Synthesis of Indole Alkaloids and Development of New Methodology

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2019

Document Version:
Publisher's PDF, also known as Version of record

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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To be defended at lecture hall B, Kemicentrum. Date 12 april 2019 at 9.00.

Faculty opponent
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Organization LUND UNIVERSITY Centre for Analysis and Synthesis Department of Chemistry	Document name: Doctoral thesis Date of issue 2019-03-19
Author(s) Anita Hoang	Sponsoring organization

Title and subtitle

Synthesis of Indole Alkaloids and Development of New Methodology

Abstract

This thesis describes our efforts towards the total synthesis of natural products and the development of a new methodology to afford a synthetically important scaffold.

Chapter 2 outlines our efforts towards the total synthesis of a marine natural product, perophoramidine as well as our completed synthesis of dehaloperophoramidine. The focus of the studies was to develop an efficient and concise strategy to afford the natural products. We aimed at utilising the inherent structure and symmetry of the natural product to encourage domino processes and gain access to the key features. The vicinal quaternary stereocenters were installed by employing Overman's diastereoselective dialkylation protocol. Two new domino processes were discovered. The first domino process led to the formation of the *ortho*-amide and careful investigation of its reactivity led to the discovery of the second domino process which ultimately delivered dehaloperophoramidine. The synthesis was completed in eight steps starting from isoindigo.

Chapter 3 describes our efforts towards the total synthesis of strictamine. The key features of strictamine that need to be addressed when pursuing the synthesis are: (i) the quaternary stereocenter, (ii) the central cyclohexane moiety (D ring) with four stereocenters, and (iii) the cage-like methanoquinolizidine core. We aimed at accessing these key features through intramolecular Heck reaction to access the central D ring with parts of the substitution pattern already present and the quaternary stereocenter. For the methanoquinolizidine core, we planned to adopt our previously described domino carbopalladation/carbonylation protocol. The synthesis is in an advanced state with two additional functionalisation left in order to access the target compound. Described in this chapter is our effort to access the core structure of strictamine with all the rings installed.

The third part of this thesis deals with the development of a new methodology to access indoline scaffolds that feature an all-carbon quaternary stereocenter. We were able to synthesise allyl anilines through the regio- and stereoselective ring-opening of vinyl aziridines with 2-iodoaniline. The final indoline scaffold was furnished by intramolecular Heck reaction with concomitant formation of the quaternary stereocenter.

Key words

Total synthesis, indole alkaloids, domino reaction, vicinal quaternary stereocenters, quaternary stereocenter, indoline synthesis, communesin alkaloids, perophoramidine, dehaloperophoramidine, akuammiline alkaloids, strictamine, intramolecular Heck reactions, domino carbopalladation carbonylation, indoline synthesis, indoline alkaloids, indole alkaloids

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language: English
ISSN and key title		ISBN 978-91-7422-645-4 (Printed) ISBN 978-91-7422-646-1 (Digital)
Recipient's notes	Number of pages 160	Price
	Security classification	

Signature _____ Date _____

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Coverphoto by Graphicriver

Faculty of Science
Department of Chemistry
Centre for Analysis and Synthesis

ISBN 978-91-7422-645-4 (Printed)
ISBN 978-91-7422-646-1 (Digital)

Printed in Sweden by Media-Tryck, Lund University
Lund 2019

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MADE IN SWEDEN

To my loving parents

Thank you for always believing in me

Table of Contents

Popular summary

Natural products are compounds that exist naturally in living organisms, *e.g.*, plants, animal and fungi. These compounds are likely biologically active and can be used as pharmaceuticals for various diseases. Evolution has made it possible for living organisms to produce these natural products as a defence mechanism against various threats. In most cases, the organism only produces a small amount of the natural product in question which makes it very difficult to get hold of a reasonable amount to study, and even more so if we would like to use it as a medicine. Furthermore, most natural products have a very complex three-dimensional structure. The complexity of these molecules makes it very difficult to synthesise them efficiently and have therefore enticed the synthetic organic community. Besides the optimal goal of accessing the natural products, method development can also lead to drug candidates with higher selectivity which ultimately means that we can use less of a drug and experience much fewer side effects. Our research interest is to develop strategies and methodologies and implement them on the syntheses of natural products. In this thesis, we have explored several strategies towards total syntheses of natural products as well as working with method development.

The first part describes our efforts towards the total synthesis of perophoramidine and its synthetic analogue, dehaloperophoramidine. Perophoramidine can be found in a marine ascidian that is native to the south Pacific ocean. We wanted to utilise the inherent structure and symmetry of the natural product in our planning to maximize the likelihood of reactions leading to so-called "domino processes". We then applied this strategy to the synthesis of perophoramidine and dehaloperophoramidine, the latter with great success. We successfully made dehaloperophoramidine in eight steps starting from isoindigo, a compound that can be easily accessed.

The second part outlines our efforts towards the total synthesis of strictamine, which is an alkaloid that can be isolated from the leaves of the *Rhazya stricta* plant. The complexity of this natural product is ascribed to the highly congested polycyclic structure. We intended to adopt a methodology that was previously disclosed in our group to construct the complex ring system found in strictamine. The synthesis is currently at an advanced state. The core structure of strictamine was established and to complete the synthesis, two additional steps are required.

The third part of this thesis deals with the development of a new methodology to access important scaffolds, indolines, that can be used in the synthesis of natural products. The indoline scaffolds are reoccurring in natural products, and many of of which have pharmaceutical properties. We were interested in synthesising indoline scaffolds that have an all-carbon quaternary stereocenter.

List of papers

This thesis is based on the following papers that will be referred to by roman numerals I-IV

I. **Concise total synthesis of dehaloperophoramidine**

Kirill Popov, Anita Hoang and Peter Somfai

Angew. Chem. Int. Ed. **2016**, *55*, 1801-1804.

I performed part of the experimental work and contributed to solving the research problems

II. **An efficient total synthesis of (±)-dehaloperophoramidine**

Anita Hoang, Kirill Popov and Peter Somfai

J. Org. Chem. **2017**, *82*, 2171-2176

I performed part of the experimental work, contributed to solving the research problems and wrote the manuscript

III. **Synthetic studies towards total synthesis of strictamine**

Anita Hoang and Peter Somfai

In Manuscript

I performed all the experimental work, contributed to solving the research problems and wrote the manuscript

IV. **Rapid construction of indoline scaffolds featuring an all-carbon quaternary stereocenter**

Anita Hoang and Peter Somfai

In Manuscript

I performed all the experimental work, contributed to solving the research problems and wrote the manuscript

Abbreviations

Bn	Benzyl
Brsm	Based on recovered starting material
COD	1,5-cyclooctadiene
d.r.	Diastereomeric ratio
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibensylidineacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAl-H	Diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-Dimethylaminopyridine
e.r.	Enantiomeric ratio
HMDS	Hexamethyldisilazane
MS	Molecular sieves
NMO	4-methylmorpholine *N*-oxide
Nu	Nucleophile
PMB	*p*-methoxybenzyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Ts	Tosyl

1 Introduction

1.1 Organic Synthesis – From Vitalism to Ideal Synthesis

The origin of life on earth is still not completely demystified. What we do know is that chemistry played a crucial role in creating life.[1] In the early days of earth history, millions chemical reactions occurred and in the event formed large organic compounds that are crucial for life as we know it. Organic chemistry is a big part of our life. Countless organic reactions occur in our body every minute to maintain our living body. In fact, organic chemistry is so essential to life that the pioneer in organic chemistry believed that organic compounds could only be produced by living organisms through "vital force" and are distinguished from inorganic compounds.[2] It would soon be discovered that organic compounds made in the laboratory are no different from organic compounds found in living organisms. The discovery by Friedrich Wöhler in 1828, when he inadvertently synthesise urea from inorganic starting material (silver cyanate and ammonium chloride), is widely accepted as the starting point of organic synthesis.[3] The realisation that organic materials can be made in the laboratory is one of the first steps towards the modern society we know today. The fruits of organic synthesis affects our daily life in a myriad of ways: new materials such as plastics, high-tech materials for computers, perfumes, new drugs to cure our diseases and much more.[4-5]

Organic synthesis can be widely divided into two area, total synthesis, and methodology development. Total synthesis is the chemical synthesis of a complex organic compound through rational combination of chemical reactions starting from commercial starting materials or simple natural compounds.[6] The organic compound in question are most often found in nature. The aim of total synthesis varies for the individual researcher; however, three main motivations are occurring. The motivations can be: (i) the need of confirming the correct structure of a complex molecule, (ii) development of new methodologies by design or serendipity, (iii) providing reasonable amount of the natural product for biological activity studies. The synthesis of a bioactive compound also gives the opportunity to modify some part of the molecule. This, in turn, can give insight into the toxicology, pharmacology, and elucidation of the biochemical and metabolic pathways. The result can be an effective drug with the least secondary effect. For

total synthesis to be fruitful and successful, it requires a repertoire of equally excellent and efficient reactions methods. The second area of organic synthesis is, therefore, the method development that focuses on development of novel and increasingly efficient reactions. Both areas are therefore highly synergistic and complementary.

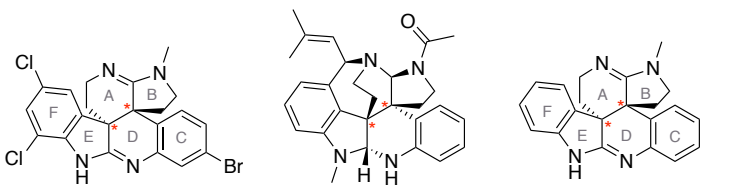
The area of organic synthesis has developed immensely since the 60s. With the toolbox and knowledge that we have today, the synthetic chemist can construct more or less any degree of structural complexity. However, there are no doubts that mother nature does syntheses much more efficient and more environmentally friendly. In fact, many of the drugs we use today are now made semi-synthetically from natural sources or by fermentations. Numerous elegant total syntheses are deemed too complicated to be useful in the pharmaceutical industry. The challenges that the synthetic community must face are the demands of providing large quantities of the desired compound in the least amount of labour and material expenses. In response to the challenges, the synthetic community must aim towards designing efficient synthetic routes and pursue the "ideal synthesis," a term first introduced by Hendrickson in 1975 where he defined it as:[7]

> "… creates a complex molecule …in a sequence of only construction reactions involving no intermediary refunctionalization, and leading directly to the target, not only its skeleton but also its correctly placed functionality."

With ideal synthesis, we are aiming to include as much constructive reactions (construction of carbon-carbon or carbon-heteroatom bonds) and strategic redox reactions as possible and limit the amount of non-strategic redox reactions, functional group manipulations and protecting group manipulations. Scalability of the synthetic steps are equally important in order to address the needs of the pharmaceutical industry. Finally, it is highly important to address the environmental and safety aspect of each synthetic steps.[8]

1.2 Studies towards perophoramidine and total synthesis of dehaloperophoramidine

Perophoramidine (**1.1**) is an indole alkaloid that exists naturally in the marine ascidian *Perophora Namei* and was first isolated by Ireland in 2002 (Figure 1.1).[9] Perophoramidine has displayed cytotoxicity against the HCT116 colon carcinoma cell line with an IC_{50} of 60 μM. The molecular architecture of perophoramidine is structurally related to the communesin alkaloids, *e.g.,* communesin F (**1.2**) found in the marine algae *Enteromorpha Intestinalis* (Figure 1.1). Communesin F has shown to exhibit insecticidal activity against instar silkworm larvae.[10] The structural similarity of perophoramidine and communesin F was initially suggested to rise from the biosynthetic origin with the former being derived from oxidative dimerization of two tryptamine units and the latter from tryptamine and aurantioclavine.[11] This notion was later confirmed by the characterization of the responsible gene cluster.[12] Although sharing similar carbon skeletal connectivity, perophoramidine exhibits halogenated aromatic rings, bis-amidine functionalities and vicinal quaternary stereocenters having *trans* relative stereochemistry. The communesin family adversely exhibits an additional azepine ring, bis-aminal functionalities and *cis* relative stereochemistry of the vicinal quaternary stereocenters. Dehaloperophoramidine (**1.3**) is the synthetic analogue of perophoramidine (**1.1**) lacking the aromatic halogens (Figure 1.1) and was first introduced in the original isolation paper. The aromatic halogens are removed through hydrogenation to provide dehaloperophoramidine.[9]



Perophoramidine (**1.1**) Communesin F (**1.2**) Dehaloperophoramidine (**1.3**)

Figure 1.1
Structure of perophoramidine, communesin F and dehaloperophoramidine

The structural motif of these alkaloids is indeed highly complex and for that reason also incited interest among synthetic chemist to pursue their total synthesis.[13-32] The most challenging motif to construct is undoubtedly the vicinal quaternary stereocenters. The construction of an all carbon quaternary stereocenter is already challenging due to the steric repulsion of the carbon substituents connecting to a centre carbon. On top of that, adding two all-carbon quaternary stereocenters next to each other and the necessity of constructing it asymmetrically further increase

the challenges. Several advances have surfaced in recent years and rely either on step-wise or simultaneous introduction of the vicinal quaternary stereocenters. From a strategic point of view, installation of the vicinal stereocenters simultaneously is the most attractive and also the most efficient procedure.[33-44]

The formidable synthetic challenges in combination with the intriguing molecular structure of perophoramidine and dehaloperophoramidine have made us interested in pursuing the total syntheses of these alkaloids. Chapter 2 outline our efforts towards total synthesis of perophoramidine and our completed synthesis of dehaloperophoramidine.

1.3 Studies towards total synthesis of strictamine

The akuammiline alkaloids are a large family of indole alkaloids that have been studied for over a century.[45] Akuammiline alkaloids can be found in plants in the south, and south-eastern Asia and inhabitants of this area have utilised plants such as *Alstonia scholaris* in traditional medicine to treat various illnesses.[46] The akuammiline alkaloids have shown to be biologically active in preliminary studies. It was found that members of this family have displayed anticancer[47-49], anti-inflammatory[50-51] and antimalarial activies[52] among others.[46, 53-56] In addition to their interesting biological properties, the intriguing molecular architecture of akuammiline alkaloids have also caught the attention of the synthetic community.[45, 57-60]

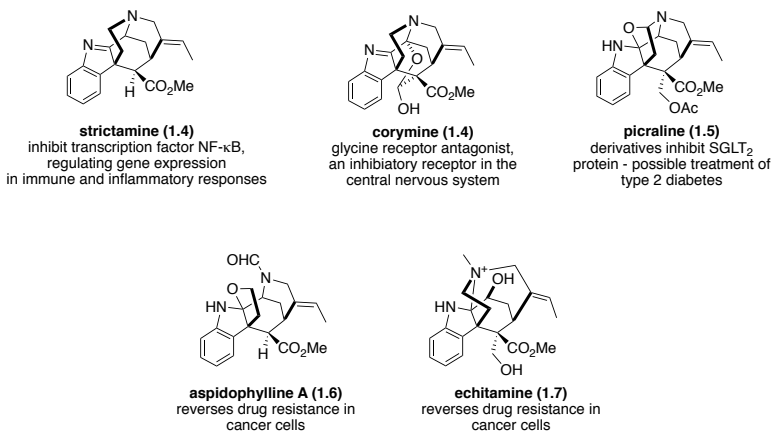


Figure 1.2
Structure of akuammiline alkaloids and their biological properties

The akuammiline alkaloids exhibit a rigid and cage-like framework that makes the total syntheses of these alkaloids challenging. There are approximately 30 known members that are fully characterised and isolated. The structural diversity of these members are mainly associated with substitution pattern on the central cyclohexane moiety. Several akuammiline alkaloids are outline in Figure 1.2

Strictamine (**1.4**) is member of the akuammiline alkaloids and was isolated in 1966 from leaves of *Rhazya Stricta.* Studies have shown that strictamine (**1.4**) displays inhibitory activity against transcription factor NF-κB important to inflammatory responses.[56, 61] Prominent structural features of strictamine are: (i) the cage-like methanoquinolizidine core, (ii) the central cyclohexane moiety with four stereocenters, where one of them is an all-carbon quaternary stereocenter, and (iii) the *E*-configured ethylidene substituent. These features are the main concern when designing a strategy towards the total synthesis.

Chapter 3 outlines our efforts to synthesise the hexacyclic core of strictamine by employing an intramolecular Heck reaction to construct the dihydrocarbazole motif and the quaternary stereocenter. Included is also our investigation of constructing the methanoquinolizidine core through a domino carbopalladation/carbonylation process

1.4 Method development for indoline scaffolds containing a quaternary stereocenter

Method development of important structural scaffolds is a fundamental research topic. The scaffolds can be used as building blocks in synthesis of biologically active and structurally interesting natural products. Its synergistic and complementary relation to total synthesis is the reason why synthetic research groups most often study both areas. Method development is crucial in cases where a specific transformation has no known methodology to rely on, or in cases where the existing methods are not suitable for the synthesis. In our case, we needed a method to rapidly construct indoline scaffolds that feature a quaternary stereocenter. Synthesis of indoline scaffolds that features a C3 all-carbon quaternary stereocenter exhibit a particular synthetic challenge due to steric reasons.[33, 62] Although many methods exist for synthesising indolines,[63-66] there are only a few protocols to install the quaternary stereocenter, and several of them involve intermediates such as 3-substituted indoles[64, 67-78] and 3,3-disubstituted oxindole.[79-82]. The interrupted Fischer indole synthesis starting from phenylhydrazines and aldehyde surrogates or ketones can give a direct access to such scaffolds. However, this protocol generally furnishes fused indoline

scaffolds.[83-84] We aimed to develop an efficient methodology to construct indoline scaffolds containing a quaternary stereocenter.

Chapter 4 describes our development of a new methodology to access indoline scaffolds that feature a quaternary stereocenter. The intramolecular Heck reaction was employed to construct the indoline scaffold with concomitant formation of the quaternary stereocenter.

1.5 Aim of the thesis

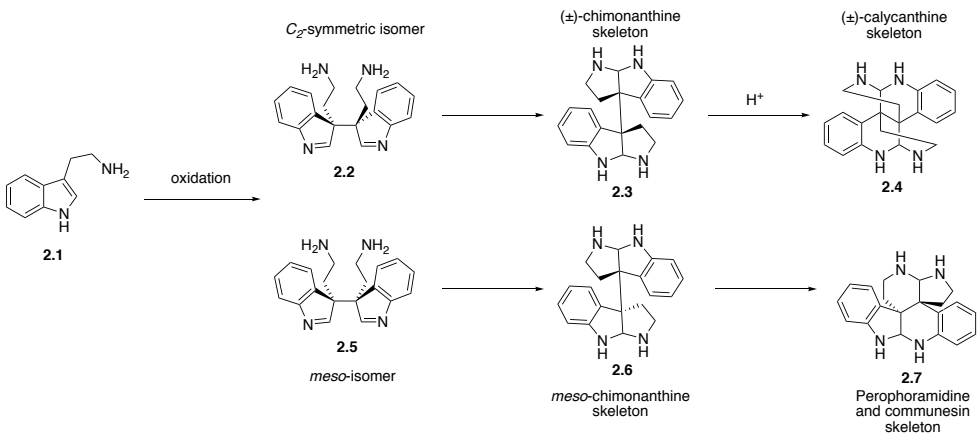
This thesis has several aims. Chapter 2 and 3 focus on the development of concise and efficient total syntheses of biologically active indole alkaloids through domino reactions and organometallic reactions. The aim of chapter 4 is to develop a methodology for the rapid construction of indoline scaffolds featuring quaternary stereocenter by adopting intramolecular Heck reaction.

2 Studies towards perophoramidine and total synthesis of dehaloperophoramidine

2.1 Background

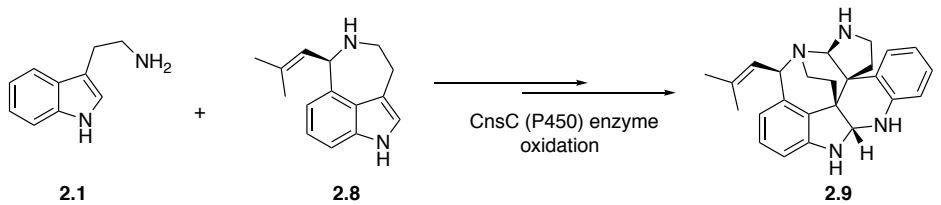
2.1.1 Biosynthesis

The skeletal arrangement of perophoramidine is shared by the calycanthaceous, chimonanthine and communesin family.[11] Natural products belonging to these families can be found in diverse sources, *e.g.*, in plants[85-87], animal[88], fungi[10], and marine organism.[9] This notion suggest a convergent evolution of these natural products which implies that these compounds are likely to be accessed by many organisms and is therefore an interesting target to study.



Scheme 2.1
Suggested biosynthesis of chimonanthine, calycanthine, perophoramidine and communesin family from oxidative dimerization of tryptamine[89]

It was suggested that the biosynthesis of chimonanthine, calycanthine, and perophoramidine involves dimerisation of two tryptamine (**2.1**) units[11] and indeed studies by Hendrickson[90] and Scott[91] supported this hypothesis (Scheme 2.1). The C_2-symmetric isomer **2.2** of the dimerised tryptamine would lead to the skeletal arrangement of (±)-chimonanthine **2.3** and (±)-calycanthine **2.4**[90] while the *meso*-isomer **2.5** would give rise to *meso*-chimonanthine **2.6,** perophoramidine and communesin skeleton **2.7**.[91] Interestingly, the biosynthesis of communesin alkaloids neither involve the C_2-symmetric isomer **2.2** or *meso*-isomer **2.5**. Instead it was suggested that core of communesin is formed through oxidative dimerisation of aurantioclavine (**2.8**)[92-94] and tryptamine (**2.1**).[11] This notion was later confirmed by genetic-inactivation studies (Scheme 2.2).[12] Important to note is that the relative diastereomeric relationship of the vicinal quaternary stereocenters of the communesin are more akin to the (±)-chimonathine which preferentially forms the connectivitiy found in calycanthine and not **2.7**. It appears that the azepine ring in aurantioclavine has bias the system towards formation of **2.9** with the skeletal arrangement related to the perophoramidine and the relative stereochemistry of vicinal quaternary stereocenters akin to the (±)-chimonathine.[11, 95-96]



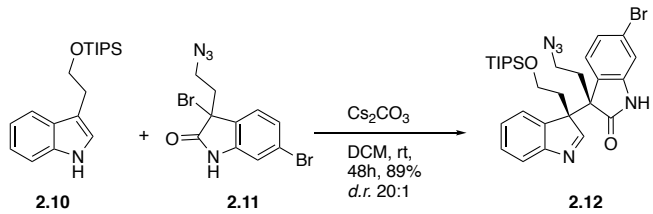
2.1 **2.8** **2.9**

Scheme 2.2
Oxidative dimerization of tryptamine and aurantioclavine catalysed by CnsC (P450) enzyme

2.1.2 State of the art – Total syntheses of perophoramidine and dehaloperophoramidine

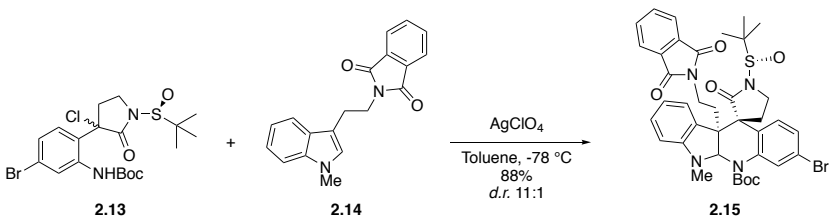
The intriguing molecular structure of perophoramidine in combination with shown biological activities has inspired many synthetic endeavours and has resulted in four total syntheses of perophoramidine[14, 28-31] (one racemic and three asymmetric) and three completed syntheses of dehaloperophoramidine[97-99]. Additionally, several synthetic studies have been reported.[13-27]

The first total synthesis of (±)-perophoramidine was reported by Fuchs and Funk in 2004.[29] The vicinal quaternary stereocenters was constructed simultaneously by employing a hetero Diels-Alder reaction with tryptophol **2.10** and bromo-oxindole **2.11** (Scheme 2.3). This approach was believed to be "biomimetic" as suggested by Stoltz.[11] The synthesis was completed in 14 steps and 4.7% overall yield with excellent diastereoselectivity.



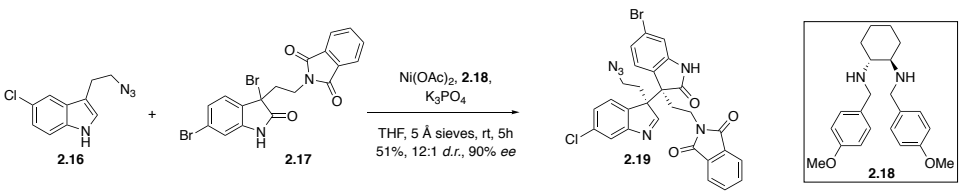
Scheme 2.3
Key step in installing the vicinal quaternary stereocenter by Fuchs and Funk

In 2010, Qin and co-workers reported the first asymmetrical total synthesis of (+)-perophoramidine.[30] The key step in this synthesis resembles the approach by Fuchs and Funk. An asymmetric hetero Diels-Alder reaction with lactam **2.13** protected with a chiral auxiliary and protected tryptamine **2.14** provided **2.15** in excellent diastereoselectivity (Scheme 2.4). The synthesis was accomplished in 17 steps and 11% overall yield and additionally aided the determination of the absolute configuration of (+)-perophoramidine.



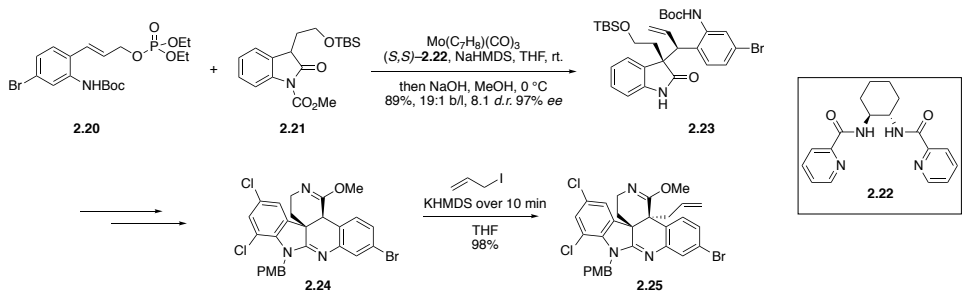
Scheme 2.4
Asymmetric hetero Diels-Alder approach to the vicinal quaternary stereocenter presented by Qin and co-workers

Wang and co-workers later presented their catalytic version of the biomimetic approach to forge the vicinal quaternary stereocenters.[31] They introduced a Ni-catalysed cycloaddition reaction using a chiral diamine ligand **2.18.** Addition of indole **2.16** to bromo-oxindole **2.17** furnished compound **2.19** in 51% yield, 12:1 d.r. and 90% *ee* (Scheme 2.5). To complete the synthesis, they use a total of 17 steps in 4.1% overall yield.



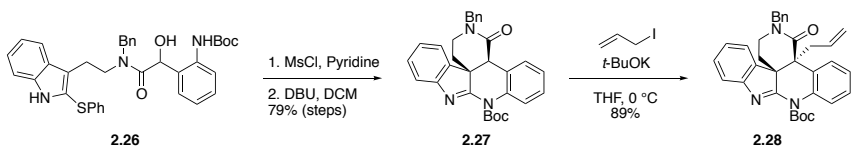
Scheme 2.5
Wang and co-workers catalytic biomimetic approach to install the vicinal quaternary stereocenters

The most recent completed total synthesis of (–)-perophoramidine was described by Trost and co-workers (Scheme 2.6).[28] Their strategy differs from previously reported syntheses in which they relied on Mo-catalysed asymmetric allylic alkylation (Mo-AAA) to form the vicinal quaternary stereocenters in a stepwise manner. The second of the vicinal quaternary stereocenters was installed by a stereoselective α-allylation of imidate **2.24**. Compound **2.25** was afforded by using KHMDS and allyl iodide.



Scheme 2.6
Mo-catalysed asymmetric allylic alkylation to form quaternary stereocenter presented by Trost and co-workers

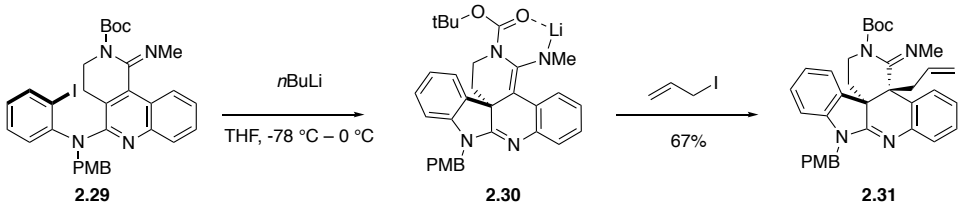
Rainier and co-workers[98] disclosed the total synthesis of (±)-dehaloperophoramidine where they employed their 2-thioindole spirocyclization methodology to afford one of the vicinal quaternary stereocenters (Scheme 2.7). Subsequent stereoselective α-allylation of the lactam delivered the vicinal quaternary stereocenters. The target compound was afforded after 18 steps and 7.5% overall yield.



Scheme 2.7
Rainer an co-workers approach to install quaternary stereocenters in their total synthesis of dehaloperophoramidine

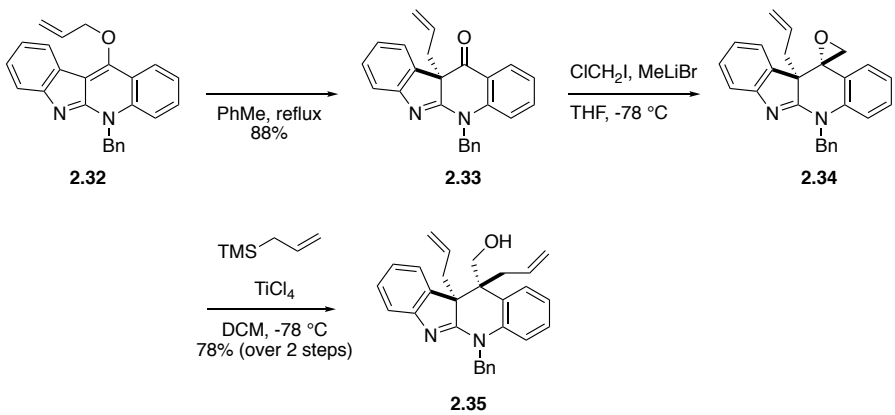
An efficient dearomatising conjugate addition-allylation strategy was presented by Takemoto and co-workers.[97] This unique approach delivered the vicinal quaternary stereocenters simultaneously. The reaction commenced with the *in situ* formation of the aryl anion followed by a conjugate addition. The final trapping of the azaenolate with allyl iodide delivered the second vicinal quaternary stereocenters diastereoselectively (Scheme 2.8). They rationalised that the observed stereoselectivity was due to the steric congestion around the concave face of the

lithium azaenolate **2.30**. Dehaloperophoramidine was synthesised in 17 steps and 9.4% overall yield by this approach.



Scheme 2.8
Dearomatizing conjugate addition-allylation strategy presented by Takemoto and co-workers

Westwood and co-workers reported the latest total synthesis of dehaloperophoramidine. They choose a stepwise approach to install the vicinal quaternary stereocenters. A [3,3]-Claisen rearrangement of vinyl ether **2.32** to allyl-ketone **2.33** delivered one of the vicinal stereocenters. The final quaternary stereocenters was achieved by a sequence of epoxidation and modified Hosomi-Sakurai reaction to afford compound **2.35** (Scheme 2.9). The total synthesis was completed in 23 steps.

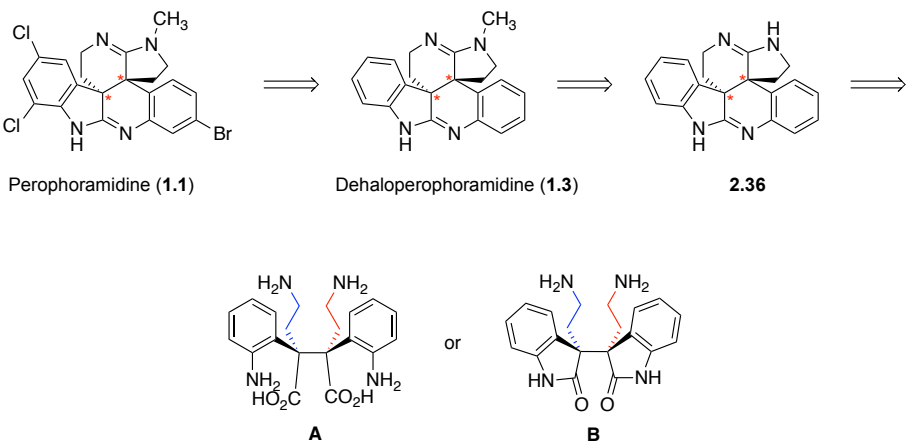


Scheme 2.9
Westwood's strategy to install the vicinal quaternary stereocenters

2.2 Structural and retrosynthetic analysis of perophoramidine and dehaloperophoramidine

The presented strategies demonstrate how synthetic challenges can encourage creative solutions. Four syntheses of perophoramidine have so far been described, and three of them rely on the biomimetic Diels-Alder reaction to install the vicinal quaternary stereocenters (*cf.* Scheme 2.3-2.5). In the case of dehaloperophoramidine, the approaches towards creating the vicinal quaternary stereocenters are more original and in several cases also shown to be highly efficient. The advantages of creating the vicinal stereocenters in a single operation can be seen in several cases and was also an approach that was most attractive to us.

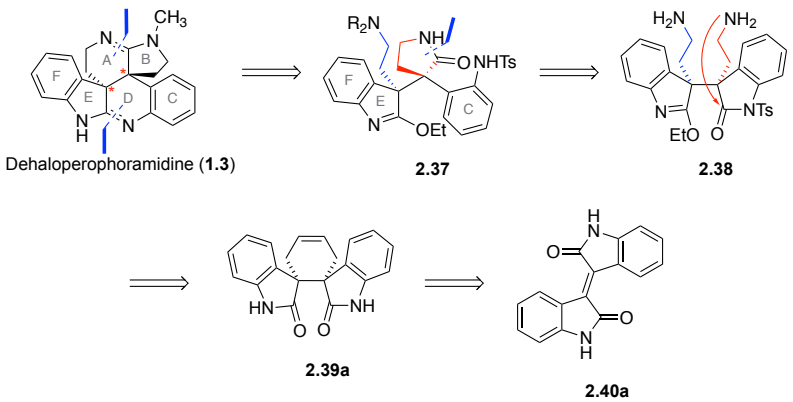
Several groups have taken inspiration from the biosynthesis of perophoramidine and created the vicinal quaternary stereocenter by mimicking nature. The intriguing biosynthesis of these natural products has also inspired us. The core structure of perophoramidine was suggested to arise from the dimerisation of two identical precursors which implies that there is a hidden symmetry element embedded in the structure.[100] Indeed, the latent symmetry element is revealed by disconnecting four C-N bonds in **2.36** resulting in σ-symmetric compound **A** or its synthetic equivalent bis-oxindole **B** (Scheme 2.10). We recognised this to be an excellent platform on to which continue our analysis.



Scheme 2.10
Disconnection of four C-N bonds in **2.36** reveals the latent symmetry of dehaloperophoramidine

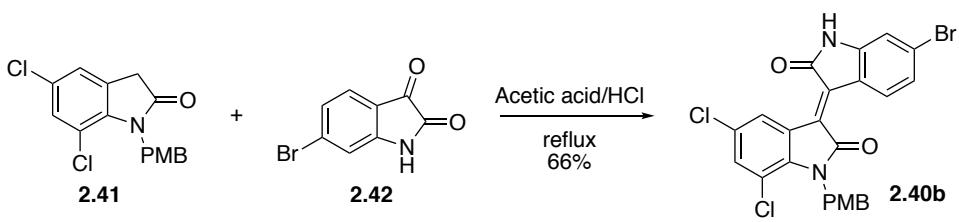
Our aim with this project was to develop an efficient route towards the hexacyclic core of perophoramidine and dehaloperophoramidine. We planned the

retrosynthesis for dehaloperophoramidine (**1.3**) in order the avoid any issue involving the halogens. Our retrosynthetic analysis was guided by the following critera: (i) introduce the vicinal quaternary stereocenters and all skeletal carbon of **1.1** and **1.3** at the beginning of the synthesis and (ii) install all necessary functional group in their correct oxidation state early in the sequence. With regards to these criteria, we then disconnected the upper A/B and lower E/D amidine to reveal lactam **2.37** (Scheme 2.11). For this compound, we appreciated that it could be derived from **2.38**, the synthetic equivalent of **B,** by kinetically controlled differentiation of the aminoethyl moieties.



Scheme 2.11
Retrosynthetic analysis of dehaloperophoramidine (**1.3**)

Compound **2.38** can be traced back to bis-oxindole **2.39a** in which the vicinal quaternary stereocenters should be accessible through Overman's diastereoselective dialkylation methodology on commercially available isoindigo **2.40a**.[40, 44] For perophoramidine (**1.1**), we planned to include the aromatic halogens at the beginning of the synthesis thus resulting our analysis to conclude with halogenated isoindigo **2.40b**, a product of condensation reaction between PMB protected 5,7-dichlorooxindole (**2.41**) and 6-bromoisatin (**2.42**)

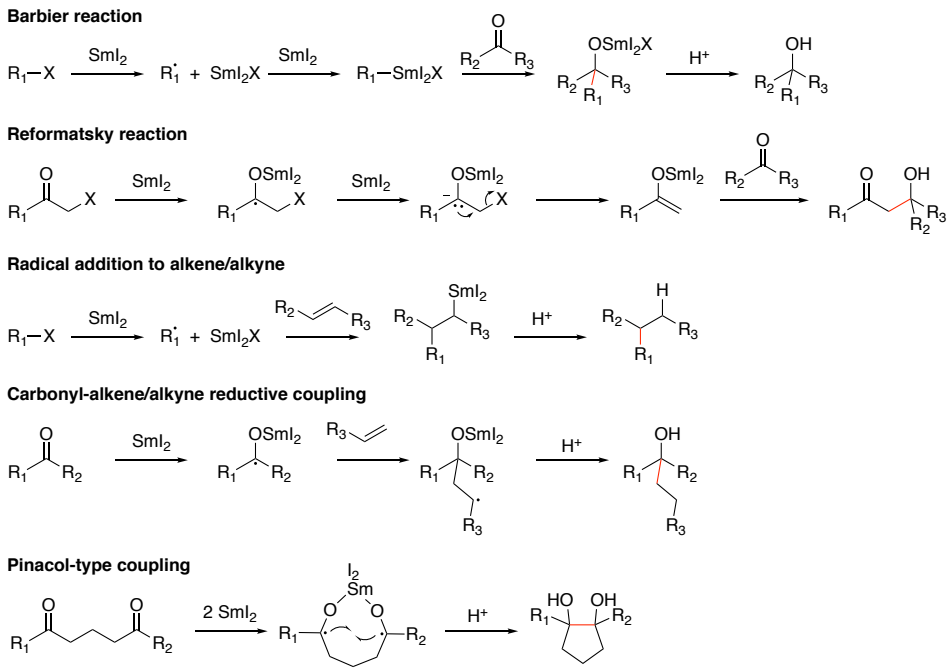


Scheme 2.12
Synthesis of dichloro-bromo-isoindigo **2.40b** by condensation of dichlorooxindole and bromoisatin

2.3 Installation of the vicinal quaternary stereocenters

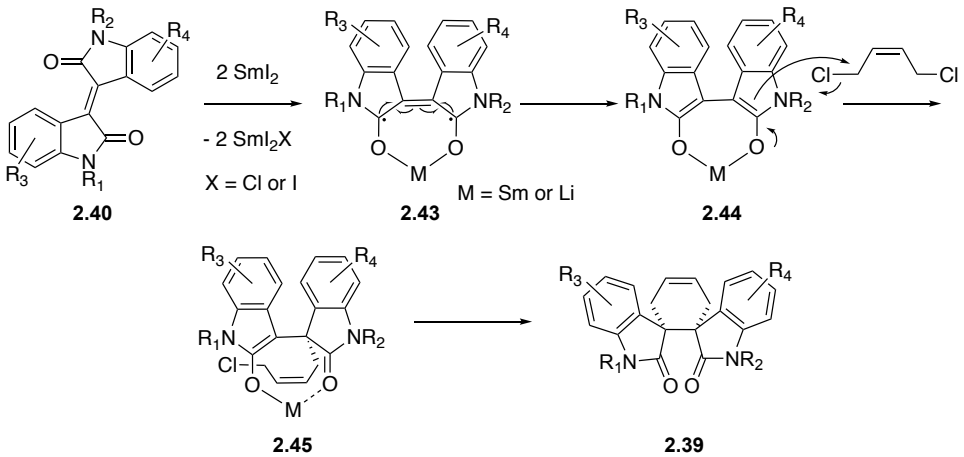
2.3.1 Samarium mediated reductive dialkylation

Samarium iodide (SmI_2) is a mild and selective one-electron reducing agent. It can participate in the reduction of halides, aldehydes, ketones, carboxylic acid and promote reductive eliminations and deoxygenation reactions. This reagent was introduced by Kagan and co-workers in 1977 where a convenient preparation method from samarium metal and diiodoethane in THF was also disclosed.[101-103] The concentration of SmI_2 prepared by this method is generally 0.1 M, and it is also commercially available. SmI_2 as a reducing agent is much more convenient to use compared to common reducing agents such as hydrogenation in Pd/C or active catalyst, alkali metals and hydrides which are highly pyrophoric. Since its introduction, several samarium-mediated reductive coupling and sequenced reaction have been developed, and new applications are steadily developed.[104-107] SmI_2 is an appreciated reducing agent owing to its property of selectively generating carbon centred radicals through a one-electron transfer process. It is therefore commonly adopted in carbon-carbon bond forming reactions (Scheme 2.13). For that reason, it is extensively adopted in natural product synthesis.[108-110]



Scheme 2.13
Samarium mediated carbon-carbon bond forming reactions

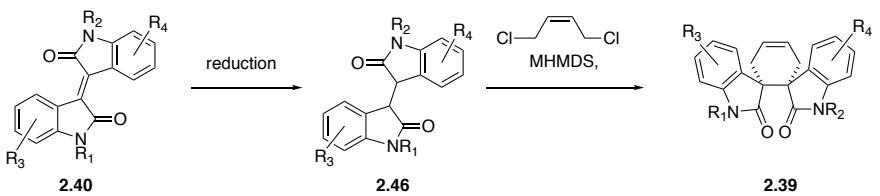
We were particularly interested in the samarium mediated reductive dialkylation of isoindigo to install the vicinal quaternary stereocenters. Through a one-electron transfer process, SmI_2 can generate dienolate **2.43** with the configuration locked by a chelating metal. The *cis*-1,4-dichloro butene adds to one face of the dienolate and the second alkylation must occur on the same face leading to the desired diastereoselectivity (Scheme 2.14).



Scheme 2.14
Mechanism of the samarium mediated reductive dialkylation

2.3.2 Diastereoselective dialkylation

For the perophoramidine isomer, there was an uncertainty if SmI_2 would be compatible with the aromatic halogens. Therefore, an alternative strategy to construct the stereocenters was planned. The vicinal quaternary stereocenters can also be introduced by dialkylation of the corresponding dihydroisoindigo with a chelating metal, *i.e.* LiHMDS, NaHMDS or KHMDS to control the diastereoselectivity (Scheme 2.15).



Scheme 2.15
Diastereoselective dialkylation using MHMDS, M=Li, Na or K

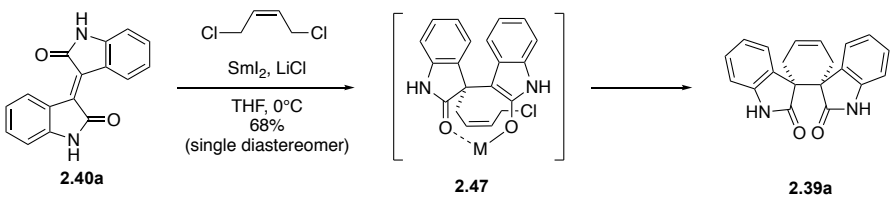
2.3.3 Aim of the project

The focus of this project was to investigate whether the samarium mediated reductive dialkylation reactions can be implemented to the synthesis of perophoramidine and dehaloperophoramidine. The ultimate goal was to access the vicinal quaternary stereocenters with the correct stereochemistry.

2.3.4 Results and Discussion

2.3.4.1 Dehaloperophoramidine isomer

We commenced the study by subjecting **2.40a** to Overman's samarium mediated reductive dialkylation[40] with *cis*-1,4-dichloro butene in THF at 0°C. To our advantage, bis-oxindole **2.39a** was afforded as a single diastereomer in 68% yield (Scheme 2.16).

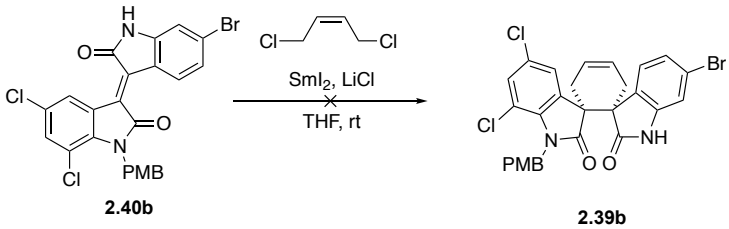


Scheme 2.16
Samarium mediated reductive dialkylation of isoindigo (**2.40**a) with *cis*-1,4-dichloro butene to afford bis-oxindole **2.39a**

It turned out, the reaction was highly capricious with the yield of **2.39a** varying from 10% to 68% at best. It came to our knowledge that the quality of the samarium metal used to prepare SmI_2 is highly crucial for the reaction outcome.[111] When using freshly prepared and titrated SmI_2, the reaction became more reliable with more consistent yield. The reaction was initially performed at room temperature. At this temperature, dienolate was formed entirely within 30 min of reaction as evidenced by the isolation of dihydroisoindigo (98%) upon hydrolytic work-up. Another indication is the change in colour from deep red to light yellow which indicates that the conjugation has changed. Upon colour change, *cis*-1,4-dichloro butene was added immediately resulting in the formation of **2.39a** together with isoindigo (**2.40a**). It was postulated that under the reaction condition, **2.40a** was regenerated through a competing E1cB reaction of monoalkylated **2.47**. We then study the effect of temperature on the reaction, and the results showed that the reaction performed best at 0°C. At higher temperature, the reaction favours the regeneration of **2.40a,** and at a lower temperature the reaction was slow and did not perform significantly better.

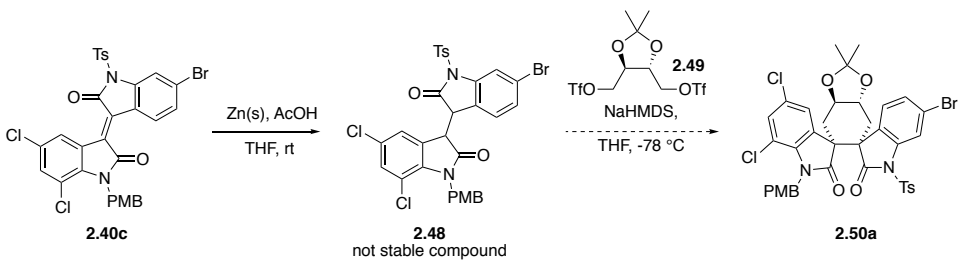
2.3.4.2 Perophoramidine isomer

For the perophoramidine project, we initially subjected halogenated isoindigo **2.40b** to identical reaction conditions at room temperature that turn out to be unsuccessful. Adding *cis*-1,4-dichloro butene to the reaction resulted only in the isolation of **2.40b** and no trace of the desired product **2.39b** (Scheme 2.17). In parallel to this, we also studied the alternative route to install the vicinal quaternary stereocenter.[35]



Scheme 2.17
Attempt to install the vicinal quaternary stereocenters by samarium mediated reductive dialkylaiton

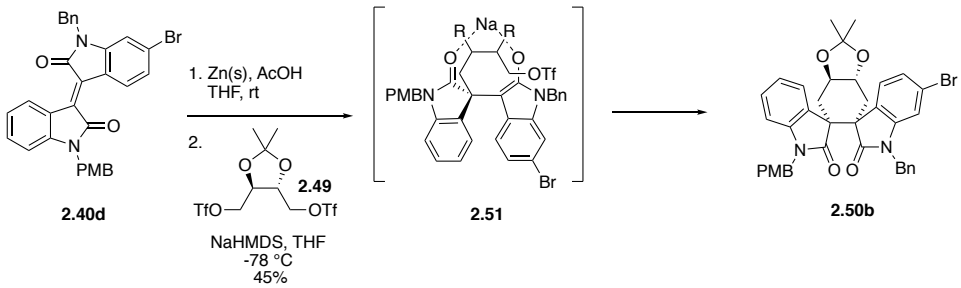
For this approach, it was necessary to protect the remaining lactam to form *N*-Ts imide **2.40c**. This stepwise procedure involves the initial reduction of **2.40c** with zinc powder and acetic acid at room temperature to afford dihydroisoindigo **2.48**. Unfortunately, this compound was not stable in air as it rapidly re-oxidises to **2.40c**. The instability of compound **2.48** made the subsequent dialkylation step not possible to perform (Scheme 2.18).



Scheme 2.18
Stepwise approach to install vicinal quaternary stereocenter

It turns out, this route was only possible for bromo isoindigo **2.40d** where the lactams are protected with *p*-methoxybenzyl and benzyl groups (Scheme 2.19). Pieces of evidence suggest that the instability of dihydroisoindigo **2.48** is caused by the electron withdrawing nature of *N*-Ts imide as the reduction of **2.40b,** and **2.40d** under identical reaction conditions delivered air stable products. Compound

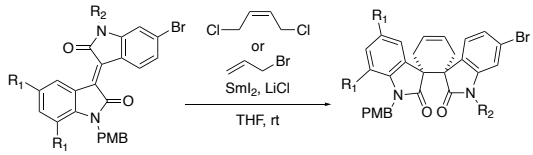
2.50b was however not useful in our continuous study towards perophoramidine considering we need the *N*-Ts imide functionality further on in the synthetic plan and existing benzyl deprotection method is not compatible with aromatic halogens. Nonetheless, this line of investigation made us reconsider the importance of the lactam protecting group in the dialkylation strategy.



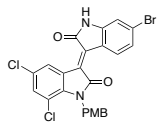
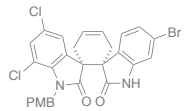
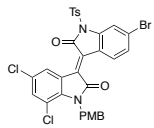
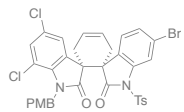
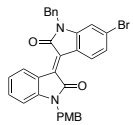
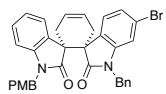
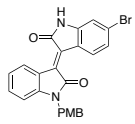
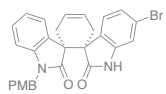
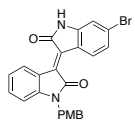
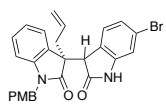
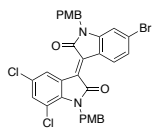
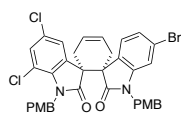
Scheme 2.19
Reduction and subsequent diastereoselective dialkylation using NaHMDS to install vicinal quaternarys stereocenter in **2.50b**

With the newfound knowledge about the system, we then resumed our investigation to the samarium mediated reductive dialkylation methodology. The reaction was repeated for compound **2.40e** (Table 2.1). However, this attempt did not furnished the dialkylated adduct instead the starting material was recovered. Initially, it was believed that SmI_2 was not compatible with aromatic halogens and as a result did not deliver the corresponding dienolate. However, when repeating the reaction with isoindigo **2.40b** we were able to isolate the corresponding dihydroisoindigo upon hydrolytic work up, which proves that the dienolate indeed formed. In order to determine if the first alkylation did take place, bromo-isoindigo **2.40e** was subjected to the reaction conditions with allyl bromide. Gratifyingly, alkylated product **2.39e'** was isolated in 24% yield together with the corresponding dihydroisoindigo. The outcome of this study indicates that SmI_2 is compatible with aromatic halogens and that the problematic step is the second alkylation since there was no trace of the bis-allyl product. Additionally, it was shown by 2D NMR studies that the allyl group was added to the oxindole moiety with the PMB protected lactam. It made clear that further experimentation with protecting groups was needed and ideally the protecting groups should be electron rich to encourage the second alkylation step. To test out our hypothesis we repeated the reaction with isoindigo **2.40d** and **2.40f** which resulted in the formation of bis-oxindole **2.39d** and **2.39f** (Table 2.1). In contrast to this advancement, exposure of **2.40c** to the same reaction conditions resulted only in recovered starting material thus implying that electron withdrawing protecting groups are not compatible with SmI_2.

Table 2.1
Attempts to construct the vicinal quaternary stereocenters by SmI_2[a]



2.40b-f **2.39b-f**

Entry	Substrates	Electrophile	Products	Yield (%)
1	 **2.40b**	*cis*-1,4-dichloro butene	 **2.39b** not formed	n.d
2	 **2.40c**	*cis*-1,4-dichloro butene	 **2.39c** not formed	n.d
3	 **2.40d**	*cis*-1,4-dichloro butene	 **2.39d**	21
4	 **2.40e**	*cis*-1,4-dichloro butene	 **2.39e** not formed	n.d
5	 **2.40e**	allyl bromide	 **2.39e'**	24
6	 **2.40f**	*cis*-1,4-dichloro butene	 **2.39f**	36

[a]Reaction conditions: Isoindigo (1 eq.), SmI_2 (0.07M, 2.6 eq.), LiCl (11 eq.) in anhydrous THF. The corresponding electrophile (1.4 eq) was added after the formation of the dienaolate. The reaction was performed at room temperature.

2.3.5 Conclusions

In conclusions, the vicinal quaternary stereocenters were successfully installed for both dehaloperophoramidine and perophoramidine by employing the samarium mediated reductive dialkylation protocol. The efficiency of the reaction was improved by performing the reaction at 0 °C. At this temperature, the dialkylation step can outcompete the E1cB pathway. It was found that the lactam protecting groups influence the outcome of the samarium reaction as well as the stability of the dihydroisoindigo. Electron donating protecting groups appears to promotes the reaction in contrast to electron withdrawing protecting groups which inhibits the reaction. Additionally, the latter also accelerates oxidation of dihydroisoindigo to isoindigo.

2.4 Desymmetrisation of compound **2.39a**

2.4.1 Desymmetrisation strategies in natural product synthesis

There are several practises that need to be attended to when striving for an efficient synthesis. If a latent symmetry of a natural product can be found, then including a desymmetrisation step can increase both efficiency and brevity of the synthetic sequence. When using a chiral catalyst or enzyme, chirality can also be induced in this step.[5, 100] There are several reported total synthesis of natural product where incorporation of a desymmetrisation step has shorten the synthesis notably.[112-114]

2.4.2 Aim of the project

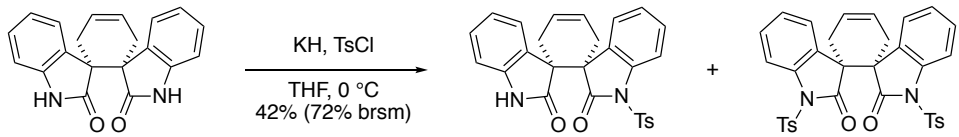
We intended that this stage of the synthesis is most suitable to perform the desymmetrisation process. Our goal was to differentiate the bis-oxindole moieties by selectively functionalise one of the carboxamide moieties in **2.39a**. This can be achieved either by attempting to form the mono *N*-Ts imide or the mono imidate.

2.4.3 Results and Discussion

2.4.3.1 Monotosylation

Initially, we attempted to form the *N*-Ts imide **2.52** by treating **2.39a** with one equivalent of potassium hydride and *p*-toluenesulfonyl chloride. However, satisfactory yield was not achieved since it was only possible to isolate the mono *N*-Ts imide **2.52** in 42% yield (72% brsm). Optimisation with various bases (NaH, Cs_2CO_3, *t*-BuOK and pyridine) and altering the temperature did not improve the

situation. The reason for the low yield is because a considerable amount of bis-*N*-Ts imide **2.53** being formed (Scheme 2.20).

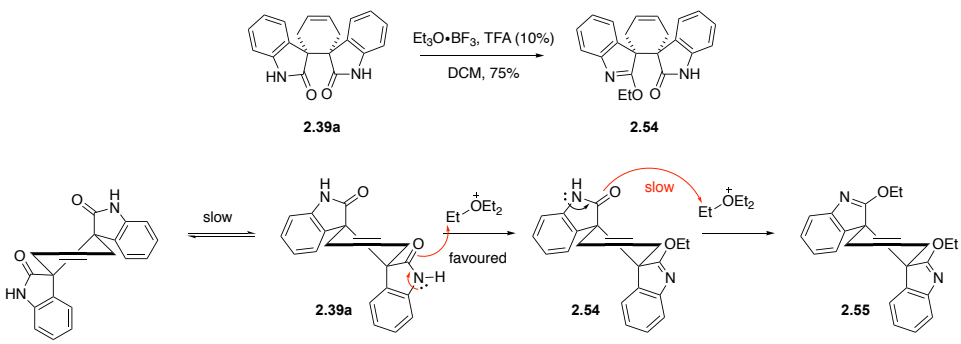


2.39a **2.52** **2.53**

Scheme 2.20
Desymmetrisation attempt by forming *N*-Ts imide.

2.4.3.2 Monoimidate formation

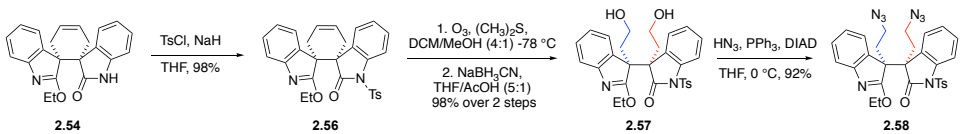
Eventually, it was found that the efficiency of the desymmetrisation could be improved to 75% by instead forming the monoimidate **2.54** using Meerwein's salt and a catalytic amount of TFA (Scheme 2.20).[115] The improved selectivity of the monoimidate is believed to be accredited to the slow conformational equilibria of the cyclohexene ring of **2.39a** that is clearly shown in the broad peaks of ^{1}H NMR spectrum of this compound. Alkylation of the equatorial carboxamide moiety is believed to be more favoured than the axial position due to steric reasons. Once the first imidate is formed, additional alkylation must take place on the less favoured axial position thus resulting in the selective imidate formation (Scheme 2.21).



Scheme 2.21
Desymmetrisation by forming the monoimidate using Meerwein's salt and catalytic amount of TFA. The selectivity is ascribed to the combination of slow conformation equilibria and steric reasons

In contrast to the this, the formation of *N*-Ts imide is not affected by steric factors since the carboxamide nitrogen is projected away from the cyclohexene moiety and should not experience much steric differentiation. With monoimidate **2.54**

secured, subsequent tosylation of the remaining lactam afforded *N*-Ts imide **2.56**. The choice of differentiating the carboxamide moieties with *N*-Ts imide and imidate was important later on in the synthesis. This compound was further elaborated to diol **2.57** through a one-pot ozonolysis/reduction of **2.56**. This material was subsequently converted to bis-azide **2.58** by employing a Mitsunobu reaction[116] with HN_3 (Scheme 2.22).



Scheme 2.22
Synthesis of bis-azide **2.58** from monoimidate **2.54**

With bis-azide **2.58** in hand, we are set to investigate the possibility of differentiating the ethyl side-chains. Hydrogenation of the bis-azide **2.58** should furnish the diamine **2.38**. The strategy was to differentiate the ethyl side-chains (blue and red in the scheme) by allowing kinetically controlled cyclisation to the *N*-Ts imide. In accordance to Baldwin's rules, the 5-exo-trig should be faster than the 6-exo-trig cyclisation. That in combination with our successful differentiation of the bis-oxindole moieties should preferentially lead to the addition of the red ethyl amino side-chain to the *N*-Ts imide which is more electrophilic than the imidate, thus forming the B ring. Ideally, the D ring could be installed by addition of the generated N-Ts anion to the imidate. However, another scenario involving the addition of the primary amine to the imidate was also anticipated. Neverthless, if the ethyl side-chains could be differentiated kinetically, this strategy would deliver the B ring and ideally the D ring, an opportunity that need to be investigated.[117]

2.4.4 Conclusions

We discovered that the conformational bias of the cyclohexene ring can be exploited to achieve a selective functionalisation of the carboxamide moiety. By forming the monoimidate, we successfully desymmetrize σ-symmetric compound **2.39a**. This compound was further transformed to the bis-azide **2.58** by a series of transformation involving the cyclohexene moiety.

2.5 Domino reactions – formation of *ortho*-amide and its reactivity

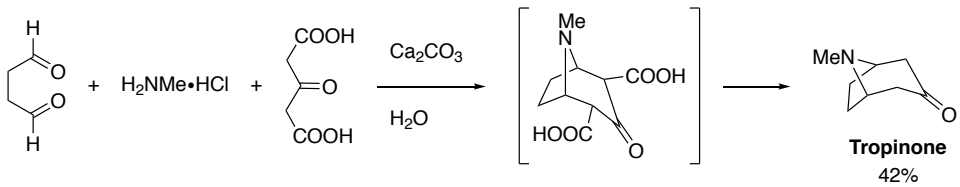
2.5.1 Domino reactions

Efficiency and conciseness is always an important matter to consider in synthesis. An excellent way to achieve this is by incorporating domino reactions into the strategy.[5] Domino reaction is not a concept that organic chemists have developed. In actuality, domino reactions are prevalent in nature. Albeit involvement of multienzymes is not directly comparable to a reaction in a flask, it still brings an appreciation for domino processes as evidence in the extensive reviews. The definition of a domino reaction was first coined by Tietze in 1993 and goes as follow:[118]

> "A domino reaction is a process involving two or more bond-forming transformation (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalyst and in which the subsequent reactions result as a consequence of the functionality formed in the previous step"

At the time, there was a need for a definition since there were various terms to describe such a process, *e.g.* tandem, consecutive, cascade and multicomponent reactions. The term tandem is however not appropriate to describe such processes considering the word tandem reflect spatial rather than time-resolved events.[119]

The first known reaction in the literature that agrees with the description above was Robinson's tropinone synthesis (Scheme 2.23).[120]



Scheme 2.23
Robinson's one step synthesis of tropinone

This synthesis indeed conveys efficiency and brevity that can be considered as almost ideal. Today, there are a plethora of domino reaction described in the literature and new methodologies keep coming.[121-128]

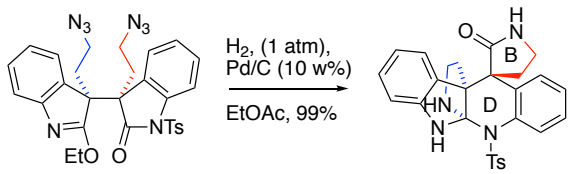
2.5.2 Aim of the project

At the planning stage, we envisioned that a domino reaction could be anticipated when differentiating the ethyl side-chain in **2.58**. In accordance to the Baldwin's rules, we anticipated that the 5-exo-trig cyclisation should be faster than the 6-exo-trig. Furthermore, nucleophilic addition to the *N*-Ts imide should be faster than addition to the imidate. We anticipated that this strategy would efficiently deliver the B-ring and potentially the D-ring, a key step that must be investigated.

2.5.3 Results and Discussion

2.5.3.1 Formation of ortho-amide

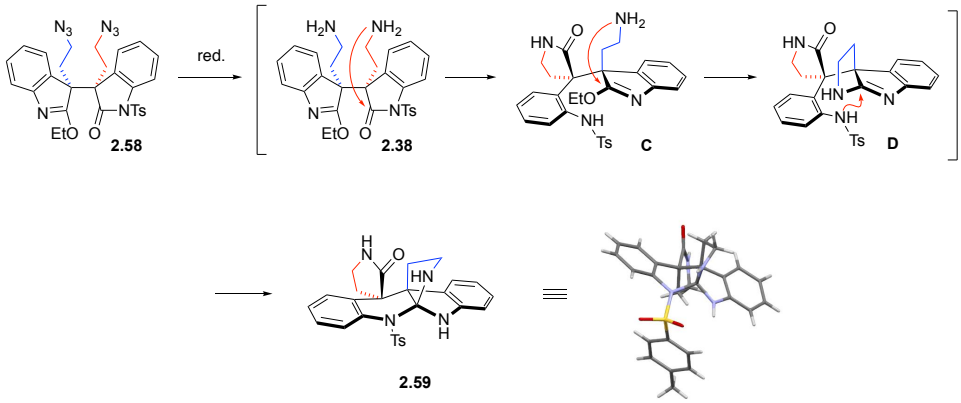
Subjecting **2.58** to the hydrogenation conditions ultimately delivered *ortho*-amide **2.59** through a domino process. Gratifyingly, our goal to differentiate the ethyl side-chains was accomplished as well as securing the B and D ring formation (Scheme 2.24). However, the ultimate formation of the *ortho*-amide was unforeseen although we suspected that the primary amine could be involved in the domino process. The structure of **2.59** was also confirmed by X-ray crystallography.



2.58 **2.59**

Scheme 2.24
Hydrogenation of bis-azide **2.58** led to the unexpected formation of ortho-amide **2.59**

It is believed that initial reduction afforded bis-amine **2.38** followed by kinetically controlled ring closure to furnish lactam **C** where the B ring is installed. The remaining aminoethyl side-chain was then added to the imidate resulting in amidine **D** which is trapped by the proximal *N*-Ts amide resulting in *ortho*-amide **2.59,** securing the formation of the D ring (Scheme 2.25).

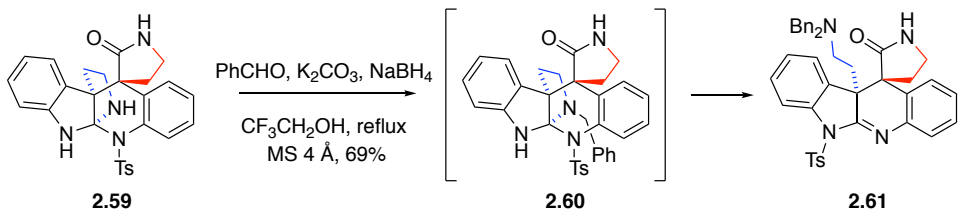


Scheme 2.25
Tentative mechanism of the formation of *ortho*-amide **2.58** from bis-azide **2.58**

At this juncture, we aimed to selectively disconnect the aliphatic amine moiety of the *ortho*-amide with concomitant formation of the lower E/D amidine or the aminal functionality. With the aminoethyl sidechain free, next was to form the final A ring, and the last challenge was to selectively *N*-methylate the pyrrolidine moiety, a challenge that has been addressed previously.[129]

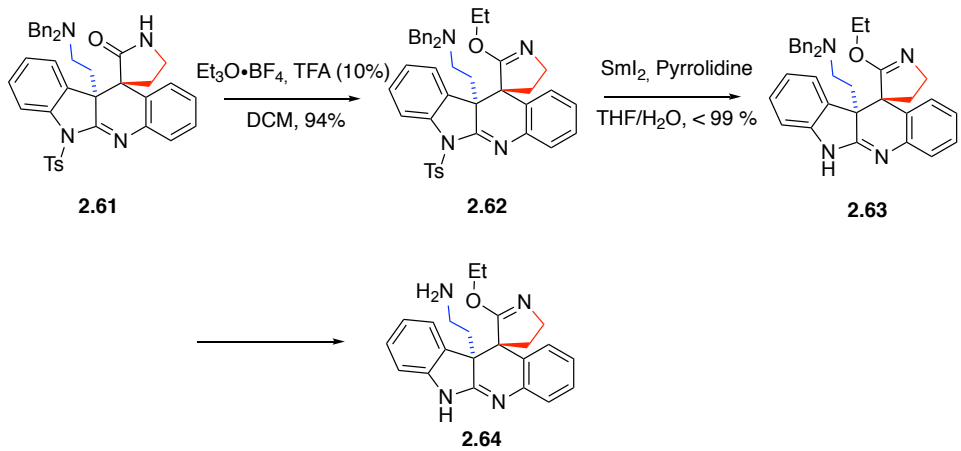
2.5.3.2 Reductive amination of the ortho amide under basic conditions

We initially attempted to reduce *ortho*-amide **2.59** to the aminal functionality by subjecting it to various reducing agents ($NaBH_4$, $NaBH_3CN$ and DIBAL-H). However, the *ortho*-amide remained untouched, and the starting material was recovered. After further studies, it was found that basic reductive amination conditions (BnCHO, $NaBH_4$, K_2CO_3 in trifluoroethanol) could deliver the desired transformation (Scheme 2.26).



Scheme 2.26
Selective disconnection of the aliphatic sidechain by reductive amination procedure to deliver amidine **2.59**

A possible mechanism involves initial alkylation of the aliphatic amine moiety to afford compound **2.60.** Subsequent reductive amination of this compound leads to the elimination of the dibenzyl aliphatic amine moiety and the formation of the lower E/D amidine. Compound **2.61** was isolated and it was noted that the *N*-Ts amide has participated in a 1,3 sulphur shift.[130] At this stage, a strategy to conclude the synthesis involves conversion of **2.61** into the corresponding imidate, removal of all protecting groups, and formation of the A/B amidine. A late-stage selective *N*-methylation would then deliver the target compound. Exposure of **2.61** to Meerwein's reagent and a catalytic amount of TFA furnished **2.62** in high yield (Scheme 2.27). Detosylation of **2.62** using SmI_2 in pyrrolidine/water provided compound **2.63** in excellent yield.[131] At this point, attempts to remove the benzyl groups through hydrogenation turned out to be problematic. When compound **2.63** was treated with various Pd sources (Pd/C, $Pd(OH)_2/C$), in different solvent mixture, at high pressure and elevated temperature only recovered starting material together with the monodebenzylated product was recovered from the reaction mixture. Small amounts of **2.64** was eventually prepared by another group member. Attempts using this material to complete the A/B ring system by intramolecular addition of the primary amine moiety onto the imidate at elevated temperatures only returned the corresponding amide. Considering this, it was decided to explore other alternatives to approach the target molecule.

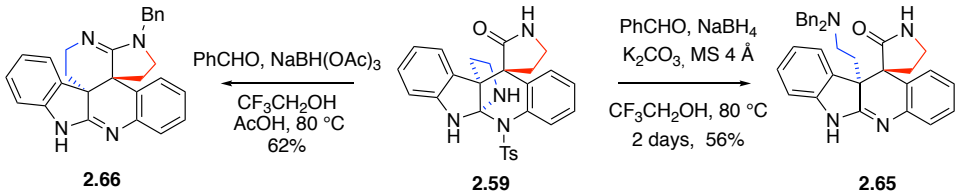


Scheme 2.27
Initial attempt to form the polycyclic core of dehaloperophoramidine

2.5.3.3 Reductive amination ortho amide under acidic conditions

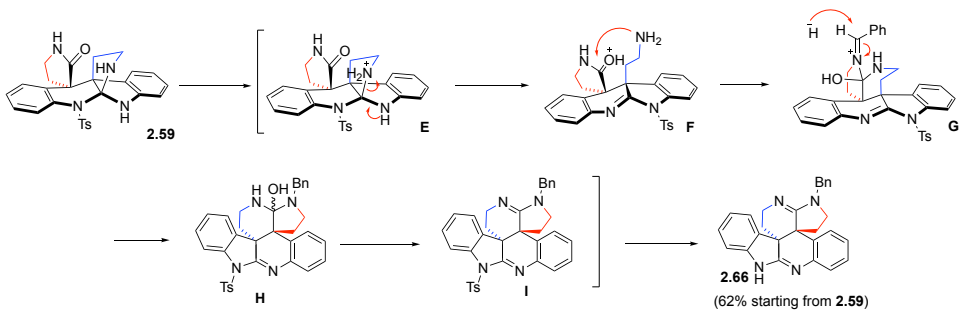
In a parallel line of investigation, it was noted that the tosyl group was removed after prolonged reaction time, affording **2.65** (Scheme 2.28). After considerable investigation, it was found that exposure of *ortho*-amide to acidic reductive

amination conditions led to the discovery of a new reaction mode. In contrast to the basic reductive amination procedure, elimination of the aliphatic side chain led instead to cyclisation with the B-ring lactam resulting in the A/B amidine. Under the reaction conditions it was noted that B-ring was selectively benzylated, ultimately affording *N*-benzyl dehaloperophoramidine **2.66** in 62% yield.



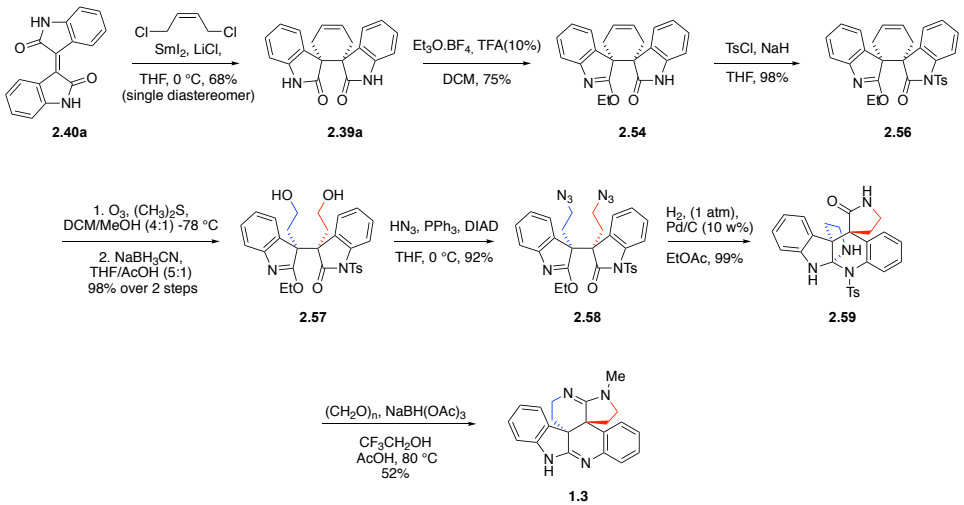
Scheme 2.28
Alternative reaction mode of the *ortho*-amide opening/cyclisation reaction

The transformation from **2.59** → **2.66**, secured several of our goals and furthermore, obviates our original concerns for the challenging late-stage *N*-alkylation step and improved the efficiency of the synthesis immensely. The mechanism of this domino process is believed to commence with the initial protonation of the aliphatic amine moiety which enables elimination of this to furnish protonated lactam **F**. The proximal aminoethyl side chain then adds to the lactam resulting in the formation of the A ring. Subsequent reductive amination of this results in intermediate **H**. The regioselectivity of the reductive amination is ascribed to the faster formation of the iminium ion from pyrrolidine than from piperidine.[132-133] Dehydration of intermediate **H** under the acidic conditions results in intermediate **I**. Finally, hydrolysis of this compound afforded **2.66** (Scheme 2.29). It was possible to isolate intermediate **H** in which 1,3 – sulphur shift has already occurred.[130] The plausibility of this proposed mechanism was investigated by subjecting intermediate **H** to acidic reaction conditions (AcOH, CF_3CH_2OH) which resulted in clean conversion into **I**.



Scheme 2.29
Proposed mechanism of the domino process leading to N-benzyl dehaloperophoramidine **2.59**

Furthermore, **2.59** was subjected to identical reaction conditions, resulting in complete recovery of the starting material. This indicates that the reductive amination proceeds before the formation of the A/B amidine moiety. Ultimately, this domino process was applied in the synthesis of dehaloperophoramidine. Compound **2.59** (1.00 g scale) was subjected to paraformaldehyde under identical reaction conditions to furnish **1.3** in 52% yield and completed the synthesis in eight steps, and 23% overall yield starting from commercially available isoindigo (**2.40a**) (Scheme 2.30).



Scheme 2.30
Eight-step total synthesis of dehaloperophoramidine (**1.3**)

2.6 Conclusions and outlook

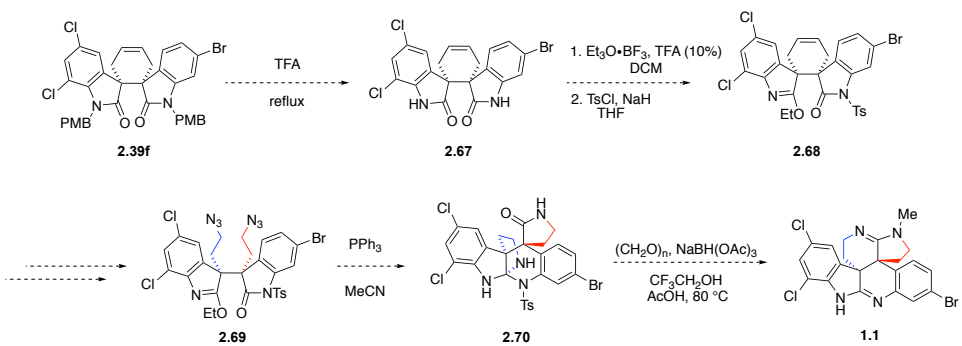
It is shown that Overman's dialkylation strategy is an effective method to construct vicinal quaternary stereocenters having *cis* relative stereochemistry. This method was adopted on the dehaloperophoramidine synthesis (Scheme 2.16). It was necessary to pay attention to the quality of the samarium metal used to prepare SmI_2 and the reaction outcome is best achieved at 0°C to eliminate competing reaction.

Desymmetrisation of σ-symmetric compound **2.39a** was achieved by exploiting the conformational bias of the cyclohexene moiety to selectively functionalise the carboxamide moiety thus furnish mono imidate **2.54** (Scheme 2.21).

Two new domino processes were discovered that improved the efficiency and brevity of the synthesis. The first domino reaction was envisioned at the planning

stage. However, the formation of the *ortho*-amide functionality was unexpected. The second domino reaction was discovered after careful investigation of reactivity of the *ortho*-amide, a transformation that was unforeseen nonetheless was significant for the efficiency of the synthesis (Scheme 2.28). It is believed the driving force for the second domino reaction is due to the thermodynamic preference of the hexacyclic motif of **1.3** and is the reason for the successful implementation in the synthesis.

For the perophoramidine isomer, it was possible to adopt the same strategy to forge the vicinal quaternary stereocenters. However, careful attention to the choice of protecting groups on the lactam moieties is required. Nonetheless, one of the key transformations was achieved and to reach the target compound **1.1**. Several modifications of the dehaloperophoramidine synthesis need to be taken in order to be applicable on **1.1**. Moving forward, we can study suitable protecting groups that are compatible with SmI_2. Alternatively, another strategy is to move forward with compound **2.39f** by removal of the PMB protecting groups. Next, the study of the selective functionalisation of the dichloro oxindole motif is necessary to plan further modification of the synthesis (Scheme 2.31). If this strategy is not fruitful, then more resources need to be focused on the initial protection step. In the case where selective functionalisation can be implemented, it is also necessary to replace the hydrogenation step to Staudinger reaction in order to not cause problems with the aromatic halogens (Scheme 2.31). In the case where the reduction of the azide by the Staudinger reaction proceeds smoothly, then the final domino reaction would furnish the target compound.



Scheme 2.31
Outlook on the perophoramidine synthesis

3 Studies towards total synthesis of strictamine

3.1 Background

3.1.1 Biosynthetic origin and etymology

The akuammiline alkaloids are a large family of monoterpene alkaloids with more than 30 members. The first known member of this family is echitamine (**1.7**) that was isolated in 1875.[134] Several of the members can be found in the akuamma seeds, which has also given the name to this family of indole alkaloids. The seeds of the akuamma plants have been used as folk medicine[52, 134-136] for centuries and studies of these alkaloids has shown that akuammiline alkaloids have a broad range of bioactivities such as anticancer[47-49], antiviral[55], anti-inflammatory[46] and antimalarial[52]. Prominent features of the akuammiline alkaloids are: (i) the cage like methanoquinolizidine that is build up by C-D-E rings, (ii) the C7 quaternary stereocenter that is part of the C ring and, (iii) the C20 ethylidene or ethyl substituent (Figure 3.1).

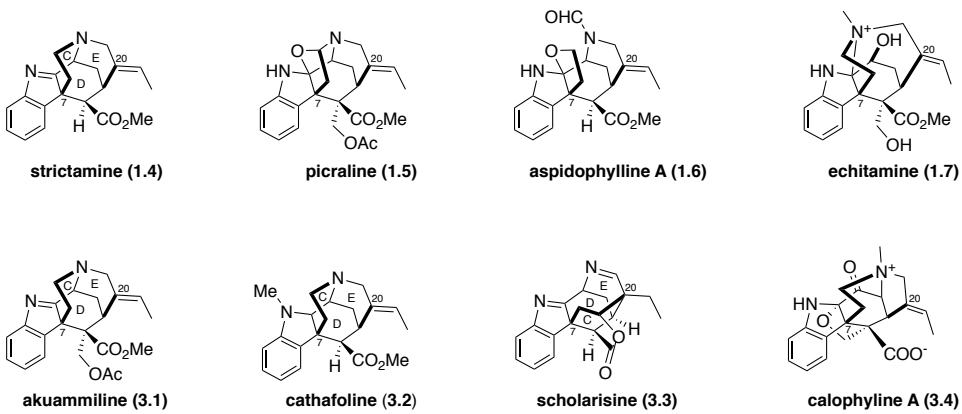
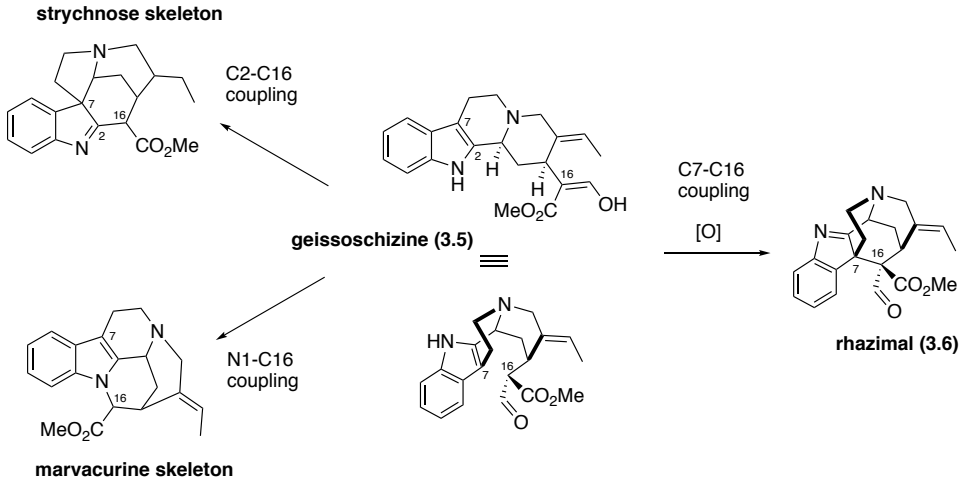


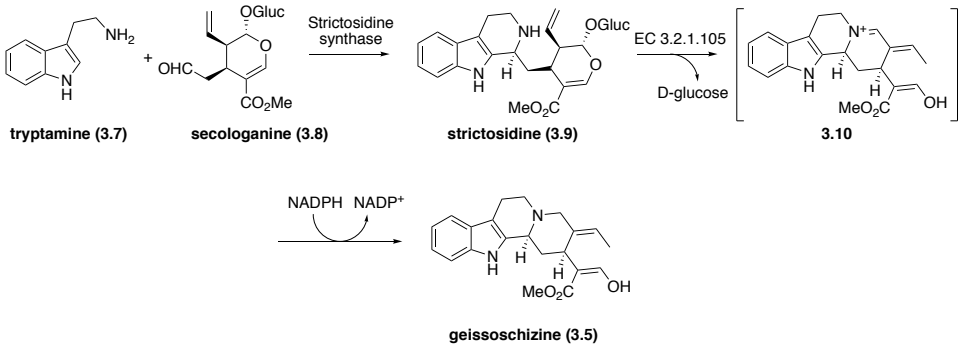
Figure 3.1
Diverse structure of akuammiline alkaloids

The biosynthesis of akuammiline alkaloid is not fully mapped. However, it is known that the structure can be traced back to geissoschizine (**3.5**).[112, 137-140] The signature methanoquinolizidine core of the akuammiline is formed by bonding C7 to C16 in **3.5** to furnish rhazimal (**3.6**), a formylated precursor of strictamine (**1.4**), the core structure from which all other members can be accessed. The mechanism of this step is still unknown. The mechanism of this step is still unknown but it is suggested occur by a one-electron oxidative coupling.[141] Geissoschizine (**3.5**) is also the biosynthetic precursor to many other monoterpene alkaloids thus links the akuammiline family to strychnose, and marvacurine alkaloids.



Scheme 3.1
Biosynthetic precursor geissoschizine (**3.5**) various coupling pattern leading to alkloids belonging to akuammiline, strychnose and marvacurine

The biosynthesis of geissoschizine commences by the formation of strictosidine (**3.9**) from tryptamine (**3.7**) and secologanine (**3.8**) through the action of strictosidine synthase. Deglucosylation of **3.9** leads to a highly reactive aglycone **3.10** that in turns give rise to diverse alkaloids. Intercepting the aglycone **3.10** with NADPH furnish geissoschizine (**3.5**).[142-144]

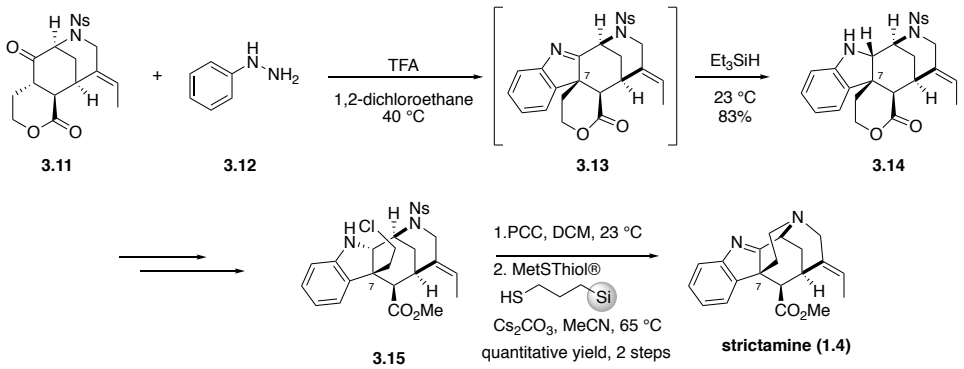


Scheme 3.2
Biosynthetic pathway to geissoschizine from tryptamine and secologanine

3.1.2 State of the art – Completed syntheses

Given the highly complex structure of akuammiline alkaloids and the broad biological activities these natural products have shown, there is no surprise that they have attracted and immense interest among synthetic chemist. Although known since the 1870s, the first total synthesis of an akuammiline alkaloid was only disclose in 2009.[145] Since then, several elegant total synthesis of akuammiline alkaloids has been disclosed. Despite the triumph, akuammiline alkaloids containing the methanoquinolizidine motif have proved to be challenging. The complexity of this structural motif has received an immense interest in the organic synthetic community and has resulted in several elegant approaches.[146-156] The first total synthesis of an akuammiline alkaloid containing this motif was reported in 2016 by Garg and co-workers[45] in their total synthesis of strictamine (**1.4**). As by now, there are four total syntheses (two asymmetric[45, 157] and two racemic[57, 158]) and four formal syntheses of strictamine (two asymmetric[159-160] and two racemic[161-162]).

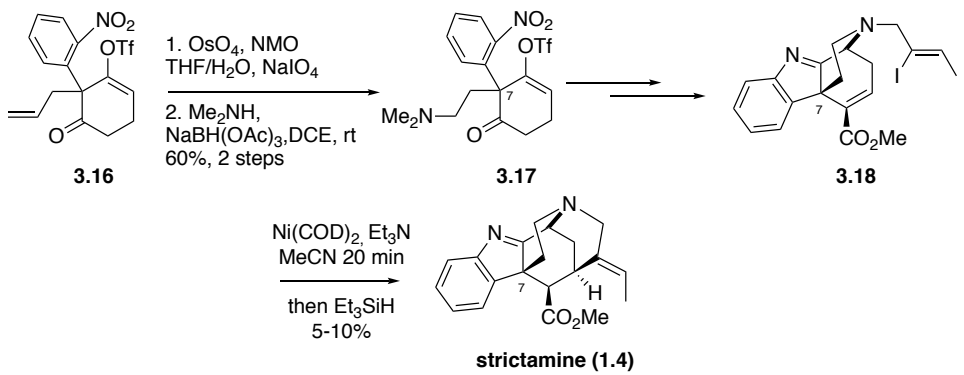
The first asymmetric total synthesis of strictamine was reported by Garg and co-workers.[45] By employing a reductive interrupted Fischer indole synthesis with compound **3.11** and **3.12**, they accomplished the enantioselective formation of the C7 quaternary stereocenter as well as forming four of the rings in strictamine. The final C ring and the methanoquinolizidine motif was constructed through an intramolecular nucleophilic substitution reaction (Scheme 3.3). This strategy was also used in the total synthesis of (–)-aspidophylline A and (–)-2*S*-cathafoline. The synthesis was completed in 25 steps with 1.7% overall yield.



3.11 **3.12** **3.13** **3.14** **3.15**

Scheme 3.3
Garg and co-workers asymmetric synthesis of strictamine

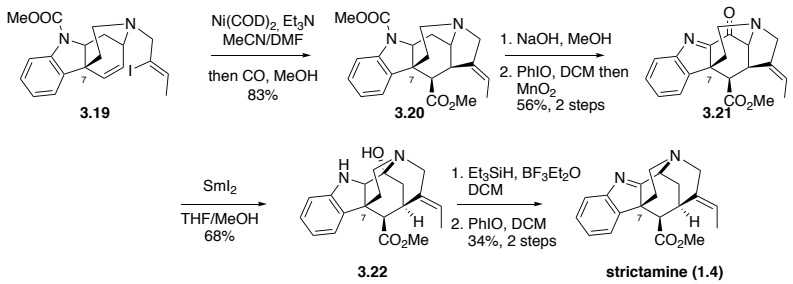
Not long after the first reported synthesis, Zhu and co-workers disclosed their total synthesis of strictamine.[57] Their strategic guidelines are: (i) install the C7 quaternary stereocenter at the beginning of the synthesis, and (ii) introduce the indolenine late in the reaction sequence. Based on this, they commenced the synthesise with the known compound **3.16**, where the quaternary stereocenter was already installed. The methanoquinolizidine motif was constructed by forming the E ring through a reductive Heck reaction using $Ni(COD)_2$ at room temperature and Et_3SiH as reducing agent. Although this strategy is a powerful method to afford the highly-strained motif, the yield remains rather poor (5-10%). This strategy was later employed by Gaich[161], Ohno[162], Qin[159] and Snyder[160] in their formal syntheses (Scheme 3.4).



3.16 **3.17** **3.18**

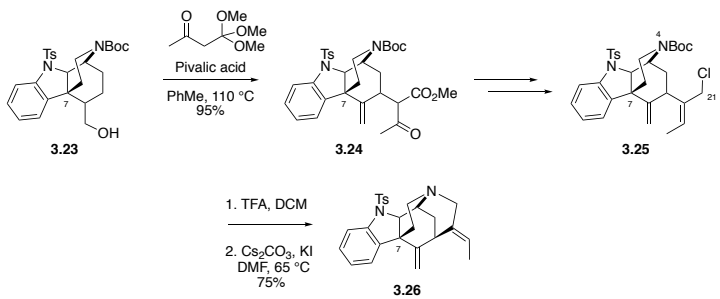
Scheme 3.4
Zhu and co-workers strategy to include the quaternary stereocenter at the beginning of the synthesis and reductive Heck reaction as the last step to form the E-ring

In 2017, Zu presented their unified total synthesis of structurally diverse akuammiline alkaloids.[158] They took inspiration from the biosynthetic strategy where it is believed that rhazimal (**3.6**) is the common intermediate in many syntheses of akuammiline alkaloids. Their retrosynthetic analysis concluded with compound **3.19** and diversify this compound to other akuammiline alkaloids. The construction of the polycyclic ring system relies on Heck carbonylation of compound **3.19** and subsequent oxidation to the shared intermediate **3.21**. The core skeletal of strictamine is achieved by a samarium mediated skeletal rearrangement to deliver skeletal connectivities of strictamine **(1.4**) and further transformation to the target compound.



Scheme 3.5
Zu and co-workers strategy to construct **3.21** as a common intermediate in the unified total synthesis of akuammiline alkaloids

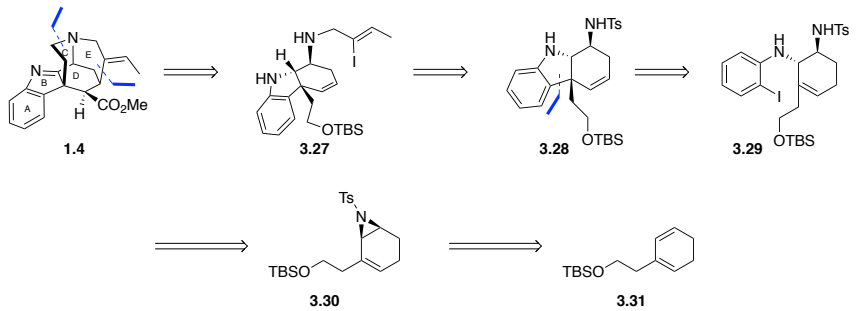
The most recent total synthesis of strictamine was reported by Qin and co-workers. Initially, they reported a formal synthesis in which they completed the synthesis using the same intermediate **3.18** as in Zhu's total synthesis. In their total synthesis, they disclosed a novel disconnection to form the E ring. Instead of forming the C20-C15 bond as in previous syntheses, they sought to go for the N4-C21 bond formation by an intramolecular nucleophilic substitution reaction of **3.25** to **3.26.** Compound **3.24** was constructed by Johnson-Claisen rearrangement of **3.23**.



Scheme 3.6
Qin's strategy to construct the methanoquinolizidine core of strictamine.

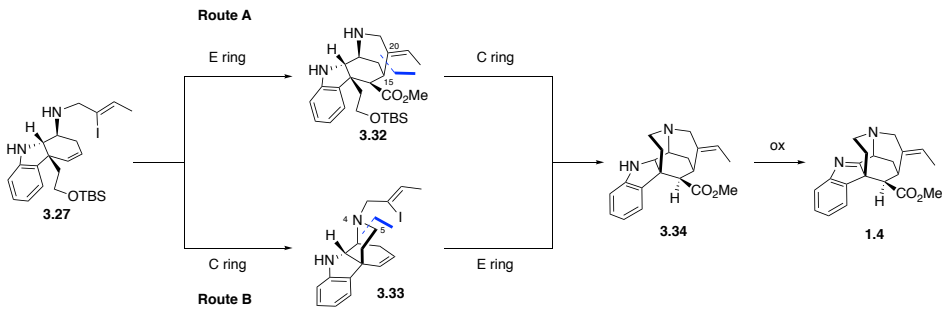
3.2 Structural and retrosynthetic analysis of strictamine

The intriguing structure of compound **1.4** and the complexity of the methanoquinolizidine motif has made us interested in developing a strategy towards this system. Our retrosynthetic analysis is outline in Scheme 3.7. We envisioned that the methanoquinolizidine core could be derived from compound **3.27**. We planned two possible series of transformation from **3.27** to **1.4**, differing in the order of ring-constructing events. In the first strategy, the E ring is installed by employing the domino carbopalladation carbonylation protocol,[163] followed by installation of the C ring. In the second strategy, the ring-constructing order is reversed (Scheme 3.8).



Scheme 3.7
Retrosynthetic analysis of strictamine

Compound **3.27** can be traced back to dihydrocarbazole **3.28** which in turn is derived from diamine **2.29** through an intramolecular Heck reaction. Diamine **2.29** can be available from aziridine **3.30** by an regio- and stereoselective ring-opening with 2-iodoaniline. Finally, aziridine **3.30** is furnished by a chemoselective aziridination of diene **3.31**.[164]

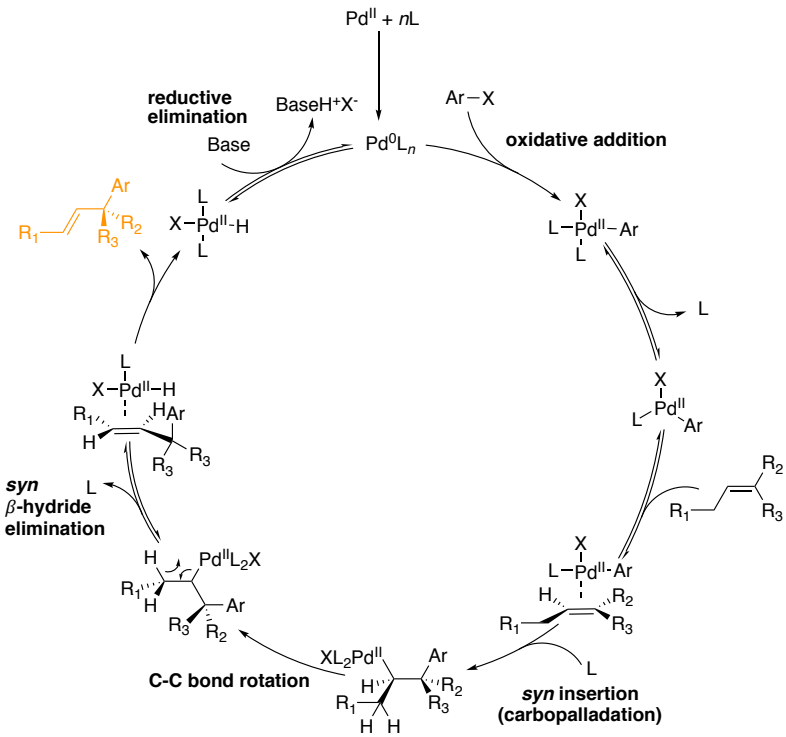


Scheme 3.8
Alternative ring cyclisation strategies

3.3 Installation of C7 quaternary stereocenter

3.3.1 Intramolecular Heck reactions

The intramolecular Heck reaction has shown to be a particularly great tool to construct stereogenic centre.[165] A metal source is required, usually Pd(0) although Ni(0) has also been used. Three mechanistic pathways have been proposed for this reaction, the neutral, cationic and anionic. The substrate that adds oxidatively to the Pd(0) species determines the mechanistic pathway. The neutral pathway is most often invoked for substrates with halogens (X = Cl, Br or I), although they can also be forced to follow the cationic pathway by adding a silver salt to the reaction mixture. Generally, the cationic pathway is invoked when X = OTf. The anionic pathway usually requires the addition of additives, *e.g.* KOAc. The neutral pathway commences with oxidative addition of an aryl/vinyl halide to Pd(0). If a Pd(II) catalyst is used or other pre-catalyst, then an initial reduction is required, generally with the phosphorus ligand or an amine. Subsequent ligand dissociation and concomitant coordination of the alkene furnishes the *syn* insertions product.



Scheme 3.9
The catalytic cycle of the Heck reaction – neutral pathway.

When the substrate is a trisubstituted alkene, the concomitant β-hydride elimination must occur on the secondary carbon thus give rise to a product that contain vinyl quaternary stereocenter. The product then dissociates from the metal centre, and the catalyst is regenerated by a base promoted reductive elimination of HX (Scheme 3.9).

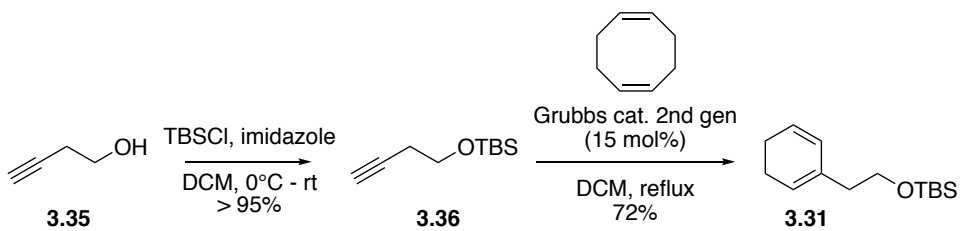
3.3.2 Aim of the project

We intended to construct the C7 quaternary stereocenter of strictamine (**1.4**) by employing the intramolecular Heck reaction. There are reported procedures where the intramolecular Heck reaction was employed to afford 3,3-disubstituted oxindole and indolines scaffolds that features an all-carbon quaternary stereocenter.[166-182] We aim to adopt this procedure to construct the dihydrocarbazole framework and the quaternary stereocenter, starting from vinyl aziridine and *o*-iodoaniline.

3.3.3 Results and Discussion

3.3.3.1 Aziridination of conjugated dienes

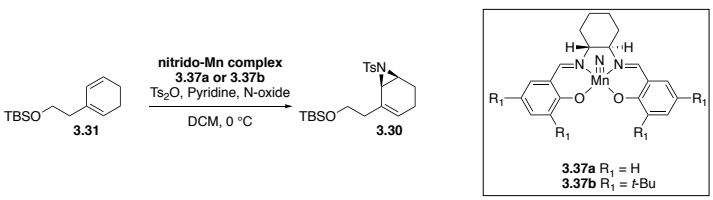
Vinyl aziridines are valuable functional groups as they serve as versatile building blocks to afford biologically and structurally important compounds.[183] A general method to furnish a vinyl aziridine involves the direct addition of a nitrene to a conjugated diene. We aimed to adopt the selective [2+1] addition of a nitridomanganese complex to diene **3.31** to afford vinyl aziridine **3.30**.[164] This method represents a reagent controlled asymmetric aziridination of conjugated dienes. Diene **3.31** is a known compound that can be accessed from 3-butynol (**3.35**) and cyclooctadiene using a Grubbs 2nd generation catalyst (Scheme 3.10).[184]



Scheme 3.10
Synthesis of diene **3.31** from TBS protected 3-butynol

Subjecting diene **3.31** to the aziridination procedure with nitridomanganese **3.37a** furnished vinyl aziridine **3.30** in 11-20% yield as a single diastereomer and regioisomer, although the enantioselectivity was rather poor (54:46 *e.r.*) (Table 3.1).[164] The remaining product mixture was an inseparable mixture and it was therefore not possible to isolate and characterise the other products. The reason for the poor performance is still ambiguous. However, it was possible to isolate *O*-Ts salicaldehyde, which suggest that hydrolysis of the salen ligand must have occurred at some point in the reaction. To eliminate this possibility, we substituted the hygroscopic pyridine-*N*-oxide to 4-phenyl pyridine *N*-oxide which is easier to handle. The yield was improved to 36%, and a consistence outcome was observed. Nitridomanganese complex **3.37b** was synthesised in order to improve the enantioselectivity of the aziridination. Unfortunately, subjecting **3.31** to complex **3.37b** left the diene untouched and the starting material was recovered.

Table 3.1
Aziridination of cyclic diene using Mn-nitrido complex **3.37a** and **3.37b**[a]



Entry	*N*-oxide	Nitrido-Mn complex	Yield[b]	e.r.[c]
1	pyridine *N*-oxide	**3.37a**	11-20%	52:48
2	4-phenylpyridine *N*-oxide	**3.37a**	36%	54:46
3	4-phenylpyridine *N*-oxide	**3.37b**	n.d.	n.d.

[a] Reaction conditions: Nitrido-Mn complex (1.6 eq.), Ts_2O (1.9 eq), *N*-oxide (1.9 eq.) Pyridine (0.8 eq.) in anhydrous DCM at 0°C for 2h. [b] Isolated yield. [c] Determined by chiral-HPLC chiralPac IA, n-Hexane/iPrOH 98:2, 1.0 mL/min

Moreover, the unsatisfying yield led us to investigate alternative methods to synthesise vinyl aziridine **3.30**. Diene **3.31** was subjected to Cu-homoscorpionate complex (Tp*Cu)[185-186], (salen)-Cu complex[187], Ag-homoscorpionate complex (Tp*Ag)[186], Jacobsen catalysts[188] and PhI=NTs and chloramine T as nitrene source (Figure 3.2). However, in none of the cases was the outcome improved compared to the use of nitridomanganese **3.37a**

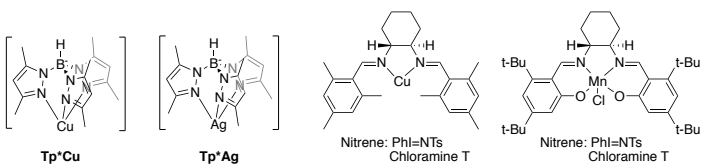
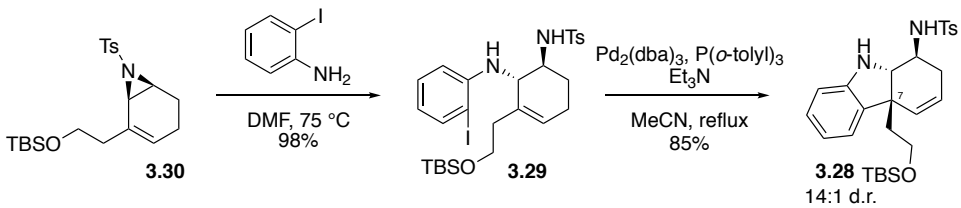


Figure 3.2
Various Cu, Ag, and Mn catalyst for vinyl aziridination

3.3.3.2 Aminolysis and intramolecular Heck reaction

Having obtained **3.30**, we then focused our attention to the regio- and stereoselective ring opening of the vinyl aziridine. Treatment of vinyl aziridine with two equivalent of 2-iodoaniline in DMF at 75 °C overnight delivered the desired product **3.29** as a single regioisomer in excellent yield. Next, was to investigate the intramolecular Heck reaction. This key reaction was interesting because control of the diastereoselectivity at the quaternary stereocenter is essential. Intramolecular Heck reaction using $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and Et_3N in MeCN (reflux, 1h), was performed on allyl aniline **3.29** resulting in isolation of dihydrocarbazole **3.28** in 85% yield and with excellent control of the diastereoselectivity (14:1 d.r.). The relative stereochemistry was determined by nOe experiments (Scheme 3.11).



Scheme 3.11
Intramolecular Heck reaction of diamine **3.29** furnished dihydrocarbazole **3.28** with quaternary stereocenter.

3.3.4 Conclusions

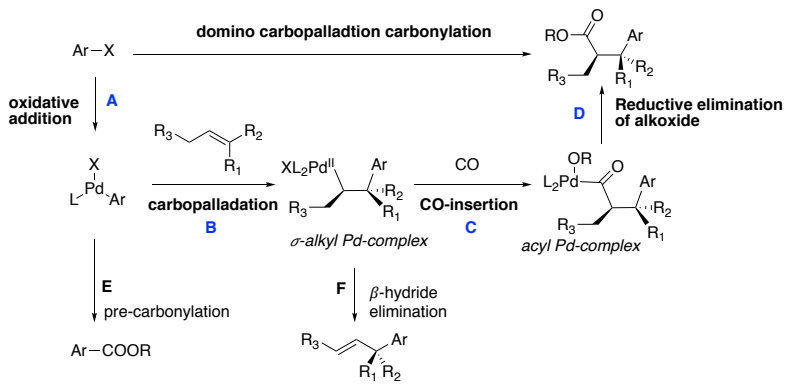
In summary, a rapid strategy to install the C7 quaternary stereocenter was developed. The vinyl aziridine **3.30** was synthesised by employing Komatsu´s selective [2+1] addition of nitrene to conjugated dienes. Subsequent ring-opening of vinyl aziridine **3.30** with 2-iodoaniline resulted in excellent regioselectivity. The intramolecular Heck reaction was employed as the key step to construct the dihydrocarbazole core of strictamine with concomitant formation of the quaternary stereocenter.

3.4 Construction of methanoquinolizidine

3.4.1 Domino carbopalladation carbonylation

The Heck reaction has been extensively studied since it was first introduced. It is a powerful tool to form C-C bonds.[165] However, its true power lies on the numerous possibilities to modify the route, especially in the case that leads to consecutive C-

C bond formations. Several methods have been reported where the σ-alkyl-Pd(II) complex (Scheme 3.12) has been intercepted with various reagents such as carbon monoxide, nitrile, and organometallic compounds thus allowing for additional C-C bonds.[189-199] In the presence of carbon monoxide, the σ-alkyl-Pd(II) complex can undergo insertion of carbon monoxide to form an acyl Pd(II) complex (step C). The catalytic cycle then terminates with reductive elimination of an alkoxide ligand to furnish the domino carbopalladation/carbonylation product (step D).



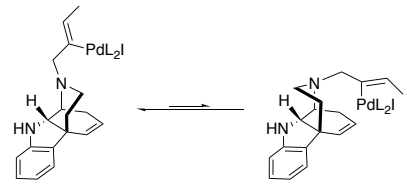
Scheme 3.12
Domino carbopalladation carbonylation sequence and possible side reactions

However, several problematic scenarios are associated with this process. Firstly, the aryl-palladium complex can undergo pre-carbonylation reaction to furnish an ester product (step E). This is especially problematic for substrates that undergo slow carbopalladation due to steric reasons. Secondly, for substrates containing β-hydrogens, the β-hydride elimination (step F) can compete with the CO-insertion (step F). Tuning of the CO pressure can nevertheless change the reaction to favour the insertion pathway. Although, the increase in pressure would also favour the pre-carbonylation step. For the desired transformation to occur, a careful investigation of suitable reaction pressure and alkoxide stoichiometry need to be done.

3.4.2 Aim of the project

We recognise this to be a good method to construct the methanoquinolizidine core of strictamine (**1.4**). In this case, the β-hydride elimination (step F) does not pose a problem. However, the pre-carbonylation (step E) can still be problematic which we aimed to circumvent by finding the balanced CO pressure and alkoxide stoichiometry. Another possible situation that can cause a problem is that the carbopalladation step requires the C-ring to be in the less favourable boat

conformer (Scheme 3.13). Nonetheless, if successful, this protocol would efficiently deliver two new C-C bonds and the methyl ester group in the correct stereochemistry, an opportunity that must be studied.



3.38
Chair Conformation

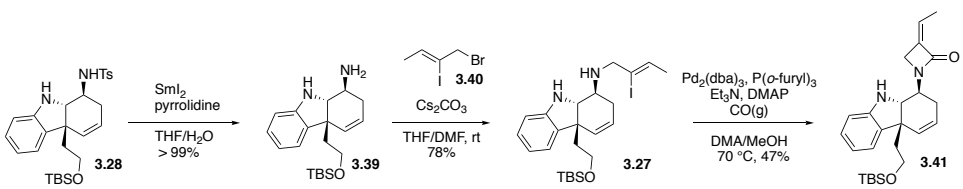
3.38
Boat Conformation

Scheme 3.13
Conformational equilibrila of σ-alkyl Pd complex **3.38**

3.4.3 Results and Discussion

3.4.3.1 C/E Route

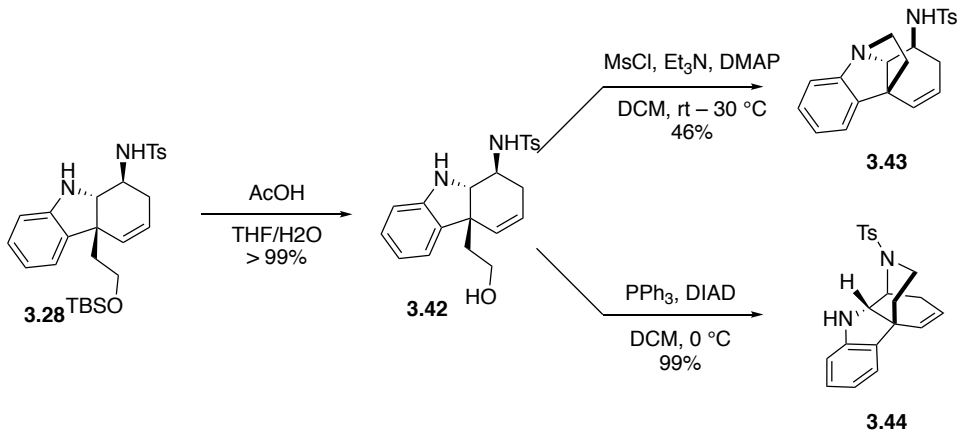
With dihydrocarbazole **3.28** in hand, we continued the synthesis by removing the tosyl group using the SmI_2/water/amine system, resulting in primary amine **3.39**.[131] Subsequent alkylation of the primary amine with (*Z*)-bromo-2-iodo-2-butene (**3.40**), afforded **3.27**. Surprisingly, subjecting allyl amine **3.27** to the domino carbopalladation/carbonylation protocol resulted in the isolation of β-lactam **3.41**. Interaction of the alkene with the Pd(II) species forces the secondary amine to be in an axial position thus placing it in close proximity to the silyloxyethyl moiety. It was speculated that the unfavourable conformation of the vinyl Pd(II) complex impedes the carbopalladation step. Additionally, the strong coordination of the secondary amine to the Pd(II) species would force the square planar Pd(II) to project away from the cyclohexene moiety thus placing the metal centre out of reach for the alkene to interact.[200] Our initial plan to first install the E ring was not possible by using compound **3.27**.



Scheme 3.14
Synthetic route to investigate E-ring closure with domino carbopalladation carbonylation

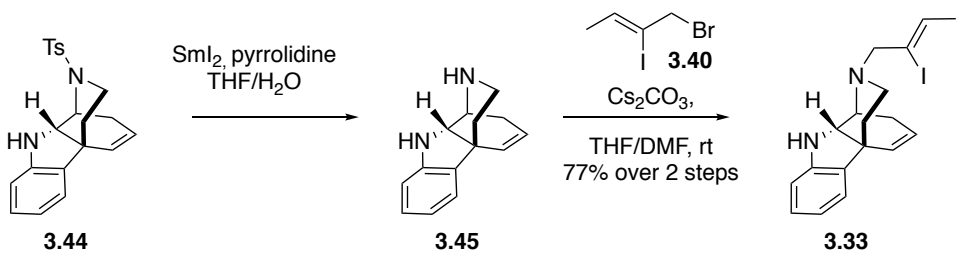
3.4.3.2 E/C Route

Our alternative plan was to close the C-ring before attempting to install the E-ring. The formation of the C-ring would prevent lactam formation and thus enable carbopalladation to proceed. Removal of the silyl group under acidic conditions delivered the alcohol **3.42** in excellent yield. We then attempted cyclisation by transforming the alcohol to the corresponding mesylate using MsCl and Et_3N in DCM at rt. However, the anticipated cyclisation did not occur, and addition of DMAP led instead to the formation of tetracyclic compound **3.43**. Eventually, it was found that subjecting alcohol **3.42** to Mitsunobu conditions afforded the desired cyclisation to compound **3.44** in excellent yield (Scheme 3.15)



Scheme 3.15
Synthetic route to construct the C-ring by intramolecular nucleophilic substitution.

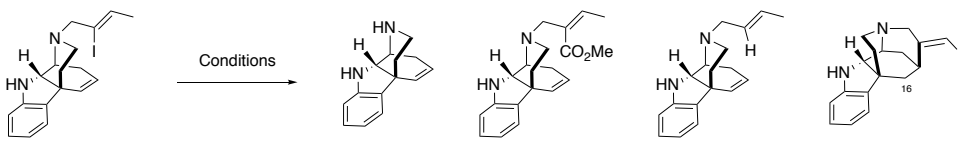
With the C-ring successfully installed, treatment of compound **3.44** to SmI_2/water/amine system followed by alkylation of this material delivered the tertiary amine **3.33** in excellent yield.



Scheme 3.16
The E/C route, construction of E-ring with domino carbopalladation carbonylation sequence

To this end, compound **3.33** was subjected to domino carbopalladation carbonylation reaction. Unfortunately, under the reaction conditions, only ester product **3.46** was isolated (Entry 1, Table 3.2). Further experimentation with other ligands were not successful (Entries 2-4, Table 3.2) and changing to $Pd(OAc)_2$ as the pre-catalyst proved to be fruitless. Moreover, the use of $Pd(OAc)_2$ resulted in formation of the reduced derivative **3.47** and de-allylated product **3.45**. The reaction was repeated with the addition of Ag_2CO_3 in order to encourage the carbopalladation step. However, this treatment was also unproductive. This indicates that carbopalladation of this cyclic system is much slower than direct carbonylation. In an effort to promote desired cyclisation, we sought to pre-form the σ-alkyl Pd(II) complex before adding CO, by using a stoichiometric amount of palladium metal. Nonetheless, the use of a stoichiometric amount of $Pd(OAc)_2$ resulted in clean removal of the alkyl side-chain to regenerate the secondary amine **3.45** (Entry 6, Table 3.2) and the use of $Pd(PPh_3)_4$ gave complex reaction mixture (Entry 7, Table 3.2). We concluded that the use of palladium would not promote the desired transformation.

Table 3.2
Attempts to install the E ring by domino Heck carbonylation



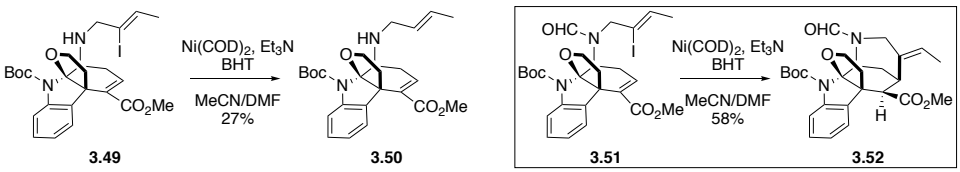
3.33 **3.45** **3.46** **3.47** **3.48**

Entry	Conditions	Result
1	$Pd_2(dba)_3$ (5 mol%), P(o-furyl)$_3$, DABCO, DMAP, DMA/MeOH (80:20), CO (1 atm), 70°C	**3.46** (91)[a]
2	$Pd_2(dba)_3$ (5 mol%), P(*o*-tolyl)$_3$, Et_3N (eq.) DMF, MeOH (5 eq.), CO (1 atm), 70°C	**3.46**[b]
3	$Pd_2(dba)_3$ (5 mol%), PPh_3, Et_3N, DMF, MeOH (5 eq.), CO (1 atm), 70°C	**3.46**[b]
4	$Pd(OAc)_2$, (2 mol%), *n*-Bu_4NCl, Et_3N, DMF, MeOH (5 eq.), CO (1 atm), 100°C	**3.46** (73%)[a] + **3.47**[c] + **3.45**[c]
5	$Pd(OAc)_2$ (1 eq.), PPh_3 (1.1 eq.), Et_3N, DMF, MeOH (5 eq.), Ag_2CO_3 (1 eq.) CO (1 atm), 100°C	**3.45** (74%)[a]
6	$Pd(PPh_3)_4$ (1 eq.), Et_3N, DMF, MeOH (5 eq.) CO (1 atm), 100°C	Complex mixture[c]
7	$Ni(COD)_2$ (3 eq.), Et_3N, MeCN/DMF (2:1), MeOH (4 eq.) CO (1 atm), rt.	**3.48** + **3.45**[c, d]
8	$Ni(COD)_2$ (3 eq.), K_2CO_3, MeCN/DMF (2:1), MeOH (4 eq.) CO (1 atm), rt.	**3.48** + **3.45**[c, d]
9	$Ni(COD)_2$ (3 eq.), MeCN/DMF (2:1), MeOH (4 eq.) CO (1 atm), rt.	**3.48** + **3.45**[c, d]

[a] Isolated yield. [b] Based on ^1H NMR analysis of the crude reaction mixture. [c] Based on ^1H NMR and LCMS analysis of the crude reaction mixture.[d] Compound **3.45** and **3.48** were inseparable using standard column chromatography and preparative TLC. dba = Dibenzylideneacetone, DABCO = 1,4-Diazabicyclo[2.2.2]octane, DMAP = 4-(Dimethylamino)pyridine, COD = 1,5-cyclooctadiene

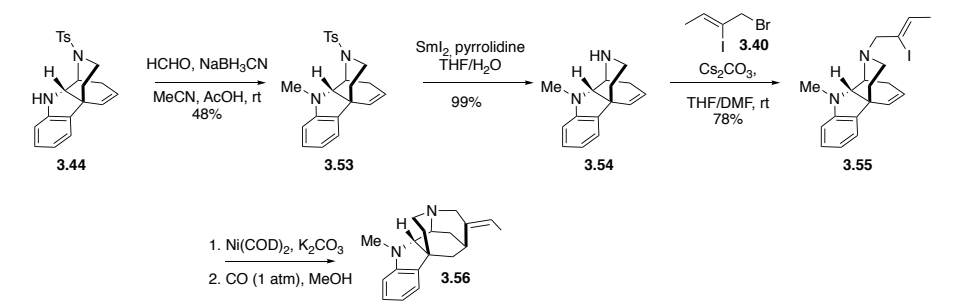
We then turned our attention to Ni(0) as it is believed to induce faster alkene insertion[201] and there is literature precedence of similar transformations using

$Ni(COD)_2$.[57, 158, 193, 197] We were pleased to find that treatment of compound **3.33** to $Ni(COD)_2$, Et_3N, $CO_{(g)}$ (1 atm), MeOH (4 eq.) in DMF at rt. resulted in compound **3.48** in which the methanoquinolizidine core was constructed. However, the methyl ester at C16 was not installed, instead a reduction has occurred on this position (Entry 8, Table 3.2). We suspected that the hydride source comes from reductive elimination of Et_3N thus attempts with K_2CO_3 (Entry 8, Table 3.2) and without base was performed (Entry 9, Table 3.2). However, the desired transformation was not achieved and compound **3.48** was isolated from the reaction mixture. It has previously been reported that the choice of *N*-protecting groups can have a dramatic influence on the outcome of these cyclisations (Scheme 3.17).[202]



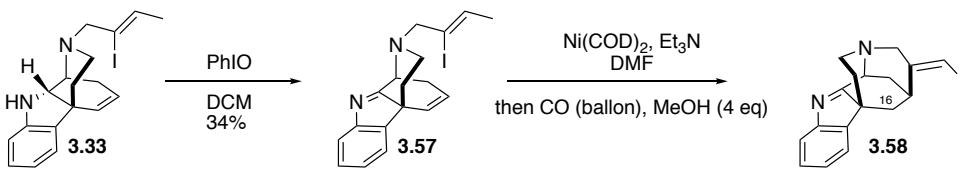
Scheme 3.17
Ma's strategy to form the E-ring in the synthesis of aspidophylline A. Protection of the amine was essential for the reaction outcome.

In regard to this, we believed that the hydrogen source could come from unprotected indoline moiety. We planned to protect the indoline nitrogen with methyl since successful cyclisation would afford cathafoline (**3.2**), another akuammiline alkaloid. Nonetheless, subjecting **3.55** to $Ni(COD)_2$ mediated cyclisation was proven to be fruitless. From ^{1}H-NMR spectroscopic and LCMS data, it seems to have formed product **3.56** containing the methanoquinolizidine core lacking the C20 ester (Scheme 3.18).



Scheme 3.18
Synthesis of *N*-Methyl analogue **3.55** from tetracyclic **3.44**

At this point, we planned to move forward by forming the indolenine before attempting cyclisation. Oxidation of the indoline **3.33** with PhIO in DCM at rt furnished indolenine **3.57** in 34% yield. This compound was subjected to the $Ni(COD)_2$ carbonylation protocol and to our disappointment, this treatment only furnished reduced product **3.58** (Scheme 3.19). The carbonyl insertion step was also not possible for this substrate. However, the carbon skeletal of strictamine was afforded. Further investigation of the reaction by varying the CO pressure need to be carried out.



Scheme 3.19
Cyclisation attempt with indolenine **3.57**

3.5 Conclusions and outlook.

It is shown that intramolecular Heck reaction is a powerful method to construct carbazole scaffold featuring quaternary stereocenter. This method provided the quaternary stereocenter in strictamine in rapid manner.

The methanoquinolizidine motif of strictamine was shown to be a daunting challenge. All method to invoke useful transformation by Pd catalyst was unsuccessful. The reason being the formation of the early ester product. Successful cyclisation was only possible with the use of $Ni(COD)_2$. However the final carbonylation was never accomplished.

In order to reach the target compound, more studies on the $Ni(COD)_2$ mediated cyclisation need to be carried out. Since the problem seems to be the insertion of carbonyl to alkyl-Ni complex, it should be interesting to study the reaction under higher CO pressure. Alternatively, it can be worth to investigation cyclisation using $Ni(CO)_4$, although it should be noted that $Ni(CO)_4$ is highly toxic.

4 Rapid construction of indoline scaffold featuring an all-carbon quaternary stereocenter

4.1 Indoline motif in natural products

Indoline is a reoccurring motif in many natural products and pharmaceuticals (Figure 4.1). Many of these have desirable bioactivities[203-204] as well as remarkable molecular architectures, which have inspired synthetic chemists to develop novel chemical transformations and synthetic strategies.[66, 72, 205-206] We intended to develop a rapid methodology towards indoline scaffolds featuring a quaternary stereocenter.

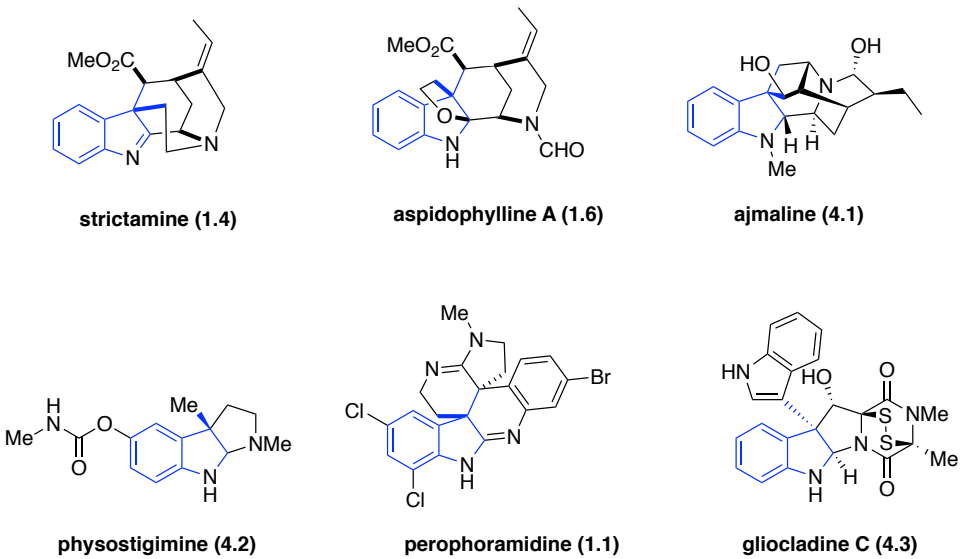
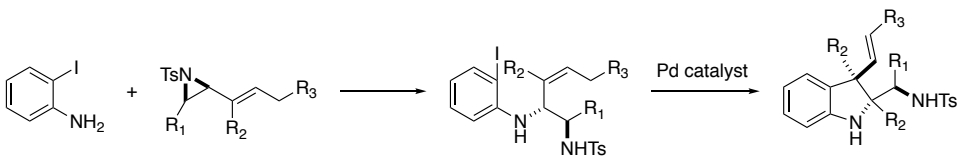


Figure 4.1
Natural products containing indoline motif that feature quaternary stereocenter

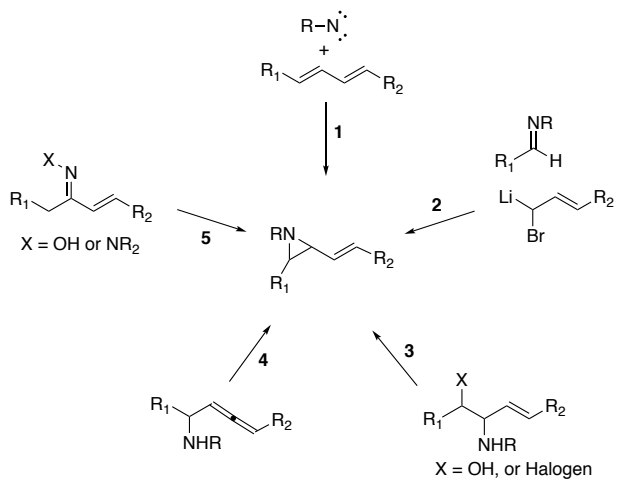
It has been proven that the intramolecular Heck reaction is a powerful tool to install quaternary stereocenters.[165] We envisioned that the indoline scaffolds could be derived from suitable allyl anilines. The allyl anilines in turn, could be afforded from vinyl aziridines



Scheme 4.1
Synthesis of indoline scaffolds featuring quaternary stereocenter

4.2 Vinyl aziridine

Vinyl aziridines have been used extensively as building blocks for synthesis of natural products.[183] It is a highly versatile functional group as it can serve as a reactive carbon electrophile and participates in ring-opening reactions with carbon and heteroatom nucleophiles. Additionally, elaboration through rearrangement provides important scaffolds in the synthesis of bioactive alkaloids and other natural products. Several methods to afford vinyl aziridine are available: (1) direct nitrene insertion (2) addition of allylic ylides to imines (3) cyclisation of amino alcohols (4) cyclisation of amino allenes (5) aziridination of α,β unsaturated oximes or hydrazones (Scheme 4.2).[183]



Scheme 4.2
Methods to afford vinyl aziridines

4.2.1 Aim of the project

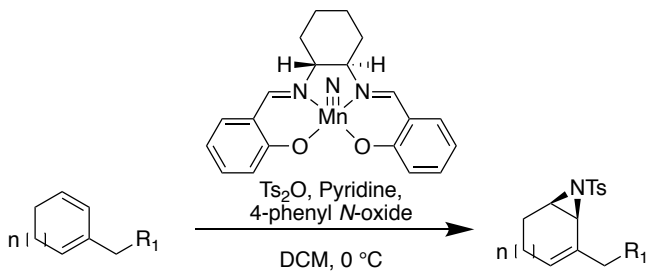
The objective for this project was to synthesise cyclic and acyclic vinyl aziridines with trisubstituted alkene. We intended to use known methods to afford the vinyl aziridines, *e.g.,* method 2 and 3.

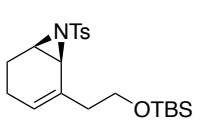
4.2.2 Results and Discussion

4.2.2.1 Direct nitrene addition to conjugated dienes

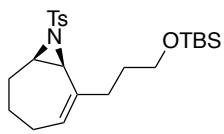
We have previously employed 1,2-addition of nitrene to conjugated diene to afford cyclic vinyl aziridine **3.31** thus we intended to use the same methodology to afford the seven-membered and eight-membered vinyl aziridines. It was possible to furnish the seven-membered aziridine **4.4** using this method however the eight-membered derivative remained untouched when subjected to the identical reaction conditions. Unfortunately, the enantioinduction of the chiral nitridomanganese complex was poor. Using the chiral HPLC, the enantiomeric purity of **3.30** was low (er 54:46).

Table 4.1
Aziridination of conjugated dienes using nitrido-Mn complex

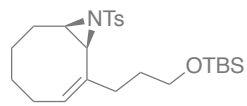




3.30
(36%)



4.4
(30%)

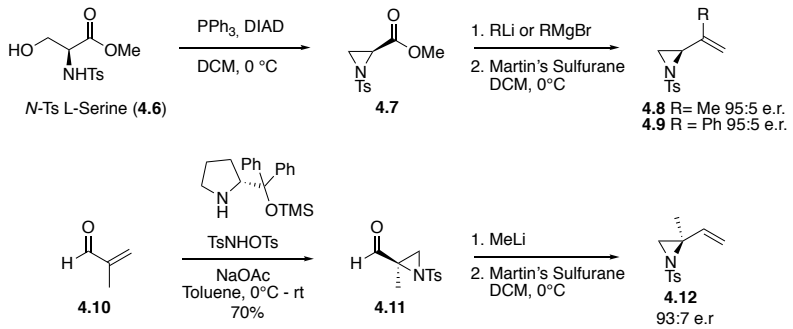


4.5

[a] Reaction conditions: Nitrido-Mn complex (1.6 eq.), Ts_2O (1.9 eq), *N*-oxide (1.9 eq.) Pyridine (0.8 eq.) in anhydrous DCM at 0°C for 2h.

4.2.2.2 Synthesis of vinyl aziridine from amino acid

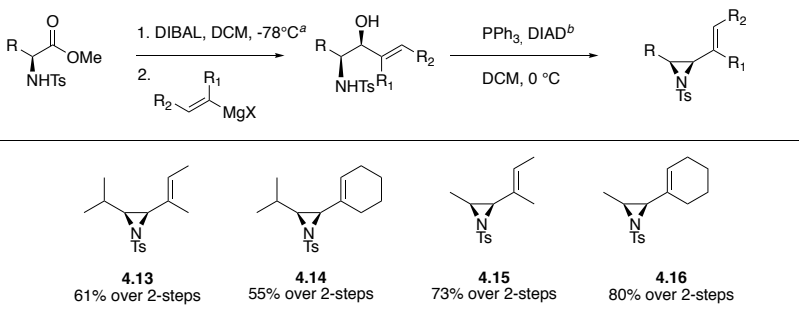
Vinyl aziridine **4.8** and **4.9** was prepared using a known procedure starting from L-serine.[207] The procedure involves initial cyclisation of the amino alcohol to aziridine **4.7**. Addition of alkyl lithium or Grignard reagent to the methyl ester followed by dehydration of the resulting alcohol afforded the vinyl aziridines (Scheme 4.3). Vinyl aziridine **4.12** afforded by enantioselective aziridination of metacrolein[208] (**4.10**) to aziridine **4.11**. Addition of methyl lithium followed by dehydration using Martin's sulfurane resulted in aziridine **4.12**.



Scheme 4.3
Synthesis of acyclic vinyl azirdines from L-serine and metacrolein

The remaining vinyl aziridines were synthesised from *N*-Ts L-alaninate and *N*-Ts L-valinate. Initially, the methyl ester was reduced to the corresponding aldehyde before attempting diastereoselective 1,2 addition using organolithium, organozinc and grignard reagent. However, the diastereoselectivity of these reaction were very poor even in the presence of a lewis acid (BBr_3, Et_2AlCl, Me_3Al).

Table 4.2
Acyclic vinyl aziridines from L-valine and L-alanine[a,b]



[a] Reaction conditions of the one-pot protocol: *N*-Ts L- amino ester (1 eq.) DIBAL-H (2 eq. 1.0M in heptane) stirred for 1-2h at -78 °C before adding the grignard reagent (3 eq. 0.5 M in Et_2O). [b] Reaction conditions: amino alcohol (1 eq.), PPh_3 (1.1 eq.) and DIAD (1.1 eq.) in DCM at 0 °C

Eventually, it was found that the best diastereoselectivity was achieved by adopting a one-pot reduction/1,2 addition procedure.[209] Reduction of the methyl ester with DIBAL-H to the aldehyde would form the chelated species **A**. The stereoselectivity was then governed by chelation controlled addition of the carbon nucleophile to the less hindered face. Subsequent cyclisation of the amino alcohol using the Mitsunobu protocol resulted in aziridine **4.13 – 4.16**.

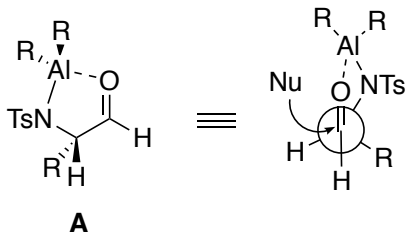


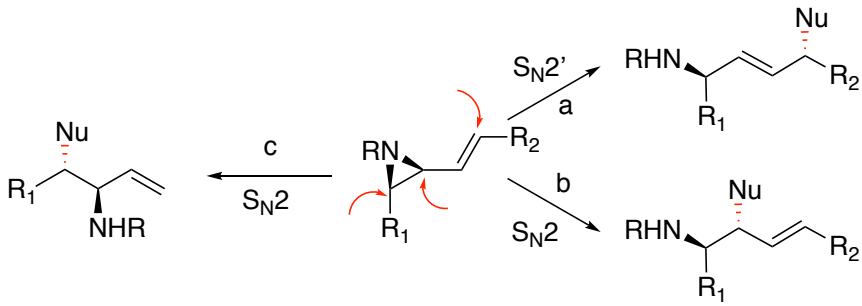
Figure 4.2
Chelation controlled addition of a carbon nucleophile

4.2.3 Conclusions

In summary, cyclic aziridines **3.30** and **4.4** were synthesised according to the [2+1] nitrene addition protocol.[164] Vinyl aziridine **4.8-4.9** and **4-12** were synthesised according to known procedures.[207-208] For the remaining vinyl aziridine **4.13-4.16** it was found that a one-pot reduction/1,2 addition protocol gave the best diastereoselectivity.

4.3 Regioselective aminolysis of vinyl aziridine

Regioselective ring opening of vinyl aziridine with a nitrogen nucleophile is a convenient and efficient method to afford the 1,2-diamino motifs. Such scaffolds are found in many biologically active compounds and natural products. The reaction can occur on or the vinylic position (S_N2' reaction, path a) giving rise to 1,4-diamino scaffolds or the allylic position (S_N2 reaction path b) leading to the 1,2-diamino scaffolds. The reaction can in principle occur on the terminal position (path c) however this is highly unfavourable (Scheme 4.4). The regioselectivity is highly affected by steric factors. Large substituents on the alkene disfavours the S_N2' path while large substituents around the aziridine disfavours the S_N2 path.



Scheme 4.4
Regioselectivity in the ring opening of vinyl aziridine

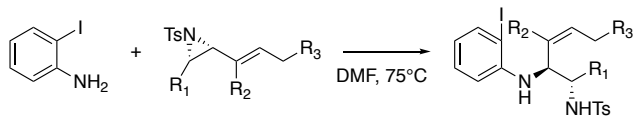
4.3.1 Aim of the project

The aim of this project was to investigate the regioselectivity in the ring opening reaction of vinyl aziridine with various substituted 2-iodoanilines. Many reports have shown that ring opening on the allylic position is the most favoured. Our goal was to access allyl anilines that are suitable for constructing the indoline scaffolds thus we aimed for the ring-opening to occur on the allylic position.

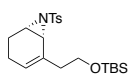
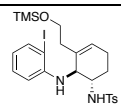
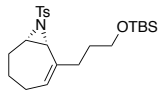
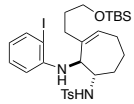
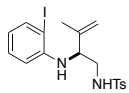
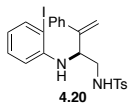
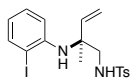
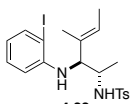
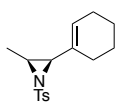
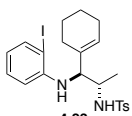
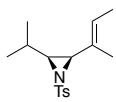
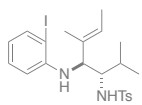
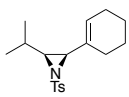
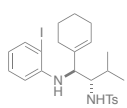
4.3.2 Results and Discussion

Treatment of vinyl aziridine **3.30** with two equivalent of 2-iodoaniline (**4.17**) in DMF at 75 °C, overnight resulted in the desired 1,2-diamino product **3.29** as the major regioisomer with trace amount of the corresponding 1,4-diamino product. The stoichiometry of the nitrogen nucleophile was crucial to afford the desired regioselectivity as it was found that the use stoichiometric amount of the nitrogen nucleophile resulted in a 2:1 product mixture with the S_N2 product as the major component. Subjecting **4.4** to identical reactions conditions afforded 1,2-diamine **4.18** in excellent yield (Entry 2, Table 4.3). For the acyclic series, vinyl aziridines **4.8 – 4.9** and **4.12** were subjected to the optimised reaction conditions and resulted in 1,2-diamine **4.19 – 4.21** in good to excellent yield and with excellent stereoselectivity (Entries 3-5, Table 4.3). Additionally, treatment of vinyl aziridine **4.13** and **4.14** to the identical reaction conditions furnished the desired product **4.22** and **4.23** in moderate yield and moderate d.r. However, when aziridine **4.15** and **4.16** were subjected to the same reaction conditions the outcomes were different. The expected products **4.24 – 4.25** were not observed at 75 °C and the starting materials were not consumed. Rising the temperature to 100 °C turned out to be favouring the S_N2' product and no trace of the desired products **4.24 – 4.25** were found. It seemed that the allylic position was blocked by the bulky isopropyl group.

Table 4.3
Ring-opening reactions of various cyclic and acyclic vinyl aziridine with 2-iodoaniline[a]



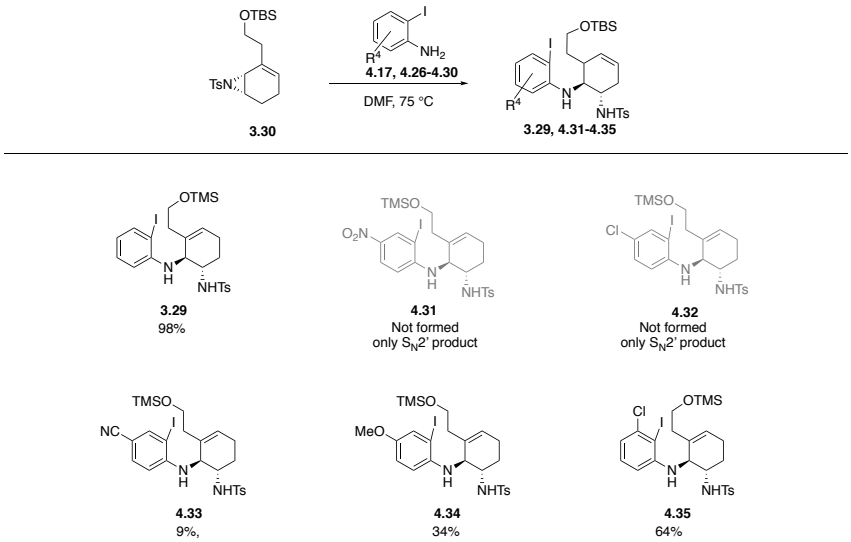
4.17 **3.30, 4.4, 4.8-4.9, 4.12 4.13-4.16** **3.29, 4.18-4.25**

Entry	Vinyl aziridine	Product	Yield (%)	e.r and d.r
1	 **3.30**	 **3.29**	98	54:46 e.r.
2	 **4.4**	 **4.18**	80	55:45 e.r.
3	 **4.8**	 **4.19**	72	95:5 e.r.
4	 **4.9**	 **4.20**	65	95:5 e.r.
5	 **4.12**	 **4.21**	70	95:5 e.r.
6	 **4.13**	 **4.22**	40	68:32 d.r.
7	 **4.14**	 **4.23**	47	72:28 d.r.
8	 **4.15**	 **4.24**	n.d.	n.d.
9	 **4.16**	 **4.25**	n.d.	n.d.

[a] Reaction condition: Vinyl aziridine (1 eq.) and 2-iodoaniline (2 eq.) were heated to 75°C in DMF

We then continued to explore other substituted 2-iodoanilines to perform ring-opening on vinyl aziridine **3.30** (Table 4.4). Ring-opening of **3.30** were performed with 2-nitro-4-nitroaniline (**4.26)**, 4-chloro-2-iodoaniline (**4.27**), 4-amino-3-iodobenzonitrile (**4.28**), 2-iodo-4-methoxyaniline (**4.29**) and 3-chloro-2-iodoaniline (**4.30)**. It was found that 2-iodoaniline with substituent on the *para* position, **4.26, 4.27** and **4.28** performed the weakest. For aniline **4.26** and **4.27** The ring opening occurred preferentially on the vinylic position and only trace amount of the desired S_N2 products **4.31** and **4.32** were observed. Aniline **4.28** performed slightly better however not to satisfactory yield. The best results were achieved for ring-opening reactions with **4.17, 4.29** and **4.30**.

Table 4.4
Ring opening of **3.30** with various anilines[a]



[a] Reaction condition: Vinyl aziridine (1 eq.) and 2-iodoaniline (2 eq.) were heated to 75°C in DMF

4.3.3 Conclusions

The ring-opening of vinyl aziridine with various substituted 2-iodoanilines was performed and in most cases delivered the desired regioisomer. It was speculated that the bulky isopropyl group hampered the ring opening on the allylic position. It was also noted that anilines with electron withdrawing substituents on the *para* position preferentially give the S_N2' products.

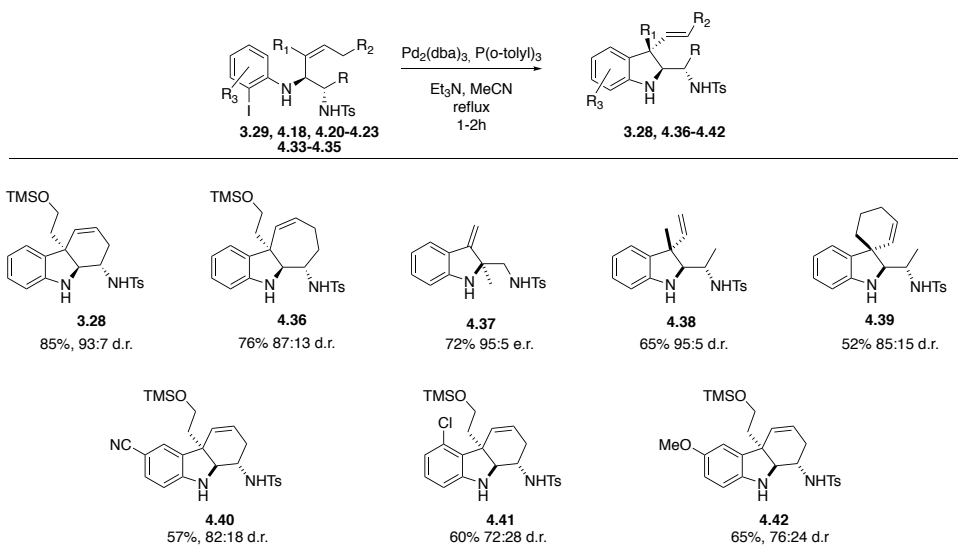
4.4 Intramolecular Heck reaction of diamine

With the allyl aniline **3.29, 4.18 – 4.23** and **4.33 – 4.35** in hand, we then shift our focus to investigate the intramolecular Heck reactions on these substrates. The aim was to construct indoline scaffolds that feature a quaternary stereocenter.

4.4.1 Results and Discussion

Intramolecular Heck reactions in $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, Et_3N in MeCN (reflux, 1h) were performed on diamine **3.29, 4.18 , 4.20 – 4.23** and **4.33 – 4.35** (Table 4.5). Indoline **3.28, 4.36 – 4.42** was afforded in good to excellent yield and with high diastereoselectivity. The relative stereochemistry of the major diastereomer was determined by nOe studies (Table 4.5).

Table 4.5
Intramolecular Heck reactions of allyl anilines to afford various indoline scaffolds with quaternary stereocentre[a]

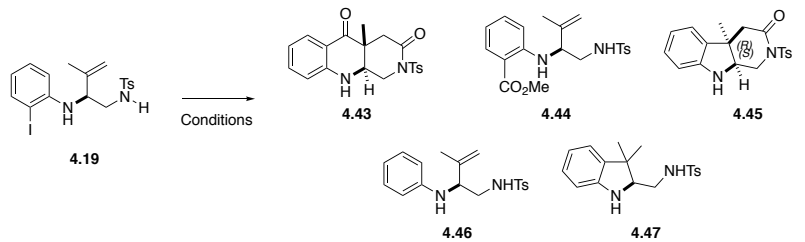


[a] Reaction condition: Allyl aniline (1 eq.), $Pd_2(dba)_3$ (15 mol%), P(*o*-tolyl)$_3$ (15 mol%), Et_3N (5 eq.) were heated to reflux in MeCN for 1-2h.

For diamine **4.19**, we wanted to investigate domino heck reactions. Diamine **4.19** was subjected to domino carbopalladation/carbonylation[163] resulting in the formation of double carbonylation product **4.43** in 68% yield, a product of direct carbonylation of the aryl-Pd(II) complex and subsequent carbopalladation carbonylation sequence of this intermediate. Addition of the proximal *N*-Ts amide to this intermediate resulted in lactam **4.43** (Entry 1, Table 4.6). We then

investigated the reductive heck reaction on the same substrate. Treatment of **4.19** to $Pd(OAc)_2$, n-Bu_4NCl and sodium formate as hydride source furnished compound **4.46** (Entry 3, Table 4.6). This indicates that direct insertion of hydride or carbonyl of the aryl-Pd complex is faster than insertion of the alkene. It is believed that the strong coordination of the 1,2-diamine motif to Pd is the reason to the slow alkene insertion.[210] Coordination of the diamine leads to locked conformation of **4.19** thus makes the alkene not available for insertion. Higher temperature will likely break up any coordination of the nitrogen to Pd. To investigate the plausibility of our initial hypothesis, we then carried out reductive heck reaction at elevated temperature (100°C). To our delight, we were able to isolate the desired indoline product **4.47** in 72% yield together with reduced diamine **4.46** (Entry 5, Table 4.6).

Table 4.6
Intramolecular domino Heck reactions



4.19 **4.43** **4.44** **4.45** **4.46** **4.47**

Entry	Pd Source	Ligand	Temperature	Quencher	Product/(yield) [f]
1 [b]	$Pd_2(dba)_3$	P(*o*-furyl)$_3$	70°C	CO (1 atm) [c]	**4.43** (68%) **4.44** (30%) **4.45** (n/a)
2 [d]	$Pd(OAc)_2$	n-Bu_4NCl	70°C	CO (1 atm) [c]	**4.43** (45%) **4.44** (55%) **4.45** (n/a)
3 [b]	$Pd_2(dba)_3$	P(*o*-furyl)$_3$	70°C	NaCOOH	**4.46** (80%) **4.47** (n/a)
4 [d]	$Pd(OAc)_2$	n-Bu_4NCl	70°C	NaCOOH	**4.46** (65%) **4.47** (n/a)
5 [d]	$Pd(OAc)_2$	n-Bu_4NCl	100°C	NaCOOH	**4.46** (10%) **4.47** (72%)
6 [d]	$Pd(OAc)_2$	n-Bu_4NCl	100°C	CO (1 atm) [e]	**4.43** (7%) **4.44** (45%) **4.45** (30%)[g],

[a] Reactions were run on 0.22 mmol scale of **4.19** in DMA and Pd source, Ligand, Et_3N (2.5 eq). [b] 5 mol% $Pd_2(dba)_3$, and 30 mol% P(*o*-furyl)$_3$. [c] Solvent mixture DMA/MeOH (80:20). [d] 2 mol% $Pd(OAc)_2$, 1 eq. n-Bu_4NCl and 1 eq. NaCOOH. [e] MeOH (1 eq). [f] isolated yields. [g] 74:26 d.r.determined by nOe experiment.

This finding inspired us to investigate the domino carbopalladation carbonylation at elevated temperature. Treatment of diamine **4.19** to $Pd(OAc)_2$, *n*-Bu_4NCl, Et_3N, CO (1 atm) in MeCN (100°C, 1h) resulted in the desired carbonylation carbopalladation product **4.45** in 30% yield together with pre-ester product **4.44** and double carbonylation product **4.43** (Entry 6, Table 4.6). These results imply that the system is more flexible at higher temperature and competition between direct carbonylation and carbopalladation after the initial oxidative addition can be altered by this method.

4.5 Conclusions and Remarks

In summary, we have developed a rapid method to construct indoline scaffolds featuring a quaternary stereocenter. The indoline scaffolds was constructed by employing the intramolecular Heck reaction on allyl anilines. Moreover, we have also demonstrated domino carbopalladation and reductive heck reaction on one of the substrates. The desired reaction outcome was made possible by studying the temperature dependence of the reaction.

5 Concluding remarks

In this thesis, we have studied total synthesis of natural products that are biologically active as well as development of a new method to construct indoline scaffolds that features a quaternary stereocenter.

Specifically, we have developed an efficient total synthesis of (±)-dehaloperophoramidine. We were able to construct the vicinal quaternary stereocenters by employing Overman's diastereoselective dialkylation protocol. Furthermore, implementation of a desymmetrisation step increased the brevity of the synthesis. The formation of the unanticipated *ortho*-amide and careful study of this functional group led to the discovery of a new domino process. The discovery of the two final domino processes was crucial for the efficiency of the synthesis.

For the study towards the synthesis of strictamine, we were able to implement the intramolecular Heck reaction to construct the indoline core of strictamine as well as the quaternary stereocenter. This indoline scaffold containing the quaternary stereocenter was elaborated to a very advanced intermediate. We sought to adopt the domino carbopalladation/carbonylation protocol and intramolecular substitution reaction to construct the cage-like methanoquinolizidine core. Our strategy to install the E ring before the C ring was however unsuccessful, and resulted in the formation of a β-lactam. By altering the order of ring-constructing event, it was possible to access four out five rings in strictamine. The final ring was possible to install using Ni mediated domino Heck reaction. Unfortunately, it was not possible to install the final methyl ester group.

Finally, we have also developed a rapid method to construct indoline scaffolds featuring a quaternary stereocenter by adopting the intramolecular Heck reactions and domino Heck reactions on allyl anilines. The allyl anilines were available from a regioselective ring-opening of vinyl aziridines with 2-iodoanilines.

6 Acknowledgment

First and foremost, I would like to thank my supervisor professor Peter Somfai, for accepting me as a PhD Student. It has been five rewarding years in your group. Thank you for sharing your knowledge about organic chemistry and all your support during my PhD study. I truly appreciate that your office was always opened to discussions about small or big problems.

I would also like to thank Filip and Peter for taking time and helped me proofread this thesis and giving me valuable feedbacks.

I would like to thank former and present members of the PS-group (Jakob, Kirill, Marvin, Angelo, Andreas, Valerio, Lu, Giovanni, and Juha) for providing a good atmosphere. Thanks to Kirill and Jakob for teaching me about total synthesis when I just started in the group and for all the useful discussions. Kirill, it was a pleasure collaborating with you on the perophoramidine/dehaloperophoramidine project. I have learned a lot from you! Special thanks to Angelo, it was never boring having you in the lab! Thank you for all the interesting discussions we had and for teaching me the best Italian words – "Jurnata rutta, rumpila tutta". Thank you Lu, for being my lab mate for the last years and all your support during this time! Thanks to all my former students for giving me the opportunity to learn with you and to be developed as a supervisor. Elisabet, thank you for helping me with the perophoramidine project. Marie and Samuel, thank you for all your help in the indoline project. Gintare for your help with producing materials for me in the strictamine project.

Thanks to all the co-workers at CAS for creating a good environment to work in. Filip, I am very grateful to have you as a friend and colleague. You inspire me! Thanks for being the best study buddy and for listening to all my problems in the lab. Thank you Maria-Luisa for your cheerfulness and your encouragement. Michaela, our trip to the Boston conferences was the best. Roman, thank you for all the coffee time and interesting discussions! Special thanks to Kristoffer, Daniel, Niels, Olga, Valtyr, and Alexander D., for making teaching fun!

I would also like to thank Maria, Bodil and Katarina for all your efforts to make CAS a pleasant work place and keeping it running smoothly! Thank Sofia, for all your help with mass spectroscopy. Karl-Erik for help with the NMR.

Thanks to all the groups that I have borrowed chemicals or equipments from.

Thanks to the Swedish Research Council, the Royal Swedish Academy of Science and the Royal Physiographic Society in Lund for financial support.

I would like to express my gratitude to my closest friends: Minh Tue, Hompe, Minh Thu and Oliver. Thank you for your support and for believing that I can make it. Without you guys, my spare time would be so boring. Thank you for creating the relaxing environment that I need to keep on going.

I would like to thank my parents, brothers and sisters for their encouragement and support during this time.

Cảm ơn bố và mẹ vì đã dành những điều tốt đẹp nhất cho con. Cảm ơn bố mẹ đã luôn luôn tin tưởng vào con và tạo đủ điều kiện cho con có được thành công ngày hôm nay.

Last but not least, I would like to give my deepest gratitude to my love. Thank you David (Trung) for your support, patience and love. Thank you for being my steady foundation during the stressful periods. Without you, this thesis would not be possible.

7 Appendix

Experimental procedures and NMR data for unpublished compounds

Isoindigo **2.40b**

To a suspension of bromo-oxindole **2.42** (1.24 g, 3.68 mmol) and PMB-dichloroisatine **2.41** (0.780 g, 3.68 mmol) in glacial AcOH (9 mL) was added catalytic amount of concentrated HCl. The orange suspension was heated to reflux and stirred for 8 h. The resulting red suspension was allowed to cool to rt. and the precipitate was then collected and washed with water, heptane and diethyl ether to yield isoindigo **2.40b** as a dark red solid (1.31 g, 66 %) ^{1}H NMR (400 MHz, DMSO) δ = 11.20 (s, 1H), 9.26 (s, 1H), 8.95 (dd, J = 29.9, 8.4 Hz, 1H), 7.58 (s, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.02 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.29 (s, 2H), 3.70 (s, 3H) ppm.

Isoindigo **2.40c**

Anhydrous DMF (20 mL) was added to a mixture of **2.40b** (500 mg, 0.943 mmol), flame dried Cs_2CO_3 (371 mg, 1.14 mmol) and DMAP (1.3 mg, 0.013 mmol). *p*-toluenesulfonyl choride (225 mg, 1.18 mmol) was added slowly under N_2(g). The resulting red solution was heated to 60 °C and stirred for 10 h. The reaction solution was then poured into aqueous NH_4Cl at 0 °C and extracted with EtOAc and dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the tosyl protected isoindigo **2.40c** (614 mg, 95 %) as dark brown solid without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.97 (d, J = 8.7 Hz, 1H), 8.79 (d, J = 2.0 Hz, 1H), 8.2 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.33 (dd, J = 8.7, 1.9 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 5.33 (s, 2H), 3.75 (s, 3H), 2.43 (s, 3H) ppm.

Isoindigo **2.40d**

Anhydrous DMF (0.35 M) was added to a mixture of isoindigo (1.0 eq), flame dried Cs_2CO_3 (1.2 eq) and DMAP (0.50 mol%). Benzyl bromide (1.2 eq) was addedslowly under N_2(g). The resulting red solution was heated to 60 °C and stirred for 48 h. The reaction The reaction solution was then poured into aqueous NH_4Cl at 0 °C and a dark maroon precipitated. The solid was collected and washed with water and thereafter heptane to yield benzyl protected isoindigo

withoutfurther purification (97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, J = 7.5 Hz, 1H), 7.36 – 7.27 (m, 8H), 7.18 (dd, J = 8.6, 1.9 Hz, 1H), 7.04 (dd, J = 11.4, 4.2 Hz, 1H), 6.86 (dd, J = 7.2, 5.3 Hz, 3H), 6.74 (d, J = 7.7 Hz, 1H), 4.99 (s, 2H), 4.94 (s, 2H), 3.77 (s, 3H).

Isoindigo **2.40e**

To a suspension of bromo-oxindole **2.42** (1.24 g, 3.68 mmol) and PMB-dichloroisatine **2.41** (0.780 g, 3.68 mmol) in glacial AcOH (9 mL) was added catalytic amount of concentrated HCl. The orange suspension was heated to reflux and stirred for 8 h. The resulting red suspension was allowed to cool to rt. and the precipitate was then collected and washed with water, heptane and diethyl ether toyield isoindigo **2.40b** as a dark red solid (1.31 g, 66 %) ^{1}H NMR (400 MHz, DMSO) δ = 9.13 (d, J = 8.5 Hz, 1H), 9.09 (dd, J = 8.5 Hz, 1H), 7.49 (s, 1H),7.20 (d, J = 8.5 1H), 7.04 – 6.99 (m, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 8.5 Hz 1H), 4.93 (s,2H), 3.77 (s, 3H) ppm.

Isoindigo **2.40f**

Anhydrous DMF (0.35 M) was added to a mixture of isoindigo **2.40b** (1.0 eq), flame dried Cs_2CO_3 (1.2 eq) and DMAP (0.50 mol%). PMB-Cl (1.2 eq) was added slowly under N_2(g). The resulting red solution was heated to 60 °C and stirred for 48 h. The reaction The reaction solution was then poured into aqueous NH_4Cl at 0 °C and a dark maroon precipitated. The solid was collected and washed with water and thereafter heptane to yield PMB protected isoindigo **2.40f** without further purification (97 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, J = 7.5 Hz, 1H), 7.36 – 7.27 (m, 8H), 7.18 (dd, J = 8.6, 1.9 Hz, 1H), 7.04 (dd, J = 11.4, 4.2 Hz, 1H), 6.86 (dd, J = 7.2, 5.3 Hz, 3H), 6.74 (d, J = 7.7 Hz, 1H), 4.99 (s, 2H), 4.94 (s, 2H), 3.77 (s, 6H).

Bisoxindole **2.50b**

To a solution of isoindigo **2.40d** (1.00 g, 1.89 mmol) in THF (18.2 mL) was added AcOH (0.60 mL, 10.6 mmol). Zinc dust (739 mg, 11.3 mmol) was added slowly at rt. The red suspension was stirred for 10 min at rt. and the reaction was complete when the red colour was disappeared. The suspension was filtered through a pad of celite and eluting with EtOAc. The eluent was dried with $MgSO_4$, filtered and solvent was removed *in vacuo* to yield bisoxindole as a white solid and was used directly in the next step. A solution of bisoxindole (150 mg, 0.27 mmol) in anhydrous THF (4ml) was cooled down to - 78 °C at which time NaHMDS (0.62 mL, 1.0M in THF) was added dropwise over 5 min and maintained at - 78 °C resulting in a deep green solution. After 1 hour, a solution of dielectrophile 7 (116 mg, 0.27 mmol) in anhydrous THF (1.4 mL) was added dropwise over 10 min at - 78 °C. The reaction solution was kept at - 78 °C for 8 h and was thereafter partitioned between EtOAc (10 mL) and Brine (10 mL) and separated. The water

phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to a white solid. The white solid was purified by flash chromatography (Heptane/EtOAc 3:1) to yield **2.50b** as a white solid (88.7 mg, 45 % 53:47 dr). Data for major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 1H), 7.38 – 7.29 (m, 4H), 6.97 (t, J = 7.6 Hz, 2H), 6.65 – 6.52 (m, 6H), 6.30 (dd, J = 7.9, 4.1 Hz, 4H), 5.85 (d, J = 8.2 Hz, 1H), 5.31 – 5.23 (m, 1H), 5.11 (d, J = 12.2 Hz, 1H), 4.36 (ddd, J = 13.0, 9.4, 4.1 Hz, 1H), 4.21 (d, J = 15.9 Hz, 1H), 3.26 (q, J = 12.0 Hz, 2H), 2.02 (ddd, J = 15.5, 9.6, 4.1 Hz, 2H), 1.57 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.2, 158.9, 144.5, 143.0, 135.2, 130.2, 129.5, 128.9, 128.8, 127.7, 127.6, 127.3,126.5, 125.9, 124.6, 122.1, 114.1, 113.3, 110.4, 110.1, 75.2, 73.1, 55.3, 55.0, 52.1,43.6, 34.7, 32.5, 31.9, 27.1 ppm.

Samarium mediated reductive alkylation

Anhydrous LiCl (896 mg, 21.1 mmol, flame-dried under vacuum) was added to **3.40** (504 mg, 1.92 mmol) which had been azeotropically dried with PhH and the mixture was left under high vacuum for 10 h at 50°C. A deoxygenated solution of samarium diiodide (55 mL, 0.09 M, 5.00 mmol) in dry THF was added quickly in one portion at rt. The vigorously stirred reaction mixture turned from blue to black over 10 min. Freshly distilled *cis*-1,4-dichloro-2 butene (280 µl mL, 2.66 mmol) was added at 0 °C. After 5 h at ambient temperature, the crude reaction mixture was poured into H_2O (50 mL). Saturated aqueous $Na_2S_2O_3$ (50 mL) was added and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were rinsed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica. Elution with n-heptane/EtOAc (2:1→1:1→1:2) gave **3.39** as pink amorphous solid.

3.39d

^{1}H NMR(500 MHz, DMSO-d_6) δ 10.24 (s, 1H), 10.12 (s, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.13 – 6.94 (m, 2H), 6.82 – 6.64 (m, 2H), 6.46 (s, 1H), 5.97 (s, 1H), 5.88 (s, 1H), 5.58 (s, 1H), 3.25 (d, J = 16.4 Hz, 1H), 2.63 (d, J = 18.9 Hz, 1H), 2.21 (d, J = 18.9 Hz, 1H), 1.85 (d, J = 17.1 Hz, 1H). ^{13}C NMR(126 MHz, DMSO-d_6) δ 177.7, 142.2, 142.1, 132.1, 130.0, 128.5, 128.2, 125.6, 124.7, 123.8, 122.6, 121.62, 120.2, 109.4, 108.7, 50.2, 47.6, 32.3, 29.9.

Aziridine **3.30**

To the nitridomangangese complex **3.37a** (26 g, 67 mmol) was added a solution of 4-phenylpyridine *N*-oxide (16 g, 168 mmol) in DCM (140 mL) and the solution was cooled to 0°C. A solution of Ts_2O (22 g, 67 mmol) in DCM (280 mL) was added dropwise followed by a solution of diene **3.31** (10 g, 42 mmol) in DCM (70 mL) and finally pyridine (2.7 mL, 34 mmol) was added. The reaction mixture was stirred at 0 °C under an inert nitrogen atmosphere until the diene was consumed according to TLC. The reaction was quenched by addition of pentane (500 mL) and Celite (500 mg) and the reaction mixture was allowed to stir for additional 10 minutes. The reaction mixture was then passed through a 10 cm pad of silica with Et_2O as eluent. The filtrate was concentrated under vacuum and the crude was purified by flash chromatography (*n*-Heptane/Ethyl acetate, 9:1) to afford aziridine **3.30** (6.2 g, 36%) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.7 Hz, 1H), 5.57 (dt, J = 4.8, 1.3 Hz, 1H), 3.58 (ddd, J = 10.1, 7.5, 6.0 Hz, 1H), 3.47 (dt, J = 10.1, 7.2 Hz, 1H), 3.30 (dd, J = 7.2, 1.3 Hz, 1H), 3.07 (dd, J = 7.2, 1.7 Hz, 1H), 2.40 (s, 3H), 2.23 (tdd, J = 5.8, 4.7, 4.1, 2.6 Hz, 2H), 2.06 – 1.80 (m, 2H), 1.51 – 1.33 (m, 1H), 0.85 (s, 9H), -0.00 (d, J = 2.9 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 135.6, 129.6, 129.5, 127.7, 127.56, 62.2, 41.9, 39.8, 39.7, 25.9, 21.6, 20.2, 18.7, 18.2, -5.3

Diamine **3.29**

A solution of aziridine **3.30** (2.7 g, 7.0 mmol) and 2-iodoaniline (2.9 mg, 14 mmol) in DMF (14 mL) was heated at 75 °C overnight. The reaction was monitored by TLC and by completion the crude was poured into water (140 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with water (4 × 50 mL), Brine (50 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography using silica gel to give compound **3.29** (2.1 g, 98%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.63 (dd, J = 7.9, 1.5 Hz, 1H), 7.34 (dd, J = 8.6, 0.7 Hz, 2H), 7.08 – 7.01 (m, 1H), 6.45 (ddd, J = 7.8, 7.2, 1.4 Hz, 1H), 6.24 – 6.19 (m, 1H), 5.79 (t, J = 3.7 Hz, 1H), 4.70 (d, J = 8.9 Hz, 1H), 4.07 (d, J = 7.7 Hz, 1H), 3.73 – 3.66 (m, 2H), 3.64 (d, J = 7.9 Hz, 1H), 3.61 – 3.54 (m, 1H), 2.48 (s, 3H), 2.32 – 2.19 (m, 2H), 2.15 (d, J = 7.0 Hz, 2H), 1.79 (dtd, J = 14.0, 8.9, 8.4, 2.6 Hz, 1H), 1.58 (s, 2H), 0.92 (s, 9H), 0.08 (d, J = 1.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 143.6, 139.3, 137.9, 132.2, 129.9, 129.7, 128.3, 127.4, 119.2, 110.8, 85.6, 62.0, 54.3, 49.4, 38.5, 26.2, 21.7, 21.5, 20.4, 18.5, 5.0.

Dihydrocarbazole **3.28**

To a stirred solution of diamine **3.29** (2.00 g, 3.19 mmol), $Pd_2(dba)_3$ (296 mg, 0,31 mmol) and P(*o*-tolyl)$_3$ (104 mg, 0.33mmol) in MeCN (20 mL) was added Et_3N (1.34 mL, 9.59 mmol) at room temperature and the solution was stirred for 1h at reflux. The solvent was removed *in vacuo*, and the reaction crude was purified by column chromatography to afford the product **3.28** (1.35 g, 85 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.63 (dd, J = 7.9, 1.5 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.04 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 6.45 (td, J = 7.5, 1.4 Hz, 1H), 6.21 (dd, J = 8.3, 1.4 Hz, 1H), 5.79 (t, 1H), 4.80 (d, J = 8.7 Hz, 1H), 3.70 (dd, J = 7.2, 6.2 Hz, 2H), 3.64 (s, 1H), 3.61 – 3.54 (m, 1H), 2.48 (s, 3H), 2.30 – 2.21 (m, 1H), 2.20 – 2.11 (m, 2H), 1.79 (dtd, J = 13.9, 8.8, 2.6 Hz, 1H), 1.59 (dt, J = 14.2, 4.1 Hz, 1H), 1.29 (s, 1H), 0.92 (s, 10H), 0.08 (d, J = 0.9 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 143.4, 139.2, 137.8, 132.0, 129.8, 129.6, 128.2, 127.3, 119.0, 110.7, 85.4, 61.9, 54.2, 49.3, 38.4, 26.0, 21.6, 21.4, 20.3, -5.1, -5.2 mp: 176.8 – 178.2 °C

Primary amine **3.39**

To a stirred deep blue solution of SmI_2 (192 mL, 14.6 mmol, 0.07 M in THF) was added a solution of **3.28** (727 mg, 1.46 mmol) in THF (15 mL) followed by H_2O (788 µl, 43.7 mmol) and pyrrolidine (2.43 mL, 29.1 mmol) under a nitrogen atmosphere. The reaction mixture immediately turned white upon addition of the amine. The reaction was stirred for 1h and monitored by TLC analysis. The reaction was then diluted with Et_2O (100 mL) and treated with a solution of potassium sodium tartrate (100 mL, 10% w/v) and potassium carbonate (100 mL, 10% w/v). The aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The reaction crude was purified by flash chromatography (Et_2O/2-i$PrNH_2$ 98:2) to provide the product **3.39** (497 mg, 99%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 6.98 (m, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.00 (dd, *J* = 9.9, 2.7 Hz, 1H), 5.74 (ddd, *J* = 10.0, 6.3, 2.0 Hz, 1H), 3.78 – 3.65 (m, 1H), 3.67 – 3.57 (m, 1H), 3.30 (d, *J* = 9.8 Hz, 1H), 2.60 (td, *J* = 10.0, 4.5 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.95 (ddd, *J* = 13.6, 8.2, 6.8 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.77 (ddd, *J* = 13.4, 7.8, 5.2 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 135.5, 131.0, 127.5, 124.3, 122.9, 118.7, 110.6, 69.5, 59.9, 50.6, 50.1, 43.4, 34.1, 26.0, 18.2, -5.3.

Secondary amine **3.27**

To a solution of **3.39 (**27 mg, 78 mmol) in THF (0.35 mL) and DMF (0.35 mL) were added 4Å molecular sieves. A solution of **3.40** in THF (0.10 mL) and DMF (0.10 mL) as added dropwise with syringe pump over 1h. The reaction was stirred in the dark at room temperature for 24h. The reaction was then filtered and the filtrate was poured into H_2O (1 mL) and extracted with Et_2O (2 × 3 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (n-Heptane/EtOAc 4:1) to provide the product **3.27** (32 mg, 78%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (td, *J* = 7.6, 1.3 Hz, 1H), 7.04 – 6.97 (m, 1H), 6.78 – 6.70 (m, 2H), 6.01 (dd, *J* = 9.9, 2.7 Hz, 1H), 5.79 – 5.71 (m, 2H), 3.76 – 3.66 (m, 1H), 3.65 – 3.56 (m, 2H), 3.41 – 3.31 (m, 2H), 2.42 – 2.30 (m, 2H), 1.95 (ddd, *J* = 13.6, 8.3, 6.8 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.72 (dt, *J* = 6.4, 1.0 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 135.4, 131.9, 131.2, 127.5, 124.0, 122.8, 118.7, 111.1, 67.7, 60.0, 58.3, 55.0, 50.2, 43.3, 29.1, 26.0, 21.7, 18.2, -5.3.

Beta lactam **3.41**

To a flame dried schlenk tube was added $Pd_2(dba)_3$ (2.3 mg, 2.5 µmol), P(*o*-furyl)3 (3.5 mg, 15 µmol) and DMAP (2.4 mg, 20 µmol). The schlenk tube was evacuated/backfilled with N_2 (3×). To this was added a solution of **7** (23 mg, 44 µmol) in dry DMA (0.8 mL) followed by dry MeOH (0.2 mL). The reaction mixture was purged with CO (3×) and kept under an atmosphere of CO (ballon) at 70°C overnight. The reaction mixture was diluted with EtOAc (5 mL) and washed with H_2O (3 × 5ml). The combined aqueous phases were extracted with EtOAc (2 × 5ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to a brown solid. The crude reaction mixture was purified by flash chromatography (Heptane/EtOAc 4:1) to provide the product **3.41** (9 mg, 47%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (td, *J* = 7.6, 1.3 Hz, 1H), 7.01 (ddd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 6.77 – 6.69 (m, 2H), 6.05 (ddd, *J* = 10.0, 2.3, 1.3 Hz, 1H), 5.80 – 5.74 (m, 1H), 5.73 – 5.67 (m, 1H), 3.80 (d, *J* = 10.1 Hz, 1H), 3.77 – 3.59 (m, 6H), 2.21 – 2.14 (m, 2H), 2.08 (dt, *J* = 7.2, 1.0 Hz, 3H), 1.98 (dt, *J* = 13.7, 7.5 Hz, 2H), 1.75 (ddd, *J* = 13.8, 6.9, 5.1 Hz, 1H), 0.89 (s, 10H), 0.03 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 148.2, 135.2, 134.4, 131.2, 127.9, 125.6, 122.8, 122.7, 118.8, 110.5, 65.3, 59.9, 52.1, 50.1, 45.3, 42.9, 26.3, 25.9, 18.2, 14.5, -5.3, -5.3.

Alcohol **3.42**

Compound **3.28** (1.24 g, 0.53 mmol) was dissolved in THF (34 mL) and H_2O (34 mL). To this was added acetic acid (120 mL) and stirred vigorously at rt. After 4h, the reaction was quenched by addition of $NaHCO_3$ (400 mL, sat. aq. soln.) and extracted with EtOAc (3 × 150 mL). The combined organic phase was washed with

Brine (200 mL), dried with $MgSO_4$ and concentrated *in vacuo* provided **3.42** (0.96 mg, 99%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 6.9 Hz, 3H), 7.08 (td, *J* = 7.6, 1.3 Hz, 1H), 6.94 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.83 (td, *J* = 7.4, 1.0 Hz, 1H), 6.64 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.89 (dt, *J* = 10.0, 1.8 Hz, 1H), 5.63 – 5.48 (m, 1H), 3.55 (dt, *J* = 12.1, 4.3 Hz, 1H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.23 – 3.08 (m, 2H), 2.42 (s, 3H), 1.97 – 1.84 (m, 3H), 1.74 (ddd, *J* = 14.3, 4.4, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 143.4, 139.2, 137.8, 132.0, 129.8, 129.6, 128.2, 127.3, 119.0, 110.7, 85.4, 61.9, 54.2, 49.3, 38.4, 26.0, 21.4, 20.3, mp: 176.4 – 177.6 °C

Amine **3.43**

To a solution of **3.42** (100 mg, 0.26 mmol) in dry DCM (10 mL) was added triethylamine (43 µL, 0.31 mmol) and methanesulfonyl chloride (40 µL, 0.51 mmol) dropwise. The mixture was stirred at rt. over 1h and then heated to reflux for additionally 1h. DMAP (3.2 mg, 0.026 mmol) was added to the reaction mixture and stirred for 2h at reflux. Reaction was quenched using NH_4Cl (2 mL, sat. aq. soln.) and extracted with DCM (3 × 5 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude reaction mixture purified by flash chromatography (DCM/MeOH 98:2) to provide the product **3.43** (44 mg, 46%) as yellow solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.49 (m, 2H), 7.19 – 7.11 (m, 2H), 6.99 (td, *J* = 7.3, 1.1 Hz, 1H), 6.98 – 6.90 (m, 1H), 6.86 (td, *J* = 7.5, 1.5 Hz, 1H), 6.51 (dt, *J* = 7.5, 0.8 Hz, 1H), 6.25 (ddd, *J* = 9.8, 3.1, 1.3 Hz, 1H), 5.74 (ddd, *J* = 9.8, 5.1, 2.1 Hz, 1H), 3.38 (ddd, *J* = 11.7, 9.2, 4.4 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.74 – 2.59 (m, 1H), 2.53 (ddd, *J* = 12.0, 8.1, 4.3 Hz, 1H), 2.43 (s, 3H), 2.23 – 2.11 (m, 1H), 2.01 – 1.84 (m, 2H), 1.53 (ddd, *J* = 10.9, 8.1, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 147.2, 142.8, 136.6, 129.4, 128.6, 127.2, 126.4, 126.0, 124.6, 120.3, 118.8, 98.4, 81.3, 67.6, 55.6, 54.7, 48.8, 34.9, 33.4, 32.2, 23.7, 21.5

Tetracyclic compound **3.44**

To a cold solution of **3.42** (234 mg, 0.61 mmol) and PPh_3 (176 mg, 0.67 mmol) in dry THF (6 mL) was added dropwise DIAD (132 µL, 0.67 mmol) at 0 °C. The reaction turned slowly yellow upon addition of DIAD. The reaction was warmed to rt. and stirred for 2h. The reaction was concentrated *in vacuo* to a yellow oil. The crude reaction mixture was purified by flash chromatography (DCM/Aceton 98:2) to provide **3.44** (154 mg, 99%) as a yellow solid. ^{1}H NMR (500 MHz**,** $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 3H), 7.14 – 7.06 (m, 2H), 6.86 (td, *J* = 7.4, 1.0 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 5.83 (ddd, *J* = 10.0, 3.5, 2.1 Hz, 1H), 5.20 – 5.10 (m, 1H), 4.64 (t, *J* = 4.6 Hz, 1H), 3.96 (ddd, *J* = 13.0, 5.2, 1.5 Hz, 1H), 3.46 (dd, *J* = 4.0, 1.2 Hz, 1H), 3.38 (td, *J* = 12.6, 4.0 Hz, 1H), 2.55 (ddt, *J* = 19.1, 5.3, 2.6 Hz, 1H), 2.44 (s, 3H), 2.12 – 2.00 (m, 2H), 1.90 (td, *J*

= 12.4, 5.2 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 137.9, 129.7, 127.9, 127.9, 126.8, 126.1, 121.8, 120.5, 111.6, 65.6, 50.7, 43.5, 40.4, 30.7, 26.5, 21.5.

Secondary amine **3.45**

To a stirred deep blue solution of SmI_2 (53 mL, 4.23 mmol, 0.07 M in THF) was added a solution of **3.44** (155 mg, 0.42 mmol) in THF (5 mL) followed by H_2O (228 µl, 12.6 mmol) and pyrrolidine (706 µl, 8.46 mmol) under a nitrogen atmosphere. The reaction mixture immediately turned white upon addition of the amine. The reaction was stirred for 1h and monitored by TLC analysis. The reaction was then diluted with Et_2O (50 mL) and treated with a solution of potassium sodium tartrate (50 mL, 10% w/v) and potassium carbonate (50 mL, 10% w/v). The aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic phases were acidified with HCl (20 mL, 1M, pH <2) and extracted with H_2O (3 × 50 mL) and the organic phase was discarded. The combined acidic aqueous phases were basified with NaOH (30 mL, 1M, pH 15) to freebase compound **3.45**. The basic aqueous phase was extracted with Et_2O (4 × 50 mL) to provide compound **3.45** (92 mg, 99%) and was used directly to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.09 (td, *J* = 7.6, 1.3 Hz, 1H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H), 6.77 (dt, *J* = 7.8, 0.8 Hz, 1H), 6.01 – 5.94 (m, 1H), 5.15 (dt, *J* = 9.8, 2.7 Hz, 1H), 3.57 (d, *J* = 3.8 Hz, 1H), 3.53 – 3.39 (m, 1H), 3.19 (ddd, *J* = 13.0, 12.0, 4.0 Hz, 1H), 2.96 (ddd, *J* = 13.0, 4.9, 1.5 Hz, 1H), 2.66 (ddt, *J* = 18.9, 5.4, 2.6 Hz, 1H), 2.21 (ddt, *J* = 18.9, 3.7, 1.6 Hz, 1H), 2.00 (ddt, *J* = 12.4, 3.8, 1.2 Hz, 1H), 1.86 (td, *J* = 12.2, 4.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 135.8, 128.7, 127.6, 127.2, 121.7, 120.0, 111.4, 68.1, 49.3, 44.1, 39.6, 32.5, 29.5.

Tertiary amine **3.33**

To a solution of **3.45** (135 mg, 64 mmol) in and DMF (3 mL) were added 4Å molecular sieves and Cs_2CO_3 (207 mg, 0.64 mmol). A solution of **3.40** in and DMF (3 mL) as added dropwise with syringe pump over 1h. The reaction was stirred in the dark at room temperature for 24h. The reaction was then filtered and the filtrate was poured into H_2O (60 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (4 × 30 mL), Brine (30 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Heptane/EtOAc 4:1) to provide the product **3.33** (190 mg, 76%) as yellow solid. R_f = 0.30 (Heptane/EtOAc 4:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.09 (td, *J* = 7.6, 1.3 Hz, 1H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.05 – 5.85 (m, 2H), 5.15 (dq, *J* = 9.7, 1.9 Hz, 1H), 3.96 (s, 1H), 3.73 (dd, *J* = 3.7, 1.2 Hz, 1H), 3.46 – 3.26 (m, 3H), 2.80 – 2.68 (m, 2H), 2.34 – 2.15 (m, 2H), 2.09 – 1.89 (m, 2H), 1.84 (dt, *J* = 6.4, 1.3 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 135.4, 131.0, 128.9, 127.5, 126.7, 121.8, 120.0, 111.5, 67.2, 66.5, 53.5, 45.2, 43.8, 31.0, 22.2, 21.7.

Methyl ester **3.46**

To a solution of **13** (8 mg, 20 µmol), DABCO (11 mg, 90 µmol) and DMAP (1.0mg, 8µmol) in anhydrous DMA (0.32 mL), and MeOH (81 µL) was added a solution of $Pd_2(dba)_3$ (102 µL, 1 µmol, 0.01 M in DMA) and P(*o*-furyl)$_3$ (306 µL, 6 µmol, 0.02 M in DMA) under N_2 at rt. The flask was purged with CO (3×, balloon) and heated to 70°C under vigorous stirring. The reaction was monitored by LCMS. The reaction was diluted with EtOAc (5 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (4 × 3 mL), Brine (3 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by preparative TLC (20 × 20 cm plate, 0.5 mm thick, DCM/MeOH 98:2) to provide **13** (6 mg, 91%) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.2 Hz, 1H), 7.12 – 7.04 (m, 1H), 6.83 (dd, *J* = 9.2, 5.6 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 5.99 – 5.88 (m, 2H), 5.13 (s, 1H), 3.79 – 3.73 (m, 3H), 3.60 (s, 1H), 3.40 (d, *J* = 36.0 Hz, 1H), 2.73 (s, 2H), 2.03 – 1.82 (m, 5H), 1.32 (d, *J* = 13.5 Hz, 3H).

Methanoquinolizidine **3.48**

$Ni(COD)_2$ (42 mg, 0.15 mmol) was weighted and added to flask inside a glove box. The reaction was then performed outside the glove box. A solution of **3.33** (20 mg, 0.05 mmol) and Et_3N (35 µL, 0.25 mmol) in MeCN/DMF (2 mL/1 mL) under nitrogen. After stirred for 4 min, the mixture was sparged with CO and added MeOH (10 µL, 0.25 mmol). The reaction was stirred for 30 min then quenched with a solution $NaHCO_3$ (10 mL, aq. sat. soln.). The MeCN was removed under *in vacuo* and the residue was extracted with EtOAc (3 × 5 mL). The combined organics were washed with water (3 × 5 mL) and brine (5 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (20 × 20 cm plate, 0.5 mm thick, DCM/MeOH 98:2) provided a mixture of **3.48** and **3.45** (16 mg).

Compound **3.53**

To a solution of **3.44** (100 mg, 0.27 mmol) in MeCN (5.5 mL) was added 37% w/w HCHO in H_2O (61 µL, 0.82 mmol) and AcOH (47 µL, 0.82 mmol). After stirring for 3 min, $NaBH_3CN$ (51 mg, 0.82 mmol) was added. The reaction was flushed with N_2 for 1 min, and stirred at room temperature. After stirring for 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and diluted with EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were washed with brine (10 mL) and dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (n-Heptane/EtOAc 4:1) provided **3.53** (50 mg, 48%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.18 (td, *J* = 7.7, 1.2 Hz, 1H), 7.10 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.84 (td, *J* = 7.4, 0.8 Hz, 1H),

6.67 (d, *J* = 7.9 Hz, 1H), 5.83 (ddd, *J* = 9.9, 4.4, 2.4 Hz, 1H), 5.21 – 5.14 (m, 1H), 4.70 (t, *J* = 4.3 Hz, 1H), 3.98 (ddd, *J* = 13.1, 5.3, 1.4 Hz, 1H), 3.43 (td, *J* = 12.7, 4.0 Hz, 1H), 2.77 – 2.69 (m, 4H), 2.44 (s, 4H), 2.14 (dt, *J* = 19.2, 2.9 Hz, 1H), 2.01 (ddd, *J* = 12.7, 4.0, 1.4 Hz, 1H), 1.84 (td, *J* = 12.4, 5.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 143.3, 137.9, 134.4, 129.9, 128.4, 128.2, 126.8, 126.2, 121.4, 119.9, 109.8, 72.3, 49.6, 42.9, 40.8, 34.7, 30.7, 26.8, 21.6.

Secondary amine **3.54**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.72 – 5.55 (m, 1H), 3.23 – 3.17 (m, 1H), 2.93 (dq, *J* = 7.3, 5.7 Hz, 1H), 2.43 (s, 3H), 2.01 – 1.86 (m, 3H), 1.80 – 1.71 (m, 1H), 1.64 – 1.46 (m, 4H), 1.09 (d, *J* = 5.8 Hz, 3H).

Tertiary amine **3.55**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.09 (m, 2H), 6.84 (td, *J* = 7.4, 1.0 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.00 – 5.86 (m, 2H), 5.18 (dq, *J* = 10.1, 1.9 Hz, 1H), 3.47 – 3.32 (m, 3H), 3.15 – 3.05 (m, 1H), 2.82 – 2.71 (m, 5H), 2.21 (q, *J* = 3.0 Hz, 2H), 2.06 – 1.90 (m, 2H), 1.85 (dt, *J* = 6.4, 1.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 135.9, 130.8, 129.3, 127.7, 126.8, 121.3, 119.5, 111.1, 109.7, 74.0, 66.7, 52.3, 45.3, 43.2, 34.9, 31.0, 30.4, 22.3, 21.7, 1.8, 1.2, 1.1.

Indolenine **3.57**

To a solution of **3.33** (50 mg, 0.13 mmol) in DCM (13 mL) was added iodosylbenzene (140 mg, 0.64 mmol). After stirring for 30 min, the mixture was filtered through a pad of Celite and washed with DCM (100 mL). The filtrate was concentrated *in vacuo*. Purification by flash chromatography (n-Heptane/EtOAc 4:1) provided **3.57** as a white solid (17 mg, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.46 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.00 (dt, *J* = 9.4, 3.3 Hz, 1H), 5.92 (qt, *J* = 6.5, 1.3 Hz, 1H), 5.72 (ddd, *J* = 9.4, 2.5, 1.7 Hz, 1H), 3.97 (d, *J* = 6.4 Hz, 1H), 3.42 (dt, *J* = 14.1, 1.2 Hz, 1H), 3.35 – 3.20 (m, 3H), 2.83 (dd, *J* = 19.4, 3.6 Hz, 1H), 2.72 – 2.60 (m, 2H), 2.15 – 2.08 (m, 1H), 1.82 (dt, *J* = 6.4, 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4, 155.7, 142.3, 132.6, 130.6, 128.1, 126.4, 125.2, 122.0, 121.0, 108.8, 65.2, 55.9, 54.7, 42.8, 36.0, 34.0, 31.9, 29.0, 22.7, 21.7, 14.2, 14.1.

Aziridine **4.4**

Synthesized according to the procedure that provided **3.31**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 2H), 7.38 – 7.31 (m, 2H), 5.52 (ddt, *J* = 7.3, 4.7, 1.3 Hz, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.22 – 3.13 (m, 2H), 2.46 (s, 3H), 2.26 – 1.84 (m, 5H), 1.81 – 1.67 (m, 1H), 1.62 – 1.44 (m, 4H), 0.90 (s, 9H), 0.09 – -0.01 (m,

6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 135.5, 133.3, 129.6, 128.6, 128.0, 62.4, 45.3, 44.7, 33.1, 30.8, 27.6, 27.5, 26.0, 21.8, 21.6, 18.3, -5.3.

N-Ts L-serine methyl ester **4.6**

To a suspension of L-serine methyl ester hydrochloride (4.76 g, 30.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added dropwise triethyl amine (8.60 mL, 61.2 mmol, 2.0 equiv) and a solution of p-toluenesulfonylchloride (5.83 g, 30.6 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL). After 12 h at 0 °C, the suspended white precipitate was filtered off under suction, and the filtrate was evaporated *in vacuo* to yield a white solid. The solid was then dissolved in ethyl acetate (50 mL), washed with $NaHCO_3$ (1.0 M aq. 40 mL), citric acid (10% w/v aq. 40 mL) and water (40 mL). Then, the organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a white powder. Recrystallization from ethyl acetate/hexanes (1/1) provided N-tosyl serine methyl ester (–)-S3 (7.49 g, 27.2 mmol, 89%) as a white crystal; mp 92-93 °C; $[\alpha]_{20D}$ –11.6 (c 1.00, CHCl3); ^{1}H NMR (500 MHz, $CDCl_3$) d 7.74 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 5.63 (d, J = 7.5 Hz, 1H), 4.01-3.97 (m, 1H), 3,89 (d, J = 3.7 Hz, 2H), 3.62 (s, 3H), 2.42 (s, 3H), 2.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) d 170.1, 143.9, 136.4, 129.8, 127.2, 63.7, 57.6, 52.9, 21.5; high resolution mass spectrum (CI) m/z 274.0744 [$(M+H)^+$; calcd for C11H16NO5S: 274.0749].

Aziridine **4.7**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 8.7, 0.7 Hz, 2H), 6.46 (s, 1H), 3.74 (s, 3H), 3.35 (dd, *J* = 7.1, 4.1 Hz, 1H), 2.77 (d, *J* = 7.1 Hz, 1H), 2.57 (d, *J* = 4.1 Hz, 1H), 2.46 (s, 3H).

Vinyl aziridine **4.8**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.06 (d, *J* = 0.5 Hz, 1H), 4.95 (app t, *J* = 1.5 Hz, 1H), 3.26 (dd, *J* = 7.1 and 4.6 Hz, 1H), 2.72 (d, *J* = 7.2 Hz, 1H), 2.45 (s, 3H), 2.30 (d, *J* = 4.6 Hz, 1H), 1.58 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 138.9, 135.2, 129.7, 127.9, 115.5, 43.3, 32.5, 21.6, 17.8

Vinyl aziridine **4.9**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.41-7.34 (m, 2H), 7.32-7.25 (m, 5H), 5.43 (s, 1H), 5.29 (s, 1H), 3.58 (dd, *J* = 6.8 and 5.2 Hz, 1H), 2.90 (d, *J* = 7.2 Hz, 1H), 2.44 (s, 3H), 2.28 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 141.7, 137.8, 134.9, 129.7, 128.4, 128.1, 127.9, 125.9, 114.7, 41.0, 34.6, 21.6.

Aziridine **4.11**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 2.86 (d, *J* = 24.2 Hz, 2H), 2.43 (d, *J* = 11.5 Hz, 5H), 1.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 145.0, 136.3, 129.9, 129.8, 129.7, 129.6, 128.8, 127.6, 52.0, 37.9, 21.8, 21.7, 21.6, 12.7.

Vinyl Aziridine **4.12**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.98 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.42 (dd, *J* = 17.3, 0.8 Hz, 1H), 5.33 (dd, *J* = 10.7, 0.8 Hz, 1H), 2.64 (d, *J* = 6.7 Hz, 2H), 2.44 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 137.6, 137.0, 129.5, 128.5, 127.4, 118.3, 49.9, 42.0, 21.6, 18.6.

Vinyl aziridine **4.13**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.56 – 5.45 (m, 1H), 3.51 (d, *J* = 7.2 Hz, 1H), 2.61 (dd, *J* = 9.8, 7.2 Hz, 1H), 2.47 (s, 3H), 1.78 – 1.63 (m, 4H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 135.3, 129.5, 128.2, 128.1, 124.5, 51.3, 45.2, 29.7, 27.3, 22.2, 21.7, 21.0, 19.2, 13.8.

Vinyl Aziridine **4.14**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 2H), 7.37 – 7.31 (m, 2H), 5.69 (dh, *J* = 3.0, 1.5 Hz, 1H), 3.34 – 3.21 (m, 1H), 2.51 (dd, *J* = 9.8, 7.2 Hz, 1H), 2.45 (s, 3H), 2.11 – 1.92 (m, 3H), 1.67 – 1.48 (m, 5H), 1.38 (dp, *J* = 9.7, 6.7 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 135.3, 129.5, 128.9, 128.1, 125.4, 52.6, 47.4, 27.4, 25.6, 24.7, 22.4, 22.3, 21.7, 20.8, 19.6.

Vinyl aziridine **4.15**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 5.48 (dddq, *J* = 8.6, 7.0, 5.3, 1.6 Hz, 1H), 3.37 (d, *J* = 7.2 Hz, 1H), 3.08 (dq, *J* = 7.3, 5.8 Hz, 1H), 2.45 (s, 4H), 1.63 – 1.55 (m, 4H), 1.45 (s, 3H), 1.14 (d, *J* = 5.8 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 135.4, 129.6, 129.4, 127.9, 127.8, 127.6, 127.2, 124.5, 45.3, 40.6, 21.8, 21.6, 13.6, 12.8.

Vinyl Aziridine **4.16**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.72 – 5.55 (m, 1H), 3.23 – 3.17 (m, 1H), 2.93 (dq, *J* = 7.3, 5.7 Hz, 1H), 2.43 (s, 3H), 2.01 – 1.86 (m, 3H), 1.80 – 1.71 (m, 1H), 1.64 – 1.46 (m, 4H), 1.09 (d, *J* = 5.8 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 135.5, 129.6, 128.7, 127.8, 125.9, 47.4, 40.9, 26.8, 24.7, 22.3, 22.2, 21.6, 11.7.

Allyl aniline **4.18**

Synthesised according to the procedure that afforded **3.29** a ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.64 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.16 (ddd, *J* = 8.4, 7.3, 1.6 Hz, 1H), 6.46 (td, *J* = 7.6, 1.4 Hz, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.87 (dd, *J* = 8.8, 4.5 Hz, 1H), 4.82 (dd, *J* = 10.0, 2.9 Hz, 1H), 4.38 (d, *J* = 7.6 Hz, 1H), 3.89 (t, *J* = 6.5 Hz, 1H), 3.84 – 3.70 (m, 1H), 3.60 (t, *J* = 6.2 Hz, 2H), 2.46 (s, 3H), 2.35 – 2.21 (m, 2H), 2.21 – 2.10 (m, 2H), 1.71 – 1.47 (m, 6H), 0.90 (s, 9H), 0.05 (d, *J* = 0.9 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 143.5, 140.8, 139.2, 137.8, 129.9, 129.8, 129.7, 127.2, 119.0, 110.4, 85.7, 62.5, 59.2, 49.7, 36.8, 31.0, 30.2, 27.4, 26.0, 26.0, 21.6, 21.5, 18.4, -5.2, -5.3.

Allyl aniline **4.19**

Synthesised according to the procedure that afforded **3.29.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.01 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 6.61 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.48 – 6.38 (m, 1H), 5.85 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.29 – 5.15 (m, 1H), 4.84 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.44 (s, 1H), 3.25 – 3.08 (m, 1H), 2.43 (s, 2H), 1.43 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 143.5, 141.0, 139.4, 136.5, 129.8, 128.6, 127.1, 119.6, 116.3, 114.4, 88.1, 57.6, 50.1, 24.3, 21.6.

Allyl aniline **4.20**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H),) 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.35– 7.30 (m, 4H) 7.28 (d, *J* = 7.7 Hz, 1H), 7.01 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 6.61 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.48 – 6.38 (m, 1H), 5.85 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.29 – 5.15 (m, 1H), 4.84 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.44 (s, 1H), 3.25 – 3.08 (m, 1H), 2.43 (s, 2H), 1.43 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 145.0, 143.6, 139.1, 136.7, 129.7, 129.6, 129.2, 128.7, 128.6, 128.2, 127.0, 127.0, 126.8, 126.3, 119.6, 115.5, 111.7. 114.4, 88.1, 57.6, 50.1, 24.3, 21.6.

Allyl aniline **4.21**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.01 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 6.61 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.49 – 6.41 (m, 1H), 5.85 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.26 (d, *J* = 0.7 Hz, 0H), 5.20 (dd, *J* = 17.6, 0.7 Hz, 1H), 4.84 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.44 (s, 1H), 3.25 – 2.96 (m, 1H), 2.43 (s, 2H), 1.43 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 143.5, 141.0, 139.4, 136.5, 129.8, 128.6, 127.1, 119.6, 116.3, 114.4, 88.1, 57.6, 50.1, 24.3, 21.6.

Allyl aniline **4.22**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.66 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.18 – 7.11 (m, 2H), 6.52 – 6.39 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 139.2, 139.0, 137.5, 132.0, 129.9, 129.9, 129.2, 129.1, 127.3, 127.2, 125.8, 124.8, 119.6, 119.3, 112.3, 112.1, 86.4, 86.4, 66.2, 57.8, 52.1, 51.2, 21.6, 19.1, 18.4, 18.2, 13.9, 13.3, 12.1.

Allyl aniline **4.23**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.65 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.16 – 7.10 (m, 1H), 6.46 (d, *J* = 7.7 Hz, 2H), 5.74 – 5.66 (m, 1H), 4.96 (d, *J* = 5.9 Hz, 1H), 3.56 (d, *J* = 7.2 Hz, 1H), 3.48 – 3.37 (m, 1H), 2.44 (s, 4H), 2.03 – 1.97 (m, 2H), 1.83 – 1.73 (m, 3H), 1.58 – 1.44 (m, 4H), 1.15 (d, *J* = 6.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 143.5, 139.0, 137.4, 133.8, 129.9, 129.2, 127.3, 127.2, 119.2, 112.2, 86.3, 65.2, 51.3, 25.1, 24.5, 22.4, 22.3, 21.6, 18.9.

Allyl aniline **4.33**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 14.4, 1.9 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.42 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 – 7.32 (m, 3H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 8.7 Hz, 1H), 5.84 (t, *J* = 3.6 Hz, 1H), 4.87 (d, *J* = 8.9 Hz, 1H), 4.59 (d, *J* = 7.6 Hz, 1H), 3.79 (d, *J* = 7.7 Hz, 1H), 3.72 – 3.67 (m, 2H), 3.50 (ddt, *J* = 9.4, 4.2, 2.7 Hz, 1H), 2.48 (s, 3H), 2.28 – 2.21 (m, 2H), 2.16 (s, 2H), 1.75 (ddd, *J* = 11.6, 6.6, 3.7 Hz, 1H), 1.55 (d, *J* = 4.3 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 143.8, 142.8, 142.5, 137.5, 133.8, 133.3, 131.3, 129.9, 128.9, 127.2, 118.5, 118.3, 113.5, 109.8, 101.1, 83.9, 61.8, 54.3, 49.2, 38.3, 26.0, 21.6, 20.3, 18.4, -5.1, -5.2.

Allyl aniline **4.34**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 8.1 Hz, 1H), 6.28 (ddd, *J* = 8.2, 2.3, 0.8 Hz, 1H), 6.15 (t, *J* = 2.2 Hz, 1H), 5.96 – 5.91 (m, 1H), 5.71 (s, 1H), 4.67 (d, *J* = 8.9 Hz, 1H), 3.85 (d, *J* = 10.2 Hz, 1H), 3.80 (s, 2H), 3.68 (t, *J* = 6.4 Hz, 3H), 2.45 (d, *J* = 11.3 Hz, 3H), 2.32 – 2.21 (m, 2H), 2.08 (d, *J* = 7.2 Hz, 2H), 1.85 – 1.74 (m, 1H), 1.56 – 1.46 (m, 1H), 0.91 (d, *J* = 3.3 Hz, 9H), 0.08 (t, *J* = 2.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 130.1, 129.8, 127.5, 127.2, 105.1, 103.4, 98.3, 61.6, 55.2, 54.5, 49.7, 38.6, 26.0, 21.6, 21.2, 20.3, -5.2.

Allyl aniline **4.35**

Synthesised according to the procedure that afforded **3.29**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 2H), 6.60 (dd, *J* = 2.3, 0.6 Hz, 1H), 6.46 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.83 – 5.75 (m, 1H), 4.95 (d, *J* = 8.4 Hz, 1H), 4.14 (d, *J* = 7.7 Hz, 1H), 3.69 (td, *J* = 6.7, 0.9 Hz, 2H), 3.59 – 3.50 (m, 1H), 2.43 (s, 3H), 2.28 – 2.10 (m, 4H), 1.85 – 1.73 (m, 1H), 1.60 (dt, *J* = 14.1, 4.3 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 6H).

Indoline **4.36**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.10 – 7.02 (m, 1H), 6.98 (td, *J* = 7.7, 1.3 Hz, 1H), 6.77 (d, *J* = 6.0 Hz, 1H), 6.74 (td, *J* = 7.4, 1.0 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 5.65 – 5.46 (m, 2H), 4.96 (dd, *J* = 13.1, 2.1 Hz, 1H), 3.70 – 3.37 (m, 5H), 2.48 (s, 3H), 2.35 – 2.08 (m, 3H), 1.72 – 1.32 (m, 7H), 0.87 (d, *J* = 2.1 Hz, 9H), 0.06 – -0.12 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 138.1, 134.7, 131.7, 129.9, 129.8, 129.8, 129.3, 127.9, 127.6, 127.2, 127.1, 127.1, 126.1, 123.4, 123.1, 75.0, 63.3, 56.1, 47.1, 32.3, 26.7, 26.0, 25.9, 24.9, 24.3, 21.6, 18.3, -5.2, -5.3, -5.3.

Indoline **4.37**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.98 (td, *J* = 7.6, 1.5 Hz, 1H), 6.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.62 (td, *J* = 7.4, 1.1 Hz, 1H), 6.37 (dd, *J* = 9.0, 7.8 Hz, 2H), 5.24 (d, *J* = 9.8 Hz, 1H), 4.99 – 4.93 (m, 1H), 3.05 (dd, *J* = 12.5, 7.1 Hz, 1H), 2.81 (dd, *J* = 12.5, 5.2 Hz, 1H), 2.45 (s, 3H), 1.28 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 142.2, 137.0, 129.7, 129.0, 127.1, 127.0, 126.8, 126.1, 119.2, 117.9, 113.2, 55.3, 52.9, 27.5, 21.5.

Indoline **4.38**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.04 (td, *J* = 7.6, 1.4 Hz, 1H), 6.85 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.74 (td, *J* = 7.4, 1.0 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 5.94 (dd, *J* = 17.8, 10.3 Hz, 1H), 5.17 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.88 (d, *J* = 9.0 Hz, 1H), 3.71 – 3.63 (m, 1H), 3.45 (d, *J* = 8.5 Hz, 1H), 2.45 (s, 2H), 1.17 (s, 2H), 1.00 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 143.5, 138.5, 137.0, 129.7, 127.9, 127.1, 123.1, 119.5, 113.9, 110.0, 73.4, 51.3, 49.7, 21.6, 20.1, 17.9.

Indoline **4.39**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.06 (td, *J* = 7.6, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.74 (td, *J* = 7.5, 1.1 Hz, 1H), 6.60 (d, *J* = 7.7

Hz, 1H), 5.90 (ddd, *J* = 10.0, 5.2, 2.4 Hz, 1H), 5.51 – 5.39 (m, 1H), 4.81 (d, *J* = 8.7 Hz, 1H), 3.80 – 3.70 (m, 1H), 3.37 (d, *J* = 8.4 Hz, 1H), 2.46 (s, 2H), 2.16 – 2.09 (m, 1H), 2.02 – 1.92 (m, 1H), 1.72 – 1.58 (m, 1H), 1.45 (dd, *J* = 12.9, 3.1 Hz, 1H), 1.20 (d, *J* = 6.7 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 138.4, 137.1, 131.5, 129.7, 129.6, 129.5, 129.2, 128.1, 127.9, 127.7, 127.1, 127.0, 125.7, 124.8, 124.1, 118.6, 109.8, 75.2, 73.6, 51.1, 48.8, 48.0, 27.3, 25.0, 22.7, 22.0, 21.6, 19.9, 17.8, 14.1.

Indoline **4.40**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.16 (m, 1H), 6.37 – 6.29 (m, 1H), 5.90 (td, *J* = 11.1, 10.5, 2.8 Hz, 1H), 5.61 (ddd, *J* = 10.0, 6.1, 2.2 Hz, 1H), 3.70 – 3.49 (m, 4H), 3.09 (qd, *J* = 9.9, 4.9 Hz, 1H), 2.49 (s, 3H), 2.09 (dt, *J* = 16.4, 5.3 Hz, 2H), 1.94 – 1.78 (m, 3H), 1.74 – 1.64 (m, 1H), 0.87 (d, *J* = 2.2 Hz, 9H) 0.02 – 0.00 (m, 6H).

Indoline **4.41**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.72 – 6.67 (m, 1H), 6.37 – 6.29 (m, 1H), 5.90 (td, *J* = 11.1, 10.5, 2.8 Hz, 1H), 5.61 (ddd, *J* = 10.0, 6.1, 2.2 Hz, 1H), 3.70 – 3.49 (m, 4H), 3.09 (qd, *J* = 9.9, 4.9 Hz, 1H), 2.49 (s, 3H), 2.09 (dt, *J* = 16.4, 5.3 Hz, 2H), 1.94 – 1.78 (m, 3H), 1.74 – 1.64 (m, 1H), 0.87 (d, *J* = 2.2 Hz, 9H) 0.02 – 0.00 (m, 6H).

Indoline **4.42**

Synthesised according to the procedure that afforded **3.28**.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.72 – 6.67 (m, 1H), 6.37 – 6.29 (m, 1H), 5.90 (td, *J* = 11.1, 10.5, 2.8 Hz, 1H), 5.61 (ddd, *J* = 10.0, 6.1, 2.2 Hz, 1H), 3.70 – 3.49 (m, 4H), 3.09 (qd, *J* = 9.9, 4.9 Hz, 1H), 2.49 (s, 3H), 2.09 (dt, *J* = 16.4, 5.3 Hz, 2H), 1.94 – 1.78 (m, 3H), 1.74 – 1.64 (m, 1H), 0.87 (d, *J* = 2.2 Hz, 9H) 0.02 – 0.00 (m, 6H).

Compound **4.45**

To a solution of **4.19** (100 mg, 22 mmol), Et_3N (76 µL, 0.55 mmol) *n*-Bu_4NCl (50mg, 0.22mmol) and MeOH (9 µL, 0.22 mmol) in anhydrous DMF, (0.7 mL), was added a solution of $Pd(OAc)_2$ (44 µL, 0.04 mmol, 0.1 M in DMA) under N_2 at rt. The flask was purged with CO (3×, balloon) and heated to 100 °C under vigorous stirring. The reaction was monitored by LCMS. The reaction was diluted with EtOAc (5 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (4 × 3 mL), Brine (3 mL) and dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (*n*-Heptane/EtOAc 4:1) to

provide **4.45** (24 mg, 30%) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.13 (td, *J* = 7.6, 1.3 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.86 (td, *J* = 7.4, 1.0 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 0H), 4.48 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.89 (t, *J* = 11.4 Hz, 1H), 3.59 (dd, *J* = 11.8, 5.2 Hz, 1H), 2.88 (dd, *J* = 17.1, 0.6 Hz, 1H), 2.83 – 2.69 (m, 1H), 2.46 (s, 2H), 1.03 (d, *J* = 0.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 149.8, 145.1, 135.8, 135.7, 129.4, 128.7, 128.2, 121.9, 120.7, 111.5, 63.3, 46.5, 44.8, 42.7, 21.7, 19.2.

Compound **4.43**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.37 – 7.32 (m, 1H), 6.84 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.74 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.67 (s, 1H), 4.08 (d, *J* = 4.6 Hz, 1H), 3.91 – 3.78 (m, 1H), 3.00 (d, *J* = 17.8 Hz, 1H), 2.46 (s, 2H), 2.24 – 2.13 (m, 1H), 2.07 (s, 1H), 1.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 167.6, 148.6, 145.3, 135.8, 129.5, 128.7, 128.5, 119.3, 116.3, 115.9, 55.2, 47.7, 43.9, 37.8, 21.7, 19.5.

Compound **4.44**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.30 (m, 4H), 6.65 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 5.00 (d, *J* = 1.4 Hz, 2H), 4.74 (t, *J* = 6.3 Hz, 1H), 3.97 (t, *J* = 6.7 Hz, 1H), 3.89 (s, 3H), 3.37 – 3.21 (m, 1H), 3.15 (ddd, *J* = 12.8, 7.4, 5.2 Hz, 1H), 2.44 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 134.6, 131.6, 129.8, 128.7, 127.1, 115.7, 114.3, 112.3, 57.8, 51.6, 45.3, 29.7, 21.5, 18.6.

Compound **4.47**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.09 – 6.96 (m, 2H), 6.77 (td, *J* = 7.4, 1.0 Hz, 1H), 6.62 (dt, *J* = 7.7, 0.9 Hz, 1H), 5.13 (t, *J* = 6.4 Hz, 1H), 3.51 (dd, *J* = 9.4, 3.6 Hz, 1H), 3.16 (ddd, *J* = 12.8, 6.2, 3.7 Hz, 1H), 3.11 – 2.98 (m, 1H), 2.46 (s, 3H), 1.19 (d, *J* = 91.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 143.7, 138.3, 136.6, 129.9, 127.6, 127.1, 121.9, 119.6, 119.5, 110.3, 110.3, 68.2, 44.2, 43.3, 27.5, 22.5, 21.6.

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