UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENT SCIENCES

School of Chemistry

STEREOSELECTIVE TOTAL SYNTHESES OF LUPIN ALKALOIDS

by

Xiang Lyu

Thesis for the degree of Doctor of Philosophy

September 2018

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING & PHYSICAL SCIENCES

Chemistry

Thesis for the degree of Doctor of Philosophy

STEREOSELECTIVE TOTAL SYNTHESES OF LUPIN ALKALOIDS

Xiang Lyu

A highly *anti*-selective formal imino-aldol methodology has been developed and applied to asymmetric total synthesis of five alkaloids, including (+)-lupinine, (–)-epitashiromine, (–)-epilamprolobine, (+)-isosophoridine and (+)-sparteine. This method combined an imino-aldol reaction and *anti*-alkylation, with a variety of (*S*)-*p*-tolylsulfinimines, to give *anti*-products with high diastereoselectivity (*dr* >10:1). Absolute stereochemical determination of the *anti*-product was proved by the synthesis of (+)-lupinine and (–)-epitashiromine in 17% and 23% overall yields respectively.

The first total synthesis of the tetracyclic lupin alkaloid (+)-isosophoridine has been completed in 10 steps in 9% overall yield. The target molecule was assembled with excellent control of contiguous stereocenters employing an *anti*-selective formal imino-aldol reaction and *N*-acyliminium cyclisation as key steps. As a part of our studies towards (+)-isosophoridine, we performed the first total synthesis of the tricyclic alkaloid (–)-epilamprolobine.

In addition, based on the *anti*-selective methodology and good understanding of *N*-acyliminium cyclisation chemistry, a total synthesis of (+)-sparteine has been achieved in 16 linear steps and 1.6% overall yield, which employed a cross metathesis to assemble the allyl silane present in the *N*-acyliminium precursor.

Table of Contents

List of Figures

DECLARATION OF AUTHORSHIP

I, Xiang Lyu

declare that this thesis entitled

STEREOSELECTIVE TOTAL SYNTHESES OF LUPIN ALKALOIDS

and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission.

Signed: ....

Date: ....

Acknowledgements

Firstly, I would like to thank my supervisor Professor Richard Brown for the opportunity to work on the total synthesis project within his group and for all of his help and guidance throughout my PhD. I am very grateful. His unwavering support and encouragement have enabled me to make this research a great success and sparked my interest in synthetic organic chemistry.

I would like to thank my secondary supervisor Dr Lynda Brown for all of her support throughout my PhD. Her advice gave me hope when I was under tremendous pressure several times.

Thank you to all group members: Azzam, Alex L, Alex P, Alex T, Aqeel, Firas, Rob G, Victor for giving me an unforgettable time. I would especially thank Katie J, Alex MI and David W for proofreading all of my posters, presentations and this thesis as well. Thank you also to Wei Sun, Zhong Wang, Dharyl, Rebecca, Faisal, Gert-Jan and the other groups on level 3 for letting me borrow chemicals and equipments. Thanks to everyone in the mass spectrometry lab for their help with compound characterisation, Neil Wells for his help with NMR experiments and Ningjin Zhang for help with X-ray analysis.

Many thanks to my close friends in Southampton, Jie Xie, Weiming Lu, Junjie Wang, Wu Chen, Zhongwei Zhao, Yangxiao Lu, Yi Qu, Zhewen Wu for their support and help.

I would like to say a huge thank you to my mother for always being supportive during my studies and always being there when I needed her. Your love and support have always enabled me to reach my goals. I thank all my family members for their caring and support during my PhD study. I know I could not have done it without them.

Finally, I would like to thank my girlfriend Hui Fang for all your help and support. Especially when things were not going very well, thank you for putting up with me and making everything seem brighter. Your love and support throughout my PhD have helped me to succeed and become the person I am today.

Definitions and Abbreviations

$[\alpha]_D$	Alpha-D
Ac	Acetyl
acac	Acetylacetonate
ADDP	1,1’-(Azodicarbonyl)dipiperidine
AIBN	2,2’-Azobis(2-methylpropionitrile)
aq.	Aqueous
atm	Atmosphere
ATMS	Allyltrimethylsilane
Boc$_2$O	Di-*tert*-butyl dicarbonate
Bn	Benzyl
Bu	Butyl
ca.	Circa
cat.	Catalytic
Cbz	Benzyloxycarbonyl
CM	Cross-metathesis
conc.	Concentrated
Cp	Cyclopentyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DIAD	Di-*iso*-propyl azodicarboxylate
DIBAL-H	Di-*iso*-butyl aluminium hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane

DMF	Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
ent	Enantiomer
epi	Epimer
equiv.	Equivalents
Et	Ethyl
ES$_+$	Electrospray ionisation (positive ion)
ES$_-$	Electrospray ionisation (negative ion)
FT	Fourier transform
g	Gram(s)
h	Hour(s)
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
i	*Iso*
IPA	*Iso*-propylalcohol
IR	Infra-red
J	Coupling constant
K	Kelvin
L	Ligand
LC-MS	Liquid chromatography mass spectroscopy
LDA	Lithium di-*iso*-propylamide
LiHMDS	Lithium hexamethyldisilazide
LRMS	Low resolution mass spectroscopy

M	Molar
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre
mmol	Millimole
Ms	Methanesulfonyl
MS	Mass Spectrometry
n	Normal
nm	Nanometres
NMO	N-Methyl morpholine-N-oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
p	*para*
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
p-tolyl	*para*-methylphenyl
Py	Pyridine
RCM	Ring-closing metathesis
RBF	Round Bottom Flask
rt	Room temperature
sat.	Saturated

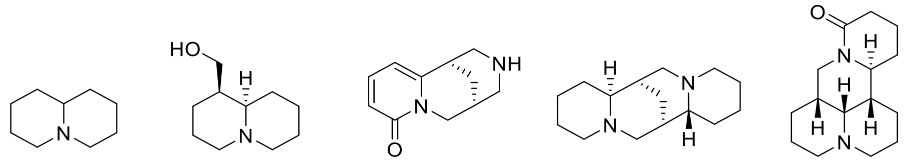
t(tert)	Tertiary
T	Temperature
T_3P	Propylphosphonic anhydride
TBAB	Tetrabutylammonium bromide
TBS	*tert*-Butyldimethylsilyl
TBSA	*tert*-Butylsulfinamide
Tf	Trifluromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri-*iso*propylsilyl
TLC	Thin-layer chromatography
TMEDA	*N*,*N*,*N*’,*N*’-Tetramethylethylenediamine
TMS	Trimethylsilyl
TsOH	*para*-Toluenesulfonic acid
UV	Ultra-violet
Δ	Heating at reflux
9-BBN	9-Borabicyclo[3.3.31]-nanone

Chapter 1: Introduction

1.1 Lupin Alkaloids Background

The lupin alkaloids, a family of *N*-heterocyclic natural products, prominently exist in *leguminous* plants, especially the subfamily *Papilionaceae*.[1] These alkaloids are bitter compounds, and together with other secondary compounds in plant tissues act as the chemical-defense against predators, such as herbivores and pathogenic microorganisms. In addition, lupin seeds have good nutritive characteristics containing 30 – 40% crude protein, which is valuable source to partially replace traditional proteins of animal origin.[2] For this reason, many plants in the legume family are important sources of food for humans and livestock, and they help to conserve soil and fix nitrogen. Before consumption, de-bittering is always required to reduce the alkaloid level, due to the fact that some quinolizidine alkaloids are toxic to humans and animals.[3]

Lupin alkaloids, which are also referred to as the quinolizidine alkaloids, possess the quinolizidine core as their main characteristic motif. The main groups of lupin alkaloids are divided into three main types (**Figure 1.1**): bicyclic alkaloids (lupinine type), tricyclic alkaloids (cytisine type), and tetracyclic alkaloids (sparteine type and matrine type).



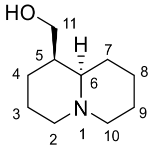
quinolizidine (–)-lupinine (–)-cytisine (+)-sparteine (–)-matrine

Figure 1.1. Some examples of lupin alkaloids.

1.2 Structural elucidation of lupinine and matrine

1.2.1 Lupinine structure elucidation

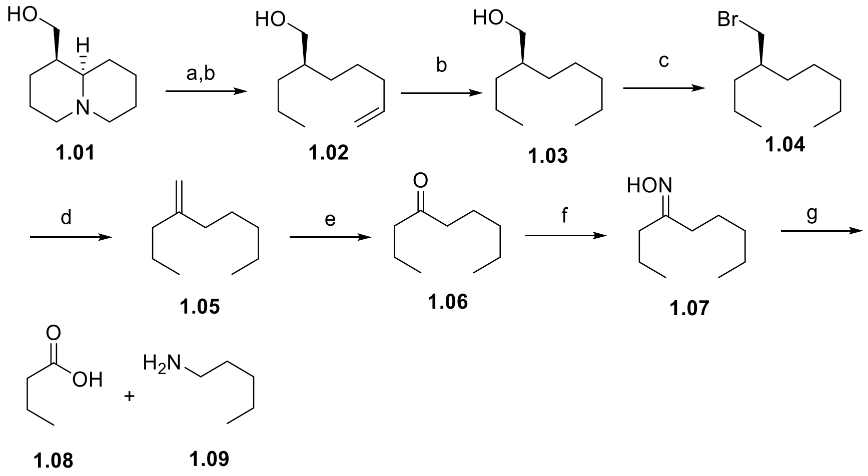
(–)-Lupinine (**1.01**), was first isolated from yellow lupin seeds by Cassola in 1835 and its molecular formula, $C_{10}H_{19}NO$, was established by Willstäter and Fourneau in 1902.[4] Numbers of subsequent investigators have proven the (–)-lupinine structure as shown in **Figure 1.2**. In the following section, some key aspects of the elucidation of lupinine will be introduced.



(–)-lupinine **1.01**

Figure 1.2. Structure of (–)-lupinine (**1.01**).

Karrer and co-workers applied a Hofmann exhaustive methylation on lupinine, with hydrogenation following each degradation stage (**Scheme 1.01**).[5] An unsaturated alcohol **1.02,** containing a primary alcohol group and a terminal double bond, was obtained before the last hydrogenation. This alcohol **1.02** showed optical activity, which indicated that at least one chiral centre in the molecule withstood the degradation process. The bromination of saturated alcohol **1.03** derived from **1.02** and subsequent elimination gave unsaturated hydrocarbon **1.05**. Due to the unsaturated hydrocarbon **1.05** being optically inactive, it was therefore confirmed that the only chiral centre in the original alcohol **1.02** was adjacent to the hydroxymethyl group. Ozonolysis of **1.05** and condensation afforded oxime **1.07**. A Beckmann rearrangement of oxime **1.08** and subsequent hydrolysis resulted in *n*-butyric acid **1.08** and *n*-amyl-amine **1.09**. The degradation structures evidently indicated that the carbon skeleton of lupinine should be that of alcohol **1.03**. Accommodating the nitrogen atom in the molecule would recreate bicyclic structural candidates such as **1.01** and **1.10** (**Figure 1.03**). Karrer *et al.*[5] proposed that the fused five-seven membered ring **1.10** was less likely than structure **1.01** with a fused six-six membered ring (**Figure 1.3**).



Scheme 1.01. *Reagents and conditions*: a) i) MeI, MeOH ii) Ag_2O, H_2O, Δ; b) H_2, Pt; c) PBr_5; d) NEt_3, Ag_2O; e) O_3; f) NH_2OH; g) i) *conc.* H_2SO_4; ii) HCl, H_2O.

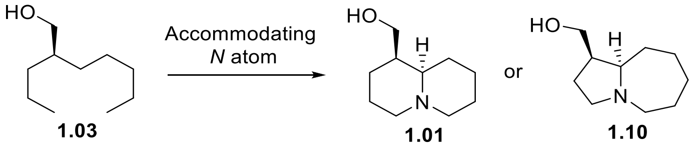
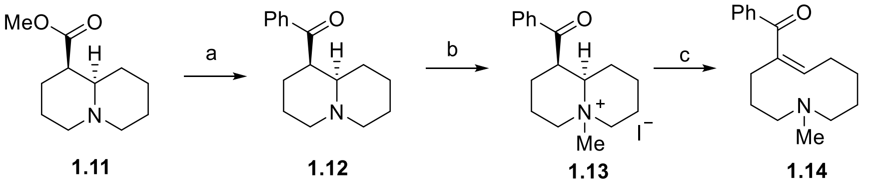


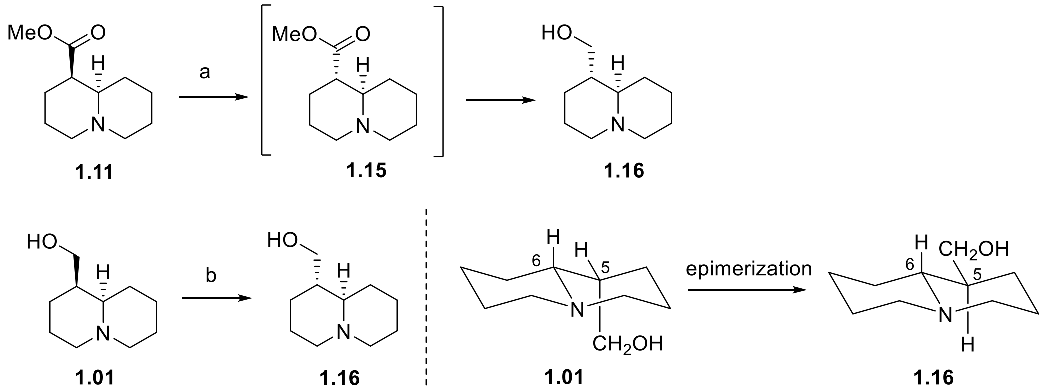
Figure 1.3. Possible structural candidates for lupinine after accommodation the nitrogen atom.

Schöpf and co-workers reported a confirmation of the *β*-relationship of the amine and alcohol group in lupinine (**Scheme 1.02**).[6] The ketone **1.12** was prepared by the reaction of phenylmagnesium bromide with lupininic acid methyl ester (**1.11**), prepared from (–)-lupinine. The methyl-ammonium salt **1.13** derived from ketone **1.12** under Hoffmann elimination conditions gave a *α,β*-unsaturated ketone (**1.14**) as a single product. The formation of *α,β*-unsaturated ketone **1.14** was typical from a *β*-amino ketone, and this result confirmed the lupinine structure for the *β*-amino alcohol.



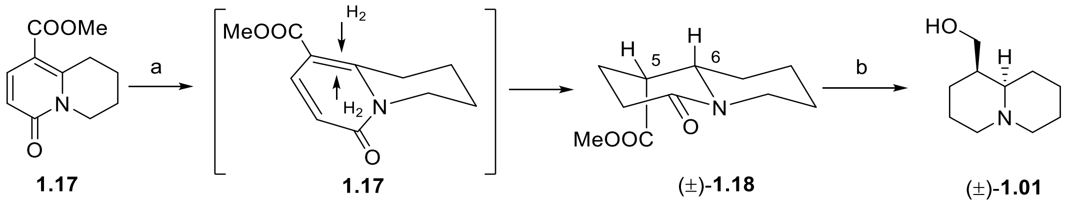
Scheme 1.02. *Reagents and conditions*: a) PhMgBr, Et_2O; b) CH_3I, MeOH; c) aq. NaOH, Δ.

As the structure of lupinine has two chiral centres, the next stage was to establish whether the hydrogens on C-5 and C-6 are *cis* or *trans*. Winterfeld and Holschneider found that methyl (–)-lupininate (**1.11**), when treated with Na in EtOH, provided a lupinine isomer: (+)-epilupinine **1.16** (**Scheme 1.03**).[7] It was considered that ester **1.11** firstly underwent epimerisation to **1.15**, then underwent Bouveault-Blanc reduction to afford epilupinine **1.16**. Direct epimerisation was also found by Winterfeld *et al*. to proceed *via* treatment of lupinine with Na in toluene under reflux leading to epilupinine **1.16** (**Scheme 1.03**).[7] In this case, the relative configuration of hydrogens on C-5 and C-6 was suggested as *cis*, since both of two above transformations corresponded to a thermodynamically preferred H_5,H_6-diaxial bonding in epilupinine (**Scheme 1.03**).



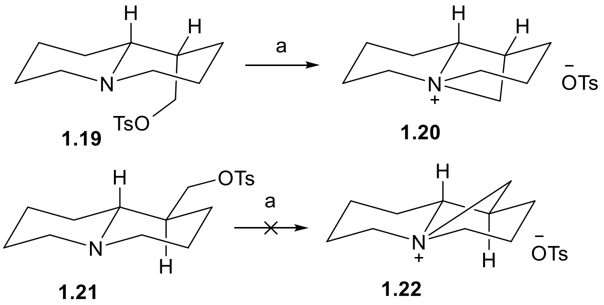
Scheme 1.03. *Reagents and conditions*: a) Na, EtOH; b) Na, PhMe, Δ.

Boekelheide and Lodge claimed proof of the *cis* stereochemistry of lupinine by the synthesis of (±)-lupinine.[8] Hydrogenation of **1.17** over Pt in neutral solution gave quinolizidone (±)-**1.18** (**Scheme 1.04**). Since the product consisted of only (±)-**1.18**, the hydrogens on C-5 and C-6 were assigned to possess a *cis* relationship. The lactam group in **1.18** was reduced by H_2 over Pt in acidic solution, and carbomethoxy group was reduced by $LiAlH_4$ to give the racemic product **1.01** which was identified as (±)-lupinine.



Scheme 1.04. *Reagents and conditions*: a) H_2, Pt, EtOH; b) i) H_2, Pt, HCl, EtOH; ii) $LiAlH_4$, Et_2O

The further confirmation of the axial position of hydroxymethyl group is provided by the self-alkylation of (–)-lupinine tosylate by Galinovsky and co-workers (**Scheme 1.05**).[9] The tosylate **1.19** of (–)-lupinine under 100 °C afforded a quaternary ammonium salt **1.20**, in contrast, the tosyl ester **1.21** of (+)-epilupinine did not react under the same conditions.



Scheme 1.05. Self-alkylation of (–)-lupinine and (+)-epilupinine tosylate *Reagents and conditions*: a) 100 ° to 150 °C.

The absolute configuration of (–)-lupinine was established by Cookson *et al.*[10] by degradation of (–)-lupinine to an optically active 4-methylnonane **1.23** (**Figure 1.4**), which has the same sign of rotation as the known absolute configuration (–)-4-methylonane.[11] Okuda and co-workers carefully repeated the degradation procedures to verify the sign of rotation.[12] Accordingly (–)-4-methylonane is (*R*) configured, allowing to assign the (–)-lupinine absolute configuration as shown in **Figure 1.4**.

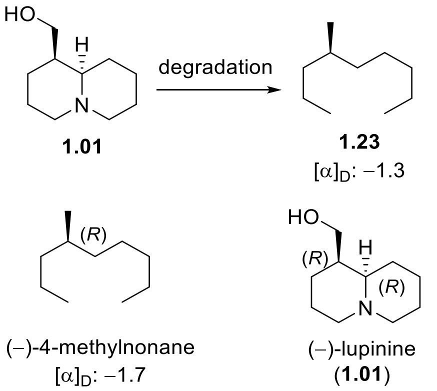
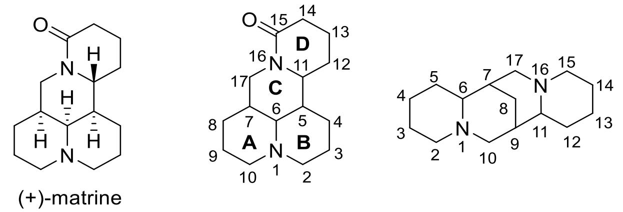


Figure 1.4. Determined absolute configuration of (–)-lupinine.

1.2.2 Matrine structure elucidation

(+)-Matrine (**1.24**) was first isolated from *Sophora flavescens* and assigned the correct molecular formula, $C_{15}H_{24}N_2O$, by Nagai.[13] It has a variety of pharmacological effects such as anticancer activity, anti-inflammatory and antiviral activities and anti-nociceptive activity.[14-15] Kushen (the dried roots of *Sophora flavescens*) is a traditional Chinese medicine, which was first recorded in the Chinese book *Shen Nong Ben Cao Jing* in 200 A.D.,[16] as a treatment for solid tumors and inflammation. Matrine has been proven to possess a strong antitumor activity *in vitro* and *in vivo*.[15] It is also the main chemical ingredient of the Fufang Kushen injection which was approved by

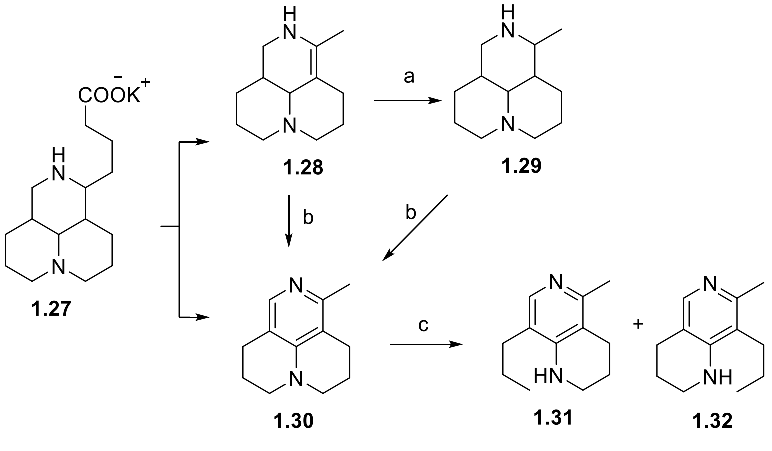
Chinese FDA in 1995 as an *anti*-cancer drug.[17] The following section will give a review of matrine structure elucidation by synthetic studies.



(+)-matrine **1.24** **1.25** **1.26**

Figure 1.5. Structure of matrine and skeletons of matrine and sparteine.

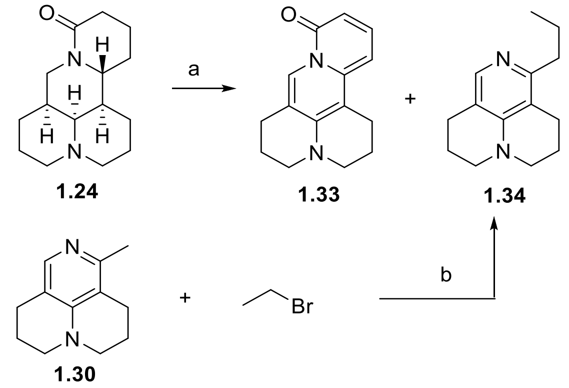
The basic skeleton of matrine type alkaloids was proposed by Tsuda as **1.25** (**Figure 1.5**), where the C$_9$-C$_{11}$ bond in sparteine (**1.26**) was cleaved and re-cyclised between C$_5$ and C$_{11}$.[18] The presence of the lactam group was proved by hydrolysis of matrine with KOH to potassium matrinate (**1.27**), $C_{15}H_{25}N_2O_2K$.[19] The nature of the A-B fused ring was established by drastic degradation by treatment of **1.27** with soda-lime distillation (**Scheme 1.06**), which gave two major products α-matrinidine (**1.28**) and dehydro-α-matrinidine (**1.30**).[20] The α-matrinidine **1.28** afforded dihydro-α-matrinidine **1.29** by hydrogenation over Pt. Under dehydrogenation conditions, **1.28** and **1.29** lost four and six hydrogen atoms respectively to give the pyridine-contained dehydro-α-matrinidine **1.30**.[21] Later in 1956, Tsuda and co-workers[22] synthesised dehydro-α-matrinidine **1.30** and showed that it was identical to the dehydrogenation product of **1.28** or **1.29**. In the same year, Okuda *et al.*[23] confirmed the *N*-COCH$_3$ derivative of **1.30** after cyanogen bromide cleavage afforded 4-aminopyridine structure **1.31** and **1.32** using UV analysis.



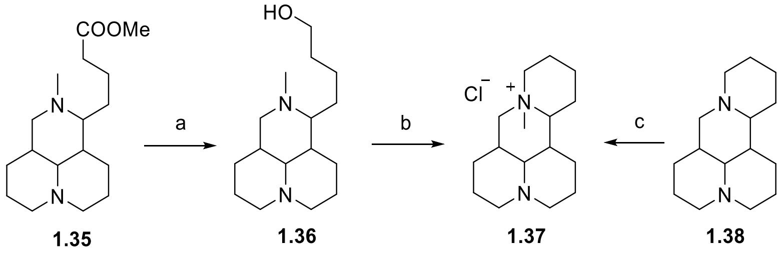
Scheme 1.06. Matrine A-B ring elucidation. *Reagents and conditions*: a) Pt, H_2; b) Pd, Δ; c) i) Ac_2O; ii) BrCN.

The nature of the C-D ring in matrine was also established by degradation studies. Dehydrogenation of matrine gave two main products octadehydromatrine **1.33** and intermediate **1.34**. Tsuda *et al.*[18]

found that treatment of **1.30** with *n*-BuLi followed by EtBr gave a product identical to **1.34** (**Scheme 1.07**). An opened and reclosed route also showed the presence of the C-D ring. The methyl methylmatrinate **1.35** was reduced by $LiAlH_4$ to give methylmatrine alcohol **1.36** (**Scheme 1.08**) and the following treatment of **1.36** with $SOCl_2$ and K_2CO_3 resulted in reclosed matridine salt **1.37**,[24] which is also obtainable directly from matridine **1.38**.[25]

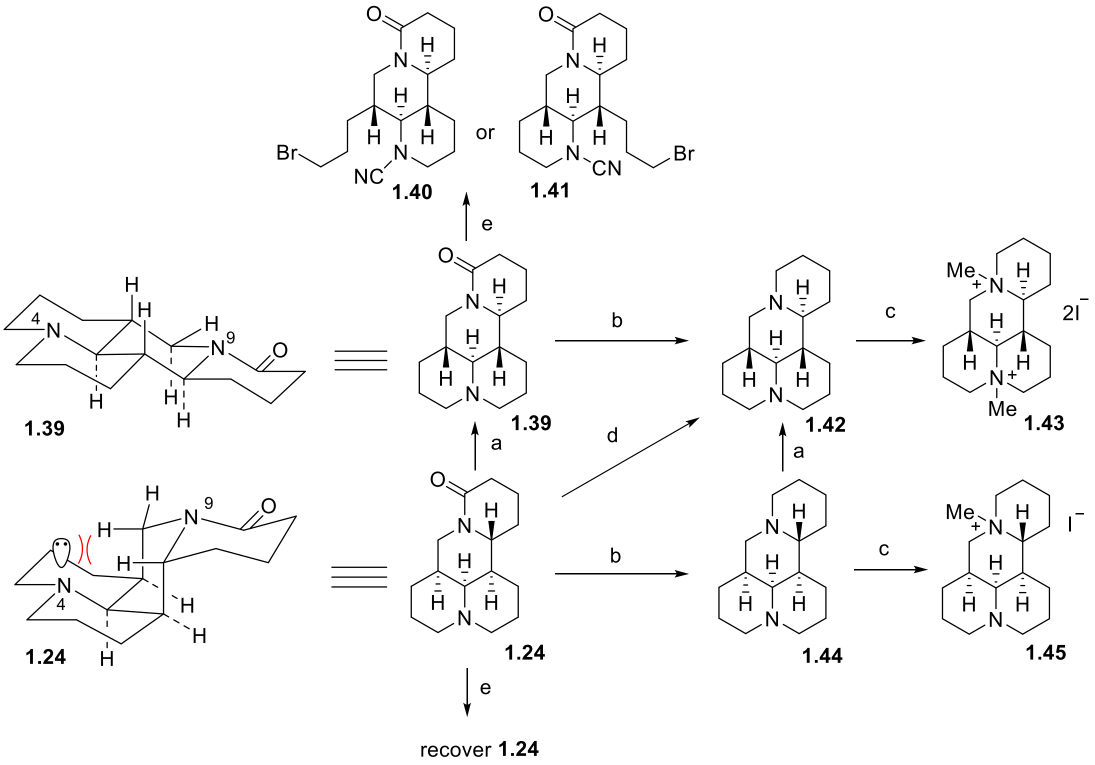


Scheme 1.07. Matrine C-D ring elucidation. *Reagents and conditions*: a) Pd, Δ; b) i) *n*-BuLi; ii) EtBr.



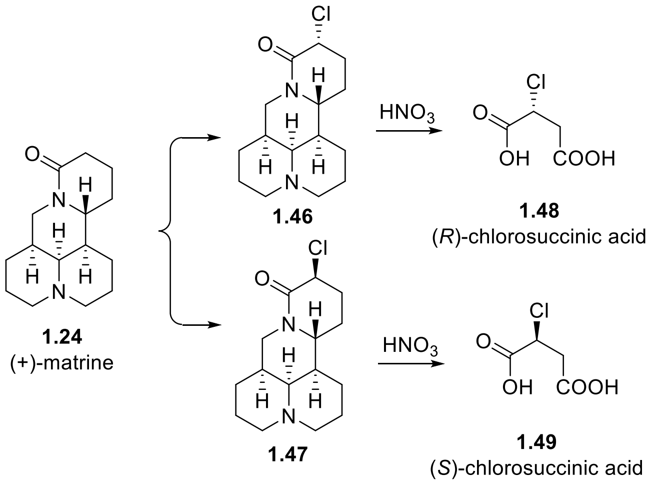
Scheme 1.08. Matrine C-D ring elucidation. *Reagents and conditions*: a) $LiAlH_4$; b) i) $SOCl_2$; ii) K_2CO_3; c) CH_3Cl.

The relative stereochemistries of matrine **1.24** and allomatrine **1.39** were proposed by Tsuda and Mishima based on the information summarised below (**Scheme 1.09**).[26] They observed that: a) cyanogen bromide did not attack matrine as the N-4 is hindered, whereas it attacked N-4 in allomatrine giving two products **1.40** and **1.41**; b) methyl-iodination of matridine (**1.44**), reduced from **1.24,** only formed monomethiodide **1.45** due to the shielded N-4**,** but in contrast allomatridine (**1.42**) gave the dimethyl iodide product **1.43**; c) isomerisation converted matrine to allomatrine at high temperature using a hydrogen transfer catalyst, identifying the allo-series as being the more thermodynamically stable; d) dehydrogenation of matrine was four times faster than that of allomatrine, and matridine (**1.44**) was two times faster than allomatridine (**1.42**), which indicated matrine had more *cis* C-H bonds than allomatrine. The assignments were supported by Bohlmann *et al.*[27-29] *via* a comparison of the dehydration rates of matrine and allomatrine with $Hg(OAc)_2$ studied by IR analysis.



Scheme 1.09. Elucidation of the relative stereochemistry of matrine and allomatrine. *Reagents and conditions*: a) Pd, Δ; or H_2, PtO_2; b) $LiAlH_4$; c) CH_3I; d) H_2, CuO, $CuCr_2O_4$; e) BrCN.

The absolute configuration of matrine was first reported by Okuda *et al.*[30] based on the degradation of 11-monochloromatrine (**Scheme 1.10**). (+)-Matrine was chlorinated under the method reported before by Okuda *et al.*[31] to give two epimeric products: 11α-chloromatrine **1.46** and 11β-chloromatrine **1.47**. These two epimers were separated by column chromatography and the chlorine atoms were assigned as either axial or equatorial in each compound by NMR and dipole moment measurements. Treatment of the separated **1.46** and **1.47** with nitric acid gave (*R*) and (*S*) chlorosuccinic acid (**1.48** and **1.49**) respectively. The absolute configuration of each chlorosuccinic acid was then confirmed by comparison to literature and from this the configuration of the initial matrine could be elucidated. The configuration of matrine was later confirmed by X-ray crystallography.[32]



Scheme 1.10. Determination of the absolute configuration of (+)-matrine.

As matrine has four asymmetric chiral centres, this leads to theoretically possible eight pairs of racemates as shown (**Figure 1.6**). Allomatrine (**1.39**) was first identified as a by-product in isomerisation of matrine prior to isolation from *Sophora genus*.[23] Isomatrine (**1.50**) was isolated in 1975 from roots of *Sophora flavescens*, and its isomerisation over PtO_2 under H_2 led to matrine (**Scheme 1.11-1**), allomatrine and recovered starting material, which clearly indicated isomatrine is a new stereoisomer of the matrine type alkaloids. The structure of isomatrine was determined by X-ray analysis by Okuda *et al.*[33] Tetrahydroneosophoramine (**1.51**) was obtained by the hydrogenation of neosophoraimine (**1.56**) over PtO_2 by Monakhova *et al.* (**Scheme 1.11-2**),[34] and its relative configuration was subsequently investigated by Ibragimov *et al.*[35] *via* X-ray analysis. There are no further records of tetrahydroneosophoramine isomerisation in the literature. Sophoridine (**1.52**) was first isolated by Orekhov[36] from the plant *Sophore alopecuroides* and the relative configuration was confirmed by Ibragimov *et al.*[37] Rulko *et al.*[38] obtained isosophoridine (**1.53**) by completely isomerising sophoridine (**1.52**) under H_2 over PtO_2 in acid at 80 °C (**Scheme 1.11-3**). The last two stereoisomers (**1.54** and **1.55**) have not yet been found or synthesised.

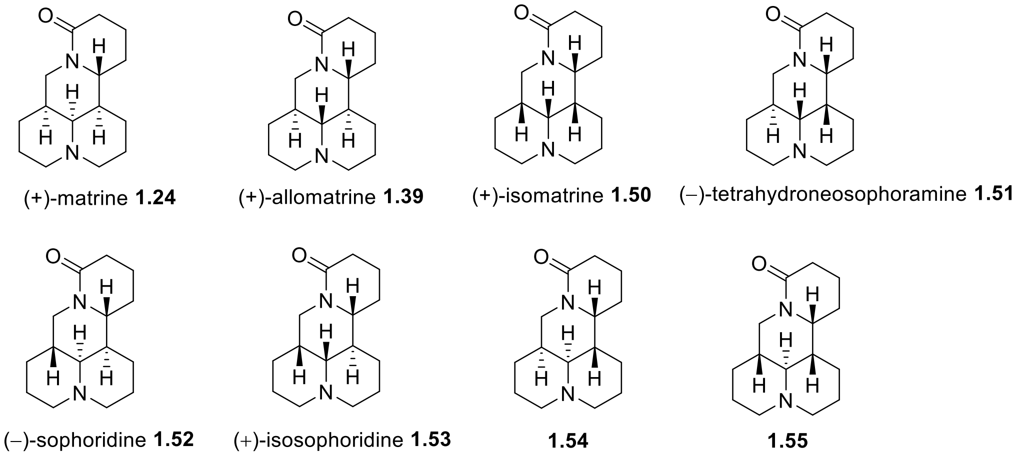
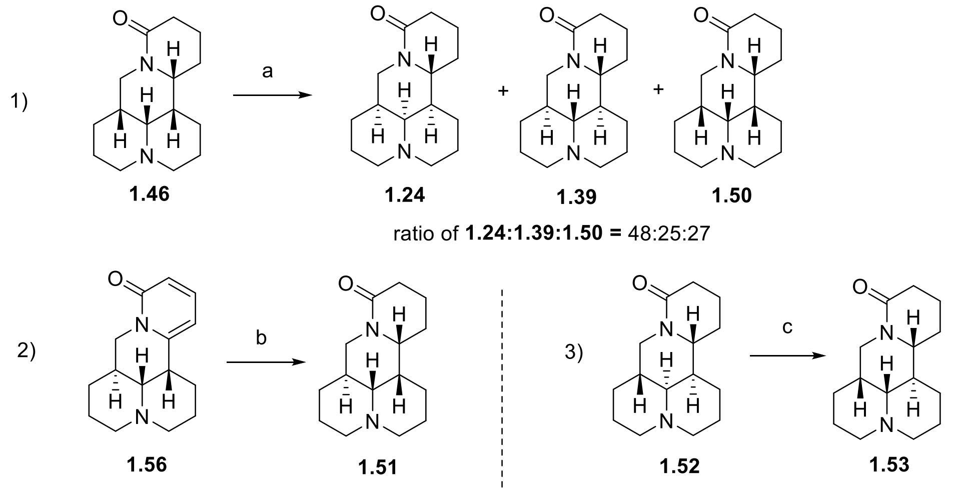


Figure 1.6. Theoretically possible diastereoisomers of matrine skeleton.



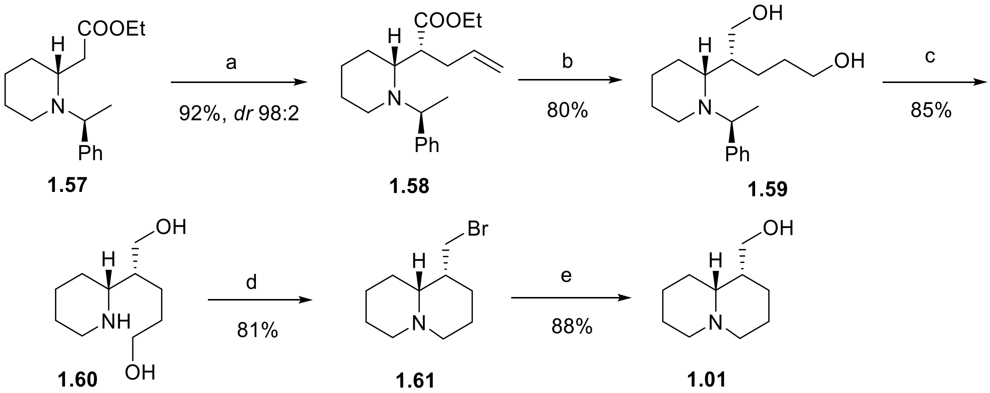
Scheme 1.11. Some transformations of matrine type diastereoisomers. *Reagents and conditions*: a) H_2O, H_2, PtO_2, Δ; b) H_2, PtO_2, EtOH; c) H_2, PtO_2, HCl, Δ.

1.3 Previous synthesis of lupinine

Lupinine is a relatively popular target for synthetic chemists to show new synthetic methods. Many racemic synthetic routes to lupinine have been published,[39-42] and here we will focus on recent enantioselective approaches towards lupinine. An overview of the synthetic work for natural occurring (–)-lupinine and its enantiomer (+)-lupinine is separately documented below in chronological order.

1.3.1 Lhommet's synthesis of (–)-lupinine

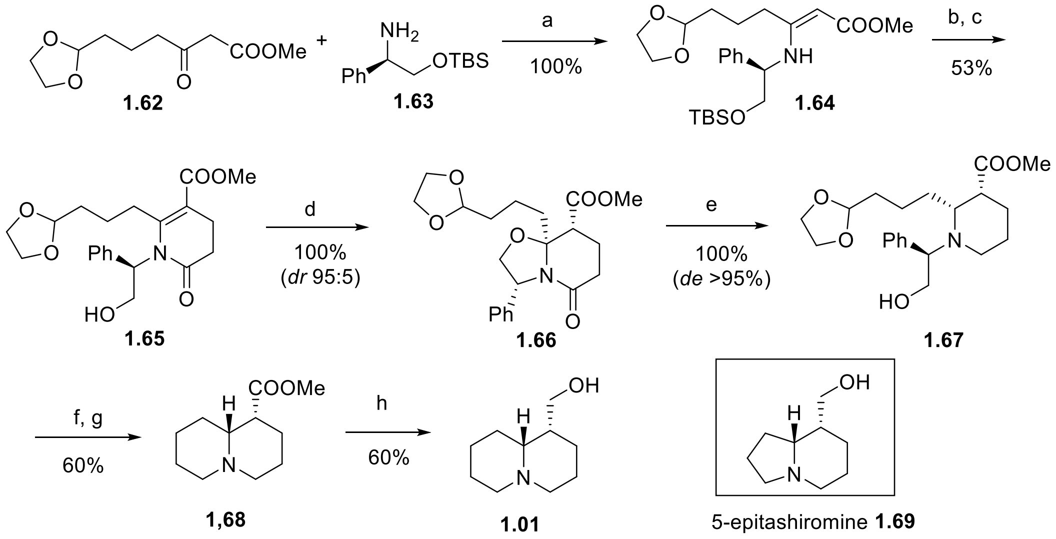
A short synthesis of (–)-lupinine was reported by Lhommet and co-workers in 2001 (**Scheme 1.12**).[43] The chiral piperidine **1.57** was treated with LDA and reacted with allyl bromide giving the corresponding allylation product **1.58** with high diastereoselectivity (*dr* 98:2). Treatment of **1.58** with excess of BH_3/THF converted both the ester and terminal alkene into primary alcohols to provide **1.59**. Debenzylation of **1.59** was accomplished by hydrogenation over a Pd catalyst. The bromination of diol **1.60** with PBr_5 followed by cyclisation afforded bromo lupinane **1.61**. The final conversion of **1.61** into (–)-lupinine (**1.01**) was completed by hydrolysis with aqueous $CuSO_4$ in DMSO.



Scheme 1.12. *Reagents and conditions*: a) i) LDA, –78 °C, THF; ii) allyl bromide; b) i) BH_3, THF; ii) HCl, MeOH; iii) H_2O_2, NaOH; c) H_2, Pd/C, MeOH; d) i) PBr_5, C_6H_6; ii) aq. NaOH; e) aq. $CuSO_4$, DMSO.

1.3.2 Agami's synthesis of (–)-lupinine

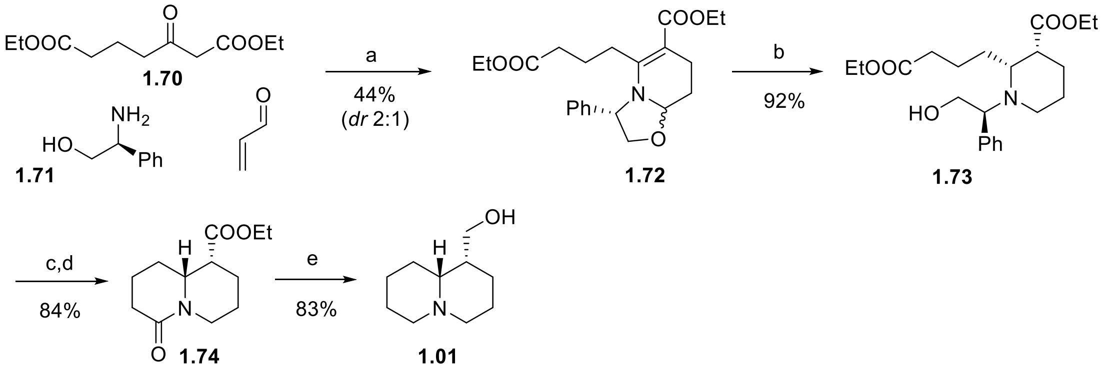
Agami *et al.*[44] reported an efficient enantioselective synthesis of (–)-lupinine in 2004 by preparing bicyclic oxazololactam **1.66** as the key intermediate (**Scheme 1.13**). The synthesis began with condensation of *β*-keto-ester **1.62** and TBS protected (*R*)-phenylglycinol (**1.63**) to give enamino ester **1.64** in quantitative yield. The aza-annulation of **1.64** with acryloyl chloride, followed by removal of silyl protected group by using HF provided alcohol **1.65**. Treatment of the alcohol **1.65** with strong base triggered an intramolecular conjugate addition providing oxazololactam **1.66** in quantitative yield with high diastereoselectivity (*dr* 95:5). The oxazololactam **1.66** was reduced by borane to piperidine **1.67** with high facial selectivity (*de* >95%). Hydrolysis of the acetal followed by cleavage of the chiral protecting group and a reductive aminocyclisation afforded the lupinic ester **1.68**. The final reduction with LiAlH$_4$ led to (–)-lupinine (**1.01**). Agami and co-workers also showed that 5-epitashiromine (**1.69**) could be obtained *via* the same synthetic strategy, utilising a *β*-keto-ester with one less carbon.



Scheme 1.13. *Reagents and conditions*: a) MeOH, Δ, 10 days; b) acryloyl chloride, THF, 0 °C, 15 min; c) HF·py, THF, rt, 20 h; d) LiHMDS, THF, 0 °C, 40 min; e) BH$_3$·THF, rt, 24 h; f) *p*-TsOH, acetone, H$_2$O; g) H$_2$, 10% Pd/C, MeOH, rt, 24 h; h) LiAlH$_4$, THF, Δ.

1.3.3 Lhommet's second synthesis of (–)-lupinine

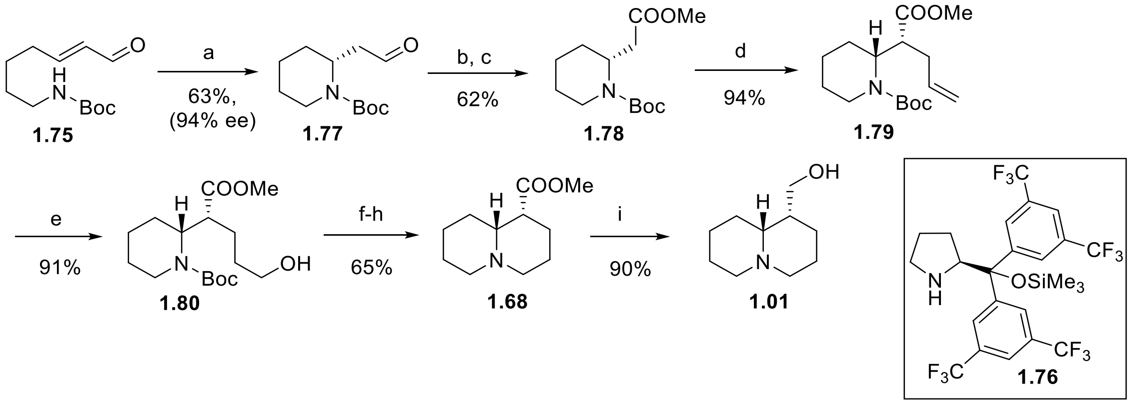
In 2008, a second synthetic route of (–)-lupinine was reported by Lohommet *et al.* based on a multicomponent condensation (**Scheme 1.14**).[45] Refluxing the *β*-ketoester **1.70**, (*S*)-phenylglycinol (**1.71**) and acrolein in toluene yielded a 2:1 mixture of bicyclic oxazolo-pyridines **1.72**. Treatment of this mixture with sodium triacetoxyborohydride in acetic acid led to the diastereoselective reduction of the double bond along with cleavage of the oxazolidine ring to afford piperidine **1.73** as a single isomer in 92% yield. Deprotection of the chiral auxiliary followed by treatment with *p*-toluenesulfonic acid gave rise to bicyclic lactam **1.74**. Double reduction of both the lactam and ester groups by lithium aluminium hydride completed the synthesis of (–)-lupinine (**1.01**).



Scheme 1.14. *Reagents and conditions*: a) 4Å molecular sieves, PhMe, Δ; b) $NaBH(OAc)_3$, MeCN, rt, 48 h; c) H_2, 10% Pd/C, EtOAc, rt, 15 h; d) *p*-TsOH, PhMe, Δ, 36 h; (e) $LiAlH_4$, THF, Δ, 2 h.

1.3.4 Fustero's synthesis of (–)-lupinine

An intramolecular aza-Michael reaction catalysed by proline derivative **1.76** was used in a short synthesis of (–)-lupinine introduced by Fustero *et al.* in 2011 (**Scheme 1.15**).[46] The *N*-Boc protected unsaturated aldehyde **1.75** was treated with the chiral diarylprolinol ether **1.76** as an organocatalysis undergoing intramolecular aza-Michael addition to afford the piperidine **1.77** in 63% yield with high enantioselectivity (94% *ee*). The aldehyde **1.77** was converted into the corresponding methyl ester **1.78** by oxidation. The following allylation installed the second stereocenter by treatment of lithium enolate derived from **1.78** with allyl iodide to afford **1.79** in 94% yield and excellent diastereoselectivity (*dr* 96:4). The sequence of hydroboration-oxidation gave the primary alcohol **1.80**. Mesylation of **1.80** and deprotection of Boc group allowed the base-induced cyclisation to give rise to (–)-methyl lupinate **1.68**. Finally, a standard reduction of **1.68** with lithium aluminium hydride produced (–)-lupinine (**1.01**) in 20% overall yield.

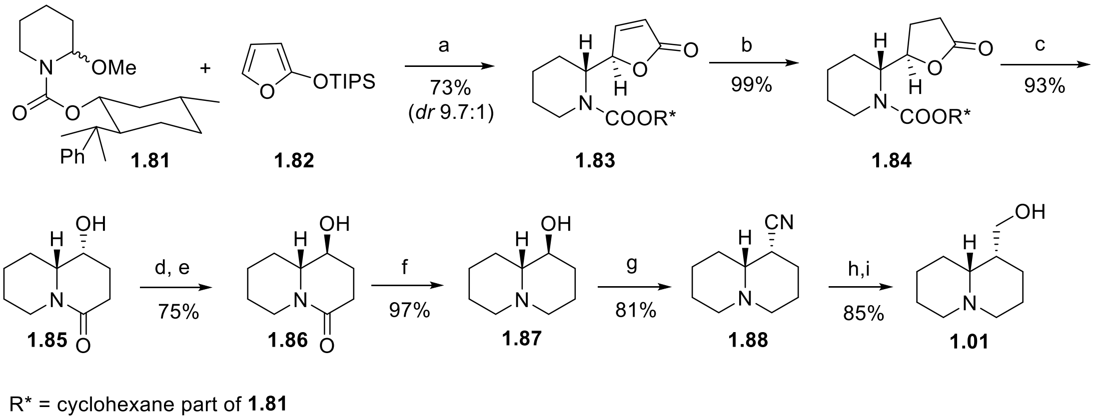


Scheme 1.15. *Reagents and conditions*: a) **1.76** (0.2 equiv), $CHCl_3$, $PhCO_2H$, –50 °C, 20 h; (b) $NaClO_2$, aq. H_2O_2(30%), KH_2PO_4, MeOH-MeCN-H_2O (1:1:1); c) $TMSCHN_2$ (2 M in Et_2O); d) LDA, Et_2O, –100 °C,

1 h, then allyl iodide, 1 h; e) $BH_3{\cdot}Me_2S$, then aq. H_2O_2 (30%), aq. NaOH (1%), EtOH, Δ, 1 h; f) Ms-Cl, NEt_3, CH_2Cl_2, 0 °C, 2 h; g) TFA, rt, 1.5 h; h) aq. NaOH, CH_2Cl_2, 0 °C; (i) $LiAlH_4$, Et_2O, Δ, 3 h.

1.3.5 Santos' synthesis of (–)-lupinine

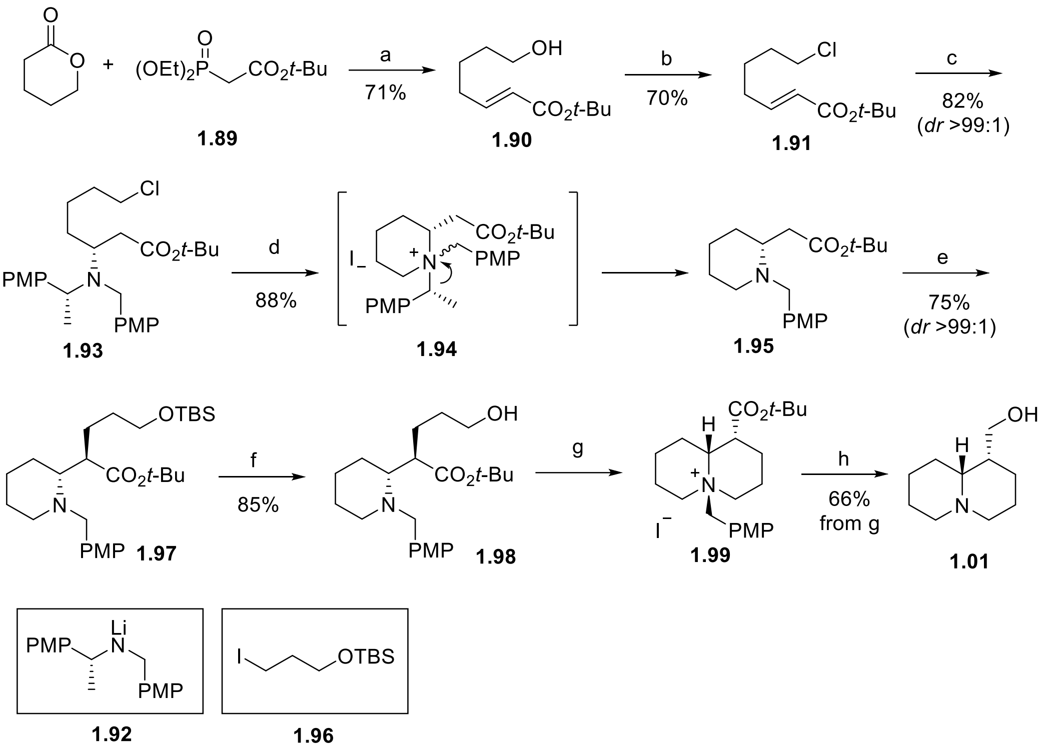
Santos *et al.*[47] in 2011 reported a (–)-lupinine synthesis using the phenylmenthol chiral auxiliary to control the intermolecular nucleophilic addition of silyloxyfurans to cyclic *N*-acyliminium ion as a key step (**Scheme 1.16**). With the TMSOTf and butylmethylimidazolinium tetrafluoroborate ($MBI{\cdot}BF_4$) as additives, the 2-silyloxyfuran **1.82** added to the *N*-acyliminium ion derived from chiral 2-methoxypoperidine carbamate **1.81** giving a 9.7:1 mixture in favour of product **1.83** in 80% yield. Catalytic hydrogenation of **1.83** followed by methanolysis afforded hydroxyl lactam **1.85** in 93% overall yield. The first Mitsunobu reaction converted the alcohol **1.85** into the corresponding epimer **1.86**. After reduction of lactam by alane (AlH_3), a second Mitsunobu inversion with cyanide gave the nitrile **1.88**, which after acid hydrolysis and further reduction by alane provided enantiomerically pure (–)-lupinine (**1.01**).



Scheme 1.16. *Reagents and conditions*: a) TMSOTf, $BMI{\cdot}BF_4$, CH_2Cl_2-THF (1:1), –78 °C, 7 h; b) H_2, 10% Pd/C, EtOAc; c) MeONa, MeOH, Δ; (d) $ClCH_2COOH$, PPh_3, DEAD, CH_2Cl_2; e) K_2CO_3, MeOH; (f) AlH_3; g) $Me_2C(OH)CN$, PPh_3, THF, then DEAD; h) HCl in $CHCl_3$ (6 M), Δ; (i) AlH_3.

1.3.6 Davies' synthesis of (–)-lupinine

The most recent report of (–)-lupinine asymmetric synthesis was described In 2014 by Davies *et al.* (**Scheme 1.17**).[48] The α,β-unsaturated ester **1.90** was formed *via* a one-pot DIBAL-H reduction/Wadsworth-Emmons reaction from δ-valerolactone. A subsequent Appel reaction converted **1.90** into chloro substituted **1.91**. Conjugated addition of chiral lithium amide **1.92** to **1.91** afforded β-amino ester **1.93** in 82% yield as a single diastereoisomer (*dr* >99:1). Piperidine **1.95** was formed *via* a quaternary ammonium species **1.94**, which resulted from the cyclisation of the amine **1.93**. Alkylation of piperidine **1.95** with iodide **1.96** gave the only *anti*-product **1.97** in 75% yield (*dr* > 99:1). Subsequent cyclisation of **1.98**, derived from **1.97** by desilylation, with I_2, imidazole and PPh_3 gave the quaternary ammonium salt **1.99**. Reduction of the ester moiety and removal of the *N*-(*p*-methoxybenzyl) group was achieved in one step by treatment of the ammonium salt with $LiAlH_4$ to give (–)-lupinine.

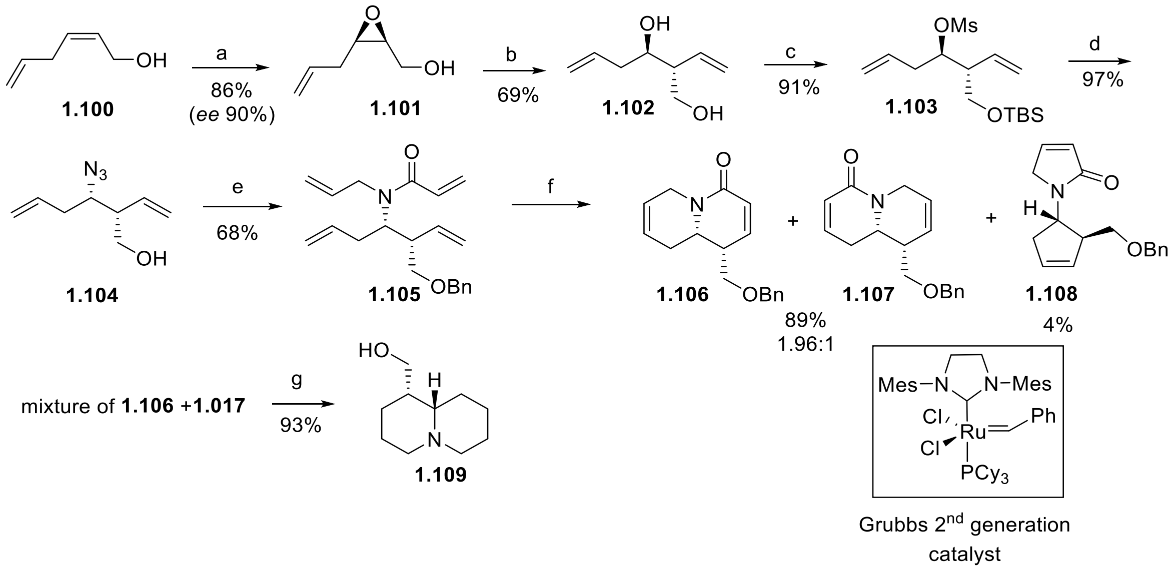


Scheme 1.17. *Reagents and conditions*: a) *n*-BuLi, DIBAL-H, THF, –78 °C to rt; b) CCl_4, PPh_3, Et_3N, MeCN, Δ; c) **1.92**, THF, –78 °C; d) NaI, MeCN, Δ; e) i) LiHMDS, THF, –78 °C; ii) **1.96**, –78 °C to rt; f) TBAF, THF; g) I_2, imidazole, PPh_3, PhMe/MeCN (4:1), 65 °C; h) $LiAlH_4$, THF, Δ.

The following section will introduce 3 synthetic routes of the unnatural occurring (+)-lupinine.

1.3.7 Ma's synthesis of (+)-lupinine

Ma *et al.*[49] in 2004 employed the Sharpless asymmetric epoxidation and double ring-closing metathesis (RCM) reactions as key steps to synthesise (+)-lupinine and other three stereoisomers of the lupinine skeleton. The route to (+)-lupinine is illustrated by **Scheme 1.18**. Asymmetric epoxidation of (*Z*)-hexa-2,5-dienol (**1.100**) in the presence of D-diethyl tartrate gave the **1.101** in 86% yield (90% *ee*). Regiospecific ring opening of **1.101** with vinyl cuprate afforded the diene **1.102**, which was converted into the diene **1.103** *via* a TBS protection of the primary alcohol and subsequent mesylation of secondary alcohol. The azide **1.104** was formed by treatment of **1.103** with NaN_3. Following *N*-allylation and acylation of the amine, derived from reduction of the azide **1.104**, afforded the RCM precursor **1.105**. When treatment of **1.105** with the Grubbs 2nd catalyst, the double metathesis yielded a mixture of **1.106** and **1.107** (1.96:1, 89%), together with trace amount of dumbbell product **1.108** (4%). Finally, the mixture **1.106** and **1.107** were performed with a sequence of hydrogenation over Pd/C and reduction with $LiAlH_4$ to afford the (+)-lupinine (**1.109**).

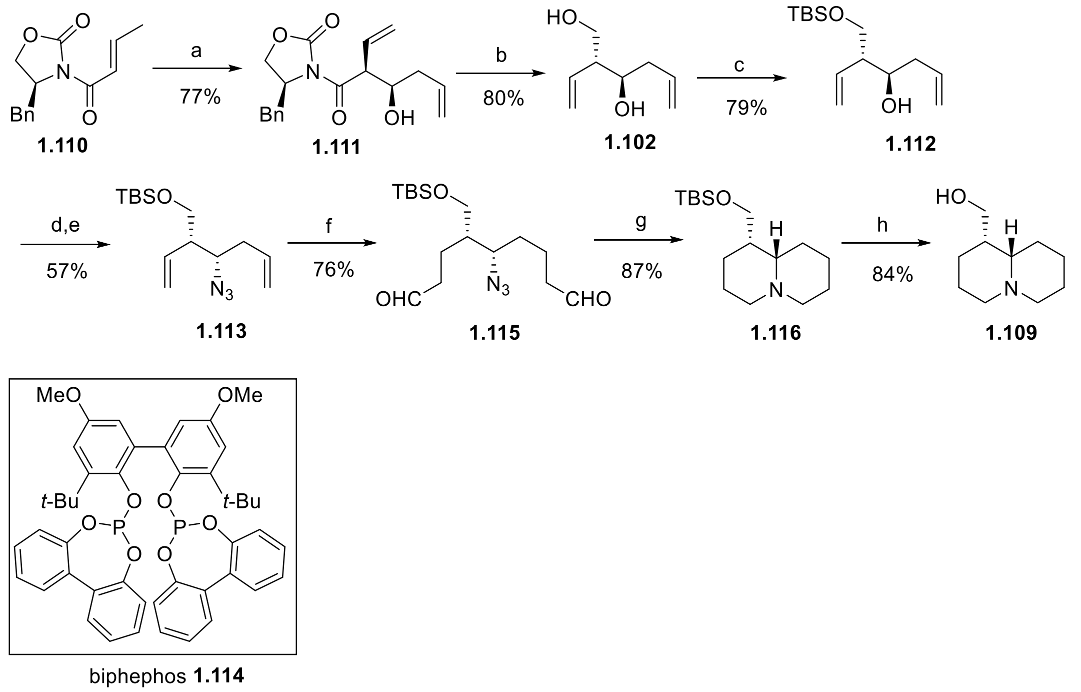


Scheme 1.18. *Reagents and conditions*: a) *t*-BuOOH, Ti(O*i*-Pr)$_4$, D-diethyl tartrate, −20 °C, CH_2Cl_2; b) i) $H_2C{=}CHMgBr$, CuI, Et_2O/THF; ii) $NaIO_4$, THF/H_2O; c) i) TBSCl, Et_3N, DMAP; ii) Ms-Cl, Et_3N, DMAP; d) i) NaN_3, HMPA; ii) TBAF; e) i) NaH, BnBr; ii) $LiAlH_4$, THF; iii) allyl bromide, K_2CO_3; iv) acryloyl chloride, Et_3N; f) 5 mol % Grubbs II, CH_2Cl_2, Δ; g) i) H_2, Pd/C; ii) $LiAlH_4$, THF, Δ.

1.3.8 Airiau's synthesis of (+)-Lupinine

In 2009 (+)-Lupinine was prepared by Airiau *et al.*[50] by a bidirectional hydroformylation and reductive bis-amination strategy (**Scheme 1.19**). The same intermediate **1.102**, used in Ma's synthetic route, was prepared by a different route. Evans aldol reaction between titanium enolate derived from **1.110** and 3-butenal afforded the *syn*-product **1.111** as a single diastereoisomer in 77% yield. Reductive cleavage of chiral auxiliary using $LiBH_4$ gave the diol **1.102**. The primary alcohol was protected as a TBS ether, and the secondary alcohol was displaced with the azide ion via the active intermediate mesylate to furnish bis-homoallylic azide **1.113**. The regioselective double hydroformylation of the terminal alkenes employing $Rh(CO)_2(acac)$ and biphephos **1.114** afforded azidodialdehyde **1.115** in 76% yield. A one-pot reduction of the azide and subsequent imine over

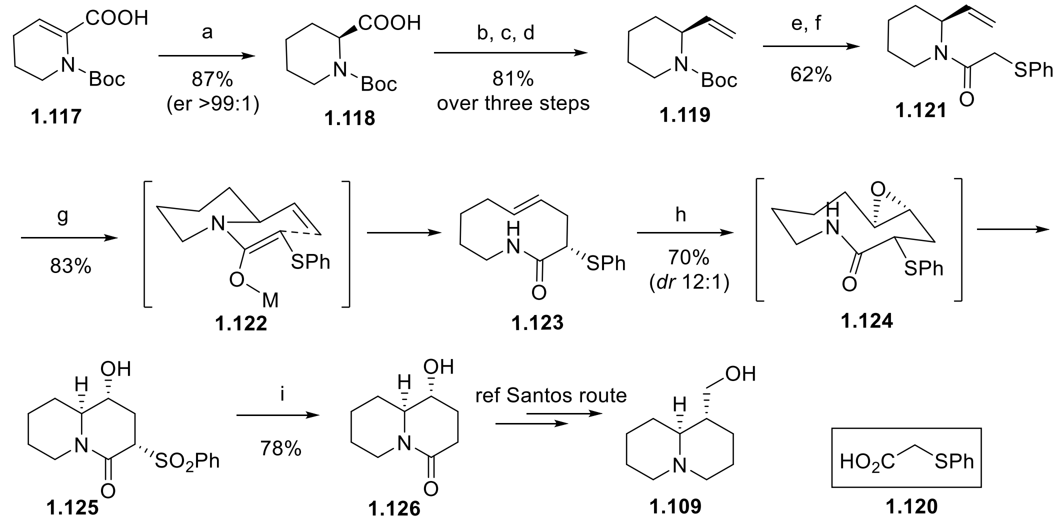
$Pd(OH)_2$ under H_2 gave the quinolizidine core **1.116** in 87% overall yield. Finally desilylation of **1.116** using TBAF completed the formation of (+)-lupinine in 8 steps with an overall yield of 15%.



Scheme 1.19. *Reagents and conditions*: a) i) $TiCl_4$, DIPEA, –78 °C, CH_2Cl_2; ii) $H_2C{=}CHCH_2CHO$, –78 °C to rt; b) $LiBH_4$; c) TBSCl, Et_3N, DMAP; d) Ms-Cl, Et_3N, DMAP; e) NaN_3, DMF; f) H_2/CO (1:1) 5 bar, 2 mol% $Rh(CO)_2(acac)$, 4 mol% biphephos **1.114**, THF, 65 °C; g) H_2 5 bar, 20 mol% $Pd(OH)_2/C$; h) TBAF, THF, 45 °C.

1.3.9 Sim's synthesis of (+)-lupinine

In 2012, a synthesis of the (+)-lupinine was reported by Sim and co-workers using aza-Claisen rearrangement as the key step (**Scheme 1.20**).[51] The Boc protected pipecolic acid **1.118** was prepared by asymmetric hydrogenation of **1.117** using Noyori catalyst.[52] Sequential borane reduction, Swern oxidation and Wittig reaction afforded the (*S*)-2-vinyl-*N*-Boc piperidine **1.119**.[53] Boc deprotection of **1.119** using TMSOTf with 2,6-lutidine and acylation with phenylthioacetic acid (**1.120**) to afforded amide **1.121**. A microwave assisted aza-Claisen rearrangement of **1.121** completed the transfer of chirality to give the ring-expanded product **1.123** in 83% yield. The oxone-induced transannulation via epoxide **1.124** gave rise to **1.125** with concomitant oxidation of the sulfide in 70% yield with good diastereoselectivity (*dr* 12:1). Cleavage of the sulfone using sodium amalgam produced the lactam **1.126**, which is the enantiomer of **1.86** in Santos' synthesis of (–)-lupinine. Then, following the same procedures described by Santos *et al.*[47], (+)-lupinine was afforded.



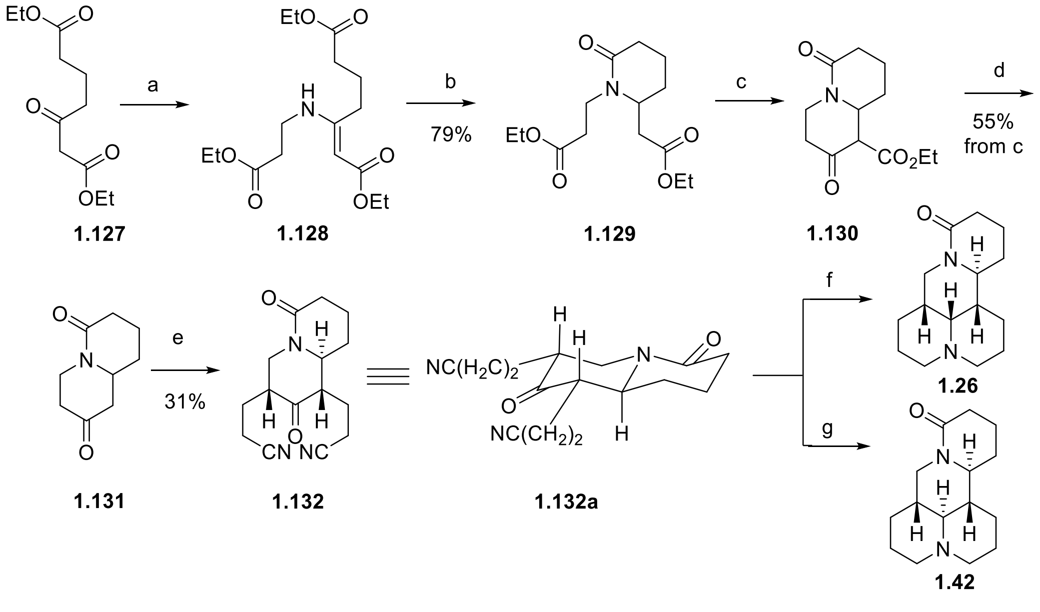
Scheme 1.20. *Reagents and conditions*: a) H_2, Noyori catalyst; b) $BH_3 \cdot THF$; c) i)DMSO, oxalyl chloride, −78 °C, CH_2Cl_2; ii) NEt_3, −78 °C, CH_2Cl_2; d) KHMDS, PH_3PCH_3Br, THF, −78 ° to 0 °C; e) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; f) **1.120**, EDC, HOBt, *N*-methylmorphline, CH_2Cl_2; g) *i*-PrMgCl, PhMe, 200 °C (microwave, 250 W); h) oxone®, MeOH/H_2O; i) 6% Na/Hg, $B(OH)_3$, MeOH.

1.4 Previous syntheses of matrine-type alkaloids

Synthesis of matrine-type alkaloids has been attempted several times, but only four racemic total syntheses and three semi-syntheses have been reported to date. There is no asymmetric access to matrine. In this section, an overview of synthetic work including matrine, allomatrine, sophoramine and isosophoramine is introduced below in chronological order.

1.4.1 Mandell's synthesis of (±)-matrine

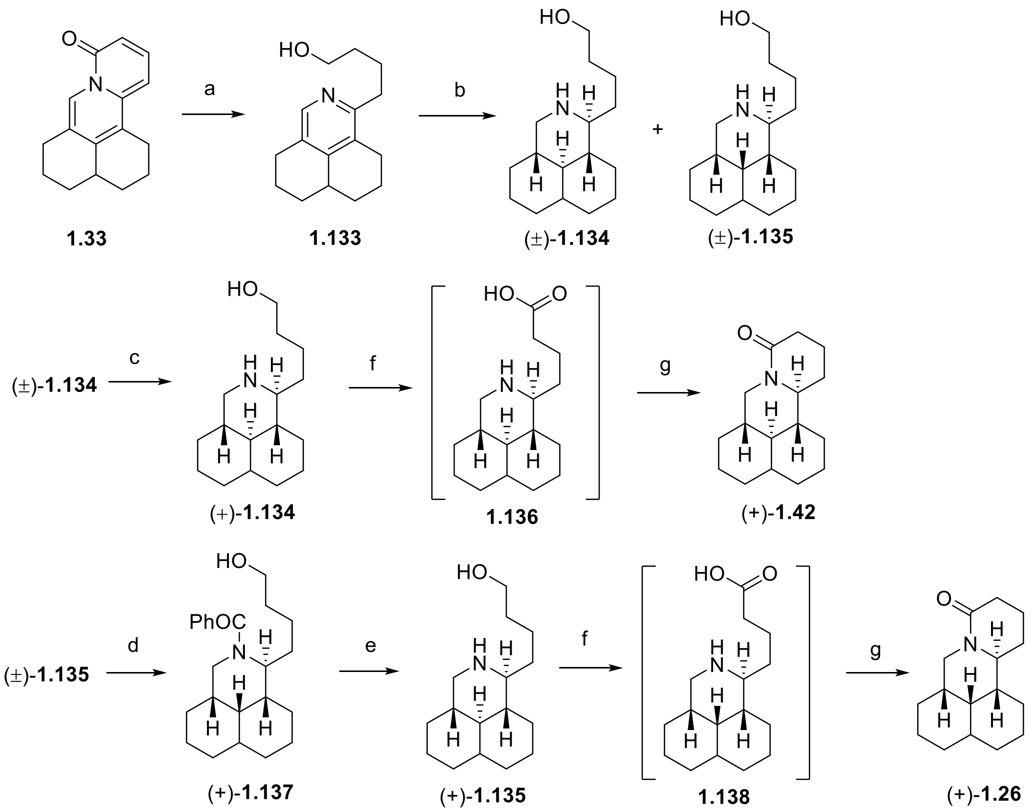
The first total synthesis of (±)-matrine was reported by Mandell *et al.* in 1963.[54] And later in 1965, Mandell and co-workers performed the same synthetic methodology to prepare both (±)-matrine (**1.26**) and (±)-allomatrine (**1.42**) as shown in **Scheme 1.21**.[55] Condensation between diethyl-3-oxo-pimalate (**1.127**) and *β*-alinine ethyl ester in refluxing benzene gave the enamine **1.128**. The crude product from the condensation was reduced with Adams catalyst and followed by heating to effect lactamization providing **1.129**. Dieckmann cyclisation of **1.129** with NaH and subsequent decarboxylation by refluxing the crude product in glacial AcOH generated the bicyclic ketone **1.131** in 55% overall yield. In order to complete bis-alkylation of **1.131**, the alkylation was repeated twice before purification to give dinitrile **1.132**. The relative stereochemistry of dinitrile **1.132** was in the most stable configuration as shown **1.132a**. Finally the reductive cyclisation afforded (±)-matrine (**1.26**) by hydrogenation of **1.132** with 5% Pd/C in AcOH. Increasing the catalyst loading to 10% Pd/C led to (±)-allomatrine (**1.42**). The synthetic products were identified by comparison of infrared spectra and melting points with authentic samples from natural sources.



Scheme 1.21. *Reagents and conditions*: a) *β*-Alanine ethyl ester, benzene, Δ; b) H_2, PtO_2; c) NaH, Δ; d) glacial AcOH, Δ; e) i) pyrrolidine, benzene; ii) acrylonitrile, EtOH, Δ, repeat steps twice; f) 5%, Pd on charcoal, H_2, 50 psi; g) 10%, Pd on charcoal, H_2, 50 psi.

1.4.2 Okuda semi-synthesis of optically active matrine and allomatrine

In 1966, Okuda *et al.*[56] reported a semi-synthesis of matrine and allomatrine from octadehydromatrine (**1.33**). A chiral resolution was performed during the synthesis, which allowed isolation of the optically pure amino alcohol intermediates (+)-matrinol and (+)-allomatrinol.



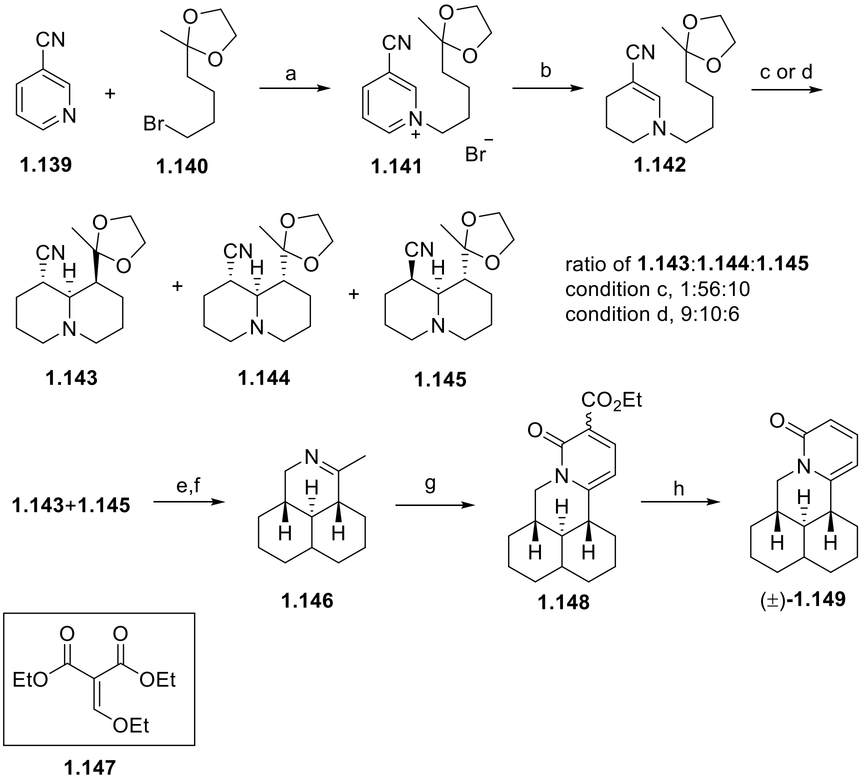
Scheme 1.22. *Reagents and conditions*: a) H_2, PtO_2, AcOH; b) Na, EtOH, Δ; c) recrystallisation with dibenzoyl-(+)-tartaric acid; d) i) PhCOCl, NaOH; ii) KOH, EtOH, Δ; iii) recrystallization with dibenzoyl-(+)-tartaric acid; e) i) $LiAlH_4$, dioxane, Δ; ii) H_2, PtO_2, MeOH; f) CrO_3, 20% H_2SO_4; g) Ac_2O, Δ.

Hydrogenation of octadehydromatrine (**1.33**), which was obtained by dehydrogenation of matrine, over PtO_2 in AcOH, gave rise to didehydomatrine **1.133** (**Scheme 1.22**). In the presence of excess Na under reflux in EtOH, **1.133** was reduced to racemic (±)-allomatrinol **1.134** and (±)-matrinol **1.135**. The racemic (±)-allomatrinol **1.134** was resolved by ecrystallisation of the dibenzoyl-(+)-tartaric acid salt of (±)-allomatrinol **1.134** from EtOH. For racemic (±)-matrinol **1.135**, it was found that efficient resolution was achieved by recrystallisation of the dibenzoyl-(+)-tartaric acid salt of

N-benzoyl-(±)-matrinol to afford pure *N*-benzoyl-(+)-matrinol (**1.137**). Reduction of (+)-**1.137** using $LiAlH_4$ and successive catalytic hydrogenation afforded (+)-matrinol (**1.135**). Both (+)-matrinol and (+)-allomatrinol were oxidised to corresponding amino acids by CrO_3, and ring-closed immediately in refluxing Ac_2O to furnish (+)-matrine (**1.26**) and (+)-allomatrine (**1.42**).

1.4.3 Wenkert's synthesis of (±)-isosophoramine

In 1973 Wenkert *et al.*[57] published the total synthesis of (±)-isosophoramine from nicotinonitrile (**Scheme 1.23**). The synthetic method is based on the sequence of hydrogenation and cyclisation of the *N*-alkyl salt of β-acylpyridine (**1.141**), which was applied in the total synthesis of (±)-lamprolobine by Wenkert and Jeffcoat previously in 1970.[58]



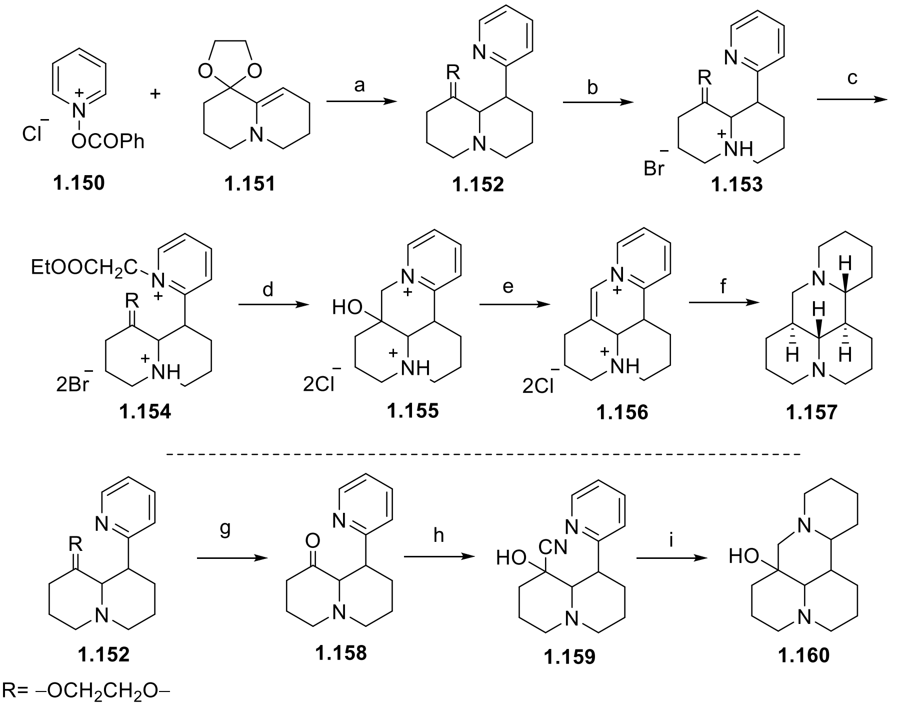
Scheme 1.23. *Reagents and conditions*: a) Δ, 3 days; b) H_2, Pd/C, NEt_3, MeOH; c) TsOH, rt, $CHCl_3$; d) TsOH, benzene, Δ; e) $LiAlH_4$, Et_2O, Δ; f) 20% HCl; g) LDA, **1.147**; h) 20% TsOH, Δ.

Alkylation of nicotinonitrile **1.139** with ketal bromide **1.140** gave a salt **1.141**, and the following catalytic hydrogenation afforded piperidine **1.142**. Acid catalysed cyclisation produced the quinolizidine core as three stereoisomers. Isomers **1.143**, **1.144** and **1.145** were obtained in 1:56:10 ratio respectively when performing reaction at rt in $CHCl_3$, while a 1:10:6 ratio was observed when the reaction was carried out in refluxing benzene. Relative stereochemistries were assigned by NMR spectroscopy combined with acid or base-induced isomerisation experiments. Treatment of **1.143** and **1.145** with $LiAlH_4$ and subsequent acid hydrolysis afforded the same tricyclic imine **1.146**, which had an all-*trans* hydrogen-arrangement determined by NMR and IR analysis. A sequence of Michael addition of imine **1.146** with ethoxymethylenemalonate (**1.147**) and lactam formation with acid treatment yielded the tetracyclic ester **1.148**. Finally decarboxylation of **1.148** in 20% H_2SO_4 afforded (±)-isosophoramine (**1.149**).

1.4.4 Saeki's synthesis of (±)-allomatridine

In 1977, Saeki *et al.*[59] reported a total synthesis of (±)-allomatridine based on enamine addition to acyl-addition of *N*-oxide pyridinium salts which they had developed previously (**Scheme 1.24**).[60] The mixture of enamine **1.151** and *N*-benzoyloxypridinium chloride **1.150** was treated with $NaBH_4$ to afford quinolizidine **1.152** *via* an addition-elimination pathway. Monohydrobromide **1.153**, obtained from treatment of **1.152** with NH_4Br, was used to prepare pyridinium salt **1.154** by reaction with ethyl bromoacetate under reflux in EtOH. Hydrolysis of ketal and ester groups in **1.154** with 20% HCl and consecutive ring closure accompanied by decarboxylation produced tetracycle **1.155**. Transformation of **1.155** into (±)-allomatridine was achieved by treatment of **1.155** with an excess amount of NEt_3, affording dehydrated intermediate **1.156**, and subsequent two-step reduction by $NaBH_4$ and hydrogenation over PtO_2. The overall yield was around 1-1.5%, and the melting point and IR spectrum of the dipicrate of the synthetic product agreed with that of allomatridine obtained from naturally occurring matrine.

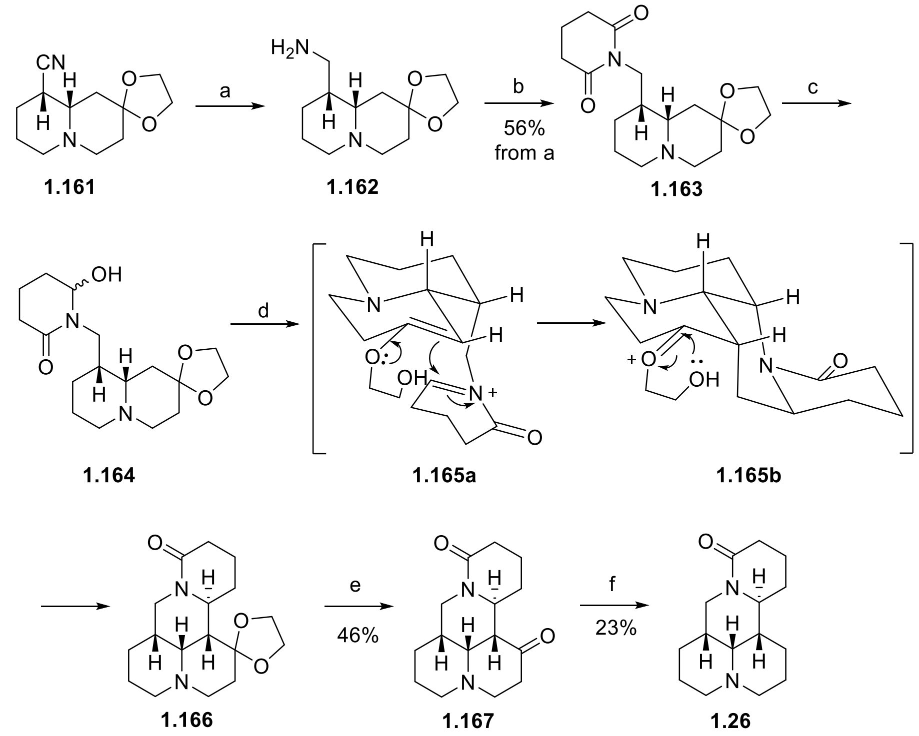
An alternative route to form tetracyclic ring was also investigated. Hydrolysis of quinolizidine **1.152** in 20% HCl under reflux gave 1-oxo-9-(2-pyridyl)quinolizidine (**1.158**), and treatment of **1.158** with excess acetone cyanohydrin yielded cyanide **1.159**. Compound **1.159** was hydrogenated in dioxane over Raney Ni at 190 °C to produce 17-hydroxyallomatrinde (**1.160**). Due to lack of enough sample of sufficient material, the further transformation of **1.160** to allomatridine was not accomplished.



Scheme 1.24. *Reagents and conditions*: a) i) CH_2Cl_2, rt; ii) $NaBH_4$, EtOH; b) NH_4Br, Δ; c) $BrCH_2COOEt$; d) 20% HCl, Δ; e) NEt_3, EtOH; f) i) $NaBH_4$, EtOH; ii) HCl; iii) H_2/PtO_2; g) 20% HCl, Δ; h) acetone cyanohydrin, CH_2Cl_2, rt; i) H_2, Raney Ni, dioxane, 190 °C.

1.4.5 Chen's synthesis of (±)-matrine

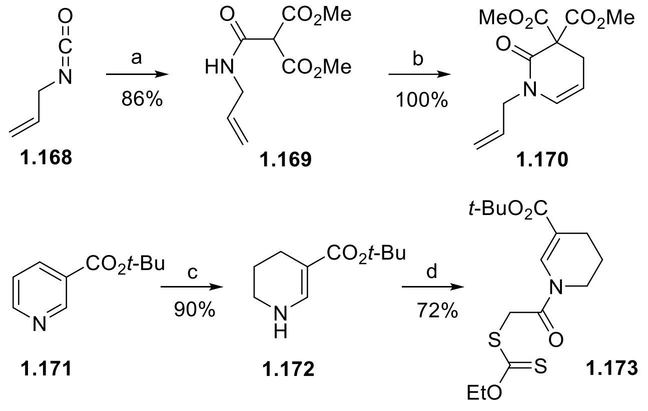
In 1986 Chen *et al.*[61] reported a total synthesis of (±)-matrine. The synthesis employed an acetal mediated *N*-acyliminium cyclisation to assemble the tetracyclic ring skeleton (**Scheme 1.25**). Chen's synthesis is built on the total synthesis of isolamprolobine, which is identical to epilamprolobine, published by Wenkert and Jeffcoat in 1970.[58] Reduction of the nitrile functionality in **1.161** by $LiAlH_4$ afforded primary amine **1.162**, which was treated with glutaric anhydride to produce glutarimide intermediate **1.163**. Treatment of **1.163** with L-selectride afforded hydroxyl lactam **1.164**, which was sequentially subjected to *N*-acyliminium cyclisation **1.165a** with MsOH to obtain the tetracyclic product **1.166**. The relative stereochemistry at the ring junctions was determined by X-ray analysis of 8-oxomatrine **1.167**, derived from **1.166** in the presence of aq. H_2SO_4. The total synthesis of (±)-matrine (**1.26**) was completed after a final reduction of **1.167** by employing Barton deoxygenation, which firstly reduced ketone to the corresponding alcohol followed by thioester formation and subsequent *n*-Bu_3SnH reduction.



Scheme 1.25. *Reagents and conditions*: a) $LiAlH_4$; b) glutaric anhydride; c) L-selectride, –30 °C; d) MsOH; e) aq. H_2SO_4; f) i) L-selectride, –78 °C; ii) 1,1'-thiocarbonyldi-imidazole, Δ; iii) *n*-Bu_3SnH, Δ.

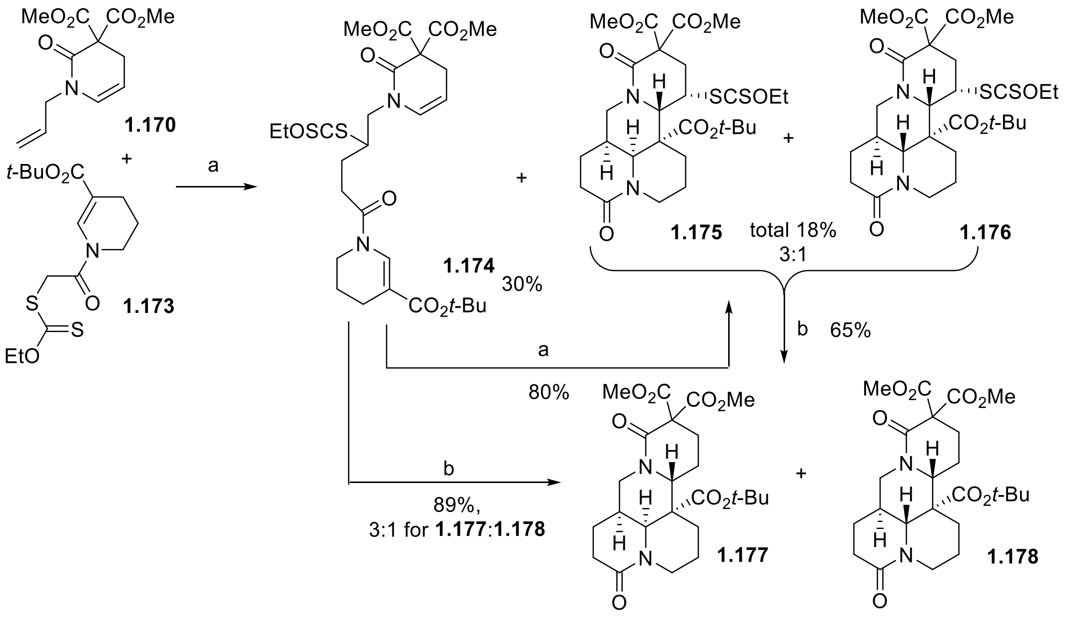
1.4.6 Zard's synthesis of (±)-matrine

In 1998, Zard *et al.*[62] developed a method that enabled assembly of the tetracyclic skeleton of matrine-type alkaloids rapidly by a radical cascade sequence from two relatively simple piperidine derivatives (**Scheme 1.26** and **Scheme 1.27**). Allyl isocyanate **1.168** was treated with the anion of dimethyl malonate to give amide **1.169** (**Scheme 1.26**). Amide **1.169** underwent Michael addition to acrolein and intramolecular condensation by heating with boric acid to afford enamide **1.170** in 86% overall yield. The xanthate **1.173** was easily prepared in three sequential steps. Catalytic hydrogenation of *tert*-butyl nicotinate **1.171** to enamine **1.172**, followed by chloro-acetylation and displacement chloride with potassium thiolate afforded ethyl xanthate **1.173** in 64% overall yield.



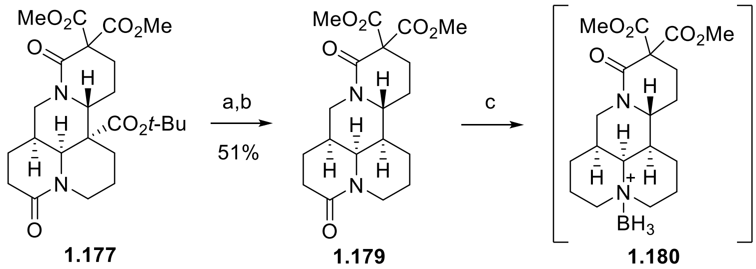
Scheme 1.26. *Reagents and conditions*: a) sodium dimethylmalonate; b) i) acrolein, TEA; ii) $B(OH)_3$, toluene, Δ; c) H_2, Pd/C; d) i) $ClCH_2COCl$, NEt_3. ii) EtOCSSK.

Using lauroyl peroxide as the radical initiator, the radical cascade reaction of **1.170** with **1.173** under reflux in benzene gave a 18% combined yield of tetracyclic derivatives **1.175** (matrine relative stereochemistry) and **1.176** (allomatrine relative stereochemistry) in a ratio of 3:1 respectively, together with bicyclic compound **1.174** in 30% yield (**Scheme 1.27**). Re-exposing compound **1.174** to the initial radical cascade conditions obtained the same mixture of **1.175** and **1.176** in 80% yield. Radical reduction of the xanthate group was achieved by treatment of mixture **1.175** and **1.176** with lauroyl peroxide in 2-propanol under reflux to give **1.177** and **1.178**. Under the same conditions, **1.174** directly generated the reduced tetracyclic products (**1.177** and **1.178**) in an excellent yield (89%), due to that the uncyclised radical intermediate abstracted hydrogen from 2-propanol relatively slower than cyclisation progressed.



Scheme 1.27. *Reagents and conditions*: a) lauroyl peroxide, benzene, Δ; b) lauroyl peroxide, 2-propanol, Δ.

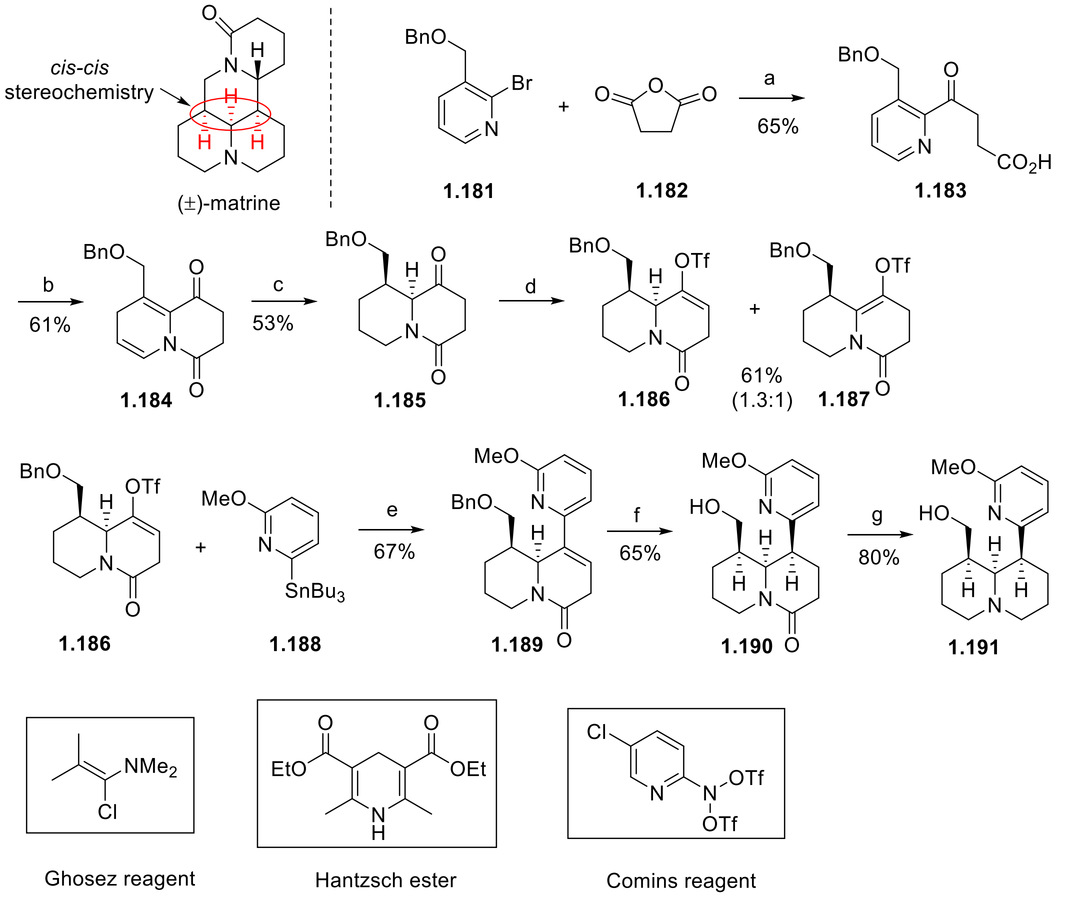
In this stage the two tetracyclic products could be separated. Matrine skeleton **1.177** was selective deprotected of *tert*-butyl ester group under acidic conditions, followed by Barton decarboxylation to afford intermediate **1.179** (**Scheme 1.28**). Selective reduction of lactam on ring A with $BH_3 \cdot SMe_2$ led to the borane complex **1.180**, which was heated with diluted HCl allowed to effect both hydrolysis and decarboxylation of the germinal diester moiety to complete the total synthesis of (±)-matrine (**1.26**).



Scheme 1.28. *Reagents and conditions*: a) TFA, CH_2Cl_2; b) $(COCl)_2$, *N*-hydroxy-4-methylthiazolinethione, NEt_3, *tert*-dodecanethiol, cyclohexane, AIBN, Δ; c) $BH_3 \cdot SMe_2$, THF; d) 2 M HCl, Δ.

1.4.7 Takemoto's stereoselective construction of AB ring system of matrine

In 2014, Takemoto *et al.*[63] developed a method for the stereoselective construction of the AB rings of the quinolizidine moiety with a *cis-cis* stereochemistry (**Scheme 1.29**). 2-Bromopyridine **1.181** was treated with *n*-BuLi and TMSCl and then with succinic anhydride to afford carboxylic acid **1.183** in 65% yield over two steps. Quinolizidine skeleton **1.184** was generated by treatment of **1.183** with Ghosez reagent followed by the Hantzsch ester. Due to instability of compound **1.184**, an immediate hydrogenation was performed over Pd/C to give ketone **1.185**, whose stereochemistry was confirmed by NOE experiments. Ketone **1.185** was converted to enol triflate **1.186** by treatment with NaHMDS and Comins reagent, but a large amount of its regio-isomer **1.187** formed together in a combined yield of 61% (**1.186**:**1.187** = 1.3:1). The desired enol triflate **1.186** could be separated by column chromatography, and subsequent Stille coupling gave **1.189** in 67% yield. Hydrogenation of **1.189** afforded **1.190** as a single isomer and selectivity provided by shielding of the top-face by the hydroxymethyl group. Finally, reduction of the lactam with $LiAlH_4$ produced the intermediate **1.191** with the required *cis-cis* stereochemistry of the AB ring. Although the tetracyclic moiety was not formed, this method still provides a rapid way to construct the quinolizidine core with the required cis-cis stereochemistry for matrine, and closure the final ring to form matrine can be achieved through intermediate **1.191** with subsequent adjustment of the oxidation levels.



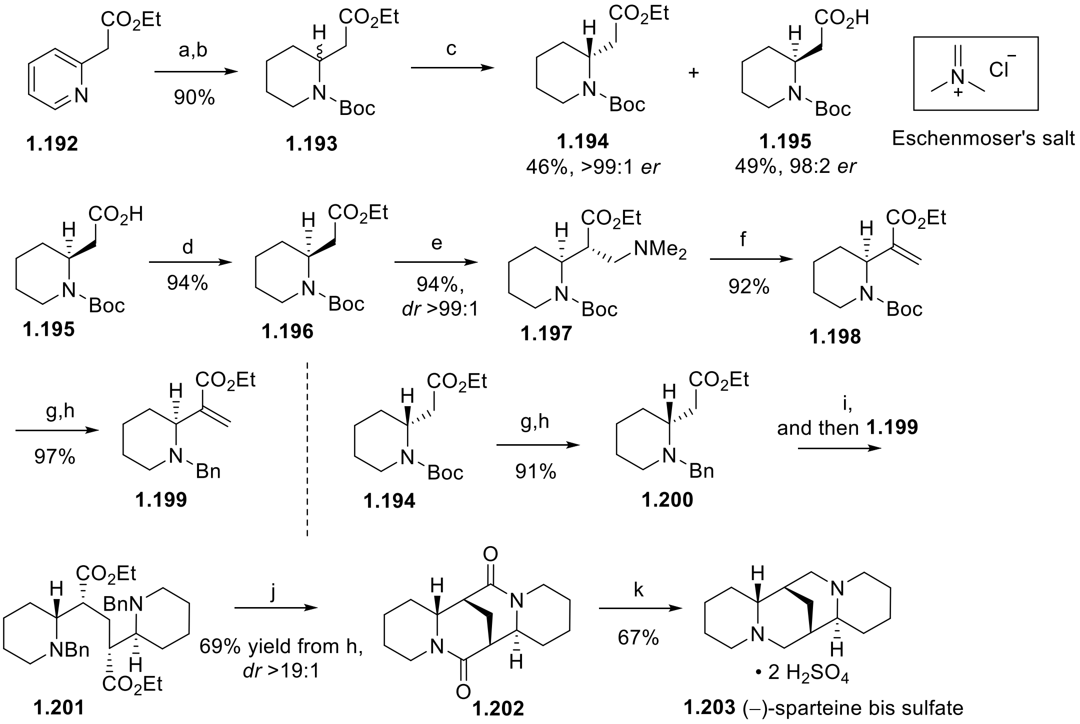
Scheme 1.29. *Reagents and conditions*: a) i) *n*-BuLi, TMSCl, Et_2O, –78 °C to rt; ii) **1.182**, $ClCH_2CH_2Cl$, 100 °C; b) i) Ghosez reagent, 4 Å MS; ii) Hantzsch ester, $ClCH_2CH_2Cl$, 0 °C to rt; c) H_2, Pd/C, EtOH; d) NaHMDS, Comins reagent, THF, –78 ° to 0 °C; e) $Pd(PPh_3)_4$, CuDPP, LiCl, THF, 50 °C; f) H_2 5 atm, Pd/C, EtOH; g) $LiAlH_4$, THF, 50 °C.

1.5 Updated synthesis of sparteine

Previous syntheses of sparteine have been reviewed by our group,[64] and this part will give an update including two enantioselective syntheses of sparteine published in 2018 by O'Brien *et al*. and Breuning *et al*.

1.5.1 O'Brien's gram-scale synthesis of (–)-sparteine

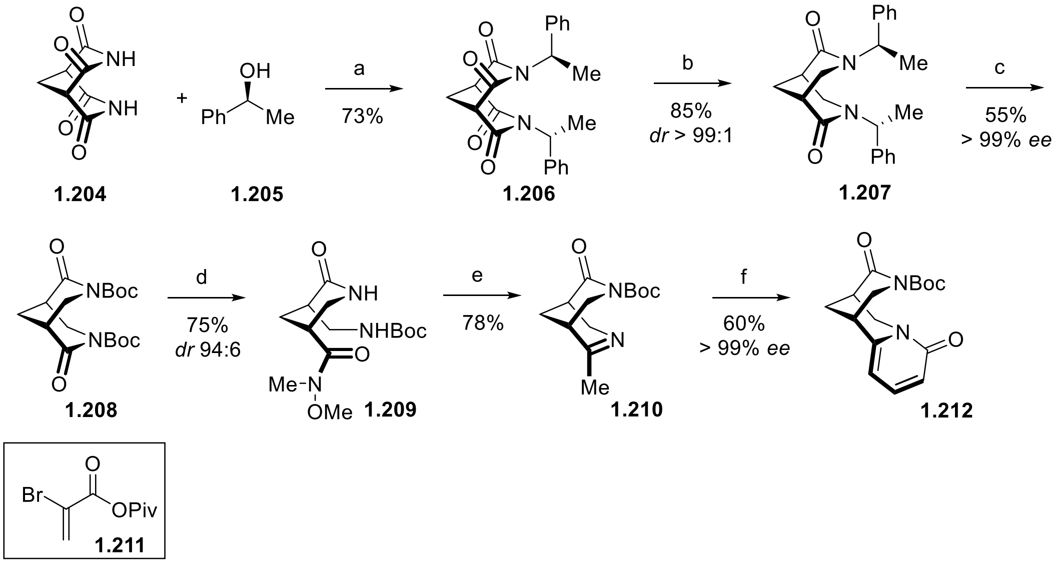
A gram-scale synthesis of (–)-sparteine was reported by O'Brien *et al.*[65] in 2018 by combining an enzymatic resolution and their earlier synthetic approach to sparteine (**Scheme 1.30**).[66] The racemic ester **1.193** was prepared by hydrogenation and Boc protection of pyridine **1.192** on a 30 g scale. An enzymatic resolution of **1.193** with lipase from *B. Cepacia* provided enantiopure ester **1.194** and acid **1.195** after aqueous work-up without any chromatography. Acid **1.195** was re-esterified and then alkylated with Eschenmoser's salt to afford **1.196**. Methylation and elimination of **1.196** gave Michael accepter **1.198** in good yield with no racemisation. All attempts to add an enolate derived from Boc protected **1.194** to **1.198** resulted in complex mixture of products. Therefore, the protecting group was switched to a Bn group to give **1.199** and **1.200** from **1.198** and **1.194** respectively. Treatment of **1.200** with LDA at –78 °C before adding **1.199** led to bis-ester **1.201** with complete control over the newly formed stereocenters, which followed the same sense as their previously reported enolate alkylation. Hydrogenolysis of **1.201** followed by *in situ* bis-lactamization afforded (+)-10,17-dioxosparteine (**1.202**). The final amide reduction completed the diastereocontrolled synthesis of (–)-sparteine (isolated as bisulfate salt **1.203**) in 10 steps in 31% yield.



Scheme 1.30. *Reagents and conditions*: a) H_2, PtO_2, EtOH, HCl; b) Boc_2O, CH_2Cl_2; c) Lipase from *B.Cepacia*, pH 7, H_2O/THF, 35 °C; d) EtOH, DCC, DMAP, MeCN; e) i) LiHMDS, THF, –78 °C; ii) Eschenmoser's salt, –78 °C to rt; f) MeI, THF; ii) DBU, toluene, Δ; g) TFA, CH_2Cl_2; h) BnBr, Na_2CO_3, CH_2Cl_2/H_2O; i) i) LDA, –78 °C, THF; ii) **1.199**, –78 °C to rt; j) i) $Pd(OH)_2$/C, NH_4HCO_2, EtOH; then K_2CO_3; k) $LiAlH_4$, THF, Δ; then H_2SO_4.

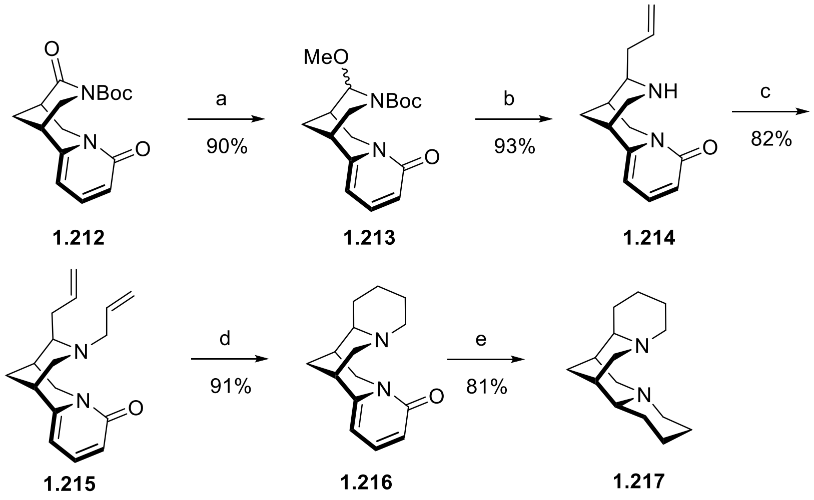
1.5.2 Breuning's synthesis of (+)-sparteine

Breuning *et al.* reported a synthesis of (+)-sparteine in 2018 by preparing the chiral bispidine core as the key step (**Scheme 1.31**).[67] The synthesis of the chiral 2,6-dioxobispidine **1.208** commenced with achiral 2,4,6,8-tetraoxobispidine **1.204**. Under Mitsunobu conditions, tetraoxobispidine **1.204** was coupled with 2 equivalents of (*S*)-phenylethanol **1.205** to give **1.206**. A two-step reduction afforded diamide **1.207** with complete regio- and stereocontrol (*dr* > 99:1), which was confirmed by X-ray crystallography. Subsequent Birch reduction to remove chiral auxiliary and *N*-Boc protection gave the chiral 2,6-dioxobispidine **1.208**. Selective opening one of the two imide groups was achieved by treatment of **1.208** with Weinreb salt/$AlMe_3$, after *N*-Boc cleavage from the imide group, to provide Weinreb amide **1.209** in 75% yield (*dr* 94:6) over two steps. A sequence of reactions with MeMgBr, *N*-Boc cleavage, imine formation and *N*-Boc re-protection furnished imine **1.210**, which was treated with α-bromoacrylic pivalic anhydride (**1.211**) and NEt_3 to afford pyridine fused bispidine **1.212**.



Scheme 1.31. *Reagents and conditions*: a) PBu_3, ADDP; b) i) $LiBHEt_3$; ii) Et_3SiH, TFA; c) i) Na, NH_3; ii) Boc_2O; d) i) HN(Me)OMe·HCl, $AlMe_3$; ii) TFA; e) i) MeMgBr; ii) $BF_3{\cdot}OEt_2$; iii)BoC_2O; f) **1.211**, NEt_3.

Their earlier investigation found that the nucleophilic attack on the bispidine imine or iminium salt would occur from the less sterically hindered *exo*-face with high selectivity.[68-69] A Sakurai allylation was introduced after reduction of **1.212** to the *N,O*-acetal to provide *exo*-substitution product **1.213** (**Scheme 1.32**). *N*-allylation of **1.214** followed by RCM and hydrogenation gave access to tetracyclic anagyrine **1.216** in good yield. Finally hydrogenation of the pyridone and reduction of amide group completed the synthesis (+)-sparteine. They also obtained (–)-sparteine following the same synthetic strategy using (*R*)-phenylethanol.



Scheme 1.32. *Reagents and conditions*: a) $NaBH_4$, HCl, MeOH; b) allyl$SiMe_3$, $BF_3{\cdot}OEt_2$; c) allyl bromide, NEt_3; d) i) Grubbs II; ii) H_2, Pd/C; e) H_2, PtO_2.

1.6 Brown group approach to lupin alkaloids

In recent years, Brown and co-workers have reported the asymmetric total synthesis of four natural products from the lupin family[70-72]: (–)-epilupinine, (+)-allomatrine, (–)-lamprolobine and (+)-β-isosparteine and one indolizidine alkaloid: (–)-tashiromine (**Figure 1.7**). The highly diastereoselective imino-aldol reaction is employed as the key step to assemble the two adjacent chiral centres at C-5 and C-6, and *N*-acyliminium chemistry to install the remaining two stereocenters in the tetracyclic alkaloids.

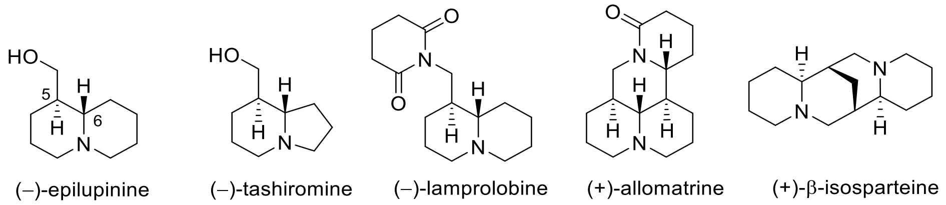
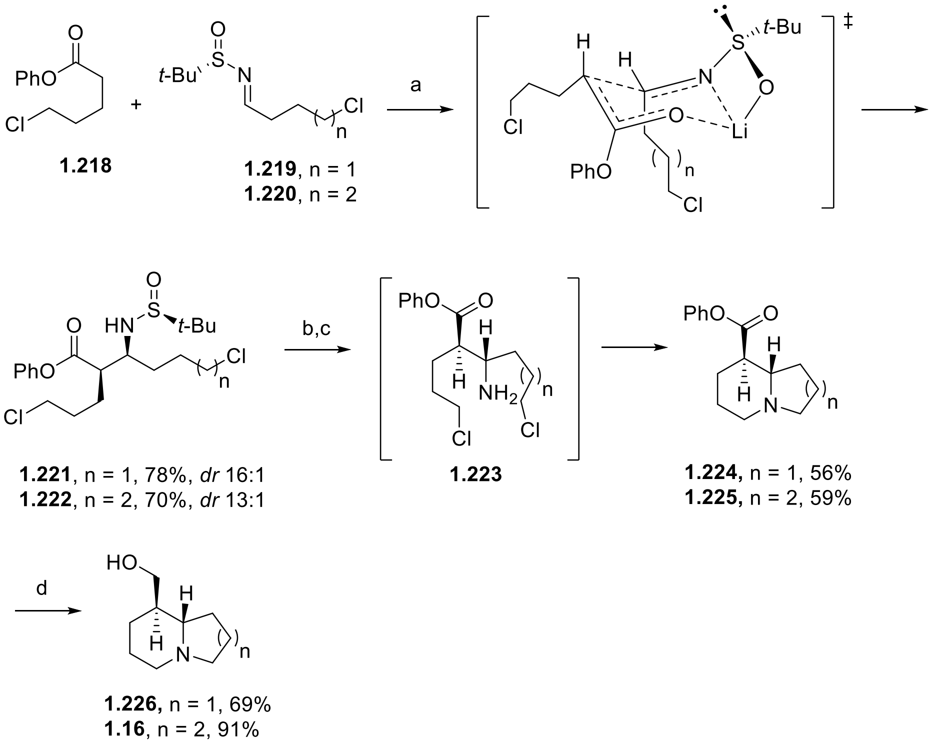


Figure 1.7. Alkaloids synthesised by Brown group.

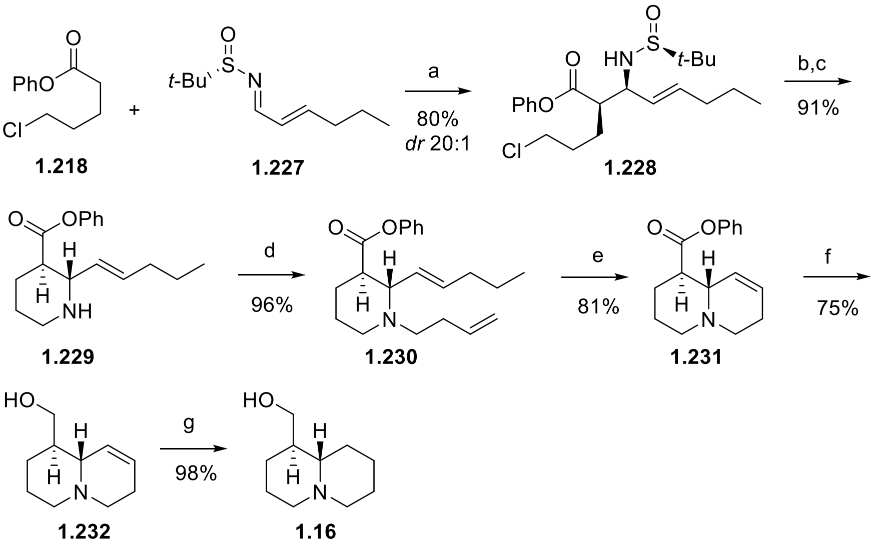
1.6.1 The total synthesis of (–)-tashiromine and (–)-epilupinine

The total synthesis of (–)-tashiromine and (–)-epilupinine was reported by the Brown group in 2011.[70] The lithium enolate derived from phenyl ester **1.218** added to chloroalkyl sulfinylimine **1.219** or **2.220** following a chair transition state to smoothly afford the β-amino ester **1.221** or **1.222**, respectively, with high diastereoselectivity, *dr* 16:1 for **1.221** and 13:1 for **1.222** in favour of *syn*-product (**Scheme 1.33**). After imino-aldol addition, **1.221** and **1.222** contained the whole frameworks of (–)-tashiromine and (–)-epilupinine. *N*-sulfinyl protecting group was removed using *conc*. HCl to furnish primary amines and the subsequent intramolecular double cyclisation under basic conditions delivered the indolizidine **1.224** and quinolizidine **1.225**. Finally, reduction by $LiAlH_4$ completed syntheses of (–)-tashiromine (**1.226**) and (–)-epilupinine (**1.16**) in 12% and 15% overall yields respectively within six-steps, or 4 steps from imine **1.219** and **1.220**.



Scheme 1.33. *Reagents and conditions*: a) LDA, THF, –78 °C; b) *conc*. HCl, dioxane; c) K_2CO_3, NaI, MeCN, rt; d) $LiAlH_4$, THF, rt.

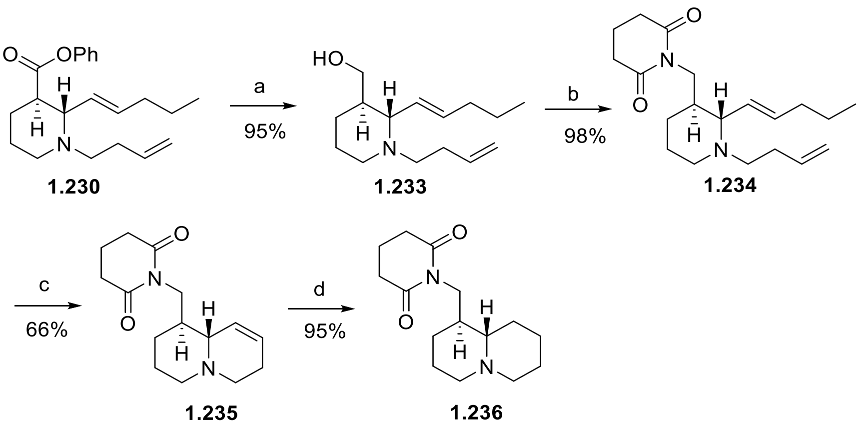
A second approach to (–)-epilupinine employed a ring closing metathesis (RCM) to form the quinolizidine core (**Scheme 1.34**).[73] The imino-aldol addition of the lithium enolate derived from phenyl ester **1.218** to *α,β*-unsaturated imine **1.227** gave the *syn*-selective *β*-amino ester **1.228** in 80% yield (*dr* 20:1). A sequence of deprotection of the *N*-sulfinyl group by *conc*. HCl and cyclisation in the presence of K_2CO_3 and NaI afforded piperidine **1.229** in 91% yield over two steps. *N*-alkylation of **1.229** with 4-bromo-but-1-ene and subsequent RCM of diene **1.230** using Grubbs 1st generation catalyst secured the bicyclic scaffold **1.231**. Reduction of ester **1.231** with $LiAlH_4$ followed by hydrogenation of unsaturated quinolizidine **1.232** over Pd/C completed the synthesis of (–)-epilupinine (**1.16**) in seven linear steps, but with an improved 39% overall yield. However, it should be noted that the yields reported in the original synthesis from 2011 were not optimised.



Scheme 1.34. *Reagents and conditions*: a) LDA, THF, –78 °C; b) *conc*. HCl, dioxane; c) K_2CO_3, NaI, MeCN, rt; d) 4-bromo-but-1-ene, K_2CO_3, MeCN, Δ; e) 10 mol% Grubbs I catalyst, CH_2Cl_2, Δ; f) $LiALH_4$, THF, 0 °C; g) H_2, Pd/C, EtOH.

1.6.2 Total synthesis of (–)-lamprolobine

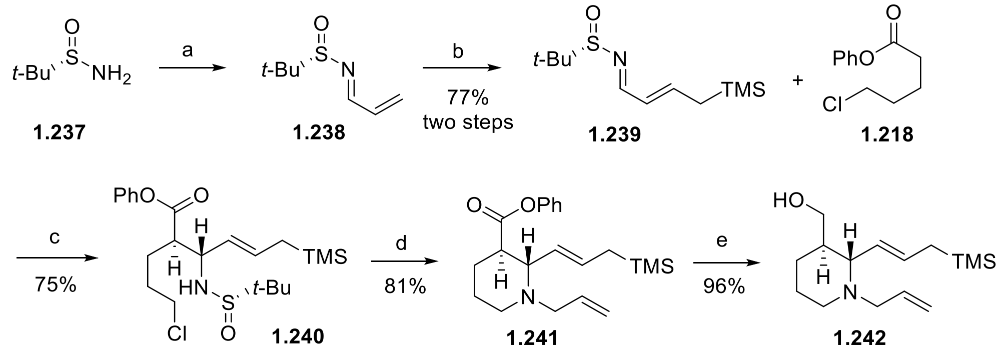
The synthesis of (–)-lamprolobine started with the piperidine **1.230** which was previously prepared as a RCM precursor in the synthesis of (–)-epilupinine.[73] Ester **1.230** was reduced to the corresponding alcohol **1.233** by $LiAlH_4$ and subsequent Mitsunobu coupling introduced glutarimide on the piperidine ring to give compound **1.234** in good yield (**Scheme 1.35**). RCM of diene **1.234** with Grubbs 1st catalyst accessed to the quinolizidine core **1.235** and final hydrogenation of **1.235** over Pd/C proceeded completed the synthesis of (–)-lamprolobine (**1.236**) in eight linear steps and 39% overall yield.



Scheme 1.35. *Reagents and conditions*: a) $LiALH_4$, THF, 0 °C; b) DIAD, PPh_3, glutarimide, THF/CH_2Cl_2; c) 10 mol% Grubbs I catalyst, CH_2Cl_2, Δ; d) H_2 , Pd/C, EtOH.

1.6.3 Total synthesis of (+)-allomatrine

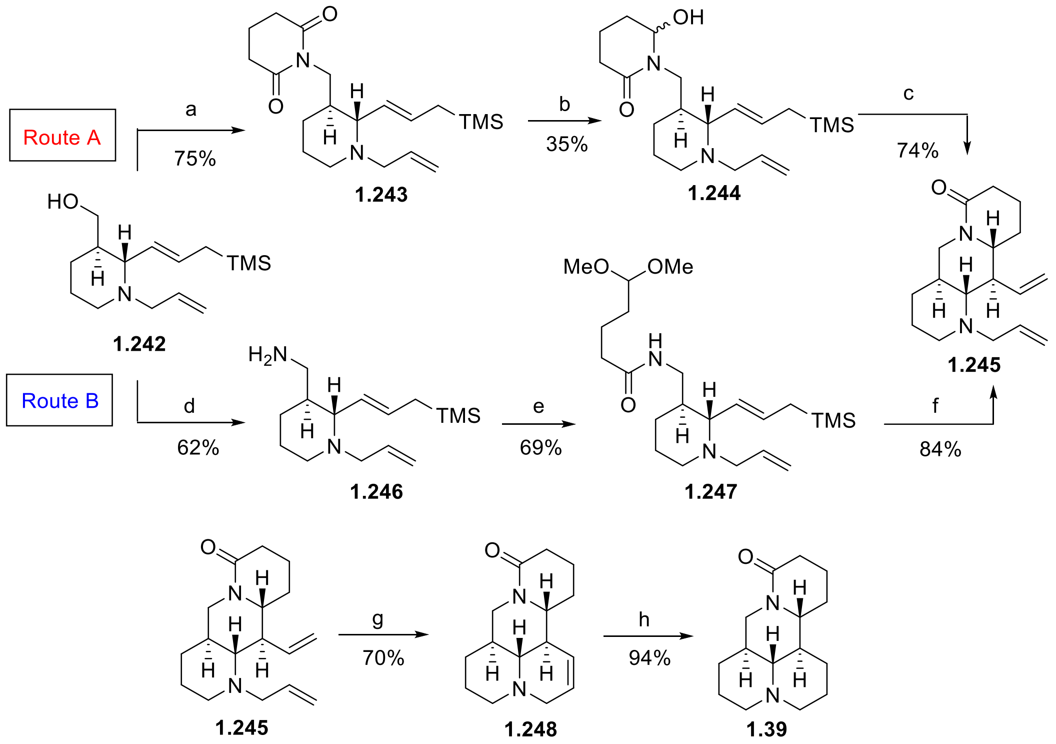
The first stereocontrolled synthesis of (+)-allomatrine was published by Brown *et al.* in 2013[71] using the well-developed imino-aldol reaction as described above and *N*-acyliminium ion cyclisation as key steps (**Scheme 1.36** and **Scheme 1.37**). Sulfinimine **1.239** was prepared in 77% yield *via* two steps through formation of sulfinimine **1.238** of acrolein followed by cross-metathesis (CM) with allyltrimethylsilane. The lithium enolate of **1.218** underwent addition to **1.239** yielding the *syn*-product **1.240** as a single diastereoisomer in 75% yield. *β*-Amino ester derivative **1.240** was subjected to sequential one-pot deprotection, cyclisation and *N*-allylation furnishing piperidine **1.241**. $LiAlH_4$ reduction of phenyl ester afforded the primary alcohol **1.242**.



Scheme 1.36. *Reagents and conditions*: a) acrolein, $Ti(OEt)_4$, THF; b) 2 mol% Hoveyda-Grubbs II catalyst, CH_2Cl_2; c) LDA, THF, –78 °C; d) i) *conc*. HCl, dioxane; ii) K_2CO_3, NaI, MeCN, rt; iii) allyl bromide, K_2CO_3, MeCN; e) $LiALH_4$, THF, 0 °C.

Two approaches were introduced to form the C-ring (**Scheme 1.37**). In route A, alcohol **1.242** was coupled with glutarimide under Mitsunobu conditions to give **1.243** in 75% yield. Reduction of **1.243** with $NaBH_4$ at –15 °C afforded the *N*-acyliminium precursor **1.244** and subsequent exposure of **1.244** with TfOH induced cyclisation to afford tricyclic diene **1.245** as the predominant diastereoisomer. The stereochemistry of **1.245** was assigned by NMR spectroscopy and latter corroborated with X-ray data for **1.248** formed by RCM. Due to reduction of **1.243** showing low efficiency, the second route B was used to access *N*-acyliminium precursor, a modified Mitsunobu coupling to introduce azide followed by reduction using $LiAlH_4$ generated amine **1.246** in 62% over two steps. 5,5-Dimethoxypentanoic acid was coupled with amine **1.246** in the presence of cyclic triphosphate coupling reagent T_3P (propylphosphonic anhydride) to form **1.247** in 69% yield. Tricyclic diene **1.245** was generated through a sequence of *N*-acyliminium ion formation and ring-closure which was initiated by treatment of acetal **1.247** with an excess of $BF_3{\cdot}OEt_2$ in 84% yield. RCM of diene **1.245** using Hoveyda-Grubbs 2nd catalyst followed by hydrogenation of 8,9-

dehydroallomatrine (**1.248**) over Pd/C completed the first total synthesis of (+)-allomatrine (**1.39**) in 13% overall yield.

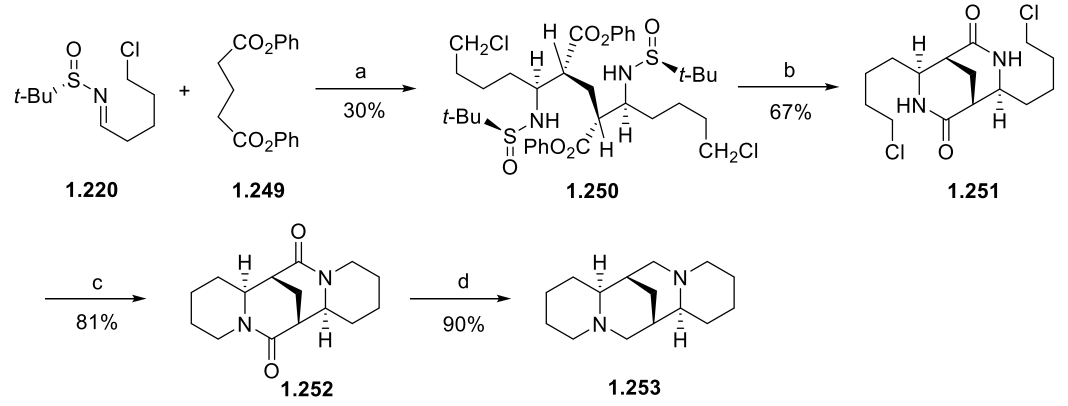


Scheme 1.37. *Reagents and conditions*: a) DIAD, PPh$_3$, glutarimide, THF/ CH$_2$Cl$_2$; b) NaBH$_4$, EtOH, HCl, –15 °C; c) TfOH, CH$_2$Cl$_2$; d) i) DIAD, PPh$_3$, (PhO)$_2$P(O)N$_3$, THF, –10 °C to rt; ii) LiAlH$_4$, Et$_2$O, 0 °C to rt; e) 5,5-dimethoxypentanoic acid, T$_3$P, NEt$_3$, EtOAc; f) BF$_3$·OEt$_2$, CH$_2$Cl$_2$; g) 5 mol% Hoveyda-Grubbs II catalyst, CH$_2$Cl$_2$, Δ; h) H$_2$, Pd/C, EtOH.

1.6.4 Total synthesis of (+)-*β*-isosparteine

In 2017, Brown *et al.*[72] published a two-directional approach to the C_2-symmetrical alkaloid (+)-*β*-isosparteine (**Scheme 1.38**). Based on previous study of imino-aldol reactions from our laboratory, the lithium enolates from phenyl esters underwent addition to alkyl- and alkenyl-substituted *tert*-butyl sulfinimines with good diastereoselectivity, tolerating a wide range of functional groups in both imine and ester substrates. A double imino-aldol addition was investigated. Deprotonation of diphenyl glutarate **1.249** with 2.2 equivalents of LDA in THF at –78 °C followed by treatment with 2 equivalents of sulfinimine **1.220** afforded double *syn* imino-adduct **1.250** in 30% yield along with a cyclised *syn* mono-imino aldol product and a mixture of cyclised and uncyclised minor double-imino aldol stereoisomers. Cleavage of the sulfinyl group from adduct **1.250** by the use of molecular iodine and subsequent neutralisation accessed the dioxobispidine **1.251.** Under basic conditions, the cyclisation took place assisted by tetrabutylammonium bromide to furnish (+)-10,17-dioxo-*β*-

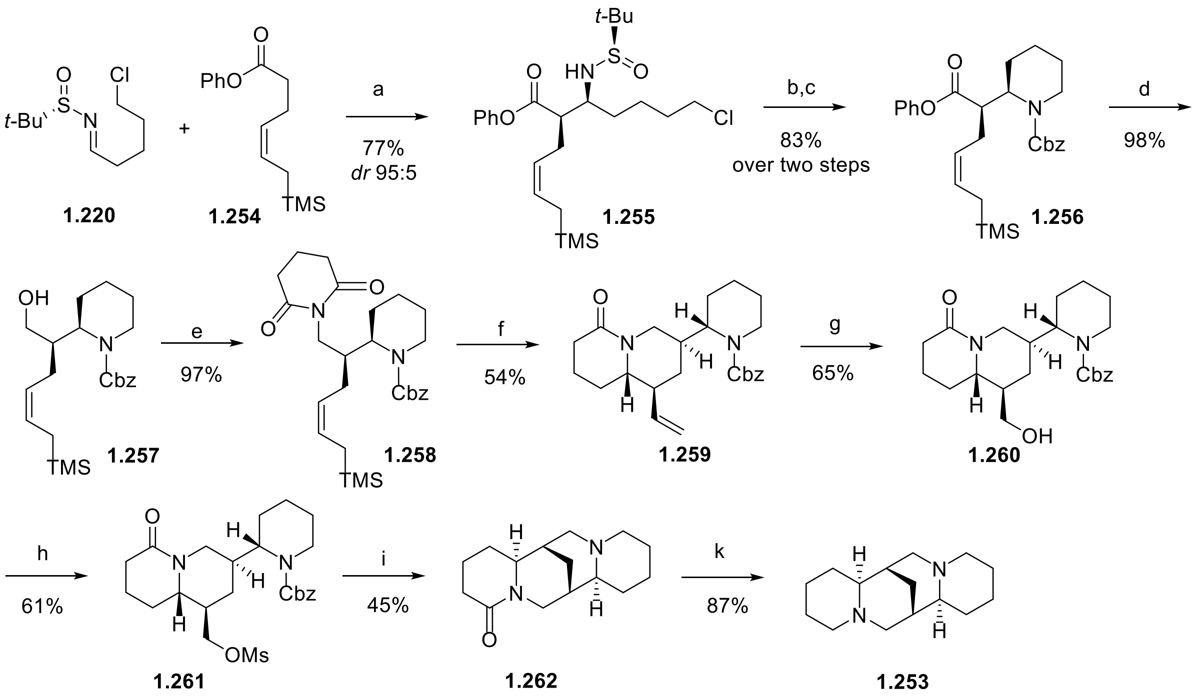
isosparteine (**1.252**). The structure was confirmed directly *via* X-ray crystallography. Following bis-lactam reduction using $LiAlH_4$ the synthesis of (+)-β-isosparteine (**1.253**) was completed in an overall 15% yield in 4 steps from imine **1.220**.



Scheme 1.38. *Reagents and conditions*: a) LDA, THF, –78 °C; b) I_2, THF/H_2O, 50 °C, then Na_2CO_3; c) K_2CO_3, KOH, TBAB, DMSO, 60 °C; d) $LiAlH_4$, THF, Δ.

1.6.5 A second total synthesis of (+)-β-isosparteine

A second total synthesis of (+)-β-isosparteine was completed by David Wheatley based on earlier advances towards this synthesis performed by Ionut-Alexandru Pop in our group (**Scheme 1.39**).[64] The allylsilane modified phenyl ester **1.254** coupled with sulfinimine **1.220** under the imino-aldol conditions to provide **1.255** in 77% yield (*dr* 95:5). A sequence of sulfinyl group removal, *N*-cyclisation and *N*-Cbz protection gave piperidine **1.256** in one pot with 83% overall yield. Reduction of **1.256** using $LiAlH_4$ followed by Mitsunobu reaction, furnished *N*-acyliminium precursor **1.258.** Treatment of **1.258** with $LiEt_3BH$ and subsequently with $BF_3{\cdot}OEt_2$ gave access to tricyclic **1.259** as a single diastereoisomer. Conversion of the terminal alkene to alcohol **1.260** was achieved by ozonolysis and reduction of **1.259** in 65% yield over two steps. The tetracycle **1.262** was formed by *N*-cyclisation, after mesylation of **1.260** and *N*-Cbz deprotection. The final reduction of the lactam group completed the total synthesis of (+)-β-isosparteine (**1.253**) in 9 steps from imine **1.220** in 5.1% overall yield.



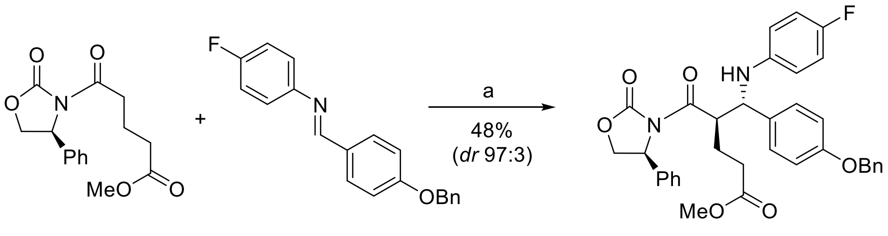
Scheme 1.39. *Reagents and conditions*: a) LDA, THF, –78 °C; b) i) *conc*. HCl, dioxane; ii) K_2CO_3, NaI, MeCN, rt; c) Cbz-Cl, K_2CO_3, THF; d) $LiALH_4$, THF; e) ADDP, PBu_3, glutarimide, THF/ CH_2Cl_2; f) i) $LiEt_3BH$, CH_2Cl_2, –78 °C; ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2; g) i) O_3, –78 °C, CH_2Cl_2; ii) $NaBH_4$, 0 °C; h) Ms-Cl, NEt_3; i) i) H_2, Pd/C, EtOH; ii) K_2CO_3, THF, Δ; k) $LiAlH_4$, THF, Δ.

1.7 Aims and Objectives

The preliminary aim of the total synthesis project is to develop a method based on imino-aldol reaction to achieve a highly *anti*-diastereoselectivity. Since access to *anti* β-amino acid derivatives is essential for the synthesis of the lupin alkaloids such as lupinine and matrine. Previous research in the Brown group has indicated that when a lithium enolate derived from phenyl ester and a chiral *t*-butyl sulfinimine are combined, the resulting imino-aldol reaction gave excellent *syn* selectivity (see before **Scheme 1.33**).[70-72] Effects to develop an *anti*-selective imino-aldol reaction of sulfinyl imines were explored, and although some modest increase in the ratio of the product was observed, no conditions offered a complete reversal in selectivity. Instead of using a chiral auxiliary located in the imine moiety, we focussed our attention on using of the Evans auxiliary to modify the nucleophilic reaction component.

1.7.1 Evans auxiliary used in *anti*-selective imino-aldol reaction

The first *anti*-selective imino-aldol reaction mediated by the Evans-type auxiliary was reported by Fuentes and co-workers, using boron enolate from chiral oxazolidinone to 4-acetoxyazetidinones.[74] Later Nagao *et al.*[75-76] observed *anti*-selectivity by using a tin enolate derived from chiral thiazolidinethione in the reaction with a cyclic iminium ion. Recently several papers have reported that titanium enolates derived from either chiral oxazolidinone or thiazolidinethione add to aromatic substituted imines with high *anti*-selectivity.[77-79] For example, a process for Ezetimibe synthesis reported by Sasikala *et al.*[79] (**Scheme 1.40**) using a titanium enolate formed by soft deprotonation of imide **1.263** and addition to the imine **1.264**, gave rise to a 97:3 *dr* in favour of *anti*-product. The proposed transition state for *anti*-selectivity was following a chelated six-membered ring (**Figure 1.8**).



Scheme 1.40. *anti*-Selective imino-aldol reaction using *N*-acyl oxazolidinone. *Reagents and conditions*: a) $TiCl_4$, $TiCl_3(O\textit{i}\text{-Pr})$, DIPEA, CH_2Cl_2, −78 °C.

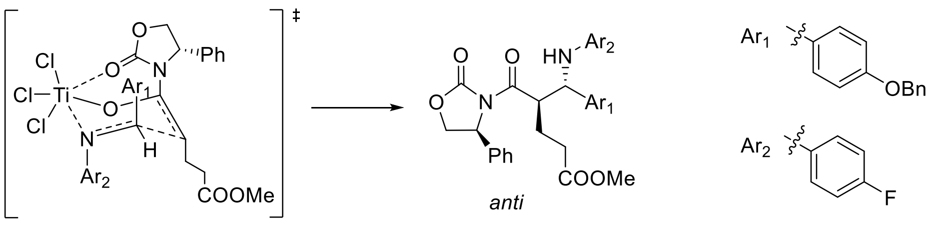


Figure 1.8. Proposed transition state for *anti*-selectivity

1.7.2 Retrosynthetic analysis of lupinine

To investigate the *anti*-selective imino-aldol methodology, we chose lupinine (**1.01**) as the target molecule due to its relatively simple structure. Based on the retrosynthetic analysis of lupinine (**Figure 1.9**), the functionalised *β*-amino acid derivative **1.267** is identified as the key intermediate for the total synthesis. The imino-aldol reaction mediated by a chiral oxazolidinone, which is expected to couple the chosen imine **1.270** and imide **1.269** to give the required stereochemistry at C-5 and C-6 on **1.01**, is the most straightforward approach to this key intermediate. Both fragments (**1.270** and imide **1.269**) contain a chloride leaving group to enable future ring closure and to avoid further functional group interconversion, as demonstrated in our epilupinine total synthesis.[70] If the *anti β*-amino acid derivative could be accessed, it would be expected that, following deprotection and cyclisation, the quinolizidine **1.266** would be obtained. A final reduction would complete the total synthesis of lupinine (**1.01**).

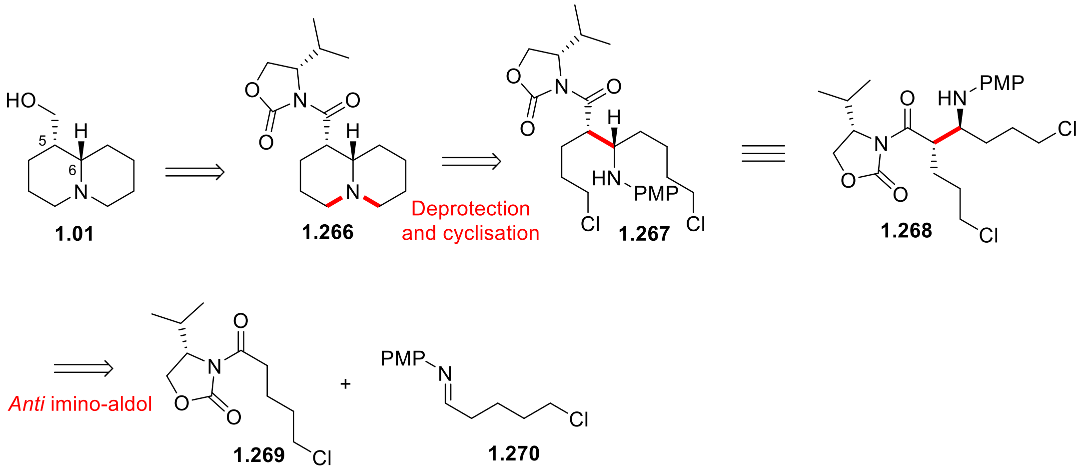


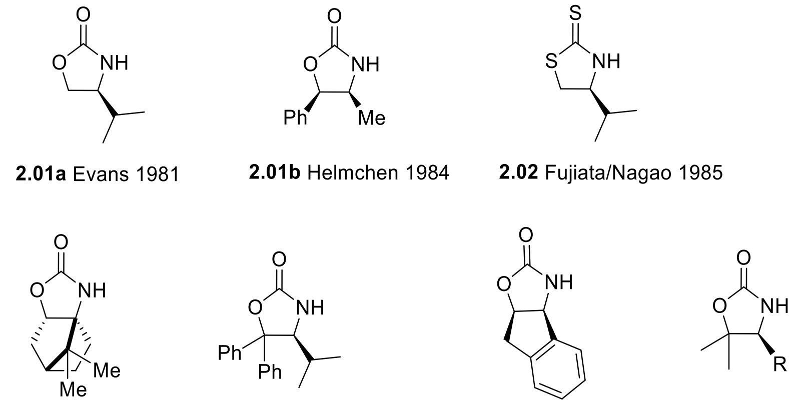
Figure 1.9. Retrosynthetic analysis of (+)-lupinine using *anti*-selective imino-aldol.

Chapter 2: Total syntheses of lupin alkaloids

The following section will discuss two investigations of *anti*-selective method for β-amino acid derivatives preparation, and applications of the excellent selectivity method to five lupin alkaloids total syntheses.

2.1. Preparation of *anti* β-amino acid derivatives using oxazolidinone chiral auxiliaries

The chiral oxazolidinone, is one of the most utilized type of auxiliaries, and was initially developed by the Evans group and applied to asymmetric aldol condensations in 1981.[80-81] Subsequently, many structural variants have been developed which show different diastereoselectivity, cleavage reactivity or complementary diastereoselectivity (**Figure 2.1**). While numerous methods exist to access oxazolidinones, the most commonly employed procedures involve α-amino acid reduction to the corresponding β-amino alcohol followed by oxazolidinone formation using phosgene or diethyl carbonate.[82] The cleavage of this type auxiliary can usually be achieved under relatively mild conditions by hydrolysis using lithium hydroperoxide (LiOOH),[83] or other methods including transesterification,[84] transamination,[85] and reduction.[86]



2.01a Evans 1981 **2.01b** Helmchen 1984 **2.02** Fujiata/Nagao 1985

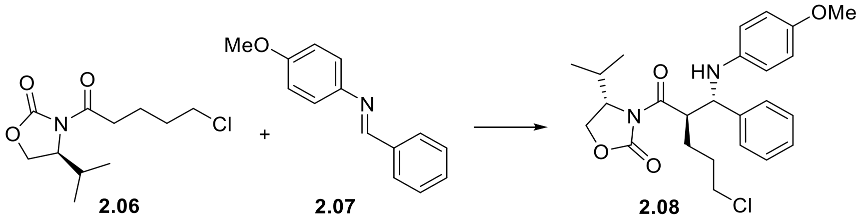
2.03 Yan 1991 **2.04a** Seebach 1998 **2.04b** Ghosh 1998 **2.05** Davies 1999

Figure 2.1. Variants developed on Evans type auxiliary.

Our early studies investigated using Evans auxiliary to develop *anti*-selective imino-aldol methodology.

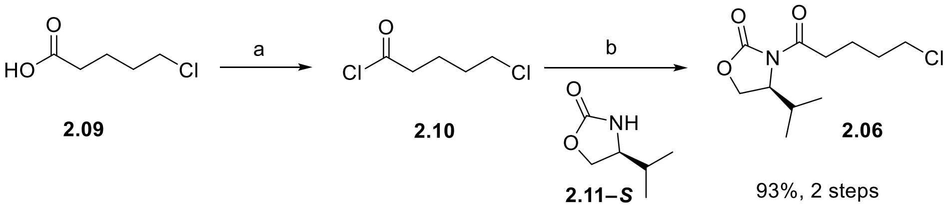
2.1.1 Model imino-aldol reaction

Initially inspired by Sasikala's work,[79] the Evans type oxazolidinone was employed in a model imino-aldol reaction to control the diastereoselectivity and afford the desired *anti* product (see before **Scheme 1.40**). We planned to use the reaction in **Scheme 2.01** as a model reaction employing *N*-acyl isopropyloxazolidinone **2.06** and a *para*-methoxy phenyl (PMP) protected imine **2.07** to investigate the diastereoselectivity, which was expected to favour the *anti*-product.



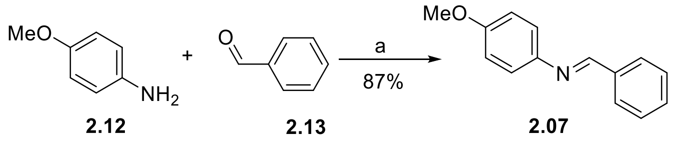
Scheme 2.01. Model imino-aldol reaction.

Following the procedures described by Hettche *et al.*,[87] commercially available 5-chloropentanoic acid (**2.09**) was treated with oxalyl chloride to afford the corresponding acid chloride **2.10** (**Scheme 2.02**). (*S*)-4-Isopropyloxazolidin-2-one (**2.11-*S***) was deprotonated using *n*-BuLi at –78 °C and freshly prepared acid chloride **2.10** was added to afford imide **2.06** with excellent yield over two steps.



Scheme 2.02 *Reagents and conditions*: a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt. b) i) **2.11-*S***, *n*-BuLi, THF, –78 °C. ii) acid chloride **2.10**.

The condensation of 4-methoxyaniline (**2.12**) and benzaldehyde (**2.13**) in the presence of anhydrous $MgSO_4$ afforded imine **2.07** (**Scheme 2.03**). It was found that purification of imine **2.07** by silica column chromatography caused a small amount of decomposition, returning some aniline and aldehyde (**Scheme 2.03**).[88] Therefore, purification was undertaken by recrystallization from hot hexane to afford **2.07** as grey crystals.



Scheme 2.03. *Reagents and conditions*: a) anhydrous $MgSO_4$, CH_2Cl_2, rt, 16 h.

With oxazolidinone **2.06** and imine **2.07** in hand, the diastereoselectivity of the imino-aldol reaction was investigated. According to the literature,[78-79] titanium enolates exhibit good *anti*-selectivity upon addition to aromatic imines. Therefore, the model reaction was performed using a titanium enolate, which was derived from of **2.06** by hard or soft enolisation methods as shown in **Table 2.01**. All the reaction results showed good selectivity obtaining one major diastereoisomer. Low yields were obtained when kinetic deprotonation of imide **2.06** by LDA, was followed by transmetalation to titanium enolate prior to the addition of imine **2.07** (Entries 1 and 2, **Table 2.01**). A significant improvement in yield was obtained when the titanium enolate was formed under soft enolisation conditions with DIPEA and $TiCl_4$ (entry 3, **Table 2.01**).

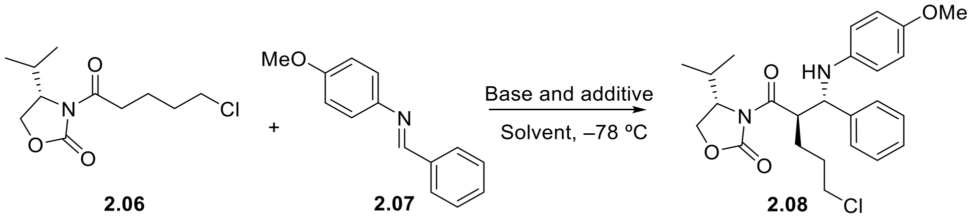
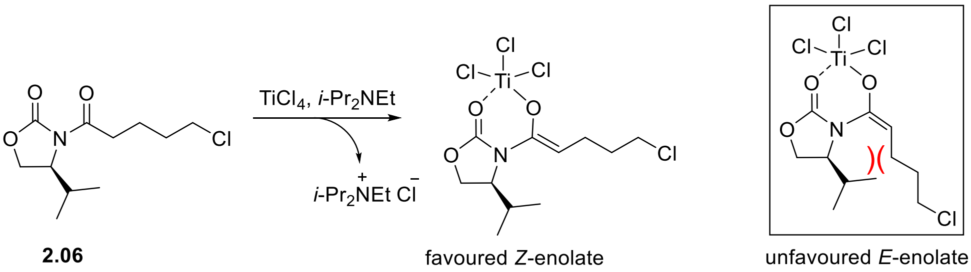


Table 2.01. Diastereomeric outcome of the model imino-aldol reactions.

Entry	Solvent	LDA	DIPEA	$TiCl_4$	Yield	*dr*[a] *anti:syn*
1	CH_2Cl_2	1.0 equiv.	—	2.0 equiv.	37%	10 : 1
2	THF	1.0 equiv.	—	2.0 equiv.	13%	13 : 1
3	CH_2Cl_2	—	1.0 equiv.	2.0 equiv.	99%	> 20:1

[a] Estimated by integration of N<u>H</u> peaks in crude ^1H NMR spectra.

Based on the extensive literature precedent associated with enolates that utilized Evans-type chiral auxiliaries,[89-90] we believed that only *Z*-enolates were operative here to avoid the steric hindrance from the *i*-Pr group (**Scheme 2.04**). With respect to the high diastereoselectivity, the dominance of the *anti*-product can be understood by a chelated chair-like transition state (**Figure 2.2**). The imine **2.07** approaches the enolate on the less hindered *Re* face and the PMP substituent on the imine would adopt an axial position in order to allow the lone pair at the imine nitrogen to coordinate with the titanium Lewis-acid. As the configuration of the C=N double bond is *E*, this would place the imine substituent in an axial position in the cyclic transition state and therefore afford the diastereoisomer possessing an *anti* configuration.



Scheme 2.04. Chelation facilitates soft enolisation to form *Z*-enolate.

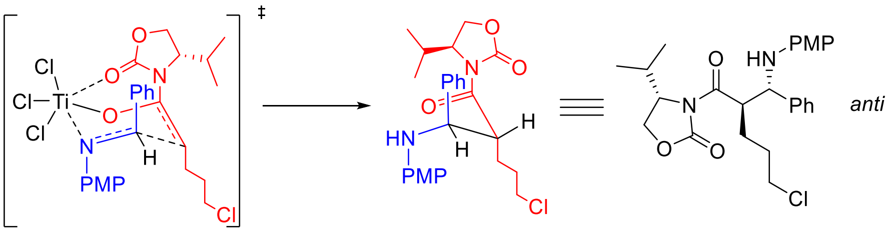
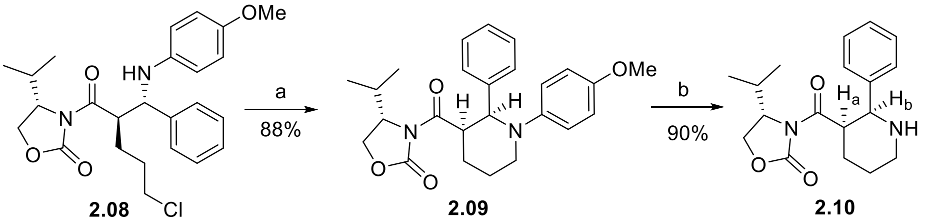


Figure 2.2. Proposed transition state for *anti*-selectivity.

Next, a cyclisation reaction on **2.08** was performed in order to confirm the relative *anti*-stereochemistry (**Scheme 2.05**). Due to the steric repulsion caused by the two aromatic rings, the cyclisation was completed only after 48 hours at room temperature with sodium iodide as catalyst to access piperidine **2.09** in 88% yield. Using a procedure described by Hughes *et al.*,[91] the oxidative cleavage of the PMP group by ceric ammonium nitrate (CAN) was undertaken to afford piperidine **2.10** in good yield.



Scheme 2.05. *Reagents and conditions*: a) K_2CO_3, NaI, MeCN, rt, 48 h. b) CAN, MeCN:H_2O (3:1), rt, 1.5 h.

Assignment of the relative stereochemistry of piperidine **2.10** was confirmed by comparison of coupling constant data in the ^{1}H NMR spectrum, which showed a vicinal coupling of 5.2 Hz between the two methine protons (H_a and H_b) in the ring. Previous work in the Brown group showed that the piperidine ring obtained from the *syn* imino-aldol adduct, which has been fully characterised, exhibited the *J* values for these two protons between 9.0 Hz to 11.0 Hz.[92] In a six-membered heterocyclic ring, the two methine protons for *syn*-product **2.13** occupy corresponding axial positions with a *trans* relationship in the chair conformation, which results in a large *J* value. For the *anti*-product (**2.14a** or **2.14b**), one of the two protons occupies an axial position and the other in the equatorial position, which leads to a smaller *J* value (**Figure 2.3**). Therefore, it is reasonable that a smaller coupling constant between H_a and H_b supports formation of the *anti*-product **2.10**.

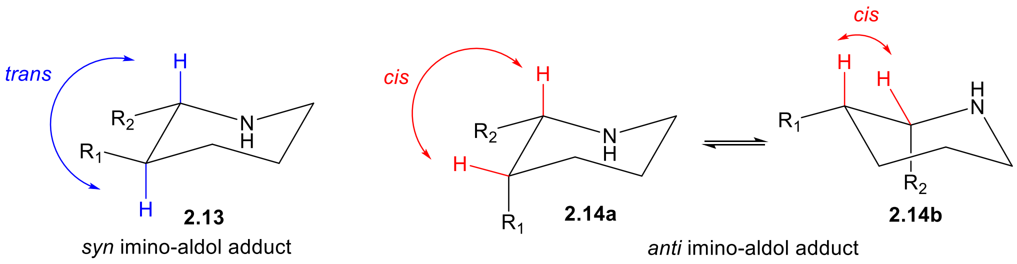
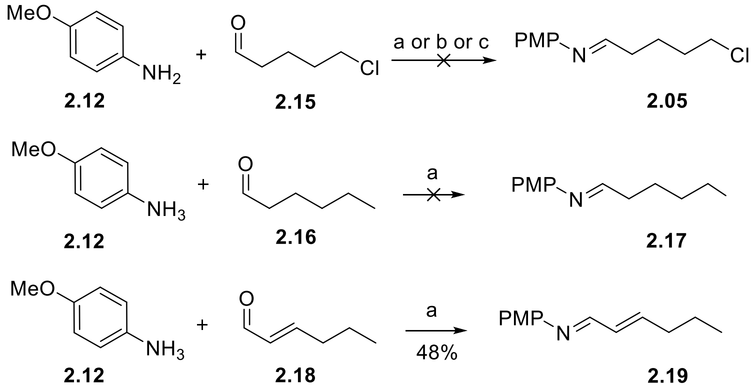


Figure 2.3. Piperidine chair structures for *syn* and *anti* imino-aldol adducts.

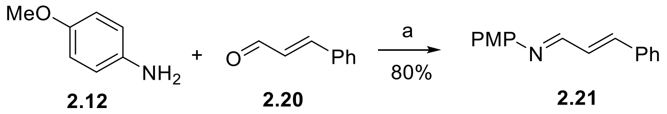
2.1.2 Attempt to extend the *anti*-selective imino-aldol to aliphatic imines

After analysing the NMR data, the relative *anti*-configuration has been confirmed. We then attempted to examine the diastereoselectivity of the reaction with aliphatic imine **2.05**. Unfortunately, imine **2.05** (**Scheme 2.06**) failed to form by condensation with methoxyaniline (**2.12**) and 5-chloropentanaldehyde (**2.15**). No clean product was isolated from the mixture. Aliphatic imine **2.05** seemed to be unstable. Then both saturated aldehyde **2.16** and α,β-unsaturated aldehyde **2.18** were used to form the corresponding imines (**Scheme 2.06**). Hexanal (**2.16**) reacted with *p*-aniline giving a complex mixture and no imine or other products could be isolated. However the (*E*)-hex-2-enal (**2.18**) afforded the desired α,β-unsaturated imine **2.19** in 48% yield. It was found that imine **2.19** was still unstable and decomposed on storage in a fridge overnight. Alternative methods were also investigated to prepare imine **2.05**, but unfortunately there were still no desired product formation, even when the reaction was undertaken at 0 °C and –10 °C.



Scheme 2.06. *Reagents and conditions*: a) anhydrous $MgSO_4$, CH_2Cl_2, rt. b) anhydrous $CuSO_4$, CH_2Cl_2, 0 °C. c) anhydrous $MgSO_4$, CH_2Cl_2, −10 °C.

Due to the poor stability of aliphatic imines, imine **2.21** was used to investigate the stereo-outcome of the imino-aldol reaction under the same conditions as the model reaction. The alkene could later serve as a functional group to form a ring by ring-closing metathesis to access the quinolizidine system. The desired imine **2.21** was synthesised in excellent yield under previously employed conditions (**Scheme 2.07**).



Scheme 2.07. *Reagents and conditions*: a) anhydrous $MgSO_4$, CH_2Cl_2, rt, 12 h.

Surprisingly none of the desired imino-aldol product was obtained and almost solely starting materials were recovered when the optimised imino-aldol conditions were employed for the reaction of imine **2.21** (**Table 2.02**, entry 1). Increasing the stoichiometry of DIPEA to 2.0 equivalents improved the reaction and after work up, the cyclised products were obtained directly. However, the diastereoselectivity of the major product was reversed and an inseparable mixture of *syn* adducts **2.23** and **2.24** was obtained. After cyclisation, the *anti*-imino aldol adduct would give the *cis* protons configuration in the piperidine ring, while the *syn*-adduct would give the *trans* protons in the piperidine ring. The relative stereochemistry was determined by coupling constant (8.6 Hz) from the two methine protons in the piperidine ring. It was found that DIPEA stoichiometry should be in excess relative to $TiCl_4$ to ensure that the reaction proceeds. It is possible that excess $TiCl_4$ could deactivate the formed enolate or amine base, although this is not clear. Unfortunately, using excess base (**Table 2.02**, entries 2 and 3), the *syn* adducts were always obtained as the major product (*anti*:*syn*, *dr* = 1:5). It may be explained by an open transition state (**Figure 2.4**). The imine approaches the less hindered face leading to *syn* adducts, which is similar to that proposed by Heathcock and co-workers in the aldol reaction.[93]

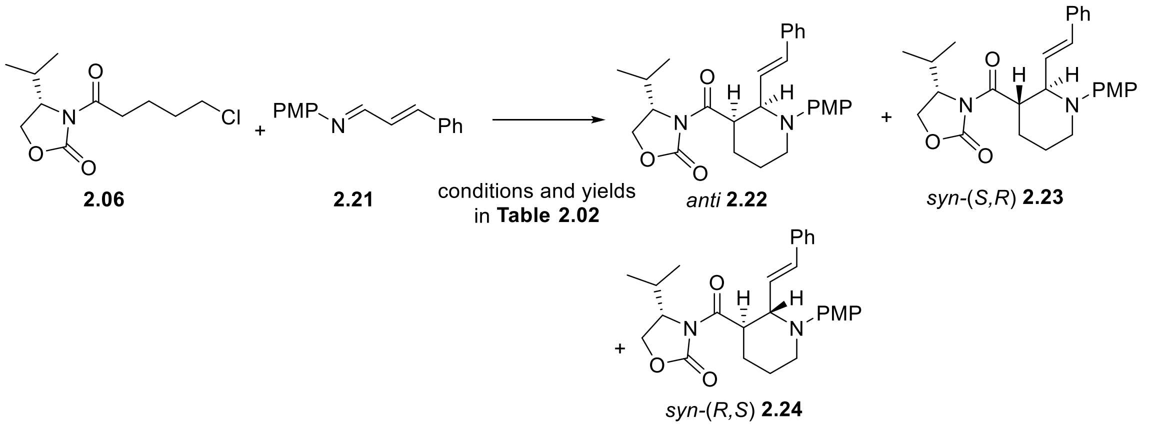
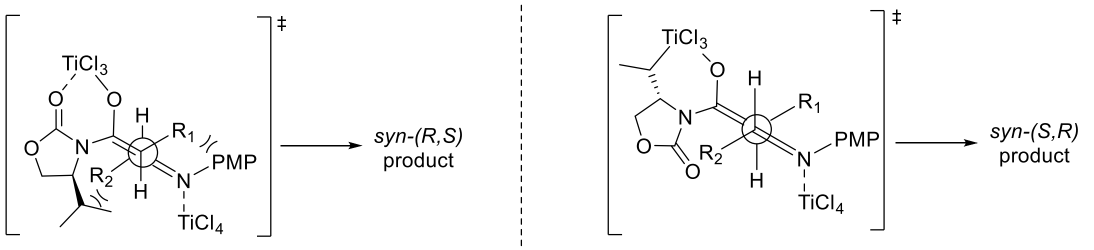


Table 2.02. Outcomes of the imino-aldol reaction between **2.06** and **2.21**.

Entry	$TiCl_4$	DIPEA	Yield[a]	*dr anti*: *syn*[b]
1	2.0 equiv.	1.0 equiv.	—	—
2	2.0 equiv.	2.0 equiv.	10%	1:5[b]
3	2.0 equiv.	3.0 equiv.	70%	1:8[b]

[a]Yield for mixture of *syn* and *anti* products
[b]Estimated by integration of H peaks on alkene in crude ^{1}H NMR.
[b]Mixture of two *syn* products.



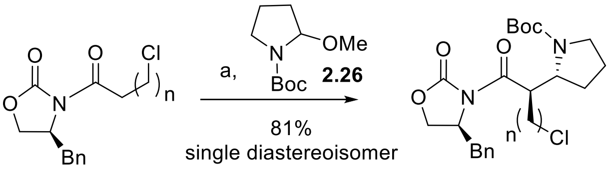
R_1: $-C_3H_6Cl$
R_2: -CH=CH-Ph

Figure 2.4. Possible open transition state leading to *syn* products.

2.1.3 Preparation of piperidine derivatives

As the imino-aldol reaction only showed good *anti* selectivity for aromatic imines, we attempted to employ cyclic *N*-acyliminium ions and the Evans imide to achieve the desired *anti* *β*-amino acid derivatives. A highly *anti*-selective imino-aldol addition was reported by Pilli *et al.*[94-95] (**Scheme**

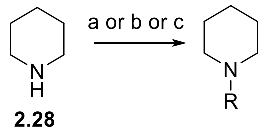
2.08), and applied in the total synthesis of (+)-isoretronecanol and (+)-epitashiromine. The *anti*-adduct **2.27** was formed as a single diastereoisomer using a titanium enolate and *N*-acyliminium ion derived from 2-methoxypyrrolidine **2.26**. Similar results were also observed by Matsumura *et al.* using the *N*-acyliminium ion derived from 2-methoxypiperidine.[96]



2.25 **2.27**

Scheme 2.08. *Reagents and conditions*: a) i) $TiCl_4$, DIPEA, –10 °C, CH_2Cl_2; ii) then **2.26**.

Therefore, we attempted to prepare 2-methoxypiperidine as the *N*-acyliminium ion precursor. A flow electrochemistry adaptation of the Shono-oxidation was used. Previous research into this method has been well developed in our group and applied in *N*-formylpyrrolidine methoxylation.[97] Piperidine (**2.28**) was protected with –Boc, –Cbz and –COOMe protecting groups and all three reactions progressed smoothly to furnish the corresponding piperidine derivatives in yields >90% (**Scheme 2.09**).

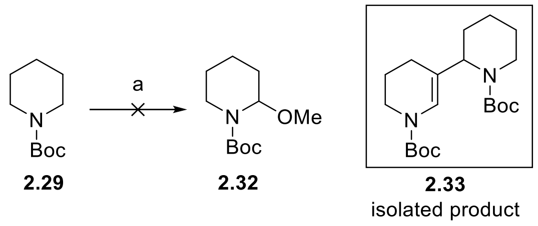


2.28

2.29, R= Boc, 95%,
2.30, R= Cbz, 90%,
2.31, R= COOMe, 90%.

Scheme 2.09. *Reagents and conditions*: a) $(Boc)_2O$, DMAP, Et_3N, rt, THF; b) Cbz-Cl, Et_3N, rt, THF c) MeOCOCl, K_2CO_3, rt, H_2O.

To access the required *N*-acyliminium ions, *N*-Boc piperidine **2.29** was first used to examine the Shono-oxidation (**Scheme 2.10**). Following the procedure reported by Mikhail *et al.*,[98] none of the desired product was observed and the NMR and MS for the isolated product indicated formation of a dimer **2.33.** The pH value of the reaction solution was checked and found to be around pH 1 after electro-oxidation. In an acidic solution the methoxylated product **2.32** would rapidly convert to enamine **2.35** *via* the *N*-acyliminium ion **2.34** (**Figure 2.5**), and then the formed enamine could add to another *N*-acyliminium ion to afford dimer **2.33**. The same problem was also observed with –Cbz and –COOMe protected piperidines.



Scheme 2.10. *Reagents and conditions*: a) -e$^-$, MeOH, Et_4NBF_4, 80 mA, 0.1 mL/min.

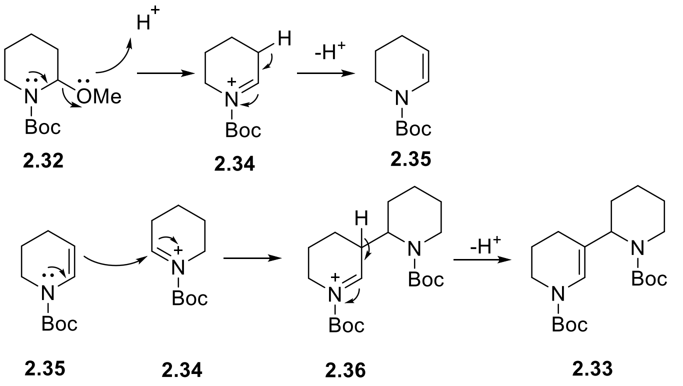
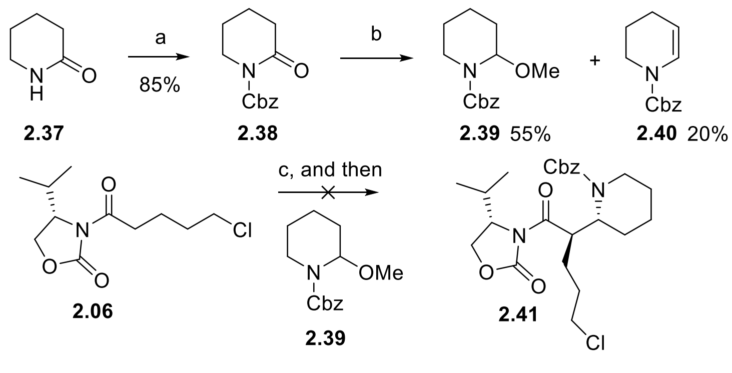


Figure 2.5. Proposed 2-methoxypiperidine **2.32** dimer formation pathway in acidic conditions.

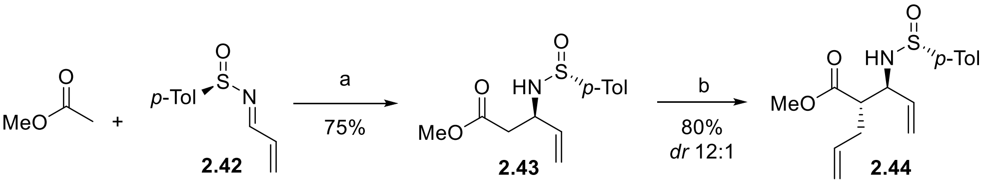
Due to this, the methoxylation of the protected piperdines using flow electrochemistry was not explored further. An alternative method was used to prepare the α-methoxypiperidine by reducing the corresponding piperidinone (**Scheme 2.11**). Piperidin-2-one (**2.37**) was deprotonated by *n*-BuLi and reacted with Cbz-Cl to afford the corresponding –Cbz protected piperidin-2-one (**2.38**) in 85% yield. Following procedures reported by Okitsu *et al.*,[99] piperidine **2.38** was reduced by $LiEt_3BH$ and quenched by acidic MeOH solution to form the α-methoxypiperidine **2.39** in 55% yield. However piperidine **2.39** was found to be unstable and easily converted to the corresponding enamine **2.40**, therefore, freshly made *N*-Cbz methoxypiperidine **2.39** was used without further purification and added to titanium enolate derived from **2.06**. Unfortunately, the imino-aldol reaction did not work under the previous optimised conditions and the starting material **2.06** was recovered together with enamine **2.40** (**Scheme 2.11**).



Scheme 2.11. *Reagents and conditions*: a) *n*-BuLi, Cbz-Cl, –78 °C, THF; b) i) $LiEt_3BH$, THF, –78 °C; ii) *p*-TsOH (10 mol%), MeOH; c) $TiCl_4$ (2 equiv), DIPEA (1 equiv), CH_2Cl_2, –78 °C.

2.2 *Anti*-alkylation of *β*-amino ester

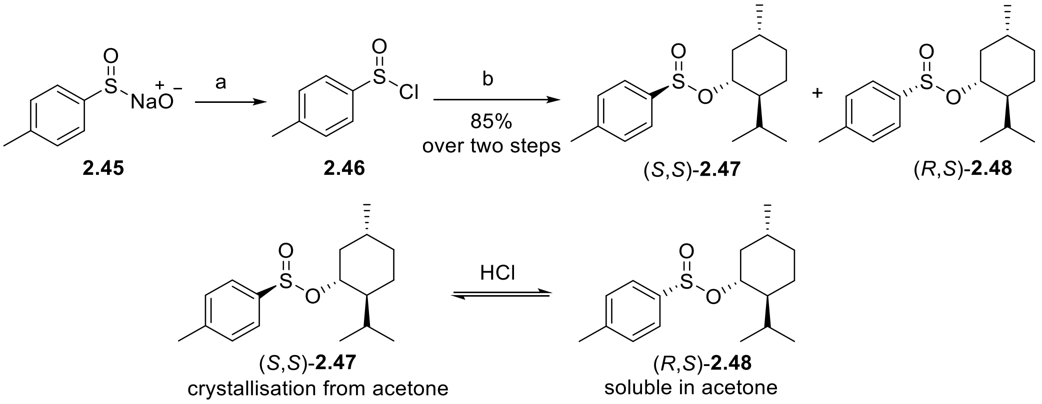
Due to the unsuccessful formation of *anti β*-amino acid derivatives using Evans imides, we switched our focus to the *anti*-alkylation of *β*-amino esters. Davis *et al.*[100] described an *anti*-alkylation method from sulfinimines **2.43** (**Scheme 2.12**). Enantiomerically pure *β*-amino ester **2.43** prepared from methyl acetate and *N*-sulfinyl imine **2.42** was deprotonated by 2 equivalents LDA and reacted with allyl iodide to afford *anti*-product **2.44** with good selectivity. It was found that the *anti*:*syn* selectivity was enhanced from 2:1 to 12:1, when 10 equivalents LiCl was added compared with no LiCl addition.



Scheme 2.12. *Reagents and conditions*: a) NaHMDS, THF, –78 °C, 2 h; b) i) LDA (2 equiv), LiCl (10 equiv), –78 °C, THF, 1 h; ii) allyl iodide, –78 °C, THF, 1 h.

2.2.1 Preparation of *p*-toluenesufinamide chiral auxiliary

In order to apply the *anti*-alkylation method as Davis described (**Scheme 2.12**), we started by preparing the *p*-toluenesufinamide chiral auxiliary. According to the procedures described by Blakemore *et al.*,[101-102] a slight modification of the Andersen method was performed on multi-gram scale for preparation of the *p*-toluenesufinamide chiral auxiliary (**Scheme 2.13**). Racemic sodium *p*-toluenesulfinate (**2.45**) was chlorinated using thionyl chloride and the resulting sulfinyl chloride (**2.46**) was coupled with (–)-menthol to afford the mixture of two diastereoisomers in 85% overall yield. The separation of the two isomers could be achieved by recrystallisation, as the (*S,S*)-isomer **2.47** is crystalline and (*R,S*)-isomer **2.48** is an oil in acetone. In the presence of catalytic amounts of hydrochloride acid, an *in-situ* epimerisation occurred. Since the (*S,S*)-isomer **2.47** selectively precipitated from acetone, the equilibration shifted towards to the formation of (*S,S*)-menthyl sulfinate **2.47** (**Figure 2.6**). A 150 g scale reaction was performed resulting in an 85% overall yield of **2.47** after dynamic kinetic resolution.



Scheme 2.13. *Reagents and conditions*: a) $SOCl_2$, CH_2Cl_2, 0 °C to rt, 4 h; b) (–)-menthol, pyridine, CH_2Cl_2, 0 °C to rt, 16 h.

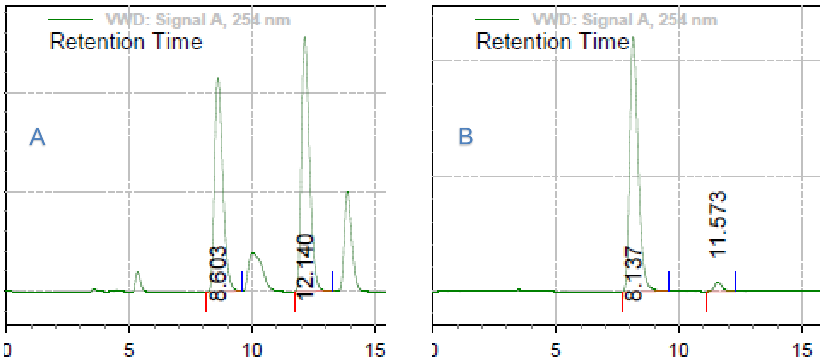
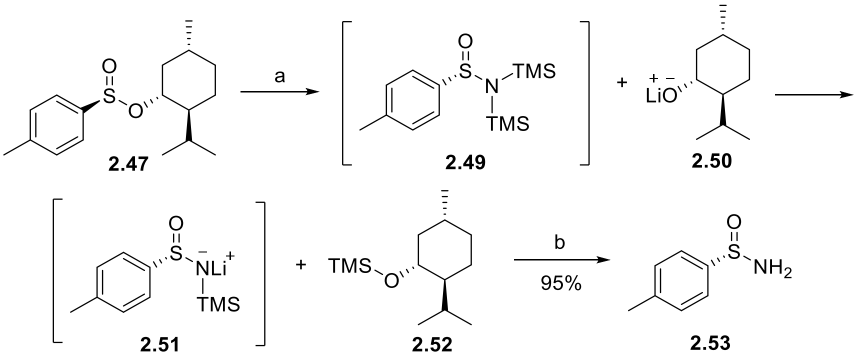


Figure 2.6. Chiral HPLC for (**A**) mixture of diastereoisomer **2.47** and **2.48**; (**B**) after dynamic resolution of **2.47**.

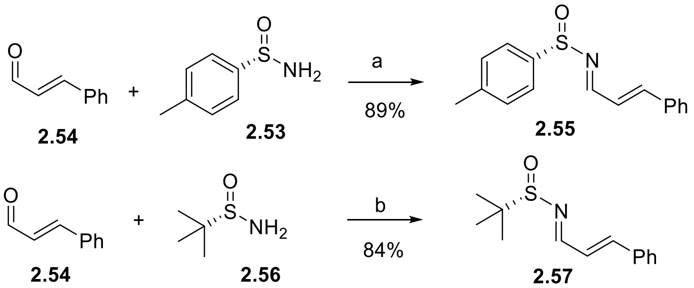
Treatment of **2.47** with LiHMDS at –78 °C and gradual warming to room temperature gave the intermediate **2.49**, in which the HMDS group replaced (–)-menthol with inversion of chirality at sulphur (**Scheme 2.14**). A silyl transfer led to the intermediate **2.51** and TMS (–)-menthol **2.52.** After work up in aqueous NH_4Cl solution, the *p*-toluenesulfinamide (**2.53**) was obtained in 95% yield by recrystallisation from hexane.



Scheme 2.14. *Reagents and conditions*: a) LiHMDS, THF, –78 °C to rt, 2 h; b) sat. NH_4Cl, 0 °C to rt, 30 min.

2.2.2 Synthesis of sulfinyl imines

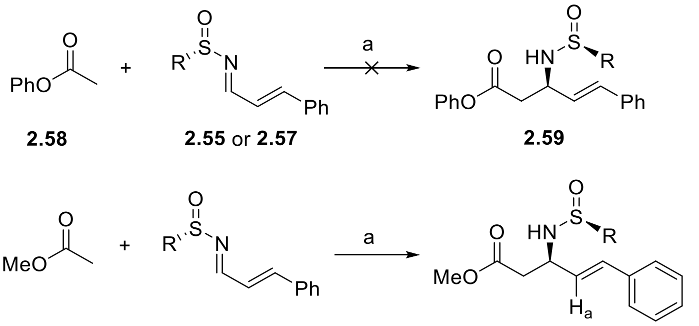
Both the *p*-toluenesulfinamide and *tert*-butylsulfinamide chiral auxiliaries were employed for the imine formation (**Scheme 2.15**). Following the procedure detailed by Davis *et al.*,[100] cinnamaldehyde (**2.54**) underwent condensation with tolyl auxiliary **2.53** affording the corresponding imine **2.55** in 89% yield. The similar condensation with commercially available *t*-butyl sulfinamide **2.56** in the presence of anhydrous $CuSO_4$ yielded sulfinyl imine **2.57** in 84%.



Scheme 2.15. *Reagents and conditions*: a) $Ti(OEt)_4$, CH_2Cl_2, rt, 12 h; b) anhydrous $CuSO_4$, CH_2Cl_2, rt, 12 h.

2.2.3 Imino-aldol reactions

Previous research in the Brown group found that phenyl esters exhibited higher diastereoselectivity in the imino-aldol reaction, in comparison to other esters such as methyl esters.[92] Therefore, the initial investigation employed phenyl acetate (**2.58**) to couple with imines (**Scheme 2.16**). No coupling reaction occurred and starting sulfinyl imine and phenol were isolated after work up. It seemed that the enolate of phenyl acetate decomposed, presumably by the ketene pathway under the reaction conditions. Treatment of methyl acetate with NaHMDS to form the corresponding enolate and then coupling with sulfinimine **2.55** or **2.57** gave good yields and excellent diastereoselectivities for the imino-aldols **2.60** and **2.61**. The *dr* of the imino-aldol products were determined by comparison of the H_a proton signals (on **2.60** or **2.61**, dd at 6.2 or 6.1 ppm) from the crude ^1H NMR spectra.

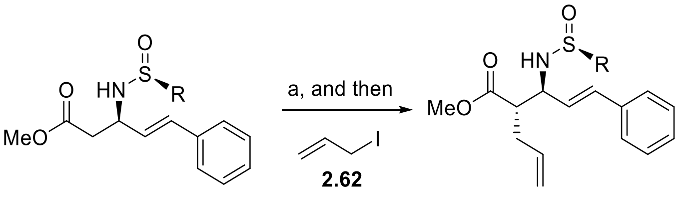


2.60 R=*p*-tolene, 81%, *dr* (>20:1),
2.61 R=*t*-butyl, 91%, *dr* (10:1).

Scheme 2.16. *Reagents and conditions*: a) i) NaHMDS, THF, –78 °C, 1 h; ii) imine **2.55** or **2.57**, THF, –78 °C , 1 h.

2.2.4 *anti*-Alkylations of *β*-amino esters

With the *β*-amino esters **2.60** and **2.61** in hand, we next investigated the selectivity of the *anti*-alkylation with the two sulfinyl chiral auxiliaries. Following the same producers reported by Davis,[100] the *β*-amino esters **2.60** and **2.61** were deprotonated with 2.5 equivalents of LDA in anhydrous THF to secure dianion formation. These were then coupled with allyl iodide in the presence of 10 equivalents of LiCl additive (**Scheme 2.17**). The results showed that both of the two esters gave the products as inseparable diastereoisomers with high yield, but with different selectivities. Ester **2.63** exhibited a *dr* of 15:1-*anti*/*syn*, which was similar with the results in literature,[100] while ester **2.64** only provided a 5.5:1 diastereoselectivity (**Figure 2.7**).



2.60, R=*p*-toluene,
2.61, R=*t*-butyl.

2.63, R=*p*-toluene, 76%, *dr* (15:1),
2.64, R=*t*-butyl, 80%, *dr* (5.5:1).

Scheme 2.17. *Reagents and conditions*: a) i) LDA (2.5 equiv), LiCl (10 equiv), THF, –78 ° to –50 °C, N_2, 1 h; ii) **2.62**, –78 °C, N_2, 1 h.

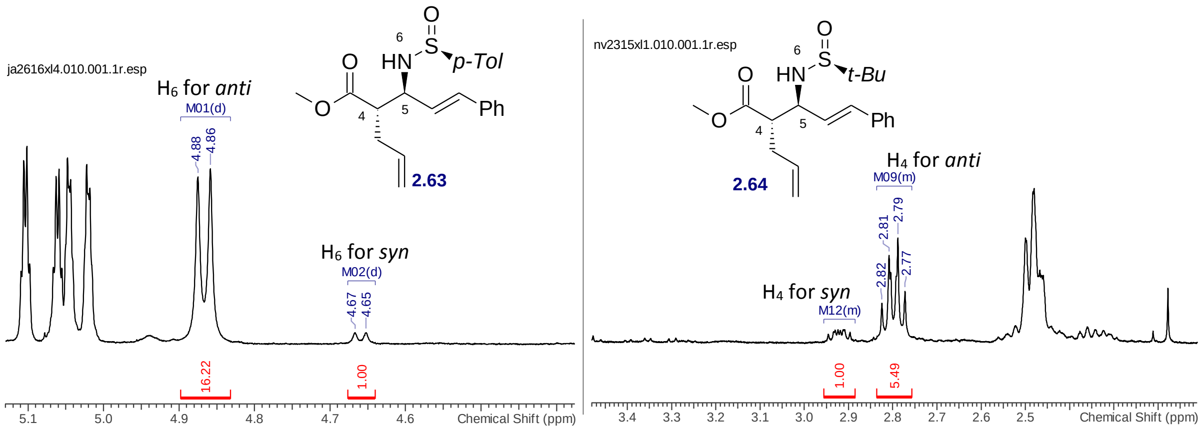


Figure 2.7. Comparison H$_4$ peaks of **2.63** and H$_6$ peaks of **2.64** in the ^{1}H NMR spectra of the *anti*-alkylation crude products.

Anti-selectivity has been generally observed in the α-alkylation of β-amino esters.[103-107] A reasonable interpretation is that the chelation of a lithium ion between the enolate oxygen and the deprotonated amino group prefers to take the half-chair conformation **2.66** with the alkene group occupying a pseudo-axial position (**Figure 2.8**). The alkylation took place by the attack of the electrophile (allyl iodide) from the opposite side of the neighbouring alkene group, resulting in the product **2.62** with *anti*-selectivity. Evidence to support the chelation transition state was reported by Wang *et al.*[106] that when NaHMDS was used as base in the similar alkylation reaction, only the *N*-alkylated product was formed. Since the sodium ion does not form a strong chelation with enolates. In the case of the *tert*-butyl group, it may destabilise the half-chair conformation and hinder the *Si* face to prevent the allyl iodide from approaching, while the *p*-toluene group could rotate to reduce steric hindrance.

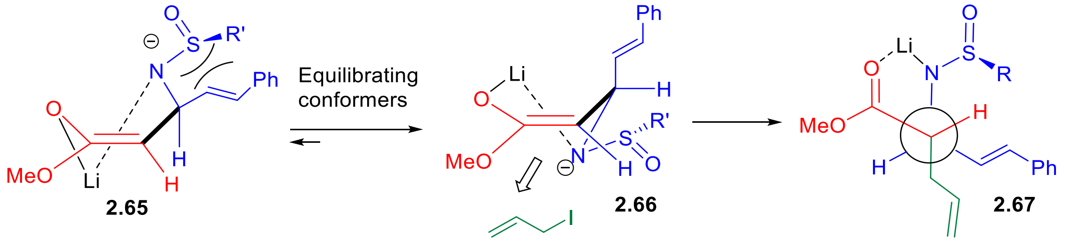
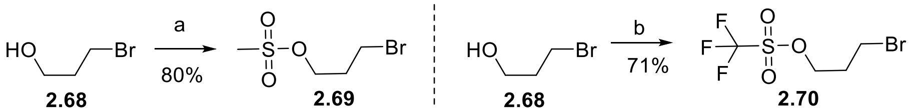


Figure 2.8. Proposed mechanism for *anti*-alkylation.

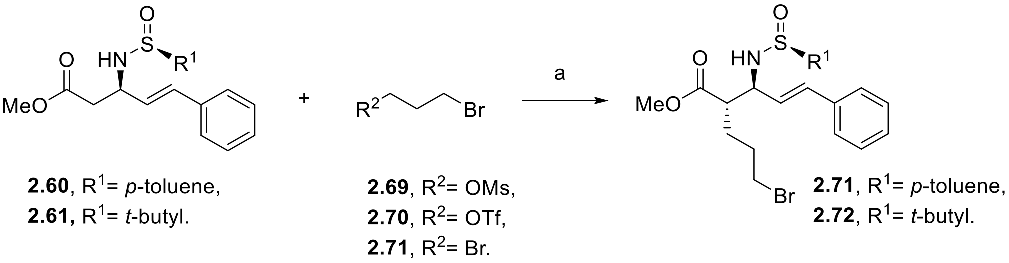
Within the sulfinyl amine literature, only a limited range of electrophiles such as MeI, allyl iodide and BnBr have been reported for this *anti*-alkylation.[100] In order to examine the reactivity of *anti*-alkylation for aliphatic examples, two more electrophiles were prepared (**Scheme 2.18**). Treatment

3-bromo-1-propanol (**2.68**) with mesyl chloride and triflic anhydride afforded the corresponding mesylate **2.69** and triflate **2.70** in good yield.



Scheme 2.18. *Reagents and conditions*: a) Ms-Cl, NEt_3,CH_2Cl_2, 0 °C to rt, 2 h; b) Tf_2O, pyridine, CH_2Cl_2, −78 °C, 1 h.

Under the previously determined dianion conditions, there was no reaction of mesylate **2.69** or aliphatic halide **2.71** and starting materials were recovered (**Scheme 2.19**). When a more active electrophile such as a triflate **2.70** was used, the reaction proceeded and exhibited similar diastereoselectivities to alkylation using allyl iodide (**Table 2.03**). Again, using a chiral auxiliary with a *p*-tolyl group gave a higher *anti*-selectivity (*dr* 10:1) compared to *tert*-butyl (*dr* 4.4:1) shown in **Figure 2.9**. When employing 1 equivalent of triflate **2.70** in the alkylation, a low yield (17%) was observed. Thus, an excess of electrophile was found to be required to achieve reaction in good yield, although it is not clear why this should be. It is possible that some of the electrophile is destroyed by reaction with chloride anion.



2.60, R^1= *p*-toluene,
2.61, R^1= *t*-butyl.

2.69, R^2= OMs,
2.70, R^2= OTf,
2.71, R^2= Br.

2.71, R^1= *p*-toluene,
2.72, R^1= *t*-butyl.

Scheme 2.19. *Reagents and conditions*: a) i) LDA (2.5 equiv), LiCl (10 equiv), THF, −78 ° to −50 °C, N_2, 1 h; ii) **2.69**, **2.70** or **2.71**, −78 °C, N_2, 1 h.

Table 2.03. Outcomes of the *anti*-alkylation with different electrophiles.

Entry	R^1	R^2	Yield %, (*dr*)[a]
1	*p*-toluene	Br	NR[b]
2	*p*-toluene	OMs	NR
3	*p*-toluene	OTf	66%, (10:1)
4	*t*-butyl	Br	NR
5	*t*-butyl	OMs	NR
6	*t*-butyl	OTf	69%, (4.4:1)

[a] Estimated by integration of NH peaks of **2.71** and MeO peak of **2.72** in the crude ^{1}H NMR spectra.
[b] NR indicated no reaction, and starting material recovered.

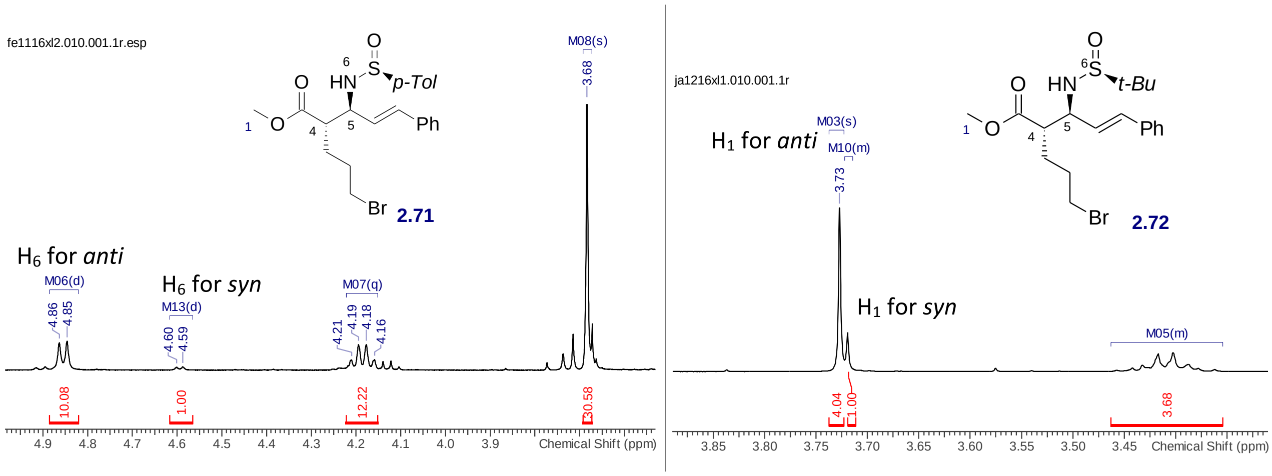


Figure 2.9. Comparison of the H_6 peak of **2.71** and H_1 peak of **2.72** in the ^{1}H NMR spectra of the *anti*-alkylation crude products.

2.3 Total synthesis of (+)-lupinine, (–)-epitashriomine and (–)-epilamprolobine

2.3.1 Re-evaluation strategy of lupinine synthesis

Since the *anti*-alkylation of *β*-amino esters successfully afforded the desired diastereoselectivity for the *anti* imino-aldols, we re-evaluated the synthetic strategy for (+)-lupinine (**Figure 2.10**). The synthesis would start from the imino-aldol reaction, coupling methyl acetate with sulfinyl imine **2.77** to access the *β*-amino ester **2.76** for controlling the first new chiral centre at C-5. The key step is *anti*-alkylation to assemble the second chiral centre at C-6 to afford **2.75**. Following a sequence of deprotection, cyclisation and *N*-alkylation would give access to piperidine **2.74**. Intermediate **2.74** would then undergo ring-closing metathesis to give quinolizidine **2.73.** Final reduction and hydrogenation would furnish the natural product (+)-lupinine **2.01**.

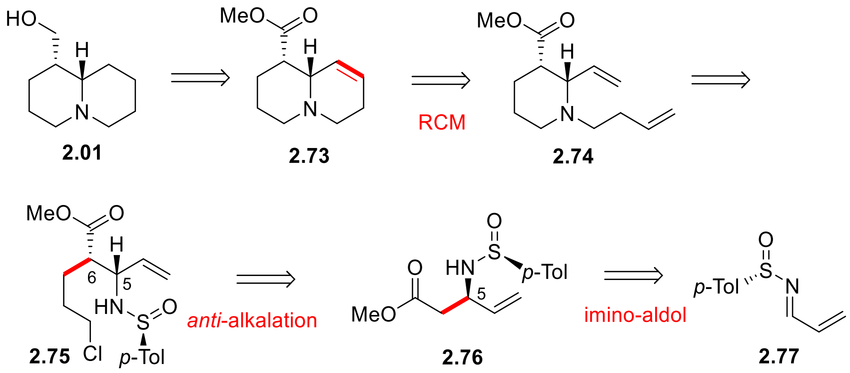
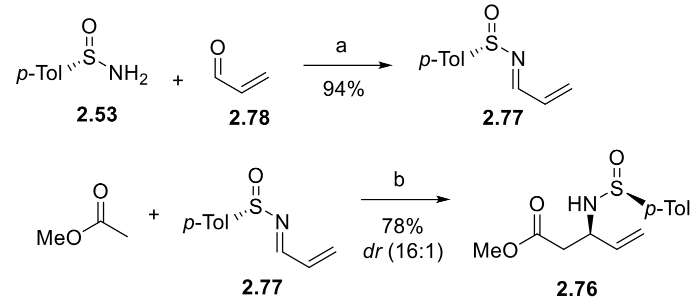


Figure 2.10. Re-evaluation strategy of (+)-lupinine synthesis.

2.3.2 Synthesis of *anti β*-amino ester 2.75

The synthesis commenced by imine condensation with chiral sulfinamide (**2.53**) and commercially available acrolein (**2.78**) to afford imine **2.77** in 94% yield using $Ti(OEt)_4$ (**Scheme 2.20**). With the imine **2.77** in hand, the initial imino-aldol reaction was performed. The sodium enolate derived from methyl acetate at –78 °C underwent smooth addition to sulfinyl imine **2.77** giving *β*-amino ester **2.76** at –78 °C. A poor yield was obtained when the reaction was carried out under a flow of N_2, even at low temperature. This was likely due to the high volatility of methyl acetate. The isolated yield was 78% on a large (5 g) scale with the excellent diastereoselectivity (*dr* 16:1). The stereochemistry of the major product can be rationalised *via* a Zimmerman-Traxler six-membered transition state model (**Figure 2.11**) and the data are consistent with previously reported examples.[100]



Scheme 2.20. *Reagents and conditions:* a) $Ti(OEt)_4$, CH_2Cl_2, rt, 12 h; b) NaHMDS, THF, –78 °C, 2 h.

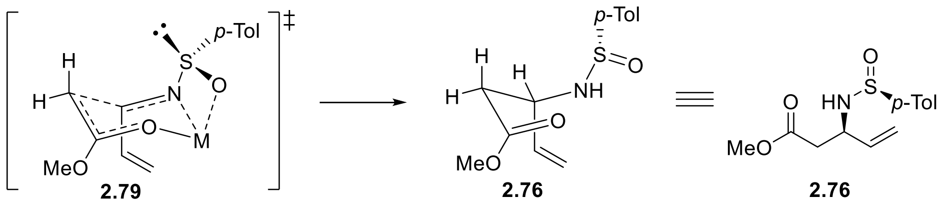
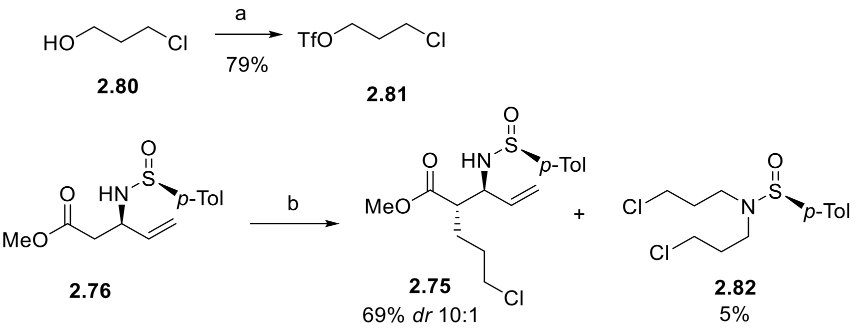


Figure 2.11. Proposed Zimmerman-Traxler transition state model for the imino-aldol reaction.[108]

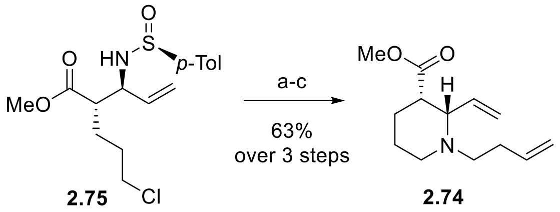
Triflate **2.81** was prepared from 3-chloro-pentanol (**2.80**) with triflic anhydride in 79% yield after distillation purification (**Scheme 2.21**). Surprisingly the colourless oily product **2.81** can be purified by column chromatography on silica, but it evaporates readily under vacuum. *Anti*-alkylation of β-amino ester **2.76** with triflate **2.81** furnished the desired product **2.75** in yields ranging between 50% and 69% yield with excellent diastereoselectivity (*dr* 10:1) and with 5% to 10% byproduct **2.82**. We supposed that the reaction is sensitive to temperature, and there is a competition between α-alkylation and *N*-alkylation as temperature increases. When the reaction was performed at –78 °C, a low yield (around 30%) was always observed and 50% β-amino ester **2.76** was recovered. It was found that the best yield (69%) was observed when the reaction was warmed to –50 °C after addition of triflate. Slightly warmer conditions of –45 °C after deprotonation gave more of undesired byproduct **2.82** (14%). Due to the high reactivity of the triflate, as the temperature increases, the nitrogen anion can react with the triflate and elimination to give byproduct **2.82**. No other byproducts can be isolated from the reaction mixture.



Scheme 2.21. *Reagents and conditions:* a) Tf_2O, pyridine, CH_2Cl_2, –78 °C, 1 h; b) i) LDA (2.5 equiv), LiCl (10 equiv), THF, –78 °C, N_2, 1 h; ii) **2.81**, –50 °C, N_2, 1 h.

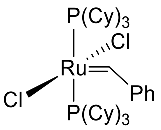
2.3.3 Attempt to close the ring *via* ring-closing metathesis

Using the conditions detailed by Ellman,[109] the *p*-toluenesulfinyl group was removed by treatment with excess acid (**Scheme 2.22**). The resulting crude ammonium salt was treated with base and catalytic NaI to access the piperidine ring. A subsequent *N*-alkylation with 4-bromo-but-1-ene in one pot afforded piperidine intermediate **2.74** in 63% overall yield.

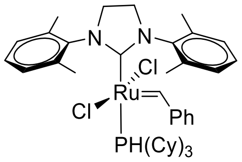


Scheme 2.22. *Reagents and conditions:* a) *conc*. HCl, dioxane, rt. b) K_2CO_3, NaI, rt, MeCN. c) 4-bromo-but-1-ene, K_2CO_3, MeCN, Δ.

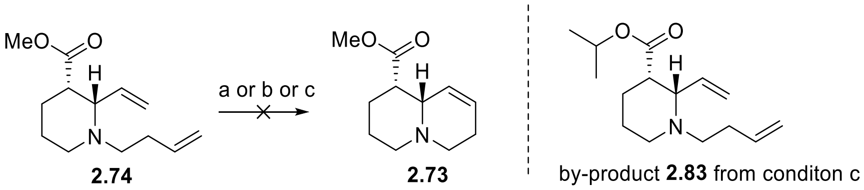
The ring-closing metathesis (RCM) of **2.74** would lead to the bicyclic quinolizidine core. Two RCM catalysts were investigated for this reaction. In the case of Grubbs 1st generation catalyst, 10 mol % of catalyst together with starting material **2.74** were heated at 45 °C in CH_2Cl_2 overnight, but no product was observed (**Scheme 2.23**). We repeated the reaction with the more active Grubbs 2nd generation catalyst at 45 °C and 100 °C in toluene, but unfortunately no desired product was formed either. According to the results, we reasoned that the basicity and nucleophilicity of the *N* atom may play a role in the RCM reaction by coordinating with the ruthenium catalyst preventing reaction progress.[110] A sub-stoichiometric amount Lewis acid Ti(O*i*-Pr)$_4$ was added into the reaction together with Grubbs 2nd generation catalyst refluxing in CH_2Cl_2. This time a trace amount by-product **2.83** was isolated. From its ^1H NMR spectrum, a clear *i*-Pr peak indicated that with the additive Ti(O*i*-Pr)$_4$, the reaction underwent trans-esterification rather than ring closure.



Grubbs Catalyst 1st Generation



Grubbs Catalyst 2nd Generation



Scheme 2.23. *Reagents and conditions:* a) 10 mol% Grubbs I or Grubbs II, reflux, CH_2Cl_2. b) 10 mol% Grubbs II, 100 °C, toluene. c) 10 mol% Grubbs II, 10 mol% $Ti(Oi\text{-}Pr)_4$, reflux, CH_2Cl_2.

As the $Ti(Oi\text{-}Pr)_4$ additive proved unsuccessful, the failed RCM may be ascribed to the terminal alkene which is closer to the ester group. It was found that a functional group with potential for coordination (ester, ketone, ether, etc.), in the starting material with a certain distance between itself and alkene to be metathesized, can inhibit the RCM reaction.[111] Since the carbonyl oxygen could direct the ruthenium catalyst to the nearest terminal alkene, it meant that after the first metathesis, an unreactive six-membered chelate with oxygen sequesters the catalyst in the form of an unproductive complex (**Figure 2.12**), which is unable to chelate the second alkene, resulting in inhibition of the cyclisation.

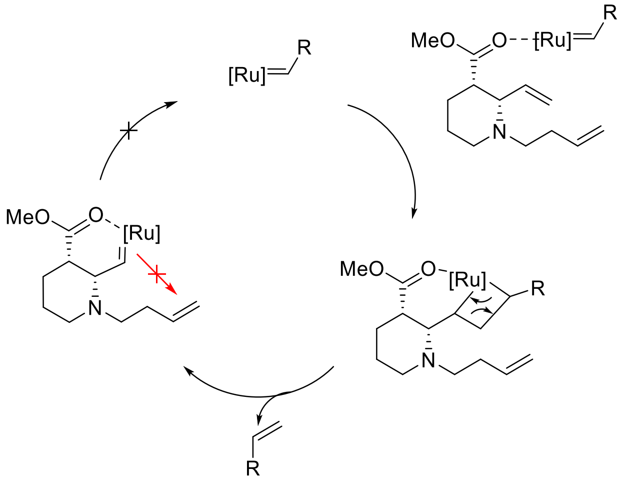
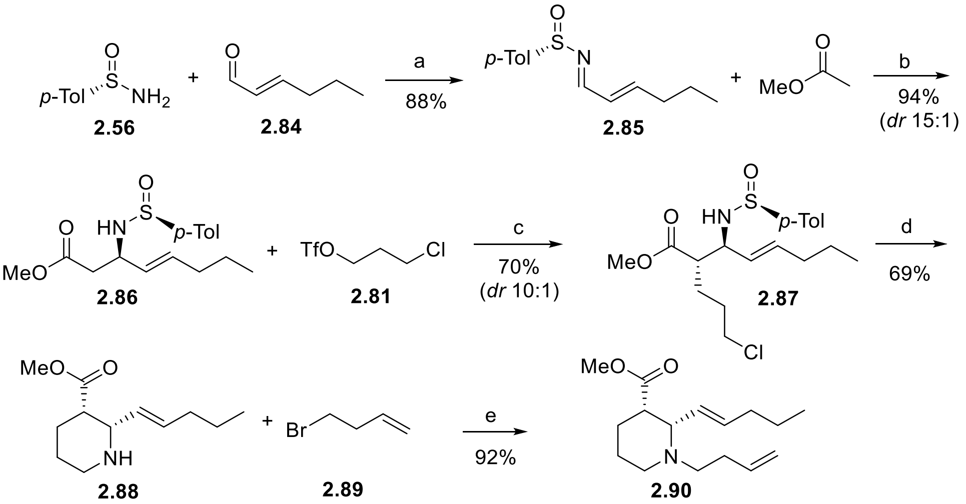


Figure 2.12. Proposed RCM inhibition pathway by 6-membered chelated structure.

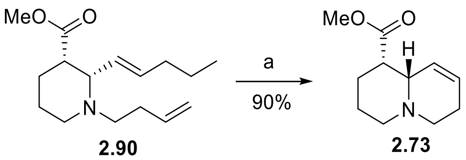
2.3.4 Synthesis of quinolizidine scaffold 2.71

To avoid formation of the unreactive metal alkene, commercially available trans-2-hexen-1-al (**2.84**) was selected to prepare the RCM precursor following the same synthetic sequence (**Scheme 2.24**). The yield for the condensation of *p*-toluene sulfinamide **2.56** with aldehyde **2.84** was 88%. The following imino-aldol reaction between **2.85** and methyl acetate was performed on 5 g scale proceeding in 94% yield with over 15:1 *dr*. The next *anti*-alkylation exhibited a reduced yield in 70% and 10:1 *dr* for two inseparable diastereoisomers under the optimised conditions. However the reaction was not always fully completed and around 20% *β*-amino ester **2.86** was recovered. The recovered starting material was resubmitted to *anti*-alkylation to provide further material to progress the synthesis. With the *anti*-product **2.87** in hand, a one-pot deprotection and cyclisation using the same conditions used previously to prepare piperidine **2.74** (in **Scheme 2.22**) gave intermediate **2.88** in 69% overall yield. This low yield was attributed mainly to the basicity of the piperidine causing a loss of material on the silica gel during chromatography. Treatment of **2.88** with 4-bromo-but-1-ene in MeCN with K_2CO_3 afforded RCM precursor **2.90** in 92% yield. Pleasingly, the minor epimer formed in *anti*-alkylation could be removed in this step by column chromatography.



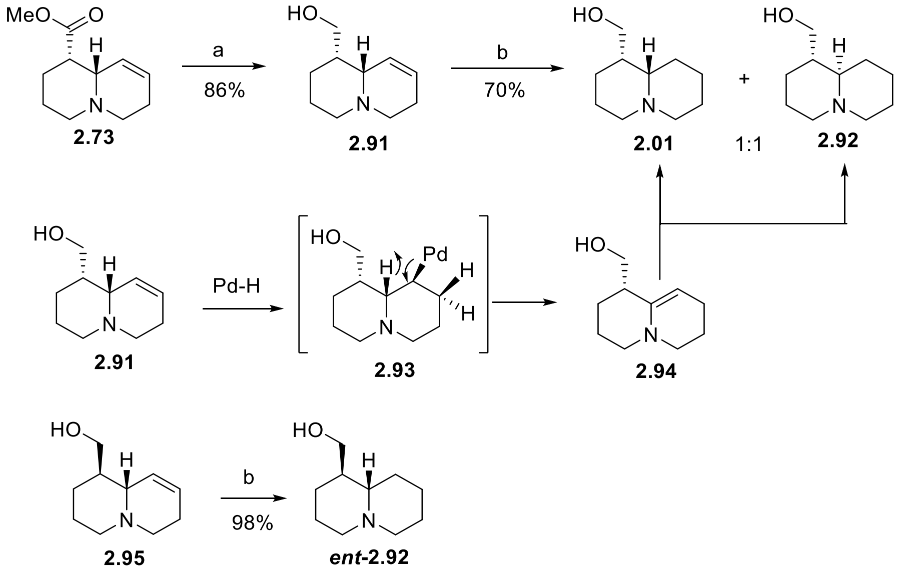
Scheme 2.24. *Reagents and conditions*: a) $Ti(OEt)_4$, CH_2Cl_2, rt. b) NaHMDS, THF, –78 °C; c) i) LDA (2.5 equiv), LiCl (10 equiv), THF, –78 °C, N_2, 1 h; ii) **2.81**, –50 °C, N_2, 1 h. d) i) *conc*. HCl, dioxane, rt; ii) K_2CO_3, NaI, rt, MeCN; e) 4-bromo-but-1-ene, K_2CO_3, MeCN, Δ.

The ring-closing metathesis was performed again with the modified intermediate **2.90** (**Scheme 2.25**). A 5 mol% loading of Grubbs 2nd catalyst with **2.90** proceeded efficiently to access the desired unsaturated quinolizidine **2.73** (in 90% yield) in 1 h under reflux in CH_2Cl_2 validating the earlier proposal. After the cyclisation, the polarity increased significantly and column chromatography purification required a highly polar eluent system. Employing the eluent system: aq. 35% $NH_4OH/MeOH/CH_2Cl_2$-1:10:100 achieved efficient purification of **2.73**.



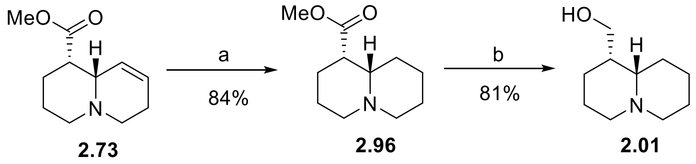
Scheme 2.25. *Reagents and conditions*: a) 5 mol% Grubbs II, reflux, CH_2Cl_2.

Quinolizidine **2.73** was reduced efficiently with $LiAlH_4$ giving the pure unsaturated (+)-lupinine precursor **2.91** in 86% yield (**Scheme 2.26**). The s hydrogenation was performed over Pt/C with H_2. After 12 h the reaction reached full conversion as monitored by LC-MS and only one new spot was observed by TLC. However, after column chromatography, the ^1H NMR spectra exhibited two peaks as a 1:1 ratio, one for lupinine another one for its epimer epilupinine. Due to the high polarity of both products, epilupinine (**2.92**) could not be separated from mixture. Therefore it was not clear which enantiomer of epilupinine we obtained. We assumed that this epimerisation occurred *via* Pd intermediate **2.93** and dehydro product (**2.94**). Palladium hydride adds to **2.91** followed by a β-elimination to afford **2.94**, which under hydrogenation conditions gave epilupinine **2.92**. Converting lupinine to epilupinine has been reported in the literature with Na in hot xylene and isomerisation of lupin alkaloids by Pd is well-known (see Introduction **1.2.2**).[112] Under the same hydrogenation conditions, epilupinine ***ent*-2.92** was obtained from quinolizidine **2.95** without epimerisation, a reaction which had previously been performed in our group by Samuel Watkin.[73]



Scheme 2.26. *Reagents and conditions*: a) $LiAlH_4$, 0 °C, N_2, CH_2Cl_2. b) 10 mol% Pd/C, H_2, EtOH.

In order to avoid the epimerisation, we modified the reaction order to carry out the hydrogenation of ester **2.73** first (**Scheme 2.27**). Fortunately, with 10 mol% Pd/C catalyst loading, the hydrogenation proceeded smoothly to afford the desired product **2.96** without epimerisation in 84% yield. Following this, the standard reduction of **2.96** with $LiAlH_4$ furnished (+)-lupinine (**2.01**), an unnatural enantiomer of a known natural product, in 85% yield as white crystals, which also allowed us to confirm the configuration by X-ray crystallography (**Figure 2.13**). As the optical rotation value of synthetic product **2.01** is consistent with recorded literature data,[70, 113] therefore we can confirm that the absolute configuration of **2.01** is (+)-lupinine.



Scheme 2.27. *Reagents and conditions*: a) 10 mol% Pd/C, H_2, EtOH. b) $LiAlH_4$, 0 °C, N_2, CH_2Cl_2.

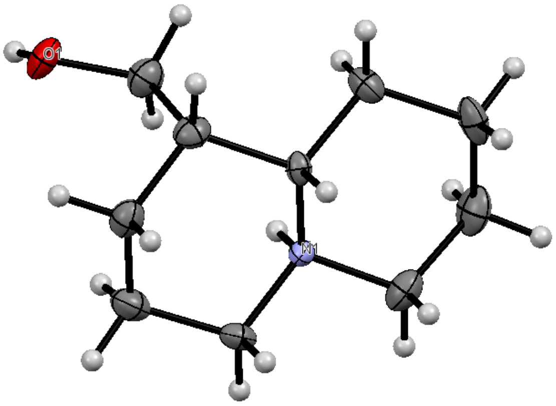


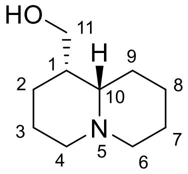
Figure 2.13. X-ray crystal structure of (+)-lupinine (**2.01**).

The asymmetric total synthesis of (+)-lupinine was achieved in 23% yield over 8 linear steps from the imine **2.85**. As the full characterisation data for (+)-lupinine is already recorded in the literature, our material was expected to be consistent (**Table 2.04**). The ^{13}C NMR data are in excellent agreement with the previously reported literature values[50] deviating by less than 0.2 ppm for each signal. The results validated our formal imino-aldol approach giving *anti β*-amino ester intermediates for application in alkaloid synthesis.

^{13}C NMR:

Assignment carbon	Literature δ ppm[a]	Recorded δ ppm[b,c]	Δ δ
C-1	38.1	38.1	0
C-2	31.5	31.3	+0.2
C-3	22.9	22.9	0
C-4	57.1	57.1	0
C-6	57.2	57.1	+0.1
C-7	25.6	25.6	0
C-8	24.6	24.6	0
C-9	29.7	29.7	0
C-10	65.1	65.1	0
C-11	66.0	65.9	+0.1

(+)-Lupinine



Optical Rotation:

[α]$_D$: +12.9 (c 0.2, EtOH, 23 °C).

Literature data:

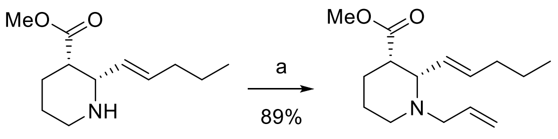
[α]$_D$: +12.7 (c 0.35, EtOH, 30 °C)[70], +19.5 (c 1.00, EtOH, 20 °C)[114], +13.4 (c 1.00, EtOH, 20 °C)[113].

Table 2.04. Comparison of literature and recorded data for (+)-lupinine (**2.01**).
[a] 100 MHz in $CDCl_3$[70]; [b] 101 MHz in $CDCl_3$; [c] current work.

2.3.5 Synthesis of (–)-epitashiromine

In previous work from the Brown group, the *syn* imino-aldol reaction has been successfully applied to the asymmetric total synthesis of tashiromine. Its epimer: epitashiromine has the same relative stereochemical requirement as lupinine. Therefore the *anti*-selective formal imino-aldol approach used for lupinine is applicable to access epitashiromine by simply changing the length of the carbon chain in the *N*-alkylation step to construct the indolizidine core.

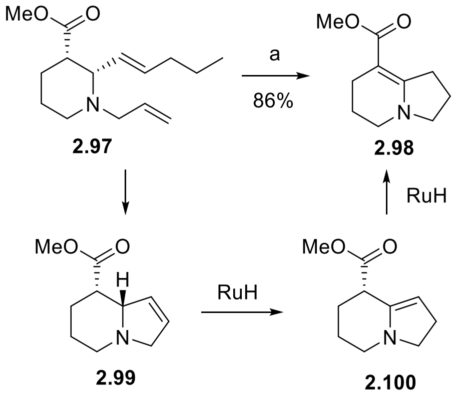
With piperidine **2.88** already in hand, the *N*-alkylation (**Scheme 2.28**) was performed with 1.5 equivalents allyl bromide in the presence of K_2CO_3. After work up and column chromatography purification, a very low isolated yield (20%) of **2.97** was obtained. This poor yield was attributed to the excess allyl bromide, as the tertiary amine could react with the excess alkylating agent to form an ammonium salt which would be lost in the aqueous phase during workup. The stoichiometry of allyl iodide was reduced to 1.01 equivalents to repeat the reaction. A significant improvement in the yield (89%) was achieved after isolation.



2.88 **2.97**

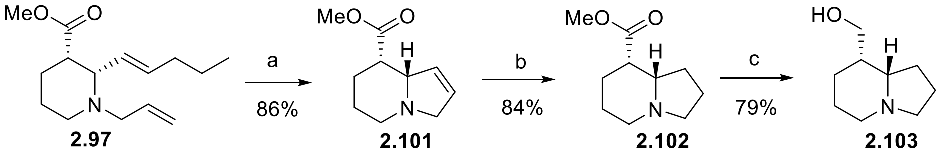
Scheme 2.28. *Reagents and conditions*: a) allyl bromide, K_2CO_3, MeCN.

Employing the same RCM conditions used in the quinolizidine formation, the diene **2.97** was treated with 5 mol% Grubbs 2nd catalyst refluxing at 40 °C in CH_2Cl_2 for 1 h (**Scheme 2.29**). The resulting highly polar indolizidine product (**2.98**) was obtained in 86% yield. Analysis of the reaction product showed that its optical rotation was zero and a further NMR evidence showed that none of the expected methine proton peaks or alkene peaks could be seen from the ^{1}H NMR spectrum. Finally, the cyclised product was confirmed to be α,β-unsaturated ester **2.98** with double bond migration. This unexpected migration did not take place in the lupinine synthesis. We concluded that the indolizidine ring had a more strained half-chair conformation than that of quinolizidine. Even a trace amount of ruthenium hydride would allow the double bond migration *via* intermediate **2.100** to the lower energy isomer **2.98** in which conjugation with the carbonyl group stabilises the structure.



Scheme 2.29. *Reagents and conditions*: a) 5 mol% Grubbs II, reflux, CH_2Cl_2.

To prevent the undesirable isomerisation, the RCM reaction was repeated at room temperature with 10 mol% of 1,4-benzoquinone as an additive to trap the ruthenium hydride (**Scheme2.30**).[115] Monitoring the reaction by TLC every 20 minutes, the diene starting material was consumed after 1 h. Fortunately the desired indolizidine **2.101** was afforded in 86% yield as a single product without isomerisation. From the experience of our previous lupinine synthesis, the hydrogenation was introduced prior to ester reduction to avoid the undesired epimerisation. These final two steps both proceeded efficiently in 84% and 79% yield respectively to furnish the final product (–)-epitashiromine (**2.103**).



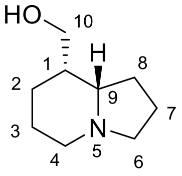
Scheme 2.30. *Reagents and conditions*: a) 5 mol% Grubbs II, 10 mol% 1,4-benzoquinone rt, CH_2Cl_2; b) 10 mol% Pd/C, H_2, EtOH; c) $LiAlH_4$, 0 °C, N_2, CH_2Cl_2.

The analytical data obtained for our synthetic product (–)-epitashiromine are in excellent agreement with the previously reported values (**Table 2.05**). The asymmetric total synthesis of (–)-epitashiromine was achieved in 8 linear steps in 20% yield. Although the optical rotation value of our synthetic product is very low, it is comparable to values reported in the literature.[116] The ^{13}C NMR data are in excellent agreement with published data, deviating by less than 0.2 ppm for each signal.

^{13}C NMR:

Assignment carbon	Literature δ ppm[a]	Recorded δ ppm[b,c]	Δ δ
C-1	35.1	35.3	–0.2
C-2	30.5	30.7	–0.2
C-3	23.1	23.3	–0.2
C-4	53.4	53.6	–0.2
C-6	54.3	54.5	–0.2
C-7	20.6	20.8	–0.2
C-8	25.7	25.9	–0.2
C-9	66.7	66.9	–0.2
C-10	65.6	65.6	0

(–)-Epitashiromine



Optical Rotation:

$[\alpha]_D$: –1.4 (c 0.3, EtOH, 23 °C).

Literature data:

$[\alpha]_D$: –1.9 (c 1.0, EtOH, 25 °C)[116], –0.96 (c 0.31, EtOH, 23 °C)[117].

Table 2.05. Comparison of literature and recorded data for (–)-epitashiromine (**2.103**).
[a] 100 MHz in $CDCl_3$[70]; [b] 101 MHz in $CDCl_3$; [c] current work.

2.3.6 Synthesis of (–)-Epilamprolobine

(–)-Epilamprolobine (**2.104**) was first isolated as a natural product from *sophora tomentosa* in 1981 by Isamu *et. al.*,[118] while its racemate has been synthesised before by Yamada and co-workers.[119] (–)-Epilamprolobine could be synthesised using the same synthetic strategy used for lupinine. An additional glutarimide ring could be introduced on the quinolizidine core of lupinine **2.01** to explore tetracyclic scaffold (**2.105**) formation (**Figure 2.14**).

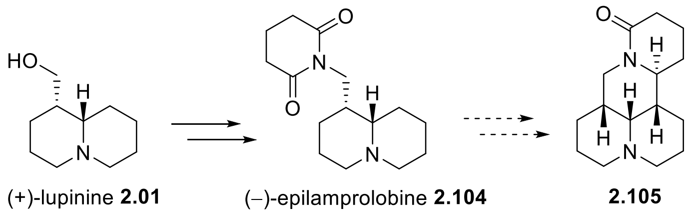
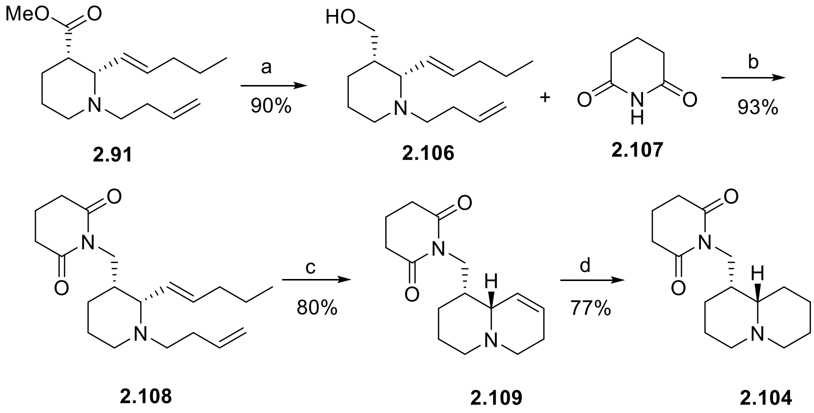


Figure 2.14. Synthesis plan for (–)-epilamprolobine.

Due to the high polarity of lupinine, it would increase the difficulty of purification if the bicyclic intermediate was directly coupled with glutarimide (**2.107**). We decided to reduce the piperidine **2.91** first (**Scheme 2.31**).

Beginning from the previously synthesised piperidine **2.91**, it was reduced using $LiAlH_4$ to afford the corresponding alcohol **2.106** in 90% yield (**Scheme 2.31**). The attempted Mitsunobu reaction to couple **2.106** and glutarimide (**2.107**) in the presence of DIAD and PPh_3 did not show a full conversion even after 48 h monitoring by LC-MS. In addition, after an acidic work up and column chromatography, the product **2.108** could not be separated from PPh_3. After three purification attempts, only 10% yield of **2.108** was obtained. Generally, the PPh_3-DIAD system is useful for acidic nucleophiles with $pK_a < 11$, while the glutarimide pK_a is around 12[120] and needs a more active coupling reagent. Therefore the ADDP/n-Bu_3P system was used, which is effective for $pK_a > 11$ nucleophiles.[121] The Mitsunobu transformation proceeded completely with the modified conditions and the product **2.108** was isolated in 93% yield by column chromatography with the eluent ($MeOH/CH_2Cl_2$ – 10:90). The following RCM reaction of diene **2.108** provided the unsaturated quinolizidine intermediate **2.109** in 80% yield. In this case, the double bond migration was not occurred without benzoquinone additive, which reinforced the proposal that unsaturated quinolizidine structure holds less strain than that of indolizidine intermediate in the half chair conformation. Finally hydrogenation of **2.109** over Pd/C completed the synthesis of enantiopure natural product (–)-epilamprolobine (**2.104**) in 77% yield.

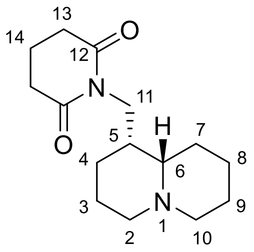


Scheme 2.31. *Reagents and conditions*: a) $LiAlH_4$, 0 °C, N_2, CH_2Cl_2. b) ADDP, n-Bu_3P, THF, rt, 24 h. c) 5 mol% Grubbs II, reflux, CH_2Cl_2; d) 10 mol% Pd/C, H_2, EtOH.

The analytical data of our synthetic sample of (–)-epilamprolobine (**2.104**) are in excellent agreement with the previously reported literature values (**Table 2.06**). The synthetic route shares the same intermediate **2.91** (**Scheme 2.31**) used in lupinine synthesis. This is the first documented asymmetric total synthesis of (–)-epilamprolobine or its enantiomer. Overall, the asymmetric total synthesis of (–)-epilamprolobine was achieved in 9 linear steps in 19% yield.

^{13}C NMR:

(–)-Epilamprolobine



Assignment carbon	Literature δ ppm[a]	Recorded δ ppm[b,c]	Δ δ
C-2	57.1	56.9	+0.2
C-3	21.0	21.1	–0.1
C-4	26.5	26.5	0
C-5	37.0	37.2	–0.2
C-6	65.2	65.2	0
C-7	29.4	29.6	–0.2
C-8	25.0	25.0	0
C-9	25.5	25.4	0.1
C-10	57.6	57.6	0
C-11	37.7	37.9	–0.2
C-12	172.8	172.9	–0.1
C-13	33.1	33.2	–0.1
C-14	17.2	17.3	–0.1

Optical Rotation:

$[\alpha]_D$: –12.0 (c 0.1, EtOH, 23 °C).

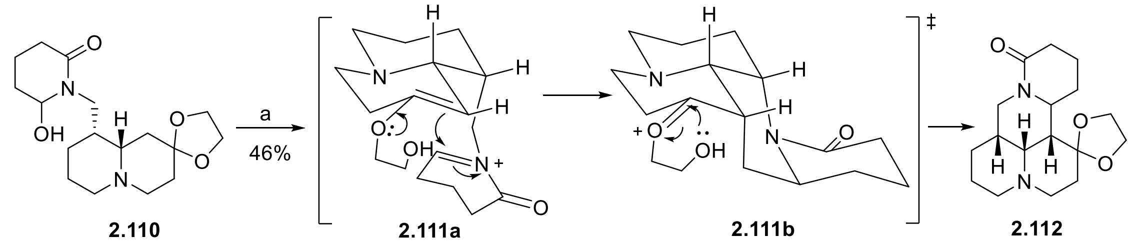
Literature data:

$[\alpha]_D$: –13.8 (c 0.34, EtOH, 23 °C)[118].

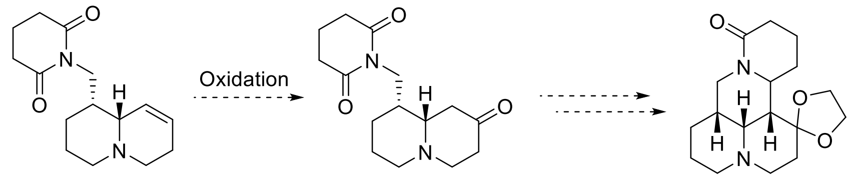
Table 2.06. Comparison of literature and recorded data for (–)-epilamprolobine (**2.104**).
[a] 25 MHz in $CDCl_3$[122]; [b] 101 MHz in $CDCl_3$; [c] current work.

2.3.7 Attempts to functionalise the unsaturated quinolizidine intermediate

In Chen's matrine total synthesis (**Scheme 2.32**),[61] the acetal **2.110** was cyclised in the presence of $MeSO_3H$ facilitated the cyclisation *via* *N*-acyliminium ion **2.111** giving the tetracyclic skeleton **2.112**. From this we proposed that if we can access the desired ketone **2.113** (**Figure 2.15**), then we could assemble tetracyclic structure **2.112** following the same strategy as Chen's matrine synthesis. Herein we attempt to oxidise the internal alkene of quinolizidine **2.109,** which was used in the synthesis of (–)-epilamprolobine, by Wacker oxidation.



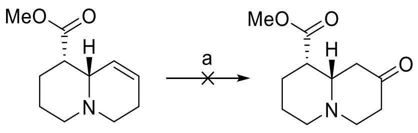
Scheme 2.32. *N*-acyliminium cyclisation in Chen's matrine total synthesis. *Reagents and conditions*: a) $MeSO_3H$, $CHCl_3$.[61]



2.109 **2.113** **2.112**

Figure 2.15. Synthesis plan for tetracyclic **2.112** based on **2.109**.

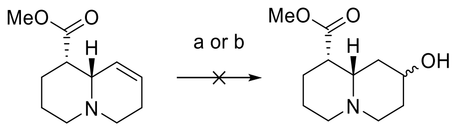
Due to the fact that the high polarity of **2.109** would increase the difficulties in separation, ester **2.96** was used instead of **2.109**. Several successful examples were reported for regioselective oxidation internal alkenes to ketones by Wacker oxidation,[123] although no *N*-heterocyclic examples were found. Recently a highly regio-selective and high yielding Wacker oxidation has been used in synthesis of (±)-vibralactone by our group,[124] therefore the same conditions were applied to **2.96**. (**Scheme 2.33**). Unfortunately, the reaction did not work and starting material was recovered.



2.96 **2.114**

Scheme 2.33. *Reagents and conditions*: a) $PdCl_2(PhCN)_2$, $CuCl_2{\cdot}2H_2O$, $AgNO_2$, O_2, rt.

An alternative way to functionalise the internal alkene is hydroboration. Treatment of **2.96** with excess of 9-BBN in THF under reflux overnight did not give any of the desired product (**Scheme 2.34**). After work up, the starting material **2.96** and cyclooctadiol by-product from 9-BBN were recovered. More forcing hydroboration conditions were applied using the microwave reactor at 110 °C for 1 h. However, even under these conditions quantitative recovery of **2.96** was observed.



2.96 **2.115**

Scheme 2.34. *Reagents and conditions*: a) i) 9-BBN, THF, reflux, 12 h; ii) aq. NaOH, H_2O_2; b) i) 9-BBN, MW, toluene, 110 °C, 1 h; ii) aq. NaOH, H_2O_2.

Attempts to functionalise the internal alkene were not successful. As the oxidation and hydroboration were unworkable for the alkene in our quinolizidine system, we moved our attention to C-C bond formation using the nucleophilic allylsilane group. However, the approach to matrine using hydroboration of the alkene to access to the desired precursor for *N*-acyliminium cyclisation is still under investigation by our group.

2.4 Total synthesis of (+)-isosophoridine

2.4.1 Retrosynthesis of (+)-isosophoridine.

Due to the lack of success in functionalising the alkene present in the quinolizidine core of **2.96**, we turned our attention to attempting to form the C-C bond using an allylsilane-based *N*-acyliminium cyclisation, which has often been used in the synthesis of quinolizidine derivatives.[125-126] (+)-Isosophoridine (**2.116**) was thought to be a good target to examine this approach. The retrosynthetic analysis of (+)-isosophoridine relies on the *anti*-diastereoselective formal imino-aldol reaction and an *N*-acyliminium cyclisation (**Figure 2.16**). The formal imino-aldol reaction of α,β-unsaturated allylsilane imine **2.123** would give the *anti* β-amino ester **2.121**. The subsequent sulfinyl deprotection, cyclisation and *N*-alkylation would afford piperidine derivative **2.120**. The glutarimide moiety could be introduced *via* a Mitsunobu reaction to access the *N*-acyliminium cyclisation precursor **2.119**. The allylsilane-based *N*-acyliminium cyclisation would be expected to give the fused tricyclic ring **2.118** and followed by RCM and hydrogenation would afford (+)-isosophoridine.

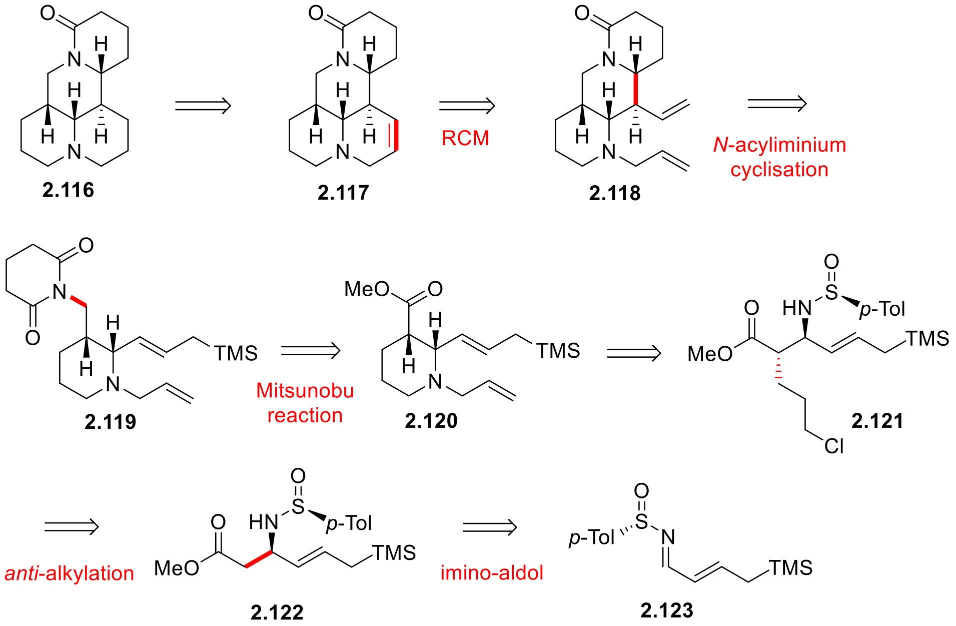
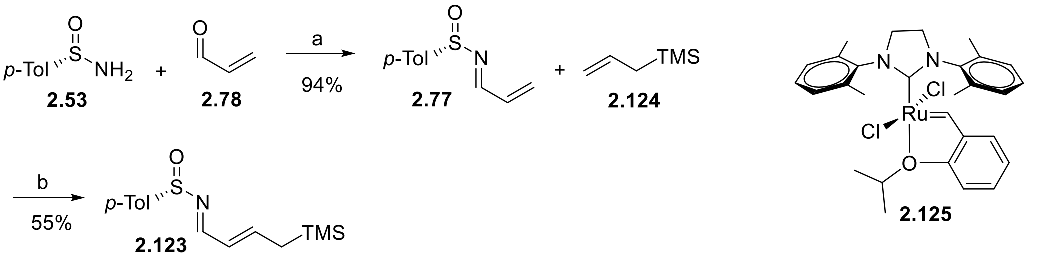


Figure 2.16. Retrosynthetic analysis of (+)-isosophoridine.

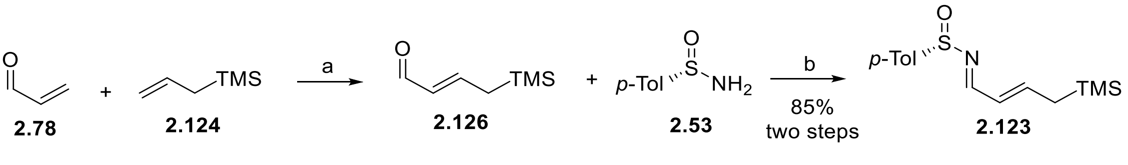
2.4.2 Preparation of imine 2.123

Following a procedure reported by Watkin *et al.*,[71] imine **2.123** was first prepared by a sequence of condensation and cross metathesis reactions (**Scheme 2.35**). Sulfinamide **2.53** was condensed with acrolein (**2.78**) in the presence of Ti(OEt)$_4$ in 94% yield. Cross metathesis with a 1:3 stoichiometry of imine **2.77** and allyltrimethylsilane (**2.124**) with 5 mol% Hoveyda-Grubbs 2nd generation catalyst (**2.125**) afforded the desired imine **2.123** in 55% yield. Increasing the reaction time and catalyst loading gave a similar yield without significant improvement.



Scheme 2.35. *Reagents and conditions*: a) Ti(OEt)$_4$, CH_2Cl_2, N_2, rt, 12 h; b) 5 mol% Hoveyda-Grubbs II, CH_2Cl_2, N_2, rt, 8 h.

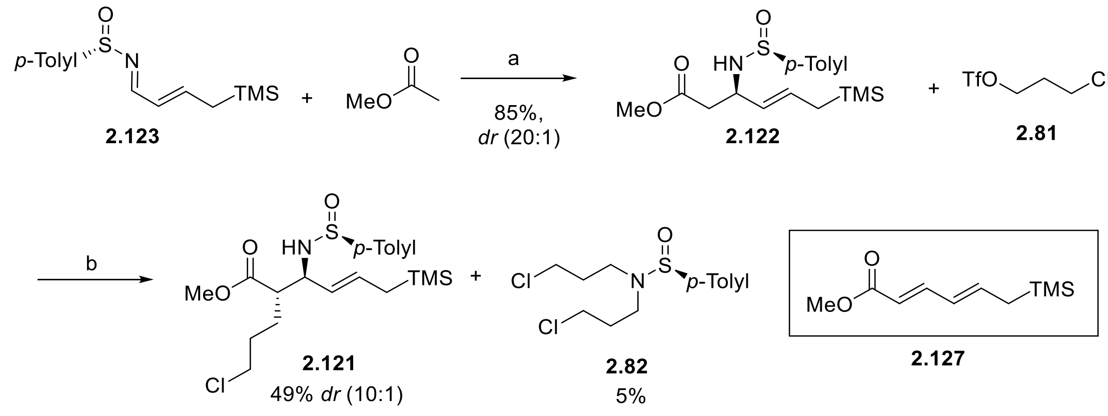
An alternative way was investigated to improve the yield for the preparation of **2.123** by reversing the order of cross metathesis and condensation steps. Aldehyde **2.126** was synthesized via cross metathesis with 1.0 equivalent of allytrimethylsilane and 3.0 equivalents acrolein (**Scheme 2.36**). The reaction was monitored by ^{1}H NMR spectroscopy until full consumption of allytrimethylsilane. Due to aldehyde volatility, only an 18% yield was obtained. A modified one-pot reaction to avoid loss of material improved the yield greatly to 85%. Reversal of the stoichiometry of acrolein: allytrimethylsilane to 1:3, meant that upon consumption of acrolein, all impurities were removed by filtration through a thin layer of silica gel. Subsequently sulfinamide **2.53** and Ti(OEt)$_4$ were added directly into the solvent mixture without concentration *in vacuo*. Upon completion of the imine condensation, imine **2.123** was obtained in 85% yield over two steps.



Scheme 2.36. *Reagents and conditions*: a) 5 mol% Hoveyda-Grubbs II, CH_2Cl_2, N_2, rt; b) Ti(OEt)$_4$, CH_2Cl_2, N_2, rt, 12 h.

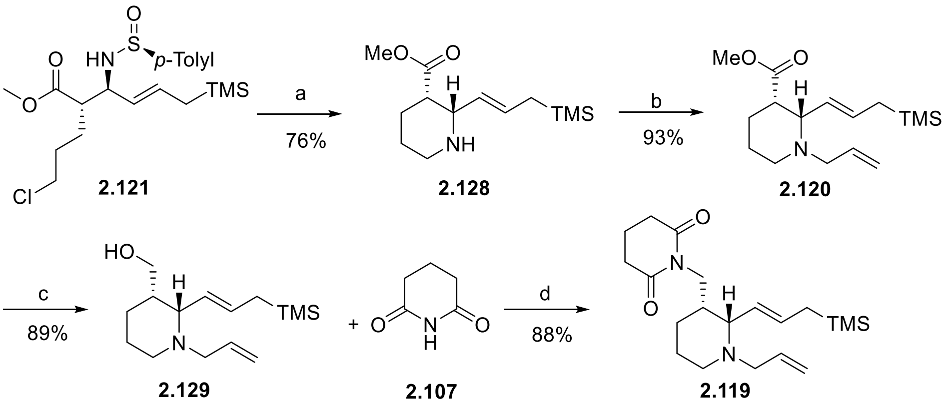
2.4.3 *Anti*-selective formal imino-aldol reaction of sulfinimine 2.123

The combined imino-aldol reaction and *anti*-alkylation were investigated for α,β-unsaturated imine **2.123** (**Scheme 2.37**). Sodium enolate derived from methyl acetate underwent addition to the imine **2.123** affording β-amino ester **2.122** in 85% yield with over 20:1 diastereoselectivity. *Anti*-alkylation was carried out by the dianion of ester **2.122** and triflate **2.81**. It was found that the reaction provided an unexpectedly low yield of only 9%, and 80% by-product **2.82** was isolated. Despite the poor yield, the reaction exhibited >15:1 diastereoselectivity for the desired product. In the previous lupinine synthesis, elimination was observed under the same conditions but to a lesser extent. It is believed that as temperature increases, the *N*-alkylation becomes competitive. Especially in this case, the TMS group would stabilise the transition state for amine elimination to form α,β-unsaturated ester. When *N*-alkylation occurred, the sulfinamine eliminated under E1 or more likely E1cB pathway and the excess triflate helped to capture the eliminated anion. An alternative elimination pathway would involve loss of the sulfinamine dianion before *N*-alkylation, although this pathway is unlikely. Only sulfinamine **2.82** was isolated from after reaction and no other side-product was separated from the mixture, such as α,β-unsaturated ester **2.127** after elimination. In order to reduce the competition from *N*-alkylation, the reaction temperature was kept at –78 °C without warming to –50 °C after addition of triflate. Under these conditions, the side reaction was significantly reduced and the yield was improved to 49% with 10:1 *dr*.



Scheme 2.37. *Reagents and conditions*: a) NaHMDS, –78 °C, THF, N_2; b) i) LDA (2.5 equiv), LiCl (10 equiv), THF, –78 °C, N_2, 1 h; ii) **2.81**, –50 °C, N_2, 1 h.

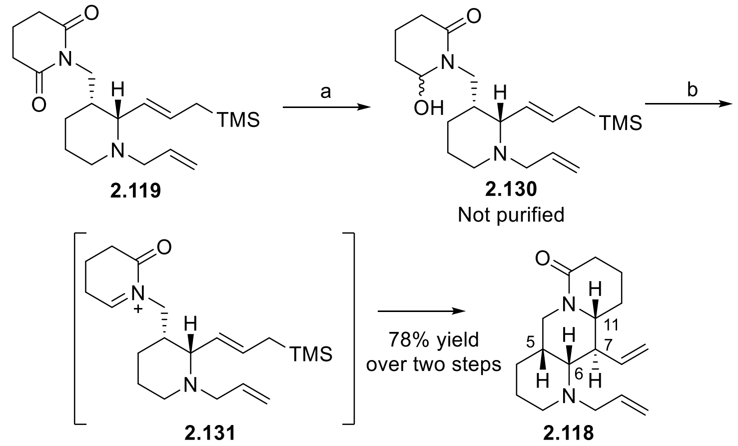
With the *anti* β-amino ester **2.121** in hand, the one-pot cleavage of the sulfinyl auxiliary using *conc*. HCl and subsequent cyclisation in the presence of K_2CO_3 and NaI allowed access to piperidine intermediate **2.128** in good yield (**Scheme 2.38**). *N*-Alkylation of **2.128** was carried out using 1.05 equivalents of allyl bromide to avoid quaternisation. Reduction of methyl ester **2.120** was successfully achieved in high yield by using $LiAlH_4$ at 0 °C. Using the optimal conditions applied in the previous synthesis of epilamprolobine, the Mitsunobu reaction of **2.129** substituted the alcohol group by glutarimide in 88%.



Scheme 2.38. *Reagents and conditions*: a) i) *conc*. HCl, dioxane, rt; ii) K_2CO_3, NaI, rt, MeCN; b) allyl bromide, K_2CO_3, MeCN, Δ; c) $LiAlH_4$, CH_2Cl_2, 0 °C; d) *n*-Bu_3P, ADDP, THF.

2.4.4 *N*-acyliminium cyclisation and access to the tetracyclic scaffold

Previous work[64] indicated that $LiEt_3BH$ is an excellent reagent to reduce glutarimide to the corresponding hydroxylactam without opening the ring. This reduction usually requires excess reducing agent to work efficiently, and previous attempts with $NaBH_4$ caused over-reduction to afford ring opened alcohol. Utilising the procedure detailed by Ionut-Alexandru Pop,[64] **2.119** was reduced in full conversion by using $LiEt_3BH$ (2.0 equiv.) at –78 °C in CH_2Cl_2 after 1.5 hours (**Scheme 2.39**). The reaction was quenched with sat. NH_4Cl before warming to room temperature. The unstable hydroxylactam may convert into the corresponding enamine on silica, so the crude product was used for the *N*-acyliminium cyclisation without purification. The crude material was dissolved in CH_2Cl_2 with excess of $BF_3{\cdot}OEt_2$ overnight to afford a single diastereoisomer **2.118** in 78% yield over two steps.



Scheme 2.39. *Reagents and conditions*: a) $LiEt_3BH$, CH_2Cl_2, –78 °C; b) $BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 12 h.

The ^1H NMR peak corresponding to H_6 on **2.118** (**Scheme 2.39**) showed a double-doublet peak with *J* values of 10.9 and 4.8 Hz, which indicated two adjacent protons one *trans* and one *cis* to H_6. This is consistent with the stereochemistry of isosophoridine. If the matrine stereochemistry had been obtained, we would have expected to see an apparent triplet peak for H_6 with a small *J* value for two *cis* protons adjacent to H_6 on each side of scaffold **2.132** (**Figure 2.17**). The relative stereochemistry was confirmed by NOESY NMR data, which indicated correlation between H_6-H_5 and H_6-H_{11} (**Figure 2.18**). Thus the single stereoisomer obtained was confirmed to be the one required for the synthesis of isosophoridine. It was envisioned that the *N*-acyliminium cyclised *via* a chair transition state where the allyl silane group occupied the equatorial position (Transition state **2.131-a** in **Figure 2.17**).

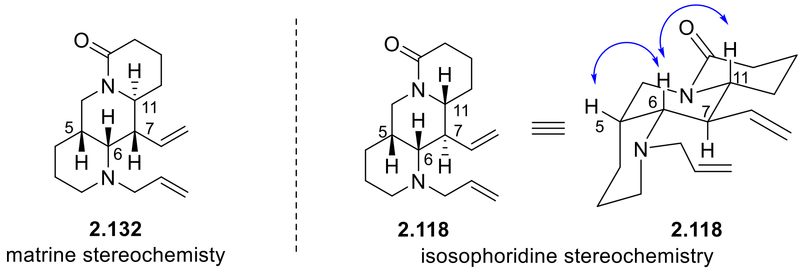
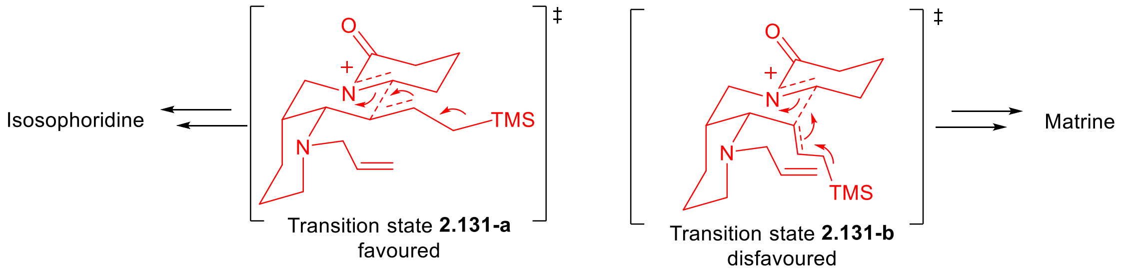


Figure 2.17. Confirmation of the relative stereochemistry of diene 2.118 by NOESY NMR data.

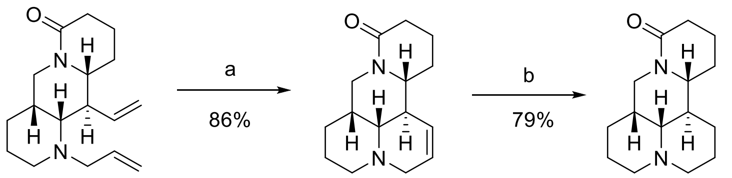


Transition state **2.131-a**
favoured

Transition state **2.131-b**
disfavoured

Figure 2.18. Proposed transition state for *N*-acyliminium cyclisation.

With **2.118** in hand, the subsequent RCM was performed (**Scheme 2.40**). Hoveyda-Grubbs 2nd generation catalysed the ring closure in CH_2Cl_2 at room temperature providing the tetracyclic product **2.117** in 86% yield after 12 h. Finally, hydrogenation over Pd/C accessed saturated product **2.116** as white crystals. At this stage, we were able to confirm our relative stereochemical assignment and absolute stereochemistry by X-ray structure data and optical rotation value for **2.131** (**Figure 2.19**). Comparing the optical rotation data with literature confirmed that the final product was the natural stereoisomer (+)-isosophoridine.



2.118

2.117

(+)-isosophoridine **2.116**

Scheme 2.40. *Reagents and conditions*: a) 5 mol% Hoveyda-Grubbs II, CH_2Cl_2, rt. b) 10 mol% Pd/C, H_2, EtOH.

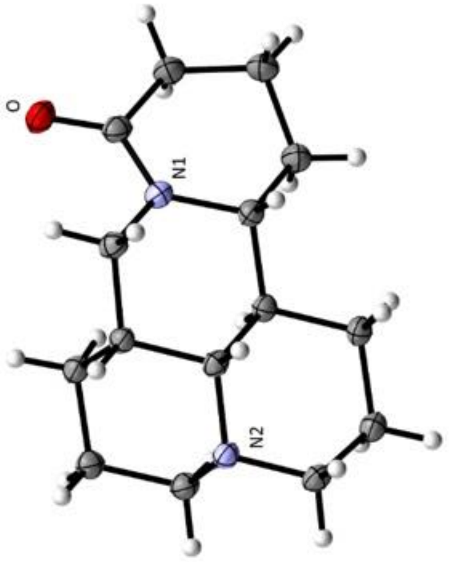


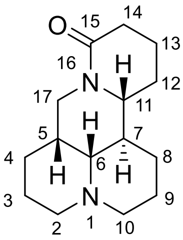
Figure 2.19. X-ray crystal structure of (+)-isosophoridine (**2.116**).

The first asymmetric total synthesis of natural product (+)-isosophoridine was achieved in 10 linear steps with a 10% overall yield. Isosophoridine was first obtained in 1962 by Rulko *et al.*[127] by completely isomerizing sophoridine over PtO_2/H_2 in acetic acid and later isolated from *Sophora alopecuroides* and *Oxytropis ochrocephala*.[128-129] All the analytical data of the synthetic material was in agreement with the sample recorded in the literature.[130] The ^{13}C NMR data was consistent with the reported literature values, deviating by less than 0.2 ppm for each signal (**Table 2.07**).

^{13}C NMR:

Assignment carbon	Literature δ ppm[a]	Recorded δ ppm[b,c]	Δ δ
C-2	45.0	45.0	0
C-3	25.6	25.8	–0.2
C-4	22.7	22.9	–0.2
C-5	35.8	35.9	–0.1
C-6	62.1	62.2	–0.1
C-7	33.3	33.3	0
C-8	26.6	26.6	0
C-9	19.0	19.1	–0.1
C-10	53.9	54.1	–0.2
C-11	59.9	60.0	–0.1
C-12	27.8	27.9	–0.1
C-13	18.9	19.0	–0.1
C-14	32.8	32.9	–0.1
C-15	169.9	169.8	+0.1
C-17	46.6	46.7	–0.1

(+)-Isosophoridine



Optical Rotation:

[α]$_D$: +99 (c 0.2, EtOH, 23 °C).

Literature data:

[α]$_D$: +101 (c 3.2, EtOH, 23 °C)[130].

Table 2.07. Comparison of literature and recorded data for (+)-isosophoridine (**2.116**).

[a] 100.5 MHz in $CDCl_3$[130]; [b] 101 MHz in $CDCl_3$; [c] current work.

2.5 Total synthesis of (+)-sparteine

2.5.1 Synthetic plan for sparteine

We next moved our attention to apply the *anti*-selective formal imino-aldol method to a well-known natural product: sparteine. Sparteine has two different relative configurations either side of the bridge (**Figure 2.20**). One side requires a *trans* hydrogen relationship and the other side of the bridge has a *cis* hydrogen relationship. The configuration of the chiral centres from *N*-acyliminium cyclisation gives the *trans* hydrogen relationship, as confirmed in the total synthesis of (+)-isosophoridine. This discovery suggested to us that the *trans* side on sparteine can be formed by *N*-acyliminium cyclisation. The *cis* part can be achieved by *anti*-selective formal imino-aldol approach, which has been successfully performed in the total syntheses of (+)-lupinine and (+)-isosophoridine.

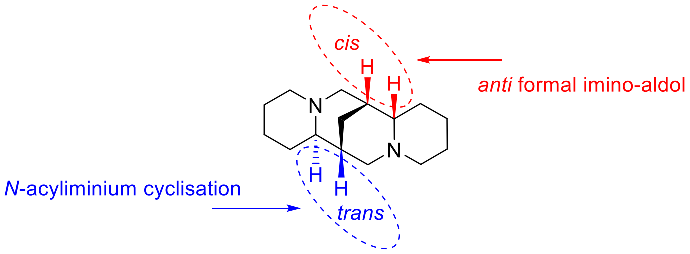


Figure 2.20. Structure of sparteine showing the *cis* and *trans* hydrogen relationships.

The synthesis of sparteine commenced with imino-aldol reaction of imine **2.141** (**Figure 2.21**). The allylic silane group installed by *anti*-alkylation of triflate **2.140** would allow access to **2.138**. The subsequent *N*-acyliminium cyclisation in the presence of a Lewis acid would cleave the sulfinyl auxiliary and cause amine addition to the iminium ion, which has been found in previous synthesis of β-isosparteine by Ionut-Alexandru Pop.[64] Therefore after cleavage of the auxiliary and cyclisation of **2.138**, the piperidine derivative **2.137** requires protection with an acid stable protecting group such as the -Cbz group to avoid this. After introducing the required *cis* stereochemistry on one side of sparteine, the Mitsunobu reaction would couple glutarimide to give imide **2.136**. The following *N*-acyliminium cyclisation would access **2.135**, which should possess the required *"trans"* relationship. Ozonolysis of **2.135** followed by reductive amination would allow access to the tetracyclic skeleton **2.134** which under reduction of the lactam would complete the total synthesis of (+)-sparteine.

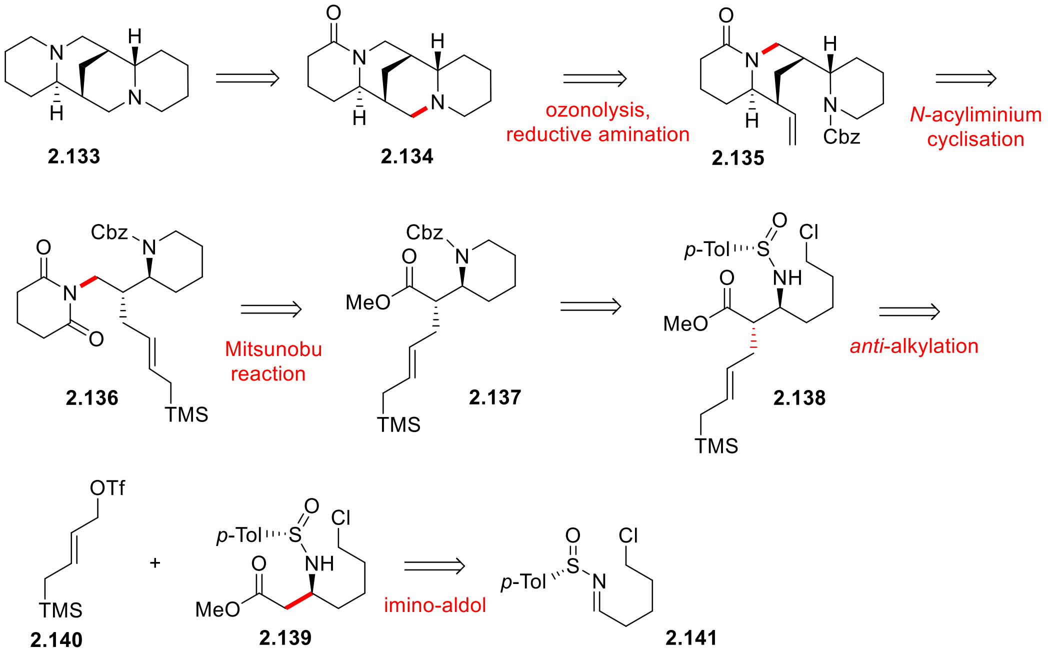
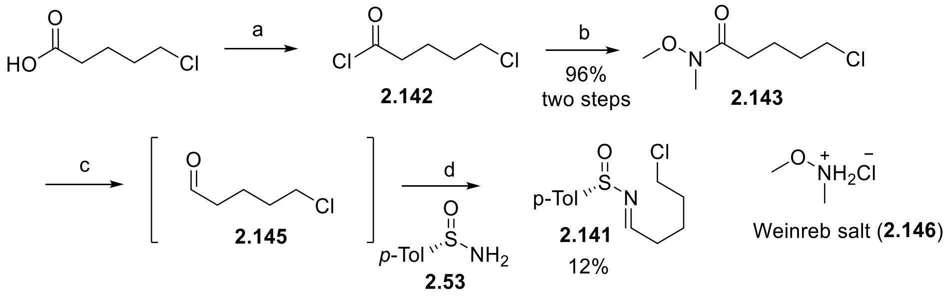


Figure 2.21. Retrosynthetic analysis of (+)-sparteine.

2.5.2 Preparation of imine 2.141

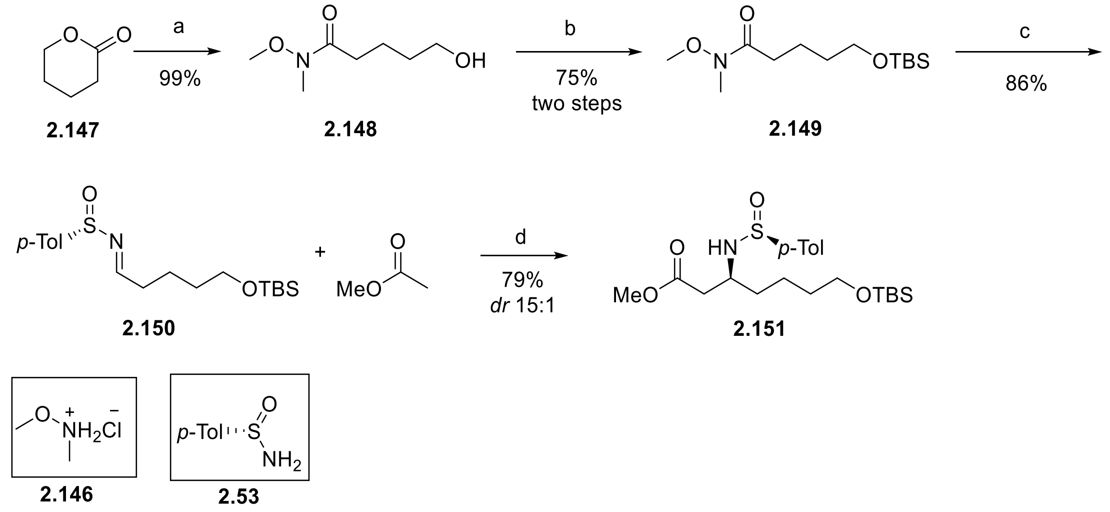
Commercially available acid 5-chlorovaleric acid was converted to the corresponding acid chloride **2.142** using oxalyl chloride (**Scheme 2.41**). The crude product without further purification, was converted to the Weinreb amide **2.143** in 96% yield over two steps. Reduction of amide **2.143** with DIBAL-H at –78 °C gave aldehyde **2.145** exclusively. The aldehyde was used directly for imine condensation with sulfinamide **2.53** due to its volatility. Following the optimum conditions used previously in the synthesis of sulfinimines, the best yield of sulfinimine **2.141** achieved was only 12% over 2 steps. Increasing the reaction time or temperature did not improve the yield. We also used the purified aldehyde **2.145** to repeat the condensation, but the yield was still very low with a large amount unreacted sulfinamide **2.53**. The poor yield of imine **2.141**, unfortunately, suggested that it is not a suitable starting material for application in the total synthesis.



Scheme 2.41. *Reagents and conditions*: a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; b) **2.146**, NEt_3, CH_2Cl_2, 0 °C to rt, 12 h; c) DIBAL-H, CH_2Cl_2, N_2, –78 °C; d) $Ti(OEt)_4$, **2.53**, CH_2Cl_2.

2.5.3 Preparation of imine 2.150 and imino-aldol reaction

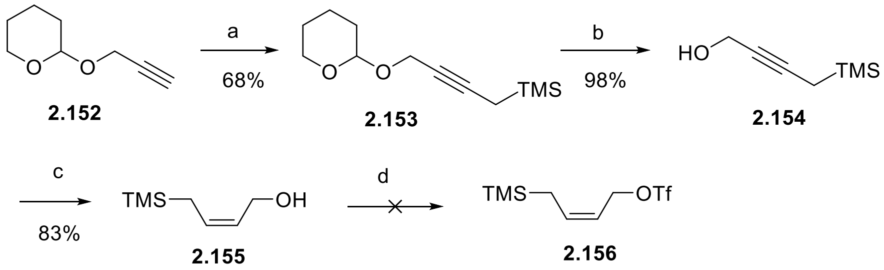
Due to the poor yield obtained for formation of halo-imine **2.141**, which we attributed to the presence of the chloro group reacting with hemiaminal intermediate, we selected a protected alcohol group to replace the terminal chloride. Following a procedure described by Flick *et al.*,[131] $AlMe_3$ was mixed with Weinreb salt (**2.146**) in CH_2Cl_2 at 0 °C for 30 min and δ-valerolactone (**2.147**) was added to afford alcohol **2.148** (**Scheme 2.42**). Primary alcohol **2.148** was protected as its TBS ether **2.149** in quantitative yield. Subsequent reduction of **2.149** with DIBAL-H and imine condensation with sulfinamide **2.53** gave access to the desired imine **2.150** in 86% yield. The four-step sequence proceeded in 64% yield for the imine **2.150** which was acceptable for a starting material preparation. Treatment of imine **2.150** with an excess the sodium enolate derived from methyl acetate resulted in β-amino ester **2.151** in 79% yield with good diastereoselectivity (*dr* 15:1).



Scheme 2.42. *Reagents and conditions*: a) $AlMe_3$, **2.146**, CH_2Cl_2, 0 °C, 30 min; then **2.147**, 12 h; b) TBDMS-Cl, NEt_3, CH_2Cl_2, rt; c) i) DIBAL-H, CH_2Cl_2, N_2, –78 °C; ii) **2.53**, $Ti(OEt)_4$, CH_2Cl_2, rt; d) NaHMDS, –78 °C, N_2, THF.

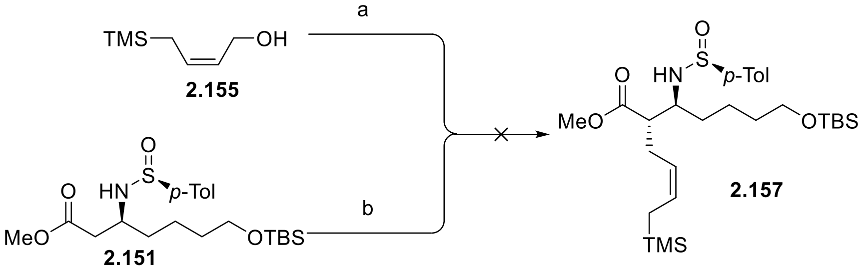
2.5.4 Attempts to introduce allyltrimethylsilane group by *anti*-alkylation

Using the produce detailed by Wender *et al.*,[132] the THP-protected propargyl alcohol **2.152** was deprotonated with *n*-BuLi followed by alkylation with iodo(trimethylsilyl)methane to afford propargyl silane **2.153**, which following deprotection with PPTS formed alcohol **2.154** in 98% yield over two steps (**Scheme 2.43**). The reduction of alcohol **2.154** with $LiAlH_4$ afforded *trans* alkene in only 43% yield in the report.[133] The *cis* alkene **2.155** could be prepared by hydrogenation with a nickel catalyst in high yield. Following the conditions detailed by Tietze *et al.*,[134] **2.155** was formed by hydrogenation in 83% yield with selectivity of over 20:1 (*cis*/*trans*). Alcohol **2.155** was treated with triflic anhydride using the same procedure employed previously (see **scheme 2.18**). Unfortunately, none of the desired product was isolated after reaction and the TLC showed a new spot on the base line.



Scheme 2.43. *Reagents and conditions*: a) i) *n*-BuLi, –78 °C, N_2, THF, 1 h; ii) $TMSCH_2I$; b) PPTS, EtOH, rt; c) $Ni(OAc)_2$, $NaBH_4$, H_2, EtOH; d) Tf_2O, pyridine, CH_2Cl_2, –78 °C, 1 h.

It is likely that the triflate **2.156** is highly unstable, as all of alcohol **2.155** was consumed. Therefore the one pot *anti*-alkylation using triflate **2.156** prepared *in situ* was explored to give access to *anti*-product (**Scheme 2.44**). The *β*-amino ester **2.151** was deprotonated by LDA in THF at –78 °C. At the same time, the alcohol **2.155** was deprotonated by *n*-BuLi and coupled with triflic anhydride. The triflation reaction mixture was transferred into the dianion solution derived from **2.151** by cannula, but the crude mass spectra did not show any evidence for the desired product. The starting *β*-amino ester was recovered. *Anti*-alkylation of the allyltrimethylsilane triflate system was unsuccessful and not explored further.

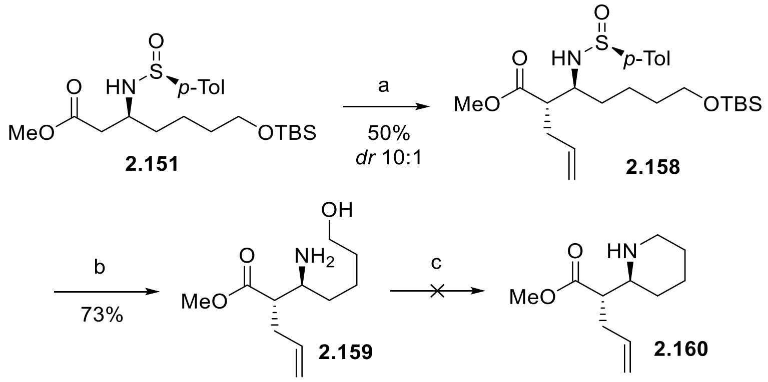


Scheme 2.44. *Reagents and conditions*: a) *n*-BuLi, TfO_2, –78 °C, N_2, Et_2O; b) LDA (2.5 equiv), LiCl (10 equiv), –78 °C, N_2, THF.

2.5.5 Alternative approach to install allyltrimethylsilane group

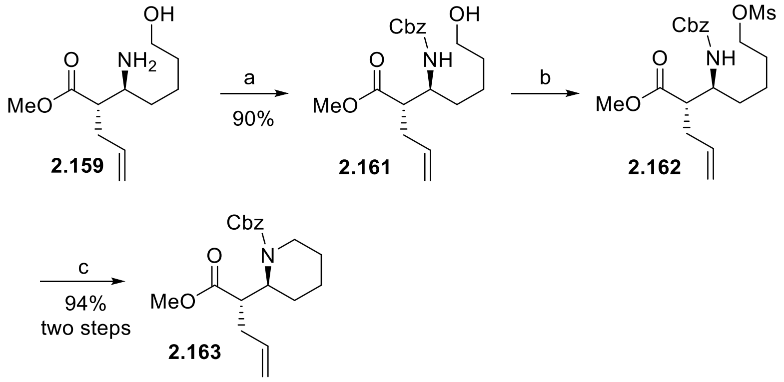
In order to install the allyl silane group into the *β*-amino ester, we moved our attention to cross metathesis reaction (CM). The synthetic route was redesigned so that the ester **2.151** underwent *anti*-alkylation with allyl iodide. Subsequent closure of the piperidine ring and protection of the amine would afford the CM precursor, in case the amine group poisoned the ruthenium catalyst.

The *anti*-alkylation of ester **2.151** with allyl iodide afforded **2.158** in 50% yield with *dr* 10:1 (**Scheme 2.45**). Both the sulfinyl group and TBS group were successfully removed in one step with *conc*. HCl in dioxane, which gave *anti-β*-amino ester **2.159** in 73% yield. Due to the high polarity of **2.159**, the work up required several extractions of the aqueous phase to ensure complete recovery of all material. Attempts to close the ring of **2.159** by an intramolecular Mitsunobu reaction failed.



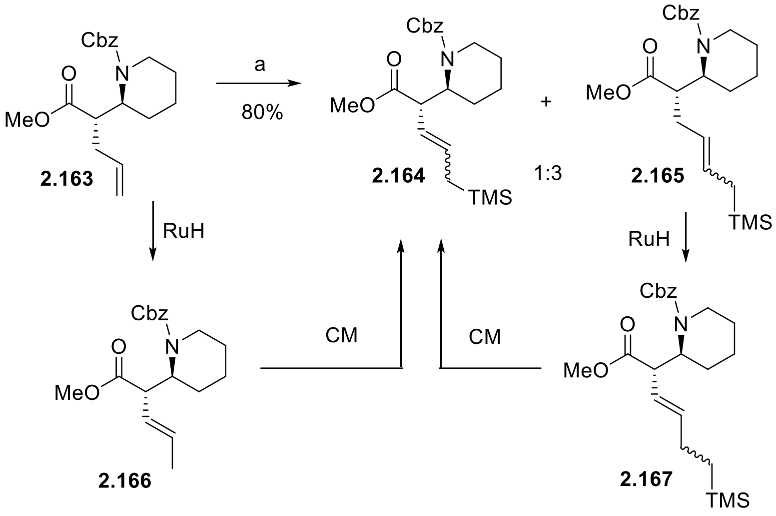
Scheme 2.45. *Reagents and conditions*: a) LDA (2.5 equiv), LiCl (10 equiv), –78 °C, N_2, then $ICH_2CH=CH_2$, THF; b) *conc.* HCl, dioxane, 12 h; c) *n*-Bu_3P, ADDP, THF.

A longer but more secure route was used to prepare piperidine **2.163** (**Scheme 2.46**). Amine **2.159** was treated with Cbz-Cl in the presence of K_2CO_3 to afford **2.161.** Treatment of alcohol **2.161** with Ms-Cl gave the corresponding mesylate **2.162** and the following cyclisation was completed smoothly in the presence of *t*-BuOK to afford piperidine **2.163** in 94% yield over 2 steps.

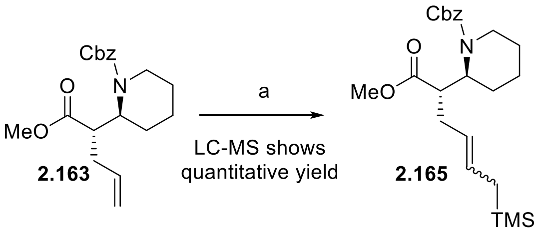


Scheme 2.46. *Reagents and conditions*: a) Cbz-Cl, K_2CO_3, THF, rt; b) Ms-Cl, NEt_3, –78 °C, CH_2Cl_2; c) MeCN, *t*-BuOK, rt, 12 h.

With the piperidine derivate **2.163** in hand, the cross metathesis reaction was investigated. Exposure of **2.163** to 5 mol% Hoveyda-Grubbs 2nd catalyst with three equivalents allyltrimethylsilane (ATMS) at room temperature provided a mixture of inseparable products **2.164** and **2.165** in 80% yield and a 3:1 ratio of desired product : byproduct (**Scheme 2.47**). The reaction was repeated and monitored by LC-MS. After one hour, there remained around 50% stating material **2.163** with a 2:1 ratio in favour of the desired product **2.165**. After two hours, the starting material was almost consumed, but the ratio of the product and byproduct increased to 1:1. It was found that increasing the amount of ATMS did not improve the desired product yield and exposure of the reaction to high temperature (45 °C) led to more byproduct formation. In addition, leaving the CM reaction for a long period increased the byproduct formation, becoming the major product. From the LC-MS, we could see a new peak with the same molecular weight as the starting material **2.163**, which was believed to be the isomer **2.166** from isomerisation of **2.163** by ruthenium hydride. The side reaction occurred with both starting material **2.166** and product **2.165**. After isomerisation, the double bond in **2.166** and **2.167** migrated and these two intermediates continued cross metathesis to give the undesired byproduct **2.164** with loss of one carbon. In order to trap the ruthenium hydride to prevent isomerisation, 5 mol% 1,4-benzoquinone was used (**Scheme 2.48**).[115] Due to lack of starting material, a small scale reaction (10 mg of **2.163**) was performed in the presence of the benzoquinone additive. This time LC-MS of the reaction exhibited full conversion to desired product **2.165** without by-product formation. Unfortunately, is was not possible to repeat this reaction on a large scale due to lack of material.



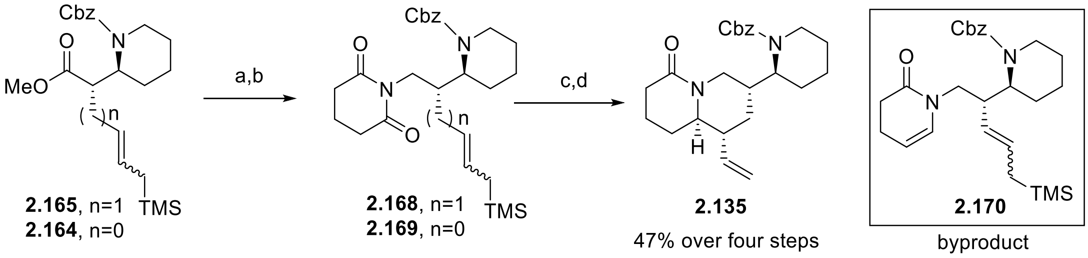
Scheme 2.47. *Reagents and conditions*: a) ATMS, 5 mol% Hoveyda-Grubbs II, CH_2Cl_2, rt.



Scheme 2.48. Small scale reaction using 1,4-benzoquinone for CM. *Reagents and conditions*: a) ATMS, 5 mol% Hoveyda-Grubbs II, 5 mol% 1,4-benzoquinone, CH_2Cl_2, rt.

2.5.6 Total synthesis of (+)-sparteine

The unseparated mixture of **2.165** and **2.164** was reduced to the corresponding alcohols with $LiAlH_4$ followed by the Mitsunobu reaction employing the conditions used in the (+)-isosophoridine synthesis (**Scheme 2.49**). Unfortunately, the resulting imides **2.168** and **2.169** were not separable. The mixture of imides was treated with $LiEt_3BH$ and subsequent addition $BF_3{\cdot}OEt_2$ to give the cyclised product **2.135**. Only one diastereoisomer was observed and the short chain by-product was unable to cyclise to the corresponding five-six membered fused ring giving rise to the enamine **2.170**. This selective cyclisation can be account for a chair-like transition state **2.168-a** as in the isosophoridine synthesis (**Figure 2.22**), with the allyl TMS group placed on more favoured equatorial position.



Scheme 2.49. *Reagents and conditions*: a) $LiAlH_4$, –78 °C, N_2, CH_2Cl_2, b) ADDP, *n*-Bu_3P, glutarimide THF; c) $LiEt_3BH$, CH_2Cl_2, –78 °C, N_2; d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt.

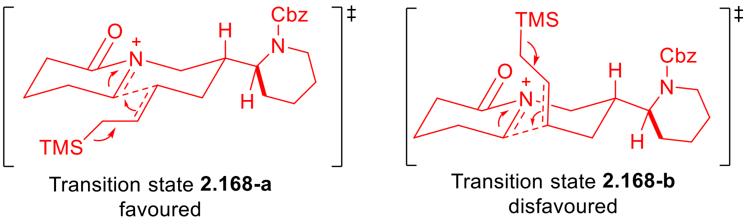
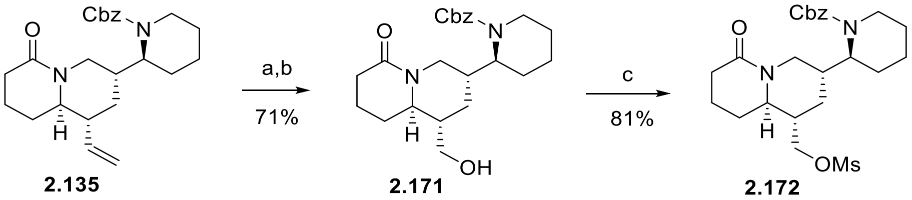


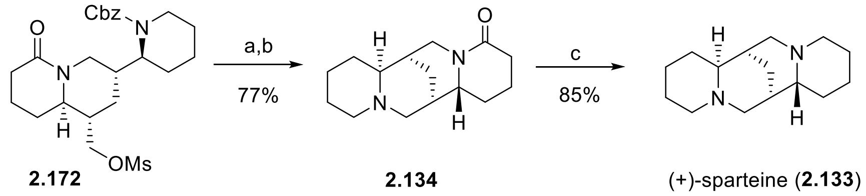
Figure 2.22. Proposed cyclisation transition states for explaining the selectivity.

In order to prove that the required configuration of sparteine has been established, the next step was to investigate the final ring closure. Employing the one-pot ozonolysis and reduction conditions described by Lv *et al.*,[135] the alkene cleavage of **2.135** was performed with O_3 at –78 °C in CH_2Cl_2 (**Scheme 2.50**). A clear indication that the reaction proceeded to completion was observed when the solution colour turned blue from colourless. A nitrogen atmosphere was introduced until the solution became colourless again, followed by slow addition of $NaBH_4$ and warming to 0 °C to afford the alcohol **2.171**. The one-pot ozonolysis and reduction provided 71% overall yield. The alcohol **2.171** was subsequently converted into mesylate **2.172** in good yield.



Scheme 2.50. *Reagents and conditions*: a) O_3, –78 °C, CH_2Cl_2; b) $NaBH_4$, 0 °C, N_2, CH_2Cl_2, c) Ms-Cl, NEt_3, –78 °C, N_2.

To avoid loss of material by column chromatography, a one-pot deprotection and cyclisation was performed (**Scheme 2.51**). Hydrogenation of **2.172** over Pd/C smoothly cleaved the Cbz protecting group and the crude mixture was obtained by evaporation of the solvent after filtration. The crude mixture was re-dissolved in THF and stirred together with K_2CO_3. The 15-oxo-sparteine (**2.134**) was successfully formed in 77% isolated yield. A final reduction of 15-oxo-sparteine (**2.134**) by $LiAlH_4$ in THF under reflux completed the total synthesis of (+)-sparteine (**2.133**).

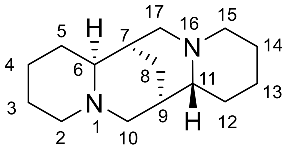


Scheme 2.51. *Reagents and conditions*: a) H_2, Pd/C, EtOH; b) K_2CO_3, THF; c) $LiAlH_4$, reflux, THF.

The asymmetric total synthesis of (+)-sparteine was achieved by 16 linear steps in 2.7% overall yield from the Weinreb amide **2.149**. All analytical data are consistent with those reported for the isolated natural product and previous reported synthetic products (**Table 2.08**).

^{13}C NMR:

(+)-Sparteine



Assignment carbon	Literature δ ppm[a]	Recorded δ ppm[b,c]	Δ δ
C-2	56.4	56.3	0.1
C-3	26.0	26.0	0
C-4	24.9	24.8	0.1
C-5	29.5	29.3	0.2
C-6	66.6	66.6	0
C-7	36.1	36.1	0
C-8	27.7	27.7	0
C-9	33.1	33.1	0
C-10	62.1	62.0	0.1
C-11	64.6	64.5	0.1
C-12	34.7	34.7	0
C-13	24.8	24.7	0.1
C-14	26.0	26.0	0
C-15	55.5	55.4	0.1
C-17	53.7	53.7	–0.1

Optical Rotation:

$[\alpha]_D$: +16 (c 0.25, EtOH, 23 °C).

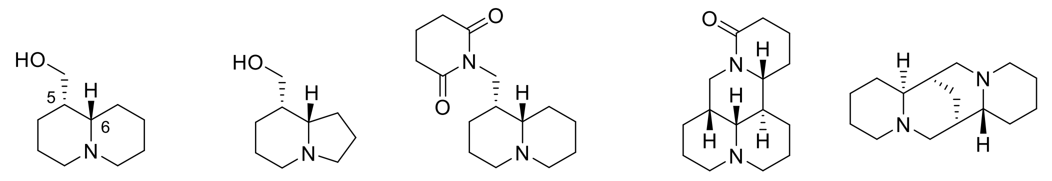
Literature data:

$[\alpha]_D$: +19.2 (c 0.5, EtOH, 23 °C)[136], $[\alpha]_D$: +21.2 (c 1.6, EtOH, 23 °C)[67].

Table 2.08. Comparison of literature and recorded data for (+)-sparteine (**2.133**).
[a] 125 MHz in $CDCl_3$[67]; [b] 101 MHz in $CDCl_3$; [c] current work.

2.6 Conclusions

In conclusion, we have developed a highly *anti*-diastereoselective formal imino-aldol strategy for alkaloid synthesis. The stereochemistry control is well established at an early stage of the synthesis of *β*-amino ester which offers advantages in higher diastereoselectivity, simpler reaction procedure and cheaper reagent costs. A selection of sulfinyl imines were used in formal *anti* imino-aldol reaction to determine the tolerance of the reaction to different functionality. And this versatile approach has been applied to asymmetric total synthesis of 5 alkaloids, including (+)-lupinine, (–)-epitashiromine, (–)-epilamprolobine, (+)-isosophoridine and (+)-sparteine (**Figure 2.23**). The total synthesis of bicyclic lupin alkaloid (+)-lupinine was successfully completed in 23% yield over 8 linear steps. The excellent stereocontrol at C-5 and C-6 was achieved by using a *p*-tolylsulfinyl auxiliary mediated imino-aldol and *anti*-alkylation reaction sequence, which provided over 10:1 *dr*. RCM was used to access the 6,6-membered bicyclic ring. This ring closure strategy allowed access 5,6-membered ring system by simply changing the length of carbon chain. Following the same reaction sequence used in (+)-lupinine, the total synthesis of (–)-epitashiromine was achieved in 8 steps in 20% yield. By coupling a glutarimide group to the same piperidine intermediate used in (+)-lupinine synthesis, the first asymmetric total synthesis of (–)-epilamprolobine was achieved in 9 steps 19% overall yield.



(+)-lupinine
8 steps, 23% yield.

(–)-epitashiromine
8 steps, 20% yield.

(–)-epilamprolobine
9 steps, 19% yield.

(+)-isosophoridine
10 steps, 10% yield.

(+)-sparteine
16 steps, 2.7% yield.

Figure 2.23. Overall yields of total syntheses of lupin alkaloids.

Two tetracyclic lupin alkaloids were formed using the *anti*-diastereoselective formal imino-aldol approach and *N*-acyliminium cyclisation as key steps. The first asymmetric total synthesis of (+)-isosophoridine was completed in 10 steps in 10% overall yield. A modified one-pot cross metathesis and imine condensation was used to prepare allylsilane-based *α,β*-unsaturated imine. The two chiral centres established by *anti*-alkylation resulted in excellent diastereocontrol of the subsequent allylsilane-induced *N*-acyliminium cyclisation. Following a similar strategy, the asymmetric total synthesis of (+)-sparteine was achieved by 16 linear steps in 2.7% overall yield. The main obstacle to be overcome in (+)-sparteine synthesis was to install allylsilane group in the *anti*-alkylation moiety. Cross metathesis caused a large amount isomerisation for a long chain system. This isomerisation was prevented by using benzoquinone as additive.

Our total syntheses were enabled by the development of key synthetic methodologies, such as *anti*-selective formal imino-aldol reaction, *N*-acyliminium cyclisation for assembling of tricyclic system and benzoquinone mediated long chain cross metathesis. These new methods offer a high degree of flexibility for the synthesis of lupin type alkaloids, and complement our previously reported *syn*-selective approach.

2.7 Future work

As an extension to this *anti*-selective formal imino-aldol method, we would like to investigate preparing chiral piperidine analogues with a wide range of different substituted sulfinyl imines. Using the synthetic route in (+)-lupinine synthesis, the cyclic amines could be rapidly assembled by a deprotection and *N*-alkylation sequence (**Figure 2.24**. These would be useful intermediates for the synthesis of bioactive compound libraries.

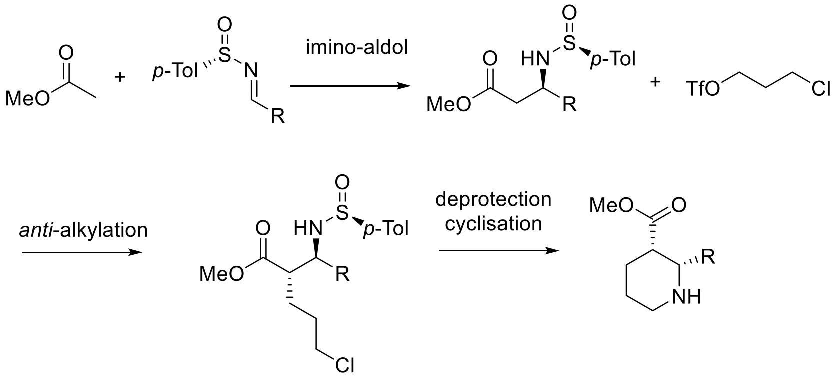


Figure 2.24. Proposed route for piperidine analogues using *anti* imino-aldol method.

There are also some improvements that could be made to the sparteine synthesis. For a (–)-sparteine synthetic route (**Figure 2.25**), the *t*-butyl sulfinyl imine with chloride at the end could be formed in a high yield. Based on previously research, the imino-aldol reaction of this chiral auxiliary afford a good selectivity. And then replacing the auxiliary by -Cbz protecting group is worth to investigate the selectivity of *anti*-alkylation. The following ring-closure would save two steps than before which used a mesylate as leaving group. In particular, the CM approach to the allyl silane intermediate using 1,4-benzoquinone to prevent isomerisation should be repeated on a larger scale. Functionalisation the internal alkene with different boron hydride reagents is still under investigation.

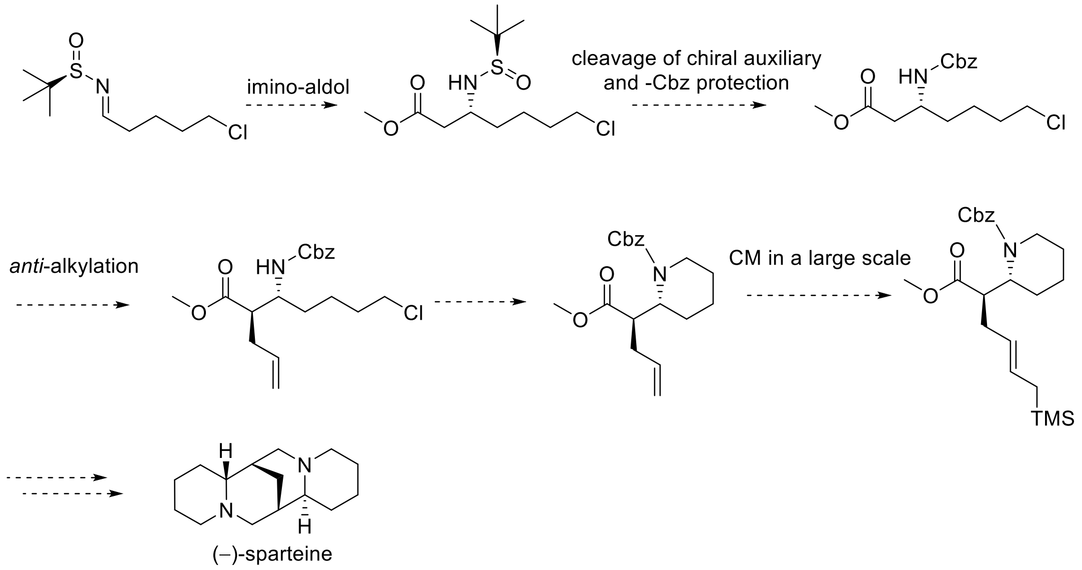


Figure 2.25. Proposed improved route for (–)-spartenine synthesis.

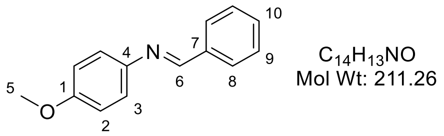
Chapter 3: Experimental

3.1 General Methods

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific or Alfa Aesar. All air/moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame-dried glassware. The solvents THF (from Na/benzophenone), CH_3CN and CH_2Cl_2 (from CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques. TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} indicator; visualised under UV light (254 nm) and/or by staining with anisaldehyde, ceric ammonium molybdate, iodine, phosphomolybdic acid, potassium permanganate or vanillin. Flash column chromatography was performed using high purity silica gel, pore size 60 Å, 230-400 mesh particle size, purchased from Merck. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-*d*$_6$ solutions (purchased from Cambridge Isotope Laboratories) at 298 K using Bruker DPX400 (400 and 101 MHz respectively) spectrometers. Chemical shifts are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra; DMSO-*d*$_6$: 2.50 ppm for ^1H NMR spectra and 39.51 ppm for ^{13}C NMR spectra; ^{19}F NMR chemical shifts were referenced to $CFCl_3$ at 0.0 ppm). To aid interpretation of the spectra for selected compounds variable temperature NMR experiments at $T = 353$ K and 373 K were conducted. All spectra were reprocessed using ACD/Labs software version 2015 or ACD/Spectrus. Coupling constants (*J*) were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), spt (septet), br (broad), and m (multiplet). Electrospray (ES) low resolution mass spectra were recorded on a Waters TQD quadrupole spectrometer. Electron impact (EI) low resolution mass spectra were recorded on a Trace 2000 Series GC-MS. High resolution mass spectra were recorded on a Bruker APEX III FT-ICR mass spectrometer. Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 fitted with a Smart Orbit Goldengate attachment using OMNIC software package. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra. Melting points were obtained using a Gallenkamp Electrothermal apparatus. Analytical HPLC was performed on an Agilent 1220 Infinity LC System utilising the Agilent EZChrom software package eluting either from Daicel Chiralcel® OD-H or AD-H columns eluting with IPA/hexane mixtures. Microwave synthesis was performed in a sealed tube using a CEM discover microwave synthesizer.

3.2 Procedures and Characterisation Data

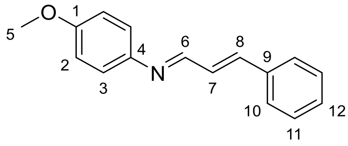
(*E*)-*N*-(4-Methoxyphenyl)-1-phenylmethanimine (2.07)



A solution of benzaldehyde (2.30 mL, 20.3 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled to 0 °C. After successively adding $MgSO_4$ (9.70 g, 80.6 mmol) and *para*-methoxyaniline (2.50 g, 20.3 mmol), the mixture was stirred under N_2 for 30 min and then allowed to warm to rt. After 12 h, $MgSO_4$ was removed by filtration and the residue was washed with CH_2Cl_2. The solvent was removed under reduced pressure and the crude material was recrystallised from petroleum ether to give a white crystalline product (3.70 g, 17.5 mmol, 87%). The physical and spectroscopic data recorded were consistent with those reported.[137]

Melting Point:	67–68 °C. (Lit.[137] 68–70 °C).
IR-FT(cm^{-1}):	1621, 1245, 1028, 831, 718.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 8.50 (s, 1H, **H**$_6$), 7.95 – 7.86 (m, 2H, **H**$_8$), 7.51 – 7.44 (m, 3H, **H**$_9$ & **H**$_{10}$), 7.29 – 7.22 (m, 2H, **H**$_3$), 6.95 (d, *J* = 8.0 Hz, 2H, **H**$_2$), 3.85 (s, 3H, **H**$_5$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 158.4 (**C**$_6$), 158.3 (**C**$_1$), 144.9 (**C**$_4$), 136.5 (**C**$_7$), 131.1 (**C**$_{10}$), 128.8 (**C**$_8$), 128.6 (**C**$_9$), 122.2 (**C**$_3$), 114.4 (**C**$_2$), 55.5 (**C**$_5$).

(1*E*,2*E*)-*N*-(4-Methoxyphenyl)-3-phenylprop-2-en-1-imine (2.21)



$C_{16}H_{15}NO$
Mol Wt: 237.30

Following the procedure described above for the synthesis of imine **2.07**, cinnamaldehyde (2.60 mL, 20.3 mmol) afforded the title compound as bright yellow crystals (2.60 g, 11.0 mmol, 80%). The physical and spectroscopic data recorded were consistent with those reported.[137]

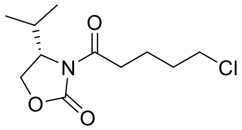
Melting Point: 118–121 °C. (Lit.[137] 119–121 °C).

IR-FT(cm^{-1}): 1627, 1246, 1029, 824, 743, 692.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.31 (t, *J* = 4.2 Hz, 1H, **H**$_6$), 7.58 – 7.51 (m, 2H, **H**$_{11}$), 7.43 – 7.32 (m, 3H, **H**$_{10}$ & **H**$_{12}$), 7.22 (d, *J* = 8.9 Hz, 2H, **H**$_3$), 7.17 – 7.08 (m, 2H, **H**$_7$ & **H**$_8$), 6.93 (d, *J* = 8.9 Hz, 2H, **H**$_2$), 3.84 (s, 3H, **H**$_5$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 159.5 (**C**$_6$), 158.4 (**C**$_1$), 144.6 (**C**$_4$), 143.0 (**C**$_8$), 135.8 (**C**$_9$), 129.4 (**C**$_{11}$), 128.9 (**C**$_7$), 128.8 (**C**$_{12}$), 127.4 (**C**$_{10}$), 122.2 (**C**$_3$), 114.5 (**C**$_2$), 55.5 (**C**$_5$).

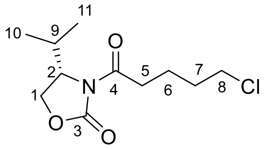
(*S*)-3-(5-Chloropentanoyl)-4-isopropyloxazolidin-2-one (2.06)



$C_{11}H_{18}ClNO_3$
Mol Wt: 247.72

By adaption of a procedure by Hettche *et al.*,[87] to a solution of 5-chlorovaleric acid (3.30 g, 24.0 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C under N_2 was added anhydrous DMF (4 drops) followed by dropwise addition of oxalyl chloride (2.40 mL, 28.8 mmol). The reaction was stirred for 1 h at 0 °C and then warmed to rt, with continued stirring for 4 h. When the reaction reached completion and gas evolution ceased, the reaction mixture was concentrated *in vacuo* giving 5-chloropentanoyl chloride as colourless oil, which was used directly in the next step.

A solution of *n*-BuLi (10.4 mL of 2.3 M in hexane, 24.0 mmol) was added dropwise to a stirred solution of (*S*)-4-isopropyl-2-oxazolidinone (2.60 g, 20.1 mmol) in anhydrous THF (80 mL) at –78 °C. After stirring the solution at –78 °C for 30 min, the freshly prepared 5-chloropentanoyl chloride was added dropwise. The mixture was stirred at –78 °C for 20 min, and then warmed to –10 °C for 2 h. The reaction was quenched with aq. K_2CO_3 (50 mL of 1.0 M) at –78 °C, then allowed to warm to rt. The phases were separated and the aqueous layer extracted with EtOAc (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:9) yielded the title product as a yellow solid (4.60 g, 18.6 mmol, 93%). The physical and spectroscopic data were consistent with those reported in literature.[87]



Melting Point: 36–38 °C. (not previously reported)

[α]$_D$: +69 (c 1.1, $CHCl_3$, 23 °C). Lit.[87] +59.4 (c 4.3, $CHCl_3$, 20 °C).

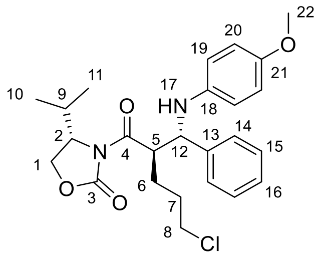
FT-IR (cm^{-1}): 2962, 2875, 1772, 1697, 1385, 1204.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 4.43 (dt, *J* = 8.2, 3.3 Hz, 1H, **H**$_2$), 4.33 – 4.16 (m, 2H, **H**$_1$), 3.56 (t, *J* = 5.9 Hz, 2H, **H**$_8$), 3.06 – 2.85 (m, 2H, **H**$_5$), 2.44 – 2.32 (m, 1H, **H**$_9$), 1.90 – 1.76 (m, 4H, **H**$_6$ & **H**$_7$), 0.92 (d, *J* = 7.0 Hz, 3H, **H**$_{10}$), 0.87 (d, *J* = 7.0 Hz, 3H, **H**$_{11}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 172.6 (**C**$_4$), 154.1 (**C**$_3$), 63.4 (**C**$_1$), 58.4 (**C**$_2$), 44.6 (**C**$_8$) 34.7 (**C**$_5$), 31.9 (**C**$_7$), 28.4 (**C**$_9$),21.7 (**C**$_6$), 18.0 (**C**$_{10}$), 14.7 (**C**$_{11}$).

LRMS: (ES+) m/z = 248.0 [M+H]$^+$.

(*S*)-3-((2*R*,3*S*)-2-(2-Chloroethyl)-4-((4-methoxyphenyl)amino)-3-phenylbutanoyl)-4-isopropyloxazolidin-2-one (2.08)



$C_{25}H_{31}ClN_2O_4$
Mol Wt: 458.98

By adaption of a procedure by Sasikal *et al.*,[79] to a solution of oxazolidinone **2.06** (0.200 g, 0.807 mmol) in anhydrous CH_2Cl_2 (5 mL) at –78 °C under N_2 was added dropwise a solution of $TiCl_4$ (1.74 mL of 1.0 M in CH_2Cl_2, 1.74 mmol) followed by anhydrous DIPEA (160 µL, 0.918 mmol). After stirring at –78 °C for 1 h, a solution of imine **2.07** (0.130 g, 0.616 mmol) in CH_2Cl_2 (5 mL) was added dropwise. This reaction was stirred for 2 h before quenching with sat. NH_4Cl (20 mL). The reaction was allowed to warm to rt and stirred for 30 min. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (hexane:acetone – 9:1 to 8:2) yielded the title product as a yellow oil (0.280 g, 0.611 mmol, 99%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.35 – 7.19 (m, 5H, **H**$_{14}$, **H**$_{15}$ & **H**$_{16}$), 6.65 (d, *J* = 8.9 Hz, 2H, **H**$_{19}$), 6.48 (d, *J* = 8.9 Hz, 2H, **H**$_{20}$), 4.82 (br s, 1H, **H**$_{17}$), 4.54 – 4.40 (m, 3H, **H**$_2$, **H**$_5$ & **H**$_{12}$), 4.34 – 4.16 (m, 2H, **H**$_1$), 3.68 (s, 3H, **H**$_{22}$), 3.58 (t, *J* = 6.0, Hz, 2H, **H**$_8$), 2.31 – 2.21 (m, 1H, **H**$_9$), 2.02 – 1.80 (m, 1H, **H**$_{6a}$), 1.72 – 1.62 (m, 2H, **H**$_7$), 1.50 – 1.38 (m, 1H, **H**$_{6b}$), 0.85 (d, *J* = 7.0 Hz, 3H, **H**$_{10}$), 0.63 (d, *J* = 7.0 Hz, 3H, **H**$_{11}$).

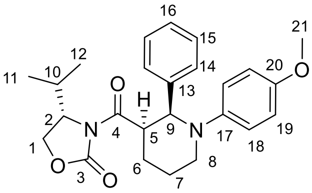
^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 175.3 (**C**$_4$), 154.7 (**C**$_3$), 152.2 (**C**$_{21}$), 141.0 (**C**$_{18}$), 140.6 (**C**$_{13}$), 128.7 (**C**$_{15}$), 127.6 (**C**$_{14}$), 127.1 (**C**$_{16}$), 115.5 (**C**$_{19}$), 114.6 (**C**$_{20}$), 63.2 (**C**$_{12}$), 62.2 (**C**$_1$), 59.2 (**C**$_2$), 55.6 (**C**$_{22}$), 47.7 (**C**$_5$), 44.3 (**C**$_8$), 30.5 (**C**$_7$), 28.2 (**C**$_6$), 28.0 (**C**$_9$), 17.9 (**C**$_{10}$), 14.2 (**C**$_{11}$).

LRMS: (ES+) m/z = 459.2 $[M+H]^+$.

Selected data for the *syn* diastereoisomer:

^{1}H NMR: ($CDCl_3$, 101 MHz) δ ppm = 5.31 (br s, 1H, N$\underline{H}$), 3.70 (s, 3H, O$\underline{Me}$)

(*S*)-4-Isopropyl-3-((3*S*,4*R*)-1-(4-methoxyphenyl)-3-phenylpiperidine-4-carbonyl)oxazolidin-2-one (2.09)



$C_{25}H_{30}N_2O_4$
Mol Wt: 422.53

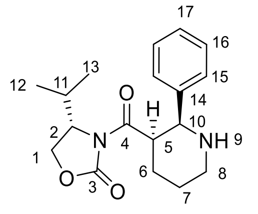
The imino-aldol adduct **2.08** (0.280 g, 0.611 mmol) was dissolved in MeCN (5 mL), then K_2CO_3 (0.690 g, 4.96 mmol) and NaI (12.4 mg, 0.0827 mmol) were added portionwise. The resulting brown solution was stirred for 48 h. The solution was removed *in vacuo*, and the residue partitioned between EtOAc:H_2O (1:1 – 20 mL) and the layers were separated. The aqueous layer was re-extracted with EtOAc (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (hexane:EtOAc – 95:5 to 80:20) gave the title piperidine as a yellow oil (0.230 g, 0.545 mmol, 88%).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.24 – 7.17 (m, 2H, $\mathbf{H}_{14}$), 7.17 – 7.07 (m, 3H, $\mathbf{H}_{15}$ & $\mathbf{H}_{16}$), 6.89 (d, *J* = 9.1 Hz, 2H, $\mathbf{H}_{18}$), 6.72 (d, *J* = 9.1 Hz, 2H, $\mathbf{H}_{19}$), 5.30 (d, *J* = 5.4 Hz, 1H, $\mathbf{H}_{9}$), 4.41 – 4.33 (m, 2H, $\mathbf{H}_{2}$ & $\mathbf{H}_{5}$), 4.21 (t, *J* = 8.9 Hz, 1H, $\mathbf{H}_{1a}$), 4.11 (dd, *J* = 8.9, 3.1 Hz, 1H, $\mathbf{H}_{1b}$), 3.71 (s, 3H, $\mathbf{H}_{21}$), 3.36 – 3.27 (m, 1H, $\mathbf{H}_{8eq}$), 3.13 – 3.01 (m, 1H, $\mathbf{H}_{8ax}$), 2.47 – 2.35 (m, 1H, $\mathbf{H}_{6eq}$), 2.13 – 2.06 (m, 1H, $\mathbf{H}_{7eq}$), 1.98 – 1.74 (m, 2H, $\mathbf{H}_{6ax}$ & $\mathbf{H}_{7ax}$), 1.73 – 1.62 (m, 1H, $\mathbf{H}_{10}$), 0.69 (d, *J* = 7.0 Hz, 3H, $\mathbf{H}_{11}$), 0.42 (d, *J* = 7.0 Hz, 3H, $\mathbf{H}_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 172.5 ($\mathbf{C}_{4}$), 153.8 ($\mathbf{C}_{3}$), 153.7 ($\mathbf{C}_{20}$), 145.0 ($\mathbf{C}_{17}$), 138.5 ($\mathbf{C}_{13}$), 129.3 ($\mathbf{C}_{15}$), 127.6 ($\mathbf{C}_{14}$), 127.1 ($\mathbf{C}_{16}$), 120.9 ($\mathbf{C}_{18}$), 114.1 ($\mathbf{C}_{19}$), 63.1 ($\mathbf{C}_{9}$), 62.3 ($\mathbf{C}_{1}$), 58.2 ($\mathbf{C}_{2}$), 55.4 ($\mathbf{C}_{21}$), 46.7 ($\mathbf{C}_{5}$), 45.0 ($\mathbf{C}_{8}$), 28.1 ($\mathbf{C}_{10}$), 23.7 ($\mathbf{C}_{6}$), 23.0 ($\mathbf{C}_{7}$), 17.9 ($\mathbf{C}_{11}$), 14.3 ($\mathbf{C}_{12}$).

LRMS: (ES+) m/z = 423.3 $[M+H]^+$.

(*S*)-4-Isopropyl-3-((2*S*,3*R*)-2-phenylpiperidine-3-carbonyl)oxazolidin-2-one (2.10)

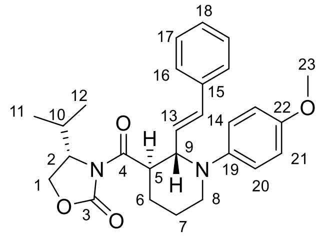


$C_{18}H_{24}N_2O_3$
Mol Wt: 316.40

By adaption of a procedure by Hughes *et al.*,[91] to a solution of **2.09** (42.0 mg, 0.0995 mmol) in MeCN (2.5 mL) at 0 °C was added a solution of ammonium cerium nitrate (0.240 g, 0.438 mmol) in H_2O (1.5 mL). Then the pH was adjusted to ~1 by addition of aq. HCl (2.0 M). The resulting solution was stirred for 2 h. The solution was basified by the addition of $NaHCO_3$ (sat.), and then extracted with EtOAc (3 x 4 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo,* providing title compound as a brown oil (28.4 mg, 0.0899 mmol, 90%).

^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 7.35 – 7.24 (m, 4H, **H_{15}** & **H_{16}**), 7.21 – 7.14 (m, 1H, **H_{17}**), 4.57 – 4.50 (m, 1H, **H_{10}**), 4.33 – 4.27 (m, 1H, **H_2**), 4.19 – 4.11 (m, 1H, **H_{1a}**), 4.05 – 4.00 (m, 2H, **H_{1b}** & **H_5**), 3.45 – 3.37 (m, 1H, **H_{8eq}**), 2.82 (td, *J* = 13.1, 3.1 Hz, 1H, **H_{8ax}**), 2.35 (br s, 1H, **H_9**), 2.13 – 2.06 (m, 2H, **H_6**), 1.80 – 1.65 (m, 2H, **H_{11}** & **H_{7eq}**), 1.58 – 1.47 (m, 1H, **H_{7ax}**), 0.66 (d, *J* = 7.0 Hz, 3H, **H_{12}**), 0.24 (d, *J* = 7.0 Hz, 3H, **H_{13}**).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 174.1 (**C_4**), 153.6 (**C_3**), 141.8 (**C_{14}**), 128.2 (**C_{16}**), 126.7 (**C_{17}**), 126.0 (**C_{15}**), 62.6 (**C_{10}**), 61.2 (**C_1**), 58.1 (**C_2**), 46.9 (**C_5**), 40.6 (**C_8**), 28.1 (**C_{11}**), 27.2 (**C_6**), 21.5 (**C_7**), 17.7 (**C_{12}**), 13.8 (**C_{13}**).
LRMS:	(ES+) m/z = 317.2 $[M+H]^+$.

1-(4-Methoxyphenyl)-2-((*E*)-styryl)piperidine-3-carbonyl)oxazolidin-2-one (2.24)



$C_{27}H_{32}N_2O_4$
Mol Wt: 448.56

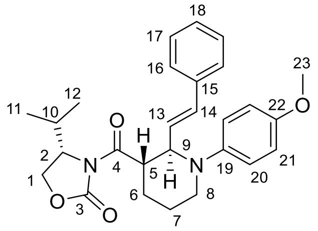
By adaption of a procedure by Sasikal *et al.*,[79] to a solution of oxazolidinone **2.06** (0.200 g, 0.807 mmol) in anhydrous CH_2Cl_2 (5 mL) at –78 °C under N_2 was added dropwise a solution of $TiCl_4$ (1.74 mL of 1.0 M in CH_2Cl_2, 1.74 mmol) followed by addition of dry DIPEA (450 µL, 2.43 mmol). After stirring at –78 °C for 1 h, a solution of imine **2.21** (0.150 g, 0.632 mmol) in CH_2Cl_2 (5 mL) was added dropwise. This reaction was stirred for 2 h before quenching with sat. NH_4Cl (20 mL). The reaction was allowed to warm to rt and stirred for 30 min. The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was a mixture of two *syn* diastereoisomers **2.24** and **2.23** (integration of $\mathbf{H}_{13}$ peak in ^{1}H NMR spectrum showed *dr* 4:3). Purification by column chromatography (hexane:acetone – 9:1 to 8:2) yielded the major diastereoisomeric piperidine as a yellow oil (0.130 g, 0.290 mmol, 38%). The relative chemistry of **2.24** and **2.23** in the piperidine ring were assigned to be *trans*, but the absolute stereochemistry was not assigned.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.22 – 7.10 (m, 5H, $\mathbf{H}_{16}$, $\mathbf{H}_{17}$ & $\mathbf{H}_{18}$), 7.05 (d, *J* = 8.8 Hz, 2H, $\mathbf{H}_{20}$), 6.75 (d, *J* = 8.8 Hz, 2H, $\mathbf{H}_{21}$), 6.31 (d, *J* = 16.1 Hz, 1H, $\mathbf{H}_{14}$), 5.97 (dd, *J* = 16.1, 8.6 Hz, 1H, $\mathbf{H}_{13}$), 4.41 (dt, *J* = 8.6, 3.1 Hz, 1H, $\mathbf{H}_{2}$), 4.22 – 4.12 (m, 2H, $\mathbf{H}_{1a}$ & $\mathbf{H}_{5}$), 4.08 (dd, *J* = 9.1, 3.1 Hz, 1H, $\mathbf{H}_{1b}$), 3.94 (t, *J* = 8.6 Hz, 1H, $\mathbf{H}_{9}$), 3.72 (s, 3H, $\mathbf{H}_{23}$), 3.21 (br dt, *J* = 11.7, 3.4 Hz, 1H, $\mathbf{H}_{8eq}$), 2.91 – 2.81 (m, 1H, $\mathbf{H}_{8ax}$), 2.10 – 1.97 (m, 2H, $\mathbf{H}_{10}$ & $\mathbf{H}_{6eq}$), 1.93 – 1.82 (m, 2H, $\mathbf{H}_{7}$), 0.91 – 0.82 (m, 1H, $\mathbf{H}_{6ax}$), 0.72 (d, *J* = 7.0 Hz, 3H, $\mathbf{H}_{11}$), 0.28 (d, *J* = 7.0 Hz, 3H, $\mathbf{H}_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 174.6 ($\mathbf{C}_{4}$), 155.9 ($\mathbf{C}_{3}$), 153.7 ($\mathbf{C}_{22}$), 145.5 ($\mathbf{C}_{19}$), 136.9 ($\mathbf{C}_{15}$), 132.8 ($\mathbf{C}_{13}$), 130.0 ($\mathbf{C}_{14}$), 128.3 ($\mathbf{C}_{16}$), 127.3 ($\mathbf{C}_{18}$), 126.2 ($\mathbf{C}_{17}$), 125.7 ($\mathbf{C}_{20}$), 113.9 ($\mathbf{C}_{21}$), 65.3 ($\mathbf{C}_{9}$), 62.7 ($\mathbf{C}_{1}$), 58.3 ($\mathbf{C}_{2}$), 55.5 ($\mathbf{C}_{8}$), 55.3 ($\mathbf{C}_{23}$), 46.4 ($\mathbf{C}_{5}$), 28.2 ($\mathbf{C}_{10}$), 27.4 ($\mathbf{C}_{6}$), 25.0 ($\mathbf{C}_{7}$), 17.9 ($\mathbf{C}_{11}$), 13.7 ($\mathbf{C}_{12}$).

LRMS: (ES+) *m/z* = 449.3 $[M+H]^+$.

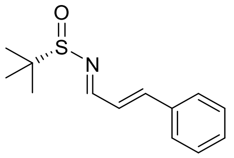
After further chromatography, the minor diastereoisomer **2.23** was obtained as an inseparable mixture with **2.24**. Selected NMR data for **2.23**:



^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 7.38 – 7.18 (m, 5H, **H**$_{16}$, **H**$_{17}$ & **H**$_{18}$), 6.72 (d, *J* = 8.8 Hz, 2H, **H**$_{20}$), 6.58 (d, *J* = 8.8 Hz, 2H, **H**$_{21}$), 6.50 (d, *J* = 15.9 Hz, 1H, **H**$_{14}$), 6.08 (dd, *J* = 15.9, 7.8 Hz, 1H, **H**$_{13}$), 4.48 – 4.45 (m, 1H, **H**$_2$), 4.37 – 4.18 (m, 3H, **H**$_1$ & **H**$_5$), 4.13 (t, *J* = 7.8 Hz, 1H, **H**$_9$), 3.72 (s, 3H, **H**$_{23}$), 3.50 – 3.47 (m, 2H, **H**$_8$), 2.35 – 2.24 (m, 1H, **H**$_{10}$), 2.02 – 1.90 (m, 1H, **H**$_{6eq}$), 1.86 – 1.68 (m, 3H, **H**$_{6ax}$ & **H**$_7$), 0.84 (d, *J* = 7.0 Hz, 3H, **H**$_{11}$), 0.68 (d, *J* = 7.0 Hz, 3H, **H**$_{12}$).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 175.2 (**C**$_4$), 154.6 (**C**$_3$), 152.4 (**C**$_{22}$), 136.4 (**C**$_{15}$), 132.6 (**C**$_{13}$ & **C**$_{19}$), 128.5 (**C**$_{16}$), 127.7 (**C**$_{18}$), 126.5 (**C**$_{17}$), 115.7 (**C**$_{20}$), 114.7 (**C**$_{21}$), 63.2 (**C**$_9$), 60.6 (**C**$_2$), 59.2 (**C**$_1$), 55.7 (**C**$_{23}$), 46.4 (**C**$_8$), 44.4 (**C**$_5$), 30.5 (**C**$_{10}$), 28.3 (**C**$_6$), 27.7 (**C**$_7$), 17.9 (**C**$_{11}$), 14. 21 (**C**$_{12}$).

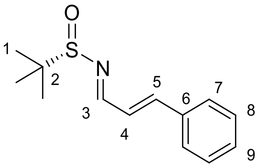
(*S*)-2-Methyl-*N*-((1*E*,2*E*)-3-phenylallylidene)propane-2-sulfinamide (2.57)



$C_{13}H_{17}NOS$
Mol Wt: 235.35

To a solution of (*S*)-*t*-butanesulfinamide (5.00 g, 41.3 mmol) and cinnamaldehyde (6.24 mL, 49.5 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under N_2 was added $Ti(OEt)_4$ (8.50 mL, 37.3 mmol) dropwise. The reaction was stirred for 1 h at rt and further $Ti(OEt)_4$ (8.50 mL, 37.3 mmol) was added dropwise. After 12 h, brine (100 mL) was added. The reaction was stirred rapidly for 5 min and filtered, washing filter cake with CH_2Cl_2 (4 × 50 mL). The phases were separated, re-extracting the aqueous layer with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) yielded the title product as a pale yellow oil (8.01 g, 34.0 mmol, 84%). The spectroscopic data were consistent with the literature.[138]

FT-IR (cm^{-1}): 1624, 1579, 1568, 1152, 1075, 749, 712, 688, 561.

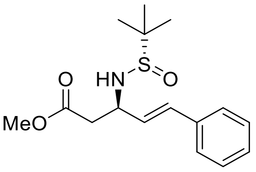


^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 8.38 (d, *J* = 9.0 Hz, 1H, **H**$_3$), 7.54 (dd, *J* = 7.7, 1.8 Hz, 2H, **H**$_7$), 7.43 – 7.37 (m, 3H, **H**$_8$ & **H**$_9$), 7.24 (d, *J* = 16.0 Hz, 1H, **H**$_5$), 7.09 (dd, *J* = 16.0, 9.0 Hz, 1H, **H**$_4$), 1.24 (s, 9H, **H**$_1$).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 163.8 (**C**$_3$), 146.4 (**C**$_5$), 135.0 (**C**$_6$), 130.2 (**C**$_9$), 129.0 (**C**$_7$), 127.9 (**C**$_8$), 125.6 (**C**$_4$), 57.6 (**C**$_2$), 22.5 (**C**$_1$).

LRMS: (ES+) *m/z* = 236.2 [M+H]$^+$.

Methyl (*R*,*E*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-phenylpent-4-enoate (2.61)

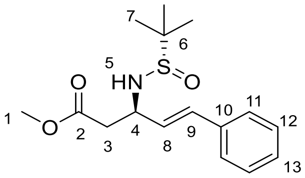


$C_{16}H_{23}NO_3S$
Mol Wt: 309.42

A solution of methyl acetate (3.72 mL, 46.8 mmol) in anhydrous THF (40 mL) was added dropwise to the RBF containing a solution of NaHMDS (51.5 mL of 1.0 M in THF, 51.5 mmol) at –78 °C under N$_2$. After addition, the N$_2$ flow was removed and the round bottom flask was sealed to avoid evaporation of volatile methyl acetate. The reaction was stirred for 1 h at –78 °C then a solution of sulfinimine **2.57** (5.50 g, 23.4 mmol) in anhydrous THF (20 mL) was added dropwise over 20 min. The reaction was stirred at –78 °C for 2 h and quenched with sat. NH$_4$Cl (10 mL) at the same temperature. The mixture was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 40 mL). The organic phases were combined, washed with brine (40 mL), dried (MgSO$_4$), and concentrated *in vacuo* to yield the crude product as a separable mixture of two diastereoisomers (integration of the N$\underline{H}$ peaks in the crude ^{1}H NMR spectrum showed *dr* 10:1). Purification by column chromatography (EtOAc:hexane – 1:9) afforded the major diastereoisomer as a yellow oil (6.51 g, 21.1 mmol, 91%).

[α]$_D$: +226 (c 0.7, $CHCl_3$, 23 °C),

FT-IR (cm^{-1}): 3206, 2953, 1731, 1169, 1048, 749, 693.



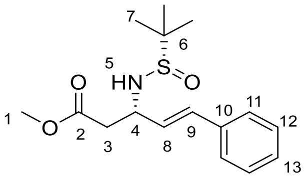
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.41 – 7.26 (m, 5H, **H**$_{11}$, **H**$_{12}$ & **H**$_{13}$), 6.64 (d, *J* = 15.9 Hz, 1H, **H**$_9$), 6.11 (dd, *J* = 15.9, 9.1 Hz, 1H, **H**$_8$), 4.44 – 4.35 (m, 2H, **H**$_4$ & **H**$_5$), 3.71 (s, 3H, **H**$_1$), 2.87 – 2.70 (m, 2H, **H**$_3$), 1.25 (s, 9H, **H**$_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 171.8 (**C**$_2$), 136.3 (**C**$_{10}$), 132.5 (**C**$_8$), 128.6 (**C**$_9$ & **C**$_{12}$), 128.0 (**C**$_{13}$), 126.6 (**C**$_{11}$), 55.7 (**C**$_4$), 54.4 (**C**$_6$), 51.9 (**C**$_1$), 40.7 (**C**$_3$), 22.7 (**C**$_7$).

LRMS: (ES+) m/z = 236.2 $[M+H]^+$.

HRMS: (ES+) for $C_{16}H_{23}NaNO_3S^+$ calculated 332.1296, found 332.1293 Da.

The minor diastereoisomer was isolated from reaction mixture as a yellow oil (0.220 g, 0.711 mmol, 3%).



FT-IR (cm^{-1}): 3208, 2952, 1735, 1165, 1051, 750, 694.

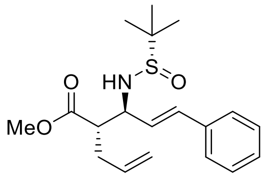
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.42 – 7.22 (m, 5H, **H**$_{11}$, **H**$_{12}$ & **H**$_{13}$), 6.65 (d, *J* = 16.0 Hz, 1H, **H**$_9$), 6.30 (dd, *J* = 16.0, 6.8 Hz, 1H, **H**$_8$), 4.42 (quin, *J* = 6.8 Hz, 1H, **H**$_4$), 3.77 (d, *J* = 6.8 Hz, 1H, **H**$_5$), 3.70 (s, 3H, **H**$_1$), 2.83 – 2.69 (m, 2H, **H**$_3$), 1.22 (s, 9H, **H**$_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 171.4 (**C**$_2$), 136.2 (**C**$_{10}$), 132.2 (**C**$_8$), 129.1 (**C**$_9$), 128.6 (**C**$_{12}$), 128.0 (**C**$_{13}$), 126.7 (**C**$_{11}$), 56.1 (**C**$_4$), 55.2 (**C**$_6$), 51.8 (**C**$_1$), 40.7 (**C**$_3$), 22.5 (**C**$_7$).

LRMS: (ES+) m/z = 310.2 $[M+H]^+$.

HRMS: (ES+) for $C_{16}H_{23}NaNO_3S^+$ calculated 332.1293, found 332.1291 Da.

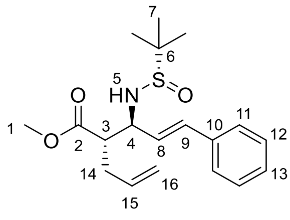
Methyl (2*S*,3*S*,*E*)-2-allyl-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-phenylpent-4-enoate (2.64)



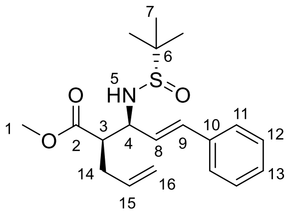
$C_{19}H_{27}NO_3S$
Mol Wt: 349.49

By adaption of a procedure by Davis *et al.*,[100] a round bottom containing LiCl (0.130 g, 3.20 mmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (800 µL of 1.0 M in THF, 0.800 mmol) was added dropwise. To the solution was added dropwise *β*-amino ester **2.61** (0.100 g, 0.323 mmol) in anhydrous THF (5 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then allyl iodide (90 µL, 0.984 mmol) in anhydrous THF (2 mL) was added dropwise and the solution was allowed to warm to –50 °C (dry ice/MeCN) and then stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (10 mL) and the phases were separated, re-extracting the aqueous layer with EtOAc (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) gave the *anti* imino-aldol as an inseparable mixture containing the *syn* isomer as a yellow oil (90.1 mg, 0.258 mmol, 80%). Integration of the **H**$_3$ peaks in the crude ^{1}H NMR spectrum allowed estimation of the *anti:syn* ratio (*dr* 5.5:1).

Data were recorded for the 5.5:1 mixture of diastereosiomers.



major *anti*-diastereoisomer



minor *syn*-diastereoisomer

^{1}H NMR: ($CDCl_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.42 – 7.24 (m, 5H, **H**$_{11}$, **H**$_{12}$, & **H**$_{13}$), 6.61 (d, *J* = 15.9 Hz, 1H, **H**$_9$), 6.07 (dd, *J* = 15.9, 7.8 Hz, 1H, **H**$_8$), 5.77 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H, **H**$_{15}$), 5.15 (br d, *J* = 17.0 Hz, 1H, **H**$_{16trans}$), 5.08 (br d, *J* = 10.1 Hz, 1H, **H**$_{16cis}$), 4.29 (br d, *J* = 5.1 Hz, 1H, **H**$_5$), 4.24 – 4.17 (m, 1H, **H**$_4$), 3.71 (s, 3H, **H**$_1$), 2.84 – 2.76 (m, 1H, **H**$_3$), 2.52 – 2.45 (m, 2H, **H**$_{14}$), 1.23 (s, 9H, **H**$_7$).

($CDCl_3$, 400 MHz, selected signals reported for the *syn* diastereoisomer) δ ppm = 6.62 (br d, *J* = 15.9 Hz, 1H, **H**$_9$), 3.70 (s, 3H, **H**$_1$), 2.96 – 2.89 (m, 1H, **H**$_3$).

^{13}C NMR: (CDCl$_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 174.0 (**C**$_2$), 136.3 (**C**$_{10}$), 134.5 (**C**$_{15}$), 133.2 (**C**$_8$), 128.6 (**C**$_{12}$), 128.2 (**C**$_{13}$), 128.0 (**C**$_9$), 126.6 (**C**$_{11}$), 117.8 (**C**$_{16}$), 58.9 (**C**$_4$), 55.9 (**C**$_6$), 51.9 (**C**$_1$), 50.3 (**C**$_3$), 33.7 (**C**$_{14}$) 22.7 (**C**$_7$).

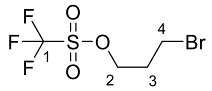
(CDCl$_3$, 101 MHz selected signals reported for the *syn* diastereoisomer) δ ppm = 171.2 (**C**$_2$), 58.3 (**C**$_4$), 32.6 (**C**$_{14}$), 22.68 (**C**$_7$),

LRMS: (ES+) m/z = 372.4 [M+H]$^+$.

Selected data for the *syn* diastereoisomer:

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 2.96 – 2.85 (m, 1H, **H**$_3$).

3-Bromopropyl trifluoromethanesulfonate (2.70)



$C_4H_6BrF_3O_3S$
Mol Wt: 271.05

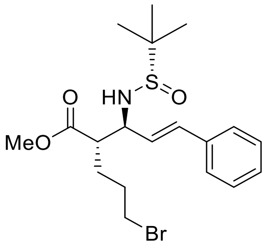
By adaption of a procedure by Hugelshofer *et al.*,[139] to a solution of 3-bromopropan-1-ol (0.250 mL, 2.76 mmol) in anhydrous CH$_2$Cl$_2$ (3 mL) at –78 °C was added pyridine (0.270 mL, 3.32 mmol). Trifluoromethanesulfonic anhydride (0.470 mL, 2.79 mmol) was added dropwise over 1 min, and stirring was continued at –78 °C for 10 min. The solution was warmed to 0 °C, then stirred at this temperature for 40 min. The reaction was quenched by dropwise addition of sat. NH$_4$Cl (10 mL) and the phases were separated, re-extracting the aqueous layer with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined, dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) gave the title product as a colourless oil (0.530 g, 1.96 mmol, 71%). The spectroscopic data were consistent with those reported in literature.[139]

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 4.72 (t, J = 6.0 Hz, 2H, **H**$_2$), 3.52 (t, J = 6.0 Hz, 2H, **H**$_4$), 2.37 (quin, J = 6.0 Hz, 2H, **H**$_3$).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 118.6 (q, $J_{C\text{-}F}$ = 319.9 Hz, **C**$_1$), 74.4 (**C**$_2$), 32.0 (**C**$_4$), 27.2 (**C**$_3$).

^{19}F NMR: (CDCl$_3$, 376 MHz) δ ppm = –74.6 (**F**).

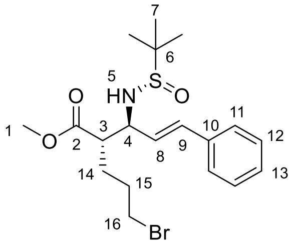
Methyl (2*S*,3*S*,*E*)-2-(3-bromopropyl)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-phenylpent-4-enoate (2.72)



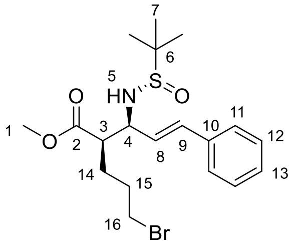
$C_{19}H_{28}BrNO_3S$
Mol Wt: 430.40

The round bottom flask containing LiCl (134 mg, 3.20 mmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (800 µL of 1.0 M in THF, 0.800 mmol) was added dropwise. To the solution was added dropwise *β*-amino ester **2.61** (100 mg, 0.323 mmol) in anhydrous THF (5 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then triflate **2.70** (260 mg, 0.959 mmol) in anhydrous THF (5 mL) was added dropwise and the solution was allowed to warm to –50 °C (dry ice/MeCN) stirring for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (10 mL) and the phases were separated, re-extracting the aqueous layer with EtOAc (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) gave the *anti* imino-aldol as an inseparable mixture containing the *syn* isomer as a yellow oil (95.8 mg, 0.222 mmol, 69%). Integration of the **H**$_3$ peaks in the crude ^{1}H NMR spectrum allowed estimation of the *anti:syn* ratio (*dr* 4.4:1).

Data were recorded for the 4.4:1 mixture of diastereoisomers.



major *anti*-diastereoisomer



minor *syn*-diastereoisomer

^{1}H NMR:	($CDCl_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.41 – 7.24 (m, 5H, **H**$_{11}$, **H**$_{12}$, & **H**$_{13}$), 6.62 (d, *J* = 15.8 Hz, 1H, **H**$_9$), 6.05 (dd, *J* = 15.8, 7.5 Hz, 1H, **H**$_8$), 4.19 (m, 2H, **H**$_5$ & **H**$_4$), 3.73 (s, 3H, **H**$_1$), 3.46 – 3.35 (m, 2H, **H**$_{16}$), 2.76 – 2.67 (m, 1H, **H**$_3$), 1.95 – 1.82 (m, 4H, **H**$_{14}$ & **H**$_{15}$), 1.24 (s, 9H, **H**$_7$). ($CDCl_3$, 400 MHz, selected signals reported for the *syn* diastereoisomer) δ ppm = 6.64 (d, *J* = 15.9 Hz, 1H, **H**$_9$), 6.11 (dd, *J* = 15.9, 8.4 Hz, 1H, **H**$_8$), 3.72 (s, 3H, **H**$_1$), 2.85 – 2.78 (m, 1H, **H**$_3$).

^{13}C NMR: ($CDCl_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 174.1 (**C**$_2$), 136.2 (**C**$_{10}$), 133.3 (**C**$_8$), 128.6 (**C**$_{12}$), 128.0 (**C**$_9$), 127.9 (**C**$_{13}$), 126.7 (**C**$_{11}$), 59.2 (**C**$_4$), 55.9 (**C**$_6$), 52.1 (**C**$_1$), 49.8 (**C**$_3$), 32.8 (**C**$_{16}$), 30.3 (**C**$_{14}$) 27.8 (**C**$_{15}$), 22.7 (**C**$_7$).

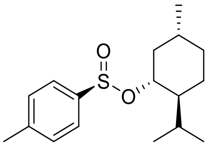
($CDCl_3$, 101 MHz selected signals reported for the *syn* diastereoisomer) δ ppm = 173.7 (**C**$_2$), 53.4 (**C**$_1$), 50.2 (**C**$_3$), 30.5 (**C**$_{16}$), 26.9 (**C**$_{15}$), 22.67 (**C**$_7$).

LRMS: (ES+) +) m/z = 452.2 $[M^{79}Br+Na]^+$ and 454.2 $[M^{81}Br+Na]^+$.

Selected data for the *syn* diastereoisomer:

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 3.72 (s, 3H, **H**$_1$), 2.85 – 2.78 (m, 1H, **H**$_3$).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate (2.47)



$C_{17}H_{26}O_2S$
Mol Wt: 294.45

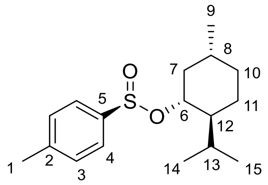
By adaption of a procedure by Blakemore *et al.,*[102] the sodium toluenesulfinate (100 g, 561 mmol) was added portion wise to thionyl chloride (61.0 mL, 842 mmol) at 0 °C over 1 h. The reaction was stirred for 3 h at 0 °C. When the gas evolution ceased, the reaction was allowed to warmed to rt and was concentrated *in vacuo*. The residue was re-dissolved in anhydrous CH_2Cl_2 (100 mL) and repeatedly concentrated *in vacuo* three times to remove excess thionyl chloride. The resulting sulfinyl chloride was as a yellow oil, which was used directly in the next step.

The freshly prepared sulfinyl chloride was dissolved in anhydrous CH_2Cl_2 (200 mL). To this solution was added dropwise a solution of (–)-menthol (132 g, 840 mmol) and pyridine (112 mL, 1400 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C over 1 h, voluminous white precipitates appearing immediately. The mixture was stirred at 0 °C for 1 h and then warmed to rt for 16 h. The reaction was quenched by dropwise addition of H_2O (200 mL). The organic layer was separated and washed with aq. HCl (2 × 100 mL of 2.0 M), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was recrystallised from acetone with *conc*. HCl (5 drops) to yield the title product as white needles (141 g, 480 mmol, 85%). The physical and spectroscopic data recorded were consistent with reported literature values.[102]

Melting Point: 101–103 °C. (Lit.[102] 106 – 108 °C).

$[\alpha]_D$: −206 (c 0.5, acetone, 23 °C). Lit.[102] −200 (c 1.5, acetone, 25 °C).

FT-IR (cm^{-1}): 2957, 2947, 1456, 1388, 1131, 952.



^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 7.61 (d, *J* = 7.8 Hz, 2H, **H**$_4$), 7.33 (d, *J* = 7.8 Hz, 2H, **H**$_3$), 4.13 (td, *J* = 10.7, 4.5 Hz, 1H, **H**$_6$), 2.43 (s, 3H, **H**$_1$), 2.32 – 2.25 (m, 1H, **H**$_{13}$), 2.19 – 2.10 (m, 1H, **H**$_{7eq}$), 1.73 – 1.66 (m, 2H, **H**$_{12}$ & **H**$_{11eq}$), 1.55 – 1.44 (m, 1H, **H**$_{7ax}$), 1.41 – 1.32 (m, 1H, **H**$_8$), 1.29 – 1.17 (m, 1H, **H**$_{10eq}$), 1.11 – 0.99 (m, 1H, **H**$_{11ax}$), 0.97 (d, *J* = 6.6 Hz, 3H, **H**$_9$), 0.89 – 0.84 (m, 4H, **H**$_{14}$ & **H**$_{10ax}$), 0.73 (d, *J* = 6.9 Hz, 3H, **H**$_{15}$).

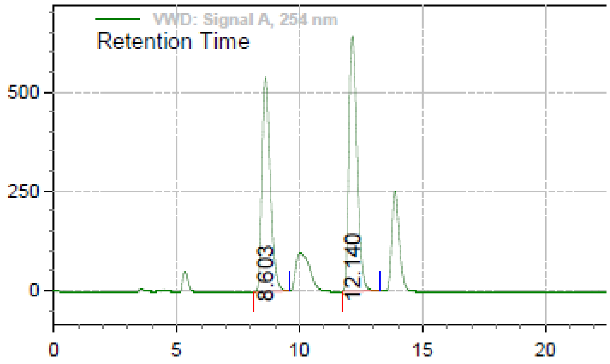
^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 143.2 (**C**$_5$), 142.4 (**C**$_2$), 129.6 (**C**$_3$), 125.0 (**C**$_4$), 80.1 (**C**$_6$), 47.9 (**C**$_{12}$), 43.0 (**C**$_7$), 34.0 (**C**$_{10}$), 31.7 (**C**$_8$), 25.2 (**C**$_{13}$), 23.2 (**C**$_{11}$), 22.1 (**C**$_9$), 21.5 (**C**$_1$), 20.9 (**C**$_{14}$), 15.5 (**C**$_{15}$).

LRMS: (ES+) m/z = 295.4 [M+H]$^+$.

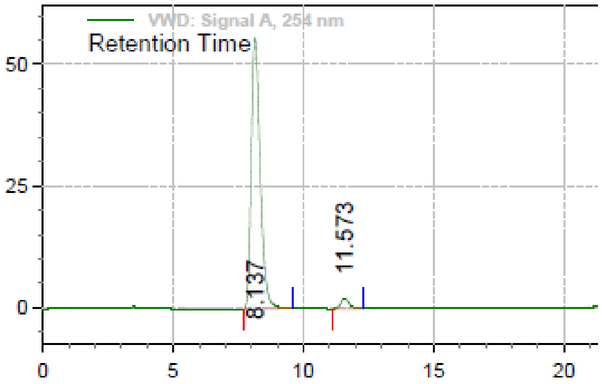
HPLC: Chiralpak® AD-H (4.6 ×250 mm, 5 µm) – (*eluent*: IPA:*n*-hexane – 1:19) – 1 mL/min

Retention time: 8.1 & 11.6 min. The ratio after resolution – 96.5:3.5.

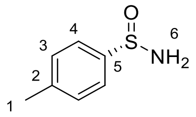
Racemic:



Desired product:



(*S*)-4-Methylbenzenesulfinamide (2.53)



C_7H_9NOS
Mol Wt: 155.22

To a solution of sulfinate **2.47** (500 mg, 1.70 mmol) in anhydrous THF (10 mL) at –78 °C under N_2 was added dropwise a solution of LiHMDS (2.30 mL of 1.0 M in THF, 2.30 mmol). The mixture was stirred at –78 °C for 30 min and then warmed to rt for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (20 mL) at 0 °C. Then the mixture was allowed to warm to rt and stirring for 1 h. The phases were separated, re-extracting the aqueous phase with EtOAc (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude material was recrystallised from hexane to yield the title product as yellow crystals (250 mg, 1.61 mmol, 95%). The physical and spectroscopic data recorded were consistent with reported values.[140]

Melting Point: 113–114 °C. (Lit.[141] 113 °C).

$[\alpha]_D$: + 81.2 (c 0.5, $CHCl_3$, 23 °C). Lit.[140] + 80.2 (c 1.1, $CHCl_3$, 23 °C).

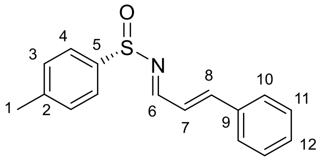
FT-IR (cm^{-1}): 3094, 1086, 1020, 806.

^1H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.64 (d, *J* = 8.1 Hz, 2H, **H_3**), 7.32 (d, *J* = 8.1 Hz, 2H, **H_4**), 4.27 (br s, 2H, **H_6**), 2.43 (s, 3H, **H_1**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 143.5 (**C_5**), 141.6 (**C_2**), 129.6 (**C_3**), 125.3 (**C_4**), 21.3 (**C_1**).

LRMS: (ES+) m/z = 156.2 $[M+H]^+$.

(*S*)-4-Methyl-*N*-((1*E*,2*E*)-3-phenylallylidene)benzenesulfinamide (2.55)



$C_{16}H_{15}NOS$
Mol Wt: 269.36

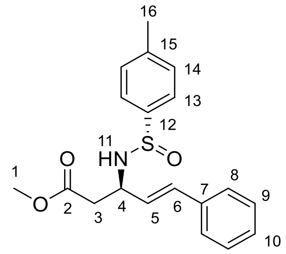
To a solution of sulfinamide **2.53** (200 mg, 1.29 mmol) and cinnamaldehyde (0.240 mL, 1.93 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under N_2 was added dropwise $Ti(OEt)_4$ (400 µL, 1.94 mmol). The reaction was stirred for 1 h and further $Ti(OEt)_4$ (400 µL, 1.94 mmol) was added dropwise. After 16 h, brine (20 mL) was added. The reaction was stirred rapidly for 5 min and filtered, washing the filter cake with CH_2Cl_2 (4 × 20 mL). The phases were separated, re-extracting the aqueous layer with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude material was recrystallised from hexane to give the title product as yellow crystals (309 mg, 1.14 mmol, 89%). The physical and spectroscopic data recorded were consistent with reported values.[142]

Melting Point: 112–113 °C. (Lit.[142] 113–114 °C).

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.56 (d, *J* = 9.3 Hz, 1H, **H**$_6$), 7.62 (d, *J* = 7.5 Hz, 2H, **H**$_4$), 7.56 – 7.51 (m, 2H, **H**$_{11}$), 7.44 – 7.39 (m, 3H, **H**$_{10}$ & **H**$_{12}$), 7.34 (d, *J* = 7.5 Hz, 2H, **H**$_3$), 7.29 (d, *J* = 15.4 Hz, 1H, **H**$_8$), 7.07 (dd, *J* = 15.4, 9.3 Hz, 1H, **H**$_7$), 2.43 (s, 3H, **H**$_1$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 161.6 (**C**$_6$), 146.9 (**C**$_8$), 141.9 (**C**$_5$), 141.8 (**C**$_2$), 134.9 (**C**$_9$), 130.4 (**C**$_{12}$), 129.9 (**C**$_3$), 129.0 (**C**$_{10}$), 128.0 (**C**$_{11}$), 125.5 (**C**$_4$), 124.6 (**C**$_7$), 21.4 (**C**$_1$).

Methyl (*R*,*E*)-5-phenyl-3-(((*S*)-*p*-tolylsulfinyl)amino)pent-4-enoate (2.60)

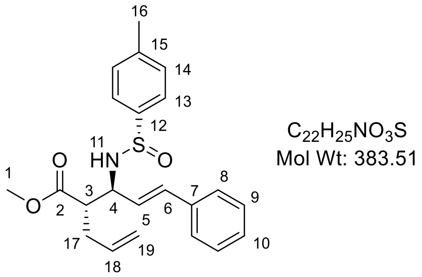


$C_{19}H_{21}NO_3S$
Mol Wt: 343.44

To a solution of methyl acetate (180 µL, 2.22 mmol) in anhydrous THF (10 mL) was added dropwise a solution of NaHMDS (2.44 mL of 1.0 M in THF, 2.44 mmol) at −78 °C under N_2. After addition, the N_2 flow was removed and the RBF was sealed to avoid evaporation of methyl acetate. The reaction was stirred for 1 h at −78 °C then a solution of sulfinimine **2.55** (300 mg, 1.11 mmol) in anhydrous THF (5 mL) was added dropwise. The reaction was stirred at −78 °C for 2 h and quenched by dropwise addition of sat. NH_4Cl (10 mL) at the same temperature. The mixture was allowed to warm to rt with rapid stirring. The phases were separated, re-extracting the aqueous layer with EtOAc (3 × 20 mL). The organic phases were combined, washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:9) afforded the diastereoisomerically pure imino-aldol adduct as a yellow oil (308 mg, 0.898 mmol, 81%). Integration of the N<u>H</u> peaks in the crude ^{1}H NMR spectrum showed *dr* 20:1.

[α]$_D$:	+317 (c 0.25, $CHCl_3$, 23 °C),
FT-IR (cm^{-1}):	3191, 3025, 2951, 1735, 1436, 1089, 1057.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 7.57 (d, *J* = 8.3 Hz, 2H, **H**$_{13}$), 7.37 – 7.32 (d, *J* = 8.3 Hz, 2H, **H**$_{14}$), 7.29 – 7.16 (m, 5H, **H**$_8$, **H**$_9$ & **H**$_{10}$), 6.61 (d, *J* = 15.8 Hz, 1H, **H**$_6$), 6.20 (dd, *J* = 15.8, 6.5 Hz, 1H, **H**$_5$), 4.81 (d, *J* = 6.5 Hz, 1H, **H**$_{11}$), 4.40 (quin, *J* = 6.5 Hz, 1H, **H**$_4$), 3.61 (s, 3H, **H**$_1$), 2.73 – 2.61 (m, 2H, **H**$_3$), 2.37 (s, 3H, **H**$_{16}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 171.1 (**C**$_2$), 142.2 (**C**$_{12}$), 141.4 (**C**$_{15}$), 136.2 (**C**$_7$), 132.6 (**C**$_5$), 129.6 (**C**$_{14}$), 128.6 (**C**$_9$), 128.5 (**C**$_{10}$), 128.0 (**C**$_6$), 126.7 (**C**$_8$), 125.5 (**C**$_{13}$), 53.3 (**C**$_4$), 51.8 (**C**$_1$), 40.8 (**C**$_3$), 21.3 (**C**$_{16}$).
LRMS:	(ES+) m/z = 366.3 [M+H]$^+$.
HRMS:	(ES+) for $C_{19}H_{21}NaNO_3S^+$ calculated 336.1139, found 336.1134 Da.

Methyl (2*S*,3*S*,*E*)-2-allyl-5-phenyl-3-(((*S*)-*p*-tolylsulfinyl)amino)pent-4-enoate (2.63)



A round bottom flask containing LiCl (25.0 mg, 595 µmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (170 µL of 1.0 M in THF, 170 µmol) was added dropwise. To the solution was added dropwise β-amino ester **2.60** (20.0 mg, 58.3 µmol) in anhydrous THF (5 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then allyl iodide (10.0 µL, 109 µmol) was added dropwise and the solution was allowed to warm to –50 °C (dry ice/MeCN), and then stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (5 mL) and the phases were separated, re-extracting the aqueous layer with EtOAc (3 × 5 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) gave the *anti* imino-aldol adduct as an inseparable mixture containing the *syn* isomer as a yellow oil (18.0 mg, 46.9 µmol, 76%). Integration of the N<u>H</u> peak in the ^{1}H NMR spectrum allowed estimation of the *anti*:*syn* ratio (*dr* ~15:1).

Data were recorded for the ~15:1 mixture of diastereoisomers.

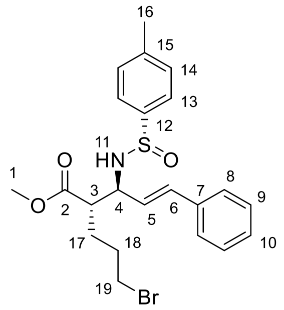
^{1}H NMR: (CDCl$_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.60 (d, *J* = 7.8 Hz, 2H, **H**$_{13}$), 7.40 (d, *J* = 7.8 Hz, 2H, **H**$_{14}$), 7.36 – 7.24 (m, 5H, **H**$_8$, **H**$_9$ & **H**$_{10}$), 6.62 (d, *J* = 15.8 Hz, 1H, **H**$_6$), 6.20 (dd, *J* = 15.8, 7.6 Hz, 1H, **H**$_5$), 5.69 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, **H**$_{18}$), 5.08 (br d, *J* = 17.1 Hz, 1H, **H**$_{19\text{trans}}$), 5.03 (br d, *J* = 10.2 Hz, 1H, **H**$_{19\text{cis}}$), 4.87 (d, *J* = 6.9 Hz, 1H, **H**$_{11}$), 4.25 – 4.18 (m, 1H, **H**$_4$), 3.66 (s, 3H, **H**$_1$), 2.74 (dt, *J* = 8.7, 6.0 Hz, 1H, **H**$_3$), 2.49 – 2.32 (m, 5H, **H**$_{16}$ & **H**$_{17}$).

^{13}C NMR: (CDCl$_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 173.7 (**C**$_2$), 142.1 (**C**$_{12}$), 141.4 (**C**$_{15}$), 136.3 (**C**$_7$), 134.5 (**C**$_{18}$), 133.2 (**C**$_5$), 129.6 (**C**$_{14}$), 128.6 (**C**$_8$), 128.4 (**C**$_{10}$), 128.0 (**C**$_6$), 126.7 (**C**$_9$), 125.6 (**C**$_{13}$), 117.6 (**C**$_{19}$), 57.8 (**C**$_4$), 51.8 (**C**$_1$), 50.3 (**C**$_3$), 33.6 (**C**$_{17}$), 21.4 (**C**$_{16}$).

Selected data for the *syn* diastereoisomer:

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 4.66 (d, *J* = 5.3 Hz, 1H, **H**$_{11}$).

Methyl (2*S*,3*S*,*E*)-2-(3-bromopropyl)-5-phenyl-3-(((*S*)-*p*-tolylsulfinyl)amino)pent-4-enoate (2.71)



$C_{22}H_{26}BrNO_3S$
Mol Wt: 464.42

A round bottom flask containing LiCl (64.0 mg, 1.50 mmol) under N$_2$ was flame-dried. After cooling to –78 °C, a solution of LDA (450 µL of 1.0 M in THF, 450 µmol) was added dropwise. To the solution was added dropwise *β*-amino ester **2.60** (50.0 mg, 145 µmol) in anhydrous THF (5 mL) and the reaction mixture was stirred at –78 °C for 1 h. Triflate **2.70** (78.0 mg, 287 µmol) in THF (5 mL) was added dropwise and the solution was allowed to warm to –50 °C (dry ice/MeCN), and then stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of sat. NH$_4$Cl (10 mL). The phases were separated, re-extracting the aqueous layer with EtOAc (3 × 10 mL). The organic phases were combined, dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH$_2$Cl$_2$ – 10:90) gave the *anti* imino-aldol adduct as an inseparable mixture containing the *syn* isomer as a yellow oil (45.0 mg, 96.9 µmol, 66%). Integration of the N$\underline{\text{H}}$ peak in the ^{1}H NMR spectrum allowed estimation of the *anti*:*syn* ratio (*dr* ~10:1).

Data were recorded for the ~10:1 mixture of diastereoisomers.

^{1}H NMR: (CDCl$_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.61 (d, *J* = 8.2 Hz, 2H, **H**$_{13}$), 7.40 (d, *J* = 8.2 Hz, 2H, **H**$_{14}$), 7.37 – 7.23 (m, 5H, **H**$_8$, **H**$_9$ & **H**$_{10}$), 6.63 (d, *J* = 15.8 Hz, 1H, **H**$_6$), 6.20 (dd, *J* = 15.8, 7.3 Hz, 1H, **H**$_5$), 4.86 (d, *J* = 7.0 Hz, 1H, **H**$_{11}$), 4.25 – 4.14 (m, 1H, **H**$_4$), 3.68 (s, 3H, **H**$_1$), 3.35 (t, *J* = 6.5 Hz, 2H, **H**$_{19}$), 2.68 – 2.60 (m, 1H, **H**$_3$), 2.43 (s, 3H, **H**$_{16}$), 1.90 – 1.67 (m, 4H, **H**$_{17}$ & **H**$_{18}$).

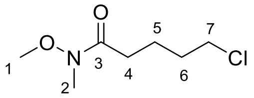
^{13}C NMR: (CDCl$_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 173.9 (**C$_2$**), 141.9 (**C$_{12}$**), 141.5 (**C$_{15}$**), 136.2 (**C$_7$**), 133.1 (**C$_5$**), 129.6 (**C$_{14}$**), 128.6 (**C$_9$**), 128.3 (**C$_6$**), 128.0 (**C$_{10}$**), 126.7 (**C$_8$**), 125.6 (**C$_{13}$**), 57.5 (**C$_4$**), 52.0 (**C$_1$**), 49.7 (**C$_3$**), 32.8 (**C$_{19}$**), 30.3 (**C$_{17}$**), 27.8 (**C$_{18}$**), 21.4 (**C$_{16}$**).

LRMS: (ES+) m/z = 486.3 [M^{79}Br+Na]$^+$ and 488.3 [M^{81}Br+Na]$^+$.

Selected data for the *syn* diastereoisomer:

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 4.59 (d, *J* = 5.5 Hz, 1H, **H$_{11}$**), 2.34 (s, 3H, **H$_{16}$**).

5-Chloro-*N*-methoxy-*N*-methylpentanamide (2.143)



$C_7H_{14}ClNO_2$
Mol Wt: 179.64

To a solution of 5-chlorovaleric acid (5.00 g, 36.6 mmol) in anhydrous CH$_2$Cl$_2$ (45 mL) at 0 °C under N$_2$ was added oxalyl chloride (3.41 mL, 40.3 mmol) dropwise, followed by DMF (3 drops). The reaction was stirred for 30 min at 0 °C and then warmed to rt and stirred for 4 h. When the gas evolution ceased, the mixture was concentrated *in vacuo* give 5-chloropentanoyl chloride as colourless oil, which was used directly in the next step.

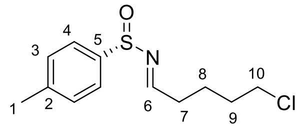
To a solution of Weinreb amine hydrochloride (4.63 g, 45.8 mmol) in anhydrous CH$_2$Cl$_2$ (150 mL) at 0 °C under N$_2$ was added NEt$_3$ (12.8 mL, 91.5 mmol) dropwise over 15 min. After stirring the mixture for 30 min at 0 °C, the freshly prepared acid chloride was added dropwise. The mixture was stirred for 30 min at 0 °C, and then warmed to rt for 12 h. The reaction was quenched by addition of sat. NH$_4$Cl (130 mL). The organic phase was separated, washed with brine (2 x 130 mL), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:9) afforded the title product as a colourless oil (6.33 g, 35.2 mmol, 96%). The spectroscopic data are consistent with those previously reported.[70]

IR-FT (cm^{-1}): 2939, 1658, 1385, 1177, 993, 750.

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 3.68 (s, 3H, **H$_1$**), 3.55 (t, *J* = 6.5 Hz, 2H, **H$_7$**), 3.17 (s, 3H, **H$_2$**), 2.46 (t, *J* = 6.8 Hz, 2H, **H$_4$**), 1.90 – 1.71 (m, 4H, **H$_5$** & **H$_6$**).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 174.0 (**C**$_3$), 61.2 (**C**$_1$), 44.7 (**C**$_7$), 32.2 (**C**$_2$ & **C**$_5$), 31.0 (**C**$_4$), 21.9 (**C**$_6$).

(*S*,*E*)-*N*-(5-Chloropentylidene)-4-methylbenzenesulfinamide (2.141)



$C_{12}H_{16}ClNOS$
Mol Wt: 257.78

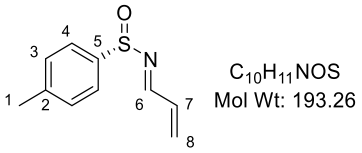
To a solution of Weinreb amide **2.143** (270 mg, 1.50 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) at –78 °C under N$_2$ was added dropwise a solution of DIBAL-H (1.80 mL of 1.0 M in CH$_2$Cl$_2$, 1.80 mmol). The reaction was stirred for 2 h at –78 °C before quenching by dropwise addition of sat. NH$_4$Cl (20 mL). The mixture was warmed to rt and stirred for 2 h. The suspension was filtered through the celite and the filter cake was washed with CH$_2$Cl$_2$ (3 x 10 mL). The organic phase was separated, washed with brine (3 x 10 mL), and dried (MgSO$_4$), to give the crude aldehyde, which was used directly in the next step.

To a solution of sulfinamide **2.53** (155 mg, 1.00 mmol) and Ti(OEt)$_4$ (0.930 mL, 4.07 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) at 0 °C under N$_2$ was added the freshly prepared aldehyde in CH$_2$Cl$_2$ (30 mL). The reaction was stirred for 30 min at 0 °C, and then warmed to rt. After 12 h, bring (20 mL) was added. The reaction was stirred rapidly for 5 min and filtered, washing the filter cake with CH$_2$Cl$_2$ (4 × 10 mL). The phases were separated, re-extracting the aqueous layer with CH$_2$Cl$_2$ (2 × 10 mL). The organic phases were combined, washed with brine (2 × 10 mL), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) afforded the title product as a pale yellow oil (48.0 mg, 0.186 mmol, 12%). The spectroscopic data are consistent with those previously reported.[143]

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 8.24 (t, *J* = 4.5 Hz, 1H, **H**$_6$), 7.56 (d, *J* = 7.9 Hz, 2H, **H**$_4$), 7.31 (d, *J* = 7.9 Hz, 2H, **H**$_3$), 3.52 (t, *J* = 6.1 Hz, 2H, **H**$_{10}$), 2.59 – 2.46 (m, 2H, **H**$_7$), 2.41 (s, 3H, **H**$_1$), 1.80 (m, 4H, **H**$_8$ & **H**$_9$).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 166.2 (**C**$_6$), 141.7 (**C**$_2$ & **C**$_5$), 129.8 (**C**$_3$), 124.5 (**C**$_4$), 44.4 (**C**$_{10}$), 35.0 (**C**$_7$), 31.8 (**C**$_9$), 22.5 (**C**$_8$), 21.4 (**C**$_1$).

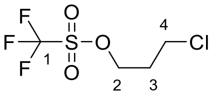
(*S*,*E*)-*N*-Allylidene-4-methylbenzenesulfinamide (2.77)



To a solution of sulfinamide **2.53** (6.00 g, 38.7 mmol) and $Ti(OEt)_4$ (32.3 mL, 141 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under N_2 was added acrolein (3.70 mL, 78.8 mmol) dropwise. The reaction mixture was stirred for 30 min at 0 °C, and then warmed to rt. After 16 h, brine (100 mL) was added. The reaction was stirred rapidly for 5 min and filtered, washing the filter cake with CH_2Cl_2 (4 × 50 mL). The phases were separated, re-extracting the aqueous layer with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) afforded the title product as a pale yellow oil (7.00 g, 36.2 mmol, 94%). The physical and spectroscopic data are consistent with those previously reported.[100]

$[\alpha]_D$:	+ 832 (c 0.5, $CHCl_3$, 23 °C). Lit.[100] + 714 (c 1.0, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	1575, 1092, 1070, 808, 556.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 8.38 (d, *J* = 9.3 Hz, 1H, **H_6**), 7.58 (d, *J* = 7.7 Hz, 2H, **H_4**), 7.31 (d, *J* = 7.7 Hz, 2H, **H_3**), 6.66 (ddd, *J* = 17.2, 10.2, 9.3 Hz, 1H, **H_7**), 6.07 – 5.99 (m, 2H, **H_8**), 2.40 (s, 3H, **H_1**).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 162.0 (**C_6**), 141.8 (**C_5**), 141.5 (**C_2**), 134.6 (**C_8**), 132.1 (**C_7**), 129.9 (**C_3**), 124.6 (**C_4**), 21.4 (**C_1**).
LRMS:	(ES+) m/z = 194.3 $[M+H]^+$.

3-Chloropropyl trifluoromethanesulfonate (2.81)

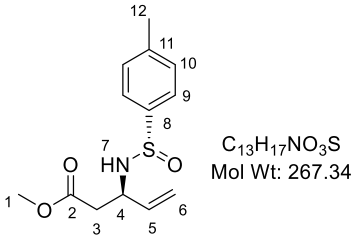


$C_4H_6ClF_3O_3S$
Mol Wt: 226.59

To a solution of 3-chloropropan-1-ol (1.40 mL, 16.8 mmol) in anhydrous CH_2Cl_2 (10 mL) at –78 °C was added pyridine (1.63 mL, 20.2 mmol). Trifluoromethanesulfonic anhydride (2.83 mL, 16.8 mmol) was added dropwise over 5 min, stirring at –78 °C for 10 min. The solution was warmed to 0 °C, then stirred at this temperature for 40 min. The reaction was quenched by dropwise addition of sat. NH_4Cl (10 mL) and the phases were separated, re-extracting the aqueous layer with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by using a Kugelrohr apparatus at 1 Torr with the heating chamber temperature 50 °C gave the title product as a colourless oil (3.34 g, 14.8 mmol, 88%). The spectroscopic data are consistent with those previously reported.[139]

^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.73 (t, J = 6.0 Hz, 2H, **H**$_2$), 3.68 (t, J = 6.0 Hz, 2H, **H**$_4$), 2.29 (quin, J = 6.0 Hz, 2H, **H**$_3$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 118.6 (q, $J_{C\text{-}F}$ = 308.9 Hz, **C**$_1$), 73.4 (**C**$_2$), 39.4 (**C**$_4$), 31.9 (**C**$_3$).
^{19}F NMR:	($CDCl_3$, 376 MHz) δ ppm = –74.7 (**F**).

Methyl (*R*)-3-(((*S*)-*p*-tolylsulfinyl)amino)pent-4-enoate (2.76)

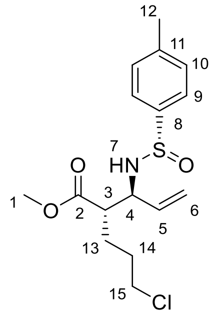


$C_{13}H_{17}NO_3S$
Mol Wt: 267.34

To a solution of methyl acetate (4.11 mL, 51.8 mmol) in anhydrous THF (30 mL) was added dropwise a solution of NaHMDS (64.8 mL of 1.0 M in THF, 64.8 mmol) at –78 °C under N_2. After addition, the N_2 flow was removed and the RBF was sealed to avoid evaporation of methyl acetate. The reaction was stirred for 1 h at –78 °C, and then a solution of sulfinimine **2.77** (5.00 g, 25.9 mmol) in anhydrous THF (20 mL) was added dropwise over 10 min. The reaction was stirred at –78 °C for 2 h and quenched by dropwise addition of sat. NH_4Cl (100 mL). The reaction was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) afforded the diastereoisomerically pure imino-aldol adduct as a yellow oil (5.40 g, 20.2 mmol, 78%). Integration of the N<u>H</u> peak in the crude ^{1}H NMR spectrum showed *dr* ~16:1. Data are consistent with those previously reported.[100]

^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 7.58 (d, *J* = 8.0 Hz, 2H, **H_9**), 7.29 (d, *J* = 8.0 Hz, 2H, **H_{10}**), 5.92 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H, **H_5**), 5.32 (dt, *J* = 17.1, 1.2 Hz, 1H, **H_{6trans}**), 5.22 (dt, *J* = 10.6, 1.2 Hz, 1H, **H_{6cis}**), 4.79 (d, *J* = 7.2 Hz, 1H, **H_7**), 4.29 – 4.19 (m, 1H, **H_4**), 3.64 (s, 3H, **H_1**), 2.69 – 2.56 (m, 2H, **H_3**), 2.40 (s, 3H, **H_{12}**).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 171.3 (**C_2**), 142.0 (**C_8**), 141.4 (**C_{11}**), 137.8 (**C_5**), 129.6 (**C_{10}**), 125.6 (**C_9**), 117.2 (**C_6**), 53.4 (**C_4**), 51.8 (**C_1**), 40.4 (**C_3**), 21.3 (**C_{12}**).
LRMS:	(ES+) m/z = 268.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{13}H_{17}NaNO_3S^+$ calculated 290.0826, found 290.0821 Da.

Methyl (2*S*,3*S*)-2-(3-chloropropyl)-3-(((*S*)-*p*-tolylsulfinyl)amino)pent-4-enoate (2.75)



$C_{16}H_{22}ClNO_3S$
Mol Wt: 343.87

A round bottom flask containing LiCl (3.50 g, 83.3 mmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (20.6 mL of 1.0 M in THF, 20.6 mmol) was added dropwise. To the solution was added dropwise β-amino ester **2.76** (2.20 g, 8.30 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then triflate **2.81** (3.70 g, 16.5 mmol) in anhydrous THF (10 mL) was added dropwise and the solution was allowed to warm to –50 °C (dry ice/MeCN), and then stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (50 mL) and the phases were separated, re-extracting the aqueous layer with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 –1:9) gave the *anti* imino-aldol adduct as an inseparable mixture containing the *syn* isomer as a yellow oil (1.97 g, 5.73 mmol, 69%). Integration of the N<u>H</u> peaks in the crude ^{1}H NMR spectrum allowed estimation of the *anti:syn* ratio (*dr* 10:1).

Data were recorded for the 10:1 mixture of diastereoisomers.

[α]$_D$: + 87.2 (c 0.25, $CHCl_3$, 25 °C).

FT-IR (cm^{-1}): 3202, 2952, 1729, 1088, 1055, 811.

^{1}H NMR: ($CDCl_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.59 (d, *J* = 8.0 Hz, 2H, **H**$_9$), 7.31 (d, *J* = 8.0 Hz, 2H, **H**$_{10}$), 5.89 (ddd, *J* = 16.9, 10.4, 6.5 Hz, 1H, **H**$_5$), 5.33 – 5.24 (m, 2H, **H**$_6$), 4.87 (d, *J* = 7.8 Hz, 1H, **H**$_7$), 4.00 – 3.92 (m, 1H, **H**$_4$), 3.67 (s, 3H, **H**$_1$), 3.47 (t, *J* = 6.4 Hz, 2H, **H**$_{15}$), 2.56 – 2.49 (m, 1H, **H**$_3$), 2.42 (s, 3H, **H**$_{12}$), 1.80 – 1.55 (m, 4H, **H**$_{13}$ & **H**$_{14}$).

^{13}C NMR: ($CDCl_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 174.0 (**C**$_2$), 141.7 (**C**$_8$), 141.5 (**C**$_{11}$), 137.5 (**C**$_5$), 129.6 (**C**$_{10}$), 125.7 (**C**$_9$), 117.6 (**C**$_6$), 57.3 (**C**$_4$), 51.9 (**C**$_1$), 49.4 (**C**$_3$), 44.3 (**C**$_{15}$), 30.2 (**C**$_{13}$), 26.5 (**C**$_{14}$), 21.4 (**C**$_{12}$).

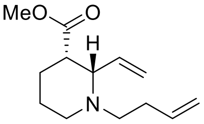
LRMS: (ES+) m/z = 344.3 $[M+H]^+$.

HRMS: (ES+) for $C_{16}H_{22}ClNO_3S^+$ calculated 366.0901, found 366.0903 Da.

Selected data for the *syn* diastereoisomer:

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 4.54 (d, *J* = 7.6 Hz, 1H, **H**$_7$).

Methyl (2*S*,3*S*)-1-(but-3-en-1-yl)-2-vinylpiperidine-3-carboxylate (2.74)



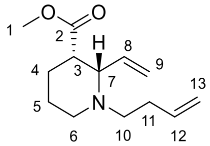
$C_{13}H_{21}NO_2$
Mol Wt: 223.32

To a solution of mixture of *anti* imino-aldol **2.75** (*dr* 10:1 with the *syn* diastereoisomer, 1.48 g, 6.64 mmol) in dioxane (20 mL) under N_2 was added dropwise *conc*. HCl (4.90 mL, 19.8 mmol). After 2 h stirring at rt, the reaction was concentrated *in vacuo*. The crude product was used directly in the next step. The crude product was re-dissolved in MeCN (20 mL), and K_2CO_3 (4.50 g, 32.6 mmol) and NaI (89.4 mg, 0.596 mmol) were added to the solution. The reaction was stirred for 16 h at rt and then concentrated *in vacuo*. The residue was re-dissolved in a mixture of EtOAc:H_2O (1:1 – 50 mL) and layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford the cyclised crude product as a yellow oil, which was used directly in the next step.

The crude material was re-dissolved in MeCN (20 mL), and 4-bromo-but-1-ene (1.40 mL, 13.3 mmol) and K_2CO_3 (1.80 g, 13.3 mmol) were added to the solution. The reaction mixture was stirred at 40 °C for 12 h. After cooling to rt, the reaction was concentrated *in vacuo*. The residue was re-dissolved in a mixture of EtOAc:H_2O (1:1 – 100 mL) and layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 4:6) gave the diastereoisomerically pure piperidine as a pale yellow oil (920 mg, 4.13 mmol, 63%).

$[\alpha]_D$: –16.1 (c 0.2, $CHCl_3$, 25 °C).

FT-IR (cm^{-1}): 2946, 2846, 1735, 1194, 1147, 992, 911.



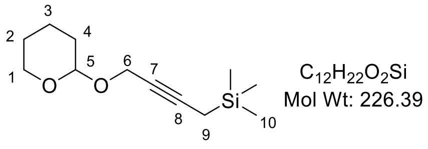
^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 6.02 (dt, *J* = 17.0, 10.2 Hz, 1H, $\mathbf{H}_8$), 5.80 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H, $\mathbf{H}_{12}$), 5.23 (dd, *J* = 10.2, 2.0 Hz, 1H, $\mathbf{H}_{9cis}$), 5.13 (dd, *J* = 17.0, 2.0 Hz, 1H, $\mathbf{H}_{9trans}$), 5.04 (dq, *J* = 17.1, 1.4 Hz, 1H, $\mathbf{H}_{13trans}$), 4.98 (ddt, *J* = 10.3, 1.4, 1.1 Hz, 1H, $\mathbf{H}_{13cis}$), 3.65 (dd, *J* = 10.2, 4.5 Hz, 1H, $\mathbf{H}_7$), 3.62 (s, 3H, $\mathbf{H}_1$), 2.84 (dt, *J* = 12.0, 4.5 Hz, 1H, $\mathbf{H}_3$), 2.65 – 2.57 (m, 1H, $\mathbf{H}_{6eq}$), 2.53 – 2.35 (m, 3H, $\mathbf{H}_{6ax}$ & $\mathbf{H}_{10}$), 2.26 – 2.15 (m, 2H, $\mathbf{H}_{11}$), 1.83 – 1.54 (m, 4H, $\mathbf{H}_4$ & $\mathbf{H}_5$).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 173.6 ($\mathbf{C}_2$), 136.8 ($\mathbf{C}_{12}$), 130.7 ($\mathbf{C}_8$), 119.8 ($\mathbf{C}_9$), 115.4 ($\mathbf{C}_{13}$), 62.6 ($\mathbf{C}_7$), 54.7 ($\mathbf{C}_{10}$), 51.4 ($\mathbf{C}_1$), 46.9 ($\mathbf{C}_6$), 46.5 ($\mathbf{C}_3$), 31.9 ($\mathbf{C}_{11}$), 24.6 ($\mathbf{C}_4$), 21.5 ($\mathbf{C}_5$).

LRMS: (ES+) *m/z* = 224.3 [M+H]$^+$.

HRMS: (ES+) for $C_{13}H_{22}NO_2^+$ calculated 224.1650, found 224.1645 Da.

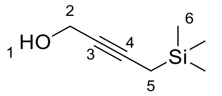
Trimethyl(4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-yn-1-yl)silane (2.153)



To a solution of 2-(2-propynyl)tetrahydro-2*H*-pyran (2.50 g, 17.8 mmol) in anhydrous THF (50 mL) was added dropwise a solution of *n*-BuLi (7.83 mL of 2.5 M in hexane, 19.6 mmol,) at –78 °C under N_2. The mixture was stirred for 15 min at –78 °C and then warmed to 0 °C for 20 min. (Iodomethyl)trimethylsilane (2.90 mL, 19.6 mmol) was added dropwise to the reaction over 5 min. The RBF was wrapped in foil and the reaction was heated at reflux for 3 h. After cooling to rt, the mixture was diluted with EtOAc (100 mL) and washed with water (50 mL), then brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) gave the title product as a colourless oil (2.74 g, 12.1 mmol, 68%). Data are consistent with those previously reported.[132]

^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.85 (t, *J* = 3.6 Hz, 1H, **H**$_5$), 4.29 (dt, *J* = 15.2, 2.5 Hz, 1H, **H**$_{6a}$), 4.23 (dt, *J* = 15.2, 2.5 Hz, 1H, **H**$_{6b}$), 3.86 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1H, **H**$_{1eq}$), 3.56 – 3.49 (m, 1H, **H**$_{1ax}$), 1.90 – 1.70 (m, 2H, **H**$_{2eq}$ & **H**$_{4eq}$), 1.68 – 1.48 (m, 6H, **H**$_{2ax}$, **H**$_3$, **H**$_{4ax}$ & **H**$_9$) 0.11 (s, 9H, **H**$_{10}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 98.4 (**C**$_5$), 86.6 (**C**$_7$), 76.6 (**C**$_8$), 64.1 (**C**$_6$), 56.8 (**C**$_1$), 32.4 (**C**$_4$), 27.5 (**C**$_3$), 21.3 (**C**$_2$), 9.3 (**C**$_9$), 0.0 (**C**$_{10}$).
LRMS:	(ES+) m/z = 227.2 $[M+H]^+$.

4-(Trimethylsilyl)but-2-yn-1-ol (2.154)



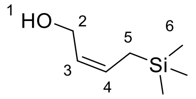
$C_7H_{14}OSi$
Mol Wt: 142.27

To a solution of PTSA (420 mg, 2.20 mmol) and pyridine (174 mg, 2.20 mmol) in EtOH (20 mL) was added **2.153** (2.50 g, 11.1 mmol) in a solution of EtOH:H_2O (40 mL, 1:1). The reaction was stirred at 55 °C for 12 h. The EtOH was removed *in vacuo*. The residue was diluted with petroleum ether (20 mL). The phases were separated, re-extracting the aqueous layer with petroleum ether (2 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford the title product as a colourless oil (1.54 g, 10.9 mmol, 98%). Data are consistent with those previously reported.[132]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 4.23 (t, *J* = 2.6 Hz, 2H, **H_2**), 1.85 (br s, 1H, **H_1**), 1.49 (t, *J* = 2.6 Hz, 2H, **H_5**), 0.1 (s, 9H, **H_6**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 86.4 (**C_3**), 79.3 (**C_4**), 53.6 (**C_2**), 9.2 (**C_5**), 0.0 (**C_6**).

(*Z*)-4-(Trimethylsilyl)but-2-en-1-ol (2.155)

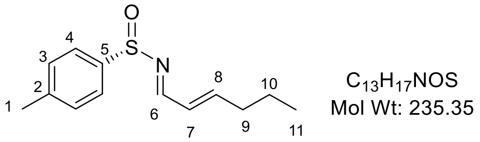


$C_7H_{16}OSi$
Mol Wt: 144.29

To a stirred solution of $Ni(OAc)_2$ (98.0 mg, 0.557 mmol) in EtOH (2 mL) was added dropwise a solution of $NaBH_4$ (0.557 mL of 1.0 M in EtOH, 0.557 mmol) at rt under N_2. The mixture turned from bright green to black immediately. After 20 min, ethylenediamine (36.0 µL, 0.557 mmol) was added. After stirring at rt for 20 min, a solution of alkyne **2.154** (630 mg, 4.44 mmol) in EtOH (5 mL) was added. The N_2 atmosphere was then replaced by H_2 and the reaction was stirred for 16 h. The reaction was quenched by addition of H_2O (10 mL), filtered through the celite, and concentrated *in vacuo*. The residue was re-dissolved in H_2O:CH_2Cl_2 (1:1, 20 mL), and the phases were separated, re-extracting the aqueous layer with CH_2Cl_2 (3 x 15 mL). The organic phases were combined, washed with sat. $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) gave the title product as colourless oil (530 mg, 3.68 mmol, 83%). Data are consistent with those previously reported.[133]

^{1}H NMR:	(CDCl$_3$, 400 MHz) δ ppm = 5.65 – 5.47 (m, 2H, **H**$_3$ & **H**$_4$), 4.16 (d, *J* = 6.5 Hz, 2H, **H**$_2$), 1.55 (d, *J* = 8.4 Hz, 2H, **H**$_5$), 1.19 (br s, 1H, **H**$_1$), 0.00 (s, 9H, **H**$_6$).
^{13}C NMR:	(CDCl$_3$, 101 MHz) δ ppm = 131.4 (**C**$_3$), 127.8 (**C**$_4$), 60.4 (**C**$_2$), 21.0 (**C**$_5$), 0.0 (**C**$_6$).

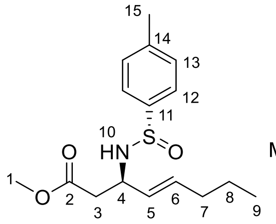
(*S*)-*N*-((1*Z*,2*E*)-Hex-2-en-1-ylidene)-4-methylbenzenesulfinamide (2.85)



To a solution of sulfinamide **2.53** (5.00 g, 32.2 mmol) and Ti(OEt)$_4$ (26.8 mL, 128 mmol) in anhydrous CH$_2$Cl$_2$ (50 mL) at 0 °C under N$_2$ was added *trans*-2-hexen-1-al (5.60 mL, 48.3 mmol). The reaction mixture was stirred for 30 min at 0 °C, and then was allowed to warm to rt. After 16 h, brine (100 mL) was added. The mixture was stirred rapidly for 20 min and filtered, washing filter cake with CH$_2$Cl$_2$ (3 x 30 mL). The organic phases were combined, washed with brine (2 x 20 mL), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) afforded the title sulfinimine as a pale yellow oil (6.60 g, 28.1 mmol, 88%).

[α]$_D$:	–290 (c 0.5, CHCl$_3$, 22 °C).
FT-IR (cm^{-1}):	2959, 2930, 1639, 1578, 1094, 1070.
^{1}H NMR:	(CDCl$_3$, 400 MHz) δ ppm = 8.35 (d, *J* = 9.3 Hz, 1H, **H**$_6$), 7.57 (d, *J* = 8.0 Hz, 2H, **H**$_4$), 7.30 (d, *J* = 8.0 Hz, 2H, **H**$_3$), 6.57 (dt, *J* =15.5, 6.8 Hz, 1H, **H**$_8$), 6.40 (ddt, *J* = 15.5, 9.3, 1.4 Hz, 1H, **H**$_7$), 2.40 (s, 3H, **H**$_1$), 2.25 (qd, *J* = 6.8, 1.4 Hz, 2H, **H**$_9$), 1.51 (sxt, *J* = 7.4 Hz, 2H, **H**$_{10}$), 0.94 (t, *J* = 7.4 Hz, 3H, **H**$_{11}$).
^{13}C NMR:	(CDCl$_3$, 101 MHz) δ ppm = 162.0 (**C**$_6$), 152.2 (**C**$_8$), 142.0 (**C**$_5$), 141.7 (**C**$_2$), 129.8 (**C**$_3$), 128.7 (**C**$_7$), 124.6 (**C**$_4$), 35.0 (**C**$_9$), 21.4 (**C**$_1$ & **C**$_{10}$), 13.7 (**C**$_{11}$).
LRMS:	(ES+) *m/z* = 236.3 [M+H]$^+$.
HRMS:	(ES+) for C$_{13}$H$_{17}$NOSNa$^+$ calculated 258.0929, found 258.0923 Da.

Methyl (*R*,*E*)-3-(((*S*)-*p*-tolylsulfinyl)amino)oct-4-enoate (2.86)

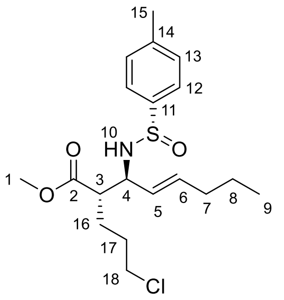


$C_{16}H_{23}NO_3S$
Mol Wt: 309.42

To a solution of methyl acetate (3.72 mL, 46.8 mmol) in anhydrous THF (40 mL) was added dropwise a solution of a solution of NaHMDS (51.5 mL of 1.0 M in THF, 51.5 mmol) at –78 °C under N_2. After addition, the N_2 flow was removed and the round bottom flask was sealed to avoid evaporation of methyl acetate. The reaction was stirred for 1 h at –78 °C then a solution of sulfinimine **2.85** (5.50 g, 23.4 mmol) in anhydrous THF (20 mL) was added dropwise over 20 min. The reaction was stirred at –78 °C for 2 h and quenched by dropwise addition of sat. NH_4Cl (40 mL) at the same temperature. The mixture was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer re-extracted with EtOAc (3 × 40 mL). The organic phases were combined, washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:9) afforded the diastereoisomerically pure imino-aldol adduct as a yellow oil (6.80 g, 22.0 mmol, 94%). Integration of the N<u>H</u> peaks in the crude ^{1}H NMR spectrum showed *dr* 15:1.

[α]$_D$:	+ 132.3 (c 0.3, $CHCl_3$, 25 °C).
FT-IR (cm^{-1}):	3189, 2955, 2927, 1736, 1169, 1089, 1055.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 7.59 (d, *J* = 8.1 Hz, 2H, **H**$_{12}$), 7.30 (d, *J* = 8.1 Hz, 2H, **H**$_{13}$), 5.76 (dtd, *J* = 15.3, 7.3, 0.8 Hz, 1H, **H**$_6$), 5.49 (ddt, *J* = 15.3, 6.5, 1.2 Hz, 1H, **H**$_5$), 4.68 (d, *J* = 6.5 Hz, 1H, **H**$_{10}$), 4.25 (quin, *J* = 6.5 Hz, 1H, **H**$_4$), 3.64 (s, 3H, **H**$_1$), 2.66 – 2.53 (m, 2H, **H**$_3$), 2.41 (s, 3H, **H**$_{15}$), 2.04 (q, *J* = 7.3 Hz, 2H, **H**$_7$), 1.41 (sxt, *J* = 7.3 Hz, 2H, **H**$_8$,), 0.9 (t, *J* = 7.3 Hz, 3H, **H**$_9$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 171.5 (**C**$_2$), 142.3 (**C**$_{11}$), 141.3 (**C**$_{14}$), 134.5 (**C**$_6$), 129.1 (**C**$_{13}$ & **C**$_5$), 125.5 (**C**$_{12}$), 53.2 (**C**$_4$), 51.8 (**C**$_1$), 41.0 (**C**$_3$), 34.3 (**C**$_7$), 22.2 (**C**$_8$), 21.4 (**C**$_{15}$), 13.6 (**C**$_9$).
LRMS:	(ES+) m/z = 310.4 [M+H]$^+$.
HRMS:	(ES+) for $C_{16}H_{23}NO_3SNa^+$ calculated 332.1291, found 332.1291 Da.

Methyl (2*S*,3*S*,*E*)-2-(3-chloropropyl)-3-(((*S*)-*p*-tolylsulfinyl)amino)oct-4-enoate (2.87)



$C_{19}H_{28}ClNO_3S$
Mol Wt: 385.95

A round bottom flask containing LiCl (1.23 g, 29.1 mmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (8.70 mL of 1.0 M in THF, 8.70 mmol) was added dropwise. To the solution was added dropwise β-amino ester **2.86** (0.900 g, 2.90 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then triflate (1.18 g, 4.40 mmol) in anhydrous THF (10 mL) was added dropwise and the solution was allowed to warm to –50 °C (dry ice/MeCN), and then stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (20 mL) and the phases were separated, re-extracting the aqueous layer with EtOAc (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) gave the *anti* imino-aldol adduct as an inseparable mixture containing the *syn* isomer as a yellow oil (783 mg, 2.03 mmol, 70%). Integration of the N$\underline{H}$ peak in the crude ^{1}H NMR spectrum allowed estimation of the *anti*:*syn* ratio (*dr* ~10:1).

Data were recorded for the ~10:1 mixture of diastereoisomers.

[α]$_D$:	+ 92.4 (c 0.3, $CHCl_3$, 25 °C).
FT-IR (cm^{-1}):	3190, 2956, 2929, 1733, 1169, 1089, 1058.
^{1}H NMR:	($CDCl_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.58 (d, *J* = 8.1 Hz, 2H, **H**$_{12}$), 7.30 (d, *J* = 8.1 Hz, 2H, **H**$_{13}$), 5.77 – 5.68 (m, 1H, **H**$_6$), 5.44 (ddt, *J* = 15.3, 7.0, 1.3 Hz, 1H, **H**$_5$), 4.65 (d, *J* = 7.0 Hz, 1H, **H**$_{10}$), 3.99 (q, *J* = 7.0 Hz, 1H, **H**$_4$), 3.66 (s, 3H, **H**$_1$), 3.48 (t, *J* = 6.2 Hz, 2H, **H**$_{18}$), 2.53 – 2.45 (m, 1H, **H**$_3$), 2.42 (s, 3H, **H**$_{15}$), 2.10 – 2.02 (m, 2H, **H**$_7$), 1.78 – 1.56 (m, 4H, **H**$_{16}$ & **H**$_{17}$), 1.42 (sxt, *J* = 7.3 Hz, 2H, **H**$_8$) 0.9 (t, *J* = 7.3 Hz, 3H, **H**$_9$).

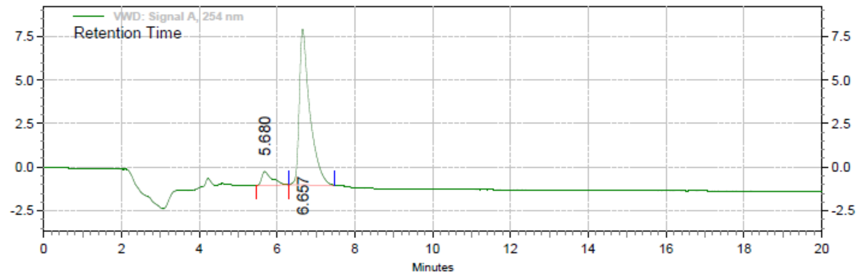
^{13}C NMR: (CDCl$_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 174.1 (**C**$_2$), 142.1 (**C**$_{11}$), 141.3 (**C**$_{14}$), 135.1 (**C**$_6$), 129.5 (**C**$_{13}$), 128.6 (**C**$_5$), 125.6 (**C**$_{12}$), 57.3 (**C**$_4$), 51.9 (**C**$_1$), 49.9 (**C**$_3$), 44.4 (**C**$_{18}$), 34.3 (**C**$_7$), 30.2 (**C**$_{17}$), 26.4 (**C**$_{16}$), 22.2 (**C**$_8$), 21.4 (**C**$_{15}$), 13.6 (**C**$_9$).

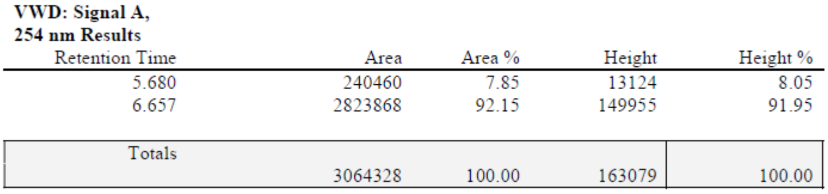
LRMS: (ES+) m/z = 386.4 [M^{35}Cl+H]$^+$ & 388.3 [M^{37}Cl+H]$^+$, 408.3 [M^{35}Cl+H]$^+$ & 410.3 [M^{37}Cl+Na]$^+$.

HRMS: (ES+) for $C_{19}H_{29}ClNO_3S^+$ calculated 386.1551, found 386.1553 Da; for $C_{19}H_{28}ClNO_3SNa^+$ calculated 408.1371, found 408.1371 Da.

HPLC: Chiralpak® AD-H (4.6 ×250 mm, 5 µm) – (*eluent*: IPA:*n*-hexane – 1:19) – 1 mL/min

Retention time: 5.7 & 6.7 min. The *dr* of *anti:syn* – 92.1:7.9.





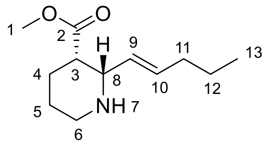
VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.680	240460	7.85	13124	8.05
6.657	2823868	92.15	149955	91.95
Totals	3064328	100.00	163079	100.00

Selected data for the *syn* diastereoisomer:

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 4.45 (d, *J* = 5.4 Hz, 1H, **H**$_{10}$), 3.65 (s, 3H, **H**$_1$).

Methyl (2*S*,3*S*)-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate (2.88)



$C_{12}H_{21}NO_2$
Mol Wt: 211.31

To a solution of the mixture of *anti* imino-aldol **2.87** (*dr* ~10:1 with the *syn* diastereoisomer, 2.00 g, 5.18 mmol) in dioxane (20 mL) under N_2 was added *conc*. HCl (1.00 mL, 11.8 mmol) dropwise. After 2 h stirring at rt, the reaction was concentrated *in vacuo.* The crude product was used directly in the next step. The crude material was re-dissolved in MeCN (20 mL), and then K_2CO_3 (3.50 g, 25.4 mmol) and NaI (75.0 mg, 0.500 mmol) were added to the solution. The reaction was stirred for 16 h at rt and then concentrated *in vacuo*. The residue was re-dissolved in a mixture of EtOAc:H_2O (1:1 – 20 mL) and layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 3:7) gave the diastereoisomerically pure piperidine as a yellow oil (746 mg, 3.59 mmol, 69%).

[α]D : + 4.2 (c 0.5, $CHCl_3$, 25 °C).

FT-IR (cm^{-1}): 2930, 2858, 1733, 1436, 1190, 1163, 968.

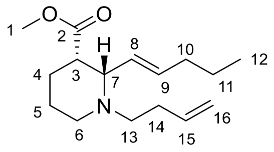
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.64 – 5.53 (m, 2H, **H_9** & **H_{10}**), 3.63 (s, 3H, **H_1**), 3.49 – 3.43 (m, 1H, **H_8**), 3.08 (dt, *J* = 13.1, 4.5 Hz, 1H, **H_{6eq}**), 2.73 – 2.64 (m, 2H, **H_3** & **H_{6ax}**), 2.00 – 1.91 (m, 4H, **H_{11}**, **H_7** & **H_{4eq}**), 1.83 – 1.64 (m, 2H, **H_{4ax}** & **H_{5eq}**), 1.47 – 1.41 (m, 1H, **H_{5ax}**), 1.35 (sxt, *J* = 7.4 Hz, 2H, **H_{12}**), 0.86 (t, *J* = 7.4 Hz, 3H, **H_{13}**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 174.2 (**C_2**), 132.0 (**C_{10}**), 129.3 (**C_9**), 58.3 (**C_8**), 51.2 (**C_1**), 44.5 (**C_6**), 44.4 (**C_3**), 34.6 (**C_{11}**), 25.6 (**C_4**), 23.1 (**C_5**), 22.4 (**C_{12}**), 13.6 (**C_{13}**).

LRMS: (ES+) m/z = 212.3 $[M+H]^+$.

HRMS: (ES+) for $C_{12}H_{22}NO_2^+$ calculated 212.1645, found 212.1648 Da.

Methyl (2*S*,3*S*)-1-(but-3-en-1-yl)-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate (2.90)



$C_{16}H_{27}NO_2$
Mol Wt: 265.40

To a solution of piperidine **2.88** (500 mg, 2.40 mmol) in MeCN (10 mL) was added 4-bromo-but-1-ene (0.400 mL, 3.94 mmol) and K_2CO_3 (552 mg, 4.00 mmol). The reaction mixture was stirred at 40 °C for 16 h, then the reaction was concentrated *in vacuo*. The residue was re-dissolved in a mixtuer of EtOAc:H_2O (1:1 – 40 mL) and layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 4:6) gave the title piperidine as a yellow oil (586 mg, 2.21 mmol, 92%).

[α]$_D$: –21.2 (c 0.3, $CHCl_3$, 25 °C).

FT-IR (cm^{-1}): 2930, 1738, 1434, 1223, 1191, 1166, 1145, 970.

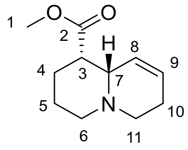
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.79 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H, **H**$_{15}$), 5.67 – 5.49 (m, 2H, **H**$_8$ & **H**$_9$), 5.04 (dq, *J* = 17.1, 1.9 Hz, 1H, **H**$_{16trans}$), 4.98 (ddt, *J* = 10.3, 1.9, 1.1 Hz, 1H, **H**$_{16cis}$), 3.64 (dd, *J* = 9.5, 4.5 Hz, 1H, **H**$_7$), 3.60 (s, 3H, **H**$_1$), 2.8 (dt, *J* = 11.8, 4.5 Hz, 1H, **H**$_3$), 2.62 – 2.55 (m, 1H, **H**$_{6eq}$), 2.51- 2.32 (m, 3H, **H**$_{13}$ & **H**$_{6ax}$), 2.30 – 2.15 (m, 2H, **H**$_{14}$), 2.07 – 1.92 (m, 2H, **H**$_{10}$), 1.81 – 1.53 (m, 4H, **H**$_4$ & **H**$_5$),1.35 (sxt, *J* = 7.3 Hz, 2H, **H**$_{11}$), 0.87 (t, *J* = 7.3 Hz, 3H, **H**$_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 173.7 (**C**$_2$), 136.9 (**C**$_{15}$), 136.4 (**C**$_9$), 121.6 (**C**$_8$), 115.4 (**C**$_{16}$), 61.6 (**C**$_7$), 54.7 (**C**$_{13}$), 51.3 (**C**$_1$), 47.1 (**C**$_6$), 46.7 (**C**$_3$), 34.7 (**C**$_{10}$), 31.9 (**C**$_{14}$), 24.7 (**C**$_4$), 22.6 (**C**$_{11}$), 21.4 (**C**$_5$), 13.5 (**C**$_{12}$).

LRMS: (ES+) *m/z* = 266.4 [M+H]$^+$.

HRMS: (ES+) for $C_{16}H_{28}NO_2^+$ calculated 266.2115, found 266.2121 Da.

Methyl (1*S*,9a*S*)-1,3,4,6,7,9a-hexahydro-2*H*-quinolizine-1-carboxylate (2.73)

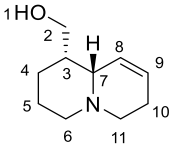


$C_{11}H_{17}NO_2$
Mol Wt: 195.26

To a solution of piperidine **2.90** (100 mg, 0.377 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2 was added Grubbs II (25.0 mg, 0.0294 mmol). The reaction was stirred under reflux for 2 h. The solvent was removed *in vacuo*. The residue was treated with EtOAc (20 mL), triturated and filtered through the celite. The filter cake was washed with EtOAc (3 × 15 mL) and the combined organics concentrated *in vacuo*. The residue was then partitioned between EtOAc:H_2O (1:1 – 40 mL) and the phases were separated. The organic phase was washed with aq. HCl (3 × 10 mL of 1.0 M). The acidic aqueous phases were combined and basified with 35% NH_4OH to pH 14. The aqueous phase was re-extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 5:95) gave the title quinolizidine as a brown oil (66.2 mg, 0.339 mmol, 90%).

$[\alpha]_D$:	+ 35.9 (c 0.1, $CHCl_3$, 25 °C).
FT-IR (cm^{-1}):	2943, 2744, 1736, 1210, 1166, 1138.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.76 – 5.68 (m, 1H, **H_9**), 5.53 (br d, *J* = 10.0 Hz, 1H, **H_8**), 3.64 (s, 3H, **H_1**), 2.99 – 2.79 (m, 3H, **H_7**, **H_{6eq}** & **H_{11eq}**), 2.66 (br q, *J* = 4.0 Hz, 1H, **H_3**), 2.45 – 2.32 (m, 2H, **H_{10eq}** & **H_{11ax}**), 2.23 – 2.09 (m, 2H, **H_{5eq}** & **H_{6ax}**), 2.09 – 1.98 (m, 1H, **H_{4eq}**), 1.92 – 1.87 (m, 1H, **H_{10ax}**), 1.61 – 1.49 (m, 2H, **H_{4ax}** & **H_{5ax}**).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 173.4 (**C_2**), 128.0 (**C_8**), 124.8 (**C_9**), 62.3 (**C_7**), 55.2 (**C_6**), 52.5 (**C_{11}**), 51.2 (**C_1**), 44.1 (**C_3**), 26.3 (**C_4**), 24.8 (**C_{10}**), 22.7 (**C_5**).
LRMS:	(ES+) m/z = 196.4 $[M+H]^+$.
HRMS:	(ES+) for $C_{11}H_{18}NO_2^+$ calculated 196.1332, found 196.1336 Da.

((1*S*,9*aS*)-1,3,4,6,7,9*a*-Hexahydro-2*H*-quinolizin-1-yl)metanol (2.91)



$C_{10}H_{17}NO$
Mol Wt: 167.25

To a solution of quinolizidine **2.73** (30.0 mg, 0.154 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of $LiAlH_4$ (0.180 mL of 1.0 M in CH_2Cl_2, 0.180 mmol) at 0 °C under N_2. The mixture was stirred for 1.5 h at the same condition. The reaction was quenched by dropwise addition of aq. NaOH (2 mL of 2.0 M) at 0 °C. The mixture was stirred for 30 min and then filtered through the celite. The filter cake was washed with CH_2Cl_2 (5 × 10 mL), and the phases were separated. The aqueous was re-extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:4) gave the title quinolizidine as a colourless oil (22.1 mg, 0.132 mmol, 86%).

$[\alpha]_D$: + 104.5 (c 0.15, $CHCl_3$, 25 °C).

FT-IR (cm^{-1}): 3364, 2933, 1464, 1075, 1033.

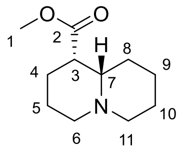
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.88 – 5.80 (m, 1H, **H_9**), 5.52 (br d, *J* = 10.0 Hz, 1H, **H_8**), 5.12 (br s, 1H, **H_1**), 4.05 (dt, *J* = 10.8, 2.6 Hz, 1H, **H_{2a}**), 3.67 (dt, *J* = 10.8, 1.6 Hz, 1H, **H_{2b}**), 2.96 (br s, 1H, **H_7**), 2.91 – 2.82 (m, 1H, **H_{6eq}**), 2.78 (dd, *J* = 10.9, 5.6 Hz, 1H, **H_{11eq}**), 2.48 – 2.37 (m, 1H, **H_{10eq}**), 2.34 – 2.14 (m, 3H, **H_{5eq}**, **H_{6ax}** & **H_{11ax}**), 2.06 – 1.87 (m, 2H, **H_{10ax}** & **H_{4eq}**), 1.72 – 1.56 (m, 3H, **H_3**, **H_{4ax}** & **H_{5ax}**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 128.2 (**C_8**), 126.1 (**C_9**), 65.8 (**C_2**), 64.3 (**C_7**), 56.3 (**C_6**), 52.1 (**C_{11}**), 38.4 (**C_3**), 30.1 (**C_4**), 25.7 (**C_{10}**), 23.4 (**C_5**).

LRMS: (ES+) m/z = 168.2 $[M+H]^+$.

HRMS: (ES+) for $C_{10}H_{18}NO^+$ calculated 168.1383, found 168.1384 Da.

Methyl (1*S*,9*aS*)-octahydro-2*H*-quinolizine-1-carboxylate (2.96)



$C_{11}H_{19}NO_2$
Mol Wt: 197.28

To a solution of quinolizidine **2.73** (50.0 mg, 0.256 mmol) in EtOH (5 mL) was added 10% wt Pd/C (28.0 mg, 0.0264 mmol). The RBF was placed under an atmosphere of H_2 and stirred rapidly. After 4 h, the mixture was filtered through the celite. The filter cake was washed with MeOH (3 × 5 mL) and the solvent was removed *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title quinolizidine as a colourless oil (43.0 mg, 0.218 mmol, 84%). Data are consistent with those previously reported.[144]

[α]$_D$: + 8.5 (c 0.1, $CHCl_3$, 25 °C). Lit.[144] + 10.2 (c 1.5, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 2933, 1738, 1442, 1207, 1156, 1127, 1112.

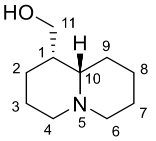
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 3.67 (s, 3H, **H**$_1$), 2.95 – 2.86 (m, 2H, **H**$_{6eq}$ & **H**$_{11eq}$), 2.61 – 2.51 (m, 1H, **H**$_3$), 2.19 – 1.90 (m, 5H, **H**$_{5eq}$, **H**$_{6ax}$, **H**$_7$, **H**$_{10eq}$ & **H**$_{11ax}$), 1.80 – 1.71 (m, 1H, **H**$_{9eq}$), 1.67 – 1.42 (m, 6H, **H**$_4$, **H**$_{5ax}$, **H**$_8$ & **H**$_{10ax}$), 1.34 – 1.19 (m, 1H, **H**$_{9ax}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 174.1 (**C**$_2$), 62.9 (**C**$_7$), 57.3 (**C**$_{11}$), 55.4 (**C**$_6$), 51.2 (**C**$_1$), 44.6 (**C**$_3$), 29.3 (**C**$_8$), 26.5 (**C**$_{10}$), 25.0 (**C**$_9$), 24.7 (**C**$_4$), 22.2 (**C**$_5$).

LRMS: (ES+) m/z = 198.4 $[M+H]^+$.

HRMS: (ES+) for $C_{11}H_{20}NO_2^+$ calculated 198.1489, found 198.1490 Da.

(+)-Lupinine (2.01)

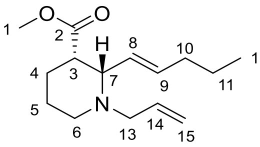


$C_{10}H_{19}NO$
Mol Wt: 169.27

To a solution of quinolizidine **2.96** (50.0 mg, 0.254 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise a solution of $LiAlH_4$ (0.300 mL of 1.0 M in CH_2Cl_2, 0.300 mmol) at 0 °C under N_2. Then the mixture was stirred for 1.5 h at the same temperature. The reaction was quenched by dropwise addition of aq. NaOH (5 mL of 2.0 M) at 0 °C. The mixture was filtered through the celite. The filter cake was washed with CH_2Cl_2 (5 × 10 mL), and the phases were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title quinolizidine as white crystals (35.0 mg, 0.207 mmol, 81%). Data are consistent with those previously reported.[70]

Melting point:	67–68 °C. (Lit.[114] 67–68 °C).
$[\alpha]_D$:	+ 12.9 (c 0.1, EtOH, 23 °C). Lit.[70] +12.7 (c 0.35, EtOH, 30 °C). Lit.[114] +19.5 (c 1.0, EtOH, 20 °C). Lit.[113] +13.4 (c 1.0, EtOH, 20 °C).
FT-IR (cm^{-1}):	3352, 2931, 2856, 2805, 1443, 1036.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.14 (ddd, *J* = 10.7, 4.7, 1.5 Hz, 1H, $\mathbf{H}_{11a}$), 3.68 (br d, *J* = 10.7 Hz, 1H, $\mathbf{H}_{11b}$), 2.84 – 2.76 (m, 2H, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{6eq}$), 2.20 – 2.07 (m, 2H, $\mathbf{H}_{10}$ & $\mathbf{H}_{3eq}$), 2.05 - 1.95 (m, 1H, $\mathbf{H}_{6ax}$), 1.87 – 1.67 (m, 4H, $\mathbf{H}_{2eq}$, $\mathbf{H}_{4ax}$, $\mathbf{H}_{8eq}$ & $\mathbf{H}_{9eq}$), 1.60 – 1.35 (m, 6H, $\mathbf{H}_1$, $\mathbf{H}_{2ax}$, $\mathbf{H}_{3ax}$, $\mathbf{H}_7$ & $\mathbf{H}_{9ax}$), 1.31 – 1.18 (m, 1H, $\mathbf{H}_{8ax}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 65.9 ($\mathbf{C}_{11}$), 65.1 ($\mathbf{C}_{10}$), 57.1 ($\mathbf{C}_6$ & $\mathbf{C}_4$), 38.2 ($\mathbf{C}_1$), 31.4 ($\mathbf{C}_2$), 29.7 ($\mathbf{C}_9$), 25.6 ($\mathbf{C}_7$), 24.6 ($\mathbf{C}_8$), 22.9 ($\mathbf{C}_3$).
LRMS:	(ES+) m/z = 170.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{10}H_{20}NO^+$ calculated 170.1539, found 170.1538 Da.

Methyl (2*S*,3*S*)-1-allyl-2-((*E*)-pent-1-en-1-yl)piperidine-3-carboxylate (2.97)

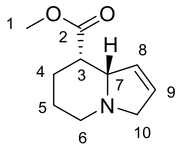


$C_{15}H_{25}NO_2$
Mol Wt: 251.37

To a solution of piperidine **2.88** (500 mg, 2.37 mmol) in MeCN (10 mL) was added allyl bromide (0.200 mL, 2.40 mmol) and K_2CO_3 (400 mg, 2.90 mmol). The reaction mixture was stirred at rt for 3 h. The solvent was removed *in vacuo*. The residue was re-dissolved in a mixture of EtOAc:H_2O (1:1 – 40 mL) and the layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 4:6) gave the title piperidine as a yellow oil (540 mg, 2.14 mmol, 89%).

[α]$_D$:	–41.4 (c 0.15, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2926, 1739, 1435, 1113, 970.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.89 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H, **H**$_{14}$), 5.65 – 5.49 (m, 2H, **H**$_8$ & **H**$_9$), 5.19 – 5.08 (m, 2H, **H**$_{15}$), 3.66 (dd, *J* = 8.9, 3.7 Hz, 1H, **H**$_7$), 3.61 (s, 3H, **H**$_1$), 3.10 (dd, *J* = 14.0, 6.0 Hz, 1H, **H**$_{13a}$), 2.96 (dd, *J* = 14.0, 6.2 Hz, 1H, **H**$_{13b}$), 2.88 – 2.81 (m, 1H, **H**$_3$), 2.61 (br d, *J* = 11.5 Hz, 1H, **H**$_{6eq}$), 2.41 (td, *J* = 11.5, 2.4 Hz, 1H, **H**$_{6ax}$), 2.07 – 1.95 (m, 2H, **H**$_{10}$), 1.83 – 1.60 (m, 4H, **H**$_4$ & **H**$_5$), 1.37 (sxt, *J* = 7.4 Hz, 2H, **H**$_{11}$), 0.89 (t, *J* = 7.4 Hz, 3H, **H**$_{12}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 173.7 (**C**$_2$), 136.8 (**C**$_9$), 136.0 (**C**$_{14}$), 121.3 (**C**$_8$), 117.3 (**C**$_{15}$), 61.8 (**C**$_7$), 58.5 (**C**$_{13}$), 51.3 (**C**$_1$), 46.6 (**C**$_6$), 46.5 (**C**$_3$), 34.8 (**C**$_{10}$), 24.6 (**C**$_5$), 22.6 (**C**$_{11}$), 21.3 (**C**$_4$), 13.5 (**C**$_{12}$).
LRMS:	(ES+) m/z = 252.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{26}NO_2^+$ calculated 252.1958, found 252.1959 Da.

Methyl (8*S*,8*aS*)-3,5,6,7,8,8*a*-hexahydroindolizine-8-carboxylate (2.101)

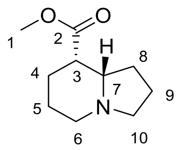


$C_{10}H_{15}NO_2$
Mol Wt: 181.24

To a solution of piperidine **2.97** (100 mg, 0.398 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2 was added Grubbs II (25.0 mg, 0.0295 mmol) and 1,4-benzoquinone (3.5 mg, 0.0324 mmol). The reaction was stirred at rt for 1 h. The solvent was removed *in vacuo*. The residue was treated with EtOAc (20 mL), triturated and filtered through the celite. The filter cake was washed with EtOAc (3 × 15 mL) and the combined organics were concentrated *in vacuo*. The residue was partitioned between EtOAc:H_2O (1:1 – 40 mL) and the phases were separated. The organics were washed with aq. HCl (3 × 10 mL of 1.0 M). The acidic aqueous phases were combined and basified with 35% NH_4OH to pH 14. The aqueous phase was re-extracted with EtOAc (3 × 20 mL). The organics were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 5:95) gave the title indolizidine as a brown oil (62.0 mg, 0.343 mmol, 86%).

$[\alpha]_D$:	–50 (c 0.1, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2946, 2776, 1734, 1437, 1212, 1162, 1121.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.96 – 5.93 (m, 1H, **H_9**), 5.80 – 5.77 (m, 1H, **H_8**), 3.66 (s, 3H, **H_1**), 3.64 – 3.59 (m, 1H, **H_{10eq}**), 3.33 – 3.20 (m, 1H, **H_7**), 3.10 – 2.97 (m, 2H, **H_{6eq}** & **H_{10ax}**), 2.92 – 2.84 (m, 1H, **H_3**), 2.41 (td, *J* = 11.1, 3.1 Hz, 1H, **H_{6ax}**), 2.17 – 1.99 (m, 2H, **H_{4eq}** & **H_{5eq}**), 1.58 – 1.40 (m, 2H, **H_{4ax}** & **H_{5ax}**)
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 173.5 (**C_2**), 132.0 (**C_9**), 126.8 (**C_8**), 69.5 (**C_7**), 58.5 (**C_{10}**), 51.2 (**C_1**), 50.8 (**C_6**), 42.1 (**C_3**), 25.5 (**C_4**), 22.6 (**C_5**).
LRMS:	(ES+) m/z = 182.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{10}H_{16}NO_2^+$ calculated 182.1176, found 182.1177 Da.

Methyl (8*S*,8*aS*)-octahydroindolizine-8-carboxylate (2.102)



$C_{10}H_{17}NO_2$
Mol Wt: 183.25

To a solution of indolizidine **2.101** (50.0 mg, 0.276 mmol) in EtOH (5 mL) was added 10% wt Pd/C (27.0 mg, 0.0255 mmol). The RBF was placed under an atmosphere of H_2 and stirred rapidly. After 4 h, the reaction was filtered through the celite. The filter cake was washed with MeOH (3 × 5 mL) and the solvent was removed *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title indolizidine as a colourless oil (43.0 mg, 0.235 mmol, 84%). Data are consistent with those previously reported.[70]

$[\alpha]_D$: + 18.1 (c 0.15, $CHCl_3$, 23 °C). Lit.[70] + 18.6 (c 0.22, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 2948, 1737, 1438, 1219, 1154.

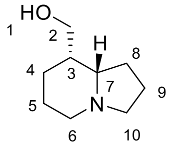
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 3.68 (s, 3H, **H**$_1$), 3.16 – 3.01 (m, 2H, **H**$_{6eq}$ & **H**$_{10eq}$), 2.85 – 2.77 (m, 1H, **H**$_3$), 2.21 – 2.16 (m, 1H, **H**$_7$), 2.13 – 1.95 (m, 4H, **H**$_{4eq}$, **H**$_{5eq}$, **H**$_{6ax}$ & **H**$_{10ax}$), 1.84 – 1.71 (m, 3H, **H**$_8$ & **H**$_{9eq}$), 1.69 – 1.40 (m, 3H, **H**$_{4ax}$, **H**$_{5ax}$ & **H**$_{9ax}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 173.5 (**C**$_2$), 64.4 (**C**$_7$), 54.8 (**C**$_{10}$), 53.0 (**C**$_6$), 51.2 (**C**$_1$), 41.8 (**C**$_3$), 26.7 (**C**$_8$), 26.2 (**C**$_4$), 22.4 (**C**$_5$), 20.6 (**C**$_9$).

LRMS: (ES+) m/z = 184.3 $[M+H]^+$.

HRMS: (ES+) for $C_{10}H_{18}NO_2^+$ calculated 184.1332, found 184.1328 Da.

(–)-Epitashiromine (2.103)

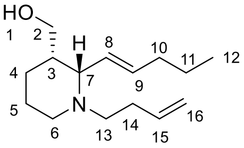


$C_9H_{17}NO$
Mol Wt: 155.24

To a solution of indolizidine **2.102** (50.0 mg, 0.273 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise a solution of $LiAlH_4$ (0.330 mL of 1.0 M in CH_2Cl_2, 0.330 mmol) at 0 °C under N_2. The reaction was stirred for 2 h at the same temperature. The reaction was quenched by dropwise addition of aq. NaOH (5 mL, 2.0 M) at 0 °C. The mixture was filtered through the celite. The filter cake was washed with CH_2Cl_2 (5 × 10 mL), and the phases were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title indolizidine as a colourless oil (34.0 mg, 0.219 mmol, 79%). Data are consistent with those previously reported.[70]

$[\alpha]_D$:	–1.4 (c 0.3, EtOH, 23 °C). Lit.[116] –1.9 (c 1.0, EtOH, 25 °C).
FT-IR (cm^{-1}):	3310, 2929, 2781, 1444, 1325, 1030.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.17 (dd, *J* = 10.8, 4.2 Hz, 1H, $\mathbf{H}_{2a}$), 3.74 (br d, *J* = 10.8 Hz, 1H, $\mathbf{H}_{2b}$), 3.14 – 3.07 (m, 1H, $\mathbf{H}_{6eq}$), 3.04 – 2.98 (m, 1H, $\mathbf{H}_{10eq}$), 2.24 (ddd, *J* = 10.1, 6.8, 2.9 Hz, 1H, $\mathbf{H}_7$), 2.11 – 2.02 (m, 1H, $\mathbf{H}_{5eq}$), 2.02 – 1.86 (m, 4H, $\mathbf{H}_{4eq}$, $\mathbf{H}_{6ax}$, $\mathbf{H}_{8eq}$ & $\mathbf{H}_{10ax}$), 1.85 – 1.64 (m, 4H, $\mathbf{H}_3$, $\mathbf{H}_{8ax}$ & $\mathbf{H}_9$), 1.64 – 1.48 (m, 2H, $\mathbf{H}_{4ax}$ & $\mathbf{H}_{5ax}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 66.9 ($\mathbf{C}_7$), 65.6 ($\mathbf{C}_2$), 54.5 ($\mathbf{C}_{10}$), 53.6 ($\mathbf{C}_6$), 35.3 ($\mathbf{C}_3$), 30.7 ($\mathbf{C}_4$), 25.9 ($\mathbf{C}_8$), 23.3 ($\mathbf{C}_5$), 20.8 ($\mathbf{C}_9$).
LRMS:	(ES+) m/z = 156.2 $[M+H]^+$.
HRMS:	(ES+) for $C_9H_{18}NO^+$ calculated 156.1383, found 156.1379 Da.

((2*S*,3*S*)-1-(But-3-en-1-yl)-2-((*E*)-pent-1-en-1-yl)piperidin-3-yl)methanol (2.106)

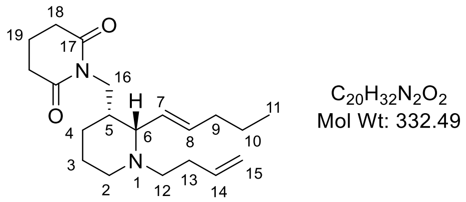


$C_{15}H_{27}NO$
Mol Wt: 237.39

To a solution of piperidine **2.91** (1.00 g, 3.77 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise a solution of $LiAlH_4$ (3.90 mL of 1.0 M in CH_2Cl_2, 3.90 mmol) at 0 °C under N_2. The reaction was stirred for 1.5 h at the same temperature. The reaction was quenched by dropwise addition of aq. NaOH (10 mL of 2.0 M) at 0 °C. The mixture was filtered through the celite. The filter cake was washed with EtOAc (5 × 10 mL), and the phases were separated. The aqueous was re-extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title piperidine as a yellow oil (810 mg, 3.42 mmol, 90%).

$[\alpha]_D$:	+ 11.4 (c 0.3, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	3338, 2926, 1641, 1376, 1077, 972.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.80 – 5.59 (m, 3H, **H_8**, **H_9** & **H_{15}**), 5.05 – 4.97 (m, 2H, **H_{16}**), 3.86 (dd, *J* = 10.7, 4.7 Hz, 1H, **H_{2a}**), 3.57 (dd, *J* = 10.7, 4.1 Hz, 1H, **H_{2b}**), 3.14 (dd, *J* = 9.0, 3.5 Hz, 1H, **H_7**), 2.80 (dd, *J* = 11.0, 7.0 Hz, 1H, **H_{6eq}**), 2.68 – 2.58 (m, 1H, **H_{13a}**), 2.37 – 2.13 (m, 4H, **H_{6ax}**, **H_{13b}** & **H_{14}**), 2.06 (q, *J* = 7.1 Hz, 2H, **H_{10}**), 2.02 – 1.89 (m, 1H, **H_{4eq}**), 1.76 – 1.73 (m, 1H, **H_3**), 1.68 – 1.55 (m, 3H, **H_{4ax}** & **H_5**), 1.42 (sxt, *J* = 7.1 Hz, 2H, **H_{11}**), 0.91 (t, *J* = 7.1 Hz, 3H, **H_{12}**).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 136.7 (**C_{15}**), 134.6 (**C_9**), 127.4 (**C_8**), 115.6 (**C_{16}**), 66.3 (**C_7**), 66.1 (**C_2**), 54.3 (**C_{13}**), 50.7 (**C_6**), 41.5 (**C_3**), 34.6 (**C_{10}**), 31.0 (**C_{14}**), 27.7 (**C_5**), 24.4 (**C_4**), 22.5 (**C_{11}**), 13.6 (**C_{12}**).
LRMS:	(ES+) *m/z* = 238.4 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{28}NO^+$ calculated 238.2165, found 238.2166 Da.

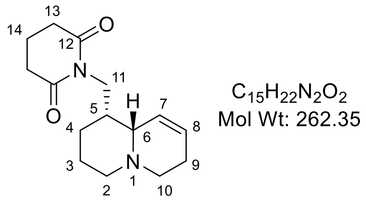
1-(((2*S*,3*R*)-1-(But-3-en-1-yl)-2-((*E*)-pent-1-en-1-yl)piperidin-3-yl)methyl)piperidine-2,6-dione (2.108)



To a solution of alcohol **2.106** (500 mg, 2.11 mmol) in anhydrous THF (5 mL) was added glutarimide (751 mg, 6.65 mmol), ADDP (1.68 g, 6.65 mmol) and *n*-Bu$_3$P (1.66 mL, 6.65 mmol) at 0 °C under N$_2$. The reaction was stirred for 24 h at rt. A mixture of EtOAc:H$_2$O (1:1 – 20 mL) was added. The phases were separated and the aqueous layer was re-extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with aq. HCl (3 × 10 mL of 0.5 M), dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography on Al$_2$O$_3$ (EtOAc:hexane – 4:6) gave the title diene as a yellow oil (650 mg, 1.96 mmol, 93%).

$[\alpha]_D$:	–42.1 (c 0.1, CHCl$_3$, 23 °C).
FT-IR (cm^{-1}):	2929, 1673, 1351, 1167, 1119.
^{1}H NMR:	(CDCl$_3$, 400 MHz) δ ppm = 5.77 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, $\mathbf{H}_{14}$), 5.71 – 5.54 (m, 2H, $\mathbf{H}_7$ & $\mathbf{H}_8$), 5.05 – 4.92 (m, 2H, $\mathbf{H}_{15}$), 3.69 (dd, *J* = 13.1, 9.5 Hz, 1H, $\mathbf{H}_{16a}$), 3.49 (dd, *J* = 13.1, 4.2 Hz, 1H, $\mathbf{H}_{16b}$), 3.32 – 3.22 (m, 1H, $\mathbf{H}_6$), 2.63 (t, *J* = 6.6 Hz, 4H, $\mathbf{H}_{18}$), 2.60 – 2.33 (m, 4H, $\mathbf{H}_2$ & $\mathbf{H}_{12}$), 2.27 – 2.13 (m, 2H, $\mathbf{H}_{13}$), 2.11 – 1.88 (m, 5H, $\mathbf{H}_5$, $\mathbf{H}_9$ & $\mathbf{H}_{19}$), 1.74 – 1.22 (m, 6H, $\mathbf{H}_3$, $\mathbf{H}_4$ & $\mathbf{H}_{10}$), 0.91 (t, *J* = 7.3 Hz, 3H, $\mathbf{H}_{11}$).
^{13}C NMR:	(CDCl$_3$, 101 MHz) δ ppm 172.6 ($\mathbf{C}_{17}$), 136.9 ($\mathbf{C}_{14}$), 136.6 ($\mathbf{C}_8$), 122.4 ($\mathbf{C}_7$), 115.3 ($\mathbf{C}_{15}$), 63.6 ($\mathbf{C}_6$), 54.6 ($\mathbf{C}_{12}$), 47.7 ($\mathbf{C}_2$), 42.4 ($\mathbf{C}_{16}$), 39.2 ($\mathbf{C}_5$), 34.8 ($\mathbf{C}_9$), 33.0 ($\mathbf{C}_{18}$), 31.6 ($\mathbf{C}_{13}$), 25.1 ($\mathbf{C}_3$), 24.5 ($\mathbf{C}_4$), 22.6 ($\mathbf{C}_{10}$), 17.2 ($\mathbf{C}_{19}$), 13.7 ($\mathbf{C}_{11}$).
LRMS:	(ES+) m/z = 333.4 $[M+H]^+$.
HRMS:	(ES+) for $C_{20}H_{33}N_2O_2^+$ calculated 333.2537, found 333.2540 Da.

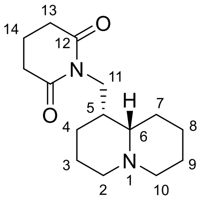
1-(((1*R*,9*aS*)-1,3,4,6,7,9*a*-Hexahydro-2*H*-quinolizin-1-yl)methyl)piperidine-2,6-dione (2.109)



To a solution of diene **2.108** (200 mg, 0.602 mmol) in anhydrous CH_2Cl_2 (10 mL) was added Hoveyda-Grubbs II (38.0 mg, 0.0607 mmol) under N_2. The reaction was heated at reflux for 2 h. The solvent was removed *in vacuo*. The residue was treated with EtOAc (20 mL), triturated and filtered through the celite. The filter cake was washed with EtOAc (3 × 15 mL) and the combined organics were concentrated *in vacuo*. The residue was then partitioned between EtOAc:H_2O (1:1 - 40 mL) and the phases were separated. The organic phase was washed with aq. HCl (3 × 10 mL of 1.0 M). The acidic aqueous phases were combined and basified with 35% NH_4OH to pH 14. The aqueous phase was re-extracted with EtOAc (3 × 20 mL). The organics were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:9) gave the title product as a yellow oil (126 mg, 0.481 mmol, 80%).

$[\alpha]_D$:	+ 13.5 (c 0.1, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2934, 2741, 1722, 1666, 1351, 1164, 1111.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.77 (dt, *J* = 9.9, 2.7 Hz, 1H, **H**$_8$), 5.63 (br d, *J* = 9.9 Hz, 1H, **H**$_7$), 4.26 (dd, *J* = 13.3, 10.6 Hz, 1H, **H**$_{11a}$), 3.66 – 3.60 (m, 1H, **H**$_{11b}$), 2.86 – 2.81 (m, 1H, **H**$_{2eq}$), 2.74 (dd, *J* = 10.9, 5.6 Hz, 1H, **H**$_{10eq}$), 2.71 – 2.65 (m, 1H, **H**$_6$), 2.63 (t, *J* = 6.5 Hz, 4H, **H**$_{13}$), 2.44 – 2.30 (m, 1H, **H**$_{9eq}$), 2.27 – 2.19 (m, 1H, **H**$_{10ax}$), 2.12 – 2.03 (m, 2H, **H**$_{2ax}$ & **H**$_{3eq}$), 1.95 – 1.87 (m, 4H, **H**$_5$, **H**$_{9ax}$ & **H**$_{14}$), 1.49 – 1.21 (m, 3H, **H**$_{3ax}$ & **H**$_4$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm 172.8 (**C**$_{12}$), 129.0 (**C**$_7$), 125.7 (**C**$_8$), 64.4 (**C**$_6$), 56.8 (**C**$_2$), 52.6 (**C**$_{10}$), 37.3 (**C**$_{11}$), 36.8 (**C**$_5$), 33.1 (**C**$_{13}$), 26.4 (**C**$_4$), 25.9 (**C**$_9$), 21.2 (**C**$_3$), 17.3 (**C**$_{14}$).
LRMS:	(ES+) m/z = 263.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{23}N_2O_2^+$ calculated 263.1754, found 263.1760 Da.

(–)-Epilamprolobine (2.104)

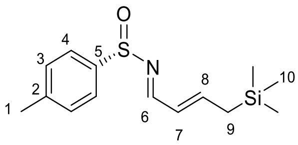


$C_{15}H_{24}N_2O_2$
Mol Wt: 264.37

To a solution of **2.109** (50.0 mg, 0.191 mmol) in EtOH (2 mL) was added 10% wt Pd/C (21.0 mg, 0.0198mmol). The RBF was placed under an atmosphere H_2 and stirred rapidly. After 4 h, the mixture was filtered through the celite. The filter cake was washed with MeOH (5 × 5 mL) and the solvent removed *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title product as white crystals (39.0 mg, 0.148mmol, 77%). Data are consistent with those previously reported.[122]

Melting Point:	62-63 °C. (Lit.[122] 66.5-67.5 °C).
[α]$_D$:	–12.0 (c 0.1, EtOH, 23 °C). Lit.[118] –13.8 (c 0.34, EtOH, 23 °C).
FT-IR (cm^{-1}):	2931, 2758, 1722, 1668, 1353, 1166, 1124.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.26 (t, *J* = 12.5 Hz, 1H, **H**$_{11a}$), 3.77 (dd, *J* = 12.5, 3.6 Hz, 1H, **H**$_{11b}$), 2.90 – 2.81 (m, 2H, **H**$_{2eq}$ & **H**$_{10eq}$), 2.64 (t, *J* = 6.5 Hz, 4H, **H**$_{13}$), 2.11 – 1.84 (m, 7H, **H**$_{2ax}$, **H**$_{3eq}$, **H**$_5$, **H**$_6$, **H**$_{10ax}$ & **H**$_{14}$), 1.82 – 1.74 (m, 1H, **H**$_{8eq}$), 1.68 – 1.51 (m, 4H, **H**$_7$, **H**$_{8ax}$ & **H**$_{9eq}$), 1.49 – 1.17 (m, 4H, **H**$_{3ax}$, **H**$_4$, & **H**$_{9ax}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm 172.9 (**C**$_{12}$), 65.2 (**C**$_6$), 57.6 (**C**$_{10}$), 56.9 (**C**$_2$), 37.9 (**C**$_{11}$), 37.2 (**C**$_5$), 33.2 (**C**$_{13}$), 29.6 (**C**$_7$), 26.5 (**C**$_4$), 25.4 (**C**$_9$), 25.0 (**C**$_8$), 21.1 (**C**$_3$), 17.3 (**C**$_{14}$).
LRMS:	(ES+) m/z = 265.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{25}N_2O_2^+$ calculated 265.1911, found 265.1908 Da.

(*S*)-4-Methyl-*N*-((1*E*,2*E*)-4-(trimethylsilyl)but-2-en-1-ylidene)benzenesulfinamide (2.123)

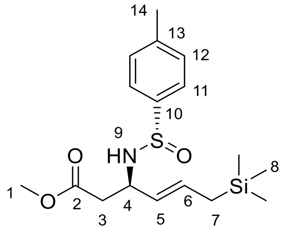


$C_{14}H_{21}NOSSi$
Mol Wt: 279.47

To a solution of acrolein (1.40 mL, 21.0 mmol) and allyltrimethylsilane (9.50 mL, 59.9 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Hoveyda-Grubbs II (313 mg, 0.500 mmol) in one portion. The reaction was stirred for 30 min at rt and token a drop of reaction mixture to check by ^1H NMR spectroscopy. When acrolein was consumed showed by ^1H NMR, the mixture was filtered through a thin silica gel, and the silica gel was washed with hexane (4 × 20 mL). To the combined organic solution was added sulfinamide **2.53** (2.80 g, 18.1 mmol) and $Ti(OEt)_4$ (8.40 mL, 36.8 mmol). The reaction was stirred at rt under N_2. After 12 h, brine (100 mL) was added. The mixture was stirred rapidly for 5 min and filtered. The filter cake was washed with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) afforded the title sulfinimine as a pale yellow oil (4.30 g, 15.3 mmol, 85%).

$[\alpha]_D$:	+ 474.9 (c 0.5, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	1575, 1091, 1070, 808, 705, 555.
^1H NMR:	($CDCl_3$, 400 MHz) δ ppm = 8.31 (d, *J* = 9.4 Hz, 1H, $\mathbf{H}_6$), 7.58 (d, *J* = 7.7 Hz, 2H, $\mathbf{H}_4$), 7.30 (d, *J* = 7.7 Hz, 2H, $\mathbf{H}_3$), 6.64 (dt, *J* = 15.2, 8.8 Hz, 1H, $\mathbf{H}_8$), 6.27 (ddt, *J* = 15.2, 9.4, 1.2 Hz, 1H, $\mathbf{H}_7$), 2.40 (s, 3H, $\mathbf{H}_1$), 1.83 (dd, *J* = 8.8, 1.2 Hz, 2H, $\mathbf{H}_9$), 0.0 (s, 9H, $\mathbf{H}_{10}$)
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm 163.9 ($\mathbf{C}_6$), 153.4 ($\mathbf{C}_8$), 144.1 ($\mathbf{C}_5$), 143.4 ($\mathbf{C}_2$), 131.6 ($\mathbf{C}_3$), 128.9 ($\mathbf{C}_7$), 126.5 ($\mathbf{C}_4$), 28.1 ($\mathbf{C}_1$), 23.2 ($\mathbf{C}_9$), 0.0 ($\mathbf{C}_{10}$).

Methyl (*R*,*E*)-3-(((*S*)-*p*-tolylsulfinyl)amino)-6-(trimethylsilyl)hex-4-enoate (2.122)

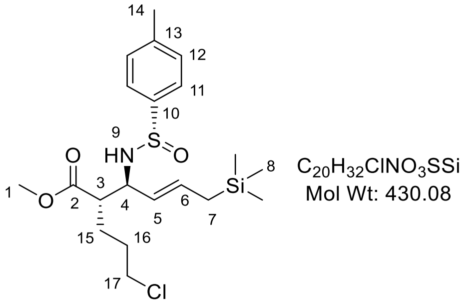


$C_{17}H_{27}NO_3SSi$
Mol Wt: 353.55

To a solution of methyl acetate (0.810 mL, 10.2 mmol) in anhydrous THF (5 mL) was added dropwise a solution of NaHMDS (11.0 mL of 1.0 M in THF, 11.0 mmol,) at –78 °C under N_2. After addition, the N_2 flow was removed and the round bottom flask was sealed to avoid evaporation of methyl acetate. The reaction was stirred for 1 h at –78 °C and then a solution of sulfinimine **2.123** (1.40 g, 5.02 mmol) in THF (5 mL) was added dropwise. The reaction was stirred at –78 °C for 2 h and quenched by dropwise addition of sat. NH_4Cl (10 mL) at the same temperature. The mixture was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) afforded the diastereoisomerically pure imino-aldol as a pale yellow oil (1.50 g, 4.25 mmol, 85%) Integration of the N<u>H</u> peaks in the crude ^{1}H NMR spectrum showed *dr* 20:1.

$[\alpha]_D$:	+ 139.4 (c 0.3, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	3183, 2952, 1736, 1246, 1054, 841.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 7.59 (d, *J* = 8.1 Hz, 2H, $\mathbf{H_{11}}$), 7.29 (d, *J* = 8.1 Hz, 2H, $\mathbf{H_{12}}$), 5.84 – 5.74 (m, 1H, $\mathbf{H_6}$), 5.30 (dd, *J* = 15.2, 6.5 Hz, 1H, $\mathbf{H_5}$), 4.63 (d, *J* = 6.5 Hz, 1H, $\mathbf{H_9}$), 4.25 (quin, *J* = 6.5 Hz, 1H, $\mathbf{H_4}$), 3.64 (s, 3H, $\mathbf{H_1}$), 2.65 – 2.51 (m, 2H, $\mathbf{H_3}$), 2.40 (s, 3H, $\mathbf{H_{14}}$), 1.57 – 1.46 (m, 2H, $\mathbf{H_7}$), 0.0 (s, 9H, $\mathbf{H_8}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm 173.4 ($\mathbf{C_2}$), 144.5 ($\mathbf{C_{10}}$), 143.2 ($\mathbf{C_{13}}$), 133.7 ($\mathbf{C_6}$), 131.5 ($\mathbf{C_{12}}$), 128.9 ($\mathbf{C_5}$), 127.4 ($\mathbf{C_{11}}$), 55.4 ($\mathbf{C_4}$), 53.7 ($\mathbf{C_1}$), 43.1 ($\mathbf{C_3}$), 24.9 ($\mathbf{C_7}$), 23.3 ($\mathbf{C_{14}}$), 0.0 ($\mathbf{C_8}$).
LRMS:	(ES+) m/z = 354.2 $[M+H]^+$, 376.4 $[M+Na]^+$.
HRMS:	(ES+) for $C_{17}H_{28}NO_3SSi^+$ calculated 354.1554, found 354.1555 Da; for $C_{17}H_{27}NO_3SSiNa^+$ calculated 376.1373, found 376.1381 Da.

(2*S*,3*S*,*E*)-2-(3-Chloropropyl)-3-(((*S*)-*p*-tolylsulfinyl)amino)-6-(trimethylsilyl)hex-4-enoate (2.121)



$C_{20}H_{32}ClNO_3SSi$
Mol Wt: 430.08

A round bottom flask containing LiCl (1.70 g, 40.5 mmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (10.0 mL of 1.0 M in THF, 10.0 mmol) was added dropwise. To the solution was added dropwise β-amino ester **2.122** (1.40 g, 3.97 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then triflate **2.81** (1.80 g, 7.96 mmol) in anhydrous THF (10 mL) was added dropwise at –78 °C, and then stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of sat. NH_4Cl (20 mL) at the same temperature. After warming up to rt, the phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) gave the *anti* imino-aldol as an inseparable mixture containing the *syn* isomer as a yellow oil (842 mg, 1.96 mmol, 49%). Integration of the N$\underline{H}$ peaks in the crude ^{1}H NMR spectrum allowed estimation of the *anti:syn* ratio (*dr* ~10:1).

Data were recorded for the ~10:1 mixture of diastereoisomers

[α]$_D$: + 75.3 (c 0.2, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 3189, 2952, 1730, 1246, 1049, 967, 841.

^{1}H NMR: ($CDCl_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.58 (d, *J* = 8.1 Hz, 2H, **H**$_{11}$), 7.30 (d, *J* = 8.1 Hz, 2H, **H**$_{12}$), 5.75 (dt, *J* = 15.2, 8.3 Hz, 1H, **H**$_6$), 5.26 (dd, *J* = 15.2, 7.0 Hz, 1H, **H**$_5$), 4.57 (d, *J* = 7.0 Hz, 1H, **H**$_9$), 4.00 (q, *J* = 7.0 Hz, 1H, **H**$_4$) 3.66 (s, 3H, **H**$_1$), 3.48 (t, *J* = 6.2 Hz, 2H, **H**$_{17}$), 2.50 – 2.44 (m, 1H, **H**$_3$), 2.42 (s, 3H, **H**$_{14}$), 1.79 – 1.61 (m, 4H, **H**$_{15}$ & **H**$_{16}$), 1.54 (br d, *J* = 8.3 Hz, 2H, **H**$_7$), 0.0 (s, 9H, **H**$_8$).

^{13}C NMR: ($CDCl_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm 175.9 (**C**$_2$), 144.2 (**C**$_{10}$), 143.2 (**C**$_{13}$), 134.3 (**C**$_6$), 131.4 (**C**$_{12}$), 128.2 (**C**$_5$), 127.5 (**C**$_{11}$), 59.7 (**C**$_4$), 53.7 (**C**$_1$), 52.1 (**C**$_3$), 46.3 (**C**$_{17}$), 32.1 (**C**$_{16}$), 28.3 (**C**$_{15}$), 25.0 (**C**$_7$), 0.0 (**C**$_8$).

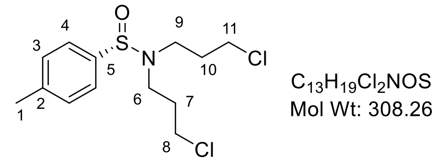
LRMS: (ES+) m/z = 452.4 [M^{35}Cl+Na]$^+$, 454.4 [M^{37}Cl+Na]$^+$.

HRMS: (ES+) for $C_{20}H_{32}ClNO_3SSiNa^+$ calculated 452.1453, found 452.1460 Da.

Selected data for the *syn* diastereoisomer:

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 4.60 (d, *J* = 6.5 Hz, 1H, **H**$_9$), 3.69 (s, 3H, **H**$_1$).

(*S*)-*N*,*N*-Bis(3-chloropropyl)-4-methylbenzenesulfinamide (2.82)



By-product isolated from above *anti*-alkylation reaction (61.0 mg, 0.198 mmol, 5%).

[α]$_D$: +106 (c 0.26, $CHCl_3$, 23 °C),

FT-IR (cm^{-1}): 2958, 1203, 1083, 1064, 753.

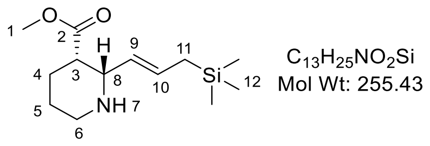
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.52 (d, *J* = 7.8 Hz, 2H, **H**$_3$), 7.32 (d, *J* = 7.8 Hz, 2H, **H**$_4$), 3.55 – 3.42 (m, 4H, **H**$_8$ & **H**$_{11}$), 3.30 – 3.15 (m, 4H, **H**$_6$ & **H**$_9$), 2.42 (s, 3H, **H**$_1$), 2.07 – 1.89 (m, 4H, **H**$_7$ & **H**$_{10}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm 141.6 (**C**$_5$), 140.3 (**C**$_2$), 129.7 (**C**$_3$), 125.9 (**C**$_4$), 45.3 (**C**$_8$ & **C**$_{11}$), 42.1 (**C**$_6$ & **C**$_9$), 31.2 (**C**$_7$ & **C**$_{10}$), 21.4 (**C**$_1$).

LRMS: (ES+) m/z = 308.3 [M^{35}Cl+Na]$^+$, 310.3 [M^{37}Cl+Na]$^+$.

HRMS: (ES+) for $C_{13}H_{20}Cl_2NOS^+$ calculated 308.0637, found 308.0634 Da.

Methyl (2*S*,3*S*)-2-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)piperidine-3-carboxylate (2.128)



To a solution of the mixture of *anti* imino-aldol **2.121** (*dr* ~10:1 with the *syn* diastereoisomer, 700 mg, 1.63 mmol) in dioxane (10 mL) was added dropwise *conc*. HCl (1.35 mL, 16.0 mmol) under N_2 dropwise. After 2 h, the reaction was concentrated *in vacuo* to give the crude product, which was used directly in next step. The crude product was re-dissolved in MeCN (20 mL) and to the solution was added K_2CO_3 (1.20 g, 8.69 mmol) and NaI (24.0 mg, 0.160 mmol). The reaction was stirred for 16 h at rt and then the solvent was removed *in vacuo*. The residue was re-dissolved in EtOAc:H_2O (1:1 – 100 mL) and the layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 3:7) gave the diastereoisomerically pure piperidine as a yellow oil (310 mg, 1.22 mmol, 76%).

[α]$_D$: + 16.3 (c 0.3, $CHCl_3$, 25 °C).

FT-IR (cm^{-1}): 3321, 2949, 1729, 1247, 1163, 848.

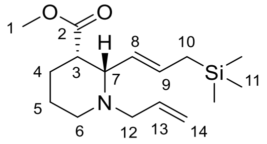
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.60 (dtd, *J* =15.4, 8.0, 1.1 Hz, 1H, $\mathbf{H}_{10}$), 5.43 (ddt, *J* = 15.4, 6.7, 1.3 Hz, 1H, $\mathbf{H}_{9}$), 3.65 (s, 3H, $\mathbf{H}_{1}$), 3.48 (dd, *J* = 6.7, 3.9 Hz, 1H, $\mathbf{H}_{8}$), 3.09 (dt, *J* = 12.8, 4.5 Hz, 1H, $\mathbf{H}_{6eq}$), 2.74 – 2.61 (m, 2H, $\mathbf{H}_{3}$ & $\mathbf{H}_{6ax}$), 2.09 – 1.89 (m, 2H, $\mathbf{H}_{4eq}$ & $\mathbf{H}_{7}$), 1.84 – 1.76 (m, 1H, $\mathbf{H}_{4ax}$), 1.75 – 1.63 (m, 1H, $\mathbf{H}_{5eq}$), 1.48 – 1.40 (m, 3H, $\mathbf{H}_{5ax}$ & $\mathbf{H}_{11}$), 0.0 (s, 9H, $\mathbf{H}_{12}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 176.2 ($\mathbf{C}_{2}$), 130.6 ($\mathbf{C}_{10}$), 129.6 ($\mathbf{C}_{9}$), 60.6 ($\mathbf{C}_{8}$), 53.3 ($\mathbf{C}_{1}$), 46.6 ($\mathbf{C}_{3}$), 46.3 ($\mathbf{C}_{6}$), 27.6 ($\mathbf{C}_{4}$), 25.2 ($\mathbf{C}_{5}$), 24.9 ($\mathbf{C}_{11}$), 0.0 ($\mathbf{C}_{12}$).

LRMS: (ES+) m/z = 256.3 $[M+H]^+$.

HRMS: (ES+) for $C_{13}H_{26}NO_2Si^+$ calculated 256.1727, found 256.1735 Da.

Methyl (2*S*,3*S*)-1-allyl-2-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)piperidine-3-carboxylate (2.120)

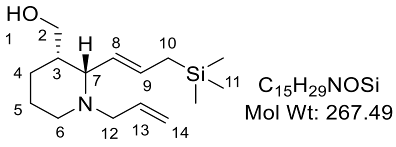


$C_{16}H_{29}NO_2Si$
Mol Wt: 295.50

To a solution of piperidine **2.128** (500 mg, 1.96 mmol) in MeCN (10 mL) was added allyl bromide (180 µL, 2.10 mmol) and K_2CO_3 (400 mg, 2.90 mmol). The reaction mixture was stirred at rt. After 3 h, the solvent was removed *in vacuo*. The residue was re-dissolved in EtOAc:H_2O (1:1 – 40 mL) and layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 4:6) gave the title piperidine as a yellow oil (540 mg, 1.83 mmol, 93%).

$[\alpha]_D$:	–8.6 (c 0.1, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2949, 1735, 1246, 1148, 1020, 967.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.85 (ddt, *J* = 17.0, 10.3, 6.4 Hz, 1H, **H_{13}**), 5.59 – 5.41 (m, 2H, **H_8** & **H_9**), 5.18 – 5.08 (m, 2H, **H_{14}**), 3.70 – 3.62 (m, 1H, **H_7**), 3.61 (s, 3H, **H_1**), 3.09 (br dd, *J* = 13.8, 6.4 Hz, 1H, **H_{12a}**), 2.93 (br dd, *J* = 13.8, 6.4 Hz, 1H, **H_{12b}**), 2.82 (dt, *J* = 11.6, 4.2 Hz, 1H, **H_3**), 2.61 – 2.53 (m, 1H, **H_{6eq}**), 2.47 – 2.35 (m, 2H, **H_{4eq}** & **H_{6ax}**), 1.82 – 1.69 (m, 2H, **H_{4ax}** & **H_{5eq}**), 1.67 – 1.39 (m, 3H, **H_{5ax}** & **H_{10}**), 0.0 (s, 9H, **H_{11}**).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 175.6 (**C_2**), 138.2 (**C_{13}**), 135.1 (**C_9**), 121.3 (**C_8**), 119.1 (**C_{14}**), 64.0 (**C_7**), 60.4 (**C_{12}**), 53.3 (**C_1**), 48.7 (**C_3**), 48.6 (**C_6**), 26.7 (**C_5**), 25.3 (**C_{10}**), 23.3 (**C_4**), 0.0 (**C_{11}**).
LRMS:	(ES+) *m/z* = 296.5 $[M+H]^+$.
HRMS:	(ES+) for $C_{16}H_{30}NO_2Si^+$ calculated 296.2040, found 296.2035 Da.

((2*S*,3*S*)-1-Allyl-2-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)piperidin-3-yl)methanol (2.129)



To a solution of piperidine **2.120** (135 mg, 0.458 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of $LiAlH_4$ (0.500 mL of 1.0 M in CH_2Cl_2, 0.500 mmol) at 0 °C under N_2. Then the mixture was stirred for 2 h at the same temperature. The reaction was quenched by dropwise addition of aq. NaOH (5 mL of 2.0 M) at 0 °C. The mixture was stirred for 30 min and filtered through the celite. The filter cake was washed with EtOAc (5 × 5 mL), and the phases were separated, re-extracting the aqueous phase with EtOAc (3 × 5 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:9) gave the title piperidine as a yellow oil (109 mg, 0.408 mmol, 89%).

$[\alpha]_D$: + 6.5 (c 0.1, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 3360, 2926, 1645, 1376, 1246, 1041, 836.

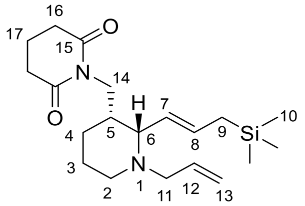
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.83 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1H, **H_{13}**), 5.67 – 5.50 (m, 2H, **H_8** & **H_9**), 5.16 – 5.08 (m, 2H, **H_{14}**), 3.81 (br dd, *J* = 10.5, 4.9 Hz, 1H, **H_{2a}**), 3.56 (dd, *J* = 10.5, 4.7 Hz, 1H, **H_{2b}**), 3.27 – 3.12 (m, 2H, **H_7** & **H_{12a}**), 2.86 (br dd, *J* = 13.9, 6.5 Hz, 1H, **H_{12b}**), 2.76 – 2.67 (m, 1H, **H_{6eq}**), 2.36 – 2.27 (m, 1H, **H_{6ax}**), 1.98 – 1.86 (m, 1H, **H_{4eq}**), 1.86 – 1.76 (m, 1H, **H_3**), 1.69 – 1.48 (m, 5H, **H_{4ax}**, **H_5** & **H_{10}**), 0.0 (s, 9H, **H_{11}**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 137.6 (**C_{13}**), 133.3 (**C_9**), 126.3 (**C_8**), 119.1 (**C_{14}**), 67.8 (**C_2** & **C_7**), 60.1 (**C_{12}**), 51.8 (**C_6**), 43.7 (**C_3**), 28.7 (**C_5**), 26.3 (**C_4**), 25.0 (**C_{10}**), 0.0 (**C_{11}**).

LRMS: (ES+) $m/z = 268.4\ [M+H]^+$.

HRMS: (ES+) for $C_{15}H_{30}NOSi^+$ calculated 268.2091, found 268.2086 Da.

1-(((2*S*,3*R*)-1-Allyl-2-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)piperidin-3-yl)methyl)piperidine-2,6-dione (2.119)

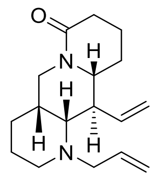


$C_{20}H_{34}N_2O_2Si$
Mol Wt: 362.59

To a solution of alcohol **2.129** (200 mg, 0.749 mmol) in anhydrous THF (5 mL) was added glutarimide (212 mg, 1.88 mmol), ADDP (475 mg, 1.88 mmol) and *n*-Bu_3P (0.463 mL, 1.88 mmol) at 0 °C under N_2. The reaction was stirred for 48 h at rt. The reaction was concentrated *in vacuo*, and the residue was re-dissolved in EtOAc:H_2O (1;1 – 20 mL). The phases were separated and the aqueous layer was re-extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with aq. HCl (3 × 10 mL of 0.5 M) and the aqueous solutions combined. The combined acidic aqueous solution was basified with 35% NH_4Cl to pH 14 and extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:9) gave the title diene as a yellow oil (240 mg, 0.663 mmol, 88%).

$[\alpha]_D$:	−74.3 (c 0.2, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2929, 1724, 1672, 1351, 1246, 1113, 849.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 5.84 (ddt, *J* = 17.0, 10.4, 6.4 Hz, 1H, **H**$_{12}$), 5.63 – 5.45 (m, 2H, **H**$_7$ & **H**$_8$), 5.15 – 5.05 (m, 2H, **H**$_{13}$), 3.73 (dd, *J* = 13.0, 9.8 Hz, 1H, **H**$_{14a}$), 3.47 (dd, *J* = 13.0, 3.9 Hz, 1H, **H**$_{14b}$), 3.25 (dd, *J* = 9.5, 3.9 Hz, 1H, **H**$_6$), 3.06 (dd, *J* = 13.8, 6.4 Hz, 1H, **H**$_{11a}$), 2.92 (dd, *J* = 13.8, 6.4 Hz, 1H, **H**$_{11b}$), 2.64 (t, *J* = 6.5 Hz, 4H, **H**$_{16}$), 2.53 – 2.48 (m, 1H, **H**$_{2eq}$), 2.38 (td, *J* = 11.4, 3.3 Hz, 1H, **H**$_{2ax}$), 2.07 – 1.98 (m, 1H, **H**$_5$), 1.92 (quin, *J* = 6.5 Hz, 2H, **H**$_{17}$), 1.72 – 1.66 (m, 1H, **H**$_{3eq}$), 1.58 – 1.45 (m, 3H, **H**$_{3ax}$ & **H**$_9$), 1.43 – 1.24 (m, 2H, **H**$_4$), 0.0 (s, 9H, **H**$_{10}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 174.4 (**C**$_{15}$), 138.3 (**C**$_{12}$), 134.6 (**C**$_8$), 122.3 (**C**$_7$), 118.6 (**C**$_{13}$), 65.9 (**C**$_6$), 60.2 (**C**$_{11}$), 48.9 (**C**$_2$), 44.3 (**C**$_{14}$), 41.4 (**C**$_5$), 34.8 (**C**$_{16}$), 27.1 (**C**$_3$), 26.2 (**C**$_4$), 25.2 (**C**$_9$), 19.0 (**C**$_{17}$), 0.0 (**C**$_{10}$).
LRMS:	(ES+) m/z = 363.5 $[M+H]^+$.
HRMS:	(ES+) for $C_{20}H_{35}N_2O_2Si^+$ calculated 363.2462, found 363.2463 Da.

(4*aR*,10*aR*,11*R*,11*aR*)-1-Allyl-11-vinyldodecahydro-7*H*-pyrido[1,2-*g*][1,6]naphthyridin-7-one (2.118)

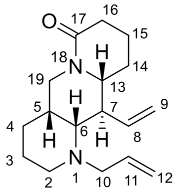


$C_{17}H_{26}N_2O$
Mol Wt: 274.41

To a solution of diene **2.119** (20.0 mg, 0.0552 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of $LiEt_3BH$ (0.110 mL of 1.0 M in THF, 0.110 mmol) at –78 °C under N_2. Then the reaction was stirred at the same temperature for 2 h. The reaction was quenched by dropwise addition of aq. HCl (2 mL of 2.0 M). The mixture was allowed to warm to rt and stirred for 1 h before basifying by addition of sat. $NaHCO_3$ (2 mL). The phase were separated and the aqueous phase was re-extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a yellow oil, which was used directly in the next step.

The crude material was re-dissolved in anhydrous CH_2Cl_2 (2 mL), and then $BF_3{\bullet}Et_2O$ (30.0 µL, 0.234 mmol) was added to the reaction at 0 °C. The reaction was stirred for 8 h at rt before quenching by addition of sat. $NaHCO_3$ (5 mL). The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (35% $NH_4OH:MeOH:CH_2Cl_2$ – 1:10:200) gave the title diene as a yellow oil (11.8 mg, 0.0430 mmol, 78%).

$[\alpha]_D$:	+ 60.7 (c 0.4, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2928, 1639, 1417, 1338, 1261, 914.



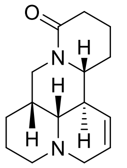
^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 5.75 (dddd, *J* = 17.3, 10.0, 7.5, 4.9 Hz, 1H, **H**$_{11}$), 5.47 (ddd, *J* = 16.9, 10.2, 9.2 Hz, 1H, **H**$_8$), 5.21 – 5.06 (m, 4H, **H**$_9$ & **H**$_{12}$), 4.62 (dd, *J* = 13.3, 2.2 Hz, 1H, **H**$_{19eq}$), 3.40 (dd, *J* = 13.6, 7.5 Hz, 1H, **H**$_{10a}$), 3.29 (dd, *J* = 13.6, 4.9 Hz, 1H, **H**$_{10b}$), 3.02 (dt, *J* = 9.7, 5.9 Hz, 1H, **H**$_{13}$), 2.78 (td, *J* = 13.8, 2.9 Hz, 1H, **H**$_{2eq}$), 2.70 (dd, *J* = 10.9, 4.8 Hz, 1H, **H**$_6$), 2.66 – 2.52 (m, 3H, **H**$_{2ax}$, **H**$_7$ & **H**$_{19ax}$), 2.44 – 2.27 (m, 2H, **H**$_{16}$), 2.08 – 1.91 (m, 2H, **H**$_5$ & **H**$_{14eq}$), 1.86 – 1.77 (m, 1H, **H**$_{15eq}$), 1.74 – 1.45 (m, 5H, **H**$_3$, **H**$_{4eq}$, **H**$_{14ax}$ & **H**$_{15ax}$), 1.33 – 1.25 (m, 1H, **H**$_{4ax}$).

^{13}C NMR: (CDCl$_3$, 101 MHz) δ ppm = 170.0 (**C**$_{17}$), 138.5 (**C**$_8$), 137.6 (**C**$_{11}$), 117.8 (**C**$_9$), 116.4 (**C**$_{12}$), 60.5 (**C**$_6$), 58.8 (**C**$_{13}$), 57.1 (**C**$_{10}$), 46.8 (**C**$_{19}$), 46.2 (**C**$_7$), 45.2 (**C**$_2$), 32.9 (**C**$_{16}$), 29.9 (**C**$_5$), 28.0 (**C**$_{14}$), 23.9 (**C**$_3$), 20.9 (**C**$_4$), 18.8 (**C**$_{15}$).

LRMS: (ES+) *m/z* = 275.4 [M+H]$^+$.

HRMS: (ES+) for $C_{17}H_{27}N_2O^+$ calculated 275.2118, found 275.2123 Da.

(4^1*R*,7*aR*,13*aS*,13*bS*)-4^1,6,7,7*a*,8,11,12,13,13*a*,13*b*-Decahydro-3*H*,5*H*,10*H*-dipyrido[2,1-*f*:3',2',1'-ij][1,6]naphthyridin-10-one (2.117)

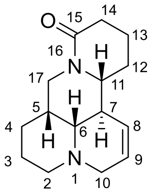


$C_{15}H_{22}N_2O$
Mol Wt: 246.35

To a solution of diene **2.118** (20.0 mg, 73.0 µmol) in anhydrous CH$_2$Cl$_2$ (2 mL) under N$_2$ was added Hoveyda-Grubbs II (4.50 mg, 7.19 µmol). The reaction was stirred at rt for 12 h. The solvent was removed *in vacuo*. The residue was treated with Et$_2$O (10 mL), triturated and filtered through the celite. The filter cake was washed with Et$_2$O (3 × 15 mL). The combined organics were washed with aq. HCl (3 × 10 mL of 1.0 M). The acidic aqueous phases were combined and basified with 35% NH$_4$OH to pH 14. The aqueous phase was re-extracted with EtOAc (3 × 10 mL) and CHCl$_3$ (3 × 10 mL). The organics were combined, dried (MgSO$_4$), and concentrated *in vacuo*. Purification by column chromatography (35% NH$_4$OH:MeOH:CH$_2$Cl$_2$ – 1:10:300) gave the title product as a yellow oil (15.5 mg, 63.0 µmol, 86%).

$[\alpha]_D$: + 87.5 (c 0.2, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 2945, 2879, 1735, 1635, 1436, 1376, 1222, 1038, 752.



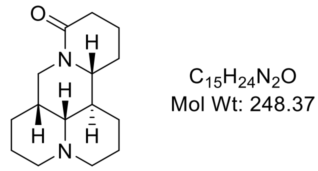
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.80 – 5.70 (m, 2H, $\mathbf{H}_{8}$ & $\mathbf{H}_{9}$), 4.73 (dd, *J* = 13.5, 1.8 Hz, 1H, $\mathbf{H}_{17eq}$), 3.82 – 3.73 (m, 1H, $\mathbf{H}_{10eq}$), 3.07 – 2.95 (m, 2H, $\mathbf{H}_{10ax}$ & $\mathbf{H}_{11}$), 2.91 (dd, *J* = 10.5, 4.2 Hz, 1H, $\mathbf{H}_{6}$), 2.74 – 2.65 (m, 2H, $\mathbf{H}_{2eq}$ & $\mathbf{H}_{17ax}$), 2.59 – 2.51 (m, 1H, $\mathbf{H}_{2ax}$), 2.51 – 2.40 (m, 2H, $\mathbf{H}_{7}$ & $\mathbf{H}_{14eq}$), 2.39 – 2.16 (m, 2H, $\mathbf{H}_{12eq}$ & $\mathbf{H}_{14ax}$), 2.01 – 1.93 (m, 1H, $\mathbf{H}_{5}$), 1.93 – 1.80 (m, 1H, $\mathbf{H}_{13eq}$), 1.79 – 1.52 (m, 5H, $\mathbf{H}_{3}$, $\mathbf{H}_{4eq}$, $\mathbf{H}_{12ax}$ & $\mathbf{H}_{13ax}$), 1.50 – 1.39 (m, 1H, $\mathbf{H}_{4ax}$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 170.2 ($\mathbf{C}_{15}$), 126.7 ($\mathbf{C}_{9}$), 123.1 ($\mathbf{C}_{8}$), 59.1 ($\mathbf{C}_{11}$), 59.0 ($\mathbf{C}_{6}$), 53.4 ($\mathbf{C}_{10}$), 47.1 ($\mathbf{C}_{2}$), 46.5 ($\mathbf{C}_{17}$), 35.0 ($\mathbf{C}_{5}$), 32.9 ($\mathbf{C}_{14}$), 32.3 ($\mathbf{C}_{7}$), 26.6 ($\mathbf{C}_{12}$), 25.6 ($\mathbf{C}_{3}$), 22.5 ($\mathbf{C}_{4}$), 19.1 ($\mathbf{C}_{13}$).

LRMS: (ES+) *m/z* = 247.4 $[M+H]^+$.

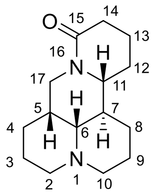
HRMS: (ES+) for $C_{15}H_{23}N_2O^+$ calculated 247.1805, found 247.1804 Da.

(+)-Isosophoridine (2.116)



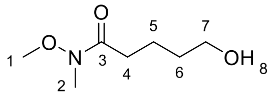
To a solution of **2.117** (10.0 mg, 40.7 µmol) in EtOH (5 mL) was added 10% wt Pd/C (4.2 mg, 3.96 µmol). The RBF was placed under H_2 atmosphere and stirred rapidly for 4 h. The mixture was filtered through the celite. The filter cake was washed with MeOH (5 × 5 mL) and the solvent was removed *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title product as pale yellow crystals (8.0 mg, 32.3 µmol, 79%). Data are consistent with those previously reported. [130]

Melting Point:	109–110 °C. (Lit.[38] 111–112 °C).
[α]$_D$:	+ 99.2 (c 0.2, EtOH, 23 °C). Lit.[130] +101 (c 3.2, EtOH, 23 °C).
FT-IR (cm^{-1}):	2925, 2852, 1637, 1440, 1344, 1274, 1112, 669.



^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.69 (dd, *J* = 13.4, 1.9 Hz, 1H, **H**$_{17eq}$), 3.02 – 2.85 (m, 4H, **H**$_{2eq}$, **H**$_{10}$ & **H**$_{11}$), 2.77 (dd, *J* = 10.6, 4.7 Hz, 1H, **H**$_6$), 2.65 (dd, *J* = 13.4, 3.5 Hz, 1H, **H**$_{17ax}$), 2.52 – 2.37 (m, 2H, **H**$_{2ax}$ & **H**$_{14eq}$), 2.35 – 2.24 (m, 1H, **H**$_{14ax}$), 2.09 – 1.99 (m, 1H, **H**$_{8eq}$), 1.95 – 1.71 (m, 5H, **H**$_{3eq}$, **H**$_5$, **H**$_7$, **H**$_{12eq}$ & **H**$_{13eq}$), 1.71 – 1.49 (m, 4H, **H**$_{3ax}$, **H**$_{4eq}$, **H**$_{8ax}$ & **H**$_{13ax}$), 1.41 – 1.23 (m, 3H, **H**$_{4ax}$ & **H**$_9$), 1.05 (qd, *J* = 12.4, 4.2 Hz, 1H, **H**$_{12ax}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 169.8 (**C**$_{15}$), 62.2 (**C**$_6$), 60.0 (**C**$_{11}$), 54.1 (**C**$_{10}$), 46.7 (**C**$_{17}$), 45.0 (**C**$_2$), 35.9 (**C**$_5$), 33.3 (**C**$_7$), 32.9 (**C**$_{14}$), 27.9 (**C**$_{12}$), 26.6 (**C**$_8$), 25.8 (**C**$_3$), 22.9 (**C**$_4$), 19.1 (**C**$_9$), 19.0 (**C**$_{13}$).
LRMS:	(ES+) *m/z* = 249.3 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{25}N_2O^+$ calculated 249.1961, found 249.1958 Da.

5-Hydroxy-*N*-methoxy-*N*-methylpentanamide (2.148)



$C_7H_{15}NO_3$
Mol Wt: 161.20

Following a procedure described by Flick *et al.*,[131] to a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (14.7 g, 150 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added dropwise a solution of $AlMe_3$ (75.0 mL of 2.0 M in hexane, 150 mmol) over 30 min. After stirring at 0 °C for 30 min, a solution of δ-valerolactone (10.0 g, 100 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise over 20 min. After 30 min stirring at the same temperature, aq. HCl (5 mL of 0.1 M) and CH_2Cl_2 (50 mL) were added. The reaction was stirred for 1 h at 0 °C before quenching by addition of sat. NH_4Cl (50 mL). The mixture was filtered through the celite, and the phases were separated. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo* to give the title Weinreb amide as a colourless oil (15.9 g, 98.8 mmol, 99%). Data are consistent with those previously reported.[131]

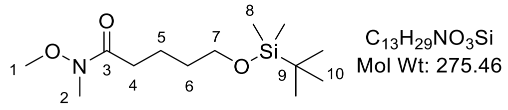
FT-IR (cm^{-1}): 3426, 1639, 1385, 1059, 996.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 3.67 (s, 3H, **H**$_1$), 3.62 (t, *J* = 6.2 Hz, 2H, **H**$_7$), 3.17 (s, 3H, **H**$_2$), 2.46 (t, *J* = 7.1 Hz, 2H, **H**$_4$), 2.32 (br s, 1H, **H**$_8$), 1.76 – 1.67 (m, 2H, **H**$_5$), 1.64 – 1.55 (m, 2H, **H**$_6$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 174.7 (**C**$_3$), 62.1 (**C**$_7$), 61.2 (**C**$_1$), 32.3 (**C**$_2$ & **C**$_6$), 31.3 (**C**$_4$), 20.3 (**C**$_5$).

LRMS: (ES+) *m/z* = 184.3 $[M+Na]^+$.

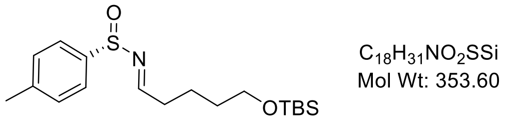
5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylpentanamide (2.149)



To a stirred solution of alcohol **2.148** (19.9 g, 124 mmol) in anhydrous CH_2Cl_2 (150 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (24.3 g, 161 mmol), followed by DMAP (0.700 g, 5.74 mmol). To the mixture was added NEt_3 (23.0 mL, 165 mmol) dropwise over 20 min at 0 °C. Then the reaction was allowed to warm to rt. After stirring for 16 h, H_2O (100 mL) was added and the layers were separated. The aqueous layer was re-extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 25:75) gave the title silyl ether as a pale yellow oil (25.5 g, 92.7 mmol, 75%).

FT-IR (cm^{-1}):	2970, 1669, 1393, 1056, 834, 773.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 3.68 (s, 3H, **H**$_1$), 3.64 (t, *J* = 6.4 Hz, 2H, **H**$_7$), 3.18 (s, 3H, **H**$_2$), 2.45 (t, *J* = 7.5 Hz, 2H, **H**$_4$), 1.74 – 1.65 (m, 2H, **H**$_5$), 1.62 – 1.53 (m, 2H, **H**$_6$), 0.90 (s, 9H, **H**$_{10}$), 0.10 (s, 6H, **H**$_8$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 174.6 (**C**$_3$), 62.9 (**C**$_7$), 61.2 (**C**$_1$), 32.5 (**C**$_6$), 32.2 (**C**$_2$), 31.7 (**C**$_4$), 26.0 (**C**$_{10}$), 21.1 (**C**$_5$), 18.3 (**C**$_9$), – 5.3 (**C**$_8$).
LRMS:	(ES+) m/z = 276.4 $[M+H]^+$.

(*S*,*E*)-*N*-(5-((*tert*-Butyldimethylsilyl)oxy)pentylidene)-4-methylbenzenesulfinamide (2.150)

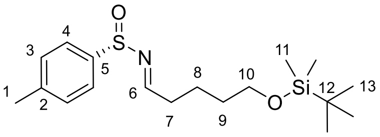


To a solution of amide **2.149** (21.8 g, 79.1 mmol) in anhydrous CH_2Cl_2 (50 mL) at −78 °C under N_2 was added dropwise a solution of DIBAL-H (95.0 mL of 1.0 M in CH_2Cl_2, 95.0 mmol) over 30 min. The reaction mixture was stirred for 2 h at −78 °C before quenching by addition of sat. NH_4Cl (150 mL). The mixture was stirred vigorously for 2 h, and then the phases were separated. The organic phase was washed with brine (3 x 50 mL) and dried ($MgSO_4$) to give the crude product, which was used directly in the next step.

To the solution of freshly prepared aldehyde was added sulfinamide **2.53** (13.6 g, 87.7 mmol) and $Ti(OEt)_4$ (50.0 mL, 237 mmol) at 0 °C under N_2. The reaction mixture was stirred for 30 min at 0 °C, and then was allowed to warm to rt. After 16 h, H_2O (100 mL) was added. The mixture was filtered through the celite and the filter cake was washed with CH_2Cl_2 (3 x 50 mL). The phases were separated, and the aqueous phase was re-extracted with CH_2Cl_2 (3 x 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) afforded the title sulfinimine as a pale yellow oil (24.0 g, 68.2 mmol, 86%).

$[\alpha]_D$: + 152.5 (c 0.1, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 2927, 2856, 1621, 1462, 1254, 1096, 835, 775.



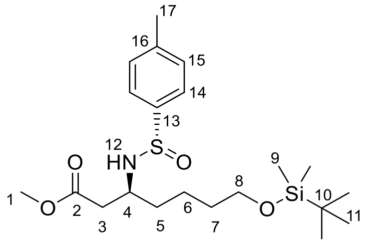
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 8.23 (t, *J* = 4.8 Hz, 1H, **H_6**), 7.56 (d, *J* = 8.2 Hz, 2H, **H_4**), 7.30 (d, *J* = 8.2 Hz, 2H, **H_3**), 3.61 (t, *J* = 6.2 Hz, 2H, **H_{10}**), 2.51 (td, *J* = 7.4, 4.8 Hz, 2H, **H_7**), 2.41 (s, 3H, **H_1**), 1.73 – 1.64 (m, 2H, **H_8**), 1.60 – 1.52 (m, 2H, **H_9**), 0.89 (s, 9H, **H_{13}**), 0.0 (s, 6H, **H_{11}**).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 167.1 (**C_6**), 141.9 (**C_5**), 141.6 (**C_2**), 129.8 (**C_3**), 124.6 (**C_4**), 62.6 (**C_{10}**), 35.7 (**C_7**), 32.1 (**C_9**), 25.9 (**C_{13}**), 21.9 (**C_1**), 21.4 (**C_8**), 18.3 (**C_{12}**), –5.3 (**C_{11}**).

LRMS: (ES+) m/z = 354.4 $[M+H]^+$.

HRMS: (ES+) for $C_{18}H_{31}NO_2SSiNa^+$ calculated 376.1737, found 376.1736 Da.

Methyl (*S*)-7-((tert-butyldimethylsilyl)oxy)-3-(((*S*)-*p*-tolylsulfinyl)amino)heptanoate (2.151)

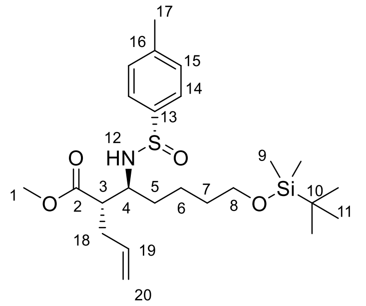


$C_{21}H_{37}NO_4SSi$
Mol Wt: 427.68

To a solution of methyl acetate (2.30 mL, 28.4 mmol) was added dropwise a solution of NaHMDS (35.5 mL of 1.0 M in THF, 35.5 mmol) at –78 °C under N_2. After addition, the N_2 flow was removed and the round bottom flask was sealed to avoid evaporation of methyl acetate. The reaction was stirred for 1 h at –78 °C and then a solution of sulfinimine **2.150** (5.00 g, 14.2 mmol) in anhydrous THF (30 mL) was added dropwise over 20 min. The reaction was stirred at –78 °C for 2 h and quenched by dropwise addition of sat. NH_4Cl (50 mL). The reaction was allowed to warm to rt with rapid stirring. The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 40 mL). The organic phases were combined, washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:9) afforded the diastereoisomerically pure imino-aldol adduct as a yellow oil (4.80 g, 11.2 mmol, 79%). Integration of the N<u>H</u> peaks in the crude ^{1}H NMR showed *dr* 15:1.

[α]$_D$:	+ 53.3 (c 0.1, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	3196, 2928, 1737, 1253, 1090, 835, 775.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 7.58 (d, *J* = 8.1 Hz, 2H, **H**$_{14}$), 7.29 (d, *J* = 8.1 Hz, 2H, **H**$_{15}$), 4.55 (d, *J* = 9.2 Hz, 1H, **H**$_{12}$), 3.72 – 3.59 (m, 6H, **H**$_1$, **H**$_4$ & **H**$_8$), 2.66 (dd, *J* = 15.8, 5.3 Hz, 1H, **H**$_{3a}$), 2.58 (dd, *J* = 15.8, 5.3 Hz, 1H, **H**$_{3b}$), 2.41 (s, 3H, **H**$_{17}$), 1.53 (s, 6H, **H**$_5$, **H**$_6$ & **H**$_7$), 0.90 (s, 9H, **H**$_{11}$), 0.05 (s, 6H, **H**$_9$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 172.0 (**C**$_2$), 142.4 (**C**$_{13}$), 141.3 (**C**$_{16}$), 129.5 (**C**$_{15}$), 125.5 (**C**$_{14}$), 62.9 (**C**$_8$), 52.8 (**C**$_1$), 51.7 (**C**$_4$), 40.4 (**C**$_3$), 35.6 (**C**$_5$), 32.4 (**C**$_7$), 26.0 (**C**$_{11}$), 22.5 (**C**$_6$), 21.3 (**C**$_{17}$), 18.4 (**C**$_{10}$), – 5.3 (**C**$_9$).
LRMS:	(ES+) m/z = 428.4 $[M+H]^+$, 450.4 $[M+Na]^+$.
HRMS:	(ES+) for $C_{21}H_{37}NO_4SSiNa^+$ calculated 450.2105, found 450.2113 Da.

Methyl (2*S*,3*S*)-2-allyl-7-((*tert*-butyldimethylsilyl)oxy)-3-(((*S*)-*p*-tolylsulfinyl)amino)heptanoate (2.158)



$C_{24}H_{41}NO_4SSi$
Mol Wt: 467.74

A round bottom flask containing LiCl (2.90 g, 69.0 mmol) under N_2 was flame-dried. After cooling to –78 °C, a solution of LDA (17.6 mL of 1.0 M in THF, 17.6 mmol) was added dropwise. To the solution was added dropwise β-amino ester **2.151** (3.00 g, 7.01 mmol) in anhydrous THF (20 mL) and the reaction mixture was stirred at –78 °C for 1 h. Then allyl iodide (1.40 mL, 15.1 mmol) was added dropwise to the reaction at –78 °C, and then stirred at this temperature for 1 h before quenching by dropwise addition of sat. NH_4Cl (50 mL). The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:CH_2Cl_2 – 1:9) gave the *anti* imino-aldol as an inseparable mixture containing the *syn* isomer as a yellow oil (1.63 g, 3.49 mmol, 50%). Integration of the N$\underline{H}$ peaks in the crude ^{1}H NMR spectrum allowed estimation of the *anti:syn* ratio (*dr* 10:1).

Data were recorded for the 10:1 mixture of diastereoisomers

[α]$_D$:	+ 60.1 (c 0.2, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	3304, 2927, 1725, 1253, 1089, 833, 773.
^{1}H NMR:	($CDCl_3$, 400 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 7.61 (d, *J* = 8.1 Hz, 2H, **H**$_{14}$), 7.29 (d, *J* = 8.1 Hz, 2H, **H**$_{15}$), 5.67 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H, **H**$_{19}$), 5.09 (br d, *J* = 17.0 Hz, 1H, **H**$_{20trans}$), 5.01 (br d, *J* = 10.2 Hz, 1H, **H**$_{20cis}$), 4.90 (d, *J* = 9.2 Hz, 1H, **H**$_{12}$), 3.65 (s, 3H, **H**$_1$), 3.62 (t, *J* = 5.8 Hz, 2H, **H**$_8$), 3.48 – 3.38 (m, 1H, **H**$_4$), 2.64 (ddd, *J* = 8.7, 6.1, 3.9 Hz, 1H, **H**$_3$), 2.52 – 2.39 (m, 4H, **H**$_{17}$ & **H**$_{18a}$), 2.32 – 2.23 (m, 1H, **H**$_{18b}$), 1.73 – 1.63 (m, 1H, **H**$_{5a}$), 1.59 – 1.38 (m, 5H, **H**$_{5b}$, **H**$_6$ & **H**$_7$), 0.90 (s, 9H, **H**$_{11}$), 0.05 (s, 6H, **H**$_9$).

^{13}C NMR: (CDCl$_3$, 101 MHz, signals reported for the *anti* diastereoisomer) δ ppm = 174.6 (**C**$_2$), 142.5 (**C**$_{13}$), 141.2 (**C**$_{16}$), 135.0 (**C**$_{19}$), 129.5 (**C**$_{15}$), 125.7 (**C**$_{14}$), 117.3 (**C**$_{20}$), 62.9 (**C**$_8$), 56.5 (**C**$_4$), 51.6 (**C**$_1$), 48.6 (**C**$_3$), 35.9 (**C**$_5$), 33.9 (**C**$_{18}$), 32.5 (**C**$_7$), 26.0 (**C**$_{11}$), 22.7 (**C**$_6$), 21.3 (**C**$_{17}$), 18.4 (**C**$_{10}$), – 5.3 (**C**$_9$).

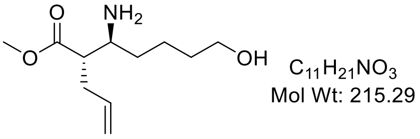
LRMS: (ES+) m/z = 468.5 [M+H]$^+$.

HRMS: (ES+) for $C_{24}H_{42}NO_4SSi^+$ calculated 468.2598, found 468.2600 Da.

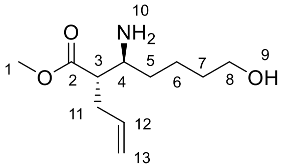
Selected data for the *syn* diastereoisomer:

^{1}H NMR: (CDCl$_3$, 400 MHz) δ ppm = 4.50 (d, *J* = 9.5 Hz, 1H, **H**$_{12}$), 3.13 – 3.09 (m, 1H, **H**$_{18a}$), 2.87 – 2.83 (m, 1H, **H**$_{18b}$).

Methyl (2*S*,3*S*)-2-allyl-3-amino-7-hydroxyheptanoate (2.159)



To a solution of the mixture of *anti* imino-aldol **2.158** (*dr* 10:1 with the *syn* diastereoisomer, 800 mg, 1.70 mmol) in dioxane:MeOH (1:1 – 10 mL) under N_2 was added *conc*. HCl (1.44 mL, 17.0 mmol) dropwise. The reaction was stirred for 16 h at rt and then the solvent was removed *in vacuo*. The residue was re-dissolved in EtOAc:sat. $NaHCO_3$ (1:1 – 20 mL) and the layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:4) gave the diastereoisomerically pure amine as a pale yellow oil (270 mg, 1.24 mmol, 73%).



[α]D : + 2.7 (c 0.2, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 3365, 2934, 1726, 1437, 1197, 1170, 918.

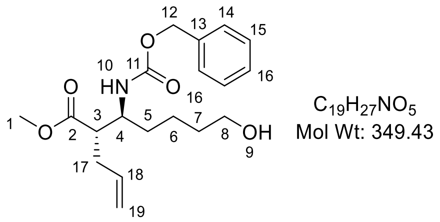
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 5.74 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H, $\mathbf{H}_{12}$), 5.12 – 5.01 (m, 2H, $\mathbf{H}_{13}$), 3.69 (s, 3H, $\mathbf{H}_1$), 3.66 (t, *J* = 6.2 Hz, 2H, $\mathbf{H}_8$), 2.90 (ddd, *J* = 8.8, 5.3, 3.7 Hz, 1H, $\mathbf{H}_4$), 2.53 – 2.29 (m, 3H, $\mathbf{H}_3$ & $\mathbf{H}_{11}$), 1.65 – 1.24 (m, 6H, $\mathbf{H}_5$, $\mathbf{H}_6$ & $\mathbf{H}_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 174.7 ($\mathbf{C}_2$), 135.2 ($\mathbf{C}_{12}$), 117.0 ($\mathbf{C}_{13}$), 62.5 ($\mathbf{C}_8$), 52.7 ($\mathbf{C}_1$), 51.5 ($\mathbf{C}_4$), 51.4 ($\mathbf{C}_3$), 35.1 ($\mathbf{C}_{11}$), 33.9 ($\mathbf{C}_5$), 32.4 ($\mathbf{C}_7$), 22.3 ($\mathbf{C}_6$).

LRMS: (ES+) *m/z* = 216.3 $[M+H]^+$.

HRMS: (ES+) for $C_{11}H_{22}NO_3^+$ calculated 216.1594, found 216.1596 Da.

Methyl (2*S*,3*S*)-2-allyl-3-(((benzyloxy)carbonyl)amino)-7-hydroxyheptanoate (2.161)



To a stirred solution of amine **2.159** (120 mg, 0.558 mmol) in anhydrous THF (5 mL) at 0 °C was added dropwise Cbz-Cl (190 mg, 1.12 mmol), followed by K_2CO_3 (306 mg, 2.24 mmol). The mixture was stirred for 16 h at rt. To the reaction was added H_2O (10 mL) and the layers were separated. The aqueous layer was re-extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:4) gave the single diastereoiosmer as a pale yellow oil (176 mg, 0.504 mmol, 90%).

$[\alpha]_D$: –14.2 (c 0.2, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 3368, 2947, 1719, 1510, 1230.

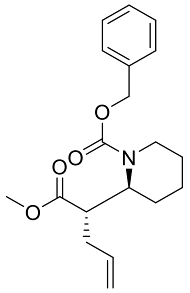
^{1}H NMR: ($CDCl_3$, 400 MHz) δ ppm = 7.41 – 7.32 (m, 5H, **H**$_{14}$, **H**$_{15}$ & **H**$_{16}$), 5.75 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, **H**$_{18}$), 5.55 (d, *J* = 10.0 Hz, 1H, **H**$_{10}$), 5.13 – 5.01 (m, 4H, **H**$_{12}$ & **H**$_{19}$), 3.94 – 3.84 (m, 1H, **H**$_4$), 3.68 (s, 3H, **H**$_1$), 3.62 (t, *J* = 6.3 Hz, 2H, **H**$_8$), 2.65 (ddd, *J* = 8.2, 6.8, 3.9 Hz, 1H, **H**$_3$), 2.48 – 2.27 (m, 2H, **H**$_{17}$), 1.64 – 1.37 (m, 6H, **H**$_5$, **H**$_6$ & **H**$_7$).

^{13}C NMR: ($CDCl_3$, 101 MHz) δ ppm = 174.8 (**C**$_2$), 156.5 (**C**$_{11}$), 136.7 (**C**$_{13}$), 134.6 (**C**$_{18}$), 128.5 (**C**$_{15}$), 128.1 (**C**$_{16}$), 128.0 (**C**$_{14}$), 117.5 (**C**$_{19}$), 66.7 (**C**$_{12}$), 62.6 (**C**$_8$), 51.7 (**C**$_1$), 51.4 (**C**$_4$), 48.6 (**C**$_3$), 34.4 (**C**$_7$), 34.3 (**C**$_{17}$), 32.3 (**C**$_5$), 22.3 (**C**$_6$).

LRMS: (ES+) m/z = 350.4 $[M+H]^+$.

HRMS: (ES+) for $C_{19}H_{27}NO_5Na^+$ calculated 372.1779, found 372.1782 Da.

Benzyl (*S*)-2-((*S*)-1-methoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate (2.163)

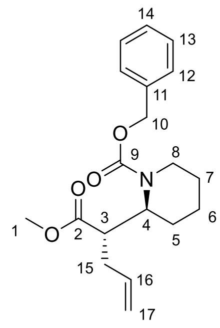


$C_{19}H_{25}NO_4$
Mol Wt: 331.41

To a solution of amide **2.161** (100 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 was added Ms-Cl (33 µL, 0.428 mmol) and NEt_3 (82 µL, 0.585 mmol) dropwise at –78 °C dropwise. The reaction was stirred for 1 h at the same temperature and brine (5 mL) was added. The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as a yellow oil, which was used directly in the next step.

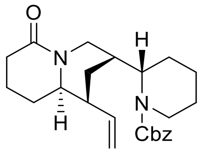
The crude material was dissolved in MeCN (5 mL), and *t*-BuOK (48.0 mg, 0.428 mmol) was added. The reaction was stirred for 12 h, and then the solvent was removed *in vacuo*. The residue was re-dissolved in a mixture of EtOAc:H_2O (1:1 – 10 mL) and the layers were separated. The aqueous layer was re-extracted with EtOAc (5 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:4) gave the title piperidine as a yellow oil (90.0 mg, 0.272 mmol, 94%).

$[\alpha]_D$:	–50.9 (c 0.5, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	2947, 1735, 1694, 1422, 1252, 1169, 1027, 698.



^{1}H NMR: **(T = 298 K)**	(CDCl$_3$, 400 MHz) δ ppm = 7.44 – 7.28 (m, 5H, $\mathbf{H}_{12}$, $\mathbf{H}_{13}$ & $\mathbf{H}_{14}$), 5.81 – 5.70 (m, 1H, $\mathbf{H}_{16}$), 5.16 – 4.95 (m, 4H, $\mathbf{H}_{10}$ & $\mathbf{H}_{17}$), 4.50 (br d, *J* = 9.4 Hz, 1H, $\mathbf{H}_4$), 4.08 (br s, 1H, $\mathbf{H}_{8eq}$), 3.50 (s, 3H, $\mathbf{H}_1$), 3.12 – 2.95 (m, 2H, $\mathbf{H}_3$ & $\mathbf{H}_{8ax}$), 2.45 – 2.30 (m, 1H, $\mathbf{H}_{15a}$), 2.30 – 2.14 (m, 1H, $\mathbf{H}_{15b}$), 1.68 – 1.35 (m, 6H, $\mathbf{H}_5$, $\mathbf{H}_6$ & $\mathbf{H}_7$).
^{1}H NMR: **(T = 363 K)**	(DMSO-*d*$_6$, 500 MHz) δ ppm = 7.38 – 7.26 (m, 5H, $\mathbf{H}_{12}$, $\mathbf{H}_{13}$ & $\mathbf{H}_{14}$), 5.76 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H, $\mathbf{H}_{16}$), 5.10 – 4.99 (m, 4H, $\mathbf{H}_{10}$ & $\mathbf{H}_{17}$), 4.38 – 4.33 (m, 1H, $\mathbf{H}_4$), 3.93 (dd, *J* = 14.6, 4.6 Hz, 1H, $\mathbf{H}_{8eq}$), 3.45 (s, 3H, $\mathbf{H}_1$), 3.08 – 2.93 (m, 2H, $\mathbf{H}_3$ & $\mathbf{H}_{8ax}$), 2.28 – 2.24 (m, 2H, $\mathbf{H}_{15}$), 1.80 (br dd, *J* = 13.4, 2.6 Hz, 1H, $\mathbf{H}_{5eq}$), 1.62 – 1.46 (m, 4H, $\mathbf{H}_{5ax,}$ $\mathbf{H}_6$ & $\mathbf{H}_{7eq}$), 1.40 – 1.27 (m, 1H, $\mathbf{H}_{7ax}$).
^{13}C NMR: **(T = 298 K)**	(CDCl$_3$, 101 MHz) δ ppm = 173.6 ($\mathbf{C}_2$), 155.1 ($\mathbf{C}_9$), 137.0 ($\mathbf{C}_{11}$), 134.8 ($\mathbf{C}_{16}$), 128.4 ($\mathbf{C}_{13}$), 127.9 ($\mathbf{C}_{12}$), 127.0 ($\mathbf{C}_{14}$), 117.1 ($\mathbf{C}_{17}$), 67.1 ($\mathbf{C}_{10}$), 53.0 ($\mathbf{C}_4$), 51.4 ($\mathbf{C}_1$), 45.2 ($\mathbf{C}_3$), 39.7 ($\mathbf{C}_8$), 33.8 ($\mathbf{C}_{15}$), 25.9 ($\mathbf{C}_6$), 25.2 ($\mathbf{C}_7$), 18.9 ($\mathbf{C}_5$).
^{13}C NMR: **(T = 363 K)**	(DMSO-*d*$_6$, 126 MHz) δ ppm = 173.4 ($\mathbf{C}_2$), 154.9 ($\mathbf{C}_9$), 137.6 ($\mathbf{C}_{11}$), 135.7 ($\mathbf{C}_{16}$), 128.7 ($\mathbf{C}_{13}$), 128.1 ($\mathbf{C}_{12}$), 127.8 ($\mathbf{C}_{14}$), 117.1 ($\mathbf{C}_{17}$), 66.7 ($\mathbf{C}_{10}$), 53.3 ($\mathbf{C}_4$), 51.4 ($\mathbf{C}_1$), 45.1 ($\mathbf{C}_3$), 40.0 ($\mathbf{C}_8$), 33.6 ($\mathbf{C}_{15}$), 25.9 ($\mathbf{C}_6$), 25.2 ($\mathbf{C}_7$), 18.8 ($\mathbf{C}_5$).
LRMS:	(ES+) m/z = 332.4 [M+H]$^+$.
HRMS:	(ES+) for $C_{19}H_{26}NO_4^+$ calculated 332.1856, found 332.1862 Da.

Benzyl (*S*)-2-((1*S*,3*R*,9*aR*)-6-oxo-1-vinyloctahydro-2*H*-quinolizin-3-yl)piperidine-1-carboxylate (2.135)



$C_{24}H_{32}N_2O_3$
Mol Wt: 396.53

To a solution of piperidine **2.163** (150 mg, 0.453 mmol) in anhydrous CH_2Cl_2 (5 mL) was added allyltrimethylsilane (0.200 mL, 1.35 mmol) and Hoveyda-Grubbs II (28.0 mg 0.0447 mmol) at rt. After stirring at the same temperature for 1 h, the mixture was filtered through the celite and the filter cake was washed with Et_2O (3 × 5 mL). The solvent was removed *in vacuo* to give a brown oil as the mixture of desired product and the alkene isomerisation / cross-metathesis product.

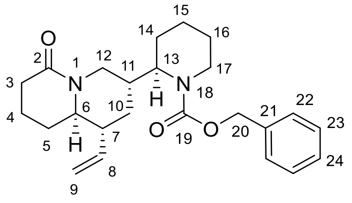
The crude material was dissolved in anhydrous CH_2Cl_2 (5 mL) and to the solution was added dropwise a solution of a solution of $LiAlH_4$ (0.460 mL of 1.0 M in CH_2Cl_2, 0.460 mmol) at 0 °C under N_2. The mixture was stirred for 2 h at the same conditions. The reaction was quenched by dropwise addition of aq. NaOH (5 mL of 2.0 M) at 0 °C. The mixture was filtered through the celite and the filter cake was washed with EtOAc (5 × 5 mL). The phases were separated and the aqueous was re-extracted with EtOAc (3 × 5 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the corresponding alcohol with the chain-shortened compound.

The crude product obtained from the last step was dissolved in anhydrous THF (5 mL). To the solution was added glutarimide (136 mg, 1.20 mmol), ADDP (303 mg, 1.20 mmol) and *n*-Bu_3P (0.300 mL, 1.20 mmol) at 0 °C under N_2. The mixture was stirred for 48 h at rt. To the solution was added EtOAc:H_2O (1:1 – 20 mL). The phases were separated and the aqueous layer was re-extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with aq. HCl (10 mL of 0.5 M), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:1) gave a yellow oil of an inseparable mixture of the desired product and chain-shortened compound (ratio 3:1 from LCMS, 150 mg, ~0.312 mmol).

The mixture (150 mg, 0.312 mmol) obtained from the last step was dissolved in anhydrous CH_2Cl_2 (2 mL), and a solution of $LiEt_3BH$ (0.450 mL of 1.0 M in CH_2Cl_2, 0.450 mmol) was added dropwise at −78 °C under N_2. After 2 h, the reaction was quenched by addition of HCl (0.5 mL of 2.0 M in EtOH). The phases were separated and the aqueous was re-extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated to 5 mL *in vacuo*. BF_3•OEt_2 (0.156 mL, 1.25 mmol) was then added to the solution at rt and the solution was stirred at the same temperature for 12 h. The reaction was quenched by addition of aq. HCl (2 mL of 2.0 M) and the acidic aqueous phases were combined, then basified with 35% NH_4OH to pH 14. The aqueous phase was re-extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (EtOAc:hexane – 1:1) gave the title product as a yellow oil (85.0 mg, 0.215 mmol, 47% overall yield).

$[\alpha]_D$: −2.8 (c 0.1, $CHCl_3$, 23 °C).

FT-IR (cm^{-1}): 2935, 1687, 1634, 1419, 1262, 1172, 1027, 727.



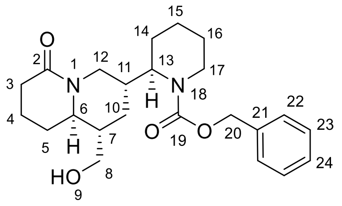
^{1}H NMR: (DMSO-d_6, 500 MHz) δ ppm = 7.39 – 7.28 (m, 5H, **H**$_{22}$, **H**$_{23}$ & **H**$_{24}$), 5.68 (ddd, *J* = 17.2, 10.3, 8.6 Hz, 1H, **H**$_8$), 5.16 – 5.04 (m, 4H, **H**$_9$ & **H**$_{20}$), 4.55 – 4.50 (m, 1H, **H**$_{12eq}$), 4.02 – 3.98 (m, 1H, **H**$_{17eq}$), 3.90 – 3.88 (m, 1H, **H**$_{13}$), 3.04 (dt, *J* = 10.0, 6.2 Hz, 1H, **H**$_6$), 2.86 (td, *J* = 13.3, 2.9 Hz, 1H, **H**$_{17ax}$), 2.25 – 1.86 (m, 6H, **H**$_3$, **H**$_{5eq}$, **H**$_7$, **H**$_{11}$ & **H**$_{12ax}$), 1.79 – 1.68 (m, 3H, **H**$_{4eq}$, **H**$_{10eq}$ & **H**$_{16eq}$), 1.62 – 1.49 (m, 5H, **H**$_{4ax}$, **H**$_{5ax}$, **H**$_{14}$ & **H**$_{15eq}$), 1.45 – 1.30 (m, 2H, **H**$_{15ax}$ & **H**$_{16ax}$), 1.16 – 1.06 (m, 1H, **H**$_{10ax}$).

^{13}C NMR: (DMSO-d_6, 126 MHz) δ ppm = 167.6 (**C**$_2$), 154.4 (**C**$_{19}$), 139.5 (**C**$_8$), 136.8 (**C**$_{21}$), 128.0 (**C**$_{23}$), 127.3 (**C**$_{22}$), 126.9 (**C**$_{24}$), 115.7 (**C**$_9$), 65.8 (**C**$_{20}$), 58.5 (**C**$_6$), 53.4 (**C**$_{13}$), 46.8 (**C**$_7$), 43.9 (**C**$_{12}$), 39.0 (**C**$_{17}$), 35.0 (**C**$_{10}$), 32.8 (**C**$_{11}$), 32.2 (**C**$_3$), 26.5 (**C**$_5$), 24.8 (**C**$_{16}$), 24.6 (**C**$_{15}$), 18.2 (**C**$_{14}$), 17.7 (**C**$_4$).

LRMS: (ES+) m/z = 397.4 $[M+H]^+$.

HRMS: (ES+) for $C_{24}H_{33}N_2O_3^+$ calculated 397.2486, found 397.2488 Da.

Benzyl (*S*)-2-((1*R*,3*R*,9*aR*)-1-(hydroxymethyl)-6-oxooctahydro-2*H*-quinolizin-3-yl)piperidine-1-carboxylate (2.171)



$C_{23}H_{32}N_2O_4$
Mol Wt: 400.52

A solution of **2.135** (200 mg, 0.505 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to –78 °C. The stirred solution was purged with ozone until the colourless solution became blue (~2 h). The ozone was removed and the mixture was purged with N_2 flow for 30 min, and then the mixture was allowed to warm to 0 °C. $NaBH_4$ (190 mg, 5.00 mmol) was added to the reaction at 0 °C under N_2. After 1 h, the reaction was quenched by dropwise addition of sat. NH_4OH (5 mL). The phases were separated and the aqueous was re-extracted with EtOAc (3 × 5 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (MeOH:EtOAc – 1:9) gave the title alcohol as a colourless oil (156 mg, 0.390 mmol, 71%).

$[\alpha]_D$:	–16.7 (c 0.2, $CHCl_3$, 23 °C).
FT-IR (cm^{-1}):	3379, 2934, 2865, 1686, 1612, 1422, 1262, 1173, 1073, 728.
^{1}H NMR: **(T = 298 K)**	($CDCl_3$, 400 MHz) δ ppm = 7.39 – 7.28 (m, 5H, **H**$_{22}$, **H**$_{23}$ & **H**$_{24}$), 5.08 (s, 2H, **H**$_{20}$), 4.56 – 4.46 (m, 2H, **H**$_9$ & **H**$_{12eq}$), 4.01 – 3.94 (m, 1H, **H**$_{17eq}$), 3.89 – 3.81 (m, 1H, **H**$_{13}$), 3.41 (t, *J* = 4.7 Hz, 2H, **H**$_8$), 3.07 (br s, 1H, **H**$_6$), 2.82 (br s, 1H, **H**$_{17ax}$), 2.24 – 2.08 (m, 2H, **H**$_3$), 2.05 – 1.97 (m, 1H, **H**$_{5eq}$), 1.94 – 1.65 (m, 5H, **H**$_{10eq}$, **H**$_{11}$, **H**$_{12ax}$, **H**$_{4eq}$ & **H**$_{16eq}$), 1.63 – 1.46 (m, 5H, **H**$_{4ax}$, **H**$_{5ax}$, **H**$_{14}$ & **H**$_{15eq}$), 1.46 – 1.23 (m, 3H, **H**$_7$, **H**$_{15ax}$ & **H**$_{16ax}$), 1.04 (br s, 1H, **H**$_{10ax}$).
^{1}H NMR: **(T = 343 K)**	(DMSO-*d*$_6$, 500 MHz) δ ppm = 7.38 – 7.27 (m, 5H, **H**$_{22}$, **H**$_{23}$ & **H**$_{24}$), 5.10 (s, 2H, **H**$_{20}$), 4.60 – 4.44 (m, 1H, **H**$_{12eq}$), 4.32 (t, *J* = 5.2 Hz, 1H, **H**$_9$), 4.06 – 3.92 (m, 1H, **H**$_{17eq}$), 3.88 (br dd, *J* = 9.1, 4.0 Hz, 1H, **H**$_{13}$), 3.49 – 3.35 (m, 2H, **H**$_8$), 3.10 – 3.05 (m, 1H, **H**$_6$), 2.86 (td, *J* = 13.3, 2.6 Hz, 1H, **H**$_{17ax}$), 2.25 – 2.10 (m, 2H, **H**$_3$), 2.06 – 1.99 (m, 1H, **H**$_{5eq}$), 1.95 – 1.83 (m, 3H, **H**$_{10eq}$, **H**$_{11}$ & **H**$_{12ax}$), 1.81 – 1.70 (m, 2H, **H**$_{4eq}$ & **H**$_{16eq}$), 1.64 – 1.48 (m, 5H, **H**$_{4ax}$, **H**$_{5ax}$, **H**$_{14}$ & **H**$_{15eq}$), 1.46 – 1.31 (m, 3H, **H**$_7$, **H**$_{15ax}$ & **H**$_{16ax}$), 1.12 – 0.99 (m, 1H, **H**$_{10ax}$).

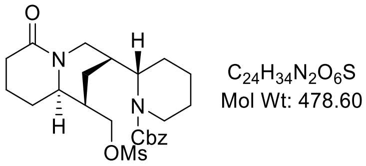
^{13}C NMR: (T = 298 K) (CDCl$_3$, 101 MHz) δ ppm = 169.5 ($\mathbf{C_{2}}$), 136.9 ($\mathbf{C_{21}}$), 128.5 ($\mathbf{C_{23}}$), 127.9 ($\mathbf{C_{22}}$), 127.7 ($\mathbf{C_{24}}$), 67.1 ($\mathbf{C_{20}}$), 63.8 ($\mathbf{C_{8}}$), 57.9 ($\mathbf{C_{6}}$), 54.1 ($\mathbf{C_{13}}$), 44.8 ($\mathbf{C_{12}}$), 44.6 ($\mathbf{C_{7}}$), 39.9 ($\mathbf{C_{17}}$), 33.3 ($\mathbf{C_{11}}$), 32.9 ($\mathbf{C_{3}}$), 32.7 ($\mathbf{C_{10}}$), 27.0 ($\mathbf{C_{5}}$), 25.4 ($\mathbf{C_{15}}$ & $\mathbf{C_{16}}$), 19.1 ($\mathbf{C_{14}}$), 18.7 ($\mathbf{C_{4}}$). (1 carbon missing: $\mathbf{C_{19}}$, observed in the V$_T$ NMR)

^{13}C NMR: (T = 343 K) (DMSO-*d*$_6$, 126 MHz) δ ppm = 167.7 ($\mathbf{C_{2}}$), 154.4 ($\mathbf{C_{19}}$), 136.8 ($\mathbf{C_{21}}$), 128.0 ($\mathbf{C_{23}}$), 127.3 ($\mathbf{C_{22}}$), 126.9 ($\mathbf{C_{24}}$), 65.8 ($\mathbf{C_{20}}$), 62.0 ($\mathbf{C_{8}}$), 57.4 ($\mathbf{C_{6}}$), 53.7 ($\mathbf{C_{13}}$), 43.9 ($\mathbf{C_{7}}$ & $\mathbf{C_{12}}$), 39.0 ($\mathbf{C_{17}}$), 33.0 ($\mathbf{C_{11}}$), 32.8 ($\mathbf{C_{3}}$), 31.9 ($\mathbf{C_{10}}$), 26.2 ($\mathbf{C_{5}}$), 24.9 ($\mathbf{C_{16}}$), 24.6 ($\mathbf{C_{15}}$), 18.2 ($\mathbf{C_{14}}$), 18.0 ($\mathbf{C_{4}}$).

LRMS: (ES+) m/z = 401.5 [M+H]$^+$.

HRMS: (ES+) for $C_{23}H_{33}N_2O_4^+$ calculated 401.2435, found 401.2439 Da.

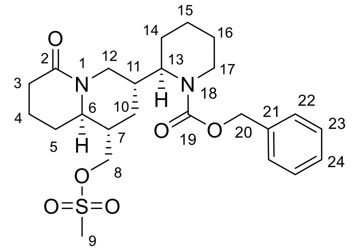
Benzyl (*S*)-2-((1*R*,3*R*,9a*R*)-1-(((methylsulfonyl)oxy)methyl)-6-oxooctahydro-2*H*-quinolizin-3-yl)piperidine-1-carboxylate (2.172)



To a solution of alcohol **2.171** (100 mg, 0.249 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) at −78 °C was added NEt$_3$ (70 µL, 0.503 mmol) and Ms-Cl (30 µL, 0.387 mmol) dropwise. The reaction was warm to 0 °C and stirred for 2 h before quenching by addition of sat. NH$_4$Cl (5 mL). The phases were separated and the aqueous layer was re-extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined, dried (MgSO$_4$), and concentrated *in vacuo*. No further purification was required, and the title mesylate was obtained as a colourless oil (95.0 mg, 0.199 mmol, 81%).

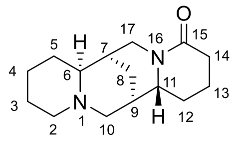
[α]$_D$: −1.5 (c 0.1, CHCl$_3$, 23 °C).

FT-IR (cm^{-1}): 2936, 2865, 1688, 1635, 1424, 1352, 1174.



^{1}H NMR: (T = 298 K)	(CDCl$_3$, 400 MHz) δ ppm = 7.39 – 7.27 (m, 5H, $\mathbf{H}_{22}$, $\mathbf{H}_{23}$ & $\mathbf{H}_{24}$), 5.16 – 5.07 (m, 2H, $\mathbf{H}_{20}$), 4.75 (br d, *J* = 11.2 Hz, 1H, $\mathbf{H}_{12eq}$), 4.33 – 3.91 (m, 4H, $\mathbf{H}_{8}$, $\mathbf{H}_{13}$ & $\mathbf{H}_{17eq}$), 3.23 – 3.11 (m, 1H, $\mathbf{H}_{6}$), 3.05 (s, 3H, $\mathbf{H}_{9}$), 2.97 – 2.91 (m, 1H, $\mathbf{H}_{17ax}$), 2.49 – 2.32 (m, 1H, $\mathbf{H}_{3eq}$), 2.34 – 2.10 (m, 2H, $\mathbf{H}_{3ax}$ & $\mathbf{H}_{5eq}$), 2.05 – 1.37 (m, 13H, $\mathbf{H}_{4}$, $\mathbf{H}_{5ax}$, $\mathbf{H}_{7}$, $\mathbf{H}_{10eq}$, $\mathbf{H}_{11}$, $\mathbf{H}_{12ax}$, $\mathbf{H}_{14}$, $\mathbf{H}_{15}$ & $\mathbf{H}_{16}$), 1.28 – 1.25 (m, 1H, $\mathbf{H}_{10ax}$).
^{1}H NMR: (T = 343 K)	(DMSO-*d*$_6$, 500 MHz) δ ppm = 7.38 – 7.28 (m, 5H, $\mathbf{H}_{22}$, $\mathbf{H}_{23}$ & $\mathbf{H}_{24}$), 5.10 (d, *J* = 2.6 Hz, 2H, $\mathbf{H}_{20}$), 4.53 (dd, *J* = 9.0, 2.3 Hz, 1H, $\mathbf{H}_{12eq}$), 4.21 (d, *J* = 4.5 Hz, 2H, $\mathbf{H}_{8}$), 4.04 – 3.97 (m, 1H, $\mathbf{H}_{17eq}$), 3.94 – 3.87 (m, 1H, $\mathbf{H}_{13}$), 3.17 – 3.15 (m, 4H, $\mathbf{H}_{6}$ & $\mathbf{H}_{9}$), 2.90 – 2.81 (m, 1H, $\mathbf{H}_{17ax}$), 2.28 – 2.12 (m, 2H, $\mathbf{H}_{3}$), 2.09 – 2.02 (m, 1H, $\mathbf{H}_{5eq}$), 2.00 – 1.88 (m, 3H, $\mathbf{H}_{10eq}$, $\mathbf{H}_{11}$ & $\mathbf{H}_{12ax}$), 1.83 – 1.72 (m, 3H, $\mathbf{H}_{4eq}$, $\mathbf{H}_{16eq}$ & $\mathbf{H}_{7}$), 1.66 – 1.50 (m, 5H, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5ax}$, $\mathbf{H}_{14}$ & $\mathbf{H}_{15eq}$), 1.48 – 1.30 (m, 2H, $\mathbf{H}_{15ax}$ & $\mathbf{H}_{16ax}$), 1.17 – 1.03 (m, 1H, $\mathbf{H}_{10ax}$).
^{13}C NMR: (T = 343 K)	(DMSO-*d*$_6$, 126 MHz) δ ppm = 167.7 ($\mathbf{C}_{2}$), 154.4 ($\mathbf{C}_{19}$), 136.8 ($\mathbf{C}_{21}$), 128.0 ($\mathbf{C}_{23}$), 127.3 ($\mathbf{C}_{22}$), 126.9 ($\mathbf{C}_{24}$), 70.7 ($\mathbf{C}_{8}$), 65.8 ($\mathbf{C}_{20}$), 56.7 ($\mathbf{C}_{6}$), 53.4 ($\mathbf{C}_{13}$), 43.8 ($\mathbf{C}_{12}$), 41.0 ($\mathbf{C}_{7}$), 39.0 ($\mathbf{C}_{17}$), 36.4 ($\mathbf{C}_{9}$), 32.8 ($\mathbf{C}_{11}$), 32.2 ($\mathbf{C}_{3}$), 31.3 ($\mathbf{C}_{10}$), 26.0 ($\mathbf{C}_{5}$), 24.8 ($\mathbf{C}_{16}$), 24.6 ($\mathbf{C}_{15}$), 18.2 ($\mathbf{C}_{14}$), 17.9 ($\mathbf{C}_{4}$).
LRMS:	(ES+) *m/z* = 479.5 [M+H]$^+$.
HRMS:	(ES+) for $C_{24}H_{35}N_2O_6^+$ calculated 479.2210, found 479.2216 Da.

(7*R*,7*aR*,14*R*,14*aS*)-Dodecahydro-2*H*,11*H*-7,14-methanodipyrido[1,2-a:1',2'-e][1,5]diazocin-11-one (2.134)



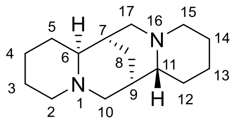
$C_{15}H_{24}N_2O$
Mol Wt: 248.37

To a solution of mesylate **2.172** (80.0 mg, 0.167 mmol) in EtOH (2 mL) was added 10% wt Pd/C (20.0 mg, 0.0189 mmol). The RBF was placed under an atmosphere of H_2 and stirred rapidly. After 2 h, the mixture was filtered through the celite. The filter cake was washed with MeOH (3 × 5 mL) and the solvent removed *in vacuo* to give the crude product as a yellow oil, which was used directly in the next step.

The crude material was dissolved in MeCN (5 mL) and to the solution was added K_2CO_3 (47.0 mg, 0.341 mmol). After stirring at rt for 12 h, the solvent was removed *in vacuo*. The residue was treated with CH_2Cl_2:H_2O (10 mL, 1:1), and the phases were separated. The aqueous layer was re-extracted with CH_2Cl_2 (5 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title product as a colourless oil (32.0 mg, 0.129 mmol, 77%). Data are consistent with those of its enantiomer previously reported.[145]

$[\alpha]_D$:	+2.8 (c 0.1, EtOH, 23 °C). Lit.[145] –9.1 (c 1.0, EtOH, 23 °C).
FT-IR (cm^{-1}):	2929, 2799, 1636, 1443, 1348, 1275.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 4.55 (dd, *J* = 13.6, 10.7 Hz, 1H, $\mathbf{H}_{17eq}$), 3.54 (ddd, *J* = 7.2, 4.8, 2.4 Hz, 1H, $\mathbf{H}_{11}$), 2.93 (dd, *J* = 13.6, 2.6 Hz, 1H, $\mathbf{H}_{17ax}$), 2.70 (br d, *J* = 11.1 Hz, 1H, $\mathbf{H}_{2eq}$), 2.61 – 2.54 (m, 1H, $\mathbf{H}_{10eq}$), 2.47 – 2.30 (m, 2H, $\mathbf{H}_{14}$), 2.07 (dd, *J* = 11.3, 2.5 Hz, 1H, $\mathbf{H}_{10ax}$), 2.01 -1.89 (m, 2H, $\mathbf{H}_{2ax}$ & $\mathbf{H}_{12eq}$), 1.87 – 1.43 (m, 10H, $\mathbf{H}_{3}$, $\mathbf{H}_{4eq}$, $\mathbf{H}_{7}$, $\mathbf{H}_{6}$, $\mathbf{H}_{8eq}$, $\mathbf{H}_{9}$, $\mathbf{H}_{12ax}$ & $\mathbf{H}_{13}$), 1.38 – 1.20 (m, 4H, $\mathbf{H}_{4ax}$, $\mathbf{H}_{5}$ & $\mathbf{H}_{8ax}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 170.5 ($\mathbf{C}_{15}$), 65.7 ($\mathbf{C}_{6}$), 61.4 ($\mathbf{C}_{10}$), 58.5 ($\mathbf{C}_{11}$), 56.1 ($\mathbf{C}_{2}$), 40.1 ($\mathbf{C}_{17}$), 36.3 ($\mathbf{C}_{9}$), 32.6 ($\mathbf{C}_{14}$), 32.0 ($\mathbf{C}_{12}$), 32.9 ($\mathbf{C}_{7}$), 29.4 ($\mathbf{C}_{5}$), 27.2 ($\mathbf{C}_{8}$), 25.7 ($\mathbf{C}_{3}$), 24.5 ($\mathbf{C}_{4}$), 20.0 ($\mathbf{C}_{13}$).
LRMS:	(ES+) m/z = 249.4 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{25}N_2O^+$ calculated 249.1961, found 249.1966 Da.

(+)-Sparteine (2.133)



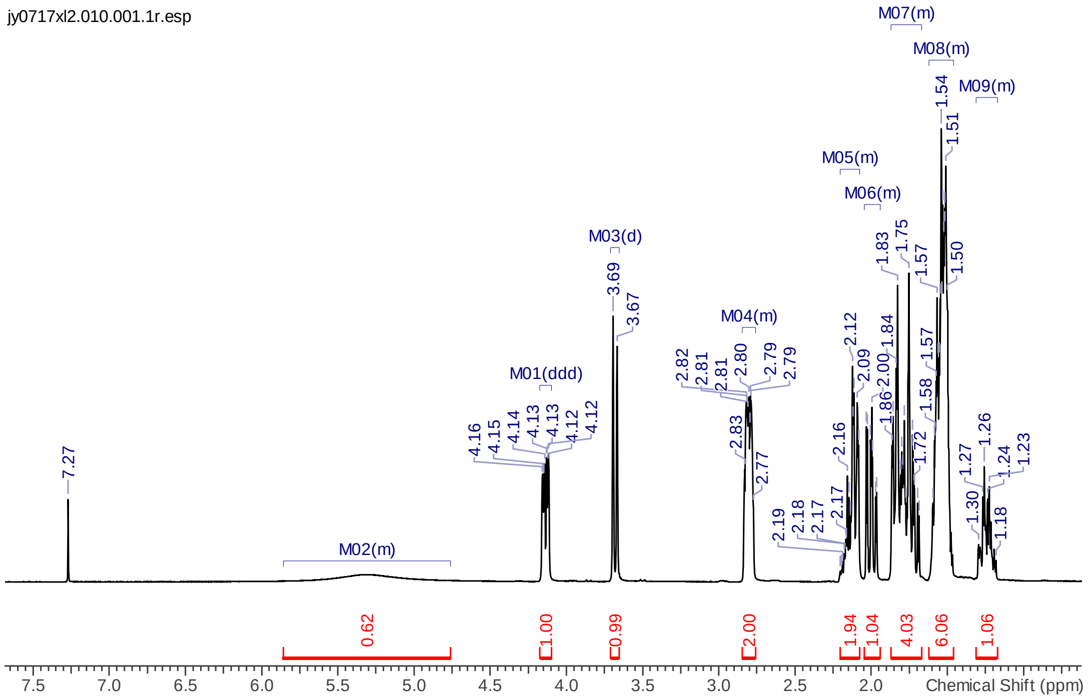
$C_{15}H_{26}N_2$
Mol Wt: 234.39

To a solution of **2.134** (10.0 mg, 0.0403 mmol) in anhydrous THF (5 mL) was added dropwise a solution of $LiAlH_4$ (0.320 mL of 1.0 M in THF, 0.320 mmol,) at 0 °C under N_2. The mixture was stirred under reflux for 2 h. After cooling to rt, the reaction was quenched by addition of aq. NaOH (2 mL, 1.0 M). The phases were separated and the aqueous was re-extracted with CH_2Cl_2 (5 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (35% NH_4OH:MeOH:CH_2Cl_2 – 1:10:200) gave the title product as a colourless oil (8.0 mg, 0.0342 mmol, 85%). Data are consistent with those previously reported.[67]

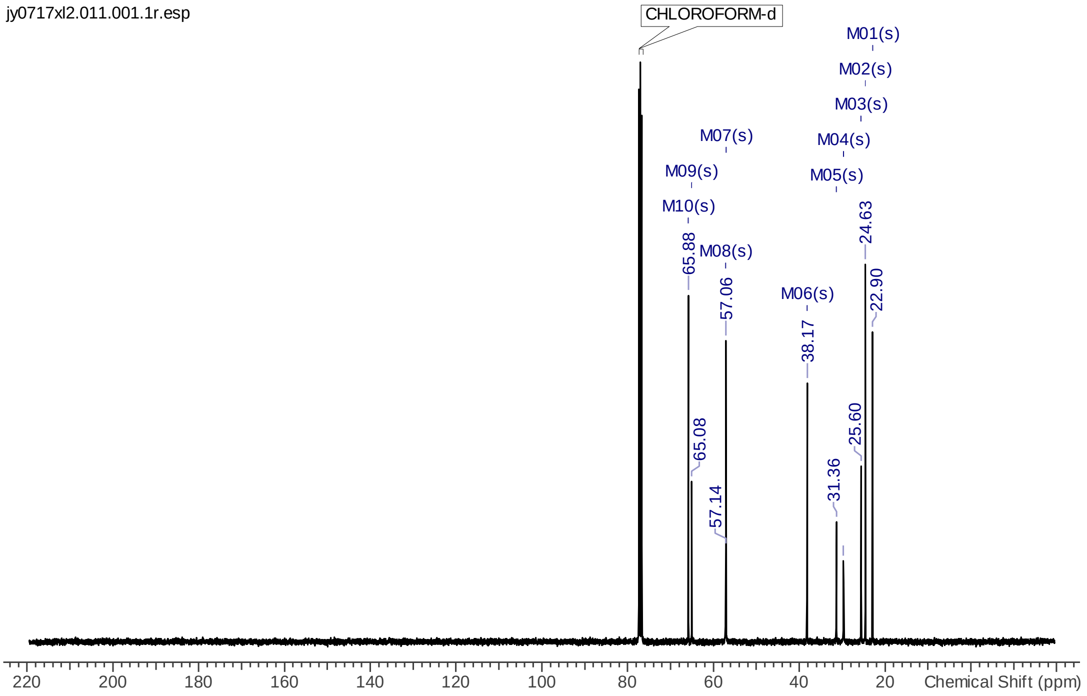
$[\alpha]_D$:	+14 (c 0.1, EtOH, 23 °C). Lit.[136] +19.2 (c 0.5, EtOH, 23 °C). Lit.[67] +21.2 (c 1.6, EtOH, 23 °C).
FT-IR (cm^{-1}):	1456, 1349, 1288, 1124, 1112, 1072, 784.
^{1}H NMR:	($CDCl_3$, 400 MHz) δ ppm = 2.80 (br d, *J* = 11.2 Hz, 1H, $\mathbf{H}_{15eq}$), 2.76 – 2.64 (m, 2H, $\mathbf{H}_{2eq}$ & $\mathbf{H}_{17eq}$), 2.54 (br d, *J* = 10.9 Hz, 1H, $\mathbf{H}_{10eq}$), 2.35 (dd, *J* = 11.1, 3.1 Hz, 1H, $\mathbf{H}_{17ax}$), 2.11 – 1.91 (m, 5H, $\mathbf{H}_{2ax}$, $\mathbf{H}_{8eq}$, $\mathbf{H}_{10ax}$, $\mathbf{H}_{11}$ & $\mathbf{H}_{15ax}$), 1.89 – 1.80 (m, 1H, $\mathbf{H}_7$), 1.78 – 1.65 (m, 3H, $\mathbf{H}_{4eq}$, $\mathbf{H}_6$ & $\mathbf{H}_{13eq}$), 1.63 – 1.43 (m, 6H, $\mathbf{H}_3$, $\mathbf{H}_9$, $\mathbf{H}_{12ax}$ & $\mathbf{H}_{14}$), 1.43 – 1.14 (m, 5H, $\mathbf{H}_{4ax}$, $\mathbf{H}_5$, $\mathbf{H}_{12eq}$ & $\mathbf{H}_{13ax}$), 1.06 (d, *J* = 11.9 Hz, 1H, $\mathbf{H}_{8ax}$).
^{13}C NMR:	($CDCl_3$, 101 MHz) δ ppm = 66.6 ($\mathbf{C}_6$), 64.5 ($\mathbf{C}_{11}$), 62.0 ($\mathbf{C}_{10}$), 56.3 ($\mathbf{C}_2$), 55.4 ($\mathbf{C}_{15}$), 53.7 ($\mathbf{C}_{17}$), 36.1 ($\mathbf{C}_7$), 34.7 ($\mathbf{C}_{12}$), 33.1 ($\mathbf{C}_9$), 29.3 ($\mathbf{C}_5$), 27.7 ($\mathbf{C}_8$), 26.0 ($\mathbf{C}_3$ & $\mathbf{C}_{14}$), 24.8 ($\mathbf{C}_4$), 24.7 ($\mathbf{C}_{13}$).
LRMS:	(ES+) m/z = 235.4 $[M+H]^+$.
HRMS:	(ES+) for $C_{15}H_{27}N_2^+$ calculated 235.2169, found 235.2170 Da.

Chapter 4: Appendix

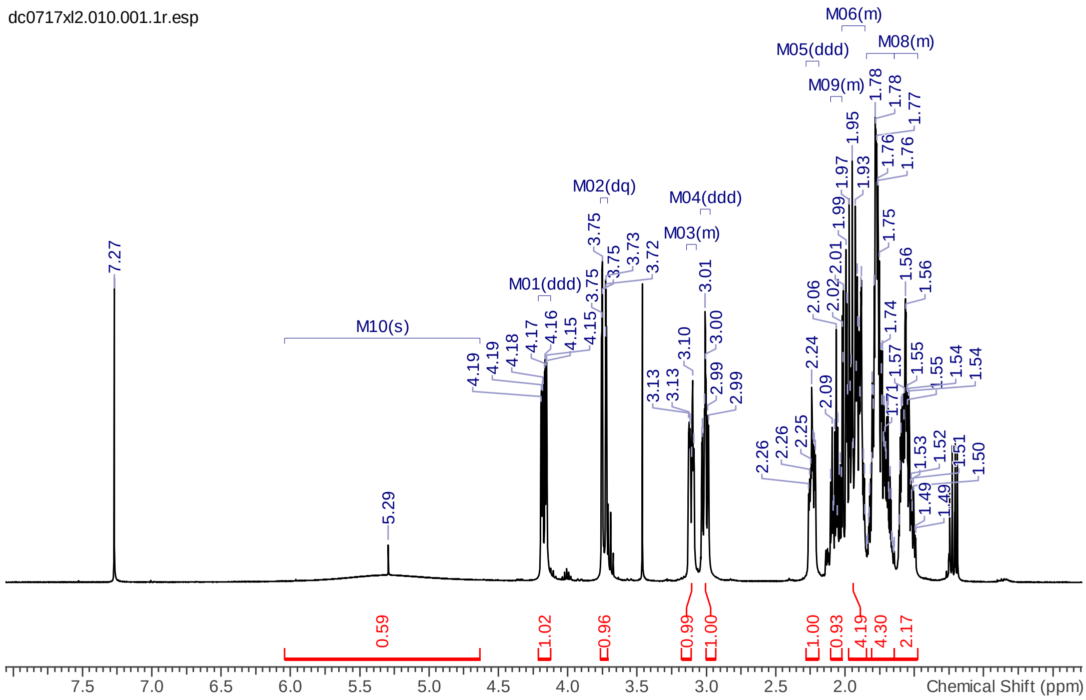
4.1 ^{1}H NMR: (+)-lupinine



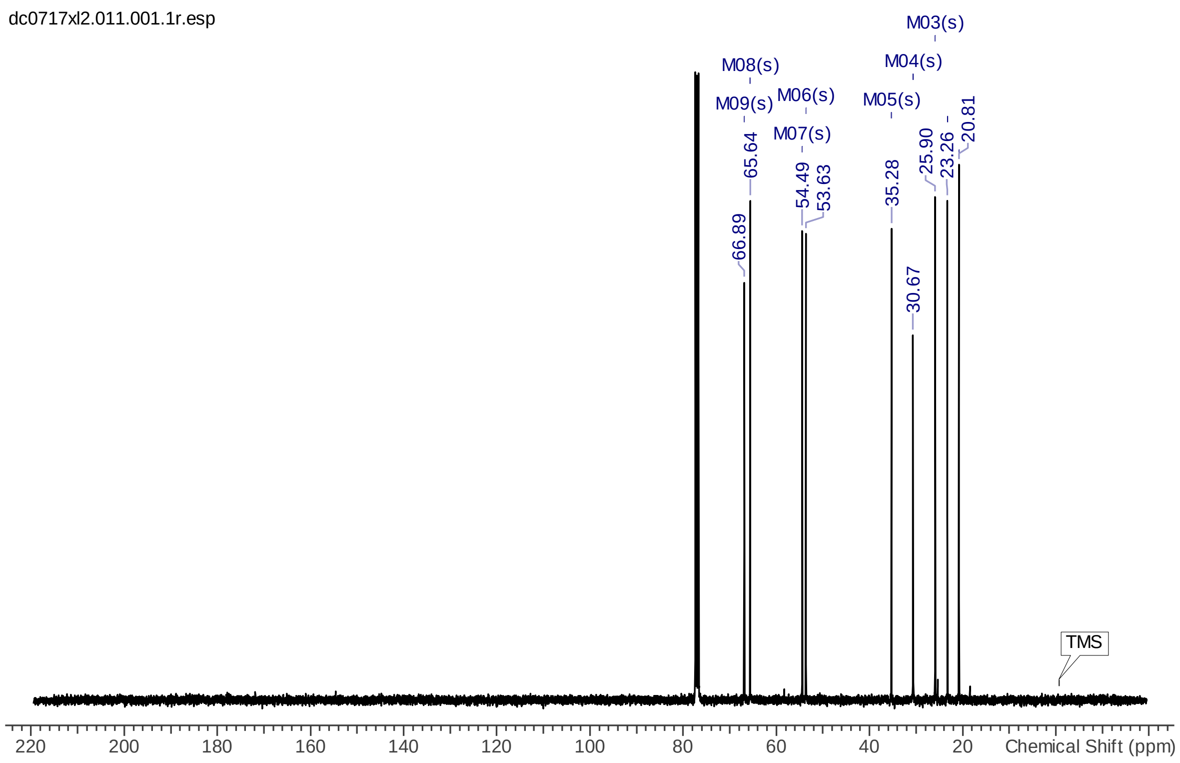
4.2 ^{13}C NMR: (+)-lupinine



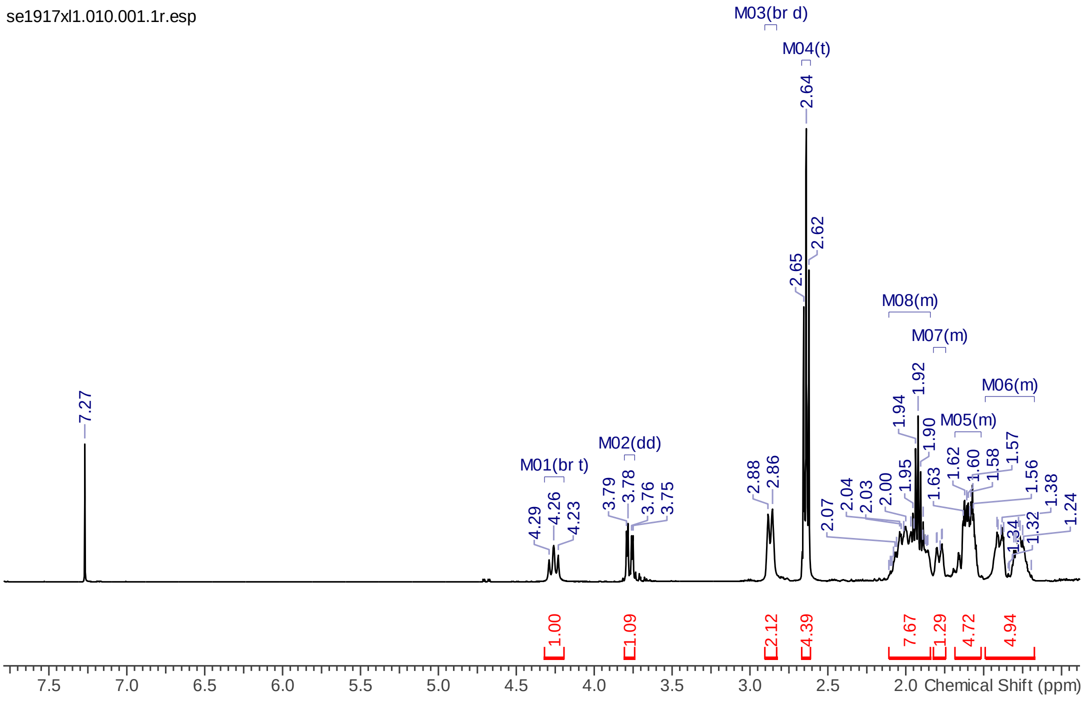
4.3 ^{1}H NMR: (–)-epilamprolobine



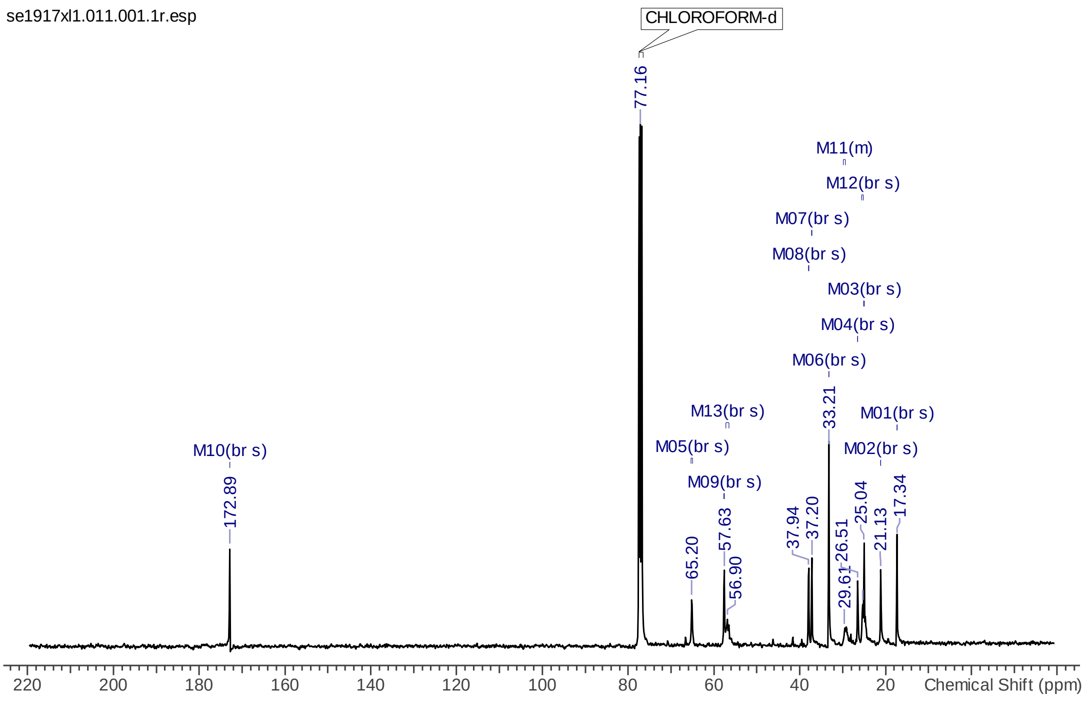
4.4 ^{13}C NMR: (–)-epilamprolobine



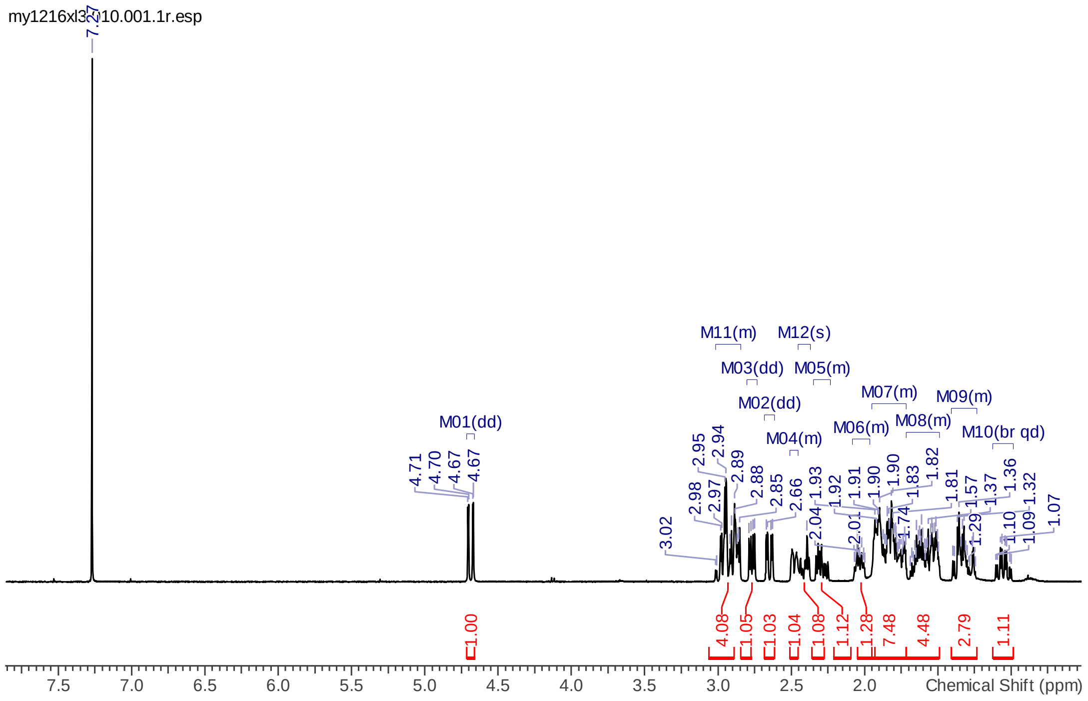
4.5 ^{1}H NMR: (–)-epilamprolobine



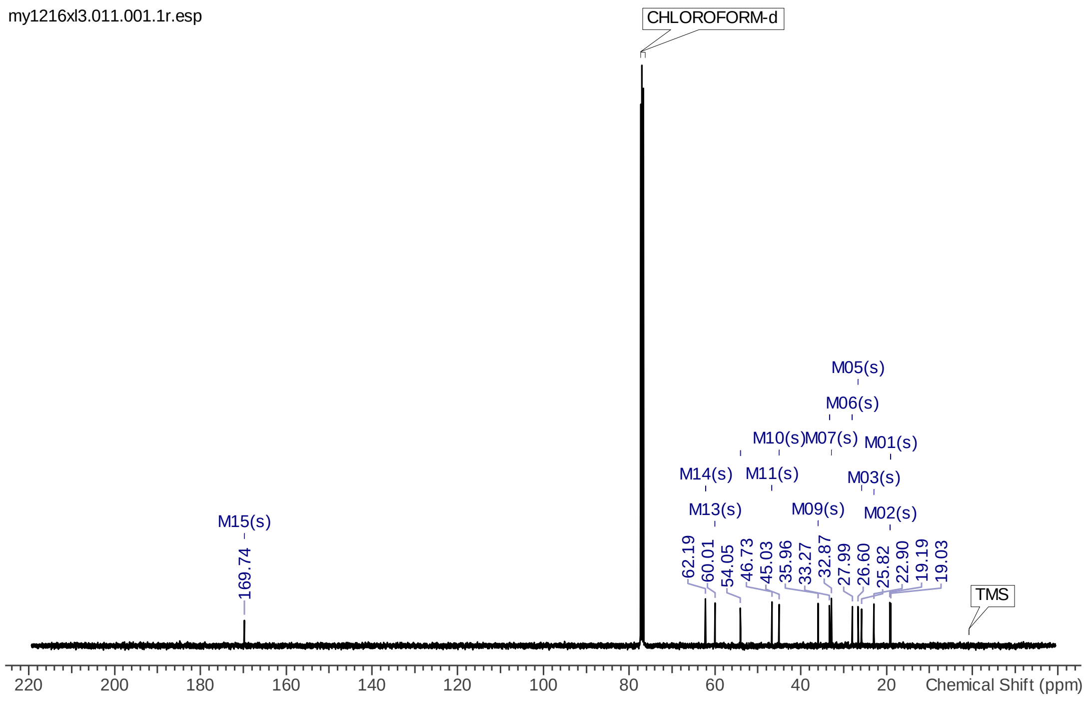
4.6 ^{13}C NMR: (–)-epilamprolobine



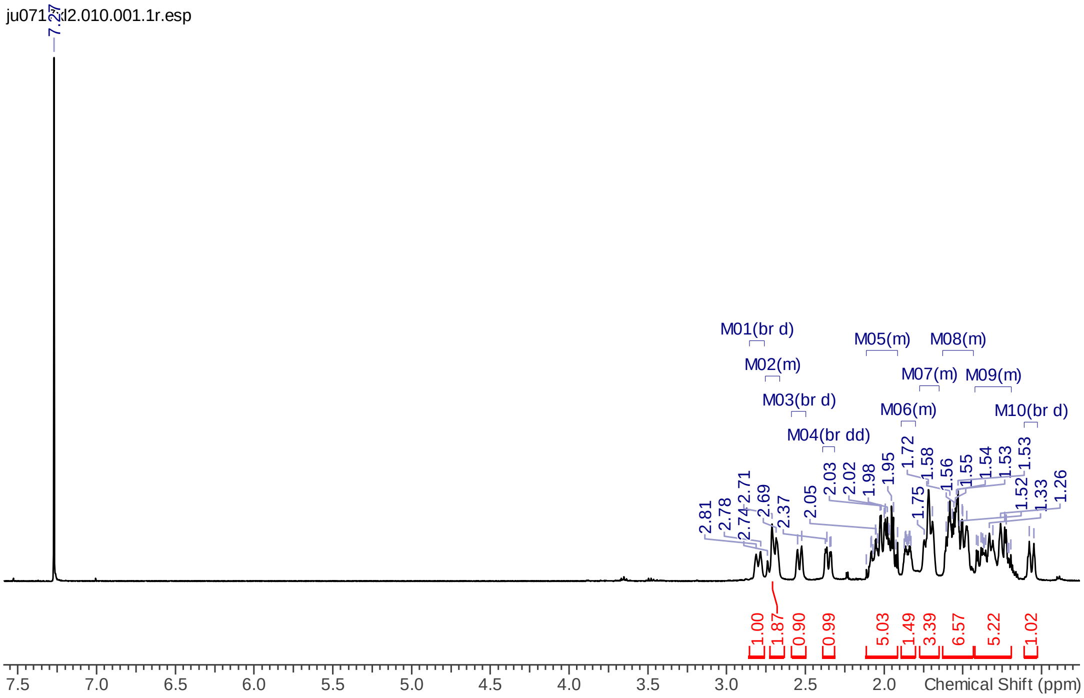
4.7 ^{1}H NMR: (+)-isosophoridine



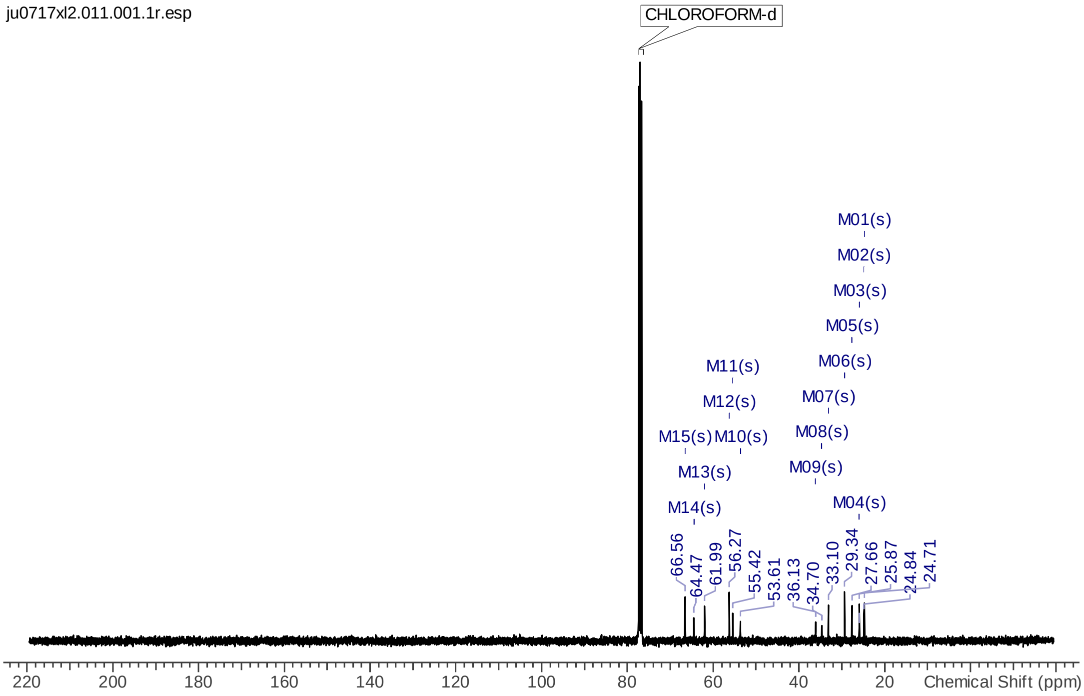
4.8 ^{13}C NMR: (+)-isosophoridine



4.9 ^{1}H NMR: (+)-sparteine



4.10 ^{13}C NMR: (+)-sparteine



Chapter 5: Reference

1. Aslanov, K. A.; Kushmuradov, Y. K.; Sadykov, A. S., Chapter 5 Lupine Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*, Brossi, A., Ed. Academic Press: 1987; Vol. 31, pp 117-192.

2. Jezierny, D.; Mosenthin, R.; Bauer, E. *Anim. Feed Sci. Technol.* **2010,** *157*, 111-128.

3. Litkey, J.; Dailey, M. W. *Am J Emerg Med* **2007,** *25*, 215-217.

4. Willstatter, R.; Fourneau, E. *Chem. Ber.* **1902**.

5. Karrer, P.; Canal, F.; Zohner, K.; Widmer, R. *Helv. Chim. Acta* **1928,** *11*, 1062-1084.

6. Schöpf, C., and Thomä, O. *Liebigs Ann. Chem* **1928,** *465*.

7. Winterfeld, K. a. H., F.W. *Ber. Dtsch. Chem. Ges* **1931,** *64*.

8. Boekelheide, V.; Lodge Jr, J. *J. Am. Chem. Soc.* **1951,** *73*, 3681-3684.

9. Galinovsky, F.; Nesvadba, H. *Monatsh. Chem* **1954,** *85*.

10. Cookson, R. *Chem. Ind. (london)* **1953**, 337-340.

11. Levene, P.; Marker, R. *J. Biol. Chem.* **1931,** *91*, 761-772.

12. Okuda, S.; Kataoka, H.; Tsuda, K. *Chem. Pharm. Bull.* **1965,** *13*, 487-491.

13. Plugge, P. *Arch. Pharm.* **1895,** *233*, 441-443.

14. Xiao, P.; Kubo, H.; Ohsawa, M.; Higashiyama, K.; Nagase, H.; Yan, Y.; Li, J.; Kamei, J.; Ohmiya, S. *Planta Med.* **1999,** *65*, 230-233.

15. Huang, J.; Xu, H. *Curr. Top. Med. Chem.* **2016,** *16*, 3365-3378.

16. Sun, M.; Cao, H.; Sun, L.; Dong, S.; Bian, Y.; Han, J.; Zhang, L.; Ren, S.; Hu, Y.; Liu, C. *Evid Based Complement Alternat Med* **2012,** *2012*.

17. Liu, Y.; Xu, Y.; Ji, W.; Li, X.; Sun, B.; Gao, Q.; Su, C. *Tumour Biol* **2014,** *35*, 5111-5119.

18. Tsuda, K. *Chem. Ber.* **1936,** *69*, 429-434.

19. Kondo, H. *Arch. Pharm.* **1928,** *266*, 1-19.

20. Kondo, H.; Ochiai, E.; Tsuda, K.; Yoshida, S. *Chem. Ber.* **1935,** *68*, 570-581.

21. Kondo, H.; Ochiai, E.; Tsuda, K. *Eur. J. Inorg. Chem.* **1935,** *68*, 1899-1904.

22. Tsuda, K.; Saeki, S.; Imura, S.; Okuda, S.; Sato, Y.; Mishima, H. *J. Org. Chem.* **1956,** *21*, 1481-1486.

23. Shigenobu, O. *Chem. Pharm. Bull.* **1956,** *4*, 257-261.

24. Ochiai, E.; Minato, H. *Yakugaku Zasshi* **1953,** *73*, 914-917.

25. Proskurnina, N.; Kuzovkov, A. *Dokl. Akad. Nauk SSSR* **1953,** *91*, 1145-1146.

26. Tsuda, K.; Mishima, H. *J. Org. Chem.* **1958,** *23*, 1179-1183.

27. Bohlmann, F.; Weise, W.; Rahtz, D.; Arndt, C. *Eur. J. Inorg. Chem.* **1958,** *91*, 2176-2189.

28. Bohlmann, F. *Eur. J. Inorg. Chem.* **1958,** *91*, 2157-2167.

29. Bohlmann, F. *Angew. Chem.* **1957,** *69*, 641-642.

30. Okuda, S.; Yoshimoto, M.; Tsuda, K.; Utzugi, N. *Chem. Pharm. Bull.* **1966,** *14*, 314-318.

31. Shigenobu, O.; Hiromitsu, K.; Kyosuke, T. *Chem & Ind (London)* **1962**, 1326.

32. Iskandarov, S.; Kamalitdinov, D. D.; Yagudaev, M.; Yunusov, S. Y. *Chem. Nat. Compd.* **1971,** *7*, 165-170.

33. Ueno, A.; Morinaga, K.; Fukushima, S.; Iitaka, Y.; Koiso, Y.; Okuda, S. *Chem. Pharm. Bull.* **1975,** *23*, 2560-2566.

34. Monakhova, T.; Tolkachev, O.; Kabanov, V.; Perel'son, M.; Proskurnina, N. *Chem. Nat. Compd.* **1974,** *10*, 477-480.

35. Ibragimov, B.; Tishchenko, G.; Kushmuradov, Y. K.; Talinov, S.; Aripov, T. *Chem. Nat. Compd.* **1982,** *18*, 66-69.

36. Leonard, N. J., Lupin alkaloids. In *The Alkaloids: Chemistry and Physiology*, Elsevier: 1953; Vol. 3, pp 119-199.

37. Ibragimov, B.; Tishchenko, G.; Kushmuradov, Y. K.; Aripov, T.; Sadykov, A. *Chem. Nat. Compd.* **1979,** *15*, 308-314.

38. Rulko, F. *Zh. Obshch. Khim.* **1962,** *32*, 1695-1699.

39. Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982,** *47*, 230-233.

40. Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988,** *53*, 3325-3330.

41. Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993,** *34*, 215-218.

42. Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1996,** *61*, 5581-5586.

43. Ledoux, S.; Marchalant, E.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **2001,** *42*, 5397-5399.

44. Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. *Tetrahedron* **2004,** *60*, 5433-5438.

45. Noel, R.; Fargeau-Bellassoued, M.-C.; Vanucci-Bacque, C.; Lhommet, G. *Synthesis* **2008,** *2008*, 1948-1954.

46. Fustero, S.; Moscardó, J.; Sánchez-Roselló, M.; Flores, S.; Guerola, M.; del Pozo, C. *Tetrahedron* **2011,** *67*, 7412-7417.

47. Santos, L. S.; Mirabal-Gallardo, Y.; Shankaraiah, N.; Simirgiotis, M. J. *Synthesis* **2011,** *2011*, 51-56.

48. Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T.; Roberts, P. M.; Schofield, T. M.; Thomson, J. E. *Chem. Commun.* **2014,** *50*, 8309-8311.

49. Ma, S.; Ni, B. *Chem. Eur. J.* **2004,** *10*, 3286-3300.

50. Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2009,** *12*, 528-531.

51. Sim, J.; Yun, H.; Jung, J.; Lee, S.; Kim, N.; Suh, Y. *Tetrahedron Lett.* **2012,** *53*, 4813-4815.

52. Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001,** *66*, 9056-9062.

53. Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000,** *2*, 155-158.

54. Mandell, L.; Singh, K.; Gresham, J.; Freeman, W. *J. Am. Chem. Soc.* **1963,** *85*, 2682-2683.

55. Mandell, L.; Singh, K.; Gresham, J.; Freeman, W. *J. Am. Chem. Soc.* **1965,** *87*, 5234-5236.

56. Okuda, S.; Yoshimoto, M.; Tsuda, K. *Chem. Pharm. Bull.* **1966,** *14*, 275-279.

57. Wenkert, E.; Chauncy, B.; Dave, K.; Jeffcoat, A. R.; Schell, F.; Schenk, H. *J. Am. Chem. Soc.* **1973,** *95*, 8427-8436.

58. Wenkert, E.; Jeffcoat, A. R. *J. Org. Chem.* **1970,** *35*, 515-517.

59. Saeki, S.; Yamashita, A.; Morinaka, Y.; Hamana, M. *Chem. Pharm. Bull.* **1977,** *25*, 79-86.

60. Saeki, S.; Yamashita, A.; Matsukura, Y.; Hamana, M. *Chem. Pharm. Bull.* **1974,** *22*, 2341-2345.

61. Chen, J.; Browne, L. J.; Gonnela, N. C. *J. Chem. Soc., Chem. Commun.* **1986**, 905-907.

62. Boiteau, L.; Boivin, J.; Liard, A.; Quicletl-Sire, B.; Zard, S. Z. *Angew. Chem. Int. Ed.* **1998,** *37*, 1128-1131.

63. Tsukano, C.; Oimura, A.; Enkhtaivan, I.; Takemoto, Y. **2014**.

64. Pop, I.-A. *Thesis* **2015**.

65. Firth, J. D.; Canipa, S. J.; Ferris, L.; O'Brien, P. *Angew. Chem. Int. Ed.* **2018,** *57*, 223-226.

66. Hermet, J.-P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830-1831.

67. Scharnagel, D.; Goller, J.; Deibl, N.; Milius, W.; Breuning, M. *Angew. Chem. Int. Ed.* **2018,** *57*, 2432-2435.

68. Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem. Eur. J.* **2009,** *15*, 12764-12769.

69. Breuning, M.; Steiner, M.; Mehler, C.; Paasche, A.; Hein, D. *J. Org. Chem.* **2008,** *74*, 1407-1410.

70. Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. *Org. Lett.* **2011,** *13*, 3988-3991.

71. Watkin, S. V.; Camp, N. P.; Brown, R. C. *Org. Lett.* **2013,** *15*, 4596-4599.

72. Al-Saffar, F. M.; Brown, R. C. *Org. Lett.* **2017,** *19*, 3502-3504.

73. Watkin, S. V. *Thesis* **2013**.

74. Fuentes, L. M.; Shinkai, I.; Salzmann, T. *J. Am. Chem. Soc.* **1986,** *108*, 4675-4676.

75. Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990,** *55*, 1148-1156.

76. Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *Tetrahedron* **1990,** *46*, 6361-6380.

77. Vaccaro, W. D.; Sher, R.; Davis Jr, H. R. *Bioorg. Med. Chem. Lett.* **1998,** *8*, 35-40.

78. Ferstl, E. M.; Venkatesan, H.; Ambhaikar, N. B.; Snyder, J. P.; Liotta, D. C. *Synthesis* **2002,** *14*, 2075-2083.

79. Sasikala, C.; Reddy Padi, P.; Sunkara, V.; Ramayya, P.; Dubey, P.; Bhaskar Rao Uppala, V.; Praveen, C. *Org. Process Res. Dev.* **2009,** *13*, 907-910.

80. Evans, D. A.; Bartroli, J.; Shih, T. *J. Am. Chem. Soc.* **1981,** *103*, 2127-2129.

81. Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387-398.

82. Gage, J. R.; Evans, D. A. *Org. Synth.* **2003,** *68*, 77-77.

83. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987,** *28*, 6141-6144.

84. Leeuwenburgh, M. A.; Geurink, P. P.; Klein, T.; Kauffman, H. F.; van der Marel, G. A.; Bischoff, R.; Overkleeft, H. S. *Org. Lett.* **2006,** *8*, 1705-1708.

85. Usui, K.; Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2015,** *56*, 1247-1251.

86. Wullschleger, C. W.; Li, J.; Edenharter, A.; Altmann, K.-H. *Synlett* **2016,** *27*, 2726-2730.

87. Hettche, F.; Reiß, P.; Hoffmann, R. W. *Chem. Eur. J.* **2002,** *8*, 4946-4956.

88. Layer, R. W. *Chem. Rev.* **1963,** *63*, 489-510.

89. Evans, D. A.; Shaw, J. T. *Angew. Chem*.

90. Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001,** *66*, 894-902.

91. Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003,** *125*, 11253-11258.

92. Cutter, A. C. *Thesis* **2012**.

93. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991,** *56*, 5747-5750.

94. Pereira, E.; de Fátima Alves, C.; Böckelmann, M. A.; Pilli, R. A. *Tetrahedron Lett.* **2005,** *46*, 2691-2693.

95. Pereira, E.; Alves, C. d. F.; Böckelmann, M. A.; Pilli, R. A. *Quim. Nova* **2008,** *31*, 771-775.

96. Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Tetrahedron* **2000,** *56*, 7411-7422.

97. Green, R. A.; Brown, R. C.; Pletcher, D. *J. Flow. Chem.* **2015,** *5*, 31-36.

98. Kabeshov, M. A.; Musio, B.; Murray, P. R.; Browne, D. L.; Ley, S. V. *Org. Lett.* **2014,** *16*, 4618-4621.

99. Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001,** *66*, 809-823.

100. Davis, F. A.; Xu, P. *J. Org. Chem.* **2011,** *76*, 3329-3337.

101. Solladié, G. *Synthesis* **1981,** *1981*, 185-196.

102. Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006,** *8*, 773-776.

103. Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987,** *28*, 3103-3106.

104. Baldwin, J. E.; Moloney, M. G.; North, M. *Tetrahedron* **1989,** *45*, 6309-6318.

105. Hanessian, S.; Margarita, R.; Hall, A.; Luo, X. *Tetrahedron Lett.* **1998,** *39*, 5883-5886.

106. Wang, J.; Hou, Y.; Wu, P.; Qu, Z.; Chan, A. S. *Tetrahedron: Asymmetry* **1999,** *10*, 4553-4561.

107. Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. *J. Org. Chem.* **2005,** *70*, 207-213.

108. Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995,** *6*, 1511-1514.

109. Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009,** *74*, 2646-2650.

110. Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005,** *7*, 871-874.

111. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992,** *114*, 7324-7325.

112. Sparatore, A.; Tasso, B.; Boido, V.; Sparatore, F. *Helv. Chim. Acta* **2005,** *88*, 245-251.

113. Rusconi, C.; Vaiana, N.; Casagrande, M.; Basilico, N.; Parapini, S.; Taramelli, D.; Romeo, S.; Sparatore, A. *Biorg. Med. Chem.* **2012,** *20*, 5980-5985.

114. Morley, C.; Knight, D. W.; Share, A. C. *Tetrahedron: Asymmetry* **1990,** *1*, 147-150.

115. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005,** *127*, 17160-17161.

116. Gavhane, K. B.; Bhorkade, S. B.; Kulkarni, M. G. *Tetrahedron: Asymmetry* **2015,** *26*, 746-750.

117. Banwell, M. G.; Beck, D. A.; Smith, J. A. *Org. Biomol. Chem.* **2004,** *2*, 157-159.

118. Murakoshi, I.; Kidoguchi, E.; Nakamura, M.; Haginiwa, J.; Ohmiya, S.; Higashiyama, K.; Otomasu, H. *Phytochemistry* **1981,** *20*, 1725-1730.

119. Yamada, Y.; Hatano, K.; Matsui, M. *Agric. Biol. Chem.* **1970,** *34*, 1536-1540.

120. Schmidt am Busch, M.; Knapp, E. W. *ChemPhysChem* **2004,** *5*, 1513-1522.

121. Swamy, K. K.; Kumar, N. B.; Balaraman, E.; Kumar, K. P. *Chem. Rev.* **2009,** *109*, 2551-2651.

122. Michael, J. P.; Jungmann, C. M. *Tetrahedron* **1992,** *48*, 10211-10220.

123. Handore, K. L.; Reddy, D. S. *Org. Lett.* **2013,** *15*, 1894-1897.

124. Leeder, A. J.; Heap, R. J.; Brown, L. J.; Franck, X.; Brown, R. C. *Org. Lett.* **2016,** *18*, 5971-5973.

125. Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998,** *9*, 4361-4368.

126. Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998,** *9*, 1823-1828.

127. Morinaga, K.; Ueno, A.; Fukushima, S.; Namikoshi, M.; Iitaka, Y.; Okuda, S. *Chem. Pharm. Bull.* **1978,** *26*, 2483-2488.

128. Kushmuradov, Y. K.; Aslanov, K. A.; Sohütte, K. R.; Kuchkarov, S. *Chem. Nat. Compd.* **1977,** *13*, 207-210.

129. Tan, C.-j.; Zhao, Y.; Goto, M.; Hsieh, K.-Y.; Yang, X.-m.; Morris-Natschke, S. L.; Liu, L.-n.; Zhao, B.-y.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2016,** *26*, 1495-1497.

130. Galasso, V.; Asaro, F.; Berti, F.; Pergolese, B.; Kovač, B.; Pichierri, F. *Chem. Phys.* **2006,** *330*, 457-468.

131. Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett.* **2008,** *10*, 1871-1874.

132. Wender, P. A.; Jeffreys, M. S.; Raub, A. G. *J. Am. Chem. Soc.* **2015,** *137*, 9088-9093.

133. Malkov, A. V.; Kysilka, O.; Edgar, M.; Kadlčíková, A.; Kotora, M.; Kočovský, P. *Chem. Eur. J.* **2011,** *17*, 7162-7166.

134. Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M. *Chem. Eur. J.* **2001,** *7*, 1304-1308.

135. Lv, C.; Yan, X.; Tu, Q.; Di, Y.; Yuan, C.; Fang, X.; Ben-David, Y.; Xia, L.; Gong, J.; Shen, Y. *Angew. Chem. Int. Ed.* **2016,** *55*, 7539-7543.

136. Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002,** *4*, 2577-2579.

137. Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2008,** *11*, 485-488.

138. Huang, Z.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005,** *2005*, 1334-1336.

139. Hugelshofer, C. L.; Mellem, K. T.; Myers, A. G. *Org. Lett.* **2013,** *15*, 3134-3137.

140. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999,** *64*, 1403-1406.

141. Fernández, I.; Alcudia, A.; Gori, B.; Valdivia, V.; Recio, R.; García, M. V.; Khiar, N. *Org. Biomol. Chem.* **2010,** *8*, 4388-4393.

142. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997,** *62*, 2555-2563.

143. Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett.* **2003,** *5*, 925-927.

144. Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903-2907.

145. Kolanoś, R.; Wysocka, W.; Kwit, M.; Gawroński, J. *Tetrahedron: Asymmetry* **2001,** *12*, 1337-1343.