University of Southampton

Faculty of Engineering and Physical Sciences

School of Chemistry

Synthesis of (+)-*β*-Isosparteine and (+)-Sparteine from *Syn* and *Anti β*-Amino Esters

by

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Thesis for the degree of Doctor of Philosophy

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Abstract

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The sparteine series of alkaloids are a subset of the lupin alkaloids, a diverse family of over 200 natural products all containing a quinolizidine core. The sparteine series itself is comprised of three stereoisomers: sparteine, *α*-isosparteine and *β*-isosparteine. Whilst these alkaloids have found use medicinally in the past, contemporary use has focused on their applications within organic synthesis as asymmetric ligands. This is best exemplified in the use of (–)-sparteine as the ligand of choice for a range of enantioselective transformations.

This thesis describes the total synthesis of (+)-*β*-isosparteine and the formal synthesis of (+)-sparteine. The synthetic strategy employed for these syntheses is based upon highly diastereoselective imino-aldol reactions of functionalised ester and *N*-sulfinylimine fragments. (+)-*β*-isosparteine was accessed by a *syn*-selective imino aldol, whereas (+)-sparteine was delivered *via* a formal *anti*-imino aldol strategy. Both syntheses would also make use of a key *N*-acyl iminium cyclisation, in order to furnish the quinolizidine core.

In order to put these syntheses into context with almost 170 years of work on the sparteine series, a comprehensive review on the synthesis of the sparteine alkaloids is included. The privilege of modern synthetic knowledge and analytical techniques are applied to the early literature, and a scholarly eye is applied to much of the early structural elucidations and syntheses.

Efforts to explore the formal *anti*-imino aldol reaction are also disclosed. Significant progress has been made on improving the substrate scope for the *anti*-alkylation step itself. These insights would lead to the successful synthesis of an *anti*-substituted piperidine, affording novel access into a privileged medicinal chemistry motif. Finally, initial progress in the intramolecular cyclisation of tethered imides to styrenes using synthetic organic electrochemistry is also disclosed.

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Research Thesis: Declaration of Authorship

Print name:	David Edward Wheatley

Title of thesis:	Synthesis of (+)-*β*-isosparteine and (+)-sparteine from *syn* and *anti β*-amino esters

I declare that this thesis 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.

Signature:		Date:	

Acknowledgements

Bear with me, this might take a while.

First and foremost, I am indebted to Professor Richard Brown, for a great many things. You gave me the chance to pursue my dream of a PhD, and while it's been a rocky road these past few years, your unending patience, encyclopaedic knowledge of why my ideas are crazy and your unwavering support throughout this journey have both meant the world to me, and helped me become a better scientist. I will miss putting the world of synthesis to rights in your office.

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I reserve a **huge** thank-you to the members of the Brown group, both past and present, for keeping me insane these past few years. I won't even try to list all the times you've helped me through the long nights. In particular; thank-you to Alex Pop for helping me find my feet; Alex Leeder for your never-ending puns and Mao-gnets; Alex MI for not letting me sashay away; Katie Jolley for all the talks, teaching and wisdom you gave; Rob Green for always telling it like it is; Ana Folgueiras for always being a pelota, Lynda Brown for always being ready to share a tale of frustration (but always with cake after!), and Sean for being quite simply the best project partner I could ever have wished for. I miss our stories already, even though I know the next chapter of all of yours will have nothing but success.

And that doesn't even cover everyone on the floor! Many names old and new: Gabriela K, Dharyl W, Thomas R, Sun-Wei, Ben J, Rachel W, Zhong, Gemma P, Rob B, Laura P, thank-you for all the fun times we've shared and the laughs we've had. My time at Southampton was made brighter by your presence, whenever we intersected. A special shout-out to Andreina P, for being my done-with-it-all weekend buddy, and Hannah F for being part of team cyclopropane (Δ).

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I would also like to thank my parents, Kevin and Elaine, for all of the support, love and kindness you have shown to me – not just regarding the PhD, but in general. I know I haven't always been the easiest, but your generosity of spirit and your (almost!) endless patience have allowed me to become the person that I am today, and more and more a person that I'm proud to be. I got there – we got there.

And finally, I can't not thank you, Rebecca. You have been such an integral part to this story over the last three years. Our conversations in the lab, shared love of sarcasm, close-fought battles in University Challenge (I've almost won a match!) and **everything** else over the past three years has honestly kept me going, especially through the times things seemed the most bleak. The time we've spent in Southampton is a story that I wouldn't change for the world. Whilst I don't know what lies ahead in the next chapter, I will treasure this tale always, in the knowledge that, eventually, both of us will get where we want – the long way around.

There is also one other message that I would like to take the time to write.

Over the course of my PhD studies (and over much of my adult life), I have suffered from mental health (MH) difficulties of one form or another, and with varying severity at times. This might surprise several people reading this, or it might surprise no-one at all; I am fairly open about my MH, and always have been. However, in my time as a student – both as an undergrad and as a postgraduate, I have noticed an undeniable trend that the incidence of people suffering MH issues is on the rise – not even just in academia, but in all walks of life.

PhD research, and all academic research at the cutting-edge, is hard. I will not dispute that for an instant. At times it's taxing, draining and soul-destroying. It is also exciting, energetic, something to take pride in, and also (to me) the most worthwhile thing I have

ever done with my life. I wouldn't trade in my experience for any other. However, I have been fortunate. I have had friends, family and colleagues there for me, who have supported me in with full knowledge of my MH history, and who have stuck with me. They have also, at times, helped me find the help I have needed in order to get back on track, and stop the dark hole of despair from swallowing me up again. I know from personal experience that there are others who are less fortunate – and perhaps some who will be reading these pages.

The acceptance of MH issues in academia, *especially* at postgraduate level, is increasing by the year. This is just as well, considering that recent research has shown that one in two PhD students experience psychological distress (*Res. Policy*, **2017**, 46, 868). Even the big names in science are finally starting to open up to the growing issue of MH in academia (*Nature*, **2018**, 556, 5), and are starting to have a conversation about it – a casual google search will show you many examples starting from the last three years.

However, this might not be enough for whoever is reading this thesis at this moment in time. So, I offer some words of wisdom from my own experiences, both for people who might have MH difficulties and for those who might want to support someone who does.

It is completely **okay** to be feeling the way you are right now. It's okay not to be okay! But, there are ways that can help you to feel better – there is, and will always be – help available to you throughout your studies. Importantly, there is always hope, even when it might seem like there isn't.

In the first instance, talk to a friend. Talk to your family. Talk to your supervisor. Talk to someone else completely removed from everything. Importantly, talk to someone. I remember a time when there was a lot of stigma around MH, and fortunately for all there is a lot more openness about the topic these days. Instead of deaf ears or shrugged shoulders, support and understanding have replaced stigma on the whole.

There are several facilities that both the University and the NHS have available that can potentially be of help. The University Enabling Services are an excellent place to start, and have several easily accessible avenues to explore. Your GP is also worth a visit, as despite all the advice I am giving, *I am not a trained healthcare professional*. I can share my experiences, but I can't offer solutions.

Regarding other options, the NHS in Southampton offers a service called "Steps to Wellbeing", which I and others have found useful (https://www.steps2wellbeing.co.uk/). Finally, the Samaritans are always available (116 123). You are more than your PhD. But in case the PhD gets more than you, be strong. Be brave. And good luck.

Acknowledgements

This Thesis is dedicated to Ted (Edward) Wheatley.

Though you didn't see it end, I know I made you proud.

Never forgotten.

Definitions and Abbreviations

$[\alpha]_D$	Alpha D
°C	Degrees Celsius
9-BBN	9-Borabicyclo[3.3.1]-nonane
Ac	Acetyl
AcOH	Acetic Acid
ADDP	1,1'-(Azodicarbonyl)dipiperidine
AM	Anti-Markovnikov
Aq	Aqueous
atm	Atmosphere
ATMS	Allyltrimethylsilane
Bn	Benzyl
br	Broad
BtH	1*H*-Benzotriazole
Bu	Butyl
ca.	Circa
Cbz	Benzyloxycarbonyl
cm	Centimetre
CM	Cross metathesis
Conc.	Concentrated
d	Doublet
d.r.	Diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride

DMAP	4-(Dimethylamino)-pyridine
DMF	*N*,*N*'-dimethylformamide
DMSO	Dimethylsulfoxide
e.e.	Enantiomeric excess
EI	Electron ionisation
Equiv.	Molar equivalents
ESI	Electrospray Ionisation
Et	Ethyl
et al.	*et alia* (Latin: and others)
FT	Fourier Transform
g	Gram
GC	Gas Chromatography
h	Hour(s)
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
i	Iso
IR	Infrared
J	Coupling constant
K	Kelvin
L	Litre
LDA	Lithium diisopropylamide
LRMS	Low-Resolution Mass Spectrometry
M	Milli
m	Multiplet
M	Molar

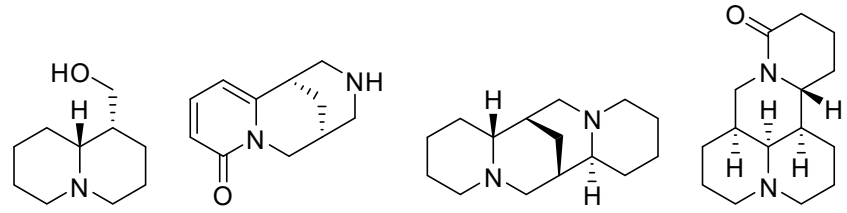
m (IR)	Medium
***m*-CPBA**	*meta*-Chloroperbenzoic acid
Me	Methyl
min	Minute(s)
Mmol	Millimole(s)
Ms	Mesyl
MS	Mass Spectrometry
MW	Molecular weight
n	Nano
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-Oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
O/N	Overnight
p	Para
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine
q	Quartet
RBF	Round Bottom Flask
RCM	Ring Closing Metathesis
R_f	Retention factor
RT	Room Temperature
s	Singlet
s (IR)	Strong
Sat.	Saturated
t	Triplet

t	Tertiary
T	Temperature
TBS	*tert*-Dibutyldimethylsilyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	Tosyl
UV	Ultraviolet
V_t	Variable Temperature
W	Weak
Δ	Heating at reflux

Chapter 1 The sparteine family of alkaloids

1.1 Introduction

The lupin (quinolizidine) alkaloids consist of a structurally diverse set of over 200 compounds, all sharing with a common quinolizidine core.[1] Known for well over 150 years, the lupin alkaloids can be divided broadly into four distinct compound classes, and have been isolated from several papilionaceous plant species[1-2]: bicyclics such as (–)-lupinine ((–)-**1.1**, *Lupinus pusillus*), tricyclics such as (–)-cytisine ((–)-**1.2**, *Anagyris foetida*), and two tetracyclic classes, exemplified by (–)-sparteine ((–)-**1.3**, *Cytisus scoparius*) and (+)-matrine ((+)-**1.4**, *Sophora pachycarpa*) (**Figure 1.1**).



(–)-lupinine **1.1** (–)-cytisine **1.2** (–)-sparteine **1.3** (+)-matrine **1.4**

Figure 1.1: Examples of common lupin alkaloids.

Lupin seeds have long been used as foodstuffs and for medicinal purposes, with many reports indicating this has been true for a period of over 3000 years.[3-4] Indeed, there has been a recent resurgence in the prospect of using lupin seeds as viable foodstuffs in agriculture, given the generally high protein levels present in the seeds.[5] One obstacle to wider uptake lies in their inherent toxicity to humans and animals, thus requiring a de-bittering process before consumption in order to lower the alkaloid levels.[6-7] Several of the lupin alkaloids have found medicinal uses in the modern day, however, with one of the most prominent being (–)-cytisine ((–)-**1.2**), marketed under the brand name Tabex® as a smoking cessation aid.[8-9]

Within the synthetic world, the members of the lupin alkaloids have often found themselves as desirable targets for total synthesis, often as ways to showcase new methodologies for use in the organic chemist's toolkit.[10-12] One of the most researched lupin alkaloids, both in terms of synthesis and application, is perhaps (–)-**1.3** .

1.1.1 (–)-Sparteine

(–)-Sparteine ((–)-**1.3**), possesses a semi-rigid bisquinolizidine structure, and has two C_2-symmetrical diastereoisomers, *α*-isosparteine (**1.5**) and *β*-isosparteine (**1.6**) (**Figure**

1.2), laevorotatory antipodes of which have also been isolated from natural sources (**Table 1.1**). Medicinally, (–)-**1.3** is the major alkaloid constituent of *Cytisus scoparius* (Scotch Broom), which has a long history of use as a herbal medicine. The plant is stated to possess a range of pharmacological effects that have been attributed to the alkaloid constituents. Indicated properties of the herbal extract include cardioactive, diuretic, peripheral vasoconstrictor and anti-haemorrhagic effects.

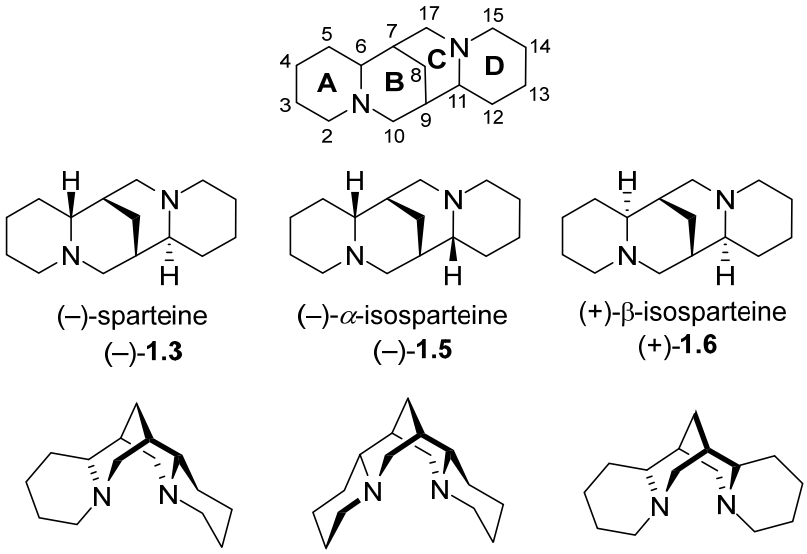
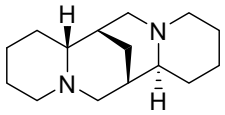
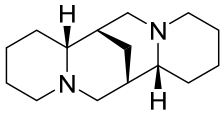
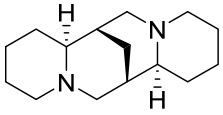


Figure 1.2: Structures of the sparteine family of stereoisomers, and numbering convention.

Table 1.1: Sparteine diastereoisomers, common synonyms and examples of occurence by optical antipode

				
Alkaloid		Sparteine	*α*-isosparteine	*β*-isosparteine
Synonyms	(+)	Pachycarpine		
	(–)	Lupinidine	Genisteine	Spartalupine, Pusilline
Occurrence	(+)	*Ammodendrin argenteum, Cytisus caucasicus, Thermopsis alpina*	*Not isolated*	*Not isolated*
	(–)	*Adenocarpys hispanicus, Cytisus scoparius, Lupinus arboreus*	*Lupinus caudatus, Sarothamnus scoparisus*	*Lupinus pusillus, Lupinus sericeus*

Biological and pharmacological evaluation of (–)-**1.3** itself is quite extensive, and has found use in clinical applications.[13-17] In the cardiovascular system, (–)-**1.3** exhibits anti-arrhythmic activity, both in humans and animals, as a result of its ability to chelate Na^+ and K^+ ions.[18] It is also able to reduce ventricular tachycardia and fibrillation incidences, and to lower the heart rate and blood pressure. However, due to several concerns about the toxicity of (–)-**1.3**, it was withdrawn for use by the FDA.[19] Despite this ban, research still continues on the use of (–)-**1.3** and its derivatives in medicinal applications.[20]

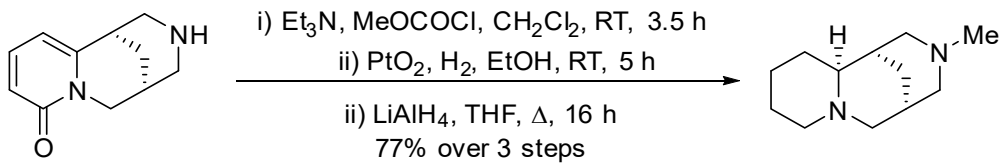
(–)-Sparteine is most familiar to synthetic chemists as a chiral diamine, used in a wide range of enantioselective transformations. Its diastereoisomers remain less well explored in this regard.[21] As shown in **Figure 1.2**, the conformations of (–)-**1.3** and its isomers can behave as bidentate ligands for a variety of metal ions, providing a chiral space suitable for enantioselective transformations. Initial work by Butte[22] and Noyori[23] explored this effect with Li^+ ions, however the enantioselectivity obtained was initially modest. Contributions by Hoppe[24] and Beak[25]expanded this significantly, leading to a large field of highly enantioselective reactions that would employ (–)-**1.3** as the source of chirality.

The myriad use of sparteine complexes for asymmetric reactions has been widely reviewed in the literature.[21, 26-27] Selected recent applications of (–)-**1.3** include chiral resolution,[28] chain homologation,[29] *α*-arylation of *O*-carbamates,[30] ring-opening polymerization[31] and desymmetrisations of *meso*-diols.[32] The eclectic nature of this list emphasizes the versatility and continuing interest in (–)-**1.3**. It is also prudent to mention that the diastereoisomers (–)-*α*-isosparteine ((–)-**1.5**) and (+)-*β*-isosparteine ((+)-**1.6**) have also found use in asymmetric synthesis, however in most cases their effect is muted compared to (–)-**1.3** itself.[33-35]

1.1.2 (+)-Sparteine Surrogate

In recent years, there has been a marked shortage of commercial sources of (–)-**1.3**, which has been noted as far back as 2010.[36-37] This scarcity of sparteine has only recently been remedied, with several chemical companies now selling gram amounts of both antipodes at time of writing, albeit at fairly modest prices. This drought led researchers to investigate other means of procuring both antipodes of **1.3**, such as a reduction/resolution route from (–)-lupanine,[38-39] however this still relies on natural product sources. An alternative solution has been the development of chiral diamine ligands for use as potential "sparteine surrogates", with O'Brien's (+)-sparteine surrogate (+)-**1.7** emerging as the ligand of choice to replace (+)-**1.3**.[40-43]

In an interesting twist to the tale of the lupin alkaloids, the preparation of **1.7** is a quite facile process from (–)-cytisine ((–)-**1.2**), involving protection of the secondary amine as the methoxy carbamate, followed by sequential reduction, first with H_2 in the presence of Adam's catalyst and finally $LiAlH_4$ to furnish (+)-**1.7** (**Scheme 1.1**). This molecule can in effect be regarded as possessing the complete ABC rings of (+)-**1.3**, whilst possessing a methyl-capped secondary amine, truncating the D ring. Rigorous testing of (+)-**1.7** with the lithiation-electrophilic trapping of *N*-Boc pyrrolidine as the model reaction gave an enantiocomplimentary e.r. when compared to (–)-**1.3**. Later studies have shown that the A ring of (–)-**1.3** is indeed essential for asymmetric induction, whilst the D ring, although working in tandem with the A ring, has a much less pronounced effect.[44]



(–)-**1.2** (+)-**1.7**

Scheme 1.1: O'Brien's original synthesis of the (+)-sparteine surrogate (+)-**1.7.**

1.1.3 Biosynthesis of the sparteine series

The unmasking of the biosynthesis of the sparteine alkaloids has been a key target of several investigations throughout the last century. Robinson communicated the first proposal of the biosynthesis as part of a set of "reasonable biosynthetic routes to a wide range of alkaloids".[45] Whilst the principles of this have merit, a fundamental flaw in Robinson's proposal originated from the use of an erroneous structure of (–)-**1.3** (**See Section 1.2.1**). Since then, the biosynthesis has been a topic of much debate in the literature, with much work done by Robinson,[46] Schöpf,[47] Schütte and Bohlmann[48-50] and Spenser.[51-52] This has led to more detailed treatments of the biosynthesis of quinolizidine alkaloids.[53-55]

1.2 Isolation and Structural Determination

It is already clear that (–)-sparteine ((–)-**1.3**) is an alkaloid with a wealth of history. There have been several past reviews of its synthesis, mostly contained within the book series *The Alkaloids*,[1-2, 56-57] complimented with an excellent micro-review by Blakemore as a preface to his total syntheses of the sparteine series.[58]

Much of the work in recent years within the Brown group has had (–)-**1.3** - along with other members of the lupin family - at its core. In our estimation, a review of the syntheses was necessary due to: a) A comprehensive review of the sparteine series has never been published, and b) The initial literature, especially the early racemic total syntheses, deserve comment with the privilege of modern analytical techniques, especially now that the full structure (–)-**1.3** is known in great detail. It is with this enquiring eye that we review the syntheses of the sparteine series in detail up to the present day.

The following section is broadly chronological in nature. Contemporary syntheses have been driven by the changing paradigms of natural product synthesis research, whereas the very early work was motivated by structural determination. Due to the time in which these early endeavors were published, they were heavily restricted by the available synthetic methods and (more importantly) analytical techniques. As such there are times where it is reasonable to both make assumptions and correct errors concerning starting

materials, compounds isolated, and the optical character of intermediates and products, given the greater knowledge available at present.

More recent synthetic approaches would emphasise aspects such as stereocontrol and methodology development, with more recent publications stressing the practicalities and scalability of the syntheses, especially due to the recent limited availability of (–)-**1.3** itself.

1.2.1 Original Isolation & Early Structural Insights

In 1851, Stenhouse reported the isolation of several new alkaloids from the plant *Cytisus Scoparisus*, one of which was given the name Sparteïn.[59] Initial experiments by Stenhouse yielded the tentative assignment of the chemical formula as $C_{15}H_{26}N_2$, which was subsequently corroborated by Mills.[60] Over the next few decades, several investigators tasked themselves with identifying the full structure of this new alkaloid (**Figure 1.3**), however a full structural and stereochemical determination of (–)-**1.3** would not be completed until well into the next century.

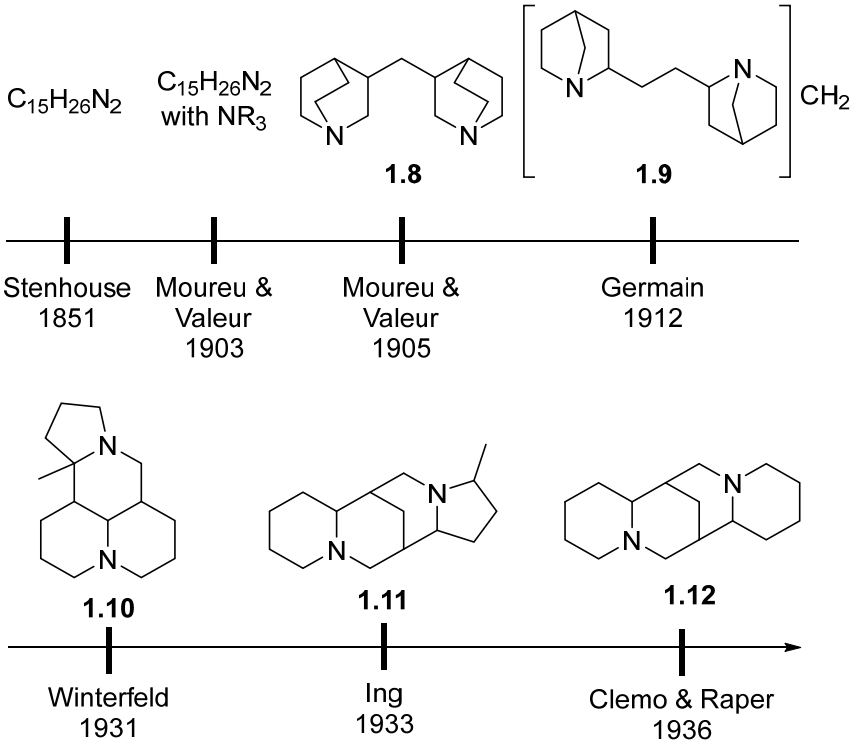


Figure 1.3: The evolution of the proposed sparteine skeleton throughout time.

Some notable insights into the structure of sparteine would be made by Moureu and Valeur, who assigned the two nitrogen atoms as tertiary, based on the observation that both could be titrated, and that the molecule formed both neutral and acid salts.[61] They also proposed that the alkaloid possessed a saturated skeleton due to the lack of reaction with permanganate reagents, and also noted that a cyclic structure was suggested by the

molecular formula.[62] Based upon these observations, they advanced the structure of sparteine to be that of diquinuclidylmethane **1.8**.[63]

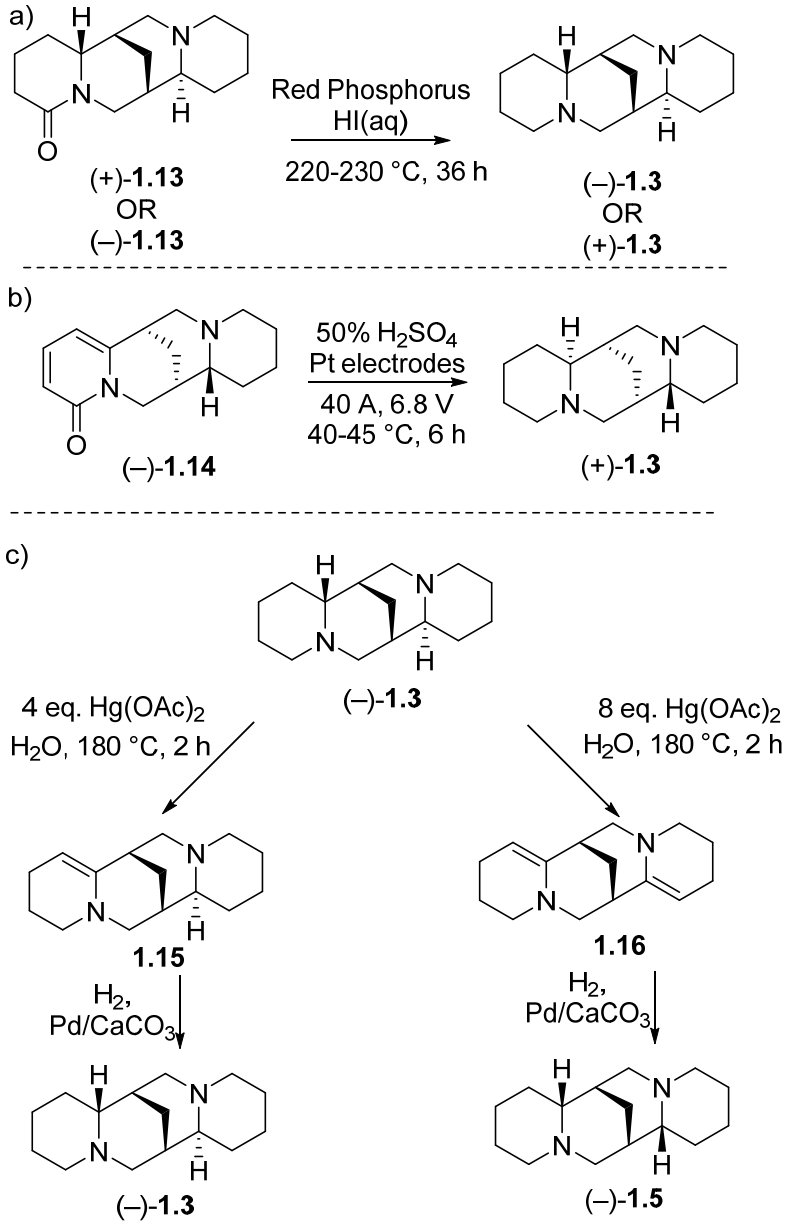
As was typical of the time, a series of degradation studies were also carried out on this alkaloid of unknown constitution. Moureu and Valeur performed an exhaustive Hoffman methylation study on the alkaloid, which had the effect of dissecting the nitrogen atoms from the sparteine scaffold to yield trimethylamine, and a compound the investigators called "sparteilene", an unsaturated hydrocarbon with chemical formula $C_{15}H_{20}$.[64] This observation was also confirmed by Willstätter and Marx.[65] The conclusion from these experiments was that there were indeed two tertiary nitrogen atoms in a symmetrically constituted molecule.

Perhaps indicating how capricious structural assignments could be at the turn of the century, structure **1.8** was not the only formula in contention for sparteine. Germain, performing an oxidation of sparteine with permanganate in phosphoric acid, obtained succinic acid as one of the products, which gave in his eyes justification to advance the structure **1.9** bearing two azabicyclo[2.2.1]heptane units, with an ethyl linker between them.[66-67] Upon inspection it is obvious that a CH_2 unit is missing from this structure, but no further evidence is offered to place this unit within the proposed structure.

1.2.2 Interconversions With Other Known Alkaloids

Following this early work in determining the molecular formula of (–)-**1.3**, there was also a drive to determine relations to other previously isolated and identified compounds from the *Leguminosae* family. As such, several investigators undertook studies with the aim of converting (–)-**1.3** into other known alkaloids.

In 1928, Clemo reported that the known alkaloid (±)-lupanine ((±)-**1.13**) could be reduced to a base of chemical formula $C_{15}H_{26}N_2$.[66] Within this report, they note that there is a possibility that this product, which they named "deoxylupanine", could correspond to (±)-**1.3**, however they were not able to conclusively prove this until 1931.[68] Reduction of either (+)- or (–)-**1.13** by heating with fuming HI and red phosphorus afforded (–)- or (+)-**1.3** respectively, as confirmed by single and mixed melting point analyses of the picrate and mono-hydroiodide salts (**Scheme 1.2a**).



Scheme 1.2: Interconversions of lupin alkaloids. a) Clemo's conversion of lupanine to sparteine. b) Ing's conversion of anagyrine to sparteine. c) Winterfeld's oxidation and reduction of sparteine to return either itself or *α*-isosparteine, dependant on the severity of oxidation conditions.

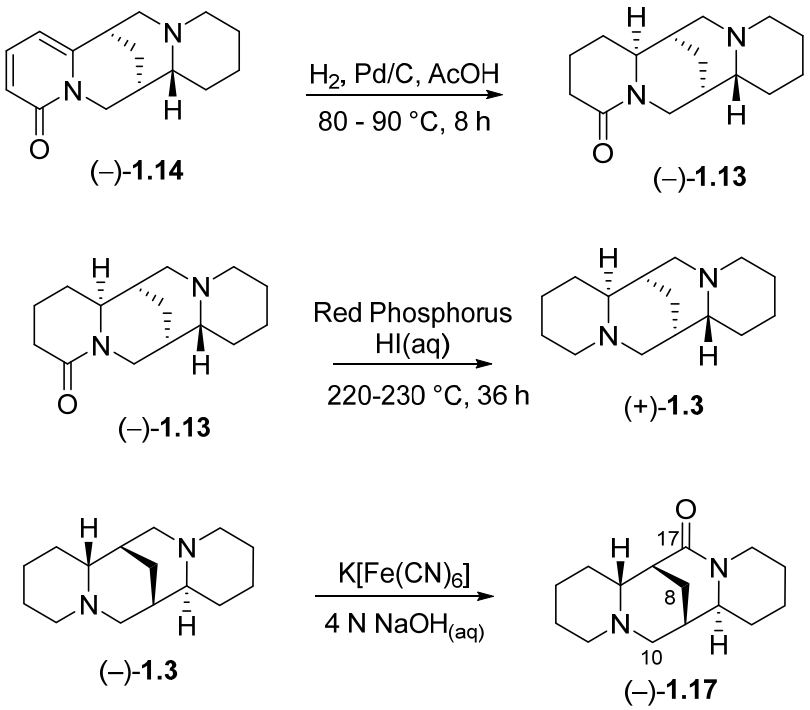
Whilst investigating two alkaloids isolated from *Anagyris Foetida* – cytisine and anagyrine - Ing noted that the electrolytic reduction of (–)-anagyrine ((–)-**1.14**) afforded a compound initially named "hexahydrodeoxyanagyrine" (**Scheme 1.2b**).[69] Comparison of the physical and chemical properties of the compound and its salts left little doubt that this reduction product was identical to (+)-**1.3**. Ing would use this information, and his previous work on the degradation of anagyrine - which had already been established to be close in structure to cytisine - to propose the structure **1.11** for sparteine, which was the first time the familiar tetracyclic structure of the alkaloid would emerge, albeit with an erroneous 5-membered ring.

The first emergence of one of the diastereoisomers of (±)-**1.3**, that of (–)-*α*-isosparteine ((–)-**1.5**), would surface in the 1934 communication of Winterfeld and Rauch on their investigations into the structures of the lupin alkaloids.[70] Their initial foray into the structural assignments of the sparteine series produced the (±)-matrine-like scaffold of **1.10**, which differed from Ing's proposed structure merely by the choice of ring-junctions.[71] They discovered that the oxidation of an authentic sample of (–)-**1.3** with four equivalents of mercuric acetate allowed the isolation of "dehydrosparteine" **1.15** (now known as (–)-Δ^5-dehydrosparteine), isolated as the free base (**Scheme 1.2c**). Hydrogenation of **1.15** returned optically pure (–)-**1.3**. More drastic oxidation conditions, using 8 equivalents of $Hg(OAc)_2$ returned a mixture of "*α*-didehydrosparteine" **1.16** ((–)-$\Delta^{5,11}$-didehydrosparteine), isolated as the bisulfate salt, and a species that the authors would call "*β*-didehydrosparteine", a brown oil admixed with **1.16** impurities. Hydrogenation of **1.16** provided a crystalline product, which the authors chose to name "*α*-isosparteine". The physical properties of this substance are consistent with contemporaneous data for (–)-**1.5**, and indeed this method has since been employed by others for the semi-synthesis of (–)-**1.5**.[34, 72-73]

The appearance of a second double oxidation product, this so-called *β*-didehydrosparteine presents an interesting predicament. The original isolation of this product by Winterfeld and Rauch was achieved only by the oiling out from a mixture of hydrogenation products; and was an impure mixture at best. The analytical data is also minimal, with only AgCl and picrate salts – and an optical rotation – being reported. As noted previously, there have been several repetitions of this methodology in the years following the original report. However, to the best of our knowledge, no other synthesis has obtained this "*β*-didehydrosparteine" since, and as such the isolation of this compound remains an anomaly.

1.2.3 Final structural determination of (–)-Sparteine

The relation of (–)-sparteine ((–)-**1.3**) to one of its oxidation products was key to the final proof of the tetracyclic structure **1.12**. One of the first oxidations carried out was that to "oxysparteine" (or "oxosparteine"), or more correctly (–)-17-oxosparteine ((–)-**1.17**) by Ahrens.[74] While the exact method used to oxidize (–)-**1.3** was not reported in the original communication, repetition of the work by Schöpf divulges the preparation as a ferricyanide oxidation carried out in alkaline conditions (**Scheme 1.3**).[75] More recent work, supported with characterization by NMR, provides confirmation that (–)-**1.17** is the obtained oxidation product from this reaction.[76-77]



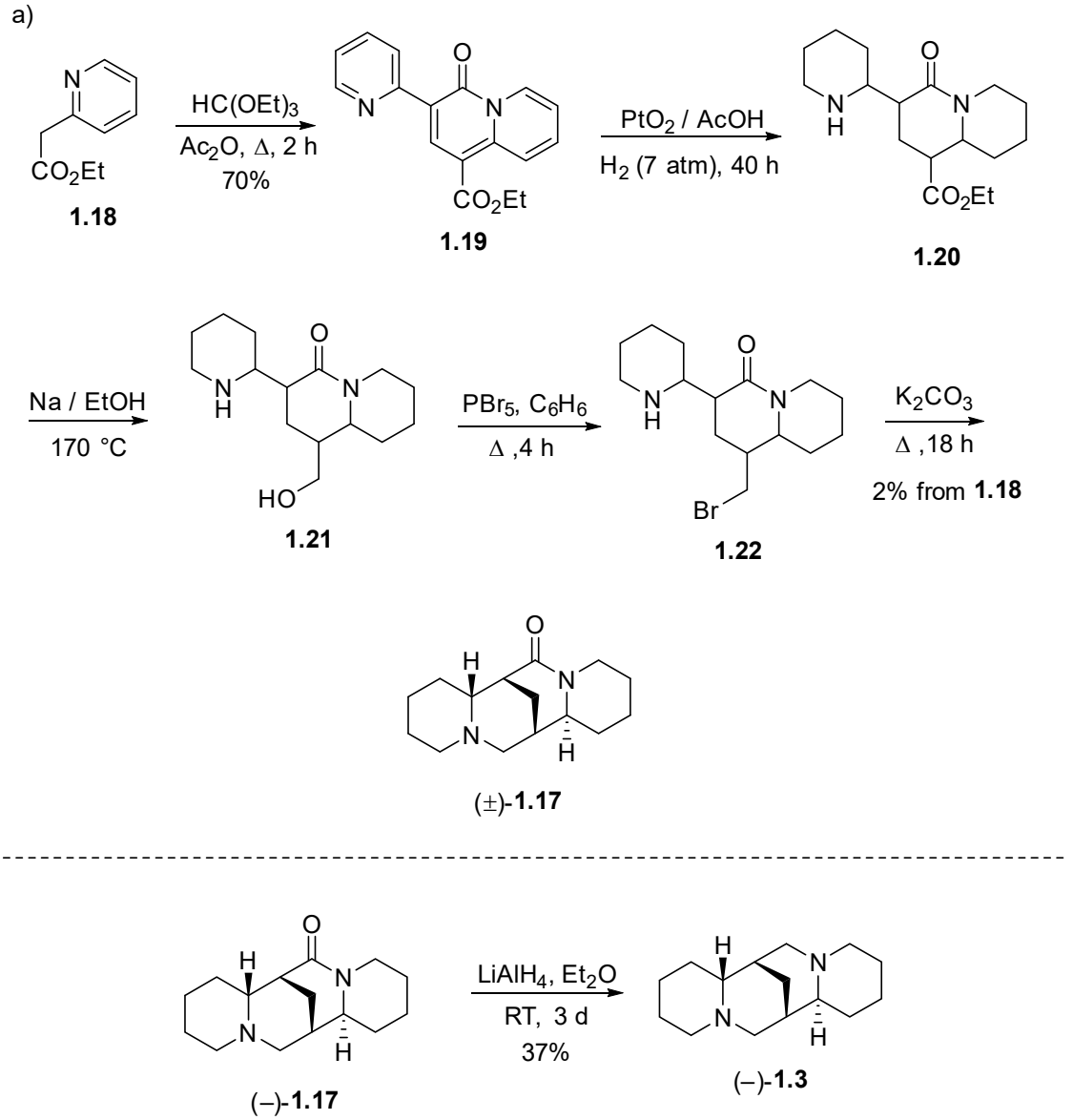
Scheme 1.3: Summary of the relation of (–)-**1.3** to its oxidation products.

Armed with the link of (–)-sparteine ((–)-**1.3**) to both (±)-lupanine (**1.13**) and (–)-anagyrine ((–)-**1.14**), Clemo and Raper, – in consultation with Ing – would propose a new structure of (–)-sparteine ((–)-**1.3**), that of the tetracyclic **1.12**, in an attempt to rationalize all the information that had been reported previously.[78] Support for Ing's previously proposed structure **1.11** had included the observation that the decomposition products of the lupin alkaloids with zinc dust gave pyrrole-like colour reactions, indicating the presence of a 5-membered ring within the skeleton. However, Clemo and Raper noted that (–)-**1.2**, the structure of which Ing had already tentatively assigned,[79] gave similar results to that of other lupin alkaloids, indicating that the 5-membered ring was produced by the reaction, not preformed in the molecule. They also used the relationship of (–)-**1.3** to its various oxidised forms (**Scheme 1.3**) to assign the carbonyl of "oxosparteine" to the C17 position, having ruled out C8 and C10 due to results of the previous degradation studies.

They also put forward a tentative stereochemical assignment for the alkaloid, however they would erroneously assign the stereochemistry present in *α*-isosparteine to that of sparteine itself. Assignment of the relative stereochemistry of the sparteine series would have to wait another 18 years, before being correctly proposed by Marion and Leonard,[80] and a further 13 years before the absolute stereochemistry was assigned by Tsuda.[81]

1.3 Initial total syntheses of the sparteine series

Having proposed the tetracyclic structure **1.12** for that of the sparteine series, the definitive proof of the structure would emerge from work in total synthesis. In 1936, a mere 85 years after the initial isolation of (–)-sparteine ((–)-**1.3**) by Stenhouse, the total synthesis of (±)-17-oxosparteine ((±)-**1.17**) was reported by Clemo, Morgan and Raper (**Scheme 1.4a**).[82] Condensation of ethyl 2-pyridylacetate (**1.18**) with triethyl orthoformate afforded unsaturated quinolizidone **1.19**. With subsequent electrolytic reduction of **1.19** proving fruitless, a stepwise approach was envisioned instead. Reduction of **1.19** to the saturated octahydroquinolizinone **1.20** followed by Bouvealt-Blanc reduction of the ester yielded alcohol **1.21**. This was then treated with PBr_3 to give primary bromide **1.22**, which cyclized in the presence of K_2CO_3 with heating in a sealed tube to obtain (±)-**1.17**.



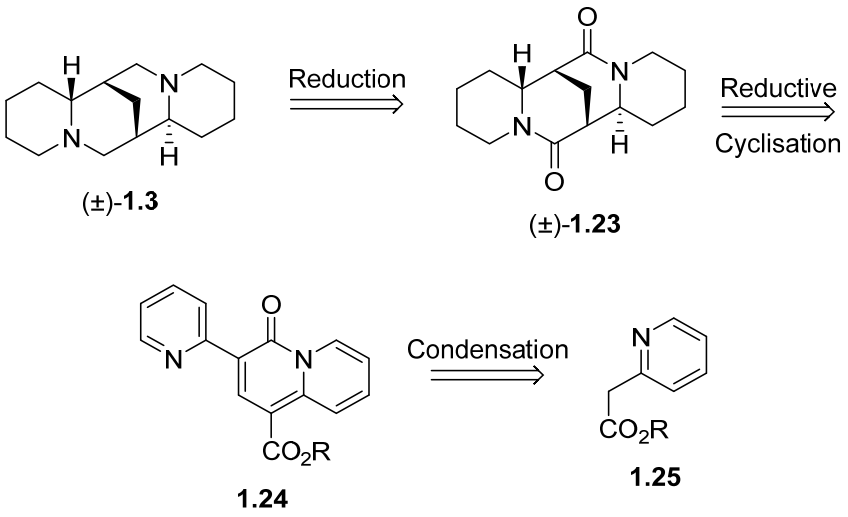
Scheme 1.4: a) Clemo's original synthesis of (±)-17-oxosparteine. b) Reduction of (–)-17-oxosparteine to (–)-sparteine using $LiAlH_4$.

The physical properties of their synthetic (±)-**1.17** were found to be consistent with those of the ferricyanide oxidation product of natural (±)-**1.3**, and as such the authors concluded that these two structures were identical, cementing the tetracyclic structure **1.12**. This is often cited as the first total synthesis of (±)-**1.3**, however in this report they were never able to reduce the lactam carbonyl with methods available at the time. It was not until 1948 that the authors were able to reduce an optically pure sample of (–)-**1.17** to (–)-**1.3** using $LiAlH_4$, thus finally completing the synthesis (**Scheme 1.4b**).[83-84]

Another curiosity disclosed within the report is that the authors state that the position of the carbonyl of (±)-**1.17** can either be at C10 or C17, and that the naming is interchangeable. This is an understandable oversight, as they had previously tentatively assigned the relative stereochemistry of (±)-**1.3** as that of (±)-**1.5** (vide supra).[78] In the privileged position of knowing the absolute structures of the sparteine series, it is clear by inspection that (±)-10-oxosparteine and (±)-**1.17** are diastereoisomers, however the reduction of either would naturally lead to (±)-**1.3**.

1.3.1 Reductive Cyclisations: The Quinolizidone variations.

Over the best part of the next two decades, inspired by the use of quinolizidone **1.19**, several reports from different groups emerged detailing total syntheses of either (±)-sparteine ((±)-**1.3**) or one of its oxidized precursors such as (±)-**1.17**. These closely related syntheses all relied on the use of a reductive cyclisation step to produce the tetracyclic skeleton (**Scheme 1.5**). The nature of these reductions often led to complicated reaction mixtures, with the reported products isolated not perhaps tallying with those that would be anticipated. Additionally, several of the reports included repetitions of the methods that others had published, with some findings deviating from the previous work.

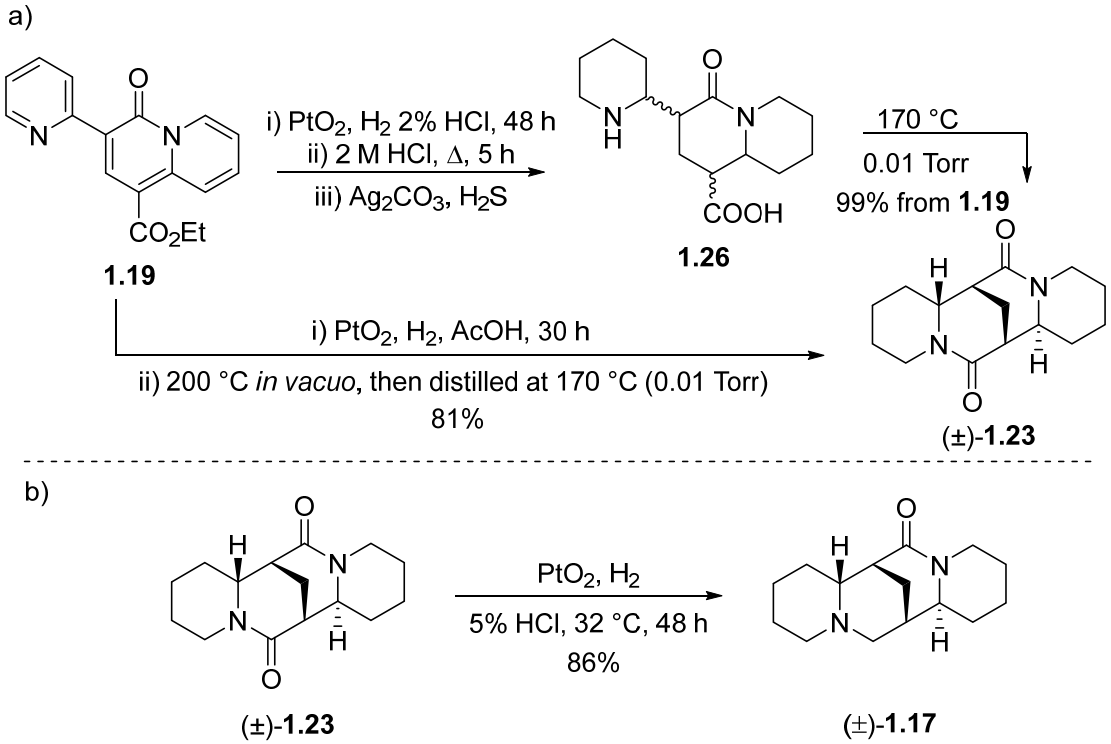


(±)-**1.3** (±)-**1.23** **1.24** **1.25**

Scheme 1.5: Generalised reductive cyclisation route towards the sparteine isomers.

In efforts to accurately represent this period of development and discovery, we have found it necessary to re-examine the primary data, armed with the privilege of modern analytical techniques and full understanding of the diastereoisomers of the sparteine series, to ascertain the products reported from the reactions undertaken. It is perhaps here that the most care and attention needs to be taken, due to the complicated interdependencies of the syntheses.

Due to the original synthesis of (±)-**1.17** producing only 0.2 g of material, Galinovsky & Kainz set themselves the task of improving and simplifying the synthesis, in the hopes to eventually obtain (±)-**1.3**.[85] They sought to do this *via* the Pt-mediated hydrogenation of quinolizidone **1.19** directly, based on their previous success with this reduction on other members of the lupin alkaloids.[86] They reduced **1.19** to the amino-alcohol **1.26** after acidic saponification and neutralisation (**Scheme 1.6a**). Vacuum distillation at elevated temperatures afforded a pale oil which the authors claimed to be (±)-10,17-dioxosparteine ((±)-**1.23**). They then reported a second method to access (±)-**1.23** directly by heating the crude product obtained after reduction *in vacuo*, followed by distillation at low pressure. Reduction of (±)-**1.23** to (±)-**1.17** was accomplished by hydrogenolysis in acid, providing product that showed physical characteristics matching the product of Clemo's previous synthesis (**Scheme 1.6b**).

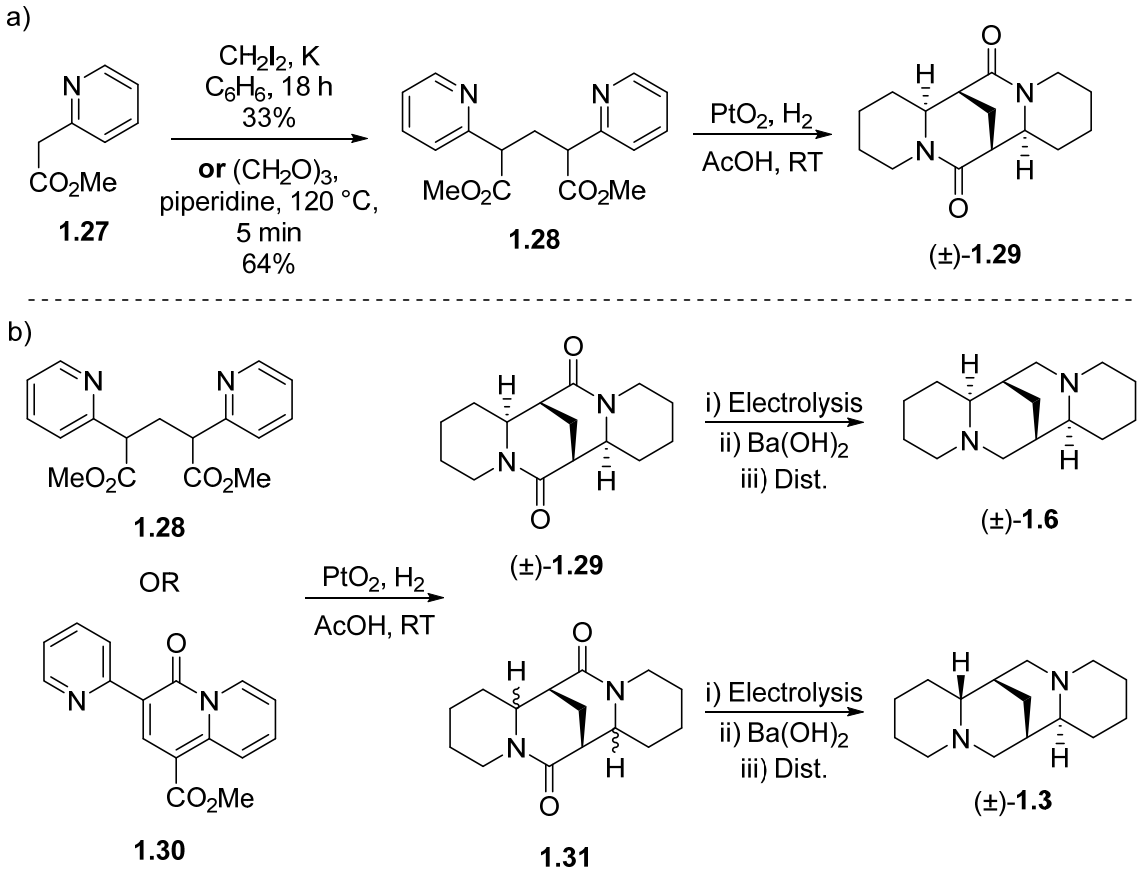


Scheme 1.6: Galinovsky and Kainz's syntheses. a) Synthesis of (±)-**1.23** *via* reduction and epimerization. b) Synthesis of (±)-**1.17** by hydrogenolysis.

It is perhaps surprising that the authors claim that only (±)-**1.23** arose from the cyclisation, however due to the relative harshness of the isolation steps, potential

epimerisations of the reaction intermediates cannot be ruled out at this stage. The reduction of (±)-**1.23** to (±)-**1.17** is as expected, with the physical data of the latter confirming the synthesis.

Shortly after Galinovsky and Kainz put forward their work on the synthesis of (±)-**1.23**, Šorm and Kiel published their efforts towards the synthesis of the sparteine series.[87] By using methyl 2-pyridylacetate (**1.27**), they synthesised glutarate **1.28** by either condensation with formaldehyde, or reaction of the potassium enolate with diiodomethane (**Scheme 1.7a**). Reduction using PtO_2 as before would lead to the eventual isolation of a dioxosparteine diastereoisomer. Although left ambiguous at the time of disclosure, comparison of physical data to contemporary sources would suggest this to be (±)-10,17-*β*-dioxoisosparteine (±)-**1.29**.[88]



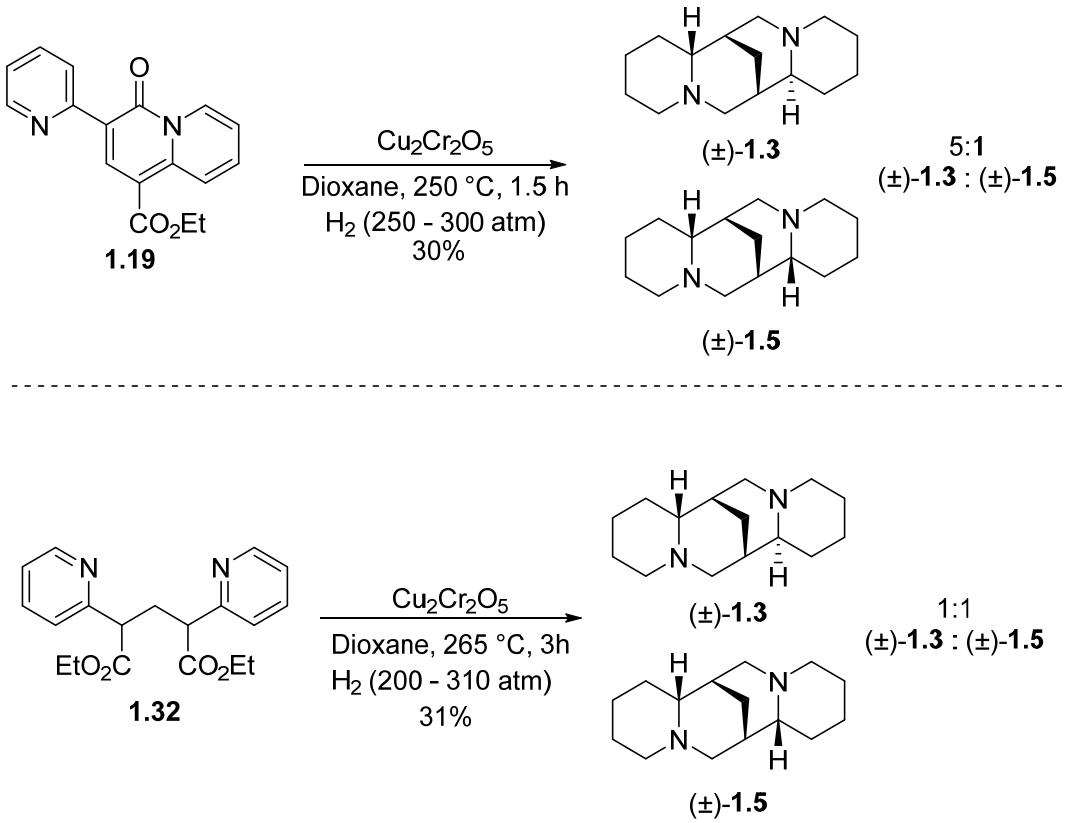
Scheme 1.7: Šorm and Kiel's efforts towards the sparteine isomers. a) Initial isolation of (±)-**1.29** (no yield was disclosed for the final reduction). b) Subsequent work resulting in the isolation of (±)-**1.6** and (±)-**1.3** (no yields were given in this report). The electrolysis step was performed with Pb electrodes in 50% H_2SO_4, 1.3 A,

Šorm and Kiel revisited the synthesis a year later, in an effort to improve the characterization of their products.[89] They noted that in their initial syntheses of **1.28**, a strongly yellow coloured by-product formed as a result of distillation, which was identified as the methyl ester analogue of quinolizidone **1.19**. Once again, **1.28** and the newly

synthesized quinolizidone **1.30** were subjected to catalytic hydrogenation over PtO_2. However, after a more meticulous isolation, two distinct products would be isolated (**Scheme 1.7b**). The original results would be confirmed by the isolation of (±)-**1.29**, however a second fraction was identified upon distillation, which the authors proposed was a mixture of further dioxosparteine isomers **1.31**. In a manner akin to Galinovsky and Kainz, the dioxosparteines were electrolytically reduced to obtain the alkaloids themselves. (±)-**1.29** was reduced to (±)-**1.6** (which was initially misidentified as (±)-**1.3**)), and the mixture of isomers **1.31** was reduced to (±)-**1.3** (originally misidentified as (±)-*α*-isosparteine (±)-**1.5**)).

In addition, this last reduction would yield another compound whose identity was never fully disclosed. However, this synthesis is notable in retrospect as this would mark the first true synthetic preparation of (±)-**1.6** – albeit misidentified at the time of publication. The results here would also check well with a related synthesis by Clemo, which proceeded from the ethyl derivative of glutarate **1.28**.[84]

The final true evolution of this procedure was reported by Leonard, at approximately the same time as Šorm and Kiel.[90] Copper chromite was employed as the catalyst, in an adaptation of their previous work on the synthesis of pyrrolizidines.[91] This shortened the synthesis of (±)-**1.3** to two steps – preparation of the quinolizidone **1.19** and then subsequent hydrogenation to (±)-**1.3** (**Scheme 3.5**). The authors provided further insight into this reaction in a full publication two years later (**Scheme 3.5**), which also included results from the ethyl glutarate **1.32**.[72]



Scheme 1.8: Leonard's syntheses of (±)-**1.3** and (±)-**1.5** *via* reductive cyclisation using copper chromite.

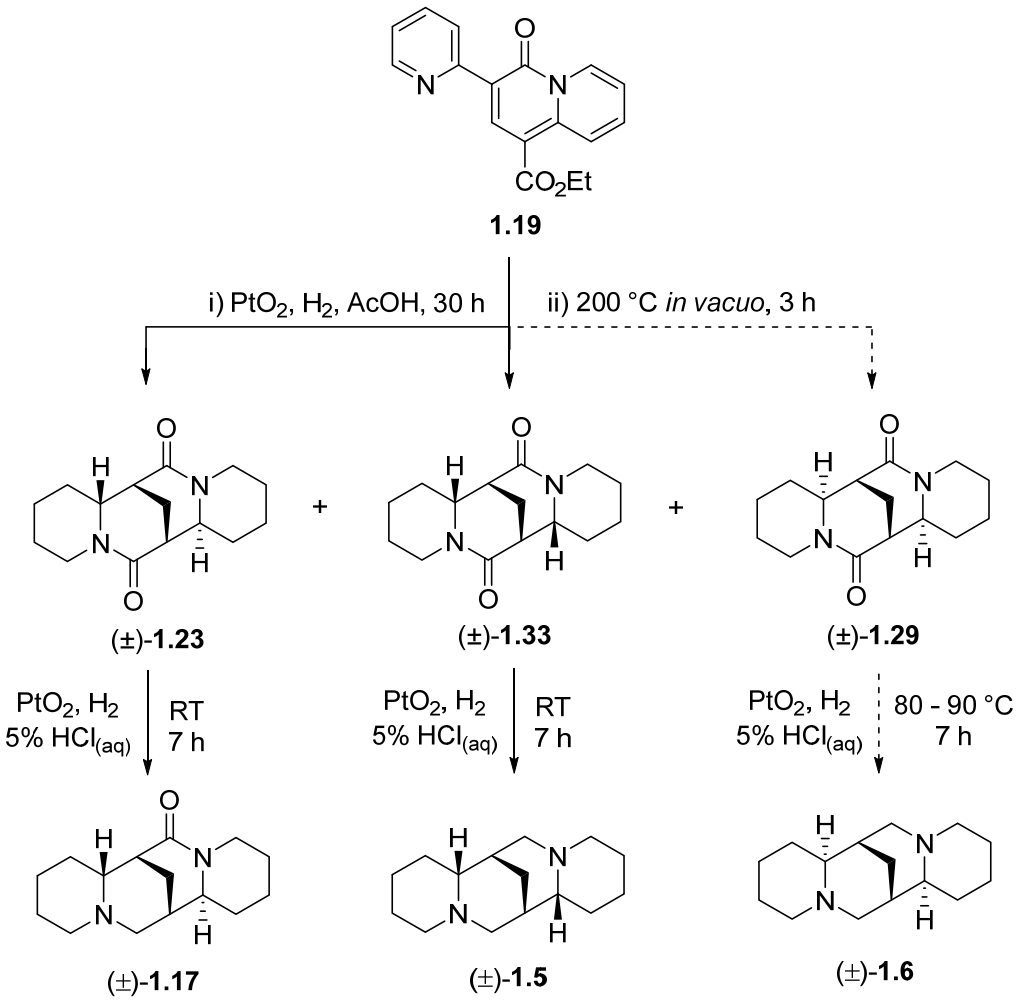
Whilst their initial communication implied that three products were isolated, the full publication discloses that two separate $C_{15}H_{26}N_2$ bases were isolated from the hydrogenation of **1.19** over copper chromite at elevated pressure and temperature, which were identified by Leonard as (±)-**1.3** and (±)-**1.5**, present in an approximate ratio of 5:1 respectively. This is the first time in the literature that (±)-**1.5** is unambiguously identified, given that the stereochemical structure of the sparteine isomers was unknown when Winterfeld coined "α-isosparteine". Data collected by Leonard was compared to the known literature, which confirmed the identify of their synthesised (±)-**1.5** as the racemate of that produced by Winterfeld. They also performed this hydrogenation with glutarate **1.32**, isolating again a mixture of (±)-**1.3** and (±)-**1.5**, this time in roughly equal amounts.

1.3.2 Attempts to amalgamate the syntheses

Quinolizidine **1.19**, and the methyl analogue, proved itself to be a key intermediate in the early total syntheses of the sparteine isomers. However, examination of the method that each used poses an interesting, if obvious question. Given the choice of reduction performed – that of hydrogenation – why would **1.19** not lead to all three possible sparteine diastereoisomers?

Two further experiments probed this question, the first published by Tsuda and Satoh in 1954.[92] Drawing on the methods developed by Galinovsky, Šorm and Kiel, they again reduced **1.19** using H_2 over PtO_2, and upon heating at 200 °C *in vacuo* obtained three separate products after chromatography, claimed to be the three dioxo-derivatives of the sparteine isomers, (±)-10,17-dioxosparteine ((±)-**1.23**), (±)-10,17-dioxo-*α*-isosparteine ((±)-**1.33**) and (±)-10,17-dioxo-*β*-isosparteine ((±)-**1.29**) (**Scheme 1.9**). Subsequent reduction of these three products would consequently lead to (±)-17-oxosparteine ((±)-**1.17**), (±)-*α*-isosparteine ((±)-**1.5**) and (±)-*β*-isosparteine ((±)-**1.6**).

However, while the data collected for (±)-**1.17** and (±)-**1.5** match other sources from the time,[72, 82, 85] the data collected for (±)-**1.6** and its precusror (±)-**1.29** are somewhat suspect. Whilst the elemental analyses of these two compounds are broadly in agreement, there was a distinct elevation in melting points of both species compared to other sources. The authors also noted that the third dioxo compound isolated required elevated temperatures for the catalytic hydrogenation to progress, which is at odds with their reported synthesis of (±)-**1.5**. It would be anticipated that both (±)-**1.33** and (±)-**1.29** would react similarly under catalytic hydrogenation conditions.



Scheme 1.9: Tsuda and Satoh's synthesis of (±)-**1.17** and (±)-**1.5**. Whilst the authors claim that (±)-**1.6** was also isolated, analytical data provided is dubious.

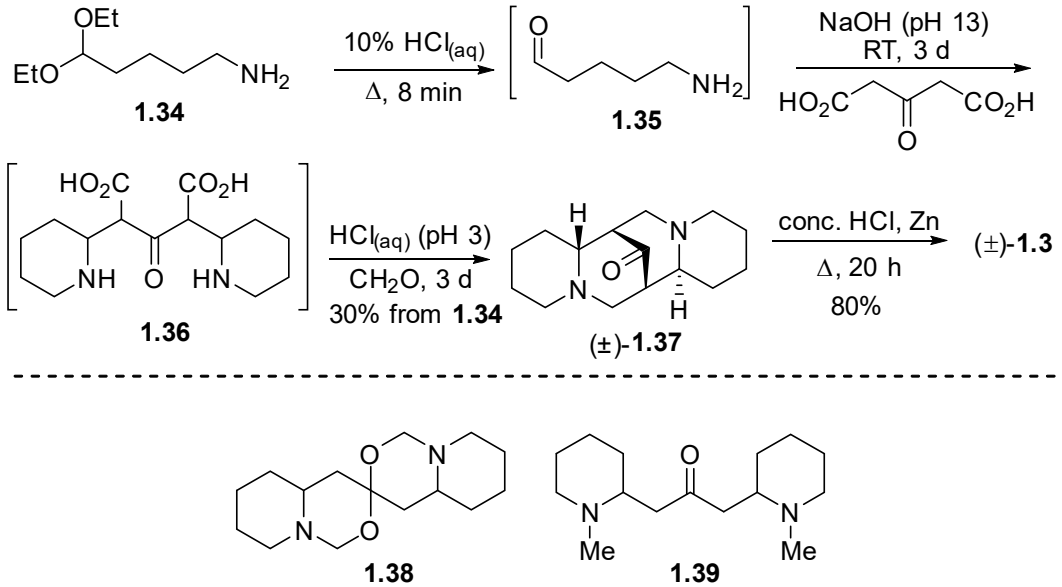
The second investigation was performed by Carmack in 1955.[73] This paper would unveil proof that (–)-*β*-isosparteine ((–)-**1.6**) was the final remaining diastereoisomer of the sparteine series, by showing that the natural product *l*-spartalupine was related to the sparteine isomers. Initial isolation of *l*-spartalupine from *Lupinus sericeus* was followed by repetition of the mercuric acetate oxidation protocol of Winterfeld and Rauch. Mild conditions again provided **1.15** and upon reduction (+)-**1.3**, whilst more drastic conditions furnished (+)-**1.5**, which confirmed the relation of (–)-**1.6** to the other isomers.

They would further repeat the synthesis of Šorm and Kiel, noting that three distinct dioxo species were isolated, which upon reduction by $LiAlH_4$, yielded the corresponding reduced diastereoisomer of the sparteine series, all of which display analytical data in agreement with contemporary sources – though it must be noted that the full experimental details, and comprehensive analyses of *all* products were not disclosed. However, this seems to support the earlier work carried out by Clemo, Galinovsky, Šorm and Kiel, Leonard and Tsuda and Satoh.

1.4 Towards stereoselective syntheses

With the structures of sparteine ((–)-**1.3**) and its diastereoisomers conclusively proven and armed with knowledge of relationships with other members of the lupin alkaloids, research shifted from structural determination towards total synthesis. Initial efforts followed closely the gradual elucidation of biosynthetic pathways and attempts to synthesise analogues of proposed biosynthetic intermediates. They would then seek to transform these compounds into the sparteine series themselves.

Whilst early work on the biosynthesis of the sparteine alkaloids by Robinson was inaccurate due to the erroneous use of the bis-quinuclidine structure **1.8**,[45] Anet extended some of these underlying ideas in a proposed total synthesis of (±)-**1.3**.[93-94] Amino aldehyde **1.35** (prepared *in situ* from acetal **1.34**) was condensed with 1,3-acetonedicarboxylic acid to form Robinson's putative biosynthetic dipiperidine intermediate **1.36** (**Scheme 1.10**). Acidification and reaction with formaldehyde gave a product that they identified as (±)-8-oxosparteine ((±)-**1.37**). Yields for these transformations were noted to be highly dependant on pH, with the highest overall yield of (±)-**1.37** reaching 30%. A final Clemmensen reduction would have afforded the target (±)-**1.3**.



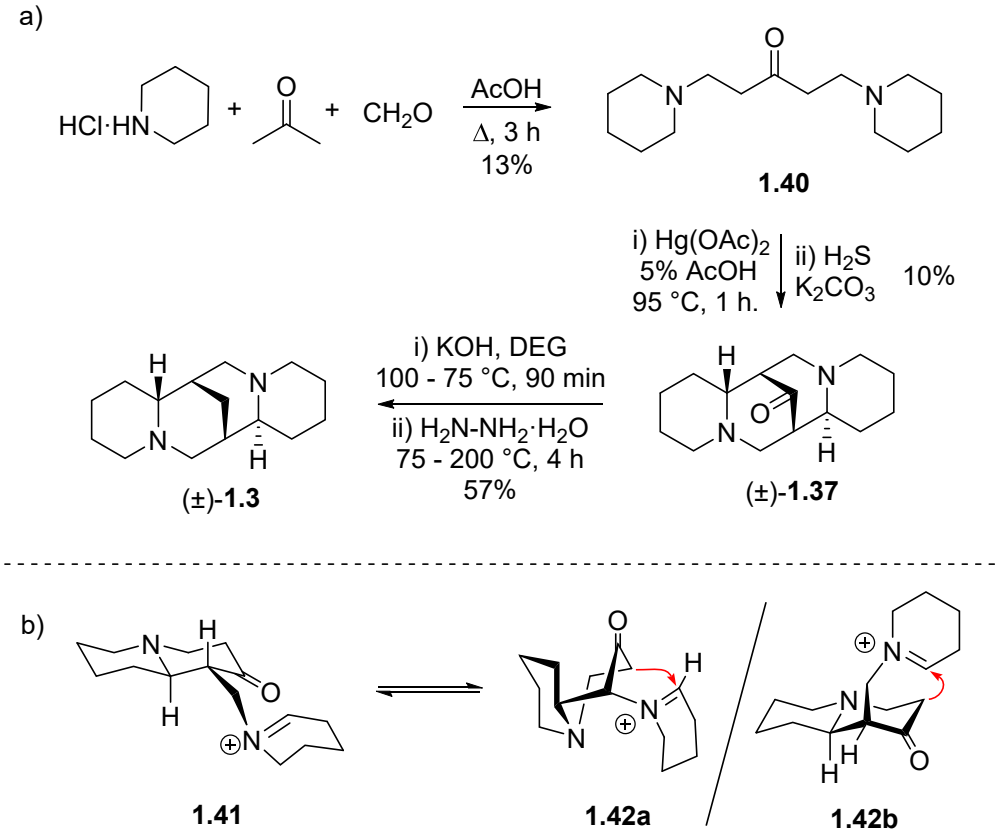
Scheme 1.10: Anet's proposed biomimetic synthesis of (±)-**1.3**. Below are the structures proposed by Rokohl and Schöpf to explain analytical irregularities in the proposed synthesis.

However, other researchers later questioned the constitution of Anet's products. Initially, Rokohl stated that a similar effort within his laboratory had already been attempted, and after reaction of 1,3-acetonedicarboxylic acid with Δ^1-piperidine at a pH of 11.5, a

spirane **1.38** was obtained.[95] Subsequently, in 1953, Schöpf reported that they were unable to observe the formation of a product with the structure of (±)-**1.37**, instead isolating **1.38** which upon Clemmensen reduction gave propanone **1.39**.[96] The physical data of these substrates would match strikingly with those reported by Anet for (±)-**1.37** and (±)-**1.3**, and the IR analysis of Anet's proposed (±)-**1.37** would also preclude the presence of a ketone. While Schöpf stops short of fully discrediting Anet's synthesis, the general agreement in the literature since is that this biomimetic synthesis did not produce the desired result.[46, 56, 58] Interestingly, spirane **1.38** was not synthetically wasteful: Schöpf would later report that (±)-**1.37** could be synthesised by the reaction of **1.38** with acetic anhydride,[97] experimental details of which would surface in 1972.[98]

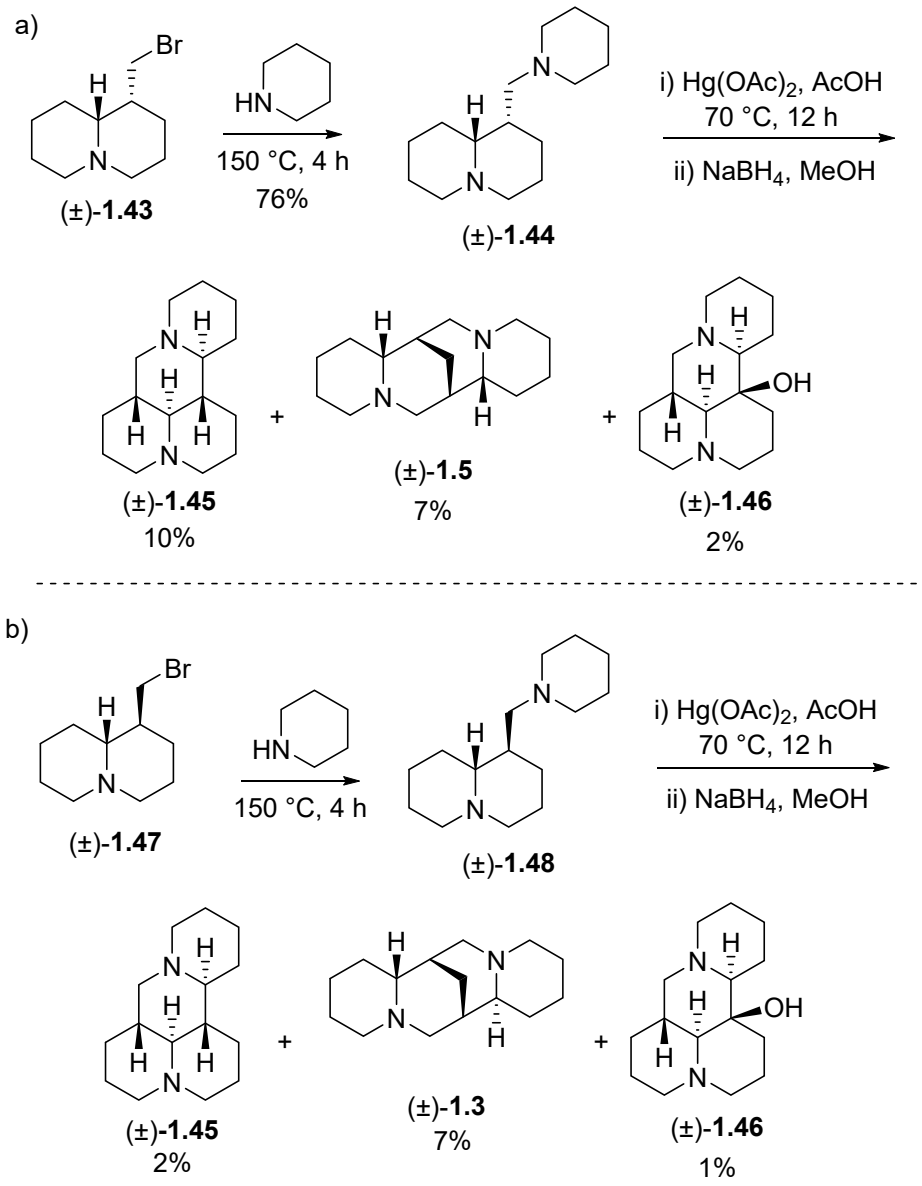
Based on a revised biosynthetic approach by Robinson,[46] van Tamelen reported a new synthesis of (±)-**1.3** in 1960,[99] with full experimental details disclosed in 1969.[100] The application of a double Mannich reaction of acetone, piperidine hydrochloride and formaldehyde gave ketone **1.40** in low yield (**Scheme 1.11a**). A second Mannich reaction of the free base was induced under oxidative conditions using mercuric acetate, leading to the isolation of (±)-**1.37**. Subsequent application of the Huang-Minlon modification of the Wolff-Kishner reduction afforded (±)-**1.3**. Comparison of the physical and spectroscopic data of the synthesised (±)-**1.3** to authentic samples established this successful biomimetic synthesis.

To account for the sole isolation of (±)-**1.37**, they proposed that the first cyclisation produced the thermodynamically more stable *trans*-quinolizidone derivative **1.41**, which could cyclise through a reactive conformation **1.42a** (**Scheme 1.11b**). However, if instead the higher energy *cis*-quinolizidine **1.42b** was obtained, this could directly cyclise instead. This proposed pathway is likely to be an oversimplification, due to the possibility for isomerisation of all intermediates under the reaction conditions by keto-enol tautomerism, and reversibility of the Mannich reactions. It should also be noted that the isolated yield of (±)-**1.37** is only 10%, and other, perhaps minor, stereoisomers may have simply been overlooked.



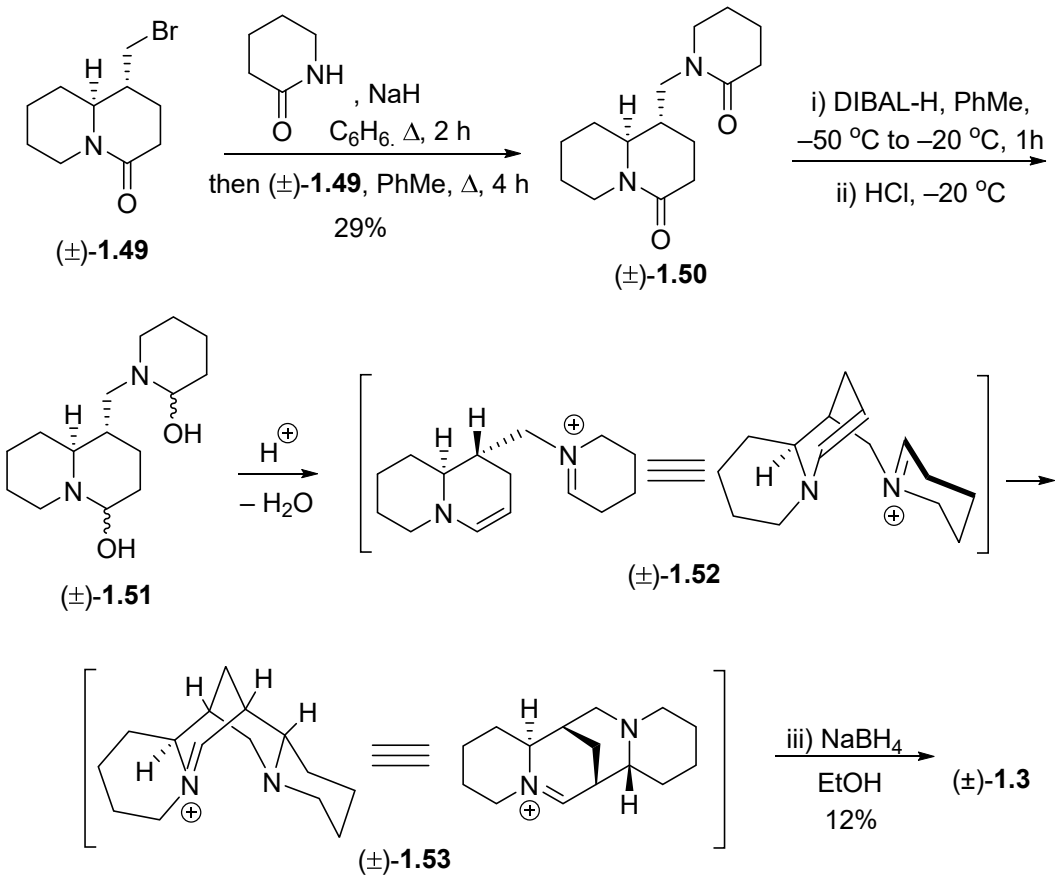
Scheme 1.11: a) van Tamelen's biomimetic synthesis of (±)-**1.3**.b) Proposed explanation to account for the formation of (±)-8-oxosparteine ((±)-**1.37**).

Bohlmann and co-workers also explored Mannich cyclisations in two further syntheses of the sparteine alkaloids, the first publication of which was in 1963, with a second following a decade later.[101-102] The initial communication detailed syntheses of (±)-**1.3** and (±)-**1.5**, alongside other related tetracyclic lupin alkaloids. Conversion of bromolupinine (±)-**1.43** to piperidinoquinolizinine (±)-**1.44** allowed an oxidation/reduction sequence to be enacted with mercuric acetate and sodium borohydride to obtain a mixture of (±)-allomatridine ((±)-**1.45**), (±)-**1.5** and (±)-5-hydroxy-allomatridine ((±)-**1.46**), isolated chromatographically in low yields (**Scheme 1.12a**). The analogous sequence performed on epi-bromolupinine ((±)-**1.47**) resulted in the isolation of (±)-**1.45**, (±)-**1.3** and (±)-**1.46**, again in low yield (**Scheme 1.12b**).



Scheme 1.12: Bohlmann's original syntheses of: a) (±)-**1.3**. b) (±)-**1.5**.

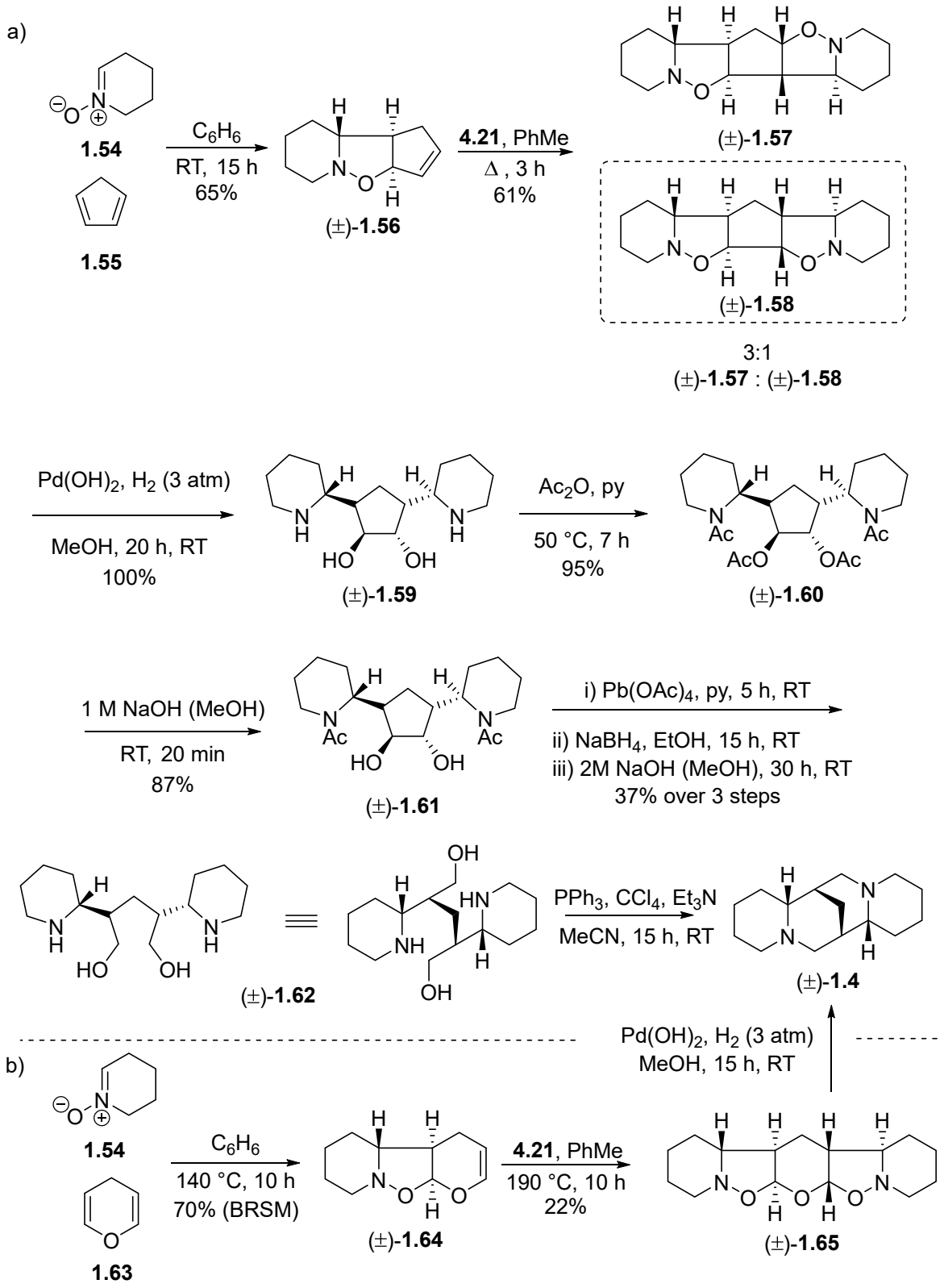
A further synthesis of (±)-**1.3** would follow, as part of an investigation into enamines generated from the reduction of lactams by DIBAL-H (**Scheme 1.13**). Deprotonation of *δ*-valerolactam and reaction with bromide (±)-**1.49** generated *bis*-lactam (±)-**1.50** in modest yield. The reduction of both lactams to the corresponding *bis*-hemiaminal (±)-**1.51** and ensuing acid treatment afforded an equilibrating mixture of enamine and imine intermediates. A productive intermediate (±)-**1.52**, where the enamine is present in the quinolizidine system can react with the piperidine iminium salt, generating iminium (±)-**1.53**. Reductive workup with $NaBH_4$ yielded (±)-**1.3** in 12% yield from bromide (±)-**1.49**.



Scheme 1.13: Bohlmann's synthesis of (±)-**1.3** *via* enamine / iminium cyclisation.

1.4.1 From nitrones to nature

Most of the reported routes towards the sparteine series have thus far centred on a similar method – non-selective approaches typically involving reductive cyclisation. Work by Kakisawa and co-workers would be the first major paradigm shift, with approaches reflecting newly established suites of chemical reactions and approaches tailored to stereoselective syntheses of specific sparteine structures.[103-104] Between two publications in 1983 and 1990, the authors disclosed two routes to (±)-*α*-isosparteine ((±)-**1.5**), based on the 1,3-cycloaddition of nitrone **1.54** (**Scheme 1.14**).



Scheme 1.14: a) Kakisawa's original route to (±)-**1.5** based on nitrone cycloaddition to cyclopentadiene **1.55**. b) Streamlined approach based on cycloaddition to 4*H*-pyran **1.63**.

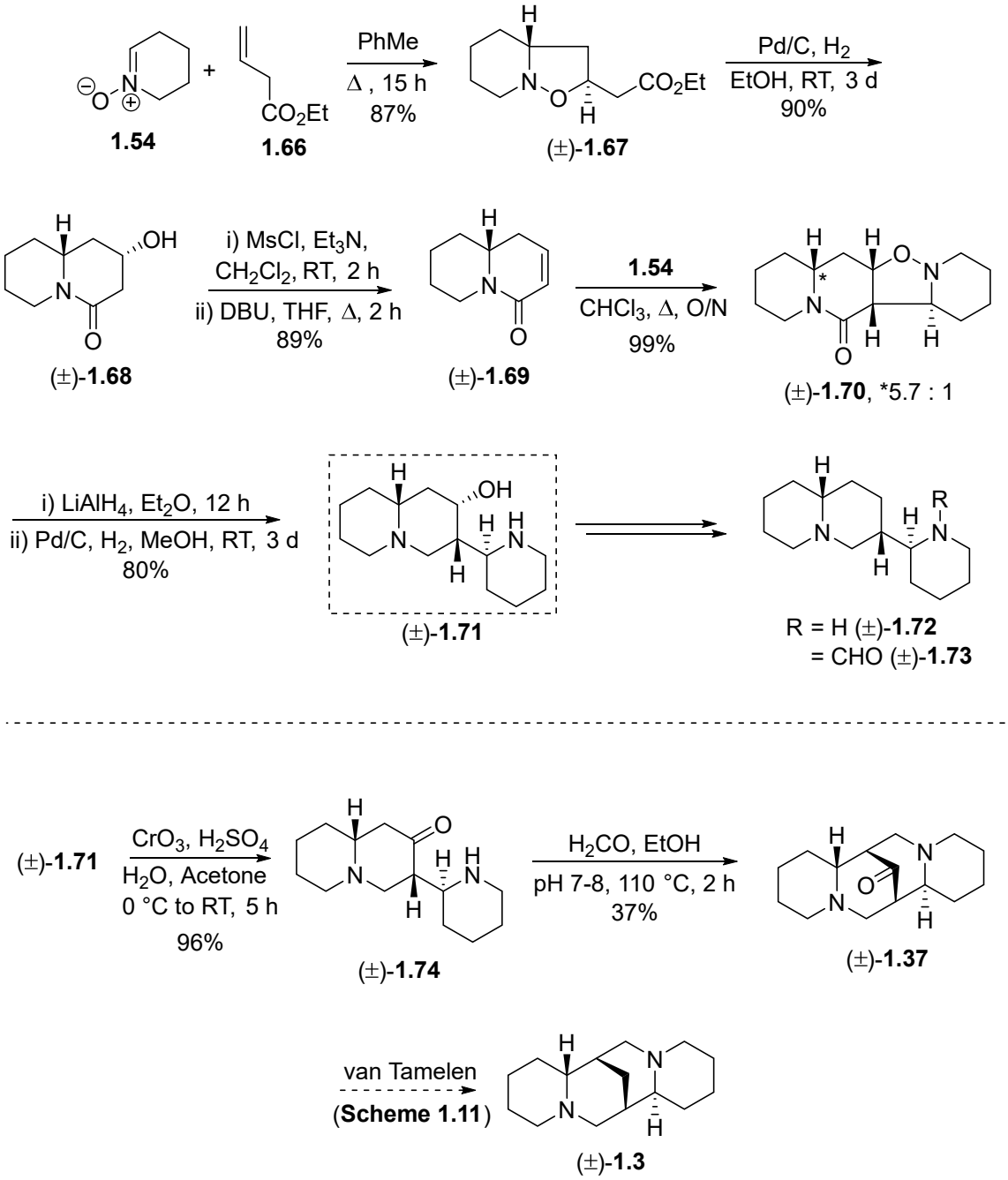
Their original synthesis began with the cycloaddition of nitrone **1.54** to cyclopentadiene **1.55** to form adduct (±)-**1.56** in good yield (**Scheme 1.14a**). By further reaction with **1.54**, a mixture of regioisomers was obtained in a 3:1 ratio of unwanted (±)-

1.57 and desired (±)-**1.58**. Performing a reductive cleavage of the N-O bonds of (±)-**1.58** using $Pd(OH)_2$ gave diol (±)-**1.59**, which was assigned as *trans* based on the lack of oxidation by periodate reagents. Cleavage of this diol necessitated diverting to (±)-**1.60** *via* global acetate protection, with selective unmasking of the diol to reveal (±)-**1.61**. The synthetic endgame could now be enacted, starting with $Pb(OAc)_4$ mediated cleavage of (±)-**1.61**, followed by reduction and deprotection steps to furnish diamino diol (±)-**1.62** in low yield. Finally, an Appel reaction yielded (±)-**1.5**, obtained *via* preparative TLC. No yield would be disclosed for this final step.

Wishing to improve upon this synthesis whilst keeping to the use of nitrone **1.54**, they instead performed a cycloaddition with diene **1.63** (**Scheme 1.14b**). This reaction proved to be capricious at best, with up to 70% of **1.63** recovered after the reaction and adduct (±)-**1.64** only isolated in modest yield. Nevertheless, further addition of **1.54** produced adduct (±)-**1.65**, which was converted to (±)-**1.5** upon reduction with $Pd(OH)_2$, which can be rationalised by reductive cleavage of the N-O bonds, cyclisation to a di-iminium species akin to (±)-**1.53**, followed by a final reductive step.

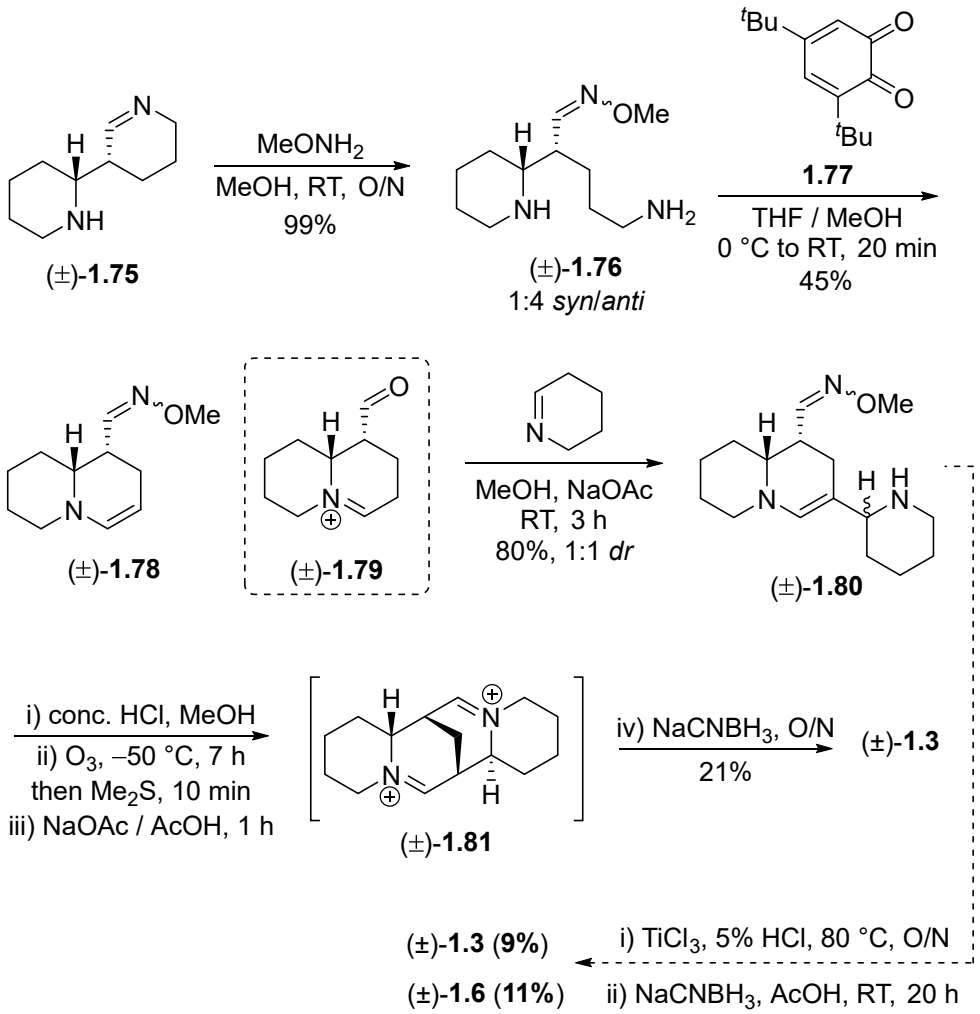
Continuing the theme of nitrone chemistry, Otomasu published a formal synthesis of (±)-**1.3** in 1987.[105] Starting from nitrone **1.54**, cyclisation onto alkene **1.66** provided *exo*-adduct (±)-**1.67**. Reductive cleavage of the N-O bond and subsequent cyclisation yielded hydroxy-quinolizidone (±)-**1.68**, which was converted into the enone (±)-**1.69** *via* mesylation and elimination. A second addition of **1.54** followed, with (±)-**1.70** formed in quantitative yield as a mixture of diastereoisomers. Lactam reduction and N-O bond fission provided the key quinolizidine (±)-**1.71**.

Originally, this key intermediate was used in the synthesis of (±)-leontiformidine ((±)-**1.72**) and (±)-leontiformine ((±)-**1.73**),[106] but the authors realised that this quinolizidine could also be converted to (±)-8-oxosparteine ((±)-**1.37**). Jones oxidation of the hydroxyl functionality provided ketone (±)-**1.74**. A final Mannich reaction afforded (±)-**1.37**, which could be further reduced under Wolff-Kishner conditions, as outlined by van Tamelen.



Scheme 1.15: Otomasu's formal synthesis of (±)-**1.3** *via* key quinolizidine derivative (±)-**1.71**.

At this point in time, several groups had elucidated possible routes for the biosynthesis of the sparteine isomers in nature. Schütte[50] and Schöpf[107] established the role of cadaverine, which was theorised to oxidise *in vivo* to Δ^1-piperidine, and then to tetrahydroanabasine (±)-**1.75**, which would eventually lead to the lupin alkaloids. This was further elaborated on by Spenser and co-workers, who disclosed their full proposal for the biosynthesis in 1988.[52] Koomen and Wanner would publish work in 1996 that would seek to prepare a synthetic analogue to one of the key intermediates in the proposed biosynthesis.



Scheme 1.16: Koomen and Wanner's synthesis of (±)-sparteine and (±)-*β*-isosparteine *via* preparation of a synthetic equivalent of the proposed biosynthetic intermediate (±)-**1.79**.

Tetrahydroanabasine (±)-**1.75**, which was prepared according to Schöpf,[107] was transformed into oxime (±)-**1.76** (**Scheme 1.16**). A mild oxidative deamination of the primary amine with *ortho*-quinone **1.77** [108] afforded bicycle (±)-**1.78**, which was the key synthetic equivalent of proposed biosynthetic intermediate (±)-**1.79**. With this key intermediate in hand, further reaction with Δ^1-piperidine gave amine (±)-**1.80**. Treatment with acid and subsequent ozonolysis would oxidatively cleaved the oxime, then reaction with NaOAc/AcOH effected an enamine/iminium tautomerization, allowing the aldehyde and piperidine moieties to adopt a *cis* configuration, enabling cyclisation to occur to 1,10:16,17-didehydrosparteinium ion (±)-**1.81**. A final reduction with $NaCNBH_3$ would provided (±)-**1.3** as the sole isolated product in low yield over the four steps from (±)-**1.80**.

Modification of the hydrolysis of (±)-**1.80** *via* $TiCl_3$/HCl at elevated temperatures was also attempted, and after cyanoborohydride reduction, both (±)-**1.3** and (±)-**1.6** were isolated in roughly equal amounts. Given that the relative stereochemistry of C6 and C7 had already been established, this observation can be rationalised using similar arguments

as before – isomerisation between reactive intermediates, with pathways leading to the *cis*-methylene bridge resulting in cyclisation to the tetracyclic structure.

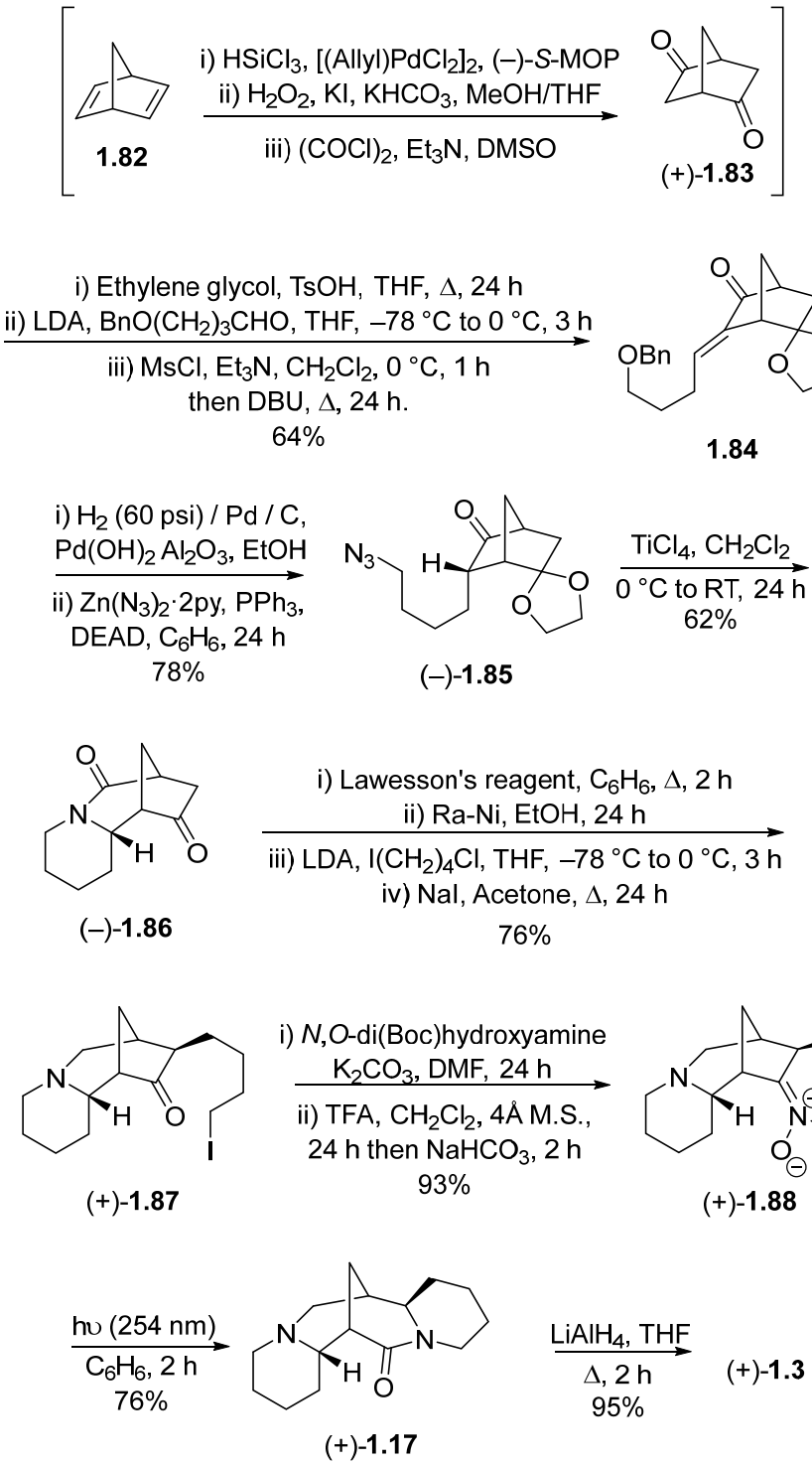
1.4.2 First asymmetric syntheses

The first asymmetric total synthesis of one of the optical antipodes of the sparteine series had to wait until well over 50 years had passed from the initial syntheses based on quinolizidone **1.19**. In 2002, Aubé and co-workers published the first total synthesis of (+)-**1.3**.[109] Based on their previous work using intramolecular Schmidt reactions,[110] a synthesis was envisioned using the coupling of two functionalised amine fragments onto a diketone scaffold, which itself was derived from 2,5-norbornadiene **1.82** (**Scheme 1.17**).

Armed with previously published preparations of (+)-**1.83**, [111-112] acetal protection of one of the ketones allowed the synthesis of mono-alkylated enone **1.84** *via* aldol condensation and elimination of the corresponding mesylate by DBU. Deprotection of the introduced alcohol followed by Mitsunobu azidation gave azide (–)-**1.85**, which in the presence of $TiCl_4$ underwent an intramolecular Schmidt reaction to afford quinolizidone (–)-**1.86**.

With this in hand, the installation of the final piperidine ring could be effected. Direct alkylation of (–)-**1.86** proved low yielding, so the alkylation was attempted on the quinolizidine derivative, accessed *via* Raney-Nickel reduction of a thio-lactam, prepared using Lawesson's reagent. Installation of a chloride chain proceeded well, yielding a single *exo* diastereoisomer, which was converted into iodide (+)-**1.87**. Whilst a second Schmidt reaction would fail to be realised, preparation of cyclic nitrone (+)-**1.88** enabled the use of a photo-Beckmann rearrangement to afford (+)-17-oxosparteine ((+)-**1.17**), and final $LiAlH_4$ reduction secured (+)-**1.3**.

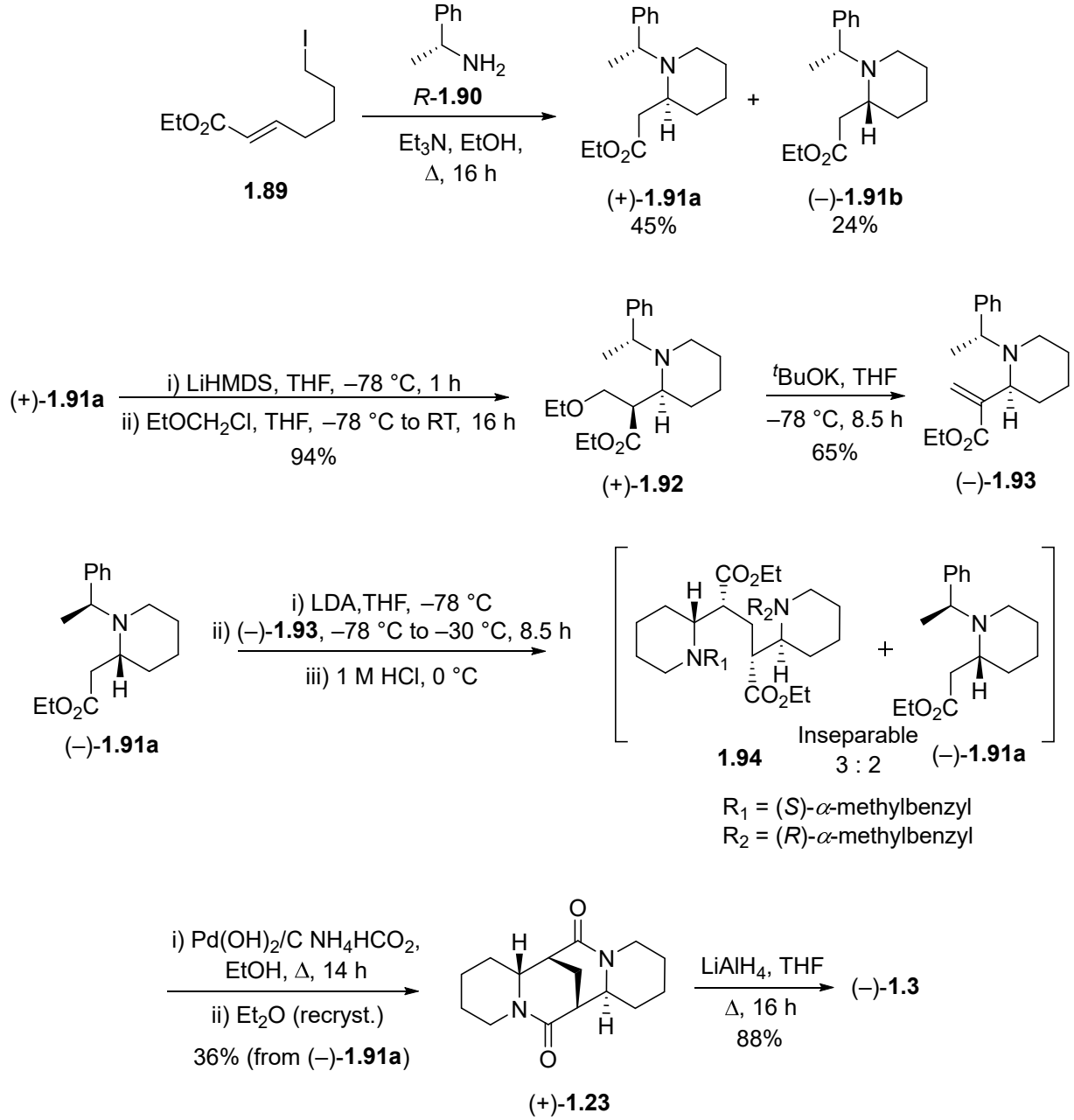
Following Aube's successful total synthesis, O'Brien and co-workers published the total synthesis of the laevorotary isomer in 2004.[113] By development of a stereoselective version of a previously published reaction by Bunce,[114] (*R*)-*α*-methylbenzylamine ((*R*)-**1.90**) was alkylated with iodide **1.89**,[115] which under the reaction conditions allowed an intramolecular conjugate addition to take place, forming *β*-amino esters (+)-**1.91a** and (–)-**1.91b** in a 2:1 ratio (**Scheme 1.18**). Allkylation of isolated (+)-**1.91a** with (chloromethoxy)ethane proceeded in excellent yield to give ester (+)-**1.92**, which was then converted into Michael acceptor (–)-**1.93** *via tert*-butoxide aided elimination. This set up the stereochemistry required at C11 and allowed for the future creation of the methylene bridgehead.



Scheme 1.17: Aube's total synthesis of (+)-**1.3**, starting from key diketone (+)-**1.83** and proceeding *via* intramolecular Schmidt reaction of azide (–)-**1.85**.

The elegance of this synthesis would emerge from the use of the enantiomer of the original *β*-amino ester, (–)-**1.91a**, as the nucleophile in the subsequent Michael addition. Prepared analogously to (+)-**1.91a**, this contained the stereochemistry required at C6, with the Michael addition proceeding to provide the required stereochemistry at the bridgehead. After workup, an inseparable mixture of the desired bicycle **1.94** and unreacted starting material would arise, in a ratio of approximately 3:2.

Extensive analysis of the NMR spectra of this mixture indicated that **1.94** was present as a single diastereoisomer. Transfer hydrogenation of this mixture using Pearlman's catalyst followed by subsequent recrystallisation from Et_2O gave (+)-10,17-dioxosparteine ((+)-**1.23**) in 36% from (–)-**1.91a**, with final $LiAlH_4$ reduction resulting in (–)-**1.3**. This would also serve to confirm the stereochemistry of **1.94** by extension.



Scheme 1.18: O'Brien's total synthesis of (–)-**1.3**, using the key reaction of Michael acceptor (–)-**1.93** in tandem with (–)-**1.91a** to effect the desired bridgehead stereochemistry.

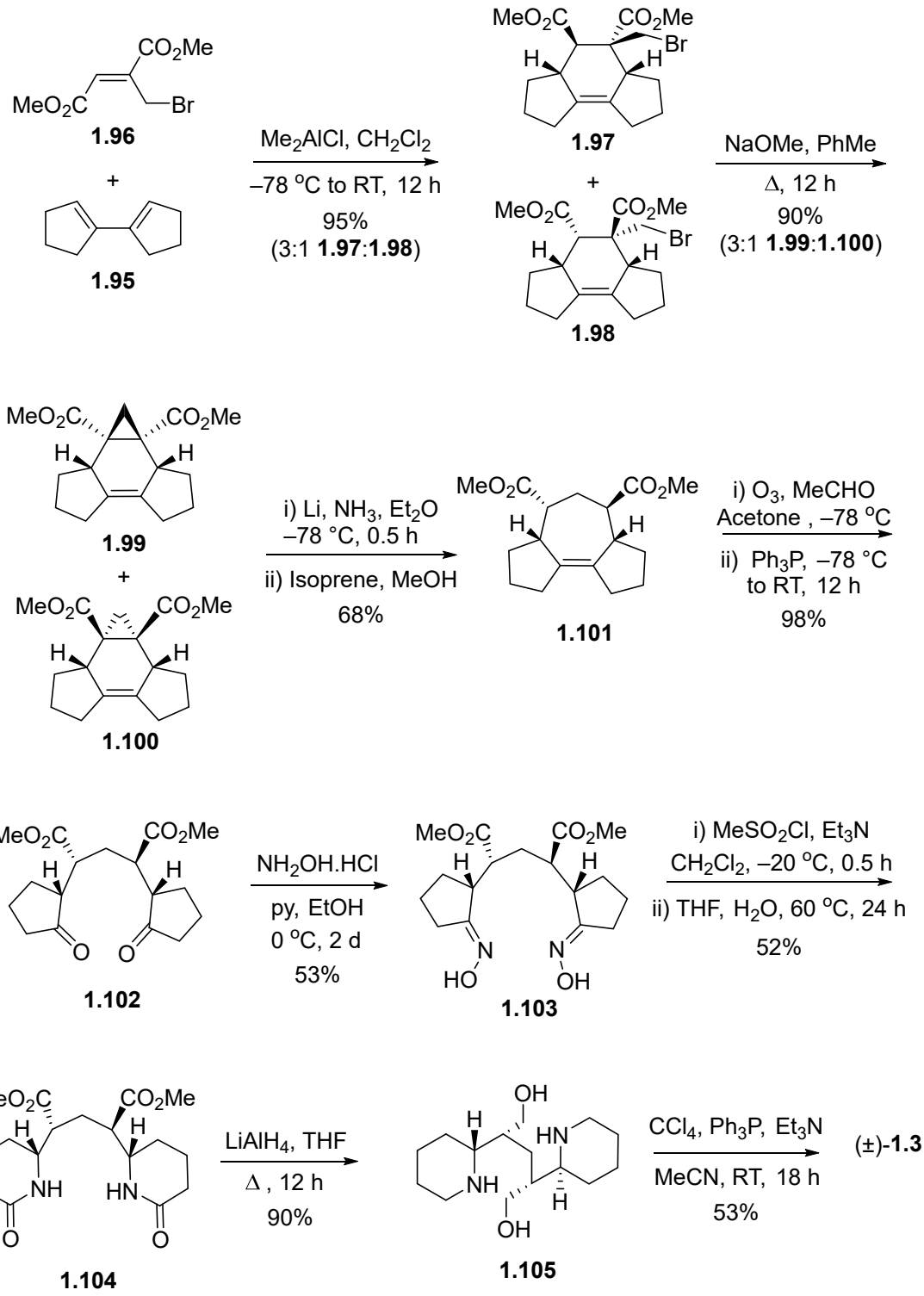
Published a mere two months after O'Brien's synthesis, Fleming and co-workers would put forward an initial synthesis of (±)-**1.3** in 2004,[116] and disclose the full methodology the next year.[117] This synthesis built upon previous disconnections of the C10-N and C17-

N bonds that were a feature of Leonard's and Kakisawa's syntheses, however in an attempt to do so in a more stereodefined manner (**Scheme 1.19**). A Diels-Alder cycloaddition was at the heart of the synthesis, however initial trials of several different coupling partners to diene **1.95** failed to realise useful products. Salvation came in the form of bromide **1.96**, which upon cycloaddition furnished a mixture of *endo*-cycloadducts **1.97** and **1.98** in a 3:1 ratio. Subsequent deprotonation and cyclisation yielded the *meso*-cyclopropanes **1.99** and **1.100**.

This mixture of *meso*-cyclopropanes converged into one product *via* a *bis*-enolate intermediate upon reaction with Li in NH_3, and subsequent reprotonation. Several different products of this reaction are possible, dependant on which face of the enolate is protonated, with the desired product being diester **1.101**. The addition of isoprene before any proton quench raised the yield of this step substantially. Two different proton quenches were used: NH_4Cl afforded **1.101** as the minor component of a mixture with the *meso*-diester, whilst MeOH provided **1.101** in a 3:1 ratio with the *meso*-diester, which was isolated in good yield. This provided the necessary relative stereochemistry for (±)-**1.3**.

Ozonolysis of the double bond also proved to be capricious, with the eventual solution utilizing acetone and acetaldehyde in the ozonolysis, trapping the intermediate ketone oxide as an ozonide. Subsequent workup with PPh_3 provided diketone **1.102** in near quantitative yield.

Compared to the first half of this synthesis, the last few steps proceeded in an uneventful manner. *Bis*-oxime **1.103** was used to effect a Beckmann rearrangement by heating the methanesulfonate salt to afford *bis*-lactam **1.104**. Reduction using $LiAlH_4$ unmasked piperidine-diol **1.105**, and using similar conditions to Kakisawa, a final Appel reaction gave (±)-**1.3**. The authors posit that this synthesis could be adapted into an asymmetric synthesis by the use of a chiral acid to effect the reprotonation of the *bis*-enolate towards **1.101**. Despite the availability of such reagents,[118] even at the time,[119] to the best of our knowledge no such approach has resulted in an asymmetric synthesis of any of the sparteine series.

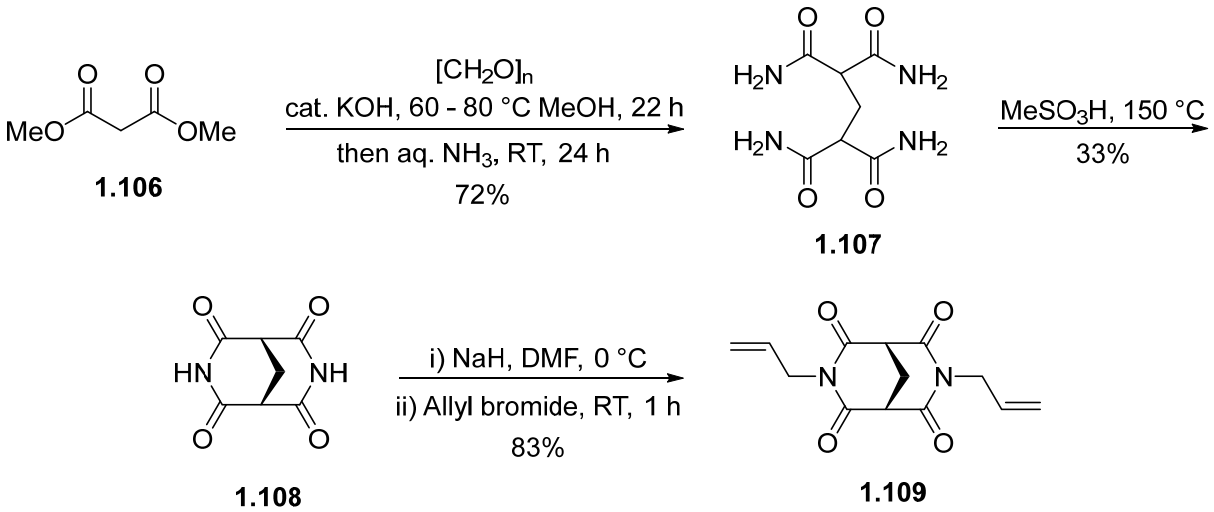


Scheme 1.19: Fleming's synthesis of (±)-**1.3** based upon cycloaddition of diene **1.95** and bromide **1.96**.

By 2008, reports of the total syntheses of (±)-**1.3**, (±)-**1.5** and (±)-**1.6**, were published by Blakemore and co-workers.[58, 88, 120] Two common themes united all three of these syntheses: they would all originate from a tetraoxobispidine core; and all would utilise an RCM approach to the target.

The synthesis of this key tetraoxobispidine core was not without incident, however. Bispidines substituted at the methylene bridge are widely known in the literature, and are commonly prepared by acidic hydrolysis of *α*,*α*'-dicyanoglutarimides, which are in turn synthesised *via* Guareschi condensation.[121] The preparation of the unsubstituted parent tetraoxobispidine would not be able to be effected using this strategy, as the reaction was prone to degradation.

Adaptation of a century-old procedure resolved the issue, starting from dimethyl malonate **1.106** (**Scheme 1.20**).[122] Transformation to tetraamide **1.107** allowed condensation by mixing with $MeSO_3H$, which provided **1.108** in modest, yet scalable yield – multigram amounts of this crystalline substance were able to be realised. Simple alkylation with NaH and allyl bromide affordrd key bispidine **1.109**. Over the three publications, the authors disclosed refinements to the yields of this synthesis: those reported in **Scheme 1.20** reflect the final, most optimised conditions.



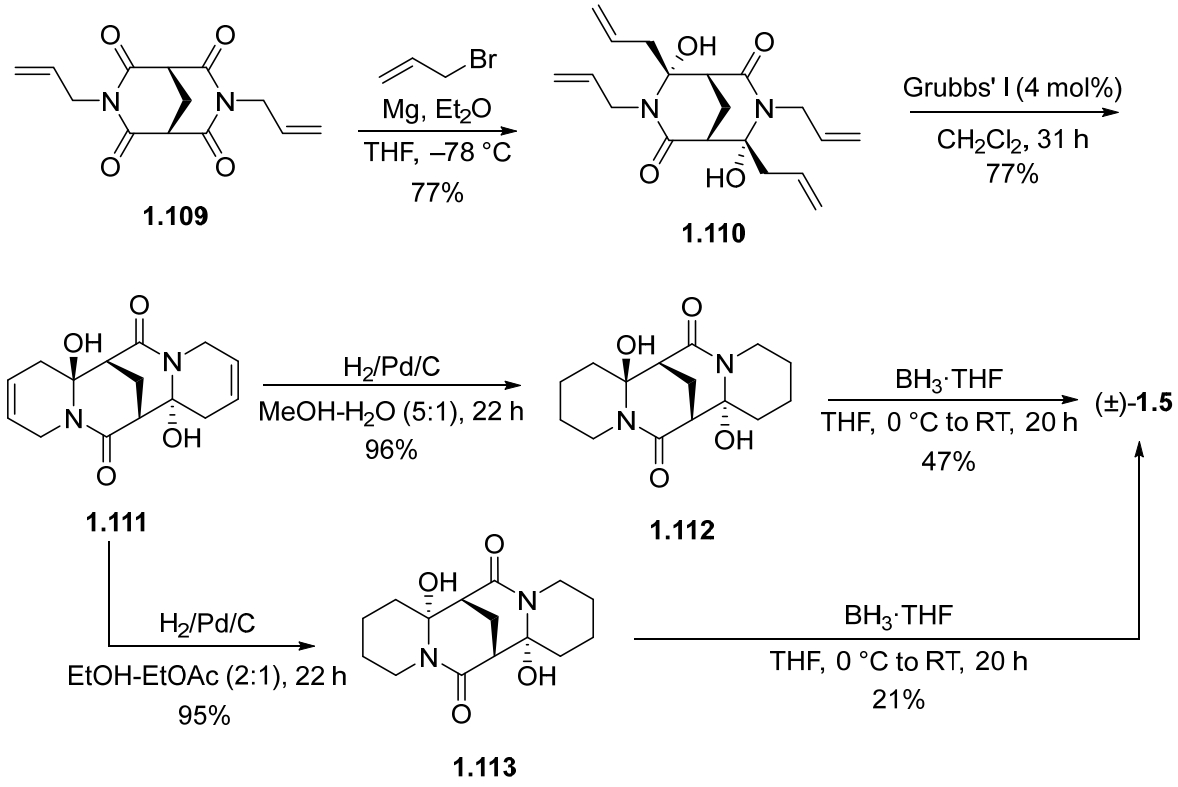
Scheme 1.20: Blakemore's synthesis of tetraoxobispidine **1.108**, and conversion to key bispidine **1.109**.

With the key bispidine **1.109** in hand, attention turned to the syntheses of the sparteine series. The most accessible initial target was (±)-*α*-isosparteine ((±)-**1.5**), which could be prepared in 4 steps from **1.109**, as disclosed in 2005 (**Scheme 1.21**). Grignard allylation of **1.109** generated bishemiaminal **1.110** as a single diastereoisomer after recrystallisation. Double RCM of this tetraene in the presence of Grubbs' I afforded the tetracyclic compound **1.111**, which was reduced first with H_2 over Pd/C to the saturated derivative **1.112**, then a final borane reduction to provide (±)-**1.4**.

The last few steps of this are of interest, as the hydrogenation step would - in differing solvents - provide different relative configurations of the alcohol groups. The more polar system of MeOH/H_2O afforded the non-symmetric bishemiaminal **1.112**, however reduction using a less polar mixture afforded the symmetric product **1.113**, with both

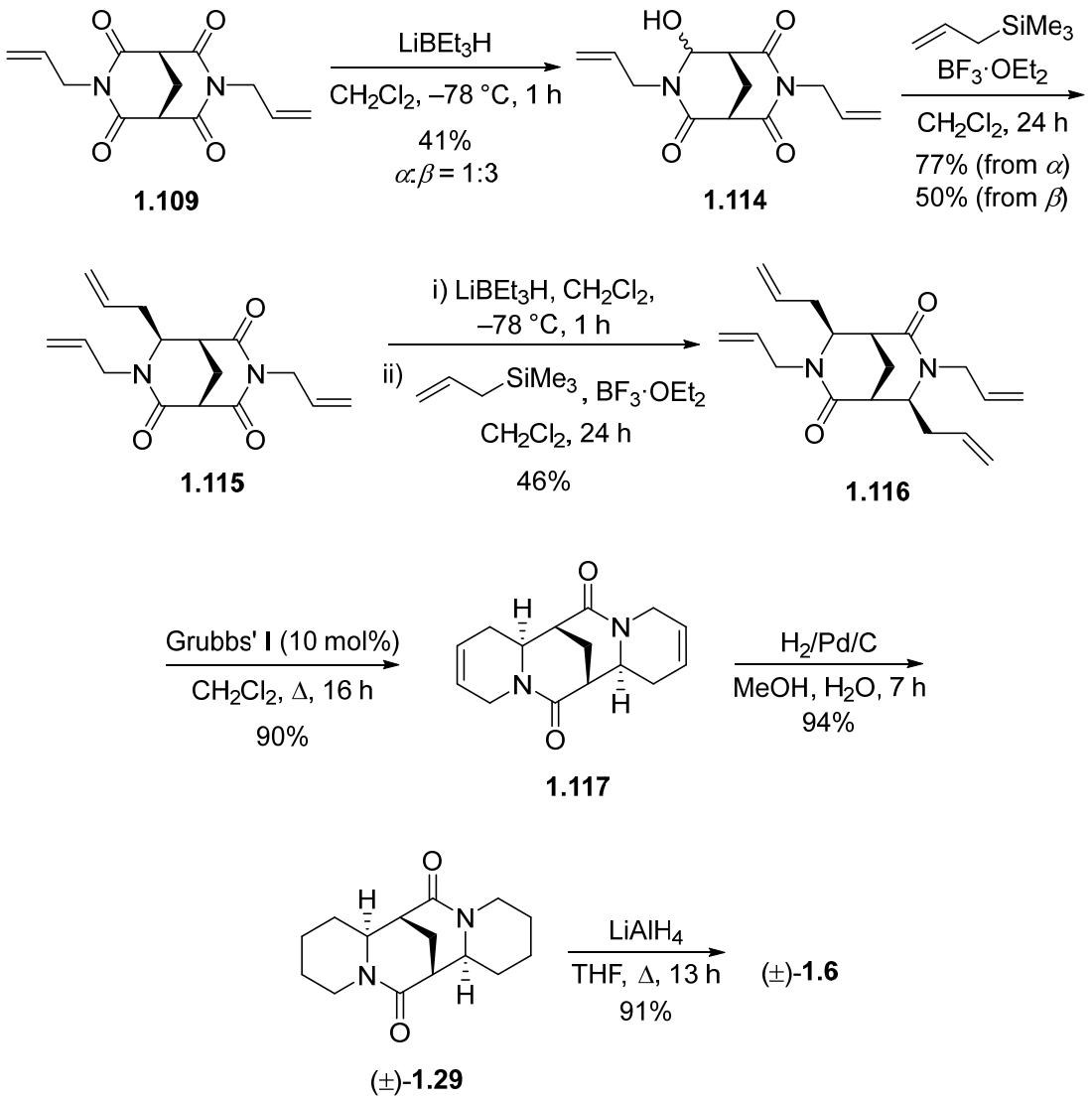
hydroxyls *trans* (*endo*) to the bridgehead. This is posited to occur *via* ring-opened amido keto tautomers.

The isolation of this symmetric product would entice the authors towards a dehydration towards (±)-10,17-dioxo-*α*-isosparteine ((±)-**1.33**), in a manner akin to the preparation of (–)-$\Delta^{5,11}$-didehydrosparteine (**1.16**). However, this approach would prove to be unsuccessful. The final borane reduction is thought to go *via* iminium intermediates, and hydride delivery would be expected to occur from the *exo* face.[123] The authors also attempted the borane reduction on **1.113**, however the yield from this step was less than half that obtained from **1.112**.



Scheme 1.21: Blakemore's total synthesis of (±)-**1.5**.

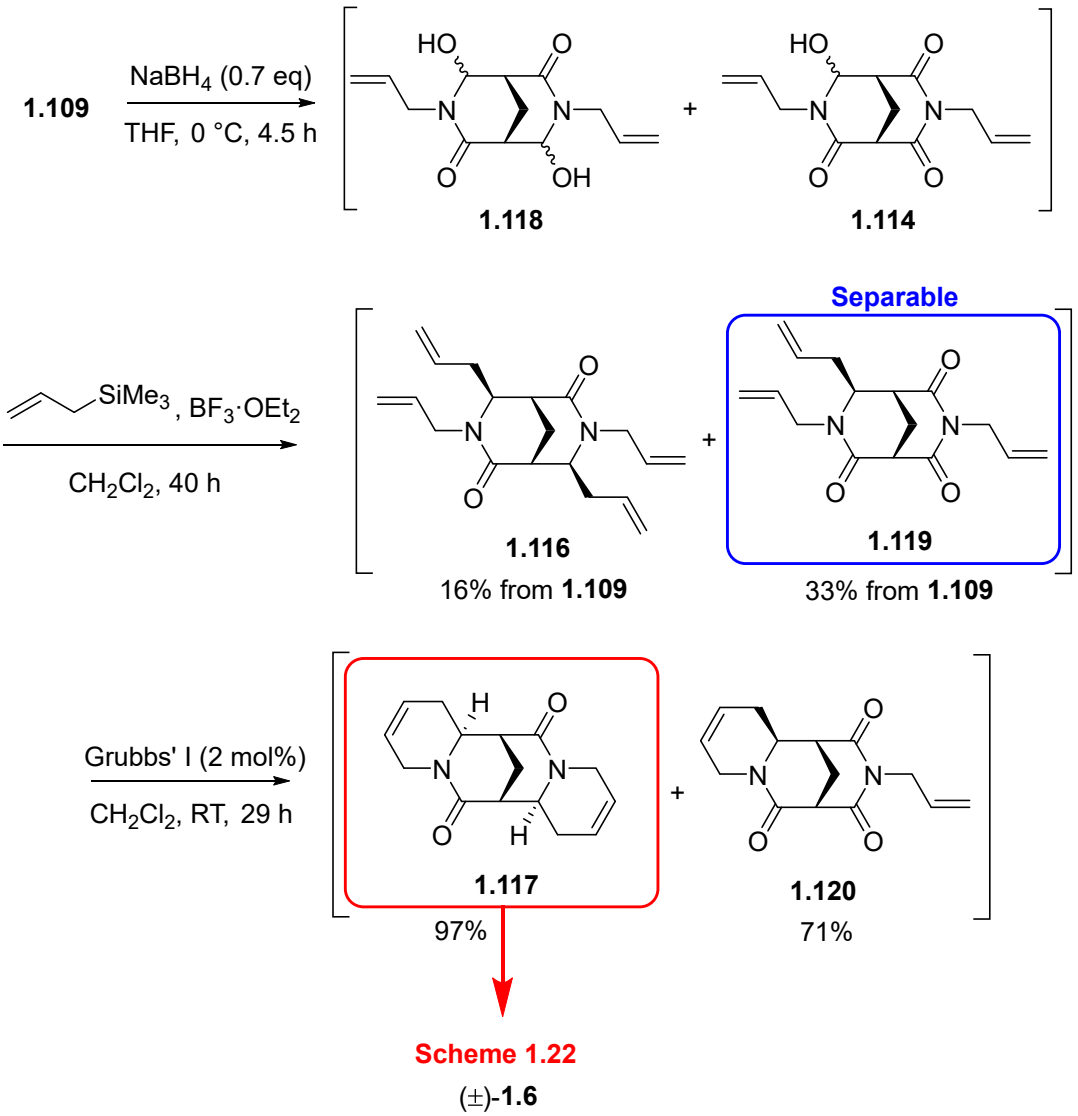
On the back of this successful synthesis, Blakemore then published the total synthesis of (±)-*β*-isosparteine ((±)-**1.6**) in 2006. Whilst the synthesis of (±)-**1.5** involved the allylation, RCM and reduction of derivatives of **1.109**, this route would call for a re-ordering of these steps. Mono-reduction of bispidine **1.109** resulted in hemiaminal **1.114**, isolated in modest yield as a mixture of anomers (**Scheme 1.22**). Subjecting this to a Sakurai allylation gave triene **1.115**, which was then converted to tetraene **1.116**, using the same stepwise reduction and allylation. RCM secured the tetracyclic compound **1.117**, which was reduced to afford (±)-10,17-dioxo-*β*-sparteine ((±)-**1.29**), which would be subjected to the now familiar $LiAlH_4$ reduction to provide (±)-*β*-isosparteine ((±)-**1.6**).



1.109 **1.114** **1.115** **1.116** **1.117** (±)-**1.29**

Scheme 1.22: Blakemore's first-generation total synthesis of (±)-*β*-isosparteine ((±)-**1.6**).

With two of the trio synthesised, the final publication in 2008 served to bring together the wealth of knowledge gained over the past few years into an improvement of the synthesis of (±)-**1.6**, and also the total synthesis of (±)-**1.3**. The previously disclosed route (**Scheme 1.22**) was hindered by the use of a stepwise process to obtain tetraene **1.116**, which could only be brought through in fairly modest yield from **1.109**. The discovery that the mono-reduction step could be bypassed by the use of $NaBH_4$ to effect a double reduction would allow a more streamlined synthesis to take place (**Scheme 1.23**).

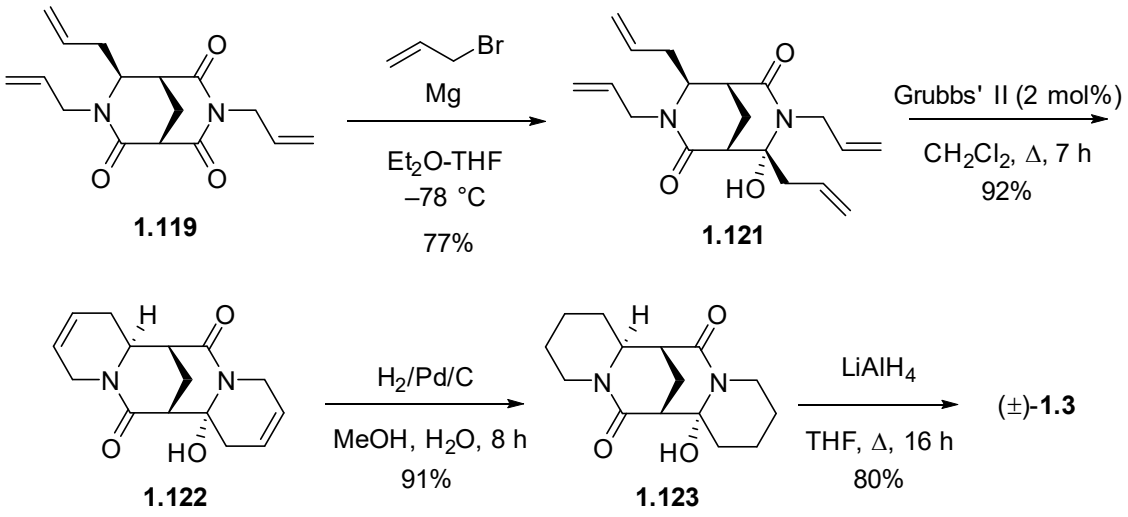


Scheme 1.23: Blakemore's second-generation synthesis of (±)-**1.6**.

Thus, **1.109** was subjected to $NaBH_4$, which would result in a mixture of mono- and doubly-reduced bispidines **1.118** and **1.114**. Sakurai allylation of this mixture would result in the corresponding triene **1.116** and tetraene **1.119**. Whilst the triene was able to be successfully purified and isolated, the tetraene was unable to be fully purified. As such, the subsequent RCM step was carried out on a mixture of **1.116** and **1.119**, which would afford both tricycle **1.117** and **1.120**, fully separable by chromatographically at this point. **1.117** would provide an intersection with the previous route (**Scheme 1.22**). This would have the effect of raising the overall yield of (±)-**1.5** from 11% to 13%.

Whilst, in isolation, this only reflects a modest increase in the yield of (±)-**1.5**, the prime benefit of this synthesis is that one of the intermediates, triene **1.109**, is also the key compound in a synthesis of (±)-**1.3** (**Scheme 1.24**). Whilst **1.116** was never fully separated from the crude products, pure **1.119** was alkylated with allylmagnesium bromide to afford tetraene **1.121** in good yield, which now contained all of the required stereochemical elements to progress. RCM to the dioxo derivative **1.122**, followed by hydrogenation gave

(±)-10,17-dioxo-6-hydroxy-*β*-isosparteine (±)-**1.123**. $LiAlH_4$ reduction obtained (±)-**1.3** and the first syntheses of all of the sparteine isomers from a single laboratory in over 50 years.

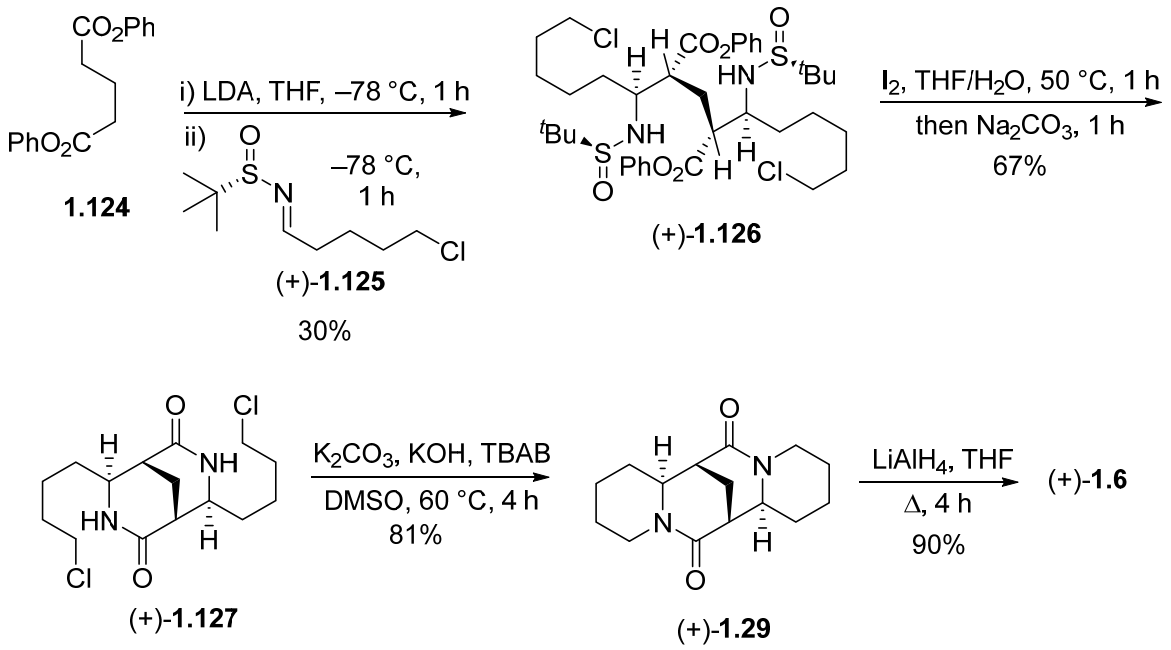


Scheme 1.24: Blakemore's total synthesis of (±)-**1.3** from triene intermediate **1.119**.

1.5 Recent endeavours

Despite the continued interest in the use of (–)-**1.3** in synthetic procedures, and even throughout the absence of commercial sources starting in 2010, it would be 8 more years before any further total syntheses of the sparteine isomers would be reported.

In 2017, Brown would report the total synthesis of (+)-*β*-isosparteine (+)-**1.6**, marking the first asymmetric total synthesis of a single antipode of either isosparteine.[124] Previous work on the synthesis of other members of the lupin alkaloids had divulged that the *syn*-relationship of many of these were conveniently accessed by the use of *tert*-butane *N*-sulfinyl auxiliaries (**See Chapter 2**).[11-12] The use of these chiral auxiliaries allowed a highly diastereoselective imino-aldol reaction to take place, in good yields and high selectivities This idea was extended to the tetracyclic skeleton of (+)-**1.6**, which possesses two such *syn*-relationships. It was envisaged that a double-imino aldol protocol could be enacted, preparing both *syn*-linkages in one step. By careful tailoring of the imine fragments, a short synthesis of (+)-**1.6** would be possible.



Scheme 1.25: Brown's total synthesis of (+)-**1.6** using *N*-sulfinylimine (+)-**1.125** to effect a double imino-aldol reaction.

With this strategy in mind, double deprotonation of diphenyl glutarate **1.124** and subsequent treatment with *N*-sulfinylimine (+)-**1.125** afforded diastereomerically pure double imino-aldol adduct (+)-**1.126** in acceptable yield (**Scheme 1.25**). Several by-products from the reaction were isolated, dominated by a cyclised single *syn*-imino aldol product. Nevertheless, the complete acyclic carbon skeleton, along with the required stereochemical complexity, had been set with a single reaction, which balanced the modest yield of the reaction. I_2 promoted cleavage of the *tert*-butanesulfinyl groups provided bispidine (+)-**1.127**, which was cyclised under basic conditions onto the strategically placed chloroalkyl chains installed in the imino-aldol reaction to yield (+)-**1.29**, which was reduced with $LiAlH_4$ to (+)-*β*-isosparteine ((+)-**1.6**).

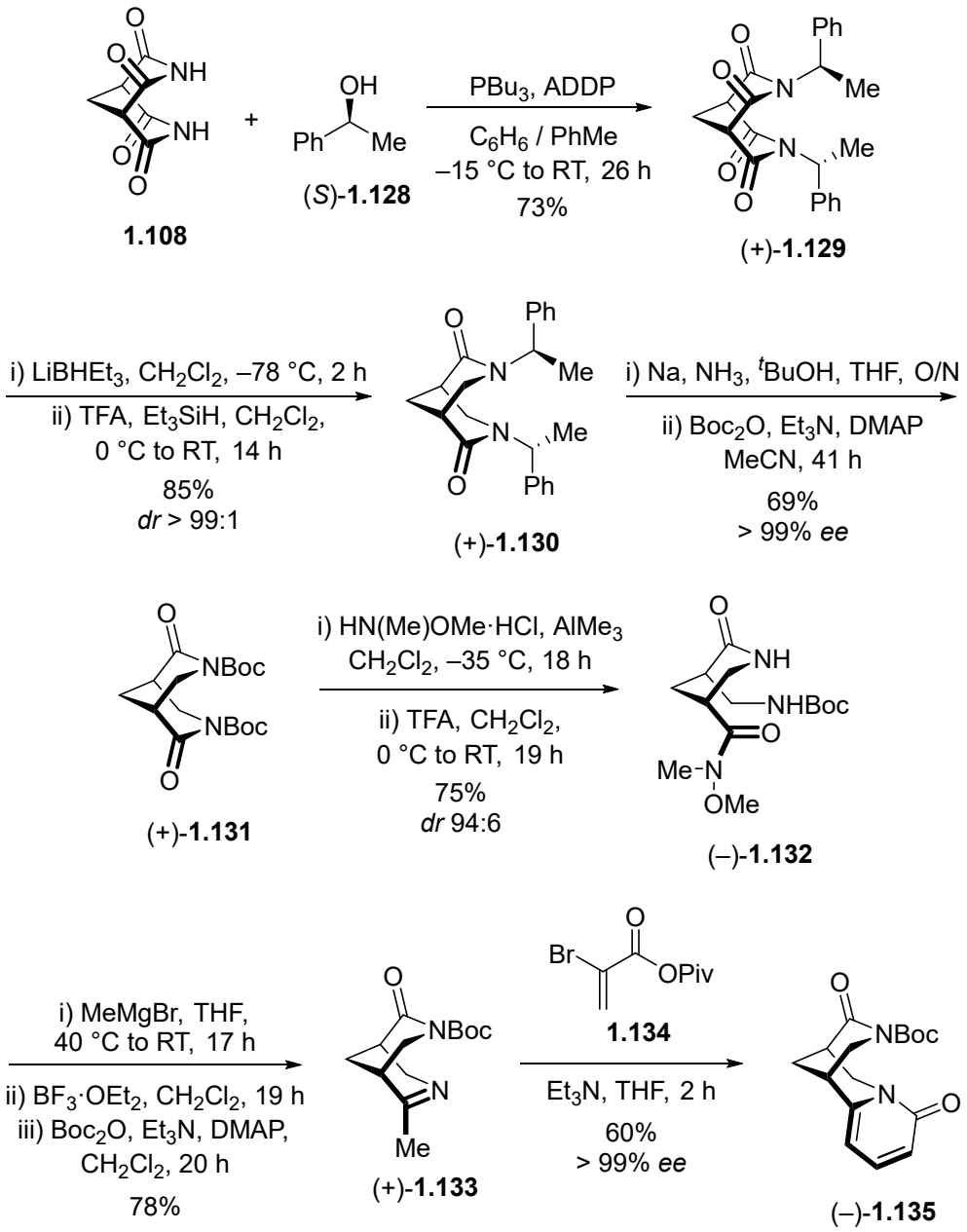
Early in 2018, Breuning and co-workers disclosed their approaches to several bisquinolizidine alkaloids, publishing the asymmetric syntheses of 21 natural products in total.[125] This tour-de-force attempted to fill a gap that had previously been left open: many of the asymmetric syntheses described thus far were specifically designed with one product in mind, and would build the tetracyclic cores of the sparteine isomers from the "outside-in" – constructing the peripheries of the molecule using selective reactions, and then building inwards.

Recognising that the bispidine **1.108** used by Blakemore (**Scheme 1.20**) was an excellent start to an "inside out" route towards the core of the lupin alkaloids, Breuning attempted to directly desymmetrize this core, building on unsuccessful attempts by Blakemore to carry this out on the di-benzyl and di-allyl derivatives of **1.108** previously.[58]

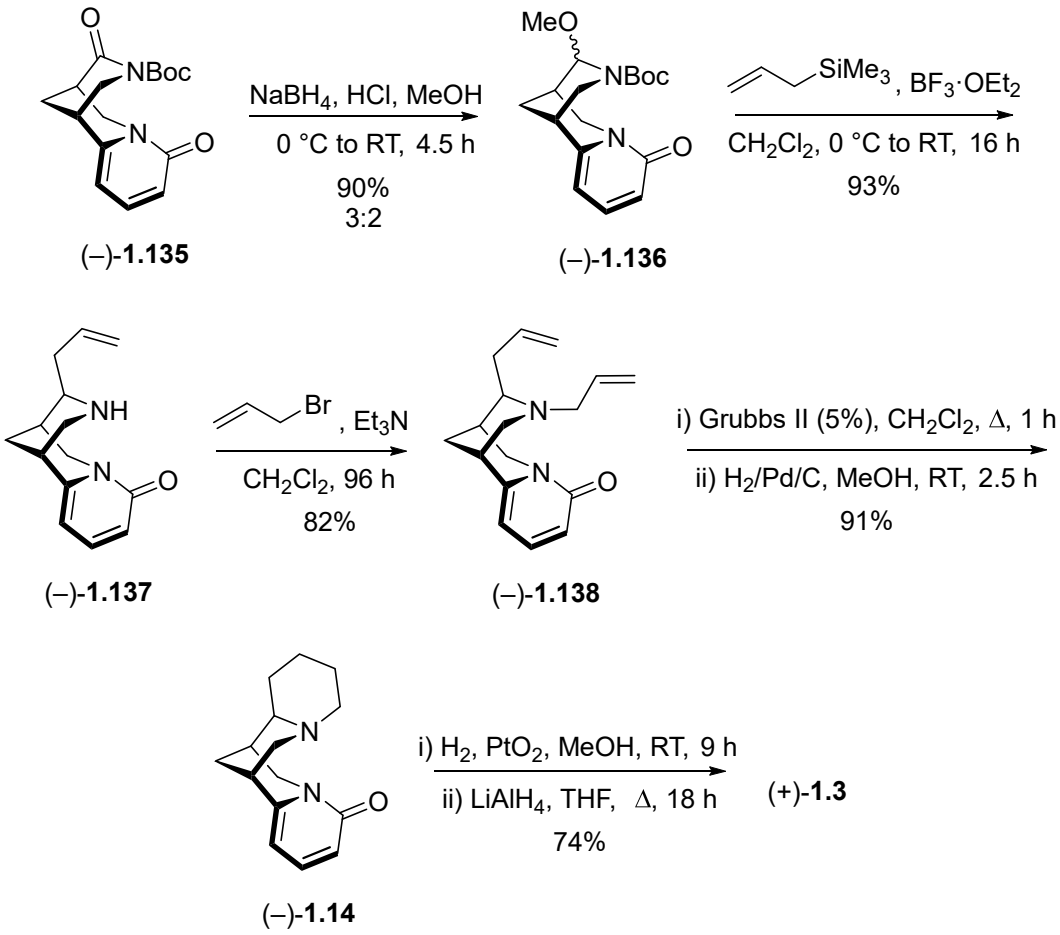
With careful manipulation, this would allow the preparation of a key late-stage tricyclic intermediate that could be further functionalised to afford the desired alkaloids. The authors would use Blakemore's originally reported synthesis of **1.108**, which would presumably suffer the same modest yields but high throughput as in the original case.[120]

The first task was to deoxygenate one pair of enantiotopic carbonyls from achiral bispidine **1.108** (**Scheme 1.26**). Reaction with (*S*)-phenylethanol ((*S*)-**1.128**) would provide diimide (+)-**1.129**, and Super-Hydride® reduction followed by treatment with TFA provided diamide (+)-**1.130** with excellent regio- and stereo-control. Birch reduction of the chiral auxiliary and subsequent Boc protection furnished the successfully desymmetrized bispidine (+)-**1.131**. Selective modification of one of the imide groups by Lewis acid-catalysed ring opening with *N*,*O*-dimethylhydroxylamine, followed by Boc deprotection of the resultant imide gave Weinreb amide (–)-**1.132**, with a slight loss in diastereoselectivity, presumably by epimerisation at the bridgehead positions (the authors noted the crucial temperature dependence of this reaction). Nucleophillic alkylation of the Weinreb amide and subsequent recyclization of the pendant amine *via* Boc deprotection, yielded cyclic imine (+)-**1.133** after reprotection. A final Michael addition to anhydride **1.134** (prepared *in situ* from pivaloyl chloride and 2-bromoacrylic acid), and elimination of HBr provided the key tricyclic bispidine (–)-**1.135**, the enantiomer of which was also readily prepared from **1.108** and (*R*)-**1.128**.

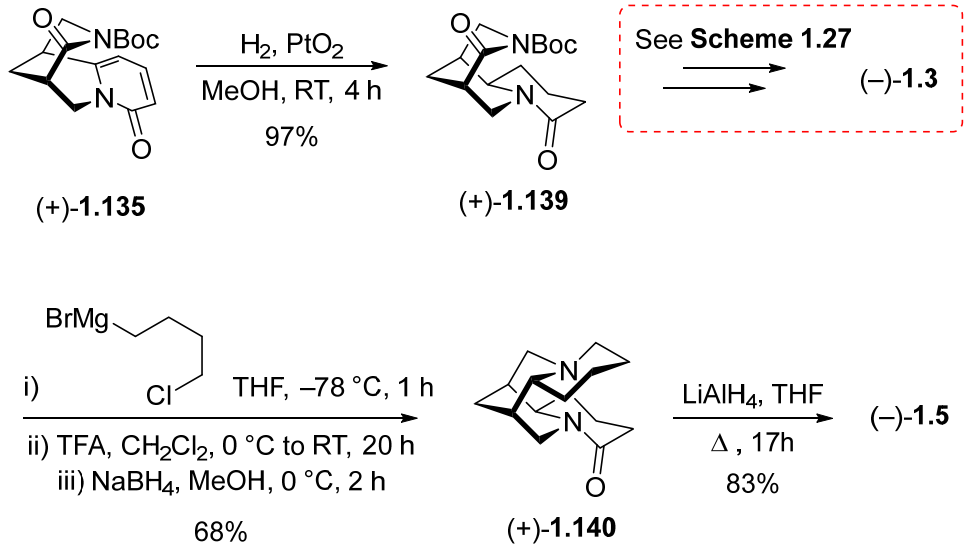
With both antipodes of key bispidine in hand, attention now turned to modification of the core to access the target alkaloids. (+)-**1.3** could be easily obtained, due to the prevalence of *exo* attack onto bispidine imines or iminium ions.[126-127] Thus, reduction of the imide functionality of (–)-**1.135** using $NaBH_4$ afforded *N*,*O*-acetal (–)-**1.136**, which was subjected to an *exo*-selective Sakurai allylation and simultaneous Boc deprotection to obtain alkene (–)-**1.137** (**Scheme 1.27**). The free amine was itself allylated to provide diene (–)-**1.138**, which after RCM and reduction afforded (–)-anagyrine ((–)-**1.14**), which was subsequently reduced to (+)-**1.3**.



Scheme 1.26: Breuning's desymmetrization of bispidine **1.108**, and subsequent preparation of key late-stage intermediate (–)-**1.135**. (The use of (*R*)-**1.128** would provide (+)-**1.135**)



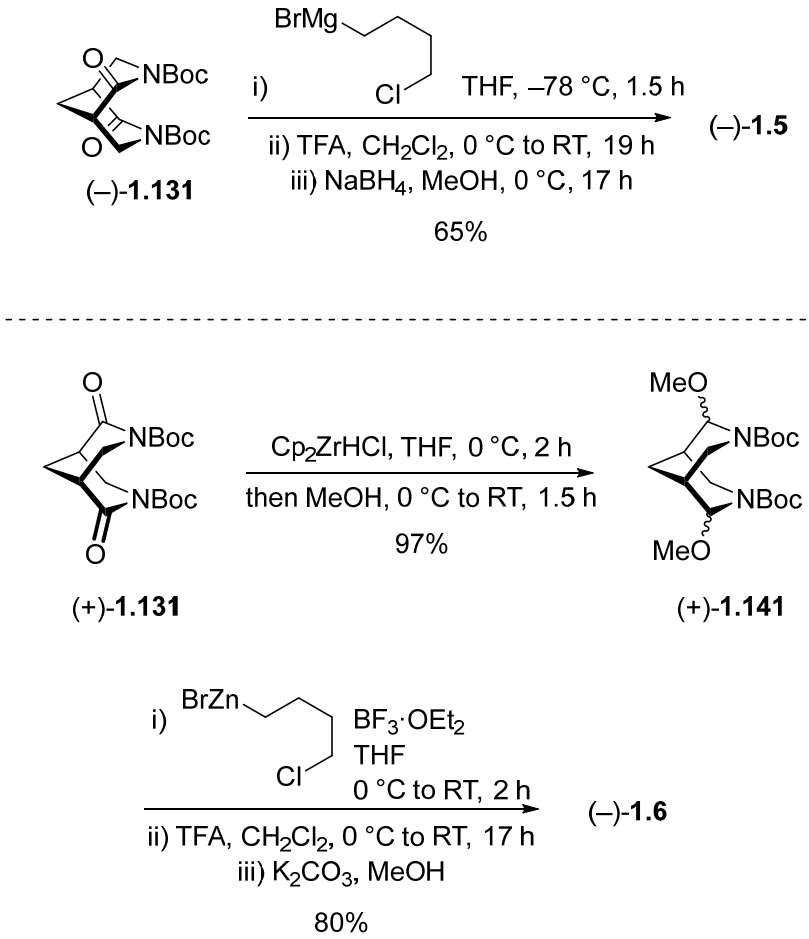
Scheme 1.27: Breuning's total synthesis of (+)-**1.3** from tricyclic bispidine (–)-**1.135**, *via* (–)-anagyrine ((–)-**1.14**).



Scheme 1.28: Use of (+)-**1.135** for the total syntheses of (–)-**1.3** by adaptation of the previously used *exo*-functionalisation, and of (–)-**1.5** by *endo*-annulation.

The corollary of *exo*-selective nucelophillic addition following a reductive step is that *endo*-selectivity can occur from addition followed by reduction. With this in mind, reduction of (+)-**1.135** would obtain piperidone (+)-**1.139**, which would be reacted with 4-

chlorobutylmagnesium bromide, followed by *N*-deprotection and reductive amination to provide the *endo*-annulated product (+)-isolupanine ((+)-**1.140**). Reduction of this would provide (–)-*α*-isosparteine ((–)-**1.5**) (**Scheme 1.28**). This route would also provide easy access to (–)-sparteine ((–)-**1.3**) by the application of the Sakurai allylation steps exemplified in **Scheme 1.27** to piperidone (+)-**1.139,** which would occur in *endo* fashion.



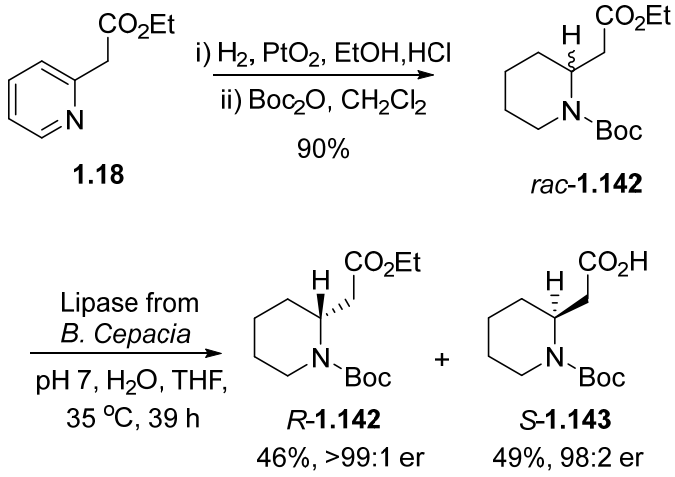
Scheme 1.29: Total syntheses of (–)-**1.5** and (–)-**1.6** following the *exo*/*endo* annulation strategy from both antipodes of bispidine **1.135**.

The ability to manipulate the *endo*/*exo* additions to this scaffold was also applied to the bispidine precursors (+)- and (–)-**1.135** (**Scheme 1.29**). Double alkylation of (–)-**1.131** followed by *N*-deprotection and reductive cyclisation as before offered a short route to (–)-**1.5**, whereas the double reduction of the imides to *N*,*O*-acetal (+)-**1.141** was effected by the use of Schwartz's reagent, which was found to be higher-yielding than other alternatives. Lewis acid assisted alkylation of the required alkyl chain, followed by cyclisation, subsequently delivered (–)-**1.6**.

The most recently reported total synthesis of the sparteine isomers was published once more by O'Brien, as a way to address supply chain issues of surrogate (–)-**1.7**, whilst

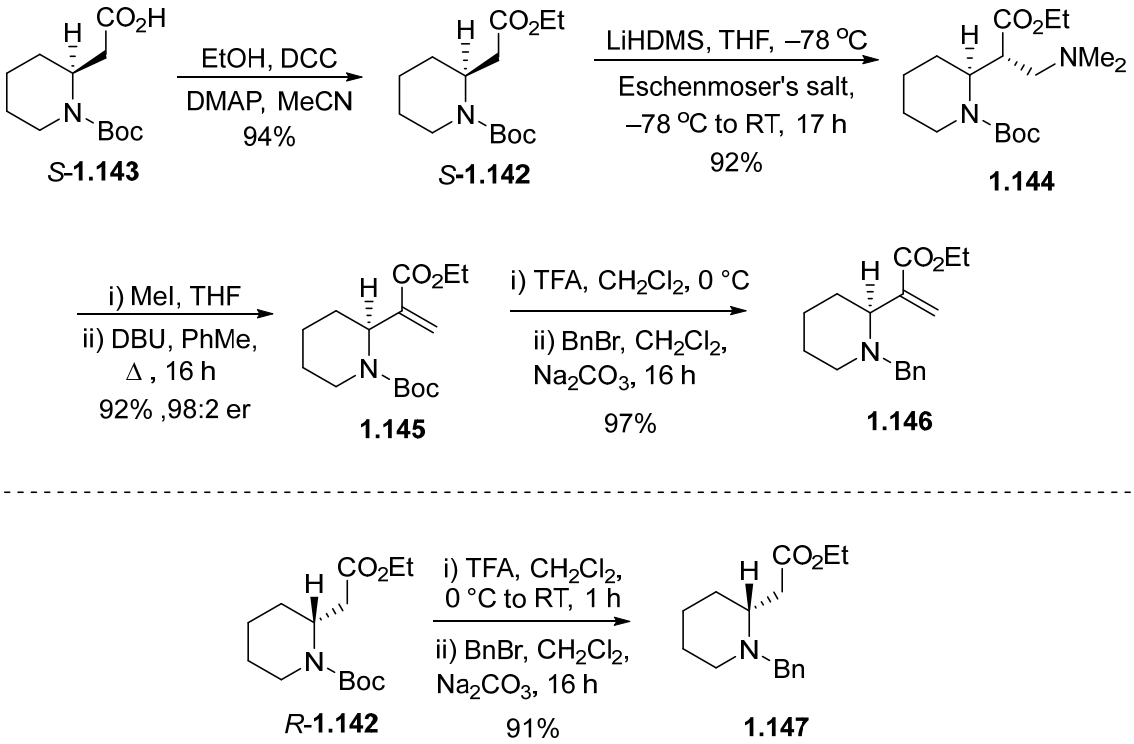
also enacting a gram-scale total synthesis of (–)-**1.3** itself.[128] Inspired to act by the lack of adoption of a scale process to (+)-**1.7** due to concerns about the availability of the natural product precursor (–)-cytisine ((–)-**1.2**), O'Brien would seek to optimise the step count, yields and scalability of his previously published efforts.

The lynchpin of the route would be in the enzymatic resolution of piperidine *rac*-**1.142**, obtained from pyridine **1.18** – reintroducing this valuable sparteine synthon over 60 years since its last use. Adaptation of a previously published resolution[129] afforded ester *R*-**1.142** and acid *S*-**1.143**, the latter of which would be a wasted byproduct in the synthesis of the surrogate (–)-**1.7** (**Scheme 1.30**). However, the realisation that these separate resolution products contained all the required atoms for (–)-**1.3** apart from the methylene bridge itself revealed a route towards the synthesis of (–)-**1.3**.



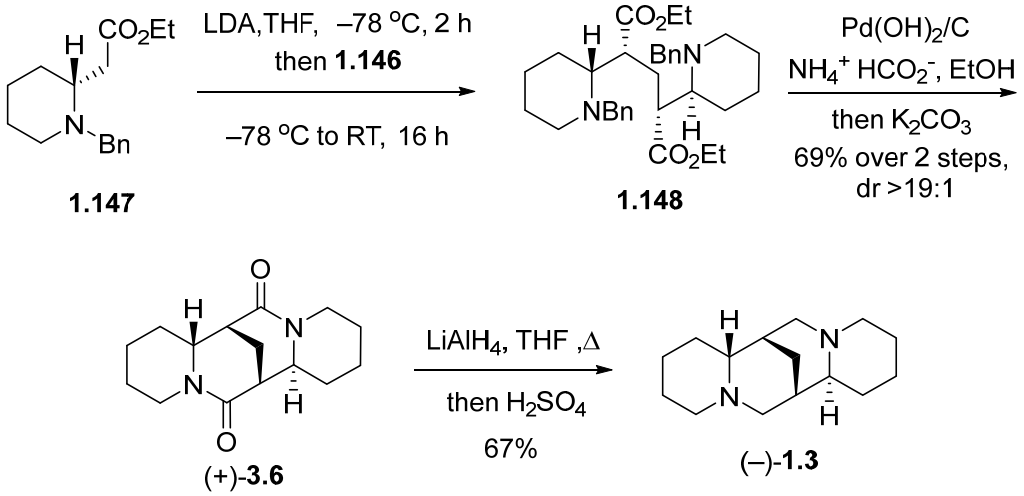
Scheme 1.30: Enzymatic resolution of *rac*-**1.142**.

By using the same approach as reported previously,[113] (*S*)-**1.143** was re-esterified to (*S*)-**1.142**, and the methylene bridge added by one-carbon homologation using Eschenmoser's salt; initially affording amine **1.144** (**Scheme 1.31**). Methylation and DBU-assisted elimination accessed Michael acceptor **1.145**. Attempts to react (*R*)-**1.142** directly produced a complex mixture of products, and as a result the Boc protecting groups of both piperidines were replaced with benzyl groups, to yield Michael acceptor **1.146** and piperidine **1.147**.



Scheme 1.31: Preparation of Michael acceptor **1.146** from resolved *S*-**1.143**, and preparation of benzyl-protected piperidine **1.147**.

Subsequent Michael addition yielded adduct **1.148**, which contained all of the necessary stereochemical information of the (–)-**1.3** skeleton (**Scheme 1.32**). Removal of the benzyl protecting groups *via* transfer hydrogenation accessed tetracycle (+)-**1.23**, which was finally reduced to furnish (–)-**1.3** in 31% yield over 10 linear steps, achieving the initial goal of improving the synthesis.



Scheme 1.32: Michael addition of **1.147** to acceptor **1.146**, allowing access to (–)-**1.3**.

1.6 Conclusions and future perspectives

Few compounds within the chemical literature have as much of a wealth of history as (–)-sparteine ((–)-**1.3**). Isolated almost 170 years ago, this review has shown that an incredible amount of research has been directed at this single alkaloid: from the initial structural determinations, discovery of its diastereoisomers, and the large array of both racemic and asymmetric syntheses that have taken place over the years. Whilst we have attempted to correct any oversights in the early literature, the efforts of all of the early researchers in this area should still be lauded – the abundance of modern analytical techniques, and thus a more complete understanding of the structure of these alkaloids, allows us to shine light into areas that were unable to be fully elucidated at the time.

(–)-Sparteine ((–)-**1.3**) will always be a tempting target for total synthesis for two reasons: (1) The complicated stereochemistry inherent to the skeleton is an excellent proving ground for showcasing new asymmetric methodology, and (2) Finding new routes towards its synthesis due to its continued use in the contemporary literature as a key component of any chemist's arsenal of ligands for enantioselective organolithium reactions. Indeed, the recent publication by O'Brien aims to tackle this very issue, and it is foreseeable that several other solutions to a scalable synthesis will appear in the near future, providing a more sustainable source of either antipode of **1.3** than present.

Chapter 2 *N*-Sulfinylimines as chiral auxiliaries

2.1 Introduction

The use of chiral auxiliaries has been at the core of asymmetric synthesis for many years. Stereoselective synthesis is a key target for organic chemists, which has led to the prevalence of general synthetic categories employed in this regard. Broadly speaking, these are:

1. Preparative resolution of mixtures of enantiomers to separate and purify one enantiomer selectively.
2. Use of the "chiral pool": enantiomerically enriched reagents as starting materials, such as natural amino acids.[130]
3. Using pre-installed components of the substrate to provide asymmetry in proximal positions, so called "substrate control".[131]
4. Use of chiral reagents to provide asymmetric induction of achiral substrates.

The latter group is perhaps the most explored, with countless reports within the literature detailing syntheses of compounds, catalysts and other frameworks that can create chirality from achiral compounds. One particular class of compounds that have found use in this area are termed chiral auxiliaries.

2.1.1 Chiral auxiliaries in asymmetric synthesis

The essence of chiral auxiliaries is covered in **Figure 2.1**. The desired substrate is reacted with a stoichiometric amount of chiral auxiliary, which then undergoes some chemical change, with the ideal of producing one diastereomeric product in preference to others. This mixture of diastereoisomers could be separated, and the desired isomer subjected to conditions facilitating the removal of the auxiliary. In some cases, an equimolar mixture of products can result, and the auxiliary is perhaps best thought of as an in-built resolving agent. In ideal scenarios, auxiliaries act as stereodirecting groups that result in almost total formation of the desired isomer preferentially.

The current trend in organic chemistry is concerned with the progress towards reactions that are less wasteful, more atom-efficient, more economical and more environmentally friendly. With this in mind, chiral auxiliaries could be argued to occupy a precarious position, as they are by design stochiometric reagents, which may only be used for a few steps before being discarded. In particular, the growing use of asymmetric catalysis has threatened to push the use of these reagents towards the perhipheries.

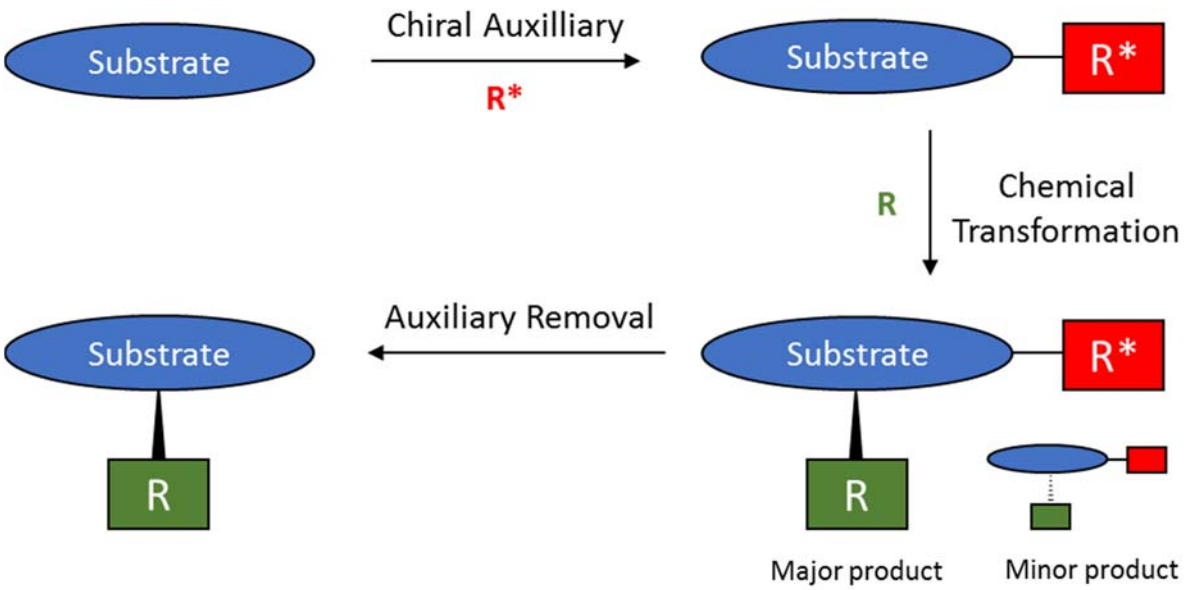
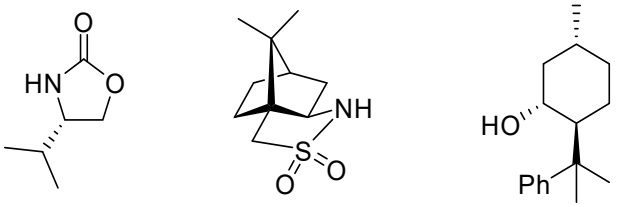


Figure 2.1: Simplified diagram of the action of a chiral auxiliary.

Nevertheless, chiral auxiliaries remain vital components of many successful syntheses of asymmetric compounds.[132] Several different classes of auxiliaries exist, and many have found ubiquitous use within organic synthesis. Some examples are listed in **Figure 2.2**, and include the Evans oxazolidinone **2.1**,[133] camphorsultam **2.2**,[134] and 8-phenylmenthol **2.3**.[135]



2.1 **2.2** **2.3**

Figure 2.2: Examples of chiral auxiliaries.

In order to be synthetically useful, these auxiliary compounds need to fulfil several criteria:

1. Cheap and readily available
2. Easily attached and removed
3. Inert to the desired chemical transformation
4. Most importantly: able to induce stereochemical effects

The work within the Brown group in recent years has featured the exploitation of one particular class of chiral auxiliaries, that of *N*-sulfinylimines. A brief review of their synthesis and a summary of relevant work done so far within the group is presented throughout the rest of this chapter.

2.2 *N*-sulfinylimines

N-sulfinylimines have become a ubiquitous chiral auxiliary within organic synthesis in recent years, due to their use as a so-called “chiral ammonia” equivalent. In general, routes towards enantiopure amines are highly sought after, given that many natural product scaffolds and promising pharmaceutical agents possess non-racemic chiral amine functionalities.[136]

One potential entry into chiral amines is by stereoselective reaction of a nucleophile with an imine, yielding an amine as the result of the reaction. There are issues with this approach – imines are often poor electrophiles on their own, and often require activation towards nucleophilic attack.[137] Both aldehyde and ketone derived imines – aldimines and ketimines respectively – can also suffer from competing side reactions upon addition, such as deprotonation and reduction. Consequently, there has been a drive to find ways to temper the proclivity of side reactions encountered in imine reactions, whilst also increasing the electrophilicity of the group and allowing facile addition of reagents across the C=N bond.

The development of *N*-sulfinylimines in the mid-70’s provided one such solution to this conundrum. By reaction of an aldehyde or ketone with a sulfinamide auxiliary, the imine exhibited an increased reactivity towards 1,2-addition of nucleophiles, increased stability which would aid isolation, reduction in propensity to undergo side reactions, and an easy cleavage of the group after the reaction under mildly acidic conditions. Whilst initially synthesised as racemates, the subsequent availability of enantiopure versions enabled the use of these groups as chiral auxiliaries.

A general overview of the properties of N-sulfinylimines are listed in **Figure 2.3**, and will be elaborated on throughout this section. The two most common *N*-sulfinylimines in contemporary use are ultimately derived from *p*-tolylsulfinylamine **2.4**, pioneered by Franklin Davis, and *tert*-butanesulfinylamine **2.5**, popularised by Jonathan Ellman (**Figure 2.4**).

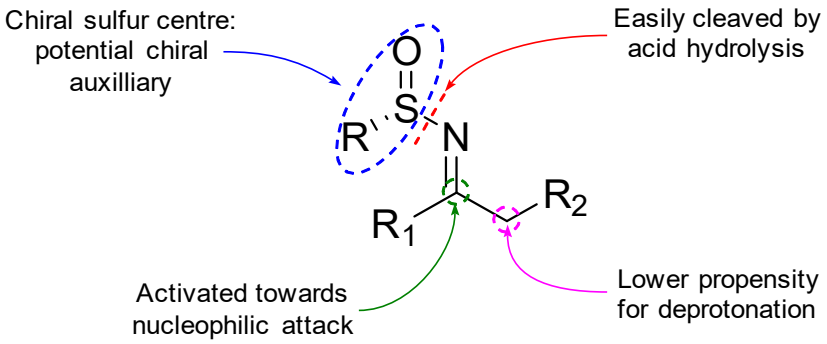


Figure 2.3: Overview of the features of *N*-sulfinylimines.

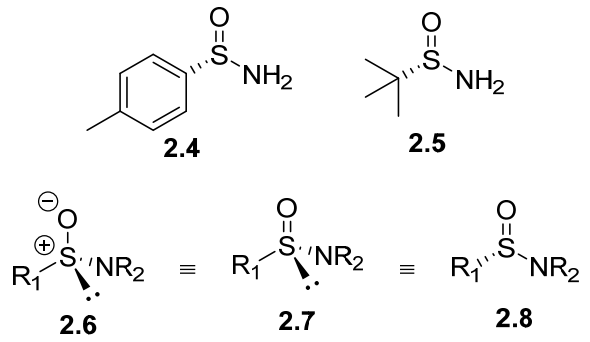


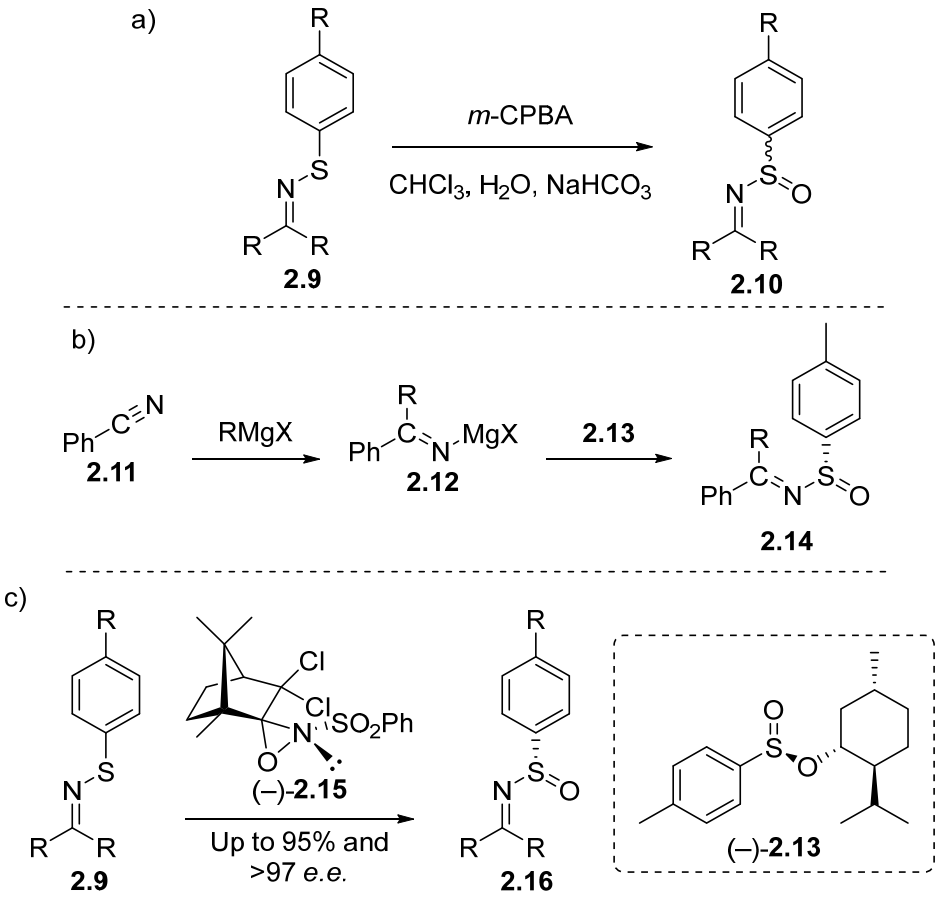
Figure 2.4: Chiral sulfinylamine auxiliaries. For clarity, the lone pair of electrons on the sulfur atom will be omitted, and the S-O bond represented as S=O.

2.2.1 Syntheses

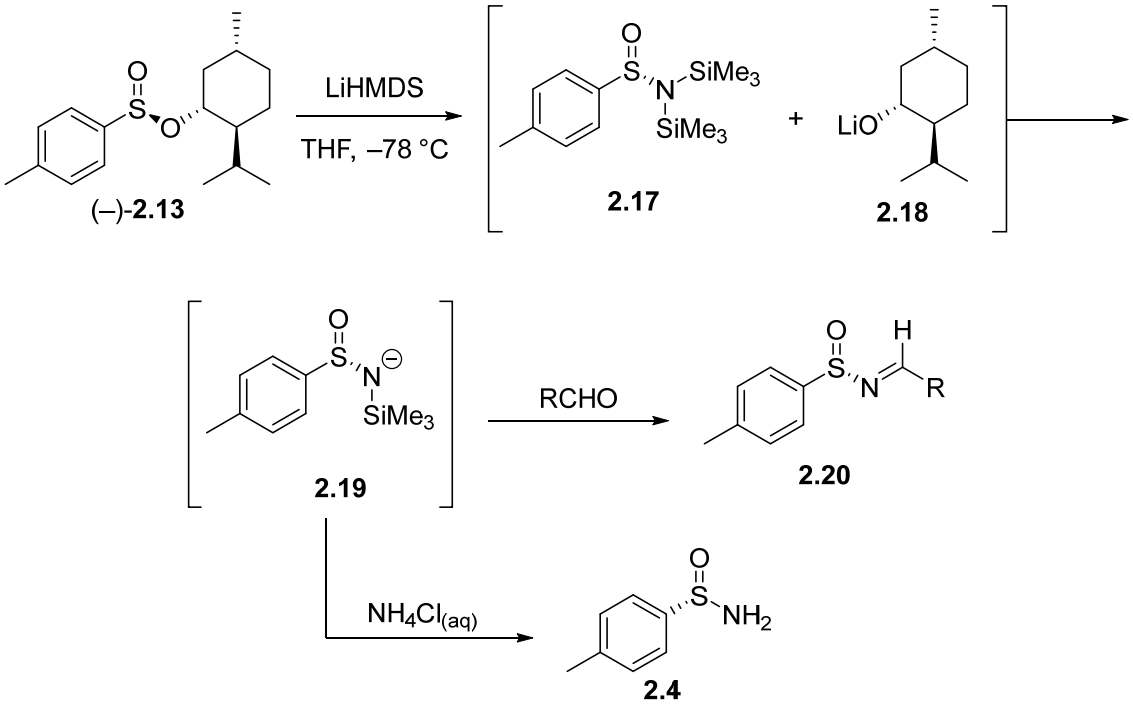
2.2.1.1 Davis *p*-tolylsulfinamide 2.4

The first *N*-sulfinylimines possessing the chiral information of **2.4** were reported by Davis in the mid 1970's. The initial discovery was reported via the oxidation of sulfenimines **2.9** using *m*-CPBA, providing racemic *N*-sulfinylimine **2.10** (**Scheme 2.1a**),[138] and were proposed as a convenient route to arenesulfenic acids.[139] The first enantiomerically pure versions were synthesised by Cozzi, who added Grignard reagents to nitriles and reacted the resulting intermediates with (–)-menthyl (*S*)-*p*-toluenesulfinate (–)-**2.13** (**Scheme 2.1b**).[140-141] A decade later, Davis would return to the synthesis *via* the oxidation of sulfenimines once again, this time using chiral oxaziridine (–)-**2.15** to yield enantioenriched *N*-sulfinylimines **2.16** as a result (**Scheme 2.1c**).[142].

The development of a convenient one-pot procedure for the synthesis of *p*-tolyl *N*-sulfinylimines drastically improved the accessibility of this chemistry.[143] In a seminal paper, Davis disclosed the treatment of (–)-**2.13** with LiHMDS, accessing *bis*-silane intermediate **2.17**, along with the concurrent formation of menthyl alkoxide **2.18** (**Scheme 2.2**). This alkoxide facilitated formation of anion **2.19**, which could be reacted with an aldehyde to afford *N*-sulfinylimine **2.20**. Due to the limited reactivity of ketones *via* this procedure, there was a need to refine this methodology further. As such, the quenching of **2.19** with $NH_4Cl_{(aq)}$ provided sulfinylamine **2.4**, enantiomerically pure after recrystallisation. This reagent permitted allow the facile preparation of a wide range of *N*-sulfinylimines from either aldehydes or ketones when used with a Lewis acidic dehydrating reagent.[144]



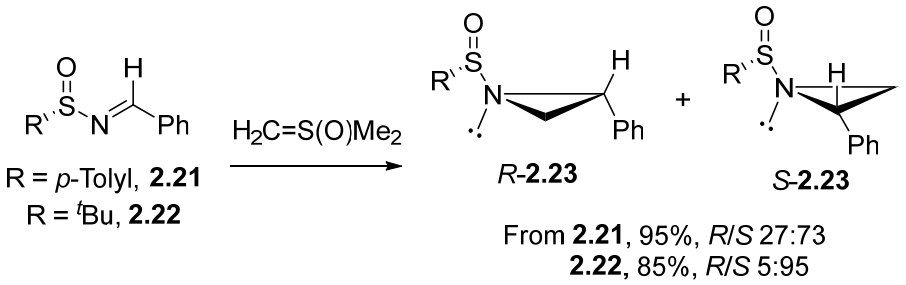
Scheme 2.1: Early *N*-sulfinylimine syntheses. a) Original synthesis by Davis using *m*-CPBA. b) First asymmetric version by Cozzi. c) Enantioselective oxidation by Davis using oxaziridine (–)-**2.15**.



Scheme 2.2: Synthesis of *N*-sulfinylimine **2.20** from (–)-**2.13**, and preparation of auxiliary **2.4** *via* quench of intermediate **2.19**.

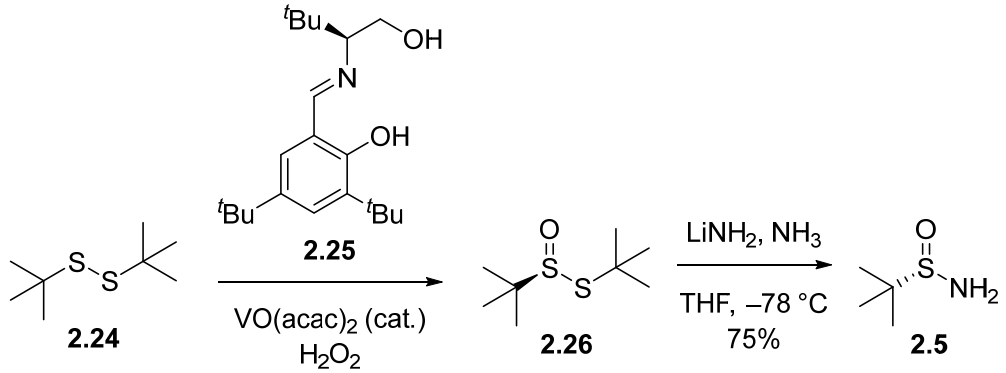
2.2.1.2 Ellman *tert*-butanesulfinamide 2.5

The use of chiral *tert*-butyl sulfoxides as stereochemical directing groups can be traced back to the work of Casey,[145] Kagan[146] and Khiar.[147] The extension of this methodology to nitrogen containing analogues was first proposed by Ruano and Fernández, who noted that the *tert*-butylsulfinyl group was the chiral auxiliary of choice in their asymmetric aziridination experiments (**Scheme 2.3**).[148] The use of the *p*-tolyl derivative **2.21**, whilst offering a higher overall yield of the diastereomeric mixture **2.23**, gave lower selectivities than the *tert*-butyl analogue **2.22**.



Scheme 2.3: Initial investigations of *tert*-butyl *N*-sulfinylimines in aziridation reactions.

Noting this increase in selectivity, but lamenting the lack of an expedient process to provide free auxiliary **2.5**, Ellman disclosed a simple two-step synthesis from commercially available and cheap *tert*-butyl disulfide (**2.24**, **Scheme 2.4**).[149] The use of catalytic $VO(acac)_2$ and stoichiometric amounts of sacrificial oxidant H_2O_2 in conjunction with a chiral Schiff base ligand **2.25** afforded thiosulfinate **2.26** with a high degree of enantioenrichment. Subsequent application of lithium amide in ammonia would furnish **2.5**, with high optical purity after a single recrystallisation.

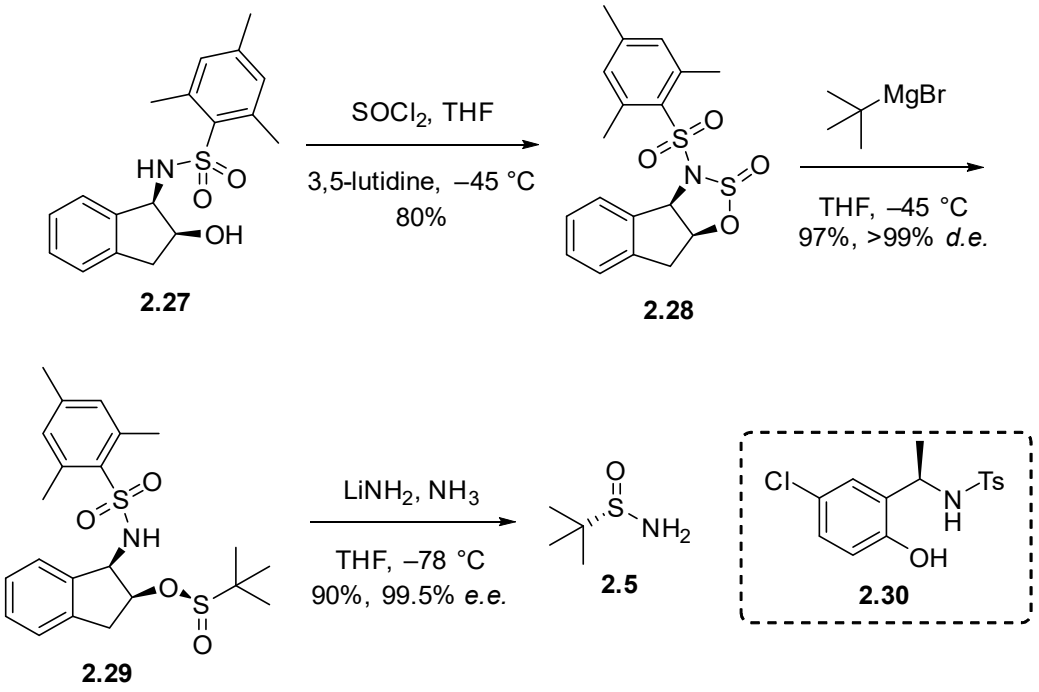


Scheme 2.4: Asymmetric synthesis of **2.5** from achiral sulphide **2.24**.

A subsequent communication from Ellman divulged additional information regarding the synthesis, in particular the further optimisation of the catalytic reaction.[150] The lowering of the catalyst loading to 0.25 mol% and **2.25** to 0.26 mol% led to the isolation of **2.26** in 92% yield and 91% *e.e.*

Several other syntheses of **2.5** were reported in the years since the initial disclosure of the catalytic route. Senanayake disclosed the preparation of **2.5** in 3 steps from substituted indanol **2.27** (**Scheme 2.5**)[151-152]. Reaction of thionyl chloride formed oxathiazolidinine **2.28**, from which an addition of *tert*-butyl Grignard provided sulfinate ester **2.29**. Liberation of the auxiliary with $LiNH_2/NH_3$ gave **2.5** as before, in >99% *e.e.* and 70% overall yield.

A further communication from Senanayake unveiled a more optimised synthesis using the same methodology, but instead starting from aminophenol **2.30**.[153] Finally, a recently patented synthesis provides **2.5** *via* resolution of a racemic mixture of **2.26**.[154] Of note is that these methods have also been applied to the synthesis of **2.4**. Whilst these approaches are higher yielding than Ellman's original communication, the simplicity and elegance of the original catalytic synthesis would appear to stand the test of time.



Scheme 2.5: Senanayake's synthesis of **2.5** *via* Grignard attack of oxathiazolidinine **2.28**.

2.3 Properties and selected reactions of *N*-sulfinylimines

2.3.1 Structural, conformational and electronic studies

Due to their use as excellent chiral nitrogen surrogates, there have been extensive investigations into the properties of *N*-sulfinylimines. In the absence of any other steric or electronic factors, *N*-sulfinylimines with unsymmetrically substituted carbon atoms can exist as a mixture of *cis* and *trans* isomers, due to the relatively low barrier of stereomutation.[155] However, Davis noted that, upon oxidation of aldimines of type **2.31**, only the *trans*

stereoisomer of *N*-sulfinylimine **2.32** was isolated.[139] They proposed that the sulfur oxygen and imine proton possessed an intramolecular hydrogen bonding interaction (**Figure 2.5**) However, they later discounted this theory after obtaining crystallographic data for *N*-benzylidene-*p*-toluenesulfinamide (**2.33**), noting that the distance between these atoms was too great to possess a hydrogen bonding interaction.[143]

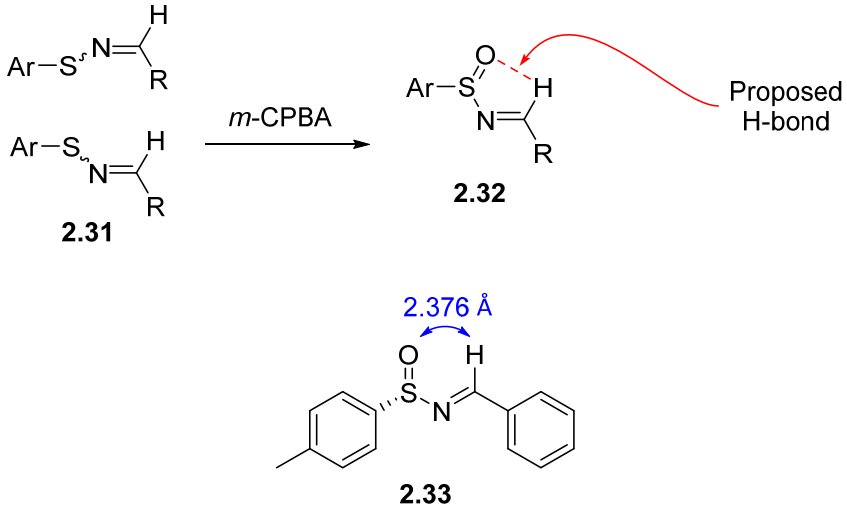


Figure 2.5: Initial proposal for observed *E*-selectivity of aldimine **2.32**, and data from crystallographic interrogation of **2.33**.

As such, their proposal would be confined to a rationale based on minimising steric interactions. They suggested that the bulky aromatic groups adopted the more stable *trans* geometry, lowering the amount of non-bonded steric interactions. DFT calculations by Bharatam probed this theory further,[156-157] showing that, in the case of simple *N*-sulfinyimine **2.34**, there was a natural tendency of the C-N-S-O atoms to adopt a semi-rigid synperiplanar arrangement, attributable to repulsion of the lone pairs of the N, S and O atoms and a negative hyperconjugation effect between the N and S=O (**Figure 2.6**). They would also show that there was a significant inversion barrier between the preferred *trans* isomer and the *cis* isomer of *c.a.* 100 kJ mol^{-1}.

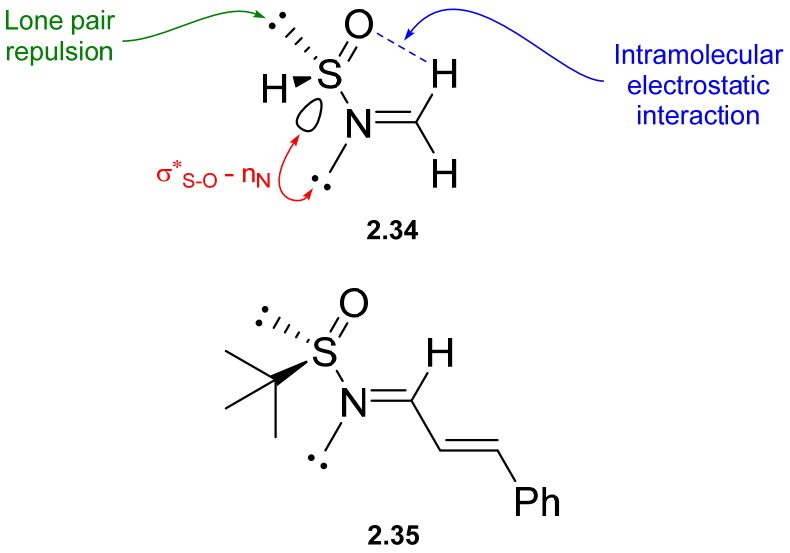


Figure 2.6: Preferred conformations of **2.34** and **2.35** based on DFT and semi-empirical AM1 calculations.

They also stated that, in part, an intramolecular electrostatic interaction of the C-H···O subunit did add further stability, however the expected interaction was only small – in the range of 1-2 kcal mol^{-1}. Ferreira *et al*. added computational examples for the *tert*-butane analogues, showing that conformation **2.35** was favoured for the corresponding cinnamaldehyde-derived *tert*-butyl analogue.[158] These conformations would also serve as models to show the origins of the facial selectivities observed in various reactions.

Bharatam *et al*. also probed the electronic properties of *N*-sulfinylimines, in efforts to quantitatively qualify the observations that the auxiliaries activate the imine towards nucleophilic attack. Computed natural charges on the atoms of structure **2.36** would confirm the presence of a strongly polarised S-O bond, with a charge of near unity present on the oxygen atom, with a large positive charge on the sulfur (**Figure 2.7**). This observation is consistent with the structural interpretations noted in **Figure 2.6**.

The sulfinyl group would also act to polarize the N=C bond, which is thought to withdraw electron density due to the inductive effect. The natural charges on two related compounds **2.37** and **2.38** are also presented, showing the key differences.[159] The net effect is to make the imine carbon significantly more electropositive, and therefore more activated towards nucleophilic attack than the non-activated analogues.

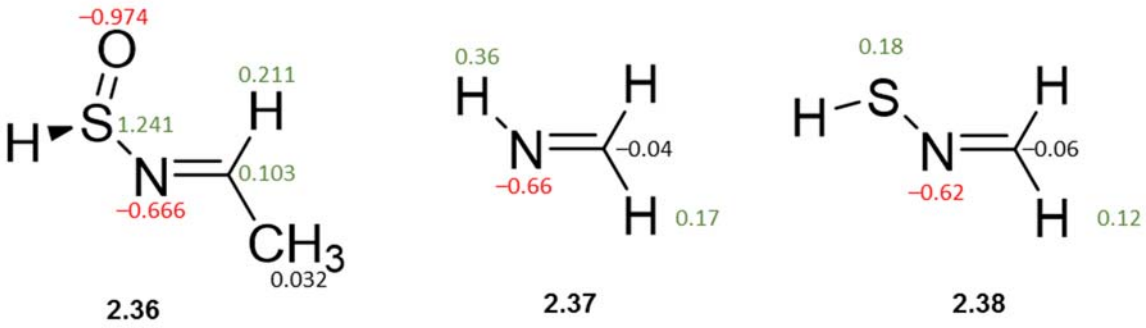
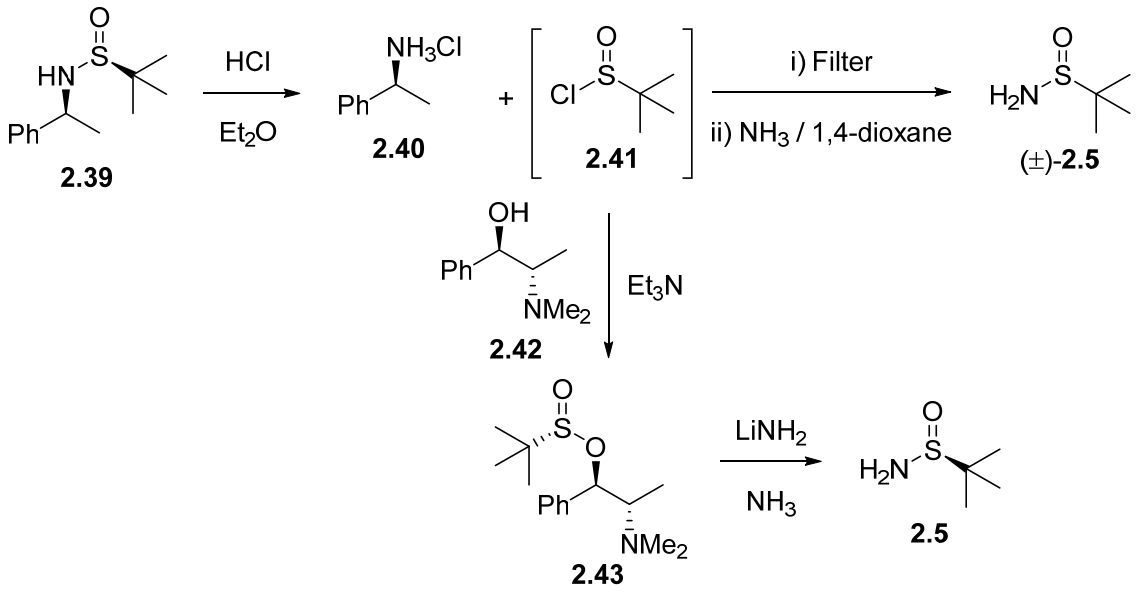


Figure 2.7: Natural charges present on **2.36**, **2.37** and **2.38**.

2.3.2 Cleavage of the auxiliary

As stated in **Section 2.1.1**, to be an effective chiral auxiliary, effective removal once the desired reaction has taken place is an essential design feature. Fortunately, the removal of both auxiliaries **2.4** and **2.5** is facile, taking place under even mildly acidic conditions, in near quantitative yields.[160-162] However, this is a wasteful process, as the deprotected auxiliary is often removed in the work up and disposed into solvent waste streams. However, there has been an interest in recent years into the fate of the deprotected auxiliary, in an effort to improve the atom economy of this reaction.

If analogy was made to Boc and *tert*-BuSO_2 protecting groups, one might expect a decomposition of the auxiliary into isobutene and SO. However, Aggarwal *et al*. showed this to be unlikely, given the known instability of SO.[163] Instead, it was proposed that the auxiliary may still be intact after deprotection, and so a protocol was enacted in order to scavenge this remaining material. Deprotection of amine **2.39** under acidic conditions and subsequent removal of the resulting salt **2.40** gave a solution of sulfinyl chloride **2.41** (**Scheme 2.6**). Subsequent treatment with NH_3 in dioxane allowed racemic auxiliary (±)-**2.5** to be recovered in excellent yield.



Scheme 2.6: Recovery of racemic auxiliary after reaction.

This was furthered by the incorporation of chiral alcohol **2.42** into the procedure. Base-assisted trapping of intermediate **2.41** provided a single diastereoisomer of sulfinate ester **2.43**, releasing the parent sulfinamide **2.5** after treatment with $LiNH_2/NH_3$. Concurrently to the publication of this article, Ellman also detailed efforts towards the recycling of **2.5**, using a similar approach but using a chiral quinidine catalyst instead.[164]

2.3.3 Reactions utilizing *N*-sulfinylimines

Due to these favourable characteristics, the use of *N*-sulfinylimines to effect asymmetric syntheses has received significant attention within the literature. Although the applications of these privileged chiral auxiliaries are too numerous to list here, several comprehensive reviews of their chemistries have been published.[158, 161, 165-166] A general overview of the transformations that can be achieved using *N*-sulfinylimines is shown in **Figure 2.8**, but this is not given as an exhaustive list.

The facial selectivities of *N*-sulfinylimine reactions are generally explained by the application of 6-membered Zimmerman-Traxler type transition states.[167] The example of Grignard addition to *N*-sulfinylimines can be used as an excellent application of this methodology. Ellman noted high levels of stereoinduction in addition reactions of a range of Grignard reagents.[168] They proposed that, upon addition of Grignard reagent to aldimine **2.44**, the cyclic transition state **2.45** would result (**Scheme 2.7**). This would place the bulky *tert*-butyl group in a *pseudo*-equatorial position, guiding Grignard addition to the *Si*-face, whilst also shielding the *Re*-face from attack. It was also found that coordinating solvents such as THF and Et_2O led to reduced selectivities, whilst CH_2Cl_2 gave elevated results, consistent with solvent effects in cyclic transition states.

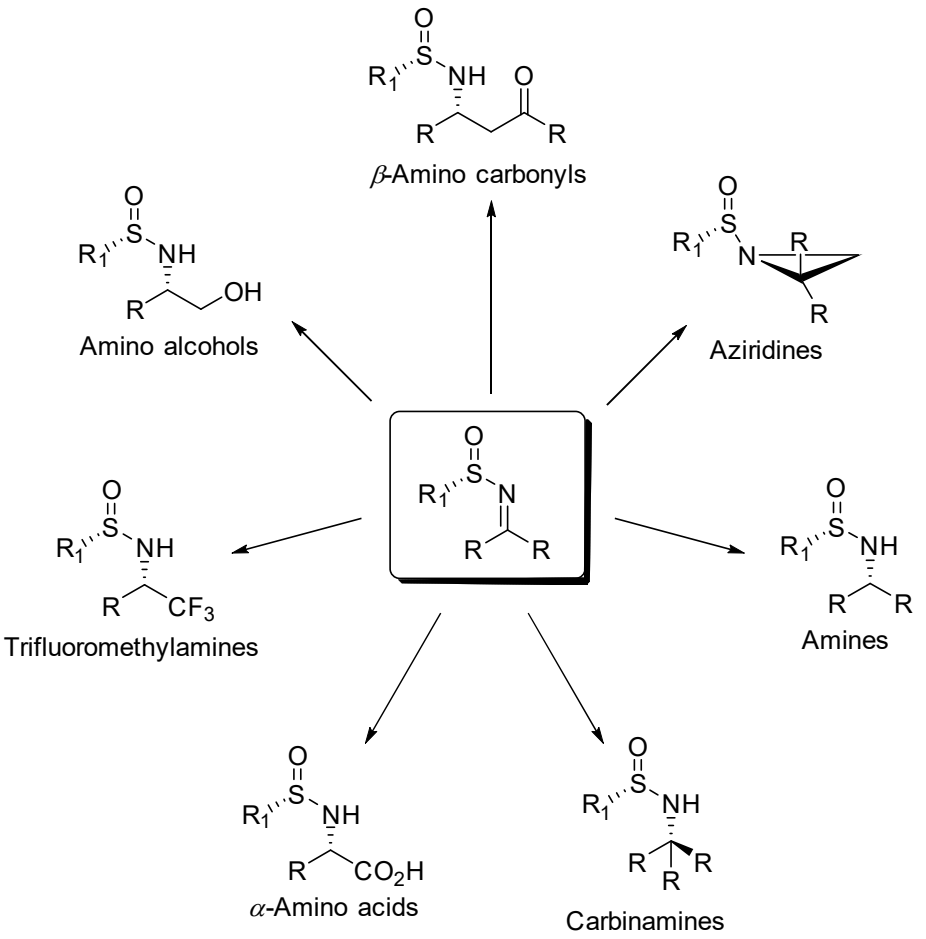
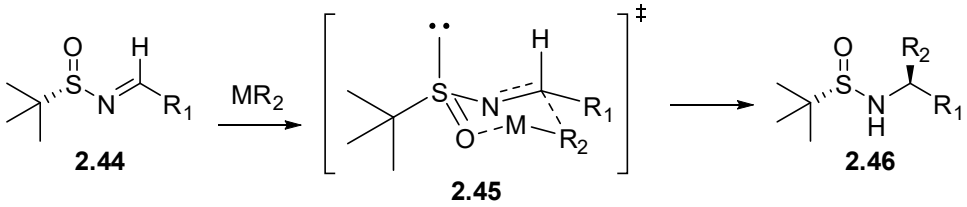


Figure 2.8: Overview of several reactions of *N*-sulfinylimines.



Scheme 2.7: Grignard addition to **2.44**, proceeding *via* cyclic transition state **2.45**.

2.4 Use within the Brown group

The Brown group's approaches towards natural products has relied heavily on *N*-sulfinylimines in order to provide *β*-amino esters in excellent yields and high diastereoselectivies. The synthesis of the lupin alkaloids, including the sparteine stereoisomers, has been a key goal of the Brown group for many years. Several of these quinolizidine alkaloids have been synthesised within the group in recent years, with some awaiting publication (**Figure 2.9**). At the centre of all of these syntheses is the preparation of *β*-amino esters by an imino-aldol reaction, which allows the construction of the necessary *syn*-stereochemistry of these alkaloids.

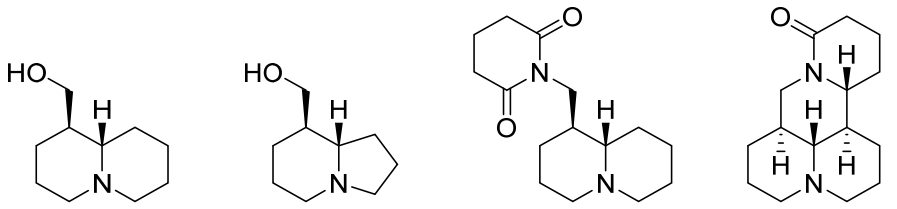


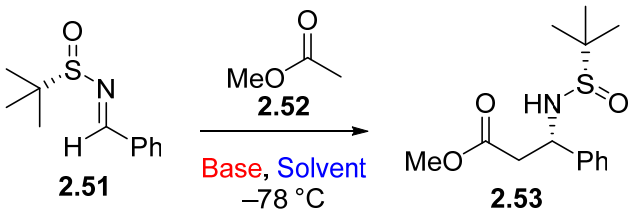
Figure 2.9: Alkaloids synthesised within the Brown group.

2.4.1 The highly diastereoselective imino-aldol reaction

Ellman extensively studied the addition of enolates to *tert*-butane *N*-sulfinylimines.[169] The development of this methodology allowed access to a wide range of chiral *β*-amino acid derivatives. Ellman's original work reacted the enolate of methyl acetate (**2.52**) with *N*-sulfinylimine **2.51**, affording *β*-amino ester **2.53** (**Table 2.1**). It is apparent that the choice of counter ion and solvent are instrumental in determining both the yield and selectivity. The use of Et_2O provided a decrease in selectivity but enhanced yield when using the Li counterion (**Table 2.1**, **Entry 2**). Upon switch to Na, Et_2O would increase the selectivity but slightly lower the yield (**Table 2.1**, **Entry 4**). The best results were noted by the transmetallation of a lithium enolate to a titanium enolate offering almost complete stereocontrol (**Table 2.1**, **Entries 5-7**).

This work was expanded to longer-chain esters, using their optimised titanium enolate conditions (**Table 2.2**).[162] The use of esters **2.54** and substituted *N*-sulfinylimines **2.55** this time provide a range of *α*-branched *β*-amino esters **2.56**. These were synthesised in good to excellent yields, and all with high diastereoselectivity (**Table 2.2**, **Entries 1-5**).

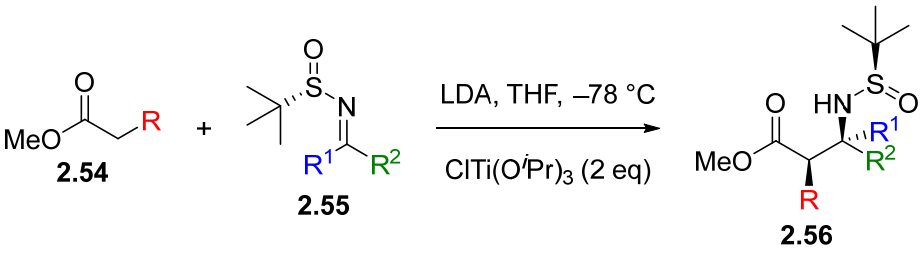
Table 2.1: Solvent and counterion effects of enolate additions to **2.51**.



Entry	Base	Solvent	Yield (%)	*d.r.*
1	LDA	THF	76	83:17
2	LDA	Et_2O	91	67:33
3	NaHMDS	THF	89	75:25
4	NaHMDS	Et_2O	78	96:4
5	LDA / 1 eq $ClTi(O^iPr)_3$	THF	90	87:13

Entry	Base	Solvent	Yield (%)	*d.r.*
6	LDA / 2 eq ClTi(O^{i}Pr)$_3$	THF	90	98:2
7	LDA / 4 eq ClTi(O^{i}Pr)$_3$	THF	90	99:1

Table 2.2: Substituent effects on yield and selectivities of longer chain esters.



Entry	R	R^1	R^2	Yield (%)	*dr*
1	Me	H	Me	96	92:7:1:0
2	Me	H	^{i}Bu	81	95:3:2:0
3	Me	H	Ph	85	96:4:0:0
4	Me	Me	Ph	81	91:9:0:0
5	Bn	H	Et	67	90:10:0:0

With these promising results, Ellman extended the work to include esters with more functionalised side chains.[170] However, this would prove capricious in its execution. The use of azide **2.57** led to decomposition under the reaction conditions. Coupling was achieved by returning to the use of NaHMDS, but with much lower selectivities (65:17:15:3). Similarly, TIPS-protected alcohol **2.58** was coupled with a much lower observed selectivity (60:20:17:3).

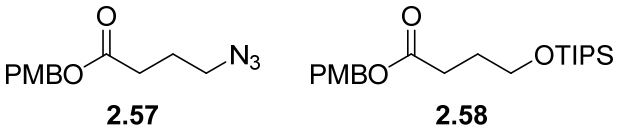
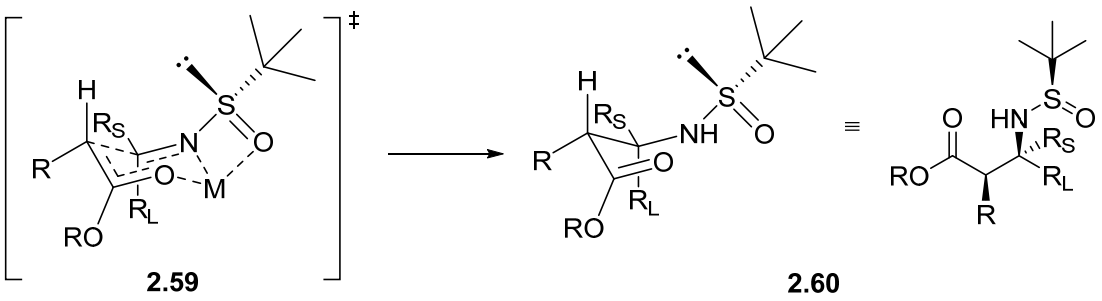


Figure 2.10: Functionalised ester fragments used in imino-aldol reactions by Ellman.

The origins of the observed diastereoselectivity were again rationalised *via* application of a Zimmerman-Traxler transition state **2.59**, which is consistent with formation of **2.60** as the major product. Salient features of the transition state are the unexpected axial orientation of the bulky imine substituent, and the chelation of both the *N* and *O* atoms of the sulfinyl group to the enolate counterion. The former can be rationalised due to the conformation of the imine, which is exclusively *trans* when R$_s$ = H and expected to still be present in the majority *trans* configuration with R$_s$ = Me. The latter is proposed to be due to

the highly coordinatively unsaturated and oxyphilic Ti(IV) counterion, which is able to accommodate tridentate coordination from the reactants (other ligands not shown).



Scheme 2.8: Proposed transition state for the *syn*-selective imino-aldol reaction.

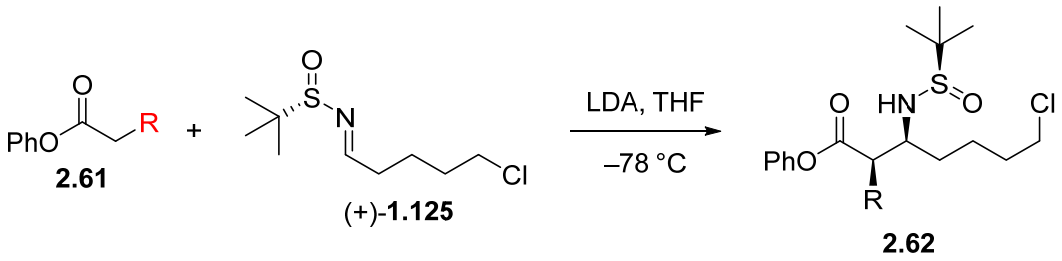
2.4.2 The Brown group's approach to functionalised fragments

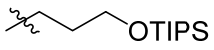
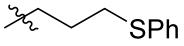
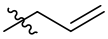
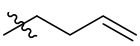
Past research within the group was focused towards a more detailed understanding of the *syn*-selective imino-aldol, and towards improving the range of functionalised fragments amenable to the reaction.

Initial investigations confirmed the importance of the Lewis acid partner in the transmetallation step.[171] It was found that large amounts of added $TiCl_4$ could reverse the facial selectivity observed, presumably by disruption of the closed-chair transition state **2.59**, possibly favouring an open transition state. We would also find that the reaction between chloroalkyl *N*-sulfinylimine and methyl ester derivatives proceeded well using a Li enolate, offering diastereoselectivities above 10:1 in favour of the desired *syn* products.

The next improvement to be made to the reaction would come from the observation that phenyl esters offered even further levels of stereocontrol in combination with a lithium enolate.[172-173] These observations led to the synthesis of a number of functionalised ester fragments **2.61**, and subsequent reaction with chloroalkyl *N*-sulfinylimine (+)-**1.125** to provide highly functionalised imino-aldol adducts **2.62** (**Table 2.3**).

Table 2.3: Initial scope of the synthesis of functionalised imino-aldol adducts **2.62**.[a] Yield of major isomer isolated after purification.



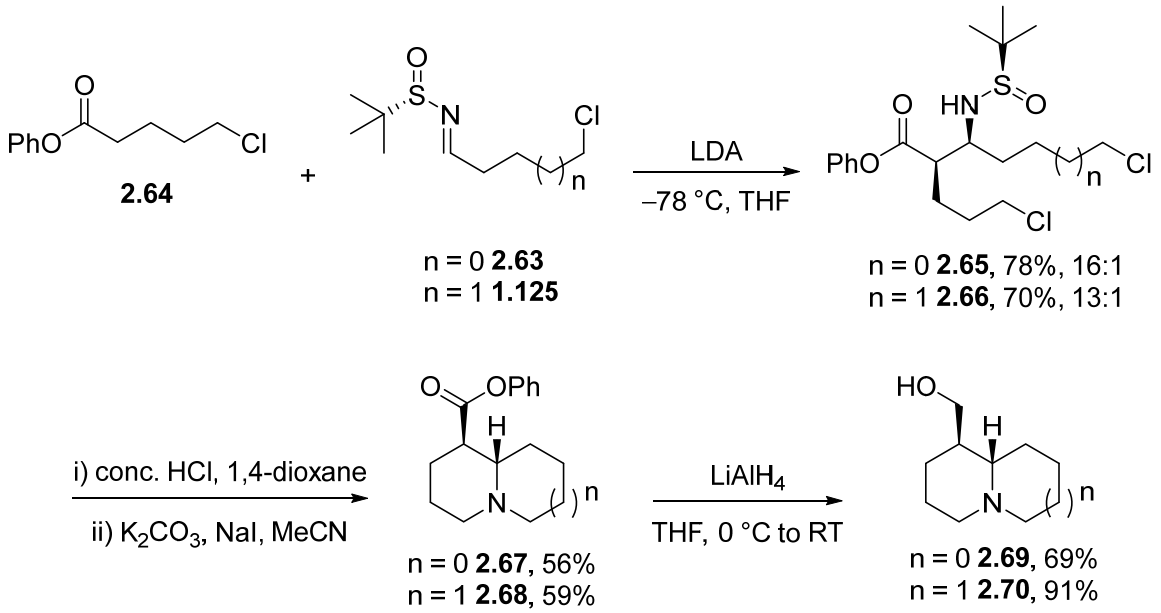
Entry	R	Yield (%)	*dr*
1		63	90:10:0:0
2		71	90:10:0:0
3		75	91:9:0:0
4		82	95:5:0:0

2.4.3 Previous total syntheses of the lupin alkaloids

The successful marriage of imine (+)-**1.125** and functionalised phenyl esters **2.61** led to the successful total syntheses of several quinolizidine alkaloids *via syn*-selective imino-aldol reactions, which are described in the ensuing sections.

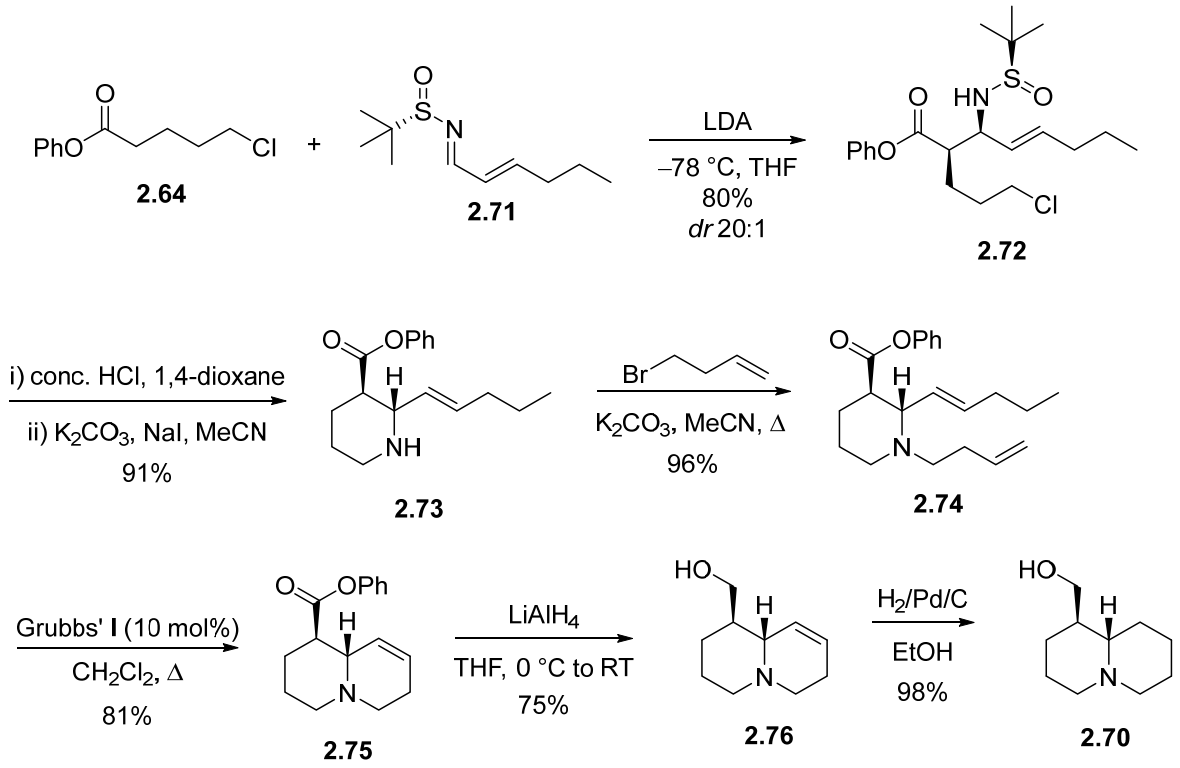
2.4.3.1 Total syntheses of (–)-epilupinine and (–)-tashiromine

Initial work on the lupin alkaloids focused on the bicyclic structures of (–)-epilupinine and (–)-tashiromine (**Scheme 2.9**).[12] Preparation of *N*-sulfinylimines **2.63** and **1.125** *via* condensation of the appropriate chloroaldehyde and Ellman sulfinylamine **2.25** allowed the imino-aldol reaction to take place, using phenyl ester **2.64** as the coupling partner. This afforded access to adducts **2.65** and **2.66** in 16:1 and 13:1 d.r. respectively, possessing the requires chain lengths and *syn*-stereochemistry. Removal of the auxiliary under acidic conditions and subsequent cyclisation using K_2CO_3 and catalytic NaI accessed quinolizidine **2.67** and indolizidine **2.68**, which were subjected to $LiAlH_4$ reduction to obtain the natural products **2.69** and **2.70** in 15% and 12% yields respectively, both in 4 steps from ester **2.64**.



Scheme 2.9: Total syntheses of (–)-**2.69** and (–)-**2.70** using *syn*-selective imino-aldol reactions.

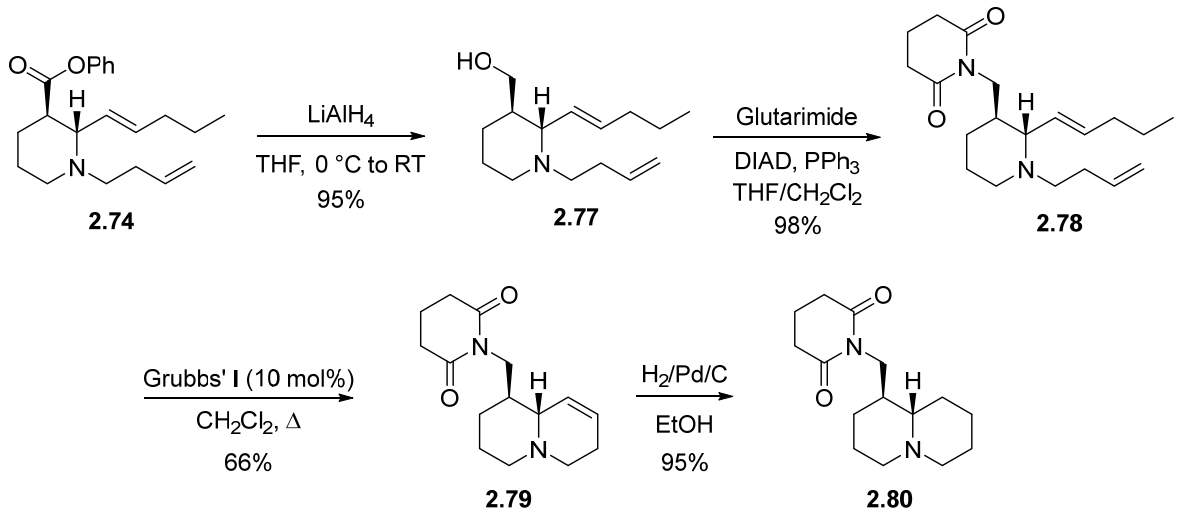
A second synthesis of (–)-**2.70** was also undertaken, which combined the use of a RCM approach in tandem with the imino-aldol reaction (**Scheme 2.10**).[173] Using *N*-sulfinylimine **2.71**, possessing olefinic functionality, imino-aldol reaction of phenyl ester **2.64** afforded *syn*-adduct **2.72** in good yield with excellent d.r. Removal of the auxiliary and piperidine cyclisation as before realised free piperidine **2.73**. Installation of a homoallylic functionality gave diene **2.74**, which is set up to form the quinolizidine skeleton using an RCM approach. Ring closure using Grubb's I yielded bicycle **2.75**, which was subjected to reduction with both $LiAlH_4$ – obtaining alcohol **2.76** – and hydrogenation to finally furnish (–)-**2.70**. Whilst containing more steps than the original synthesis, the overall yield of (–)-**2.70** in this case was 39%, in seven steps from ester **2.64**. This constitutes a marked improvement from the original communication; although it should be noted that there was no attempt to optimise the earlier synthesis.



Scheme 2.10: Second generation total synthesis of (–)-**2.70**, utilising an RCM approach.

2.4.3.2 Total synthesis of (–)-lamprolobine

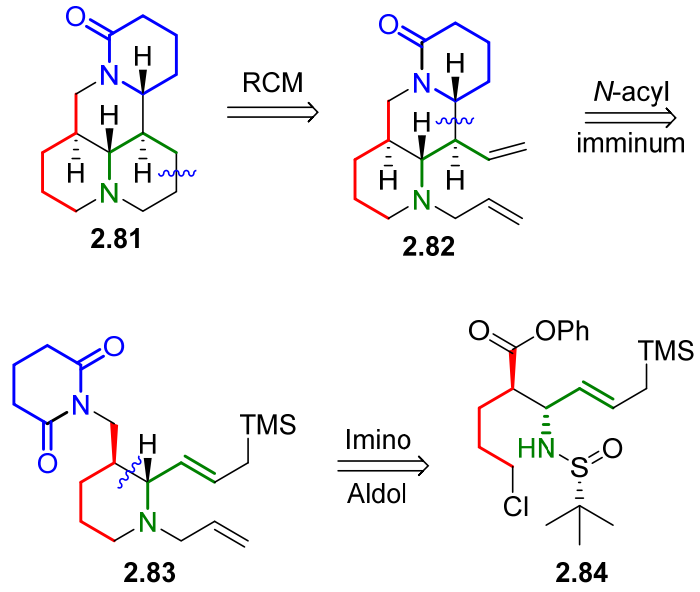
In addition to allowing access to (–)-**2.70**, the RCM approach also offered an intermediate that could be readily converted to (–)-lamprolobine ((–)-**2.80**).[173] Reduction of **2.74** to alcohol **2.77** allowed Mitsunobu coupling with glutarimide to afford imide **2.78** (**Scheme 2.11**). RCM of the diene functionality as conducted previously afforded access to quinolizidine derivative **2.79**, which was hydrogenated to provide (–)-**2.80** in 39% yield over eight steps.



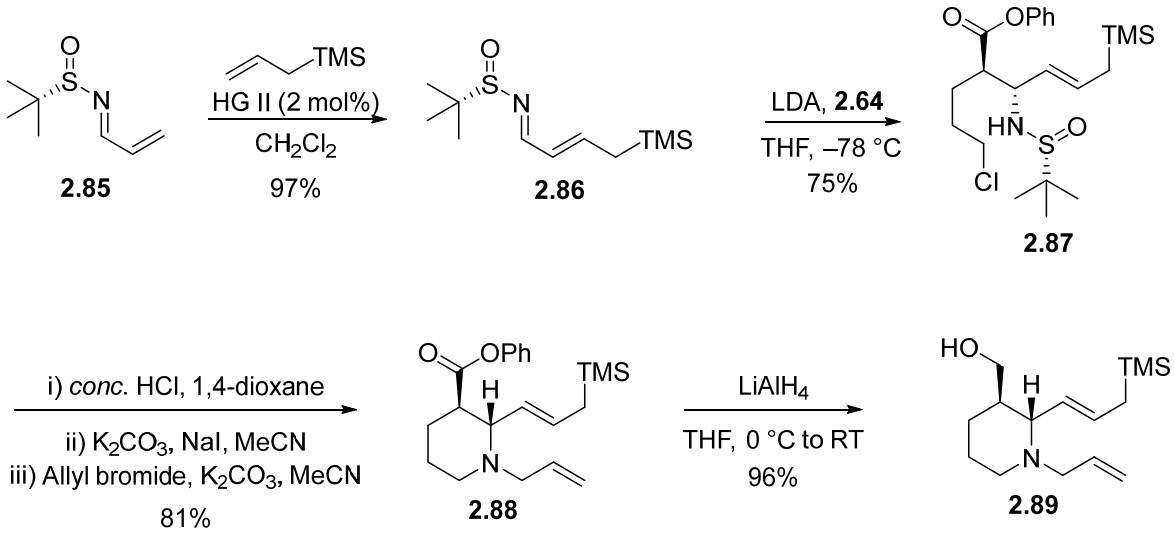
Scheme 2.11: Total synthesis of (–)-**2.80** *via* a Mitsunobu route from intermediate **2.74**.

2.4.3.3 Total synthesis of (+)-allomatrine

Having now established reliable and robust methods for the synthesis of several simple bicyclic lupin alkaloids, attention turned into elaborating these methods into syntheses of alkaloids possessing more stereochemically complex quinolizidine cores. With this in mind, the first stereocontrolled synthesis of (+)-allomatrine ((+)-**2.81**) was reported from this laboratory in 2013.[11, 173] The synthesis would still rely on the key imino-aldol reaction, however an extra element was needed to cyclise to the tetracycle. By extending the idea of using the imide moiety from the synthesis of (–)-**2.80**, a scenario was envisaged where one cyclisation would proceed *via* an *N*-acyl iminium ion (**Scheme 2.12**).



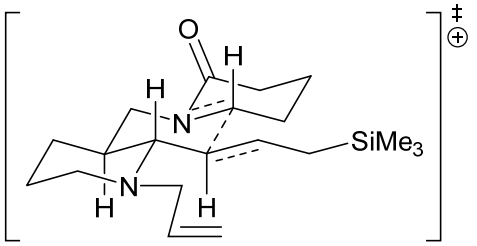
Scheme 2.12: Retrosynthesis of (+)-**2.81**, with the three key synthetic transformations highlighted. Colour added for emphasis of carbon chain sources.



Scheme 2.13: Synthesis of key piperidine intermediate **3.27**

This strategy relied on *N*-sulfinylimine **2.85**, prepared in one step from sulfinylamine **2.25** and acrolein (**Scheme 2.13**). Installation of an allylsilane was achieved *via* CM of allyltrimethylsilane, which gave silane **2.86**, the nucleophilic partner for the later *N*-acyliminium cyclisation. Reaction with the lithium enolate of ester **2.64** provided imino-aldol adduct **2.87** as a single diastereoisomer in good yield. This *β*-amino ester was subjected to the same one-pot deprotection and cyclisation procedure as before, with the addition of an *N*-alkylation step with allyl bromide, furnishing alkylated piperidine **2.88**, which was further reduced to the alcohol **2.89** by $LiAlH_4$.

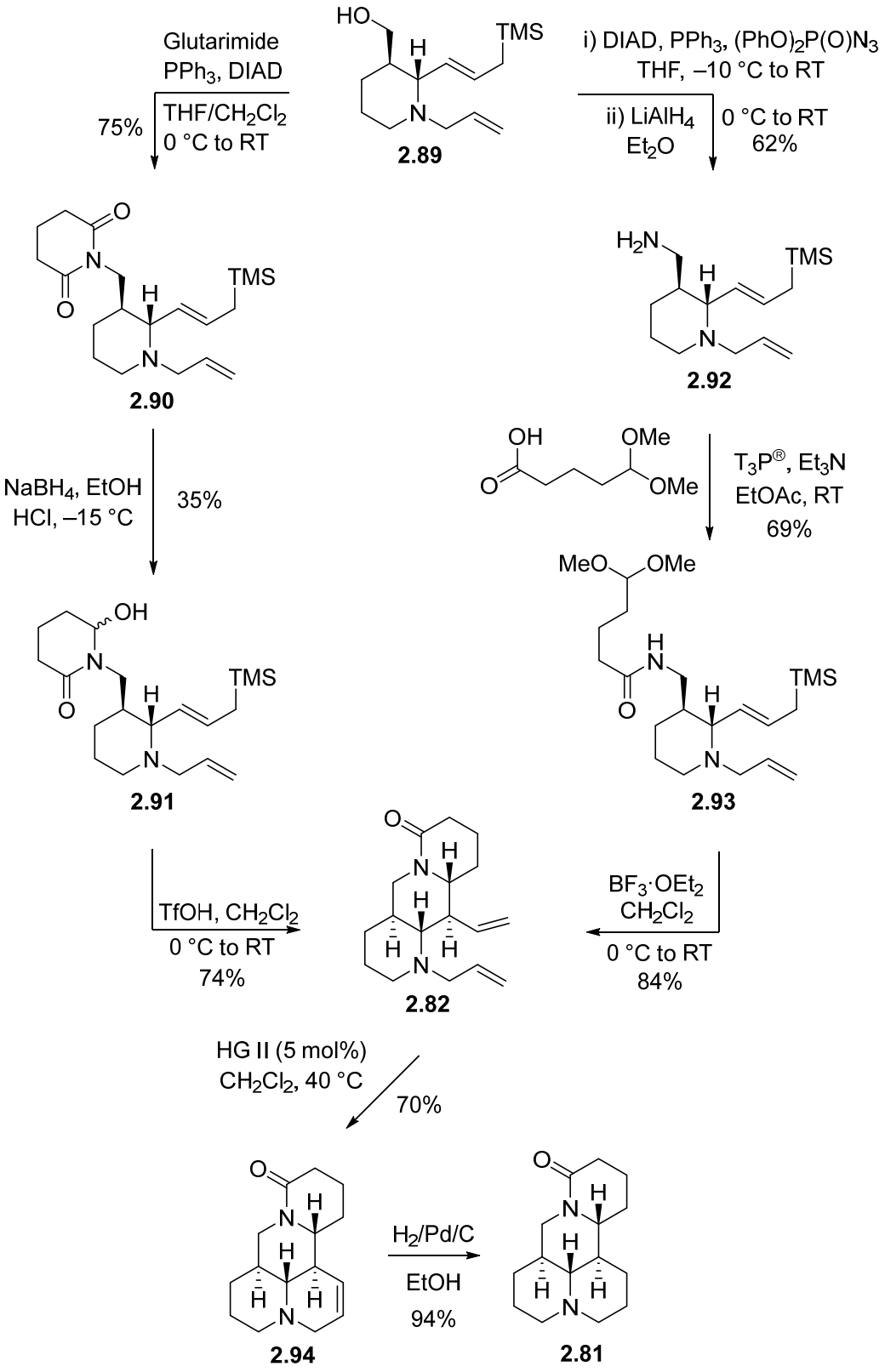
With this key intermediate in hand, attention turned to the completion of the synthesis. Two distinct methods of preparing an *N*-acyliminium precursor were examined, both utilising a Mitsunobu reaction of the pendant alcohol (**Scheme 2.14**). The first sequence attempted was the substitution of glutarimide to give imide **2.90**, which could be reduced in the presence of $NaBH_4$ to hemiaminal **2.91**. Addition of TfOH would promote the *N*-acyliminium cyclisation in order to give tricycle **2.82**, with all of the needed stereochemistry for **2.81** set. The stereochemical outcome of this reaction can be rationalised by considering a *trans*-decalin chairlike arrangement **2.93** in the transition state (**Figure 2.11**).[174]



2.93

Figure 2.11: Proposed transition state for the *N*-acyliminium reaction towards **2.82**.

Whilst successful in providing the desired diene **2.82**, the yield of the reductive step between **2.90** and **2.91** was lower than desired. As such, an alternative route was designed. One-pot Mitunobu azidation and reduction yielded amine **2.92**. Coupling this primary amine to 5,5-dimethoxypentanoic acid in the presence of propylphosphonic anhydride (T3P®) gave acetal **2.93**, a viable *N*-acyliminium precursor in a much better yield over the equivalent two steps. Treatment with Lewis acid once again provided tricycle **2.82**, this time in a much improved yield compared to the original transformation. Having now established an acceptable route to intermediate **2.82**, the synthesis could be completed: RCM using Hoveyda-Grubbs II provided 8,9-dehydoallomatrine **2.94**, which was successfully hydrogenated over Pd/C to afford **2.81** in 13% overall yield over 13 steps.

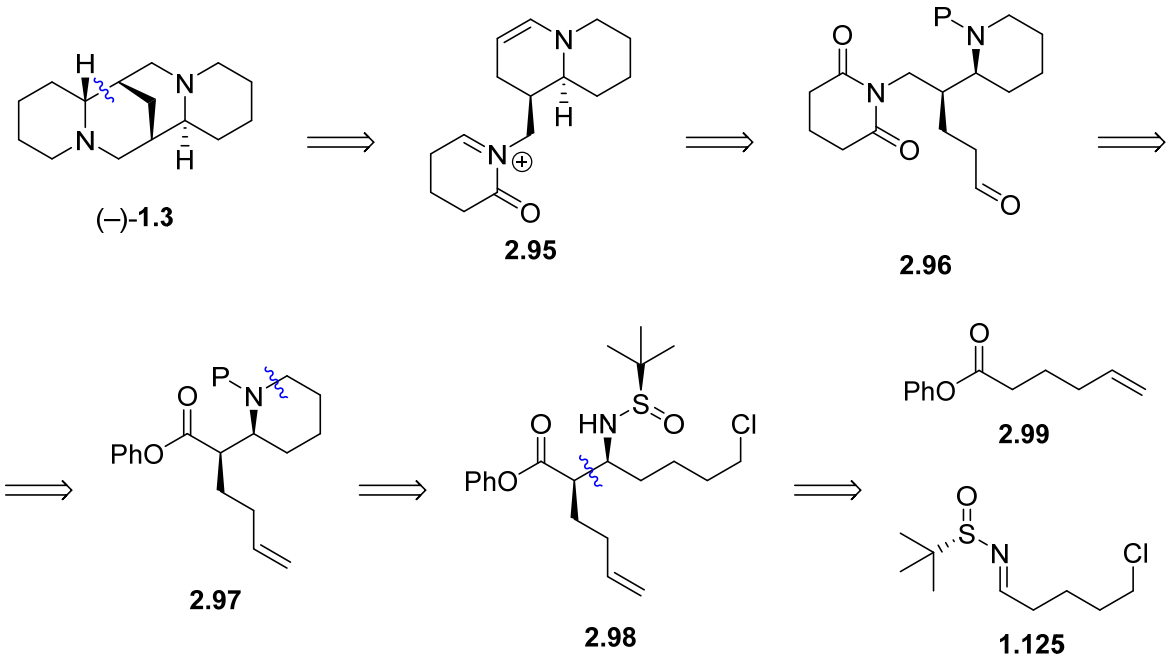


Scheme 2.14: Completion of the total synthesis of (+)-allomatrine ((+)-**2.81**), proceeding *via* the use of two different *N*-acyliminium processes.

2.4.4 Progress towards the total synthesis of (+)-*β*-isosparteine

With one structural isomer of the tetracyclic $C_{15}H_{26}N_2$ series successfully synthesised, work within the group progressed towards the sparteine stereoisomeric series. Initial work within this area was conducted by Alex Ionut-Pop, as part of his Doctoral Thesis.[172] The initial strategy focused on an attempted synthesis of (–)-sparteine (**1.3**) by adapting the *N*-acyliminium approach used in the group's previous total syntheses. The initial retrosynthetic analysis is shown in **Scheme 2.15**, beginning from the highly diastereoselective *syn* imino-aldol reaction between functionalised fragments **2.99** and **1.125** to form adduct **2.98**.

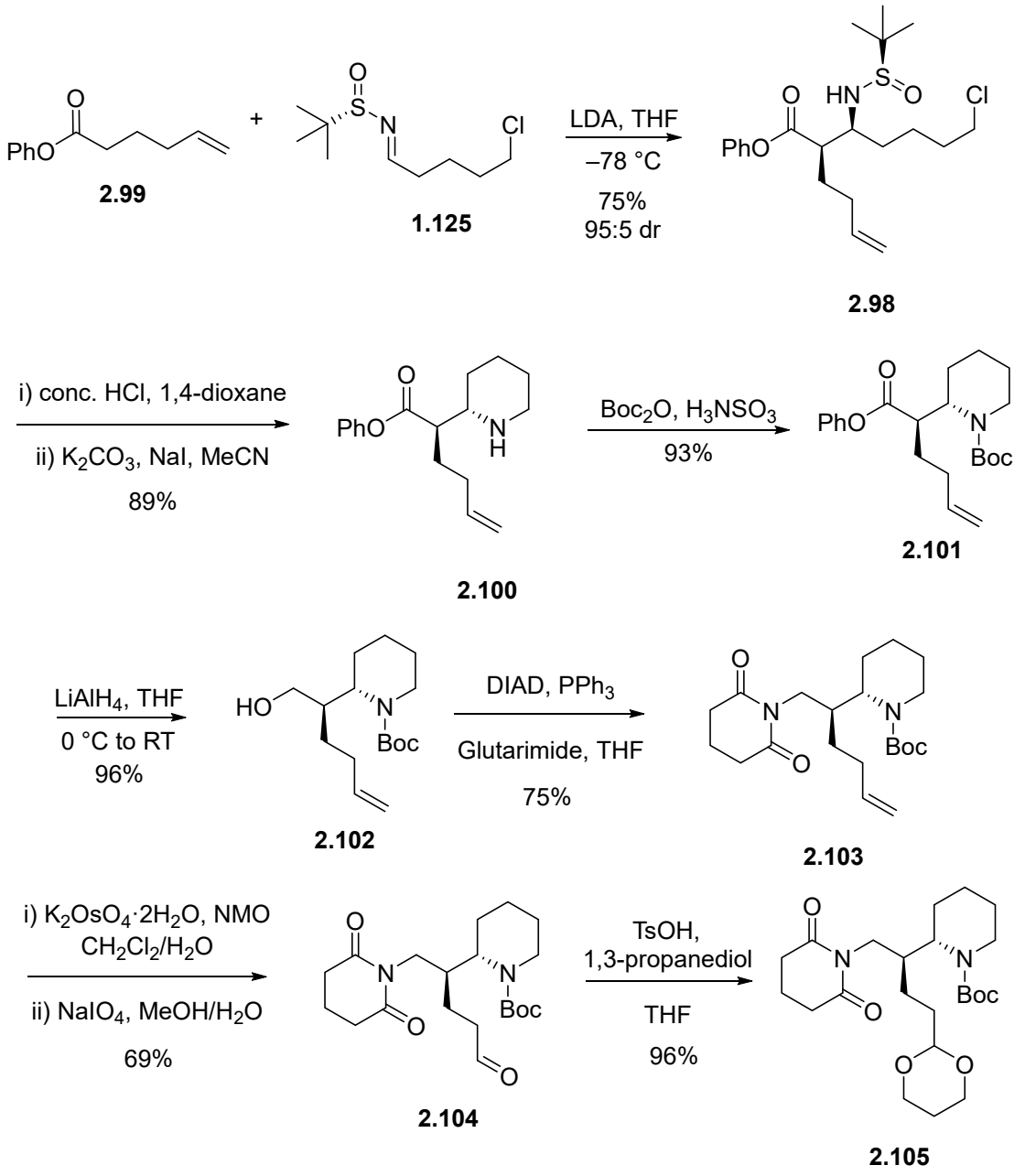
Removal of the sulfinylimine, cyclisation and reprotection would provide piperidine **2.97**, which could undergo reduction and replacement of the ester functionality with glutarimide to provide an alkene, whose latent aldehyde functionality could be unmasked by oxidative cleavage, to give aldehyde **2.96**. Reduction to the corresponding hydroxylactam and treatment with Lewis acid would theoretically provide *N*-acyl iminium **2.95** after initial intramolecular cyclisation to the quinolizidine, which would then further cyclise to providing (–)-**1.3** after amide reduction.



Scheme 2.15: Initial retrosynthetic analysis of (–)-**1.3**.

In order to enact this plan, the functionalised fragments **2.99** and **1.125** were prepared from their corresponding commercially available carboxylic acids. Using the optimised *syn* imino-aldol conditions developed previously, these two fragments were coupled to afford imino-aldol adduct **2.98** in good yield and excellent diastereoselectivity (**Scheme 2.16**). Removal of the sulfinylimine moiety and subsequent cyclisation provided piperidine **2.100**, which was subsequently Boc-protected to give ester **2.101**. Installation of the glutarimide would be effected by the reduction of ester **2.101** to alcohol **2.102**, which was then coupled

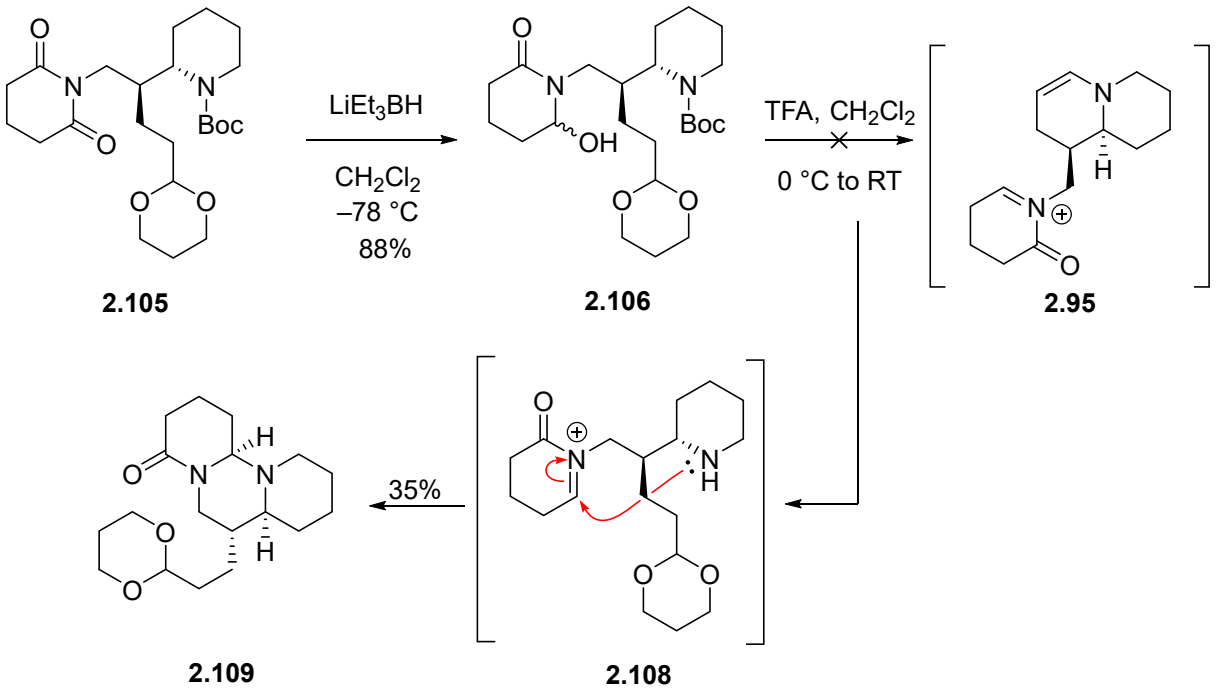
with glutarimide under Mitsunobu conditions to furnish alkene **2.103**. Catalytic ozonolysis and diol cleavage with $NaIO_4$ unmasked aldehyde **2.104**, which was protected as its cyclic acetal **2.105**.



Scheme 2.16: Synthesis of *N*-acyliminium precursor **2.105**, starting from fragments **2.99** and **1.125**.

The switch from $NaBH_4$ to the adaption of a procedure from Grigg using Super-Hydride® ($LiEt_3BH$) afforded hemiaminal **2.106** as a 1:1 mixture of epimers in good yield (**Scheme 2.17**).[175] The subsequent attempt to perform the domino cyclisation to the tetracyclic skeleton through imine **2.107** would not succeed: instead, the *N*-acyliminium was

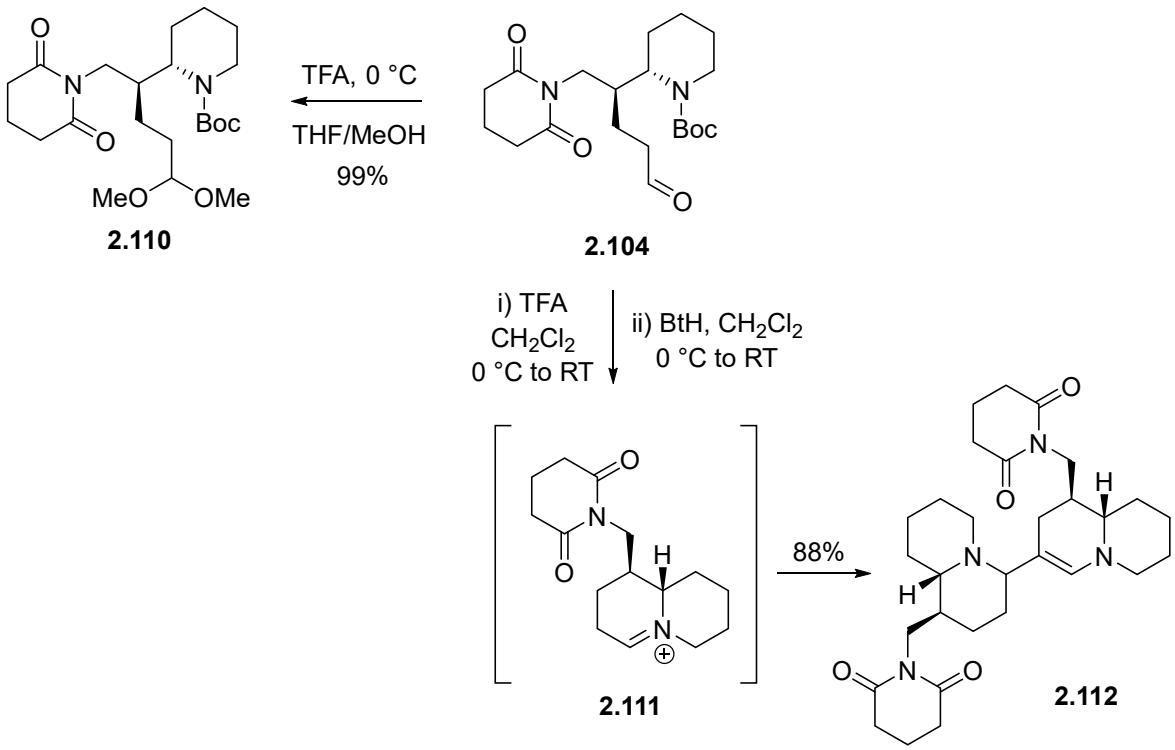
believed to be formed concurrent with Boc-deprotection under the reaction conditions, leading to the undesired intramolecular cyclisation exemplified by **2.108**, resulting in low yield of tricyclic **2.109**.



Scheme 2.17: Outcome of attempted *N*-acyliminium cyclisation from precursor **2.105**.

Whilst this initial attempt was unsuccessful, a further attempt of the N-acyl iminium cyclisation would be attempted *via* modification of a late-stage intermediate: aldehyde **2.104**. Using a method described by Hiemstra *et al.*, it was proposed that the use of BtH could trap an iminium generated *in situ*, which would allow further modification of the intermediate.[176]

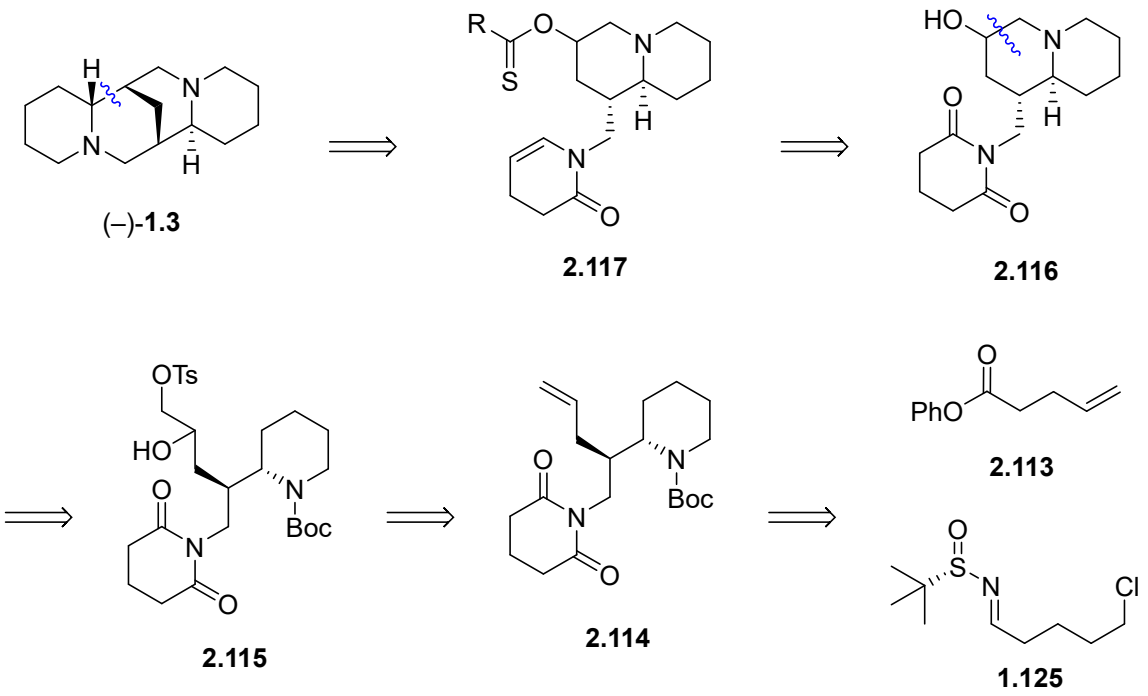
As such, treatment of aldehyde **2.104** with a Brønsted acid would effect a Boc-deprotection and intramolecular cyclisation to a quinolizidine intermediate that could be trapped with BtH. An initial attempt using TFA in THF/MeOH would yield no Boc deprotection; instead realizing a quantitative acetalisation of the aldehyde to afford acetal **2.110** (**Scheme 2.18**). Modification of the reaction conditions to prevent the possibility of acetalisation would effect the desired Boc-deprotection and presumed cyclisation to quinolizidine **2.111**. However, attempts to trap the iminium intermediate with either BtH or MeOH proved unsuccessful; isolating only the dimeric species **2.112** in high yield.



Scheme 2.18: Attempted trapping of the *in situ* generated iminium **2.111** with BtH.

2.4.4.1 Alternate xanthate cyclisation

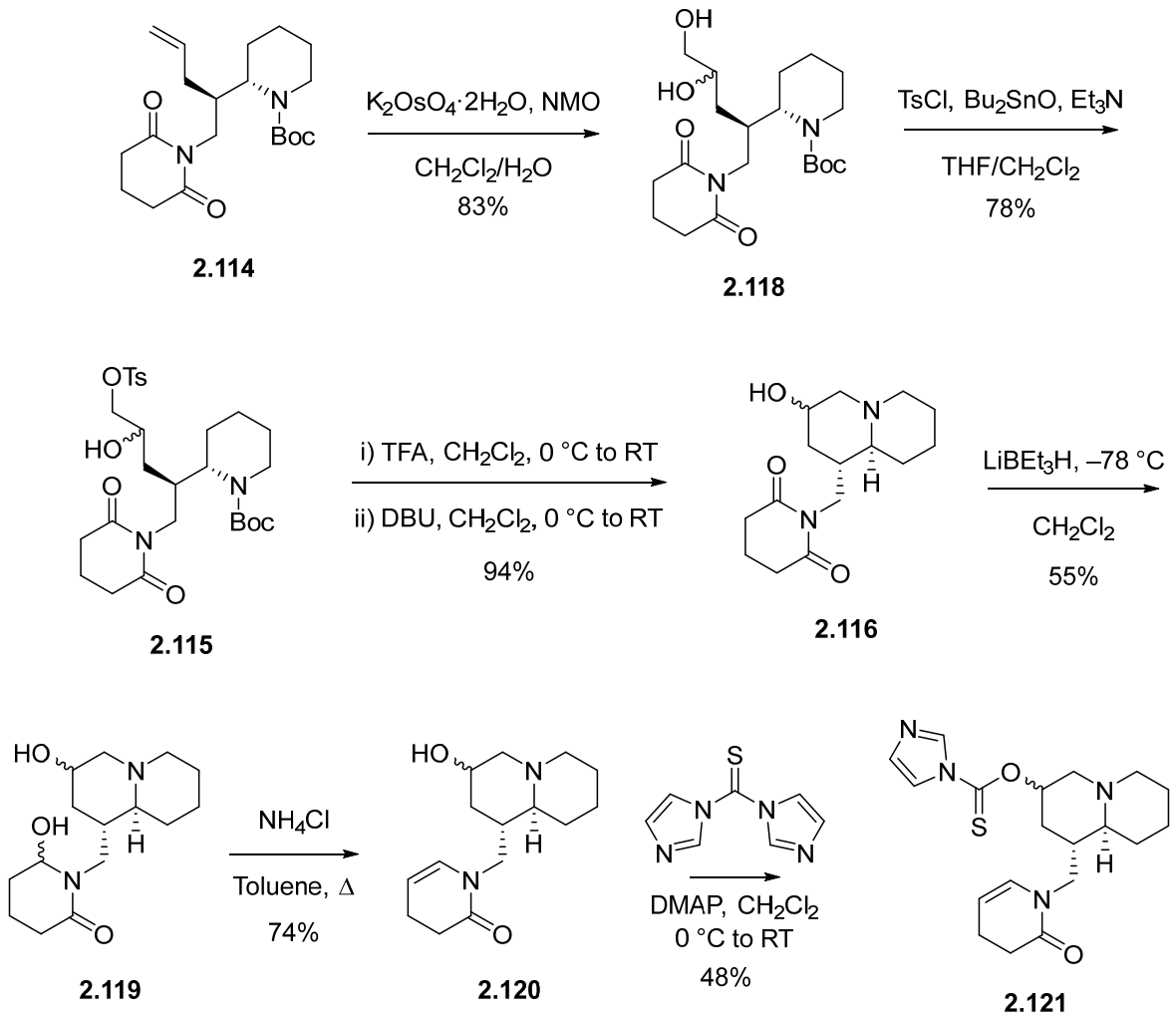
With the desired cyclisation being unable to be realised under the current route, an alternative approach was sought. A radical cyclisation route, as reported by Zard towards the synthesis of the related alkaloid matrine, was thought to be achievable, and would require only small changes to the substrates used previously.[177] An imino-aldol reaction between new phenyl ester **2.113** and *N*-sulfinylimine **1.125** would give, using similar chemical modifications as before, alkene **2.114** (**Scheme 2.19**). Dihydroxylation and selective tosylation of the resultant primary alcohol would afford tosylate **2.115**, which could then be cyclised onto the deprotected piperidine to yield quinolizidine **2.116**. Enamide formation *via* reduction of the imide, and xanthate formation from the secondary alcohol would give radical precursor **2.117**, which could then undergo radical cyclisation to the tetracyclic skeleton, where a final $LiAlH_4$ reduction would provide (–)-**1.3**.



Scheme 2.19: Alternative retrosynthesis of (–)-**1.3** using a radical cyclisation approach.

Using the same approach outlined in **Scheme 2.16**, the use of ester **2.113** and *N*-sulfinylimine **1.125** provided alkene **2.114** in 5 steps and a 31% overall yield. Dihydroxylation of the alkene led to the formation of diol **2.118**, which was transformed into tosylate **2.115** (**Scheme 2.20**). Boc-deprotection followed by cyclisation with DBU afforded quinolizidine **2.116**, with the secondary hydroxyl moiety in place to attach the needed thiocarbamate. Formation of the enamide would commence first: treatment of the imide with $LiBEt_3H$ as before provided hemiaminal **2.119**, which upon heating with NH_4Cl afforded enamide **2.120** in good yield over the two steps. With this in place, the reaction of the alcohol with 1,1'-thiocarbonyldiimidazole assisted by DMAP furnished the desired radical precursor **2.121**.

Two sets of conditions were employed to initiate the radical cyclisation. First, sub-stoichiometric lauroyl peroxide in refluxing benzene was used, however no evidence of the desired cyclisation was obtained, and the starting material degraded under the reaction conditions. Secondly, standard Barton-McCombie conditions were trialled – the use of AIBN and tris(trimethylsilyl)silane under microwave conditions also failed to enact the desired cyclisation, also leading to degradation of the starting material. As such, a revised approach to the synthesis of the sparteine-type tetracyclic lupin alkaloids was needed.



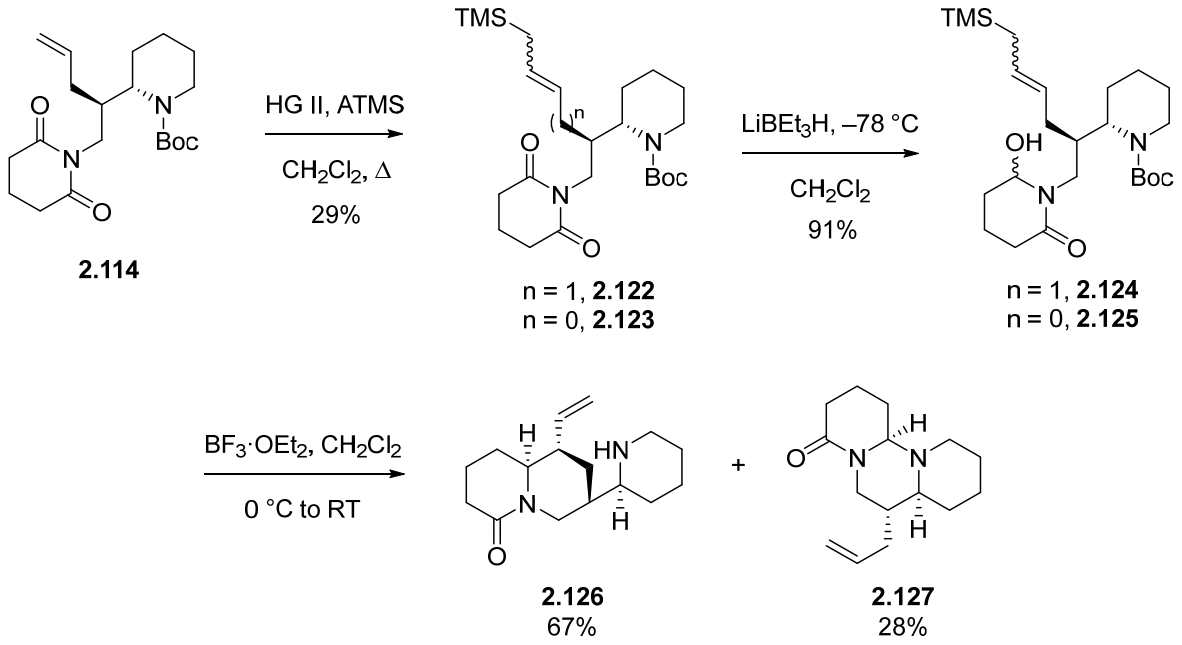
Scheme 2.20: Synthesis of radical cyclisation precursor **2.121** from key intermediate **2.114**.

2.4.4.2 Allylsilane approach

It was thought returning to the use of the allylsilane *N*-acylimminium mediated approach used for the syntheses of (+)-allomatrine (**Section 2.2.3**) that this problem could be solved. Indeed, one of the intermediates used in the radical cyclisation approach could be amenable to a late-stage modification, in order to effect the total synthesis. As such, alkene **2.114** would be subjected to standard olefin metathesis conditions in order to provide an inseparable mixture of alkenes **2.122** and **2.123**, both as 2:1 mixtures of E/Z isomers, in fairly low yield (**Scheme 2.21**). The loss of one carbon unit in the course of the metathesis step is thought to be related to catalyst degradation, and will be the subject of future discussions (**see Section 5.2**).

Regardless of the low yield in this step, the lack of material due to this being a late-stage modification led to expeditious exploration of further steps of the synthesis. This mixture of alkenes **2.122** and **2.123** was therefore taken forward to the *N*-acyliminium precursors **2.124** and **2.125**. Treatment of this mixture with $BF_3{\cdot}OEt_2$ would afford two

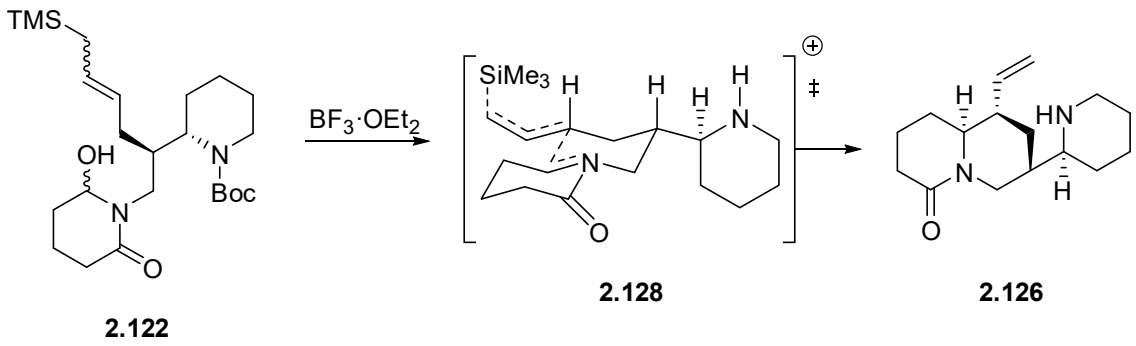
products, the desired quinolizidone structure **2.126**, and an undesired tricyclic compound **2.127**.



Scheme 2.21: Modification of intermediate **2.114** in order to investigate an *N*-acyliminium cyclisation.

The presence of undesired by-product **2.127** can be explained by the effect of Boc-deprotection under the reaction conditions – concomitant formation of the desired iminium would allow for an intramolecular cyclisation to occur from the deprotected piperidine, resulting in the formation of **2.127** after protodesilation of the allylsilane moiety. Whilst an unproductive cyclisation, the relative rate of allylsilane attack onto the iminium would appear to be faster, resulting in a larger percentage of the desired quinolizidone skeleton **2.126**.

However, quinolizidone **2.126** would offer insight into the rest of this synthesis – the stereochemistry obtained from the cyclisation would allow for the total synthesis of (+)-*β*-isosparteine (**1.6**), not (–)-spartiene (**1.3**). The formation of the *syn*-stereochemistry - and the isolation of only one diastereoisomer – can again be readily explained by considering a chair-like transition state **2.128** for the reaction (**Scheme 2.22**).



2.122 **2.128** **2.126**

Scheme 2.22: Proposed transition state **3.64** for the *N*-acyliminium reaction**.**

2.5 Conclusions

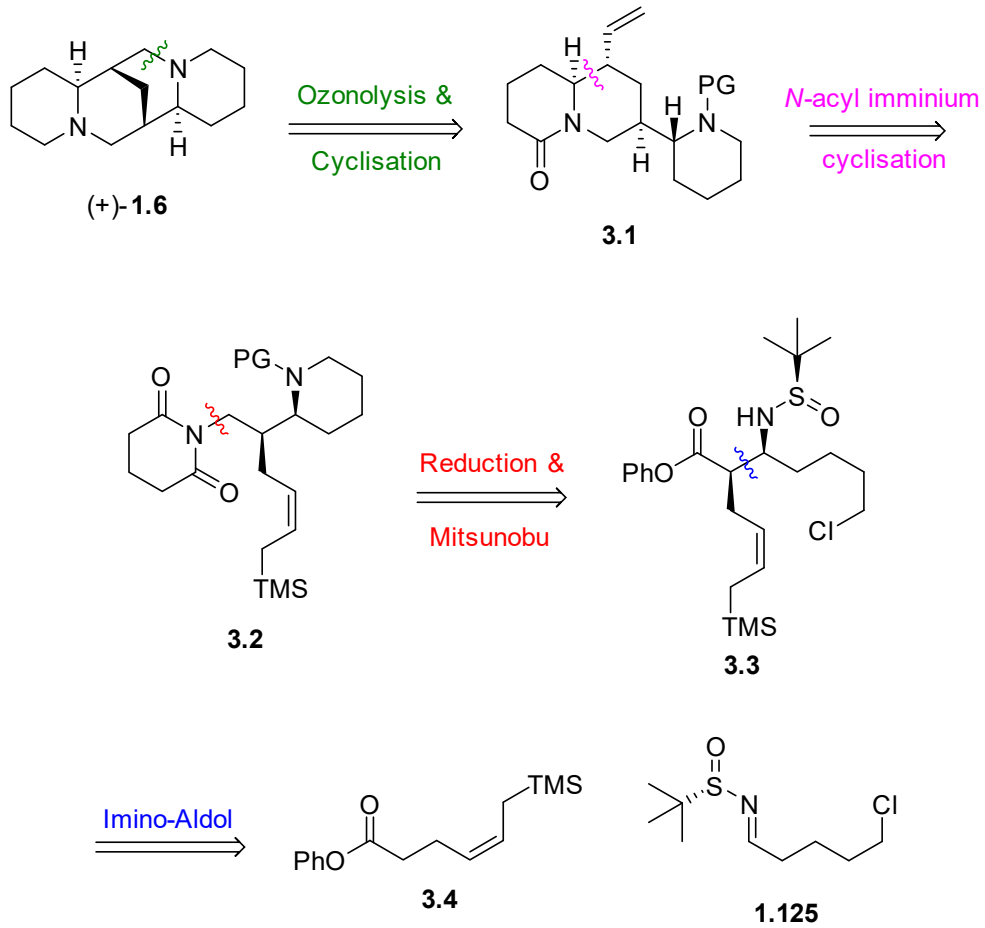
The development, syntheses and uses of two important *N*-sulfinylamide auxiliaries within the literature – **2.4** and **2.5** – have been presented within this chapter. Their transformation into *N*-sulfinylimine compounds, as well as a brief overview of their electronic and structural properties has also been included. Their use as important building blocks for a variety of chiral nitrogen-containing compounds has also been expanded upon.

The Brown group's approach to the Lupin alkaloids relies heavily on *N*-sulfinylimines, and as such a review of past syntheses of several alkaloids - (−)-epilupinine ((−)-**2.70**), (−)-tashiromine ((−)-**2.69**) and (+)-allomatrine ((+)-**2.81**) - is also included. Particular note is paid to the two key steps in their synthesis, that of the highly diastereoselective imino-aldol reaction and *N*-acyliminium cyclisations. Finally, a summary of the group's previous approaches to (+)-*β*-isosparteine ((+)-**1.6**) is divulged.

Chapter 3 The total synthesis of (+)-*β*-isosparteine

3.1 Project aims and initial approach

Given the relative success in the *N*-acyliminium approach to quinolizidine **2.126**, the precedent for a total synthesis of (+)-*β*-isosparteine ((+)-**1.6**) would appear to be set. However, a repetition of the overall route thus far would be suboptimal, due to the yield of the olefin metathesis step. Our thoughts were drawn towards redesigning the synthesis, and introducing the allylsilane moiety as part of the initial imino-aldol fragments. It would also be prudent to replace the Boc protecting group with one that would survive the *N*-acyliminium step, in order to eliminate the reaction pathway to produce tricycle **2.127**.



Scheme 3.1: Retrosynthetic analysis of (+)-**1.6**, with the four key steps emphasised.

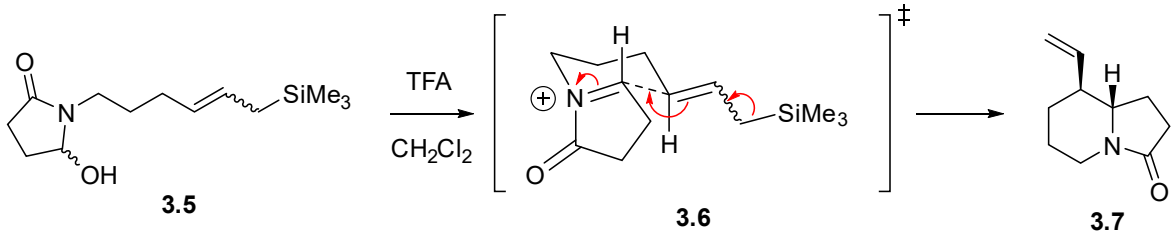
As such, the approach to (+)-**1.6** was designed in order to take advantage of the early inclusion of an allylsilane motif, and also to "design out" some of the complications of the earlier approach. It was therefore envisaged that (+)-**1.6** could be constructed by the unmasking of a primary alcohol from alkene **3.1**, followed by its transformation into a leaving group for attack by the deprotected piperidine (**Scheme 3.1**). Quinolizidone **3.1** would itself be made by the key *N*-acyliminium cyclisation, requiring the use of imide **3.2** as the

precursor. As seen previously, this type of structure could be made from the Mitsunobu reaction of the fully reduced ester **3.3**, which would also be used to form the initial piperidine by base-assisted alkylation of the deprotected amine. Finally, **3.3** would be the logical consequence of a *syn*-selective imino-aldol reaction of fragments **3.4** and **1.125**.

3.2 Fragment syntheses

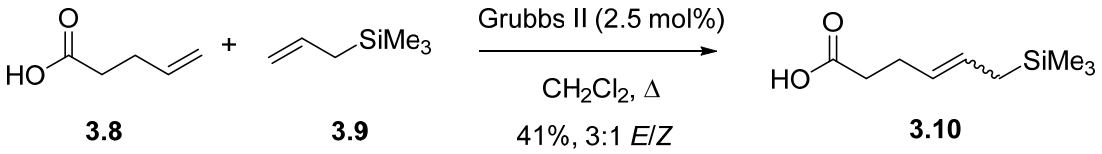
3.2.1 Design

In designing this new synthesis, one of the key considerations was whether the alkene geometry of **3.4** was a significant factor. The examination of the proposed transition state **2.128** would appear to indicate that the alkene geometry is irrelevant: the allylsilane moiety will adopt a *pseudo*-equatorial geometry in the transitions state, regardless of whether the alkene is *E* or *Z*. This conclusion is backed up by work of McElhinney *et al*., in the total synthesis of the related alkaloid tashiromine.[178] They would show that the *N*-acyliminium cyclisation of an allylsilane **3.7** would proceed with a high degree of stereocontrol, where the nuclophillic addition of the allylsilane moiety would occur through chair-like transition state **3.8** (Scheme **3.2**). A 96:4 mixture of *syn* and *anti* diastereoisomers of **3.9** was generated in 85% yield, starting from a 3:1 mixture of *E*/*Z* alkene isomers.



Scheme 3.2: *N*-acyliminium cyclisation of **3.7**, with proposed transition state **3.8** shown.

As such, the inclusion of either a *cis* or *trans* alkene becomes a matter purely of design choice – which would be easiest to install within the phenyl fragment? A relatively easy approach would appear to be the direct olefin metathesis of acid **3.8** and allyltrimethylsilane **3.9**, affording acid **3.10**, which could easily be esterified (**Scheme 3.3**). Indeed, this was an approach carried out by Alex Ionut-Pop in the last weeks of his Doctoral studies, albeit with a relatively low yield.[172] The isolation of the alkene in low yield was thought to be due to the relatively fast rates of homodimerization of both the terminal olefin and allylsilane, which is a common issue within cross metathesis.[179] As is also typical of olefin cross-metathesis, an inseparable mixture of *E*/*Z* alkenes were obtained. Whilst not detrimental within the new route, the use of a sole alkene isomer within the synthesis would be a boon, greatly simplifying analysis and perhaps purifications.



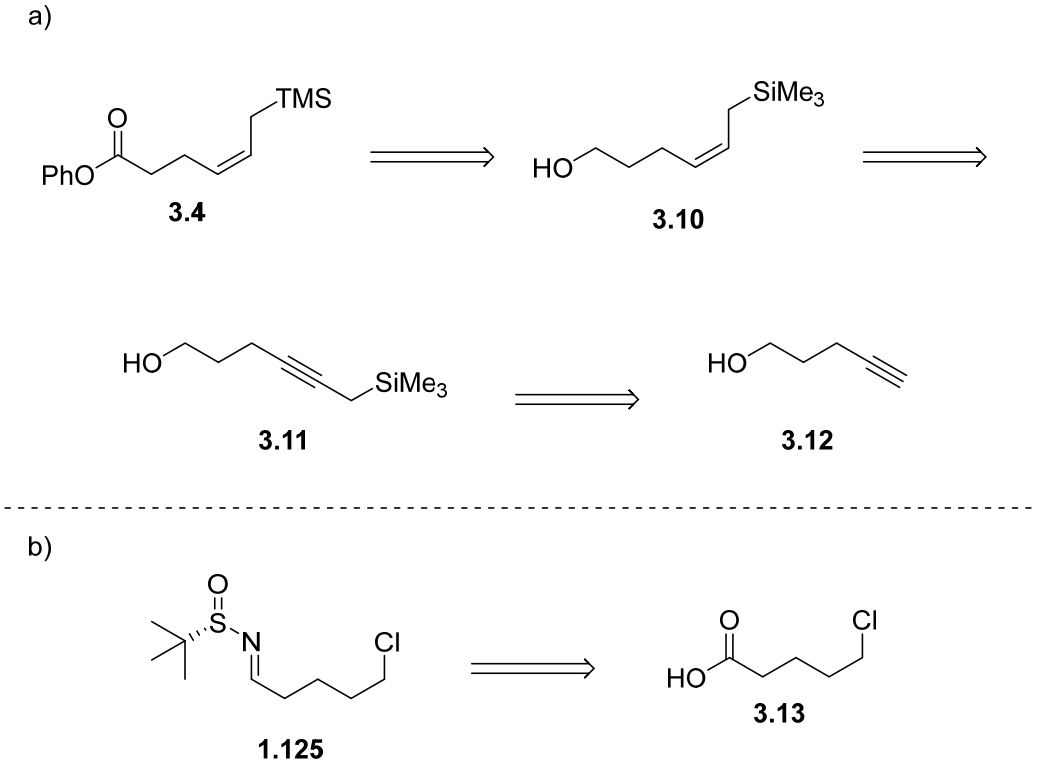
3.8 **3.9** **3.10**

Scheme 3.3: Olefin metathesis attempt towards ester **3.4**.

As such, it was decided to attempt to synthesise **3.4** with *cis* geometry, as a route that would be operationally simple, and potentially amenable to scale up. One of the more obvious routes to a *Z*-alkene is that of reduction of an alkyne under Lindlar conditions. The poisoned Pd catalyst effects the reduction of triple bonds to corresponding double bonds, with minimal over-reduction. Alkene hydrogenation itself is a stereospecific process, occurring via *syn*-addition of hydrogen to give the *cis* alkene preferentially. Due to the fairly robust nature of a Lindlar hydrogenation, it was initially decided to include this in the route, thereby necessitating the inclusion of an alkyne.

The retrosynthetic analysis of **3.4** would therefore start from commercially available alcohol **3.12** (**Scheme 3.4a**). Protection, alkylation and deprotection would provide silane **3.11**, which could then be reduced under Lindlar conditions to the *Z*-alkene **3.10**. Oxidation and esterification would then provide the desired phenyl ester **3.4**.

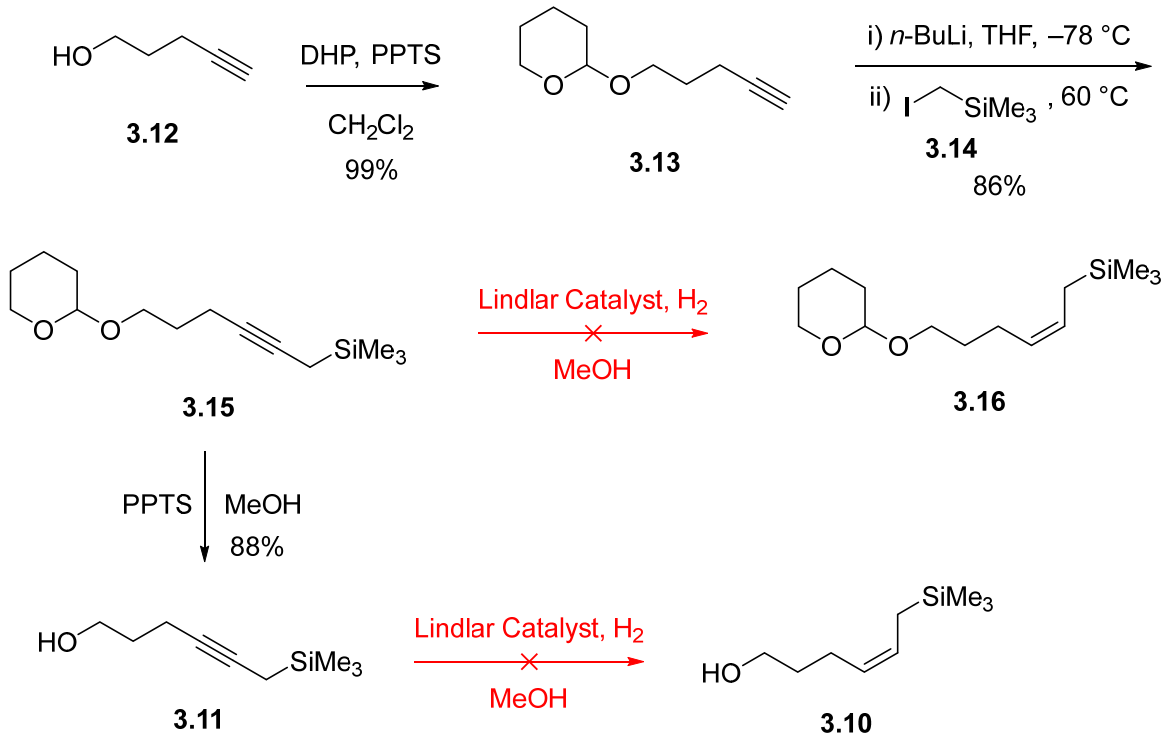
The synthesis of the *N*-sulfinylimine fragment, however, would be more straightforward. As such, the general route previously established for the synthesis would be followed, starting from acid **3.13**.[172] Conversion to the corresponding Weinreb amide would allow condensation to take place between the Ellman sulfinylamine **2.25** and 5-chloropentanal, generated *in situ* from reduction of the Weinreb amide (**Scheme 3.4b**).



Scheme 3.4: Fragment retrosyntheses. a) Ester fragment **3.4** from commercial alcohol **3.12**. b) *N*-sulfinylimine fragment from acid **3.13**.

3.2.2 Synthesis of phenyl ester 3.4

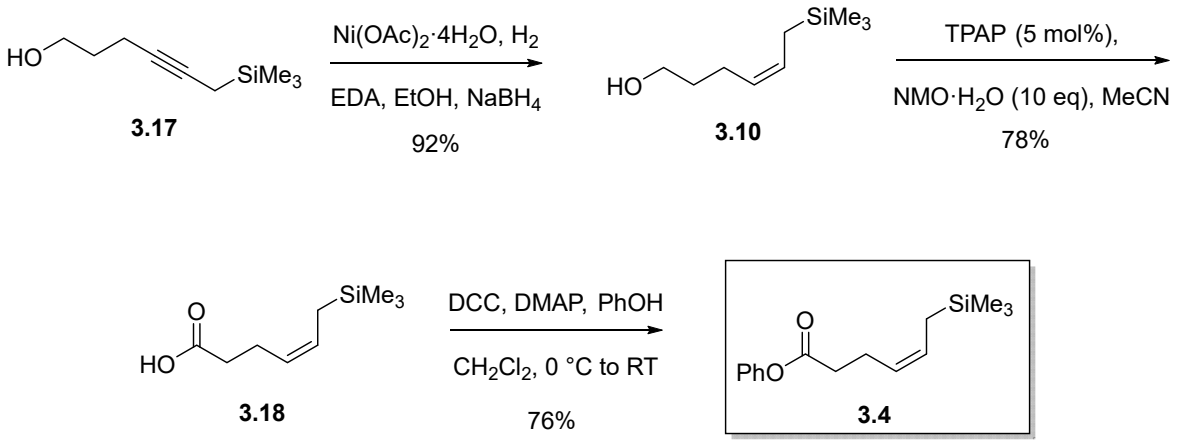
With a plan in place, the start of the total synthesis began in earnest. 4-Pentyn-1-ol **3.12** was protected as THP ether **3.13** in order to allow the subsequent alkylation of the alkyne using iodide **3.14**, ultimately providing alkyne **3.15** (**Scheme 3.5**). Alkyne **3.15** was subjected to a standard Lindlar hydrogenation, where disappointingly no reaction was observed to take place, even after several attempts. The initial conclusion reached was that the THP ring of **3.15** may hinder the reaction; disrupting the ability of the substrate to coordinate to the catalyst surface. As such, **3.15** was deprotected in order to trial the hydrogenation of alcohol **3.17**. However, this approach too would lead to failure, and **3.17** proved as capricious as the protected derivative to reduce under these conditions.



Scheme 3.5: Initial synthesis of protected alkyne **3.15** and unsuccessful attempts at Lindlar reduction.

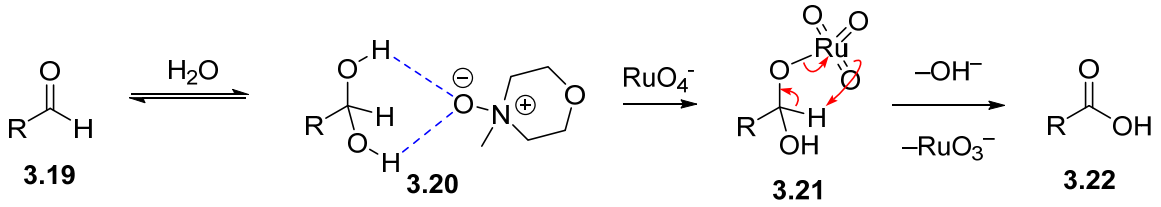
This was especially surprising, given that literature precedent existed for the reduction of **3.17** in this fashion.[180] This opens up the possibility of the use of a sub-standard catalyst batch, or perhaps unidentified impurities in the starting materials, leading to further poisoning of the catalyst. However, further examination of the literature also unveiled an alternative set of conditions for this hydrogenation; the use of so-called "P-2 Ni", first reported as a hydrogenation catalyst by Brown.[181-182] This hydrogenation involves the preparation of a Nickel-boride catalyst *in situ via* the reduction of $Ni(OAc)_2{\cdot}4H_2O$ with a methanolic solution of $NaBH_4$, and has been shown to be a highly versatile hydrogenation catalyst.[183] The addition of EDA to the reaction has also been shown to drastically improve the hydrogenation selectivity, approaching >100/1 *Z*/*E*. Pleasingly, substrate **3.11** has also been reduced using this catalyst by Hiemstra and Speckamp.[174]

The alternative hydrogenation approach would be attempted on alcohol **3.17**, and to great relief the desired *Z*-alkene **3.10** was isolated in excellent yield, with minimal (<5% by ^{1}H NMR) over-reduction (**Scheme 3.6**). The rest of the fragment synthesis would pass without incident: oxidation of alcohol **3.10** to acid **3.18** was achieved by the use of a modification of the standard TPAP/NMO oxidation of alcohols to aldehydes by the use of $NMO{\cdot}H_2O$, as published by Stark.[184]



Scheme 3.6: Completion of the synthesis of fragment **3.4**.

In their communication, Stark proposes that the NMO·H_2O plays a dual role, acting not only as co-oxidant in order to turn over the Ru(VII) catalyst, but also to stabilise the aldehyde hydrate intermediate needed to further oxidise the substrate (**Scheme 3.7**). After initial oxidation of alcohol to aldehyde **3.19**, the NMO could act to stabilise the hydrate in a manner akin to complex **3.20**, which would allow a second action of the regenerated Ru(VII) oxidant to complete the oxidation to acid **3.22**, proceeding *via* complex **3.21**.



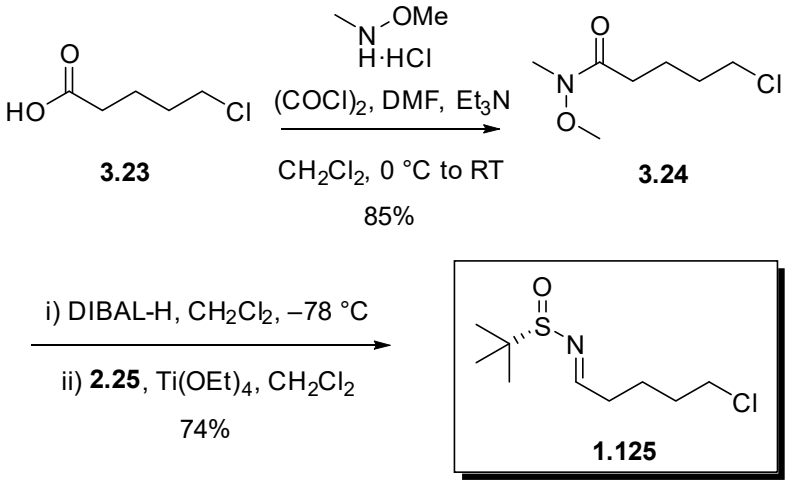
Scheme 3.7: Proposed mechanism for the NMO·H_2O assisted TPAP oxidation of aldehydes to carboxylic acids.

Adapting the methodology would allow access to acid **3.18** in good yield, and proved amenable to larger scale. It is worth noting that several different oxidation steps were attempted on **3.10**, including oxidation by IBX, TEMPO, PDC and under Swern conditions. However, these methods either proved lower-yielding, led to degradation of the starting material, or proved too unwieldy to use in larger scale reactions. Finally, esterification of acid **3.18** under standard Steglich conditions would furnish the desired phenyl ester fragment **3.4**, in 41% overall yield over 6 steps. The design of the synthesis was robust enough to provide **3.4** on a multigram scale, with over 10 g of substrate able to be brought through.

3.2.3 Synthesis of *N*-sulfinylimine 1.125

With the desired phenyl ester fragment **3.4** in place, attention turned to the preparation of *N*-sulfinylimine **1.125**. The synthesis of this is well practised within the group, as it has been the foundation for several previous investigations of the lupin alkaloids. As such, the

standard protocol for its synthesis was followed (**Scheme 3.8**).[185] Formation of Weinreb amide **3.24** from 5-chlorovaleric acid (**3.23**) allowed access to 5-chloropentanal *in situ via* DIBAL-H reduction. Condensation with Ellman auxiliary **2.25** afforded the desired *N*-sulfinylimine fragment in 63% yield over the two steps.



Scheme 3.8: Synthesis of *N*-sulfinylimine **1.125**.

3.3 Towards the *N*-acyliminium precursor

3.3.1 Imino-aldol reaction and piperidine cyclisation

With the two fragments **3.4** and (+)-**1.125** in hand, the next step was to combine them using a highly diastereoselective imino-aldol reaction. Using conditions developed within the group previously (*vide supra*), the lithium enolate of **3.4** was reacted with imine (+)-**1.125** to provide adduct **3.3** in high yield and a 95:5 d.r. (*syn*/*anti*) (**Scheme 3.9**). The d.r. of the reaction was calculated by the integration of the NH signal of **3.3**, as shown in **Figure 3.1**. The major *syn* diastereoisomer is visible at 4.25 ppm, whilst the minor *anti* diastereoisomer is present at 4.50 ppm.

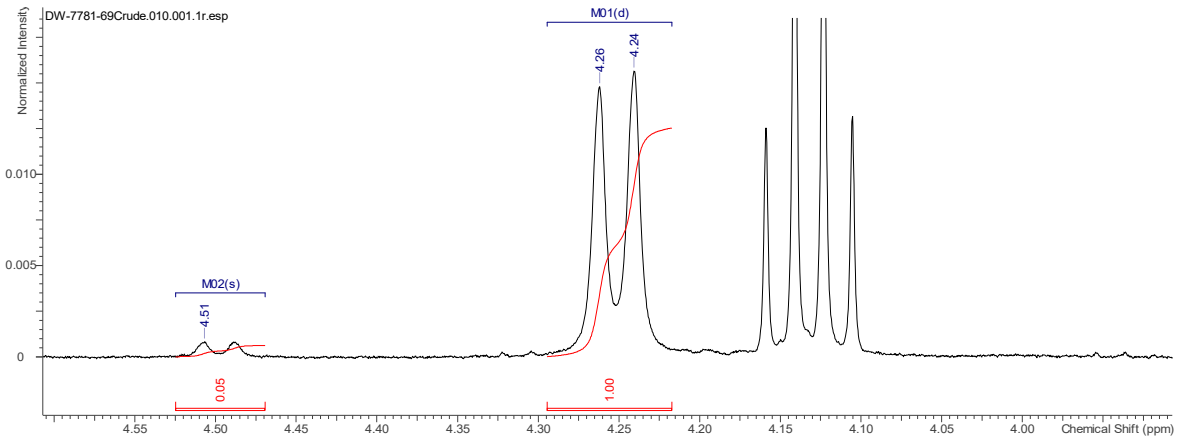
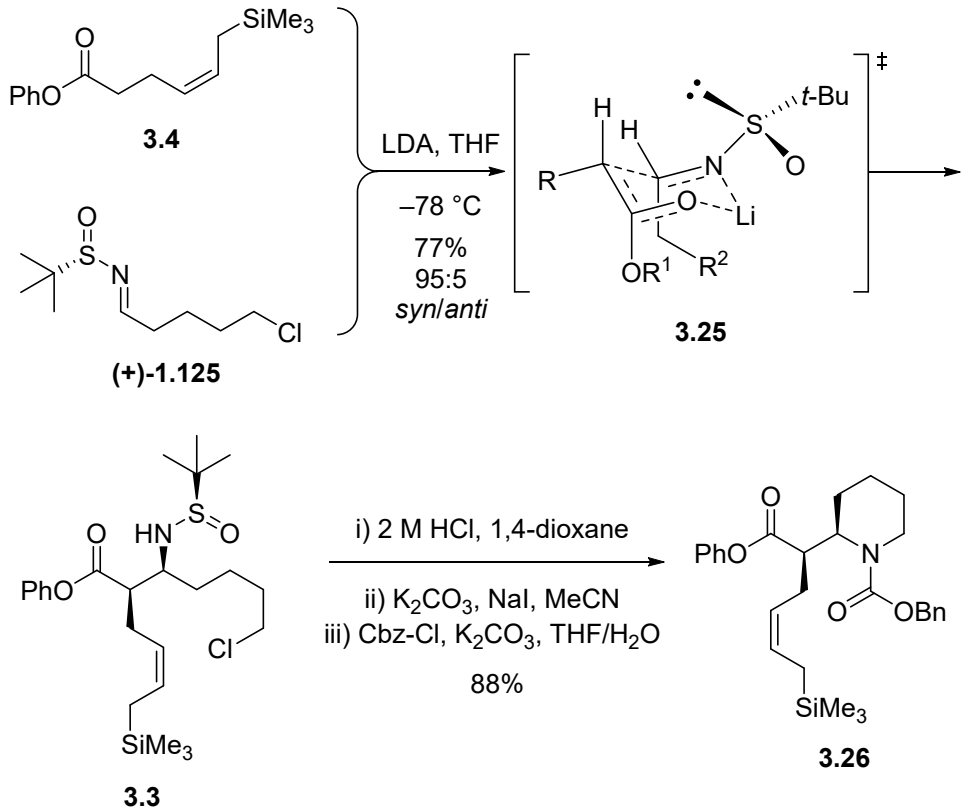


Figure 3.1: Comparison of the NH doublets of the *anti*/syn product in the ^{1}H NMR of the crude reaction mixture of the imino-aldol reaction of **3.4** and **3.7**.

The stereochemical outcome of this reaction can be rationalised by the application of a Zimmerman-Traxler type transition state, as shown by **3.25** (**See Section 2.4.1.1**). The reactants adopt a chair conformation, with the ester carbon chain *pseudo*-equatorial and the imine carbon chain *pseudo*-axial, due to the both *trans* nature of the imine and in order to minimise 1,2-allylic strain.[11-12, 158] The sulfinyl group is aligned as to shield the *Re* face of the imine, thus favouring approach of the enolate from the *Si* face. The initial relative *syn* stereochemistry was tentatively assigned by analogy to previous syntheses reported from this laboratory, with the hope that either a future intermediate would provide an opportunity for an absolute determination, or that on successful completion of the synthesis, the initial assignments would be verified by the comparison of the synthesised (+)-**1.6** to literature data.



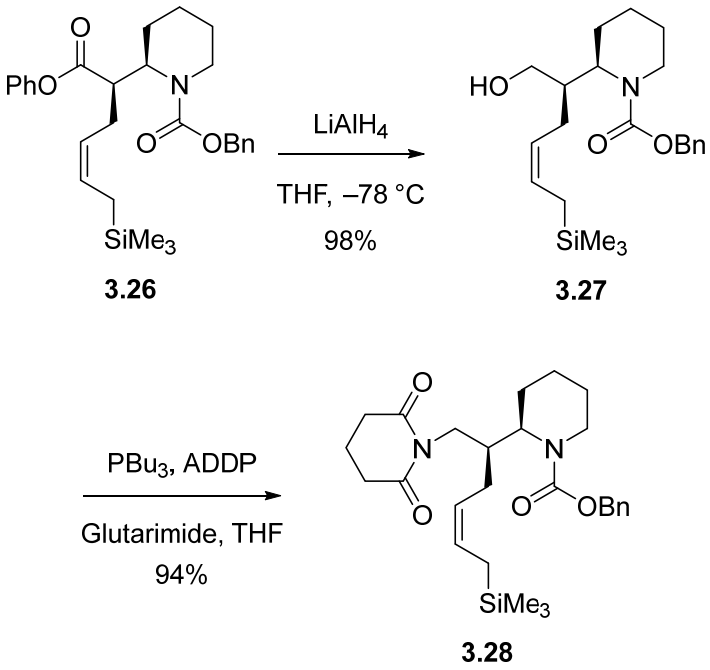
Scheme 3.9: Key imino-aldol reaction to form **3.3** and subsequent cyclisation to protected piperidine **3.26**.

With imino-aldol adduct **3.3** successfully obtained, the next step was to close the first of the four required rings of the tetracyclic structure. Treatment of **3.3** with 2 M HCl effected the deprotection of the sulfinyl auxiliary. Addition of K_2CO_3 and NaI enabled the cyclisation of the unmasked amine with the pre-installed chloroalkyl chain to afford a piperidine. Initial

trials would isolate the piperidine at this point, however the isolated yields were always lower than were expected, attributed to losses in the workup. As such, it was instead decided to add a third step and directly re-protect the free piperidine. The Cbz protecting group was chosen as a viable option, as it would remain unaffected by the rest of the proposed synthetic transformations, including the future *N*-acyliminium cyclisation. This three step protocol would result in the isolation of protected piperidine **3.26** in excellent overall yield.

3.3.2 Preparation of the *N*-acyliminium precursor

With **3.26** in hand, the next step would be the installation of the necessary imide motif to enable the *N*-acyliminium cyclisation. Reduction of the ester **3.26** to the corresponding alcohol **3.27** proceeded smoothly in near quantitative yield, allowing the use of a Mitsunobu reaction to install the needed glutarimide (**Scheme 3.10**).



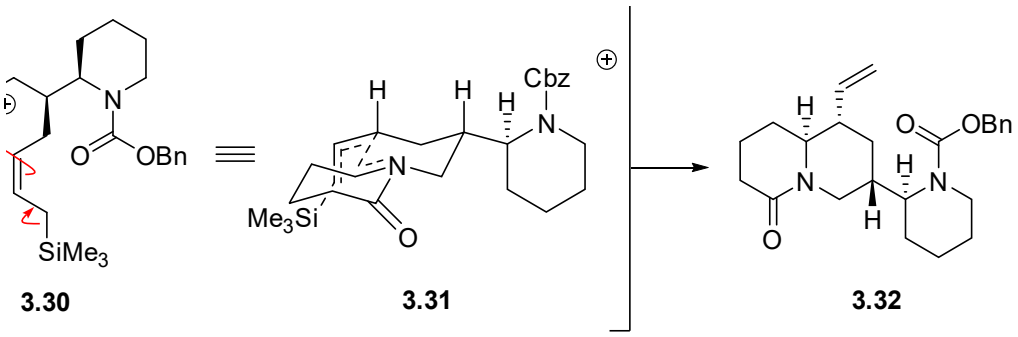
Scheme 3.10: Synthesis of *N*-acyliminium precursor **3.28**.

As with many Mitsunobu protocols, several different azo coupling partners were available to us, such as DEAD and DIAD, which are typically used in this type of reaction. DEAD however has fallen out of favour in recent years, due to the associated risks beholden to this chemical, such as its shock sensitivity and tendency to be explosive at elevated temperatures.[186] Whilst DIAD is much safer, both of these reagents also have a propensity to complicate purification due to the presence of several by-products, such as: alkylated hydrazine derivatives due to incomplete reaction; the starting material itself; and also the stochiometric urea byproduct, which is often soluble in the reaction medium. This has necessitated the development of newer azo coupling partners.[187]

We were particularly drawn to one such reagent, ADDP.[188] This has been noted to work particularly well with pronucleophiles that have pK_a values greater than 11. A pK_a value of 11.75 has been determined for glutarimide, and as such would fit into this category.[189] Another benefit is that the urea byproduct is known to precipitate out in THF, which aides in purification. Drawbacks of ADDP are that the reagent is more expensive than DIAD, and is also best paired with a more σ-donating phosphine, such as PBu_3. Using this combination of phosphine and azo reagent, imide **3.28** was obtained in excellent yield, after an initial trituration with hexane and subsequent chromatographic purification.

3.4 *N*-acyliminium cyclisation and completion of the synthesis

With precursor compound **3.28** successfully obtained, the synthetic endgame could now be enacted. Using the conditions previously employed for the synthesis of (+)-allomatrine,[11] treatment of imide **3.28** with Super-Hydride® accessed hemiaminal **3.29** (**Scheme 3.11**). However, unlike the previous approaches towards (–)-sparteine (*vide supra*), this intermediate was not isolated, due to stability concerns – it was feared that over long time periods, premature elimination of the hydroxyl group would lead to enamine formation, rendering the substrate inert to the desired cyclisation.

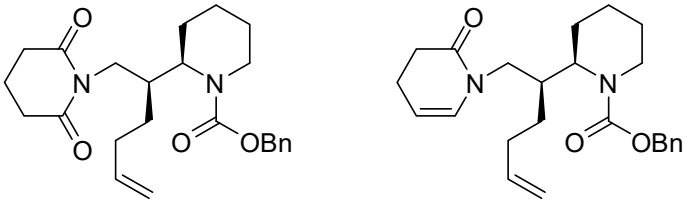


Scheme 3.11: *N*-acyliminium cyclisation to provide quinolizidone **3.32**.

As such, **3.29** was immediately converted to quinolizidone **3.32** by reaction with the Lewis acid $BF_3{\cdot}OEt_2$. Disappointingly, the yield for this two-step process was lower than anticipated at 54%. However, after purification, only one diastereoisomer of **3.32** was isolated, and subsequent work on this cyclisation by Xiang Lyu as part of a synthesis of (+)-

sparteine ((+)-**1.3**) would add support to there being a sole diastereomeric product from this step, rationalised by the favoured transition state **3.31**.[185]

As such, it was prudent to consider possible by-products of the reaction, shown in **Figure 3.2**. Two immediate compounds are apparent, alkene **3.33** and enamide **3.34**. The former is the result of an incomplete reduction by $LiBEt_3H$, whereas the latter is the result of enamine formation in the reaction. Both are assumed to have undergone protodesilylation, given the large excess of Lewis acid used in the reaction.



3.33 **3.34**

Figure 3.2: Possible by-products from the *N*-acyliminium cyclisation.

^1H NMR analysis of the crude reaction mixture proved capricious, due to signal broadening in the NMR. This is expected to be caused by amide rotomers, present due to the Cbz protecting group. As such, we turned to MS analysis in order to probe the course of the reaction further. Analysis of the crude ESI^+ MS would prove to be the key to deciphering the course of the reaction in this instance (**Figure 3.3**). Due to the presence of only two peaks in the mass spectrum, that of product at 3.93 min and a peak indicative of byproduct **3.33** at 4.26 min, the tentative conclusion drawn was that the reductive step was suspect in this transformation. It is possible, however, that under electrospray conditions, the observed ions are the result of degradation processes during sample acquisition. Unfortunately, lack of material this late into the synthesis did not allow for any further determination.

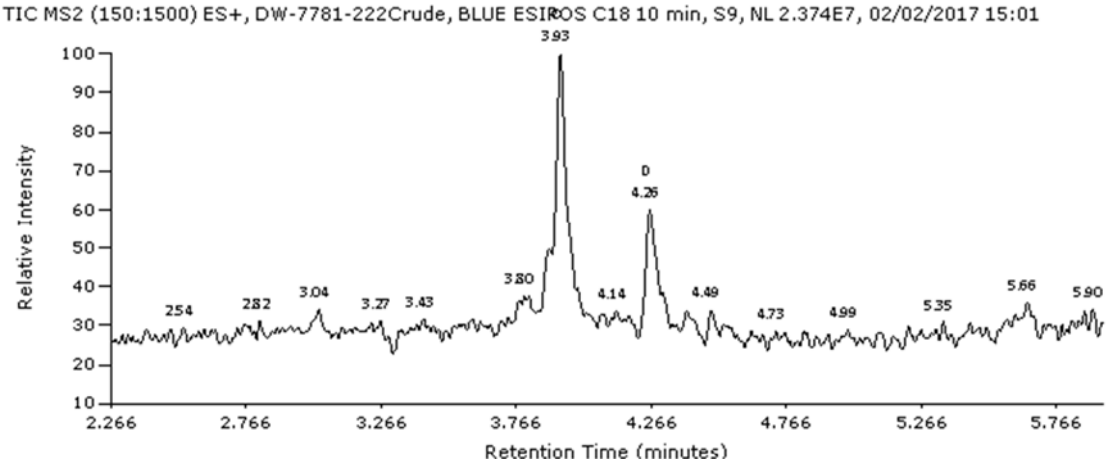
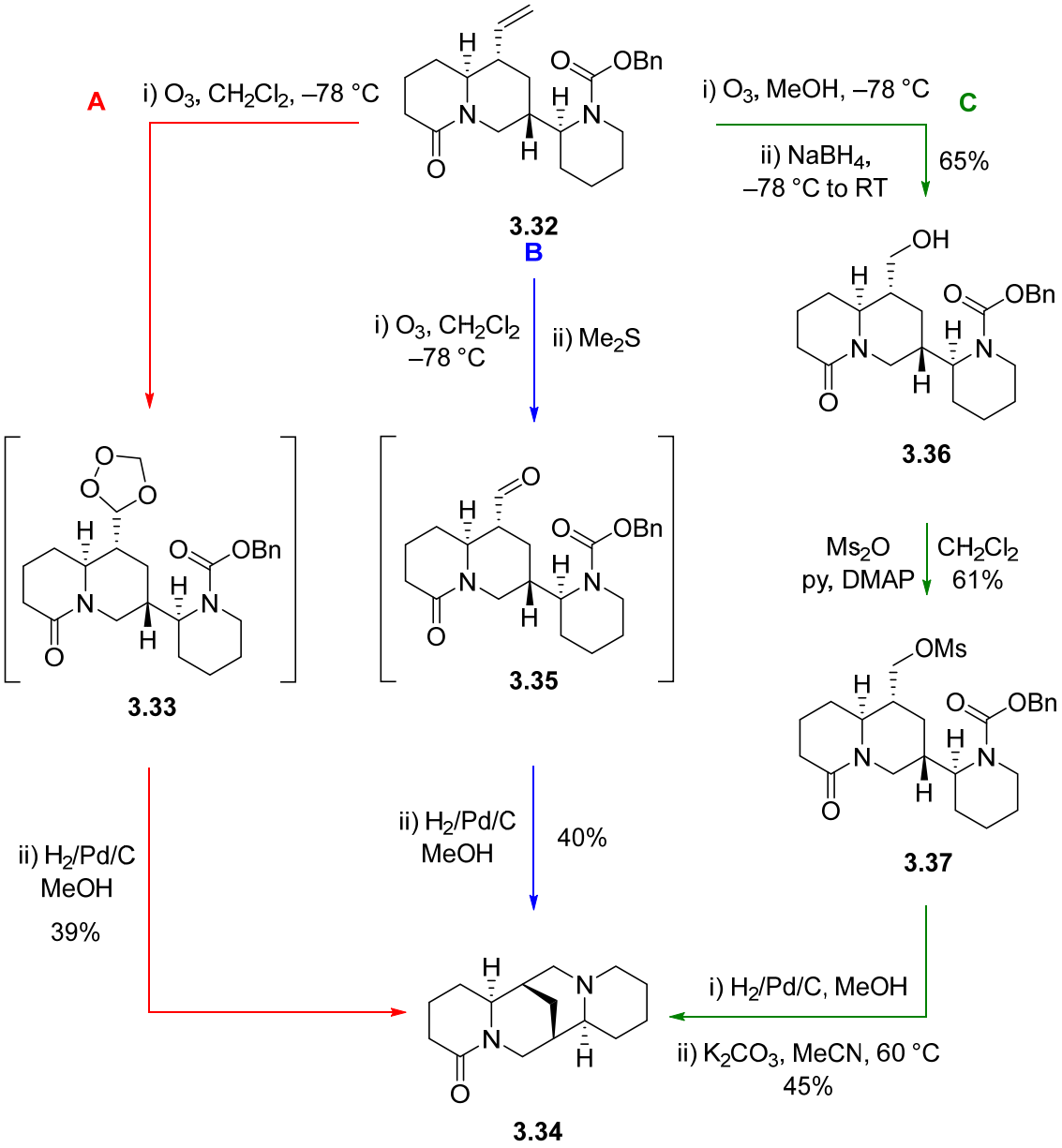


Figure 3.3: TIC of the crude reaction mixture of **3.29** to **3.32** (ESI^+). 3.93 min = 397.4 m/z corresponding to **3.32**. 4.26 min = 413.4 m/z corresponding to theoretical byproduct **3.33**.

3.4.1 Final cyclisation approaches

Undeterred, the last part of the synthesis would be enacted in short order. In order to do this, the latent aldehyde functionality of alkene **3.32** would need to be unmasked. Initially, it was thought that a direct approach would be amenable, proceeding by ozonolysis of the alkene and direct hydrogenation of the ozonide intermediate **3.33**.

Whilst an unusual approach, there is precedent within the literature,[190-192] and also more specific communications more tailored to a direct reductive amination approach.[193] As such, it was felt that it was a method worth pursuing, and **3.32** was subjected to O_3 to afford the ozonide **3.33**, which was immediately subjected to catalytic hydrogenation (**Scheme 3.12**) as shown by pathway **A**. Pleasingly, quinolizidine **3.34** was isolated, albeit in modest yield, even after several attempts to optimise the reaction,

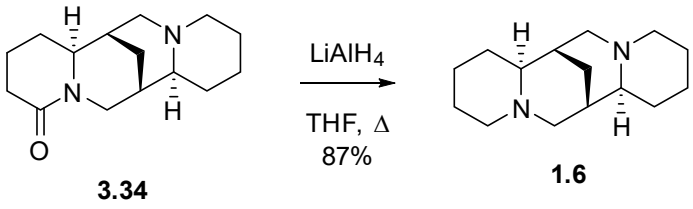


Scheme 3.12: Routes attempted from quinolizidone **3.32** to tetracyclic **3.34**.

Given the limited quantity of **3.32** available at this late stage, it was decided to attempt a more conventional ozonolysis approach, where the initial ozonide is reacted with Me_2S in order to form aldehyde **3.35**, as shown by pathway **B**. Frustratingly, this too proved low yielding after several attempts, and was roughly on par with the more direct approach. Finally, the stepwise approach shown by pathway **C** was attempted, whereby reductive workup of the ozonolysis with $NaBH_4$ would furnish alcohol **3.36**. This would then be converted into mesylate **3.37**, which was then subjected to catalytic hydrogenation and, upon completion, basic conditions to afford tetracycle **3.34** in 16% overall yield over the three steps.

Despite the low overall yield of the stepwise approach, this became the more favoured route to take given the variability of yields from routes **A** and **B**. Given that several operations are occurring in a "single step" in these latter two approaches, it becomes harder to pinpoint areas of potential improvement, whereas the analytical data collected for **3.36** and **3.37** allow definitive determination of what occurs in each reaction.

However, now that the tetracyclic lactam **3.34** was in our hands, the final step was to reduce this to our target, (+)-*β*-isosparteine ((+)-**1.6**). Literature precedent for the $LiAlH_4$ reduction of the analogous structure possessing the (–)-sparteine ((–)-**1.3**) configuration was followed, and allowed the successful isolation of (+)-**1.6** in high yield, also serving to confirm the absolute stereochemical assignments of the preceding synthetic intermediates (**Scheme 3.13**).[58, 124] This would mark the second successful total synthesis of this compound from our laboratory, and our first synthesis of one of the sparteine isomers using an imino-aldol / *N*-acyliminium approach.

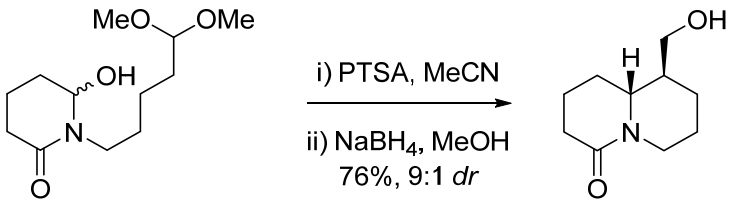


3.34 **1.6**

Scheme 3.13: Final reduction of lactam **3.34** to the target alkaloid (+)-**1.6**.

3.5 Returning to the acetal cyclisation approach

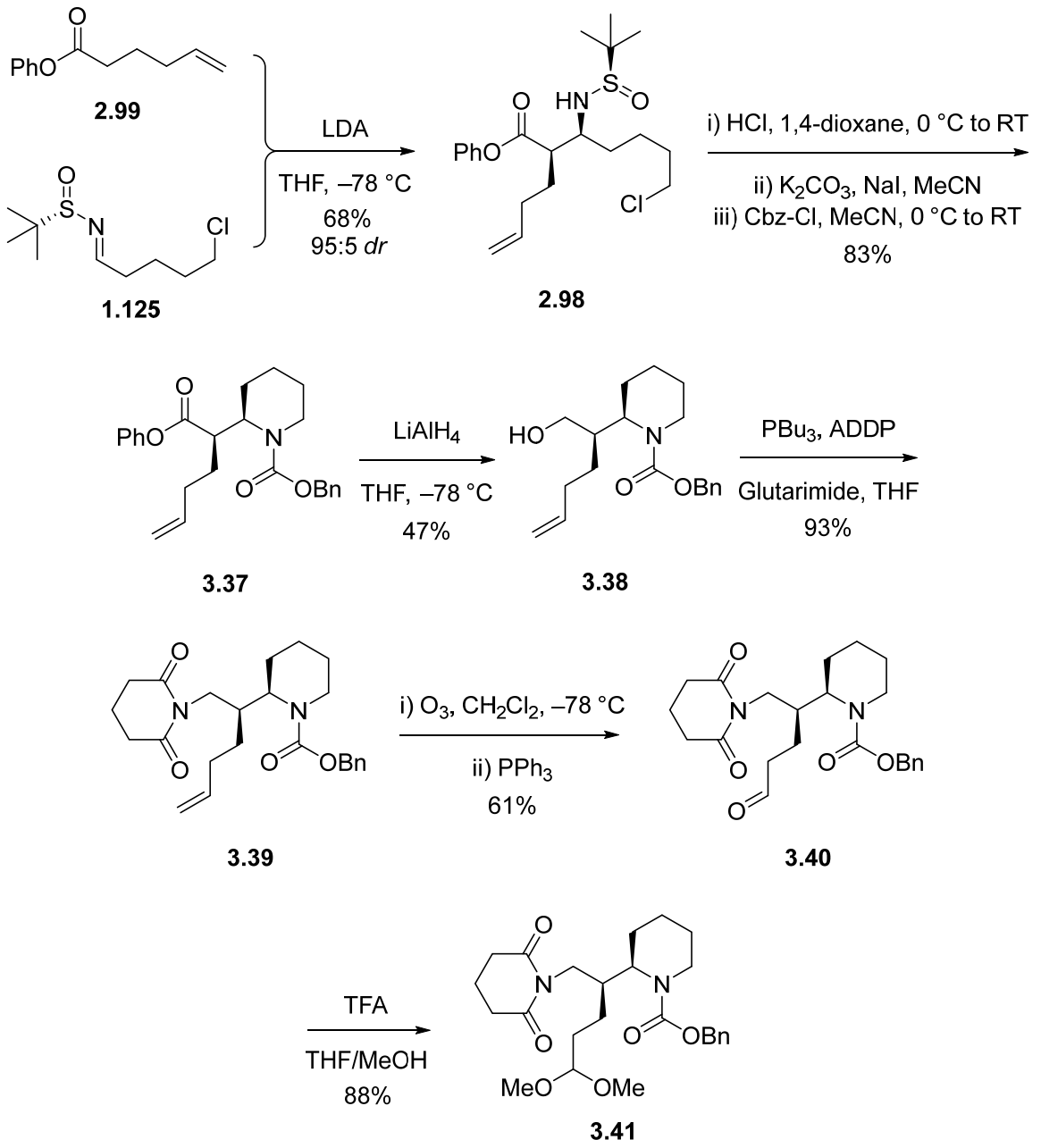
Concurrent to the work on the *N*-acyliminium total synthesis route, we were intrigued by a publication from Koley *et al*., describing the cyclisation of a number of [m, n, 0] bicyclic scaffolds *via* reductive coupling of *N*-acyliminium and enol functionalities (**Scheme 3.14**).[194] The exploration of this intramolecular Mannich reaction was enticing, as it would allow for the completion of an earlier attempted route by Alex Ionut-Pop (**See Section 2.2.4**).[172]



3.35 **3.36**

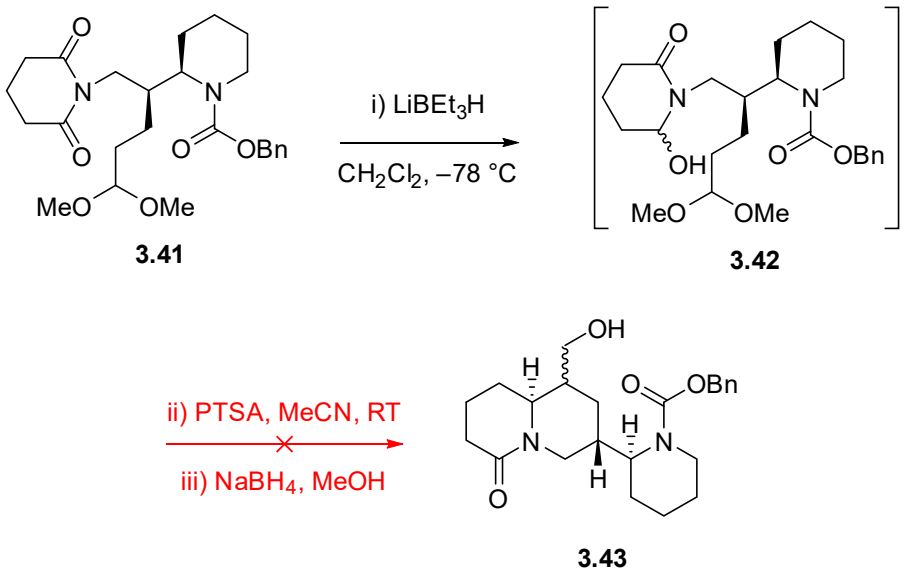
Scheme 3.14: Example of the intramolecular Mannich reaction conducted by Koley.[194]

Following the same methodology employed in the total synthesis, phenyl ester **2.99** and *N*-sulfinylimine **1.125** were combined to furnish adduct **2.98** in good yield and high diastereoselectivity (**Scheme 3.15**). As before, the three-step deprotection-cyclisation-protection strategy was employed to provide protected piperidine **3.37** in good yield over the three steps. The ester was subsequently reduced with $LiAlH_4$, obtaining alcohol **3.38** in an unexpectedly modest yield. The optimised Mitsunobu conditions were employed to provide imide **3.39** in excellent yield. Finally, ozonolysis to aldehyde **3.40** was followed by acetalisation in the presence of TFA and MeOH to obtain dimethyl acetal **3.41** in good yields for both steps.



Scheme 3.15: Synthesis of intramolecular Mannich cyclisation precursor **3.41**.

With acetal **3.41** in hand, the cyclisation protocol could be attempted (**Scheme 3.16**). Treatment of **3.41** with Super-Hydride® afforded hemiaminal **3.42**, which was immediately used without purification. Following the addition of PTSA, MS analysis of the reaction gave rise to a feature consistent with the evolution of the intermediate aldehyde, but on completion of the protocol by the addition of $NaBH_4$, no pure product could be isolated from the reaction mixture, despite repeated attempts to isolate this chromatographically. Due to the success of the total synthesis of (+)-*β*-isosparteine ((+)-**1.6**) by the *N*-acyliminium approach, no further work was conducted around this cyclisation.



3.41 **3.42** **3.43**

Scheme 3.16: Attempted cyclisation of acetal **3.41** using an intramolecular Mannich cyclisation.

3.6 Conclusions

The asymmetric total synthesis of (+)-*β*-isosparteine ((+)-**1.6**) has been achieved in 2% overall yield over 18 linear steps. The design of two specifically functionalised fragments: phenyl ester **3.4** and *N*-sulfinylimine **1.125**, allowed the use of a highly diastereoselective imino-aldol reaction to establish one of the two necessary *syn* linkages within the target alkaloid. Subsequent modifications to the carbon skeleton would allow the use of a diastereoselective *N*-acyliminium cyclisation, furnishing key quinolizidine **3.32**. Several different reductive transformations towards the tetracyclic structure were attempted, with a stepwise reduction-mesylation-cyclisation approach proving the most reliable.

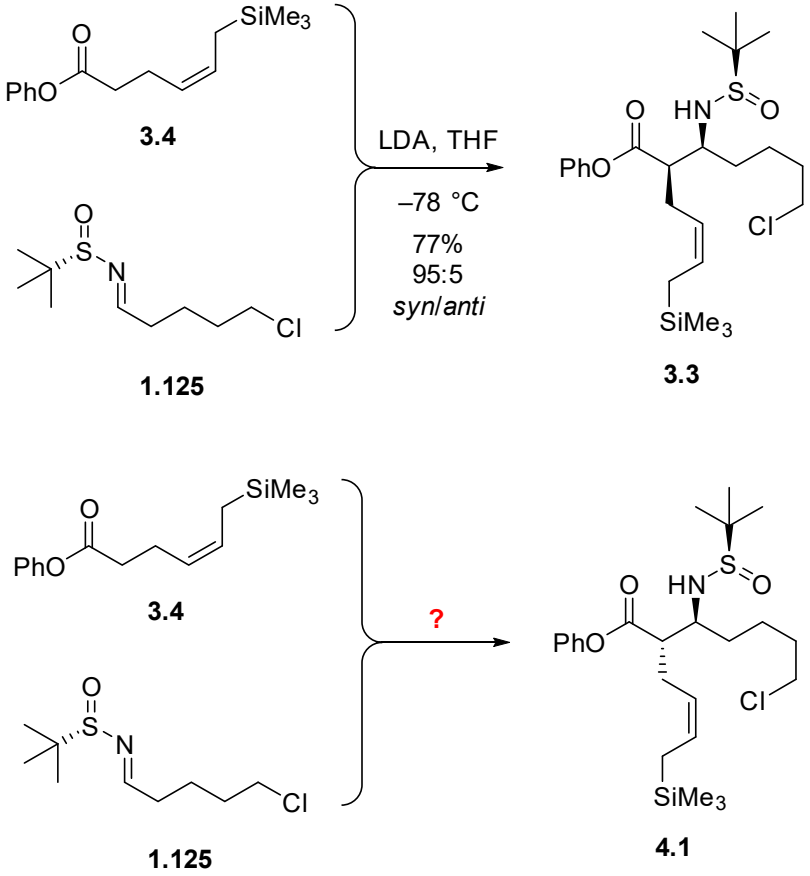
The successful conclusion of this total synthesis would allow the elaboration of this methodology to the total synthesis of (+)-sparteine ((+)-**1.3**) as part of a colleague's doctoral studies.[185] And finally, whilst the intramolecular Mannich reaction was never fully studied, the precedent towards the study of this reaction in the synthesis of the sparteine alkaloids has been established, with a robust synthetic route found towards the necessary intermediate.

Chapter 4 *Anti*-alkylations of *β*-amino esters

4.1 Introduction

The total synthesis of (+)-*β*-isosparteine ((+)-**1.6**) was, at its heart, an excellent showcase of the utility of the highly diastereoselective *syn* imino-aldol reaction within our hands. Indeed, the completion of the synthesis marked the 5th lupin alkaloid synthesised within the group, and was completed alongside another synthesis of (+)-**1.5** which has since been reported from our laboratory.[124] The use of the imino-aldol reaction to form the *syn β*-amino ester **3.3** gave us easy entry to substituted piperidine **3.27**, due to the inclusion of a chloroalkyl chain in the initial *N*-sulfinylimine used.

An open question throughout the synthesis was whether the corresponding *anti* amino-ester **4.1** could be synthesised (**Scheme 4.1**). This would therefore allow a synthesis of (+)-sparteine ((+)-**1.3**) by extension of the methodology outlined before.



Scheme 4.1: Potential scope of *anti* imino-aldol reaction to give ester **4.1**.

It is obvious, however, that there is a fundamental flaw with this logic. The very reasons that make the *N*-sulfinylimine an excellent choice for the *syn* product preclude its

use in a two-component coupling towards an *anti β*-amino ester. As previously mentioned, the proposed transition state of this reaction is formed in such a way as to highly favour attack of the lithium enolate onto the *Re* face of the *N*-sulfinylimine, leading to the *syn* product (**See Section 3.3.1**). As such, it seems unlikely that a change in the conditions will lead to a reversal of the selectivity – we would instead expect for the selectivity towards the *syn* product merely to worsen. Indeed, scouring of the literature for a precedent for this kind of transformation only supported the conclusion that this was an ill-advised avenue to tread.

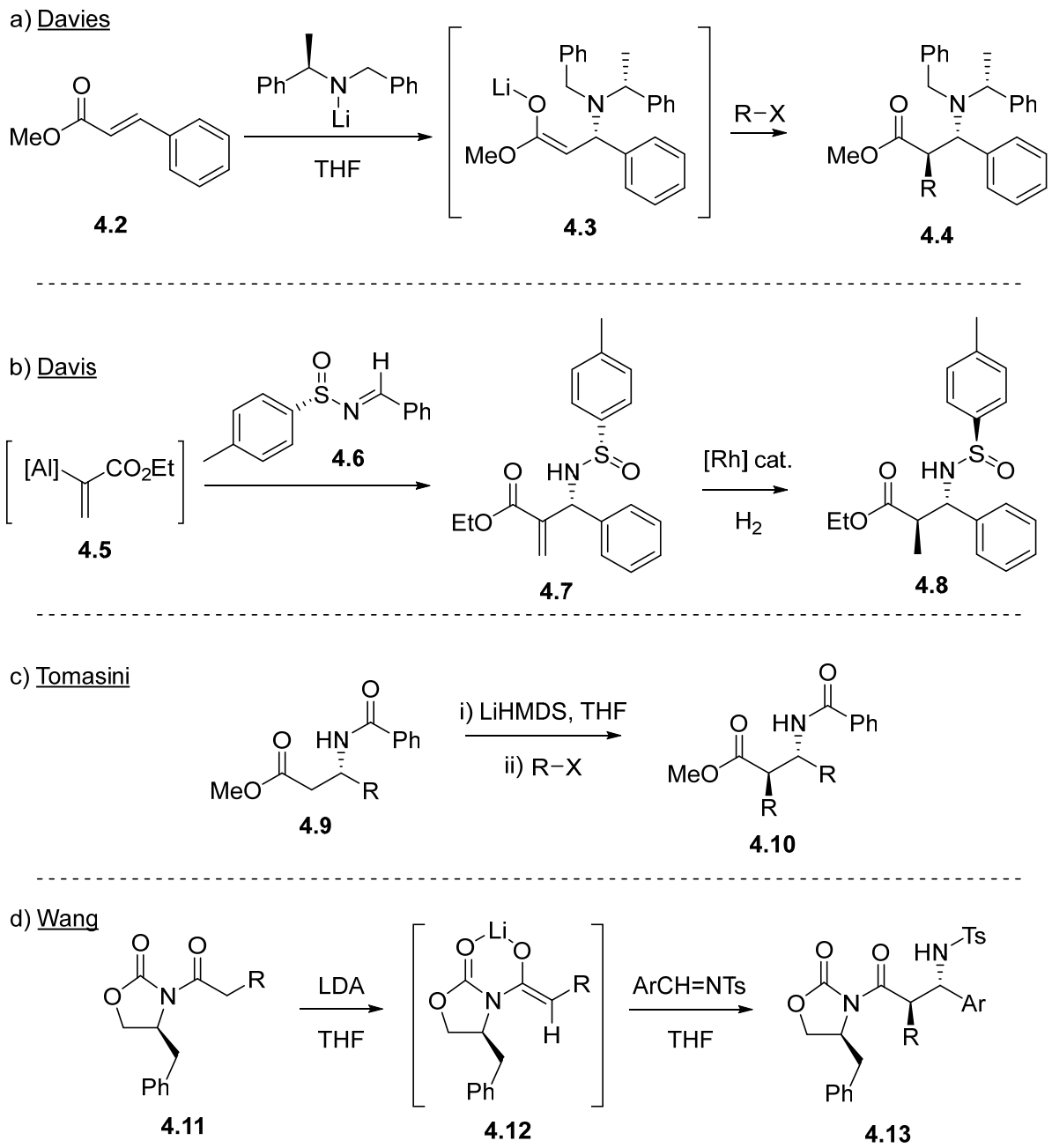
4.1.1 The formal *anti* imino-aldol reaction

However, *anti* substituted *β*-amino esters are well known within the literature, and as such there has been much discussion of ways in which to synthesise these important compounds, with methods such as modification of the chiral pool, asymmetric catalysis, and auxiliary-based approaches.[195-197]

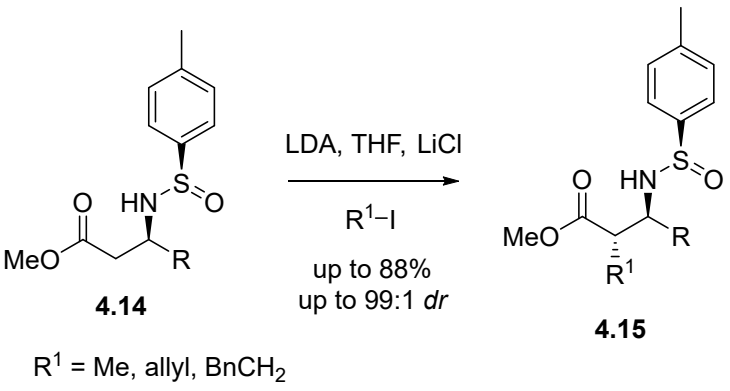
By way of examples; Davies reported the conjugate addition of lithiated (*R*)-*N*-benzyl-*N*-*α*-methylbenzylamides onto crotonate and cinnamate esters, providing modest to high diastereoselectivities of *anti* products. (**Scheme 4.2a**).[198] Davis outlined the synthesis of *anti β*-amino esters utilising selective hydrogenation of aza-Morita-Baylis-Hillman adducts under control of a chiral Rh catalyst (**Scheme 4.2b**).[199] Tomasini published the diastereoselective synthesis of *anti β*-amino esters *via* the reaction of alkylating agents with the di-anion of benzamino methyl esters (**Scheme 4.2c**)[200] It would also be remiss not to mention approaches reliant on derivatives of Evans' oxazolidinoes, an example of which was demonstrated by Wang (**Scheme 4.2d**).[201]

Three of these examples have one key element in common – instead of one reaction that can install the required *anti* stereochemistry in one step, usually a stepwise approach is followed to furnish the desired *anti* relationship. One particular approach that caught our eye was published by Davis, where alkylation of the dianion of chiral *β*-amino ester **4.14** in the presence of LiCl with several iodide alkylating agents provided *anti β*-amino esters **4.15**, progressing with high diastereoselectivities and in high yields (**Scheme 4.3**).[202]

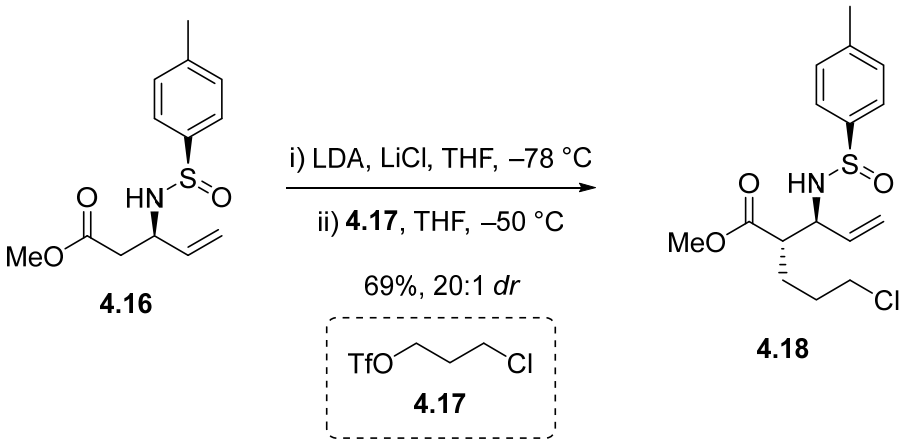
This approach also made use of a chiral sulfinyl auxiliary, and it was thought that adoption of this methodology would allow access to the necessary *anti* stereochemistry needed for the synthesis of several more lupin alkaloids. As part of his doctoral studies, Lyu Xiang proposed the use of a new electrophile as the alkylating agent, triflate **4.17**. By adapting Davis' method, ester **4.16** was alkylated with this highly electrophilic alkylating agent, furnishing *anti* substituted *β*-amino ester **4.18** in good yield and high *dr*. (**Scheme 4.4**).[185]



Scheme 4.2: Selected examples of the synthesis of *anti*-substituted *β*-amino esters.

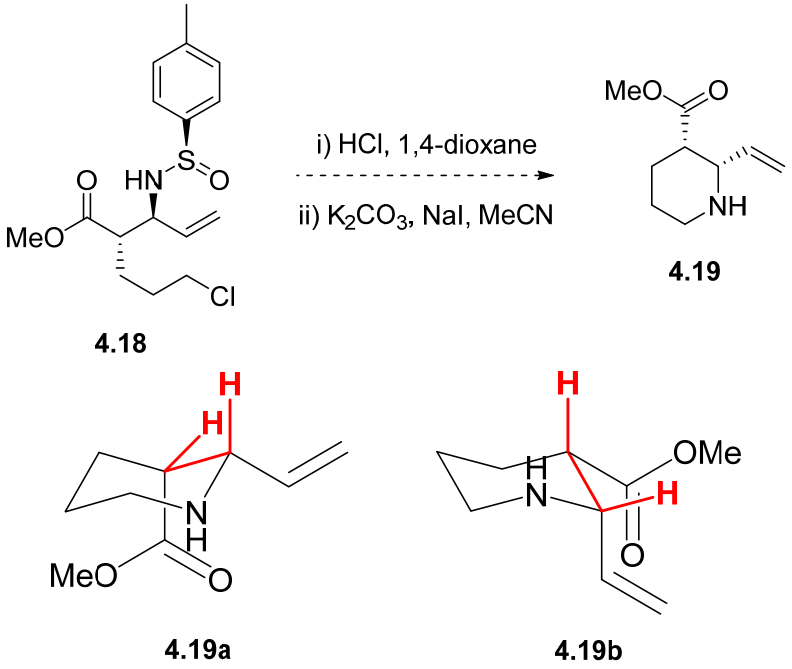


Scheme 4.3: The *anti* alkylation of some *β*-amino esters by Davis *et al*.



Scheme 4.4: Use of triflate **4.17** to install a chloroalkyl motif *via anti* alkylation of ester **4.16**.

Whilst the original use of this *anti*-alkylation would be the synthesis of various lupin alkaloids, the use of this reaction would also bear fruit in another direction. Employing the acid deprotection and basic cyclisation conditions used previously (**See Section 3.3.1**) would give easy access to *cis* substituted piperidine **4.19** (**Scheme 4.5**).

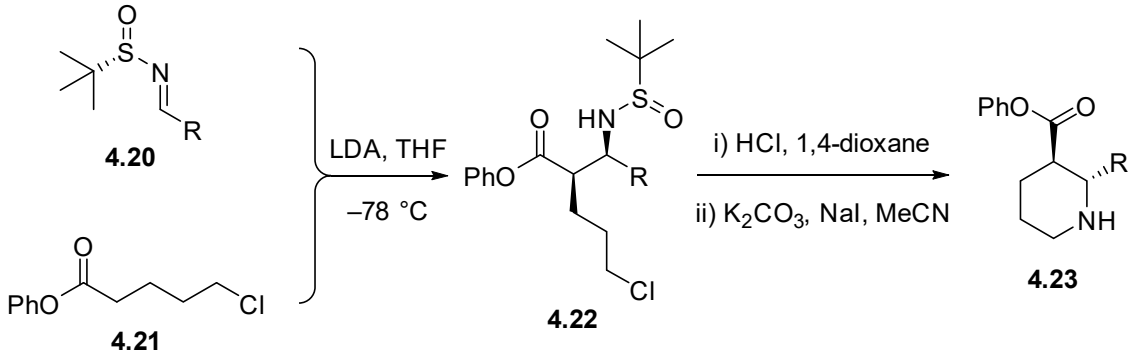


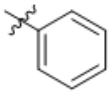
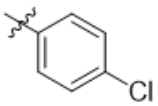
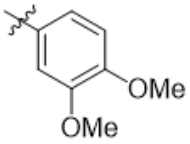
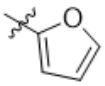
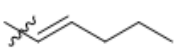
Scheme 4.5: Proposed synthesis of *cis* substituted piperidine **4.19**, with conformers **4.19a** and **4.19b**.

Piperidines are a privileged structural motif within chemistry. Indeed, nitrogen heterocycles are one of the most significant structural components of pharmaceuticals, with a recent review highlighting the incorporation of the piperidine unit into 72 different new drugs approved by the FDA in recent years, with di-substituted piperidines accounting for over 60% of the total.[203] The corollary of being a highly desirable motif is that there has been much investigation into the synthesis of the piperidine structure.[204] As such, the development of a route into 2,3-disubstituted piperidines is obviously of great interest.

As part of her doctoral studies, Amanda Cutter investigated the use of the *syn* imino-aldol reaction towards this goal, and synthesised a small library of chiral piperidines, prepared *via* an imino-aldol reaction (**Table 4.1**).[171] It was thought that establishing a small library of corresponding *cis*-substituted piperidines, and the fleshing out of her original work, would represent a short and robust synthesis of these important saturated *N*-heterocycles.

Table 4.1: Summary of results from Amanda Cutter's syntheses of *syn* di-substituted piperidines, as part of her doctoral studies.[171] [a]Yield over the three steps from **4.21**.

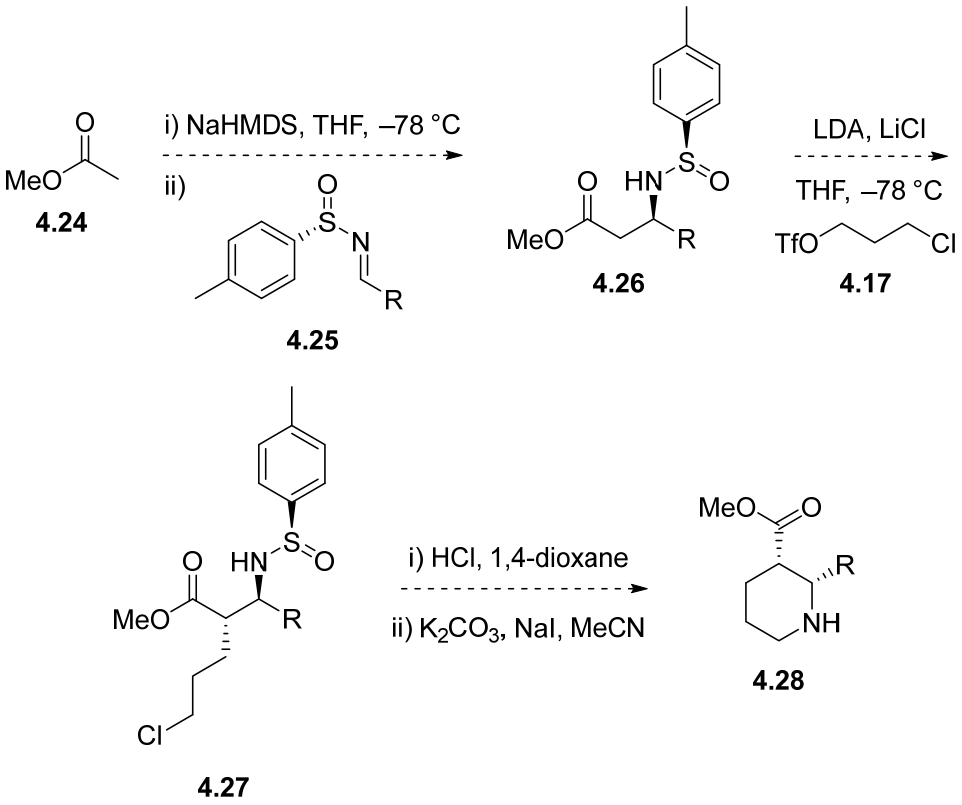


Entry	R	Product	Overall Yield (%)[a]	*dr*
1		**4.23a**	25	73:23:4
2		**4.23b**	22	76:15:9
3		**4.23c**	13	95:5
4		**4.23d**	49	85:11:4
5		**4.23e**	26	89:11

4.2 Initial trials of the *anti*-alkylation

Having now established the goal of the project, the next step was to put in place a plan to enable its execution. Taking inspiration from the substrates used in Davis' original communication, the use of an ester derived from *p*-tolyl *N*-sulfinylimine **2.24** was favoured,

due to the observation of lower diastereoselectivities in the *anti* alkylation step when using the Ellman *tert*-butyl *N*-sulfinylimine **2.25**.[185, 199] As such, a route was initiated whereby the reaction of various substituted *N*-sulfinyl imines **4.25** with the sodium enolate of methyl acetate (**4.26**) would give *β*-amino ester **4.24** in high diastereoselectivity (**Scheme 4.6**). Subsequent *anti* alkylation with triflate **4.17** would yield the *anti* adduct **4.27**, which could then be subjected to the standard deprotection and cyclisation conditions to furnish *cis* substituted piperidine **4.28**.

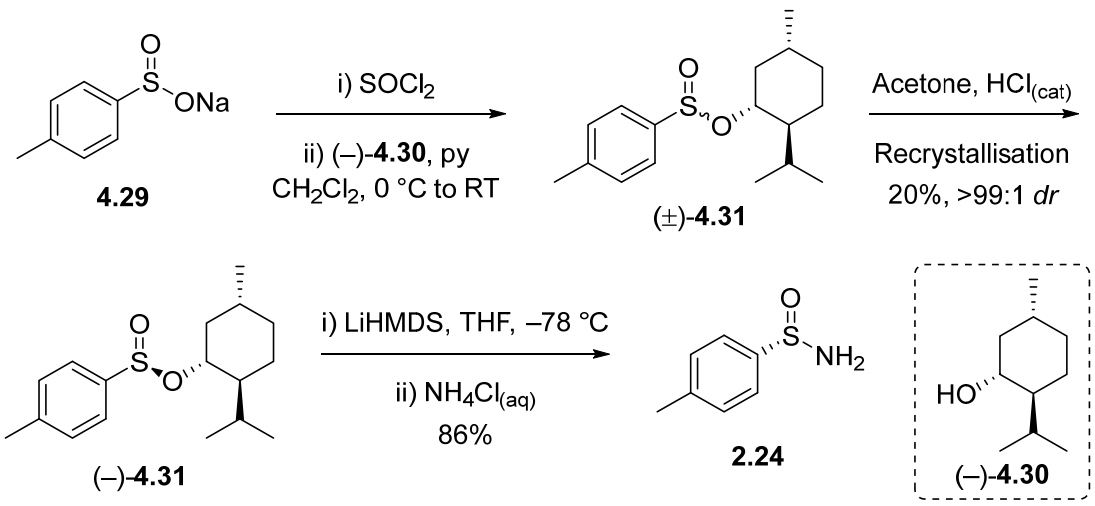


Scheme 4.6: Proposed route to *anti* substituted piperidine analogues **4.28**.

Work began in earnest, commencing with the synthesis of the Davis sulfinamide **2.24**. Whilst commercially available, the high cost of either antipode was deemed too great. As such, the auxiliary was prepared on a multi-gram scale in-house, from the commercially available sodium salt of *p*-toluenesulfinate (**4.29**) and (–)-menthol ((–)-**4.30**) by a slight modification of a well-known literature preparation (**Scheme 4.7**).[205]

Conversion of sulfinate **4.29** to the corresponding acid chloride allowed subsequent reaction with (–)-**4.30**, in the presence of pyridine, to afford sulfinate **4.31** as a mixture of diastereoisomers. Recrystallisation of the crude mixture afforded (*S*)-(–)-menthyl-*p*-toluenesulfinate preferentially, and further equilibration of the mixture could be achieved by the addition of small amounts of *conc*. HCl, allowing for the collection of further crops of the desired product. A final recrystallisation step afforded (–)-**4.31** with a *dr* of over 99:1, as confirmed by HPLC analysis. Whilst the yield for this step within the literature is often above 60%, in our hands the yield of this step was always mediocre at best, attributed to lackluster

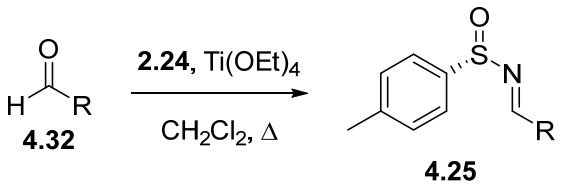
recrystallisations. Nevertheless, reaction of (–)-**4.31** with LiHMDS, and subsequent work-up with $NH_4Cl_{(aq)}$ allowed the isolation of auxiliary **2.24**, accessed on a multigram scale.

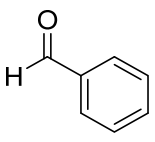
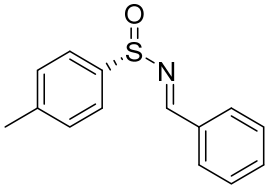


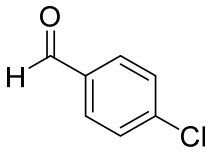
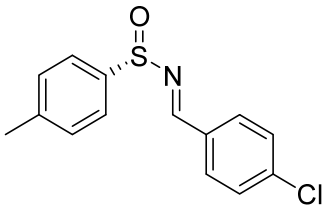
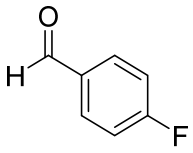
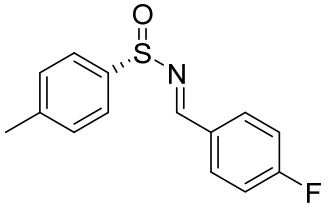
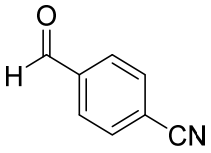
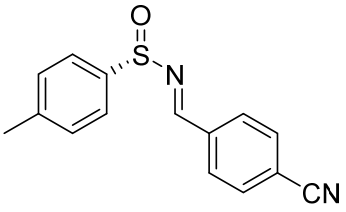
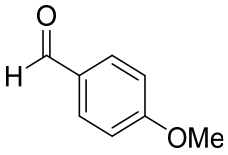
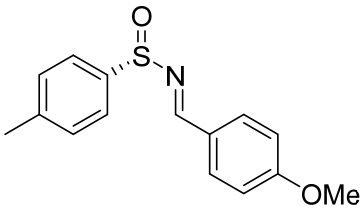
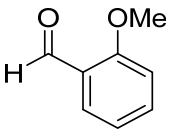
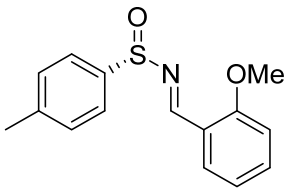
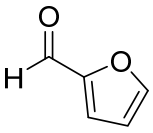
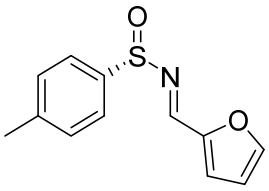
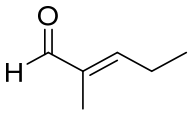
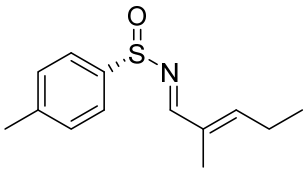
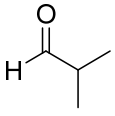
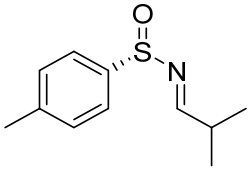
Scheme 4.7: Preparation of Davis *p*-toluene *N*-sulfinylamide auxiliary **2.24**.

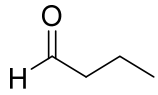
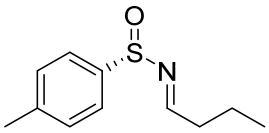
With copious amounts of the needed auxiliary in hand, the next task was to obtain a series of *N*-sulfinylimine analogues. Condensation of **2.24** with a mixture of commercially available or easily synthesised aldehydes provided, after workup, a series of analogues in generally good to excellent yields. (**Table 4.2**). Compounds isolated in low yield were observed to have protons at the C_α position, which could cause unwanted side-reactions under the reaction conditions (**Table 4.2**, **Entries 8-10**). An emphasis was to be put on fragments that have medicinally relevant functionalities, but also possessing groups that can fully test the scope of the reaction. *N*-sulfinylimine **4.25a** was chosen as the model substrate for further testing, as *anti* alkylations of the *β*-amino ester derivative have been reported previously.

Table 4.2: Preparation of *N*-sulfinylimines **4.25**. [a]Prepared from propionaldehyde, according to the procedure of Behr *et al*.[206]



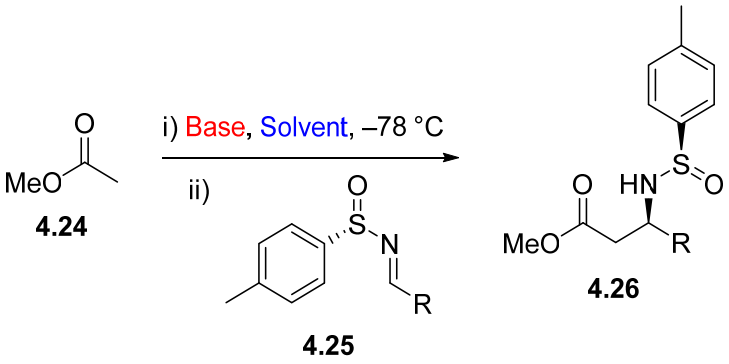
Entry	Aldehyde		Product		Yield (%)
1	**4.32a**		**4.25a**		90

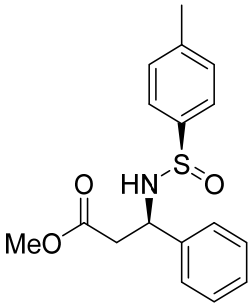
Entry	Aldehyde		Product		Yield (%)
2	**4.32b**		**4.25b**		93
3	**4.32c**		**4.25c**		91
4	**4.32d**		**4.25d**		79
5	**4.32e**		**4.25e**		91
6	**4.32f**		**4.25f**		94
7	**4.32g**		**4.25g**		66
8	**4.32h**		**4.25h**		62
9	**4.32i**		**4.25i**		25

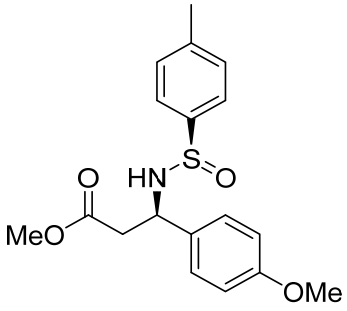
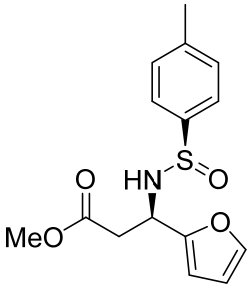
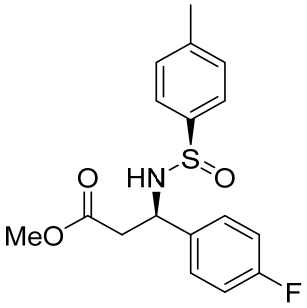
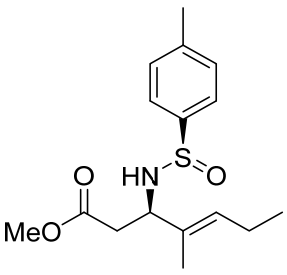
Entry	Aldehyde	Product	Yield (%)
10	**4.32j** 	**4.25j** 	66

Several of these substrates were thus taken forward to the next stage by the reaction with **4.24** (**Table 4.3**). Initial trials were conducted using the conditions established in the prior art, using NaHMDS in THF, however this was shown to be lower in both yield and *dr* than had been anticipated. Switching solvents to Et_2O (**Entries 1 & 2**) gave a much higher yield, and also resulted in a greatly elevated diastereoselectivity. The effect of the base was briefly investigated, however the observed selectivity upon changing the counterion from Na^+ to Li^+ was minimal (**Entries 5 & 6**). Five different *β*-amino esters were prepared, with **4.26a** prepared on a multi-gram scale in order to investigate the next steps.

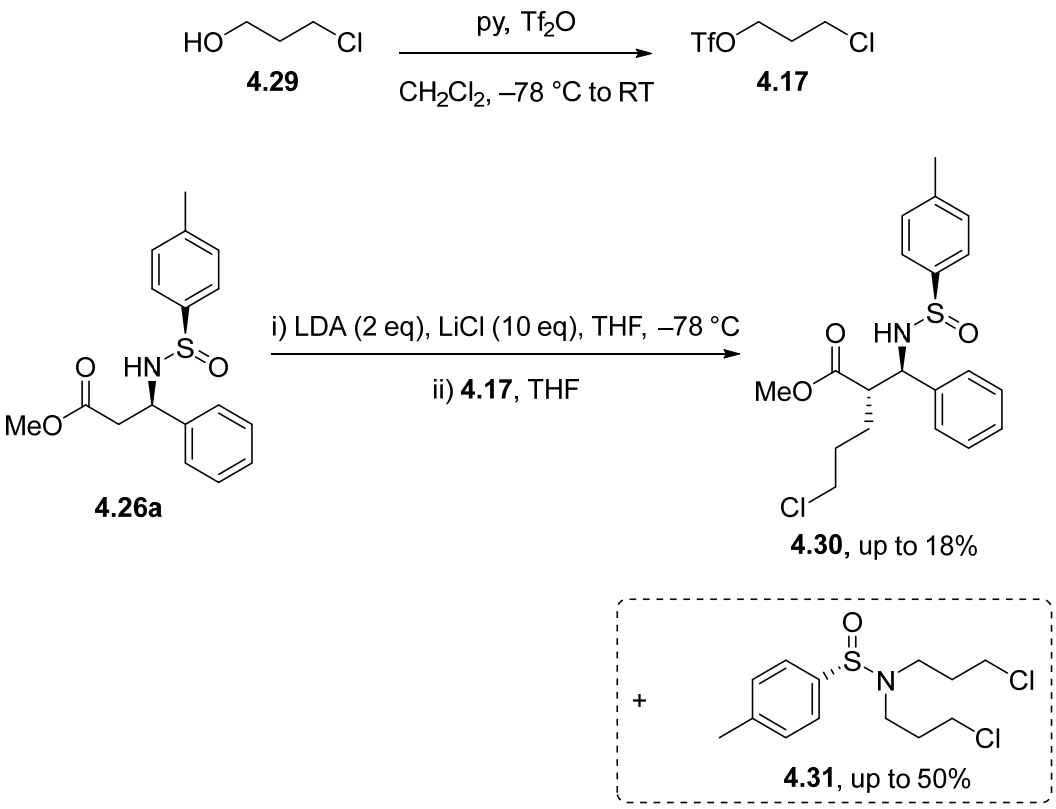
Table 4.3: Optimisations and sample throughput of *N*-sulfinylimines to *β*-amino esters **4.26**. [a] *dr* measured by integration of the NH peak in the ^{1}H NMR of the crude reaction mixture. [b] *dr* measured by HPLC analysis of the crude reaction mixture.



Entry	Imine	Base	Solvent	Product	Yield (%)	*dr* (*R*,*S* : *S*,*S*)
1	**4.25a**	NaHMDS	THF	**4.26a** 	59	9:1[a]
2		NaHMDS	Et_2O		76	24:1[a]

Entry	Imine	Base	Solvent		Product	Yield (%)	*dr* (*R*,*S* : *S*,*S*)
3	**4.25e**	NaHMDS	Et_2O	**4.26b**		44	49:1[b]
4	**4.25f**	NaHMDS	THF	**4.26f**		42	2:1[a]
5	**4.25c**	NaHMDS	THF	**4.26c**		53	77:33[a]
6		LiHMDS	THF			69	5:1[a]
7	**4.25h**	NaHMDS	THF	**4.26h**		41	78:22[a]

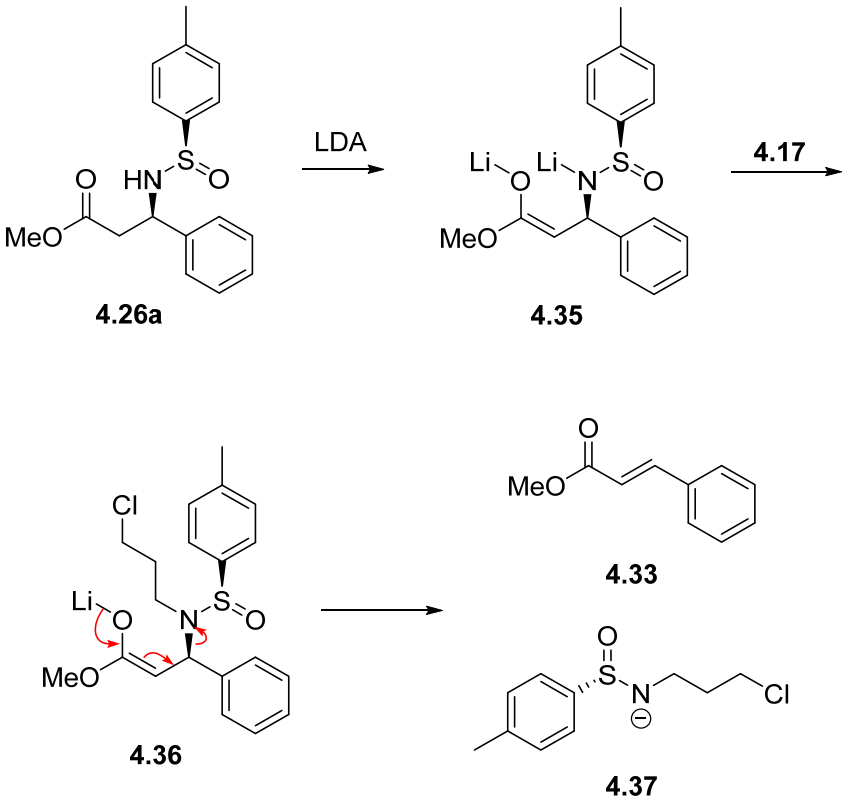
With **4.26a** prepared, the attempts at the *anti* alkylation began in earnest, with high expectations due to the precedent set previously within the group. Triflate **4.17** was prepared in one step from commercially available alcohol **4.29**, and was used to effect the subsequent alkylation (**Scheme 4.8**). However, from the outset, the idea of a quick route to access di-substituted piperidines **4.28** became immediately frustrated. The *anti*-alkalyation reaction using **4.17** returned consistently low yields of **4.30**, and large amounts of a byproduct, *bis*-chloropropylated sulfinylamine **4.31**.



Scheme 4.8: Preparation of triflate **4.17** and subsequent use in *anti* alkylation.

The appearance and high yield of this byproduct, while disappointing, can be rationalised by considering the sequence of events in the reaction. Initial formation of the di-anion **4.35** could be followed by *N*-alkylation, instead of the desired α-alkylation (**Scheme 4.9**). This would lead to intermediate **4.36**, which could then undergo a retro-Michael elimination to afford methyl cinnamate **4.33** and mono-alkylated anion **4.37**, which could undergo a second alkylation to ultimately give **4.31**.

We have previously noted that there is a large temperature dependency of this reaction.[185] Conducting the alkylation of **4.16** at –78 °C led to low overall yields of the alkylated product **4.18**, but also low yields of **4.31**. Raising the temperature slightly to –50 °C improved the yield drastically, and still kept the level of byproduct to acceptable levels. However, warming even slightly above this temperature led to larger amounts of **4.31**, which led to the conclusion that at higher temperatures, the highly reactive triflate electrophile **4.17** can react with the nitrogen anion more preferentially, leading to large amounts of **4.31** being produced. Given that we were seeing low overall yields of **4.30** and significant amounts of **4.31** even at these low temperatures, it was concluded that **4.17** was too reactive to be successfully used in our approach. A final note is that, despite exhaustive efforts, **4.33** was never successfully isolated from the crude reaction mixture, however Davis does report isolation of this byproduct in his *anti* alkylation work.[202]

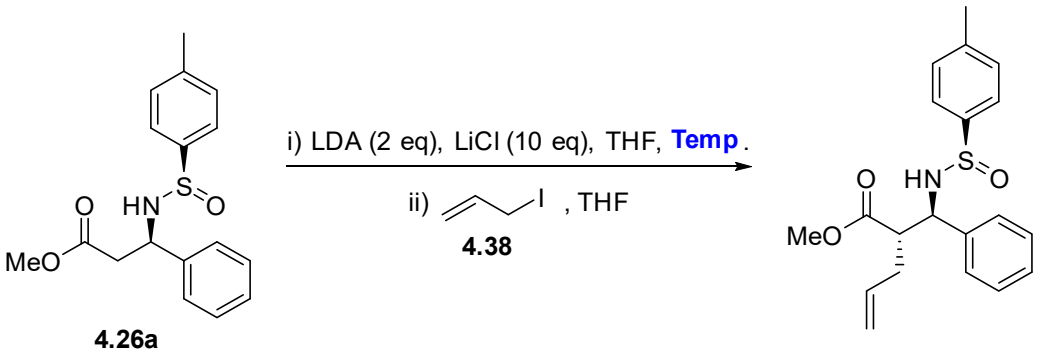


Scheme 4.9: Possible side reaction upon double deptotonation of ester **4.26a**, ultimately leading to side product **4.31**.

4.2.1 Re-evaluation of the route

With the use of triflate **4.17** deemed unsuitable for use, we were interested to see if there were other directions we could explore towards the desired di-substituted piperidines. We were once again drawn towards the initial work conducted by Davis, and re-examined their published syntheses. We were particularly heartened by the successful *anti* alkylation of **4.26a** with allyl iodide, occurring in good yield and with a 92:8 *dr*. As such, our focus shifted from the use of the more direct 3-carbon linker **4.17** into one of elaborating the terminal alkene installed by alkylation with allyl iodide. **4.26a** was again used as the model substrate for these investigations, due to the literature precedent afforded by Davis. Pleasingly, the use of allyl iodide **4.38** would afford the *anti* alkylated product **4.39** in high yield and excellent *dr* (**Table 4.4**).

Table 4.4: Temperature optimisation of the *anti* alkylation of **4.26a** to afford **4.39**.[a] *dr* calculated by integration of the NH peak in the ^{1}H NMR of the crude product.



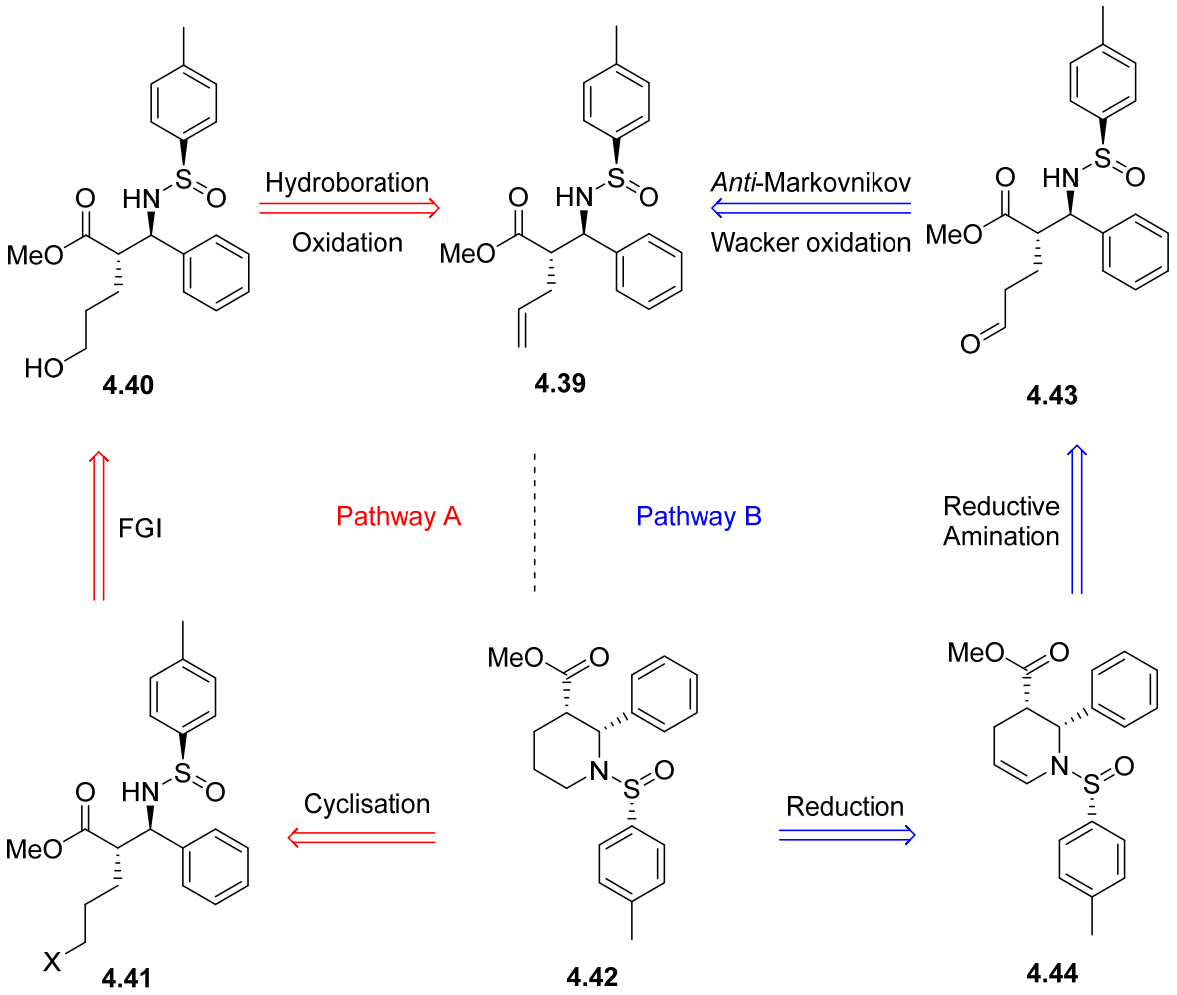
Entry	Temperature / °C	Yield (%)	*dr* (*syn*/*anti*)[a]
1	–78	38	>99:1
2	–50	63	>99:1

4.3 Initial elaboration of pendant alkene

With the successful synthesis of **4.39**, the question of how to best elaborate this into our desired piperidines came into focus. Initially, two different approaches were thought of: hydroboration / oxidation of the alkene to pendant alcohol **4.40**, which could be then transformed into alkyl halide **4.41** – leaving us with the original compound we had sought (**Scheme 4.10** Pathway A); or an *anti*-Markovnikov Wacker oxidation of the alkene to corresponding aldehyde **4.43**, followed by reductive amination to **4.42** *via* intermediate **4.44** (**Scheme 4.10** Pathway B). Both of these routes have merit, and both would increase the total step count by the same amount. As such, it was decided to attempt *both* routes, and see which could be effected most efficiently.

4.3.1 Pathway A: Hydroboration / Oxidation

The use of borane reagents to effect the transformation of double or triple bonds into other functionalities is well known in organic chemistry. The first use of a tandem hydroboration / oxidation reaction to transform an olefin into a new *anti*-Markovnikov alcohol was reported by Brown in 1959.[207] This would, along with his other many contributions to the field of organoboranes, eventually lead to his award of the Nobel Prize in Chemistry in 1979, along with Wittig. Many researchers have explored the chemistry of organoboranes in the years since, leading to a plethora of modern uses for these reagents.[208-209]



Scheme 4.10: Possible new pathways for the synthesis of **4.42** from alkene **4.39.**

Our interest was in the use of these organoboranes in order to hydroborate the alkene, with a subsequent oxidative work-up to access pendant alcohol **4.40**. A range of reagents are available to us, exemplified in **Figure 4.1**.[210] Borane complexed with either THF or Lewis acids, such as **4.45** and **4.46**, are known to be highly reactive species with lower Markovnikov / *Anti*-Markovnikov (M/AM) selectivity. Alkylboranes such as disiamylborane **4.47** and 9-BBN **4.48** are widely used for their generally good reactivity and M/AM selectivity, whilst dialkyloxyboranes such as pinacolborane (Bpin, **4.49**) are generally used as boranes in the catalytic preparation of cross-coupling precursors.

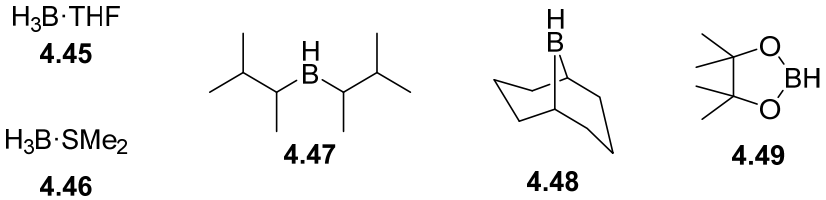
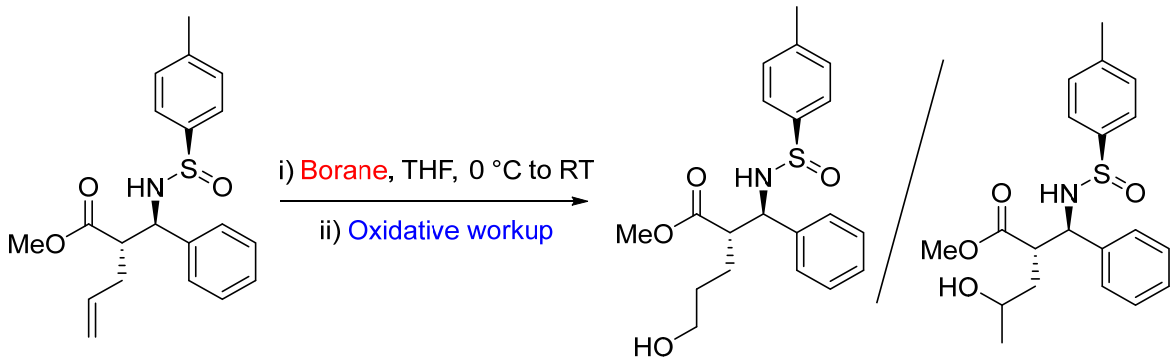


Figure 4.1: Examples of organoborane reagents.

With a wide range of organoborane reagents at our disposal, trials of this reaction began in earnest (**Table 4.5**). The use of 9-BBN never resulted in the desired product, which

was attributed to the degradation of the reagent upon storage. However, a fresh stock of **4.48** also failed to provide any reaction (**Entries 1 & 2**). Complex **4.46** provided a higher yield and acceptable M/AM selectivity. A further improvement of the yield occurred when switching to more mild conditions in the workup, with the removal of NaOH prevented ester hydrolysis (**Entries 3 & 4**). Finally, complex **4.45** was trialled, providing a similar yield and selectivity to **4.46**. The attempt to use the mild oxidant $NaBO_3$ resulted in no product being isolated. The shift downfield of the NH signal in the ^1H NMR from 5.23 to 5.62 ppm would indicate the oxidation of the sulfinyl auxiliary to the sulfonyl derivative, resulting in none of the desired product **4.40** being observed (**Entries 5 & 6**).

Table 4.5: Results of hydroboration/oxidation trials of alkene **4.39**. [a] M/AM selectivity estimated from the integration of the NH signal in the ^1H NMR of the crude product.



4.39 **4.40** **4.50**

Entry	Borane	Oxidative Workup	Yield (%)	M:AM (4.50 : 4.40)
1	**4.48**	MeOH / NaOH / H_2O_2 / RT	0	-
2	**4.48**	NaOAc / H_2O / H_2O_2 / 50 °C	0	-
3	**4.46**	MeOH / NaOH / H_2O_2 / RT	32	15:85
4	**4.46**	NaOAc / H_2O / H_2O_2 / 50 °C	48	12:82
5	**4.45**	NaOAc / H_2O / H_2O_2 / 60 °C	42	10:90
6	**4.45**	$NaBO_3$ / H_2O / RT	0	-

4.3.2 Pathway B: *Anti*-Markovnikov Wacker oxidation

With the hydroboration route providing us with unexpected complications, our attention turned instead to the use of an alternative oxidative step, the Wacker oxidation. This process traces its origin to the conversion of ethylene to acetaldehyde, in the presence of stoichiometric quantities of $PdCl_2$. The development of a catalytic process, termed the Tsuji-Wacker oxidation, has led to widespread adoption of this process in synthetic

laboratories for the conversion of alkenes to ketones.[211-212] The generally accepted mechanism for the catalytic version is shown in **Scheme 4.2**. Formation of an η^2-Pd-alkene complex is followed by hydroxy-palladation. Subsequent *β*-hydride elimination affords the corresponding enol, which tautomerises to the desired ketone product, and releases the reduced Pd^0 catalyst, which is in turn reoxidised to Pd^{II} by the presence of an oxidant species.

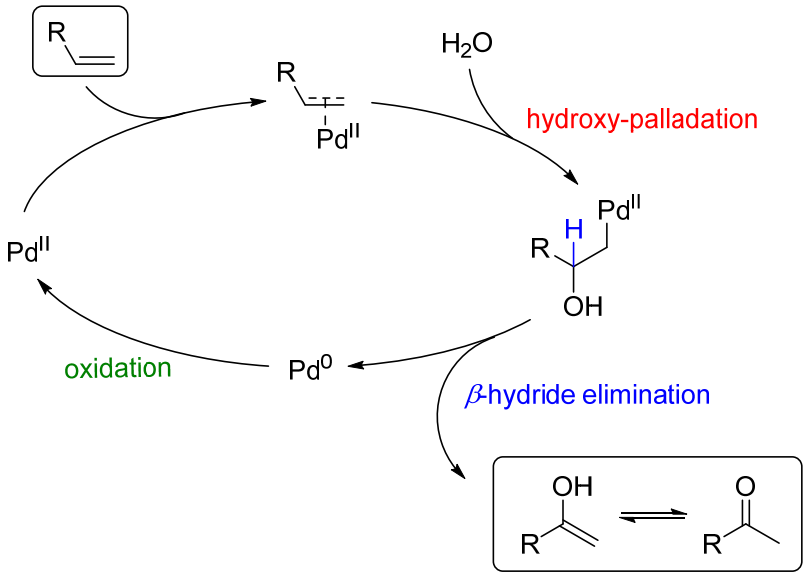


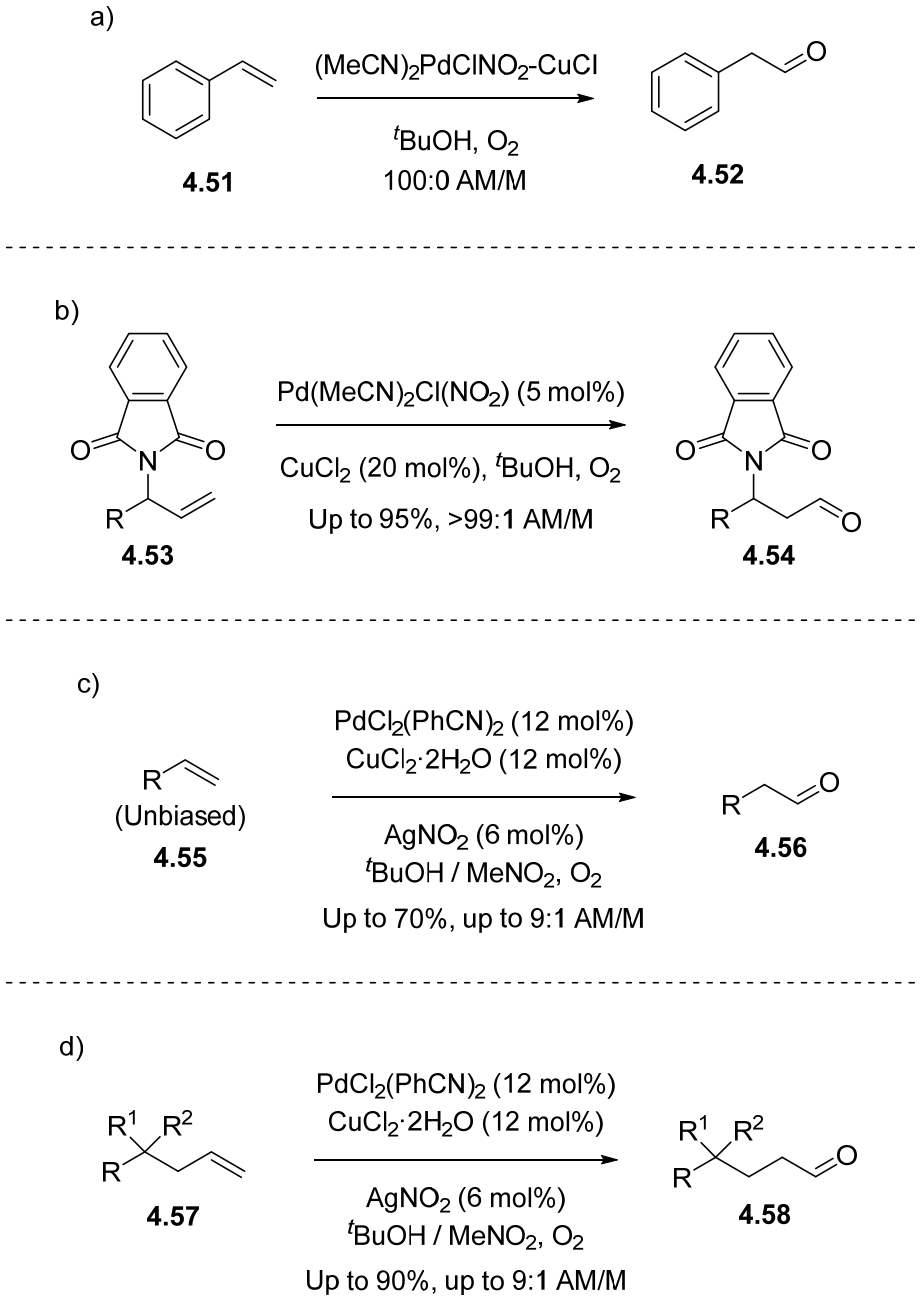
Figure 4.2: General mechanism for Tsuji-Wacker oxidation.[212]

4.3.2.1 Palladium Nitrite catalyst system

In recent years, there has been much development of this reaction, tailored towards the formation of the *anti*-Markovnikov aldehyde product. Aldehydes have been isolated as unwanted byproducts in the Markovnikov Wacker oxidation previously, or as the minor byproduct in specific reactions, often involving an "activated" alkene with the ability to chelate the Pd catalyst.[213-214] More direct investigations towards improving the aldehyde selectivity would begin with Feringa, who would disclose the use of a nitrite-modified Pd catalyst, increasing the propensity of aldehyde formation from linear olefins, albeit only providing aldehydes selectively with styrene (**Scheme 4.11a**).[215-216] Further development by Feringa realised the selective oxidation of a phthalimide-protected allylic amine to the aldehyde, which was rationalised by coordination of the protecting group to the Pd catalyst (**Scheme 4.11b**).[217]

The next iteration in the use of the Pd-NO_2 catalyst system was outlined by Grubbs, who would innovate a Pd-NO_2 catalyst assembled *in situ* that would react with unbiased terminal alkenes in an AM fashion (**Scheme 4.11c**).[218] They would posit that the lack of selectivity noticed in previous reactions was due to the inefficient generation of an aldehyde-selective species from *tert*-butyl nitrite, and as such they would combine a catalytic *tert*-

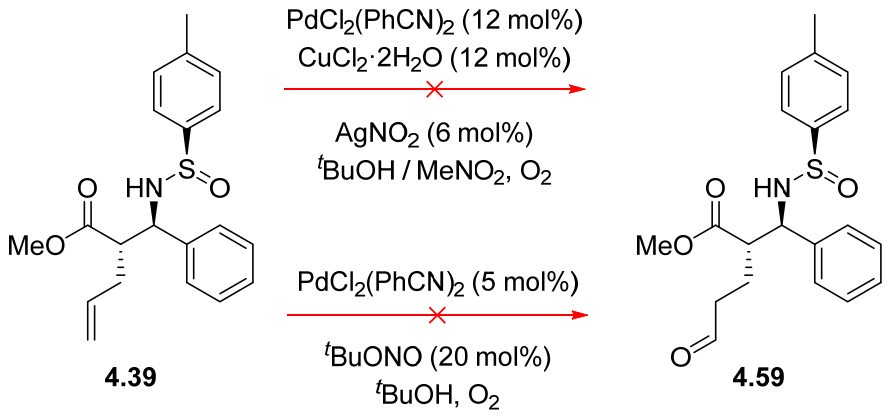
butyl nitrite species, $AgNO_2$ with $PdCl_2$ and $CuCl_2$ co-catalysts. This would dramatically increase the AM selectivity obtained for a wide range of unbiased olefin substrates with various distal functionalities present. They would propose that the reaction would progress *via* a radical pathway, where the aldehyde selectivity would be enhanced due to the stabilisation of the secondary radical intermediate. Grubbs has also successfully applied these conditions to hindered terminal alkenes, and also the use of a formal AM hydroamination process (**Scheme 4.11d**).[219]



Scheme 4.11: Evolution of the palladium-nitrite catalyst system.

4.3.2.2 Oxidative approach using the AM Wacker protocol

Based upon these precedents, and especially heartened by the use of this process on hindered substrates bearing similar functionalities possessed by **4.39**, we applied the optimised conditions developed by Grubbs to our substrate. Disappointingly, upon exposure of this catalyst system, no reaction seemed to take place, even after prolonged reaction times. The conditions were altered, instead using ^{t}BuONO in a procedure reported by Kang, however this would still prove ineffective.[220]

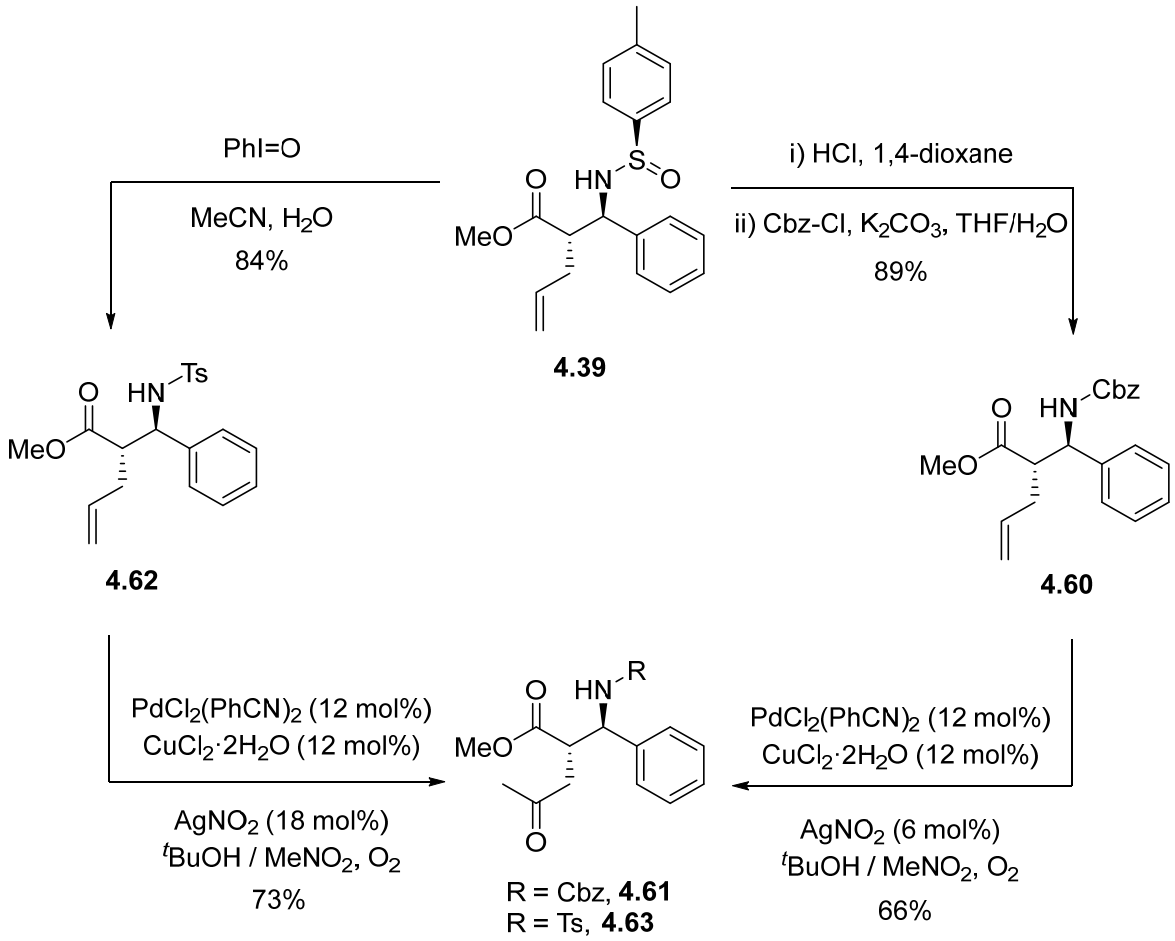


Scheme 4.12: Unsuccessful attempts to perform the AM Wacker oxidation on alkene **4.39**.

We surmised that the sulfinyl group may be impeding the process, as the sulfur could preferentially coordinate the Pd species. It was decided to attempt this process in the absence of this potential problem: **4.39** was deprotected, and then re-protected with the Cbz group, affording carbamate **4.60**. This was subjected to the Grubbs AM Wacker conditions, affording the Markovnikov product, ketone **4.61**. Similarly, oxidation of **4.39** using a mild iodosylbenzene oxidant furnished tosylate **4.62**. AM Wacker conditions would, again, provide the corresponding ketone **4.63**.

Whilst unsuccessful at providing the AM product, we were tickled to notice that the ketone product was being afforded in good yields. Our initial conclusion of interference of the sulfinyl group would also seem to be vindicated by the successful reaction of the sulfonate derivative. However, it was also clear that other interferences were occurring from our substrate. We supposed that both the NH and carbonyl O functionalities could also act as coordination sites for the Pd catalyst, exemplified in **Figure 4.3**. The ester functionality could act to anchor the Pd catalyst close to the alkene, but so could the amine functionality shown in **4.65**. Attack of adventitious water could then be enabling the Markovnikov oxidation to then take place.

It was envisaged that the easiest coordination to supress would be the ester *via* reduction and then subsequent protection as a silyl ether. Submitting this substrate to the Wacker conditions would therefore hopefully provide the aldehyde product.



Scheme 4.13: Reprotection of **4.39** and subsequent AM Wacker oxidation attempts.

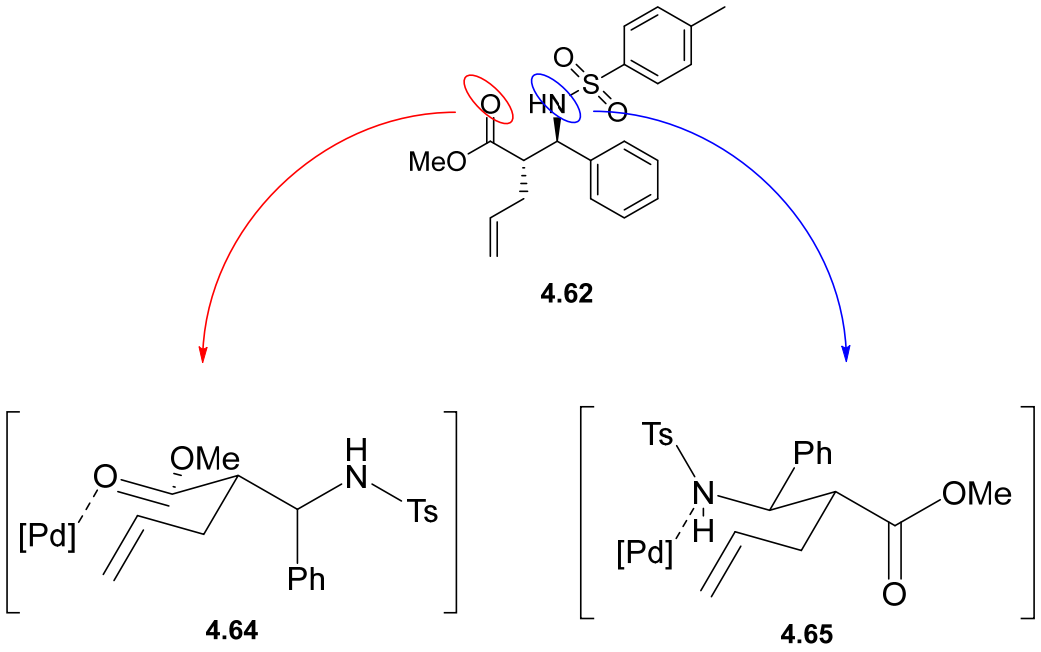
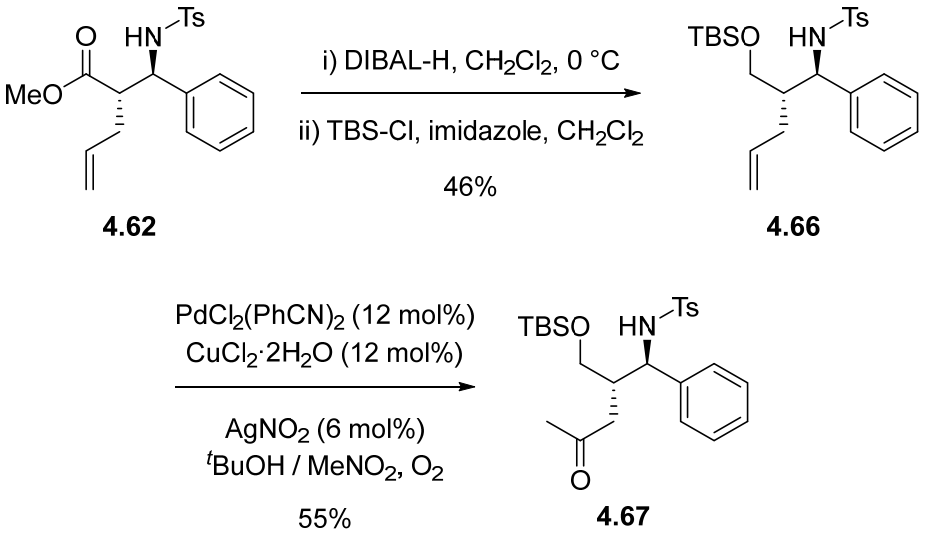


Figure 4.3: Possible coordination of Pd catalyst to **4.62**, resulting in Markovnikov addition.

As such, ester **4.62** was reduced using an excess of DIBAL-H, and the resultant alcohol protected with TBS-Cl to provide silyl ether **4.66** (**Scheme 4.14**). Much to our chagrin, the Wacker oxidation would once again yield ketone **4.67** as the sole product. This

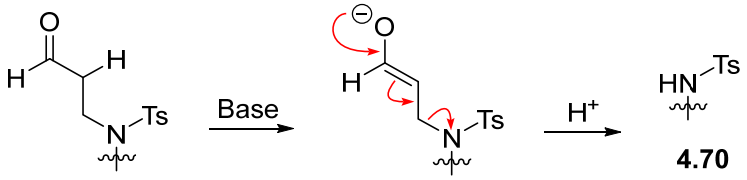
would present us with a quandary. It would seem apparent that the nitrogen functionality was responsible for the lack of aldehyde selectivity, but the way to remove this effect was less clear.



4.62 **4.66** **4.67**

Scheme 4.14: Unsuccessful attempt at the AM Wacker oxidation of silyl ether **4.66**.

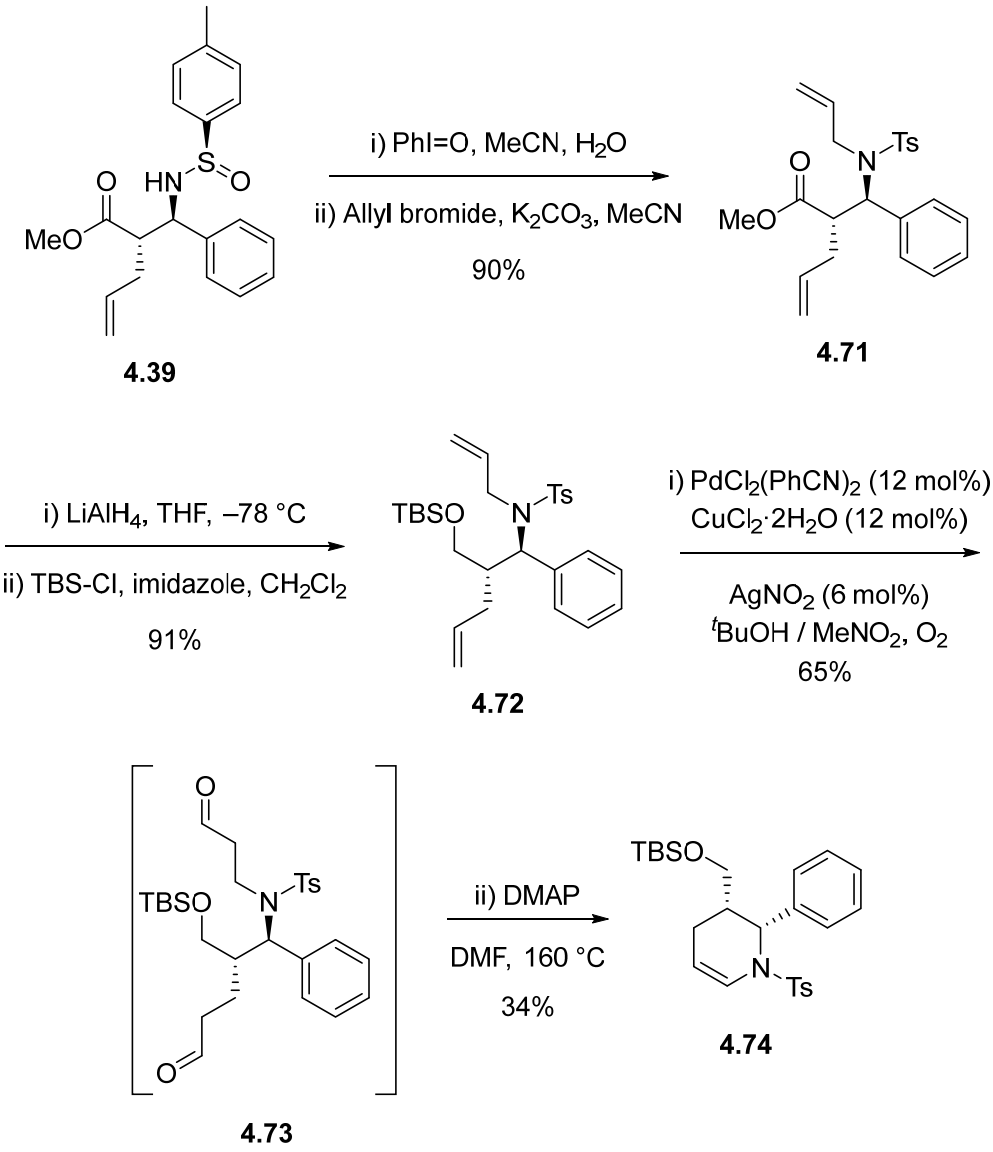
We were intrigued by the idea of blocking this functionality with a group that could be removed as a part of a cyclisation step. An elegant solution was thought to be the use of a *β*-amino aldehyde as this blocking group, which itself could be the product of an AM Wacker oxidation. It was hoped that upon exposure to a non-nucleophillic base, deprotonation of the C_α position of **4.68** would lead to enolate **4.69**, which would then undergo the retro-Michael elimination to give acrolein and amine **4.70**.



4.68 **4.69** **4.70**

Scheme 4.15: Supposed retro-Michael reaction of protected *β*-amino aldehyde **4.68**.

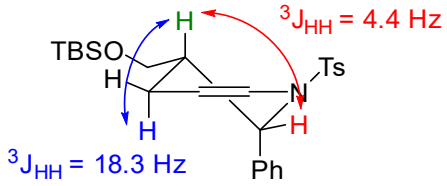
This would perhaps seem a tall order, however precedent presented itself upon consulting the work of Basavaiah[221] and Spaller,[222] who had both noticed this type of elimination in their substrates, albeit as unwanted byproducts of their syntheses. As such, oxidation of the sulfinyl **4.39** to the sulfone **4.62** was followed by *N*-alkylation with allyl bromide to give diene **4.71** (**Scheme 4.16**). TBS protection of the alcohol resulting from reduction of the ester would access diene **4.72**, which was then subjected to the AM-Wacker oxidation conditions.



Scheme 4.16: Synthesis of **4.74** *via* retro-Michael elimination of punitive intermediate **4.73**, prepared from alkene **4.39**.

Whereas with the previous attempts, the aldehyde appeared to be the minor byproduct in the oxidation (analysis of the ^{1}H NMR of the crude product giving >20:1 ketone/aldehyde), pleasingly the evolution of several aldehyde peaks were now observed after the AM-Wacker oxidation. However, analysis of the crude was complex, indicating the formation of several other products as part of the reaction. As such, the retro-Michael reaction was attempted on a portion of this mixture, using the conditions published by Basavaiah. To our delight, protected enamine **4.74** was isolated in modest yield from this two-step reaction sequence. The conformation of the protected alcohol chain and the phenyl ring were able to be proven at this point, after careful coupling constant analysis (**Figure 4.4**). Despite several attempts, the overall yield of this process could not be improved upon, likely due to there still being appreciable amounts of the Markovnikov ketone product

produced in the Wacker oxidation. Therefore, although an interesting synthetic diversion, this method to obtain our wanted piperidines was not further explored.



4.74

Figure 4.4: Coupling constant analysis of half-chair structure **4.74**.

4.4 Alternative alkylating agents

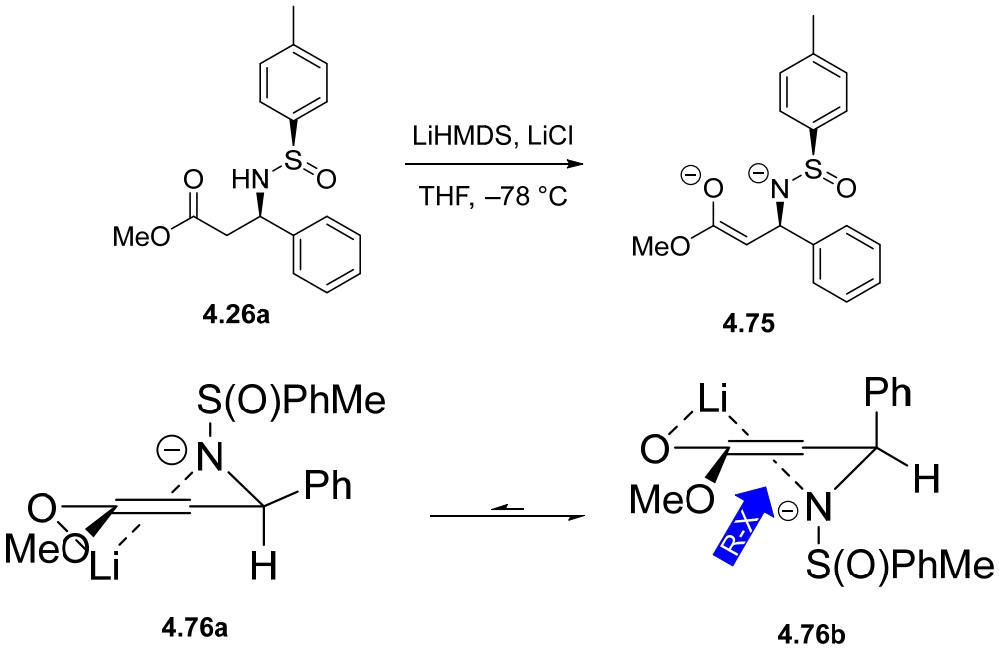
Whist obviously disappointed at the only modest success at preparing pipiridines *via* an AM-Wacker oxidation, there were other methods left at our disposal. With the pendant alkene seemingly at a dead end, it was decided to explore other possible electrophiles for use in the *anti* alkylation step. We had previously noted that only three alkylating agents – methyl iodide, allyl iodide and benzyl iodide – were used in Davis' original communication, and supposed that this did not represent the only agents that could be used in this reaction.[202]

4.4.1 Mechanistic considerations

At this stage, consideration of the course of the reaction is prudent, as this might reveal some insight into what makes an ideal alkylating agent. The alkylation of a chiral *β*-amino ester is analogous to that of the Fráter-Seebach alkylation of chiral *β*-hydroxyl esters.[223-225] The double deprotonation of our substrate **4.26a** leads to the dianion species **4.75**, which is proposed to exist as a half-chair conformation (**Scheme 4.17**).[202, 226] This could be either one of species **4.76a** and **4.76b**, with the phenyl ring occupying a *pseudo*-equatorial or *pseudo*-axial position respectively. **4.76b** is proposed to be the more favoured conformation, as it is able to minimise steric interactions between the sulfinylimine moiety and the phenyl ring itself. Attack of the electrophile would thereby result in the alkylation occurring with *anti* selectivity.

The scope of the reported electrophiles used for the alkylation of *β*-amino esters is somewhat narrow, however. Early reports of this alkylation used substrates similar to the three noted in Davis' communication, with scant innovation. Indeed, the only early alternatives that could be found were Seebach's use of benzaldehyde[227] and Chamberlin's use of iodoethane (noting that the reaction was allowed to progress for 15 days with constant cooling).[228] Hanessian *et al* published the *anti* alkylation of aspartate derivatives,

using a wide variety of iodides or bromides that all possessed an allyl unit adjacent to the side of nucleophilic attack, all with good to excellent yields and good to excellent diastereoselectivity.[229]



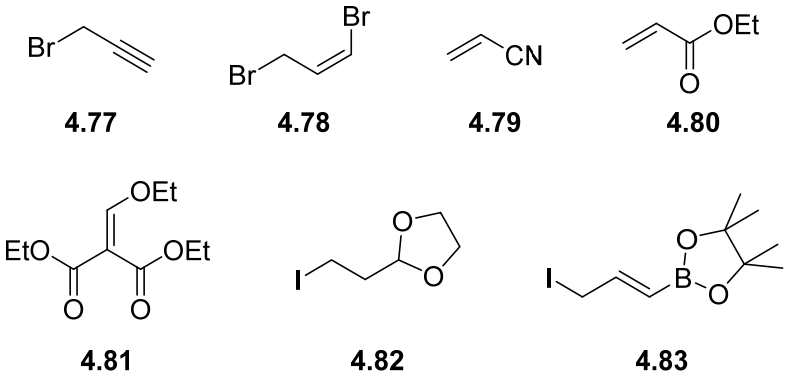
Scheme 4.17: Proposed conformation of dianion **4.75**, indicating the trajectory of alkylation.

What is clear from these examples is that the use of some sort of stabilised electrophile appears necessary to achieve high yields and high selectivities. In several cases where longer chain alkyl halides were used, yields and selectivities declined drastically.[230] It would therefore seem likely that there would be some stabilising interaction within the transition state from this element of conjugation, leading to a lowering of the energy in the transition state and a subsequent rise in the yield of the reaction at lower temperatures.

4.4.2 Choice of electrophile

This important piece of information would inform our design of a new alkylating agent substantially. Paired with our desire to effect a piperidine ring closure after the alkylation, a series of potential electrophiles were decided upon (**Figure 4.5**). These exhibit the characteristics needed, with propargyl bromide **4.77** and 1,3-dibromopropene **4.78** exemplifying substrates with good conjugation to the S_N2 centre. Michael acceptors **4.79**, **4.80** and **4.81** were also thought to be amenable to the reaction, and carried functionalities that could be easily manipulated subsequently to effect ring closure. Iodide **4.82** was thought worthy of an attempt – even if this did not possess the exact properties we required, the short alkyl chain and ease of elaboration presented an attractive diversion. Finally,

iodide **4.83** was thought to be an interesting substrate, as the tethered alkenylboronic acid could provide access to further chemical transformations.



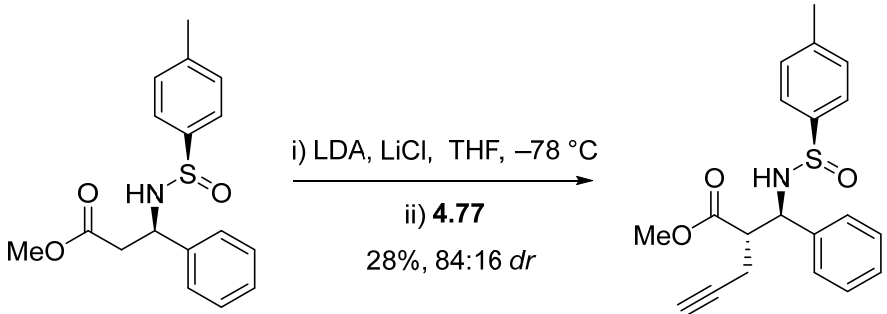
4.77 **4.78** **4.79** **4.80**

4.81 **4.82** **4.83**

Figure 4.5: Potential electrophilic partners for the *anti* alkylation step.

4.4.3 Propargyl bromide and subsequent re-examination of the reaction

The easiest new electrophile to test was propargyl bromide **4.77**. A successful *anti* alkylation of this substrate could open up several new pathways towards the cyclisation, including hydrozirconation,[231] and an alternative hydroboration. As such, ester **4.26a** was subjected to the standard *anti* alkylation conditions, and to our surprise alkyne **4.84** was only isolated in 28% yield, with much diminished selectivity (**Scheme 4.18**). This result was unexpected, as for all intents and purposes, **4.77** should have been an excellent electrophilic partner for this reaction, and there are reports of the successful alkylation in a similar manner, albeit with low selectivity.[232]



4.26a **4.84**

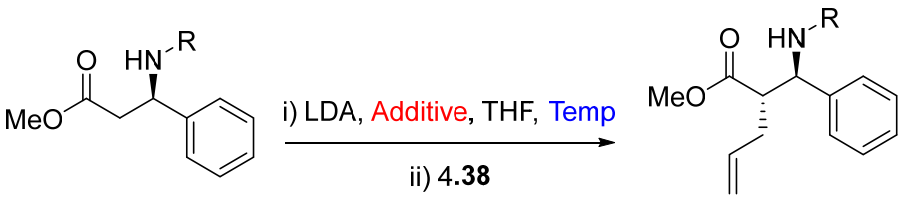
Scheme 4.18: Initial *anti* alkylation attempt using **4.77**.

Based on this result, we were interested in whether the LiCl additive was responsible for this lowered yield. Classically, the addition of an additive to lithium enolate formations is used in order to break up the aggregation of the enolates in solution. The enolates of *β*-amino esters are known to exist as hexamers in solution.[233-234] This propensity of aggregation is often a cause of long reaction times, lower yields, and lowered selectivities. By breaking up the aggregation with additives such as LiCl, HMPA or DMPU, it has been

suggested that the intramolecular chelation shown in **Scheme 4.17** can take place, enhancing the selectivities obtained from these reactions.

However, the literature also has examples of *anti* alkylations of *β*-amino esters involving no addition additive in the reaction.[225, 228, 235] As such, we were interested in taking a step back and evaluating the influence of LiCl on the *anti* alkylation of our substrate **4.26a**, the results of which are summarised in **Table 4.6**. As we were conducting these investigations, we were also curious as to whether it was possible to conduct the alkylation using the alternative Cbz-protected substrate **4.85**, in order to prevent any possible issues arising from the previously seen *N*-alkylation. We returned to our model reaction, using allyl iodide **4.38** in order to investigate this, and as such we could compare these new reactions to those already reported (**Table 4.4**).

Table 4.6: Investigation and further optimisation of the *anti* alkylation of *β*-amino esters.



R = S(O)PhMe, **4.26a**
R = Cbz, **4.85**

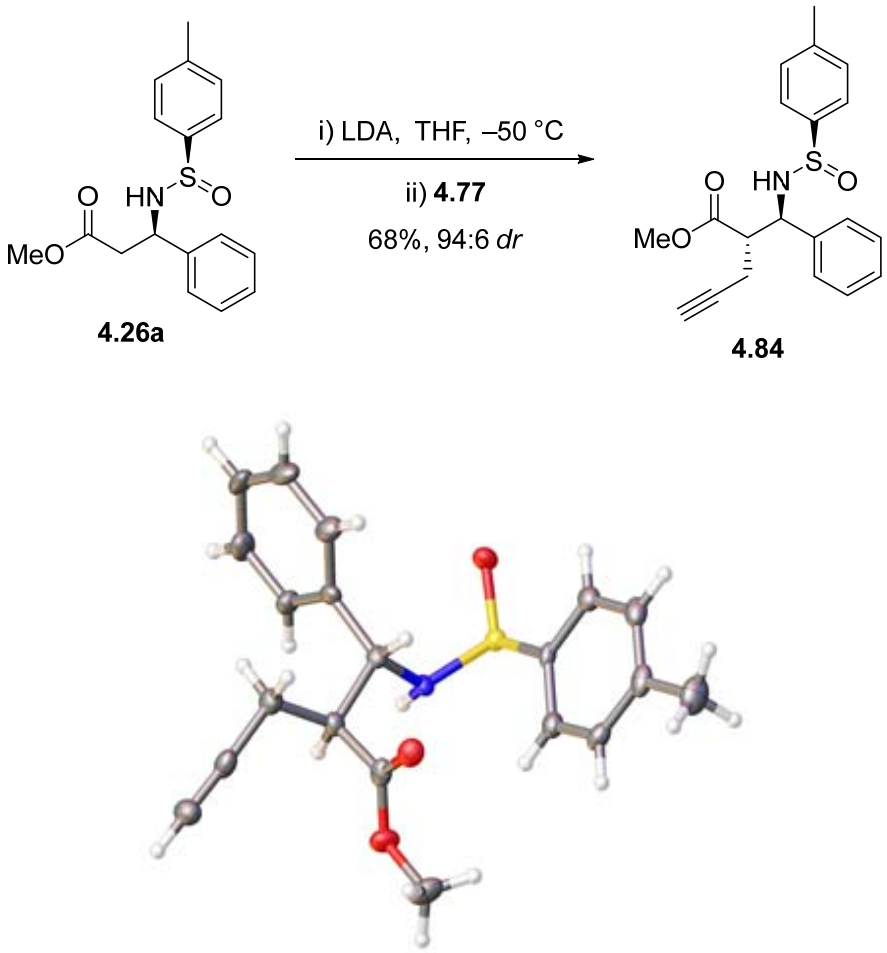
R = S(O)PhMe, **4.39**
R = Cbz, **4.60**

Entry	Substrate	Additive	Temp / °C	Product	Yield	*dr* (*anti*/*syn*)
1	**4.26a**	LiCl (10 eq)	–78	**4.39**	38	>99:1
2	**4.26a**	LiCl (10 eq)	–50	**4.39**	63	>99:1
3	**4.26a**	None	–20	**4.39**	74	97:3
4	**4.85**	LiCl (10 eq)	–50	**4.60**	73	93:7
5	**4.85**	None	–50	**4.60**	88	93:7

These results indicated that the LiCl may not be critical with our substrates; while there is a small decrease in the observed *dr* of the reaction, the substantial increase in yield offsets this drawback (**Table 4.6**, **Entries 1-3**). Importantly, substitution of the sulfinyl group with the Cbz group would also provide access to the *anti* alkylated derivatives in high yields and good *dr*. This reaction would also offer one other benefit – no *N*-alkylated byproducts were observed in the reaction, preventing the complications of the *bis*-chloropropyl byproduct **4.31**. The yields from the Cbz substrate were also highly reproducable.

Armed with this new information, we attempted the alkylation with **4.77** again, without the presence of added LiCl. To our great delight, the reaction proceeded in good yield and

high diastereoselectivity (**Scheme 4.19**). The serendipity of a crystalline product allowed the unambiguous determination of the absolute stereochemistry, and offer proof that we were indeed forming the *anti* alkylated products in our investigations.

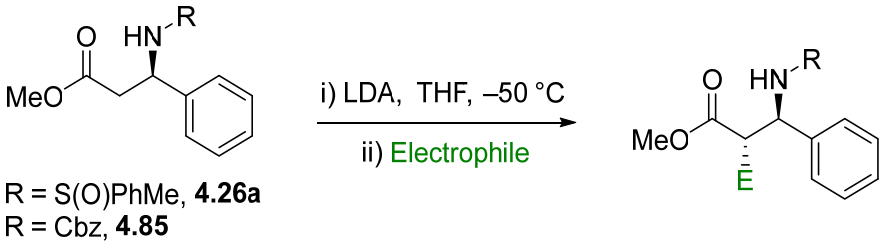


Scheme 4.19: Revised synthesis of alkyne **4.84**. The solved crystal structure of **4.84** is shown, with thermal ellipsoids drawn at the 50% probability level.

4.4.4 Further *anti* alkylation attempts

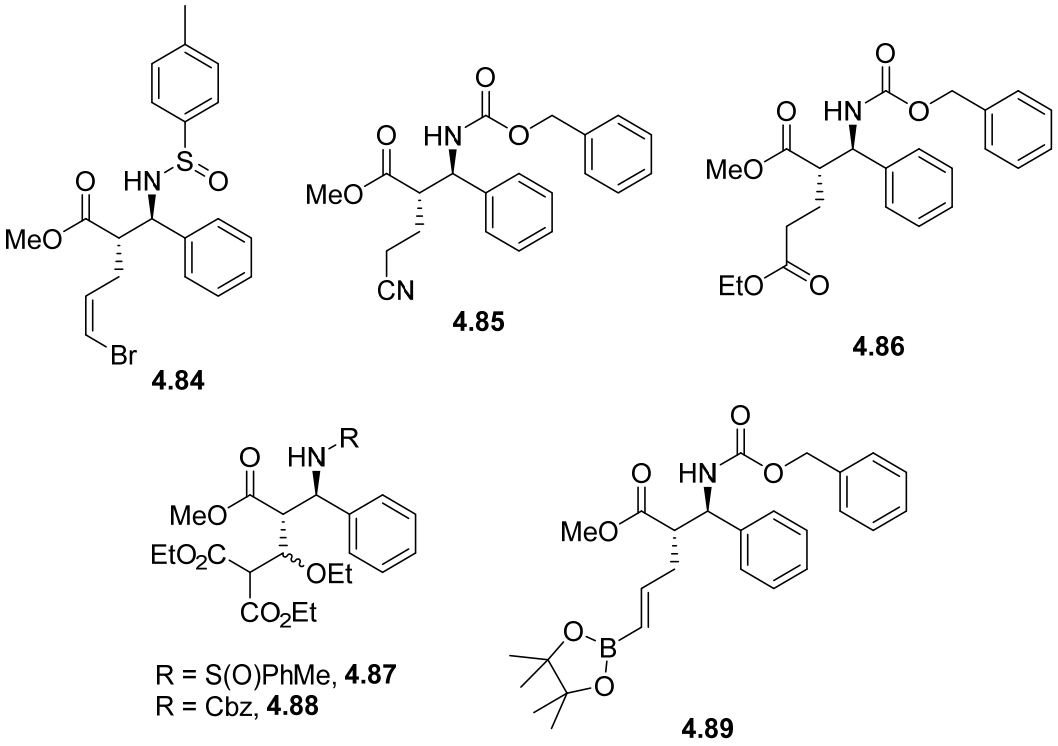
With robust methods for the successful alkylation with propargyl bromide **4.77**, attention could now be focused on the alkylations of several of the other substrates mentioned previously (**Figure 4.5**). Given the propensity of LiCl to cause problems, as well as the added complication of *bis*-chloropropyl byproduct **4.31**, it was decided to attempt some of these alkylations using the Cbz protected substrate **4.84**, given the higher yields and significant simplification of the reaction that it afforded. As such, a variety of electrophiles were trialled using these conditions, summarised in **Table 4.7**, with potential products from the reaction shown in **Figure 4.6**. Two of our planned electrophiles were not commercially available, and were thus synthesised as shown in **Scheme 4.20**.

Table 4.7: Attempted *anti* alkylations of **4.85**, and comparisons to the analogous alkylation of the original sulfinyl substrate **4.26a**.[a] Yield of a mixture of **4.89** and unknown impurities.



R = S(O)PhMe, **4.26a**
R = Cbz, **4.85**

Entry	Substrate	Electrophile	Product	Yield (%)	*dr* (syn/*anti*)
1	**4.26a**	**4.78**	**4.84**	19	83:17
2	**4.85**	**4.79**	**4.85**	0	-
3	**4.85**	**4.80**	**4.86**	0	-
4	**4.26a**	**4.81**	**4.87**	19	98:2
5	**4.85**	**4.81**	**4.88**	0	-
6	**4.85**	**4.83**	**4.89**	72[a]	-



4.84 **4.85** **4.86**

R = S(O)PhMe, **4.87**
R = Cbz, **4.88**

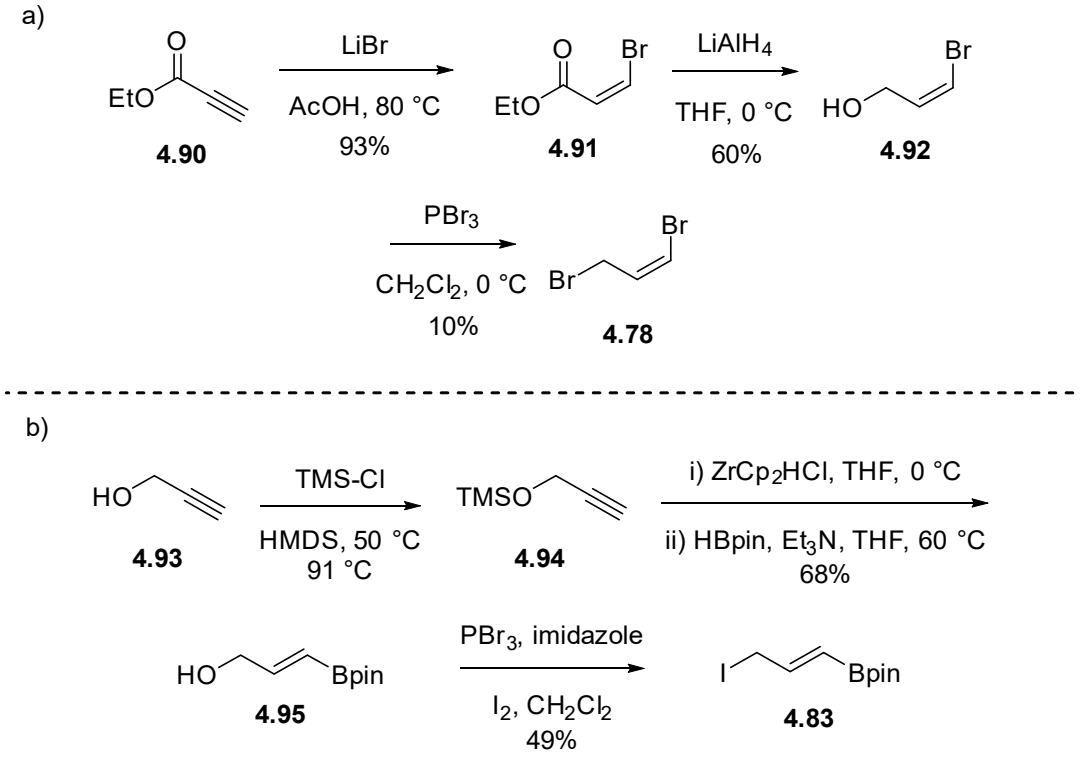
4.89

Figure 4.6: Potential products from the electrophile investigation detailed in **Table 4.7**.

As can be seen from **Table 4.7**, the electrophiles used were universally poor substrates. Dibromoalkene **4.78** proved more capricious to isolate than was anticipated, and as such was used directly after the bromination of alcohol **4.91** without further purification; this could explain the relatively low yield of the reaction (**Table 4.7**, **Entry 1**).

Michael acceptors **4.79** and **4.80** did not proceed, confirmed by ^{1}H NMR and MS analysis (**Table 4.7**, **Entries 2 & 3**). The use of a more electrophilic Michael acceptor **4.81** did progress the reaction, however impure product could only be isolated even after repeated purification, precluding the further investigation of this reaction.

The most interesting result came from the use of iodide **4.83**, the reaction of which would appear to have furnished alkenyl boronic ester **4.89** as indicated by NMR and MS analysis. However, a definitive assignment is not possible, as this was isolated as an impure mixture even after several attempts at purification. It is supposed that the alkenyl boronic acid is susceptible to elimination under the slightly acidic conditions of silica, leading to the perpetual isolation of impure product despite repeated purification attempts. Time constraints did not allow for the further interrogation of this substrate, however the use of **4.83** as a novel 3-carbon aldehyde surrogate warrants further investigation.



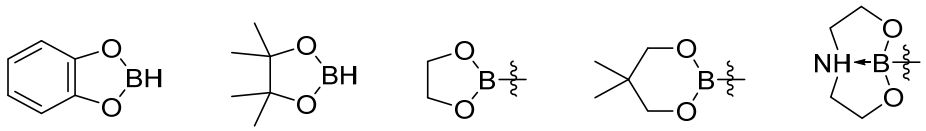
Scheme 4.20: Syntheses of dibromide **4.78** and iodide **4.83**.

4.5 Pathway A(2) – Return to the boron strategy

With an approach based upon an alternative electrophilic partner not offering any solutions, it was decided to attempt another strategy. Ongoing literature research would provide us with a possible solution to the problems with our original hydroboration strategy (**See Section 4.3.1**). The application of a metal-catalysed hydroboration of alkene **4.39** or **4.60** would give rise to a boronic ester, which could be further elaborated in a number of ways.

Metal-catalysed hydroboration of olefins has been studied greatly in the past few decades.[236-238] One important class of products accessed *via* this technique are boron esters, which find use as the quintessential coupling partner of halides within the Pd catalysed Suzuki-Miyaura reaction, oft cited as one of the most important reaction developments in the 20th century.[239] An amenable catalyst for this process is [$RhCl(PPh_3)_3$], better known as Wilkinson's catalyst. This Rh^I catalyst has found ubiquitous use within chemistry, and is used for processes such as hydrogenation,[240] hydrosilylation[241] and, gratifyingly, hydroboration.[242]

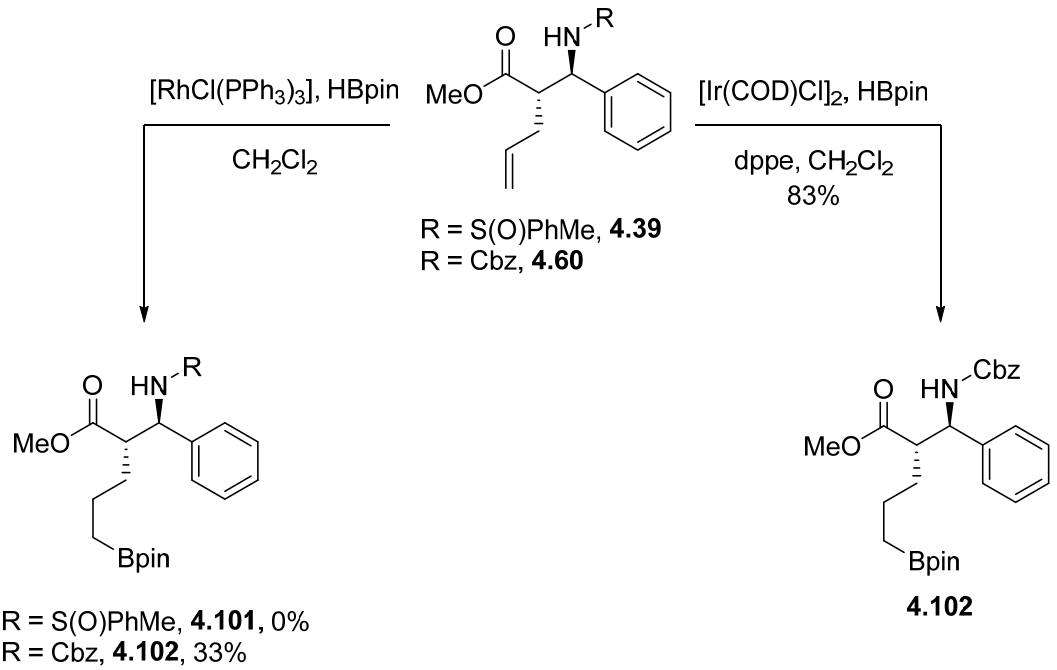
Early processes would use catecholborane (Bcat, **4.96**) as the hydroboration partner, however the relative reticence towards isolation of these derivatives has seen pinacolborane (Bpin, **4.97**) rise in popularity, due to increased stability and subsequent ease of isolation (**Figure 4.7**). Other borane derivatives have been exploited within the literature, such as ethylene glycol esters (Beg, **4.98**), *bis*(neopentyl glycol) esters (Bneop, **4.99**) and diethanolamine derivatives **4.100**.



4.96 **4.97** **4.98** **4.99** **4.100**

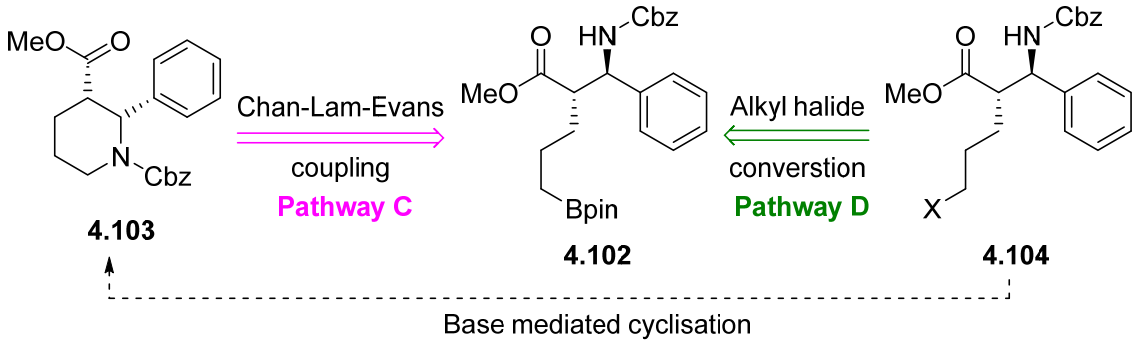
Figure 4.7: Examples of boranes and boronate esters.

Given the relative ease of the hydroboration of olefins with Wilkinson's catalyst, we were minded to attempt this reaction on our substrates. Initial trials with alkene **4.39** proceeded with degradation of starting material, and no observable product evolution by MS. As such, the Cbz-protected derivative **4.60** was used instead (**Scheme 4.21**). A relatively small amount of product **4.102** was formed, unfortunately also concurrently with the reduced alkane byproduct. This would force us to seek alternative reaction conditions to install the boron ester. The use of an iridium catalyst to effect the hydroboration, in a procedure reported by Miyaura, would allow the isolation of the desired boron ester **4.102** in a pleasing 83% yield.[243]



Scheme 4.21: Preparation of boron ester derivatives *via* metal-catalysed hydroboration of HBpin.

With this new functionality present, we would once again find ourselves in a position where several different strategies could allow access to the piperidine product. The option of oxidation to the alcohol derivative was still present, however we were curious if either a more direct approach, or elaboration of more recent chemistry, would provide the solution (**Scheme 4.22**). As such, two pathways became apparent: the use of a Chan-Lam-Evans reaction to directly couple the boron ester and carbamate (**Pathway C**), or by the transformation of the boron ester into an alkyl halide and subsequent cyclisation (**Pathway D**).



Scheme 4.22: New routes towards piperidine **4.103**.

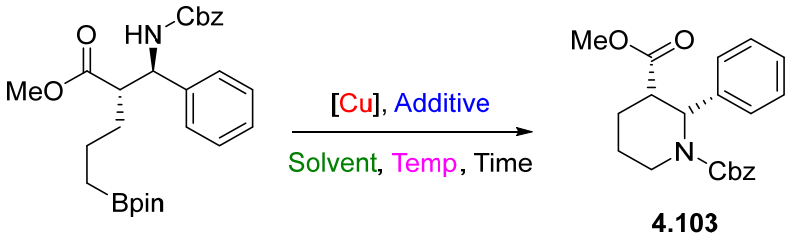
4.5.1 Chan-Lam-Evans approach (Pathway C)

The Chan-Lam-Evans coupling is used to couple boronic acids/esters, stannanes or siloxanes with heteroatom-containing substrates, such as those containing nitrogen, oxygen and sulfur.[244-245] Whilst originally used to couple aromatic substrates, recent

endeavours have been focused in part towards expanding the repertoire of this reaction. The scope of heteroatom substrates have been dramatically increased, and the range of boron esters has been expanded to non-aromatic systems, such as alkyl boronic esters.[246-247]

Relatively little work has been reported on a direct coupling of alkylboronic esters to amides,[248-249] and even less on the coupling to carbamates.[250] It was enticing to us to attempt the cross-coupling on our substrate, as this would be a useful addition to the established literature. As such, we would expose boronic ester **4.102** to a range of established Chan-Lam-Evans coupling conditions in an effort to provide precedent for a further examination of this methodology (**Table 4.8**).

Table 4.8: Attempted intramolecular Chan-Lam-Evans coupling of boronic ester **4.102**. In cases where sub-stochiometric amounts of Cu was used, O_2 was used as an oxidant.



4.102 **4.103**

Entry	Copper source	Additive	Solvent	Temperature / °C	Time / h	Yield (%)
1	$Cu(OAc)_2$ (5 mol%)	$(^tBuO)_2$ (2 eq)	PhMe	50	16	-
2	$Cu(OAc)_2$ (1.1 eq)	Et_3N (5 eq)	MeCN	80	24	-
3	$Cu(OAc)_2$ (2.5 eq)	^{t}BuOK (5 eq)	1,4-dioxane	110	72	-
4	$Cu(OAc)_2$ (1.1 eq)	py	MeCN	80	72	-
5	$Cu(OAc)_2$ (1 eq)	DMAP (3 eq), NaHMDS (1 eq)	PhMe	100	72	-
6	$Cu(acac)_2$ (1.1 eq)	$(^tBuO)_2$ (2 eq), KO^{t}Bu (1.1 eq)	^{t}BuOH	75	24	-
7	CuI (1.1 eq)	$(^tBuO)_2$ (3 eq), KO^{t}Bu (1.6 eq)	^{t}BuOH	70	24	-
8	CuI (20 mol%)	DMAP (40 mol%), Cs_2CO_3 (2 eq)	DMF	80	24	-

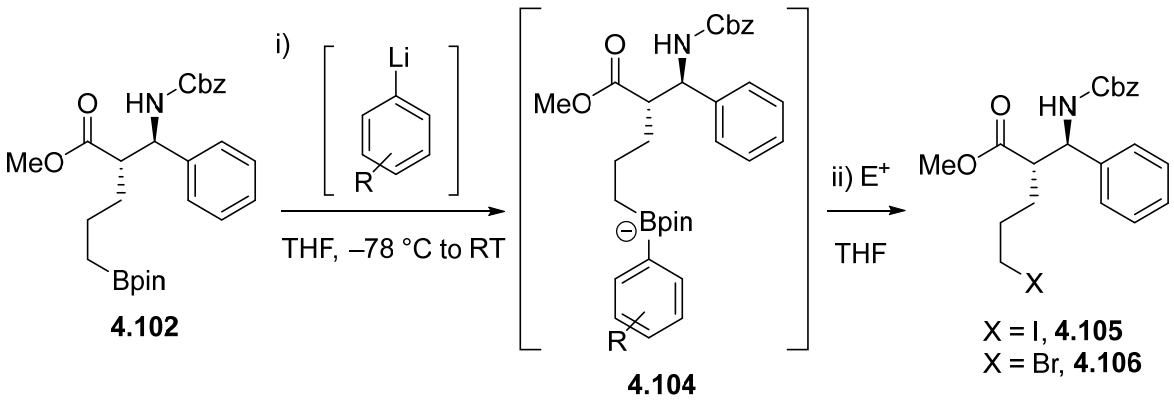
Entry	Copper source	Additive	Solvent	Temperature / °C	Time / h	Yield (%)
9	CuI (20 mol%)	DMAP (40 mol%), Cs_2CO_3 (2 eq)	MeCN	60	24	-
10	CuI (1 eq)	DMAP (2 eq), Cs_2CO_3 (2 eq)	MeCN	60	24	-

Disappointingly, the desired intramolecular cross-coupling was not able to be realised, despite the variation of several different parameters. Carbamate derivatives are known to be frustrating partners in the Chan-Lam-Evans reaction, and we suppose that the inherent lack of reactivity and steric bulk are key factors in the failure of this reaction to proceed.

4.5.2 Alkyl halide conversion (Pathway D)

Given the inability to effect a direct coupling, the final option considered was to convert the boronic ester into a functionality that was more amenable to cyclisation. We were intrigued by a report by Aggarwal of the conversion of boronic esters into reactive nucleophiles by the addition of an aryllithium reagent.[251] The reaction of this ate-complex with a series of electrophiles occurred in good to high yields, and in their case, high enantiospecificity. Due to **4.102** being a primary alkyl boronic ester, this was not a concern, however the innate high-yielding methodology was certainly of interest.

Table 4.9: Synthesis of alkyl halides **4.105** and **4.106** *via* aryllithium addition to boron ester **4.102** and subsequent electrophilic quench of intermediate **4.104**. [a] Isolated as a *ca* 1:1 mixture.

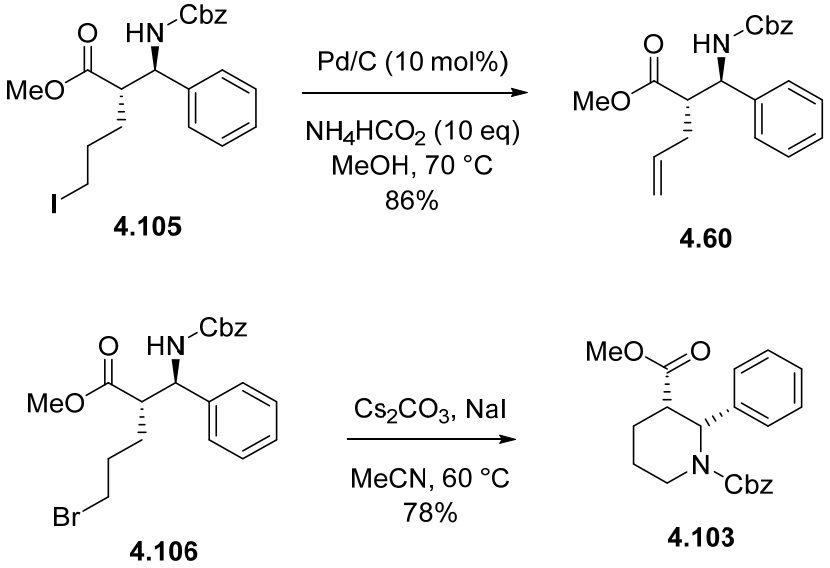


Entry	Aryl	Electrophile	Product	Yield (%)
1	4-bromobenzotrifluoride	NIS	**4.105** / **4.106**	54[a]
2	PhBr	I_2	**4.105**	14

Entry	Aryl	Electrophile	Product	Yield (%)
3	3,5-$(CF_3)_2C_6H_3Br$	NBS	**4.106**	21

Pleasingly, when adapting the protocol of Aggarwal to our substrate, we found that the alkyl halides were able to be accessed. Of note is that a prolonged reaction time when using 4-bromobenzotrifluoride produced both the desired iodide **4.105**, but also bromide **4.106** (**Table 4.9**, **Entry 1**). We attribute this to a background Finkelstein-type reaction occurring from the LiBr byproduct formed in the reaction. The use of more electron-withdrawing aromatics proved beneficial, as compared to an "electron neutral" aromatic ring (**Table 4.9**, **Entry 2**). The use of Aggarwal's "ideal" electron withdrawing aromatic group and NBS as the electrophilic quenching agent proved the most amenable to forming bromide **4.106** in excellent purity, albeit in an unoptimized 21% yield (**Table 4.9**, **Entry 3**).

Whilst optimisation of the reaction was not achieved, with desired alkyl halides in hand, the final ring closure to our desired piperidine seemed within our grasp. Two different steps were attempted: the first was transfer hydrogenation of iodide **4.98** with the hope that Cbz deprotection would take place with an additional *in situ* cyclisation of the pendant iodide (**Scheme 4.23**). Disappointingly, upon reaction only alkene **4.60** was isolated in excellent yield, which can be attributed to elimination of the iodide under the reaction conditions.

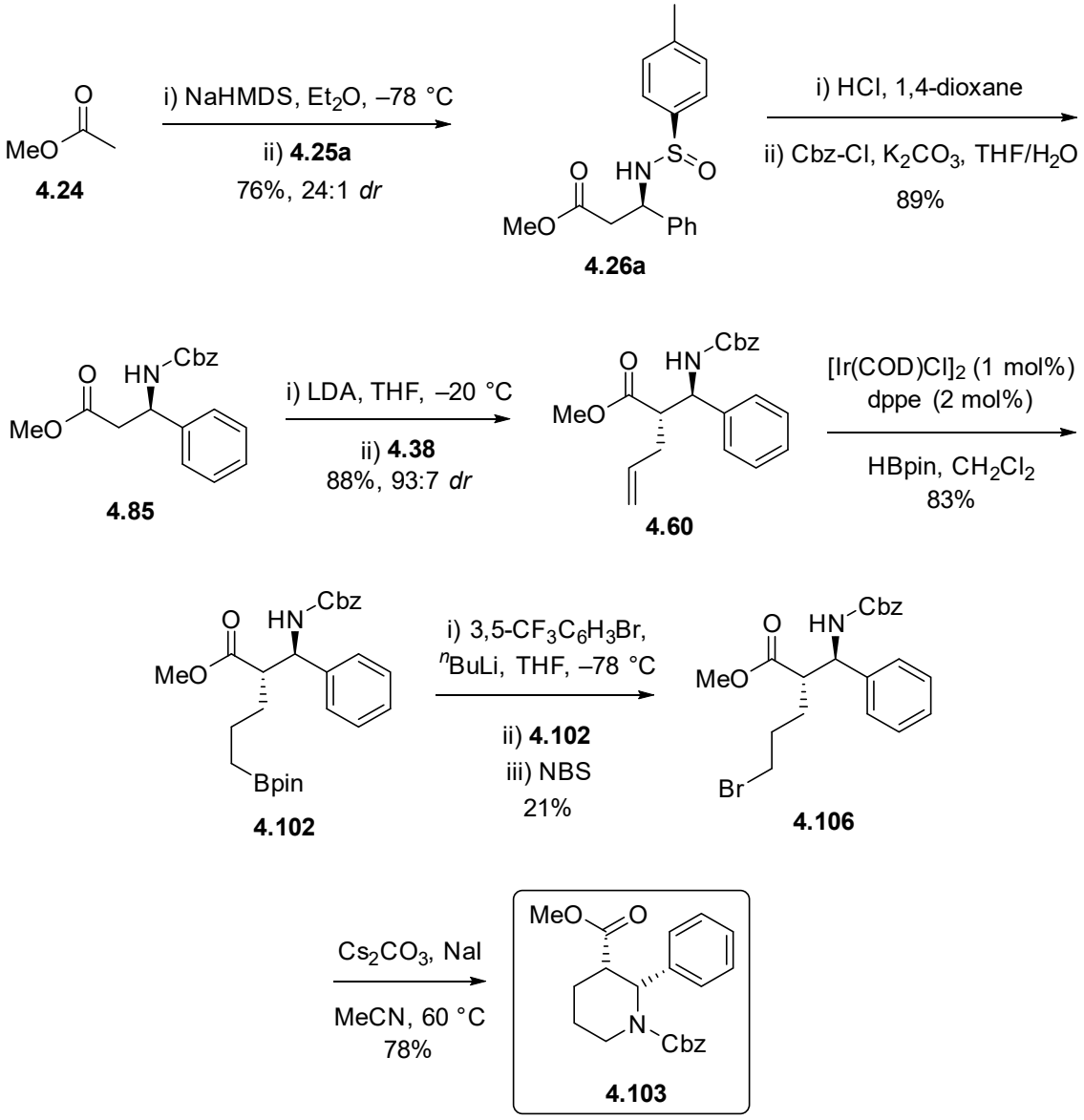


Scheme 4.23: Attempted transfer hydrogenation of **4.105**, and cyclisation of **4.106** to desired piperidine **4.96**.

We would attempt a more straightforward cyclisation on bromide **4.106**, using Cs_2CO_3 and NaI. The use of these more forcing conditions to close the alkyl halide chain were born from our observations that the carbamate moiety is reluctant to deprotonate, while the use of much stronger bases carries risks of epimerisation (*vide infra*). To our overwhelming relief, piperidine **4.103** was isolated in excellent yield. Whilst a need to optimise the

formation of the alkyl halide remains, the successful isolation of piperidine **4.103** would mark a successful conclusion to this project.

4.6 Conclusions and future work



Scheme 4.24: Synthesis of **4.103** from **4.24** and **4.25a**, carried out in 8% overall yield in 6 steps from the starting materials.

Careful investigation and optimisation of the *anti* alkylation of *β*-amino esters **4.26a** and **4.85** provided piperidine **4.103** in 8% overall yield over 6 transformations from *N*-sulfinyl imine **4.25a**. A sequence of methodologies, including hydroboration, AM-Wacker oxidation, Chan-Lam-Evans and boronate-assisted alkyl halide formation were attempted, with the latter sequence eventually bearing fruit. The entire synthetic route is summarised in **Scheme 4.24**. It is envisioned that a library of *cis*-substituted piperidines could be synthesised easily using this methodology, and would compliment the existing prior art well.

Several *anti* alkylations of the *β*-amino esters were carried out using novel electrophilic partners for the reaction, with several showing potential for further analysis. In particular, iodide **4.83** shows significant promise as a 3-carbon aldehyde surrogate, as well as being a potential substrate in further reactions by its own right, for instance as a coupling partner in *N*-acyliminium cyclisations.[252]

Finally, although the ambition of an Anti-Markovnikov Wacker oxidation of alkenes **4.39** and **4.60** was never realised, the tandem process on diene **4.72** represents a novel way of making tosyl-protected cyclic enamines. With further tailoring of the substrate used, this could represent a good (albeit circuitous) route towards these scaffolds.

Chapter 5 Formal synthesis of (+)-sparteine

5.1 Old syntheses and new ideas

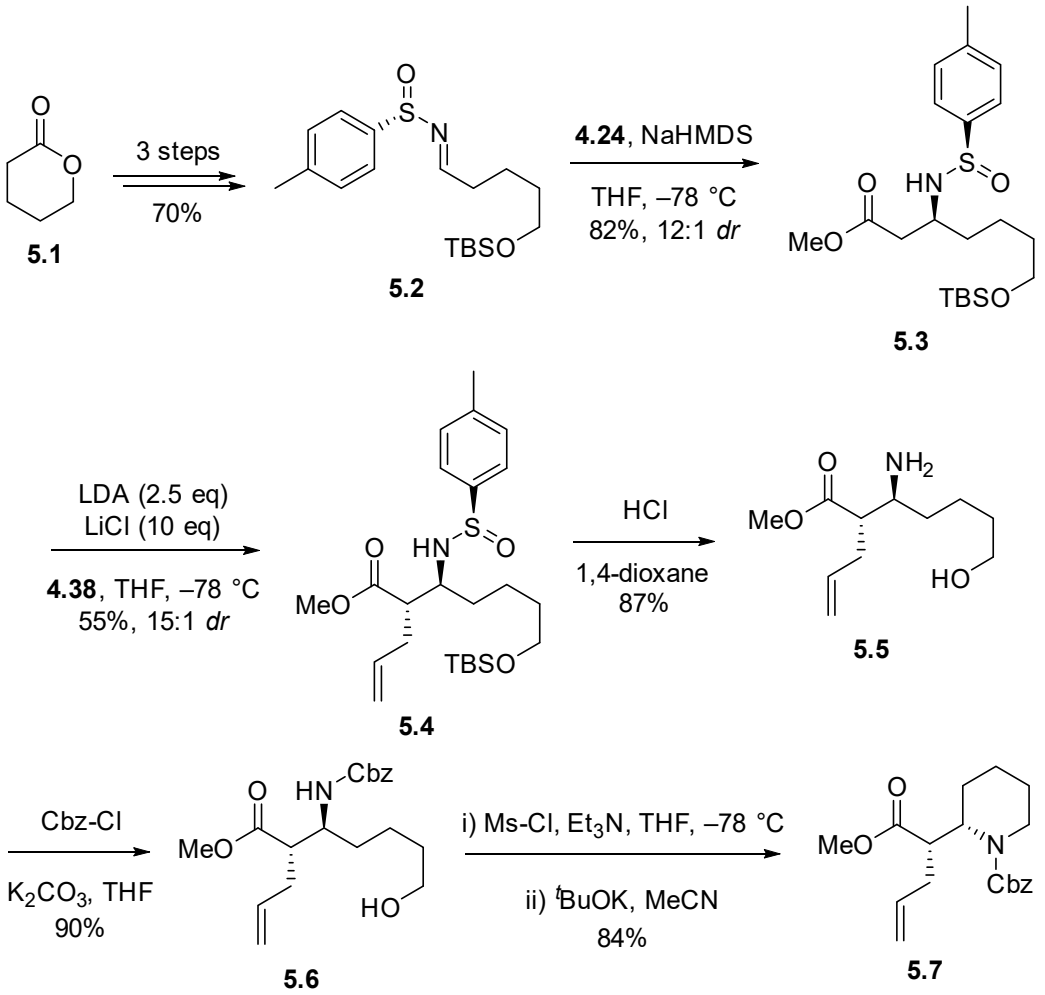
Armed with the wealth of knowledge obtained from our work on the *anti* alkylations of *β*-amino esters, the opportunity arose to use this knowledge to improve upon the total synthesis of (+)-sparteine ((+)-**1.3**) previously conducted by Lyu Xiang as part of his doctoral studies.[185] Inspired by the combination of the *β*-isosparteine route (**Chapter 3**), and using the *anti* alkylation approach, he completed the total synthesis of (+)-**1.3** in 16 linear steps and a 2% overall yield.

This route was based and built around our early applications of the *anti* alkylation approach, and the use of the Davis sulfinylamide **2.24**. As such, there were several early steps that were un-optimised, and the chance to increase the yields and the accessibility of this synthesis was appealing. Finally, it was believed that in the original synthesis, the menthol precursor to **2.24** was not isolated in enantiopure form, which had detrimental effects as the synthesis progressed. We would therefore look to redesign the initial half of the synthesis, using the *anti* alkylation experience we now possessed.

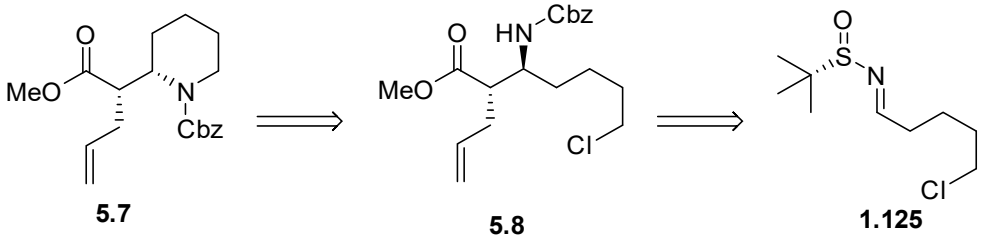
The synthesis of key piperidine **5.7** is shown in **Scheme 5.1**. The initial formation of *N*-sulfinyl imine **5.2** would start from *δ*-valerolactone **5.1**. Preparation of a Weinreb amide would be effected by opening of the lactone with $AlMe_3$ in the presence of *N*,*O*-dimethylhydroxylamine. TBS protection of the resultant alcohol and DIBAL-H reduction to provide the aldehyde derivative *in situ* would allow condensation with sulfinylamide **2.24** to provide **5.2** in 70% overall yield over the three steps.

As before, reaction with the sodium enolate of methyl acetate **4.24** formed *β*-amino ester **5.3** in high yield and with good selectivity. *Anti* alkylation with allyl iodide **4.38** in the presence of LiCl gave alkene **5.4**, which was converted to the Cbz-protected amine **5.6** *via* sulfinyl deprotection to amine **5.5**, which also deprotected the alcohol moiety. Finally, base-assisted cyclisation of a mesylate derivative afforded alkene **5.7** in 20% overall yield over the 9 steps.

We would instead plan to access **5.7** from the cyclisation of alkene **5.8**, which in turn could be accessed from a highly diastereoselective imino-aldol reaction between methyl acetate **4.24** and *N*-sulfinyl imine **1.125** (**Scheme 5.2**). A subsequent protecting group swap to the Cbz group could then be effected, and *anti* alkylation followed by cyclisation of the alkylchloride group onto the carbamate would then afford **5.7**.



Scheme 5.1: Initial synthesis of alkene **5.7** by Xiang Lyu (9 steps, 20% yield).



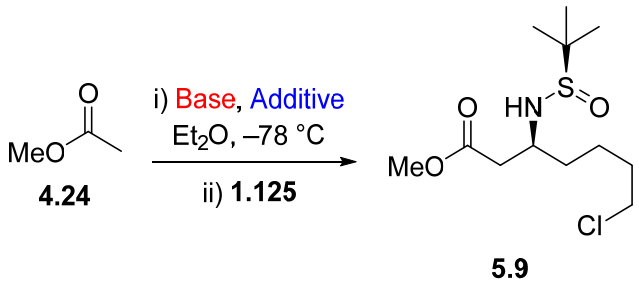
Scheme 5.2: New retrosynthetic approach to alkene **5.7**.

5.2 Forward synthesis and new distractions

With this new approach in mind, the forward synthesis could begin in earnest. Using *N*-sulfinylimine **1.125**, the imino-aldol reaction with **4.24** was attempted. We would start with our previously refined conditions, using NaHMDS to form the sodium enolate of **4.24**, followed by reaction with *N*-sulfinyl imine **1.125** (**Table 5.1**). Much to our dismay, only low yields were obtained, with only 19% of the desired *β*-amino ester isolated, albeit in good *dr* (**Entry 1**). Changing the conditions to a much slower addition of a solution of **1.125** to the pre-formed enolate would only improve the yield to 34% (**Entry 2**). Using LDA as a base

gave a modest improvement in yield, however with a loss of selectivity (**Entry 3**). The use of LiHMDS resulted in an interesting reversal of selectivity (**Entry 4**). Finally, transmetallation of the enolate counterion from Li to Ti resulted in a vast improvement to both the yield and the selectivity (**Entry 5**). The result of the enolate transmetallation was consistent with observations reported by Ellman regarding the synthesis of *β*-amino esters.[166]

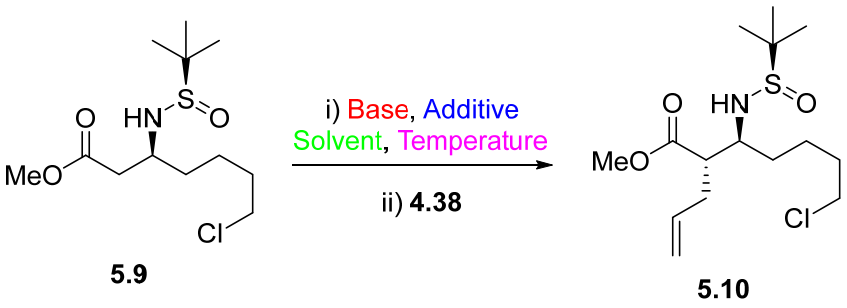
Table 5.1: Optimisation of the imino-aldol reaction between **4.24** and **1.125**.[a] *dr* measured by integration of the NH peak in the ^{1}H NMR of the crude reaction mixture. [b] Addition of **1.125** *via* syringe pump (0.25 mL min^{-1} over 70 min).



Entry	Base	Additive	Yield (%)	*dr* (*R*,*S* : *S*,*S*)[a]
1	NaHMDS	-	19	9:1
2	NaHMDS	Slow addition[b]	34	9:1
3	LDA	-	40	7:3
4	LiHMDS	-	-	4:6
5	LDA	ClTi(O^{i}Pr)$_3$	67	98:2

With the synthesis of **5.9** complete, we were interested as to whether a direct *anti* alkylation of this *β*-amino ester with allyl iodide **4.38** was possible, as this would allow access to the desired alkene derivative in very short order. The exploration of this reaction is summarised in **Table 5.2**. The use of our previously explored conditions afforded **5.10** in low yield and only a 2:1 *dr* (**Entry 1**). Switching the solvent to Et$_2$O completely retarded the reaction, even with increased temperature (**Entries 2 and 3**). Changing the base to LiHMDS afforded similar yields of product with a slight reduction in selectivity (**Entry 4**). Finally, the addition of HMPA as an additive also afforded **5.10** in low yield, with reduced selectivities (**Entries 5 and 6**). We suppose that the steric bulk of the *tert*-butyl group on the sulfinyl auxiliary is responsible for this decrease in selectivity, especially compared to the *p*-tolyl auxiliary used in **Chapter 4**.

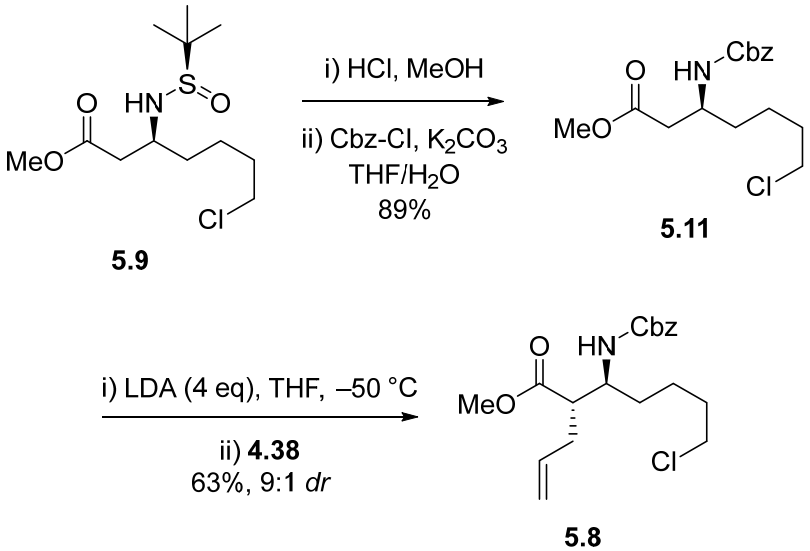
Table 5.2: Optimisation of the synthesis of *anti* alkylated *β*-amino ester **5.10**. [a] *dr* measured by integration of the NH peak in the ^{1}H NMR of the crude reaction mixture



5.9 **5.10**

Entry	Base	Additive	Solvent	Temperature / °C	Yield (%)	*dr* (*anti* : *syn*)[a]
1	LDA (3 eq)	-	THF	–50	27	2:1
2	LDA (3 eq)	-	Et_2O	–50	0	-
3	LDA (3 eq)	-	Et_2O	–20	0	-
4	LiHMDS (3 eq)	-	THF	–20	23	3:2
5	LDA (3 eq)	HMPA (4 eq)	THF	–78	17	3:2
6	LDA (4 eq)	HMPA (4 eq)	Et_2O	–78	-	1:1

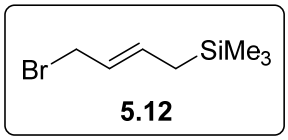
With these disappointing – but not completely unexpected – results, we returned to the original plan; performing the *anti* alkylation on the Cbz-protected derivative. As such, deprotection of the sulfinyl auxiliary and subsequent replacement with the Cbz-protecting group afforded carbamate **5.11** in good yield (**Scheme 5.3**). Gratifyingly, the use of our now standard *anti* alkylation conditions provided alkene **5.8** easily, both in good yield and *dr*



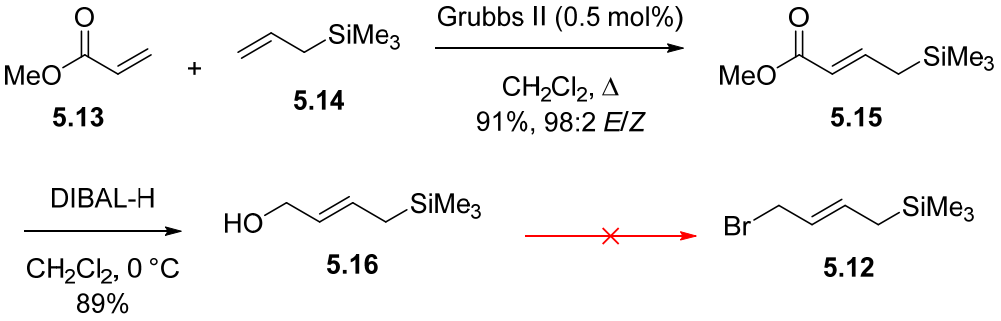
5.9 **5.11** **5.8**

Scheme 5.3: Synthesis of **5.8** *via anti* alkylation of **5.11**.

With this successful *anti* alkylation, we were also interested to see whether we could bring another facet of our *anti* alkylation experience to bear – the use of another tailored substrate as the alkylation partner. Given that we would later want to install an allylsilane motif to effect our *N*-acyl iminium cyclisation, we believed that the use of fragment **5.12** would provide easy access to this functionality (**Scheme 5.4**). However, despite the high yielding olefin metathesis between acrylate **5.13** and allylsilane **5.14** to ester **5.15**, and the subsequent high yielding reduction to alcohol **5.16**, the bromide **5.12** proved too elusive for us to isolate. Several reaction conditions were attempted, including standard Appel conditions[253] and bromination *via* reaction of LiBr with the mesylate derivative *in situ*.[254] However, we believe that **5.12** is highly volatile, and potentially highly reactive and unstable towards isolation, necessitating a re-examination of its synthesis in the future.



5.12

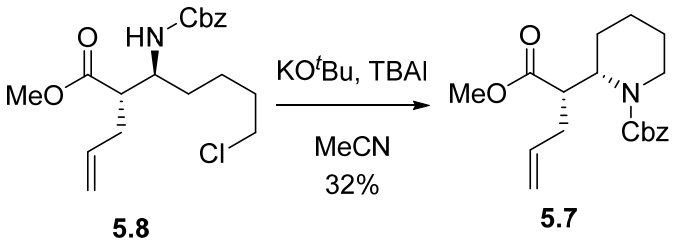


5.13 **5.14** **5.15** **5.16** **5.12**

Scheme 5.4: Attempted synthesis of allylsilane fragment **5.12**.

Thus, we would return to completing the formal synthesis, with just the cyclisation remaining. The cyclisation of the chloroalkyl moiety onto the carbamate presented us with a problem, due to the innate resistance of the carbamate to deprotonation. However, cyclised piperidine **5.7** was successfully synthesised by base-assisted cyclisation, albeit in poor yield (**Scheme 5.5**). This was attributed to degradation of the KO^{t}Bu used – the presence of water within the stored reagent was believed to introduce hydroxide, the effect of which would be to hydrolyse the ester. We also observed some epimerisation of the C_α stereogenic centre in reactions using this tainted batch of KO^{t}Bu, which also affected the yield.

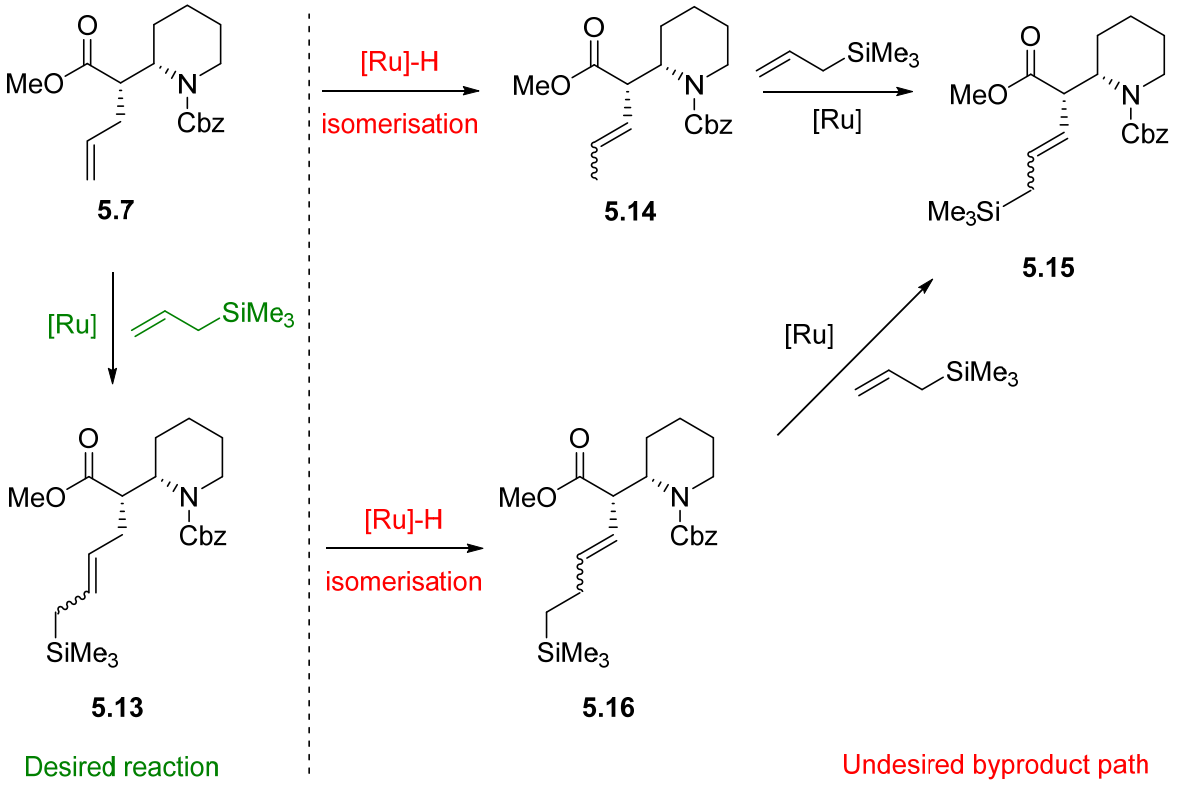
Nevertheless, the isolation of **5.7** completed our goal of a formal synthesis, intersecting with the original route outlined in **Scheme 5.1** in 10% overall yield over a streamlined 6 steps from 5-chlorovaleric acid.**3.13**. Time precluded the optimisation of this reaction, however a proposed solution was enacted in a related synthesis (**See Section 5.3**).



5.8 **5.7**

Scheme 5.5: Completion of the formal synthesis of (+)-**1.3** by synthesis of alkene **5.7**.

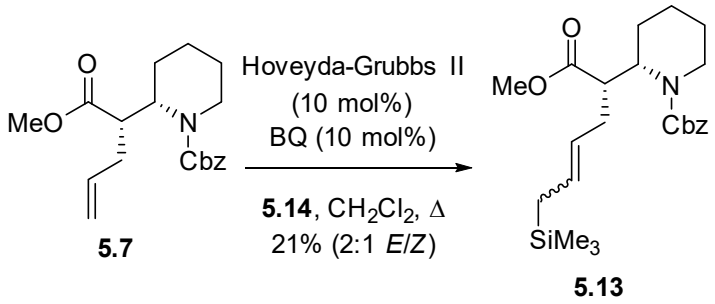
At this point, there was a further chance to improve the original synthesis of (+)-**1.3**, as it transpired that the next step, an olefin metathesis reaction between alkene **5.7** and silane **5.14** suffered from undesirable byproduct formation. We believed that scission of a CH_2 unit was occurring, catalysed by the decomposition of the ruthenium catalyst *in situ*, leading to ruthenium hydride assisted isomerisation pathways (**Scheme 5.6**). This would in turn lead to an undesired chain shortening, leading to alkene **5.15**, which was inseparable from the desired product **5.13**.



Scheme 5.6: Desired olefin metathesis reaction and undesired side reactions catalysed by a ruthenium hydride species.

These undesired isomerisation / chain shortening pathways have been reported previously within the literature, and have been the subject of several investigations. [255-256] We were particularly intrigued by the publication from Grubbs, where the use of 1,4-benzoquinone effectively suppressed ruthenium hydride formation. Armed with this information, **5.7** was subjected to standard olefin metathesis conditions, with the addition of

BQ to suppress hydride formation. Pleasingly, our initial experiments led to isolation of **5.13** with only 4% (by ^{1}H NMR) isomerisation, albeit in a modest 21% yield (**Scheme 5.7**). Time and material constraints did not allow us to further refine this reaction in this instance, however we would return to this reaction in a related synthesis (**See Section 5.3**).

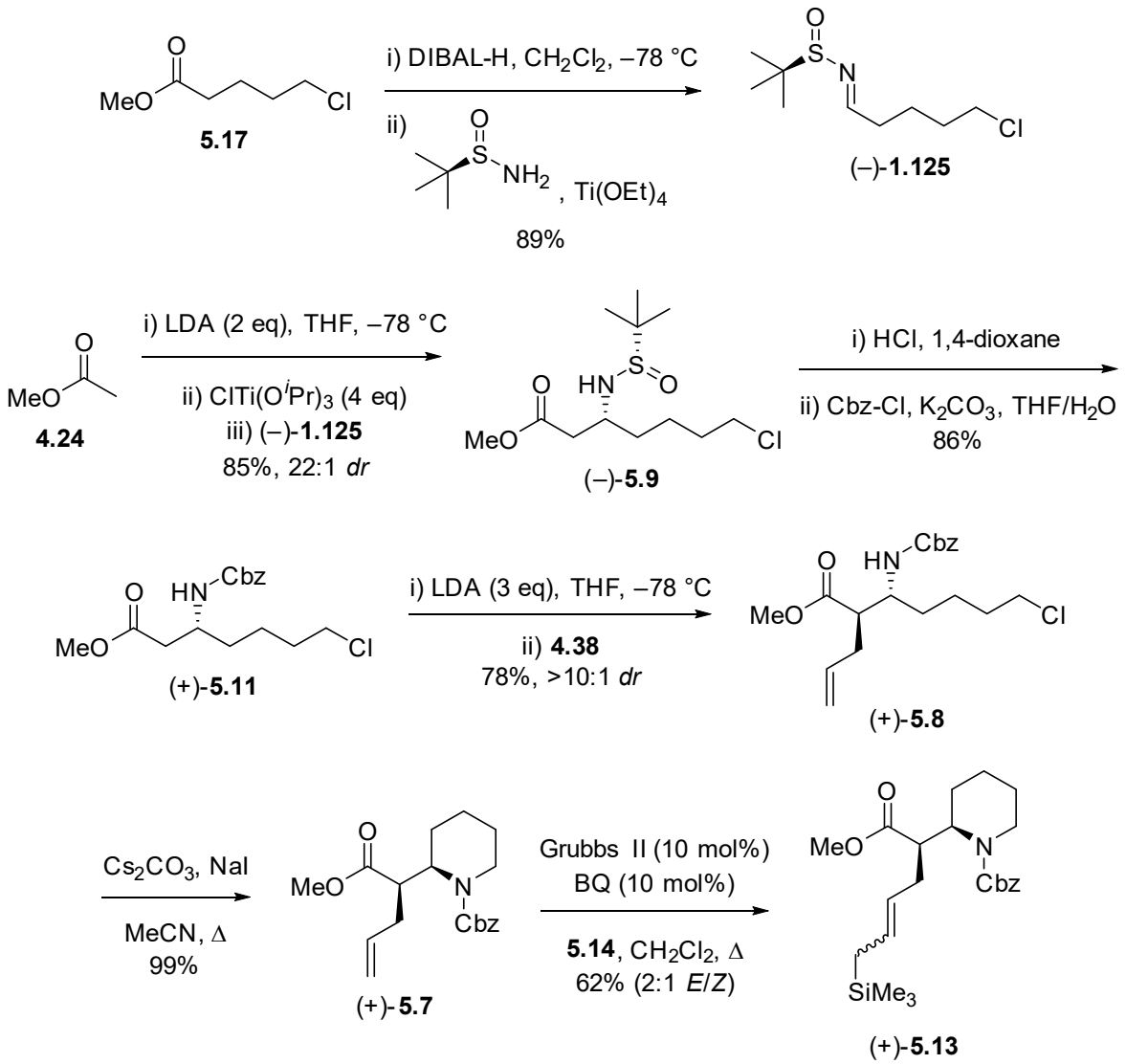


Scheme 5.7: BQ moderated olefin metathesis of alkene **5.7**.

5.3 Progress towards a gram-scale synthesis of (–)-sparteine

With the successful optimisation of the initial half of the total synthesis, we wished to showcase our route in the completion of a gram-scale total synthesis, in order to better prove the efficacy of our route compared to recent contemporary syntheses.[125, 128] Due to the ubiquity of use of (–)-**1.3** within the literature, we set our sights on elaborating our method to a gram scale preparation of this antipode, using the methods we have brought to fruition in the total and formal synthesises of (+)-**1.3**. This would also allow us one last chance to optimise the last remaining reactions, such as the chloroalkyl cyclisation and cross metathesis steps.

The synthesis commenced with the preparation of (–)-**1.125**, using the commercially available *R*-enantiomer of the Ellman auxiliary **2.25**. The imino-aldol reaction using acetate **4.24** proceeded smoothly *via* transmetallation to titanium as before, providing *β*-amino ester (–)-**5.9** in excellent yield and high *dr*. The protecting group swap of the sulfinyl to carboxybenzyl group afforded carbamate (+)-**5.11**, which then underwent an *anti* alkylation using allyl iodide **4.38** to furnish alkene (+)-**5.8** in good yield and with high selectivity. The interrogation of cyclisation strategies on this substrate revealed Cs_2CO_3 to be the optimal base to effect the cyclisation, in the presence of 1 equivalent of NaI. As such, piperidine (+)-**5.7** was synthesised in quantitative yield, with no epimerisation or saponification observed. Finally, BQ assisted cross metathesis of the alkene moiety with silane **5.14** afforded allylsilane (+)-**5.13** in good yield with only a minor trace of the chain shortened byproduct.



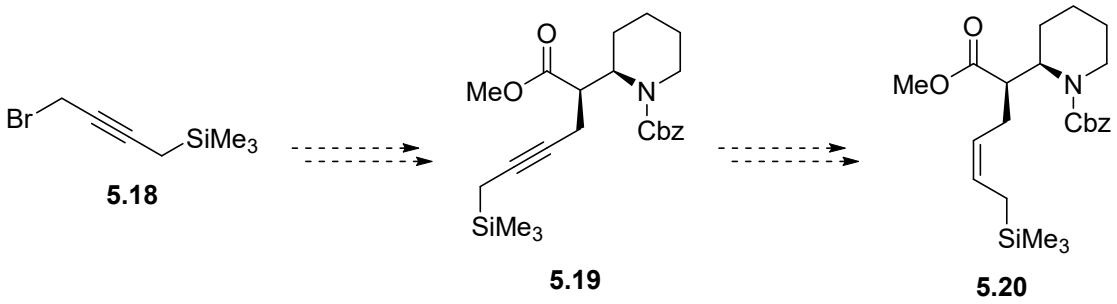
Scheme 5.8: Progress towards a gram-scale synthesis of (+)-**1.3**, conducted jointly with Lyu Xiang.

5.4 Conclusions and future work

Whilst the full synthesis was not completed within the timescale allowed, comparison of this streamlined route to the original (+)-**1.3** synthesis is positive – the original route provided (–)-**5.7** in 20% yield over 9 linear steps, whereas the revised approach afforded the optical antipode (+)-**5.7** in a vastly improved 50% yield in only 5 steps. Significant progress in the cross metathesis step would also be achieved, substantially lowering the amount of byproduct isolated.

Whilst the remainder of the synthesis remains to be completed, a further optimisation of the route could be effected, drawing on the experience of *anti* alkylations gained within this project, and also avoiding the troublesome cross metathesis step (**Scheme 5.9**). The preparation alkyne **5.18** could allow direct access to *anti* alkylated *β*-amino ester **5.19**, which

could then be reduced under Lindlar or P2-Ni conditions to allylsilane **5.20**. Precedent in the literature exists for the selective reduction of the alkyne moiety over the Cbz protecting group, and this could be a useful modification of the synthesis, with the preparation of **5.19** expected to proceed with high *dr* (**See Section 4.4.3**).



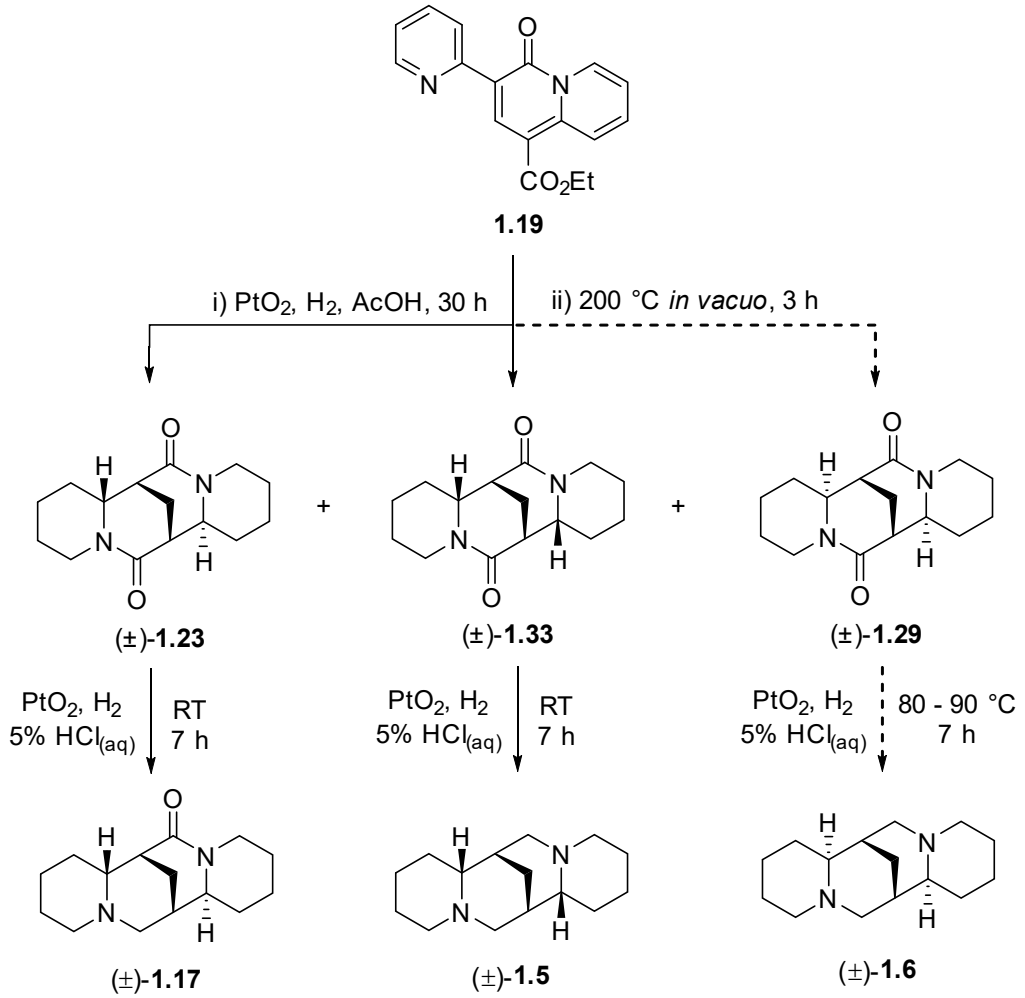
Scheme 5.9: Proposed streamlining of the total synthesis of (–)-**1.3**.

Chapter 6 Synthetic potpourri

6.1 Investigations into the original (±)-sparteine syntheses

6.1.1 Inconsistencies within the original literature

While compiling the review into the syntheses of the sparteine series, we were interested in interrogating the original quinolizidone based syntheses of the sparteine series (**See Section 1.3.1**). The overall route, summarised elegantly by the work of Satoh and Tsuda, is that of a catalytic reductive cyclisation of key quinolizidine **1.19** in order to afford the dioxo species (±)-**1.23**, (±)-**1.29** and (±)-**1.33** (**Scheme 6.1**).[92] However, although they would claim to isolate three different diastereoisomers of sparteine, this is at odds with reports from Clemo, Leonard, Galinovsky & Kainz, and Sorm & Kiel, whose efforts would isolate either (±)-sparteine ((±)-**1.3**) itself, one or other of the diastereoisomers, or all three.

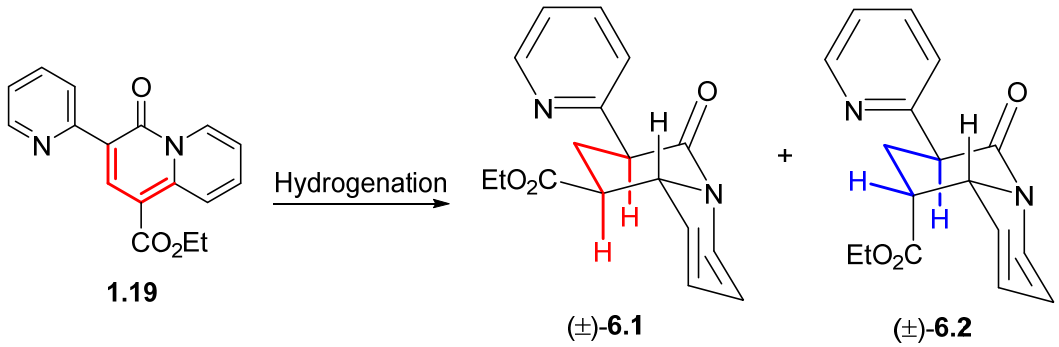


Scheme 6.1: Satoh and Tsuda's proposed syntheses of key sparteine alkaloids.

Unpicking exactly which of the sparteine series were synthesized in these early, groundbreaking experiments is inherently complicated due to the relative lack of analytical techniques available to the investigators at the time. Elemental analysis and melting point data were the tools of the trade, and routine IR analysis - which the later authors used to compare their products - was not available in most laboratories until the late 1950's. Given that the relative stereochemistry present in the sparteine series would also not be completely confirmed until the mid-1960's, it is understandable why – in some cases – products have been misidentified, or even missed, in these communications. Whilst assembling our review, we thought it of value to interrogate this reductive cyclisation further.

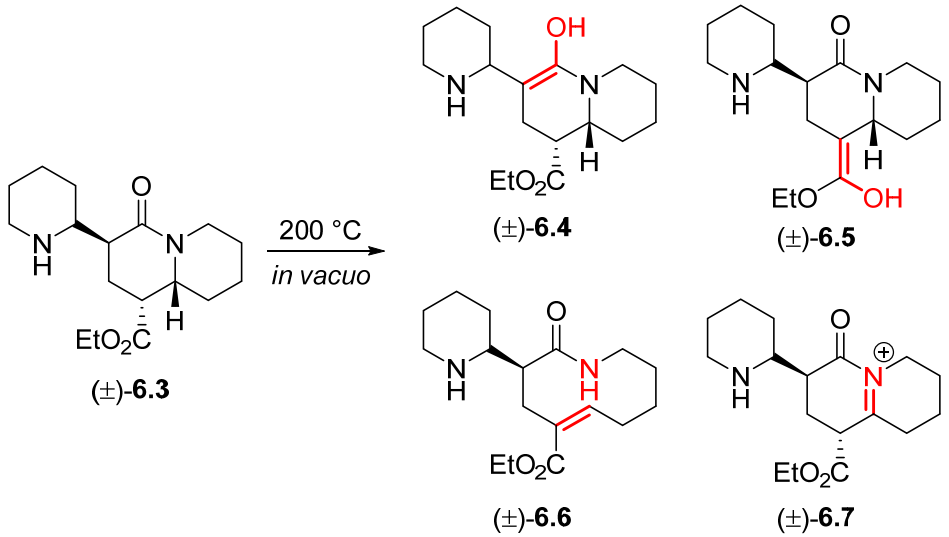
6.1.2 Discussion of these early syntheses

Assuming the stepwise hydrogenation of the double bonds of **3.2**, we can imagine a situation where only the bonds surrounding the future bridgehead of the tetracyclic structure have been reduced (**Scheme 6.2**). Using a non-selective hydrogenation, this would lead either to the *cis* intermediate (±)-**6.1** which would be expected to cyclise, or the *trans* structure (±)-**6.2** which would be unable to do so.



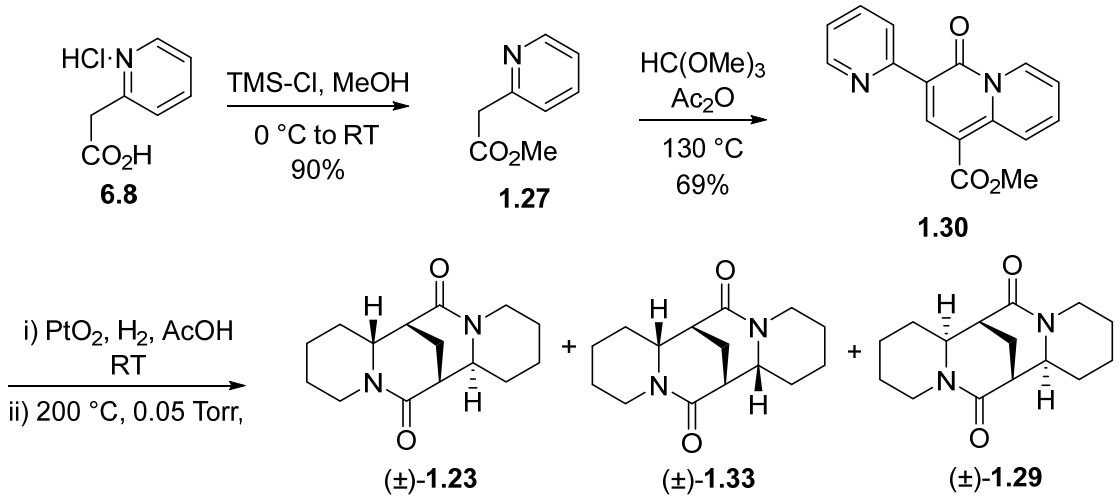
Scheme 6.2: Representation of the two possible relative stereochemistries at the bridgehead.

Under the reaction conditions most often employed, that of heating the crude reduction product *in vacuo* for prolonged periods of time, it is likely that several epimerization events occur, summarized in **Scheme 6.3**. This would have the effect of turning the unwanted *trans* (±)-**6.2** into a structure with a *cis* bridgehead, which would be able to cyclise to the tetracyclic structure. It is also possible that once formed, the dioxo compounds (±)-**1.23**, (±)-**1.33** and (±)-**1.29** could continue to interconvert under these harsh conditions, which would offer an explanation as to why some of the published syntheses report the isolation of only one product, some two and others all three diastereoisomers. The lack of high-field NMR when these accounts were published would have not allowed the determination of these complex mixtures of diastereoisomers.



Scheme 6.3: Possible epimerisations of *trans* structure (±)-**6.3**.

Due to the contradictory nature of products reported in these early syntheses, and lack of NMR data to determine precisely what products were synthesized, we were interested in performing an independent verification of these syntheses ourselves, with a view to establishing the product distribution of the dioxo species after the reductive cyclisation step. As such, we sought to repeat these reactions, and use the privilege of modern analytical techniques to probe the products obtained.



Scheme 6.4: Independent replication of the reductive cyclisation step. GC analysis gave the ratio of (±)-**1.23** : (±)-**1.33** : (±)-**1.29** as approximately 3:1:1.

As such, acid **6.8** was converted to methyl ester **1.27**, and then condensed with methyl orthoformate to afford quinolizidone **1.30** (**Scheme 6.4**). By employing the conditions of Šorm and Kiel,[89] **1.30** was hydrogenated over PtO_2 to afford a mixture of cyclized dioxo species, and what appeared to be uncyclized *trans* species akin to (±)-**6.2**. By heating this crude mixture *in vacuo* at 200 °C, a mixture of (±)-**1.23**, (±)-**1.33** and (±)-**1.29** was obtained. GC analysis of this mixture revealed that these were present in an approximate ratio of

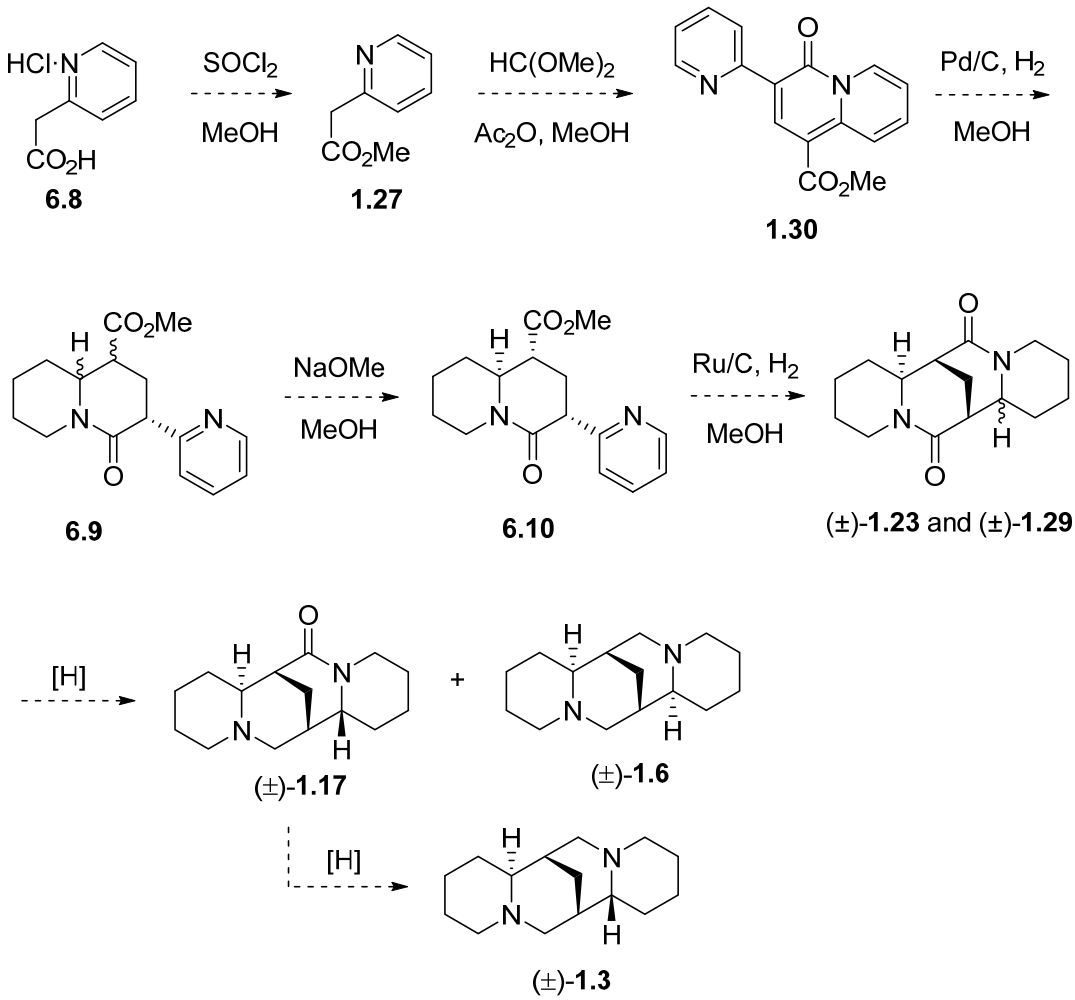
3:1:1, respectively. Further heating of the mixture of the dioxo compounds would fail to change this ratio, leading us to conclude that no further epimerisation occurs once the dioxo species have been formed.

These results served to show that in previous syntheses using a reductive cyclisation step, followed by heating *in vacuo*, all of the dioxosparteine diastereoisomers would have been formed. That not all of these were isolated can be attributed to both (±)-**1.33** and (±)-**1.29** being present as only minor components of the mixture, and to the incomplete understanding of the full stereochemical picture of the sparteine series. For example, (±)-**1.6** was only proven to be a diastereoisomer towards the end of these syntheses, and as such it is not surprising that the isolation of this material was erroneously reported by investigators.

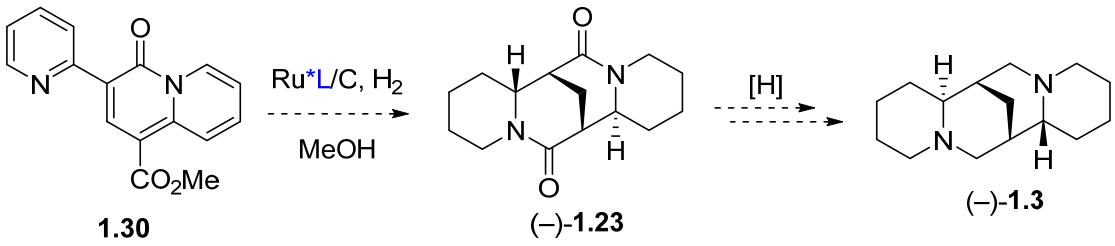
6.1.3 Further investigations

Whilst undertaking this work, it occurred to us that this synthesis of the dioxo species – and ultimately the sparteine series itself – could be amenable to a concise flow synthesis. The formation of quinolizidine **1.30** could be achieved from pyridine salt **6.8** and ester **1.27**. Palladium catalysed hydrogenation under flow conditions is purported to give a mixture of reduced quinolizidone species **6.9**, which has been shown to be epimerizable to the more stable structure **6.10**.[257] A further hydrogenation of the pyridine ring[258] would afford a mixture of (±)-**1.23** and (±)-**1.29**, which could be reduced in flow, first to a mixture of (±)-17-oxosparteine ((±)-**1.17**) and *β*-isosparteine ((±)-**1.6**), which at this stage could be separated due to the crystalline nature of (±)-**1.17**. A final reduction would then afford (±)-**1.3**.

It could also be possible to modify this synthesis further by the use of a chiral ruthenium catalyst to effect the hydrogenation of quinolizidine **1.30**. As it has been shown that quinolizidine **6.10** can be formed by a hydrogenation / epimerization protocol, it is conceivable that the judicious use of a chiral ruthenium hydrogenation catalyst that could effect the hydrogenation of both the pyridine and quinolizidone motifs asymmetrically could access (–)-10,17-dioxosparteine ((–)-**1.23**) directly. This could then be easily reduced fully in flow to the desired alkaloid (–)-**1.3**. In principle, a careful tailoring of this flow hydrogenation step could provide access to all of the sparteine series.



Scheme 6.5: Proposed flow synthesis of (±)-**1.3**, *via* adaptation of the reductive cyclisation route of quinolizidine **1.30**.



Scheme 6.6: Proposed asymmetric flow synthesis of (–)-**1.3**, using an asymmetric ruthenium based catalyst.

6.2 Adventures in organic electrosynthesis

6.2.1 Introduction

All chemical transformations involve the transfer of electrons. Examples of this are oxidative processes in which electrons are lost, or reductive processes in which electrons are gained. Organic chemists use reagents in order to effect these processes, and this art has been refined over the last several centuries. Concurrently with the development of organic synthesis, investigations into the use of electricity to directly mediate reactions have also taken place.

In recent years, it has been noted that we are close to a renaissance of synthetic organic electrochemistry, with several notable reviews on the subject published in recent years, such as by Baran[259] and Waldvogel,[260] and the availability of preparative methods for lab-scale syntheses.[261] In particular, the use of electric current as an inexpensive reagent replacing conventional oxidation and reducing agents is becoming more mainstream, due to the inherent sustainability and often improved safety aspects compared to traditional reagents.[262]

6.2.2 Flow electrosynthesis

One aspect of electrochemistry that has received significant attention in recent years is that of flow electrosynthesis. This involves the marriage of flow chemistry and electrochemical techniques. Flow chemistry provides the advantage of rapid mixing of reactants and targeted heating or cooling of the reaction, which reduces the risk of runaway reactions. This has led to improved safety aspects of reactions, and has provided opportunities for easy scale up of reactions.[263-264] As previously discussed, electrochemistry provides the potential for cheaper and tunable reactions.

The uptake of flow electrosynthesis in a routine laboratory setting has often been hampered by a lack in knowledge transfer of the techniques necessary to support flow electrosynthesis, or the lack of equipment and support designed specifically for non-electrochemists.[265] Literature reactions are often undertaken in beaker cells or H-cells, which provide the convenience of equipment (as these can be built from equipment often found in organic labs), however are inherently disadvantageous due to the often low yields, long reaction times and irreproducible conditions.

There are now, however, many reports in the literature of microflow electrochemical cells for organic synthesis applications.[266] These have the benefit of small interelectrode gaps, often in the micrometer regime, which reduce reaction times by lowering the distance

of mass transfer to the electrode surfaces. This can also lead to a reduced amount of supporting electrolyte needed to aid the reaction; and in some cases, this supporting electrolyte can be removed altogether. These reactions can also often achieve high conversions in a single pass of material, as opposed to other setups which require the recycling of material through the electrode (**Figure 6.1**).[267]

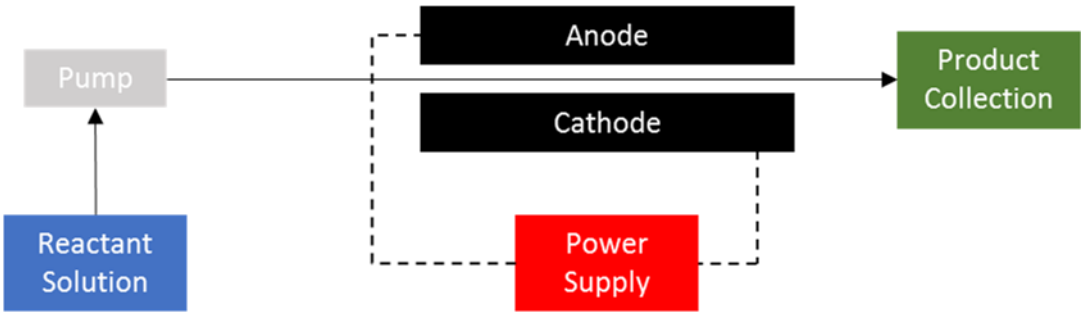
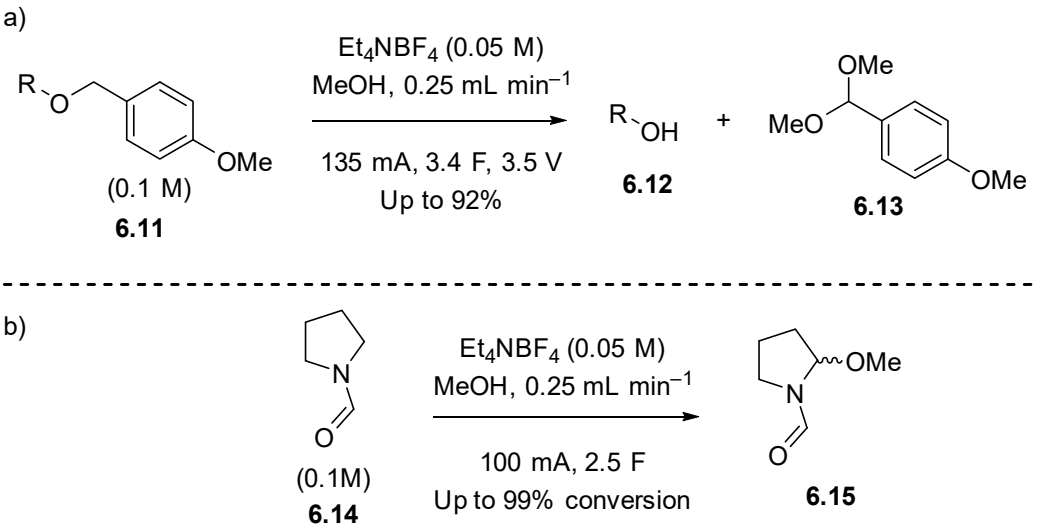


Figure 6.1: Schematic representation of a microflow electrochemical reactor.

The Brown group has been at the forefront of the development of these extended channel electrochemical flow reactors, and has a proven track record of innovating on design and application.[268-270] The latest development within the group was the Ammonite series of reactors, conducted in conjunction with Cambridge Reactor Design (**Figure 6.2**).[271] This cell consists of undivided parallel plate electrodes, with a perfluoroelastomer gasket sandwiched inbetween in order to achieve a narrow interelectrode gap (250 – 750 μm), whilst also providing a long electrolysis channel (1 m) in which to flow the electrolyte.

This cell has been used within the group to cleave protecting groups, such as 4-methoxybenzyl (PMB) ethers,[271-272] and perform the methoxylation of *N*-formylpyrrolidine,[271] all with high conversions and isolated yields (**Scheme 6.7**). Efforts have also been directed into modelling the effects of surfactants on the electrosynthesis reaction itself.[273]



Scheme 6.6: Reports from the Brown group using flow electrosynthesis. a) Deprotection of PMB ethers. b) Methoxylation of *N*-formylpyrrolidine.

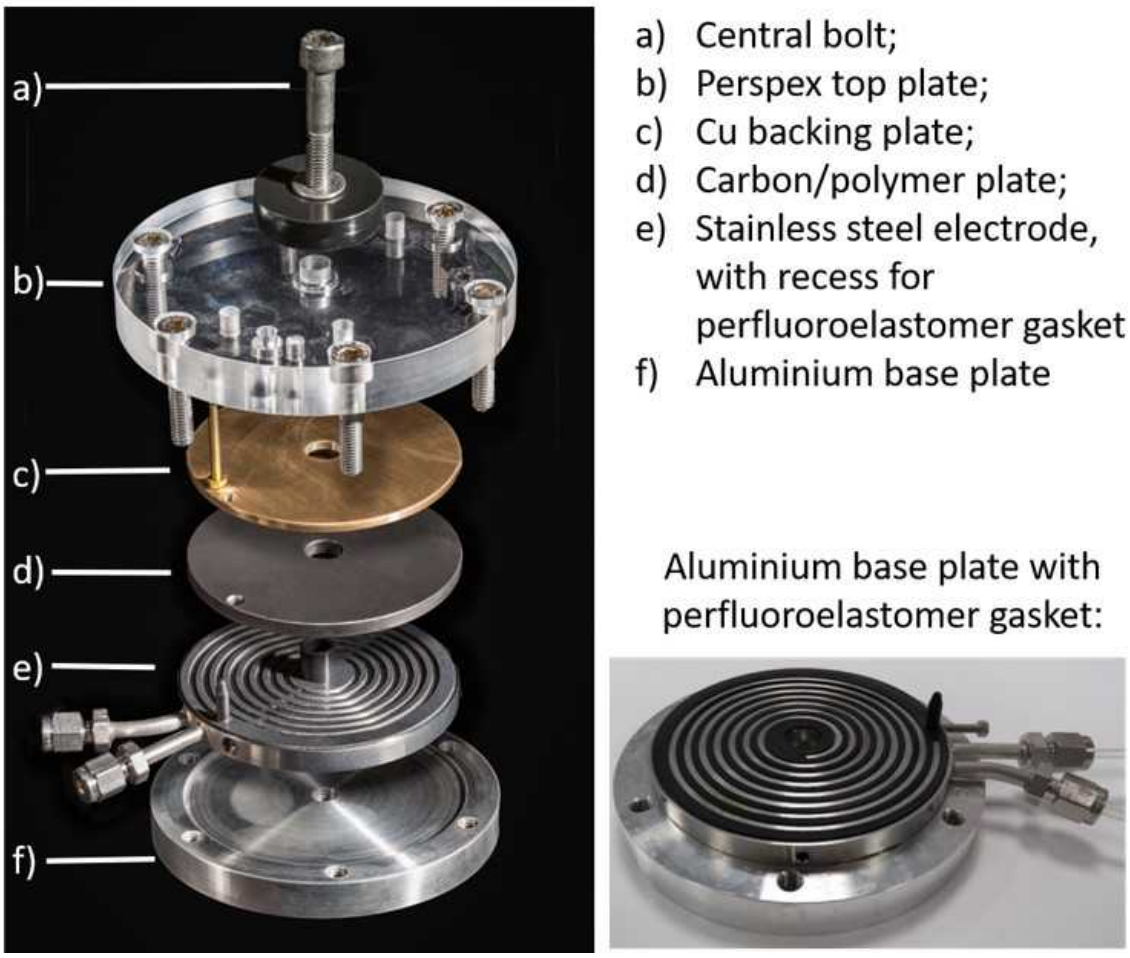


Figure 6.2: Expanded view of the Ammonite 8 reactor, highlighting the cell construction.

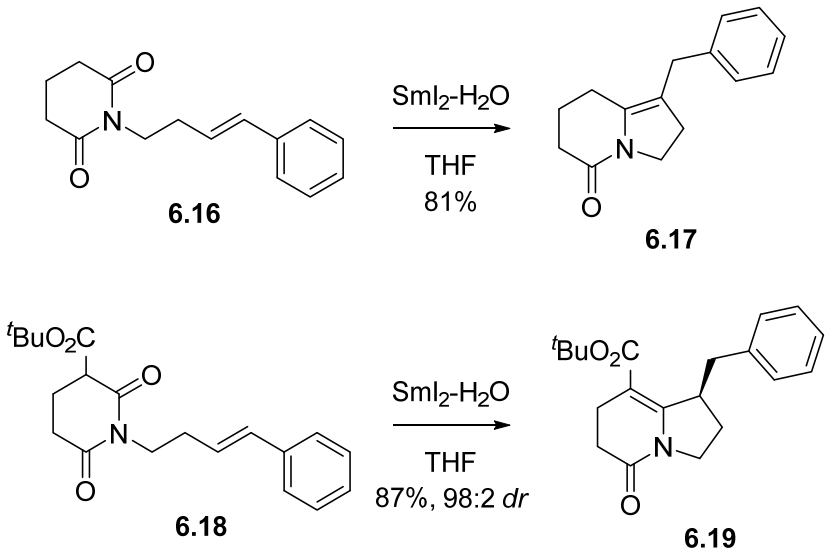
As part of our continued efforts into expanding the portfolio of synthetic transformations achieved within the Ammonite cell, we were interested in two different cyclisation reactions that could take place under electrolytic conditions.

6.2.3 Reductive cyclisations of imides onto styrenes

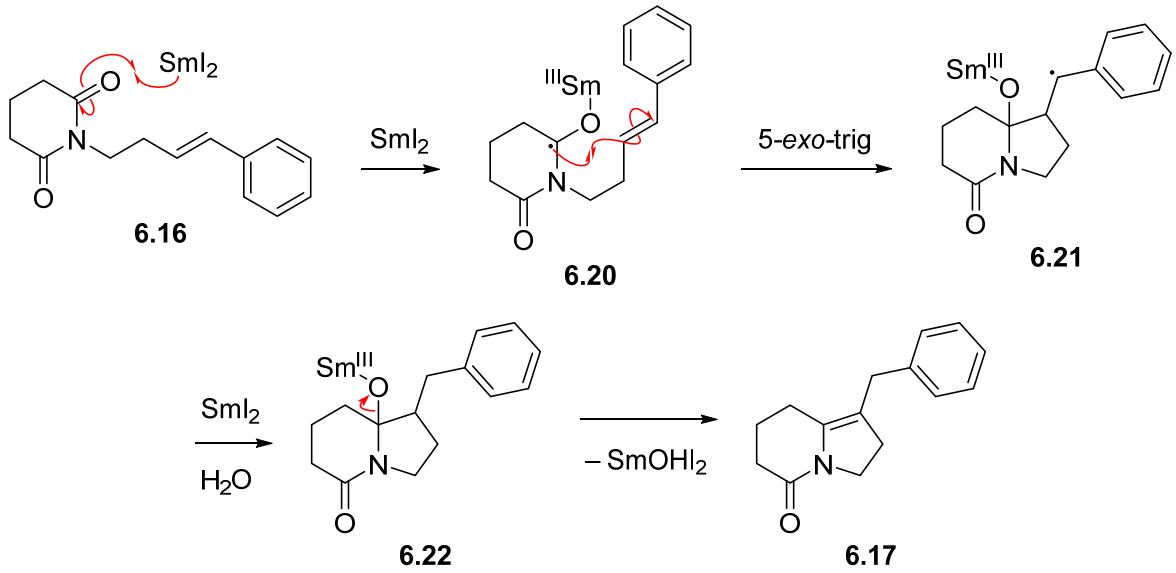
Whilst searching for potential ways to improve the *N*-acyliminium reaction used in the total synthesis of (+)-*β*-isosparteine ((+)-**1.5**), we were drawn to work by Szostak on the synthesis of indolizidine skeletons *via* an aminoketyl radical approach.[274] This would build upon their earlier work synthesising 2-azabicyles using SmI_2-H_2O,[275] and was further evidence of the synthetic utility of SmI_2, a well known single-electron transfer reagent.[276] The use of appropriate ligands and additives allows fine-tuning of this reagent to effect transformations in a chemoselective manner.

The initial report by Szostak described the preparation of indolizidine scaffold **6.17** in a single reaction from tethered imide **6.16**, in high yield (**Scheme 6.7**). The position of the double bond could be controlled by the addition of an ester moiety as part of the imide, as in the case of the cyclisation of **6.18** to **6.19**. The course of the reaction is purported to

proceed akin to **Scheme 6.8**. Initial formation of amidyl radical **6.20** would allow a 5-*exo*-trig cyclisation to occur, affording **6.21**. Further reduction with SmI_2 and protonation by H_2O would give intermediate **6.22**, which could then undergo elimination facilitated by hydroxide to provide indolizidine **6.17**. This mechanism also explains the formation of **6.19**, due to the favoured loss of the proton at the C_α position to the ester moiety.



Scheme 6.7: SmI_2 mediated reductive cyclisations of tethered imides.



Scheme 6.8: Purported reaction mechanism of the SmI_2 mediated reductive cyclisation to afford indolizidine **6.17**.

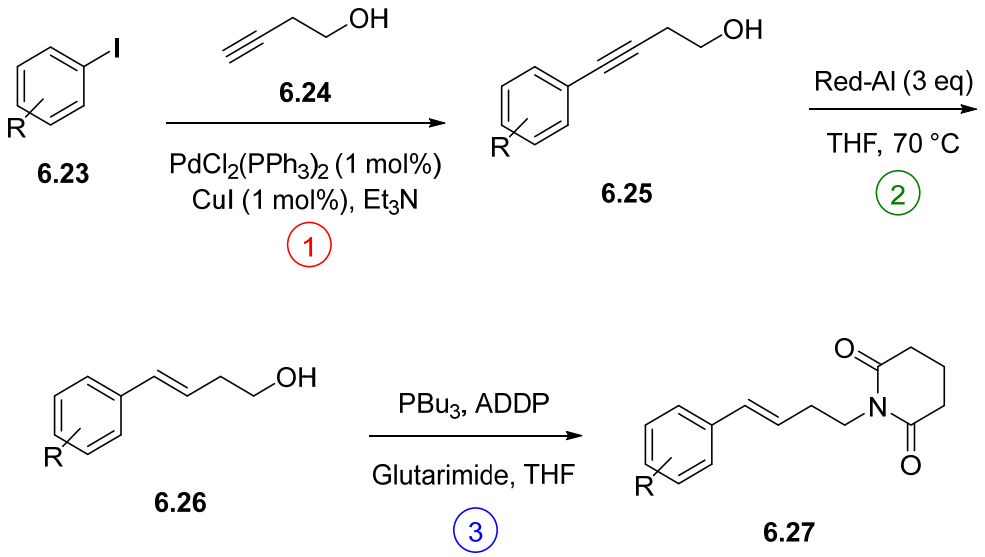
6.2.3.1 Synthesis of trial compounds

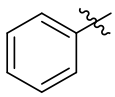
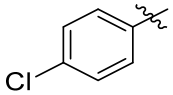
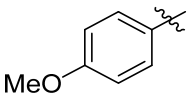
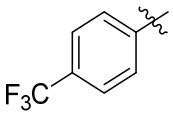
It was thought that the use of flow electrosynthesis would be amenable to this cyclisation, as the use of electricity as an electron source is analogous to the role played by SmI_2. Careful tuning of the reaction conditions could also introduce the base needed in

order to facilitate the last elimination step, however the isolation of an intermediate akin to **6.22** would also be an acceptable goal.

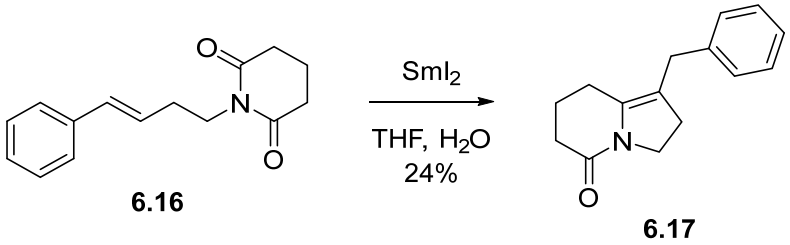
The first step in exploring this reaction was to synthesise a small library of test compounds, in order to probe the efficacy of this cyclisation. Taking inspiration from Szostak's initial substrates, a series of tethered imines were synthesised according to **Table 6.1**. Sonogashira coupling of substituted aromatic iodides **6.23** to homopropargyl alcohol **6.24** was realised by adapting a procedure by Gong, affording alkynes **6.25**.[277] Selective reduction to the *E* alkenes **6.26** was achieved by the use of Red-Al, which is known to reduce alkynes with proximal alcohols in this way.[278] This set up the use of our previously employed and optimised Mitsunobu protocol, in order to install the imide functionality on the pendant alcohol, affording tethered imides **6.27**.

Table 6.1: Syntheses of tethered imides **6.27**.



Entry	Aromatic Group	Yield 1 (%)	Product	Yield 2 (%)	Product	Yield 3 (%)	Product
1		95	**6.26a**	94	**6.27a**	85	**6.16**
2		73	**6.26b**	75	**6.27b**	60	**6.16b**
3		96	**6.26c**	78	**6.27c**	77	**6.16c**
4		77	**6.26d**	-	**6.27d**	-	**6.16d**

All of the substrates were synthesised successfully, in good to excellent yields and all with the expected excellent *E* selectivity (all isolated >50:1 *E*/*Z*). The final step before probing the reaction was to repeat the procedure outlined by Szostak – this would not only provide us with pure **6.17** to use when analysing the electrochemical reaction, but also as a useful comparison between the batch process with SmI_2 and our proposed electrosynthesis. As such, the SmI_2 mediated reaction was carried out as shown in **Scheme 6.9**. In our hands, despite several attempts, the reaction only progressed to a 24% yield. We credit this to the use of commercially available SmI_2, which could degrade while stored. It is best prepared immediately before use.[279] However, enough material was synthesised over several attempts to use for comparative purposes, and as such the reaction was not investigated further.



6.16 **6.17**

Scheme 6.9: Synthesis of indolizidine **6.17** using the method of Szostak.[274]

6.2.3.2 Electrosynthesis reaction

Armed with this result, and the synthesised substrates, we were eager to explore the reaction using an electrolytic approach. Whilst the ultimate aim was to use the Ammonite flow cell, our initial investigation relied on the use of a beaker cell in order to investigate this unknown reaction, as we had at this point little experience in performing reductions using the Ammonite.

As such, a beaker cell system was designed, as shown schematically in **Figure 6.3**. Reactions were run using 60 mL of a 10% aqueous solution of MeCN, containing 0.3 M Et_4NBF_4 as supporting electrolyte and 0.05 M of substrate, stirred within a beaker. A graphite anode was submerged into the solution (Approximate area in solution: 12 cm^2). A spiral strip of copper was used as the cathode, which was also submerged into the solution (Approximate area in solution: 72 cm^2).

The current used for the electrolysis was determined using **Equation 6.1**, where the minimum cell current required for full conversion, $I_{cell,minimum}$ (amps) is given by:

$$I_{cell,minimum} = mnF/t \quad (\mathbf{6.1})$$

where *m* is the number of moles of reactant, *n* the number of electrons per reactant molecule involved in the synthesis reaction, *F* (C $mole^{-1}$) the Faraday constant (the charge on a mole of electrons) and *t* (s) the time for the total reactant solution containing *m* moles of reactant

is allowed to react. Assuming, as shown in **Scheme 6.8**, this process involves two electrons overall, and that the reaction would be allowed to progress for an hour, the minimum required current using 3 mmol of substrate is 160 mA. It was decided to set the current for the initial reaction at 150 mA, in order to suppress any potential side reactions that may occur whilst investigating this novel chemistry.

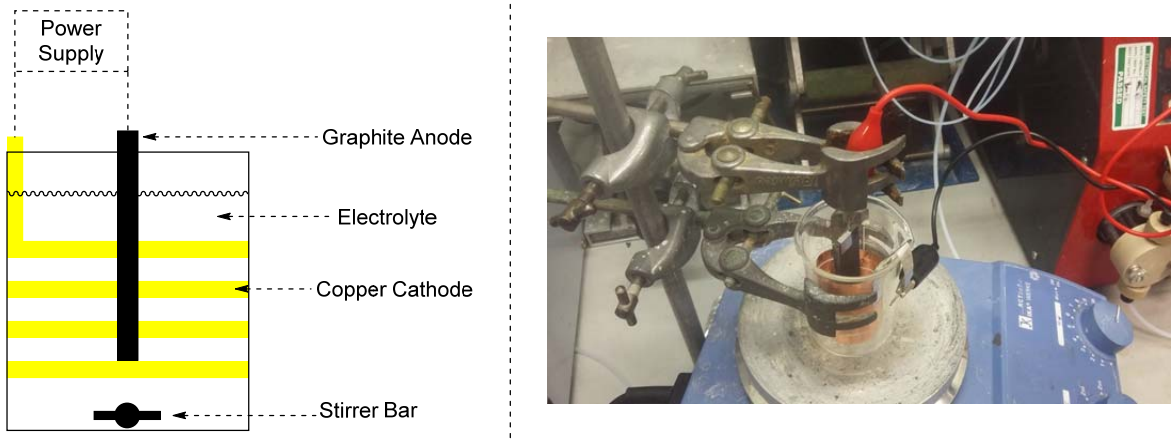


Figure 6.3: Left: Schematic representation of the beaker cell. Right: Picture of the setup in reality.

TLC monitoring of the reaction evidenced the formation of a new species, with an amount of starting material still present. Perplexingly, the R_f of the new species was not similar to **6.17** – indeed, there was no spot present within the crude reaction mixture after 1 hour that was similar to the target indolizidine. Isolation of this new species by chromatography afforded a white crystalline solid, the NMR analysis of which was not immediately forthcoming with information. Fortunately, the crystalline nature of the product offered the opportunity to collect an X-Ray crystal structure of the product, which was – to our great astonishment – confirmed to be that of fused tricyclic **6.29**, isolated in 12% yield (**Figure 6.4**)!

The generation of **6.29** offered us a rare and serendipitous compound, with seemingly no direct analogues present within the chemical literature. The nearest structures that could be found were **6.30**, isolated by Kanoh as a result of the Lewis acid mediated isomerisation of oxetane imides,[280] and Zard's synthesis of **6.31** as an unintended byproduct of the oxidation of an alkylidene-cyclobutane system (**Figure 6.5**).[281] The isolation of **6.29** would also indicate to us that an oxidative process took place under the reaction conditions, instead of our desired reductive cyclisation.

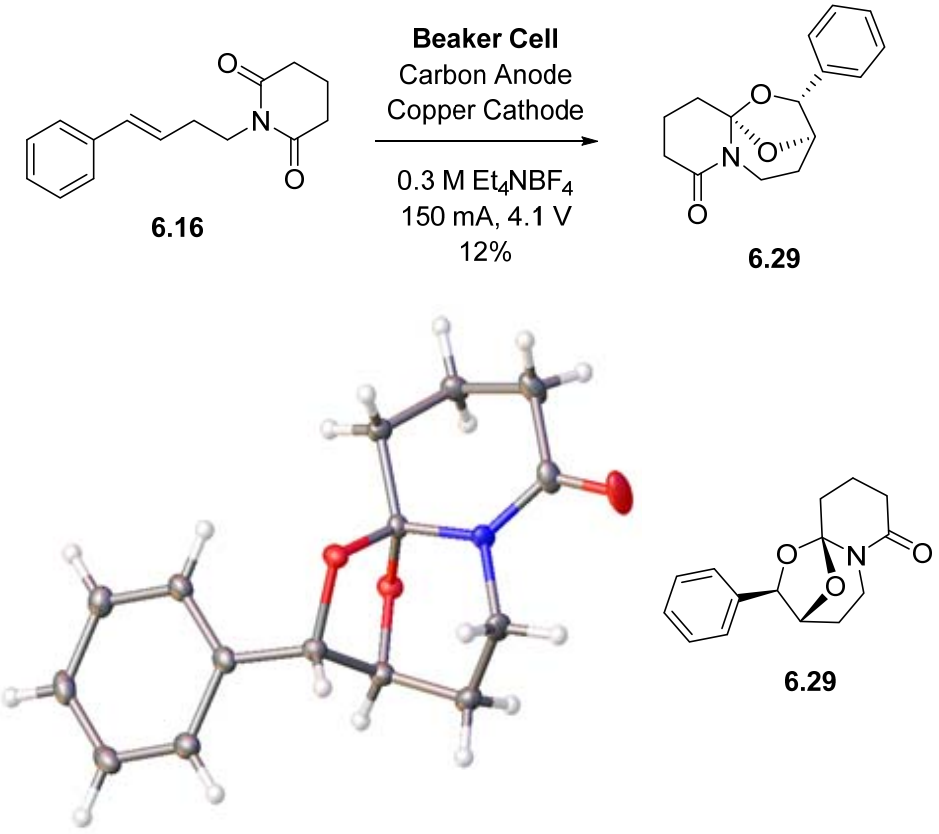


Figure 6.4: Oxidation of **6.16**, and the solved crystal structure of **6.29**, with thermal ellipsoids drawn at the 50% probability level. **6.29** was recrystallised by slow diffusion from CH_2Cl_2 / hexane.

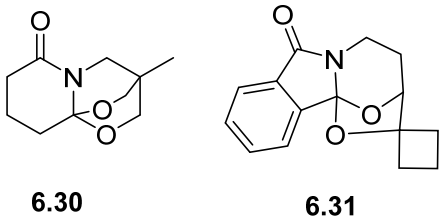
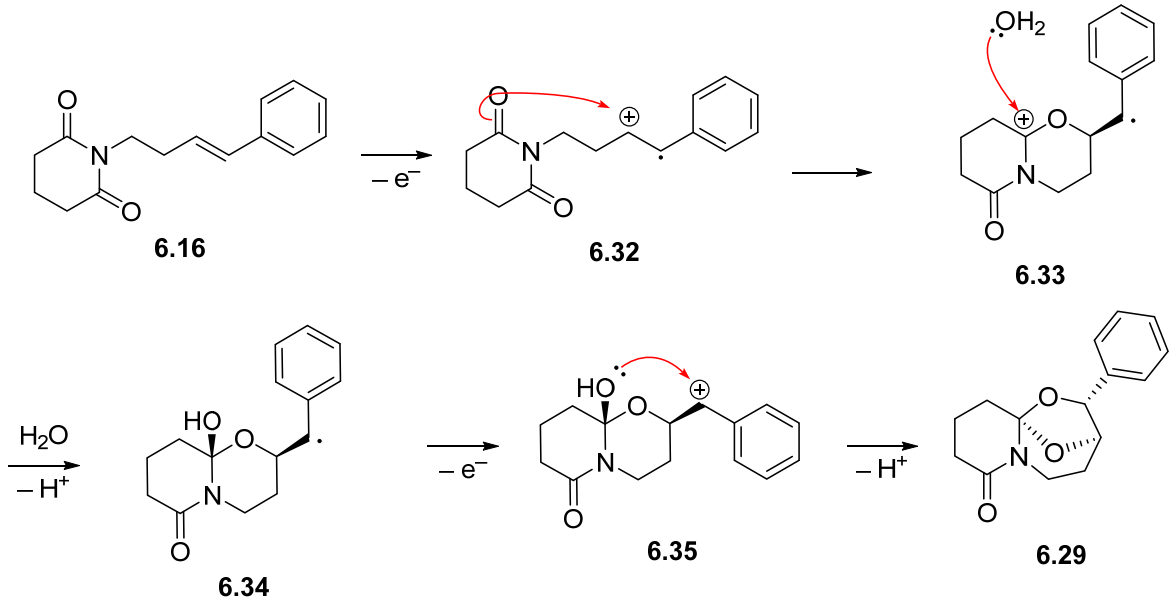


Figure 6.5: Similar compounds of the amido-orthoformate class within the literature.

^{1}H NMR analysis of **6.29**, conducted in tandem with the solved crystal structure, revealed several interesting insights. The benzylic proton at 5.16 ppm appears as a singlet, which would indicate an orthogonal relationship to the neighbouring C<u>H</u>O proton. Application of the Karplus equation in this situation would lead to a small ^{3}J coupling, which would appear to not be resolved in this instance. Analysis of the crystal structure shows a dihedral angle of 91.1 °C, which would support this claim. The C<u>H</u>O signal itself at 4.55 ppm appears as a broad singlet, indicative of an unresolved coupling to the adjacent C<u>H</u>$_2$ group. The presence of the electronegative O atom in the *β* position may be responsible for this small, unresolved ^{3}J coupling in this instance.

A proposed mechanism for this is shown in **Scheme 6.10**. Initial oxidation of the styrene would lead to species **6.32**, which could then undergo cyclisation with one of the

imide carbonyls to form bicycle **6.33**. The cation could then be attacked by water, which would yield hemiacetal **6.34**. A second oxidation event would lead to cation **6.35**, which would then undergo a final cyclisation to provide amido-orthoformate **6.29**.



Scheme 6.10: Proposed mechanism of the oxidative cyclisation of **6.16**.

An important feature to note was the observed evolution of gas at the copper cathode as the reaction progressed. This can be rationalised by counter electrode reaction, shown in **Equation 6.2**.

$$2\,H^{+}_{(aq)} + 2\,e^{-} \rightarrow H_{2(g)} \quad \textbf{(6.2)}$$

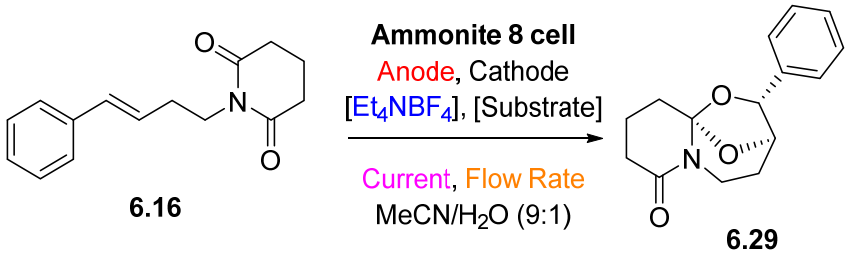
In order for any electrochemical process to occur, there must be both an oxidative and reductive process taking place at all times, in order to close the circuit. In the absence of substrate in the electrolyte, the MeCN and H_2O present would fulfil these functions, which is known to lead to a myriad of reaction products.[282] The presence of substrate within the cell would not curtail these other oxidations and reductions, but allow a new pathway to take place concurrently. The logical consequence of the proposed 2-electron oxidative mechanism in **Scheme 6.10** is the evolution of two protons, which would also serve the needed counter electrode reaction. Our proposed oxidative 2-electron process shown in **Scheme 6.10** serves to provide the ingredients for the counter electrode reaction.

6.2.3.3 Further trials

With this rather surprising compound successfully synthesised, attention would be turned towards attempts to optimise this reaction in the Ammonite reactor. Our aim was to try, as best we could, to replicate the conditions in the batch reactor. Whilst we were constrained to the use of a carbon polymer anode (CPA) and stainless steel (SS) cathode,

we could ensure a long residence time within the cell itself in order to try and drive the reaction towards completion. These results are summarised in **Table 6.2**.

Table 6.2: Synthesis of **6.29** in Ammonite 8 flow electrosynthesis cell. Reactions carried out using 5 mL solutions of electrolyte. [a]Reaction carried out on 50 mL sample.



6.16 **6.29**

Entry	Anode	Cathode	[Et_4NBF_4] / M	[Substrate] / M	Current / mA	Flow rate / mL min^{-1}	Yield (%)
1	CPA	SS	0.3	0.05	40	0.13	16
2		SS	0.3	0.05	40	0.13	14
3		SS	0.05	0.1	80	0.25	12
4[a]		SS	0.05	0.1	82	0.25	9

As can be seen, this short initial reaction screening did not produce any meaningful improvement to the yield of the reaction. The only common thread with all of the conditions trialled was a laborious isolation of the pure compound by chromatography, and the presence of several impurities that were not able to be categorically identified. It is assumed that the amido-orthoformate structure is unstable to acid, which could explain why chromatographic purifications were capricious. It is obvious, however, that more work is needed in optimising the synthesis of this interesting compound.

6.2.3.4 Attempt to effect the original reductive cyclisation

Whilst the isolation of the oxidative product **6.29** was an exciting diversion, the formation of **6.17** was also a target. As there was no evidence of the formation of this indolizidine in either the batch cell or under flow conditions, it was thought that the use of a divided cell would be of benefit. Due to the Ammonite 8 being - by design - unsuitable for this, the reaction was initially attempted in a batch divided cell. A standard H-cell setup was used, as shown schematically in **Figure 6.6**.

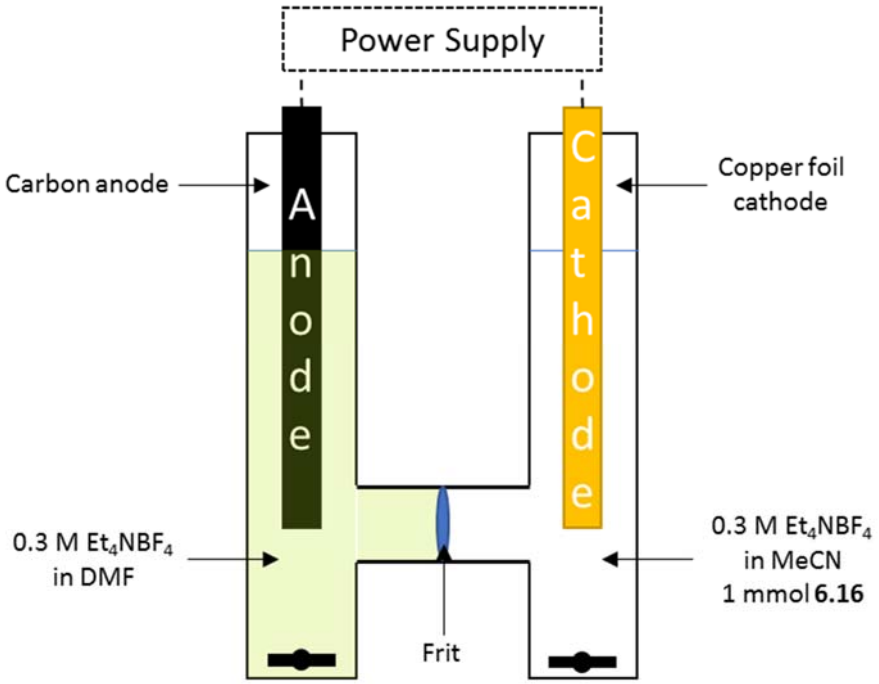
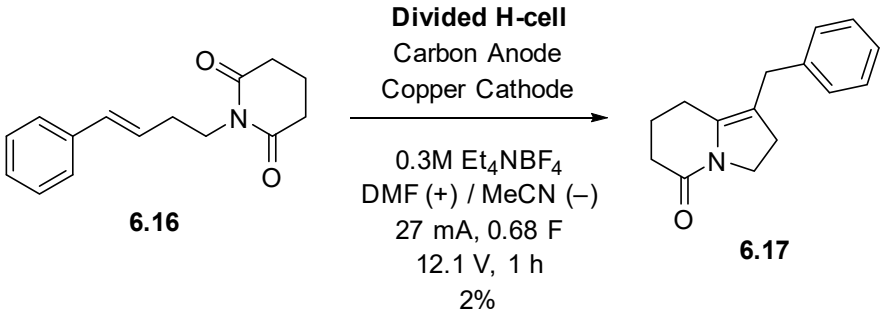


Figure 6.6: Schematic diagram of H-cell setup used to investigate the reductive cyclisation.

Unlike the undivided cells used previously, the divided cell is set up to only allow the substrate to undergo *either* an oxidation or reduction, dependant on the compartment the substrate is placed in. The use of two different electrolyte solutions and a physical barrier to diffusion of substrate – in this case a fritted plug – keeps the substrate solely in one compartment whilst allowing the electrolysis reaction to take place.

As such, a solution of 1 mmol of **6.16** in MeCN with 0.3 M of Et_4NBF_4 as supporting electrolyte was added to the cathodic chamber, where a copper foil electrode (Submerged surface area approximately 4.5 cm^2) was suspended. Simultaneously, a solution of 0.3 M Et_4NBF_4 in DMF was added to the anodic chamber, and a carbon electrode (Submerged surface area approximately 3.0 cm^2) suspended. A current of 27 mA was applied across the cell, requiring a voltage of 12.1 V. As before, gas evolution occurred at the copper cathode. The reaction was stopped after 1 h, and the crude cathodic product was purified using column chromatography. To our delight, **6.17** was isolated as a component of this mixture, albeit with only ca 5 mg of compound isolated (**Scheme 6.10**).



Scheme 6.10: Overall reaction of tethered imide **6.16** to indolizidine **6.17**.

6.3 Conclusions and future work

In this section, the synthesis of a mixture of dioxosparteine diastereoisomers has been achieved by the use of the original routes proposed for their synthesis. The determination of the ratio of (±)-**1.23** : (±)-**1.33** : (±)-**1.29** as 3:1:1 adds valuable insight into the early syntheses of these compounds, and provides a reasonable explanation as to the often conflicting accounts of their isolation from reactions that should – in principle – afford all of the possible diastereoisomers. A novel flow synthesis has also been proposed, based upon the early work using quinolizidine **1.19** as a key component, which could provide new life for this old synthetic route.

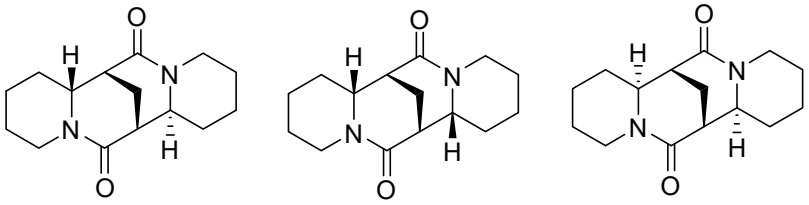


Figure 6.7: Dioxosparteine diastereoisomers revisited as part of our review of the sparteine family of alkaloids.

Efforts towards the flow electrosyntheses of two cyclic species **6.17**, **6.29** have also been disclosed. Whilst these approaches are preliminary in scope at present, the contemporary re-discovery of a novel class of structures, tentatively named “amido-orthoformates” within the scant literature available, is an exciting prospect for future study, and a small library of easily accessible substrates have been synthesised in order to aid future work in this area.

Also, the successful application – albeit in an incredibly modest yield – of the desired reductive cyclisation under batch conditions is also hugely promising, and it is hoped that the Brown group’s current efforts towards the construction of a divided flow cell could be used to further probe this chemistry.

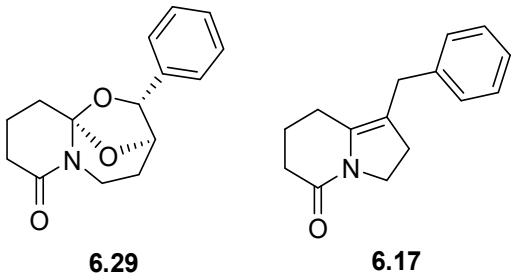


Figure 6.7: Synthesised compounds in our preliminary application of flow electrosynthesis to the cyclisation of various substrates.

Chapter 7 Experimental

7.1 General Methods

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Fluorochem or Apollo Scientific. All air or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame-dried glassware. The solvents THF (from Na/benzophenone), MeCN and CH_2Cl_2 (from CaH_2) were distilled before use, and where appropriate, other reagents and solvents were purified using standard techniques. Anhydrous MeOH was bought from Fischer Scientific. TLC was performed on aluminium-precoated plates coated with silica gel 60 containing F_{254} indicator: visualised under UV light (254 nm) and/or by staining with potassium permanganate, vanillin, nihydrin or iodoplatin. Flash column chromatography was performed using high purity silica gel: Geduran®, pore size 60 Å, 230-400 mesh particle size, purchased from Merck.

Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as neat liquids on a Nicolet iS5 spectrometer, equipped with an Attenuated Total Reflection (ATR) attachment featuring a laminated diamond crystal, using the OMNIC software package. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra. Optical rotations were collected on an Optical Activity PolAAr 2001 machine. The solvents used for the measurement of the optical activity are detailed in the experimental. Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (purchased from Cambridge Isotope Laboratories, Inc.) at 298K using Bruker AVII400 or AVIIHD400 (400 MHz and 101 MHz respectively) FT-NMR spectrometers. Chemical shift values (δ) are reported in ppm relative to residual solvent ($CDCl_3$: δ 7.27 ppm for ^{1}H, δ 77.00 ppm for ^{13}C; DMSO-d_6: δ 2.50 ppm for ^{1}H, δ 39.52 ppm for ^{13}C). ^{19}F NMR is referenced internally to $CFCl_3$ (0.00 ppm). ^{11}B NMR was obtained by subtracting the borosilicate background signal of the NMR tube, and referenced to $BF_3{\cdot}OEt_2$ in $CDCl_3$ (0.00 ppm). All spectra were reprocessed using ACD/Labs software version: S30S41. 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), sept (septet), br (broad) and m (multiplet). Compounds containing N-Cbz protecting groups exhibited broadening of peaks in the NMR due to restricted rotation. To aid in interpretation of spectra for selected compounds, variable temperature NMR experiments at T = 353 K were conducted.

Electrospray low-resolution mass spectra were recorded on a Waters ZMD quadrupole spectrometer, or a Waters (Manchester, UK) TQD triple quadrupole analyser. High resolution mass spectra were recorded on a Bruker APEX III FT-ICR mass spectrometer.

Analytical HPLC was performed on an Agilent 1220 Infinity LC System, using the Agilent EZChrom software package, eluting from either Daicel Chiralcel® OD-H, AD-H or OD-Z columns, eluting with IPA/hexane mixtures.

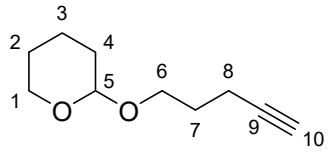
Analytical GC was performed using a Shimadzu GC-2014 equipped with an autosampler and FID detector. The GC was fitted with an Agilent technologies HP5 column with the following dimensions; length – 30 m, internal diameter – 0.32 mm and film thickness – 0.25 μm. The results were processed using GC Solution Lite software. Separations were carried out using He as a carrier gas with a flow rate of 2.37 mL min^{-1} through the column. A split injection was conducted using a split ratio of 100:1. The injection and detector temperatures were maintained at 200 °C and 255 °C respectively. The oven temperature was initially held at 80 °C and then programmed to increase at 20 °C min^{-1} to 250 °C, where it was held constant for 5 min.

7.2 Procedures and Characterisation Data

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

7.2.1.1 *N*-acyliminium route

3.13: 2-(Pent-4-yn-1-yloxy)tetrahydro-2*H*-pyran



$C_{10}H_{16}O_2$

168.24 g mol^{-1}

To a solution of 3,4-dihydro-2*H*-pyran (18.20 mL, 193 mmol) in anhydrous CH_2Cl_2 (400 mL) was added 4-pentyn-1-ol (12.0 mL, 128 mmol) and PPTS (1.65 g, 6.42 mmol). The resulting colourless solution was stirred for 24 h at RT. The reaction mixture was then washed with H_2O (2 x 100 mL), sat. $NaHCO_3$ (2 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a colourless oil. Purification by chromatography (silica, CH_2Cl_2 : pet. ether. 70:30) afforded the title compound as a colourless oil (1.89 g, 11.2 mmol, 99%).

R_f 0.36 (CH_2Cl_2 : pet. ether. 70:30)

FT-IR (neat) ν_{max}: 3294, 2940, 2850, 1135, 1119, 1061 cm^{-1}

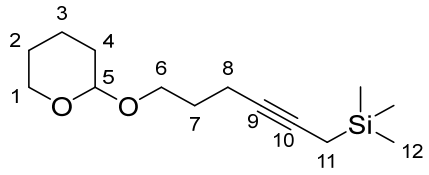
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.61 (t, *J* = 3.5 Hz, 1H, **H5**), 3.93 – 3.75 (m, 2H, **H1'**, **H6'**), 3.58 – 3.43 (m, 2H, **H1''**, **H6''**), 2.32 (tdd, J = 7.7, 3.2, 1.2 Hz, 2H, **H8**), 1.95 (t, *J* = 2.7 Hz, 1H, **H10**), 1.87 – 1.78 (m, 3H, **H2'**, **H7**), 1.77 – 1.68 (m, 1H, **H4'**), 1.65 – 1.50 (m, 4H, **H2'**, **H3**, **H4''**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 98.81 (**CH**, **C5**), 83.99 (**C**, **C9**), 68.40 (**CH**, **C10**), 65.78 (**CH_2**, **C6**), 62.21 (**CH_2**, **C1**), 30.66 (**CH_2**, **C4**), 28.69 (**CH_2**, **C7**), 25.46 (**CH_2**, **C3**), 19.50 (**CH_2**, **C2**), 15.33 (**CH_2**, **C8**) ppm.

LRMS (ES^+) *m/z* 169.1 $[M+H]^+$, 191.2 $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[283]

3.15: Trimethyl(6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-2-yn-1-yl)silane



$C_{14}H_{26}O_2Si$

254.45 g mol^{-1}

To a solution of alkyne **3.13** (1.67 g, 9.93 mmol) in anhydrous THF (20 mL) at ─30 °C was added *n*-BuLi (2.3 M in hexanes, 5.11 mL, 10.4 mmol) over 30 min. The dark-brown solution was stirred for 30 min at this temperature, and a further 15 min at 0 °C. (Iodomethyl)trimethylsilane (1.55 mL, 10.4 mmol) was added dropwise over 20 min, and the reaction warmed to 60 °C and stirred for 22 h. The resulting light-brown solution was cooled to RT and the reaction quenched with sat. $NH_4Cl_{(aq)}$ (20 mL). The phases were separated, and the aqueous layer extracted with EtOAc (3 x 20 mL), washed with brine (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a light brown oil. Purification by chromatography (silica, EtOAc:hexane - 5:95) afforded the title compound as a colourless oil (2.18 g, 8.57 mmol, 86%).

R_f 0.60 (CH_2Cl_2:pet. ether. 70:30)

FT-IR (neat) ν_{max}: 2944, 2872, 1248, 1160, 1076 cm^{-1}

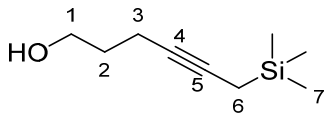
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.59 (dd, *J* = 4.0, 2.6 Hz, 1H, **H5**), 3.92 – 3.78 (m, 2H, **H6**, **H1**), 3.54 – 3.43 (m, 2H, **H6**, **H1**), 2.31 - 2.22 (m, 2H, **H8**), 1.88 – 1.66 (m, 4H, **H7**, **THP**), 1.63 – 1.47 (m, 4H, **THP**), 1.41 (t, *J* = 2.6 Hz, 2H, **H11**), 0.09 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 98.74 (**CH**, **C5**), 78.06 (**C**, **C9**), 77.63 (**C**, **C10**), 68.15 (**CH_2**, **C1**), 62.07 (**CH_2**, **C6**), 30.66 (**THP**), 29.59 (**CH_2**, **C7**), 25.47 (**THP**), 19.49 (**THP**), 15.77 (**CH_2**, **C8**), 6.89 (**CH_2**, **C11**), –2.11 (**Me_3Si**) ppm.

LRMS (ES^+) *m/z* 255.3 $[M+H]^+$, 277.3 $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[284]

3.11: 6-(Trimethylsilyl)hex-4-yn-1-ol



$C_9H_{18}OSi$

170.33 g mol^{-1}

To a solution of alkyne **3.15** (206 mg, 810 µmol) in MeOH (3 mL) was added PPTS (21 mg, 83.4 µmol). The colourless solution was stirred for 22 h, then concentrated *in vacuo*. Purification by chromatography (silica, EtOAc:hexane 20:80) afforded the title compound as a colourless oil (121 mg, 0.710 µmol, 88%).

R_f 0.49 (EtOAc:hexane 40:30)

FT-IR (neat) ν_{max}: 3332 (br), 2953 (m), 1397 (w), 1248 (s), 1169 (w), 1056 (m) cm^{-1}

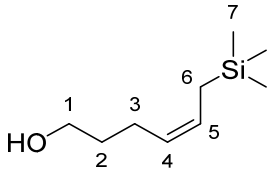
^{1}H NMR ($CDCl_3$ 400 MHz) δ = 3.71 (t, *J* = 6.2 Hz, 2H, **H1**), 2.24 (tt, *J* = 6.9, 2.7 Hz, 2H, **H3**), 1.69 (quin, *J* = 6.5 Hz, 2H, **H2**), 1.38 (t, *J* = 2.6 Hz, 2H, **H6**), 0.08 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 78.11 (**C**, **C5**), 77.90 (**C**, **C4**), 61.91 (**CH_2**, **C1**), 31.88 (**CH_2**, **C2**), 15.50 (**CH_2**, **C3**), 6.81 (**CH_2**, **C6**), –2.19 (**Me_3Si**) ppm.

LRMS (ES^+) *m/z* 171.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[285]

3.10: (*Z*)-6-(Trimethylsilyl)hex-4-en-1-ol



$C_9H_{20}OSi$

172.34 g mol^{-1}

To a solution of $Ni(OAc)_2{\cdot}4H_2O$ (3.05 g, 12.0 mmol) in anhydrous EtOH (60 mL) under N_2 was added 12 mL of a 1 M solution of $NaBH_4$ in EtOH. The mixture turned from turquoise to black instantly after addition. The mixture was then put under an atmosphere of H_2, and EDA (1.64 mL, 24.3 mmol) was added dropwise over 2 min. The mixture was stirred for 10 min, then alkyne **3.17** (16.4 g, 96.3 mmol) in anhydrous EtOH (9 mL) was added dropwise over 5 min. The reaction was stirred for 7 h, placed under a N_2 atmosphere for 16 h, and then resubmitted to an H_2 atmosphere for a further 2 h. The mixture was filtered through activated charcoal to afford a lilac coloured filtrate. The filter pad was washed with CH_2Cl_2 (3 x 100 mL) and the filtrate concentrated *in vacuo*. Purification by chromatography (silica, EtOAc:hexane 20:80) afforded the title compound as a colourless oil (15.3 g, 172 mmol, 92%).

R_f 0.52 (EtOAc:hexane 40:60)

FT-IR (neat) ν_{max}: 3330 (br), 3006 (w), 2953 (m), 1417 (w), 1392 (w), 1247 (s), 1151 (m), 1058 (m) cm^{-1}

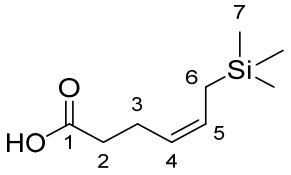
^{1}H NMR ($CDCl_3$ 400 MHz) δ = 5.48 – 5.39 (m, 1H, **H5**), 5.32 – 5.23 (m, 1H, **H4**), 3.66 (t, *J* = 6.5 Hz, 2H, **H1**), 3.48 (s, 1H, **OH**), 2.08 (q, *J* = 6.9 Hz, 2H, **H3**), 1.68 – 1.59 (m, 2H, **H2**), 1.48 (dd, *J* = 29.7, 8.6 Hz, 2H, **H6**), 0.00 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 126.59 (**CH**, **C4**), 126.23 (**CH**, **C5**), 62.74 (**CH_2**, **C1**), 32.66 (**CH_2**, **C2**), 23.36 (**CH_2**, **C3**), 18.44 (**CH_2**, **C6**), –1.83 (**Me_3Si**) ppm.

LRMS (ES^+) *m/z* 173.30 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[286]

3.18: (4*Z*)-6-(Trimethylsilyl)hex-4-enoic acid



$C_9H_{28}O_2Si$

186.33 g mol^{-1}

To a solution of alcohol **3.10** (2.00 g, 11.6 mmol) in MeCN (45 mL) was added NMO·H_2O (15.4 g, 113 mmol) in 5 g portions. The cloudy mixture was stirred for 20 min, then TPAP (400 mg, 1.14 mmol) was added in one portion, upon which the reaction turned a green-black colour. The reaction was stirred for 45 min then quenched by the addition of IPA (50 mL). The reaction was concentrated in vacuo, then filtered through a silica plug eluting with EtOAc (1% AcOH, 500 mL). The filtrate was concentrated *in vacuo* to afford a yellow oil. Purification by chromatography (silica, EtOAc:hexane 40:60) afforded the title compound as a pale yellow oil (2.08 g, 11.2 mmol, 96%).

R_f 0.20 (EtOAc:hexane 40:60)

FT-IR (neat) ν_{max}: 3010 (br), 2954 (m), 1708 (s), 1414 (m), 1247 (s), 1210 (m), 1150 (m) cm^{-1}.

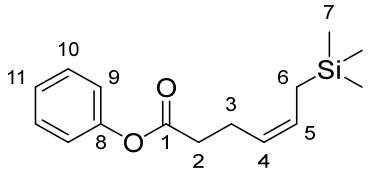
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.48 (dtt, 10.8, 8.8, 1.5 Hz, 1H, **H5**). 5.25 (dtt, *J* = 10.9, 6.9, 1.3 Hz, 1H, **H4**), 2.44 – 2.38 (m, 2H, **H2**), 2.38 – 2.30 (m, 2H, **H3**), 1.50 (d, *J* = 8.6 Hz, 2H, **H6**), 0.02 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 178.55 (**C**, **C1**), 127.46 (**CH**, **C5**), 124.65 (**CH**, **C4**), 33.95 (**CH_2**, **C2**), 22.34 (**CH_2**, **C3**), 18.56 (**CH_2**, **C6**), –2.15 (**Me_3Si**) ppm.

LRMS (ES^-) *m/z* 185.5 $[M-H]^-$.

Physical and spectroscopic data are consistent with reported values.[287]

3.4: Phenyl (*Z*)-6-(trimethylsilyl)hex-4-enoate



$C_{15}H_{22}O_2Si$

262.42 g mol^{-1}

To a solution of acid **3.18** (2.08 g, 11.2 mmol) in CH_2Cl_2 (56 mL) was added DCC (2.53 g, 12.3 mmol), DMAP (136 mg, 1.12 mmol) and phenol (2.10 g, 1.96 mL, 22.3 mmol) sequentially over 10 min. The white suspension was stirred for 60 h. The mixture was concentrated *in vacuo* to yield a white solid. The residue was taken up in Et_2O (40 mL), and the suspension filtered through a pad of celite and the filter pad washed with Et_2O (150 mL). The solution was concentrated in vacuo to *ca*. 40 mL, then washed with 2 M HCl (50 mL), sat. $NaHCO_{3\,(aq)}$ (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil. Purification by chromatography (silica, EtOAc:hexane 1:99) afforded the title compound as a colourless oil (2.29 g, 8.73 mmol, 78 %).

R_f 0.88 (EtOAc:hexane 40:60)

FT-IR (neat) ν_{max}: 3009 (w), 2953 (w), 1760 (s), 1593 (w), 1493 (m), 1417 (w), 1359 (w), 1247 (s), 1195 (s), 1161 (s), 1120 (s) cm^{-1}.

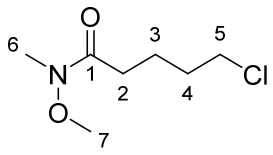
^{1}H NMR ($CDCl_3$ 400 MHz) δ = 7.39 (t, *J* = 7.5 Hz, 2H, **H10**), 7.26 – 7.21 (m, 1H, **H11**), 7.10 (dd, *J* = 8.6, 1.1 Hz, 2H, **H9**), 5.59 – 5.49 (m, 1H, **H5**), 5.39 – 5.30 (m, 1H, **H4**), 2.65 – 2.59 (m, 2H, **H2**), 2.47 (q, *J* = 7.4 Hz, 2H, **H3**), 1.56 (d, *J* = 8.7 Hz, 2H, **H6**), 0.05 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.78 (**C**, **C1**), 150.74 (**C**, **C8**), 129.33 (**CH**, **C10**), 127.54 (**CH**, **C5**), 125.67 (**CH**, **C11**), 124.60 (**CH**, **C4**), 121.56 (**CH**, **C9**), 34.44 (**CH_2**, **C2**), 22.59 (**CH_2**, **C3**), 18.60 (**CH_2**, **C6**), –1.83 (**Me_3Si**) ppm.

LRMS (ES$^+$) *m/z* 263.29 [M+H]$^+$.

HRMS (ES$^+$) for $C_{15}H_{22}NaO_2Si^+$, calculated 285.1281 found 285.1285.

3.24: 5-Chloro-*N*-methoxy-*N*-methylpentanamide



$C_7H_{14}ClNO_2$

179.64 g mol^{-1}

A solution of 5-chlorovaleric acid (10.0 mL, 85.7 mmol) in anhydrous CH_2Cl_2 (100 mL) was cooled to 0 °C. Oxalyl chloride (7.97 mL, 94.2 mmol) was added dropwise, along with DMF (10 drops). The reaction was stirred at 0 °C for 30 min, warmed to RT and stirred a further 2.5 h until gas evolution had ceased. A solution of *N*,*O*-dimethylhydroxylamine hydrochloride (10.4 g, 107 mmol) in anhydrous CH_2Cl_2 (300 mL) was cooled to 0 °C. Et_3N (29.9 mL, 214 mmol) was added, and the resultant white suspension was stirred at this temperature for 30 min. The freshly prepared acid chloride was added *via* cannula over 40 min at 0 °C, and the reaction warmed to RT and stirred for 24 h. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$ (200 mL). The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (400 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, EtOAc:hexane 20:80) afforded the title compound as a colourless oil (14.5 g, 80.7 mmol, 94%).

R_f 0.30 (EtOAc:hexane 40:60)

FT-IR (neat) ν_{max}: 2939 (br), 1658 (s), 1440 (m), 1415 (m), 1320 (w), 1177 (m), 1105 (w) cm^{-1}.

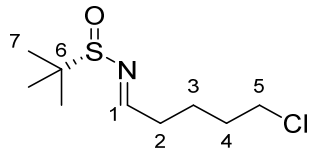
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.66 (s, 3H, **H1**), 3.54 (t, *J* = 6.4 Hz, 2H, **H5**), 3.16 (s, 3H, **H6**), 2.45 (t, *J* = 6.9 Hz, 2H, **H2**), 1.87 – 1.72 (m, 4H, **H3**, **H4**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 173.92 (**C**, **C1**), 61.21 (**CH_3**, **C7**), 44.66 (**CH_2**, **C5**), 32.13 (**CH_3**, **C6**, **C4**), 30.95 (**CH_2**, **C2**). 21.89 (**CH_2**, **C3**) ppm.

LRMS (ES^+) *m/z* 180.1 $[M^{35}Cl+H]^+$, 182.2 $[M^{37}Cl+H]^+$, 202.2 $[M^{35}Cl+Na]^+$, 204.2 $[M^{37}Cl+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[288]

(+)-1.125: (+)-(*S*)-*N*-[(1*E*)-5-Chloropentylidene]-2-methylpropane-2-sulfinamide



$C_9H_{18}ClNOS$

223.76 g mol^{-1}

A solution of amide **3.24** (6.39 g, 35.6 mmol) in anhydrous CH_2Cl_2 (90 mL) was cooled to –78 °C. DIBAL-H (1 M in CH_2Cl_2, 42.7 mL) was added dropwise over 20 min *via* dropping funnel, and the reaction stirred at this temperature for 1.5 h. The reaction was quenched with 2 M HCl (100 mL), and the reaction stirred vigorously for 2 h until the white emulsion disappeared. The phases were separated, and the organic layer washed with brine (100 mL) and dried ($MgSO_4$).

To a suspension of (*S*)-(–)-2-methyl-2-propanesulfinamide (4.74 g, 39.1 mmol) and $Ti(OEt)_4$ (29.8 mL, 142 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C was added the freshly prepared aldehyde dropwise *via* cannula over 45 min. The mixture was stirred at this temperature for 1 h. The reaction was allowed to warm to RT then stirred for a further 16 h. The reaction was quenched by addition to brine (150 mL) and H2O (100 mL). The cream-coloured mixture was stirred for 30 min, then filtered through a pad of celite, and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a pale yellow oil. Purification by chromatography (silica, EtOAc/hexane 3:7 to 1:1) afforded the title compound as a colourless oil (5.86 g, 26.2 mmol, 74%).

R_f 0.38 (EtOAc:hexane 40:60)

$[\alpha]_D$ +227.6 (*c*. 1.18, $CHCl_3$)

FT-IR (neat) ν_{max}: 2957 (br), 1622 (s), 1475 (m), 1456 (m), 1363 (m), 1312 (w), 1184 (w), 1078 (s), 1017 (w) cm^{-1}.

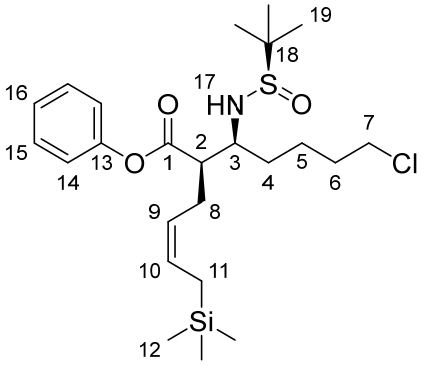
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.07 (t, *J* = 4.4 Hz, 1H, **H1**), 3.55 (t, *J* = 6.2 Hz, 2H, **H5**), 2.56 (td, *J* = 7.0, 4.5 Hz, 2H, **H2**), 1.90 – 1.75 (m, 4H, **H3**, **H4**), 1.19 (s, 9H, **H7**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 168.67 (**CH**, **C1**), 56.53 (**C**, **C6**), 44.39 (**CH_2**, **C5**), 35.16 (**CH_2**, **C2**), 31.85 (**CH_2**, **C4**), 22.60 (**CH_2**, **C3**), 22.30 (**CH_3**, **C7**) ppm.

LRMS (ES^+) *m/z* 224.2 $[M^{35}Cl+H]^+$, 226.1 $[M^{37}Cl+H]^+$, 264.1 $[M^{37}Cl+Na]^+$, 266.1 $[M^{37}Cl+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[12]

3.3: (+)-Phenyl (2*R*,3*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-7-chloro-2-((*Z*)-4-(trimethylsilyl)but-2-en-1-yl)heptanoate



$C_{24}H_{40}ClNO_3SSi$

486.18 g mol^{-1}

A solution of LDA (1.73 M in THF, 3.47 mL, 11.7 mmol) was cooled to –78 °C. Ester **3.4** (1.5 g, 5.72 mmol) in anhydrous THF (15 mL) was added dropwise over 20 min. The mixture was stirred for 1.5 h, then *N*-sulfinylimine (+)-**1.125** (1.02 g, 4.57 mmol) in anhydrous THF (5 mL) was added dropwise over 20 min. The resulting orange solution was stirred for 3 h at –78 °C. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (20 mL), warmed to RT and stirred for 30 min. The phases were separated, and the aqueous extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the crude product gives d.r. 95:5 *syn*/*anti*). Purification by chromatography (silica, EtOAc:hexane 20:80) afforded the major diastereomer as a viscous yellow oil (1.71 g, 3.52 mmol, 77 %).

R_f 0.24 (EtOAc:hexane 20:80)

$[\alpha]_D$ +23.0 ° (*c*. 1.14 $CHCl_3$)

FT-IR (neat) ν_{max}: 2953 (br), 1754 (m), 1592 (w), 1492 (w), 1456 (w), 1391 (w), 1247 (m), 1190 (s), 1161 (s), 1126 (s), 1068 (s) cm^{-1}.

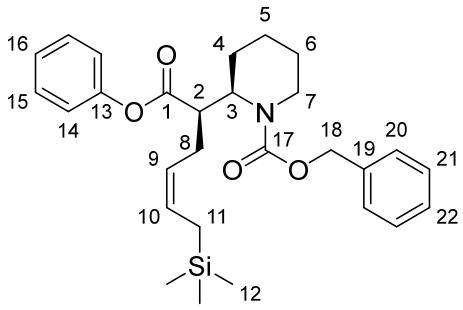
^{1}H NMR ($CDCl_3$ 400 MHz) δ = 7.42 – 7.35 (m, 2H, **H15**), 7.24 (tt *J* = 7.3, 1.2 Hz, 1H, **H16**), 7.11 – 7.05 (m, 2H, **H14**), 5.65 – 5.53 (m, 1H, **H10**), 5.42 – 5.31 (m, 1H, **H9**), 4.23 (d, *J* = 8.7 Hz, 1H, **H17**), 3.58 – 3.47 (m, 3H, **H3**, **H7**), 3.25 (td, *J* = 7.6, 4.2 Hz, 1H, **H2**), 2.62 – 2.52 (m, 1H, **H8'**), 2.46 – 2.35 (m, 1H, **H8''**), 1.89 – 1.45 (m, 8H, **H4**, **H5**, **H6**, **H11**), 1.24 (s, 9H, **H19**), 0.03 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.48 (**C**, **C1**), 150.31 (**C**, **C13**), 129.45 (**CH**, **C15**), 128.75 (**CH**, **C10**), 126.01 (**CH**, **C16**), 123.05 (**CH**, **C9**), 121.48 (**CH**, **C14**), 57.47 (**CH**, **C3**), 56.10 (**C**, **C18**), 50.54 (**CH**, **C2**), 44.71 (**CH_2**, **C7**), 32.01 (**CH_2**, **C4**), 31.02 (**CH_2**, **C6**), 26.14 (**CH_2**, **C8**), 23.57 (**CH_2**, **C11**), 22.70 (**CH_3**, **C19**), 18.79 (**CH_2**, **C5**), –1.80 (**Me_3Si**) ppm.

LRMS (ES$^+$) *m/z* 486.45 [M^{35}Cl+H]$^+$, 488.4 [M^{37}Cl+H]$^+$, 508.4 [M^{35}Cl+Na]$^+$, 510.4 [M^{37}Cl+Na]$^+$.

HRMS (ES$^+$) for $C_{24}H_{41}ClNO_3SSi^+$ [M+H]$^+$, calculated 486.2259 found 486.2270.

3.26: (–)-Benzyl (*R*)-2-((*R*,*Z*)-1-oxo-1-phenoxy-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate



$C_{28}H_{37}NO_4Si$

479.69 g mol^{-1}

To a solution of imino-aldol adduct **3.3** (3.22 g, 6.62 mmol) in 1,4-dioxane (100 mL) under N_2 at 0 °C was added HCl (2 M, 3.64 mL, 7.29 mmol). The mixture was warmed to RT and stirred for 3 h. The solvent was removed *in vacuo*, and the residue dissolved in CH_2Cl_2 (20 mL) and evaporated (three times) to yield a pale yellow oil. The oil was redissolved in MeCN (100 mL) and K_2CO_3 (4.58 g, 33.1 mmol) was added, along with NaI (93 mg, 662 µmol). The resulting bright yellow suspension was stirred at RT for 24 h. The reaction mixture was concentrated *in vacuo*, and the yellow solid residue partitioned between EtOAc/H_2O (40 mL, 1:1). The phases were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil.

The crude piperidine was dissolved in anhydrous MeCN (35 mL) and then K_2CO_3 (1.83 g, 13.2 mmol) was added. The mixture was stirred for 20 min, and then benzyl chloroformate (1.49 mL, 9.93 mmol) was added dropwise over 5 min. The yellow suspension was stirred for 16 h. The reaction was quenched by the addition of H_2O (30 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification by chromatography (silica, EtOAc:hexane 5:95) afforded the title compound as a pale yellow oil (2.63 g, 5.48 mmol, 83%).

R_f 0.90 (EtOAc:hexane 40:60)

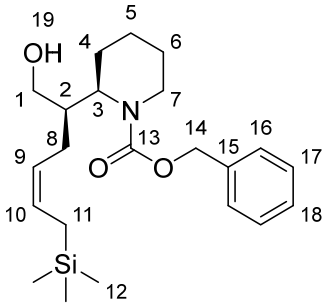
$[\alpha]_D$ –24.9° (*c*. 1.00 $CHCl_3$)

FT-IR (neat) ν_{max}: 2948 (m), 1754 (s), 1695 (s), 1592 (w), 1492 (m), 1421 (s), 1353 (w), 1334 (w), 1311 (w), 1246 (s), 1161 (s), 1123 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.24 – 7.46 (m, 8H, **H15**, **H16**, **H20**, **H21**, **H22**), 7.04 (br d, *J* = 7.7 Hz, 2H, **H14**), 5.5 (q, *J* = 9.3 Hz, 1H, **H10**), 5.33 (br d, *J* = 7.6 Hz, 1H, **H9**), 5.22 – 5.01 (m, 2H, **H18**), 4.54 (br s, 1H, **H3(ax)**), 4.01 (br s, 1H, **H7(eq)**), 3.32 – 3.22 (m, 1H, **H2**), 2.99 – 2.77 (m, 1H, **H7(ax)**), 2.35 (dt, *J* = 14.0, 9.8 Hz, 1H, **H8'**), 2.07 (br s,

	1H, **H8''**), 1.75 - 1.28 (m, 8H, **H4**, **H5**, **H6**, **H11**), 0.03 (s, 9H, **Me_3Si**) ppm.
^{13}C NMR	(101 MHz, DMSO-d_6): δ = 172.31 (**C**, **C1**), 154.88 (**C**, **C17**), 150.13 (**C**, **C13**), 136.77 (**C**, **C19**), 129.63 (**Ar**), 128.38 (**Ar**), 127.96 (**Ar**), 127.82 (**CH**, **C10**), 127.32 (**Ar**), 126.04 (**Ar**), 122.74 (**CH**, **C9**), 121.53 (**Ar**), 66.36 (**CH_2**, **C18**), 52.00 (**CH**,**C3**), 44.84 (**CH**,**C2**), 38.90 (**CH_2**,**C7**), 27.25 (**CH_2**,**C4**), 26.85 (**CH_2**,**C8**), 24.91 (**CH_2**,**C6**), 18.56 (**CH_2**,**C5**), 18.06 (**CH_2**,**C11**), –1.83 (**Me_3Si**) ppm.
^{1}H NMR (V_T, T = 353K)	(500 MHz, DMSO-d_6): δ = 7.44 – 7.40 (m, 2H, **H15**), 7.39 – 7.33 (m, 4H, **H20**, **H21**), 7.33 – 7.29 (m, 1H, **H22**), 7.27 (ddt, *J* = 8.0, 6.9, 1.0 Hz, 1H, **H16**), 7.08 – 7.04 (m, 2H, **H14**), 5.53 (dddt, *J* = 10.8, 9.3, 8.00, 1.5 Hz, 1H, **H10**), 5.38 – 5.30 (m, 1H, **H9**), 5.14 (s, 2H, **H18**), 4.56 (br d, *J* = 10.9 Hz, 1H, **H3(ax)**), 4.04 (br dd, *J* = 13.9, 4.0 Hz, 1H, **H7(eq)**), 3.24 (td, *J* = 10.8, 4.4 Hz, 1H, **H2**), 2.88 (br t, *J* = 12.5 Hz, 1H, **H7(ax)**), 2.37 (dddd, *J* = 14.7, 10.4, 7.9, 1.2 Hz, 1H, **H8'**), 2.21 – 2.13 (m, 1H, **H8''**), 1.79 – 1.61 (m, 5H, **H4**, **H5**, **H6(eq)**), 1.51 (ddd, *J* = 13.8, 9.2, 0.8 Hz, 1H, **H11'**), 1.46 – 1.35 (m, 2H, **H6(ax) & H11''**), 0.02 (s, 9H, **Me_3Si**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d_6): δ = 171.66 (**C**,**C1**), 154.52 (**C**,**C17**), 149.95 (**C**,**C13**), 136.55 (**C**,**C19**), 129.07 (**CH**,**C15**), 127.89 (**CH**,**C20**), 127.48 (**CH**,**C22**), 127.31 (**CH**,**C10**), 126.90 (**CH**,**C21**), 125.44 (**CH**,**C16**), 122.54 (**CH**,**C9**), 120.93 (**CH**,**C14**), 66.03 (**CH_2**,**C18**), 51.89 (**CH**,**C3**), 44.87 (**CH**,**C2**), 38.80 (**CH_2**,**C7**), 26.77 (**CH_2**,**C4**), 26.47 (**CH_2**,**C8**), 24.38 (**CH_2**,**C6**), 18.21 (**CH_2**,**C5**), 17.70 (**CH_2**,**C11**), –2.23 (**Me_3Si**) ppm.
LRMS	(ES^+) *m/z* $[M+H]^+$ 480.5, $[M+Na]^+$ 502.5.
HRMS	(ES^+) for $C_{28}H_{38}NO_4Si^+$ $[M+H]^+$, calculated 480.2565 found 480.2568.

3.27: (–)-Benzyl (*R*)-2-(*R*,*Z*)-1-hydroxy-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate



$C_{22}H_{35}NO_3Si$

389.61 g mol^{-1}

To a solution of ester **3.26** (135 mg, 280 µmol) in anhydrous THF (2 mL) at 0 °C was added $LiAlH_4$ (1 M in THF, 310 µL, 310 µmol) dropwise over 5 min. The pale yellow mixture was stirred for 2 h by which time the solution had turned colourless. The reaction was quenched by the slow addition of H_2O (1 mL), 20% NaOH (1 mL) and H_2O (2 mL) and stirred for 16 h. The phases were separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (3 x 20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. Purification by chromatography (silica, EtOAc:hexane 20:80) afforded the title compound as a colourless oil (108 mg, 280 µmol, 98%).

R_f 0.57 (EtOAc:hexane 40:60)

$[\alpha]_D$ **–**23.9° (*c*. 1.05 $CHCl_3$)

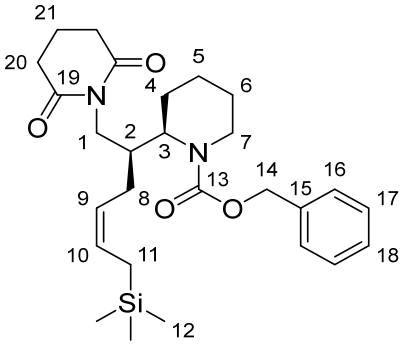
FT-IR (neat) ν_{max}: 3461 (br), 2946 (m), 2340 (w), 1670 (s), 1497 (w), 1425 (s), 1351 (w), 1311 (w), 1246 (s), 1173 (m), 1073 (m), 1028 (m) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36 – 7.26 (m, 5H, **H16**, **H17**, **H18**), 5.44 – 5.34 (m, 1H, **H10**), 5.32 – 5.22 (m, 1H, **H9**), 5.06 (br s, 2H, **H14**), 4.44 (t, *J* = 4.8 Hz, 1H, **H19**), 4.20 (br dd, *J* = 10.6, 3.7 Hz, 1H, **H3(ax)**), 3.96 (br d, *J* = 11.3 Hz, 1H, **H7(eq)**), 3.43 (br t, *J* = 3.6 Hz, 2H, **H1**), 2.78 (br s, 1H, **H7(ax)**), 2.04 – 1.93 (m, 1H, **H8'**), 1.92 – 1.76 (m, 3H, **H2**, **H4(eq)**, **H8''**), 1.60 – 1.26 (m, 7H, **H4(ax)**, **H5**, **H6**, **H11**), –0.05 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.75 (**C**, **C13**), 137.17 (**C**, **C15**), 128.30 (**CH**, **C16**), 127.62 (**CH**, **C18**), 127.18 (**CH**, **C17**), 126.17 (**CH**, **C10**), 125.88 (**CH**, **C9**), 65.92 (**CH_2**, **C14**), 59.31 (**CH_2**, **C1**), 51.88 (**CH**, **C3**), 39.09 (**CH_2**, **C7**), 38.29 (**CH**, **C2**), 26.04 (**CH_2**, **C4**), 25.34 (**CH_2**, **C6**), 24.53 (**CH_2**, **C8**), 18.83 (**CH_2**, **C5**), 17.84 (**CH_2**, **C11**), –1.77 (**Me_3Si**) ppm.

^{1}H NMR (V_T, T = 353K)	(500 MHz, DMSO-d_6): δ = 7.37 – 7.32 (m, 4H, **H16**, **H17**), 7.32 – 7.27 (m, 1H, **H18**), 5.43 – 5.35 (m, 1H, **H10**), 5.33 – 5.27 (m, 1H, **H9**), 5.08 (s, 2H, **H14**), 4.20 (ddd, *J* = 10.4, 5.1, 1.7 Hz, 1H, **H3(ax)**), 4.17 (t, *J* = 4.9 Hz, 1H, **H19**), 4.02 – 3.95 (m, 1H, **H7(eq)**), 3.47 (t, *J* = 4.0 Hz, 2H, **H1**), 2.81 (td, *J* = 13.3, 2.8 Hz, 1H, **H7(ax)**), 2.04 – 1.95 (m, 1H, **H8'**), 1.95 – 1.86 (m, 3H, **H2**, **H4(eq)**, **H8''**), 1.62 – 1.31 (m, 7H, **H4(ax), H5**, **H6**, **H11**), –0.02 (s, 9H, **Me_3Si**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d_6): δ = 154.52 (**C**, **C13**), 136.90 (**C**, **C15**), 127.82 (**CH**, **C16**), 127.13 (**CH**, **C18**), 126.78 (**CH**, **C17**), 125.63 (**CH**, **C10**), 125.55 (**CH**, **C9**), 65.60 (**CH_2**, **C14**), 59.74 (**CH_2**, **C1**), 52.03 (**CH**, **C3**), 38.93 (**CH_2**, **C7**), 38.55 (**CH**, **C2**), 25.75 (**CH_2**, **C4**), 24.81 (**CH_2**, **C6**), 24.57 (**CH_2**, **C8**), 18.50 (**CH_2**, **C5**), 17.48 (**CH_2**, **C11**), –2.17 (**Me_3Si**) ppm.
LRMS	(ES^+) *m/z* 390.4 $[M+H]^+$, 412.4 $[M+Na]^+$.
HRMS	(ES^+) for $C_{22}H_{36}NO_3Si^+$ $[M+H]^+$, calculated 390.2459 found 390.2458.

3.28: (–)-Benzyl (*R*)-2-((*S*,*Z*)-1-(2,6-dioxopiperidin-1-yl)-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate



$C_{27}H_{40}N_2O_4Si$

484.71 g mol^{-1}

To a solution of alcohol **3.27** (440 mg, 1.12 mmol) in anhydrous THF (5 mL) was added glutarimide (250 mg, 2.23 mmol), ADDP (560 mg, 2.24 mmol) and tributylphosphine (0.56 mL, 2.23 mmol) sequentially. The colourless solution turned bright yellow on addition of ADDP, turning colourless after approximately 5 min following the addition of tributylphosphine. The reaction was stirred at RT for 48 h. The reaction was quenched by the addition of H_2O (10 mL). The phases were separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid. The residue was suspended in hexane (50 mL) and filtered, washing the filter pad through with hexane (3 x 50 mL). The filtrate was then concentrated *in vacuo* to yield a colourless oil. Purification by chromatography (EtOAc:hexane 20:80) afforded the title compound as a colourless oil (525 mg, 1.08 mmol, 97 %).

R_f 0.38 (EtOAc:hexane 40:60)

$[\alpha]_D$ –83.1° (*c*. 1.11 $CHCl_3$)

FT-IR (neat) ν_{max}: 2950 (br), 1724 (s), 1672 (s), 1498 (w), 1424 (m), 1390 (w), 1340 (s), 1259 (s), 1246 (s), 1167 (m), 1128 (s), 1071 (m), 1042 (m), 1028 (m), 1005 (w) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.39 7.27 (m, 5H, **H16**, **H17**, **H18**), 5.28 (q, *J* = 9.1 Hz, 1H, **H10**), 5.15 – 5.17 (m, 1H, **H9**), 5.05 (s, 2H, **H14**), 4.02 – 3.89 (m, 2H, **H3(ax)**, **H7(eq)**), 3.77 (dd, *J* = 13.0, 9.7 Hz, 1H, **H1'**), 3.50 (dd, *J* = 13.0, 4.5 Hz, 1H, **H1''**), 2.78 – 2.64 (m, 1H, **H7(ax)**), 2.64 – 2.53 (m, 4H, **H20**), 2.44 – 2.33 (m, 1H, **H2**), 1.89 – 1.73 (m, 5H, **H4'**, **H8**, **H21**), 1.68 – 1.50 (m, 3H, **H5, H6'**), 1.48 – 1.21 (m, 4H, **H4''**, **H6''** & **H11**), –0.09 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.84 (**C**, **C19**), 154.63 (**C**, **C13**), 137.00 (**C**, **C15**), 128.34 (**CH**, **C16**), 127.73 (**CH**, **C18**), 127.33 (**CH**, **C17**), 125.85

(**CH_2 C9**), 125.55 (**CH**, **C10**), 66.09 (**CH_2**, **C14**), 53.35 (**CH**, **C3**), 40.98 (**CH_2**, **C1**), 39.41 (**CH_2**, **C7**), 34.39 (**CH**, **C2**), 32.26 (**CH_2**, **C20**), 26.54 (**CH_2**, **C8**), 26.35 (**CH_2**, **C4**), 24.98 (**CH_2**, **C6**), 18.62 (**CH_2**, **C5**), 17.94 (**CH_2**, **C11**), 16.42 (**CH_2**, **C21**), –1.76 (**Me_3Si**) ppm.

^{1}H NMR (V_T, T = 353K)

(500 MHz, DMSO-d_6): δ = 7.38 – 7.32 (m, 4H, **H16**, **H17**), 7.32 – 7.28 (m, 1H, **H18**), 5.33 – 5.26 (m, 1H, **H10**), 5.19 – 5.13 (m, 1H, **H9**), 5.07 (s, 2H, **H14**), 4.01 (dq, *J* = 10.8, 2.5 Hz, 1H, **H3(ax)**), 3.95 (br dd, *J* = 13.7, 4.3 Hz, 1H, **H7(eq)**), 3.79 (dd, *J* = 13.1, 9.1 Hz, 1H, **H1'**), 3.56 (dd, *J* = 13.1, 4.8 Hz, 1H, **H1''**), 2.75 (td, *J* = 13.3, 2.9 Hz, 1H, **H7(ax)**), 2.58 (td, *J* = 6.5, 1.4, 4H, **H20**), 2.45 – 2.37 (m, 1H, **H2**), 1.91 – 1.76 (m, 5H, **H4(eq)**, **H8**, **H21**), 1.70 – 1.52 (m, 3H, **H5, H6'**), 1.51 – 1.43 (tdd, *J* = 13.3, 5.1, 3.8 Hz, 1H, **H4(ax)**), 1.41 – 1.26 (m, 3H, **H6''**, **H11**), –0.05 (s, 9H, **Me_3Si**) ppm.

^{13}C NMR (V_T, T = 353K)

(126 MHz, DMSO-d_6): δ = 172.30 (**C**, **C19**), 154.41 (**CH**, **C13**), 136.74 (**C**, **C15**), 127.86 (**CH**, **C16**), 127.21 (**CH**, **C18**), 126.88 (**CH**, **C17**), 125.47 (**CH**, **C9**), 125.19 (**CH**, **C10**), 65.76 (**CH_2**, **C14**), 53.27 (**CH**, **C3**), 40.78 (**CH_2**, **C1**), 39.21 (**CH_2**, **C7**), 34.71 (**CH**, **C2**), 31.98 (**CH_2**, **C20**), 26.29 (**CH_2**, **C8**), 25.88 (**CH_2**, **C4**), 24.45 (**CH_2**, **C6**), 18.31 (**CH_2**, **C5**), 17.55 (**CH_2**, **C11**), 16.04 (**CH_2**, **C21**), –2.17 (**Me_3Si**) ppm.

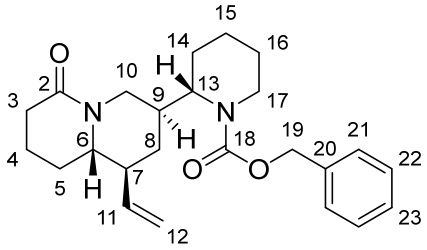
LRMS

(ES^+) *m/z* 485.5 $[M+H]^+$, 507.5 $[M+Na]^+$.

HRMS

(ES^+) for $C_{27}H_{41}N_2O_4Si^+$ $[M+H]^+$, calculated 485.2830 found 485.2836.

3.32: (–)-Benzyl (*S*)-((1*S*,3*S*,9a*S*)-6-oxo-1-vinyloctahydro-2*H*-quinolizin-3-yl)piperidine-1-carboxylate



$C_{24}H_{32}N_2O_3$

396.53 g mol^{-1}

To a solution of imide **3.28** (514 mg, 1.06 mmol) in anhydrous CH_2Cl_2 (5.5 mL) at –78 °C was added lithium triethylborohydride (1 M in THF, 2.12 mL, 2.12 mmol) dropwise over 5 min. The reaction was stirred for 3 h. The reaction was quenched with 2 M HCl (2 mL), warmed to RT and stirred for 45 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (3 x 10), dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil.

The crude hydroxylactam was dissolved in anhydrous CH_2Cl_2 (5.5 mL) and cooled to 0 °C. Boron trifluoride diethyl etherate (0.65 mL, 5.30 mmol) was added dropwise over 2 min. The reaction was warmed to RT and stirred for 2 h. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (3 mL) and stirred for 30 min. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a colourless oil.

Purification by chromatography (silica, EtOAc:hexane 20:80) afforded the title compound as a colourless oil (226 mg, 0.571 mmol, 54 %).

R_f 0.18 (EtOAc:hexane 90:10)

$[\alpha]^{20}_D$ –111.1° (*c*. 1.11 $CHCl_3$)

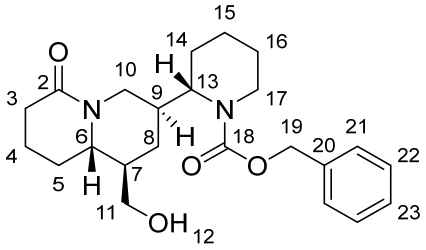
FT-IR (neat) ν_{max}: 2937 (m), 2864 (m), 1689 (s), 1636 (s), 1497 (w), 1421 (s), 1347 (m), 1306 (w), 1301 (w), 1253 (s), 1172 (w), 1154 (s), 1071 (m), 1029 (m), 1002 (w) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.41 – 7.24 (m, 5H, **H21**, **H22**, **H23**), 5.56 (br s, 1H, **H11**), 5.21 – 4.92 (m, 4H, **H12**, **H19**), 4.65 (br d, *J* = 11.9 Hz, **H10(eq)**), 4.00 – 3.82 (m, 2H, **H13(ax)**, **H17(eq**)), 3.03 (br s, 1H, **H6(ax)**), 2.76 (br s, 1H, **H17(ax)**), 2.28 – 1.80 (m, 6H, **H3**, **H9(ax)**, **H5'**, **H10(ax)**, **H7(eq)**), 1.77 – 1.63 (m, 2H, **H4'**, **H14'**), 1.62 – 1.38 (m, 7H, **H8'**, **H5''**, **H16'**, **H15**, **H4''**, **H14''**) 1.37 – 1.23 (m, 1H, **H16''**), 1.05 (br s, 1H, **H8''**) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.02 (**C**, **C2**), 154.69 (**C**, **C18**), 139.95 (**CH**, **C11**), 137.16 (**C**, **C20**), 128.35 (**CAr**), 127.68 (**CAr**), 116.00 (**CH_2**

	C12), 65.93 (**CH_2**, **C19**), 58.53 (**CH**, **C6**), 53.14 (**CH**, **C13**), 47.11 (**CH**, **C7**), 44.43 (**CH_2**, **C10**), 39.10 (**CH_2**, **C17**), 34.40 (**CH_2**, **C8**), 32.72 (**CH**, **C9**), 32.52 (**CH_2**, **C3**), 26.79 (**CH_2**, **C5**), 25.88 (**CH_2**, **C14**), 25.07 (**CH_2**, **C16**), 18.53 (**CH_2**, **C15**), 17.97 (**CH_2**, **C4**) ppm.
^{1}H NMR (V_T, T = 353K)	(500 MHz, DMSO-d_6): δ = 7.37 – 7.28 (m, 5H, **H21**, **H22**, **H23**), 5.60 (ddd, *J* = 17.27, 10.17, 8.65 Hz, 1H, **H11**), 5.13 – 5.01 (m, 4H, **H12, H19**), 4.68 (ddd, *J* = 12.60, 4.01, 2.52 Hz, 1H, **H10(eq)**), 3.95 (br d, *J* = 13.6, 3.9 Hz, 1H, **H17(eq)**), 3.90 (ddd, *J* = 10.4, 5.0, 1.8 Hz, 1H, **H13(ax)**), 3.03 (dt, *J* = 10.4, 6.4 Hz, 1H, **H6(ax)**), 2.78 (td, *J* = 13.2, 2.5 Hz, 1H, **H17(ax)**), 2.29 – 2.14 (m, 2H, **H3**), 2.06 (t, *J* = 12.1 Hz, 1H, **H10(ax)**), 2.05 – 1.97 (m, 1H, **H7**), 1.96 – 1.87 (m, 2H, **H5'**, **H9(ax)**), 1.78 – 1.68 (m, 2H, **H4'**, **H14'**), 1.63 – 1.44 (m, 7H, **H4''**, **H5''**, **H8(eq)**, **H14''**, **H15**, **H16'**), 1.41 – 1.30 (m, 1H, **H16''**), 1.07 (app q, *J* = 12.7, 12.0 Hz, 1H, **H8(ax)**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d_6): δ = 168.56 (**C**, **C2**), 155.37 (**C**, **C18**), 140.38 (**CH**, **C11**), 137.74 (**C**, **C20**), 128.77 (**CAr**), 128.10 (**CAr**), 127.79 (**CAr**), 116.28 (**CH_2**, **C12**), 66.55 (**CH_2**, **C19**), 59.37 (**CH**, **C6**), 53.89 (**CH**, **C13**), 47.59 (**CH**, **C7**), 45.19 (**CH_2**, **C10**), 39.84 (**CH_2**, **C17**), 35.08 (**CH_2**, **C8**), 33.76 (**CH**, **C9**), 33.08 (**CH_2**, **C3**), 27.41 (**CH_2**, **C5**), 26.31 (**CH_2**, **C14**), 25.45 (**CH_2**, **C16**), 19.09 (**CH_2**, **C15**), 18.62 (**CH_2**, **C4**) ppm.
LRMS	(ES^+) *m/z* 397.4 $[M+H]^+$, 419.4 $[M+Na]^+$.
HRMS	(ES^+) for $C_{24}H_{32}N_2O_3^+$ $[M+H]^+$, calculated 397.2486 found 397.2477

3.36: (–)-Benzyl (*S*)-2-((1*R*,3*S*,9a*S*)-1-(hydroxymethyl)-6-oxooctahydro-2*H*-quinolizin-3-yl)piperidine-1-carboxylate



$C_{23}H_{32}N_2O_4$

400.52 g mol^{-1}

A solution of alkene **3.32** (170 mg, 431 µmol) in anhydrous MeOH (8.5 mL) was cooled to –78 °C. O_3 in O_2 was bubbled through the solution for 15 min at this temperature until the characteristic blue colour of ozone appeared. The solution was then sparged with O_2 for 15 min. $NaBH_4$ (162 mg, 4.29 mmol) was then added in one portion, and the cloudy suspension warmed to RT and stirred for 2 h. The reaction was quenched with 2 M HCl (4 mL), and the reaction diluted with CH_2Cl_2 (10 mL). The phases were separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a pale yellow oil. Purification by chromatography (silica, EtOAc:MeOH 95:5) afforded the title compound as a yellow oil (112 mg, 280 µmol, 65 %).

R_f 0.31 (9:1 EtOAc:MeOH)

$[\alpha]_D$ –55.8° (*c*. 1.00, $CHCl_3$)

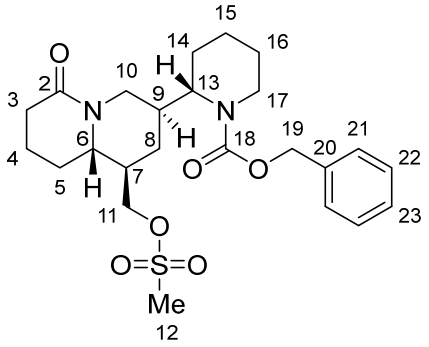
FT-IR (neat) ν_{max}: 3415 (br), 2934 (m), 2866 (m), 1693 (s), 1615 (s), 1425 (m), 1350 (w), 1257 (m), 1173 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41 – 7.27 (m, 5H, **H21**, **H22**, **H23**), 5.31 – 4.95 (m, 2H, **H19**), 4.92 – 4.76 (m, 1H, **H10(eq)**), 4.17 – 3.88 (m, 3H, **H12**, **H13(ax)**, **H17(eq)**), 3.63 – 3.43 (m, 2H, **H11**), 3.19 – 3.03 (m, 1H, **H6**), 2.81 – 2.60 (m, 1H, **H17(ax)**), 2.46 – 2.34 (m, 1H, **H3(eq)**), 2.32 – 2.20 (m, 1H, **H3(ax)**), 2.18 – 1.74 (m, 7H, **H4**, **H5(eq)**, **H9**, **H14**, **H10(ax)**), 1.72 – 1.31 (m, 7H, **H5(ax)**, **H7**, **H8(eq)**, **H15**, **H16**), 1.20 – 0.94 (m, 1H, **H8(ax)**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.09 (**C**, **C2**), 155.73 (**C**, **C18**), 136.93 (**C**, **C20**), 128.37 (**Ar**), 128.02 (**Ar**), 127.72 (**Ar**), 66.86 (**CH_2**, **C19**), 63.73 (**CH_2**, **C11**), 58.06 (**CH**, **C6**), 53.77 (**CH**, **C13**), 45.22 (**CH_2**, **C10**), 44.55 (**CH**, **C7**), 39.79 (**CH_2**, **C17**), 33.39 (**CH**, **C9**), 32.80 (**CH_2**, **C3**), 31.07 (**CH_2**, **C8**), 27.08 (**CH_2**, **C5**), 25.96 (**CH_2**, **C14**), 25.36 (**CH_2**, **C16**), 19.00 (**CH_2**, **C15**), 18.67 (**CH_2**, **C4**) ppm.

^{1}H NMR (V_T, T = 353K)	(DMSO-d_6, 500 MHz): δ = 7.39 – 7.32 (m, 4H, **H22**, **H21**), 7.33 – 7.28 (m, 1H, **H23**), 5.10 (s, 2H, **H19**), 4.68 (ddd, *J* = 12.5, 3.8, 2.5 Hz, 1H, **H10(eq)**), 4.24 (t, *J* = 5.0 Hz, 1H, **H12**), 3.96 (br dd, *J* = 13.6, 4.1 Hz, 1H, **H17(eq)**), 3.90 (ddd, *J* = 10.2, 4.7, 1.7 Hz, 1H, **H13**), 3.40 (td, *J* = 4.6, 2.5 Hz, 2H, **H11**), 3.13 – 3.07 (m, 1H, **H6**), 2.78 (td, *J* 13.2, 2.5 Hz, 1H, **17(ax)**), 2.24 (dtd, *J* = 16.8, 5.7, 1.0 Hz, 1H, **H3(eq)**), 2.16 (ddd, *J* = 16.9, 9.3, 5.5 Hz, 1H, **H3(ax)**), 2.09 – 2.02 (m, 1H, **H5(eq)**), 1.99 (t, *J* = 12.0 Hz, 1H, **H10(ax)**), 1.87 (qt, *J* = 11.3, 3.6 Hz, 1H, **H9**), 1.79- 1.42 (m, 9H, **H4**, **H5(ax)**, **H8(eq)**, **H14**, **H15**, **H16(eq)**), 1.42 – 1.30 (m, 2H, **H7**, **H16(ax)**), 1.08 (app q, *J* = 12.1 Hz, 1H, **H8(ax)**) ppm.
^{13}C NMR (V_T, T = 353K)	(DMSO-d_6, 126 MHz): δ = 167.72 (**C**, **C2**), 154.51 (**C**, **C18**), 136.87 (**C**, **C20**), 127.90 (**CH**, **C22**), 127.17 (**CH**, **C23**), 126.85 (**CH**, **C21**), 65.69 (**CH_2**, **C19**), 62.10 (**CH_2**, **C11**), 57.62 (**CH**, **C6**), 53.23 (**CH**, **C13**), 44.41 (**CH_2**, **C10**), 43.86 (**CH**, **C7**), 39.01 (**CH_2**, **C17**), 33.24 (**CH**, **C9**), 32.21 (**CH_2**, **C3**), 31.02 (**CH_2**, **C8**), 26.17 (**CH_2**, **C5**), 25.46 (**CH_2**, **C14**), 24.60 (**CH_2**, **C16**), 18.25 (**CH_2**, **C15**), 18.06 (**CH_2**, **C4**) ppm.
LRMS	(ES$^+$) *m/z* 401.5 $[M+H]^+$, 423.5 $[M+Na]^+$.
HRMS	(ES$^+$) for $C_{23}H_{33}N_2O_4^+$ $[M+H]^+$, calculated 401.2435 found 401.2443

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



$C_{24}H_{34}N_2O_6S$

478.60 g mol^{-1}

To a solution of alcohol **3.36** (112 mg, 282 µmol) in anhydrous CH_2Cl_2 (4.5 mL) was added pyridine (0.14 mL, 1.73 mmol) and DMAP (2 mg, 16.4 µmol). The colourless solution was stirred at room temperature for 20 min, then methanesulfonic anhydride (146 mg, 842 µmol) was added in one portion. The reaction was stirred for 6 h, over which time the solution turned a cloudy orange. The reaction was quenched with H_2O (4 mL), and stirred for a further 30 min. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange oil. Purification by chromatography (silica, EtOAc:MeOH 95:5) afforded the title compound as a pale yellow oil (81 mg, 169 µmol, 61%).

R_f 0.31 (9:1 EtOAc:MeOH)

$[\alpha]_D$ –42.7 ° (*c*. 0.37, $CHCl_3$)

FT-IR (neat) ν_{max} 2934 (w), 2863 (w), 1690 (s), 1637 (s), 1425 (m), 1353 (s), 1265 (m), 1174 (s), 1156 (m), 1094 (w) cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ = 7.41 – 7.28 (m, 5H, **H21**, **H22**, **H23**), 5.07 (s, 2H, **H19**), 4.65 (br d, *J* = 11.0 Hz, 1H, **H10(eq)**), 4.23 – 4.11 (m, 2H, **H11**), 3.98 – 3.84 (m, 2H, **H13(ax)**, **H17(eq)**), 3.21 – 3.09 (m, 4H, **H6(ax)**, **H12**), 2.79 (br s, 1H, **H17(ax)**), 2.30 – 2.11 (m, 2H, **H3**), 2.10 – 1.87 (m, 3H, **H5(eq)**, **H9(ax)**, **H10(ax)**), 1.79 – 1.39 (m, 10H, **H4**, **H5(ax)**, **H7(ax)**, **H8(eq)**, **H14**, **H15**, **H16(eq)**), 1.37 – 1.27 (m, 1H, **H16(ax)**), 1.09 (q, *J* = 12.3 Hz, 1H, **H8(ax)**) ppm.

^{13}C NMR (DMSO-*d*$_6$, 101 MHz) δ =185.15 (**C**, **C2**), 154.76 (**C**, **C18**), 137.09 (**C**, **C20**), 128.41 (**CH**, **C22**), 127.73 (**CH**, **C23**), 127.34 (**CH**, **C21**), 71.31 (**CH_2**, **C11**), 66.14 (**CH_2**, **C19**), 56.92 (**CH**, **C6**), 53.22 (**CH**, **C13**), 44.29 (**CH_2**, **C10**), 41.06 (**CH**, **C7**), 39.09 (**CH_2**, **C17**), 36.37 (**CH_3**, **C12**), 32.83

(**CH**, **C9**), 32.47 (**CH_2**, **C3**), 30.72 (**CH_2**, **C8**), 26.14 (**CH_2**, **C5 & C14**), 25.16 (**CH_2**, **C16**), 18.55 (**CH_2**, **C15**), 18.16 (**CH_2**, **C4**) ppm.

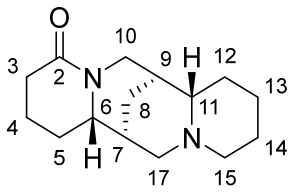
^{1}H NMR (V_T, T = 353K) (500 MHz, DMSO-d_6): δ = 7.40 – 7.23 (m, 2H, **H21**, **H22**), 7.33 – 7.28 (m, 1H, **H23**), 5.09 (d, *J* = 1.6 Hz, 2H, **H19**), 4.68 (ddd, *J* = 12.3, 3.9, 2.4 Hz, 1H, **H10(eq)**), 4.16 (d, *J* = 4.2 Hz, 2H, **H11**), 3.96 (br dd, *J* = 13.6, 3.7 Hz, 1H, **H17(eq)**), 3.91 (ddd, *J* = 10.5, 4.3, 1.6 Hz, 1H, **H13(ax)**), 3.19 – 3.13 (m, 1H, **H6(ax)**), 3.11 (s, 3H, **H12**), 2.81 (td, *J* = 13.4, 2.7 Hz, 1H, **H17(ax)**), 2.26 (dt, *J* = 16.7, 5.7 Hz, 1H, **H3(eq)**), 2.19 (ddd, *J* = 16.7, 8.8, 5.5 Hz, 1H, **H3(ax)**), 2.11 – 2.01 (m, 2H, **H5(eq)**, **H10(ax)**), 1.93 (qt, *J* = 11.3, 3.4 Hz, 1H, **H9(ax)**), 1.80 – 1.69 (m, 4H, **H4(eq)**, **H7(ax)**, **H8(eq)**, **H14(eq)**), 1.67 – 1.54 (m, 5H, **H4(ax)**, **H5(ax)**, **H15**, **H16(eq)**), 1.53 – 1.44 (m, 1H, **H14(ax)**), 1.40 – 1.31 (m, 1H, **H16(ax)**), 1.10 (app q, *J* = 12.5, 11.7 Hz, 1H, **H8(ax)**) ppm.

^{13}C NMR (V_T, T = 353K) (126 MHz, DMSO-d_6): δ = 167.75 (**C**, **C2**), 154.53 (**C**, **C18**), 136.79 (**C**, **C20**), 127.92 (**CH**, **C22**), 127.23 (**C**, **C23**), 70.77 (**CH_2**, **C11**), 65.78 (**CH_2**, **C19**), 56.86 (**CH**, **C6**), 53.04 (**CH**, **C13**), 44.18 (**CH_2**, **C10**), 40.96 (**CH**, **C7**), 39.01 (**CH_2**, **C17**), 36.38 (**CH_3**, **C12**), 32.97 (**CH**, **C9**), 32.10 (**CH_2**, **C3**), 30.45 (**CH_2**, **C8**), 25.92 (**CH_2**, **C5**), 25.42 (**CH_2**, **C14**), 24.53 (**CH_2**, **C16**), 18.19 (**CH_2**, **C15**), 17.86 (**CH_2**, **C4**) ppm.

LRMS $(ES)^+$ *m/z* = 479.4 $[M+H]^+$, 501.5 $[M+Na]^+$.

HRMS $(ES)^+$ for $C_{24}H_{35}N_2O_6S^+$ $[M+H]^+$ calculated 479.2210 found 479.2214.

3.34: (+)-(7*S*,7a*S*,14*S*,14a*S*)-dodecahydro-2*H*,11*H*-7,14-methanodipyrido[1,2-a:1',2'-e][1,5]diazocin-11-one



$C_{15}H_{24}N_2O$

248.37 g mol^{-1}

To a solution of mesylate **3.37** (69 mg, 140 µmol) in anhydrous MeOH (2 mL) was added palladium on carbon (10%, 16 mg, 144 µmol). The cloudy black mixture was stirred under an H_2 atmosphere for 16 h. The reaction mixture was filtered through celite, the filter pad was washed with MeOH (3 x 10 mL), and the filtrate concentrated *in vacuo* to yield a pale yellow oil. This residue was redissolved in MeCN (4 mL), and K_2CO_3 (100 mg, 720 µmol) was added in one portion. The mixture was heated to 60 °C and stirred for 16 h. The reaction was quenched with H_2O (4 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a pale brown oil (16 mg, 64 µmol, 45 %).

R_f 0.31 (9:1 EtOAc:MeOH)

$[\alpha]_D$ +12.4° (*c*. 0.25, $CHCl_3$)

FT-IR (neat) ν_{max} 2927 (s), 2853 (m), 1639 (s), 1443 (w), 1343 (w), 1269 (w), 1159 (w) cm^{-1}.

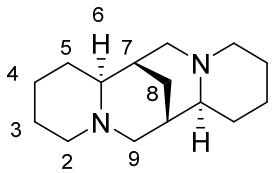
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 4.77 (dd, *J* = 13.6, 10.8 Hz, 1H, **H10(eq)**), 3.62 (ddd, *J* = 9.4, 4.8, 2.9 Hz, 1H, **H6(ax)**), 3.12 (dd, *J* = 11.1, 2.5 Hz, 1H, **H17(eq)**), 2.87 (ddd, *J* = 13.5, 12.6, 3.0 Hz, 1H, **H15(eq)**), 2.82 (ddt, *J* = 13.8, 4.1, 1.8 Hz, 1H, **H15(ax)**), 2.73 (dd, *J* = 13.6, 1.9 Hz, 1H, **H10(ax)**), 2.59 (dt, *J* = 12.1, 2.3 Hz, 1H, **H11(ax)**), 2.45 – 2.32 (m, 2H, **H3**), 2.25 (ddd, *J* = 11.1, 2.8, 1.8 Hz, 1H, **H17(ax)**), 1.95 – 1.83 (m, 3H, **H5(eq)**, **H9(eq)**, **H13(eq)**), 1.82 – 1.61 (m, 5H, **H4**, **H7(eq)**, **H12(eq)**, **H14(eq)**), 1.59 – 1.42 (m, 3H, **H5(ax)**, **H8(eq)**, **H13(ax)**), 1.31 (dtd, *J* = 13.1, 3.8, 1.8 Hz, 1H, **H8(ax)**), 1.21 – 1.15 (m, 1H, **H14(ax)**), 1.06 (br dd, *J* = 13.0, 2.6 Hz, 1H, **H12(ax)**) ppm.

^{13}C NMR ($CDCl_3$, 126 MHz) δ = 170.47 (**C**, **C2**), 61.96 (**CH**, **C11**), 57.84 (**CH**, **C6**), 54.91 (**CH_2**, **C15**), 50.60 (**CH_2**, **C17**), 45.57 (**CH_2**, **C10**), 36.47 (**CH**, **C7**), 32.65 (**CH_2**, **C3**), 32.03 (**CH_2**, **C5**), 31.64 (**CH**, **C9**), 25.75 (**CH_2**, **C13**), 22.51 (**CH_2**, **C12**), 19.96 (**CH_2**, **C8**), 19.86 (**CH_2**, **C4**), 19.36 (**CH_2**, **C14**) ppm.

LRMS (ES)$^+$ *m/z* = 249.3 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{25}N_2O^+$ $[M+H]^+$ calculated 249.1961 found 249.1961.

(+)-1.6: (+)-*β*-isosparteine



$C_{15}H_{26}N_2$

234.39 g mol^{-1}

To a solution of amide **3.34** (10 mg, 40 µmol) in anhydrous THF (1 mL) under N_2 was added $LiAlH_4$ (1 M in THF, 320 µL, 320 µmol) dropwise. The solution was heated to reflux and stirred for 16 h. The reaction mixture was diluted with Et_2O (1 mL) and the reaction quenched by the dropwise addition of *sat*. $Na_2SO_{4(aq)}$ until effervescence ceased. The phases were separated, and the aqueous layer extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale brown oil. The crude product was dissolved in Et_2O (2 mL) and *conc*. HCl was added (3 drops). The solution was agitated and then concentrated *in vacuo* to yield a pale yellow solid. The residue was dissolved in hexane (3 mL) and the organic layer decanted off. This was repeated three times. The residue was then dissolved in EtOAc (3 mL), and 20% $NaOH_{(aq)}$ (1 mL) added. The phases were separated and the aqueous extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound as a pale brown oil (8 mg, 34 µmol, 87%).

R_f 0.10 (75:25:2.5 CH_2Cl_2:MeOH:NH_4OH)

$[\alpha]_D$ +11.0° (*c* = 0.1, absolute EtOH)

FT-IR (neat) ν_{max}: 2926 (s), 2851 (m), 2805 (w), 1457 (w), 1443 (w), 1129 (w) cm^{-1}.

^{1}H NMR ($CHCl_3$, 400 MHz) δ = 3.03 (dd, *J* = 10.8, 6.6 Hz, 2H, **H10(eq)**), 2.81 (dt, *J* = 12.6, 1.9 Hz, 2H, **H2(eq)**), 2.46 (td, *J* = 12.9, 2.1 Hz, 2H, **H2(ax)**), 2.28 (d, *J* = 10.0 Hz, 2H, **H6(ax)**), 2.18 (d, *J* = 10.7 Hz, 2H, **H10(ax)**), 1.77 (m, 2H, **H4(eq)**), 1.72 – 1.49 (m, 8H, **H3(eq)**, **H5(eq)**, **H7(ax)**, **H8**), 1.46 – 1.17 (m, 6H, **H3(ax)**, **H4(ax)**, **H5(ax)**) ppm.

^{13}C NMR ($CHCl_3$, 101 MHz) δ = 62.81 (**CH**, **C6**), 55.13 (**CH_2**, **C2**), 54.97 (**CH_2**, **C9**), 34.43 (**CH**, **C7**), 28.68 (**CH_2**, **C5**), 25.44 (**CH_2**, **C4**), 22.67 (**CH_2**, **C3**), 19.81 (**CH_2**, **C8**) ppm.

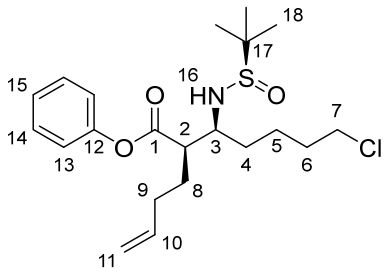
LRMS (ES^+) *m/z* = 235.4 $[M+H]^+$.

HRMS (ES^+) for $C_{15}H_{27}N_2^+$, calculated 235.2169 found 235.2170.

Physical and spectroscopic data are consistent with the literature.[34, 124]

7.2.1.2 Acetal route

2.98: (+)-(Phenyl (2*R*,3*S*)-2-(but-3-en-1-yl)-3-(((*S*)-*tert*-butylsulfinyl)amino)-7-chloroheptanoate



$C_{21}H_{32}ClNO_3S$

414.00 g mol^{-1}

A solution of LDA (5.52 mL, 2 M in THF, 11.0 mmol) was cooled to −78 °C. A solution of ester **2.99** (2.00 g, 10.5 mmol) in anhydrous THF (50 mL) was added dropwise at this temperature. The orange solution was stirred for 1 h, then a solution of *N*-sulfinylimine (+)-**1.125** (1.88 g, 8.41 mmol) in anhydrous THF (5 mL) was added over 30 min. The solution was stirred for 2 h, then quenched by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL). The mixture was warmed to RT and stirred for 1 h. The phases were separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 95:5 *syn*/*anti*). Purification by chromatography (silica, 2:8 EtOAc / hexane) afforded the title compound as a yellow oil (2.38 g, 5.75 mmol, 68%).

R_f 0.31 (2:8 EtOAc:hexane)

$[\alpha]_D$ +15.9° (*c*. 1.02, $CHCl_3$)

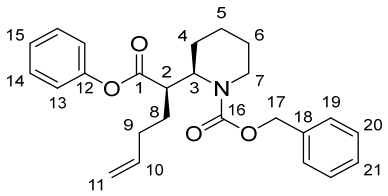
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.45 – 7.37 (m, 2H, **H14**), 7.29 – 7.23 (m, 1H, **H15**), 7.13 – 7.06 (m, 2H, **H13**), 5.85 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H, **H10**), 5.12 (dq, *J* = 17.1, 1.6 Hz, 1H, **H11'**), 5.08 – 5.04 (m, 1H, **H11''**), 4.17 (d, *J* = 8.3 Hz, 1H, **H16**), 3.56 (t, *J* = 6.4, 2H, **H7**), 3.53 – 3.45 (m, 1H, **H3**), 3.18 (ddt, *J* = 9.3, 4.7 Hz, 1H, **H2**), 2.35 – 2.14 (m, 2H, **H9**), 2.11 – 1.99 (m, 1H, **H8'**), 1.90 – 1.46 (m, 7H, **H4**, **H5**, **H6**, **H8''**), 1.25 (s, 9H, **H18**).ppm.

^{13}C NMR ($CDCl_3$, 10 MHz) δ = 172.60 (**C**, **C1**), 150.32 (**C**, **C12**), 137.21 (**CH**, **C10**), 129.57 (**CH**, **C14**), 126.14 (**CH**, **C15**), 121.49 (**CH**, **C13**), 115.97 (**CH_2**, **C11**), 58.25 (**CH**, **C3**), 56.21 (**C**, **C17**), 49.98 (**CH**, **C2**), 44.76 (**CH_2**, **C7**), 32.10 (**CH_2**, **C6**), 31.87 (**CH_2**, **C9**), 31.46 (**CH_2**, **C4**), 28.01 (**CH_2**, **C8**), 23.65 (**CH_2**, **C5**), 22.77 (**CH_3**, **C18**). ppm.

LRMS $(ES)^+$ *m/z* = 436.1 $[M^{35}Cl+H]^+$, 438.1 $[M^{37}Cl+H]^+$.

Physical and spectroscopic data are consistent with the literature.[172]

3.37: (+)-Benzyl (*R*)-2-((*R*)-1-oxo-1-phenoxyhex-5-en-2-yl)piperidine-1-carboxylate



$C_{25}H_{29}NO_4$

407.51 g mol^{-1}

A solution of imino-aldol adduct **2.98** (2.2 g, 5.31 mmol) in 1,4-dioxane (88 mL) under N_2 was cooled to 0 °C. To the yellow solution was added conc. HCl (1.33 mL, 15.9 mmol) dropwise over 5 min. The solution was warmed to RT and stirred for 2 h. The solution was concentrated *in vacuo*, and the white residue dissolved in CH_2Cl_2 (50 mL) and evaporated (three times) to yield a pale yellow solid.

The residue was redissolved in MeCN (88 mL). K_2CO_3 (3.67 g, 26.6 mmol) and NaI (80 mg, 0.53 mmol) were added in one portion, and the resulting bright yellow mixture stirred for 60 h. The mixture was concentrated *in vacuo*, and the residue partitioned between EtOAc/H_2O (1:1, 50 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil.

The crude piperidine was dissolved in MeCN (25 mL), then K_2CO_3 (1.07 g, 7.74 mmol) was added. The mixture was stirred for 10 min, then benzyl chloroformate (0.77 mL, 5.42 mmol) was added dropwise over 5 min. The reaction was stirred for 16 h, then quenched by addition of H_2O (10 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 5:95 to 20:80 EtOAc/hexane) afforded the title compound as a yellow oil (1.79 g, 4.39 mmol, 83 %).

R_f 0.62 (4:6 EtOAc:hexane)

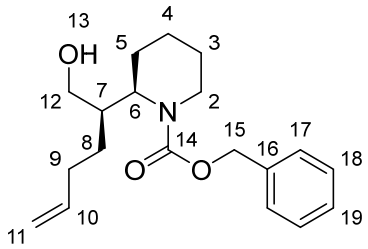
$[\alpha]_D$ +5.00° (*c*. 1.37, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44 – 7.22 (m, 8H, **H14**, **H15**, **H19**, **H20**, **H21**), 7.12 – 6.95 (m, 2H, **H13**), 5.92 – 5.67 (m, 1H, **H10**), 5.29 – 4.98 (m, 4H, **H11**, **H17**), 4.80 – 4.56 (m, 1H, **H3**), 4.30 – 4.05 (m, 1H, **H7(eq)**), 3.20 (td, *J* = 11.2, 3.6 Hz, 1H, **H2**), 2.90 – 2.68 (m, 1H, **H7(ax)**), 2.34 – 1.41 (m, 10H, **H4**, **H5**, **H6**, **H8**, **H9**) ppm.

^{13}C NMR (101 MHz, CDCl3): δ = 172.79 (**C**, **C1**), 155.64 (**C**, **C16**), 150.43 (**C**, **C12**), 137.12 (**CH**, **C10**), 129.45 (**Ar**), 128.47 (**Ar**), 127.94 (**Ar**), 121.35 (**CH**, **C13**), 115.78 (**CH_2**, **C11**), 67.19 (**CH_2**, **C17**), 52.44 (**CH**, **C3**), 44.83

	(**CH**, **C2**), 39.38 (**CH_2**, **C7**), 31.46 (**CH_2**, **C9**), 28.27 (**CH_2**, **C8**), 27.88 (**CH_2**, **C4**), 25.14 (**CH_2**, **C6**), 19.08 (**CH_2**, **C5**) ppm.
^{1}H NMR (V_T, T = 353K)	(500 MHz, DMSO-d6): δ = 7.47 – 7.41 (m, 2H, **H14**), 7.38 – 7.26 (m, 6H, **H15**, **H19**, **H20**, **H21**), 7.14 – 7.07 (m, 2H, **H13**), 5.80 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H, **H10**), 5.14 (d, *J* = 2.6 Hz, 2H, **H17**), 5.06 – 4.98 (m, 2H, **H11**), 4.51 (br d, *J* = 11.1 Hz, 1H, **H3**), 4.06 – 3.98 (m, 1H, **H7(eq)**), 3.25 (td, *J* = 10.8, 3.8 Hz, 1H, **H2**), 2.85 (br t, *J* = 12.3 Hz, 1H, **H7(ax)**), 2.21 – 2.06 (m, 2H, **H9**), 1.86 – 1.59 (m, 6H, **H6(eq)**, **H5**, **H4**, **H8'**), 1.58 – 1.50 (m, 1H, **H8''**), 1.45 – 1.34 (m, 1H, **H6(ax)**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d6): δ = 171.94 (**C**, **C11**), 154.53 (**C**, **C16**), 149.88 (**C**, **C12**), 137.18 (**CH**, **C10**), 136.61 (**CH**, **C18**), 129.14 (**CH**, **C14**), 127.90 (**CH**, **C20**), 127.32 (**CH**, **C21**), 127.01 (**CH**, **C19**), 125.52 (**CH**, **C15**), 120.96 (**CH**, **C13**), 114.94 (**CH_2**, **C11**), 66.02 (**CH_2**, **C17**), 51.99 (**CH**, **C3**), 44.09 (**CH**, **C2**), 38.74 (**CH_2**, **C7**), 30.26 (**CH_2**, **C9**), 27.97 (**CH_2**, **C8**), 26.80 (**CH_2**, **C4**), 24.36 (**CH_2**, **C6**), 18.19 (**CH_2**, **C5**) ppm.
LRMS	(ES^+) *m/z* 408.5 $[M+H]^+$, 430.5 $[M+Na]^+$.
HRMS	(ES^+) for $C_{25}H_{29}NNaO_4^+$ $[M+Na]^+$, calculated 430.1989 found 430.2000.

3.38: (−)-Benzyl (*S*)-2-((*R*)-1-hydroxyhex-5-en-2-yl)piperidine-1-carboxylate



$C_{19}H_{27}NO_3$

317.43 g mol^{-1}

A solution of ester **3.37** (1.62 g, 3.98 mmol) in anhydrous THF (20 mL) was cooled to 0 °C. $LiAlH_4$ (1 M in THF, 4.37 mL, 4.37 mmol) was added dropwise. The yellow solution was stirred for 1 h, then cooled to 0 °C and quenched by the slow addition of Rochelle's salt (20 mL). The mixture was stirred for 12 h. The phases were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. Purification by chromatography (silica, 30:70 EtOAc/hexane) afforded the title compound as a colourless oil (595 mg, 1.87 mmol, 47%).

R_f 0.34 (4:6 EtOAc:hexane)

$[\alpha]_D$ −26.9 ° (*c*. 1.06, $CHCl_3$)

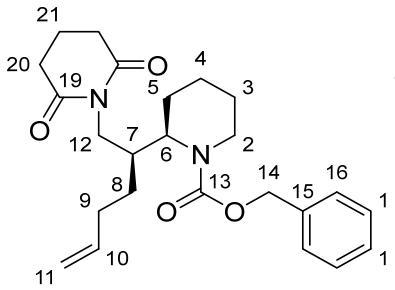
^{1}H NMR (400 MHz, CDCl3): δ = 7.39 – 7.28 (m, 5H, **H19**, **H18**, **H17**), 5.75 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, **H10**), 5.14 (s, 2H, **H15**), 5.03 – 4.93 (m, 2H, **H11**), 4.34 – 4.25 (m, 1H, **H6**), 4.16 – 4.05 (m, 1H, **H2(eq)**), 3.73 – 3.61 (m, 2H, **H12**), 2.83 – 2.72 (m, 1H, **H2(ax)**), 2.25 – 2.13 (m, 1H, **H9'**), 2.045 – 1.79 (m, 3H, **H9''**, **H7**, **H5(eq)**), 1.64 – 1.44 (m, 5H, **H5(ax)**, **H4**, **H3**), 1.44 – 1.37 (m, 2H, **H8**) ppm.

^{13}C NMR (101 MHz, CDCl3): δ = 155.96 (**C**, **C14**), 138.63 (**CH**, **C10**), 136.96 (**C**, **C16**), 128.40 (**CH**, **C18**), 127.80 (**CH**, **C19**), 127.67 (**CH**, **C17**), 114.76 (**CH_2**, **C11**), 66.96 (**CH_2**, **C15**), 61.37 (**CH_2**, **C12**), 51.94 (**CH**, **C6**), 39.71 (**CH_2**, **C2**), 38.14 (**CH**, **C7**), 31.00 (**CH_2**, **C9**), 26.38 (**CH_2**, **C5**), 25.93 (**CH_2**, **C8**), 25.26 (**CH_2**, **C3**), 19.92 (**CH_2**, **C4**) ppm.

^{1}H NMR (V_T, T = 353K) (500 MHz, DMSO-d6): δ = 7.37 – 7.32 (m, 4H, **H17**, **H18**), 7.31 – 7.29 (m, 1H, **H19**), 5.75 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H, **H10**), 5.09 (s, 2H, **H15**), 4.98 – 4.89 (m, 2H, **H11**), 4.98 – 4.92 (m, 1H, **H11'**), 4.92 – 4.89 (m, 1H, **H11'**), 4.21 (t, *J* = 5.0 Hz, 1H, **H13**), 4.17 (ddd, *J* = 10.9, 5.1, 1.8 Hz, 1H, **H6**), 3.99 – 3.94 (m, 1H, **H2(eq)**), 3.54 – 3.43 (m, 2H, **H12**), 2.77 (td, *J* = 13.3, 2.9 Hz, 1H, **H2(ax)**), 2.17 – 2.08 (m, 1H, **H9'**), 2.01 – 1.84 (m, 3H, **H5(eq)**, **H7**, **H9''**), 1.62 – 1.48 (m, 3H, **H3(eq)**, **H4**), 1.47 – 1.21 (m, 4H, **H3(ax)**, **H5(ax)**, **H8**) ppm.

^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d6): δ = 154.55 (**C**, **C14**), 138.78 (**CH**, **C10**),136.98 (**C**, **C16**), 127.85 (**CH**, **C18**), 127.15 (**CH**, **C19**), 126.82 (**CH**, **C17**), 113.79 (**CH_2**, **C11**), 65.56 (**CH_2**, **C15**), 59.41 (**CH_2**, **C12**), 51.80 (**CH**, **C6**), 38.85 (**CH_2**, **C2**), 36.90 (**CH**, **C7**), 30.13 (**CH_2**, **C9**), 26.11 (**CH_2**, **C8**), 25.75 (**CH_2**, **C5**), 24.81 (**CH_2**, **C3**), 18.45 (**CH_2**, **C4**) ppm.
LRMS	(ES^+) *m/z* 318.5 $[M+H]^+$, 340.5 $[M+Na]^+$.
HRMS	(ES^+) for $C_{19}H_{28}NO_3^+$ $[M+H]^+$ calculated 318.2064 found 318.2064.

3.39: (−)-Benzyl (*S*)-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)hex-5-en-2-yl)piperidine-1-carboxylate



$C_{24}H_{32}N_2O_4$

412.53 g mol^{-1}

To a solution of alcohol **3.38** (485 mg, 1.53 mmol) in anhydrous THF (8 mL) was added glutarimide (345 mg, 3.06 mmol), ADDP (768 mg, 3.06 mmol) and tributylphosphine (618 mg, 763 µL, 3.06 mmol. The solution turned bright orange on addition of ADDP, and off-yellow after 5 min upon addition of PBu_3. The solution was stirred for 40 h, then quenched by the addition of H_2O (8 mL). The phases were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). The mixture was acidified with 2M HCl (1 mL) in order to aid separation. The combined organic layers were washed with 2M HCl (40 mL), brine (40 mL), dried ($MgSO_4$) then concentrated *in vacuo* to afford the crude product as a colourless oil. Purification by chromatography (silica, 40:60 EtOAc/hexane) afforded the title compound as a colourless oil (585 mg, 1.42 mmol, 93%).

R_f 0.1 (3:7 EtOAc/hexane)

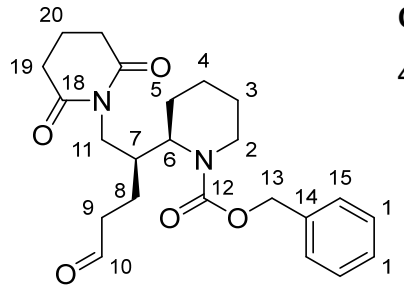
$[\alpha]_D$ -55.5 (*c*. 0.83 $CHCl_3$).

^{1}H NMR (400 MHz, CDCl3): δ = 7.38 – 7.27 (m, 5H, **H16**, **H17**, **H18**), 5.64 (ddt, *J* = 16.8, 10.1, 6.8 Hz, 1H, **H10**), 5.19 – 5.08 (m, 2H, **H14**), 4.95 – 4.83 (m, 2H, **H11**), 4.20 – 4.02 (m, 2H, **H2(eq)**, **H6**), 3.95 (br t, *J* = 10.8 Hz, 1H, **H12'**), 3.59 (dd, *J* = 13.1, 4.0 Hz, 1H, **H12''**), 2.75 (br t, *J* = 12.5 Hz, 1H, **H2(ax)**), 2.64 (t, *J* = 6.5 Hz, 4H, **H20**), 2.47 – 2.36 (m, 1H, **H7**), 2.08 – 1.97 (m, 2H, **H9**), 1.96 – 1.82 (m, 3H, **H5(eq)**, **H21**), 1.82 – 1.68 (m, 1H, **H4(eq)**), 1.67 – 1.36 (m, 4H, **H3**, **H4(ax)**, **H5(ax)**), 1.31 – 1.14 (m, 2H, **H8**) ppm.

^{13}C NMR (101 MHz, CDCl3): δ = 172.71 (**C**, **C19**), 155.48 (**C**, **C13**), 138.93 (**CH**, **C10**), 136.90 (**C**, **C15**), 128.39 (**Ar**), 127.81 (**Ar**), 114.27 (**CH_2**, **C11**), 66.97 (**CH_2**, **C14**), 52.69 (**CH**, **C6**), 40.39 (**CH_2**, **C12**), 39.87 (**CH_2**, **C2**), 33.37 (**CH**, **C7**), 32.95 (**CH_2**, **C20**), 29.67 (**CH_2**, **C9**), 27.37 (**CH_2**, **C8**), 26.65 (**CH_2**, **C5**), 25.38 (**CH_2**, **C3**), 19.04 (**CH_2**, **C4**), 17.00 (**CH_2**, **C21**) ppm.

^{1}H NMR (V_T, T = 353K)	(500 MHz, DMSO-d6): δ = 7.38 – 7.27 (m, 5H, **H16**, **H17**, **H18**), 5.68 – 5.59 (m, 1H, **H10**), 5.11 (d, *J* = 12.8 Hz, 1H, **H14'**), 5.08 (d, *J* = 12.8 Hz, 1H, **H14'**), 4.89 – 4.86 (m, 1H, **H11'**), 4.85 (t, *J* = 1.47 Hz, 1H, **H11''**), 4.03 – 3.98 (m, 1H, **H6**), 3.98 – 3.93 (m, 1H, **H2(eq)**), 3.79 (dd, *J* = 13.2, 9.1 Hz, 1H, **H12'**), 3.54 (dd, *J* = 13.2, 4.5 Hz, 1H, **H12''**), 2.73 (td, *J* = 13.3, 3.0 Hz, 1H, **H2(ax)**), 2.62 (t, *J* = 6.5 Hz, 4H, **H20**), 2.37 – 2.30 (m, 1H, **H7**), 2.03 – 1.91 (m, 2H, **H9**), 1.86 – 1.79 (m, 3H, **H5(eq)**, **H21**), 1.73 – 1.62 (m, 1H, **H4(eq)**), 1.61 – 1.51 (m, 2H, **H3(eq)**, **H4(ax)**), 1.51 – 1.42 (m, 1H, **H5(ax)**), 1.40 – 1.29 (m, 1H, **H3(ax)**), 1.25 – 1.11 (m, 2H, **H8**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d6): δ = 172.51 (**C**, **C19**), 154.42 (**C**, **C13**), 138.62 (**CH**, **C10**), 136.80 (**C**, **C15**), 127.88 (**CH**, **C17**), 127.24 (**CH**, **C18**), 126.94 (**CH**, **C16**), 113.79 (**CH_2**, **C11**), 65.77 (**CH_2**, **C14**), 52.43 (**CH**, **C6**), 39.64 (**CH_2**, **C12**), 39.20 (**CH_2**, **C2**), 33.33 (**CH**, **C7**), 32.02 (**CH_2**, **C20**), 29.10 (**CH_2**, **C9**), 27.01 (**CH_2**, **C8**), 25.86 (**CH_2**, **C5**), 24.51 (**CH_2**, **C3**), 18.29 (**CH_2**, **C4**), 16.16 (**CH_2**, **C21**) ppm.
LRMS	(ES$^+$) *m/z* 413.5 $[M+H]^+$, 435.5 $[M+Na]^+$.
HRMS	(ES$^+$) for $C_{24}H_{32}N_2NaO_4^+$ $[M+Na]^+$ calculated 435.2254 found 435.2253.

3.40: Benzyl (*S*)-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)-5-oxopentan-2-yl)piperidine-1-carboxylate



$C_{24}H_{32}N_2O_4$

414.50 g mol^{-1}

A solution of alkene **3.39** (523 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C. O_3 in O_2 was bubbled through the rapidly stirred solution for 2 h until a deep blue colour was observed. The solution was then sparged with O_2 for 15 min. Iodine paper confirmed the absence of peroxides at this time. To the solution was added triphenylphosphine (831 mg, 3.17 mmol), and stirred for 24 h at RT. A deep amber colour appeared 5 min after warming. H_2O (5 mL) was added, and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. Purification by chromatography (silica, 1:1 EtOAc/hexane) afforded the title compound as a colourless oil (323 mg, 779 µmol, 61 %).

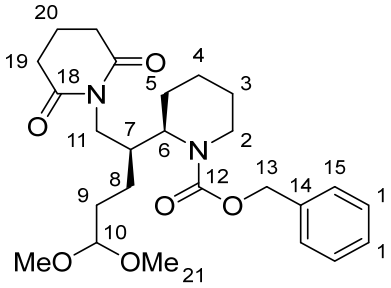
R_f 0.1 (3:7 EtOAc/hexane)

^{1}H NMR (400 MHz, CDCl3): δ = 9.76 – 9.34 (m, 1H, **H10**), 7.40 – 7.28 (m, 5H, **H15**, **H16**, **H17**), 5.30 – 4.94 (m, 2H, **H13**), 4.25 – 3.79 (m, 3H, **H2(eq)**, **H6**, **H11'**), 3.56 (dd, *J* = 13.2, 3.6 Hz, 1H, **H11''**), 2.74 (br t, *J* = 13.5 Hz, 1H, **H2(ax)**), 2.65 (br t, *J* = 6.5 Hz, 4H, **H19**), 2.57 – 2.21 (m, 2H, **H7**, **H9'**), 2.00 – 1.29 (m, 11H, **H3**, **H4**, **H5**, **H8, H9''**, **H20**) ppm.

LRMS (ES$^+$) *m/z* 415.5 $[M+H]^+$, 437.5 $[M+Na]^+$.

HRMS (ES$^+$) for $C_{23}H_{30}N_2NaO_5^+$ $[M+Na]^+$ calculated 437.2047 found 437.2054.

3.41: Benzyl (*S*)-2-((*S*)-1-(2,6-dioxopiperidin-1-yl)-5,5-dimethoxypentan-2-yl)piperidine-1-carboxylate



$C_{24}H_{32}N_2O_4$

460.57 g mol^{-1}

To a solution of aldehyde **3.40** (295 mg, 0.712 mmol) in THF/MeOH (6 mL, 2:3) was added TFA (53 µL, 712 µmol) dropwise. The solution was stirred for 60 h before quenching with $NaHCO_3$ (5 mL). The layers were separated and the aqueous extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a colourless oil (289 mg, 630 µmol, 88%).

R_f 0.65 (1:1 EtOAc/hexane)

^{1}H NMR (400 MHz, CDCl3): δ = 7.39 – 7.28 (m, 5H, **H15**, **H16**, **H17**), 5.16 (d, *J* = 12.2 Hz, 1H, **H13'**), 5.10 (d, *J* = 12.7 Hz, 1H, **H13''**), 4.16 (t, *J* = 5.6 Hz, 1H, **H10**), 4.14 – 3.89 (m, 3H, **H2(eq)**, **H6**, **H11'**), 3.57 (dd, *J* = 13.2, 4.1 Hz, 1H, **H11''**), 3.23 (s, 3H, **H21'**), 3.21 (s, 3H, **H21''**), 2.76 (br t, *J* = 13.4 Hz, 1H, **H2(ax)**), 2.66 (t, *J* = 6.5 Hz, 4H, **H19**), 2.53 – 2.42 (m, 1H, **H7**), 1.94 (quin, *J* = 6.4 Hz, 2H, **H20**), 1.85 (br d, *J* = 14.3 Hz, 1H, **H9'**), 1.80 – 1.70 (m, 1H, **H4(eq)**), 1.68 – 1.38 (m, 6H, **H3**, **H4(ax)**, **H5**, **H9''**) 1.24 – 1.15 (m, 2H, **H8**) ppm.

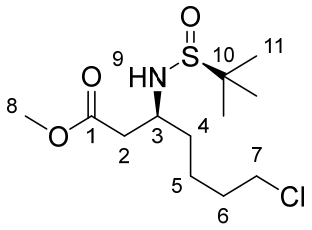
^{13}C NMR (101 MHz, CDCl3): δ = 172.84 (**C**, **C18**), 155.53 (**C**, **C12**), 128.45 (**Ar**), 127.88 (**Ar**), 104.84 (**CH**, **C10**), 67.11 (**CH_2**, **C13**), 52.90 (**C6**, **C21'**), 52.35 (**CH_3**, **C21''**), 40.31 (**CH_2**, **C11**), 39.92 (**CH_2**, **C2**), 33.06 (**CH_2**, **C19**), 33.04 (**CH**, **C7**), 28.14 (**CH_2**, **C3**), 26.75 (**CH_2**, **C9**), 25.63 (**CH_2**, **C5**), 22.34 (**CH_2**, **C8**), 19.19 (**CH_2**, **C4**), 16.99 (**CH_2**, **C20**) ppm.

LRMS (ES$^+$) *m/z* 483.6 [M+Na]$^{+\cdot}$

HRMS (ES$^+$) for $C_{25}H_{36}N_2NaO_6^+$ [M+Na]$^+$ calculated 483.2466 found 483.2474.

7.2.2 Formal synthesis of (+)-sparteine / gram scale synthesis of (–)-sparteine

(+)-5.9: (+)-Methyl (*S*)-3-(((*S*)-tert-butylsulfinyl)amino)-7-chloroheptanoate



$C_{12}H_{24}ClNO_3S$

297.84 g mol^{-1}

A solution of LDA (14.2 mL of a 1.94 M solution in THF, 27.5 mmol) and anhydrous THF (50 mL) was cooled to –78 °C. Methyl acetate (1.31 mL, 26.8 mmol) was added dropwise to the yellow coloured solution. The solution was stirred for 30 min, then a solution of $ClTi(O^iPr)_3$ (56.3 mL of a 1 M solution in hexanes, 56.3 mmol) was added dropwise. The solution was stirred at this temperature for 45 min, upon which the solution changed to a deep red colour, and a solution of imine (+)-**1.125** (3.00 g, 13.4 mmol) in anhydrous THF (20 mL) was added over 20 min. The reaction was stirred for 3 h, then quenched with $NH_4Cl_{(sat)}$ (30 mL) and warmed to RT.

The solution was poured into brine (200 mL) then diluted with EtOAc (200 mL), and the resulting cream-coloured suspension stirred for 30 min. The organic layer was decanted, and a futher portion of EtOAc (200 mL) added, and stirred for 30 min. The organic layer was again decanted, and the remaining aqueous layer extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil (integration of the NH peak in the NMR of the crude product gives d.r. 95:5 *R*:*S*). Purification by chromatography (silica, 4:6 to 6:4 $Et_2O/CHCl_3$) afforded the title compound as a yellow oil (2.67 g, 8.96 mmol, 67%).

R_f 0.03 (4:6 EtOAc:hexane)

$[\alpha]^{21}_D$ +45.0 ° (*c* = 0.97, $CHCl_3$)

FT-IR (neat) ν_{max}: 3446 (w), 3216 (w), 2952 (m), 1732 (s), 1437 (m), 1198 (m), 1049 (s) cm^{-1}.

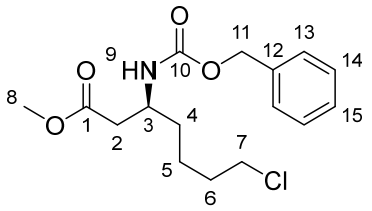
^{1}H NMR ($CHCl_3$, 400 MHz) δ = 4.12 (d, *J* = 8.6 Hz, 1H, **H9**), 3.69 (s, 3H, **H8**), 3.60 – 3.49 (m, 3H, **H3**, **H7**), 2.80 (dd, *J* = 16.1, 5.4 Hz, 1H, **H2'**), 2.62 (dd, *J* = 16.1, 5.4 Hz, 1H, **H2''**), 1.86 – 1.71 (m, 2H, **H6**), 1.68 – 1.42 (m, 4H, **H4**, **H5**), 1.22 (s, 9H, **H11**) ppm.

^{13}C NMR ($CHCl_3$, 101 MHz) δ = 172.32 (**C**, **C1**), 55.93 (**C**, **C10**), 53.67 (**CH**, **C3**), 51.70 (**CH_3**, **C8**), 44.72 (**CH_2**, **C7**), 40.24 (**CH_2**, **C2**), 34.70 (**CH_2**, **C4**), 32.01 (**CH_2**, **C6**), 23.27 (**CH_2**, **C5**), 22.66 (**CH_3**, **C11**) ppm.

LRMS (ES^+) *m/z* = 298.4 $[M^{35}Cl+H]^+$, 300.4 $[M^{37}Cl+H]^+$

HRMS (ES^+) for $C_{12}H_{25}ClNO_3S^+$, calculated 298.1238 found 298.1239.

(–)-5.11: (–)-Methyl (*S*)-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate



$C_{16}H_{22}ClNO_4$

327.81 g mol^{-1}

To solution of sulfinylamine **5.9** (1.00 g, 3.36 mmol) in anhydrous MeOH (10 mL) was added HCl (3.36 mL of a 4 M solution in 1,4-dioxane, 13.4 mmol). The yellow solution was stirred for 3.5 h, then concentrated *in vacuo*. The oily yellow residue was dissolved in CH_2Cl_2 (5 mL) and concentrated *in vacuo*. This was repeated two more times.

The residue was then dissolved in THF/H_2O (10 mL, 1:1), and K_2CO_3 (697 mg, 5.04 mmol) and CBz-Cl (0.72 mL, 5.04 mmol) were added. The yellow suspension was stirred for 1 h. The phases were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 0:1 to 1:1 Et_2O/hexane) afforded the title compound as a colourless oil (984 mg, 3.00 mmol, 89%).

R_f 0.61 (4:6 EtOAc:hexane)

$[\alpha]^{21}_D$ –16.9 ° (*c* = 1.03, $CHCl_3$)

FT-IR (neat) ν_{max}: 3333 (br), 2950 (w), 1718 (s), 1696 (s), 1521 (m), 1437 (m), 1235 (br), 1063 (m) cm^{-1}.

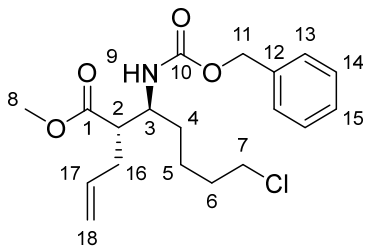
^{1}H NMR ($CHCl_3$, 400 MHz) δ = 7.42 – 7.27 (m, 5H, **H13**, **H14**, **H15**), 5.23 (d, *J* = 9.1 Hz, 1H, **H9**), 5.10 (s, 2H, **H11**), 4.05 – 3.93 (m, 1H, **H3**), 3.68 (s, 3H, **H8**), 3.52 (t, *J* = 6.4 Hz, 2H, **H7**), 2.64 – 2.48 (m, 2H, **H2**), 1.87 – 1.60 (m, 2H, **H6**), 1.65 – 1.42 (m, 4H, **H4**, **H5**) ppm.

^{13}C NMR ($CHCl_3$, 101 MHz) δ = 171.89 (**C**, **C1**), 155.80 (**C**, **C10**), 136.48 (**C**, **C12**), 128.50 (**CH**, **C14**), 128.10 (**CH**, **C15**), 128.05 (**CH**, **C13**), 66.67 (**CH_2**, **C11**), 51.70 (**CH_3**, **C8**), 47.86 (**CH**, **C3**), 44.68 (**CH_2**, **C7**), 38.76 (**CH_2**, **C2**), 33.61 (**CH_2**, **C4**), 32.06 (**CH_2**, **C6**), 23.40 (**CH_2**, **C5**) ppm.

LRMS (ES^+) *m/z* = 328.4 $[M^{35}Cl+H]^+$, 330.3 $[M^{37}Cl+H]^+$

HRMS (ES^+) for $C_{16}H_{22}ClNNaO_4^+$, calculated 350.1130 found 350.1135.

(–)-5.8: (–)-Methyl (2*S*,3*S*)-2-allyl-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate



$C_{19}H_{26}ClNO_4$

367.87 g mol^{-1}

A solution of LDA (2.06 mL of a 1.94 M solution, 4.00 mmol) was cooled to –50 °C. A solution of carbamate **5.11** (328 mg, 1.00 mmol) in anhydrous THF (5 mL) was added dropwise, and the resulting orange solution was stirred for 45 min. Allyl iodide (0.23 mL. 2.50 mmol) was added dropwise at this temperature, and the resulting yellow solution stirred for 4 h. The reaction was then quenched at –50°C with sat. $NH_4Cl_{(aq)}$ (5 mL) and warmed to RT. The layers were separated and the aqueous extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil (integration of the NH peak in the NMR of the crude product gives d.r. 9:1 *anti*:*syn*). Purification by chromatography (silica, 1:19 to 1:5 EtOAc/hexane) afforded the title compound as a yellow oil (233 mg, 0.63 mmol, 63%).

R_f 0.76 (4:6 EtOAc:hexane)

$[\alpha]^{21}_D$ –24.2 ° (*c* = 0.75, $CHCl_3$)

FT-IR (neat) ν_{max}: 3336 (br), 2951 (w), 1721 (s), 1642 (w), 1508 (m), 1227 (s) cm^{-1}.

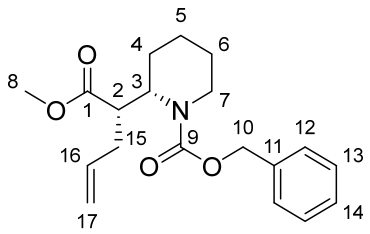
^{1}H NMR ($CHCl_3$, 400 MHz) δ = 7.40 – 7.29 (m, 5H, **H13**, **H14**, **H15**), 5.75 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, **H17**), 5.55 (d, *J* = 9.9 Hz, 1H, **H9**), 5.21 – 4.98 (m, 4H, **H11**, **H18**), 3.92 – 3.84 (m, 1H, **H3**), 3.68 (s, 3H, **H8**), 3.56 – 3.40 (m, 2H, **H7**), 2.65 (ddd, *J* = 8.1, 6.9, 3.8 Hz, 1H, **H2**), 2.46 – 2.37 (m, 1H, **H16'**), 2.37 – 2.27 (m, 1H, **H16''**), 1.87 – 1.67 (m, 2H, **H6**), 1.56 – 1.39 (m, 4H, **H4**, **H5**) ppm.

^{13}C NMR ($CHCl_3$, 101 MHz) δ = 174.75 (**C**, **C1**), 156.35 (**C**, **C10**), 136.64 (**C**, **C12**), 134.48 (**CH**, **C17**), 128.48 (**CH**, **C14**), 128.06 (**CH**, **C15**), 127.99 (**CH**, **C13**), 117.55 (**CH_2**, **C18**), 66.66 (**CH_2**, **C11**), 51.64 (**CH_3**, **C8**), 51.33 (**CH**, **C3**), 48.45 (**CH**, **C2**), 44.68 (**CH_2**, **C7**), 34.21 (**CH_2**, **C16**), 33.86 (**CH_2**, **C4**), 32.16 (**CH_2**, **C6**), 23.39 (**CH_2**, **C5**) ppm.

LRMS (ES$^+$) *m/z* = 368.4 [M^{35}Cl+H]$^+$, 370.4 [M^{37}Cl+H]$^+$

HRMS (ES$^+$) for $C_{19}H_{26}ClNNaO_4^+$, calculated 390.1443 found 390.1443.

(–)-5.7: (–)-Benzyl (*S*)-2-((*S*)-1-methoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate



$C_{19}H_{25}NO_4$

331.41 g mol^{-1}

To a solution of chloride **5.8** (110 mg, 0.30 mmol) in anhydrous MeCN (2 mL) was added KO*t*Bu (51 mg, 0.45 mmol) and TBAI (22 mg, 68 µmol). The suspension was stirred for 24 h and then concentrated *in vacuo* to yield a yellow residue. Purification by chromatography (silica, 1:9 EtOAc/hexane) afforded the title compound as a colourless oil (32 mg, 100 µmol, 32%).

R_f 0.14 (EtOAc/hexane 1:9)

$[\alpha]^{21}_D$ –35.2 ° (*c* = 0.25, $CHCl_3$)

FT-IR (neat) ν_{max}: 3487 (w, br), 2947 (w), 1734 (s), 1693 (s), 1421 (s), 1251 (m), 1168 (m), 1026 (m) cm^{-1}.

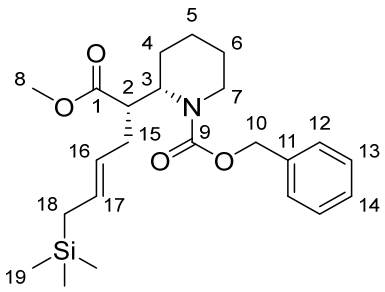
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.40 – 7.27 (m, 5H, **H12**, **H13**, **H14**), 5.80 – 5.67 (m, 1H, **H16**), 5.11 – 4.96 (m, 4H, **H10**, **H17**), 4.32 (dd, *J* = 11.0, 3.4 Hz, 1H, **H3(ax)**), 3.90 (dd, *J* = 13.6, 3.2 Hz, 1H, **H7(eq)**), 3.41 (s, 3H, **H8**), 3.06 (td, *J* = 10.3, 4.4 Hz, 1H, **H2**), 2.95 (t, *J* = 11.9 Hz, 1H, **H7(ax)**), 2.29 – 2.14 (m, 2H, **H15**), 1.78 (d, *J* = 13.8 Hz, 1H, **H4 (eq)**), 1.63 – 1.38 (m, 4H, **H4(ax)**, **H5**, **H6(eq)**), 1.36 – 1.20 (m, 1H, **H6(ax)**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz) δ = 173.02 (**C**, **C1**), 154.16 (**C**, **C9**), 136.99 (**C**, **C11**), 135.20 (**CH**, **C16**), 128.31 (**CH**, **C13**), 127.69 (**CH**, **C14**), 127.35 (**CH**, **C12**), 116.96 (**CH_2**, **C17**), 66.14 (**CH_2**, **C10**), 52.63 (**CH**, **C3**), 51.07 (**CH_3**, **C8**), 44.08 (**CH**, **C2**), 39.09 (**CH_2**, **C7**), 33.21 (**CH_2**, **C15**), 25.36 (**CH_2**, **C4**), 24.85 (**CH_2**, **C6**), 18.20 (**CH_2**, **C5**) ppm.

^{1}H NMR (V_T, T = 353K) (500 MHz, DMSO-d_6): δ = 7.39 – 7.28 (m, 5H, **H12**, **H13**, **H14**), 5.76 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H, **H16**), 5.08 (d, *J* = 12.7 Hz, 1H, **H10'**), 5.07 (dq, 17.2, 1.5 Hz, 1H, **H17'**), 5.02 (d, *J* = 12.7 Hz, 1H, **H10''**), 5.01 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, **H17''**), 4.35 (ddd, *J* = 10.8, 5.0, 2.0 Hz, 1H, **H3(ax)**), 3.96 – 3.90 (m, 1H, **H7(eq)**), 3.45 (s, 3H, **H8**), 3.07 – 3.01 (m, 1H, **H2**), 2.97 (td, *J* = 13.4, 3.0 Hz, 1H, **H7(ax)**), 2.28 – 2.23 (m, 2H,

	H15), 1.82 – 1.76 (m, 1H, **H4(eq)**), 1.63 – 1.44 (m, 4H, **H4(ax)**, **H5**, **H6(eq)**), 1.39 – 1.26 (m, 1H, **H6(ax)**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d_6): δ =. 172.49 (**C**, **C1**), 153.95 (**C**, **C9**), 136.70 (**C**, **C11**), 134.82 (**CH**, **C16**), 127.83 (**CH**, **C13**), 127.20 (**CH**, **C14**), 126.91 (**CH**, **C12**), 116.27 (**CH_2**, **C17**), 65.82 (**CH_2**, **C10**), 52.40 (**CH**, **C3**), 50.49 (**CH_3**, **C8**), 44.12 (**CH**, **C2**), 38.95 (**CH_2, C7**), 32.73 (**CH_2**, **C15**), 25.04 (**CH_2**, **C4**), 24.33 (**CH_2**, **C6**), 17.90 (**CH_2**, **C5**) ppm.
LRMS	(ES^+) *m/z* = 332.3 $[M+H]^+$, 354.3 $[M+Na]^+$

(–)-5.13: (–)-Benzyl (*S*)-2-((*S*,*E*)-1-methoxy-1-oxo-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate



$C_{23}H_{35}NO_4Si$

417.62 g mol^{-1}

To a solution of alkene **5.7** (79 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (2 mL) was added allyltrimethylsilane (0.11 mL, 0.72 mmol) and benzoquinone (2 mg, 18 µmol), followed by Hoveyda-Grubbs II (8 mg, 13 µmol). The reaction was stirred at RT for 24 h, turning from yellow to light green. The reaction mixture was filtered through a plug of Celite®, and the filter cake washed with Et_2O (5 x 5 mL). The filtrate was concentrated *in vacuo* to afford the crude product as a green oil admixed with green solid. Purification by chromatography (silica, EtOAc/hexane 1:9) afforded the title compound as a colourless oil (21 mg, 50 µmol, 21%, ≈2:1 *E*/*Z*)

R_f 0.37 (EtOAc/hexane 1:4)

$[\alpha]^{21}_D$ –29.9 ° (*c* = 0.25, $CHCl_3$)

FT-IR (neat) ν_{max}: 2950 (m), 2161 (w), 1738 (s), 1699 (s), 1422 (m), 1248 (m), 1169 (m) cm^{-1}.

^{1}H NMR ($CHCl_3$, 400 MHz) δ = 7.44 – 7.26 (m, 5H, **H12**, **H13**, **H14**), 5.53 – 5.42 (m, 1H, **H17**), 5.25 – 5.03 (m, 3H, **H16**, **H10**), 4.57 – 4.37 (m, 1H, **H3(ax)**, 4.19 – 3.99 (m, 1H, **H7(eq)**), 3.49 (s, 3H, **H8**), 3.11 – 2.88 (m, 2H, **H2**, **H7(ax)**), 2.46 – 2.23 (m, 1H, **H15'**), 2.21 – 2.08 (m, 1H, **H15''**), 1.85 – 1.72 (m, 1H, **H4(eq)**), 1.69 – 1.33 (m, 7H, **H4(ax)**, **H5**, **H6**, **H18**), 0.01 (s, 3H, **Me$_3$Si** (*Z*)), −0.02 (s, 6H, **Me$_3$Si** (*E*)) ppm.

^{13}C NMR ($CHCl_3$, 101 MHz) δ = 173.72 (**C**, **C1**), 155.07 (**C**, **C9**), 136.99 (**C**, **C11**), 129.36 (**ArCH**), 128.37 (**CH**, **C17**), 128.18 (**ArCH**), 127.83 (**ArCH**), 124.25 (**CH**, **C16**), 67.00 (**CH$_2$**, **C10**), 52.95 (**CH**, **C3**), 51.33 (**CH$_3$**, **C8**), 45.70 (**CH**, **C2**), 39.64 (**CH$_2$**, **C7**), 32.92 (**CH$_2$**, **C15**), 25.94 (**CH$_2$**, **C4**), 25.51 (**CH$_2$**, **C6**), 18.88 (**CH$_2$**, **C5**), −1.80 (**CH$_3$**, **C19** (*Z*)), −2.08 (**CH$_3$**, **C19** (*E*)) ppm.

^{1}H NMR (V_T, T = 353K) (DMSO-d_6, 500 MHz) (***E* isomer**) δ = 7.39 – 7.32 (m, 4H, **H12**, **H13**), 7.32 – 7.28 (m, 1H, **H14**), 5.45 (dtt, *J* = 15.2, 7.9, 1.7 Hz, 1H, **H17**), 5.19 (dtt, *J* = 15.2, 6.8, 1.3 Hz, 1H, **H16**), 5.08 (d, *J* = 13.1 Hz, 1H,

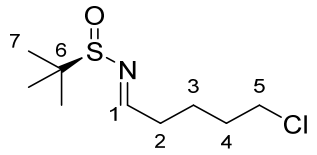
H10'), 5.01 (d, *J* = 13.1 Hz, 1H, **H10''**), 4.33 (ddd, *J* = 11.3, 5.5, 2.5 Hz, 1H, **H3(ax)**), 3.92 (dt, *J* = 13.9, 3.9 Hz, 1H, **H7(eq)**), 3.44 (s, 3H, **H8**), 3.00 – 2.92 (m, 2H, **H2**, **H7(ax)**), 2.33 – 2.13 (m, 2H, **H15**), 1.83 – 1.74 (m, 1H, **H4(eq)**), 1.63 – 1.25 (m, 7H, **H4(ax)**, **H5**, **H6**, **H18**), −0.03 (s, 9H, **H19**) ppm.

^{13}C NMR (V_T, T = 353K) (DMSO-d_6, 126 MHz) (***E* isomer**) δ = 172.62 (**C**, **C1**), 153.93 (**C**, **C9**), 136.73 (**C**, **C11**), 128.15 (**CH**, **C17**), 127.82 (**CH**, **C13**), 127.19 (**CH**, **C14**), 126.90 (**CH**, **C12**), 124.15 (**CH**, **C6**), 65.79 (**CH_2**, **C10**), 52.33 (**CH**, **C3**), 50.41 (**CH_3**, **C8**), 44.85 (**CH**, **C2**), 38.95 (**CH_2**, **C7**), 31.82 (**CH_2**, **C15**), 25.07 (**CH_2**, **C4**), 24.36 (**CH_2**, **C6**), 21.80 (**CH_2**, **C18**), 17.94 (**CH_2**, **C5**), −2.49 (**CH_3**, **Me_3Si**) ppm.

LRMS (ES^+) *m/z* = 418.4 $[M+H]^+$, 440.4 $[M+Na]^+$

HRMS (ES^+) for $C_{23}H_{35}NNaO_4Si^+$, calculated 440.2228 found 440.2234.

(–)-1.125: (–)-(*R,E*)-*N*-(5-Chloropentylidene)-2-methylpropane-2-sulfinamide



$C_9H_{18}ClNOS$

223.76 g mol^{-1}

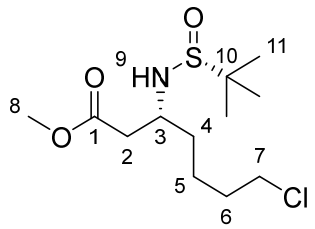
Methyl 5-chloropentanoate (2.00 g, 13.3 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL). The colourless solution was cooled to –78 °C, then DIBAL-H (14.6 mL, 1.0 M in CH_2Cl_2, 14.6 mmol) was added dropwise. The mixture was stirred at this temperature for 2 h, then quenched by the dropwise addition of sat. Rochelle's salt (20 mL). The emulsion was stirred for 2 h, until both phases became clear. The solution was filtered through Celite®, separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and used without further purification.

To this solution was added **(+)-2.25** (1.80 g, 14.6 mmol) and $Ti(OEt)_4$ (5.60 mL, 26.6 mmol). The reaction was stirred at RT for 12 h, then quenched by the addition of brine (100 mL). The yellow suspension was vigorously stirred for 5 min, then filtered. The filter cake was washed with CH_2Cl_2 (3 x 30 mL). The layers were separated, and the organic phase washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 1:4 EtOAc / hexane) afforded the title compound as a pale yellow oil (2.60 g, 11.7 mmol, 89%).

$[\alpha]^{20}_D$ –226.2 (*c*. 0.71, $CHCl_3$)

Physical and spectroscopic data are consistent with the enantiomer **(+)-1.125**.

(–)-5.9-: (–)-Methyl (*R*)-3-(((*R*)-tert-butylsulfinyl)amino)-7-chloroheptanoate



$C_{12}H_{24}ClNO_3S$

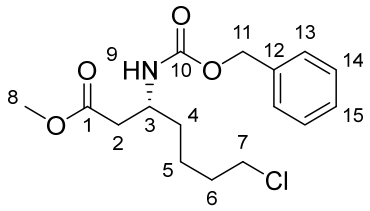
297.84 g mol^{-1}

A solution of LDA (28.6 mL, 1.92 M in THF, 54.9 mmol) and anhydrous THF (100 mL) was cooled to –78 °C. Methyl acetate (2.60 mL, 53.6 mmol) was added dropwise. The solution was stirred for 30 min at this temperature, then a solution of $TiCl(O^iPr)_3$ (113 mL, 1.0 M in hexanes, 113 mmol) was added dropwise. The solution was stirred for 45 min, during which time it turned a blood-red colour. A solution of imine **(–)-1.125** (6.00 g, 26.8 mmol) in anhydrous THF (40 mL) was added dropwise at this temperature. The reaction was stirred for 1 h and quenched at –78 °C by dropwise addition of sat. $NH_4Cl_{(aq)}$ (60 mL), and warmed to RT. The solution was diluted with EtOAc (100 mL) and brine (200 mL), and the resulting cream-coloured solution filtered through Celite®, and the filter cake washed with EtOAc (3 x 50 mL). The layers were separated, and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, 15:85 EtOAc / CH_2Cl_2) afforded the title compound as a yellow oil (6.78 g, 22.8 mmol, 85%). Integration of the OMe peaks in the crude ^{1}H NMR gave a *d.r.* of 22:1 (*R*,*R*:*S*,*R*).

$[\alpha]^{21}_D$ –41.5° (*c* = 0.71, $CHCl_3$)

Physical and spectroscopic data are consistent with the enantiomer **(+)-5.9**.

(+)-5.11: (+)-Methyl (*R*)-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate



$C_{16}H_{22}ClNO_4$

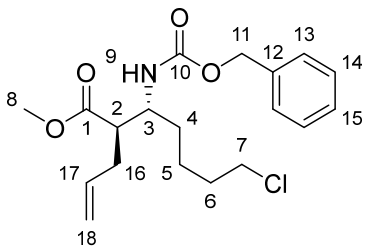
327.81 g mol^{-1}

A solution of sulfinylamine **(–)-5.9** (10.0 g, 33.6 mmol) in 1,4-dioxane (50 mL) was cooled to 0 °C. *Conc.* HCl (8.65 mL, 101 mmol) was added dropwise. The solution was stirred at this temperature for 1 h, then warmed to RT and concentrated *in vacuo*. The oily yellow residue was dissolved in CH_2Cl_2 (20 mL) and concentrated *in vacuo*. This was repeated 3 times. The residue was redissolved in THF (50 mL), and K_2CO_3 (6.90 g, 50.5 mmol) and Cbz-Cl (7.20 mL, 50.4 mmol) added. The reaction was stirred for 1 h, before the addition of H_2O (20 mL). The phases were separated, and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 15:85 Et_2O / hexane) afforded the title compound as a pale yellow oil (9.45 g, 28.8 mmol, 86%).

$[\alpha]^{21}_D$ +16.6 ° (*c* = 1.5, $CHCl_3$)

Physical and spectroscopic data are consistent with the enantiomer **(–)-5.11**.

(+)-5.8: (+)-Methyl (2*R*,3*R*)-2-allyl-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate



$C_{19}H_{26}ClNO_4$

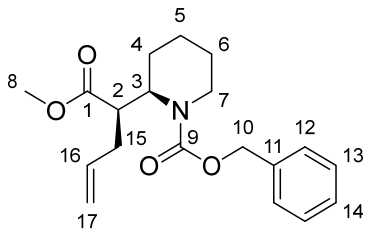
367.87 g mol^{-1}

A solution of LDA (15.2 mL. 2.0 M in THF, 30.4 mmol) was cooled to –78 °C. A solution of ester **(+)-5.11** (3.30 g, 10.1 mmol) in anhydrous THF (20 mL) was added dropwise, and the yellow-orange solution stirred at this temperature for 1 h. Allyl iodide (2.30 mL, 25.3 mmol) was added dropwise, and the solution stirred a further 4 h at this temperature. The reaction was quenched by addition of sat. $NH_4Cl_{(aq)}$ (20 mL) and warmed to RT. The phases were separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil (Integration of the NH peaks in the crude ^{1}H NMR gives *syn*/*anti* >10:1). Purification by chromatography (silica, 15:85 EtOAc / hexane) gave the title compound as a yellow oil (2.90 g, 7.90 mmol, 78%).

$[\alpha]^{21}_D$ +24.1 ° (*c* = 1.6, $CHCl_3$)

Physical and spectroscopic data are consistent with the enantiomer **(–)-5.8***.*

(+)-5.7: (+)-Benzyl (*R*)-2-((*R*)-1-methoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate



$C_{19}H_{25}NO_4$

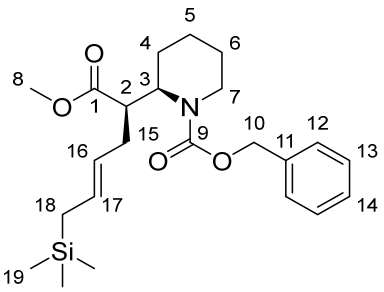
331.41 g mol^{-1}

To a solution of carbamate **(+)-5.8** (1.00 g, 2.72 mmol) in anhydrous MeCN (5 mL) was added Cs_2CO_3 (3.54 g, 10.9 mmol) and NaI (410 mg, 2.72 mmol). The resulting yellow suspension was refluxed at 105 °C for 48 h. The reaction was cooled to RT and the suspension filtered, with the residues washed with MeCN (3 x 10 mL). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, 5:95 EtOAc / hexane) afforded the title compound as a yellow oil (900 mg, 2.71 mmol, 99%).

$[\alpha]^{21}_D$ +53.3 ° (*c* = 1.3, $CHCl_3$)

Physical and spectroscopic data are consistent with the enantiomer **(–)-5.7**.

(+)-5.13: (+)-Benzyl (*R*)-2-((*R*,E)-1-methoxy-1-oxo-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate



$C_{23}H_{35}NO_4Si$

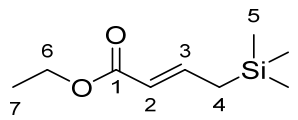
417.62 g mol^{-1}

A solution of alkene **(+)-5.7** (331 mg, 1.00 mmol), allyltrimethylsilane (0.79 mL, 5.00 mmol), 1,4-benzoquinone (11 mg, 10 mol%) and Hoveyda-Grubbs II (30 mg, 5 mol was heated to 60 °C for 50 min, before a further portion of catalyst (15 mg, 2.5 mol%) was added. The solution was heated for a further 20 min, then cooled to RT. The reaction was quenched by the addition of EtOAc / H_2O (20 mL, 1:1). The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 2:8 EtOAc / hexane) afforded the title compound as a colourless oil (260 mg, 620 µmol, 62%, ≈2:1 *E*/*Z*).

$[\alpha]^{21}_D$ 31.3 ° (*c* = 0.25, $CHCl_3$)

Physical and spectroscopic data are consistent with the enantiomer **(–)-5.13**.

5.15: Ethyl (*E*)-4-(trimethylsilyl)but-2-enonate



$C_8H_{16}O_2Si$

186.33 g mol^{-1}

Adapting the procedure of Cossy[289], to a solution of ethyl acrylate (12.2 mL, 120 mmol) in anhydrous CH_2Cl_2 (120 mL) was added allyltrimethylsilane (9.54 mL, 60.0 mmol), followed by Grubbs II (235 mg, 300 μmol). The resulting dark brown solution was heated to reflux and stirred for 21 h. The solution was concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, 1:99 to 1:9 Et_2O/pet. ether) afforded the title compound as a colourless oil (10.1 g, 54.4 mmol, 49:1 E/Z, 91%).

R_f 0.89 (4:6 EtOAc:hexane)

FT-IR (neat) ν_{max}: 2956 (w), 1713 (s), 1639 (m), 1314 (m), 1249 (m), 1124 (s), 1047 (m) cm^{-1}.

^{1}H NMR ($CHCl_3$, 400 MHz) δ = 7.04 (dt, *J* = 15.4, 8.9 Hz, 1H, **H3**), 5.66 (dt, *J* = 15.4, 1.3 Hz, 1H, **H2**), 4.17 (q, *J* = 7.2 Hz, 2H, **H6**), 1.73 (dd, *J* = 8.9, 1.3 Hz, 2H, **H4**), 1.28 (t, *J* = 7.2 Hz, 3H, **H7**), 0.06 (s, 9H, **H5**) ppm.

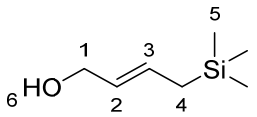
^{13}C NMR ($CHCl_3$, 101 MHz) δ = 166.87 (**C**, **C1**), 147.82 (**CH**, **C3**), 119.05 (**CH**, **C2**), 59.83 (**CH_2**, **C6**), 24.83 (**CH_2**, **C4**), 14.30 (**CH_3**, **C7**), −1.86 (**CH_3**, **C5**) ppm.

LRMS (ES$^+$) *m/z* = 187.2 [M+H]$^+$.

HRMS (ES$^+$) for $C_9H_{18}NaO_2Si^+$, calculated 209.0968 found 209.0957.

Physical and spectroscopic data are consistent with reported values.[289]

5.16: (*E*)-4-(Trimethylsilyl)but-2-en-1-ol



$C_7H_{16}OSi$

144.29 g mol^{-1}

Adapting the procedure of Kočovský,[290] a solution of ester **5.15** (8.00 g, 42.9 mmol) in anhydrous CH_2Cl_2 (110 mL) was cooled to 0 °C. DIBAL-H (98.7 mL of a 1 M solution in CH_2Cl_2, 98.7 mL) was added dropwise over 30 min. The solution was stirred for 2 h, over which time it was warmed to RT. The reaction was cooled back to 0 °C and quenched by the addition of sat. Rochelle's salt (110 mL), warmed to RT and stirred for a further 2 h. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a colourless oil. Purification by chromatography (silica, 3:7 to 4:6 Et_2O/pet. ether.) afforded the title compound as a colourless oil (5.50 g, 38.1 mmol, 89%).

R_f 0.21 (2:8 EtOAc / hexane)

FT-IR (neat) ν_{max}: 3323 (br), 2954 (w), 1660 (w), 1247 (m) cm^{-1}.

^{1}H NMR ($CHCl_3$, 400 MHz) δ = 5.7 (dtt, *J* = 15.3, 8.4, 1.2 Hz, 1H, **H3**), 5.51 (dtt, *J* = 15.3, 6.3, 1.2 Hz, 1H, **H2**), 4.07 (t, *J* = 5.2 Hz, 2H, **H1**), 1.50 (d, *J* = 8.4 Hz, 2H, **H4**), 1.18 (t, *J* = 5.2 Hz, 1H, **H6**), 0.01 (s, 9H, **H5**) ppm.

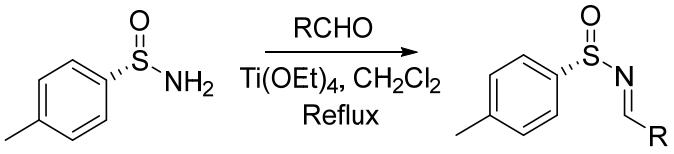
^{13}C NMR ($CHCl_3$, 101 MHz) δ = 130.56 (**CH**, **C3**), 127.45 (**CH**, **C2**), 64.17 (**CH_2**, **C1**), 22.77 (**CH_2**, **C4**), −2.01 (**CH_3**, **Me_3Si**) ppm.

LRMS (EI) *m/z* = 126.2 (3%) $[M\text{-}H_2O]^{\cdot+}$, 111.2 (21%) $[M\text{-}MeOH]^{\cdot+}$, 75.1 (72%), 73.1 (58%) $(TMS)^{\cdot+}$

Physical and spectroscopic data are consistent with reported values.[290]

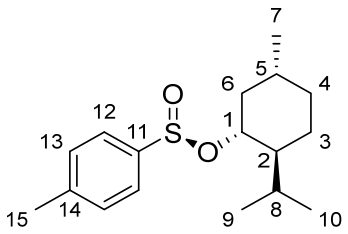
7.2.3 Imino-Aldol Methodology

7.2.3.1 General method for the synthesis of *N*-sulfinyl imines



To a stirred solution of (+)-**2.24** (1 eq) in anhydrous CH_2Cl_2 (0.2 M) was added $Ti(OEt)_4$ (4 eq), followed by aldehyde (1.1 eq). The clear yellow solution was heated to 40 °C for 4 h. The solution was allowed to cool to RT, and then poured into brine (100 mL), and stirred for 30 min, precipitating a yellow solid. The mixture was filtered, and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude *N*-sulfinyl imine. Purification by chromatography (silica, EtOAc:pet. ether) or recrystallisation (pet. ether:CH_2Cl_2 19:1) afforded the pure product.

4.31: (–)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*R*)-4-methylbenzenesulfinate



$C_{17}H_{26}O_2S$

294.45 g mol^{-1}

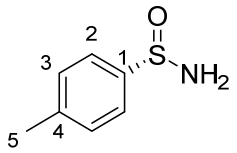
Adapting the procedure of Posner,[13] $SOCl_2$ (103 mL, 1.42 mol) was cooled to 0 °C. *p*-Toluenesulfinic acid sodium salt (100 g, 515 mmol) was added portionwise over 45 min, over which time the suspension turned yellow. Upon complete addition, the solution was stirred for 3 h. Anhydrous CH_2Cl_2 (100 mL) was added, and the solution concentrated *in vacuo* to remove excess $SOCl_2$. This was repeated three times, to leave a yellow oil. Separately, a solution of (–)-menthol (96.6 g, 618 mmol), pyridine (83.0 mL, 1.03 mol) in anhydrous CH_2Cl_2 (300 mL) was cooled to 0 °C. This solution was added *via* cannula to the freshly prepared acid chloride, which was warmed to RT and stirred for 16 h.

The reaction was quenched by the addition of H_2O (300 mL) and stirred for 15 min. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil admixed with white solid. Purification by recrystallisation (acetone) afforded over 2 crops the title compound as long white needles (30.8 g, 105 mmol, 20%).

MP	104.6 – 105.7 °C
FT-IR	(neat) ν_{max}: 3058 (w), 2917 (w), 1603 (m), 1571 (m), 1097 (s), 1069 (s) cm^{-1}.
$[\alpha]_D$	–197.2 ° (*c* = 1.03, Acetone)
^{1}H NMR	($CDCl_3$, 400 MHz) δ = 7.61 (d, *J* = 8.3 Hz, 2H, **H12**), 7.32 (d, *J* = 8.1 Hz, 2H, **H13**), 4.13 (td, *J* = 10.7 Hz, 4.5 Hz, 1H, **H1**), 2.42 (s, 3H, **H15**), 2.33 – 2.44 (m, 1H, **H6(eq)**), 2.14 (sptd, *J* = 7.2, 2.6 Hz, 1H, **H8**), 1.75 – 1.64 (m, 2H, **H3(eq)**, **H4(eq)**), 1.57 – 1.43 (m, 1H, **H5(ax)**), 1.41 – 1.31 (m, 1H, **H2(ax)**), 1.23 (q, *J* = 12.4 Hz, 1H, **H6(ax)**), 1.14 – 0.99 (m, 1H, **H4(ax)**), 0.97 (d, *J* = 6.6 Hz, 3H, **H7**), 0.95 – 0.79 (m, 4H, **H3(ax)**, **H10**), 0.73 (d, *J* = 6.9 Hz, 3H, **H9**) ppm.
^{13}C NMR	($CDCl_3$, 101 MHz) δ = 143.20 (**C**, **C11**), 142.37 (**C**, **C14**), 129.58 (**CH**, **C13**), 124.96 (**CH**, **C12**), 80.06 (**CH**, **C1**), 47.84 (**CH**, **C2**), 42.93 (**CH_2**, **C6**), 34.00 (**CH_2**, **C3**), 31.71 (**CH**, **C5**), 25.20 (**CH**, **C8**), 23.14 (**CH_2**, **C4**), 22.05 (**CH_3**, **C7**), 21.47 (**CH_3**, **C15**), 20.83 (**CH_3**, **C10**), 15.45 (**CH_3**, **C9**) ppm.
LRMS	(ES^+) *m/z* = 295.4 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[291]

2.24: (+)-(*S*)-4-Methylbenzenesulfinamide



C_7H_9NOS

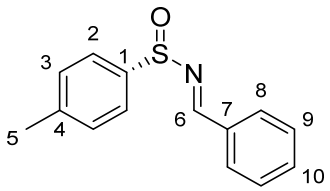
155.22 g mol^{-1}

A solution of sulfinate **4.31** (20.0 g, 67.9 mmol) in anhydrous THF (150 mL) under N_2 was cooled to ─78 °C. LiHMDS (1 M in THF, 88.5 mL, 88.5 mmol) was added dropwise over 20 min at this temperature. The reaction was warmed to RT and stirred for 1 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (150 mL) and stirred for a further 30 min. The phases were separated and the aqueous layer extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a light brown solid. Purification by recrystallisation (hexane:EtOAc 10:1) afforded the title compound as long pale brown needles (9.02 g, 58.1 mmol, 86%).

R_f	0.09 (EtOAc:hexane 4:6)
MP	113.0 – 113.6 °C
FT-IR	(neat) ν_{max}: 3191 (m), 3095 (m), 1572 (m), 1087 (m), 1020 (s) cm^{-1}.
$[\alpha]^{23}_D$	+81.0 ° (*c*. 1.01 $CHCl_3$)
^{1}H NMR	($CDCl_3$, 500 MHz) δ = 7.64 – 7.60 (m, 2H, **H2**), 7.33 – 7.28 (m, 2H, **H3**), 4.37 (br s, 2H, N**H_2**), 2.42 (s, 3H, **H5**) ppm.
^{13}C NMR	($CDCl_3$, 126 MHz) δ = 143.43 (**C**, **C1**), 141.48 (**C**, **C4**), 129.59 (**CH**, **C3**), 125.37 (**CH**, **C2**), 21.35 (**CH_3**, **C5**) ppm.
LRMS	(ES^+) *m/z* 156.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[292]

4.25a: (+)-(*S*,*E*)-*N*-Benzylidene-4-methylbenzenesulfinamide



$C_{14}H_{13}NOS$

243.32 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (2.12 g, 8.69 mmol, 90%) as a pale yellow solid.

R_f 0.53 (40:60 EtOAc/hexane)

MP 84.0 – 85.0 °C

FT-IR (neat) ν_{max}: 3059 (w), 1603 (s), 1574 (m), 1495 (m), 1097 (s), 1069 (s) cm^{-1}.

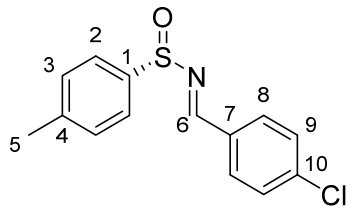
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.77 (s, 1H, **H6**), 7.90 – 7.82 (m, 2H, **H8**), 7.65 (d, *J* = 8.2 Hz, 2H, **H2**), 7.54 – 7.43 (m, 3H, **H9**, **H10**), 7.32 (d, *J* = 8.1 Hz, 2H, **H3**), 2.41 (s, 3H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 160.64 (**CH**, **C6**), 141.78 (**C**, **C1**), 141.72 (**C**, **C4**), 133.89 (**C**, **C7**), 132.57 (**CH**, **C10**), 129.83 (**CH**, **C3**), 129.58 (**CH**, **C8**), 128.88 (**CH**, **C9**), 124.79 (**CH**, **C2**), 21.40 (**CH_3**, **C5**) ppm.

LRMS (ES^+) *m/z* 244.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[293]

4.25b: (+)-(*S*,*E*)-*N*-(4-Chlorobenzylidene)-4-methylbenzenesulfinamide



$C_{14}H_{12}ClNOS$

277.77 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (1.67 g, 6.01 mmol, 93%) as a white powdery solid.

R_f 0.53 (40:60 EtOAc/hexane)

MP 119.2 – 120.6 °C

FT-IR (neat) ν_{max}: 3053 (w), 2921 (w), 1910 (w), 1608 (s), 1592 (s), 1486 (m), 1405 (m), 1103 (s) cm^{-1}.

$[\alpha]^{23}_D$ +56 ° (*c*. 1.2, $CHCl_3$)

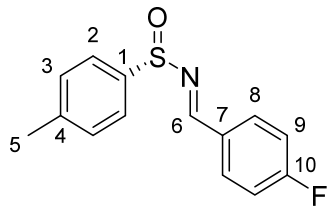
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.72 (s, 1H, **H6**), 7.79 (d, *J* = 8.5 Hz, 2H, **H8**), 7.63 (d, *J* = 8.1 Hz, 2H, **H2**), 7.43 (d, *J* = 8.5 Hz, 2H, **H9**), 7.32 (d, *J* = 8.1 Hz, 2H, **H3**), 2.41 (s, 3H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 159.33 (**CH**, **C6**), 141.83 (**C**, **C4**), 141.59 (**C**, **C7**), 138.80 (**C**, **C10**), 132.38 (**C**, **C1**), 130.71 (**CH**, **C8**), 129.88 (**CH**, **C3**), 129.26 (**CH**, **C9**), 124.75 (**CH**, **C2**), 21.40 (**CH_3**, **C5**), ppm.

LRMS (ES^+) *m/z* 278.2 $[M^{35}Cl+H]^+$, 280.2 $[M^{37}Cl+H]^+$.

Physical and spectroscopic data are consistent with reported values.[292]

4.25c: (+)-(*S*,*E*)-*N*-(4-Fluorobenzylidene)-4-methylbenzenesulfinamide



$C_{14}H_{12}FNOS$

261.31 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the title compound as fine yellow crystals (2.30 g, 8.80 mmol, 91%).

MP 119.8 – 121.6 °C

FT-IR (neat) ν_{max}: 3054 (w), 2889 (w), 1609 (s), 1581 (s), 1505 (m), 1224 (m), 1094 (s), 1072 (s) cm^{-1}.

$[\alpha]^{23}_{D}$ +100.1 ° (*c* = 0.39, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.72 (s, 1H, **H6**), 7.86 (dd, *J* = 8.8, 5.4 Hz, 2H, **H8**), 7.64 (d, *J* = 8.2 Hz, 2H, **H2**), 7.32 (d, *J* = 8.0 Hz, 2H, **H3**), 7.14 (t, *J* = 8.6 Hz, 2H, **H9**), 2.41 (s, 3H, **H5**) ppm.

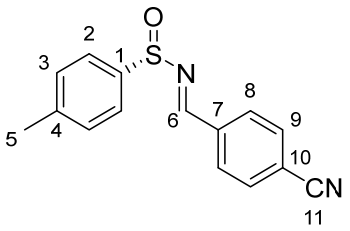
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 165.34 (d, *J* = 254.6 Hz, **C**, **C10**), 159.20 (**CH**, **C6**), 141.79 (**C**, **C4**), 141.69 (**C**, **C1**), 131.78 (d, *J* = 9.5 Hz, **CH**, **C8**), 130.31 (d, *J* = 3.0 Hz, **C**, **C7**), 129.85 (**CH**, **C3**), 124.74 (**CH**, **C2**), 116.16 (d, *J* = 22.0 Hz, **CH**, **C9**), 21.40 (**CH_3**, **C5**) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz) δ = –105.82 ppm.

LRMS (ES^+) *m/z* 262.2 $[M+H]^+$

Physical and spectroscopic data are consistent with reported values.[294]

4.25d: (+)-(*S*,*E*)-*N*-(4-Cyanobenzylidene)-4-methylbenzenesulfinamide



$C_{15}H_{12}N_2OS$

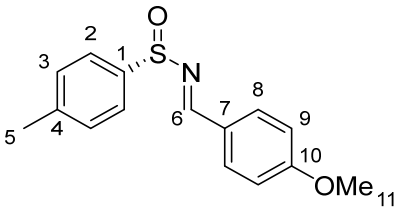
268.33 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (0.98 g, 4.22 mmol, 79%) as a pale yellow solid.

R_f	0.55 (40:60 EtOAc/hexane)
MP	145.6 – 146.9 °C
FT-IR	(neat) ν_{max}: 3087 (w), 2920 (w), 2229 (m), 1594 (m), 1101 (s), 1074 (w) cm^{-1}.
$[\alpha]^{23}_D$	+31.8 ° (*c* = 0.52, $CHCl_3$)
^{1}H NMR	($CDCl_3$, 400 MHz) δ = 8.77 (s, 1H, **H6**), 7.95 (dt, *J* = 8.4, 1.5 Hz, 2H, **H8**), 7.75 (dt, *J* = 8.3, 1.7 Hz, 2H, **H9**), 7.63 (dt, *J* = 8.2, 2.2 Hz, 2H, **H2**), 7.34 (d, *J* = 8.0 Hz, 2H, **H3**), 2.41 (s, 3H, **H5**) ppm.
^{13}C NMR	($CDCl_3$, 101 MHz) δ = 158.74 (**CH**, **C6**), 142.1 (**C**, **C4**), 140.85 (**C**, **C1**), 137.26 (**C**, **C7**), 132.63 (**CH**, **C9**), 129.96 (**CH**, **C3**), 129.80 (**CH**, **C8**), 124.66 (**CH**, **C2**), 118.00 (**C**, **C11**), 115.61 (**C**, **C10**), 21.41 (**CH_3**, **C5**) ppm.
LRMS	(ES^+) *m/z* 269.3 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[293]

4.25e: (+)-(*S*,*E*)-*N*-(4-Methoxybenzylidene)-4-methylbenzenesulfinamide



$C_{15}H_{15}NO_2S$

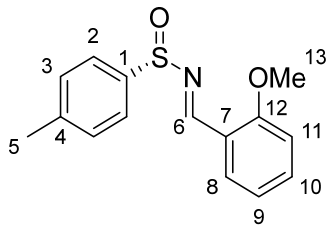
273.35 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (1.60g, 5.86 mmol, 91%) as a white solid.

MP	140.7 – 142.4 °C
FT-IR	(neat) ν_{max}: 3018 (w), 2955 (w), 1911 (w), 1591 (s), 1511 (s), 1306 (m), 1017 (m) cm^{-1}.
$[\alpha]^{23}_D$	+45.3 ° (*c* = 0.47, $CHCl_3$)
^{1}H NMR	($CDCl_3$, 400 MHz) δ = 8.69 (s, 1H, **H6**), 7.81 (d, *J* = 8.8 Hz, 2H, **H8**), 7.64 (d, *J* = 8.3 Hz, 2H, **H2**), 7.31 (d, *J* = 8.0 Hz, 2H, **H3**), 6.95 (d, *J* = 8.8 Hz, 2H, **H9**), 3.86 (s, 3H, **H11**), 2.40 (s, 3H, **H5**) ppm.
^{13}C NMR	($CDCl_3$, 101 MHz) δ = 163.20 (**C**, **C10**), 159.78 (**CH**, **C6**), 142.28 (**C**, **C1**), 141.60 (**C**, **C4**), 131.54 (**CH**, **C8**), 129.80 (**CH**, **C3**), 127.06 (**C**, **C7**), 124.83 (**CH**, **C2**), 114.31 (**CH**, **C9**), 55.49 (**CH_3**, **C11**), 21.42 (**CH_3**, **C5**) ppm.
LRMS	(ES^+) 274.3 $[M+H]^+$, 296.2 $[M+Na]^+$ *m/z*

Physical and spectroscopic data are consistent with reported values.[294]

4.25f: (+)-(*S*,*E*)-*N*-(2-Methoxybenzylidene)-4-methylbenzenesulfinamide



$C_{15}H_{15}NO_2S$

273.35 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (1.65 g, 6.04 mmol, 94%) as an off-white solid.

MP 81.7 – 82.4 °C

FT-IR (neat) ν_{max}: 3025 (w), 2945 (w), 1586 (s), 1468 (s), 1344 (m), 1249 (s), 1068 (s) cm^{-1}.

$[\alpha]^{23}_D$ +332.4 ° (*c* = 0.39, $CHCl_3$)

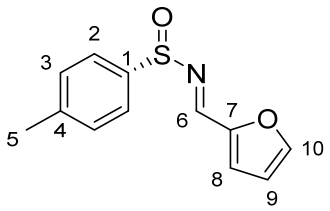
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.26 (s, 1H, **H6**), 7.98 (dd, *J* = 7.8, 1.8 Hz, 1H, **H8**), 7.65 (d, *J* = 8.3 Hz, 2H, **H2**), 7.46 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H, **H10**), 7.33 – 7.28 (m, 2H, **H3**), 7.01 - 6.97 (m, 1H, **H9**), 6.97 – 6.92 (m, 1H, **H11**), 3.90 (s, 3H, **H13**), 2.40 (s, 3H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 159.73 (**C**, **C12**), 155.68 (**CH**, **C6**), 142.24 (**C**, **C1**), 141.47 (**C**, **C4**), 134.08 (**CH**, **C10**), 129.73 (**CH**, **C3**), 128.45 (**CH**, **C8**), 124.82 (**CH**, **C2**), 122.55 (**C**, **C7**), 120.62 (**CH**, **C9**), 111.29 (**CH**, **C11**), 55.51 (**CH_3**, **C13**), 21.37 (**CH_3**, **C5**) ppm.

LRMS (ES^+) 274.3 $[M+H]^+$, 296.3 $[M+Na]^+$ *m/z.*

Physical and spectroscopic data are consistent with reported values.[294]

4.25g: (*S*,*E*)-*N*-(Furan-2-ylmethylene)-4-methylbenzenesulfinamide



$C_{12}H_{11}NO_2S$

233.29 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (0.98 g, 4.22 mmol, 66%) as a pale yellow solid.

R_f 0.40 (40:60 EtOAc/hexane)

MP 73.2 – 74.4 °C

FT-IR (neat) ν_{max}: 3120 (w), 1605 (s), 1545 (m), 1472 (m), 1086 (s), 1068 (s) cm^{-1}.

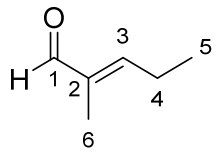
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.59 (s, 1H, **H6**), 7.65 – 7.61 (m, 3H, **H2**, **H10**), 7.31 (d, *J* = 8.0 Hz, 2H, **H3**), 7.04 (dd, *J* = 3.6, 0.6 Hz, 1H, **H8**), 6.57 (dd, *J* = 3.6, 1.8 Hz, 1H, **H9**), 2.40 (s, 3H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 150.53 (**C**, **C7**), 147.70 (**CH**, **C6**), 147.06 (**CH**, **C10**), 141.89 (**C**, **C4**), 141.61 (**C**, **C1**), 129.88 (**CH**, **C3**), 124.70 (**CH**, **C2**), 119.35 (**CH**, **C8**), 112.56 (**CH**, **C9**), 21.43 (**CH_3**, **C5**) ppm.

LRMS (ES^+) *m/z* 234.2 $[M+H]^+$, 256.2 $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[295]

4.32h: (*E*)-2-Methylpent-2-enal



$C_6H_{10}O$

98.15 g mol^{-1}

Following the method of Behr,[18] to a solution of NaOH (4%, 10 mL) was added propionaldehyde (6.21 mL). The milk-white suspension was heated to 60 °C, and stirred for 2 h, upon which it became a yellow solution. The reaction was cooled to RT. The phases were separated, and the aqueous phase washed with pentane (3 x 20 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* (500 mBar, 20 °C bath temp) to afford the crude product as a colourless oil. Purification by distillation (136 °C, 760 Torr) afforded the title compound as a colourless oil (1.61 g, 16.4 mmol, 38%).

FT-IR (neat) ν_{max}: 2971 (w), 2878 (w), 1683 (s), 1642 (s), 1220 (m), 1042 (m) cm^{-1}.

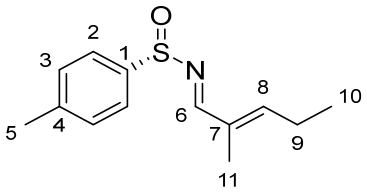
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.40 (s, 1H, **H1**), 6.48 (tq, *J* = 7.3, 1.3 Hz, 1H, **H3**), 2.37 (quind, *J* = 7.5 Hz, 0.8 Hz, 2H, **H4**), 1.74 (d, *J* = 1.2 Hz, 3H, **H6**), 1.12 (t, *J* = 7.6 Hz, 3H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.41 (**CH**, **C1**), 156.23 (**CH**, **C3**), 138.80 (**C**, **C2**), 22.29 (**CH_2**, **C4**), 12.80 (**CH_3**, **C5**), 9.10 (**CH_3**, **C6**) ppm.

LRMS (EI) *m/z* = 98.1 (67%) $[M]^{\cdot+}$, 83.1 (16%) $[M-CH_3]^{\cdot+}$, 69.1 (28%) $[M-C_2H_5]^{\cdot+}$, 55.1 (37%), 41.1 (100%).

Physical and spectroscopic data are consistent with reported values.[206]

4.25h: (+)-(*S*)-4-Methyl-N-((1*E*,2*E*)-2-methylpent-2-en-1-ylidene)benzenesulfinamide



$C_{13}H_{17}NOS$

235.35 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (1.40 g, 5.95 mmol, 62%) as pale yellow oil.

R_f 0.51 (40:60 EtOAc/hexane)

FT-IR (neat) ν_{max}: 2968 (w), 1636 (m), 1577 (s), 1097 (s) cm^{-1}.

$[\alpha]^{23}_D$ +564.0 ° (*c* = 1.1, $CHCl_3$)

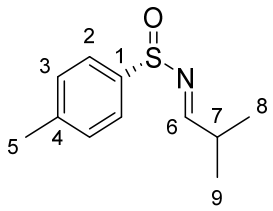
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.28 (s, 1H, **H6**), 7.59 (d, *J* = 8.3 Hz, 2H, **H2**), 7.29 (d, *J* = 8.0 Hz, 2H, **H3**), 6.26 (td, *J* = 7.4, 1.0 Hz, 1H, **H8**), 2.40 (s, 3H, **H5**), 2.30 (quin, *J* = 7.5 Hz, 2H, **H15**), 1.87 (d, *J* = 0.8 Hz, 3H, **H11**), 1.07 (t, *J* = 7.6 Hz, 3H, **H10**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 164.68 (**CH**, **C6**), 150.34 (**CH**, **C8**), 142.56 (**C**, **C1**), 141.35 (**C**, **C4**), 134.32 (**C**, **C7**), 129.68 (**CH**, **C3**), 124.77 (**CH**, **C2**), 22.26 (**CH_2**, **C9**), 21.37 (**CH_3**, **C5**), 13.05 (**CH_3**, **C10**), 11.15 (**CH_3**, **C11**) ppm.

LRMS (ES^+) 236.3 $[M+H]^+$, 258.2 $[M+Na]^+$ *m/z*.

HRMS (ES^+) for $C_{13}H_{17}NNaOS^+$, calculated 258.0923 found 258.0929.

4.25i: (+)-(*S*,*E*)-4-Methyl-*N*-(2-methylpropylidene)benzenesulfinamide



$C_{11}H_{15}NOS$

209.31 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (504 mg, 2.41 mmol, 25%) as a colourless oil.

FT-IR (neat) ν_{max}: 2967 (w), 1618 (s), 1463 (m), 1096 (s) cm^{-1}.

$[\alpha]^{23}_D$ +324.0 ° (*c* = 1.1, $CHCl_3$)

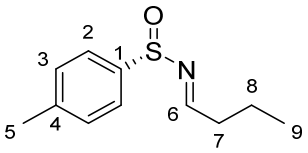
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.15 (d, *J* = 4.7 Hz, 1H, **H6**), 7.56 (d, *J* = 8.6 Hz, 2H, **H2**), 7.30 (d, *J* = 8.0 Hz, 2H, **H3**), 2.68 (dtd, *J* = 13.8, 6.9, 4.5 Hz, 1H, **H7**), 2.41 (s, 3H, **H5**), 1.16 (d, *J* = 4.8 Hz, 3H, **H8/H9**), 1.14 (d, J = 4.7 Hz, 3H, **H8/H9**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.26 (**CH**, **C6**), 142.02 (**C**, **C1**), 141.58 (**C**, **C4**), 129.78 (**CH**, **C3**), 124.65 (**CH**, **C2**), 34.66 (**CH**, **C7**), 21.42 (**CH_3**, **C5**), 18.78 (**CH_3**, **C8/C9**), 18.74 (**CH_3**, **C8/C9**) ppm.

LRMS (ES^+) 210.3 $[M+H]^+$, 232.3 $[M+Na]^+$ *m/z.*

HRMS (ES^+) for $C_{11}H_{15}NNaOS^+$, calculated 232.0767 found 232.0769.

4.25j: (+)-((*S*,*E*)-*N*-butylidene-4-methylbenzenesulfinamide



$C_{11}H_{15}NOS$

209.31 g mol^{-1}

Prepared according to General Procedure 7.2.3.1 to give the target compound (895 mg, 4.28 mmol, 66%) as a colourless oil.

R_f 0.38 (2:8 EtOAc/hexane)

FT-IR (neat) ν_{max}: 2961 (w), 1620 (s), 1093 (s), 1071 (s) cm^{-1}.

$[\alpha]^{23}_D$ +220.9 ° (*c* = 0.81, $CHCl_3$).

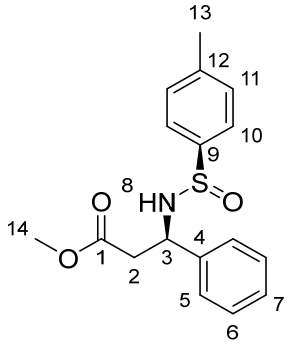
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.23 (t, *J* = 4.8 Hz, 1H, **H6**), 7.56 (d, *J* = 8.7 Hz, 2H, **H2**), 7.30 (d, *J* = 8.0 Hz, 2H, **H3**), 2.46 (td, *J* = 7.3, 4.9 Hz, 2H, **H7**), 2.40 (s, 3H, **H5**), 1.64 (sxt, *J* = 7.4 Hz, 2H, **H8**), 0.95 (t, *J* = 7.4 Hz, 3H, **H9**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 167.16 (**CH**, **C6**), 141.80 (**C**, **C1**), 141.59 (**C**, **C4**), 129.73 (**CH**, **C3**), 124.49 (**CH**, **C2**), 37.74 (**CH_2**, **C7**), 21.37 (**CH_3**, **C5**), 18.79 (**CH_2**, **C8**), 13.61 (**CH_3**, **C9**) ppm.

LRMS (ES^+) 210.3 $[M+H]^+$, 232.3 $[M+Na]^+$ *m/z.*

Physical and spectroscopic data are consistent with reported values.[296]

4.26a: (+)-Methyl (*R*)-3-phenyl-3-(((*S*)-*p*-tolylsulfinyl)amino)propanoate



$C_{17}H_{19}NO_3S$

317.40 g mol^{-1}

A solution of NaHMDS (24.9 mL of a 2 M solution in THF, 49.78 mmol) was cooled to ─78 °C. Methyl acetate (2.43 mL, 49.8 mmol) was added dropwise over 5 min. The solution was stirred for 1 h at this temperature. A solution of *N*-sulfinyl imine **4.25a** (4.84 g, 19.9 mmol) in THF (75 mL) was added dropwise over 15 min, and the reaction stirred for a further 2 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL) and warmed to RT. The phases were separated and the aqueous extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 9:1 *R*:*S*). Purification by chromatography (silica, 1:9 EtOAc:CH_2Cl_2) afforded the title compound as a white solid (3.71 g, 11.7 mmol, 59%).

A solution of NaHMDS (13.2 mL of a 2 M solution in THF, 26.4 mmol) and anhydrous Et_2O (120 mL) was cooled to –78 °C. Methyl acetate (1.29 mL, 1.96 mmol) was added dropwise, and the solution stirred at this temperature for 1 h. A solution of *N*-sulfinyl imine **4.25a** (2.57 g, 10.6 mmol) in anhydrous Et_2O (80 mL) was added dropwise at this temperature over 10 min. The solution was stirred for a further 2 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL) and warmed to RT. The phases were separated and the aqueous extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as an inseparable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 24:1 *R*:*S*). Purification by chromatography (silica, 1:9 EtOAc:CH_2Cl_2) afforded the title compound as a white solid (2.56 g, 8.07 mmol, 76%).

R_f 0.18 (EtOAc:hexane 4:6)

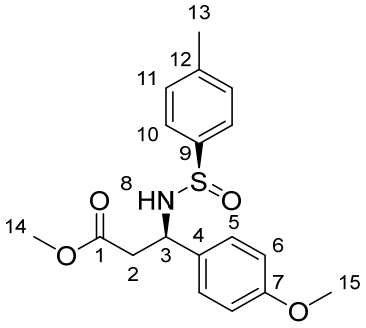
MP 88.1 – 89.5 °C

FT-IR (neat) ν_{max}: 3137 (br), 2952 (w) , 1726 (s), 1434 (m), 1230 (m), 1044 (s) cm^{-1}.

$[\alpha]^{23}_{D}$	+104.7 ° (*c* = 1.06, $CHCl_3$)
^{1}H NMR	($CDCl_3$, 400 MHz) δ = 7.61 (d, *J* = 8.2 Hz, 2H, **H10**), 7.45 – 7.36 (m, 4H, **H5**, **H6**), 7.35 – 7.29 (m, 3H, **H7**, **H11**), 4.99 (br d, *J* = 5.4 Hz, 1H, **H8**), 4.92 (q, *J* = 6.0 Hz, 1H, **H3**), 3.61 (s, 3H, **H14**), 2.86 (d, *J* = 6.4 Hz, 2H, **H2**), 2.42 (s, 3H, **H13**) ppm.
^{13}C NMR	($CDCl_3$, 101 MHz) δ = 171.26 (**C**, **C1**), 142.30 (**C**, **C9**), 141.45 (**C**, **C12**), 140.36 (**C**, **C4**), 129.58 (**CH**, **C11**), 128.78 (**CH**, **C6**), 128.08 (**CH**, **C7**), 127.21 (**CH**, **C5**), 125.35 (**CH**, **C10**), 54.82 (**CH**, **C3**), 51.85 (**CH_3**, **C14**), 42.04 (**CH_2**, **C2**), 21.86 (**CH_3**, **C13**) ppm.
LRMS	(ES^+) *m/z* 318.3 $[M+H]^+$, 340.3 $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[297]

4.26e: (+)-Methyl (*R*)-3-(4-methoxyphenyl)-3-(((*S*)-*p*-tolylsulfinyl)amino)propanoate



$C_{18}H_{21}NO_4S$

347.43 g mol^{-1}

A solution of NaHMDS (4.58 mL of a 2 M solution in THF, 9.15 mmol) and anhydrous Et_2O (30 mL) was cooled to –78 °C. Methyl acetate (0.45 mL, 9.15 mmol) was added dropwise, and the solution stirred for 1 h. A solution of imine **4.25e** (1.00 g, 3.66 mL) in anhydrous Et_2O (40 mL) was added dropwise, and the reaction stirred at this temperature for 2.5 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL), and warmed to RT. The phases were separated and the aqueous extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a yellow oil (HPLC analysis of the crude reaction mixture gave d.r. 98:2 *R*/*S*). Purification by chromatography (silica, 4:6 – 8:2 EtOAc/pet. ether) afforded the title compound as an off-yellow oil (557 mg, 1.60 mmol, 44 %).

R_f 0.15 (EtOAc:hexane 4:6)

FT-IR (neat) ν_{max}: 3184 (br), 2952 (w), 1733 (s), 1611 (w), 1513 (m), 1246 (s), 1031 (s) cm^{-1}.

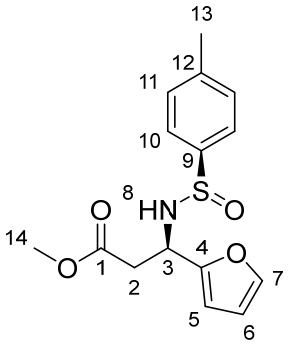
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.59 (d, *J* = 8.6 Hz, 2H, **H10**), 7.35 (d, *J* = 8.8 Hz, 2H, **H5**), 7.32 – 7.28 (m, 2H, **H11**), 6.91 (d, *J* = 8.8 Hz, 2H, **H6**), 4.95 (d, *J* = 5.1 Hz, 1H, **H8**), 4.90 – 4.83 (m, 1H, **H3**), 3.81 (s, 3H, **H15**), 3.60 (s, 3H, **H14**), 2.82 (d, *J* = 6.6 Hz, 2H, **H2**), 2.41 (s, 3H, **H13**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.28 (**C**, **C1**), 159.31 (**C**, **C7**), 142.28 (**C**, **C9**), 141.34 (**C**, **C12**), 132.19 (**C**, **C4**), 129.51 (**CH**, **C11**), 128.47 (**CH**, **C5**), 125.30 (**CH**, **C10**), 114.10 (**CH**, **C6**), 55.21 (**CH_3**, **C15**), 54.16 (**CH**, **C3**), 51.77 (**CH_3**, **C14**), 42.07 (**CH_2**, **C2**), 21.31 (**CH_3**, **C13**) ppm.

LRMS (ES$^+$) *m/z* 348.3 [M+H]$^+$, 370.3 [M+Na]$^+$.

HRMS (ES$^+$) for $C_{18}H_{21}NNaO_4S^+$, calculated 370.1083 found 370.1087.

4.26f: Methyl (*R*)-3-(furan-2-yl)-3-(((*S*)-*p*-tolylsulfinyl)amino)propanoate



$C_{15}H_{17}NO_4S$

307.36 g mol^{-1}

A solution of NaHMDS (9.70 mL of a 1 M solution in THF, 9.70 mmol) was cooled to –78 °C. Methyl acetate (0.77 mL, 9.65 mmol) was added dropwise, and the orange solution stirred for 1 h. A solution of imine **4.25f** (900 mg, 3.86 mmol) in anhydrous THF (12 mL) was added dropwise over 5 min, and the solution stirred at this temperature for a further 2 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (15 mL) and warmed to RT. The phases were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 2:1 *R*:*S*). Purification by chromatography (silica, 5:95 EtOAc/CH_2Cl_2) afforded the title compound as a brown solid (504 mg, 1.64 mmol, 42%).

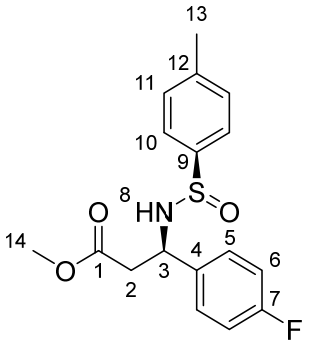
FT-IR (neat) ν_{max}: 3163 (br), 2959 (w), 1736 (s), 1594 (w), 1435 (m), 1162 (m), 1035 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.60 (d, *J* = 8.4 Hz, 2H, **H10**), 7.39 (t, *J* = 1.4 Hz, 1H, **H7**), 7.31 (d, *J* = 8.0 Hz, 2H, **H11**), 6.36 – 6.32 (m, 2H, **H5**, **H6**), 5.01 (d, *J* = 7.8 Hz, 1H, **H8**), 4.91 (dt, *J* = 7.7, 6.1 Hz, 1H, **H3**), 3.64 (s, 3H, **H14**), 2.95 (dd, *J* = 16.3, 6.3 Hz, 1H, **H2'**), 2.88 (dd, *J* = 16.3, 6.2 Hz, 1H, **H2''**), 2.42 (s, 3H, **H13**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.04 (**C**, **C1**), 153.13 (**C**, **C4**), 142.34 (**CH**, **C7**), 141.78 (**C**, **C9**), 141.48 (**C**, **C12**), 129.56 (**CH**, **C11**), 125.56 (**CH**, **C10**), 110.47 (**CH**, **C6**), 107.57 (**CH**, **C5**), 51.87 (**CH_3**, **C14**), 49.05 (**CH**, **C3**), 39.40 (**CH_2**, **C2**), 21.34 (**CH_3**, **C13**) ppm.

LRMS (ES^+) *m/z* 308.4 $[M+H]^+$, 330.3 $[M+Na]^+$.

4.26c: Methyl (*R*)-3-(4-fluorophenyl)-3-(((*S*)-*p*-tolylsulfinyl)amino)propanoate



$C_{17}H_{18}FNO_3S$

335.39 g mol^{-1}

A solution of NaHMDS (7.23 mL of a 1 M solution in THF, 7.23 mmol) was cooled to –78 °C. Methyl acetate (0.57 mL, 7.23 mmol) was added dropwise, and the orange solution stirred for 1 h. A solution of imine **4.25c** (754 mg, 2.89 mmol) in anhydrous THF (8 mL) was added dropwise over 5 min, and the solution stirred at this temperature for 3 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (15 mL) and warmed to RT. The phases were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 77:33 *R*:*S*). Purification by chromatography (silica, 5:95 EtOAc/CH_2Cl_2) afforded the title compound as a yellow oil (459 mg, 1.52 mmol, 53%).

Alternatively, to a solution of LiHMDS (1.93 mL of a 1 M solution in THF, 1.93 mL) was cooled to –78 °C. Methyl acetate (0.15 mL, 1.93 mmol) was added dropwise, and the orange solution stirred for 1 h. A solution of imine **4.25c** (200 mg, 0.77 mmol) in anhydrous THF (4 mL) was added dropwise over 5 min, and the solution was stirred at this temperature for 2 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL) and warmed to RT. The phases were separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 5:1 *R*:*S*). Purification by chromatography (silica, 1:9 EtOAc/CH_2Cl_2) afforded the title compound as a yellow oil (178 mg, 0.53 mmol, 69%).

R_f 0.40 (1:9 EtOAc/CH_2Cl_2)

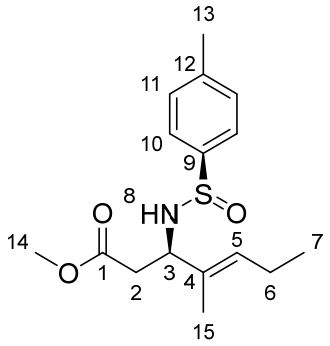
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.60 (d, *J* = 8.2 Hz, 2H, **H10**), 7.40 (dd, *J* = 8.6 , 5.3 Hz, 2H, **H5**), 7.32 (d, *J* = 8.1 Hz, 2H, **H11**), 7.08 (t, *J* = 8.6 Hz, 2H, **H6**), 4.97 (d, *J* = 5.3 Hz, 1H, **H8**), 4.88 (q, *J* = 6.2 Hz, 1H, **H3**), 3.62 (s, 3H, **H14**), 2.83 (d, *J* = 6.4 Hz, 2H, **H2**), 2.43 (s, 3H, **H13**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.14 (**C**, **C1**), 142.06 (**C**, **C9**), 141.61 (**C**, **C12**), 136.1 (d, *J* = 3.7 Hz, **C**, **C4**), 129.86 (**CH**, **C11**), 128.98 (d, *J* = 8.1 Hz, **CH**, **C5**), 125.32 (**CH**, **C10**), 115.72 (d, *J* = 22.0 Hz, **CH**, **C6**), 54.04 (**CH**, **C3**), 51.92 (**CH_3**, **C14**), 42.01 (**CH_2**, **C2**), 21.39 (**CH_3**, **C13**) ppm *(**C7** not observed)*.

^{19}F NMR ($CDCl_3$, 376 MHz) δ = –114.21 ppm.

LRMS (ES^+) *m/z* 336.3 $[M+H]^+$, 358.3 $[M+Na]^+$.

4.26h: (+)-Methyl (*R*,*E*)-4-methyl-3-(((*S*)-*p*-tolylsulfinyl)amino)hept-4-enoate



$C_{16}H_{23}NO_3S$

309.42 g mol^{-1}

A solution of NaHMDS (10.6 mL of a 1 M solution in THF, 10.6 mmol) was cooled to –78 °C. Methyl acetate (0.84 mL, 10.6 mmol) was added, and the orange solution stirred for 1 h. A solution of imine **4.25h** (1.00 g, 4.25 mmol) in anhydrous THF (12 mL) was added dropwise over 5 min. The solution was stirred at this temperature for 90 min. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (20 mL) and warmed to RT. The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a separable mixture of diastereoisomers (integration of the NH peak in the NMR of the crude product gives d.r. 78:22 *R*:*S*). Purification by chromatography (silica, 5:85 to 3:7 EtOAc/CH_2Cl_2) afforded the title compound as a yellow oil (536 mg, 1.73 mmol, 41%).

R_f 0.14 (1:9 EtOAc/CH_2Cl_2)

FT-IR (neat) ν_{max}: 3195 (br), 2962 (w), 1738 (s), 1596 (w), 1436 (m), 1089 (s), 1053 (s) cm^{-1}.

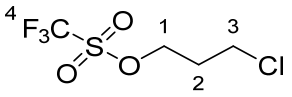
$[\alpha]^{23}_D$ +93.6 ° (*c* = 1.16, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.59 (d, *J* = 8.2 Hz, 2H, **H10**), 7.29 (d, *J* = 8.0 Hz, 2H, **H11**), 5.58 (t, *J* = 7.0 Hz, 1H, **H5**), 4.50 (d, *J* = 4.2 Hz, 1H, **H8**), 4.30 – 4.21 (m, 1H, **H3**), 3.64 (s, 3H, **H14**), 2.63 (dd, *J* = 15.7, 7.8 Hz, 1H, **H2'**), 2.58 (dd, *J* = 15.3, 6.0 Hz, 1H, **H2''**), 2.41 (s, 3H, **H13**), 2.13 – 2.02 (m, 2H, **H6**), 1.69 (s, 3H, **H15**), 0.98 (t, *J* = 7.5 Hz, 3H, **H7**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.61 (**C**, **C1**), 142.58 (**C**, **C9**), 141.26 (**C**, **C12**), 132.38 (**CH**, **C5**), 131.60 (**C**, **C4**), 129.52 (**CH**, **C11**), 125.27 (**CH**, **C10**), 58.32 (**CH**, **C3**), 51.79 (**CH_3**, **C14**), 39.46 (**CH_2**, **C2**), 21.35 (**CH_3**, **C13**), 21.09 (**CH_2**, **C6**), 13.75 (**CH_3**, **C7**), 11.90 (**CH_3**, **C15**) ppm.

LRMS (ES^+) *m/z* 310.7 $[M+H]^+$, 332.6 $[M+Na]^+$.

4.17: 3-Chloropropyl trifluoromethanesulfonate



$C_4H_6ClF_3O_3S$

226.59 g mol^{-1}

A solution of 3-chloro-1-propanol (3.6 mL, 43.1 mmol), CH_2Cl_2 (100 mL) and pyridine (4.11 mL, 50.78 mmol) was cooled to –78 °C. Trifluoromethanesulfonic anhydride (7.83 mL, 50.8 mmol) was added dropwise over 10 min. The solution was stirred for 15 min at this temperature, then warmed to RT and stirred for a further 90 min. The reaction was quenched by the addition of 1 M HCl (100 mL). The phases were separated, and the organic phase was washed with sat. $NaHCO_3$ (150 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a yellow oil. Purification by short-path distillation (70 °C at 0.6 mBar) afforded the title compound as a colourless oil (7.38 g, 34.6 mmol, 80%).

FT-IR (neat) ν_{max}: 1410 (s), 1198 (s), 1140 (s), 926 (s) cm^{-1}.

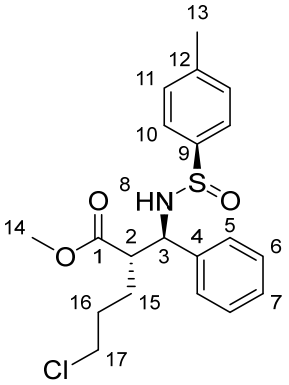
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.73 (t, *J* = 5.9 Hz, 2H, **H1**), 3.68 (t, *J* = 6.1 Hz, 2H, **H3**), 2.29 (quin, *J* = 6.0 Hz, 2H, **H2**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 118.59 (q, *J* = 320 Hz, **C**, **C4**), 73.43 (**CH_2**, **C1**), 39.41 (**CH_2**, **C3**), 31.93 (**CH_2**, **C2**) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz) δ = –74.84 (s, **CF_3**) ppm.

Physical and spectroscopic data are consistent with reported values.[298]

4.30: (+)-Methyl (*S*)-5-chloro-2-((*R*)-phenyl(((*S*)-p-tolylsulfinyl)amino)methyl)pentanoate



$C_{20}H_{24}ClNO_3S$

393.93 g mol^{-1}

To a solution of LDA (1.73 mL of a 1.53 M solution, 2.65 mmol) was added dried LiCl (449 mg, 10.6 mmol) in one portion, and the suspension cooled to –78 °C and stirred for 10 min. A solution of ester **4.26a** (335 mg, 1.06 mmol) in anhydrous THF (4 mL) was added dropwise, and stirred for 1 h at this temperature. A solution of triflate **4.17** (480 mg, 2.12 mmol) in anhydrous THF (1 mL) was then added dropwise, and the solution stirred for 1 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL) and then warmed to RT. The phases were separated and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 5:95 EtOAc/CH_2Cl_2) afforded the title compound as a yellow oil (73 mg, 0.19 mmol, 18%).

R_f 0.31 (EtOAc:CH_2Cl_2 1:9)

FT-IR (neat) ν_{max}: 3191 (br), 2952 (w), 1733 (s), 1597 (w), 1454 (m), 1201 (m), 1090 (s), 1058 (s) cm^{-1}.

$[\alpha]^{23}_D$ +84.7 ° (*c* = 1.2, $CHCl_3$)

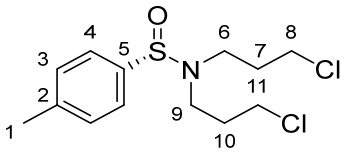
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55 (d, *J* = 8.2, 2H, **H10**), 7.42 – 7.28 (m, 7H, **H5**, **H6**, **H7**, **H11**), 5.14 (d, *J* = 6.6 Hz, 1H, **H8**), 4.58 (t, *J* = 6.9 Hz, 1H, **H3**), 3.61 (s, 3H, **H14**), 3.45 (td, *J* = 6.4, 2.1 Hz, 2H, **H17**), 2.76 (ddd, *J* = 9.0, 7.0, 5.1 Hz, 1H, **H2**), 2.42 (s, 3H, **H13**), 1.80 – 1.51 (m, 4H, **H15**, **H16**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.04 (**C**, **C1**), 142.10 (**C**, **C9**), 141.41 (**C**, **C12**), 140.27 (**C**, **C4**), 129.53 (**CH**, **C11**), 128.72 (**CH**, **C6**), 128.02 (**CH**, **C7**), 127.11 (**CH**, **C5**), 125.50 (**CH**, **C10**), 59.55 (**CH**, **C6**), 51.93 (**CH**, **C2**), 51.71 (**CH_3**, **C14**), 44.10 (**CH_2**, **C17**), 30.09 (**CH_2**, **C16**), 27.22 (**CH_2**, **C15**), 21.35 (**CH_3**, **C13**) ppm.

LRMS (ES$^+$) *m/z* 394.4 [M^{35}Cl+H]$^+$, 396.4 [M^{37}Cl+H]$^+$

HRMS (ES$^+$) for $C_{20}H_{24}ClNNaO_3S^+$, calculated 416.1058 found 416.1062.

4.31: (+)-(*S*)-*N*,*N*-*bis*(3-Chloropropyl)-4-methylbenzenesulfinamide



$C_{13}H_{19}Cl_2NOS$

308.26 g mol^{-1}

Isolated as a byproduct from the *anti* alkylation of ester **4.26a.**

R_f 0.6 (EtOAc:Ch_2Cl_2 1:9)

FT-IR (neat) ν_{max}: 2958 (w), 1736 (s), 1203 (m), 1083 (m), 1064 (m), 753 (s), cm^{-1}.

$[\alpha]^{23}_D$ +106 ° (*c* = 0.26, $CHCl_3$)

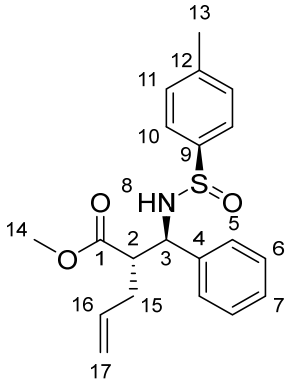
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.52 (d, *J* = 7.8 Hz, 2H, **H3**), 7.32 (d, *J* = 7.8 Hz, 2H, **H4**), 3.55 – 3.42 (m, 4H, **H8**, **H11**), 3.30 – 3.15 (m, 4H, **H6**, **H9**), 2.42 (s, 3H, **H1**), 2.07 – 1.89 (m, 4H, **H7**, **H10**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 141.61 (**C**, **C5**), 140.30 (**C**, **C2**), 129.73 (**CH**, **C3**), 125.90 (**CH**, **C4**), 45.32 (**CH_2**, **C8 & C11**), 42.11 (**CH_2**, **C6 & C9**), 31.25 (**CH_2**, **C7 & C10**), 21.43 (**CH_3**, **C1**) ppm.

LRMS (ES^+) *m/z* 308.3 $[M^{35}Cl+H]^+$, 310.3 $[M^{37}Cl+H]^+$

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

4.39: (+)-Methyl (*S*)-2-((*R*)-phenyl(((*S*)-p-tolylsulfinyl)amino)methyl)pent-4-enoate



$C_{20}H_{23}NO_3S$

357.47 g mol^{-1}

A solution of LDA (1.50 mL of a 2 M solution in THF, 3.00 mmol) was cooled to –20 °C. A solution of ester **4.26a** (318 mg, 1.00 mmol) in anhydrous THF (5 mL) was added dropwise. The orange solution was stirred for 1 h. A solution of allyl iodide (0.23 mL, 2.50 mmol) in anhydrous THF (5 mL) was added dropwise at this temperature, turning the solution yellow. The solution was stirred for 1 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and warmed to RT. The phases were separated and the aqueous extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. HPLC analysis of the crude product gave a d.r. of 97:3 (*anti/syn).* Purification by chromatography (silica, 1:9 EtOAc/CH_2Cl_2) afforded the title compound as a viscous yellow oil (265 mg, 0.74 mmol, 74%).

R_f 0.24 (EtOAc:hexane 4:6)

FT-IR (neat) ν_{max}: 3194 (br), 2950 (w), 1734 (s), 1642 (w), 1598 (w), 1455 (m), 1169 (m), 1089 (s), 1059 (s) cm^{-1}.

$[\alpha]^{23}_D$ +105.4 (*c* = 0.9, $CHCl_3$)

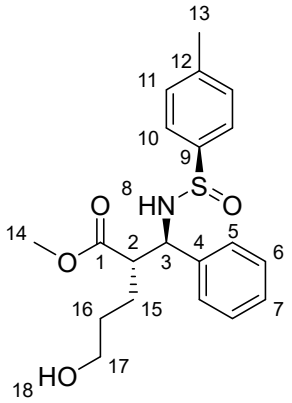
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55 (d, *J* = 8.2 Hz, 2H, **H10**), 7.42 – 7.28 (m, 7H, **H5**, **H6**, **H7**, **H11**), 5.66 (ddt, *J* = 16.8, 10.3, 6.7 Hz, 1H, **H16**), 5.17 (d, *J* = 6.5 Hz, 1H, **H8**), 5.09 – 4.97 (m, 2H, **H17**), 4.62 (t, *J* = 6.5 Hz, 1H, **H3**), 3.59 (s, 3H, **H14**), 2.85 (ddd, *J* = 9.0, 7.0, 5.4 Hz, 1H, **H2**), 2.42 (s, 3H, **H13**), 2.38 – 2.28 (m, 1H, **H15'**), 2.25 – 2.16 (m, 1H, **H15''**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 173.80 (**C**, **C1**), 142.26 (**C**, **C9**), 141.30 (**C**, **C12**), 140.30 (**C**, **C4**), 134.13 (**CH**, **C16**), 129.49 (**CH**, **C11**), 128.68 (**CH**, **C6**), 127.98 (**CH**, **C7**), 127.27 (**CH**, **C5**), 125.48 (**CH**, **C10**), 117.66 (**CH_2**, **C17**), 59.48 (**CH**, **C3**), 52.14 (**CH**, **C2**), 51.75 (**CH_3**, **C14**), 34.13 (**CH_2**, **C15**), 21.33 (**CH_3**, **C13**) ppm.

LRMS (ES$^+$) *m/z* 358.4 [M+H]$^+$, 380.4 [M+Na]$^+$.

Physical and spectroscopic data are consistent with reported values.[202]

4.40: (+)-Methyl (*S*)-5-hydroxy-2-((*R*)-phenyl(((*S*)-*p*-tolylsulfinyl)amino)methyl) pentanoate



$C_{20}H_{25}NO_4S$

375.48 g mol^{-1}

A solution of alkene **4.39** (164 mg, 0.46 mmol) in anhydrous THF (3 mL) was cooled to 0 °C. BH_3•THF (0.69 mL of a 1 M solution in THF, 0.69 mmol) was added dropwise. The solution was warmed to RT and stirred for 2 h, before being cooled to 0 °C. A solution of NaOAc (2.8 mL of a 1 M solution in MeOH, 2.8 mmol) was added, causing effervescence. When this ceased (*ca* 2 min), a solution of H_2O_2 (0.3 mL, 30% wt H_2O, 2.76 mmol) was added dropwise, and the reaction heated to 60 °C for 16 h. The reaction was cooled to RT and diluted with H_2O (3 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a colourless oil (integration of the NH peak in the NMR of the crude product gives 9:1 *AM*/*M* product). Purification by chromatography (silica, 8:2 EtOAc/pet. ether) afforded the title compound as a colourless oil (73 mg, 0.19 mmol, 42%).

R_f 0.12 (EtOAc:CH_2Cl_2 1:9)

FT-IR (neat) ν_{max}: 3300 (br), 2949 (w), 1724 (s), 1454 (m), 1087 (s), 1052 (s) cm^{-1}.

$[\alpha]^{23}_D$ +58.3 (*c* = 0.55, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56 (d, *J* = 8.2 Hz, 2H, **H10**), 7.42 – 7.29 (m, 7H, **H5**, **H6**, **H7**, **H11**), 5.27 (d, *J* = 7.0 Hz, 1H, **H8**), 4.67 (t, *J* = 6.7 Hz, 1H, **H3**), 3.68 – 3.49 (m, 5H, **H14**, **H17**), 2.83 (dt, *J* = 7.2, 6.5 Hz, 1H, **H2**), 2.43 (s, 3H, **H13**), 1.96 (br s, 1H, **H18**), 1.75 – 1.47 (m, 4H, **H15**, **H16**) ppm.

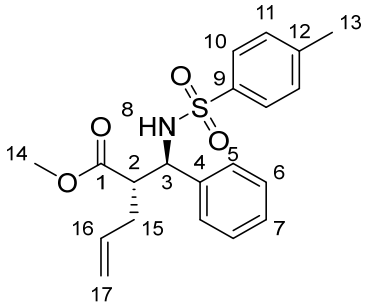
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.45 (**C**, **C1**), 142.24 (**C**, **C9**), 141.44 (**C**, **C12**), 140.70 (**C**, **C4**), 129.56 (**CH**, **C11**), 128.66 (**CH**, **C6**), 127.86 (**CH**, **C7**), 127.00 (**CH**, **C5**), 125.53 (**CH**, **C10**), 62.10 (**CH_2**, **C17**), 59.87 (**CH**, **C3**),

51.90 (**CH**, **C2**), 51.79 (**CH_3**, **C14**), 30.10 (**CH_2**, **C16**), 26.22 (**CH_2**, **C15**), 21.35 (**CH_3**, **C13**) ppm.

LRMS (ES^+) *m/z* 376.3 $[M+H]^+$, 398.3 $[M+Na]^+$.

HRMS (ES^+) for $C_{20}H_{25}NNaO_4S^+$, calculated 398.1397 found 398.1394.

4.62: (+)-Methyl (*S*)-2-((*R*)-((4-methylphenyl)sulfonamido)(phenyl)methyl)pent-4-enoate



$C_{20}H_{23}NO_4S$

373.47 g mol^{-1}

Adapting the procedure of Malacria,[299] to a solution of sulfinamide **4.39** (202 mg, 0.56 mmol) in MeCN (4 mL) and H_2O (0.1 mL) was added iodosobenzene (245 mg, 1.12 mmol). The yellow suspension was stirred for 22 h, and the reaction concentrated *in vacuo* to afford a yellow solid residue. Purification by chromatography (silica, 1:4 EtOAc/pet. ether) afforded the title compound as an off-white solid (174 mg, 0.47 mmol, 84%).

R_f 0.50 (EtOAc:hexane 4:6)

FT-IR (neat) ν_{max}: 3280 (br), 1738 (s), 1720 (s), 1330 (m), 1161 (s) cm^{-1}.

$[\alpha]^{23}_D$ +22.0 ° (*c* = 0.7, $CHCl_3$)

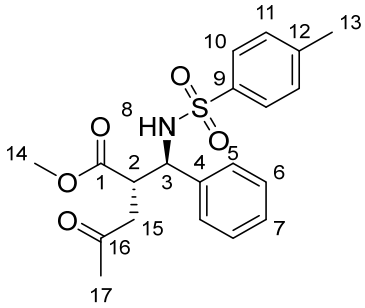
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.48 (d, *J* = 8.6 Hz, 2H, **H10**), 7.14 – 7.09 (m, 3H, **H6**, **H7**), 7.04 (d, *J* = 8.1 Hz, 2H, **H11**), 6.99 – 6.94 (m, 2H, **H5**), 6.04 (d, *J* = 9.3 Hz, 1H, **H8**), 5.71 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H, **H16**), 5.10 – 5.03 (m, 2H, **H17**), 4.63 (dd, *J* = 9.3, 5.6 Hz, 1H, **H3**), 3.52 (s, 3H, **H14**), 2.77 (dt, *J* = 8.5, 6.0 Hz, 1H, **H2**), 2.48 – 2.37 (m, 1H, **H15'**), 2.36 – 2.25 (m, 4H, **H13**, **H15''**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.01 (**C**, **C1**), 142.78 (**C**, **C12**), 138.87 (**C**, **C4**), 137.96 (**C**, **C9**), 133.93 (**CH**, **C16**), 129.10 (**CH**, **C11**), 128.35 (**CH**, **C6**), 127.42 (**CH**, **C7**), 126.88 (**CH**, **C10**), 126.30 (**CH**, **C5**), 117.99 (**CH_2**, **C17**), 58.28 (**CH**, **C3**), 51.83 (**CH_3**, **C14**), 51.75 (**CH**, **C2**), 34.38 (**CH_2**, **C15**), 21.35 (**CH_3**, **C13**) ppm.

LRMS (ES$^+$) *m/z* 374.3 $[M+H]^+$, 396.3 $[M+Na]^+$.

HRMS (ES$^+$) for $C_{20}H_{23}NNaO_4S^+$, calculated 396.1240 found 396.1245.

4.63: (+)-Methyl (*S*)-2-((*R*)-((4-methylphenyl)sulfonamido)(phenyl)methyl)-4-oxopentanoate



$C_{20}H_{23}NO_5S$

389.47 g mol^{-1}

Adapting the method of Grubbs and Stoltz,[219] a solution of alkene **4.62** (51 mg, 0.14 mmol) in ^{t}BuOH/$MeNO_2$ (15:1, 1.6 mL) was spared with O_2. Separately, a mixture of $Pd(PhCN)_2Cl_2$ (6 mg, 16 µmol), $CuCl_2$•$2H_2O$ (3 mg, 16 µmol) and $AgNO_2$ (3 mg, 21 µmol) was sparged with O_2, and then the solution of substrate was added, forming a brown suspension. This was stirred for 21 h, and the reaction quenched by the addition of H_2O (2 mL). The solution was diluted with CH_2Cl_2 (2 mL), the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, 4:6 EtOAc/pet. ether) afforded the title compound as a yellow oil (39 mg, 0.10 mmol, 73%).

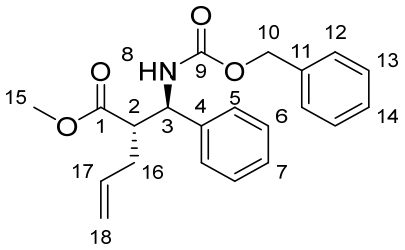
R_f 0.22 (EtOAc:hexane, 4:6)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.49 (d, *J* = 9.3 Hz, 2H, **H10**), 7.16 – 7.11 (m, 3H, **H6**, **H7**), 7.07 (d, *J* = 8.2 Hz, 2H, **H11**), 7.04 – 7.00 (m, 2H, **H5**), 5.99 (d, *J* = 9.4 Hz, 1H, **H8**), 4.59 (dd, *J* = 9.4, 5.0 Hz, 1H, **H3**), 3.53 (s, 3H, **H14**), 3.31 (td, *J* = 6.9, 5.1 Hz, 1H, **H2**), 2.89 (dd, *J* = 18.5, 7.2 Hz, 1H, **H15'**), 2.82 (dd, *J* = 18.5, 7.0 Hz, 1H, **H15''**), 2.31 (s, 3H, **H13**), 2.14 (s, 3H, **H17**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 205.60 (**C**, **C16**), 173.69 (**C**, **C1**), 143.01 (**C**, **C12**), 138.44 (**C**, **C4**), 137.55 (**C**, **C9**), 129.23 (**CH**, **C11**), 128.29 (**CH**, **C6**), 127.46 (**CH**, **C7**), 126.88 (**CH**, **C10**), 126.27 (**CH**, **C5**), 57.41 (**CH**, **C3**), 52.03 (**CH_3**, **C14**), 46.12 (**CH**, **C2**), 42.92 (**CH_2**, **C15**), 29.94 (**CH_3**, **C17**), 21.36 (**CH_3**, **C13**) ppm.

LRMS (ES^+) *m/z* 390.3 $[M+H]^+$, 412.3 $[M+Na]^+$.

4.60: (+)-Methyl (*S*)-2-((*R*)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)pent-4-enoate



$C_{21}H_{23}NO_4$

353.42 g mol^{-1}

To a solution of dry LiCl (3.92 g, 42.4 mmol) in anhydrous THF (132 mL) was added LDA (13.9 mL of a 2 M solution in THF, 27.8 mmol) was added, and the suspension cooled to –50 °C. A solution of carbamate **4.85** (2.90 g, 9.25 mmol) in anhydrous THF (46 mL) was added dropwise over 15 min. The orange solution was stirred for 1 h. A solution of allyl iodide (2.12 mL, 23.1 mmol) was added dropwise over 10 min, turning the solution yellow. The solution was stirred for a further 90 min at this temperature. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL) and warmed to RT. The phases were separated and the aqueous diluted with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. HPLC analysis of the crude productgave a d.r. of 95:5 (*anti*/*syn*). Purification by chromatography (silica, 3:17 EtOAc/pet. ether) afforded the title compound as a yellow oil (2.88 g, 8.15 mmol, 88%).

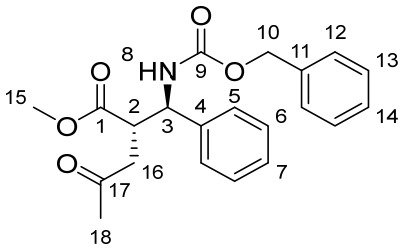
Alternatively, to a solution of ester **4.39** (1.25 g, 3.50 mmol) in 1,4-dioxane (18 mL) was added conc. HCl (0.90 mL, 10.5 mmol). The yellow solution was stirred for 4 h, and then concentrated *in vacuo* to leave an oily residue. The residue was dissolved in CH_2Cl_2 (20 mL) and concentrated *in vacuo* three times to leave a yellow solid, which was redissolved in THF/H_2O (20 mL, 1:1). K_2CO_3 (2.42 g, 17.5 mmol) was added in one portion, followed by benzyl chloroformate (0.75 mL, 5.25 mmol). The yellow solution was stirred for 2 h, then diluted with 10 mL EtOAc and the phases separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 1:4 EtOAc/pet. ether) afforded the title compound as a yellow oil (1.10 g, 3.10 mmol, 89%).

R_f 0.23 (EtOAc:hexane 2:8)

FT-IR (neat) ν_{max}: 3330 (br), 2980 (w), 1717 (s, br), 1497 (m), 1232 (s) cm^{-1}.

$[\alpha]^{23}_{D}$	+ 11.1 (*c* = 0.7, $CHCl_3$)
^{1}H NMR	(DMSO-d_6, 400 MHz) δ = 7.96 (d, *J* = 9.5 Hz, 1H, **H8**), 7.41 – 7.20 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.64 – 5.51 (m, 1H, **H17**), 5.05 – 4.85 (m, 4H, **H10**, **H18**), 4.74 (t, *J* = 9.9 Hz, 1H, **H3**), 3.56 (s, 3H, **H15**), 2.87 (td, *J* = 10.4, 4.2 Hz, 1H, **H2**), 2.12 – 2.01 (m, 1H, **H16'**), 1.84 – 1.74 (m, 1H, **H16''**) ppm.
^{13}C NMR	(DMSO-d_6, 101 MHz) δ = 173.04 (**C**, **C1**), 155.12 (**C**, **C9**), 140.55 (**C**, **C4**), 136.96 (**C**, **C11**), 134.61 (**CH**, **C17**), 128.34 (**CH**, **Ar**), 128.23 (**CH**, **Ar**), 127.70 (**CH**, **Ar**), 127.54 (**CH**, **C12**), 127.43 (**CH**, **Ar**), 127.25 (**CH**, **C5**), 116.91 (**CH_2**, **C18**), 65.26 (**CH_2**, **C10**), 56.57 (**CH**, **C3**), 51.27 (**CH_3**, **C15**), 50.69 (**CH**, **C2**), 33.78 (**CH_2**, **C16**) ppm.
^{1}H NMR (V_T, T = 353K)	(DMSO-d_6, 500 MHz) δ = 7.54 (br s, 1H, **H8**), 7.38 – 7.24 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.62 (dddd, *J* = 17.1, 10.2, 7.4, 6.5 Hz, 1H, **H17**), 5.06 – 4.88 (m, 4H, **H10**, **H18**), 4.80 (t, *J* = 9.4 Hz, 1H, **H3**), 3.57 (s, 3H, **H15**), 2.93 (td, *J* = 9.7, 4.6 Hz, 1H, **H2**), 2.13 (dddt, *J* = 14.4, 10.1, 7.7, 1.4 Hz, 1H, **H16'**), 1.93 (dddt, *J* = 14.3, 6.3, 4.7, 1.4 Hz, 1H, **H16''**) ppm.
^{13}C NMR (V_T, T = 353K)	(DMSO-d_6, 126 MHz) δ = 172.61 (**C**, **C1**), 154.76 (**C**, **C9**), 140.24 (**C**, **C4**), 136.72 (**C**, **C11**), 134.32 (**CH**, **C17**), 127.88 (**CH**, **Ar**), 127.80 (**CH**, **Ar**), 127.21 (**CH**, **Ar**), 127.00 (**CH**, **C12**), 126.95 (**CH**, **Ar**), 126.78 (**CH**, **C5**), 116.32 (**CH_2**, **C18**), 65.03 (**CH_2**, **C10**), 56.23 (**CH**, **C3**), 50.74 (**CH_3**, **C15**), 50.25 (**CH**, **C2**), 33.21 (**CH_2**, **C16**) ppm.
LRMS	(ES^+) *m/z* 354.3 $[M+H]^+$, 376.3 $[M+Na]^+$.
HRMS	(ES^+) for $C_{21}H_{23}NNaO_4^+$, calculated 376.1519 found 376.1523.

4.61: (+)-Methyl (*S*)-2-((*R*)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-4-oxopentanoate



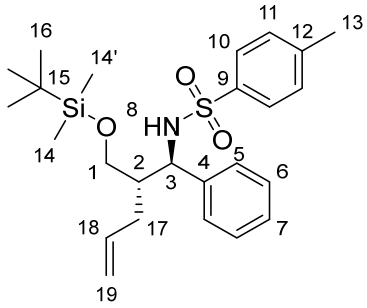
$C_{21}H_{23}NO_5$

369.42 g mol^{-1}

Adapting the method of Grubbs and Stoltz,[219] a solution of alkene **4.60** (50 mg, 0.14 mmol) in ^{t}BuOH/$MeNO_2$ (15:1, 2 mL) was spared with O_2. Separately, a mixture of $Pd(PhCN)_2Cl_2$ (5 mg, 14 µmol), $CuCl_2$•$2H_2O$ (3 mg, 14 µmol) and $AgNO_2$ (1 mg, 7 µmol) was sparged with O_2, and then the solution of substrate was added, forming a brown suspension. This was stirred for 21 h, and the reaction quenched by the addition of H_2O (2 mL). The solution was diluted with CH_2Cl_2 (2 mL), the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, 3:7 EtOAc/pet. ether) afforded the title compound as a yellow oil (34 mg, 92 µmol, 66%).

R_f	0.16 (EtOAc:hexane 3:7)
FT-IR	(neat) ν_{max}: 3350 (br), 2952 (w), 1716 (s, br), 1522 (m), 1238 (m) cm^{-1}.
$[\alpha]^{23}_D$	+44.3 ° (*c* = 0.7, $CHCl_3$)
^{1}H NMR	($CDCl_3$, 400 MHz) δ = 7.39 – 7.20 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.95 (d, *J* = 7.8 Hz, 1H, **H8**), 5.16 – 5.01 (m, 2H, **H10**), 4.98 – 4.89 (m, 1H, **H3**), 3.55 (s, 3H, **H15**), 3.41 – 3.33 (m, 1H, **H2**), 2.91 (dd, *J* = 18.3, 8.3 Hz, 1H, **H16'**), 2.63 (dd, *J* = 18.3, 5.6 Hz, 1H, **H16''**), 2.10 (s, 3H, **H18**) ppm.
^{13}C NMR	($CDCl_3$, 101 MHz) δ = 205.45 (**C**, **C17**), 173.79 (**C**, **C1**), 155.80 (**C**, **C9**), 139.85 (**C**, **C4**), 136.35 (**C**, **C11**), 128.66 (**Ar**), 128.48 (**Ar**),128.12 (**Ar**), 127.75 (**Ar**), 126.19 (**Ar**), 66.93 (**CH_2**, **C10**), 55.58 (**CH**, **C3**), 51.95 (**CH_3**, **C15**), 45.64 (**CH**, **C2**), 43.42 (**CH_2**, **C16**), 29.85 (**CH_3**, **C18**) ppm.
LRMS	(ES$^+$) *m/z* 370.4 [M+H]$^+$, 392.3 [M+Na]$^+$.
HRMS	(ES$^+$) for $C_{21}H_{23}NNaO_5^+$, calculated 392.1468 found 392.1471.

4.66: (*N*-((1*R*,2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-phenylpent-4-en-1-yl)-4-methylbenzenesulfonamide



$C_{25}H_{37}NO_3SSi$

459.72 g mol^{-1}

A solution of ester **4.62** (50 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (1 mL) was cooled to 0 °C. DIBAL-H (0.28 mL of a 1 M solution in CH_2Cl_2, 0.28 mmol) was added, and the solution stirred at this temperature for 1 h. A further portion of DIBAL-H (0.14 mL of a 1 M solution in CH_2Cl_2, 0.14 mmol) was added, and the solution stirred a further 1 h. The reaction was quenched by the slow addition of sat. Rochelle's salt (4 mL), warmed to RT and stirred for 2 h. The phases were separated and the aqueous extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude alcohol as a colourless oil.

The crude alcohol was redissolved in CH_2Cl_2 (1 mL). Imidazole (15 mg, 0.23 mmol) and TBS-Cl (27 mg, 0.17 mmol) were added sequentially, and the cloudy white solution stirred for 16 h. The reaction was quenched by the addition of H_2O (1 mL) and stirred for 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a colourless oil. Purification by chromatography (silica, 1:99 EtOAc/pet. ether) afforded the title compound as a colourless oil (28 mg, 60 µmol, 46%).

R_f 0.33 (EtOAc/hexane 1:99)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.5, (d, *J* = 8.3 Hz, 2H, **H10**), 7.19 – 7.13 (m, 3H, **H6**, **H7**), 7.12 – 7.07 (m, 4H, **H5**, **H11**), 6.7 (d, *J* = 6.9 Hz, 1H, **H8**), 5.70 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, **H18**), 5.06 – 4.96 (m, 2H, **H19**), 4.60 (dd, *J* = 6.7, 4.9 Hz, 1H, **H3**), 3.55 (dd, *J* = 11.0, 2.6 Hz, 1H, **H1'**), 3.44 (dd, *J* = 11.0, 3.8 Hz, 1H, **H1''**), 2.35 (s, 3H, **H13**), 2.20 – 2.13 (m, 2H, **H17**), 1.72 – 1.64 (m, 1H, **H2**), 0.99 (s, 9H, **H16**), 0.069 (s, 3H, **H14/H14'**), 0.065 (s, 3H, **H14/H14'**) ppm.

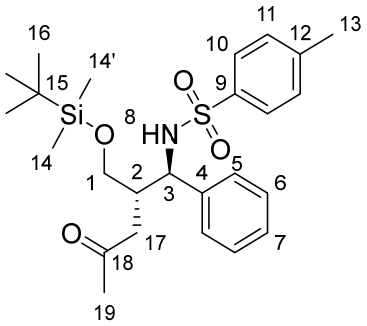
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 142.39 (**C**, **C12**), 140.62 (**C**, **C4**), 138.55 (**C**, **C9**), 135.86 (**CH**, **C18**) 129.06 (**CH**, **C11**), 128.02 (**CH**, **C6**), 128.82 (**CH**, **C7**, **C10**), 126.74 (**CH**, **C5**), 117.21 (**CH_2**, **C19**), 62.26 (**CH_2**, **C1**), 60.86 (**CH**,

C3), 45.29 (**CH**, **C4**), 33.36 (**CH_2**, **C17**), 25.82 (**CH_3**, **C16**), 21.37 (**CH_3**, **C13**), 18.00 (**C**, **C15**), –5.71 (**CH_3**, **C14/C14'**), –5.79 (**CH_3**, **C14/C14'**) ppm.

LRMS (ES^+) *m/z* 460.5 $[M+H]^+$, 482.5 $[M+Na]^+$.

HRMS (ES^+) for $C_{25}H_{38}NO_3SSi^+$, calculated 460.2336 found 460.2344.

4.67: *N*-((1*R*,2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-oxo-1-phenylpentyl)-4-methylbenzenesulfonamide



$C_{25}H_{37}NO_4SSi$

475.72 g mol^{-1}

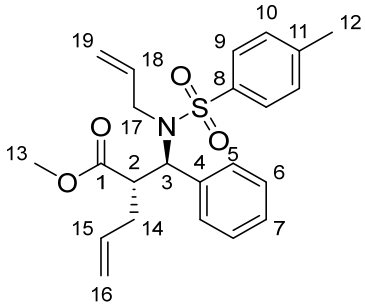
A solution of alkene **4.66** (28 mg, 61 µmol) in ^{t}BuOH/$MeNO_2$ (15:1, 1 mL) was sparged with O_2. Separately, a mixture of $Pd(PhCN)_2Cl_2$ (2 mg, 6 µmol), $CuCl_2$•$2H_2O$ (1 mg, 4 µmol) and $AgNO_2$ (1 mg, 4 µmol) was sparged with O_2, and then the solution of substrate was added, forming a brown suspension. The solution was stirred for 2 h, after which the reaction was quenched by the addition of H_2O (1 mL). The solution was diluted with CH_2Cl_2 (2 mL), the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a yellow oil (16 mg, 0.034 mmol, 55%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.52 (d, *J* = 8.3 Hz, 2H, **H10**), 7.20 – 7.13 (m, 3H, **H6**, **H7**), 7.12 – 7.07 (m, 4H, **H5**, **H11**), 6.59 (d, *J* = 7.8 Hz, 1H, **H8**), 4.61 (dd, *J* = 7.8, 4.3 Hz, 1H, **H3**), 3.53 (dd, *J* = 10.6, 2.5 Hz, 1H, **H1'**), 3.38 (dd, *J* = 10.5, 3.1 Hz, 1H, **H1'**), 2.67 (dd, *J* = 18.8, 6.5 Hz, 1H, **H17'**), 2.60 (dd, *J* = 18.5, 6.6 Hz, 1H, **H17''**), 2.37 – 2.29 (m, 4H, **H2**, **H13**), 2.09 (s, 3H, **H19**), 0.97 (s, 9H, **H16**), 0.039 (s, 3H, **H14/H14'**), 0.038 (s, 3H, **H14/H14'**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.24 (**C**, **C18**), 142.57 (**C**, **C12**), 139.95 (**C**, **C4**), 138.30 (**C**, **C9**), 129.18 (**CH**, **C11**), 128.08 (**CH**, **C6**), 126.93 (**CH**, **C7**), 126.80 (**CH**, **C10**), 126.53 (**CH**, **C5**), 62.84 (**CH_2**, **C1**), 60.17 (**CH**, **C3**), 42.61 (**CH_2**, **C17**), 40.07 (**CH**, **C2**), 30.42 (**CH_3**, **C19**), 25.81 (**CH_3**, **C16**), 21.35 (**CH_3**, **C13**), 17.98 (**C**, **C15**), –5.73 (**CH_3**, **C14/C14'**), –5.86 (**CH_3**, **C14/C14'**) ppm.

LRMS (ES^+) *m/z* 458.5 $[M–H_2O+H]^+$.

4.71: (+)-Methyl (*S*)-2-((*R*)-((*N*-allyl-4-methylphenyl)sulfonamido)(phenyl)methyl)pent-4-enoate



$C_{23}H_{27}NO_4S$

413.53 g mol^{-1}

To a solution of sulfinylamine **4.39** (800 mg, 2.24 mmol) in MeCN (10 mL) and H_2O (0.4 mL) was added iodosylbenzene (986 mg, 4.48 mmol). The yellow suspension was stirred for 48 h, then filtered and concentrated *in vacuo* to yield the crude tosylate as a yellow oil. The crude tosylate was redissolved in MeCN (10 mL). K_2CO_3 (3.10 g, 22.4 mmol) and allyl bromide (1.94 mL, 22.4 mmol) were added sequentially, and the yellow suspension stirred for 48 h. The reaction was quenched by the addition of H_2O (10 mL), diluted with EtOAc (20 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 1:9-2:8 EtOAc/hexane) afforded the title compound as a colourless oil (749 mg, 2.01 mmol, 90%).

R_f 0.74 (EtOAc/hexane 4:6).

FT-IR (neat) ν_{max}: 2981 (w), 1735 (s), 1496 (w), 1436 (w), 1334 (m), 1155 (s), 1089 (m) cm^{-1}

$[\alpha]^{23}_D$ +45.1 ° (*c* = 1.05, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.50 (d, *J* = 9.6 Hz, 2H, **H9**), 7.36 – 7.29 (m, 5H, **H5**, **H6**, **H7**), 7.15 (d, *J* = 8.0 Hz, 2H, **H10**), 5.68 (dddd, *J* = 16.8, 10.4, 7.8, 6.1 Hz, 1H, **H15**), 5.49 (dddd, *J* = 17.2, 10.1, 7.0, 6.0 Hz, 1H, **H18**), 5.22 (d, *J* = 11.8 Hz, 1H, **H3**), 5.13 – 4.89 (m, 4H, **H16**, **H19**), 3.83 – 3.65 (m, 5H, **H17**, **H13**), 3.57 (ddd, *J* = 11.6, 10.9, 3.4 Hz, 1H, **H2**), 2.37 (s, 3H, **H12**), 2.25 – 2.14 (m, 1H, **H14'**), 2.06 – 1.97 (m, 1H, **H14''**) ppm.

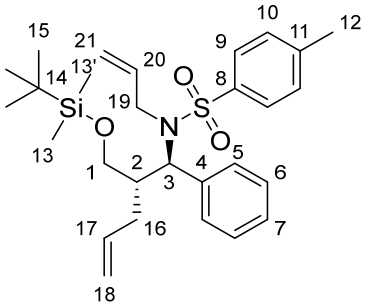
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 173.49 (**C**, **C1**), 142.99 (**C**, **C11**), 137.94 (**C**, **C8**), 135.68 (**C**, **C4**), 135.13 (**CH**, **C18**), 134.16 (**CH**, **C15**), 129.30 (**CH**, **C6**), 129.11 (**CH**, **C10**), 128.59 (**CH**, **C5**), 128.39 (**CH**, **C7**), 127.78 (**CH**, **C9**), 117.64 (**CH_2**, **C19**), 117.14 (**CH_2**, **C16**), 63.22 (**CH**, **C3**), 51.70 (**CH_3**,

C13), 48.74 (**CH_2**, **C17**), 48.29 (**CH**, **C2**), 34.85 (**CH_2**, **C14**), 21.40 (**CH_3**, **C12**) ppm.

LRMS (ES^+) *m/z* 414.4 $[M+H]^+$, 436.3 $[M+Na]^+$.

HRMS (ES^+) for $C_{23}H_{27}NNaO_4S^+$, calculated 436.1553 found 436.1554.

4.72: (+)-*N*-Allyl-*N*-((1*R*,2*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-phenylpent-4-en-1-yl)-4-methylbenzenesulfonamide



$C_{28}H_{41}NO_3SSi$

499.79 g mol^{-1}

A solution of ester **4.71** (614 mg, 1.48 mmol) in anhydrous THF (15 mL) was cooled to –78 °C. A solution of $LiAlH_4$ (2.96 mL of a 1 M solution in THF, 2.96 mmol) was added dropwise, and the colourless solution stirred for 2 h. The solution was warmed to 0 °C and stirred for a further 2.5 h. The reaction was quenched at this temperature with MeOH until effervescence ceased (approx.. 1 mL), and then sat. Rochelle's salt (15 mL) added, and the suspension stirred for 2 h, until both phases became clear. The phases were separated and the aqueous phase extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude alcohol as a colourless oil.

The crude alcohol was dissolved in anhydrous CH_2Cl_2 (15 mL). Imidazole (302 mg, 4.44 mmol) and TBS-Cl (335 mg, 2.22 mmol) was added, and the white suspension stirred at RT for 22 h. The reaction was quenched by the addition of H_2O (10 mL), and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a colourless oil. Purification by chromatography (1:9 EtOAc/pet. ether) afforded the title compound as a colourless oil (718 mg, 1.35 mmol, 91%).

R_f 0.66 (EtOAc/hexane 4:6).

FT-IR (neat) ν_{max}: 3075 (w), 2928 (m), 1599 (w), 1337 (m), 1161 (s), 1090 (s) cm^{-1}

$[\alpha]^{23}_D$ +72.0 ° (*c* = 0.54, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44 (d, *J* = 8.3 Hz, 2H, **H10**), 7.28 – 7.25 (m, 5H, **H5**, **H6**, **H7**), 7.17 (d, *J* = 8.0 Hz, 2H, **H9**), 5.71 (dddd, *J* = 16.9, 10.2, 8.0, 6.4 Hz, 1H, **H17**), 5.56 (dddd, *J* = 17.0, 10.2, 8.1, 5.3 Hz, 1H, **H20**), 5.13 (dd, *J* = 17.2, 1.4 Hz, 1H, **H21'**), 5.04 (dd, *J* = 10.0, 1.1 Hz, 1H, **H21''**) 4.97 (dt, *J* = 10.2, 1.0 Hz, 1H, **H18'**), 4.80 (ddt, *J* = 17.0, 2.2, 1.3 Hz, 1H, **H18''**), 4.78 (d, *J* = 12.0 Hz, 1H, **H3**), 3.89 (ddt, *J* = 16.3, 5.1, 1.6 Hz, 1H, **H1'**), 3.81 – 3.70 (m, 3H, **H1''**, **H19**), 2.65 – 2.56 (m,

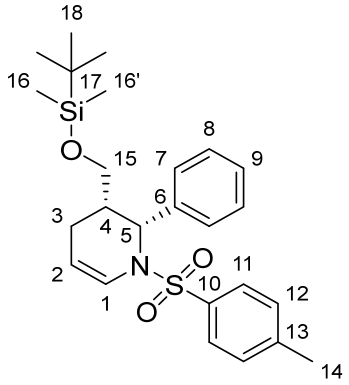
1H, **H2**), 2.37 (s, 3H, **H12**), 2.13 (dddd, *J* = 14.1, 4.8, 3.3, 1.7 Hz, 1H, **H16'**), 1.93 – 1.83 (m, 1H, **H16''**), 0.94 (s, 9H, **H15**), 0.10 (s, 3H, **H13/H13'**), 0.07 (s, 3H, **H13/H13'**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 142.75 (**C**, **C11**), 138.38 (**C**, **C8**), 136.96 (**C**, **C4**), 135.41 (**CH**, **C20**), 134.94 (**CH**, **C17**), 129.61 (**CH**, **C5**), 129.21 (**CH**, **C9**), 128.24 (**CH**, **C6**), 127.83 (**CH**, **C7**), 127.36 (**CH**, **C10**), 117.63 (**CH_2**, **C21**), 117.04 (**CH_2**, **C18**), 62.44 (**CH**, **C3**), 61.42 (**CH_2**, **C19**), 48.51 (**CH_2**, **C1**), 40.94 (**CH**, **C2**), 32.01 (**CH_2**, **C16**), 25.98 (**CH_3**, **C15**), 21.40 (**CH_3**, **C12**), 18.26 (**C**, **C14**), –5.34 (**CH_3**, **C13/C13'**), –5.46 (**CH_3**, **C13/C13'**) ppm.

LRMS (ES^+) *m/z* 500.5 $[M+H]^+$, 522.5 $[M+Na]^+$.

HRMS (ES^+) for $C_{28}H_{42}NO_3SSi^+$, calculated 500.2649 found 500.2658.

4.74: (2*R*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine



$C_{25}H_{35}NO_3SSi$

457.70 g mol^{-1}

A solution of alkene **4.73** (100 mg, 0.20 mmol) in ^{t}BuOH/$MeNO_2$ (2 mL, 15:1) was sparged with O_2. Separately, a mixture of $Pd(PhCN)_2Cl_2$ (13 mg, 30 µmol), $CuCl_2$•$2H_2O$ (6 mg, 30 µmol) and $AgNO_2$ (3 mg, 20 µmol) was sparged with O_2, and then the solution of substrate added, forming a brown suspension. The suspension was stirred under an O_2 atmosphere for 16 h. The reaction was diluted with CH_2Cl_2 (3 mL) and then absorbed onto silica. Purification by chromatography afforded an inseparable mixture of dialdehyde and ketone (70 mg, 0.13 mmol, 65%) which was used directly in the next step.

The mixture of isomers (35 mg, 0.07 mmol) were redissolved in anhydrous DMF (2 mL). DMAP (10 mg, 80 µmol) was added, and the solution heated to 160 °C and stirred for 16 h. The reaction was cooled to RT and diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were washed with H_2O (3 x 5 mL), brine (3 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a colourless oil. Purification by chromatography (silica, 1:9 EtOAc/hexane) afforded the title compound as a colourless oil (11 mg, 24 µmol, 22% over two steps).

R_f 0.65 (EtOAc/hexane 4:6).

FT-IR (neat) ν_{max}: 2953 (w), 1647 (w), 1348 (m), 1256 (w), 1168 (s), 1091 (m) cm^{-1}

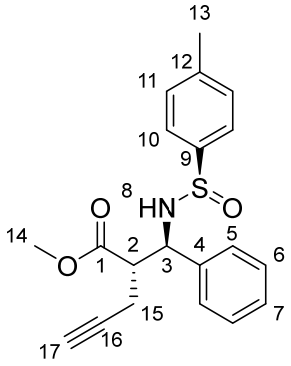
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56 (d, *J* = 8.5 Hz, 2H, **H11**), 7.23 – 7.15 (m, 7H, **H7**, **H8**, **H9**, **H12**), 6.98 (dt, *J* = 8.3, 1.1 Hz, 1H, **H1**), 5.24 (d, *J* = 4.4 Hz, 1H, **H5(ax)**), 5.07 (ddd, *J* = 8.1, 5.9, 2.0 Hz, 1H, **H2**), 3.28 (dd, *J* = 10.3, 5.0 Hz, 1H, **H15'**), 2.96 (t, *J* = 10.1 Hz, 1H, **H15''**), 2.38 (s, 3H, **H14**), 1.81 – 1.68 (m, 2H, **H3(eq)**, **H4(eq)**), 1.54 – 1.42 (ddt, *J* = 18.3, 13.2, 2 Hz, 1H, **H3(ax)**), 0.92 (s, 9H, **H18**), 0.00 (s, 3H, **H16/H16'**), –0.04 (s, 3H, **H16/H16'**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 143.13 (**C**, **C13**), 137.61 (**C**, **C6**), 136.31 (**C**, **C10**), 129.44 (**CH**, **C12**), 127.92 (**CH**, **C8**), 127.75 (**CH**, **C7**), 127.30 (**CH**, **C9**), 126.89 (**CH**, **C11**), 125.87 (**CH**, **C1**), 106.08 (**CH**, **C2**), 63.09 (**CH_2**, **C15**), 57.44 (**CH**, **C5**), 38.84 (**CH**, **C4**), 25.84 (**CH_3**, **C18**), 21.47 (**CH_3**, **C14**), 20.07 (**CH_2**, **C3**), 18.09 (**C**, **C17**), –5.53 (**CH_3**, **C16/C16'**), –5.57 (**CH_3**, **C16/C16'**) ppm.

LRMS (ES^+) *m/z* 458.5 $[M+H]^+$, 480.5 $[M+Na]^+$.

HRMS (ES^+) for $C_{25}H_{36}NO_3SSi^+$, calculated 458.2180 found 458.2187.

4.84: (+)-Methyl (*S*)-2-((*R*)-phenyl(((*R*)-*p*-tolylsulfinyl)amino)methyl)pent-4-ynoate



$C_{20}H_{21}NO_3S$

355.455 g mol^{-1}

A solution of LDA (0.26 mL, 1.86 M in THF, 0.48 mmol) was cooled to −50 °C. A solution of ester **4.26a** (60 mg, 0.19 mmol) in anhydrous THF (1 mL) was added, and the orange solution stirred at this temperature for 1 h. Propargyl bromide (50 µL of an 80% solution in PhMe, 0.48 mmol) in THF (2 mL) was added dropwise, and the solution stirred for 2 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL) and warmed to RT. The phases were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil (integration of the NH peak in the NMR of the crude product gives *d.r*. 93:7). Purification by chromatography (silica, 5:95 – 10:90 EtOAc / CH_2Cl_2) afforded the title compound as a yellow solid (45 mg, 0.13 mmol, 68%).

R_f 0.11 (EtOAc/hexane 2:8).

FT-IR (neat) ν_{max}: 3264 (w), 3195 (w), 2913 (w), 2113 (w), 1725 (s), 1600 (w), 1435 (m), 1046 (s) cm^{-1}

$[\alpha]^{23}_D$ +90.8 (*c* = 0.55, $CHCl_3$)

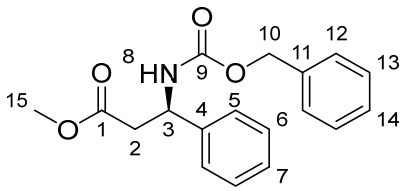
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56 (d, *J* = 8.1 Hz. 2H, **H10**), 7.42 – 7.29 (m, 7H, **H5**, **H6**, **H7**, **H11**), 5.26 (d, *J* = 6.4 Hz, 1H, **H8**), 4.78 (t, *J* = 6.4 Hz, 1H, **H3**), 3.65 (s, 3H, **H14**), 2.98 (q, *J* = 6.9 Hz, 1H, **H2**), 2.45 – 2.40 (m, 5H, **H13**, **H15**), 2.02 (t, *J* = 2.7 Hz, 1H, **H17**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.72 (**C**, **C1**), 142.22 (**C**, **C9**), 141.40 (**C**, **C12**), 139.47 (**C**, **C4**), 129.57 (**CH**, **C11**), 128.78 (**CH**, **C6**), 128.21 (**CH**, **C7**), 127.36 (**CH**, **C5**), 125.44 (**CH**, **C10**), 80.16 (**C**, **C16**), 70.98 (**CH**, **C17**), 58.80 (**CH**, **C3**), 52.17 (**CH_3**, **C14**), 51.04 (**CH**, **C2**), 21.36 (**CH_3**, **C13**), 19.56 (**CH_2**, **C15**) ppm.

LRMS (ES$^+$) *m/z* 356.2 $[M+H]^+$, 378.2 $[M+Na]^+$.

HRMS (ES$^+$) for $C_{20}H_{22}NO_3S^+$, calculated 356.1315 found 356.1307.

4.85: (+)-Methyl (*R*)-3-(((benzyloxy)carbonyl)amino)-3-phenylpropanoate



$C_{18}H_{19}NO_4$

313.35 g mol^{-1}

To a solution of sulfinylamine **4.26a** (500 mg, 1.58 mmol) in 1,4-dioxane (8 mL) was added conc. HCl (0.5 mL, 4.74 mmol). The yellow solution was stirred for 3 h. The solution was concentrated *in vacuo* to afford a solid yellow residue. The residue was dissolved in CH_2Cl_2 (10 mL) and concentrated *in vacuo*. This was repeated three times. To the yellow residue was added THF/H_2O (8 mL, 1:1). K_2CO_3 (1.09 g, 7.90 mmol) and Cbz-Cl (0.34 mL, 2.37 mmol). The yellow suspension was stirred for 1 h. The suspension was diluted with EtOAc (10 mL), and the phases separated. The aqueous phase was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a yellow oil. Purification by chromatography (silica, 3:7 EtOAc/hexane) afforded the title compound as a colourless oil, which solidified on standing to a white solid (455 mg, 1.45 mmol, 92%).

R_f 0.11 (EtOAc/hexane 2:8).

MP 57.1 – 58.5 °C

FT-IR (neat) ν_{max}: 3310 (br), 2953 (w), 1726 (s), 1689 (s), 1548 (s), 1250 (s) cm^{-1}

$[\alpha]^{23}_D$ +17.3 (*c* = 0.55, $CHCl_3$)

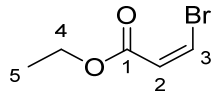
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.93 (d, *J* = 8.6 Hz, 1H, **H8**), 7.38 – 7.20 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.06 – 4.93 (m, 3H, **H3**, **H10**), 3.55 (s, **H15**), 2.80 (dd, *J* = 15.6, 9.3 Hz, 1H, **H2'**), 2.72 (d, *J* = 15.4, 6.8 Hz, 1H, **H2''**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz) δ = 170.53 (**C**, **C1**), 155.27 (**C**, **C9**), 142.38 (**C**, **C4**), 136.98 (**C**, **C11**), 128.29 (**CH**, **Ar**), 128.26 (**CH**, **Ar**), 127.73 (**CH**, **Ar**), 127.63 (**CH**, **Ar**), 127.09 (**CH**, **Ar**), 126.25 (**CH**, **Ar**), 65.28 (**CH_2**, **C10**), 51.55 (**CH**, **C3**), 51.33 (**CH_3**, **C15**), 40.76 (**CH_2**, **C2**) ppm.

LRMS (ES$^+$) *m/z* 314.3 $[M+H]^+$, 336.3 $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[300]

4.91: Ethyl (*Z*)-3-bromoacrylate



$C_5H_7BrO_2$

179.01 g mol^{-1}

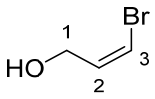
Following the procedure of Lu,[301] to a solution of ethyl propiolate (5.17 mL, 51.0 mmol) in MeCN (50 mL) was added LiBr (5.53 g, 63.7 mmol) and AcOH (3.65 mL, 63.7 mmol). The white suspension was heated to 80 °C and stirred for 16 h. The mixture was cooled to RT and quenched by the addition of H_2O (50 mL). K_2CO_3 was added until effervescence ceased. The phases were separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a yellow oil (8.49 g, 47.4 mmol, 93%). The compound was used without further purification.

R_f 0.81 (EtOAc/hexane 2:8).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.98 (d, *J* = 8.3 Hz, 1H, **H3**), 6.61 (d, *J* = 8.3 Hz, 1H, **H2**), 4.24 (q, *J* = 7.1 Hz, 2H, **H4**), 1.31 (t, *J* = 7.1 Hz, 3H, **H5**) ppm.

Spectroscopic data was consistent with reported values.[301]

4.92: (*Z*)-3-bromoprop-2-en-1-ol



C_3H_5BrO

136.98 g mol^{-1}

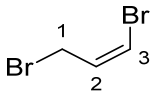
Following the procedure of Taylor,[302] a solution of ester **4.91** (3.00 g, 16.8 mmol) in anhydrous THF (40 mL) was cooled to 0 °C. $LiAlH_4$ (11.1 mL, 1 M in THF, 11.1 mL) was added dropwise at this temperature. The yellow solution was stirred for 1 h and quenched by the addition of H_2O (0.5 mL), 2 M NaOH (1.5 mL) and H_2O (3 mL). The mixture was stirred vigorously for 30 min. The white solids were filtered, and the filtrate washed with sat. $NaHCO_{3(aq)}$ (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a colourless oil (1.38 g, 10.1 mmol, 60%). The compound was used without further purification.

R_f 0.44 (EtOAc/hexane 2:8).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.37 (dt, *J* = 7.3, 6.0 Hz, 1H, **H2**), 6.28 (dt, *J* = 7.3, 1.6 Hz, 1H, **H3**), 4.33 (dd, *J* = 6.0, 1.6 Hz, 2H, **H1**) ppm.

Spectroscopic data was consistent with reported values.[302]

4.78: (*Z*)-1,3-dibromoprop-1-ene



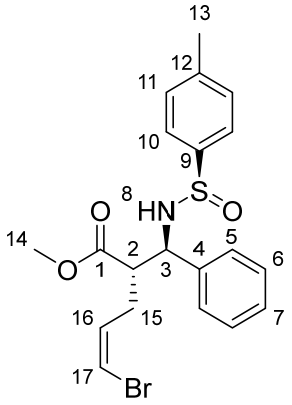
$C_3H_4Br_2$

199.87 g mol^{-1}

A solution of alcohol **4.92** (760 mg, 5.55 mmol) in anhydrous CH_2Cl_2 (15 mL) was cooled to −20 °C. PBr_3 (0.78 mL, 8.33 mmol) was added dropwise, and the brown mixture stirred at this temperature for 2 h. The reaction was quenched by the addition of sat. $NaHCO_3$ (10 ml) and warmed to RT. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil. Purification by short-path distillation (30 mBar, 70 °C) afforded the title compound as a colourless oil (108 mg, 0.54 mmol, 10%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.43 (q, *J* = 7.4 Hz, 1H, **H2**), 6.39 (d, *J* = 7.4 Hz, 1H, **H3**), 4.08 (d, *J* = 7.4 Hz, 2H, **H1**) ppm.

4.84: Methyl (*S*,*Z*)-5-bromo-2-((*R*)-phenyl(((*R*)-p-tolylsulfinyl)amino)methyl)pent-4-enoate



$C_{20}H_{22}BrNO_3S$

436.36 g mol^{-1}

A solution of LDA (0.26 mL, 1.86 M, 0.48 mmol) was cooled to −50 °C. A solution of ester **4.26a** (50 mg, 0.16 mmol) in anhydrous THF (1 mL) was added, and the orange solution stirred for 1 h. A solution of bromide **4.78** (80 mg, 0.40 mmol) in anhydrous THF (2 mL) was added dropwise at this temperature, and the solution stirred for 3 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL) and warmed to RT. The phases were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil. Purification by chromatography (silica, 1:9 EtOAc / CH_2Cl_2) afforded the title compound as a yellow oil (12 mg, 30 µmol, 19%, 83:17 *dr*).

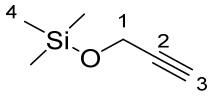
R_f 0.33 (EtOAc/CH_2Cl_2 1:9).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56 (d, *J* = 8.4 Hz, 2H, **H10**), 7.43 – 7.29 (m, 7H, **H5**, **H6**, **H7**, **H11**), 6.21 (dt, *J* = 7.1, 1.3 Hz, 1H, **H17**), 6.02 (q, *J* = 7.1 Hz, 1H, **H16**), 5.11 (d, *J* = 6.2 Hz, 1H, **H8**), 4.63 (t, *J* = 6.8 Hz, 1H, **H3**). 3.62 (s, 3H, **H14**), 2.91 (ddd, *J* = 9.2, 7.3, 5.3 Hz,1H, **H2**), 2.54 – 2.44 (m, 1H, **H15'**), 2.42 (s, 3H, **H13**), 2.28 (dddd, *J* = 14.7, 6.9, 5.4, 1.5 Hz, 1H, **H15''**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 173.38 (**C**, **C1**), 142.09 (**C**, **C9**), 141.42 (**C**, **C12**), 139.65 (**C**, **C4**), 130.51 (**CH**, **C16**), 129.56 (**CH**, **C11**), 128.78 (**CH**, **C6**), 128.19 (**CH**, **C7**), 127.42 (**CH**, **C5**), 125.48 (**CH**, **C10**), 110.45 (**CH**, **C17**), 59.30 (**CH**, **C3**), 52.06 (**CH_3**, **C14**), 51.06 (**CH**, **C2**), 30.02 (**CH_2**, **C15**), 21.36 (**CH_3**, **C13**) ppm.

LRMS (ES$^+$) *m/z* 436.1 [M^{79}Br+H]$^+$, 438.2 [M^{81}Br+H]$^+$.

4.94: Trimethyl(prop-2-yn-1-yloxy)silane



$C_6H_{12}OSi$

128.25 g mol^{-1}

To a solution of propargyl alcohol (5.83 mL, 100 mmol) and HMDS (10.5 mL, 50.0 mmol) was added TMS-Cl (0.63 mL, 5.00 mmol). The yellow solution was heated to 50 °C and stirred for 16 h. Purification by short-path distillation (60 °C at 30 mBar) afforded the title compound as a colourless oil (11.7 g, 91.1 mmol, 91%).

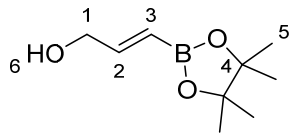
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.29 (d, *J* = 2.4 Hz, 2H, **H1**), 2.40 (t, *J* = 2.4 Hz, 1H, **H3**), 0.18 (s, 9H, **H4**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 82.18 (**C**, **C2**), 73.01 (**CH**, **C3**), 50.80 (**CH_2**, **C1**), –0.40 (**CH_3**, **C4**) ppm.

LRMS (ES^+) *m/z* $[M+H]^+$, $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[303]

4.95: (*E*)-3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol



$C_9H_{17}BO_3$

184.04 g mol^{-1}

A solution of Cp_2ZrCl_2 (1.14 g, 3.90 mmol) in anhydrous THF (20 mL) was cooled to 0 °C. DIBAL-H (3.90 mL, 1 M in THF, 3.90 mmol) was added dropwise, and the solution stirred at this temperature for 1 h. A solution of alkyne **4.94** (5.00 g, 39.0 mmol), Et_3N (0.54 mL, 3.90 mmol) and pinacolborane (5.94 mL, 40.9 mmol) in anhydrous THF (30 mL) was added dropwise at this temperature. The solution was warmed to RT and stirred for 22 h. The reaction was quenched with 2 M HCl (20 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a pale yellow oil. Purification by chromatography (silica, 20:80 – 30:70 EtOAc/pet. ether) afforded the title compound as a colourless oil (4.88 g, 26.5 mmol, 68%).

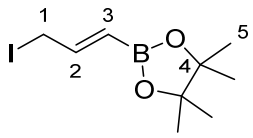
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.74 (dt, *J* = 18.2, 4.2 Hz, 1H, **H2**), 5.7 (dt, *J* = 18.2, 1.9 Hz, 1H, **H3**), 4.23 (br s, 2H, **H1**), 1.69 (br s, 1H, **H6**), 1.27 (s, 12H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 151.72 (**CH**, **C2**), 116.78 (**CH**, **C3**), 83.29 (**C**, **C4**), 64.50 (**CH_2**, **C1**), 24.72 (**CH_3**, **C5**) ppm.
(***C3*** *not observed by 1D data, assigned by HSQC*).

LRMS (ES$^+$) *m/z* 184.2 [M^{10}B+H]$^+$, 185.2 [M^{11}B+H]$^+$.

Physical and spectroscopic data are consistent with reported values.[304]

4.83: (*E*)-2-(3-Iodoprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



$C_9H_{16}BIO_2$

293.94 g mol^{-1}

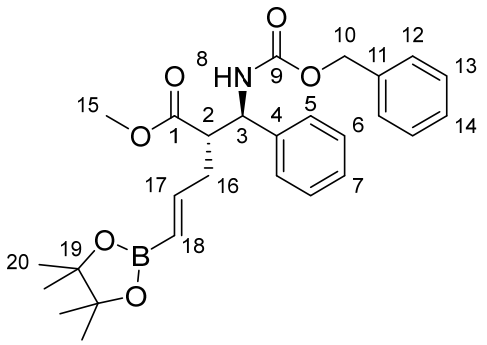
A solution of alcohol **4.95** (400 mg, 2.17 mmol) in CH_2Cl_2 (11 mL) was cooled to 0 °C. Imidazole (177 mg, 2.60 mmol), PPh_3 (682 mg, 2.60 mmol) and I_2 (660 mg, 2.60 mmol) were added sequentially, and the reaction excluded from light. The orange suspension was warmed to RT and stirred for 3 h. The reaction was diluted with pentane (10 mL) and filtered through Celite®. The filter cake was further washed with pentane (3 x 10 mL) and the filtrate concentrated *in vacuo* to yield the crude product as a white solid residue. Purification by chromatography (silica, 1:9 EtOAc / pet. ether.) afforded the title compound as a yellow oil (315 mg, 1.07 mmol, 49%). The compound was stored in darkness at 4 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.71 (dt, *J* = 17.5, 7.7 Hz, 1H, **H2**), 5.58 (dt, *J* = 17.5, 1.0 Hz, 1H, **H3**), 3.91 (dd, *J* = 7.7, 1.0 Hz, 2H, **H1**), 1.27 (s, 12H, **H5**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 148.31 (**CH**, **C2**), 83.29 (**C**, **C4**), 64.50 (**CH_2**, **C1**), 24.72 (**CH_3**, **C5**) ppm.
(***C3** not observed*).

Physical and spectroscopic data are consistent with reported values.[305]

4.89: Methyl (*S*,*E*)-2-((*R*)-phenyl(((*R*)-p-tolylsulfinyl)amino)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enoate



$C_{26}H_{34}BNO_5S$

483.43 g mol^{-1}

A solution of LDA (1.82 mL of a 1.80 M solution n THF, 3.27 mL) was cooled to −50 °C. A solution of ester **4.85** (340 mg, 1.09 mmol) in anhydrous THF (5 mL) was added dropwise at this temperature, and the orange solution stirred for 1 h. A solution of iodide **4.83** (802 mg, 2.73 mmol) in anhydrous THF (10 mL) was added dropwise at this temperature over 5 min. The orange solution was stirred for 2 h, then quenched by the addition of sat. $NH_4Cl_{(aq)}$ (10 mL). The mixture was warmed to RT. The phases were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, prewashed with Et_3N (1% in eluent), 15:85 – 25:75 EtOAc/hexane) afforded the title compound admixed with an unknown impurity (374 mg, 0.78 mmol, 72%)

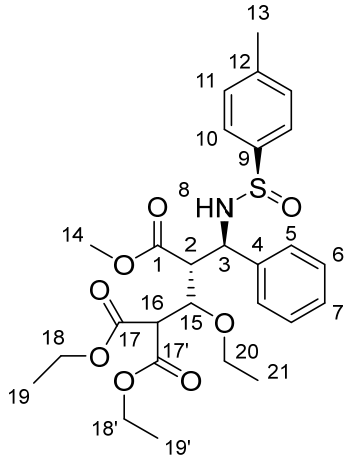
R_f 0.34 (EtOAc/hexane 2:8).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44 – 7.15 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 6.52 (dt, *J* = 17.9, 6.5 Hz, 1H, **H17**), 6.18 (d, *J* = 8.5 Hz, 1H, **H8**), 5.49 (dt, *J* = 17.9, 1.4 Hz, 1H, **H18**), 5.16 – 4.92 (, 3H, **H3**, **H10**), 3.51 (s, 3H, **H15**), 3.02 – 2.91 (m, 1H, **H2**), 2.64 – 2.37 (m, 2H, **H16**), 1.26 (s, 12H, **H20**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.09 (**C**, **C1**), 155.82 (**C**, **C9**), 148.87 (**CH**, **C17**), 140.40 (**C**, **C4**), 136.44 (**C**, **C11**), 128.59 (**CH**, **ArCH**), 128.46 (**CH**, **ArCH**), 128.08 (**CH**, **C12**), 127.58 (**CH**, **ArCH**), 126.70 (**CH**, **ArCH**), 126.11 (**CH**, **ArCH**), 83.18 (**C**, **C19**), 66.84 (**CH_2**, **C10**), 55.83 (**CH**, **C3**), 51.67 (**CH_3**, **C15**), 50.20 (**CH**, **C2**), 36.27 (**CH_2**, **C16**), 24.71 (**CH_3**, **C20**) ppm.

LRMS (ES$^+$) *m/z* 479.5 [M^{10}B+H]$^+$, 481.5 [M^{11}B+H]$^+$.

4.87: 1,1-Diethyl 3-methyl (2*R*,3*R*,4*R*)-2-ethoxy-4-phenyl-4-(((*R*)-p-tolylsulfinyl)amino)butane-1,1,3-tricarboxylate



$C_{27}H_{35}NO_8S$

533.64 g mol^{-1}

A solution of LDA (0.52 mL, 1.86 M in THF, 0.96 mmol) was cooled to −50 °C. A solution of ester **4.26a** (100 mg, 0.32 mmol) in anhydrous THF (2 mL) was added dropwise at this temperature, and the orange solution stirred for 1 h. A solution of diethyl ethoxymethylenemalonate (0.16 mL, 0.80 mmol) in anhydrous THF (4 mL) was added dropwise, and the solution stirred at this temperature for 2.5 h. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$ (6 mL) and warmed to RT. The phases were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a brown oil. Purification by chromatography (silica, 1:9 EtOAc/CH_2Cl_2) afforded the title compound as a yellow oil (32 mg, 60 µmol, 19%).

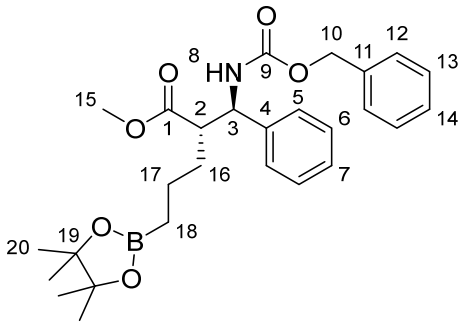
R_f 0.34 (EtOAc/CH_2Cl_2 1:9).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.59 (d, *J* = 8.2 Hz, 2H, **H10**), 7.39 – 7.26 (m, 7H, **H5**, **H6**, **H7**, **H11**), 5.62 (d, *J* = 6.8 Hz, 1H, **H8**), 5.12 (dd, *J* = 6.8, 4.1 Hz, 1H, **H3**), 4.44 (dd, *J* = 7.6, 5.4 Hz, 1H, **H15**), 4.30 – 4.07 (m, 4H, **H18**, **H18'**), 3.69 – 3.61 (m, 2H, **H20**), 3.57 – 3.51 (m, 4H, **H14**, **H16**), 3.38 (dd, *J* = 7.6, 4.1 Hz, 1H, **H2**), 2.42 (s, 3H, **H13**), 1.27 (2 x t, *J* = 7.1 Hz, 6H, **H19** or **H19'**), 1.08 (t, *J* = 7.0 Hz, 3H, **H21**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.99 (**C**, **C1**), 167.46 (**C**, **C17** or **C17'**), 166.81 (**C**, **C17** or **C17'**), 142.99 (**C**, **C9**), 141.21 (**C**, **C12**), 140.62 (**C**, **C4**), 129.49 (**CH**, **C11**), 128.42 (**CH**, **C6**), 127.69 (**CH**, **C7**), 127.09 (**CH**, **C5**), 125.31 (**CH**, **C10**), 75.97 (**CH**, **C15**), 67.63 (**CH_2**, **C20**), 61.56 (**CH_2**, **C18** or **C18'**), 61.46 (**CH_2**, **C18** or **C18'**), 58.92 (**CH**, **C3**), 55.39 (**CH**, **C3**), 55.34 (**CH_3**,

C14),. 51.76 (**CH**, **C16**), 21.31 (**CH_3**, **C13**), 15.37 (**CH_3**, **C21**), 14.03 (**CH_3**, **C19** or **C19'**), 13.97 (**CH_3**, **C19** or **C19'**) ppm.

4.102: (+)-Methyl (*S*)-2-((*R*)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate



$C_{27}H_{36}BNO_6$

481.40 g mol^{-1}

To a solution of alkene **4.60** (52 mg, 0.15 mmol) in anhydrous THF (1 mL) was added Wilkinson's catalyst (7 mg, 7.5 µmol), followed by pinacolborane (40 µL, 0.30 mmol). The purple solution was stirred for 48 h, and the reaction was quenched by the addition of H_2O (0.1 mL) and MeOH (3 mL). The solution was absorbed onto silica. Purification by chromatography (silica, 2:8 EtOAc/pet. ether) afforded the title compound as a colourless oil (23 mg, 50 µmol, 33%).

Alternatively, adapting the procedure of Miyaura,[243] to a solution of alkene **4.60** (1.00 g, 2.83 mmol) in anhydrous CH_2Cl_2 (15 mL) was added $[Ir(COD)Cl]_2$ (19 mg, 30 µmol) and dppe (25 mg, 60 µmol), forming a purple coloured solution. Pinacolborane (0.57 mL, 3.96 mmol) was then added, and the solution stirred for 24 h. The reaction was quenched by the dropwise addition of MeOH (4 mL), causing a slight effervescence. The solution was absorbed onto silica. Purification by chromatography (silica, 1:9 to 3:7 EtOAc/hexane) afforded the title compound as a colourless oil (1.13 g, 2.35 mmol, 83%).

R_f 0.19 (EtOAc/hexane 2:8).

FT-IR (neat) ν_{max}: 3332 (br), 2978 (w), 1721 (s), 1703 (s), 1499 (m), 1372 (s), 1217 (s), 1144 (s) cm^{-1}

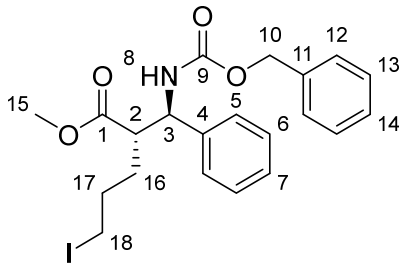
$[\alpha]^{23}_D$ +3.73 (*c* = 1.1, $CHCl_3$)

^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.91 (d, *J* = 9.5 Hz, 1H, **H8**), 7.36 – 7.19 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.05 – 4.86 (m, 2H, **H10**), 4.66 (t, *J* = 10.1 Hz, 1H, **H3**), 3.58 (s, 3H, **H15**), 2.74 (td, *J* = 10.7, 3.8 Hz, 1H, **H2**), 1.38 – 0.90 (m, 16H, **H16**, **H17**, **H20**), 0.51 (td, *J* = 7.3, 2.2 Hz, 2H, **H18**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz) δ = 173.84 (**C**, **C1**), 155.08 (**C**, **C9**), 140.90 (**C**, **C4**), 137.00 (**C**, **C11**), 128.26 (**CH**, **Ar**), 128.22 (**CH**, **Ar**), 127.66 (**CH**, **Ar**), 127.49 (**CH**, **Ar**), 127.25 (**CH**, **Ar**), 127.22

	(**CH**, **Ar**), 82.48 (**C**, **C19**), 65.18 (**CH_2**, **C10**), 57.05 (**CH**, **C3**), 51.28 (**CH_3**, **C15**), 50.96 (**CH**, **C2**), 31.69 (**CH_2**, **C16**), 24.46 (**CH_3**, **C20**), 24.42 (**CH_3**, **C20**), 21.33 (**CH_2**, **C17**) 10.11 (**CH_2**, **C18**) ppm. (***C18*** *not observed by 1D data, assigned by HSQC*).
^{1}H NMR (V_T, T = 353K)	(500 MHz, DMSO-d_6): δ = 7.49 (br s, 1H, **H8**), 7.36 – 7.22 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.03 (d, *J* = 12.8 Hz, 1H, **H10'**), 4.95 (d, *J* = 13.1 Hz, 1H, **H10''**), 4.73 (t, *J* = 9.6 Hz, 1H, **H3**), 3.58 (s, 3H, **H15**), 2.82 (td, *J* = 10.0, 4.0 Hz, 1H, **H2**), 1.46 – 1.35 (m, 1H, **H16'**), 1.29 – 1.11 (m, 3H, **H16''**, **H17**), 1.11 (s, 12H, **H20**), 0.55 (t, *J* = 7.3 Hz, 2H, **H18**) ppm.
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d_6): δ = 173.38 (**C**, **C1**), 154.73 (**C**, **C9**), 140.59 (**C**, **C4**), 136.75 (**C**, **C11**), 127.79 (**CH**, **Ar**), 127.77 (**CH**, **Ar**), 127.17 (**CH**, **Ar**), 126.94 (**CH**, **C12**), 126.78 (**CH**, **C5**), 126.75 (**CH**, **Ar**), 82.14 (**C**, **C19**), 64.95 (**CH_2**, **C10**), 56.68 (**CH**, **C3**), 50.69 (**CH_3**, **C15**), 50.46 (**CH**, **C2**), 31.34 (**CH_2**, **C16**), 24.11 (**CH_3**, **C20**), 20.90 (**CH_2**, **C17**), 9.90 (**CH_2**, **C18**) ppm. (***C18*** *observed as broad signal by 1D data, assigned by HSQC*).
^{11}B NMR	(160 MHz, DMSO-d_6): δ = 33.58 (s, pin**B**-CH_2) ppm
LRMS	(ES^+) *m/z* 481.5 [$M^{10}B$+H]$^+$, 482.5 [$M^{11}B$+H]$^+$.
HRMS	(ES^+) for $C_{27}H_{37}BNO_6^+$, calculated 482.2713 found 482.2719.

4.105: Methyl (*S*)-2-((*R*)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-5-iodopentanoate



$C_{21}H_{24}INO_4$

481.33 g mol^{-1}

Adapting the procedure of Aggarwal,[251] a solution of bromobenzene (30 µL, 0.25 mmol) in anhydrous THF (2 mL) was cooled to –78 °C. ^{n}BuLi (0.10 mL of a 2.5 M solution in hexanes, 0.25 mmol) was added, and the solution stirred for 1 h. A solution of boronic ester **4.102** (100 mg, 0.21 mmol) in anhydrous THF (1 mL) was added dropwise at this temperature. The solution was stirred for 30 min, warmed to RT and stirred a further 30 min. I_2 (82 mg, 0.32 mmol) in anhydrous THF (1 mL) was added, and the purple solution stirred for 1 h. The reaction was quenched by the addition of sat. $Na_2S_2O_{3\,(aq)}$ (4 mL). The mixture was diluted with EtOAc (3 mL), the phases separated and the aqueous layer extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a yellow oil. Purification by chromatography (silica, 1:9 EtOAc/pet. ether) afforded the title compound as a colourless oil (50 mg, 0.10 mmol, 49%).

R_f 0.13 (EtOAc/hexane 2:8).

FT-IR (neat) ν_{max}: 3332 (br), 2950 (w), 1718 (s), 1498 (s), 1219 (s) cm^{-1}

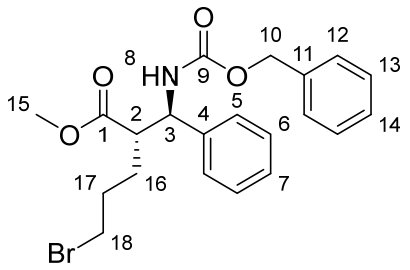
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.94 (d, *J* = 9.5 Hz, 1H, **H8**), 7.40 – 7.22 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 5.02 (d, *J* = 13.0 Hz, 1H, **H10'**), 4.91 (d, *J* = 13.0 Hz, 1H, **H10''**), 4.72 (t, *J* = 9.9 Hz, 1H, **H3**), 3.59 (s, 3H, **H15**), 3.17 – 3.01 (m, 2H, **H18**), 2.81 (dt, *J* = 10.3, 4.0 Hz, 1H, **H2**), 1.66 – 1.35 (m, 3H, **H16'**, **H17**), 1.19 – 1.08 (m, 1H, **H16''**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz) δ = 173.57 (**C**, **C1**), 155.16 (**C**, **C9**), 140.57 (**C**, **C4**), 136.98 (**C**, **C11**), 128.38 (**CH**, **Ar**), 128.27 (**CH**, **Ar**), 127.73 (**CH**, **Ar**), 127.57 (**CH**, **Ar**), 127.45 (**CH**, **Ar**), 127.28 (**CH**, **Ar**), 65.28 (**CH_2**, **C10**), 56.80 (**CH**, **C3**), 51.50 (**CH_3**, **C15**), 49.97 (**CH**, **C2**), 30.45 (**CH_2**, **C17**), 30.21 (**CH_2**, **C16**), 7.55 (**CH_2**, **C18**) ppm.

LRMS (ES$^+$) *m/z* 482.3 [M+H]$^+$, 504.3 [M+Na]$^+$.

HRMS (ES$^+$) for $C_{21}H_{25}INO_4^+$, calculated 482.0823 found 482.0832.

4.106: Methyl (*S*)-2-((*R*)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-5-bromopentanoate



$C_{21}H_{24}BrNO_4$

434.33 g mol^{-1}

Adapting the procedure of Aggarwal,[251] a solution of 1,3-bis (trifluoromethyl)-5-bromobenzene (40 µL, 0.25 mmol) in anhydrous THF (1 mL) was cooled to –78 °C. ^{n}BuLi (0.13 mL, 2.0 M in hexanes, 0.23 mmol) was added. The light yellow solution was stirred at this temperature for 30 min, then a solution of boronic ester **4.102** (100 mg, 0.21 mmol) in anhydrous THF (1 mL) was added. The solution was stirred for 30 min at this temperature, warmed to RT and stirred a further 30 min. A solution of NBS (45 mg, 0.25 mmol) in THF (1 mL) was added, turning the solution a cloudy yellow. The solution was stirred for 16 h, before being quenched by the addition of sat. $Na_2S_2O_{3(aq)}$ (3 mL) and EtOAc (3 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a pale yellow oil. Purification by chromatography (silica, 5:95 to 20:80 EtOAc / hexane) afforded the title compound as a pale yellow oil (19 mg, 40 µmol, 21%).#

R_f 0.27 (EtOAc/hexane 4:6).

$[\alpha]^{23}_D$ +2.0 (*c* = 0.95, $CHCl_3$)

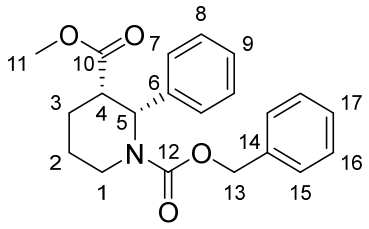
FT-IR (neat) ν_{max}: 3338 (w), 2951 (w), 1719 (s), 1499 (m), 1247 (m), 700 (m) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42 – 7.18 (m, 10H, **H5**, **H6**, **H7**, **H12**, **H13**, **H14**), 6.18 (d, *J* = 9.2 Hz, 1H, **H8**), 5.14 (d, *J* = 12.4 Hz, 1H, **H10'**), 5.08 (d, *J* = 12.4 Hz, 1H, **H10''**), 5.00 (dd, *J* = 9.2, 5.5 Hz, 1H, **H3**), 3.54 (s, 3H, **H15**), 3.42 – 3.30 (m, 2H, **H18**), 2.86 (dd, *J* = 13.3, 5.5 Hz, 1H, **H2**), 2.01 – 1.54 (m, 4H, **H16**, **H17**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.47 (**C**, **C1**), 155.92 (**C**, **C9**), 140.29 (**C**, **C4**), 136.39 (**C**, **C11**), 128.64 (**CH**, **C6**), 128.49 (**ArCH**), 128.09 (**ArCH**), 127.63 (**ArCH**), 126.01 (**CH**, **C5**), 66.89 (**CH_2**,

	C10), 55.69 (**CH**, **C3**), 51.80 (**CH_3**, **C15**), 50.26 (**CH**, **C2**), 32.57 (**CH_2**, **C18**), 30.30 (**CH_2**, **C17**), 28.86 (**CH_2**, **C16**) ppm.
LRMS	(ES^+) *m/z* 434.3 $[M^{79}Br+H]^+$, 436.3 $[M^{81}Br+H]^+$.
HRMS	(ES^+) for $C_{21}H_{24}BrNNaO_4^+$, calculated 456.0781 found 456.0790.

4.103: (+)-1-Benzyl 3-methyl (2*R*,3*S*)-2-phenylpiperidine-1,3-dicarboxylate



$C_{21}H_{23}NO_4$

353.42 g mol^{-1}

To a solution of bromide **4.106** (19 mg, 40 µmol) in anhydrous MeCN (1 mL) was added Cs_2CO_3 (65 mg, 0.20 mmol) and NaI (7 mg, 40 µmol), and the yellow suspension heated to 80 °C and stirred for 7 h. The mixture was cooled to RT, and H_2O (3 mL) added. The solution was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by chromatography (silica, 15:85 EtOAc / hexane) afforded the title compound as a pale yellow oil (11 mg, 30 µmol, 78%).#

R_f 0.31 (EtOAc/hexane 4:6).

$[\alpha]^{23}_D$ +114.5 (*c* = 0.5, $CHCl_3$)

FT-IR (neat) ν_{max}: 3032 (w), 2950 (w), 1732 (s), 1694 (s), 1421 (m), 1250 (m), 1154 (m) cm^{-1}

^{1}H NMR ($DMSO\text{-}d_6$, 400 MHz) δ = 7.43 – 7.11 (m, 10H, **H7**, **H8**, **H9**, **H15**, **H16**, **H17**), 5.87 – 5.66 (m, 1H, **H5(ax)**), 5.22 – 5.04 (m, 2H, **H13**), 3.91 (br d, *J* = 13.5 Hz, 1H, **H1(eq)**), 3.53 (s, 3H, **H11**), 3.15 – 3.01 (m, 1H, **H4(eq)**), 2.72 (td, *J* = 13.5, 3.1 Hz, 1H, **H1(ax)**), 2.02 – 1.65 (m, 3H, **H2(eq)**, **H3**), 1.58 – 1.42 (m, 1H, **H2(ax)**) ppm.

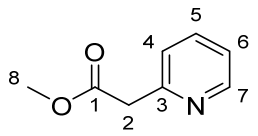
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.24 (**C**, **C10**), 154.46 (**C**, **C12**), 138.26 (**ArC**), 136.75 (**ArC**), 128.49 (**ArCH**), 128.40 (**ArCH**), 127.86 (**ArCH**), 127.52 (**ArCH**), 127.46 (**ArCH**), 127.24 (**ArCH**), 66.55 (**CH_2**, **C13**), 54.34 (**CH**, **C5**), 51.60 (**CH_3**, **C11**), 43.56 (**CH**, **C4**), 39.51 (**CH_2**, **C1**), 24.13 (**CH_2**, **C2**), 20.85 (**CH_2**, **C3**) ppm.

^{1}H NMR (V_T, T = 353K) ($DMSO\text{-}d_6$, 500 MHz) δ = 7.38 – 7.28 (m, 7H, **H8**, **H9**, **H15**, **H16**), 7.27 – 7.23 (m, 1H, **H17**), 7.22 – 7.18 (m, 2H, **H7**), 5.77 (d, *J* = 5.5 Hz, 1H, **H5(ax)**, 5.17 (d, *J* = 12.7 Hz, 1H, **H13'**), 5.12 (d, *J* = 12.7 Hz, 1H, **H13''**), 3.97 – 3.91 (m, 1H, **H1(eq)**), 3.54 (s, 3H, **H11**), 3.09 – 3.06 (m, 1H, **H4(eq)**), 2.81 (td, *J* = 13.3,

	3.3 Hz, 1H, **H1(ax)**), 2.08 – 1.87 (m 2H, **H3**), 1.81 – 1.74 (m, 1H, **H2(eq)**), 1.53 (qt, *J* = 12.9, 4.9 Hz, 1H, **H2(ax)**).
^{13}C NMR (V_T, T = 353K)	(126 MHz, DMSO-d_6): δ = 171.65 (**C**, **C10**), 154.39 (**C**, **C12**), 138.07 (**C**, **C6**), 136.48 (**C**, **C14**), 127.91 (**CH**, **C8** & **C16**), 127.34 (**CH**, **C9**), 127.16 (**CH**, **C7**), 127.01 (**CH**, **C15**), 126.72 (**CH**, **C17**), 66.19 (**CH_2**, **C13**), 54.35 (**CH**, **C5**), 50.96 (**CH_3**, **C11**), 43.69 (**CH**, **C4**), 39.01 (**CH_2**, **C1**), 23.59 (**CH_2**, **C2**), 20.51 (**CH_2**, **C3**).
LRMS	(ES^+) *m/z* 353.4 $[M+H]^+$, 375.4 $[M+Na]^+$.
HRMS	(ES^+) for $C_{21}H_{23}NNaO_4^+$, calculated 376.1519 found 376.1523.

7.2.4 Sparteine Review

1.27: Methyl 2-(pyridin-2-yl)acetate



$C_8H_9NO_2$

151.17 g mol^{-1}

A mixture of pyridin-2-yl acetic acid hydrochloride (10.0 g, 57.6 mmol) and anhydrous MeOH (70 mL) was cooled to 0 °C. TMS-Cl (14.6 mL, 115 mmol) was added dropwise over 10 min, and the yellow solution was warmed to RT and stirred for 16 h. The solution was concentrated *in vacuo* to afford a light brown residue. The residue was dissolved in sat. $NaHCO_{3(aq)}$ (100 mL), and the aqueous solution extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound as a yellow oil (7.79 g, 51.6 mmol, 90%).

FT-IR (neat) ν_{max}: 3011 (w), 2953 (w), 1733 (s), 1592 (m), 1435 (s), 1255 (s), 1156 (s) cm^{-1}.

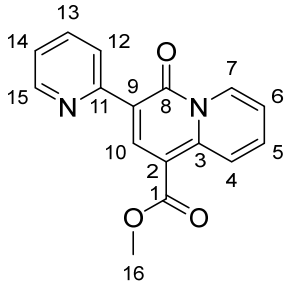
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.56 (dd, *J* = 4.9, 0.7 Hz, 1H, **H7**), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H, **H5**), 7.29 (d, *J* = 7.7 Hz, 1H, **H4**), 7.19 (ddd, *J* = 7.7, 4.9, 0.7 Hz, 1H, **H6**), 3.86 (s, 2H, **H2**), 3.73 (s, 3H, **H8**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.04 (**C**, **C1**), 154.35 (**C**, **C3**), 149.53 (**CH**, **C7**), 136.61 (**CH**, **C5**), 123.79 (**CH**, **C4**), 122.09 (**CH**, **C6**), 52.12 (**CH_3**, **C8**), 43.76 (**CH_2**, **C2**) ppm.

LRMS (ES^+) *m/z* 152.2 $[M+H]^+$, 174.3 $[M+Na]^+$.

Physical and spectroscopic data are consistent with reported values.[306]

1.30: Methyl 4-oxo-3-(pyridin-2-yl)-4H-quinolizine-1-carboxylate



$C_{16}H_{12}N_2O_3$

280.28 g mol^{-1}

A solution of ester **1.27** (5.00 g, 17.8 mmol), acetic anhydride (5.0 mL) and trimethyl orthoformate (5.17 mL) was heated to 130 °C and stirred for 4 h, during which time the solution turned a brown colour, admixed with yellow solid. The suspension was cooled to RT and concentrated *in vacuo* to a brown residue. The residue was partitioned between CH_2Cl_2 / H_2O (20 mL, 1:1). The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as an orange powder. Purification by recrystallisation (Toluene / pet. ether 1:1) afforded the title compound as bright yellow needles (3.22 g, 11.5 mmol, 69%).

MP 171.2 – 172.3 °C

FT-IR (neat) ν_{max}: 3119 (w), 2994 (w), 1699 (s), 1661 (s), 1626 (s), 1582 (m), 1494 (s), 1428 (s), 1199 (s) cm^{-1}.

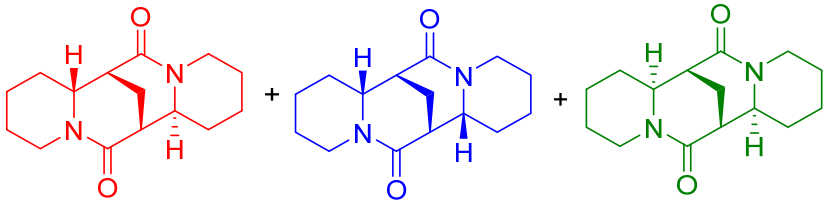
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.55 – 9.50 (m, 2H, **H7**, **H10**), 9.37 (d, *J* = 9.1 Hz, 1H, **H4**), 8.72 (d, *J* = 4.0 Hz, 1H, **H15**), 8.63 (d, *J* = 8.1 Hz, 1H, **H12**), 7.82 – 7.72 (m, 2H, **H5**, **H13**), 7.30 (td, *J* = 7.2, 1.3 Hz, 1H, **H6**), 7.23 (dd, *J* = 7.0, 4.0 Hz, 1H, **H14**), 3.96 (s, 3H, **H16**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 165.90 (**C**, **C1**), 157.19 (**C**, **C8**), 153.54 (**C**, **C11**), 149.21 (**CH**, **C15**), 144.85 (**C**, **C3**), 140.66 (**CH**, **C10**), 136.39 (**CH**, **C13**), 134.16 (**CH**, **C5**), 129.18 (**CH**, **C7**), 124.20 (**CH**, **C4**), 123.74 (**CH**, **C12**), 121.93 (**CH**, **C14**), 116.80 (**CH**, **C6**), 115.40 (**C**, **C9**), 102.73 (**C**, **C2**), 51.95 (**CH_3**, **C16**) ppm.

LRMS (ES^+) *m/z* 281.3 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[257]

Mixture of (±)-10,17-dioxosparteine (1.23), (±)-10,17-dioxo-*α*-isosparteine (1.33) and (±)-10,17-dioxo-*β*-isosparteine (1.29)



(±)-**1.23** (±)-**1.33** (±)-**1.26**

$C_{15}H_{22}N_2O_2$

262.35 g mol^{-1}

Adapting the procedure of Sǒrm and Kiel,[89] to a solution of quinolizidine **1.30** in glacial AcOH (40 mL) was added PtO_2 (225 mg, 14 mol%). The bright yellow suspension was put under an H_2 atmosphere, and stirred at RT for 6 days, until the solution had turned completely colourless, admixed with brown solid. The suspension was filtered through Celite®, and the filter cake washed with MeOH (3 x 50 mL). The solution was concentrated *in vacuo* to yield a yellow oil. The crude mixture of hydrogenated products was heated *in vacuo* in a Kugelrohr apparatus (250 °C, 0.6 mBar) for 3 h, and residual acetic acid distilled off to yield the title mixture of dioxosparteines as a brown gum (1.28 g, 4.88 mmol, 68%).

GC-FID analysis of this mixture gave the ratio of (±)-**1.23** : (±)-**1.33** : (±)-**1.29** as ≈3:1:1. Retention times were confirmed by the analysis of mixtures of (±)-**1.23** + (±)-**1.29** and (±)-**1.33** + (±)-**1.23**, obtained from attempted separation of the diastereoisomers by chromatography (silica, 89:10:1 CH_2Cl_2 : MeOH : NH_4OH).

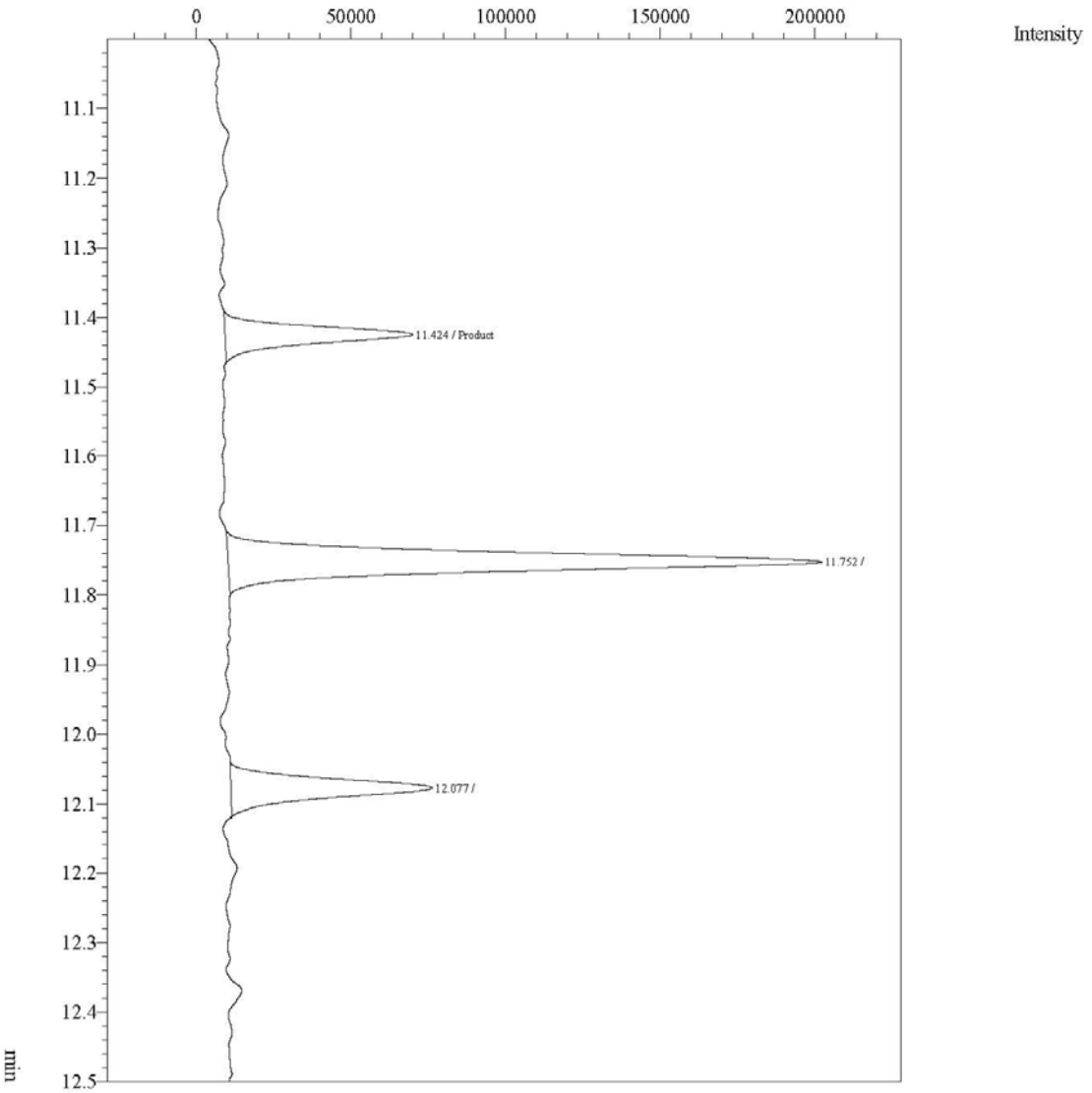
^{13}C NMR ($CDCl_3$, 101 MHz)

(±)-1.23:δ = 170.17 (**C**), 166.34 (**C**), 59.90 (**CH**), 59.10 (**CH**), 43.33 (**CH_2**), 42.69 (**CH**), 42.20 (**CH_2**), 41.89 (**CH**), 32.51 (**CH_2**), 31.18 (**CH_2**), 25.08 (**CH_2**), 24.92 (**CH_2**), 24.80 (**CH_2**), 24.12 (**CH_2**), 21.80 (**CH_2**) ppm.

(±)-1.33 δ = 167.83 (**C**), 58.77 (**CH**), 42.32 (**CH_2**), 41.78 (**CH**), 31.20 (**CH_2**), 25.17 (**CH_2**), 24.34 (**CH_2**), 24.28 (**CH_2**) ppm.

(±)-1.26 δ = 168.99 (**C**), 60.39 (**CH**), 43.42 (**CH_2**), 42.55 (**CH**), 32.16 (**CH_2**), 25.22 (**CH_2**). 24.84 (**CH_2**), 18.74 (**CH_2**) ppm.

^{13}C NMR values were consistent with those previously reported.[124]

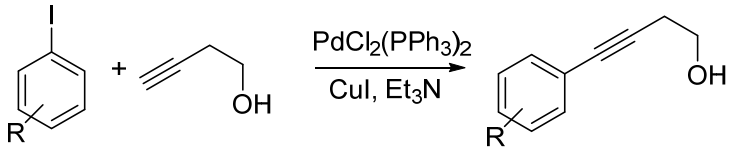


Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	11.424	96643	58964	0.000	ppm		2	Product
2	11.752	338277	188650	0.000				
3	12.077	117178	64531	0.000				
Total		552098	312145					

Figure 7.1: GC analysis of the crude mixture of dioxosparteines. Retention times: 11.42 ((±)-**1.26**), 11.75 ((±)-**1.23**), 12.08 ((±)-**1.33**) min.

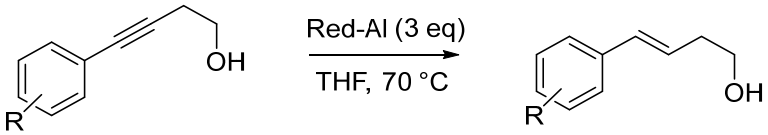
7.2.5 Organic electrosynthesis

7.2.5.1 General method for the synthesis of substituted aryl alkynes



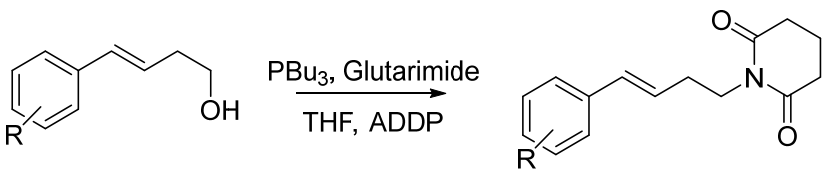
Following a procedure by Gong,[1] a solution of iodo-arene (1.1 equiv) and 3-butyn-1-ol (1.0 equiv) in Et_3N was added to a suspension of $Pd(PPh_3)Cl_2$ (1 mol%) and CuI (1 mol%) in Et_3N at RT under an inert atmosphere. The orange mixture was stirred at RT for 16 h, and then diluted with EtOAc (30 mL), and the solid residues filtered off. The filtrate was concentrated *in vacuo* to afford an orange oil. Purification by chromatography (silica, EtOAc:pet. ether. 5:95 – 20:80) afforded the pure product.

7.2.5.2 General method for the Red-Al reduction of aryl alkynes



A solution of aryl alkyne (1.0 equiv) in anhydrous THF (0.2 M) under an inert atmosphere was cooled to 0 °C. A solution of Red-Al (60% wt. in toluene, 3.0 equiv) was added dropwise at this temperature, and vigorous effervescence was observed. The reaction was heated at 80 °C for 16h, and then cooled to 0 °C. The reaction was quenched by the slow addition of sat. Rochelle's salt, and the resulting suspension stirred for 2 h. The phases were separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product. Purification by chromatography (silica, EtOAc:pet. ether. 40:60) afforded the pure product.

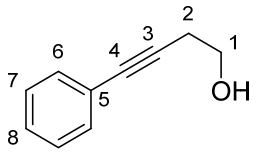
7.2.5.3 General procedure for the synthesis of *N*-alkylated gluratimides



To a solution of aryl alkene (1.0 equiv), glutarimide (1.5 equiv) and ADDP (1.5 equiv) in anhydrous THF at 0 °C was added PBu_3 (1.5 equiv) dropwise. The solution turned from a clear yellow to a light brown suspension. The mixture was stirred for 16 h, then the reaction was quenched with 2M $HCl_{(aq)}$ and stirred a further 30 min. The clear yellow solution was

diluted with EtOAc (20 mL) and the phases separated. The aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a light brown solid. Purification by chromatography (silica, EtOAc:pet. ether. 10:90) or by recrystallisation (CH_2Cl_2:hexane 1:19) afforded the pure product as long white needles.

6.26a: 4-Phenylbut-3-yn-1-ol



$C_{10}H_{10}O$

146.19 g mol^{-1}

Prepared according to general procedure 7.2.5.1 to give the title compound as a dark orange oil (4.15 g, 28.4 mmol, 95%).

R_f 0.30 (EtOAc:hexane 4:6)

FT-IR (neat) ν_{max}: 3330 (br), 2884 (w), 1598 (w), 1489 (m), 1041 (s) cm^{-1}.

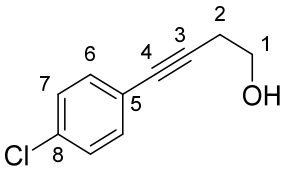
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.46 – 7.40 (m, 2H, **H6**), 7.32 – 7.27 (m, 3H, **H7**, **H8**), 3.81 (t, *J* = 6.4 Hz, 2H, **H1**), 2.69 (t, *J* = 6.4 Hz, 2H, **H2**), 2.30 (br s, 1H, **OH**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 131.58 (**CH**, **C6**), 128.17 (**CH**, **C7**), 127.84 (**CH**, **C8**), 123.28 (**C**, **C5**), 86.37 (**C**, **C3**), 82.31 (**C**, **C4**), 61.05 (**CH_2**, **C1**), 23.69 (**CH_2**, **C2**) ppm.

LRMS (ES^+) *m/z* 147.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[307]

6.26b: 4-(4-Chlorophenyl)but-3-yn-1-ol



$C_{10}H_9ClO$

180.63 g mol^{-1}

Prepared according to general procedure 7.2.5.1 to give the title compound as light brown crystals (1.26 g, 6.98 mmol, 73%).

R_f 0.28 (EtOAc:hexane 4:6)

MP 52.8 – 53.7 °C

FT-IR (neat) ν_{max}: 3285 (br), 2883 (w), 1910 (w), 1591 (w), 1488 (m), 1096 (s), 1039 (s) cm^{-1}

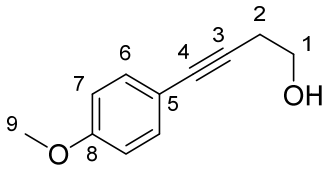
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35 (d, *J* = 8.6 Hz, 2H, **H6**), 7.28 (d, *J* = 8.6 Hz, 2H, **H7**), 3.83 (q, *J* = 6.3 Hz, 2H, **H1**), 2.70 (t, *J* = 6.2 Hz, 2H, **H2**), 1.78 (t, *J* = 6.3 Hz, 1H, **OH**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 133.92 (**C**, **C8**), 132.89 (**CH**, **C6**), 128.57 (**CH**, **C7**), 121.83 (**C**, **C5**), 67.43 (**C**, **C3**), 61.38 (**C**, **C4**), 61.08 (**CH_2**, **C1**), 23.81 (**CH_2**, **C2**) ppm.

LRMS (ES^+) *m/z* 181.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[308]

6.26c: 4-(4-methoxyphenyl)but-3-yn-1-ol



$C_{11}H_{12}O_2$

176.22 g mol^{-1}

Prepared according to general procedure 7.2.5.1 to give the title compound as a yellow solid (3.27 g, 18.7 mmol, 96%).

R_f 0.22 (EtOAc:hexane 4:6)

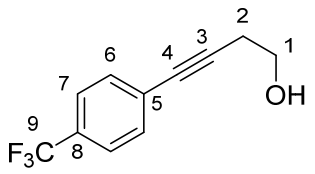
MP 55.0 – 56.3 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36 (d, *J* = 9.2 Hz, 2H, **H6**), 6.83 (d, *J* = 9.2 Hz, 2H, **H7**), 3.84 – 3.81 (m, 5H, **H1**, **H9**), 2.69 (t, *J* = 6.2 Hz, 2H, **H2**), 1.83 (br s, 1H, **OH**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 159.34 (**C**, **C8**), 133.04 (**CH**, **C6**), 115.44 (**C**, **C5**), 113.88 (**CH**, **C7**), 84.64 (**C**, **C3**), 82.35 (**C**, **C4**), 61.25 (**CH_2**, **C1**), 55.27 (**CH_3**, **C9**), 23.87 (**CH_2**, **C2**) ppm.

Physical and spectroscopic data are consistent with reported values.[309]

6.26d: 4-(4-(Trifluoromethyl)phenyl)but-3-yn-1-ol



$C_{11}H_9F_3O$

214.19 g mol^{-1}

Prepared according to general procedure 7.2.5.1 to give the title compound as a fine yellow powder (2.76 g, 12.9 mmol, 77%).

R_f 0.30 (EtOAc:hexane 4:6)

MP 38.1 – 39.1 °C

FT-IR (neat) ν_{max}: 3299 (br), 2890 (w), 1614 (m), 1405 (m), 1318 (s), 1125 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56 (d, *J* = 8.4 Hz, 2H, **H7**), 7.51 (d, *J* = 8.7 Hz, 2H, **H6**), 3.85 (q, *J* = 6.2 Hz, 2H, **H1**), 2.73 (t, *J* = 6.3 Hz, 2H, **H2**), 1.8 (t, *J* = 6.2 Hz, 1H, **OH**) ppm.

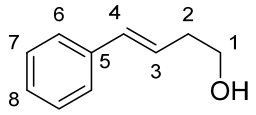
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 131.9 (**CH**, **C6**), 129.71 (q, J = 32.3 Hz, **C**, **C8**), 127.21 (**C**, **C5**), 125.18 (q, *J* = 3.9 Hz, **CH**, **C7**), 123.93 (q, *J* = 272.2 Hz, **C**, **C9**), 89.22 (**C**, **C3**), 81.22 (**C**, **C4**), 61.01 (**CH_2**, **C1**), 23.81 (**CH_2**, **C2**) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz) δ = –63.05 (s, 3F, **CF_3**) ppm.

LRMS (ES^+) *m/z* 215.2 $[M+H]^+$.

HRMS (ES^+) for $C_{11}H_{10}F_3O^+$ $[M+H]^+$, calculated 215.0678 found 215.0681.

6.27a: (*E*)-4-Phenylbut-3-en-1-ol



$C_{10}H_{12}O$

148.21 g mol^{-1}

Prepared according to general procedure 7.2.5.2 to give the target compound as a light brown oil (4.76g, 32.1 mmol, 94%).

R_f 0.30 (EtOAc:hexane 4:6)

FT-IR (neat) v_{max}: 3318 (br), 2931 (br), 1598 (w), 1493 (m), 1448 (m), 1043 (s) cm^{-1}

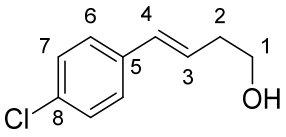
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40 – 7.35 (m, 2H, **H6**), 7.35 – 7.29 (m, 2H, **H7**), 7.23 (tt, *J* = 7.2, 1.5 Hz, 1H, **H8**), 6.52 (d, *J* = 15.8 Hz, 1H, **H4**), 6.22 (dt, *J* = 15.8, 7.2 Hz, 1H, **H3**), 3.77 (t, *J* = 6.3 Hz, 2H, **H1**), 2.50 (qd, *J* = 6.6, 1.3 Hz, 2H, **H2**), 1.75 (br s, 1H, **OH**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 137.20 (**C**, **C5**), 132.74 (**CH**, **C4**), 128.49 (**CH**, **C7**), 127.22 (**CH**, **C8**), 126.31 (**CH**, **C3**), 126.03 (**CH**, **C6**), 61.98 (**CH_2**, **C1**), 36.35 (**CH_2**, **C2**) ppm.

LRMS (ES^+) *m/z* 149.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[310]

6.27b: (*E*)-4-(4-Chlorophenyl)but-3-en-1-ol



$C_{10}H_{11}ClO$

182.65 g mol^{-1}

Prepared according to general procedure 7.2.5.2 to give the target compound as a pale yellow oil (912 mg, 5.00 mmol, 75%).

R_f 0.26 (EtOAc:hexane 4:6)

FT-IR (neat) ν_{max}: 3365 (br), 2935 (w), 1702 (m), 1661 (s), 1490 (s), 1351 (m), 1089 (s) cm^{-1}

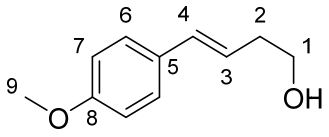
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31 – 7.25 (m, 4H, **H6**, **H7**), 6.46 (dt, *J* = 15.9, 1.2 Hz, 1H, **H4**), 6.20 (dt, *J* = 15.9, 7.1 Hz, 1H, **H3**), 3.77 (t, *J* = 6.2 Hz, 2H, **H1**), 2.49 (qd, *J* = 6.6, 1.2 Hz, 2H, **H2**), 1.50 (br s, 1H, **OH**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 135.73 (**C**, **C8**), 132.80 (**C**, **C5**), 131.51 (**CH**, **C4**), 128.64 (**CH**, **C7**), 127.26 (**CH**, **C6**), 127.16 (**CH**, **C3**), 61.94 (**CH_2**, **C1**), 36.34 (**CH_2**, **C2**) ppm.

LRMS (ES^+) *m/z* 183.2 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[311]

6.27c: (*E*)-4-(4-methoxyphenyl)but-3-en-1-ol



$C_{11}H_{14}O_2$

178.23 g mol^{-1}

Prepared according to general procedure 7.2.5.2 to give the title compound as a yellow solid (1.86 g, 10.4 mmol, 78%).

R_f 0.26 (EtOAc:hexane 4:6)

MP 79.1 – 80.0 °C

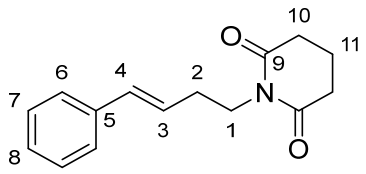
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31 (d, *J* = 8.7 Hz, 2H, **H6**), 6.86 (d, *J* = 8.7 Hz, 2H, **H7**), 6.46 (d, *J* = 15.8 Hz, 1H, **H4**), 6.06 (dt, *J* = 15.8, 7.2 Hz, 1H, **H3**), 3.81 (s, 3H, **H9**), 3.75 (t, *J* = 6.2 Hz, 2H, **H1**), 2.48 (dtd, *J* = 7.2, 6.2, 1.4 Hz, 2H, **H2**), 1.48 (br s, 1H, **OH**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 158.95 (**C**, **C8**), 132.30 (**CH**, **C4**), 130.02 (**C**, **C5**), 127.19 (**CH**, **C6**), 123.96 (**CH**, **C3**), 113.93 (**CH**, **C7**), 62.08 (**CH_2**, **C1**), 55.28 (**CH_3**, **C9**), 36.39 (**CH_2**, **C2**) ppm.

LRMS (ES^+) *m/z* 179.3 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[312]

6.16: (*E*)-1-(4-Phenylbut-3-en-1-yl)piperidine-2,6-dione



$C_{15}H_{17}NO_2$

243.31 g mol^{-1}

Prepared according to general procedure 7.2.5.3 to give the title compound as long white needles (5.58 g, 22.9 mmol, 85%).

R_f 0.23 (EtOAc:hexane 4:6)

MP 108.3 – 110.1 °C

FT-IR (neat) ν_{max}: 2962 (w), 1715 (m), 1661 (s), 1492 (m), 1431 (m), 1348 (s), 1108 (s) cm^{-1}

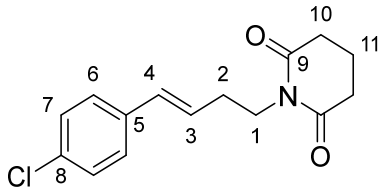
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 – 7.28 (m, 4H, **H6**, **H7**), 7.24 – 7.18 (m, 1H, **H8**), 6.38 (d, *J* = 15.8 Hz, 1H, **H4**), 6.14 (dt, *J* = 15.9, 7.6 Hz, 1H, **H3**), 3.94 (t, *J* = 7.2 Hz, 2H, **H1**), 2.63 (t, *J* = 6.5 Hz, 4H, **H10**), 2.46 (qd, *J* = 7.3, 1.3 Hz, 2H, **H2**), 1.89 (quin, *J* = 6.6 Hz, 2H, **H11**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.48 (**C**, **C9**), 137.36 (**C**, **C5**), 132.01 (**CH**, **C4**), 128.50 (**CH**, **C7**), 127.13 (**CH**, **C8**), 126.86 (**CH**, **C3**), 126.06 (**CH**, **C6**), 38.76 (**CH_2**, **C1**), 32.86 (**CH_2**, **C10**), 31.68 (**CH_2**, **C2**), 17.11 (**CH_2**, **C11**) ppm.

LRMS (ES^+) *m/z* 244.3 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[274]

6.16b: (*E*)-1-(4-(4-Chlorophenyl)but-3-en-1-yl)piperidine-2,6-dione



$C_{15}H_{16}ClNO_2$

277.75 g mol^{-1}

Prepared according to general procedure 7.2.5.3 to give the title compound as long white needles (772 mg, 2.78 mmol, 60%).

R_f 0.21 (EtOAc:hexane 4:6)

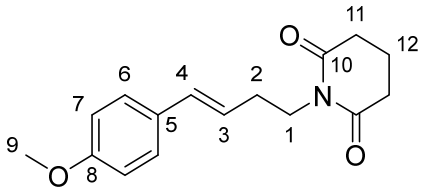
MP 74.1 – 76.3 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28 – 7.20 (m, 4H, **H6**, **H7**), 6.32 (dt, *J* = 15.9, 0.2 Hz, 1H, **H4**), 6.12 (dt, *J* = 15.7, 7.3 Hz, 1H, **H3**), 3.92 (t, *J* = 7.2 Hz, 2H, **H1**), 2.62 (t, *J* = 6.5 Hz, 4H, **H10**), 2.44 (qd, *J* = 7.2, 1.2 Hz, 2H, **H2**), 1.89 (quin, *J* = 6.5 Hz, 2H, **H11**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.43 (**C**, **C9**), 135.83 (**C**, **C8**), 132.70 (**C**, **C5**), 130.71 (**CH**, **C4**), 128.62 (**CH**, **C7**), 127.65 (**CH**, **C3**), 127.24 (**CH**, **C6**), 38.63 (**CH_2**, **C1**), 32.82 (**CH_2**, **C10**), 31.66 (**CH_2**, **C2**), 17.08 (**CH_2**, **C11**) ppm.

LRMS (ES^+) *m/z* 278.2 $[M+H]^+$.

6.16c: (*E*)-4-(4-methoxyphenyl)but-3-en-1-ol



$C_{16}H_{19}NO_3$

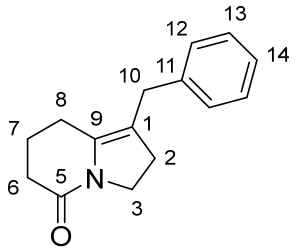
273.33 g mol^{-1}

Prepared according to general procedure 7.2.5.3 to give the title compound (as long white needles 2.12 g, 7.76 mmol, 77%).

R_f	0.20 (EtOAc:hexane 4:6)
MP	82.4 – 83.8 °C
^{1}H NMR	($CDCl_3$, 400 MHz) δ = 7.28 – 7.23 (m, 2H, **H6**), 6.86 – 6.81 (m, 2H, **H7**), 6.32 (d, *J* = 15.8 Hz, 1H, **H4**), 5.99 (dt, *J* = 15.9, 7.5 Hz, 1H, **H3**), 3.92 (t, *J* = 7.2 Hz, 2H, **H1**), 3.8 (s, 3H, **H9**), 2.62 (t, *J* = 6.6 Hz, 4H, **H11**), 2.42 (qd, *J* = 7.3, 1.3 Hz, 2H, **H2**), 1.88 (quin, *J* = 6.6 Hz, 2H, **H12**) ppm.
^{13}C NMR	($CDCl_3$, 101 MHz) δ = 172.46 (**C**, **C10**), 158.87 (**C**, **C8**), 131.37 (**CH**, **C4**), 130.20 (**C**, **C5**), 127.15 (**CH**, **C6**), 124.61 (**CH**, **C3**), 113.92 (**CH**, **C7**), 55.24 (**CH_3**, **C9**), 38.86 (**CH_2**, **C1**), 32.85 (**CH_2**, **C11**), 31.64 (**CH_2**, **C10**), 17.09 (**CH_2**, **C12**) ppm.
LRMS	(ES^+) *m/z* 274.3 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[274]

6.17: 1-Benzyl-2,6,7,8-tetrahydroindolizin-5(3*H*)-one



$C_{15}H_{17}NO$

227.31 g mol^{-1}

Following the procedure of Szostak,[37] to a rapidly stirred solution of imide **6.16a** (300 mg, 1.23 mmol) in THF (9 mL) and H_2O (13.3 mL, 600 eq) was added SmI_2 (0.1M in THF, 36.9 mL, 3.69mmol). The solution immediately turned a deep burgundy red. After approximately 1 min, the solution turned a cloudy white. The solution was sparged with air for 5 min in order to quench any remaining SmI_2.The solution was diluted with Et_2O (20 mL) and 1M HCl (20 mL), upon which the mixture turned a pale orange. The phases were separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange oil. Purification by chromatography (silica, EtOAc:pet. ether 4:6 to 8:2) afforded the title compound as a brown oil (66 mg, 0.29 mmol, 24%).

Alternatively, to an H-cell (**See Figure 6.6**) was added a solution of 0.3 M Et_4NBF_4 (652 mg) in DMF in one compartment. Simultaneously, a solution of 0.3 M Et_4NBF_4 (652 mg) and imide **6.16a** (244 mg, 1.00 mmol) was added to the other compartment. A carbon anode (submerged area = 3.0 cm^2) and copper foil cathode (submerged area = 4.5 cm^2) were added to the DMF (anodic) and MeCN (cathodic) chambers respectively. A current of 27 mA was applied, resulting in an overall voltage of 12.1 V. The solutions in each chamber were stirred for 1 h. Gas evolution was seen to occur at the copper cathode, and the DMF solution slowly turned bark brown over this time, whilst the MeCN solution turned a pale orange. The anodic solution was collected and concentrated *in vacuo* to yield a brown residue. The residue was diluted in EtOAc (50 mL) and filtered to remove residual Et_4NBF_4, and the filtrate concentrated *in vacuo* to afford a brown oil. Purification by chromatography (silica, 1:1 – 0:1 CH_2Cl_2 / EtOAc) afforded the title compound as a brown oil (5 mg, 2.20 µmol, 2%).

R_f 0.11 (EtOAc:hexane 4:6)

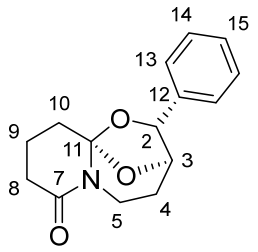
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31 (t, *J* = 7.3 Hz, 2H, **H13**), 7.23 (t, *J* = 7.1 Hz, 1H, **H14**), 7.14 (d, *J* = 7.1 Hz, 2H, **H12**), 3.82 (t, *J* = 8.3 Hz, 2H, **H3**), 3.41 (s, 2H, **H10**), 2.56 – 2.50 (m, 2H, **H8**), 2.50 – 2.38 (m, 4H, **H2**, **H6**), 1.87 (quin, *J* = 6.3 Hz, 2H, **H7**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.81 (**C**, **C5**), 139.18 (**C**, **C111**), 133.46 (**C**, **C9**), 128.58 (**CH**, **C13**), 128.37 (**CH**, **C12**), 126.32 (**CH**, **C14**), 116.33 (**C**, **C1**), 43.53 (**CH_2**, **C3**), 33.67 (**CH_2**, **C10**), 32.27 (**CH_2**, **C6**), 29.74 (**CH_2**, **C2**), 21.55 (**CH_2**, **C8**), 19.84 (**CH_2**, **C7**) ppm.

LRMS (ES^+) *m/z* 228.3 $[M+H]^+$.

Physical and spectroscopic data are consistent with reported values.[274]

6.29: 2-Phenylhexahydro-3,10a-epoxypyrido[2,1-b][1,3]oxazepin-7(8*H*)-one



$C_{15}H_{17}NO_3$

259.31 g mol^{-1}

To a 100 mL beaker was added 60 mL of a 0.3 M solution of Et_4NBF_4 (3.90 g) in MeCN / H_2O (9:1). Imide **6.16a** (729 mg, 3 mmol) was added. To the beaker was added a coiled copper foil cathode (**See Figure 6.3**) (submerged area 72 cm^2) and a graphite anode (submerged area 12 cm^2). The colourless solution was stirred and a current of 157 mA was passed through the solution, resulting in an overall voltage of 4.1 V. The colourless solution was stirred for 1 h, over which time it turned a pale orange colour. The electrolyte was concentrated *in vacuo* to yield a brown residue. The residue was diluted in EtOAc (100 mL) and filtered to remove Et_4NBF_4. The filtrate was concentrated *in vacuo* to afford a brown oil. Purification by chromatography (silica, 4:6 – 10:0 EtOAc / pet. ether) afforded the title compound as a white powdery solid (91 mg, 0.35 mmol, 12%).

Alternatively, 5 mL of a 0.3 M solution of Et_4NBF_4 (326 mg) containing 0.05 M of imide **6.16a** (61 mg) in MeCN / H_2O (9:1) was passed through the Ammonite 8 reactor at a flow rate of 0.13 ml min^{-1}. A carbon polymer anode and stainless steel cathode were used. The current was set to 40 mA, resulting in a voltage of 3.2 V. The pale orange product was collected, and concentrated *in vacuo* to a brown residue. The residue was diluted in EtOAc (10 mL) and filtered to remove Et_4NBF_4. The filtrate was concentrated *in vacuo* to yield a brown oil. Purification by chromatography (silica, 4:6 – 10:0 EtOAc / pet. ether) afforded the title compound as a white powdery solid (11 mg, 0.04 mmol, 16%).

R_f 0.16 (EtOAc:hexane 4:6)

FT-IR (neat) ν_{max}: 2952 (w), 1640 (s), 1435 (m), 1407 (m), 1256 (m), 1003 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40 – 7.30 (m, 5H, **H13**, **H14**, **H15**), 5.16 (s, 1H, **H2**), 4.55 (br s, 1H, **H3**), 4.55 (dd, *J* = 13.6, 6.9 Hz, 1H, **H5(eq)**), 3.31 (td, *J* = 13.0, 5.1 Hz, 1H, **H5(ax)**, 2.53 – 2.31 (m, 4H, **H8**, **H10**), 2.23 – 2.12 (m, 1H, **H4(eq)**), 1.97 – 1.88 (m, 2H, **H9**), 1.84 – 1.77 (m, 1H, **H4(ax)**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 169.04 (**C**, **C7**), 140.67 (**C**, **C12**), 128.59 (**CH**, **C14**), 128.18 (**CH**, **C15**), 125.82 (**CH**, **C13**), 113.15 (**C**, **C11**), 81.19

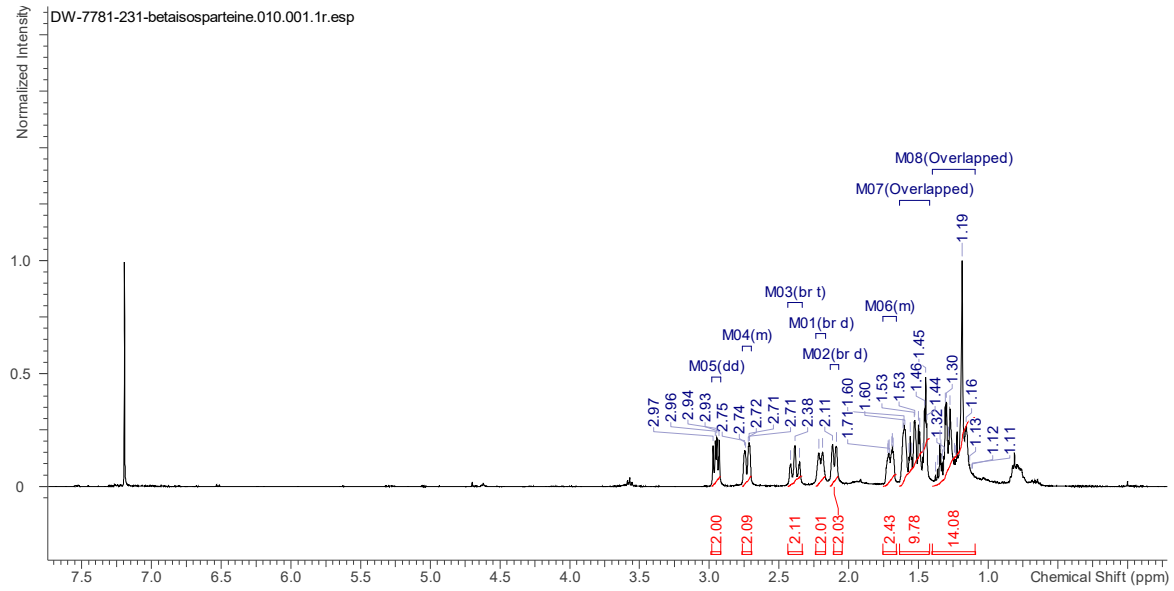
(**CH**, **C2**), 80.54 (**CH**, **C3**), 34.32 (**CH_2**, **C5**), 32.46 (**CH_2**, **C8** or **C10**), 32.41 (**CH_2**, **C8** or **C10**), 27.83 (**CH_2**, **C4**), 17.79 (**CH_2**, **C9**) ppm.

LRMS (ES^+) *m/z* 260.3 $[M+H]^+$.

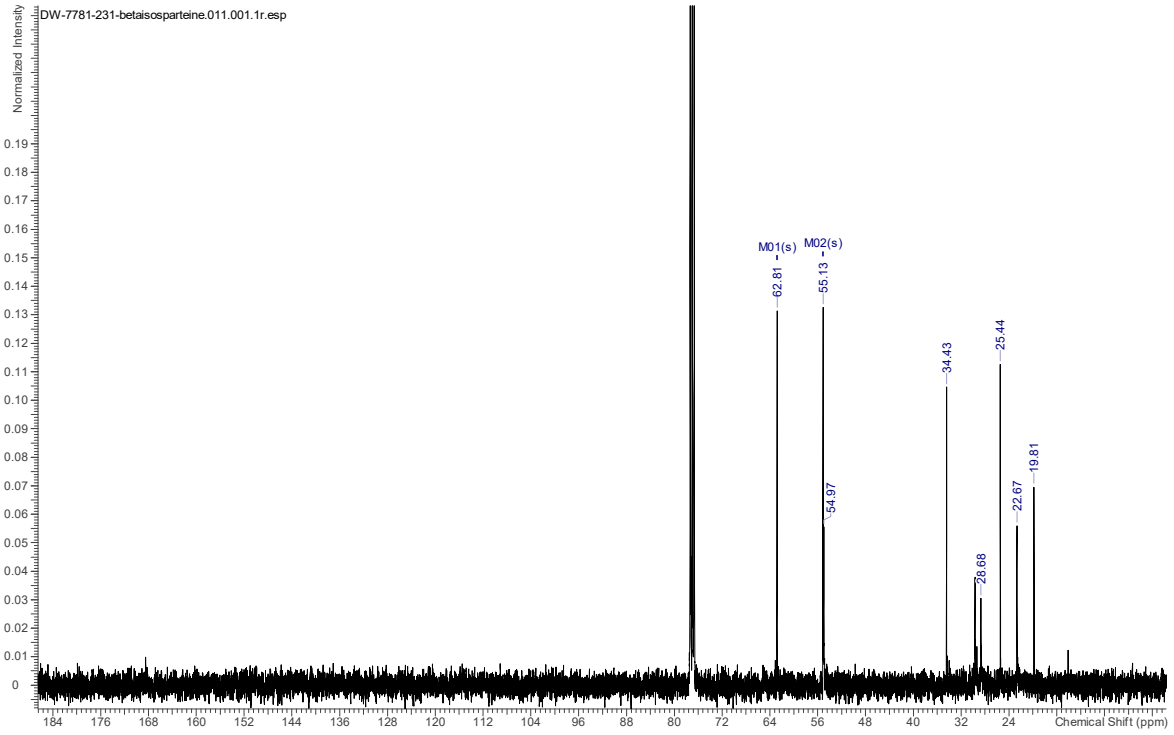
Appendix A Supplementary Data

A.1 NMR of (+)-1.6

A.1.1 ^{1}H NMR



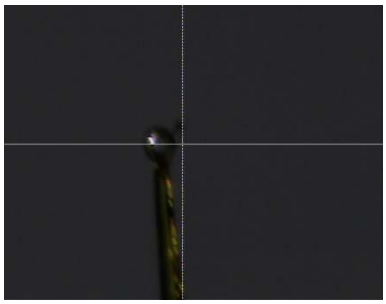
A.1.2 ^{13}C NMR



A.2 X-Ray Crystallography Data

A.2.1 *Anti*-alyklation product 4.84

Submitted by: **David Wheatley**
Supervisor: **Richard Brown**
Solved by: **Mark Edward Light**
X-ray ID: **2018sot0012_R1_100K**



Crystal Data and Experimental

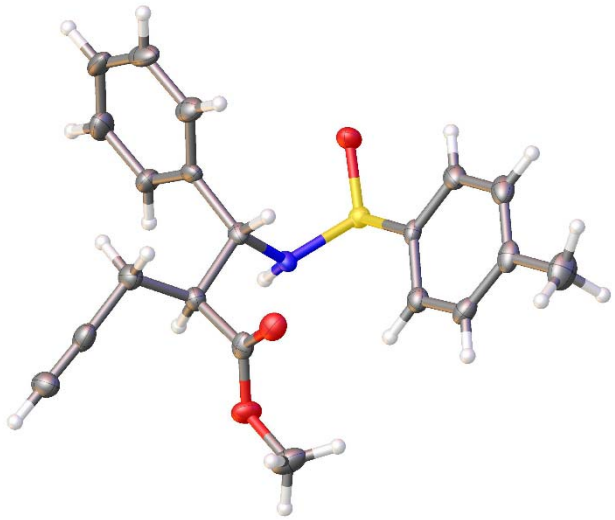


Figure 3: Thermal ellipsoids drawn at the 50% probability level.

Experimental. Single clear colourless needle-shaped crystals **DW/8572/43 P** were recrystallised from a mixture of DCM and hexane by slow evaporation. A suitable crystal 0.08×0.01×0.01 mm^3 was selected and mounted on a MITIGEN holder with silicon oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program using the Intrinsic Phasing solution method and by using **Olex2** (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{20}H_{21}NO_3S$, M_r = 355.44, hexagonal, $P6_5$ (No. 170), a = 19.2925(14) Å, b = 19.2925(14) Å, c = 8.8857(4) Å, α = 90°, β = 90°, γ = 120°, V = 2864.2(4) Å^3, T = 100(2) K, Z = 6, Z' = 1, μ(MoK$_\alpha$) = 0.187, 29895 reflections measured, 4830 unique (R_{int} = 0.0982) which were used in all calculations. The final wR_2 was 0.1142 (all data) and R_1 was 0.0752 (I > 2(I)).

Compound	**DW/8572/43 P**
Formula	$C_{20}H_{21}NO_3S$
$D_{calc.}$/ g cm^{-3}	1.236
μ/mm^{-1}	0.187
Formula Weight	355.44
Colour	clear colourless
Shape	needle
Size/mm^3	0.08×0.01×0.01
T/K	100(2)
Crystal System	hexagonal
Flack Parameter	0.03(5)
Hooft Parameter	0.02(4)
Space Group	$P6_5$
a/Å	19.2925(14)
b/Å	19.2925(14)
c/Å	8.8857(4)
α/°	90
β/°	90
γ/°	120
V/Å^3	2864.2(4)
Z	6
Z'	1
Wavelength/Å	0.71073
Radiation type	MoK$_\alpha$
Θ_{min}/°	2.111
Θ_{max}/°	28.500
Measured Refl.	29895
Independent Refl.	4830
Reflections with I >2(I)	3889

R_{int}	0.0982
Parameters	232
Restraints	1
Largest Peak	0.458
Deepest Hole	-0.352
GooF	1.058
wR_2 (all data)	0.1142
wR_2	0.1083
R_1 (all data)	0.0975
R_1	0.0752

Structure Quality Indicators

Reflections:

Refinement:

A clear colourless needle-shaped crystal with dimensions 0.08×0.01×0.01 mm^3 was mounted on a MITIGEN holder with silicon oil. X-ray diffraction data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100(2) K.

Data were measured using profile data from ω-scans of 0.5 ° per frame for 10.0 s using MoK_α radiation (Rotating-anode X-ray tube, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrysAlisPro** (Rigaku, V1.171.39.46b, 2018).The maximum resolution achieved was Θ = 28.500°.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.46b, 2018) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.46b, 2018) on 3810 reflections, 13 % of the observed reflections. Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.46b, 2018) software that corrects for Lorentz polarisation. The final completeness is 99.90 % out to 28.500° in Θ.

A multi-scan absorption correction was performed using CrysAlisPro 1.171.39.46b (Rigaku Oxford Diffraction, 2018) using spherical harmonics as implemented in SCALE3 ABSPACK.. The absorption coefficient μ of this material is 0.187 mm^{-1} at this wavelength (λ = 0.711Å) and the minimum and maximum transmissions are 0.611 and 1.000

The structure was solved in the space group $P6_5$ (# 170) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2016/6 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Most hydrogen atom positions were calculated geometrically and refined using the riding model, but some hydrogen atoms were refined freely.

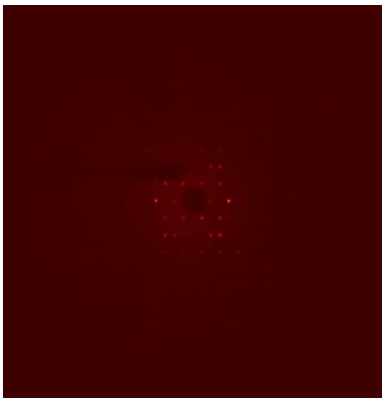
_refine_special_details: Solvent masking used, suspected solvent is water.

_exptl_absorpt_process_details: CrysAlisPro 1.171.39.46b (Rigaku Oxford Diffraction, 2018) using spherical harmonics as implemented in SCALE3 ABSPACK.

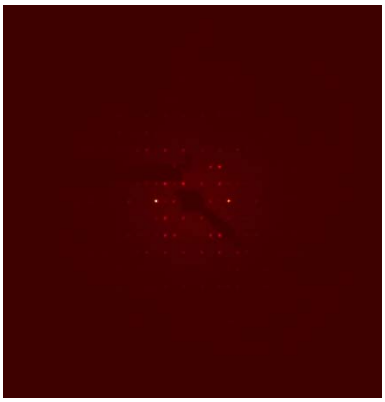
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 6 and Z' is 1.

The Flack parameter was refined to 0.03(5). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.02(4). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

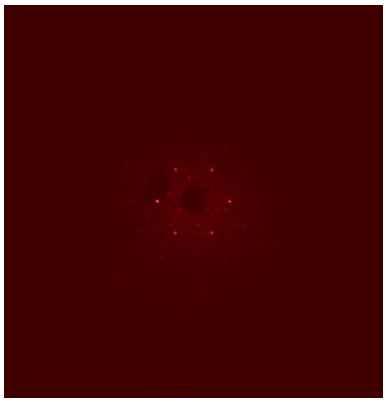
Generated images



0kl

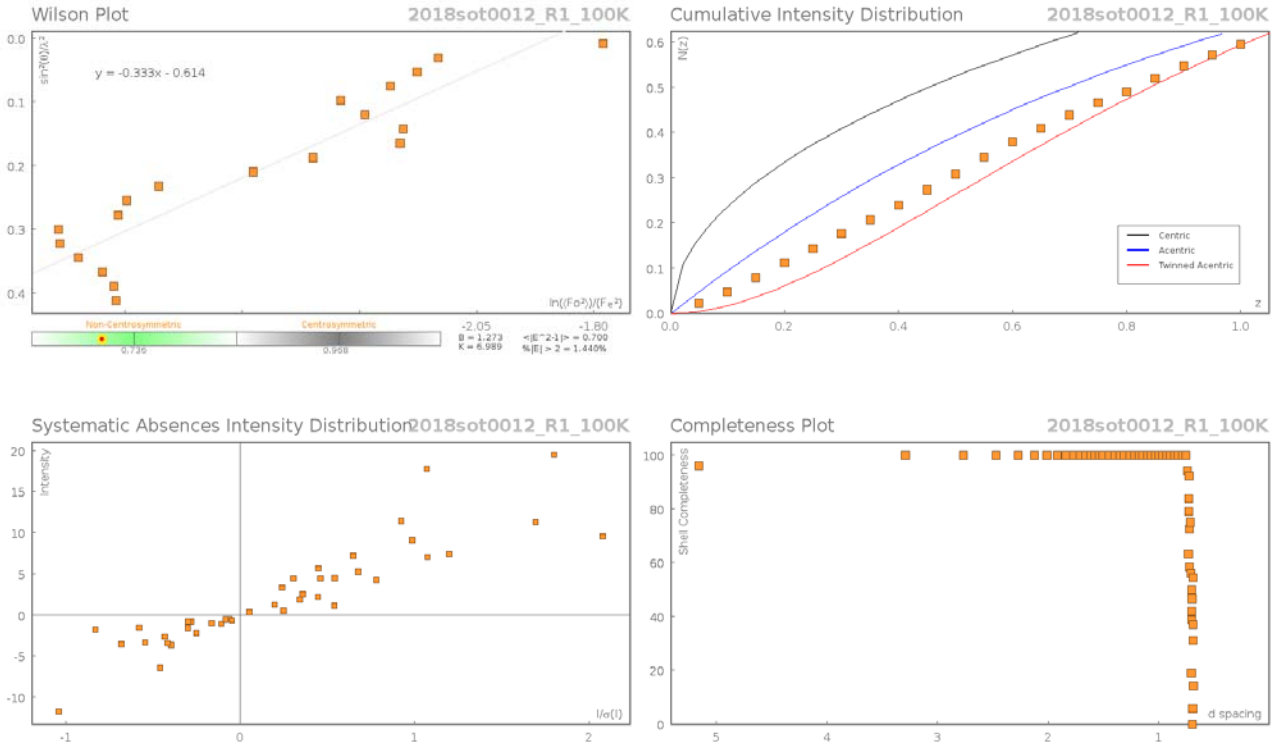


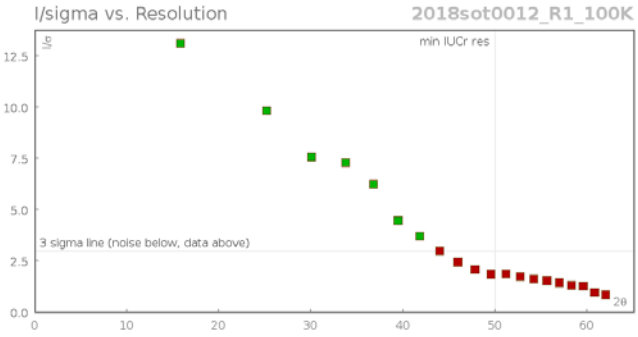
h0l



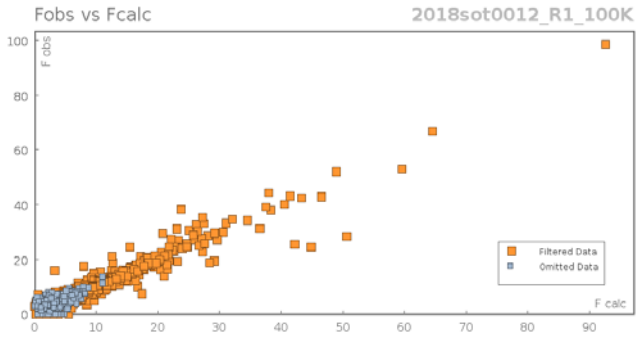
hk0

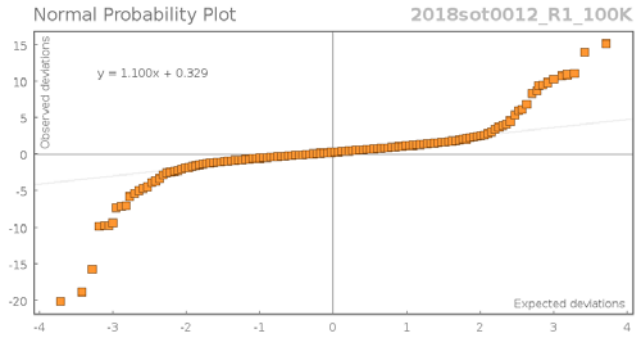
Data Plots: Diffraction Data





Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	29937	Unique reflections	4830
Completeness	0.998	Mean I/σ	11.92
hkl_{max} collected	(28, 22, 12)	hkl_{min} collected	(-21, -27, -12)
hkl_{max} used	(0, 25, 11)	hkl_{min} used	(-21, 0, -11)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.74
d_{max} used	9.65	d_{min} used	0.74
Friedel pairs	5415	Friedel pairs merged	0
Inconsistent equivalents	0	R_{int}	0.0982
R_{sigma}	0.0898	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(10920, 6050, 1995, 359, 84)	Maximum multiplicity	22
Removed systematic absences	42	Filtered off (Shel/OMIT)	924

Images of the Crystal on the Diffractometer

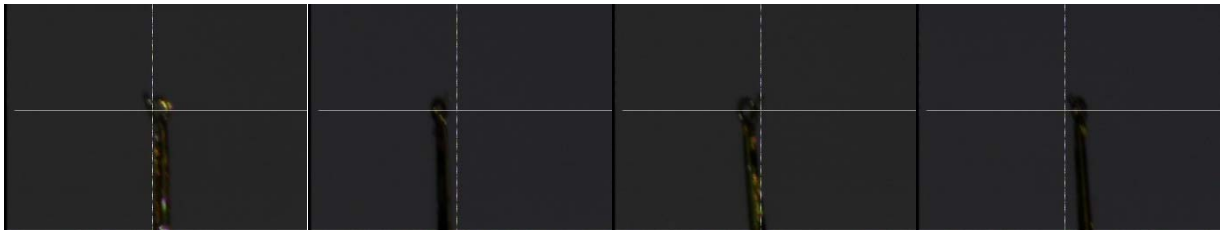


Table 2: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **2018sot0012_R1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
S1	7750.2(7)	418.8(7)	3600.6(11)	18.8(2)
O2	6606(2)	1842.4(19)	5555(3)	26.8(8)
O1	7419.4(19)	-404.4(19)	4220(3)	25.0(8)
O3	7862.6(19)	2852.2(19)	5322(4)	28.4(8)
N1	7963(2)	1108(2)	4920(4)	17.5(8)
C12	6906(3)	421(3)	2761(4)	17.8(9)
C2	7587(3)	2511(3)	9150(5)	28.5(12)
C13	6937(3)	1137(3)	2416(5)	23.5(10)
C15	5660(3)	400(3)	1151(5)	27.1(11)
C19	7310(3)	2143(3)	5846(5)	23.3(10)
C3	7330(3)	1721(3)	8468(5)	26.7(10)
C5	7449(3)	942(3)	6251(5)	20.0(10)
C14	6308(3)	1117(3)	1632(5)	25.0(11)
C16	5652(3)	-302(3)	1495(5)	29.4(12)
C17	6269(3)	-300(3)	2309(5)	23.9(10)
C1	7801(3)	3133(3)	9732(5)	31.0(12)
C4	7662(3)	1775(3)	6874(5)	22.7(10)
C9	7677(4)	-488(3)	9688(6)	40.1(15)
C11	6867(3)	-261(3)	7951(5)	31.0(12)
C10	6938(4)	-714(3)	9077(5)	38.0(14)
C8	8349(4)	180(3)	9162(6)	38.1(13)
C18	5006(3)	396(4)	224(6)	41.7(14)
C6	7541(3)	426(3)	7419(5)	22.0(10)

Atom	x	y	z	U_{eq}
C7	8287(3)	641(3)	8023(5)	28.4(11)
C20	7561(3)	3258(3)	4382(6)	37.9(14)

Table 3: Anisotropic Displacement Parameters (×10⁴) **2018sot0012_R1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	20.4(6)	19.7(6)	17.2(4)	0.3(4)	1.3(5)	10.5(5)
O2	30(2)	31.1(19)	26.2(17)	0.5(14)	3.7(15)	20.2(17)
O1	31(2)	18.8(18)	27.1(16)	-1.7(14)	-4.2(14)	14.0(16)
O3	30.6(19)	22.4(17)	35.2(18)	5.1(16)	-1.0(16)	15.5(16)
N1	16(2)	15.6(19)	17.4(17)	-1.4(14)	0.5(15)	5.1(17)
C12	16(2)	26(2)	11(2)	-0.1(17)	-0.5(16)	10(2)
C2	40(3)	34(3)	18(2)	3(2)	1(2)	24(3)
C13	24(3)	26(3)	17(2)	-0.1(19)	0.7(18)	11(2)
C15	22(3)	42(3)	16(2)	0(2)	2.7(19)	15(2)
C19	30(3)	30(3)	18(2)	-3.2(19)	1(2)	20(2)
C3	32(3)	26(3)	22(2)	0(2)	3(2)	14(2)
C5	18(2)	20(2)	17(2)	0.2(18)	2.9(18)	6(2)
C14	30(3)	31(3)	19(2)	5(2)	3.2(19)	19(2)
C16	25(3)	33(3)	20(2)	0(2)	1.5(19)	7(2)
C17	24(3)	24(3)	19(2)	0.5(18)	3.1(19)	8(2)
C1	37(3)	25(3)	29(3)	0(2)	4(2)	14(2)
C4	27(2)	21(2)	19(2)	-2(2)	-2(2)	11(2)
C9	80(5)	28(3)	20(2)	3(2)	-4(3)	32(3)
C11	41(3)	27(3)	24(2)	5(2)	10(2)	16(3)
C10	59(4)	23(3)	27(3)	7(2)	17(3)	16(3)
C8	55(4)	34(3)	29(3)	-3(2)	-15(3)	25(3)
C18	32(3)	58(4)	34(3)	2(3)	-5(3)	22(3)
C6	32(3)	15(2)	18(2)	-2.2(17)	2.1(19)	11(2)
C7	39(3)	24(3)	22(2)	3(2)	-4(2)	16(2)
C20	43(3)	35(3)	42(3)	15(3)	7(3)	23(3)

Table 4: Bond Lengths in Å for **2018sot0012_R1_100K**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.489(3)	C15	C16	1.381(7)
S1	N1	1.662(4)	C15	C18	1.503(7)
S1	C12	1.793(4)	C19	C4	1.510(6)
O2	C19	1.207(6)	C3	C4	1.536(6)
O3	C19	1.330(6)	C5	C4	1.550(6)
O3	C20	1.452(6)	C5	C6	1.509(6)
N1	C5	1.472(5)	C16	C17	1.391(7)
C12	C13	1.388(6)	C9	C10	1.378(8)
C12	C17	1.377(6)	C9	C8	1.375(8)
C2	C3	1.476(7)	C11	C10	1.380(7)
C2	C1	1.175(7)	C11	C6	1.395(7)
C13	C14	1.382(6)	C8	C7	1.390(7)
C15	C14	1.389(7)	C6	C7	1.392(7)

Table 5: Bond Angles in ° for **2018sot0012_R1_100K**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	N1	113.25(18)	C16	C15	C14	118.1(4)
O1	S1	C12	104.5(2)	C16	C15	C18	121.3(5)
N1	S1	C12	98.8(2)	O2	C19	O3	123.4(4)
C19	O3	C20	115.1(4)	O2	C19	C4	124.5(4)
C5	N1	S1	121.5(3)	O3	C19	C4	112.2(4)
C13	C12	S1	120.5(3)	C2	C3	C4	113.3(4)
C17	C12	S1	118.2(4)	N1	C5	C4	105.2(3)
C17	C12	C13	120.9(4)	N1	C5	C6	114.1(4)
C1	C2	C3	177.8(5)	C6	C5	C4	112.4(3)
C14	C13	C12	118.9(4)	C13	C14	C15	121.6(5)
C14	C15	C18	120.6(5)	C15	C16	C17	121.5(5)

Atom	Atom	Atom	Angle/°
C12	C17	C16	119.0(5)
C19	C4	C3	108.7(4)
C19	C4	C5	108.9(4)
C3	C4	C5	112.0(4)
C8	C9	C10	120.3(5)
C10	C11	C6	120.4(5)
C9	C10	C11	120.0(5)
C9	C8	C7	120.3(5)
C11	C6	C5	119.9(4)
C7	C6	C5	120.9(4)
C7	C6	C11	119.1(4)
C8	C7	C6	119.8(5)

Table 6: Hydrogen Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **2018sot0012_R1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H13	7372.94	1623.24	2706.95	28
H3A	6750.4	1419.94	8429.99	32
H3B	7505.6	1430.21	9106.12	32
H5	6890.37	669.13	5917	24
H14	6318.56	1594.14	1421.43	30
H16	5224.26	-787.26	1175.75	35
H17	6251.36	-778.41	2544.86	29
H1A	7971	3625.32	10192.13	37
H4	8245.03	2119.11	6894.04	27
H9	7722.16	-788.91	10459.63	48
H11	6366.51	-414.87	7542.9	37
H10	6486.44	-1172.43	9423.13	46
H8	8847.39	325.37	9569.71	46
H18A	4874.13	776.89	629.95	63
H18B	4541.14	-128.39	245.75	63
H18C	5186.01	537.84	-795.97	63
H7	8743.59	1090.61	7665.53	34
H20A	7338.62	2956.65	3475.64	57
H20B	7990.68	3782.67	4132.08	57
H20C	7153.11	3304.31	4916.68	57
H1	8490(30)	1370(20)	5110(40)	8(10)

Table 7: Solvent masking (Olex2) information for **2018sot0012_R1_100K**.

No	x	y	z	V	e	Content
1	0.000	0.000	-0.167	213.1	66.2	water

Citations

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2018).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

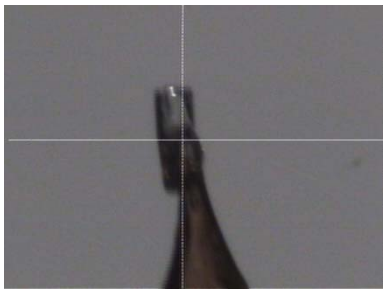
Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

A.2.2 Electrochemical product 6.29

2017sot0037_K1_100K

Submitted by: **David Wheatley**
Supervisor: **Richard C Brown**
Solved by: **Mark Edward Light**
X-ray ID: **2017sot0037_K1_100K**



Crystal Data and Experimental

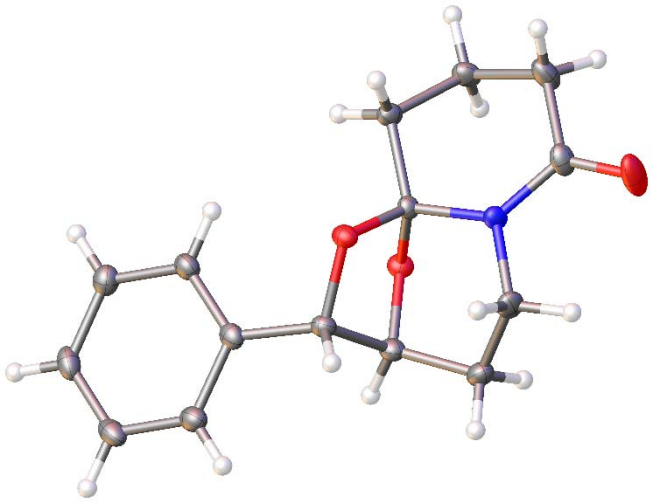


Figure 4: Thermal ellipsoids drawn at the 50% probability level, second molecule in the asymmetric unit omitted for clarity.

Experimental. Single clear colourless prism-shaped crystals of (**DW/8238/IF1C2**) were recrystallised from a mixture of DCM and hexane by slow evaporation. A suitable crystal (0.21×0.10×0.07) mm^3 was selected and mounted on a MITIGEN holder silicon oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{15}H_{17}NO_3$, M_r = 259.29, monoclinic, $P2_1/c$ (No. 14), a = 10.5176(8) Å, b = 19.3524(4) Å, c = 19.9938(16) Å, β = 141.147(16)°, α = γ = 90°, V = 2552.9(6) Å^3, T = 100(2) K, Z = 8, Z' = 2, μ(MoK$_\alpha$) = 0.094, 34273 reflections measured, 6470 unique (R_{int} = 0.0292) which were used in all calculations. The final wR_2 was 0.1172 (all data) and R_1 was 0.0549 (I > 2(I)).

Compound	**DW/8238/IF1C2**
Formula	$C_{15}H_{17}NO_3$
$D_{calc.}$/ g cm^{-3}	1.349
μ/mm^{-1}	0.094
Formula Weight	259.29
Colour	clear colourless
Shape	prism
Size/mm^3	0.21×0.10×0.07
T/K	100(2)
Crystal System	monoclinic
Flack Parameter	**None**
Hooft Parameter	**None**
Space Group	$P2_1/c$
a/Å	10.5176(8)
b/Å	19.3524(4)
c/Å	19.9938(16)
α/°	90
β/°	141.147(16)
γ/°	90
V/Å^3	2552.9(6)
Z	8
Z'	2
Wavelength/Å	0.71073
Radiation type	MoK_α
Θ_{min}/°	2.965
Θ_{max}/°	28.495
Measured Refl.	34273
Independent Refl.	6470
Reflections Used	6033
R_{int}	0.0292

Parameters	343
Restraints	0
Largest Peak	0.379
Deepest Hole	-0.266
GooF	1.175
wR_2 (all data)	0.1172
wR_2	0.1145
R_1 (all data)	0.0602
$\boldsymbol{R_1}$	**0.0549**

Structure Quality Indicators

Reflections:	d min (Mo) 0.74	I/σ 26.1	Rint 2.92%	complete at 2θ=57° 100%
Refinement:	Shift 0.000	Max Peak 0.4	Min Peak -0.3	GooF 1.175

A clear colourless prism-shaped crystal with dimensions 0.21×0.10×0.07 mm^3 was mounted on a MITIGEN holder silicon oil. X-ray diffraction data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100(2) K.

Data were measured using profile data from ω-scans of 1.0 ° per frame for 10.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015).The maximum resolution achieved was Θ = 28.495°.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) on 14544 reflections, 42 % of the observed reflections. Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software that corrects for Lorentz polarisation. The final completeness is 99.90 % out to 28.495° in Θ.

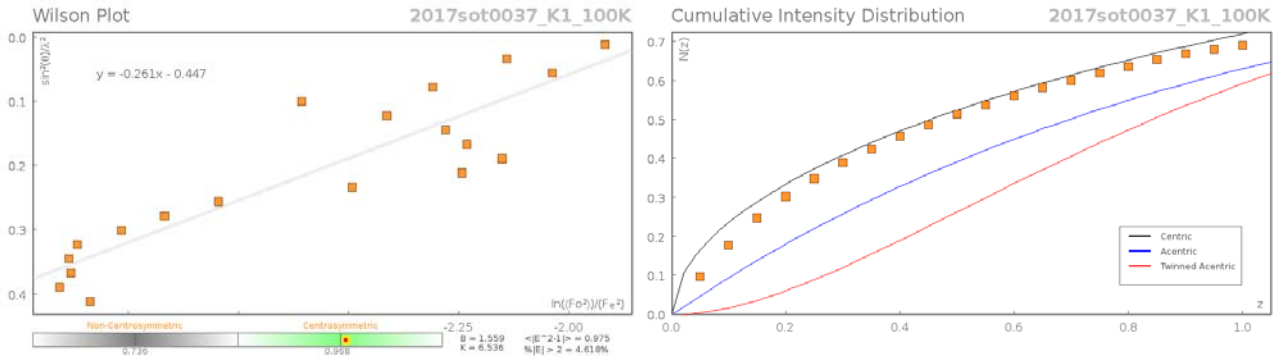
A multi-scan absorption correction was performed using CrysAlisPro 1.171.39.9g (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient μ of this material is 0.094 mm^{-1}, at this wavelength (λ = 0.71073Å) and the minimum and maximum transmissions are 0.76603 and 1.00000.

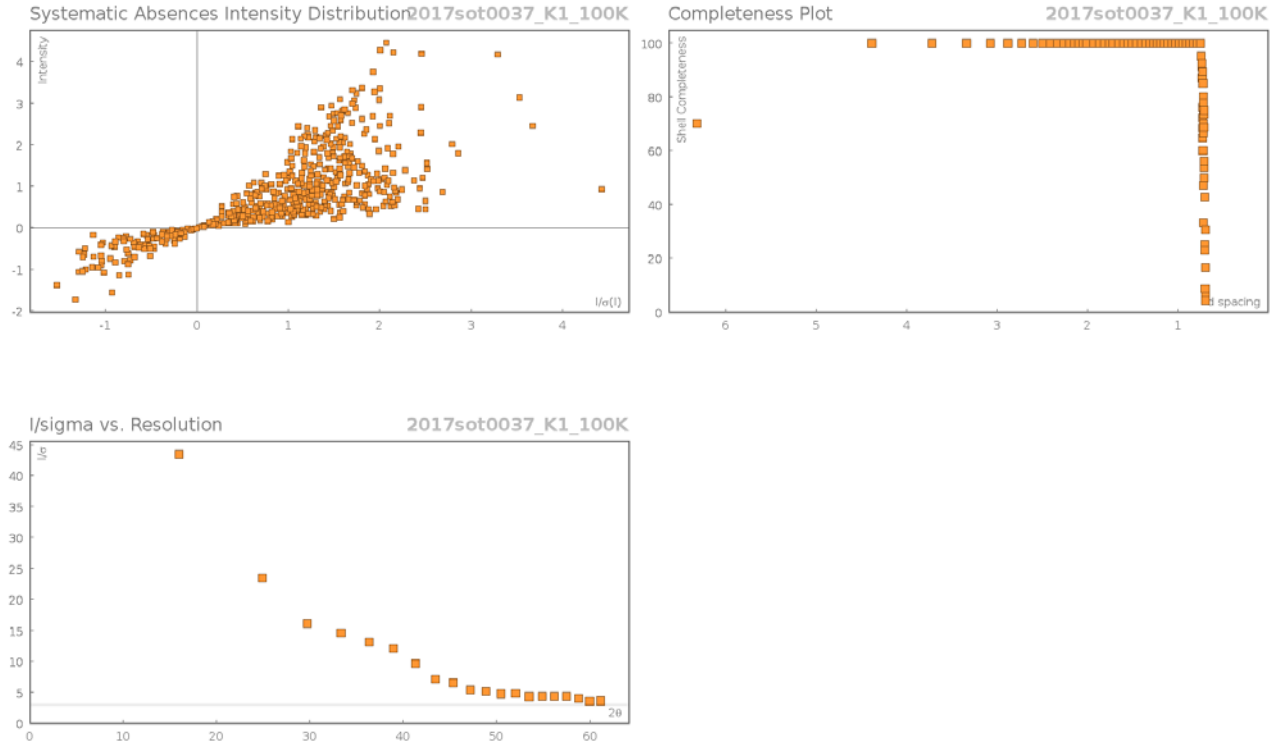
The structure was solved in the space group P2$_1$/c (# 14) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2016/6 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

_exptl_absorpt_process_details: CrysAlisPro 1.171.39.9g (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

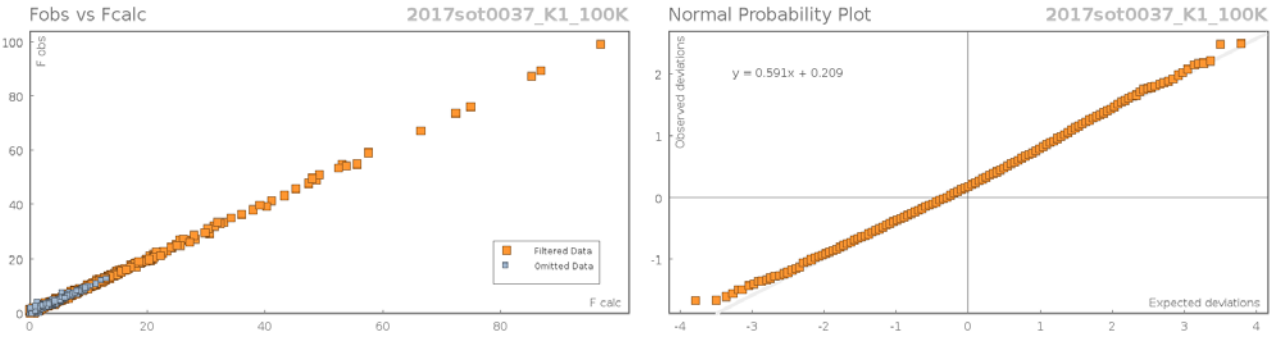
The value of Z' is 2. This means that there are two independent molecules in the asymmetric unit.

Data Plots: Diffraction Data





Data Plots: Refinement and Data



Reflection Statistics

Total reflections (after filtering)	34960	Unique reflections	6470
Completeness	1.0	Mean I/σ	26.12
hkl_{max} collected	(14, 26, 28)	hkl_{min} collected	(-15, -27, -21)
hkl_{max} used	(8, 25, 26)	hkl_{min} used	(-14, 0, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.74
d_{max} used	6.87	d_{min} used	0.74

Friedel pairs	6529	Friedel pairs merged	1
Inconsistent equivalents	4	R_{int}	0.0292
R_{sigma}	0.0232	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(9901, 6860, 3352, 640, 128, 10)	Maximum multiplicity	19
Removed systematic absences	687	Filtered off (Shel/OMIT)	1977

Images of the Crystal on the Diffractometer

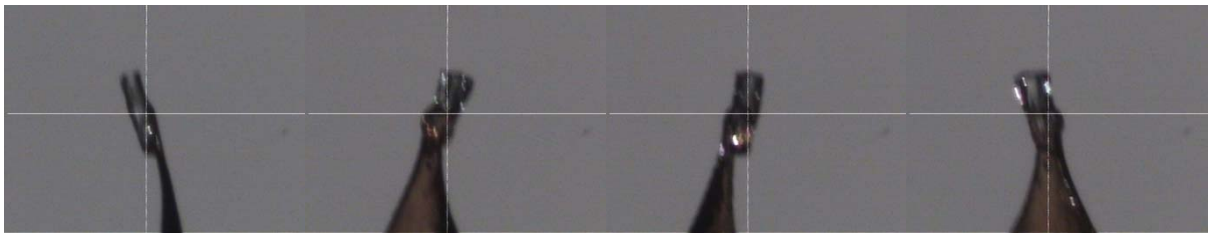


Table 8: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **2017sot0037_K1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
C101	6541(2)	5624.0(8)	7405.1(11)	18.9(3)
C102	8309(2)	5338.5(8)	8390.2(12)	21.7(3)
C103	9557(2)	5729.3(8)	9313.1(12)	22.4(3)
C104	9027(2)	6403.2(8)	9254.3(12)	22.9(3)
C105	7266(2)	6688.3(8)	8270.5(12)	20.0(3)
C106	6018(2)	6302.5(7)	7338.5(11)	16.8(3)
C107	4221(2)	6654.9(7)	6277.4(11)	15.6(3)
C108	4856(2)	7044.2(7)	5901.5(11)	17.2(3)
C109	3368(2)	7611.3(7)	5098.8(12)	21.1(3)
C110	1214(2)	7330.3(7)	4198.3(12)	20.6(3)
C111	2808.7(19)	6193.6(7)	4732.5(10)	13.1(2)
C112	2606(2)	5480.2(7)	4362.7(11)	17.2(3)
C113	2139(2)	5502.5(8)	3429.5(11)	20.1(3)
C114	146(2)	5883.6(9)	2505.2(12)	24.6(3)

Atom	x	y	z	U_{eq}
C115	-35(2)	6557.3(8)	2807.9(11)	20.6(3)
N101	1210.8(17)	6661.4(6)	3849.8(9)	15.6(2)
O101	2758.4(14)	6165.5(5)	5423.9(7)	15.3(2)
O102	4705.5(14)	6491.5(5)	5355.9(7)	15.1(2)
O103	-1299.5(19)	6988.2(7)	2124.7(9)	34.6(3)
C201	12354(2)	6044.3(8)	7311.1(12)	23.5(3)
C202	14166(2)	5781.4(8)	8300.9(13)	26.4(3)
C203	14424(2)	5685.1(8)	9087.5(12)	27.2(4)
C204	12870(3)	5848.3(8)	8889.3(12)	27.5(3)
C205	11055(2)	6115.7(8)	7899.3(12)	22.2(3)
C206	10782(2)	6218.2(7)	7106.5(11)	18.2(3)
C207	8806(2)	6512.9(7)	6047.0(11)	17.1(3)
C208	8966(2)	7162.6(7)	5675.4(11)	16.2(3)
C209	7025(2)	7585.2(7)	4882.6(11)	18.2(3)
C210	5191(2)	7141.6(8)	3942.2(11)	18.6(3)
C211	7716(2)	6332.7(7)	4505.2(11)	15.9(3)
C212	8153(2)	5790.3(8)	4161.7(12)	22.6(3)
C213	7260(2)	5981.2(9)	3124.2(13)	26.2(3)
C214	4985(2)	6036.7(8)	2269.7(12)	22.4(3)
C215	4336(2)	6510.1(8)	2567.0(12)	23.0(3)
N201	5712.6(17)	6658.9(6)	3611.2(9)	15.9(2)
O201	7822.4(15)	6029.3(5)	5193.7(8)	19.2(2)
O202	9191.4(14)	6857.8(5)	5108.0(8)	16.2(2)
O203	2628(2)	6751.8(8)	1880.3(10)	53.8(5)

Table 9: Anisotropic Displacement Parameters (×10⁴) **2017sot0037_K1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C101	20.2(7)	21.1(7)	15.3(6)	-0.8(5)	13.9(6)	-1.1(5)
C102	22.9(7)	22.1(7)	21.2(7)	3.5(6)	17.4(7)	2.7(6)
C103	17.2(7)	30.0(8)	14.8(6)	4.2(6)	11.1(6)	-1.0(6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C104	22.5(7)	27.2(8)	16.1(7)	-4.6(6)	14.3(6)	-8.9(6)
C105	23.6(7)	19.3(7)	18.9(7)	-2.6(5)	17.0(6)	-3.8(6)
C106	18.0(6)	19.9(7)	15.4(6)	-0.6(5)	13.7(6)	-2.5(5)
C107	16.5(6)	15.2(6)	15.3(6)	-2.5(5)	12.4(6)	-1.9(5)
C108	17.9(6)	16.7(7)	16.3(6)	-2.8(5)	13.2(6)	-3.5(5)
C109	27.5(8)	14.3(6)	21.8(7)	-1.0(5)	19.3(7)	-0.9(6)
C110	24.1(7)	15.2(7)	20.9(7)	2.3(5)	17.1(7)	6.6(6)
C111	11.0(6)	14.4(6)	11.5(6)	0.9(5)	8.2(5)	1.3(5)
C112	16.3(6)	13.7(6)	15.8(6)	-0.7(5)	11.1(6)	1.3(5)
C113	20.2(7)	19.1(7)	17.8(7)	-2.7(5)	14.0(6)	1.9(5)
C114	22.5(7)	30.1(8)	14.7(6)	-0.4(6)	12.9(6)	6.3(6)
C115	17.5(7)	26.3(8)	16.0(7)	3.8(6)	12.5(6)	6.4(6)
N101	14.6(5)	13.9(5)	13.4(5)	0.5(4)	9.7(5)	3.2(4)
O101	15.3(5)	16.5(5)	15.4(4)	-2.5(4)	12.3(4)	-3.4(4)
O102	12.2(4)	16.8(5)	15.6(5)	-1.7(4)	10.6(4)	-1.7(4)
O103	34.2(7)	41.1(7)	18.8(5)	11.9(5)	18.2(6)	23.0(6)
C201	17.8(7)	26.6(8)	19.2(7)	4.7(6)	12.7(6)	-0.2(6)
C202	17.5(7)	22.1(8)	24.1(8)	4.0(6)	12.3(7)	0.7(6)
C203	22.9(8)	17.1(7)	14.9(7)	2.0(5)	8.0(6)	0.6(6)
C204	36.8(9)	19.9(7)	17.2(7)	1.3(6)	18.9(7)	2.1(7)
C205	26.8(8)	16.9(7)	20.2(7)	-0.3(5)	17.6(7)	0.2(6)
C206	16.6(6)	14.6(6)	16.6(6)	1.1(5)	11.2(6)	-1.7(5)
C207	14.1(6)	18.2(7)	15.6(6)	1.5(5)	10.7(6)	-1.0(5)
C208	16.2(6)	15.8(6)	15.1(6)	-0.3(5)	11.7(6)	-1.0(5)
C209	20.3(7)	16.9(7)	17.3(6)	1.4(5)	14.6(6)	2.1(5)
C210	16.3(6)	20.7(7)	17.2(6)	1.8(5)	12.6(6)	4.2(5)
C211	11.6(6)	15.3(6)	15.3(6)	-0.1(5)	9.1(6)	-0.6(5)
C212	13.6(6)	21.0(7)	23.4(7)	-5.0(6)	11.9(6)	0.0(5)
C213	29.6(8)	25.5(8)	35.3(9)	-11.5(7)	28.2(8)	-8.7(6)
C214	28.3(8)	19.5(7)	19.2(7)	0.2(5)	18.5(7)	0.9(6)
C215	22.9(7)	20.6(7)	16.0(7)	2.0(5)	12.7(6)	3.9(6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N201	12.5(5)	17.4(6)	14.0(5)	0.7(4)	9.4(5)	1.3(4)
O201	15.8(5)	16.8(5)	15.7(5)	1.0(4)	10.0(4)	-3.5(4)
O202	14.7(5)	16.8(5)	17.4(5)	-2.9(4)	12.6(4)	-3.6(4)
O203	31.9(7)	63.7(10)	15.4(6)	-2.2(6)	5.7(6)	28.9(7)

Table 10: Bond Lengths in Å for **2017sot0037_K1_100K**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C101	C102	1.392(2)	C201	C202	1.390(2)
C101	C106	1.389(2)	C201	C206	1.400(2)
C102	C103	1.388(2)	C202	C203	1.385(2)
C103	C104	1.387(2)	C203	C204	1.385(3)
C104	C105	1.389(2)	C204	C205	1.395(2)
C105	C106	1.394(2)	C205	C206	1.387(2)
C106	C107	1.514(2)	C206	C207	1.508(2)
C107	C108	1.5365(19)	C207	C208	1.5351(19)
C107	O101	1.4445(16)	C207	O201	1.4517(17)
C108	C109	1.522(2)	C208	C209	1.5196(19)
C108	O102	1.4455(16)	C208	O202	1.4527(17)
C109	C110	1.522(2)	C209	C210	1.531(2)
C110	N101	1.4689(17)	C210	N201	1.4755(18)
C111	C112	1.5008(18)	C211	C212	1.508(2)
C111	N101	1.4626(17)	C211	N201	1.4723(18)
C111	O101	1.4251(16)	C211	O201	1.4188(17)
C111	O102	1.4117(16)	C211	O202	1.4072(16)
C112	C113	1.515(2)	C212	C213	1.513(2)
C113	C114	1.523(2)	C213	C214	1.513(2)
C114	C115	1.511(2)	C214	C215	1.513(2)
C115	N101	1.3584(18)	C215	N201	1.3528(19)
C115	O103	1.2249(18)	C215	O203	1.221(2)

Table 11: Bond Angles in ° for **2017sot0037_K1_100K**.

Atom	Atom	Atom	Angle/°
C106	C101	C102	120.24(14)
C103	C102	C101	120.19(14)
C104	C103	C102	119.87(14)
C103	C104	C105	119.88(14)
C104	C105	C106	120.62(14)
C101	C106	C105	119.19(13)
C101	C106	C107	121.94(12)
C105	C106	C107	118.70(13)
C106	C107	C108	111.23(11)
O101	C107	C106	112.26(11)
O101	C107	C108	102.26(10)
C109	C108	C107	112.80(12)
O102	C108	C107	99.92(10)
O102	C108	C109	108.62(11)
C108	C109	C110	110.52(12)
N101	C110	C109	109.10(12)
N101	C111	C112	112.71(11)
O101	C111	C112	110.15(11)
O101	C111	N101	108.56(10)
O102	C111	C112	111.81(11)
O102	C111	N101	108.57(11)
O102	C111	O101	104.69(10)
C111	C112	C113	111.46(12)
C112	C113	C114	109.16(12)
C115	C114	C113	114.56(12)
N101	C115	C114	118.05(13)
O103	C115	C114	120.45(13)
O103	C115	N101	121.48(14)
C111	N101	C110	113.40(11)
C115	N101	C110	120.08(12)
C115	N101	C111	126.04(12)
C111	O101	C107	108.12(10)
C111	O102	C108	102.57(10)
C202	C201	C206	120.13(15)
C203	C202	C201	120.29(16)
C202	C203	C204	120.03(14)
C203	C204	C205	119.81(15)
C206	C205	C204	120.73(15)
C201	C206	C207	121.53(13)
C205	C206	C201	119.01(14)
C205	C206	C207	119.46(13)
C206	C207	C208	116.04(11)
O201	C207	C206	110.39(11)
O201	C207	C208	101.86(11)
C209	C208	C207	112.39(12)
O202	C208	C207	101.05(11)
O202	C208	C209	107.92(11)
C208	C209	C210	111.32(12)
N201	C210	C209	110.67(11)
N201	C211	C212	113.65(11)
O201	C211	C212	109.39(12)
O201	C211	N201	108.18(11)
O202	C211	C212	111.65(11)
O202	C211	N201	108.12(11)

Atom	Atom	Atom	Angle/°
O202	C211	O201	105.46(11)
C211	C212	C213	111.75(13)
C212	C213	C214	108.22(13)
C213	C214	C215	113.56(13)
N201	C215	C214	117.85(13)
O203	C215	C214	120.61(14)
O203	C215	N201	121.54(15)
C211	N201	C210	114.06(11)
C215	N201	C210	120.15(12)
C215	N201	C211	125.59(12)
C211	O201	C207	108.62(10)
C211	O202	C208	102.74(10)

Table 12: Hydrogen Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **2017sot0037_K1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H101	5689.28	5353.95	6776.07	23
H102	8662.7	4874.88	8431.11	26
H103	10771.86	5535.49	9983.56	27
H104	9865.67	6669.27	9885.7	27
H105	6909.64	7150.64	8232.42	24
H107	3559.87	6978.54	6329.63	19
H108	6272.88	7224.4	6516.41	21
H10A	3731.23	7797.45	4802.06	25
H10B	3452.14	7993.46	5461.17	25
H11A	697.99	7272.07	4448.46	25
H11B	316.89	7659.31	3593.85	25
H11C	1507.47	5231.18	4148.58	21
H11D	3883.81	5222.76	4958.78	21
H11E	2034.11	5026.49	3208.67	24
H11F	3244.03	5742.84	3641.47	24
H11G	-12.15	5978.33	1956.62	30
H11H	-981.26	5577.12	2180.39	30
H201	12181.26	6106.01	6772.6	28
H202	15232.53	5667.45	8438.1	32
H203	15667.03	5506.96	9763.41	33
H204	13040.96	5778.27	9426.04	33
H205	9993.56	6228.87	7766.39	27
H207	7893.82	6608.49	6062.03	21
H208	10168.89	7449.82	6291.92	19
H20A	7154.47	7971.68	4614.26	22
H20B	6812.82	7784.4	5246.48	22
H21A	4732.35	6877	4150.24	22

Atom	x	y	z	U_{eq}
H21B	4063.85	7444.32	3335.72	22
H21C	7580.97	5342.6	4075.02	27
H21D	9637.54	5733.81	4724.1	27
H21E	7598.61	5623.15	2927.37	31
H21F	7824.13	6427.83	3201.35	31
H21G	4424.09	5569.87	2122.17	27
H21H	4399.62	6209.1	1605.6	27

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