation furnished key vinyl iodide **2.196** in 69% yield over 3 steps. After intensive screening of the reaction conditions and modifications of the initial substrate, the desired intramolecular 1,4-addition reaction to form the bridged system could not be accomplished.

With the same strategy in mind, enamin(on)e **2.226** was synthesized from common intermediate **2.211** in order to reach vobasidines B (**2.3**) and D (**2.4**). Once more, the desired cyclization could not be achieved under various conditions.



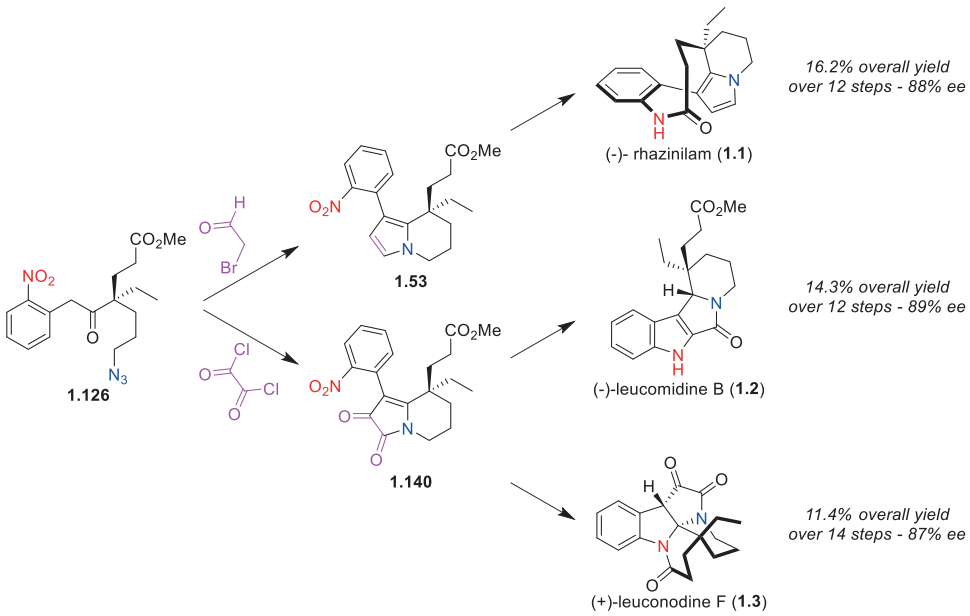
Scheme 143 Overview of the synthetic studies towards the sarpagine-type indoles discussed in the second part

We then moved to an approach towards the synthesis of macroline-based indoles. 3,5-Diepi-alstonerine (**2.228**) was chosen as a first target to explore the feasibility of forming the required bridged azabicyclo[3.3.1]nonane system from 8-membered cyclic enone **2.211**. After deprotection of the alcohol and subsequent esterification with acetoacetic acid, an intramolecular 1,4-addition reaction was carried out with excellent diastereoselectivity to deliver the *cis*-fused rings system in **2.231** in 87% yield over 3 steps. The following steps, involving a reduction / cyclization sequence, failed due to the instability of the intermediates.

Finally, we shifted our synthetic studies towards *N*(1)-demethyl-3,5-diepi-alstolactone (**2.239**), closely related to **2.228**. Triflation of 1,3-ketolactone **2.231** and reduction of the resulting vinyl triflate afforded corresponding conjugated lactone **2.241** in 72% yield over 2 steps, with a remarkable control of the desired (*E*)-configuration. After removal of both *N*-protecting groups, chemoselective reduction of the ketone, without reduction of the conjugated lactone moiety, furnished alcohol **2.240** in 77% yield over 2 steps. Thermolysis of the latter under slightly acidic conditions afforded the desired bridged system **2.239** in 79% yield *via* a dehydration / transannulation process. From aldehyde **2.184** and imide **2.182**, the desired *N*(1)-demethyl-3,5-diepi-alstolactone (**2.239**) was synthesized in 19 steps and in a noteworthy 9.5% overall yield with 99% ee.

General Conclusion

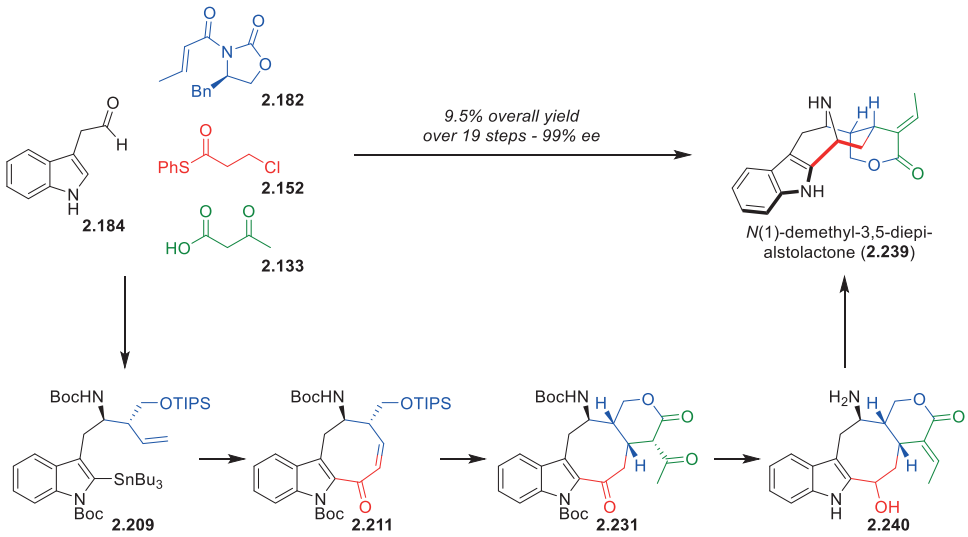
In conclusion, we developed a divergent total synthesis of three structurally distinct natural products of the *Aspidosperma* family: (-)-rhazinilam (**1.1**), (-)-leucomidine B (**1.2**) and (+)-leuconodine F (**1.3**) (Scheme 144). First, from advanced intermediate **1.126**, tetrahydroindolizine **1.53** was synthesized in a one-pot fashion *via* a tandem Staudinger / aza-Wittig reaction followed by formal [3+2] cycloaddition of the resulting tetrahydropyridine **1.129** with 2-bromoacetaldehyde. Compound **1.53** was then converted into (-)-rhazinilam (**1.1**) by way of a reduction / hydrolysis / lactamization sequence.



Scheme 144 Divergent total synthesis of (-)-rhazinilam, (-)-leucomidine B and (+)-leuconodine F

1,3-Dioxopyrrole **1.140**, a precursor towards (-)-leucomidine B (**1.2**) and (+)-leuconodine F (**1.3**), was next obtained by reacting the same cyclic imine **1.129** with oxalyl chloride as cycloaddition partner. In order to control the second stereogenic center in **1.2**, a substrate-directed diastereoselective hydrogenation of the sterically unbiased double bond was accomplished by coordination of the acid derivative of ester **1.140** with a homogeneous palladium catalyst. The nitroaryl moiety was reduced under the same reaction conditions and the resulting aniline condensed spontaneously onto the ketone to form the indole core, which after one-pot esterification, afforded **1.2**. In the case of **1.3**, the dioxopyrrole moiety in **1.140** was protected against reductive conditions by taking advantage of its intrinsic sensitivity towards nucleophiles. We were then able to perform a hydrolysis / reduction sequence followed by lactamization and one-pot acid-catalyzed transannulation to furnish desired **1.3**.

Next, we moved to the synthetic studies towards the *Sarpagan* family. After the exploration of several strategies and natural products, we accomplished the enantioselective total synthesis of the macroline-related *N*(1)-demethyl-3,5-diepi-alstolactone (**2.239**) (Scheme 145). First, the advanced 8-membered cyclic enone **2.211** was synthesized from **2.209** *via* incorporation of the vinyl ketone unit, using the mild Liebeskind-Srogl coupling with thioester **2.152**, followed by ring-closing metathesis of the resulting diene. After alcohol deprotection of **2.211** and esterification with acetoacetic acid **2.133**, the key intramolecular 1,4-addition reaction of the corresponding 1,3-ketoester onto the enone function occurred with complete diastereoselectivity to afford the *cis*-fused rings system **2.231**. The subsequent conversion of the ketolactone moiety in **2.231** into the corresponding conjugated lactone was achieved with excellent (*E*)-selectivity *via* a triflation / Pd-catalyzed reduction sequence. After Boc-deprotections and chemoselective reduction of the ketone to alcohol **2.240**, the second key cyclization, involving a dehydration / transannulation process, was accomplished under slightly acidic and thermal conditions to afford the desired bridged system **2.239**.



Scheme 145 Enantioselective total synthesis of N(1)-demethyl-3,5-diepi-alstolactone

For the future work, it would be interesting to develop a new route for the synthesis of the starting materials in order to obtain the desired relative stereochemistry and therefore access the natural product alstolactone (**2.6**). The early incorporation of the methyl group on the indole nitrogen should also be considered as the late-stage methylation would be a difficult task. Indeed, the selective indole methylation in presence of secondary amine has been reported *via* the deprotonation of the indole core with a strong base. However, double bond isomerization of the conjugated lactone moiety could occur under these conditions.

For a more personal point of view, the PhD was a fantastic experience. I had the opportunity to develop and improve my skills on a panoply of reactions and on a wide range of scale (from 0.3 mol to 3 μmol). With the thesis itself and the various MOM (Molecule Of the Month) meetings organized by the different groups in organic chemistry, I also had the occasion to develop better analytical capabilities and a critical mind in order to design viable retrosyntheses and corresponding forward syntheses. Along the way, I had the privilege to work with amazing people and in a good working atmosphere. I would like once again to thank Pr. Jieping Zhu for having given me the opportunity to grow as a chemist and as a person among his group and under his expert guidance.

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Experimental Part

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 in a glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) and stirring unless otherwise noted. When needed, the glassware was dried overnight in an oven (T > 100 °C) or under vacuum with a heat gun (T > 200 °C).

When solvents were indicated as dry they were either purchased as such, distilled prior to use or dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubbs' design[1]. Only CF_3CH_2OH was dried by stirring over molecular sieves 3 Å for several hours and then filtered under argon. When solvents were indicated as degassed they were evacuated and refilled with argon multiple times under vigorous stirring.

Flash column chromatography was performed using SiliaFlash® P60 (SiliCycle) silica: 40-63 µm (230-400 mesh) silica.

Reactions were monitored using Merck Kieselgel 60F254 aluminium plates. TLC were visualized by UV fluorescence (254 nm) then one of the following: phosphomolybdic acid (mainly), ninhydrin, p-anisaldehyde, vanillin or $KMnO_4$.

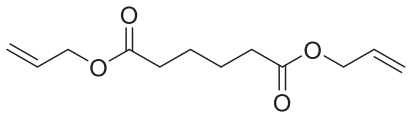
NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DPX-400 spectrometer at room temperature, ^1H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (*ref: $CDCl_3$ [^1H: 7.26, ^{13}C: 77.2], CD_3OD [^1H: 3.31, ^{13}C: 49.0], $(CD_3)_2CO$ [^1H: 2.05, ^{13}C: 29.8 & 206.3]*). 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, COSY and/or HSQC and/or HMBC experiments were carried out 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 were reported in cm^{-1}. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

(*S*)-tBuPHOX was synthesized following the procedure described in the literature.[2]

Experimental Procedures and Characterization Data of PART I

*Diallyl adipate (**1.116**)*

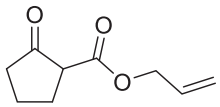


To a suspension of adipic acid (30.0 g, 205.3 mmol, 1.0 equiv) in allyl alcohol (210 mL, 3080 mmol, 15.0 equiv) at 0 °C was added dropwise TMSCl (105.0 mL, 821.2 mmol, 4.0 equiv). The mixture was warmed to rt and stirred for 12 h. Volatiles were then removed under reduced pressure. The residue was dissolved in EtOAc, washed with a saturated aqueous solution of $NaHCO_3$ (twice) and with brine (once), dried over Na_2SO_4, filtered and concentrated until dryness to afford 46.4 g (quantitative yield) of pure diallyl adipate (**1.116**) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 5.91 (ddt, *J* = 17.1, 10.5, 5.5 Hz, 2H), 5.31 (dq, *J* = 17.1, 1.5 Hz, 2H), 5.23 (dq, *J* = 10.5, 1.5 Hz, 2H), 4.57 (dt, *J* = 5.5, 1.5 Hz, 4H), 2.39-2.33 (m, 4H), 1.74-1.63 (m, 4H).

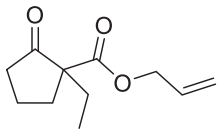
^{13}C NMR (100MHz, $CDCl_3$): δ 173.1 (2Cq), 132.4 (2C), 118.4 (2C), 65.2 (2C), 34.0 (2C), 24.5 (2C).

*Allyl 2-oxocyclopentane-1-carboxylate (**1.117**)*



To a suspension of NaH (60 wt.% in mineral oil, 9.04 g, 225.6 mmol, 1.1 equiv) in toluene (120 mL) at 0 °C was added dropwise allyl alcohol (4.20 mL, 61.5 mmol, 0.3 equiv). The mixture was warmed to rt and a solution of diallyl adipate (**1.116**, 46.4 g, 205.1 mmol, 1.0 equiv) in toluene (60 mL) was added dropwise. The resulting mixture was stirred at rt for 10 min and then at 95 °C for 1.5 h. The mixture was cooled to rt, diluted with water, acidified with 2 N HCl until pH 2-3 and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated until dryness. The crude β-keto ester **1.117** was used directly in the next step.

*Allyl 1-ethyl-2-oxocyclopentane-1-carboxylate (**1.114**)*



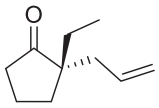
To a solution of crude β-keto ester **1.117** (205.1 mmol, 1.0 equiv) in acetone (300 mL, 0.67 M) were added K_2CO_3 (56.7 g, 410.2 mmol, 2.0 equiv) and ethyl iodide (33.0 mL, 410.2 mmol, 2.0 equiv). The resulting mixture was stirred at 50 °C for 12 h. Another portion of K_2CO_3 (28.3 g, 205.1 mmol, 1.0 equiv) and ethyl iodide (16.5 mL, 205.1 mmol, 1.0 equiv) were added and the mixture was stirred at 50 °C for additional 24 h. The mixture was cooled to rt and filtered. The filter cake was washed with acetone and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with brine (twice), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 10/1) afforded 31.0 g (77% yield over 2 steps) of allyl β-keto ester **1.114** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 5.87 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.59 (dt, *J* = 5.6, 1.4 Hz, 2H), 2.56 – 2.46 (m, 1H), 2.45 – 2.36 (m, 1H), 2.30 – 2.20 (m, 1H), 2.05 – 1.86 (m, 4H), 1.65 (dq, *J* = 13.9, 7.5 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 215.0 (Cq), 170.9 (Cq), 131.9, 118.5, 65.9, 61.1, 38.3, 32.4, 26.9, 19.7, 9.4.

The spectroscopic data of this compound are in agreement with these reported in the literature.[3]

*(S)-2-Allyl-2-ethylcyclopentan-1-one (**1.113**)*



In a dried flask under Ar were added [$Pd_2(dba)_3$] (583.3 mg, 0.637 mmol, 0.025 equiv) and (*S*)-tBuPHOX (617.0 mg, 1.59 mmol, 0.0625 equiv). The flask was evacuated for 10 min and refilled with THF (dry and degassed, 408 mL, 0.063 M) *via* cannula. The flask was purged 3 times (vacuum-Ar) and stirred at 25 °C (oil bath at 28 °C) for 30 min. Then neat allyl β-keto ester **1.114** (5.00 g, 25.5 mmol, 1.0 equiv) was added in one portion by syringe and the flask was purged again 3 times (vacuum-Ar). The resulting mixture was stirred at 25 °C (oil bath at 27 °C) for 3 h. The mixture was concentrated under reduced pressure (water bath at 25 °C) and purified by FCC (PE/EtOAc: 20/1) to afford 3.37 g (87% yield) of volatile alkene **1.113** as a colorless oil.

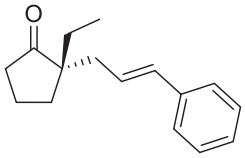
^{1}H NMR (400MHz, $CDCl_3$): δ 5.75 – 5.60 (m, 1H), 5.07 – 5.05 (m, 1H), 5.04 – 5.01 (m, 1H), 2.23 – 2.17 (m, 2H), 2.15 (m, 2H), 1.91 – 1.79 (m, 4H), 1.46 (q, *J* = 7.5 Hz, 2H), 0.83 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 223.1 (Cq), 134.2, 118.1, 52.1 (Cq), 39.5, 38.7, 32.4, 28.0, 18.9, 8.6.

$[\alpha]_D^{24}$ = -20 (*c* 0.5, CH_2Cl_2); lit. $[\alpha]_D^{25.2}$ = -18.55 (*c* 1.050, CH_2Cl_2, 86% ee).

The spectroscopic data of this compound are in agreement with these reported in the literature.[3]

*(S)-2-Cinnamyl-2-ethylcyclopentan-1-one (**1.118**)*



In a dried flask under Ar charged with alkene **1.113** (60.0 mg, 0.394 mmol, 1.0 equiv) in CH_2Cl_2 (dry and degassed, 20 mL, 0.02 M) were added styrene (74 µL, 0.788 mmol, 2.0 equiv) and Grubbs 2nd generation catalyst (33.1 mg, 0.039 mmol, 0.1 equiv). The resulting mixture was stirred at rt for 12 h. The mixture was diluted with 1 N HCl and extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 25/1) afforded 36.2 mg (40% yield) of compound **1.118** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 4H), 7.25 – 7.16 (m, 1H), 6.40 (dt, *J* = 15.6, 1.3 Hz, 1H), 6.10 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.39 – 2.26 (m, 2H), 2.24 (m, 2H), 1.96 – 1.83 (m, 4H), 1.52 (dq, *J* = 7.5, 1.4 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 223.2 (Cq), 137.5 (Cq), 133.2, 128.7 (2C), 127.3, 126.2 (2C), 125.9, 52.6 (Cq), 38.7 (2C), 32.4, 28.3, 18.9, 8.7.

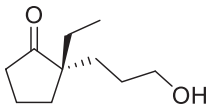
IR: υ (cm^{-1}) 3027 (w), 2963 (w), 2882 (w), 1730 (s), 1454 (w), 1161 (w), 970 (m), 741 (s), 695 (s).

HRMS: (ESI) calcd for $C_{16}H_{21}O^+$ $[M+H]^+$ 229.1587; found 229.1592.

e.r: 93/7 – **ee** = 86%

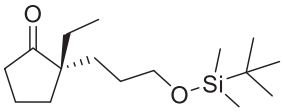
$[\alpha]_D^{26}$ = -47 (*c* 0.7, $CHCl_3$)

*(S)-2-Ethyl-2-(3-hydroxypropyl)cyclopentan-1-one (**1.119**)*



In a dried flask under Ar charged with BH_3•THF (1 M in THF, 52.6 mL, 52.6 mmol, 2.5 equiv) at 0 °C was added dropwise 2-methylbut-2-ene (12.3 mL, 115.6 mmol, 5.5 equiv). The resulting mixture was stirred at 0 °C for 3 h. In a second dried flask under Ar charged with alkene **1.113** (3.20 g, 21.0 mmol, 1.0 equiv) in dry THF (42 mL, 0.5 M) at 0 °C was added dropwise the *in-situ* prepared disiamylborane by cannula. The resulting mixture was stirred at rt for 2 h. Then H_2O_2 (30% in H_2O, 21 mL, 1 mL/mmol) and NaOH (15% in H_2O, 21 mL, 1 mL/mmol) were carefully added dropwise at 0 °C and the mixture was stirred vigorously at rt for 1 h. The mixture was diluted with brine and extracted with EtOAc (4 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated until dryness. The crude alcohol **1.119** was used directly in the next step.

*(S)-2-(3-((tert-Butyldimethylsilyl)oxy)propyl)-2-ethylcyclopentan-1-one (**1.120**)*



To a solution of crude alcohol **1.119** (21.0 mmol, 1 equiv) in DMF (21 mL, 1 M) were added imidazole (2.15 g, 32.5 mmol, 1.5 equiv) and TBSCl (3.80 g, 25.2 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 12 h. The mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 20/1) afforded 5.08 g (85% yield over 2 steps) of ketone **1.120** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 3.55 (t, *J* = 6.1 Hz, 2H), 2.25 – 2.18 (m, 2H), 1.91 – 1.78 (m, 4H), 1.56 – 1.29 (m, 6H), 0.88 (s, 9H), 0.82 (t, *J* = 7.5 Hz, 3H), 0.03 (s, 6H).

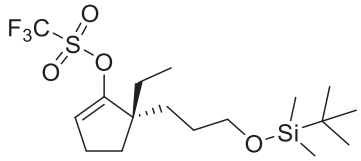
^{13}C NMR (100MHz, $CDCl_3$): δ 223.5 (Cq), 63.6, 51.7 (Cq), 38.5, 33.3, 30.8, 27.7, 27.6, 26.1 (3C), 18.8, 18.5 (Cq), 8.6, -5.1 (2C).

IR: υ (cm^{-1}) 2954 (w), 2930 (w), 2857 (w), 1735 (m), 1462 (w), 1254 (w), 1097 (s), 835 (s), 775 (s).

HRMS: (ESI) calcd for $C_{16}H_{33}O_2Si^+$ $[M+H]^+$ 285.2244; found 285.2233.

$[\alpha]_D^{27}$ = -3 (*c* 1.0, $CHCl_3$)

*(S)-5-(3-((tert-Butyldimethylsilyl)oxy)propyl)-5-ethylcyclopent-1-en-1-yl trifluoromethanesulfonate (**1.111**)*



In a dried flask under Ar charged with ketone **1.120** (4.72 g, 16.6 mmol, 1.0 equiv) in dry THF (33 mL, 0.5 M) at -78 °C was added dropwise LiHMDS (1 M in THF, 18.3 mL, 18.3 mmol, 1.1 equiv). The resulting mixture was stirred at -78 °C for 45 min. Then a solution of $PhNTf_2$ (7.11 g, 19.9 mmol, 1.2 equiv) in dry THF (33 mL) was added dropwise at -78 °C and the mixture was stirred for 12 h while slowly warming to rt. The mixture was diluted with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 40/1) afforded 6.37 g (92% yield) of vinyl triflate **1.111** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 5.62 (t, *J* = 2.6 Hz, 1H), 3.66 – 3.53 (m, 2H), 2.38 – 2.24 (m, 2H), 1.89 – 1.77 (m, 2H), 1.56 – 1.37 (m, 6H), 0.89 (s, 9H), 0.87 (t, *J* = 7.6 Hz, 3H), 0.04 (s, 6H).

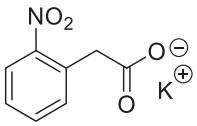
^{13}C NMR (100MHz, $CDCl_3$): δ 152.5 (Cq), 118.6 (q, *J* = 320.1 Hz, Cq), 113.9, 63.5, 50.5 (Cq), 33.7, 30.4, 30.2, 27.8, 26.3, 26.1 (3C), 18.5 (Cq), 8.5, -5.19, -5.17.

IR: υ (cm^{-1}) 2954 (w), 2932 (w), 2859 (w), 1658 (w), 1422 (m), 1250 (m), 1209 (s), 1142 (s), 1101 (m), 1074 (m), 835 (s), 775 (m).

HRMS: (ESI) calcd for $C_{17}H_{32}F_3O_4SSi^+$ $[M+H]^+$ 417.1737; found 417.1746.

$[\alpha]_D^{25}$ = +9 (*c* 1.0, $CHCl_3$)

*Potassium 2-(2-nitrophenyl)acetate (**1.112**)*



To a solution of 2-nitrophenylacetic acid (30.0 g, 165.6 mmol, 1.0 equiv) in EtOH (330 mL, 0.5 M) at rt was added dropwise a solution of *t*-BuOK (18.6 g, 165.6 mmol, 1.0 equiv) in EtOH (330 mL, 0.5 M). The resulting mixture was stirred at rt for 1 h and volatiles were then removed under

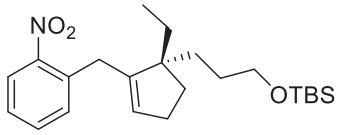
reduced pressure. The resulting solid was washed several times with Et_2O and dried under vacuum to afford 36.4 g (quantitative yield) of potassium carboxylate **1.112** as a white solid.

^{1}H NMR (400MHz, CD_3OD): δ 7.98 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.64 – 7.51 (m, 1H), 7.49 – 7.35 (m, 2H), 3.88 (s, 2H).

^{13}C NMR (100MHz, CD_3OD): δ 177.5 (Cq), 150.9 (Cq), 134.9 (Cq), 134.3, 134.0, 128.3, 125.6, 43.7.

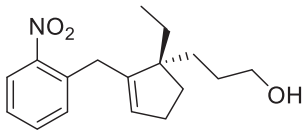
The spectroscopic data of this compound are in agreement with these reported in the literature.[4]

*(S)-tert-Butyl(3-(1-ethyl-2-(2-nitrobenzyl)cyclopent-2-en-1-yl)propoxy)dimethylsilane (**1.110**)*



A dried flask under Ar was charged with potassium carboxylate **1.112** (3.95 g, 18.0 mmol, 2.5 equiv), $[PdCl(allyl)]_2$ (131.7 mg, 0.360 mmol, 0.05 equiv) and X-PHOS (514.9 mg, 1.08 mmol, 0.15 equiv) and was then evacuated for 10 min. The flask was refilled with Ar and a solution of vinyl triflate **1.111** (3.00 g, 7.20 mmol, 1.0 equiv) in diglyme (72 mL, 0.1 M) was added. The resulting suspension was purged 3 times (vacuum-Ar) and quickly warmed to 140 °C. The mixture was stirred for 2 h while the solution turned to black and CO_2 evolution was observed. The mixture was cooled to rt, diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered through a pad of Celite® and concentrated under reduced pressure (water bath at 60 °C). Purification by FCC (PE/EtOAc: 40/1) afforded 2.11 g of an inseparable mixture of cyclopentene **1.110** and 2-nitrotoluene (1/1.2 based on ^{1}H NMR) corresponding to 1.50 g (~52% yield) of cyclopentene **1.110**. The mixture was used directly in the next step.

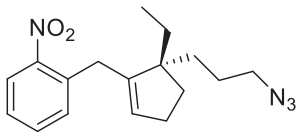
*(S)-3-(1-Ethyl-2-(2-nitrobenzyl)cyclopent-2-en-1-yl)propan-1-ol (**1.124**)*



In a flask under Ar charged with cyclopentene **1.110** (1.50 g, 3.72 mmol, 1.0 equiv) in MeOH (15 mL, 0.25 M) was added dropwise AcCl (53 µL, 0.744 mmol, 0.2 equiv). The resulting mixture

was stirred at rt for 1 h and volatiles were then removed under reduced pressure. The crude alcohol **1.124** was used directly in the next step.

(S)-1-((5-(3-Azidopropyl)-5-ethylcyclopent-1-en-1-yl)methyl)-2-nitrobenzene (1.125)



In a flask under Ar charged with crude alcohol **1.124** (3.72 mmol, 1.0 equiv) in DMF (37 mL, 0.1 M) were added dropwise Et_3N (1.04 mL, 7.44 mmol, 2.0 equiv) and then MsCl (0.432 mL, 5.58 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 5 h. Then NaN_3 (725.5 mg, 11.2 mmol, 3.0 equiv) was added portionwise and the mixture was stirred vigorously at rt for additional 12 h. The mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 40/1) afforded 980.0 mg (~84% yield over 2 steps / 43% yield over 3 steps) of cyclopentene **1.125** as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.91 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.38 (dt, *J* = 8.2, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.79 (quint, *J* = 2.1 Hz, 1H), 3.55 – 3.40 (m, 2H), 3.36 – 3.22 (m, 2H), 2.11 (m, 2H), 1.86 – 1.67 (m, 2H), 1.64 – 1.42 (m, 6H), 0.86 (t, *J* = 7.4 Hz, 3H).

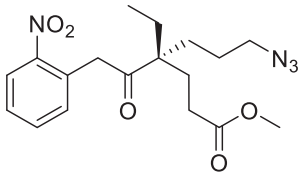
^{13}C NMR (100MHz, $CDCl_3$): δ 149.9 (Cq), 145.7 (Cq), 135.1 (Cq), 133.2, 132.9, 127.4, 127.1, 124.8, 53.6 (Cq) , 52.4, 36.0, 32.5, 31.6, 31.1, 30.7, 24.2, 8.7.

IR: υ (cm^{-1}) 2939 (w), 2852 (w), 2092 (s), 1525 (s), 1451 (w), 1349 (m), 1258 (w), 861 (w), 784 (m), 717 (m).

HRMS: (APPI) calcd for $C_{17}H_{22}N_4O_2$ [M+] 314.1743; found 314.1738.

$[\alpha]_D^{24}$ = +29 (*c* 1.0, $CHCl_3$)

*Methyl (R)-7-azido-4-ethyl-4-(2-(2-nitrophenyl)acetyl)heptanoate (**1.126**)*



In a flask charged with cyclopentene **1.125** (980.0 mg, 3.12 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (4/1, 20 mL / 5 mL, 0.125 M) was added $NaHCO_3$ (78.6 mg, 0.935 mmol, 0.3 equiv) and the mixture was cooled to -78 °C. O_3 was bubbled until the yellow solution turned to blue (1-2 min). Ar was bubbled to remove excess of O_3 and the mixture was warmed to 0 °C. Ac_2O (1.18 mL, 12.5 mmol, 4.0 equiv) and then Et_3N (0.869 ml, 6.23 mmol, 2.0 equiv) were added and the resulting mixture was stirred at rt for 3 h. The mixture was diluted with water and extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 4/1) afforded 1.08 g (92% yield) of ketoester **1.126** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.09 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.30 (s, 2H), 3.66 (s, 3H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.25 – 2.16 (m, 2H), 2.06 – 1.96 (m, 2H), 1.79 – 1.64 (m, 4H), 1.50 – 1.40 (m, 2H), 0.85 (t, *J* = 7.5 Hz, 3H).

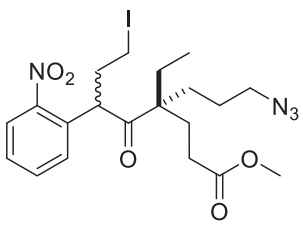
^{13}C NMR (100MHz, $CDCl_3$): δ 209.0 (Cq), 173.8 (Cq), 149.7 (Cq), 133.4, 133.3, 130.3 (Cq), 128.4, 125.3, 53.6 (Cq), 51.9 (2C), 43.4, 30.6, 28.8, 28.6, 26.8, 23.5, 8.23.

IR: υ (cm^{-1}) 2950 (w), 2879 (w), 2096 (s), 1735 (s), 1704 (m), 1526 (s), 1350 (s), 789 (w), 727 (m).

HRMS: (ESI) calcd for $C_{18}H_{25}N_4O_5^+$ $[M+H]^+$ 377.1819; found 377.1830.

$[\alpha]_D^{23}$ = -0.7 (*c* 1.0, $CHCl_3$)

*Methyl 4-(3-azidopropyl)-4-ethyl-8-iodo-6-(2-nitrophenyl)-5-oxooctanoate (**1.127**)*



In a dried flask under N_2 charged with ketoester **1.126** (100.0 mg, 0.266 mmol, 1.0 equiv) in dry DMF (5 mL, 0.05 M) at 0 °C was added NaH (60 wt.% in mineral oil, 11.7 mg, 0.292 mmol, 1.1 equiv) and the resulting mixture was stirred at 0°C for 30 min while the solution turned to blue. Phenyl vinyl selenone (62.9 mg, 0.292 mmol, 1.1 equiv) was added and the mixture was stirred at rt for 1 h. Another portion of phenyl vinyl selenone (62.9 mg, 0.292 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for additional 1 h. The mixture was cooled to 0 °C, acetic acid (46 µL, 0.797 mmol, 3.0 equiv) and sodium iodide (238.9 mg, 1.59 mmol, 6.0 equiv) were added and the resulting mixture was stirred at 40 °C for 1.5 h. The mixture was diluted with a half-saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/AcOEt : 5/1) afforded 84.5 mg (60% yield) of iodide **1.127** as a light yellow oil. A mixture of diastereoisomers in 1/1 ratio was observed based on ^{1}H NMR.

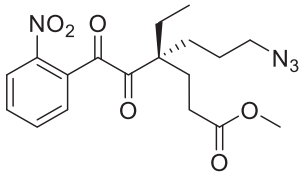
^{1}H NMR (400MHz, $CDCl_3$): δ 7.89 – 7.79 (m, 1H), 7.62 – 7.52 (m, 2H), 7.47 – 7.40 (m, 1H), 5.01 – 4.92 (m, 1H), 3.64 (s, 1.5H), 3.62 (s, 1.5H), 3.24 – 3.12 (m, 1H), 3.10 – 2.98 (m, 2H), 2.96 – 2.87 (m, 1H), 2.53 – 2.30 (m, 2H), 2.06 – 0.91 (m, 10H), 0.67 (t, *J* = 7.4 Hz, 1.5H), 0.61 (t, *J* = 7.4 Hz, 1.5H).

^{13}C NMR (100MHz, $CDCl_3$): δ 211.6 (Cq), 211.5 (Cq), 173.4 (Cq), 173.2 (Cq), 150.0 (Cq), 149.9 (Cq), 133.2, 131.13 (Cq), 131.10 (Cq), 129.4, 128.74, 128.71, 125.2, 125.1, 55.2 (Cq), 51.93, 51.90, 51.7, 51.5, 45.9, 45.8, 39.8, 29.9, 29.8, 28.9, 28.8, 27.7, 27.2, 26.4, 26.0, 23.6, 8.3, 8, 1.7, 1.6.

IR: υ (cm^{-1}) 2950 (w), 2878 (w), 2097 (s), 1737 (s), 1699 (m), 1527 (s), 1437 (w), 1352 (m), 1258 (w), 1174 (w), 788 (w), 745 (w).

HRMS: (ESI) calcd for $C_{20}H_{28}IN_4O_5^+$ $[M+H]^+$ 531.1099; found 531.1105.

*Methyl 7-azido-4-ethyl-4-(2-(2-nitrophenyl)-2-oxoacetyl)heptanoate (**1.83**)*



In a tube charged with ketoester **1.126** (100.0 mg, 0.266 mmol, 1.0 equiv) in DMF (5.3 mL, 0.05 M) was added portionwise 1,2-diiodoethane (82.4 mg, 0.292 mmol, 1.1 equiv) and then Cs_2CO_3 (190.4 mg, 0.584 mmol, 2.2 equiv). The resulting mixture was stirred at rt for 6 h. The mixture was diluted with a half-saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc

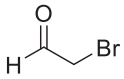
(3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 5/1) afforded 82.3 mg (79% yield) of diketone **1.83** as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.76 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.67 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.52 (dd, *J* = 1.2, 8.0 Hz, 1H), 3.63 (s, 3H), 3.34-3.24 (m, 2H), 2.21 (s, 4H), 2.00-1.92 (m, 4H), 1.53-1.40 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 200.6, 188.1, 173.8, 147.2, 134.7, 133.7, 131.9, 130.1, 123.8, 52.5, 51.8 (2C), 30.2, 28.7, 28.3, 26.1, 23.4, 8.1.

The spectroscopic data of this compound are in accord with these reported in the literature.[5]

*2-Bromoacetaldehyde (**1.131**)*

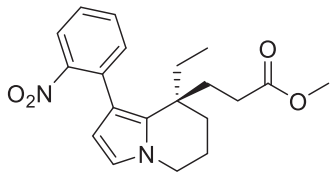


TFA (7.2 mL, 97.5 mmol, 3.0 equiv) was added dropwise to neat 2-bromo-1,1-diethoxyethane (5.0 mL, 32.5 mmol, 1.0 equiv) and the resulting mixture was stirred at rt for 12 h. The mixture was diluted with minimum of CH_2Cl_2 and carefully quenched with a saturated aqueous solution of $NaHCO_3$ until neutral pH. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure (water bath at 0 °C, P~100 mmbar) to remove most of CH_2Cl_2 and ethyl 2,2,2-trifluoroacetate formed during the reaction. The residue was then distilled with the receiving flask cooled at -78 °C. The distillation was started at 0 °C (P~100 mmbar) to remove remaining excess of CH_2Cl_2. The residue was then heated at 25 °C - 40 °C (P~5 mmbar) to afford 4.48 g of lachrymal 2-bromoacetaldehyde (**1.131**, 49 wt.% in CH_2Cl_2, ~55% yield).

^{1}H NMR (400MHz, $CDCl_3$): δ 9.54 (t, *J* = 2.6 Hz, 1H), 3.85 (d, *J* = 2.6 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 192.0, 34.8.

*Methyl (R)-3-(8-ethyl-1-(2-nitrophenyl)-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (**1.53**)*



In a dried sealed tube under Ar charged with ketoester **1.126** (100.0 mg, 0.266 mmol, 1.0 equiv) in CH_3CN (5.3 mL, 0.05 M) was added PPh_3 (76.7 mg, 0.292 mmol, 1.1 equiv). The resulting mixture was stirred at 70 °C for 3 days. The mixture was cooled to rt, $NaHCO_3$ (133.9 mg, 1.59 mmol, 6.0 equiv) and then 2-bromoacetaldehyde (**1.131**, 49 wt.% in CH_2Cl_2, 333.2 mg, 1.33 mmol, 5.0 equiv) were added and the mixture was stirred at 70 °C for additional 6 h. The mixture was cooled to rt, diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc/Et_3N: 30/10/0.5) afforded 72.0 mg (76% yield) of tetrahydroindolizine **1.53** as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.79 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.52 – 7.36 (m, 3H), 6.54 (d, *J* = 2.8 Hz, 1H), 6.02 (d, *J* = 2.8 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.60 (s, 3H), 2.30 – 2.12 (m, 2H), 1.99 – 1.83 (m, 2H), 1.79 – 1.71 (m, 1H), 1.71 – 1.63 (m, 2H), 1.62 – 1.50 (m, 2H), 1.38 (br. s, 1H), 0.76 (t, *J* = 7.5 Hz, 3H).

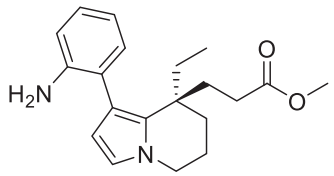
^{13}C NMR (100MHz, $CDCl_3$): δ 174.3 (Cq), 150.6 (Cq), 133.7, 133.4 (Cq), 131.1, 130.4 (Cq), 127.6, 123.7, 118.9, 114.6 (Cq), 110.6, 51.5, 46.1, 39.3 (Cq), 35.9, 34.8, 30.0 (2C), 21.2, 9.1.

IR: υ (cm^{-1}) 2952 (w), 2875 (w), 1734 (s), 1527 (s), 1352 (m), 1199 (m), 1171 (m), 754 (w), 697 (w).

HRMS: (ESI) calcd for $C_{20}H_{25}N_2O_4^+$ $[M+H]^+$ 357.1809; found 357.1813.

$[\alpha]_D^{24}$ = +66 (*c* 0.5, $CHCl_3$)

*Methyl (R)-3-(1-(2-aminophenyl)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (**1.132**)*



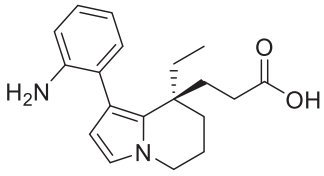
In a flask under Ar charged with tetrahydroindolizine **1.53** (60.0 mg, 0.168 mmol, 1.0 equiv) in MeOH (1.7 mL, 0.1 M) was added Pd/C (10 wt.%, 17.9 mg, 0.017 mmol, 0.1 equiv). The resulting mixture was stirred under H_2 atmosphere (1 atm) at rt for 30 min. The mixture was purged with Ar and filtered through a pad of Celite®. The filter cake was washed with MeOH (3 times) and the filtrate was concentrated until dryness. The crude aniline **1.132** as a colorless oil was used directly in the next step. A mixture of rotamers in 1/1 ratio was observed based on ^{1}H NMR.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.13 – 7.04 (m, 2H), 6.74 – 6.65 (m, 2H), 6.57 (d, *J* = 2.7 Hz, 1H), 6.02 (d, *J* = 2.7 Hz, 0.5H), 5.99 (d, *J* = 2.7 Hz, 0.5H), 3.98 – 3.84 (m, 2H), 3.74 – 3.53 (m, 5H), 2.27 (t, *J* = 8.1 Hz, 1H), 2.19 (t, *J* = 8.1 Hz, 1H), 2.04 – 1.83 (m, 2H), 1.81 – 1.65 (m, 3H), 1.64 – 1.34 (m, 3H), 0.82 (t, *J* = 7.4 Hz, 1.5H), 0.73 (t, *J* = 7.4 Hz, 1.5H).

^{13}C NMR (100MHz, $CDCl_3$): δ 174.6, 145.7, 131.7, 131.2, 131.1, 128.0, 124.5, 124.3, 119.1, 117.6, 117.5, 116.2, 114.9, 114.7, 110.3, 110.2, 51.7, 51.6, 46.3, 39.5, 39.4, 36.1, 34.6, 34.5, 33.4, 30.7, 30.4, 29.9, 29.8, 21.5, 21.2, 9.5, 9.4.

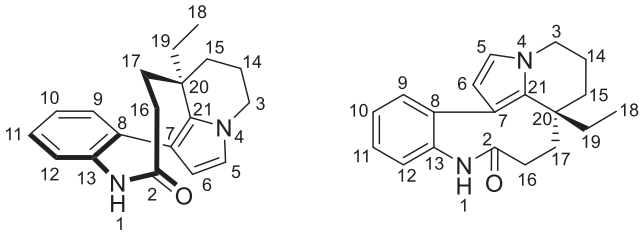
The spectroscopic data of this compound are in agreement with these reported in the literature.[6]

(R)-3-(1-(2-Aminophenyl)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoic acid (1.133)



In a flask charged with crude aniline **1.132** (55.0 mg, 0.168 mmol, 1.0 equiv) in MeOH (1.7 mL, 0.1 M) was added a solution of KOH (94.3 mg, 1.68 mmol, 10.0 equiv) in H_2O (1.7 mL, 1 M). The resulting mixture was stirred at rt for 12 h. The mixture was diluted with CH_2Cl_2 and 1 N HCl was added until pH 1-2. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (twice). The aqueous phase was saturated with NaCl and further extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4, filtered and concentrated until dryness. The crude amino acid **1.133** as an orange oil was used directly in the next step.

*(-)-Rhazinilam (**1.1**)*



In a dried flask under Ar charged with crude amino acid **1.133** (0.168 mmol, 1.0 equiv) in CH_2Cl_2 (8.4 mL, 0.02 M) were added Et_3N (94 µL, 0.672 mmol, 4.0 equiv), HOBt (34.1 mg, 0.252 mmol, 1.5 equiv) and EDCI.HCl (48.3 mg, 0.252 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 3 h. The mixture was diluted with 1 N HCl and extracted with CH_2Cl_2 (4 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 3/7) afforded 39.2 mg (79% yield over 3 steps) of (-)-rhazinilam (**1.1**) as a white powder.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.43 (dd, *J* = 7.4, 1.9 Hz, 1H^9), 7.38 – 7.27 (m, 2H^{10,11}), 7.21 (dd, *J* = 7.4, 1.2 Hz, 1H^{12}), 6.62 (s, 1H^1), 6.51 (d, *J* = 2.7 Hz, 1H^5), 5.76 (d, *J* = 2.7 Hz, 1H^6), 4.01 (dd, *J* = 12.1, 5.4 Hz, 1H^{3a}), 3.79 (dt, *J* = 12.1, 4.8 Hz, 1H^{3b}), 2.52 – 2.32 (m, 2H^{16a,17a}), 2.31 – 2.16 (m, 1H^{14a}), 2.00 – 1.92 (m, 1H^{16b}), 1.92 – 1.81 (m, 1H^{14b}), 1.72 (dt, *J* = 13.4, 3.1 Hz, 1H^{15a}), 1.58 – 1.41 (m, 3H^{15b,17b,19a}), 1.25 (dq, *J* = 14.5, 7.3 Hz, 1H^{19b}), 0.72 (t, *J* = 7.3 Hz, 3H^{18}).

^{13}C NMR (100MHz, $CDCl_3$): δ 177.5 (Cq^2), 140.5 (Cq^8), 138.2 (Cq^{13}), 131.6 (C^9), 130.7 (Cq^{21}), 128.1 (C^{11}), 127.4 (C^{10}), 127.0 (C^{12}), 119.3 (C^5), 117.4 (Cq^7), 109.7 (C^6), 46.2 (C^3), 39.0 (Cq^{20}), 36.8 (C^{17}), 33.2 (C^{15}), 30.3 (C^{19}), 28.2 (C^{16}), 19.6 (C^{14}), 8.3 (C^{18}).

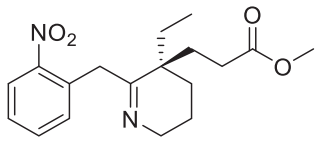
IR: υ (cm^{-1}) 3212 (w), 3056 (w), 2960 (w), 2915 (w), 2873 (w), 1667 (s), 1622 (w), 1393 (m), 1198 (m), 799 (m), 756 (s), 702 (s).

HRMS: (ESI) calcd for $C_{19}H_{23}N_2O^+$ $[M+H]^+$ 295.1805; found 295.1805.

e.r: 94/6 – **ee** = 88%

$[\alpha]_D^{25}$ = -365 (*c* 0.5, $CHCl_3$); lit.[7] $[\alpha]_D^{24}$ = -421 (*c* 0.973, $CHCl_3$)

Methyl (R)-3-(3-ethyl-2-(2-nitrobenzyl)-3,4,5,6-tetrahydropyridin-3-yl)propanoate (1.129)



In a dried sealed tube under Ar charged with ketoester **1.126** (200.0 mg, 0.531 mmol, 1.0 equiv) in CH_3CN (10.6 mL, 0.05 M) was added PPh_3 (167.2 mg, 0.635 mmol, 1.2 equiv). The resulting mixture was stirred at 70 °C for 4 days. The mixture was concentrated until dryness and purified by FCC (PE/EtOAc/Et_3N: 30/10/0.5) to afford 152.0 mg (86% yield) of imine **1.129** as an orange viscous oil (which solidified in the freezer).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.50 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.36 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.00 (s, 2H), 3.70 (s, 3H), 3.41 – 3.31 (m, 2H), 2.37 (ddd, *J* = 15.8, 11.4, 6.0 Hz, 1H), 2.26 (ddd, *J* = 15.8, 11.4, 4.6 Hz, 1H), 2.03 (ddd, *J* = 14.2, 11.4, 4.6 Hz, 1H), 1.83 (ddd, *J* = 14.2, 11.4, 5.8 Hz, 1H), 1.75 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.69 – 1.59 (m, 1H), 1.59 – 1.50 (m, 2H), 1.50 – 1.43 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

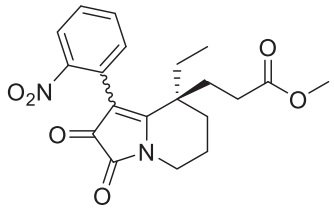
^{13}C NMR (100MHz, $CDCl_3$): δ 174.2 (Cq), 170.0 (Cq), 150.8 (Cq), 133.2 (Cq), 132.9, 132.8, 127.5, 124.6, 52.0, 49.6, 42.2 (Cq), 38.7, 33.9, 31.7, 29.7, 28.5, 20.0, 8.8.

IR: υ (cm^{-1}) 2938 (w), 2866 (w), 1734 (s), 1653 (w), 1526 (s), 1437 (w), 1355 (s), 1302 (w), 1196 (m), 1177 (m), 786 (w), 710 (m).

HRMS: (ESI) calcd for $C_{18}H_{25}N_2O_4^+$ $[M+H]^+$ 333.1809; found 333.1804.

$[\alpha]_D^{26}$ = -36 (*c* 0.5, $CHCl_3$)

Methyl (R)-3-(8-ethyl-1-(2-nitrophenyl)-2,3-dioxo-2,3,5,6,7,8-hexahydroindolizin-8-yl) propanoate (1.140)



In a dried flask under Ar charged with oxalyl chloride (28 µL, 0.331 mmol, 1.1 equiv) in dry CH_2Cl_2 (3 mL) at 0 °C was added dropwise a solution of imine **1.129** (100.0 mg, 0.301 mmol, 1.0 equiv) and Et_3N (105 µL, 0.752 mmol, 2.5 equiv) in dry CH_2Cl_2 (3 mL). The resulting mixture was stirred

at 0 °C for 5 min and then at rt for 1 h. The mixture was diluted with 2 N HCl and extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated until dryness to afford 116.0 mg (quantitative yield) of pure 2,3-dioxopyrrole **1.140** as a red oil. Due to an atropisomerism, a mixture of diastereoisomers in 1/1 ratio was observed based on ^{1}H NMR.

^{1}H NMR (400MHz, $CDCl_3$): 8.19 (dd, *J* = 8.2, 1.4 Hz, 0.5H), 8.12 (dd, *J* = 8.2, 1.4 Hz, 0.5H), 7.67 – 7.59 (m, 1H), 7.58 – 7.51 (m, 1H), 7.36 – 7.29 (m, 1H), 3.79 – 3.38 (m, 5H), 2.48 – 2.28 (m, 1H), 2.28 – 2.16 (m, 1H), 1.92 – 1.53 (m, 7H), 1.53 – 1.42 (m, 0.5H), 1.28 – 1.16 (m, 0.5H), 0.99 (t, *J* = 7.4 Hz, 1.5H), 0.78 (t, *J* = 7.4 Hz, 1.5H).

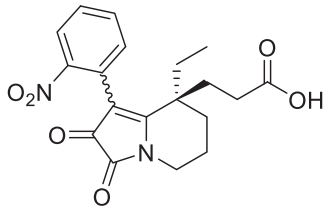
^{13}C NMR (100MHz, $CDCl_3$): 183.0 (Cq), 182.8 (Cq), 173.0 (Cq), 172.9 (Cq), 170.5 (Cq), 170.4 (Cq), 158.2 (Cq), 158.0 (Cq), 149.1 (Cq), 148.6 (Cq), 133.5 (2C), 133.4, 133.3, 129.99, 129.95, 126.2, 126.1, 125.8, 125.6, 109.2 (Cq), 108.7 (Cq), 52.1, 51.9, 41.84 (Cq), 41.78 (Cq), 40.0, 39.9, 34.0, 33.1, 32.6, 31.6, 29.8, 29.2, 27.7 (2C), 18.4, 18.2, 8.9, 8.4.

IR: υ (cm^{-1}) 2956 (w), 2880 (w), 1739 (s), 1718 (s), 1525 (s), 1392 (m), 1346 (s), 1174 (m), 727 (s).

HRMS: (ESI) calcd for $C_{20}H_{23}N_2O_6^+$ $[M+H]^+$ 387.1551; found 387.1562.

$[\alpha]_D^{24}$ = -82 (*c* 1.0, $CHCl_3$)

*(R)-3-(8-Ethyl-1-(2-nitrophenyl)-2,3-dioxo-2,3,5,6,7,8-hexahydroindolizin-8-yl)propanoic acid (**1.144**)*



To a solution of 2,3-dioxopyrrole **1.140** (116.0 mg, 0.301 mmol, 1.0 equiv) in THF (6 mL, 0.05 M) was added dropwise a solution of KOH (168.9 mg, 3.01 mmol, 10.0 equiv) in H_2O (6 mL, 0.5 M). The resulting mixture was stirred at rt for 12 h. The mixture was diluted with CH_2Cl_2 and 2 N HCl was added until pH 1-2. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc/AcOH: 10/40/0.5) afforded 97.7 mg of acid **1.144**. The product was contaminated with a small amount (<10%) of adducts, presumably formed by 1,4-addition to the 2,3-dioxopyrrole, which can be converted back to acid **1.144**. Thus, the residue was dissolved in toluene/CH_2Cl_2 (5/1) and TFA (~100 equiv) was added

dropwise. After stirring at rt for 1 h, volatiles were evaporated under reduced pressure and traces of TFA were removed by coevaporation with toluene (twice) to afford 97.2 mg (87% yield) of pure acid **1.144** as a red foam. Due to an atropisomerism, a mixture of diastereoismers in 1/1 ratio was observed based on ^{1}H NMR.

^{1}H NMR (400MHz, $(CD_3)_2CO$): δ 10.50 (br. s, 1H), 8.23 – 8.10 (m, 1H), 7.84 – 7.63 (m, 2H), 7.62 – 7.52 (m, 1H), 3.74 – 3.45 (m, 2H), 2.66 – 2.45 (m, 1H), 2.38 – 2.27 (m, 1H), 2.03 – 1.86 (m, 2.5H), 1.87 – 1.63 (m, 4.5H), 1.55 (dq, *J* = 14.8, 7.4 Hz, 0.5H), 1.33 (dq, *J* = 14.8, 7.4 Hz, 0.5H), 1.07 (t, *J* = 7.4 Hz, 1.5H), 0.82 (t, *J* = 7.4 Hz, 1.5H).

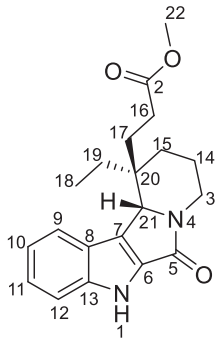
^{13}C NMR (100MHz, $(CD_3)_2CO$): δ 183.8 (Cq), 183.7 (Cq), 174.1 (Cq), 173.9 (Cq), 172.0 (Cq), 171.6 (Cq), 159.0 (Cq), 158.9 (Cq), 150.3 (Cq), 149.7 (Cq), 134.6, 134.5, 134.34, 134.31, 130.7, 130.6, 127.6, 127.5, 126.2, 125.9, 109.4 (Cq), 108.9 (Cq), 42.6 (Cq), 42.5 (Cq), 40.44, 40.39, 35.0, 33.6, 33.4, 32.7, 29.8 (overlapped with the acetone peak), 29.2 (overlapped with the acetone peak), 28.4, 28.1, 19.3, 18.8, 9.0, 8.6.

IR: υ (cm^{-1}) 3450-2500 (br), 2971 (w), 2882 (w), 1741 (s), 1711 (s), 1524 (s), 1392 (m), 1344 (s), 1174 (m), 725 (s).

HRMS: (ESI) calcd for $C_{19}H_{21}N_2O_6^+$ $[M+H]^+$ 373.1394; found 373.1402.

$[\alpha]_D^{25}$ = +52 (*c* 1.0, $CHCl_3$)

*(-)-Leucomidine B (**1.2**)*



In a dried flask under Ar charged with acid **1.144** (97.2 mg, 0.261 mmol, 1.0 equiv) in CF_3CH_2OH (dry and degassed, 10.5 mL, 0.025 M) at 0 °C was added $Pd(TFA)_2$ (8.7 mg, 0.026 mmol, 0.1 equiv). The resulting mixture was stirred under H_2 atmosphere (1 atm) for 12 h while slowly warming to rt. The solution initially red turned to yellow (double bond reduced) and finished colorless (double bond and nitro reduced). The mixture was purged with Ar and refluxed for 4 h to complete cyclization to indole. The mixture was cooled to 0 °C and $TMSCHN_2$ (2 M in hexane,

653 µL, 1.31 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C until complete esterification (< 5 min). The mixture was stirred at 0°C for additional 15 min to quench excess of $TMSCHN_2$ with CF_3CH_2OH. The mixture was filtered through a pad of Celite® and the filter cake was washed with MeOH (3 times). The filtrate was concentrated until dryness to afford crude (-)-leucomidine B (**1.2**) with a d.r of 12/1 based on ^1H NMR. The crude yellow solid was washed 3 times with cold MeOH (-20 °C) to afford (-)-leucomidine B (**1.2**) with 95% of purity (contaminated with 5% of the wrong diastereoisomer, corresponding to a d.r. of 20/1 based on ^1H NMR). The obtained whitish solid was purified by FCC (CH_2Cl_2/MeOH: 98/2) to afford 62.9 mg (71% yield) of pure (-)-leucomidine B (**1.2**) as a white powder.

^1H NMR (400MHz, $CDCl_3$): δ 10.88 (s, 1H[1]), 7.70 (dd, *J* = 8.1, 1.1 Hz, 1H[9]), 7.62 (dd, *J* = 8.3, 1.1 Hz, 1H[12]), 7.31 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H[11]), 7.20 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H[10]), 4.54 – 4.43 (m, 1H[3a]), 4.30 (s, 1H[21]), 3.80 (s, 3H[22]), 2.99 (ddd, *J* = 13.1, 11.5, 4.8 Hz, 1H[3b]), 2.78 – 2.65 (m, 1H[16a]), 2.63 – 2.51 (m, 1H[16b]), 2.26 – 2.14 (m, 2H[17]), 1.79 – 1.72 (m, 1H[15a]), 1.72 – 1.59 (m, 2H[14]), 1.58 – 1.48 (m, 1H[15b]), 1.15 (dq, *J* = 14.6, 7.4 Hz, 1H[19a]), 0.70 (dq, *J* = 14.6, 7.4 Hz, 1H[19b]), 0.57 (t, *J* = 7.4 Hz, 3H[18]).

^{13}C NMR (100MHz, $CDCl_3$): δ 174.3 (Cq[2]), 162.0 (Cq[5]), 141.8 (Cq[13]), 135.4 (Cq[6]), 126.8 (Cq[7]), 124.2 (C[11]), 122.2 (Cq[8]), 121.0 (C[10]), 120.7 (C[9]), 113.9 (C[12]), 63.3 (C[21]), 52.1 (C[22]), 39.7 (C[3] + Cq[20]), 32.4 (C[17]), 29.9 (C[15]), 29.0 (C[16]), 23.4 (C[19]), 20.9 (C[14]), 7.5 (C[18]).

^1H NMR (400MHz, $CDCl_3$/CD_3OD: 1/1): δ 7.67 (dd, *J* = 8.1, 1.1 Hz, 1H[9]), 7.49 (dd, *J* = 8.3, 1.1 Hz, 1H[12]), 7.26 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H[11]), 7.15 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H[10]), 4.35 (s, 1H[21]), 4.34 – 4.27 (m, 1H[3a]), 3.78 (s, 3H[22]), 2.98 (ddd, *J* = 13.1, 11.5, 4.8 Hz, 1H[3b]), 2.78 – 2.66 (m, 1H[16a]), 2.66 – 2.53 (m, 1H[16b]), 2.22 – 2.12 (m, 2H[17]), 1.79 – 1.73 (m, 1H[15a]), 1.72 – 1.61 (m, 2H[14]), 1.61 – 1.53 (m, 1H[15b]), 1.12 (dq, *J* = 14.6, 7.4 Hz, 1H[19a]), 0.66 (dq, *J* = 14.6, 7.4 Hz, 1H[19b]), 0.57 (t, *J* = 7.4 Hz, 3H[18]).

^{13}C NMR (100MHz, $CDCl_3$/ CD_3OD: 1/1): δ 175.3 (Cq[2]), 162.7 (Cq[5]), 142.2 (Cq[13]), 135.2 (Cq[6]), 127.5 (Cq[7]), 124.8 (C[11]), 122.5 (Cq[8]), 121.3 (C[10]), 121.0 (C[9]), 114.0 (C[12]), 63.4 (C[21]), 52.4 (C[22]), 40.2 (Cq[20]), 40.1 (C[3]), 32.7 (C[17]), 30.1 (C[15]), 29.2 (C[16]), 23.7 (C[19]), 21.2 (C[14]), 7.6 (C[18]).

IR: υ (cm^{-1}) 3110 (w), 3067 (w), 2947 (w), 2866 (w), 1730 (m), 1663 (s), 1427 (m), 1375 (w), 1283 (m), 1180 (w), 741 (s).

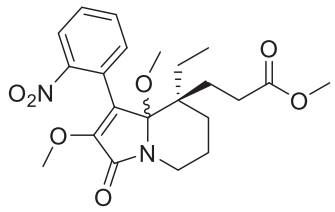
HRMS: (ESI) calcd for $C_{20}H_{25}N_2O_3^+$ $[M+H]^+$ 341.1860; found 341.1875.

e.r: 94.5/5.5 – **ee** = 89%

$[\alpha]_D^{27}$ = -21 (*c* 1.0, $CHCl_3$)

$[\alpha]_D^{27}$ = -29 (*c* 0.3, $CHCl_3$); lit.[8] $[\alpha]_D^{24}$ = -18 (*c* 0.3, $CHCl_3$)

*Methyl 3-((8R)-8-ethyl-2,8a-dimethoxy-1-(2-nitrophenyl)-3-oxo-3,5,6,7,8,8a-hexahydroindolizin-8-yl) propanoate (**1.152**)*



In a dried flask under Ar charged with 2,3-dioxopyrrole **1.140** (116.0 mg, 0.301 mmol, 1.0 equiv) in dry MeOH (15 mL, 0.02 M) was added DIPEA (262 µL, 1.51 mmol, 5.0 equiv). The resulting mixture was stirred at rt for 1 h. Then $TMSCHN_2$ (2 M in hexane, 753 µL, 1.51 mmol, 5.0 equiv) was added dropwise at 0 °C and the mixture was stirred at rt for additional 30 min. Excess of $TMSCHN_2$ was quenched by adding dropwise AcOH (172 µL, 3.01 mmol, 10.0 equiv) at 0 °C. Then 2/3 of MeOH was evaporated under reduced pressure and the mixture was diluted with CH_2Cl_2 and 1 N HCl. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 3/1) afforded 121.0 mg (93% yield) of compound **1.152** as a yellow oil. A mixture of diastereoisomers in 1/1 ratio was observed based on ^{1}H NMR.

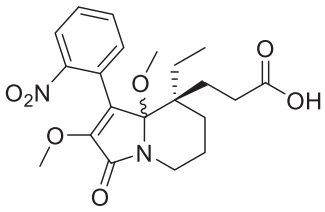
^{1}H NMR (400MHz, $CDCl_3$): δ 7.86 – 7.81 (m, 1H), 7.80 – 7.75 (m, 1H), 7.58 – 7.51 (m, 1H), 7.46 – 7.37 (m, 1H), 4.17 – 4.09 (m, 1H), 4.07 (s, 1.5H), 4.07 (s, 1.5H), 3.66 (s, 1.5H), 3.58 (s, 1.5H), 3.05 (s, 1.5H), 3.03 (s, 1.5H), 2.79 – 2.60 (m, 1.5H), 2.38 – 2.25 (m, 0.5H), 2.24 – 2.00 (m, 1.5H), 1.99 – 1.84 (m, 1H), 1.76 – 1.48 (m, 4.5H), 1.47 – 1.34 (m, 1.5H), 1.33 – 1.18 (m, 0.5H), 0.83 (t, *J* = 7.6 Hz, 1.5H), 0.76 (t, *J* = 7.6 Hz, 1.5H).

^{13}C NMR (100MHz, $CDCl_3$): δ 174.8 (Cq), 174.1 (Cq), 162.70 (Cq), 162.66 (Cq), 149.9 (Cq), 149.8 (Cq), 149.5 (Cq), 149.3 (Cq), 132.2, 131.9, 129.4, 129.2, 128.7, 128.6, 126.1 (Cq), 126.0 (Cq), 125.32, 125.27, 118.4 (Cq), 118.3 (Cq), 97.0 (Cq), 96.5 (Cq), 57.89, 57.87, 51.9, 51.6, 49.0, 43.98 (Cq), 43.96 (Cq), 35.9, 35.8, 30.4, 29.7, 29.6, 28.4, 28.0, 26.2, 25.5, 25.2, 20.1, 20.0, 9.8, 7.9.

IR: υ (cm^{-1}) 2956 (w), 2876 (w), 1735 (m), 1704 (s), 1641 (m), 1532 (s), 1358 (m), 1340 (m), 1072 (m).

HRMS: (ESI) calcd for $C_{22}H_{28}N_2NaO_7^+$ $[M+Na]^+$ 455.1789; found 455.1801.

*3-((8R)-8-Ethyl-2,8a-dimethoxy-1-(2-nitrophenyl)-3-oxo-3,5,6,7,8,8a-hexahydroindolizin-8-yl) propanoic acid (**1.153**)*



To a solution of compound **1.152** (121.0 mg, 0.280 mmol, 1.0 equiv) in MeOH (10 mL, 0.03 M) was added dropwise a solution of KOH (314.0 mg, 5.60 mmol, 20.0 equiv) in H_2O (5 mL, 1.1 M). The resulting mixture was stirred at rt for 12 h. The mixture was diluted with CH_2Cl_2 and 1 N HCl was added until pH 1-2. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated until dryness. The crude acid **1.153** as a yellow oil was used directly in the next step. A mixture of diastereoisomers in 1/1 ratio was observed based on ^{1}H NMR.

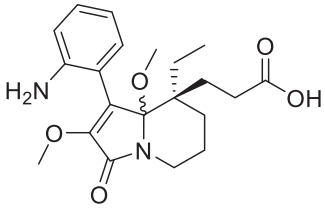
^{1}H NMR (400MHz, CD_3OD): δ 7.93 – 7.81 (m, 2H), 7.69 – 7.61 (m, 1H), 7.57 – 7.48 (m, 1H), 4.13 – 4.03 (m, 1H), 3.97 (s, 1.5H), 3.96 (s, 1.5H), 3.09 (s, 1.5H), 3.07 (s, 1.5H), 2.80 – 2.63 (m, 1.5H), 2.35 – 2.25 (m, 0.5H), 2.24 – 2.10 (m, 1H), 2.09 – 1.90 (m, 1.5H), 1.73 – 1.50 (m, 4.5H), 1.50 – 1.41 (m, 1H), 1.40 – 1.25 (m, 1H), 0.83 (t, *J* = 7.6 Hz, 1.5H), 0.79 (t, *J* = 7.6 Hz, 1.5H).

^{13}C NMR (100MHz, CD_3OD): δ 178.0, 177.6, 164.3, 164.3, 151.1, 151.1, 150.7, 150.6, 133.5, 133.2, 130.7, 130.5, 130.3, 130.2, 126.9, 126.7, 126.3, 126.2, 120.8, 120.7, 98.4, 97.9, 58.5, 49.4, 49.3, 45.3, 45.1, 36.9, 36.9, 31.0, 30.6, 30.3, 29.5, 28.9, 27.0, 26.4, 26.3, 20.9, 10.0, 8.0.

IR: υ (cm^{-1}) 3450-2650 (br), 2948 (w), 2875 (w), 1703 (s), 1639 (m), 1532 (s), 1358 (m), 1340 (m), 1073 (m), 738 (m).

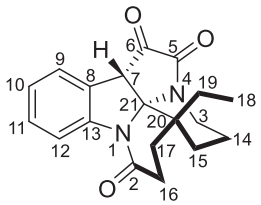
HRMS: (ESI) calcd for $C_{21}H_{26}N_2NaO_7^+$ $[M+Na]^+$ 441.1632; found 441.1632.

*3-((8R)-1-(2-Aminophenyl)-8-ethyl-2,8a-dimethoxy-3-oxo-3,5,6,7,8,8a-hexahydroindolizin-8-yl) propanoic acid (**1.154**)*



In a flask under Ar charged with crude acid **1.153** (0.280 mmol, 1.0 equiv) in dry MeOH (14 mL, 0.02 M) was added Pd/C (10 wt.%, 59.6 mg, 0.056 mmol, 0.2 equiv). The resulting mixture was stirred under H_2 atmosphere (1 atm) at rt for 1 h. The mixture was purged with Ar and filtered through a pad of Celite®. The filter cake was washed with MeOH (3 times) and the filtrate was concentrated under reduced pressure. Traces of MeOH were removed by coevaporation with $CHCl_3$ (twice) and the residue was dried under vacuum. The crude amino acid **1.154** as a white solid was used directly in the next step.

*(+)-Leuconodine F (**1.3**)*



In a dried flask under Ar charged with crude amino acid **1.154** (0.280 mmol, 1.0 equiv) in dry CH_2Cl_2 (14 mL, 0.02 M) were added Et_3N (156 µL, 1.12 mmol, 4.0 equiv), HOBt (56.8 mg, 0.420 mmol, 1.5 equiv) and EDCI.HCl (80.5 mg, 0.420 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 12 h. Dry CH_2Cl_2 (14 mL) and TFA (5.4 mL, 70.0 mmol, 250 equiv) were then added and the mixture was stirred at rt for additional 4 h. Excess of TFA were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, cooled to 0 °C, and a saturated aqueous solution of $NaHCO_3$ was added dropwise until neutral pH. The two layers were separated and the neutral aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with 1 N HCl (once) and the acidic aqueous phase was further extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine (once), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc: 1/2) afforded 48.1 mg (53% yield over 3 steps) of (+)-leuconodine F (**1.3**) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.80 (dd, *J* = 7.7, 1.2 Hz, 1H^{12}), 7.35 (dt, , *J* = 7.7, 1.2 Hz, 1H^{11}), 7.20 (dd, *J* = 7.7, 1.2 Hz, 1H^{9}), 7.14 (dt, *J* = 7.7, 1.2 Hz, 1H^{10}), 4.22 (s, 1H^{7}), 4.13 – 4.04 (m, 1H^{3a}), 3.08 (ddd, *J* = 12.7, 10.7, 3.9 Hz, 1H^{3b}), 2.84 (ddd, *J* = 19.4, 13.4, 6.4 Hz, 1H^{16a}), 2.57 (ddd, *J* = 19.4, 5.9, 1.5 Hz, 1H^{16b}), 2.09 – 1.91 (m, 2H^{15a,17a}), 1.79 – 1.56 (m, 4H^{14,15b,17b}), 1.46 (dq, *J* = 14.3, 7.3 Hz, 1H^{19a}), 1.22 (dq, *J* = 14.3, 7.3 Hz, 1H^{19b}), 0.90 (t, *J* = 7.3 Hz, 3H^{18}).

^{13}C NMR (100MHz, $CDCl_3$): δ 192.5 (Cq^{6}), 172.5 (Cq^{2}), 157.7 (Cq^{5}), 142.7 (Cq^{13}), 130.0 (C^{11}), 126.3 (Cq^{8}), 126.0 (C^{10}), 125.2 (C^{9}), 121.1 (C^{12}), 87.6 (Cq^{21}), 53.5 (C^{7}), 37.9 (C^{3}), 37.7 (Cq^{20}), 29.6 (C^{16}), 27.8 (C^{17}), 26.7 (C^{19}), 26.4 (C^{15}), 20.3 (C^{14}), 7.4 (C^{18}).

IR: υ (cm^{-1}) 2963 (w), 2868 (w), 1768 (s), 1716 (s), 1687 (s), 1474 (m), 1349 (m), 1279 (m), 1164 (m), 1145 (s), 762 (m), 735 (m).

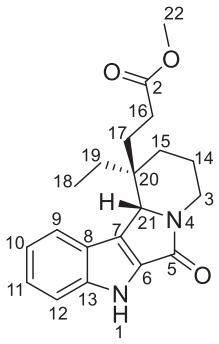
HRMS: (ESI) calcd for $C_{19}H_{20}N_2NaO_3^+$ $[M+Na]^+$ 347.1366; found 347.1366.

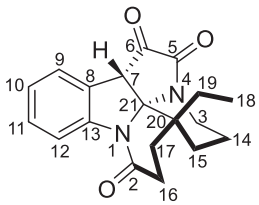
e.r: 93.5/6.5 – **ee** = 87%

$[\alpha]_D^{25}$ = +94 (*c* 1.0, $CHCl_3$)

$[\alpha]_D^{25}$ = +98 (*c* 0.05, $CHCl_3$); lit.[9] $[\alpha]_D^{25}$ = +94 (*c* 0.05, $CHCl_3$)

NMR Chemical Shifts for Natural and Synthetic (-)-Leucomidine B and (+)-Leuconodine F



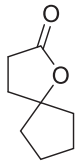


	(-)-leucomidine B ($CDCl_3/CD_3OD$:1/1)				(+)-leuconodine F ($CDCl_3$)			
	^1H		^{13}C		^1H		^{13}C	
Position[a]	Natural[8]	Synthetic	Natural[8]	Synthetic	Natural[9]	Synthetic	Natural[9]	Synthetic
2			175.3	175.3			172.2	172.5
3	4.30 2.98	4.34-4.27 2.98	40.1	40.1	4.11 3.10	4.13-4.04 3.08	37.8	37.9
5	-	-	162.8	162.7	-	-	157.5	157.7
6	-	-	127.6[b]	135.2[b]	-	-	192.5	192.5
7	-	-	135.2[b]	127.5[b]	4.23	4.22	53.4	53.5
8	-	-	128.2[c]	122.5[c]			126.2	126.3
9	7.68	7.67	121.4	121.0	7.22	7.20	125.1	125.2
10	7.16	7.15	122.5[c]	121.3[c]	7.16	7.14	125.9	126.0
11	7.27	7.26	124.8	124.8	7.37	7.35	129.9	130.0
12	7.49	7.49	114.1	114.0	7.82	7.80	121.0	121.1
13			142.5	142.2			142.6	142.7
14	1.69 1.60	1.72-1.61 1.72-1.61	21.2	21.2	1.70	1.79-1.56	20.1	20.3
15	1.76 1.59	1.79-1.73 1.61-1.53	30.1	30.1	2.05 1.70	2.09-1.91 1.79-1.56	26.3	26.4
16	2.74 2.60	2.78-1.66 2.66-2.53	29.2	29.2	2.86 2.59	2.84 2.57	29.5	29.6
17	2.18	2.22-2.12	32.7	32.7	1.98 1.66	2.09-1.91 1.79-1.56	26.6[d]	27.8[d]
18	0.58	0.57	7.6	7.6	0.92	0.90	7.3	7.4
19	1.12 0.67	1.12 0.66	23.7	23.7	1.49 1.23	1.46 1.22	27.7[d]	26.7[d]
20	-	-	40.2	40.2	-	-	37.6	37.7
21	4.36	4.35	63.8	63.4	-	-	88.0	87.6
22	3.78	3.78	52.4	52.4	-	-	-	-

(a) The numbering used is the biogenetic one proposed by Le Men and Taylor.[10]
(b) The assignments of C6 and C7 are supported by 2D correlations in HMBC experiment.
(c) The assignment of C8 and C10 are supported by 2D correlations in HSQC and HMBC experiments. Besides, in the ^{13}C NMR spectrum, no peak was observed at 128.2 ppm.
(d) The assignments of C17 and C19 are supported by 2D correlations in HSQC and HMBC experiments.

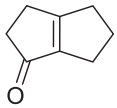
Experimental Procedures and Characterization Data of PART II

*1-oxaspiro[4.4]nonan-2-one (**2.90**)*



In a dried flask under Ar charged with magnesium (6.07 g; 249.8 mmol; 2.5 equiv.) in suspension in THF (62.5 mL) was added dropwise 1,4-dibromobutane (13.1 mL; 109.9 mmol; 1.1 equiv) at a sufficient rate to maintain a gentle reflux. At the end of addition, the mixture was stirred at reflux for 3 h. The mixture was cooled to -10 °C and a solution of succinic anhydride (10.0 g; 99.9 mmol; 1.0 equiv) in THF (150 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 3 h and then at rt for 12 h. The mixture was cooled to 0 °C and quenched by dropwise addition of 4 N HCl (300 mL). The biphasic mixture was stirred at 40 °C for 1 h and extracted with Et_2O (x2) and CH_2Cl_2 (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure (water bath at 25°C) to afford crude spirolactone **2.90** which was used directly as such in the next step.

*3,4,5,6-tetrahydropentalen-1(2H)-one (**2.91**)*



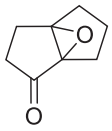
In a dried flask under Ar charged with methanesulfonic acid (345 mL) was added portionwise phosphorus pentoxide (42.5 g; 299.7 mmol; 3.0 equiv) and the resulting mixture was stirred at 50 °C until complete dissolution of P_2O_5. The mixture was then transferred by canula to a dried flask under Ar charged with crude spirolactone **2.90** and the resulting mixture was stirred at rt for 60 h. The mixture was cooled to 0 °C, ice water was added and the mixture was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with a half-saturated aqueous solution of $NaHCO_3$ (x1) and water (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 6.52 g (53% yield over 2 steps) of enone **2.91** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 2.75 – 2.68 (m, 2H), 2.56 – 2.46 (m, 4H), 2.39 – 2.27 (m, 4H).

^{13}C NMR (100MHz, $CDCl_3$): δ 204.1 (Cq), 187.5 (Cq), 149.0 (Cq), 41.2, 32.1, 27.9, 25.8, 24.5.

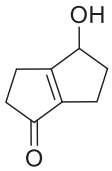
The spectroscopic data of this compound are in accord with these reported in the literature.[11]

*tetrahydro-1H,4H-3a,6a-epoxypentalen-1-one (**2.92**)*



In a flask charged with enone **2.91** (4.37 g; 35.8 mmol; 1.0 equiv) in MeOH (71.8 mL) was added dropwise at 0 °C H_2O_2 (30% in H_2O; 16.2 mL; 143.1 mmol; 4.0 equiv) and then NaOH (1 N in H_2O; 3.6 mL; 3.6 mmol; 0.1 equiv) and the resulting mixture was stirred at 0 °C for 3 h. The mixture was diluted with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (x4). Note: if an emulsion appeared, addition of few water helped to break it. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude epoxide **2.92** which was used directly as such in the next step.

*4-hydroxy-3,4,5,6-tetrahydropentalen-1(2H)-one (**2.93**)*



In a flask charged with crude epoxide **2.92** was added $HClO_4$ (5% in H_2O; 350 mL) and the resulting mixture was stirred at rt for 3 h. The mixture was cooled to 0 °C and solid $NaHCO_3$ was added portionwise until neutral pH. The mixture was then saturated with solid NaCl and extracted with CH_2Cl_2 (x7). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (100% EtOAc) afforded 1.73 g (35% yield over 2 steps) of allylic alcohol **2.93** as a white solid.

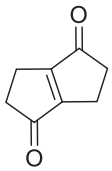
^{1}H NMR (400MHz, $CDCl_3$): δ 4.98 (dd, *J* = 5.1, 7.5 Hz, 1H), 2.85 – 2.64 (m, 4H), 2.56 – 2.44 (m, 2H), 2.33 – 2.22 (m, 1H), 2.16 (ddt, *J* = 14.2, 8.9, 5.1 Hz, 1H), 1.96 (br s, 1H).

^{13}C NMR (100MHz, $CDCl_3$): δ 204.9 (Cq), 184.1 (Cq), 150.0 (Cq), 74.4, 41.0, 38.7, 23.3, 22.9.

IR: υ (cm^{-1}) 3348 (m), 2922 (w), 2859 (w), 1672 (s), 1636 (s), 1430 (w), 1388 (w), 1330 (m), 1284 (m), 1185 (m), 1071 (s), 1035 (m), 948 (w), 795 (w), 721 (w).

HRMS: (ESI) calcd for $C_8H_{11}O_2^+$ $[M+H]^+$ 139.0754; found 139.0759.

*2,3,5,6-tetrahydropentalene-1,4-dione (**2.88**)*



To a suspension of PCC (624 mg; 2.89 mmol; 2.0 equiv) and Celite (624 mg) in CH_2Cl_2 (9 mL) was added dropwise at rt a solution of allylic alcohol **2.93** (200 mg; 1.45 mmol; 1.0 equiv) in CH_2Cl_2 (2 mL). The resulting mixture was stirred at rt for 3 h, diluted with Et_2O and stirred at rt for additional 1 h. The black suspension was filtered through a pad of Celite and the filter cake was washed with Et_2O. The filtrate was concentrated under reduced pressure and purified by FCC (PE/EtOAc : 1/1) to afford 173 mg (88% yield) of enedione **2.88** as a white solid.

Or

In a flask charged with enone **2.91** (200 mg; 1.64 mmol; 1.0 equiv) in 1,2-DCE (24.6 mL) was added portionwise PCC (3.53 g; 16.4 mmol; 10 equiv) and the resulting mixture was stirred at 80 °C for 12 h. The mixture was diluted with Et_2O, filtered through a pad of Fluorisil and the filter cake was washed with Et_2O (several times) and with Et_2O/CH_2Cl_2 (1/1, once at the end). The filtrated was concentrated under reduced pressure and purified by FCC (PE/EtOAc : from 2/1 to 1/1) to afford 48.8 mg (24% recovered) of starting enone **2.91** and 33.9 mg (15% yield) of desired enedione **2.88**. On 10 mg scale, 39% of **2.91** and 32% of **2.88** were obtained.

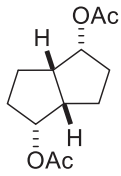
^{1}H NMR (400MHz, $CDCl_3$): δ 2.9 (dd, *J* = 5.7, 2.9 Hz, 4H), 2.70 – 2.63 (m, 4H).

^{13}C NMR (100MHz, $CDCl_3$): δ 204.8 (2Cq), 173.3 (2Cq), 41.0 (2C), 20.8 (2C).

IR: υ (cm^{-1}) 2965 (w), 2926 (w), 1688 (s), 1448 (m), 1407 (w), 1326 (m), 1188 (s), 1139 (w), 1037 (s), 1008 (m), 965 (m), 786 (m), 660 (m).

HRMS: (ESI) calcd for $C_8H_9O_2^+$ $[M+H]^+$ 137.0597; found 137.0596.

octahydropentalene-1,4-diyl diacetate (2.96)



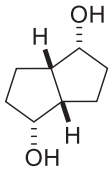
In a flask charged with 1,5-cyclooctadiene (1.2 mL; 10.0 mmol ; 1.0 equiv) in glacial acetic acid (20 mL) was added portionwise lead(IV) acetate (4.87 g; 11.0 mmol; 1.1 equiv) and then palladium(II) acetate (112.3 mg; 0.5 mmol; 0.05 equiv). The resulting mixture was stirred at rt for 36 h. AcOH was removed under reduced pressure and the residue was diluted with water and extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 1.9 g (84% yield) of diacetate **2.96** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 5.08 (q, *J* = 6.7 Hz, 2H), 2.76 – 2.64 (m, 2H), 2.04 (s, 6H), 1.83 – 1.64 (m, 4H), 1.6 3– 1.54 (m, 2H), 1.53 – 1.42 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 170.9 (2Cq), 77.3 (2C), 44.8 (2C), 32.4 (2C), 23.0 (2C), 21.3 (2C).

The spectroscopic data of this compound are in accord with these reported in the literature.[12]

octahydropentalene-1,4-diol (2.97)



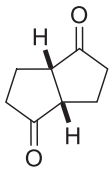
In a flask charged with diacetate **2.96** (1.9 g; 8.39 mmol; 1.0 equiv) in MeOH (42 mL) was added portionwise Dowex 1x8 (OH- form; 3.8 g) and the resulting suspension was stirred vigorously at rt for 24 h. Solids were filtered off, washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 1.16 g (97% yield) of diol **2.97**.

^{1}H NMR (400MHz, $CDCl_3$): δ 3.96 – 3.91 (m, 2H), 3.02 (s, 2H), 2.58 – 2.50 (m, 2H), 1.94 – 1.87 (m, 2H), 1.86 – 1.68 (m, 4H), 1.67 – 1.58 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 72.9 (2C), 49.0 (2C), 39.2 (2C), 20.4 (2C).

The spectroscopic data of this compound are in accord with these reported in the literature.[12]

*hexahydropentalene-1,4-dione (**2.98**)*



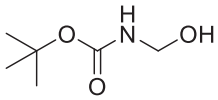
To a suspension of PCC (7.03 g; 32.6 mmol; 4.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise a solution of diol **2.97** (1.16 g; 8.16 mmol; 1.0 equiv) in CH_2Cl_2 (12 mL). The resulting mixture was stirred at rt for 5 h, diluted with Et_2O and stirred at rt for additional 2 h. The black suspension was filtered through a pad of Celite and the filter cake was washed with Et_2O. The filtrate was concentrated under reduced pressure and purified by FCC (PE/EtOAc : 1/1) to afford 852 mg (76% yield) of diketone **2.98**.

^{1}H NMR (400MHz, $CDCl_3$): δ 2.94 – 2.86 (m, 2H), 2.42 – 2.30 (m, 2H), 2.23 – 2.14 (m, 4H), 2.13 – 1.98 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 220.4 (2Cq), 49.6 (2C), 37.7 (2C), 23.1 (2C).

The spectroscopic data of this compound are in accord with these reported in the literature.[12]

*tert-butyl (hydroxymethyl)carbamate (**2.102**)*



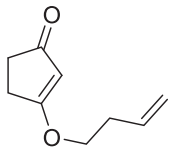
A flask was charged with *tert*-butyl carbamate (1.0 g; 8.54 mmol; 1.0 equiv), paraformaldehyde (359 mg; 11.95 mmol; 1.4 equiv) and sodium carbonate (453 mg; 4.27 mmol; 0.5 equiv). Water (12.8 mL) was added and the resulting suspension was stirred at 80 °C until complete dissolution of solids and then was stirred at rt for 12 h. The mixture was extracted with EtOAc (x3) and the combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : from 2/1 to 1/1) afforded 704 mg (56% yield) of hemiaminal **2.102** as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 5.82 – 5.41 (2x br s, 1H), 4.90 – 4.78 (m, 1H), 4.65 (d, *J* = 7.3 Hz, 1H), 1.83 (br s, 1H), 1.45 (s, 9H).

^{13}C NMR (100MHz, $CDCl_3$): δ 156.3 (Cq), 80.3 (Cq), 68.8, 28.4.

The spectroscopic data of this compound are in accord with these reported in the literature.[13]

*3-(but-3-en-1-yloxy)cyclopent-2-en-1-one (**2.106**)*



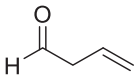
In a flask charged with 1,3-cyclopentanedione (1.0 g; 10.2 mmol; 1.0 equiv) in acetone (15 mL) was added portionwise potassium carbonate (1.69 g; 12.2 mmol; 1.2 equiv) and then dropwise 4-bromobut-1-ene (1.14 mL; 11.2 mmol; 1.1 equiv). The resulting suspension was stirred at reflux for 24 h, cooled to rt and solids were filtered off. Solids were washed with acetone and the filtrate was concentrated under reduced pressure to afford 712 mg (46% yield) of O-alkylated product **2.106**. NMR of solids revealed a mixture of salts and starting 1,3-cyclopentanedione.

^{1}H NMR (400MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.30 (br s, 1H), 5.20 – 5.10 (m, 2H), 4.02 (t, *J* = 6.7 Hz, 2H), 2.63 – 2.59 (m, 2H), 2.52 (tq, *J* = 6.7, 1.3 Hz, 2H), 2.47 – 2.40 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 206.1 (Cq), 190.2 (Cq), 133.3, 118.0, 105.0, 71.1, 34.1, 33.0, 28.6.

The spectroscopic data of this compound are in accord with these reported in the literature.[14]

*but-3-enal (**2.108**)*

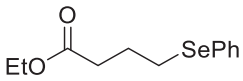


To a suspension of DMP (4.67 g; 11.0 mmol; 1.1 equiv) in CH_2Cl_2 (20 mL) was added dropwise a solution of but-3-en-1-ol (0.85 mL; 10.0 mmol; 1.0 equiv) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at rt for 3.5 h, solids were filtered off and were washed with CH_2Cl_2. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ containing 8 g of $Na_2S_2O_3$ (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure (P = 650 mmbar; T = 30 °C) to afford 12.9 g of a solution of aldehyde **2.108** in CH_2Cl_2 (NMR ratio **2.108**/CH_2Cl_2 : 1/18; ~0.57 g of **2.108**; ~81% yield).

^{1}H NMR (400MHz, $CDCl_3$): δ 9.70 (t, *J* = 1.9 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.29 (dq, *J* = 10.3, 1.5 Hz, 1H), 5.22 (dq, *J* = 17.2, 1.5 Hz, 1H), 3.20 (dq, *J* = 6.9, 1.9 Hz, 2H).

The spectroscopic data of this compound are in accord with these reported in the literature.[15]

*ethyl 4-(phenylselanyl)butanoate (**2.110**)*



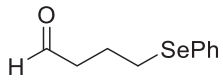
In a dried flask under Ar charged with diphenyl diselenide (4.68 g; 15.0 mmol; 1.0 equiv) in EtOH (150 mL) was added portionwise at 0 °C $NaBH_4$ (1.31 g; 34.5 mmol; 2.3 equiv). Then, a solution of ethyl 4-bromobutanoate (4.73 mL; 33.0 mmol; 2.2 equiv) in EtOH (30 mL) was added dropwise at 0 °C and the mixture was slowly warmed to 55 °C and stirred 2 h. The mixture was cooled to rt, water (10 mL) was added dropwise and then 3/4 of EtOH were removed under reduced pressure. The concentrated solution was diluted with water and extracted with Et_2O (x4). The combined organic layers were washed with brine (x2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 20/1) afforded 8.01 g (98% yield) of ester **2.110** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.54 – 7.48 (m, 2H), 7.31 – 7.23 (m, 3H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.02 (p, *J* = 7.3 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 172.1 (Cq), 132.5 (2C), 129.9 (Cq), 128.7(2C), 126.6, 60.0, 33.6, 26.8, 25.2, 14.1.

The spectroscopic data of this compound are in accord with these reported in the literature.[16]

*4-(phenylselanyl)butanal (**2.111**)*



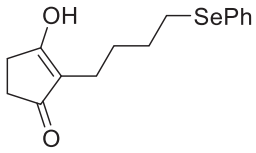
In a dried flask under Ar charged with ester **2.110** (7.70 g; 28.4 mmol; 1.0 equiv) in CH_2Cl_2 (56.8 mL) was added over 5 min at -78 °C DIBAL (1.2 M in toluene; 24.8 mL; 29.8 mmol; 1.05 equiv). The resulting mixture was stirred 15 min at -78 °C and then quenched by dropwise addition of water (50 mL). The mixture was warmed to rt, diluted with 2 N HCl until complete dissolution of the white precipitates and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 10/1) afforded 5.73 g (89% yield) of aldehyde **2.110** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.3 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.29 – 7.22 (m, 3H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.59 (td, *J* = 7.1, 1.3 Hz, 2H), 2.01 (p, *J* = 7.1 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 201.6, 132.9 (2C), 129.8 (Cq), 129.3 (2C), 127.2, 43.7, 27.2, 22.6.

The spectroscopic data of this compound are in accord with these reported in the literature.[17]

*3-hydroxy-2-(4-(phenylselanyl)butyl)cyclopent-2-en-1-one (**2.112**)*



In a flask charged with 1,3-cyclopentanedione (686.7 mg; 7.0 mmol; 1.0 equiv), aldehyde **2.111** (4.77 g; 21.0 mmol; 3.0 equiv) and Hantzsch Ester (1.86 g; 7.4 mmol; 1.05 equiv) in CH_2Cl_2 (23 mL) was added in one portion *L*-proline (40.3 mg; 0.35 mmol; 0.05 equiv). The resulting mixture was stirred at rt for 4 h, then diluted with 1 N HCl and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc/MeOH : 10/1/0) afforded 2.58 g (81% recovered) of starting aldehyde **2.111**, then (PE/EtOAc/MeOH : 1/5/0; elution until strong yellow spot) afforded various impurities and finally (PE/EtOAc/MeOH : 0/95/5) afforded 2.07 g (96% yield) of 1,3-diketone **2.112** as a white solid.

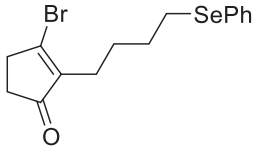
^{1}H NMR (400MHz, $CDCl_3$): δ 10.35 (br s, 1H), 7.49 – 7.43 (m, 2H), 7.25 – 7.16 (m, 3H), 2.91 (t, *J* = 7.3 Hz, 2H), 2.53 (s, 4H), 2.19 (t, *J* = 7.5 Hz, 2H), 1.76 – 1.62 (m, 2H), 1.60 – 1.49 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 198.6 (2Cq), 132.4 (2C), 130.7 (Cq), 129.1 (2C), 126.7, 118.1 (Cq), 30.7 (2C), 29.9, 28.2, 27.8, 20.4.

IR: υ (cm^{-1}) 3086 (w), 2948 (w), 2921 (w), 2852 (w), 1715 (s), 1637 (m), 1448 (w), 1281 (s), 1263 (s), 1193 (m), 1123 (m), 1080 (m), 1001 (m), 907 (s).

HRMS: (ESI) calcd for $C_{15}H_{18}NaO_2Se^+$ $[M+Na]^+$ 333.0370; found 333.0368.

*3-bromo-2-(4-(phenylselanyl)butyl)cyclopent-2-en-1-one **2.113***



In a dried flask under Ar charged with 1,3-diketone **2.112** (500 mg; 1.62 mmol; 1.0 equiv) in $CHCl_3$ (6.5 mL) was added dropwise at rt PBr_3 (230 µL; 2.43 mmol; 1.5 equiv) and the resulting mixture

was stirred at reflux for 7 h. The mixture was cooled to rt, diluted with CH_2Cl_2 and added dropwise to water at 0 °C. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (x1) and brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 424 mg (70% yield) of crude vinyl bromide **2.113**.

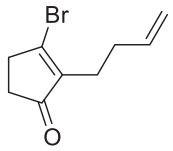
^{1}H NMR (400MHz, $CDCl_3$): 7.53 – 7.43 (m, 2H), 7.30 – 7.19 (m, 4H), 2.95 – 2.85 (m, 4H), 2.54 – 2.48 (m, 2H), 2.27 (tt, *J* = 7.5, 1.3 Hz, 2H), 1.69 (dtd, *J* = 8.9, 7.7, 7.1, 5.6 Hz, 2H), 1.62 – 1.50 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 203.8 (Cq), 156.4 (Cq), 144.9 (Cq), 132.8 (2C), 130.4 (Cq), 129.1 (2C), 126.9, 36.0, 35.3, 29.9, 27.6, 27.3, 24.3.

IR: υ (cm^{-1}) 3082 (w), 2945 (w), 2899 (w), 1711 (s), 1623 (m), 1430 (w), 1267 (m), 1193 (w), 1121 (w), 1011 (w), 922 (m), 647 (m).

HRMS: (ESI) calcd for $C_{15}H_{18}BrOSe^+$ $[M+H]^+$ 372.9706; found 372.9707.

3-bromo-2-(but-3-en-1-yl)cyclopent-2-en-1-one ***2.103***



In a flask charged with crude vinyl bromide **2.113** (300 mg; 0.806 mmol; 1.0 equiv) in MeOH/H_2O (7/1; 4.0 mL) was added portionwise $NaHCO_3$ (81.3 mg; 0967 mmol; 1.2 equiv) and then $NaIO_4$ (413.8 mg; 1.93 mmol; 2.4 equiv). The resulting mixture was stirred at 60 °C for 16 h and then 2/3 of MeOH were removed under reduced pressure. The concentrated solution was diluted with CH_2Cl_2, washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 10/1) afforded 117.4 mg (68% yield) of alkene **2.103** as a light yellow oil.

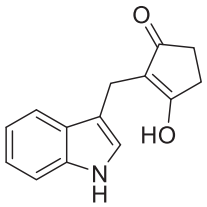
^{1}H NMR (400MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H), 2.97 – 2.86 (m, 2H), 2.56 – 2.51 (m, 2H), 2.41 – 2.34 (m, 2H), 2.26 – 2.15 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 203.8 (Cq), 156.6 (Cq), 144.5 (Cq), 137.5, 115.5, 36.1, 35.3, 31.2, 24.4.

IR: υ (cm^{-1}) 3084 (w), 2927 (w), 1704 (s), 1628 (m), 1440 (w), 1342 (w), 1274 (m), 1198 (w), 1077 (w), 994 (w), 914 (m), 635 (m).

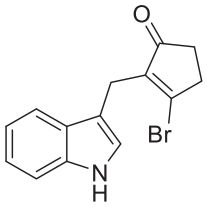
HRMS: (ESI) calcd for $C_9H_{12}BrO^+$ $[M+H]^+$ 215.0066; found 215.0065.

*2-((1H-indol-3-yl)methyl)-3-hydroxycyclopent-2-en-1-one (**2.121**)*



A flask was charged homogeneously with indole-3-carboxaldehyde (7.40 g; 51.0 mmol; 1.0 equiv), 1,3-cyclopentanedione (5.0 g; 51.0 mmol; 1.0 equiv), Hantzsch Ester (12.9 g; 51.0 mmol; 1.0 equiv) and *L*-proline (293.6 mg; 2.55 mmol; 0.05 equiv). MeOH (170 mL) was added in one portion and the resulting mixture was stirred at rt for 12 h. Volatiles were removed under reduced pressure and traces of MeOH was coevaporated with $CHCl_3$. The crude 1,3-diketone **2.121** was directly used as such in the next step.

*2-((1H-indol-3-yl)methyl)-3-bromocyclopent-2-en-1-one **2.122***



In a dried flask under Ar charged with crude 1,3-diketone **2.121** in suspension in THF (170 mL) was added dropwise at rt PBr_3 (14.5 mL; 153.0 mmol; 3.0 equiv). The resulting mixture was stirred at reflux (oil bath at 70 °C) for 12 h. The mixture was cooled to rt, diluted with CH_2Cl_2 (300 mL) and water (18 mL; ~20 equiv) was added dropwise. The resulting mixture was stirred 30 min at rt, filtered through a pad of Celite and the filter cake was washed with CH_2Cl_2. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 6.87 g (46% yield over 2 steps) of vinyl bromide **2.122** as a white solid.

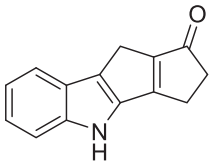
^{1}H NMR (400MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.79 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.32 (dt, *J* = 8.2, 1.2 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.14 (s, 1H), 7.12 (ddd, *J* = 7.7, 7.0, 1.2 Hz, 1H), 3.74 (q, *J* = 1.1 Hz, 2H), 2.94 – 2,97 (m, 2H), 2.56 – 2.48 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 203.7 (Cq), 156.3 (Cq), 144.2 (Cq), 136.1 (Cq), 127.2 (Cq), 123.3, 122.1, 119.6, 119.5, 111.7 (Cq), 111.1, 36.1, 35.3, 20.7.

IR: υ (cm^{-1}) 3293 (w), 2987 (w), 2909 (w), 1688 (s), 1622 (m), 1424 (w), 1294 (m), 1235 (m), 1079 (m), 930 (w), 814 (w), 751 (s).

HRMS: (ESI) calcd for $C_{14}H_{13}BrNO^+$ $[M+H]^+$ 290.0175; found 290.0176.

2,3,4,9-tetrahydro-1H-pentaleno[1,2-b]indol-1-one ***2.119***



A flask charged with vinyl bromide **2.122** (876.0 mg; 3.02 mmol; 1.0 equiv), palladium(II) acetate (67.8 mg; 0.302 mmol; 0.1 equiv); triphenylphosphine (158 mg; 0.604 mmol; 0.2 equiv) and potassium carbonate (834.5 mg; 6.04 mmol; 2.0 equiv) was evacuated for 15 min and then refilled with Ar. Degassed DMF was added in one portion and the resulting mixture was stirred at 60 °C for 12 h. The mixture was cooled to rt, diluted with EtOAc, filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure and purified twice by FCC (CH_2Cl_2/MeOH : 95/5) to afford impure enone **2.119** (contaminated mainly with triphenylphosphine oxide and other minor impurities). After recrystallization in EtOAc, 220 mg (35% yield) of pure enone **2.119** was obtained. Note: On 13 mg scale, purification by prep TLC afforded 6.2 mg (66% yield) of enone **2.119**.

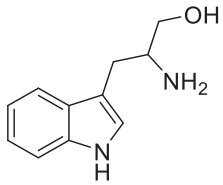
^{1}H NMR (400MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.26 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.19 (dd, *J* = 7.9, 7.1 Hz, 1H), 3.46 (s, 2H), 3.04 – 2.87 (m, 4H).

^{13}C NMR (100MHz, $CDCl_3$): δ 199.9 (Cq), 171.4 (Cq), 150.0 (Cq), 141.7 (Cq), 140.6 (Cq), 133.4 (Cq), 124.2 (Cq), 124.0, 121.1, 120.2, 112.7, 40.6, 26.3, 23.2.

IR: υ (cm^{-1}) 3137 (w), 2919 (w), 1633 (s), 1527 (w), 1474 (m), 1412 (m), 1364 (s), 1325 (m), 1244 (m), 1163 (m), 1013 (w), 775 (m), 746 (s), 720 (s).

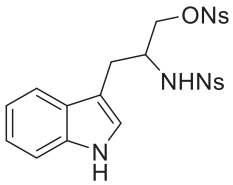
HRMS: (ESI) calcd for $C_{14}H_{12}NO^+$ $[M+H]^+$ 210.0913; found 210.0915.

*2-amino-3-(1H-indol-3-yl)propan-1-ol (**2.136**)*



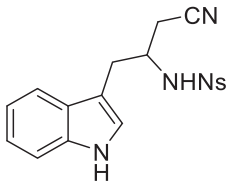
In a dried flask under Ar charged with *DL*-tryptophan (2.04 g; 10.0 mmol; 1.0 equiv) in THF (50 mL) was added portionwise at 0 °C $LiAlH_4$ (1.52 g; 40.0 mmol; 4.0 equiv) and the resulting mixture was stirred at reflux for 12 h. To the mixture cooled at 0 °C was added dropwise sequentially water (1.5 mL), 15% NaOH (1.5 mL) and water (4.5 mL). The resulting suspension was stirred at rt for 15 min, filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate was concentrated to afford crude amino alcohol **2.136** which was used directly as such in the next step.

*4-(3-(1H-indol-3-yl)-2-((2-nitro-4-sulfophenyl)amino)propoxy)-3-nitrobenzenesulfonic acid (**2.137**)*



In a dried flask under Ar charged with crude amino alcohol **2.136** in CH_2Cl_2 (20 mL) was added at 0 °C pyridine (3.22 mL; 40.0 mmol; 4.0 equiv) and then in one portion NsCl (5.54 g; 25.0 mmol; 2.5 equiv). The resulting mixture was stirred at rt for 12 h and then diluted with CH_2Cl_2 and 1 N HCl. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with a mixture brine / 1 N HCl (3/1; x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude dinosylated product **2.137** which was used directly as such in the next step.

4-((1-cyano-3-(1H-indol-3-yl)propan-2-yl)amino)-3-nitrobenzenesulfonic acid (2.138)



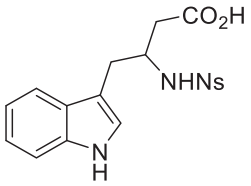
In a flask charged with crude dinosylated product **2.137** in DMF/H_2O (9/1; 50 mL) was added in one portion KCN (977 mg; 15.0 mmol; 1.5 equiv) and the resulting mixture was stirred at rt for 17 h. The mixture was diluted with EtOAc and a half-saturated aqueous solution of $NaHCO_3$. The two layers were separated and the aqueous phase was extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (solid deposition; PE/EtOAc : 3/2) afforded 2.56 g (67% yield over 3 steps) of nitrile **2.138** as a light yellow solid.

^{1}H NMR (400MHz, $CDCl_3$/CD_3OD : 1/1): δ 7.62 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.41 (td, *J* = 8.1, 1.4 Hz, 1H), 7.26 (td, *J* = 7.9, 1.3 Hz, 1H), 7.21 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.13 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.01 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 6.99 (s, 1H), 6.86 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.00 – 3.89 (m, 1H), 3.10 (dd, *J* = 14.7, 5.2 Hz, 1H), 2.94 (dd, *J* = 14.7, 9.7 Hz, 1H), 2.91 – 2.78 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$/CD_3OD : 1/1): δ 147.0 (Cq), 137.1 (Cq), 133.8, 133.1 (Cq), 132.8, 130.3, 126.9 (Cq), 125.4, 124.9, 122.0, 119.6, 118.3, 117.9 (Cq), 112.1, 109.0 (Cq), 52.2, 30.6, 25.7.

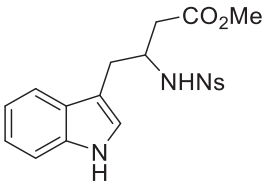
The spectroscopic data of this compound are in accord with these reported in the literature.[18]

4-(1H-indol-3-yl)-3-((2-nitro-4-sulfophenyl)amino)butanoic acid (2.139)



In a flask under Ar, nitrile **2.138** (1.23 g; 3.20 mmol; 1.0 equiv) was dissolved in NaOH (5% in H_2O; degassed; 32 mL) and the resulting mixture was stirred at 100 °C for 14 h. The mixture was cooled to 0 °C, quenched with 4 N HCl until pH 2-3 and then extracted with CH_2Cl_2 (x4). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude acid **2.139** which was used directly as such in the next step.

*4-((1-(1H-indol-3-yl)-4-methoxy-4-oxobutan-2-yl)amino)-3-nitrobenzenesulfonic acid (**2.130**)*



In a dried flask under Ar charged with crude acid **2.139** in MeOH (32 mL) was added dropwise at rt TMSCl (812 µL; 6.40 mmol; 2.0 equiv) and the resulting mixture was stirred at rt for 6 h. Volatiles were removed under reduced pressure and the residue was diluted with CH_2Cl_2 and 1 N HCl. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 3/2) afforded 1.02 g (76% yield over 2 steps) of ester **2.130** as a light orange oil.

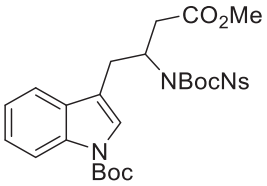
^{1}H NMR (400MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.85 – 7.81 (m, 1H), 7.53 – 7.49 (m, 1H), 7.43 – 7.36 (m, 2H), 7.35 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.16 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.07 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.92 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 5.76 (d, *J* = 5.8 Hz, 1H), 4.21 – 4.06 (m, 1H), 3.71 (s, 3H), 3.13 (ddd, *J* = 14.7, 5.3, 1.0 Hz, 1H), 2.92 (dd, *J* = 16.6, 4.4 Hz, 1H), 2.86 (dd, *J* = 14.7, 9.2 Hz, 1H), 2.66 (dd, *J* = 16.6, 7.6 Hz, 1H).

^{13}C NMR (100MHz, $CDCl_3$): 171.8 (Cq), 146.6 (Cq), 136.4 (Cq), 133.3 (Cq), 133.1, 132.6, 130.5, 126.8 (Cq), 125.2, 123.8, 122.2, 119.9, 118.8, 111.3, 110.6 (Cq), 51.99, 51.97, 40.4, 31.1.

IR: υ (cm^{-1}) 3401 (w), 1724 (m), 1536 (s), 1415 (w), 1339 (m), 1208 (w), 1163 (s), 1079 (m), 855 (w), 738 (s), 650 (m).

HRMS: (ESI) calcd for $C_{19}H_{19}N_3NaO_6S^+$ $[M+Na]^+$ 440.0887; found 440.0886.

*tert-butyl 3-(2-((N-(tert-butoxycarbonyl)-4-nitrophenyl)sulfonamido)-4-methoxy-4-oxobutyl)-1H-indole-1-carboxylate (**2.143**)*



In a dried flask under Ar charged with ester **2.130** (209 mg; 0.50 mmol; 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added portionwise at rt Boc_2O (273 mg; 1.25 mmol; 2.5 equiv) and then DMAP

(3.1 mg; 0.025 mmol; 0.05 equiv). The resulting mixture was stirred at rt for 12 h and then volatiles were removed under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 1.02 g (96% yield) of diBoc product **2.143** (mixture of rotamers in 8/1 ratio) as a light yellow foam.

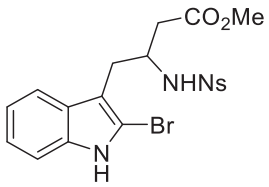
^{1}H NMR (400MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.54 – 7.48 (m, 1H), 7.46 (s, 1H), 7.37 – 7.24 (m, 3H), 5.17 (p, *J* = 7.5 Hz, 1H), 3.65 (s, 3H), 3.50 – 3.40 (dd, *J* = 14.2, 8.2 Hz, 1H), 3.33 (dd, *J* = 14.2, 7.3 Hz, 1H), 3.05 (dd, *J* = 10.7, 6.8 Hz, 2H), 1.66 (s, 9H), 1.35 (s, 9H).

^{13}C NMR (100MHz, $CDCl_3$): 171.6 (Cq), 150.3 (Cq), 149.7 (Cq), 147.9 (Cq), 135.6 (Cq), 133.9 (Cq), 133.7, 131.4, 131.3 (Cq), 130.4 (Cq), 124.9, 124.8, 124.1, 123.1, 119.7, 116.6, 115.3, 85.5 (Cq), 83.8 (Cq), 56.0, 52.0, 38.6, 28.8, 28.3 (3C), 27.9 (3C).

IR: υ (cm^{-1}) 2978 (w), 1730 (s), 1543 (m), 1455 (w), 1366 (s), 1257 (m), 1147 (s), 1089 (m), 1017 (w), 852 (w), 767 (m), 722 (m).

HRMS: (ESI) calcd for $C_{29}H_{35}N_3NaO_{10}S^+$ $[M+Na]^+$ 640.1935; found 640.1934.

*4-((1-(2-bromo-1H-indol-3-yl)-4-methoxy-4-oxobutan-2-yl)amino)-3-nitrobenzenesulfonic acid (**2.141**)*



In a dried flask under Ar charged with ester **2.130** (400 mg; 0.96 mmol; 1.0 equiv) in $CHCl_3$/THF (1/1; 10 mL) was added over 1 h at -10 °C pyridinium tribromide (90% purity; 357.5 mg; 1.01 mmol; 1.05 equiv). The resulting mixture was stirred at -10 °C for 1 h and then quenched with an aqueous solution of 10% $Na_2S_2O_3$. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 393 mg (83% yield) of bromoindole **2.141** as a yellow foam.

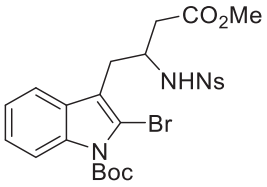
^{1}H NMR (400MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.85 – 7.80 (m, 1H), 7.59 – 7.54 (m, 1H), 7.48 – 7.40 (m, 2H), 7.36 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.97 (ddd, *J* = 8.0, 6.3, 1.9 Hz, 1H), 5.90 (d, *J* = 6.8 Hz, 1H), 4.23 (dqd, *J* = 9.0, 6.8, 4.5 Hz, 1H), 3.70 (s, 3H), 3.04 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.93 (dd, *J* = 14.6, 9.0 Hz, 1H), 2.85 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.69 (dd, *J* = 16.8, 6.9 Hz, 1H).

^{13}C NMR (100MHz, $CDCl_3$): δ 171.8 (Cq), 146.7 (Cq), 135.9 (Cq), 133.8 (Cq), 133.1, 132.6, 130.2, 127.2 (Cq), 125.2, 122.6, 120.6, 118.2, 110.7 (Cq), 110.6, 109.9 (Cq), 52.0, 51.8, 39.9, 30.5.

IR: υ (cm^{-1}) 3332 (w), 2983 (w), 1732 (s), 1538 (s), 1453 (w), 1399 (m), 1357 (s), 1313 (s), 1255 (m), 1212 (m), 1167 (s), 1100 (s), 765 (s), 733 (s), 656 (s).

HRMS: (ESI) calcd for $C_{19}H_{18}BrN_3NaO_6S^+$ $[M+Na]^+$ 517.9992; found 517.9999.

*tert-butyl 2-bromo-3-(4-methoxy-2-((4-nitrophenyl)sulfonamido)-4-oxobutyl)-1H-indole-1-carboxylate (**2.144**)*



In a dried flask under Ar charged with bromoindole **2.141** (165 mg; 0.331 mmol; 1.0 equiv) in CH_2Cl_2 (1.7 mL) was added portionwise at rt Boc_2O (76 mg; 0.348 mmol; 1.05 equiv) and then DMAP (2.0 mg; 0.017 mmol; 0.05 equiv). The resulting mixture was stirred at rt for 3 h and then quenched with an aqueous solution of 10% $KHSO_4$. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 188 mg (95% yield) of protected bromoindole **2.144** as a light yellow foam.

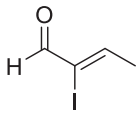
^{1}H NMR (400MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz 1H), 7.66 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.46 – 7.35 (m, 2H), 7.29 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.22 – 7.12 (m, 2H), 5.97 (d, *J* = 7.6 Hz, 1H), 4.39 – 4.23 (m, 1H), 3.73 (s, 3H), 3.10 – 2.95 (m, 2H), 2.86 (dd, *J* = 16.9, 4.3 Hz, 1H), 2.76 (dd, *J* = 16.9, 6.9 Hz, 1H).

^{13}C NMR (100MHz, $CDCl_3$): δ 171.7 (Cq), 148.7 (Cq), 146.5 (Cq), 136.3 (Cq), 134.1 (Cq), 133.0, 132.4, 129.8, 128.2 (Cq), 125.1, 124.7, 123.3, 118.44 (Cq), 118.36, 115.4, 110.7 (Cq), 85.5 (Cq), 52.1, 51.4, 40.4, 30.7, 28.3 (3C).

IR: υ (cm^{-1}) 3287 (w), 2957 (w), 1722 (s), 1621 (w), 1540 (m), 1440 (m), 1336 (m), 1218 (m), 1163 (s), 1072 (m), 737 (s).

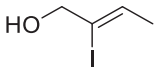
HRMS: (ESI) calcd for $C_{24}H_{26}BrN_3NaO_8S^+$ $[M+Na]^+$ 618.0516; found 618.0521.

*(Z)-2-iodobut-2-enal (**2.149**)*



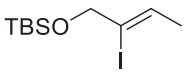
In a flask charged with (*E*)-crotonaldehyde (5.0 g; 71.3 mmol; 1.0 equiv) in THF/H_2O (1/1; 300 mL) was added sequentially at 0 °C K_2CO_3 (11.8 g; 85.6 mmol; 1.2 equiv), molecular iodine (36.2 g; 142.7 mmol; 2.0 equiv) and DMAP (1.74 g; 14.3 mmol; 0.2 equiv). The resulting mixture was stirred at rt for 5 h and diluted with EtOAc and an aqueous solution of 3 M $Na_2S_2O_3$ (150 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (x2). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude iodoenal **2.149** which was used directly as such in the next step.

*(Z)-2-iodobut-2-en-1-ol (**2.150**)*



In a flask charged with crude iodoenal **2.149** in THF/H_2O (9/1; 150 mL) was added portionwise at rt $NaBH_4$ (1.35 g; 35.7 mmol; 0.5 equiv) and the resulting mixture was stirred at rt for 1 h. The mixture was quenched with few water until the gaz evolution ceased and 2/3 of THF were removed under reduced pressure. The concentrated solution was diluted with water and extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude allylic alcohol **2.150** which was used directly as such in the next step.

*(Z)-tert-butyl((2-iodobut-2-en-1-yl)oxy)dimethylsilane (**2.133**)*



In a dried flask under Ar charged with crude allylic alcohol **2.150** in CH_2Cl_2 (150 mL) was added at rt imidazole (7.28 g; 107.0 mmol; 1.5 equiv). After complete dissolution of the base, TBSCl (12.9 g; 85.6 mmol; 1.2 equiv) was added portionwise and the resulting mixture was stirred at rt for 12 h. The mixture was diluted with water and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under

reduced pressure. Purification by FCC (100% PE) afforded 11.7 g (53% yield over 3 steps) of vinyl iodide **2.133** as a colorless oil.

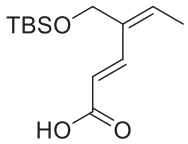
^{1}H NMR (400MHz, $CDCl_3$): δ 5.98 (qt, *J* = 6.5, 1.6 Hz, 1H), 4.26 (p, *J* = 1.6 Hz, 2H), 1.79 (dt, *J* = 6.5, 1.6 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (100MHz, $CDCl_3$): δ 128.9, 109.0 (Cq), 71.7, 26.0 (3C), 21.3, 18.6 (Cq), -5.1 (2C).

IR: υ (cm^{-1}) 2953 (w), 2928 (w), 2855 (w), 1472 (w), 1256 (w), 1131 (w), 1094 (m), 1055 (w), 902 (w), 835 (s), 776 (s), 669 (m).

HRMS: (ESI) calcd for $C_{10}H_{23}OSi^+$ $[M\text{-}I+H+H]^+$ 187.1513; found 187.1514.

*(2E,4E)-4-(((tert-butyldimethylsilyl)oxy)methyl)hexa-2,4-dienoic acid (**2.155**)*



A flask charged with $Pd(OAc)_2$ (71.9 mg; 0.320 mmol; 0.05 equiv), PPh_3 (168.0 mg; 0.640 mmol; 0.1 equiv) and K_2CO_3 (2.66 g; 19.2 mmol; 3.0 equiv) was evacuated for 15 min and then was refilled with Ar. A degassed solution of vinyl iodide **2.133** (2.0 g; 6.40 mmol; 1.0 equiv) and acrylic acid (659 µL; 9.61 mmol; 1.5 equiv) in DMF (32 mL) was added in one portion and the resulting mixture was stirred at 95 °C for 12 h. The mixture was cooled to rt and diluted with CH_2Cl_2 (60 mL) and water (40 mL). 1 N HCl was added until pH 5 (~35 mL). The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (1x100 mL + 3x50 mL). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 917 mg (56% yield) of conjugated acid **2.155** as a yellow oil.

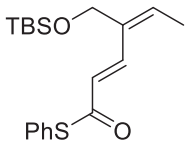
^{1}H NMR (400MHz, $CDCl_3$): δ 11.40 (br s, 1H), 7.78 (dd, *J* = 16.1, 0.9 Hz, 1H), 6.18 (q, *J* = 7.4 Hz, 1H), 5.93 (d, *J* = 16.1 Hz, 1H), 4.30 (p, *J* = 1.4 Hz, 2H), 1.92 (dt, *J* = 7.4, 1.4 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (100MHz, $CDCl_3$): δ 173.0 (Cq), 140.7, 134.6 (Cq), 134.2, 116.7, 63.9, 26.0 (3C), 18.5 (Cq), 13.9, -5.2 (2C).

IR: υ (cm^{-1}) 2951 (w), 2930 (w), 2857 (w), 2573 (w), 1687 (s), 1614 (m), 1417 (w), 1313 (m), 1284 (m), 1253 (m), 1207 (m), 1114 (s), 943 (m), 837 (s), 777 (s).

HRMS: (ESI) calcd for $C_{13}H_{23}O_3Si$ [M-H] 255.1416; found 255.1419.

*S-phenyl (2E,4E)-4-(((tert-butyldimethylsilyl)oxy)methyl)hexa-2,4-dienethioate (**2.153**)*



In a dried flask charged with conjugated acid **2.155** (129 mg; 0.503 mmol; 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise at rt oxalyl chloride (52 µL; 0.604 mmol; 1.2 equiv) and the resulting mixture was stirred at rt for 2 h. Volatiles were removed under reduced pressure and the crude acyl chloride was dissolved in CH_2Cl_2 (2.5 mL) and cooled to -40 °C. In a second dried flask charged with Et_3N (70 µL; 0.503 mmol; 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise at rt PhSH (49 µL; 0.478 mmol; 0.95 equiv). The resulting mixture was stirred at rt for 10 min, cooled to -40 °C and added dropwise to the acyl chloride solution (protected from light with aluminium foil). The resulting mixture was stirred at -40 °C for 1 h, then diluted with CH_2Cl_2 and washed with 1 N HCl (x1) and water (x1). The combined aqueous layer were extracted with CH_2Cl_2 (x1) and was then discarded. The combined organic layers were washed with a saturated aqueous solution of Na_2CO_3 (x1) and water (x1). The combined aqueous layer were extracted with CH_2Cl_2 (x1) and was then discarded. The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 20/1) afforded 144 mg (86% yield) of conjugated thioester **2.153** as a colorless oil.

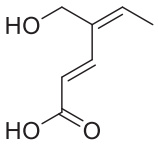
^{1}H NMR (400MHz, $CDCl_3$): δ 7.68 (dd, *J* = 15.8, 0.9 Hz, 1H), 7.53 – 7.36 (m, 5H), 6.31 (d, *J* = 15.8 Hz, 1H), 6.22 (q, *J* = 7.4 Hz, 1H), 4.30 (p, *J* = 1.3 Hz, 2H), 1.91 (dt, *J* = 7.4, 1.3 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (100MHz, $CDCl_3$): δ 188.6 (Cq), 135.30, 135.27, 134.7 (2C), 134.6 (Cq), 129.5, 129.3 (2C), 128.0 (Cq), 123.7, 64.1, 26.1 (3C), 18.5 (Cq), 14.0, -5.2 (2C).

IR: υ (cm^{-1}) 3383 (w), 2965 (w), 2926 (w), 2880 (w), 1727 (m), 1691 (m), 1479 (w), 1442 (w), 1290 (w), 1205 (w), 1024 (s), 1001 (m), 746 (s), 690 (s).

HRMS: (ESI) calcd for $C_{13}H_{15}O_2S^+$ $[M\text{-}TBS+H+H]^+$ 235.0787; found 235.0788.

*(2E,4E)-4-(hydroxymethyl)hexa-2,4-dienoic acid (**2.156**)*



In a flask charged with conjugated acid **2.155** (257 mg; 1.0 mmol; 1.0 equiv) in THF (8 mL) was added dropwise at rt 1 N HCl (4 mL; 4.0 mmol; 4.0 equiv) and the resulting biphasic mixture was vigorously stirred at rt for 1 h. The mixture was diluted with brine and then extracted with EtOAc (x4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 142 mg (quant. yield) of hydroxy acid **2.156** as a white solid.

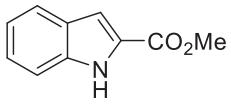
^{1}H NMR (400MHz, $CDCl_3$/CD_3OD : 1/1): δ 7.67 (dd, *J* = 16.0, 0.9 Hz, 1H), 6.09 (q, *J* = 7.2 Hz, 1H), 5.97 (d, *J* = 16.0 Hz, 1H), 4.20 (br s, 2H), 1.88 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$/CD_3OD : 1/1): δ 170.3 (Cq), 139.5, 135.5 (Cq), 134.7, 118.4, 63.7, 13.7.

IR: υ (cm^{-1}) 3235 (w), 2956 (w), 2856 (w), 2674 (w), 2580 (w), 1682 (s), 1610 (m), 1421 (m), 1313 (m), 1287 (s), 1202 (m), 1098 (s), 936 (m), 871 (s), 690 (s).

HRMS: (ESI) calcd for $C_7H_9O_3$ [M-H] 141.0552; found 141.0556.

methyl 1H-indole-2-carboxylate (2.169)



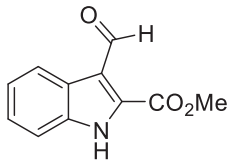
In a flask charged with indole-2-carboxylic acid (15.0 g; 93.1 mmol; 1.0 equiv) in MeOH (186 mL) was added dropwise at rt H_2SO_4 conc. (7.44 mL; 139.6 mmol; 1.5 equiv) and the resulting mixture was stirred at reflux for 12 h. The mixture was cooled to rt and then to 0 °C and the resulting suspension was filtered. Solids were washed with a saturated aqueous solution of $NaHCO_3$ (2x75 mL) and water (2x75 mL). The solids remaining in the filtrate was filtered and washed with a saturated aqueous solution of $NaHCO_3$ (1x45 mL) and water (2x45 mL). The combined solids were dried under reduced pressure to afford 15.0 g (92% yield) of ester **2.169** as a light brown solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.71 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.17 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 3.97 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 162.7 (Cq), 137.0 (Cq), 127.5 (Cq), 127.1, 125.4, 122.6, 120.8, 112.0, 108.8, 52.0.

The spectroscopic data of this compound are in accord with these reported in the literature.[19]

*methyl 3-formyl-1H-indole-2-carboxylate (**2.170**)*



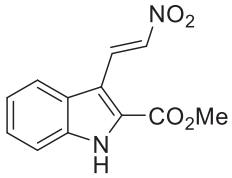
In a dried flask under Ar charged with DMF (23.1 mL; 299.7 mmol; 3.5 equiv) was added dropwise at 0 °C $POCl_3$ (8.38 mL; 89.9 mmol; 1.05 equiv). After 5-10 min, a solution of ester **2.169** (15.0 g; 85.6 mmol; 1.0 equiv) in DMF (30 mL) was added dropwise at 0 °C and the resulting mixture was stirred at rt for 30 min and then at 60 °C for 3.5 h. The mixture was cooled to rt, poured into ice (~350 mL) and neutralized with a saturated solution of Na_2CO_3 until pH 8. The resulting suspension was filtered and solids were washed with water (2x100 mL) and dried under reduced pressure to afford 17.3 g (99% yield) of aldehyde **2.170** as a light yellow solid.

^{1}H NMR (400MHz, DMSO-*d*$_6$): δ 12.85 (br s, 1H), 10.59 (s, 1H), 8.23 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.39 (m, 1H), 7.29 (m, 1H), 3.98 (s, 3H).

^{13}C NMR (100MHz, DMSO-*d*$_6$): δ 187.6, 160.7 (Cq), 135.9 (Cq), 132.5 (Cq), 126.0, 124.8 (Cq), 123.6, 122.5, 118.6 (Cq), 113.3, 52.9.

The spectroscopic data of this compound are in accord with these reported in the literature.[20]

*methyl (E)-3-(2-nitrovinyl)-1H-indole-2-carboxylate (**2.171**)*



To a suspension under Ar of aldehyde **2.170** (8.13 g; 40.0 mmol; 1.0 equiv) in $MeNO_2$ (160 mL) was added in one portion at rt NH_4OAc (dried before use; 3.39 g; 44.0 mmol; 1.1 equiv) and the resulting mixture was stirred at reflux (oil bath at 105 °C) for 2 h behind a safety shield. The suspension was cooled to rt, diluted with water (80 mL) and then the biphasic mixture was cooled to 0 °C. The suspension was filtered and solids were washed with water (2x80 mL) and dried under reduced pressure to afford 8.64 g (88% yield) of nitrovinyl **2.171** as a light green solid.

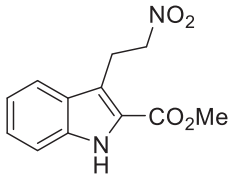
^{1}H NMR (400MHz, DMSO-*d*$_6$): δ 12.92 (s, 1H), 8.99 (d, *J* = 13.8 Hz, 1H), 8.17 (d, *J* = 13.8 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 3.97 (s, 3H).

^{13}C NMR (100MHz, DMSO-*d*$_6$): δ 160.9 (Cq), 136.7 (Cq), 135.8, 132.1, 129.8 (Cq), 126.2, 124.5 (Cq), 123.1, 122.1, 113.7, 111.3 (Cq), 52.7.

IR: υ (cm^{-1}) 3306 (w), 2958 (w), 1677 (m), 1621 (w), 1516 (w), 1462 (w), 1315 (s), 1283 (s), 1234 (s), 1155 (w), 990 (w), 965 (m), 741 (s), 723 (s).

HRMS: (ESI) calcd for $C_{12}H_{10}N_2NaO_4^+$ [M+Na]$^+$ 269.0533; found 269.0532.

methyl 3-(2-nitroethyl)-1H-indole-2-carboxylate (2.167)



To a partial suspension of vinylnitro **2.171** (6.16 g; 25.0 mmol; 1.0 equiv) in $CHCl_3$/MeOH (1/1; 50 mL) was added at rt $NaBH_4$ (473 mg; 12.5 mmol; 0.5 equiv) every 15 min until 3.0 equivalents of $NaBH_4$ were reached (1.25 h). The resulting mixture was stirred at rt for additional 2 h. Note: The yellow suspension turned to an orange suspension then to an orange solution and finally to a light yellow / colorless solution. The mixture was diluted with CH_2Cl_2 (50 mL) and quenched with a aqueous solution of 10% $KHSO_4$ until pH 2. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (solid deposition; PE/EtOAc : 2/1) afforded 1.1 g (89% yield) of aliphatic nitro **2.167** as a white solid.

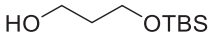
^{1}H NMR (400MHz, $CDCl_3$): δ 8.90 (s, 1H), 7.71 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.20 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 4.69 (dd, *J* = 7.8, 7.1 Hz, 2H), 3.98 (s, 3H), 3.81 (dd, *J* = 7.8, 7.1 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 162.1 (Cq), 135.9 (Cq), 127.6 (Cq), 126.4, 124.0 (Cq), 121.2, 120.3, 117.9 (Cq), 112.1, 75.3, 52.2, 23.3.

IR: υ (cm^{-1}) 3338 (m), 2955 (w), 1677 (s), 1544 (s), 1461 (m), 1381 (m), 1333 (m), 1261 (s), 1198 (m), 1100 (m), 971 (m), 853 (w), 777 (m), 745 (s).

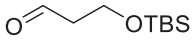
HRMS: (ESI) calcd for $C_{12}H_{11}N_2O_4$ [M-H] 247.0719; found 247.0720.

*3-((tert-butyldimethylsilyl)oxy)propan-1-ol (**2.173**)*



To a suspension under Ar of NaH (60% in mineral oil; prewashed with PE three times; 2.0 g; 50.0 mmol; 1.0 equiv) in THF (80 mL) was added dropwise at rt propane-1,3-diol (3.62 mL; 50.0 mmol; 1.0 equiv). The resulting mixture was stirred at rt for 1h then cooled to 0 °C. A solution of TBSCl (7.54 g; 50.0 mmol; 1.0 equiv) in THF (20 mL) was added dropwise and the mixture was stirred at rt for additional 1 h. The mixture was diluted with Et_2O, washed with a saturated solution of Na_2CO_3 (x1) and brine (x3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude monoprotected diol **2.173** which was used directly as such in the next step.

*3-((tert-butyldimethylsilyl)oxy)propanal (**2.165**)*



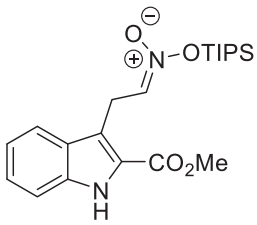
In a dried flask under Ar charged with oxalyl chloride (5.15 mL; 60.0 mmol; 1.2 equiv) in CH_2Cl_2 (200 mL) was added dropwise at -78 °C DMSO (8.52 mL; 120.0 mmol; 2.4 equiv). After stirring at -78 °C for 15 min, crude monoprotected diol **2.173** was added dropwise. After stirring at -78 °C for additional 30 min, Et_3N (34.8 mL; 250.0 mmol; 5.0 equiv) was added dropwise. The resulting mixture was stirred at -78 °C for 15 min and then at rt for 1 h. The mixture was diluted with CH_2Cl_2 (250 mL) and washed with water (1x200 mL). The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (1x100 mL) and was then discarded. The combined organic layers were washed with an aqueous solution of 10% $KHSO_4$ (1x200 mL). The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (1x100 mL) and was then discarded. The combined organic layers were washed with an aqueous solution of 1% $KHSO_4$ (1x100 mL), a saturated aqueous solution of $NaHCO_3$ (1x100 mL) and brine (1x200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by distillation (P=1 mmbar; T=45 °C; T oil bath from 65 to 95 °C) afforded 7.68 g (82% over 2 steps) of aldehyde **2.165** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 9.80 (t, *J* = 2.1 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.60 (td, *J* = 6.0, 2.1 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100MHz, $CDCl_3$): δ 202.2 (Cq), 57.6, 46.7, 26.0 (3C), 18.4 (Cq), -5.3 (2C).

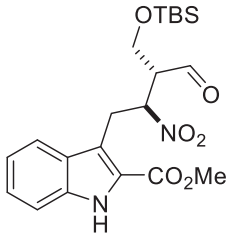
The spectroscopic data of this compound are in accord with these reported in the literature.[21]

*methyl (E)-3-(2-(oxido((triisopropylsilyl)oxy)azanylidene)ethyl)-1H-indole-2-carboxylate (**2.166**)*



In a dried flask under Ar charged with aliphatic nitro **2.167** (497 mg; 2.00 mmol; 1.0 equiv) in CH_2Cl_2 (6 mL) was added dropwise at 0 °C TIPSCl (449 μL; 2.10 mmol; 1.05 equiv). After stirring at 0 °C for 5 min, DBU (320 μL; 2.14 mmol; 1.07 equiv) was added over a period of 30-60 seconds and the resulting mixture was stirred at 0 °C for 30 min. The mixture was then diluted with CH_2Cl_2 (60 mL), washed with water (1x30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude silyl nitronate **2.166** was directly used as such in the next step.

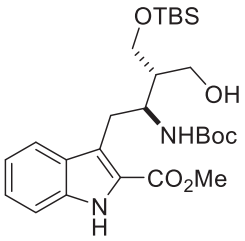
*methyl 3-(4-((tert-butyldimethylsilyl)oxy)-3-formyl-2-nitrobutyl)-1H-indole-2-carboxylate (**2.164**)*



A flask charged with the MacMillan catalyst *cis* 5-benzyl-2-(tert-butyl)-3-methylimidazolidin-4-one (98.5 mg; 0.40 mmol; 0.2 equiv), CAN (2.25 g; 4.10 mmol; 2.05 equiv) and $NaHCO_3$ (336.0 mg; 4.00 mmol; 2.0 equiv) was evacuated for 15 min, refilled with Ar and cooled to -78 °C. Cold degassed THF (-78 °C; 10 mL) was added in one portion followed by addition of H_2O (72 μL; 4.00 mmol; 2.0 equiv). The resulting suspension was purged three times (vacuum-Ar). Aldehyde **2.165** (753.4 mg; 4.00 mmol; 2.0 equiv) and a cold solution of crude silyl nitronate **2.166** in degassed THF (-78 °C; 5 mL) were added sequentially at -78 °C and the suspension was purged additional three times (vacuum-Ar). The resulting mixture was stirred at -30 °C for 20 h. The mixture was cooled to -78 °C and diluted with cold Et_2O (-78 °C; 100 mL). After stirring at -78 °C for 5 min the suspension was filtered through a pad of Celite. The reaction flask and the pad were washed with additional Et_2O (~100 mL). While the filtrate was still cold, it was washed with water

(3x50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude nitroaldehyde **2.164** was directly used as such in the next step.

*methyl 3-(2-((tert-butoxycarbonyl)amino)-4-((tert-butyldimethylsilyl)oxy)-3-(hydroxymethyl)butyl)-1H-indole-2-carboxylate (**2.174**)*



In a flask under Ar charged with crude nitroaldehyde **2.164** in MeOH (20 mL) was added at 0 °C Boc_2O (646 mg; 3.00 mmol; 1.5 equiv) and then $NiCl_2.H_2O$ (951 mg; 4.00 mmol; 2.0 equiv). After complete dissolution of solids, $NaBH_4$ (378 mg; 10.0 mmol; 5.0 equiv) was added portionwise at 0 °C and the resulting black suspension was stirred at 0 °C for 30 min. Additional Boc_2O (218 mg; 1.0 mmol; 0.5 equiv) and $NaBH_4$ (378 mg; 10.0 mmol; 5.0 equiv) were added portionwise and the resulting mixture was stirred at rt for 45 min. Then, 2/3 of MeOH were removed under reduced pressure (water bath at 35 °C). The concentrated mixture was diluted with CH_2Cl_2 and washed with a half-saturated aqueous solution of NH_4Cl (x1). The aqueous phase was extracted with CH_2Cl_2 (x3) and the combined organic layers were dried over Na_2SO_4, filtered through a pad of Celite and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 168 mg (17% yield over 3 steps) of *N*-protected amino alcohol **2.174**. Note: The same 3-step process was carried out on 0.050 mmol and 0.15 mmol and gave respectively 8.3 mg (33%) and 23.5 mg (31%) of desired product **2.174**.

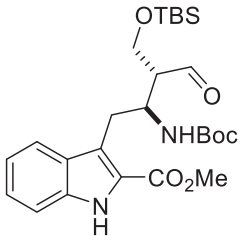
^{1}H NMR (400MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.15 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H), 5.56 (d, *J* = 8.6 Hz, 1H), 4.02 (td, *J* = 11.0, 10.3, 4.3 Hz, 1H), 3.92 (s, 3H), 3.91 – 3.80 (m, 3H), 3.49 (dd, *J* = 13.6, 5.0 Hz, 1H), 3.23 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.98 (s, 1H), 1.90 (q, *J* = 5.6 Hz, 1H), 1.59 (s, 1H), 1.21 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (100MHz, $CDCl_3$): δ 162.8 (Cq), 156.2 (Cq), 136.0 (Cq), 128.3 (Cq), 126.0, 123.4 (Cq), 122.6 (Cq), 121.2, 120.6, 111.8, 78.8 (Cq), 63.8, 62.1, 52.6, 52.0, 46.6, 28.4, 28.3 (3C), 26.0 (3C), 18.3 (Cq), -5.4 (2C).

IR: υ (cm^{-1}) 3367 (w), 2955 (m), 2926 (m), 2855 (w), 1695 (s), 1513 (w), 1457 (m), 1367 (w), 1321 (w), 1253 (s), 1170 (m), 1097 (m), 839 (m), 779 (m), 746 (m).

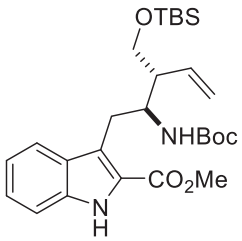
HRMS: (ESI) calcd for $C_{26}H_{42}N_2NaO_6Si^+$ $[M+Na]^+$ 529.2704; found 529.2714.

*methyl 3-(2-((tert-butoxycarbonyl)amino)-4-((tert-butyldimethylsilyl)oxy)-3-formylbutyl)-1H-indole-2-carboxylate (**2.163a**)*



To a suspension under Ar of DMP (143 mg; 0.336 mmol; 1.2 equiv) in CH_2Cl_2 (1.4 mL) was added dropwise at 0 °C a solution of protected amino alcohol **2.174** (142 mg; 0.280 mmol; 1.0 equiv) in CH_2Cl_2 (1.4 mL). The resulting mixture was stirred at rt for 3 h, then diluted with CH_2Cl_2 and washed with a mixture of saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ (1/1, x2). The aqueous phase was extracted with CH_2Cl_2 (x2) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde **2.163a** was directly used as such in the next step.

*methyl 3-(-2-(((tert-butoxycarbonyl)amino)-3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-2-carboxylate (**2.163**)*



A flask charged with methyltriphenylphosphonium bromide (550 mg; 1.54 mmol; 5.5 equiv) and *t*-BuOK (157 mg; 1.40 mmol; 5.0 equiv) was dried under vacuum, then refilled with Ar and cold to 0 °C. A cold solution of THF (0 °C; 4.2 mL) was added in one portion and the resulting suspension was stirred at 0 °C for 1 h. A solution of crude aldehyde **2.163a** in THF (1.4 mL) was added dropwise at 0 °C and the mixture was stirred at rt for 2 h. The mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl (x2). The aqueous phase was extracted with EtOAc (x2) and the combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 4/1) afforded 93 mg (66% yield over 2 steps) of vinyl **2.163** as a white foam.

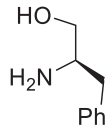
^{1}H NMR (400MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.12 (ddd, *J* = 8.0, 6.6, 1.2 Hz, 1H), 5.88 (ddd, *J* = 17.1, 10.6, 8.0 Hz, 1H), 5.33 – 5.08 (m, 3H), 4.18 (dq, *J* = 10.6, 6.2, 5.1 Hz, 1H), 3.91 (s, 3H), 3.82 (dd, *J* = 10.1, 8.0 Hz, 1H), 3.70 (dd, *J* = 10.1, 6.1 Hz, 1H), 3.31 (dd, *J* = 13.5, 5.2 Hz, 1H), 3.21 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.55 (dd, *J* = 10.6, 6.2 Hz, 1H), 1.17 (s, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 162.9 (Cq), 155.4 (Cq), 136.03 (Cq), 135.99, 128.5 (Cq), 125.7, 123.7 (Cq), 121.9 (Cq), 121.3, 120.3, 118.1, 111.8, 78.4 (Cq), 63.8, 53.0, 51.8, 49.3, 28.2 (3C), 28.0, 26.1 (3C), 18.3 (Cq), -5.3, -5.4.

IR: υ (cm^{-1}) 3329 (w), 2953 (w), 2928 (w), 2859 (w), 1695 (s), 1502 (w), 1456 (m), 1367 (m), 1251 (s), 1172 (s), 1097 (s), 1066 (m), 1005 (m), 920 (w), 837 (s), 777 (s), 742 (s).

HRMS: (ESI) calcd for $C_{27}H_{42}N_2NaO_5Si^+$ $[M+Na]^+$ 525.2755; found 525.2754.

*(R)-2-amino-3-phenylpropan-1-ol (**2.186**)*



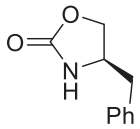
In a dried flask under Ar charged with *D*-phenylalanine (33.0 g; 200 mmol; 1.0 equiv) in THF (400 mL) was added in one portion at 0 °C $NaBH_4$ (18.9 g; 500 mmol; 2.5 equiv). A solution of molecular iodine (50.7 g; 200 mmol; 1.0 equiv) in THF (200 mL) was added dropwise at 0 °C over a period of 1.5 h. The resulting suspension was stirred at rt for 5 h and then at reflux for 12 h. The suspension was cooled to 0 °C and MeOH (200 mL) was added dropwise. After stirring at rt for 30 min, the resulting clear solution was concentrated under reduced pressure. The residue was dissolved in a freshly prepared KOH aqueous solution (80 g in 400 mL) and stirred at rt for 5 h. The mixture was then extracted with CH_2Cl_2 (6x200 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by recrystallization in EtOAc (100 mL; reflux and slowly cooled to -20 °C, 12 h; after filtration, solids were washed with PE twice) afforded 25.4 g (84% yield) of amino alcohol **2.186** as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 2H), 7.25 – 7.15 (m, 3H), 3.64 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.38 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.19 – 3.05 (m, 1H), 2.80 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.54 (dd, *J* = 13.5, 8.4 Hz, 1H), 1.78 (br s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 138.8 (Cq), 129.4 (2C), 128.8 (2C), 126.7, 66.6, 54.4, 41.2.

The spectroscopic data of this compound are in accord with these reported in the literature.[22]

*(R)-4-benzyloxazolidin-2-one (**2.187**)*



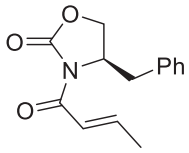
To a suspension of amino alcohol **2.186** (25.4 g; 168 mmol; 1.0 equiv) in diethyl carbonate (41.7 mL; 344 mmol; 2.05 equiv) was added in one portion at rt K_2CO_3 (2.3 g; 16.8 mmol; 0.1 equiv). The mixture was heated to 120 °C (oil bath) and stirred until complete dissolution of amino alcohol **2.186**. The mixture was then further heated to 140 °C and stirred 2 h while EtOH was distilled. The mixture was cooled to rt, diluted with CH_2Cl_2 (200 mL) and washed with brine (150 mL). The aqueous phase was extracted with CH_2Cl_2 (3x100 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure (the greatest possible amount of residual diethyl carbonate was removed as this stage). Purification by recrystallization in EtOAc/hexane (2/1, 75 mL; reflux and slowly cooled to -20 °C, 12 h; after filtration, solids were washed with PE twice) afforded 20.7 g (70% yield) of oxazolidinone **2.187** as a white solid. The mother liquor was concentrated under reduced pressure and purified by FCC (PE/EtOAc : 1/2) to afford additional 3.4 g (11% yield) of **2.187**. Combined yield: 81%.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.20 – 7.13 (m, 2H), 5.48 (br s, 1H), 4.46 (t, *J* = 8.3 Hz, 1H), 4.15 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.13 – 4.04 (m, 1H), 2.88 (d, *J* = 6.8 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 159.3 (Cq), 136.1 (Cq), 129.2 (2C), 129.1 (2C), 127.4, 69.8, 53.9, 41.6.

The spectroscopic data of this compound are in accord with these reported in the literature.[22]

*(R,E)-4-benzyl-3-(but-2-enoyl)oxazolidin-2-one (**2.182**)*



In a dried flask charged with oxazolidinone **2.187** (22.5 g; 127 mmol; 1.0 equiv) in THF (450 mL) was added dropwise at -78 °C *n*-BuLi (2.4 M in hexane; 52.9 mL; 127 mmol, 1.0 equiv). After stirring at -78 °C for 15 min, crotonyl chloride (13.4 mL; 140 mmol; 1.1 equiv) was added dropwise. The resulting mixture was stirred at -78 °C for 15 min and then slowly warmed to rt over 1.5 h. The mixture was quenched by dropwise addition of a saturated aqueous solution of

NH_4Cl (5-10 mL) and 2/3 of THF were removed under reduced pressure. The concentrated solution was diluted with EtOAc (300 mL) and a saturated aqueous solution of NH_4Cl (200 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (2x150 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1x150 mL) and brine (1x150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 3/1) afforded 28.3 g (91% yield) of imide **2.182** as a white solid.

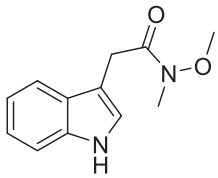
^{1}H NMR (400MHz, $CDCl_3$): δ 7.39 – 7.18 (m, 7H), 4.74 (ddt, *J* = 9.5, 7.5, 3.3 Hz, 1H), 4.25 – 4.16 (m, 2H), 3.34 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.81 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.00 (d, *J* = 5.3 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 165.1 (Cq), 153.6 (Cq), 147.1, 135.5 (Cq), 129.6 (2C), 129.1 (2C), 127.4, 122.0, 66.2, 55.4, 38.0, 18.7.

$[\alpha]_D^{23.4}$ = -69.7 (*c* 0.5, $CHCl_3$); lit. $[\alpha]_D^{23}$ = -70.6 (*c* 0.5, $CHCl_3$).

The spectroscopic data of this compound are in accord with these reported in the literature.[23]

*2-(1H-indol-3-yl)-N-methoxy-N-methylacetamide (**2.188**)*



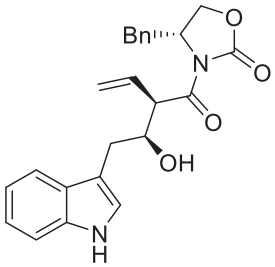
To a suspension under Ar of indole-3-acetic acid (52.6 g; 300 mmol; 1.0 equiv) in CH_2Cl_2 (600 mL) was added portionwise at 0 °C CDI (58.4 g; 360 mmol; 1.2 equiv) and the resulting mixture was stirred at rt for 2 h. Note: The starting mixture became a clear solution before turning back to a suspension. The mixture was cooled to 0 °C, N,O-dimethylhydroxylamine hydrochloride (43.9 g; 450 mmol; 1.5 equiv) was added portionwise and the resulting mixture was stirred at rt for additional 12 h. The mixture was diluted with water (500 mL), extracted with CH_2Cl_2 (2x100 mL) and the aqueous phase was then discarded. The combined organic layers were washed with 1 N HCl (1x250 mL) and the acidic aqueous phase was extracted with CH_2Cl_2 (1x100 mL). The combined organic layers were washed with brine (1x250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by recrystallization in EtOAc (250 mL; reflux and slowly cooled to -20 °C, 12 h; after filtration, solids were washed with PE twice) afforded 63.2 g (97% yield) of Weinreb amide **2.188** as a beige solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.18 (td, *J* = 8.0, 7.5, 1.3 Hz, 1H), 7.15 – 7.09 (m, 2H), 3.92 (s, 2H), 3.66 (s, 3H), 3.22 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 173.2 (Cq), 136.3 (Cq), 127.5 (Cq), 123.5, 121.9, 119.5, 118.8, 111.4, 108.7 (Cq), 61.5, 32.5, 29.1.

The spectroscopic data of this compound are in accord with these reported in the literature.[24]

*(R)-4-benzyl-3-((R)-2-((S)-1-hydroxy-2-(1H-indol-3-yl)ethyl)but-3-enoyl)oxazolidin-2-one (**2.181**)*



In a dried flask under Ar charged with Weinreb amide **2.188** (8.73 g; 40.0 mmol; 1.0 equiv) in CH_2Cl_2 (200 mL) was added dropwise at -78 °C DIBAL (1.2 M in toluene; 40 mL; 48.0 mmol; 1.2 equiv) and the resulting mixture was stirred at -78 °C for 1 h. The mixture was quenched by dropwise addition of MeOH (485 μL; 0.3 equiv) at -78 °C. After the gas evolution stopped, the cold bath was removed and the mixture was diluted with CH_2Cl_2 (100 mL) and washed with an aqueous solution of 10% $KHSO_4$ (1x200 mL) until a yellow/light orange color persisted (~5 min). Note: After adding $KHSO_4$, the starting yellow solution became blue, then green, then red and finished yellow/light orange. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were washed with brine (1x200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Under Ar, the crude aldehyde **2.184** was dissolved in CH_2Cl_2 (40 mL) and stirred over molecular sieves 3 Å (powder) for 0.5 – 1 h.

In parallel, in a dried flask under Ar charged with imide **2.182** (4.91 g; 20.0 mmol; 1.0 equiv) in CH_2Cl_2 (60 mL) was added dropwise at -78 °C *n*-Bu_2BOTf (1 M in CH_2Cl_2; 22.0 mL; 1.1 equiv). After stirring at -78 °C for 5 min, Et_3N (3.90 mL; 28.0 mmol; 1.4 equiv) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h and then at 0 °C for 15-20 min. The mixture was cooled to -78 °C and the crude solution of aldehyde **2.184** in CH_2Cl_2 prepared above was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and then at 0 °C for 1 h.

The mixture was quenched at 0 °C by sequential dropwise addition of buffer pH 7 (40 mL) and H_2O_2 (30% in H_2O; 40 mL) and the resulting biphasic mixture was vigorously stirred at 0 °C for 45 min and then at rt for 15 min. The mixture was diluted with CH_2Cl_2 (80 mL) and water (80 mL)

and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2x100 mL) and was then discarded. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1x150 mL) and the basic aqueous phase was extracted with CH_2Cl_2 (1x100 mL) and was then discarded. The combined organic layers were washed with brine (1x150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : from 2/1 to 3/2) afforded 6.0 g (74% yield) of aldol adduct **2.181** as a light brown foam.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.22 – 7.07 (m, 5H), 6.21 – 6.07 (m, 1H), 5.52 – 5.48 (m, 1H), 5.46 (s, 1H), 4.64 (dd, *J* = 9.1, 4.2 Hz, 1H), 4.54 (ddt, *J* = 9.5, 7.9, 3.0 Hz, 1H), 4.41 (td, *J* = 6.5, 4.2 Hz, 1H), 4.07 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.00 (dd, *J* = 8.9, 7.9 Hz, 1H), 3.20 (dd, *J* = 13.4, 3.0 Hz, 1H), 3.09 – 2.96 (m, 2H), 2.90 (s, 1H), 2.73 (dd, *J* = 13.4, 9.5 Hz, 1H).

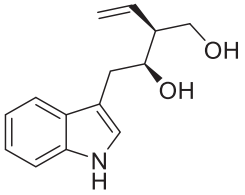
^{13}C NMR (100MHz, $CDCl_3$): δ 173.8 (Cq), 152.9 (Cq), 136.4 (Cq), 135.1 (Cq), 131.7, 129.6 (2C), 129.0 (2C), 127.6 (Cq), 127.5, 123.2, 122.2, 121.8, 119.5, 119.0, 111.7 (Cq), 111.3, 71.7, 66.0, 55.1, 51.8, 37.7, 30.4.

IR: υ (cm^{-1}) 3374 (w), 3081 (w), 2954 (w), 2916 (w), 2857 (w), 1772 (m), 1685 (m), 1457 (m), 1361 (m), 1211 (s), 1082 (m), 996 (m), 928 (w), 817 (w), 740 (s), 702 (s).

HRMS: (ESI) calcd for $C_{24}H_{24}N_2NaO_4^+$ $[M+Na]^+$ 427.1628; found 427.1620.

$[\alpha]_D^{28.8}$ = -16.0 (*c* 1.0, $CHCl_3$)

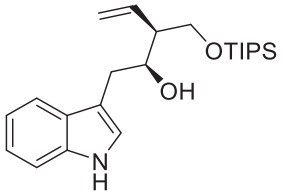
*(2S,3S)-4-(1H-indol-3-yl)-2-vinylbutane-1,3-diol (**2.189**)*



In a flask under Ar charged with aldol adduct **2.181** (5.90 g; 14.6 mmol; 1.0 equiv) in THF (73 mL) was added dropwise sequentially at 0 °C MeOH (1.20 mL; 29.2 mmol; 2.0 equiv) and a freshly prepared solution of $LiBH_4$ (635 mg; 29.2 mmol, 2.0 equiv) in THF (30 mL). The resulting mixture was stirred at 0 °C for 30 min and then NaOH (10% in H_2O; 60 mL) was added dropwise at 0 °C. The resulting biphasic mixture was stirred vigorously at rt for 10 min and extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to afford crude diol **2.189** which was used directly as such in the next step.

*(2S,3S)-1-(1H-indol-3-yl)-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-2-ol (**2.190**)*



In a dried flask under Ar charged with crude diol **2.189** in CH_2Cl_2 (73 mL) was added portionwise at rt imidazole (1.29 g; 19.0 mmol; 1.3 equiv). After complete dissolution of the base, the mixture was cooled to 0 °C, TIPSCl (3.43 mL; 16.0 mmol; 1.1 equiv) was added dropwise and the resulting mixture was stirred at rt for 12 h. The mixture was diluted with water and extracted with CH_2Cl_2 (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 5/1) afforded 4.74 g (84% yield over 2 steps) of compound **2.190** as a light yellow oil, then (PE/EtOAc : 1/2) afforded 2.03 g (78% recovered) of oxazolidinone **2.187**.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.65 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 7.9, 7.0, 1.2 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 6.14 (ddd, *J* = 17.3, 10.4, 9.1 Hz, 1H), 5.29 (dd, *J* = 10.4, 2.1 Hz, 1H), 5.19 (dd, *J* = 17.3, 2.1 Hz, 1H), 4.34 (td, *J* = 6.9, 2.5 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.14 (s, 1H), 2.94 (d, *J* = 6.9 Hz, 2H), 2.33 (tdd, *J* = 9.1, 4.9, 2.5 Hz, 1H), 1.12 – 1.02 (m, 21H).

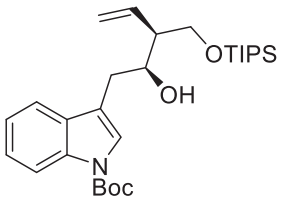
^{13}C NMR (100MHz, $CDCl_3$): δ 136.5 (Cq), 135.5, 127.8 (Cq), 122.7, 122.1, 119.4, 119.2, 118.4, 113.0 (Cq), 111.2, 73.2, 67.7, 49.7, 31.1, 18.1 (6C), 11.9 (3C).

IR: υ (cm^{-1}) 3414 (w), 3059 (w), 2942 (m), 2866 (m), 1459 (m), 1425 (w), 1338 (w), 1247 (w), 1091 (s), 997 (m), 920 (m), 883 (m), 740 (s), 679 (s).

HRMS: (ESI) calcd for $C_{23}H_{38}NO_2Si^+$ $[M+H]^+$ 388.2666; found 388.2666.

$[\alpha]_D^{28.5}$ = -1.1 (*c* 1.0, $CHCl_3$)

*tert-butyl 3-((2S,3S)-2-hydroxy-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.180**)*



In a dried flask under Ar charged with compound **2.190** (4.47 g; 11.5 mmol; 1.0 equiv) in CH_2Cl_2 (115 mL) was added dropwise at rt a solution of Boc_2O (2.64 g; 12.1 mmol; 1.05 equiv) in CH_2Cl_2 (35 mL). DMAP (70 mg; 0.58 mmol; 0.05 equiv) was then added in one portion at rt and the resulting mixture was stirred at rt for 4 h. The mixture was diluted with water and extracted with CH_2Cl_2 (x2). The combined organic layers were washed with brine (x1) dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 10/1) afforded 5.09 g (91% yield) of alcohol **2.180** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): 8.13 (br d, *J* = 8.4 Hz, 1H), 7.56 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.46 (s, 1H), 7.31 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.23 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 6.12 (ddd, *J* = 17.3, 10.4, 9.2 Hz, 1H), 5.30 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.19 (dd, *J* = 17.3, 2.0 Hz, 1H), 4.33 (dt, *J* = 6.9, 2.4 Hz, 1H), 3.94 (d, *J* = 4.6 Hz, 2H), 3.22 (s, 1H), 2.86 (d, *J* = 6.9 Hz, 2H), 2.34 (tdd, *J* = 9.2, 4.6, 2.4 Hz, 1H), 1.66 (s, 9H), 1.17 – 0.98 (m, 21H).

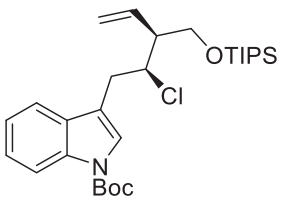
^{13}C NMR (100MHz, $CDCl_3$): δ 149.9 (Cq), 135.7 (Cq), 135.1, 130.9 (Cq), 124.4, 123.9, 122.5, 119.3, 118.7, 117.7 (Cq), 115.4, 83.5 (Cq), 72.7, 67.6, 49.8, 30.8, 28.4 (3C), 18.1 (6C), 11.9 (3C).

IR: υ (cm^{-1}) 3473 (w), 3055 (w), 2953 (w), 2930 (w), 2857 (w), 1733 (s), 1456 (m), 1371 (s), 1255 (s), 1159 (s), 1091 (s), 1020 (m), 839 (s), 773 (s), 746 (s).

HRMS: (ESI) calcd for $C_{28}H_{45}NNaO_4Si^+$ $[M+Na]^+$ 510.3010; found 510.3005.

$[\alpha]_D^{28.7}$ = -5.6 (*c* 1.0, $CHCl_3$)

*tert-butyl 3-((2S,3S)-2-chloro-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.193**)*



In a dried flask under Ar charged with $SOCl_2$ (2.53 mL; 34.9 mmol; 5.0 equiv) in 1,2-DCE (70 mL) was added dropwise at 0 °C 2,6-lutidine (8.88 mL; 76.7 mmol; 11.0 equiv). After stirring at 0 °C for 5-10 min, a solution of alcohol **2.180** (3.40 g; 6.97 mmol; 1.0 equiv) in 1,2-DCE (35 mL) was added dropwise at 0 °C over a period of 10 min and the resulting mixture was stirred at rt for 12 h. The mixture was diluted with CH_2Cl_2, washed with water (x1) and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were washed with brine (x1) dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 97/3) afforded 3.13 g (89% yield) of chloride **2.193** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.13 (br d, *J* = 8.4 Hz 1H), 7.51 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.44 (s, 1H), 7.31 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.21 (ddd, *J* = 7.9, 7.2, 1.2 Hz, 1H), 5.87 (ddd, *J* = 17.2, 10.4, 9.0 Hz, 1H), 5.31 (dd, *J* = 10.4, 1.9 Hz, 1H), 5.21 (dd, 17.2, 1.9 Hz, 1H), 4.78 (td, *J* = 7.5, 2.2 Hz, 1H), 3.83 (t, *J* = 9.6 Hz, 1H), 3.64 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.21 – 3.04 (m, 2H), 2.61 (tdd, *J* = 9.0, 5.2, 2.2 Hz, 1H), 1.67 (s, 10H), 1.09 – 0.93 (m, 21H).

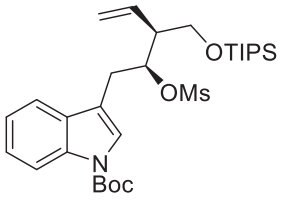
^{13}C NMR (100MHz, $CDCl_3$): δ 149.8 (Cq), 135.6 (Cq), 133.5, 130.4 (Cq), 124.5, 124.1, 122.6, 120.1, 119.1, 117.1 (Cq), 115.4, 83.6, 64.1, 61.1, 51.5, 32.8, 28.4 (3C), 18.1 (6C), 12.1 (3C).

IR: υ (cm^{-1}) 3073 (w), 2924 (w), 2853 (w), 1731 (s), 1456 (m), 1373 (s), 1255 (s), 1159 (s), 1093 (m), 1001 (w), 927 (w), 841 (m), 750 (m), 696 (w).

HRMS: (ESI) calcd for $C_{28}H_{44}ClNNaO_3Si^+$ $[M+Na]^+$ 528.2671; found 528.2672.

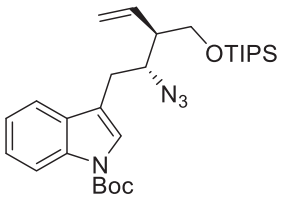
$[\alpha]_D^{30.1}$ = -13.7 (*c* 0.25, $CHCl_3$)

*tert-butyl 3-((2S,3S)-2-((methylsulfonyl)oxy)-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.192**)*



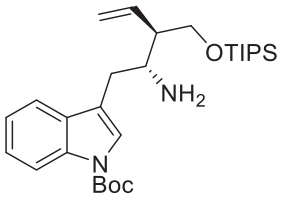
In a dried flask under Ar charged with alcohol **2.180** (4.50 g; 9.23 mmol; 1.0 equiv) in CH_2Cl_2 (92 mL) was added dropwise sequentially at 0 °C Et_3N (1.93 mL; 13.8 mmol; 1.5 equiv) and MsCl (857 µL; 11.1 mmol; 1.2 equiv) and the resulting mixture was stirred at rt for 1 h. The mixture was diluted with water and extracted with CH_2Cl_2 (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude mesylate **2.192** which was used directly as such in the next step.

*tert-butyl 3-((2R,3R)-2-azido-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.194**)*



In a dried flask under Ar charged with crude mesylate **2.192** was added in one portion at rt a solution of TBAAz (5.25 g; 18.5 mmol; 2.0 equiv) in MeCN (37 mL). After complete dissolution of crude **2.192**, the resulting mixture was stirred at 60-65 °C for 20 h. The mixture was cooled to rt and volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with water (x1). The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude azide **2.194** which was used directly as such in the next step.

*tert-butyl 3-((2R,3R)-2-amino-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.195**)*



In a flask under Ar charged with crude azide **2.194** in THF/H_2O (2/1; 84 mL) was added portionwise at rt PPh_3 (3.63 g; 13.9 mmol; 1.5 equiv) and the resulting mixture was stirred at 35-40 °C for 12 h. Volatiles were removed under reduced pressure and residual water were coevaporated with toluene. Purification by FCC (PE/EtOAc/Et_3N) : 80/20/1) afforded 2.91 g (65% yield over 3 steps) of amine **2.195** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.45 (s, 1H), 7.31 (ddd, *J* = 8.5, 7.2, 1.2 Hz, 1H), 7.22 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1H), 6.01 – 5.84 (m, 1H), 5.23 (s, 1H), 5.22 – 5.18 (m, 1H), 3.96 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.88 (dd, *J* = 10.1, 6.2 Hz, 1H), 3.37 (ddd, *J* = 10.6, 6.4, 2.8 Hz, 1H), 3.08 (dd, *J* = 14.2, 2.8 Hz, 1H), 2.42 (dd, *J* = 14.2, 10.6 Hz, 1H), 2.39 – 2.30 (m, 1H), 1.66 (s, 9H), 1.47 (br s, 2H), 1.12 – 1.04 (m, 21H).

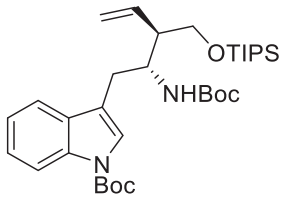
^{13}C NMR (100MHz, $CDCl_3$): δ 149.9 (Cq), 137.4, 135.9 (Cq), 130.8 (Cq), 124.5, 123.8, 122.5, 119.4, 118.6 (Cq), 118.0, 115.4, 83.5 (Cq), 65.1, 52.9, 51.2, 30.7, 28.4 (3C), 18.2 (6C), 12.1 (3C).

IR: υ (cm^{-1}) 3061 (w), 2938 (m), 2866 (m), 1733 (m), 1456 (m), 1371 (s), 1255 (s), 1159 (s), 1091 (s), 1018 (m), 883 (m), 767 (s), 746 (s), 681 (s).

HRMS: (ESI) calcd for $C_{28}H_{47}N_2O_3Si^+$ $[M+H]^+$ 487.3350; found 487.3352.

$[\alpha]_D^{26.6}$ = +11.2 (*c* 1.0, $CHCl_3$)

*tert-butyl 3-((2R,3R)-2-((tert-butoxycarbonyl)amino)-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.208**)*



In a flask under Ar charged with amine **2.195** (2.60 g; 5.34 mmol; 1.0 equiv) in CH_2Cl_2 (27 mL) was added dropwise at 0 °C a solution of Boc_2O (1.40 g; 6.41 mmol; 1.2 equiv) in CH_2Cl_2 (11 mL). The resulting mixture was stirred at 0 °C for 3 h and then at rt for 1 h. Volatiles were removed under reduced pressure and the residue was purified by FCC (PE/EtOAc : 10/1) to afford 2.90 g (93% yield) of Boc amine **2.208** as a colorless oil. Based on ^{1}H NMR, the product was obtained as a 6/1 mixture of two rotamers at rt.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.41 (s, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.02 – 5.83 (m, 1H), 5.61 (d, *J* = 8.6 Hz, 1H), 5.17 – 5.05 (m, 2H), 4.17 – 4.08 (m, 1H), 4.05 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.80 (dd, *J* = 10.2, 4.2 Hz, 1H), 2.99 (d, *J* = 6.9 Hz, 2H), 2.37 – 2.29 (m, 1H), 1.66 (s, 9H), 1.40 (s, 9H), 1.17 – 1.00 (m, 21H).

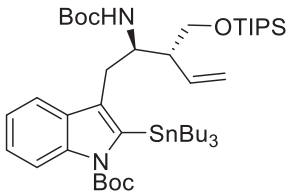
^{13}C NMR (100MHz, $CDCl_3$): δ 155.8 (Cq), 149.8 (Cq), 137.8, 135.6 (Cq), 131.1 (Cq), 124.4, 123.7, 122.6, 119.5, 117.6 (Cq), 117.3, 115.2, 83.5 (Cq), 78.7 (Cq), 64.7, 52.7, 47.0, 28.5 (3C), 28.4 (3C), 27.6, 18.2 (6C), 12.0 (3C).

IR: υ (cm^{-1}) 3310 (w), 3065 (w), 2978 (w), 2940 (w), 2866 (w), 1737 (m), 1714 (s), 1602 (m), 1521 (m), 1413 (m), 1367 (m), 1324 (m), 1247 (s), 1161 (s), 1118 (s), 1072 (m), 1006 (m), 879 (m), 833 (m), 760 (s).

HRMS: (ESI) calcd for $C_{33}H_{54}N_2NaO_5Si^+$ $[M+Na]^+$ 609.3694; found 609.3695.

$[\alpha]_D^{29.9}$ = +14.4 (*c* 1.0, $CHCl_3$)

*tert-butyl 3-((2R,3R)-2-((tert-butoxycarbonyl)amino)-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-2-(tributylstannyl)-1H-indole-1-carboxylate (**2.209**)*



In a dried flask under Ar charged with 2,2,6,6-tetramethylpiperidine (3.17 mL; 18.7 mmol; 3.8 equiv) in THF (15 mL) was added dropwise at -78 °C *n*-BuLi (2.4 M in hexane; 7.20 mL; 17.3 mmol, 3.5 equiv) and the resulting mixture was stirred at -78 °C for 30 min. In a second dried flask under Ar charged with Boc amine **2.208** (2.90 g; 4.94 mmol; 1.0 equiv) in THF (25 mL) was added dropwise at -78 °C the freshly prepared LiTMP solution. The resulting mixture was stirred at -78 °C for 1 h and then *n*-Bu_3SnCl (5.36 mL; 19.8 mmol; 4.0 equiv) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 30 min and then quenched by dropwise addition of a saturated aqueous solution of $NaHCO_3$ at -78 °C. The mixture was warmed to 0 °C and extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/Et_3N : 97/3) afforded 4.09 g (95% yield) of tin partner **2.209** as a light yellow oil. Based on ^1H NMR, the product was obtained as a 2/1 mixture of two rotamers at rt.

^1H NMR (400MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 2/3H), 7.64 (d, *J* = 7.9 Hz, 1/3H), 7.24 – 7.11 (m, 2H), 5.92 (dt, *J* = 18.5, 9.6 Hz, 2/3H), 5.86 – 5.75 (m, 1/3H), 5.34 (d, *J* = 8.5 Hz, 2/3H), 5.29 – 5.17 (m, 2/3H), 5.16 – 5.01 (m, 4/3H), 4.39 (d, *J* = 8.5 Hz, 1/3H),.4.31 (br s, 1/3H), 4.17 (brs, 2/3H), 4.04 (dd, *J* = 10.4, 4.0 Hz, 2/3H), 3.92 – 3.77 (m, 4/3H), 3.08 – 2.98 (m, 1H), 2.97 – 2.86 (m, 2/3H), 2.59 – 2.46 (m, 2/3H), 2.41 (s, 2/3H), 1.68 (s, 9H), 1.58 – 1.42 (m, 8H), 1.39 – 1.24 (m, 13H), 1.18 – 1.03 (m, 27H), 0.88 (t, *J* = 7.3 Hz, 9H).

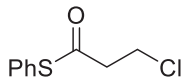
^{13}C NMR (100MHz, $CDCl_3$): δ 155.6 (Cq), 152.4 (Cq), 139.7 (Cq), 137.6, 137.5 (Cq), 132.8 (Cq), 129.5 (Cq), 123.5, 122.2, 119.5, 117.4, 115.2, 83.7 (Cq), 78.4 (Cq), 64.8, 52.9, 48.3, 38.7, 31.6, 29.3 (3C), 28.3 (6C), 27.6 (3C), 18.2 (6C), 13.9 (3C), 13.7 (3C), 12.1 (3C).

IR: υ (cm^{-1}) 3416 (w), 3082 (w), 2955 (m), 2924 (m), 2866 (m), 1708 (s), 1496 (m), 1450 (m), 1371 (s), 1330 (m), 1242 (m), 1164 (s), 1103 (s), 1068 (m), 1014 (m), 881 (m), 771 (m), 746 (m), 677 (m), 650 (m).

HRMS: (ESI) calcd for $C_{45}H_{81}N_2O_5SiSn^+$ $[M+H]^+$ 877.4931; found 877.4932.

$[\alpha]_D^{27.4}$ = +14.5 (*c* 1.0, $CHCl_3$)

*S-phenyl 3-chloropropanethioate (**2.152**)*



In a dried flask under Ar charged with 3-chloropropanoyl chloride (2.10 mL; 22.0 mmol; 1.1 equiv) in CH_2Cl_2 (150 mL) was added dropwise at -78 °C over a period of 45 min a solution of thiophenol (2.04 mL; 20.0 mmol; 1.0 equiv) and Et_3N (2.79 mL; 20.0 mmol; 1.0 equiv) in CH_2Cl_2 (50 mL). The resulting mixture was stirred 12 h while slowly warmed to rt. The mixture was quenched with water, the two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x1). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 97/3) afforded 3.41 g (85% yield) of thioester **2.152** as a colorless oil.

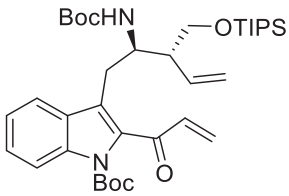
^{1}H NMR (400MHz, $CDCl_3$): δ 7.43 (s, 5H), 3.80 (t, *J* = 6.7 Hz, 2H), 3.12 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 194.5 (Cq), 134.6, 129.9, 129.5, 127.1 (Cq), 45.9, 38.8.

IR: υ (cm^{-1}) 3055 (w), 2967 (w), 1702 (s), 1479 (w), 1440 (w), 1338 (w), 1296 (w), 1166 (w), 1051 (s), 968 (m), 879 (w), 746 (s), 688 (s).

HRMS: (ESI) calcd for $C_9H_{10}ClOS^+$ $[M+H]^+$ 201.0135; found 201.0138.

*tert-butyl 2-acryloyl-3-((2R,3R)-2-((tert-butoxycarbonyl)amino)-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.210**)*



A dried flask charged with $Pd_2(dba)_3$ (408 mg; 0.445 mmol; 0.1 equiv), $AsPh_3$ (136 mg; 0.445 mmol; 0.1 equiv) and CuDPP (1.50 g; 5.34 mmol; 1.2 equiv) was evacuated for 30 min and then refilled with Ar. A solution of tin partner **2.209** (3.90 g; 4.45 mmol; 1.0 equiv) and thioester **2.152** (938 mg; 4.67 mmol; 1.05 equiv) in degassed hexane/THF (3/1; 70 mL) was added in one portion at rt. The resulting suspension was purged three times (vacuum-Ar) and then vigorously stirred at rt for 12 h. The mixture was diluted with PE/EtOAc (9/1) and filtered through a pad of silica. The pad was washed with with PE/EtOAc (8/2) until all dba ligand was eluted (yellow color). The filtrate was concentrated under reduced pressure and purified by FCC (PE/EtOAc/Et_3N :

95/3/2) to afford 2.57 g (90% yield) of diene **2.210** as a light yellow oil. Based on ^{1}H NMR, the product was obtained as a 5/1 mixture of two rotamers at rt.

^{1}H NMR (400MHz, $CDCl_3$): 8.10 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.65 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.06 (d, *J* = 17.5 Hz, 1H), 6.01 – 5.89 (m, 2H), 5.87 (d, *J* = 10.5 Hz, 1H), 5.16 – 5.03 (m, 2H), 4.11 – 4.01 (m, 2H), 3.80 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.05 (dd, *J* = 14.0, 6.7 Hz, 1H), 2.92 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.40 – 2.29 (m, 1H), 1.57 (s, 9H), 1.30 (s, 9H), 1.18 – 1.03 (m, 21H).

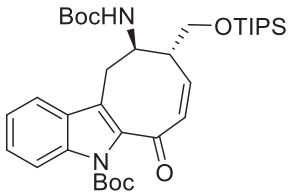
^{13}C NMR (100MHz, $CDCl_3$): δ 187.9 (Cq), 155.9 (Cq), 149.6 (Cq), 137.9, 137.3, 136.4 (Cq), 133.9(Cq), 129.3 (Cq), 128.2, 126.9, 123.9 (Cq), 123.7, 121.4, 117.4, 115.4, 85.4 (Cq), 78.4 (Cq), 64.5, 52.9, 47.8, 28.5 (3C), 28.0 (3C), 27.7, 18.2 (6C), 12.0 (3C).

IR: υ (cm^{-1}) 3348 (w), 3067 (w), 2957 (m), 2922 (s), 2855 (m), 1737 (m), 1714 (m), 1502 (m), 1461 (m), 1369 (s), 1328 (s), 1253 (m), 1159 (s), 1105 (s), 1018 (m), 883 (m), 750 (m).

HRMS: (ESI) calcd for $C_{36}H_{56}N_2NaO_6Si^+$ $[M+Na]^+$ 663.3800; found 663.3807.

$[\alpha]_D^{28.8}$ = +31.5 (*c* 1.0, $CHCl_3$)

tert-butyl (9R,10R,Z)-10-((tert-butoxycarbonyl)amino)-6-oxo-9-(((triisopropylsilyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (2.211)



In a dried flask (250 mL) under Ar charged with diene **2.210** (500 mg; 0.780 mmol; 1.0 equiv) in degassed 1.2-DCE (39 mL) was added dropwise a degassed solution of Grubbs calatyst 2nd generation (33 mg; 0.039 mmol; 0.05 equiv) in 1,2-DCE (0.5 mL). The resulting mixture was stirred at 80 °C for 6 h. The mixture was cooled to rt, Grubbs II (0.05 equiv) in 1,2-DCE (0.5 mL) was added and the resulting mixture was stirred at 80 °C for additional 12 h. The mixture was cooled to rt, Grubbs II (0.05 equiv) in 1,2-DCE (0.5 mL) was added and the resulting mixture was stirred at 80 °C for additional 6 h. The mixture was cooled to rt, Grubbs II (0.05 equiv) in 1,2-DCE (0.5 mL) was added and the resulting mixture was stirred at 80 °C for additional 6 h. The mixture was concentrated under reduced pressure and purified by FCC (PE/EtOAc : 10/1) to afford 408 mg (85% yield) of cyclic enone **2.211** as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 6.65 (dd, *J* = 12.3, 8.6 Hz, 1H), 6.50 (d, *J* = 12.3 Hz, 1H), 4.41 (d, *J* = 8.3 Hz, 1H), 4.28 – 4.15 (m, 1H), 3.89 (dd, *J* = 9.8, 4.6 Hz, 1H), 3.76 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.50 (dd, *J* = 14.4, 2.8 Hz, 1H), 2.97 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.84 – 2.71 (m, 1H), 1.57 (s, 9H), 1.44 (s, 9H), 1.14 – 0.99 (m, 21H).

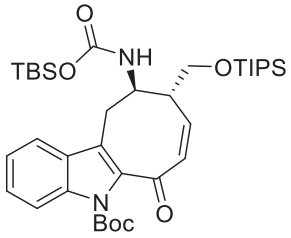
^{13}C NMR (100MHz, $CDCl_3$): δ 183.2 (Cq), 155.3 (Cq), 149.9 (Cq), 144.6, 138.5 (Cq), 137.4 (Cq), 135.2, 129.5 (Cq), 128.2, 125.2 (Cq), 123.2, 121.1, 114.3, 84.4 (Cq), 79.6 (Cq), 63.1, 53.9, 44.6, 28.5 (3C), 27.8 (3C), 27.5, 18.1 (6C), 12.0 (3C).

IR: υ (cm^{-1}) 3310 (w), 3057 (w), 2974 (w), 2940 (w), 2866 (w), 1737 (m), 1714 (s), 1602 (m), 1521 (m), 1413 (m), 1367 (m), 1324 (m), 1247 (s), 1161 (s), 1118 (s), 1072 (m), 1006 (m), 879 (m), 833 (m), 760 (s).

HRMS: (ESI) calcd for $C_{34}H_{52}N_2NaO_6Si^+$ $[M+Na]^+$ 635.3487; found 635.3492.

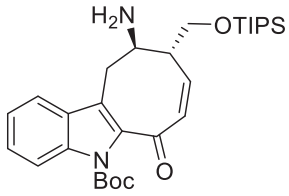
$[\alpha]_D^{29.0}$ = +84.6 (*c* 1.0, $CHCl_3$)

*tert-butyl (9R,10R,Z)-10-((((tert-butyldimethylsilyl)oxy)carbonyl)amino)-6-oxo-9-(((triisopropylsilyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.212**)*



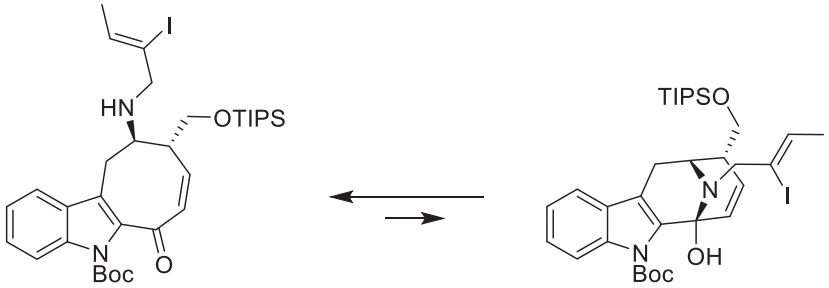
In a dried flask under Ar charged with cyclic enone **2.211** (100 mg; 0.163 mmol; 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C 2,6-lutidine (76 μL; 0.653 mmol; 4.0 equiv) and then TBSOTf (112 μL; 0.489 mmol; 3.0 equiv). The resulting mixture was stirred at rt for 1 h. The mixture was quenched by a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 (x4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude silyl carbamate **2.212** which was used directly as such in the next step.

*tert-butyl (9R,10R,Z)-10-amino-6-oxo-9-(((triisopropylsilyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.213**)*



In a dried flask under Ar charged with crude silyl carbamate **2.212** in Et_2O (6.5 mL) was added dropwise at 0 °C HCl (1 M in Et_2O; 1.63 mL; 1.63 mmol; 10 equiv) and the resulting mixture was stirred at 0 °C for 1 h. The mixture was quenched by a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 (x4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude amine **2.213** which was used directly as such in the next step.

*tert-butyl (9R,10R,Z)-10-(((Z)-2-iodobut-2-en-1-yl)amino)-6-oxo-9-(((triisopropylsilyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.196**)*



In a dried flask under Ar charged with crude amine **2.213** in DMF (3.3 mL) was added dropwise at rt DIPEA (86 μL; 0.489 mmol; 3.0 equiv) and then (*Z*)-1-bromo-2-iodobut-2-ene **2.25** (213 mg; 0.815 mmol; 5.0 equiv). The resulting mixture was stirred at rt for 24 h. The mixture was diluted with EtOAc and washed with water. The two layers were separated and the aqueous phase was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc/Et_3N : 95/5/0.25) afforded 78 mg (69% yield over 3 steps) of allylic amine **2.196** as a light yellow oil. Based on ^1H NMR, the product was obtained as a 12/1 mixture of ketone and corresponding hemiaminal at rt.

^1H NMR (400MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 6.74 (dd, *J* = 12.2, 8.8 Hz, 1H), 6.46 (dd, *J* = 12.2,

1.4 Hz, 1H), 5.86 (q, *J* = 6.4 Hz, 1H), 4.06 – 3.95 (m, 2H), 3.81 (d, *J* = 14.0 Hz, 1H), 3.56 (d, *J* = 14.0 Hz, 1H), 3.31 (d, *J* = 14.2 Hz, 1H), 3.14 (br d, *J* = 11.0 Hz, 1H), 2.93 (dd, *J* = 14.2, 4.2 Hz, 1H), 2.86 – 2.73 (m, 1H), 1.76 (d, *J* = 6.4 Hz, 2H), 1.71 (s, 1H), 1.56 (s, 9H), 1.15 – 0.99 (m, 21H).

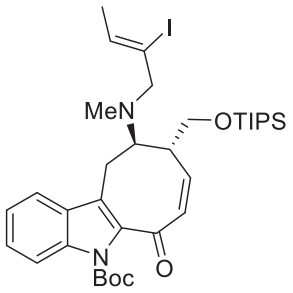
^{13}C NMR (100MHz, $CDCl_3$): δ 183.6 (Cq), 149.9 (Cq), 147.5, 138.5 (Cq), 137.6 (Cq), 134.3, 131.6, 129.6 (Cq), 128.2, 125.1 (Cq), 123.2, 120.6, 114.6, 110.1 (Cq), 84.3 (Cq), 64.0, 60.0, 59.4, 46.2, 27.8 (3C), 26.0, 21.9, 18.3 (6C), 12.1 (3C).

IR: υ (cm^{-1}) 3034 (w), 2940 (m), 2866 (m), 1739 (s), 1637 (m), 1612 (m), 1452 (m), 1353 (s), 1324 (s), 1247 (s), 1157 (s), 1097 (s), 1016 (s), 883 (m), 800 (s), 750 (s), 681 (s).

HRMS: (ESI) calcd for $C_{33}H_{50}IN_2O_4Si^+$ $[M+H]^+$ 693.2579; found 693.2586.

$[\alpha]_D^{28.1}$ = +21.4 (*c* 0.3, $CHCl_3$)

*tert-butyl (9R,10R,Z)-10-(((Z)-2-iodobut-2-en-1-yl)(methyl)amino)-6-oxo-9-(((triisopropylsilyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.215**)*



In a flask under Ar charged with allylic amine **2.196** (45 mg; 0.0650 mmol; 1.0 equiv) in MeOH (1.3 mL) was added at rt $NaBH_3CN$ (20 mg; 0.325 mmol; 5.0 equiv) and then formaldehyde (37%wt in H_2O; 48 μL; 0.650 mmol; 10 equiv). The resulting mixture was stirred at rt for 12 h. Volatiles were removed under reduced pressure and the residue was diluted with CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc/Et_3N : 95/5/0.25) afforded 41 mg (89% yield) of methylamine **2.215** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 6.76 (dd, *J* = 12.2, 8.5 Hz, 1H), 6.42 (d, *J* = 12.2 Hz, 1H), 5.80 (q, *J* = 6.4 Hz, 1H), 4.07 – 3.91 (m, 2H), 3.48 – 3.20 (m, 5H), 2.81 (dd, *J* = 14.9, 6.2 Hz, 1H), 2.01 (s, 3H), 1.77 (d, *J* = 6.4 Hz, 3H), 1.58 (s, 9H), 1.16 – 0.97 (m, 21H).

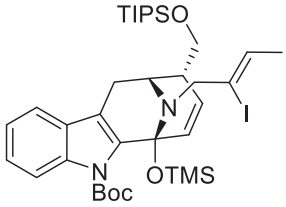
^{13}C NMR (100MHz, $CDCl_3$): δ 183.3 (Cq), 150.1 (Cq), 148.4, 139.0 (Cq), 137.7 (Cq), 133.6, 131.9, 128.1 (Cq), 128.0, 126.9 (Cq), 122.8, 121.2, 114.9, 110.4 (Cq), 84.2 (Cq), 65.6 (3C), 42.6, 36.2, 27.8(3C), 22.8, 21.8, 18.3 (6C), 12.1 (3C).

IR: υ (cm^{-1}) 3059 (w), 2940 (m), 2864 (w), 1739 (m), 1637 (m), 1614 (m), 1452 (m), 1411 (w), 1351 (s), 1328 (m), 1244 (m), 1157 (s), 1109 (s), 1089 (s), 1018 (m), 883 (m), 800 (s), 771 (s), 750 (s), 685 (m).

HRMS: (ESI) calcd for $C_{34}H_{52}IN_2O_4Si^+$ $[M+H]^+$ 707.2736; found 707.2746.

$[\alpha]_D^{28.2}$ = +36.9 (*c* 0.3, $CHCl_3$)

*tert-butyl (6S,9R,10R)-12-((Z)-2-iodobut-2-en-1-yl)-9-(((triisopropylsilyl)oxy)methyl)-6-((trimethylsilyl)oxy)-6,9,10,11-tetrahydro-5H-6,10-epiminocycloocta[b]indole-5-carboxylate (**2.219**)*



In a dried flask under Ar charged with allylic amine **2.196** (53 mg; 0.0765 mmol; 1.0 equiv) and imidazole (36.5 mg; 0.536 mmol; 7.0 equiv) in 1,2-DCE (1.9 mL) was added rt TMSCl (49 μL; 0.383 mmol; 5.0 equiv). The resulting mixture was stirred at 45 °C for 12 h. The mixture was cooled to rt, diluted with water and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc/Et_3N : 95/4/1) afforded 55 mg (94% yield) of hemiaminal **2.219** as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.21 (td, *J* = 8.1 Hz, 1H), 7.18 (td, *J* = 7.4, 1.2 Hz, 1H), 6.50 (dd, *J* = 10.2, 3.1 Hz, 1H), 5.90 (q, *J* = 6.4 Hz, 1H), 5.55 (dd, *J* = 10.2, 1.7 Hz 1H), 3.86 – 3.73 (m, 3H), 3.64 (t, *J* = 9.9 Hz, 1H), 3.11 – 3.00 (m, 1H), 2.91 (dd, *J* = 17.9, 8.1 Hz, 1H), 2.68 (d, *J* = 15.2 Hz, 1H), 2.43 (d, *J* = 17.9 Hz, 1H), 1.78 (d, *J* = 6.4 Hz, 3H), 1.71 (s, 9H), 1.15 – 1.00 (m, 21H), 0.28 (s, 9H).

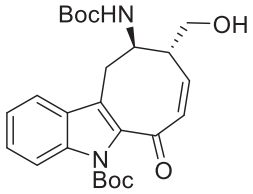
^{13}C NMR (100MHz, $CDCl_3$): δ 149.8 (Cq), 140.0 (Cq), 136.2 (Cq), 133.8, 130.8, 128.9 (Cq), 126.0, 123.8, 122.1, 118.4, 115.8 (Cq), 114.2, 109.1 (Cq), 84.9 (Cq), 83.2 (Cq), 64.6, 57.9, 50.7, 43.3, 28.6 (3C), 21.8, 18.2 (6C), 16.6, 12.2 (3C), 2.4 (3C).

IR: υ (cm^{-1}) 3034 (w), 2955 (m), 2922 (m), 2864 (m), 1747 (m), 1454 (m), 1369 (m), 1323 (m), 1257 (s), 1159 (s), 1120 (s), 1070 (s), 1018 (s), 979 (m), 883 (m), 846 (s), 804 (s), 744 (s), 685 (m).

HRMS: (ESI) calcd for $C_{36}H_{58}IN_2O_4Si_2^+$ $[M+H]^+$ 765.2974; found 765.2981.

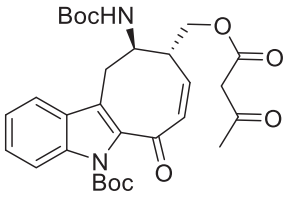
$[\alpha]_D^{27.9}$ = +51.2 (*c* 1.0, $CHCl_3$)

*tert-butyl (9R,10R,Z)-10-((tert-butoxycarbonyl)amino)-9-(hydroxymethyl)-6-oxo-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.223**)*



In a dried flask under Ar charged with cyclic enone **2.211** (200 mg; 0.326 mmol; 1.0 equiv) in THF (8.2 mL) was added dropwise at 0 °C glacial acetic acid (24 μL; 0.408 mmol; 1.25 equiv) and then TBAF (1 M in THF; 816 μL; 0.816 mmol; 2.5 equiv). The resulting mixture was stirred at rt for 3 h. The mixture was diluted with EtOAc and washed with water. The two layers were separated and the aqueous phase was extracted with EtOAc (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude alcohol **2.223** which was used directly as such in the next step.

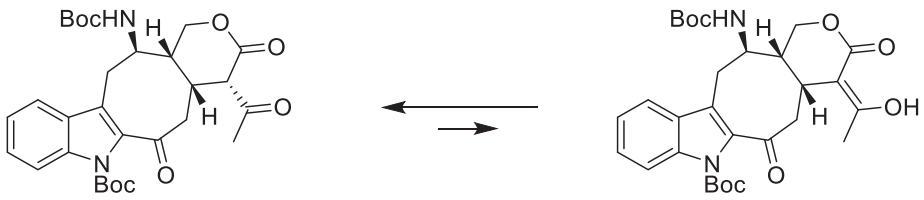
*tert-butyl (9R,10R,Z)-10-((tert-butoxycarbonyl)amino)-6-oxo-9-(((3-oxobutanoyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.232**)*



In a dried flask under Ar charged with crude alcohol **2.223**, EDCI.HCl (200 mg; 1.04 mmol; 3.2 equiv) and DMAP (4.0 mg; 0.033 mmol; 0.1 equiv) in CH_2Cl_2 (7.2 mL) was added dropwise at 0 °C acetoacetic acid **2.233** (100 mg; 0.978 mmol; 3.0 equiv) and then DIPEA (341 μL; 1.96 mmol;

6.0 equiv). The resulting mixture was stirred at rt for 3 h and then volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed with an aqueous solution of 10% $KHSO_4$ (x2). The combined acidic aqueous layers were extracted with EtOAc (x1) and was then discarded. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (x2). The combined basic aqueous layers were extracted with EtOAc (x1) and was then discarded. The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude 1,3-ketoester **2.232** which was used directly as such in the next step.

tert-butyl (4S,4aR,13R,13aR)-4-acetyl-13-((tert-butoxycarbonyl)amino)-3,6-dioxo-3,4,4a,5,6,12,13,13a-octahydropyrano[3',4':5,6]cycloocta[1,2-b]indole-7(1H)-carboxylate (2.231)



In a dried flask under Ar charged with crude 1,3-ketoester **2.232** and molecular sieves 4 Å (815 mg) in acetone (33 mL) was added portionwise Cs_2CO_3 (319 mg; 0.978 mmol; 3.0 equiv) and the resulting mixture was stirred at 55 °C for 12 h. The mixture was cooled to rt and glacial acetic acid (200 µL; 3.5 mmol; 11 equiv) was added dropwise. After stirring at rt for 5-10 min, the mixture was diluted with EtOAc, filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by FCC (CH_2Cl_2/MeOH : 98/2) to afford 154 mg (87% yield over 3 steps) of 1,3-ketolactone **2.231** as a light yellow solid. Based on ^{1}H NMR, the product was obtained as a mixture of ketone and its enol tautomer at rt (ratio ketone/enol ranging from 7/1 to 19/1).

^{1}H NMR (400MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 4.27 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.22 (d, *J* = 9.9 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.83 (d, *J* = 7.0 Hz, 1H), 3.42 (dd, *J* = 15.5, 2.9 Hz, 1H), 3.30 (dd, *J* = 15.5, 4.0 Hz, 1H), 3.23 (dd, *J* = 13.2, 4.6 Hz, 1H), 3.09 – 2.97 (m, 1H), 2.54 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.48 (s, 3H), 1.91 – 1.74 (m, 1H), 1.61 (s, 9H), 1.45 (s, 9H).

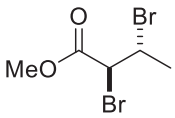
^{13}C NMR (100MHz, $CDCl_3$): δ 201.3 (Cq), 193.7 (Cq), 167.5 (Cq), 155.1 (Cq), 149.4 (Cq), 137.2 (Cq), 136.0 (Cq), 129.2 (Cq), 127.9, 123.7, 120.2, 120.0 (Cq), 114.9, 85.5 (Cq), 80.4 (Cq), 69.9, 60.2, 50.8, 48.1, 40.6, 32.4, 30.7, 28.5 (3C), 28.0 (3C), 27.8.

IR: υ (cm^{-1}) 3364 (w), 3055 (w), 2959 (w), 2924 (w), 1718 (s), 1695 (m), 1506 (w), 1456 (w), 1367 (s), 1330 (m), 1240 (m), 1159 (s), 1062 (m), 843 (w), 752 (m).

HRMS: (ESI) calcd for $C_{29}H_{36}N_2NaO_8^+$ $[M+Na]^+$ 563.2364; found 563.2364.

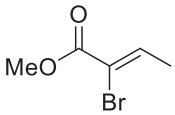
$[\alpha]_D^{29.6}$ = -82.4 (*c* 0.5, $CHCl_3$)

*methyl (2S,3R)-2,3-dibromobutanoate (**2.242a**)*



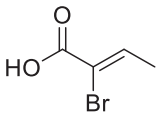
In a dried flask under Ar charged with methyl crotonate (2.1 mL; 20.0 mmol; 1.0 equiv) in CH_2Cl_2 (25 mL) was added dropwise at 0 °C over a period of 1 h Br_2 (1.1 mL; 22.0 mmol; 1.1 equiv). The resulting mixture was stirred 15 min at 0 °C and then at rt for 1 h. The mixture was concentrated under reduced pressure (P = 10 mmbar; T = 35 °C) to afford crude dibrominated product **2.242a** which was used directly as such in the next step.

*methyl (Z)-2-bromobut-2-enoate (**2.242b**)*



A solution under Ar of crude dibrominated product **2.242a** in DMSO/H_2O (95/5; 60 mL) was stirred at 85 °C for 16 h. The mixture was cooled to rt and poured into a cold half-saturated aqueous solution of $NaHCO_3$ (120 mL) and the biphasic mixture was then extracted with Et_2O (x2). The combined organic layers were washed with brine (x1), dried over Na_2SO_4, filtered and concentrated under reduced pressure (P = 10 mmbar; T = 35 °C) to afford crude conjugated ester **2.242b** as a *Z*/*E* mixture (8/1). The crude mixture was used directly as such in the next step.

*(Z)-2-bromobut-2-enoic acid (**2.242**)*



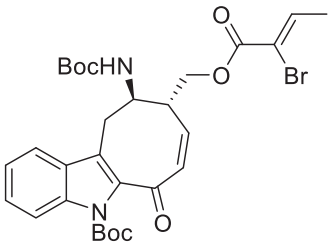
In a flask under Ar charged with crude conjugated ester **2.242b** in THF (20 mL) was added dropwise at rt a solution of LiOH (1.44 g; 60.0 mmol; 3.0 equiv) in H_2O (20 mL) and the resulting mixture was stirred at rt for 12 h. The mixture was quenched with an aqueous solution of 10% $KHSO_4$ (150 mL) and was then extracted with EtOAc (x2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude acid **2.242** as a *Z*/*E* mixture (8/1). The crude solids were washed with PE (1x10 mL and then 1x5 mL) and dried under reduced pressure to afford 2.12 g (64% over 3 steps) of pure (*Z*)-acid **2.242**.

^{1}H NMR (400MHz, $CDCl_3$): δ 10.93 (br s, 1H), 7.55 (q, *J* = 6.9 Hz, 1H), 2.00 (d, *J* = 6.9 Hz, 4H).

^{13}C NMR (100MHz, $CDCl_3$): δ 168.1 (Cq), 144.9, 116.7 (Cq), 18.3.

The spectroscopic data of this compound are in accord with these reported in the literature.[25]

*tert-butyl (9R,10R,Z)-9-((((Z)-2-bromobut-2-enoyl)oxy)methyl)-10-((tert-butoxycarbonyl)amino)-6-oxo-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.242**)*



The same TIPS-deprotection / esterification procedure to reach 1,3-ketoester **2.232** was followed. Starting from cyclic enone **2.211** (50 mg; 0.0816 mmol) and using (*Z*)-2-bromobut-2-enoic acid **2.242c** as esterification partner, 43 mg (87% over 2 steps) of desired ester **2.242** was obtained after purification by FCC (PE/EtOAc : 75/25).

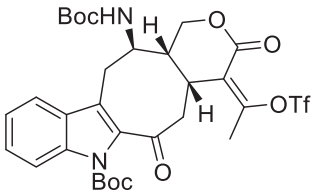
^{1}H NMR (400MHz, $CDCl_3$): 8.06 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.36 (q, *J* = 6.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.56 – 6.51 (m, 2H), 4.42 (dd, *J* = 11.4, 3.3 Hz, 1H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.23 (dt, *J* = 10.9, 3.3 Hz, 1H), 3.39 (dd, *J* = 14.4, 2.6 Hz, 1H), 3.15 – 3.03 (m, 2H), 1.94 (d, *J* = 6.8 Hz, 3H), 1.56 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (100MHz, $CDCl_3$): δ 182.6 (Cq), 162.2 (Cq), 155.2 (Cq), 149.7 (Cq), 143.1, 142.3, 138.7 (Cq), 137.4 (Cq), 136.1, 129.1 (Cq), 128.6, 124.3 (Cq), 123.5, 120.8, 117.1 (Cq), 114.5, 84.6 (Cq), 80.3 (Cq), 66.5, 53.6, 42.1, 28.5 (3C), 27.79, 27.75 (3C), 18.1.

IR: υ (cm^{-1}) 3377 (w), 2959 (w), 2889 (w), 1725 (m), 1446 (w), 1367 (w), 1247 (w), 1166 (s), 1068 (s), 1037 (s), 927 (s), 854 (m), 764 (w).

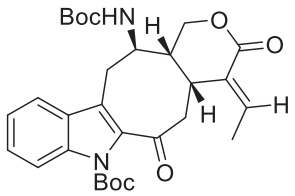
HRMS: (ESI) calcd for $C_{29}H_{35}BrN_2NaO_7^+$ $[M+Na]^+$ 625.1520; found 625.1517.

*tert-butyl (4aR,13R,13aR,Z)-13-((tert-butoxycarbonyl)amino)-3,6-dioxo-4-(1-(((trifluoromethyl)sulfonyl)oxy)ethylidene)-3,4,4a,5,6,12,13,13a-octahydropyrano[3',4':5,6]cycloocta[1,2-b]indole-7(1H)-carboxylate (**2.234**)*



In a dried sealed tube under Ar charged with 1,3-ketolactone **2.231** (40 mg; 0.0740 mmol; 1.0 equiv) and molecular sieves 4 Å (120 mg) in THF (0.55 mL) was added in one portion at rt Cs_2CO_3 (60 mg; 0.185 mmol; 2.5 equiv). The resulting suspension was stirred at rt for 1 h at 500-600 rpm and then a solution of $PhNTf_2$ (32 mg; 0.0888 mmol; 1.2 equiv) in THF (0.55 mL) was added dropwise. The resulting suspension was stirred at rt for 1 h at 500-600 rpm, then for 1 h at 1000-1200 rpm and finally for additional 2 h at 500-600 rpm. Note: after stirring at 1000-1200 rpm, the Cs_2CO_3 should become a very thin powder in suspension and not a powder staying mainly in the bottom of the tube. Volatiles were removed at rt under reduced pressure and the residue was dissolved in $CHCl_3$. The resulting suspension was filtered through cotton and the filter cake was washed with $CHCl_3$. The filtrate was concentrated under reduced pressure to afford crude triflate **2.234** which was used directly as such in the next step.

*tert-butyl (4aR,13R,13aR,E)-13-((tert-butoxycarbonyl)amino)-4-ethylidene-3,6-dioxo-3,4,4a,5,6,12,13,13a-octahydropyrano[3',4':5,6]cycloocta[1,2-b]indole-7(1H)-carboxylate (**2.241**)*



A dried sealed tube charged with crude triflate **2.234**, $Pd(OAc)_2$ (3.3 mg; 0.0148 mmol; 0.2 equiv) and PPh_3 (9.7 mg; 0.0370 mmol; 0.5 equiv) was evacuated for 15 min and then refilled with Ar. Dried and degassed DMF (1.9 mL) was added at rt in one portion followed by dropwise addition of Et_3N (103 μL; 0.740 mmol; 10 equiv) and then of HCO_2H (14 μL; 0.370 mmol; 5.0 equiv). The resulting mixture was stirred at 60 °C for 3 h. The mixture was cooled to rt, diluted with EtOAc and washed with water. The two layers were separated and the aqueous phase was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by FCC (PE/EtOAc : 2/1) afforded 28 mg (72% yield over 2 steps) of conjugated lactone **2.241** as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 6.79 (q, *J* = 7.2 Hz, 1H), 4.38 (d, *J* = 9.9 Hz, 1H), 4.25 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.96 – 3.73 (m, 2H), 3.27 – 3.14 (m, 2H), 3.09 (dd, *J* = 15.2, 3.5 Hz, 1H), 2.90 (d, *J* = 6.9 Hz, 2H), 2.14 – 2.01 (m, 1H), 1.91 (d, *J* = 7.2 Hz, 3H), 1.59 (s, 9H), 1.47 (s, 9H).

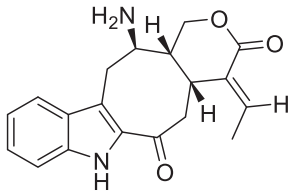
^{13}C NMR (100MHz, $CDCl_3$): δ 197.0 (Cq), 169.2 (Cq), 155.2 (Cq), 149.0 (Cq), 139.8, 136.2 (Cq), 136.0 (Cq), 131.7 (Cq), 129.2 (Cq), 126.7, 123.7, 119.6, 115.6 (Cq), 115.5, 85.9 (Cq), 80.4 (Cq), 68.7, 52.8, 51.9, 43.0, 34.0, 28.5 (3C), 28.0 (3C), 26.7, 14.2.

IR: υ (cm^{-1}) 3392 (w), 3050 (w), 3006 (w), 2955 (w), 2925 (w), 2851 (w), 1736 (s), 1688 (s), 1640 (m), 1498 (m), 1364 (m), 1314 (m), 1240 (s), 1162 (s), 1070 (m), 1019 (m), 871 (m), 746 (s), 721 (s), 669 (m).

HRMS: (ESI) calcd for $C_{29}H_{36}N_2NaO_7^+$ $[M+Na]^+$ 547.2415; found 547.2420.

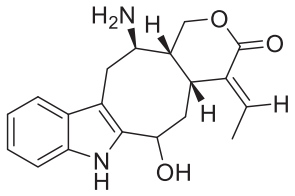
$[\alpha]_D^{29.7}$ = +83.1 (*c* 0.5, $CHCl_3$)

*(4aR,13R,13aR,E)-13-amino-4-ethylidene-4a,5,7,12,13,13a-hexahydropyrano[3',4':5,6]cycloocta[1,2-b]indole-3,6(1H,4H)-dione (**2.245**)*



In a dried sealed tube under Ar charged with conjugated lactone **2.241** (10.0 mg; 0.0191 mmol; 1.0 equiv) in CH_2Cl_2 (0.96 mL) was added dropwise at 0 °C $BF_3.OEt_2$ (19 µL; 0.152 mmol; 8.0 equiv). The resulting mixture was stirred at 0 °C for 5 min and then at rt for 4 h. Note: when the reaction was warmed to rt, a yellow suspension appeared. The mixture was diluted with CH_2Cl_2 and quenched with a saturated aqueous solution of Na_2CO_3. The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude amine **2.245** which was used directly as such in the next step.

*(4aR,13R,13aR,E)-13-amino-4-ethylidene-6-hydroxy-4,4a,5,6,7,12,13,13a-octahydropyrano[3',4':5,6]cycloocta[1,2-b]indol-3(1H)-one (**2.240**)*



In a dried tube under Ar charged with crude amine **2.245** and K_2CO_3 (1.3 mg; 0.0096 mmol; 0.5 equiv) in MeOH/$CHCl_3$ (2/1; 0.96 mL) was added in one portion $CeCl_3$ (14 mg; 0.0573 mmol; 3.0 equiv). The resulting mixture was stirred at rt for 5-10 min and then cooled to -40 °C (dry ice / acetonitrile). Four portion of $NaBH_4$ (3.6 mg; 0.0955 mmol; 5.0 equiv) were added at -40 °C over 3 h. When the 20 equiv of $NaBH_4$ were reached, the mixture was stirred at -40 °C for an additional 1 h. The mixture was then slowly diluted with CH_2Cl_2 and, still at -40 °C, quenched with a saturated aqueous solution of Na_2CO_3. While stirring vigorously, the mixture was warmed to rt and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (x5) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by preparative TLC (EtOAc/Et_3N : 96/4) afforded 4.8 mg (77% yield over 2 steps) of alcohol **2.240** as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.19 – 7.07 (m, 2H), 6.63 (q, *J* = 7.2 Hz, 1H), 5.16 (dd, *J* = 11.1, 3.7 Hz, 1H), 4.46 (dd, *J* = 11.7, 5.1 Hz, 1H), 3.68 (t, *J* = 11.7 Hz, 1H), 3.15 (dd, *J* = 15.0, 4.0 Hz, 1H), 3.09 – 2.95 (m, 2H), 2.88 (ddd, *J* = 10.4, 4.0, 2.3 Hz, 1H), 1.97 – 1.93 (m, 1H), 1.91 (d, *J* = 7.2 Hz, 3H), 1.80 (q, *J* = 11.8 Hz, 1H), 1.64 (br s, 3H), 1.55 – 1.46 (m, 1H).

^{13}C NMR (100MHz, $CDCl_3$): δ 170.8 (Cq), 137.1 (Cq), 136.6, 134.9 (Cq), 134.0 (Cq), 129.7 (Cq), 121.7, 120.1, 118.3, 111.5, 104.5 (Cq), 70.5, 68.1, 55.0, 47.3, 43.4, 33.9, 30.8, 13.8.

^{1}H NMR (400MHz, $CDCl_3$ / CD_3OD: 1/1): δ 7.57 (d hidden under $CDCl_3$, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.15 – 6.95 (m, 2H), 6.60 (q, *J* = 7.2 Hz, 1H), 5.13 (dd, *J* = 10.9, 3.5 Hz, 1H), 4.32 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.70 (t, *J* = 11.6 Hz, 1H), 3.28 – 3.15 (m, 1H), 3.13 – 3.00 (m, 2H), 2.92 (br s, 1H), 1.97 (d, *J* = 12.0 Hz, 1H), 1.92 (d, *J* = 7.2 Hz, 3H), 1.77 (q, *J* = 12.0 Hz, 1H), 1.66 – 1.52 (m, 1H).

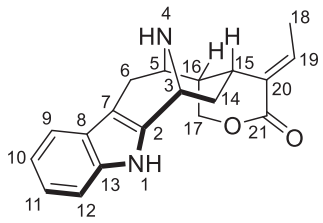
^{13}C NMR (100MHz, $CDCl_3$ / CD_3OD: 1/1): δ 172.3 (Cq), 139.2 (Cq), 137.9, 135.9 (Cq), 134.4 (Cq), 129.9 (Cq), 121.6, 120.1, 118.2, 112.0, 103.7 (Cq), 70.5, 67.8, 55.0, 47.5, 43.7, 34.4, 30.2, 13.8.

IR: υ (cm^{-1}) 3337 (w), 3059 (w), 2957 (w), 2922 (w), 2853 (w), 1673 (s), 1631 (m), 1571 (m), 1419 (m), 1109 (s), 1014 (w), 829 (m), 748 (m), 650 (s).

HRMS: (ESI) calcd for $C_{19}H_{22}N_2NaO_3^+$ $[M+Na]^+$ 349.1523; found 349.1529.

$[\alpha]_D^{26.5}$ = +166.7 (*c* 0.25, $CHCl_3$)

*N(1)-demethyl-3,5-diepi-alstolactone (**2.239**)*



Note: Traces of other solvents in starting alcohol **2.240** were coevaporated with TFE three times before use.

In a dried sealed tube under Ar charged with alcohol **2.240** (9.0 mg; 0.0276 mmol; 1.0 equiv) was added in one portion at rt TFE (5.5 mL; 0.005 M) and the tube was purged 5 times (vacuum – Ar). The resulting solution was stirred at 105 °C for 24 h. The mixture was cooled to rt and volatiles were removed under reduced pressure. Purification by preparative TLC (ALUMINA; Elution: 100% EtOAc; Extraction of **2.239** on alumina with MeOH) afforded 6.7 mg (79% yield) of *N*(1)-demethyl-3,5-diepi-alstolactone (**2.239**) as a white solid.

^{1}H NMR (400MHz, CD_3OD): δ 7.42 (d, *J* = 7.7 Hz, $1H^{9}$), 7.32 (d, *J* = 8.0 Hz, $1H^{12}$), 7.07 (dd, *J* = 8.0, 7.1 Hz, $1H^{11}$), 7.02 – 6.96 (dd, *J* = 7.7, 7.1 Hz, $1H^{10}$), 6.81 (qd, *J* = 7.4, 2.9 Hz, $1H^{19}$), 4.33 (t, *J* = 3.0 Hz, $1H^{3}$), 4.30 (dd, *J* = 10.6, 2.7 Hz, $1H^{17a}$), 4.10 (t, *J* = 10.6 Hz, $1H^{17b}$), 3.69 (dd, *J* = 7.1, 3.9 Hz, $2H^{5}$), 3.14 (dd, *J* = 16.6, 7.1 Hz, $1H^{6a}$), 2.72 (br t, *J* = 11.8 Hz, $1H^{15}$), 2.56 (d, *J* = 16.6 Hz, $1H^{6b}$), 2.36 (dt, *J* = 12.8, 3.0 Hz, $1H^{14a}$), 2.21 (tt, *J* = 11.8, 3.3 Hz, $1H^{16}$), 1.77 (td, *J* = 12.8, 3.0 Hz, $1H^{14b}$), 1.59 (dd, *J* = 7.4, 1.8 Hz, $3H^{18}$).

^{13}C NMR (100MHz, CD_3OD): δ 170.6 (Cq^{21}), 143.1 (C^{19}), 137.5 (Cq^{13}), 136.3 (Cq^{2}), 132.2 (Cq^{20}), 128.0 (Cq^{8}), 122.2 (C^{11}), 119.9 (C^{10}), 118.6 (C^{9}), 112.1 (C^{12}), 108.7 (Cq^{7}), 71.2 (C^{17}), 49.2 (C^{5} hidden under MeOD), 48.6 (C^{3} hidden under MeOD), 46.4 (C^{16}), 36.0 (C^{14}), 33.0 (C^{15}), 23.4 (C^{6}), 15.6 (C^{18}).

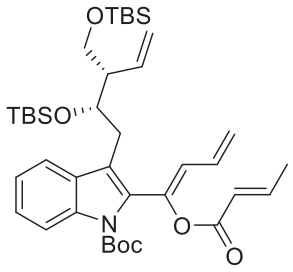
IR: υ (cm^{-1}) 3287 (w), 3053 (w), 2965 (w), 2914 (w), 2846 (w), 1697 (s), 1625 (m), 1568 (m), 1446 (m), 1329 (w), 1298 (w), 1211 (s), 1152 (m), 1072 (m), 1022 (m), 951 (w), 854 (m), 806 (m), 733 (s), 689 (m), 652 (m).

HRMS: (ESI) calcd for $C_{19}H_{21}N_2O_2^+$ $[M+H]^+$ 309.1598; found 309.1598.

$[\alpha]_D^{29.3}$ = -19.1 (*c* 0.5, MeOH)

Side Products of Part II

*tert-butyl 2-((Z)-1-(((E)-but-2-enoyl)oxy)buta-1,3-dien-1-yl)-3-((2S,3S)-2-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate (**2.201**)*



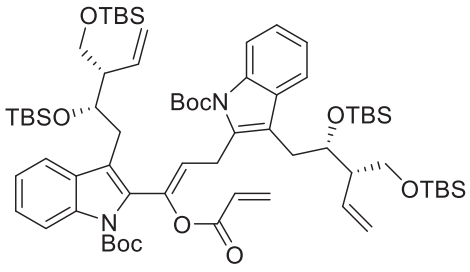
^{1}H NMR (400MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.00 (dq, *J* = 14.2, 7.0 Hz, 1H), 6.60 – 6.48 (m, 2H), 5.97 (ddd, *J* = 18.1, 10.5, 8.4 Hz, 1H), 5.86 (dd, *J* = 15.5, 2.1 Hz, 1H), 5.40 – 5.31 (m, 1H), 5.27 – 5.13 (m, 3H), 4.44 (d, *J* = 10.1 Hz, 1H), 3.81 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.64 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.14 (dd, *J* = 14.0, 10.1 Hz, 1H), 2.88 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.39 (q, *J* = 7.4 Hz, 1H), 1.87 (dd, *J* = 7.0, 1.7 Hz, 3H), 1.60 (s, 9H), 0.89 (s, 9H), 0.80 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), -0.11 (s, 3H), -0.65 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 163.8, 150.0, 146.8, 139.0, 136.8, 136.2, 131.6, 130.1, 129.8, 125.4, 122.6, 122.6, 122.2, 121.8, 120.2, 119.1, 118.4, 115.2, 83.4, 72.1, 63.1, 53.0, 30.2, 28.1 (3C), 26.2 (3C), 26.1 (3C), 18.4, 18.32, 18.28, -4.7, -5.06, -5.11, -5.2.

IR: υ (cm^{-1}) 3051 (w), 2961 (w), 2924 (w), 2857 (w), 1727 (m), 1465 (w), 1371 (m), 1321 (m), 1247 (m), 1159 (m), 1091 (s), 1028 (m), 929 (w), 833 (s), 767 (s).

HRMS: (ESI) calcd for $C_{39}H_{61}NNaO_6Si_2^+$ $[M+Na]^+$ 718.3930; found 718.3926.

*di-tert-butyl 2,2'-((Z)-1-(acryloyloxy)prop-1-ene-1,3-diyl)bis(3-((2S,3S)-2-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-en-1-yl)-1H-indole-1-carboxylate) (**2.202**)*



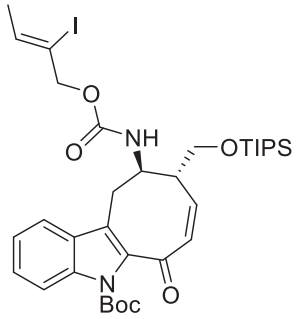
^{1}H NMR (400MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.08 (m, 4H), 6.39 (d, *J* = 17.3 Hz, 1H), 6.13 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.96 (dt, *J* = 18.1, 9.6 Hz, 1H), 5.85 – 5.77 (m, 2H), 5.66 (ddd, *J* = 18.1, 10.1, 7.9 Hz, 1H), 5.22 (d, *J* = 9.8 Hz, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 4.91 (dd, *J* = 17.5, 2.2 Hz, 1H), 4.79 (d, *J* = 9.4 Hz, 1H), 4.36 (t, *J* = 7.4 Hz, 2H), 3.98 (dd, *J* = 8.2, 3.4 Hz, 2H), 3.61 (q, *J* = 9.8 Hz 2H), 3.51 (dd, *J* = 9.9, 7.1 Hz, 1H), 3.44 (dd, *J* = 9.9, 6.9 Hz, 1H), 3.00 (dd, *J* = 14.1, 9.6 Hz, 1H), 2.89 – 2.81 (m, 3H), 2.19 (dq, *J* = 16.4, 7.7 Hz, 2H), 1.67 (s, 9H), 1.56 (s, 9H), 0.90 (s, 9H), 0.84 (s, 9H), 0.77 (s, 9H), 0.66 (s, 9H), 0.04 (s, 3H), -0.02 – -0.07 (m, 9H), -0.14 (s, 6H), -0.20 (s, 3H), -0.72 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 163.0, 150.5, 150.0, 138.5, 136.4, 136.1, 135.9, 135.8, 135.5, 131.7, 131.1, 130.2, 130.0, 128.2, 125.1, 123.6, 122.4, 122.0, 120.6, 120.5, 119.0, 118.7, 118.0, 116.7, 115.8, 115.2, 83.7, 83.2, 71.6, 70.6, 63.8, 63.5, 52.6, 51.2, 31.0, 30.8, 28.5 (3C), 28.1 (3C), 26.2 (3C), 26.1 (3C), 26.04 (3C), 25.99, 25.94 (3C), 24.8, 18.3, 18.23, 18.22, 18.17, -4.1, -4.6, -4.7, -5.10, -5.15, -5.21, -5.22, -5.3.

IR: υ (cm^{-1}) 3071 (w), 2955 (w), 2930 (w), 2857 (w), 1733 (m), 1457 (w), 1363 (m), 1328 (m), 1255 (m), 1153 (s), 1097 (s), 1035 (m), 837 (s), 775 (s), 742 (m), 673 (w).

HRMS: (ESI) calcd for $C_{68}H_{110}N_2NaO_{10}Si_4^+$ $[M+Na]^+$ 1249.7130; found 1249.7152.

*tert-butyl (9R,10R,Z)-10-(((((Z)-2-iodobut-2-en-1-yl)oxy)carbonyl)amino)-6-oxo-9-(((triisopropylsilyl)oxy)methyl)-6,9,10,11-tetrahydro-5H-cycloocta[b]indole-5-carboxylate (**2.214**)*



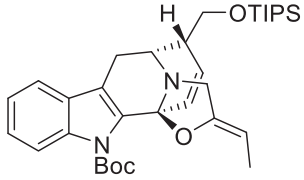
^{1}H NMR (400MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.69 (dd, *J* = 12.2, 8.7 Hz, 1H), 6.51 (d, *J* = 12.2 Hz, 1H), 6.00 (q, *J* = 6.3 Hz, 1H), 4.84 (d, *J* = 12.8 Hz, 1H), 4.70 (d, *J* = 12.8 Hz, 1H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.32 (br t, *J* = 8.9 Hz, 1H), 3.88 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.77 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.40 (dd, *J* = 14.4, 2.6 Hz, 1H), 3.05 (dd, *J* = 14.4, 4.1 Hz, 1H), 2.89 – 2.77 (m, 1H), 1.80 (d, *J* = 6.3 Hz, 3H), 1.58 (s, 9H), 1.11 – 0.98 (m, 21H).

^{13}C NMR (100MHz, $CDCl_3$): δ 183.2 (Cq), 155.1 (Cq), 149.8 (Cq), 144.6, 143.2 (Cq), 138.5 (Cq), 135.3, 135.0, 129.2 (Cq), 128.3, 124.4 (Cq), 123.7, 120.9, 114.4, 102.3 (Cq), 84.5 (Cq), 72.6, 62.9, 54.0, 44.7, 27.9, 27.8 (3C), 21.8, 18.1 (6C), 12.0 (3C).

IR: υ (cm^{-1}) 3312 (w), 2926 (m), 2864 (m), 1733 (s), 1637 (m), 1521 (m), 1461 (m), 1365 (m), 1326 (s), 1232 (s), 1159 (s), 1116 (s), 1014 (m), 883 (m), 754 (m), 687 (m).

HRMS: (ESI) calcd for $C_{34}H_{50}IN_2O_6Si^+$ $[M+H]^+$ 737.2477; found 737.2487.

tert-butyl (5R,11bS,14R,Z)-2-ethylidene-14-(((triisopropylsilyl)oxy)methyl)-2,3,5,6-tetrahydro-11H-11b,5-prop[1]enooxazolo[3',2':1,2]pyrido[3,4-b]indole-11-carboxylate (SP2)



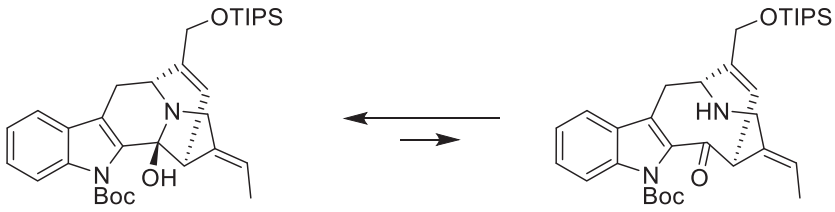
^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 10.1, 2.8 Hz, 1H), 5.62 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.24 (q, *J* = 6.7 Hz, 1H), 4.11 (t, *J* = 6.6 Hz, 1H), 3.72 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.59 (d, *J* = 11.4 Hz, 1H), 3.54 (t, *J* = 10.2 Hz, 1H), 3.40 (dt, *J* = 11.4, 2.3 Hz, 1H), 3.26 – 3.15 (m, 1H), 3.05 (dd, *J* = 18.0, 6.6 Hz, 1H), 2.92 (d, *J* = 18.0 Hz, 1H), 1.74 (s, 9H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.12 – 0.98 (m, 21H).

^{13}C NMR (100MHz, $CDCl_3$): δ 150.5 (Cq), 149.8 (Cq), 136.8 (Cq), 136.2 (Cq), 131.9, 129.1, 128.5 (Cq), 124.7, 122.5, 118.7, 115.5, 113.4 (Cq), 91.6, 90.0 (Cq), 84.2 (Cq), 63.8, 51.0, 48.6, 43.4, 28.4 (3C), 18.2 (6C), 17.7, 12.1 (3C), 10.4.

IR: υ (cm^{-1}) 2953 (w), 2926 (w), 2864 (w), 1737 (m), 1637 (w), 1459 (w), 1357 (m), 1326 (m), 1253 (m), 1157 (s), 1097 (s), 1022 (m), 883 (w), 800 (m), 754 (m), 675 (w).

HRMS: (ESI) calcd for $C_{33}H_{49}N_2O_4Si^+$ $[M+H]^+$ 565.3456; found 565.3460.

*tert-butyl (1S,5R,11bS,E)-2-ethylidene-11b-hydroxy-12-(((triisopropylsilyl)oxy)methyl)-1,2,3,5,6,11b-hexahydro-11H-1,5-ethenoindolizino[8,7-b]indole-11-carboxylate (**SP3**)*



Based on ^{1}H NMR, the product was obtained as a 9/1 mixture of hemiaminal and ketone at rt.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 6.9 Hz, 1H), 5.26 (q, *J* = 6.8 Hz, 1H), 4.21 – 3.96 (m, 4H), 3.86 (d, *J* = 6.9 Hz, 1H), 3.42 (d, *J* = 15.5 Hz, 1H), 3.35 (d, *J* = 16.1 Hz, 1H), 2.84 (d, *J* = 16.1 Hz, 1H), 1.76 (d, *J* = 6.8 Hz, 3H), 1.72 (s, 9H), 1.05 – 0.96 (m, 21H).

^{13}C NMR (100MHz, $CDCl_3$): δ 152.0 (Cq), 143.9 (Cq), 136.2 (Cq), 134.1 (Cq), 132.2 (Cq), 128.8 (Cq), 125.9, 124.8, 123.1, 118.8, 117.5 (Cq), 116.1, 112.3, 89.1 (Cq), 85.4 (Cq), 64.6, 64.1, 56.8, 46.6, 28.4 (3C), 26.2, 18.1 (6C), 15.3, 12.1 (3C).

IR: υ (cm^{-1}) 2959 (w), 2924 (w), 2863 (w), 1729 (w), 1457 (w), 1367 (w), 1323 (w), 1261 (m), 1151 (w), 1087 (s), 1018 (s), 798 (s).

HRMS: (ESI) calcd for $C_{33}H_{49}N_2O_4Si^+$ $[M+H]^+$ 565.3456; found 565.3464.

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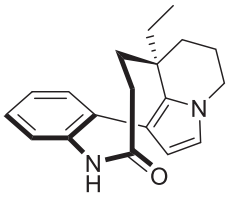
NMR Spectra of the Synthesized Targets



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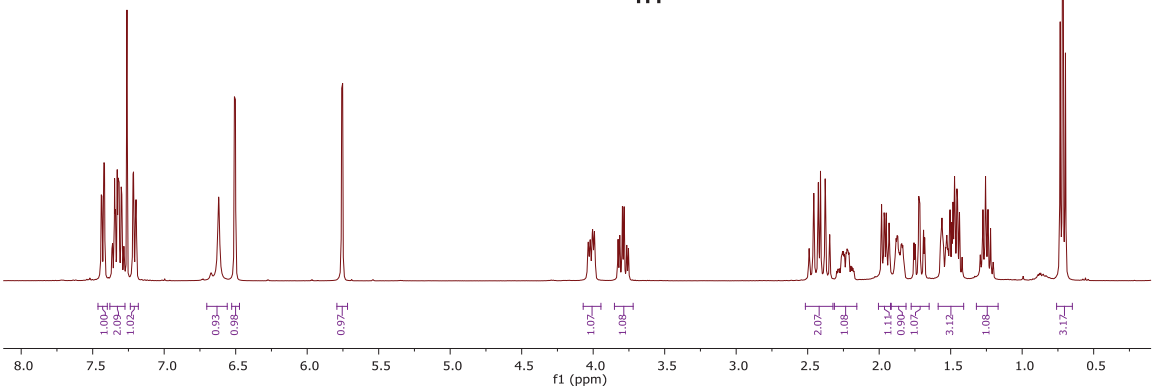

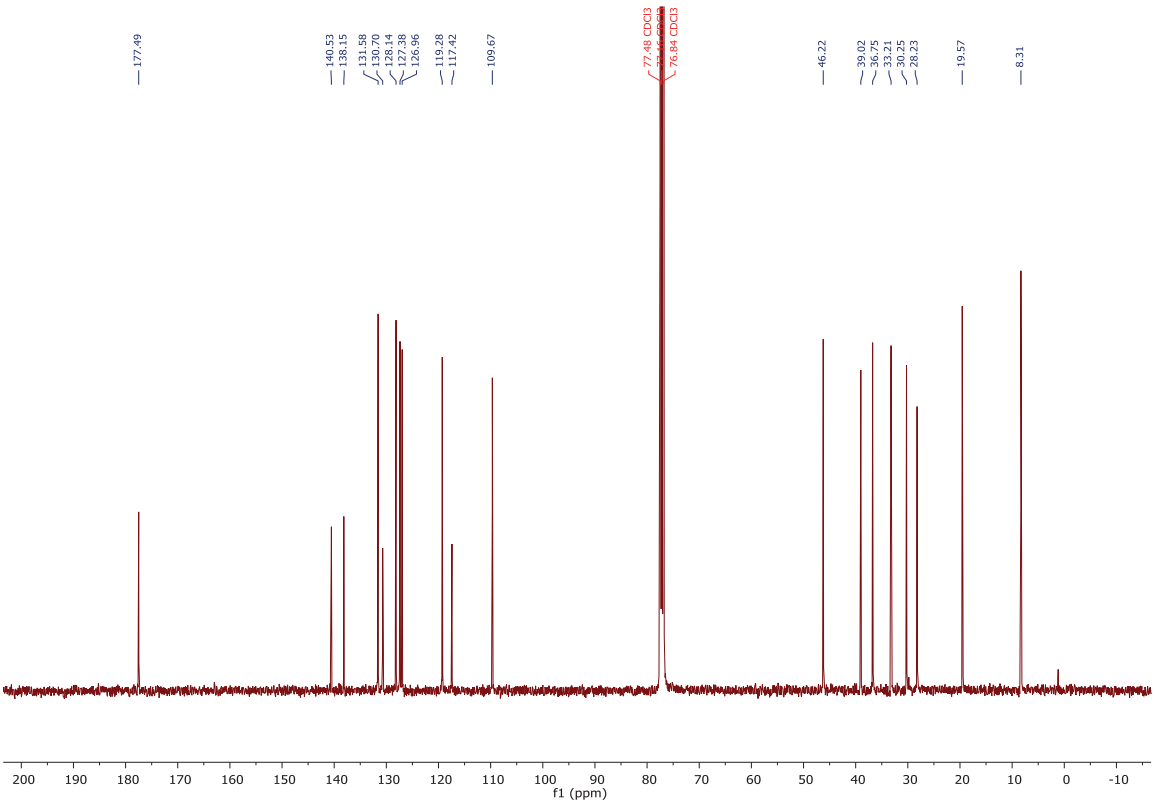

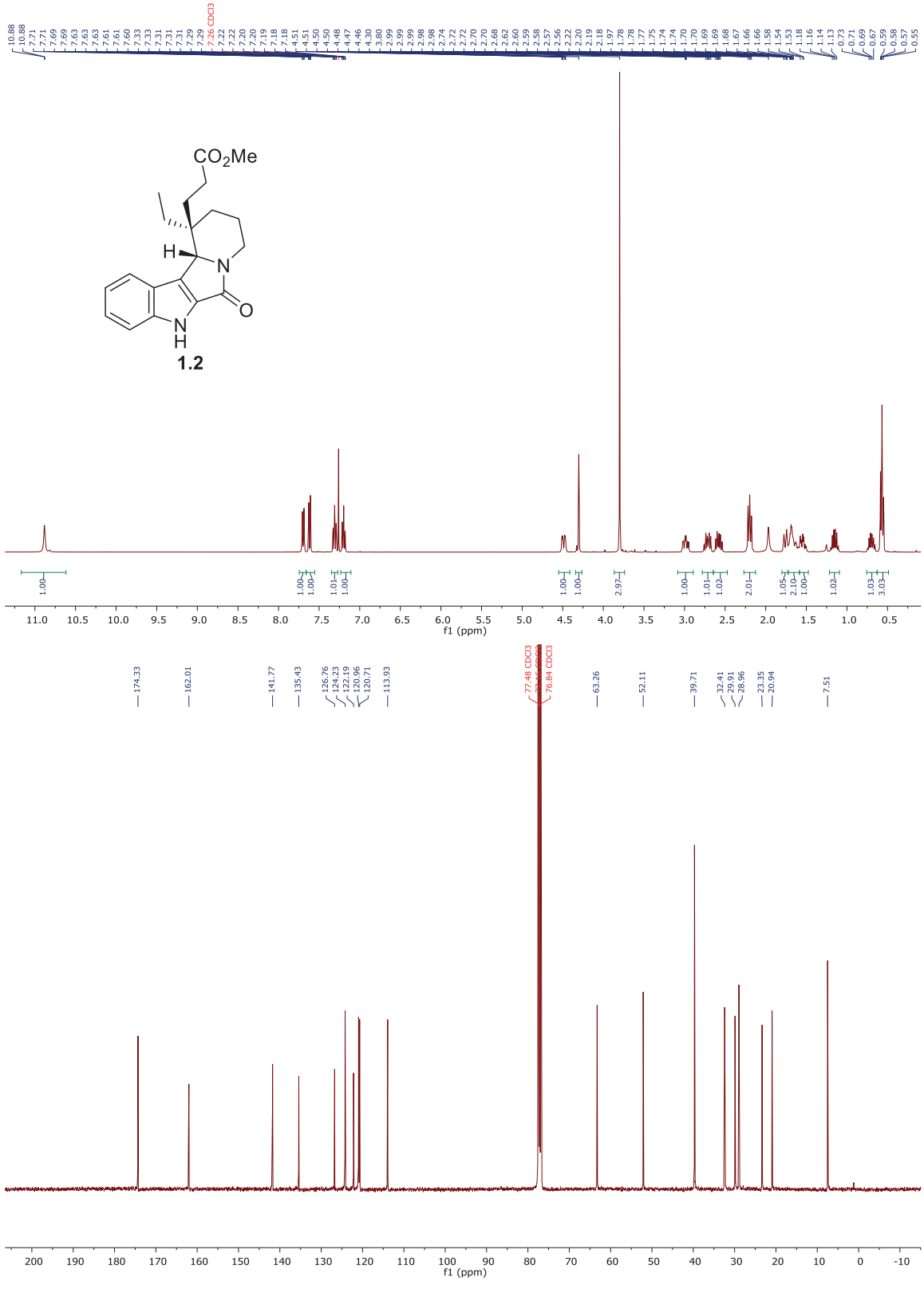
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N
H
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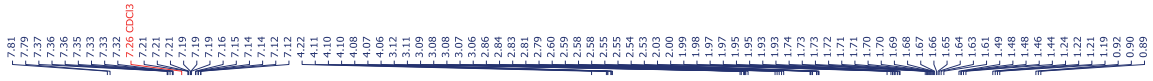
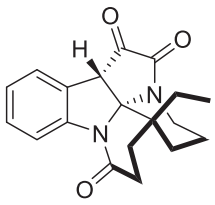
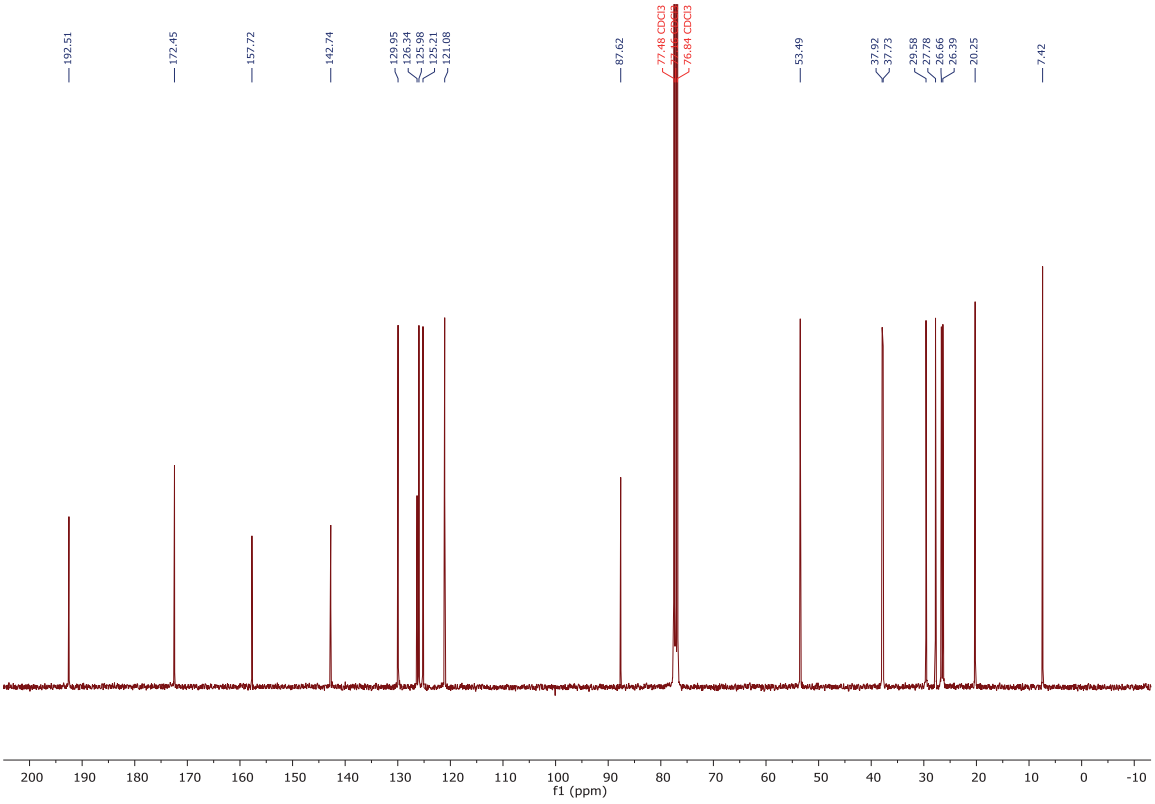
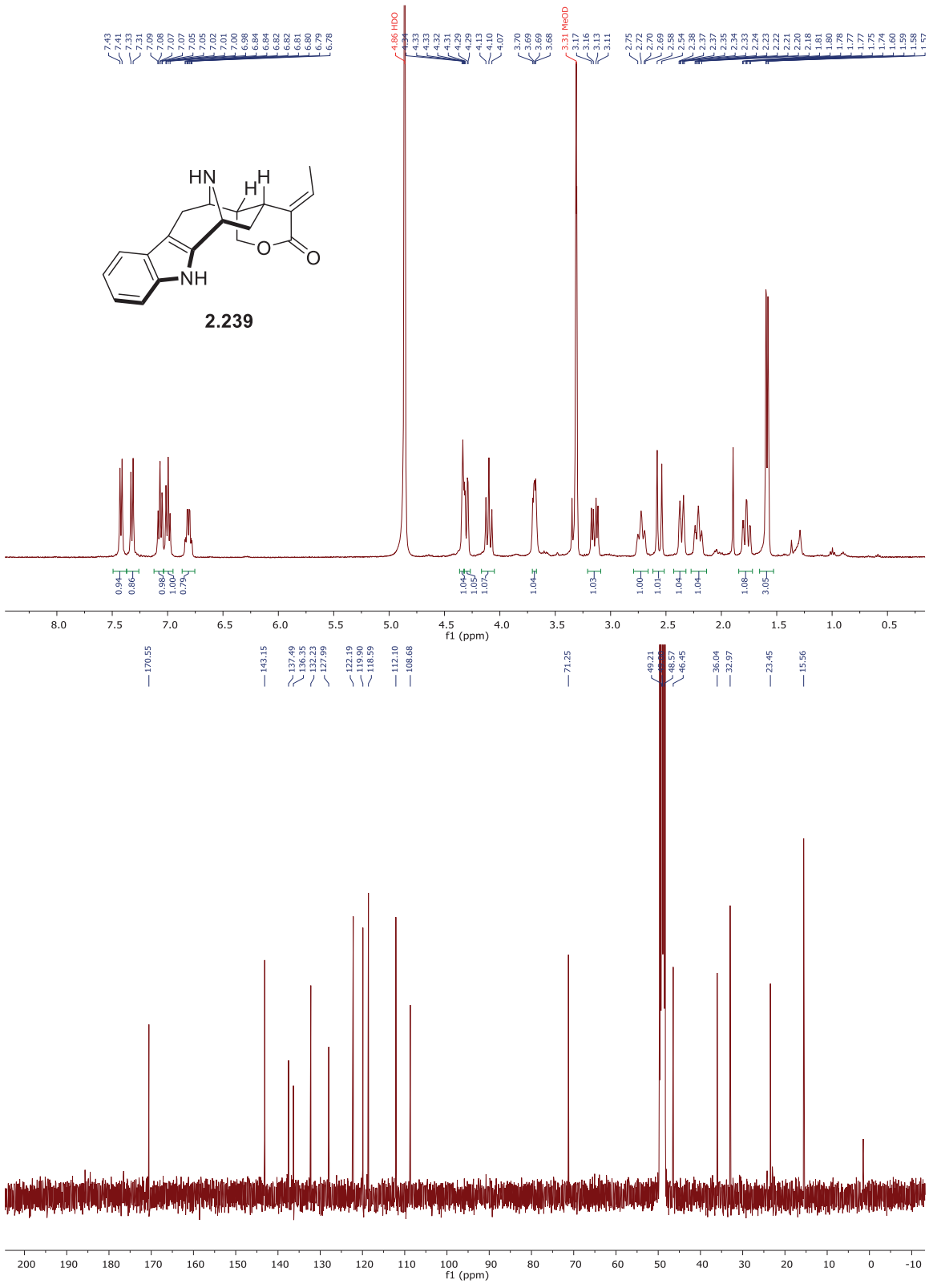
f1 (ppm)
f1 (ppm)





1.3

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f1 (ppm)
f1 (ppm)

Curriculum Vitae

Dylan DAGONEAU
Avenue de France 64 – 1004 Lausanne (Switzerland)
0041 78 956 11 54
dylan-61@hotmail.fr

French Citizen
27 years old, Single
Swiss B work permit
Driving licence

Organic Chemist

Education:

2013-2017: **PhD student** in the group of **Pr. Jieping ZHU** – **EPFL** – 4 years – Lausanne (Switzerland)

- ✓ **Total Synthesis** of Monoterpene Indole Alkaloids
  Dagoneau, D.; Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 760-763.
- ✓ Responsible for the UPLC-MS proper functioning and maintenance
- ✓ 600h as teaching assistant for exercises and practical courses in chemistry.

2013: **Engineer's Degree** in **Chemistry** and **Materials** from **ENSICAEN** and a **Master of Research Degree** in **Organic Chemistry** – Caen (France)

2010: **D.U.T in Chemistry** (Technical University Diploma) – I.U.T Le Mans (France)

2008: **Baccalauréat in Science** (french secondary school diploma), engineering sciences and physics/chemistry specialities – Rémi Belleau Secondary School, Nogent-le-Rotrou (France)

Employment History:

March-August 2013: **Chemical engineer internship** in **Discovery** – **Janssen-Cilag** (Johnson & Johnson group) – 6 months – Val-de-Reuil (France)

- ✓ Multistep synthesis of potent biologically active compounds
- ✓ Chemistry of various heterocycles and organometallics

April-August 2012: **Chemical engineer internship** – Dipartimento di Chimica « Ugo Schif » (Università degli Studi di Firenze) – 4 months – Florence (Italy)

- ✓ Chemistry of sulfur aromatic heterocycles

2011-2012: **ENSICAEN's 2nd year project** – LCMT – Caen (France)

- ✓ Chemistry of fluorosulfones

Summer 2011: **Laboratory technician** – Valois (Aptar Group) – 7 weeks – Verneuil-sur-Avre (France)

- ✓ Leak testing, dynamometer, precision weighing
- ✓ Establishment of database and protocols

2010-2011: **ENSICAEN's 1st year project** – LCMT – Caen (France)

- ✓ Chemistry of [2.2]paracyclophanes

April-June 2010: **Chemical technician internship** – Thépenier Pharma Industrie – 10 weeks – St Langis-Lès-Mortagne (France)

- ✓ Quality Control under the European Pharmacopoeia

LANGUAGES:

French:	Mother tongue
English:	B2 level (TOEIC: 940/990) – Knowledge of chemistry vocabulary
German:	High school level
Spanish:	Basic communication skills

COMPUTER SKILLS:

- ✓ ***Chemistry:*** ChemDraw, MestReNova, Mercury
- ✓ ***Office Pack:*** Word, PowerPoint, Excel
- ✓ ***Programming:*** Basis in Language C, HTML, CSS and JAVA; GRAFCET
- ✓ ***Solid Modeling:*** Solidworks

INTERESTS:

- ✓ Traveling and discovery of other cultures
- ✓ Computer hardware