
A Cascade Approach Towards the Gephyrotoxins

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Dedication

This thesis is dedicated to my grandpa, William Elliot Simpson, who passed away during the first two months of my graduate studies.

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory, Mansfield Road, Oxford between October 2008 and December 2011. The dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

A handwritten signature in black ink, appearing to read 'Stephen Wallace', followed by a period.

Stephen Wallace

Acknowledgements

I would like to begin by thanking the Department of Chemistry at the University of Oxford and the Engineering and Physical Sciences Research Council for funding my DPhil studies.

On a more personal note; I have been so fortunate to spend the past three years within such a friendly, inspiring and nurturing research group. For this I have to primarily thank my supervisor Dr Martin D. Smith; whose guidance and vivacious interest in chemistry have made my time in the Smith Group such a joy. My time spent in “Team Cascade” on such a challenging project, as well as teaching me determination and perseverance, has given me so much pleasure.

I have formed so many wonderful friendships during my time in Oxford. I can’t begin to name and thank you all individually, and duly. To all the members of the Smith Group, past and present; I have been so lucky to work with you all. To everyone else, you know who you are, thank you. The last three years have been so much fun!

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Thank you to my amazing mum, my gorgeous little sister, my dad and my godmother for all your love, gin and support. You are all a part of everything I am and have accomplished over the years.

Finally, thank you to Phil. I simply could not have done this without you. I love you dearly.

Abbreviations

Ac	acetyl	DMF	<i>N,N</i> -dimethylformamide
alk	alkyl	DMP	Dess-Martin periodinane
anh.	anhydrous	DMSO	dimethylsulfoxide
aq.	aqueous	DQF	Double Quantum Filtered
atm.	atmospheres	dr	diastereomeric ratio
BAIB	(diacetoxyiodo)benzene	EI	Electron Impact Ionisation
Bn	benzyl	eq.	equivalents
Boc	<i>tert</i> -butoxycarbonyl	ESI	Electrospray Ionisation
BOM	benzyloxymethylene	Et	ethyl
brsm	based on reacted starting material	eV	electron volts
Bu	butyl	h	hours
Bz	benzoyl	HMBC	Heteronuclear Multiple Bond Correlation
cat.	catalytic	HPLC	High Performance Liquid Chromatography
COSY	Correlation Spectroscopy	HSQC	Heteronuclear Single Quantum Correlation
Cy	cyclohexyl	<i>i</i>	<i>iso</i>
Δ	reflux	imid.	imidazole
DCM	dichloromethane	IPA	<i>iso</i> -propyl alcohol
DFT	Density Functional Theory	IR	infrared
DIBAL-H	diisobutylaluminium hydride	<i>L</i>-Selectride®	lithium tri- <i>sec</i> -butylborohydride
DMAP	4-(dimethylamino)pyridine		

M	mol dm ⁻³	PS	polymer-supported
mCPBA	<i>meta</i> -chloroperbenzoic acid	pTSA	<i>para</i> -toluenesulfonic acid
Me	methyl	py.	pyridine
min	minutes	quant.	quantitative
mol	mole	rac	racemic
MOM	methoxymethyl	Red-Al	sodium <i>bis</i> (2-methoxyethoxy)- aluminium hydride
Ms	methanesulfonyl	rt	room temperature
MS	molecular sieves/mass spectrometry	SM	starting material
μw	microwaves	t	<i>tertiary</i>
n	<i>neo</i>	TBAF	tetrabutylammonium fluoride
N	normal	TBAI	tetrabutylammonium iodide
NMR	Nuclear Magnetic Resonance	TBDPS	tertiary-butyl diphenylsilyl
nOe	Nuclear Overhauser Effect	TBME	tertiary-butyl methyl ether
NOESY	Nuclear Overhauser Effect Spectroscopy	TBS	tertiary-butyl dimethylsilyl
p	<i>para</i>	TEBH	triethylborohydride
PCC	pyridinium chlorochromate	TEMPO	2,2,6,6-tetramethyl-1- piperidinyloxy, free radical
Ph	phenyl	tert	<i>tertiary</i>
PMB	<i>para</i> -methoxybenzyl	TES	triethylsilyl
ppm	parts per million	TFA	trifluoroacetic acid
Pr	propyl		

THF	tetrahydrofuran	TOCSY	Total Correlation Spectroscopy
THP	tetrahydropyranyl		
TIPS	triisopropylsilyl	tol	toluene
t_{mix}	mixing time	TS	transition state
TMS	trimethylsilyl	UV	ultra-violet

“The pathways of synthesis are circuitous, bumpy, and even treacherous. Seldom do straight lines suffice to connect points in a synthesis of real consequence. For younger and more optimistic enthusiasts, it is appropriate to underscore the uncertainties, the detours and, yes, the frustrations associated with Organic Synthesis. Success is often a prize reserved for those who temper noble ideas with appropriate measures of realism and scepticism. Given the episodic nature of our science, wisdom may well be more valuable than cleverness.” **Prof. Samuel Danishefsky**

“The feature of constant struggle to surmount obstacles, coupled with serendipity, is often underappreciated, even though it is pivotal for invention, discovery, and, dare we say, adventure and excitement in chemical synthesis.” **Prof. K. C. Nicolaou**

“... I want to tear off the mask of nature, and stare into the face of God.” **Dr Sheldon Cooper**

Abstract

The aim of this project was to develop a cascade approach towards perhydropyrrolo-[1,2-*a*]-quinolines and to apply this to the asymmetric synthesis of the gephyrotoxin alkaloids.

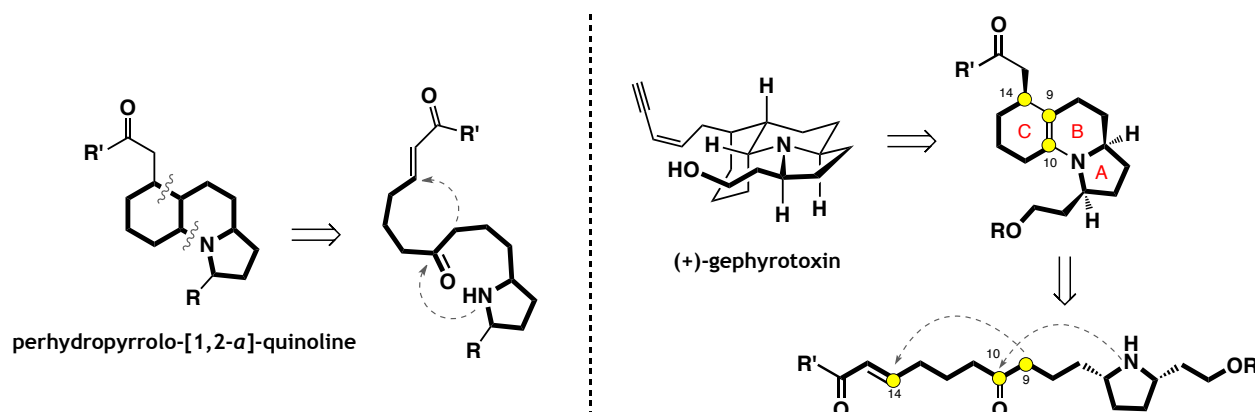
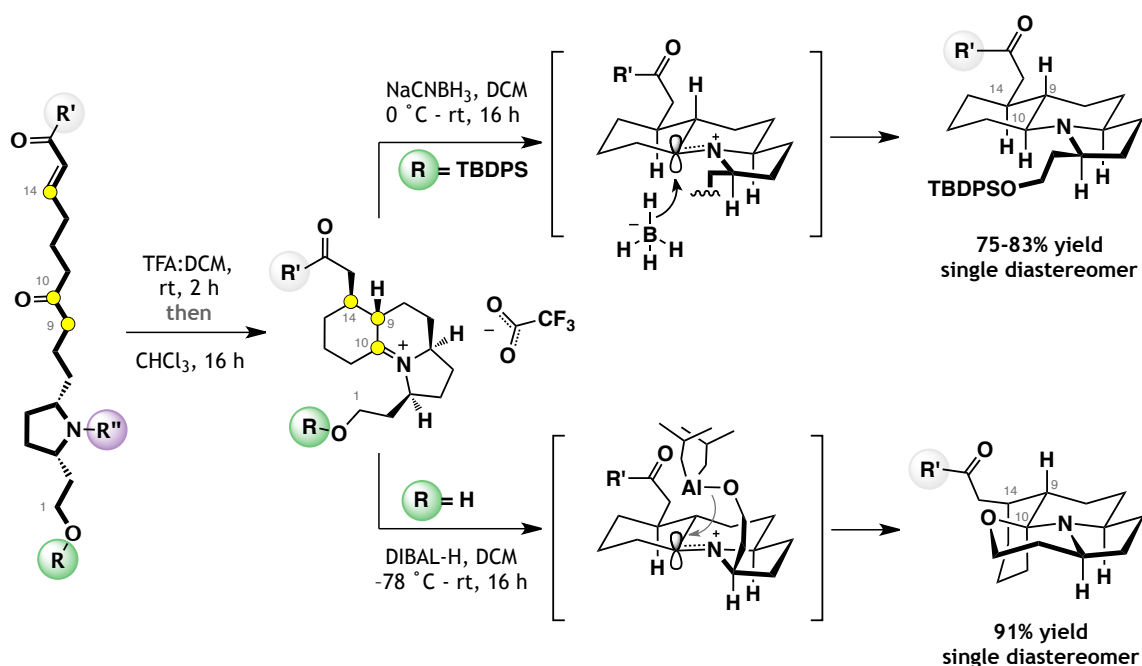


Figure I

Chapters Two and Three outline the development of a synthetic route towards a range of cascade precursors, whilst Chapter Four outlines investigations into the enamine-Michael cascade. Central to understanding the cascade process was the discovery that the major product of the enamine-Michael cascade was an unusual tricyclic hydroquininium salt. This can subsequently be engaged in a diastereoselective inter- or intramolecular reduction to afford either a *trans*-perhydro-[1,2-*a*]-quinoline or a tetracyclic amina in high overall yield depending on the C1 oxygen substituent.



Scheme I

A Comment on Nomenclature

Throughout this thesis the carbon atoms of each compound in Chapters One, Two and Three will be numbered as they are numbered in the target cascade precursor molecule. This system is sustained throughout the following discussion on perhydropyrroloquinolines in Chapter Four.

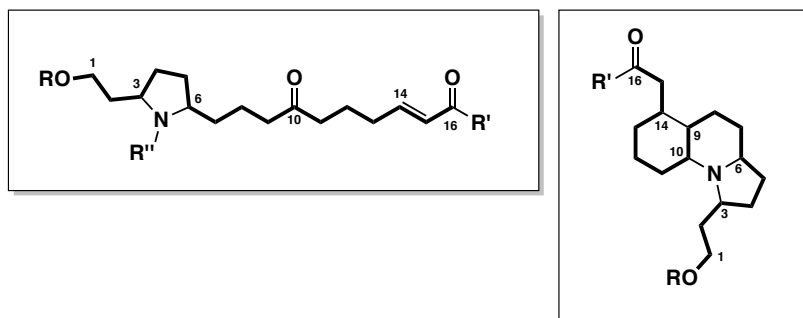


Figure II

This numbering system is distinct from that which has been traditionally used when referencing the gephyrotoxins, but is a system that I believe maximises clarity within this piece of work. Where required in the experimental section, extraneous functional groups will be numbered following their respective sequence, but will be followed by a dash.

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Chapter 1 Introduction

1.1 Alkaloids from Amphibian Skin

Over the past four decades amphibian skins have provided a diverse array of over 800 biologically active, lipid-soluble alkaloids populating over 20 structural classes that are as yet unknown elsewhere in Nature.^{1, 2} These alkaloids mainly include: histrionicotoxins, batrachotoxins, gephyrotoxins and epibatidines from neotropical poison frogs of the *Dendrobatidae* genus; the steroidal samandarines from salamanders, the pumiliotoxins (*allo*- and *homo*-pumiliotoxin) and various decahydroquinolines from the *Mantellidae*, *Dendrobatidae*, *Bufonidae* and *Myobatrachidae* genera of anurans; a huge variety of “izidines” (pyrrolizidines, spiropyrrolizidines, cyclopentapyrrolizidines, indolizidines, quinolizidines and lehmizidines), pyrrolidines, piperidines, pseudophrynamines, coccinellines and a variety of yet unclassified alkaloids of undetermined structures (Figure 1.1).

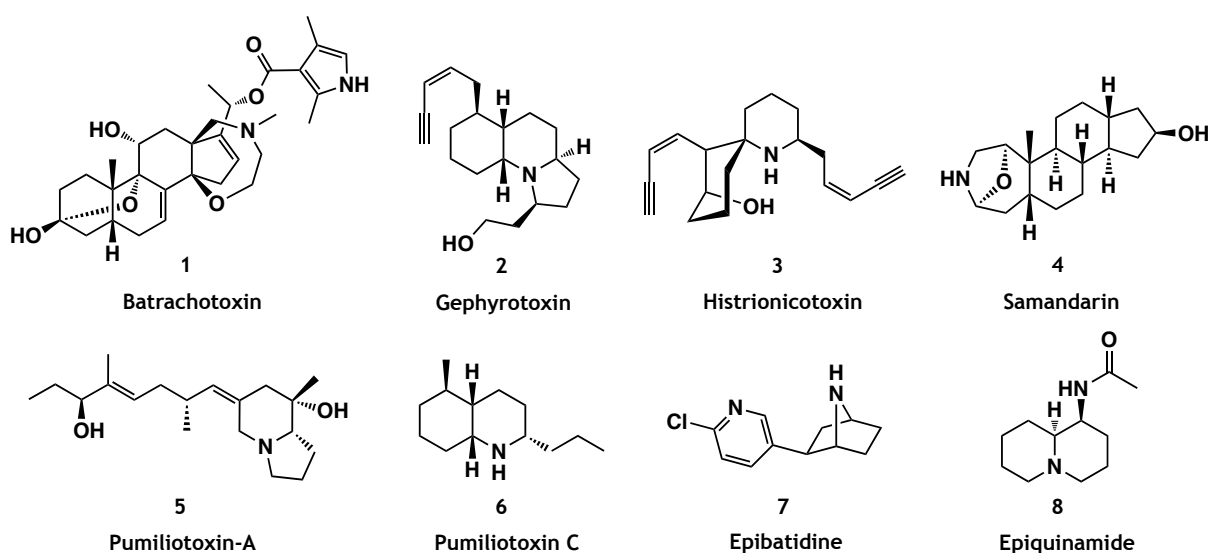


Figure 1.1

With the exception of the pseudophrynamines and the samandarines, most alkaloids found in amphibian skin appear to have been sequestered from dietary arthropods found in the world's rainforests, including beetles (batrachotoxins/coccinelline-like tricyclics), ants/mites (pumiliotoxins, histrionicotoxins, and gephyrotoxins) and millipedes (spiropyrrolizidines) – although only a few of these alkaloids have been directly detected in their native arthropods.²

1.2 The Gephyrotoxins

1.2.1 Origin, Structure and Biological Properties

(+)-Gephyrotoxin **2** and (+)-dihydrogephyrotoxin **9** are the parent members of a small family of dendrobatid alkaloids first isolated from the harlequin poison dart frog *Dendrobates histrionicus* found near Guayacana, Columbia in 1974 (Figure 1.2).³ The central structure of the gephyrotoxins consists of a saturated perhydropyrrolo-[1,2-*a*]-quinoline housing five stereocentres, three of which are contiguous. The core heterocycle is flanked by a primary alcohol and a *cis*-eneyne or a *cis*-diene side-chain. The tricyclic structure of (+)-gephyrotoxin (previously termed HTX-D) was assigned by X-ray diffraction of its hydrobromide salt along with that of (+)-dihydrogephyrotoxin by Daly *et al.* in 1977.⁴

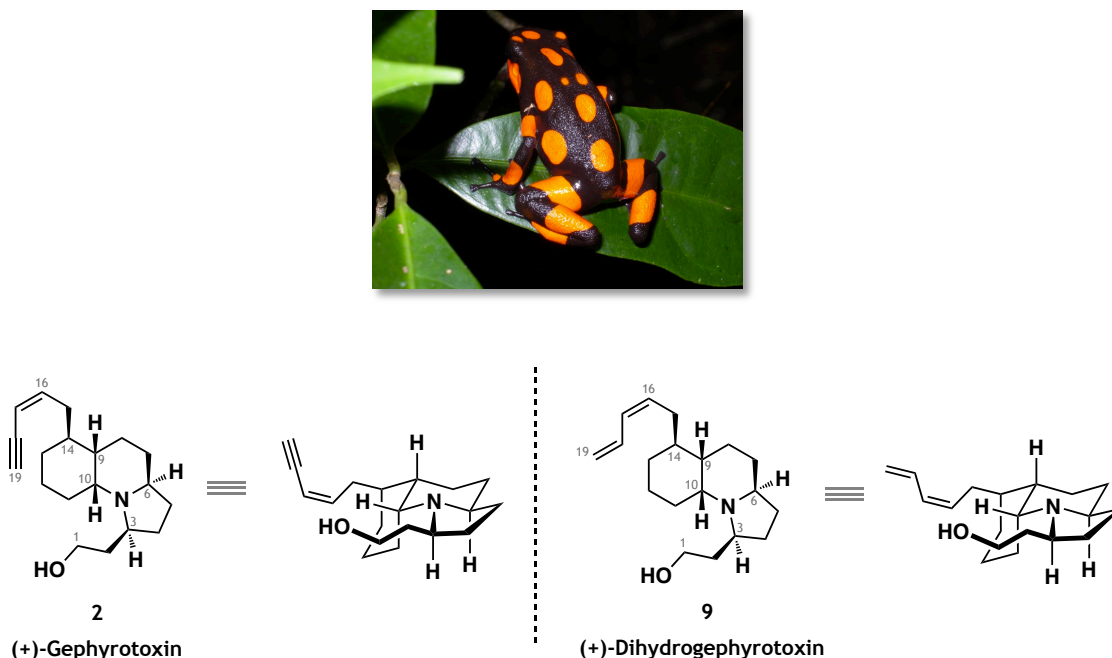


Figure 1.2

As is accepted with many other amphibian alkaloids, the presence of gephyrotoxins in anuran skin exudate is not a consequence of its native biosynthesis as a defense toxin, but a result of dietary accumulation from rainforest arthropods.⁵ (+)-Gephyrotoxin is believed to be a secondary metabolite originating from neotropical mimicrine ants.^{5,6} Even so, the precise biosynthetic mechanism for the endogenous synthesis of the gephyrotoxins has not been reported to-date, and its function within the native ant is virtually uninvestigated.

In general, dendrobatid alkaloids exhibit remarkable effects on the ion-conductance of chemosensitive and voltage-sensitive muscle and nerve channels and are highly toxic.^{1, 7}

(+)-Gephyrotoxin is, however, relatively non-toxic.⁸ Reduction in spontaneous activity in mice was observed after an 80 µg intravenous dose of (+)-gephyrotoxin, compared to batrachotoxin (**1**), which caused death in less than one minute upon administration of a 1 µg dose.⁴ Studies have demonstrated that (+)-gephyrotoxin has complex and unique effects on cholinergic transmission at the neuromuscular junction.⁹ *In vitro*, (+)-gephyrotoxin blocks neuromuscular transmission by reversible antagonism of the muscarinic acetylcholine complex, causing a moderate blockade of the receptor channel in its open conformation.¹⁰ At the same time (+)-gephyrotoxin inhibits ligand-binding sites associated with the receptor-gated ion channel without inhibiting ligand binding to the acetylcholine recognition site.¹¹ (+)-Gephyrotoxin also appears to be a selective noncompetitive blocker of ganglionic versus neuromuscular nicotinic receptor channels.¹¹ The catalytic hydrogenation of both (+)-gephyrotoxin and (+)-dihydrogephyrotoxin affords unnatural (+)-perhydrogephyrotoxin **10**, which has received considerable interest, as it constitutes the most potent member of this alkaloid class (Figure 1.3).^{4,9,12,13,14,15,16,17}

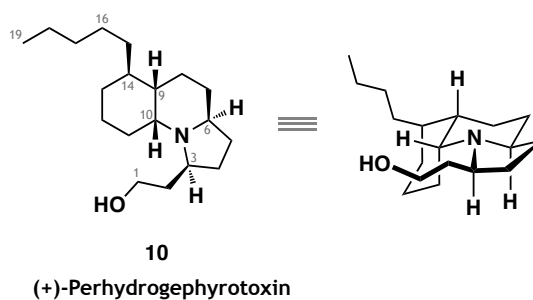


Figure 1.3

The natural abundance of the gephyrotoxins is extremely low; 15 mg of (+)-gephyrotoxin and 1 mg of (+)-dihydrogephyrotoxin were isolated from the methanolic skin extracts of 3200 frogs, alongside larger quantities of various indolizidines (previously termed ‘gephyrotoxins’) and histrionicotoxins.⁴ The low natural abundance and unique neurological profile of the gephyrotoxins has led to synthetic interest in these alkaloids from several laboratories over the past 30 years.^{18,19,20,21,22,23,24,25} However, the last reported total synthesis of any member of the gephyrotoxin family was in 1983 and no reports of further biological profiling have been published since.

1.2.2 Kishi's Asymmetric Synthesis and Structural Disagreement

There have been four total syntheses and four formal syntheses of gephyrotoxin to-date.^{18,19,20,21,22,23,24,25} The only reported asymmetric total synthesis of (+)-gephyrotoxin has been by Kishi *et al.* in 1980 (Figure 1.4).²¹ This asymmetric synthesis was adapted from the first ever total synthesis of gephyrotoxin, a previous racemic approach by the same research group, with asymmetry being chiral pool-derived.²⁰ Key to Kishi's approach to (+)-gephyrotoxin is the preparation of tricyclic vinylogous amide **13**, which was achieved in 19 steps from *L*-pyroglutamic acid **11** *via* the condensation and cyclisation of *cis*-2,5-disubstituted pyrrolidine **12** and cyclohexane-1,3-dione. This intermediate has been the focus of many studies since the publication of this synthesis, with itself serving as the target of a racemic and an asymmetric formal synthesis by other research groups.^{22,24}

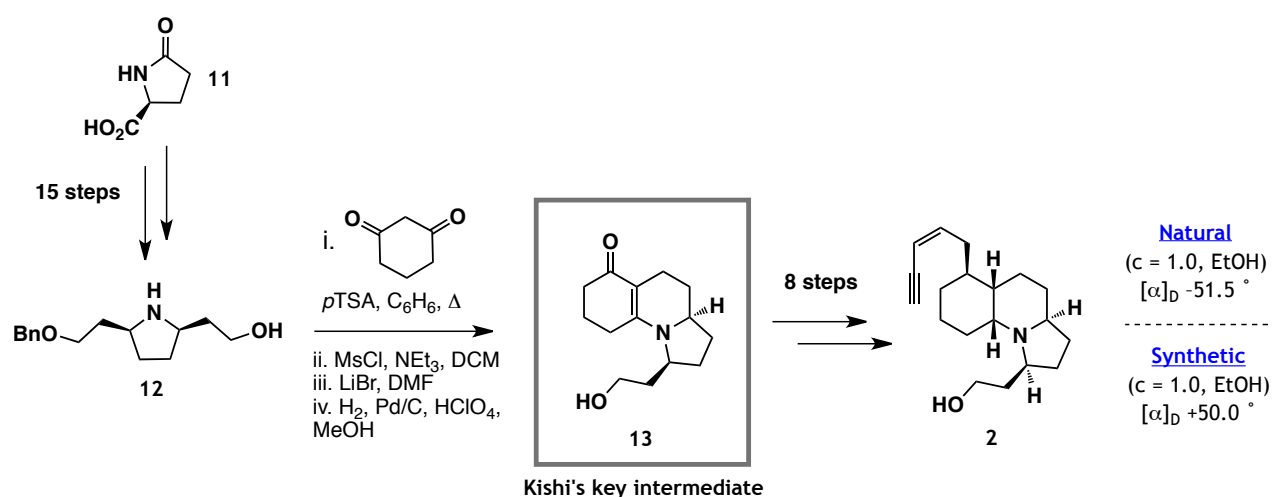


Figure 1.4

Kishi's asymmetric synthesis sparked debate in the alkaloid community, as optical rotation measurements suggested that the absolute configuration of natural gephyrotoxin as assigned by Daly *et al.* should be revised. Re-examination of the original X-ray diffraction data by Daly *et al.* found no mis-assignment, and there has been no asymmetric total synthesis of gephyrotoxin since, or a more modern X-ray diffraction study to resolve this structural discontinuity.^{*4,26,27,28,29}

* Daly *et al.* established the absolute configuration of natural gephyrotoxin hydrobromide from the anomalous scattering of the bromide ion, with an agreement factor of 8.1% for the (+)-enantiomer and 10.5% for the (-)-enantiomer using the Bijvoet method and a Hamilton R-test.⁴ They suggest that the difference in absolute configuration could be due to the different year during which the natural samples were collected.

1.3 Previous Synthetic Approaches

In general, strategies towards the synthesis of the perhydroquinoline core of the gephyrotoxins have focused upon construction of the central piperidine ring as a key disconnection, using pre-installed chirality at C9, C10 and C14 to direct the diastereoselectivity of the process in many cases (Figure 1.5). Elegant approaches have included a Schmidt reaction (Pearson, green),²³ a contrasteric iminium reduction (Overman, blue),¹⁸ an *ortho*-quinodimethane *aza*-Diels Alder reaction (Ito, orange),²² a tandem Knoevenagel-6 π -electrocyclisation (Hsung, red),²⁴ and a carbinolamide-derived *N*-acyl imminium formate reduction (Hart, purple).¹⁹

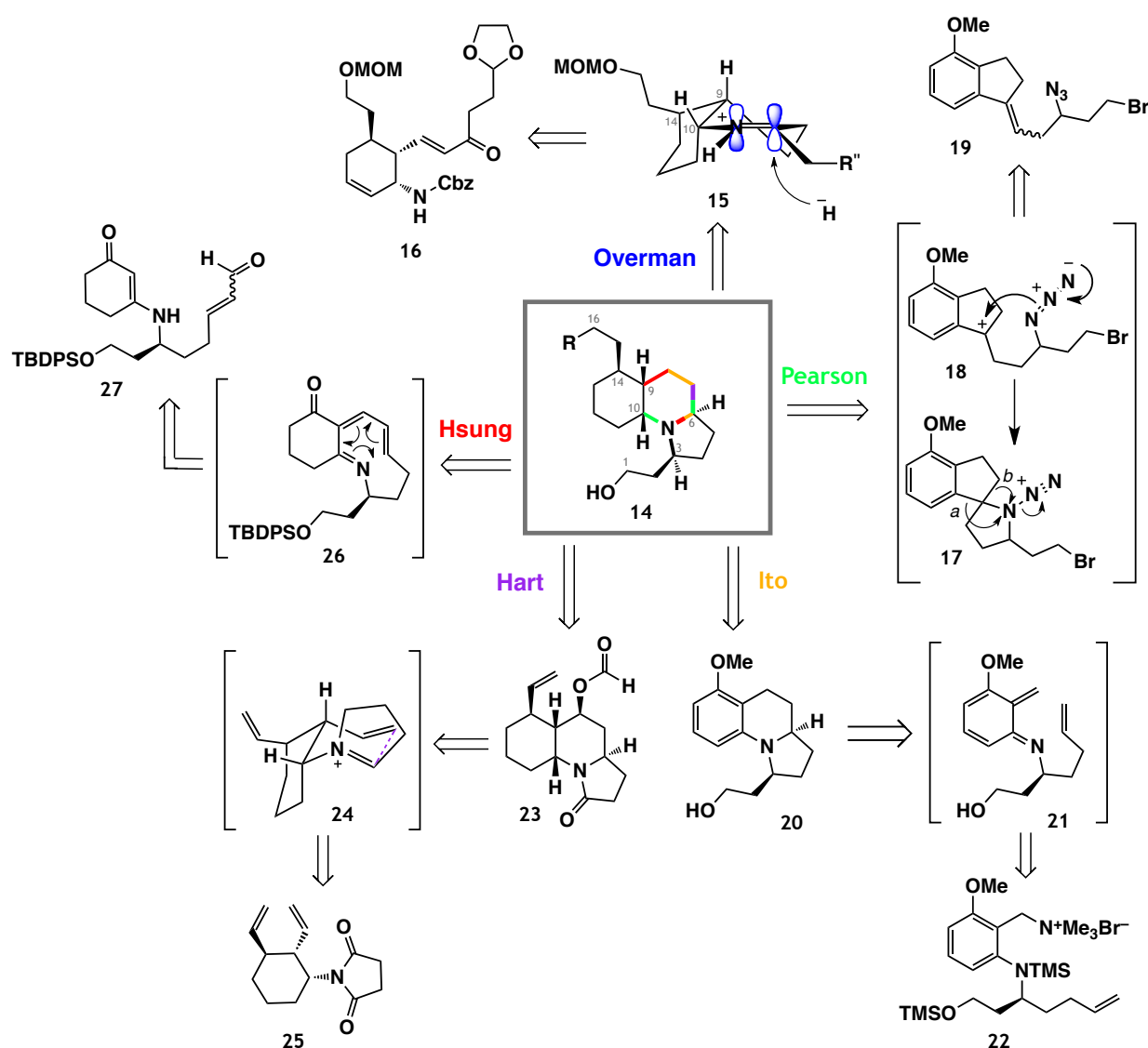
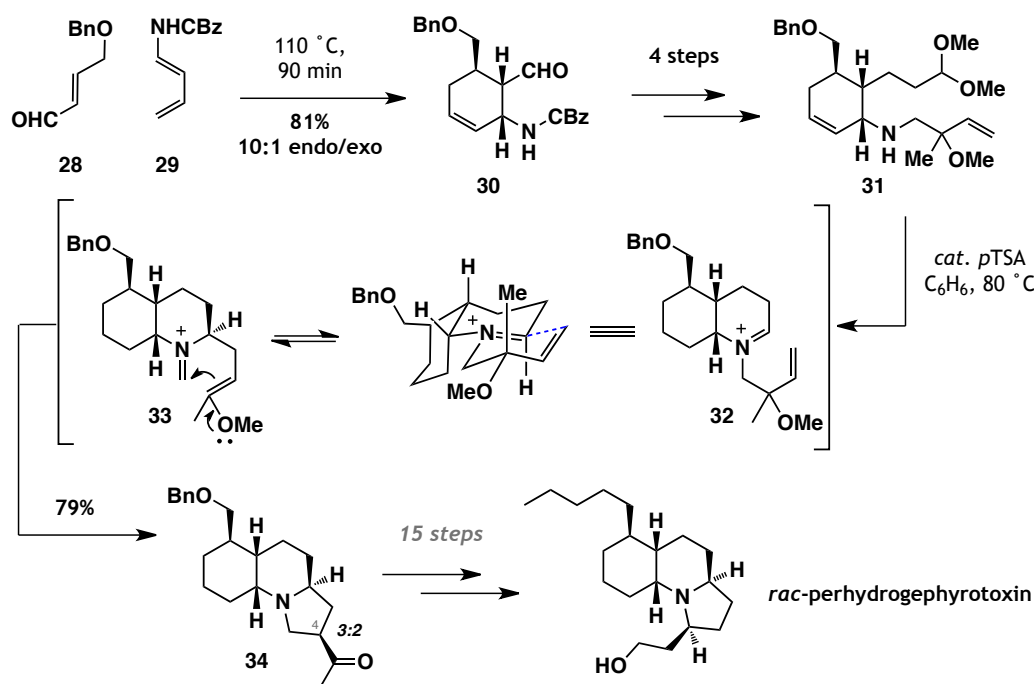


Figure 1.5

To-date, the most elegant approach to the heterocyclic core of the gephyrotoxins is outlined in Overman's synthesis of racemic perhydrogephyrotoxin in 1980.¹³ Initially, Overman *et al.* set the

relative orientation of the C9/C10 stereocentres *via* the thermal [4+2] cycloaddition of butenal **28** and *trans*-butadiene carbamate **29** to afford **30** as a 10:1 mixture of *endo*-/*exo*- cycloadducts (Scheme 1.1). Compound **30** is transformed through a sequence of four steps to the key homoallylic amine **31**. When refluxed in benzene in the presence of catalytic *p*TSA **31** undergoes an intramolecular iminium ion formation, 2-azonia-[3,3]-sigmatropic rearrangement and tandem Mannich reaction to afford the perhydropyrrolo-[1,2-*a*]-quinoline core of the gephyrotoxins as a 3:2 mixture of C4 epimers. The [3,3]-sigmatropic rearrangement occurs stereoselectively across the convex face of the intermediate iminium ion **32** to set the absolute configuration of the C6 stereocentre. This annulation cascade forms the central core of the gephyrotoxins in just 6 steps and 32% overall yield from butadiene **29**. As powerful as this strategy is, completion of the total synthesis of racemic perhydrogephyrotoxin required a further 15 linear steps and dramatically reduced the overall efficiency of the synthesis.



Scheme 1.1

1.4 Retrosynthetic Strategy

The retrosynthetic strategy outlined in this thesis will focus upon simultaneous disconnection of the N-C10 and C9-C14 bonds and assembly of the B- and C-rings of the gephyrotoxins in a single step *via* the enamine-Michael intramolecular cascade cyclisation of **37** (Figure 1.6). Michael addition of a transient C9 enamine onto a propargylic ester at C14 will yield dienyl-carbamate **35** after isomerisation. This will allow for investigation into the stereoselective hydrogenation of **35** to set

the relative configuration at C9, C10 and C14. The C16-19 side chain can then be installed *via* a Yamamoto-Peterson *cis*-enyne olefination of the corresponding C16 aldehyde. A further retrosynthetic analysis of the cascade precursor will be discussed in Chapters 2 and 3.

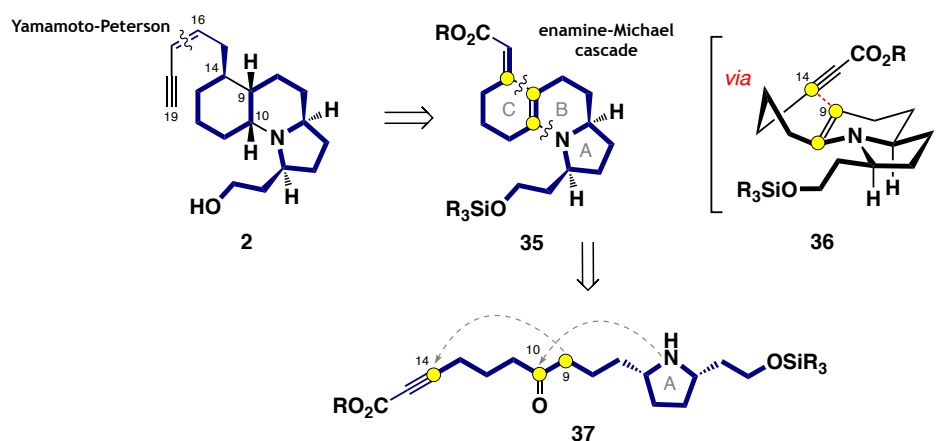
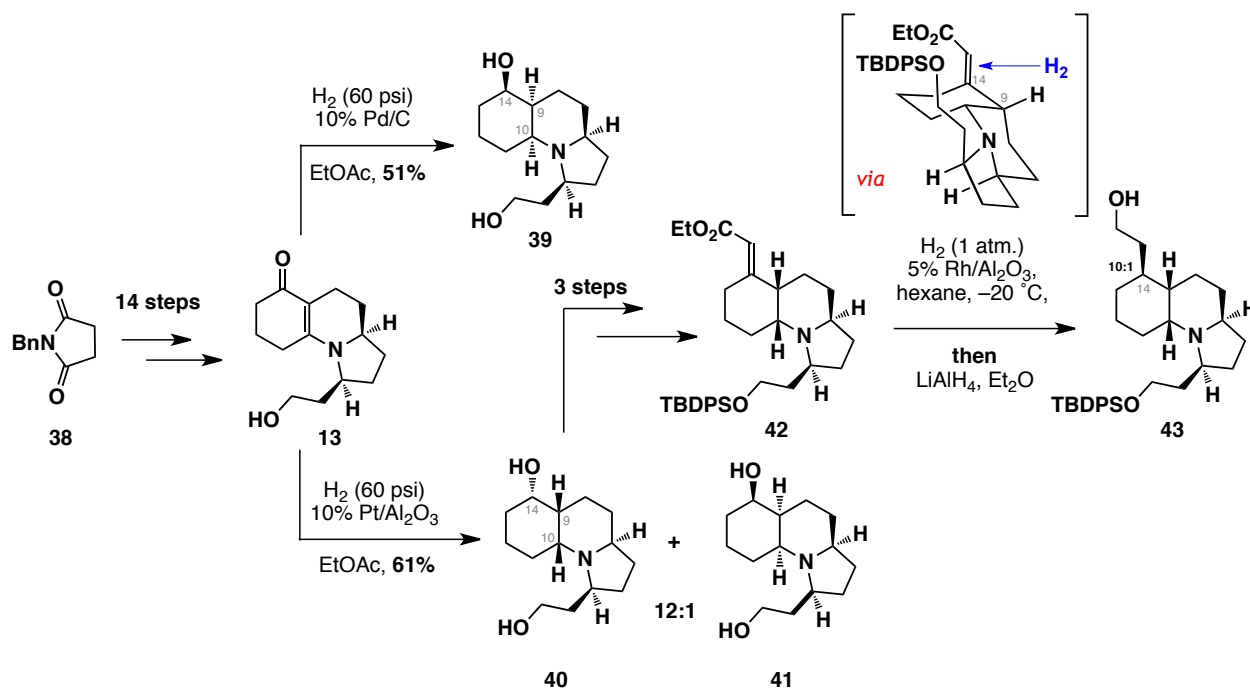


Figure 1.6

Our aim to investigate the stereoselective reduction of dienyl carbamate **35** stems from the unusual substrate and reagent effects first reported by Kishi *et al.* in 1980, during his racemic synthesis of gephyrotoxin.²⁰ Once again, central to Kishi's synthetic strategy is the formation of tricyclic vinylogous amide **13**, which he synthesises in 14 steps from *N*-benzylsuccinimide **38** (Scheme 1.2). The hydrogenation of **13** in ethyl acetate using Pd/C under 4 atm. pressure of hydrogen affords perhydroquinoline **39** in 51% yield as a single diastereomer. Interestingly, the relative stereochemical outcome of this reaction can be entirely reversed by using an alumina-supported catalyst (12:1 dr, **40:41**). Additionally, hydrogenation of late-stage acrylate **42** using alumina-supported rhodium in cold hexanes under an atmospheric pressure of hydrogen affords perhydroquinoline **43** as a 10:1 mixture of C14 diastereomers. The stereoselectivity of this reduction is dictated by the presence of the bulky silyl ether, as analogous hydrogenation of the corresponding primary alcohol affords a 1:1 mixture of C14 diastereomers. Unfortunately, a rationale for this observed stereoselectivity was not presented in this report, but is presumably a steric effect that translates to facial selectivity in the hydrogenation.



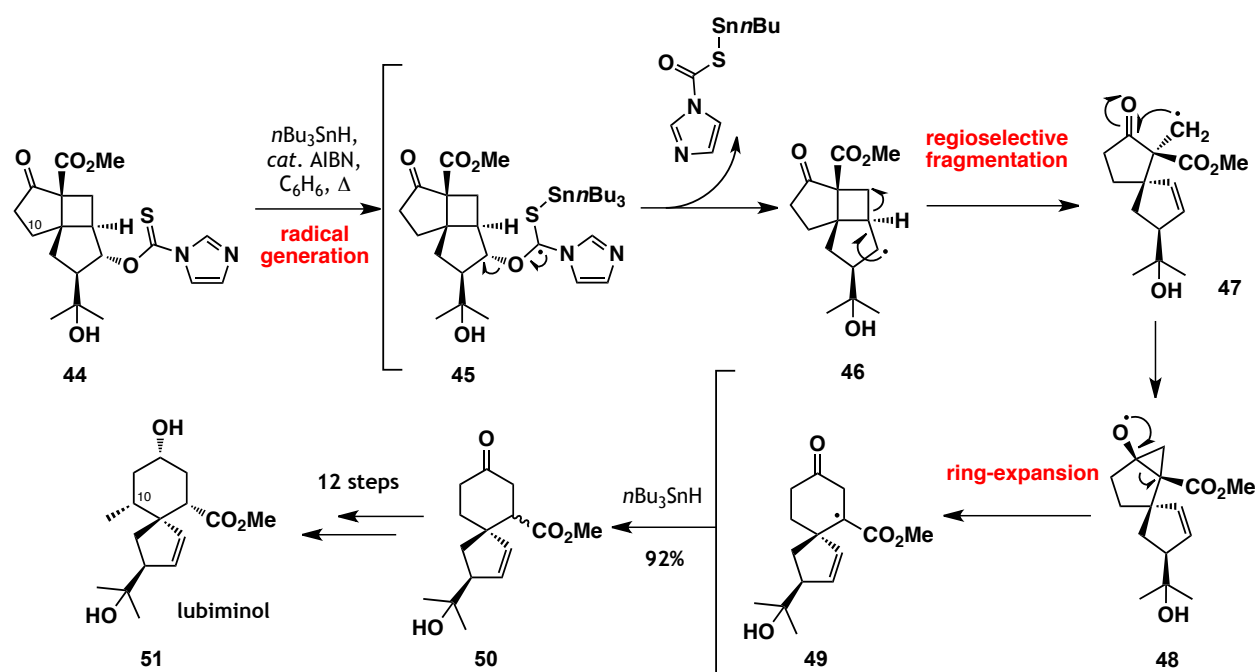
Scheme 1.2

1.5 Reaction Cascades: a strategic perspective

Complexity-generating cascade sequences present an attractive and alternative approach to step-wise procedures in target-oriented synthesis.^{30,31} It is an approach that can impart striking novelty, efficiency and elegance to an overall synthetic strategy. A single reaction cascade has the potential to allow access to high levels of molecular complexity in a controlled and selective fashion; however, this *must* be accompanied by an efficient and tractable synthesis of a polyfunctionalised, and often stereodefined, precursor molecule. The design and implementation of reaction cascades in natural product synthesis further represents a daring and significant intellectual challenge, yet has the potential to contribute to both the science and art of total synthesis.

However, the application of reaction cascades in chemical synthesis must also be approached with a degree of trepidation. Reaction cascades can frequently proceed in the absence of chemo- and/or stereoselectivity, resulting in multiple near-isomeric products being generated, requiring arduous purifications to isolate the desired product in ultimately low yield. Attempts to address or circumnavigate these issues can often dramatically diminish the intended elegance and efficiency of a cascade approach. The successful avoidance of these problems can only occur by a combination of careful retrosynthetic planning and reaction execution.

An example of the unpredictable nature of cascades can be found in Crimmins's racemic synthesis of lubiminol, **51**.³² The synthetic strategy focused on a key radical-initiated fragmentation and ring-expansion cascade of tricyclic cyclobutane **44** to afford the 6,5-spirocyclic core of the natural product (Scheme 1.3). This plan was elegant as it easily allowed for the construction of the challenging C5 all-carbon quaternary stereocentre by a stereoselective intramolecular photochemical [2+2]-cycloaddition. Tin hydride-initiated fragmentation of the thiocarbamate in model system **44** smoothly preceded a cyclobutane fragmentation and Dowd-Beckwith ring-expansion cascade to afford the spirocyclic product **50** in 92% yield after radical termination.

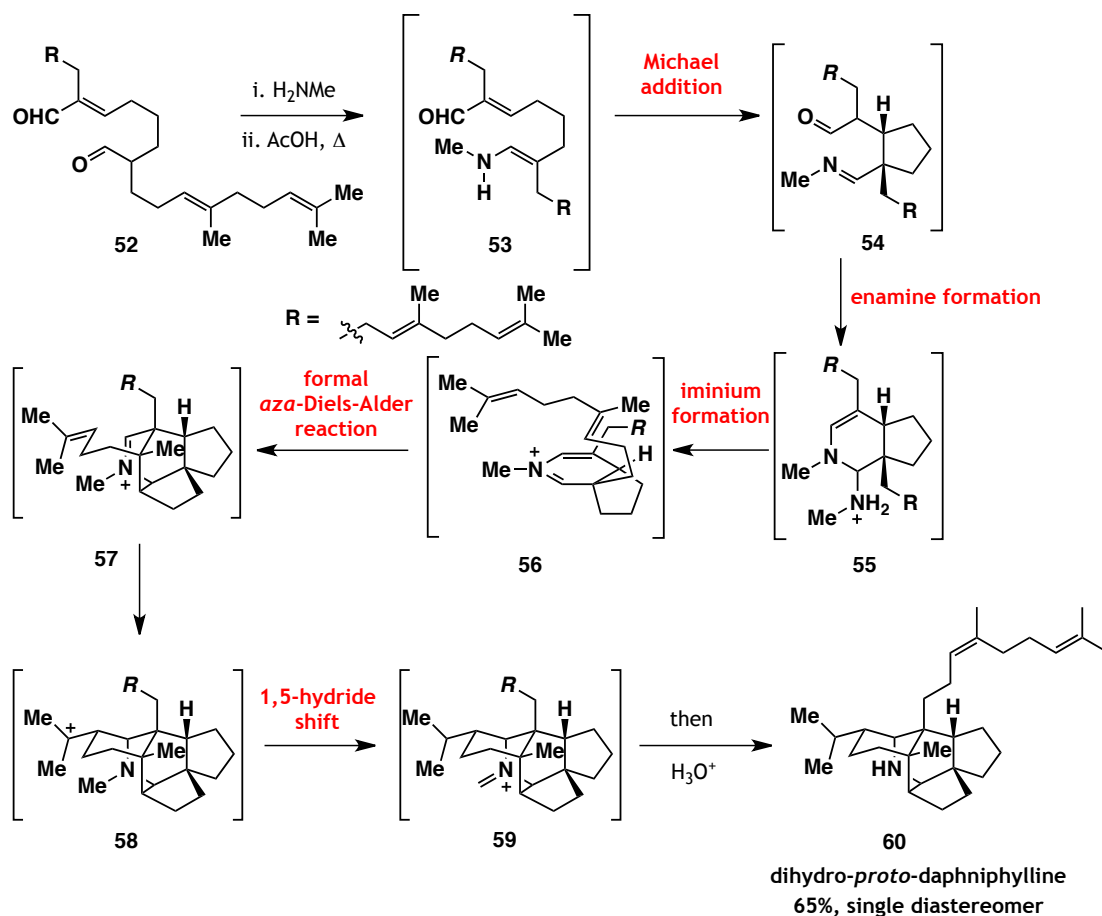


Scheme 1.3

However, when the fully substituted cascade substrate was synthesised bearing a methyl group at C10, the cascade sequence afforded multiple species, none of which were the desired product. The reason for this dramatic and deleterious effect of the seemingly benign remote C10 methyl group is unclear. The authors postulate that steric, competing radical propagation processes and/or more subtle conformational effects may be at work. Nevertheless, progression of the unsubstituted analogue **50** allowed for a late-stage introduction of the C10 stereocentre; however this required significant elongation and complication of the final stages of the total synthesis.

One of the most celebrated and elegant examples of a cascade approach in total synthesis is Heathcock's remarkable synthesis of dihydro-*proto*-daphniphylline.^{33,34} This approach is notable as it provides an example of a cascade sequence that is conceptually similar to our approach in terms

of imine/enamine activation and tandem Michael addition chemistry. The cascade is initiated by the intermolecular condensation of methylamine with the most reactive aldehyde in **52** to afford enamine **53** (Scheme 1.4). This then undergoes a cascade intramolecular Michael addition/condensation/*aza*-Diels-Alder/Prins reaction and [1,5]-hydride shift sequence to afford dihydro-*proto*-daphniphylline **60** after hydrolysis of the product iminium **59** upon work-up.[†] This single cascade sequence forms one heterocyclic ring, four carbocyclic rings and eight stereocentres with exquisite stereocontrol.



Scheme 1.4

The studies outlined in this thesis will further demonstrate the utility of multi-bond-forming reaction cascades of this mode in the synthesis of polycyclic alkaloids.

[†] **57** may not form by a concerted *aza*-Diels-Alder cycloaddition, but *via* a Prins cyclisation to form the second five-membered ring and a second nucleophilic ring closure between the resulting enamine and the tertiary carbocation.

Chapter 2 Synthesis of the Gephyrotoxin A-ring

2.1 1st Generation Strategy

2.1.1 Retrosynthetic Analysis

A principal feature of the cascade precursor **61** is a *cis*-2,5-disubstituted pyrrolidine set within a functionalised sixteen-carbon backbone. Strategically, the most attractive approach generating this arrangement would be *via* the convergent cross-metathesis of allyl pyrrolidine **62** and enone propargylic ester **65**. The pyrrolidine **62** could be prepared *via* a substrate-directed cyclisation, with chirality being derived from a suitably functionalised sulfinamide derivative **63**. Both the sulfinamide **63** and enone propargylic ester **65** could be accessed from commercial material (Figure 2.1).

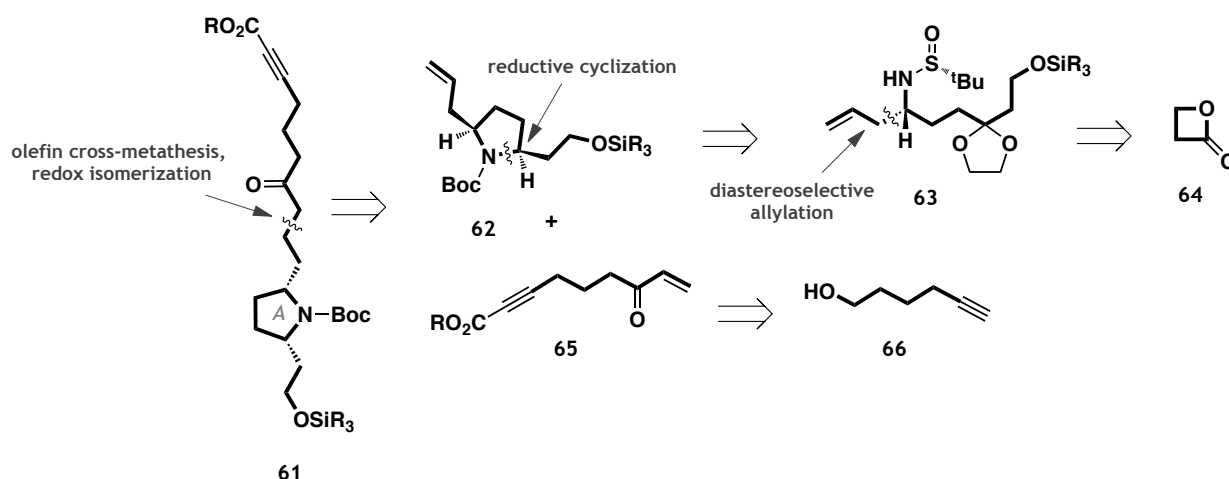
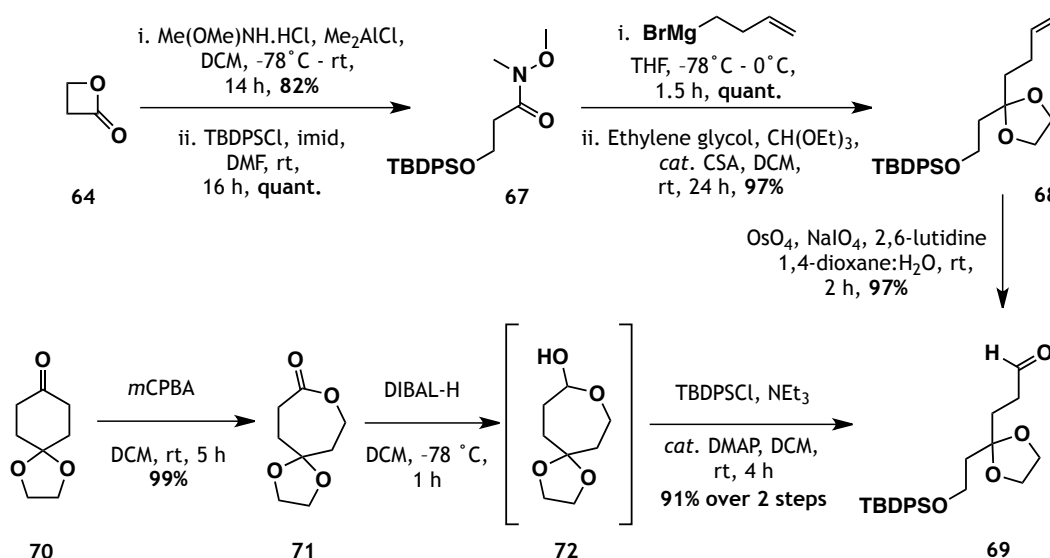


Figure 2.1

2.1.2 Synthesis of the *homo*-Allyl Sulfinamide

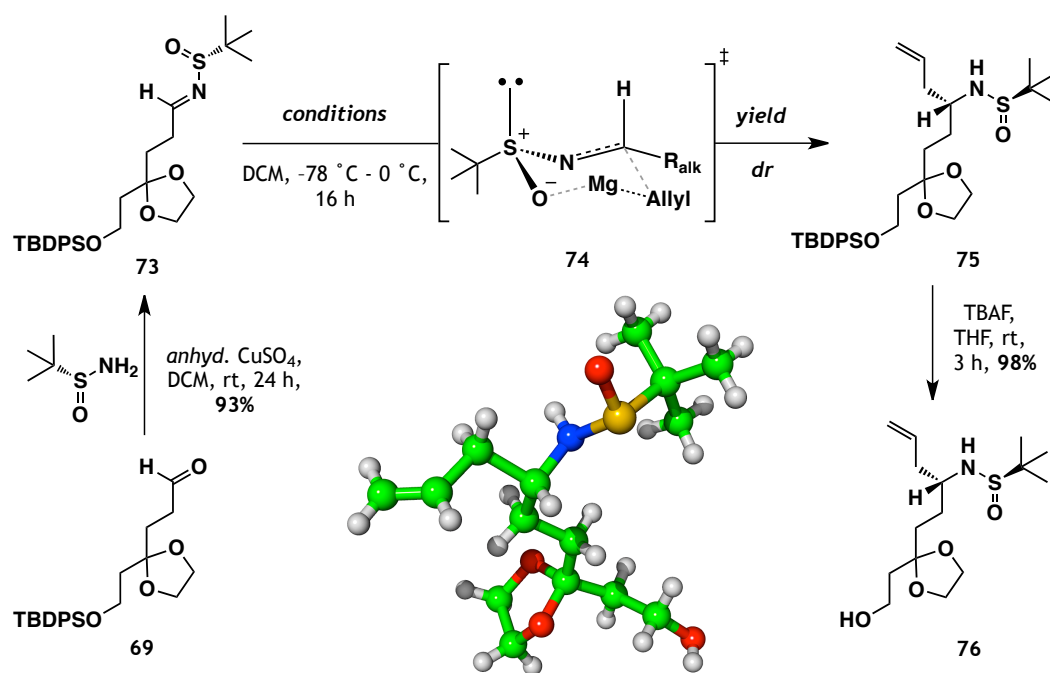
Commercially available β -propiolactone **64** was transamidated with the dimethylaluminium amide of *N*-*O*-dimethylhydroxylamine to afford the corresponding Weinreb amide in high yield.³⁵ Protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether gave **67**, which was transformed to the corresponding ketone *via* a butenyl Grignard addition in quantitative yield. Maintaining a low temperature during the organometallic addition was essential to avoid β -elimination of the silyl ether in **67**. Formation of ketal **68** under mildly acidic conditions at room temperature and oxidation of the terminal double bond under Lemieux-Johnson conditions afforded aldehyde **69** in 94% yield over 2 steps.³⁶ Although this route proved efficient, it was anticipated that the symmetry present in **69** would allow for a more efficient synthesis of this intermediate, and avoid the use of superstoichiometric aluminium, and osmium tetroxide at the

outset of the synthetic sequence. To this end, aldehyde **69** was also synthesised in three steps from commercially available *mono*-protected cyclohexane-1,4-dione **70**. Initial desymmetrisation *via* a Baeyer-Villiger oxidation afforded ϵ -caprolactone ketal **71** in near-quantitative yield. This was followed by a reductive lactol opening under basic conditions in the presence of *tert*-butyl(chloro)diphenylsilane to afford aldehyde **69** in 90% yield over 3 steps (Scheme 2.1).³⁷



Scheme 2.1

Aldehyde **69** was transformed to its corresponding sulfinyl aldimine **73** under mildly acidic conditions at room temperature. The *tert*-butylsulfinimine chiral auxiliary led to exceptional diastereocontrol in the allylation of aldimine **73** with allyl Grignard reagents, affording *homo*-allyl sulfinamine **75** in 99% yield (Scheme 2.2, Table 2.1).³⁸ The observed sense of asymmetric induction is chelation controlled and is consistent with the formation of a well-defined Zimmerman-Traxler-like transition state, **74**, whereby magnesium coordinates to the oxygen of the sulfoxide, and the *tert*-butyl group and the alkyl chain of the aldimine adopt a favourable 1,3-diequatorial orientation. The organometallic nucleophile is hence preferentially delivered to the *Si*-face of the aldimine. Desilylation of **75** yielded the primary alcohol **76** as a crystalline solid, from which structural confirmation of the relative configuration was achieved by X-ray diffraction.



Scheme 2.2

Conditions	Yield	dr
Allylmagnesium bromide	95%	44:1
Allylmagnesium chloride	98%	46:1
Allylmagnesium chloride*	99%	58:1

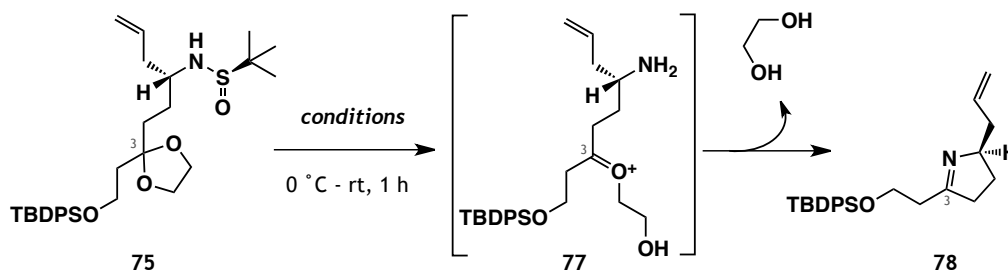
Table 2.1

2.1.3 A Diastereoselective Reductive Amination

The hydrolysis of the ketal in **75** would now allow for a diastereoselective reductive amination to form the key pyrrolidine ring system. A range of Brønsted- and Lewis-acidic hydrolysis conditions were screened, all of which failed to afford the desired keto-sulfinamide. In all cases, decomposition of **75** was observed under highly acidic conditions and hydrolysis of the terminal silyl ether was facile when the reaction was conducted at elevated temperatures. However, when **75** was treated with TFA in DCM at 0 °C and warmed to room temperature over 1 h a sequence of *N*-desulfinylation, oxonium cation formation and intramolecular cyclisation was observed to form Δ^1 -pyrroline **78** after an aqueous work-up (Scheme 2.3). This process was also effective using HCl or

* Allylmagnesium chloride was added *via* syringe-pump over 4 h.

$\text{BF}_3 \cdot \text{OEt}_2$ in methanol (Table 2.2). The Δ^1 -pyrroline ring system was confirmed by the characteristic NMR resonance of C3 at 176 ppm and the IR absorbance of the C=N bond at 1643 cm^{-1} .³⁹

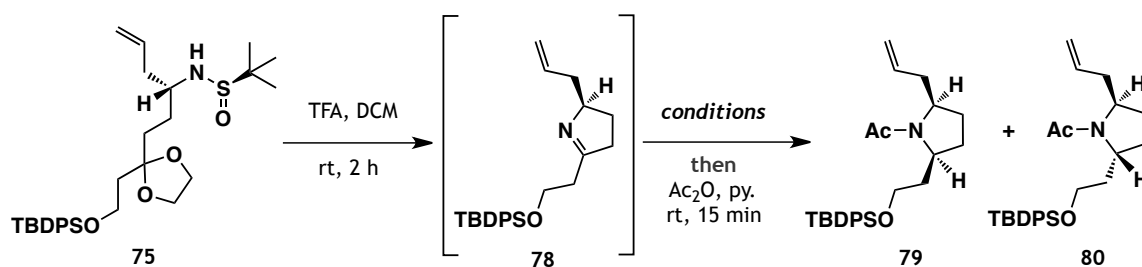


Scheme 2.3

Conditions	Yield
TFA, DCM	67%
HCl, MeOH	66%
$\text{BF}_3 \cdot \text{OEt}_2$, MeOH	58%

Table 2.2

It was postulated that both the absolute configuration at C6 and the constrained nature of the Δ^1 -pyrroline ring-system would allow for a degree of facial discrimination in the reduction of **78**. For each reducing agent that was examined, a sample of sulfinamide **75** was cyclised to Δ^1 -pyrroline **78** using TFA and then directly reduced after a basic work-up. A range of hydride reducing agents were screened and in each case the resulting pyrrolidine was functionalised as its *N*-Ac derivative in order to ease purification (Scheme 2.4, Table 2.3).



Scheme 2.4

[H ⁻]	Solvent	Temp.	Yield (over 2 steps)	dr (<i>cis:trans</i>)
Et ₃ SiH, AcOH	DCM	-78 °C – rt	no reaction	-
Ph ₃ SiH, AcOH	DCM	0 °C – rt	no reaction	-
Ph ₃ SiH, BF ₃ •OEt ₂	DCM	-78 °C – rt	no reaction	-
NaBH(OAc) ₃ , AcOH	DCM	-78 °C – rt	53%	1.8:1
NaBH(OAc) ₃ , AcOH	DCM	0 °C – rt	63%	1.4:1
L-Selectride®, AcOH	DCM	0 °C – rt	no reaction	-
L-Selectride®, AcOH	DCM	0 °C – reflux	decomposition	-
DIBAL-H	THF	-78 °C – 0 °C	58%	2.0:1
DIBAL-H	DCM	-78 °C – 0 °C	57%	2.5:1
DIBAL-H [†]	DCM	-78 °C – 0 °C	63%	1:0
DIBAL-H [†]	THF	-78 °C – 0 °C	60%	1:0

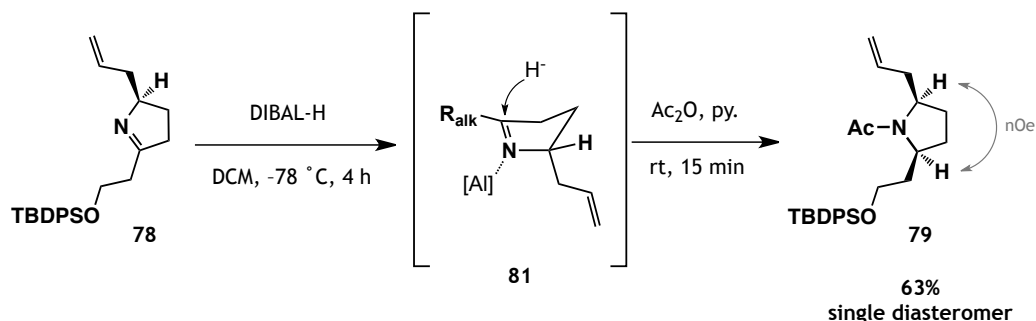
Table 2.3

It was found that upon syringe-pump addition of DIBAL-H to a solution of **78** at -78 °C *N*-Ac pyrrolidine **79** was isolated in good overall yield and as a single diastereomer (Table 2.3). Analysis of **79** *via* a 1D nOe experiment showed the *cis*-substituted pyrrolidine to be the major diastereomer. The diastereoselectivity of this process arises from delivery of hydride to the least hindered *Si*-face of the pyrroline carbon-nitrogen double bond. This would proceed through *endo*-ring puckered intermediate **81**, as dictated by the *pseudo*-axial allyl side-chain (Scheme 2.5).^{‡,40}

[†] DIBAL-H was added *via* syringe-pump over 4 h.

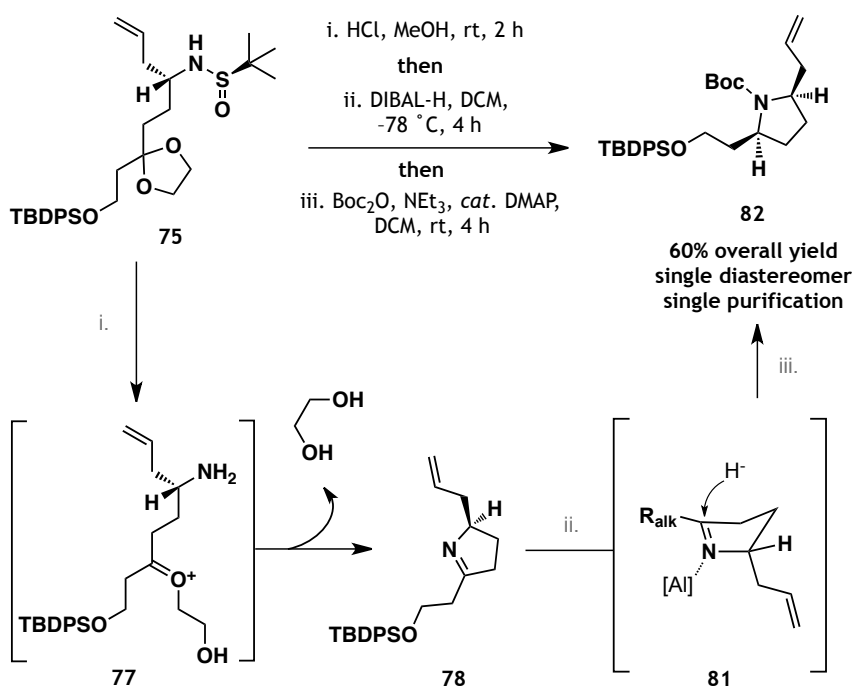
[‡] The stereoselective reduction of a Δ¹-pyrroline using DIBAL-H has previously been reported, but no mechanistic rationale was given.⁴⁰

The stereocontrolled reduction of **81** using DIBAL-H is similar to studies by Woerpel *et al.*, who report the stereoselective reduction of polysubstituted five-membered oxonium cations.⁴¹ It is suggested that these systems may hold analogy to nitrogen-containing heterocycles.



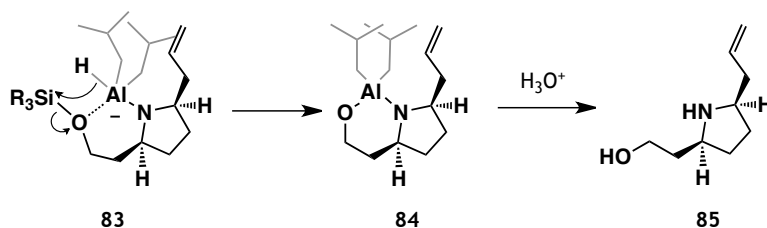
Scheme 2.5

Pleasingly, these reaction conditions can be used in a three-step, single purification sequence. Cyclisation of **75** using HCl afforded pyrroline **78**, which was immediately reduced using DIBAL-H and protected as its *N*-Boc derivative to afford the *cis*-2,5-pyrrolidine metathesis fragment **82** in 60% overall yield and as a single diastereomer (Scheme 2.6).



Scheme 2.6

When performing this reductive amination on a gram scale we were hindered by hydrolysis and polymerisation of the Δ^1 -pyrroline intermediate and by an aluminum-assisted β -desilylation process which was rapid at temperatures above $-60\text{ }^{\circ}\text{C}$ (Scheme 2.7).⁴²



Scheme 2.7

Attempts were made to chemoselectively re-protect the resulting crude pyrrolidine **85**, however multiple products were observed in all cases, including *mono*- and *bis*-*O*-/*N*-Boc-protected pyrrolidines and significant intramolecular carbamate formation. This necessitated the design of an alternative, more scalable route towards *N*-Boc pyrrolidine **82**.

2.2 2nd Generation Strategy

2.2.1 Retrosynthetic Analysis

In-line with work by Enkisch *et al.* it was rationalised that the relative stereochemistry of the pyrrolidine ring could be installed by intramolecular conjugate addition of a sulfinamide anion to an appended acrylate (Figure 2.2).⁴³ By directly progressing the resulting pyrrolidine sulfinamide, the chiral auxiliary could be used as both a stereodirecting element in the preceding alkylation and as a subsequent protecting group within the remainder of the synthesis. This strategy would disconnect pyrrolidine **87** to acrylate **88**, which we believed could be accessed from commercial material.

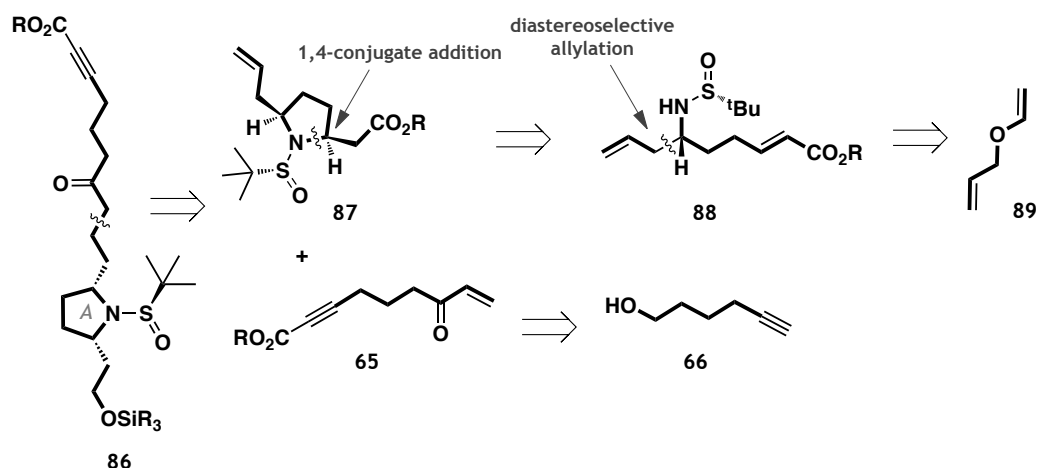
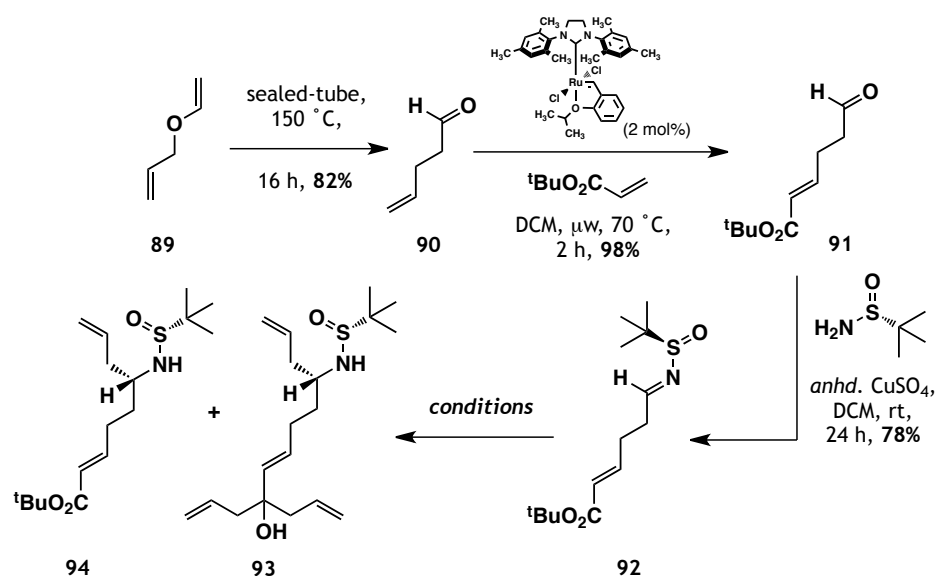


Figure 2.2

2.2.2 Synthesis of the *homo*-Allyl Sulfinamide

Allyl vinyl ether **89** was transformed to aldehyde acrylate **91** *via* a thermally induced Claisen rearrangement followed by a microwave-accelerated cross-metathesis with *tert*-butyl acrylate in the presence of the Hoveyda-Grubbs second-generation catalyst in excellent overall yield (Scheme 2.8).⁴⁴ The chiral auxiliary was installed under mildly acidic conditions to afford sulfinyl aldimine **92** in 78% yield. Treatment of **92** with sub- and super-stoichiometric allyl magnesium chloride showed both a lack of reactivity and chemoselectivity, affording starting material, the desired *homo*-allylic sulfinamide **94** and the tertiary alcohol double-addition product **93** (Table 2.4).

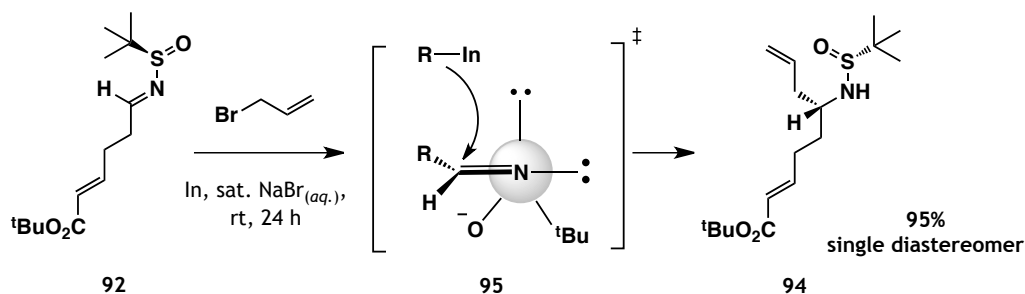


Scheme 2.8

Conditions	Yield	94:93
AllylMgCl (1.3 eq.), DCM, $-78\text{ }^\circ\text{C}$ – rt, 16 h	64% (70% brsm)	1:1
AllylMgCl, (0.9 eq.), DCM, $-78\text{ }^\circ\text{C}$ – rt, 16 h	44% (87% brsm)	6:1
AllylBr (5 eq.), In, sat. NaBr _(aq.) , rt, 24 h	95%	1:0

Table 2.4

However, by employing the method of Sun *et al.*, using elemental indium and allyl bromide in saturated aqueous sodium bromide it was possible to effect the allylation of **92** with complete chemo- and diastereocontrol to afford homo-allyl sulfonamide **94** in 95% yield (Scheme 2.9).⁴⁵



Scheme 2.9

In such a highly coordinating and ionic solvent, the sense of asymmetric induction is consistent with addition of the organoindium nucleophile to the *Si*-face of the imine *via* an open transition-

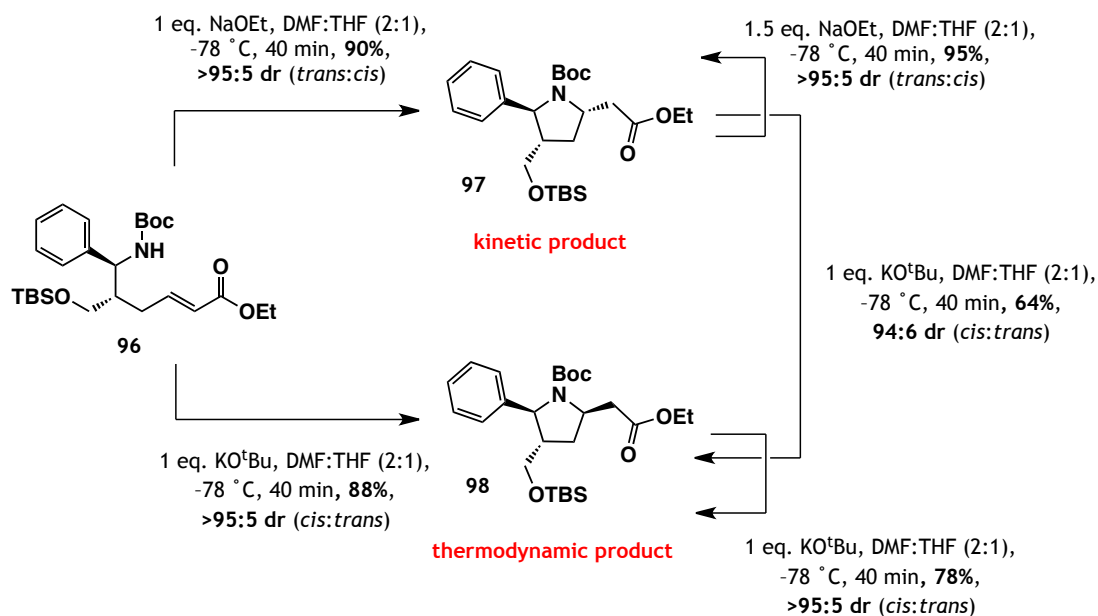
state intermediate **95**, whereby facial selectivity arises through steric repulsion from the highly-solvated sulfoxide oxygen and the *tert*-butyl group of the auxiliary (Scheme 2.9).^{§ 46,47}

2.2.3 Intramolecular Conjugate Addition and Ester Reduction

Enkisch *et al.* have reported the intramolecular conjugate addition of various *N*-Boc amino acrylates such as **96** to afford 2,5-disubstituted pyrrolidines.⁴³ By careful choice of solvent and base it is possible to select for either the kinetic or thermodynamic pyrrolidine products in high yield and diastereoselectivity. On the basis of DFT, NMR and X-Ray diffraction studies the *cis*-2,5-pyrrolidine **98** was shown to be the thermodynamic product, and the *trans*-isomer **97** to be the kinetic product (Scheme 2.10).

[§] As to whether C-C bond forming occurs *via* an In(I) or an In(III) species is not known. Current evidence suggests that the precise nature of the organoindium species is highly solvent dependant, yet strongly suggests the prevalence of a transient but discrete indium(I) organometallic in the indium-mediated allylation reaction in aqueous media. The formation of an allylindium (I) species as opposed to allylindium (III) intermediate is consistent with the relatively low 1st ionisation potential of indium relative to its 2nd and 3rd ionisation potentials, compared to those of other metals with similar chemistries. Additionally, organoindium chemistry does not suffer from carbonyl reduction or pinacol-reductive coupling by-products, commonly observed in the analogous chemistries of zinc and tin. This observation could go in part to explaining the high degree of chemoselectivity observed in this transformation.

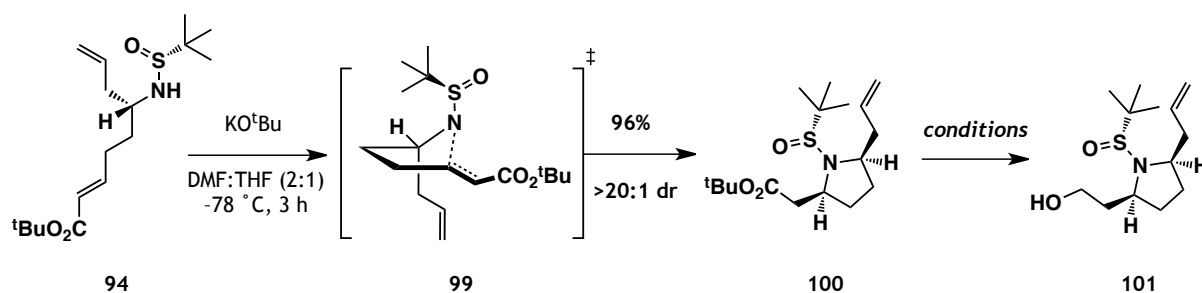
Metal	Ionisation Potential (eV)		
	1 st	2nd	3rd
In	5.79	18.86	28.03
Mg	7.65	15.04	80.14
Zn	9.39	17.96	39.70
Sn	7.34	14.63	30.49



Scheme 2.10

Pleasingly, using analogous conditions to Enkisch *et al.*, formation of the sulfinamide anion of **94** using potassium *tert*-butoxide and intramolecular conjugate addition at -78 °C in a DMF/THF mixture afforded *N*-sulfinyl pyrrolidine **100** in excellent yield and diastereoselectivity (Scheme 2.11). This cyclisation is presumed to be analogous to that involving **96**, affording the *cis*-2,5 diastereoisomer as the thermodynamic product.**

** We cannot be certain whether the conjugate addition of **94** is kinetically or thermodynamically controlled without studying the isomerisation of the *trans*-2,5-pyrrolidine under identical reaction conditions.



Scheme 2.11

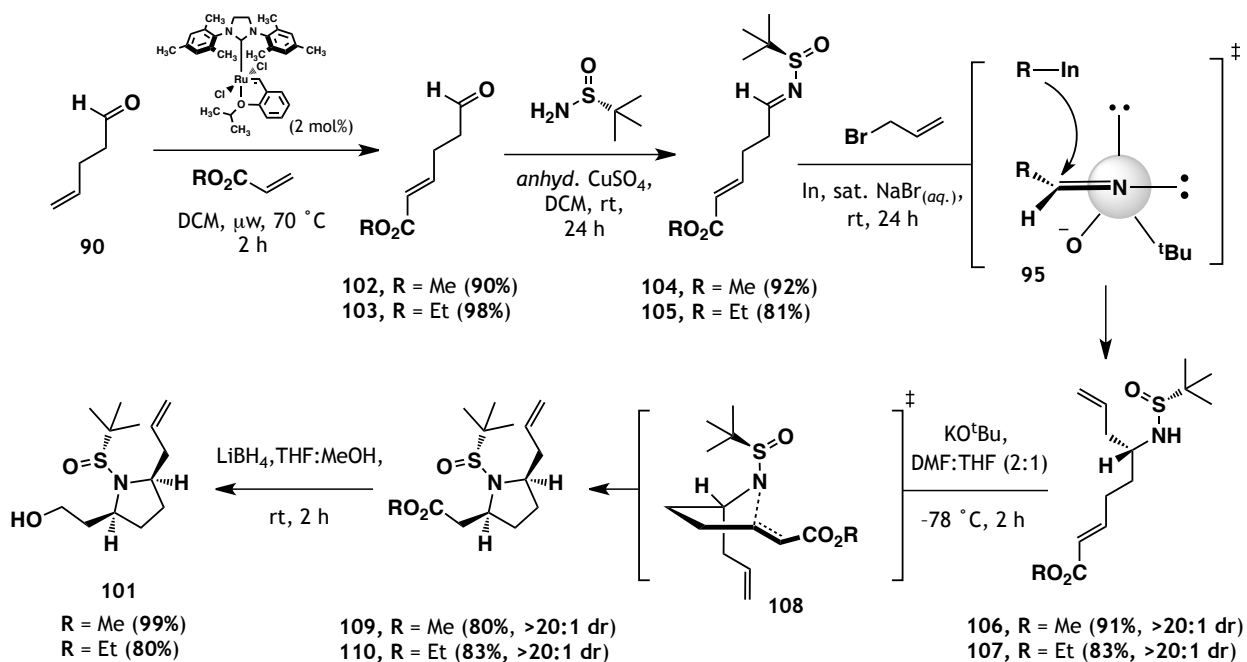
Conditions	Yield
LiAlH ₄ (3 eq.), Et ₂ O, 0 °C, 4h	No reaction
LiAlH ₄ (3 eq.), THF, reflux, 16h	53% (64% brsm)
LiBH ₄ (4 eq.), THF:MeOH, rt, 4h	No reaction
LiBH ₄ (4 eq.), THF:MeOH, reflux, 16h	42% (70% brsm)

Table 2.5

The *tert*-butyl ester was inert to reduction using a range of hydride reducing agents. When **100** was refluxed in the presence of superstoichiometric lithium aluminium hydride, and lithium borohydride in methanol 1°-alcohol **101** was only isolated in moderate yield, with *N*-desulfinylation being observed along with product formation (Table 2.5).

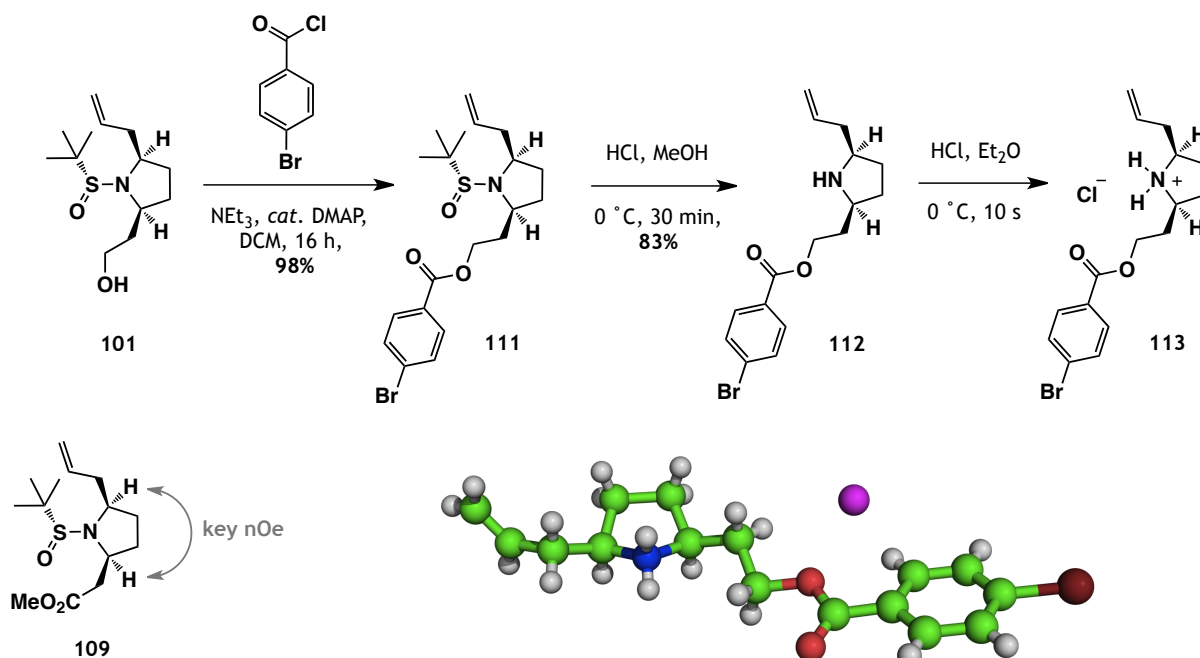
2.2.4 Methyl and Ethyl Ester Synthesis

It was anticipated that the indium-mediated allylation reaction might also be chemoselective in the presence of a less-hindered ester. To this end, sulfinyl aldimines **104** and **105** containing pendant methyl and ethyl esters were synthesised analogously to the *tert*-butyl ester example (Scheme 2.12). The indium-mediated allylation occurred once again with complete chemo- and diastereocontrol and in excellent yield. The intramolecular conjugate addition was also efficient and diastereoselective in both cases. Gratifyingly, the reduction of the less substituted esters to the corresponding 1° alcohol **101** was extremely facile and high-yielding in both examples when using LiBH₄ in a THF/MeOH mixture at room-temperature.



Scheme 2.12

The relative configuration of the pyrrolidine ring-system was confirmed *via* a nOe enhancement between *H*3 and *H*6 in **109**, and *via* the analysis of *p*-bromobenzoate **113** by X-ray diffraction (Scheme 2.13).

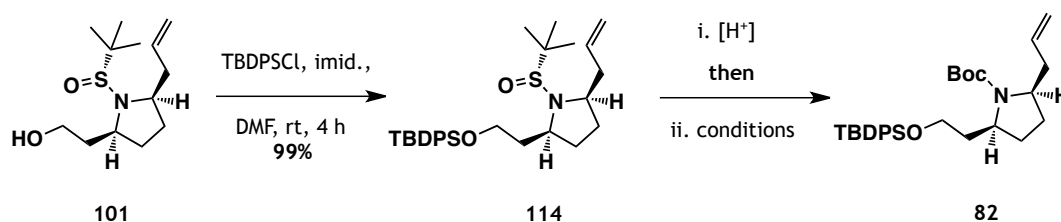


Scheme 2.13

2.2.5 Choice of *N*-Protecting Group

At this stage it was decided to progress the *N*-Boc pyrrolidine derivative as well as the *N*-sulfinyl derivative towards the cascade precursor manifold. The tertiary sulfinamide had been very labile under a variety of Brønsted- and Lewis-acidic conditions during the initial reductive amination study (Scheme 2.3, Table 2.2), and had also shown a degree of thermal instability during the reduction of **100** (Scheme 2.11, Table 2.5). Progression of both functional derivatives would allow us to assess the suitability of the tertiary sulfinamide as a robust nitrogen protecting group relative to the Boc carbamate. If so, this would allow for a shorter synthesis of the cascade precursor, and would avoid a mid-stage auxiliary-to-protecting group manipulation.

To this end, primary alcohol **101** was protected as its corresponding *tert*-butyldiphenyl silyl ether in near-quantitative yield (Scheme 2.14). The desulfinylation of **114** was rapid when using either TFA or methanolic HCl, and the Boc carbamate could be introduced efficiently after a formal deprotonation of the subsequent pyrrolidine using sodium hydride (Table 2.6). The NMR data for this product is identical to **82** (Scheme 2.6).



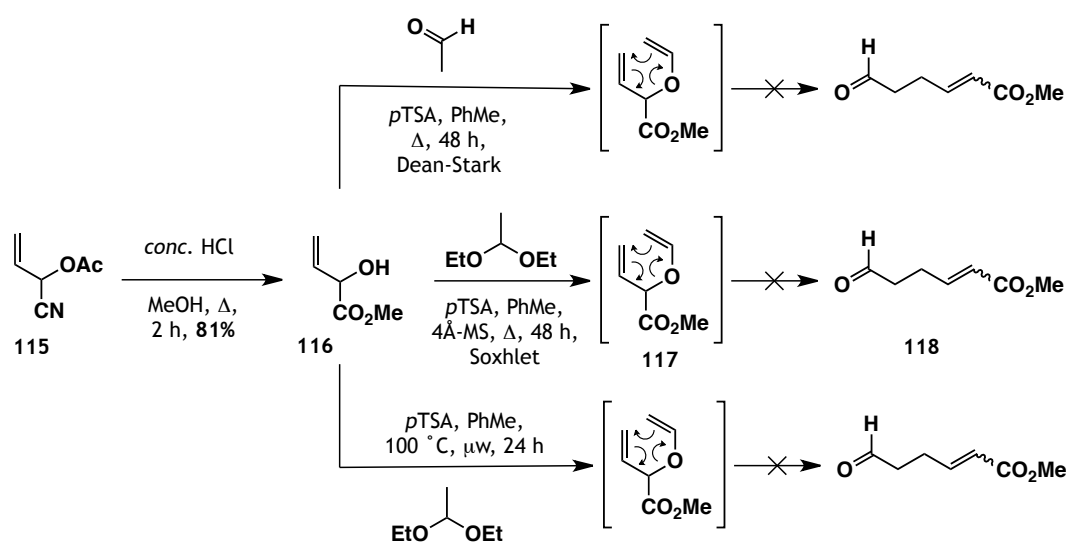
Scheme 2.14

[H ⁺]	Conditions	Overall Yield
TFA, 0 °C, DCM	Boc ₂ O, NEt ₃ , <i>cat.</i> DMAP, rt, DCM, 16 h	37%
HCl, 0 °C, MeOH	Boc ₂ O, NEt ₃ , <i>cat.</i> DMAP, rt, DCM, 16 h	52%
HCl, 0 °C, MeOH	Boc ₂ O, <i>cat.</i> DMAP, Δ, THF, 16 h	65%
HCl, 0 °C, MeOH	Boc ₂ O, <i>cat.</i> DMAP, Δ, MeCN, 16 h	68%
HCl, 0 °C, MeOH	Boc ₂ O, NaHCO ₃ , <i>cat.</i> DMAP, 80 °C, H ₂ O:dioxane, 16 h	73%
HCl, 0 °C, MeOH	Boc ₂ O, NaH, 0 °C – rt, THF, 5 h	79%

Table 2.6

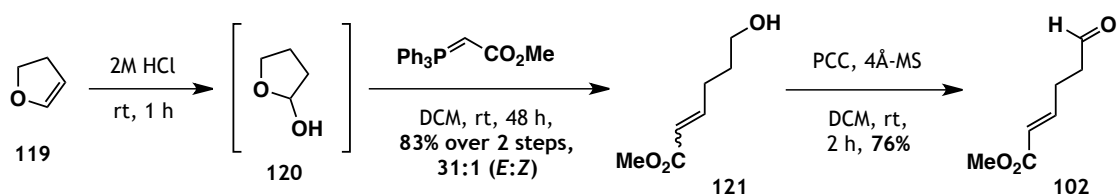
2.2.6 Scale-Up

With minor modifications, this route was performed on a multi-gram scale without any appreciable deterioration in yield. A redesign of the initial sequence was necessary to avoid the use of expensive quantities of ruthenium carbene catalyst during the first step of the synthesis. It was initially envisioned that multi-gram quantities of aldehyde acrylate **102** could be accessed *via* the Claisen rearrangement of allyl vinyl ether derivative **117**. Hydroxy butenoate **116** was synthesised *via* the reaction of commercially available cyanopropenyl acetate **115** in refluxing methanolic HCl in excellent yield (Scheme 2.15).⁴⁸ When the Claisen rearrangement was attempted using acetaldehyde under Dean-Stark conditions no product was observed and we were unable to appreciably consume starting material due to the high volatility of acetaldehyde (bp 20 °C). The use of the diethylacetal as a high-boiling acetaldehyde equivalent (bp 102 °C) under Soxhlet extraction conditions as described by Motherwell *et al.* also failed to afford any product.⁴⁹ No product was observed when this reaction was performed under microwave irradiation (Scheme 2.15).



Scheme 2.15

Multi-gram quantities of aldehyde acrylate **102** was synthesised *via* the acid-catalysed hydration of 2,3-dihydrofuran **119**, Wittig olefination of the resultant furanol and oxidation with PCC to afford **102** in 63% overall yield (Scheme 2.16).^{50,51}



Scheme 2.16

2.3 Route Selection

Although the initial route (Route A) proved beneficial from a small-scale step-efficiency perspective, the problems associated with the large-scale synthesis of the reactive Δ^1 -pyrroline **78** and its subsequent reduction using DIBAL-H precluded its use. The second route (Route B) allowed for the synthesis of *multi-gram* quantities of *N*-Boc and *N*-sulfinyl pyrrolidines **82** and **114**. As such, Route B represented the most optimal approach towards the asymmetric synthesis of the allyl pyrrolidine metathesis fragments (Figure 2.3).

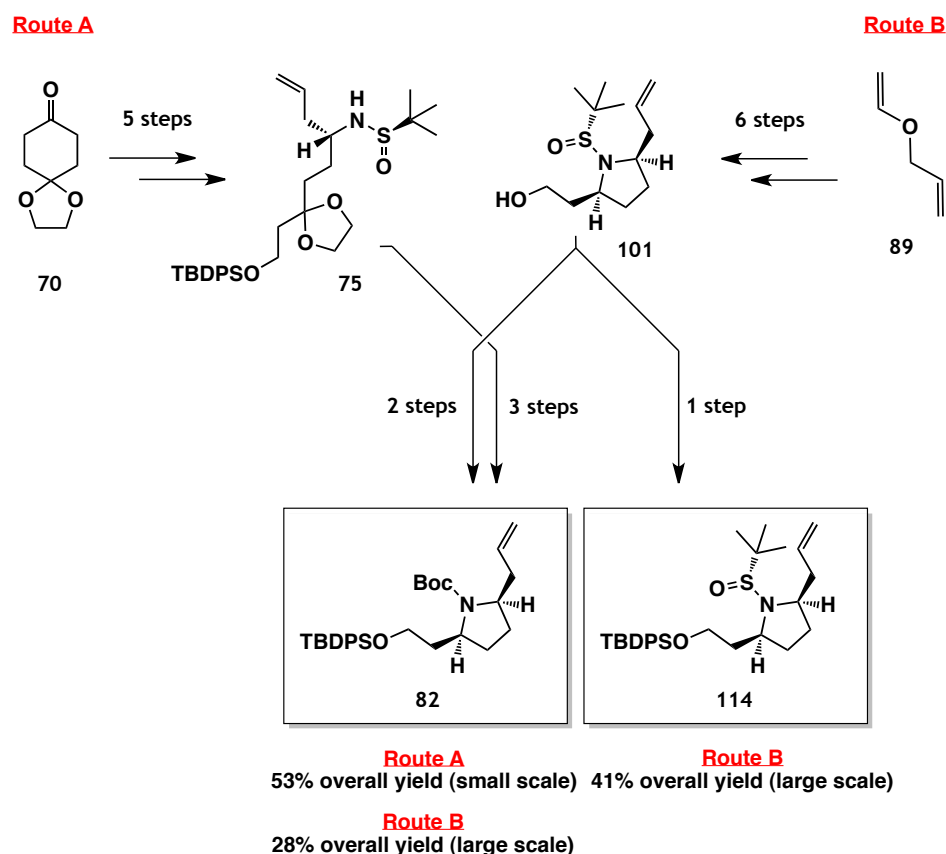


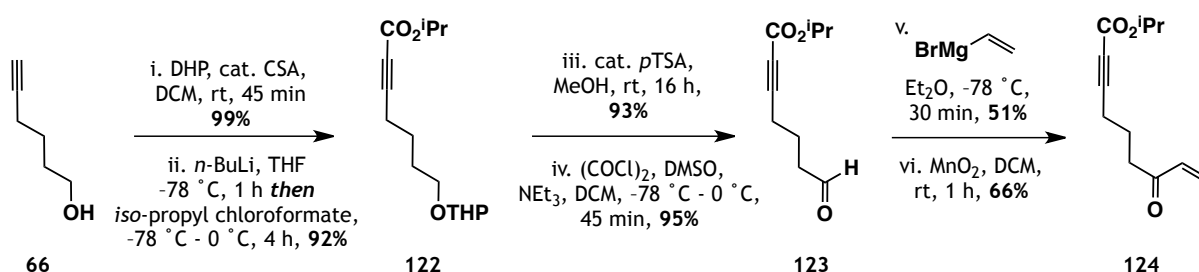
Figure 2.3

Chapter 3 Synthesis of the Cascade Precursor

3.1 1st Generation Strategy

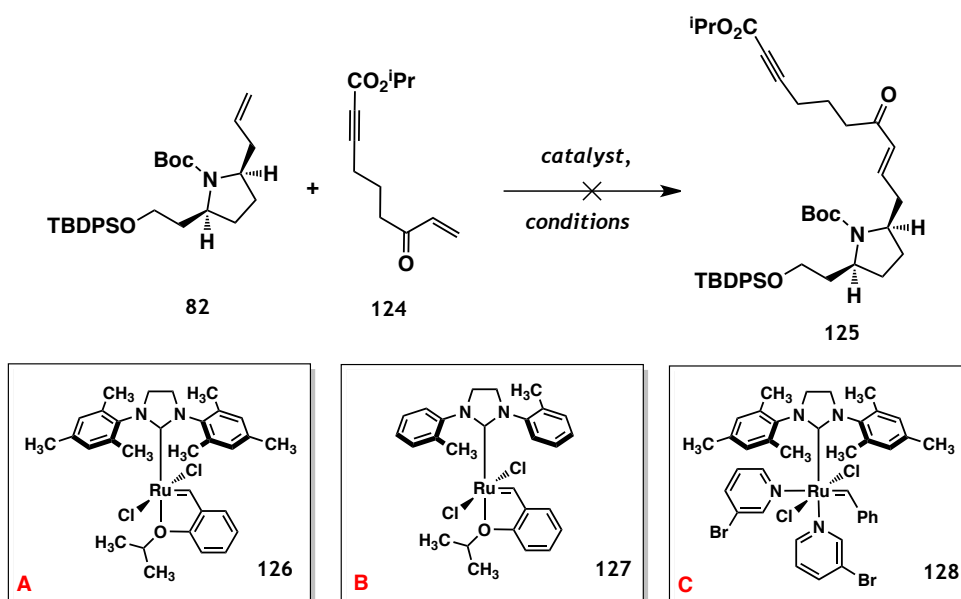
3.1.1 A Cross-Metathesis Approach

The second metathesis fragment **124** was synthesised in six steps from commercially available hexyn-1-ol **66**. Initial formation of the THP-ether **122** and acylation of the corresponding lithium acetylide afforded propargylic ester **122**. Deprotection under acidic conditions was followed by Swern oxidation, vinyl Grignard addition and allylic oxidation with manganese dioxide to afford **124** in 27% overall yield. The diminished yield in the final two steps of this sequence is a consequence of poor chemoselectivity in the Grignard addition and the instability of **124** to chromatography on silica gel (Scheme 3.1).



Scheme 3.1

The cross-metathesis of **124** with allyl pyrrolidine **82** was unsuccessful under a variety of reaction conditions (Scheme 3.2, Table 3.1), returning the allyl pyrrolidine unchanged and a polymer of **124**. A trace of the self-crossed product of **82** was observed after prolonged reaction times.



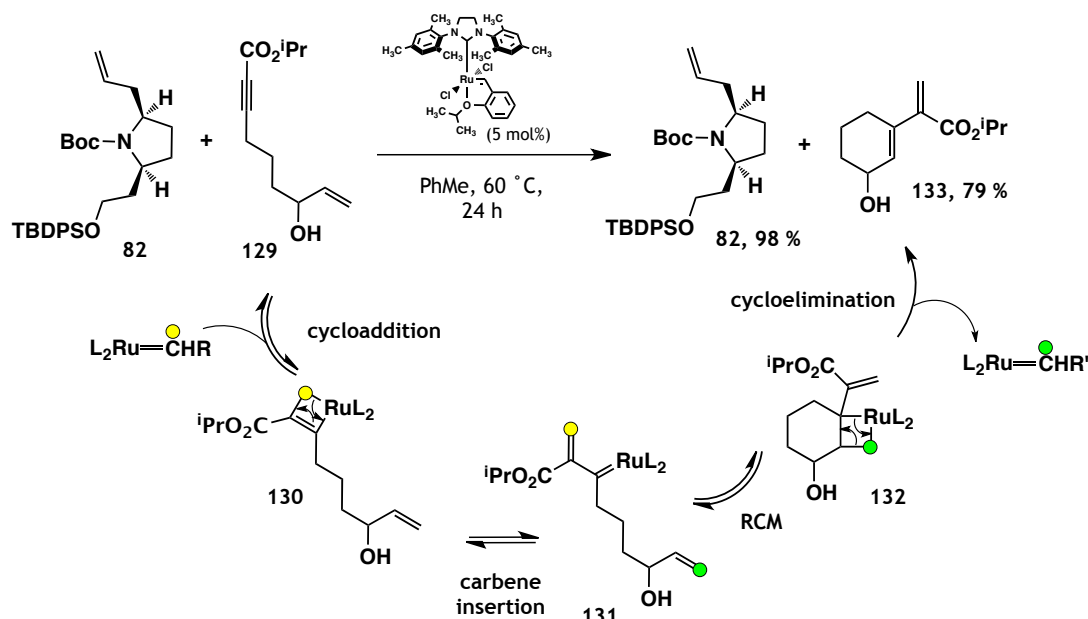
Scheme 3.2

Catalyst (10 mol%)	Conditions	Yield
A	DCM, 40 °C, 48 h	no product
A	PhMe, 60 °C, 24 h	no product
A	PhMe, 80 °C, 24 h	no product
A	DCM, 60 °C, μ w, 40 min	no product
A	DCM, 100 °C, μ w, 60 min	no product
A	DCM, 60 °C, μ w, 40 min (+15 mol% Ti(O ^{<i>i</i>} Pr) ₄)	no product
B	PhMe, 80 °C, 48 h	no product
B	DCM, 60 °C, μ w, 40 min	no product
C	PhMe, 80 °C, 48 h	no product

Table 3.1

When the allylic alcohol **129** was used, the cycloisomerised product **133** was isolated in 79% yield (Scheme 3.3). Formation of this cyclic allylic alcohol indicated that catalyst initiation was occurring by cyclometallation of the alkyne in **129** and not at the allylic alcohol, followed by a Chauvin-type

“yne-then-ene” mechanism.⁵² After insertion of the ruthenium carbene, **131** undergoes a cycloisomerisation *via* a ring-closing metathesis and cycloelimination to afford allylic alcohol **133**.⁵³



Scheme 3.3

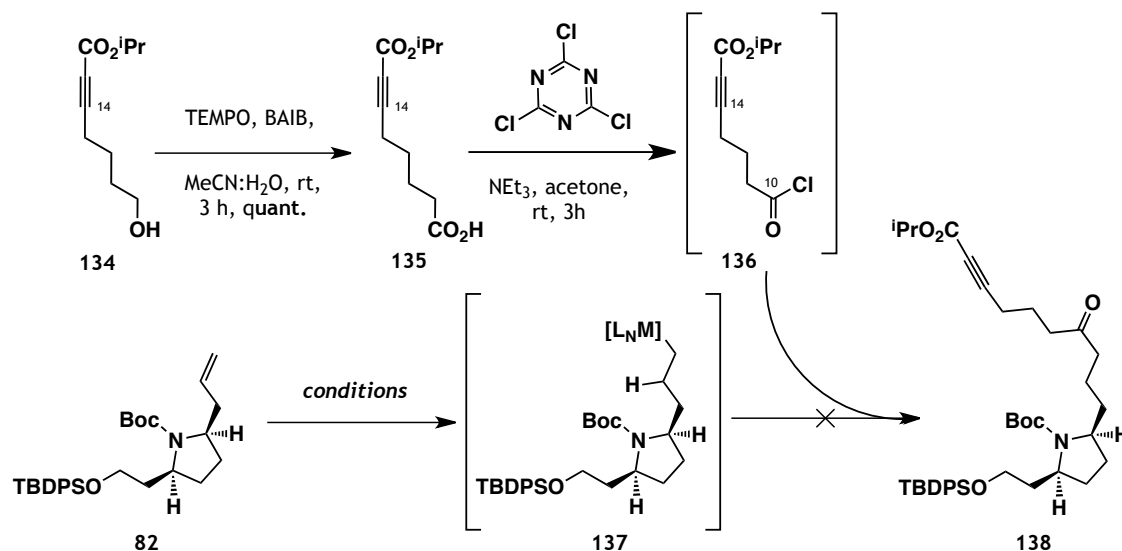
This observation indicated that the cross-metathesis of allyl pyrrolidine **82** and either enone **124** or allylic alcohol **129** in the presence of a propargylic ester would be a highly unfavourable process.

3.1.2 A Cross-Coupling Approach

Further attempts to assemble the cascade precursor included a hydrometallation-cross-coupling strategy. The interception of a preformed organometallic **137**, derived from hydrometallation of allyl pyrrolidine **82**, with acyl chloride **136** would form the requisite C-C bond and assemble the cascade precursor **138**. Acid chloride **136** was synthesised from the primary alcohol **134** *via* a high-yielding TEMPO-BAIB oxidation followed by reaction with cyanuric chloride (Scheme 3.4). Formation of the acid chloride was confirmed by its characteristic C10 ¹³C-NMR resonance at 168 ppm.⁵⁴ Hydroboration of **82** using 9-BBN consumed starting material in both cases, however the subsequent cross-coupling using a palladium(0) catalyst did not afford any detectable product, even under rigorously anhydrous reaction conditions using Schlenk apparatus (Table 3.2).⁵⁵ The hydrozirconation of **82** using the Schwartz reagent consumed starting material, however no product

* Ambiguity remains as to the predominant mechanistic pathway in Ru-alkylidene ene-yne cycloisomerisations. The possibility of an “ene-then-yne” mechanism cannot be discounted.

was observed upon reaction with acyl chloride **136** (Table 3.2). It is anticipated that the lack of product formation in both cases was due to competing β -hydride elimination of the intermediate organometallic and/or competing intramolecular carbopalladation pathways.[†]



Scheme 3.4

Conditions	Yield
9-BBN, THF, rt, 16 h then 136 then Pd(PPh ₃) ₄ , KOAc, THF, rt, 16 h	0%
9-BBN, THF, rt, 16 h then 136 then Pd(PPh ₃) ₄ , KOAc, THF, Δ , 3 h	0%
(Cp) ₂ ZrCl ₂ , LiTEBH, THF, -78 °C, 1 h, rt then 136 , 1 h, rt, dark	0%
(Cp) ₂ ZrCl ₂ , LiTEBH, THF, -78 °C, 1 h, rt then 136 , CuBr·SMe ₂ , 16 h, 40 °C, dark	0%

Table 3.2

3.2 2nd Generation Strategy

3.2.1 Retrosynthetic Analysis

Owing to the lack of success with the fully substituted C9-C16 fragment attention was turned to installing the terminal acetylene at a late-stage *via* the homologation of a C14 aldehyde. This disconnects the cascade precursor to allyl pyrrolidine **62** and δ -valerolactone-derived enone **139** (Figure 3.1).

[†] In each case, the Schwartz reagent was freshly prepared by the reaction of (Cp)₂ZrCl₂ and LiTEBH in anhydrous THF, and the reaction kept in the dark.

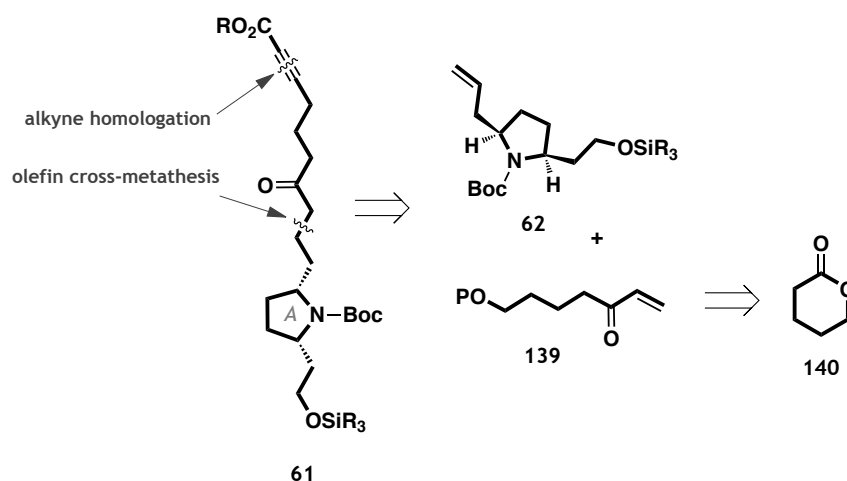
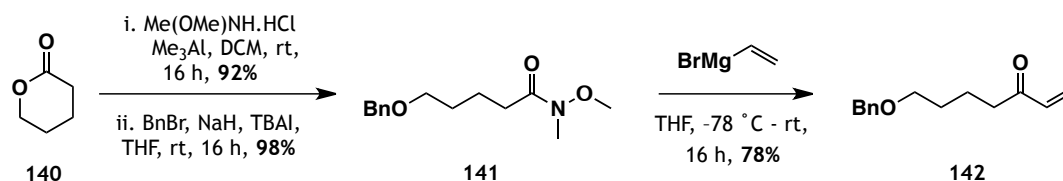


Figure 3.1

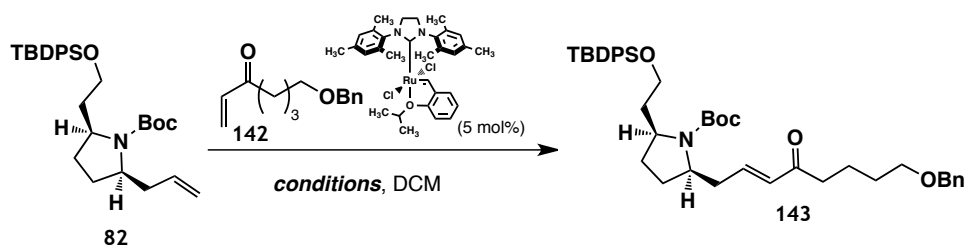
3.2.2 A Cross-Metathesis-Homologation Approach

Commercially available δ -valerolactone **140** was transamidated with the dimethylaluminium amide of *N*-*O*-dimethylhydroxylamine to afford the corresponding Weinreb amide in excellent yield. Protection of the 1°-alcohol as its benzyl ether **141** was followed by a vinyl Grignard addition to afford enone **142** in 70% overall yield (Scheme 3.5).



Scheme 3.5

Cross-metathesis of enone **142** and *N*-Boc pyrrolidine **82** occurred efficiently under microwave irradiation in the presence of the Hoveyda-Grubbs second-generation catalyst to yield pyrrolidine enone **143** in excellent yield and exclusive *E*-selectivity (Scheme 3.6, Table 3.3). By contrast, under thermal initiation the cross-metathesis required three days to consume starting material using the same catalyst loading.

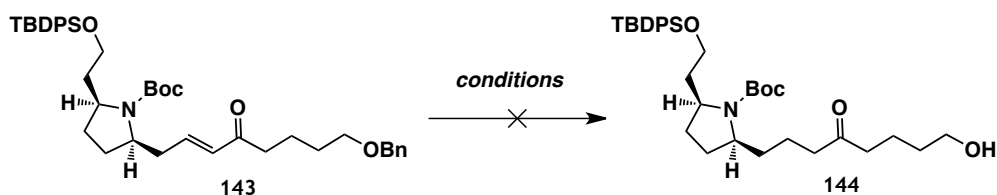


Scheme 3.6

Conditions	Time	Yield
40 °C	72 h	80%
μ w, 70 °C	6 h	95%

Table 3.3

The C=C reduction and *O*-debenzylation of **143** was attempted under a range of hydrogenation conditions, using pressures of up to 5 atm. of hydrogen and various Brønsted-acids (Scheme 3.7, Table 3.4). In all cases, only the corresponding *O*-benzylated pyrrolidine ketone was observed by ^1H -NMR analysis of the crude reaction mixtures.

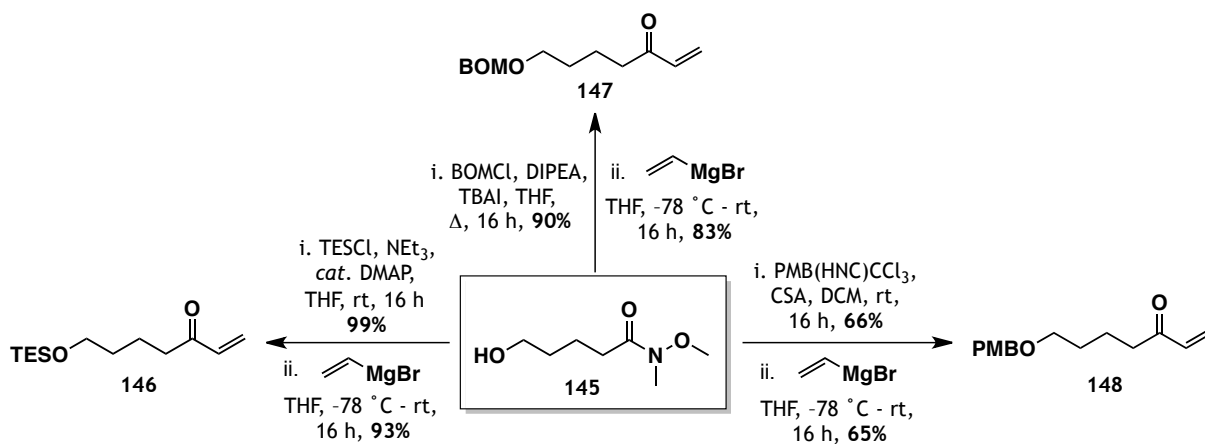


Scheme 3.7

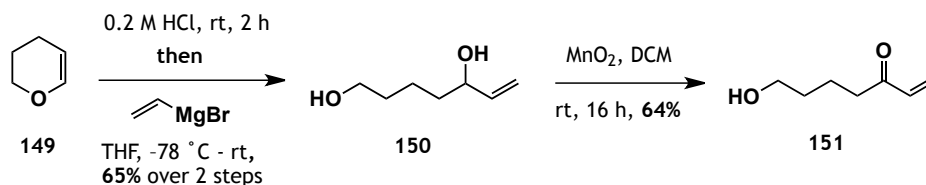
Conditions (% by weight of catalyst)	Solvent	H ₂ (atm.)	Temp (°C)	Time (h)	C=C reduction
H ₂ , Pd/C (10%)	EtOH	1	rt	48	>90%
H ₂ , Pd/C (10%)	EtOAc	1	rt	48	>90%
H ₂ , Pd/C (10%)	THF	1	50	48	>90%
H ₂ , Pd/C (10%)	EtOH	3	rt	1	>90%
H ₂ , Pd/C (20%)	EtOH	5	rt	4	>90%
H ₂ , Pd/C (50%)	EtOH	5	rt	18	>90%
H ₂ , Pd/C (50%), <i>cat.</i> AcOH	EtOH	1	rt	18	>90%
H ₂ , Pd/C (50%), HCO ₂ H	MeOH	1	rt	18	>90%
H ₂ , Pd(OH) ₂ (100%)	EtOAc	1	rt	48	>90%
H ₂ , Rh/Al ₂ O ₃ (100%)	Et ₂ O	1	rt	48	>90%

Table 3.4

A small series of *O*-protected analogues were synthesised *via* an analogous transamidation-protection-vinylation sequence (Scheme 3.8). Protecting groups were chosen for their lability to hydrogenation, and included TES (**146**), BOM (**147**) and PMB ethers (**148**) as well as the unprotected analogue **151**.^{56,57} The unprotected analogue **151** was synthesised in 3 steps from 2,3-dihydropyran **149** in 42% overall yield *via* an acid-catalysed hydration, lactol vinylation and chemoselective allylic oxidation with manganese dioxide (Scheme 3.9).^{58,59,60,61}

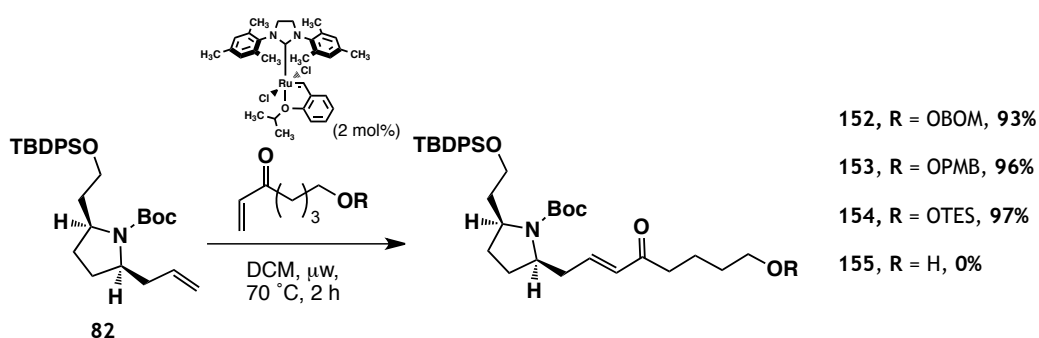


Scheme 3.8



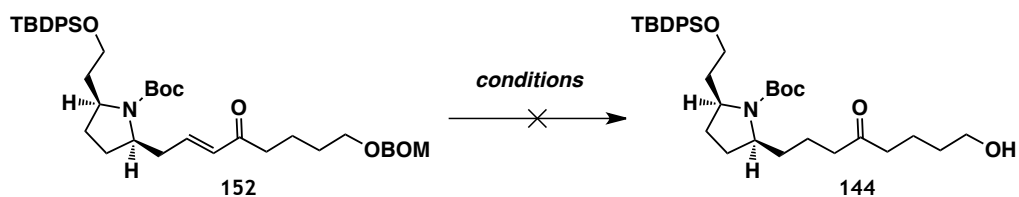
Scheme 3.9

All of the O-protected derivatives underwent cross-metathesis with allyl pyrrolidine **82** under microwave irradiation to afford the corresponding pyrrolidine enones **152-154** in excellent yield and with complete *E*-selectivity (Scheme 3.10). The cross-metathesis of hydroxyl-enone **151** with pyrrolidine **82** gave a complex mixture with no trace of the desired product by ¹H-NMR and ESI-MS.



Scheme 3.10

The BOM-protected alcohol **152** was also inert to deprotection under a range of hydrogenation conditions, with the C=C reduced keto-pyrrolidine being the major product in all cases (Scheme 3.11, Table 3.5).

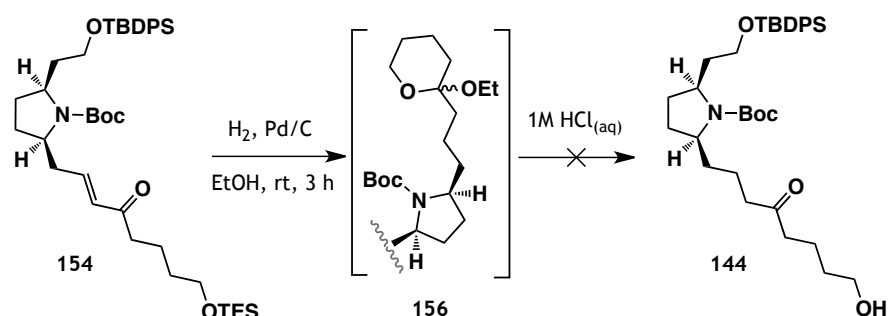


Scheme 3.11

Conditions	Solvent	H ₂ (atm.)	Temp (°C)	Time (h)	C=C reduction
H ₂ , Pd(OH) ₂ (1 eq.)	THF	1	rt	18	>90%
H ₂ , Pd(OH) ₂ (1 eq.)	EtOH	1	rt	18	>80%
H ₂ , Pd(OH) ₂ (1 eq.)	EtOH	1	40	66	>90%
H ₂ , Pd/C (1 eq.)	EtOH	1	rt	18	>90%
H ₂ , PtO ₂ (20%)	EtOH	1	rt	26	>90%
H ₂ , PtO ₂ (20%)	EtOH:AcOH	4	rt	16	>90%

Table 3.5

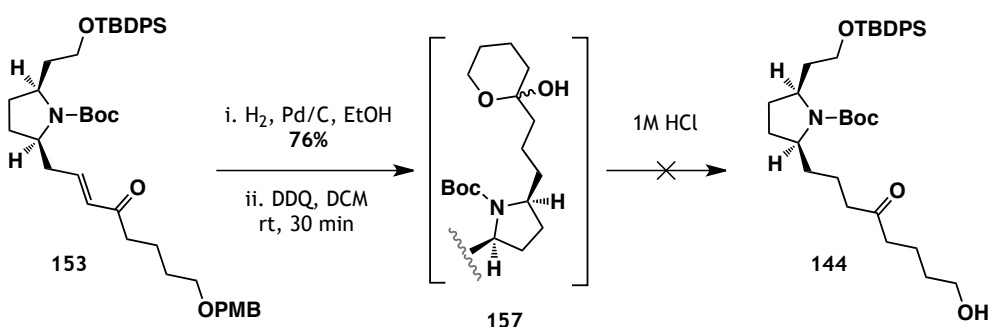
When subjected to hydrogenation over palladium on carbon the *O*-TES derivative **154** underwent C=C bond reduction, *O*-desilylation and cyclisation to form a diastereomeric mixture of pyran acetals **156**. Hydrolysis of the pyran acetal during the reaction work-up using 1M HCl initiated polymerisation of the product, with only traces of the desired δ -hydroxyketone **144** observed by ESI-MS (Scheme 3.12).



Scheme 3.12

The *O*-PMB derivative **153** underwent C=C bond reduction under standard hydrogenation conditions. Oxidative deprotection with DDQ proceeded efficiently, but the reagent-derived acidic

hydroquinone by-product promoted pyran cyclisation (Scheme 3.13). Even when this reaction was carried out in pH 7 buffer, purification on silica gel initiated cyclisation and decomposition of the product.



Scheme 3.13

3.3 3rd Generation Strategy

3.3.1 Retrosynthetic Analysis

We significantly altered our approach at this point, with the aim of avoiding homologation at C14 *via* the aldehyde oxidation level by installing the C14 electrophile *via* a late-stage cross-metathesis reaction. The introduction of a prochiral sp² centre in the cascade precursor **160** would now require the chirality present in the intermediate enamine during the cascade to impart facial selectivity in the Michael addition. Examination of a plausible transition state intermediate **159** suggested that the required absolute configuration at C14 would be favourable under Zimmerman-Traxler control (Figure 3.2). The corresponding *N*-Boc cascade precursor **161** disconnects to allyl-pyrrolidine **62** *via* two cross-metathesis reactions and an alkylation (Figure 3.3).

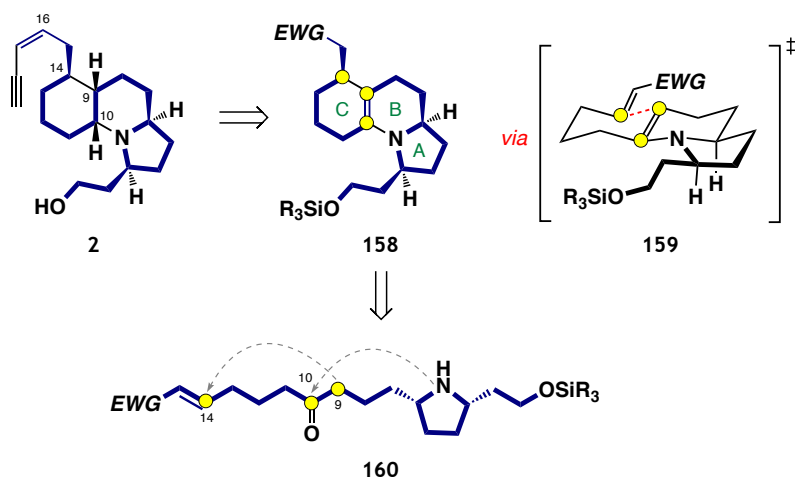
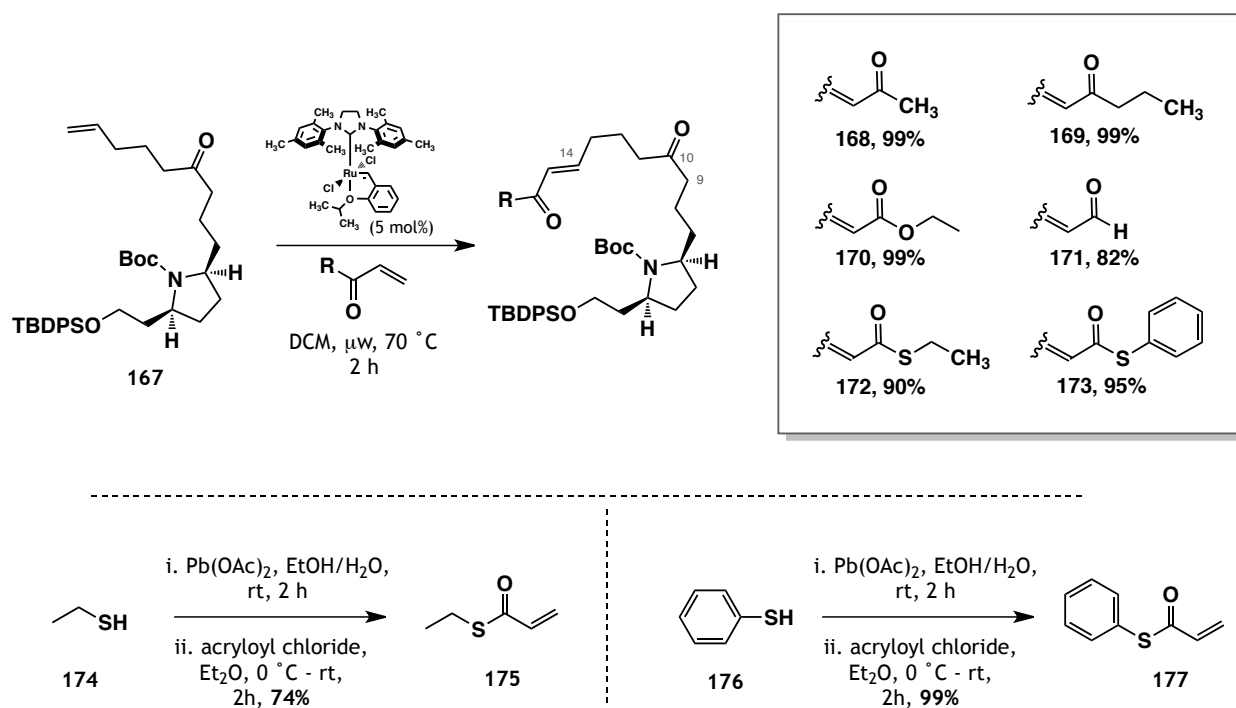


Figure 3.2

Pentenyl ketone **167** served as a divergent intermediate for the introduction of a set of C16 electrophiles by cross-metathesis. The metathesis reactions occurred with exclusive *E*-selectivity and high yield in all cases (Scheme 3.15). The acrolein-derived cascade precursor **171** was prepared, as it would allow for introduction of the unsaturated side-chain of the gephyrotoxins after the cascade.[§] Due to stability issues with **171**, acrylates **170**, **172** and **173** were chosen as *pro*-aldehyde equivalents and *neo*-propyl derivative **169** was chosen to demonstrate that the saturated side-chain of the perhydrogephyrotoxin could be introduced prior to the cascade. Ethyl- and phenyl-thioacrylates (**175** and **177**) were synthesised from their corresponding lead(II) thiolate complexes by reaction with acroloyl chloride (Scheme 3.15).⁶⁴



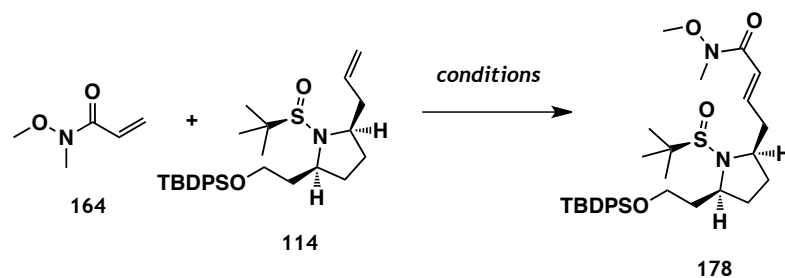
Scheme 3.15

3.4 Synthesis of the *N*-Sulfinyl Cascade Precursor

By comparison, the construction of the *N*-sulfinyl cascade precursor required a higher degree of optimisation. Cross-metathesis of **114** with acrylamide **164** under microwave irradiation at 70 °C resulted in partial *N*-desulfinylation and *O*-desilylation and afforded the product **178** in moderate yield (Scheme 3.16, Table 3.6). Conducting the reaction at room temperature afforded starting material after 48 h. Elevating the temperature to 30 °C saw consumption of starting material after

[§] The acroloyl derivative **171** was very unstable and had fully decomposed after 3 h at room temperature, precluding its characterisation by NMR and MS. It was therefore synthesised when required, and used immediately.

48 h and afforded the product in improved yield; however, partial *N*-desulfinylation was also observed under these conditions.

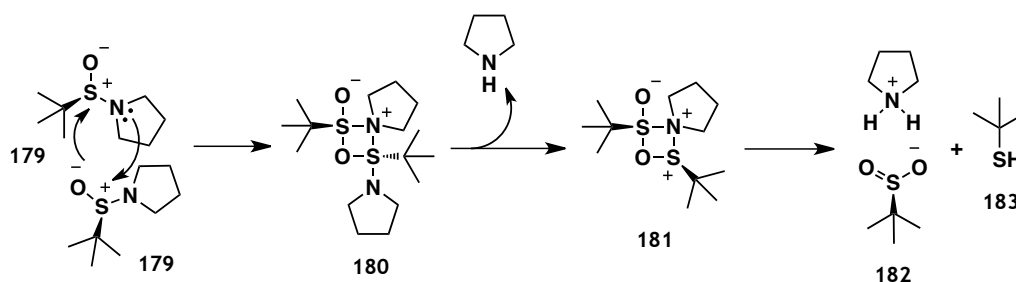


Scheme 3.16

Conditions	Temperature	Time	Yield
Hoveyda-Grubbs II (5 mol%), μ w, DCM	70 °C	2 h	52%
Hoveyda-Grubbs II (5 mol%), DCM	30 °C	48 h	66%

Table 3.6

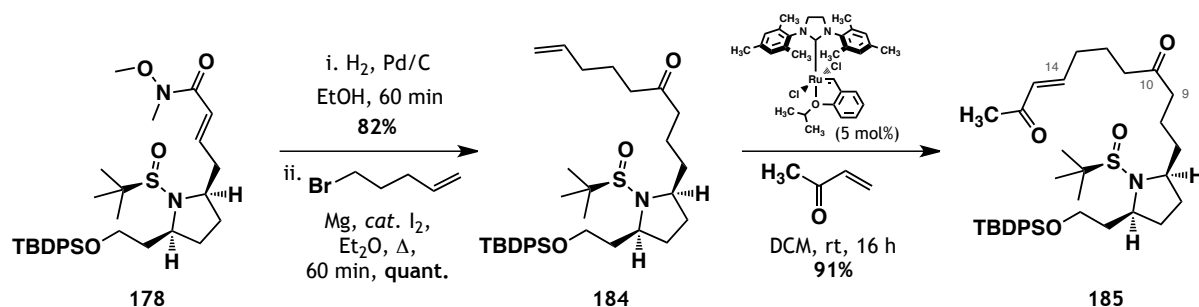
The thermal rearrangement of primary *tert*-butylsulfonamides is reported to be facile at room temperature and is particularly efficient at elevated temperatures and/or under microwave irradiation.⁶⁵ Whilst the thermally-induced decomposition of a tertiary sulfonamide has not been reported to date, it is assumed that the mechanism of tertiary sulfonamide decomposition is analogous to that reported for primary sulfonamides (Scheme 3.17). The production of *tert*-butylsulfinic acid by this proposed mechanism could account for the degree of desilylation observed under the reaction conditions.



Scheme 3.17

The hydrogenation of acrylamide **178** occurred in good yield – albeit with desulfinylation being observed once again – and Grignard alkylation proceeded smoothly to afford **184** in near-

quantitative yield (Scheme 3.18). In order to avoid *N*-desulfinylation, the final cross-metathesis reaction with methyl vinyl ketone was performed at room temperature over 16 h and afforded the *N*-sulfinyl cascade precursor **185** in excellent yield and with exclusive *E*-selectivity (Scheme 3.18).^{**}



Scheme 3.18

3.5 Overview

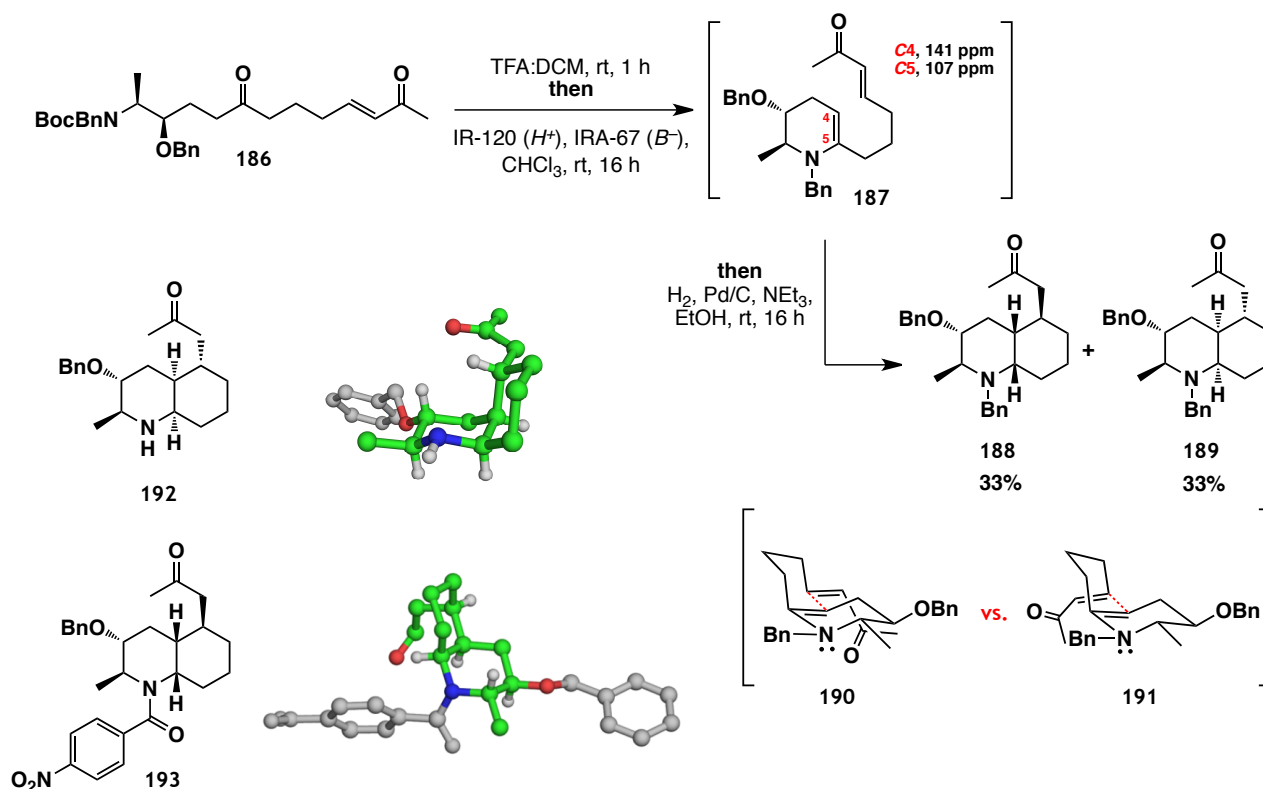
This approach of linchpin metathesis-reduction-alkylation and a final cross-metathesis provided a robust and efficient method by which to introduce the C10-C16 section of the cascade precursor. By careful reaction execution, this sequence could be adapted to synthesise both the *N*-Boc and the *N*-sulfinyl pyrrolidine cascade precursors. Inclusion of a late-stage cross-metathesis allowed for a range of functionalised cascade precursors to be synthesised, facilitating access to the C16-C19 side-chains of every member of the gephyrotoxins.

^{**} Meticulous care was taken throughout this sequence to avoid exposure of any of these intermediates to an acidic work-up protocol and/or elevated temperatures for prolonged periods of time.

Chapter 4 The Enamine-Michael Cascade

4.1 Previous Studies

Previous investigations have demonstrated an intramolecular enamine-Michael cascade in the assembly of decahydroquinoline frameworks.⁶⁶ After acidic deprotection of the Boc carbamate, **186** engages in an intramolecular enamine-Michael cascade to afford decahydroquinolines **188/189** in good overall yield after hydrogenation (Scheme 4.1). Polymer-supported Brønsted acidic and Brønsted basic resins are used to generate the intermediate enamine **187**, which can be isolated, and characterised by ¹³C-NMR. On the basis of X-ray diffraction studies it was shown that the cascade proceeds *via* a non-facially selective Michael addition followed by a substrate-directed stereoselective hydrogenation. This is rationalised by examination of both plausible transition states **190** and **191** for the Michael addition; whereby when the bulky benzyl ether occupies an equatorial position, neither *pro*-chiral face of the electrophile appears to be favoured when positioned *pseudo*-axial or *pseudo*-equatorial.

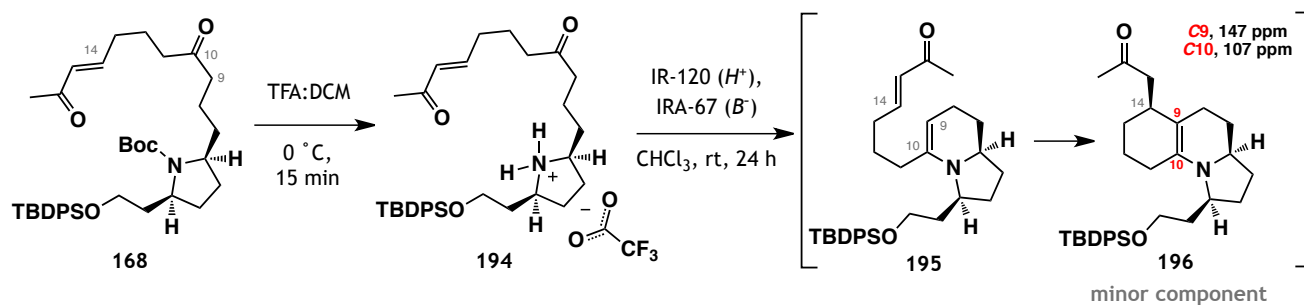


Scheme 4.1

It is anticipated that the additional 5-membered ring constraint within the intermediate enamine of the proposed gephyrotoxin enamine-Michael cascade will impart a higher level of facial selectivity in this process.

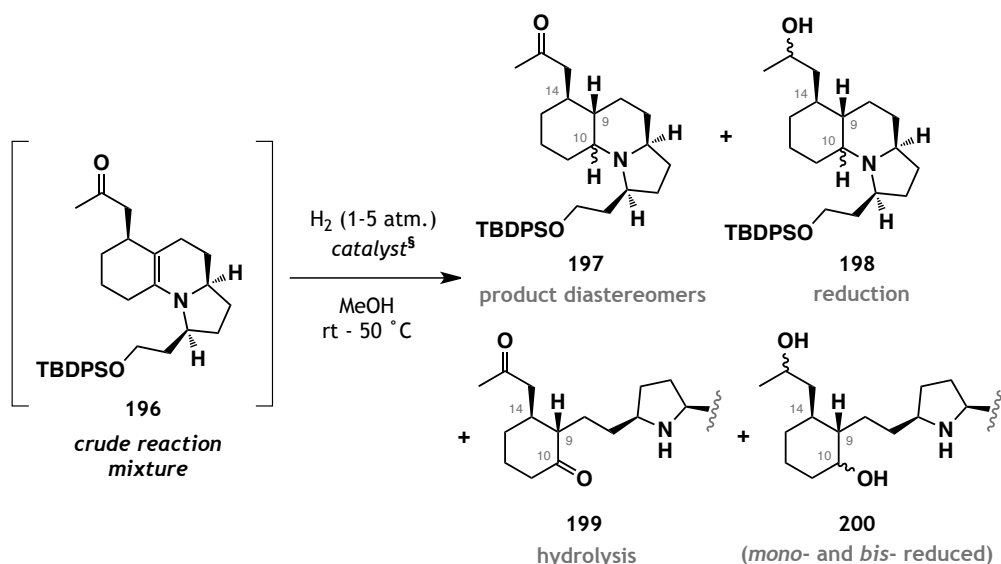
4.2 The Methyl Ketone Derivative

In line with these previous studies, the methyl ketone analogue **168** seemed a suitable compound for initial examination. Deprotection of **168** proceeded efficiently in 15 min using TFA to afford **194** and after concentration the crude mixture was exposed to PS-H⁺/B⁻ resins in chloroform over 24 h. Analysis of the filtrate by ¹H-NMR indicated that cyclisation and Michael addition had occurred. However, a mixture of compounds was formed, with only a minor component of the crude material being attributable to the tricyclic enamine **196** by ¹³C-NMR (Scheme 4.2).



Scheme 4.2

The hydrogenation of the crude reaction mixture under a variety of conditions afforded a mixture of species, including product diastereomers, as well as hydrolysis and polymerisation products (Scheme 4.3). Under increased pressures of hydrogen, secondary alcohol reduction products were also detected by ESI-MS. Isolation of a pure sample of perhydropyrroloquinoline could not be achieved by column chromatography or preparative HPLC.

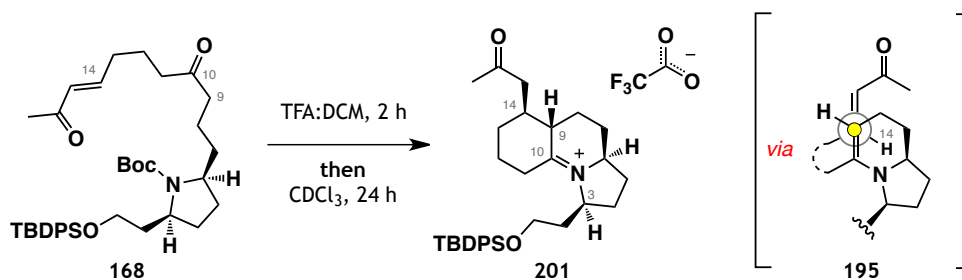


Scheme 4.3

However, when bicyclic enamine **195** was left in CDCl_3 over 16 h at room temperature, Michael addition was observed in the absence of any other additional reagents. This result was significant as it indicated that Michael addition was facile in only mildly acidic chloroform, and that the process appeared to be diastereoselective by ^1H - and ^{13}C -NMR.* On the basis of NMR evidence this compound was assigned as octahydro-quinninium trifluoroacetate **201** (Scheme 4.4). The unusual hydroquininium ring system was confirmed by the characteristic NMR resonances of C10 (190 ppm) and H3 (4.7 ppm) and their coupling by HMBC verifying through-bond connectivity (Figure 4.1). The high diastereoselectivity of this process is presumably kinetically controlled, and may be rationalised by presentation of the C14 electrophile to the least hindered face of the intermediate bicyclic enamine **195**, with projection of the side-chain enone away from the concave bulk of the intermediate bicycle. If this stereochemical model were correct, then the enamine-Michael cascade had set the correct configuration at C9 *and* at C14.

[§] Catalysts screened included Pd/C, Pd(OH)₂, PtO₂ and Rh/Al₂O₃ in methanol under 1-5 atm. of hydrogen and at reaction temperatures of up to 50 °C.

* High diastereoselectivity in this process was dependant upon the removal of water released from condensation of the intermediate ammonium salt **194**. This required deprotection and cyclisation using TFA for 2 h and azeotropic removal of the excess acid and water.



Scheme 4.4

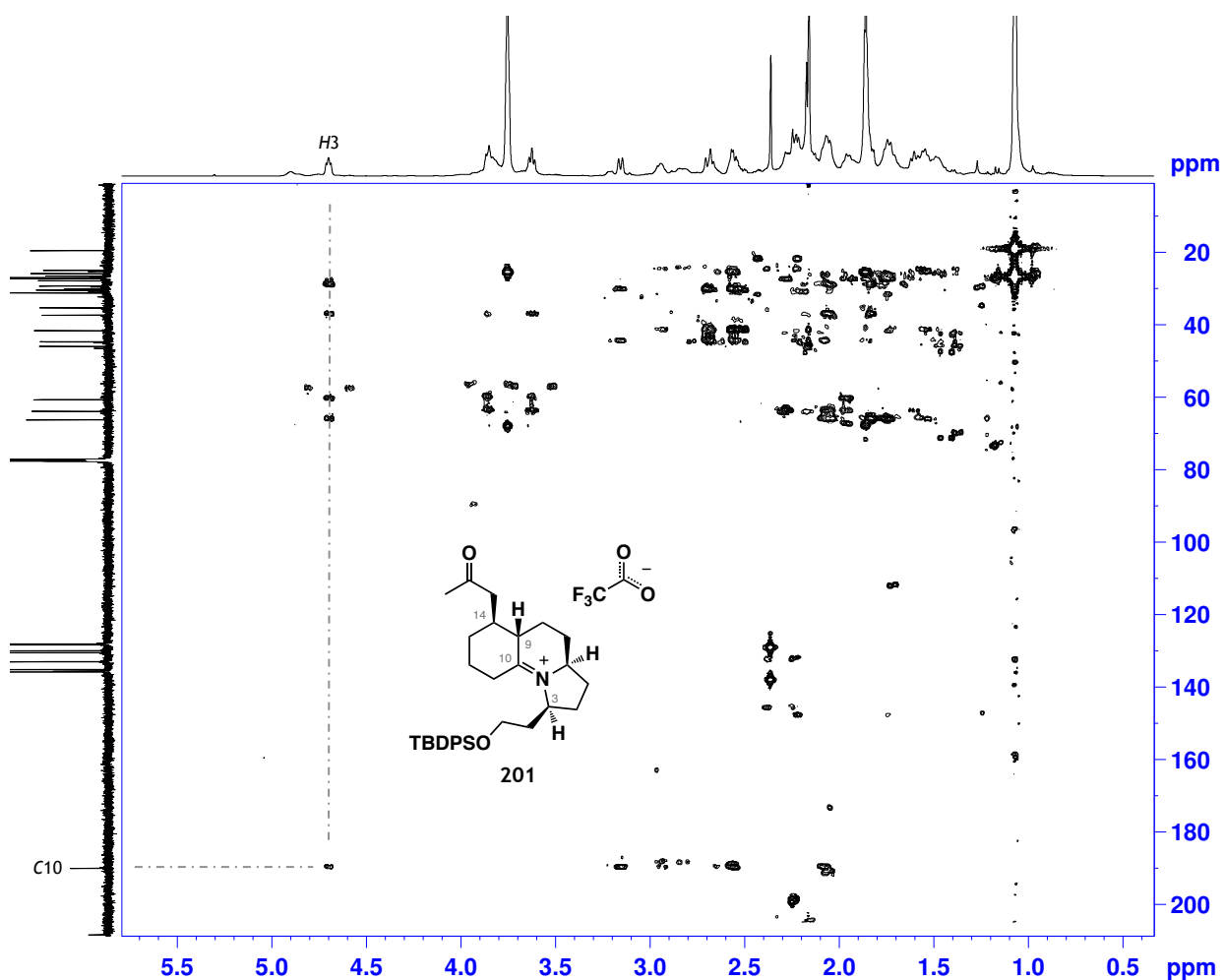
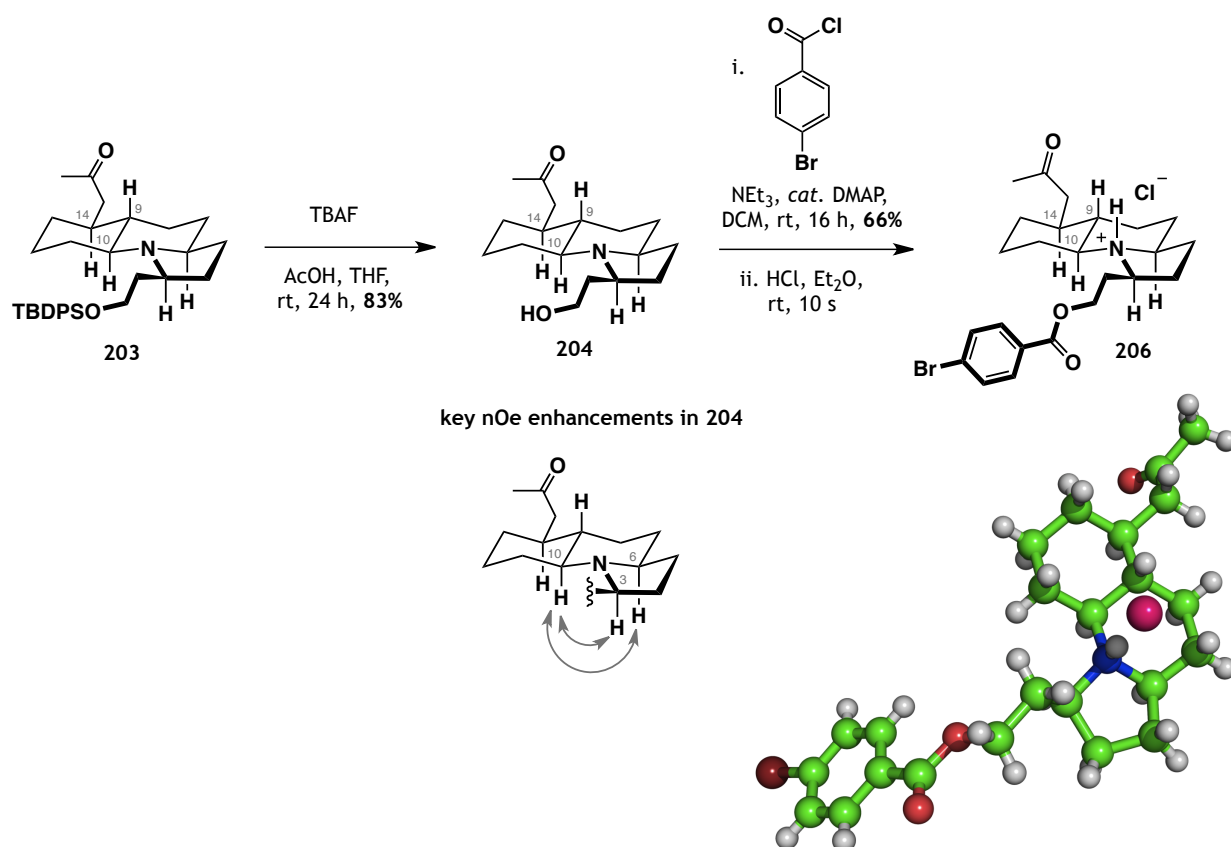


Figure 4.1

When quininium **201** was treated with sodium cyanoborohydride in DCM, chemoselective reduction of the iminium ion was observed to afford *trans*-perhydropyrroloquinoline **203** in 83% overall yield, and as a single diastereoisomer (Scheme 4.5). The selectivity in this process is dictated by stereoelectronics, whereby a *trans*-diaxial alignment of the approaching hydride nucleophile and



Scheme 4.6

The ¹H- and ¹³C-NMR spectra of **203**, **204** and **205** proved difficult to assign as a result of the highly congested upfield region in the ¹H-NMR spectrum and the highly-split diastereotopic nature of all ten geminal proton pairs. To do so, focus was placed on the relatively dispersed signals in the ¹³C-NMR spectrum and used to track local heteronuclear connectivity *via* a 2D HSQC-TOCSY experiment (Figure 4.2). By resolving a 2D TOCSY experiment in the carbon dimension this allowed for the iterative mapping of local ²J_{C-H} couplings within the upfield region of the ¹H-NMR.[‡]

[‡] The mixing time for the TOCSY experiment was kept short (25 ms) to avoid extensive transfer of magnetisation throughout what is essentially one spin-system. The HSQC spectrum of **205** (red (-ve)/blue (+ve)) is overlaid upon the HSQC-TOCSY spectrum of **205** (black).

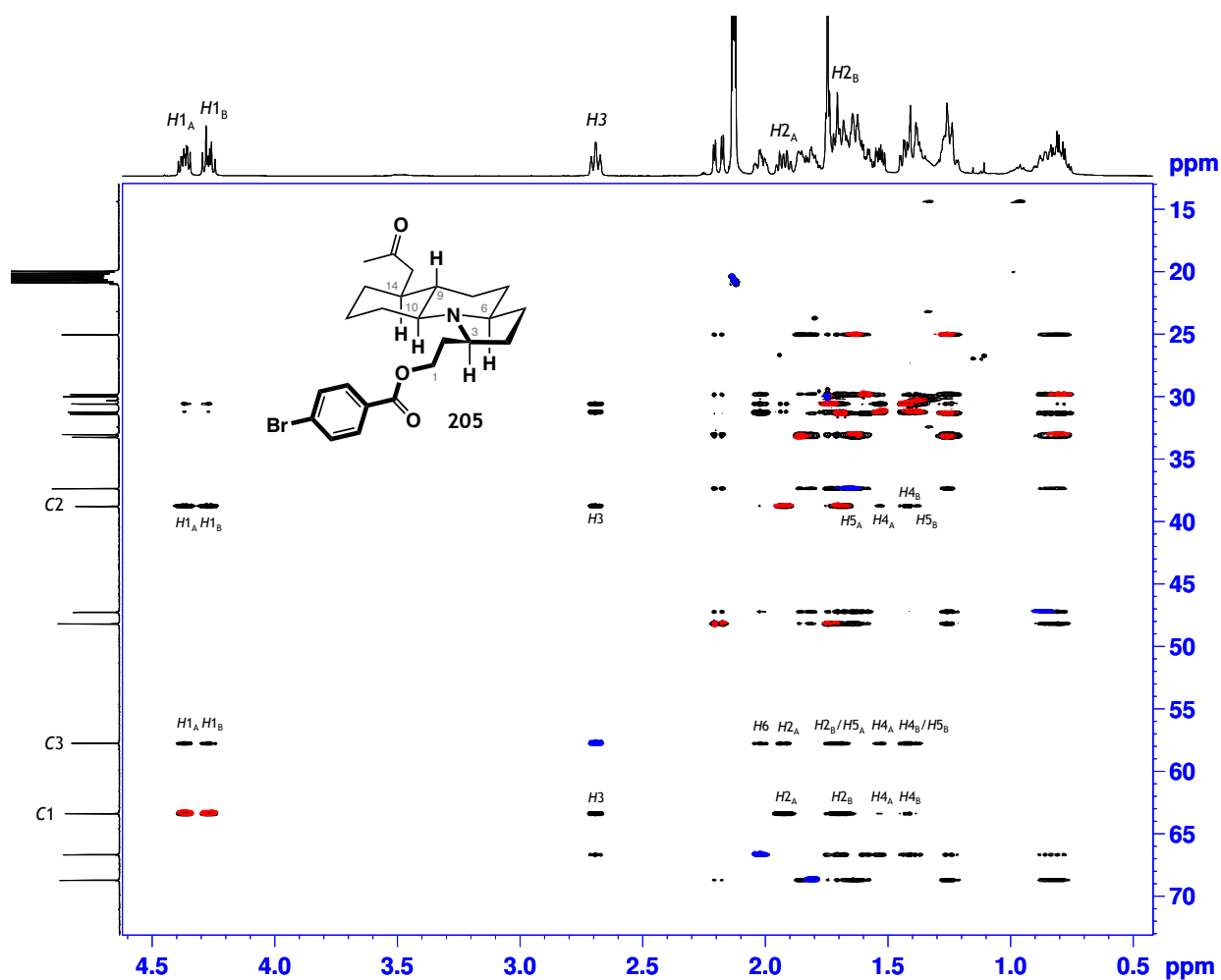
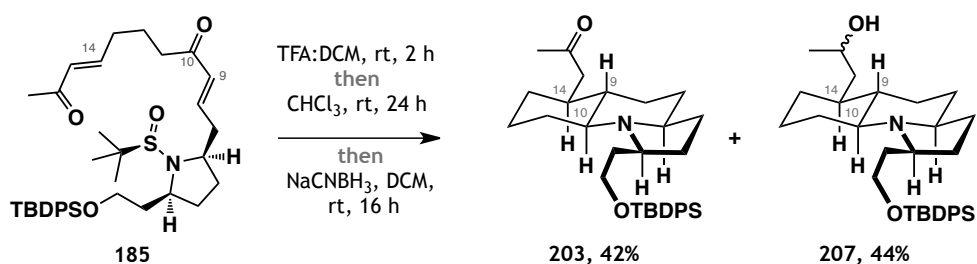


Figure 4.2

4.3 The N-Sulfinyl Cascade

When *N*-sulfinyl derivative **185** was subjected to the cascade sequence *trans*-perhydropyrroloquinoline **203** was isolated in 42% yield, along with 44% of the corresponding secondary alcohol **207** as a mixture of C16 diastereomers (Scheme 4.7).



Scheme 4.7

The reduced yield and chemoselectivity for this example is likely a consequence of the production of *tert*-butyl sulfinic acid during the acidic deprotection, allowing for facile carbonyl reduction. Whilst this example proved less efficient, strategically this system remains attractive and warrants further optimisation.

4.4 Examining Further C16 Derivatives

4.4.1 Reactivity

The success of the methyl ketone system was precluded by both the incorrect configuration at C10 in **203** and its unsuitability for further elaboration of the C17-C19 side-chain. To this end, the cascade precursors **169-173** synthesised in Chapter 3 were examined for analogous reactivity by ¹H-NMR. Each compound was deprotected under acidic conditions, concentrated and the progress of Michael addition analysed *via* a ¹H-NMR time-course experiment in CDCl₃. Following the relative integration of the H15 proton in each case allowed the rate of Michael addition to be determined (Figure 4.3). The acrylate **170** showed a distinct lack of reactivity, with Michael addition having only reached 20% conversion after 2 months in CDCl₃. The acrolein **171** showed comparable kinetics to the methyl ketone example; however, the formyl hydroquininium product of the Michael addition was extremely unstable and had fully decomposed after 16 h at room temperature. The ethyl thioacrylate **172** was sluggish to undergo Michael addition, with only 60% consumption of starting material being observed after 8 days. The more reactive phenyl thioacrylate **173** however showed promising results, with 80% consumption of starting material observed after 10 h at room temperature.

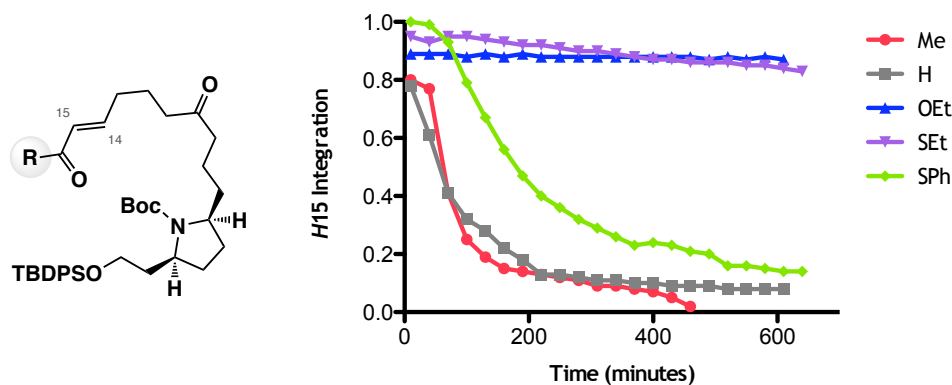
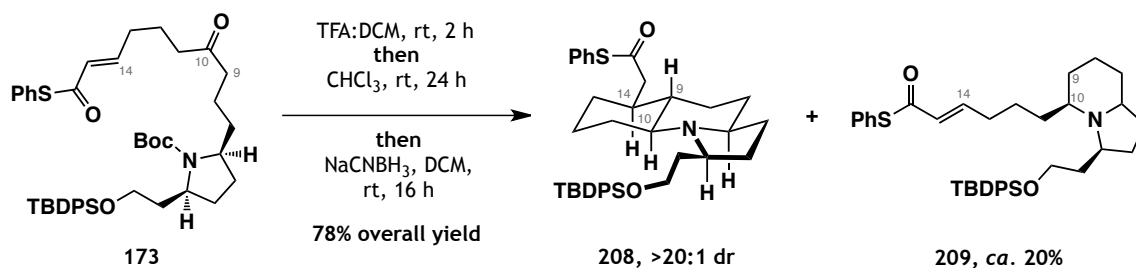


Figure 4.3

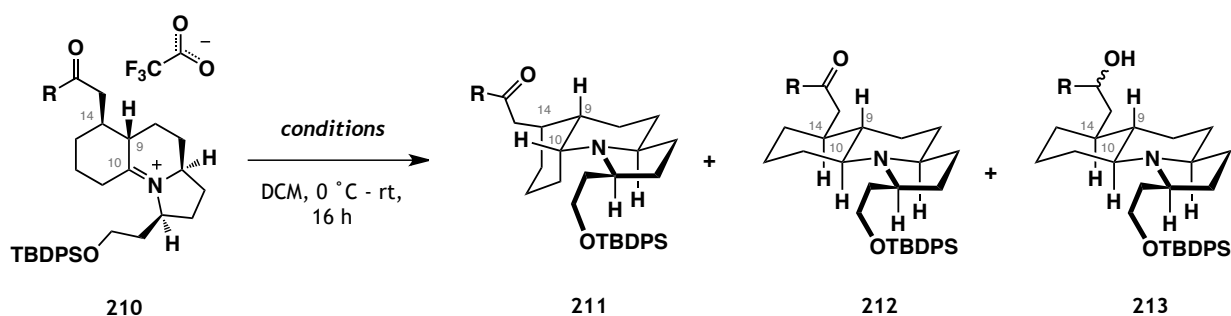
Although the NMR experiments had shown that the phenyl thioester **173** cyclised with favourable kinetics, reduction with sodium cyanoborohydride afforded tricyclic thioester **208** alongside *ca.* 20% of uncyclised indolizidine **209** (Scheme 4.8). Extensive attempts were made to separate **208** from this uncyclised material, however separation could never be completely achieved by flash chromatography or preparative HPLC.



Scheme 4.8

4.4.2 Examining Various Reducing Agents

A small set of borohydride reducing agents was screened in order to assess the generality of this stereoselective reduction process. In all examples, *trans*-perhydroquinoline **212** was isolated as a single diastereomer, with only concurrent degrees of ketone reduction being observed when more Brønsted acidic reducing agents were employed (Scheme 4.9, Table 4.1).



Scheme 4.9

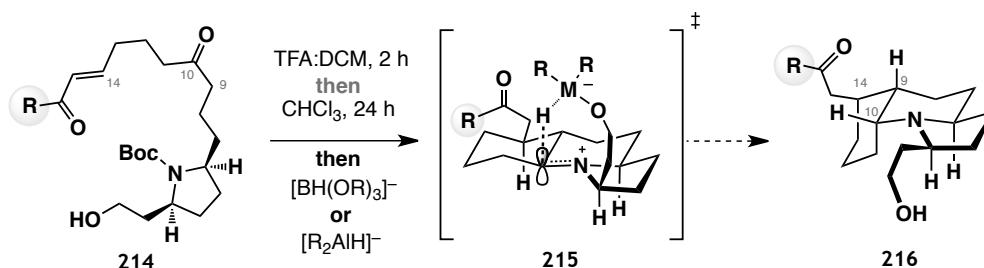
R	Conditions	Yield	211:212:213
Me	NaCNBH ₃	83%	0:1:0
Me	NaBH(OAc) ₃	79%	0:10:1
Me	BH _{4-n} (CO ₂ R) _n , R = 2-ethylhexanoic acid	75%	0:5:1
SPh	NaCNBH ₃	79%	0:1:0

Table 4.1

Further expansion of this hydride screen was not undertaken as, in line with our studies, this stereoelectronic effect has been shown to predominate with a range of reducing agents, in a number of systems.^{67, 68, 69, 70, 71, 72, 73} It seemed unlikely that an intermolecular reduction which is so predominantly dictated by stereoelectronics could be reversed on the basis of manipulating steric influence. As such, we progressed to examining *substrate*-directed intramolecular reductions of the hydroquininium salt.

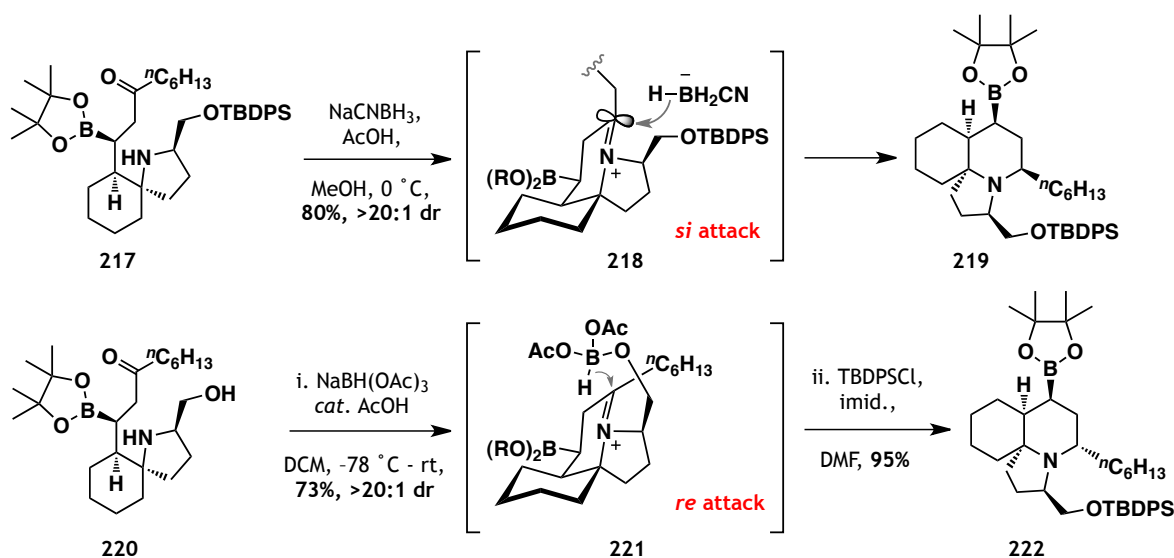
4.5 A Directed Reduction Approach

It was anticipated that it would be possible to reverse the undesired stereoselectivity of this process *via* the directed intramolecular reduction of quininium **215** by a hydride source that was chelated by the oxygen atom at C1 (Scheme 4.10). This tethered reduction approach would allow for the absolute configuration at C3 to direct the facial selectivity of the reduction to the *Si*-face of the iminium *via* an 8-membered cyclic chelate. Suitable Lewis acidic reagents would include various substituted acyloxyborohydrides and trivalent aluminium hydrides. Such an approach has found widespread use in the synthesis of stereoregular polyols whereby 1,3-stereoiduction is Zimmerman-Traxler-controlled and is highly *anti*-selective.^{74,75}



Scheme 4.10

The application of stereoselective directed iminium reductions has previously been demonstrated in alkaloid synthesis. Chifolini *et al.* demonstrated the late-stage directed reduction of the intermediate iminium **221**, formed from condensation of keto-pyrrolidine **220**, using sodium triacetoxyborohydride in the presence of catalytic acetic acid (Scheme 4.11).⁷⁶ Analogous to our study, in the presence of the protected silyl ether intermediate, iminium **218** undergoes an undesired stereoelectronic reduction *via* axial-/concave-addition of hydride to afford the epimeric core of the cylindricine alkaloids **219**. This process is particularly interesting as it proceeds *via* a thermodynamically stable iminium conformer and the reduction proceeds *via* a 7-membered boron-chelate within a congested polycyclic framework.

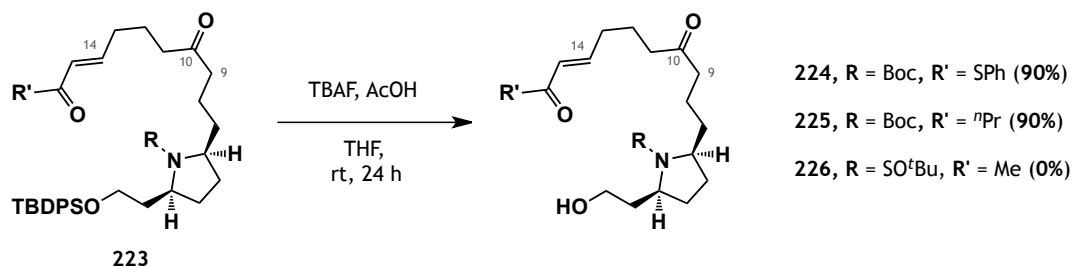


Scheme 4.11

4.5.1 The Cascade in the Presence of a Primary Alcohol

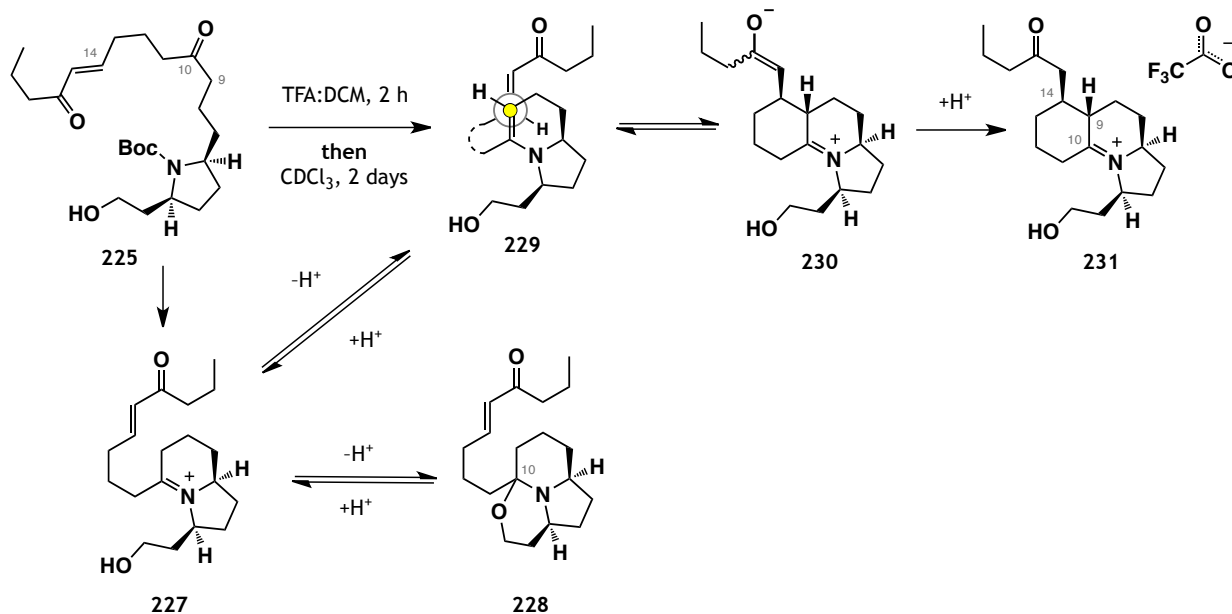
To this end, primary alcohol derivatives **224** and **225** were synthesised by desilylation of **173** and **169** under buffered TBAF conditions (Scheme 4.12). Buffering the reaction with acetic acid was essential to avoid enolisation and polymerisation of the substrate. It was not possible to synthesise

the *N*-sulfinyl primary alcohol derivative **226** under these conditions, as *N*-desulfinylation was facile in the presence of acetic acid.



Scheme 4.12

Deprotection of **225** and kinetic analysis by ¹H-NMR indicated Michael addition had occurred after two days at room temperature. The cyclisation is notably slower in this system, which is presumably a consequence of a competing equilibrium between iminium **227** and hemiaminal **228** (Scheme 4.13).



Scheme 4.13

For the phenyl thioester **224**, the cascade achieves only *ca.* 50% conversion after 20 h at room temperature, compared to *ca.* 80% conversion in the silyl ether system after 11 h (Figure 4.4).

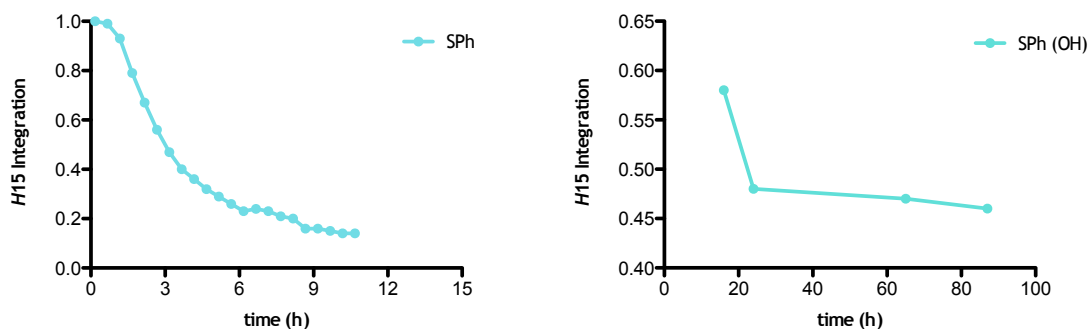


Figure 4.4

4.5.2 A Boron-chelate Approach

By analysis and comparison of the ^{13}C -NMR spectrum of **204** with that of (+)-gephyrotoxin it became apparent that C3, C6 and C10 within either a *cis*- or *trans*-decalin-based perhydroquinoline ring-system possessed marked differences in NMR resonances (Table 4.2).⁷⁷ Based on these characteristics, when screening various reduction conditions the crude reaction mixtures were analysed by ^{13}C -NMR to qualitatively assess the diastereoselectivity arising from each reagent.[§]

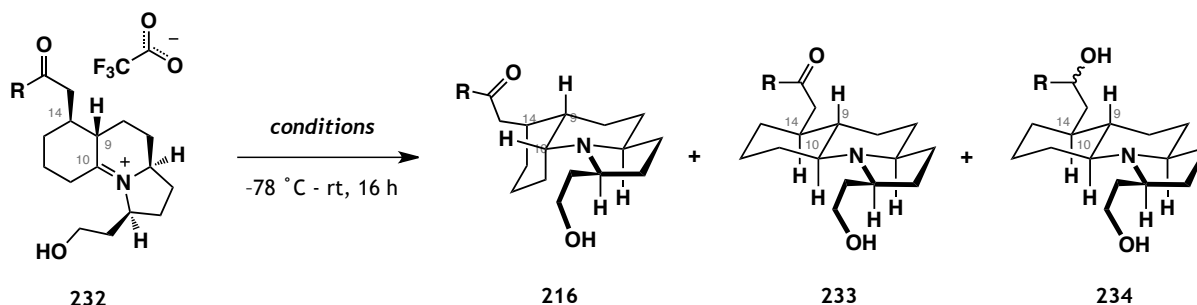
	C3 (δ , ppm)	C6 (δ , ppm)	C10 (δ , ppm)
(+)-gephyrotoxin	55.4	56.0	50.3
204	59.9	67.2	68.6

Table 4.2

When using sodium cyanoborohydride, reduction of both the *neo*-propyl ketone and phenyl thioester quininium derivatives afforded *trans*-hydroquinolines **233** as single diastereomers. Reduction using tetramethylammonium triacetoxyborohydride also afforded *trans*-hydroquinoline **233** as a single diastereoisomer, with concurrent C16 ketone reduction in the *neo*-propyl system.⁷⁴ Interestingly, when employing triacetoxyborohydride in the presence of catalytic acetic acid, analogous to Chiofolini *et al.*, we observed a 10:1 mixture of *trans*- and *cis*-hydroquinoline diastereomers **233/216** respectively (R = *n*Pr, Table 4.3). The *cis*-hydroquinoline **216** was tentatively identified by the indicative ^{13}C -NMR resonances of C3 (56.0 ppm), C6 (56.3 ppm) and C10 (50.9 ppm), which were comparable to (+)-gephyrotoxin. Unfortunately, this compound was only

[§] Products were not isolated by silica gel chromatography and product distributions are based on relative integrations, where possible, in the crude ^1H -NMR spectrum.

produced in <10% yield and could not be separated from *trans*-hydroquinoline **233**, uncyclised indolizidine and diastereomeric secondary alcohol by-products **234** (Scheme 4.14).

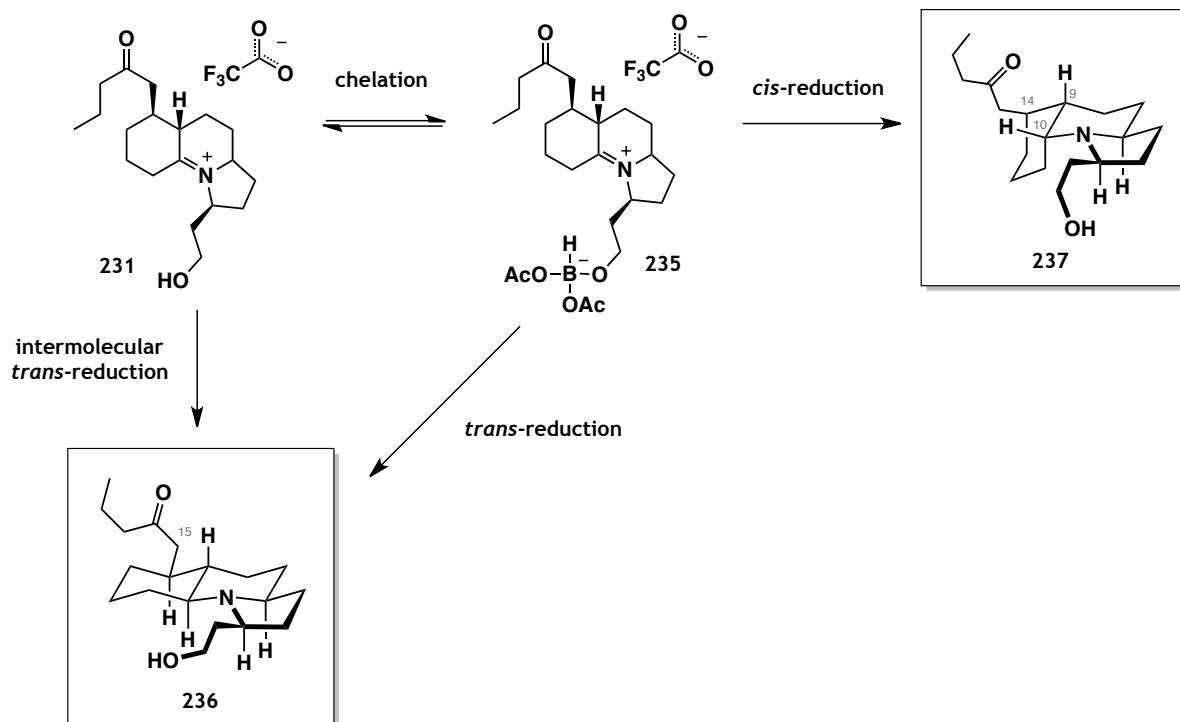


Scheme 4.14

R	Conditions	Yield	216:233:234
ⁿ Pr	NaCNBH ₃	>75%	0:1:0
SPh	NaCNBH ₃	>70%	0:1:0
SPh	NaBH(OAc) ₃ , <i>cat.</i> AcOH	-	0:1:0
SPh	Me ₄ N ⁺ [BH(OAc) ₃], AcOH:MeCN	75%	0:1:0
ⁿ Pr	NaBH(OAc) ₃ , <i>cat.</i> AcOH	>80%	1:10:1
ⁿ Pr	NaBH(CO ₂ R) ₃ , R = 2-ethylhexanoic acid	-	0:5:1
ⁿ Pr	Me ₄ N ⁺ [BH(OAc) ₃], AcOH:MeCN	>80%	0:2:1
ⁿ Pr	Me ₄ N ⁺ [BH(OAc) ₃], <i>cat.</i> AcOH, acetone	-	0:5:1

Table 4.3

The diastereoselectivity of this example can be explained through consideration of both a chelated and non-chelated borohydride intermediate (Scheme 4.15). In the presence of a competing intermolecular *anti*-selective reduction pathway, the diastereoselectivity of this process is likely a consequence of either the slow rate of formation of the initial boron chelate **235**, or a lack of facial selectivity by the intermediate cyclic chelate. As such, we thought that it would be useful to examine more Lewis acidic reducing agents. If the tethered reduction were *cis*-selective, then increasing the relative rate of formation of the initial metal chelate would translate to higher levels of *cis*-selectivity in the subsequent reduction.

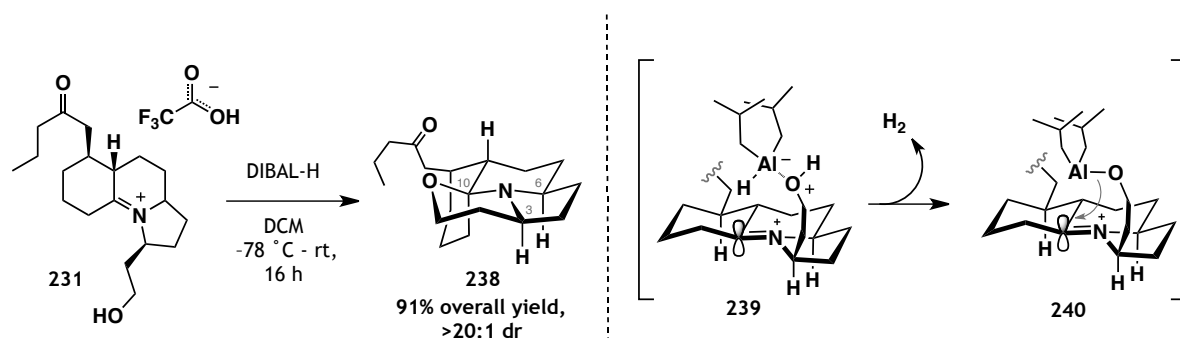


Scheme 4.15

4.5.3 An Aluminium-Chelate Approach

Aluminium-based reducing reagents were attractive alternatives to borohydrides, as they are more Lewis acidic and their hydridic reactivity is conditional upon dative complexation by a Lewis base. Such aluminium-directed reductions have been reported, and are considered as a complimentary class of reagents to borohydrides for directed stereoselective reductions.^{75,78,79,80,81,82} Curiously, when the intermediate iminium **231** was treated with 1 equivalent of DIBAL-H at $-78\text{ }^{\circ}\text{C}$ in DCM and slowly warmed to room-temperature over 16 h neither diastereomeric reduction products were detected, but instead the tetracyclic aminor **238** in 91% overall yield as a single diastereomer (Scheme 4.16). This compound presumably arises through intramolecular delivery of a nucleophilic *oxo*-aluminium species **240**. The ^{13}C -NMR spectrum of **238** suggested that addition had occurred to the *Si*-face of the iminium (C3 (51.9 ppm), C6 (56.9 ppm), Table 4.4). The aminor structure was confirmed by the deshielded ^{13}C -NMR resonance of C10 at 88.4 ppm, and by an HMBC correlation between *H*1 and C10, verifying through-bond connectivity (Figure 4.5).^{**}

^{**} Unambiguous confirmation of this tetracyclic structure required analysis by 2D HSQC-TOCSY and DQF-COSY NMR experiments.



Scheme 4.16

	C3 (δ,ppm)	C6 (δ,ppm)	C10 (δ,ppm)
(+)-gephyrotoxin	55.4	56.0	50.3
238	51.9	56.9	88.4

Table 4.4

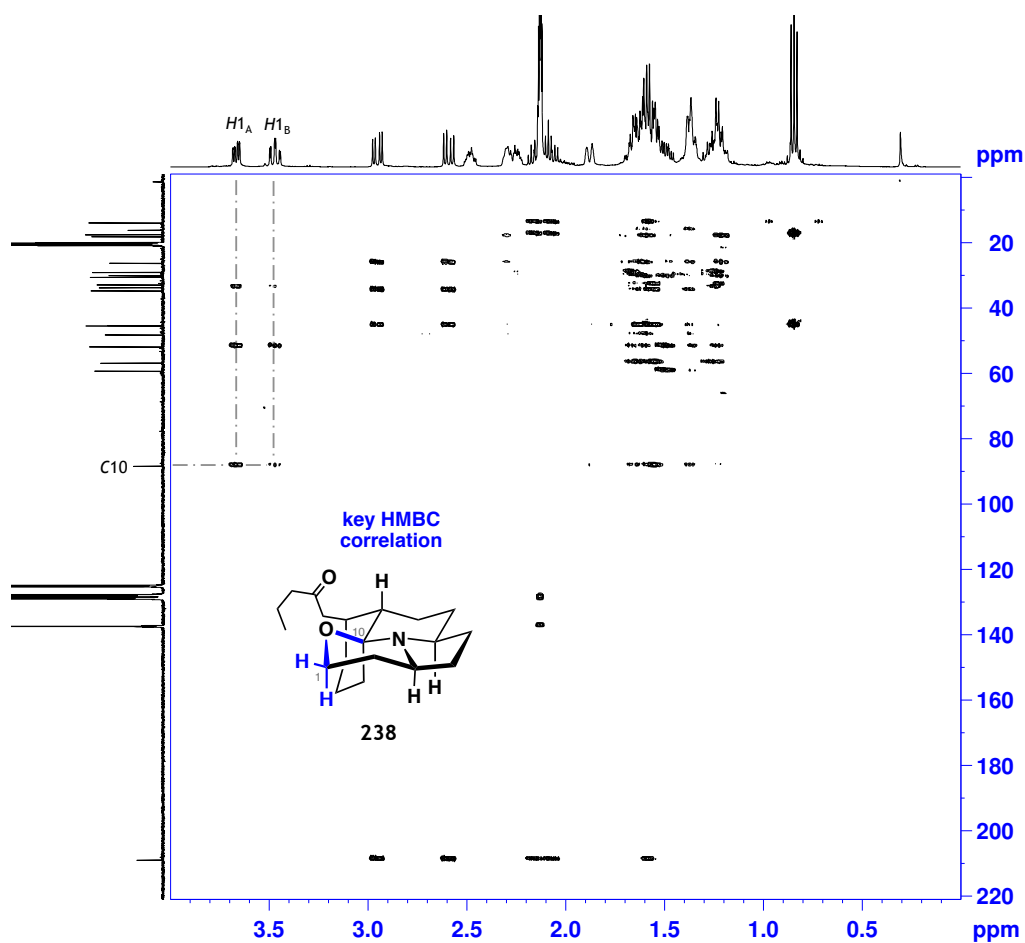
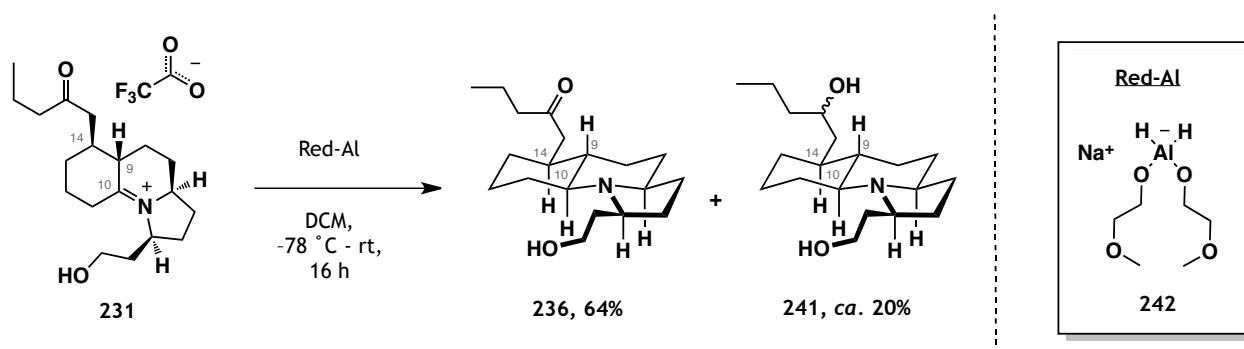


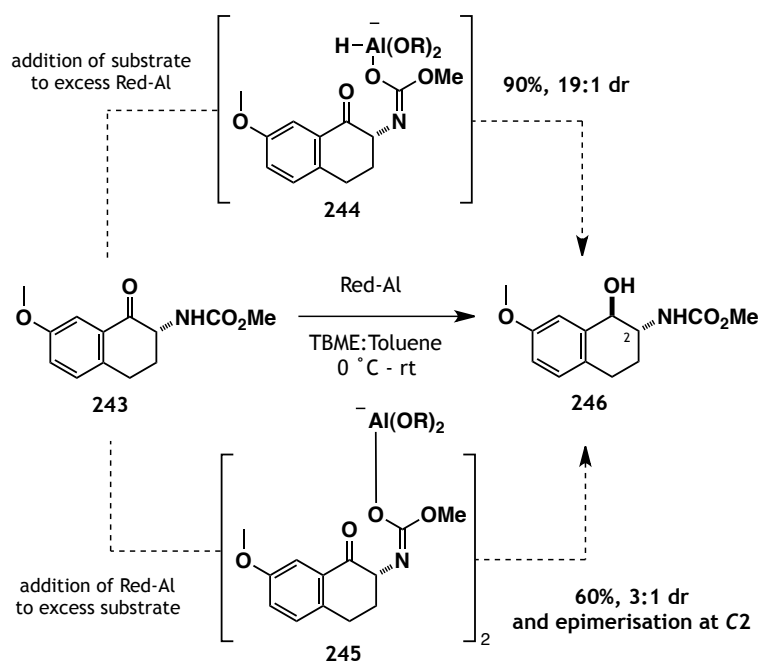
Figure 4.5

It was anticipated that if a tetrasubstituted hydroaluminate of the form $M^+[(RO)_2AlH_2]^-$ were used an *oxo*-aluminium intermediate could be formed *in situ* to produce a species which was still hydridic, and able to reduce the tethered quininium. However, when hydroxyl quininium **231** was reduced by drop-wise addition of Red-Al at $-78\text{ }^\circ\text{C}$ in DCM *trans*-**236** was afforded along with secondary alcohol **241** (Scheme 4.17).



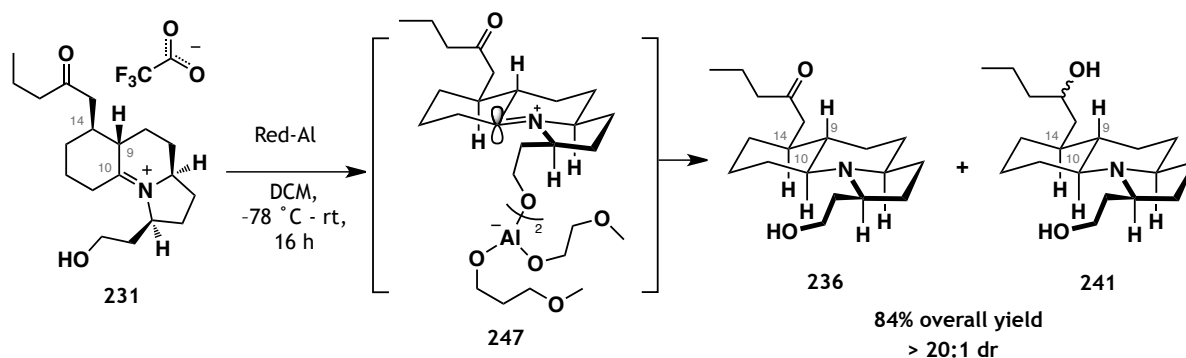
Scheme 4.17

Melillo *et al.* have demonstrated a highly diastereoselective amide-directed reduction of tetralone **243**, *via* formation of a chelated monohydric aluminate intermediate **244** (Scheme 4.18).⁸³ Interestingly, they reported that in the presence of excess substrate the rate of reaction was markedly reduced, and the substrate was epimerised at C2. This was rationalised by the formation of dimeric tetrakisalkoxyaluminate **245** and subsequent intermolecular reduction and racemisation. By slow addition of substrate to a solution of Red-Al at $-78\text{ }^\circ\text{C}$ Melillo *et al.* were able to overcome this and afford the chelation reduction product **246** in high yield and diastereoselectivity.



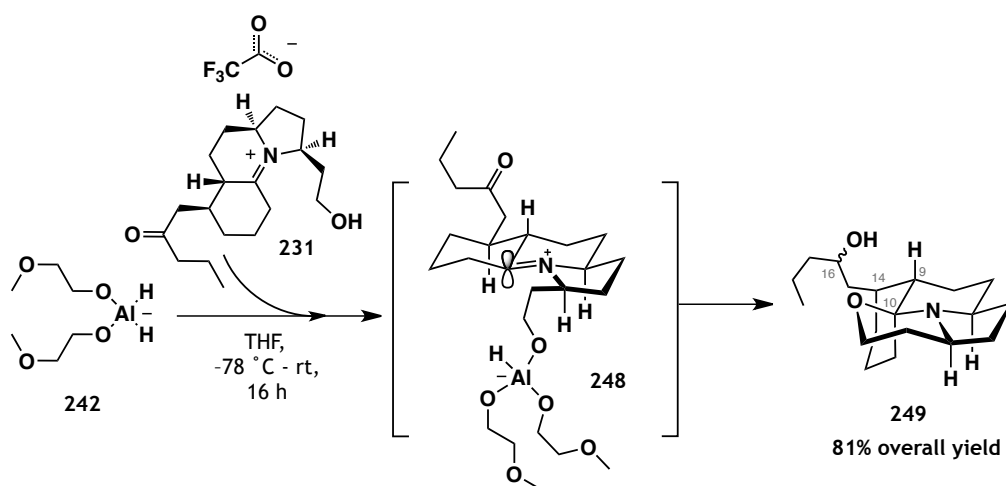
Scheme 4.18

Akin to this study, it was postulated that in the presence of excess substrate, Red-Al reacts with quininium **231** to form a dimeric tetrakisalkoxyaluminate **247**. This would then afford *trans*-**236** via a subsequent intermolecular reduction by Red-Al (Scheme 4.19).



Scheme 4.19

When a solution of quininium **231** was slowly added to a solution of Red-Al in THF at -78 °C tetracyclic aminal **249** was formed as a 1:1 mixture of C16 diastereomers (Scheme 4.20). Although this suggested that we could overcome the formation of dimeric aluminate **247** by using a reverse-addition protocol, the intramolecular *oxo*-aluminate addition is still the more favourable process.

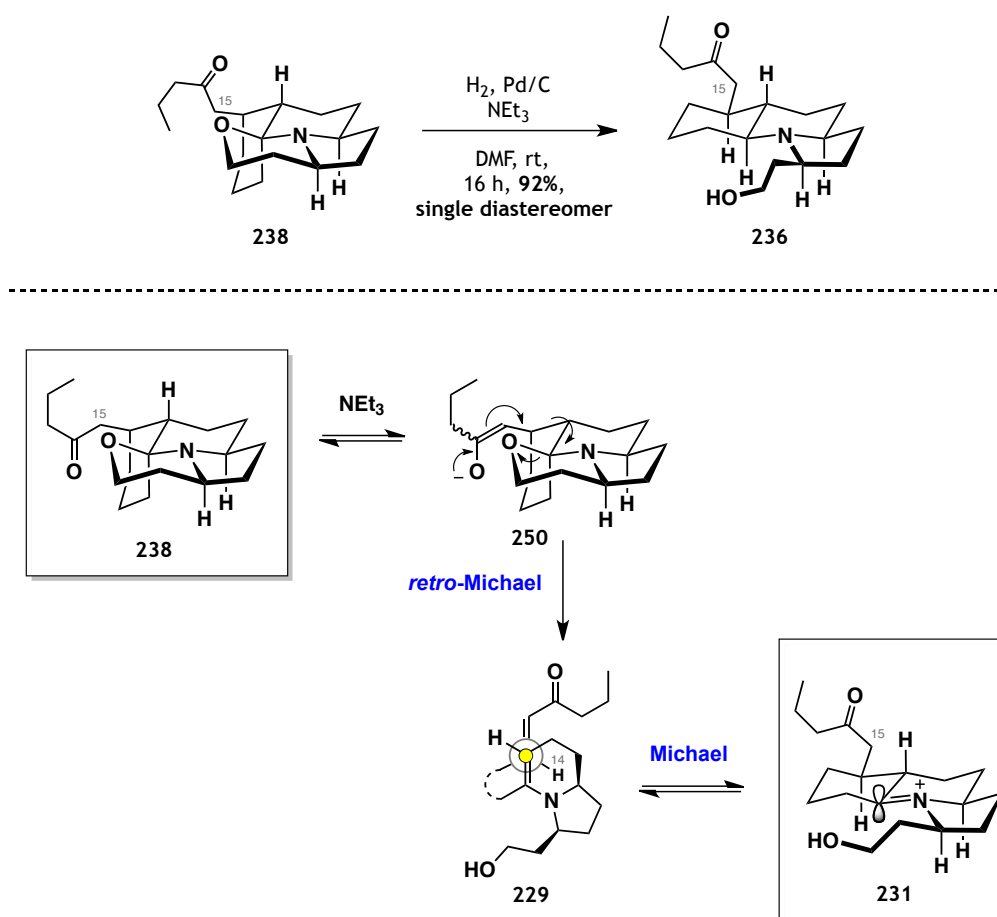


Scheme 4.20

This study indicated that the hydride reducing agent must be of sufficient Lewis acidity to initiate rapid formation of a substrate-reagent chelate. However, the resulting chelate must not be nucleophilic enough to favour intramolecular amination over intramolecular reduction. Although sufficiently Lewis acidic, the nucleophilicity of an *oxo*-aluminium intermediate unfortunately precluded the use of aluminium hydride reducing agents in this system.

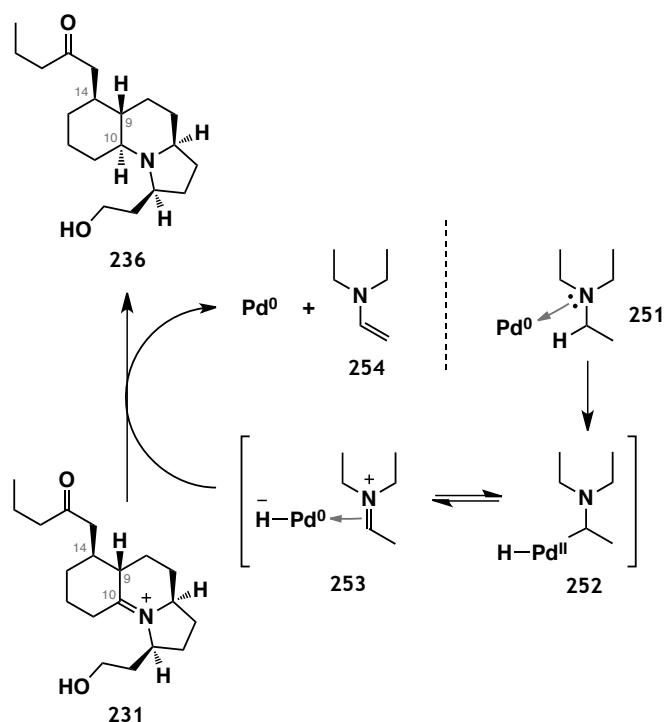
4.5.4 Amino Reactivity: current studies

Whilst examining its reactivity, it was found that the catalytic hydrogenation of amination **238** using triethylamine-buffered palladium-on-carbon under 1 atm. of hydrogen afforded *trans*-perhydroquinoline **236** in excellent yield and as a single diastereomer (Scheme 4.21).⁸⁴ In light of this result, it seems possible that triethylamine enters amination **238** into equilibrium with its open-chain iminium *via* reversible enolate formation at C15 and a *retro*-Michael-Michael process to afford hydroquininium **231**.



Scheme 4.21

It seemed unusual that hydrogenation of the transient hydroquininium **231** should occur so stereoselectively if the reduction was proceeding *via* a traditional Horiuti-Polyani-like mechanism. This is evidenced by our previous attempts at the stereoselective hydrogenation of the cascade intermediates using Pd/C, $\text{Pd}(\text{OH})_2$, PtO_2 and Rh/ Al_2O_3 (Scheme 4.3). In line with studies by Coquerel *et al.* it is possible that palladium(0) forms a trialkyliminiumpalladium hydride species **253** *via* oxidative addition to triethylamine (Scheme 4.22).^{85,86,87,88,89,90,91} This palladium hydride species is then able to reduce hydroquininium **231** in an intermolecular stereoelectronically-directed manner, akin to our previous studies, to afford *trans*-perhydroquinoline **236**.



Scheme 4.22

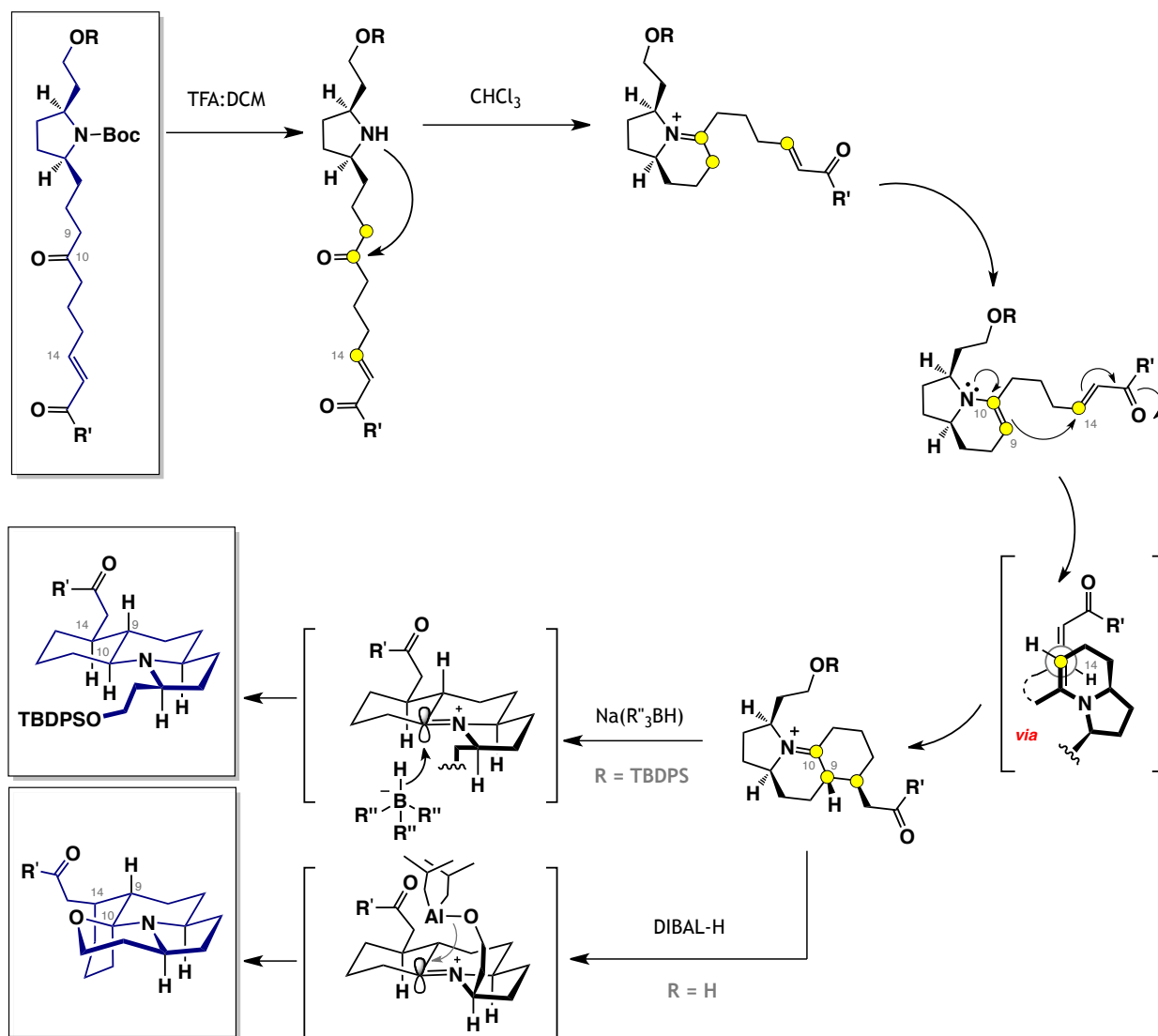
This palladium hydride intermediate has reported use in a number of transformations, including the C=C reduction of various α,β -unsaturated carbonyl/nitrile compounds, and in the redox isomerisation of secondary allylic alcohols.⁸⁵

Chapter 5 Summary

5.1 Overview

This study represents a method whereby we can engage homochiral polyfunctionalised molecules in an intramolecular enamine-Michael cascade to afford perhydropyrrolo-[1,2-*a*]-quinolines with high levels of stereocontrol. The process is highly complexity-generating, occurs under very mild reaction conditions, forms two rings and three contiguous stereocentres in a single-flask procedure, and assembles alkaloid-like molecular scaffolds. We have discovered that the enamine-Michael cascade sequence affords an unusual hydroquininium salt and undergoes a stereoelectronically-directed diastereoselective reduction with borohydride to afford *trans*-substituted hydroquinoline ring-systems. The cascade sequence is compatible with a tethered primary alcohol, and we have demonstrated that we can utilise this in the directed nucleophilic addition of a chelated *oxo*-aluminium intermediate to afford a tetracyclic aminal with equally high levels of diastereocontrol.

We can reduce the aminoral to its *trans*-hydroquinoline efficiently and stereoselectively using a transient triethyliminium palladium hydride *via* a *retro*-Michael-Michael-reduction process.



Scheme 5.1

5.2 Outlook

The successful completion of the asymmetric synthesis of the gephyrotoxins using the chemistry outlined in this thesis relies on two remaining strategies. The success of the tethered-reduction approach – whether it is by intermediate chelation and reduction during the cascade, or by a method to transform the tetracyclic aminoral – will come by heuristic selection of the correct conditions for this transformation. Studies outlined in Chapter Four have indicated that the reduction of hydroquininium **231** has a strong stereoelectronic preference in the presence of a tethered primary alcohol, and successfully overcoming this will rely on rapid chelation kinetics and a high degree of facial selectivity by the 8-membered chelate. The second strategy requires a greater

level of redesign. By truncating the carbon skeleton in the cascade precursor by one carbon at C1 would allow for a much more rigid 7-membered chelate, and fall in-line with studies reported by Cuifolini *et al.* This strategy will require a redesign of the asymmetric synthesis of the allyl pyrrolidine metathesis fragment, and a one-carbon homology at the end of the total synthesis (Figure 5.1).

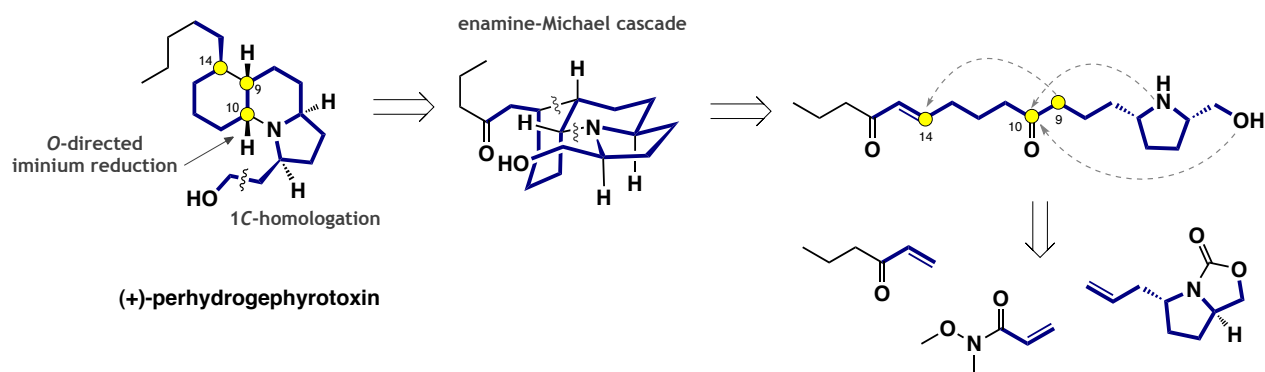


Figure 5.1

Chapter 6 Experimental

6.1 General Experimental Procedures

6.1.1 Solvents and Reagents

Non-aqueous reactions were carried out in oven-dried glassware and under an inert atmosphere of argon unless stated otherwise. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. DCM, diethyl ether, THF, methanol, acetonitrile and toluene were purified by filtration through activated alumina columns, employing the method of Grubbs *et al.*⁹² A pH7 buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 mL). All other reagents and solvents were used as supplied without prior purification. All water used experimentally was distilled. Brine refers to a saturated solution of sodium chloride in water. Rochelle's salt refers to a saturated solution of sodium potassium tartrate in water.

6.1.2 Chromatography

Thin layer chromatography (TLC) was performed on aluminium plates coated with Merck 60 F₂₅₄ silica and visualisation was achieved by using UV light or by staining with potassium permanganate. Flash column chromatography was carried out using Merck Kieselgel (230-400 mesh) or silica gel 60 (0.043-0.063 mm, VWR).

6.1.3 Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker DRX500 (^1H : 500 MHz, ^{13}C : 125 MHz), AVII500 (^1H : 500 MHz, ^{13}C : 125 MHz), AVII500 with 5mm $^{13}\text{C}(^1\text{H})$ dual cryoprobe (^1H : 500 MHz, ^{13}C : 125 MHz), AV400 (^1H : 400 MHz, ^{13}C : 101 MHz). Chemical shifts are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants, J , are measured to the nearest 0.1 Hz and are presented as observed. Chemical shifts are quoted in ppm with signal splittings recorded as follows: chemical shift δ /ppm (number of protons, multiplicity, coupling constant J /Hz, assignment) [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sextet, sextet; septet, septet; m, multiplet].

6.1.4 Infrared Spectroscopy

Infrared spectra were recorded neat either on a Bruker Tensor 27 FTIR fitted with an attenuated total reflectance attachment with internal referencing, or as a thin film on NaCl plates on a Bruker Tensor 27 FTIR with internal calibration. Only structurally important absorptions are quoted. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

6.1.5 Mass Spectrometry

Low-resolution mass spectra were recorded on a Micro Mass LCT Premier spectrometer under conditions of electrospray ionisation (ESI). Accurate mass measurements were performed on a Bruker microTOF spectrometer under conditions of electrospray ionisation (ESI) or field ionisation (FI). Values are reported as a ratio of mass to charge in Daltons.

6.1.6 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter (using the sodium D line, 589 nm) with a path length of 1 dm and are quoted in $\text{deg dm}^{-1} \text{cm}^{-1} \text{g}^{-1}$.

6.1.7 Melting Point

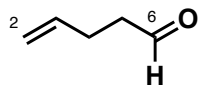
Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

6.1.8 Indicators

The indicator used in the titration of *n*-butyllithium was either 1,10-phenanthroline or diphenylacetic acid.

6.2 Experimental

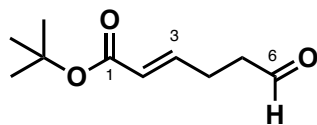
4-pentenal (**90**)



Allyl vinyl ether (5 mL, 46.4 mmol) was heated to 150 °C in a sealed-tube (Ace) for 16 h. After this time the reaction mixture was cooled to room temperature and the product distilled under vacuum to yield 4-pentenal **90** as a pungent colourless liquid (3.22 g, 83%) (bp 105 °C , 760 mmHg). δ_{H} (400 MHz, CDCl_3) 9.77 (1H, t, J 1.6, *H*₆), 5.82 (1H, ddt, J 17.0, 10.4, 6.5, *H*₃), 5.08-4.99 (2H, m, *H*₂), 2.55-2.51 (2H, m, *H*₅), 2.41-2.35 (2H, m, *H*₄); δ_{C} (101 MHz, CDCl_3) 201.8 (*C*₆), 136.4 (*C*₃), 115.6 (*C*₂), 42.7 (*C*₅), 26.1 (*C*₄); ν_{max} (film)/ cm^{-1} 1723 (*C*=O), 1642 (*C*=C). This data is in accordance with the literature.^{93*}

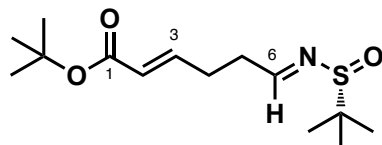
* **90** was very volatile such that accurate MS analysis was not possible under conditions of ESI or FI.

(E)-tert-butyl 6-oxohex-2-enoate (91)



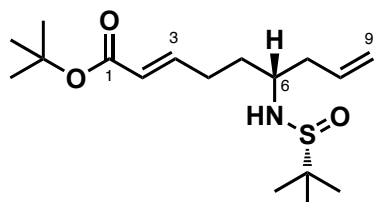
Hoveyda-Grubbs second-generation catalyst (3.2 mg, 5.1 mmol) was added to a solution of 4-pentenal **90** (25 μ L, 0.25 mmol) and *tert*-butyl acrylate (0.37 mL, 2.53 mmol) in DCM (0.5 mL) in a microwave vial. The reaction mixture was stirred at 70 °C under microwave irradiation for 2 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (10% EtOAc in petrol) to yield aldehyde acrylate **91** as a colourless oil (45.5 mg, 98%). δ_{H} (400 MHz, CDCl_3) 9.79 (1H, t, J 1.1, *H*6), 6.82 (1H, dt, J 15.6, 6.6, *H*3), 5.77 (1H, app dt, J 15.6, 1.6, *H*2), 2.64-2.60 (2H, m, *H*5), 2.53-2.47 (2H, m, *H*4), 1.47 (9H, s, *t*Bu); δ_{C} (101 MHz, CDCl_3) 200.6 (*C*6), 165.6 (*C*1), 145.0 (*C*3), 124.1 (*C*2), 80.4 (*t*Bu (4° carbon)), 41.9 (*C*5), 28.1 (*t*Bu), 24.2 (*C*4); ν_{max} (film)/ cm^{-1} 1716 (C=O aldehyde, C=O ester); low resolution ESI-MS $[\text{M}+\text{Na}+\text{MeOH}]^+$ 239.14 (aldehyde hemiacetal).

(2E,6E)-tert-butyl 6-(((R)-tert-butylsulfinyl)imino)hex-2-enoate (92)



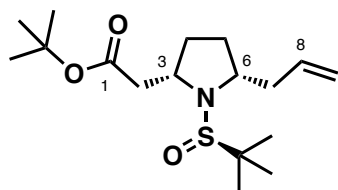
(R)-2-methylpropane sulfinamide (38 mg, 0.31 mmol) was added to aldehyde **91** (63 mg, 0.34 mmol) and anhydrous copper sulfate (0.2 g, 1.25 mmol) in DCM (5 mL). The reaction mixture was stirred at room temperature for 24 h, then filtered through a short pad of Celite® and the cake washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel chromatography (10-30% EtOAc in petrol) to yield sulfinyl aldimine **92** as a pale yellow oil (70 mg, 78%). δ_{H} (400 MHz, CDCl_3) 8.08 (1H, t, J 4.0, H6), 6.85 (1H, dt, J 15.6, 6.7, H3), 5.79 (1H, dt, J 15.6, 1.6, H2), 2.72-2.67 (2H, m, H5), 2.57-2.51 (2H, m, H4), 1.47 (9H, s, ^tBu (sulfinamide)), 1.19 (9H, s, ^tBu (ester)); δ_{C} (101 MHz, CDCl_3) 167.7 (C6), 165.6 (C1), 145.3 (C3), 124.3 (C2), 80.3 (^tBu (4° carbon, ester)), 56.7 (^tBu (4° carbon, sulfinamide)), 34.4 (C5), 28.1 (^tBu (ester)), 27.3 (C4), 22.3 (^tBu (sulfinamide)); ν_{max} (film)/ cm^{-1} 1713 (C=O), 1655 (C=C), 1624 (C=N); ESI-MS calcd. for $\text{C}_{14}\text{H}_{25}\text{NNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 310.1447, found 310.1447; $[\alpha]_{\text{D}}^{23}$ -188.9 (*c* 0.5, CH_2Cl_2).

(*R,E*)-tert-butyl 6-((*R*)-1,1-dimethylethylsulfinamido)nona-2,8-dienoate (94**)**



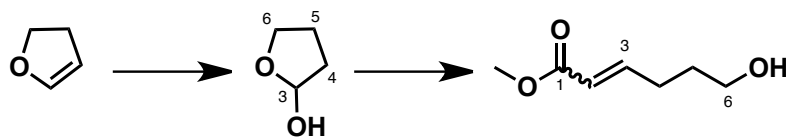
Allyl bromide (0.34 mL, 3.97 mmol) was added dropwise to a solution of sulfinyl aldimine **92** (228 mg, 0.79 mmol) and indium powder (456 mg, 3.97 mmol) in aqueous sodium bromide (sat., 15 mL). The reaction mixture was stirred for 24 h at room temperature, diluted with H₂O (100 mL) and extracted with CHCl₃:IPA (3:1, 3 x 200 mL). The combined organics were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by silica gel chromatography (20-40% EtOAc in petrol) to yield *homo*-allyl sulfinamide **94** as a colourless oil (247 mg, 95%). δ_{H} (400 MHz, CDCl₃) 6.83 (1H, dt, *J* 15.6, 6.9, *H*3), 5.82-5.72 (2H, m, *H*8, *H*2), 5.18-5.14 (2H, m, *H*9), 3.33 (1H, dquin, *J* 12.4, 6.1, *H*6), 3.22 (1H, d, *J* 6.5, NH), 2.45-2.16 (4H, m, *H*7, *H*4), 1.75-1.55 (2H, m, *H*5), 1.47 (9H, s, *t*Bu (sulfinamide)), 1.20 (9H, s, *t*Bu (ester)); δ_{C} (101 MHz, CDCl₃) 165.9 (C1), 146.8 (C3), 133.6 (C2), 123.5 (C8), 119.3 (C9), 80.2 (*t*Bu (ester, 4° carbon)), 55.9 (*t*Bu (sulfinamide, 4° carbon)), 54.5 (C6), 40.4 (C7), 33.4 (C5), 28.13 (*t*Bu (ester)), 28.09 (C4), 22.7 (*t*Bu (sulfinamide)); ν_{max} (film)/cm⁻¹ 3225 (N-H), 1714 (C=O), 1054 (S=O); ESI-MS calcd. for C₁₇H₃₁NNaO₃S [M+Na]⁺ 352.1917, found 352.1919; [α]_D²⁶ -39.0 (*c* 1.0, CH₂Cl₂).

***tert*-butyl 2-((2*S*,5*R*)-5-allyl-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)acetate (**100**)**



Potassium *tert*-butoxide (87 mg, 0.78 mmol) was added to a solution of *homo*-allyl sulfinamide **94** (232 mg, 0.71 mmol) in DMF:THF (1 ml : 0.5 mL) at -78°C . The reaction mixture was stirred at -78°C for 3 h and then ammonium chloride (sat., aq., 200 mL). The mixture was warmed to room temperature and stirred vigorously until the bi-phasic mixture became homogeneous. The organics were separated and the aqueous phase further extracted with CHCl_3 :IPA (3:1, 3 x 50 mL). The combined organics were washed with a saturated aqueous solution of magnesium sulfate, dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (20-40% EtOAc in petrol) to yield sulfinyl pyrrolidine **100** as a colourless oil (222 mg, 96% (98% brsm)). δ_{H} (500 MHz, CDCl_3) 5.74 (1H, dddd, J 16.7, 10.6, 7.9, 6.0, H_8), 5.13-5.07 (2H, m, H_9), 4.11-4.04 (1H, m, H_6), 4.02-3.97 (1H, m, H_3), 2.64 (1H, dd, J 15.1, 5.7, H_{7A}), 2.38-2.31 (2H, m, H_{2A} , H_{7B}), 2.24-2.13 (2H, m, H_{2B} , H_{5A}), 1.77-1.74 (1H, m, H_{4A}), 1.83-1.64 (2H, m, H_{4B} , H_{5B}), 1.49 (tBu (ester)), 1.26 (tBu (sulfinamide)); δ_{C} (126 MHz, CDCl_3) 170.3 (C1), 135.2 (C8), 117.2 (C9), 80.8 (tBu (ester, 4° carbon)), 64.0 (C6), 56.9 (tBu (sulfinamide, 4° carbon)), 53.2 (C3), 44.6 (C7), 40.2 (C2), 31.0 (C4), 29.6 (C5), 28.1 (tBu (ester)), 23.6 (tBu (sulfinamide)); ν_{max} (film)/ cm^{-1} 1730 (C=O), 1075 (S=O); ESI-MS calcd. for $\text{C}_{17}\text{H}_{31}\text{NNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 352.1917, found 352.1912; $[\alpha]_{\text{D}}^{23}$ -18.5 (c 0.4, CHCl_3).

(E)-methyl 6-hydroxyhex-2-enoate (121)



2,3-Dihydrofuran (8 mL, 0.11 mol) was added dropwise over 20 min to a stirring solution of $\text{HCl}_{(\text{aq})}$ (2 M, 20 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h, then basified with saturated aqueous sodium bicarbonate solution until CO_2 had stopped being released and the solution was at pH 7. The aqueous solution was extracted with chloroform (6 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to yield tetrahydrofuran-2-ol (**120**) as a pale yellow oil of *ca.* 90% purity by NMR spectroscopy, which was used without further purification. δ_{H} (400 MHz, CDCl_3) 5.55 (1H, ddd, J 4.5, 2.9, 1.5, H_3), 4.06 (1H, td, J 8.2, 5.3, $H_{6\text{A}}$), 3.89-3.83 (1H, m, $H_{6\text{B}}$), 2.90-2.82 (1H, br d, J 12.3, OH), 2.12-2.02 (1H, m, $H_{5\text{A}}$), 2.00-1.82 (3H, m, H_4 , $H_{5\text{B}}$); δ_{C} (101 MHz, CDCl_3) 98.4 (C3), 67.4 (C6), 33.2 (C4), 23.4 (C5); ν_{max} (film)/ cm^{-1} 3389 (br, O-H), 1717 (C=O); FI-MS calcd. for $\text{C}_4\text{H}_8\text{O}_2$ $[\text{M}]^+$ 88.0524, found 88.0523. This data is in accordance with the literature.⁹⁴

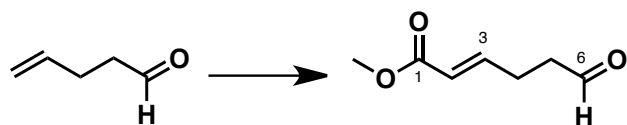
Methyl (triphenylphosphoranylidene) acetate (9.11 g, 27.2 mmol) was added to a solution of the crude tetrahydrofuran-2-ol (1.0 g, 11.4 mmol) in DCM (15 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for 48 h. After this time the reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (10-35% EtOAc in petrol) to yield acrylates **121** as a 31:1 mixture of partially separable geometrical isomers (1.26 g, 77%).

trans-**121**: δ_{H} (400 MHz, CDCl_3) 6.99 (1H, dt, J 15.7, 7.0, H_3), 5.86 (1H, app dt, J 15.7, 1.6, H_2), 3.73 (3H, s, OCH_3), 3.67 (2H, t, J 6.4, H_6), 2.31 (2H, app qd, J 7.5, 1.5, H_4), 1.73 (2H, dt, J 14.4, 7.0, H_5), 1.62 (1H, br s, OH); δ_{C} (101 MHz, CDCl_3) 167.1 (C1), 148.8 (C3), 121.3 (C2), 61.9 (C6), 51.4 (OCH_3), 30.9 (C5), 28.5 (C4); ν_{max} (film)/ cm^{-1} 3395 (broad, O-H), 1720 (C=O); FI-MS calcd. for $\text{C}_7\text{H}_{12}\text{O}_3$ $[\text{M}]^+$ 144.0786, found 144.0783. This data is in accordance with the literature.⁹⁴

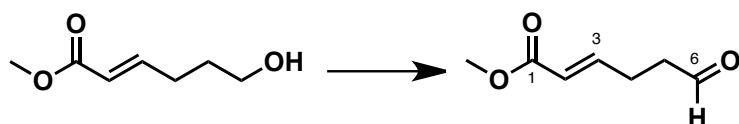
cis-**121**: δ_{H} (400 MHz, CDCl_3) 6.24 (1H, dt, J 11.5, 8.2, H_3), 5.86 (1H, dt, J 11.5, 1.4, H_2), 3.71 (3H, s, CH_3), 3.61 (2H, t, J 6.0, H_6), 2.73 (2H, dtd, J 8.2, 7.1, 1.2, H_4), 2.66 (1H, br s, OH), 1.72 (2H, app dt, J 13.5, 6.5, H_5); δ_{C} (101 MHz, CDCl_3) 167.4 (C1), 149.6 (C3), 120.3 (C2), 61.0 (C6), 51.3 (OCH_3), 31.0 (C5),

25.0 (C4); $\nu_{\max}$ (film)/ cm^{-1} 3379 (br, O-H), 1720 (C=O); 1645 (C=C); low resolution ESI-MS $[\text{M}+\text{Na}]^+$ 167.07. This data is in accordance with the literature.⁹⁴

(E)-methyl 6-oxohex-2-enoate (102)



Method A: Hoveyda-Grubbs second-generation catalyst (3.2 mg, 5.1 mmol) was added to a solution of 4-pentenal **90** (25 μ L, 0.25 mmol) and methyl acrylate (0.23 mL, 2.55 mmol) in DCM (0.5 mL) in a microwave vial. The reaction mixture was stirred at 70 °C under microwave irradiation for 2 h (exclusive of ramping time). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (5-10% EtOAc in petrol) to yield aldehyde acrylate **102** as a colourless oil (32.5 mg, 90%).

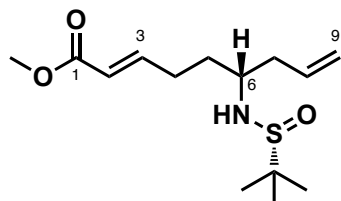


Method B: A solution of *trans*-**121** (3.49 g, 24.2 mmol) in DCM (50 mL) was transferred *via* cannula over 10 min to a solution of pyridinium chlorochromate (10.4 g, 48.5 mmol) and pre-activated 4Å molecular sieves (17 g) in DCM (150 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h after which the reaction mixture was filtered through a short pad of Fluorisil®. The cake was washed with Et₂O (200 mL), DCM (200 mL), EtOAc (400 mL) and the combined organics were concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography (5-10% EtOAc in petrol) to yield aldehyde acrylate **102** as a pale yellow oil (2.61 g, 76%). δ_{H} (400 MHz, CDCl₃) 9.73 (1H, t, J 1.0, H₆), 6.88 (1H, dt, J 15.7, 6.7, H₃), 5.80 (1H, dt, J 15.7, 1.6, H₂), 3.66 (3H, s, OCH₃), 2.61-2.57 (2H, m, H₅), 2.50-2.44 (2H, m, H₄); δ_{C} (101 MHz, CDCl₃) 200.3 (C₆), 166.6 (C₁), 146.7 (C₃), 121.9 (C₂), 51.4 (OCH₃), 41.7 (C₅), 24.3 (C₄); ν_{max} (film)/cm⁻¹ 1716 (C=O aldehyde), 1658 (C=O ester); low resolution ESI-MS [M+Na]⁺ 165.06. This data is in accordance with the literature.⁹⁴

COC(=O)/C=C/CC/C=N/S(=O)(C)C(C)C

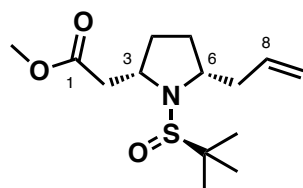
77

(*R,E*)-methyl 6-((*R*)-1,1-dimethylethylsulfinamido)nona-2,8-dienoate (106**)**



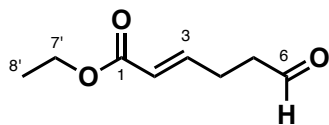
Allyl bromide (5.83 mL, 66.5 mmol) was added dropwise to a solution of sulfinyl aldimine **104** (3.26 g, 13.3 mmol) and indium powder (7.64 g, 66.5 mmol) in aqueous sodium bromide (saturated, 200 mL). The reaction mixture was stirred for 24 h at room temperature, diluted with H₂O (100 mL) and extracted with CHCl₃:IPA (3:1, 3 x 200 mL). The combined organics were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by silica gel chromatography (30-50% EtOAc in petrol) to yield *homo*-allyl sulfinamide **106** as a colourless oil (3.46 g, 91%). δ_{H} (400 MHz, CDCl₃) 6.91 (1H, dt, *J* 15.6, 7.0, *H*3), 5.87-5.68 (2H, m, *H*2, *H*8), 5.15-5.04 (2H, m, *H*9), 3.69 (3H, s, OCH₃), 3.30 (1H, dquin, *J* 12.4, 6.2, *H*6), 3.22 (1H, d, *J* 6.6, NH), 2.42-2.17 (4H, m, *H*7, *H*4), 1.73-1.54 (2H, m, *H*5), 1.18 (9H, s, *t*Bu); δ_{C} (101 MHz, CDCl₃) 166.8 (C1), 148.4 (C3), 133.6 (C8), 121.4 (C2), 119.3 (C9), 55.9 (*t*Bu (4° carbon), 54.4 (C6), 51.4 (OCH₃), 40.4 (C7), 33.3 (C5), 28.2 (C4), 22.6 (*t*Bu); ν_{max} (film)/cm⁻¹ 3222 (N-H), 723 (C=O), 1049 (S=O); ESI-MS calcd. for C₁₄H₂₅NNaO₃S [M+Na]⁺ 310.1447, found 310.1450; $[\alpha]_{\text{D}}^{26}$ -41.4 (*c* 0.05, CH₂Cl₂).

methyl 2-((2*S*,5*R*)-5-allyl-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)acetate (109**)**



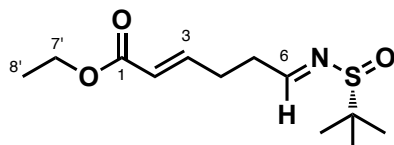
Potassium *tert*-butoxide (1.46 g, 13.0 mmol) was added to a solution of *homo*-allyl sulfinamide **106** (3.39 g, 11.8 mmol) in DMF:THF (100 ml : 50 mL) at -78°C . The reaction mixture was stirred at -78°C for 3 h and then aqueous ammonium chloride (sat., 200 mL) was slowly added. The mixture was warmed to room temperature and stirred vigorously until the biphasic mixture became homogeneous. The organics were separated and the aqueous phase further extracted with CHCl_3 :IPA (3:1, 3 x 50 mL). The combined organics were washed with an aqueous solution of magnesium sulfate (sat. 100 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (20-40% EtOAc in petrol) to yield sulfinyl pyrrolidine **109** as a colourless oil (2.72 g, 80% (91% brsm)). δ_{H} (400 MHz, CDCl_3) 5.73-5.63 (1H, m, H_8), 5.07-5.02 (2H, m, H_9), 4.10-4.03 (1H, m, H_3), 3.94 (1H, ddt, J 11.5, 6.1, 2.9, H_6), 3.65 (3H, s, OCH_3), 2.62 (1H, dd, J 15.2, 6.2, H_{2A}), 2.42 (1H, dd, J 15.2, 7.9, H_{2B}), 2.32-2.26 (1H, m, H_{7A}), 2.19-2.05 (2H, m, H_{7B} , H_{4A}), 1.78-1.58 (3H, m, H_5 , H_{4B}), 1.19 (9H, s, ^tBu); δ_{C} (101 MHz, CDCl_3) 171.4 (C_1), 135.0 (C_8), 117.1 (C_9), 63.9 (C_3), 56.9 (^tBu (4° carbon)), 53.3 (C_6), 51.5 (OCH_3), 42.8 (C_2), 40.3 (C_7), 30.9 (C_5), 29.7 (C_4), 23.4 (^tBu); ν_{max} (film)/ cm^{-1} 1739 ($\text{C}=\text{O}$), 1070 ($\text{S}=\text{O}$); ESI-MS calcd. for $\text{C}_{14}\text{H}_{25}\text{NNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 310.1447, found 310.1444; $[\alpha]_{\text{D}}^{26} -7.6$ (c 0.01, CH_2Cl_2).

(E)-ethyl 6-oxohex-2-enoate (103)



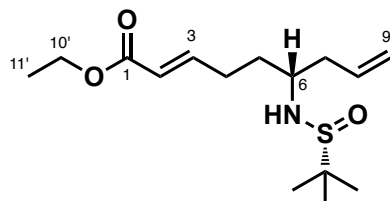
Hoveyda-Grubbs second-generation catalyst (3.2 mg, 5.1 mmol) was added to a solution of 4-pentenal **90** (25 μ L, 0.25 mmol) and ethyl acrylate (0.28 mL, 2.53 mmol) in DCM (0.5 mL) in a microwave vial. The reaction mixture was stirred at 70 °C under microwave irradiation for 2 h (exclusive of ramping time). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (5-10% EtOAc in petrol) to yield aldehyde acrylate **103** as a colourless oil (38.9 mg, 98%). δ_{H} (400 MHz, CDCl_3) 9.80 (1H, t, J 1.0, H_6), 6.94 (1H, dt, J 15.7, 6.6, H_3), 5.85 (1H, app dt, J 15.7, 1.6, H_2), 4.19 (2H, q, J 7.1, $H_{7'}$), 2.66-2.63 (2H, m, H_5), 2.56-2.51 (2H, m, H_4), 1.29 (3H, t, J 7.1, $H_{8'}$); δ_{C} (101 MHz, CDCl_3) 200.3 (C_6), 166.2 (C_1), 146.3 (C_3), 122.5 (C_2), 60.3 ($C_{7'}$), 41.8 (C_5), 24.4 (C_4), 14.2 ($C_{8'}$); ν_{max} (film)/ cm^{-1} 1718 ($\text{C}=\text{O}$ aldehyde, $\text{C}=\text{O}$ ester), 1655 ($\text{C}=\text{C}$); low resolution ESI-MS $[\text{M}+\text{MeOH}+\text{Na}]^+$ 211.10 (aldehyde hemiacetal). This data is in accordance with the literature.⁹⁴

(3*E*,6*E*)-ethyl 6-(((*R*)-*tert*-butylsulfinyl)imino)hex-1-enoate (105**)**



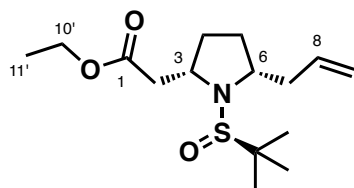
(*R*)-2-methylpropane sulfinamide (212 mg, 1.75 mmol) was added to aldehyde **103** (300 mg, 1.92 mmol) and anhydrous copper sulfate (1.12 g, 7.0 mmol) in DCM (10 mL). The reaction mixture was stirred at room temperature for 24 h, then filtered through a short pad of Celite® and the cake washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel chromatography (10-40% EtOAc in petrol) to yield sulfinyl aldimine **105** as a pale yellow oil (365 mg, 81%). δ_{H} (400 MHz, CDCl₃) 8.04 (1H, t, J 3.9, *H*₆), 6.92 (1H, dt, J 15.7, 6.7, *H*₃), 5.83 (1H, dt, J 15.7, 1.6, *H*₂), 4.13 (2H, q, J 7.1, *H*_{7'}), 2.69-2.64 (2H, m, *H*₅), 2.56-2.50 (2H, m, *H*₄), 1.23 (3H, t, J 7.1, *H*_{8'}), 1.14 (9H, s, *t*Bu); δ_{C} (101 MHz, CDCl₃) 167.5 (*C*₆), 166.2 (*C*₁), 146.6 (*C*₃), 122.5 (*C*₂), 60.2 (*C*_{7'}), 56.6 (*t*Bu (4° carbon)), 34.2 (*C*₅), 27.4 (*C*₄), 22.3 (*t*Bu), 14.2 (*C*_{8'}); ν_{max} (film)/cm⁻¹ 1719 (C=O), 1655 (C=C), 1624 (C=N), 1085 (S=O); ESI-MS calcd. for C₁₂H₂₁NNaO₃S [M+Na]⁺ 282.1134, found 282.1124; $[\alpha]_{\text{D}}^{26}$ -183.4 (c 0.5, CH₂Cl₂).

(*R,E*)-ethyl 6-((*R*)-1,1-dimethylethylsulfinamido)nona-2,8-dienoate (107**)**



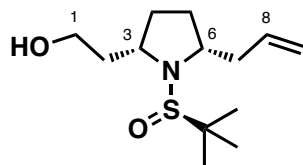
Allyl bromide (0.39 mL, 4.49 mmol) was added dropwise to a solution of sulfinyl aldimine **105** (258 mg, 0.9 mmol) and indium powder (516 mg, 4.49 mmol) in aqueous sodium bromide (sat., 15 mL). The reaction mixture was stirred for 24 h at room temperature, then diluted with H₂O (100 mL) and extracted with CHCl₃:IPA (3:1, 3 x 200 mL). The combined organics were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by silica gel chromatography (20-50% EtOAc in petrol) to yield *homo*-allyl sulfinamide **107** as a colourless oil (262 mg, 87%). δ_{H} (400 MHz, CDCl₃) 6.94 (1H, dt, J 15.6, 6.9, *H*3), 5.82 (1H, app dt, J 15.6, 1.6, *H*2), 5.28-5.72 (1H, m, *H*8), 5.19-5.14 (2H, m, *H*9), 4.19 (2H, q, J 7.1, *H*10'), 3.35 (1H, sextet, J 6.4, *H*6), 3.23 (1H, d, J 6.5, NH), 2.46-2.20 (4H, m, *H*7, *H*4), 1.75-1.58 (2H, m, *H*5), 1.29 (3H, t, J 7.1, *H*11'), 1.21 (9H, s, *t*Bu); δ_{C} (101 MHz, CDCl₃) 166.5 (*C*1), 148.1 (*C*3), 133.6 (*C*8), 121.8 (*C*2), 119.4 (*C*9), 60.2 (*C*10'), 55.9 (*t*Bu (4° carbon)), 54.4 (*C*6), 40.4 (*C*7), 33.3 (*C*5), 28.2 (*C*4), 22.7 (*t*Bu), 14.3 (*C*11'); ν_{max} (film)/cm⁻¹; ESI-MS calcd. for C₁₅H₂₇NNaO₃S [M+Na]⁺ 324.1604, found 324.1597; $[\alpha]_{\text{D}}^{26}$ -38.2 (c 0.8, CH₂Cl₂).

ethyl 2-((2*S*,5*R*)-5-allyl-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)acetate (110**)**



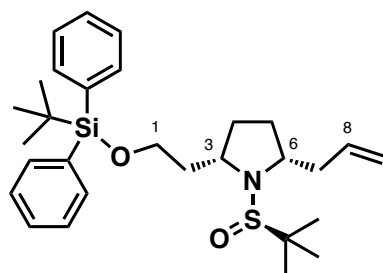
Potassium *tert*-butoxide (101 mg, 0.9 mmol) was added to a solution of *homo*-allyl sulfonamide **107** (247 mg, 0.82 mmol) in DMF:THF (1 ml : 0.5 mL) at -78°C . The reaction mixture was stirred at -78°C for 3 h and then ammonium chloride (sat., aq., 200 mL) was slowly added. The mixture was warmed to room temperature and stirred vigorously until the bi-phasic mixture became homogeneous. The organics were separated and the aqueous phase further extracted with CHCl_3 :IPA (3:1, 3 x 50 mL). The combined organics were washed with a saturated aqueous solution of magnesium sulfate, dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (20-60% EtOAc in petrol) to yield sulfinyl pyrrolidine **110** as a colourless oil (205 mg, 83% (86% brsm)). δ_{H} (400 MHz, CDCl_3) 5.74-5.63 (1H, m, H_8), 5.07-5.02 (2H, m, H_9), 4.11 (2H, q, J 7.1, $H_{10'}$), 4.09-4.03 (1H, m, H_3), 3.95 (1H, ddt, J 11.3, 6.0, 2.8, H_6), 2.62 (1H, dd, J 15.1, 6.0, H_{2A}), 2.40 (1H, dd, J 15.2, 8.0, H_{2B}), 2.32-2.26 (1H, m, H_{7A}), 2.19-2.06 (2H, m, H_{4A} , H_{7B}), 1.78-1.58 (3H, m, H_{4B} , H_5), 1.25 (3H, t, J 7.1, $H_{11'}$), 1.20 (9H, s, $t\text{Bu}$); δ_{C} (101 MHz, CDCl_3) 170.9 (C_1), 135.0 (C_8), 117.1 (C_9), 63.9 (C_3), 60.4 ($C_{10'}$), 56.9 ($t\text{Bu}$ (4° carbon)), 53.2 (C_6), 43.1 (C_2), 40.2 (C_7), 30.9 (C_5), 29.7 (C_4), 23.5 ($t\text{Bu}$), 14.2 ($C_{11'}$); ν_{max} (film)/ cm^{-1} 1735 ($\text{C}=\text{O}$), 1074 ($\text{S}=\text{O}$); ESI-MS calcd. for $\text{C}_{15}\text{H}_{27}\text{NNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 324.1604, found 324.1594; $[\alpha]_{\text{D}}^{26}$ -8.2 (c 0.9, CH_2Cl_2).

2-((2S,5R)-5-allyl-1-((R)-tert-butylsulfinyl)pyrrolidin-2-yl)ethanol (101**)**



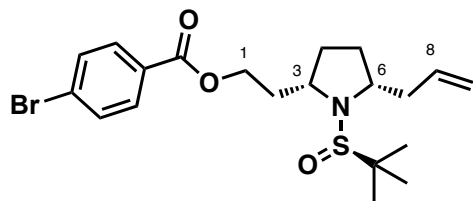
Lithium borohydride (2.0 M solution in THF, 12.6 mL, 25.2 mmol) was added to a solution of sulfinyl pyrrolidine **109** (1.81 g, 6.31 mmol) in THF (50 mL) at 0 °C. MeOH (7 mL) was added dropwise to this solution over a period of 5 min and the resulting mixture warmed to room temperature and stirred for 2 h. After this period water (50 mL) was slowly added and the mixture was extracted with Et₂O (3 x 50 mL). The combined organics were washed with brine (50 mL) and dried over sodium sulfate. The crude mixture was purified by silica gel chromatography (2-5% MeOH in Et₂O) to yield alcohol **101** as a colourless oil (1.62 g, 99%). δ_{H} (400 MHz, CDCl₃) 5.74-5.64 (1H, m, *H*₈), 5.07-5.02 (2H, m, *H*₉), 3.92 (1H, ddt, *J* 11.2, 6.2, 2.9, *H*₆), 3.80 (1H, quin, *J* 7.1, *H*₃), 3.75-3.63 (2H, m, *H*₁), 2.47 (1H, br s, OH), 2.33-2.29 (1H, m, *H*_{7A}), 2.15-2.03 (2H, m, *H*_{7B}, *H*_{4A}), 1.88 (1H, dq, *J* 13.4, 6.6, *H*_{2A}), 1.75-1.62 (3H, m, *H*_{2B}, *H*₅), 1.58 (1H, dddd, *J* 12.0, 11.1, 7.6, 8.5, *H*_{4B}), 1.23 (9H, s, *t*Bu); δ_{C} (101 MHz, CDCl₃) 135.1 (*C*₈), 117.1 (*C*₉), 64.1 (*C*₃), 59.9 (*C*₁), 57.3 (*t*Bu (4° carbon)), 53.6 (*C*₆), 40.9 (*C*₂), 40.5 (*C*₇), 30.9 (*C*₅), 29.7 (*C*₄), 23.7 (*t*Bu); ν_{max} (film)/cm⁻¹ 3399 (O-H), 1041 (S=O); ESI-MS calcd. for C₁₃H₂₅NNaO₂S [M+Na]⁺ 282.1498, found 282.1499; [α]_D²⁶ -9.8 (*c* 0.9, CH₂Cl₂).

(2R,5S)-2-allyl-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-((*R*)-*tert*-butylsulfinyl)pyrrolidine (114**)**



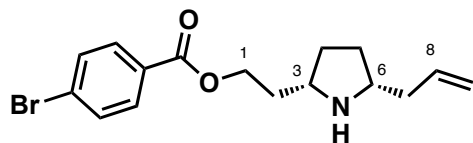
tert-Butyl(chloro)diphenylsilane (2.41 mL, 9.27 mmol) was added dropwise to a stirring solution of alcohol **101** (1.2 g, 4.63 mmol) and imidazole (0.69 g, 10.2 mmol) in DMF (7 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was diluted with Et₂O (50 mL) and sodium bicarbonate solution (sat., aq., 50 mL) was added. The organics were separated and the aqueous phase extracted with Et₂O (2 x 50 mL). The combined organics were washed with magnesium sulfate (sat., aq., 50 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-50% Et₂O in petrol) to yield silyl ether **114** as a colourless oil (2.27 g, 99%). δ_{H} (400 MHz, CDCl₃) 7.68 (4H, ddd, *J* 7.8, 3.8, 1.7, Ar*H*), 7.46-7.37 (6H, m, Ar*H*), 5.74-5.64 (1H, m, *H*₈), 5.06-5.02 (2H, m, *H*₉), 3.94 (1H, ddt, *J* 11.3, 6.2, 2.9, *H*₆), 3.86-3.78 (1H, m, *H*₃), 3.76-3.67 (2H, m, *H*₁), 2.28-2.24 (1H, m, *H*_{7A}), 2.09-1.99 (2H, m, *H*_{4A}, *H*_{7B}), 1.96-1.88 (1H, m, *H*_{2A}), 1.75-1.59 (3H, m, *H*_{2B}, *H*₅), 1.51 (1H, ddt, *J* 12.1, 11.1, 7.9, *H*_{4B}), 1.19 (9H, s, *t*Bu sulfinamide), 1.07 (9H, s, *t*Bu silyl ether); δ_{C} (101 MHz, CDCl₃) 135.6 (Ar), 135.3 (C₈), 133.7 (Ar (4°)), 129.6 (Ar), 127.7 (Ar), 116.9 (C₉), 64.9 (C₃), 61.4 (C₁), 56.9 (*t*Bu sulfinamide (4° carbon)), 52.8 (C₆), 41.3 (C₂), 40.4 (C₇), 31.1 (C₅), 29.7 (C₄), 26.9 (*t*Bu silyl ether), 23.8 (*t*Bu sulfinamide), 19.2 (*t*Bu silyl ether (4° carbon)); ν_{max} (film)/cm⁻¹ 1075 (S=O); ESI-MS calcd. for C₂₉H₄₃NNaO₂SSi [M+Na]⁺ 520.2676, found 520.2684; [α]_D²⁴ -9.0 (*c* 0.5, CH₂Cl₃).

2-((2S,5R)-5-allyl-1-((R)-tert-butylsulfinyl)pyrrolidin-2-yl)ethyl 4-bromobenzoate (111**)**



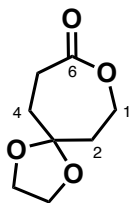
4-Bromobenzoyl chloride (119 mg, 0.54 mmol) was added to a stirring solution of alcohol **101** (70 mg, 0.27 mmol), NEt_3 (0.15 mL, 1.08 mmol) and DMAP (~1 mg) in DCM (2 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h, then diluted with DCM (10 mL) and sodium bicarbonate (sat., aq., 10 mL) was added. The organics were separated and the aqueous phase extracted with DCM (3 x 20 mL). The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30-60% Et_2O in petrol) to yield 4-bromobenzoate **111** as a pale yellow oil (117 mg, 98%). δ_{H} (500 MHz, CDCl_3) 7.96-7.93 (2H, m, ArH), 7.66-7.58 (2H, m, ArH), 5.81-5.71 (1H, m, H8), 5.14-5.08 (2H, m, H9), 4.43 (2H, t, J 6.6, H1), 4.06-4.01 (1H, m, H6), 3.89 (1H, quin, J 7.4, H3), 2.42-2.35 (1H, m, H7A), 2.23-2.12 (3H, m, H2A, H4A, H7B), 1.94 (1H, dtd, J 12.2, 6.1, H2B), 1.86-1.63 (3H, m, H4B, H5), 1.30 (9H, s, tBu); δ_{C} (126 MHz, CDCl_3) 165.8 (C=O), 135.0 (C8), 131.8 (Ar), 131.1 (Ar), 129.0 (Ar), 128.2 (Ar), 117.2 (C9), 64.6 (C3), 62.6 (C1), 57.2 (tBu (4° carbon)), 53.1 (C6), 40.4 (C7), 37.2 (C2), 31.1 (C4), 29.7 (C5), 23.7 (tBu); ν_{max} (film)/ cm^{-1} 1721 (C=O), 1102 (S=O); ESI-MS calcd. for $\text{C}_{20}\text{H}_{28}^{79}\text{BrNNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 464.0865, found 464.0864, $\text{C}_{20}\text{H}_{28}^{81}\text{BrNNaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 466.0846, found 466.0844; $[\alpha]_{\text{D}}^{24}$ -1.4 (c 0.6, CHCl_3).

2-((2*S*,5*R*)-5-allylpyrrolidin-2-yl)ethyl 4-bromobenzoate (**112**)



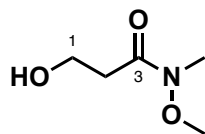
HCl (2.0 M in Et₂O, 0.63 mL, 1.27 mmol) was added dropwise to a stirring solution of sulfinyl pyrrolidine **111** (112 mg, 0.25 mmol) in MeOH (5 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min, diluted with CHCl₃ (2 mL) and sodium bicarbonate (sat., aq., 5 mL) was added. The organics were removed under reduced pressure and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organics were washed with H₂O (10 mL) and brine (10 mL) before being dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (80-100% Et₂O then 95:5:1 Et₂O:MeOH:NEt₃) to yield pyrrolidine **112** as a colourless oil (71 mg, 83%). δ_{H} (400 MHz, d₈-toluene) 7.78-7.75 (2H, m, ArH), 7.21-7.17 (2H, m, ArH), 5.78 (1H, ddt, J 17.2, 10.2, 7.0, H₈), 5.09-5.00 (2H, m, H₉), 4.31 (1H, dt, J 11.0, 6.9, H_{1A}), 4.20 (1H, dt, J 11.0, 6.4, H_{1B}), 2.92-2.84 (2H, m, H₃, H₆), 2.13-2.07 (3H, m, H₇, NH), 1.69-1.58 (4H, m, H₂, H_{4A}, H_{5A}), 1.29-1.18 (2H, m, H_{4B}, H_{5B}); δ_{C} (101 MHz, d₈-toluene) 165.5 (C=O), 137.5 (Ar (4° carbon)), 137.0 (C₈), 131.9 (Ar), 131.4 (Ar), 130.0 (Ar (4° carbon)), 116.0 (C₉), 63.8 (C₁), 58.5 (C₆), 55.9 (C₃), 41.8 (C₇), 36.5 (C₂), 31.5 (C₄), 30.7 (C₅); ν_{max} (film)/cm⁻¹ 3074 (N-H), 1718 (C=O); ESI-MS calcd. for C₁₆H₂₁⁷⁹BrNO₂ [M+H]⁺ 338.0750, found 338.0741, C₁₆H₂₁⁸¹BrNO₂ [M+H]⁺ 340.0730, found 340.0724; [α]_D²³ +6.8 (c 0.5, CHCl₃).

1,4,8-trioxaspiro[4.6]undecan-9-one (71)



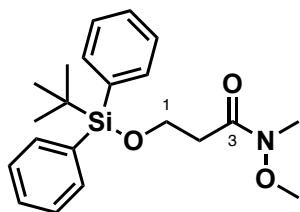
3-Chloroperbenzoic acid (16.7 g, 96.8 mmol) was added slowly to a stirring solution of cyclohexane-1,4-dione mono-ethylene glycol ketal (7.6 g, 48.7 mmol) in DCM (100 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction was cooled to 0 °C and sodium thiosulfate (sat., aq., 100 mL) was slowly added. The organics were separated and the aqueous phase washed with DCM (3 x 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (40-80% Et₂O in petrol) to yield ϵ -caprolactone ketal **71** as a colourless oil (8.32 g, 99%). δ_{H} (500 MHz, CDCl₃) 4.27-4.25 (2H, m, *H*1), 3.99-3.93 (4H, m, ketal (CH₂)₂), 2.68-2.65 (2H, m, *H*5), 1.98-1.96 (2H, m, *H*2), 1.88-1.86 (2H, m, *H*4); δ_{C} (126 MHz, CDCl₃) 175.8 (C6), 108.2 (C3), 65.2 (ketal (CH₂)₂), 64.7 (C1), 39.4 (C2), 33.1 (C4), 29.2 (C5); ν_{max} (film)/cm⁻¹ 1728 (C=O); low resolution ESI-MS 195.07 [M+Na]⁺. This data is in accordance with the literature.³⁷

3-hydroxy-*N*-methoxy-*N*-methylpropanamide



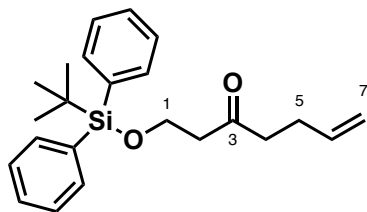
Dimethylaluminum chloride (1 M solution in hexanes, 13.8 mL, 13.8 mmol) was transferred *via* cannula to a stirring solution of *N,O*-dimethylhydroxylamine hydrochloride (1.34 g, 13.8 mmol) at -78°C in DCM (10 mL). The mixture was warmed to room temperature and stirred for 40 min, before being cooled to -78°C , when β -propiolactone (0.436 mL, 6.9 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 14 h, diluted with DCM (20 mL) and Rochelle's Salt (sat., aq., 20 mL) was added slowly. The resulting biphasic solution was stirred vigorously for 16 h, the organics extracted and the aqueous phase washed with chloroform (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0 to 5% MeOH in Et₂O) to yield the primary alcohol as a colourless oil (755 mg, 82%). δ_{H} (400 MHz, CDCl₃) 3.79 (2H, q, J 5.2, *H*1), 3.61 (3H, s, OCH₃), 3.37 (1H, br s, OH), 3.11 (3H, s, NCH₃), 2.60 (2H, t, J 5.3, *H*2); δ_{C} (101 MHz, CDCl₃) 173.5 (C3), 61.2 (C1), 58.0 (OCH₃), 34.0 (NCH₃), 31.8 (C2); ν_{max} (film)/cm⁻¹ 3419 (O-H), 1641 (C=O); ESI-MS calcd. for C₅H₁₁NNaO₃ [M+Na]⁺ 156.0631, found 156.0633.

3-((*tert*-butyldiphenylsilyl)oxy)-*N*-methoxy-*N*-methylpropanamide (**67**)



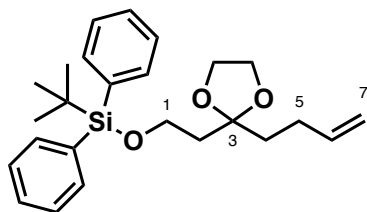
tert-Butylchlorodiphenylsilane (182 μ L, 0.7 mmol) was added dropwise to a stirring solution of the primary alcohol (85 mg, 0.64 mmol) and imidazole (96 mg, 1.4 mmol, 2.2 equiv) at 0 °C in anhydrous DMF (3 mL). The mixture was warmed to room temperature and stirred for 16 h, diluted with EtOAc (10 mL) and sodium bicarbonate (sat., aq., 20 mL) was added. The phases were separated and the aqueous phases washed with EtOAc (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (15:1 to 10:1 petrol:EtOAc) to yield silyl ether **67** as a colourless oil (236 mg, 100%). δ_{H} (400 MHz, CDCl_3) 7.70-7.67 (4H, m, ArH), 7.45-7.37 (6H, m, ArH), 4.01 (2H, t, J 6.8, H1), 3.67 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 2.72 (2H, t, J 6.4, H2), 1.05 (9H, s, tBu); δ_{C} (63 MHz, CDCl_3) 172.7 (C3), 136.0 (Ar), 134.1 (Ar), 130.1 (Ar), 128.2 (Ar), 61.7 (OCH_3), 60.6 (C1), 35.5 (C2), 32.4 (NCH_3), 27.3 (tBu), 19.6 (tBu (4° carbon)); ν_{max} (film)/ cm^{-1} 1664 (C=O); ESI-MS calcd. for $\text{C}_{21}\text{H}_{30}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 372.1989, found 372.1991.

1-((*tert*-butyldiphenylsilyl)oxy)hept-6-en-3-one



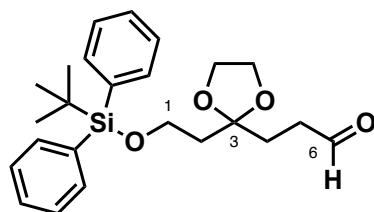
4-Butenylmagnesium bromide (0.5 M solution in THF, 3.6 mL, 1.68 mmol) was added dropwise to a stirring solution of hydroxamate **67** (208 mg, 0.56 mmol) in THF (2 mL) at -78°C . The solution was slowly warmed to 0°C and stirred for 1.5 h, diluted with Et₂O (20 mL) and HCl (1 M, 10 mL) was added slowly. The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5% EtOAc in petrol) to yield the butenyl ketone as a pale yellow oil (205 mg, 100%). δ_{H} (400 MHz, CDCl₃) 7.68-7.65 (4H, m, ArH), 7.47-7.37 (6H, m, ArH), 5.82 (1H, ddt, J 17.0, 10.4, 6.6, H₆), 5.04 (1H, app dq, J 17.1, 1.7, H₇_{trans}), 4.99 (1H, app dq, J 10.2, 1.4, H₇_{cis}), 3.95 (2H, t, J 6.2, H₁), 2.64 (2H, t, J 6.2, H₂), 2.59 (2H, t, J 7.4, H₄), 2.37-2.32 (2H, m, H₅), 1.04 (9H, s, ^tBu); δ_{C} (101 MHz, CDCl₃) 209.1 (C₃), 137.1 (C₆), 135.6 (Ar), 133.4 (Ar), 129.7 (Ar), 127.7 (Ar), 115.2 (C₇), 59.8 (C₁), 45.5 (C₂), 42.8 (C₄), 27.5 (C₅), 26.8 (^tBu), 19.1 (^tBu (4° carbon)); ν_{max} (film)/cm⁻¹ 1665 (C=O); ESI-MS calcd. for C₂₃H₃₄NO₂Si [M+H₂O]⁺ ketone hemiacetal 384.2350, found 384.2353.

(2-(2-(but-3-en-1-yl)-1,3-dioxolan-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (68)



Ethylene glycol (0.56 mL, 10 mmol), triethyl orthoformate (0.22 mL, 1.5 mmol) and ($\pm$)- β -camphorsulfonic acid (23 mg, 0.1 mmol) were added to a stirring solution of butenyl ketone (366 mg, 1.0 mmol) in DCM (10 mL) at room temperature. The mixture was stirred at room temperature for 24 h, diluted with DCM (20 mL) and sodium bicarbonate (sat., aq., 50 mL) was added. The phases were separated and the aqueous phase was washed with DCM (3 $\times$ 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0 - 5% EtOAc in petrol) to yield ketal **68** as a pale yellow oil (395 mg, 97%). δ_{H} (400 MHz, CDCl_3) 7.75-7.69 (4H, m, ArH), 7.44-7.38 (6H, m, ArH), 5.80 (1H, ddt, J 17.0, 10.3, 6.6, H_6), 4.99 (1H, app dq, J 17.1, 1.7, $H_{7\text{trans}}$), 4.93 (1H, app dq, J 10.2, 1.5, $H_{7\text{cis}}$), 3.85 (4H, m, ketal), 3.79 (2H, t, J 7.1, H_1), 2.13-2.07 (2H, m, H_5), 1.94 (2H, t, J 7.2, H_2), 1.73-1.69 (2H, m, H_4), 1.10 (9H, s, $t\text{Bu}$); δ_{C} (101 MHz, CDCl_3) 138.5 (C6), 135.6 (Ar), 133.8 (Ar), 129.7 (Ar), 127.7 (Ar), 114.2 (C7), 110.2 (C3), 64.8 (ketal), 60.1 (C1), 39.7 (C4), 36.7 (C2), 27.9 (C5), 26.6 ($t\text{Bu}$), 19.0 ($t\text{Bu}$ (4° carbon)); ν_{max} (film)/ cm^{-1} 1111 (C-O-C ketal); ESI-MS calcd. for $\text{C}_{25}\text{H}_{35}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 411.2350, found 411.2352.

3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1,3-dioxolan-2-yl)propanal (**69**)

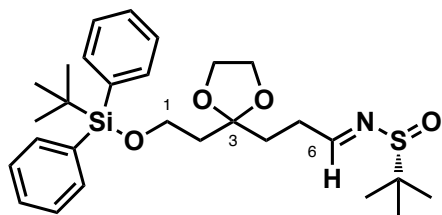


Method A: Osmium tetroxide (68.5 mg, 0.27 mmol) and sodium *meta*-periodate (11.7 g, 54.7 mmol) were added to a stirring solution of ketal **68** (5.53 g, 13.5 mmol), and 2,6-lutidine (2.96 mL, 27.6 mmol) in 1,4-dioxane:H₂O (3:1, 200 mL). The mixture was stirred at room temperature for 2 h, diluted with EtOAc (100 mL) and brine (100 mL) was added. The phases were separated and the aqueous phase washed with EtOAc (3 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10 - 20% EtOAc in petrol) to yield aldehyde **69** as a dark brown oil (5.4 g, 97%).

Method B: Diisobutylaluminum hydride (1 M solution in hexanes, 8.0 mL, 8.0 mmol) was added dropwise to a solution of ϵ -caprolactone ketal **71** (1.15 g, 6.7 mmol) in DCM (20 mL) at -78 °C. The solution was maintained at -78 °C for a further 2 h then diluted with DCM (100 mL) and Rochelle's Salt (sat., aq., 10 mL) and sodium bicarbonate (sat., aq., 10 mL) was added slowly. The resulting mixture was warmed to room temperature and stirred vigorously for 1 h. Sodium bicarbonate (5 g) and sodium sulfate (5 g) was added and the mixture filtered through a pad of Celite®. The cake was washed with DCM (3 x 100 mL) and concentrated under reduced pressure to afford the crude lactol. Triethylamine (1.21 mL, 8.7 mmol) and DMAP (38 mg, 0.31 mmol) were added to a stirring solution of crude lactol in DCM (15 mL). The resulting mixture was cooled to 0 °C and *tert*-butyl(chloro)diphenylsilane (1.92 mL, 7.38 mmol) was added dropwise over 5 min. The mixture was warmed to room temperature and stirred for 5 h, diluted with DCM (50 mL) and sodium bicarbonate was added (sat., aq., 50 mL). The phases were separated and the aqueous phase was washed with DCM (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (20 - 50% Et₂O in petrol) to yield aldehyde **69** as a colourless oil (2.52 g, 91% over 2 steps). δ_{H} (400 MHz, CDCl₃) 9.66 (1H, t, J 2.1, H₆), 7.69-7.67 (4H, m, ArH), 7.46-7.37 (6H, m, ArH), 3.85 (4H, m, ketal), 3.77 (2H, t, J 6.9, H₁), 2.40 (2H, td, J 7.0, 2.1, H₅), 2.08 (2H, t, J 7.0, H₄), 1.89 (2H, t, J 6.9, H₂), 1.05 (9H, s, ^tBu); δ_{C} (63 MHz, CDCl₃) 202.5 (C₆), 136.0 (Ar), 134.1 (Ar), 130.1 (Ar), 128.2

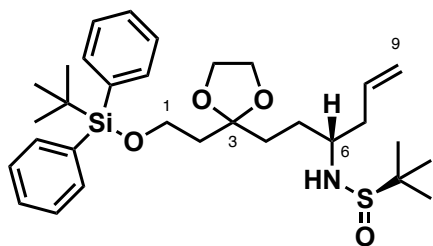
(Ar), 110.1 (C3), 65.2 (ketal), 60.5 (C1), 40.3 (C5), 38.7 (C2), 30.9 (C4), 27.3 (tBu), 19.6 (tBu (4° carbon)); ν_{max} (film)/cm⁻¹ 1723 (C=O), 1110 (C-O-C ketal); ESI-MS calcd. for C₂₄H₃₃O₄Si [M+H]⁺ 413.2143, found 413.2145.

(*R,E*)-*N*-(3-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1,3-dioxolan-2-yl)propylidene)-2-methylpropane-2-sulfinamide (73)



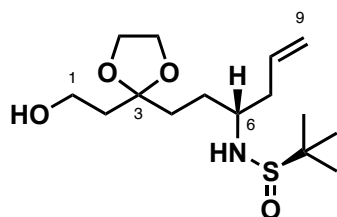
(*R*)-2-Methylpropane sulfinamide (78.3 mg, 0.65 mmol) was added to a stirring solution of aldehyde **69** (292.8 mg, 0.71 mmol) and anhydrous copper sulfate (418 mg, 2.62 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 24 h. After this time the reaction was filtered through a pad of Celite® and the cake was washed with DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel chromatography (40-45% Et₂O in petrol) to yield sulfinyl aldimine **73** as a pale yellow oil (304.5 mg, 92%, 99% brsm). δ_{H} (400 MHz, CDCl₃) 8.06 (1H, t, *J* 4.3, *H*₆), 7.69-7.66 (4H, m, *ArH*), 7.46-7.36 (6H, m, *ArH*), 3.92-3.80 (4H, m, ketal), 3.77 (2H, t, *J* 7.0, *H*₁), 2.58-2.53 (2H, m, *H*₅), 2.01 (2H, app tt, *J* 15.6, 7.6, *H*₄), 1.91 (2H, t, *J* 7.0, *H*₂), 1.18 (9H, s, *t*Bu (sulfinamide)), 1.04 (*t*Bu (silyl ether)); δ_{C} (101 MHz, CDCl₃) 169.4 (*C*₆), 135.6 (*Ar*), 133.7 (*Ar*), 129.6 (*Ar*), 127.7 (*Ar*), 109.8 (*C*₃), 64.8 (ketal), 60.0 (*C*₁), 56.5 (*t*Bu (sulfinamide, 4° carbon)), 39.7 (*C*₂), 33.0 (*C*₄), 30.56 (*C*₅), 26.8 (*t*Bu (silyl ether)), 22.3 (*t*Bu (sulfinamide)), 19.1 (*t*Bu (silyl ether, 4° carbon)); ν_{max} (film)/cm⁻¹ 1623 (C=N), 1109 (C-O-C ketal); ESI-MS calcd. for C₃₀H₄₈N₃O₄SSi [M+MeCN+NH₄]⁺ 574.3129, found 574.3139; $[\alpha]_{\text{D}}^{25}$ -76.0 (*c* 0.73, CH₂Cl₂).

(R)-N-((R)-1-(2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1,3-dioxolan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfonamide (75)



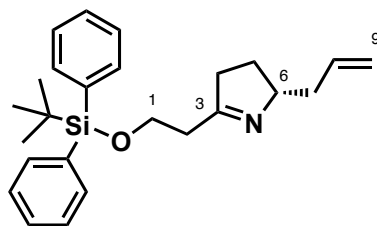
Allylmagnesium chloride (2.0 M solution in THF, 2.7 mL, 5.38 mmol) was added to a stirring solution of sulfinyl aldimine **73** (1.26 g, 2.45 mmol) in DCM (30 mL) at -78°C over a period of 4 h. The mixture was stirred at -78°C for 16 h, warmed to 0°C , diluted with DCM (30 mL) and ammonium chloride (sat., aq., 40 mL) was added. The resulting biphasic solution was stirred vigorously for 10 min, the phases separated and the aqueous layer washed with DCM (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (35% EtOAc in cyclohexane) to yield homoallyl sulfonamide **75** as a pale yellow oil (1.34 g, 99%, 58:1 dr). **Major diastereomer:** δ_{H} (400 MHz, CDCl_3) 7.68-7.66 (4H, m, ArH), 7.45-7.36 (6H, m, ArH), 5.80-5.69 (1H, m, H8), 5.16-5.12 (2H, m, H9), 3.87-3.82 (4H, m, ketal), 3.75 (2H, t, J 7.32, H1), 3.26 (1H, sextet, J 6.4, H6), 3.17 (1H, d, J 6.6, NH), 2.39-2.26 (2H, m, H7), 1.91 (2H, t, J 7.3, H2), 1.75-1.39 (4H, m, H5, H4), 1.16 (9H, s, *t*Bu (sulfonamide)), 1.05 (9H, s, *t*Bu (silyl ether)); δ_{C} (101 MHz, CDCl_3) 135.5 (Ar), 134.0 (C8), 133.8 (Ar), 129.6 (Ar), 127.7 (Ar), 119.1 (C9), 110.2 (C3), 64.7 (ketal), 60.1 (C1), 55.8 (*t*Bu (sulfonamide, 4° carbon)), 55.1 (C6), 40.6 (C7), 39.7 (C2), 33.4 (C4), 28.9 (C5), 26.8 (*t*Bu (silyl ether)), 22.7 (*t*Bu (sulfonamide)), 19.1 (*t*Bu (silyl ether, 4° carbon)); ν_{max} (film)/ cm^{-1} 1639 (C=C), 1069 (S=O); ESI-MS calcd. for $\text{C}_{31}\text{H}_{47}\text{NNaO}_4\text{SSi}$ $[\text{M}+\text{Na}]^+$ 580.2887, found 580.2891; $[\alpha]_{\text{D}}^{25} -24.3^{\circ}$ (c 1.08, CH_2Cl_2). **Minor diastereomer:** δ_{H} (400 MHz, MeOD) 7.69-7.66 (4H, m, ArH), 7.46-7.37 (6H, m, ArH), 5.80 (1H, ddt, J 17.0, 10.1, 7.0, H8), 5.10-5.03 (2H, m, H9), 3.87-3.79 (4H, m, ketal), 3.76 (2H, t, J 7.2, H1), 3.36-3.30 (1H, m, H6), 2.77 (1H, d, J 6.9, NH), 2.39 (1H, dd, J 14.0, 6.6, H7_A), 2.24 (1H, dd, J 14.0, 7.9, H7_B), 1.91 (2H, t, J 7.3, H2), 1.78-1.59 (4H, m, H4, H5), 1.17 (9H, s, *t*Bu (sulfonamide)), 1.04 (9H, s, *t*Bu (silyl ether)); δ_{C} (101 MHz, MeOD) 136.2 (C8), 135.7 (Ar), 133.9 (Ar, 4° carbon), 129.9 (Ar), 127.8 (Ar), 116.2 (C9), 110.5 (C3), 64.8 (ketal), 60.4 (C1), 56.3 (*t*Bu (4° carbon, sulfonamide)), 54.7 (C6), 43.3 (C7), 39.8 (C2), 33.4 (C4), 29.2 (C5) 26.5 (*t*Bu (silyl ether)), 22.3 (*t*Bu (sulfonamide)), 19.0 (*t*Bu (4° carbon, silyl ether)); ν_{max} (film)/ cm^{-1} 1642 (C=C), 1067 (S=O); ESI-MS calcd. for $\text{C}_{31}\text{H}_{47}\text{NNaO}_4\text{SSi}$ $[\text{M}+\text{Na}]^+$ 580.2887, found 580.2895; $[\alpha]_{\text{D}}^{25} -30.7^{\circ}$ (c 1.0, CHCl_3).

(R)-N-((R)-1-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfonamide (76)



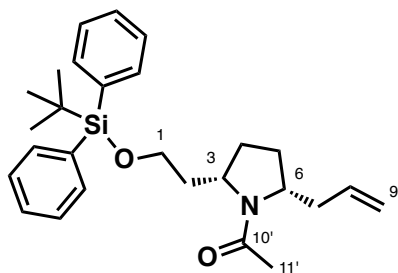
Tetrabutylammonium fluoride (1.0 M solution in THF, 0.29 mL, 0.29 mmol) was added to a stirring solution of homoallyl sulfonamide **75** at 0 °C in THF (10 mL). The reaction mixture was warmed to room temperature and stirred for 3 h, diluted with chloroform (10 mL) and brine (10 mL) was added. The organics were extracted and the aqueous phase washed with chloroform (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5% MeOH in Et₂O) to yield alcohol **75** as a colourless oil (81.1 mg, 98%). Alcohol **76** was recrystallized from chloroform:hexane (1:1) to give a colourless solid. δ_{H} (400 MHz, CDCl₃) 5.81-5.70 (1H, m, *H*8), 5.16-5.12 (2H, m, *H*9), 4.00-3.92 (4H, m, ketal), 3.71 (2H, br q, *J* 5.2, 4.4, *H*1), 3.34-3.26 (2H, m, *H*6, NH), 2.86 (1H, br t, *J* 4.8, OH), 2.36-2.34 (2H, m, *H*7), 1.89 (2H, t, *J* 5.6, *H*2), 1.80-1.71 (1H, m, *H*4_A), 1.68-1.47 (3H, m, *H*4_B, *H*5), 1.19 (9H, s, *t*Bu); δ_{C} (101 MHz, CDCl₃) 133.9 (C8), 119.1 (C9), 111.8 (C3), 64.8 (ketal), 58.7 (C1), 55.8 (*t*Bu (4° carbon)), 54.8 (C6), 40.4 (C7), 38.2 (C2), 32.9 (C4), 29.1 (C5), 22.7 (*t*Bu); ν_{max} (film)/cm⁻¹ 3397 (O-H), 1050 (S=O); ESI-MS calcd. for C₁₅H₂₉NNaO₄S [M+Na]⁺ 342.1710, found 342.1706; $[\alpha]_{\text{D}}^{25}$ -39.0 (*c* 1.08, CHCl₃); melting point 78 °C.

2-allyl-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3,4-dihydro-2*H*-pyrrole (78)



Trifluoroacetic acid (165 mL, 2.15 mmol) was added dropwise to a stirring solution of homoallyl sulfonamide **75** (77 mg, 0.14 mmol) in DCM (15 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h, concentrated under reduced pressure, redissolved in DCM (20 mL) and sodium bicarbonate (20 mL) was added. The biphasic mixture was stirred vigorously for 15 min. The layers were separated and the aqueous phase washed with DCM (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (20% EtOAc in petrol) to yield Δ^1 -pyrroline **78** as a light brown oil (36 mg, 67%). δ_{H} (500 MHz, CDCl_3) 7.68-7.66 (4H, m, ArH), 7.45-7.36 (6H, m, ArH), 5.84 (1H, ddt, J 17.1, 10.2, 7.0, H_8), 5.08 (1H, d, J 17.2, $H_{9\text{trans}}$), 5.04 (1H, d, J 10.2, $H_{9\text{cis}}$), 4.04 (1H, br quin, J 7.6, H_6), 3.93 (2H, t, J 6.4, H_1), 2.66-2.42 (5H, m, H_2 , $H_{4\text{A}}$, $H_{5\text{A}}$, $H_{7\text{A}}$), 2.18 (1H, dt, J 14.1, 7.2, $H_{7\text{B}}$), 2.02 (1H, m, $H_{4\text{B}}$), 1.50 (1H, ddt, J 12.9, 9.9, 6.7, $H_{5\text{B}}$), 1.05 (9H, s, $t\text{Bu}$); δ_{C} (126 MHz, CDCl_3) 176.0 (C3), 135.8 (C8), 135.6 (Ar), 134.9 (Ar), 129.6 (Ar), 127.6 (Ar), 116.5 (C9), 71.9 (C6), 61.6 (C1), 40.6 (C7), 37.8 (C2), 36.9 (C4), 27.7 (C5), 26.8 ($t\text{Bu}$), 19.2 ($t\text{Bu}$ silyl (4° carbon)); ν_{max} (film)/ cm^{-1} 1685 (C=N), 1642 (C=C); ESI-MS calcd. for $\text{C}_{25}\text{H}_{34}\text{NO}_4\text{Si}$ $[\text{M}+\text{H}]^+$ 392.2404, found 392.2402; $[\alpha]_{\text{D}}^{25}$ -2.0 (c 1.0, CH_2Cl_2).

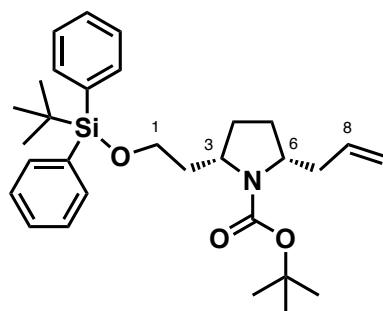
1-((2*R*,5*S*)-2-allyl-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)pyrrolidin-1-yl)ethanone (79)



HCl (4 M solution in 1,4-dioxane, 0.56 mL, 0.56 mmol) was added dropwise to a stirring solution of homo-allyl sulfonamide **75** (84 mg, 0.15 mmol) in MeOH (15 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h, cooled to 0 °C, diluted with DCM (15 mL) and sodium bicarbonate (sat., aq., 30 mL) was added. The biphasic solution was warmed to room temperature and stirred vigorously for 15 min. The organic phase was separated and the aqueous phase extracted with CHCl₃:IPA (3:1, 3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude Δ¹-pyrroline was used without further purification. Diisobutylaluminum hydride (1 M solution in hexanes, 0.6 mL, 0.6 mmol) was added dropwise to a solution of crude Δ¹-pyrroline **78** in DCM (10 mL) at -78 °C over a period of 4 h. After this period the solution was maintained at -78 °C for a further 2 h then diluted with DCM (100 mL) and Rochelle's Salt (sat., aq., 50 mL) was added slowly. The resulting mixture was warmed to room temperature and stirred vigorously for 16 h. After this period the phases were separated and aqueous phase extracted with CHCl₃:IPA (3:1, 3 x 50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude pyrrolidine was used without further purification. Acetic anhydride (1 mL, 10.6 mmol) was added dropwise to a stirring solution of crude pyrrolidine in pyridine (2 mL). The resulting solution was stirred at room temperature for 15 minutes, diluted with DCM (10 mL) and sodium bicarbonate (sat., aq., 20 mL) was added. The aqueous phase was washed with DCM (3 x 20 mL), the combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (1-10% Et₂O in petrol) to yield *N*-Ac pyrrolidine **79** as a colourless oil (46.8 mg, 60%). δ_H (500 MHz, d₆-DMSO, 380 K) 7.67-7.64 (4H, m, ArH), 7.49-7.42 (6H, m, ArH), 5.81-5.71 (1H, m, H₈), 5.08-5.01 (2H, m, H₉), 4.02-3.99 (1H, br m, H₃), 3.93-3.90 (1H, br m, H₆), 3.81-3.72 (2H, m, H₁), 2.97 (3H, s, H_{11'}), 2.11 (1H, dt, J 14.9, 7.7, H_{7A}), 1.93-1.84 (3H, m, H_{2A}, H_{4A}, H_{7B}), 1.69-1.59 (4H, m, H_{2B}, H_{4B}, H₅), 1.06 (9H, s, ^tBu); δ_C (126 MHz, d₆-DMSO, 380 K) 168.1 (C_{10'}), 136.3 (Ar), 135.2 (C₈), 134.5 (Ar), 129.9 (Ar), 127.9 (Ar), 116.9 (C₉), 61.6 (C₁), 56.2 (C₃), 55.8

(C6), 38.7 (C7), 37.8 (C2), 28.8 (C5), 28.5 (C4), 26.6 (tBu (silyl ether)), 22.3 (C11'), 18.7 (tBu (silyl ether, 4° carbon)); ν_{max} (film)/ cm^{-1} 1644 (C=O); ESI-MS calcd. for $\text{C}_{27}\text{H}_{37}\text{NNaO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 458.2486, found 458.2476; $[\alpha]_{\text{D}}^{23} +11.2$ (c 1.0, CHCl_3).

(2R,5S)-tert-butyl-2-allyl-5-(1-((tert-butyldiphenylsilyl)oxy)ethyl)pyrrolidine-1-carboxylate (82)

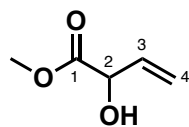


Method A: HCl (2.0 M in Et₂O, 0.25 mL, 0.50 mmol) was added dropwise to a stirring solution of sulfinyl pyrrolidine **114** (50 mg, 0.10 mmol) in MeOH (2 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min before being diluted with CHCl₃ (2 mL) and sodium bicarbonate (sat., aq., 5 mL) was added. The organics were removed under reduced pressure and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organics were washed with H₂O (10 mL) and brine (10 mL) before being dried over sodium sulfate and concentrated under reduced pressure to yield crude pyrrolidine as a colourless oil which was used without further purification. Sodium hydride (60% dispersion in mineral oil, 6 mg, 0.15 mmol) was added to a solution of crude pyrrolidine in THF (2 mL) at 0 °C and stirred for 30 min. After this period di-*tert*-butyl dicarbonate (46 mg, 0.20 mmol) was added and the reaction was warmed to room temperature and stirred for 15 h. After this period sodium bicarbonate (sat., aq., 10 mL) was added and extracted with Et₂O (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (2-5% Et₂O in petrol) to yield *N*-Boc pyrrolidine **82** as a colourless oil (38 mg, 79% overall yield).

Method B: HCl (4 M solution in 1,4-dioxane, 0.56 mL, 2.26 mmol) was added dropwise to a stirring solution of homo-allyl sulfonamide **75** (84 mg, 0.15 mmol) in MeOH (15 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h, then diluted with DCM (15 mL), cooled to 0 °C and sodium bicarbonate solution (sat., aq., 30 mL) was added. The biphasic solution was warmed to room temperature and stirred vigorously for 15 min. The organic phase was separated and the aqueous phase extracted with CHCl₃:IPA (3:1, 3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude Δ¹-pyrroline was used without further purification. Diisobutylaluminum hydride (1M solution in hexanes, 0.6 mL, 0.6 mmol) was added drop wise to a solution of crude Δ¹-pyrroline in DCM at

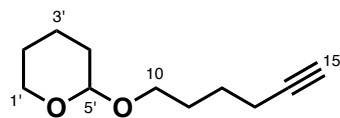
-78 °C over a period of 4 h. After this period the solution was maintained at -78 °C for a further 2 h before Rochelle's Salt (sat., aq., 50 mL) was slowly added. The resulting heterogeneous mixture was warmed to room temperature, where it gradually became biphasic, and was stirred vigorously for 16 h. After this period the phases were separated and aqueous phase extracted with CHCl₃:IPA (3:1, 3 x 50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. Crude pyrrolidine was used without further purification. Triethylamine was added to a stirring solution of crude pyrrolidine in DCM (2 mL) at 0 °C and stirred for 10 min. After this period di-*tert*-butyl dicarbonate (69 mg, 0.32 mmol) and DMAP (~1 mg) was added and the reaction mixture warmed to room temperature and stirred for 5 h, diluted with DCM (10 mL) and sodium bicarbonate (sat., aq., 10 mL) was added. The phases were separated and the aqueous phase extracted with DCM (3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (1-10% Et₂O in petrol) to yield *N*-Boc pyrrolidine **82** (46.8 mg, 60% over 3 steps) as a colourless oil. δ_{H} (500 MHz, d₈-toluene, 363 K) 7.79-7.75 (4H, m, ArH), 7.28-7.23 (6H, m, ArH), 5.74 (1H, ddt, J 17.2, 10.1, 7.1, *H*₈), 5.03-4.95 (2H, m, *H*₉), 3.96-3.90 (1H, m, *H*₃), 3.86-3.75 (3H, m, *H*₁, *H*₆), 2.60-2.54 (1H, m, *H*_{7A}), 2.27-2.20 (1H, m, *H*_{2A}), 2.14-2.06 (1H, m, *H*_{7B}), 1.67-1.55 (3H, m, *H*_{2B}, *H*₅), 1.51-1.40 (11H, m, *H*₄, *t*Bu (Boc)), 1.17 (*t*Bu (silyl ether)); δ_{C} (126 MHz, d₈-toluene, 363 K) 154.5 (Boc), 137.4 (Ar), 135.9 (Ar), 135.8 (C8), 134.7 (Ar), 130.0 (Ar), 116.4 (C9), 78.6 (*t*Bu (Boc), 4° carbon), 62.7 (C1), 58.4 (C6), 56.6 (C3), 40.4 (C7), 39.5 (C2), 30.0 (C4), 29.3 (C5), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 19.4 (*t*Bu (silyl ether, 4° carbon)); ν_{max} (film)/cm⁻¹ 1692 (C=O); ESI-MS calcd. for C₃₀H₄₃NNaO₃Si [M+Na]⁺ 516.2904, found 516.2906; $[\alpha]_{\text{D}}^{23}$ +12.8 (c 1.05, CHCl₃).

methyl 2-hydroxybut-3-enoate (**116**)



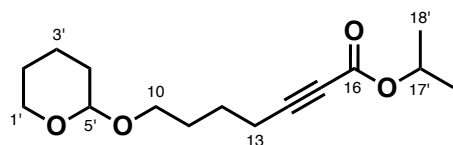
Concentrated HCl (12 M, 4.5 mL) was added dropwise over 30 min to a stirring solution of cyanopropenyl acetate **115** (2.3 mL, 18.9 mmol) in MeOH (3 mL). The resulting solution was heated to reflux and stirred for 2 h, cooled to room temperature, filtered and concentrated under reduced pressure. The crude residue was dissolved in Et₂O (50 mL) and washed with sodium bicarbonate (sat., aq., 100 mL) and H₂O (100 mL). The phases were separated and the aqueous phases extracted with 3:1 CHCl₃:IPA (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was distilled under reduced pressure to yield hydroxyl butenoate **116** as a colourless oil (1.68 g, 81%) (bp 65 °C , 20 mmHg). δ_{H} (400 MHz, CDCl₃) 5.92 (1H, ddd, J 17.1, 10.4, 5.1, *H*₃), 5.49 (1H, ddd, J 17.1, 1.8, 1.2, *H*_{4trans}), 5.26 (1H, ddd, J 10.4, 1.8, 1.2, *H*_{4cis}), 4.67 (1H, dt, J 5.1, 1.8, *H*₂), 3.79 (3H, s, OCH₃), 3.07 (1H, br s, OH); δ_{C} (101 MHz, CDCl₃) 173.6 (C1), 134.2 (C3), 117.1 (C4), 71.5 (OCH₃), 52.8 (C2); ν_{max} (film)/cm⁻¹ 3477 (O-H), 1738 (C=O); low resolution ESI-MS 139.04 [M+Na]⁺. This data is in accordance with the literature.⁹⁵

2-(hex-5-yn-1-yloxy)tetrahydro-2H-pyran



(±)-Camphor-10-sulfonic acid (206 mg, 0.89 mmol) was added to a stirring solution of 3,4-dihydropyran (4.54 mL, 48.7 mmol) and 5-hexyn-1-ol (4.8 mL, 44.3 mmol) in DCM (20 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min and then warmed to room temperature and stirred for 45 min. Sodium bicarbonate (sat., aq., 50 mL) was added, the phases separated and the aqueous phase extracted with DCM (3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (3-5% Et₂O in petrol) to yield tetrahydropyran ether as a colourless oil (8.01 g, 99%). δ_{H} (400 MHz, CDCl₃) 4.58 (1H, t, J 3.4, *H*5'), 3.86 (1H, ddd, J 11.1, 7.7, 3.4, *H*1'_A), 3.77 (1H, dt, J 9.6, 6.3, *H*10_A), 3.51 (1H, dt, J 10.8, 5.2, *H*1'_B), 3.42 (1H, dt, 9.6, 6.1, *H*10_B), 2.24 (2H, td, J 6.9, 2.6, *H*13), 1.95 (1H, td, J 2.8, 0.8, *H*15), 1.83 (1H, qd, J 9.1, 3.4, *H*4'_A), 1.76-1.47 (9H, m, *H*2', *H*3', *H*4'_B, *H*11, *H*12); δ_{C} (101 MHz, CDCl₃) 98.7 (*C*5'), 84.3 (*C*14), 68.4 (*C*15), 66.8 (*C*10), 62.2 (*C*1'), 30.7 (*C*4'), 28.8 (*C*11), 25.4 (*C*2'), 25.3 (*C*12), 19.6 (*C*3'), 18.2 (*C*13); ν_{max} (film)/cm⁻¹ 2117 (alkyne); ESI-MS calcd. for C₁₁H₁₈NaO₂ [M+Na]⁺ 205.1199, found 205.1197. This data is in accordance with the literature.⁹⁶

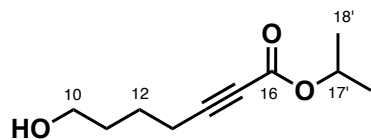
isopropyl 7-((tetrahydro-2H-pyran-2-yl)oxy)hept-2-ynoate (122**)**



*Propargylic ester **122** was synthesized using Brandsma's inverse addition protocol.⁹⁷*

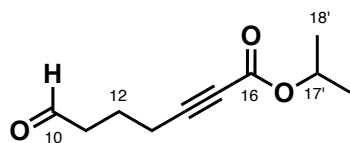
n-Butyllithium (1.3 M in hexanes) was added dropwise to a stirring solution of tetrahydropyran ether (613 mg, 3.36 mmol) in THF (5 mL) at -78°C . The solution was stirred at -78°C for 1 h and then isopropylchloroformate (1.0 M solution in toluene, 5.0 mL, 5.0 mmol) was added dropwise over a period of 10 min. The resulting mixture was stirred at -78°C for 1 h and then slowly warmed to 0°C over a period of 3 h. After this period the reaction was diluted with Et_2O (20 mL) and ammonium chloride (sat., aq., 20 mL) was added. The organics were separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-20% Et_2O in petrol) to yield propargylic ester **122** as a yellow oil (881.8 mg, 92%). δ_{H} (400 MHz, CDCl_3) 5.03 (1H, septet, J 6.3, $H_{17'}$), 4.53 (1H, t, J 3.5, $H_{5'}$), 3.81 (1H, ddd, J 11.2, 7.6, 3.5, $H_{1'A}$), 3.72 (1H, dt, J 9.7, 6.1, H_{10A}), 3.49-3.44 (1H, m, $H_{1'B}$), 3.37 (1H, dt, J 9.7, 5.8, H_{10B}), 2.34 (2H, t, J 6.5, H_{13}), 1.83-1.74 (1H, m, $H_{4'A}$), 1.70-1.62 (5H, m, $H_{3'A}$, H_{11} , H_{12}), 1.57-1.46 (4H, m, $H_{2'}$, $H_{3'B}$, $H_{4'B}$), 1.25 (6H, d, J 6.3, $H_{18'}$); δ_{C} (101 MHz, CDCl_3) 153.3 (C_{16}), 98.8 ($C_{5'}$), 88.6 (C_{14}), 73.6 (C_{15}), 69.6 ($C_{17'}$), 66.6 (C_{10}), 62.3 ($C_{1'}$), 30.7 ($C_{4'}$), 28.8 (C_{11}), 25.4 ($C_{2'}$), 24.5 (C_{12}), 21.6 ($C_{18'}$), 19.6 ($C_{3'}$), 18.5 (C_{13}); ν_{max} (film)/ cm^{-1} 2236 (alkyne), 1711 ($\text{C}=\text{O}$); ESI-MS calcd. for $\text{C}_{15}\text{H}_{24}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 291.1567, found 291.1563.

isopropyl 7-hydroxyhept-2-ynoate (**134**)



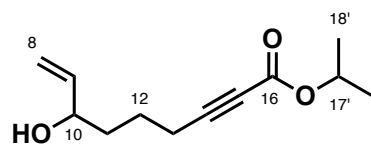
p-Toluenesulfonic acid monohydrate (22 mg, 0.12 mmol) was added to a stirring solution of propargylic ester **122** (791 mg, 2.95 mmol) in MeOH (15 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h, pH 7 buffer (20 mL) was added and the MeOH was removed under reduced pressure. The aqueous phase was washed with CHCl₃:IPA (3:1, 3 x 20 mL) and the combined organic extracts dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (1:1 Et₂O:petrol) to yield primary alcohol **134** as a colourless oil (503.2 mg, 93%). δ_{H} (400 MHz, CDCl₃) 4.99 (1H, septet, J 6.3, *H*17'), 3.60-3.56 (2H, m, *H*10), 2.62 (1H, br s, OH), 2.34-2.29 (2H, m, *H*13), 1.63-1.58 (4H, m, *H*11, *H*12), 1.22 (6H, d, J 6.3, *H*18'); δ_{C} (101 MHz, CDCl₃) 153.5 (*C*16), 88.7 (*C*14), 73.6 (*C*15), 69.7 (*C*17'), 61.7 (*C*10), 31.5 (*C*11), 23.9 (*C*12), 21.6 (*C*18'), 18.4 (*C*13); ν_{max} (film)/cm⁻¹ 3419 (O-H), 2236 (alkyne), 1645 (C=O); ESI-MS calcd. for C₁₀H₁₆NaO₃ [M+Na]⁺ 207.0992, found 207.0989.

isopropyl 7-oxohept-2-ynoate (**123**)



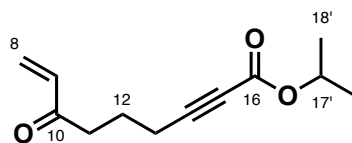
DMSO (0.38 mL, 4.45 mmol) was added dropwise to a stirring solution of oxalyl chloride (0.39 mL, 4.45 mmol) in DCM (10 mL) at -78°C . The mixture was stirred at -78°C for 15 min then a solution of primary alcohol (409 mg, 2.22 mmol) in DCM (2 mL) was added dropwise *via* cannula. The mixture was stirred at -78°C for 15 min and then triethylamine (1.55 mL, 11.11 mmol) was added dropwise. The mixture was stirred at -78°C for 15 min and then warmed to room temperature was stirred for 15 min. After this period H_2O (10 mL) was added and the aqueous phase extracted with DCM (2×10 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-20% Et_2O in petrol) to yield aldehyde **123** as a colourless oil (383.8 mg, 95%). δ_{H} (400 MHz, CDCl_3) 9.74 (1H, d, J 1.0, H_{10}), 5.01 (1H, septet, J 6.3, $H_{17'}$), 2.58 (2H, t, J 7.2, H_{11}), 2.36 (2H, t, J 7.0, H_{13}), 1.85 (2H, quin, J 7.0, H_{12}), 1.23 (6H, d, J 6.3, $H_{18'}$); δ_{C} (101 MHz, CDCl_3) 201.0 (C_{10}), 153.1 (C_{16}), 87.2 (C_{14}), 74.2 (C_{15}), 69.7 ($\text{C}_{17'}$), 42.3 (C_{11}), 21.6 ($\text{C}_{18'}$), 19.9 (C_{12}), 17.9 (C_{13}); ν_{max} (film)/ cm^{-1} 2237 (alkyne), 1699 ($\text{C}=\text{O}$); ESI-MS calcd. for $\text{C}_{11}\text{H}_{18}\text{NaO}_4$ $[\text{M}+\text{Na}+\text{MeOH}]^+$ (aldehyde hemiacetal) 237.1097, found 237.1095.

isopropyl 7-hydroxynon-8-en-2-ynoate (**129**)



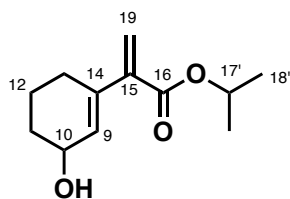
Vinylmagnesium bromide (1.0 M solution in THF, 2.3 mL, 2.3 mmol) was added over a period of 30 min to a stirring solution of aldehyde **123** (377 mg, 2.07 mmol) in Et₂O (10 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min, warmed to 0 °C and HCl_(aq) (0.25 M, 50 mL) was added. The aqueous phase was extracted with CHCl₃ (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (50-90% Et₂O in petrol) to yield allylic alcohol **129** as a colourless oil (222 mg, 51%). δ_{H} (400 MHz, CDCl₃) 5.85 (1H, ddd, J 17.1, 10.5, 6.4, *H*₉), 5.23 (1H, dt, J 17.2, 1.2, *H*_{8trans}), 5.11 (1H, dt, J 10.4, 1.2, *H*_{8cis}), 5.06 (1H, septet, J 6.4, *H*_{17'}), 4.12 (1H, q, J 5.3, *H*₁₀), 2.36 (2H, t, J 6.1, *H*₁₃), 1.85 (1H, br s, OH), 1.74-1.60 (4H, m, *H*₁₁, *H*₁₂), 1.27 (6H, d, J 6.3, *H*_{18'}); δ_{C} (101 MHz, CDCl₃) 153.4 (*C*₁₆), 140.8 (*C*₉), 115.0 (*C*₈), 88.5 (*C*₁₄), 73.7 (*C*₁₅), 72.5 (*C*₁₀), 69.7 (*C*_{17'}), 35.8 (*C*₁₁), 23.4 (*C*₁₂), 21.6 (*C*_{18'}), 18.6 (*C*₁₃); ν_{max} (film)/cm⁻¹ 3399 (O-H), 2237 (alkyne), 1706 (C=O); ESI-MS calcd. for C₁₂H₁₈NaO₃ [M+Na]⁺ 233.1148, found 233.1147.

isopropyl 7-oxonon-8-en-2-ynoate (**124**)



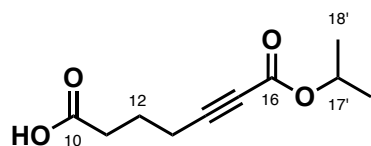
Manganese dioxide (pre-activated, 3.37 g, 38.8 mmol) was added to a stirring solution of allylic alcohol **129** (163 mg, 0.78 mmol) in DCM (30 mL) at room temperature. The mixture was stirred at room temperature for 1 h and then filtered through a short pad of Celite®. The cake was washed with DCM (3 x 30 mL) and the combined organic filtrates concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10% Et₂O in petrol) to yield enone **124** as a pale yellow oil (106 mg, 66%). δ_{H} (400 MHz, CDCl₃) 6.35 (1H, dd, J 17.7, 10.5, *H*₉), 6.25 (1H, d, J 17.7, *H*_{8trans}), 5.85 (1H, d, J 10.5, *H*_{8cis}), 5.07 (1H, septet, J 6.25, *H*_{17'}), 2.74 (2H, t, J 7.1, *H*₁₁), 2.41 (2H, t, J 6.9, *H*₁₃), 1.90 (2H, quin, J 7.0, *H*₁₂), 1.28 (6H, d, J 6.3, *H*_{18'}); δ_{C} (101 MHz, CDCl₃) 199.5 (C10), 153.2 (C16), 136.4 (C9), 128.4 (C8), 87.7 (C14), 74.1 (C15), 69.7 (C17'), 37.8 (C11), 21.6 (C18'), 21.5 (C12), 18.0 (C13); ν_{max} (film)/cm⁻¹ 2238 (alkyne), 1705 (broad, C=O ketone, C=O ester); ESI-MS calcd. for C₁₂H₁₆NaO₃ [M+Na]⁺ 231.0992, found 231.0991.

isopropyl 2-(3-hydroxycyclohex-1-en-1-yl)acrylate (**133**)



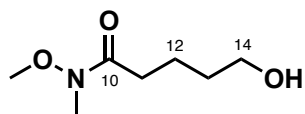
Hoveyda-Grubbs second-generation catalyst (4.2 mg, 6.7 mmol) was added to a solution of allylic alcohol **129** (28 mg, 0.13 mmol) in toluene (1 mL). The reaction mixture was warmed to 60 °C and stirred for 24 h, cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (20-40% EtOAc in petrol) to yield alcohol **133** as a colourless oil (21.8 mg, 79%). δ_{H} (500 MHz, CDCl_3) 5.98 (1H, app t, J 1.7, H_9), 5.84 (1H, s, $H_{19\text{A}}$), 5.57 (1H, s, $H_{19\text{B}}$), 5.10 (1H, septet, J 6.3, $H_{17'}$), 4.32-4.30 (1H, m, H_{10}), 2.23-2.09 (2H, m, H_{13}), 1.90 (1H, dtd, J 11.9, 5.9, 2.9, $H_{11\text{A}}$), 1.85-1.75 (2H, m, $H_{12\text{A}}$, OH), 1.66 (1H, app dddd, J 9.5, 7.2, 5.2, 2.2, $H_{12\text{B}}$), 1.59 (1H, dtd, J , 12.6, 6.4, 3.2, $H_{11\text{B}}$), 1.29 (6H, d, J 6.3, $H_{18'}$); δ_{C} (126 MHz, CDCl_3) 166.8 (C16), 143.2 (C15), 136.7 (C14), 130.0 (C9), 121.7 (C19), 68.4 (C17'), 66.1 (C10), 31.4 (C11), 26.7 (C13), 21.8 (C18'), 19.2 (C12); ν_{max} (film)/ cm^{-1} 3411 (O-H), 1716 (C=O); ESI-MS calcd. for $\text{C}_{12}\text{H}_{18}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 233.1148, found 233.1144.

7-isopropoxy-7-oxohept-5-ynoic acid (**135**)



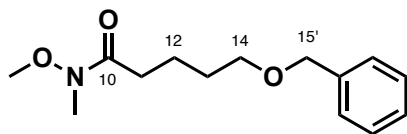
TEMPO (20 mg, 0.12 mmol) then (diacetoxyiodo)benzene (447 mg, 1.39 mmol) were added to a stirring solution of alcohol **134** (116 mg, 0.63 mmol) in H₂O:MeCN (1:1, 2 mL) at room temperature. The bright orange mixture was stirred at room temperature for 3 h, HCl_(aq) (1 M, 10 mL) added and the aqueous phase extracted with Et₂O (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (40-50% Et₂O in petrol (0.1% AcOH)) to yield carboxylic acid **135** as a colourless oil (124.2 mg, 100%). δ_{H} (400 MHz, CDCl₃) 11.36 (1H, br s, COOH), 5.05 (1H, septet, J 6.3, H17'), 2.50 (2H, t, J 7.3, H11), 2.42 (2H, t, J 7.0, H13), 1.89 (2H, quin, J 7.1, H12), 1.26 (6H, d, J 6.3, H18'); δ_{C} (101 MHz, CDCl₃) 179.0 (C10), 153.2 (C16), 87.1 (C14), 74.2 (C15), 69.8 (C17'), 32.5 (C11), 22.4 (C12), 21.6 (C18'), 17.9 (C13); ν_{max} (film)/cm⁻¹ 2240 (alkyne), 1709 (br, C=O ketone, C=O carboxylic acid); ESI-MS calcd. for C₁₀H₁₄NaO₄ [M+Na]⁺ 221.0784, found 221.0783.

5-hydroxy-*N*-methoxy-*N*-methylpentanamide (145)



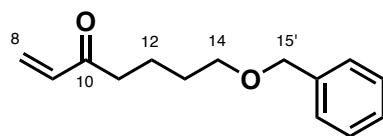
Trimethyl aluminium (2 M solution in hexanes, 97 mL, 193.9 mmol) was added *via* cannula to a stirring solution of *N,O*-dimethylhydroxylamine hydrochloride (12.28 g, 193.9 mmol) at -78°C in DCM (100 mL) over a period of 30 min. The mixture was warmed to room temperature and stirred for 20 h, cooled to -78°C and δ -valerolactone (6 mL, 64.7 mmol) in DCM (25 mL) was added slowly *via* cannula over 15 min. The mixture was warmed to room temperature and stirred for 5 h, diluted with DCM (30 mL) and Rochelle's Salt (sat., aq., 30 mL) was added slowly. The resulting biphasic solution was stirred vigorously for 16 h, the phases separated and the aqueous phase washed with CHCl_3 :IPA (3:1, 4 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0-5% MeOH in Et_2O) to yield Weinreb amide **145** as a colourless oil (9.54 g, 92%). δ_{H} (400 MHz, CDCl_3) 3.68 (3H, s, OCH_3), 3.64 (2H, q, J 6.4, H_{14}), 3.18 (3H, s, NCH_3), 2.51-2.43 (2H, m, H_{11}), 2.38-1.85 (1H, br s, OH), 1.78-1.68 (2H, m, H_{12}), 1.66-1.56 (2H, m, H_{13}); δ_{C} (126 MHz, CDCl_3) 174.7 (C_{10}), 62.1 (C_{14}), 61.2 (OCH_3), 32.3 (NCH_3), 32.2 (C_{11}), 31.3 (C_{13}), 20.3 (C_{12}); ν_{max} (film)/ cm^{-1} 3409 (O-H), 1638 (C=O); ESI-MS calcd. for $\text{C}_7\text{H}_{15}\text{NNaO}_3$ $[\text{M}+\text{Na}]^+$ 184.0944, found 184.0941. This data is in accordance with the literature.⁹⁸

5-(benzyloxy)-*N*-methoxy-*N*-methylpentanamide (**141**)



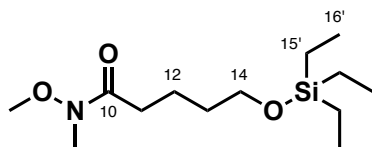
Benzyl bromide (3.94 mL, 33.1 mmol) and tetrabutylammonium iodide (0.85 g, 3.31 mmol) were added to a stirring solution of Weinreb amide **145** (1.78 g, 11 mmol) in THF (20 mL). The mixture was cooled to 0 °C and NaH (60 wt% dispersion in mineral oil, 0.88 g, 22.1 mmol) was added over a 1 h period. The mixture was stirred at 0 °C for 1 h and was then warmed to room temperature and stirred for 16 h. After this time MeOH (5 mL) was added dropwise followed by NH₄Cl (sat., aq., 30 mL). The phases were separated and the aqueous phase washed with DCM (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (20-30% EtOAc in petrol) to yield benzyl ether **141** as a pale yellow oil (2.65 g, 96%). δ_{H} (500 MHz, CDCl₃) 7.37-7.31 (4H, m, ArH), 7.30-7.24 (1H, m, ArH), 4.51 (2H, s, H_{15'}), 3.66 (3H, s, OCH₃), 3.51 (2H, t, J 6.2, H₁₄), 3.18 (3H, s, NCH₃), 2.46 (2H, t, J 7.1, H₁₁), 1.78-1.64 (4H, m, H₁₂, H₁₃); δ_{C} (126 MHz, CDCl₃) 174.5 (C₁₀), 138.6 (Ar), 128.3 (Ar), 127.6 (Ar), 127.5 (Ar), 72.9 (C_{15'}), 70.1 (C₁₄), 61.2 (OCH₃), 32.2 (NCH₃), 31.6 (C₁₁), 29.4 (C₁₃), 21.4 (C₁₂); ν_{max} (film)/cm⁻¹ 1660 (C=O); ESI-MS calcd. for C₁₄H₂₁NNaO₃ [M+Na]⁺ 274.1414, found 274.1409.

14-(benzyloxy)hept-8-en-10-one (**142**)



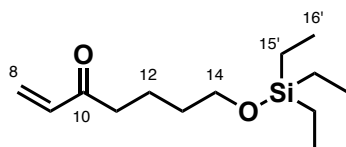
Vinylmagnesium bromide (1.0 M solution in THF, 1.59 mL, 1.59 mmol) was added dropwise to a stirring solution of Weinreb amide **141** (100 mg, 0.4 mmol) in THF (5 mL) at -78°C . The mixture was warmed to room temperature and stirred for 16 h. After this time the reaction was cooled to -78°C , diluted with DCM (100 mL) and ammonium chloride (sat., aq., 100 mL) was added. The mixture was stirred at -78°C for 30 min, 0°C for 30 min and then at room temperature for 60 min. The phases were separated and the aqueous phase washed with DCM (3×25 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5-10% EtOAc in petrol) to yield enone **142** as a pale yellow oil (68 mg, 78%). δ_{H} (500 MHz, CDCl_3) 7.37-7.33 (4H, m, ArH), 7.31-7.27 (1H, m, ArH), 6.35 (1H, dd, J 17.7, 10.6, H_9), 6.21 (1H, d, J 17.7, $H_{8\text{trans}}$), 5.82 (1H, d, J 10.6, $H_{8\text{cis}}$), 4.50 (2H, s, $H_{15'}$), 3.50 (2H, t, J 6.3, H_{14}), 2.62 (2H, t, J 7.3, H_{11}), 1.77-1.71 (2H, m, H_{13}), 1.68-1.63 (2H, m, H_{12}); δ_{C} (126 MHz, CDCl_3) 200.7 (C10), 138.5 (Ar), 136.5 (C9), 128.3 (Ar), 128.0 (C8), 127.6 (Ar), 127.5 (Ar), 72.9 (C15'), 70.0 (C14), 39.3 (C11), 29.2 (C13), 20.7 (C12); ν_{max} (film)/ cm^{-1} 1699 (C=O); ESI-MS calcd. for $\text{C}_{14}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 241.1199, found 241.1196.

***N*-methoxy-*N*-methyl-5-((triethylsilyl)oxy)pentanamide**



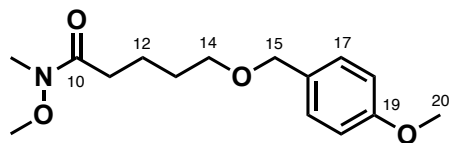
Triethylamine (0.56 mL, 4.04 mmol) was added to a stirring solution of alcohol **145** (260 mg, 1.61 mmol) and DMAP (2.0 mg, 0.16 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and chlorotriethylsilane (0.54 mL, 3.23 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 16 h, diluted with Et₂O (20 mL) and pH 7 buffer (20 mL) was added. The organics were extracted and the aqueous phase washed with Et₂O (3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5-20% EtOAc in petrol) to yield the silyl ether as a colourless oil (440 mg, 99%). δ_{H} (400 MHz, CDCl₃) 3.61 (3H, s, OCH₃), 3.56 (2H, t, J 6.4, H₁₄), 3.10 (3H, s, NCH₃), 2.38 (2H, t, J 7.5, H₁₁), 1.69-1.58 (2H, m, H₁₂), 1.52 (2H, app sextet, J 7.2, H₁₃), 0.89 (9H, t, J 8.0, H_{16'}), 0.52 (6H, q, J 7.9, H_{15'}); δ_{C} (101 MHz, CDCl₃) 174.6 (C₁₀), 62.7 (C₁₄), 61.2 (OCH₃), 32.5 (C₁₃), 32.3 (NCH₃), 31.6 (C₁₁), 21.1 (C₁₂), 6.7 (C_{15'}), 4.4 (C_{16'}); ν_{max} (film)/cm⁻¹ 1671 (C=O); ESI-MS calcd. for C₁₃H₂₉NNaO₃Si [M+Na]⁺ 298.1809, found 298.1811.

7-((triethylsilyl)oxy)hept-1-en-3-one (**146**)



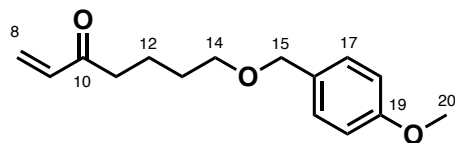
Vinylmagnesium bromide (1.0 M in THF, 5.8 mL, 5.8 mmol) was added dropwise to a stirring solution of silyl ether (400 mg, 1.45 mmol) in THF (15 mL) at -78°C . The mixture was warmed to room temperature and stirred for 16 h, cooled to -78°C , diluted with DCM (200 mL) and ammonium chloride (sat., aq., 200 mL) was added slowly. The mixture was stirred at -78°C for 30 min, 0°C for 30 min and then at room temperature for 60 min. The phases were separated and the aqueous phase washed with DCM (3 x 50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (2-5% EtOAc in petrol) to yield enone **146** as a colourless oil (326.4 mg, 93%). δ_{H} (500 MHz, CDCl_3) 6.35 (1H, dd, J 17.7, 10.6, H_9), 6.21 (1H, dd, J 17.7, 1.2, $H_{8\text{trans}}$), 5.81 (1H, dd, J 10.6, 1.2, $H_{8\text{cis}}$), 3.62 (2H, t, J 6.4, H_{14}), 2.61 (2H, t, J 7.4, H_{11}), 1.73-1.65 (2H, m, H_{12}), 1.58-1.52 (2H, m, H_{13}), 0.95 (9H, t, J 8.0, $H_{16'}$), 0.59 (6H, q, J 8.0, $H_{15'}$); δ_{C} (126 MHz, CDCl_3) 200.8 (C10), 136.5 (C9), 127.9 (C8), 62.5 (C14), 39.3 (C11), 32.3 (C13), 20.5 (C12), 6.8 (C15'), 4.4 (C16'); ν_{max} (film)/ cm^{-1} 1684 (C=O); ESI-MS calcd. for $\text{C}_{13}\text{H}_{26}\text{NaO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 265.1594, found 265.1597.

***N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*-methylpentanamide**



4-Methoxybenzyl trichloroacetimidate (0.4 mL, 41.94 mmol) was added dropwise to a stirring solution of alcohol **145** (0.26 g, 1.61 mmol) and (±)-camphor-10-sulfonic acid (23 mg, 97 μmol) in DCM (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h, diluted with DCM (10 mL) and sodium bicarbonate (sat., aq., 20 mL) was added. The phases were separated and the aqueous phase washed with DCM (3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-40% EtOAc in petrol) to yield the PMB-ether as a pale yellow oil (340 mg, 75%). δ_{H} (400 MHz, CDCl_3) 7.23 (2H, d, J 8.7, $H_{17'}$), 6.84 (2H, d, J 8.7, $H_{18'}$), 4.40 (2H, s, $H_{15'}$), 3.77 (3H, s, $H_{20'}$), 3.63 (3H, s, OCH_3), 3.45 (2H, t, J 6.2, H_{14}), 3.14 (3H, s, NCH_3), 2.42 (2H, t, J 7.1, H_{11}), 1.74-1.59 (4H, m, H_{12} , H_{13}); δ_{C} (101 MHz, CDCl_3) 174.4 (C_{10}), 159.1 ($\text{C}_{19'}$), 130.7 ($\text{C}_{16'}$), 129.2 ($\text{C}_{17'}$), 113.7 ($\text{C}_{18'}$), 72.5 ($\text{C}_{15'}$), 69.8 (C_{14}), 61.2 (OCH_3), 55.2 ($\text{C}_{20'}$), 32.1 (NCH_3), 31.6 (C_{11}), 29.4 (C_{13}), 21.4 (C_{12}); ν_{max} (film)/ cm^{-1} 1659 ($\text{C}=\text{O}$); ESI-MS calcd. for $\text{C}_{15}\text{H}_{23}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 304.1519, found 304.1529.

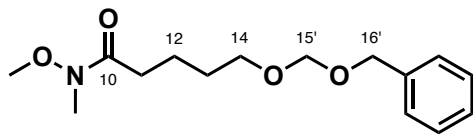
7-((4-methoxybenzyl)oxy)hept-1-en-3-one (148)



Vinylmagnesium bromide (1.0 M in THF, 1.0 mL, 1.0 mmol) was added dropwise to a stirring solution of PMB-ether (69 mg, 0.25 mmol) in THF (5 mL) at -78°C . The mixture was warmed to room temperature and stirred for 16 h, cooled to -78°C , diluted with DCM (100 mL) and ammonium chloride (sat., aq., 100 mL) was added slowly. The mixture was stirred at -78°C for 30 min, 0°C for 30 min and then at room temperature for 60 min. The phases were separated and the aqueous phase washed with DCM (3 x 25 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0-20% EtOAc in petrol) to yield enone **148** as a colourless oil (39.6 mg, 65%).

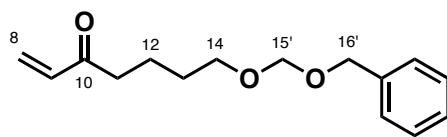
δ_{H} (400 MHz, CDCl_3) 7.26 (2H, d, J 8.2, $H_{17'}$), 6.88 (2H, d, J 8.5, $H_{18'}$), 6.35 (1H, dd, J 17.7, 10.5, H_9), 6.18 (1H, dd, J 17.6, 0.6, $H_{8\text{trans}}$), 5.81 (1H, dd, J 10.6, 0.5, $H_{8\text{cis}}$), 4.43 (2H, s, $H_{15'}$), 3.81 (3H, s, $H_{20'}$), 3.46 (2H, t, J 6.2, H_{14}), 2.61 (2H, t, J 7.2, H_{11}), 1.76-1.68 (2H, m, H_{12}), 1.68-1.60 (2H, m, H_{13}); δ_{C} (101 MHz, CDCl_3) 200.8 (C10), 159.1 (Ar (4° carbon)), 136.5 (C9), 130.6 (Ar (4° carbon)), 129.3 (Ar), 128.0 (C8), 113.8 (Ar), 72.6 (C15'), 69.7 (C14), 55.3 (C20'), 39.2 (C11), 29.2 (C13), 20.7 (C12); ν_{max} (film)/ cm^{-1} 1680 (C=O); ESI-MS calcd. for $\text{C}_{15}\text{H}_{20}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 271.1305, found 271.1305.

5-((benzyloxy)methoxy)-*N*-methoxy-*N*-methylpentanamide



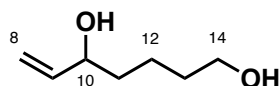
Benzyl chloromethyl ether (0.25 mL, 1.83 mmol) was added dropwise to a stirring solution of alcohol **145**, *N,N'*-diisopropylethylamine (0.43 mL, 2.49 mmol) and tetrabutylammonium iodide (123 mg, 0.33 mmol) in THF (9 mL) at room temperature. The mixture was refluxed at 70 °C for 14 h, cooled to room temperature, diluted with Et₂O (50 mL) and sodium bicarbonate (sat., aq., 20 mL) was added. The phases were separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30-50% EtOAc in petrol) to yield the BOM-ether as a pale yellow oil (400 mg, 90%). δ_{H} (500 MHz, CDCl₃) 7.35-7.25 (5H, m, ArH), 4.74 (2H, s, H16'), 4.59 (2H, s, H15'), 3.65 (3H, s, OCH₃), 3.60 (2H, t, J 6.4, H14), 3.16 (3H, s, NCH₃), 2.45 (2H, t, J 7.2, H11), 1.76-1.70 (2H, m, H12), 1.68-1.63 (2H, m, H13); δ_{C} (126 MHz, CDCl₃) 174.3 (C10), 137.9 (Ar (4°)), 128.4 (Ar), 127.8 (Ar), 127.6 (Ar), 94.6 (C16'), 69.2 (C15'), 67.7 (C14), 61.2 (OCH₃), 32.1 (NCH₃), 31.5 (C11), 29.4 (C13), 21.4 (C12); ν_{max} (film)/cm⁻¹ 1664 (C=O); ESI-MS calcd. for C₁₅H₂₃NNaO₄ [M+Na]⁺ 304.1519, found 304.1520.

(benzyloxy)methoxyhept-8-en-10-one (147)



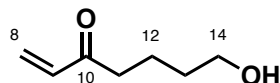
Vinyl magnesium bromide (1.0 M in THF, 1.1 mL, 1.1 mmol) was added dropwise to a stirring solution of BOM-ether (72.1 mg, 0.27 mmol) in THF (5 mL) at -78°C . The mixture was warmed to room temperature and stirred for 16 h, cooled to -78°C , diluted with DCM (200 mL) and ammonium chloride (sat. aq., 100 mL) was added. The mixture was stirred at -78°C for 30 min, 0°C for 30 min and then at room temperature for 60 min. The phases were separated and the aqueous phase washed with DCM (3 x 25 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5-15% EtOAc in petrol) to yield enone **147** as a colourless oil (55.4 mg, 83%). δ_{H} (400 MHz, CDCl_3) 7.36-7.27 (5H, m, ArH), 6.36 (1H, dd, J 17.7, 10.5, H_9), 6.22 (1H, dd, J 17.6, 0.7, $H_{8\text{trans}}$), 5.83 (1H, dd, J 10.5, 0.7, $H_{8\text{cis}}$), 4.76 (2H, s, $H_{16'}$), 4.61 (2H, s, $H_{15'}$), 3.61 (2H, t, J 6.2, H_{14}), 2.63 (2H, t, J 7.2, H_{11}), 1.77-1.70 (2H, m, H_{12}), 1.67-1.60 (2H, m, H_{13}); δ_{C} (101 MHz, CDCl_3) 200.6 (C_{10}), 137.9 (Ar (4°)), 136.5 (C_9), 128.4 (Ar), 128.0 (C_8), 127.9 (Ar), 127.7 (Ar), 94.6 ($\text{C}_{16'}$), 69.3 ($\text{C}_{15'}$), 67.6 (C_{14}), 39.2 (C_{11}), 29.2 (C_{13}), 20.7 (C_{12}); ν_{max} (film)/ cm^{-1} 1710 ($\text{C}=\text{O}$); ESI-MS calcd. for $\text{C}_{15}\text{H}_{20}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 271.1305, found 271.1312.

hept-6-ene-1,5-diol (**150**)



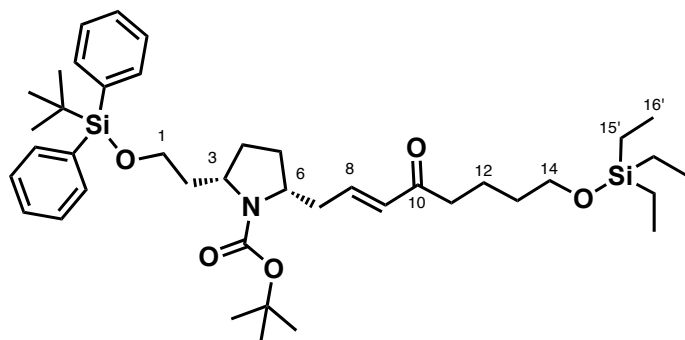
HCl_(aq) (0.2 M, 3 mL) was added to neat 3,4-dihydro-2*H*-pyran (1 mL, 10.9 mmol) at room temperature and stirred for 1.5 h, diluted with H₂O (10 mL) and extracted with DCM (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure to yield crude tetrahydro-2*H*-pyran-2-ol as a colourless oil (0.995 g, 30:1 equilibrium mixture of hemiacetal:aldehyde isomers by ¹H-NMR spectroscopy) which was used without further purification. Vinylmagnesium bromide (1.0 M in THF, 24.4 mL, 24.4 mmol) was added dropwise to a solution of crude tetrahydro-2*H*-pyran-2-ol (0.995 g) in THF (10 mL) at -78 °C. The reaction was slowly warmed to room temperature and stirred for 16 h, diluted with DCM (20 mL) and HCl_(aq) (0.2 M, 10 mL) was added. The mixture was filtered and washed with DCM (3 x 20 mL). The combined organic filtrates were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (40-70% EtOAc in petrol) to yield heptene diol **150** as a colourless oil (823 mg, 65% over 2 steps). δ_{H} (400 MHz, CDCl₃) 5.85 (1H, ddd, *J* 17.1, 10.6, 6.3, *H*₉), 5.21 (1H, d, *J* 17.2, *H*_{8_{trans}}), 5.09 (1H, d, *J* 10.4, *H*_{8_{cis}}), 4.09 (1H, q, *J* 6.1, *H*₁₀), 3.62 (2H, t, *J* 6.3, *H*₁₄), 2.51 (s, 2H, 2 x OH), 1.62-1.36 (6H, m, *H*₁₂, *H*₁₃, *H*₁₄); δ_{C} (101 MHz, CDCl₃) 141.2 (C₉), 114.6 (C₈), 72.9 (C₁₀), 62.4 (C₁₄), 36.5 (C₁₁), 32.3 (C₁₃), 21.5 (C₁₂); ν_{max} (film)/cm⁻¹ 3317 (br OH), 1644 (C=C); ESI-MS calcd. for C₇H₁₄NaO₂ [M+Na]⁺ 153.0886, found 153.0882.

7-hydroxyhept-1-en-3-one (**151**)



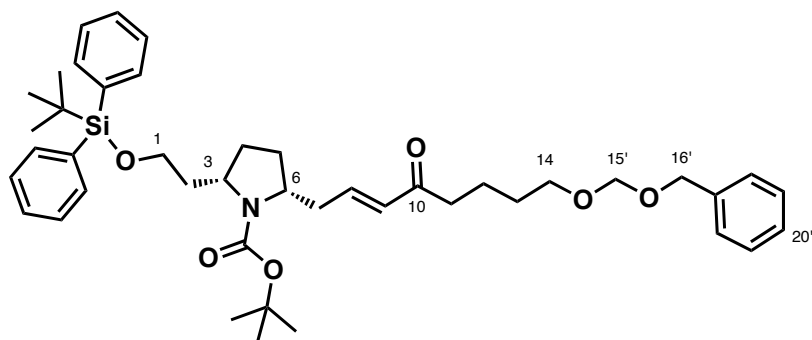
Pre-activated manganese dioxide (1.34 g, 23.1 mmol) was added to a stirring solution of heptene diol **150** (100 mg, 0.77 mmol) in DCM (50 mL) at room temperature. The mixture was stirred for 13 h, before being filtered through a short pad of Celite®. The cake was washed with DCM (3 x 50 mL) and the filtrate concentrated under reduced pressure. The crude material was purified by silica gel chromatography (60-70% Et₂O in petrol) to yield enone **151** as a colourless oil (63 mg, 64%). δ_{H} (400 MHz, CDCl₃) 6.34 (1H, dd, J 17.7, 10.4, *H*₉), 6.21 (1H, dd, J 17.7, 1.3, *H*_{8_{trans}}), 5.82 (1H, dd, J 10.4, 1.3, *H*_{8_{cis}}), 3.62 (2H, t, J 6.3, *H*₁₄), 2.63 (2H, t, J 7.1, *H*₁₁), 2.14 (1H, br s, OH), 1.74-1.66 (2H, m, *H*₁₂), 1.60-1.53 (2H, m, *H*₁₃); δ_{C} (101 MHz, CDCl₃) 201.0 (C10), 136.4 (C9), 128.5 (C8), 62.2 (C14), 39.1 (C11), 32.1 (C13), 19.9 (C12); ν_{max} (film)/cm⁻¹ 3410 (O-H), 1679 (C=O); ESI-MS calcd. for C₇H₁₂NaO₂ [M+Na]⁺ 151.0730, found 151.0725.

(2*S*,5*R*)-*tert*-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-((*E*)-4-oxo-8-((triethylsilyl)oxy)oct-2-en-1-yl)pyrrolidine-1-carboxylate (154**)**



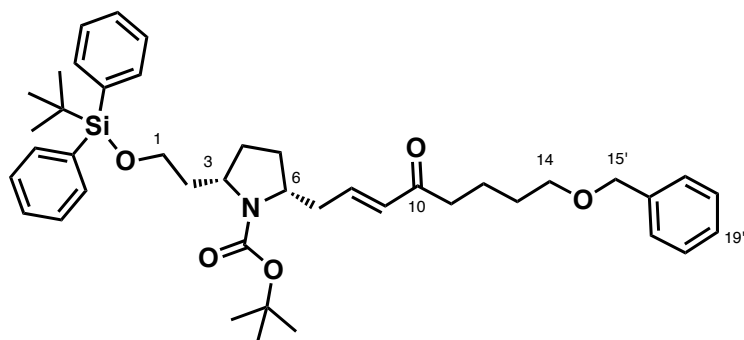
Hoveyda-Grubbs second-generation catalyst (27 mg, 43.1 μmol) was added to a solution of allyl pyrrolidine **82** (425 mg, 0.86 mmol) and enone **146** (292 mg, 1.21 mmol) in DCM (5 mL) in a microwave vial. The reaction mixture was stirred at 70 °C under microwave irradiation for 6 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (1-7% EtOAc in petrol) to yield pyrrolidine enone **154** as a pale brown oil (592 mg, 97%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.79-7.74 (3H, m, ArH), 7.27-7.26 (4H, m, ArH), 7.10-7.00 (3H, m, ArH), 6.71 (1H, dt, J 15.8, 7.6, H_8), 6.04 (1H, d, J 15.8, H_9), 3.92-3.88 (1H, m, H_6), 3.86-3.76 (3H, m, H_1 , H_3), 3.60 (2H, t, J 6.3, H_{14}), 2.55 (1H, dt, J 13.3, 6.2, H_{7A}), 2.39 (2H, t, J 7.2, H_{11}), 2.22 (1H, dq, J 12.7, 6.3, H_{2A}), 2.10-2.07 (1H, m, H_{7B}), 1.74 (2H, quin, J 7.4, H_{12}), 1.68-1.49 (6H, m, H_{2B} , H_{4A} , H_5 , H_{13}), 1.43 (9H, s, $t\text{Bu}$ (Boc)), 1.37-1.30 (1H, m, H_{4B}), 1.20 (9H, s, $t\text{Bu}$ (silyl ether)), 1.02 (3H, t, J 7.9, $H_{16'}$), 0.62 (2H, q, J 7.9, $H_{15'}$); δ_{C} (126 MHz, d_8 -toluene, 363 K) 197.8 (C10), 154.6 (Boc), 142.2 (C8), 137.7 (Ar), 135.9 (Ar), 134.6 (Ar, 4° carbon), 132.4 (C9), 129.8 (Ar), 79.0 ($t\text{Bu}$ (Boc, 4° carbon)), 62.9 (C14), 62.6 (C1), 57.9 (C6), 56.7 (C3), 40.1 (C11), 39.5 (C2), 39.1 (C7), 33.0 (C13), 30.1 (C5), 29.6 (C4), 28.5 ($t\text{Bu}$ (Boc)), 27.2 ($t\text{Bu}$ (silyl ether)), 21.1 (C12), 19.4 ($t\text{Bu}$ (silyl ether, 4° carbon)), 6.8 (C16'), 5.1 (C15'); ν_{max} (film)/ cm^{-1} 1692 (br, C=O ketone and carbamate), 1632 (C=C); ESI-MS calcd. for $\text{C}_{41}\text{H}_{65}\text{NNaO}_5\text{Si}_2$ $[\text{M}+\text{Na}]^+$ 730.4293, found 730.4294; $[\alpha]_{\text{D}}^{25} +9.0$ (c 1.0, CHCl_3).

(2*R*,5*S*)-*tert*-butyl-2-((*E*)-8-((benzyloxy)methoxy)-4-oxooct-2-en-1-yl)-5-((*tert*-butyldiphenylsilyl)oxy)ethyl)pyrrolidine-1-carboxylate (152**)**



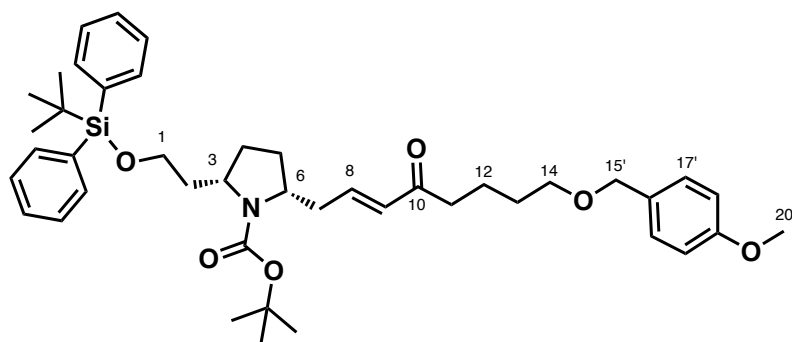
Hoveyda-Grubbs second-generation catalyst (1 mg, 1.6 μmol) was added to a solution of allyl pyrrolidine **82** (16 mg, 32 μmol) and enone **147** (12 mg, 49 μmol) in DCM (1 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}\text{C}$ under microwave irradiation for 6 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (10-40% Et_2O in petrol) to yield pyrrolidine enone **152** as a pale brown oil (21.5 mg, 93%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.79-7.76 (4H, m, ArH), 7.29-7.24 (8H, m, ArH), 7.17 (2H, t, J 7.4, ArH), 7.09-7.06 (1H, m, ArH), 6.71 (1H, dt, J 15.8, 7.4, H8), 6.03 (1H, app dt, J 15.8, 1.4, H9), 4.62 (2H, s, H15'), 4.51 (2H, s, H16'), 3.93 (1H, m, H6), 3.85-3.76 (3H, m, H1, H3), 3.48 (2H, t, J 6.4, H14), 2.55 (1H, dt, J 13.3, 6.3, H7_A), 2.36 (2H, t, J 7.2, H11), 2.23 (1H, dq, J 12.8, 6.3, H2_A), 2.13-2.07 (1H, m, H7_B), 1.72 (2H, quin, J 7.4, H12), 1.65-1.52 (6H, m, H2_B, H4_A, H5, H13), 1.43 (9H, s, *t*Bu (Boc)), 1.38-1.30 (1H, m, H4_B), 1.18 (9H, s, *t*Bu (silyl ether)); δ_{C} (126 MHz, d_8 -toluene, 363 K) 197.7 (C10), 154.6 (Boc), 142.3 (C8), 139.1 (Ar), 137.7 (Ar (silyl ether)), 136.0 (Ar (silyl ether)), 134.6 (Ar (silyl ether, 4 $^{\circ}$ carbon)), 132.4 (C9), 129.8 (Ar (silyl ether)), 128.4 (Ar), 128.1 (Ar), 127.5 (Ar), 95.0 (C15'), 79.0 (*t*Bu (Boc, 4 $^{\circ}$ carbon)), 69.6 (C16'), 68.0 (C14), 62.6 (C1), 57.9 (C6), 56.7 (C3), 40.0 (C11), 39.5 (C2), 39.1 (C7), 30.0 (C5), 29.8 (C4), 29.6 (C13), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 21.3 (C12), 19.4 (*t*Bu (silyl ether, 4 $^{\circ}$ carbon)); ν_{max} (film)/ cm^{-1} 1690 (br, C=O ketone and carbamate), 1630 (C=C); ESI-MS calcd. for $\text{C}_{43}\text{H}_{59}\text{NNaO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 736.4004, found 736.4002; $[\alpha]_{\text{D}}^{23}$ +8.0 (*c* 0.6, CHCl_3).

(2*R*,5*S*)-*tert*-butyl-2-((*E*)-8-(benzyloxy)-4-oxooct-2-en-1-yl)-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)pyrrolidine-1-carboxylate (143**)**



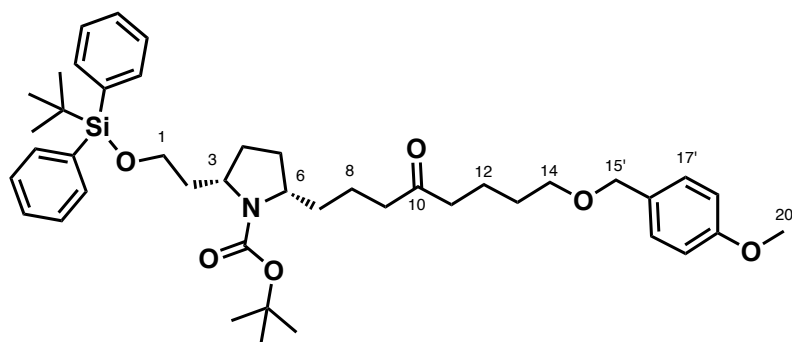
Hoveyda-Grubbs second-generation catalyst (0.7 mg, 1.1 μmol) was added to a solution of allyl pyrrolidine **82** (11 mg, 22 μmol) and enone **142** (7 mg, 33 μmol) in DCM (1 mL) in a microwave vial. The reaction mixture was stirred at 70 °C under microwave irradiation for 6 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (1-10% EtOAc in petrol) to yield pyrrolidine enone **143** as a pale brown oil (14.5 mg, 95%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.79-7.74 (4H, m, ArH), 7.27-7.22 (8H, m, ArH), 7.17 (2H, t, J 7.5, $H_{18'}$), 7.08-7.06 (1H, m, ArH), 6.70 (1H, dt, J 15.5, 7.6, H_8), 6.02 (1H, d, J 15.8, H_9), 4.34 (2H, s, $H_{15'}$), 3.93-3.88 (1H, m, H_6), 3.86-3.75 (3H, m, H_1 , H_3), 3.35 (2H, t, J 6.3, H_{14}), 2.54 (1H, dt, J 13.2, 6.4, H_{7A}), 2.37 (2H, t, J 7.2, H_{11}), 2.22 (1H, dq, J 12.7, 6.4, H_{2A}), 2.10-2.02 (1H, m, H_{7B}), 1.73 (2H, quin, J 7.4, H_{12}), 1.67-1.51 (6H, m, H_{2B} , H_{4A} , H_5 , H_{13}), 1.43 (9H, s, $t\text{Bu}$ (Boc)), 1.36-1.30 (1H, m, H_{4B}), 1.18 (9H, s, $t\text{Bu}$ (silyl ether)); δ_{C} (126 MHz, d_8 -toluene, 363 K) 197.8 (C_{10}), 154.7 (Boc), 142.2 (C_8), 137.2 (Ar, silyl ether), 135.9 (Ar, silyl ether), 134.2 (Ar, silyl ether, 4° carbon), 129.8 (Ar, silyl ether), 132.4 (C_9), 129.8 (Ar), 128.3 (Ar), 128.1 (Ar), 127.9 (Ar), 79.0 (Boc ($t\text{Bu}$, 4° carbon)), 73.0 ($C_{15'}$), 70.4 (C_{14}), 62.6 (C_1), 57.9 (C_6), 56.7 (C_3), 40.1 (C_{11}), 39.5 (C_2), 39.1 (C_7), 30.0 (C_5), 29.8 (C_4), 29.2 (C_{13}), 28.6 ($t\text{Bu}$ (Boc)), 27.2 ($t\text{Bu}$ (silyl ether)), 21.4 (C_{12}), 19.4 ($t\text{Bu}$ (silyl ether, 4° carbon)); ν_{max} (film)/ cm^{-1} 1690 (br, C=O ketone and carbamate), 1631 (C=C); ESI-MS calcd. for $\text{C}_{42}\text{H}_{57}\text{NNaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 706.3898, found 706.3907; $[\alpha]_{\text{D}}^{23} +6.2$ (c 0.35, CHCl_3).

(2*S*,5*R*)-*tert*-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-((*E*)-8-((4-methoxybenzyl)oxy)-4-oxooct-2-en-1-yl)pyrrolidine-1-carboxylate (153**)**



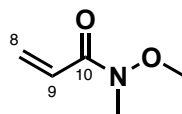
Hoveyda-Grubbs second-generation catalyst (17 mg, 26.3 μmol) was added to a solution of allyl pyrrolidine **82** (259 mg, 0.53 mmol) and enone **148** (182 mg, 0.74 mmol) in DCM (3 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}\text{C}$ under microwave irradiation for 6 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (0-10% EtOAc in petrol) to yield pyrrolidine enone **153** as a pale brown oil (359 mg, 96%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.78-7.74 (4H, m, ArH (silyl ether)), 7.29-7.23 (6H, m, ArH (silyl ether)), 7.18 (2H, d, J 8.7, $H_{17'}$), 6.78 (2H, d, J 8.7, $H_{18'}$), 6.69 (1H, dt, J 15.8, 7.5, H_8), 6.02 (1H, dt, J 16.0, 1.5, H_9), 4.32 (2H, s, $H_{15'}$), 3.90 (1H, tt, J 8.0, 4.1, H_6), 3.84-3.74 (3H, m, H_1 , H_3), 3.45 (3H, s, $H_{20'}$), 3.36 (2H, t, J 6.3, H_{14}), 2.56-2.51 (1H, m, H_{7A}), 2.38 (2H, t, J 7.2, H_{11}), 2.25-2.18 (1H, m, H_{2A}), 2.14-2.08 (1H, m, H_{7B}), 1.74 (2H, quin, J 7.5, H_{12}), 1.66-1.50 (6H, m, H_{2B} , H_{4A} , H_5 , H_{13}), 1.42 (9H, s, $t\text{Bu}$ (Boc)), 1.38-1.29 (1H, m, H_{4B}), 1.17 (9H, s, $t\text{Bu}$ (silyl ether)); δ_{C} (126 MHz, d_8 -toluene, 363 K) 197.5 (C_{10}), 159.4 ($\text{C}_{19'}$), 154.2 (Boc), 141.9 (C_8), 137.1 (Ar (silyl ether)), 135.5 (Ar (silyl ether)), 134.2 (Ar (silyl ether, 4° carbon), 132.1 (C_9), 131.3 ($\text{C}_{16'}$), 129.4 (Ar (silyl ether)), 128.7 ($\text{C}_{17'}$), 113.8 ($\text{C}_{18'}$), 78.6 (Boc (4° carbon)), 72.4 ($\text{C}_{15'}$), 69.7 (C_{14}), 62.2 (C_1), 57.5 (C_6), 56.3 (C_3), 54.5 ($\text{C}_{20'}$), 39.7 (C_{11}), 39.1 (C_2), 38.7 (C_7), 29.6 (C_5), 29.5 (C_4), 29.2 (C_{13}), 28.2 ($t\text{Bu}$ (Boc)), 26.9 ($t\text{Bu}$ (silyl ether)), 21.1 (C_{12}), 19.1 ($t\text{Bu}$ (silyl ether, 4° carbon)); ν_{max} (film)/ cm^{-1} 1689 (br, C=O ketone and carbamate), 1629 (C=C); ESI-MS calcd. for $\text{C}_{43}\text{H}_{59}\text{NNaO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 736.4004, found 736.4004; $[\alpha]_{\text{D}}^{23} +7.7$ (c 0.86, CHCl_3).

(2*S*,5*S*)-*tert*-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-(8-((4-methoxybenzyl)oxy)-4-oxooctyl)pyrrolidine-1-carboxylate



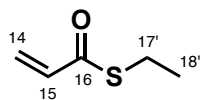
Palladium on carbon (24 mg, 10 wt% Pd) was added to a stirring solution of pyrrolidine enone **153** (239 mg, 0.34 mmol) in EtOH (5 mL). The resulting mixture was degassed (x 3) with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered through a short plug of Celite®. The cake was washed with DCM (3 x 10 mL) and the organic filtrates concentrated under reduced pressure. The crude material was purified by silica gel chromatography (1-10% EtOAc in petrol) to yield the keto-pyrrolidine as a colourless oil (240 mg, 76%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.80-7.75 (4H, m, ArH (silyl ether)), 7.29-7.26 (6H, m, ArH (silyl ether)), 7.18 (2H, d, J 8.6, $H_{17'}$), 6.78 (2H, d, J 8.6, $H_{18'}$), 4.33 (2H, s, $H_{15'}$), 3.96-3.91 (1H, m, H_6), 3.87-3.79 (3H, m, H_1 , H_3), 3.44 (3H, s, $H_{20'}$), 3.35 (2H, t, J 6.2, H_{14}), 2.30-2.23 (1H, m, H_{2A}), 2.16 (2H, t, J 7.2, H_{11}), 2.12 (2H, dt, J 4.4, 2.2, H_9), 1.82-1.74 (1H, m, H_{7A}), 1.71-1.29 (20H, m, H_{2B} , H_4 , H_5 , H_8 , H_{12} , H_{13} , $t\text{Bu}$ (Boc)), 1.28-1.20 (1H, m, H_{7B}), 1.18 (9H, s, $t\text{Bu}$ (silyl ether)); δ_{C} (126 MHz, d_8 -toluene, 363 K) 208.2 (C10), 159.6 (C19'), 154.6 (Boc), 137.2 (Ar (silyl ether)), 136.0 (Ar (silyl ether)), 134.3 (Ar (silyl ether, 4° carbon)), 131.4 (C16'), 129.9 (Ar (silyl ether)), 129.2 (C17'), 114.0 (C18'), 78.5 (Boc (4° carbon)), 72.7 (C15'), 70.0 (C14), 62.5 (C1), 58.3 (C6), 56.4 (C3), 54.6 (C20'), 42.38 (C11), 42.36 (C9), 39.6 (C2), 35.8 (C7), 30.3 (C4), 30.1 (C13), 29.8 (C5), 28.6 ($t\text{Bu}$ (Boc)), 27.2 ($t\text{Bu}$ (silyl ether)), 23.2 (C12), 21.1 (C8), 19.5 ($t\text{Bu}$ (silyl ether, 4° carbon)); ν_{max} (film)/ cm^{-1} 1713 (C=O, ketone), 1689 (C=O, Boc); ESI-MS calcd. for $\text{C}_{43}\text{H}_{61}\text{NNaO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 738.4160, found 738.4163; $[\alpha]_{\text{D}}^{23} +5.9$ (c 0.4, CHCl_3).

***N*-methoxy-*N*-methylacrylamide (164)**



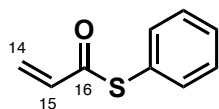
N,N-Dimethylhydroxylamine hydrochloride (3.6 g, 36.9 mmol) was added to a suspension of sodium bicarbonate (6.2 g, 73.8 mmol) in DCM (100 mL) and stirred at room temperature for 10 min. The resulting mixture was cooled to 0 °C and stirred vigorously whilst acryloyl chloride (3 mL, 36.9 mmol) was added slowly over a period of 10 min. During this time a sustained release of carbon dioxide occurred. The reaction mixture was then warmed to room temperature and stirred for 60 min before sodium sulfate was added (50 g). The reaction mixture was stirred vigorously for 5 min and filtered to yield acrylamide **164** as a pungent colourless liquid (4.17 g, 98%). δ_{H} (400 MHz, CDCl_3) 6.71 (1H, dd, J 17.1, 10.4, H_9), 6.40 (1H, dd, J 17.1, 2.0, $H_{8\text{trans}}$), 5.73 (1H, dd, J 10.4, 2.0, $H_{8\text{cis}}$), 3.69 (3H, s, OCH_3), 3.24 (3H, s, NCH_3); δ_{C} (101 MHz, CDCl_3) 166.4 (C10), 128.9 (C8), 125.9 (C9), 61.7 (OCH_3), 32.3 (NCH_3); ν_{max} (film)/ cm^{-1} 1659 (C=O); low resolution ESI-MS 138.05 $[\text{M}+\text{Na}]^+$. This data is in accordance with the literature.⁹⁹

S-ethyl prop-2-enethioate (**175**)



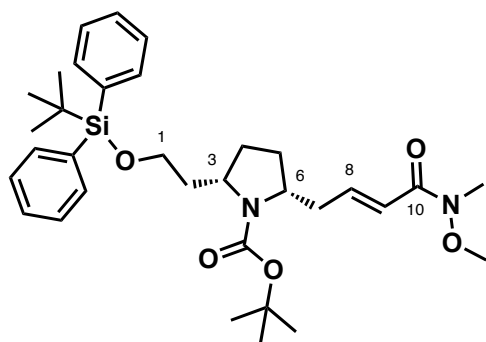
A 0 °C solution of ethanethiol (8.19 mL, 110 mmol) in ethanol (20 mL) was transferred *via* cannula over 30 min to a solution of lead (II) acetate (21 g, 55.4 mmol) in ethanol (40 mL) and H₂O (60 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h before the yellow solid was collected *via* suction filtration. The solids were washed sequentially with H₂O (100 mL), ethanol (100 mL) and Et₂O (100 mL) to yield lead (II) ethylsulfide as a crude yellow solid (16.53 g). Acryloyl chloride (1.23 mL, 15.12 mmol) was added over 1 h to a 0 °C suspension of crude lead (II) ethylsulfide (2.74 g) in Et₂O (20 mL). The resulting mixture was warmed to room temperature and stirred for 1 h, then filtered and the solids washed with Et₂O (2 x 15 mL). Et₂O was distilled from the combined organic filtrates and the product was then distilled under reduced pressure (65 °C, 20 mmHg) to yield ethyl thioacrylate **175** as a pungent clear liquid (1.30 g, 74%). δ_{H} (400 MHz, CDCl₃) 6.42-6.28 (1H, m, *H*₁₅), 6.30 (1H, dd, *J*, 17.2, 1.6, *H*_{14trans}), 5.67 (1H, dd, *J* 9.8, 1.6, *H*_{14cis}), 2.97 (2H, q, *J* 7.4, *H*_{17'}), 1.30 (3H, t, *J* 7.4, *H*_{18'}); δ_{C} (101 MHz, CDCl₃) 190.5 (C₁₆), 135.1 (C₁₅), 126.1 (C₁₄), 23.2 (C_{17'}), 14.7 (C_{18'}); ν_{max} (film)/cm⁻¹ 1739 (C=O); FI-MS calcd. for C₅H₈OS [M]⁺ 116.0296, found 116.0299. This data is in accordance with the literature.¹⁰⁰

S-phenyl prop-2-enethioate (**177**)



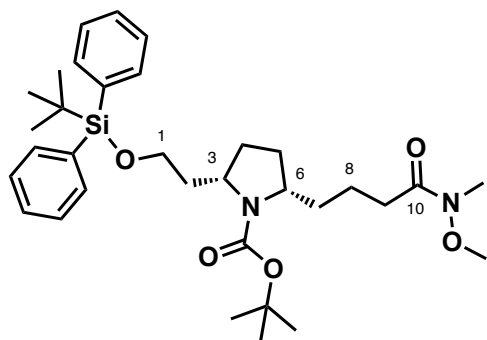
A 0 °C solution of thiophenol (5.38 mL, 52.7 mmol) in ethanol (10 mL) was transferred *via* cannula over 30 min to a solution of lead (II) acetate (10 g, 26.4 mmol) in ethanol (20 mL) and H₂O (28 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h before the yellow solid was collected *via* filtration. The solids were washed sequentially with H₂O (100 mL), ethanol (100 mL) and Et₂O (100 mL) to yield lead (II) phenylsulfide as a crude yellow solid (10.87 g). Acryloyl chloride (1.60 mL, 19.7 mmol) was added over 1 h to a 0 °C suspension of crude lead (II) phenylsulfide (4.32 g) in Et₂O (20 mL). The resulting mixture was warmed to room temperature and stirred for 1 h, then filtered, the solids washed with Et₂O (2 x 15 mL) and the combined organic filtrates were concentrated under reduced pressure. The crude material was purified by silica gel chromatography (1-3% Et₂O in petrol) to yield phenyl thioacrylate **177** as a pungent colourless oil (3.20 g, 99%). δ_{H} (400 MHz, CDCl₃) 7.51-7.43 (5H, m, ArH), 6.49 (1H, dd, J 17.2, 9.5, H₁₅), 6.42 (1H, dd, J 17.2, 1.7, H_{14trans}), 5.79 (1H, dd, J 9.5, 1.7, H_{14cis}); δ_{C} (101 MHz, CDCl₃) 188.4 (C₁₆), 134.6 (Ar-C), 134.4 (C₁₅), 129.6 (Ar-C), 129.3 (Ar-C), 127.5 (C₁₄), 127.2 (Ar-4° carbon); ν_{max} (film)/cm⁻¹ 1680 (C=O); low resolution ESI-MS 187.03 [M+Na]⁺. This data is in accordance with the literature.¹⁰⁰

(2S,5R)-tert-butyl-2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-((E)-4-(methoxy(methyl)amino)-4-oxobut-2-en-1-yl)pyrrolidine-1-carboxylate (166**)**



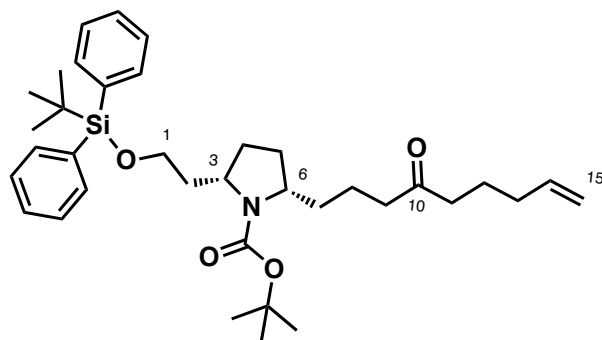
Hoveyda-Grubbs second-generation catalyst (32 mg, 50.8 μmol) was added to a solution of *N*-Boc pyrrolidine **82** (501 mg, 1.02 mmol) and acrylamide **164** (0.35 g, 3.05 mmol) in DCM (5 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}\text{C}$ under microwave irradiation for 3 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (10-30% EtOAc in petrol) to yield pyrrolidine acrylamide **166** as a light brown foam (480 mg, 81%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.79-7.75 (4H, m, ArH), 7.29-7.23 (6H, m, ArH), 6.11-6.98 (1H, m, H8), 6.46 (1H, dt, J 15.4, 1.4, H9), 3.94-3.89 (1H, m, H6), 3.86-3.72 (3H, m, H1, H3), 3.29 (3H, s, OCH₃), 2.99 (3H, s, NCH₃), 2.68-2.63 (1H, m, H7_A), 2.24 (2H, app dtd, J 19.5, 12.9, 7.0, H2_A, H7_B), 1.65-1.54 (3H, m, H2_B, H5), 1.49-1.38 (11H, m, ^tBu Boc, H4), 1.18 (9H, s, ^tBu silyl ether); δ_{C} (126 MHz, d_8 -toluene, 363 K) 166.9 (C10), 154.5 (Boc), 143.4 (C8), 137.4 (Ar), 135.9 (Ar), 134.7 (Ar (4 $^{\circ}$)), 129.8 (Ar), 121.8 (C9), 78.9 (^tBu (Boc, 4 $^{\circ}$ carbon)), 62.6 (C1), 61.0 (OCH₃), 58.1 (C6), 56.7 (C3), 39.4 (C2), 39.0 (C7), 32.2 (NCH₃), 30.0 (C4), 29.6 (C5), 28.5 (^tBu (Boc)), 27.2 (^tBu (silyl ether)), 19.4 (^tBu (silyl ether, 4 $^{\circ}$ carbon)); ν_{max} (film)/cm⁻¹ 1689 (C=O, Boc), 1666 (C=O, α,β -unsaturated Weinreb amide), 1636 (C=C); ESI-MS calcd. for C₃₃H₄₈N₂NaO₅Si [M+Na]⁺ 603.3225, found 603.3226; [α]_D²⁶ +16.1 (*c* 1.66, CHCl₃).

(2*S*,5*S*)-tert-butyl 2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(4-(methoxy(methyl)amino)-4-oxobutyl)pyrrolidine-1-carboxylate



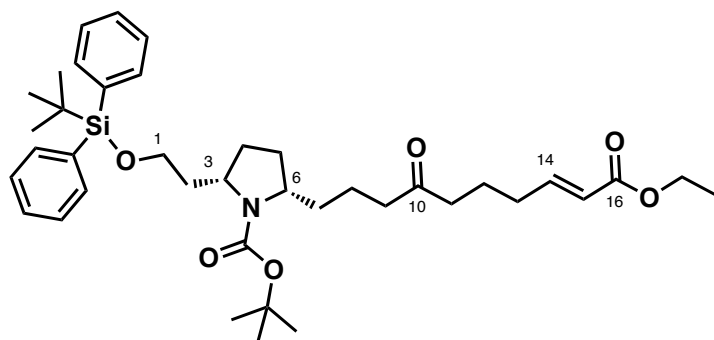
Palladium on carbon (14 mg, 10 wt% Pd) was added to a stirring solution of pyrrolidine acrylamide **166** (137 mg, 0.24 mmol) in EtOH (3 mL). The resulting mixture was degassed (x 3) with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 2 h and then filtered through a short plug of Celite®. The cake was washed with DCM (3 x 10 mL) and the organic filtrates concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-30% EtOAc in petrol) to yield the Weireb amide as a colourless oil (139 mg, 100%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.77-7.73 (4H, m, ArH), 7.25-7.20 (6H, m, ArH), 3.93-3.89 (1H, br m, H3), 3.84-3.73 (3H, m, H1, H6), 3.23 (3H, s, OCH₃), 2.90 (3H, s, NCH₃), 2.35 (2H, t, J 7.3, H9), 2.25 (1H, dq, J 12.9, 6.4, H2_A), 1.90-1.83 (1H, m, H7_A), 1.77-1.54 (5H, m, H2_B, H5, H8), 1.52-1.39 (11H, H4, ^tBu (Boc)), 1.35 (1H, dtd, J 13.3, 8.6, 5.1, H7_B), 1.15 (^tBu (silyl ether)); δ_{C} (126 MHz, d_8 -toluene, 363 K) 174.3 (C10), 154.8 (Boc), 137.4 (Ar), 136.0 (Ar), 134.8 (Ar), 129.7 (Ar), 78.5 (^tBu (Boc), 4° carbon), 62.7 (C1), 60.6 (OCH₃), 58.6 (C6), 56.5 (C3), 39.8 (C2), 36.4 (C7), 32.3 (NCH₃), 32.1 (C9), 30.2 (C4), 30.0 (C5), 28.6 (^tBu (Boc)), 27.3 (^tBu (silyl ether)), 21.7 (C8), 19.5 (^tBu (silyl ether), 4° carbon); ν_{max} (film)/cm⁻¹ 1688 (C=O, Boc); ESI-MS calcd. for C₃₃H₅₀N₂NaO₅Si [M+Na]⁺ 605.3381, found 605.3382; $[\alpha]_{\text{D}}^{23}$ +7.3 (c 1.33, CHCl₃).

(2*S*,5*S*)-tert-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-(4-oxonon-8-en-1-yl)pyrrolidine-1-carboxylate (167**)**



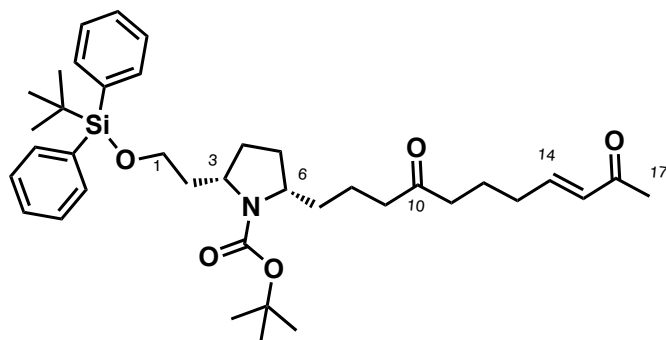
5-Bromo-1-pentene (0.51 mL, 4.32 mmol) was added over a period of 10 min to a solution of magnesium turnings (210 mg, 8.65 mmol) and iodine (~1 mg) in Et₂O (2 mL) at 45 °C such as to maintain the reaction mixture at a gentle reflux. The reaction was stirred at 45 °C for 60 min, then cooled to 0 °C and transferred *via* cannula to a solution of Weinreb amide (839 mg, 1.44 mmol) in Et₂O (10 mL) at 0 °C. The reaction mixture was then heated to reflux and stirred for 60 min, diluted with Et₂O (20 mL), cooled to 0 °C and ammonium chloride (sat., aq., 20 mL) was added. The phases were separated and the aqueous phase extracted with Et₂O (3 x 30 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-40% Et₂O in petrol) to yield pentenyl ketone **167** as a colourless oil (771 mg, 90%). δ_{H} (500 MHz, d₈-toluene, 363 K) 7.79-7.75 (4H, m, ArH), 7.28-7.25 (6H, m, ArH), 5.70 (1H, ddt, J 17.0, 10.3, 6.7, *H*₁₄), 5.00-4.92 (2H, m, *H*₁₅), 3.95-3.90 (1H, m, *H*₃), 3.86-3.73 (3H, m, *H*₁, *H*₆), 2.25 (1H, dq, J 12.9, 6.4, *H*_{2A}), 2.18-2.11 (4H, m, *H*₉, *H*₁₁), 1.98-1.93 (2H, m, *H*₁₃), 1.81-1.74 (1H, m, *H*_{7A}), 1.71-1.36 (18H, m, *H*_{2B}, *H*₄, *H*₅, *H*₈, *H*₁₂, *t*Bu (Boc)), 1.28-1.20 (1H, m, *H*_{7B}), 1.18 (9H, s, *t*Bu (silyl ether)); δ_{C} (126 MHz, d₈-toluene, 363 K) 207.8 (*C*₁₀), 154.8 (Boc), 138.3 (*C*₁₄), 137.4 (Ar), 136.0 (Ar), 134.7 (Ar), 129.8 (Ar), 114.9 (*C*₁₅), 78.6 (*t*Bu (Boc, 4° carbon)), 62.7 (*C*₁), 58.5 (*C*₆), 56.5 (*C*₃), 42.6 (*C*₁₁), 41.8 (*C*₉), 39.8 (*C*₂), 36.2 (*C*₇), 33.4 (*C*₁₃), 30.3 (*C*₄), 29.9 (*C*₅), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 23.3 (*C*₁₂), 20.9 (*C*₈), 19.5 (*t*Bu (silyl ether, 4° carbon)); ν_{max} (film)/cm⁻¹ 1713 (C=O, ketone), 1689 (C=O, Boc), 1642 (C=C); ESI-MS calcd. for C₃₆H₅₃NNaO₄Si [M+Na]⁺ 614.3636, found 614.3627; [α]_D²⁶ +7.4 (*c* 0.01, CHCl₃).

(2S,5S)-tert-butyl 2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-((E)-10-ethoxy-4,10-dioxodec-8-en-1-yl)pyrrolidine-1-carboxylate (170**)**



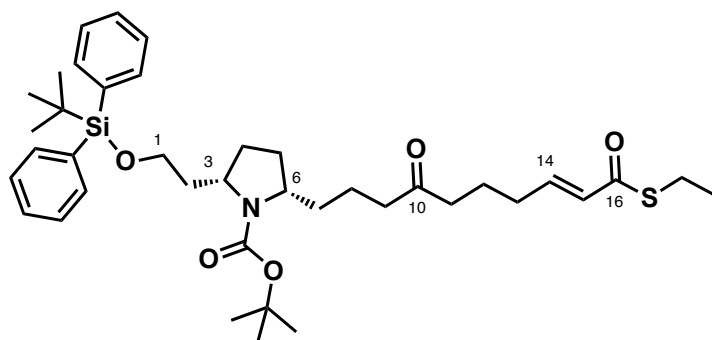
Hoveyda-Grubbs second-generation catalyst (17 mg, 26.6 μmol) was added to a solution of pentenyl ketone **167** (315 mg, 0.53 mmol) and ethyl acrylate (0.23 mL, 2.13 mmol) in DCM (3 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}\text{C}$ under microwave irradiation for 2 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (10-20% Et_2O in petrol) to yield pyrrolidine keto-acrylate **170** as a pale brown oil (350 mg, 99%). δ_{H} (500 MHz, d_8 -toluene, 363 K) 7.79-7.75 (4H, m, ArH), 7.29-7.24 (6H, m, ArH), 6.89 (1H, dt, J 15.6, 7.0, H14), 5.80 (1H, dt, J 15.5, 1.3, H15), 4.07 (2H, q, J 7.1, H17'), 3.96-3.90 (1H, m, H3), 3.86-3.74 (3H, m, H1, H6), 2.26 (1H, dtd, J 12.9, 7.3, 5.4, H2_A), 2.17-2.09 (2H, m, H11), 2.03 (2H, t, J 7.2, H9), 1.94-1.89 (2H, m, H13), 1.80-1.73 (1H, m, H7_A), 1.70-1.36 (18H, m, H2_B, H4, H5, H8, H12, ^tBu (Boc)), 1.27-1.21 (1H, m, H7_B), 1.18 (9H, s, ^tBu (silyl ether)), 1.09 (3H, t, J 7.1, H18'); δ_{C} (126 MHz, d_8 -toluene, 363 K) 207.5 (C10), 165.7 (C16), 154.9 (Boc), 147.5 (C14), 136.0 (Ar), 134.8 (Ar), 129.8 (Ar), 128.0 (Ar), 122.7 (C15), 78.7 (^tBu (Boc), 4 $^{\circ}$ carbon), 62.7 (C1), 59.8 (C17'), 58.5 (C6), 56.6 (C3), 42.6 (C9), 41.6 (C11), 39.9 (C2), 36.2 (C7), 31.6 (C13), 30.4 (C4), 30.0 (C5), 28.7 (^tBu (Boc)), 27.3 (^tBu (silyl ether)), 22.5 (C12), 21.0 (C8), 19.5 (^tBu (silyl ether), 4 $^{\circ}$ carbon), 14.3 (C18'); ν_{max} (film)/ cm^{-1} 1717 (C=O, α,β -unsaturated ester), 1688 (br, C=O, ketone and Boc), ESI-MS calcd. for $\text{C}_{39}\text{H}_{57}\text{NNaO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 686.3847, found 686.3842; $[\alpha]_{\text{D}}^{23}$ +9.5 (c 1.05, CHCl_3).

(2*S*,5*S*)-tert-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-((*E*)-4,10-dioxoundec-8-en-1-yl)pyrrolidine-1-carboxylate (168**)**



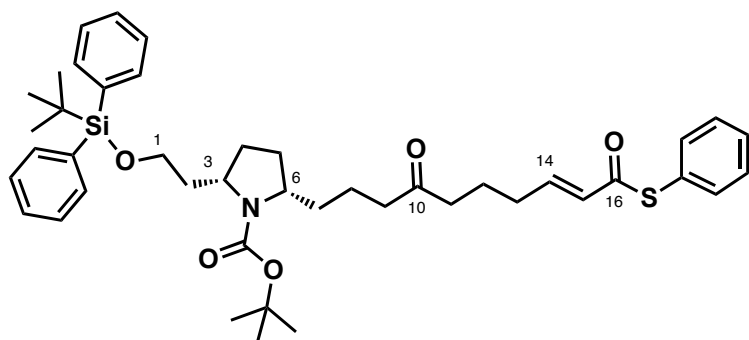
Hoveyda-Grubbs second-generation catalyst (3 mg, 5.4 μmol) was added to a solution of pentenyl ketone **167** (64 mg, 0.11 mmol) and 3-butene-2-one (44 μL , 0.54 mmol) in DCM (1 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}\text{C}$ under microwave irradiation for 2 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (20-50% Et₂O in petrol) to yield pyrrolidine keto-enone **168** as a pale yellow oil (67 mg, 98%). δ_{H} (500 MHz, *d*₈-toluene, 363 K) 7.80-7.75 (4H, m, ArH), 7.29-7.24 (6H, m, ArH), 6.46 (1H, dt, *J* 15.9, 6.9, *H*₁₄), 5.92 (1H, dt, *J* 15.9, 1.5, *H*₁₅), 3.96-3.90 (1H, m, *H*₃), 3.86-3.74 (3H, m, *H*₁, *H*₆), 2.26 (1H, dtd, *J* 12.9, 7.3, 5.5, *H*_{2A}), 2.20-2.09 (2H, m, *H*₁₁), 2.05 (2H, t, *J* 7.2, *H*₉), 1.92-1.88 (5H, m, *H*₁₃, *H*₁₇), 1.81-1.74 (1H, m, *H*_{7A}), 1.72-1.35 (18H, m, *H*_{2B}, *H*₄, *H*₅, *H*₈, *H*₁₂, *t*Bu (Boc)), 1.28-1.21 (1H, m, *H*_{7B}), 1.18 (9H, s, *t*Bu (silyl ether)); δ_{C} (126 MHz, *d*₈-toluene, 363 K) 207.5 (C₁₀), 195.3 (C₁₆), 154.8 (Boc), 145.2 (C₁₄), 137.7 (Ar), 135.9 (Ar), 134.7 (Ar), 132.0 (C₁₅), 129.8 (Ar), 78.7 (*t*Bu (Boc), 4 $^{\circ}$ carbon), 62.7 (C₁), 58.4 (C₆), 56.6 (C₃), 42.6 (C₉), 41.6 (C₁₁), 39.8 (C₂), 36.2 (C₇), 31.8 (C₁₃), 30.3 (C₄), 29.9 (C₅), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 26.5 (C₁₇), 22.5 (C₁₂), 20.9 (C₈), 19.4 (*t*Bu (silyl ether), 4 $^{\circ}$ carbon)); ν_{max} (film)/cm⁻¹ 1713 (C=O, ketone), 1687 (C=O (Boc and α,β -unsaturated ketone), 1628 (C=C); ESI-MS calcd. for C₃₈H₅₅NNaO₅Si [M+Na]⁺ 656.3742, found 656.3744; $[\alpha]_{\text{D}}^{26} +8.8$ (*c* 1.0, CHCl₃).

(2*S*,5*S*)-*tert*-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-((*E*)-10-(ethylthio)-4,10-dioxodec-8-en-1-yl)pyrrolidine-1-carboxylate (172**)**



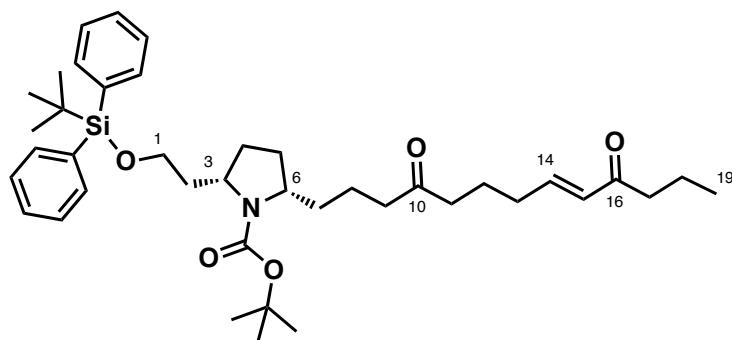
Hoveyda-Grubbs second-generation catalyst (0.8 mg, 1.3 μmol) was added to a solution of pentenyl ketone **167** (15.5 mg, 26.2 μmol) and *S*-ethyl prop-2-enethioate **175** (15 μL , 0.13 mmol) in DCM (1 mL) in a microwave vial. The reaction mixture was stirred at 70 °C under microwave irradiation for 2 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (10-40% Et₂O in petrol) to yield pyrrolidine keto-acrylate **172** as a pale yellow oil (16 mg, 90%). δ_{H} (500 MHz, *d*₈-toluene, 363 K) 7.80-7.74 (4H, m, ArH), 7.29-7.22 (6H, m, ArH), 6.77 (1H, dt, *J* 15.5, 6.9, *H*₁₄), 6.01 (1H, dt, *J* 15.5, 1.6, *H*₁₅), 3.96-3.90 (1H, m, *H*₃), 3.87-3.73 (3H, m, *H*₁, *H*₆), 2.82 (2H, q, *J* 7.4, *H*_{17'}), 2.26 (1H, dtd, *J* 13.0, 7.3, 5.5, *H*_{2A}), 2.15-2.11 (2H, m, *H*₉), 2.01 (2H, t, *J* 7.1, *H*₁₁), 1.86 (2H, qd, *J* 7.2, 1.5, *H*₁₃), 1.80-1.74 (1H, m, *H*_{7A}), 1.70-1.38 (18H, m, *H*_{2B}, *H*₄, *H*₅, *H*₈, *H*₁₂, *t*Bu (Boc)), 1.27-1.21 (1H, m, *H*_{7B}), 1.18 (9H, s, *t*Bu (silyl ether)), 1.13 (3H, t, *J* 7.4, *H*_{18'}); δ_{C} (126 MHz, *d*₈-toluene, 363 K) 207.3 (*C*₁₀), 188.4 (*C*₁₆), 154.8 (Boc), 143.7 (*C*₁₄), 137.4 (Ar), 135.9 (Ar), 134.7 (Ar), 129.8 (Ar), 127.9 (*C*₁₅), 78.7 (*t*Bu (Boc), 4° carbon)), 62.7 (*C*₁), 58.4 (*C*₆), 56.6 (*C*₃), 42.5 (*C*₉), 41.5 (*C*₁₁), 39.8 (*C*₂), 36.1 (*C*₇), 31.5 (*C*₁₃), 30.3 (*C*₄), 29.9 (*C*₅), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 23.0 (*C*_{17'}), 22.4 (*C*₁₂), 20.9 (*C*₈), 19.4 (*t*Bu (silyl ether), 4° carbon)), 14.7 (*C*_{18'}); ν_{max} (film)/cm⁻¹ 1713 (C=O, ketone), 1688 (br, C=O (Boc and thioester)), 1633 (C=C); ESI-MS calcd. for C₃₉H₅₇NNaO₅SSi [M+Na]⁺ 702.3619, found 702.3641; [α]_D²³ +7.6 (*c* 0.61, CHCl₃).

(2*S*,5*S*)-tert-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-((*E*)-4,10-dioxo-10-(phenylthio)dec-8-en-1-yl)pyrrolidine-1-carboxylate (173**)**



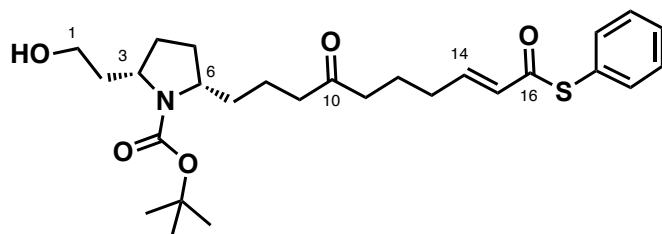
Hoveyda-Grubbs second-generation catalyst (3 mg, 4.7 μmol) was added to a solution of pentenyl ketone **167** (55 mg, 93 μmol) and *S*-phenyl prop-2-enethioate **177** (61 mg, 0.37 mmol) in DCM (1 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}\text{C}$ under microwave irradiation for 2 h (exclusive of ramping time), cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (20-50% Et₂O in petrol) to yield pyrrolidine keto-acrylate **173** as a pale yellow oil (67 mg, 98%). δ_{H} (500 MHz, d₈-toluene, 363 K) 7.79-7.76 (4H, m, SiArH), 7.42-7.39 (2H, m, SArH), 7.28-7.25 (6H, m, SiArH), 7.12-7.05 (3H, m, SArH), 6.82 (1H, dt, J 15.5, 6.9, *H*₁₄), 6.05 (1H, dt, J 15.5, 1.6, *H*₁₅), 3.96-3.91 (1H, m, *H*₃), 3.85-3.76 (3H, m, *H*₁, *H*₆), 2.26 (1H, dtd, J 12.9, 7.3, 5.5, *H*_{2A}), 2.14-2.11 (2H, m, *H*₉), 2.02 (2H, t, J 7.2, *H*₁₁), 1.88 (2H, qd, J 7.3, 1.3, *H*₁₃), 1.81-1.75 (1H, m, *H*_{7A}), 1.70-1.37 (18H, m, *H*_{2B}, *H*₄, *H*₅, *H*₈, *H*₁₂, *t*Bu (Boc)), 1.28-1.21 (1H, m, *H*_{7B}), 1.18 (9H, s, *t*Bu (silyl ether)); δ_{C} (126 MHz, d₈-toluene, 363 K) 207.4 (*C*₁₀), 188.3 (*C*₁₆), 154.8 (Boc), 145.1 (*C*₁₄), 137.5 (Ar, silyl ether and thioester), 135.9 (Ar, silyl ether), 134.7 (Ar, silyl ether and thioester), 129.8 (Ar, silyl ether), 129.1 (*C*₁₅), 127.9 (Ar, thioester), 125.3 (Ar, thioester), 78.7 (*t*Bu (Boc), 4 $^{\circ}$ carbon), 62.7 (*C*₁), 58.4 (*C*₆), 56.6 (*C*₃), 42.5 (*C*₉), 41.5 (*C*₁₁), 39.8 (*C*₂), 36.1 (*C*₇), 31.6 (*C*₁₃), 30.3 (*C*₄), 29.9 (*C*₅), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 22.3 (*C*₁₂), 20.9 (*C*₈), 19.4 (*t*Bu (silyl ether), 4 $^{\circ}$ carbon)); ν_{max} (film)/cm⁻¹ 1686 (br, C=O (Boc, ketone and thioester)), 1633 (C=C); ESI-MS calcd. for C₄₃H₅₇NNaO₅SSi [M+Na]⁺ 750.3619, found 750.3625; $[\alpha]_{\text{D}}^{23} +7.0$ (*c* 1.0, CHCl₃).

(2*S*,5*S*)-tert-butyl-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-((*E*)-4,10-dioxotridec-8-en-1-yl)pyrrolidine-1-carboxylate (169**)**



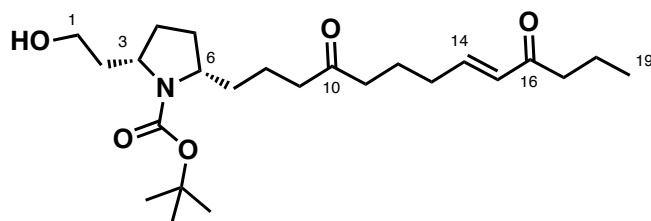
Hoveyda-Grubbs second-generation catalyst (5 mg, 8.1 μ mol) was added to a solution of pentenyl ketone **167** (97 mg, 0.16 mmol) and 1-hexene-3-one (96 μ L, 0.82 mmol) in DCM (2 mL) in a microwave vial. The reaction mixture was stirred at 70 $^{\circ}$ C under microwave irradiation for 2 h (exclusive of ramping time). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (20–40% Et₂O in petrol) to yield pyrrolidine keto-enone **169** as a colourless oil (107.3 mg, 99%). δ_{H} (500 MHz, d₈-toluene, 363 K) 7.80–7.76 (4H, m, ArH), 7.29–7.25 (6H, m, ArH), 6.59 (1H, dt, J 15.8, 6.9, *H*₁₄), 5.97 (1H, dt, J 15.9, 1.5, *H*₁₅), 3.96–3.91 (1H, m, *H*₃), 3.87–3.75 (3H, m, *H*₁, *H*₆), 2.29–2.23 (3H, m, *H*_{2A}, *H*₁₇), 2.16 (2H, t, J 7.1, *H*₁₁), 2.12 (2H, app dt, J 4.4, 2.2, *H*₉), 1.93 (2H, tdd, J 7.5, 6.8, 1.5, *H*₁₃), 1.81–1.73 (1H, m, *H*_{7A}), 1.72–1.47 (10H, m, *H*_{2B}, *H*₄, *H*_{5A}, *H*₈, *H*₁₂, *H*₁₈), 1.45 (9H, s, *t*Bu (Boc)), 1.45–1.37 (1H, m, *H*_{5B}), 1.28–1.21 (1H, m, *H*_{7B}), 1.18 (9H, s, *t*Bu (silyl ether)), 0.88 (3H, t, J 7.4, *H*₁₉); δ_{C} (126 MHz, d₈-toluene, 363 K) 207.5 (C₁₀), 197.7 (C₁₆), 154.8 (Boc), 144.4 (C₁₄), 137.6 (Ar), 135.9 (Ar), 134.7 (Ar), 131.2 (C₁₅), 129.8 (Ar), 78.7 (*t*Bu (Boc), 4 $^{\circ}$ carbon), 62.7 (C₁), 58.4 (C₆), 56.6 (C₃), 42.6 (C₉), 42.3 (C₁₇), 41.6 (C₁₁), 39.8 (C₂), 36.2 (C₇), 31.8 (C₁₃), 30.3 (C₄), 29.9 (C₅), 28.6 (*t*Bu (Boc)), 27.2 (*t*Bu (silyl ether)), 22.6 (C₁₂), 20.9 (C₈), 19.4 (*t*Bu (silyl ether), 4 $^{\circ}$ carbon), 17.8 (C₁₈), 13.7 (C₁₉); ν_{max} (film)/cm^{–1} 1713 (C=O, ketone), 1687 (br, C=O, α,β -unsaturated ketone and Boc); ESI-MS calcd. for C₄₀H₅₉NNaO₅Si [M+Na]⁺ 684.4055, found 685.4064; $[\alpha]_{\text{D}}^{23}$ +5.1 (c 0.16, CHCl₃).

(2S,5S)-tert-butyl-2-((E)-4,10-dioxo-10-(phenylthio)dec-8-en-1-yl)-5-(2-hydroxyethyl)pyrrolidine-1-carboxylate (224**)**



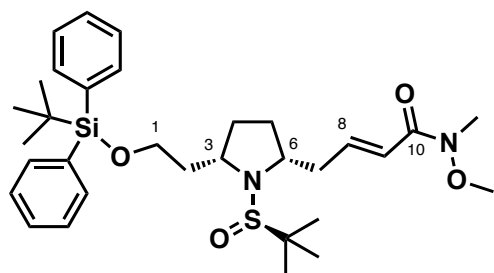
Tetrabutylammonium fluoride (1.0 M in THF, 1.39 mL, 1.39 mmol) was added dropwise to a stirring solution of silyl ether **173** (101 mg, 0.14 mmol) and acetic acid (95 μ L, 1.67 mmol) in THF (5 mL) at 0 °C. The solution was warmed to room temperature and stirred for 16 h, diluted with Et₂O (10 mL) and ammonium chloride (sat., aq., 10 mL) was added. The organics were extracted and washed with H₂O (10 mL) and brine (10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0-2% MeOH in Et₂O) to yield primary alcohol **224** as a colourless oil (61.5 mg, 90%). δ_{H} (500 MHz, d₈-toluene, 363 K) 7.42 (2H, m, ArH), 7.07-7.05 (3H, m, ArH), 6.81 (1H, dt, J 15.1, 7.3, H₁₄), 6.04 (1H, d, J 15.4, H₁₅), 4.19-4.06 (1H, br m, H₃), 3.72-3.58 (3H, m, H₁, H₆), 3.39-2.68 (1H, br s, OH), 2.09 (2H, t, J 6.7, H₉), 1.98 (2H, t, J 6.8, H₁₁), 1.86 (2H, q, J 7.0, H₁₃), 1.81-1.74 (1H, m, H_{7A}), 1.72-1.59 (2H, m, H_{4A}, H_{5A}), 1.57-1.50 (6H, m, H₂, H₈, H₁₂), 1.45 (9H, s, ^tBu (Boc)), 1.42-1.31 (2H, m, H_{4B}, H_{5B}), 1.25-1.20 (1H, m, H_{7B}); δ_{C} (126 MHz, d₈-toluene, 363 K) 207.1 (C₁₀), 186.1 (C₁₆), 154.8 (Boc), 144.9 (C₁₄), 137.5 (Ar), 134.7 (Ar), 129.1 (C₁₅), 128.1 (Ar), 125.3 (Ar), 79.5 (^tBu (Boc), 4° carbon), 59.7 (C₁), 58.7 (C₆), 55.9 (C₃), 42.5 (C₉), 41.5 (C₁₁), 40.2 (C₂), 36.4 (C₇), 31.6 (C₁₃), 30.6 (C₄), 30.3 (C₅), 28.5 (^tBu (Boc)), 22.3 (C₁₂), 20.7 (C₈); ν_{max} (film)/cm⁻¹ 3424 (br, O-H), 1684 (br, C=O (Boc, ketone and thioester)); ESI-MS calcd. for C₂₇H₃₉NNaO₅S [M+Na]⁺ 512.2441, found 512.2442; $[\alpha]_{\text{D}}^{23}$ +17.8 (c 0.8, CHCl₃).

(2*S*,5*S*)-*tert*-butyl-2-((*E*)-4,10-dioxotridec-8-en-1-yl)-5-(2-hydroxyethyl)pyrrolidine-1-carboxylate (225**)**



Tetrabutylammonium fluoride (1.0 M in THF, 1.5 mL, 1.50 mmol) was added dropwise to a stirring solution of silyl ether **169** (100 mg, 0.15 mmol) and acetic acid (0.1 mL, 1.82 mmol) in THF (5 mL) at 0 °C. The solution was warmed to room temperature and stirred for 16 h, diluted with Et₂O (10 mL) and ammonium chloride solution (sat., aq., 10 mL) was added. The organics were extracted and washed with H₂O (10 mL) and brine (10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0-2% MeOH in Et₂O) to yield primary alcohol **225** as a colourless oil (57.6 mg, 90%). δ_{H} (500 MHz, d₈-toluene, 363 K) 6.58 (1H, dt, J 15.8, 6.9, *H*₁₄), 5.96 (1H, dt, J 15.8, 1.5, *H*₁₅), 4.12-4.05 (1H, m, *H*₃), 3.73-3.58 (3H, m, *H*₁, *H*₆), 3.18-2.62 (1H, br s, OH), 2.25 (2H, t, J 7.2, *H*₁₇), 2.13-2.10 (2H, m, *H*₁₁), 2.05 (2H, t, J 7.1, *H*₉), 1.95-1.90 (2H, m, *H*₁₃), 1.80-1.73 (1H, m, *H*_{7A}), 1.72-1.50 (10H, m, *H*₂, *H*_{4A}, *H*_{5A}, *H*₈, *H*₁₂, *H*₁₈), 1.47 (9H, s, *t*Bu), 1.43-1.32 (2H, m, *H*_{4B}, *H*_{5B}), 1.27-1.20 (1H, m, *H*_{7B}), 0.88 (3H, t, J 7.4, *H*₁₉); δ_{C} (126 MHz, d₈-toluene, 363 K) 207.3 (*C*₁₀), 197.7 (*C*₁₆), 156.0 (Boc), 144.3 (*C*₁₄), 131.3 (*C*₁₅), 79.5 (*t*Bu (Boc, 4° carbon)), 59.7 (*C*₁), 58.7 (*C*₆), 55.9 (*C*₃), 42.5 (*C*₉), 42.3 (*C*₁₇), 41.6 (*C*₁₁), 40.2 (*C*₂), 36.4 (*C*₇), 31.8 (*C*₁₃), 30.6 (*C*₄), 30.3 (*C*₅), 28.5 (*t*Bu (Boc)), 22.6 (*C*₁₂), 20.7 (*C*₈), 17.8 (*C*₁₈), 13.7 (*C*₁₉); ν_{max} (film)/cm⁻¹ 1712 (C=O ketone), 1666 (br, C=O (Boc and α,β -unsaturated ketone)); 1631 (C=C); ESI-MS calcd. for C₂₄H₄₁NNaO₅ [M+Na]⁺ 446.2877, found 446.2885; $[\alpha]_{\text{D}}^{23}$ +16.5 (*c* 1.1, CHCl₃).

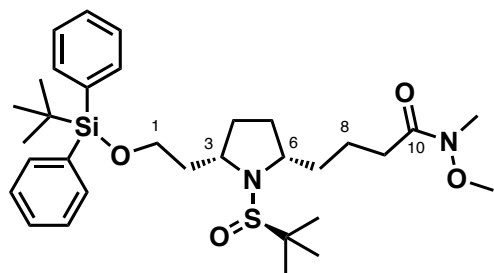
(*E*)-4-((2*R*,5*S*)-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)-*N*-methoxy-*N*-methylbut-2-enamide (178)



Hoveyda-Grubbs second-generation catalyst (51 mg, 81.4 μmol) was added to a solution of allyl pyrrolidine **114** (564 mg, 1.13 mmol) and acrylamide **164** (0.33 mL, 2.84 mmol) in DCM (5 mL). The reaction mixture was stirred at 35 $^{\circ}\text{C}$ for 24 h, cooled to room temperature and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (50-100% EtOAc in petrol, then 95:5 EtOAc:MeOH) to yield pyrrolidine acrylamide **178** (437 mg, 66%, 40:1 mixture of partially separable *E*:*Z* olefin isomers.[†] δ_{H} (400 MHz, CDCl_3) 7.68-7.63 (4H, m, ArH), 7.45-7.36 (6H, m, ArH), 6.95 (1H, m, H8), 6.49-6.39 (1H, m, H9), 4.07-4.02 (1H, m, H6), 3.87-3.79 (1H, m, H3), 3.74-3.66 (5H, m, H1, OCH₃), 3.24 (3H, s, NCH₃), 2.45-2.38 (1H, m, H7_A), 2.30-2.21 (1H, m, H7_B), 2.08-2.01 (1H, m, H2_A), 1.96-1.83 (2H, m, H2_B, H5_A), 1.79-1.59 (2H, m, H4_A, H5_B), 1.57-1.39 (1H, m, H4_B), 1.18 (9H, s, ^tBu (sulfinamide)), 1.06 (9H, s, ^tBu (silyl ether)); δ_{C} (126 MHz, CDCl_3) 166.4 (C10), 143.5 (C8), 135.6 (Ar), 133.7 (Ar), 129.7 (Ar), 127.7 (Ar), 120.6 (C9), 64.9 (C3), 61.7 (OCH₃), 61.3 (C1), 57.0 (^tBu (sulfinamide) (4 $^{\circ}$ carbon)), 52.3 (C6), 41.2 (C2), 39.0 (C7), 32.4 (NCH₃), 31.6 (C5), 29.8 (C4), 26.9 (^tBu (silyl ether)), 23.6 (^tBu (sulfinamide)), 19.1 (^tBu (silyl ether, 4 $^{\circ}$ carbon)); ν_{max} (film)/ cm^{-1} 1665 (C=O), 1635 (C=C), 1081 (S=O); ESI-MS calcd. for $\text{C}_{32}\text{H}_{48}\text{N}_2\text{NaO}_4\text{SSi}$ $[\text{M}+\text{Na}]^+$ 607.2996, found 607.2999; $[\alpha]_{\text{D}}^{24}$ -8.0 (*c* 0.25, CHCl_3).

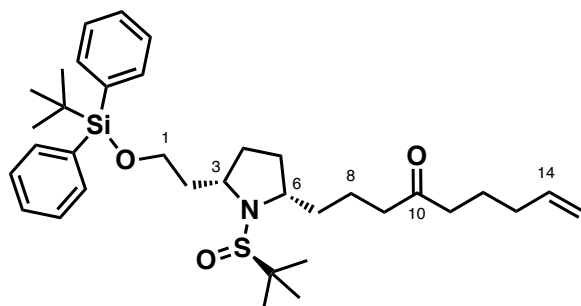
[†] A pure sample of the *E*-isomer was fully characterized and the mixture carried forward without any further attempts at purification.

4-((2*S*,5*S*)-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)-*N*-methoxy-*N*-methylbutanamide



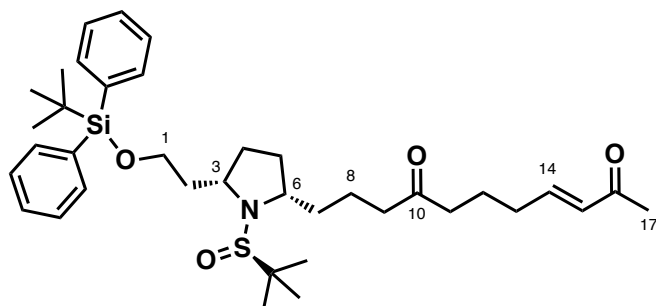
Palladium hydroxide (14 mg, 20 wt% Pd) was added to a stirring solution of pyrrolidine acrylamide *cis-/trans*-**178** (425 mg, 0.73 mmol) in EtOH (5 mL). The resulting mixture was degassed (x 3) with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 2 h then filtered through a short plug of Celite®. The cake was washed with DCM (3 x 10 mL) and the organic filtrates concentrated under reduced pressure. The crude material was purified by silica gel chromatography (50-90% EtOAc in petrol) to yield the saturated Weireb amide as a colourless oil (370 mg, 87%). δ_{H} (500 MHz, CDCl_3) 7.68-7.64 (4H, m, ArH), 7.44-7.36 (6H, m, ArH), 3.85-3.77 (2H, m, H3, H6), 3.71-3.64 (5H, m, H1, OCH₃), 3.17 (3H, s, NCH₃), 2.47-2.36 (2H, m, H9), 2.04-1.98 (1H, m, H4_A), 1.92-1.85 (1H, m, H2_A), 1.72-1.68 (2H, m, H5), 1.67-1.47 (5H, m, H2_B, H4_B, H7_A, H8), 1.41-1.33 (1H, m, H7_B), 1.16 (9H, s, ^tBu (sulfinamide)), 1.05 (9H, s, ^tBu (silyl ether)); δ_{C} (101 MHz, CDCl_3) 174.1 (C10), 135.6 (Ar), 133.7 (Ar), 129.6 (Ar), 127.6 (Ar), 64.7 (C3), 61.4 (OCH₃), 61.2 (C1), 56.9 (^tBu (sulfinamide, 4° carbon)), 53.4 (C6), 41.3 (C2), 35.8 (C7), 32.2 (NCH₃), 31.6 (C9), 31.3 (C5), 29.9 (C4), 26.9 (^tBu (silyl ether)), 23.6 (^tBu (sulfinamide)), 22.1 (C8), 19.2 (^tBu (silyl ether, 4° carbon)); ν_{max} (film)/cm⁻¹ 1667 (C=O), 1085 (S=O); ESI-MS calcd. for C₃₂H₅₀N₂NaO₄SSi [M+Na]⁺ 609.3153, found 609.3152; $[\alpha]_{\text{D}}^{24} +6.2$ (c 0.5, CHCl_3).

1-((2*S*,5*S*)-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)non-8-en-4-one (184)



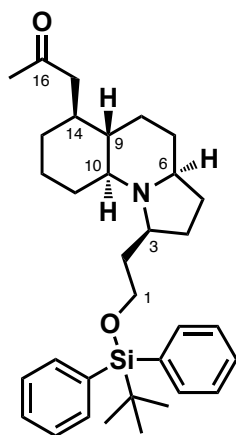
5-Bromo-1-pentene (0.22 mL, 1.87 mmol) was added over a period of 10 min to a solution of magnesium turnings (91 mg, 3.74 mmol) and iodine (~1 mg) in Et₂O (2 mL) at 45 °C such as to maintain the reaction mixture at a gentle reflux. The reaction was stirred at 45 °C for 60 min, cooled to 0 °C and transferred *via* cannula to a solution of Weinreb amide (365 mg, 0.62 mmol) in Et₂O (10 mL) at 0 °C. The reaction mixture was then heated to reflux and stirred for 60 min, diluted with Et₂O (20 mL), cooled to 0 °C and ammonium chloride (sat., aq., 20 mL) was added. The phases were separated and the aqueous phase extracted with Et₂O (3 x 30 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30-70 % Et₂O in petrol) to yield pentenyl ketone **184** as a colourless oil (369.8 mg, 100%). δ_{H} (500 MHz, CDCl₃) 7.71-7.60 (4H, m, ArH), 7.49-7.35 (6H, m, ArH), 5.76 (1H, ddt, J 17.1, 10.3, 6.7, H₁₄), 5.04-4.96 (2H, m, H₁₅), 3.83-3.75 (2H, m, H₃, H₆), (2H, ddABq, H₁), 2.45-2.33 (4H, m, H₉, H₁₁), 2.08-1.98 (3H, m, H_{7A}, H₁₃), 1.91-1.85 (1H, m, H_{2A}), 1.72-1.64 (3H, m, H_{4A}, H₁₂), 1.62-1.39 (5H, m, H_{2B}, H_{5A}, H_{7B}, H₈), 1.34-1.27 (2H, m, H_{4B}, H_{5B}), 1.16 (9H, s, ^tBu (sulfinamide)), 1.05 (9H, s, ^tBu (silyl ether)); δ_{C} (126 MHz, CDCl₃) 210.4 (C₁₀), 137.9 (C₁₄), 135.6 (Ar), 133.7 (Ar, 4° carbon), 129.6 (Ar), 127.6 (Ar), 115.2 (C₁₅), 64.7 (C₃), 61.4 (C₁), 56.9 (^tBu (sulfinamide, 4° carbon)), 53.3 (C₆), 42.3 (C₁₁), 41.9 (C₉), 41.3 (C₂), 35.6 (C₇), 33.1 (C₁₃), 31.3 (C₅), 29.9 (C₄), 26.9 (^tBu (silyl ether)), 23.6 (^tBu (sulfinamide)), 22.8 (C₁₂), 21.3 (C₈), 19.2 (^tBu (silyl ether, 4° carbon)); ν_{max} (film)/cm⁻¹ 1715 (C=O), 1640 (C=C), 1074 (S=O); ESI-MS calcd. for C₃₅H₅₃NNaO₃SSi [M+Na]⁺ 618.3408, found 618.3404; [α]_D²³ +6.4 (c 0.44, CHCl₃).

(E)-11-((2*S*,5*S*)-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)undec-3-ene-2,8-dione (185)



Hoveyda-Grubbs second-generation catalyst (19 mg, 31.0 μmol) was added to a solution of pentenyl ketone **184** (369 mg, 0.62 mmol) and 3-butene-2-one (0.25 mL, 3.10 mmol) in DCM (3 mL). The reaction mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (30-70% EtOAc in petrol) to yield pyrrolidine keto-enone **185** as a pale brown oil (358.2 mg, 91%). δ_{H} (400 MHz, CDCl_3) 7.67-7.63 (4H, m, ArH), 7.45-7.36 (6H, m, ArH), 6.75 (1H, dt, J 16.0, 6.9, H_{14}), 6.07 (1H, dt, J 16.0, 1.5, H_{15}), 3.83-3.76 (2H, m, H_3 , H_6), 3.72-3.64 (2H, m, H_1), 2.46-2.32 (4H, m, H_9 , H_{11}), 2.26-2.19 (5H, m, H_{13} , H_{17}), 2.06-1.98 (1H, m, H_{7A}), 1.88 (1H, app dq, J 13.2, 6.5, H_{2A}), 1.76 (2H, quin, J 7.4, H_{12}), 1.70-1.66 (2H, m, H_4), 1.63-1.38 (5H, m, H_{2B} , H_{5A} , H_{7B} , H_8), 1.35-1.24 (1H, m, H_{5B}), 1.16 (9H, s, $t\text{Bu}$ (sulfinamide)), 1.05 (9H, s, $t\text{Bu}$ (silyl ether)); δ_{C} (101 MHz, CDCl_3) 209.5 (C_{10}), 198.5 (C_{16}), 147.1 (C_{14}), 135.6 (Ar), 133.7 (Ar, 4° carbon), 131.7 (C_{15}), 129.6 (Ar), 127.6 (Ar), 64.7 (C_3), 61.3 (C_1), 56.8 ($t\text{Bu}$ (sulfinamide), 4° carbon), 53.2 (C_6), 42.3 (C_{11}), 41.7 (C_9), 41.3 (C_2), 35.5 (C_7), 31.7 (C_{13}), 31.3 (C_5), 29.9 (C_4), 26.94 (C_{17}), 26.85 ($t\text{Bu}$ (silyl ether)), 23.6 ($t\text{Bu}$ (sulfinamide)), 21.9 (C_{12}), 21.2 (C_8), 19.1 ($t\text{Bu}$ (silyl ether), 4° carbon)); ν_{max} (film)/ cm^{-1} 1713 ($\text{C}=\text{O}$), 1675 ($\text{C}=\text{O}$ (α,β -unsaturated)), 1087 ($\text{S}=\text{O}$); ESI-MS calcd. for $\text{C}_{37}\text{H}_{55}\text{NNaO}_4\text{SSi}$ $[\text{M}+\text{Na}]^+$ 660.3513, found 660.3517; $[\alpha]_{\text{D}}^{23} +5.7$ (c 1.1, CHCl_3).

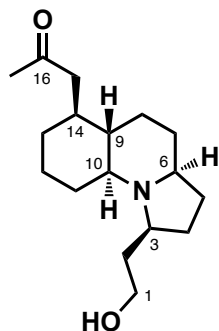
1-((1*S*,3*aS*,5*aS*,6*S*,9*aS*)-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)dodecahydropyrrolo-[1,2-*a*]-quinolin-6-yl)propan-2-one (203)



Trifluoroacetic acid (0.17 mL, 2.22 mmol) was added dropwise to a stirring solution of **168** (29 mg, 47 μ mol) in DCM (0.5 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h, concentrated under reduced pressure and azeotroped with toluene (3 x 1 mL). The resulting colourless oil was dissolved in CHCl₃ (1 mL) and stirred at room temperature for 24 h. After this period the solution was concentrated under reduced pressure and azeotroped again with toluene (1 mL). The crude oil was dissolved in DCM (2 mL) and cooled to 0 °C. Sodium cyanoborohydride (3.5 mg, 56 μ mol) was added to a stirring solution of crude hydroquininium at 0 °C. The solution was warmed to room temperature and stirred for 16 h, diluted with DCM (10 mL), cooled to 0 °C and sodium bicarbonate (sat., aq., 10 mL) was added. The phases were separated and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5-40% (90:10:0.15 CHCl₃:MeOH:NH₄OH) in CHCl₃ to yield perhydro-pyrroloquinoline **203** as a pale yellow oil (19.7 mg, 83%). δ_{H} (500 MHz, d₈-toluene, 363 K) 7.78-7.74 (4H, m, ArH), 7.27-7.25 (6H, m, ArH), 3.83 (1H, ddd, J 10.4, 7.0, 4.8, H1_A), 3.77-3.71 (1H, m, H1_B), 2.88-2.81 (1H, m, H3), 2.26 (1H, dd, J 16.1, 4.1, H15_A), 2.06-1.98 (3H, m, H2_A, H6, H11_A), 1.90-1.83 (1H, m, H10), 1.82 (1H, dd, J 16.1, 7.8, H15_B), 1.78 (3H, s, H17), 1.71-1.57 (6H, m, H2_B, H4_A, H7_A, H11_B, H12_A, H14), 1.49 (1H, ddd, J 10.6, 7.1, 4.0, H5_A), 1.42-1.21 (6H, m, H4_B, H5_B, H7_B, H8_A, H12_B, H13_A), 1.18 (9H, s, ^tBu), 1.06-0.75 (3H, m, H8_B, H9, H13_B); δ_{C} (126 MHz, d₈-toluene, 363 K) 205.2 (C16), 136.0 (Ar), 134.8 (Ar), 129.8 (Ar), 128.1 (Ar), 69.5 (C10), 67.2 (C6), 62.5 (C1), 58.3 (C3), 48.4 (C15), 47.3 (C9), 42.9 (C2), 37.8 (C14), 33.5 (C8), 33.2 (C11), 32.6 (C5), 31.1 (C7), 30.2 (C17), 30.1 (C4),

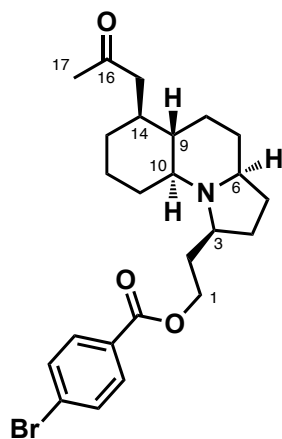
29.7 (C13), 26.8 (tBu), 25.1 (C12), 19.4 (tBu, 4° carbon); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1715 (C=O); ESI-MS calcd. for $\text{C}_{33}\text{H}_{48}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 518.3449, found 518.3460. $[\alpha]_{\text{D}^{23}} +7.5$ (c 0.71, CHCl_3).

1-((1*S*,3*aS*,5*aS*,6*S*,9*aS*)-1-(2-hydroxyethyl)dodecahydropyrrolo-[1,2-*a*]-quinolin-6-yl)propan-2-one (204)



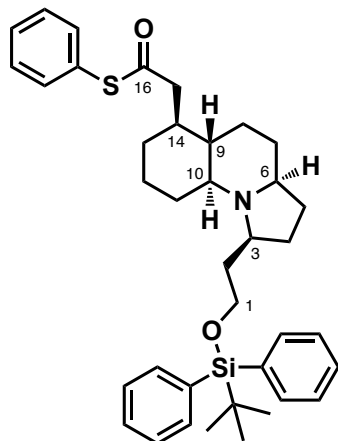
Tetrabutylammonium fluoride (1.0 M in THF, 0.97 mL, 0.97 mmol) was added dropwise to a stirring solution of silyl ether **203** (50 mg, 96.7 μ mol) and acetic acid (66 μ L, 1.16 mmol) in THF (3 mL) at 0 °C. The solution was warmed to room temperature and stirred for 16 h, diluted with Et₂O (10 mL) and ammonium chloride (sat., aq., 10 mL) was added. The aqueous phase was basified to pH 14 using NaOH (20 % aqueous solution, 10 mL) and the product extracted with Et₂O (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (20% (9:1:0.15 CHCl₃:MeOH:NH₄OH) in CHCl₃) to yield primary alcohol **204** as a colourless oil (21.9 mg, 81%). δ_{H} (700 MHz, d₈-toluene) 5.85-5.35 (1H, br s, OH), 4.03 (1H, td, J 11.4, 1.6, H_{1A}), 3.77 (1H, dtd, J 11.0, 7.3, 3.5, 1.4, H_{1B}), 2.90-2.87 (1H, m, H₃), 2.09-2.05 (1H, m, H_{15A}), 2.01 (1H, ddt, J 14.8, 11.4, 3.7, H_{2A}), 1.93-1.88 (1H, m, H₆), 1.84-1.80 (1H, m, H_{11A}), 1.73 (3H, s, H₁₇), 1.71-1.61 (5H, m, H_{4A}, H₁₀, H_{12A}, H₁₄, H_{15B}), 1.60-1.50 (5H, m, H₅, H_{8A}, H_{11B}, H_{13A}, H₁₈), 1.48-1.45 (1H, m, H_{7A}), 1.42-1.39 (1H, m, H_{4B}), 1.25-1.15 (2H, m, H_{8B}, H_{12B}), 1.11-1.06 (1H, m, H_{2B}), 0.81-0.70 (3H, m, H_{7B}, H₉, H_{13B}); δ_{C} (101 MHz, d₈-toluene) 205.8 (C₁₆), 68.7 (C₁₀), 67.3 (C₆), 60.1 (C₃), 59.9 (C₁), 48.1 (C₁₅), 47.4 (C₉), 37.4 (C₁₄), 37.2 (C₂), 32.9 (C₁₁), 32.8 (C₈), 32.4 (C₅), 31.5 (C₇), 30.1 (C₁₇), 29.6 (C₄), 29.58 (C₁₃), 25.0 (C₁₂); ν_{max} (film)/cm⁻¹ 3392 (br, OH), 1708 (C=O); ESI-MS calcd. for C₁₇H₃₀NO₂ [M+H]⁺ 280.2271, found 280.2277; $[\alpha]_{\text{D}}^{23}$ +3.4 (c 0.7, CHCl₃).

2-((1*S*,3*aS*,5*aS*,6*S*,9*aS*)-6-(2-oxopropyl)dodecahydropyrrolo-[1,2-*a*]-quinolin-1-yl)ethyl 4-bromobenzoate (205)



Triethylamine (30 μ L, 0.22 mmol) was added to a stirring solution of alcohol **204** (14.5 mg, 52 μ mol) and DMAP (~1 mg) in DCM (2 mL) at room temperature. The mixture was stirred at room temperature for 10 min, cooled to 0 °C and 4-bromobenzoyl chloride (23 mg, 0.1 mmol) was added. The resulting solution was warmed to room temperature and stirred for 16 h, diluted with DCM (10 mL), cooled to 0 °C and sodium bicarbonate (sat., aq., 10 mL) was added. The aqueous phase was extracted with DCM (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10-20% (9:1:0.15 CHCl_3 :MeOH: NH_4OH) in CHCl_3) to yield benzoyl ester **205** as a colourless oil (16 mg, 67%). δ_{H} (500 MHz, d_8 -toluene) 7.78 (2H, dt, J 8.5, 2.0, ArH), 7.20 (2H, dt, J 9.0, 2.0, ArH), 4.37 (1H, ddd, J 11.0, 7.5, 5.5, H_{1A}), 4.27 (1H, dt, J 11.0, 7.4, H_{1B}), 2.71-2.67 (1H, m, H_3), 2.19 (1H, dd, 16.1, 4.0, H_{15A}), 2.02 (1H, tdd, J 10.8, 4.1, 2.1, H_6), 1.95-1.89 (1H, m, H_{2A}), 1.88-1.78 (2H, m, H_{10} , H_{11A}), 1.76-1.51 (11H, m, H_{2B} , H_{4A} , H_{7A} , H_{8A} , H_{12A} , H_{13A} , H_{14} , H_{15B} , H_{17}), 1.54 (1H, dq, J 10.9, 3.6, H_{5A}), 1.46-1.32 (2H, m, H_{4B} , H_{5B}), 1.31-1.20 (3H, m, H_{7B} , H_{11B} , H_{12B}), 0.91-0.75 (3H, m, H_{8B} , H_9 , H_{13B}); δ_{C} (126 MHz, d_8 -toluene) 205.8 (C16), 165.5 (ester), 131.8 (Ar), 131.3 (Ar), 129.2 (Ar), 128.2 (Ar), 68.7 (C10), 66.7 (C6), 63.4 (C1), 57.8 (C3), 48.2 (C15), 47.3 (C9), 38.8 (C2), 37.4 (C14), 33.3 (C11), 33.1 (C8), 31.4 (C7), 31.3 (C5), 30.6 (C4), 30.0 (C17), 29.9 (C13), 25.1 (C12); ν_{max} (film)/ cm^{-1} 1718 (br C=O (ketone and ester); ESI-MS calcd. for $\text{C}_{24}\text{H}_{33}^{79}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 462.1638, found 462.1633, $\text{C}_{24}\text{H}_{33}^{81}\text{BrNO}_3$ $[\text{M}+\text{Na}]^+$ 464.1619, found 464.1615; $[\alpha]_{\text{D}}^{23}$ -6.6 (c 0.48, CHCl_3).

S-phenyl-2-((1S,3aS,5aS,6S,9aS)-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)dodecahydropyrrolo-[1,2-*a*]-quinolin-6-yl)ethanethioate
(208)

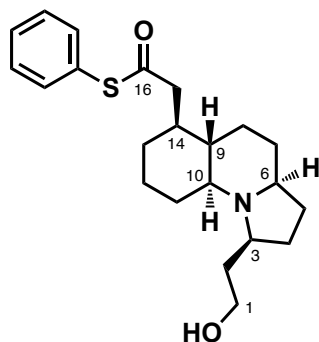


Trifluoroacetic acid (0.2 mL, 2.61 mmol) was added dropwise to a stirring solution of **173** (43 mg, 59 μ mol) in DCM (0.6 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h, concentrated under reduced pressure and azeotroped with toluene (3 x 1 mL). The resulting colourless oil was dissolved in CHCl₃ (1 mL) and stirred at room temperature for 24 h, concentrated under reduced pressure and azeotroped again with toluene (1 mL). The crude oil was dissolved in DCM (2 mL) and cooled to 0 °C. Sodium cyanoborohydride (4.5 mg, 71 μ mol) was added to a stirring solution of crude hydroquininium at 0 °C. The solution was warmed to room temperature and stirred for 16 h, diluted with DCM (10 mL), cooled to 0 °C and sodium bicarbonate (sat., aq., 10 mL) added. The phases were separated and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (*column 1*: 10% (9:1:0.15 CHCl₃:MeOH:NH₄OH) in CHCl₃, *column 2*: 0-2% MeOH (+0.2% NH₄OH) in DCM) to yield perhydro-pyrroloquinoline **208** as a pale yellow oil (28 mg, 78%).[‡] δ_{H} (500 MHz, d₈-toluene, 363 K) 7.82-7.77 (4H, m, Ar (silyl ether)), 7.43-7.36 (2H, m, Ar (thioester)), 7.30-7.23 (6H, m, Ar (silyl ether)), 7.12-7.05 (3H, m, Ar (thioester)), 3.87-3.80 (1H, m, H_{1A}), 3.80-3.73 (1H, m, H_{1B}), 2.84-2.77 (1H, m, H₃), 2.66 (1H, dd, J 15.0, 4.0, H_{15A}), 2.22 (1H, dd, J 15.0, 8.2, H_{15B}), 2.06-1.93 (3H, m, H_{2A}, H₆, H_{11A}), 1.89-1.74 (3H, m, H_{7A}, H₁₀, H_{13A}), 1.73-1.62 (3H, m, H_{4A}, H_{12A}, H₁₄), 1.62-1.53 (1H, m, H_{2B}),

[‡] Full characterisation of **208** was not possible due to the presence of *ca.* 25 % of inseparable uncyclised indolizidine. ¹H- and ¹³C-NMR resonances are quoted from this mixture, as is IR and accurate MS data. An optical rotation measurement was not recorded.

1.53-1.46 (1H, m, H_{5A}), 1.42-1.29 (5H, m, H_{4B} , H_{5B} , H_{7B} , H_{11B} , H_{13A}), 1.28-1.21 (2H, m, H_{8A} , H_{12B}), 1.18 (9H, s, t Bu), 1.07-0.92 (2H, m, H_{8B} , H_9), 0.88-0.77 (1H, m, H_{13B}); δ_C (126 MHz, $CDCl_3$) 197.3 (C16), 134.4 (Ar, silyl ether), 134.39 (Ar, thioester), 132.6 (Ar, silyl ether), 132.56 (Ar, thioester), 129.5 (Ar, silyl ether), 129.3 (Ar, thioester), 128.0 (Ar, thioester), 127.4 (Ar, silyl ether), 69.2 (C10), 66.8 (C6), 62.5 (C1), 58.1 (C3), 48.6 (C15), 47.4 (C9), 43.3 (C2), 39.7 (C14), 33.1 (C11), 32.8 (C5), 31.6 (C8), 31.4 (C7), 30.0 (C4), 28.6 (C13), 27.2 (t Bu), 25.0 (C12), 19.4 (t Bu, 4° carbon); ν_{max} (film)/ cm^{-1} 1689 (C=O); ESI-MS calcd. for $C_{38}H_{50}NO_2SSi$ $[M+H]^+$ 612.3326, found 612.3333.

S-phenyl-2-((1S,3aS,5aS,6S,9aS)-1-(2-hydroxyethyl)dodecahydropyrrolo[1,2-a]quinolin-6-yl)ethanethioate (233)

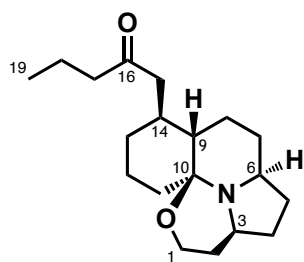


Trifluoroacetic acid (0.14 mL, 1.8 mmol) was added dropwise to a stirring solution of **224** (21 mg, 43 μ mol) in DCM (0.4 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h, concentrated under reduced pressure and azeotroped with toluene (3 x 1 mL). The resulting colourless oil was dissolved in CHCl₃ (1 mL) and stirred at room temperature for 72 h, concentrated under reduced pressure and azeotroped again with toluene (1 mL). In a separate flask, acetic acid (0.19 mL, 3.3 mmol) was added to a stirring solution of tetramethylammonium triacetoxymethylborohydride (90 mg, 0.34 mmol) in acetonitrile (0.2 mL). The resulting mixture was stirred at room temperature for 30 min, cooled to -40 °C and a solution of the crude cascade mixture added in acetonitrile (1 mL) *via* cannula. The solution was stirred at -40 °C for 16 h, diluted with Et₂O (10 mL), water (10 mL) was added and the mixture warmed to room temperature. The aqueous phase was basified to pH 14 using NaOH (20% aqueous solution, 10 mL) and the product extracted with Et₂O (3 x 10 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (*column 1*: 20% (9:1:0.15 CHCl₃:MeOH:NH₄OH) in CHCl₃, *column 2*: 0-2% MeOH (+0.2% NH₄OH) in DCM) to yield primary alcohol **233** as a colourless oil (12 mg, 75%).[§] δ_{H} (500 MHz, CDCl₃) 7.47-7.28 (5H, m, ArH), 6.61-6.30 (1H, br s, OH), 4.04 (1H, td, J 11.1, 2.0, H1_A), 3.74-3.70 (1H, m, H1_B), 3.31-3.24 (1H, m, H3), 2.86 (1H, dd, J 15.0, 4.5, H15_A), 2.39 (1H, dd, J 15.0, 8.7, H15_B), 2.28-2.20 (1H, m, H6), 2.17-1.87 (7H, m, H2_A, H4_A, H7_A, H10, H11_A, H13_A), 1.85-1.69 (4H, m, H5, H12_A, H14), 1.66-1.53 (4H, m, H4_B, H8_A, H11_B), 1.37-1.21 (4H, m, H2_B, H7_B, H12_B), 1.17-0.95 (3H, m, H8_B, H9, H13_B); δ_{C} (126 MHz, CDCl₃) 197.3 (C16), 134.4 (Ar), 132.6 (Ar), 129.5 (Ar), 128.0 (Ar), 68.3 (C10), 67.2 (C6), 60.1 (C3), 59.98 (C1),

[§] Full characterisation was not possible due to the presence of *ca.* 20 % of inseparable uncyclised indolizidine. Major ¹H- and ¹³C-NMR resonances are quoted from this mixture, as is IR and accurate MS data. An optical rotation measurement was not recorded.

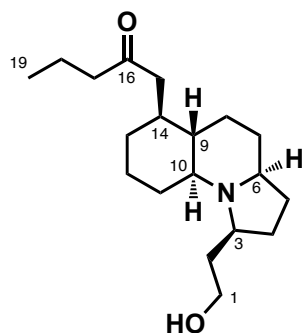
49.1 (C15), 47.1 (C9), 36.5 (C14), 36.2 (C2), 32.5 (C11), 32.1 (C5), 32.0 (C8), 31.0 (C7), 29.3 (C4), 29.2 (C13), 24.5 (C12); ν_{max} (film)/ cm^{-1} 3391 (br OH), 1689 (C=O); ESI-MS calcd. for $\text{C}_{22}\text{H}_{32}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 374.2148, found 374.2141.

1-((1*S*,4*aS*,7*aS*,9*aS*,11*aS*)-dodecahydro-1*H*-benzo[*e*][1,3]oxazino[4,3,2-*cd*]indolizin-1-yl)pentan-2-one (238)



Trifluoroacetic acid (0.3 mL, 3.92 mmol) was added dropwise to a stirring solution of **225** (37 mg, 87.5 μ mol) in DCM (0.9 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h, concentrated under reduced pressure and azeotroped with toluene (3 x 1 mL). The resulting colourless oil was dissolved in CHCl₃ (1 mL) and stirred at room temperature for 72 h, concentrated under reduced pressure and azeotroped again with toluene (1 mL). The crude oil was dissolved in DCM (3 mL), cooled to -78 °C and diisobutylaluminum hydride (1.0 M in cyclohexanes, 90 μ L, 90 μ mol) was added dropwise. The solution was gradually warmed to room temperature over a period of 16 h, diluted with DCM (10 mL) and sodium bicarbonate (sat., aq., 10 mL) was added. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (5-40% (90:10:0.15 CHCl₃:MeOH:NH₄OH) in CHCl₃ to yield aminal **238** as a pale yellow oil (24.2 mg, 91%). δ_{H} (500 MHz, d₈-toluene) 3.67 (1H, ddd, J 11.8, 5.3, 1.3, *H*1_A), 3.47 (1H, td, J 12.2, 2.9, *H*1_B), 2.95 (1H, dd, J 17.6, 6.7, *H*15_A), 2.59 (1H, dd, J 17.6, 7.7, *H*15_B), 2.51-2.45 (1H, m, *H*3), 2.32-2.27 (1H, m, *H*14), 2.26-2.21 (1H, m, *H*6), 2.15-2.14 (1H, m, *H*17_A), 2.08-2.02 (1H, m, *H*17_B), 1.91-1.85 (1H, m, *H*11_A), 1.52-1.46 (10H, m, *H*2_A, *H*4_A, *H*5_A, *H*7_A, *H*8_A, *H*9, *H*12_A, *H*13_A, *H*18), 1.41-1.32 (4H, m, *H*2_B, *H*8_B, *H*12_B, *H*13_B), 1.31-1.17 (4H, m, *H*4_B, *H*5_B, *H*7_B, *H*11_B), 0.85 (3H, t, J 7.4, *H*19); δ_{C} (126 MHz, d₈-toluene) 209.0 (*C*16), 88.4 (*C*10), 59.3 (*C*1), 56.9 (*C*6), 51.9 (*C*3), 48.2 (*C*15), 45.5 (*C*9), 45.4 (*C*17), 34.7 (*C*14), 33.8 (*C*2), 32.9 (*C*7), 30.6 (*C*4), 30.1 (*C*13), 29.1 (*C*5), 26.3 (*C*8), 18.2 (*C*12), 17.6 (*C*18), 16.2 (*C*11), 14.0 (*C*19); ν_{max} (film)/cm⁻¹ 1712 (C=O); ESI-MS calcd. for C₁₉H₃₂NO₂ [*M*+*H*]⁺ 306.2428, found 306.2431; [α]_D²³ -3.4 (*c* 0.18, CHCl₃).

1-((1*S*,3*aS*,5*aS*,6*S*,9*aS*)-1-(2-hydroxyethyl)dodecahydropyrrolo[1,2-*a*]quinolin-6-yl)pentan-2-one (236)



Palladium on carbon (0.7 mg, 10 wt% Pd) was added to a stirring solution of aminal **238** (7 mg, 23 μ mol) and triethylamine (32 μ L, 0.23 mmol) in DMF (2 mL). The resulting mixture was degassed (x 3) with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered through a short plug of Celite®. The cake was washed with DCM (3 x 10 mL) and the organic filtrates concentrated under reduced pressure to yield perhydro-pyrroloquinoline **236** as a pale yellow oil (6 mg, 92%). δ_{H} (500 MHz, d_8 -toluene) 4.04 (1H, td, 11.5, 1.5, H_{1A}), 3.78 (1H, dtd, J 11.4, 3.5, 1.5, H_{1B}), 2.92-2.87 (1H, m, H_3), 2.14-2.09 (1H, m, H_{15A}), 2.06-1.97 (3H, m, H_{2A} , H_{17}), 1.94-1.88 (1H, m, H_6), 1.84-1.81 (1H, m, H_{11A}), 1.74-1.60 (6H, m, H_{4A} , H_{5A} , H_{10} , H_{12A} , H_{14} , H_{15B}), 1.59-1.48 (6H, m, H_{5B} , H_{8A} , H_{11B} , H_{13A} , H_{18}), 1.43-1.33 (1H, m, H_{4B} , H_{7A}), 1.30-1.16 (2H, m, H_{8B} , H_{12B}), 1.08 (1H, ddt, J 14.4, 3.3, 1.7, H_{2B}), 0.86 (3H, t, J 7.4, H_{19}), 0.83-0.70 (3H, m, H_{7B} , H_9 , H_{13B}); δ_{C} (126 MHz, d_8 -toluene) 208.3 (C_{16}), 68.6 (C_{10}), 67.2 (C_6), 60.1 (C_3), 59.9 (C_1), 47.4 (C_9), 47.3 (C_{15}), 45.5 (C_{17}), 37.3 (C_{14}), 37.2 (C_2), 33.0 (C_{11}), 32.9 (C_8), 32.4 (C_5), 31.6 (C_7), 29.64 (C_4), 29.62 (C_{13}), 25.1 (C_{12}), 17.5 (C_{18}), 14.0 (C_{19}); ν_{max} (film)/ cm^{-1} 3315 (OH), 1712 (C=O); ESI-MS calcd. for $C_{19}H_{34}NO_2$ $[M+H]^+$ 308.2584, found 308.2598; $[\alpha]_{\text{D}}^{23}$ +4.5 (c 0.4, CHCl_3).

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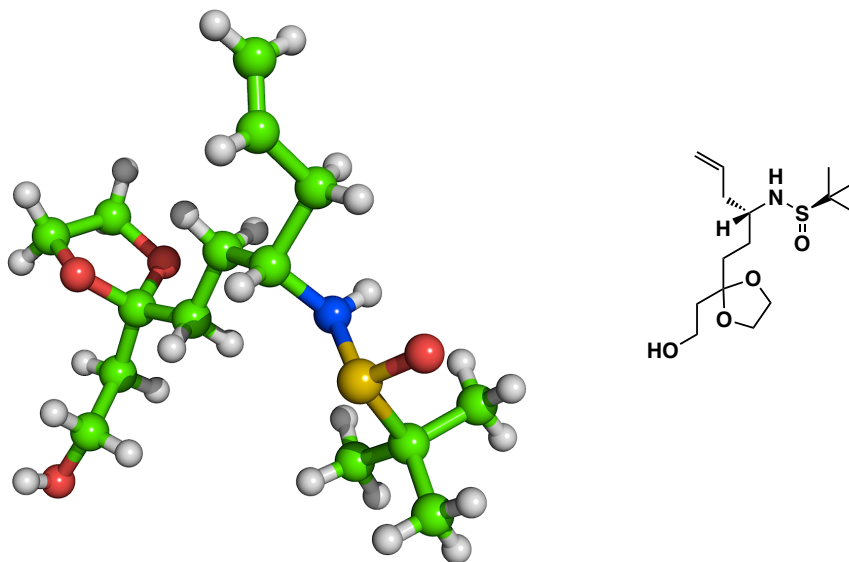
Chapter 8 Appendices

8.1 Appendix 1

8.1.1 X-ray Diffraction Data

Further data may be found on the attached CD for 002sw09 (**76**), 6392 (**113**) and DIA0146 (**206**). Key data and refinements for each structure are presented in this appendix.

(R)-N-((R)-1-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide (76)

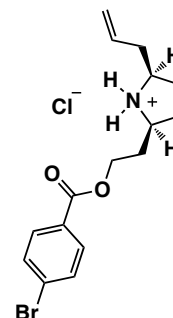
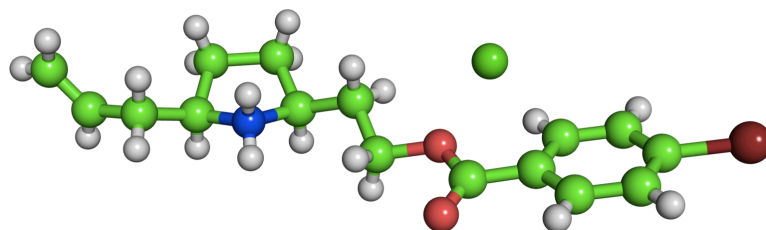


Key data and refinement for the crystal structure of 76

Identification code	002sw09
Empirical formula	C ₁₅ H ₂₉ NO ₄ S
Formula Weight	319.48
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21

Unit cell dimensions	a = 5.6430(1) Å	$\alpha = 90^\circ$
	b = 16.7335(3) Å	$\beta = 90^\circ$
	c = 18.8335(4) Å	$\gamma = 90^\circ$
Volume	1778.39 Å ³	
Z	4	
Density (calculated)	1.193 mg/m ³	
Absorption coefficient	0.196 mm ⁻¹	
F(000)	696	
Crystal size	0.50 x 0.06 x 0.03 mm ³	
Theta range for data collection	5.140 to 27.491 °	
Index ranges	-7≤h≤7, -21≤k≤21, -24≤l≤24	
Reflections collected	14071	
Independent reflections	4071 [R(int) = 0.0308]	
Completeness to theta = 74.841 °	98.9 %	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.9	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4049 / 52 / 219	
Goodness-of-fit on F ²	0.9099	
Final R indices [I>2sigma(I)]	R1 = 0.0349, wR2 = 0.0762	
R indices (all data)	R1 = 0.0431, wR2 = 0.0848	
Absolute structure parameter	0.03(7)	
Largest diff. peak and hole	0.20 and -0.23 e.Å ⁻³	

(2R,5S)-2-allyl-5-(2-((4-bromobenzoyl)oxy)ethyl)pyrrolidin-1-ium chloride (113)

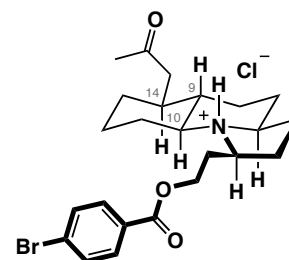
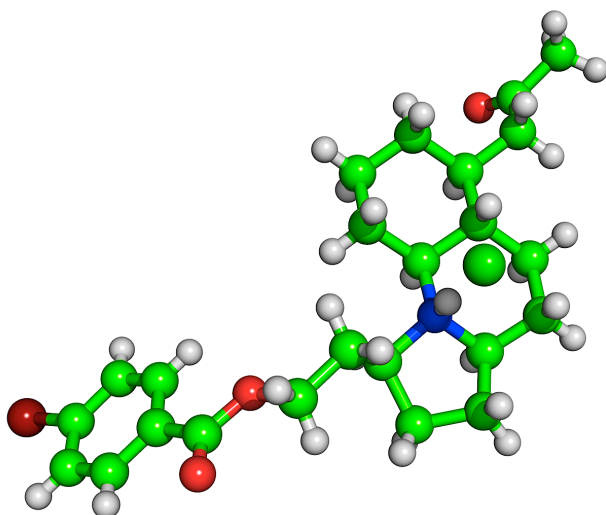


Key data and refinement for the crystal structure of 113

Identification code	6392
Empirical formula	C ₁₆ H ₂₁ BrClNO ₂
Formula Weight	374.70
Temperature	150 K
Wavelength	1.54180 Å
Crystal system	Monoclinic
Space group	P 1 21 1
Unit cell dimensions	$a = 7.9526(3) \text{ Å}$ $\alpha = 90^\circ$ $b = 7.1224(3) \text{ Å}$ $\beta = 104.354(4)^\circ$ $c = 15.4107(6) \text{ Å}$ $\gamma = 90^\circ$
Volume	845.64(6) Å ³
Z	2
Density (calculated)	1.471 mg/m ³
Absorption coefficient	4.795 mm ⁻¹
F(000)	384
Crystal size	0.1000 x 0.100 x 0.010 mm ³
Theta range for data collection	2.960 to 76.368 °
Index ranges	-9 ≤ h ≤ 9, -8 ≤ k ≤ 7, -19 ≤ l ≤ 16

Reflections collected	8812
Independent reflections	3192 [R(int) = 0.037]
Completeness to theta = 74.841 °	99.6 %
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.95 and 0.86
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3191 / 1 / 191
Goodness-of-fit on F ²	0.9786
Final R indices [I>2sigma(I)]	R1 = 0.0304, wR2 = 0.0733
R indices (all data)	R1 = 0.0330, wR2 = 0.0750
Absolute structure parameter	-0.022(19)
Largest diff. peak and hole	0.42 and -0.47 e.Å ⁻³

(1S,3aS,5aS,6S,9aS,10R)-1-(2-((4-bromobenzoyl)oxy)ethyl)-6-(2-oxopropyl)dodecahydro-1H-pyrrolo[1,2-a]quinolin-10-ium chloride (206)



Key data and refinement for the crystal structure of 206

Identification code	DIA0146	
Empirical formula	C ₂₄ H ₃₃ BrClNO ₃	
Formula Weight	498.89	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 10.2492(2) Å	α = 90 °
	b = 7.5316(2) Å	β = 106.004(2) °
	c = 16.0050(4) Å	γ = 90 °
Volume	1187.59(5) Å ³	
Z	2	
Density (calculated)	1.395 mg/m ³	
Absorption coefficient	1.868 mm ⁻¹	

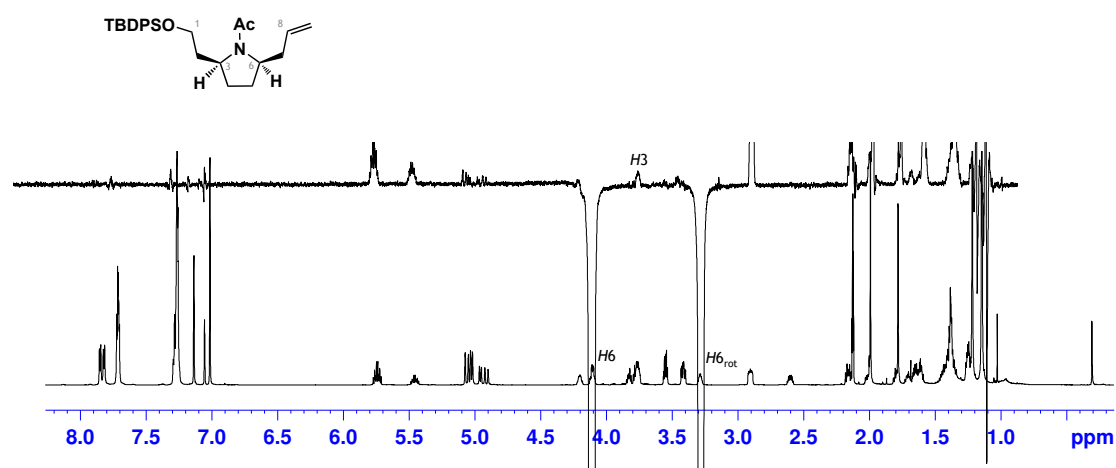
F(000)	520
Crystal size	0.0100 × 0.010 × 0.010 mm ³
Theta range for data collection	2.004 to 28.470 °
Index ranges	-14 ≤ h ≤ 13, -10 ≤ k ≤ 8, -21 ≤ l ≤ 21
Reflections collected	16829
Independent reflections	5634 [R(int) = 0.058]
Completeness to theta = 25.053 °	98.3 %
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.78
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5153 / 1 / 272
Goodness-of-fit on F ²	1.0086
Final R indices [I > 2σ(I)]	R1 = 0.0426, wR2 = 0.1086
R indices (all data)	R1 = 0.0439, wR2 = 0.1118
Absolute structure parameter	-0.026(8)
Largest diff. peak and hole	1.26 and -1.49 e.Å ⁻³

8.2 Appendix 2

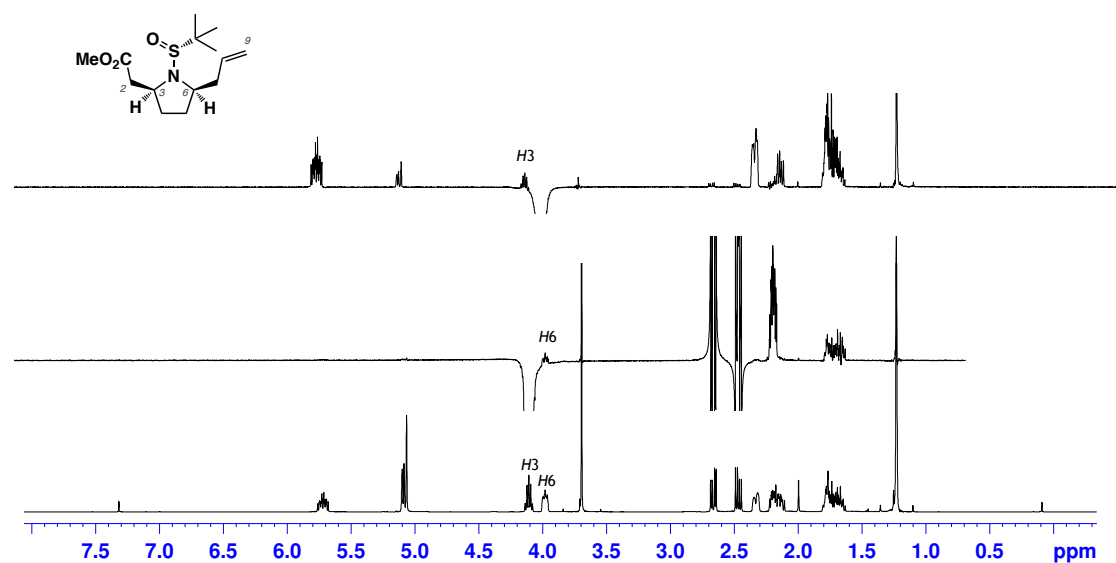
8.2.1 1D nOe Data

The annotated 1D gradient NOESY spectra of **79**, **109** and **204** are presented in this appendix. Key pre-saturation and enhancement peaks are indicated ($t_{\text{mix}} = 800$ ms).

1-((2*R*,5*S*)-2-allyl-5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)pyrrolidin-1-yl)ethanone (**79**)



methyl 2-((2*S*,5*R*)-5-allyl-1-((*R*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)acetate (**109**)



1-((1*S*,3*aS*,5*aS*,6*S*,9*aS*)-1-(2-hydroxyethyl)dodecahydropyrrolo[1,2-*a*]quinolin-6-yl)propan-2-one (204)

