

Total Synthesis of Aspidosperma Family Indole Alkaloids through the iORC Domino Process

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PAR

Olivier WAGNIÈRES

acceptée sur proposition du jury:

Prof. N. Cramer, président du jury

Prof. J. Zhu, directeur de thèse

Dr T. Gaich, rapporteuse

Prof. H.-U. Reissig, rapporteur

Prof. J. Waser, rapporteur



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FÉDÉRALE DE LAUSANNE

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Il faut toujours connaître les limites du possible.
Pas pour s'arrêter, mais pour tenter l'impossible
dans les meilleurs conditions

— Roman Gary

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Lausanne, June 8, 2015

O. W.

Abstract

This thesis describes a unified strategy for the synthesis of monoterpene indole alkaloids of the *Aspidosperma* family. These syntheses feature two key steps: (1) a palladium-catalyzed decarboxylative vinylation that provides quick access to cyclopentene intermediates containing all of the carbons present in the natural products and (2) an integrated oxidation/reduction/cyclization (*i*ORC) sequence for skeletal reorganisation that converts the cyclopentenones to the corresponding pentacyclic structures of the natural products. By incorporation of a geometric constraint to the *i*ORC substrates, both the chemoselectivity (C7 *versus* N1 cyclization) and the stereoselectivity (*trans*- versus *cis*-fused ring system) of the cyclization process can be controlled. Using this method, we achieved the total synthesis of racemic aspidospermidine and dehydroaspidospermidine in seven steps; both of which feature a *cis*-fused ring system. We then accomplished a ten-steps synthesis of kopsihainanine A featuring a *trans*-fused ring system. The work towards the total synthesis of aspidalbidine and kopsinitarine E using the same two key steps was attempted, but was not completed in the time provided. This PhD will also cover our synthetic efforts towards the alkaloid minfiensine, featuring a domino reduction/cyclization sequence performed prior to the development of the *i*ORC process.

Keywords: natural product, indole alkaloids, domino reaction, *i*ORC, total synthesis, minfiensine, aspidospermidine, dehydroaspidospermidine, vincadifformine, aspidalbidine, kopsihainanine A, kopsinitarine E.

Résumé

Cette thèse décrit une stratégie unifiée pour la synthèse d'alkaloïdes indoliques monoterpéniques de la famille des *Aspidosperma*. Ces synthèses présentent deux étapes clés : (1) une vinylation décarboxylante catalysée au palladium, qui fournit un accès rapide aux intermédiaires cyclopenténiques contenant tous les carbones présents dans les produits naturels ciblés et (2) une séquence domino d'oxydation/réduction/cyclisation intégrée (ORCi) permettant une réorganisation du squelette des cyclopentènes en leurs structures pentacycliques équivalentes. Par incorporation d'une contrainte géométrique aux substrats de l'ORCi, tant la chimiosélectivité (cyclisation en C7 ou N1) que la stéréosélectivité (systèmes cycliques fusionnés en *trans* ou en *cis*) du procédé de cyclisation peuvent être contrôlées. En utilisant cette méthode, nous avons achevé la synthèse totale racémique de l'aspidospermidine et de la déhydroaspidospermidine en sept étapes ; les deux présentant un système cyclique fusionné en *cis*. Nous avons ensuite accompli la synthèse totale racémique de la kopsihainanine A en dix étapes et présentant un système cyclique fusionné en *trans*. Le travail vers la synthèse totale de l'aspidalbidine et la kopsinitarine E utilisant ces deux étapes clés ont été tentées, mais ne furent pas complétées dans le temps imparti. Ce doctorat couvre aussi nos efforts de synthèse de la minfiensine, utilisant une séquence domino de réduction/cyclisation antérieure au développement du procédé ORCi.

Mots-Clés : produit naturel, alkaloïde indolique, réaction domino, ORCi, synthèse totale, minfiensine, aspidospermidine, déhydroaspidospermidine, vincadifformine, aspidalbidine, kopsihainanine A, kopsinitarine E.

List of Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Boc	<i>Tert</i> -butyloxycarbonyl
Bn	Benzyl
Bp	Boiling Point
BRSM	Based on Recovered Starting Material
Bu	Butyl
Bz	Benzoyl
Cbz	Carboxybenzyl
CMPI	2-Chloro-1-methylpyridinium iodide
COSY	Correlation Spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl Carbodiimide
DCM	Dichloromethane
DEAD	Diethyl Azodicarboxylate
DEG	Diethylene Glycol
DIBAL-H	Diisobutylaluminum Hydride
DIPEA	N,N-Diisopropylethylamine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMAP	4-Dimethylaminopyridine
DMBA	1,3-Dimethylbarbituric Acid
CMBP	(Cyanomethylene)tributylphosphorane
DMP	Dess-Martin Periodinane

List of Abbreviations

DMSO	Dimethylsulfoxide
dr	Diastereoisomeric Ratio
E	Entgegen
ee	Enantiomeric Excess
Et	Ethyl
FCC	Flash Column Chromatography
Glc	Glucose
HATU	(1-Bis(dimethylamino)methylene-1H-1,2,3-triazolo [4,5- <i>b</i>]pyridinium 3-oxid Hexafluorophosphate)
HFIP	Hexafluoroisopropyl Alcohol
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single-Quantum Correlation
IBX	2-Iodoxybenzoic Acid
IEDDA	Inverse Electron Demand Diels-Alder
INEPT	Insensitive Nuclei Enhanced by Polarization Transfer
<i>i</i> ORC	Integrated Oxidation/Reduction/Cyclization
IR	Infra-Red
KHMDS	Potassium Bis(trimethylsilyl)amide
LDA	Lithium Diisopropylamine
LDMA	Lithium Dimethylamine
LiHMDS	Lithium Bis(trimethylsilyl)amide
mCPBA	<i>Meta</i> -chloroperoxybenzoic Acid
MCR	Multicomponent Reaction
Me	Methyl
Mps	<i>para</i> -Methoxyphenylsulfonamide
Ms	Mesyl
MTBE	Methyl <i>Tert</i> -butyl Ether
MVK	Methyl Vinyl Ketone
MW	Micro-Wave

Nap	Naphthyl
NHC	N-Heterocyclic Carbene
Ns	Nosyl
NMR	Nuclear Magnetic resonance
NPIF	(<i>ortho</i> -Nitrophenyl)phenyliodonium Fluoride
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
PE	Petroleum Ether
pfp	Pentafluorophenyl
Ph	Phenyl
pin	Pinacol
PMB	<i>p</i> -Methoxybenzyl
Pr	Propyl
quant.	Quantitative Yield
Rf	Retention Factor
RCM	Ring Closing Metathesis
RT	Room Temperature
TBA	Tribromoacetic Acid
TBAC	Tetrabutylammonium Chloride
TBAF	Tetrabutylammonium Fluoride
TBDPS	<i>Tert</i> -butyldiphenylsilyl
TBS or TBDMS	<i>Tert</i> -butyldimethylsilyl
TCAC	Trichloroacetyl Chloride
TES	Triethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
Tf	Triflate
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography

List of Abbreviations

TMS	Trimethylsilyl
TPAP	Tetrapropylammonium Perruthenate
Ts	Tosyl
TSE	Trimethylsilylethyl
TTF	Tetrathiafulvalene
TTMSS	Tris(trimethylsilyl)silane
UV	Ultra-Violet
Z	Zusammen

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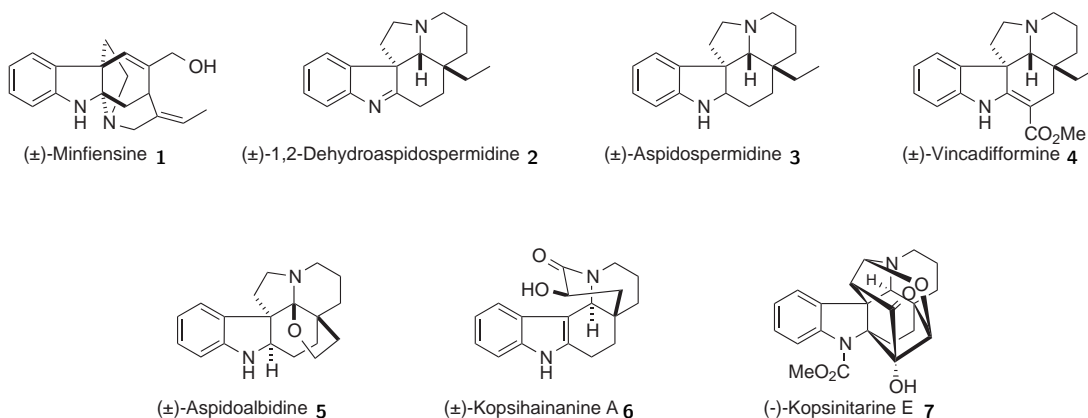
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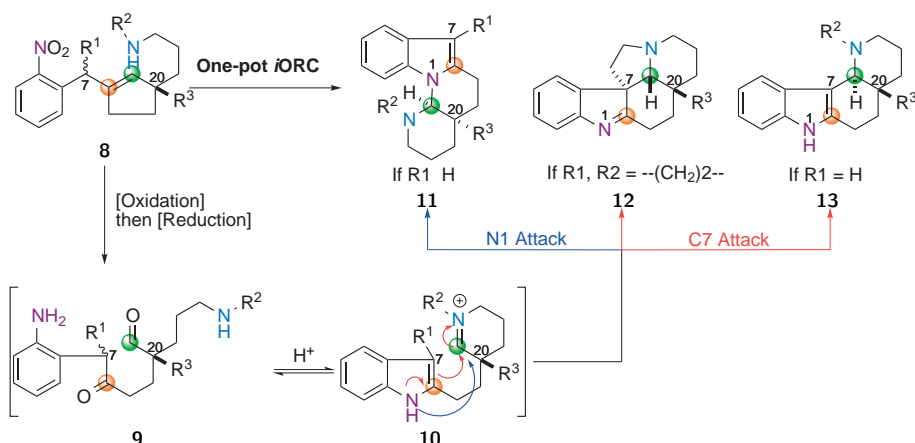
General Introduction

The *Aspidosperma* family is one of the largest family of monoterpene indole alkaloids comprising over 250 members. This group of alkaloids can be found mostly in plants of the *Apocynaceae* family, essentially present in tropical forest. These monoterpene indole alkaloids fascinate the scientific community due to their congested polycyclic structures, high substitution patterns, and multiple stereocenters. These challenging features inspired chemists for decades, and pushed them to develop new methodologies toward the synthesis of complex heterocycles. One of the main research areas of our group is the development of domino reactions, and their use in the construction of substituted indoles. So far many palladium-catalysed syntheses as well as multicomponent reactions for the formation of substituted indoles were developed by our group. In a continuation of this work, we are always looking for new ways to build in a late-stage the indole polycyclic core of indole alkaloids *via* domino processes.

This thesis focuses on the use of a domino reaction called an *integrated oxidation/reduction/cyclization (iORC)* process to reach various members of the *aspidosperma* family of monoterpene indole alkaloids, specifically the natural products **1-7**.



Our idea was to start from stable and easily accessible 1-(2-nitrobenzyl)-cyclopentene derivative **8**. After an oxidative cleavage of the double bond and reduction of the nitro group, we should obtain putative diaminodicarbonyl intermediate **9** that should spontaneously cyclize into iminium indole intermediate **10**.



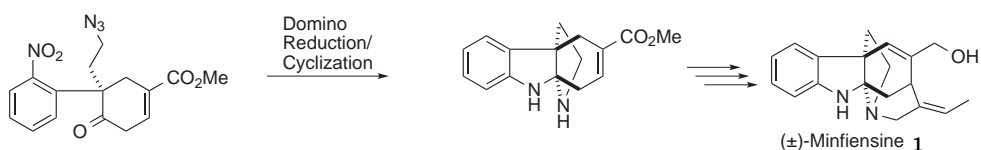
We can notice that **10** has two nucleophilic positions: the N1 and C7 position. It is well known that the C7 position is more nucleophilic than the N1. Nevertheless, if C7 is already substituted with a bulky R¹ group, the attack should occur from the nucleophilic nitrogen N1 and give tetracyclic aminal **11** bearing a *cis*-fused [6,6] ring system. This example, a total synthesis of (±)-Goniomitine has been done previously in our lab, and will be detailed in **1.3.1**.

To force the attack from the C7 position, we envisaged two solutions. i) A structural constrain, such as a tether between R¹ and R² would help force the regioselectivity and give the *cis*-fused [6,6] ring system **12**. ii) By removing all sterical hindrance in R¹, the regioselectivity for the C7 attack could be high, allowing us to reach tetracyclic structure **13**. In this example, we would like to address in more details the diastereocontrol of the *i*ORC, as we plan to force the cyclization in a *trans*-fused [6,6] ring system.

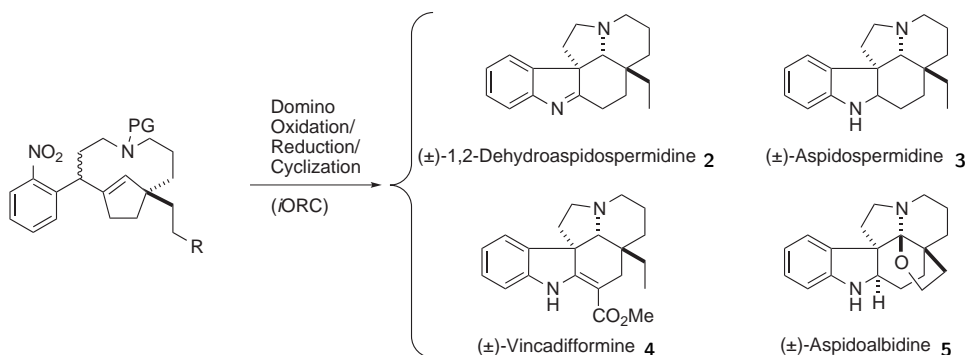
It is important to note that stereogenic centre C7 temporarily becomes sp² hybridized during the *i*ORC and therefore, loses all stereochemical information. Therefore, the C20 quaternary centre will control the diastereoselectivity of the cyclization.

This thesis will start with a brief summary and state of the art of the topics related to this work, namely indole alkaloids, the use of domino process in their total synthesis, and an introduction to the *i*ORC, along with the other syntheses done using this domino process (**Chapter 1**).

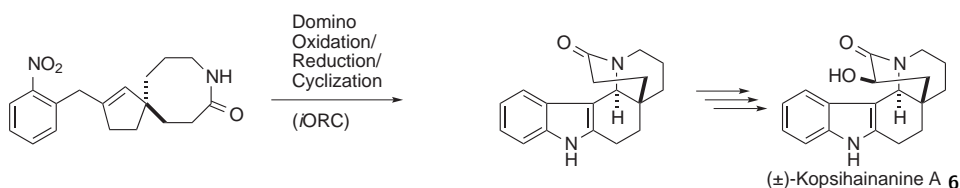
Afterward, this thesis will cover the work done toward the total synthesis of minfiensine **1**, which used an early version of the *i*ORC, lacking the oxidation step (**Chapter 2**).



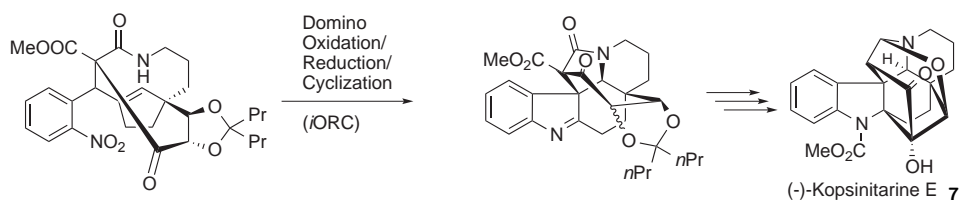
The next two chapters cover the synthesis of aspidospermidine **3**, dehydroaspidospermidine **2** and vincadifformine **4** (**Chapter 3**), and our approach toward the synthesis of aspi-doalbidine **5** (**Chapter 4**) by using the *i*ORC and taking advantage of structure-induced strain to promote the C7-C21 bond formation as key step.



The next chapter investigates more into detail the regio- and stereoselectivity of the unrestrained *i*ORC, and of their use in the total synthesis of kopsihainanine A **6** (**Chapter 5**).



The last chapter covers our approach toward the synthesis of kopsinitarine E **7** using the *i*ORC on a much more complex substrate (**Chapter 6**).



Background

The chemistry of natural products has captivated the scientific community for hundreds of years. Since the first reported isolation of an alkaloid (morphine) in 1805 by Sertürner,¹ chemists have fought many intellectual battles trying to reproduce the wonders of Nature in their flasks. Nature provides us with unlimited numbers of organic compounds, with a large spectrum of molecular masses, of complexity, of heteroatoms, and of many more features, each of them being an intellectual challenge. It is a fascinating field, that contains many sophisticated aspects. The starting point of all this is of course the isolation of the products from various biological media, such as bark of trees, algae, bacteria, or even mammals.

Every compound produced by a biological entity has a specific purpose. The direct consequence of this is the numerous biological effects caused by many of these natural products. These biological properties will often be a strong driving force for the synthetic study of a given natural product. The most potent compounds are often present in negligible quantity inside the biological entity. Therefore the study of such compounds is near impossible due to the tremendous amount of biomass which would be needed to extract a sufficient amount of said compound. This is without mentioning the difficulty to gain access to such a quantity of biomass. A relevant example would be the polyketide (+)-discodermolide, which was isolated in 1990 by Gunasekera and co-workers.² This natural product was isolated from the deep-sea sponge *Discodermia dissoluta*, who grows only at more than 33 m deep in the Caribbean sea. In addition to the difficult access to the biomass, the quantity of (+)-discodermolide present within is small. Only 7 mg of compound per 434 g of sponge was found. It is therefore easy to imagine why the synthesis of such compounds is so attractive, allowing scientists to have easier access to the product in sufficient amounts. It will also give the chemists the ability to make derivatives of a given product, in the optic of increasing some of its biological effects, such as anti cancer or antimicrobial properties.

¹Sertürner, F. J. *Pharm. Aertzte. Apoth. Chem.* **1805**, 13, 229–243

²Gunasekera, S. P.; Gunasekera, M.; Longley, R. E. *J. Org. Chem.* **1990**, 55, 4912–4915

The total syntheses which constitute the body of this work are monoterpene indole alkaloids. Therefore, the first section of this chapter will go more into detail on indole alkaloids and their biosynthesis. As our synthetic strategy revolve around a domino reaction for the late-stage formation of the indole core of these natural products, we will give some examples of the synthesis of indole alkaloids which involved a key domino sequence. We will then introduce our *iORC per se* as well as the other work done with this method.

1.1 Monoterpene Indole Alkaloids

Alkaloids are natural products that can be extracted from the alkaline aqueous phase resulting from treatment of the corresponding biomass, as most of the time they present a basic nitrogen atom. They are produced by a large variety of biological entities and are classified by their skeleton structure. Amongst these alkaloids, we will focus on the products containing an indole moiety.³ A large number of them were discovered by extracting plants or fungi, which were known to have some beneficial effect in traditional medicine. For example the plants of the *Strychnos* genus are a major source of numerous alkaloids, these plants have been used in traditional and conventional medicine for ages. A famous example is the poison strychnine, extracted from the specie *Strychnos nux vomica*, it has been used since the ancient Chinese era. The beneficial effects of plant extracts from the *Strychnos* genus were also exploited in different traditional medicines. Naturally, the biological properties of these plants attracted the attention of chemists which led to the isolation of strychnine by Pelletier and Caventou in 1819.⁴ This was the first monoterpene indole alkaloid isolated. Since then, more than 2000 monoterpene indole alkaloids were discovered. Due to their potent biological activities,⁵ and their challenging polycyclic structure, numerous laboratories have spent years extracting, identifying or synthesizing these alkaloids.

As a result of this strong interest from the scientific community, a large number of reviews and books on indole alkaloids already exist.⁶ Therefore, instead of making a full ac-

³For a review on indole alkaloids, see for example Grundon, M. E.; Saxton, J. E. In *The Alkaloids*, Grundon, M. E., Ed.; The Alkaloids, Vol. 6; Royal Society of Chemistry: Cambridge, 1976; Chapter 10, pp 189–251

⁴Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1819**, *10*, 142–177

⁵For relevant examples, see a) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662; b) Kutchan, T. M. In *Alkaloids Chem. Biol.* 1998; Vol. 50; Chapter 7, pp 257–316; c) Frederich, M.; Hayette, M.-P.; Tits, M.; De Mol, P.; Angenot, L. *Antimicrob. Agents Chemother.* **1999**, *43*, 2328–2331; d) Leclercq, J.; De Pauw-Gillet, M.-C.; Bassleer, R.; Angenot, L. *J. Ethnopharmacol.* **1986**, *15*, 305–316; e) Gong, Z.; Sun, L.-r.; Cao, X.; Li, S.-j.; Zhu, X.-h.; Gao, T.-m. *Nan Fang Yi Ke Da Xue Xue Bao* **2008**, *28*, 2121–2125; f) Baliga, M. S.; Jagetia, G. C.; Ulloor, J. N.; Baliga, M. P.; Venkatesh, P.; Reddy, R.; Rao, K. V. N. M.; Baliga, B. S.; Devi, S.; Raju, S. K.; Veeresh, V.; Reddy, T. K.; Bairy, K. L. *Toxicol. Lett.* **2004**, *151*, 317–326

⁶For reviews on monoterpene indole alkaloids, see: a) Saxton, J. E. *The Alkaloids* **1998**, *51*, 343–376; b) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843–868; c) Lopchuk, J. M. *Prog. Heterocycl. Chem.* **2011**, *23*, 1–25; d) Hájíček, J. *Collect. Czechoslov. Chem. Commun.* **2012**, *76*, 2023–2083

count on the topic of the synthesis of indole alkaloids, we will only introduce the biosynthesis of this class of natural products.

1.1.1 Biosynthesis of monoterpene Indole Alkaloids

The biosynthetic pathway of most monoterpene indole alkaloids are already established and well studied.⁷ Secologanine **14** and tryptamine **15** are the core building blocks to most, if not all, of the monoterpene indole alkaloids (**Scheme 1.1**). They are synthesised respectively from 1-deoxy-D-glucose 5-phosphate **16** and tryptophan **17**. After an enzymatic Pictet Spengler reaction between these two products, strictosidine **18** is obtained. After removal of the glucose, some rearrangements lead to 4,21-dehydrogeissoschizine **19**. This ammonium salt can lead to the *Yohimbinoid* Family, or be reduced into geissoschizine **20**, which is a precursor of the *Ajmalicine* family. The *Cinchona* alkaloids are also derived from strictosidine **18**.

From strictosidine **18** and geissoschizine **20** is derived the uniform numbering system of indole alkaloids proposed by Taylor and Le Men in 1965.⁸ We will use this numbering for the attribution of the NMR spectra as soon as an intermediate bearing all the carbons of the natural products is reached.

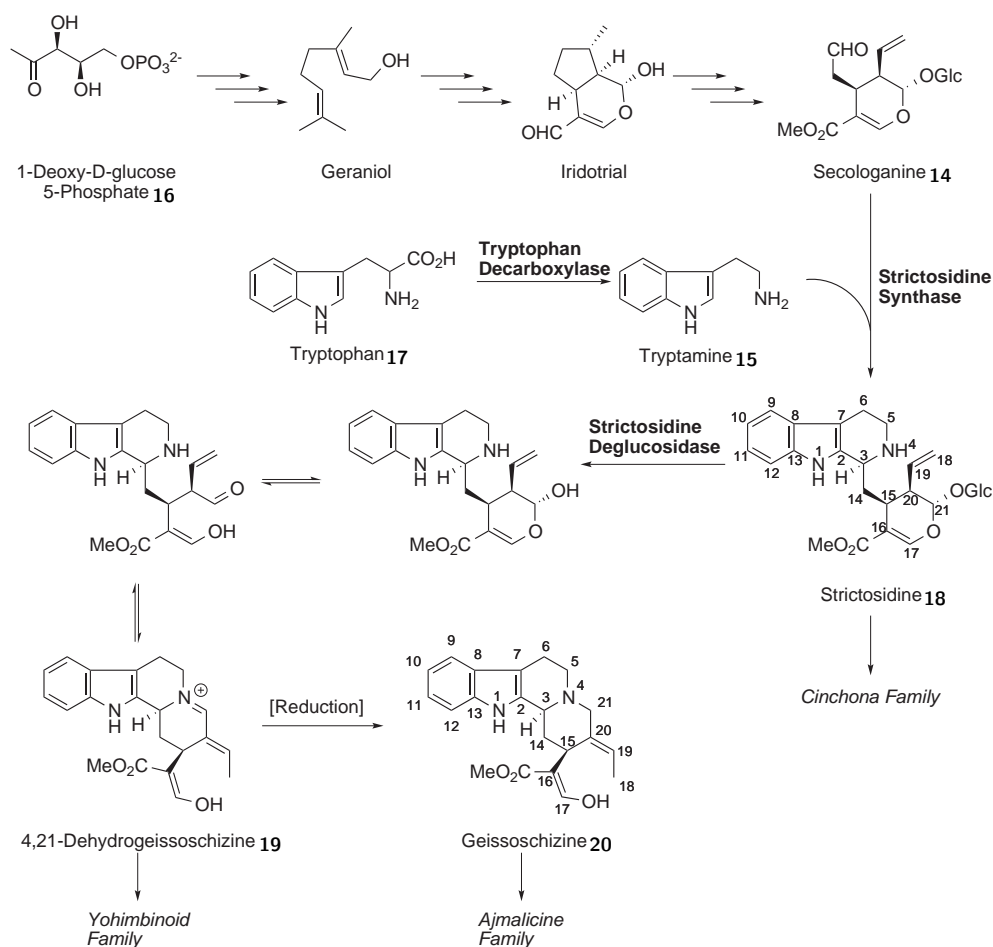
From geissoschizine **20** to *aspidosperma* alkaloids, the mechanism is less understood. Many enzymes involed in the process haven't been isolated or identified. Nevertheless, there are a few theories and some isolated intermediates that allowed chemists to hypothesise a mechanism (**Scheme 1.2**).^{7,9}

After an oxidation, geissoschizine **20** could cyclise to intermediate **21**, an *akuammiline* precursor, that could rearrange into preakuammicine **22** (a precursor of *akuammicine* alkaloids). Then, the iminium would be reduced to afford stemmadenine **23**. From this alkaloid, an isomerisation of the double bond, followed by opening of the macrocycle through enzymatic dehydroxylation would afford *Iboga* precursor **24**. This intermediate could undergo a Diels-Alder cycloaddition into tabersonine **25**. A simple reduction into vincadifformine **4** gives an entrance into the *vinca*, *aspidosperma*, *strychnos* alkaloids and few other families.

⁷ O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, 23, 532–547

⁸ Le Men, J.; Taylor, W. I. *Experientia* **1965**, 21, 508–510

⁹; a) Scott, A. I.; Qureshi, A. A. *J. Am. Chem. Soc.* **1969**, 91, 5874–5876; b) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, 87, 1580–1589



Scheme 1.1 – Biosynthetic pathway to geissoschizine from tryptamine and secologanine

1.2 The Domino Process in Total Synthesis of Indole Alkaloids

Using domino reactions¹⁰ has diverse advantages in organic synthesis mostly less work-up and purification steps, meaning cheaper and faster reaction sequences. It is then not surprising if a myriad of groups applied them in total synthesis. A tremendous number of total syntheses using domino reactions already exist (and it would take many books to cover them).

Domino processes by themselves are not new. Many classical chemical reactions, like Mannich reactions¹¹ are by definitions domino processes. Therefore, it is easy to imagine the tremendous amount of examples of domino reactions accessible in the literature. The

¹⁰Tietze, L. F. *Chem. Rev.* **1996**, 96, 115–136

¹¹Mannich, C.; Krösche, W. *Arch. Pharm. (Weinheim)*. **1912**, 250, 647–667

Geissoschizine **20**

[Oxidation]

MeO₂C CHO

21

[Rearrangement]
[Reduction]

MeO₂C CHO

[Reduction]

Preakuammicine **22**

Akuammiline Family

Stemmadenine **23**

[Reduction]

Vincadifformine **4**

Aspidosperma Family
Strychnos Family

Tabersonine **25**

[Diels-Alder]

24

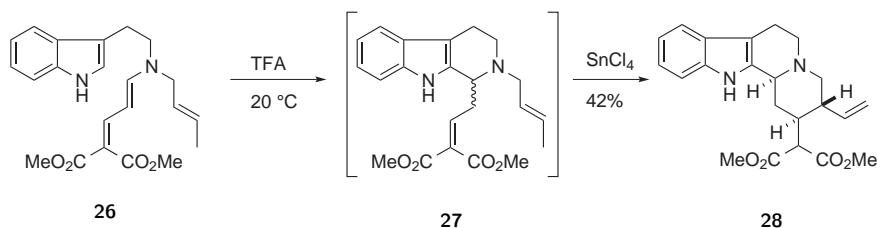
Iboga Family

fascination of chemists for these processes lies in the elegance and almost artistic fashion to perform chemical transformations. The simple reasoning to not just quench the resulting intermediate into a given product A, but instead having it reacting with another substrate toward a more complex product B is somewhat appealing. Lots of work were already done in this field, and multiple reviews on the use of domino reaction in total synthesis already exist.^{10,12} We will only present some selected total syntheses of indole alkaloids that are using domino reactions as key steps.

9

1.2.1 *Corynanthe* Type Indole Alkaloid Synthesis by Tietze

In 1992, Tietze and co-worker reported a synthesis of the tetracyclic core of *corynanthe* alkaloids by the use of a domino Pictet-Spengler/intramolecular ene reaction (**Scheme 1.3**).¹³ Intermediate **26** submitted to acidic medium went through a Pictet-Spengler cyclization into tricycle **27**. This intermediate could be isolated in 66% yield. If SnCl₄ was added to the reaction mixture, an intramolecular ene reaction occurred to give racemic *corynanthe* core **28**.



Scheme 1.3 – Domino Pictet-Spengler/intramolecular ene reaction for the synthesis of *corynanthe* family indole alkaloids

It is an interesting example of an ene reaction in a domino process. The ene reaction has most of the time a high activation energy, which makes it more difficult to be included in a domino process (often in the presence of other reagents or reactive intermediates).

1.2.2 *Strictosidine* Analogues Synthesis by Tietze

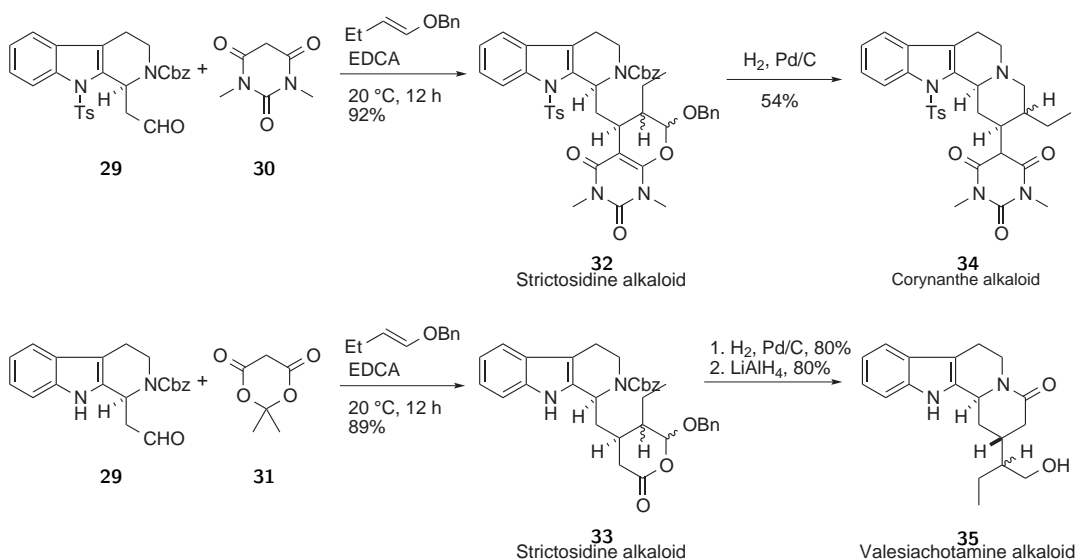
Between 1994 and 1997, Tietze published the syntheses of *strictosidine* type structure using a Domino Knoevenagel/hetero-Diels-Alder pathway (**Scheme 1.4**).¹⁴ After a Knoevenagel condensation of aldehyde **29** with dimethylbarbituric acid **30** or Meldrum's acid **31**, a hetero-Diels-Alder with as dienophile (E)-((but-1-en-1-yloxy)methyl)benzene produced the two *strictosidine* analogues **32** and **33** respectively. These products were converted into *corynanthe* alkaloid **34** or *valesiachotamine* alkaloid **35** by hydrogenolysis of the Cbz and Bz groups.

These examples illustrate the principle of a divergent strategy, where from the same starting material and different reagents, different alkaloids (here *corynanthe* alkaloid and *valesiachotamine* alkaloid) can be reached.

¹³Tietze, L. F.; Wichmann, J. *Angew. Chem. Int. Ed.* **1992**, 31, 1079–1080

¹⁴a) Tietze, L.-F.; Bachmann, J.; Schul, W. *Angew. Chem. Int. Ed.* **1988**, 27, 971–973; b) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, 26, 1185–1194; c) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Zhou, Y.; Raschke, T. *Liebigs Ann.* **1997**, 881–886

1.2. The Domino Process in Total Synthesis of Indole Alkaloids



Scheme 1.4 – Domino Knoevenagel/hetero-Diels-Alder reaction for the synthesis of *strictosidine*-type indole alkaloid

1.2.3 Corey's Total Synthesis of (-)-Aspidophytine

In 1999, Corey and co-workers reported the use of a domino Mannich/allylation sequence to reach aspidophytine **36** (**Scheme 1.5**).¹⁵ Starting from indole **37** and dialdehyde **38**, an acid-catalyzed condensation into iminium **39** took place. The indole moiety of this reactive intermediate cyclized on the iminium, forming indolenium salt **40**. This intermediate cyclized again into pentacycle **41**. *In situ* isomerization of the enamine into an iminium, followed by reduction with NaBH_3CN afforded pentacycle **42** in 66% yield from the starting amine and dialdehyde. This intermediate was converted to (-)-aspidophytine **36** in 6 steps. This synthesis is an elegant example of using indole reactivity to perform multiple cyclizations in one domino process.

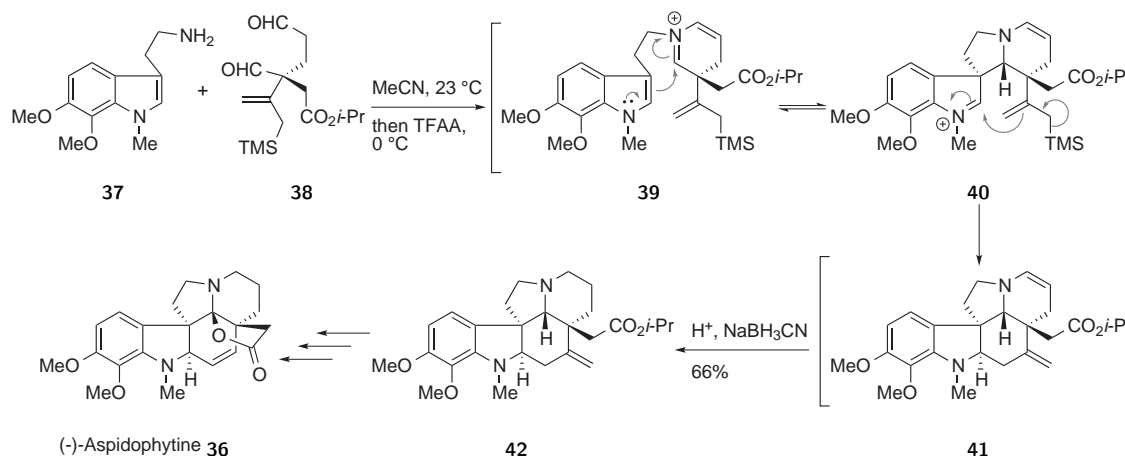
1.2.4 Boger's Total Synthesis of (-)-Vindorosine

Boger and co-workers reported in 2006 a total synthesis of (-)-vindorosine **43** *via* an inverse electron demand Diels–Alder reaction (IEDDA)/(1,3)-dipolar cycloaddition domino process (**Scheme 1.6**).¹⁶ From intermediate **44**, an IEDDA between the electron-rich dienophile and the 1,3,4-oxadiazole moiety afforded intermediate **45**. Subsequent elimination of nitrogen furnished dipolar intermediate **46** that underwent a (3+2) cycloaddition into ether-bridged

¹⁵He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772

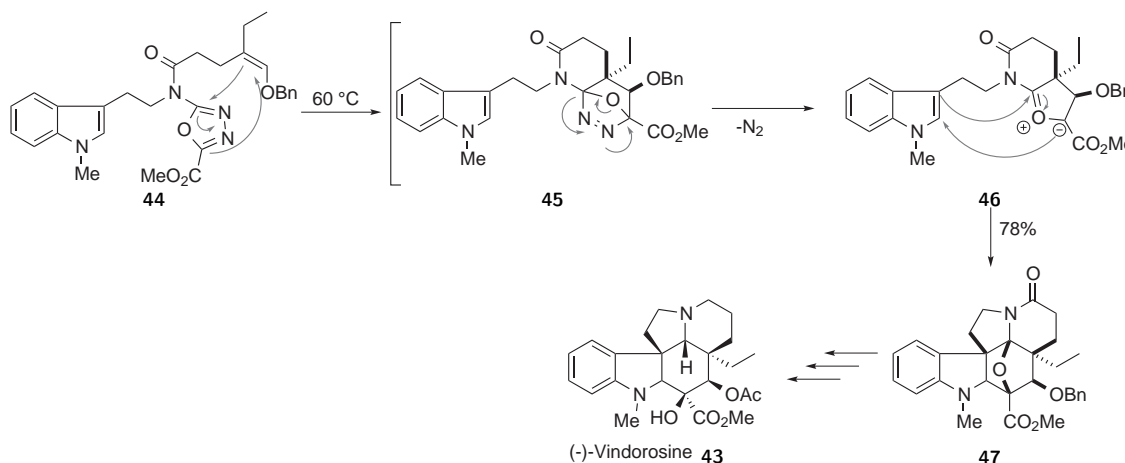
¹⁶Elliott, G. I.; Velcicky, J.; Ishikawa, H.; Li, Y.; Boger, D. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 620–622

Chapter 1: Background



Scheme 1.5 – Domino Cyclizations for a total synthesis of (-)-aspidophytine

product **47**. Both enantiomers of **47** were separated, and (-)-vindorosine **43** was then reached in 7 additional steps.



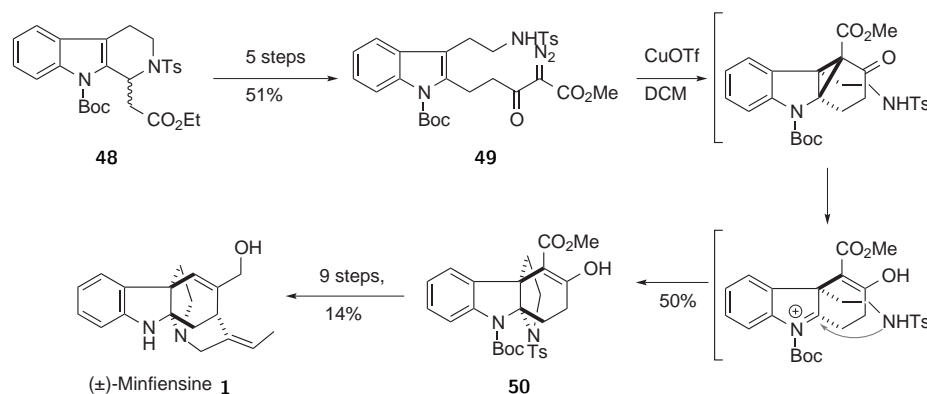
Scheme 1.6 – Domino IEDDA/(1,3)-dipolar cycloaddition for a total synthesis of (-)-vindorosine

Diels-Alder and retro Diels-Alder reactions are often used in domino reactions, as they often display good regio and diastereoselectivity and the resulting olefin can undergo subsequent transformations.

1.2.5 Qin's Total Synthesis of (±)-Minfiensine

Qin and co-workers illustrated in 2008 the efficiency of a cyclopropanation/retro-Mannich/cyclization domino sequence towards total synthesis of minfiensine

(**Scheme 1.7**).¹⁷ Starting directly with indole structure **48** (obtained in 3 steps from tryptamine with 70% yield), they obtained diazo ketone **49**. It then cyclized in the presence of copper triflate through a one-pot cyclopropanation/ring opening/ring closing cascade reaction to form intermediate **50**. (±)-Minfiensine **1** was then reached in 9 more steps.



Scheme 1.7 – Domino cyclopropanation/retro-mannich/cyclization process in Qin's total synthesis of (±)-minfiensine

The release of the ring strain of a cyclopropane is a good driving force for developing a process that does not require harsh conditions. It allows more flexibility in the development of one-pot procedures.

1.2.6 Danishefsky's Total Synthesis of (-)-Phalarine

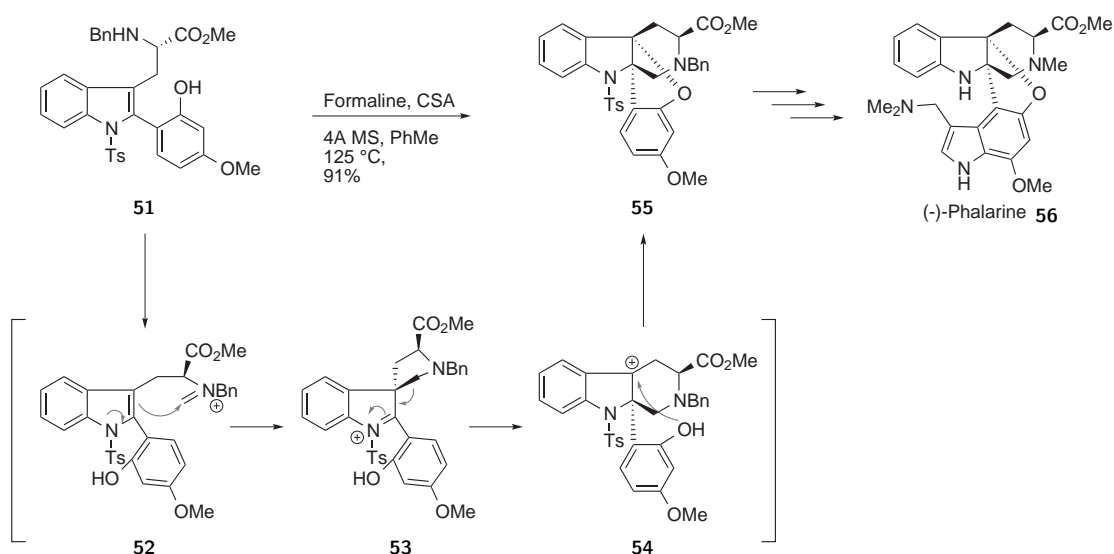
Danishefsky reported in 2010 a total synthesis of the furanobisindole alkaloid (-)-phalarine (**Scheme 1.8**).¹⁸ Starting from aminoester derivative **51**, their reaction sequence began with a Pictet Spengler reaction with formaldehyde into iminium salt **52**. Subsequent attack from the C3 position of the indole gave indolenium intermediate **53**. This was followed by a Wagner-Meerwein rearrangement into carbocation **54**. The carbocation was then trapped by the phenol moiety affording **55** in 91% yield as a single diastereoisomer. Ten more steps were necessary to reach enantiopure (-)-phalarine **56**.

1.3 The *i*ORC Process and Related Total Syntheses

The Michael and Mannich additions are amongst the most powerful tools for C-C bond formation. Despite being well established reactions, Michael and Mannich reactions are still

¹⁷Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, 47, 3618–3621

¹⁸Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, 132, 8506–8512



Scheme 1.8 – Domino Pictet-Spengler/Cationic cyclization pathway in a total synthesis of (-)-phalarine

being studied and improved every year.

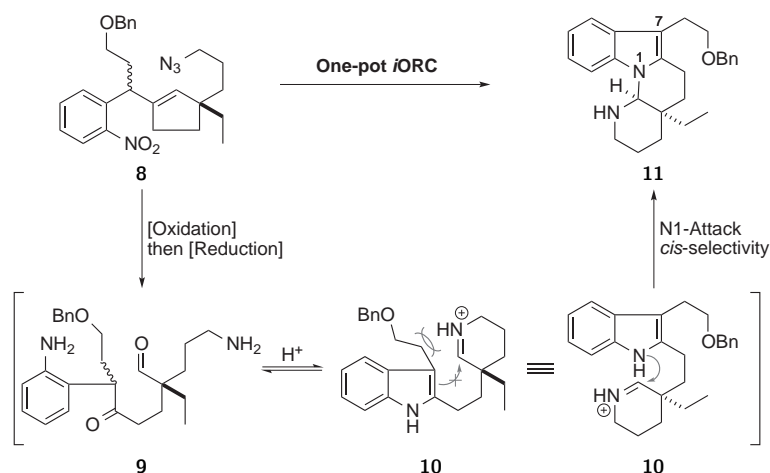
Intramolecular Mannich reactions between indole derivatives and imine or iminium species are well described systems.¹⁹ Nonetheless, the one-pot sequential condensations of on one hand a 2-aminophenylacetyl ketone moiety to form the indole and on the other an amine and carbonyl group to form an activated imine followed by reaction of these two species *in situ* haven't been exploited to the best of our knowledge. The reason is the difficulty to obtain a stable intermediate with amines and carbonyles groups without prior unwanted condensation or polymerization. The first concept of the *i*ORC was to form these two amines and carbonyl groups *in situ* in a domino process (**Scheme 1.9**). From stable and easily accessible 1-(2-nitrobenzyl)-cyclopentene derivative **8**, an oxidative cleavage of the double bond²⁰ and reduction of the nitro group,²¹ afforded putative diaminodicarbonyl intermediate **9** that should spontaneously cyclize into iminium indole intermediate **10** (*cf.* **General Introduction**).

We can notice that **10** has two nucleophilic positions: the N1 and C7 position. It is well known that the C7 position is more nucleophilic than the N1. Nevertheless, as C7 is already substituted with a bulky alkyl group, the attack occurred from the nucleophilic nitrogen N1 and gave the tetracyclic aminal **11** bearing the desired *cis*-fused [6,6] ring system.

¹⁹ Shiri, M. *Chem. Rev.* **2012**, *112*, 3508–3549

²⁰ a) Criegee, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 745–752; b) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990–3001

²¹ Ono, N., *The Nitro Group in Organic Synthesis*; Feuer, H., Ed.; John Wiley & Sons, 2003: 2001



Scheme 1.9 – General pathway of the *i*ORC domino process for the total synthesis of goniomitine

1.3.1 Total Synthesis of (±)-Goniomitine

In 2013, Zhu and co-workers published the total synthesis of goniomitine using the *i*ORC domino sequence (**Scheme 1.10**).²² This synthesis was the proof of concept for this domino process.

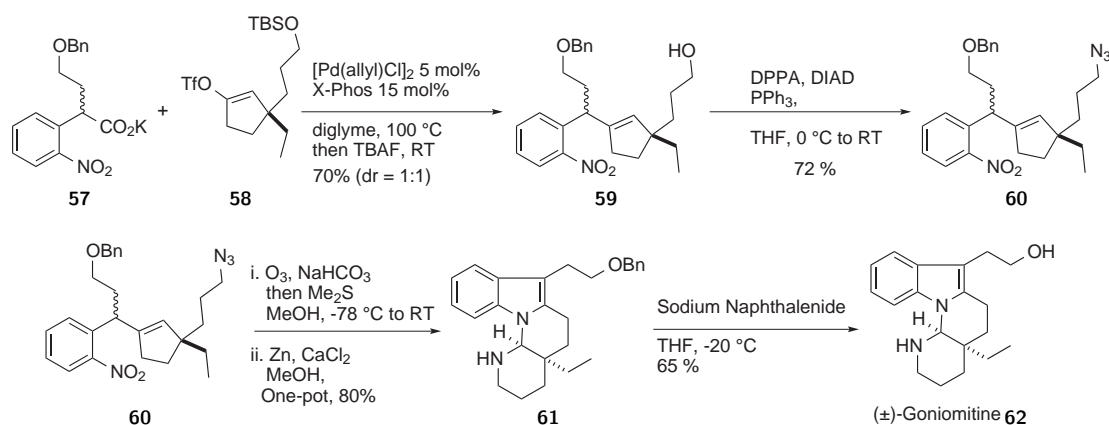
From easily accessible potassium salt **57** and vinyl triflate **58**, a palladium-catalyzed decarboxylative coupling followed by *in situ* deprotection of the silyl group afforded the alcohol **59**. After a Mitsunobu reaction to form the azide **60**, the key step could be attempted. As planned, the bulky $\text{CH}_2\text{CH}_2\text{OBn}$ chain blocked the attack from the C7 position and only the attack from the nitrogen was observed with full diastereocontrol. After ozonolysis and subsequent reduction of both nitro and azide groups, O-benzylgoniomitine **61** was isolated as the only product in 80% yield. Deprotection of the benzyl group under standard conditions afforded racemic goniomitine **62** in 65% yield.

1.3.2 Total Synthesis of leuconolam–leuconoxine–mersicarpine

In the end of 2013, our group published a domino sequence similar to the *i*ORC process in order to reach the leuconolam–leuconoxine–mersicarpine skeleton (**Scheme 1.11**).²³ In this case, the domino sequence is not anymore an *i*ORC, because the oxidation of the olefin was performed as a separate operation, and the reduction/cyclization sequence was refined to incorporate a lactamization and further oxidation steps. Nonetheless, the reaction pathway

²²Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, 52, 3272–3276

²³Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, 135, 19127–19130



Scheme 1.10 – Total Synthesis of goniomitine **62** using an *i*ORC domino process

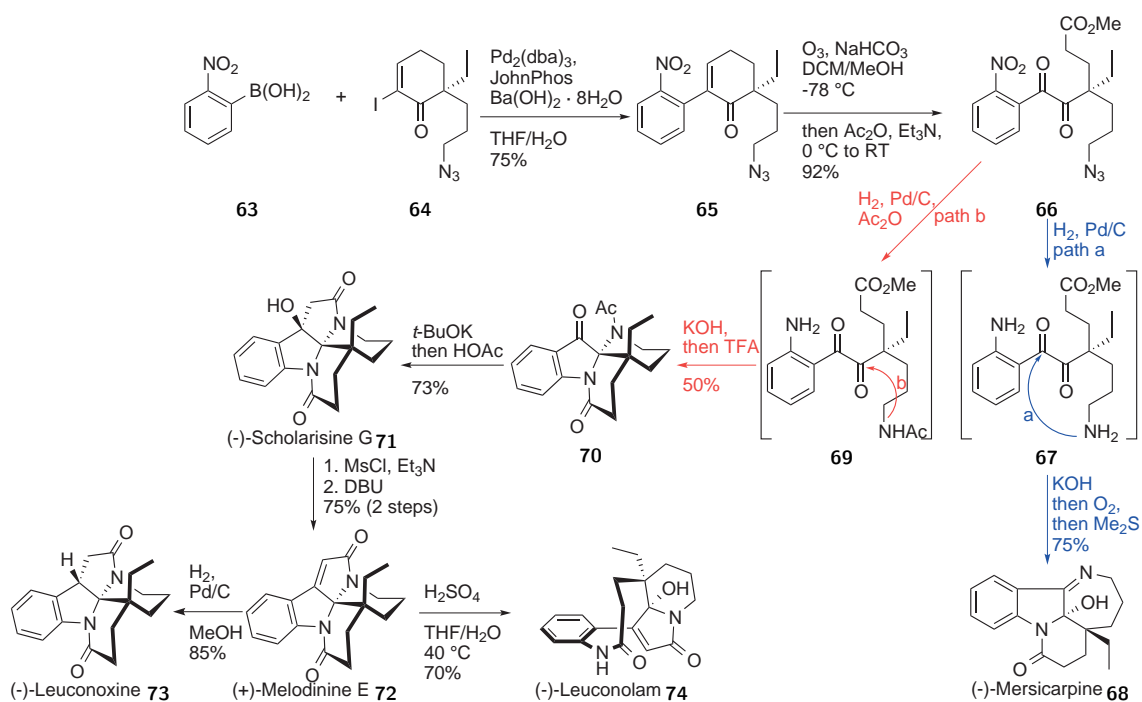
has strong similarities with our former *i*ORC.

From boronic acid **63** and iodoenone **64**, a Suzuki-Miyaura coupling afforded **65**, then an ozonolysis afforded methyl ester **66**. Following the idea of the *i*ORC, the following step was the reduction of both the nitro group and the azide, giving the two amines needed for the cyclizations. A careful optimization allowed for selectivity between pathways a and b. Following pathway a, the alkyl amine **67** cyclized on the aryl ketone, to afford a 1H-3-aminoindole. This intermediate underwent lactamization of the ester by the indole nitrogen promoted by KOH, followed by *in situ* oxidation with oxygen and reduction with Me_2S to yield (-)-mersicarpine **68** which was isolated with 75% yield.

When acetic anhydride was used during the first reduction step (path b), the azide moiety was converted into an acetamine group (**69**). After two consecutive cyclizations, intermediate **70** was isolated in 50% yield. This intermediate is a precursor to scholarizine G, but is lacking the C6-C7 bond (the acetyl did not cyclize on the 3-oxindole). Submitting this intermediate to a strong base afforded (-)-scholarisine G **71** in 73% yield. Further transformations of this natural product allowed our laboratory to reach (+)-meoldinine E **72**, (-)-leuconoxine **73** and (-)-leuconolam **74**.

This work demonstrates the high versatility of the *i*ORC process. Its potency to reach a large variety of families of monoterpene indole alkaloid is quite exceptional.

1.3. The *i*ORC Process and Related Total Syntheses



Scheme 1.11 – Total Synthesis of (-)-mersicarpine **68**, (-)-scholarisine G **71**, (+)-melodinine E **72**, (-)-leuconoxine **73** and (-)-leuconolam **74**

Approach Towards the Total Synthesis of Minfiensine

In 1989, Massiot and co-workers discovered an indole alkaloid named (+)-minfiensine **1**, which possess an unprecedented pentacyclic structure. They isolated this new alkaloid from the African plant *Strychnos minfiensis* (**Figure 2.1**).²⁴

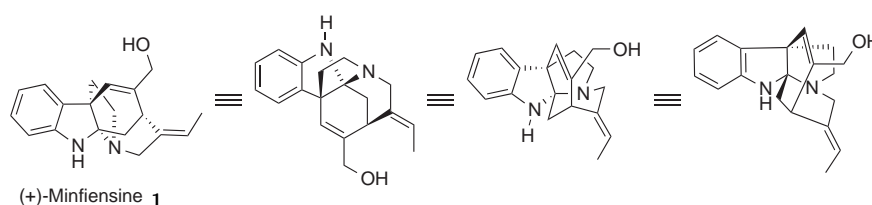


Figure 2.1 – Different representations of the indole alkaloid minfiensine **1**

This *strychnos* indole alkaloid raised the attention of the scientific community due to its highly congested pentacyclic ring system that presents an interesting synthetic challenge. In addition, different members of the *strychnos* indole alkaloid family have shown interesting anticancer activities.²⁵ The pentacyclic core of this alkaloid was unique until 2012, when Morita and co-workers found in the *Alstonia* plant an indole alkaloid with a similar polycyclic system named (+)-alsmaphorazine C (**Figure 2.2**).²⁶ The challenge of this quite unique congested skeleton encouraged many laboratories to search for a synthetic route and, until now, five laboratories have achieved the total synthesis of minfiensine.

²⁴ Massiot, G.; Thépenier, P.; Jacquier, M. J.; Le Men-Olivier, L.; Delaude, C. *Heterocycles* **1989**, 29, 1435–1438

²⁵ a) Leewanich, P.; Tohda, M.; Matsumoto, K.; Subhadhirasakul, S.; Takayama, H.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **1997**, 332, 321–326; b) Leewanich, P.; Tohda, M.; Matsumoto, K.; Subhadhirasakul, S.; Takayama, H.; Watanabe, H. *Biol. Pharm. Bull.* **1996**, 19, 394–399; c) Maier, A.; Maul, C.; Zerlin, M.; Grabley, S.; Thiericke, R. *J. Antibiot.* **1999**, 52, 952–959

²⁶ Koyama, K.; Hirasawa, Y.; Nugroho, A. E.; Kaneda, T.; Hoe, T. C.; Chan, K.-L.; Morita, H. *Tetrahedron* **2012**, 68, 1502–1506

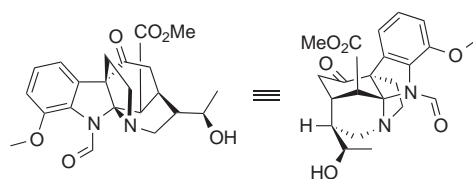
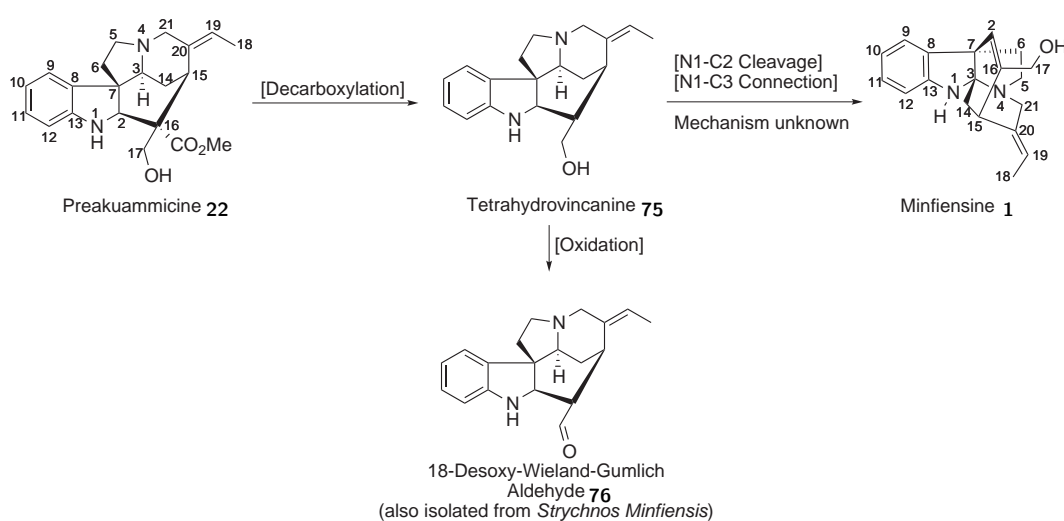


Figure 2.2 – The indole alkaloid (+)-alsmaphorazine C

To the best of our knowledge, no biosynthetic pathway of minfiensine is reported. It is reasonable to postulate that minfiensine **1** originates from preakuammicine **22** (Scheme 2.1), as minfiensine's structure is closely related to some members of the akuammine indole alkaloid family. The first step is probably a decarboxylation, leading to tetrahydrovincanine **75**. This structure is closely related to 18-desoxy-Wieland-Gumlish aldehyde **76** isolated from the same plant as minfiensine **1**. From here, the remaining steps to go from tetrahydrovincanine **75** to minfiensine **1** are the cleavage of the N1-C2 bond and the formation of the N1-C3 bond. Unfortunately, there are no explanation so far on the enzymatic pathway leading to minfiensine **1**.

Scheme 2.1 – Hypothesis of biosynthetic pathway for akuammine alkaloid minfiensine **1**

2.1 Previous Syntheses

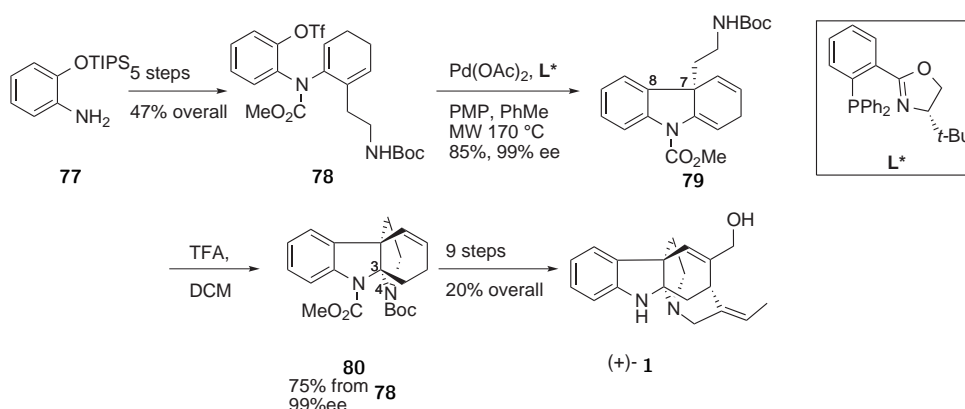
16 years after the isolation of minfiensine **1**, Overman and co-workers reported the first synthetic pathway to enantiopure alkaloid **1** in 21 steps and 3.2% overall yield,²⁷ which has since

²⁷ Dounay, A. B.; Overman, L. E.; Wroblewski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187

then been improved in 2008 to 15 steps and 6.5% overall yield.²⁸ Qin and co-workers reported in 2008 a synthesis of the racemic alkaloid in 18 steps and 0.4% overall yield (See **1.2.5**).¹⁷ A major breakthrough came from the MacMillan group the year after, who obtained the enantiopure alkaloid in only 9 steps and 21% yield.²⁹ Finally the group of Padwa and Qiu synthesized (±)-minfiensine in 2011, the former in 11 steps and 3.3% overall yield³⁰ and the latter in 10 steps and 6.2% overall yield³¹ respectively.

2.1.1 Overman's Synthesis of (+)-Minfiensine

Overman's group published the first synthesis of (+)-minfiensine **1** starting from **77** (Scheme 2.2). Five steps were needed to convert this amine into enamine intermediate **78**. Then by using a catalytic asymmetric Heck-iminium ion cyclization sequence, indoline derivative **79** was obtained. Acidification of the reaction mixture resulted in the N4 attack of the C3 position, closing the aминаl ring, affording **80**. Nine more steps were required to reach (+)-minfiensine **1**.^{27,28}



Scheme 2.2 – Overman's Synthesis of (+)-minfiensine **1**

Using the Pfaltz ligand for the formation of **79**, they were able to form the quaternary center on the C7 with full enantiocontrol, which then dictated the stereoselectivity of the aминаl formation.

²⁸Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wroblewski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377

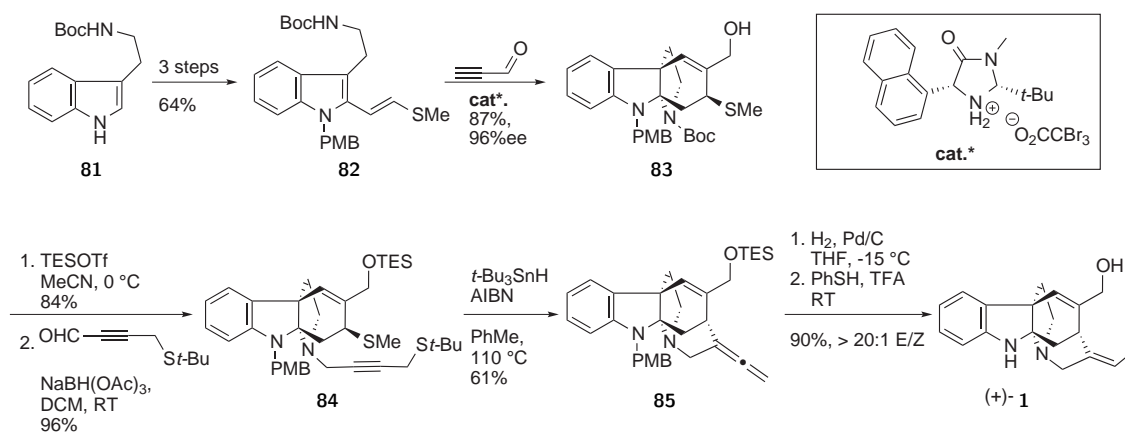
²⁹Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607

³⁰a) Bobeck, D. R.; France, S.; Leverett, C. A.; Sánchez-Cantalejo, E.; Padwa, A. *Tetrahedron Lett.* **2009**, *50*, 3145–3147; b) Li, G.; Padwa, A. *Org. Lett.* **2011**, *13*, 3767–3769

³¹Liu, P.; Wang, J.; Zhang, J.; Qiu, F. G. *Org. Lett.* **2011**, *13*, 6426–6428

2.1.2 MacMillan's Synthesis of (+)-Minfiensine

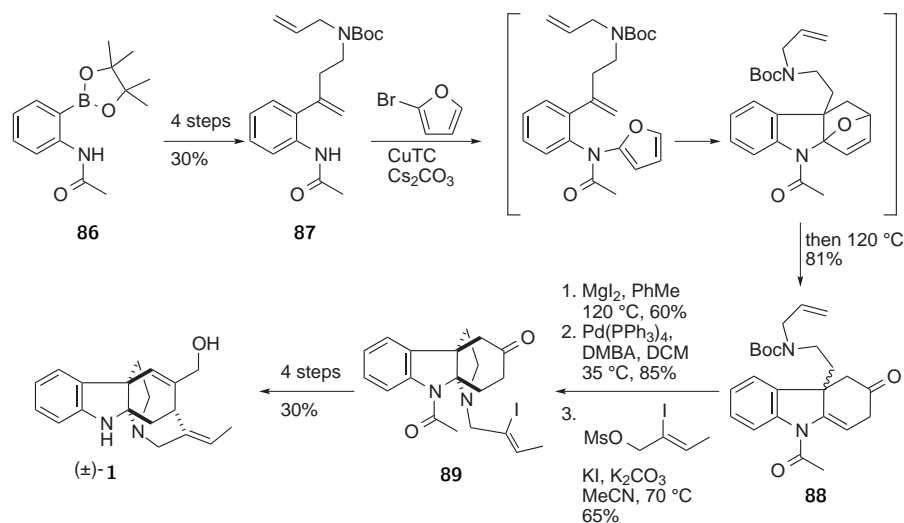
In 2009, a short enantioselective synthesis was published by MacMillan and co-workers.²⁹ Their synthesis of (+)-minfiensine **1** started with protected tryptamine **81**, synthesizing diene **82** in three steps (**Scheme 2.3**). This diene reacted with propionaldehyde after activation by a chiral organocatalyst. The resulting Diels-Alder product spontaneously cyclized with the Boc-protected amine to afford **83** with good yield and ee.

Scheme 2.3 – MacMillan's Synthesis of (+)-Minfiensine **1**

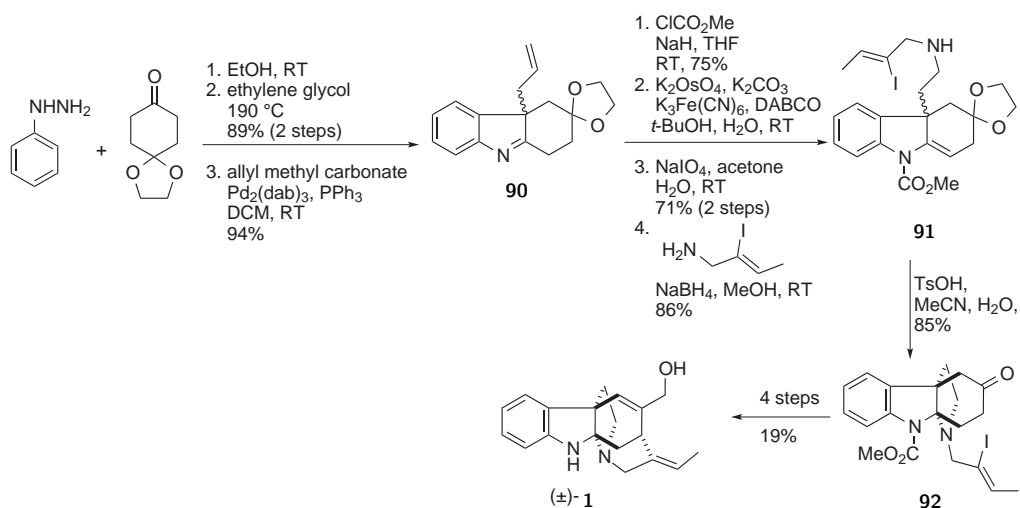
After protection of the alcohol and alkylation of the amine (**84**), a radical 6-exo-*dig* cyclization closed the last ring of the natural product and form the allene **85**. A palladium catalyzed hydrogenation afforded the *E* alkene with high selectivity. Finally, deprotection gave (+)-minfiensine **1**.

2.1.3 Padwa's Synthesis of (±)-Minfiensine

The strategy of Padwa and co-workers is shown in **Scheme 2.4**.³⁰ Starting from **87**, obtained in 4 steps from **86**, they decided to build the indole moiety using a domino cross-coupling/Diels-Alder/rearrangement process to reach **88**. After this, Boc deprotection with MgI₂ with spontaneous cyclization to form the aminal moiety, palladium-catalyzed deallylation, and N-allylation afforded **89**. Finally, a Heck-type reaction closed the last ring of the racemic natural product and (±)-minfiensine **1** was obtained in 4 more steps *via* functional group interconversions.



Scheme 2.4 – Padwa's synthesis of (±)-minfiensine **1** using a domino Cross-coupling/Diels-Alder/rearrangement process



Scheme 2.5 – Qiu's total synthesis of (±)-minfiensine

2.1.4 Qiu's Synthesis of (±)-Minfiensine

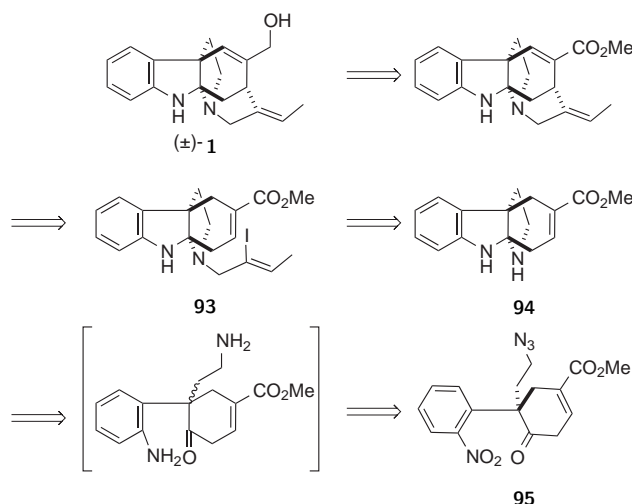
In Qiu's strategy (**Scheme 2.5**),³¹ the indole is formed using the Fisher indole synthesis as the first step. The quaternary carbon at the C7 position was then installed with a palladium catalyzed allylation to reach intermediate **90**. Protection of the indolenine moiety followed by a two-step oxidative cleavage of the terminal olefin and reductive amination of the resulting aldehyde afforded **91**. It was then cyclized at the C3 position to form aminal **92**. A Heck-type reaction allowed them to close the last ring of the pentacyclic core to reach racemic

minfiensine **1** after functional group interconversions.

2.2 Synthetic Studies of Minfiensine

These strategies, elegant as they are, all form the indole in an early stage, or start from an indole derivative (tryptamine). As far as we know, nobody has yet attempted to form both C-N bonds of the aminal in one step. This approach could be a powerful tool for the formation of indole alkaloids. With this in mind, we undertook the synthesis of minfiensine **1** featuring our domino process.

From a retrosynthetic point of view (**Scheme 2.6**), (±)-minfiensine **1** can be easily obtained from **93**, following a similar Heck-type reaction as described in other syntheses.³²



Scheme 2.6 – Retrosynthetic analysis of (±)-minfiensine

The key step would be the formation of **94** through a reduction/cyclization sequence. To the best of our knowledge, such strategy was not yet described to reach this type of alkaloid. We planed to use a reductive domino double cyclization sequence in which the aminal was formed from a ketone and two latent amine functions (**95**). This reaction had the great advantage of creating the two amino functions *in situ*, avoiding excessive protection/deprotection steps. We can consider this domino process as an early version of our *i*ORC process, that did not include the oxidation step.

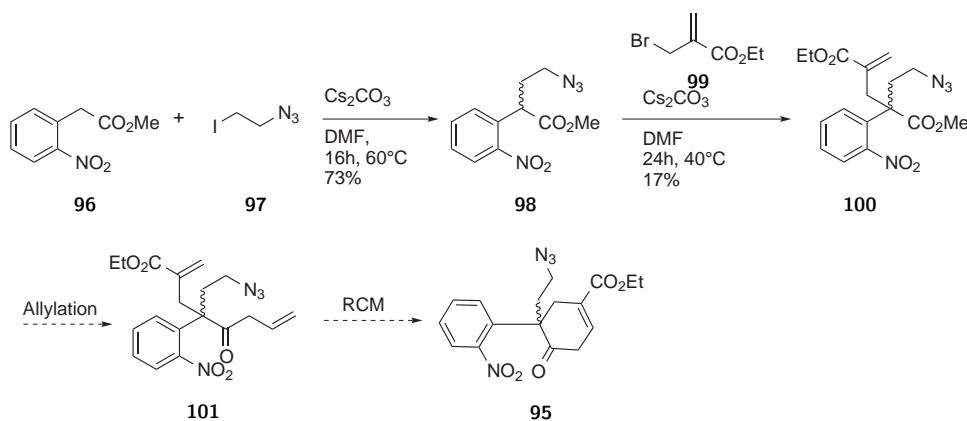
We can notice the presence in the key intermediate of the quaternary center in what

³²a) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473; b) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877–8879

would be the C7 position of the future alkaloid structure. This stereocentre should direct the diastereoselectivity of the different cyclisations. As our first plan was to reach intermediate **95** and study the feasibility of the key reaction of our synthesis, we decided not to focus on the chirality of this stereocentre for the moment, but to dedicate our efforts to a racemic version of the synthesis with the possibility to develop subsequently an enantioselective version.

2.2.1 Key Intermediate Formation: Intramolecular RCM Strategy

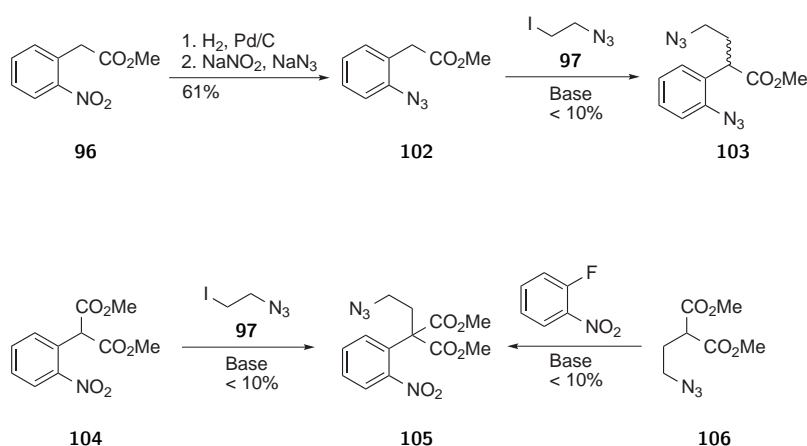
We pursued several strategies to obtain intermediate **95**. Our first idea (**Scheme 2.7**) was to perform an alkylation and an allylation on methyl 2-(2-nitrophenyl)acetate **96**. Alkylation with **97**, would afford ester **98**. Subsequent allylation with **99** would generate 2,2-disubstituted arylacetate **100**. With this straightforward approach it was, in theory, possible to reach allyl ketone **101** from methyl ester **100** and then form highly functionalized cyclohex-3-en-1-one derivative **95** by ring closing metathesis (RCM).



Scheme 2.7 – First pathway to the key intermediate

The α position of the ester has a low pKa value due to the strong electron withdrawing effect of the *o*-nitrophenyl group. This makes the anion a poor nucleophile. Furthermore, after the first addition, this position becomes quite hindered which makes the attack on the electrophile more difficult. The formation of this quaternary center was therefore a major issue in this strategy. When we inverted the sequence and started by adding **99**, which worked well, the anion from this allylated product was not sufficiently nucleophilic to add onto **97** and no desired compound **100** was obtained. The more reactive methacrylate derivative **99** had therefore to be added in the second step. After careful screening of diverse bases and temperature, the yield of the first addition was pushed to a promising 73%, but the second addition to form **100** was more tedious. Even after optimizing the base (amines, lithium bases, alcoholates, carbonate bases with or without crown ether), the solvent and the temperature,

the yield never exceeded 17%. This reaction resulted either in recovering the starting material, or decomposition if the temperature was too high or the base too strong. We attempted to modify the nucleophile, using an azidophenyl acetate **102** instead of the nitrophenyl acetate **96**, but all alkylations tried on this substrate resulted in degradation of the reagent and a messy reaction mixture. It is noteworthy that such alkylation on 2-(2-azidophenyl)acetyl acid derivatives were never reported. We also attempted to form malonate compound **105**. Sadly, the poor reactivity of the anion was again troublesome and the quaternary carbon was unreachable by alkylation (from **104**) or S_NAr (from **106**) regardless of our efforts. Reactions with similar substrates are known, but only on less bulky substituents, or with more activated electrophiles.³³ The conversion after 24 h was less than 10% in the best conditions.



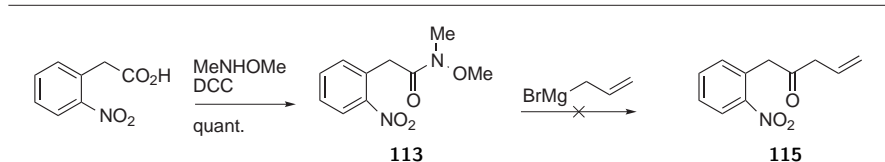
Scheme 2.8 – Attempts on malonate derivatives or azidophenyl derivative

At this stage, we reasoned we could not afford such a poor yield for the formation of this quaternary centre. We needed a way to force the anion to react and increase the yield. It was decided to attempt the cross-metathesis first, and then form the quaternary centre intramolecularly.

2.2.2 Key Intermediate Formation: Cross Metathesis

For this strategy, we needed at first to change the ester of **98** to an allyl ketone. Several pathways were attempted. The results are shown in **Scheme 2.9**. We first saponified ester **98** to

³³Only example of S_NAr reaction of α -alkyl substituted malonate with 2-fluoronitrobenzene, see: a) Ueno, M.; Yonemoto, M.; Hashimoto, M.; Wheatley, A. E. H.; Naka, H.; Kondo, Y. *Chem. Commun.* **2007**, 2264–2266; For examples of alkylation on α -arylmalonate, see also b) Selvakumar, N.; Reddy, B. Y.; Azhagan, A. M.; Khera, M. K.; Babu, J. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, 44, 7065–7069; c) Hong, S.; Jung, M.; Park, Y.; Ha, M. W.; Park, C.; Lee, M.; Park, H. G. *Chem. Eur. J.* **2013**, 19, 9599–9605; d) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M. H.; Jew, S. S.; Park, H. G. *J. Am. Chem. Soc.* **2011**, 133, 4924–4929; e) Hirschhäuser, C.; Parker, J. S.; Perry, M. W. D.; Haddow, M. E.; Gallagher, T. *Org. Lett.* **2012**, 14, 4846–4849



tion of the starting material. The desired allyl ketone **110** was never observed.

We therefore decided to try different types of allylations. In an attempt to make the reaction smoother, we planned to use an aldehyde instead of an acyl chloride. Here again, allylation of aldehyde **111** was not trivial. Numerous Lewis acids were tried in combination with allyltrimethylsilane, or different allyl-metal species. These attempts resulted only in degradation, except for allyl cerium complexes, formed *in situ* from cerium chloride and allylmagnesium bromide³⁶ afforded the desired product, though the yield remained low (<20%). After many trials, we finally found that Brown Allylation of aldehyde **111** with an allylboronic acid pinacol ester worked well to afford homoallylic alcohol **112** in good yield as a mixture of two diastereoisomers.³⁷ From this intermediate, formation of both TES-protected alcohol **114** and allyl ketone **110** proceeded smoothly.

With allyl products **110**, **112** and **114** in our hand, we could attempt the cross metathesis with different acrylates (**Scheme 2.10**).³⁸ Unfortunately, all possible combinations of the three acrylates **99**, **116**, **117** with unprotected alcohol **112**, TES-protected alcohol **114** or the oxidized allyl ketone **110** did not provide the desired olefin when using either Grubbs II or Hoveyda-Grubbs II. Only starting material and degradation was observed. An attempt was made after tethering the two olefins by esterification, but resulting compound **119** also failed to undergo the RCM to **120**. This behaviour might be due to the presence of an azide group. Some ruthenium catalysts are known to react with azides³⁹ and the phosphine in the Grubbs II catalyst could also reduce the azide group. Examples of metathesis with substrates bearing an azide moiety are sparse and are often described as troublesome, giving low yields, especially if the azide group is close to the olefin.⁴⁰

Since the metathesis proved unfruitful, we planned to screen conditions for a Baylis Hillman reaction^{38,41} on aldehyde **128** (**Scheme 2.11**), but only degradation was observed.

Takeuchi, H.; Shiobara, Y.; Kawamoto, H.; Koyama, K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 321–327

³⁶Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398

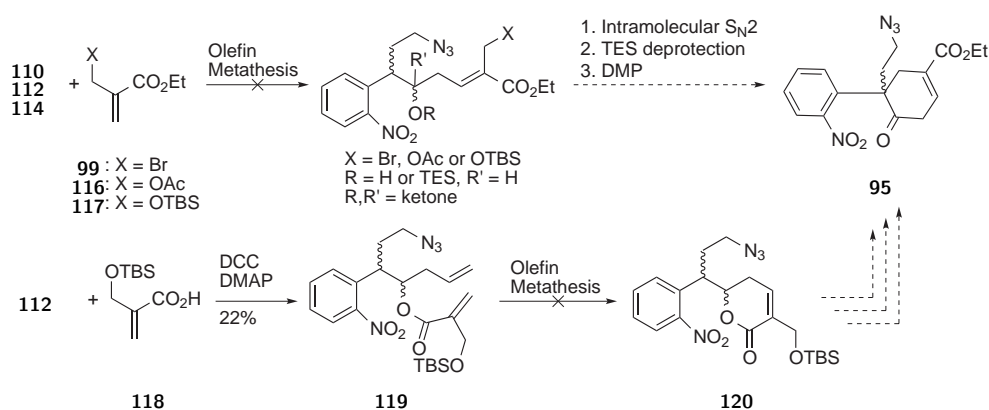
³⁷a) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868–1874; b) Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443–7448

³⁸Aouzal, R.; Prunet, J. *Org. Biomol. Chem.* **2009**, *7*, 3594–3598

³⁹a) Caselli, A.; Gallo, E.; Ragaini, F.; Ricatto, E.; Abbiati, G.; Cenini, S. *Inorganica Chim. Acta* **2006**, *359*, 2924–2932; b) He, J.; Yamaguchi, K.; Mizuno, N. *J. Org. Chem.* **2011**, *76*, 4606–4610; c) Risse, J.; Scopelliti, R.; Severin, K. *Organometallics* **2011**, *30*, 3412–3418

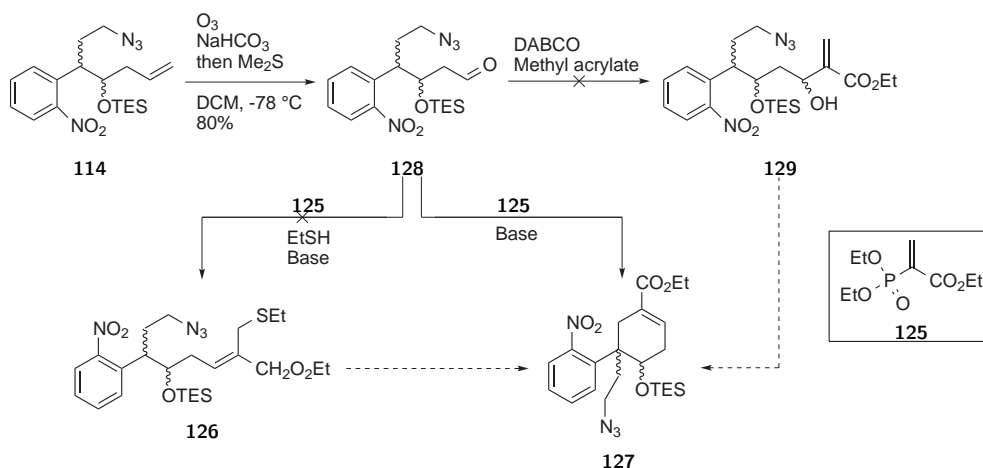
⁴⁰a) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413–415; b) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929–4938; c) Chang, C. W.; Chen, Y. N.; Adak, A. K.; Lin, K. H.; Tzou, D. L. M.; Lin, C. C. *Tetrahedron* **2007**, *63*, 4310–4318; d) Kanemitsu, T.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4541–4544; e) Rai, A. N.; Basu, A. *Org. Lett.* **2004**, *6*, 2861–2863; f) Busscher, G. E.; van den Broek, S. B. A. M. W.; Rutjes, F. P. J. T.; van Delft, F. L. *Tetrahedron* **2007**, *63*, 3183–3188; g) Chaudhari, V. D.; Ajish Kumar, K. S.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805–5807; h) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508–6514; i) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879–8882

⁴¹Basavaiah, D.; Rao, P. *Tetrahedron* **1996**, *52*, 8001–8062



Scheme 2.10 – Attempts to perform the metathesis before the formation of the quaternary center.

Horner–Wadsworth–Emmons reaction with ethyl 2-(diethylphosphono)acrylate **125** and an external nucleophile did not afford **126**.⁴² Attempts without external nucleophile to reach directly cyclized **127** has proven unsuccessful.



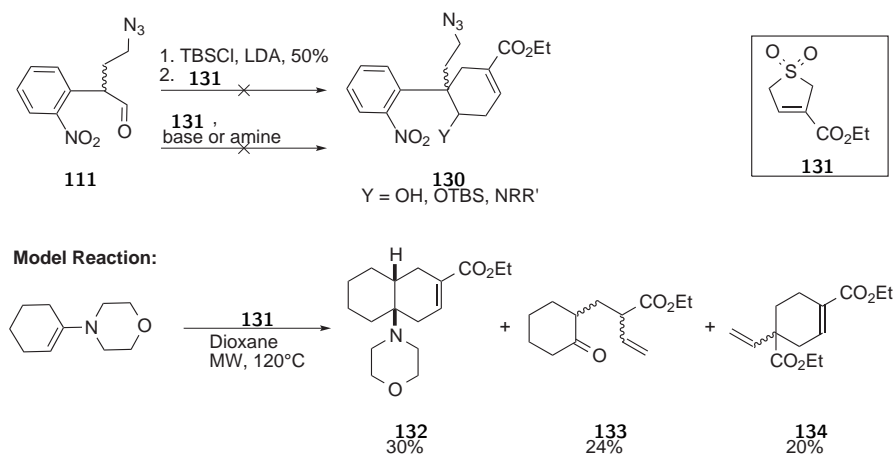
Scheme 2.11 – Morita-Baylis-Hillman or Horner–Wadsworth–Emmons reaction for the formation of **127**

After encountering so many problems at this stage of the synthesis, we decided to change our strategy in order to reach our key intermediate. We reasoned that because it contains a cyclohexenone ring, we could probably attempt to form it *via* a Diels-Alder reaction.

⁴²Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, *43*, 1259–1262

2.2.3 Key Intermediate Formation: Cycloaddition Strategies

Our first cycloaddition strategy relied on an IEDDA reaction (**Scheme 2.12**). Starting from aldehyde **111**, formation of a silyl enolate⁴³ followed by cycloaddition with 2-buta-1,3-dienoate ethyl ester should afford desired cyclohexene **130**. The diene needed for the reaction proven not to be stable, but could be formed *in situ* by heating sulfonene **131**.



Scheme 2.12 – IEDDA to the key intermediate and model reaction for the cycloaddition on an enamine

This diene precursor is easily synthesised⁴⁴ and is well described in IEDDA reactions with electron rich dienophiles to afford structures with the desired regioselectivity.⁴⁵ Unfortunately, all our attempts at forming **130** were unsuccessful and only resulted in degradation. Instead, we envisaged to perform the cycloaddition using a base (enolate formation) or an amine (enamine formation). After a few unsuccessful trials with aldehyde **111**, we decided to use a model substrate to continue studying this reaction. We decided to use the commercially available N-morpholinocyclohex-1-ene as enamine for this cycloaddition.⁴⁶ The main difficulty encountered during this reaction was the easy polymerization of both starting materials. Product formation could only be observed under microwave assisted conditions. But the best yield which could be obtained was 30% of *cis*-fused cycloadduct **132**, along with sig-

⁴³ a) Takasu, K.; Tanaka, T.; Azuma, T.; Takemoto, Y. *Chem. Commun.* **2010**, 46, 8246–8248; b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, 68, 7565–7581

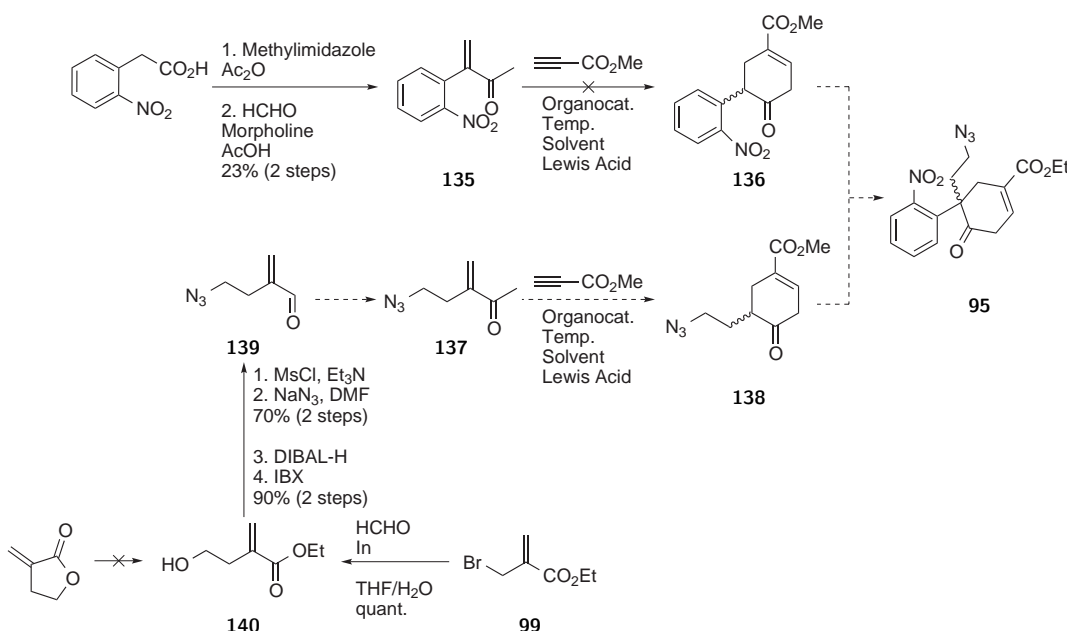
⁴⁴ a) Trost, B. M.; Huang, X. *Chem. Asian J.* **2006**, 1, 469–478; b) McIntosh, J. J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, 43, 4431–4433; c) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, 56, 226–231; d) Leonard, J.; Hague, A. B.; Jones, M. F.; Ward, R. A. *Synthesis* **2000**, 32, 507–509; e) Johnson, J. W.; Evanoff, D. P.; Savard, M. E.; Lange, G.; Ramadhar, T. R.; Assoud, A.; Taylor, N. J.; Dmitrienko, G. I. *J. Org. Chem.* **2008**, 73, 6970–6982; f) Andrade, G. S.; Berkner, J. E.; Liotta, C. L.; Eckert, C.; Schiraldi, D. A.; Andersen, A.; Collard, D. M. *Synth. Commun.* **2003**, 33, 3643–3650

⁴⁵ a) Vasil'ev, A. A.; Serebryakov, E. P. *Russ. Chem. Rev.* **2001**, 70, 735–776; b) Lathbury, D. C.; Parsons, P. J.; Pinto, I. J. *Chem. Soc. Chem. Commun.* **1988**, 81–82

⁴⁶ a) Pottie, I. R.; Nandaluru, P. R.; Benoit, W. L.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *J. Org. Chem.* **2011**, 76, 9015–9030; b) Backvall, J.-E.; Rise, F. *Tetrahedron Lett.* **1989**, 30, 5347–5348

nificant amount of side-product **133** and a large amount of diene dimer **134** (described as an important competitive reaction).⁴⁷ The addition of a Lewis acid to this reaction resulted in a higher polymerization rate. Attempts to tune the electron density of diene by modifying the ester moiety of the sulfolene were done. But other sulfolene derivatives were too unstable to handle.

We therefore decided to rely on another cycloaddition for the formation of this cyclohexene derivatives (**Scheme 2.13**). Cycloaddition between electron-poor triple bonds and electron rich dienes are well described in the literature.⁴⁸ We chose two vinyl ketones (**135** and **137**) as potential precursor to the diene needed for the reaction. We believed that the corresponding enolates, enamines or silyl enol ethers of these methyl enones would be suitable partners for a Diels-Alder reaction with methyl propiolate as dienophile. Resulting cycloadducts **136** or **138**, thus obtained, should be easily transformed into key intermediate **95**.



Scheme 2.13 – New cycloaddition strategy to reach key intermediate

The regioselectivity of this type of cycloadditions is known to match the one required for our strategy.^{48c,49} The electron demand seems to be good in our case, having an elec-

⁴⁷ a) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem. Int. Ed.* **1998**, 37, 3262–3265; b) Alanine, A. I.; Fishwick, C. W.; Jones, A. D.; Mitchell, M. B. *Tetrahedron Lett.* **1989**, 30, 5653–5654

⁴⁸ a) Yates, P.; Gomes, A.; Burnell, D.; Cong, D.; Sawyer, J. *Can. J. Chem.* **1989**, 67, 37–47; b) Olsen, R. K.; Feng, X. *Tetrahedron Lett.* **1991**, 32, 5721–5724; c) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, 126, 1352–1353; d) Ackland, D. J.; Pinhey, J. T. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2689–2694

⁴⁹ a) Ghosh, A.; Chakraborty, I.; Adarsh, N. N.; Lahiri, S. *Tetrahedron* **2010**, 66, 164–171; b) Lahiri, S.; Yadav, S.;

tron deficient dienophile and an electron-rich diene. The main risk was that the nitrophenyl group would diminish the electron density of the diene. However we believed a correct catalyst should help us overcome this difficulty.

In the forward synthesis, intermediates **135** and **137** could be rapidly obtained as shown in **Scheme 2.13**, 2-(2-nitrophenyl)acetic acid could be converted to enone **135** using a Dakin-West reaction⁵⁰ followed by a Knoevenagel Condensation.⁵¹

We first attempted to reach alcohol **140** in one step by opening tulipane,⁵² but this reaction proven to be messy and resulted in a low yield. We returned to using bromomethacrylate **99** (obtained in 2 steps); Homologation with formaldehyde and indium gave the desired alcohol **140** in good yield. Azidation and reduction into aldehyde **139** proceeded smoothly. Unfortunately, our attempts toward converting the aldehyde to methyl ketone **137** showed no desired product in all our attempts, resulting only polymerization of the acrolein moiety. The results of a model study (see below) prompted us to change our strategy before we could optimize the formation of **137**.

From compound **135**, we attempted to form the diene using a base (formation of an enolate), a silyl enolate (TBS or TMS enolate), or methylbenzylamine (as organocatalyst) followed by cycloaddition with methylpropiolate. Only starting material or decomposition was observed. Modification of the reactions conditions (Temperature, solvent, Lewis-acids) only changed the speed of decomposition. A more active dienophile such as prop-2-ynal²⁹ was used without anymore success. Desired compound **136** was never observed. Probably the electron-withdrawing effects of the nitrophenyl substituent decreased too strongly the electron density of the diene making it unreactive towards Diels-Alder reaction. Another reason could be the steric clash between the aryl and the silyl group. This steric repulsion would increase the energy required to pass from the unreactive *s-trans* to the reactive *s-cis* intermediate.⁵³

When 3-methylbut-3-en-1-one was used as a diene precursor (model substrate of **137**, **Scheme 2.14**), the desired product **141a** could only be observed in low yield, as an inseparable mixture with isomers **141b** and **141c**.^{48b} Considering how poor the regioselectivity was, and how easily the double bond in **141a** could migrate to **141b**, we decided not to pursue

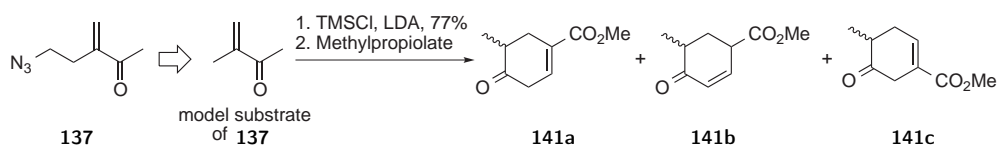
Chanda, M.; Chakraborty, I.; Chowdhury, K.; Mukherjee, M.; Choudhury, A. R.; Guru Row, T. N. *Tetrahedron Lett.* **2005**, 46, 8133–8136; c) Yadav, S.; Banerjee, S.; Maji, D.; Lahiri, S. *Tetrahedron* **2007**, 63, 10979–10990; d) Maiti, B. C.; Lahiri, S. *Tetrahedron* **1997**, 53, 13053–13062; e) Xiao, T.; Dong, X.; Tang, Y.; Zhou, L. *Adv. Synth. Catal.* **2012**, 354, 3195–3199; f) Smith, D. L. L.; Chidipudi, S. R.; Goundry, W. R.; Lam, H. W. *Org. Lett.* **2012**, 14, 4934–4937; g) Takasu, K.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2008**, 49, 4220–4222

⁵⁰a) Danheiser, R. *Tetrahedron* **1983**, 39, 935–947; b) Tran, K.-V.; Bickar, D. *J. Org. Chem.* **2006**, 71, 6640–6643

⁵¹Okuro, K.; Gurnham, J.; Alper, H. *J. Org. Chem.* **2011**, 76, 4715–4720

⁵²Mendgen, T.; Scholz, T.; Klein, C. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 5757–5762

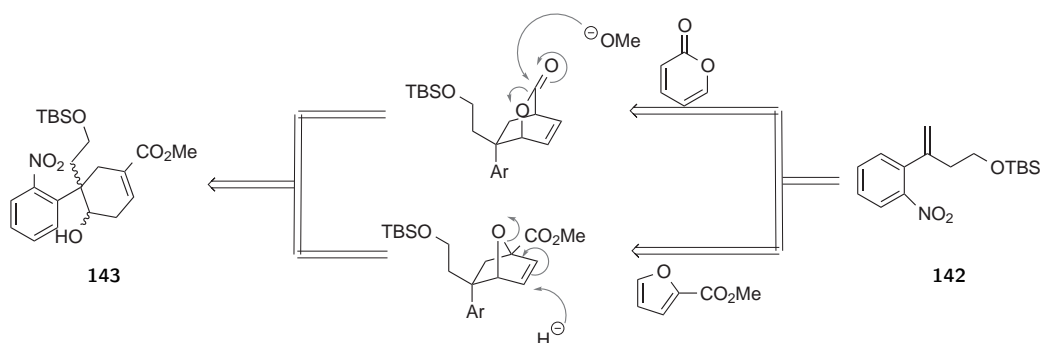
⁵³Sauer, J. *Angew. Chem. Int. Ed.* **1967**, 6, 16–33



Scheme 2.14 – Test of cycloaddition

further this synthetic pathway.

Our last attempt was with the Diels-Alder reaction shown in **Scheme 2.15**. From dienophile **142**, a cycloaddition with either described 2H-pyran-2-one or the commercially available methyl furane-2-carboxylate could be considered. Similar bridged bicyclic structures are known to be easy to open.⁵⁴ The opening of our cycloadduct should afford intermediate **143**.



Scheme 2.15 – New cycloaddition pathway

The pyranone is known to react with electron poor dienophiles,⁵⁵ and the regioselectivity can vary according to literature. But in comparison with the work of Markó and co-workers,⁵⁶ the possibility of having a good regioselectivity was high despite the need for high pressure and harsh reaction conditions. As for the furane, some examples exist, even if most of the Diels-Alder reaction used in similar molecules are intramolecular, like in the work of Padwa and co-workers⁵⁷ or Kitagawa and co-workers.⁵⁸

To synthesise dienophile **142**, we first substituted the ester **96** with iodoalkane **144** to

⁵⁴ a) Markó, I. E.; Seres, P.; Swarbrick, T. M.; Staton, I.; Adams, H. *Tetrahedron Lett.* **1992**, 33, 5649–5652; b) Posner, G. H.; Suh, B. C.; Petersen, K. S.; Dolan, P.; Agoston, E. S.; Kensler, T. W.; Koh, J. T.; Peleg, S. *J. Steroid Biochem. Mol. Biol.* **2007**, 103, 213–221; c) Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, 35, 7545–7548; d) Shin, I. J.; Choi, E. S.; Cho, C. G. *Angew. Chem. Int. Ed.* **2007**, 46, 2303–2305

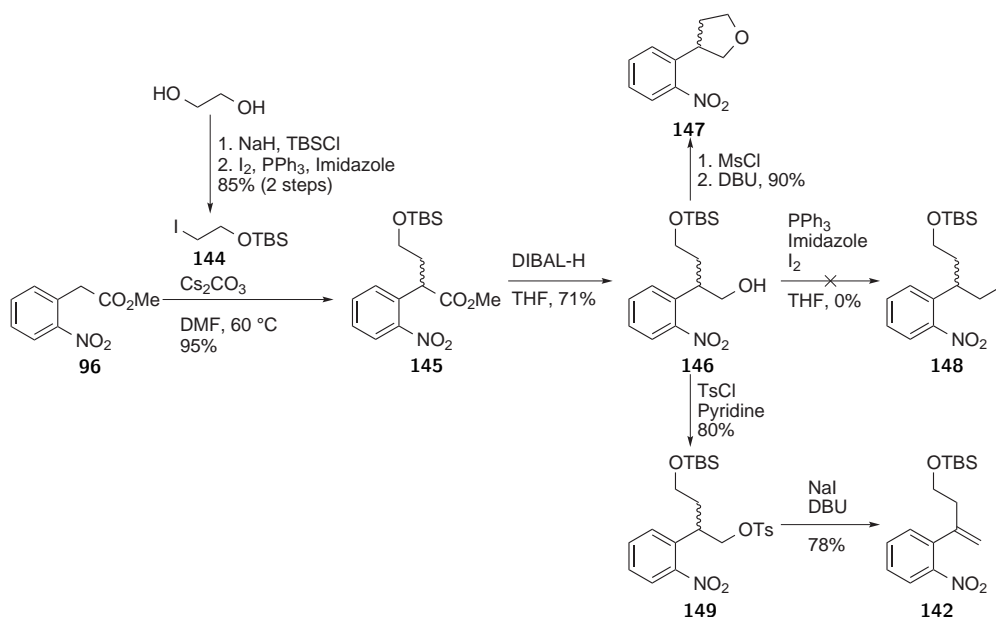
⁵⁵ Pfaff, E.; Pleningner, H. *Chem. Ber.* **1982**, 115, 1967–1981

⁵⁶ Swarbrick, T. M.; Markó, I. E.; Kennard, L. *Tetrahedron Lett.* **1991**, 32, 2549–2552

⁵⁷ Padwa, A.; Crawford, K. R.; Straub, C. S.; Pieniazek, S. N.; Houk, K. N. *J. Org. Chem.* **2006**, 71, 5432–5439

⁵⁸ Nakamura, M.; Takahashi, I.; Yamada, S.; Dobashi, Y.; Kitagawa, O. *Tetrahedron Lett.* **2011**, 52, 53–55

afford ester **145** (Scheme 2.16). After a reduction, we obtained alcohol **146**. Mesylation of alcohol **146** followed by elimination under basic conditions only afforded side-product **147** instead of olefin **142**. Iodination of **146** resulted only in traces of desired iodine **148**, the reaction yielding mostly overiodinated products and degradation. To our delight, tosylate **149** was stable enough to prevent the cyclization and was readily eliminated to olefin **142** in the presence of DBU and NaI.



Scheme 2.16 – Synthesis of the dienophile **142**

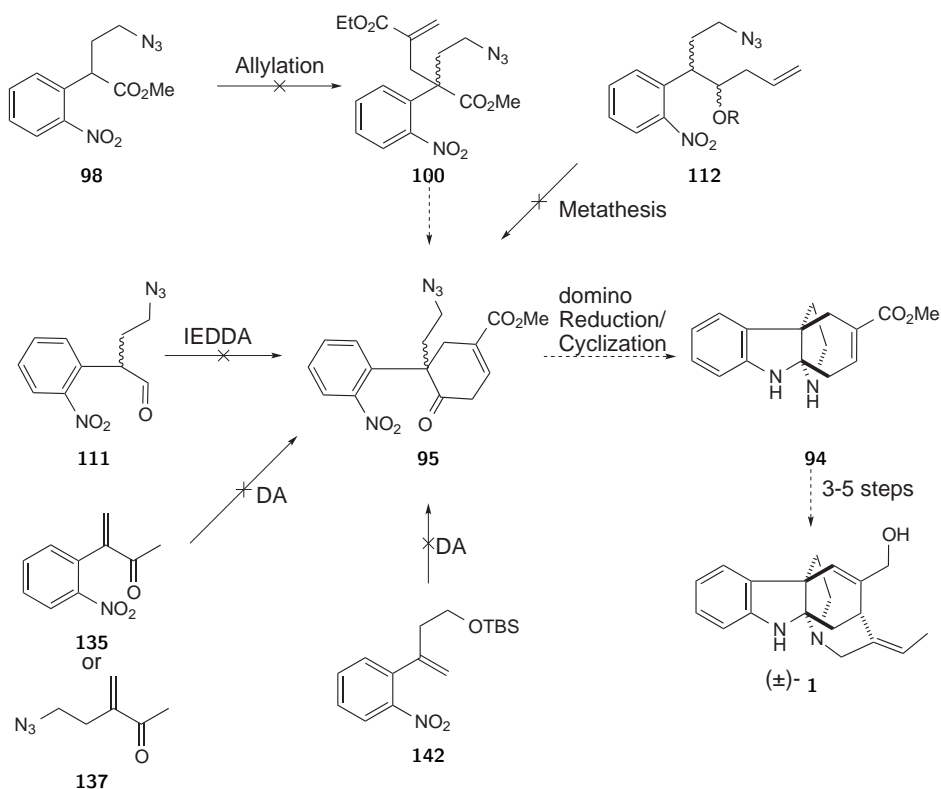
Unfortunately, no reaction was observed when using lewis acids, high temperatures (up to 200 °C. Above, degradation was observed) and high pressures (up to 200 bar) for the pyranone or furane substrates. This lack of reactivity toward Diels-Alder reaction was probably due to steric hindrance of the dienophile.

After considering the strategies already reported and the length of our current strategies, the decision was taken to suspend our efforts toward the synthesis of minfiensine and to change targets.

2.3 Conclusion

In summary, the total synthesis of minfiensine was attempted using a reduction/cyclization domino sequence as a key step. The key intermediate needed for this domino sequence was never reached due to the steric hindrance around the quaternary center and the easy isomer-

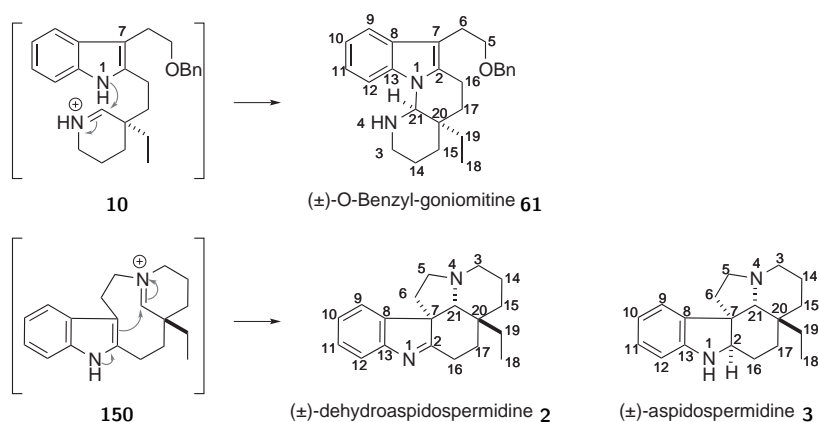
ization of the olefine. Multiple strategies were attempted (summarized in **Scheme 2.17**). Our lack of success with these strategies, combined with the efficient syntheses published previously and the growing number of steps required to overcome the problems encountered convinced us to suspend our efforts towards this natural product, and change targets.



Scheme 2.17 – Summary of the different strategies used in this chapter

Dehydroaspidospermidine and Aspidospermidine

During the synthetic studies of minfiensine, our laboratory developed the *i*ORC process to target goniomitine (*cf.* **Section 1.3**). As shown in **Scheme 3.1**, the C7 position of *i*ORC iminium intermediate **10** was too hindered, and only cyclization *via* the nucleophilic N1 was observed, giving (±)-O-benzylgoniomitine as the sole product. The diastereoselectivity was controlled by the quaternary center C20.



Scheme 3.1 – Cyclization to (±)-aspidospermidine and (±)-dehydroaspidospermidine

In this new project, we wanted to apply the *i*ORC domino process to reach aspidospermidine-type alkaloids. We postulated that a tether between the N4 iminium and the C7 (**150**) would force the cyclization to take place between C7 and C21 carbons. The installation of this connection would not be redundant steps, as this tether exists in the aspidospermidine-type natural products. As first target, we chose the dehydroaspidospermidine **2** and aspidospermidine **3**. The pentacyclic skeleton of aspidospermidine has received attention as a testing ground for the evaluation of new reactions and synthetic strategies. It

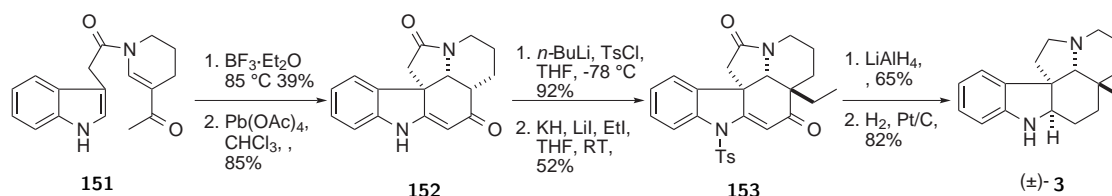
was then natural to start from this alkaloid to investigate our *i*ORC sequence, before moving to more complicated structures (*cf.* **Chapter 4 and 6**).

3.1 Aspidospermidine, Background

(+)-Aspidospermidine **3** was first isolated by Biemann and co-workers in 1961⁵⁹ during a mass spectrometry study of the indole alkaloids from the bark of *Aspidosperma Quebracho-Blanco*. In this same paper, they also observed (+)-1,2-dehydroaspidospermidine **2** and reduced it to (+)-aspidospermidine **3** using zinc. From a biosynthetic point of view, this alkaloid comes from (+)-vincadifformine **4** (*cf.* **Section 1.1.1**), where a simple decarboxylation would afford (+)-dehydroaspidospermidine **2**, and further reduction would give aspidospermidine **3**. The pentacyclic structure of the *aspidosperma* family is an interesting synthetic challenge that pushed many chemists to pursue this synthesis. As a result, more than thirty total syntheses of aspidospermidine **3** are published so far. Most of them could be divided into three categories: Starting from an indole derivative, from a tryptamine derivative, or the syntheses where the indole is formed during the synthesis.

3.1.1 Previous syntheses from tryptamine derivatives

Wenkert and co-workers in 1983⁶⁰ made the tryptamine derivative **151** and used it in an intramolecular cycloaddition reaction to form (after oxidation with lead tetraacetate) intermediate **152** (**Scheme 3.2**). In 1991, they published the route to the natural product from intermediate **152**.⁶¹ Tosylation followed by diastereoselective alkylation afforded intermediate **153**. Further reductions gave racemic aspidospermidine **3**.



Scheme 3.2 – (±)-Aspidospermidine syntheses from Kunesch and co-workers

Two similar enantiospecific total syntheses are shown in **Scheme 3.3**, from Fuji and co-workers in 1990 and Tomioka and co-workers in 2009.

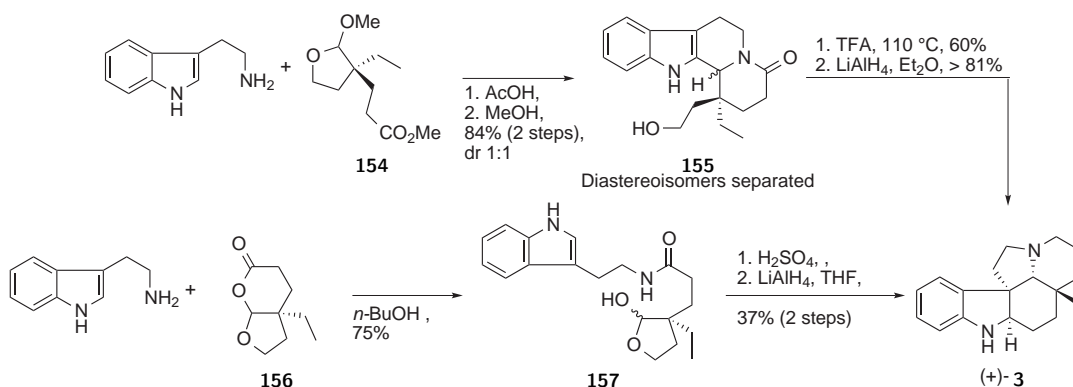
⁵⁹Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, 2, 485–492

⁶⁰Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, 39, 3719–3724

⁶¹Le Menez, P.; Kunesch, N.; Liu, S.; Wenkert, E. *J. Org. Chem.* **1991**, 56, 2915–2918

Fuji's group published in 1987 and 1990⁶² a synthesis using the Pictet-Spengler reaction between tryptamine and acetal derivative **154** to reach intermediate **155**. From here, an acid catalyzed ring closing/rearrangement sequence followed by reduction with LiAlH_4 gave (+)-aspidospermidine **3**. The intermediate **154** was also synthesized by Wee and co-workers in 2001 in a synthesis of other *Vinca* alkaloids.⁶³

The group of Tomioka used a similar strategy.⁶⁴ Condensation of tryptamine with lactone **156** afforded intermediate **157**. Intramolecular Pictet-Spengler reaction followed by LiAlH_4 reduction allowed them to reach the natural product.



Scheme 3.3 – (+)-Aspidospermidine syntheses from Fuji and Tomioka

MacMillan and co-workers recently published an enantioselective total synthesis of aspidospermidine **3** (**Scheme 3.4**),⁶⁵ where the route toward the natural product started with tryptamine derivative **158**. A new cascade reaction featuring a cycloaddition of **158** with propionaldehyde using an imidazolidinone catalyst, followed by 5-*exo-trig* cyclization with the internal secondary amine afforded **159** in good yield and excellent ee. A Wittig reaction, N-Boc deprotection and N-allylation provided indoline derivative **160**. A Heck cyclization closed the last ring to afford **161**, which upon reduction provided (+)-aspidospermidine **3**.

3.1.2 Previous syntheses from indole derivatives

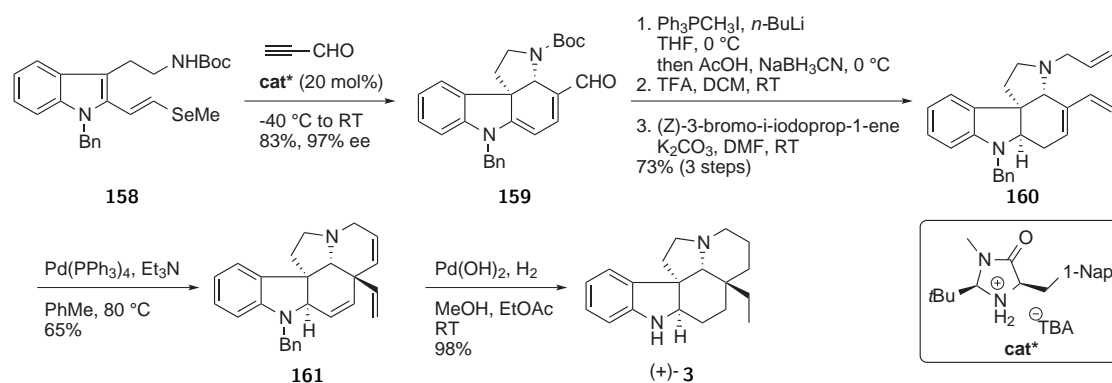
Many groups developed methodologies to functionalize or substitute the indole moiety, and the development of total syntheses using these new reactions is frequent. Here are some relevant examples of syntheses of aspidospermidine **3** starting from an indole derivative other

⁶²a) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901–7903; b) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517–521

⁶³Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **2001**, *66*, 8935–8943

⁶⁴Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653–655

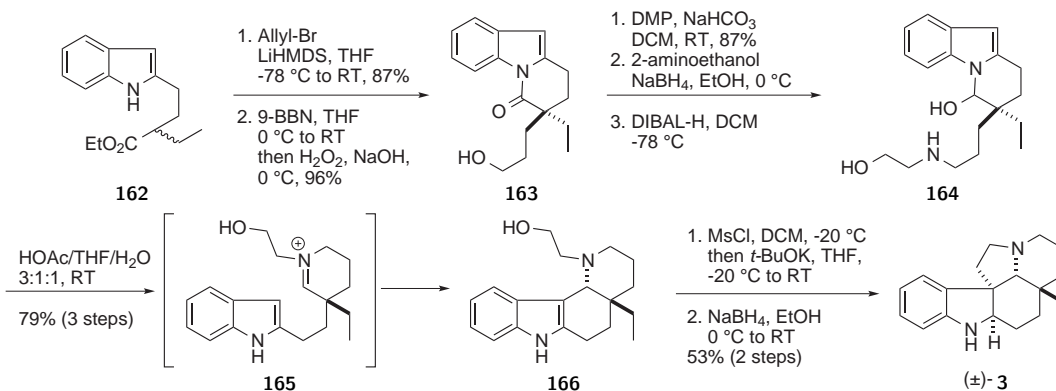
⁶⁵Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188



Scheme 3.4 – MacMillan's total synthesis of (+)-aspidospermidine

than tryptamine.

Bach's group published in 2012 a total synthesis of (±)-aspidospermidine **3** (Scheme 3.5),⁶⁶ using a newly developed palladium-catalyzed 2-alkylation of indoles, allowing them to build precursor **162**. Allylation followed by hydroboration of the newly installed double bond afforded intermediate **163**. Oxidation of the alcohol, reductive amination and reduction of the amide afforded hemiaminal **164**. Under acidic conditions, this hemiaminal was dehydrated to iminium **165** which underwent a Mannich-type reaction to afford **166**. The last ring was closed in one step, affording (±)-dehydroaspidospermidine **2**, that was then reduced with NaBH₄ to (±)-aspidospermidine **3**.



Scheme 3.5 – Bach's strategy, starting from indole

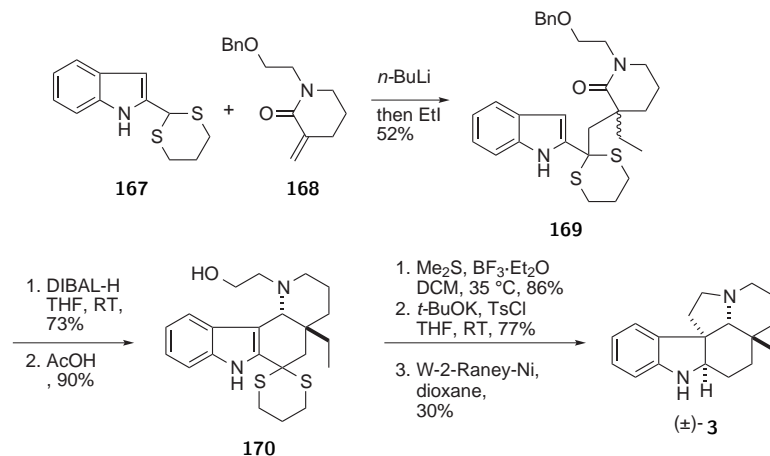
A similar strategy to close the last ring of aspidospermidine **3** was used by Rubiralta's group in 1996 (Scheme 3.6).⁶⁷ Rubiralta synthesized aspidospermidine **3** starting from dithiane **167**. 1,4-addition on enone **168** afforded racemic **169**. A reduction/cyclization protocol

⁶⁶Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563–14572

⁶⁷Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882–7888

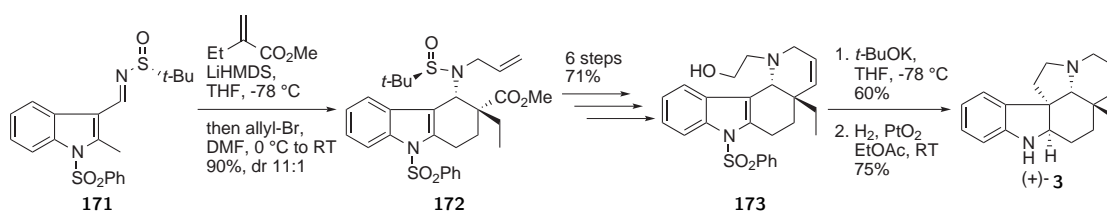
3.1. Aspidospermidine, Background

was performed to reach intermediate **170**. Closing the last ring by a nucleophilic substitution, and subsequent reduction of the dithiane afforded a mixture of (±)-aspidospermidine **3** and (±)-dehydroaspidospermidine **2**.



Scheme 3.6 – Rubiralta's synthesis of aspidospermidine

Andrade and co-workers reached (+)-aspidospermidine **3** in 2013 (**Scheme 3.7**).⁶⁸ Starting from chiral N-sulfinyl indole **171**, a domino Michael/Manich/N-alkylation afforded **172** with good diastereoselectivity. Intermediate **173** was then reached in 6 steps from the N-sulfinyl derivative **172**. The sequence include a reduction of the ester into an aldehyde, a Wittig reaction and a RCM to close the azacyclohexene ring. Finally, a Bosch-Rubiralta spirocyclization⁶⁹ closed the last ring, and a reduction afforded the natural product.



Scheme 3.7 – Andrade's synthesis of (+)-aspidospermidine

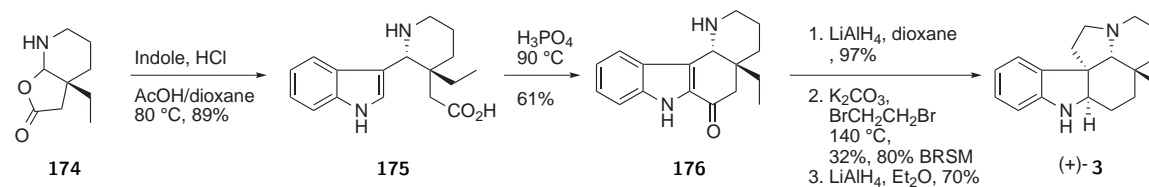
Wenkert in 1988⁷⁰ decided to reach (+)-dehydroaspidospermidine **2** and (+)-aspidospermidine **3** from amlalactone **174** (**Scheme 3.8**). Acidic treatment of **174** with indole afforded **175** as a single diastereoisomer. Cyclization of **175** into **176** in phosphoric acid proceeded with 61% yield. Reduction of amide and double substitution with ethylene bromide afforded dehydroaspidospermidine, that was converted into aspidospermidine with

⁶⁸Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334–13337

⁶⁹Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591–5597

⁷⁰Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953–1957

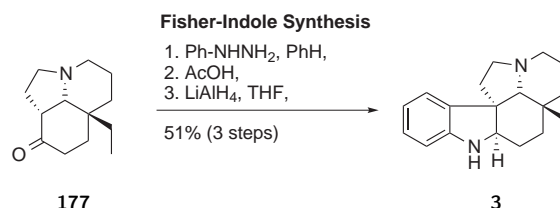
LiAlH_4 . Waser and co-workers reached Wenkert's intermediate **176** in a formal synthesis of aspidospermidine **3** using a homo-Nazarov reaction on an aminocyclopropane derivative.⁷¹



Scheme 3.8 – Wenkert's synthesis of (+)-aspidospermidine

3.1.3 Syntheses of aspidospermidine with formation of the indole ring

The most common way to synthesize the aspidospermidine **3** was first described by Stork and co-workers in 1963 in a total synthesis of aspidospermine,⁷² and applied later on by Aubé and co-workers for aspidospermidine.⁷³ Tricyclic **177** was used in a Fisher indole synthesis to afford dehydroaspidospermidine. Reduction of indolenine moiety gave aspidospermidine **3**. Many groups targeted intermediate **177** for the total synthesis⁷⁴ or the formal synthesis⁷⁵ of aspidospermidine **3**.



Scheme 3.9 – Aubé's indole synthesis of aspidospermidine

⁷¹ a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, 49, 5767–5770; b) De Simone, F.; Waser, J. *Synlett* **2011**, 22, 589–593; c) De Simone, F.; Waser, J. *Chimia* **2012**, 66, 233–236

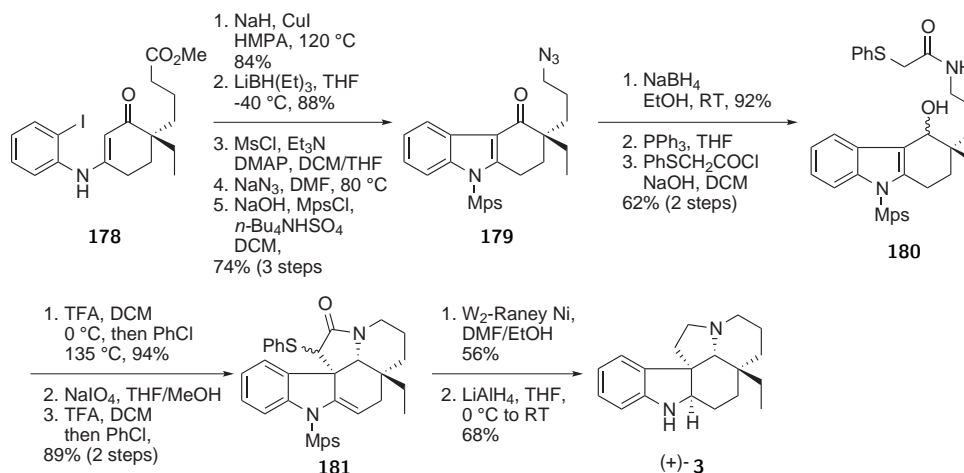
⁷² Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, 85, 2872–2873

⁷³ Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, 2, 1625–1627

⁷⁴ a) Callier-Dublanche, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, 64, 4803–4816; b) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, 8, 831–834; c) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L. J.; Orea, L.; Bernès, S.; Enríquez, R. G. *Arkivoc* **2003**, 185–192; d) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, 66, 5893–5901; e) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, 74, 2290–2300; f) Cho, H.-K.; Tam, N. T.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2010**, 31, 3382–3384; g) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed.* **2007**, 46, 6159–6162; h) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, 73, 7498–7508; i) Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, 70, 10645–10652; j) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941–2943

⁷⁵ a) Banwell, M. G.; Smith, J. A. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2613–2618; b) Huang, J.-Z.; Jie, X.-K.; Wei, K.; Zhang, H.; Wang, M.-C.; Yang, Y.-R. *Synlett* **2013**, 24, 1303–1306; c) Pearson, W. H.; Aponick, A. *Org. Lett.* **2006**, 8, 1661–1664

In 1994, Angelo and co-workers⁷⁶ reached the natural compound from **178** (**Scheme 3.10**). Copper-assisted cyclization created the indole ring, and a few functional group interconversions afforded **179**. Reduction of the carbonyl group, followed by Staudinger reduction and N-acylation provided **180**. Acidic treatment allowed them to eliminate the alcohol, and cyclize the amine on the C21 position. Subsequent oxidation of the thioether to sulfoxide followed by a Pummerer rearrangement afforded **181**. Desulfurization and reduction of the amide and enamine moieties afforded the natural product.



Scheme 3.10 – Angelo's synthesis of (+)-aspidospermidine with formation of the indole ring

Murphy and co-workers published in 1999⁷⁷ a synthesis of (±)-aspidospermidine (**Scheme 3.11**), using their previously developed tetrathiafulvalene (TTF)-mediated radical-polar crossover reaction.⁷⁸ This reaction extruded nitrogen from **182** and formed the aryl radical. A cyclization on the double bond gave benzylic radical that was oxidized to the benzylic cation and trapped with water. The formed alcohol was oxidized with PCC to afford **183**. This intermediate was transformed into **184** in six steps. A Heck-type reaction on **184** closed the last ring. Reduction and deprotection of **184** afforded aspidospermidine **3**.

One year after, Murphy's group reached the same precursor **184** from alcohol **185**.⁷⁹ A five step procedure converted **185** into **186**. Azidation of primary alcohol afforded **187**. An iodoazide radical cascade cyclization closed both 5 membered rings, and N-allylation with (Z)-3-bromo-1-iodopropene afforded **184**.

Another interesting example is the racemic synthesis of (±)-rhazinilam and

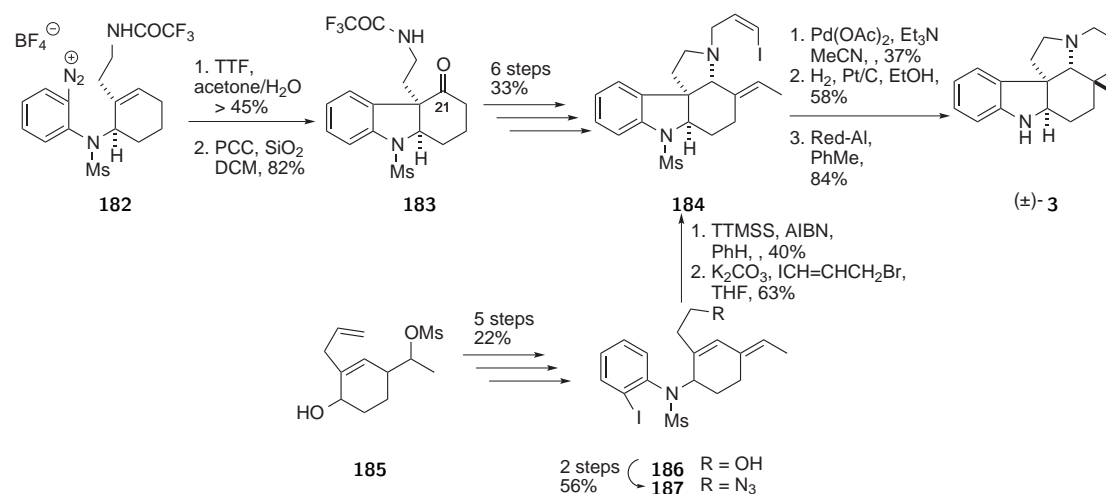
⁷⁶Desmaeele, D.; D'Angelo, J. *J. Org. Chem.* **1994**, 59, 2292–2303

⁷⁷Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc. Perkin Trans. 1* **1999**, 995–1002

⁷⁸Fletcher, R.; Kizil, M.; Lampard, C.; Murphy, J. A.; Roome, S. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2341–2352

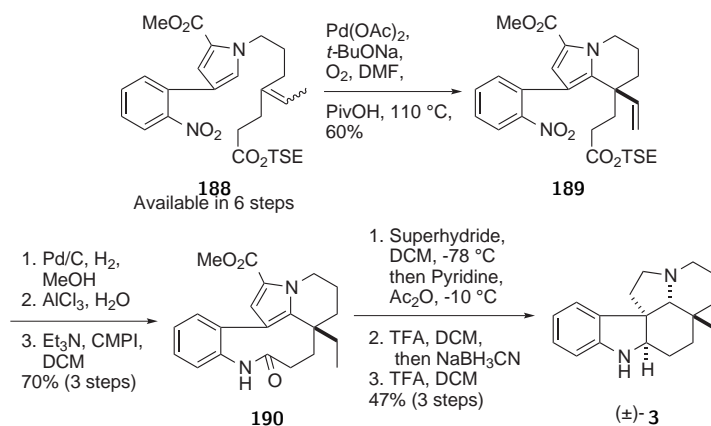
⁷⁹Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, 2, 3599–3601

Chapter 3: Dehydroaspidospermidine and Aspidospermidine



Scheme 3.11 – Murphy's Syntheses of (±)-aspidospermidine with formation of the indole ring

its subsequent transformation into (±)-aspidospermidine **3** by Gaunt and co-workers (**Scheme 3.12**).⁸⁰ Using the pyrrol derivative **188**, a palladium-catalyzed C-H alkenylation reaction afforded the intermediate **189**. Reduction of the vinyl group and the nitro group, followed by macrolactamization using 2-chloro-1-methylpyridinium iodide (CMPI) as coupling reagent afforded 2-methoxycarbonyl-rhazinilam **190**. From here, a three-steps reductive transannular cyclization process afforded (±)-aspidospermidine **3**.



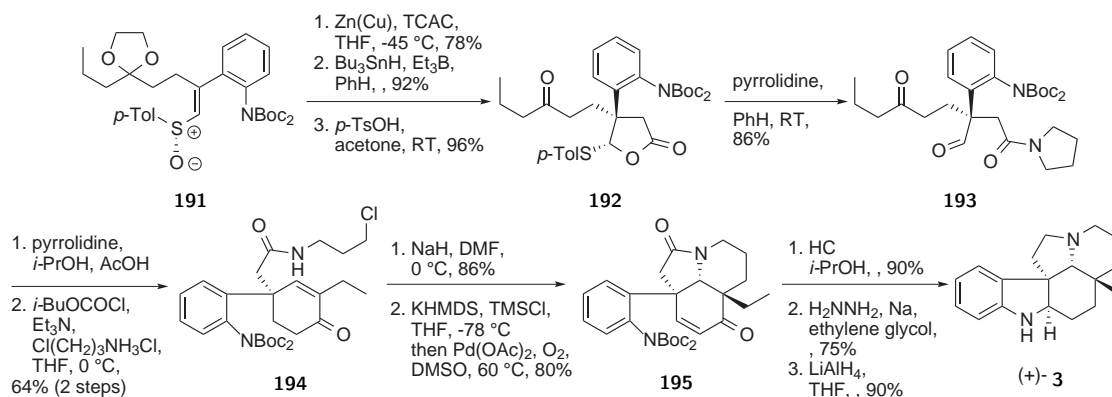
Scheme 3.12 – Gaunt's Synthesis of (±)-aspidospermidine with formation of the indole ring

In 2002, Marino finished a total synthesis of (+)-aspidospermidine⁸¹ with a late-stage closing of the indole ring (**Scheme 3.13**). Starting from the chiral sulfoxide **191**, a ketene lactonization with trichloroacetyl chloride (TCAC), followed by reduction and deprotection

⁸⁰ McMurray, L.; Beck, E. M.; Gaunt, M. *J. Angew. Chem. Int. Ed.* **2012**, *51*, 9288–9291

⁸¹ Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399

of the acetal provided lactone **192**. Lactone opening with pyrrolidine, afforded aldehyde **193**. Subsequent aldol condensation and amidation provided **194**. Intramolecular aza-Michael addition followed by cyclization of the resulting enolate on the alkyl chloride and Saegusa reaction gave enone **195**. Boc deprotection followed by Wolff-Kishner reduction afforded (+)-aspidospermidine **3**.



Scheme 3.13 – Marino's Syntheses of (+)-aspidospermidine with formation of the indole ring

Banwell in 2005 started from precursor **196** for a racemic synthesis of aspidospermidine **3** (**Scheme 3.14**).⁸² An Ullmann cross-coupling with *o*-nitroiodobenzene followed with saponification of the acetate and azidation of the resulting alcohol afforded **197**. Refluxing this azide in benzene forced an azacyclopropanation to afford **198**. Acidic treatment of this cyclopropane gave the chloride derivative **199**. Subjecting this intermediate to reducing conditions like $\text{TiCl}_3/\text{NH}_4\text{OAc}$, followed by N-acylation with 2-chloroacetyl chloride afforded indole **200**. Halogen exchange, followed with cyclization and reduction afforded (\pm)-aspidospermidine **3** (3-step protocol developed by Toczko and Heathcock)⁸³ in high yield.

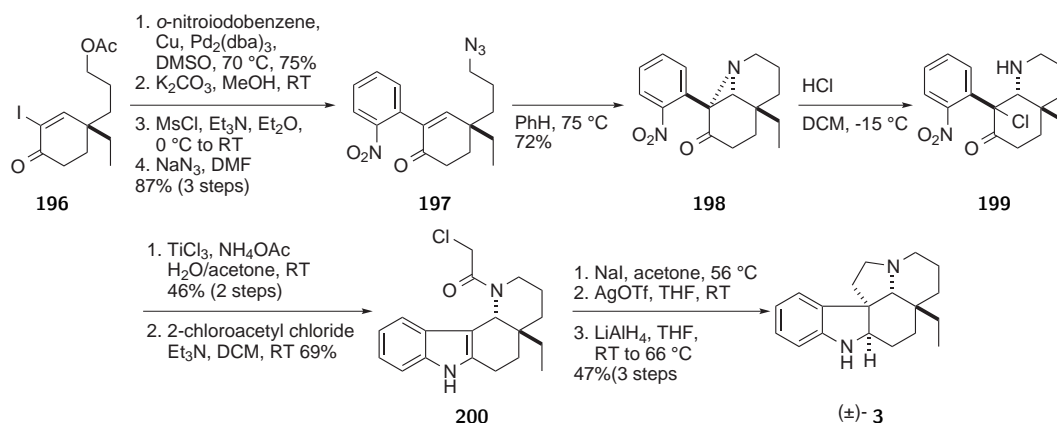
Rawal in 2002⁸⁴ reported a catalytic enantioselective Diels-Alder reaction between diene **201** and ethylacrolein using antimonate salt of Jacobsen's chiral Cr^{III} -salen complex⁸⁵ (**Scheme 3.15**). The resulting aldehyde **202** was submitted to a Wittig reaction and RCM reaction to afford bicyclic structure **203**. (*o*-Nitrophenyl)phenyliodonium fluoride (NPIF) reagent arylated the silyl enolate and provided the nitrophenyl derivative **204**. A reduction of the nitro function provided indole derivative **205**. Deprotection of the amine with trimethylsilyl iodide followed by N-alkylation with 2-bromoethanol, mesylation of the alcohol and cyclization gave 1,2,14,15-tetrahydroaspidospermidine **206**. Reduction of both double bonds gave

⁸²a) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, 3, 213–215; b) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, 58, 722–737

⁸³Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, 65, 2642–2645

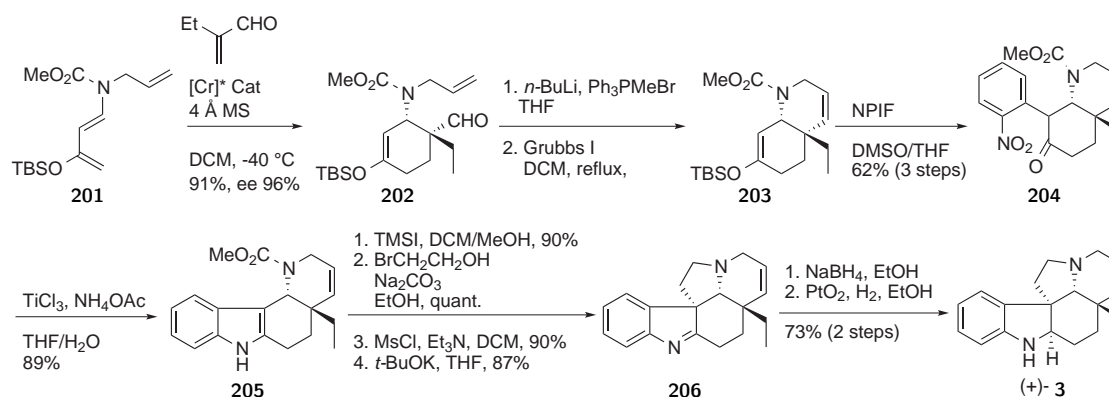
⁸⁴Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, 124, 4628–4641

⁸⁵Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, 117, 5897–5898



Scheme 3.14 – Banwell's Synthesis of (±)-aspidospermidine with formation of the indole ring

(+)-aspidospermidine **3** in good yield.



Scheme 3.15 – Rawal's synthesis of (+)-aspidospermidine with formation of the indole ring

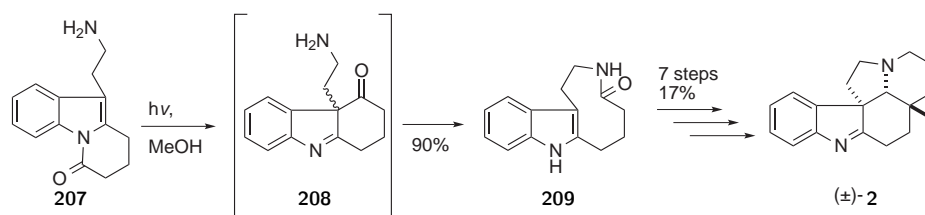
3.2 Dehydroaspidospermidine

Dehydroaspidospermidine **2** was isolated from the same tree as aspidospermidine **3**. It is the oxidized version of aspidospermidine, having an indolenine ring instead of an indoline.

Most of the syntheses of aspidospermidine pass by dehydroaspidospermidine with a subsequent reduction, and few papers synthesized aspidospermidine and oxidized it into dehydroaspidospermidine. Hence they were already discussed in the previous section. One of the few groups who synthesized dehydroaspidospermidine **3** without involving aspidospermidine **3** was Ban and co-workers in 1981⁸⁶ (**Scheme 3.16**). They reported an effective pho-

⁸⁶a) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990–6992; b) Ban, Y.; Yoshida, K.; Goto, J.;

3.3. Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine



Scheme 3.16 – Ban's synthesis of (±)-dehydroaspidospermidine

toisomerization of amine **207** into amine **208** that spontaneously cyclize into the amide **209**. With just a few protections, alkylations and deprotections, they achieved the synthesis of (±)-dehydroaspidospermidine **2** in seven steps and 17% overall yield.

Other syntheses of aspidospermidine and dehydroaspidospermidine are reported. But the syntheses above are amongst the most relevant ones.⁸⁷

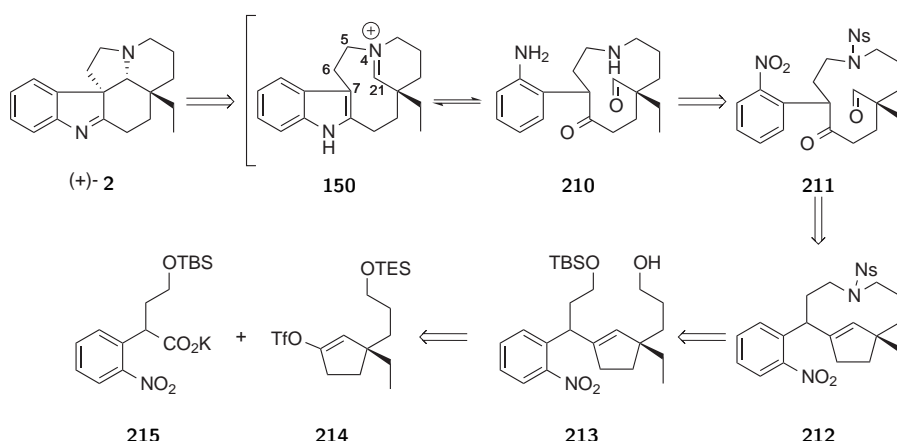
3.3 Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine

We could see that forming the indole moiety of aspidospermidine in a late-stage fashion is an interesting idea, as it reduces the sensitivity of the substrate toward acidic media, and diminishes the need for protecting groups. In addition, exploiting the reactivity of the indole during its formation, as a domino process could be a powerful tool to cyclize other rings. These are the power of our *i*ORC process we wished to emphasize.

From a retrosynthetic point of view, 1,2-dehydroaspidospermidine **2** could be reached from iminium **150** (**Scheme 3.17**). The cyclization of this intermediate could only happen between the C7 and C21 due to the tether N4-C5-C6-C7. This intermediate contains an enamine and an iminium group. These functional groups could arise from their respective amino and carbonyl groups (intermediate **210**). The aniline moiety could arise from a nitrobenzene, and the secondary amine from a protected amino group (Intermediate **211**). We chose a nitrophenylsulfonamide protecting group due to the mild deprotection conditions that were

Oishi, T.; Takeda, E.; Ishigamori *Tetrahedron* **1983**, 39, 3657–3668

⁸⁷ See also a) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915–916; b) Mandal, S. B.; Giri, V. S.; Pakrashi, S. C. *Heterocycles* **1988**, 27, 11–12; c) Mandal, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, 53, 4236–4241; d) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, 59, 7677–7682; e) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.-i.; Ishibashi, H. *Angew. Chem. Int. Ed.* **2013**, 52, 906–910; f) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, 52, 4117–4121; g) Xia, G.; Han, X.; Lu, X. *Org. Lett.* **2014**, 16, 2058–2061; h) Jiao, L.; Bach, T. *Synthesis* **2014**, 46, 35–41



Scheme 3.17 – Retrosynthesis of dehydroaspidospermidine

compatible with our *i*ORC sequence.⁸⁸

The aldehyde **211** could result from an ozonolysis of **212**. This macrocycle is the key intermediate we planned to use for our key step. From this intermediate to dehydroaspidospermidine, we hope the whole sequence would be performed in a one pot fashion.

We planned to make macrocycle **212** from **213** by N-alkylation or Mitsunobu reactions with H_2NNs . This monoprotected diol could be the result of a decarboxylative coupling between potassium salt **215** and vinyl triflate **214**. This palladium-catalyzed decarboxylative coupling between potassium 2-(2-nitrophenyl)acetate derivatives and vinyl triflates was developed by Zhu and co-workers in 2013.²² This reaction is a key point of our *i*ORC strategy, as it allows us to build a large variety of precursors for our key domino process. A remarkable feature of this coupling is its ability to assemble intermediates bearing all the carbons needed in the natural product.

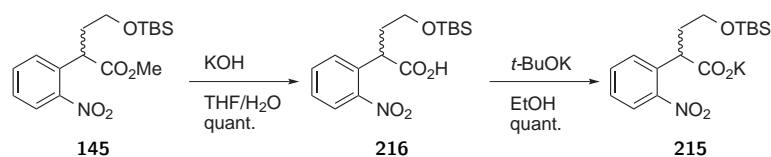
3.3.1 Key Intermediate Formation

The two partners of the decarboxylative coupling are easy to access. First, the potassium salt **215** had to be synthesised (Scheme 3.18). Starting from ester **145** (already synthesized in Section 2.2.3), we saponified the methyl ester with KOH, and treated the resulting acid **216** with equimolar amount of potassium *tert*-butoxyde to reach potassium salt **215**.

Then, the vinyl triflate needed for the decarboxylative coupling had to be synthesized (Scheme 3.19). Starting from the commercially available **217**, the enone **218** was obtained

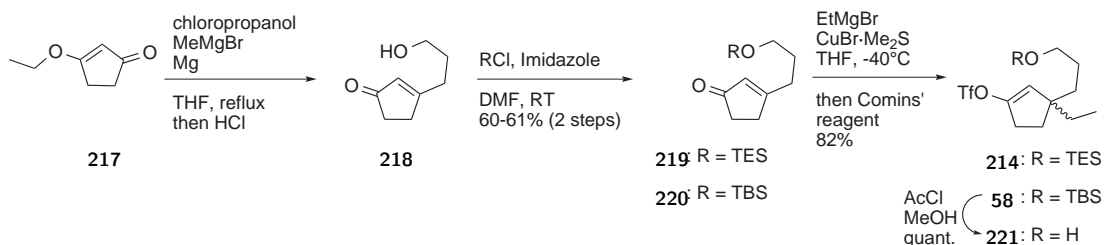
⁸⁸Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, 36, 6373–6374

3.3. Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine



Scheme 3.18 – Synthesis of the potassium salt

after 1,2-addition of a Normant-type Grignard reagent,⁸⁹ followed by strong acidic work-up to eliminate ethanol. Silylation of the primary alcohol gave either TES-protected **219** or TBS-protected **220**. These enone derivatives could undergo a copper-assisted 1,4 addition, followed by the trapping of the enolate with Comins' reagent, to give the corresponding vinyl triflate **214** or **58**. Deprotection of this last one afforded free alcohol **221**.



Scheme 3.19 – Synthesis of vinyl triflates

It is noteworthy that the only important stereocenter of the natural product, *i.e.* the one that will control the diastereochemical outcome of the *i*ORC is formed in a copper-assisted 1,4-addition. We naturally envisioned to make this addition enantioselective using reported procedures.

Copper-catalysed enantioselective 1,4-addition on enone are well described in the literature. Nevertheless, most examples are reported on linear or unstrained cyclic enones. The enantioselective conjugate addition of nucleophiles to cyclopentenones is a challenging process that has rarely been achieved. The main examples are from Copper-catalyzed addition of organomagnesium nucleophiles,⁹⁰ silver catalyzed organoaluminium nucleophiles⁹¹ and palladium-catalyzed conjugate addition of arylboronic acid.⁹²

The route toward our vinyl triflate was already optimized and seemed to work well with copper-assisted 1,4-addition. We were hoping Alexakis' N-heterocarbene (NHC) ligands

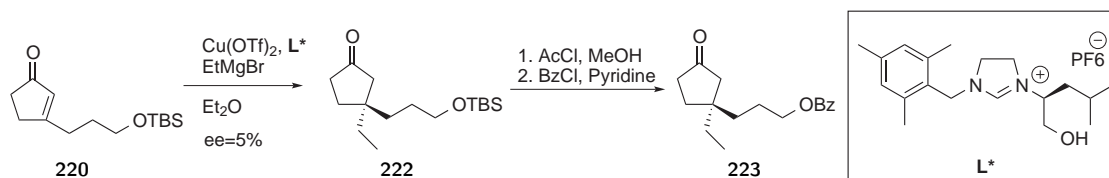
⁸⁹ Cahiez, G.; Alexakis, A.; Normant, J. *Tetrahedron Lett.* **1978**, *19*, 3013–3014

⁹⁰ See Germain, N.; Schlaefli, D.; Chellat, M.; Rosset, S.; Alexakis, A. *Org. Lett.* **2014**, *16*, 2006–2009

⁹¹ See May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 7358–7362

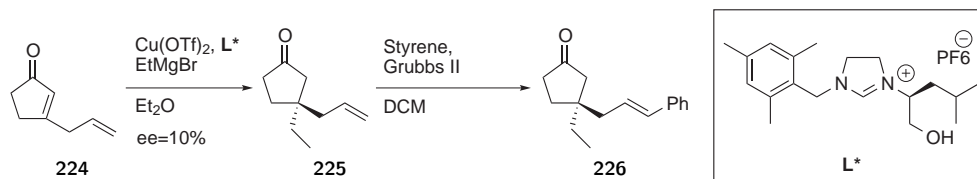
⁹² See Gottumukkala, A. L.; Matcha, K.; Lutz, M.; De Vries, J. G.; Minnaard, A. J. *Chem. Eur. J.* **2012**, *18*, 6907–6914

with catalytic amount of copper could work in our synthesis.⁹³ The trials were done on our enone **220** (Scheme 3.20). The newly formed cyclopentanone **222** was benzoylated in order to measure the ee (UV detector). Despite our efforts, the copper catalyzed conjugate addition using Alexakis ligand afforded **222** with a maximum of 5% ee.



Scheme 3.20 – Asymmetric 1,4-addition trials

The lack of stereoselectivity might come from the size of the alkyl chain. Most of the examples described in the development of this ligand were done on simple cyclopentenone with small substituents (Me, Et). Therefore, we synthesized the allylcyclopentenone **224**⁹⁴ and used the same conditions (Scheme 3.21). The ketone **225** was obtained in good yield, but after cross metathesis to **226** (for UV activity), the measured ee was 10%. An improvement not good enough to continue with this catalyst.



Scheme 3.21 – Asymmetric 1,4-addition trials

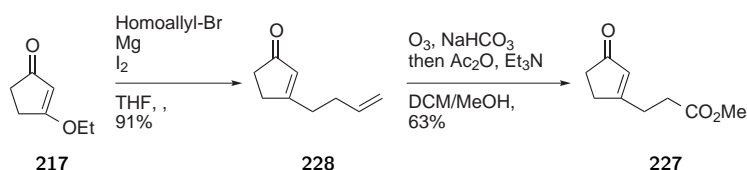
We wanted to pursue the 1,4-addition with Hoveyda's methodology, using AlEt₃ and his silver-catalyst. The substrate **227** (Scheme 3.22) was chosen to be optimal, due to the chelating effect of ester. Homoallylation of **217** afforded substituted enone **228**. Selective ozonolysis of terminal double bond afforded ester **227**. After discussion with Professor Hoveyda, a sample of **227** was sent to his group for preliminary trials on enantioselective addition. The results were promising, but showed some trouble for the one-pot triflation of the enolate. A higher temperature is needed to form the enol triflate, and Dieckmann condensation would occur. no further work was done for an enantioselective synthesis, as we focused our effort on the racemic synthesis.

Continuing with racemic vinyl triflates, we performed the decarboxylative coupling with potassium salt **215** following the conditions optimised in our laboratory

⁹³ Germain, N.; Magrez, M.; Kehrl, S.; Mauduit, M.; Alexakis, A. *Eur. J. Org. Chem.* **2012**, 5301–5306

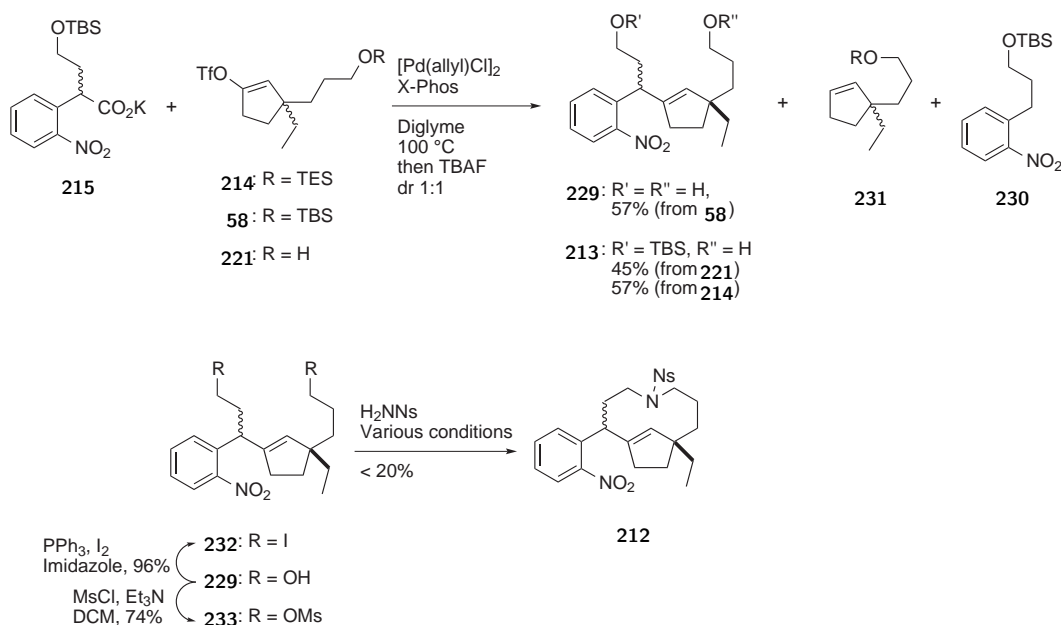
⁹⁴ Moore, S. P.; Coote, S. C.; O'Brien, P.; Gilday, J. *Org. Lett.* **2006**, 8, 5145–5148

3.3. Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine



Scheme 3.22 – Substrate preparation for asymmetric 1,4-addition trials

(**Scheme 3.23**).²² We planned to reach diol **229** and monoprotected diol **213**. It was previously observed that this decarboxylative coupling produce had as major side-product the protodecarboxylation product **230**, and reduced triflate **231**. The formation of these side-products was increased if the free alcohol **221** was used. In order to improve the yield of **213**, we opted for the TES-protected vinyl triflate **214** as it could be removed selectively, and used 1.2-1.5 equivalent of potassium salt **215**.



Scheme 3.23 – Macrocyclisation attempts

From the diol **229**, we performed multiple attempts on double N-alkylation with *o*-nitrophenylsulfonamide, as described in the literature.⁹⁵ Double S_N2 on the diiodine **232** or

⁹⁵ a) Zaimoku, H.; Nishide, H.; Nishibata, A.; Goto, N.; Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2013**, *15*, 2140–2143; b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137–2139; c) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, *59*, 8571–8587; d) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891–1893; e) Shimada, N.; Abe, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11824–11826; f) Schneider, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4217–4219; g) Pan, G.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 4801–4811; h) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246–10247; i) Yang, Y.-R.; Lai, Z.-W.; Shen, L.; Huang, J.-Z.; Wu, X.-D.; Yin, J.-L.; Wei, K. *Org. Lett.* **2010**, *12*, 3430–3433

the dimesylate **233** were tried. Unfortunately, the double N-alkylation process has proven ineffective, showing lack of reactivity and easy degradation of our substrate.

The double Mitsunobu of diol **229** was also troublesome.⁹⁶ During the Mitsunobu (**Scheme 3.24**), triphenylphosphine and DEAD first react to form intermediate **234**. In the presence of alcohol, this intermediate is in equilibrium with reactive species **235** and unreactive intermediate **236**.⁹⁷ The mechanism of the Mitsunobu reaction has been well studied and it was shown that intermediate **234** is in some cases an inhibitor of the reaction.⁹⁸ This may explain why an excess of the alcohol is often needed to improve the yield, as the equilibrium will be pushed in favor of **235** and **236**. Since the alcohol is sometimes difficult to obtain (as in our case, the alcohol is our substrate, and the nucleophile is commercially available), it would be interesting if it could be used as limiting reagent. In this purpose, Walker in 1995⁹⁸ showed that using neopentyl alcohol could push the equilibrium away from **234**. As neopentyl alcohol is hindered, the S_N2 reaction of **235** where R = neopentyl will be too slow compared to the substrate, and the only reactive species will be the intermediate **235** with desired substrate R-OH, leading to an improvement of the yield. In our case, when trying the double Mitsunobu on **229**, one possibility would be that intermediate **236** was too favorable, and the reaction was slow. Yet, it is known that sulfonamide, like H_2NNs or H_2NTs could react in the presence of PPh_3 and DEAD (or DIAD) to give undesired **237**.^{96e,99} This side-reaction would compete with the desired Mitsunobu and consume the starting material. If the presence of the two alcohols on the molecule slow down the Mitsunobu reaction, this side-reaction would become the fastest one, and low conversion was achieved, as all the phosphine and amine were consumed. Even (cyanomethylene)tributylphosphorane (CMBP) described to prevent formation of **237**^{96d} showed no good reactivity with our substrate.

In order to obtain the macrocycle **212**, we decided to go through the monoprotected alcohol **213** and perform a two step procedure (**Scheme 3.25**). Having only one alcohol on the molecule seems to accelerate the Mitsunobu reaction and allow the product to be formed before the side product **237**. Deprotecting the TBS in a one-pot fashion, we could obtain the amino alcohol **239** in good yield using a variation of Walker's conditions.⁹⁸ The macrocyclisation was again performed with a Mitsunobu reaction. Optimization of the stoichiometry and concentration allowed us to push the cyclization yield up to 81%. We also attempted to mesy-

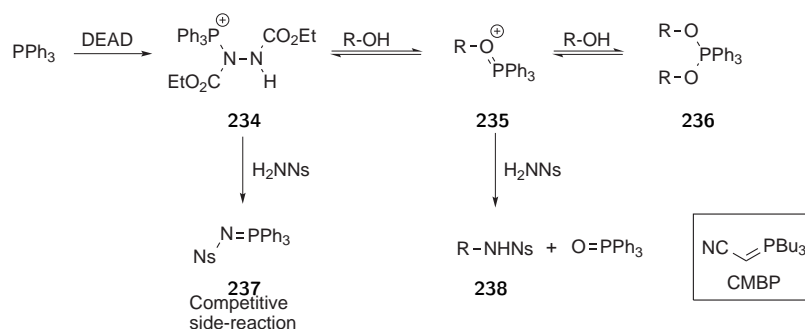
⁹⁶For reviews and mechanistic studies on Mitsunobu, see: a) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753; b) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045–3049; c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257–259; d) Sakamoto, I.; Nishii, T.; Ozaki, E.; Kaku, H.; Tanaka, M.; Tsunoda, T. *Chem. Pharm. Bull.* **2005**, *53*, 1508–1509; e) Tsunoda, T.; Yamamoto, H.; Goda, K.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2457–2458; f) Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977–2980; g) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236; h) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164

⁹⁷Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235–4238

⁹⁸Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352–5355

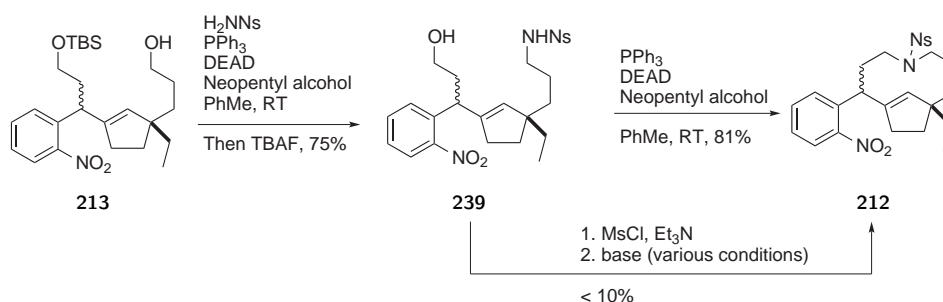
⁹⁹Pomerantz, M.; Chou, W. N.; Witczak, M. K.; Smith, C. G. *J. Org. Chem.* **1987**, *52*, 159–163

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Scheme 3.24 – Mitsunobu mechanism

late the alcohol and perform an intramolecular N-alkylation reaction, but it proved inferior to Mitsunobu conditions.



Scheme 3.25 – Macrocyclisation toward **212**

During the study of macrocycle **212**, we were able to obtain a monocrystal of one of the diastereoisomer, and obtained an X-ray structure (**Figure 3.1**). One can observe the bent structure of the bridged olefin, showing the strain present in this structure (in solid state).¹⁰⁰

3.3.2 IORC sequence and endgame

With macrocycle **212** in hand, we could start studying its reactivity toward our *i*ORC domino sequence (**Scheme 3.26**). Our original plan was to use ozonolysis for the cleavage of the olefin. The advantage of this reaction was of course the possibility to remove the oxidant (ozone) by bubbling argon or nitrogen through the solution, making it the perfect tool for a one-pot processes. There are a few conditions known to influence ozonolysis. The main modifications in an ozonolysis are the solvent (DCM or MeOH are the most common ones), with or without Na₂CO₃, and quenching the ozonide with Me₂S or PPh₃. We found that the cleanest reaction condition with our substrate was the standard one, in DCM without base

¹⁰⁰Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102–15108

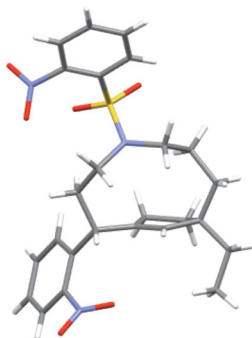
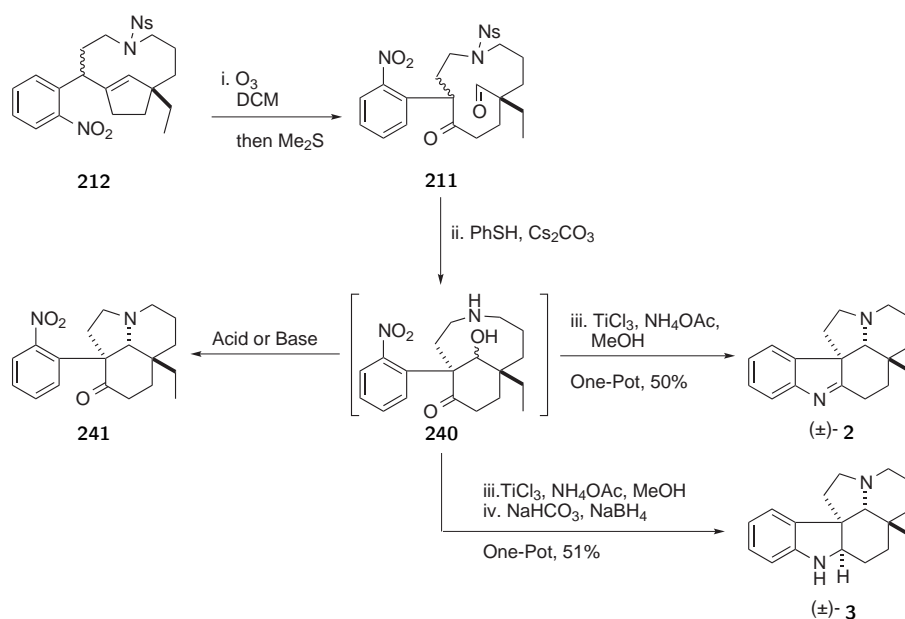


Figure 3.1 – X-Ray structure of one diastereoisomer of the key intermediate **212**

and by quenching the reaction with Me_2S . The aldehyde intermediate **211** could be observed after work-up, but was not stable on silicagel. We decided then to continue with the one-pot procedure. Deprotection of the nosyl group appeared to have a rate dependent on the solvent. When the reaction mixture was kept in DCM, the deprotection took 24 h to reach completion. However, if MeCN was added, the reaction was finished in 2 h. Unfortunately, the intermediate at this stage was impossible to analyse. No product could be obtained after an aqueous work-up. Simple filtration and evaporation afforded a crude mixture, which NMR showed to have some aldol condensation between the C7 and the C21 (**240**). At that stage, we attempted to have the cyclized adduct **241**. After the deprotection, the screening of Brønsted acids, Brønsted bases, Lewis acids, solvents and temperatures were done, but no desired product was ever observed. We expected the cyclization to be easier on the indole moiety, and decided to continue with the one-pot procedure.

The reduction step was the main problem of the *i*ORC. Many reduction conditions exist for reducing nitroaryl groups,¹⁰¹ but the reducing conditions should not touch any iminium/imine/aldehyde/enamine intermediates. The conditions should be slightly acidic to promote the cyclizations, and the intermediates as well as final product should be stable enough in the reaction conditions to avoid degradation. As hydrogenations gave no reactions of degradations, activated zinc powder with HCl 0.5 M gave (\pm)-dehydroaspidospermidine **2**, but only in low yield. All other attempted combinations of Zinc or Iron with various acids

¹⁰¹ For some examples of nitroaryl reductions, see: a) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, 5, 2497–2500; b) Bunce, R. A.; Nammalwar, B. J. *Heterocycl. Chem.* **2009**, 46, 172–177; c) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. J. *Am. Chem. Soc.* **1988**, 110, 2242–2248; d) Heller, G.; Lauth, H.; Buchwaldt, A. *Berichte der Dtsch. Chem. Gesellschaft* **1922**, 55, 483–489; e) Ho, T. T.-L.; Wong, C. M. C. *Synthesis* **1974**, 6, 45–45; f) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, 1, 673–676; g) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, 48, 2066–2069; h) Royer, D.; Wong, Y.-S.; Plé, S.; Chiaroni, A.; Diker, K.; Lévy, J. *Tetrahedron* **2008**, 64, 9607–9618; i) Sachs, F.; Kantorowicz, H. *Berichte der Dtsch. Chem. Gesellschaft* **1906**, 39, 2754–2762; j) Snape, T. *Synlett* **2008**, 19, 2689–2691; k) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, 14, 5621–5623



Scheme 3.26 – iORC sequence

resulted in full degradation. To our delight, reduction using TiCl_3 ^{101e-g,i} afforded the desired natural product with up to 50% yield after tuning of the stoichiometry, pH of the solution (NH_4OAc as buffer) and reaction time. By quenching the excess of TiCl_3 with aqueous NaHCO_3 , and adding excess of NaBH_4 in a one-pot fashion, (±)-aspidospermidine **3** would be isolated with similar yield.

3.4 Vincadifformine

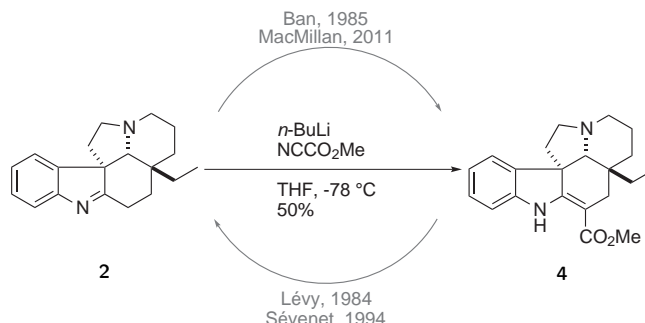
Vincadifformine **4** was isolated in 1962,¹⁰² from the leaves of the tree *Vinca Difformis*. It is an indole alkaloid of the *Aspidosperma* family. Its biosynthesis is fully detailed in 1.1.1. Its first total synthesis was from Kutney and co-workers in 1968.¹⁰³ Since then, numerous total syntheses were achieved.^{68,104} The synthetic connection between dehydroaspidospermidine

¹⁰² Djerassi, C.; Budzikiewicz, H.; Wilson, J.; Gosset, J.; Men, J. L.; Janot, M.-M. *Tetrahedron Lett.* **1962**, 3, 235–239

¹⁰³ Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Nelson, V. R. *J. Am. Chem. Soc.* **1968**, 90, 3891–3893

¹⁰⁴ a) Barsi, M.-C.; Das, B. C.; Fourrey, J.-L.; Sundaramoorthi, R. *J. Chem. Soc. Chem. Commun.* **1985**, 88–89; b) J.-Y. Laronze, P.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 15, 491–494; c) Kalaus, G.; Greiner, I.; Kajtar-Peredy, M.; Brlik, J.; Szabo, L.; Szantay, C. *J. Org. Chem.* **1993**, 58, 1434–1442; d) Kalaus, G.; Kiss, M.; Kajtar-Peredy, M.; Brick, J.; Szabó, L.; Szántay, C. *Heterocycles* **1985**, 23, 2783–2787; e) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, 40, 1519–1522; f) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, 63, 2172–2183; g) Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *J. Org. Chem.* **1979**, 44, 2477–2480; h) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *J. Org. Chem.* **1979**, 44, 1063–1068; i) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, 50, 924–929; j) Kuehne, M. E.; Roland, D. M.; Hafter, R. J.

2 and vincadifformine **4** was already known in both directions^{65,105} (**Scheme 3.27**). Using Mander's reagent, dehydroaspidospermidine was converted into vincadifformine with 50% yield.⁶⁵



Scheme 3.27 – Synthetic connection between vincadifformine and dehydroaspidospermidine

3.5 Quebrachamine

Quebrachamine **242** is an *Aspidosperma* alkaloid highly related to dehydroaspidospermidine **2** (**Scheme 3.28**). It was first isolated by Hesse in 1882¹⁰⁶ but no structure was given. In 1951, Gellert found a new alkaloid called kamassine¹⁰⁷ but found out it was quebrachamine **242** one year later.¹⁰⁸ Its correct structure was hypothesized by Witkop in 1960,¹⁰⁹ before it was confirmed by Biemann one year after.¹¹⁰ Since then, more than twenty syntheses (total and formal) were published.^{62,70,72,74g,84,86b,111}

Org. Chem. **1978**, 43, 3705–3710; k) Kuehne, M. E.; Wang, T.; Seaton, P. J. *J. Org. Chem.* **1996**, 61, 6001–6008; l) Lewin, G.; Bernadat, G.; Aubert, G.; Cresteil, T. *Tetrahedron* **2013**, 69, 1622–1627; m) Pandey, G.; C, P. K. *Org. Lett.* **2011**, 13, 4672–4675

¹⁰⁵ a) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron* **1985**, 41, 5495–5501; b) Hugel, G.; Lévy, J. *Tetrahedron* **1984**, 40, 1067–1073; c) David, B.; Sevenet, T.; Thoison, O.; Awang, K.; Pais, M.; Wright, M.; Guenard, D. *Bioorg. Med. Chem. Lett.* **1997**, 7, 2155–2158

¹⁰⁶ Hesse, O. *Justus Liebig's Ann. der Chemie* **1882**, 211, 249–282

¹⁰⁷ Schlittler, E.; Gellert, E. *Helv. Chim. Acta* **1951**, 34, 920–923

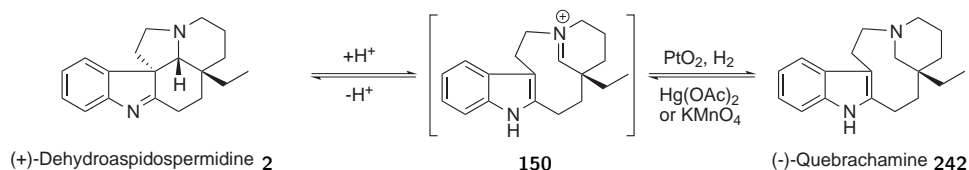
¹⁰⁸ Gellert, E.; Witkop, B. *Helv. Chim. Acta* **1952**, 35, 114–115

¹⁰⁹ Kny, H.; Witkop, B. *J. Org. Chem.* **1960**, 25, 635–637

¹¹⁰ Biemann, K.; Spiteller, G. *Tetrahedron Lett.* **1961**, 2, 299–304

¹¹¹ a) Ziegler, F. E.; Kloek, J. a.; Zoretic, P. a. *J. Am. Chem. Soc.* **1969**, 91, 2342–2346; b) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlatts, I. *J. Am. Chem. Soc.* **1970**, 92, 1727–1735; c) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, 98, 3022–3023; d) Giri, V. S.; Ali, E.; Satyesh, C. *J. Heterocycl. Chem.* **1980**, 17, 1133–1134; e) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1980**, 616–617; f) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, 103, 6990–6992; g) Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1981**, 1153–1155; h) Wenkert, E.; Halls, T. D.; Kwart, L. D.; Magnusson, G.; Showalter, H. *Tetrahedron* **1981**, 37, 4017–4025; i) Temme, O.; Taj, S.-A.; Andersson, P. G. *J. Org. Chem.* **1998**, 63, 6007–6015; j) Wee, A. G.; Yu, Q. *Tetrahedron* **1998**, 54, 13435–13448; k) Amat, M.; Lozano, O.;

One possible biosynthetic pathway of quebrachamine **242** is from dehydroaspidospermidine **2**. Biemann already suggest a possible connection between these two alkaloids in his structure determination of the aspido-spermidine.⁵⁹ Previous studies by Schmid,¹¹² Trotte¹¹³ and Rawal⁸⁴ have reported the possible synthetic connection between these two natural compounds, going from aspido-spermidine and dehydroaspido-spermidine to quebrachamine and *vice versa* (**Scheme 3.28**). The reaction should pass by the same iminium intermediate **150** used in our *i*ORC.



Scheme 3.28 – Possible biosynthetic pathway of quebrachamine

Iminium intermediates similar to **150** have already been reported for the synthesis of quebrachamine.^{87c} Therefore, we planed to intercept iminium **150** in our domino sequence by using stronger reducing conditions to obtain quebrachamine **242** instead of dehydroaspido-spermidine **2**. Unfortunately, the formation of quebrachamine has proven unsuccessful using the *i*ORC domino process. Only dehydroaspido-spermidine or degradation were observed.

3.6 Conclusion

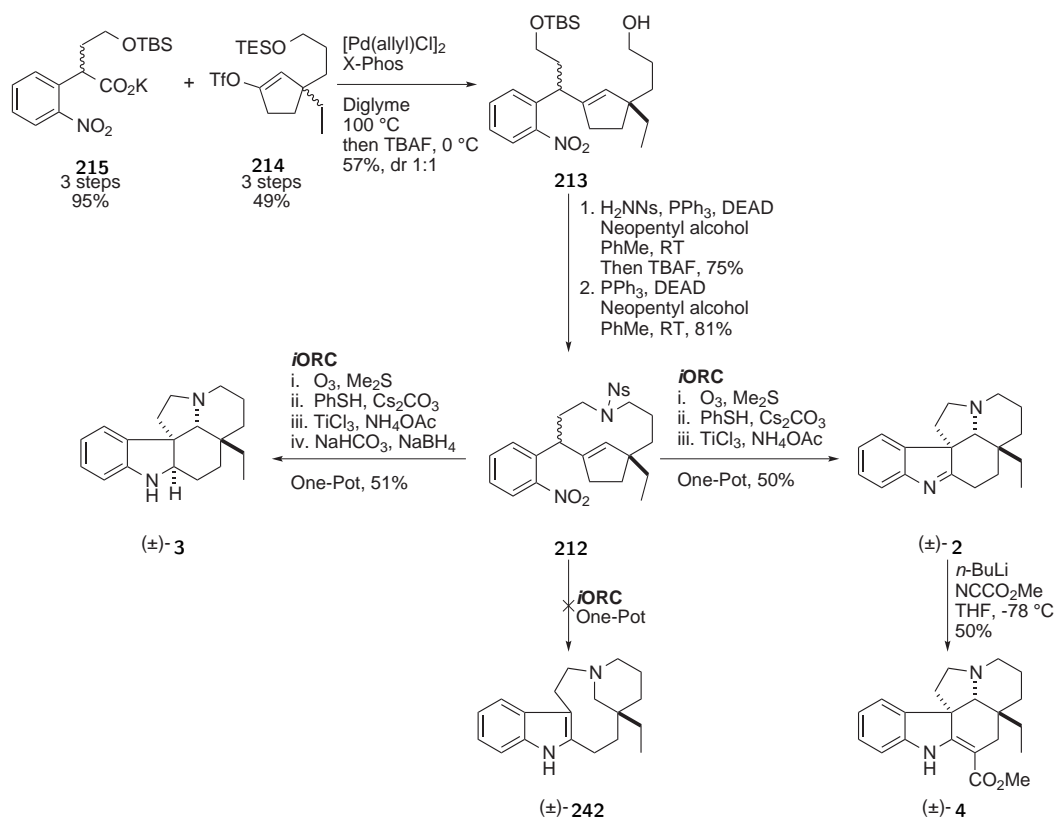
In summary, the total syntheses of (±)-aspido-spermidine **3**, (±)-dehydroaspido-spermidine **2** and (±)-vincadifformine **4** were accomplished (**Scheme 3.29**).¹⁰⁰ From the potassium carbonate **215** and vinyl triflate **214**, a decarboxylative coupling developed in our laboratory allowed us to build intermediate **213** bearing all the carbons needed in the natural product. Two consecutive Mitsunobu reactions afforded the macrocyclic key intermediate **212** in good yield. Our key *i*ORC sequence did a full skeleton reorganization in a diastereoselective fashion, allowing us to reach either (±)-dehydroaspido-spermidine **2** or (±)-aspido-spermidine **3**. A known procedure allowed us to reach (±)-vincadifformine **4** in 50% yield.

Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, 72, 4431–4439; sl) Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 1072–1077; m) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, 131, 943–953; n) Nidhiry, J. E.; Prasad, K. R. *Tetrahedron* **2013**, 69, 5525–5536; o) Hsu, S. W.; Cheng, H. Y.; Huang, A. C.; Ho, T. L.; Hou, D. R. *Eur. J. Org. Chem.* **2014**, 3109–3115; p) Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, 10, 2501–2512

¹¹² Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964**, 47, 1147–1152

¹¹³ Camerman, A.; Camerman, N.; Kutney, J.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, 6, 637–642

Chapter 3: Dehydroaspidospermidine and Aspidospermidine



Scheme 3.29 – Summary of the total synthesis of aspidospermidine, dehydroaspidospermidine and vincadifformine

These syntheses showed the power of our *i*ORC domino sequence, and the simple synthesis of precursor **212** motivated us to pursue other natural products with similar key steps.

Approach Towards the Total Synthesis of Aspidoalbidine

(+)-Aspidoalbidine (or (+)-fendleridine) **5** is an *aspidosperma* alkaloid isolated in 1966 by Burnell and co-workers from the seeds of *Aspidosperma fendleri* (**Figure 4.1**). The name fendleridine was based on the name of the tree.¹¹⁴ Although in 1963, Brown isolated (+)-N-acetylaspidoalbidine **244**,¹¹⁵ they gave the name "aspidoalbidine" to the postulated simplest member by analogy to aspidospermidine, discovered by Biemann two years before.⁵⁹ While both names seemed to be used nowadays for this natural product, we will use aspidoalbidine as it relates better to the *aspidosperma* family to which it belongs.

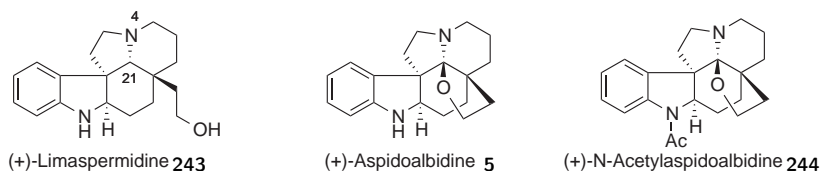


Figure 4.1 – Structures of limaspermidine **243**, aspidoalbidine **5** and N-acetylaspidoalbidine **244**

The biosynthesis of this alkaloid seems to arise from limaspermidine (18-hydroxyaspidospermidine) **243** *via* oxidation of the N4-C21 bond and cyclization.

4.1 Previous Syntheses of Aspidoalbidine

Few syntheses of both aspidoalbidine **5** and N-acetylaspidoalbidine **244** are reported. Most of them followed the biosynthetic pathway. They reached first limaspermidine, oxidized the N1-C21 bond and the alcohol group cyclized spontaneously on the iminium moiety. This

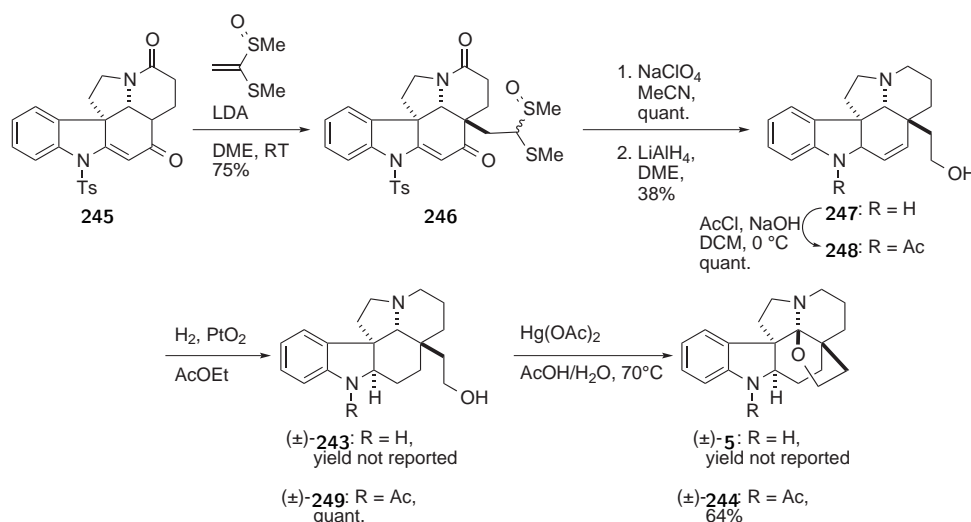
¹¹⁴Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1966**, *44*, 28–31

¹¹⁵Brown, K.; Budzikiewicz, H.; Djerassi, C. *Tetrahedron Lett.* **1963**, *4*, 1731–1736

last oxidation step required the protection of the indole moiety, which is the main reason why most of the groups targeted N-acetylaspidoalbidine.

4.1.1 Ban's Syntheses of (±)-N-Acetylaspidoalbidine and (±)-Aspidoalbidine

In 1975, Ban and co-workers reported the first total synthesis of (±)-N-acetylaspidoalbidine **244**,¹¹⁶ and one year later reported the first total synthesis of (±)-aspidoalbidine **5** (Scheme 4.1).¹¹⁷ Starting from pentacyclic intermediate **245**. Michael addition with ketene thioacetal monoxide provided intermediate **246**. Hydrolysis of thioacetal group followed by reduction with LiAlH₄ provided alcohol derivative **247**. Selective acetylation of indole afforded **248**. Hydrogenation on both **247** and **248** with Adams' catalyst afforded (±)-limaspermidine **243** and (±)-N-acetyllimaspermidine **249** respectively. Final oxidation of N1-C21 bond with mercury acetate in acidic medium afforded (±)-aspidoalbidine **5** or (±)-N-acetylaspidoalbidine **244**.



Scheme 4.1 – Ban's synthesis of (±)-N-acetylaspidoalbidine and (±)-aspidoalbidine

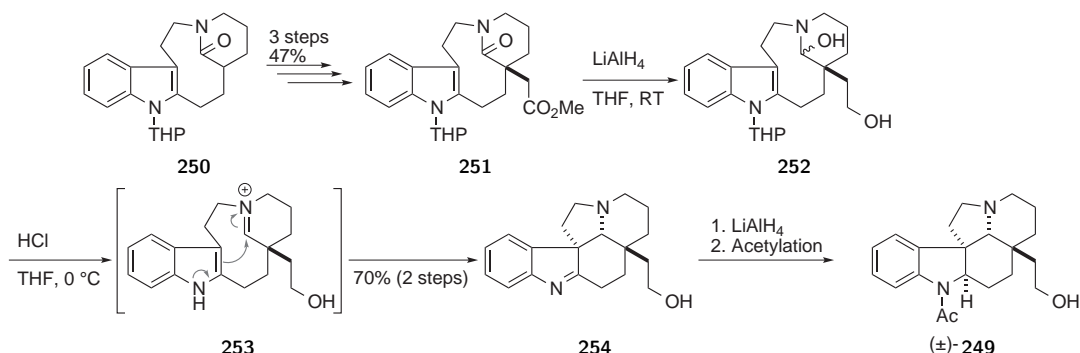
In 1987, Ban and co-workers reported a formal synthesis of (±)-N-acetylaspidoalbidine **244** (Scheme 4.2).¹¹⁸ From the indole-protected precursor **250**, addition of methyl oxalate, Wolff-Kishner reduction and esterification afforded methyl ester derivative **251**. Reduction gave hemiaminal derivative **252**. Under acidic conditions, the THP was cleaved and the hemiaminal was dehydrated to form iminium salt **253**, which cy-

¹¹⁶Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, 16, 727–730

¹¹⁷Ban, Y.; Honma, Y.; Ohnuma, T. *Heterocycles* **1976**, 5, 47–51

¹¹⁸Yoshida, K.; Sakum, Y.; Ban, Y. *Heterocycles* **1987**, 25, 47–50

clized into (\pm)-dehydrolimaspermidine **254**. Reduction and acetylation afforded (\pm)-N-acetylillaspermidine **249** as the precursor of (\pm)-N-acetylaspidoalbidine **244**



Scheme 4.2 – Ban's formal synthesis of (\pm)-N-acetylaspidoalbidine

4.1.2 Overman's Formal Synthesis of (\pm)-N-Acetylaspidoalbidine

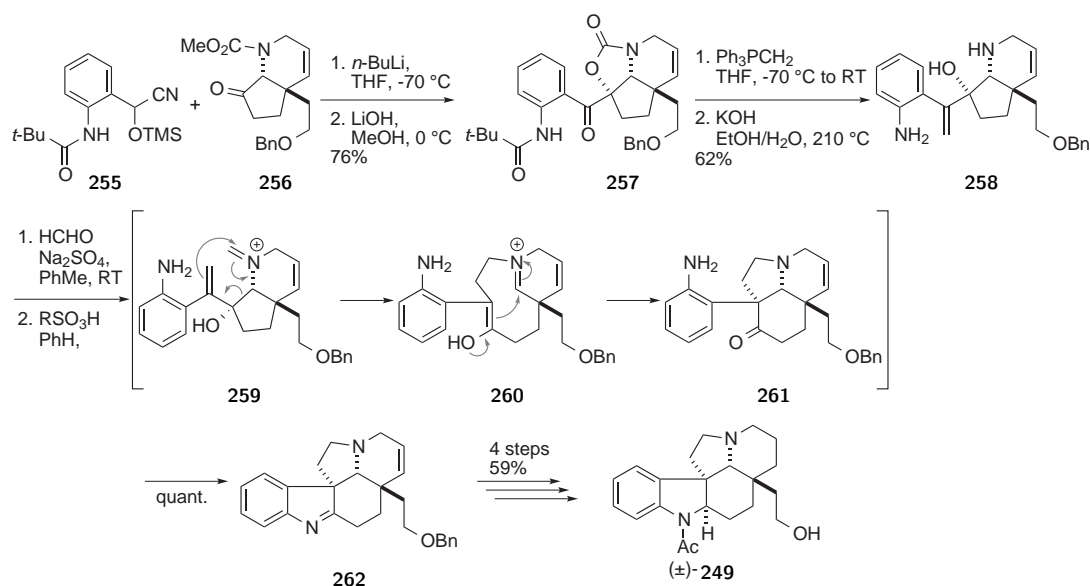
In 1991, Overman published a formal synthesis of (\pm)-N-acetylaspidoalbidine involving a tandem aza-Cope rearrangement/Mannich cyclization sequence as a key step (**Scheme 4.3**).¹¹⁹ Addition of **255** on ketone **256** followed by intramolecular acylation afforded lactone **257** in 76% yield. Wittig reaction followed by lactone opening gave key intermediate **258**. The key-step started with formation of iminium **259**. Oxy-cope rearrangement gave enol intermediate **260** and Mannich cyclization afforded ketone derivative **261**, that condensed into indolenine **262**. A four steps sequence allowed Overman and co-workers to reach (\pm)-N-acetylillaspermidine **249**.

4.1.3 Boger's Synthesis of (\pm)-Aspidoalbidine

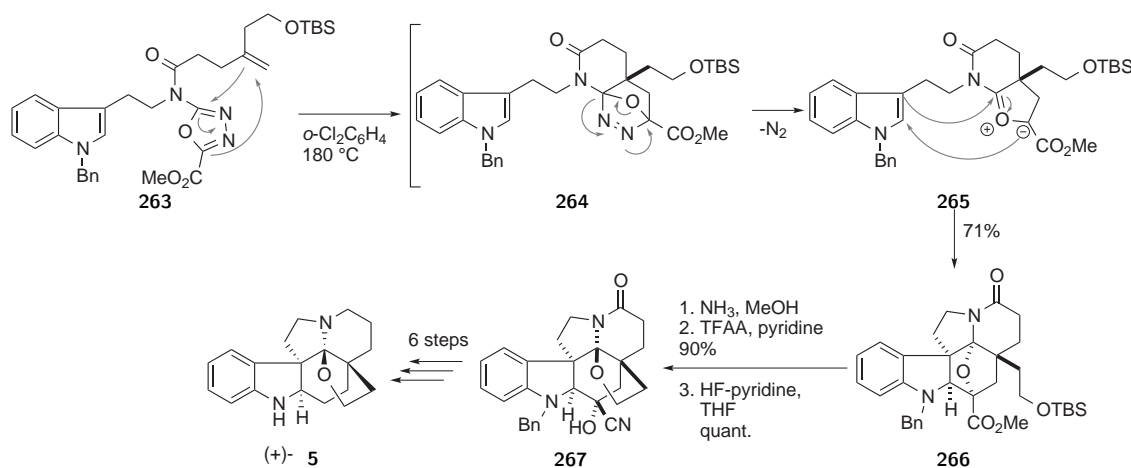
Boger and co-workers reported in 2010 a total synthesis of (\pm)-aspidoalbidine¹²⁰ using their emblematic domino IEDDA/(1,3)-dipolar cycloaddition sequence (also presented for their total synthesis of vindorosine in **Section 1.2.4**). From intermediate **263** (**Scheme 4.4**), a thermal IEDDA occurred and afforded intermediate **264**. Release of nitrogen resulted in dipolar intermediate **265**. A (1,3)-dipolar cycloaddition afforded polycyclic structure **266** in 71% yield from **263**. Conversion of the ester to the primary amide followed by dehydration to the nitrile and deprotection of silyl ether with HF resulted in the cyclized aspidoalbidine-core **267**. Six steps were needed to reach aspidoalbidine **5**. Separation of enantiomers four steps before the end allowed them to reach the enantiopure form of the natural product.

¹¹⁹Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610

¹²⁰Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012



Scheme 4.3 – Overman's Formal Synthesis of (±)-N-acetylaspidoalbidine

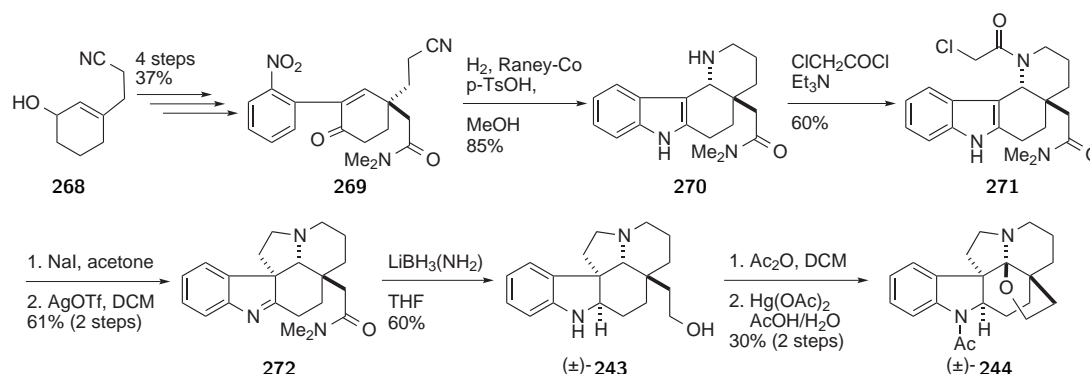


Scheme 4.4 – Boger's Total Synthesis of aspidalbidine

4.1.4 Banwell's Synthesis of (±)-N-Acetylspidoalbidine

In 2012, Banwell and co-workers published a total synthesis of (±)-N-acetylaspidoalbidine **244** (Scheme 4.5).^{101k} Nitrile derivative **268** was converted in four steps into the enone intermediate **269**. A domino reduction/cyclization sequence using Raney-Cobalt and TsOH afforded tetracyclic intermediate **270**. Alkylation of the amine gave **271**, and cyclization provided the pentacyclic structure **272**. (±)-Limaspermidine **243** was obtained after reduction of the amide, and Ban's procedure¹¹⁷ allowed them to reach (±)-N-acetylspidospermidine **244**.

Attempts to reproduce Ban's conversion of (\pm)-limaspermidine **243** into (\pm)-aspidalbidine **5** (without protection of indole) were not successful.



Scheme 4.5 – Banwell's Total Synthesis of (\pm)-N-acetylaspidalbidine

4.1.5 Shao's Formal Synthesis of (+)-Aspidalbidine

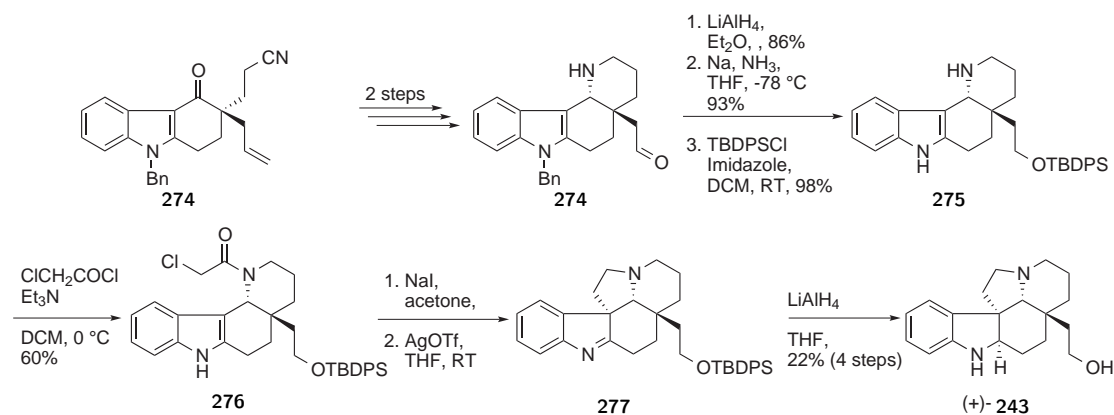
Shao and co-workers published in 2013¹²¹ a formal synthesis of (+)-N-acetylaspidalbidine similar to Banwell's work (see above). Having developed a palladium-catalyzed decarboxylative allylation, they used this methodology to build indole precursor **273** (**Scheme 4.6**). Reductive cyclization of the cyano group on the ketone, followed by oxidation resulted in aldehyde **274**. Reduction of aldehyde with LiAlH_4 , followed by benzyl deprotection and alcohol protection afforded intermediate **275**. Following Banwell's route, alkylation of amine afforded **276**, which was cyclized in two steps into protected (+)-dehydrolimaspermidine **277**. Reduction of **277** with LiAlH_4 afforded (+)-limaspermidine **243** as precursor of (+)-aspidalbidine.

4.1.6 Canesi's Formal Synthesis of (\pm)-N-Acetylaspidalbidine

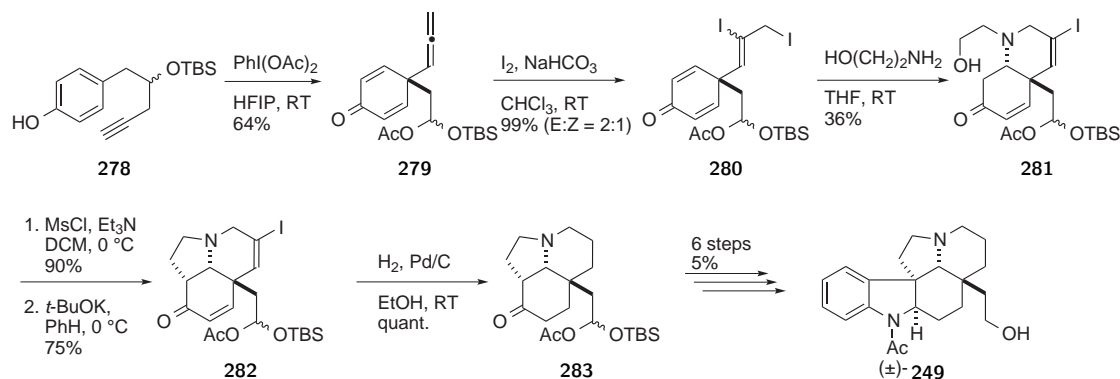
In 2012, Canesi and co-workers developed an oxidative 1,3-alkyl shift process and used it in the formal synthesis of (\pm)-N-acetylaspidalbidine (**Scheme 4.7**).¹²² From alkyne **278**, their 1,3-alkyl shift process afforded alkene **279** in good yield. Diiodination gave olefin **280** as a mixture of isomers. Amination and intramolecular 1,4-addition provided intermediate **281** in low yield, as only one isomer of **280** had the correct conformation to favor the cyclization.

¹²¹ Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444–11449; Correction in Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2014**, *79*, 829–829

¹²² Guérard, K. C.; Guérinot, A.; Bouchard-Aubin, C.; Ménard, M. A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121–2133



Scheme 4.6 – Shao's Formal Synthesis of (+)-aspidalbidine



Scheme 4.7 – Canesi's Formal Synthesis of (±)-N-acetylaspidoalbidine

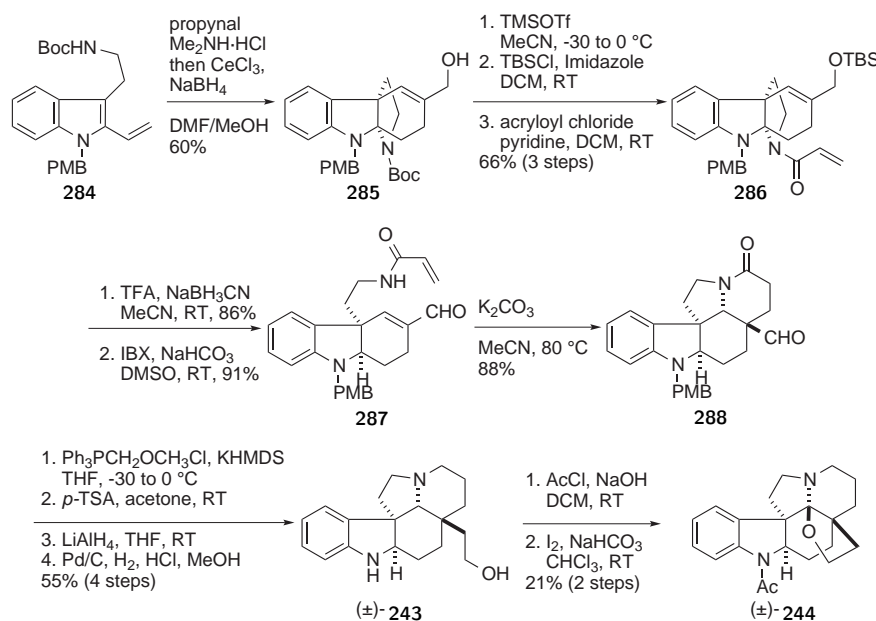
Mesylation of the alcohol followed by cyclization afforded tricyclic structure **282**. Hydrogenolysis of the iodide and hydrogenation of the two olefins afforded intermediate **283**. From this intermediate, six steps (deprotection of the aldehyde moiety and its reduction into alcohol, Fischer indole synthesis, reduction and acetylation) provided (±)-N-acetylmaspermidine **249**.

4.1.7 Qiu's Total Synthesis of (±)-N-Acetylaspidoalbidine

In 2014, Qiu and co-workers reported a Diels-Alder cycloaddition between tryptamine derivative **284** and propynal (Scheme 4.8).¹²³ The resulting cycloadduct **285** was transformed to **286** by a three steps sequence. Reduction of the aminal followed by oxidation of alcohol afforded aldehyde **287**. Domino Michael addition gave pentacyclic intermediate **288**.

¹²³Jin, J.; Qiu, F. G. *Adv. Synth. Catal.* **2014**, 356, 340–346

Wittig reaction followed by functional group manipulations afforded (±)-limaspermidine **243**. Qiu and co-workers attempted to change the oxidation conditions to reach (±)-N-acetylaspidalbidine **244**. Nevertheless, most reported conditions for tertiary amine oxidation suffered from irreproducibility and non completion of the reaction. Iodine oxidation of tertiary amine (reported on alkaloids by Szántay in 2001)¹²⁴ gave the final product in 21% yield.



Scheme 4.8 – Qiu's Total Synthesis of (±)-N-acetylaspidalbidine

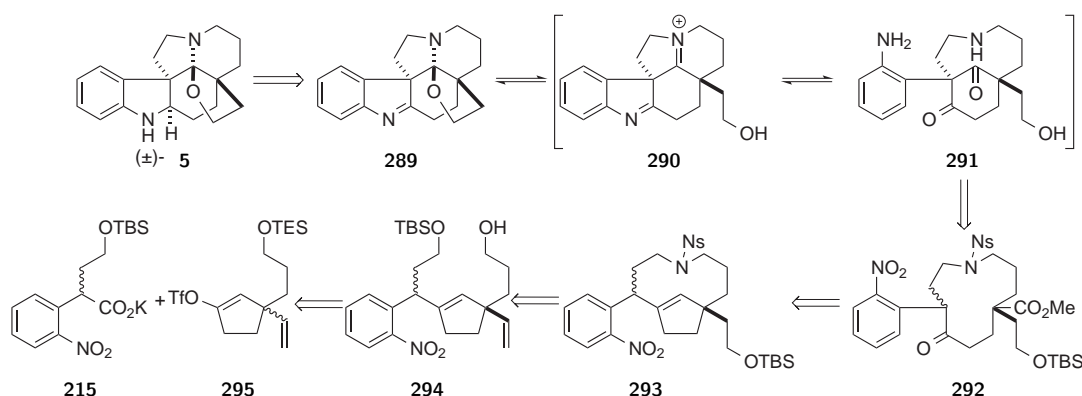
4.2 Synthetic Studies of Aspidalbidine

Considering the close relation between aspidospermidine and aspidalbidine, we decided to pursue the total synthesis of this *Aspidosperma* alkaloid. As most previous syntheses passed by 18-hydroxyaspidospermidine (limaspermidine), then oxidize the C21-N4 bond into its iminium form, we wanted to see if similar iminium intermediates were not readily accessible through our *i*ORC process.

From a retrosynthetic analysis perspective (**Scheme 4.9**), (±)-aspidalbidine **5** could arise from (±)-dehydroaspidalbidine **289**. Disconnecting the amination ether would give the iminium **290**. Following the *i*ORC disconnection (*cf.* **Chapter 3**), we can consider the disconnection of the iminium moiety and indolenine moiety to the putative diamino-dicarbonyl

¹²⁴Moldvai, I.; Szántay, C.; Szántay, C. *Heterocycles* **2001**, 55, 2147–2155

intermediate **291**. This intermediate could result from the reduction of a nitro group, the deprotection of a secondary amine, and intramolecular Dieckmann condensation from macrocycle **292**. If we compare this intermediate with aldehyde **211** in **Scheme 3.17**, the only difference in the key step would be to perform the ozonolysis from **293** with a work-up leading to the methyl ester instead of aldehyde. Cyclopentene derivative **293** is again closely related to the key intermediate **212** used for aspidospermidine. Taking inspiration from the aspidospermidine synthesis presented in the previous chapter, we could reach this 10-membered ring by two Mitsunobu reaction and a hydroboration from precursor **294**. This precursor could arise from our palladium-catalyzed decarboxylative coupling between potassium carboxylate **215** and vinyl triflate derivative **295**.

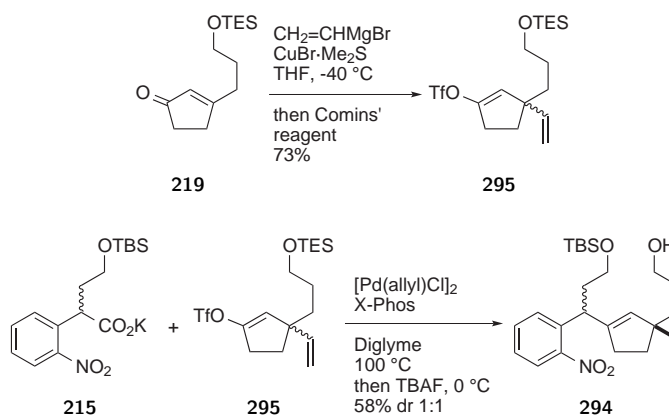


Scheme 4.9 – Retrosynthetic analysis of aspidalbidine

4.2.1 Key intermediate synthesis

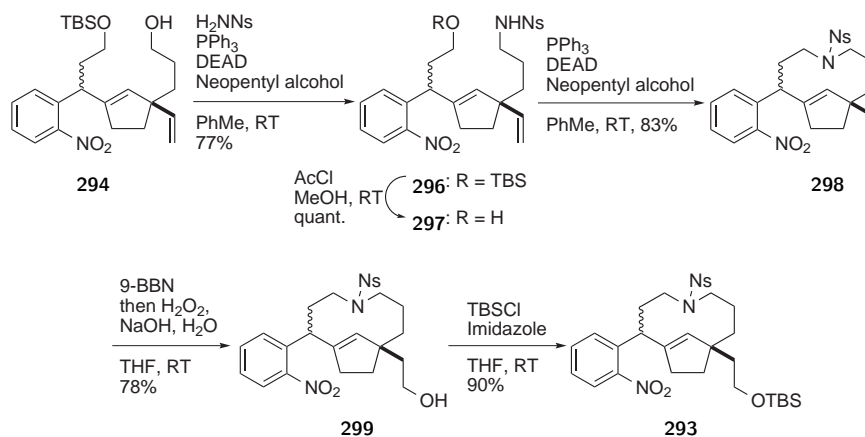
The synthesis of potassium carboxylate **215** was already detailed in **3.3.1**. For the vinyl triflate derivative **295**, we decided to follow the same strategy as for triflate derivative **214** (with ethyl instead of vinyl, see **3.3.1**). We planned that the presence of the vinyl group instead of an ethyl moiety would not interfere with the synthetic route used in the total synthesis of aspidospermidine. Starting from TES-protected enone **219** (**Scheme 4.10**). A copper-assisted 1,4-addition of vinylmagnesium bromide, followed by trapping of the enolate with Comins' reagent afforded triflate derivative **295**. To our delight, the palladium-catalyzed decarboxylative coupling between potassium carboxylate **215** and vinyl triflate derivative **295** afforded product **294** as a mixture of diastereoisomers in 58% yield.

From monoprotected diol **294**, Mitsunobu reaction with nosylamine afforded protected aminoalcohol **296** (**Scheme 4.11**). Deprotection with catalytic amount of HCl in methanol gave aminoalcohol **297**. A second Mitsunobu afforded desired macrocycle **298**. The results of this cyclization was different from the aspidospermidine case. In large scale,



Scheme 4.10 – Synthesis of triflate and decarboxylative coupling

dimerization of **297** appeared as major side-product (60%). To avoid this side-reaction, higher dilution had to be used in the scale up of this intramolecular Mitsunobu reaction. Selective anti-Markovnikov hydroxylation of terminal double bond in the presence of more hindered olefins were already described in the literature, using hindered borane like Cy_2BH ,¹²⁵ *thexylborane*¹²⁶ or 9-BBN.¹²⁷ In our case, attempts with these boranes as well as simpler ones were performed. Only 9-BBN afforded alcohol **299** with good yield. Finally, protection with TBSCl gave **293**.



Scheme 4.11 – Mitsunobu cyclization

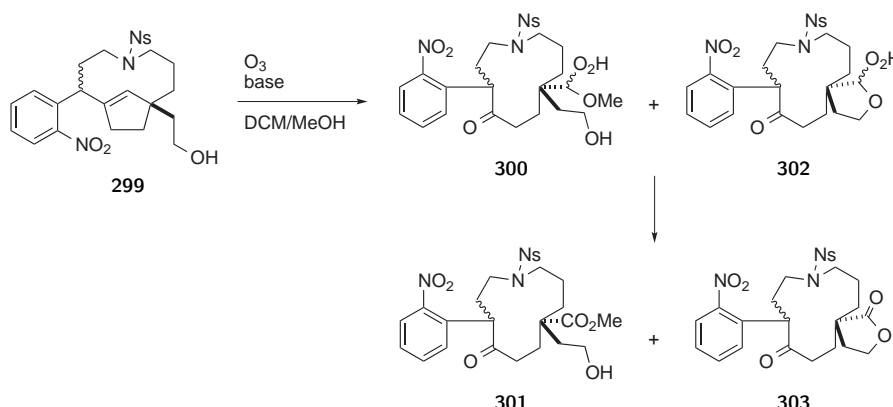
¹²⁵ Jiao, L.; Lin, M.; Zhuo, L. G.; Yu, Z. X. *Org. Lett.* **2010**, *12*, 2528–2531

¹²⁶ Nagaoka, H.; Shibuya, K.; Yamada, Y. *Tetrahedron* **1994**, *50*, 661–688

¹²⁷ a) San Feliciano, A.; Medardea, M.; Toméa, F.; Caballeroa, E.; Hebreroa, B.; del Corrala, J. M. M.; Barrerob, A. E. *Tetrahedron* **1989**, *45*, 1815–1822; b) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379; c) Yu, M.; Ibrahim, I.; Hasegawa, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 2788–2799

4.2.2 *i*ORC Study

Our first ozonolysis attempts were on free alcohol **299** (Scheme 4.12). Many conditions were reported on ozonolysis to afford a methyl ester instead of aldehyde.¹²⁸ If an ozonolysis is performed in the presence of methanol and a mild base, peroxide **300** should be formed. Quenching this peroxide into methyl ester **301** is a well described procedure, commonly performed by treatment with acids,¹²⁹ hypochlorites,¹³⁰ $\text{Ac}_2\text{O}/\text{Et}_3\text{N}$ ¹³¹ or $\text{Ac}_2\text{O}/\text{pyridine}$.¹³² If the base used during ozonolysis is strong (NaOH, or sodium methanolate), direct formation of methyl ester **301** should be observed. In our case, all attempts gave dirty mixture of peroxide **302** and lactone **303** with poor mass balance. Methyl peroxide **300** or methyl ester **301** were never observed. The reason could be that the intramolecular cyclization was faster than the attack of the solvent, or methyl ester was formed, but lactonization happened under the reaction conditions. It is also possible that methyl peroxide degraded before conversion to methyl ester. In any case, if lactonization was easy, removing the methanol in the reaction mixture should favor it, and in fact reaction was much cleaner without methanol. Unfortunately, using Ac_2O and Et_3N provided large amount of peroxide **302** and low conversion into lactone **303**. Amongst all the conditions tried, only $\text{Ca}(\text{OCl})_2$ afforded lactone **303** cleanly with good yield (70%).



Scheme 4.12 – Ozonolysis mechanism

Now that ozonolysis was optimized, we looked into the rest of the domino sequence (Scheme 4.13). Large scale ozonolysis of **299** afforded lactone **303** with reproducible yield. We

¹²⁸ Lee, D. G.; Chen, T. In *Compr. Org. Chem. V7 Oxidations*, Trost, B. M., Fleming, I., Eds.; Pergamon, Oxford: 1991, pp 541–591

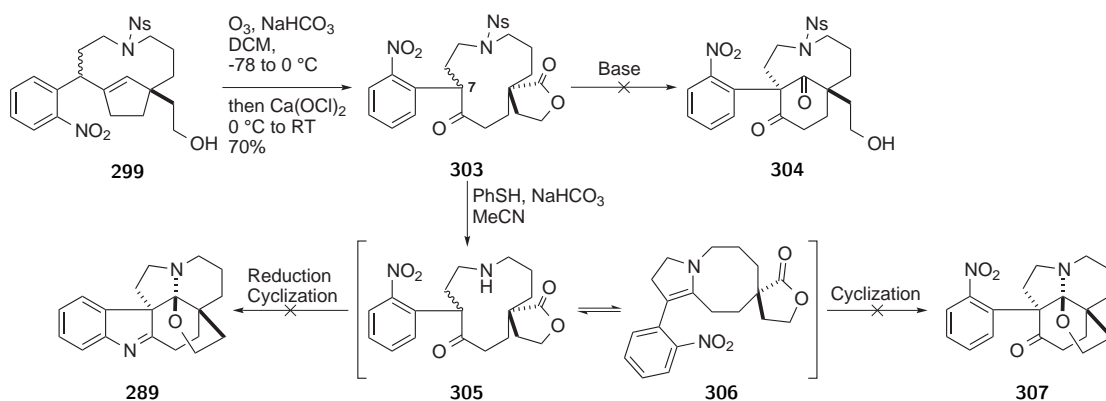
¹²⁹ Keul, H.; Griesbaum, K. *Can. J. Chem.* **1980**, *58*, 2049–5054

¹³⁰ Fisher, T. J.; Dussault, P. H. *Tetrahedron Lett.* **2010**, *51*, 5615–5617

¹³¹ Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867–3870

¹³² Lee, S.-g.; WooLim, C.; EuiSong, C.; HanPark, D. *Synth. Commun.* **1996**, *26*, 4623–4631

first attempted direct Dieckmann cyclization using organic or inorganic bases, in different solvents at various temperature. It was possible to observe which conditions could deprotonate substrate **303** (DBU, $> 50^{\circ}\text{C}$), as the reaction was performed on each diastereoisomer separately and epimerization could be observed when deprotonation at C7 occurred. However, no cyclization into **304** was observed.

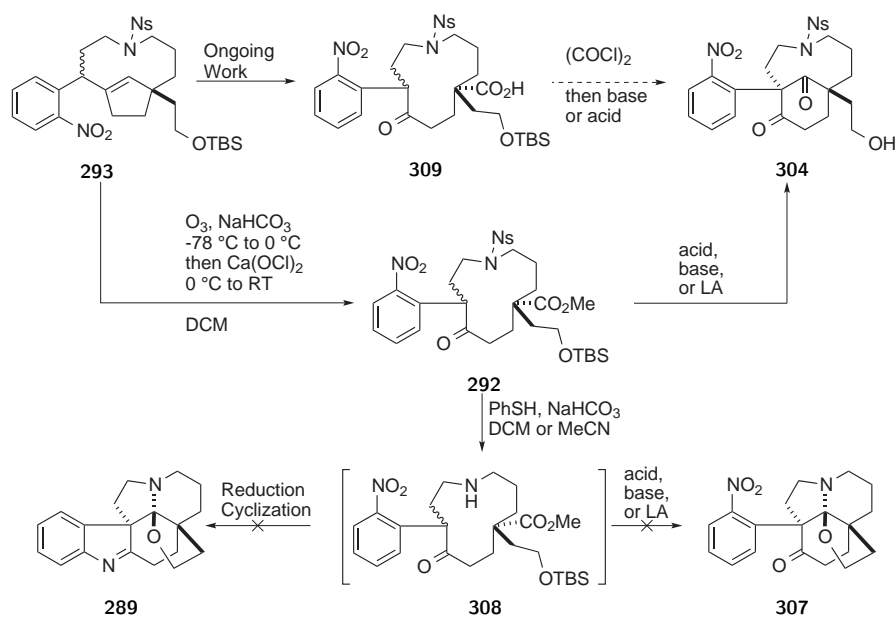


Scheme 4.13 – Study of key step

Deprotection of nosyl group afforded an unstable crude mixture of amine **305** and presumably enamine **306**. The deprotection was much cleaner if performed in acetonitrile compared to DCM. Cyclization attempts into **307** were attempted with various bases, acids or Lewis acids, but without success. We thought that as the C7 position of **305** needed to be activated, it would be beneficial to already reduce the nitro group, in order to form the indole. The position C7 would then be nucleophilic with milder activation conditions. Unfortunately, only degradation was observed no matter the reduction conditions tried or the acidity of the solution. Never any dehydroaspidoalbidine **289** was observed.

One of the problems may come from the conformation of the lactone moiety that disfavors any type of cyclization. We decided then to use the TBS-protected precursor **293** to avoid lactone formation (Scheme 4.14).

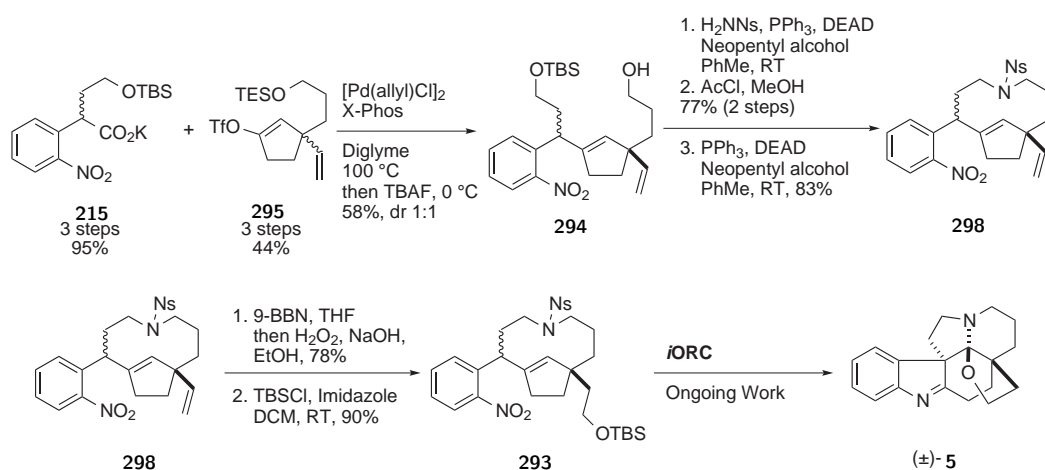
The work toward the total synthesis of aspidoalbidine is unfortunately not finished at the moment. Preliminary results showed that synthesis of methyl ester **292** was less clean than lactone **303**. From ester **292** Dieckmann condensation to **304** has proven unsuccessful under Brønsted acid, Brønsted base or Lewis acid conditions. When stronger conditions were used, degradation appeared. Deprotection of **308** gave unstable amine derivative **308** that could not be converted into tricyclic intermediate **307** or dehydroaspidoalbidine **289**. The ozonolysis of **293** into acid **309** is still ongoing. We planned to activate acid **309** via the corresponding acid chloride to facilitate the Dieckmann cyclization.



Scheme 4.14 – Study of key step

4.3 Conclusion

By changing the ethyl into a vinyl group, we could synthesize vinyl triflate **295** with similar route as for aspidospermidine (Scheme 4.15). Decarboxylative coupling with potassium salt **215** afforded intermediate **294**. Two successive Mitsunobu reactions allowed us to reach ten-membered ring **298**. Hydroboration followed by silyl protection gave the key intermediate **293** needed for our *i*ORC process. Unfortunately, this key domino process proceeded less easily than for the previous examples. The Dieckmann condensation was difficult, or the product too unstable to be observed. The study of our key step is still ongoing.



Scheme 4.15 – Summary of the synthetic efforts towards aspidalbidine

Kopsihainanine A

The *Apocynaceae* is a family of tropical or subtropical floral plants, which most of the members are poisonous and produce milky latex. The *Kopsia* genus of this family is widely distributed in Asia and Australia and is rich in alkaloids. From the leaves of *Kopsia hainanensis*, a plant used in Chinese medicine, Gao and co-workers in 2011 isolated two monoterpene indole alkaloids, (+)-kopsihainanine A **6** and (+)-kopsihainanine B **310** (Figure 5.1).¹³³ (+)-Kopsihainanine A **6** possess a unusual 6/5/6/6/6 pentacyclic structure.

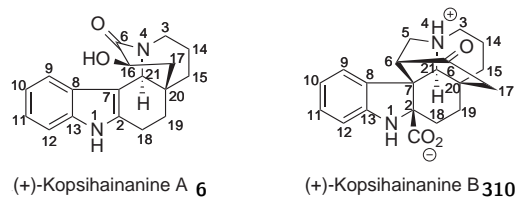


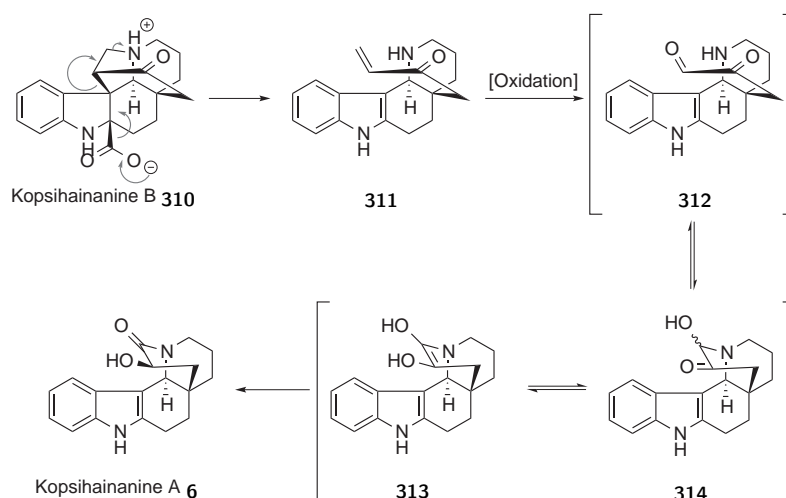
Figure 5.1 – (+)-kopsihainanine A **6** and (+)-kopsihainanine B **310**

Gao and co-workers suggested the biosynthesis of kopsihainanine A **6** from kopsihainanine B **310** (Scheme 5.1). Decarboxylation and retro-Michael gave vinylketone structure **311**. An oxidation of the terminal olefin afforded glyoxal intermediate **312**. This intermediate should condense into the hemiaminal **313**, and has keto-enol equilibrium with diol **313** and kopsihainanine A **6**.

Even without any reported biosynthesis of kopsihainanine B **310**, we could postulate a biosynthetic pathway (Scheme 5.2). From vincadifformine **4**, an oxidation into minovincine **315** occurred. Kutney postulated in 1971 that this oxidation is more likely to happen at this stage instead of happening on an earlier intermediate.¹³⁴ We postulated that an intramolecular conjugated addition of minovincine **315** could afford **316**. Similar cyclizations were de-

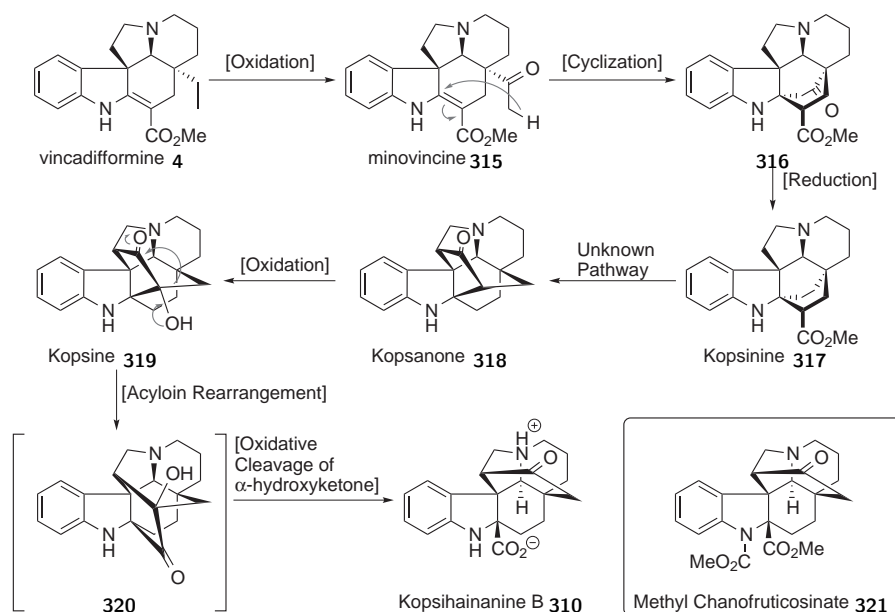
¹³³Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, 9, 5334–5336

¹³⁴Kutney, J. P.; Beck, J. E.; Eggers, N. J.; Hanssen, H. W.; Sood, R. S.; Westcott, N. D. *J. Am. Chem. Soc.* **1971**, 93, 7322–7324



Scheme 5.1 – Suggested biosynthesis of kopsihainanine A **6** from kopsihainanine B **310**

scribed during the biomimetic synthesis of kopsijasminilam¹³⁵ and pauciflorine A and B by Kuehne and co-workers.¹³⁶



Scheme 5.2 – Postulated biosynthesis of kopsihainanine B

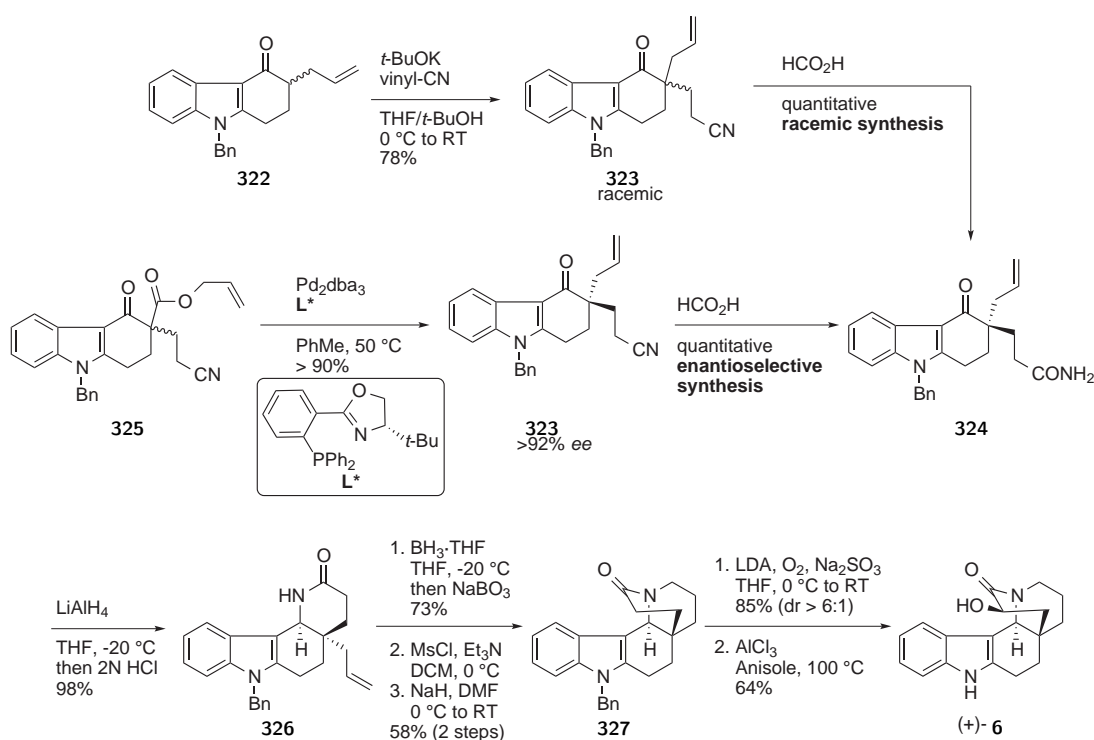
Reduction of the ketone would afford kopsinine **317**. From this alkaloid, the cyclization of C6 on C22 is required. Kuehne and co-workers showed similar transformation in acidic

¹³⁵Kuehne, M. E.; Li, Y. L.; Wei, C. Q. *J. Org. Chem.* **2000**, 65, 6434–6440

¹³⁶Kuehne, M. E.; Li, Y. L. *Org. Lett.* **1999**, 1, 1749–1750; Corrections in Kuehne, M. E.; Li, Y. L. *Org. Lett.* **2000**, 2, 97–97

media in 1985.¹³⁷ Such cyclization would convert kopsinine **317** into kopsanone **318**. The selective α -keto hydroxylation of C16 carbon is needed to reach kopsine **319**. Such hydroxylation was performed on similar substrate in 10 steps by Magnus in a racemic total synthesis of kopsine in 1989.¹³⁸ From kopsine **319**, acyloin rearrangement could afford α -hydroxyketone **320**.¹³⁹ This α -hydroxyketone structure is also present in the alkaloid dasyrachine, found in *Kopsia dasyrachis* by Kam and co-workers.¹⁴⁰ They found in the same plant methyl chanofrutosinate **321**,¹⁴¹ which is closely related to kopsihainanine B **310**. Therefore we suggested an oxidative cleavage of the α -hydroxyketone moiety of **320** to reach kopsihainanine B **310**

5.1 Previous Syntheses of Kopsihainanine A



Scheme 5.3 – Previous syntheses of kopsihainanine A 6

Up to date, four total syntheses were published. The first three are shown in **Scheme 5.3**. The difference between these three syntheses resides on the route towards cyano

¹³⁷Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, 50, 4790–4796

¹³⁸Magnus, P.; Katoh, T.; Matthews, I. R.; Huffman, J. C. *J. Am. Chem. Soc.* **1989**, 111, 6707–6711

¹³⁹Govindachari, T. R.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1963**, 46, 433–444

¹⁴⁰Kam, T. S.; Subramaniam, G.; Chen, W. *Phytochemistry* **1999**, 51, 159–169

¹⁴¹Kam, T. S.; Choo, Y. M.; Chen, W.; Yao, J. X. *Phytochemistry* **1999**, 52, 959–963

intermediate **323**. The first one was a racemic total synthesis by She and co-workers in 2012.¹⁴² Starting from ketone **322**, conjugate addition afforded racemic cyano derivative **323**. In 2013, Lupton and co-workers¹⁴³ and Shao and co-workers^{87f} published at the same time a palladium-catalyzed decarboxylative allylation of precursor **325** using PHOX-type ligand to reach one enantiomer of **323**.

From this intermediate, hydrolysis of the cyano group into primary amide derivative **324** followed by reduction with LiAlH₄ afforded cyclized intermediate **326**. Anti-Markovnikov hydroxylation of allyl group followed by mesylation and cyclization afforded protected 16-dehydroxykopsihainanine A **327**. Oxidation of α position of amide followed by deprotection gave alkaloid **6**. It is interesting to report that She did obtain an aluminum complex of kopsihainanine A due to the last deprotection step. The product they obtained was not soluble in CDCl₃, in opposition to the isolated natural product. Shao, using the same last step for the synthesis (deprotection of the N-Benzyl protected indole using AlCl₃) observed the same solubility issue. But after treatment of the natural product with Rochelle's salt, the free natural product was obtained.

Last year, Mukai and co-workers reported a new strategy for a total synthesis of (+)-kopsihainanine A **6**.¹⁴⁴ From precursor **328**, a similar palladium-catalyzed decarboxylative allylation gave **329** with excellent ee. Deprotection of both Boc and Bz group afforded intermediate **330**. Bischler-Napieralski reaction followed by NaBH₄ reduction converted **330** into **331**. Boc and Cbz protection followed by dihydroxylation gave diol intermediate **332**. Cbz deprotection and oxidation with IBX afforded α -ketonamide intermediate **333**. Reduction with NaBH₄ and Boc deprotection afforded the natural product (+)-**6**.

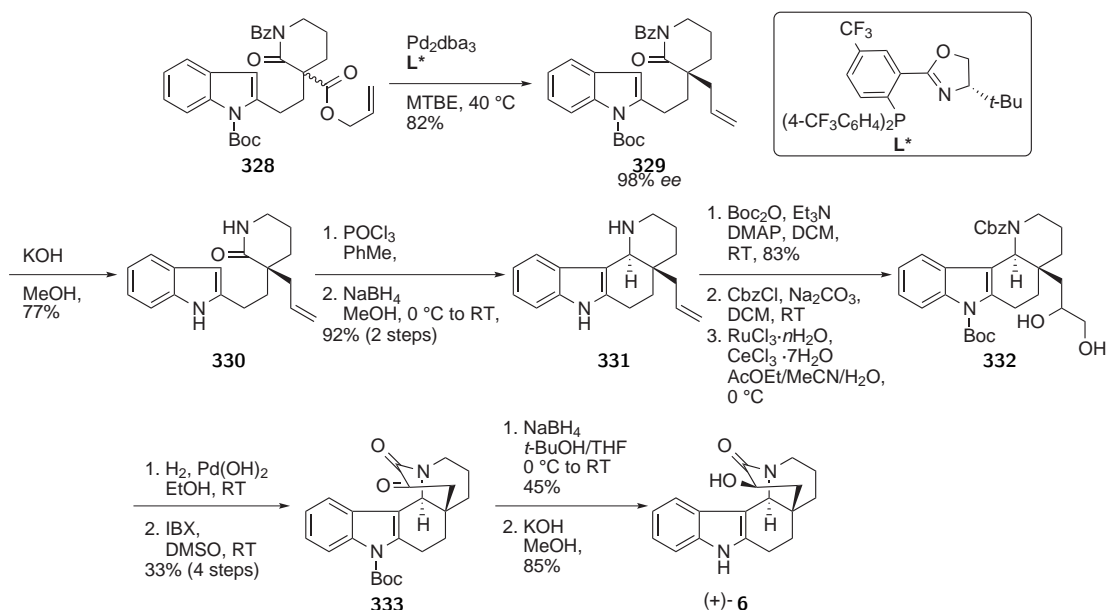
5.2 Retrosynthetic Study

In our previous uses of our *i*ORC domino process, we showed that with bulky group in the position 3 of indole, the intermediate **10** would cyclize from N1 to afford protected (\pm)-goniomitine **61** (**Scheme 5.5**). With a tether, we could force the cyclization from **150** to (\pm)-dehydroaspidospermidine **2** and (\pm)-aspidospermidine **3**. However, both cyclizations gave *cis*-fused [6,6] ring systems. By targeting (\pm)-kopsihainanine A **6**, we planned to address two questions: (1) Will the cyclization of **334** (without tether) still be highly regioselective for the C7 attack? And (2) How to force the *trans*-fused [6,6] ring systems needed for (\pm)-kopsihainanine A **6**?

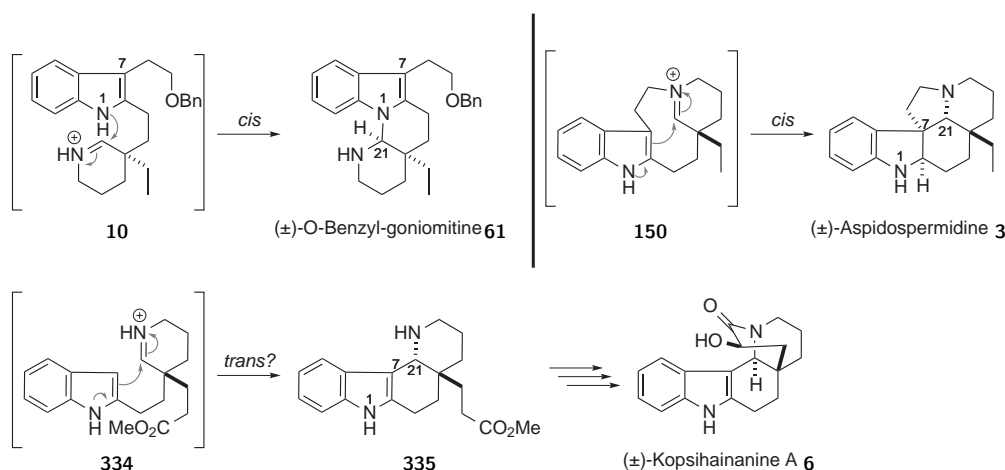
¹⁴²Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chemistry* **2012**, *18*, 6729–6732

¹⁴³Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116

¹⁴⁴Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.* **2014**, *50*, 5782–5785



Scheme 5.4 – Mukai's synthesis of (+)-kopsihainanine A 6

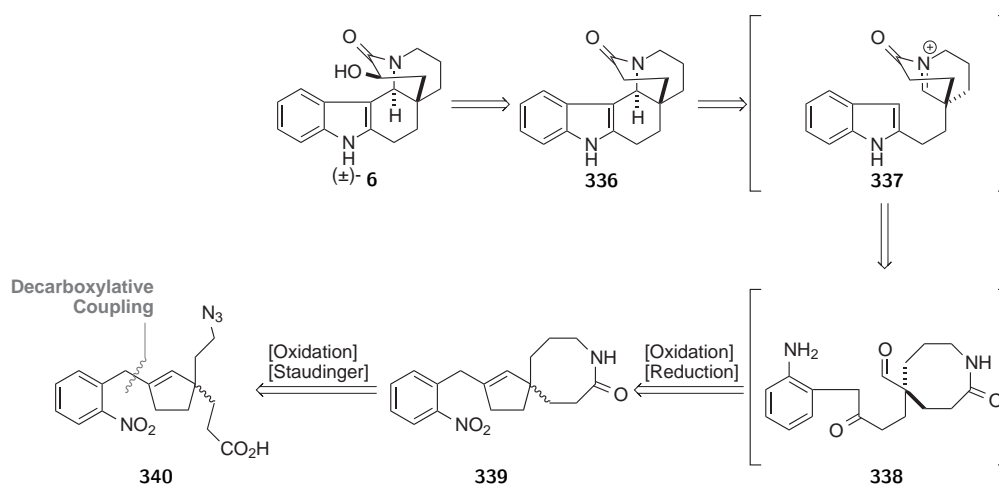


Scheme 5.5 – iORC cyclization: Diastereoselectivity issue

The regioselectivity should not be troublesome, as other similar transformation happened with good yields, but almost all the examples gave *cis*-selectivity. Which mean the diastereoselectivity will be a problem. If we manage to control these two factors, we would obtain intermediate 335, which could be transformed in few steps into the racemic alkaloid (±)-6.

On a retrosynthetic perspective, (±)-kopsihainanine A 6 could be obtained from 336 in a similar way as the previous syntheses (Scheme 5.6). To force the *trans*-selectivity, we de-

cided to already have the amide bond on iminium intermediate **337**. This way, the cyclization in *trans* should be favoured. This amide formation is not a redundant step for the synthesis, as it is present in the natural product. Following our *i*ORC procedure, this iminium could arise from the putative dicarbonyl intermediate **338**. As the previous cases, forming the aniline from a nitrophenyl moiety, and the two carbonyl by an ozonolysis resulted in synthon **339**. A Staudinger lactamization from the azide and a carboxylic acid leads us to precursor **340**. This precursor could be reached *via* the same palladium-catalyzed decarboxylative coupling as the aspidospermidine, using slightly different starting materials.



Scheme 5.6 – Retrosynthesis of kopsihainanine A 6

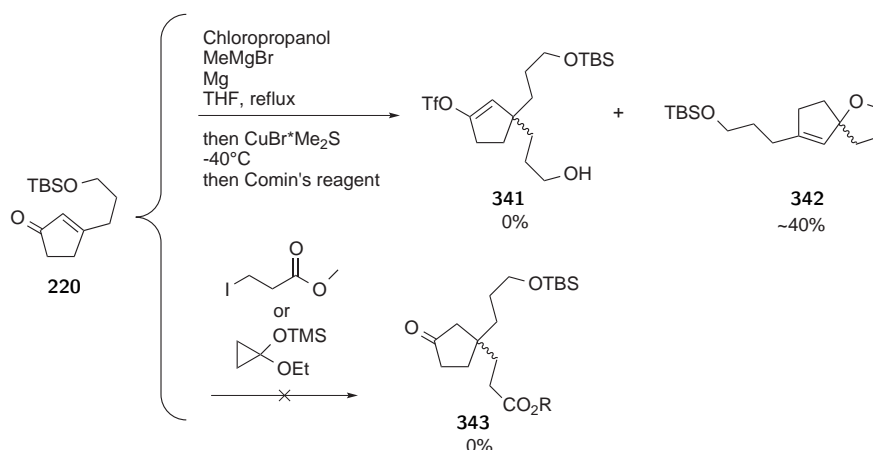
5.3 Synthetic studies of Kopsihainanine A

In order to reach precursor **340**, we planned to start from **220** (*cf.* Chapter 3). A chain with a carboxylic acid precursor should be added (Scheme 5.7). Our first attempt was with Normant-type Grignard reagent,⁸⁹ which did not give desired product **341** but only yielded 1,2-adduct **342**. Organozinc generated either from methyl 3-iodopropanoate¹⁴⁵ or from (1-Ethoxycyclopropoxy)trimethylsilane¹⁴⁶ resulted in messy reactions or degradations. Desired 1,4-adduct **343** was never observed.

To avoid these difficulties, we chose to perform a 1,4 homoallylation using similar conditions as before and oxidize the olefin on a late stage. Trapping of the enolate with Comins' reagent gave vinyl triflate **344**. Our palladium-catalyzed decarboxylative coupling between

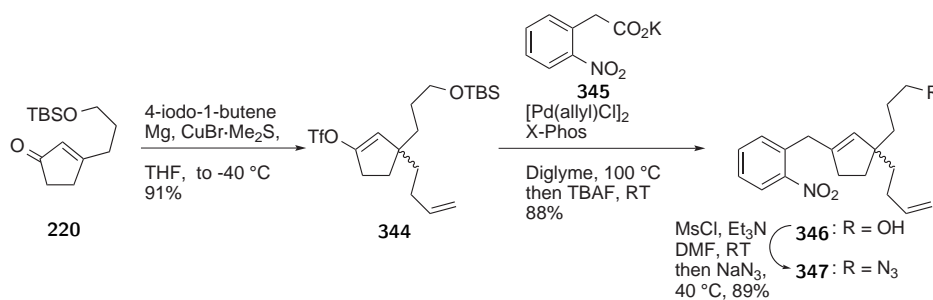
¹⁴⁵ a) Charette, A. B.; Beauchemin, A.; Marcoux, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 5114–5115; b) Wang, J.-X.; Fu, Y.; Hu, Y.; Wang, K. *Synthesis* **2003**, *35*, 1506–1510; c) Tamaru, Y.; Gavryushin, A.; Knochel, P. In *e-EROS Encycl. Reagents Org. Synth.* John Wiley & Sons, Ltd: 2009

¹⁴⁶ Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83–86



Scheme 5.7 – attempts of direct 1,4-Addition

triflate **344** and potassium salt **345** afforded compound **346** in good yield. We could observe the improvement of the yield compared to our previous syntheses due to the low steric hindrance of this potassium salt. One-pot azidation of the alcohol gave intermediate **347**.

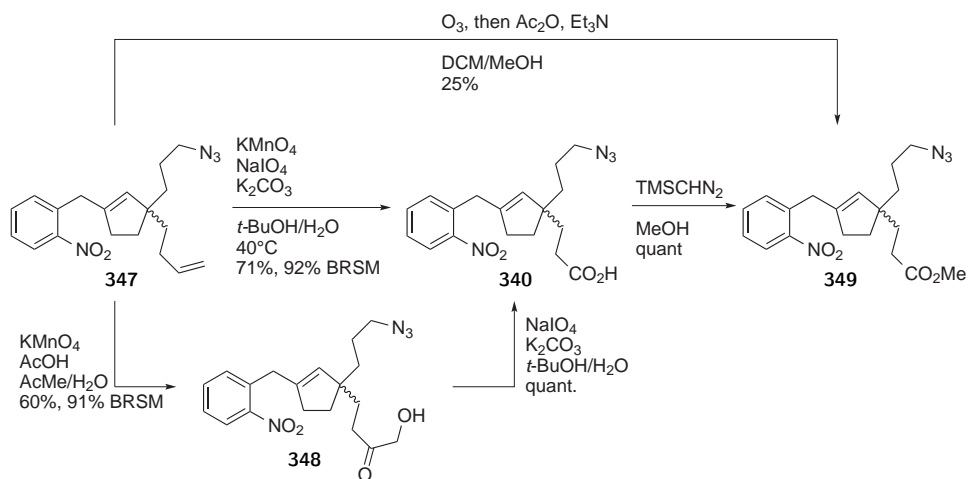


Scheme 5.8 – Synthetic studies of kopsihainanine A 6

At this stage, an oxidation of the terminal olefin of **347** into the methyl ester is required. The presence of the second olefin made this oxidation quite challenging (**Scheme 5.9**). Ozonolysis under non-reductive conditions ($\text{Ac}_2\text{O}/\text{Et}_3\text{N}$) gave directly the methyl ester **349** with 25% yield. When a Lemieux-Johnson or Lemieux Von-Rudloff oxidation were attempted,¹⁴⁷ we could notice that a catalytic amount of osmium or manganate was not sufficient, no matter how much of the co-catalyst was used. No conversion was observed until more than 1.0 equivalent of the metal was added. And as soon as the stoichiometry was passed, the reaction occurred. This finding was unexpected and suggested that the first equiv-

¹⁴⁷ a) Lemieux, R. U.; Rudloff, E. V. *Can. J. Chem.* **1955**, 33, 1701–1709; b) Rudloff, E. V. *Can. J. Chem.* **1955**, 33, 1714–1719; c) Wee, A. G.; Liu, B. In *e-EROS Encycl. Reagents Org. Synth.* John Wiley & Sons, Ltd: Chichester, UK, 2001; d) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc. Chem. Commun.* **1985**, 1359–1362; e) Majetich, G.; Hull, K. *Tetrahedron* **1987**, 43, 5621–5635

alent of oxidant was somehow complexed with the substrate. Potassium permanganate being cheaper and safer than osmium tetroxide, we focused our effort on the Lemieux Von-Rudloff oxidation ($\text{KMnO}_4/\text{NaIO}_4$).



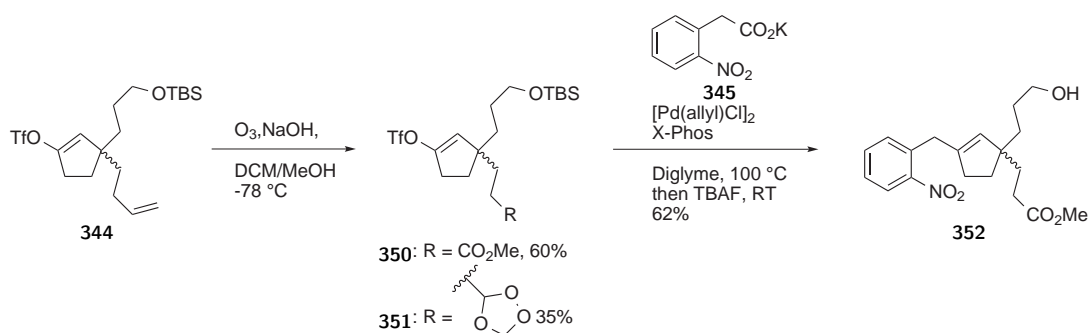
Scheme 5.9 – Lemieux Von-Rudloff Oxidation

As shown in **Scheme 5.9**, the hydroxyketone **348** was first formed, and then oxidized by NaIO_4 or KMnO_4 into the carboxylic acid **340**. Use of TMS-diazomethane gave the methyl ester **349**. The optimization of the permanganate oxidation was somehow tedious. The first oxidation of the terminal olefin into the hydroxyketone happened in few second. The subsequent oxidation into the carboxylic acid was much slower. If harsher conditions were applied, the trisubstituted olefin started to get oxidized.

On small scale, the standard one-pot Lemieux Von-Rudloff worked well, giving carboxylic acid in 71% yield and 91% BRSM. But when the reaction was run on 0.5-1.5 mmol, the yield dropped to 40-50%. A more robust version of this oxidation could be done stepwise on 3 mmol scale, using only KMnO_4 to reach cleanly the hydroxyketone, and after work-up oxidising it into the carboxylic acid using only NaIO_4 .

As an attempt to improve the overall yield, oxidation of homoallyl group was tried before the decarboxylative coupling (**Scheme 5.10**). A short screening of previously tried conditions showed us that enolate moiety of intermediate **344** was highly sensitive to oxidation. Fortunately, careful ozonolysis in the presence of NaOH could afford methyl ester **350** along with minor quantity of ozonide **351**. As the terminal olefin was slightly more reactive than the vinyl triflate, if ozone was highly diluted and added slowly, the reaction could be stopped when all the terminal olefin had reacted without formation of overoxidation products.

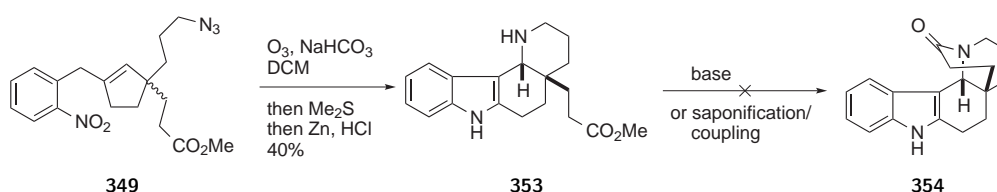
Decarboxylative coupling with potassium salt **345** afforded ester derivative **352**. As the



Scheme 5.10 – Oxidation pathway employing ozone

overall yield of both decarboxylative coupling and oxidation was lower than before, we kept the pathway coupling-azidation-Lemieux-von-Rudloff.

From methyl ester **349**, preliminary studies on our *i*ORC showed that cyclization would occur exclusively from C7, no trace of the attack from nucleophilic N1 was observed. Unfortunately, the *cis*-selectivity was observed as predicted. Optimized conditions used zinc in acidic medium to reduce the azide and nitro groups, and afforded 40% of intermediate **353**. We were wondering if lactamization of **353** into **354** could take place. However, only degradation were observed when bases were applied,¹⁴⁸ tautomeric catalyst (hydroxypyridine)¹⁴⁹ or coupling on the aminoacid derivative of **353**.¹⁵⁰

Scheme 5.11 – *i*ORC on precursor **349**

As the regioselectivity was not an issue, we pursue our plan to form lactam **339**. Even if eight-membered ring are not easy to make, the Thorpe-Ingold effect of the spirocyclopentene should help the cyclization.¹⁵¹ From acid **340**, direct anhydrous Staudinger lactamization¹⁵² or Staudinger reduction followed by coupling reaction¹⁵³ did not provided the desired lactam.

¹⁴⁸ Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268–3272

¹⁴⁹ Rony, P. R. *J. Am. Chem. Soc.* **1969**, *91*, 6090–6096

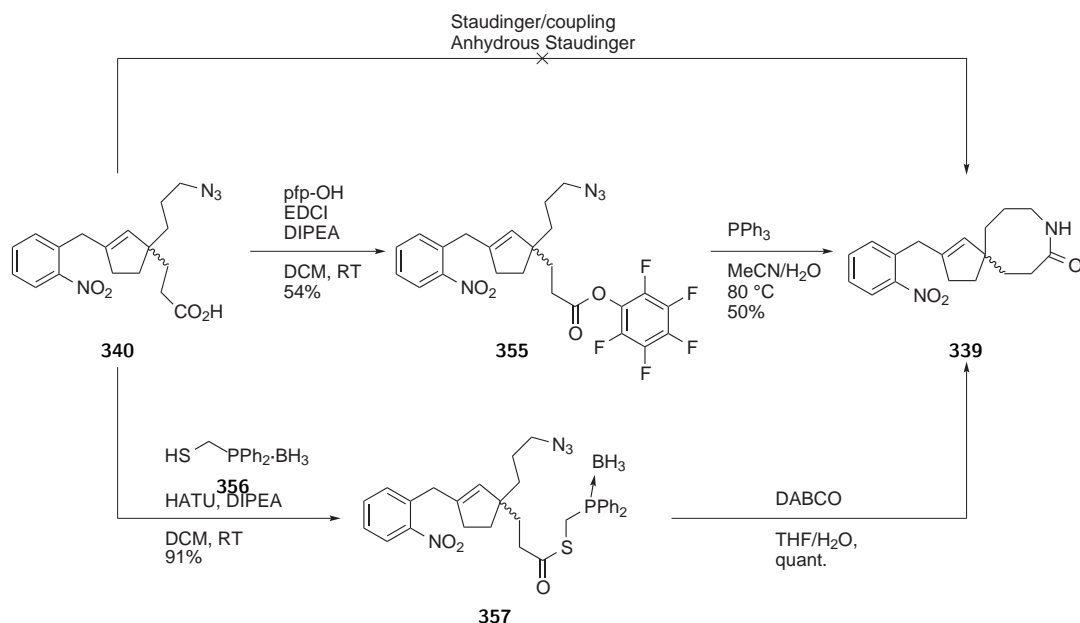
¹⁵⁰ Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369–2376

¹⁵¹ Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106

¹⁵² Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12036–12040

¹⁵³ a) Yamamoto, Y.; Furuta, T. *Chem. Lett.* **1989**, *18*, 797–800; b) Szemes, F.; Rybár, A.; Uhrin, D.; Solčániová, E. *Chem. Pap.* **1991**, *45*, 667–675; c) Falcone, B. V.; Creighton, C. J.; Parker, M. H.; Reitz, A. B. *Synth. Commun.* **2008**, *38*,

Pentafluorophenyl ester **355** was made with EDCI as coupling agent, and Staudinger reaction afforded lactam **339**.¹⁵⁴ However, the combined yield of both step was low.



Scheme 5.12 – Different lactamization pathways

Using Maarseveen's Staudinger ligation methodology,¹⁵⁵ the coupling between thio-phosphine ligand **356** and acid **340** afforded thioether **357** with good yield if HATU and DIPEA were used. Releasing the phosphine with DABCO¹⁵⁶ allowed the intramolecular Staudinger lactamization of **357** to take place, affording lactam **339** quantitatively.

Having lactam **339** in hand, optimization of our *i*ORC could be done. During the oxidation step, the presence of base (NaHCO_3) gave dirty mixtures. When Me_2S was used as reducing agent, careful analysis of the crude mixture revealed the presence of the two intermediate **358** and **359**. The ratio between them was dependant on the conditions. Similar cyclizations were already observed by Schultz and co-workers in 1999.¹⁵⁷ A surprising observation was the formation of **358** as major product if Me_2S was used, and **359** if PPh_3 was

411–418

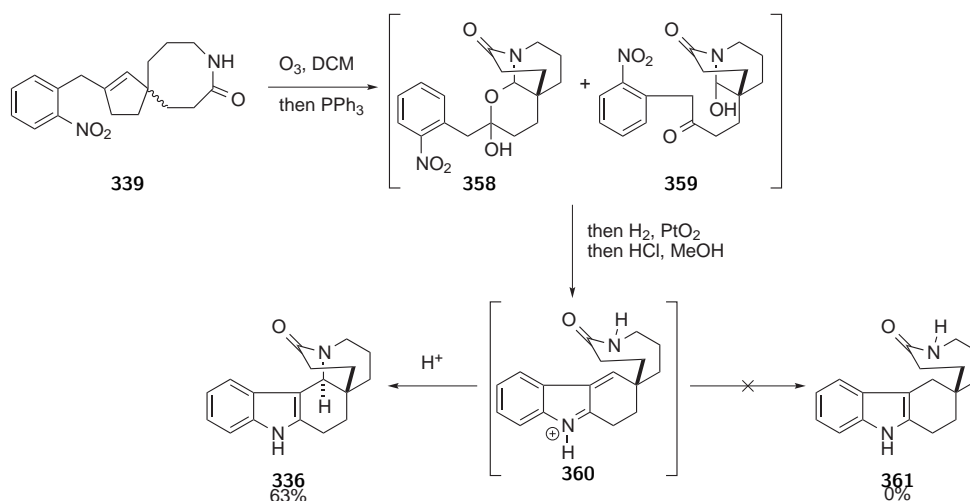
¹⁵⁴ For macrolactamization of Pentafluorophenyl ester and azide into eight-membered ring lactams, see a) Koizumi, Y.; Kobayashi, H.; Wakimoto, T.; Furuta, T.; Fukuyama, T.; Kan, T. *J. Am. Chem. Soc.* **2008**, *130*, 16854–16855; b) Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383–2388

¹⁵⁵ a) David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4373–4375; Other examples of the use of this thiophosphane ligand, see b) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Org. Chem.* **2002**, *67*, 4993–4996; c) Parkhouse, S. M.; Garnett, M. C.; Chan, W. C. *Bioorg. Med. Chem.* **2008**, *16*, 6641–6650; d) Carroll, L.; Boldon, S.; Bejot, R.; Moore, J. E.; Declerck, J.; Gouverneur, V. *Org. Biomol. Chem.* **2011**, *9*, 136–140

¹⁵⁶ Dang, H.-S.; Diart, V.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1033–1041

¹⁵⁷ Schultz, A. G.; Dai, M. *Tetrahedron Lett.* **1999**, *40*, 645–648

used. The cleanest reaction happened when the ozonide was quenched with PPh_3 , giving exclusively **359**. During the optimization of the reduction of nitro group, we observed that most reduction conditions afforded unstable side-product **361**, with only traces of desired product **336**. Reduction with zinc or TiCl_3 in acidic media afforded **361** as only product. This side-product would be due to the reactive iminium intermediate **360**. The strongly activated olefin was easily reduced and the difficulty was to find reducing conditions strong enough to reduce the nitro group, but mild enough to allow intermediate **360** to cyclize into **336** before being reduced to **361**. Raney Nickel Hydrogenation in acidic conditions seemed to give desired product **336** without the side-product, but in low yield. If Raney Nickel was used in neutral or basic anhydrous conditions (wash of the raney nickel with dry THF), an unstable polar intermediate that couldn't be analysed was formed. If acid was added on this unknown intermediate after full conversion, this intermediate would cyclized into desired product **336**. Using this method, the yield could be pushed to 58%, but the yields were not reproducible, due to the difficulties to control the stoichiometry of the Nickel (slurry solution in H_2O). Adams' catalyst showed similar activity as Raney nickel, but could be weighted. As a results, the yield could be improved to 63% as a single diastereoisomer with no traces of side-product **361**.



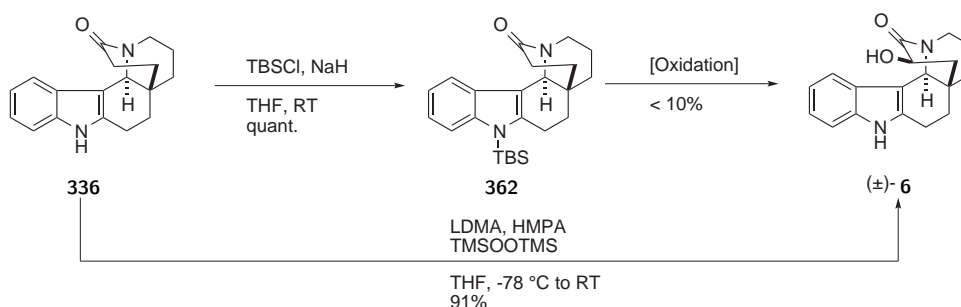
Scheme 5.13 – *i*ORC on precursor **339** and endgame

For the end game (**Scheme 5.14**), we first considered to protect the indole moiety of **336** *in situ* with TMS ¹⁵⁸ or COO^- ,¹⁵⁹ followed by the oxidation conditions used by She (LDA, O_2 , $\text{Na}_2\text{S}_2\text{O}_3$), and removal of the protecting group in the work-up. Unfortunately, the oxidation was not successful. We decided to first optimise the oxidation with a more stable

¹⁵⁸ a) Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Heterocycles* **1991**, 32, 685–692; b) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. L.; Tester, J. W. *Org. Biomol. Chem.* **2005**, 3, 3767–3781

¹⁵⁹ Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, 26, 5935–5938

protecting group, like TBS (**362**). Surprisingly, every oxidations resulted in deprotection of the indole. When the protected indole **362** was treated with strong base at -50°C , deprotection occurred. Similar results were observed with Boc or TIPS-protected indole. However, we noticed that even if the deprotected indole was present, the oxidation still occurred with low yield. We decided to directly optimize the oxidation on the free indole. α -Hydroxylation of amide are well described in literature, and many conditions exists.¹⁶⁰ Deep screening of this last oxidation step were performed, and optimum conditions happened to be lithium dimethylamine (LDMA), HMPA and bis(trimethylsilyl)peroxide. Under these conditions, the desired alkaloid was obtained with 91% yield as single diastereoisomer. Using LDMA as the base was essential for the success of the above transformation, as other bulkier bases led essentially to no reaction or degradation depending on the nature of the oxidant. The result is in line with She's observation that the amide enolate is difficult to form because of the steric hindrance around the α -pseudoaxial proton of the amide.



Scheme 5.14 – Final oxidation toward (±)-kopsihainanine A **6**

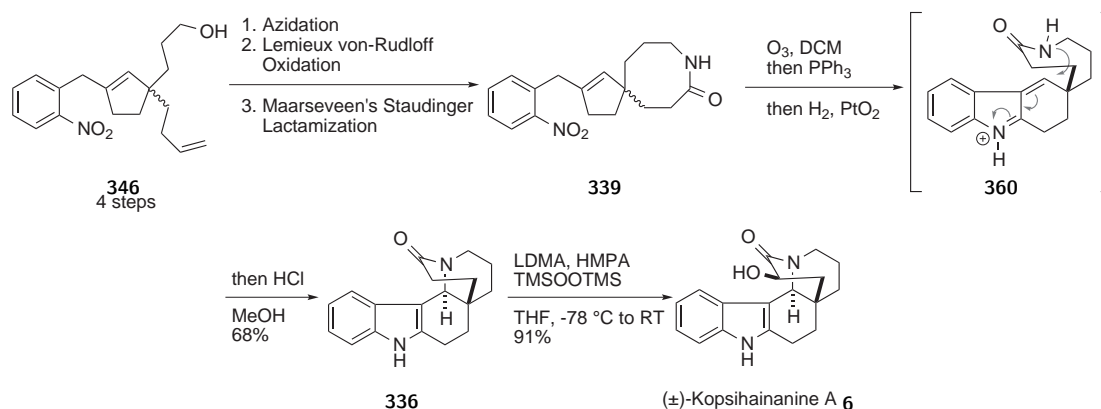
5.4 Conclusion

In summary, the total synthesis of (±)-kopsihainanine A **6** was accomplished (**Scheme 5.15**).¹⁰⁰ Once again, our palladium-catalyzed decarboxylative coupling afforded an intermediate bearing all the carbons needed for the natural product (**346**). An azidation, followed by regioselective Lemieux von-Rudloff oxidation of the terminal double bond and a Staudinger lactamization developed by Maarseveen and co-workers allowed us to reach eight-membered lactam **339** efficiently. Finally, our *i*ORC could cyclize on C7 with a *trans*-selectivity (through intermediate **360**) to afford 18-dehydroxykopsihainanine A **336**. Oxidation of **336** was performed with LDMA and bistrimethylsilylperoxide to afford (±)-kopsihainanine A **6** in 91% as a single diastereoisomer. We demonstrated that selectivity

¹⁶⁰For a review, see Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. In *Org. React.* 2004; Vol. 62, p 1, , and references cited within

of the cyclization could be achieved by design of our *i*ORC precursor. Macrolactamization of precursor reversed the selectivity of our *i*ORC process from *cis* to *trans*.

Oxidation with a non hindered base as LDMA afforded the final alkaloid in good yield without any need for protection of the indol nitrogen. This work showed us the importance to design the *i*ORC precursor in order to select the *cis/trans* diastereoselectivity of the cyclization.



Scheme 5.15 – *i*ORC on precursor **339** and endgame

Approach Towards the Total Synthesis of Kopsinitarine E

In 1994 and 1996, Kam and co-workers discovered in the leaves of Malayan tree *Kopsia teoi* four unprecedented cage-like structures they called kopsinitarine A-D **363-366** (Figure 6.1).¹⁶¹ A decade later, they reported kopsinitarine E **7**, found in the same plant specie.¹⁶²

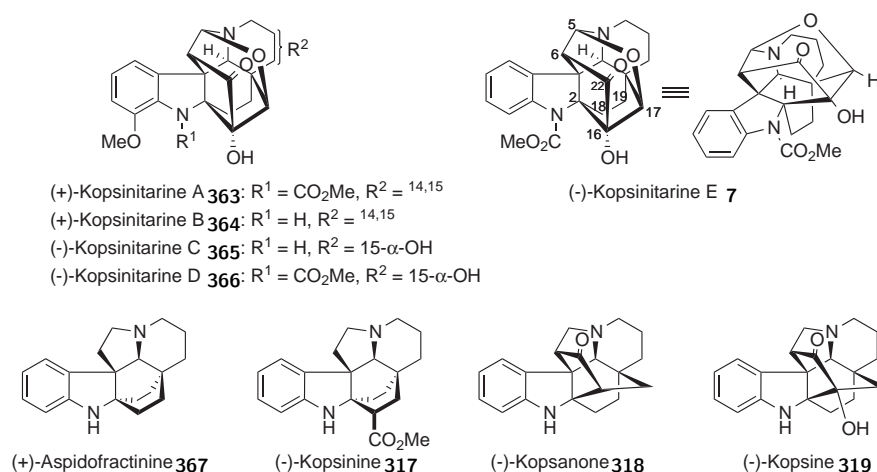


Figure 6.1 – Kopsinitarine A-E and some related alkaloids

These alkaloids possess the *Kopsia* pentacyclic skeleton, with the C18 connected to the C2 position. C17 is oxidized to create an additional bridged hemiaminal ether moiety with oxidized C5. C16 is also oxidized and formed a bridged α -hydroxy-ketone with the C22 carbonyl, which itself is connected to C6. As a result, these structures form congested cage-like skeletons. The complexity of such highly oxidised structures makes their synthesis a fascinat-

¹⁶¹a) Kam, T.-S.; Yoganathan, K.; Chuah, C.-H. *Tetrahedron Lett.* **1994**, 35, 4457–4460; b) Kam, T.-S.; Yoganathan, K.; Wei, C. *J. Nat. Prod.* **1996**, 59, 1109–1112

¹⁶²Lim, S.-H.; Sim, K.-M.; Abdullah, Z.; Hiraku, O.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, 70, 1380–1383

ing challenge. To this day and to the best of our knowledge, no total synthesis of kopsinitarine A-E has been reported.

However, some related alkaloids were synthesized. For example aspidofractinine **367**¹⁶³ and kopsinine **317**^{65,163b,164} possess a similar C2-C16 connection, but not the bridged hemiaminal or bridged ketone of the kopsinitarine structure. Kopsanone **318**^{65,163b,165} and kopsine **319**¹³⁸ are to our knowledge the closest structures to the kopsinitarine skeleton that have been synthesized.

No reports on the potential biosynthetic pathway of kopsinitarines skeletons are reported. Nevertheless, there is one report from Kam and co-workers in 2001,¹⁶⁶ in which they isolated kopsilosine C **368** (an oxidized version of kopsinine **317**) from *Kopsia singaporensis*,¹⁶⁷ and used electrochemical oxidation to reach the cage-like structure of the kopsinitarine skeleton (**Scheme 6.1**). By submitting natural product **368** to an anodic oxidation with 0.95 V in an attempt to form dimeric indole alkaloid structures, they obtained 12-demethoxykopsinitarine D **371** as a side-product with 17% yield.

From a mechanistic point of view, they suggested first the oxidation of the tertiary amine to form iminium intermediate **369**, from this intermediate, equilibration of this iminium moiety to its enamine form, followed by intramolecular enamine-ester reaction, creates the C6-C22 bond. However from this point, in order to have cyclisation of the C17 alcohol on the iminium, epimerization of the C17 center is required. *Via* which mechanism this epimerization occurs is not known. Once iminium **370** is reached, the alcohol on the C17 position and the iminium moiety have the proper conformation for cyclisation to reach 12-demethoxykopsinitarine D **371**. Such a transformation sequence could be similar to the biosynthetic pathway.

6.1 Synthetic Studies of Kopsinitarine E

The skeleton of kopsinitarine alkaloids, with its congested cage-like structure and the high number of C-O bonds it possesses represents an appealing challenge. Hence we chose

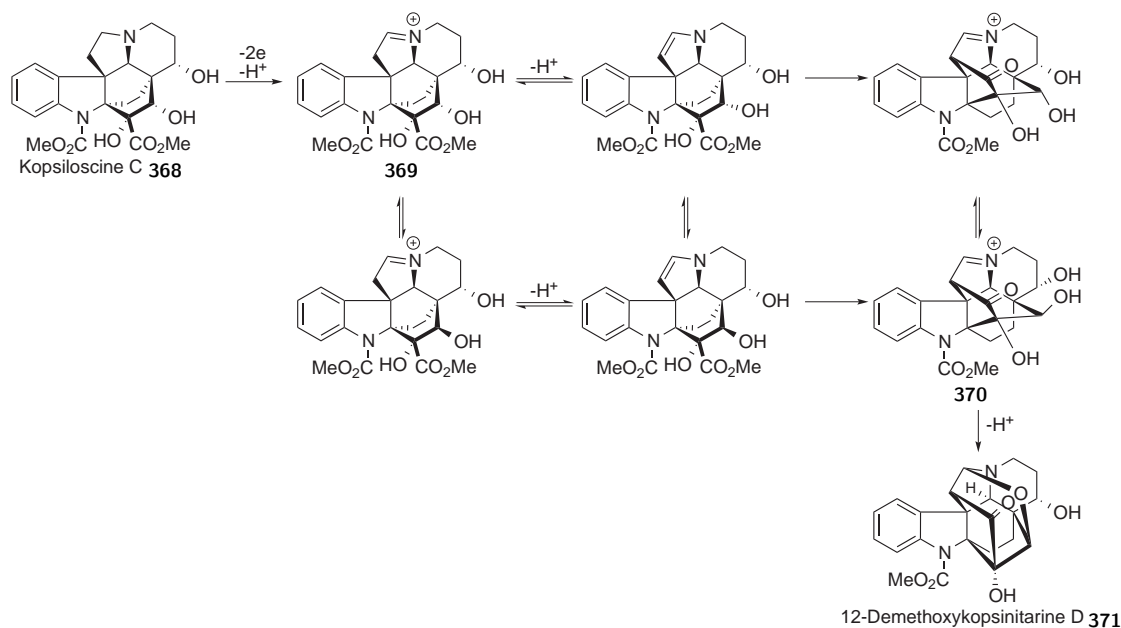
¹⁶³See a) Kinoshita, H.; Ohnuma, T.; Oishi, T.; Ban, Y. *Chem. Lett.* **1986**, 15, 927–930; b) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, 74, 6035–6041; c) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, 50, 4790–4796

¹⁶⁴See a) Magnus, P.; Brown, P. *J. Chem. Soc. Chem. Commun.* **1985**, 184–186; b) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.-i.; Yamamoto, Y.; Tomioka, K. *Chem. Asian J.* **2012**, 7, 2196–2198; c) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.-i.; Yamamoto, Y.; Tomioka, K. *Tetrahedron* **2013**, 69, 3264–3273; d) Xie, J.; Wolfe, A. L.; Boger, D. L. *Org. Lett.* **2013**, 15, 868–870

¹⁶⁵Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, 105, 2086–2087

¹⁶⁶Kam, T.-S.; Lim, T.-M.; Tan, G.-H. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1594–1604

¹⁶⁷Subramaniam, G.; Kam, T. S. *Helv. Chim. Acta* **2008**, 91, 930–937



Scheme 6.1 – Electrochemical cyclization of kopsinitarine skeleton

kopsinitarine E **7** as our next target. Its structure is highly related to aspidospermidine. We were therefore convinced that the *i*ORC method would allow us to readily form the core structure of this alkaloid. The difficulty lies in the high number of reactive sites this alkaloid shows (α -hydroxyketone, indole, hemiaminal ether). Targeting such complex alkaloid would require to have a highly functionalized *i*ORC precursor. Therefore, we planned to use this synthesis to investigate the sensitivity of our key step towards the presence of a large number of functional groups.

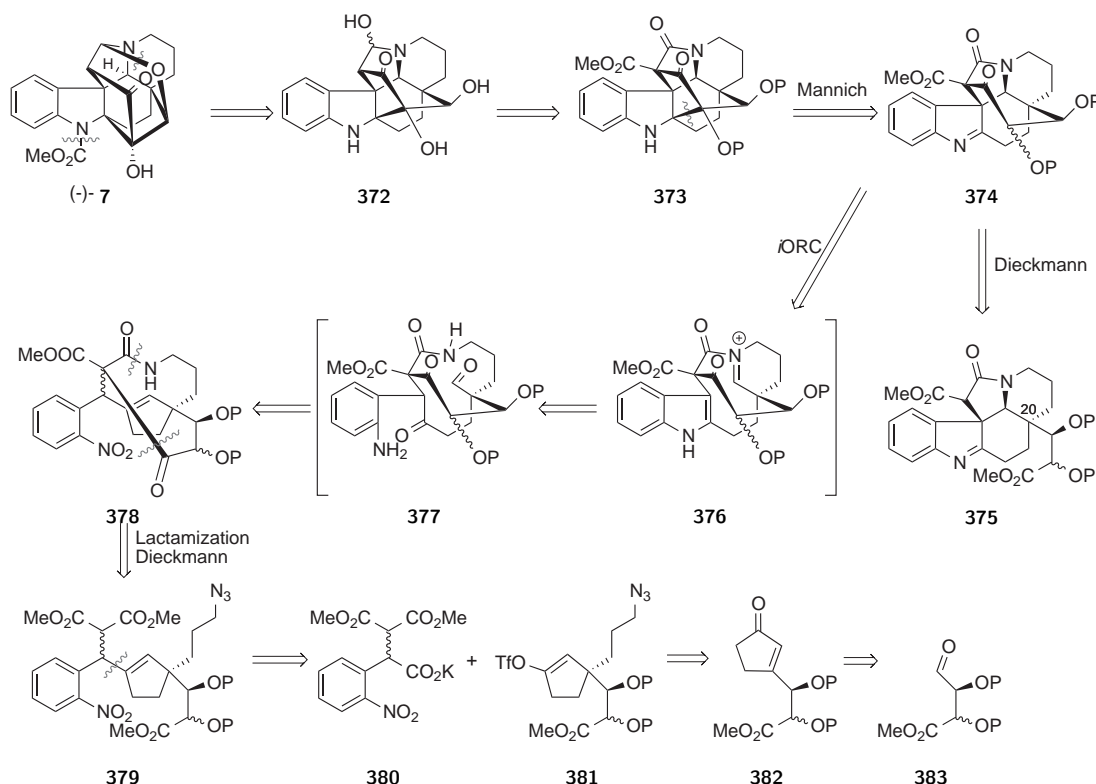
6.1.1 Retrosynthetic Approach

From a retrosynthetic perspective (Scheme 6.2), kopsinitarine E **7** could arise from precursor **372** through indole protection and cyclization of the C17 alcohol on the C5 hemiaminal.¹⁶⁸ This cyclization would require the correct stereochemistry on C17. Intermediate **372** would come from **373** through reduction of the amide moiety,¹⁶⁹ decarboxylation of quaternary ester and deprotection of the diol moiety. The indoline of **373** could be the result of an intramolecular Mannich reaction on indolenine **374**. This step would mean that the stere-

¹⁶⁸For the formation of hemiaminal and hemiaminal ether in C5 position, see a) Kam, T.-S.; Lim, T.-M.; Choo, Y.-M. *Tetrahedron* **1999**, 55, 1457–1468; b) Hájíček, J. *Collect. Czechoslov. Chem. Commun.* **2007**, 72, 821–898; c) Lim, K.-H.; Low, Y.-Y.; Tan, G.-H.; Kam, T.-S.; Lim, T.-M. *Helv. Chim. Acta* **2008**, 91, 1559–1566

¹⁶⁹For selective reduction of amide in the presence of ketone, see Preparation of Taxol and Docetaxel Through Primary Amines. Patent, WO9623780 (A1), 1996

ochemistry of the C16 carbon before this step is not relevant for our synthesis. From the previous *i*ORC processes described in **Chapter 5**, we knew that controlling the diastereoselectivity of our key domino process would be challenging. To force the cyclization of the fused [6,6] ring system in a *trans* fashion, we needed to already have the connection between C6 and C22. If we disconnect this bond (Dieckmann cyclization), any *i*ORC to form precursor **375** would give the undesired *cis* selectivity. To circumvent this, we have to perform the *i*ORC before this disconnection. Following our *i*ORC, indolenine **374** could result from the cyclization of iminium **376**. This structure would come from aldehyde intermediate **377**, which in turn would arise from the ozonolysis and reduction of nitroaryl intermediate **378**.



Scheme 6.2 – Retrosynthetic analysis of kopsinitarine E 7

This key intermediate could be reached from a Dieckmann condensation and Staudinger lactamization of azide precursor **379**. For the lactamization, saponification of one of the methyl esters of the malonate moiety is needed. Theoretically, it should be easier to saponify a malonate ester than the C20 methyl ester.¹⁷⁰ We planned to reach intermediate **379** from potassium salt **380** and vinyl triflate **381** via our palladium-catalyzed decarboxylative coupling as used in our previous syntheses. This vinyl triflate could result from enone **382**, using conjugated 1,4-addition and enol trapping with Comins' reagent. A Stetter reac-

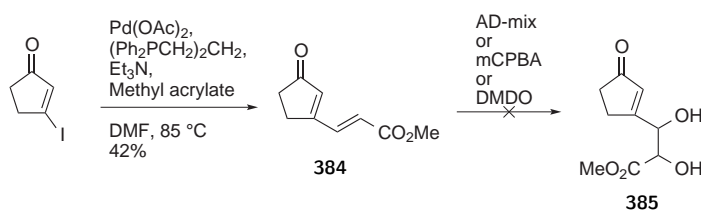
¹⁷⁰ Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, 67, 5269–5278

tion¹⁷¹ followed by aldol condensation could form enone **382** from aldehyde **383**. We are hoping that the diol moiety on enantiopure enone **382** would help direct the nucleophile during the conjugate addition and allow us to form the quaternary center of vinyl triflate **381** in a diastereoselective fashion.

The choice of protecting group on the diol moiety would depend on the stereochemistry used. Dieckmann condensation to afford **378** would be favoured if the ester is close to the 1,3-dicarbonyl position. This conformation will require a different protecting group depending on the diol configuration. If we use a *syn*-diol, as in mesotartaric acid derivatives, a cyclic ketal protecting group would be a good choice. Nonetheless, if the two alcohols are *anti* as in D-tartaric acid, such cyclic protection would push away the ester and the cyclization might become difficult. Two silyl or benzyl groups would therefore be a better choice.

6.1.2 Synthetic Route Towards Cyclopentenone **382**

Our first synthetic attempts towards cyclopentenone derivative **382** started with known 3-iodocyclopentenone¹⁷² (**Scheme 6.3**). A Heck coupling with methyl acrylate afforded **384**.¹⁷³ We anticipated that the trans-disubstituted olefin would be more accessible than the cyclic trisubstituted one and could therefore be oxidized selectively. Unfortunately, all our dihydroxylation attempts with oxidants such as AD-mix, mCPBA or DMDO resulted in messy mixtures and no diol **385** was observed.



Scheme 6.3 – First pathway to enone derivatives

We decided to develop a synthesis to reach derivatives of aldehyde **383**. This strategy was chosen due to the relation between aldehyde **383** and chiral pool reagents such as tartaric acids (meso- or D-), isoascorbic acid, or monosaccharids (L-erythrose or L-threose).

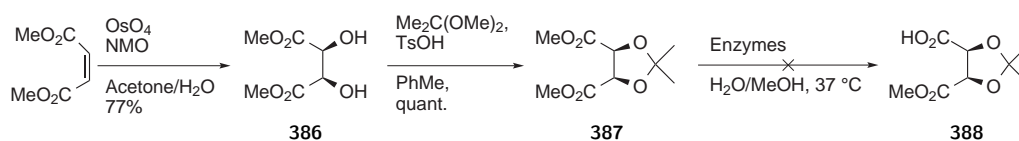
We first planned to reach this aldehyde from dimethyl *meso*-tartrate **386**, synthesized

¹⁷¹ Stetter, H.; Schreckenberger, M. *Angew. Chem. Int. Ed.* **1973**, 12, 81–81

¹⁷² Lemi re, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, 131, 2993–3006

¹⁷³ Duvvuru, D.; Betzer, J.-F.; Retailleau, P.; Frison, G.; Marinetti, A. *Adv. Synth. Catal.* **2011**, 353, 483–493

by dihydroxylation of maleic acid¹⁷⁴ (**Scheme 6.4**). Protection of the diol moiety afforded **387**. A desymmetrisation of **387** was planned using enzymes, as good ee's and yields were reported on many meso-1,2-diester substrates.¹⁷⁵ Even if some examples on five-membered ring meso-1,2-diester showed inferior results,¹⁷⁶ we were confident in this strategy since the D-tartrate derivative of our substrate seemed to be working well.¹⁷⁷ However, the selective saponification of the desired ester function proved unsuccessful after using a range of esterases (porcine liver esterase, hog liver esterase, or liver acetone powder), yielding only traces of the desired acid.



Scheme 6.4 – First pathway to aldehyde derivatives

We then turned our attention to our study on enantiopure derivatives from the chiral pool. As such, we targeted derivatives of unnatural dimethyl D-(-)-tartrate (**Scheme 6.5**). Double TBS protection proceeded smoothly to afford **389**¹⁷⁸ but selective reduction of one of the methyl ester did not afford alcohol **390** or aldehyde **391**. When a reducing agent like DIBAL-H (with or without MgBr₂),¹⁷⁹ BH₃·Me₂S/NaBH₄,¹⁸⁰ or NaBH₄/LiCl¹⁸¹ was used, a messy reaction or reduction of both esters was observed. A second attempt *via* the saponification of one ester¹⁸² followed by BH₃ reduction of the acid to alcohol,¹⁸³ acid chloride for-

¹⁷⁴ Crout, D. H. G.; Gaudet, V. S. B.; Hallinan, K. O. *J. Chem. Soc. Perkin Trans. 1* **1993**, 805–812

¹⁷⁵ See a) Boland, W.; Niedermeyer, U.; Jaenicke, L. *Helv. Chim. Acta* **1985**, 68, 2062–2073; b) Häbich, D.; Hartwig, W. *Tetrahedron Lett.* **1987**, 28, 781–784; c) Van der Eycken, J.; Vandewalle, M.; Heinemann, G.; Laumen, K.; Schneider, M. P.; Kredel, J.; Sauer, J. *J. Chem. Soc. Chem. Commun.* **1989**, 306–308; d) Kocienski, P.; Stocks, M.; Donald, D.; Perry, M. *Synlett* **1990**, 1, 38–39; e) Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J.; Buendia, J. *Tetrahedron Lett.* **1992**, 33, 4889–4892

¹⁷⁶ See a) Gais, H. J.; Buelow, G.; Zatorski, A.; Jentsch, M.; Maidonis, P.; Hemmerle, H. *J. Org. Chem.* **1989**, 54, 5115–5122; b) Rosenquist, A. S.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B.; Kady, M. M.; Christensen, S. B. *Acta Chem. Scand.* **1992**, 46, 1127–1129; c) Renold, P.; Tamm, C. *Tetrahedron Asymmetry* **1993**, 4, 1047–1050

¹⁷⁷ Piel, J.; Boland, W. *Tetrahedron Lett.* **1997**, 38, 6387–6390

¹⁷⁸ Hiyama, T.; Minami, T.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1995**, 68, 364–372

¹⁷⁹ a) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, 56, 417–420; b) Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1996**, 61, 2986–2987

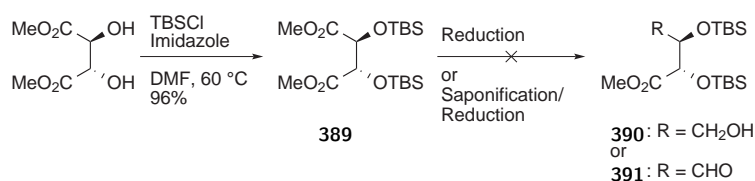
¹⁸⁰ Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 13, 1389–1392

¹⁸¹ Mahadevegowda, S. H.; Khan, F. A. *Tetrahedron* **2013**, 69, 8494–8504

¹⁸² Trost, B. M.; Miede, F. *J. Am. Chem. Soc.* **2014**, 136, 3016–3019

¹⁸³ a) Gutman, A. L.; Boltanski, A. *J. Chem. Soc. Perkin Trans. 1* **1989**, 47–49; b) Homer, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, 120, 7738–7748; c) Candy, M.; Tomas, L.; Parat, S.; Heran, V.; Bienaymé, H.; Pons, J. M.; Bressy, C. *Chem. Eur. J.* **2012**, 18, 14267–14271

mation/reduction,¹⁸⁴ or thioesterification/reduction^{182,185} was attempted. These attempts only resulted in messy reactions with no traces of the desired product observed.



Scheme 6.5 – Aldehyde derivatives from dimethyl D-(-)-tartrate

Another precursor from the chiral pool studied was D-isoascorbic acid, an epimer of vitamin C. A described procedure allowed us to convert this product into 2,3-O-isopropylidene-D-erythrone lactone **392** (**Scheme 6.6**).¹⁸⁶ We were planning to open the lactone with methanol to reach **393** and oxidize the alcohol moiety into an aldehyde. Unfortunately, the basic conditions needed for the opening of the lactone epimerized the product and only *trans* **394** was observed. As the use of Et₃N¹⁸⁷ did not result in good yields, we used sodium methoxide as nucleophile¹⁸⁸ to obtain **394** in 63% yield. Other lactone opening conditions were attempted to avoid this epimerization, such as MeMgCl or Ti(OiPr)₄ in MeOH. Saponification with LiOH in water was also tried. These reactions only resulted in degradation of the starting lactone. The major problem of this strategy lied in the polarity of these compounds. All these derivatives are highly water-soluble and could not be extracted. In addition, the products were too sensitive to be distilled. The oxidation of alcohol **394** proved to be not trivial. Among all the conditions attempted (IBX, DMP, PCC, PDC, TPAP, Swern, Parikh-Doering, Corey-Kim, Oppenauer), the Swern oxidation using DIPEA seemed to be the cleanest. As no aqueous work-up was possible, this aldehyde was used in the following reaction after filtration. Unfortunately, Stetter reaction on aldehyde **395** with NHC catalyst¹⁸⁹ gave **396** with unreproducible results since the stoichiometry and purity of aldehyde **395** could not be controlled.

In an attempt to diminish the polarity and volatility of intermediates **392-396**, we decided to change the acetonide for a more hydrophobic group and chose 4-heptylidene ketal **397** (**Scheme 6.7**). This bulkier protecting group allowed these intermediates to be extracted

¹⁸⁴a) Bartlett, P. a.; Johnson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 7792–7793; b) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.* **1985**, *28*, 1847–1853; c) De Meijere, A.; Bagutski, V.; Zeuner, E.; Fischer, U. K.; Rheinberger, V.; Moszner, N. *Eur. J. Org. Chem.* **2004**, 3669–3678

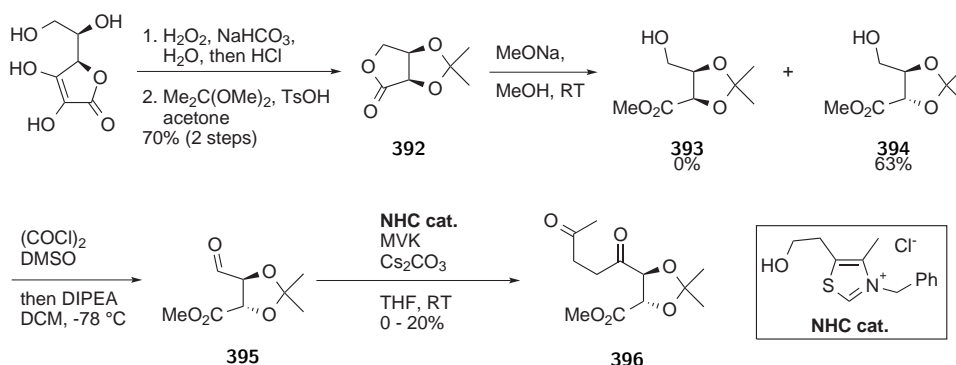
¹⁸⁵D'Aniello, E.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870–4871

¹⁸⁶Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1985**, *63*, 127

¹⁸⁷Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924–5927

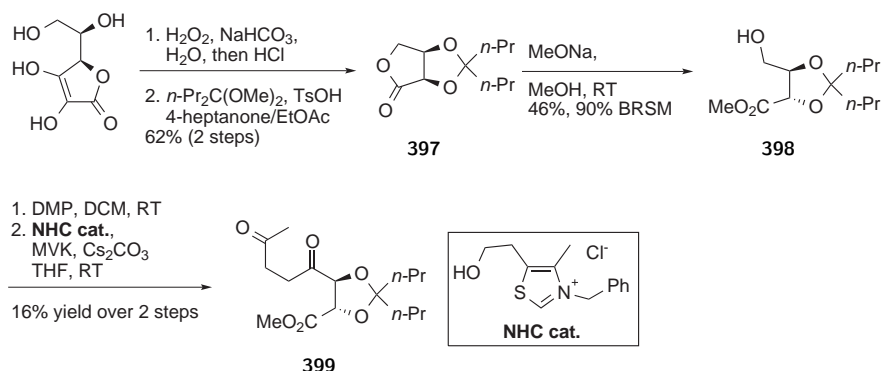
¹⁸⁸Guo, H.; Kim, C. U.; Lee, I. Y.; Mitchell, M. L.; Rhodes, G.; Son, J. C.; Xu, L. Novel HIV reverse transcriptase inhibitors. Patent, WO2009005674 (A2), 2009

¹⁸⁹Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589–5591



Scheme 6.6 – Aldehyde derivatives from D-isoascorbic acid

and purified more easily. Unfortunately, it also seemed to change the equilibrium of the lactone opening reaction and conversion of **397** into ester **398** could not be driven to completion. An optimum yield of 46% of ester **398** was obtained with 90% yield based on recovered starting materials. Optimization of the alcohol oxidation and the Stetter reaction¹⁹⁰ was still ongoing at the end of this thesis. Currently, optimal conditions give 16% yield of desired 1,4-diketone **399**.



Scheme 6.7 – New strategy from D-isoascorbic acid

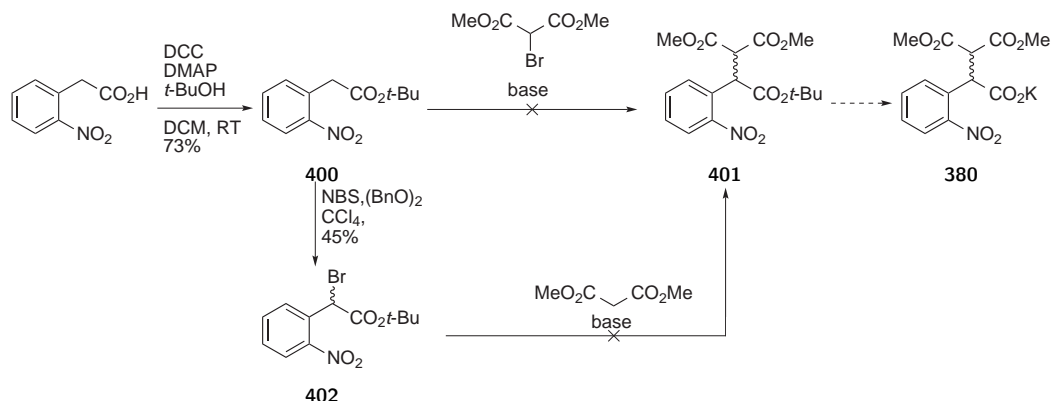
6.1.3 Synthetic attempts towards potassium salt **380**

In order to reach potassium salt **380** we planned to start from ester **400** obtained by esterification of 2-(2-nitrophenyl)acetic acid with *tert*-butyl alcohol (Scheme 6.8).¹⁹¹ Alkylation of **400** with dimethyl bromomalonate to afford **401** were attempted without success. The simi-

¹⁹⁰ Novák, L.; Rohály, J.; Gálik, G.; Fekete, J.; Varjas, L.; Szántay, C. *Liebigs Ann. der Chemie* **1986**, 509–524

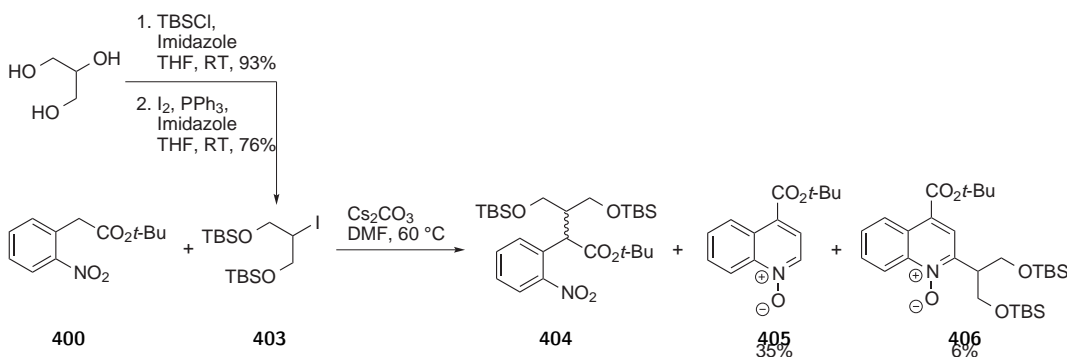
¹⁹¹ Riss, P. J.; Kroll, C.; Nagel, V.; Rösch, F. *Bioorg. Med. Chem. Lett.* **2008**, 18, 5364–5367; See also Flitsch, W.; Rußkamp, P. *Liebigs Ann. der Chemie* **1985**, 1398–1412

lar pKa of both electrophile and nucleophile, caused proton transfer and subsequent degradation of the electrophile. Reversing the reactivity by using dimethyl malonate and bromide derivative **402**¹⁹² proved unsuccessful as well, intermediate **401** was never observed.



Scheme 6.8 – First Pathway to potassium salt **380**

In an attempt to have a more suitable electrophile, we tried using iodide **403** (obtained in two steps from glycerol) to alkylate **400**. To our surprise, instead of adduct **404**, a mixture of quinoline 1-oxide derivatives **405** and **406** were obtained in 41% yield, with **405** being the major product.



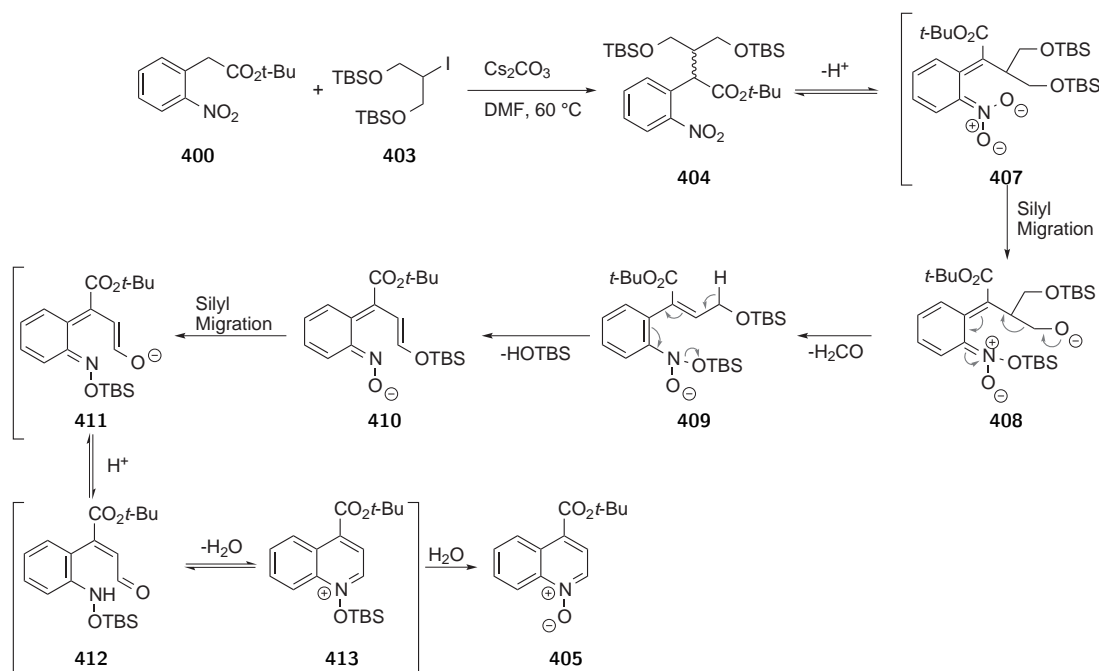
Scheme 6.9 – Second Pathway to potassium salt **380**

A possible mechanism is shown in **Scheme 6.10**. After the desired nucleophilic substitution, deprotonation of the substrate could occur, leading to **407**. This intermediate could undergo a 1,8-O,O-silyl migration to reach **408**. To the best of our knowledge, 1,8-silyl migrations have not been reported yet,¹⁹³ but it is conceivable that the rigidity of the structure **407** allowed the required promiscuity between the silylated alcohol and the nitro group. Silylated

¹⁹²Grewer, C.; Madani Mobarekeh, S. A.; Watzke, N.; Rauen, T.; Schaper, K. *Biochemistry* **2001**, *40*, 232–240

¹⁹³For a review, see Kira, M.; Iwamoto, T. In *Chem. Org. Silicon Compd.* Rappoport, Z., Apeloig, Y., Eds.; John Wiley & Sons, Ltd: 2001; Vol. 3; Chapter 16, pp 0–471, and references cited within

nitro groups have been previously reported.¹⁹⁴ In these studies they underline the weakness of the resulting N–OSi bond, this could explain how we lost both silyl groups during the reaction. We postulated that formaldehyde could be eliminated from **408** to afford anionic intermediate **409**. It would then be conceivable to have elimination of TBSOH from intermediate **410**. This intermediate would again have the correct conformation for a 1,8-silyl migration towards enolate **411**. This structure would be in equilibrium with aldehyde **412**, that could condense into **413**. Hydrolysis of the silyl group would give observed side-product **405**.



Scheme 6.10 – Mechanism hypothesis for the formation of quinoline 1-oxide **405**

Considering the trouble encountered with these derivatives, we decided to modify our strategy. We hoped to reach potassium salt **380** from olefin **414** (**Scheme 6.11**). However, Knoevenagel reaction¹⁹⁵ with ester **400** has proven unsuccessful. Attempts to transform bromide derivative **402** into a phosphine derivative¹⁹⁶ to perform a Wittig-type reaction with dimethyl ketomalonate resulted only in a messy reaction mixture.

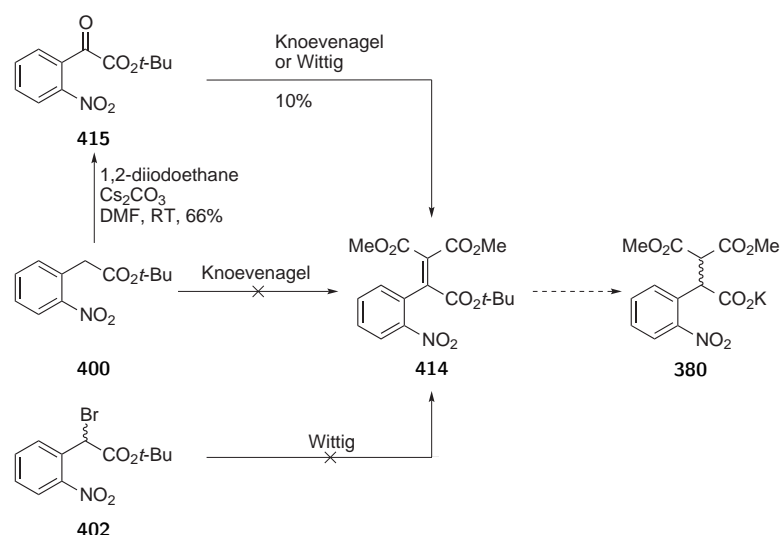
Oxidation of ester **400** to keto ester **415** (unpublished procedure from our labora-

¹⁹⁴ a) Tishkov, A. A.; Dilman, A. D.; Faustov, V. I.; Birukov, A. A.; Lysenko, K. S.; Belyakov, P. A.; Ioffe, S. L.; Strelenko, Y. A.; Antipin, M. Y. *J. Am. Chem. Soc.* **2002**, *124*, 11358–11367; b) Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Russ. Chem. Bull.* **1996**, *45*, 856–862; c) Dilman, A. D.; Lyapkalo, I. M.; Belyakov, P. A.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2000**, *49*, 1649–1650

¹⁹⁵ Craig, R. Synthesis of Electron-Poor tetrasubstituted olefins and their reactions with electron-rich comonomers., Ph.D. Thesis, University of Arizona, 1982

¹⁹⁶ a) Nader, F. W.; Brecht, A.; Kreis, S. *Chem. Ber.* **1986**, *119*, 1208–1216; b) Ianni, A.; Waldvogel, S. R. *Synthesis* **2006**, *38*, 2103–2112

tory),¹⁹⁷ followed by Knoevenagel condensation¹⁹⁸ with dimethyl malonate afforded olefin **414**. However, the yield was low due to the four electron-withdrawing groups making this product highly unstable. When using $\text{TiCl}_4 \cdot \text{THF}$ and pyridine, our best reaction conditions, only 10% yield of olefin **414** was obtained. Horner–Wadsworth–Emmons reaction with phosphorylated derivatives of malonic ester¹⁹⁹ were attempted but did not afford any product **414**.



Scheme 6.11 – Third Pathway to potassium salt **380**

Since potassium salt **380** seemed troublesome to synthesise, we planned to change strategy from our decarboxylative coupling to a Heck, or reductive Heck, reaction (Scheme 6.12). Knoevenagel condensation of dimethyl malonate or Meldrum's acid with 2-nitrobenzaldehyde afforded compounds **417**²⁰⁰ and **418**²⁰¹ respectively. Heck,²⁰² or reductive Heck,²⁰³ reactions with vinyl triflate **419** as model substrate should allow us to reach the scaffold we needed for our synthesis. During this screening, Palladium catalysts ($\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ or $\text{Pd}(\text{PPh}_3)_4$), were tested with or without ligands (PPh_3 , $\text{P}(n\text{Bu})_3$, dppp, dppe,

¹⁹⁷The reported procedures for similar oxidation were unsuccessful in our case. See a) Nagano, T.; Kobayashi, S. *Chem. Lett.* **2008**, 37, 1042–1043; b) Moriyama, K.; Takemura, M.; Togo, H. *Org. Lett.* **2012**, 14, 2414–2417

¹⁹⁸a) Rakufs, K.; Verevkin, S. P.; Keller, M.; Beckhaus, H.-D.; Rüchardt, C. *Liebigs Ann.* **1995**, 1483–1493; b) Sylla, M.; Joseph, D.; Chevallier, E.; Camara, C.; Dumas, F. *Synthesis* **2006**, 38, 1045–1049; c) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, 10, 2801–2804; d) Mukherjee, H.; Martinez, C. A. *ACS Catal.* **2011**, 1, 1010–1013; e) Yu, J.; Li, N.; Chen, D.-F.; Luo, S.-W. *Tetrahedron Lett.* **2014**, 55, 2859–2864

¹⁹⁹a) Cai, X.; Liu, Z.; Yang, Z. *Huaxue Yanjiu* **2006**, 17, 41–43; b) Sal'keeva, L. K.; Taishibekova, E. K.; Minaeva, E. V.; Shibaeva, A. K.; Kasenov, R. Z.; Sal'keeva, A. K.; Muratbekova, A. A. *Russ. J. Gen. Chem.* **2013**, 83, 659–662

²⁰⁰Mase, N.; Horibe, T. *Org. Lett.* **2013**, 15, 1854–1857

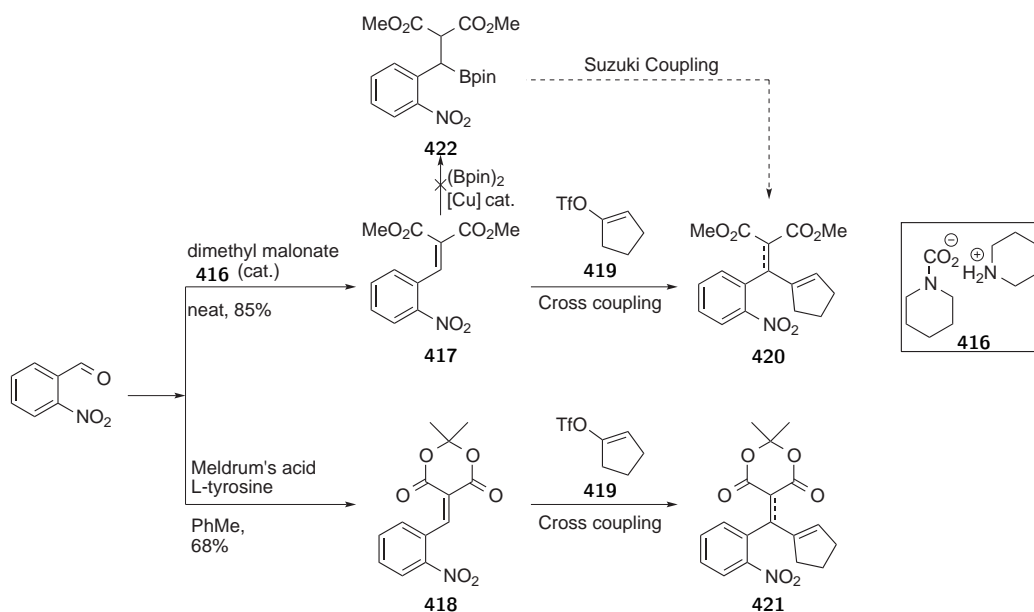
²⁰¹Thirupathi, G.; Venkatanarayana, M.; Dubey, P. K.; Kumari, Y. B. *Org. Chem. Int.* **2012**, 191584

²⁰²See, *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; John Wiley & Sons, Ltd: 2009

²⁰³See Yang, X.; Ma, S.; Du, Y.; Tao, Y. *Chinese J. Org. Chem.* **2013**, 33, 2325

X-Phos, BINAP, NHC or AsPh_3), base (Et_3N , piperidine, or K_2CO_3), additives (TBAC) and hydride sources (HCO_2H or HCO_2Na) in various solvents such as DMF, MeCN or water in oxygen-free conditions. In most attempts, the starting materials were unreactive at less than 60°C . When heated more, one could observe the disappearance of vinyl triflate, suggesting the palladium oxidative addition was working, but the coupling with the olefin never occurred. All vinyl triflate was consumed, while olefin **417** was recovered. In all attempts using olefin **418**, degradation of the olefin occurred at higher temperature ($>80^\circ\text{C}$).

Direct cobalt-catalyzed conjugate addition of triflate reagents into similar activated double bond were attempted,²⁰⁴ as well as alkenylchromium reagents prepared from **419**.²⁰⁵ Both reactions showed only degradations, apparently due to sensitivity of the nitrophenyl moiety to metals.



Scheme 6.12 – Heck, reductive Heck and Suzuki attempts towards **420** or **421**

Finally, synthesis of boronic ester **422** was planned in prevision of a Suzuki coupling with triflate **419**. Unfortunately, copper-catalyzed 1,4-Addition of pinacol diborane to reach **422** has proven unsuccessful.²⁰⁶ The borane was not stable enough and total protodeboronation was observed. We are currently exploring similar couplings with model triflate **419**.

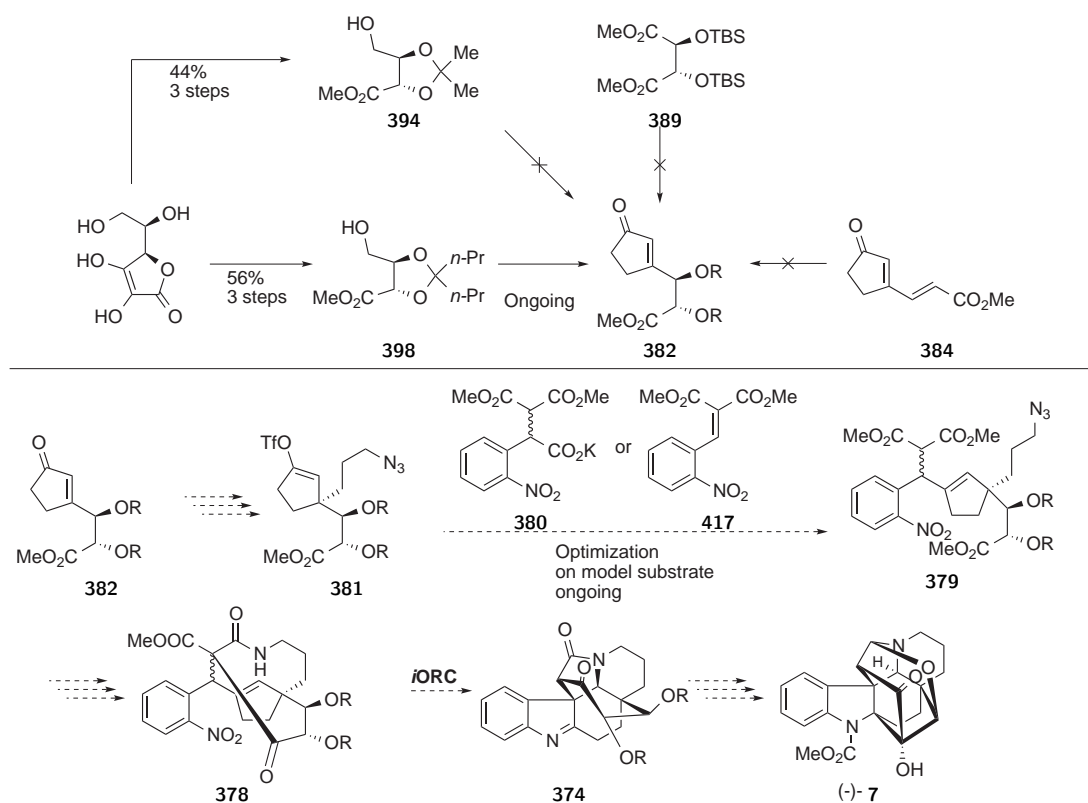
²⁰⁴ a) Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* **2006**, *71*, 6130–6134; b) Amatore, M.; Gosmini, C. *Synlett* **2009**, *20*, 1073–1076

²⁰⁵ Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050

²⁰⁶ a) Ito, H.; Yamanaka, H.; Tateiwa, J.-i.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825; b) Mun, S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887–4889; c) Chea, H.; Sim, H. S.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855–858; d) Thorpe, S. B.; Calderone, J. A.; Santos, W. L. *Org. Lett.* **2012**, *14*, 1918–1921; e) Stavber, G.; Časar, Z. *Appl. Organomet. Chem.* **2013**, *27*, 159–165

6.2 Conclusion

In summary, we studied the total synthesis of kopsinitarine E **7** *via* a palladium-catalyzed coupling/*i*ORC pathway. Several attempts were made for the synthesis of the starting materials needed for the decarboxylative or Heck coupling (**Scheme 6.13**). The formation of enone **382** was attempted from various pathways, such as dihydroxylation of **384**, desymmetrisation of *meso*-tartrate derivative **389**, or from isopropylidene ketal **394**. Unfortunately no success were obtained with these strategies. On the last one, the high solubility of such ketal intermediates caused many difficulties. By changing the protecting group of **394** for the 4-heptylidene ketal **398**, the solubility issue could be solved and preliminary results towards enone **382** seemed promising. The optimisation of the route towards enone **382** is still ongoing. The plan was to convert this enone in vinyl triflate **381** using a conjugate addition and trapping of the enolate with Comins' reagent. Using **417** or **380** as coupling partner with **381**, we planned to reach **379**. This intermediate could be cyclized into **378**, which would be the *i*ORC precursor to reach indole intermediate **374**. Few more reactions should allow us to reach kopsinitarine E **7**. Many attempts were done towards the potassium carboxylate **380**, without success. Alkylation, Wittig-type reaction or Knoevenagel reaction did not succeed to afford desired product. For this reason, the Heck coupling was chosen due to the easy access to olefin **417**. Preliminary results on Heck and reductive Heck using **417** with a known vinyl triflate as model substrate did not presented promising results so far. Nevertheless, as many other coupling reactions are conceivable, this total synthesis is still pursued.



Scheme 6.13 – Current State of the Synthetic Study of Kopsinitarine E

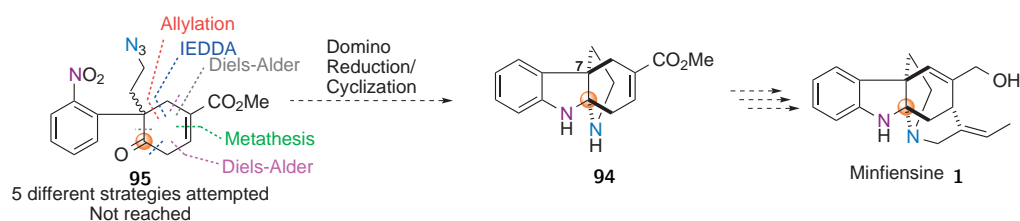
General Conclusion

In summary, we developed a domino sequence called an integrated oxidation/reduction/cyclization (*i*ORC) process allowing us to reach easily the polycyclic core of *Aspidosperma* alkaloids. This reaction uses latent functionalities hidden within molecules, like double bonds, and nitro or azide to generate *in situ* carbonyls and amines which in turn spontaneously condense to form three or more cycles during a skeletal rearrangement process that affords the indole polycyclic skeleton of our target products with a high degree of chemo-, regio-, and diastereoselectivity.

Our first target was minfiensine **1** (**Scheme 7.1**). The goal of this strategy was to reach intermediate **95**, and to perform a domino reduction/cyclization sequence. This represented an unpolished version of our *i*ORC which lacked the oxidation step. Such a reaction should have allowed us to reach aminal **94**, which could supposedly be transformed into minfiensine **1** in a short and straightforward manner. In our synthetic study towards minfiensine **1**, five main strategies were attempted in order to reach key intermediate **95**. Instalment of the quaternary C7 center by allylation or alkylation failed due to the steric hindrance around this center. Cross metathesis of an allyl ketone to install the olefin moiety did not succeed due to the incompatibility of our substrate with metathesis catalysts. Furthermore, the various cycloadditions to afford the cyclohexenone moiety proved unsuccessful. Cyclohexenone structure **95** proved difficult to reach and our synthetic route became too long to remain attractive. It was therefore decided to stop this synthesis and focus on our newly developed *i*ORC.

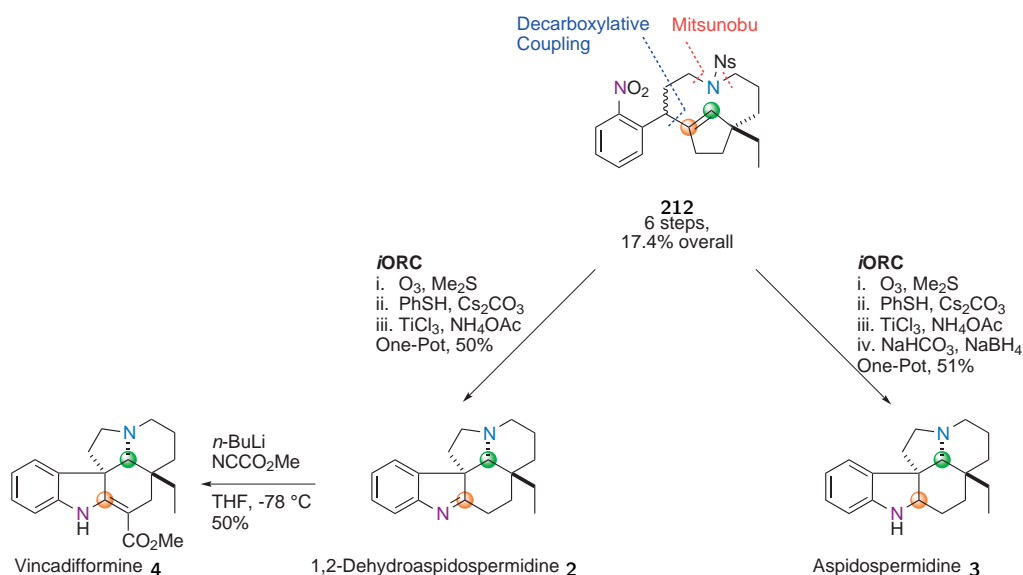
The next studies focused on the use of our domino *i*ORC sequence. We first chose to target aspidospermidine **3** and dehydroaspidospermidine **2** (**Scheme 7.2**). The key macrocycle **212** was reached in only 6 steps and 17.4% overall yield featuring our palladium-catalyzed decarboxylative coupling to build in one step a compound having all the carbons needed for the synthesis of the natural product. Two consecutive Mitsunobu reactions closed the macrocycle needed in our key intermediate **212**. Our key domino process allowed us to reach se-

Chapter 7: General Conclusion



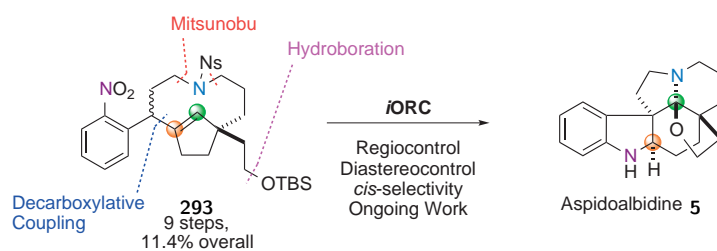
Scheme 7.1 – Summary of the synthetic study towards minfiensine **1** and the different strategies attempted to reach **94**

lectively dehydroaspidospermidine **2** or aspidospermidine **3** with an optimised yield of 50% from **212**. Full diastereocontrol was observed as we formed a *cis*-fused [6,6] ring system. From dehydroaspidospermidine **2**, vincadifformine **4** could be synthesized in one step and 50% yield.



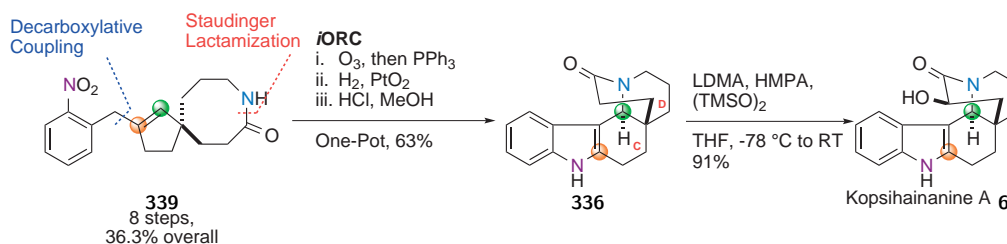
Scheme 7.2 – Summary of the total synthesis of dehydroaspidospermidine **2**, aspidospermidine **3** and vincadifformine **4**

Following a similar synthetic route as for aspidospermidine, we attempted to reach aspidoalbidine **5** with our *i*ORC (**Scheme 7.3**) from macrocycle **293**, obtained in 9 steps and 11.4% overall yield. This macrocycle was obtained using a palladium-catalyzed decarboxylative coupling to link the two main fragments of the molecule and two Mitsunobu reactions to close the ten-membered ring. Anti-Markovnikov hydroxylation of the terminal olefin afforded the primary alcohol moiety of key intermediate **293**. Our key-step is still under development at this time and aspidoalbidine **5** has not yet been reached though we believe this is just a matter of time until we obtain our target structure.



Scheme 7.3 – Summary of the synthetic study towards aspidoalbidine **5**

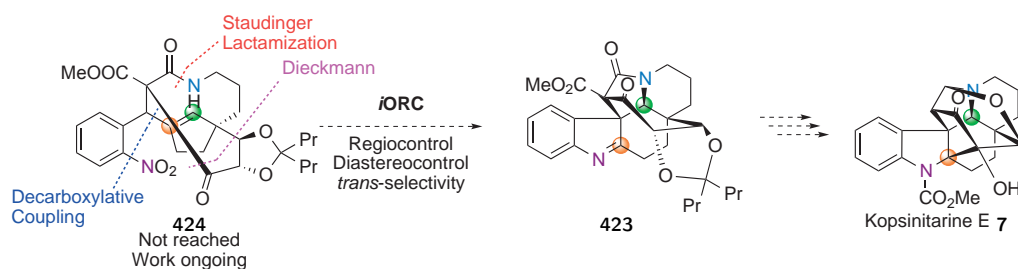
As all these previous examples of *i*ORC domino process gave *cis*-fused [6,6] ring system, we decided to change the diastereoselectivity of this reaction and force the reaction into giving a *trans*-fused [6,6] ring system. This would allow us to reach kopsihainanine A **6** (**Scheme 7.4**). In order to change the selectivity, we introduced a constrain in the key intermediate to push the reaction towards our desired conformation. We formed 8-membered ring **339** in 8 steps and 36% overall yield, featuring our palladium-catalyzed decarboxylative coupling, and a Staudinger lactamization. To our delight, performing our key domino process on this lactam allowed us to reach intermediate **336** with a *trans*-fused C/D ring system in 63% yield with full stereocontrol. An α -keto hydroxylation concluded our total synthesis of racemic kopsihainanine A **6** in 91% yield.



Scheme 7.4 – Summary of the total synthesis of kopsihainanine A **6**

Our final synthetic study was designed to see how far could we go for generating molecular complexity by the *i*ORC process (**Scheme 7.5**). We targeted kopsinitarine E **7** *via* indole-nine **423**. This intermediate was supposed to be reached by performing our *i*ORC domino process on highly substituted precursor **424**. Unfortunately, the presence of these functional groups made the synthesis of precursor **424** challenging. This project was still at an early stage.

To conclude, we were able to demonstrate the power of our *i*ORC and our ability to control the cyclization step from a regioselective perspective (goniomitine *versus* aspidospermidine), as well as a diastereoselective perspective (aspidospermidine *versus* kopsihainanine A). The quaternary center in C20 of these *aspidosperma* alkaloids is the one controlling the



Scheme 7.5 – Summary of the synthetic study towards kopsinitarine E 7

relative stereoselectivity, and if the formation of this center could be done in an enantioselective manner, the total syntheses of these alkaloids would become enantioselective. We are currently considering this synthetic challenge. Nonetheless, such domino processes have some drawbacks. The sensitivity of the key step towards the reductive conditions used makes this transformation challenging, as a slightly different substrate requires totally different reductive conditions to achieve good yields. In addition, we sometimes experienced troubles to reach *i*ORC precursors as for the synthesis of kopsinitarine E or minfiensine. However, the ability to trigger such skeleton rearrangement and form complex polycyclic indole skeletons from simple precursors is certainly a great asset and a significant addition to the strategies available for the total synthesis of indole alkaloids, and could allow easy synthetic entry into many other families of indole alkaloids.

Experimental Section

8.1 General Remarks

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka, TCI and VWR international) and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) unless otherwise noted. When needed, glassware was dried overnight in an oven ($T > 100\text{ }^{\circ}\text{C}$) or under vacuum with a heat gun ($T > 200\text{ }^{\circ}\text{C}$).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb's design.²⁰⁷

Reactions heated by microwave irradiation were performed in a CEM Discover SP microwave instrument.

Flash column chromatographies²⁰⁸ were performed using Silicycle P60 silica: 230-400 mesh (40-63 μm) silica.

Reactions were monitored using Merck Kieselgel 60F254 aluminium or glass backed plates. TLC's were visualized by UV fluorescence (254 nm) then one of the following: KMnO_4 , PMA, ninhydrin, pancaldi, *p*-anisaldehyde, vanillin.

NMR spectra were recorded on a Bruker AvanceIII-400, Bruker Avance-400, Bruker DRX-400, or Bruker AvanceII-800 spectrometer at room temperature, ^1H frequency is at 400.13 MHz,

²⁰⁷Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 15, 1518–1520

²⁰⁸Still, W.; Kahn, M. J. *Org. Chem.* **1978**, 43, 2923–2925

Chapter 8: Experimental Section

^{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 ppm for proton and 0.1 ppm for carbon (*ref*: CHCl_3 [^1H : 7.26 ppm, ^{13}C : 77.2 ppm], MeOH [^1H : 3.31 ppm, ^{13}C 49.0 ppm], DMSO [^1H : 2.50 ppm, ^{13}C 39.5 ppm]). 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. COSY, HSQC, and HMBC experiments were used to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra are reported in cm^{-1} . Abbreviations used are: *w* (weak), *m* (medium), *s* (strong) and *br* (broad).

Mass spectra were obtained by using a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI^+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Specific optical rotations $[\alpha]_D$ were obtained with a Jasco P-2000 polarimeter (589 nm).

Enantiomeric excesses were determined with a Thar SFC Investigator system using chiral stationary phase columns by comparing the samples with the appropriate racemic samples, column and elution details specified in each entry.

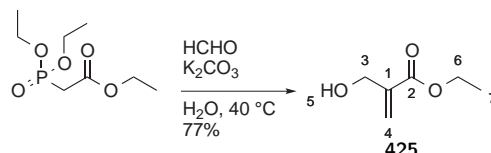
Melting points are uncorrected and were recorded on a Stuart SMP30 melting point apparatus.

When a rigorously inert and dry atmosphere was needed reactions were carried out in a Pure-Lab HE 4GB 2500 Glove-box System from Innovative Technologies inc.

For all general procedures the order of addition of reagents has to be respected.

8.2 Experimental Procedures of Chapter 2

Ethyl 2-(hydroxymethyl)acrylate **425**



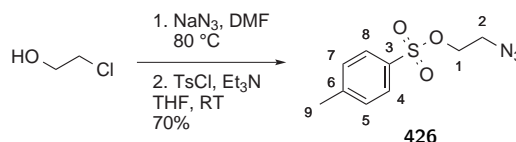
Following a reported procedure,²⁰⁹ a solution of paraformaldehyde (4.8 g, 0.16 mol, 4.0 equiv) in H₂O (11 mL) and phosphoric acid (1.0 M solution, 0.40 mL) was heated to 90 °C for 5 h. The reaction mixture was allowed to cool down to RT, and triethyl phosphonoacetate (8.0 mL, 40 mmol) was added. A solution of K₂CO₃ (6.1 g, 40 mmol, 1.0 equiv) in H₂O (6.0 mL) was added dropwise carefully, by avoiding the reaction mixture to go higher than 40 °C. The reaction was then stirred at 40 °C for 5 minutes. The reaction mixture was then cooled down to 0 °C. Brine and Et₂O were added to the mixture. The solution was then extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by vacuum distillation (Bp = 55 °C/0.1 mbar) afforded compound **425** as a colorless oil (4.0 g, 77% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁰

¹H NMR (400 MHz, CDCl₃): δ 6.25 (s, 1H, C⁴-H), 5.82 (s, 1H, C⁴-H), 4.32 (d, *J* = 6.6 Hz, 2H, C³-H), 4.24 (q, *J* = 7.1 Hz, 2H, C⁶-H), 2.36 (t, *J* = 6.6 Hz, 1H, O⁵-H), 1.31 (t, *J* = 7.1 Hz, 3H, C⁷-H).

¹³C NMR (101 MHz, CDCl₃): δ 166.5 (C²), 139.6 (C¹), 125.8 (C⁴), 62.8 (C⁶), 61.0 (C³), 14.3 (C⁷).

*R*_f(PE/EtOAc 8:2) = 0.2.

2-azidoethyl 4-methylbenzenesulfonate **426**



²⁰⁹Villieras, J; Rambaud, M *Org. Synth.* **1988**, 66, 220

²¹⁰Patil, S.; Chen, L.; Tanko, J. M. *Tetrahedron Lett.* **2014**, 55, 7029–7033

Following a reported procedure,²¹¹ to a solution of 2-chloroethanol (4.3 mL, 63 mmol) in DMF (20 mL) was added sodium azide (5.7 g, 88 mmol, 1.4 equiv). The solution was stirred at 80 °C for 24 h. The reaction mixture was allowed to cool down to RT, and then filtered through Celite. The Celite was washed with THF and the solution was directly used for the next reaction.

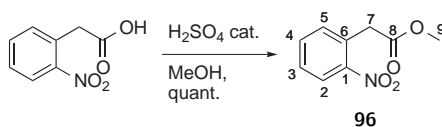
To the crude 2-azidoethanol in solution (THF/DMF 2:1) was added triethylamine (26 mL, 0.19 mol, 3.0 equiv) and tosyl chloride (14 g, 72 mmol, 1.2 equiv). The mixture was stirred overnight. The solution was then concentrated *in vacuo*, diluted in DCM and washed with H₂O, 1 M HCl, 10% NaOH, brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 5:1) afforded compound **426** as a yellow oil (11 g, 70% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹¹

¹H NMR (400 MHz, CDCl₃): δ 7.82 (d, J = 8.3 Hz, 2H, C^{4,8}-H), 7.37 (d, J = 8.3 Hz, 2H, C^{5,7}-H), 4.16 (t, J = 5.2 Hz, 2H, C²-H), 3.48 (t, J = 5.2 Hz, 2H, C¹-H), 2.46 (s, 3H, C⁹-H).

¹³C NMR (101 MHz, CDCl₃): δ 145.3 (C³), 132.6 (C⁶), 130.0 (C^{5,7}), 128.0 (C^{4,8}), 68.1 (C¹), 49.6 (C²), 21.7 (C⁹).

R_f (PE/EtOAc 8:2) = 0.28.

methyl 2-(2-nitrophenyl)acetate **96**



To a solution of 2-(2-nitrophenyl)-acetic acid (10.0 g, 55.0 mmol) in methanol (300 mL) was added 3.0 mL of conc. H₂SO₄. The solution was heated at reflux for 2 h. The solution was then concentrated under reduced pressure, diluted with EtOAc, washed with saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude compound **96** thus obtained was used for the next step without further purification (yellow wax, 10.7 g). The spectroscopic data of this compound were in accord with those reported in the literature.²¹² The compound was used without further purification.

¹H NMR (400 MHz, CDCl₃): δ 8.12 (dd, J = 7.9, 1.2 Hz, 1H, C²-H), 7.60 (td, J = 7.9, 1.2 Hz, 1H, C⁴-H), 7.48 (td, J = 7.9, 1.2 Hz, 1H, C³-H), 7.36 (dd, J = 7.9, 1.2 Hz, 1H, C⁵-H), 4.03 (s, 2H, C⁷-H), 3.71 (s, 3H, C⁹-H).

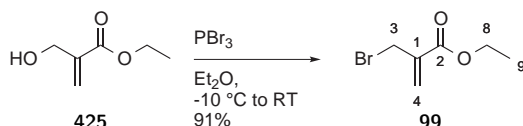
²¹¹Macleod, E.; Lang, S.; Murphy, J. A. *Synlett* **2010**, 21, 529–534

²¹²Lee, S.; Lim, H.-J.; Cha, K. L.; Sulikowski, G. A. *Tetrahedron* **1997**, 53, 16521–16532

^{13}C NMR (101 MHz, CDCl_3): δ 170.5 (C^8), 148.9 (C^1), 133.7 (C^4), 133.5 (C^5), 129.9 (C^3), 128.8 (C^6), 125.5 (C^2), 52.4 (C^9), 39.7 (C^7).

R_f (EtOAc) = 0.71.

Ethyl 2-(bromomethyl)acrylate **99**



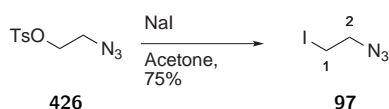
Following a reported procedure,²¹⁰ to a solution of acrylate **425** (8.0 g, 61 mmol) in Et_2O (65 mL) at $-10\text{ }^\circ\text{C}$ was added dropwise PBr_3 (2.3 mL, 25 mmol, 0.40 equiv). The solution was stirred and allowed to warm up slowly to RT over a period of 4 h. The solution was then cooled down to $-10\text{ }^\circ\text{C}$, water was added slowly, and the mixture was extracted with Et_2O . The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by vacuum distillation (Bp = $55\text{ }^\circ\text{C}/8.0\text{ mbar}$) afforded compound **99** as a colorless oil (11 g, 91% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁰

^1H NMR (400 MHz, CDCl_3): δ 6.33 (d, $J = 0.7\text{ Hz}$, 1H, $\text{C}^4\text{-H}$), 5.94 (d, $J = 0.7\text{ Hz}$, 1H, $\text{C}^4\text{-H}$), 4.27 (q, $J = 7.1\text{ Hz}$, 2H, $\text{C}^8\text{-H}$), 4.18 (d, $J = 0.8\text{ Hz}$, 2H, $\text{C}^3\text{-H}$), 1.33 (t, $J = 7.1\text{ Hz}$, 3H, $\text{C}^9\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 165.0 (C^2), 137.7 (C^1), 129.1 (C^4), 61.5 (C^8), 29.5 (C^3), 14.3 (C^9).

R_f (PE/EtOAc 8:2) = 0.68.

2-azidoiodoethane **97**



Sodium iodide (4.7 g, 31 mmol, 1.5 equiv) was added to a solution of **426** (5.0 mL, 21 mmol) in acetone (100 mL). The solution was stirred at reflux for 18 h. The reaction mixture was allowed to cool down to RT, and concentrated under reduced pressure. Water was added and the mixture was extracted with Et_2O . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by vacuum distillation (Bp

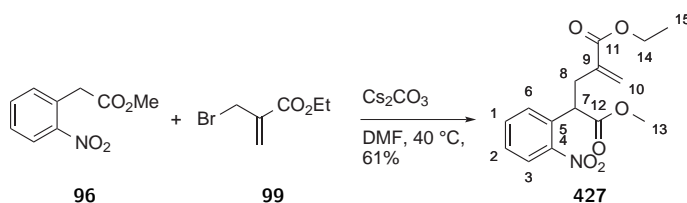
= 70 °C/20 mbar) afforded compound **97** as a colorless oil (3.1 g, 75% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹¹

¹H NMR (400 MHz, CDCl₃): δ 3.66 (t, J = 7.1 Hz, 2H, C²–H), 3.25 (t, J = 7.1 Hz, 2H, C¹–H).

¹³C NMR (101 MHz, CDCl₃): δ 53.1 (C²), 1.0 (C¹).

R_f (PE/EtOAc 5:1) = 0.78.

1-ethyl 5-methyl 2-methylene-4-(2-nitrophenyl)-pentanedioate **427**



The ester **96** (0.20 g, 1.0 mmol) was dissolved in DMF (1.0 mL). The acrylate **99** was added (0.12 g, 1.2 mmol, 1.2 equiv), followed by cesium carbonate (0.33 g, 2.0 mmol, 2.0 equiv). The reaction mixture was then stirred at 45 °C for 9 h. The solution was then cooled down to RT, acidified with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/DCM 1:1) afforded compound **427** as a yellow oil (0.19 g, 61% yield).

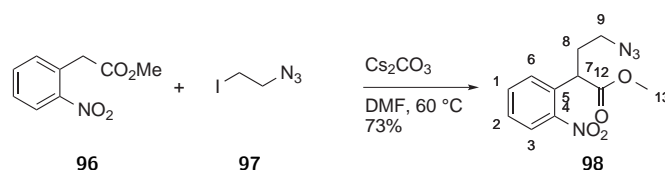
¹H NMR (400 MHz, CDCl₃): δ 7.89 (dd, J = 7.8, 1.1 Hz, 1H, C³–H), 7.57 (td, J = 7.8, 1.1 Hz, 1H, C¹–H), 7.49 (dd, J = 7.8, 1.3 Hz, 1H, C⁶–H), 7.42 (td, J = 7.8, 1.3 Hz, 1H, C²–H), 6.11 (d, J = 1.0 Hz, 1H, C¹⁰–H), 5.42 (d, J = 1.0 Hz, 1H, C¹⁰–H), 4.55 (t, J = 8.1 Hz, 1H, C⁷–H), 4.20 (q, J = 7.2 Hz, 2H, C¹⁴–H), 3.66 (s, 3H, C¹³–H), 3.24 (dd, J = 14.1, 8.1 Hz, 1H, C⁸–H), 2.82 (dd, J = 14.1, 8.1 Hz, 1H, C⁸–H), 1.29 (t, J = 7.2 Hz, 3H, C¹⁵–H).

¹³C NMR (101 MHz, CDCl₃): δ 172.4 (C¹²), 166.5 (C¹¹), 149.5 (C⁴), 137.2 (C⁹), 133.1 (C¹), 132.98 (C⁵), 130.7 (C⁶), 128.4 (C²), 127.9 (C¹⁰), 124.9 (C³), 61.1 (C¹⁴), 52.4 (C¹³), 45.7 (C⁷), 35.3 (C⁸), 14.3 (C¹⁵).

IR: 1736 (s), 1714 (s), 1527 (s), 1352 (m), 1194 (s).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₅H₁₈NO₆⁺: 308.1134; Found: 308.1126.

R_f (PE/DCM 1:1) = 0.23.

methyl 4-azido-2-(2-nitrophenyl)butanoate 98

The ester **96** (0.20 g, 1.0 mmol) was dissolved in DMF (2.0 mL). Compound **97** was added (0.43 g, 2.1 mmol, 2.0 equiv), followed by cesium carbonate (0.33 g, 2.1 mmol, 2.0 equiv). The reaction mixture was then stirred at 60 °C for 18 h. The solution was then cooled down to RT, acidified with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (toluene) afforded compound **98** as a yellow oil (0.19 g, 73% yield).

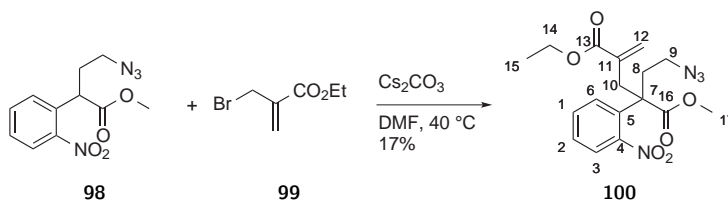
¹H NMR (400 MHz, CDCl₃): δ 7.95 (dd, J = 7.9, 1.2 Hz, 1H, C³-H), 7.61 (td, J = 7.9, 1.2 Hz, 1H, C¹-H), 7.50-7.42 (m, 2H, C^{2,6}-H), 4.29 (t, J = 7.2 Hz, 1H, C⁷-H), 3.67 (s, 3H, C¹³-H), 3.46-3.29 (m, 2H, C⁹-H), 2.50 (dq, J = 14.2, 7.0 Hz, 1H, C⁸-H), 2.09 (dq, J = 14.2, 7.0 Hz, 1H, C⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 172.3 (C¹²), 149.1 (C⁴), 133.4 (C¹), 132.8 (C⁵), 130.3 (C⁶), 128.6 (C²), 125.2 (C³), 52.5 (C¹³), 49.3 (C⁹), 44.1 (C⁷), 31.9 (C⁸).

IR: 2098 (w), 1734 (w), 1528 (s), 1352 (w).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₁H₁₂N₄NaO₄⁺: 287.0751; Found: 287.0754.

R_f (Toluene) = 0.45.

5-ethyl 1-methyl 2-(2-azidoethyl)-4-methylene-2-(2-nitrophenyl)pentanedioate 100

The ester **98** (30 mg, 0.12 mmol) was dissolved in DMF (0.30 mL). Compound **99** was added (27 mg, 0.14 mmol, 1.2 equiv), followed by cesium carbonate (75 mg, 0.18 mmol, 1.5 equiv). The reaction mixture was then stirred at 40 °C for 24 h. The solution was then cooled down

to RT, acidified with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **100** as a yellow oil (7.7 mg, 17% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.96 (dd, J = 7.9, 1.4 Hz, 1H, C³-H), 7.58 (td, J = 7.9, 1.4 Hz, 1H, C¹-H), 7.47 (td, J = 7.9, 1.1 Hz, 1H, C²-H), 7.33 (dd, J = 7.9, 1.1 Hz, 1H, C⁶-H), 6.26 (d, J = 1.1 Hz, 1H, C¹²-H), 5.41 (d, J = 1.1 Hz, 1H, C¹²-H), 4.01-3.84 (m, 2H, C¹⁴-H), 3.68 (s, 3H, C¹⁷-H), 3.63 (d, J = 13.8 Hz, 1H, C¹⁰-H), 3.35-3.16 (m, 2H, C⁹-H), 3.12 (d, J = 13.8 Hz, 1H, C¹⁰-H), 2.44-2.28 (m, 2H, C⁸-H), 1.16 (t, J = 7.1 Hz, 3H, C¹⁵-H).

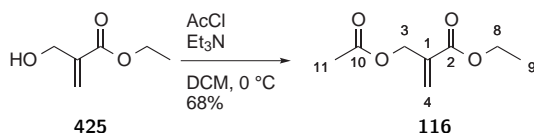
¹³C NMR (101 MHz, CDCl₃): δ 172.5 (C¹⁶), 166.9 (C¹³), 149.9 (C⁴), 136.2 (C¹¹), 134.0 (C⁵), 132.4 (C²), 130.3 (C¹²), 129.1 (C⁶), 128.3 (C¹), 126.0 (C³), 61.0 (C¹⁴), 52.1 (C¹⁷), 52.0 (C⁷), 47.5 (C⁹), 38.1 (C¹⁰), 35.0 (C⁸), 14.0 (C¹⁵).

IR: 2924 (s), 2851 (w), 2099 (m), 1718 (m), 1530 (s), 1357 (w).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₇H₂₁N₄O₆⁺: 377.1456; Found: 377.1464.

R_f (DCM) = 0.5.

ethyl 2-(acetoxymethyl)acrylate **116**



Following a reported procedure,²¹³ to a solution of acrylate **425** (50 mg, 0.38 mmol) in DCM (1.5 mL) at 0 °C was added dropwise Et₃N (80 μ L, 0.58 mmol, 1.5 equiv). Acetyl chloride (40 μ L, 0.58 mmol, 1.5 equiv) was then added dropwise. The solution was stirred for 20 min. The mixture was quenched with brine. The phases were separated and the aqueous one was washed with DCM. The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **116** as a yellow oil (45 mg, 68% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹³

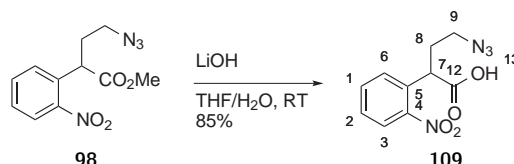
¹H NMR (400 MHz, CDCl₃): δ 6.36 (d, J = 1.1 Hz, 1H, C⁴-H), 5.83 (d, J = 1.1 Hz, 1H, C⁴-H), 4.81 (s, 2H, C³-H), 4.24 (q, J = 7.1 Hz, 2H, C⁸-H), 2.10 (s, 3H, C¹¹-H), 1.31 (t, J = 7.1 Hz, 3H, C⁹-H).

²¹³Kang, S.; Shi, Q.; Ha, M. W.; Ku, J.-M.; Cheng, M.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *Tetrahedron* **2010**, 66, 4326-4329

^{13}C NMR (101 MHz, CDCl_3): δ 170.6 (C^{10}), 165.3 (C^2), 135.6 (C^1), 127.4 (C^4), 62.6 (C^3), 61.1 (C^8), 21.0 (C^{11}), 14.3 (C^9).

R_f (DCM) = 0.54.

4-azido-2-(2-nitrophenyl)butanoic acid **109**



To a solution of ester **98** (0.50 g, 1.9 mmol) in a mixture of THF/ H_2O (1:1, 20 mL) was added LiOH (91 mg, 3.8 mmol, 2.0 equiv). The solution was stirred at RT for 3 h. HCl (1.0 M) was then added and the solution was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded acid **109** as a yellow oil (0.40 g, 85% yield).

^1H NMR (400 MHz, CDCl_3): δ 8.00 (dd, J = 8.1, 1.3 Hz, 1H, $\text{C}^3\text{-H}$), 7.64 (td, J = 8.1, 1.3 Hz, 1H, $\text{C}^1\text{-H}$), 7.52-7.45 (m, 2H, $\text{C}^{2,6}\text{-H}$), 4.32 (t, J = 7.1 Hz, 1H, $\text{C}^7\text{-H}$), 3.42 (dt, J = 13.6, 7.1 Hz, 1H, $\text{C}^9\text{-H}$), 3.30 (dt, J = 13.6, 7.1 Hz, 1H, $\text{C}^9\text{-H}$), 2.52 (dq, J = 14.1, 7.1 Hz, 1H, $\text{C}^8\text{-H}$), 2.10 (dq, J = 14.1, 7.1 Hz, 1H, $\text{C}^8\text{-H}$).

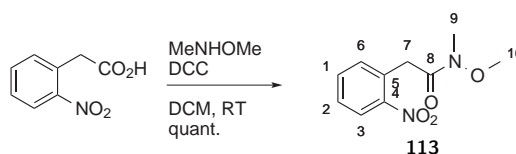
^{13}C NMR (101 MHz, CDCl_3): δ 176.9 (C^{12}), 149.0 (C^4), 133.7 (C^5), 132.4 (C^6), 130.9 (C^1), 129.0 (C^2), 125.5 (C^3), 49.3 (C^9), 44.5 (C^7), 31.5 (C^8).

IR: 2926 (w), 2856 (w), 2750 (w), 2635 (w), 2571 (w), 2102 (w), 1701 (s), 1612 (w), 1578 (w), 1518 (s), 1431 (m), 1410 (m), 1342 (s), 1241 (s), 938 (m), 706 (s).

HRMS: ($\text{ESI}^+ -$) m/z : $[\text{M} - \text{H}]^-$ Calcd for $\text{C}_{10}\text{H}_9\text{N}_4\text{O}_4^-$: 249.0624; Found: 249.0631.

R_f (EtOAc) = 0.61.

N-methoxy-N-methyl-2-(2-nitrophenyl)acetamide **113**



Chapter 8: Experimental Section

To a solution of 2-(2-nitrophenyl)acetic acid (50 mg, 0.27 mmol) in DCM (0.60 mL) at 0 °C was added freshly distilled N,O-dimethylhydroxylamine (25 mg, 0.41 mmol, 1.5 equiv) and DCC (62 mg, 0.30 mmol, 1.1 equiv). The solution was stirred at RT for 24 h. HCl (1.0 M) was then added and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (EtOAc) afforded pure Weinreb amide **113** as a yellow oil (60 mg, quantitative yield).

¹H NMR (400 MHz, CDCl₃): δ 8.09 (dd, $J = 7.7, 1.4$ Hz, 1H, C³–H), 7.58 (td, $J = 7.7, 1.4$ Hz, 1H, C¹–H), 7.45 (td, $J = 7.7, 1.3$ Hz, 1H, C²–H), 7.36 (dd, $J = 7.7, 1.3$ Hz, 1H, C⁶–H), 4.17 (s, 2H, C⁷–H), 3.81 (s, 3H, C¹⁰–H), 3.22 (s, 3H, C⁹–H).

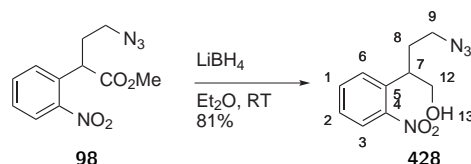
¹³C NMR (101 MHz, CDCl₃): δ 170.5 (C⁶), 149.2 (C⁴), 133.5 (C⁶), 133.4 (C¹), 130.7 (C⁵), 128.3 (C²), 125.2 (C³), 61.3 (C¹⁰), 37.9 (C⁷), 32.4 (C⁹).

IR: 2936 (w), 2856 (w), 2359 (w), 2342 (w), 1665 (s), 1525 (s), 1350 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₀H₁₃N₂O₄⁺: 225.0870; Found: 225.0869.

R_f (PE/EtOAc 8:2) = 0.07.

4-azido-2-(2-nitrophenyl)butan-1-ol **428**



To a solution of ester **98** (6.7 g, 25 mmol) in Et₂O (25 mL) was added LiBH₄ (1.1 g, 51 mmol, 2.0 equiv). The solution was stirred at RT for 2 h. Saturated NH₄Cl was then added and the solution was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (DCM) afforded compound **428** as an orange oil (4.8 g, 81% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.77 (dd, $J = 7.8, 1.3$ Hz, 1H, C³–H), 7.61 (td, $J = 7.8, 1.3$ Hz, 1H, C¹–H), 7.50 (dd, $J = 7.8, 1.3$ Hz, 1H, C⁶–H), 7.41 (td, $J = 7.8, 1.3$ Hz, 1H, C¹–H), 3.86 (dd, $J = 9.3, 5.3$ Hz, 2H, C¹²–H), 3.49 (tt, $J = 9.3, 5.9$ Hz, 1H, C⁷–H), 3.37–3.15 (m, 2H, C⁹–H), 2.15 (dtd, $J = 14.0, 7.6, 5.6$ Hz, 1H, C⁸–H), 1.97 (dtd, $J = 14.0, 7.6, 5.6$ Hz, 1H, C⁸–H), 1.70 (t, $J = 5.3$ Hz, 1H, O¹³–H).

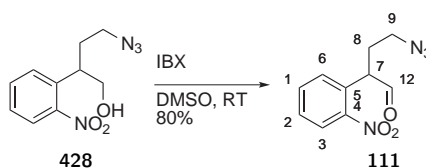
¹³C NMR (101 MHz, CDCl₃): δ 151.2 (C⁴), 135.5 (C⁵), 132.7 (C¹), 128.4 (C⁶), 127.73 (C²), 124.3 (C³), 66.5 (C¹²), 49.4 (C⁹), 39.5 (C⁷), 31.1 (C⁸).

IR: 2920 (w), 2878 (w), 2360 (w), 2094 (s), 1520 (s), 1353 (s), 1038 (m).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₁₀H₁₃N₄O₃⁺: 237.0982; Found: 237.0992.

R_f (DCM) = 0.19.

4-azido-2-(2-nitrophenyl)butan-1-al **111**



To a solution of alcohol **428** (4.5 g, 19 mmol) in DMSO (20 mL) was added IBX (6.0 g, 25 mmol, 1.3 equiv). The solution was stirred at RT for 3 h. Saturated NaHCO₃ was then added and the solution was filtered and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **111** as an orange oil (3.5 g, 80% yield).

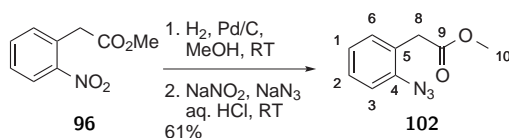
¹H NMR (400 MHz, CDCl₃): δ 9.75 (s, 1H, C¹²-H), 8.02 (dd, *J* = 7.9, 1.0 Hz, 1H, C³-H), 7.67 (td, *J* = 7.9, 1.0 Hz, 1H, C¹-H), 7.52 (td, *J* = 7.9, 1.0 Hz, 1H, C²-H), 7.31 (dd, *J* = 7.9, 1.0 Hz, 1H, C⁶-H), 4.28 (t, *J* = 7.6 Hz, 1H, C⁷-H), 3.40 (dt, *J* = 13.1, 6.7 Hz, 1H, C⁹-H), 3.31 (dt, *J* = 13.1, 6.7 Hz, 1H, C⁹-H), 2.52 (ddt, *J* = 14.2, 7.6, 6.7 Hz, 1H, C⁸-H), 2.02 (ddt, *J* = 14.2, 7.6, 6.7 Hz, 1H, C⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 197.9 (C¹²), 149.8 (C⁴), 133.7 (C⁵), 131.2 (C²), 130.7 (C⁶), 129.1 (C¹), 125.5 (C³), 51.4 (C⁷), 49.1 (C⁹), 29.0 (C⁸).

IR: 2934 (w), 2838 (w), 2725 (w), 2097 (s), 1724 (s), 1523 (s), 1348 (s).

HRMS: (ESI⁺) *m/z*: [M - N + H]⁺ Calcd for C₁₀H₁₁N₃O₃⁺: 221.0795; Found: 221.0805.

R_f (DCM) = 0.73.

methyl 2-(2-azidophenyl)acetate **102**

A solution of **96** (1.0 g, 5.1 mmol) in methanol (10 mL) under nitrogen was treated with 10% palladium on activated charcoal (0.25 g, 5.0 mol%). The nitrogen atmosphere was then replaced by hydrogen. The solution was stirred for 4 h. It was then filtered through Celite, washed with saturated NaHCO₃ and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give the crude amine that was used without further purification.

The crude amine was dissolved in aqueous HCl (2.0 M, 30 mL). A solution of NaNO₂ (0.50 g, 7.2 mmol, 1.4 equiv) in 6.0 mL H₂O was added dropwise. After 15 min, a solution of NaN₃ (0.40 g, 6.1 mmol, 1.2 equiv) in 6.0 mL H₂O was added carefully. The reaction mixture was stirred for 3 h. The solution was then extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **102** as a yellow oil (0.59 g, 61% yield).

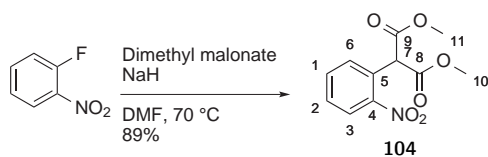
¹H NMR (400 MHz, CDCl₃): δ 7.36 (td, J = 7.9, 1.3 Hz, 1H, C²-H), 7.25 (dd, J = 7.9, 1.3 Hz, 1H, C⁶-H), 7.19 (dd, J = 7.9, 1.1 Hz, 1H, C³-H), 7.14 (td, J = 7.9, 1.1 Hz, 1H, C¹-H), 3.73 (s, 3H, C¹⁰-H), 3.64 (s, 2H, C⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 171.6 (C⁹), 138.7 (C⁴), 131.5 (C⁶), 128.8 (C²), 125.6 (C⁵), 124.8 (C¹), 118.2 (C³), 52.2 (C¹⁰), 36.5 (C⁸).

IR: 2953 (w), 2120 (s), 1737 (s), 1491 (m), 1286 (s), 1161 (s), 750 (s).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₉H₉N₃NaO₂⁺: 214.0587; Found: 214.0592.

R_f (DCM) = 0.7.

dimethyl 2-(2-nitrophenyl)malonate **104**

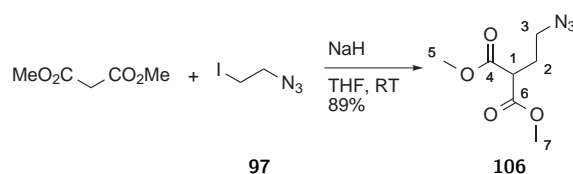
To a suspension of NaH (60% in oil, 0.60 g, 1.4 mmol, 2.2 equiv) in DMF (9.0 mL) at 0 °C was added dimethyl malonate (1.7 g, 1.3 mmol, 2.0 equiv) dropwise. A solution of *o*-fluoronitrobenzene (0.70 mL, 0.6 mmol) in DMF (2.0 mL) was then added dropwise. The solution was then heated at 70 °C for 2 h. The reaction mixture was then cooled down, quenched with saturated NH₄Cl, then extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **104** as a yellow oil (0.14 g, 89% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁴

¹H NMR (400 MHz, CDCl₃): δ 8.09 (dd, *J* = 7.8, 1.1 Hz, 1H, C³-H), 7.67 (td, *J* = 7.8, 1.1 Hz, 1H, C¹-H), 7.54 (td, *J* = 7.8, 1.4 Hz, 1H, C²-H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H, C⁶-H), 5.35 (s, 1H, C⁷-H), 3.82 (s, 6H, C^{10,11}-H).

¹³C NMR (101 MHz, CDCl₃): δ 167.7 (C^{8,9}), 148.7 (C⁴), 133.6 (C¹), 131.4 (C⁶), 129.4 (C²), 127.9 (C⁵), 125.3 (C³), 54.1 (C⁷), 53.2 (C^{10,11}).

R_f (DCM) = 0.17.

dimethyl 2-(2-azidoethyl)malonate **106**



To a suspension of NaH (60% in oil, 23 mg, 1.0 mmol, 1.3 equiv) in THF (1.0 mL) at 0 °C was added dimethyl malonate (0.10 g, 0.76 mmol) dropwise. After 15 minutes, 1-azido-2-iodoethane **97** (0.20 g, 1.0 mmol, 1.3 equiv) was added dropwise. The solution was then stirred at RT overnight. The reaction mixture was then cooled down, quenched with saturated NH₄Cl, then extracted with EtOAc. Purification by FCC (PE/EtOAc 8:2) afforded compound **106** as a yellow oil (0.14 g, 89% yield).

¹H NMR (400 MHz, CDCl₃): δ 3.79 (s, 6H, C^{5,7}-H), 3.56 (t, *J* = 7.2 Hz, 1H, C¹-H), 3.42 (t, *J* = 6.6 Hz, 2H, C³-H), 2.20 (dt, *J* = 7.2, 6.5 Hz, 2H, C²-H).

¹³C NMR (101 MHz, CDCl₃): δ 169.2 (C^{4,6}), 52.8 (C^{5,7}), 49.1 (C¹), 48.7 (C³), 28.2 (C²).

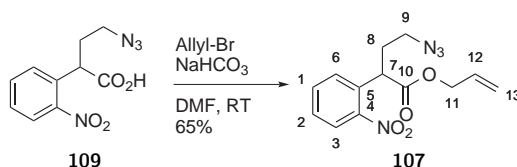
IR: 2955 (w), 2924 (w), 2853 (w), 2099 (s), 1732 (s), 1437 (m), 1343 (w), 1250 (m), 1155 (s).

²¹⁴Goetz, F. J.; Hirsch, J. A.; Augustine, R. L. *J. Org. Chem.* **1983**, *48*, 2468–2472

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₇H₁₁N₃NaO₄⁺: 224.0642; Found: 224.0635.

R_f (PE/EtOAc 7:3) = 0.67.

allyl 4-azido-2-(2-nitrophenyl)butanoate 107



To a solution of acid **109** (0.60 g, 2.4 mmol) in DMF (4.8 mL) was added NaHCO₃ (0.20 g, 2.6 mmol, 1.1 equiv) and allyl bromide (1.4 g, 12 mmol, 5.0 equiv). The solution was stirred at RT for 48 h. The mixture was then concentrated under reduced pressure, diluted with DCM, washed with H₂O, saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (DCM) afforded compound **107** as a yellow oil (0.45 g, 65% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.95 (dd, *J* = 8.0, 1.2 Hz, 1H, C³-H), 7.61 (td, *J* = 8.0, 1.2 Hz, 1H, C¹-H), 7.51-7.42 (m, 2H, C^{2,6}-H), 5.82 (ddt, *J* = 17.2, 10.6, 5.7 Hz, 1H, C¹²-H), 5.27-5.18 (m, 2H, C¹³-H), 4.65-4.56 (m, 2H, C¹¹-H), 4.31 (t, *J* = 7.1 Hz, 1H, C⁷-H), 3.48-3.30 (m, 2H, C⁹-H), 2.51 (m, 1H, C⁸-H), 2.11 (m, 1H, C⁸-H).

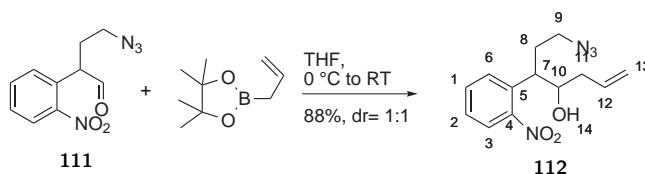
¹³C NMR (101 MHz, CDCl₃): δ 171.5 (C¹⁰), 149.2 (C⁴), 133.4 (C¹), 132.8 (C⁵), 131.5 (C¹²), 130.3 (C⁶), 128.6 (C²), 125.2 (C³), 118.7 (C¹³), 66.0 (C¹¹), 49.4 (C⁹), 44.2 (C⁷), 31.9 (C⁸).

IR: 2926 (w), 2865 (w), 2361 (w), 2337 (w), 2097 (s), 1734 (s), 1526 (s), 1351 (s), 1170 (s).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₁₃H₁₄N₄NaO₄⁺: 313.0907; Found: 313.09165.

R_f (DCM) = 0.49.

7-azido-5-(2-nitrophenyl)hept-1-en-4-ol 112



To a solution of allylboronic acid pinacol ester (1.6 mL, 8.5 mmol, 1.7 equiv) in THF (20 mL)

at 0 °C was added the aldehyde **111** (1.2 g, 4.9 mmol). The solution was stirred at 0 °C for 3 h, and then at RT overnight. Saturated aqueous NaHCO₃ was added, and the mixture was stirred for 30 min at RT. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:1) afforded compound **112** as a yellow oil (1.2 g, 88% yield as an inseparable mixture of two diastereoisomers).

¹H NMR (400 MHz, CDCl₃): δ 7.72 (m, 1H, C³-H), 7.59 (m, 1H, C¹-H), 7.51 (m, 1H, C²-H), 7.40 (m, 1H, C⁶-H), 5.76 (m, 1H, C¹²-H), 5.23-5.10 (m, 2H, C¹³-H), 3.88 (m, 1H, C¹⁰-H), 3.36 (m, 1H, O¹⁴-H), 3.25-3.10 (m, 2H, C⁹-H), 2.36 (m, 1H, C⁷-H), 2.21-1.83 (m, 4H, C^{8,11}-H).

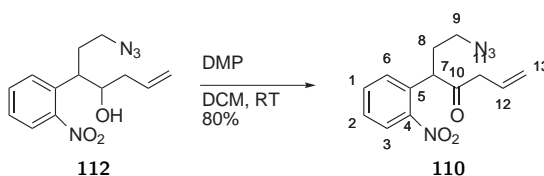
¹³C NMR (101 MHz, CDCl₃): δ 151.9 (C⁴), 151.3 (C⁴), 135.4 (C⁵), 134.5 (C⁵), 133.9 (C¹²), 133.9 (C¹²), 132.5 (C¹), 132.3 (C¹), 129.9 (C⁶), 128.9 (C⁶), 127.7 (C²), 127.6 (C²), 124.1 (C³), 123.8 (C³), 119.3 (C¹³), 119.1 (C¹³), 73.5 (C¹⁰), 72.9 (C¹⁰), 49.5 (C⁹), 49.4 (C⁹), 42.2 (C¹¹), 41.5 (C¹¹), 39.9 (C⁷), 39.8 (C⁷), 32.0 (C⁸), 30.3 (C⁸).

IR: 3436 (w), 3079 (w), 2936 (w), 2878 (w), 2096 (s), 1730 (w), 1524 (s), 1355 (s), 1251 (m), 998 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₁₃H₁₆N₄NaO₃⁺: 299.1115; Found: 299.1124.

R_f (DCM) = 0.48.

7-azido-5-(2-nitrophenyl)hept-1-en-4-one **110**



To a solution of alcohol **112** (3.0 mg, 0.010 mmol) in DCM (1.0 mL) was added DMP (8.0 mg, 0.020 mmol, 1.8 equiv). The solution was stirred at RT for 1 h. Aqueous 2% NaOH was then added and the solution was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **110** as a yellow oil (2.2 mg, 80% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.90 (dd, *J* = 7.9, 1.2 Hz, 1H, C³-H), 7.59 (td, *J* = 7.9, 1.2 Hz, 1H, C¹-H), 7.46 (td, *J* = 7.9, 1.1 Hz, 1H, C²-H), 7.33 (dd, *J* = 7.9, 1.1 Hz, 1H, C⁶-H), 5.81 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H, C¹²-H), 5.14 (dd, *J* = 10.1, 1.2 Hz, 1H, C¹³-H), 5.04 (dd, *J* = 17.1, 1.2 Hz, 1H, C¹³-H), 4.48 (t, *J* = 7.1 Hz, 1H, C⁷-H), 3.35-3.13 (m, 4H, C^{9,11}-H), 2.38 (ddt,

$J = 16.9, 7.1, 6.9 \text{ Hz}$, 1H, C⁸–H), 1.94 (ddt, $J = 16.9, 7.1, 6.9 \text{ Hz}$, 1H, C⁸–H).

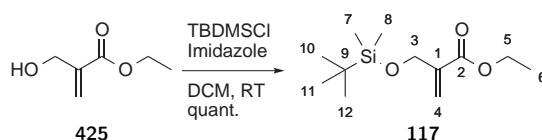
¹³C NMR (101 MHz, CDCl₃): δ 205.7 (C¹⁰), 150.0 (C⁴), 133.4 (C¹), 131.9 (C⁵), 129.9 (C⁶), 129.7 (C¹²), 128.7 (C²), 125.0 (C³), 119.5 (C¹³), 49.2 (C⁹), 49.0 (C⁷), 47.0 (C¹¹), 31.4 (C⁸).

IR: 2958 (w), 2929 (w), 2854 (w), 2096 (s), 1716 (m), 1526 (s), 1350 (s), 1259 (s), 788 (s).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₃H₁₄N₄NaO₃⁺: 297.0958; Found: 297.0969.

R_f (DCM) = 0.71.

ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-acrylate **117**



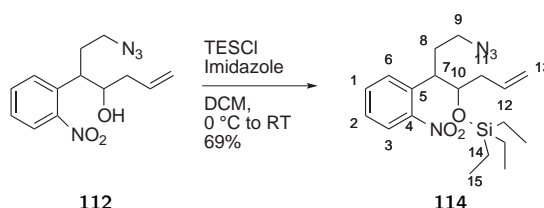
Following a reported procedure,²¹⁵ the acrylate **425** (1.2 g, 9.2 mmol) was dissolved in DCM (30 mL). Imidazole (1.6 g, 24 mmol, 2.5 equiv) was added slowly, followed by TBSCl (1.5 g, 10 mmol, 1.1 equiv). The mixture was stirred for 2 h and then quenched with saturated NaHCO₃. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **117** as a colorless oil (2.3 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁵

¹H NMR (400 MHz, CDCl₃): δ 6.25 (q, $J = 2.0 \text{ Hz}$, 1H, C⁴–H), 5.90 (q, $J = 2.0 \text{ Hz}$, 1H, C⁴–H), 4.37 (t, $J = 2.0 \text{ Hz}$, 2H, C³–H), 4.22 (q, $J = 7.1 \text{ Hz}$, 2H, C⁵–H), 1.30 (t, $J = 7.1 \text{ Hz}$, 3H, C⁶–H), 0.92 (s, 9H, C^{10,11,12}–H), 0.09 (s, 6H, C^{7,8}–H).

¹³C NMR (101 MHz, CDCl₃): δ 166.0 (C²), 139.9 (C¹), 123.6 (C⁴), 61.5 (C³), 60.5 (C⁵), 25.9 (C⁹), 18.4 (C^{10,11,12}), 14.2 (C⁶), -5.4 (C^{7,8}).

R_f (DCM) = 0.17.

²¹⁵Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695–2698

((7-azido-5-(2-nitrophenyl)hept-1-en-4-yl)oxy)-triethylsilane 114

The compound **112** (0.10 g, 0.36 mmol) was dissolved in DCM (1.0 mL) at 0 °C. Imidazole (0.12 mL, 0.72 mmol, 2.0 equiv) and TESCl (0.10 g, 1.5 mmol, 4.0 equiv) were added. The reaction mixture was stirred for 1 h at 0 °C, then 1 h at RT. The solution was then quenched with saturated NaHCO₃ and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **114** as a yellow oil (97 mg, 69% yield as an inseparable mixture of two diastereoisomers).

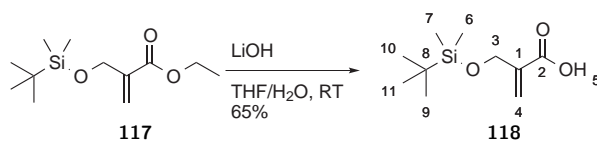
¹H NMR (400 MHz, CDCl₃): δ 7.72 (m, 1H, C³-H), 7.54 (m, 1H, C¹-H), 7.47 (m, 1H, C²-H), 7.37 (m, 1H, C⁶-H), 5.72 (m, 1H, C¹²-H), 5.03-4.90 (m, 2H, C¹³-H), 3.96 (m, 1H, C¹⁰-H), 3.41-3.22 (m, 2H, C⁹-H), 3.11 (m, 1H, C⁷-H), 2.34-1.94 (m, 4H, C^{8,11}-H), 1.02-0.85 (m, 9H, C¹⁵-H), 0.64-0.48 (m, 6H, C¹⁴-H).

¹³C NMR (101 MHz, CDCl₃): δ 151.2 (C⁴), 135.8 (C⁵), 135.1 (C⁵), 133.5 (C¹²), 133.4 (C¹²), 132.0 (C¹), 132.0 (C¹), 130.2 (C⁶), 129.8 (C⁶), 127.4 (C²), 127.4 (C²), 124.2 (C³), 123.9 (C³), 117.9 (C¹³), 75.0 (C¹⁰), 74.8 (C¹⁰), 49.6 (C⁷), 49.6 (C⁷), 40.7 (C⁹), 40.4 (C¹¹), 40.0 (C¹¹), 32.0 (C⁸), 28.3 (C⁸), 6.9 (C¹⁵), 5.0 (C¹⁴).

IR: 2957 (w), 2877 (w), 2099 (w), 1528 (w), 1355 (w), 905 (s), 726 (s).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₁₉H₃₁N₄O₃Si⁺: 391.2160; Found: 391.2179.

R_f (PE/EtOAc 9:1) = 0.59.

2-((*tert*-butyldimethylsilyloxy)methyl)acrylic acid 118

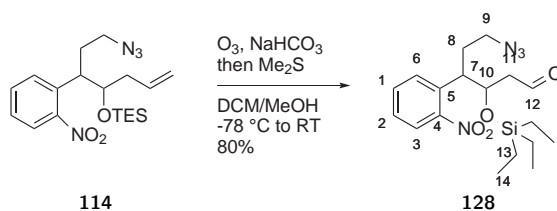
Following a reported procedure,²¹⁶ to a solution of acrylate **117** (20 mg, 0.080 mmol) in a mixture of THF/H₂O (1:1, 0.50 mL) was added LiOH (4.0 mg, 0.16 mmol, 2.0 equiv). The reaction mixture was stirred overnight at RT. It was then quenched with saturated NH₄Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product **118** thus obtained was used for the next step without further purification as a colorless oil (11 mg, 65% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁷

¹H NMR (400 MHz, CDCl₃): δ 6.40 (q, J = 2.0 Hz, 1H, C⁴-H), 6.03 (q, J = 2.0 Hz, 1H, C⁴-H), 4.38 (t, J = 2.0 Hz, 2H, C³-H), 0.93 (s, 9H, C^{9,10,11}-H), 0.10 (s, 6H, C^{6,7}-H).

¹³C NMR (101 MHz, CDCl₃): δ 170.5 (C²), 138.9 (C¹), 126.4 (C⁴), 61.3 (C³), 25.9 (C⁸), 18.4 (C^{9,10,11}), -5.4 (C^{6,7}).

R_f (PE/EtOAc 5:5) = 0.50.

6-azido-4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-hexanal **128**



To a solution of compound **114** (0.10 g, 0.25 mmol) in a mixture DCM/MeOH (1:1, 1.0 mL) at -78 °C was added NaHCO₃ (60 mg, 0.63 mmol, 2.5 equiv). O₃ was then bubbled through the solution for 20 s. Argon was bubbled through the solution to remove the ozone and Me₂S (excess) was added to the solution. It was then allowed to warm up to RT. The mixture was stirred for 4 h. The mixture was then filtered through Celite and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **128** as a slightly yellow oil (79 mg, 80% yield as an inseparable mixture of two diastereoisomers).

¹H NMR (400 MHz, CDCl₃): δ 9.69 (m, 1H, C¹²-H), 7.76 (m, 1H, C³-H), 7.59 (m, 1H, C¹-H), 7.49-7.31 (m, 2H, C^{2,6}-H), 4.53 (m, 1H, C¹⁰-H), 3.42 (m, 1H, C⁷-H), 3.23-3.05 (m, 2H, C⁹-H), 2.64-2.42 (m, 2H, C¹¹-H), 2.39-1.83 (m, 2H, C⁸-H), 1.03-0.85 (m, 9H, C¹⁴-H), 0.70-0.55 (m, 6H, C¹³-H).

²¹⁶Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. *Synlett* **2009**, 20, 2997-2999

²¹⁷Adams, R. S.; Calderwood, E. F.; Gould, A. E.; Greenspan, P. D.; Lamarche, M. J.; Tian, Y.; Vos, T. J. Cinnamide and hydrocinnamide derivatives with kinase inhibitory activity. US Patent Application Publication, US2006160803 (A1) (US), 2006

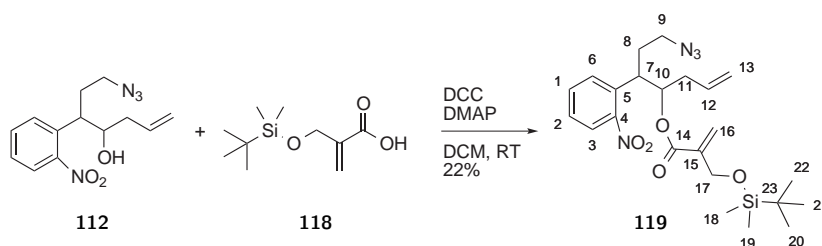
^{13}C NMR (101 MHz, CDCl_3): δ 200.2 (C^{12}), 200.2 (C^{12}), 151.4 (C^4), 134.4 (C^5), 133.4 (C^5), 132.4 (C^1), 132.1 (C^1), 130.1 (C^6), 129.1 (C^6), 128.1 (C^2), 128.0 (C^2), 124.3 (C^3), 123.8 (C^3), 70.9 (C^{10}), 70.1 (C^{10}), 50.1 (C^7), 49.4 (C^7), 43.1 (C^9), 41.8 (C^{11}), 41.4 (C^{11}), 31.6 (C^8), 30.1 (C^8), 6.9 (C^{14}), 5.0 (C^{13}).

IR: 2957 (w), 2877 (w), 2099 (s), 1725 (w), 1529 (s), 1356 (m), 1244 (w), 1114 (w), 1007 (w), 746 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_4\text{NaO}_4\text{Si}^+$: 415.1772; Found: 415.1781.

R_f (PE/EtOAc 8:2) = 0.48.

7-azido-5-(2-nitrophenyl)hept-1-en-4-yl 2-((*tert*-butyldimethylsilyloxy)methyl)-acrylate **119**



To a solution of the alcohol **112** (40 mg, 0.15 mmol) and the acid **118** (40 mg, 0.18 mmol, 1.2 equiv) in DCM (1.0 mL) at 0 °C was added DCC (0.16 g, 0.75 mmol, 5.0 equiv), followed by DMAP (9.4 mg, 0.080 mmol, 0.50 equiv). The reaction mixture was stirred for 30 min at 0 °C, and then overnight at RT. The reaction was then quenched with saturated NaHCO_3 . The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product **119** was then used without further purification as a yellow oil (16 mg, 22% yield as an inseparable mixture of two diastereoisomers).

^1H NMR (400 MHz, CDCl_3): δ 7.76 (m, 1H, $\text{C}^3\text{-H}$), 7.61 (m, 1H, $\text{C}^1\text{-H}$), 7.54-7.41 (m, 2H, $\text{C}^{2,6}\text{-H}$), 6.24 (m, 1H, $\text{C}^{16}\text{-H}$), 5.93 (m, 1H, $\text{C}^{16}\text{-H}$), 5.66 (m, 1H, $\text{C}^{12}\text{-H}$), 5.34 (m, 1H, $\text{C}^{10}\text{-H}$), 5.12-5.00 (m, 2H, $\text{C}^{13}\text{-H}$), 4.48-4.30 (m, 2H, $\text{C}^{17}\text{-H}$), 3.66 (m, 1H, $\text{C}^7\text{-H}$), 3.27-3.05 (m, 2H, $\text{C}^9\text{-H}$), 2.35-2.16 (m, 2H, $\text{C}^{11}\text{-H}$), 2.13 (m, 1H, $\text{C}^8\text{-H}$), 1.94 (m, 1H, $\text{C}^8\text{-H}$), 1.02-0.88 (m, 9H, $\text{C}^{20,21,22}\text{-H}$), 0.21-0.05 (m, 6H, $\text{C}^{18,19}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 165.3 (C^{14}), 164.9 (C^{14}), 151.3 (C^4), 139.5 (C^{15}), 134.3 (C^{12}), 132.8 (C^5), 132.5 (C^5), 132.4 (C^1), 132.3 (C^1), 128.7 (C^6), 128.2 (C^6), 128.0 (C^{16}), 124.5 (C^2), 124.3 (C^2), 124.0 (C^3), 118.8 (C^{13}), 118.6 (C^{13}), 75.4 (C^{10}), 74.8 (C^{10}), 61.5 (C^{17}), 61.3 (C^{17}), 49.1

Chapter 8: Experimental Section

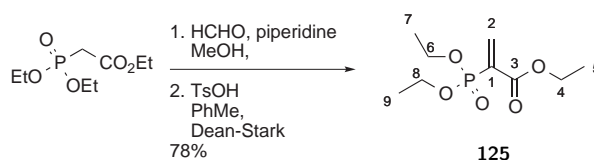
(C⁷), 49.0 (C⁷), 39.9 (C⁹), 39.6 (C⁹), 37.3 (C¹¹), 37.2 (C¹¹), 31.8 (C⁸), 30.6 (C⁸), 25.9 (C²³), 18.4 (C^{20,21,22}), -5.4 (C^{18,19}).

IR: 2954 (w), 2930 (w), 2885 (w), 2857 (w), 2098 (m), 1715 (m), 1529 (s), 1356 (m), 1260 (s), 1091 (s), 839 (s), 780 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₃H₃₄N₄NaO₅Si⁺: 497.2191; Found: 497.2200.

R_f (PE/EtOAc 9.5:0.5) = 0.19.

ethyl 2-(diethoxyphosphoryl)acrylate **125**



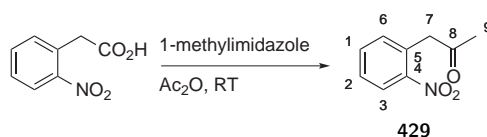
Following a reported procedure,^{44e} a solution of paraformaldehyde (2.5 g, 82 mmol, 2.0 equiv) in MeOH (100 mL) and piperidine (0.40 mL, 4.1 mmol, 0.1 equiv) was stirred at RT. Triethyl phosphonoacetate (9.2 g, 41 mmol) was added over 30 minutes. The solution was then refluxed for 24 h. The solvent was evaporated under reduced pressure. The crude compound was dissolved in toluene (100 mL). *p*-Toluenesulfonic acid monohydrate (0.80 g, 4.1 mmol, 0.10 equiv) was added and the solution was refluxed with a Dean-Stark apparatus for 8 h. Purification by vacuum distillation (Bp = 90 °C/1.0 mbar) afforded compound **125** as a colorless oil (7.6 g, 78% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁸

¹H NMR (400 MHz, CDCl₃): δ 7.00 (dd, *J* = 42.0, 1.6 Hz, 1H, C²-H), 6.76 (dd, *J* = 20.4, 1.6 Hz, 1H, C²-H), 4.30 (q, *J* = 7.2 Hz, 2H, C⁴-H), 4.29-4.11 (m, 4H, C^{6,8}-H), 1.41-1.30 (m, 9H, C^{5,7,9}-H).

¹³C NMR (101 MHz, CDCl₃): δ 163.8 (d, *J* = 16 Hz, C³), 143.3 (d, *J* = 5 Hz, C²), 133.2 (d, *J* = 186 Hz, C¹), 62.8 (d, *J* = 6 Hz, C^{6,8}), 61.6 (s, C⁴), 16.4 (d, *J* = 7 Hz, C^{7,9}), 14.1 (s, C⁵).

R_f(EtOAc) = 0.44.

²¹⁸ a) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, 50, 8412–8415; b) Cherkasov, A. R.; Galkin, V. I.; Sibgatullin, I. M.; Khusainova, N. G.; Zyablikova, T. A.; Buzykin, B. I.; Cherkasov, R. A. *Russ. J. Gen. Chem.* **2001**, 71, 343–347; c) Galvez-Ruano, E.; Bellanato, J.; Fernandez-Ibañez, M.; Sainz-Diaz, C.; Arias-Perez, M. *J. Mol. Struct.* **1986**, 142, 397–402

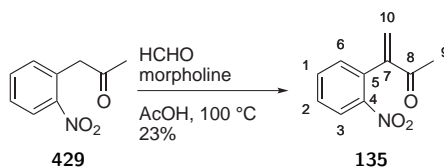
1-(2-nitrophenyl)propan-2-one 429

Following a reported procedure,⁵¹ to a solution of 2-(2-nitrophenyl)acetic acid (9.5 g, 52 mmol) in Ac₂O (25 mL) at RT was added 1-methylimidazole (2.1 mL, 51 mmol, 0.5 equiv). The solution was stirred for 12 h. It was then poured into water. The crude product was extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The crude compound **429** thus obtained was used for the next step without further purification as a yellow oil. The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁹

¹H NMR (400 MHz, CDCl₃): δ 8.12 (dd, J = 7.9, 1.1 Hz, 1H, C³-H), 7.60 (td, J = 7.9, 1.1 Hz, 1H, C¹-H), 7.47 (td, J = 7.9, 1.2 Hz, 1H, C²-H), 7.28 (dd, J = 7.9, 1.2 Hz, 1H, C⁶-H), 4.13 (s, 2H, C⁷-H), 2.33 (s, 3H, C⁹-H).

¹³C NMR (101 MHz, CDCl₃): δ 203.7 (C⁸), 148.7 (C⁴), 133.7 (C¹), 133.6 (C⁶), 130.5 (C⁵), 128.5 (C²), 125.4 (C³), 48.7 (C⁷), 30.1 (C⁹).

R_f (PE/EtOAc 6.5:3.5) = 0.5.

3-(2-nitrophenyl)but-3-en-2-one 135

Following a reported procedure,⁵¹ a solution of crude 1-(2-nitrophenyl)propan-2-one **429** (From 52 mmol of 2-(2-nitrophenyl)acetic acid), morpholine (1.1 g, 13 mmol, 0.25 equiv), and 37% HCHO in H₂O (13 mL) in AcOH (55 mL) was heated at 100 °C for 24 h. The solution was concentrated under reduced pressure, and Et₂O and H₂O were added. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **135** as a slightly yellow wax (2.3 g, 23% yield in two

²¹⁹Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fetting, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 2062–2065

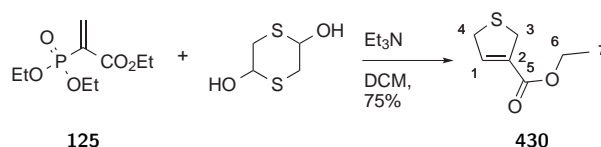
steps). The spectroscopic data of this compound were in accord with those reported in the literature.⁵¹

¹H NMR (400 MHz, CDCl₃): δ 8.10 (dd, $J = 7.8, 1.2$ Hz, 1H, C³-H), 7.64 (td, $J = 7.8, 1.2$ Hz, 1H, C¹-H), 7.52 (td, $J = 7.8, 1.3$ Hz, 1H, C²-H), 7.32 (dd, $J = 7.8, 1.3$ Hz, 1H, C⁶-H), 6.29 (s, 1H, C¹⁰-H), 6.02 (s, 1H, C¹⁰-H), 2.49 (s, 3H, C⁹-H).

¹³C NMR (101 MHz, CDCl₃): δ 197.3 (C⁸), 148.4 (C⁴), 133.7 (C¹), 133.4 (C⁵), 132.1 (C⁶), 129.3 (C⁷), 129.3 (C²), 125.6 (C¹⁰), 124.6 (C³), 26.3 (C⁹).

R_f (PE/Et₂O 8:2) = 0.07.

ethyl 2,5-dihydrothiophene-3-carboxylate **430**

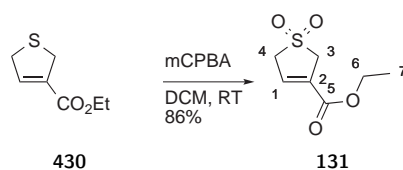


Following a reported procedure,^{44b} a solution of 1,4-dithiane-2,5-diol (0.46 g, 3.0 mmol, 0.60 equiv) and Et₃N (0.90 mL, 6.5 mmol, 1.3 equiv) in DCM (37 mL) was heated at reflux. A solution of the acrylate **125** (1.2 g, 5.0 mmol) in DCM (5.0 mL) was added dropwise. The reaction mixture was stirred at reflux for 4 h. When the reaction was finished, the mixture was cooled down, diluted with DCM, washed with HCl (5%), brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by vacuum distillation (Bp = 190 °C/1.5 mbar) afforded compound **430** as a colorless oil (0.59 g, 75% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²⁰

¹H NMR (400 MHz, CDCl₃): δ 6.91 (m, 1H, C¹-H), 4.24 (q, $J = 7.1$ Hz, 2H, C⁶-H), 4.01-3.85 (m, 4H, C^{3,4}-H), 1.32 (t, $J = 7.1$ Hz, 3H, C⁷-H).

R_f (PE/Et₂O 8:2) = 0.42.

²²⁰Martyres, D. H.; Baldwin, J. E.; Adlington, R. M.; Lee, V.; Probert, M. R.; Watkin, D. J. *Tetrahedron* **2001**, 57, 4999–5007

ethyl 2,5-dihydrothiophene-3-carboxylate **131**

Following a reported procedure,^{44b} a solution of **430** (0.30 g, 1.9 mmol) in DCM (3.0 mL) was stirred at 0 °C when a solution of mCPBA (0.85 g, 3.8 mmol, 2.0 equiv) in DCM (10 mL) was added dropwise. The mixture was allowed to warm up slowly (3 h) and then stirred overnight at RT. The solution was then filtered, washed with saturated Na₂CO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **131** as a colorless oil (0.31 g, 86% yield).

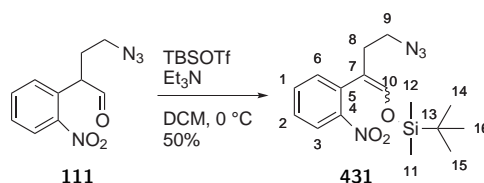
¹H NMR (400 MHz, CDCl₃): δ 7.03 (m, 1H, C¹-H), 4.28 (q, *J* = 7.1 Hz, 2H, C⁶-H), 4.03-3.98 (m, 4H, C^{3,4}-H), 1.32 (t, *J* = 7.1 Hz, 3H, C⁷-H).

¹³C NMR (101 MHz, CDCl₃): δ 162.0 (C⁵), 133.1 (C¹), 130.3 (C²), 61.8 (C³), 57.8 (C⁶), 55.1 (C⁴), 14.2 (C⁷).

IR: 2983 (w), 2939 (w), 1716 (s), 1632 (w), 1316 (s), 1266 (s), 1213 (s), 1135 (m), 1072 (s), 1018 (w), 731 (w).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₇H₁₀NaO₄S⁺: 213.0197; Found: 213.0203.

R_f(PE/Et₂O 8:2) = 0.07.

((4-azido-2-(2-nitrophenyl)but-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane **431**

A solution of the aldehyde **111** (0.10 g, 0.43 mmol) in DCM (1.0 mL) was stirred at 0 °C. Et₃N (0.30 mL, 2.1 mmol, 5.0 equiv) was added, followed by TBSOTf (0.20 mL, 0.86 mmol, 2.0 equiv). The reaction mixture was stirred for 5 h at 0 °C. DCM was added, followed by aqueous 5% NaHCO₃. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1)

afforded compound **431** as a yellow oil (75 mg, 50% yield as a mixture of inseparable isomers. Ratio: 1:1.5).

¹H NMR (400 MHz, CDCl₃): δ 7.87 (dd, J = 7.9, 1.4 Hz, 1H, C³-H, minor), 7.81 (dd, J = 8.0, 1.5 Hz, 1H, C³-H, major), 7.58-7.49 (m, 2H, C¹-H, minor+major), 7.42-7.30 (m, 4H, C^{2,6}-H, minor+major), 6.35 (s, 1H, C¹⁰-H, minor), 6.33 (s, 1H, C¹⁰-H, major), 3.35 (t, J = 7.3 Hz, 2H, C⁹-H, minor), 3.30 (t, J = 7.5 Hz, 2H, C⁹-H, major), 2.71 (t, J = 7.5 Hz, 2H, C⁸-H, major), 2.61 (t, J = 7.3 Hz, 2H, C⁸-H, minor), 0.96 (s, 9H, C^{14,15,16}-H, major), 0.71 (s, 9H, C^{14,15,16}-H, minor), 0.18 (s, 6H, C^{11,12}-H, major), 0.03 (s, 6H, C^{11,12}-H, minor).

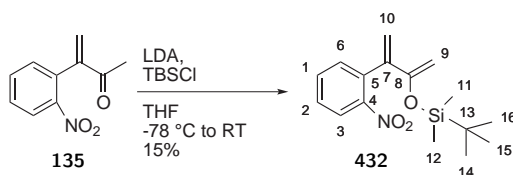
¹³C NMR (101 MHz, CDCl₃): δ 150.0 (C⁴, minor+major), 140.7 (C¹⁰, major), 138.8 (C¹⁰, minor), 134.4 (C¹, major + minor), 132.4 (C⁵, minor + major), 131.2 (C⁶, major + minor), 127.9 (C², major), 127.7 (C², minor), 124.4 (C³, major), 124.3 (C³, minor), 115.9 (C⁷, major), 113.6 (C⁷, minor), 50.5 (C⁹, minor), 49.6 (C⁹, major), 32.5 (C⁸, minor), 28.6 (C⁸, major), 25.7 (C^{14,15,16}, major), 25.4 (C^{14,15,16}, minor), 18.3 (C¹⁸, major), 18.1 (C¹⁸, minor), -5.2 (C^{11,12}, major), -5.5 (C^{11,12}, minor)

IR: 2954 (w), 2931 (w), 2858 (w), 2095 (m), 1650 (w), 1527 (s), 1353 (w), 1256 (m), 1179 (s), 838 (s), 784 (s).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₆H₂₄N₄NaO₃Si⁺: 371.1510; Found: 371.1505.

R_f(PE/Et₂O 9:1) = 0.58.

tert*-butyldimethyl((3-(2-nitrophenyl)but-3-en-2-yl)oxy)silane **432*



Diisopropylamine (0.040 mL, 0.29 mmol, 1.4 equiv) was stirred at -78 °C when *n*-BuLi was added dropwise (1.6 M solution in Et₂O, 0.18 mL, 0.29 mmol, 1.4 equiv). The solution was stirred for 30 minutes. THF (1.0 mL) was then added and the solution was stirred for 5 minutes. A solution of ketone **135** (40 mg, 0.21 mmol) in THF (0.50 mL) was added dropwise. The reaction mixture was stirred for 30 minutes. TBSCl (44 mg, 0.29 mmol, 1.4 equiv) was then added. The solution was stirred for 30 minutes, then 15 minutes at RT. It was then quenched with saturated NaHCO₃. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9.5:0.5) afforded compound **432** as a yellow oil (9.6 mg, 15% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.85 (dd, $J = 7.8, 0.9$ Hz, 1H, $\text{C}^3\text{-H}$), 7.65–7.56 (m, 2H, $\text{C}^{1,6}\text{-H}$), 7.39 (td, $J = 7.8, 1.1$ Hz, 1H, $\text{C}^2\text{-H}$), 5.66 (s, 1H, $\text{C}^{10}\text{-H}$), 5.44 (s, 1H, $\text{C}^{10}\text{-H}$), 4.48 (m, 1H, $\text{C}^9\text{-H}$), 3.45 (m, 1H, $\text{C}^9\text{-H}$), 1.02 (s, 9H, $\text{C}^{14,15,16}\text{-H}$), 0.37 (s, 3H, $\text{C}^{11}\text{-H}$), 0.10 (s, 3H, $\text{C}^{12}\text{-H}$).

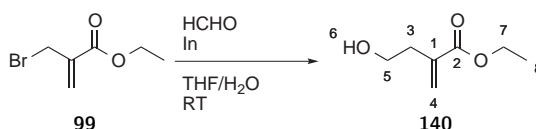
^{13}C NMR (101 MHz, CDCl_3): δ 155.1 (C^8), 149.0 (C^4), 143.7 (C^7), 135.6 (C^5), 132.8 (C^1), 132.5 (C^6), 128.7 (C^2), 124.2 (C^3), 115.8 (C^{10}), 95.6 (C^9), 25.9 ($\text{C}^{14,15,16}$), 18.4 (C^{13}), -4.5 ($\text{C}^{11,12}$),

IR: 2956 (w), 2930 (w), 2857 (w), 1586 (w), 1529 (s), 1472 (w), 1350 (s), 1257 (m), 1218 (m), 1017 (m), 826 (s), 784 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_3\text{Si}^+$: 306.1520; Found: 306.1526.

$R_f(\text{PE}/\text{Et}_2\text{O } 9:1) = 0.33$.

ethyl 4-hydroxy-2-methylenebutanoate **140**



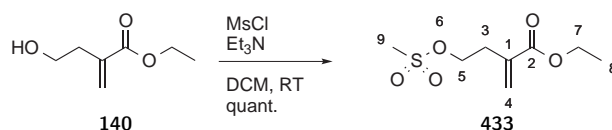
Following a reported procedure,²²¹ to a solution of the acrylate **99** (2.5 g, 11 mmol) in a mixture of THF/ H_2O (1:1, 33 mL) was added indium (1.3 g, 11 mmol, 1.0 equiv) followed by aqueous 37% formaldehyde (0.75 mL, 11 mmol, 1.0 equiv). The mixture was stirred at RT overnight. The reaction was quenched with HCl (2.0 M) and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 5:1) afforded compound **140** as a yellow oil (1.6 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²¹

^1H NMR (400 MHz, CDCl_3): δ 6.25 (s, 1H, $\text{C}^4\text{-H}$), 5.69 (s, 1H, $\text{C}^4\text{-H}$), 4.24 (q, $J = 7.1$ Hz, 2H, $\text{C}^7\text{-H}$), 3.83 (t, $J = 5.7$ Hz, 2H, $\text{C}^5\text{-H}$), 2.61 (t, $J = 5.7$ Hz, 2H, $\text{C}^3\text{-H}$), 1.32 (t, $J = 7.1$ Hz, 3H, $\text{C}^8\text{-H}$), OH peak not observed.

^{13}C NMR (101 MHz, CDCl_3): 168.3 (C^2), 137.7 (C^1), 127.8 (C^4), 62.4 (C^5), 61.5 (C^7), 35.4 (C^3), 14.2 (C^8).

$R_f(\text{PE}/\text{EtOAc } 9:1) = 0.07$.

²²¹Nagano, H.; Kuwahara, R.; Yokoyama, F. *Tetrahedron* **2007**, 63, 8810–8814

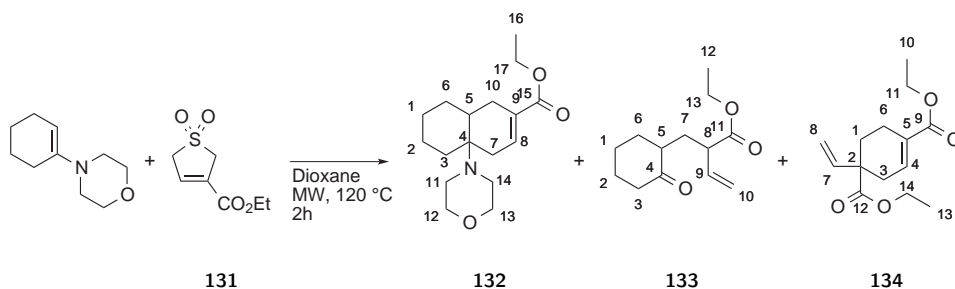
ethyl 2-methylene-4-((methylsulfonyl)oxy)-butanoate **433**

To a solution of the acrylate **140** (3.0 g, 20 mmol) in DCM (70 mL) at 0 °C was added Et₃N (5.7 mL, 40 mmol, 2.0 equiv) followed by MsCl (3.2 mL, 40 mmol, 2.0 equiv). The mixture was stirred at RT overnight. The reaction was quenched with saturated NH₄Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded compound **433** as a yellow oil (4.4 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²²

¹H NMR (400 MHz, CDCl₃): δ 6.31 (s, 1H, C⁴-H), 5.73 (d, *J* = 1.0 Hz, 1H, C⁴-H), 4.37 (t, *J* = 6.6 Hz, 2H, C⁵-H), 4.22 (q, *J* = 7.1 Hz, 2H, C⁷-H), 2.99 (s, 3H, C⁹-H), 2.76 (t, *J* = 6.6 Hz, 2H, C³-H), 1.31 (t, *J* = 7.1 Hz, 3H, C⁸-H).

¹³C NMR (101 MHz, CDCl₃): 166.3 (C²), 135.2 (C¹), 128.4 (C⁴), 68.0 (C⁵), 61.0 (C⁷), 37.4 (C⁹), 32.3 (C³), 14.2 (C⁸).

R_f(PE/EtOAc 8:2) = 0.16.

ethyl 4a-morpholino-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-2-carboxylate **132**

To a solution of 1-(N-morpholino)cyclohex-1-ene (22 mg, 0.13 mmol) in dioxane (0.50 mL) was added **131** (30 mg, 0.16 mmol, 1.2 equiv). The solution was then heated by microwave irradiation (150 W) at 120 °C for 2 h. HCl (1.0 M) was added and the reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over

²²²Jaegli, S. Approche vers la synthèse d'analogues de la Rustmicine et nouvelles voies d'accès à des spiro-oxindoles par réactions domino palladocatalysées., Ph.D. Thesis, Paris Sud XI, 2008

Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compounds **132**, **133** and **134**. The spectroscopic data of compound **134** were in accord with those reported in the literature.²²³

Compound 132:

Red oil, 12 mg, 30% yield.

¹H NMR (400 MHz, CDCl₃): δ 6.83 (m, 1H, C⁸-H), 4.19 (q, J = 7.1 Hz, 2H, C¹⁷-H), 3.76-3.57 (m, 4H, C^{12,13}-H), 2.60-2.41 (m, 4H, C^{11,14}-H), 2.45 (m, 1H, C⁷-H), 2.30-2.20 (m, 2H, C^{7,10}-H), 2.09 (d, J = 19.2 Hz, 1H, C¹⁰-H), 1.99 (m, 1H, C⁵-H), 1.68-1.21 (m, 11 H).

¹³C NMR (101 MHz, CDCl₃): δ 167.5, 136.8, 128.3, 68.0, 60.3, 44.8, 33.6, 32.0, 29.7, 28.1, 27.5, 27.4, 22.7, 21.8, 14.3.

IR: 2925 (m), 2852 (w), 2811 (w), 1708 (s), 1658 (w), 1451 (w), 1247 (s), 1155 (m), 1118 (s).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₇H₂₈NO₃⁺: 294.2069; Found: 294.2070.

R_f(PE/EtOAc 8:2) = 0.38.

Compound 133:

yellow oil, 7.0 mg, 24% yield as an inseparable mixture of two diastereoisomers.

¹H NMR (400 MHz, CDCl₃): δ 5.87-5.67 (m, 1H, C⁹-H), 5.24-5.03 (m, 2H, C¹⁰-H), 4.24-4.05 (m, 2H, C¹³-H), 3.24-3.06 (m, 1H, C⁸-H), 2.44-2.22 (m, 4H, C^{5,3}-H), 2.15-2.00 (m, 2 H), 1.91-1.79 (m, 1 H), 1.72-1.60 (m, 2 H), 1.44-1.30 (m, 1 H), 1.29-1.21 (m, 4H, C¹²-H).

¹³C NMR (101 MHz, CDCl₃): δ 174.0, 173.9, 136.0, 135.9, 117.7, 117.3, 60.7, 48.1, 47.9, 47.8, 42.3, 34.6, 34.2, 31.7, 31.6, 28.2, 28.1, 25.2, 14.2.

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₃H₂₁O₃⁺: 225.1491; Found: 225.1495.

R_f(PE/EtOAc 8:2) = 0.67.

Compound 134:

slightly yellow oil, 8.0 mg, 20% yield (calculated based on sulfonene **131**).

²²³Xu, S.; Chen, R.; He, Z. *J. Org. Chem.* **2011**, 76, 7528–7538

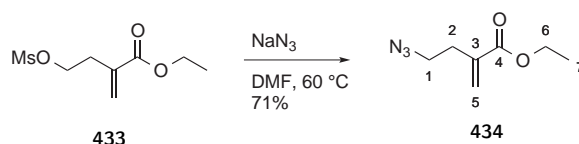
^1H NMR (400 MHz, CDCl_3): δ 6.96 (m, 1H, $\text{C}^4\text{-H}$), 5.88 (dd, $J = 17.5, 10.7$ Hz, 1H, $\text{C}^7\text{-H}$), 5.15 (dd, $J = 10.7, 0.5$ Hz, 1H, $\text{C}^8\text{-H}$), 5.11 (dd, $J = 17.5, 0.5$ Hz, 1H, $\text{C}^8\text{-H}$), 4.24-4.10 (m, 4H, $\text{C}^{11,14}\text{-H}$), 2.80 (m, 1H, $\text{C}^3\text{-H}$), 2.40-2.28 (m, 3H, $\text{C}^{3,6}\text{-H}$), 2.07 (m, 1H, $\text{C}^1\text{-H}$), 1.78 (m, 1H, $\text{C}^1\text{-H}$), 1.31-1.21 (m, 6H, $\text{C}^{10,13}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 174.4 (C^{12}), 167.0 (C^9), 139.6 (C^7), 136.8 (C^4), 129.6 (C^5), 115.1 (C^8), 61.0 (C^{11}), 60.4 (C^{14}), 47.2 (C^2), 32.2 (C^3), 29.7 (C^6), 21.7 (C^1), 14.3 (C^{13}), 14.1 (C^{10}).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{21}\text{O}_4^+$: 253.1440; Found: 253.1438.

R_f (PE/EtOAc 8:2) = 0.67.

ethyl 4-azido-2-methylenebutanoate **434**



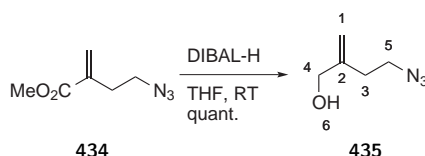
Following a known procedure,²²² mesylate **433** (0.50 g, 2.3 mmol) was dissolved in DMF (25 mL). NaN_3 (0.22 g, 3.4 mmol, 1.5 equiv) was added and the solution was heated to 60 °C overnight. The reaction was allowed to cool down to room temperature, and saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded azide **434** as a colorless oil (0.27 g, 71%). The spectroscopic data of this compound were in accord with those reported in the literature.²²²

^1H NMR (400 MHz, CDCl_3): δ 6.29 (s, 1H, $\text{C}^5\text{-H}$), 5.69 (s, 1H, $\text{C}^5\text{-H}$), 4.23 (q, $J = 7.1$ Hz, 2H, $\text{C}^6\text{-H}$), 3.44 (t, $J = 6.9$ Hz, 2H, $\text{C}^1\text{-H}$), 2.61 (t, $J = 6.9$ Hz, 2H, $\text{C}^2\text{-H}$), 1.31 (t, $J = 7.2$ Hz, 3H, $\text{C}^7\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 166.5 (C^4), 137.0 (C^3), 127.6 (C^5), 61.0 (C^6), 50.1 (C^1), 31.9 (C^2), 14.3. (C^7).

IR: 2983 (w), 2935 (w), 2095 (s), 1713 (s), 1447 (w), 1299 (m), 1199 (s), 1150 (s), 1024 (m), 953 (m).

R_f (PE/EtOAc 8:2) = 0.82.

4-azido-2-methylenebutan-1-ol **435**

To a solution of ester **434** (50 mg, 0.32 mmol) in THF (5.0 mL) was added dropwise DIBALH (1 M solution in toluene, 0.96 mL, 0.96 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 16 h. Saturated Rochelle's salts was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude alcohol **435** was used directly in the next step without further purification.

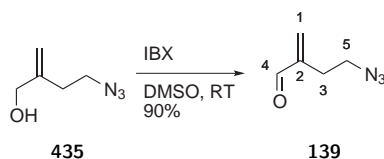
^1H NMR (400 MHz, CDCl_3): δ 5.16 (s, 1H, $\text{C}^1\text{-H}$), 4.99 (s, 1H, $\text{C}^1\text{-H}$), 4.11 (s, 2H, $\text{C}^4\text{-H}$), 3.44 (t, $J = 7.0$ Hz, 2H, $\text{C}^5\text{-H}$), 2.39 (t, $J = 7.0$ Hz, 2H, $\text{C}^3\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 145.3 (C^2), 112.7 (C^1), 66.0 (C^4), 50.0 (C^5), 32.4 (C^3).

IR: 3338 (br w), 2928 (w), 2875 (w), 2090 (s), 1263 (m), 1023 (m), 904 (m).

No HRMS could be obtained from this structure due to its instability.

R_f (PE/EtOAc 7:3) = 0.33.

4-azido-2-methylenebutan-1-al **139**

To a solution of alcohol **435** (40 mg, 0.31 mmol) in DMSO (2.0 mL) was added IBX (0.18 g, 0.62 mmol, 2.0 equiv) and the reaction mixture was stirred for 1 h. The mixture was filtered, saturated NaHCO_3 was added and the mixture was extracted with Et_2O . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 7:3) afforded aldehyde **139** as a colorless oil (35 mg, 90%).

^1H NMR (400 MHz, CDCl_3): δ 9.55 (s, 1H, $\text{C}^4\text{-H}$), 6.40 (s, 1H, $\text{C}^1\text{-H}$), 6.15 (s, 1H, $\text{C}^1\text{-H}$), 3.41 (t, $J = 6.8$ Hz, 2H, $\text{C}^5\text{-H}$), 2.55 (t, $J = 6.8$ Hz, 2H, $\text{C}^3\text{-H}$).

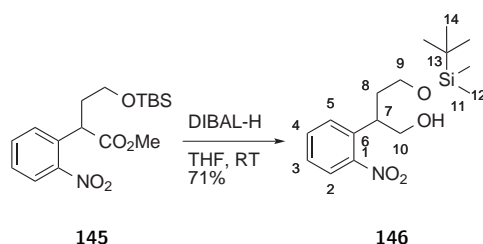
^{13}C NMR (101 MHz, CDCl_3): δ 194.0 (C^4), 146.3 (C^2), 136.4 (C^1), 49.3 (C^5), 27.9 (C^3).

IR: 2932 (w), 2823 (w), 2090 (s), 1686 (s), 1260 (m), 954 (m).

No HRMS could be obtained from this structure due to its instability.

R_f (PE/EtOAc 7:3) = 0.59.

4-(*tert*-butyldimethylsilyloxy)-2-(2-nitrophenyl)butan-1-ol 146



To a solution of ester **145** (50 mg, 0.14 mmol) in THF (5.0 mL) was added dropwise DIBALH (1 M solution in toluene, 0.42 mL, 0.42 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 0.5 h. Saturated Rochelle's salts was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (9:1 PE/EtOAc) afforded the desired alcohol **146** as a yellow oil (32 mg, 71% yield).

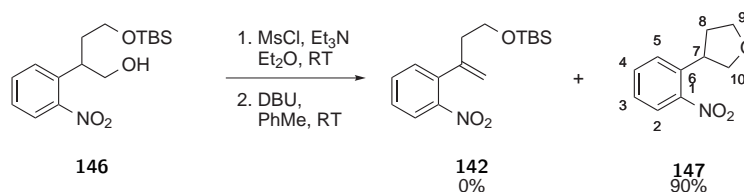
^1H NMR (400 MHz, CDCl_3): δ 7.74 (m, 1H, $\text{C}^2\text{-H}$), 7.56-7.54 (m, 2H, $\text{C}^{3,5}\text{-H}$), 7.35 (m, 1H, $\text{C}^4\text{-H}$), 3.85 (dd, $J = 4.4$ Hz, 2H, $\text{C}^{10}\text{-H}$), 3.70 (m, 1H, $\text{C}^9\text{-H}$), 3.60 (m, 1H, $\text{C}^9\text{-H}$), 3.47 (m, 1H, $\text{C}^7\text{-H}$), 2.03 (m, 1H, $\text{C}^8\text{-H}$), 1.93 (m, 1H, $\text{C}^8\text{-H}$), 0.88 (s, 9H, $\text{C}^{14}\text{-H}$), 0.03 (s, 3H, $\text{C}^{12}\text{-H}$), 0.03 (s, 3H, $\text{C}^{12}\text{-H}$), OH peak not observed.

^{13}C NMR (101 MHz, CDCl_3): δ 150.6 (C^1), 137.8 (C^6), 132.7 (C^3), 129.0 (C^5), 127.3 (C^4), 124.2 (C^2), 66.7 (C^{10}), 61.7 (C^9), 40.2 (C^7), 35.9 (C^8), 26.0 (C^{14}), 18.3 (C^{13}), -5.4 (C^{12}).

IR: 3366 (br w), 2930 (m), 2857 (m), 1527 (s), 1358 (m), 1256 (w), 837 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_4\text{Si}^+$: 326.1782; Found: 326.1792.

R_f (PE/EtOAc 8:2) = 0.32.

3-(2-nitrophenyl)tetrahydrofuran **147**

To a solution of the alcohol **146** (63 mg, 0.19 mmol) in Et₂O (2.0 mL) was added triethylamine (60 μ L, 0.43 mmol, 2.2 equiv) followed by MsCl (16 μ L, 0.21 mmol, 1.1 equiv). After 1 h, the reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude mesyl alcohol was dissolved in toluene (2.0 mL), and DBU (40 μ L, 0.29 mmol, 1.5 equiv) was added. The reaction was stirred for 0.5 h at room temperature. Water was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (9:1 PE/EtOAc) afforded the side-product **147** as a yellow oil (33 mg, 90% yield). The desired elimination product **142** was not observed.

¹H NMR (400 MHz, CDCl₃): δ 7.77 (m, 1H, C²-H), 7.61-7.52 (m, 2H, C^{3,5}-H), 7.35 (m, 1H, C⁴-H), 4.08-3.99 (m, 2H, C^{9,10}-H), 3.96-3.81 (m, 3H, C^{7,9,10}-H), 2.49 (m, 1H, C⁸-H), 2.04 (m, 1H, C⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.3 (C¹), 138.4 (C⁶), 133.1 (C³), 128.2 (C⁵), 127.2 (C⁴), 124.0 (C²), 74.4 (C¹⁰), 68.3 (C⁹), 39.5 (C⁷), 34.8 (C⁸).

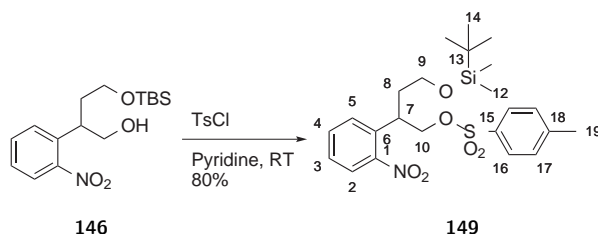
IR: 2930 (w), 2866 (w), 1525 (s), 1355 (m).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₁₀H₁₂NO₃⁺: 194.0812; Found: 194.0811.

R_f (PE/EtOAc 8:2) = 0.26.

4-((*tert*-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butyl
sulfonate **149**

4-methylbenzene-



To a solution of the alcohol **146** (50 mg, 0.15 mmol) in pyridine (1.0 mL) at 0 °C was added tosyl chloride (44 mg, 0.23 mmol, 1.5 equiv). The solution was stirred at room temperature for 2 h. Aqueous 1 M HCl was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (9:1 PE/EtOAc) afforded the tosylate **149** as a yellow oil (58 mg, 80% yield).

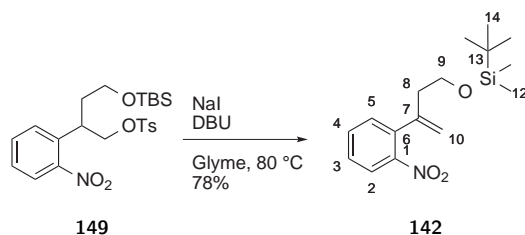
¹H NMR (400 MHz, CDCl₃): δ 7.74 (dd, *J* = 8.1, 1.3 Hz, 1H, C²-H), 7.65 (d, *J* = 8.3 Hz, 2H, C¹⁶-H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H, C⁴-H), 7.42 (dd, *J* = 7.9, 1.3 Hz, 1H, C⁵-H), 7.36 (m, 1H, C³-H), 7.35-7.18 (m, 2H, C¹⁷-H), 4.28 (d, *J* = 5.3 Hz, 2H, C¹⁰-H), 3.73 (m, 1H, C⁷-H), 3.52 (m, 1H, C⁹-H), 3.41 (m, 1H, C⁹-H), 2.43 (s, 3H, C¹⁹-H), 2.00-1.91 (m, 2H, C⁸-H), 0.80 (s, 9H, C¹⁴-H), -0.09 (s, 3H, C¹²-H), -0.09 (s, 3H, C¹²-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.5 (C¹), 144.8 (C¹⁵), 134.6 (C⁶), 132.6 (C⁴), 132.6 (C¹⁸), 129.8 (C¹⁷), 129.5 (C⁵), 127.8 (C¹⁶), 127.3 (C³), 124.5 (C²), 72.6 (C¹⁰), 60.0 (C⁹), 35.8 (C⁷), 34.2 (C⁸), 25.8 (C¹⁴), 21.7 (C¹⁹), 18.2 (C¹³), -5.6 (C¹²).

IR: 2953 (w), 2930 (w), 2857 (w), 1527 (s), 1358 (s), 1177 (s), 1098 (m), 966 (m), 837 (s), 780 (s).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₃H₃₃NNaO₆SSi⁺: 502.1690; Found: 502.1699.

R_f (PE/EtOAc 8:2) = 0.5.

tert*-butyldimethyl((3-(2-nitrophenyl)but-3-en-1-yl)oxy)silane **142*

To a solution of the tosylate **149** (20 mg, 0.042 mmol) in glyme (0.50 mL) was added NaI (13 mg, 0.065 mmol, 2.0 equiv) and DBU (12 μ L, 0.065 mmol, 2.0 equiv). The mixture was heated at 80 $^\circ$ C overnight. Saturated NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (95:5 PE/EtOAc) afforded the olefin **142** as a yellow oil (10 mg, 78% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.88 (dd, J = 7.8, 1.1 Hz, 1H, C²-H), 7.54 (td, J = 7.8, 1.3 Hz, 1H, C³-H), 7.40 (m, 1H, C⁴-H), 7.34 (dd, J = 7.8, 1.3 Hz, 1H, C⁵-H), 5.22 (q, J = 1.2 Hz, 1H, C¹⁰-H), 5.03 (m, 1H, C¹⁰-H), 3.69 (t, J = 6.8 Hz, 2H, C⁹-H), 2.59 (td, J = 6.8, 0.8 Hz, 2H, C⁸-H), 0.85 (s, 9H, C¹⁴-H), -0.01 (s, 6H, C¹²-H).

¹³C NMR (101 MHz, CDCl₃): δ 148.2 (C¹), 144.5 (C⁶), 138.3, (C⁹), 132.6 (C⁵), 131.4 (C³), 128.0 (C⁴), 124.1 (C²), 116.1 (C¹⁰), 61.8 (C⁹), 40.0 (C⁸), 25.9 (C¹⁴), 18.2 (C¹³), -5.4 (C¹²).

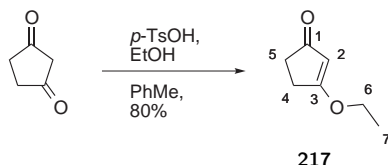
IR: 2953 (w), 2929 (w), 2885 (w), 2856 (w), 1527 (s), 1471 (w), 1349 (m), 1255 (m), 1096 (s), 933 (w), 906 (w), 834 (s), 776 (s).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₆H₂₆NO₃Si⁺: 308.1676; Found: 308.1700.

R_f (PE/EtOAc 8:2) = 0.8.

8.3 Experimental Procedures of Chapter 3

3-ethoxycyclopent-2-en-1-one 217



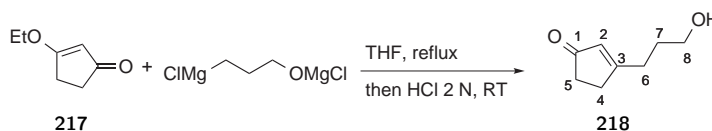
Following a reported procedure,²²⁴ to a solution of 1,3-cyclopentadione (20 g, 0.20 mol) and EtOH (46 mL, 0.83 mol, 4.0 equiv) in toluene (200 mL) was added *p*-TsOH (0.3 g, 2.0 mmol, 1.0 mol%). The reaction mixture was heated at refluxing temperature for 16 h. Water was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded pure enone **217** as a yellow oil (21 g, 80% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²⁵

¹H NMR (400 MHz, CDCl₃): δ 5.28 (s, 1H, C²-H), 4.04 (q, *J* = 7.1 Hz, 2H, C⁶-H), 2.62-2.58 (m, 2H, C⁵-H), 2.46-2.41 (m, 2H, C⁴-H), 1.41 (t, *J* = 7.1 Hz, 3H, C⁷-H).

¹³C NMR (101 MHz, CDCl₃): δ 206.1 (C¹), 190.2 (C³), 104.7 (C²), 67.7 (C⁶), 34.0 (C⁵), 28.6 (C⁴), 14.2 (C⁷).

R_f (EtOAc) = 0.46.

3-(3-hydroxypropyl)cyclopent-2-en-1-one 218



Following a reported procedure,²² to a solution of 3-chloropropanol (2.4 mL, 29 mmol, 2.0 equiv) in THF (45 mL) at -78 °C was added dropwise a solution of MeMgCl (3 M in THF, 9.5 mL, 29 mmol, 2.0 equiv). The solution was allowed to warm to RT. When no more gas was produced, magnesium turning (0.76 g, 31 mmol, 2.2 equiv) was added and the mixture was

²²⁴Kikani, B. B.; Mckee, J. R.; Zanger, M. *Synthesis* **1991**, 23, 176–176

²²⁵Reimann, E; Poeschl, K *Pharmazie* **1995**, 50, 589–592

heated at reflux for 3 h. To the above freshly prepared Grignard reagent solution at refluxing temperature was added dropwise a solution of 3-ethoxycyclopent-2-en-1-one **217** (1.8 g, 14 mmol) in THF (45 mL) over 20 min. The reaction mixture was stirred at refluxing temperature for 2 h before being allowed to cool down to RT. The reaction was quenched by slow addition of saturated aqueous NH_4Cl . DCM and 2 M HCl was added to the reaction mixture and the biphasic reaction mixture was stirred vigorously for 3 h. The layers were separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give crude enone **218** as a yellow oil (1.4 g), which was used for the next reaction without further purification. An analytical sample was obtained by FCC (EtOAc) to give **218** as a colorless oil. The spectroscopic data of this compound were in accord with those reported in the literature.²²

^1H NMR (400 MHz, CDCl_3): δ 5.96 (t, $J = 1.4$ Hz, 1H, $\text{C}^2\text{-H}$), 3.70 (t, $J = 7.1$ Hz, 2H, $\text{C}^8\text{-H}$), 2.62-2.57 (m, 2H, $\text{C}^5\text{-H}$), 2.52 (t, $J = 7.1$ Hz, 2H, $\text{C}^6\text{-H}$), 2.43-2.38 (m, 2H, $\text{C}^4\text{-H}$), 1.92 (br s, 1H, $\text{C}^8\text{-OH}$), 1.85 (quintet, $J = 7.1$ Hz, 2H, $\text{C}^7\text{-H}$).

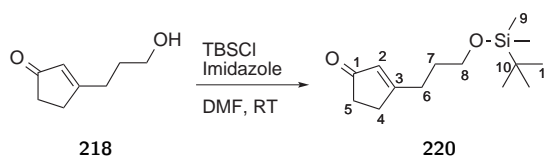
^{13}C NMR (101 MHz, CDCl_3): δ 210.3 (C^1), 182.7 (C^3), 129.6 (C^2), 62.1 (C^8), 35.4 (C^5), 31.8 (C^6), 30.1 (C^7 or C^4), 30.0 (C^7 or C^4).

IR: 3402 (br w), 2936 (w), 2867 (w), 1703 (s), 1673 (s), 1611 (s), 1437 (w), 1190 (w), 1056 (m),

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_8\text{H}_{13}\text{O}_2^+$: 141.0910; Found: 141.0909.

R_f (EtOAc) = 0.23.

3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclopent-2-en-1-one **220**



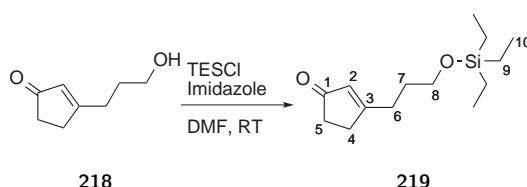
Following a reported procedure,²² to a solution of crude **218** (obtained from 14 mmol of 3-ethoxycyclopent-2-en-1-one) in DMF (100 mL) at 0 °C were added imidazole (1.5 g, 22 mmol, 1.5 equiv) and TBSCl (2.4 g, 16 mmol, 1.1 equiv). The solution was stirred at RT for 3 h. Saturated aqueous NaHCO_3 was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 4:1) afforded compound **220** as a slightly yellow oil (2.2 g, 60% yield over two steps). The spectroscopic data of this compound were in accord with those reported in the literature.²²

^1H NMR (400 MHz, CDCl_3): δ 5.95 (s, 1H, $\text{C}^2\text{-H}$), 3.66 (t, $J = 6.1$ Hz, 2H, $\text{C}^8\text{-H}$), 2.62-2.57 (m, 2H, $\text{C}^5\text{-H}$), 2.48 (t, $J = 7.5$ Hz, 2H, $\text{C}^6\text{-H}$), 2.43-2.38 (m, 2H, $\text{C}^4\text{-H}$), 1.80 (tt, $J = 7.5, 6.1$ Hz, 2H, $\text{C}^7\text{-H}$), 0.89 (s, 9H, $\text{C}^{11}\text{-H}$), 0.05 (s, 6H, $\text{C}^9\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 210.2 (C^1), 183.0 (C^3), 129.6 (C^2), 62.4 (C^8), 35.5 (C^5), 31.8 (C^6), 30.3 (C^7 or C^4), 30.2 (C^7 or C^4), 26.1 (C^{11}), 18.5 (C^{10}), -5.2 (C^9).

R_f (EtOAc) = 0.87.

3-(3-((triethylsilyl)oxy)propyl)cyclopent-2-en-1-one **219**



To a solution of crude **218** (obtained from 14 mmol of 3-ethoxycyclopent-2-en-1-one) in DMF (100 mL) at 0 °C were added imidazole (1.5 g, 22 mmol, 1.5 equiv) and TESCl (2.6 mL, 16 mmol, 1.1 equiv) were added. The solution was stirred at RT for 3 h. Saturated aqueous NaHCO_3 was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **219** as a yellow oil (2.2 g, 61% yield over two steps).

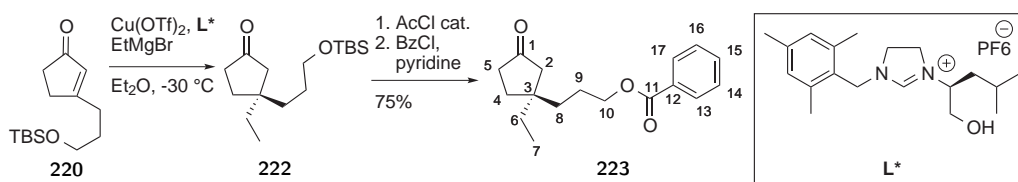
^1H NMR (400 MHz, CDCl_3): δ 5.94 (t, $J = 1.4$ Hz, 1H, $\text{C}^2\text{-H}$), 3.65 (t, $J = 6.4$ Hz, 2H, $\text{C}^8\text{-H}$), 2.62-2.56 (m, 2H, $\text{C}^5\text{-H}$), 2.48 (t, $J = 8.0$ Hz, 2H, $\text{C}^6\text{-H}$), 2.42-2.37 (m, 2H, $\text{C}^4\text{-H}$), 1.80 (tt, $J = 8.0, 6.4$ Hz, 2H, $\text{C}^7\text{-H}$), 0.95 (t, $J = 7.9$ Hz, 9H, $\text{C}^{10}\text{-H}$), 0.59 (q, $J = 7.9$ Hz, 6H, $\text{C}^9\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 210.2 (C^1), 183.0 (C^3), 129.6 (C^2), 62.0 (C^8), 35.5 (C^5), 31.8 (C^6), 30.3 (C^7 or C^4), 30.2 (C^7 or C^4), 6.9 (C^{10}), 4.5 (C^9).

IR: 2953 (w), 2912 (w), 2876 (w), 1708 (s), 1676 (w), 1617 (w), 1097 (s), 1009 (w), 732 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{27}\text{O}_2\text{Si}^+$: 255.1775; Found: 255.1781.

R_f (PE/EtOAc 1:1) = 0.5.

3-(1-ethyl-3-oxocyclopentyl)propyl benzoate **223**

Following a reported procedure,^{93,226} to a solution of $\text{Cu}(\text{OTf})_2$ (1.6 mg, 0.0045 mmol, 0.75 mol%) and the ligand (2.4 mg, 0.0060 mmol, 1.0 mol%) in Et_2O (2.0 mL) at -30°C was added dropwise a solution of EtMgBr (3.0 M in Et_2O , 0.24 mL, 1.2 equiv). The mixture was stirred for 40 min at -30°C . Then, a solution of **220** (0.15 g, 0.60 mmol) in Et_2O (6.0 mL) was added dropwise to the mixture *via* an automatic syringe pump over 30 min, and the mixture was stirred for 2 h. The reaction mixture was quenched by dropwise addition of a saturated NH_4Cl solution at -30°C , and the reaction mixture was allowed to warm up to RT. The mixture was extracted with Et_2O . The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude compound **222** thus obtained was used for the next step without further purification.

To a solution of the crude ketone **222** (obtained from 0.60 mmol of enone **220**) in MeOH (7.0 mL) was added acetyl chloride (8.0 μL , 20 mol%) at 0°C . The reaction mixture was stirred at RT for 2 h. The solution was concentrated *in vacuo*. The crude alcohol thus obtained was used for the next step without further purification.

The crude alcohol was dissolved in DCM (10 mL) and stirred at 0°C . Pyridine (95 μL , 1.4 mmol, 2.0 equiv) and benzoyl chloride (0.11 mL, 0.90 mmol, 1.5 equiv) were added. The reaction mixture was stirred for 2 h. Aqueous 1 M HCl was added. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (9:1 PE/EtOAc) afforded benzoyl ester **223** as a colorless oil (0.12 g, 75%, ee=5%).

^1H NMR (400 MHz, CDCl_3): δ 8.03 (dd, $J = 8.2, 1.4$ Hz, 2H, $\text{C}^{13,17}\text{-H}$), 7.56 (m, 1H, $\text{C}^{15}\text{-H}$), 7.45 (dd, $J = 8.2, 1.4$ Hz, 2H, $\text{C}^{14,16}\text{-H}$), 4.32 (t, $J = 6.5$ Hz, 2H, $\text{C}^{10}\text{-H}$), 2.28 (t, $J = 8.0$ Hz, 2H, $\text{C}^5\text{-H}$), 2.13 (d, $J = 18.0$ Hz, 1H, $\text{C}^2\text{-H}$), 2.08 (d, $J = 18.0$ Hz, 1H, $\text{C}^2\text{-H}$), 1.90-1.78 (m, 2H, $\text{C}^4\text{-H}$), 1.78-1.74 (m, 2H, $\text{C}^9\text{-H}$), 1.57-1.49 (m, 2H, $\text{C}^8\text{-H}$), 1.46 (q, $J = 7.3$ Hz, 2H, $\text{C}^6\text{-H}$), 0.88 (t, $J = 7.3$ Hz, 3H, $\text{C}^7\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 220.0 (C^{11}), 167.1 (C^1), 133.4 (C^{15}), 130.7 (C^{12}), 130.0 (C^{13}),

²²⁶The chiral ligand used for enantioselective 1,4 additions on cyclopentenone was kindly provided by Professor Alexakis (Geneva University).

Chapter 8: Experimental Section

128.9 (C¹⁴), 65.7 (C¹⁰), 51.1 (C²), 42.8 (C³), 36.9 (C⁵), 33.9 (C⁸), 33.2 (C⁴), 30.1 (C⁶), 24.3 (C⁹), 9.0 (C⁷).

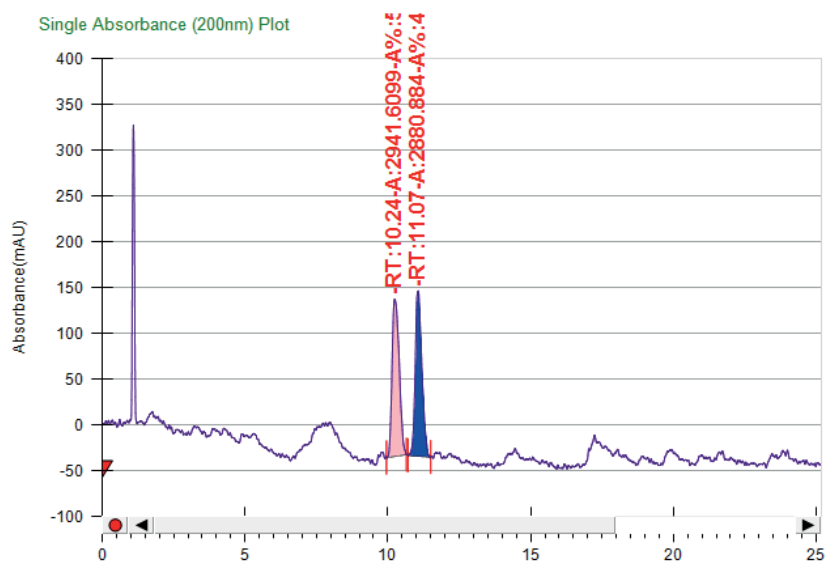
IR: 2957 (w), 1737 (s), 1718 (s), 1281 (s), 1069 (m), 1028 (m), 714 (m).

HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₇H₂₃O₃⁺: 275.1647; Found: 275.1644.

R_f (PE/Et₂O/Et₃N 8:2) = 0.6.

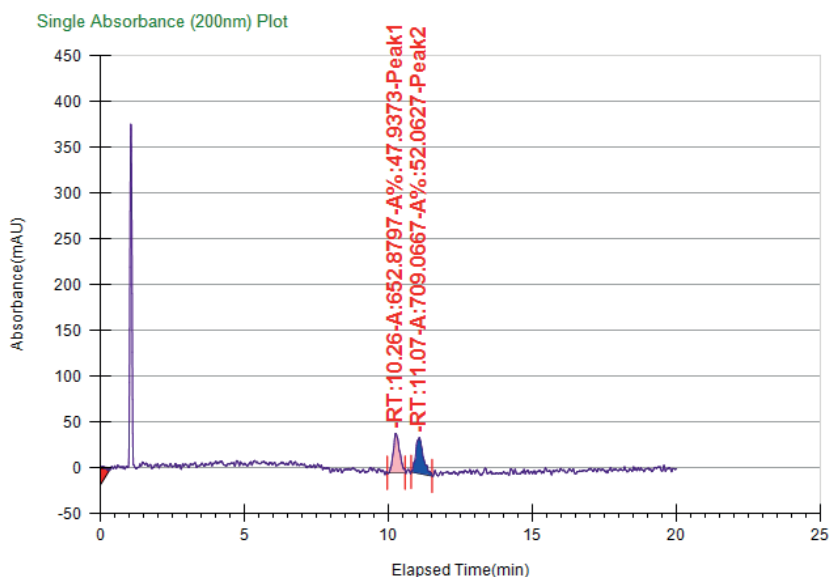
Co-Solvent %	Total Flow	Column	Co-Solvent	Back Pressure
5	4	IC	MeOH	150

Peak #	Ret. Time	Area	Area %
1	10.24 min	2941.6099	50.5215
2	11.07 min	2880.884	49.4785

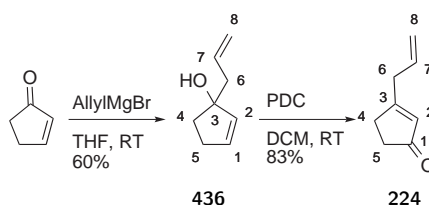


Co-Solvent %	Total Flow	Column	Co-Solvent	Back Pressure
5	4	IC	MeOH	150

Peak #	Ret. Time	Area	Area %
1	10.26 min	652.8797	47.9373
2	11.07 min	709.0667	52.0627



3-allylcyclopent-2-en-1-one **224**



Following a known procedure,⁹⁴ a solution of cyclopent-2-en-1-one (1.2 mL, 15 mmol) in THF (2.4 mL) was added dropwise to a stirred solution of allylmagnesium bromide (1 M in Et₂O, 18 mL, 18 mmol, 1.2 equiv) at 0 °C. The mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was cooled to 0 °C, 15 mL of a saturated solution of NH₄Cl were added and the mixture was stirred at RT for 15 min. The aqueous layer was extracted with Et₂O and the combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by Kugelrohr distillation (Bp = 120-130 °C/1.2 mmHg) afforded product **436** as a colorless oil (1.1 g, 60% yield). The spectroscopic data of this compound were in accord with those reported in the literature.⁹⁴

Pyridium dichromate (5.5 g, 15 mmol, 2.0 equiv) was added in one portion to a stirred solution of **436** (0.90 g, 7.2 mmol, 1.0 equiv) in DCM (9.0 mL) at RT. The resulting brown suspension was stirred for 6 h. Et₂O was added and the solid residue was removed by filtration through a plug of silica gel, and washed with Et₂O. The filtrate was concentrated *in vacuo*. Purification by Kugelrohr distillation (Bp= 118-128 °C/1.2 mmHg) afforded product **224** as a colorless oil (0.73 g, 83% yield). The spectroscopic data of this compound were in accord with those reported in the literature.⁹⁴

Compound 436

¹H NMR (400 MHz, CDCl₃): δ 5.91-5.80 (m, 2H, C^{7,2}-H), 5.70 (dt, *J* = 5.6, 2.2 Hz, 1H, C¹-H), 5.22-5.01 (m, 2H, C⁸-H), 2.50 (dddt, *J* = 17.0, 8.7, 4.6, 2.3 Hz, 1H, C⁵-H), 2.41 (dt, *J* = 7.4, 1.2 Hz, 2H, C⁶-H), 2.29 (dddt, *J* = 17.0, 8.7, 4.6, 2.3 Hz, 1H, C⁵-H), 2.04 (ddd, *J* = 13.4, 8.7, 4.6 Hz, 1H, C⁴-H), 1.83 (ddd, *J* = 13.4, 8.7, 4.6 Hz, 1H, C⁴-H), OH peak not observed.

R_f (PE/EtOAc 1:1) = 0.67.

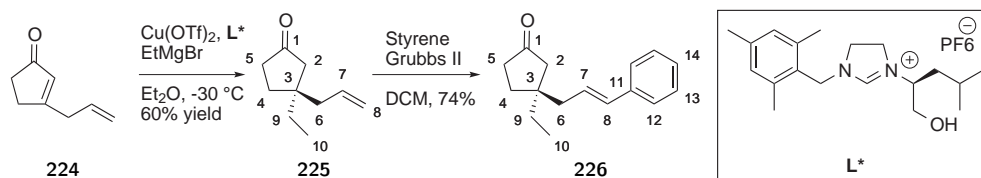
Compound 224

¹H NMR (400 MHz, CDCl₃): δ 5.94 (s, 1H, C²-H), 5.91-5.77 (m, 1H, C⁷-H), 5.19 (m, 1H, C⁸-H), 5.13 (m, 1H, C⁸-H), 3.13 (d, *J* = 6.9 Hz, 2H, C⁶-H), 2.62-2.55 (m, 2H, C⁴-H), 2.42-2.38 (m, 2H, C⁵-H).

¹³C NMR (101 MHz, CDCl₃): δ 210.0 (C¹), 180.6 (C³), 132.9 (C⁷), 130.2 (C²), 118.4 (C⁸), 38.0 (C⁶), 35.5 (C⁵), 31.4 (C⁴).

R_f (PE/EtOAc 1:1) = 0.44.

Enantioselective synthesis of 3-allyl-3-ethylcyclopentan-1-one **226**



Following a reported procedure,⁹³ to a solution of Cu(OTf)₂ (1.6 mg, 0.0045 mmol, 0.75 mol%) and the ligand (2.4 mg, 0.0060 mmol, 1.0 mol%) in Et₂O (2.0 mL) at -30 °C was added dropwise

a solution of EtMgBr (3 M in Et₂O, 0.24 mL, 1.2 equiv). The mixture was stirred for 40 min at -30 °C. Then, a solution of **224** (73 mg, 0.60 mmol) in Et₂O (6.0 mL) was added dropwise to the mixture *via* an automatic syringe pump over 30 min, and the mixture was stirred for 2 h. The reaction mixture was quenched by dropwise addition of a saturated NH₄Cl solution at -30 °C, and the reaction mixture was allowed to warm up to RT. The mixture was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (9:1 PE/Et₂O) afforded product **225** as a colorless oil (55 mg, 60% yield).

To a solution of compound **225** (27 mg, 0.18 mmol) and styrene (84 μL, 0.36 mmol, 2.0 equiv) in DCM (18 mL) was added Grubbs II catalyst (30 mg, 0.036 mmol, 0.20 equiv). The reaction mixture was stirred at RT overnight. It was then heated at 30 °C for 4 h. Aqueous 1 M HCl was added, and the mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/Et₂O 10:0 to 9:1) afforded **226** as a colorless oil (16 mg, 40%, ee = 10%).

Compound 225

¹H NMR (400 MHz, CDCl₃): δ 5.77 (ddt, *J* = 16.7, 10.5, 7.4 Hz, 1H, C⁷-H), 5.13-5.01 (m, 2H, C⁸-H), 2.26 (t, *J* = 8.0 Hz, 2H, C⁵-H), 2.14 (d, *J* = 7.4 Hz, 2H, C⁶-H), 2.12 (d, *J* = 7.8 Hz, 1H, C²-H), 2.03 (d, *J* = 7.8 Hz, 1H, C²-H), 1.89-1.72 (m, 2H, C⁴-H), 1.44 (q, *J* = 7.4 Hz, 2H, C⁹-H), 0.89 (t, *J* = 7.4 Hz, 3H, C¹⁰-H).

¹³C NMR (101 MHz, CDCl₃): δ 219.5 (C¹), 134.3 (C⁷), 118.0 (C⁸), 49.9 (C²), 42.7 (C⁶), 41.4 (C³), 36.6 (C⁵), 32.2 (C⁴), 30.6 (C⁹), 8.5 (C¹⁰).

IR: 2963 (w), 2921 (w), 1741 (s), 1462 (w), 1405 (w), 1166 (w), 915 (w).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₁₀H₁₇O⁺: 153.1279; Found: 153.1361.

R_f (PE/Et₂O 3:2) = 0.50.

Compound 226

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.28 (4H, m, C^{12,13}-H), 7.23 (m, 1H, C¹⁴-H), 6.43 (dt, *J* = 15.8, 1.3 Hz, 1H, C⁸-H), 6.17 (dt, *J* = 15.4, 7.5 Hz, 1H, C⁷-H), 2.30 (t, *J* = 5.2 Hz, 2H, C⁵-H), 2.28 (dd, *J* = 2.6, 4.1 Hz, 2H, C⁶-H), 2.19 (d, *J* = 18.1 Hz, 1H, C²-H), 2.09 (d, *J* = 18.1 Hz, 1H, C²-H), 1.89-1.71 (m, 2H, C⁴-H), 1.49 (q, *J* = 7.4 Hz, 2H, C⁹-H), 0.93 (t, *J* = 7.4 Hz, 3H, C¹⁰-H).

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^{13}C NMR (101 MHz, CDCl_3): δ 219.9 (C^1), 137.1 (C^{11}), 132.9 (C^8), 128.4 (C^{13}), 127.1 (C^{14}), 125.9 (C^{12}), 125.8 (C^7), 49.8 (C^2), 43.2 (C^3), 40.3 (C^5), 36.5 (C^6), 32.1 (C^4), 30.7 (C^9), 8.5 (C^{10}).

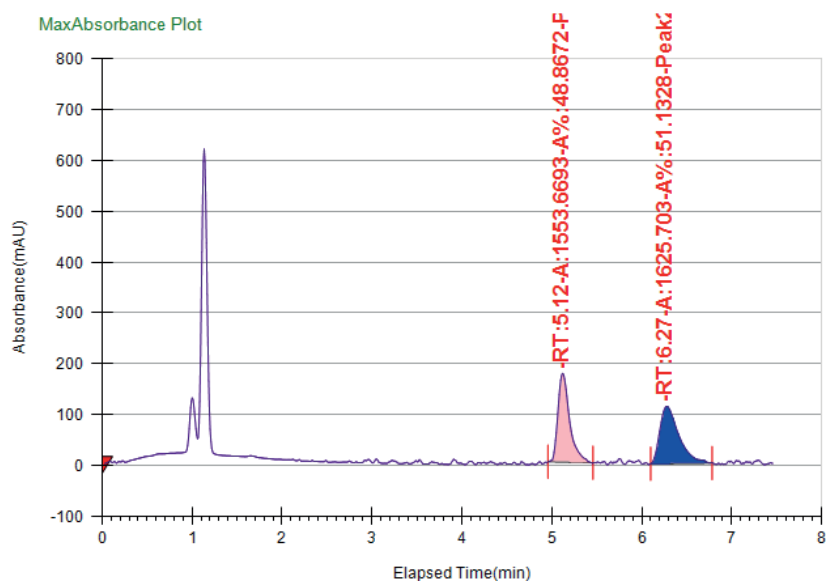
IR: 2961 (w), 2923 (w), 1739 (s), 1450 (w), 1160 (w), 967 (m), 737 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{21}\text{O}^+$: 229.1592; Found: 229.1585.

R_f (PE/ Et_2O 9:1) = 0.16.

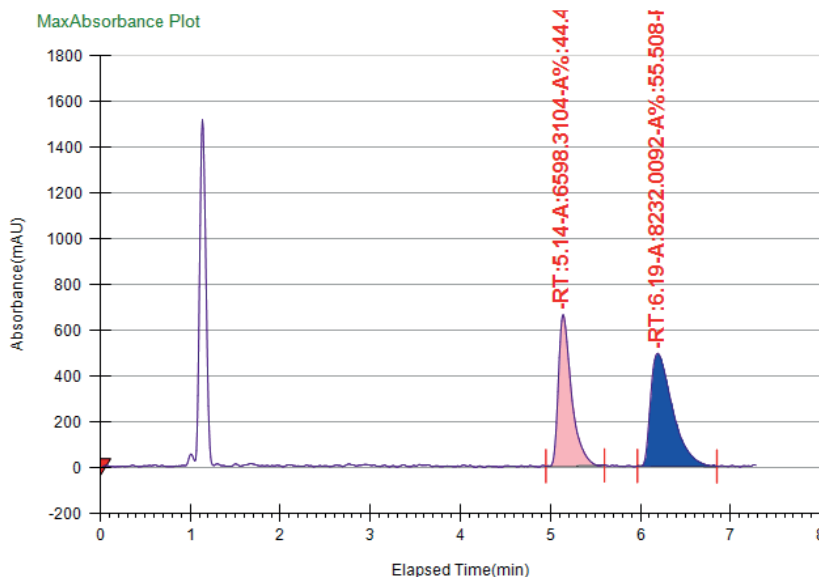
Co-Solvent %	Total Flow	Column	Co-Solvent	Back Pressure
5	4	AD-H	MeOH	150

Peak #	Ret. Time	Area	Area %
1	5.12 min	1553.6693	48.8672
2	6.27 min	1625.703	51.1328

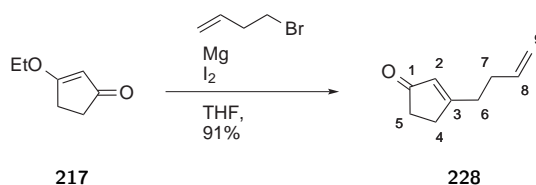


Co-Solvent %	Total Flow	Column	Co-Solvent	Back Pressure
5	4	AD-H	MeOH	150

Peak #	Ret. Time	Area	Area %
1	5.14 min	6598.3104	44.492
2	6.19 min	8232.0092	55.508



3-(but-3-en-1-yl)cyclopent-2-en-1-one **228**



Following a reported procedure,⁹⁴ to a suspension of magnesium turning (0.92 g, 38 mmol, 2.0 equiv) in THF (50 mL) at RT was added I_2 (one crystal), and the solution was heated to 60 °C. 4-bromo-1-butene (2.2 mL, 22 mmol, 1.2 equiv) was added dropwise, keeping a gentle reflux. After addition, the mixture was heated to refluxing temperature for 1 h. Then, a solution of 3-ethoxycyclopent-2-en-1-one **217** (2.4 g, 18 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred for 30 min at reflux. The reaction mixture was cooled down to RT. The reaction was quenched with aqueous NH_4Cl . 2 M HCl was then added, followed by DCM. The biphasic mixture was stirred for 30 min. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/ Et_2O 1:1) afforded the pure product **228** as colorless oil (2.2 g,

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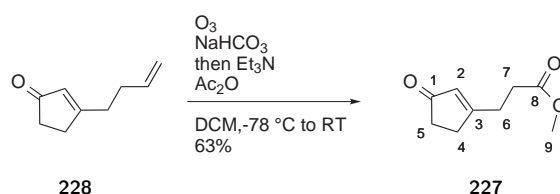
91% yield). The spectroscopic data of this compound were in accord with those reported in the literature.⁹⁴

¹H NMR (400 MHz, CDCl₃): δ 5.96 (quint, J = 1.4 Hz, 1H, C²-H), 5.80 (ddt, J = 17.0, 10.3, 6.5 Hz, 1H, C⁸-H), 5.06 (dq, J = 17.0, 1.5 Hz, 1H, C⁹-H), 5.02 (dq, J = 10.3, 1.5 Hz, 1H, C⁹-H), 2.60-2.56 (m, 2H, C⁴-H), 2.51 (t, J = 7.4 Hz, 2H, C⁶-H), 2.41-2.38 (m, 2H, C⁵-H), 2.38-2.31 (m, 2H, C⁷-H).

¹³C NMR (101 MHz, CDCl₃): δ 210.1 (C¹), 182.1 (C³), 136.9 (C⁸), 129.9 (C²), 115.9 (C⁹), 35.4 (C⁵), 32.8 (C⁶), 31.7 (C⁴), 31.1 (C⁷).

R_f (PE/Ether 1:1) = 0.30

methyl 3-(3-oxocyclopent-1-en-1-yl)propanoate **227**



To a solution of the enone **228** (1.0 g, 7.3 mmol) in DCM/MeOH (2:1, 15 mL) was added NaHCO₃ (0.12 g, 15 mmol, 2.0 equiv). The reaction mixture was cooled down to -78 °C, and ozone was bubbled through the solution. When the blue color persisted, argon was bubbled through the solution for 10 min. Triethylamine (2.0 mL, 14 mmol, 2.0 equiv), and Ac₂O (1.3 mL, 14 mmol, 1.9 equiv) were added, and the mixture was stirred at RT for 2 h. Water was added. The mixture was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/Et₂O 1:9) afforded product **227** as a colorless oil (0.77 g, 63% yield).

¹H NMR (400 MHz, CDCl₃): δ 5.94 (m, 1H, C²-H), 3.70 (s, 3H, C⁹-H), 2.73 (m, 2H, C⁷-H), 2.66-2.59 (m, 4H, C^{5,6}-H), 2.42 (m, 2H, C⁴-H).

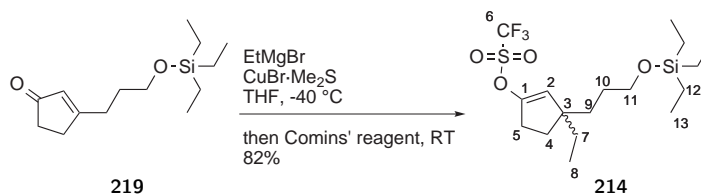
¹³C NMR (101 MHz, CDCl₃): δ 209.7 (C¹), 180.4 (C³), 172.7 (C⁸), 129.6 (C²), 52.1 (C⁹), 35.4 (C⁵), 31.8 (C^{6or7}), 31.5 (C^{6or7}), 28.6 (C⁴).

IR: 2955 (w), 2924 (w), 2852 (w), 1737 (s), 1703 (s), 1616 (m), 1437 (m), 1175 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₉H₁₃O₃⁺: 169.0859; Found: 169.0858.

R_f (Ether) = 0.4

3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate **214**



To a suspension of $\text{CuBr}\cdot\text{Me}_2\text{S}$ (5.7 g, 28 mmol, 2.0 equiv) in THF (85 mL) at -78°C was added dropwise EtMgBr (3 M in THF, 18 mL, 55 mmol, 4.0 equiv). The reaction mixture was stirred at -78°C for 1 h and then warmed to -40°C . To the above prepared cuprate solution was added dropwise a solution of the ketone **219** (3.5 g, 14 mmol) in THF (30 mL) while keeping the solution below -40°C . The reaction mixture was stirred at -40°C for 3 h. A solution of Comins' reagent (10.8 g, 28 mmol, 2.0 equiv) in THF (30 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to RT, and stirred for 24 h. The reaction was quenched with NH_4Cl . The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 20:1) afforded compound **214** as a colorless oil (4.7 g, 82% yield).

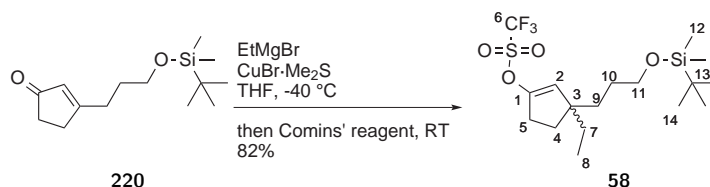
^1H NMR (400 MHz, CDCl_3): δ 5.42 (t, $J = 1.6$ Hz, 1H, $\text{C}^2\text{-H}$), 3.58 (t, $J = 5.9$ Hz, 2H, $\text{C}^{11}\text{-H}$), 2.57 (td, $J = 7.9, 1.6$, 2H, $\text{C}^5\text{-H}$), 1.81-1.76 (m, 2H, $\text{C}^4\text{-H}$), 1.49-1.40 (m, 6H, $\text{C}^{7,9,10}\text{-H}$), 0.95 (t, $J = 7.9$ Hz, 9H, $\text{C}^{13}\text{-H}$), 0.84 (t, $J = 7.4$ Hz, 3H, $\text{C}^8\text{-H}$), 0.59 (t, $J = 7.9$ Hz, 6H, $\text{C}^{12}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 148.0 (C^1), 124.7 (C^2), 118.7 (q, $J = 320.3$ Hz, C^6), 63.6 (C^{11}), 48.9 (C^3), 35.6 (C^9), 32.4 (C^7), 31.5 (C^4), 31.1 (C^5), 28.0 (C^{10}), 8.8 (C^8), 6.9 (C^{13}), 4.6 (C^{12}).

IR: 2957 (w), 2878 (w), 1421 (w), 1214 (w), 1141 (w), 1089 (w), 906 (s), 729 (s).

HRMS: (ESI $^+$) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{32}\text{F}_3\text{O}_4\text{SSi}^+$: 417.1737; Found: 417.1728.

R_f (PE/EtOAc 95:5) = 0.48.

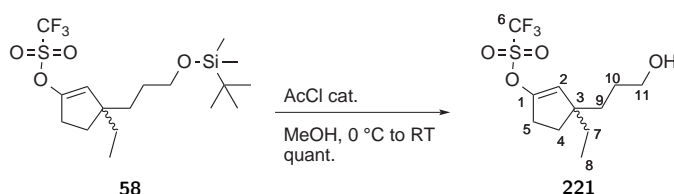
3-ethyl-3-(3-((dimethyltertbutylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 58


To a suspension of $\text{CuBr}\cdot\text{Me}_2\text{S}$ (5.7 g, 28 mmol, 2.0 equiv) in THF (85 mL) at -78°C was added dropwise EtMgBr (3 M in THF, 18 mL, 55 mmol, 4.0 equiv). The reaction mixture was stirred at -78°C for 1 h and then warmed to -40°C . To the above prepared cuprate solution was added dropwise a solution of the ketone **220** (3.5 g, 14 mmol) in THF (30 mL) while keeping the solution below -40°C . The reaction mixture was stirred at -40°C for 3 h. A solution of Comins' reagent (11 g, 28 mmol, 2.0 equiv) in THF (30 mL) was added. The reaction mixture was allowed to warm to RT, and stirred for 24 h. The reaction was quenched with NH_4Cl . The reaction mixture was diluted with water and extracted with EtOAc . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/ EtOAc 40:1) afforded compound **58** as a colorless oil (4.7 g, 82% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²

^1H NMR (400 MHz, CDCl_3): δ 5.42 (t, $J = 1.4$ Hz, 1H, $\text{C}^2\text{-H}$), 3.58 (t, $J = 5.4$ Hz, 2H, $\text{C}^{11}\text{-H}$), 2.57 (td, $J = 7.9, 1.4$ Hz, 2H, $\text{C}^5\text{-H}$), 1.83-1.77 (m, 2H, $\text{C}^4\text{-H}$), 1.49-1.39 (m, 6H, $\text{C}^{7,9,10}\text{-H}$), 0.89 (s, 9H, $\text{C}^{14}\text{-H}$), 0.84 (t, $J = 7.4$ Hz, 3H, $\text{C}^8\text{-H}$), 0.04 (s, 6H, $\text{C}^{12}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 148.0 (C^1), 124.8 (C^2), 118.7 (q, $J = 322.2$ Hz, C^6), 63.6 (C^{11}), 48.9 (C^3), 35.6 (C^9), 32.4 (C^7), 31.5 (C^4), 31.1 (C^5), 28.0 (C^{10}), 26.1 (C^{14}), 18.5 (C^{13}), 8.8 (C^8), -5.2 (C^{12}).

R_f (PE/ EtOAc 10:1) = 0.8.

3-ethyl-3-(3-hydroxypropyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 221


To a solution of **58** (14 g, 33 mmol) in MeOH (100 mL) at 0°C was added acetyl chloride

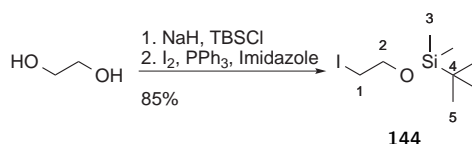
(0.23 mL, 3.3 mmol, 0.10 equiv). After stirring at RT for 1 h, the reaction mixture was concentrated *in vacuo* to afford **221** as a yellowish oil (10 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²² The product thus obtained was used for the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ 5.41 (s, 1H, C²-H), 3.62 (t, J = 6.0 Hz, 2H, C¹¹-H), 2.57 (td, J = 7.3, 1.1 Hz, 2H, C⁵-H), 1.82-1.75 (m, 2H, C⁴-H), 1.54 (s, 1H, C¹¹-OH), 1.55-1.40 (m, 6H, C^{7,9,10}-H), 0.84 (t, J = 7.5 Hz, 3H, C⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 148.1 (C¹), 124.6 (C²), 118.7 (q, J = 319.4 Hz, C⁶), 63.4 (C¹¹), 48.9 (C³), 35.6 (C⁹), 32.4 (C⁷), 31.4 (C⁴), 31.1 (C⁵), 27.9 (C¹⁰), 8.8 (C⁸).

R_f (PE/EtOAc 1:1) = 0.56.

tert*-butyl(2-iodoethoxy)dimethylsilane **144*



Following a reported procedure,²²⁷ ethylene glycol (3.0 mL, 54 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 2.2 g, 54 mmol, 1.0 equiv) in THF (100 mL) at 0 °C. The reaction mixture was stirred at RT for 1 h. TBSCl (7.2 g, 54 mmol, 1.0 equiv) was added at 0 °C and the mixture was stirred for 1 h at RT. The reaction was quenched with saturated NH₄Cl and the reaction mixture was extracted with EtOAc. The combined organic phases were washed with saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford the crude monoprotected diol as a colorless oil.

To a solution of the crude monoprotected diol in THF (300 mL) were added imidazole (5.5 g, 81 mmol, 1.5 equiv) and PPh₃ (18 g, 70 mmol, 1.3 equiv). The solution was cooled down to 0 °C and iodine (16 g, 65 mmol, 1.2 equiv) was added slowly. The resulting mixture was stirred at RT for 1 h, quenched with saturated Na₂S₂O₃, diluted with saturated NH₄Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE) afforded compound **144** as a colorless oil (13 g, 85% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²⁶

¹H NMR (400 MHz, CDCl₃): δ 3.83 (t, J = 7.0 Hz, 2H, C²-H), 3.20 (t, J = 7.0 Hz, 2H, C¹-H),

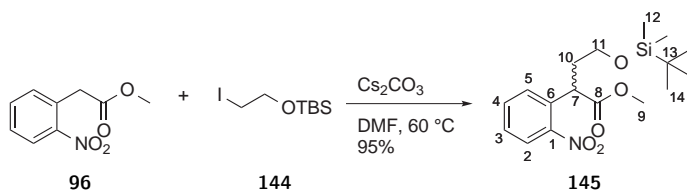
²²⁷Yamashita, S.; Iso, K.; Hiram, M. *Org. Lett.* **2008**, *10*, 3413–3415

0.90 (s, 9H, C⁵-H), 0.08 (s, 6H, C³-H).

¹³C NMR (101 MHz, CDCl₃): δ 64.4 (C²), 26.0 (C⁵), 16.4 (C⁴), 7.2 (C¹), -5.1 (C³).

*R*_f (PE) = 0.26.

methyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoate **145**

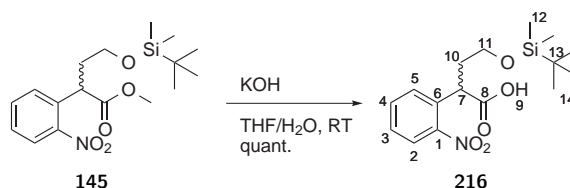


To a solution of the ester **96** (10 g, 51 mmol) and the iodide **144** (16 g, 56 mmol, 1.1 equiv) in DMF (300 mL) was added Cs₂CO₃ (25 g, 77 mmol, 1.5 equiv). The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was allowed to cool down to RT. Water was added and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded compound **145** as a yellow wax (17 g, 95% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²

¹H NMR (400 MHz, CDCl₃): δ 7.91 (dd, *J* = 7.7, 1.3 Hz, 1H, C²-H), 7.57 (td, *J* = 7.7, 1.3 Hz, 1H, C⁴-H), 7.51 (dd, *J* = 7.7, 1.5 Hz, 1H, C⁵-H), 7.41 (td, *J* = 7.7, 1.5 Hz, 1H, C³-H), 4.40 (t, *J* = 7.2 Hz, 1H, C⁷-H), 3.70-3.63 (m, 1H, C¹¹-H), 3.66 (s, 3H, C⁹-H), 3.52 (ddd, *J* = 10.3, 7.4, 5.3 Hz, 1H, C¹¹-H), 2.45 (dtd, *J* = 13.9, 7.2, 5.5 Hz, 1H, C¹⁰-H), 2.00 (dtd, *J* = 13.9, 7.2, 5.7 Hz, 1H, C¹⁰-H), 0.87 (s, 9H, C¹⁴-H), 0.01 (s, 3H, C¹²-H), 0.00 (s, 3H, C¹²-H).

¹³C NMR (101 MHz, CDCl₃): δ 173.2 (C⁸), 149.4 (C¹), 133.8 (C⁶), 133.1 (C⁴), 130.9 (C⁵), 128.2 (C³), 125.0 (C²), 60.5 (C¹¹), 52.4 (C⁹), 43.3 (C⁷), 35.6 (C¹⁰), 26.0 (C¹⁴), 18.4 (C¹³), -5.4 (C¹²).

*R*_f (PE/EtOAc 9:1) = 0.43.

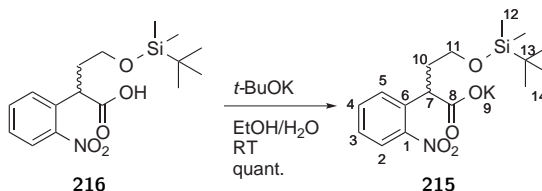
4-((*tert*-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoic acid **216**

To a solution of the ester **145** (2.0 g, 5.7 mmol) in THF (50 mL) was added a solution of aqueous 10% KOH (10 mL). The reaction mixture was stirred until complete consumption of the ester. Water was added and the reaction mixture was acidified to pH 5-6 with 1 M HCl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford carboxylic acid **216** as a yellow oil (1.9 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²² The compound was used for the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ 10.78 (br s, 1H, O⁹-H), 7.95 (dd, J = 7.8, 1.4 Hz, 1H, C²-H), 7.58 (td, J = 7.8, 1.4 Hz, 1H, C⁴-H), 7.50 (dd, J = 7.8, 1.5 Hz, 1H, C⁵-H), 7.43 (td, J = 7.8, 1.5 Hz, 1H, C³-H), 4.41 (t, J = 7.0 Hz, 1H, C⁷-H), 3.69 (dt, J = 10.4, 5.3 Hz, 1H, C¹¹-H), 3.51 (ddd, J = 10.4, 8.0, 5.3 Hz, 1H, C¹¹-H), 2.47 (dddd, J = 14.0, 8.1, 7.0, 5.3 Hz, 1H, C¹⁰-H), 2.01 (ddt, J = 14.0, 7.0, 5.3 Hz, 1H, C¹⁰-H), 0.86 (s, 9H, C¹⁴-H), 0.00 (two s, 6H, C¹²-H).

¹³C NMR (101 MHz, CDCl₃): δ 178.7 (C⁸), 149.1 (C¹), 133.3 (C⁶), 133.2 (C⁴), 131.2 (C⁵), 128.4 (C³), 125.1 (C²), 60.5 (C¹¹), 43.9 (C⁷), 35.1 (C¹⁰), 25.9 (C¹⁴), 18.3 (C¹³), -5.4 (C¹²).

R_f (PE/EtOAc 8:2) = 0.24.

potassium 4-((*tert*-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoate **215**

Following a reported procedure,²² to a solution of crude acid **216** (1.9 g, 5.7 mmol) in EtOH (50 mL) was added dropwise a solution of *t*-BuOK (0.64 g, 5.7 mmol, 1.0 equiv) in EtOH (5.0 mL). The reaction mixture was stirred for 1 h, then concentrated *in vacuo* and coevaporated with toluene to afford the crude carboxylate **215** as a white amorphous solid (2.2 g,

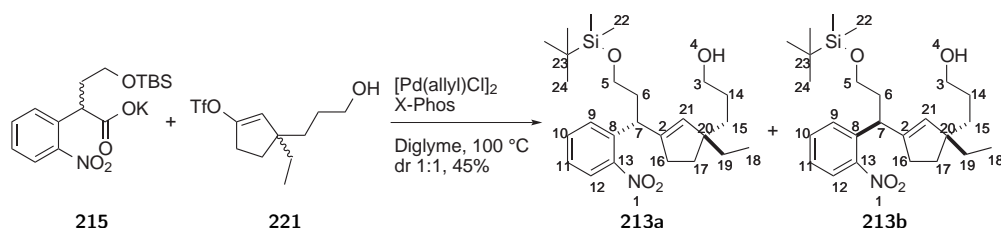
quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²² This compound was used for the next step without further purification.

¹H NMR (400 MHz, CD₃OD): δ 7.79 (dd, J = 8.2, 1.4 Hz, 1H, C²-H), 7.68 (dd, J = 7.7, 1.6 Hz, 1H, C⁴-H), 7.58 (td, J = 7.7, 1.4 Hz, 1H, C⁵-H), 7.38 (ddd, J = 8.1, 7.3, 1.5 Hz, 1H, C³-H), 4.41 (t, J = 7.2 Hz, 1H, C⁷-H), 3.65 (ddd, J = 10.0, 6.4, 6.1 Hz, 1H, C¹¹-H), 3.60 (ddd, J = 10.0, 7.0, 6.8 Hz, 1H, C¹¹-H), 2.38 (dq, J = 13.5, 7.2 Hz, 1H, C¹⁰-H), 2.01 (dq, J = 13.5, 7.2 Hz, 1H, C¹⁰-H), 0.87 (s, 9H, C¹⁴-H), 0.00 (two s, 6H, C¹²-H).

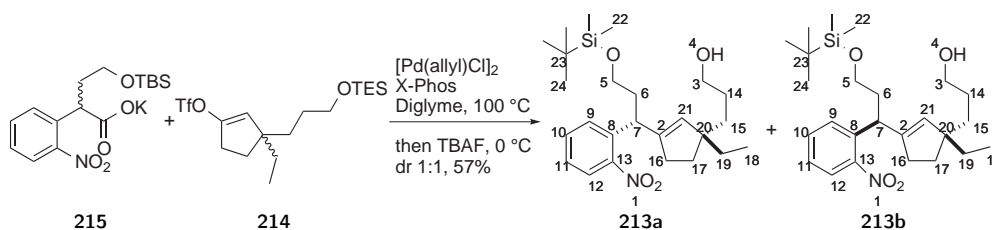
¹³C NMR (101 MHz, CD₃OD): δ 179.8 (C⁸), 151.7 (C¹), 138.1 (C⁶), 133.6 (C⁴), 131.6 (C⁵), 128.2 (C³), 125.2 (C²), 62.9 (C¹¹), 47.5 (C⁷), 38.2 (C¹⁰), 26.6 (C¹⁴), 19.2 (C¹³), -5.1 (C¹²).

3-(3-(3-((*tert*-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propan-1-ol **213**

From free alcohol **221**



An oven-dried flask was charged with salt **215** (2.0 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%) and allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **221** (1.3 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The two diastereoisomers were separated by FCC (PE/EtOAc 8:2), giving **213a** and **213b** as yellow oils (0.89 g, 45% yield, dr 1:1).

From TES-protected alcohol **214**

An oven-dried flask was charged with salt **215** (2.0 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%) and allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **214** (1.8 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was cooled down to 0 °C, and TBAF (1 M solution in THF, 5 mL, 5 mmol, 1.1 equiv) was added dropwise. The reaction was monitored by TLC until total conversion. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The two diastereoisomers were separated by FCC (PE/EtOAc 8:2), giving **213a** and **213b** as yellow oils (1.1 g, 57% yield, dr 1:1).

Compound **213a**

¹H NMR (400 MHz, CDCl₃): δ 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H, C¹²-H), 7.49 (td, *J* = 7.8, 1.5 Hz, 1H, C¹⁰-H), 7.38 (dd, *J* = 7.8, 1.5 Hz, 1H, C⁹-H), 7.30 (td, *J* = 7.8, 1.5 Hz, 1H, C¹¹-H), 5.25 (d, *J* = 1.7 Hz, 1H, C²¹-H), 4.07 (t, *J* = 7.4 Hz, 1H, C⁷-H), 3.59 (t, *J* = 6.4 Hz, 2H, C³-H), 3.53 (t, *J* = 6.8 Hz, 2H, C⁵-H), 2.18-1.89 (m, 4H, C^{6,15}-H), 1.70 (br s, 1H, O⁴-H), 1.66-1.53 (m, 2H, C¹⁷-H), 1.49-1.41 (m, 2H, C¹⁴-H), 1.40-1.31 (m, 4H, C^{16,19}-H), 0.85 (s, 9H, C²⁴-H), 0.78 (t, *J* = 7.5 Hz, 3H, C¹⁸-H), -0.02 (s, 6H, C²²-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.7 (C¹³), 144.1 (C²), 137.8 (C⁸), 133.0 (C²¹), 132.3 (C¹⁰), 129.2 (C⁹), 127.0 (C¹¹), 124.0 (C¹²), 63.8 (C³), 61.2 (C⁵), 51.8 (C²⁰), 37.4 (C⁷), 37.1 (C⁶), 35.3 (C¹⁵), 33.6 (C¹⁶), 33.5 (C¹⁷), 32.1 (C¹⁹), 28.3 (C¹⁴), 26.0 (C²⁴), 18.4 (C²³), 9.1 (C¹⁸), -5.3 (C²²).

IR: 3378 (br w), 2930 (w), 2856 (w), 1527 (s), 1462 (w), 1356 (m), 1254 (m), 1099 (s), 1061 (m), 834 (s), 777 (s).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₂₅H₄₂NO₄Si⁺: 448.2878; Found: 448.2885.

R_f (PE/EtOAc 6:4) = 0.43.

Compound 213b

^1H NMR (400 MHz, CDCl_3): δ 7.67 (dd, $J = 7.7, 1.5$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.48 (td, $J = 7.7, 1.5$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.38 (dd, $J = 7.7, 1.6$ Hz, 1H, $\text{C}^9\text{-H}$), 7.29 (td, $J = 7.7, 1.6$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.26 (d, $J = 1.9$ Hz, 1H, $\text{C}^{21}\text{-H}$), 4.11 (t, $J = 7.3$ Hz, 1H, $\text{C}^7\text{-H}$), 3.58 (t, $J = 6.5$ Hz, 2H, $\text{C}^3\text{-H}$), 3.52 (t, $J = 6.8$ Hz, 2H, $\text{C}^5\text{-H}$), 2.16-2.00 (m, 3H, $\text{C}^{6,15}\text{-H}$), 1.95 (dq, $J = 13.6, 6.8$ Hz, 1H, $\text{C}^6\text{-H}$), 1.73 (br s, 1H, $\text{O}^4\text{-H}$), 1.57 (t, $J = 7.4$ Hz, 2H, $\text{C}^{17}\text{-H}$), 1.50-1.40 (m, 2H, $\text{C}^{14}\text{-H}$), 1.40-1.30 (m, 4H, $\text{C}^{16,19}\text{-H}$), 0.84 (s, 9H, $\text{C}^{24}\text{-H}$), 0.77 (t, $J = 7.3$ Hz, 3H, $\text{C}^{18}\text{-H}$), -0.03 (s, 6H, $\text{C}^{22}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 150.7 (C^{13}), 143.9 (C^2), 137.7 (C^8), 133.2 (C^{21}), 132.2 (C^{10}), 129.1 (C^9), 127.0 (C^{11}), 124.0 (C^{12}), 63.7 (C^3), 61.1 (C^5), 51.8 (C^{20}), 37.3 (C^7), 36.9 (C^6), 35.3 (C^{15}), 33.4 (C^{16}), 33.3 (C^{17}), 32.1 (C^{19}), 28.3 (C^{14}), 26.0 (C^{24}), 18.4 (C^{23}), 9.1 (C^{18}), -5.3 (C^{22}).

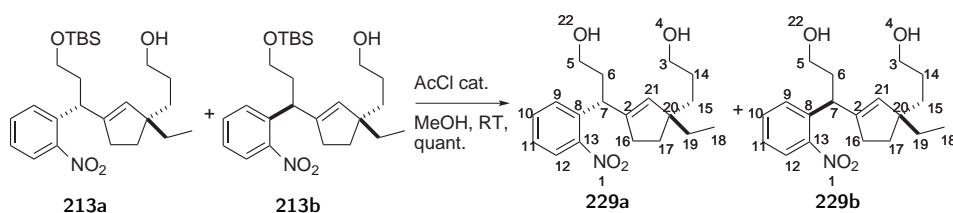
IR: 3362 (br w), 2934 (w), 2856 (w), 1527 (s), 1463 (w), 1356 (m), 1254 (m), 1099 (s), 1062 (m), 834 (s), 778 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{42}\text{NO}_4\text{Si}^+$: 448.2878; Found: 448.2876.

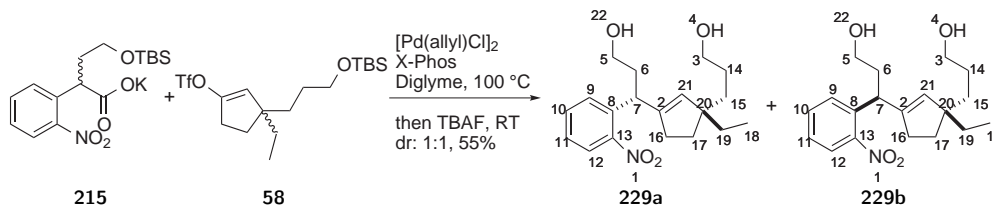
R_f (PE/EtOAc 6:4) = 0.57.

3-(3-(3-(hydroxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propan-1-ol 229

From 213



To a solution of compounds **213a/213b** (dr 1:1, 2.7 g, 6.0 mmol) in MeOH (50 mL) at 0 °C was added dropwise acetyl chloride (40 μL , 0.60 mmol, 10 mol%). The reaction was stirred at RT for 1 h, then concentrated *in vacuo*. The crude alcohols **229a/229b** (2.0 g, quantitative yield, no change in dr) thus obtained was used for the next step without further purification.

From TBS-protected alcohol **58**

An oven-dried flask was charged with salt **215** (dr 1:1, 2.0 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%) and allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **58** (1.8 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100°C for 2 h. The reaction mixture was cooled down to RT, and TBAF (1 M solution in THF, 13 mL, 13 mmol, 3.0 equiv) was added dropwise. The reaction was monitored by TLC until total conversion. Saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers **229a** and **229b** as yellow oils (0.81 g, 55% yield, dr 1:1).

Compound **229a**

^1H NMR (400 MHz, CDCl_3): δ 7.67 (dd, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.51 (td, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.38 (dd, $J = 7.7, 1.6$ Hz, 1H, $\text{C}^9\text{-H}$), 7.31 (td, $J = 7.7, 1.6$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.29 (d, $J = 1.7$ Hz, 1H, $\text{C}^{21}\text{-H}$), 4.06 (t, $J = 7.4$ Hz, 1H, $\text{C}^7\text{-H}$), 3.61–3.48 (m, 4H, $\text{C}^{3,5}\text{-H}$), 2.46 (br s, 2H, $\text{O}^{4,22}\text{-H}$), 2.20 (ddt, $J = 13.2, 6.6, 6.6$ Hz, 1H, $\text{C}^6\text{-H}$), 2.14–2.04 (m, 1H, $\text{C}^{15}\text{-H}$), 2.04–1.92 (m, 2H, $\text{C}^{6,15}\text{-H}$), 1.65–1.50 (m, 2H, $\text{C}^{17}\text{-H}$), 1.49–1.39 (m, 2H, $\text{C}^{14}\text{-H}$), 1.40–1.30 (m, 4H, $\text{C}^{16,19}\text{-H}$), 0.76 (t, $J = 7.4$ Hz, 3H, $\text{C}^{18}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 150.8 (C^{13}), 143.9 (C^2), 137.3 (C^8), 133.3 (C^{21}), 132.5 (C^{10}), 129.2 (C^9), 127.2 (C^{11}), 124.0 (C^{12}), 63.7 (C^3), 60.8 (C^5), 51.9 (C^{20}), 37.5 (C^7), 36.9 (C^6), 35.2 (C^{15}), 33.5 (C^{16}), 33.5 (C^{17}), 32.1 (C^{19}), 28.2 (C^{14}), 9.1 (C^{18}).

IR: 3343 (br w), 2937 (w), 2875 (w), 1525 (s), 1451 (w), 1355 (m), 1052 (m), 909 (m), 731 (s).

HRMS: (ESI $^+$) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4^+$: 334.2013; Found: 334.2001.

R_f (PE/EtOAc 4:6) = 0.22.

Compound 229b

^1H NMR (400 MHz, CDCl_3): δ 7.67 (dd, $J = 7.7, 1.7$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.50 (td, $J = 7.7, 1.7$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.38 (dd, $J = 7.7, 1.6$ Hz, 1H, $\text{C}^9\text{-H}$), 7.31 (td, $J = 7.7, 1.6$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.31 (d, $J = 1.8$ Hz, 1H, $\text{C}^{21}\text{-H}$), 4.03 (t, $J = 7.5$ Hz, 1H, $\text{C}^7\text{-H}$), 3.61-3.48 (m, 4H, $\text{C}^{3,5}\text{-H}$), 2.50 (br s, 2H, $\text{O}^{4,22}\text{-H}$), 2.19 (ddt, $J = 13.5, 13.0, 6.7$ Hz, 1H, $\text{C}^6\text{-H}$), 2.14-2.04 (m, 1H, $\text{C}^{15}\text{-H}$), 2.02-1.91 (m, 2H, $\text{C}^{6,15}\text{-H}$), 1.59-1.53 (m, 2H, $\text{C}^{17}\text{-H}$), 1.50-1.41 (m, 2H, $\text{C}^{14}\text{-H}$), 1.40-1.30 (m, 4H, $\text{C}^{16,19}\text{-H}$), 0.77 (t, $J = 7.4$ Hz, 3H, $\text{C}^{18}\text{-H}$).

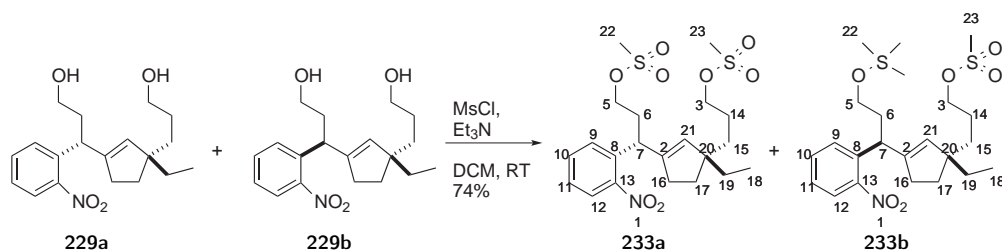
^{13}C NMR (101 MHz, CDCl_3): δ 150.7 (C^{13}), 143.9 (C^2), 137.4 (C^8), 133.2 (C^{21}), 132.5 (C^{10}), 129.2 (C^9), 127.2 (C^{11}), 123.9 (C^{12}), 63.7 (C^3), 60.7 (C^5), 51.9 (C^{20}), 37.5 (C^7), 37.0 (C^6), 35.3 (C^{15}), 33.7 (C^{16}), 33.3 (C^{17}), 32.2 (C^{19}), 28.2 (C^{14}), 9.2 (C^{18}).

IR: 3330 (br w), 2937 (w), 2875 (w), 1525 (s), 1461 (w), 1355 (m), 1052 (m), 910 (w), 855 (w), 784 (m), 732 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4^+$: 334.2013; Found: 334.2012.

R_f (PE/EtOAc 4:6) = 0.22.

3-(-1-ethyl-3-(-3-((methylsulfonyl)oxy)-1-(2-nitrophenyl)propyl)cyclopent-2-en-1-yl)propyl methanesulfonate 233



To a solution of diols **229a/229b** (dr 1:1, 50 mg, 0.15 mmol) in DCM (15 mL) at 0 °C was added Et_3N (63 μL , 0.50 mmol, 3.0 equiv) and MsCl (29 μL , 0.37 mmol, 2.5 equiv). The reaction mixture was stirred at RT until complete consumption of the starting material. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the pure compounds **233a/233b** as a mixture of two diastereoisomers (yellow oils, 54 mg, 74% yield, no change in dr).

Compound 233a

¹H NMR (400 MHz, CDCl₃): δ 7.75 (dd, $J = 7.9, 1.3$ Hz, 1H, C¹²-H), 7.58 (td, $J = 7.9, 1.3$ Hz, 1H, C¹⁰-H), 7.41-7.35 (m, 2H, C^{9,11}-H), 5.31 (d, $J = 1.4$ Hz, 1H, C²¹-H), 4.25-4.05 (m, 5H, C^{5,7,14}-H), 3.00 (s, 3H, C²³-H), 2.97 (s, 3H, C²²-H), 2.41 (dq, $J = 14.3, 6.9$ Hz, 1H, C⁶-H), 2.23 (dq, $J = 14.3, 7.3$ Hz, 1H, C⁶-H), 2.15 (m, 1H, C¹⁵-H), 2.02 (m, 1H, C¹⁵-H), 1.72-1.62 (m, 3H, C^{17,14}-H), 1.55 (m, 1H, C¹⁴-H), 1.45-1.34 (m, 4H, C^{16,19}-H), 0.80 (t, $J = 7.5$ Hz, 3H, C¹⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.6 (C¹³), 143.7 (C²), 136.0 (C⁸), 133.2 (C²¹), 133.0 (C¹⁰), 129.0 (C⁹), 127.9 (C¹¹), 124.4 (C¹²), 71.0 (C³), 67.5 (C⁵), 51.9 (C²⁰), 37.6 (C⁷), 37.5 (C²²), 37.5 (C²³), 34.8 (C¹⁵), 33.7 (C^{6or16}), 33.6 (C^{6or16}), 33.4 (C¹⁷), 32.1 (C¹⁹), 25.0 (C¹⁴), 9.1 (C¹⁸).

IR: 2959 (w), 2941 (w), 2851 (w), 1526 (m), 1350 (s), 1172 (s), 958 (m), 918 (m), 815 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₁H₃₂NO₈S₂⁺: 490.1564; Found: 490.1508.

R_f (PE/EtOAc 4:6) = 0.58.

Compound 233b

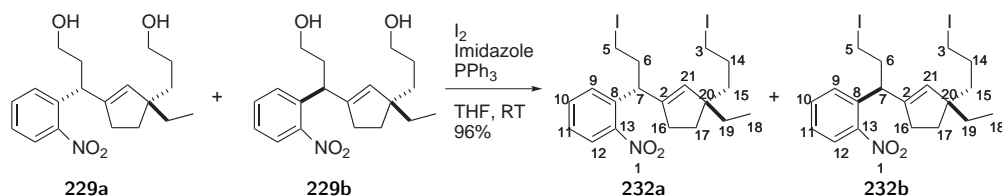
¹H NMR (400 MHz, CDCl₃): δ 7.74 (dd, $J = 7.6, 1.4$ Hz, 1H, C¹²-H), 7.56 (td, $J = 7.6, 1.4$ Hz, 1H, C¹⁰-H), 7.31 (td, $J = 7.6, 1.5$ Hz, 2H, C^{9,11}-H), 5.33 (d, $J = 1.3$ Hz, 1H, C²¹-H), 4.28-4.05 (m, 5H, C^{5,7,14}-H), 3.01 (s, 3H, C²³-H), 2.97 (s, 3H, C²²-H), 2.39 (dq, $J = 14.1, 7.0$ Hz, 1H, C⁶-H), 2.23 (dq, $J = 14.1, 7.0$ Hz, 1H, C⁶-H), 2.13 (ddd, $J = 16.1, 7.8, 7.2$ Hz, 1H, C¹⁵-H), 2.02 (ddd, $J = 16.1, 7.8, 7.2$ Hz, 1H, C¹⁵-H), 1.70-1.55 (m, 4H, C^{14,17}-H), 1.46-1.35 (m, 4H, C^{16,19}-H), 0.8 (t, $J = 7.0$ Hz, 3H, C¹⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.6 (C¹³), 143.5 (C²), 136.1 (C⁸), 133.3 (C²¹), 132.8 (C¹⁰), 129.0 (C⁹), 127.8 (C¹¹), 124.4 (C¹²), 70.9 (C³), 67.5 (C⁵), 51.9 (C²⁰), 37.6 (C⁷), 37.5 (C^{22or23}), 37.4 (C^{22or23}), 35.0 (C¹⁵), 33.6 (C^{6or16}), 33.6 (C^{6or16}), 33.2 (C¹⁷), 33.1 (C¹⁹), 24.9 (C¹⁴), 9.2 (C¹⁸).

IR: 2960 (w), 2942 (w), 2850 (w), 1527 (m), 1351 (s), 1173 (s), 967 (m), 919 (m), 815 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₁H₃₂NO₈S₂⁺: 490.1564; Found: 490.1563.

R_f (PE/EtOAc 4:6) = 0.58.

1-(1-(3-ethyl-3-(3-iodopropyl)cyclopent-1-en-1-yl)-3-iodopropyl)-2-nitrobenzene 232


To a solution of diols **229a/229b** (dr 1:1, 50 mg, 0.15 mmol) in THF (15 mL) at 0 °C was added imidazole (34 mg, 0.50 mmol, 3.0 equiv) and PPh₃ (97 mg, 0.37 mmol, 2.5 equiv), followed by portionwise addition of iodine (84 mg, 0.33 mmol, 2.2 equiv). The reaction mixture was stirred at RT until complete consumption of the starting material. The reaction mixture was poured into saturated aqueous NH₄Cl, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the pure compounds **232a/232b** as a mixture of two diastereoisomers (yellow oils, 80 mg, 96% yield, no change in dr).

Compound 232a

¹H NMR (400 MHz, CDCl₃): δ 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H, C¹²-H), 7.56 (td, *J* = 8.0, 1.5 Hz, 1H, C¹⁰-H), 7.40-7.34 (m, 2H, C^{9,11}-H), 5.30 (d, *J* = 1.9 Hz, 1H, C²¹-H), 4.04 (t, *J* = 7.4 Hz, 1H, C⁷-H), 3.19-3.12 (m, 2H, C³-H), 3.11 (ddd, *J* = 9.7, 9.6, 6.1 Hz, 1H, C⁵-H), 3.04 (ddd, *J* = 9.7, 9.6, 6.1 Hz, 1H, C⁵-H), 2.47 (dq, *J* = 14.1, 6.9 Hz, 1H, C⁶-H), 2.33 (ddt, *J* = 13.9, 9.3, 6.6 Hz, 1H, C⁶-H), 2.15 (ddd, *J* = 15.8, 7.7, 7.7 Hz, 1H, C¹⁶-H), 2.02 (ddd, *J* = 15.8, 7.7, 7.7 Hz, 1H, C¹⁶-H), 1.73 (quint, *J* = 7.16 Hz, 2H, C¹⁴-H), 1.69-1.50 (m, 2H, C¹⁷-H), 1.42 (q, *J* = 7.8 Hz, 2H, C¹⁹-H), 1.41-1.34 (m, 2H, C¹⁵-H), 0.80 (t, *J* = 7.5 Hz, 3H, C¹⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.7 (C¹³), 143.3 (C²), 136.2 (C⁸), 133.3 (C²¹), 132.8 (C¹⁰), 129.0 (C⁹), 127.6 (C¹¹), 124.4 (C¹²), 52.0 (C²⁰), 42.5 (C⁷), 40.3 (C¹⁵), 38.4 (C⁶), 33.7 (C^{16or17}), 33.5 (C^{16or17}), 32.3 (C¹⁹), 29.6 (C¹⁴), 9.1 (C¹⁸), 8.1 (C³), 2.8 (C⁵).

IR: 2933 (w), 2918 (w), 2848 (w), 1526 (s), 1458 (w), 1353 (m), 1230 (w), 1172 (w), 786 (w), 746 (w).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₁₉H₂₅I₂NNaO₂⁺: 575.9867; Found: 575.9861.

R_f (PE/EtOAc 8:2) = 0.42.

Compound 232b

¹H NMR (400 MHz, CDCl₃): δ 7.74 (dd, J = 8.4, 1.4 Hz, 1H, C¹²-H), 7.54 (td, J = 7.5, 1.4 Hz, 1H, C¹⁰-H), 7.39-7.34 (m, 2H, C^{9,11}-H), 5.30 (d, J = 1.7 Hz, 1H, C²¹-H), 4.06 (t, J = 7.4 Hz, 1H, C⁷-H), 3.16 (t, J = 6.6 Hz, 2H, C³-H), 3.10 (ddd, J = 9.5, 9.4, 6.1 Hz, 1H, C⁵-H), 3.03 (ddd, J = 9.5, 9.4, 6.1 Hz, 1H, C⁵-H), 2.46 (m, 1H, C⁶-H), 2.32 (m, 1H, C⁶-H), 2.14 (ddd, J = 15.8, 7.7, 7.4 Hz, 1H, C¹⁶-H), 2.02 (ddd, J = 15.8, 7.7, 7.4 Hz, 1H, C¹⁶-H), 1.79-1.65 (m, 2H, C¹⁴-H), 1.60 (t, J = 7.4 Hz, 2H, C¹⁷-H), 1.46-1.33 (m, 2H, C¹⁵-H), 1.36 (q, J = 7.5 Hz, 2H, C¹⁹-H), 0.80 (t, J = 7.5 Hz, 3H, C¹⁸-H).

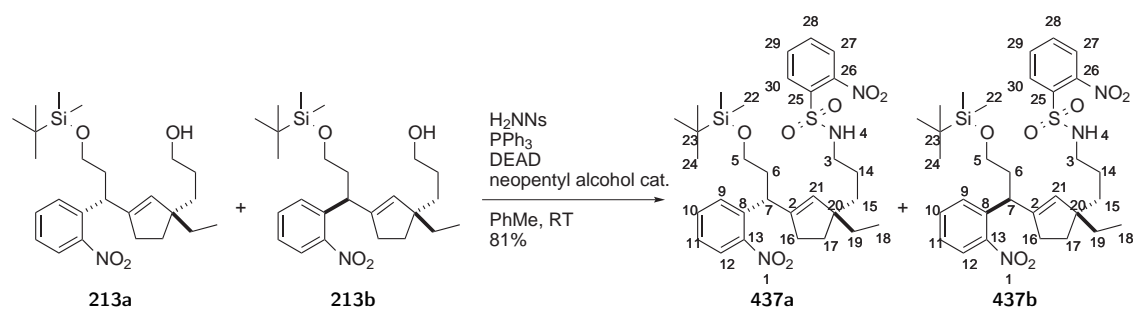
¹³C NMR (101 MHz, CDCl₃): δ 150.8 (C¹³), 143.2 (C²), 136.2 (C⁸), 133.6 (C²¹), 132.7 (C¹⁰), 128.9 (C⁹), 127.6 (C¹¹), 124.4 (C¹²), 51.9 (C²⁰), 42.5 (C⁷), 40.3 (C¹⁵), 38.3 (C⁶), 33.5 (C^{16or17}), 33.4 (C^{16or17}), 32.1 (C¹⁹), 29.4 (C¹⁴), 9.2 (C¹⁸), 8.1 (C³), 2.8 (C⁵).

IR: 2956 (w), 2932 (w), 2847 (w), 1525 (s), 1447 (w), 1353 (m), 1230 (w), 1170 (w), 909 (w), 855 (w), 783 (w), 733 (m).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₉H₂₅I₂NNaO₂⁺: 575.9867; Found: 575.9870.

R_f (PE/EtOAc 8:2) = 0.42.

N-(3-(-3-(-3-((*tert*-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propyl)-2-nitrobenzenesulfonamide 437



To a solution of alcohols **213a/213b** (dr 1:1, 60 mg, 0.13 mmol), neopentyl alcohol (5.8 mg, 0.060 mmol, 0.40 equiv), *o*-nitrophenylsulfonamide (53 mg, 0.27 mmol, 2.0 equiv) and PPh₃ (35 mg, 0.13 mmol, 1.0 equiv) in toluene (4.0 mL) at RT was added DEAD (40 wt.% in toluene, 60 μ L, 0.13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh₃ (35 mg, 0.13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 60 μ L, 0.13 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine,

dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers **437a** and **437b** as yellow oils (67 mg, 81% yield, no change in dr).

Compound 437a

¹H NMR (400 MHz, CDCl₃): δ 8.13 (m, 1H, C³⁰-H), 7.84 (m, 1H, C²⁷-H), 7.76-7.71 (m, 2H, C^{28,29}-H), 7.70 (d, *J* = 7.8 Hz, 1H, C¹²-H), 7.54 (t, *J* = 7.8 Hz, 1H, C¹⁰-H), 7.36 (d, *J* = 7.8 Hz, 1H, C⁹-H), 7.33 (t, *J* = 7.8 Hz, 1H, C¹¹-H), 5.24 (t, *J* = 5.8 Hz, 1H, C⁴-H), 5.14 (d, *J* = 1.4 Hz, 1H, C²¹-H), 4.05 (t, *J* = 7.2 Hz, 1H, C⁷-H), 3.56-3.46 (m, 2H, C⁵-H), 3.07 (q, *J* = 6.6 Hz, 2H, C³-H), 2.20-2.06 (m, 2H, C^{6,16}-H), 2.02-1.88 (m, 2H, C^{6,16}-H), 1.58 (m, 1H, C¹⁷-H), 1.46-1.35 (m, 3H, C^{14,17}-H), 1.32-1.23 (m, 4H, C^{15,19}-H), 0.85 (s, 9H, C²⁴-H), 0.73 (t, *J* = 7.4 Hz, 3H, C¹⁸-H), -0.02 (s, 6H, C²²-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.7 (C¹³), 148.3 (C²⁶), 144.8 (C²), 137.6 (C⁸), 134.1 (C²⁵), 133.6 (C²⁸), 132.9 (C²⁹), 132.5 (C¹⁰), 132.3 (C²¹), 131.2 (C³⁰), 129.2 (C⁹), 127.2 (C¹¹), 125.5 (C²⁷), 124.1 (C¹²), 61.1 (C⁵), 51.8 (C²⁰), 44.8 (C³), 37.5 (C⁷), 37.1 (C⁶), 36.2 (C¹⁵), 33.8 (C¹⁶), 33.4 (C¹⁷), 32.2 (C¹⁹), 26.1 (C²⁴), 25.3 (C¹⁴), 18.4 (C²³), 9.1 (C¹⁸), -5.3 (C²²).

IR: 3353 (br w), 2950 (m), 2932 (m), 2856 (m), 1721 (w), 1529 (s), 1358 (s), 1256 (m), 1169 (s), 1100 (s), 836 (s), 781 (s).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₃₁H₄₆N₃O₇SSi⁺: 632.2820; Found: 632.2820.

R_f (PE/EtOAc 6:4) = 0.57.

Compound 437b

¹H NMR (400 MHz, CDCl₃): δ 8.14 (m, 1H, C³⁰-H), 7.86 (m, 1H, C²⁷-H), 7.77-7.72 (m, 2H, C^{28,29}-H), 7.69 (dd, *J* = 7.9, 1.1 Hz, 1H, C¹²-H), 7.51 (t, *J* = 7.9 Hz, 1H, C¹⁰-H), 7.36 (d, *J* = 7.9 Hz, 1H, C⁹-H), 7.32 (t, *J* = 7.9 Hz, 1H, C¹¹-H), 5.26 (t, *J* = 6.0 Hz, 1H, C⁴-H), 5.16 (s, 1H, C²¹-H), 4.13 (t, *J* = 7.3 Hz, 1H, C⁷-H), 3.54-3.46 (m, 2H, C⁵-H), 3.11-3.03 (m, 2H, C³-H), 2.08 (dq, *J* = 13.9, 7.0 Hz, 1H, C⁶-H), 2.01 (t, *J* = 7.2 Hz, 2H, C¹⁶-H), 1.95 (dq, *J* = 14.0, 7.0 Hz, 1H, C⁶-H), 1.53 (dd, *J* = 14.3, 8.2 Hz, 1H, C¹⁷-H), 1.44 (dd, *J* = 14.3, 7.6 Hz, 1H, C¹⁷-H), 1.42-1.35 (m, 2H, C¹⁴-H), 1.31-1.22 (m, 4H, C^{15,19}-H), 0.86 (s, 9H, C²⁴-H), 0.73 (t, *J* = 7.4 Hz, 3H, C¹⁸-H), 0.02 (s, 6H, C²²-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.8 (C¹³), 148.2 (C²⁶), 144.4 (C²), 137.4 (C⁸), 134.1 (C²⁵), 133.6 (C²⁸), 132.9 (C²¹), 132.8 (C²⁹), 132.3 (C¹⁰), 131.2 (C³⁰), 129.0 (C⁹), 127.1 (C¹¹), 125.5 (C²⁷), 124.2 (C¹²), 61.1 (C⁵), 51.8 (C²⁰), 44.8 (C³), 37.3 (C⁶), 36.6 (C¹⁵), 36.3 (C⁷), 33.3 (C¹⁶), 32.9 (C¹⁷), 32.2 (C¹⁹), 26.1 (C²⁴), 25.2 (C¹⁴), 18.4 (C²³), 9.2 (C¹⁸), -5.3 (C²²).

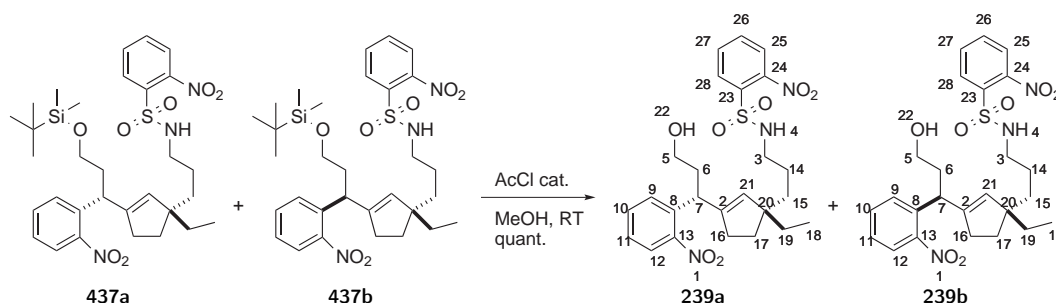
IR: 3329 (br w), 2953 (w), 2934 (w), 2856 (w), 1723 (s), 1528 (s), 1353 (s), 1249 (s), 1168 (s), 1097 (s), 1063 (s), 836 (s), 779 (s), 740 (s).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₃₁H₄₆N₃O₇SSi⁺: 632.2820; Found: 632.2806,.

R_f (PE/EtOAc 6:4) = 0.57.

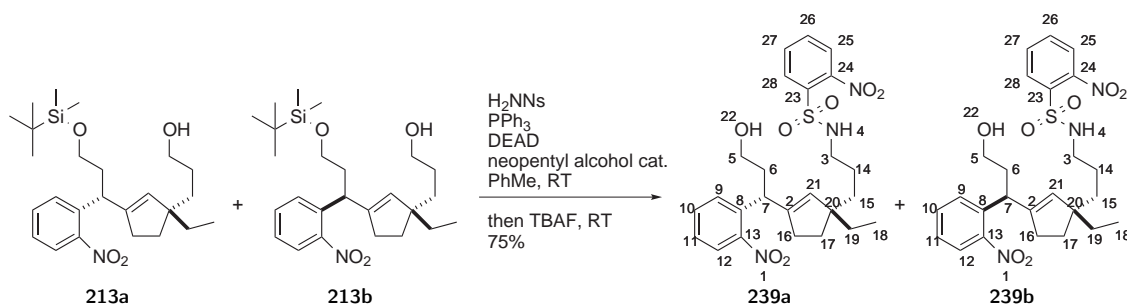
N-(3-(-1-ethyl-3-(-3-hydroxy-1-(2-nitrophenyl)propyl)cyclopent-2-en-1-yl)-propyl)-2-nitrobenzenesulfonamide 239

From TBS-protected alcohol 437



To a solution of compounds **437a/437b** (dr 1:1, 3.2 g, 5.0 mmol) in MeOH (50 mL) at 0 °C was added dropwise acetyl chloride (30 μ L, 0.50 mmol, 10 mol%). After stirring for 1 h at RT, the reaction mixture was concentrated *in vacuo*. The crude compounds **239a/239b** thus obtained was used for the next step without further purification (2.6 g, quantitative yield, no change in dr).

From monoprotected diol 213



To a solution of alcohols **213a/213b** (dr 1:1, 60 mg, 0.13 mmol), neopentyl alcohol (5.8 mg, 0.060 mmol, 0.40 equiv), *o*-nitrophenylsulfonamide (53 mg, 0.27 mmol, 2.0 equiv) and PPh₃

(35 mg, 0.13 mmol, 1.0 equiv) in toluene (4.0 mL) at RT was added DEAD (40 wt.% in toluene, 60 μ L, 0.13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh₃ (35 mg, 0.13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 60 μ L, 0.13 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. TBAF (1 M solution in THF, 0.39 mL, 0.39 mmol, 3.0 equiv) was added and the reaction mixture was stirred at RT for 3 h. Saturated aqueous NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers **239a** and **239b** as a mixture (yellow oil, 50 mg, 75% yield, no change in dr).

Compound 239a

¹H NMR (400 MHz, CDCl₃): δ 8.13 (m, 1H, C²⁸-H), 7.85 (m, 1H, C²⁵-H), 7.77-7.71 (m, 2H, C^{26,27}-H), 7.69 (d, J = 7.5 Hz, 1H, C¹²-H), 7.56 (t, J = 7.0 Hz, 1H, C¹⁰-H), 7.40-7.31 (m, 2H, C^{9,11}-H), 5.27 (br s, 1H, N⁴-H), 5.21 (s, 1H, C²¹-H), 4.05 (t, J = 6.9 Hz, 1H, C⁷-H), 3.61 (m, 1H, C⁵-H), 3.52 (m, 1H, C⁵-H), 3.07 (q, J = 6.4 Hz, 2H, C³-H), 2.21 (m, 1H, C⁶-H), 2.10 (m, 1H, C¹⁶-H), 2.04-1.88 (m, 2H, C^{6,16}-H), 1.58 (m, 1H, C¹⁷-H), 1.47-1.36 (m, 3H, C^{14,17}-H), 1.35-1.22 (m, 4H, C^{15,19}-H), 0.73 (t, J = 7.4 Hz, 3H, C¹⁸-H), OH peak not observed.

¹³C NMR (101 MHz, CDCl₃): δ 150.9 (C¹³), 148.2 (C²⁴), 144.7 (C²), 137.1 (C⁸), 134.0 (C²³), 133.7 (C²⁶), 132.9 (C²¹), 132.7 (C²⁷), 132.5 (C¹⁰), 131.2 (C²⁸), 129.2 (C⁹), 127.4 (C¹¹), 125.5 (C²⁵), 124.0 (C¹²), 60.8 (C⁵), 51.8 (C²⁰), 44.8 (C³), 37.5 (C⁷), 37.0 (C⁶), 36.2 (C¹⁵), 33.7 (C¹⁶), 33.4 (C¹⁷), 32.2 (C¹⁹), 25.4 (C¹⁴), 9.1 (C¹⁸).

IR: 3565 (br w), 3354 (br w), 2937 (w), 2852 (w), 1525 (m), 1352 (m), 1165 (m), 1051 (w), 909 (m), 730 (s).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₂₅H₃₁N₃NaO₇S⁺: 540.1775; Found: 540.1771.

R_f (PE/EtOAc 4:6) = 0.48.

Compound 239b

¹H NMR (400 MHz, CDCl₃): δ 8.14 (m, 1H, C²⁸-H), 7.87 (m, 1H, C²⁵-H), 7.78-7.72 (m, 2H, C^{26,27}-H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H, C¹²-H), 7.52 (td, J = 7.6, 1.6 Hz, 1H, C¹⁰-H), 7.38-7.31 (m, 2H, C^{9,11}-H), 5.28 (t, J = 6.2 Hz, 1H, N⁴-H), 5.22 (d, J = 1.8 Hz, 1H, C²¹-H), 4.07 (t, J = 7.1 Hz, 1H, C⁷-H), 3.61 (m, 1H, C⁵-H), 3.52 (m, 1H, C⁵-H), 3.07 (q, J = 6.7 Hz, 2H, C³-H), 2.19 (m, 1H, C⁶-H), 2.02-1.91 (m, 3H, C^{6,16}-H), 2.55-1.35 (m, 4H, C^{14,17}-H), 1.35-1.23 (m, 4H, C^{15,19}-H), 0.74 (t, J = 7.5 Hz, 3H, C¹⁸-H), OH peak not observed.

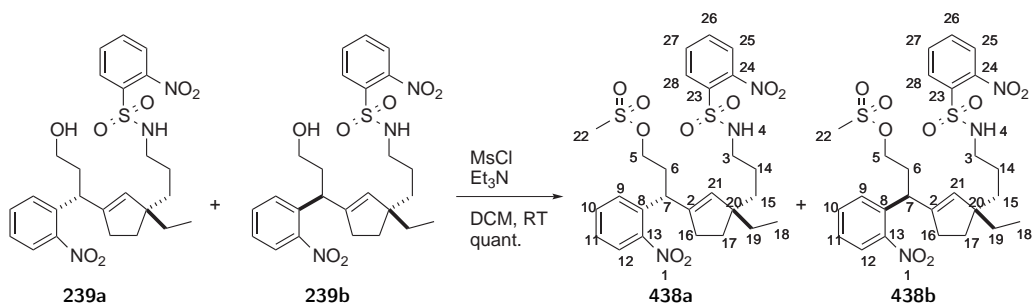
^{13}C NMR (101 MHz, CDCl_3): δ 150.9 (C^{13}), 148.2 (C^{24}), 144.5 (C^2), 137.0 (C^8), 134.1 (C^{23}), 133.7 (C^{26}), 132.9 (C^{21}), 132.7 (C^{27}), 132.6 (C^{10}), 131.2 (C^{28}), 129.2 (C^9), 127.4 (C^{11}), 125.5 (C^{25}), 124.1 (C^{12}), 60.8 (C^5), 51.8 (C^{20}), 44.7 (C^3), 37.4 (C^6), 36.8 (C^{15}), 36.2 (C^7), 33.4 (C^{16}), 33.2 (C^{17}), 32.2 (C^{19}), 25.2 (C^{14}), 9.1 (C^{18}).

IR: 3566 (br w), 3341 (br w), 2935 (w), 2853 (w), 1526 (s), 1358 (s), 1166 (s), 1061 (w), 741 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{NaO}_7\text{S}^+$: 540.1775; Found: 540.1786.

R_f (PE/EtOAc 4:6) = 0.48.

3-(3-ethyl-3-(3-((2-nitrophenyl)sulfonamido)propyl)cyclopent-1-en-1-yl)-3-(2-nitrophenyl)propyl methanesulfonate **438**



To a solution of alcohols **239a/239b** (dr 1:1, 20 mg, 0.040 mmol) in DCM (1.0 mL) at RT was added triethylamine (8.0 μL , 0.060 mmol, 1.5 equiv) and MsCl (3.7 μL , 0.050 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred for 0.5 h. Saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product thus obtained was used for the next step without further purification (24 mg, quantitative yield, no change in dr). An analytical sample was obtained by FCC (PE/EtOAc 4:6) to afford **438a** and **438b** (yellow oils).

Compound **438a**

^1H NMR (400 MHz, CDCl_3): δ 8.13 (m, 1H, $\text{C}^{28}\text{-H}$), 7.85 (m, 1H, $\text{C}^{25}\text{-H}$), 7.77-7.71 (m, 3H, $\text{C}^{12,26,27}\text{-H}$), 7.59 (t, $J = 7.8$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.39 (t, $J = 7.8$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.36 (d, $J = 7.8$ Hz, 1H, $\text{C}^9\text{-H}$), 5.32 (t, $J = 6.4$ Hz, 1H, $\text{N}^4\text{-H}$), 5.26 (m, 1H, $\text{C}^{21}\text{-H}$), 4.21 (dt, $J = 9.9, 6.5$ Hz, 1H, $\text{C}^5\text{-H}$), 4.13 (dt, $J = 9.9, 6.5$ Hz, 1H, $\text{C}^5\text{-H}$), 4.09 (t, $J = 7.4$ Hz, 1H, $\text{C}^7\text{-H}$), 3.07 (q, $J = 6.4$ Hz, 2H, $\text{C}^3\text{-H}$), 2.99 (s, 3H, $\text{C}^{22}\text{-H}$), 2.38 (dddd, $J = 14.2, 7.1, 7.1, 7.0$ Hz, 1H, $\text{C}^6\text{-H}$), 2.22 (dddd,

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$J = 14.2, 7.1, 7.1, 7.0$ Hz, 1H, C⁶-H), 2.10 (m, 1H, C¹⁶-H), 1.96 (m, 1H, C¹⁶-H), 1.64-1.54 (m, 2H, C¹⁷-H), 1.49-1.40 (m, 2H, C¹⁴-H), 1.35-1.27 (m, 4H, C^{15,19}-H), 0.74 (t, $J = 7.3$ Hz, 3H, C¹⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.6 (C¹³), 148.2 (C²⁴), 143.3 (C²), 136.0 (C⁸), 134.0 (C²³), 133.7 (C²⁶), 133.6 (C²¹), 133.0 (C^{10or27}), 132.9 (C^{10or27}), 131.2 (C²⁸), 129.0 (C⁹), 127.9 (C¹¹), 125.5 (C²⁵), 124.4 (C¹²), 67.5 (C⁵), 51.9 (C²⁰), 44.7 (C³), 37.6 (C²²), 37.5 (C⁷), 36.0 (C¹⁵), 33.4 (C⁶), 33.4 (C¹⁶), 33.4 (C¹⁷), 32.1 (C¹⁹), 25.4 (C¹⁴), 9.1 (C¹⁸).

IR: 3343 (br w), 2930 (w), 2853 (w), 1529 (s), 1355 (s), 1172 (s), 976 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₆H₃₄N₃O₉S₂⁺: 596.1731; Found: 596.1722.

R_f (PE/EtOAc 6:4) = 0.48.

Compound 438b

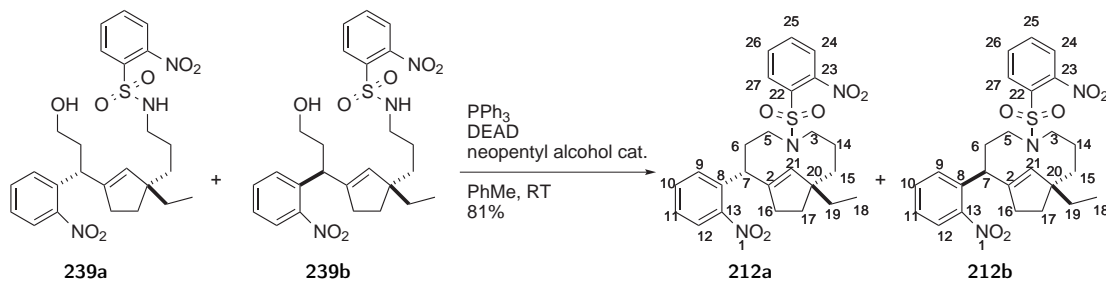
¹H NMR (400 MHz, CDCl₃): δ 8.14 (m, 1H, C²⁸-H), 7.86 (m, 1H, C²⁵-H), 7.78-7.71 (m, 3H, C^{12,26,27}-H), 7.55 (t, $J = 7.7$ Hz, 1H, C¹⁰-H), 7.41-7.34 (m, 2H, C^{9,11}-H), 5.35 (t, $J = 5.7$ Hz, 1H, N⁴-H), 5.28 (s, 1H, C²¹-H), 4.23 (dt, $J = 10.0, 7.0$ Hz, 1H, C⁵-H), 4.15 (dt, $J = 10.0, 7.0$ Hz, 1H, C⁵-H), 4.06 (t, $J = 7.4$ Hz, 1H, C⁷-H), 3.11-3.04 (m, 2H, C³-H), 3.00 (s, 3H, C²²-H), 2.35 (m, 1H, C⁶-H), 2.22 (m, 1H, C⁶-H), 2.09-1.94 (m, 2H, C¹⁶-H), 1.55-1.48 (m, 2H, C¹⁷-H), 1.47-1.39 (m, 2H, C¹⁴-H), 1.36-1.28 (m, 4H, C^{15,19}-H), 0.76 (t, $J = 7.4$ Hz, 3H, C¹⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.5 (C¹³), 148.2 (C²⁴), 143.2 (C²), 136.2 (C⁸), 134.0 (C²³), 133.6 (C²⁶), 133.5 (C²¹), 132.9 (C²⁷), 132.9 (C¹⁰), 131.2 (C²⁸), 128.9 (C⁹), 127.8 (C¹¹), 125.5 (C²⁵), 124.5 (C¹²), 67.6 (C⁵), 52.0 (C²⁰), 44.7 (C³), 37.6 (C²²), 37.4 (C⁷), 36.2 (C¹⁵), 33.6 (C⁶), 33.6 (C¹⁶), 33.2 (C¹⁷), 32.2 (C¹⁹), 25.3 (C¹⁴), 9.2 (C¹⁸).

IR: 3329 (br w), 2938 (w), 2852 (w), 1528 (s), 1353 (s), 1171 (s), 970 (w), 921 (w), 786 (w), 743 (w).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₂₆H₃₃N₃NaO₉S₂⁺: 618.1550; Found: 618.1541.

R_f (PE/EtOAc 6:4) = 0.48.

1-ethyl-8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene 212

To a solution of alcohols **239a/239b** (dr 1:1, 68 mg, 0.13 mmol), neopentyl alcohol (5.8 mg, 0.060 mmol, 0.40 equiv) and PPh_3 (35 mg, 0.13 mmol, 1.0 equiv) in toluene (4.5 mL) at RT was added DEAD (40 wt.% in toluene, 60 μL , 0.13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh_3 (35 mg, 0.13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 60 μL , 0.13 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. Saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers **212a** and **212b** as yellow prism and yellow oil, respectively (53 mg, 81% yield, no change in dr).

Compound 212a

mp= 188.6-189 °C (CHCl_3 / C_7H_{16}).

^1H NMR (400 MHz, CDCl_3): δ 7.91 (dd, $J = 7.4, 2.0$ Hz, 1H, $\text{C}^{27}\text{-H}$), 7.74-7.65 (m, 3H, $\text{C}^{12,25,26}\text{-H}$), 7.59 (dd, $J = 7.3, 1.9$ Hz, 1H, $\text{C}^{24}\text{-H}$), 7.55 (td, $J = 7.7, 1.3$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.47 (dd, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^9\text{-H}$), 7.35 (td, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.47 (s, 1H, $\text{C}^{21}\text{-H}$), 4.33 (dd, $J = 12.3, 3.2$ Hz, 1H, $\text{C}^7\text{-H}$), 4.03 (dd, $J = 15.6, 7.2$ Hz, 1H, $\text{C}^5\text{-H}$), 3.73 (ddd, $J = 15.3, 10.3, 4.9$ Hz, 1H, $\text{C}^3\text{-H}$), 2.80 (dd, $J = 15.6, 8.6$ Hz, 1H, $\text{C}^5\text{-H}$), 2.72 (ddd, $J = 15.0, 6.7, 2.4$ Hz, 1H, $\text{C}^3\text{-H}$), 2.68-2.54 (m, 2H, $\text{C}^{6,16}\text{-H}$), 2.13 (ddd, $J = 14.5, 7.2, 3.2$ Hz, 1H, $\text{C}^6\text{-H}$), 2.03 (m, 1H, $\text{C}^{14}\text{-H}$), 1.82-1.63 (m, 3H, $\text{C}^{16,17}\text{-H}$), 1.53 (dd, $J = 14.6, 6.7$ Hz, 1H, $\text{C}^{15}\text{-H}$), 1.42-1.20 (m, 4H, $\text{C}^{14,15,19}\text{-H}$), 0.75 (t, $J = 7.5$ Hz, 3H, $\text{C}^{18}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 150.3 (C^{13}), 149.1 (C^{23}), 141.9 (C^2), 136.2 (C^{21}), 136.1 (C^8), 133.7 (C^{25}), 132.3 (C^{10}), 131.4 (C^{26}), 131.2 (C^{22}), 130.6 (C^{27}), 128.6 (C^9), 127.2 (C^{11}), 124.4 (C^{12}), 124.1 (C^{24}), 56.6 (C^3), 54.8 (C^5), 53.5 (C^{20}), 43.0 (C^7), 40.3 (C^{15}), 35.7 (C^6), 33.9 (C^{19}), 32.6 (C^{17}), 31.4 (C^{16}), 28.2 (C^{14}), 9.4 (C^{18}).

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IR: 2960 (w), 2934 (w), 2849 (w), 1544 (s), 1529 (s), 1465 (w), 1355 (s), 1164 (m), 784 (m), 755 (m).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₂₅H₃₀N₃O₆S⁺: 500.1850; Found: 500.1860.

R_f (PE/EtOAc 4:6) = 0.59.

Compound 212b

¹H NMR (400 MHz, CDCl₃): δ 7.91 (dd, *J* = 7.5, 1.9 Hz, 1H, C²⁷-H), 7.78 (dd, *J* = 7.8, 1.4 Hz, 1H, C¹²-H), 7.70 (td, *J* = 7.5, 1.9 Hz, 1H, C²⁵-H), 7.66 (td, *J* = 7.5, 1.8 Hz, 1H, C²⁶-H), 7.60 (dd, *J* = 7.8, 1.5 Hz, 1H, C⁹-H), 7.57 (dd, *J* = 7.5, 1.8 Hz, 1H, C²⁴-H), 7.54 (td, *J* = 7.8, 1.4 Hz, 1H, C¹⁰-H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H, C¹¹-H), 5.63 (s, 1H, C²¹-H), 3.85 (dd, *J* = 11.5, 3.4 Hz, 1H, C⁷-H), 3.54 (ddd, *J* = 15.4, 7.5, 2.1 Hz, 1H, C⁵-H), 3.27 (m, 1H, C³-H), 3.07 (m, 1H, C³-H), 2.94 (ddd, *J* = 15.4, 7.2, 2.6 Hz, 1H, C⁵-H), 2.54 (dddd, *J* = 15.2, 11.4, 7.2, 2.1 Hz, 1H, C⁶-H), 2.44-2.36 (m, 2H, C¹⁶-H), 2.17 (ddt, *J* = 15.3, 7.9, 3.3 Hz, 1H, C⁶-H), 1.80-1.63 (m, 3H, C^{14,15,17}-H), 1.58 (ddd, *J* = 13.6, 8.4, 3.7 Hz, 1H, C¹⁷-H), 1.53-1.43 (m, 2H, C¹⁹-H), 1.42-1.38 (m, 2H, C^{14,15}-H), 0.85 (t, *J* = 7.5 Hz, 3H, C¹⁸-H).

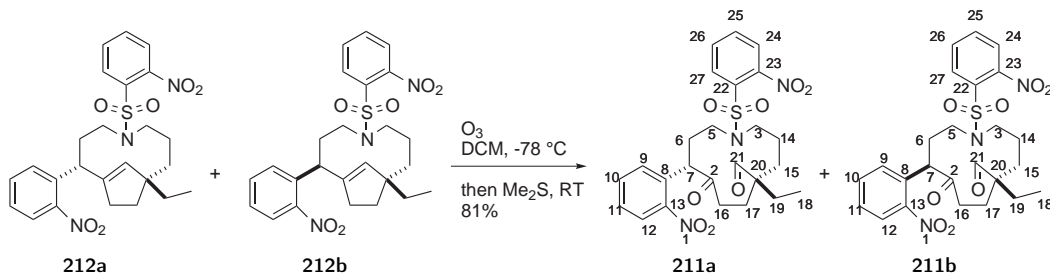
¹³C NMR (101 MHz, CDCl₃): δ 149.7 (C¹³), 149.0 (C²³), 140.7 (C²), 137.6 (C²¹), 137.4 (C⁸), 133.7 (C²⁵), 132.9 (C¹⁰), 131.4 (C²⁶), 131.2 (C²²), 131.0 (C²⁷), 129.6 (C⁹), 127.4 (C¹¹), 124.5 (C¹²), 124.0 (C²⁴), 54.5 (C²⁰), 52.5 (C³), 48.7 (C⁵), 42.1 (C⁷), 39.2 (C¹⁶), 38.3 (C¹⁵), 35.6 (C⁶), 33.3 (C¹⁹), 32.1 (C¹⁷), 22.3 (C¹⁴), 9.8 (C¹⁸).

IR: 2958 (w), 2932 (w), 2850 (w), 1545 (s), 1526 (s), 1462 (w), 1354 (s), 1165 (m), 782 (m), 734 (m).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₂₅H₃₀N₃O₆S⁺: 500.1850; Found: 500.1843.

R_f (PE/EtOAc 4:6) = 0.59.

5-ethyl-9-(2-nitrophenyl)-1-((2-nitrophenyl)sulfonyl)-8-oxoazacycloundecane-5-carbaldehyde **211**



A solution of the macrocycle **212** (dr 1:1, 10 mg, 0.020 mmol) in DCM (0.50 mL) was stirred at -78°C . Ozone was bubbled through the solution until a blue color appears (approximately 15 s). Argon was then bubbled through the solution for 10 min. Me_2S (0.10 mL) was added and the reaction mixture was stirred overnight at RT. The reaction mixture was concentrated *in vacuo*. Purification by FCC (PE/EtOAc 4:6) afforded the compound **211** as a yellow oil (8.6 mg, 81% yield, no change in dr).

Compound 211a

^1H NMR (400 MHz, CDCl_3): δ 9.45 (s, 1H, $\text{C}^{21}\text{-H}$), 7.89 (dd, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.83 (dd, $J = 8.1, 0.9$ Hz, 1H, $\text{C}^{27}\text{-H}$), 7.71 (td, $J = 7.5, 1.5$ Hz, 1H, $\text{C}^{25}\text{-H}$), 7.67 (td, $J = 7.5, 1.6$ Hz, 1H, $\text{C}^{26}\text{-H}$), 7.55 (dd, $J = 7.6, 1.5$ Hz, 1H, $\text{C}^{24}\text{-H}$), 7.50 (td, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.41 (td, $J = 7.7, 1.0$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.22 (dd, $J = 7.7, 1.0$ Hz, 1H, $\text{C}^9\text{-H}$), 5.25 (dd, $J = 11.4, 2.1$ Hz, 1H, $\text{C}^7\text{-H}$), 3.70-3.54 (m, 1H, $\text{C}^3\text{-H}$), 3.27 (dd, $J = 15.1, 5.5$ Hz, 1H, $\text{C}^5\text{-H}$), 3.12 (m, 1H, $\text{C}^5\text{-H}$), 2.82 (dt, $J = 13.1, 2.6$ Hz, 1H, $\text{C}^3\text{-H}$), 2.69 (m, 1H, $\text{C}^{16}\text{-H}$), 2.29 (m, 1H, $\text{C}^6\text{-H}$), 2.14 (m, 1H, $\text{C}^6\text{-H}$), 2.04-1.92 (m, 3H, $\text{C}^{15,17}\text{-H}$), 1.88 (m, 1H, $\text{C}^{16}\text{-H}$), 1.71 (td, $J = 13.7, 5.9$ Hz, 1H, $\text{C}^{17}\text{-H}$), 1.63-1.43 (m, 2H, $\text{C}^{19}\text{-H}$), 0.95-0.70 (m, 2H, $\text{C}^{14}\text{-H}$), 0.79 (t, $J = 7.5$ Hz, 3H, $\text{C}^{18}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 211.6 (C^2), 206.0 (C^{21}), 150.5 (C^{13}), 149.2 (C^{23}), 134.0 (C^{10}), 132.9 (C^{25}), 131.8 (C^8), 131.5 ($\text{C}^{26\text{or}27}$), 131.4 ($\text{C}^{26\text{or}27}$), 130.1 (C^{22}), 130.0 (C^9), 128.7 (C^{11}), 125.3 (C^{12}), 124.0 (C^{24}), 53.0 (C^{20}), 51.5 (C^3), 49.3 (C^7), 46.0 (C^5), 36.9 (C^{16}), 32.1 (C^6), 27.9 (C^{15}), 27.4 (C^{19}), 25.4 (C^{17}), 20.5 (C^{14}), 8.6 (C^{18}).

IR: 2961 (w), 2878 (w), 1711 (m), 1545 (s), 1529 (s), 1465 (w), 1373 (s), 1354 (s), 1171 (m), 785 (m), 745 (m), 731 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_8\text{S}^+$: 532.1748; Found: 532.1754.

R_f (PE/EtOAc 4:6) = 0.47.

Compound 211b

¹H NMR (400 MHz, CDCl₃): δ 9.41 (s, 1H, C²¹-H), 7.86 (dd, J = 7.8, 1.4 Hz, 1H, C¹²-H), 7.85 (dd, J = 7.7, 1.3 Hz, 1H, C²⁷-H), 7.69 (td, J = 7.7, 1.3 Hz, 1H, C²⁵-H), 7.65 (td, J = 7.7, 1.4 Hz, 1H, C²⁶-H), 7.54 (dd, J = 7.7, 1.4 Hz, 1H, C²⁴-H), 7.53 (td, J = 7.8, 1.3 Hz, 1H, C¹⁰-H), 7.43 (td, J = 7.8, 1.0 Hz, 1H, C¹¹-H), 7.22 (dd, J = 7.8, 1.0 Hz, 1H, C⁹-H), 5.31 (dd, J = 11.5, 1.9 Hz, 1H, C⁷-H), 3.61 (td, J = 13.1, 3.1 Hz, 1H, C³-H), 3.26 (dd, J = 15.0, 5.3 Hz, 1H, C⁵-H), 3.06 (ddd, J = 15.2, 12.5, 4.8 Hz, 1H, C⁵-H), 2.87 (dd, J = 14.7, 10.9 Hz, 1H, C¹⁶-H), 2.71 (dt, J = 13.3, 2.7 Hz, 1H, C³-H), 2.26 (m, 2H, C^{6,17}-H), 2.12 (m, 1H, C⁶-H), 2.00 (dd, J = 14.7, 10.3 Hz, 1H, C¹⁶-H), 1.92-1.70 (m, 3H, C^{15,17}-H), 1.77 (q, J = 7.7 Hz, 2H, C¹⁹-H), 1.31-1.12 (m, 2H, C¹⁴-H), 0.76 (t, J = 7.5 Hz, 3H, C¹⁸-H).

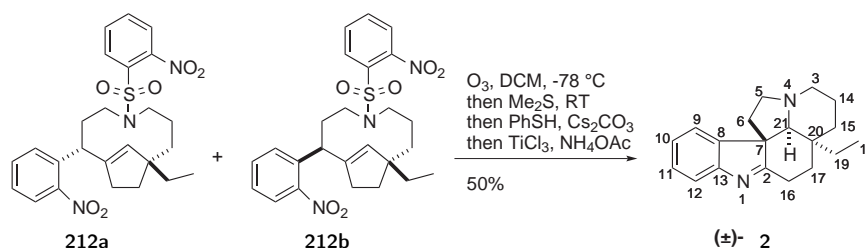
¹³C NMR (101 MHz, CDCl₃): δ 212.7 (C²), 205.9 (C²¹), 150.5 (C¹³), 149.1 (C²³), 134.0 (C¹⁰), 133.0 (C²⁵), 131.8 (C⁸), 131.3 (C^{26or27}), 131.3 (C^{26or27}), 130.0 (C²²), 129.8 (C⁹), 128.7 (C¹¹), 125.3 (C¹²), 124.0 (C²⁴), 53.0 (C²⁰), 51.4 (C³), 48.9 (C⁷), 46.0 (C⁵), 34.4 (C¹⁶), 32.3 (C⁶), 30.5 (C¹⁵), 27.3 (C¹⁹), 23.3 (C¹⁷), 21.7 (C¹⁴), 8.7 (C¹⁸).

IR: 2963 (w), 2932 (w), 2878 (w), 1713 (m), 1544 (s), 1528 (s), 1465 (w), 1352 (s), 1168 (m), 912 (w), 852 (w), 782 (m), 733 (m), 674 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₅H₃₀N₃O₈S⁺: 532.1748; Found: 532.1754.

R_f (PE/EtOAc 4:6) = 0.47.

(±)-1,2-dehydroaspidospermidine 2



A solution of the macrocycles **212a/212b** (dr 1:1, 10 mg, 0.020 mmol) in DCM (0.50 mL) was stirred at -78 °C. Ozone was bubbled through the solution until a blue color appeared (approximately 15 s). Argon was then bubbled through the solution for 10 min. Me₂S (50 μ L) was added and the reaction mixture was stirred overnight at RT. Cesium carbonate (20 mg, 0.060 mmol, 3.0 equiv) and thiophenol (6.0 μ L, 0.060 mmol, 3.0 equiv) were added. The reaction mixture was stirred at RT for 24 h. Methanol (0.20 mL) was then added, followed by aqueous NH₄OAc (2.5 M solution in H₂O, 0.30 mL). A mixture of TiCl₃ (20% in aqueous 3%

HCl, 60 μ L, 0.10 mmol, 5.0 equiv) and aqueous NH_4OAc (2.5 M solution in H_2O , 0.3.0 mL) was then added dropwise. The dark purple solution was stirred at RT for 30 min. The reaction mixture was then poured into saturated aqueous NaHCO_3 . The mixture turned black. EtOAc was added and, after vigorous shaking, the mixture turned to white. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc/ Et_3N 90:10:2) afforded (\pm)-1,2-dehydroaspidospermidine **2** as a colorless oil (2.8 mg, 50% yield, single diastereoisomer). The spectroscopic data of this compound were in accord with those reported in the literature.⁶⁶

^1H NMR (400 MHz, CDCl_3): δ 7.51 (d, J = 7.3 Hz, 1H, $\text{C}^{12}\text{-H}$), 7.33 (d, J = 7.3 Hz, 1H, $\text{C}^9\text{-H}$), 7.29 (td, J = 7.3, 1.3 Hz, 1H, $\text{C}^{11}\text{-H}$), 7.16 (td, J = 7.3, 1.0 Hz, 1H, $\text{C}^{10}\text{-H}$), 3.18 (t, J = 7.5 Hz, 2H, $\text{C}^{3,5}\text{-H}$), 3.11 (ddd, J = 14.4, 11.8, 5.3 Hz, 1H, $\text{C}^{16}\text{-H}$), 2.76 (ddd, J = 14.4, 10.5, 3.6 Hz, 1H, $\text{C}^{16}\text{-H}$), 2.59 (ddd, J = 11.5, 8.4, 5.7 Hz, 1H, $\text{C}^5\text{-H}$), 2.46 (td, J = 12.8, 3.3 Hz, 1H, $\text{C}^{17}\text{-H}$), 2.40 (s, 1H, $\text{C}^{21}\text{-H}$), 2.14-2.06 (m, 2H, $\text{C}^{3,6}\text{-H}$), 1.85 (qt, J = 13.4, 4.7 Hz, 1H, $\text{C}^{14}\text{-H}$), 1.65 (dd, J = 12.2, 5.4 Hz, 1H, $\text{C}^6\text{-H}$), 1.61-1.52 (m, 2H, $\text{C}^{14,17}\text{-H}$), 1.47 (dd, J = 13.7, 2.7 Hz, 1H, $\text{C}^{15}\text{-H}$), 1.00 (td, J = 13.6, 5.0 Hz, 1H, $\text{C}^{15}\text{-H}$), 0.70 (dq, J = 14.5, 7.4 Hz, 1H, $\text{C}^{19}\text{-H}$), 0.64 (dq, J = 14.5, 7.4 Hz, 1H, $\text{C}^{19}\text{-H}$), 0.49 (t, J = 7.4 Hz, 3H, $\text{C}^{18}\text{-H}$).

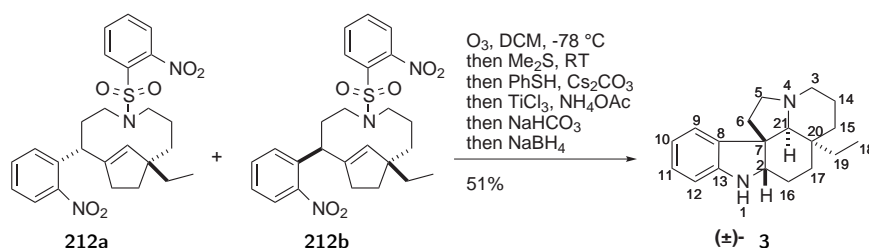
^{13}C NMR (101 MHz, CDCl_3): δ 192.5 (C^2), 154.7 (C^{13}), 147.3 (C^8), 127.6 (C^{11}), 125.3 (C^{10}), 121.1 (C^9), 120.3 (C^{12}), 79.2 (C^{21}), 61.5 (C^7), 54.7 (C^5), 52.2 (C^3), 36.7 (C^{20}), 35.3 (C^6), 33.4 (C^{15}), 29.9 (C^{19}), 27.4 (C^{17}), 23.9 (C^{16}), 22.2 (C^{14}), 7.4 (C^{18}).

IR: 2933 (m), 2773 (m), 1575 (m), 1456 (m), 1324 (w), 1251 (w), 1194 (w), 1123 (w), 1014 (w), 751 (w), 615 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2^+$: 281.2012; Found: 281.2008.

R_f (PE/EtOAc/ Et_3N 4:4:0.5) = 0.54 (red to blue with molybdenate stain).

(\pm)-aspidospermidine **3**



A solution of the macrocycles **212a/212b** (dr 1:1, 10 mg, 0.020 mmol) in DCM (0.50 mL) was

stirred at -78°C . Ozone was bubbled through the solution until a blue color appeared (approximately 15 s). Argon was then bubbled through the solution for 10 min. Me_2S (0.050 mL) was added and the reaction mixture was stirred overnight at RT. Cesium carbonate (20 mg, 0.060 mmol, 3.0 equiv) and thiophenol (6.0 μL , 0.060 mmol, 3.0 equiv) were added. The reaction mixture was stirred at RT for 24 h. Methanol (0.20 mL) was then added, followed by aqueous NH_4OAc (2.5 M solution in H_2O , 0.30 mL). A mixture of TiCl_3 (20% in aqueous 3% HCl , 60 μL , 0.10 mmol, 5.0 equiv) and aqueous NH_4OAc (2.5 M solution in H_2O , 0.30 mL) was then added dropwise. The dark purple solution was stirred at RT for 30 min. Saturated aqueous NaHCO_3 (1.0 mL) was then added. The mixture turned black, and after vigorous stirring for 15 min, the mixture turned to white. NaBH_4 (7.6 mg, 0.20 mmol, 10 equiv) was then added, and the mixture was stirred for 2 h. EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/ EtOAc / Et_3N 90:10:2) afforded (\pm)-aspidospermidine **3** as a colorless oil (2.9 mg, 51% yield, single diastereoisomer). The spectroscopic data of this compound were in accord with those reported in the literature.⁷⁰

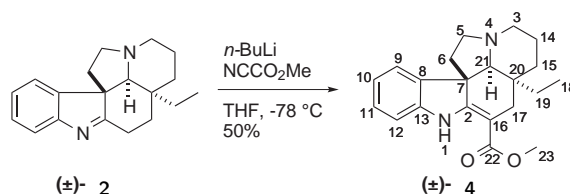
^1H NMR (800 MHz, CDCl_3): δ 7.08 (d, J = 7.5 Hz, 1H, $\text{C}^9\text{-H}$), 7.02 (td, J = 7.6, 1.0 Hz, 1H, $\text{C}^{11}\text{-H}$), 6.73 (td, J = 7.2, 0.7 Hz, 1H, $\text{C}^{10}\text{-H}$), 6.64 (d, J = 7.8 Hz, 1H, $\text{C}^{12}\text{-H}$), 3.51 (dd, J = 11.1, 6.2 Hz, 1H, $\text{C}^2\text{-H}$), 3.12 (td, J = 8.9, 2.7 Hz, 1H, $\text{C}^5\text{-H}$), 3.06 (m, 1H, $\text{C}^3\text{-H}$), 2.29 (dt, J = 13.0, 8.6 Hz, 1H, $\text{C}^6\text{-H}$), 2.24 (dt, J = 10.1, 8.6 Hz, 1H, $\text{C}^5\text{-H}$), 2.21 (s, 1H, $\text{C}^{21}\text{-H}$), 2.01-1.90 (m, 2H, $\text{C}^{3,16}\text{-H}$), 1.74 (qt, J = 13.1, 3.9 Hz, 1H, $\text{C}^{14}\text{-H}$), 1.66-1.61 (m, 2H, $\text{C}^{15,17}\text{-H}$), 1.51 (m, 1H, $\text{C}^{14}\text{-H}$), 1.50-1.45 (m, 2H, $\text{C}^{6,19}\text{-H}$), 1.39 (dt, J = 13.9, 2.7 Hz, 1H, $\text{C}^{17}\text{-H}$), 1.11 (td, J = 13.4, 4.8 Hz, 1H, $\text{C}^{15}\text{-H}$), 1.05 (dt, J = 13.7, 2.9 Hz, 1H, $\text{C}^{16}\text{-H}$), 0.87 (dq, J = 14.4, 7.9 Hz, 1H, $\text{C}^{19}\text{-H}$), 0.63 (t, J = 7.5 Hz, 3H, $\text{C}^{18}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 149.5 (C^{13}), 135.9 (C^8), 127.2 (C^{11}), 123.0 (C^9), 119.1 (C^{10}), 110.5 (C^{12}), 71.4 (C^{21}), 65.8 (C^2), 54.0 (C^3), 53.5 (C^7), 53.2 (C^5), 39.0 (C^6), 35.8 (C^{20}), 34.6 (C^{15}), 30.1 (C^{19}), 28.2 (C^{17}), 23.2 (C^{16}), 21.9 (C^{14}), 7.0 (C^{18}).

IR: 3361 (w), 2930 (m), 2778 (w), 2772 (w), 1729 (w), 1607 (w), 1481 (m), 1462 (m), 1332 (w), 1259 (m), 1179 (w), 1024 (m), 905 (w), 737 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{27}\text{N}_2^+$: 283.2169; Found: 283.2107.

R_f (PE/ EtOAc / Et_3N 4:4:0.5) = 0.25 (red to blue with molybdenate stain).

(±)-vincadifformine 4

To a solution of (±)-1,2-dehydroaspidospermidine **2** (10 mg, 0.036 mmol) in THF (0.50 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise $n\text{-BuLi}$ (1.1 M in THF, $36\text{ }\mu\text{L}$, 0.036 mmol, 1.0 equiv). The solution was stirred for 30 min. Methyl cyanofomate ($4.5\text{ }\mu\text{L}$, 0.058 mmol, 1.6 equiv) was added dropwise. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min, and allowed to warm to $0\text{ }^\circ\text{C}$. The reaction was monitored by TLC. After complete consumption of the starting material, saturated aqueous NaHCO_3 was added slowly, and the reaction mixture was warmed up to RT. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/Et₂O/Et₃N 80:10:2) afforded (±)-vincadifformine **4** as a colorless oil (6.0 mg, 50% yield, single diastereoisomer). The spectroscopic data of this compound were in accord with those reported in the literature.⁷⁰

¹H NMR (400 MHz, CDCl₃): δ 8.89 (s, 1H, N¹-H), 7.18 (d, $J = 7.6\text{ Hz}$, 1H, C⁹-H), 7.12 (t, $J = 7.1\text{ Hz}$, 1H, C¹¹-H), 6.85 (t, $J = 7.4\text{ Hz}$, 1H, C¹⁰-H), 6.79 (d, $J = 7.6\text{ Hz}$, 1H, C¹²-H), 3.76 (s, 3H, C²³-H), 3.12 (m, 1H, C³-H), 2.92 (t, $J = 7.4\text{ Hz}$, 1H, C⁵-H), 2.72 (d, $J = 15.1\text{ Hz}$, 1H, C¹⁷-H), 2.55 (ddd, $J = 11.4, 8.2, 4.6\text{ Hz}$, 1H, C⁵-H), 2.45 (d, $J = 0.9\text{ Hz}$, 1H, C²¹-H), 2.40 (td, $J = 10.7, 3.0\text{ Hz}$, 1H, C³-H), 2.27 (dd, $J = 15.2, 1.6\text{ Hz}$, 1H, C¹⁷-H), 2.05 (ddd, $J = 11.3, 11.3, 6.5\text{ Hz}$, 1H, C⁶-H), 1.88-1.76 (m, 2H, C¹⁴-H), 1.70 (dd, $J = 11.5, 4.8\text{ Hz}$, 1H, C⁶-H), 1.21 (m, 1H, C¹⁵-H), 0.96 (m, 1H, C¹⁹-H), 0.88 (m, 1H, C¹⁵-H), 0.62 (m, 1H, C¹⁹-H), 0.57 (t, $J = 7.0\text{ Hz}$, 3H, C¹⁸-H).

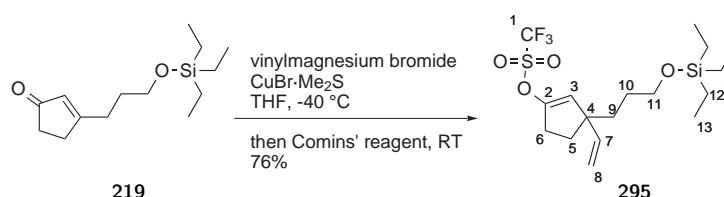
¹³C NMR (101 MHz, CDCl₃): δ 169.4 (C²²), 168.0 (C²), 143.5 (C¹³), 138.1 (C⁸), 127.6 (C¹¹), 121.1 (C⁹), 120.6 (C¹⁰), 109.5 (C¹²), 92.8 (C¹⁶), 72.9 (C²¹), 55.16 (C⁷), 51.9 (C³), 51.1 (C⁵), 50.9 (C²³), 45.4 (C⁶), 38.4 (C²⁰), 33.0 (C¹⁵), 29.4 (C¹⁹), 25.6 (C¹⁷), 22.3 (C¹⁴), 7.3 (C¹⁸).

IR: 3378 (br m), 2927 (s), 2854 (m), 2776 (w), 1736 (w), 1676 (s), 1609 (s), 1464 (w), 1437 (w), 1252 (m), 1159 (s).

HRMS: (ESI⁺) m/z : $[\text{M} + \text{H}]^+$ Calcd for C₂₁H₂₇N₂O₂⁺: 339.2067; Found: 339.2063.

R_f (PE/Et₂O/Et₃N 8:2:0.5) = 0.4 (red to blue with molybdenate stain).

8.4 Experimental Procedures of Chapter 4

3-vinyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate **295**

To a suspension of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (5.7 g, 28 mmol, 2.0 equiv) in THF (85 mL) at -78°C was added dropwise vinylmagnesium bromide (0.8 M in THF, 69 mL, 55 mmol, 4.0 equiv). The reaction mixture was stirred at -78°C for 1 h and then warmed to -40°C . To the above prepared cuprate solution was added dropwise a solution of the ketone **219** (3.5 g, 14 mmol) in THF (30 mL) while keeping the solution below -40°C . The reaction mixture was stirred at -40°C for 3 h. A solution of Comins' reagent (11 g, 28 mmol, 2.0 equiv) in THF (30 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to RT, and stirred for 24 h. The reaction was quenched with NH_4Cl . The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 20:1) afforded compound **295** as a colorless oil (4.2 g, 73% yield).

^1H NMR (400 MHz, CDCl_3): δ 5.73 (dd, $J = 17.5, 10.8$ Hz, 1H, $\text{C}^7\text{--H}$), 5.55 (t, $J = 1.6$ Hz, 1H, $\text{C}^3\text{--H}$), 5.01 (dd, $J = 10.8, 1.9$ Hz, 1H, $\text{C}^{8a}\text{--H}$), 4.96 (dd, $J = 17.5, 1.9$ Hz, 1H, $\text{C}^{8b}\text{--H}$), 3.58 (t, $J = 5.8$ Hz, 2H, $\text{C}^{11}\text{--H}$), 2.68–2.50 (m, 2H, $\text{C}^6\text{--H}$), 1.99–1.85 (m, 2H, $\text{C}^5\text{--H}$), 1.59–1.42 (m, 4H, $\text{C}^{9,10}\text{--H}$), 0.95 (t, $J = 7.8$ Hz, 9H, $\text{C}^{13}\text{--H}$), 0.59 (q, $J = 7.8$ Hz, 6H, $\text{C}^{12}\text{--H}$).

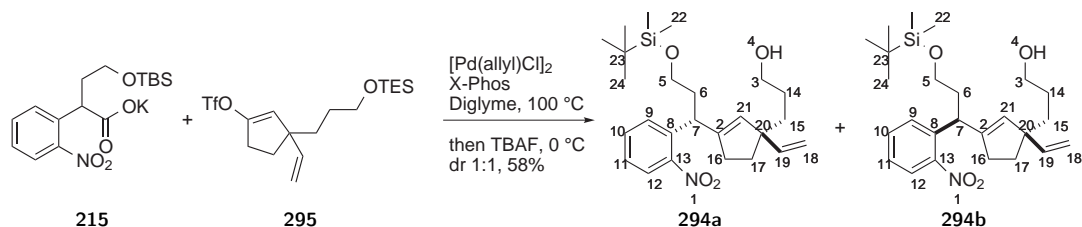
^{13}C NMR (101 MHz, CDCl_3): δ 149.1 (C^2), 143.8 (C^7), 122.7 (C^3), 118.4 (q, $J = 338.0$ Hz, C^1), 112.7 (C^8), 63.1 (C^{11}), 51.4 (C^4), 36.6 (C^9), 34.0 (C^5), 30.3 (C^6), 28.4 (C^{10}), 6.9 (C^{13}), 4.5 (C^{12}).

IR: 2954 (m), 2910 (w), 2878 (w), 1661 (w), 1425 (m), 1221 (s), 1142 (m), 1097 (m), 1006 (w), 914 (m), 839 (w), 741 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{29}\text{F}_3\text{NaO}_4\text{Si}^+$: 437.1400; Found: 437.1400.

R_f (PE/EtOAc 10:1) = 0.88

3-(-3-((-3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-vinylcyclopent-2-en-1-yl)propan-1-ol 294



An oven-dried flask was charged with salt **215** (10 g, 27 mmol, 1.2 equiv), X-Phos (1.6 g, 3.3 mmol, 15 mol%), allylpalladium chloride dimer (0.20 g, 0.55 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (150 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **295** (9.0 g, 22 mmol) in diglyme (150 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was cooled down to 0 °C, and TBAF (1 M solution in THF, 24 mL, 24 mmol, 1.1 equiv) was added dropwise. The reaction was monitored by TLC until total conversion. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The two diastereoisomers were separated by FCC (PE/EtOAc 8:2), giving **294a** and **294b** as yellow oils (5.7 g, 58% yield, dr 1:1).

Compound 294a

¹H NMR (400 MHz, CDCl₃): δ 7.70 (dd, J = 7.8, 1.2 Hz, 1H, C¹²-H), 7.51 (td, J = 7.8, 1.2 Hz, 1H, C¹⁰-H), 7.38 (dd, J = 7.8, 1.2 Hz, 1H, C⁹-H), 7.32 (td, J = 7.8, 1.2 Hz, 1H, C¹¹-H), 5.83 (dd, J = 17.5, 10.1 Hz, 1H, C¹⁹-H), 5.40 (m, 1H, C²¹-H), 4.92 (dd, J = 10.1, 1.6 Hz, 1H, C¹⁸-H), 4.91 (dd, J = 17.5, 1.6 Hz, 1H, C¹⁸-H), 4.17 (t, J = 7.4 Hz, 1H, C⁷-H), 3.65-3.59 (m, 2H, C³-H), 3.51-3.50 (m, 2H, C⁵-H), 2.19-2.03 (m, 3H, C^{6,15}-H), 1.97 (m, 1H, C⁶-H), 1.80-1.67 (m, 2H, C¹⁷-H), 1.54-1.46 (m, 4H, C^{14,16}-H), 0.86 (s, 9H, C^{3'}-H), -0.09 (s, 6H, C^{1'}-H), OH peak not observed.

¹³C NMR (101 MHz, CDCl₃): δ 150.8 (C¹³), 145.5 (C¹⁹), 145.2 (C²), 137.4 (C⁸), 132.4 (C¹⁰), 131.2 (C²¹), 129.1 (C⁹), 127.1 (C¹¹), 124.2 (C¹²), 111.2 (C¹⁸), 63.7 (C³), 61.1 (C⁵), 54.5 (C²⁰), 37.4 (C⁷), 36.9 (C⁶), 36.2 (C¹⁵), 35.8 (C¹⁷), 32.6 (C¹⁶), 28.7 (C¹⁴), 26.1 (C^{3'}), 18.4 (C^{2'}), -5.3 (C^{1'}).

IR: 3354 (br w), 2931 (m), 2856 (w), 1528 (s), 1357 (m), 1255 (m), 1101 (s), 1061 (m), 836 (s), 777 (s).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₂₅H₃₉NNaO₄Si⁺: 468.2541; Found: 468.2549.

R_f (PE/EtOAc 6:4) = 0.60

Compound 294b

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.71 (dd, $J = 7.8, 1.5$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.51 (td, $J = 7.8, 1.5$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.39 (dd, $J = 7.8, 1.5$ Hz, 1H, $\text{C}^9\text{-H}$), 7.33 (td, $J = 7.8, 1.5$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.83 (dd, $J = 14.0, 10.7$ Hz, 1H, $\text{C}^{19}\text{-H}$), 5.40 (m, 1H, $\text{C}^{21}\text{-H}$), 4.93 (dd, $J = 14.0, 1.3$ Hz, 1H, $\text{C}^{18}\text{-H}$), 4.89 (dd, $J = 10.7, 1.3$ Hz, 1H, $\text{C}^{18}\text{-H}$), 4.12 (t, $J = 7.4$ Hz, 1H, $\text{C}^7\text{-H}$), 3.64-3.59 (m, 2H, $\text{C}^3\text{-H}$), 3.57-3.50 (m, 2H, $\text{C}^5\text{-H}$), 2.25-2.12 (m, 2H, $\text{C}^{6,15}\text{-H}$), 2.06 (m, 1H, $\text{C}^{15}\text{-H}$), 1.97 (m, 1H, $\text{C}^6\text{-H}$), 1.84-1.78 (m, 2H, $\text{C}^{17}\text{-H}$ and $\text{C}^3\text{-OH}$), 1.68 (m, 1H, $\text{C}^{17}\text{-H}$), 1.55-1.45 (m, 4H, $\text{C}^{14,16}\text{-H}$), 0.85 (s, 9H, $\text{C}^3\text{-H}$), -0.02 (s, 6H, $\text{C}^{1'}\text{-H}$).

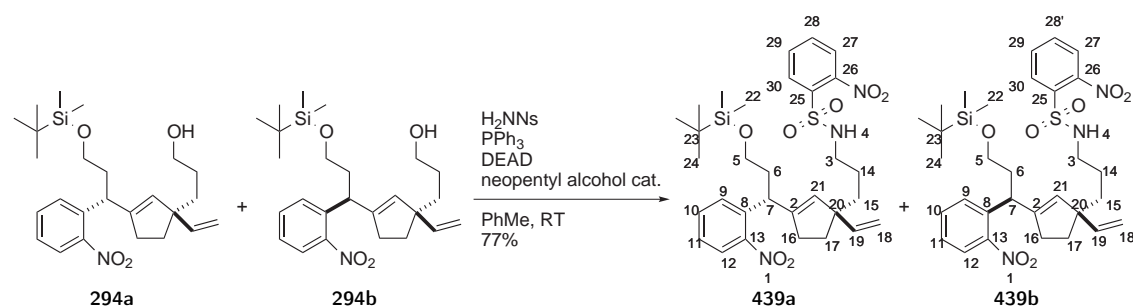
$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 150.7 (C^{13}), 145.6 (C^2), 145.3 (C^{19}), 137.6 (C^8), 132.4 (C^{10}), 131.0 (C^{21}), 129.2 (C^9), 127.1 (C^{11}), 124.2 (C^{12}), 111.4 (C^{18}), 64.0 (C^3), 61.1 (C^5), 54.6 (C^{20}), 37.6 (C^7), 37.2 (C^6), 36.2 (C^{15}), 35.9 (C^{17}), 33.0 (C^{16}), 28.7 (C^{14}), 26.1 ($\text{C}^{3'}$), 18.4 ($\text{C}^{2'}$), -5.3 ($\text{C}^{1'}$).

IR: 3352 (br w), 2929 (m), 2857 (w), 1528 (s), 1358 (m), 1255 (m), 1102 (s), 1062 (m), 835 (s), 778 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{25}\text{H}_{39}\text{NNaO}_4\text{Si}^+$: 468.2541; Found: 468.2544.

R_f (PE/EtOAc 6:4) = 0.48

N-(3-(3-(3-((*tert*-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-vinylcyclopent-2-en-1-yl)propyl)-2-nitrobenzenesulfonamide 439



To a solution of alcohols **294a/294b** (dr 1:1, 6.0 g, 13 mmol), neopentyl alcohol (0.58 g, 6.0 mmol, 0.40 equiv), *o*-nitrophenylsulfonamide (5.3 g, 27 mmol, 2.0 equiv) and PPh_3 (3.5 g, 13 mmol, 1.0 equiv) in toluene (400 mL) at RT was added DEAD (40 wt.% in toluene, 6.0 mL, 13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh_3 (3.5 g, 13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 6.0 mL, 13 mmol, 1.0 equiv) were added. The reaction mixture was

stirred for one more hour. Saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (DCM) afforded the two diastereoisomers **439a** and **439b** as yellow oils (6.3 g, 77% yield, no change in dr).

Compound 439a

^1H NMR (400 MHz, CDCl_3): δ 8.13 (m, 1H, $\text{C}^{30}\text{-H}$), 7.85 (m, 1H, $\text{C}^{27}\text{-H}$), 7.76-7.69 (m, 3H, $\text{C}^{12,28,29}\text{-H}$), 7.54 (td, $J = 7.5, 1.6$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.37 (d, $J = 7.5$ Hz, 1H, $\text{C}^9\text{-H}$), 7.34 (t, $J = 7.5$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.72 (dd, $J = 17.2, 10.5$ Hz, 1H, $\text{C}^{19}\text{-H}$), 5.28-5.22 (m, 2H, $\text{C}^{4,21}\text{-H}$), 4.88 (dd, $J = 10.5, 1.4$ Hz, 1H, $\text{C}^{18}\text{-H}$), 4.84 (dd, $J = 17.2, 1.4$ Hz, 1H, $\text{C}^{18}\text{-H}$), 4.09 (t, $J = 7.3$ Hz, 1H, $\text{C}^7\text{-H}$), 3.75-3.45 (m, 2H, $\text{C}^5\text{-H}$), 3.10-3.04 (m, 2H, $\text{C}^3\text{-H}$), 2.23-2.09 (m, 2H, $\text{C}^{6,17}\text{-H}$), 2.05-1.91 (m, 2H, $\text{C}^{6,17}\text{-H}$), 1.75 (ddd, $J = 13.1, 9.2, 5.0$ Hz, 1H, $\text{C}^{16}\text{-H}$), 1.60-1.50 (m, 1H, $\text{C}^{16}\text{-H}$), 1.49-1.35 (m, 4H, $\text{C}^{14,15}\text{-H}$), 0.85 (s, 9H, $\text{C}^{24}\text{-H}$), -0.02 (s, 6H, $\text{C}^{22}\text{-H}$),

^{13}C NMR (101 MHz, CDCl_3): δ 150.7 (C^{13}), 148.3 (C^{26}), 146.2 (C^2), 144.8 (C^{19}), 137.3 (C^8), 134.0 (C^{25}), 133.6 (C^{28}), 132.9 (C^{21}), 132.5 (C^{29}), 131.2 (C^{10}), 130.3 (C^{30}), 129.2 (C^9), 127.3 (C^{11}), 125.5 (C^{27}), 124.2 (C^{12}), 111.7 (C^{18}), 61.0 (C^5), 54.4 (C^{20}), 44.6 (C^3), 37.6 (C^7), 37.1 ($\text{C}^{6\text{or}15}$), 37.0 ($\text{C}^{6\text{or}15}$), 35.8 (C^{16}), 33.1 (C^{17}), 26.1 (C^{24}), 25.6 (C^{14}), 18.4 (C^{23}), -5.3 (C^{22}).

IR: 3352 (w), 2950 (w), 2930 (w), 2856 (w), 1540 (s), 1527 (s), 1413 (m), 1356 (s), 1255 (m), 1167 (s), 1100 (s), 853 (s), 836 (s), 779 (s), 742 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{31}\text{H}_{43}\text{N}_3\text{NaO}_7\text{SSi}^+$: 652.2483; Found: 652.2482.

R_f (DCM) = 0.39

Compound 439b

^1H NMR (400 MHz, CDCl_3): δ 8.13 (m, 1H, $\text{C}^{30}\text{-H}$), 7.86 (m, 1H, $\text{C}^{27}\text{-H}$), 7.76-7.72 (m, 2H, $\text{C}^{28,29}\text{-H}$), 7.70 (dd, $J = 8.0, 1.2$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.51 (m, 1H, $\text{C}^{10}\text{-H}$), 7.40-7.30 (m, 2H, $\text{C}^{9,11}\text{-H}$), 5.71 (dd, $J = 12.0, 18.4$ Hz, 1H, $\text{C}^{19}\text{-H}$), 5.29 (m, 1H, $\text{C}^{21}\text{-H}$), 5.25 (t, $J = 5.5$ Hz, 1H, $\text{N}^4\text{-H}$), 4.91-4.80 (m, 2H, $\text{C}^{18}\text{-H}$), 4.18 (t, $J = 7.4$ Hz, 1H, $\text{C}^7\text{-H}$), 3.56-3.47 (m, 2H, $\text{C}^5\text{-H}$), 3.11-3.05 (m, 2H, $\text{C}^3\text{-H}$), 2.10 (m, 1H, $\text{C}^6\text{-H}$), 2.07-2.01 (m, 2H, $\text{C}^{17}\text{-H}$), 1.96 (m, 1H, $\text{C}^6\text{-H}$), 1.71 (m, 1H, $\text{C}^{16}\text{-H}$), 1.63-1.53 (m, 1H, $\text{C}^{16}\text{-H}$), 1.48-1.35 (m, 4H, $\text{C}^{14,15}\text{-H}$), 0.86 (s, 9H, $\text{C}^{24}\text{-H}$), -0.1 (s, 6H, $\text{C}^{22}\text{-H}$),

^{13}C NMR (101 MHz, CDCl_3): δ 150.8 (C^{13}), 148.2 (C^{26}), 145.6 (C^2), 144.9 (C^{19}), 137.1 (C^8), 134.1 (C^{25}), 133.6 (C^{28}), 132.9 (C^{21}), 132.4 (C^{29}), 131.3 (C^{10}), 130.8 (C^{30}), 129.0 (C^9), 127.2 (C^{11}), 125.5 (C^{27}), 124.2 (C^{12}), 111.5 (C^{18}), 61.0 (C^5), 54.3 (C^{20}), 44.6 (C^3), 37.3 (C^7), 36.9 (C^{15}), 36.6 (C^6),

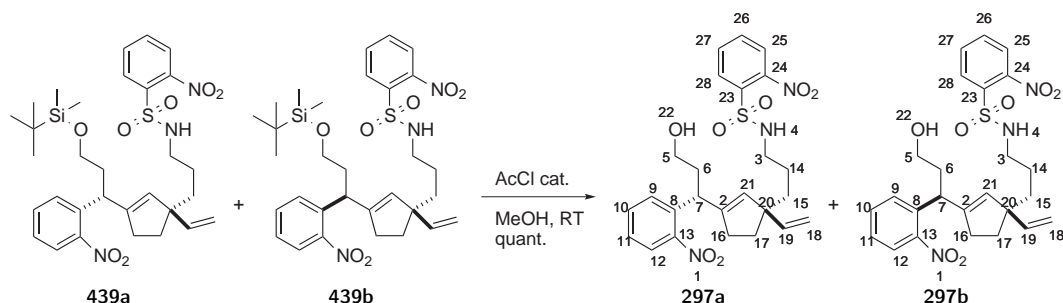
35.8 (C¹⁶), 32.2 (C¹⁷), 26.1 (C²⁴), 25.5 (C¹⁴), 18.4 (C²³), -5.3 (C²²).

IR: 3346 (w), 2951 (w), 2929 (w), 2855 (w), 1542 (s), 1527 (s), 1414 (w), 1357 (s), 1255 (m), 1169 (s), 1100 (s), 853 (m), 835 (s), 780 (s), 741 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₃₁H₄₃N₃NaO₇SSi⁺: 652.2483; Found: 652.2486.

R_f (DCM) = 0.39

N-(3-(3-(3-hydroxy-1-(2-nitrophenyl)propyl)-1-vinylcyclopent-2-en-1-yl)propyl)-2-nitrobenzenesulfonamide 297



To a solution of compounds **439a/439b** (dr 1:1, 6.3 g, 10 mmol) in MeOH (100 mL) at 0°C was added dropwise acetyl chloride (60 μ L, 1.0 mmol, 10 mol%). After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. The crude compound **440** thus obtained (5.2 g, quantitative yield, no change in dr) was used for the next step without further purification.

Compound 297a

¹H NMR (400 MHz, CDCl₃): δ 8.12 (m, 1H, C²⁸-H), 7.84 (m, 1H, C²⁵-H), 7.76-7.72 (m, 2H, C^{26,27}-H), 7.69 (dd, *J* = 8.0, 1.3 Hz, 1H, C¹²-H), 7.56 (td, *J* = 8.0, 1.3 Hz, 1H, C¹⁰-H), 7.37 (dd, *J* = 8.0, 1.3 Hz, 1H, C⁹-H), 7.35 (td, *J* = 8.0, 1.3 Hz, 1H, C¹¹-H), 5.71 (dd, *J* = 17.2, 10.7 Hz, 1H, C¹⁹-H), 5.33 (m, 1H, C²¹-H), 5.30 (m, 1H, N⁴-H), 4.87 (dd, *J* = 10.7, 1.3 Hz, 1H, C¹⁸-H), 4.83 (dd, *J* = 17.2, 1.3 Hz, 1H, C¹⁸-H), 4.08 (t, *J* = 7.8 Hz, 1H, C⁷-H), 3.60 (m, 1H, C⁵-H), 3.51 (m, 1H, C⁵-H), 3.11-3.03 (m, 2H, C³-H), 2.22 (m, 1H, C⁶-H), 2.12 (m, 1H, C¹⁷-H), 2.03-1.90 (m, 2H, C^{6,17}-H), 1.74 (ddd, *J* = 12.8, 8.8, 5.0 Hz, 1H, C¹⁶-H), 1.54 (ddd, *J* = 12.8, 8.8, 6.1 Hz, 1H, C¹⁶-H), 1.49-1.35 (m, 4H, C^{14,15}-H), OH peak not observed.

¹³C NMR (101 MHz, CDCl₃): δ 150.9 (C¹³), 148.2 (C²⁴), 146.1 (C²), 144.7 (C¹⁹), 136.9 (C⁸), 134.0 (C²³), 133.7 (C²⁶), 132.9 (C²¹), 132.7 (C²⁷), 131.2 (C¹⁰), 130.5 (C²⁸), 129.2 (C⁹), 127.5 (C¹¹),

125.5 (C²⁵), 124.1 (C¹²), 111.8 (C¹⁸), 60.7 (C⁵), 54.4 (C²⁰), 44.5 (C³), 37.7 (C⁷), 37.0 (C^{6or15}), 37.0 (C^{6or15}), 35.8 (C¹⁶), 33.0 (C¹⁷), 25.6 (C¹⁴).

IR: 3323 (w), 3081 (w), 2935 (w), 2847 (w), 2357 (w), 2323 (w), 1541 (s), 1525 (s), 1342 (s), 1165 (m), 915 (m), 854 (m), 786 (m), 733 (s).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₂₅H₂₉N₃NaO₇S⁺: 538.1618; Found: 538.1619.

R_f (PE/EtOAc 4:6) = 0.50

Compound 297b

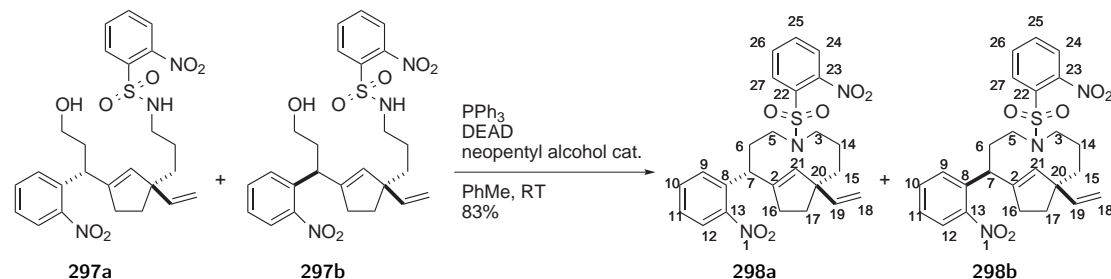
¹H NMR (400 MHz, CDCl₃): δ 8.13 (m, 1H, C²⁸-H), 7.86 (m, 1H, C²⁵-H), 7.77-7.73 (m, 2H, C^{26,27}-H), 7.69 (dd, *J* = 7.7, 1.7 Hz, 1H, C¹²-H), 7.53 (td, *J* = 7.7, 1.7 Hz, 1H, C¹⁰-H), 7.35 (d, *J* = 7.7 Hz, 1H, C⁹-H), 7.34 (m, 1H, C¹¹-H), 5.72 (dd, *J* = 17.6, 10.5 Hz, 1H, C¹⁹-H), 5.35 (m, 1H, C²¹-H), 5.29 (t, *J* = 5.9 Hz, 1H, N⁴-H), 4.88 (dd, *J* = 10.5, 1.4 Hz, 1H, C¹⁸-H), 4.84 (dd, *J* = 17.6, 1.4 Hz, 1H, C¹⁸-H), 4.12 (m, 1H, C⁷-H), 3.61 (m, 1H, C⁵-H), 3.53 (m, 1H, C⁵-H), 3.13-3.02 (m, 2H, C³-H), 2.20 (m, 1H, C⁶-H), 2.06-1.93 (m, 3H, C^{6,17}-H), 1.70 (m, 1H, C¹⁶-H), 1.64-1.56 (m, 1H, C¹⁶-H), 1.49-1.37 (m, 4H, C^{14,15}-H), OH peak not observed.

¹³C NMR (101 MHz, CDCl₃): δ 150.9 (C¹³), 148.2 (C²⁴), 145.6 (C²), 144.9 (C¹⁹), 136.7 (C⁸), 134.0 (C²³), 133.7 (C²⁶), 132.9 (C²¹), 132.6 (C²⁷), 131.2 (C¹⁰), 130.8 (C²⁸), 129.1 (C⁹), 127.5 (C¹¹), 125.5 (C²⁵), 124.1 (C¹²), 111.6 (C¹⁸), 60.8 (C⁵), 54.4 (C²⁰), 44.6 (C³), 37.6 (C⁷), 36.9 (C^{6or15}), 36.7 (C^{6or15}), 35.7 (C¹⁶), 32.6 (C¹⁷), 25.5 (C¹⁴).

IR: 3349 (w), 3075 (w), 2945 (w), 2877 (w), 1540 (s), 1525 (s), 1415 (w), 1358 (s), 1165 (m), 1031 (w), 913 (w), 854 (w), 783 (m), 731 (m).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₂₅H₂₉N₃NaO₇S⁺: 538.1618; Found: 538.1620.

R_f (PE/EtOAc 4:6) = 0.50

(E)-8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-1-vinyl-5-azabicyclo[7.2.1]dodec-9(12)-ene 298

To a solution of alcohols **297a/297b** (dr 1:1, 0.10 g, 0.19 mmol), neopentyl alcohol (7.5 mg, 0.078 mmol, 0.40 equiv), and PPh_3 (50 mg, 0.19 mmol, 1.0 equiv) in toluene (40 mL) at RT was added DEAD (40 wt.% in toluene, 85 μL , 0.19 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh_3 (50 mg, 0.19 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 85 μL , 0.19 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. Saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/DCM 1:9) afforded the two diastereoisomers **298a** and **298b** as yellow oils (78 mg, 83% yield, no change in dr).

Compound 298a

^1H NMR (400 MHz, CDCl_3): δ 7.91 (dd, $J = 7.4, 1.8$ Hz, 1H, $\text{C}^{27}\text{-H}$), 7.75-7.65 (m, 3H, $\text{C}^{12,25,26}\text{-H}$), 7.61-7.53 (m, 2H, $\text{C}^{10,24}\text{-H}$), 7.48 (dd, $J = 7.5, 1.8$ Hz, 1H, $\text{C}^9\text{-H}$), 7.36 (td, $J = 7.5, 1.8$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.87 (dd, $J = 17.1, 11.0$ Hz, 1H, $\text{C}^{19}\text{-H}$), 5.58 (m, 1H, $\text{C}^{21}\text{-H}$), 4.96 (dd, $J = 17.1, 1.7$ Hz, 1H, $\text{C}^{18}\text{-H}$), 4.88 (dd, $J = 11.0, 1.7$ Hz, 1H, $\text{C}^{18}\text{-H}$), 4.36 (dd, $J = 12.7, 2.8$ Hz, 1H, $\text{C}^7\text{-H}$), 4.04 (dd, $J = 15.5, 7.2$ Hz, 1H, $\text{C}^5\text{-H}$), 3.77 (ddd, $J = 14.9, 9.9, 5.0$ Hz, 1H, $\text{C}^3\text{-H}$), 2.84-2.61 (m, 4H, $\text{C}^{3,5,6,17}\text{-H}$), 2.17-2.03 (m, 2H, $\text{C}^{14,16}\text{-H}$), 1.94-1.83 (m, 2H, $\text{C}^{6,17}\text{-H}$), 1.83-1.69 (m, 2H, $\text{C}^{14,16}\text{-H}$), 1.69-1.61 (m, 1H, $\text{C}^{15}\text{-H}$), 1.42 (m, 1H, $\text{C}^{15}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 150.3 (C^{13}), 149.1 (C^{23}), 147.2 (C^{19}), 143.2 (C^2), 135.9 (C^8), 134.4 (C^{21}), 133.8 (C^{25}), 132.4 (C^{10}), 131.4 (C^{26}), 131.0 (C^{27}), 130.6 (C^{22}), 128.6 (C^9), 127.4 (C^{11}), 124.4 (C^{12}), 124.1 (C^{24}), 110.8 (C^{18}), 56.7 (C^3), 55.4 (C^5), 55.1 (C^{20}), 43.1 (C^7), 39.4 (C^{15}), 35.9 (C^6), 35.4 (C^{16}), 31.4 (C^{17}), 28.0 (C^{14}).

IR: 2938 (w), 2913 (w), 2852 (w), 1544 (s), 1527 (s), 1465 (w), 1353 (s), 1164 (m), 1126 (w), 913 (w), 852 (w), 784 (m), 755 (m), 732 (m),

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₅H₂₇N₃NaO₆S⁺: 520.1513; Found: 520.1512.

R_f (DCM) = 0.5

Compound 298b

¹H NMR (400 MHz, CDCl₃): δ 7.91 (m, 1H, C²⁷-H), 7.79 (dd, *J* = 8.0, 1.1 Hz, 1H, C¹²-H), 7.73-7.65 (m, 2H, C^{25,26}-H), 7.63-7.52 (m, 3H, C^{9,10,24}-H), 7.35 (td, *J* = 8.0, 1.1 Hz, 1H, C¹¹-H), 5.99 (dd, *J* = 17.6, 10.3 Hz, 1H, C¹⁹-H), 5.73 (m, 1H, C²¹-H), 4.98 (dd, *J* = 17.6, 1.7 Hz, 1H, C¹⁸-H), 4.93 (dd, *J* = 10.3, 1.7 Hz, 1H, C¹⁸-H), 3.88 (dd, *J* = 11.4, 3.4 Hz, 1H, C⁷-H), 3.53 (ddd, *J* = 15.4, 6.8, 1.7 Hz, 1H, C⁵-H), 3.27 (m, 1H, C³-H), 3.10 (m, 1H, C³-H), 2.98 (ddd, *J* = 15.4, 6.8, 1.7 Hz, 1H, C⁵-H), 2.58 (m, 1H, C⁶-H), 2.51-2.38 (m, 2H, C¹⁷-H), 2.19 (m, 1H, C⁶-H), 1.89 (m, 1H, C¹⁶-H), 1.83-1.69 (m, 3H, C^{14,15,16}-H), 1.61-1.40 (m, 2H, C^{14,15}-H).

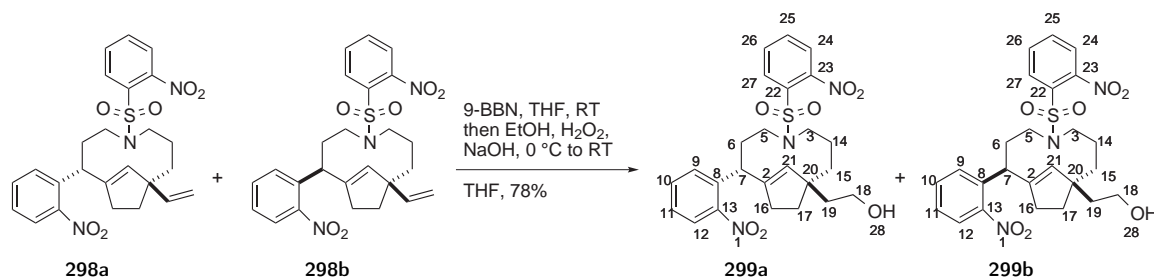
¹³C NMR (101 MHz, CDCl₃): δ 149.7 (C¹³), 149.0 (C²³), 146.6 (C¹⁹), 141.9 (C²), 137.2 (C⁸), 135.8 (C²¹), 133.8 (C²⁵), 133.0 (C¹⁰), 131.4 (C²⁶), 131.0 (C^{27or22}), 131.0 (C^{27or22}), 129.6 (C⁹), 127.5 (C¹¹), 124.6 (C¹²), 124.0 (C²⁴), 111.9 (C¹⁸), 56.3 (C²⁰), 52.5 (C³), 48.9 (C⁵), 41.9 (C⁷), 39.0 (C¹⁷), 37.9 (C¹⁵), 35.5 (C⁶), 34.3 (C¹⁶), 22.3 (C¹⁴).

IR: 2929 (w), 2849 (w), 1544 (s), 1525 (s), 1373 (m), 1354 (s), 1165 (w), 1126 (w), 912 (w), 853 (w), 782 (w), 732 (w),

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₂₅H₂₈N₃O₆S⁺: 498.1693; Found: 498.1690.

R_f (DCM) = 0.5

(E)-2-(8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-en-1-yl)ethan-1-ol **299**



To a solution of olefins **298a/298b** (dr 1:1, 78 mg, 0.16 mmol) in THF (10 mL) at RT was added 9-BBN (0.5 M in THF, 0.32 mL, 0.32 mmol, 2.0 equiv). After stirring for 2 h at RT, EtOH (0.50 mL), NaOH (6 M in H₂O, 0.50 mL) and H₂O₂ (30% in H₂O, 0.40 mL) were added at 0 °C.

The reaction mixture was stirred at 0 °C for 15 minutes, and then at RT for 2 h. Saturated aqueous Na₂S₂O₃ was added, followed by saturated aqueous NH₄Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 5:5) afforded the two diastereoisomers **299a** and **299b** as yellow oils (65 mg, 78% yield, no change in dr).

Compound 299a

¹H NMR (400 MHz, CDCl₃): δ 7.91 (m, 1H, C²⁷-H), 7.75-7.65 (m, 3H, C^{12,25,26}-H), 7.62-7.54 (m, 2H, C^{10,24}-H), 7.48 (m, 1H, C⁹-H), 7.37 (m, 1H, C¹¹-H), 5.60 (m, 1H, C²¹-H), 4.28 (dd, *J* = 13.0, 3.0 Hz, 1H, C⁷-H), 4.04 (dd, *J* = 16.5, 7.5 Hz, 1H, C⁵-H), 3.76 (ddd, *J* = 15.0, 10.0, 5.0 Hz, 1H, C³-H), 3.70-3.59 (m, 2H, C¹⁸-H), 2.79 (dd, *J* = 16.5, 7.5 Hz, 1H, C⁵-H), 2.74-2.53 (m, 3H, C^{3,6,17}-H), 2.15 (m, 1H, C⁶-H), 2.05 (m, 1H, C¹⁴-H), 1.83-1.63 (m, 5H, C^{14,16,17,19}-H), 1.62-1.50 (m, 2H, C^{15,19}-H), 1.34 (m, 1H, C¹⁵-H), 1.25 (br m, 1H, O²⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.3 (C¹³), 149.1 (C²³), 142.4 (C²), 135.8 (C⁸), 135.7 (C²¹), 133.8 (C²⁵), 132.5 (C¹⁰), 131.4 (C²⁶), 131.0 (C²⁷), 130.6 (C²²), 128.5 (C⁹), 127.4 (C¹¹), 124.4 (C¹²), 124.1 (C²⁴), 60.1 (C¹⁸), 56.6 (C³), 54.8 (C⁵), 52.0 (C²⁰), 44.0 (C¹⁹), 43.0 (C⁷), 41.6 (C¹⁵), 35.6 (C⁶), 33.2 (C¹⁶), 31.2 (C¹⁷), 28.1 (C¹⁴).

IR: 3342 (w), 2928 (m), 2852 (w), 1544 (s), 1527 (s), 1465 (w), 1351 (s), 1164 (m), 1006 (w), 852 (w), 784 (m), 756 (m), 731 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₅H₂₉N₃NaO₇S⁺: 538.1618; Found: 538.1620.

R_f (PE/EtOAc 4:6) = 0.2

Compound 299b

¹H NMR (400 MHz, CDCl₃): δ 7.90 (m, 1H, C²⁷-H), 7.78 (m, 1H, C¹²-H), 7.73-7.64 (m, 2H, C^{25,26}-H), 7.60-7.51 (m, 3H, C^{9,10,24}-H), 7.35 (m, 1H, C¹¹-H), 5.71 (s, 1H, C²¹-H), 3.87 (dd, *J* = 11.7, 2.9 Hz, 1H, C⁷-H), 3.77-3.65 (m, 2H, C¹⁸-H), 3.54 (ddd, *J* = 16.6, 7.8, 2.0 Hz, 1H, C⁵-H), 3.26 (m, 1H, C³-H), 3.07 (m, 1H, C³-H), 2.96 (ddd, *J* = 16.6, 7.8, 2.0 Hz, 1H, C⁵-H), 2.57 (m, 1H, C⁶-H), 2.47-2.34 (m, 2H, C¹⁶-H), 2.18 (m, 1H, C⁶-H), 1.88-1.62 (m, 6H, C^{14,15,17,19}-H), 1.52-1.36 (m, 2H, C^{14,15}-H), 1.25 (br s, 1H, O²⁸-H).

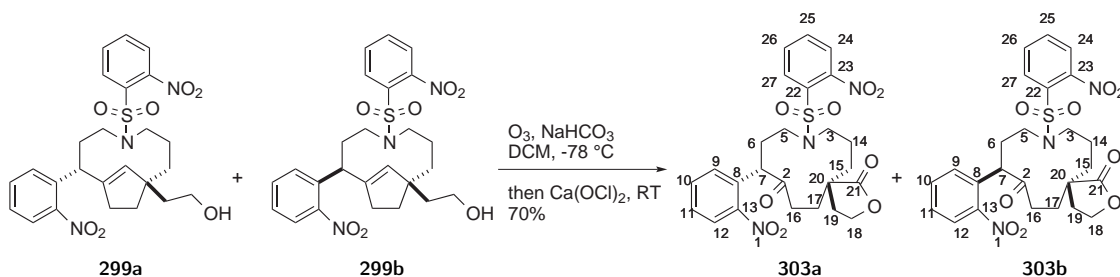
¹³C NMR (101 MHz, CDCl₃): δ 149.7 (C¹³), 149.0 (C²³), 141.3 (C²), 137.3 (C⁸), 137.0 (C²¹), 133.8 (C²⁵), 133.0 (C¹⁰), 131.5 (C²⁶), 131.1 (C²²), 131.0 (C²⁷), 129.5 (C¹¹), 127.5 (C⁹), 124.6 (C¹²), 124.1 (C²⁴), 60.6 (C¹⁸), 52.6 (C²⁰), 52.4 (C³), 48.9 (C⁵), 43.7 (C¹⁹), 42.0 (C⁷), 39.0 (C^{15or16}), 39.0 (C^{15or16}), 35.4 (C⁶), 33.1 (C¹⁷), 22.2 (C¹⁴).

IR: 3362 (w), 2929 (w), 2849 (w), 1546 (s), 1525 (s), 1373 (m), 1353 (s), 1165 (m), 1043 (w), 1004 (w), 910 (w), 853 (w), 788 (w), 732 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₅H₂₉N₃NaO₇S⁺: 538.1618; Found: 538.1623.

R_f (PE/EtOAc 4:6) = 0.2

12-(2-nitrophenyl)-9-((2-nitrophenyl)sulfonyl)-2-oxa-9-azaspiro[4.10]pentadecane-1,13-dione **303**



A suspension of macrocycles **299a/299b** (dr 1:1, 50 mg, 0.10 mmol) and NaHCO₃ (17 mg, 0.20 mmol, 2.0 equiv) in DCM (0.50 mL) was stirred at -78 °C. Ozone was bubbled through the solution until full conversion was observed by TLC. Argon was then bubbled through the mixture for 10 min. The mixture was then stirred at 0 °C for 15 min. Ca(OCl)₂ (29 mg, 0.20 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 24 h at RT. The reaction mixture was filtered through Celite and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 4:6) afforded the two diastereoisomers **303a** and **303b** as yellow foams (38 mg, 70% yield, no change in dr).

Compound 303a

¹H NMR (400 MHz, CDCl₃): δ 7.91 (dd, *J* = 7.1, 1.6 Hz, 1H, C²⁷-H), 7.86 (dd, *J* = 7.6, 1.1 Hz, 1H, C¹²-H), 7.71 (td, *J* = 7.1, 1.6 Hz, 1H, C²⁵-H), 7.68 (td, *J* = 7.1, 1.6 Hz, 1H, C²⁶-H), 7.57-7.51 (m, 2H, C^{10,24}-H), 7.42 (td, *J* = 7.6, 1.1 Hz, 1H, C¹¹-H), 7.31 (dd, *J* = 7.6, 1.1 Hz, 1H, C⁹-H), 5.25 (dd, *J* = 11.7, 2.3 Hz, 1H, C⁷-H), 4.31-4.20 (m, 2H, C¹⁸-H), 3.55 (m, 1H, C³-H), 3.41-3.15 (m, 3H, C^{5,16}-H), 2.86 (m, 1H, C³-H), 2.40 (m, 1H, C⁶-H), 2.31-2.11 (m, 4H, C^{6,15,17,19}-H), 2.05-1.88 (m, 3H, C^{15,16,19}-H), 1.55-1.20 (m, 3H, C^{14,17}-H).

¹³C NMR (101 MHz, CDCl₃): δ 211.3 (C²), 180.0 (C²¹), 150.3 (C¹³), 149.2 (C²³), 134.1 (C¹⁰), 133.1 (C²⁵), 131.8 (C⁸), 131.5 (C²⁶), 131.4 (C²⁷), 130.5 (C²²), 130.0 (C⁹), 128.7 (C¹¹), 125.3 (C¹²), 124.0 (C²⁴), 64.9 (C¹⁸), 51.1 (C³), 50.3 (C⁷), 46.4 (C⁵), 44.3 (C²⁰), 35.8 (C¹⁹), 35.3 (C¹⁶), 32.1 (C⁶),

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29.5 (C¹⁵or¹⁷), 29.3 (C¹⁵or¹⁷), 22.0 (C¹⁴).

IR: 2930 (w), 2863 (w), 1764 (m), 1711 (w), 1545 (s), 1529 (s), 1456 (w), 1360 (s), 1356 (s), 1169 (m), 1028 (w), 849 (w), 780 (w), 742 (m), 733 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₅H₂₇N₃NaO₉S⁺: 568.1360; Found: 568.1366.

R_f (PE/EtOAc 1:9) = 0.44

Compound 303b

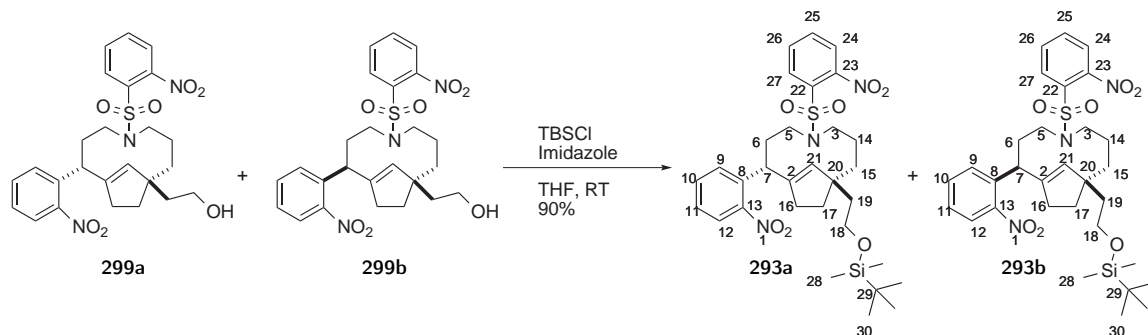
¹H NMR (400 MHz, CDCl₃): δ 7.86 (dd, *J* = 7.6, 1.6 Hz, 1H, C¹²–H), 7.83 (dd, *J* = 7.5, 1.7 Hz, 1H, C²⁷–H), 7.71 (td, *J* = 7.5, 1.7 Hz, 1H, C²⁵–H), 7.65 (td, *J* = 7.5, 1.7 Hz, 1H, C²⁶–H), 7.54 (dd, *J* = 7.5, 1.7 Hz, 1H, C²⁴–H), 7.53 (td, *J* = 7.6, 1.6 Hz, 1H, C¹⁰–H), 7.44 (td, *J* = 7.6, 1.6 Hz, 1H, C¹¹–H), 7.22 (dd, *J* = 7.6, 1.6 Hz, 1H, C⁹–H), 5.36 (dd, *J* = 11.4, 2.6 Hz, 1H, C⁷–H), 4.38–4.30 (m, 2H, C¹⁸–H), 3.59 (td, *J* = 13.0, 2.9 Hz, 1H, C³–H), 3.30 (dd, *J* = 15.0, 5.0 Hz, 1H, C⁵–H), 3.10 (m, 1H, C⁵–H), 2.88 (dd, *J* = 15.0, 10.0 Hz, 1H, C¹⁶–H), 2.78–2.64 (m, 2H, C^{3,17}–H), 2.42 (ddd, *J* = 12.9, 5.9, 3.2 Hz, 1H, C¹⁹–H), 2.30 (td, *J* = 12.9, 3.7 Hz, 1H, C⁶–H), 2.22–1.99 (m, 4H, C^{6,15,16,19}–H), 1.77 (td, *J* = 12.9, 3.7 Hz, 1H, C¹⁵–H), 1.67 (dd, *J* = 11.2, 15.4 Hz, 1H, C¹⁷–H), 1.62–1.52 (m, 1H, C¹⁴–H), 1.45 (m, 1H, C¹⁴–H).

¹³C NMR (101 MHz, CDCl₃): δ 210.9 (C²), 179.9 (C²¹), 150.6 (C¹³), 149.1 (C²³), 134.0 (C¹⁰), 133.1 (C²⁵), 131.7 (C⁸), 131.4 (C²⁶), 131.1 (C²⁷), 129.8 (C⁹ and C²² superimposed), 128.8 (C¹¹), 125.3 (C¹²), 124.0 (C²⁴), 65.3 (C¹⁸), 51.3 (C³), 48.5 (C⁷), 46.0 (C⁵), 45.9 (C²⁰), 36.7 (C¹⁹), 36.2 (C¹⁶), 32.1 (C⁶), 30.8 (C¹⁷), 30.3 (C¹⁵), 21.5 (C¹⁴).

IR: 2923 (w), 2852 (w), 1761 (m), 1715 (w), 1543 (s), 1530 (s), 1456 (w), 1374 (s), 1359 (s), 1164 (w), 1027 (w), 915 (w), 748 (w).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₅H₂₇N₃NaO₉S⁺: 568.1360; Found: 568.1373.

R_f (PE/EtOAc 1:9) = 0.65

(E)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene 293

To a solution of macrocycles **299a/299b** (dr 1:1, 50 mg, 0.10 mmol) and Imidazole (14 mg, 0.20 mmol, 2.0 equiv) in THF (0.50 mL) at RT was added TBSCl (23 mg, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred for 2 h. Water was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers **293a** and **293b** as colorless oils (57 mg, 90% yield, no change in dr).

Compound 293a

¹H NMR (400 MHz, CDCl₃): δ 7.91 (dd, $J = 7.8, 1.7$ Hz, 1H, C²⁷-H), 7.74-7.65 (m, 3H, C^{12,25,26}-H), 7.59 (dd, $J = 7.8, 1.7$ Hz, 1H, C²⁴-H), 7.55 (td, $J = 7.8, 1.2$ Hz, 1H, C¹⁰-H), 7.46 (dd, $J = 7.8, 1.2$ Hz, 1H, C⁹-H), 7.35 (td, $J = 7.8, 1.2$ Hz, 1H, C¹¹-H), 5.51 (s, 1H, C²¹-H), 4.30 (dd, $J = 12.4, 3.4$ Hz, 1H, C⁷-H), 4.03 (dd, $J = 15.1, 6.6$ Hz, 1H, C⁵-H), 3.74 (ddd, $J = 15.0, 10.0, 5.0$ Hz, 1H, C³-H), 3.59 (t, $J = 7.0$ Hz, 2H, C¹⁸-H), 2.78 (dd, $J = 15.1, 8.5$ Hz, 1H, C⁵-H), 2.70 (m, 1H, C³-H), 2.65-2.52 (m, 2H, C^{6,17}-H), 2.12 (ddd, $J = 15.3, 7.6, 3.4$ Hz, 1H, C⁶-H), 2.02 (m, 1H, C¹⁴-H), 1.83-1.73 (m, 3H, C^{16,17}-H), 1.71-1.53 (m, 4H, C^{14,15,19}-H), 1.30 (m, 1H, C¹⁵-H), 0.87 (s, 9H (C³⁰), 0.04 (s, 3H, C²⁸-H), 0.02 (s, 3H, C²⁸-H).

¹³C NMR (101 MHz, CDCl₃): δ 150.3 (C¹³), 149.1 (C²³), 142.1 (C²), 136.0 (C⁸), 135.8 (C²¹), 133.8 (C²⁵), 132.3 (C¹⁰), 131.4 (C²⁶), 131.1 (C²⁷), 130.6 (C²²), 128.6 (C⁹), 127.3 (C¹¹), 124.4 (C¹²), 124.1 (C²⁴), 60.6 (C¹⁸), 56.6 (C³), 54.8 (C⁵), 51.7 (C²⁰), 44.2 (C¹⁹), 43.0 (C⁷), 40.8 (C¹⁵), 35.8 (C⁶), 33.6 (C¹⁶), 31.3 (C¹⁷), 28.0 (C¹⁴), 26.1 (C³⁰), 18.4 (C²⁹), -5.2 (C²⁸), -5.2 (C²⁸).

IR: 2929 (w), 2851 (w), 1545 (s), 1529 (s), 1465 (w), 1357 (s), 1251 (w), 1164 (m), 1090 (m), 852 (m), 837 (s), 779 (s), 754 (m).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₃₁H₄₃N₃NaO₇SSi⁺: 652.2483; Found: 652.2491.

R_f (PE/EtOAc 6:4) = 0.55

Compound 293b

^1H NMR (400 MHz, CDCl_3): δ 7.88 (dd, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{27}\text{-H}$), 7.74 (dd, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.66 (td, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{25}\text{-H}$), 7.63 (td, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{26}\text{-H}$), 7.55 (dd, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{24}\text{-H}$), 7.53 (dd, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^9\text{-H}$), 7.49 (td, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.31 (td, $J = 7.3, 2.0$ Hz, 1H, $\text{C}^{11}\text{-H}$), 5.65 (s, 1H, $\text{C}^{21}\text{-H}$), 3.81 (dd, $J = 10.1, 4.3$ Hz, 1H, $\text{C}^7\text{-H}$), 3.70-3.57 (m, 2H, $\text{C}^{18}\text{-H}$), 3.50 (dd, $J = 15.8, 7.2$ Hz, 1H, $\text{C}^5\text{-H}$), 3.21 (m, 1H, $\text{C}^3\text{-H}$), 3.05 (m, 1H, $\text{C}^3\text{-H}$), 2.90 (dd, $J = 15.8, 7.2$ Hz, 1H, $\text{C}^5\text{-H}$), 2.48 (m, 1H, $\text{C}^6\text{-H}$), 2.41-2.29 (m, 2H, $\text{C}^{16}\text{-H}$), 2.14 (m, 1H, $\text{C}^6\text{-H}$), 1.81 (m, 1H, $\text{C}^{17}\text{-H}$), 1.75-1.57 (m, 5H, $\text{C}^{14,15,17,19}\text{-H}$), 1.44-1.33 (m, 2H, $\text{C}^{14,15}\text{-H}$), 0.84 (s, 9H, $\text{C}^{30}\text{-H}$), 0.00 (s, 6H, $\text{C}^{28}\text{-H}$).

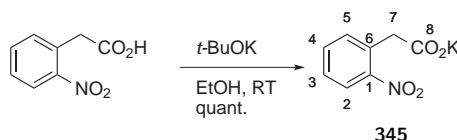
^{13}C NMR (101 MHz, CDCl_3): δ 149.6 (C^{13}), 148.9 (C^{23}), 140.7 (C^2), 137.3 (C^{21}), 137.2 (C^8), 133.6 (C^{25}), 132.8 (C^{10}), 131.3 (C^{26}), 131.1 (C^{22}), 130.9 (C^{27}), 129.4 (C^{11}), 127.3 (C^9), 124.4 (C^{12}), 123.9 (C^{24}), 60.8 (C^{18}), 52.4 (C^3), 52.1 (C^{20}), 48.4 (C^5), 43.6 (C^{19}), 41.7 (C^7), 39.1 (C^{16}), 38.6 (C^{15}), 35.4 (C^6), 33.1 (C^{17}), 26.0 (C^{30}), 22.0 (C^{14}), 18.3 (C^{29}), -5.2 (C^{28}).

IR: 2929 (w), 2855 (w), 1545 (s), 1526 (s), 1460 (w), 1373 (m), 1356 (m), 1254 (w), 1167 (m), 1125 (w), 1090 (m), 852 (m), 837 (s), 777 (s), 744 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{31}\text{H}_{43}\text{N}_3\text{NaO}_7\text{SSi}^+$: 652.2483; Found: 652.2500.

R_f (PE/EtOAc 6:4) = 0.55

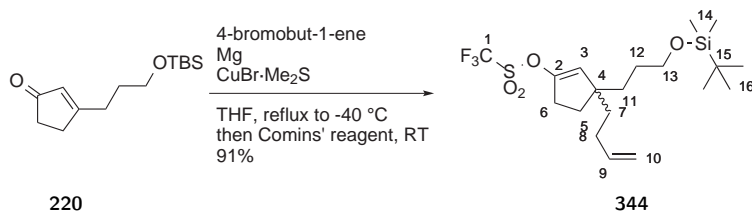
8.5 Experimental Procedures of Chapter 5

potassium 2-(2-nitrophenyl)acetate **345**

To a solution of 2-(2-nitrophenyl)acetic acid (10 g, 55 mmol) in EtOH (100 mL) was added dropwise a solution of *t*-BuOK (6.2 g, 55 mmol, 1.0 equiv) in EtOH (20 mL). The reaction mixture was stirred for 1 h, and then concentrated *in vacuo*. The crude salt **345** thus obtained was used for the next step without further purification (white solid, 12 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²

¹H NMR (400 MHz, MeOD): δ 7.98 (dd, J = 8.6, 1.5 Hz, 1H, C²-H), 7.57 (td, J = 7.5, 1.5 Hz, 1H, C⁴-H), 7.44-7.38 (m, 2H, C^{3,5}-H), 3.88 (s, 2H, C⁷-H).

¹³C NMR (101 MHz, MeOD): δ 177.6 (C⁸), 155.1 (C¹), 135.0 (C⁶), 134.5 (C⁴), 134.2 (C⁵), 128.5 (C³), 125.7 (C²), 43.9 (C⁷).

3-(but-3-en-1-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate **344**

To a solution of 4-bromobut-1-ene (2.4 mL, 24 mmol, 4.0 equiv) in THF (100 mL) was added magnesium turning (0.57 g, 24 mmol, 4.0 equiv) and the mixture was heated to reflux for 3 h. The mixture was then cooled down to -78 °C, CuBr·Me₂S (2.4 g, 12 mmol, 2.0 equiv) was added and the mixture was stirred for 1 h. The reaction mixture was then warmed up to -40 °C, and a solution of the enone **220** (1.5 g, 5.9 mmol) in THF (20 mL) was added dropwise. The reaction mixture was then stirred for 3 h. A solution of Comins' reagent (4.6 g, 12 mmol, 2.0 equiv) in THF (20 mL) was added, and the reaction mixture was stirred at RT for 24 h. Saturated NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic

phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded the vinyl triflate **344** as a colorless oil (2.4 g, 91% yield).

^1H NMR (400 MHz, CDCl_3): δ 5.80 (ddt, $J = 17.2, 10.1, 6.6$ Hz, 1H, $\text{C}^9\text{-H}$), 5.44 (s, 1H, $\text{C}^3\text{-H}$), 5.01 (dd, $J = 17.2, 1.9$ Hz, 1H, $\text{C}^{10}\text{-H}$), 4.94 (dd, $J = 10.1, 1.9$ Hz, 1H, $\text{C}^{10}\text{-H}$), 3.61-3.53 (m, 2H, $\text{C}^{13}\text{-H}$), 2.61-2.55 (m, 2H, $\text{C}^6\text{-H}$), 2.05-1.95 (m, 2H, $\text{C}^8\text{-H}$), 1.82 (t, $J = 7.6$ Hz, 2H, $\text{C}^5\text{-H}$), 1.53-1.47 (m, 2H, $\text{C}^7\text{-H}$), 1.47-1.43 (m, 4H, $\text{C}^{11,12}\text{-H}$), 0.89 (s, 9H, $\text{C}^{16}\text{-H}$), 0.04 (s, 6H, $\text{C}^{14}\text{-H}$).

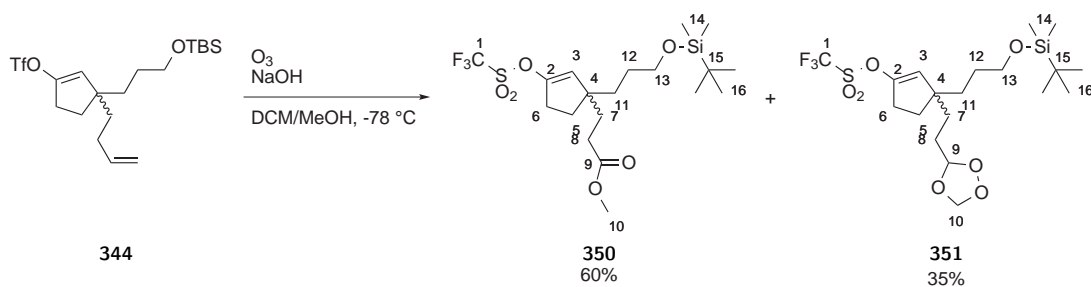
^{13}C NMR (101 MHz, CDCl_3): δ 148.1 (C^2), 138.8 (C^9), 124.7 (C^3), 118.7 (q, $J = 319.9$ Hz, C^1), 114.6 (C^{10}), 63.5 (C^{13}), 48.5 (C^4), 39.1 (C^7), 36.0 (C^{11}), 32.0 (C^5), 31.0 (C^6), 29.0 (C^8), 28.0 (C^{12}), 26.1 (C^{16}), 18.5 (C^{15}), -5.2 (C^{14}).

IR: 2941 (w), 2931 (w), 2858 (w), 1660 (w), 1643 (w), 1424 (m), 1251 (m), 1210 (s), 1141 (s), 1096 (s), 912 (s), 835 (s), 776 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{34}\text{F}_3\text{O}_4\text{SSi}^+$: 443.1894; Found: 443.1893.

R_f (PE/EtOAc 95:5) = 0.72.

methyl 3-(1-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)propanoate **350 and 3-(2-(1,2,4-trioxolan-3-yl)ethyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate **351****



To a solution of the olefin **344** (50 mg, 0.11 mmol) in DCM (1.0 mL) was added a solution of NaOH (23 mg, 0.56 mmol, 5.0 equiv) in MeOH (0.25 mL). The mixture was cooled to -78°C , and ozone was bubbled through the reaction mixture. The reaction mixture turned yellow, followed by decoloration and subsequent blue coloration. When the blue color appeared, argon was bubbled through the solution, and the mixture was warmed up to 0°C . Water and ether were added, and the biphasic mixture was stirred for 1 h. The two layers were separated and the aqueous layer was extracted with ether. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded prod-

uct **350** (colorless oil, 31 mg, 60% yield) along with the side product **351** (colorless oil, mixture of 2 diastereoisomers, dr 1:1, 19 mg, 35% yield).

Compound 350

¹H NMR (400 MHz, CDCl₃): δ 5.39 (t, J = 1.6 Hz, 1H, C³-H), 3.66 (s, 3H, C¹⁰-H), 3.60-3.55 (m, 2H, C¹³-H), 2.58 (td, J = 7.6, 1.5 Hz, 2H, C⁶-H), 2.26 (t, J = 8.3 Hz, 2H, C⁸-H), 1.89-1.69 (m, 4H, C^{5,7}-H), 1.49-1.42 (m, 4H, C^{11,12}-H), 0.87 (s, 9H, C¹⁶-H), 0.03 (s, 6H, C¹⁴-H).

¹³C NMR (101 MHz, CDCl₃): δ 174.1 (C⁹), 148.5 (C²), 123.9 (C³), 118.7 (d, J = 321.0 Hz, C¹), 63.3 (C¹³), 51.8 (C¹⁰), 48.2 (C⁴), 36.2 (C¹¹), 34.7 (C⁷), 31.5 (C⁵), 31.0 (C⁶), 29.6 (C⁸), 27.9 (C¹²), 26.0 (C¹⁶), 18.4 (C¹⁵), -5.2 (C¹⁴).

IR: 2952 (w), 2932 (w), 2858 (w), 1740 (m), 1423 (m), 1209 (s), 1141 (s), 1098 (m), 914 (m), 835 (s), 776 (m).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₉H₃₄F₃O₆SSi⁺: 475.1792; Found: 475.1792.

R_f (PE/EtOAc 95:5) = 0.36.

Compound 351 (mixture of diastereoisomers, dr 1:1)

¹H NMR (400 MHz, CDCl₃): δ 5.42 (m, 1H, C³-H), 5.17 (s, 1H, C¹⁰-H), 5.13 (td, J = 4.07, 0.8 Hz, 1H, C⁹-H), 5.04 (s, 1H, C¹⁰-H), 3.61-3.55 (m, 2H, C¹³-H), 2.59 (td, J = 7.7, 2.0 Hz, 2H, C⁶-H), 1.87-1.77 (m, 2H, C⁵-H), 1.72-1.64 (m, 2H, C⁸-H), 1.58-1.51 (m, 2H, C⁷-H), 1.48-1.42 (m, 4H, C^{11,12}-H), 0.88 (s, 9H, C¹⁶-H), 0.04 (s, 6H, C¹⁴-H).

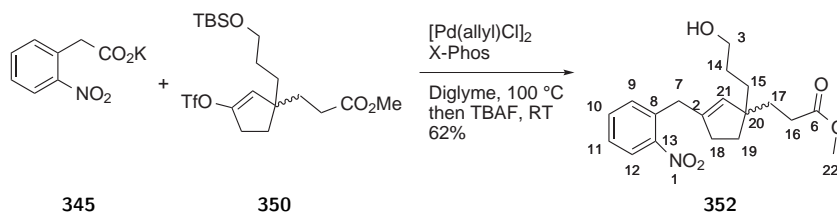
¹³C NMR (101 MHz, CDCl₃): δ 148.4 (C²), 124.1 (C³), 118.7 (d, J = 320.5 Hz, C¹), 103.7 (C⁹), 94.2 (C¹⁰), 63.3 (C¹³), 48.1 (C⁴), 36.1 (C¹¹), 36.0 (C¹¹), 33.4 (C⁷), 31.7 (C⁵), 31.7 (C⁵), 31.0 (C⁶), 27.9 (C¹²), 26.8 (C⁸), 26.1 (C¹⁶), 18.5 (C¹⁵), -5.2 (C¹⁴).

IR: 2958 (w), 2933 (w), 2890 (w), 2859 (w), 1663 (w), 1422 (m), 1251 (w), 1210 (s), 1141 (s), 1099 (m), 1055 (m), 914 (m), 835 (s), 777 (m).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₉H₃₃F₃NaO₇SSi⁺: 513.1561; Found: 513.1553.

R_f (PE/EtOAc 95:5) = 0.30.

methyl 3-(1-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanoate **352**



An oven-dried flask was charged with salt **345** (0.12 g, 0.53 mmol, 1.2 equiv), X-Phos (32 mg, 0.066 mmol, 15 mol%), allylpalladium chloride dimer (4.0 mg, 0.011 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (3.0 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **350** (0.21 g, 0.44 mmol) in diglyme (3.0 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and TBAF (1 M in THF, 1.3 mL, 1.3 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 2 h. Saturated aqueous NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded the pure product **352** as a yellow oil (0.13 g, 62% yield).

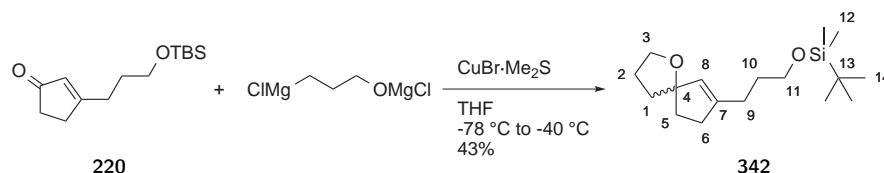
¹H NMR (400 MHz, CDCl₃): δ 7.88 (dd, J = 1.0, 7.8 Hz, 1H, C¹²-H), 7.53 (td, J = 1.1, 7.8 Hz, 1H, C¹⁰-H), 7.37 (td, J = 1.3, 7.8 Hz, 1H, C¹¹-H), 7.32 (dd, J = 7.6, 1.8 Hz, 1H, C⁹-H), 4.84 (s, 1H, C²¹-H), 3.67 (s, 2H, C⁷-H), 3.63 (s, 3H, C²²-H), 3.58 (t, J = 6.1 Hz, 2H, C³-H), 2.25 (t, J = 7.2 Hz, 2H, C¹⁶-H), 2.22-2.16 (m, 2H, C¹⁸-H), 1.76-1.64 (m, 4H, C^{17,19}-H), 1.49-1.22 (m, 4H, C^{14,15}-H), OH peak not observed.

¹³C NMR (101 MHz, CDCl₃): δ 174.8 (C⁶), 149.6 (C¹³), 141.8 (C²), 134.7 (C⁸), 133.0 (C¹⁰), 132.6 (C⁹), 132.4 (C²¹), 127.5 (C¹¹), 124.9 (C¹²), 63.7 (C³), 51.7 (C²⁰), 51.5 (C²²), 36.0 (C¹⁵), 35.1 (C¹⁸), 35.0 (C⁷), 34.7 (C¹⁷), 33.9 (C¹⁹), 30.0 (C¹⁶), 28.1 (C¹⁴).

IR: 3397 (br w), 2940 (w), 2847 (w), 1735 (m), 1526 (s), 1436 (w), 1353 (m), 1199 (w), 1172 (w), 1055 (w).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₉H₂₆NO₅⁺: 348.1806; Found: 348.1807.

R_f (PE/EtOAc 6:4) = 0.11.

(3-(1-oxaspiro[4.4]non-6-en-7-yl)propoxy)(*tert*-butyl)dimethylsilane 342

To a solution of 3-chloropropan-1-ol (2.0 mL, 24 mmol, 4.0 equiv) in THF (100 mL) at 0 °C was added MeMgBr (1.2 M in THF, 20 mL, 24 mmol, 4.0 equiv). The mixture was then warmed up to RT, and magnesium turning (0.57 g, 24 mmol, 4.0 equiv) was added. The mixture was heated to reflux for 3 h. The solution was then cooled down to -78 °C, CuBr·Me₂S (2.4 g, 12 mmol, 2.0 equiv) was added and the solution was stirred for 1 h. The reaction mixture was then warmed up to -40 °C, and a solution of enone **220** (1.5 g, 5.9 mmol) in THF (20 mL) was added dropwise. The reaction mixture was then stirred at -40 °C for 3 h. Saturated NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compound **342** as a colorless oil (0.75 g, 43% yield).

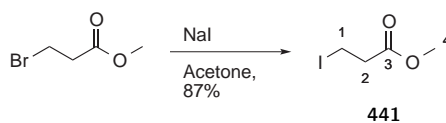
¹H NMR (400 MHz, CDCl₃): δ 5.33 (s, 1H, C⁸-H), 3.81 (t, *J* = 6.8 Hz, 2H, C³-H), 3.61 (t, *J* = 6.4 Hz, 2H, C¹¹-H), 2.40 (m, 1H, C⁵-H), 2.19 (m, 1H, C⁵-H), 2.14-2.08 (m, 2H, C⁹-H), 2.01 (ddd, *J* = 13.5, 8.9, 4.6 Hz, 1H, C⁶-H), 1.94 (t, *J* = 6.8 Hz, 2H, C²-H), 1.91 (m, 1H, C⁶-H), 1.85-1.78 (m, 2H, C¹-H), 1.73-1.64 (m, 2H, C¹⁰-H), 0.89 (s, 9H, C¹⁴-H), 0.04 (s, 6H, C¹²-H).

¹³C NMR (101 MHz, CDCl₃): δ 148.3 (C⁷), 128.0 (C⁸), 94.5 (C⁴), 67.0 (C³), 63.0 (C¹¹), 37.5 (C⁶), 36.8 (C¹), 33.8 (C⁵), 30.8 (C¹⁰), 27.7 (C⁹), 26.5 (C²), 26.1 (C¹⁴), 18.5 (C¹³), -5.1 (C¹²).

IR: 2953 (m), 2930 (m), 2856 (m), 1471 (w), 1254 (w), 1096 (m), 1046 (w), 835 (s), 775 (s).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₁₇H₃₂NaO₂Si⁺: 319.2069; Found: 319.2068.

R_f (PE/EtOAc 1:1) = 0.48.

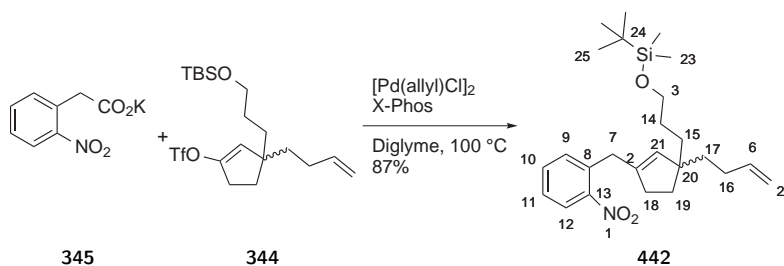
methyl 3-iodopropionate 441

Following a known procedure,²²⁸ a suspension of sodium iodide (5.4 g, 36 mmol, 1.3 equiv) in acetone (20 mL) was heated to reflux. Ethyl bromopropionate (3.0 mL, 28 mmol) was added dropwise over 30 min. The reaction mixture was heated for 4 h. The mixture was allowed to cool down to RT, diluted with diethyl ether (20 mL), and filtered. The filtrate was washed with 2% NaOH, water, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude compound **441** thus obtained was used for the next step without further purification (colourless oil, 5.8 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²⁸

¹H NMR (400 MHz, CDCl₃): δ 3.71 (s, 3H, C⁴-H), 3.31 (t, *J* = 7.1 Hz, 2H, C¹-H), 2.97 (t, *J* = 7.1 Hz, 2H, C²-H).

¹³C NMR (101 MHz, CDCl₃): δ 171.6 (C³), 52.1 (C⁴), 38.5 (C²), -3.8 (C¹).

(3-(1-(but-3-en-1-yl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propoxy)(*tert*-butyl)-dimethylsilane 442



An oven-dried flask was charged with salt **345** (1.2 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%), allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added. The reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **344** (2.0 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded the pure product **442** as a yellow oil (1.6 g, 87% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 7.8 Hz, 1H, C¹²-H), 7.51 (td, *J* = 7.8, 1.4 Hz, 1H, C¹⁰-H), 7.36 (t, *J* = 7.8 Hz, 1H, C¹¹-H), 7.33 (d, *J* = 7.8 Hz, 1H, C⁹-H), 5.79 (ddt, *J* = 16.0, 10.1, 6.5 Hz, 1H, C⁶-H), 4.97 (dd, *J* = 16.0, 1.6 Hz, 1H, C²²-H), 4.96 (s, 1H, C²¹-H),

²²⁸Chow, C. P.; Shea, K. J. *J. Am. Chem. Soc.* **2005**, 127, 3678–3679

4.89 (d, $J = 10.1$ Hz, 1H, C²²-H), 3.67 (s, 2H, C⁷-H), 3.55 (t, $J = 6.4$ Hz, 2H, C³-H), 2.22 (t, $J = 7.2$ Hz, 2H, C¹⁸-H), 2.01-1.88 (m, 2H, C¹⁶-H), 1.68 (t, $J = 7.2$ Hz, 2H, C¹⁹-H), 1.47-1.24 (m, 6H, C^{14,15,17}-H), 0.88 (s, 9H, C²⁵-H), 0.04 (s, 6H, C²³-H).

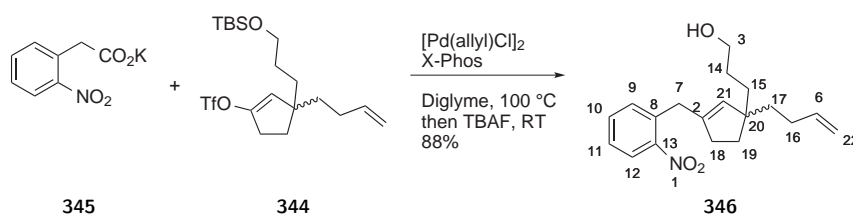
¹³C NMR (101 MHz, CDCl₃): δ 149.7 (C¹³), 140.5 (C²), 139.8 (C⁶), 135.0 (C⁸), 134.2 (C²¹), 132.8 (C¹⁰), 132.3 (C⁹), 127.3 (C¹¹), 124.8 (C¹²), 113.9 (C²²), 64.1 (C³), 51.7 (C²⁰), 39.1 (C¹⁷), 35.8 (C¹⁸), 34.9 (C¹⁹), 34.8 (C⁷), 34.5 (C¹⁵), 29.3 (C¹⁶), 28.4 (C¹⁴), 26.1 (C²⁵), 18.5 (C²⁴), -5.1 (C²³).

IR: 2929 (m), 2854 (w), 1528 (s), 1462 (w), 1353 (m), 1255 (m), 1095 (s), 835 (s), 776 (s).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₅H₄₀NO₃Si⁺: 430.2772; Found: 430.2771.

R_f (PE/EtOAc 9:1) = 0.61.

3-(1-(but-3-en-1-yl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propan-1-ol **346**



An oven-dried flask was charged with salt **345** (1.2 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%), allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added. The reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate **344** (2.0 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and TBAF (1 M in THF, 14 mL, 14 mmol, 3.0 equiv) was added. The reaction mixture was then stirred until complete consumption of intermediate **442**. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded the pure product **346** as a yellow oil (1.2 g, 88% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.88 (dd, $J = 7.8, 1.5$ Hz, 1H, C¹²-H), 7.52 (td, $J = 7.8, 1.5$ Hz, 1H, C¹⁰-H), 7.37 (td, $J = 7.8, 1.5$ Hz, 1H, C¹¹-H), 7.33 (d, $J = 7.8$ Hz, 1H, C⁹-H), 5.78 (ddt, $J = 17.5, 10.2, 6.6$ Hz, 1H, C⁶-H), 4.97 (dd, $J = 17.5, 2.1$ Hz, 1H, C²²-H), 4.92-4.86 (m, 2H, C^{21,22}-H), 3.68 (s, 2H, C⁷-H), 3.58 (t, $J = 6.3$ Hz, 2H, C³-H), 2.23 (t, $J = 7.3$ Hz, 2H, C¹⁸-H), 2.02-1.87 (m, 2H, C¹⁶-H), 1.74-1.63 (m, 2H, C¹⁹-H), 1.49-1.22 (m, 6H, C^{14,15,17}-H), OH peak not observed.

Chapter 8: Experimental Section

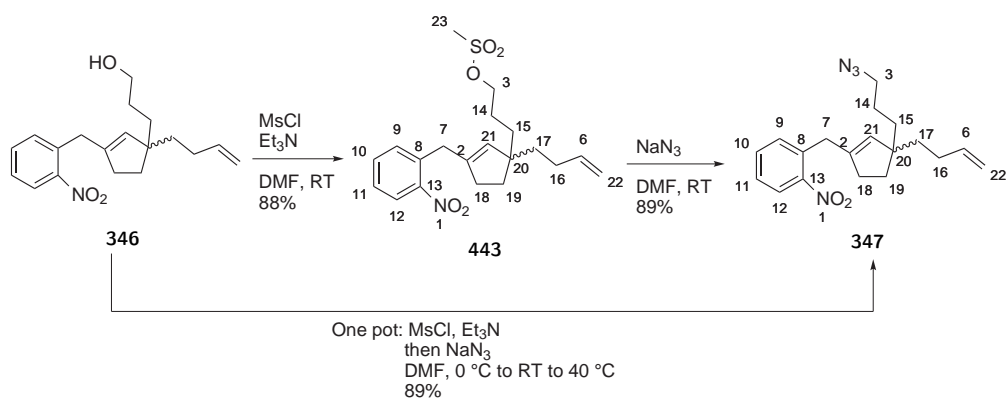
^{13}C NMR (101 MHz, CDCl_3): δ 149.7 (C^{13}), 140.8 (C^2), 139.7 (C^6), 134.9 (C^8), 133.7 (C^{21}), 132.9 (C^{10}), 132.4 (C^9), 127.4 (C^{11}), 124.8 (C^{12}), 113.9 (C^{22}), 63.8 (C^3), 51.7 (C^{20}), 39.2 (C^{17}), 35.8 (C^{18}), 35.0 (C^{19}), 34.9 (C^7), 34.4 (C^{15}), 29.3 (C^{16}), 28.2 (C^{14}).

IR: 3354 (br w), 2934 (w), 2848 (w), 1526 (s), 1450 (w), 1353 (w), 1054 (w), 908 (s), 730 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{25}\text{NNaO}_3^+$: 338.1727; Found: 338.1716.

R_f (PE/EtOAc 6:4) = 0.39.

1-((3-(3-azidopropyl)-3-(but-3-en-1-yl)cyclopent-1-en-1-yl)methyl)-2-nitrobenzene **347**



Stepwise preparation of **347**

To a solution of the alcohol **346** (1.0 g, 3.2 mmol) and Et_3N (0.60 mL, 4.8 mmol, 1.5 equiv) in DMF (60 mL) at $0\text{ }^\circ\text{C}$ was added MsCl (0.27 mL, 3.5 mmol, 1.1 equiv). The reaction mixture was stirred at RT for 30 min, and then water was added. The mixture was extracted with EtOAc . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/ EtOAc 8:2) afforded the pure product **443** as a yellow oil (1.1 g, 88% yield).

To a refluxing solution of the mesylate **443** (1.0 g, 2.5 mmol) in DCM (50 mL) was added NaN_3 (0.50 g, 7.6 mmol, 3.0 equiv). The reaction mixture was stirred for 3 h, and then water was added. The mixture was extracted with EtOAc . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/ EtOAc 8:2) afforded the azide **347** as a yellow oil (0.76 g, 89% yield).

One-pot preparation of 347

To a solution of the alcohol **346** (1.0 g, 3.2 mmol) and Et₃N (0.60 mL, 4.8 mmol, 1.5 equiv) in DMF (60 mL) at 0 °C was added MsCl (0.27 mL, 3.5 mmol, 1.1 equiv). The reaction mixture was then stirred at RT for 30 min. NaN₃ (0.62 g, 9.5 mmol, 3.0 equiv) was added and the reaction mixture was stirred at 40 °C for 3 h. Water was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over NaSO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the azide **347** as a yellow oil (0.96 g, 89% yield).

Mesyl alcohol 443

¹H NMR (400 MHz, CDCl₃): δ 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H, C¹²-H), 7.53 (td, *J* = 7.8, 1.3 Hz, 1H, C¹⁰-H), 7.38 (td, *J* = 7.8, 1.4 Hz, 1H, C¹¹-H), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H, C⁹-H), 5.78 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H, C⁶-H), 4.97 (dd, *J* = 17.1, 1.9 Hz, 1H, C²²-H), 4.93-4.85 (m, 2H, C^{21,22}-H), 4.17 (td, *J* = 6.5, 0.9 Hz, 2H, C³-H), 3.68 (s, 2H, C⁷-H), 3.00 (s, 3H, C²³-H), 2.25 (t, *J* = 7.1 Hz, 2H, C¹⁸-H), 1.97-1.87 (m, 2H, C¹⁶-H), 1.72 (ddt, *J* = 13.6, 8.5, 6.6 Hz, 1H, C¹⁹-H), 1.66 (ddt, *J* = 13.6, 8.5, 6.6 Hz, 1H, C¹⁹-H), 1.66-1.58 (m, 2H, C¹⁴-H), 1.47-1.30 (m, 4H, C^{15,17}-H).

¹³C NMR (101 MHz, CDCl₃): δ 149.7 (C¹³), 141.5 (C²), 139.4 (C⁶), 134.7 (C⁸), 133.0 (C²¹), 132.9 (C¹⁰), 132.4 (C⁹), 127.5 (C¹¹), 124.9 (C¹²), 114.1 (C²²), 71.0 (C³), 51.6 (C²⁰), 39.2 (C¹⁷), 37.5 (C²³), 35.6 (C¹⁸), 35.1 (C¹⁹), 35.0 (C⁷), 34.2 (C¹⁵), 29.2 (C¹⁶), 24.8 (C¹⁴).

IR: 2933 (w), 2848 (w), 1526 (s), 1353 (s), 1175 (s), 953 (m), 917 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₀H₂₇NNaO₅S⁺: 416.1502; Found: 416.1495.

R_f (PE/EtOAc 6:4) = 0.60.

Azide 347

¹H NMR (400 MHz, CDCl₃): δ 7.89 (dd, *J* = 7.8, 1.4 Hz, 1H, C¹²-H), 7.53 (td, *J* = 7.8, 1.4 Hz, 1H, C¹⁰-H), 7.37 (td, *J* = 7.8, 1.5 Hz, 1H, C¹¹-H), 7.33 (dd, *J* = 7.8, 1.5 Hz, 1H, C⁹-H), 5.79 (ddt, *J* = 17.2, 10.2, 6.6 Hz, 1H, C⁶-H), 4.98 (dd, *J* = 17.2, 1.9 Hz, 1H, C²²-H), 4.93-4.88 (m, 2H, C^{21,22}-H), 3.68 (s, 2H, C⁷-H), 3.22 (t, *J* = 6.8 Hz, 2H, C³-H), 2.25 (td, *J* = 7.4, 2.0 Hz, 2H, C¹⁸-H), 1.96-1.88 (m, 2H, C¹⁶-H), 1.72 (ddt, *J* = 13.7, 7.8, 6.6 Hz, 1H, C¹⁹-H), 1.66 (ddt, *J* = 13.7, 7.8, 6.6 Hz, 1H, C¹⁹-H), 1.50-1.30 (m, 6H, C^{14,15,17}-H).

¹³C NMR (101 MHz, CDCl₃): δ 149.7 (C¹³), 141.3 (C²), 139.5 (C⁶), 134.8 (C⁸), 133.3 (C²¹), 132.9

Chapter 8: Experimental Section

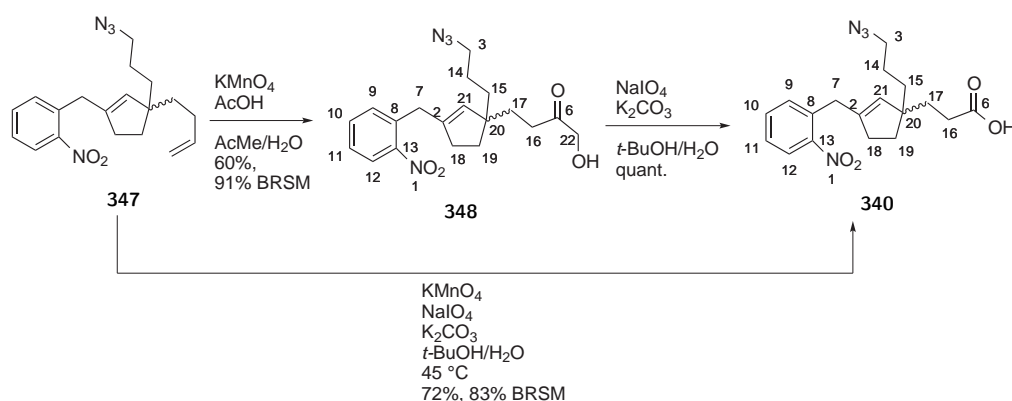
(C¹⁰), 132.3 (C⁹), 127.5 (C¹¹), 124.9 (C¹²), 114.1 (C²²), 52.3 (C³), 51.8 (C²⁰), 39.2 (C¹⁷), 37.0 (C¹⁸), 35.0 (C¹⁹), 34.9 (C⁷), 34.3 (C¹⁵), 29.2 (C¹⁶), 24.4 (C¹⁴).

IR: 2934 (w), 2847 (w), 2093 (s), 1526 (s), 1352 (m), 910 (m), 736 (m).

Anal. Calcd for C₁₉H₂₄N₄O₂: C, 67.04; H 7.11; N 16.46. Found: C 66.74; H 7.10; N 16.15.

R_f (PE/EtOAc 6:4) = 0.88.

4-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)-1-hydroxybutan-2-one **348** and 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanoic acid **340**



Stepwise preparation of **340**

To a solution of the olefin **347** (20 mg, 0.059 mmol) in acetone/water/AcOH (5:1:0.1, 1.5 mL) at RT was added a solution of KMnO_4 (14 mg, 0.088 mmol, 1.5 equiv) in a mixture of acetone/water (5:1, 1.0 mL). After 15 seconds of vigorous stirring, the reaction mixture was poured into an ice-cooled saturated Na_2SO_3 solution, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude hydroxyketone **348** (13 mg, 60%, 91% BRSM) thus obtained was used for the next step without further purification. An analytical sample was obtained by FCC (PE/EtOAc 8:2) to afford compound **348** as a yellow oil.

To a solution of hydroxyketone **348** (13 mg, 0.035 mmol) in *t*-BuOH (2.0 mL) was added a solution of NaIO_4 (26 mg, 0.12 mmol, 2.0 equiv) in aqueous K_2CO_3 (5 %, 1.0 mL), and the reaction mixture was stirred at 50°C . The reaction mixture was cooled down to 0°C , and saturated aqueous Na_2SO_3 was added until the color disappeared. The aqueous solution was acidified

to pH 2-3, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc/AcOH 8:2:0.1) afforded the acid **340** as a yellow oil (13 mg, quantitative yield).

One-pot preparation of **340**

To a solution of the olefin **347** (20 mg, 0.059 mmol) in *t*-BuOH/water/ (3:1, 1.5 mL) at 45 °C was added a solution of KMnO_4 (14 mg, 0.088 mmol, 1.5 equiv), NaIO_4 (64 mg, 0.30 mmol, 5.0 equiv) in 5% aqueous K_2CO_3 (1.0 mL). After 60 seconds of vigorous stirring, the reaction mixture was poured into an ice-cooled saturated Na_2SO_3 solution, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc/AcOH 8:2:0.1) afforded the acid **340** as a yellow oil (15 mg, 72%, 83% BRSM).

Hydroxyketone **348**

^1H NMR (400 MHz, CDCl_3): δ 7.89 (dd, $J = 7.7, 1.5$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.54 (td, $J = 7.7, 1.5$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.40 (td, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.32 (dd, $J = 7.7, 1.4$ Hz, 1H, $\text{C}^9\text{-H}$), 4.76 (quint., $J = 1.7$ Hz, 1H, $\text{C}^{21}\text{-H}$), 4.24 (s, 2H, $\text{C}^{22}\text{-H}$), 3.68 (s, 2H, $\text{C}^7\text{-H}$), 3.22 (t, $J = 6.7$ Hz, 2H, $\text{C}^3\text{-H}$), 2.31-2.22 (m, 4H, $\text{C}^{16,18}\text{-H}$), 1.74-1.59 (m, 4H, $\text{C}^{17,19}\text{-H}$), 1.52-1.42 (m, 2H, $\text{C}^{14}\text{-H}$), 1.39-1.31 (m, 2H, $\text{C}^{15}\text{-H}$). OH not observed.

^{13}C NMR (101 MHz, CDCl_3): δ 210.3 (C^6), 149.6 (C^{13}), 142.7 (C^2), 134.4 (C^8), 133.1 (C^{10}), 132.5 (C^9), 131.8 (C^{21}), 127.7 (C^{11}), 125.0 (C^{12}), 68.2 (C^{22}), 52.1 (C^3), 51.5 (C^{20}), 37.5 (C^{15}), 35.3 (C^7), 35.1 (C^{18}), 34.1 (C^{17}), 33.6 (C^{19}), 33.1 (C^{16}), 24.4 (C^{14}).

IR: 3445 (br w), 2935 (w), 2852 (w), 2095 (s), 1718 (m), 1525 (s), 1353 (m), 1067 (w),

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{24}\text{N}_4\text{NaO}_4^+$: 395.1690; Found: 395.1701.

R_f (PE/EtOAc/AcOH 6/3.5/0.5) = 0.4.

Carboxylic acid **340**

^1H NMR (400 MHz, CDCl_3): δ 7.93 (dd, $J = 7.8, 1.4$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.53 (td, $J = 7.8, 1.4$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.38 (td, $J = 7.8, 1.4$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.32 (d, $J = 7.8$ Hz, 1H, $\text{C}^9\text{-H}$), 4.84 (s, 1H, $\text{C}^{21}\text{-H}$), 3.68 (s, 2H, $\text{C}^7\text{-H}$), 3.22 (t, $J = 6.7$ Hz, 2H, $\text{C}^3\text{-H}$), 2.32-2.20 (m, 4H, $\text{C}^{16,18}\text{-H}$), 1.73-1.64 (m, 4H, $\text{C}^{17,19}\text{-H}$), 1.53-1.44 (m, 2H, $\text{C}^{14}\text{-H}$), 1.40-1.32 (m, 2H, $\text{C}^{15}\text{-H}$). OH not observed.

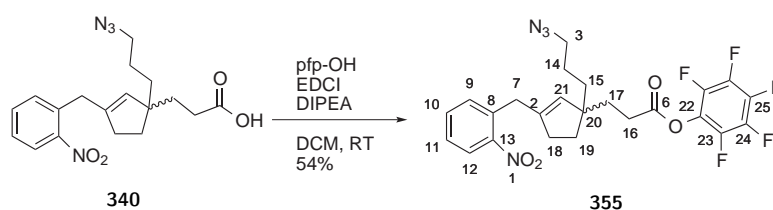
^{13}C NMR (101 MHz, CDCl_3): δ 178.0 (C^6), 149.6 (C^{13}), 142.5 (C^2), 134.5 (C^8), 133.0 (C^{10}), 132.4 (C^9), 132.0 (C^{21}), 127.6 (C^{11}), 124.9 (C^{12}), 52.2 (C^3), 51.5 (C^{20}), 37.2 (C^{15}), 35.2 (C^{18}), 34.9 (C^7), 34.5 (C^{17}), 33.7 (C^{19}), 29.5 (C^{16}), 24.4 (C^{14}).

IR: 2923 (w), 2854 (w), 2095 (w), 1704 (s), 1526 (s), 1352 (m), 1298 (w),

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{NaO}_4^+$: 381.1533; Found: 381.1547.

R_f (PE/EtOAc/AcOH 6/3.5/0.5) = 0.56.

pentafluorophenyl 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)-propanoate **355**



To a solution of the acid **340** (20 mg, 0.056 mmol) and pentafluorophenol (10 mg, 0.056 mmol, 1.0 equiv) in DCM (2.0 mL) was added EDCI (11 mg, 0.056 mmol, 1.0 equiv) and DIPEA (9.6 mL, 0.067 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h. Saturated NaHCO_3 solution was added and the mixture was extracted with EtOAc. The combined organic phases were washed with 1 M HCl, water, brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the ester **355** as a yellow oil (16 mg, 54%).

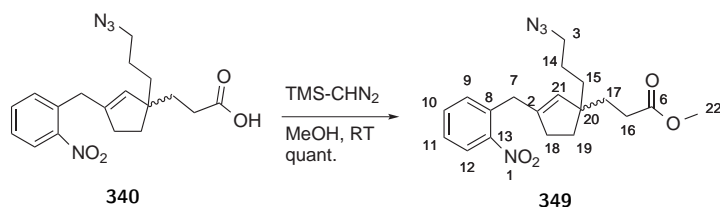
^1H NMR (400 MHz, CDCl_3): δ 7.90 (dd, $J = 1.2, 8.1$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.54 (td, $J = 1.3, 7.5$ Hz, 1H, $\text{C}^{10}\text{-H}$), 7.40 (td, $J = 1.4, 8.1$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.34 (dd, $J = 1.2, 7.6$ Hz, 1H, $\text{C}^9\text{-H}$), 4.88 (m, 1H, $\text{C}^{21}\text{-H}$), 3.70 (s, 2H, $\text{C}^7\text{-H}$), 3.27-3.22 (m, 2H, $\text{C}^3\text{-H}$), 2.57-2.51 (m, 2H, $\text{C}^{16}\text{-H}$), 2.35-2.28 (m, 2H, $\text{C}^{18}\text{-H}$), 1.82-1.72 (m, 4H, $\text{C}^{17,19}\text{-H}$), 1.56-1.44 (m, 2H, $\text{C}^{14}\text{-H}$), 1.43-1.33 (m, 2H, $\text{C}^{15}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 170.1 (C^6), 149.6 (C^{13}), 143.1 (C^2), 142.8-136.1 (m, C^{22-25}), 134.4 (C^8), 133.0 (C^{10}), 132.4 (C^9), 131.5 (C^{21}), 127.7 (C^{11}), 124.9 (C^{12}), 52.1 (C^3), 51.6 (C^{20}), 37.3 (C^{15}), 35.2 (C^{18}), 35.0 (C^7), 34.5 (C^{17}), 33.6 (C^{19}), 29.3 (C^{16}), 24.4 (C^{14}).

IR: 2926 (w), 2851 (w), 2095 (m), 1786 (w), 1518 (s), 1351 (m), 1088 (m), 993 (s), 733 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{24}\text{H}_{21}\text{F}_5\text{N}_4\text{NaO}_4^+$: 547.1375; Found: 547.1375.

R_f (PE/EtOAc/AcOH 8:2) = 0.2.

methyl 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanoate
349

To a solution of the acid **340** (12 mg, 0.033 mmol) in MeOH (1.0 mL) was added TMS-diazomethane (1 M in THF) dropwise until the yellow color persisted and no more bubbling was observed (approximately 0.050 mL, 1.5 equiv). Excess of diazomethane was quenched by addition of acetic acid (2 drops). The reaction mixture was concentrated *in vacuo*, and the crude mixture was filtered through a plug of silica gel (PE/EtOAc 8:2) to afford the methyl ester **349** as a yellow oil (12 mg, quantitative yield).

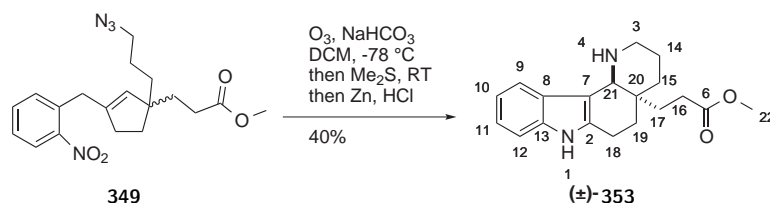
¹H NMR (400 MHz, CDCl₃): δ 7.88 (dd, J = 7.6, 1.5 Hz, 1H, C¹²-H), 7.53 (td, J = 7.6, 1.5 Hz, 1H, C¹⁰-H), 7.37 (td, J = 7.6, 1.4 Hz, 1H, C¹¹-H), 7.31 (dd, J = 7.6, 1.4 Hz, 1H, C⁹-H), 4.83 (m, 1H, C²¹-H), 3.66 (s, 2H, C⁷-H), 3.63 (s, 3H, C²²-H), 3.21 (t, J = 6.8 Hz, 2H, C³-H), 2.25 (t, J = 7.3 Hz, 2H, C¹⁸-H), 2.21-2.15 (m, 2H, C¹⁶-H), 1.70-1.62 (m, 4H, C^{17,19}-H), 1.51-1.42 (m, 2H, C¹⁴-H), 1.37-1.28 (m, 2H, C¹⁵-H).

¹³C NMR (101 MHz, CDCl₃): δ 174.6 (C⁶), 149.5 (C¹³), 142.2 (C²), 134.4 (C⁸), 132.9 (C¹⁰), 132.3 (C⁹), 132.1 (C²¹), 127.5 (C¹¹), 124.8 (C¹²), 52.1 (C³), 51.6 (C²⁰), 51.4 (C²²), 37.0 (C¹⁵), 35.0 (C¹⁸), 34.8 (C⁷), 34.6 (C¹⁷), 33.7 (C¹⁹), 29.9 (C¹⁶), 24.3 (C¹⁴).

IR: 2933 (w), 2846 (w), 2095 (s), 1736 (s), 1526 (s), 1436 (w), 1352 (m), 1260 (w).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₉H₂₄N₄NaO₄⁺: 395.1690; Found: 395.1688.

R_f (PE/EtOAc/ 8:2) = 0.50.

(±)-methyl 3-(2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazol-4a-yl)-propanoate 353

To a solution of methyl ester **349** (20 mg, 0.054 mmol) at -78°C in DCM (0.50 mL) was added NaHCO_3 (9.0 mg, 0.11 mmol, 2.0 equiv). Ozone was bubbled through the solution until the blue color persisted. Argon was then bubbled through the solution for 15 minutes. Me_2S (excess) was added and the reaction mixture was stirred at RT overnight. Methanol (0.20 mL) was added, followed by HCl (0.5 M aqueous solution, 0.11 mL, 1.0 equiv) and zinc powder (0.18 g, 2.7 mmol, 50 equiv). The reaction was stirred for 30 min. Aqueous NaHCO_3 was added, and the reaction mixture was extracted with EtOAc . The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/ EtOAc / Et_3N 3:5:0.2) afforded the pure product **(±)-353** as colourless oils (6.7 mg, 40% yield).

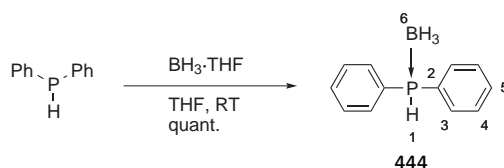
^1H NMR (400 MHz, CDCl_3): δ 7.84 (br s, 1H, $\text{N}^1\text{-H}$), 7.56 (d, $J = 7.1$ Hz, 1H, $\text{C}^9\text{-H}$), 7.26 (d, $J = 7.1$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.10 (td, $J = 7.1, 1.5$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.07 (td, $J = 7.1, 1.2$ Hz, 1H, $\text{C}^{10}\text{-H}$), 3.73 (s, 1H, $\text{C}^{21}\text{-H}$), 3.60 (s, 3H, $\text{C}^{22}\text{-H}$), 3.03 (br d, $J = 12.9$ Hz, 1H, $\text{C}^3\text{-H}$), 2.82-2.69 (m, 3H, $\text{C}^{3,18}\text{-H}$), 2.47-2.23 (m, 3H, $\text{N}^4\text{-H}$, $\text{C}^{16}\text{-H}$), 1.87-1.72 (m, 2H, $\text{C}^{17,14}\text{-H}$), 1.67-1.36 (m, 6H, $\text{C}^{14,15,17,19}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 174.8 (C^6), 136.3 (C^{13}), 133.8 (C^2), 127.5 (C^8), 121.3 (C^{11}), 119.6 (C^{10}), 117.8 (C^9), 112.3 (C^7), 110.6 (C^{12}), 56.7 (C^{21}), 51.8 (C^{22}), 46.2 (C^3), 34.5 (C^{20}), 34.4 (C^{15}), 32.4 (C^{17}), 28.9 (C^{16}), 24.6 (C^{19}), 22.9 (C^{14}), 20.2 (C^{18}).

IR: 3342 (w), 2929 (m), 2850 (w), 1731 (s), 1436 (m), 1315 (w), 1254 (w), 741 (w),

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2^+$: 313.1911; Found: 313.1899.

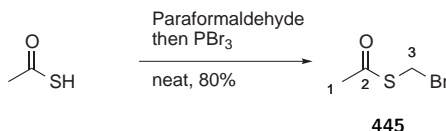
R_f (PE/ EtOAc / Et_3N 3:5:0.5) = 0.17.

Diphenylphosphine borane complex 444

Following a reported procedure,²²⁹ diphenylphosphine (10 g, 54 mmol) in THF (0.10 mL) was added dropwise to a solution of $\text{BH}_3\cdot\text{THF}$ in THF (1 M, 54 mL, 54 mmol, 1.0 equiv) at 0 °C. The mixture was stirred for 30 minutes at RT, and then concentrated *in vacuo*. The oily residue was dissolved in DCM, filtered and concentrated *in vacuo*. The crude complex **444** thus obtained was used for the next step without further purification (colorless wax, 11 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²⁹

^1H NMR (400 MHz, CDCl_3): δ 7.72-7.65 (m, 4H, $\text{C}^3\text{-H}$), 7.55-7.50 (m, 2H, $\text{C}^5\text{-H}$), 7.50-7.43 (m, 4H, $\text{C}^4\text{-H}$), 6.31 (dq, $J = 379.0, 7.0$ Hz, 1H, $\text{P}^1\text{-H}$), 1.07 (br q, $J = 91.7$ Hz, 3H, $\text{B}^6\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 133.0 (d, $J = 9.2$ Hz, C^3), 131.7 (d, $J = 1.7$ Hz, C^5), 129.11 (d, $J = 10.4$ Hz, C^4), 126.3 (d, $J = 56.3$ Hz, C^2).

Bromomethyl thioacetate 445

Following a reported procedure,^{155c} a mixture of thioacetic acid (8.0 g, 0.12 mol) and paraformaldehyde (3.6 g) was stirred at 80 °C for 18 h. The reaction mixture was cooled down to 0 °C. Then, PBr_3 (21 g, 80 mmol, 0.70 equiv) was added at 0 °C, and the reaction mixture was stirred at RT for 15 minutes. The reaction mixture was quenched with ice, and extracted with Et_2O . The combined organic phases were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC ($\text{PE}/\text{Et}_2\text{O}/\text{Et}_3\text{N}$ 3:7) afforded product **445** as a yellow oil (16 g, 80% yield). The spectroscopic data of this compound were in accord with those reported in the literature.^{155c}

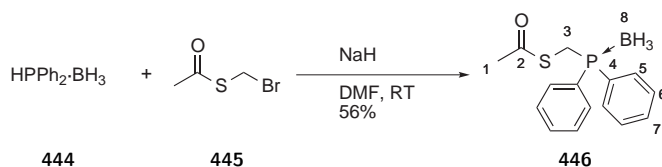
^1H NMR (400 MHz, CDCl_3): δ 4.69 (s, 2H, $\text{C}^3\text{-H}$), 2.38 (s, 3H, $\text{C}^1\text{-H}$).

²²⁹Busacca, C. A.; Farber, E.; Deyoung, J.; Campbell, S.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Lee, H.; Ma, S.; Reeves, D.; Shen, S.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5594–5597

^{13}C NMR (101 MHz, CDCl_3): δ 191.9 (C^2), 30.5 (C^3), 26.4 (C^1).

R_f (Ether) = 0.8.

S-((diphenylphosphino)methyl) ethanethioate borane complex **446**



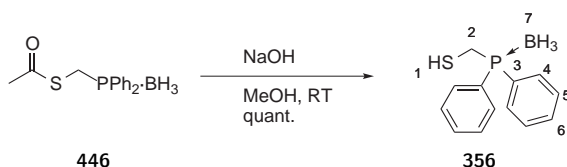
Following a reported procedure,^{155b} to a solution of the phosphine borane complex **444** (11 g, 54 mmol) in DMF (100 mL) at 0 °C was added NaH (60% in mineral oil, 2.2 g, 54 mmol, 1.0 equiv). When the gas evolution stopped, the thioester **445** (9.1 g, 54 mmol, 1.0 equiv) was added. The reaction was stirred at RT overnight. Saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the pure product **446** as a colorless oils (8.7 g, 56% yield). The spectroscopic data of this compound were in accord with those reported in the literature.^{155b}

^1H NMR (400 MHz, CDCl_3): δ 7.74-7.66 (m, 4H, $\text{C}^5\text{-H}$), 7.55-7.42 (m, 6H, $\text{C}^{6,7}\text{-H}$), 3.71 (d, $J = 6.8$ Hz, 2H, $\text{C}^3\text{-H}$), 2.25 (s, 3H, $\text{C}^1\text{-H}$), 1.40-0.40 (m, 3H, $\text{B}^8\text{-H}$),

^{13}C NMR (101 MHz, CDCl_3): δ 193.4 (C^2), 132.6 (d, $J = 8.3$ Hz, C^5), 131.9 (C^7), 129.0 (d, $J = 9.8$ Hz, C^6), 127.7 (d, $J = 55.6$ Hz, C^4), 30.2 (C^1), 23.9 (d, $J = 35.5$ Hz, C^3),

R_f (PE/EtOAc 8:2) = 0.36.

(diphenylphosphino)methanethiol borane complex **356**



Following a reported procedure,^{155a} compound **446** (8.7 g, 30 mmol) was dissolved in MeOH (60 mL). NaOH (2.4 g, 60 mmol, 2.0 equiv) in MeOH (10 mL) was added dropwise. The reaction mixture was stirred for 2 h, and then concentrated *in vacuo*. Saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The combined organic phases were

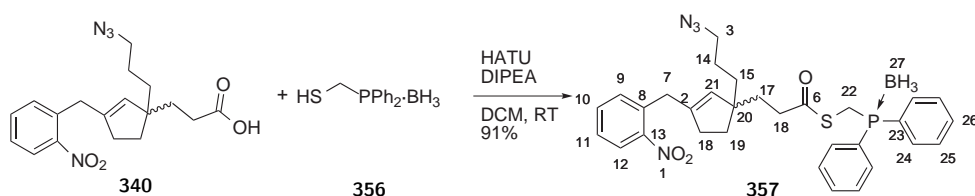
washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded product **356** as a colorless oil (7.4 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.^{155a}

^1H NMR (400 MHz, CDCl_3): δ 7.75-7.67 (m, 4H, $\text{C}^4\text{-H}$), 7.57-7.44 (m, 6H, $\text{C}^{5,6}\text{-H}$), 3.19 (dd, $J = 8.2, 6.1$ Hz, 2H, $\text{C}^2\text{-H}$), 1.88 (ddd, $J = 15.5, 8.2, 6.6$ Hz, 1H, $\text{S}^1\text{-H}$), 1.03 (q, $J = 95.6$ Hz, 3H, $\text{B}^7\text{-H}$),

^{13}C NMR (101 MHz, CDCl_3): δ 132.7 (d, $J = 7.5$ Hz, C^4), 131.8 (C^6), 129.1 (d, $J = 10.5$ Hz, C^5), 127.9 (d, $J = 55.9$ Hz, C^3), 19.8 (d, $J = 32.5$ Hz, C^2),

R_f (PE/EtOAc 8:2) = 0.43.

S-((diphenylphosphino)methyl) 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)-cyclopent-2-en-1-yl)propanethioate borane complex 357



To a solution of the acid **340** (0.20 g, 0.56 mmol) in DCM (10 mL) was added compound **356** (0.14 g, 0.56 mmol, 1.0 equiv). The solution was cooled down to 0°C . HATU (0.26 g, 0.67 mmol, 1.2 equiv) and DIPEA (0.12 mL, 0.67 mmol, 1.2 equiv) were added, and the solution was stirred at RT for 1 h. Saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The combined organic phases were washed with NaHCO_3 , brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded product **357** as a yellow oil (0.31 g, 91% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.88 (d, $J = 7.8$ Hz, 1H, $\text{C}^{12}\text{-H}$), 7.73-7.65 (m, 4H, $\text{C}^{24}\text{-H}$), 7.53-7.48 (m, 3H, $\text{C}^{10,26}\text{-H}$), 7.48-7.41 (m, 4H, $\text{C}^{25}\text{-H}$), 7.38 (t, $J = 7.8$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.30 (d, $J = 7.8$ Hz, 1H, $\text{C}^9\text{-H}$), 4.76 (s, 1H, $\text{C}^{21}\text{-H}$), 3.69 (d, $J = 6.8$ Hz, 2H, $\text{C}^{22}\text{-H}$), 3.64 (s, 2H, $\text{C}^7\text{-H}$), 3.20 (t, $J = 6.4$ Hz, 2H, $\text{C}^3\text{-H}$), 2.36-2.29 (m, 2H, $\text{C}^{16}\text{-H}$), 2.26-2.17 (m, 2H, $\text{C}^{18}\text{-H}$), 1.68-1.54 (m, 2H, $\text{C}^{19}\text{-H}$), 1.51-1.45 (m, 2H, $\text{C}^{17}\text{-H}$), 1.45-1.37 (m, 2H, $\text{C}^{14}\text{-H}$), 1.32-1.23 (m, 2H, $\text{C}^{15}\text{-H}$), Broad signals of the BH_3 between 0.7 and 1.7 ppm were lost in the background

^{13}C NMR (101 MHz, CDCl_3): δ 197.3 (C^6), 149.6 (C^{13}), 142.7 (C^2), 132.7 (C^8), 133.1 (C^{10}), 132.7 (d, $J = 9.4$ Hz, C^{24}), 132.4 (C^9), 131.9 (d, $J = 1.6$ Hz, C^{26}), 131.8 (C^{21}), 129.0 (d, $J = 10.2$ Hz, C^{25}), 127.8 (d, $J = 53.5$ Hz, C^{23}), 127.6 (C^{11}), 124.9 (C^{12}), 52.1 (C^3), 51.3 (C^{20}), 39.7 (C^{16}), 37.2 (C^{15}),

Chapter 8: Experimental Section

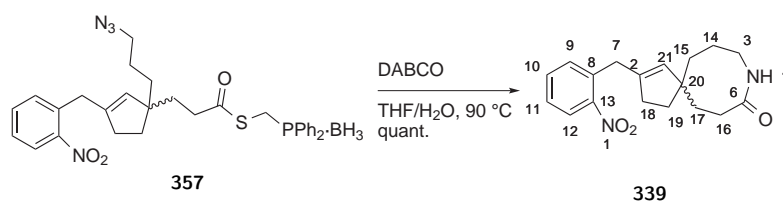
35.2 (C¹⁷), 35.1 (C¹⁸), 34.9 (C⁷), 33.6 (C¹⁹), 24.3 (C¹⁴), 23.6 (d, $J = 35.6$ Hz, C²²).

IR: 2924 (w), 2852 (w), 2385 (m), 2093 (s), 1697 (m), 1525 (s), 1436 (m), 1351 (m), 1261 (w), 1108 (w), 1058 (m), 741 (s), 703 (s),

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₃₁H₃₆BN₄NaO₃PS⁺: 609.2231; Found: 609.2231.

R_f (PE/EtOAc 6:3) = 0.60.

2-(2-nitrobenzyl)-9-azaspiro[4.7]dodec-1-en-8-one **339**



To a refluxing solution of thioester **357** (0.80 g, 1.4 mmol) in THF/H₂O (99:1, 150 mL) was added DABCO (0.30 g, 2.7 mmol, 2.0 equiv). The reaction mixture was stirred at reflux for 24 h. The reaction mixture was cooled down to RT, and water was added. The mixture was extracted with EtOAc. The combined organic phases were washed with NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (EtOAc/MeOH 98:2) afforded the product **339** as a yellow wax (0.43 g, quantitative yield).

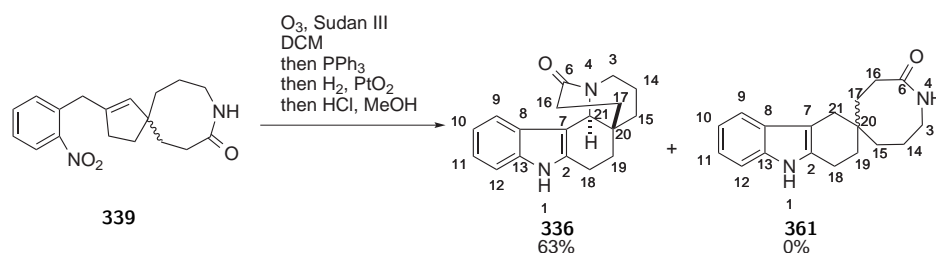
¹H NMR (400 MHz, CDCl₃): δ 7.88 (dd, $J = 7.8, 1.4$ Hz, 1H, C¹²-H), 7.53 (td, $J = 7.8, 1.4$ Hz, 1H, C¹⁰-H), 7.38 (td, $J = 7.8, 1.2$ Hz, 1H, C¹¹-H), 7.32 (dd, $J = 7.8, 1.2$ Hz, 1H, C⁹-H), 5.70 (m, 1H, C⁴-H), 5.21 (s, 1H, C²¹-H), 3.70 (s, 2H, C⁷-H), 3.29-3.21 (m, 2H, C³-H), 2.40 (t, $J = 6.7$ Hz, 2H, C¹⁶-H), 2.25-2.17 (m, 2H, C¹⁸-H), 1.78-1.68 (m, 4H, C^{17,19}-H), 1.65-1.55 (m, 4H, C^{14,15}-H).

¹³C NMR (101 MHz, CDCl₃): δ 178.4 (C⁶), 149.7 (C¹³), 140.9 (C²), 134.5 (C⁸), 133.8 (C¹⁰), 133.0 (C⁹), 132.3 (C²¹), 127.6 (C¹¹), 124.9 (C¹²), 51.1 (C²⁰), 41.9 (C³), 39.5 (C¹⁷), 38.3 (C¹⁹), 34.9 (C⁷), 33.5 (C^{15or18}), 33.4 (C^{15or18}), 30.8 (C¹⁶), 28.5 (C¹⁴).

IR: 3236 (br w), 2928 (m), 2852 (w), 1659 (s), 1525 (s), 1438 (w), 1355 (m), 1193 (w).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₁₈H₂₃N₂O₃⁺: 315.1703; Found: 315.1695.

R_f (EtOAc/MeOH 98:2) = 0.21.

(±)-16-dehydroxykopsihainanine A 336

To a solution of the lactam **339** (10 mg, 0.031 mmol) in DCM (0.30 mL) was added 0.10 mg of Sudan III. The solution was cooled down to -78°C and ozone was bubbled through the reaction mixture until the red color disappeared. Argon was then bubbled through the solution for 5 minutes, and PPh_3 (16 mg, 0.062 mmol, 2.0 equiv) was added. After 5 minutes, the reaction was allowed to warm to RT, and stirred for 30 minutes. PtO_2 (7.0 mg, 0.031 mmol, 1.0 equiv) and MeOH (0.30 mL) were added, and the flask was flushed with hydrogen. The mixture was stirred vigorously under H_2 atmosphere for 1.5 h. The hydrogen was replaced by argon, and HCl (1 M aqueous solution, 60 μL , 2.0 equiv) was added. The reaction mixture was stirred for 1 h at 50°C . Aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 3:7) afforded product (±)-**336** as a white amorphous solid (5.5 mg, 63% yield).

If Zinc/HCl or $\text{TiCl}_3/\text{NH}_4\text{OAc}$ were used as reducing agents instead of H_2/PtO_2 , the unstable side product **361** was observed as main product.

Compound 336

^1H NMR (400 MHz, CDCl_3): δ 7.79 (br s, 1H, $\text{C}^1\text{-H}$), 7.69 (d, $J = 7.6$ Hz, 1H, $\text{C}^9\text{-H}$), 7.26 (m, 1H, $\text{C}^{12}\text{-H}$), 7.12 (td, $J = 7.6, 0.9$ Hz, 1H, $\text{C}^{11}\text{-H}$), 7.03 (td, $J = 7.6, 0.9$ Hz, 1H, $\text{C}^{10}\text{-H}$), 4.41 (dd, $J = 12.9, 5.4$ Hz, 1H, $\text{C}^3\text{-H}$), 4.34 (s, 1H, $\text{C}^{21}\text{-H}$), 3.15 (td, $J = 12.9, 3.2$ Hz, 1H, $\text{C}^3\text{-H}$), 3.03 (m, 1H, $\text{C}^{18}\text{-H}$), 2.77 (m, 1H, $\text{C}^{18}\text{-H}$), 2.10-2.04 (m, 2H, $\text{C}^{17}\text{-H}$), 2.00-1.85 (m, 4H, $\text{C}^{16,19}\text{-H}$), 1.73-1.67 (m, 2H, $\text{C}^{15}\text{-H}$), 1.58-1.47 (m, 2H, $\text{C}^{14}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 186.0 (C^6), 136.3 (C^{13}), 133.2 (C^2), 125.1 (C^8), 121.9 (C^{11}), 120.4 (C^9), 119.8 (C^{10}), 111.3 (C^7), 110.4 (C^{12}), 64.4 (C^{21}), 53.8 (C^3), 40.0 (C^{15}), 37.1 (C^{20}), 35.0 (C^{17}), 34.6 (C^{19}), 27.8 (C^{16}), 22.5 (C^{14}), 19.8 (C^{18}).

IR: 3274 (br w), 2923 (m), 2853 (w), 1655 (s), 1464 (m), 1331 (w), 1244 (w), 1168 (w), 741 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₁₈H₂₀N₂NaO⁺: 303.1468; Found: 303.1456.

R_f (EtOAc/MeOH 2:8) = 0.45.

Compound 361

¹H NMR (400 MHz, CDCl₃): δ 7.08 (br, s, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 1H), 7.15 (td, *J* = 7.0, 1.4 Hz, 1H), 7.11 (td, *J* = 7.0, 1.4 Hz, 1H), 6.36 (br, s, 1H), 3.60-3.40 (m, 2H), 2.82-2.75 (m, 2H), 2.71 (d, *J* = 15.3 Hz, 1H), 2.58 (m, 1H), 2.59 (d, *J* = 15.3 Hz, 1H), 2.48 (m, 1H), 1.98 (m, 1H), 1.92-1.72 (m, 5H), 1.68-1.62 (m, 2H).

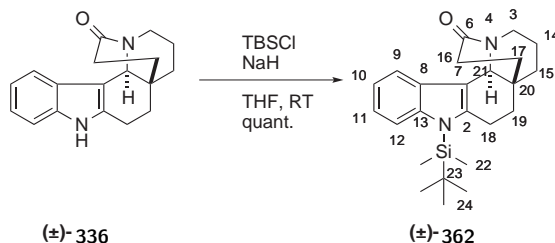
Compound **361** proved unstable at RT and fully degraded before ¹³C NMR analysis and 2D spectra could be done.

IR: 3380 (br w), 2955 (s), 2924 (s), 2853 (w), 1733 (w), 1647 (m), 1463 (m), 1397 (w), 1016 (w), 749 (m).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₁₈H₂₂N₂NaO⁺: 305.1624; Found: 305.1629.

R_f (EtOAc/MeOH/Et₃N 95:5:0.2) = 0.28

(±)-1-tributyl dimethylsilyl-16-dehydroxykopsihainanine A **362**



To a solution of (±)-**336** (10 mg, 0.036 mmol) in THF (0.50 mL) at 0 °C was added NaH (60% in mineral oil, 2.9 mg, 0.072 mmol, 2.0 equiv), followed by TBSCl (11 mg, 0.072 mmol, 2.0 equiv). The reaction mixture was stirred at RT for 2 h. Aqueous NH₄Cl was added. The mixture was extracted with EtOAc. The combined organic phases were washed with saturated NaHCO₃, water, brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 1:1) afforded product (±)-**362** as a white amorphous solid (14 mg, quantitative yield).

¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, *J* = 7.8 Hz, 1H, C⁹-H), 7.48 (d, *J* = 7.8 Hz, 1H, C¹²-H), 7.07 (td, *J* = 7.8, 1.4 Hz, 1H, C¹¹-H), 7.02 (t, *J* = 7.8 Hz, 1H, C¹⁰-H), 4.41 (dd, *J* = 12.8, 5.1 Hz, 1H, C³-H), 4.32 (s, 1H, C²¹-H), 3.15 (td, *J* = 12.8, 3.3 Hz, 1H, C³-H), 2.99 (m, 1H, C¹⁸-H),

2.86 (m, 1H, C¹⁸-H), 2.10-2.04 (m, 2H, C¹⁷-H), 2.00-1.88 (m, 3H, C^{16,19}-H), 1.79 (ddd, $J = 12.9, 11.1, 6.0$ Hz, 1H, C¹⁵-H), 1.71-1.64 (m, 2H, C^{14,15}-H), 1.60-1.45 (m, 2H, C^{14,16}-H), 0.91 (s, 9H, C²⁴-H), 0.68 (s, 6H, C²²-H).

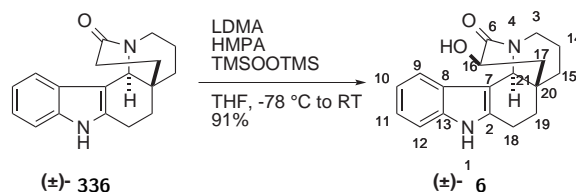
¹³C NMR (101 MHz, CDCl₃): δ 185.9 (C⁶), 142.4 (C¹³), 139.4 (C²), 128.1 (C⁸), 121.4 (C¹¹), 120.3 (C⁹), 119.8 (C¹⁰), 114.5 (C⁷), 114.0 (C¹²), 64.7 (C²¹), 53.7 (C³), 39.9 (C¹⁵), 36.2 (C²⁰), 35.3 (C¹⁷), 35.0 (C¹⁹), 27.7 (C¹⁶), 26.9 (C²⁴), 23.2 (C¹⁸), 22.5 (C¹⁴), 20.7 (C²³), -0.3 (C²²).

IR: 2929 (w), 2856 (w), 1677 (m), 1452 (m), 1256 (m), 1131 (w), 988 (w), 898 (w), 823 (s), 730 (s).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₄H₃₅N₂OSi⁺: 395.2513; Found: 395.2519.

R_f (EtOAc/MeOH 3:7) = 0.57.

(±)-Kopsihainanine A 6



To a solution of dimethylamine (2 M in THF, 0.20 mL, 0.40 mmol, 14 equiv) and HMPA (0.14 mL, 0.84 mmol, 30 equiv) in THF (1.2 mL) at -78 °C was added *n*-BuLi (1.42 M in hexane, 0.24 mL, 0.34 mmol, 12 equiv). The mixture was stirred at RT for 15 min. This mixture was added dropwise to a solution of (±)-**336** (8.0 mg, 0.028 mmol) in THF (1.2 mL) at 0 °C. The reaction mixture was stirred at RT for 15 min. The reaction mixture was cooled down to -78 °C, and bis(trimethylsilyl) peroxide (0.18 mL, 0.88 mmol, 30 equiv) was added. The reaction mixture was warmed to RT over 1 h. Aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by preparative TLC (PE/EtOAc 3:7) afforded the pure (±)-kopsihainanine A **6** as a white amorphous solid (7.5 mg, 91% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁴⁴

¹H NMR (400 MHz, CDCl₃): δ 7.84 (br s, 1H, C¹-H), 7.62 (d, $J = 7.8$ Hz, 1H, C⁹-H), 7.27 (m, 1H, C¹²-H), 7.13 (t, $J = 7.8$ Hz, 1H, C¹¹-H), 7.04 (t, $J = 7.8$ Hz, 1H, C¹⁰-H), 4.43 (dd, $J = 13.4, 5.6$ Hz, 1H, C³-H), 4.36 (s, 1H, C²¹-H), 4.02 (dd, $J = 10.6, 8.4$ Hz, 1H, C¹⁶-H), 3.55 (br s, 1H, C¹⁶-OH), 3.26 (td, $J = 12.9, 3.1$ Hz, 1H, C³-H), 3.09 (m, 1H, C¹⁸-H), 2.78 (dd, $J = 17.5, 6.5$ Hz, 1H, C¹⁸-H), 2.38 (dd, $J = 14.1, 8.8$ Hz, 1H, C¹⁷-H), 1.99-1.92 (m, 2H, C^{14,19}-H),

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1.82 (ddd, $J = 13.7, 12.2, 6.5$ Hz, 1H, C¹⁹-H), 1.75-1.68 (m, 2H, C¹⁵-H), 1.60 (m, 1H, C¹⁴-H), 1.27 (m, 1H, C¹⁷-H),

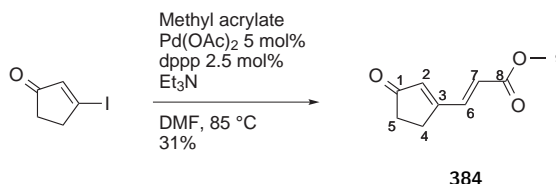
¹³C NMR (101 MHz, CDCl₃): δ 186.0 (C⁶), 136.4 (C¹³), 133.2 (C²), 124.8 (C⁸), 122.2 (C¹¹), 120.0 (C⁹), 119.9 (C¹⁰), 110.6 (C¹²), 110.0 (C⁷), 68.9 (C¹⁶), 63.9 (C²¹), 54.0 (C³), 39.6 (C¹⁵), 37.8 (C²⁰), 37.5 (C¹⁷), 34.7 (C¹⁹), 22.0 (C¹⁴), 19.8 (C¹⁸).

IR: 3394 (br w), 3314 (br w), 2925 (m), 2853 (w), 1660 (s), 1465 (m), 1329 (w), 1223 (w), 1134 (m), 1091 (m), 1037 (w), 736 (s).

HRMS: (ESI⁺) m/z : [M + Na]⁺ Calcd for C₁₈H₂₀N₂NaO₂⁺: 319.1417; Found: 319.1418.

R_f (PE/EtOAc 3:7) = 0.30.

8.6 Experimental Procedures of Chapter 6

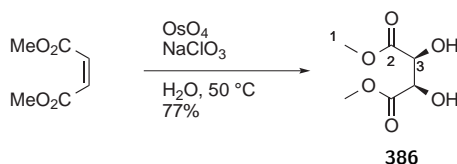
methyl (E)-3-(3-oxocyclopent-1-en-1-yl)acrylate **384**

Following a reported procedure,¹⁷³ to a solution of 3-iodopentenone¹⁷² (1.0 g, 4.8 mmol, 1.0 equiv) in DMF (20 mL) was added methyl acrylate (1.1 mL, 12 mmol, 2.5 equiv), Pd(OAc)₂ (54 mg, 0.24 mmol, 5.0 mol%), dppp (50 mg, 0.12 mmol, 2.5 mol%) and Et₃N (1.3 mL, 9.6 mmol, 2.0 equiv). The mixture was heated at 85 °C for 16 h. The reaction mixture was allowed to cool down to RT, and quenched with 0.5 M HCl. The mixture was extracted with EtOAc. The combined organic phases were washed with NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 1:1) afforded compound **384** as a white solid (0.22 g, 31% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁷³

¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, J = 15.9 Hz, 1H, C⁶–H), 6.37–6.30 (m, 2H, C^{2,7}–H), 3.82 (s, 3H, C⁹–H), 2.81–2.76 (m, 2H, C⁵–H), 2.56–2.50 (m, 2H, C⁴–H).

¹³C NMR (101 MHz, CDCl₃): δ 208.8 (C¹), 168.3 (C⁸), 166.2 (C³), 138.6 (C²), 136.1 (C⁶), 125.0 (C⁷), 52.3 (C⁹), 35.1 (C⁵), 27.0 (C⁴).

R_f (PE/EtOAc 1:1) = 0.44

dimethyl meso tartrate **386**

Following a reported procedure,²³⁰ to a solution of NaClO₃ (1.2 g, 11 mmol, 1.3 equiv) and OsO₄ (90 mg, 0.21 mmol, 2.5 mol%) in H₂O (14 mL) was added dropwise dimethyl maleate

²³⁰Milas, N. A.; Terry, E. M. *J. Am. Chem. Soc.* **1925**, 47, 1412–1418

(1.1 mL, 8.6 mmol). The reaction mixture was stirred at 50 °C overnight. The reaction mixture was then allowed to cool down. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added, followed by magnesium silicate (1 g). The slurry mixture was filtered. The filtrate was brought to pH 2, and the solution was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by recrystallisation ($\text{Et}_2\text{O}/\text{PE}$) afforded pure compound **386** as a white solid (1.2 g, 77% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²³¹

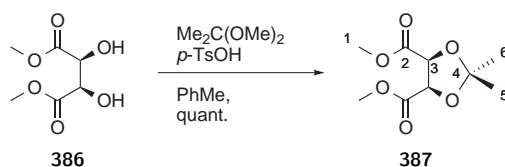
mp = 113.5–114.8 °C ($\text{Et}_2\text{O}/\text{PE}$)

^1H NMR (400 MHz, CDCl_3): δ 4.58 (s, 2H, $\text{C}^3\text{--H}$), 3.82 (s, 6H, $\text{C}^1\text{--H}$), 3.12 (br s, 2H, $\text{O}^3\text{--H}$),

^{13}C NMR (101 MHz, CDCl_3): δ 171.53 (C^2), 73.1 (C^3), 53.1 (C^1).

R_f (EtOAc) = 0.17

dimethyl dioxolane meso tartrate **387**



To a solution of dimethyl tartrate **386** (1.0 g, 5.6 mmol) in toluene (20 mL) was added 2,2-dimethoxypropane (1.0 mL, 8.4 mmol, 1.5 equiv) and *p*-TsOH (96 mg, 0.56 mmol, 0.10 equiv). The reaction mixture was then heated to reflux with a Dean-Stark apparatus for 16 h. The reaction mixture was then allowed to cool down, and saturated aqueous NaHCO_3 was added. The mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude compound **387** thus obtained (1.2 g, quantitative yield) was used for the next step without further purification. The spectroscopic data of this compound were in accord with those reported in the literature.²³²

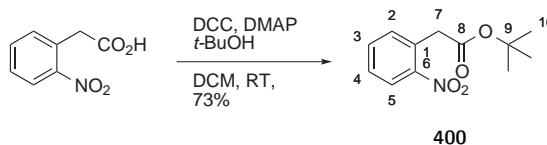
^1H NMR (400 MHz, CDCl_3): δ 4.82 (s, 2H, $\text{C}^3\text{--H}$), 3.72 (s, 6H, $\text{C}^1\text{--H}$), 1.62 (s, 3H, $\text{C}^{5\text{or}6}\text{--H}$), 1.39 (s, 3H, $\text{C}^{5\text{or}6}\text{--H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 168.7 (C^2), 113.1 (C^3), 76.4 (C^3), 52.6 (C^1), 26.7 ($\text{C}^{5\text{or}6}$), 25.8 ($\text{C}^{5\text{or}6}$).

R_f (EtOAc) = 0.83

²³¹ Dinca, E.; Hartmann, P.; Smrček, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, 4461–4482

²³² de Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V.; Evidente, A.; Piccialli, G. *J. Org. Chem.* **2000**, 65, 3432–3442

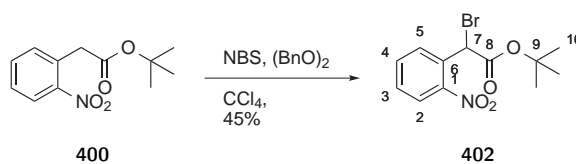
tert-butyl 2-(2-nitrophenyl)acetate 400

To a solution of 2-(2-nitrophenyl)acetic acid (1.0 g, 5.5 mmol) in DCM (20 mL) was added DCC (1.7 g, 8.3 mmol, 1.5 equiv), DMAP (0.30 g, 0.25 mmol, 0.50 equiv) and dry *t*-BuOH (1.2 g, 17 mmol, 3.0 equiv). The reaction mixture was stirred overnight. DCM was added and the organic phase was washed with saturated aqueous NH_4Cl , NaHCO_3 , brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 3:1) afforded pure ester **400** as a yellow oil (0.95 g, 73% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²³³

^1H NMR (400 MHz, CDCl_3): δ 8.09 (dd, $J = 7.5, 1.3$ Hz, 1H, $\text{C}^5\text{-H}$), 7.58 (td, $J = 7.5, 1.3$ Hz, 1H, $\text{C}^3\text{-H}$), 7.45 (td, $J = 7.5, 1.3$ Hz, 1H, $\text{C}^4\text{-H}$), 7.34 (dd, $J = 7.5, 1.3$ Hz, 1H, $\text{C}^2\text{-H}$), 3.94 (s, 2H, $\text{C}^7\text{-H}$), 1.44 (s, 9H, $\text{C}^{10}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 169.3 (C^8), 149.0 (C^6), 133.5 (C^1), 133.4 (C^3), 130.5 (C^2), 128.5 (C^4), 125.3 (C^5), 81.9 (C^9), 41.1 (C^7), 28.1 (C^{10}).

R_f (PE/EtOAc 1:1) = 0.77

tert-butyl 2-bromo 2-(2-nitrophenyl)acetate 402

Following a reported procedure,¹⁹² dibenzoyl peroxide (97 mg, 0.40 mmol, 0.10 equiv) was added to a solution of ester **400** (0.95 g, 4.0 mmol) and NBS (0.78 g, 4.4 mmol, 1.1 equiv) in CCl_4 (20 mL). The reaction mixture was heated to refluxing temperature for 72 h. The reaction mixture was filtered on a plug of Celite. Additional NBS (0.78 g, 4.4 mmol, 1.1 equiv) and dibenzoyl peroxide (97 mg, 0.40 mmol, 0.10 equiv) were added, and the mixture was stirred for an additional 48 h. The mixture was filtered again, and poured into water. The mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over

²³³Shi, D. D.; Trigo, F. F.; Semmelhack, M. F.; Wang, S. S.-H. *J. Am. Chem. Soc.* **2014**, *136*, 1976–1981

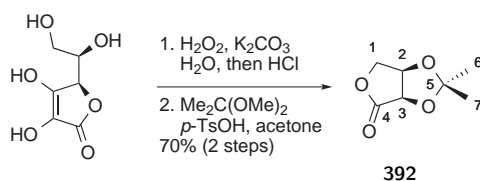
Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded pure ester **402** as a yellow oil (0.57 g, 45% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁹²

¹H NMR (400 MHz, CDCl₃): δ 8.03–7.98 (m, 2H, C^{2,5}–H), 7.69 (td, J = 7.7, 1.7 Hz, 1H, C⁴–H), 7.52 (td, J = 7.7, 1.7 Hz, 1H, C³–H), 5.96 (s, 1H, C⁷–H), 1.48 (s, 9H, C¹⁰–H).

¹³C NMR (101 MHz, CDCl₃): δ 166.7 (C⁸), 147.9 (C¹), 133.8 (C⁴), 133.3 (C⁵), 131.7 (C⁶), 129.7 (C³), 124.9 (C²), 83.9 (C⁹), 44.5 (C⁷), 27.8 (C¹⁰).

R_f (PE/EtOAc 9:1) = 0.48

2,3-O-Isopropylidene-D-Erythrolactone **392**



Following a reported procedure,¹⁸⁶ to a solution of erythorbic acid (35 g, 0.20 mol) in H₂O (500 mL) at 0 °C was slowly added K₂CO₃ (42 g, 0.40 mol, 2.0 equiv). H₂O₂ (30 % in H₂O, 45 mL, 0.45 mol, 2.3 equiv) was then added dropwise over 10 min. The reaction mixture was stirred for 5 minutes before removing the ice bath and heating the mixture to 42 °C. The reaction mixture was stirred for 30 min, and then activated charcoal (8.0 g) was added. The mixture was stirred at 80 °C for 30 min. The hot mixture was filtered through a plug of Celite and acidified to pH 1 with 6 M HCl. Concentration *in vacuo* afforded a pale yellow solid (84 g). Acetone (180 mL) was added followed by MgSO₄ (50 g), 2,2-dimethoxypropane (350 mL, 2.8 mol, 14 equiv) and *p*-TsOH (0.42 g, 2.0 mmol, 1.0 mol%). The suspension was stirred at RT for 16 h. The reaction mixture was cooled down to 0 °C. Et₂O (500 mL) and triethylamine (62 mL, 0.44 mol, 2.2 equiv) were added, and the reaction mixture was filtered and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 1:1) afforded pure compound **392** as a white solid (22 g, 70% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁸⁶

mp = 66.0–66.5 °C (Et₂O/PE)

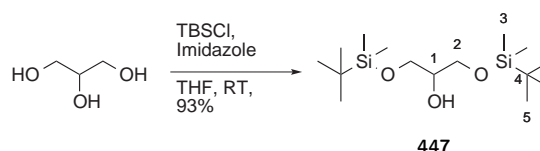
$[\alpha]_D^{23}$ -113.5 (c = 1.11, H₂O)

¹H NMR (400 MHz, CDCl₃): δ 4.88 (m, 1H, C²–H), 4.74 (d, J = 5.2 Hz, 1H, C³–H), 4.48–4.38 (m, 2H, C¹–H), 1.48 (s, 3H, C^{6or7}–H), 1.39 (s, 3H, C^{6or7}–H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.3 (C^4), 114.1 (C^5), 75.6 (C^2), 74.7 (C^3), 70.3 (C^1), 26.9 ($\text{C}^{6\text{or}7}$), 25.8 ($\text{C}^{6\text{or}7}$).

R_f (DCM) = 0.39

1,5-bis(dimethyltertbutylsilyl)glycerol **447**



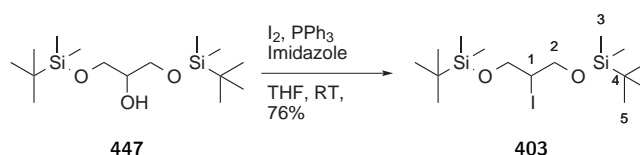
Following a reported procedure,²³⁴ to a solution of glycerol (5.0 g, 54 mmol) in THF (100 mL) were added TBSCl (17 g, 0.11 mol, 2.1 equiv) and imidazole (8.0 g, 0.12 mol, 2.2 equiv). The reaction mixture was stirred overnight at RT. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded pure compound **447** as a colorless oil (16 g, 93% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²³⁴

^1H NMR (400 MHz, CDCl_3): δ 3.69–3.58 (m, 5H, $\text{C}^{1,2}\text{--H}$), 0.89 (s, 18H, $\text{C}^5\text{--H}$), 0.06 (s, 12H, $\text{C}^3\text{--H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 72.0 (C^1), 63.6 (C^2), 26.0 (C^5), 18.4 (C^4), -5.3 (C^3).

R_f (PE/EtOAc 9:1) = 0.26

1,3-bis(dimethyltertbutylsilyloxy)-2-iodopropane **403**



To a solution of protected alcohol **447** (8.0 g, 25 mmol), PPh_3 (9.2 g, 35 mmol, 1.4 equiv) and imidazole (2.7 g, 40 mmol, 1.6 equiv) in THF (400 mL) at 0°C was added slowly iodine (7.6 g, 30 mmol, 1.2 equiv). The reaction mixture was stirred at RT for 3 h, and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added. The reaction mixture was diluted with H_2O , and extracted with EtOAc.

²³⁴Casida, J. E.; Gulevich, A. G.; Sarpong, R.; Bunnelle, E. M. *Bioorg. Med. Chem.* **2010**, *18*, 1942–1947

Chapter 8: Experimental Section

The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded pure iodide **403** as a colorless oil (8.2 g, 76% yield).

^1H NMR (400 MHz, CDCl_3): δ 4.09 (quint, $J = 5.7$ Hz, 1H, $\text{C}^1\text{-H}$), 3.85 (d, $J = 5.7$ Hz, 4H, $\text{C}^2\text{-H}$), 0.90 (s, 18H, $\text{C}^5\text{-H}$), 0.08 (s, 6H, $\text{C}^3\text{-H}$), 0.07 (s, 6H, $\text{C}^3\text{-H}$).

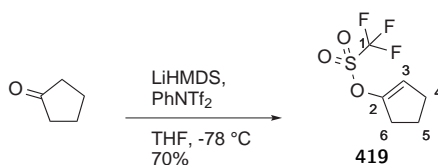
^{13}C NMR (101 MHz, CDCl_3): δ 64.7 (C^2), 36.7 (C^1), 26.0 (C^5), 18.5 (C^4), -5.1 (C^3), -5.2 (C^3).

IR: 2955 (w), 2929 (w), 2864 (w), 2857 (w), 1472 (w), 1253 (m), 1136 (w), 1074 (m), 833 (s), 775 (s).

HRMS: (ESI^+) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{36}\text{IO}_2\text{Si}_2^+$: 431.1293; Found: 431.1285.

R_f (PE/EtOAc 9:1) = 0.74

cyclopent-1-en-1-yl trifluoromethanesulfonate **419**



Following a reported procedure,²³⁵ to a solution of cyclopentanone (2.0 mL, 23 mmol) in THF (35 mL) at -78°C was added dropwise LiHMDS (0.8 M solution in THF, 28 mL, 23 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min. A solution of phenyl triflimide (8.0 g, 23 mmol, 1.0 equiv) in THF (35 mL) was added and the reaction mixture was stirred for 30 min before being allowed to warm up to RT. The reaction mixture was then stirred at RT for 18 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE) afforded pure vinyl triflate **419** as a colorless oil (3.4 g, 70% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²³⁵

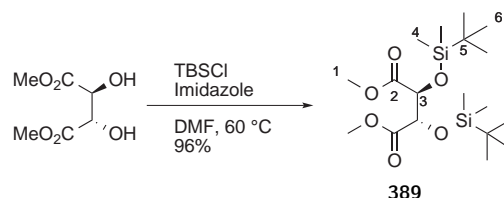
^1H NMR (400 MHz, CDCl_3): δ 5.63 (m, 1H, $\text{C}^3\text{-H}$), 2.64-2.52 (m, 2H, $\text{C}^6\text{-H}$), 2.46-2.35 (m, 2H, $\text{C}^4\text{-H}$), 2.09-1.97 (m, 2H, $\text{C}^5\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 149.7 (C^2), 118.7 (q, $J = 320.7$ Hz (C^1), 117.9 (C^3), 30.9 (C^6), 28.1 (C^4), 21.0 (C^5).

²³⁵ Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143–2146

R_f (PE) = 0.45

2,3-bis(tertbutyldimethyl)-1,4-dimethyl-D-tartrate **389**



Following a reported procedure,¹⁷⁸ to a solution of dimethyl D-tartrate (5.0 g, 28 mmol) in DMF (26 mL) were added TBSCl (13 g, 84 mmol, 3.0 equiv) and Imidazole (5.8 g, 84 mmol, 3.0 equiv). The reaction mixture was stirred overnight at 60 °C. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded pure compound **389** as a colourless oil (11 g, 96% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁷⁸

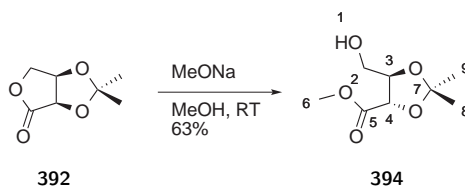
$[\alpha]_D^{22}$ -48.99 (c = 2.03, CHCl_3)

^1H NMR (400 MHz, CDCl_3): δ 4.64 (s, 2H, $\text{C}^3\text{-H}$), 3.72 (s, 6H, $\text{C}^1\text{-H}$), 0.87 (s, 18H, $\text{C}^6\text{-H}$), 0.08 (s, 6H, $\text{C}^4\text{-H}$), -0.01 (s, 6H, $\text{C}^{4'}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 171.4 (C^2), 74.9 (C^3), 52.0 (C^1), 25.7 (C^6), 18.4 (C^5), -4.6 (C^4), -5.2 ($\text{C}^{4'}$).

R_f (PE/EtOAc 9:1) = 0.60

methyl (4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate **394**



To a solution of lactone **392** (1.0 g, 6.3 mmol) in MeOH (60 mL) was added MeONa (5.4 M in MeOH, 1.2 mL, 6.3 mmol, 1.0 equiv). The reaction mixture was stirred at RT for 24 h. 4 M HCl was added until pH 7, and the solution was concentrated *in vacuo*. Purification by FCC

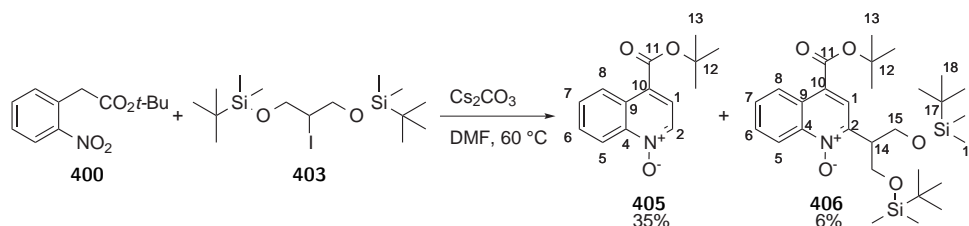
(PE/EtOAc 4:6) afforded pure compound **394** as a colorless oil (0.75 g, 63% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²³⁶ The expected (4R,5R) diastereoisomer was not observed.²³⁷

¹H NMR (400 MHz, CDCl₃): δ 4.48 (d, J = 7.8 Hz, 1H, C⁴-H), 4.25 (dt, J = 7.8, 2.9 Hz, 1H, C³-H), 3.96 (dd, J = 12.7, 2.9 Hz, 1H, C²-H), 3.80 (s, 3H, C⁶-H), 3.76 (dd, J = 12.7, 2.9 Hz, 1H, C²-H), 1.90 (br s, 1H, O¹-H), 1.49 (s, 3H, C^{8or9}-H), 1.45 (s, 3H, C^{8or9}-H).

¹³C NMR (101 MHz, CDCl₃): δ 171.4 (C⁵), 111.5 (C⁷), 79.2 (C³), 75.0 (C⁴), 61.9 (C²), 52.7 (C⁶), 26.9 (C^{8or9}), 25.8 (C^{8or9}).

R_f (PE/EtOAc 2:8) = 0.60

4-(tert-butoxycarbonyl)quinoline 1-oxide **405** and 4-(tert-butoxycarbonyl)-2-(2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)quinoline 1-oxide **406**



To a solution of ester **400** (50 mg, 0.21 mmol) and iodide **403** (0.10 g, 0.23 mmol, 1.1 equiv) in DMF (1.0 mL) was added Cs₂CO₃ (0.21 g, 0.63 mmol, 3.0 equiv). The reaction mixture was stirred at 60 °C overnight. H₂O was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 9:1) afforded pure compounds **405** as a colorless oil (18 mg, 35% yield) and pure compound **406** as a yellow oil (7.0 mg, 6% yield). The spectroscopic data of compound **405** were in accord with those reported in the literature.²³⁸

Compound **405**

¹H NMR (400 MHz, CDCl₃): δ 9.02 (d, J = 7.8 Hz, 1H, C⁵-H), 8.75 (d, J = 7.8 Hz, 1H, C⁸-H), 8.49 (d, J = 7.2 Hz, 1H, C²-H), 7.89 (d, J = 7.2 Hz, 1H, C¹-H), 7.76 (t, J = 7.8 Hz, 1H, C⁷-H),

²³⁶Kothari, A.; Qureshi, M. K. N.; Beck, E. M.; Smith, M. D. *Chem. Commun.* **2007**, 2814–2816

²³⁷Gypser, A.; Petersek, M.; Scharf, H.-D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1013–1016

²³⁸Pagar, V. V.; Jadhav, A. M.; Liu, R. S. *J. Am. Chem. Soc.* **2011**, 133, 20728–20731

7.71 (t, $J = 7.8$ Hz, 1H, C⁶-H), 1.65 (s, 9H, C¹³-H).

¹³C NMR (101 MHz, CDCl₃): δ 164.1 (C¹¹), 142.2 (C⁴), 134.5 (C²), 130.4 (C⁷), 130.0 (C⁶), 128.5 (C¹⁰), 126.9 (C⁵), 125.4 (C⁹), 124.2 (C¹), 119.9 (C⁸), 83.0 (C¹²), 28.3 (C¹³).

R_f (PE/EtOAc 9:1) = 0.10

Compound 406

¹H NMR (400 MHz, CDCl₃): δ 8.98 (d, $J = 7.8$ Hz, 1H, C⁶-H), 8.80 (d, $J = 7.8$ Hz, 1H, C⁸-H), 7.97 (s, 1H, C¹-H), 7.75 (t, $J = 7.8$ Hz, 1H, C⁷-H), 7.68 (t, $J = 7.8$ Hz, 1H, C⁶-H), 4.16-4.06 (m, 5H, C^{14,15}-H), 1.65 (s, 9H, C¹³-H), 0.82 (s, 18H, C¹⁸-H), 0.01 (s, 6H, C¹⁶-H), -0.07 (s, 6H, C^{16'}-H).

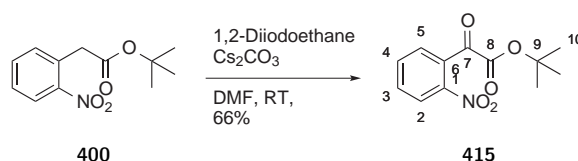
¹³C NMR (101 MHz, CDCl₃): δ 164.7 (C¹¹), 147.1 (C²), 142.3 (C⁴), 130.1 (C⁶), 129.0 (C⁷), 127.0 (C¹⁰), 126.7 (C⁸), 125.4 (C¹), 123.6 (C⁹), 120.0 (C⁵), 82.7 (C¹²), 60.1 (C¹⁵), 44.6 (C¹⁴), 28.4 (C¹³), 26.0 (C¹⁸), 18.3 (C¹⁷), -5.4 (C¹⁶).

IR: 2934 (w), 2857 (w), 1714 (w), 1251 (m), 1156 (s), 837 (s).

HRMS: (ESI⁺) m/z : [M + H]⁺ Calcd for C₂₉H₅₀NO₅Si₂⁺: 548.3222; Found: 548.3224.

R_f (PE/EtOAc 9:1) = 0.41

tert-butyl 2-(2-nitrophenyl)-2-oxoacetate 415



Following a procedure developed in our laboratory, to a solution of ester **400** (1.0 g, 4.2 mmol) in DMF (80 mL) were added 1,2-diiodoethane (1.3 g, 4.6 mmol, 1.1 equiv) and Cs₂CO₃ (3.0 g, 11 mmol, 2.5 equiv). The reaction mixture was stirred at RT for 4 h. H₂O was added and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded pure compound **415** as a yellow wax (0.70 g, 66% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.17 (d, $J = 7.4$ Hz, 1H, C²-H), 7.80 (td, $J = 7.4, 1.4$ Hz, 1H, C⁴-H), 7.71 (td, $J = 7.4, 1.4$ Hz, 1H, C³-H), 7.63 (dd, $J = 7.4, 1.4$ Hz, 1H, C⁵-H), 1.50 (s, 9H,

C¹⁰–H).

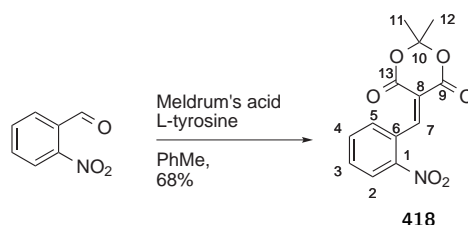
¹³C NMR (101 MHz, CDCl₃): δ 185.0 (C⁷), 158.6 (C⁸), 147.9 (C¹), 134.8 (C³), 133.5 (C⁶), 132.3 (C⁴), 130.4 (C⁵), 123.9 (C²), 85.3 (C⁹), 27.7 (C¹⁰).

IR: 2983 (w), 2933 (w), 1755 (m), 1717 (s), 1526 (s), 1372 (m), 1346 (s), 1254 (m), 1210 (s), 1153 (s), 984 (m), 845 (m), 830 (m), 789 (m), 740 (s), 705 (s).

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₁₂H₁₃NNaO₅⁺: 274.0686; Found: 274.0688.

R_f (PE/EtOAc 8:2) = 0.43

2,2-dimethyl-5-(2-nitrobenzylidene)-1,3-dioxane-4,6-dione **418**



To a solution of 2-nitrobenzaldehyde (6.0 g, 40 mmol) and Meldrum's acid (5.8 g, 40 mmol, 1.0 equiv) in toluene (100 mL) was added L-tyrosine (1.5 g, 8.0 mmol, 0.20 equiv). The reaction mixture was heated to reflux with a Dean-Stark apparatus for 16 h. H₂O was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded pure compound **418** as a yellow solid (7.5 g, 68% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²³⁹

mp = 117.0–118.5 °C (EtOH).

¹H NMR (400 MHz, CDCl₃): δ 8.78 (s, 1H, C⁷–H), 8.29 (d, *J* = 8.4 Hz, 1H, C²–H), 7.74 (t, *J* = 8.4 Hz, 1H, C⁴–H), 7.64 (t, *J* = 8.4 Hz, 1H, C³–H), 7.49 (d, *J* = 8.4 Hz, 1H, C⁵–H), 1.82 (s, 6H, C^{11,12}–H).

¹³C NMR (101 MHz, CDCl₃): δ 161.7 (C^{9or13}), 159.1 (C^{9or13}), 155.9 (C⁷), 146.4 (C¹), 133.9 (C⁴), 131.0 (C³), 130.4 (C⁵), 130.0 (C⁶), 125.0 (C²), 117.9 (C⁸), 105.6 (C¹⁰), 27.9 (C¹¹), 27.9 (C¹²).

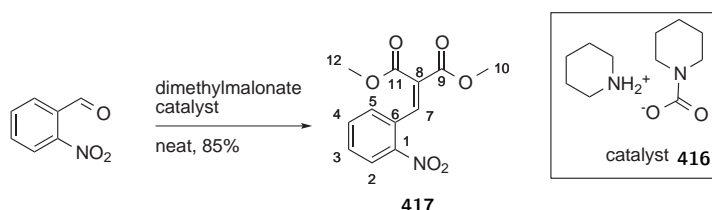
IR: 2999 (w), 2365 (w), 2338 (w), 1766 (w), 1733 (s), 1522 (s), 1344 (s), 1283 (s), 1198 (s), 1033 (w), 933 (m), 799 (w), 727 (m).

²³⁹Le, W.-J.; Lu, H.-F.; Zhou, J.-T.; Cheng, H.-L.; Gao, Y.-H. *Tetrahedron Lett.* **2013**, 54, 5370–5373

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₁₃H₁₁NNaO₆⁺: 300.0479; Found: 300.0475.

R_f (PE/EtOAc 7:3) = 0.50

dimethyl 2-(2-nitrobenzylidene)malonate **417**



Following a reported procedure,²⁰⁰ to a solution of 2-nitrobenzaldehyde (4.0 g, 27 mmol) in dimethyl malonate (3.0 mL, 27 mmol, 1.0 equiv) was added catalyst **416**²⁴⁰ (2.7 g, 14 mmol, 0.50 equiv). The reaction mixture was stirred at RT for 16 h. H₂O was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 7:3) afforded pure compound **417** as a yellow solid (6.0 g, 85% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²⁰⁰

mp= 67.0-68.2 °C (Toluene / PE).

¹H NMR (400 MHz, CDCl₃): δ 8.23-8.18 (m, 2H, C^{2,7}-H), 7.65 (t, *J* = 7.1 Hz, 1H, C⁴-H), 7.57 (t, *J* = 7.1 Hz, 1H, C³-H), 7.40 (d, *J* = 7.1 Hz, 1H, C⁵-H), 3.87 (s, 3H, C^{10or12}-H), 3.60 (s, 3H, C^{10or12}-H).

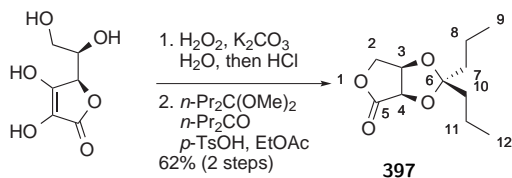
¹³C NMR (101 MHz, CDCl₃): δ 165.4 (C^{9or11}), 163.8 (C^{9or11}), 147.1 (C¹), 141.9 (C⁷), 134.0 (C⁴), 130.4 (C³), 130.4 (C⁶), 130.0 (C⁵), 128.5 (C⁸), 125.2 (C²), 53.0 (C^{10or12}), 52.6 (C^{10or12}).

IR: 3122 (w), 3005 (w), 2954 (w), 2851 (w), 1718 (s), 1520 (s), 1437 (m), 1341 (s), 1266 (s), 1223 (s), 1070 (s), 977 (m), 939 (m), 843 (m), 793 (m), 744 (s), 697 (m).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₁₂H₁₁NNaO₆⁺: 288.0479; Found: 288.0483.

R_f (PE/EtOAc 7:3) = 0.35

²⁴⁰ Catalyst **416** was prepared by adding dry ice into a solution of piperidine (5.0 mL) in Et₂O (10 mL). The catalyst precipitated and was filtered off, washed with Et₂O and dried.

2,3-O-Isoheptylidene-D-Erythrolactone 397

To a solution of 4-heptanone (60 mL, 0.43 mol) in MeOH (400 mL) was added trimethyl orthoformate (56 mL, 0.52 mol, 1.2 equiv) and *p*-TsOH (0.80 g, 4.0 mmol, 1.0 mol%). A distillation head was connected to the flask, and the mixture was stirred at 70 °C for 2 h, distilling the methyl formate formed. The reaction mixture was then heated to 100 °C, to distill the MeOH and the unreacted trimethyl orthoformate. The crude 4,4-dimethoxyheptane thus obtained was used in the reaction without further purification.

To a solution of erythorbic acid (35 g, 0.20 mol) in H₂O (500 mL) at 0 °C was slowly added K₂CO₃ (42 g, 0.40 mol, 2.0 equiv). H₂O₂ (30 % in H₂O, 45 mL, 0.45 mol, 2.3 equiv) was then added dropwise over 10 min. The reaction mixture was stirred for 5 minutes at 0 °C and then 30 min at 42 °C. Activated charcoal (8.0 g) was then added. The mixture was stirred at 80 °C for 30 min. The hot mixture was filtered through a plug of Celite and acidified to pH 1 with 6 M HCl. Concentration *in vacuo* afforded a pale yellow solid (84 g). AcOEt (180 mL) was added followed by MgSO₄ (50 g), the freshly prepared 4,4-dimethoxyheptane and *p*-TsOH (0.42 g, 2.0 mmol, 1.0 mol%). The suspension was stirred at RT for 16 h. The reaction mixture was cooled down to 0 °C. Et₂O (500 mL) and triethylamine (62 mL, 0.44 mol, 2.2 equiv) were added, and the reaction mixture was filtered and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 7:3) afforded pure compound **397** as a colourless oil (27 g, 62% yield).

$[\alpha]_D^{22}$ -113.9 (*c* = 0.49, CHCl₃)

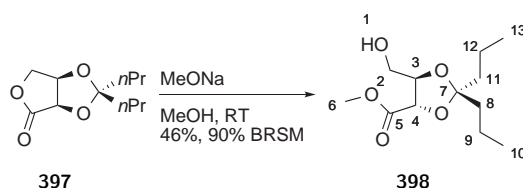
¹H NMR (400 MHz, CDCl₃): δ 4.87 (m, 1H, C³-H), 4.74 (m, 1H, C⁴-H), 4.49-4.35 (m, 2H, C²-H), 1.68-1.55 (m, 4H, C^{7,10}-H), 1.43-1.30 (m, 4H, C^{8,11}-H), 0.97-0.84 (m, 6H, C^{9,12}-H).

¹³C NMR (101 MHz, CDCl₃): δ 174.0 (C⁵), 117.8 (C⁶), 75.8 (C³), 75.0 (C⁴), 70.5 (C²), 39.7 (C^{7or10}), 39.3 (C^{7or10}), 17.4 (C^{8or11}), 16.6 (C^{8or11}), 14.4 (C^{9or12}), 14.2 (C^{9or12}).

IR: 2961 (m), 2875 (w), 1783 (s), 1466 (w), 1379 (w), 1180 (m), 1111 (w), 1063 (m), 989 (w), 946 (w).

HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₁₁H₁₉O₄⁺: 215.1278; Found: 215.1281.

R_f (DCM) = 0.38

methyl (4S,5R)-5-(hydroxymethyl)-2,2-dipropyl-1,3-dioxolane-4-carboxylate **398**

To a solution of lactone **397** (0.86 g, 4.0 mmol) in MeOH (40 mL) was added MeONa (5.4 M in MeOH, 0.74 mL, 4.0 mmol, 1.0 equiv). The reaction mixture was stirred at RT for 24 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 7:3) afforded pure compound **398** as a colorless oil (0.45 g, 46% yield, 90% BRSM).

$[\alpha]_D^{22}$ -6.7 ($c = 0.39$, CHCl_3)

^1H NMR (400 MHz, CDCl_3): δ 4.44 (d, $J = 8.4$ Hz, 1H, $\text{C}^4\text{-H}$), 4.19 (dt, $J = 8.4, 3.3$ Hz, 1H, $\text{C}^3\text{-H}$), 3.97 (dd, $J = 12.1, 3.3$ Hz, 1H, $\text{C}^2\text{-H}$), 3.80 (s, 3H, $\text{C}^6\text{-H}$), 3.77 (m, 1H, $\text{C}^2\text{-H}$), 1.90 (br s, 1H, $\text{C}^1\text{-H}$), 1.70-1.62 (m, 4H, $\text{C}^{8,11}\text{-H}$), 1.47-1.36 (m, 4H, $\text{C}^{9,12}\text{-H}$), 0.92 (t, $J = 7.4$ Hz, 6H, $\text{C}^{10,13}\text{-H}$).

^{13}C NMR (101 MHz, CDCl_3): δ 171.2 (C^5), 114.7 (C^7), 79.3 (C^3), 75.2 (C^4), 62.0 (C^2), 52.6 (C^6), 39.7 ($\text{C}^{8\text{or}11}$), 39.7 ($\text{C}^{8\text{or}11}$), 17.4 (C^9), 16.8 (C^{12}), 14.5 (C^{10}), 14.4 (C^{13}).

IR: 3482 (w), 2960 (m), 2935 (w), 2875 (w), 1758 (m), 1741 (m), 1457 (w), 1438 (w), 1379 (w), 1294 (m), 1197 (m), 1169 (m), 1109 (s), 1050 (m), 957 (m), 907 (m), 840 (m).

HRMS: (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{22}\text{NaO}_5^+$: 269.1359; Found: 269.1358.

R_f (PE/EtOAc 6:4) = 0.50

Notes and Bibliography

- [1] Sertürner, F. *J. Pharm. Aerzte. Apoth. Chem.* **1805**, *13*, 229–243
- [2] Gunasekera, S. P.; Gunasekera, M.; Longley, R. E. *J. Org. Chem.* **1990**, *55*, 4912–4915
- [3] Grundon, M. F.; Saxton, J. E. In *The Alkaloids*, Grundon, M. F., Ed.; The Alkaloids, Vol. 6; Royal Society of Chemistry: Cambridge, 1976; Chapter 10, pp 189–251
- [4] Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1819**, *10*, 142–177
- [5] a) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662; b) Kutchan, T. M. In *Alkaloids Chem. Biol.* 1998; Vol. 50; Chapter 7, pp 257–316; c) Frederich, M.; Hayette, M.-P.; Tits, M.; De Mol, P.; Angenot, L. *Antimicrob. Agents Chemother.* **1999**, *43*, 2328–2331; d) Leclercq, J.; De Pauw-Gillet, M.-C.; Bassleer, R.; Angenot, L. *J. Ethnopharmacol.* **1986**, *15*, 305–316; e) Gong, Z.; Sun, L.-r.; Cao, X.; Li, S.-j.; Zhu, X.-h.; Gao, T.-m. *Nan Fang Yi Ke Da Xue Xue Bao* **2008**, *28*, 2121–2125; f) Baliga, M. S.; Jagetia, G. C.; Ulloor, J. N.; Baliga, M. P.; Venkatesh, P.; Reddy, R.; Rao, K. V. N. M.; Baliga, B. S.; Devi, S.; Raju, S. K.; Veeresh, V.; Reddy, T. K.; Bairy, K. L. *Toxicol. Lett.* **2004**, *151*, 317–326
- [6] a) Saxton, J. E. *The Alkaloids* **1998**, *51*, 343–376; b) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843–868; c) Lopchuk, J. M. *Prog. Heterocycl. Chem.* **2011**, *23*, 1–25; d) Hájíček, J. *Collect. Czechoslov. Chem. Commun.* **2012**, *76*, 2023–2083
- [7] O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547
- [8] Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510
- [9] ; a) Scott, A. I.; Qureshi, A. A. *J. Am. Chem. Soc.* **1969**, *91*, 5874–5876; b) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580–1589
- [10] Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136
- [11] Mannich, C.; Krösche, W. *Arch. Pharm. (Weinheim)*. **1912**, *250*, 647–667
- [12] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186
- [13] Tietze, L. F.; Wichmann, J. *Angew. Chem. Int. Ed.* **1992**, *31*, 1079–1080

- [14] a) Tietze, L.-F.; Bachmann, J.; Schul, W. *Angew. Chem. Int. Ed.* **1988**, *27*, 971–973; b) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, *26*, 1185–1194; c) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Zhou, Y.; Raschke, T. *Liebigs Ann.* **1997**, 881–886
- [15] He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772
- [16] Elliott, G. I.; Velcicky, J.; Ishikawa, H.; Li, Y.; Boger, D. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 620–622
- [17] Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618–3621
- [18] Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506–8512
- [19] Shiri, M. *Chem. Rev.* **2012**, *112*, 3508–3549
- [20] a) Criegee, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 745–752; b) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990–3001
- [21] Ono, N., *The Nitro Group in Organic Synthesis*; Feuer, H., Ed.; John Wiley & Sons, 2003: 2001
- [22] Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3272–3276
- [23] Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127–19130
- [24] Massiot, G.; Thépenier, P.; Jacquier, M. J.; Le Men-Olivier, L.; Delaude, C. *Heterocycles* **1989**, *29*, 1435–1438
- [25] a) Leewanich, P.; Tohda, M.; Matsumoto, K.; Subhadhirasakul, S.; Takayama, H.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **1997**, *332*, 321–326; b) Leewanich, P.; Tohda, M.; Matsumoto, K.; Subhadhirasakul, S.; Takayama, H.; Watanabe, H. *Biol. Pharm. Bull.* **1996**, *19*, 394–399; c) Maier, A.; Maul, C.; Zerlin, M.; Grabley, S.; Thiericke, R. *J. Antibiot.* **1999**, *52*, 952–959
- [26] Koyama, K.; Hirasawa, Y.; Nugroho, A. E.; Kaneda, T.; Hoe, T. C.; Chan, K.-L.; Morita, H. *Tetrahedron* **2012**, *68*, 1502–1506
- [27] Dounay, A. B.; Overman, L. E.; Wroblewski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187
- [28] Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wroblewski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377
- [29] Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607

-
- [30] a) Bobeck, D. R.; France, S.; Leverett, C. A.; Sánchez-Cantalejo, E.; Padwa, A. *Tetrahedron Lett.* **2009**, *50*, 3145–3147; b) Li, G.; Padwa, A. *Org. Lett.* **2011**, *13*, 3767–3769
- [31] Liu, P.; Wang, J.; Zhang, J.; Qiu, F. G. *Org. Lett.* **2011**, *13*, 6426–6428
- [32] a) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473; b) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877–8879
- [33] a) Ueno, M.; Yonemoto, M.; Hashimoto, M.; Wheatley, A. E. H.; Naka, H.; Kondo, Y. *Chem. Commun.* **2007**, 2264–2266; b) Selvakumar, N.; Reddy, B. Y.; Azhagan, A. M.; Khera, M. K.; Babu, J. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7065–7069; c) Hong, S.; Jung, M.; Park, Y.; Ha, M. W.; Park, C.; Lee, M.; Park, H. G. *Chem. Eur. J.* **2013**, *19*, 9599–9605; d) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M. H.; Jew, S. S.; Park, H. G. *J. Am. Chem. Soc.* **2011**, *133*, 4924–4929; e) Hirschhäuser, C.; Parker, J. S.; Perry, M. W. D.; Haddow, M. F.; Gallagher, T. *Org. Lett.* **2012**, *14*, 4846–4849
- [34] a) Bartoli, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1985**, *26*, 115–118; b) Bartoli, G.; Marcantoni, E.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1988**, *29*, 2251–2254
- [35] a) Takeuchi, H.; Maeda, M.; Mitani, M.; Koyama, K. *J. Chem. Soc. Chem. Commun.* **1985**, 287–289; b) Takeuchi, H.; Shiobara, Y.; Kawamoto, H.; Koyama, K. *J. Chem. Soc. Perkin Trans. I* **1990**, 321–327
- [36] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398
- [37] a) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868–1874; b) Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443–7448
- [38] Aouzal, R.; Prunet, J. *Org. Biomol. Chem.* **2009**, *7*, 3594–3598
- [39] a) Caselli, A.; Gallo, E.; Ragaini, F.; Ricatto, F.; Abbiati, G.; Cenini, S. *Inorganica Chim. Acta* **2006**, *359*, 2924–2932; b) He, J.; Yamaguchi, K.; Mizuno, N. *J. Org. Chem.* **2011**, *76*, 4606–4610; c) Risse, J.; Scopelliti, R.; Severin, K. *Organometallics* **2011**, *30*, 3412–3418
- [40] a) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413–415; b) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929–4938; c) Chang, C. W.; Chen, Y. N.; Adak, A. K.; Lin, K. H.; Tzou, D. L. M.; Lin, C. C. *Tetrahedron* **2007**, *63*, 4310–4318; d) Kanemitsu, T.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4541–4544; e) Rai, A. N.; Basu, A. *Org. Lett.* **2004**, *6*, 2861–2863; f) Busscher, G. E.; van den Broek, S. B. A. M. W.; Rutjes, F. P. J. T.; van Delft, F. L. *Tetrahedron* **2007**, *63*, 3183–3188; g) Chaudhari, V. D.; Ajish Kumar, K. S.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805–5807; h) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508–6514; i) Randl, S.; Blechert, S. *J. Org. Chem.*

2003, 68, 8879–8882

- [41] Basavaiah, D.; Rao, P. *Tetrahedron* **1996**, 52, 8001–8062
- [42] Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, 43, 1259–1262
- [43] a) Takasu, K.; Tanaka, T.; Azuma, T.; Takemoto, Y. *Chem. Commun.* **2010**, 46, 8246–8248; b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, 68, 7565–7581
- [44] a) Trost, B. M.; Huang, X. *Chem. Asian J.* **2006**, 1, 469–478; b) McIntosh, J. J. M.; Sieler, R. R. A. *J. Org. Chem.* **1978**, 43, 4431–4433; c) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, 56, 226–231; d) Leonard, J.; Hague, A. B.; Jones, M. F.; Ward, R. A. *Synthesis* **2000**, 32, 507–509; e) Johnson, J. W.; Evanoff, D. P.; Savard, M. E.; Lange, G.; Ramadhar, T. R.; Assoud, A.; Taylor, N. J.; Dmitrienko, G. I. *J. Org. Chem.* **2008**, 73, 6970–6982; f) Andrade, G. S.; Berkner, J. E.; Liotta, C. L.; Eckert, C.; Schiraldi, D. A.; Andersen, A.; Collard, D. M. *Synth. Commun.* **2003**, 33, 3643–3650
- [45] a) Vasil'ev, A. A.; Serebryakov, E. P. *Russ. Chem. Rev.* **2001**, 70, 735–776; b) Lathbury, D. C.; Parsons, P. J.; Pinto, I. J. *J. Chem. Soc. Chem. Commun.* **1988**, 81–82
- [46] a) Pottie, I. R.; Nandaluru, P. R.; Benoit, W. L.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *J. Org. Chem.* **2011**, 76, 9015–9030; b) Backvall, J.-E.; Rise, F. *Tetrahedron Lett.* **1989**, 30, 5347–5348
- [47] a) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem. Int. Ed.* **1998**, 37, 3262–3265; b) Alanine, A. I.; Fishwick, C. W.; Jones, A. D.; Mitchell, M. B. *Tetrahedron Lett.* **1989**, 30, 5653–5654
- [48] a) Yates, P.; Gomes, A.; Burnell, D.; Cong, D.; Sawyer, J. *Can. J. Chem.* **1989**, 67, 37–47; b) Olsen, R. K.; Feng, X. *Tetrahedron Lett.* **1991**, 32, 5721–5724; c) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, 126, 1352–1353; d) Ackland, D. J.; Pinhey, J. T. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2689–2694
- [49] a) Ghosh, A.; Chakraborty, I.; Adarsh, N. N.; Lahiri, S. *Tetrahedron* **2010**, 66, 164–171; b) Lahiri, S.; Yadav, S.; Chanda, M.; Chakraborty, I.; Chowdhury, K.; Mukherjee, M.; Choudhury, A. R.; Guru Row, T. N. *Tetrahedron Lett.* **2005**, 46, 8133–8136; c) Yadav, S.; Banerjee, S.; Maji, D.; Lahiri, S. *Tetrahedron* **2007**, 63, 10979–10990; d) Maiti, B. C.; Lahiri, S. *Tetrahedron* **1997**, 53, 13053–13062; e) Xiao, T.; Dong, X.; Tang, Y.; Zhou, L. *Adv. Synth. Catal.* **2012**, 354, 3195–3199; f) Smith, D. L. L.; Chidipudi, S. R.; Goundry, W. R.; Lam, H. W. *Org. Lett.* **2012**, 14, 4934–4937; g) Takasu, K.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2008**, 49, 4220–4222
- [50] a) Danheiser, R. *Tetrahedron* **1983**, 39, 935–947; b) Tran, K.-V.; Bickar, D. *J. Org. Chem.*

2006, 71, 6640–6643

- [51] Okuro, K.; Gurnham, J.; Alper, H. *J. Org. Chem.* **2011**, 76, 4715–4720
- [52] Mendgen, T.; Scholz, T.; Klein, C. D. *Bioorg. Med. Chem. Lett.* **2010**, 20, 5757–5762
- [53] Sauer, J. *Angew. Chem. Int. Ed.* **1967**, 6, 16–33
- [54] a) Markó, I. E.; Seres, P.; Swarbrick, T. M.; Staton, I.; Adams, H. *Tetrahedron Lett.* **1992**, 33, 5649–5652; b) Posner, G. H.; Suh, B. C.; Petersen, K. S.; Dolan, P.; Agoston, E. S.; Kensler, T. W.; Koh, J. T.; Peleg, S. *J. Steroid Biochem. Mol. Biol.* **2007**, 103, 213–221; c) Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, 35, 7545–7548; d) Shin, I. J.; Choi, E. S.; Cho, C. G. *Angew. Chem. Int. Ed.* **2007**, 46, 2303–2305
- [55] Pfaff, E.; Plieninger, H. *Chem. Ber.* **1982**, 115, 1967–1981
- [56] Swarbrick, T. M.; Markó, I. E.; Kennard, L. *Tetrahedron Lett.* **1991**, 32, 2549–2552
- [57] Padwa, A.; Crawford, K. R.; Straub, C. S.; Pieniazek, S. N.; Houk, K. N. *J. Org. Chem.* **2006**, 71, 5432–5439
- [58] Nakamura, M.; Takahashi, I.; Yamada, S.; Dobashi, Y.; Kitagawa, O. *Tetrahedron Lett.* **2011**, 52, 53–55
- [59] Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, 2, 485–492
- [60] Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, 39, 3719–3724
- [61] Le Menez, P.; Kunesch, N.; Liu, S.; Wenkert, E. *J. Org. Chem.* **1991**, 56, 2915–2918
- [62] a) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, 109, 7901–7903; b) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, 55, 517–521
- [63] Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **2001**, 66, 8935–8943
- [64] Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, 11, 653–655
- [65] Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, 475, 183–188
- [66] Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, 134, 14563–14572
- [67] Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, 61, 7882–7888

- [68] Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334–13337
- [69] Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591–5597
- [70] Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953–1957
- [71] a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 5767–5770; b) De Simone, F.; Waser, J. *Synlett* **2011**, *22*, 589–593; c) De Simone, F.; Waser, J. *Chimia* **2012**, *66*, 233–236
- [72] Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873
- [73] Iyengar, R.; Schildknecht, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625–1627
- [74] a) Callier-Dublanche, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, *64*, 4803–4816; b) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831–834; c) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L. J.; Orea, L.; Bernès, S.; Enríquez, R. G. *Arkivoc* **2003**, 185–192; d) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893–5901; e) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290–2300; f) Cho, H.-K.; Tam, N. T.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2010**, *31*, 3382–3384; g) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 6159–6162; h) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498–7508; i) Iyengar, R.; Schildknecht, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645–10652; j) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941–2943
- [75] a) Banwell, M. G.; Smith, J. A. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2613–2618; b) Huang, J.-Z.; Jie, X.-K.; Wei, K.; Zhang, H.; Wang, M.-C.; Yang, Y.-R. *Synlett* **2013**, *24*, 1303–1306; c) Pearson, W. H.; Aponick, A. *Org. Lett.* **2006**, *8*, 1661–1664
- [76] Desmaeele, D.; D'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292–2303
- [77] Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc. Perkin Trans. 1* **1999**, 995–1002
- [78] Fletcher, R.; Kizil, M.; Lampard, C.; Murphy, J. A.; Roome, S. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2341–2352
- [79] Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599–3601
- [80] McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 9288–9291
- [81] Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399

-
- [82] a) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, 3, 213–215; b) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, 58, 722–737
- [83] Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, 65, 2642–2645
- [84] Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, 124, 4628–4641
- [85] Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, 117, 5897–5898
- [86] a) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, 103, 6990–6992; b) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E.; Ishigamori *Tetrahedron* **1983**, 39, 3657–3668
- [87] a) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915–916; b) Mandal, S. B.; Giri, V. S.; Pakrashi, S. C. *Heterocycles* **1988**, 27, 11–12; c) Mandal, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, 53, 4236–4241; d) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, 59, 7677–7682; e) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.-i.; Ishibashi, H. *Angew. Chem. Int. Ed.* **2013**, 52, 906–910; f) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, 52, 4117–4121; g) Xia, G.; Han, X.; Lu, X. *Org. Lett.* **2014**, 16, 2058–2061; h) Jiao, L.; Bach, T. *Synthesis* **2014**, 46, 35–41
- [88] Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, 36, 6373–6374
- [89] Cahiez, G.; Alexakis, A.; Normant, J. *Tetrahedron Lett.* **1978**, 19, 3013–3014
- [90] Germain, N.; Schlaefli, D.; Chellat, M.; Rosset, S.; Alexakis, A. *Org. Lett.* **2014**, 16, 2006–2009
- [91] May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2008**, 47, 7358–7362
- [92] Gottumukkala, A. L.; Matcha, K.; Lutz, M.; De Vries, J. G.; Minnaard, A. J. *Chem. Eur. J.* **2012**, 18, 6907–6914
- [93] Germain, N.; Magrez, M.; Kehrli, S.; Mauduit, M.; Alexakis, A. *Eur. J. Org. Chem.* **2012**, 5301–5306
- [94] Moore, S. P.; Coote, S. C.; O'Brien, P.; Gilday, J. *Org. Lett.* **2006**, 8, 5145–5148
- [95] a) Zaimoku, H.; Nishide, H.; Nishibata, A.; Goto, N.; Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2013**, 15, 2140–2143; b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, 124, 2137–2139; c) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, 59, 8571–8587; d) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, 5, 1891–1893; e) Shimada, N.; Abe,

Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11824–11826; f) Schneider, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4217–4219; g) Pan, G.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 4801–4811; h) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246–10247; i) Yang, Y.-R.; Lai, Z.-W.; Shen, L.; Huang, J.-Z.; Wu, X.-D.; Yin, J.-L.; Wei, K. *Org. Lett.* **2010**, *12*, 3430–3433

[96] a) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753; b) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045–3049; c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257–259; d) Sakamoto, I.; Nishii, T.; Ozaki, F.; Kaku, H.; Tanaka, M.; Tsunoda, T. *Chem. Pharm. Bull.* **2005**, *53*, 1508–1509; e) Tsunoda, T.; Yamamoto, H.; Goda, K.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2457–2458; f) Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977–2980; g) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236; h) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164

[97] Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235–4238

[98] Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352–5355

[99] Pomerantz, M.; Chou, W. N.; Witczak, M. K.; Smith, C. G. *J. Org. Chem.* **1987**, *52*, 159–163

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

[101] a) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497–2500; b) Bunce, R. A.; Nammalwar, B. *J. Heterocycl. Chem.* **2009**, *46*, 172–177; c) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242–2248; d) Heller, G.; Lauth, H.; Buchwaldt, A. *Berichte der Dtsch. Chem. Gesellschaft* **1922**, *55*, 483–489; e) Ho, T. T.-L.; Wong, C. M. C. *Synthesis* **1974**, *6*, 45–45; f) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673–676; g) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066–2069; h) Royer, D.; Wong, Y.-S.; Plé, S.; Chiaroni, A.; Diker, K.; Lévy, J. *Tetrahedron* **2008**, *64*, 9607–9618; i) Sachs, E.; Kantorowicz, H. *Berichte der Dtsch. Chem. Gesellschaft* **1906**, *39*, 2754–2762; j) Snape, T. *Synlett* **2008**, *19*, 2689–2691; k) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621–5623

[102] Djerassi, C.; Budzikiewicz, H.; Wilson, J.; Gosset, J.; Men, J. L.; Janot, M.-M. *Tetrahedron Lett.* **1962**, *3*, 235–239

[103] Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Nelson, V. R. *J. Am. Chem. Soc.* **1968**, *90*, 3891–3893

[104] a) Barsi, M.-C.; Das, B. C.; Fourrey, J.-L.; Sundaramoorthi, R. *J. Chem. Soc. Chem. Commun.* **1985**, 88–89; b) J.-Y. Laronze, P.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron*

Lett. **1974**, *15*, 491–494; c) Kalaus, G.; Greiner, I.; Kajtar-Peredy, M.; Brlik, J.; Szabo, L.; Szantay, C. *J. Org. Chem.* **1993**, *58*, 1434–1442; d) Kalaus, G.; Kiss, M.; Kajtár-Peredy, M.; Brick, J.; Szabó, L.; Szántay, C. *Heterocycles* **1985**, *23*, 2783–2787; e) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519–1522; f) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172–2183; g) Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *J. Org. Chem.* **1979**, *44*, 2477–2480; h) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *J. Org. Chem.* **1979**, *44*, 1063–1068; i) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924–929; j) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705–3710; k) Kuehne, M. E.; Wang, T.; Seaton, P. J. *J. Org. Chem.* **1996**, *61*, 6001–6008; l) Lewin, G.; Bernadat, G.; Aubert, G.; Cresteil, T. *Tetrahedron* **2013**, *69*, 1622–1627; m) Pandey, G.; C, P. K. *Org. Lett.* **2011**, *13*, 4672–4675

[105] a) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron* **1985**, *41*, 5495–5501; b) Hugel, G.; Lévy, J. *Tetrahedron* **1984**, *40*, 1067–1073; c) David, B.; Sevenet, T.; Thoison, O.; Awang, K.; Pais, M.; Wright, M.; Guenard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155–2158

[106] Hesse, O. *Justus Liebig's Ann. der Chemie* **1882**, *211*, 249–282

[107] Schlittler, E.; Gellért, E. *Helv. Chim. Acta* **1951**, *34*, 920–923

[108] Gellért, E.; Witkop, B. *Helv. Chim. Acta* **1952**, *35*, 114–115

[109] Kny, H.; Witkop, B. *J. Org. Chem.* **1960**, *25*, 635–637

[110] Biemann, K.; Spitteller, G. *Tetrahedron Lett.* **1961**, *2*, 299–304

[111] ; a) Ziegler, F. E.; Kloek, J. a.; Zoretic, P. a. *J. Am. Chem. Soc.* **1969**, *91*, 2342–2346; b) Kutney, J. P.; Abdurahman, N.; Gletsos, C.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727–1735; c) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 3022–3023; d) Giri, V. S.; Ali, E.; Satyesh, C. *J. Heterocycl. Chem.* **1980**, *17*, 1133–1134; e) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1980**, 616–617; f) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990–6992; g) Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1981**, 1153–1155; h) Wenkert, E.; Halls, T. D.; Kwart, L. D.; Magnusson, G.; Showalter, H. *Tetrahedron* **1981**, *37*, 4017–4025; i) Temme, O.; Taj, S.-A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007–6015; j) Wee, A. G.; Yu, Q. *Tetrahedron* **1998**, *54*, 13435–13448; k) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439; sl) Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 1072–1077; m) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943–953; n) Nidhiry, J. E.; Prasad, K. R. *Tetrahedron* **2013**, *69*, 5525–5536; o) Hsu, S. W.; Cheng, H. Y.; Huang, A. C.; Ho, T. L.; Hou, D. R. *Eur. J. Org. Chem.* **2014**, 3109–3115; p) Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen,

- J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512
- [112] Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1147–1152
- [113] Camerman, A.; Camerman, N.; Kutney, J.; Piers, E.; Trotter, J. *Tetrahedron Lett.* **1965**, *6*, 637–642
- [114] Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1966**, *44*, 28–31
- [115] Brown, K.; Budzikiewicz, H.; Djerassi, C. *Tetrahedron Lett.* **1963**, *4*, 1731–1736
- [116] Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, *16*, 727–730
- [117] Ban, Y.; Honma, Y.; Ohnuma, T. *Heterocycles* **1976**, *5*, 47–51
- [118] Yoshida, K.; Sakum, Y.; Ban, Y. *Heterocycles* **1987**, *25*, 47–50
- [119] Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610
- [120] Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012
- [121] Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444–11449; Correction in Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2014**, *79*, 829–829
- [122] Guérard, K. C.; Guérinot, A.; Bouchard-Aubin, C.; Ménard, M. A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121–2133
- [123] Jin, J.; Qiu, F. G. *Adv. Synth. Catal.* **2014**, *356*, 340–346
- [124] Moldvai, I.; Szántay, C.; Szántay, C. *Heterocycles* **2001**, *55*, 2147–2155
- [125] Jiao, L.; Lin, M.; Zhuo, L. G.; Yu, Z. X. *Org. Lett.* **2010**, *12*, 2528–2531
- [126] Nagaoka, H.; Shibuya, K.; Yamada, Y. *Tetrahedron* **1994**, *50*, 661–688
- [127] a) San Feliciano, A.; Medardea, M.; Toméa, F.; Caballeroa, E.; Hebreroa, B.; del Corrala, J. M. M.; Barrerob, A. F. *Tetrahedron* **1989**, *45*, 1815–1822; b) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379; c) Yu, M.; Ibrahim, I.; Hasegawa, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 2788–2799

-
- [128] Lee, D. G.; Chen, T. In *Compr. Org. Chem. V7 Oxidations*, Trost, B. M., Fleming, I., Eds.; Pergamon, Oxford: 1991, pp 541–591
- [129] Keul, H.; Griesbaum, K. *Can. J. Chem.* **1980**, *58*, 2049–5054
- [130] Fisher, T. J.; Dussault, P. H. *Tetrahedron Lett.* **2010**, *51*, 5615–5617
- [131] Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867–3870
- [132] Lee, S.-g.; WooLim, C.; EuiSong, C.; HanPark, D. *Synth. Commun.* **1996**, *26*, 4623–4631
- [133] Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334–5336
- [134] Kutney, J. P.; Beck, J. E.; Eggers, N. J.; Hanssen, H. W.; Sood, R. S.; Westcott, N. D. *J. Am. Chem. Soc.* **1971**, *93*, 7322–7324
- [135] Kuehne, M. E.; Li, Y. L.; Wei, C. Q. *J. Org. Chem.* **2000**, *65*, 6434–6440
- [136] Kuehne, M. E.; Li, Y. L. *Org. Lett.* **1999**, *1*, 1749–1750; Corrections in: Kuehne, M. E.; Li, Y. L. *Org. Lett.* **2000**, *2*, 97–97
- [137] Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790–4796
- [138] Magnus, P.; Katoh, T.; Matthews, I. R.; Huffman, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 6707–6711
- [139] Govindachari, T. R.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 433–444
- [140] Kam, T. S.; Subramaniam, G.; Chen, W. *Phytochemistry* **1999**, *51*, 159–169
- [141] Kam, T. S.; Choo, Y. M.; Chen, W.; Yao, J. X. *Phytochemistry* **1999**, *52*, 959–963
- [142] Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chemistry* **2012**, *18*, 6729–6732
- [143] Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116
- [144] Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.* **2014**, *50*, 5782–5785
- [145] a) Charette, A. B.; Beauchemin, A.; Marcoux, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 5114–5115; b) Wang, J.-X.; Fu, Y.; Hu, Y.; Wang, K. *Synthesis* **2003**, *35*, 1506–1510; c) Tamaru, Y.; Gavryushin, A.; Knochel, P. In *e-EROS Encycl. Reagents Org. Synth.* John Wiley & Sons, Ltd: 2009
- [146] Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83–86

- [147] a) Lemieux, R. U.; Rudloff, E. V. *Can. J. Chem.* **1955**, *33*, 1701–1709; b) Rudloff, E. V. *Can. J. Chem.* **1955**, *33*, 1714–1719; c) Wee, A. G.; Liu, B. In *e-EROS Encycl. Reagents Org. Synth.* John Wiley & Sons, Ltd: Chichester, UK, 2001; d) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc. Chem. Commun.* **1985**, 1359–1362; e) Majetich, G.; Hull, K. *Tetrahedron* **1987**, *43*, 5621–5635
- [148] Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268–3272
- [149] Rony, P. R. *J. Am. Chem. Soc.* **1969**, *91*, 6090–6096
- [150] Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369–2376
- [151] Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106
- [152] Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12036–12040
- [153] a) Yamamoto, Y.; Furuta, T. *Chem. Lett.* **1989**, *18*, 797–800; b) Szemes, F.; Rybár, A.; Uhrín, D.; Solčániová, E. *Chem. Pap.* **1991**, *45*, 667–675; c) Falcone, B. V.; Creighton, C. J.; Parker, M. H.; Reitz, A. B. *Synth. Commun.* **2008**, *38*, 411–418
- [154] a) Koizumi, Y.; Kobayashi, H.; Wakimoto, T.; Furuta, T.; Fukuyama, T.; Kan, T. *J. Am. Chem. Soc.* **2008**, *130*, 16854–16855; b) Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383–2388
- [155] a) David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4373–4375; b) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Org. Chem.* **2002**, *67*, 4993–4996; c) Parkhouse, S. M.; Garnett, M. C.; Chan, W. C. *Bioorg. Med. Chem.* **2008**, *16*, 6641–6650; d) Carroll, L.; Boldon, S.; Bejot, R.; Moore, J. E.; Declerck, J.; Gouverneur, V. *Org. Biomol. Chem.* **2011**, *9*, 136–140
- [156] Dang, H.-S.; Diart, V.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1033–1041
- [157] Schultz, A. G.; Dai, M. *Tetrahedron Lett.* **1999**, *40*, 645–648
- [158] a) Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Heterocycles* **1991**, *32*, 685–692; b) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. L.; Tester, J. W. *Org. Biomol. Chem.* **2005**, *3*, 3767–3781
- [159] Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935–5938
- [160] For a review, see Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. In *Org. React.* 2004; Vol. 62, p 1, , and references cited within

-
- [161] a) Kam, T.-S.; Yoganathan, K.; Chuah, C.-H. *Tetrahedron Lett.* **1994**, 35, 4457–4460; b) Kam, T.-S.; Yoganathan, K.; Wei, C. *J. Nat. Prod.* **1996**, 59, 1109–1112
- [162] Lim, S.-H.; Sim, K.-M.; Abdullah, Z.; Hiraku, O.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, 70, 1380–1383
- [163] a) Kinoshita, H.; Ohnuma, T.; Oishi, T.; Ban, Y. *Chem. Lett.* **1986**, 15, 927–930; b) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, 74, 6035–6041; c) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, 50, 4790–4796
- [164] a) Magnus, P.; Brown, P. *J. Chem. Soc. Chem. Commun.* **1985**, 184–186; b) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.-i.; Yamamoto, Y.; Tomioka, K. *Chem. Asian J.* **2012**, 7, 2196–2198; c) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.-i.; Yamamoto, Y.; Tomioka, K. *Tetrahedron* **2013**, 69, 3264–3273; d) Xie, J.; Wolfe, A. L.; Boger, D. L. *Org. Lett.* **2013**, 15, 868–870
- [165] Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, 105, 2086–2087
- [166] Kam, T.-S.; Lim, T.-M.; Tan, G.-H. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1594–1604
- [167] Subramaniam, G.; Kam, T. S. *Helv. Chim. Acta* **2008**, 91, 930–937
- [168] a) Kam, T.-S.; Lim, T.-M.; Choo, Y.-M. *Tetrahedron* **1999**, 55, 1457–1468; b) Hájíček, J. *Collect. Czechoslov. Chem. Commun.* **2007**, 72, 821–898; c) Lim, K.-H.; Low, Y.-Y.; Tan, G.-H.; Kam, T.-S.; Lim, T.-M. *Helv. Chim. Acta* **2008**, 91, 1559–1566
- [169] Preparation of Taxol and Docetaxel Through Primary Amines. Patent, WO9623780 (A1), 1996
- [170] Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, 67, 5269–5278
- [171] Stetter, H.; Schreckenber, M. *Angew. Chem. Int. Ed.* **1973**, 12, 81–81
- [172] Lemièr, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhiman, A. L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, 131, 2993–3006
- [173] Duvvuru, D.; Betzer, J.-E.; Retailleau, P.; Frison, G.; Marinetti, A. *Adv. Synth. Catal.* **2011**, 353, 483–493
- [174] Crout, D. H. G.; Gaudet, V. S. B.; Hallinan, K. O. *J. Chem. Soc. Perkin Trans. 1* **1993**, 805–812
- [175] a) Boland, W.; Niedermeyer, U.; Jaenicke, L. *Helv. Chim. Acta* **1985**, 68, 2062–2073; b) Häbich, D.; Hartwig, W. *Tetrahedron Lett.* **1987**, 28, 781–784; c) Van der Eycken, J.; Vandewalle, M.; Heinemann, G.; Laumen, K.; Schneider, M. P.; Kredel, J.; Sauer, J. *J. Chem. Soc. Chem.*

Commun. **1989**, 306–308; d) Kocienski, P.; Stocks, M.; Donald, D.; Perry, M. *Synlett* **1990**, 1, 38–39; e) Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J.; Buendia, J. *Tetrahedron Lett.* **1992**, 33, 4889–4892

[176] a) Gais, H. J.; Buelow, G.; Zatorski, A.; Jentsch, M.; Maidonis, P.; Hemmerle, H. *J. Org. Chem.* **1989**, 54, 5115–5122; b) Rosenquist, A. s.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B.; Kady, M. M.; Christensen, S. B. g. *Acta Chem. Scand.* **1992**, 46, 1127–1129; c) Renold, P.; Tamm, C. *Tetrahedron Asymmetry* **1993**, 4, 1047–1050

[177] Piel, J.; Boland, W. *Tetrahedron Lett.* **1997**, 38, 6387–6390

[178] Hiyama, T.; Minami, T.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1995**, 68, 364–372

[179] a) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, 56, 417–420; b) Maeda, H.; Kraus, G. a. *J. Org. Chem.* **1996**, 61, 2986–2987

[180] Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 13, 1389–1392

[181] Mahadevegowda, S. H.; Khan, F. A. *Tetrahedron* **2013**, 69, 8494–8504

[182] Trost, B. M.; Miege, F. *J. Am. Chem. Soc.* **2014**, 136, 3016–3019

[183] a) Gutman, A. L.; Boltanski, A. *J. Chem. Soc. Perkin Trans. 1* **1989**, 47–49; b) Homer, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, 120, 7738–7748; c) Candy, M.; Tomas, L.; Parat, S.; Heran, V.; Bienaymé, H.; Pons, J. M.; Bressy, C. *Chem. Eur. J.* **2012**, 18, 14267–14271

[184] a) Bartlett, P. a.; Johnson, C. R. *J. Am. Chem. Soc.* **1985**, 107, 7792–7793; b) Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.* **1985**, 28, 1847–1853; c) De Meijere, A.; Bagutski, V.; Zeuner, F.; Fischer, U. K.; Rheinberger, V.; Moszner, N. *Eur. J. Org. Chem.* **2004**, 3669–3678

[185] D’Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, 61, 4870–4871

[186] Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1985**, 63, 127

[187] Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, 13, 5924–5927

[188] Guo, H.; Kim, C. U.; Lee, I. Y.; Mitchell, M. L.; Rhodes, G.; Son, J. C.; Xu, L. Novel HIV reverse transcriptase inhibitors. Patent, WO2009005674 (A2), 2009

[189] Galopin, C. C. *Tetrahedron Lett.* **2001**, 42, 5589–5591

[190] Novák, L.; Rohály, J.; Gálik, G.; Fekete, J.; Varjas, L.; Szántay, C. *Liebigs Ann. der Chemie*

1986, 509–524

[191] Riss, P. J.; Kroll, C.; Nagel, V.; Rösch, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5364–5367; See also Flitsch, W.; Rußkamp, P. *Liebigs Ann. der Chemie* **1985**, 1398–1412

[192] Grewer, C.; Madani Mobarekeh, S. A.; Watzke, N.; Rauen, T.; Schaper, K. *Biochemistry* **2001**, *40*, 232–240

[193] For a review, see Kira, M.; Iwamoto, T. In *Chem. Org. Silicon Compd.* Rappoport, Z., Apeloig, Y., Eds.; John Wiley & Sons, Ltd: 2001; Vol. 3; Chapter 16, pp 0–471, and references cited within

[194] a) Tishkov, A. A.; Dilman, A. D.; Faustov, V. I.; Birukov, A. A.; Lysenko, K. S.; Belyakov, P. A.; Ioffe, S. L.; Strelenko, Y. A.; Antipin, M. Y. *J. Am. Chem. Soc.* **2002**, *124*, 11358–11367; b) Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Russ. Chem. Bull.* **1996**, *45*, 856–862; c) Dilman, A. D.; Lyapkalo, I. M.; Belyakov, P. A.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2000**, *49*, 1649–1650

[195] Craig, R. Synthesis of Electron-Poor tetrasubstituted olefins and their reactions with electron-rich comonomers., Ph.D. Thesis, University of Arizona, 1982

[196] a) Nader, F. W.; Brecht, A.; Kreisz, S. *Chem. Ber.* **1986**, *119*, 1208–1216; b) Ianni, A.; Waldvogel, S. R. *Synthesis* **2006**, *38*, 2103–2112

[197] a) Nagano, T.; Kobayashi, S. *Chem. Lett.* **2008**, *37*, 1042–1043; b) Moriyama, K.; Take-mura, M.; Togo, H. *Org. Lett.* **2012**, *14*, 2414–2417

[198] a) Rakufs, K.; Verevkin, S. P.; Keller, M.; Beckhaus, H.-D.; Rüchardt, C. *Liebigs Ann.* **1995**, 1483–1493; b) Sylla, M.; Joseph, D.; Chevallier, E.; Camara, C.; Dumas, F. *Synthesis* **2006**, *38*, 1045–1049; c) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804; d) Mukherjee, H.; Martinez, C. A. *ACS Catal.* **2011**, *1*, 1010–1013; e) Yu, J.; Li, N.; Chen, D.-F.; Luo, S.-W. *Tetrahedron Lett.* **2014**, *55*, 2859–2864

[199] a) Cai, X.; Liu, Z.; Yang, Z. *Huaxue Yanjiu* **2006**, *17*, 41–43; b) Sal'keeva, L. K.; Taishibekova, E. K.; Minaeva, E. V.; Shibaeva, a. K.; Kasenov, R. Z.; Sal'keeva, a. K.; Muratbekova, a. a. *Russ. J. Gen. Chem.* **2013**, *83*, 659–662

[200] Mase, N.; Horibe, T. *Org. Lett.* **2013**, *15*, 1854–1857

[201] Thirupathi, G.; Venkatanarayana, M.; Dubey, P. K.; Kumari, Y. B. *Org. Chem. Int.* **2012**, 191584

[202] See, *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; John Wiley & Sons, Ltd: 2009

- [203] See Yang, X.; Ma, S.; Du, Y.; Tao, Y. *Chinese J. Org. Chem.* **2013**, *33*, 2325
- [204] a) Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* **2006**, *71*, 6130–6134; b) Amatore, M.; Gosmini, C. *Synlett* **2009**, *20*, 1073–1076
- [205] Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050
- [206] a) Ito, H.; Yamanaka, H.; Tateiwa, J.-i.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825; b) Mun, S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887–4889; c) Chea, H.; Sim, H. S.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855–858; d) Thorpe, S. B.; Calderone, J. A.; Santos, W. L. *Org. Lett.* **2012**, *14*, 1918–1921; e) Stavber, G.; Časar, Z. *Appl. Organomet. Chem.* **2013**, *27*, 159–165
- [207] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520
- [208] Still, W.; Kahn, M. *J. Org. Chem.* **1978**, *43*, 2923–2925
- [209] Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220
- [210] Patil, S.; Chen, L.; Tanko, J. M. *Tetrahedron Lett.* **2014**, *55*, 7029–7033
- [211] Macleod, F.; Lang, S.; Murphy, J. A. *Synlett* **2010**, *21*, 529–534
- [212] Lee, S.; Lim, H.-J.; Cha, K. L.; Sulikowski, G. A. *Tetrahedron* **1997**, *53*, 16521–16532
- [213] Kang, S.; Shi, Q.; Ha, M. W.; Ku, J.-M.; Cheng, M.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *Tetrahedron* **2010**, *66*, 4326–4329
- [214] Goetz, F. J.; Hirsch, J. A.; Augustine, R. L. *J. Org. Chem.* **1983**, *48*, 2468–2472
- [215] Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695–2698
- [216] Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. *Synlett* **2009**, *20*, 2997–2999
- [217] Adams, R. S.; Calderwood, E. F.; Gould, A. E.; Greenspan, P. D.; Lamarche, M. J.; Tian, Y.; Vos, T. J. Cinnamide and hydrocinnamide derivatives with kinase inhibitory activity. US Patent Application Publication, US2006160803 (A1) (US), 2006
- [218] a) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8412–8415; b) Cherkasov, A. R.; Galkin, V. I.; Sibgatullin, I. M.; Khusainova, N. G.; Zyablikova, T. A.; Buzykin, B. I.; Cherkasov, R. A. *Russ. J. Gen. Chem.* **2001**, *71*, 343–347; c) Galvez-Ruano, E.; Bellanato, J.; Fernandez-Ibañez, M.; Sainz-Diaz, C.; Arias-Perez, M. *J. Mol. Struct.* **1986**, *142*, 397–402

-
- [219] Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fettingner, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 2062–2065
- [220] Martyres, D. H.; Baldwin, J. E.; Adlington, R. M.; Lee, V.; Probert, M. R.; Watkin, D. J. *Tetrahedron* **2001**, *57*, 4999–5007
- [221] Nagano, H.; Kuwahara, R.; Yokoyama, F. *Tetrahedron* **2007**, *63*, 8810–8814
- [222] Jaegli, S. Approche vers la synthèse d'analogues de la Rustmicine et nouvelles voies d'accès à des spiro-oxindoles par réactions domino palladocatalysées., Ph.D. Thesis, Paris Sud XI, 2008
- [223] Xu, S.; Chen, R.; He, Z. *J. Org. Chem.* **2011**, *76*, 7528–7538
- [224] Kikani, B. B.; Mckee, J. R.; Zanger, M. *Synthesis* **1991**, *23*, 176–176
- [225] Reimann, E.; Poeschl, K. *Pharmazie* **1995**, *50*, 589–592
- [226] The chiral ligand used for enantioselective 1,4 additions on cyclopentenone was kindly provided by Professor Alexakis (Geneva University).
- [227] Yamashita, S.; Iso, K.; Hiramata, M. *Org. Lett.* **2008**, *10*, 3413–3415
- [228] Chow, C. P.; Shea, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 3678–3679
- [229] Busacca, C. A.; Farber, E.; Deyoung, J.; Campbell, S.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Lee, H.; Ma, S.; Reeves, D.; Shen, S.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5594–5597
- [230] Milas, N. A.; Terry, E. M. *J. Am. Chem. Soc.* **1925**, *47*, 1412–1418
- [231] Dinca, E.; Hartmann, P.; Smrček, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, 4461–4482
- [232] de Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V.; Evidente, A.; Piccialli, G. *J. Org. Chem.* **2000**, *65*, 3432–3442
- [233] Shi, D. D.; Trigo, F. F.; Semmelhack, M. E.; Wang, S. S.-H. *J. Am. Chem. Soc.* **2014**, *136*, 1976–1981
- [234] Casida, J. E.; Gulevich, A. G.; Sarpong, R.; Bunelle, E. M. *Bioorg. Med. Chem.* **2010**, *18*, 1942–1947
- [235] Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143–2146

Notes and Bibliography

- [236] Kothari, A.; Qureshi, M. K. N.; Beck, E. M.; Smith, M. D. *Chem. Commun.* **2007**, 2814–2816
- [237] Gypser, A.; Peterek, M.; Scharf, H.-D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1013–1016
- [238] Pagar, V. V.; Jadhav, A. M.; Liu, R. S. *J. Am. Chem. Soc.* **2011**, 133, 20728–20731
- [239] Le, W.-J.; Lu, H.-F.; Zhou, J.-T.; Cheng, H.-L.; Gao, Y.-H. *Tetrahedron Lett.* **2013**, 54, 5370–5373
- [240] Catalyst **416** was prepared by adding dry ice into a solution of piperidine (5.0 mL) in Et₂O (10 mL). The catalyst precipitated and was filtered off, washed with Et₂O and dried.

Olivier WAGNIÈRES

Organic Chemist

Chemin des Avelines 12 03.04.1987
CH-1004 Lausanne Swiss
Switzerland olivier.wagnieres@epfl.ch
+41 (0) 794736317

EDUCATION

- PhD Candidate in Organic synthesis** 2011! 2015
Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Laboratory of Synthesis and Natural Products (LSPN)
PhD Advisor: Prof. Jieping ZHU
- M.S. in Molecular and Biological Chemistry** 2009! 2011
Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Grade average: **5.63/6** (Ranking: 2nd over 33 students)
Thesis topic: *Exploiting new organometallic chemistry and reactivity for N-Heterocycles* (achieved **6/6**)
Thesis Advisor: Professor Timothy C. Gallagher (University of Bristol)
- B.S. in Chemistry** 2005! 2009
Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Grade average: **5.53/6**

PUBLICATIONS

- Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.*, **2014**, 136(42), 15102-15108
- Sarkar, R.; Ahuja, P.; Vasos, P. R.; Bornet, A.; Wagnières, O.; Bodenhause, G. *Progress in Nuclear Magnetic Resonance Spectroscopy*, **2010**, 51(1), 83-90

AWARDS

Runner up for the Best Oral Presentation (Organic Chemistry Session) at the Fall Meeting of the Swiss Chemical Society 2014

SYMPOSIUMS AND SUMMER SCHOOLS

- | | |
|---|------------|
| Fall Meeting of the Swiss Chemical Society 2014, Lausanne, Switzerland
Oral Presentation (Runner up Prize) | 09.2014 |
| Belgian Organic Synthesis Symposium 2014, Louvain-La-Neuve, Belgium
Poster Presentation | 06.2014 |
| Fall Meeting of the Swiss Chemical Society 2013, Lausanne, Switzerland
Poster Presentation | 09.2013 |
| Swiss Summer School 2013 - Synthesis & Catalysis, Villars, Switzerland
-Poster Presentation | 08.2013 |
| Fall Meeting of the Swiss Chemical Society 2011, Lausanne, Switzerland | 09.2011 |
| CUSO Summer School 2011 - Challenges in Organic Chemistry, Villars, Switzerland | 08-09.2011 |

TEACHING, EMPLOYMENT & INTERNSHIP

- Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland 2011-2014
- Teaching duties**
659 hours of teaching done during my PhD, Including:
- Supervision for Master Thesis
 - Class exercises preparation and following corrections for students from bachelor to master level.
 - Practical course for 1st and 2nd year Bachelor as well as 1st year Master.
 - Preparation, supervision and correction of the exams for bachelor classes.

Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Internship in the Laboratory of Biomolecular Magnetic Resonance

Summer 2009

- Studies of molecules in Long-lived coherence state
- Helped in the development of the NMR sequence
- Development of Matlab program to analyze the results

Skills: analysis skills, Problem-solving skills, Informatics skills

Metaphysics SA, Ste-Croix, Switzerland

Summer 2008

Software Tester

- Debugging new fire-detection software

LANGUAGES

French	Mother language
English	Fluent (C1)
Chinese	Beginner (A2)
German	Basics
Italian	Basics

OTHER SKILLS

IT	Good experience in LATEX and Microsoft office. Basic skills in Matlab and Mathematica, C, C++ and Visual Basic
Technical	I was responsible of HPLC and GC/MS during my PhD for four years, including maintenance and simple reparation. I'm familiar with Gloveboxes, SFC, UPLC/MS and NMR.

INTERESTS

Game of Go	Good level (3 kyu); Ex-president of the Yverdon-les-Bains Go-club; Financial responsible of the EPFL Go-club.
Violin	5 years of daily practicing.
Sport	I practice hiking, swimming and occasionally jogging.