Cascade approaches to decahydroquinoline ring systems

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A dissertation presented in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

University of Oxford

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July 2010

Declaration

This dissertation describes work carried out in the University Chemical Laboratory, Cambridge between October 2006 and September 2008 and the Chemical Research Laboratory, Oxford between October 2008 and July 2010. The dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

Hannah Lingard

Acknowledgements

I am so very grateful to my supervisor, Dr Martin Smith, for giving me the opportunity to work on an exciting and challenging project, for his boundless enthusiasm and never-ending supply of ideas when mine have run out, for his invaluable advice on matters both chemistry-related and otherwise, and for creating such a fantastic group of people to work with in the Smith group.

I must also thank my industrial supervisor, Dr David Dean, for his kindness and many helpful suggestions over the course of our CASE meetings.

Working in the Smith group has been a wonderful experience, and I feel very lucky to have worked with so many brilliant people and made some amazing friends. Special thanks must go to Dr Chris Jones for first making me feel welcome, Elle Maciver (favourite conference buddy!) Peter Knipe for skilled *cis*-decalin drawing and excellent music taste, Stephen Wallace (Team Cascade!), Dr Anthony Coyne, Dr Rhian Thomas, Dr Pranjal Baruah, Dr Khurram Qureshi, Dr Abhishek Kothari, Craig Johnston, Caroline Stovold, Joe Marshall, Peter Davey, Dai Yeo, Laura Manicassamy, Jens Wegner, Jana Franke, Fiona Truscott, Alex Putau, Russell Currie and Konstantin Poscharny, you have all helped to make the last (almost) four years both memorable and fun, in and out of the lab. Thank you particularly to those of you who have helped me over the last few months with proofreading and finishing this!

Liz Jones has been an amazing friend, thank you so much for all your support and all the exciting times we've had – feels like a long time since we first met in lab 180! I look forward to our next adventure.

Many thanks are also due to Dr Stuart Warren for being an inspirational undergraduate supervisor and a good friend, and Dr David Fox who gave me my first taste of research, I wouldn't have made it this far without the strong foundations you both laid.

I would like to thank the many members of staff in both the Cambridge and Oxford departments who have been so helpful to me over the years. Special thanks to Dr Barbara Odell for her patience with my many VT NMRs, Dr Tim Claridge for his invaluable help with solving my very complex structures through 2D NMR and Dr Amber Thompson for my crystal structures.

My life and this DPhil would be much poorer if it wasn't for Dr Sam Thompson and I am grateful every day that Martin didn't take your advice back in summer 2006! Thank you from the bottom of my heart for being a wonderful support and for all your chemistry advice (even if I don't always take it!). I couldn't have done it without you.

Finally thank you to my wonderful parents and brother whose unconditional love and support have helped me every step of the way.

Abbreviations

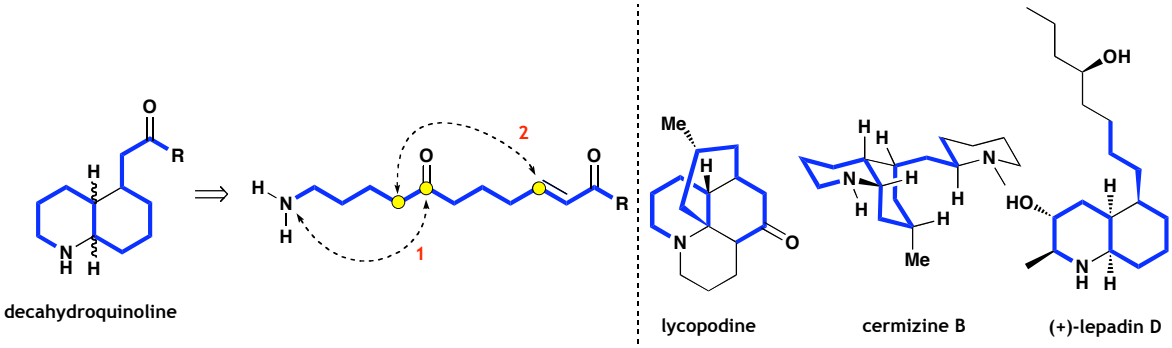
4PAA	4-(2-piperidyl) acetoacetate
Ac	acetyl
aq	aqueous
atm.	atmospheres
Bn	benzyl
Boc	tertiary-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CM	cross metathesis
COSY	Correlation Spectroscopy
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
de	diastereomeric excess
(-)-DET	(-)-diethyl tartrate
DIAD	di*iso*propyl azodicarboxylate
DIBAL-H	di*iso*butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
eq.	equivalents
Et	ethyl
h	hours

HKR	hydrolytic kinetic resolution
HMBC	Heteronuclear Multiple-Bond Correlation
HSQC	Heteronuclear Single Quantum Correlation
i	*iso*
imid.	imidazole
IPA	*iso*propyl alcohol
LDA	lithium di*iso*propylamide
LHMDS	lithium hexamethyldisilazide
M	mol dm^{-3}
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minutes
mol	mole
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves/mass spectrometry
n	*neo*
N	normal
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
[O]	oxidation
o/n	overnight
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million

Pr	propyl
p-TSA	*para*-toluenesulfonic acid
pyr.	pyridine
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
ROM	ring-opening metathesis
rt	room temperature
SAE	Sharpless asymmetric epoxidation
SES	trimethylsilylethanesulfonyl
SM	starting material
t	tertiary
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	tertiary-butyldiphenylsilyl
TBS	tertiary-butyldimethylsilyl
TDS	thexyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMS	trimethylsilyl
tol.	toluene
TPAP	tetrapropylammonium perruthenate
Troc	2,2,2-trichloroethyloxycarbonyl
Ts	toluenesulfonyl
TS	transition state
UV	ultra-violet

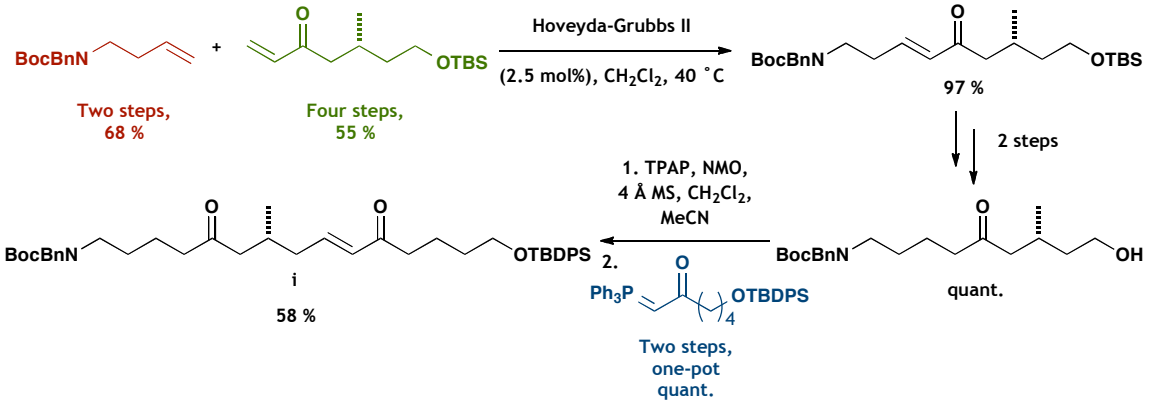
Abstract

The aims of this project were to develop a cascade approach towards decahydroquinoline frameworks (Scheme **I**) and apply this to the synthesis of decahydroquinoline-containing natural products such as lycopodine, cermizine B and lepadin D (Scheme **I**).



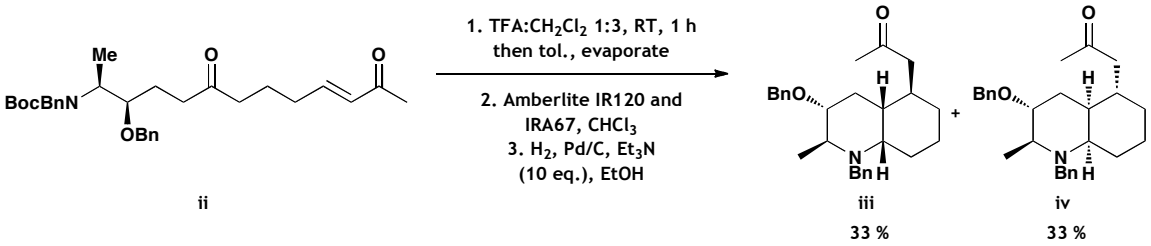
Scheme I

Several linear precursors were synthesized *via* a modular strategy. For example, lycopodine linear precursor **i** was synthesized in a total of 12 steps (Scheme **II**).



Scheme II

Conditions for cyclization and hydrogenation were tested, with the diastereoselectivity examined in each system. For example, the lepadin linear precursor **ii** produced two decahydroquinolines **iii** and **iv** upon cyclization (Scheme **III**).



Scheme III

It was found that the diastereoselectivity was dependent on the ring substituents and variation of the hydrogenation conditions could change the facial selectivity of enamine reduction.

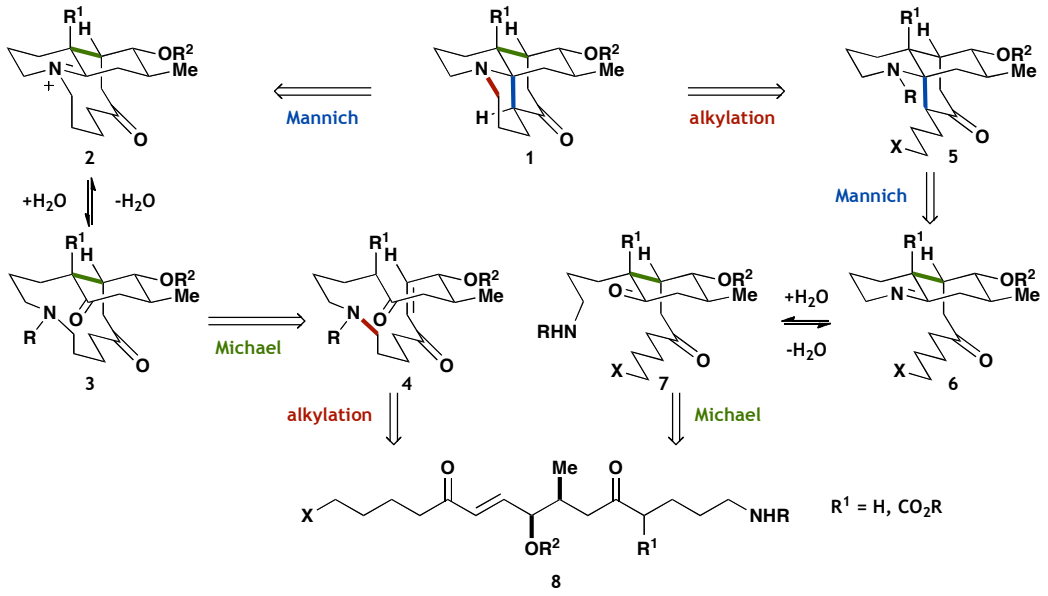
1 Introduction

1.1 Polycyclic molecules from linear precursors

Construction of complex polycyclic systems from relatively simple linear precursors is an attractive approach for synthetic chemists both from a strategic and a pragmatic point of view. There is the potential to rapidly increase complexity in an efficient manner requiring few steps, minimal purification and producing little waste. Moreover, approaches of this kind often involve elegant disconnections and innovative exploitation of known reactions as well as the development of new processes. Most importantly there is the potential to form several rings and, concomitantly, several stereocentres in a controlled fashion to access desired scaffolds for both natural and unnatural products.

1.1.1 A stepwise approach

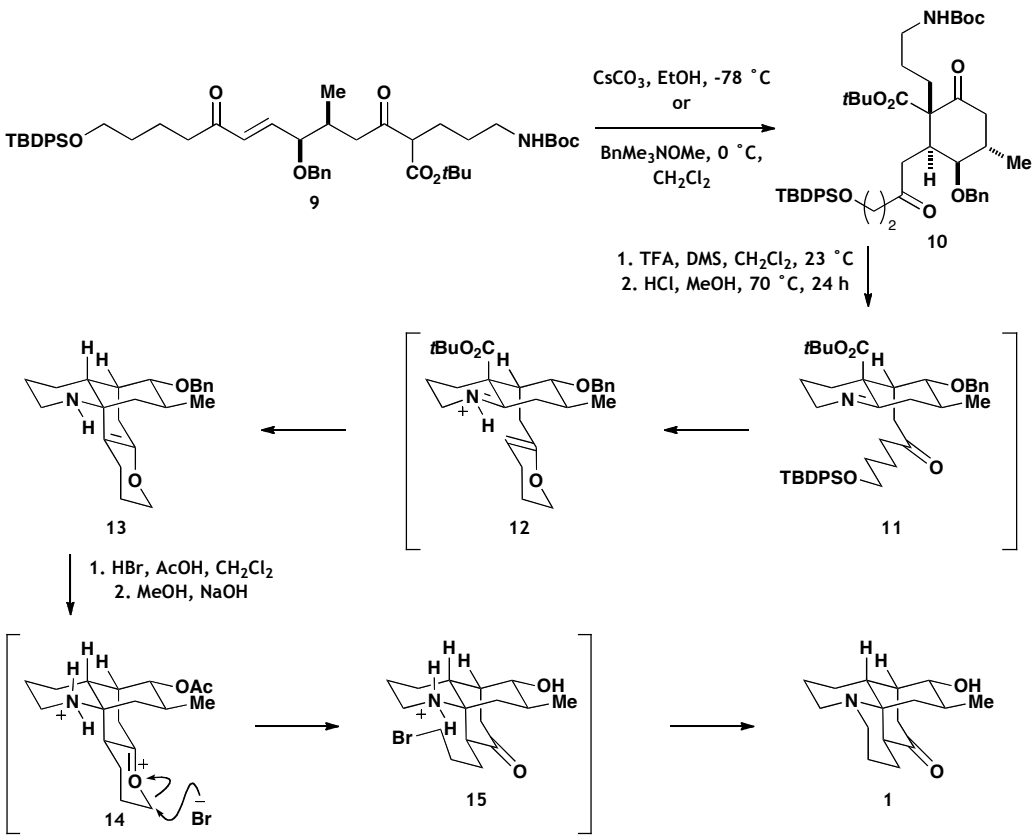
One possibility for this "linear to polycyclic" approach is to construct a molecule containing the necessary functional groups and then induce it to cyclize in a stepwise manner. We are particularly interested in polycyclic systems containing a decahydroquinoline motif and so this introduction will mainly focus on these types of molecules. An example of using this strategy to form a decahydroquinoline-containing system is the total synthesis of clavolonine **1**, as demonstrated by Evans.[1] Two viable routes for the cyclization were envisaged (Scheme **1**), either by the initial formation of a macrocycle, or a linear pathway that forms the rings in succession.



Scheme 4

The two routes could start from common linear precursor **8**. The planned macrocyclic route would involve intramolecular alkylation forming macrocycle **4**, followed by transannular Michael addition to form **3**, condensation of the amine with one of the ketones to give **2** and a Mannich-type cyclization to close the final ring. In the other more pragmatic route, the first step utilizes a Michael addition to give **7**, followed by condensation of the amine with the ketone. An intramolecular Mannich gives **5** and finally alkylation of the amine would yield clavolonine **1**.

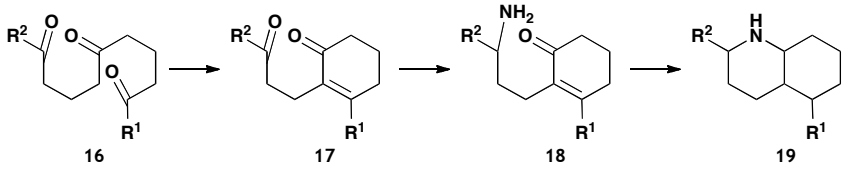
Both routes were investigated, but it was found that only the linear route was successful due to problems with differentiating the carbonyl groups in the macrocycle **4** during the condensation step. The most efficient route started from the linear precursor **9** (Scheme **2**). Treatment of **9** with base induced cyclization to form cyclohexanone **10** as the first ring in this process. This was followed by a series of cyclizations induced by treatment with acid: Removal of the *N*-Boc protecting group using TFA allowed condensation with the ketone to give bicyclic imine **11**. Further cyclizations were promoted by subjecting imine **11** to methanolic HCl to yield tetracycle **13**. Finally the tetracycle could be rearranged to yield clavolonine **1**.



Scheme 5

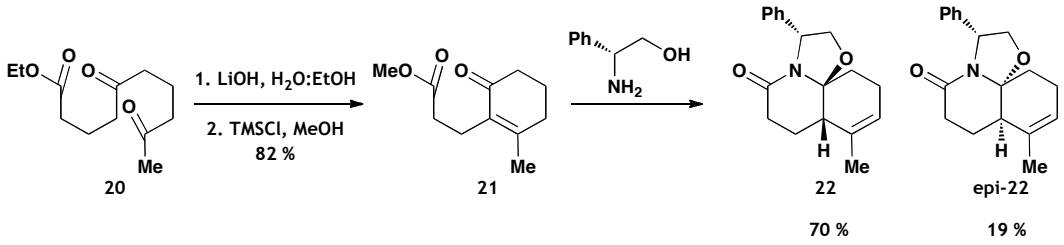
We hope to exploit a related sequence in our synthesis of decahydroquinoline ring systems.

Recently an approach to decahydroquinoline systems from linear precursors has been outlined by Amat, Bosch *et al*.[2] The biosynthetic origin of decahydroquinoline amphibian alkaloids such as pumiliotoxin C is as yet an unresolved question. One possibility could be that they derive from the polyketide pathway by aminocyclization of straight-chain 1,5-polycarbonyl products (Scheme **3**).[3] This route is reminiscent of Robinson's synthesis of tropinone[4] which will be examined itself in due course.



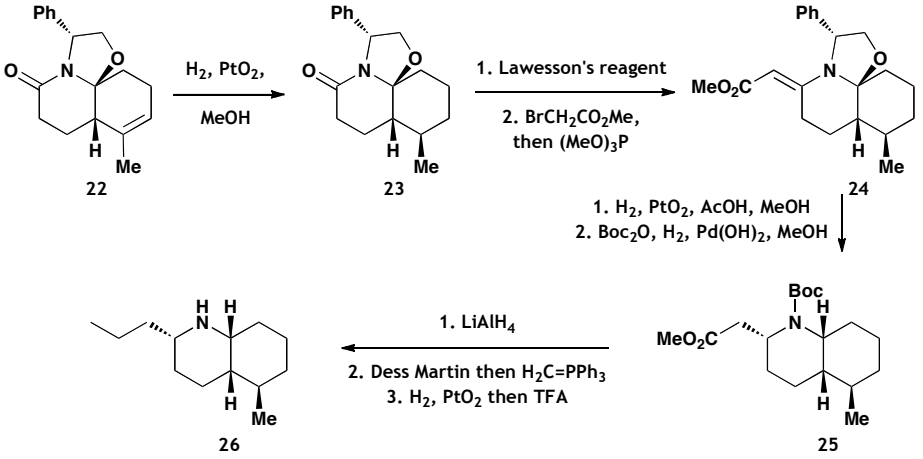
Scheme 6

Amat *et al.* noticed a reaction of this nature taking place in an attempted synthesis of (+)-anaferine and decided to explore it further. They found they were able to effect the stepwise cyclization of a linear precursor **20** to form a tricyclic product **22** in pleasing yield (Scheme **4**).



Scheme 7

Sequential treatment of diketoester **20** with aqueous lithium hydroxide in ethanol and trimethylsilyl chloride in methanol promoted cyclization to cyclohexenone **21** in good yield. Cyclization with (*R*)-phenylglycinol stereoselectively provided tricyclic lactam **22** in 70 % yield, with a further 19 % yield of epi-**22**. Tricyclic lactam **22** could be transformed to (-)-pumiliotoxin C **26** in a further 8 steps (Scheme **5**).

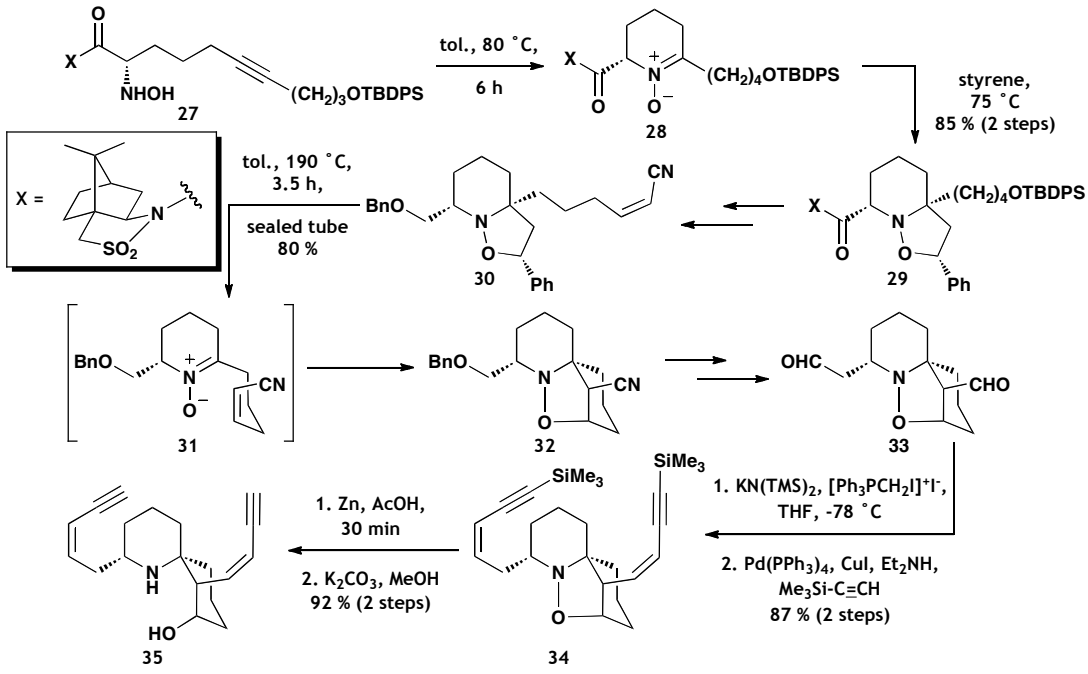


Scheme 8

Hydrogenation of **22** delivered the hydrogen *anti* to the ring-junction substituents to give tricycle **23**. Eschenmoser sulfide contraction led to formation of *β*-enamino ester **24** which could then be subjected to further hydrogenation conditions. Use of a platinum catalyst in acidic conditions allowed hydrogenation of the alkene from the top face in this case (the same face as the ring junction substituents and methyl side chain) and also promoted

cleavage of the C-O bond. Subsequent hydrogenolysis of the *N*-benzyl group using Pearlman's catalyst in the presence of Boc anhydride led to formation of decahydroquinoline **25**. All that remained was to elaborate the ester into the *n*-propyl sidechain and deprotect the amine which was achieved in a further three steps to yield (-)-pumiliotoxin C **26**.

Other alkaloid frameworks have been accessed by stepwise approaches from linear precursors. The synthesis of (-)-histrionicotoxin **35** in the laboratory of Andrew Holmes involves a number of cyclization steps starting from a linear precursor (Scheme **6**).[5]

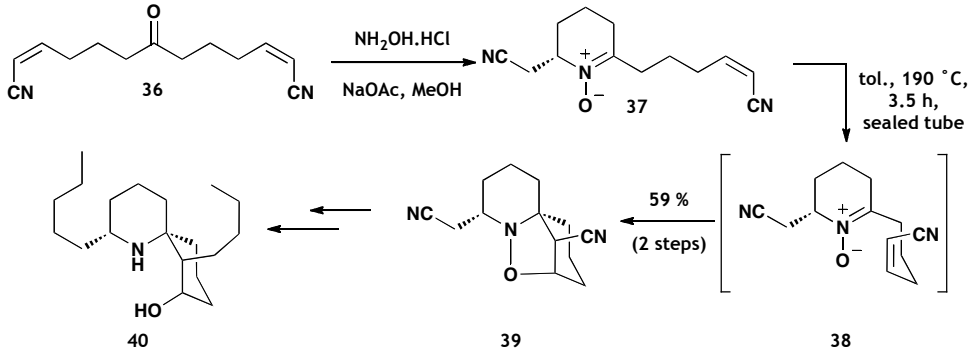


Scheme 9

Amido-alkyne **27** (prepared as a single diastereoisomer using Oppolzer's hydroxyamination[6] protocol) was heated in toluene to promote the intramolecular cyclization to give nitrone **28**, which was immediately used in a 1,3-dipolar cycloaddition with styrene to give isoxazolidine **29** as a single diastereo- and regioisomer. Further steps were needed to remove the chiral auxiliary and elaborate the bicycle to α,β-unsaturated nitrile **30**, ready for the key retrocycloaddition-cycloaddition step. Holmes *et al.* found that the best conditions for this process were heating in toluene at 190 °C in a sealed tube to

yield tricycle **32** with very high regioselectivity, *via* postulated intermediate nitrone **31** with loss of styrene. Thus the second ring of the natural product and three new stereocentres are formed in a single process. This tricycle can be elaborated to the natural product *via* transformation of both the protected alcohol and the nitrile to aldehydes and installation of the two identical sidechains using palladium-mediated coupling reactions. This is followed by reduction of the N-O bond using zinc dust and desilylation to yield (-)-histrionicotoxin **35** in 16 % overall yield.

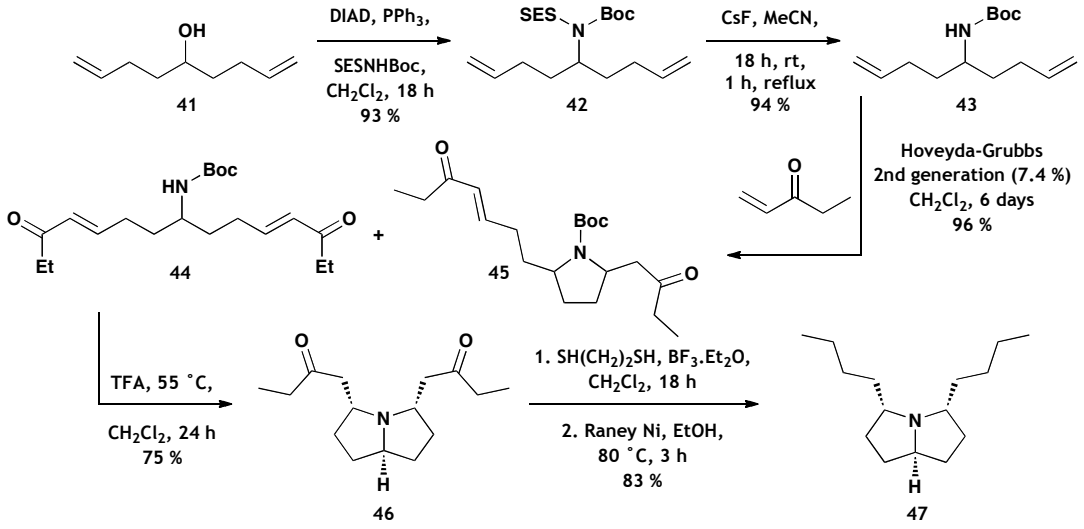
An interesting synthesis of a very similar molecule, (±)-perhydrohistrionicotoxin **40** was carried out in the group of Stockman (Scheme **7**).[7] The same key cycloaddition step is used, but in this (racemic) synthesis the initial linear precursor **36** is symmetrical and is prepared *via* dialkylation of 1,3-dithiane.



Scheme 10

Treatment of symmetrical ketone **36** with hydroxylamine hydrochloride and sodium acetate in methanol lead directly to formation of nitrone **37**, *via* oxime formation, intramolecular Michael addition and a 1,4-proton shift. The nitrone could then be directly transformed into tricycle **39** by using Holmes' conditions of heating in toluene at 190 °C in a sealed tube. Tricycle **39** is very similar to **32** above and can be transformed into (±)-perhydrohistrionicotoxin **40** in three further steps (DIBAL-H reduction of the two nitriles to aldehydes, Wittig reaction and hydrogenation) and an overall yield of 11 % from 1,3-dithiane.

The Stockman group have extended their use of symmetrical linear precursors to access a range of natural and unnatural molecules. An excellent example of this with regard to our ambitions for making polycyclic molecules is their route to alkaloid *cis*-223B **47** in the first published total synthesis of this system (Scheme **8**).[8]



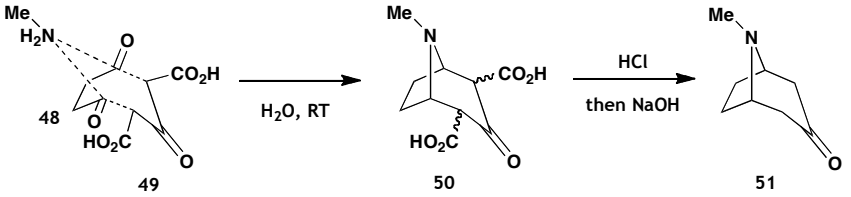
Scheme 11

The synthesis starts from symmetrical alcohol **41**, derived from addition of 3-butenyl-magnesium bromide to ethyl formate. A Mitsonobu reaction installs the protected amine followed by mono-deprotection to give symmetrical amine **43**. Double cross metathesis with 1-penten-3-one gave a mixture of the desired linear precursor **44** and some monocyclized pyrrolidine **45** which could be treated as the mixture with TFA in dichloromethane to remove the Boc group and induce cyclization. Double conjugate addition of the amine into the two Michael acceptors yields bicyclic pyrrolizidine **46** as a single diastereoisomer in excellent yield for a double cyclization process. Removal of the ketone groups by dithiane formation and Raney nickel reduction gives alkaloid *cis*-223B **47** in just seven steps and 43 % overall yield. This sequence shows the power of cascade processes to form polycyclic systems in a single synthetic step and we will focus on cascade approaches to complex molecules for the remainder of this discussion.

1.1.2 Cascade Reactions

Cascade reactions[9] can be used to great effect in synthetic strategies, providing elegant and efficient routes to a range of products. They present an interesting alternative to linear stepwise procedures in the synthesis of complex natural products and have the potential to be more economical than traditional methods due to the rapid increase in complexity possible in one step. This, however, must be balanced by the ease with which the cascade precursor(s) may be generated; the application of cascade reactions in the field of natural product synthesis can be intellectually and strategically demanding.

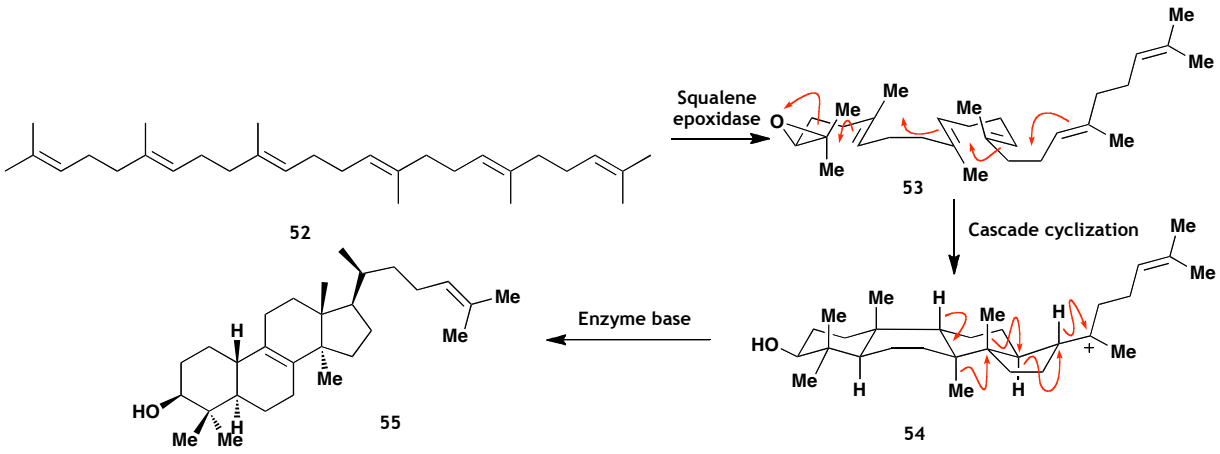
An early example of a cascade approach to a natural product is Robinson's one-pot synthesis of tropinone **51** (Scheme **9**).[4]



Scheme 12

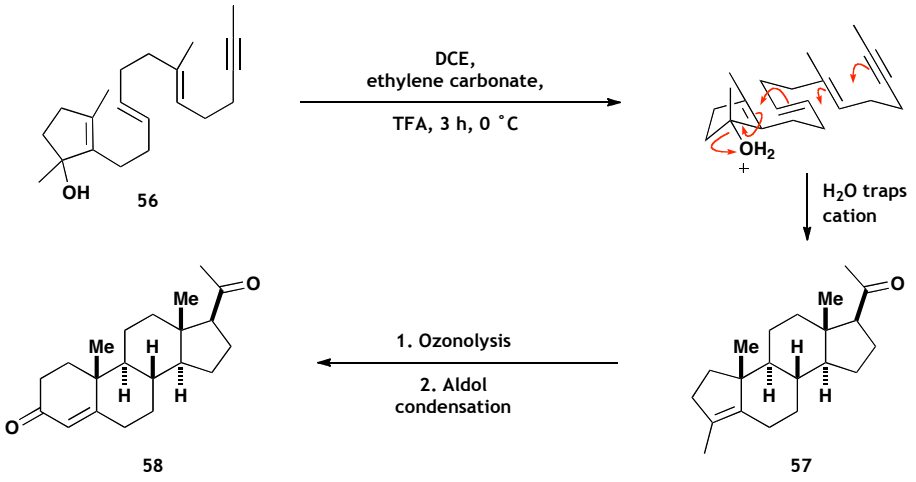
This biomimetic synthesis of tropinone involves the condensation of methylamine with a dialdehyde **48** and nucleophilic addition of a ketodiacid **49** into the activated iminium species. Decarboxylation of the resultant bicycle **50** yields tropinone **51**.

Cascade sequences such as this tropinone condensation are common in nature and often a synthesis will hope to exploit the knowledge of a biosynthetic pathway in forming a cascade approach to a natural product. The cascade cyclization of squalene **52** (Scheme **10**) to form lanosterol **55** is part of the biosynthetic pathway to cholesterol.[10]



Scheme 13

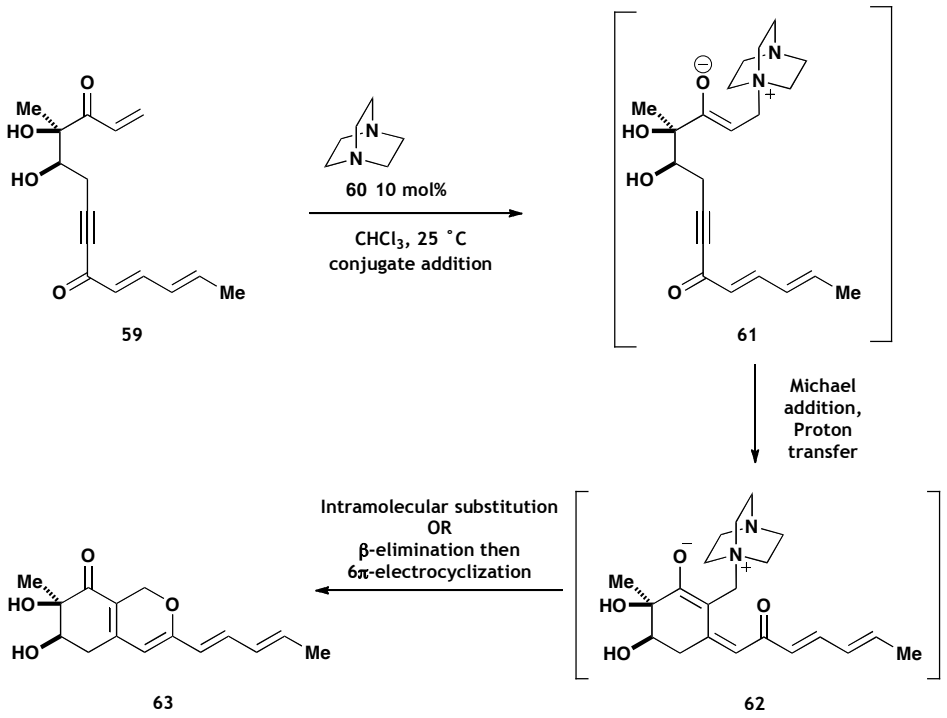
Knowledge of this cascade has been exploited in a number of biomimetic cyclizations including the synthesis of progesterone **58**,[11, 12] but these tend to proceed *via* an all-chair transition state instead of a chair-boat-chair since the transition state is not controlled by an enzyme (Scheme **11**).



Scheme 14

These cascades to form steroids are examples of electrophile-driven cyclization sequences. These differ slightly from the system we hope to use, which relies on a nucleophile-driven approach.

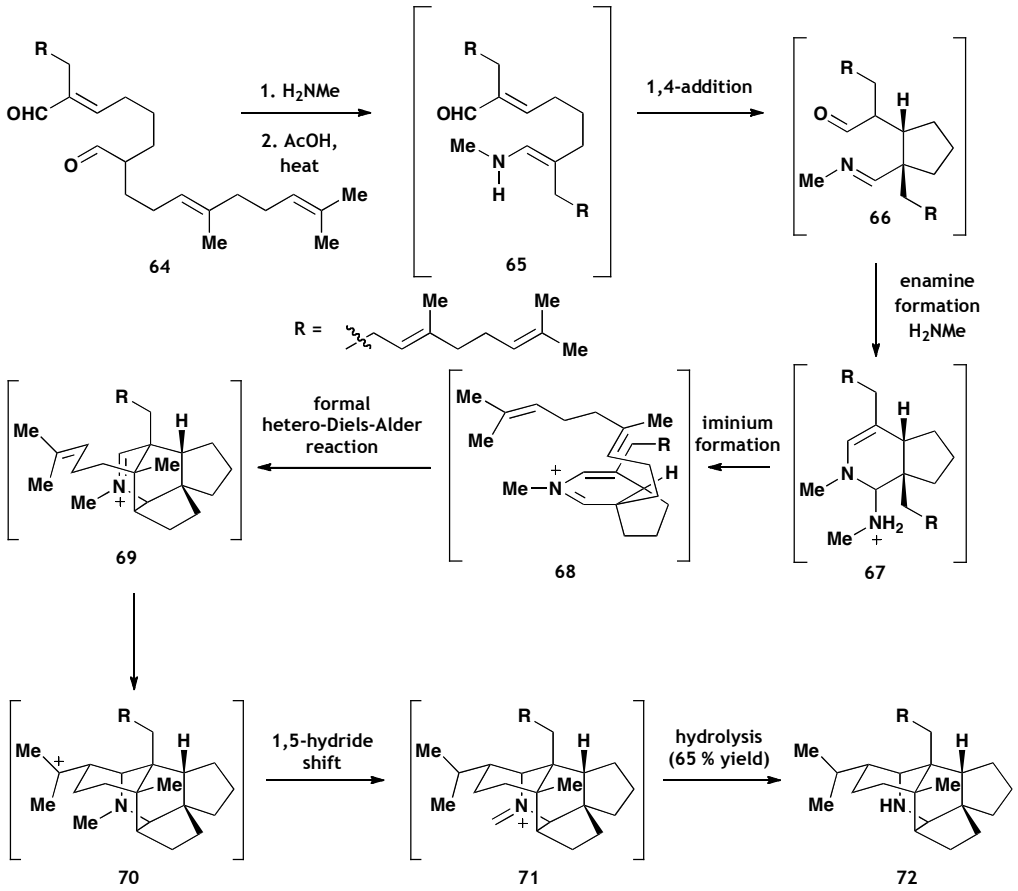
There are many examples of cascade reactions which employ this type of approach, for example in the total synthesis of (+)-harziphilone **63** (Scheme **12**).[13]



Scheme 15

DABCO **60** is used as a nucleophile to initiate a cascade that consists of a Michael addition to give **62** followed by intramolecular substitution or elimination and 6π-electrocyclization to give (+)-harziphilone **63** in a 70% yield.

Heathcock's remarkable synthesis of dihydro-*proto*-daphniphylline **72** (Scheme **13**)[14, 15] provides an example of a cascade which is conceptually similar to the approach we hope to exploit in terms of imine/enamine activation.



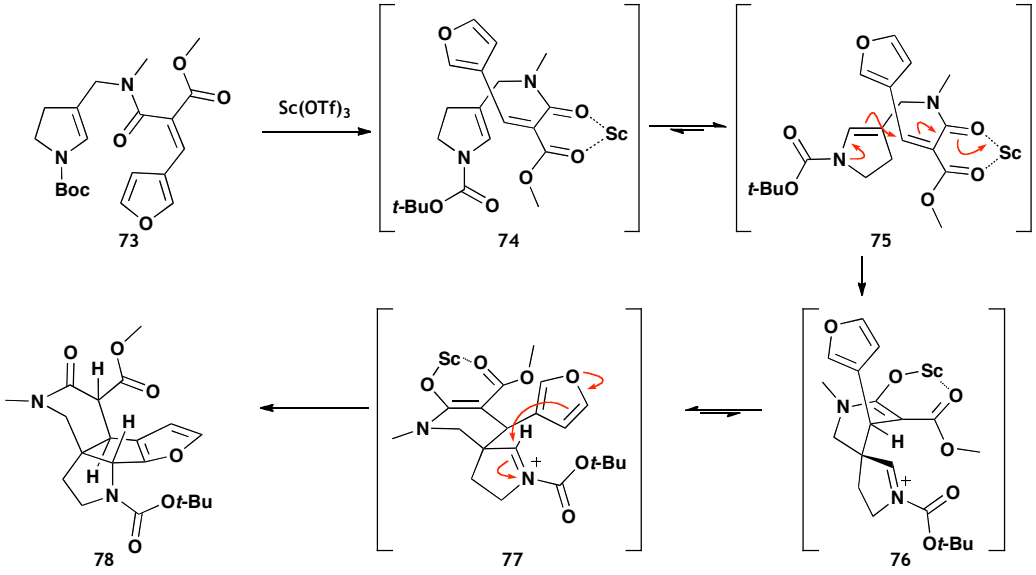
Scheme 16

The whole sequence forms five rings and eight stereogenic centres in a completely diastereoselctive fashion. The first step initiates the cascade by condensation of methylamine with the most reactive aldehyde to give the secondary enamine **65**. Intramolecular Michael addition of enamine **65** onto the enal group (forming the first ring) is followed by further condensation and cyclization to form iminium ion **68**. The formal hetero-Diels-Alder to give **69** may proceed *via* a Prins cyclization forming the second five-membered ring, followed by ring closure between the resulting enamine and tertiary carbocation, instead of a concerted Diels-Alder cycloaddition. The fifth and final ring is formed by another Prins cyclization and a 1,5-hydride shift from the methyl group of the tertiary amine to the carbocation completes the cascade to yield **71**. Hydrolysis of the iminium ion on work-up furnishes dihydro-*proto*-daphniphylline **72**. Interestingly, if ammonia is used instead of methylamine, a different product is formed with an isopropenyl side chain instead of the isopropyl group, and in a lower yield. Use of

methylamine allows differentiation between the three similar olefins in the polycyclic product in the hydride shift step and aids the progress of the cascade by stabilising the iminium and enamine intermediates.

This cascade sequence provides a good precedent for the initiation and direction of a cascade reaction sequence using the dual reactivity of enamines/imines; we hope to exploit this in our approaches to polycyclic nitrogen-containing frameworks.

Funk's studies towards nakadomarin A also include a cascade sequence exploiting this dual reactivity as a key step (Scheme **14**).[16]



Scheme 17

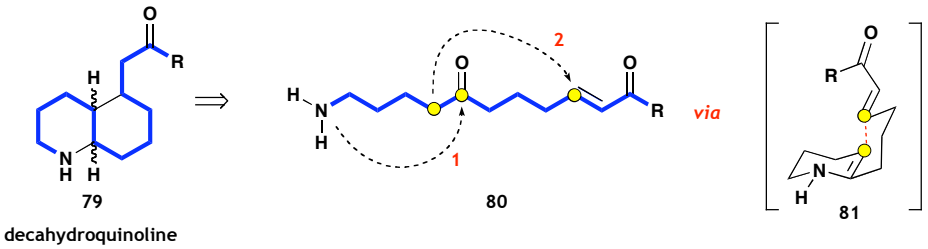
Treatment of enecarbamate **73** with scandium triflate promotes the intramolecular Michael addition into the malonate-like acceptor. This can occur *via* one of two boat-like transition states, **74** or **75**. The *syn* transition state **74** is destabilized by both a steric interaction between the *N*-Boc group and the methyl ester and an electrostatic interaction between the developing positive charge on the nitrogen and the carbonyl carbon of the ester. The *anti* transition state **75** is therefore favoured, and cyclization to form the first ring of the cascade occurs to give iminium ion **76**. This iminium ion can rotate to give the alternative boat conformer **77** with the furan group in an equatorial position before the second cyclization

occurs, accounting for the observed diastereoselectivity. Trapping of the iminium ion by the electron-rich furan and re-aromatization yields tetracycle **78**, a precursor to nakadomarin A.

Taking these elegant cascade syntheses as an inspiration for our own work and as an ideal to work towards, discussion will now focus on cascade approaches to decahydroquinoline-type skeletons.

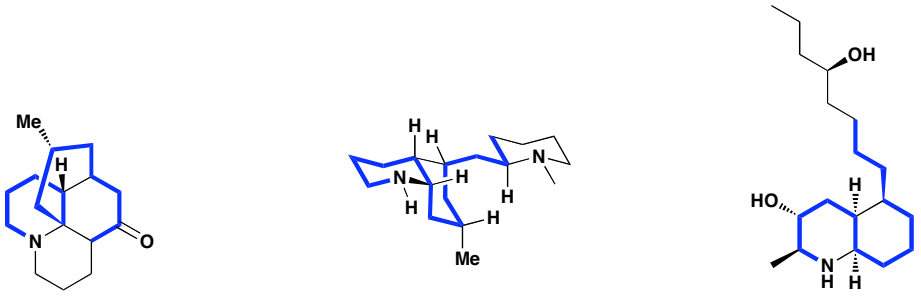
1.2 Aims of the project: Decahydroquinoline skeletons

We were interested in examining whether the rapid complexity-building nature of cascades could be exploited to give access to molecules containing a decahydroquinoline motif. We proposed to disconnect decahydroquinoline skeletons back to a common linear precursor which would be able to carry out a multiple-ring-forming cascade in the forward direction. A nucleophile-driven cascade starting with a linear precursor such as **80** (Scheme **15**) was envisaged. This contains a protected amine and two ketones, one of which will be *α,β*-unsaturated. Deprotection of the amine would allow condensation with the first ketone (**1**) to form an enamine, which would then carry out a Michael addition (**2**) into the *α,β*-unsaturated ketone to form the second ring of the decahydroquinoline. Further reactions of the resulting iminium ion or reduction of the resulting enamine would result in the formation of a decahydroquinoline skeleton containing at least three new stereocentres in one step.



Scheme 18

A cascade approach to these types of structures would be useful for the synthesis of many naturally-occuring alkaloids as the decahydroquinoline skeleton appears in several families of natural products. These include the lycopodium alkaloids (such as lycopodine **82** and cermizine B **83**, Figure **1**) and the lepadins (such as lepadin D **84**, Figure **1**).



82 Lycopodine

83 Cermizine B

84 (+)-Lepadin D

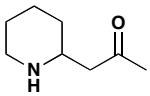
Figure 1

We proposed to investigate the stereochemistry of our nucleophilic cascade cyclizations with respect to nitrogen-containing polycyclic molecules and in particular we hoped to form the skeletons of some of the natural products containing the decahydroquinoline motif. In order to do this, we needed to develop a modular route to our linear precursors in order to access them quickly. We required a route which could easily be modified so that we could decorate the backbone with appropriate stereocentres, such as the methyl groups in lycopodine **82** and cermizine B **83**, or the methyl and hydroxy groups in lepadin D **84**.

2 The lycopodium alkaloids

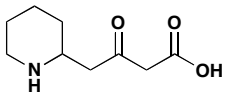
We initially focussed on the lycopodium alkaloids, a group of structurally related quinolizine, pyridine or α-pyridone alkaloids.[17] Lycopodine (Scheme **16**), originally identified in *Lycopodium* (sensu lato),[18, 19] is typical of this group of complex polycyclic nitrogen-containing natural products. Within the lycopodium group there are four distinct sub-classes: lycopodine, lycodine, fawcettimine and miscellaneous classes. The two alkaloids that we initially chose to examine belong to the lycopodine class (lycopodine **82**) and miscellaneous class (cermizine B **83**)[20] but we believe that our methodology could be extended to alkaloids within the other sub-classes as well. *In vitro* and *in vivo* pharmacological studies have demonstrated that lycopodium alkaloids are potential therapies for cardiovascular and neuromuscular diseases, and diseases related to cholinesterase activity.[21-23] Therefore there is considerable interest in evaluating other lycopodium alkaloids and developing efficient routes to these materials.

We were particularly interested in the lycopodium alkaloids because of their mutual structural features. The lycopodium alkaloids come from common biogenic precursors (shown to be pelletierine **85** and 4PAA **86**, see Figure **2**)[24, 25] and are thus structurally related. We therefore believe they can be disconnected back to a shared motif.



85

Pelletierine

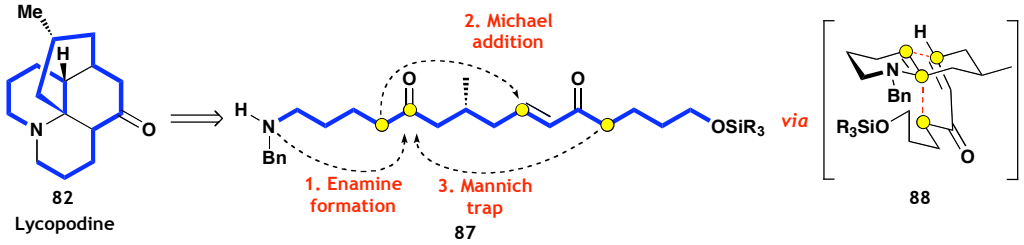


86

4PAA

Figure 2

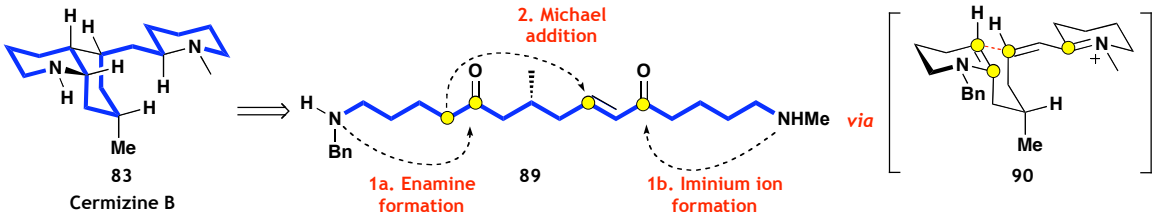
Looking more closely at the two examples we have chosen, we can see that both molecules have a common (and simple) disconnection. For example, lycopodine **82** can be disconnected across four bonds (black bonds, Scheme **16**) to give rise to the linear precursor **87**.



Scheme 19

In the forward direction of the cascade, enamine formation (**1**) would be followed by a Michael addition (**2**), tautomerization of the resulting enol, and trapping of the iminium ion resulting from the Michael addition (**3**). This cascade would form the first three rings of lycopodine in one step and the final ring could be closed by displacement of an activated alcohol by the amine.

This system can easily be modified to access another lycopodium alkaloid, cermizine B **83**. We can make three disconnections (black bonds, Scheme **17**) to give rise to the linear precursor **89,** which differs from the lycopodine precursor only in the presence of a second amine instead of the primary alcohol.



Scheme 20

In the cascade we again envisage enamine formation (**1a**), but in this molecule a second amine can condense with the *α,β*-unsaturated ketone to form an activated *α,β*-unsaturated iminium ion (**1b**), which should promote the Michael addition (**2**). Reduction of the resulting bicyclic iminium ion and *exo*-cyclic enamine from the correct face would result in the entire cermizine B skeleton.

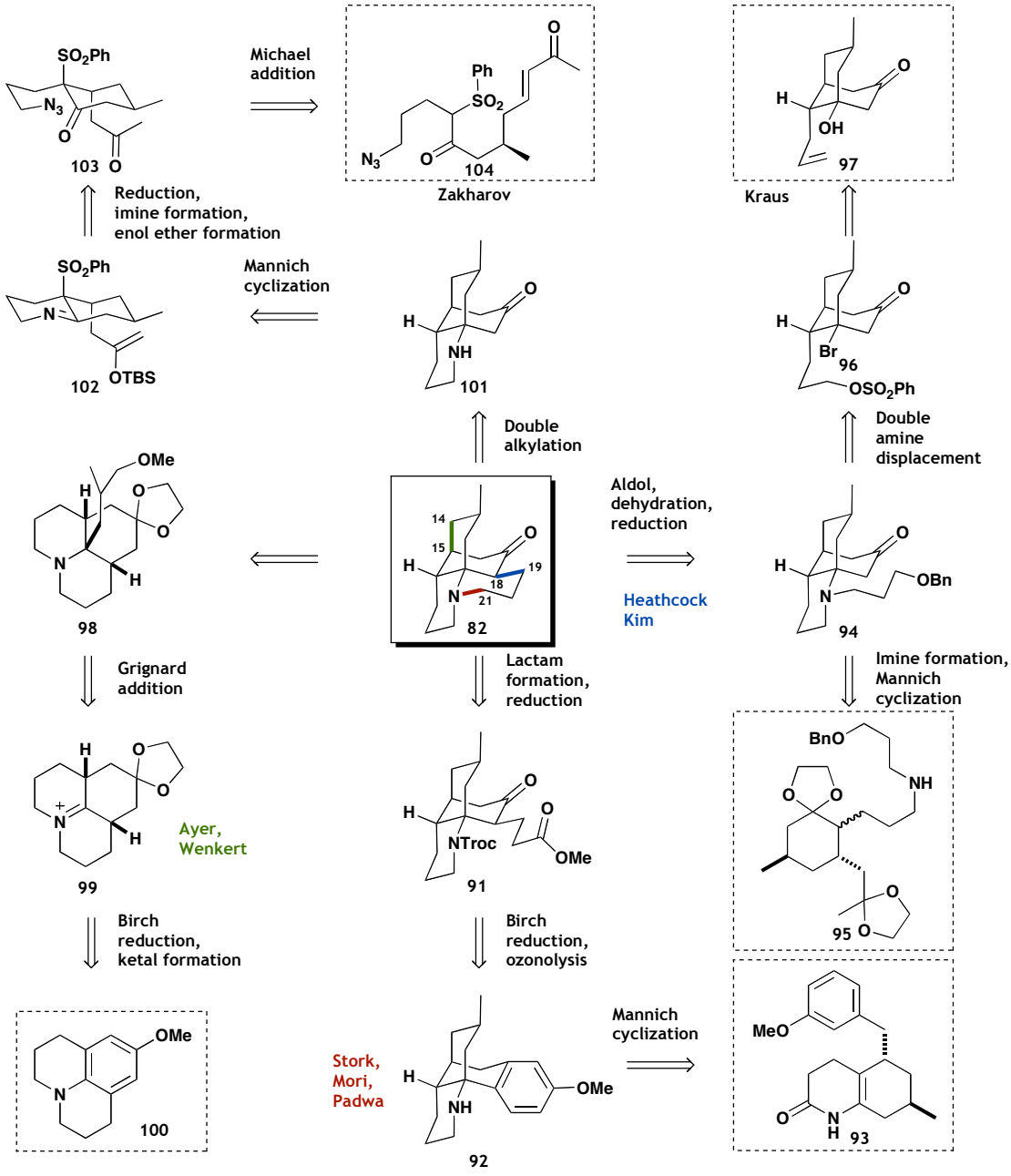
2.1 Previous approaches to lycopodine and cermizine-type frameworks

2.1.1 Previous approaches to lycopodine

Several syntheses of lycopodine have been reported since its isolation in 1881.[18] There have been five main approaches to disconnecting lycopodine, four of which are detailed in scheme **18**.

Stork,[26] Mori[27] and Padwa[28] all make an initial disconnection across the N-C_{21} bond (shown in red) to give tricycle **91**, which is derived from the arene-bridged decahydroquinoline **92**. In Stork and Mori's syntheses this is constructed by addition of the electron-rich aromatic ring into the acyl-iminium ion derived from **93**. We also intend to use *N*-alkylation as the final bond-forming event in our synthesis of lycopodine.

Heathcock,[29, 30] Kim[31, 32] and Kraus[33, 34] make their first disconnection across the C_{18}-C_{19} bond adjacent to the ketone (shown in blue) to give tricycle **94**. In Heathcock's synthesis the rings containing the ketone and the amine are formed in a single process, under thermodynamic control, from substituted cyclohexane **95**. Heathcock uses a Mannich reaction to form the quaternary centre and we intend to exploit this iminium trap in the course of our cascade. Kraus builds the amine ring onto bridged bicycle **97**.



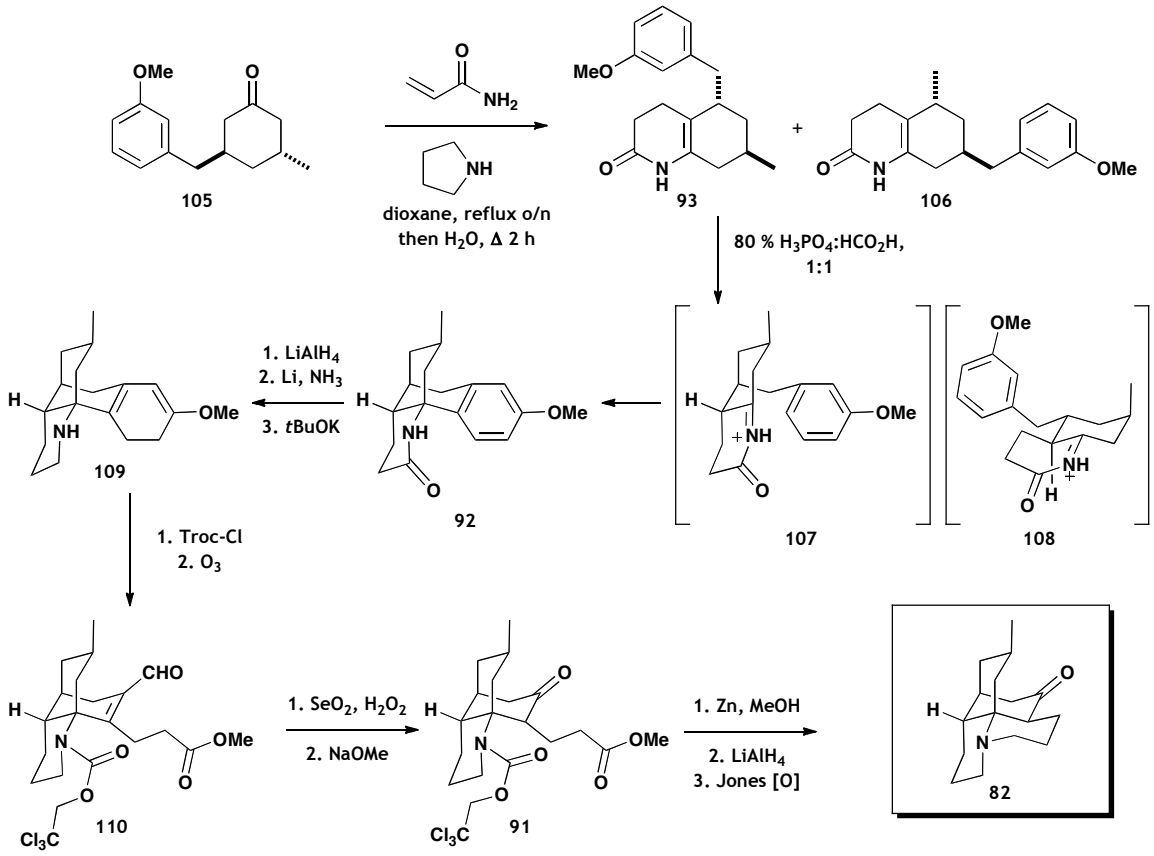
Scheme 21

Ayer[35] and Wenkert[36] both use approaches from tricyclic hydrojulolidine-type frameworks such as **99**, derived from 9-methoxyjulolidine **100** in the case of Ayers. Here the initial disconnection is the C_{14}-C_{15} bond on the ring containing the methyl stereocentre (shown in green). Again this process exploits the reactivity of iminium ions to form the crowded quaternary stereocentre.

Finally, in the only enantioselective total synthesis of lycopodine, Zakharov[37] makes the initial disconnections across both the N-C_{21} (red) and C_{18}-C_{19} (blue) bonds to leave the tricycle **101**. The quaternary centre is once again formed from bicycle **102** by a Mannich-type process, further validating our strategy of using a similar approach to form this bond. The imine which will become the piperidine ring is formed by condensation of an amine onto a ketone derived from azido-cyclohexanone **103** which suggests that imine formation followed by Mannich reaction is a reasonable way to form these two bonds. Finally the first ring is formed by a Michael addition of an enolate into an α,β-unsaturated ketone in a manner analogous to the process we plan to use: we intend that the enamine derived from our amine-ketone condensation will carry out this Michael addition.

We hope to incorporate aspects from all of these approaches into our synthetic route to lycopodine. In the interests of brevity, a full description of each individual synthesis is not desirable; some of the syntheses do however merit closer examination and these are detailed in the following section.

The first total synthesis of lycopodine was carried out by Stork in 1968 (Scheme **19**).[26] Ketone **105** is formed in five steps from *meta*-methoxybenzaldehyde and is then treated with pyrrolidine to form an enamine in the presence of acrylamide, which results in the formation of the two isomeric quinolones **93** and **106**. The desired isomer **93** is separable by crystallization and is subsequently treated with acid to induce the key Mannich cyclization step.



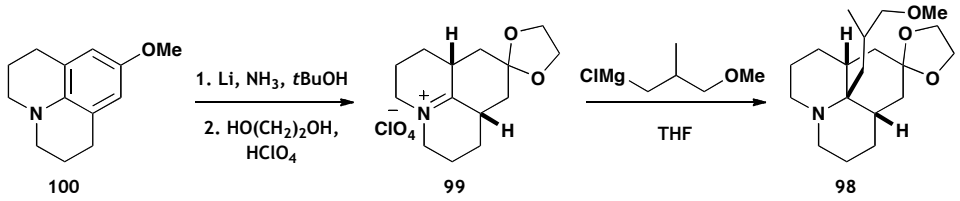
Scheme 22

The enamine can protonate on either face but only one intermediate (**107**) is reactive, due to the remoteness of the nucleophilic aromatic ring, when protonation occurs on the bottom (as drawn) face (**108**). Therefore only the desired isomer **107** reacts, resulting in formation of the tricyclic product **92**, in which the first three rings of lycopodine have been formed, in a manner similar to our strategic plan. It is clear that kinetic control can be used to direct the stereochemistry of ring formation to a high level of selectivity in this system and we will need to take into account the influence of both kinetic and thermodynamic factors to allow formation of the correct tricyclic compound in our cascade synthesis.

All that remains is to transform the aromatic ring into appropriate groups to be used to construct the fourth ring. Reduction of the amide followed by Birch reduction and isomerization to the conjugated diene sets the stage, and the resulting amine is protected as a carbamate. Finally, ozonolysis of the more electron rich alkene unmasks an aldehyde and

an ester (**110**), ready for elaboration to lycopodine. Baeyer-Villiger oxidation of the aldehyde followed by saponification reveals the desired ketone **91**. Deprotection of the amine (zinc dust), cyclization onto the ester and reduction of the lactam completes the final ring of lycopodine, whilst a final oxidation step is required to return the ketone to the correct oxidation state. Thus Stork completes the first synthesis of lycopodine **82** in 17 steps and 1.1 % overall yield, using exquisite substrate-directed control of stereochemistry to carry out the key Mannich reaction and set the stereochemistry of the tricycle.

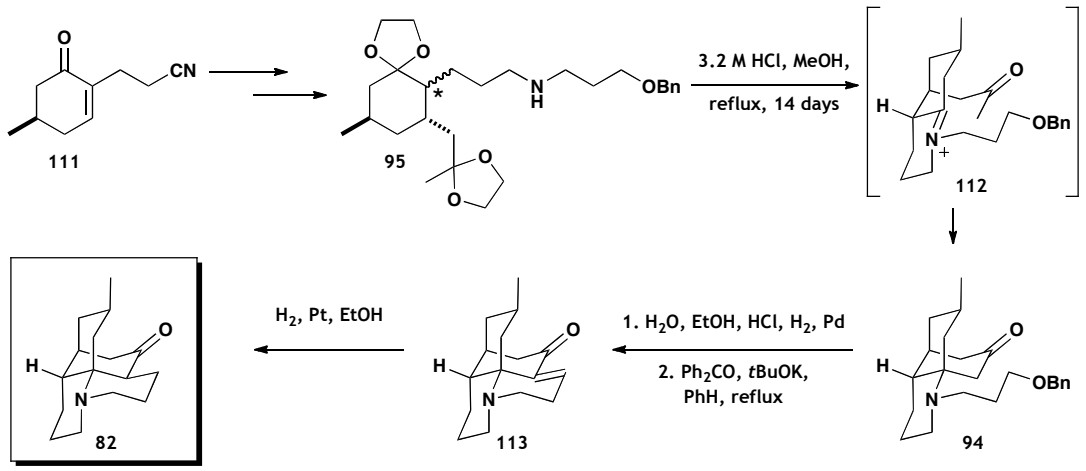
At the same time Ayer published his synthesis of lycopodine (Scheme **20**).[35]



Scheme 23

The known 9-methoxyjulolidine **100** is used as a starting point; Birch reduction and ketal formation yield the ammonium salt **99** and a Grignard addition into iminium ion **99** installs the last few carbons needed to form the skeleton of lycopodine. This is an excellent example of how addition into an iminium ion can be used even in highly congested systems such as tricycle **99** to form quaternary centres. The amine **98** is transformed into lycopodine in a further eleven steps, including oxidation state changes and isomerization of two stereocentres.

Eleven years later, Heathcock published his highly efficient approach (Scheme **21**).[29, 30]

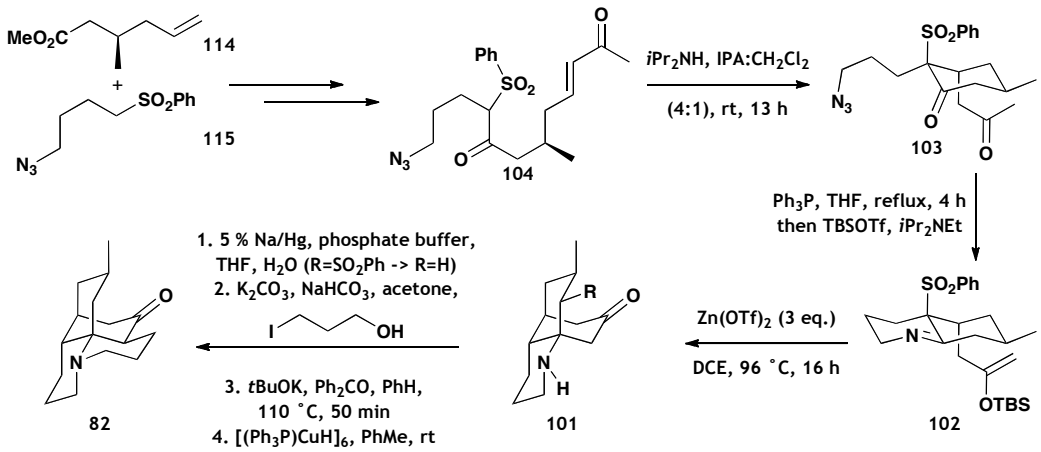


Scheme 24

Known cyanoenone **111** is converted in 5 steps to amino diketal **95**, which upon treatment with HCl in methanol slowly (14 days, reflux) cyclizes, again *via* a Mannich process, to the tricyclic amino ketone **94** as a single diastereoisomer. This is despite the presence of epimers at the marked position (*) in the starting amine and is a result of thermodynamic stereocontrol: the marked centre (*) can epimerize under the reaction conditions, and only the bicycle **112** resulting from the side chain being on the bottom face (*syn* to the ketone side chain) is able to form the third ring *via* trapping of the iminium ion. As in Stork's synthesis, a mixture of thermodynamic and kinetic effects are used to control the stereochemistry of an addition into an iminium ion to furnish the desired tricyclic amine **94**; this further supports the hypothesis that our cascade approach may be successful.

The tricycle **94** is easily converted to lycopodine *via* deprotection of the alcohol, oxidation and aldolization followed by dehydration to form the last ring. Finally hydrogenation gives lycopodine **82** in just 9 steps and 17.7 % from cyanoenone **111** and overall 13 steps and 16.6 % from 5-methylcyclohexane-1,3-dione.

Finally, in 2008 the first (and only) enantioselective total synthesis of lycopodine was published by Zakharov *et al* (Scheme **22**).[37]



Scheme 25

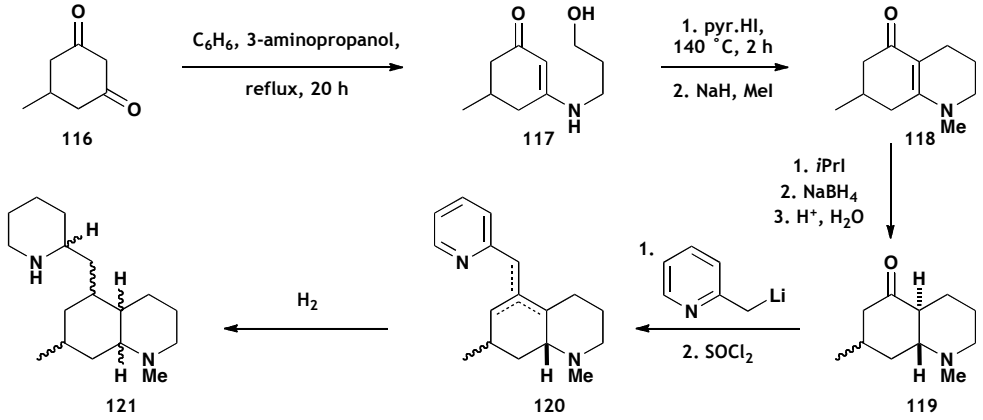
Linear precursor **104** is generated in two steps from ester **114** (which is itself synthesized in two steps from a commercially available acyl sultam) and sulfone **115** (two steps from commercially available 1,4-dibromobutane). The rings are then formed in a rapid stepwise process; first a stereoselective Michael addition results in only one isomer, which the authors hypothesize is due to 1,2-steric interations between the sulfone and α,β-unsaturated ketone. This forces them to adopt a pseudoaxial conformation in the transition state, as seen in the product **103**. Staudinger reduction of the azide leads to spontaneous generation of the imine to give the second ring, and silyl enol ether formation sets the stage for the key Mannich cyclization. Treatment of **102** with zinc (II) triflate led to the formation of tricycle **101**, where the sulfone has carried out an unusual 1,3-rearrangement, perhaps generating a more reactive intermediate for the Mannich cyclization. Finally, desulfurization followed by alkylation, cyclization to form the last ring and reduction yielded lycopodine **82**.

We intend to use similar processes for creation of each of the four rings in our synthesis, so it is encouraging to see that bond formation occurs successfully here. However, the challenge in our system will be to not only form the necessary bonds for three of the rings in a single cascade process, but to do so with the correct stereochemistry as well. The only stereodirecting element in our system will be a single methyl group, just as in the Zakharov system. We believe this stereocentre has the potential to direct facial selectivity

of a Michael addition in the context of a triple ring-forming process, even in the absence of the sulfone used by Zakharov *et al*.

2.1.2 Previous approaches to structures related to cermizine B

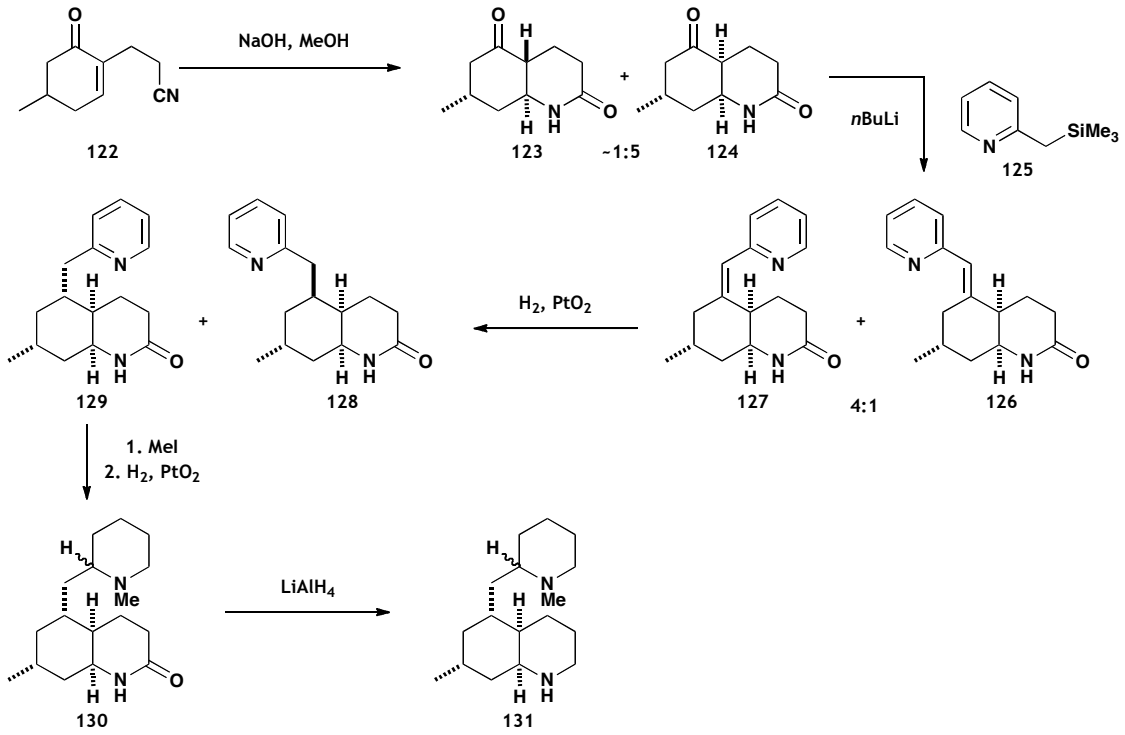
To date no syntheses of cermizine B have been reported; however, the carbon skeleton has succumbed to a number of synthetic efforts. In 1978 after the isolation of phlegmarine which bears this decahydroquinoline – piperidine type structure a short synthesis of this framework was attempted by Nyembo *et al*. (Scheme **23**).[38]



Scheme 26

Construction of the decahydroquinoline fragment[39] began with condensation of dihydroorcinol **116** with 3-aminopropanol to give vinylogous amide **117**. Cyclization under acidic conditions followed by methylation of the nitrogen gave bicycle **118**. A three-step reduction process produced the *trans*-ring junction in **119** and the piperidine fragment was installed by addition of a lithiated 2-methylpyridine. Dehydration using thionyl chloride gave a mixture of alkene isomers which were hydrogenated without further purification to yield tricycle **121** as a mixture of two compounds which were not assigned. This suggests that controlling the selectivity of the hydrogenation in this system may be challenging.

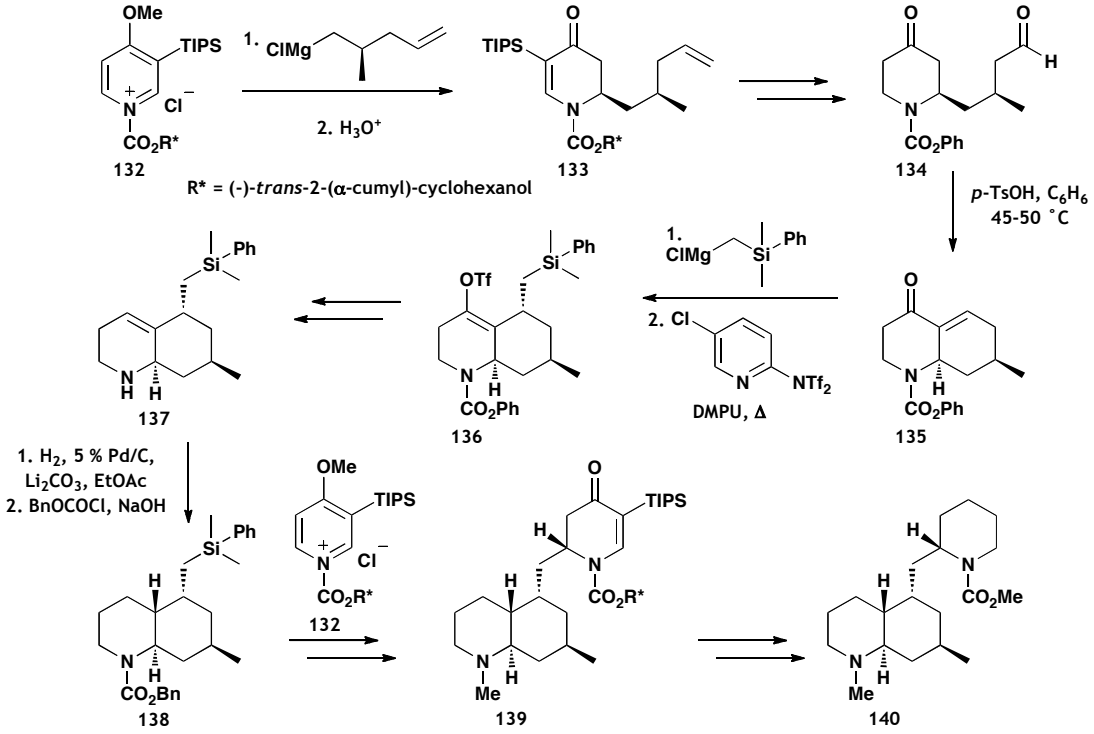
In 1981 Maclean *et al.* also reported a route to this framework (Scheme **24**).[40]



Scheme 27

The synthesis starts with cyano-ketone **122** which is the same starting point that Heathcock uses in his synthesis of lycopodine. Cyclization using methanolic NaOH led to a mixture of bicyclic lactams **123** and **124**. Olefination of the major product **124** using lithiated silylmethylpyridine **125** resulted in a mixture of alkene isomers **126** and **127** which could be separated and hydrogenated using Adam's catalyst. Hydrogenation of *cis* isomer **127** led only to (all *syn*) **129** but hydrogenation of **126** gave a mixture of (*syn*) **129** and the major product **128**. The authors decided to pursue the synthesis using (all *syn*) **129** as they believed that this was most likely to be the stereochemistry found in the natural product. Formation of the ammonium salt on the pyridine ring followed by hydrogenation led to tricycle **130** which was a mixture of epimers at the stereocentre on the piperidine ring. Finally treatment with lithium aluminium hydride reduced the lactam **130** to yield the decahydroquinoline-piperidine structure **131**. Again this synthesis demonstrates the importance of finding conditions which will be selective for the hydrogenation as at several stages a mixture of products was observed in this system.

An asymmetric synthesis of a similar framework was completed in 1999 by Comins *et al*.[41] They completed the synthesis of N_α-acetyl-N_β-methylphlegmarine **140** which is an unusual lycopodium alkaloid since it has a *trans*-ring-junction on the decahydroquinoline (Scheme **25**).



Scheme 28

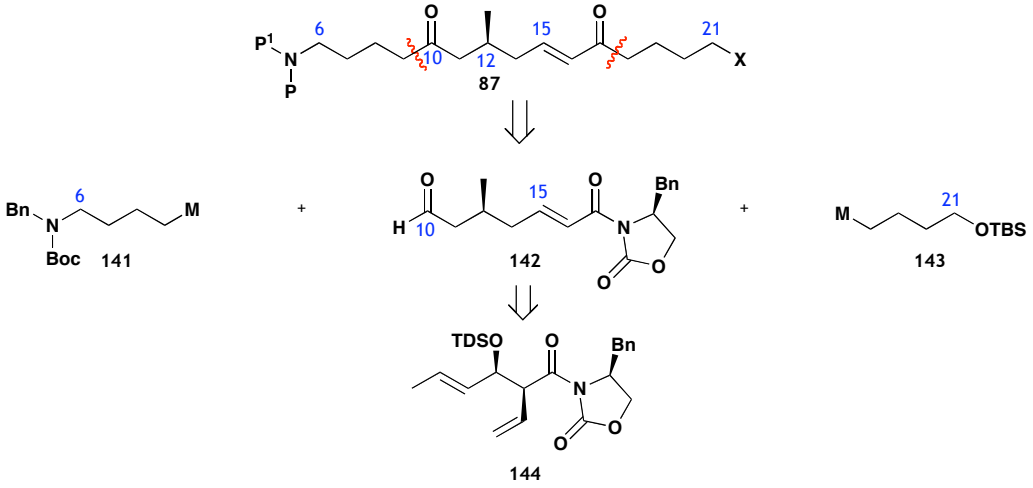
The synthesis begins with a Grignard addition into chiral acylpyridium salt **132** followed by hydrolysis to give vinylogous amide **133** with a dr of 94:6. **133** can be transformed into keto-aldehyde **134** which can be cyclized under acidic conditions to give bicyclic enone **135**. Addition of a silyl Grignard occurred with complete diastereoselectivity followed by triflate formation to give **136**. Transformation to octahydroquinoline **137** was followed by hydrogenation to give 89:11 selectivity in favour of the *trans* ring junction isomer and acylation of the amine gave decahydroquinoline **138**. Finally transformation of the silyl group into a Grignard and addition into another equivalent of chiral acylpyridium salt **132** installed the final ring and stereocentre needed for the natural product in **139**. Some further reduction and deprotection steps were necessary to furnish the natural product **140**. This

route shows that hydrogenation can be very selective in these systems and also that use of a chiral auxiliary may be necessary for high levels of stereocontrol.

2.2 Initial approaches

2.2.1 An Evans boron aldol

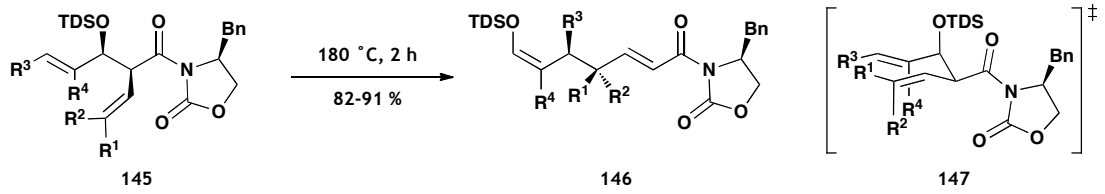
We initially focussed on the linear precursor for the lycopodium alkaloids. Our first attempt involved making two key disconnections around the central fragment which contains the methyl stereocentre (Scheme **26**).



Scheme 29

Disconnections can be made between C_9-C_{10} and C_{18}-C_{19} to yield a 1,7-dicarbonyl fragment **142**, where the groups attached to C_{10} and C_{18} allow chemoselectivity between the two carbonyls. This chiral aldehyde may be formed from a silyloxy-Cope rearrangment of a boron aldol adduct **144**.[42] Differentiated organometallic additions into both carbonyls (**141** into C_{10} followed by **143** into C_{18}) would complete the synthesis of the linear precursor. This route should allow access to enantioenriched precursor **87**.

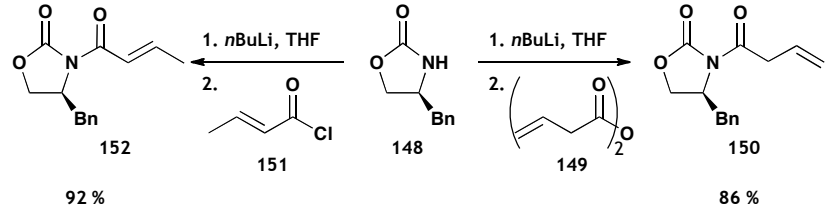
We considered that using an Evans boron aldol followed by a (stereospecific) silyloxy-Cope rearrangement to generate the correct stereochemistry in the linear precursor would be an effective strategy. This silyloxy-Cope rearrangement of *syn* aldol products has been used to good effect in several systems by Schneider (Scheme **27**).[42]



Scheme 30

Schneider found that the rearrangement could tolerate a methyl group at either R^1 or R^2 and that R^3 and R^4 could both be methyl, or R^3 could be other alkyl, silyl or stannyl groups while R^4 remained a proton. The stereoselectivity of the Cope rearrangement arises from the reaction proceeding *via* transition state **147**, where the carboximide is pseudoequatorial and the silyloxy group pseudoaxial. Schneider has gone on to use this reaction in the asymmetric syntheses of a number of systems[43-45] and we hoped it would prove equally amenable to our synthesis of lycopodine.

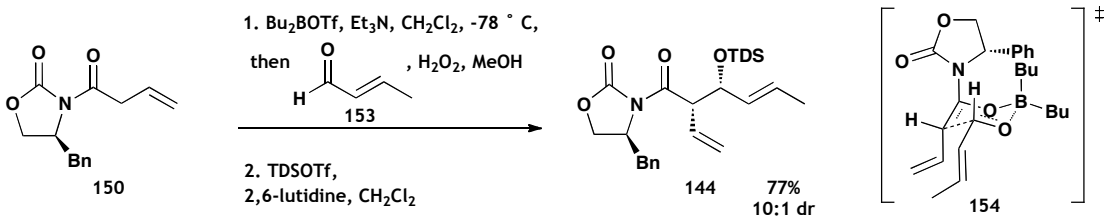
Accordingly, Evans chiral auxiliary, oxazolidinone **148**, was generated from L-phenylalanine in two steps[46, 47] (it is also commercially available). The Evans chiral auxiliary was treated with *n*-butyllithium and then either vinyl acetic anhydride **149** or crotonyl chloride **151** to form the two aldol substrates **150** and **152** (Scheme **28**).



Scheme 31

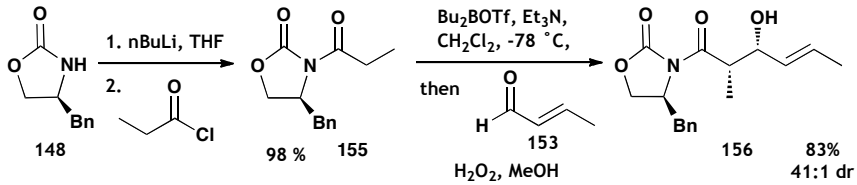
We envisaged that either *N*-acyl oxazolidinone **150** or **152** (Scheme **28**) could take part in an Evans boron aldol reaction to produce the requisite adduct **144** (Scheme **26**). Our initial attempt with the *β,γ*-unsaturated *N*-acyl oxazolidinone **150** was successful (Scheme **29**). Treatment of **150** with dibutylboron triflate (commercially available 1 M solution in dichloromethane), triethylamine and crotonaldehyde **153** followed by protection of the crude aldol adduct gave the protected aldol product **144** in 77 % isolated yield and good dr (10:1) on a small scale (30 mg). The major diastereoisomer was assumed to be as shown, in

accordance with generation of a *Z*-enolate leading to the *syn* aldol product *via* the Zimmerman-Traxler transition state **154**, which is the most stable TS with the dipoles of the oxazolidinone and the aldehyde opposing.



Scheme 32

However, this result proved to be unrepeatable: the boron aldol reaction is capricious. We believed that the dibutylboron triflate was the limiting reagent and hence we attempted to isolate this from a reaction between tributylborane and triflic acid, but this proved unproductive (the product decomposed during attempted distillation). We also examined a similar approach that involved making the dibutylboron triflate or diethylboron triflate *in situ*, but these reactions were unsuccessful for both the *β,γ*-unsaturated *N*-acyl oxazolidinone substrate **150** and the *α,β*-unsaturated *N*-acyl oxazolidinone substrate **152**. To ensure that the conditions were appropriate for substrates of this nature, a boron-mediated aldol reaction between the *N*-propionyl oxazolidinone substrate **155** and crotonaldehyde **153** was examined (Scheme **30**). Treatment of this *N*-acyl oxazolidinone **155** with dibutylboron triflate, formed *in situ*, followed by triethylamine and crotonaldehyde **153** resulted in formation of the aldol adduct **156** in 83 % isolated yield and excellent dr (41:1). Again the stereochemistry of the major diastereoisomer is assumed to be that given by a transition state analogous to **154** above.



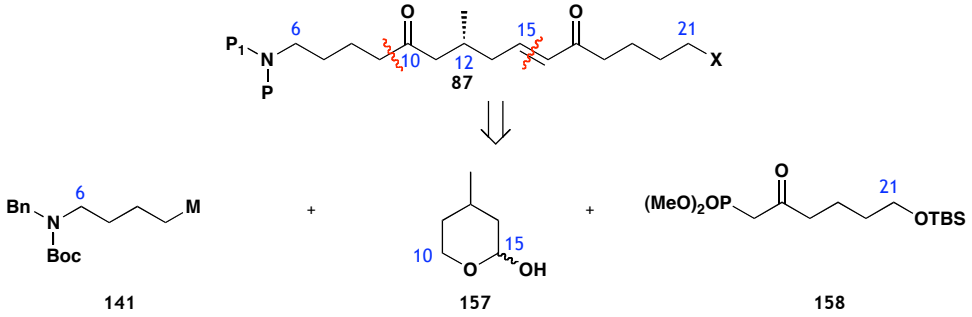
Scheme 33

Unfortunately this success could not be extended to either of the alkene-containing *N*-acyl oxazolidinones, despite subjecting both to the same conditions. It was concluded that the

two *N*-acyl oxazolidinones **150** and **152** are poor substrates for the Evans' boron aldol reaction, and we resolved to pursue a different route to the target molecule **87**.

2.2.2 An alternative approach

Our second approach to our linear precursor again involved two disconnections (Scheme **31**).



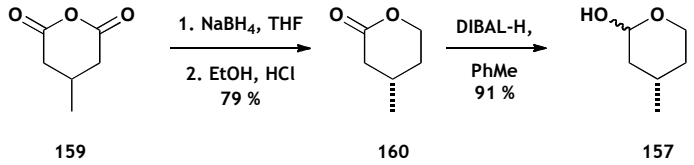
Scheme 34

Here the disconnections are made between C_9-C_{10} and the C_{15}-C_{16} alkene so that the linear precursor can be formed with a Horner-Wadsworth-Emmons reaction of the phosphonate **158** with lactol **157** and (after adjustment of oxidation states) an organometallic addition by protected amine **141**.

The strategy for this route required a 1,5-relationship between two heteroatoms attached to what would become C_{10} and C_{15} in the linear precursor, with a methyl group at what would become C_{12}. The lactol **157** (Scheme **32**) is a good starting point for this, as it contains C_{15} in the correct oxidation state without the need for protection of the C_{10} heteroatom functionality. After functionalization of C_{15}, we can envisage that the unmasked C_{10} alcohol may then be oxidised and further manipulated.

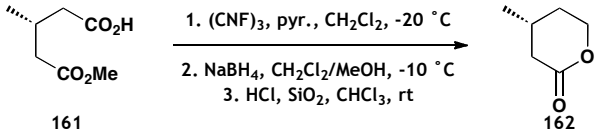
To access lactol **157** we decided to begin from 3-methyl glutaric anhydride **159** (Scheme **32**). Treatment of the anhydride **159** with sodium borohydride afforded lactone **160** in 79 %

yield. Further reduction of the lactone **160** with DIBAL-H gave lactol **157** in 91 % isolated yield.



Scheme 35

In the first instance we decided to explore this sequence using the racemic lactol **157**.† However it should be possible to form lactone **157** as a single diastereoisomer, for example A. B. Smith III's syntheses of lyconadin A and lyconadin B[49] use commercially available (although expensive, £182 for 5 mL) methyl (*R*)-3-methylglutarate **161** to form lactone **162** as a single enantiomer (Scheme **33**).



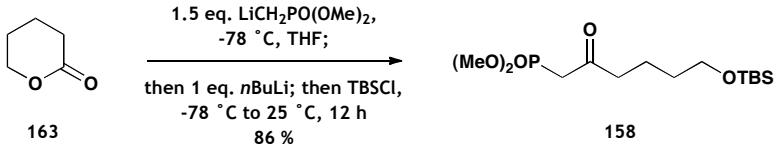
Scheme 36

Activation of the acid followed by reduction and cyclization under acidic conditions furnished lactone **162** as a single enantiomer. We planned to use a similar sequence to render our synthesis asymmetric in the future, and believe that the necessary ester-acid could be derived by desymmetrization of 3-methyl glutaric anhydride with a suitable chiral amine catalyst.[50]

With the lactol **157** in hand, it was decided to attach the C_{10}-C_{15} side chain by a Horner-Wadsworth-Emmons reaction using the phosphonate **158** (Scheme **34**) derived from *δ*-valerolactone in one step.[51] *δ*-Valerolactone **163** was ring-opened with lithiated methyl

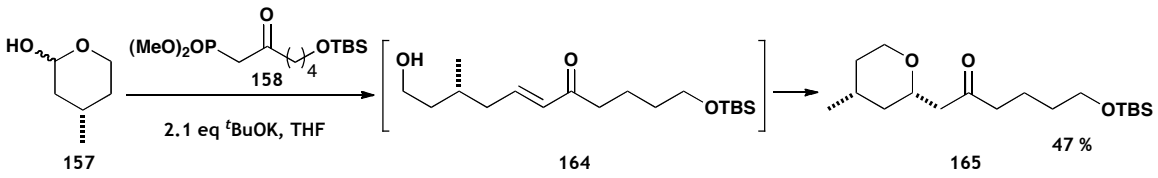
†According to the conventions defined by H. Maehr for graphical representation of stereochemistry, (48. H. Maehr, *J. Chem. Ed.*, **1985**, 114-120.) solid and broken wedged bonds are used to denote absolute configuration of the chiral element, whereas solid and broken bold line bonds are used to denote the relative configuration of a racemic compound. This convention is adhered to throughout the manuscript.

dimethyl phosphonate and the resultant primary alcohol was protected *in situ* with *tert*-butyldimethylsilyl chloride, to produce phosphonate **158** in 86 % yield.



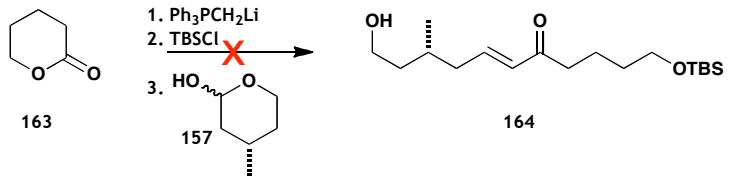
Scheme 37

We envisaged that a Horner-Wadsworth-Emmons reaction could then be carried out using this phosphonate **158** and the lactol **157**, derived above. A number of different conditions were tested, including varying the base (from sodium hydride to LHMDS to potassium *tert*-butoxide) and varying the equivalents of base (from 1.5 to 2 to 5). However, in all cases the desired α,β-unsaturated ketone **164** was not isolated. Instead, varying yields of the tetrahydropyran **165** (Scheme **35**) resulting from conjugate addition of the free hydroxy group, produced from the ring opening of the lactol, into the α,β-unsaturated ketone **164** were isolated as a mixture of diastereomers, with the remaining material being unreacted lactol. The major diastereomer was tentatively assigned as shown.



Scheme 38

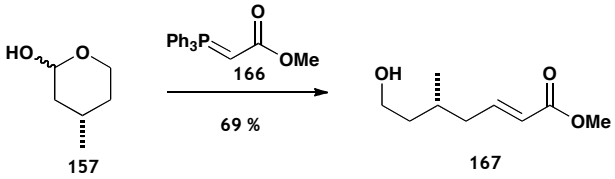
Forming the ylid from methyl triphenylphosphonium bromide and δ-valerolactone was also examined (Scheme **36**)[52] as we hoped that the lower pKa of a phosphonium ylid (7.1)[53] as compared to a phosphonate (18.6)[54] could help prevent deprotonation of the alcohol and subsequent cyclization. However although formation of the ylid was successful this also failed to show any improvement in the olefination result.



Scheme 39

Trying the Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions,[55] where we hoped that the use of a weak base would be gentle enough to prevent the conjugate addition from occurring, failed to produce any desired product.

We decided to carry out a test reaction to ensure that the lactol **157** was a suitable substrate for olefination reactions. Lactol **157** was treated with methyl (triphenylphosphoranylidene) acetate **166** to give the α,β-unsaturated ester **167** in a good yield of 69 % (Scheme **37**).



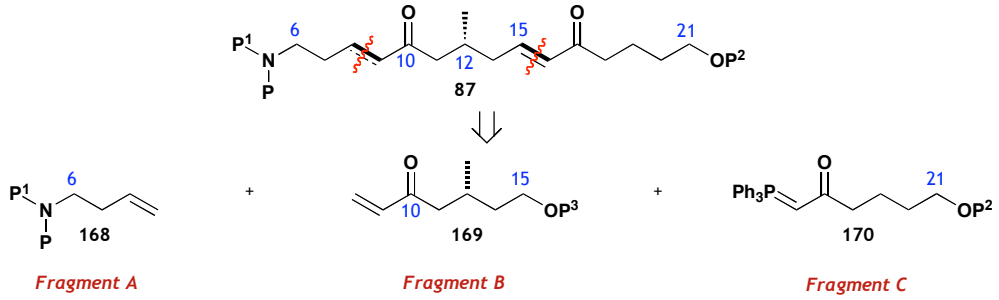
Scheme 40

We concluded from this result that the α,β-unsaturated ketone, formed *in situ* from the Horner-Wadsworth-Emmons or Wittig reactions, was simply too reactive towards the conjugate addition, and so another route that does not involve liberation of a free hydroxy group when forming the ketone was needed.

2.3 A new modular approach

2.3.1 A linear precursor for lycopodine

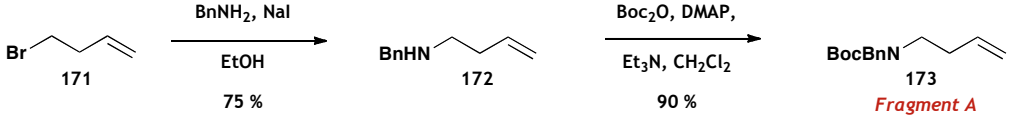
Our third and successful synthetic route to the linear precursor again involved only minor alterations from the previous disconnections. We again chose to disconnect across two bonds, leading to three similarly sized fragments (Scheme **38**).



Scheme 41

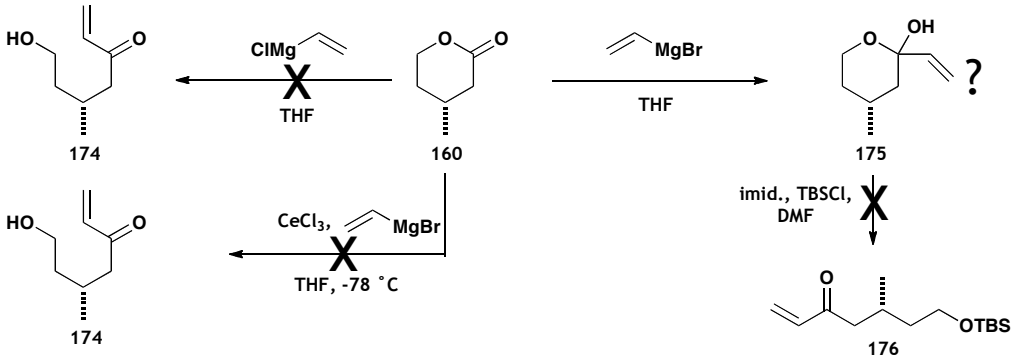
We can install an alkene between C_8-C_9 and disconnect across that bond, leaving us with an amine **168** and an α,β-unsaturated ketone **169**, which can be joined in the forward direction by transition-metal catalyzed cross metathesis. We also disconnect across the C_{15}-C_{16} alkene as before and again hope to form this bond in the forward direction by an olefination reaction, this time perhaps a Wittig reaction using ylid **170**. Our strategy of first joining amine **168** and ketone **169** and then reducing out the alkene before deprotecting the alcohol allows us to avoid any of the alkoxide conjugate addition problems we saw in the previous system.

We found that displacing the bromide in 4-bromo-1-butene with benzylamine, followed by Boc protection, furnished us with the doubly protected cross-metathesis precursor **173** in just two steps and good yield (Scheme **39**).



Scheme 42

We next turned our attention to synthesis of the electron-poor cross metathesis precursor, α,β-unsaturated ketone **169** (Scheme **38**). We initially hoped to access this *via* vinyl Grignard addition into the lactone **160** that we had previously used in the synthesis of lactol **157**.

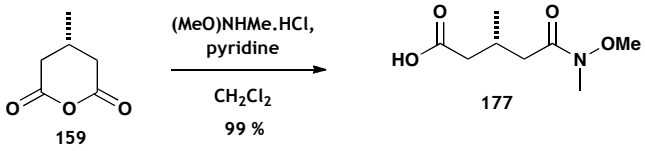


Scheme 43

However it soon became clear that the rapid one-step addition into the lactone to form the desired ketone was not a viable strategy. Additions using vinylmagnesium bromide or chloride failed to return any of the desired product **174**, instead resulting in almost complete recovery of starting material in each case. Suspecting that there might be a little of hemiacetal **175** present which must be in equilibrium with our desired keto-alcohol, we attempted to trap out the primary alcohol with a silyl protecting group to no avail. The high levels of recovered starting material in each case suggested that the Grignard reagent was acting as a base and deprotonating α to the lactone before addition could occur. Attempts to increase the nucleophilicity by transmetallating to the cerium organometallic reagent did not result in any appreciable improvement.

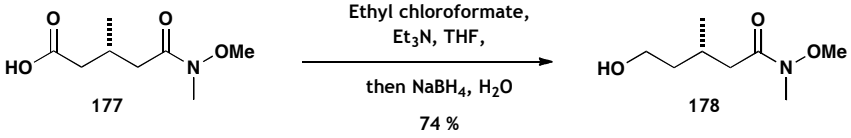
A more pragmatic approach was needed so we decided to first form the Weinreb amide and subsequently add the vinyl Grignard. We initially planned to make the Weinreb amide directly from the lactone **160**, however the reduction of the cyclic anhydride **159** to the lactone was proving capricious, with yields ranging from 30 % to 79 %. We decided instead to first make the Weinreb amide directly from the anhydride and then reduce the resulting acid (Schemes **41** and **42**). 3-Methyl glutaric anhydride **159** was treated with *N,O*-dimethylhydroxylamine hydrochloride and pyridine in dichloromethane to yield Weinreb

amide **177** in excellent yield. Again we believe that it would be possible to form Weinreb amide **177** in an asymmetric fashion using routes similar to those previously described for the lactone **162** in section **2.2.2**.



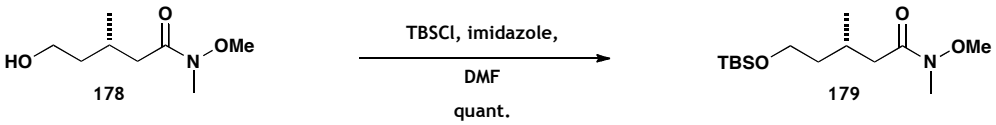
Scheme 44

After an abortive attempt to reduce the acid using borane (no reaction) the reduction was carried out by forming the mixed anhydride using ethyl chloroformate, followed by reduction with sodium borohydride to form alcohol **178** in good yield (Scheme **42**).



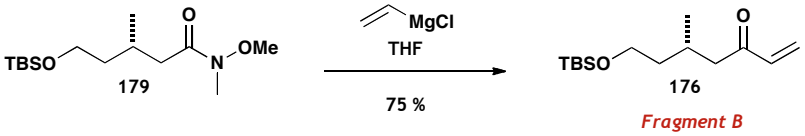
Scheme 45

Protection of the alcohol with TBSCl proceeded in excellent yield (Scheme **43**).



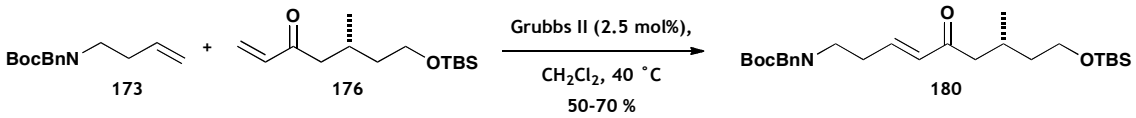
Scheme 46

Finally, vinyl addition into the Weinreb amide **179** produced *α,β*-unsaturated ketone **176** in four steps from commercially available starting materials and good yield (Scheme **44**).



Scheme 47

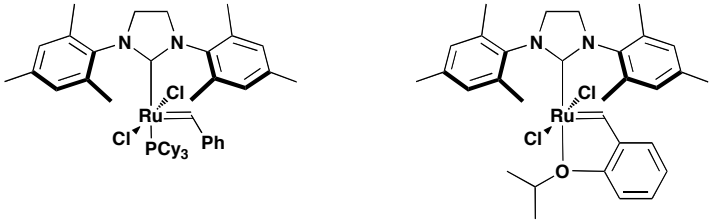
We then turned our attention to coupling the two alkenes *via* cross metathesis (Scheme **45**).



173 176 180

Scheme 48

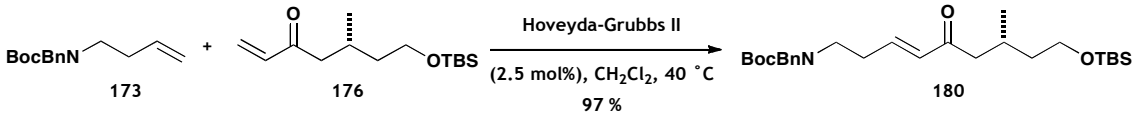
Treatment of amine **173** and ketone **176** with Grubbs II catalyst (*N*-heterocyclic carbene ruthenium complex **181**, Figure **3**) in dichloromethane at 40 ˚C led to formation of desired *α,β*-unsaturated ketone **180** in yields of between 50 – 70 %, and always as the *E*-alkene isomer. We believe this to be due to thermodynamic control of the metathesis reaction, which can isomerize any *Z*-alkene formed under the reaction conditions to the more stable *E*-alkene.



181 182

Figure 3

We wondered if altering the catalyst to the slightly more stable Hoveyda-Grubbs II (**182**, Figure **3**) would improve our yield (Scheme **46**). Hoveyda-Grubbs II is known to be more reactive than Grubbs II at lower temperatures and is particularly good at effecting cross metathesis reactions with electron-poor olefins such as *α,β*-unsaturated ketone **176**.[56]



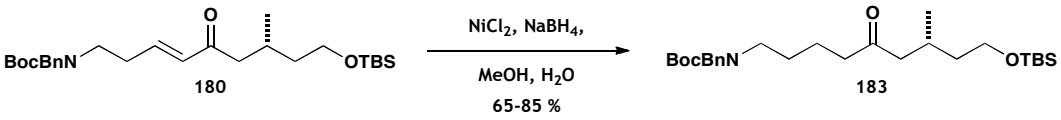
173 176 180

Scheme 49

Alkenes **173** and **176** were treated with Hoveyda-Grubbs II catalyst **182** (2.5 mol%) and heated to 40 ˚C in dichloromethane overnight. The improved reactivity and stability of the catalyst had a pleasing effect on the reaction. Cross-metathesis proceeded extremely efficiently to yield *α,β*-unsaturated ketone **180** in excellent yield and as a single alkene

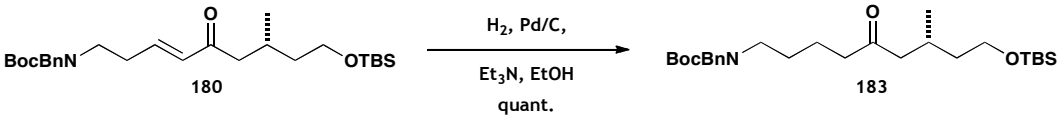
isomer – again the thermodynamic *E*-alkene, suggesting that olefin isomerization is favoured using this catalyst too.

We initially considered reducing the alkene using nickel boride (formed *in-situ* from nickel chloride and sodium borohydride, Scheme **47**). This reaction failed to go to completion, and coupled with the toxicity of the reagents this led us to seek an alternative reduction protocol.



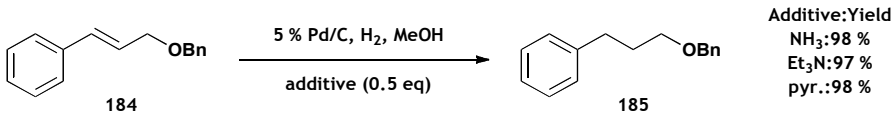
Scheme 50

We decided to examine hydrogenation with a palladium on carbon catalyst and a catalyst poison to prevent hydrogenolysis of the benzyl ether or other over-reduction (Scheme **48**).



Scheme 51

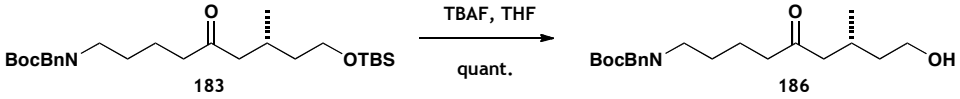
Hydrogenation under standard conditions, with triethylamine present to temper the reactivity of the palladium catalyst, worked extremely well with no hydrogenolysis of the benzyl group, and formed ketone **183** in excellent yield. These conditions were derived from work carried out by Sajiki and Hirota[57] on prevention of hydrogenolysis of *O*-benzyl ethers under hydrogenation conditions. The authors tested a range of amine bases and found that triethylamine, ammonia or pyridine all functioned equally well to prevent hydrogenolysis of aliphatic *O*-benzyl groups (Scheme **49**) but that to prevent hydrogenolysis of aromatic *O*-benzyl ethers an amine containing multiple chelating groups, such as 1,10-phenanthroline, was necessary.



Scheme 52

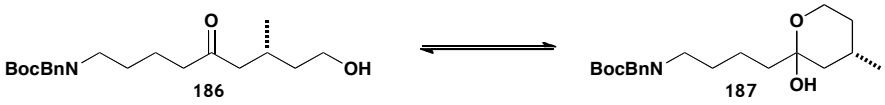
Our slightly modified conditions used an excess of triethylamine which seemed to work well in this system and so we did not attempt to alter the proportions.

The silyl protecting group was removed by treating silyl ether **183** with TBAF in THF to yield primary alcohol **186** in excellent yield (Scheme **50**) ready for oxidation and olefination with our third fragment, ylid **170**, to form the linear precursor.



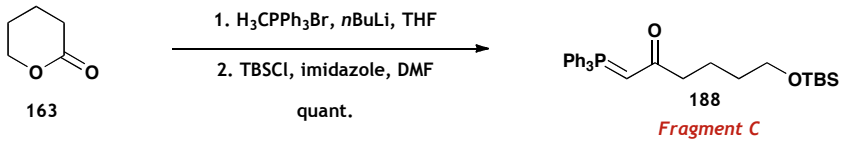
Scheme 53

When characterizing alcohol **186** we had to obtain ^{1}H and ^{13}C NMR spectra at high temperature in DMSO-d_6 due to the rotameric nature of the Boc group. This was common for most of the compounds we made, however it was interesting to note that in this system at high temperature, the equilibrium between the open chain alcohol **186** and the closed ring hemiacetal **187** (Scheme **51**) was shifted completely in the direction of the hemiacetal. This was evidenced by a lack of a ketone peak in the ^{13}C spectra and the appearance of a peak at 96.4 ppm which is diagnostic for an acetal or hemiacetal carbon.



Scheme 54

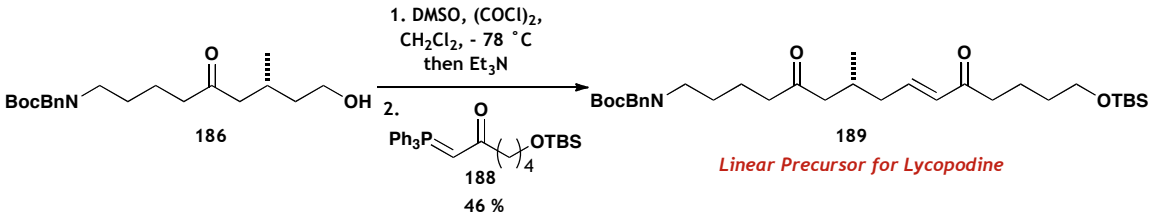
The requisite ylid can be synthesized in a one pot procedure from *δ*-valerolactone **163** (Scheme **52**).[52]



Scheme 55

Methyl triphenylphosphonium bromide was treated with *n*-butyllithium and *δ*-valerolactone **163** was added to the freshly formed methylene ylid. The resulting alkoxide was trapped out with TBSCl to form the ylid **188** in excellent yield.

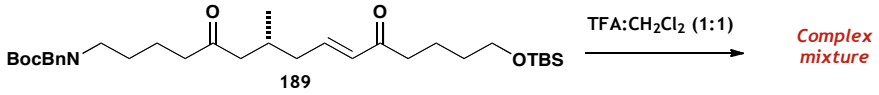
With the free alcohol **186** and ylid **188** in hand, we were ready to form our first linear precursor.



Scheme 56

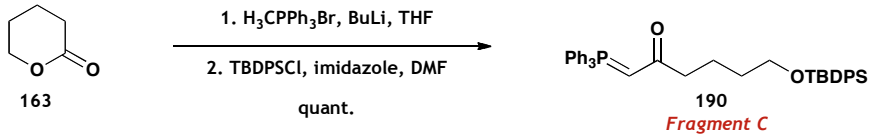
Alcohol **186** was subjected to Swern oxidation conditions to form the aldehyde and immediately treated with ylid **188** to form linear precursor **189** in moderate yield (Scheme **53**).

Having formed our first linear precursor we were eager to begin efforts towards cascade cyclizations. However, we found that upon treatment of our linear precursor **189** with TFA to remove the Boc group, the TBS moiety was concomitantly removed and this resulted in a complex mixture of products (Scheme **54**).



Scheme 57

We reasoned that removal of the TBS group allowed the free alcohol to react with one of the ketones in either an intra- or intermolecular fashion as well as carrying out other possible processes that we hadn't considered. We realised that in order to prevent side reactions we needed to replace the TBS group with a less acid-labile protecting group.



Scheme 58

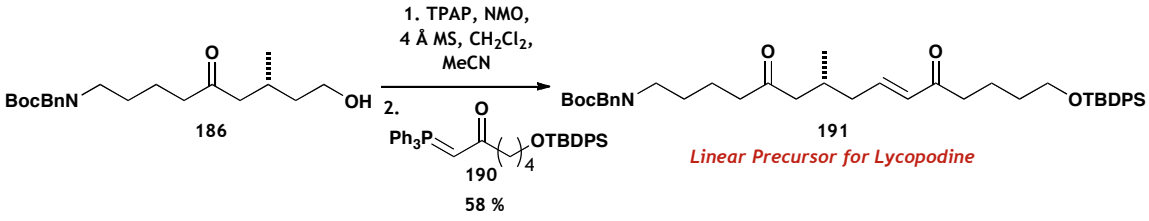
Using the same conditions previously described and replacing TBSCl with TBDPSCl, we were able to access ylid **190** again in two steps in one pot from δ-valerolactone **163** in excellent yield (Scheme **55**).

We decided to examine the oxidation-Wittig sequence more closely and try to improve the moderate yield. It appeared that the oxidation was the limiting step in this process so we looked at a series of different oxidation conditions (Table **1**).

Conditions	Aldehyde
TPAP, NMO, 4 Å MS, CH_2Cl_2	25 % conversion by NMR
TPAP, NMO, 4 Å MS, CH_2Cl_2, MeCN	62 % conversion by NMR
PDC, 4 Å MS, CH_2Cl_2	25 % conversion by NMR
PCC, 4 Å MS, CH_2Cl_2	22 % conversion by NMR
Pyr-SO_3, DMSO, Et_3N	By TLC before w/u, not in NMR
Dess-Martin Periodinane, CH_2Cl_2	40 % conversion by NMR
DMSO, oxalyl chloride, CH_2Cl_2 then Et_3N	50 % conversion by NMR

Table 1

It appeared that TPAP in a solvent mixure of dichloromethane and acetonitrile was the best oxidant, and so we used these conditions in an oxidation-Wittig sequence (Scheme **56**).

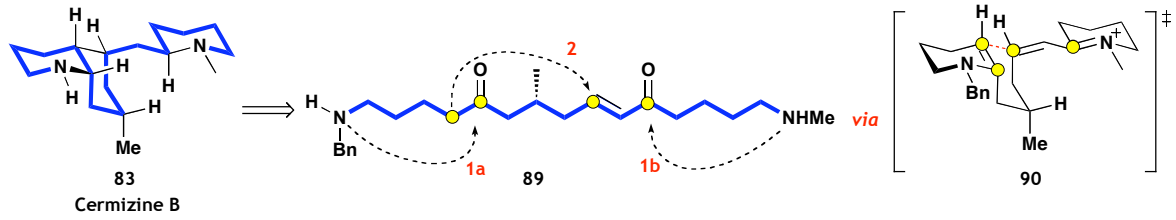


Scheme 59

Treatment of alcohol **186** with catalytic TPAP and NMO as co-oxidant, followed by treatment of the resulting aldehyde with ylid **190**, led to formation of diketone **191** in a gratifyingly improved yield of 58 %.

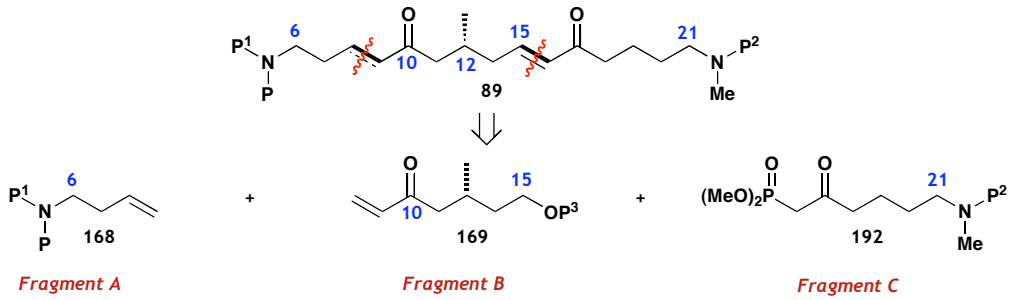
2.3.2 A linear precursor for cermizine B

We next turned our attention to the formation of a second linear precursor for cermizine B. This diketone **89** is very similar to that for lycopodine, differing only in the fact that we replace the primary alcohol with an amine, and we plan to carry out a similar cascade sequence to form the alkaloid (Scheme **57**).



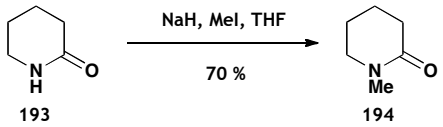
Scheme 60

We can disconnect this linear precursor in a similar manner to that for lycopodine (Scheme **58**).



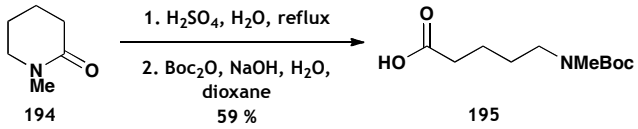
Scheme 61

We disconnect across the same bonds as in the lycopodine case; breaking the C_8-C_9 alkene to join *via* cross-metathesis in the forward direction, and cleaving the C_{15}-C_{16} alkene to be formed by olefination in the forward direction. In this case we chose to use a Horner-Wadsworth-Emmons reaction, as formation of the phosphonate was well precedented in the literature. This leaves us with the amine **168** and α,β-unsaturated ketone **169**, which can be formed using the same procedures as for the lycopodine system, and a third fragment; amino-phosphonate **192** which could be made from δ-valerolactam **193** (Scheme **59**).



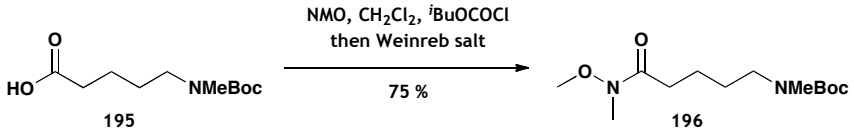
Scheme 62

δ-Valerolactam **193** was deprotonated using sodium hydride and alkylated on nitrogen with iodomethane to produce tertiary lactam **194**. Unfortunately lactam **194** could not be transformed to the relevant Weinreb amide directly using a Lewis acid such as trimethylaluminium, as would be the case for a lactone. Instead we followed literature procedures to open the lactam to the *δ*-amino acid and protect the resulting secondary amine with a Boc group to give **195** (Scheme **60**).



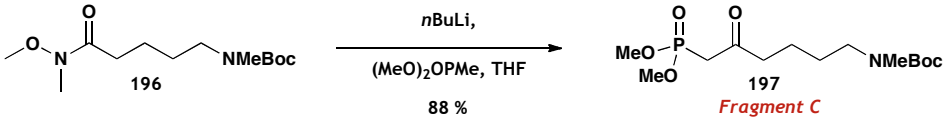
Scheme 63

The acid **195** could then be treated with *iso*-butyl chloroformate to form the mixed anhydride and addition of *N,O*-dimethylhydroxylamine hydrochloride resulted in formation of the Weinreb amide **196** in a respectable yield (44 %) from lactam **194** over three steps (Scheme **61**).



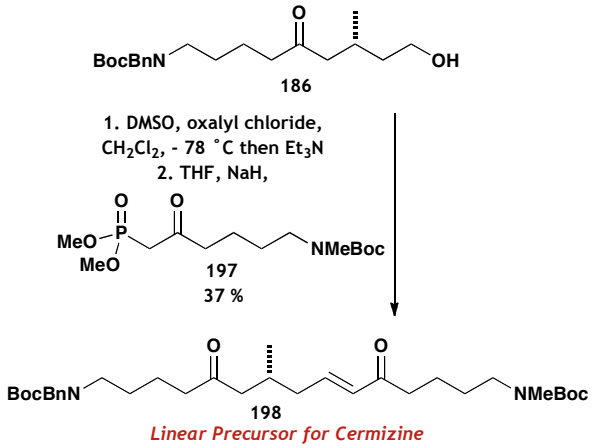
Scheme 64

Finally, dimethyl methyl phosphonate could be deprotonated using *n*-butyllithium and added into the Weinreb amide to form phosphonate **197** in good yield (Scheme **62**).



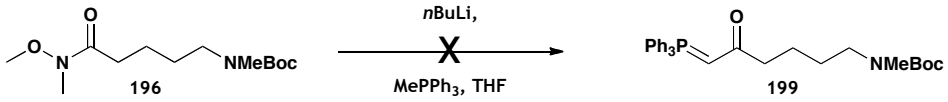
Scheme 65

With phosphonate **197** in hand we were able to form the linear precursor for cermizine B using a similar oxidation-olefination process to that used previously (Scheme **63**).



Scheme 66

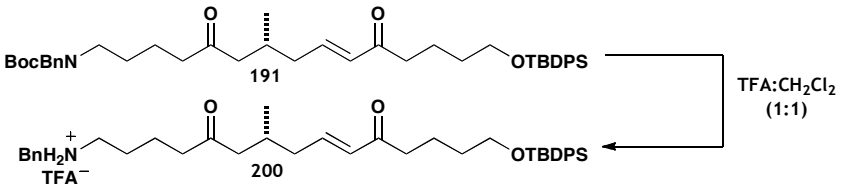
Alcohol **186** was oxidized to the aldehyde using a Swern reaction and the resulting aldehyde was treated with phosphonate **197**, which had been deprotonated with sodium hydride. Diketone **198** was formed in a disappointing yield of 37 %. We feel that further optimization could improve the yield to make it comparable with the lycopodine linear precursor. An attempt was made to form the ylid **199** instead of the phosphonate from the Weinreb amide **196** but unfortunately this reaction was not productive (Scheme **64**).



Scheme 67

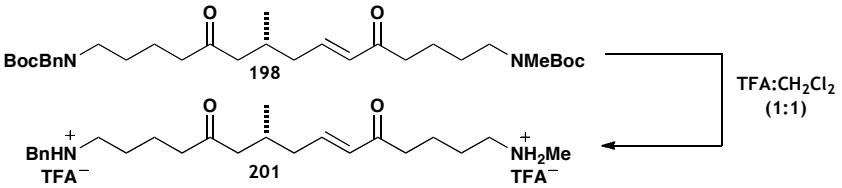
2.3.3 First cascades

With two linear precursors in hand, we turned our attention to attempting to initiate a cascade. We initially looked at simply treating our linear precursors with TFA (Scheme **65**), reasoning that this should deprotect the amine and perhaps the presence of acid would catalyze iminium/enamine formation.



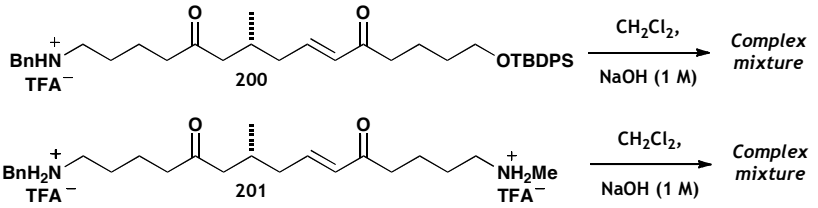
Scheme 68

However we found that treatment of our linear precursor **191** with TFA simply resulted in formation of the TFA salt **200**. Our second system gave a similar result (Scheme **66**).



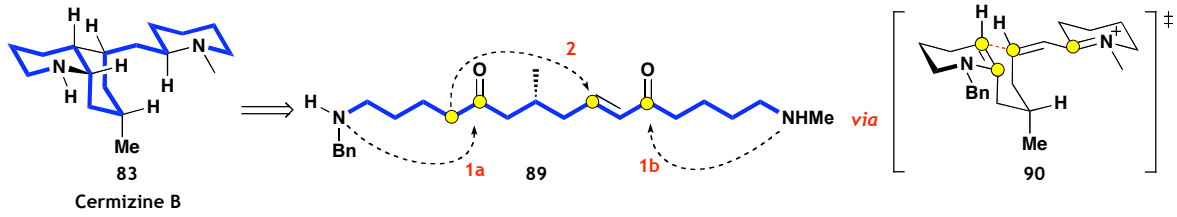
Scheme 69

We realized that we needed to free-base the amine before any further reaction could take place and so we tried evaporating the TFA:CH_2Cl_2 solvent mixture, then washing our TFA salts **200** or **201** with aqueous sodium hydroxide. However in both cases this resulted in a complex mixture of products (Scheme **67**).

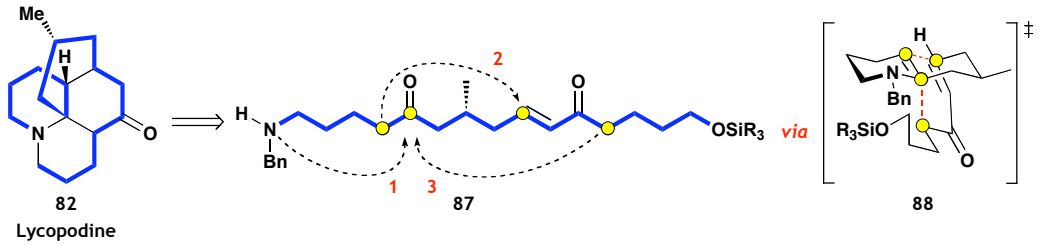


Scheme 70

Undeterred we decided to submit our complex mixture to a range of reduction conditions, reasoning that if we had formed any iminium/enamine ring systems we would be able to purify them more easily once they were reduced to less reactive amines. We focussed at first on the cermizine B system since we felt that this might be the easier cascade to manage; it required only two amine condensations (1a and 1b, Scheme **68**) and one Michael addition (2, Scheme **68**) in contrast to the condensation (1, Scheme **69**), Michael addition (2, Scheme **69**) and Mannich trap (3, Scheme **69**) we needed in our lycopodine system.



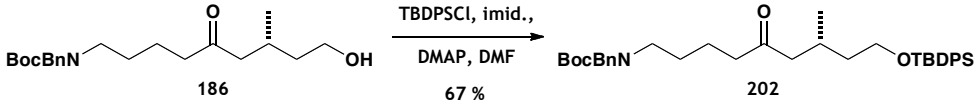
Scheme 71



Scheme 72

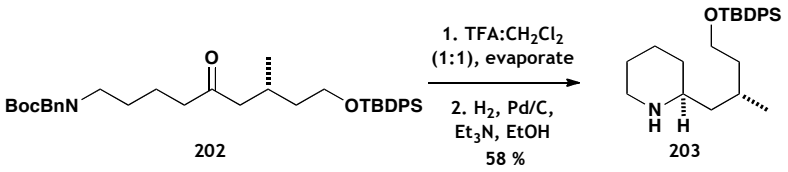
Unfortunately hydrogenation under a range of pressures, solvents and catalysts, and Birch reduction using Li/NH_3, all led to a complex mixture of products. We suspected that this could be due to the high levels of reactivity of our liberated enamine and the fact that our fully reduced product might be polar and difficult to isolate by column chromatography. We also suspected that during the evaporation of the TFA:CH_2Cl_2 mixture the fact that the dichloromethane would be removed first was resulting in exposure of our compound to high concentrations of TFA, potentially leading to unwanted side reactions under these highly acidic conditions.

We decided to go back and look at a simplified system to see if we could optimize conditions for formation of one ring, reasoning that a reliable procedure for the formation of a single ring would aid us in subsequent cascade cyclizations. We knew that a TBS group would not survive Boc deprotection but we found that we could reprotect our primary alcohol **186** using TBDPSCl to generate silyl ether **202** in good yield (Scheme **70**).



Scheme 73

We hoped that we could use this simpler linear precursor to form a piperidine *via* deprotection of our amine, iminium/enamine formation and reduction. We decided to try the reduction using the conditions we had used for alkene hydrogenation after cross-metathesis with triethylamine as a catalyst poison. We hoped that tempering the reactivity of our hydrogenation catalyst might prevent hydrogenolysis of the benzyl group and thus result in fewer purification problems.

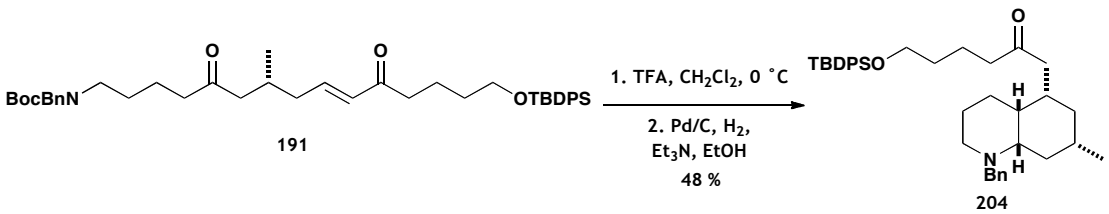


Scheme 74

We were pleased to discover that upon treatment of our truncated linear precursor **202** with TFA, evaporation of the solvent mixture and subjection of the resulting residue to our modified hydrogenation conditions we were able to isolate piperidine **203** as a single diastereoisomer in a good yield of 58 %. The stereochemistry was tentatively assigned as shown. Surprisingly hydrogenolysis of the benzyl group had occurred; however, purification of the product by flash column chromatography was not problematic and we felt that this augured well for use in our more complex cascade systems.

2.3.4 A cascade in the lycopodine system

With new hope we turned our attention back to the lycopodine linear precursor. We felt that the presence of a single amine and one Boc group would aid us in following the reaction. Accordingly, we subjected our lycopodine linear precursor **191** to a similar set of conditions as those which had produced the piperidine (Scheme **72**).



Scheme 75

We were extremely pleased to find that decahydroquinoline **204** is formed as a single diastereoisomer in moderate yield from linear precursor **191** in a two-step cascade process (Scheme **72**). Characterization of this bicycle was a challenging process and it was important to prove the connectivity of the system by tracing the 2D NMR spectroscopic correlations for key residues. Accordingly, we acquired COSY and HMBC spectra in order to follow the connectivity of the molecule by NMR spectroscopy.

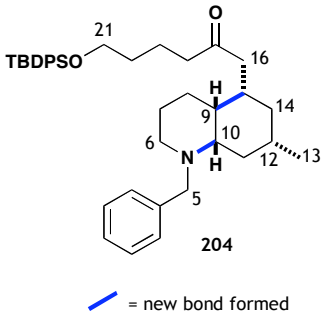
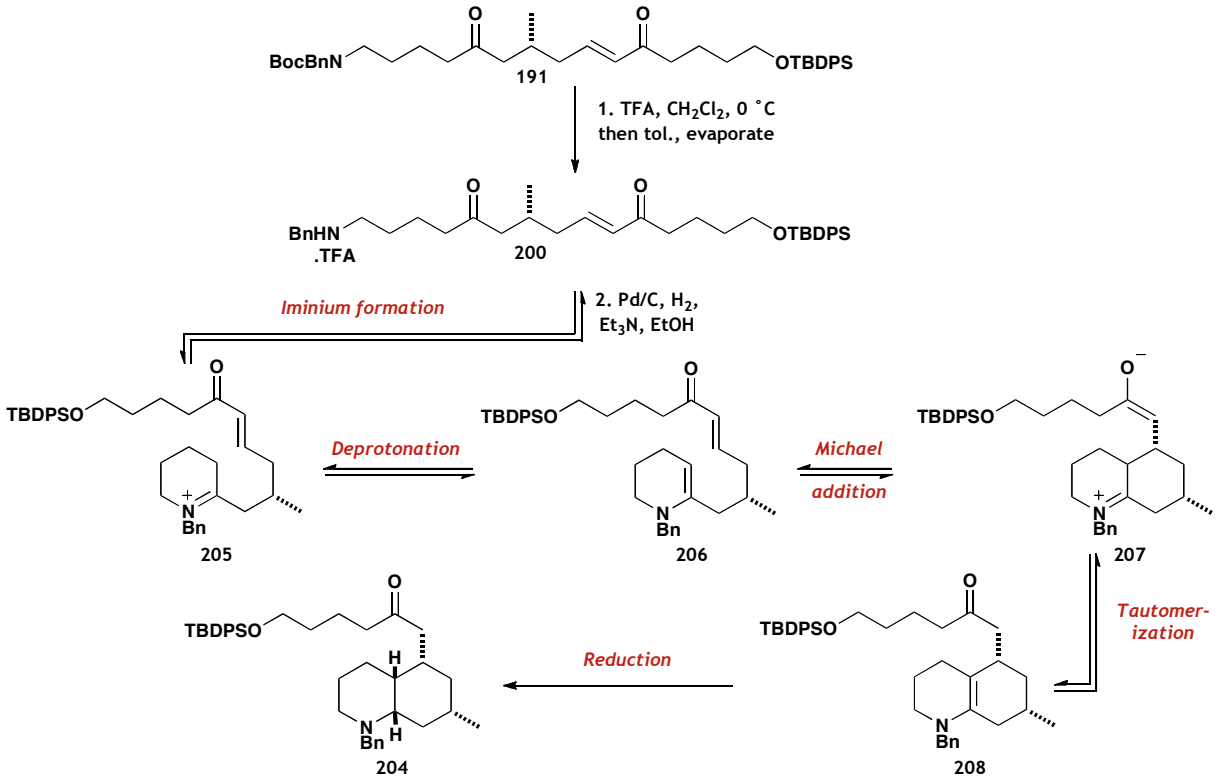


Figure 4

Using the numbering system shown above (Figure **4**) we were able to observe a number of key correlations in both the COSY and HMBC. The *N*-benzyl protons 5 and 5′ couple to carbons 6 and 10 in the HMBC suggesting that there is a bond between the amine and carbon 10; consistent with formation of the piperidine ring. Ring-junction proton 10 couples to protons 9 and also 6 (weakly) in the COSY and to carbons 15 and 6 in the HMBC, further reinforcing the connectivity of the piperidine ring and showing that formation of the cyclohexane ring has also been completed. Ring-junction proton 9 couples to proton 15 in the COSY and carbon 15 in the HMBC, proving that a bond has formed between carbons 9 and 15 and that we have indeed succeeded in forming a decahydroquinoline structure.

To rationalize the formation of this decahydroquinoline we must examine the cascade sequence in a little more detail. Treatment of linear precursor **191** with TFA in dichloromethane (1:1) removed the Boc protecting group from the amine. To prevent problems with highly acidic conditions during evaporation we diluted the reaction mixture nearly 8-fold with toluene before evaporation so that the TFA was co-evaporated

and not left behind to expose the molecule to concentrated acid. Upon evaporation, the TFA salt **200** remained (Scheme **73**), which we could then subject to the hydrogenation conditions we have previously used. Upon exposure to these conditions we believe that the first event to occur is free-basing of the TFA salt by the triethylamine (Scheme **73**).



Scheme 76

Liberation of the amine allows it to condense with the ketone, forming iminium ion **205**. A further deprotonation event (again possibly mediated by triethylamine) furnishes the enamine **206**, which carries out the Michael addition to form bicycle **207**. The zwitterion **207** can tautomerize to the enamine **208**, which is finally reduced to the decahydroquinoline **204**. The presence of the triethylamine catalyst poison tempers the reactivity of the palladium catalyst, slowing the hydrogenation process and preventing reduction of the alkene in the linear precursor before the two rings have formed. Instead we only see hydrogenation after the two rings of the decahydroquinoline have formed. No reduced linear precursor is observed.

In addition we only observe formation of one diastereoisomer, assigned by NOE experiments (**209**, Figure **5**), where the methyl group and side chain are on one face (probably in the less hindered equatorial positions) and the ring junction protons are on the opposite face. We believe that this is simply due to the steric bulk of the side-chain and methyl group forcing hydrogenation to occur exclusively on the opposite face.

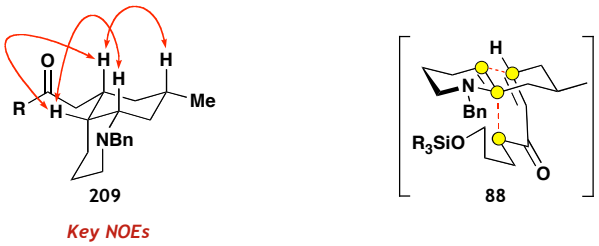
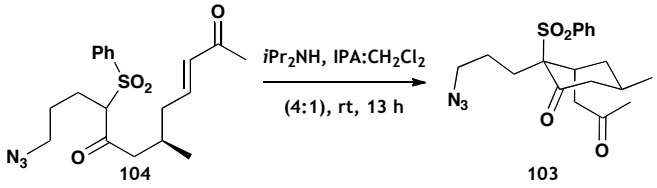


Figure 5

We have managed to form two rings in a single process in a completely diastereoselective manner, creating three new stereocentres. However this decahydroquinoline does not possess the correct stereochemistry for lycopodine; in lycopodine the methyl group and the side chain are on opposite faces of the ring we have formed. Furthermore, in order to form the skeleton for lycopodine, we need to form *three* rings in a single step with the correct stereochemistry, which would require the zwitterion **207** (Scheme **73**, above) to carry out a Mannich cyclization from the enol onto the iminium ion instead of tautomerizing to the enamine. Unfortunately this is impossible to achieve given the stereochemistry of the bicyclic compound, in which the methyl group and side chain are on the same face. For the correct Mannich addition to occur the two groups must be on opposite faces of the ring (**88**, Figure **5**), with the enol side-chain in the sterically disfavoured axial position. If the two groups were on the same face as in our system (**207**, Scheme **73**) the Mannich cyclization would be possible only if both groups adopted sterically disfavoured axial positions. This is unlikely to occur, and even if it could happen, the tricycle formed would not have the desired stereochemistry.

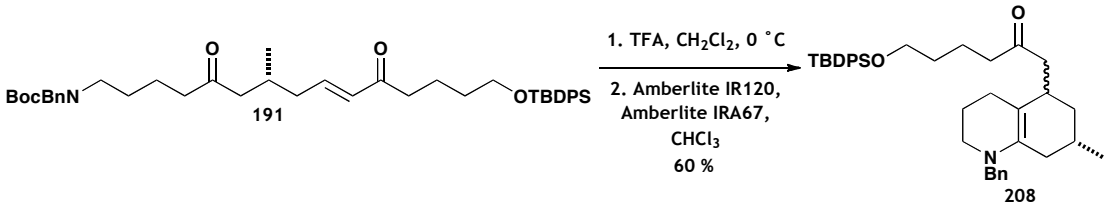
This is in contrast to Zakharov's system in which the Michael addition delivers only the desired diastereoisomer **103** with the methyl group on one face and the ketone side-chain

on the opposite face (Scheme **74**). Perhaps this is due to the presence of the sulfone encouraging the enone to lie on the opposite face to itself.



Scheme 77

Reasoning that the enamine **208** must be in equilibrium with both zwitterion **207** and enamine **206** (Scheme **73**, above), we wondered if we could find some conditions to encourage the reversibility of the Michael addition. If we could induce the Michael addition to occur on the opposite face we believed that the Mannich addition might be rapid and this would allow us to form the desired tricycle in accordance with the Curtin-Hammett principle. We believed that under the catalyst-poisoned hydrogenation conditions our linear precursor was being exposed to an environment that was both acidic (from the Pd/C) and basic (Et_3N), and we sought a more effective version of these acid/base conditions to encourage reversibility and closing of the third ring. We considered using site isolated solid supported acid and base and decided on using two types of Amberlite (Scheme **75**).

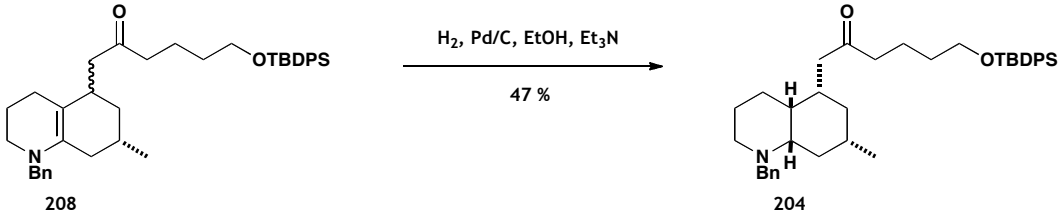


Scheme 78

Linear precursor **191** was treated with TFA in dichloromethane as before, to produce the TFA salt of the deprotected amine. The solvent was evaporated and the salt redissolved in chloroform and treated with Amberlite IR120 (a resin with sulfonic acid functionality) and Amberlite IRA67 (a resin with amine base functionality). The solid-supported base deprotonates the ammonium salt, which allows the amine to condense with the ketone, which may also be protonated by the solid-supported acid. The base will then encourage

enamine formation, followed by activation of the Michael acceptor by the acid ready for the conjugate addition. The Michael addition results in formation of the bicyclic enamine **208** which appears to exist as a 2:1 mixture of inseparable diastereoisomers, with the major one assumed to be the same stereochemistry as the saturated bicycle **204** formed previously. The key spectroscopic indication showing the presence of this enamine was observation of peaks in the ^{13}C NMR spectrum at 141.0 and 106.9 ppm corresponding to the carbons α and β to the amine in the enamine alkene. Despite the fact that one of the diastereoisomers present should have the correct stereochemistry for the lycopodine Mannich trap, we unfortunately did not observe any formation of our desired tricyclic compound.

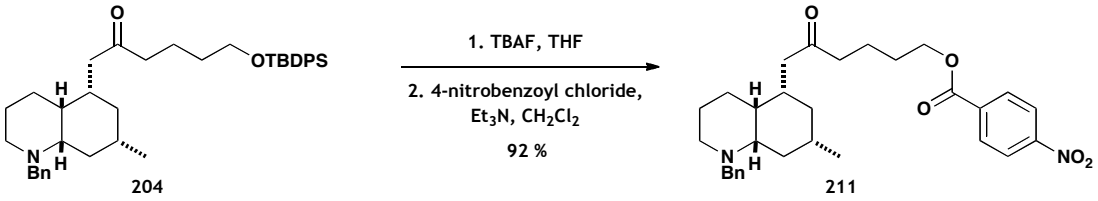
We could hydrogenate enamine **208** under the same conditions as used previously (Scheme **76**).



Scheme 79

Treatment of the enamine **208** with triethylamine-poisoned palladium on carbon under an atmosphere of hydrogen led to formation of the previously observed bicycle **204** in moderate yield. We did not observe formation of any other diastereoisomers, but speculate that perhaps the other diastereoisomer was more difficult to hydrogenate for steric reasons, and hence the unreduced enamine was lost during flash column chromatography. Hydrogen appears to be delivered from the opposite face to that which the methyl and ketone sidechains are on. We can postulate that this is simply due to steric reasons, as the hydrogen is being delivered to the least hindered face of the bicyclic enamine which is fairly flat.

In order to prove the stereochemistry of our decahydroquinoline we wanted to obtain an X-ray structure. To this end, we attempted to make a crystalline derivative of bicycle **204** (Scheme **77**).



Scheme 80

TBAF was used to deprotect the primary alcohol in decahydroquinoline **204** and the resulting alcohol was esterified with 4-nitrobenzoyl chloride to form ester **211** in excellent yield. Unfortunately ester **211** was not crystalline and all attempts to form a salt using various acids such as *p*-TSA and HCl did not result in any crystalline derivatives. We concluded that there were just too many long hydrocarbon chains in our molecule for it to crystallize effectively. However the NOE results were conclusive so we remained positive of our stereochemical assignment.

At this stage we had to face the possibility that although we had managed to form two rings, two new bonds and three new stereocentres, we would not be able to form our tricyclic compound, and thus completion of lycopodine appeared to be a distant possibility. However, we were confident in our ability to form decahydroquinoline type skeletons and so decided to focus our efforts on another family of alkaloids containing this type of skeleton: the lepadins.

3 The lepadins

There are eight naturally occurring lepadins, assigned as A-H (Figure **6**).

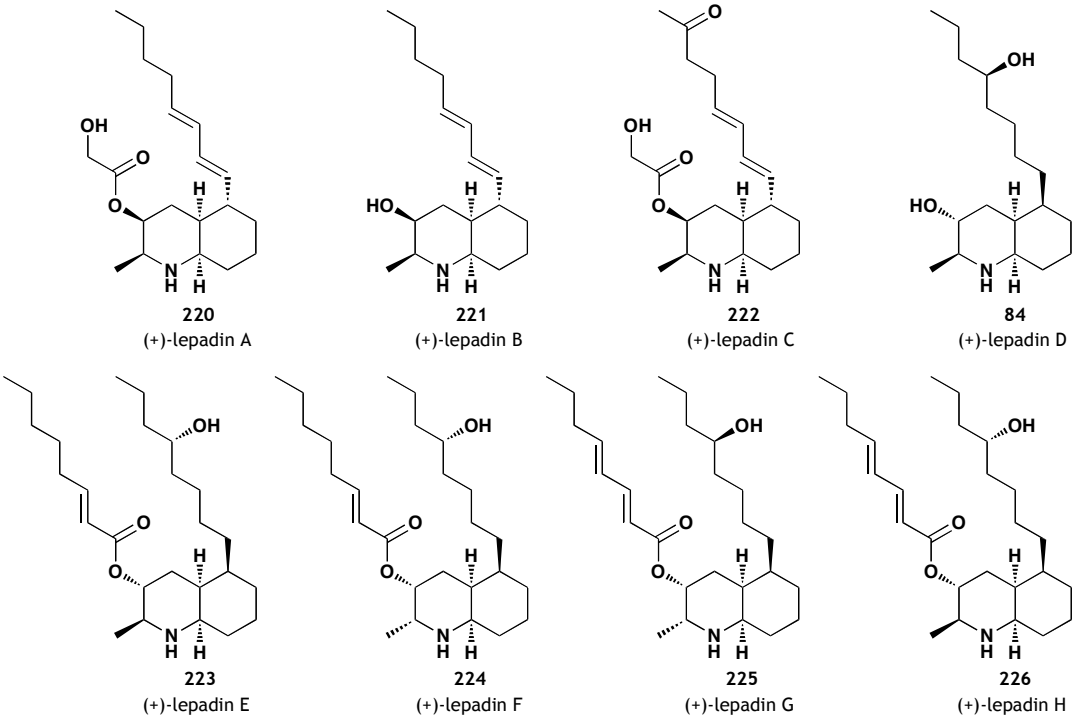
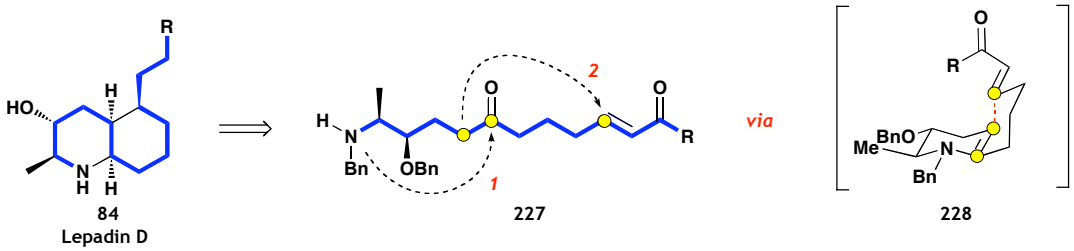


Figure 6

Lepadins A-C (**220**, **221**, **222**) were the first to be isolated from the flatworm *Prostheceraeus villatus* and its tunicate prey *Clavelina ledadiformis*, in the North Sea between 1991-5.[58, 59] However, since our cascade approach to a decahydroquinoline skeleton had so far resulted in structures of the type where the ring junction protons were on the opposite face to the adjacent side chain, we were initially most interested in lepadins D-H as these molecules share those structural features. Lepadins D-F (**84**, **223**, **224**) were isolated by Wright and König in 2002 from tunicates of the genus *Didemnum*,[60] and in the same year Caroll isolated lepadins F-H (**224**, **225**, **226**) from a Great Barrier Reef ascidian, *Aplidium tabascum*.[61] Biological studies have shown varying levels of activity and selectivity against human cancer cell lines,[58] malaria and trypanosomes.[60]

Taking lepadin D **84** as an example, we can see that all eight lepadins share a common and simple disconnection, which is also closely related to the disconnection we have used for the lycopodium alkaloids (Scheme **78**).



Scheme 81

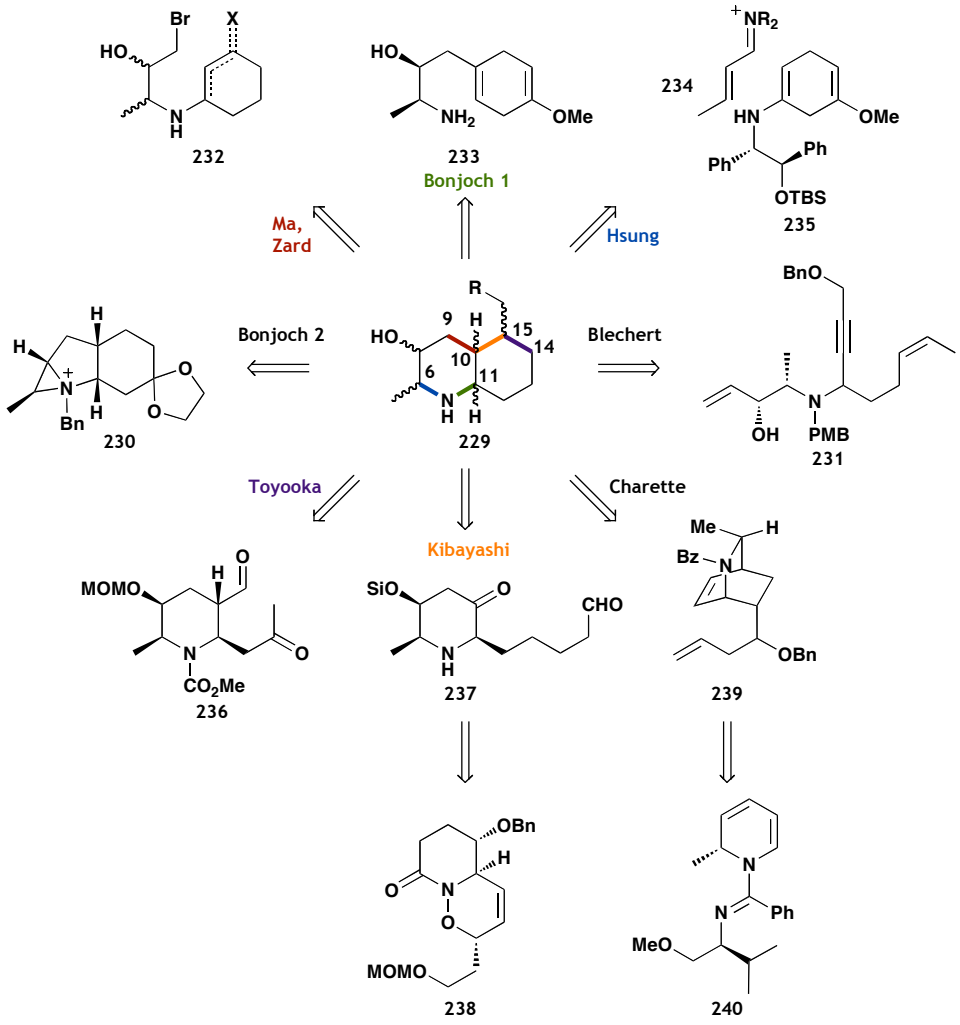
Disconnecting across the black bonds (**84**, Scheme **78**) takes us back to linear precursor **227**, which, like those for the lycopodium alkaloids, contains an amine in a 1,5 relationship with a ketone and a further α,β-unsaturated ketone which can act as a Michael acceptor. In the forward direction of the cascade, we expect enamine formation (1) to be followed by a Michael addition (2), as before, to form the bicycle. In this case a final reduction would lead to the desired decahydroquinoline skeleton ready for side chain elaboration to form lepadin D. We believe that this approach could potentially be modified to allow access to all eight of the lepadins, wherein we would just need to vary the stereocentres α- and β- to the amine, the facial selectivity of the reduction step and the final side chain elaboration.

3.1 Previous approaches to the lepadins

There have been a number of synthetic approaches to the lepadins, mainly towards lepadins A-C. However lepadins D-H have also been successfully accessed. There are four main approaches that have been used to access the decahydroquinoline skeleton needed for the lepadins (Scheme **79**). Most syntheses have started from one of the two rings and built the second ring onto either the piperidine or cyclohexane ring. However there are two approaches which are distinct: in one of Bonjoch's routes (2, Scheme **79**)[62] to decahydroquinoline skeletons he uses a ring expansion approach from a 6,5,3-tricycle such as **230**. Addition of silver acetate allows acetate mediated opening of the strained aziridine-type ring to give the desired 6,6-bicycle with the methyl and alcohol stereocentres correctly

installed for elaboration to lepadins D, E and H. Blechert also uses a different approach,[63] treating ene-yne-ene precursor **231** with a metathesis catalyst which allows formation of both rings of the skeleton in a single process, although using different reactivity to that which we hope to exploit in our two-ring-forming cascade.

Examining those routes which have started from the cyclohexane-type ring first, we see that a number of different disconnections have been used. Ma[64, 65] and Zard[66] both disconnect across the C_9-C_{10} bond (red) in **229** to give a structure like **232** (Scheme **79**) but form this bond very differently; Zard uses a radical-mediated cyclization while Ma's approach involves a Bayliss-Hillman type alkylative cyclization. Bonjoch's other approach (1, Scheme **79**)[67] to decahydroquinoline skeletons involves disconnection across the N-C_{11} bond (green) in **229** to give amine **233**, which cyclizes upon treatment with acid and is derived from Birch reduction of an aryl ring. Hsung uses his *aza*-[3+3] annulation strategy,[68] disconnecting across both the N-C_6 (blue) and C_9-C_{10} (red) bonds to give unsaturated iminium ion **234** and enamine **235**. This strategy showcases the nucleophilic nature of an *N*-benzyl enamine, which we hope to exploit in our cascade sequence.

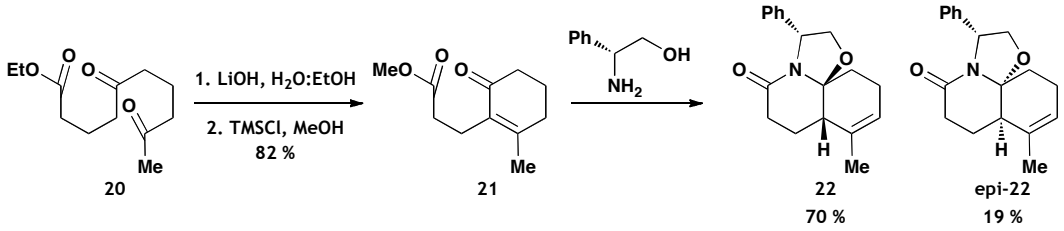


Scheme 82

Looking at the approaches which start from the piperidine ring, perhaps the simplest disconnection is between C_{14}-C_{15} (purple) which is Toyooka's aldol cyclization[69, 70] in the forward direction to form the second ring from keto-aldehyde **236** (Scheme **79**). Kibayashi[71, 72] also uses an aldol approach to form the second ring from keto-aldehyde **237**, although disconnecting across a different bond, C_{10}-C_{15} (orange). These syntheses both demonstrate the reliable nature of the aldol reaction for forming 6-membered rings in a Robinson annulation-type fashion. The most interesting part of Kibayashi's sequence, however, is perhaps his acylnitroso-Diels-Alder reaction used to form the piperidine ring, yielding **238**. Finally, Charette[73] uses a ring-opening/ring-closing metathesis approach to

form the all-carbon ring of the decahydroquinoline from **239**, deriving the piperidine ring from an asymmetric dearomatization of pyridine to give **240**.

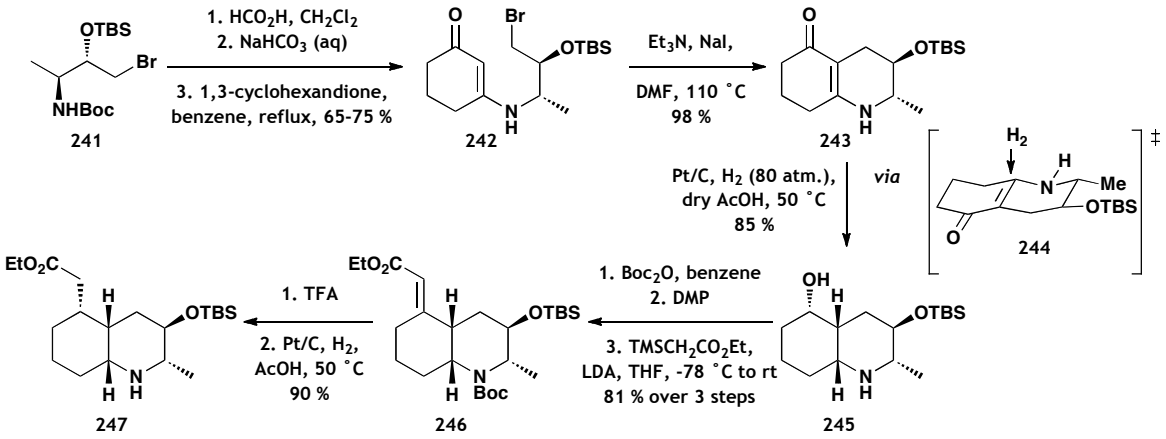
Recently Amat and Bosch have disclosed an approach to decahydroquinoline skeletons from linear precursors in a stepwise manner (Scheme **80**).[2] This was discussed earlier (section **1.1** of the introduction) but bears repeating here.



Scheme 83

Sequential treatment of diketoester **20** with aqueous lithium hydroxide in ethanol and trimethylsilyl chloride in methanol promoted cyclization to cyclohexenone **21** in good yield. Cyclization with (*R*)-phenylglycinol stereoselectively provided tricyclic lactam **22** in 70 % yield, with a further 19 % yield of epi-**22**. The authors went on to transform tricyclic lactam **22** to (-)-pumiliotoxin C in a further 8 steps. This synthesis again demonstrates the effectiveness of the Robinson annulation in these ring forming processes, as well as the utility of nucleophilic amines for forming the piperidine ring of the decahydroquinoline.

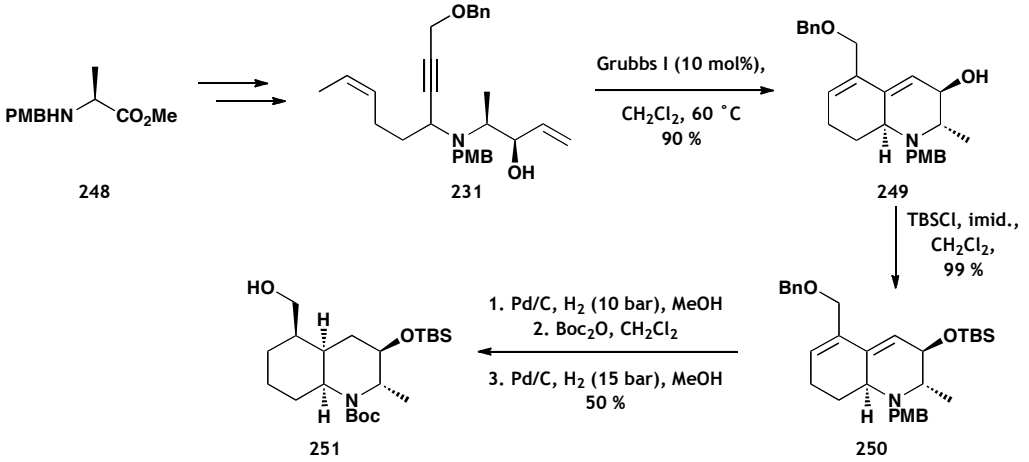
Looking at some of these syntheses in a little more detail, we first turn our attention to those routes approaching lepadins D-H as these are the structures that we initially hope to access. Ma synthesised lepadins A-E and H all from protected amino alcohol **241**, derived from L-alanine (Scheme **81**).[64, 65] This gives us a useful starting point for obtaining chiral starting materials.



Scheme 84

Boc deprotection of **241** gave the formic acid salt of the amine. Attempts to condense the salt with 1,3-cyclohexandione were very poor yielding (~10 %) but upon treatment with aqueous sodium bicarbonate to form the free amine, subsequent condensation reactions were much improved to form vinylogous amide **242**. Bayliss-Hillman type alkylative cyclization with triethylamine and sodium iodide gave bicycle **243** in excellent yield, ready for the three key stereocentres (across the ring junction and the side chain) to be set. Hydrogenation of bicycle **243** using a platinum on carbon catalyst in dry acetic acid led to decahydroquinoline **245** as a single isomer in very good yield. It is suggested that the selectivity is due to the axial attack of hydrogen from the less hindered *Re* face of the bicycle (**244**). It is difficult to see how one face of this bicycle is less hindered than the other but nevertheless a single diastereoisomer is formed. Finally a side chain must be installed to allow access to the lepadins. For lepadins D-E and H it was necessary for the side chain to be on the opposite face to the ring junction protons. This was established by hydrogenation of the alkene **246**, derived from a Peterson olefination, again using a platinum on carbon catalyst in dry acetic acid, with the hydrogen similarly being delivered onto the convex face of the *cis*-decalin to give amine **247** in excellent yield and de (>95 %). The facial selectivity of hydrogenation will be critical in our system too, once we have formed the two rings of the decahydroquinoline.

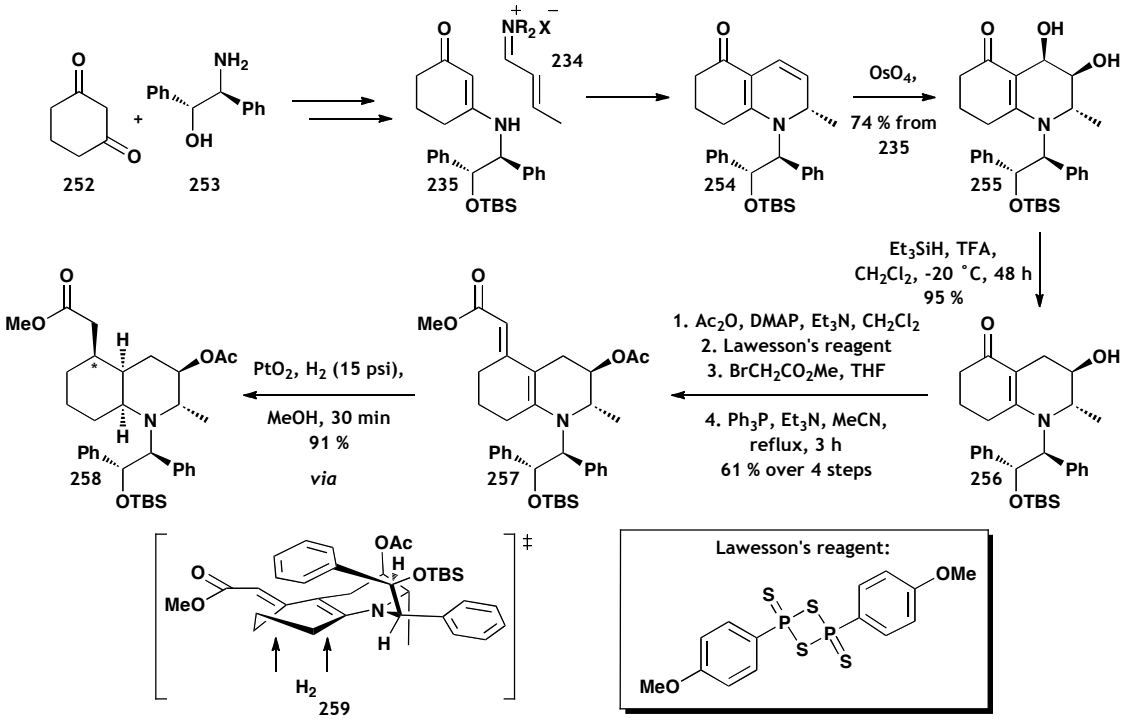
In 2008 Blechert[63] published his synthesis of *ent*-Lepadin F and G utilizing a very nice ene-yne-ene ring closing metathesis (Scheme **82**).



Scheme 85

Protected amino ester **248** (derived from L-alanine) was transformed to the metathesis precursor **231** in four steps. Again we note that L-alanine may be a useful source of chirality for our system. Treatment of **231** with the more reactive catalysts Grubbs II and Hoveyda-Grubbs II resulted in either no reaction (in the case of the former) or formation of significant amounts of byproducts. However, the use of the less stable catalyst Grubbs I at an elevated temperature of 60 °C in dichloromethane resulted in an excellent yield of the desired bicycle **249**. Silyl protection of the secondary alcohol provided silyl ether **250**, where the bulky group on the alcohol could help to direct hydrogenation of the two alkenes. Indeed hydrogenation of **250** using a palladium on carbon catalyst and a hydrogen pressure of 10 bar resulted in complete reduction of both alkenes, with the hydrogen delivered onto the bottom face of the bicycle, and concomitant cleavage of the PMB group. Boc protection of the newly liberated amine and hydrogenolysis of the benzyl group gave decahydroquinoline **251** with the side chain on the opposite face to the ring junction protons. Elaboration of this bicycle to what turned out to be *ent*-lepadins F and G allowed the relative stereochemistry of the natural products to be confirmed for the first time.

Lepadin F was also prepared by Hsung using his *aza*-[3+3] annulation (Scheme **83**).[68]

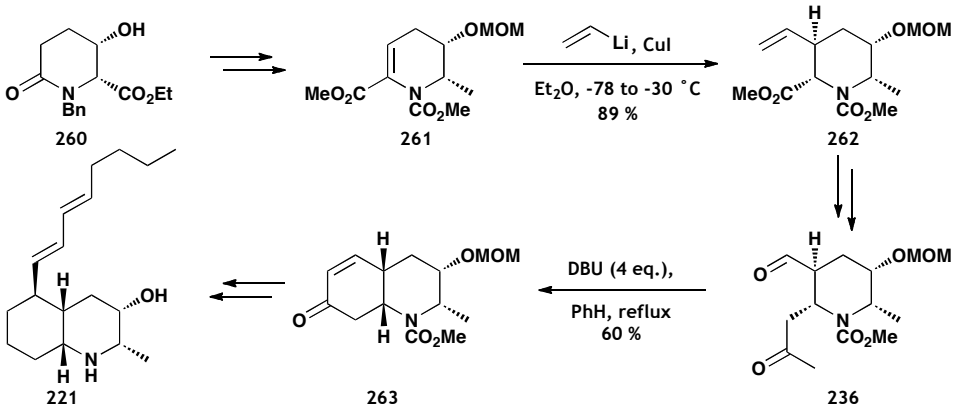


Scheme 86

Known diol **255**[74] was prepared by annulation of vinylogous amide **235** and iminium ion **234** followed by dihydroxylation. Triethylsilane in the presence of TFA was used to remove the unwanted hydroxyl group to give alcohol **256**. Unsuccessful attempts were made to hydrogenate the enamine at this stage, with reduction of the ketone being the major unwanted side reaction. Instead, after acylation of alcohol **256**, Eschenmoser's episulfide contraction[75, 76] was used to lead to doubly vinylogous amide ester **257**, ready for hydrogenation and the setting of the three key stereocentres as before. Hydrogenation proceeded smoothly using Adam's catalyst[77] and a hydrogen pressure of 15 psi to yield decahydroquinoline **258** with the desired stereochemistry (5:1 mixture of epimers at *). Here the hydrogen has been delivered onto the bottom face of the bicycle and it appears that the chiral auxiliary on the amine shields the top face from reduction (**259**, Scheme **83**). Use of a chiral protecting group such as α-methylbenzyl on the amine may be a strategy for us to consider if our reduction step proves unselective. This decahydroquinoline could be elaborated to lepadin F in 12 steps.

Other syntheses of the lepadins have mainly been focussed on lepadins A-C and lepadin B has proven a particularly tractable target.

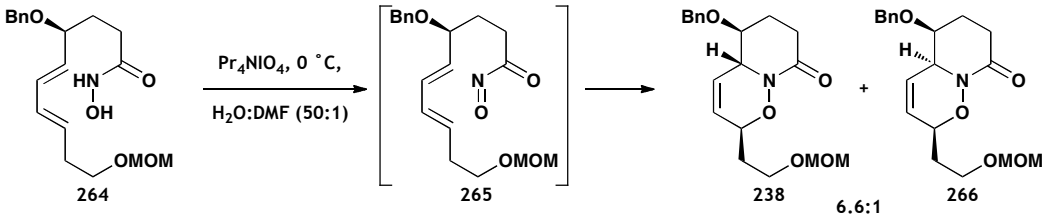
Toyooka's enantioselective total synthesis of lepadin B[69, 70] is a good example of the use of an intramolecular aldol reaction as a key step, an approach taken by more than one group (Scheme **84**).



Scheme 87

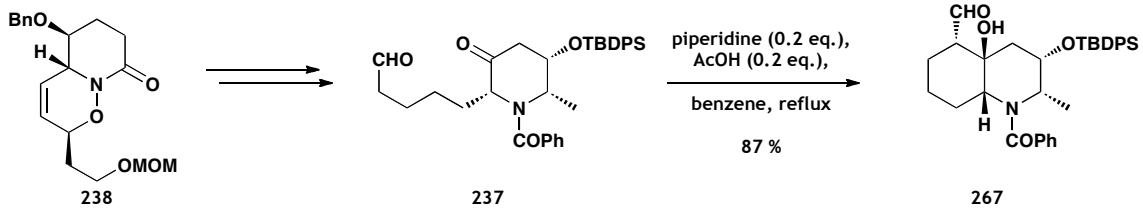
Transformation of known lactam **260**[78] into an enol triflate allows formation of vinyl ester **261**. Treatment with vinyl cuprate leads to Michael addition, giving functionalized piperidine **262** as a single diastereoisomer in excellent yield, which after further elaboration delivers aldol substrate keto-aldehyde **236**. After some optimization it was found that heating **236** in refluxing benzene with four equivalents of DBU were the best conditions for the aldol transformation, forming bicycle **263** in good yield and pleasing diastereoselectivity (14:1 *cis*:*trans* at the ring junction). This is attributed to the fact that aldol cyclization is much slower when the ketone and aldehyde lie *trans*-diaxial and so the centre α to the aldehyde is epimerized in most of the substrate before cyclization takes place; epimerization is fast compared to cyclization in the *trans* system. This is a nice demonstration of thermodynamic control giving the desired stereochemistry in a bicyclic system. The synthesis of lepadin B **221** was completed *via* a Michael addition, decarbonylation and Julia olefination.

A pericyclic approach has also been used to access the lepadin skeleton. Kibayashi used an acylnitroso Diels-Alder reaction in his route to lepadins A-C (Scheme **85**).[71, 72]



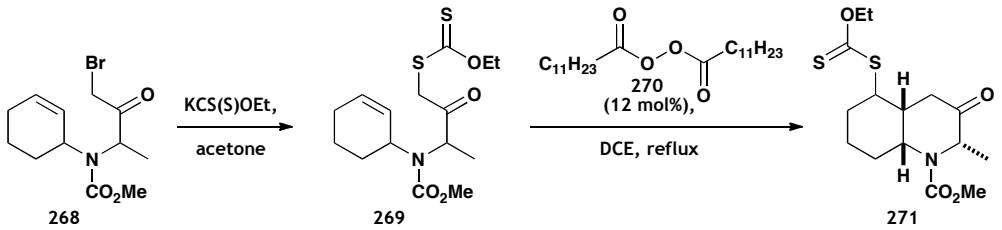
Scheme 88

With the chirality being initially derived from (*S*)-malic acid, hydroxamic acid **264** was synthesized and then exposed to hypervalent iodine, resulting in oxidation to **265** and spontaneous cycloaddition to form the bicyclic compounds **238** and **266**. The diastereoselectivity is moderate in aqueous DMF (6.6:1) but much improved from the initial results in chloroform (1.7:1). The desired diastereoisomer can be separated, and after several steps including cleavage of the N-O bond, introduction of the methyl group α- to the amine and the hydroxy group β- to the amine and installation of the required side chain, an aldol reaction is again used to close the second ring of the lepadin skeleton (Scheme **86**). Treatment of keto-aldehyde **237** with catalytic piperidine and acetic acid in refluxing benzene gave decahydroquinoline **267** in very good yield as a single diastereoisomer. Lepadins A, B and C were synthesized from a common late-stage intermediate.



Scheme 89

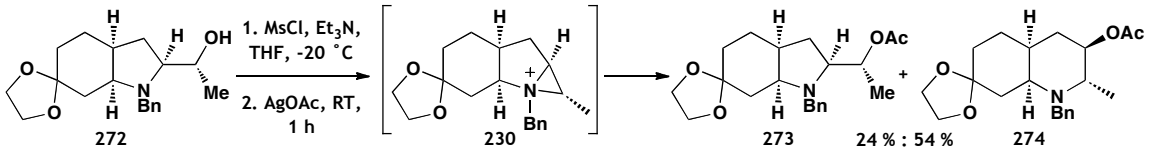
A different approach for closing the second ring was used in Zard's racemic synthesis of lepadin B:[66] a xanthate-mediated radical cyclization (Scheme **87**).



Scheme 90

The selectivity seen here for formation of the *cis* ring junction of a decalin has some precedent in the literature.[79] It is suggested that the relative stereochemistry of the methyl group is a result of equilibration to the thermodynamic equatorial product due to the presence of a trace of lauric acid deriving from the dilauroyl peroxide **270**. Again this suggests that thermodynamic control is the best method for controlling the stereochemistry of these ring systems.

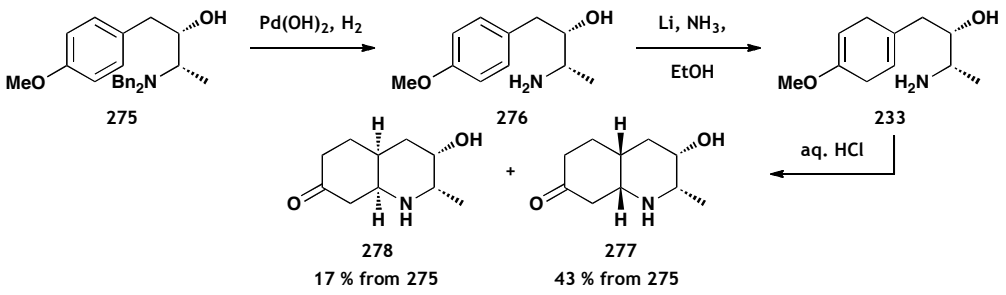
An interesting method was used by Bonjoch in one of his approaches to the *cis*-decahydroquinoline skeleton required for lepadin synthesis (Scheme **88**).[62]



Scheme 91

This ring expansion approach involves intramolecular diplacement of a mesylate by the amine of an octahydroindole to form an aziridinium ion **230**, which can then be opened at one of two sites, leading to either acylated starting material **273** or the ring expanded product **274**, which is the correct stereochemistry for elaboration to lepadins D, E and H.

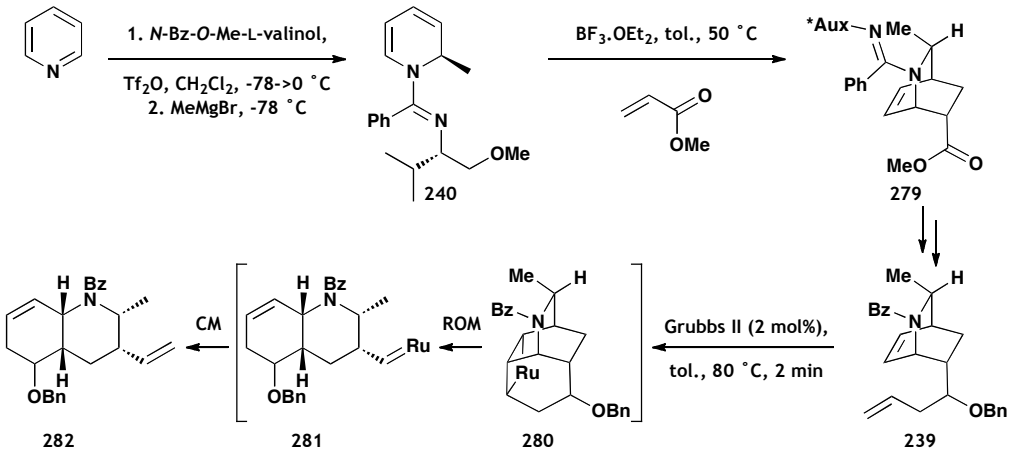
Another possible approach (again taken by Bonjoch) to this type of decahydroquinoline skeleton involves Birch reduction of an arene with a pendant L-alanine-derived sidechain such as **276** (Scheme **89**).[67]



Scheme 92

Starting from the *N,N*-dibenzyl protected amino alcohol **275**, hydrogenolysis of both benzyl groups using Pearlman's catalyst yields free amine **276**, which can be subjected to Birch reduction followed by an acidic work-up to give decahydroquinolines **277** and **278**. The *aza*-1,4-addition is stereoselective, giving only the *cis* ring junction products, presumably due to the fact that the amine is tethered on one face. The facial selectivity for the ring junction protons could be reversed by protecting the secondary alcohol as a methyl ether, leading to a 39 % yield of **278** with 17 % of **277**.

Another approach which starts from an aromatic ring was used by Charette in his synthesis of lepadin B.[73] He utilized his pyridine dearomatization methodology to form the piperidine ring of the decahydroquinoline and then used ring-opening/ring-closing metathesis to install the second ring (Scheme **90**).

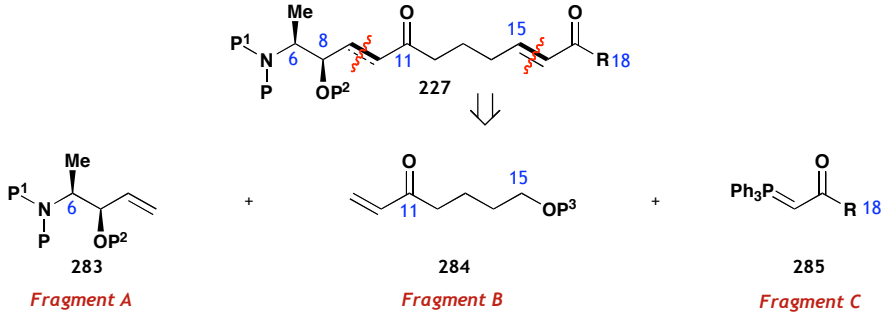


Scheme 93

Pyridine can be regio- and diastereoselectively dearomatized to give dihydropyridine **240**, which can then be used in an *endo*-selective Diels-Alder reaction to yield bridged bicycle **279**. After several synthetic manipulations, including installation of the homoallyl sidechain, the system was ready for the cross metathesis reaction. After examination of a number of conditions it was found that the best yield (79 %) was obtained by heating the substrate **239** with the Grubbs II catalyst in toluene at 80 ˚C for just two minutes. The mechanism was investigated and the authors believe that the reaction proceeds *via* initial cross metathesis of the catalyst with the terminal alkene, followed by a ring-closing metathesis with the endocyclic alkene leading to **280** and then ring-opening metathesis to give the desired decahydroquinoline skeleton **281**.

3.2 A linear precursor for the lepadins

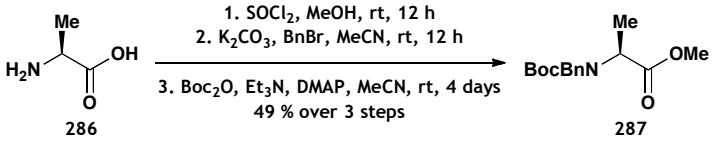
We wanted to use the same modular approach to our linear precursor for the lepadins as we had used in forming our previous systems for the lycopodium alkaloids. Accordingly, we disconnected our starting molecule across the same two bonds (Scheme **91**).



Scheme 94

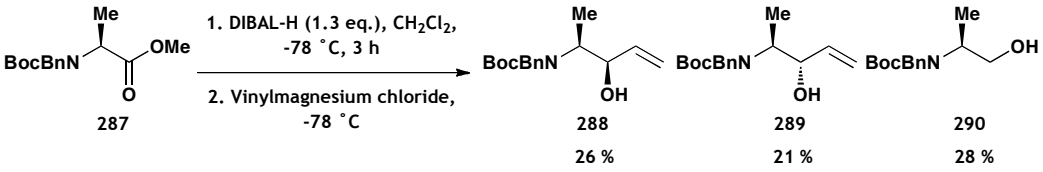
Again we can install an alkene between C_9-C_{10} and disconnect across that bond, leaving us with an amine **283** and an α,β-unsaturated ketone **284** which can be joined in the forward direction by transition-metal catalyzed cross metathesis. We also cleave the C_{15}-C_{16} alkene, as before, and again hope to form this bond in the forward direction by carrying out a Wittig reaction employing ylid **285**.

In this system our amine fragment **283** is considerably more complex than in the lycopodium system; it now contains two stereocentres which must be set correctly, and the alkene is much more sterically hindered which may prove problematic for the cross-metathesis step. However we were confident that we could overcome these potential obstacles and began our synthesis of the amine fragment by considering ester **287** (Scheme **92**).



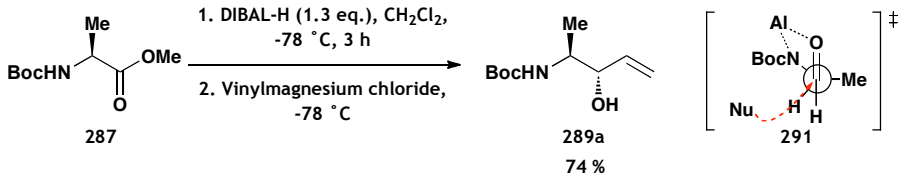
Scheme 95

Previous work within the group had shown that ester **287** could be prepared from L-alanine **286** in three steps and good overall yield.[80] Fortunately a large stock of this ester had been prepared and so armed with this we began examining approaches to our linear precursor. Again previous work had shown that ester **287** could be converted to secondary alcohols **288** and **289** as well as primary alcohol **290** in a one-pot process (Scheme **93**).[80]



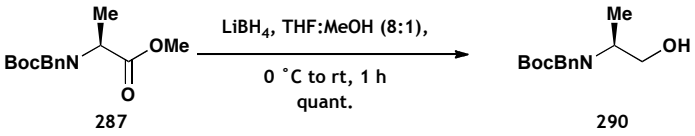
Scheme 96

Treatment of ester **287** with DIBAL-H to reduce it to the aldehyde, followed by addition of vinylmagnesium chloride into the reaction mixture, resulted in an approximately 1:1:1 mixture of the three alcohols **288**, **289**, and **290**. In contrast, when this procedure was carried out in the absence of the *N*-benzyl group (Scheme **94**), the result was a 74 % yield of alcohol **289a** with a dr of 10:1. The stereocontrol arises in this system *via* the chelation controlled transition state model **291**, which is favoured in the absence of the *N*-benzyl group and in the presence of the Lewis-acidic aluminium for chelation.



Scheme 97

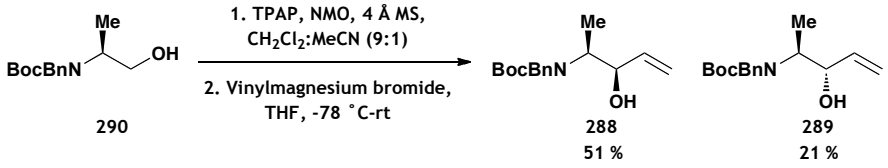
We realized that if we wanted to form either of the alcohols **288** or **289** (**288** useful for lepadins D, E and H, **289** useful for lepadins A-C) we needed to find an improved method. Accordingly we looked at carrying out the step-wise procedure.



Scheme 98

Ester **287** was reduced with lithium borohydride to give the primary alcohol **290**, which proceeded quantitatively (Scheme **95**).

Oxidation of the primary alcohol **290** to the aldehyde using catalytic TPAP with NMO as co-oxidant followed by vinyl Grignard addition led to formation of alcohol **288** and **289** in 72 % overall yield and with a d.r. of 2.5:1 (Scheme **96**).



Scheme 99

Here the major isomer is arising from the polar Felkin-Anh type transition state **292** (Figure **7**), which is favoured under these conditions with the sterically hindered protected nitrogen and magnesium, which has decreased chelating properties when compared with aluminium. The minor diastereomer arises from the chelation-controlled transition state **293**, which was previously favoured in the absence of the *N*-benzyl protecting group.

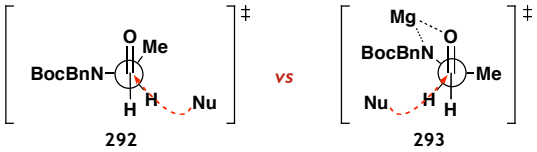
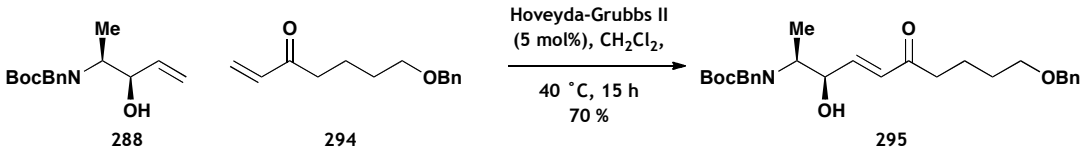


Figure 7

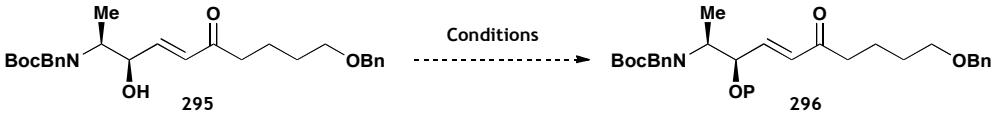
The two alcohols were separable by flash column chromatography and we decided to proceed with alcohol **288** initially. This meant that we would in the first instance be focusing on lepadins D, E and H, as these contain the appropriate stereochemistry of the alcohol and methyl group. However alcohol **289** contains the correct stereochemistry for accessing lepadins A-C so may also prove useful. It may also be interesting to examine whether the stereochemistry of the alcohol has any effect on the stereocontrol of the cascade cyclization reaction, so access to both diastereoisomers is important.

Previous work in the group had shown that alcohol **288** could be used directly in a cross metathesis reaction (Scheme **97**).[80]



Scheme 100

Amine **288** and ketone **294** could be treated with Hoveyda-Grubbs II catalyst in dichloromethane and heated at 40 °C overnight to produce a good yield of *α,β*-unsaturated ketone **295**. Again a stock of some of this *α,β*-unsaturated ketone **295** remained and so we examined whether the secondary alcohol could now be protected as a silyl ether (Scheme **98**, table **2**).



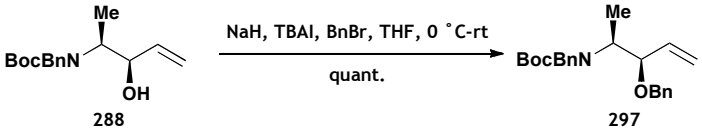
Scheme 101

Conditions	Result
TBDPSCl, imid., DMAP, DMF	Recovered SM
TIPSCl, imid., DMAP, DMF	Recovered SM
TBSOTf, 2,6-lutidine, CH_2Cl_2	Recovered SM

Table 2

We initially wanted to install a bulky silyl group which would not be acid labile such as TBDPS or TIPS, since we knew that a TBS group would be removed by TFA when we began our cyclization cascade, and we preferred to keep the alcohol protected at that stage to prevent unwanted side reactions. However neither TBDPS, TIPS nor even TBS proved amenable to silylating our alcohol. It appeared that the secondary alcohol was too sterically hindered for us to install any synthetically useful silyl protecting groups. We concluded that we needed instead to protect the secondary alcohol before cross metathesis.

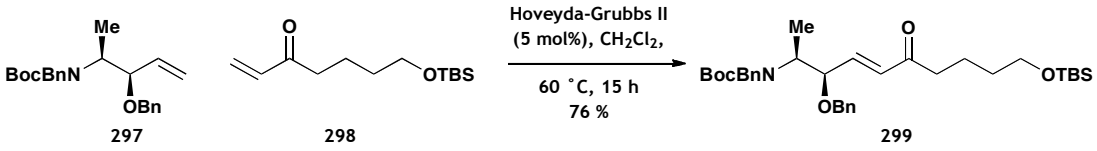
Since previous work in the group had shown that increasing the steric bulk of the alcohol on the amine fragment could be detrimental to the yield for cross metathesis, we opted to protect the secondary alcohol as a benzyl ether rather than a bulkier silyl ether (Scheme **99**), whilst protecting the primary alcohol on the ketone fragment as a silyl ether to maintain protecting group orthogonality.



Scheme 102

Treatment of alcohol **288** with sodium hydride and benzyl bromide with catalytic iodide lead to formation of benzyl ether **297** in quantitative yield. Our second fragment for cross metathesis had been synthesized before within the group and can be made in three steps

from δ-valerolactone.[80] With our two alkenes in hand we turned our attention to the cross metathesis reaction (Scheme **100**).



Scheme 103

We were very pleased to find that when amine **297** and ketone **298** were treated with Hoveyda-Grubbs II catalyst in dichloromethane at 60 °C overnight, α,β-unsaturated ketone **299** was formed in a gratifying yield of 76 %. Since our amine fragment is sterically hindered around the alkene we wondered if substituting Hoveyda Grubbs III (where the mesityl groups have been substituted by 2-tolyl groups) for Hoveyda Grubbs II might improve the yield, since the third generation catalyst has been shown to give improved yields for alkenes bearing substitution at the allylic position[81] (Table **3**).

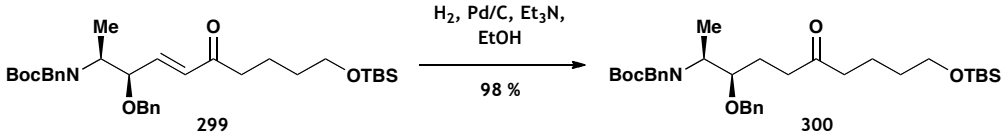
Conditions for cross-metathesis	Yield (%)
Hoveyda-Grubbs III (5 mol%), CH_2Cl_2, 40 °C	23
Hoveyda-Grubbs III (5 mol%), CH_2Cl_2, 50 °C	26
Hoveyda-Grubbs III (5 mol%), CH_2Cl_2, 60 °C	46
Hoveyda-Grubbs II (5 mol%), CH_2Cl_2, 60 °C	76

Table 3

However in our hands we found that the change of catalyst actually resulted in a significant decrease in yield, from 76 % down to as low as 23 % if we carried the reaction out at 40 °C. Even raising the temperature to 60 °C, our optimum temperature for Hoveyda-Grubbs II, only resulted in a slight increase in yield, to 46 %. Reasoning that 76 % was a fine yield for such a challenging cross-metathesis we decided to press on and form the primary alcohol we needed, ready for coupling of the third fragment.

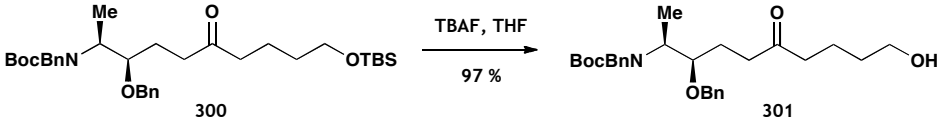
We were pleased to see that utilizing the same conditions as we had used previously in the lycopodium system, we were able to produce very similar results. Hydrogenation of α,β-unsaturated ketone **299** using palladium on carbon and triethylamine as a catalyst poison

produced ketone **300** in excellent yield, with no hydrogenolysis of either the *O*-benzyl ether or *N*-benzyl protecting groups (Scheme **101**).



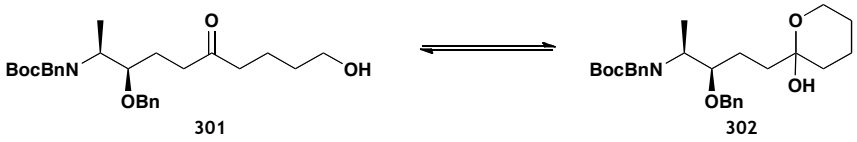
Scheme 104

Treatment of silyl ether **300** with TBAF in tetrahydrofuran led to removal of the silyl group and produced the primary alcohol **301** in excellent yield (Scheme **102**), ready for oxidation and the subsequent Wittig reaction.



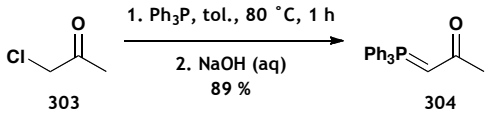
Scheme 105

Again we found that when characterizing this alcohol at high temperature in DMSO-d_6 the equilibrium between the open chain alcohol **301** and the closed ring hemiacetal **302** (Scheme **103**) was shifted completely towards the hemiacetal. We see no ketone peak in the ^{13}C NMR spectrum and observe a peak at 95.7 ppm corresponding to the hemiacetal carbon.



Scheme 106

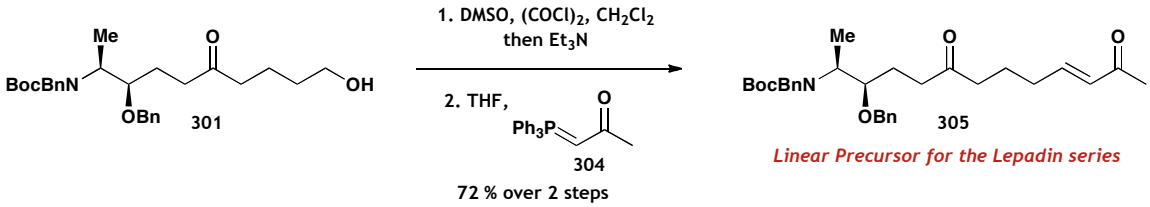
We decided to perform our initial studies using an ylid derived from chloroacetone as a model system to optimize our cascade procedure. We would subsequently either elaborate the resulting decahydroquinoline to install the correct side chain or alter our ylid accordingly.



Scheme 107

With this in mind, chloroacetone **303** was treated with triphenylphosphine in toluene at 80 ˚C to form the phosphonium chloride salt, followed by deprotonation of the salt with aqueous sodium hydroxide solution to form ylid **304** in good yield (Scheme **104**).

We now turned our attention to forming the last bond needed to complete our linear cascade precursor (Scheme **105**).

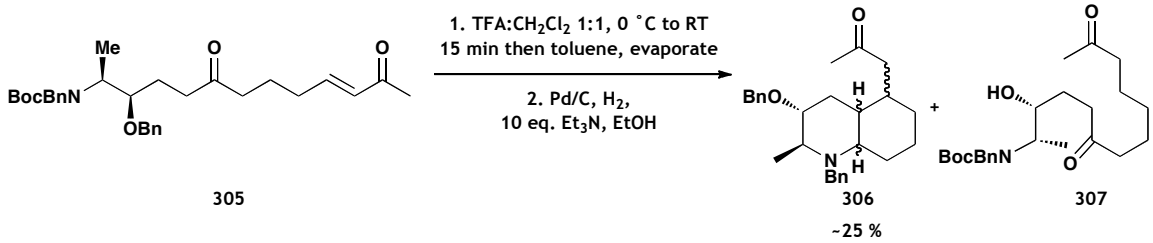


Scheme 108

We initially oxidized the alcohol using catalytic TPAP as this had worked well in our lycopodine system; in this new system over the two steps, TPAP oxidation followed by Wittig olefination gave a combined yield of 60 %. We decided to try a Swern oxidation as this had worked well in the other system, and previous work on a similar system to ours in the group suggested this would work well. We were delighted to find that upon oxidation of alcohol **301** to the aldehyde using Swern conditions followed by treatment with ylid **304**, we were able to form diketone **305** in a good yield of 72 % over the two steps.

3.3 Cascades in the lepadin system

With our lepadin linear precursor in hand we were ready to attempt the cascade. We initially used the same conditions that had been successful in decahydroquinoline formation in our lycopodine system (Scheme **106**).

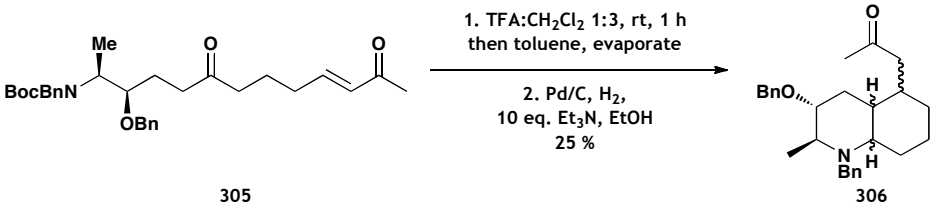


Scheme 109

We were pleased to find that on the first attempt, treatment of our linear precursor **305** with TFA in dichloromethane (1:1) to form the TFA salt, followed by hydrogenation in the presence of triethylamine and a palladium on carbon catalyst, gave us what appeared to be decahydroquinoline **306** as a mixture of diastereoisomers in moderate yield. However, mass spectrometry also showed the presence of a second product where no cyclization had taken place; the alkene and one benzyl group had been removed but the Boc group remained. We were unable to isolate this compound for further characterization but clearly we needed to find conditions where the Boc group was completely removed to improve our yield of cyclized product.

We first examined changing the reagent for deprotection. Having found literature precedence for deprotection of a Boc group using ceric ammonium nitrate,[82] we decided to attempt deprotection under these conditions. However treatment of linear precursor **305** with ceric ammonium nitrate in acetonitrile at room temperature failed to effect any removal of the Boc group and all we saw was recovered starting material.

Our next attempt involved only a small change to our original conditions (Scheme **107**).

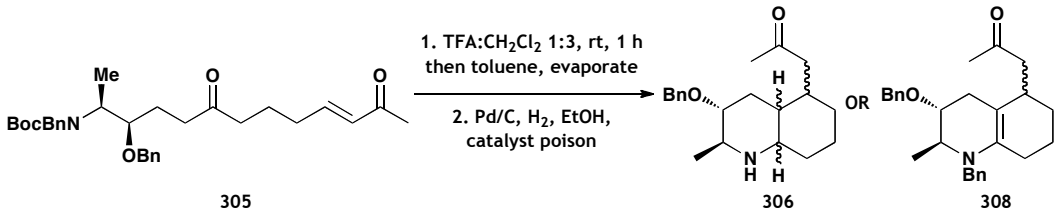


305 306

Scheme 110

We discovered that if we altered the proportions of TFA and dichloromethane from 1:1 to 1:3 and carried out the deprotection at room temperature for one hour we no longer observed the linear compound **307** by mass spectrometry or otherwise. However, our yield of decahydroquinoline **306** (still a mixture of diastereoisomers) did not seem to have improved. We wondered if the problem might be over-reduction, preventing the Michael addition from occurring, and removal of the benzyl groups allowing multiple side

reactions to occur. We examined whether changing the catalyst poison would improve our yield (Table **4**/Scheme **108**).[57]



305 306 308

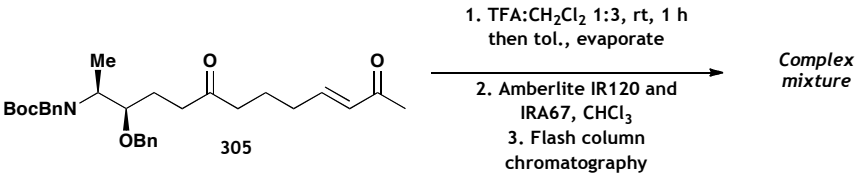
Scheme 111

Catalyst poison	Result
Et_3N (1 eq.)	Bicycle **306** by MS, none isolated
Ethylenediamine (10 eq.)	Enamine **308** by MS, none isolated
1,10-phenanthroline (10 eq.)	Enamine **308** by MS, none isolated
Ethylenediamine (1 eq.)	Complex mixture
1,10-phenanthroline (1 eq.)	Complex mixture

Table 4

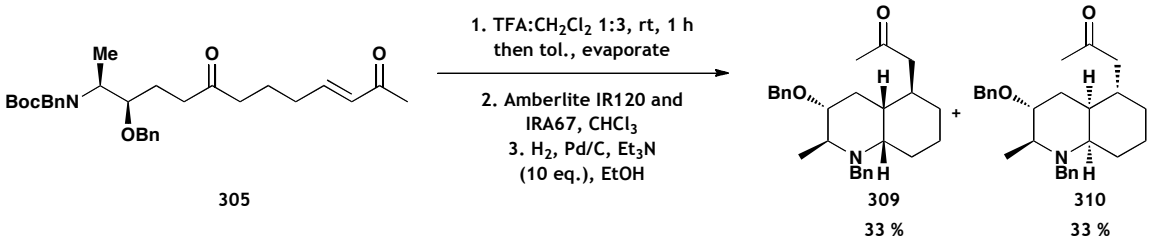
It appeared that reducing the amount of triethylamine improved the reactivity of the catalyst but the product became much more difficult to isolate and we suspected that many side reactions were taking place. Hirota *et al.*, who carried out the work on using amines to poison palladium catalysts, suggested that ethylenediamine and 1,10-phenanthroline were more effective catalyst poisons. We found that using 10 equivalents of either of these two catalyst poisons shut down hydrogenation completely, with only the enamine and/or iminium bicycles visible by mass spectrometry; we were unable to isolate either of these. Reducing the number of equivalents of catalyst resulted in a complex mixture and so we resolved to stick with our original conditions for the hydrogenation since these were the only ones which had enabled isolation of any of our desired product.

We decided to examine what would happen if we treated our TFA salt with the solid supported acid and base conditions used in the lycopodine system, reasoning that if we could isolate the enamine we could at least be sure it was forming and we could then hydrogenate it.



Scheme 112

Upon treatment of our TFA salt, derived from linear precursor **305**, with Amberlite IR120 and Amberlite IRA67, we could see a peak corresponding to formation of the enamine by mass spectrometry. However all attempts to examine the enamine by ^{1}H NMR spectroscopy (either crude or after purification on triethylamine doped silica) were fruitless. We concluded that the enamine we form in this system must be more reactive than our previous enamine. We therefore decided to attempt the three-step sequence of deprotection, solid supported acid/base and hydrogenation without isolation of any intermediates (Scheme **110**).



Scheme 113

We were happy to discover that this sequence of conditions worked well. Linear precursor **305** was treated with TFA in dichloromethane followed by evaporation from toluene to form the TFA salt. Treatment of the salt with solid-supported acid and base to form the enamine and subsequent hydrogenation under our now standard conditions led to formation of decahydroquinolines **309** and **310** as a 1:1 mixture of diastereoisomers and a pleasing overall yield of 66 %. Now that we had access to greater quantities of our decahydroquinolines we were able to separate the two isomers by flash column chromatography for thorough characterization.

We again needed to prove that we had formed the two rings of the decahydroquinoline by examining the COSY and HMBC spectra of our two diastereomers. Looking initially at decahydroquinoline **310** we numbered our structure as shown (Figure **8**).

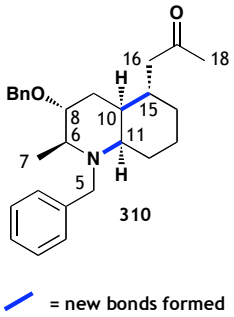


Figure 8

We were able to observe coupling between *N*-benzyl protons 5 and 5′ and carbon 11 in the HMBC, suggesting that a bond had been formed between the amine and carbon 11 to give the piperidine ring. Furthermore, looking at ring-junction proton 11 we could see coupling to protons 10 and 15 (weakly) in the COSY which suggested that the second ring had also formed. Ring junction proton 10 was observed to couple to protons 11 and 15 in the COSY and carbons 15 and 16 in the HMBC which confirmed the formation of a bond between carbons 10 and 15 and thus creation of the cyclohexane ring of the decahydroquinoline structure.

We carried out a similar analysis for our second diastereoisomer **309**, numbering the structure in the same manner (Figure **9**).

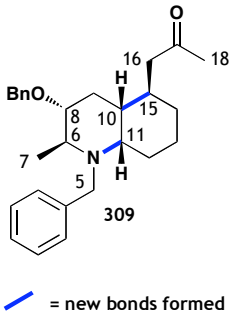
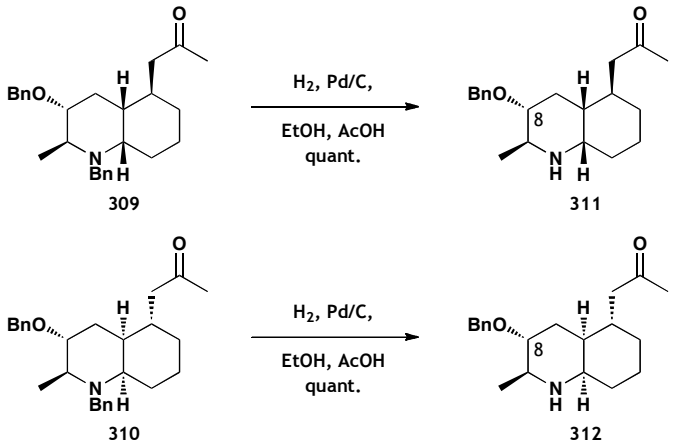


Figure 9

We again observed coupling between *N*-benzyl protons 5 and 5′ and carbon 11 in the HMBC, confirming the formation of a bond between the nitrogen and carbon 11 and construction of the piperidine ring of the bicycle. However, confirmation of the cyclohexane ring of the decahydroquinoline by 2D NMR experiments was more challenging. The only coupling observed with atoms in the cyclohexane ring was a very weak correlation between ring-junction proton 10 and proton 14′ which we did not feel was sufficient evidence to be certain that the second ring-forming event had taken place. The similarity of the chemical shifts of the protons and carbons to those in our first system were promising and mass spectrometry was also encouraging. The fact that in the HSQC we could observe that protons 10 and 11 were both methine rather than methylene groups was also encouraging. Realizing that we needed to confirm the stereochemistry of the three new stereocentres we had formed in each system, we decided to go on to crystallize each diastereoisomer to allow X-ray analysis.

The decahydroquinolines **309** and **310** were not crystalline, so in order to carry out X-ray diffraction studies we first of all hoped to hydrogenolyse the benzyl protecting groups (Scheme **111**).

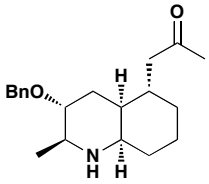


Scheme 114

Hydrogenation of decahydroquinolines **309** and **310** using a palladium on carbon catalyst in ethanol with a drop of acetic acid resulted in removal of one benzyl group in both cases. We expected that the *O*-benzyl ether would be easier to remove but were surprised to see

that instead the *N*-benzyl protecting group was removed in each case to give amines **311** and **312**. We could confirm this by the observation of coupling between proton 8 and the *O*-benzyl carbon in the HMBC of each diastereoisomer.

Amine **312** was crystalline and a small crystal was obtained.† We were delighted to be able to carry out X-ray diffraction studies to give a crystal structure (Figure **10**).



312

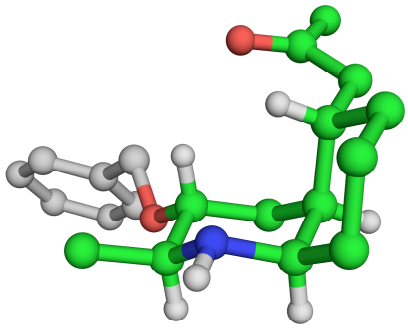
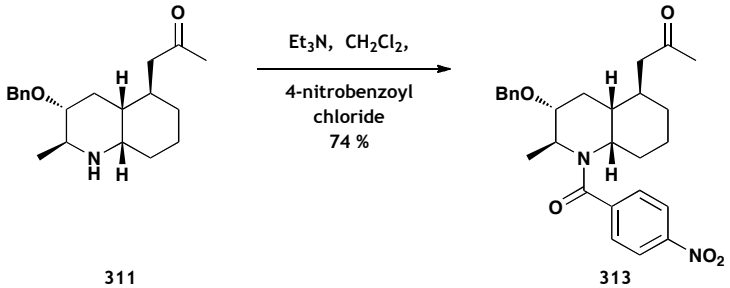


Figure 10

The crystal structure shows that the methyl group and benzyl ether are both in the sterically less demanding equatorial positions and the ring junction protons and the ketone side-chain are all on the same face which in this case is the same face as the benzyl ether.

Amine **311** was not crystalline at this stage and so required further derivatization (Scheme **112**).



311 313

Scheme 115

†In both cases the compounds were very difficult to crystallize and only a small crystal could be obtained, which required use of the high intensity X-ray source at the Diamond synchrotron in Didcot. Please see appendix for further crystal structure data.

Amine **311** was treated with triethylamine and 4-nitrobenzoyl chloride to give crystalline amide **313** in good yield. We were able to crystallize this amide and again obtain a crystal structure (Figure **11**).†

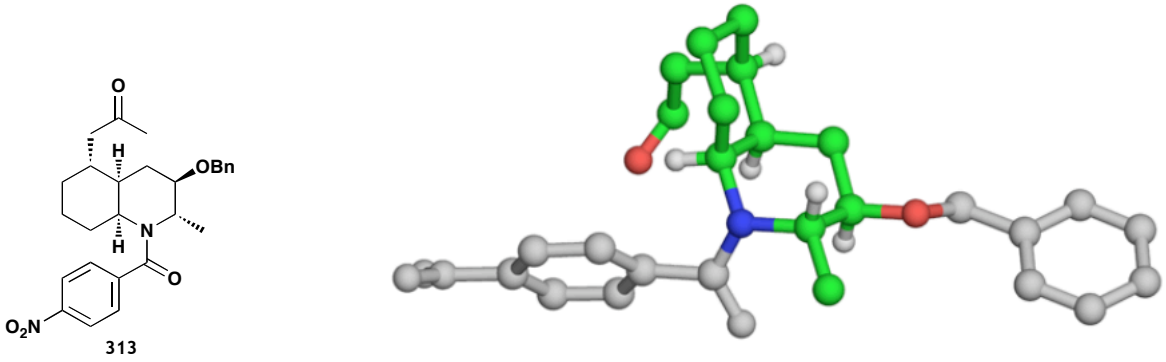


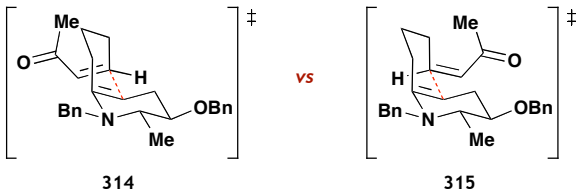
Figure 11

The crystal structure shows that, again, the methyl group and benzyl ether are both in the sterically less demanding equatorial positions and the ring junction protons and the ketone side chain are all on the same face, which in this case is the same face as the methyl group. The ketone side chain is in an axial position in this diastereoisomer. It also becomes clear upon viewing this crystal structure why we failed to see any coupling between the ring junction proton 10 and proton 15 adjacent to the ketone side chain in the COSY experiment. We can measure the dihedral angle between H^{10} and H^{15} and we find it to be 75.2˚. On the basis of the idealized Karplus equation we would therefore expect the coupling constant between the two protons to be of the order of 1 Hz, a small value which is consistent with our observations in the COSY.

We can therefore conclude that in the cascade our Michael addition is completely non-stereoselective but that there is a high level of selectivity in the hydrogenation process. If

† In both cases the compounds were very difficult to crystallize and only a small crystal could be obtained, which required use of the high intensity X-ray source at the Diamond synchrotron in Didcot. Please see appendix for further crystal structure data.

we place the methyl and *O*-benzyl groups in equatorial positions, there are two possible transition states for the Michael addition, **314** and **315** (Figure **12**).



314 315

Figure 12

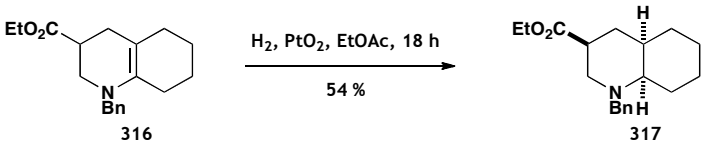
We can observe that neither transition state appears to be particularly favoured. In transition state **314** the enone is in a pseudoaxial position but there are no C-H bonds on the adjacent ring to destabilize it. Conversely in transition state **315** the enone is in the pseudoequatorial position which is usually considered to be more stable, but here there is a methylene group on the adjacent ring which may have some steric interactions with the enone.

Considering the hydrogenation step, if we examine the crystal structure of **312** we can see that there appears to be very little steric difference between the two faces. The stereochemistry of the ring junction protons and ketone side-chain in this decahydroquinoline is correct for lepadins A-C, but we would need the benzyl ether to be on the opposite face. We do have access to this arrangement of stereochemistry in the linear precursor and efforts towards this cyclization are examined in section **3.4**.

In the crystal structure of **313** it appears that if anything, the hydrogen has been delivered onto the more hindered face, past the axial ketone side-chain. Perhaps the oxygen of the ketone is involved in coordination of the catalyst and delivery of the hydrogen to this face. However in order to form lepadins D, E and H we need to select for hydrogenation on the opposite face to the ketone side chain.

We examined hydrogenation of similar systems in the literature. Brimble and coworkers hydrogenate benzyl protected bicyclic enamine **316** using platinum oxide in ethyl acetate

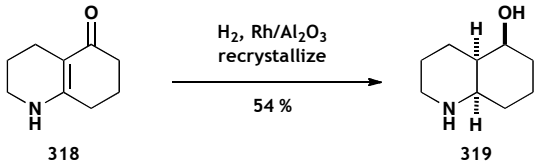
to give racemic decahydroquinoline **317**, with the ring junction protons on the opposite face to the ester side chain (Scheme **113**).[83]



Scheme 116

Varying the protecting group on nitrogen produced no improvement in yield except for the use of (*R*)-α-methyl benzyl which increased the yield to 72 %, perhaps because of the inherent steric bias due to the stereocentre on the protecting group.

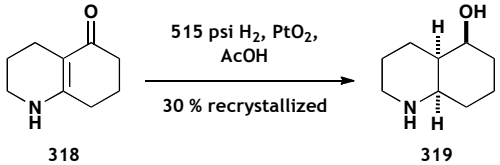
Kozlowski and coworkers hydrogenated the bicyclic vinylogous amide **318** using a rhodium on alumina catalyst (Scheme **114**).[84]



Scheme 117

Hydrogenation of **318** resulted in the delivery of hydrogen from the same face for all three new stereogenic centres. This suggests that as expected the alkene portion is reduced first and this then directs the reduction of the ketone as hydrogen approaches from the least hindered convex face.

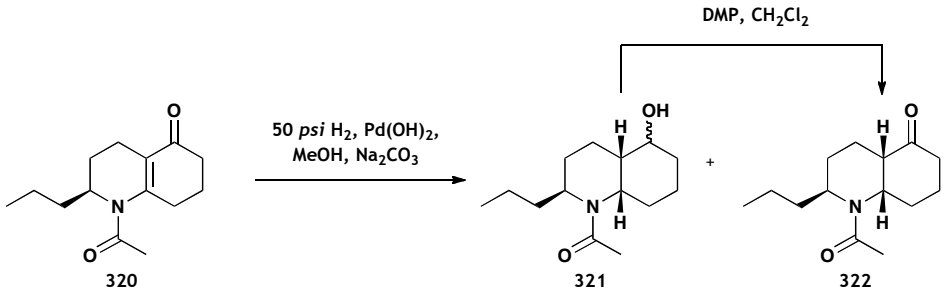
High pressure and acidic conditions were also employed by LeBel *et al.* in their hydrogenation of the same vinylogous amide **318** (Scheme **115**).[85]



Scheme 118

Under their conditions, vinylogous amide **318** was subjected to high pressure hydrogen in acetic acid in the presence of Adam's catalyst to yield bicycle **319** which could be recrystallized as a single diastereoisomer. The hydrogen in this system has again all been delivered from one face which suggests that again hydrogenation of the alkene occurs first, followed by reduction of the ketone from the least hindered convex face.

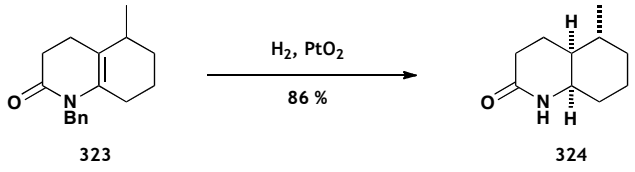
Hsung *et al.* used high pressure hydrogenation conditions for their vinylogous amide **320** (Scheme **116**).[86]



Scheme 119

Treatment of **320** with hydrogen using Pearlman's catalyst in methanol with a sodium carbonate additive resulted in complete reduction of the alkene portion, with the hydrogen being delivered from the same face as the *n*-propyl sidechain. The ketone was also reduced in some of the product but no selectivity was observed for this centre. Oxidation of the alcohol **321** to the ketone resulted in a 70 % overall yield of decahydroquinoline **322** from starting material **320**.

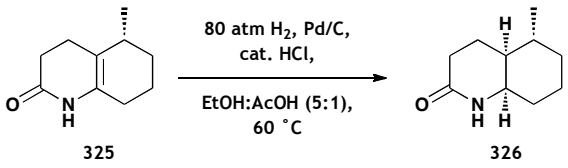
Enamide **323** was hydrogenated by Padwa and coworkers using Adam's catalyst (Scheme **117**).[87]



Scheme 120

Hydrogenation of **323** led to delivery of hydrogen from the same face as the methyl sidechain to yield amide **324** in good yield as a single diastereomer. The *N*-benzyl protecting group was also removed in this process.

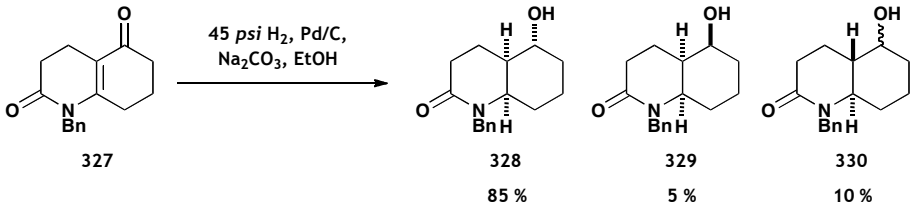
Murahashi and coworkers also used high pressure hydrogenation conditions for reduction of their identical bicyclic enamide **325**, as a single enantiomer this time (Scheme **118**).[88]



Scheme 121

Treatment of enamide **325** under high pressure at 60 °C with catalytic HCl in acetic acid/ethanol with a palladium on carbon catalyst again lead to a highly diastereoselective (98:2) hydrogenation, where the hydrogen was delivered from the same face as the methyl side chain.

Stille *et al*. also used a high pressure hydrogenation approach to reduce bicycle **327** (Scheme **119**).[89]

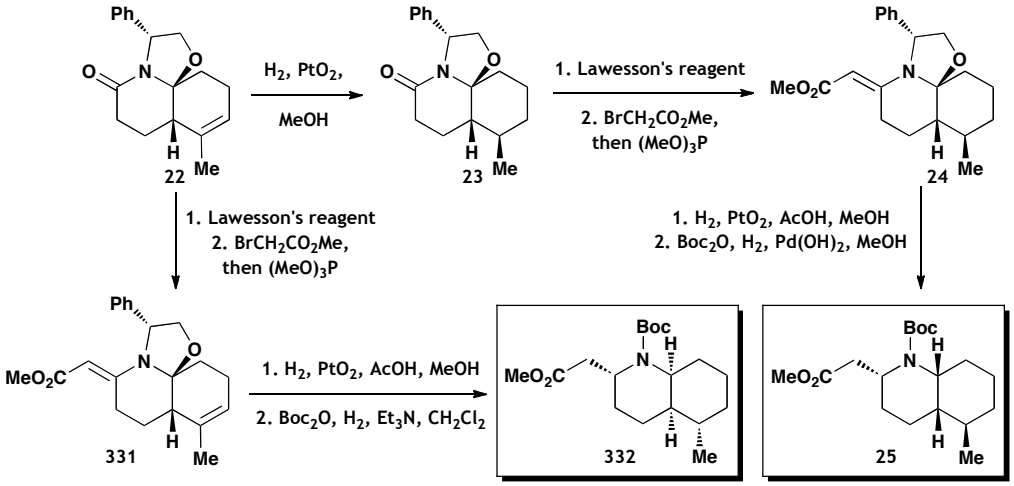


Scheme 122

Hydrogenation of **327** at 45 psi using a palladium on carbon catalyst in ethanol with sodium carbonate additive resulted in amide **328** as the major product, where the hydrogen has been delivered from one face to reduce the alkene portion and the other face to reduce the ketone. This is in contrast to the similar systems above (Schemes **114** and **115**) where hydrogen was delivered from the same face for all three stereocentres, as in the minor product **329**. This leads us to speculate that perhaps in this system different factors are affecting the selectivity; perhaps the ketone is reduced first and then the alkene is

reduced from the opposite face. Even more surprising in this system was the presence of 10 % of the *trans*-decalin **330** (where the alcohol is a mixture of epimers), which may result from protonation of the enamine and reduction of the resulting imine from the opposite face, or epimerization of the proton α to the ketone before it is reduced itself, a result not seen in any of the other systems examined. Under these basic conditions the *N*-benzyl protecting group was not removed.

It is also worth revisiting one of the systems discussed in the introduction to this document. Amat and Bosch recently described a biomimetic approach to decahydroquinoline systems[2] and encountered some interesting selectivity when forming the saturated bicycle (Scheme **120**).

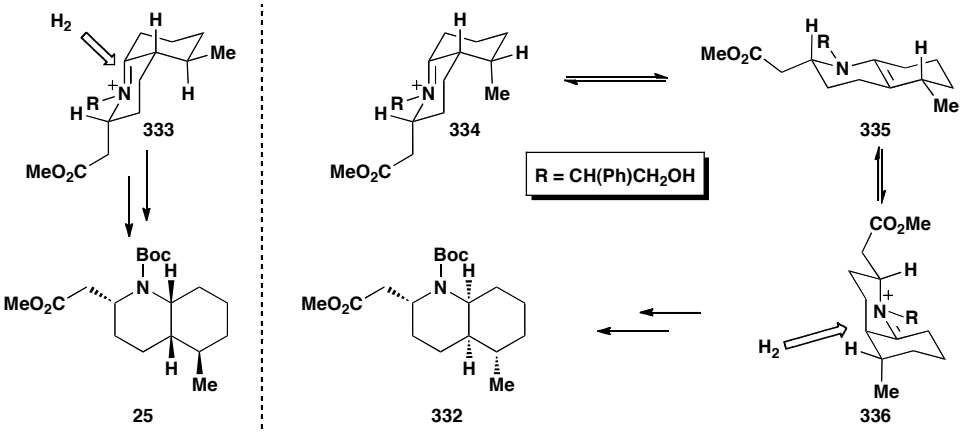


Scheme 123

In their approach to (-)-pumiliotoxin C, the authors found that hydrogenation of the alkene first led to approach of hydrogen from the bottom face of the tricycle leading to the methyl group being positioned on the top face in **23**. This group then directed the formation of further stereocentres, resulting in a successful synthesis of (-)-pumiliotoxin C. It is worth noting however, that reversal of the order of the first two steps of this endgame (reduction of the alkene and sulfide contraction) leads to a complete switch in stereochemistry of the final decahydroquinoline **332**.

The authors postulate that this may be due to the change in order of the hydrogenation of the alkenes. Thus in the first sequence, the axial C-O bond prevents hydrogenation of the endocyclic alkene from the top face, resulting in the methyl group being up, which then directs hydrogenation of the exocyclic alkene to occur on the opposite face to the methyl group, giving the observed stereochemistry in **25**. In the second sequence, the exocyclic alkene is reduced first and this blocks the bottom face, resulting in a down methyl group when the endocyclic alkene is hydrogenated to give **332**.

Subsequently the C-O bond must be broken *via* an acid-promoted iminium formation (Scheme **121**).

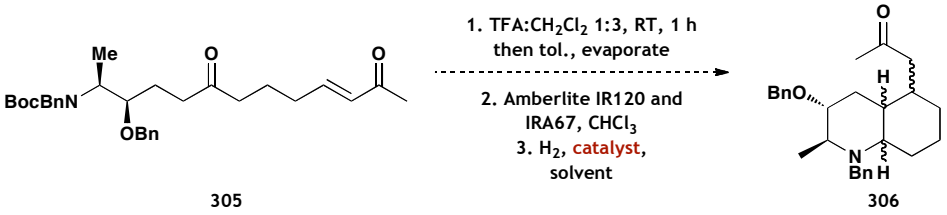


Scheme 124

In the first system this iminium ion **333** contains an equatorial methyl group and so this is the most stable conformer and is reduced directly to the product **25**. In contrast, in the second system iminium ion **334** contains an axial methyl group, destabilizing the iminium ion and causing it to proceed, *via* enamine **335**, to the iminium ion with the more stable conformation **336**. Hydrogenation of this isomer from the convex face leads to the total inversion of configuration we observe in **332**. These observations of the capricious nature of these systems with respect to facial selectivity of hydrogenation may prove important in our own studies towards decahydroquinoline systems.

The outcome of this short survey of the literature is that very small changes in either substrate or conditions for hydrogenation can result in either a complete switch of selectivity or even a loss of selectivity. It appeared that for many systems it was possible to find conditions which would give high levels of selectivity, which was encouraging. It was therefore apparent that we should survey a series of hydrogenation conditions to discover whether we could alter the selectivity in our system.

With this in mind we tried varying our hydrogenation catalyst (Scheme **122**) in the third step of our cascade process. We had enough material to try three sets of conditions, so we chose three of the most commonly used sets of conditions from the literature. Specifically we used two sets of conditions from Hsung's recent further studies towards the lepadin skeleton[90] using two different platinum catalysts, and rhodium on alumina as a third system and the results are displayed in table **5**.



305 306

Scheme 125

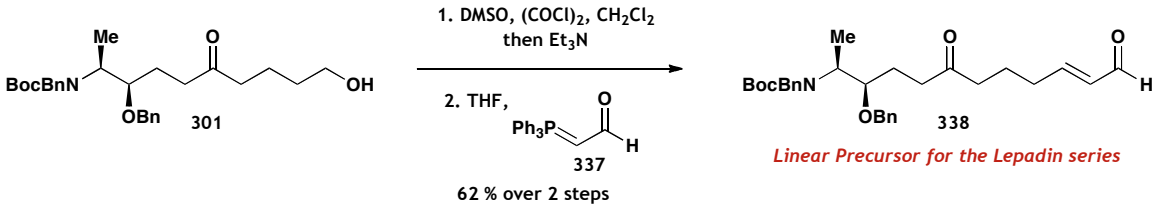
Conditions	Result
Pt/C, AcOH	No hydrogenation by MS
PtO_2, MeOH	Product bicycle 306 observed by MS but unable to isolate
Rh/Al_2O_3	No hydrogenation by MS

Table 5

Neither rhodium on alumina nor platinum on carbon returned any useful products. No hydrogenation was visible by MS and we were unable to isolate any recognizable products after purification. Using Adam's catalyst initially looked more promising since mass spectrometry analysis showed the presence of a peak corresponding to bicycle **306**. However we were unable to confirm product formation by crude ^1H NMR spectroscopy, and our attempts to isolate the bicycle or any other products were unsuccessful.

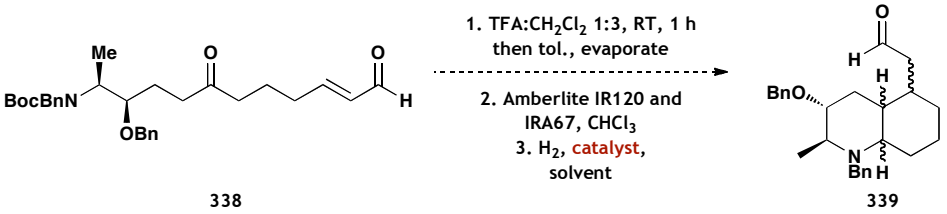
We remain confident that given more time and more linear precursor we would be able to develop conditions for a stereoselective hydrogenation leading to our desired diastereoisomer, unfortunately a lack of material and time constraints prevented us from carrying out further studies in the context of this report.

We were also interested in examining whether we could carry out the cyclization using an *α,β*-unsaturated aldehyde as the Michael acceptor instead of our enone. This would potentially allow us to use iminium catalysis to control the Michael addition as well as giving us a more convenient handle for elaboration of the side-chain after cyclization. Accordingly we carried out the oxidation-Wittig process using aldehyde ylid **337** (Scheme **123**).



Scheme 126

Oxidation of alcohol **301** and olefination with ylid **337** proceeded smoothly to give a second linear precursor for the lepadins **338** in a respectable yield over the two steps. We tested the linear precursor under a series of cyclization conditions (Scheme **124**/Table **6**).



Scheme 127

Conditions	Result
Pd/C, 10 eq. Et_3N, EtOH	No hydrogenation by MS
Pd/C, EtOH	No hydrogenation by MS
PtO_2, EtOH	No hydrogenation by MS

Table 6

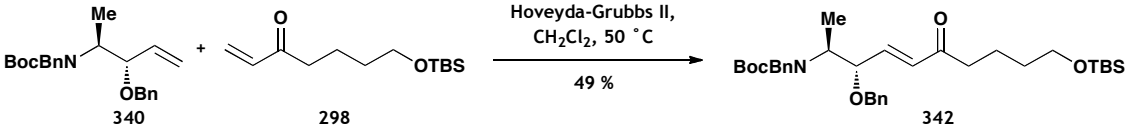
Unfortunately under a range of hydrogenation conditions we failed to observe any formation of our desired decahydroquinoline **339**. We did observe a peak in the MS in each case which could correspond to the bicyclic enamine but it appeared that hydrogenation was significantly more challenging in this system. At this stage we decided to concentrate our efforts on the ketone linear precursors as we had much more precedent for the formation of decahydroquinolines in these systems.

3.4 Another linear precursor for the lepadins

Having examined the stereochemistry of our two diastereoisomers from our first lepadin linear precursor, we wondered whether changing the stereochemistry of the secondary alcohol would affect the stereochemistry in the cascade step. In particular we were interested in whether we would be able to access the decahydroquinolines with the correct stereochemistry for lepadins A-C at the ring junction protons and ketone side-chain if we varied the stereochemistry of the alcohol. Accordingly we looked at forming a linear precursor from amine **289** (Scheme **125**).

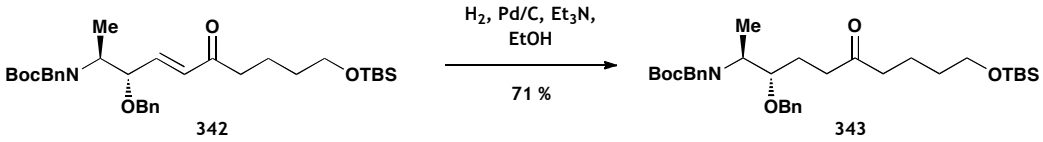
Scheme 128

Secondary alcohol **289** can be protected as the benzyl ether **340** which proceeds in only moderate yield, the main byproduct being the oxazolidinone **341** formed either by addition of the alcohol into the Boc group, or closure of the Boc carbonyl oxygen onto the vinyl iodide formed by displacement of benzyl alcohol by iodide. This was not a problem in the first system, but the change of stereochemistry has made this a more favourable reaction in this system. The methyl and vinyl groups can now both occupy psuedoequatorial positions in the five membered ring formed (**341**), so assuming the transition state is product-like, in accordance with the Hammond postulate, oxazolidinone formation is more favourable than in the original system, where one substituent was forced to adopt a pseudoaxial position. However with the amine fragment in hand we could try the cross metathesis reaction (Scheme **126**).



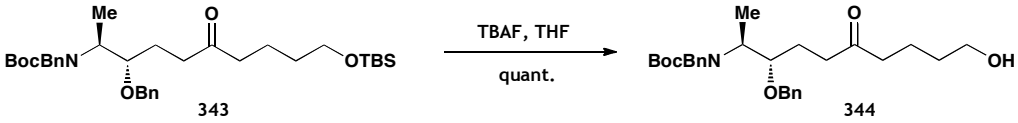
Scheme 129

Amine **340** can be combined with ketone **298** and treated with Hoveyda-Grubbs II catalyst in dichloromethane at 50 °C (Scheme **126**) to form α,β-unsaturated ketone **342** which proceeds in moderate yield. We speculate that the drop in yield may be due to the change in stereochemistry at the alcohol, increasing the steric crowding around the alkene.



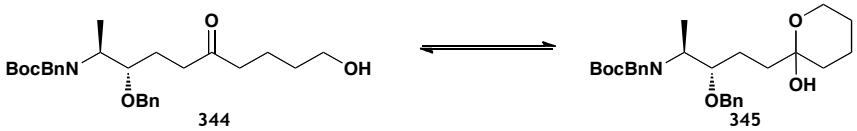
Scheme 130

Hydrogenation under the same catalyst poisoned conditions as we had previously used (Scheme **127**) proceeded in good yield to give **343**, but the yield was still much lower when compared with the other system.



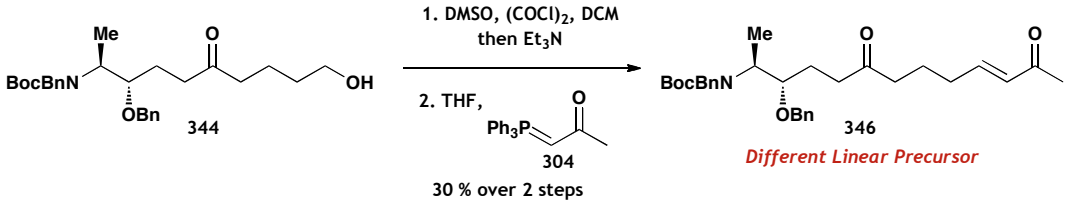
Scheme 131

We were pleased that the deprotection of the silyl ether **343** proceeded in excellent yield to give alcohol **344** (Scheme **128**). Again we found that when characterizing this alcohol at high temperature in DMSO-d_6 the equilibrium between the open chain alcohol **344** and closed ring hemiacetal **345** (Scheme **129**) is shifted completely towards the hemiacetal. We see no ketone peak in the ^{13}C NMR spectrum and we observe a peak at 95.9 ppm corresponding to the hemiacetal carbon.



Scheme 132

We were now ready for addition of the final fragment to form the linear precursor (Scheme

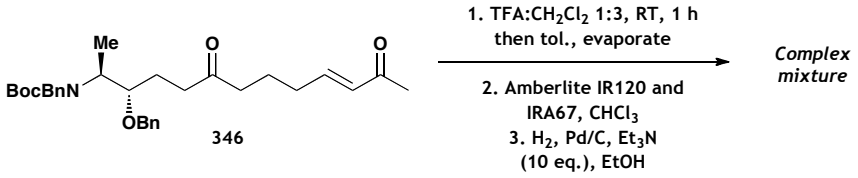


130).

Scheme 133

Oxidation of alcohol **344** using Swern conditions and Wittig olefination with ylid **304** proceeded in poor but unoptimized yield to give linear precursor **346**.

We were now ready to examine the cascade in this new system. Disappointingly, treatment of linear precursor **346** under the same cascade conditions used in our previous system resulted in no production of any desired decahydroquinolines. Instead by mass spectrometry we could see formation of enamine/iminium ion after the solid-supported acid and base step, but were unable to isolate any bicyclic molecules. The reaction only yielded a complex mixture (Scheme **131**).

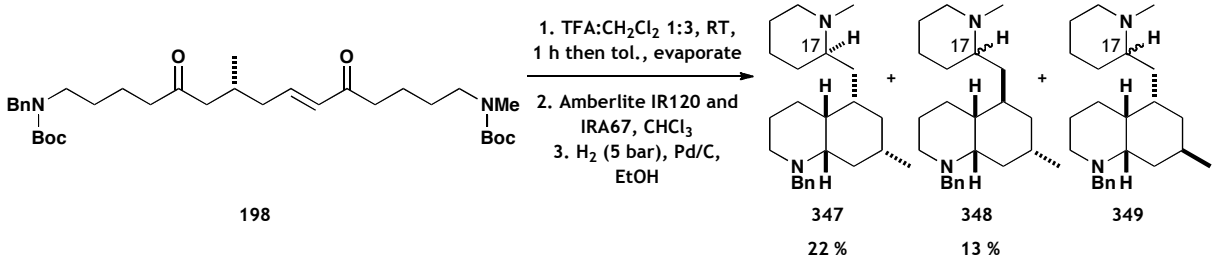


Scheme 134

It is to be expected that hydrogenation would be more difficult in this system since either the methyl group or the benzyl ether must now occupy axial positions in the cyclized product therefore there is probably a greater degree of steric hindrance to approaching at least one face of the bicyclic enamine. We remain confident that given enough material and time we would be able to find conditions which would effect a reduction in this system, by varying catalyst and solvent conditions and perhaps increasing the hydrogen pressure.

3.5 A return to the cermizine B system

Now that we had considerably more experience of the formation of decahydroquinolines from linear precursors containing an amine, a ketone and an enone, we decided to reexamine the possibility of cascades using the linear precursor we had formed for the cermizine B system. To this end we decided to subject our cermizine linear precursor **198** to the optimized cascade conditions that we had found worked best in the lepadin system (Scheme **132**).



Scheme 135

Treatment of linear precursor **198** with TFA to remove both Boc groups was followed by the addition of solid-supported acid and base to promote cyclization. Finally we found that slightly more forcing conditions for hydrogenation were necessary in this system and so our reaction mixture was subjected to hydrogen at a pressure of 5 bar using palladium on carbon as a catalyst and lacking the triethylamine catalyst poison that we usually use to temper the hydrogenation/hydrogenolysis reaction.

We were delighted to find that under these conditions we were able to form what appeared to be three major products, tricyclic molecules **347**, **348** and **349** as a mixture of diastereoisomers. We were able to isolate two of the three major diastereoisomers but in each case the major diastereoisomer also contained a little of another, minor diastereoisomer. In the case of **347** the ratio was around 3:1, in **348** the ratio was around 2:1. We wondered if instead of being another diastereomer, the smaller set of peaks in each case could be due to the presence of two rotameric forms, but heating the tricycle **347** to 90 ˚C in d_6-DMSO failed to show any coalescence of peaks in the ^{1}H NMR spectrum. We speculated that this minor product in each case was due to the epimer at the stereocentre on the piperidine ring, proton 17. Unfortunately we were unable to isolate the compound

that we believe to be the third diastereoisomer, **349**, and only observed its presence in crude ^{1}H NMR spectra.

Again it was necessary to confirm the connectivity of these tricyclic systems by careful analysis of correlations in the COSY and HMBC spectra.

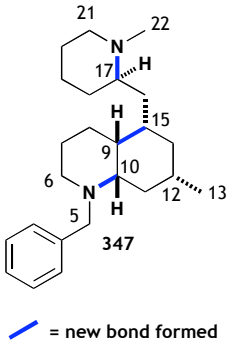


Figure 13

Using the numbering system shown (Figure **13**), in tricycle **347** we observe coupling between benzyl protons 5 and 5′ with carbon 10 in the HMBC which is in accord with a bond being formed between the benzyl-protected nitrogen and carbon 10: confirming formation of the first ring. We also see coupling between the *N*-methyl protons 22 and carbon 17 in the HMBC validating that the second piperidine ring has been generated. Finally we observe coupling between proton 9 and proton 15 in the COSY, and proton 9 and carbon 15 in the HMBC. This confirms that a bond has formed between carbons 9 and 15 to complete the decahydroquinoline system.

Looking at our second tricycle we were able to carry out a similar analysis.

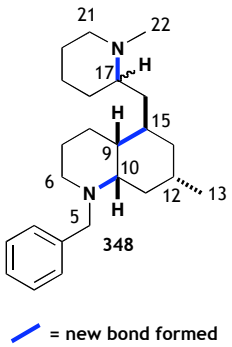
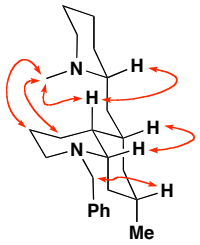


Figure 14

Using the numbering system shown above (Figure **14**), in tricycle **348** we again observe coupling between benzyl protons 5 and 5′ and carbon 10 in the HMBC confirming formation of a bond between the benzyl protected nitrogen and carbon 10 to form the lower piperidine ring. We observe coupling between the *N*-methyl protons 22 and carbon 17 in the HMBC which shows that the pendant piperidine ring has also formed. Finally we can confirm formation of the cyclohexane ring and therefore the decahydroquinoline structure by the observation of coupling between proton 9 and carbon 15 in the HMBC.

The tricycle **347** is an oil and so we were unable to obtain a single crystal for X-ray diffraction studies to confirm the stereochemistry. However we were able to acquire NOESY correlations which were very useful in assigning the stereochemistry of the tricycle (Figure **15**).



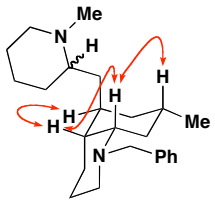
347

Figure 15

It appears that the methyl group and the side chain containing the piperidine ring are on the same face, probably both in the sterically less hindered equatorial positions on the *cis*-decahydroquinoline. This is perhaps not surprising as the transition state for the Michael addition probably places these two groups in the thermodynamically favoured positions. The protons on the ring junction are on the opposite face to the methyl group and side-chain which is consistent with the hydrogen approaching the intermediate enamine from the less hindered face. Finally the stereocentre on the piperidine ring appears to have the proton on the same face as the protons on the decahydroquinoline when drawn in this orientation. It is hard to see where the selectivity is derived from on this ring but perhaps

during hydrogenation the ring is oriented in a similar position thus allowing hydrogen to approach from the least hindered face past the other hydrogens.

We also acquired NOESY correlations for tricycle **348** which is again an oil and so not suitable for crystallization (Figure **16**).



348

Figure 16

In this case we observe that the piperidine side-chain and the ring junction protons are on the same face, similar to the structures we have observed in our lepadins system. This is in agreement with the proton NMR where we see a much smaller splitting between the *N*-benzyl protons (~0.1 ppm compared with >1.0 ppm in the system **347** above and the lycopodine system), which we also observe in our two lepadin decahydroquinolines (there is no splitting in **310** and a splitting of ~0.3 ppm in **309**). The methyl group appears to be on the opposite face so that either the methyl group or the piperidine side-chain have to sit in a sterically more hindered axial position. Unfortunately we were unable to assign the stereochemistry on the piperidine ring in this tricycle but since it exists as a 2:1 mixture it is likely there is very little difference in energy between the two structures. The selectivity around the decahydroquinoline is more difficult to explain here since the hydrogen seems to have been delivered from the more sterically hindered face but it is difficult to know what these systems look like before hydrogenation and there may not be much difference between the faces.

We were unable to isolate a third compound, **349**, which we believe to be a third diastereoisomer of the tricycle. However from examination of the crude ^{1}H NMR we believe that the stereochemistry may correspond to that shown in **349** (Figure **17**) since in this system we again see a large splitting of the *N*-benzyl protons which seems to

correspond to the side-chain being on the opposite face to the ring junction protons. We remain confident that with more time and material we would be able to isolate and characterize this third isomer successfully.

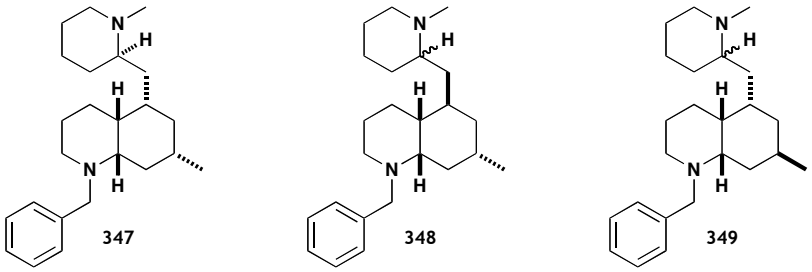
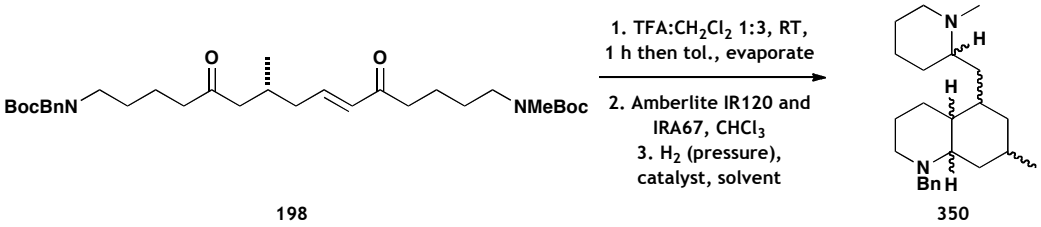


Figure 17

We decided to test some different hydrogenation conditions to try and obtain selectivity in the hydrogenation step since we believed it was in this process that the lack of selectivity was occurring. Accordingly we looked at using lower pressures and different catalysts for the process (Scheme **133**, Table **7**).



Scheme 136

catalyst	solvent	H_2 pressure	time	outcome
Pd/C	EtOH	3 bar	16 h	mixture of **347**, **348** and **349**
Pd/C	EtOH/Et_3N (1 eq.)	5 bar	16 h	mixture of **347**, **348** and **349**
PtO_2	MeOH	5 bar	16 h	mixture of **347**, **348** and **349**
Rh/Al_2O_3	EtOAc	Atmospheric	72 h	33 % yield of **347**

Table 7

We were elated to observe that using rhodium on alumina as a catalyst, the hydrogenation, while slow at atmospheric pressure, produced only one major diastereoisomer **347**, with the presece of the epimer at carbon 17 remaining. The stereochemistry we observe in **347** is not quite the correct stereochemistry for Cermizine B but nevertheless being able to

selectively form one major diastereoisomer is very gratifying. Our product does appear to possess the same stereochemistry as the pair of diastereoisomers **131** synthesized by MacLean *et al.* in 1981, discussed in section **2.1.2**,[40] however this does not correspond to any of the naturally occurring phlegmarine skeletons that have so far been isolated.[38]

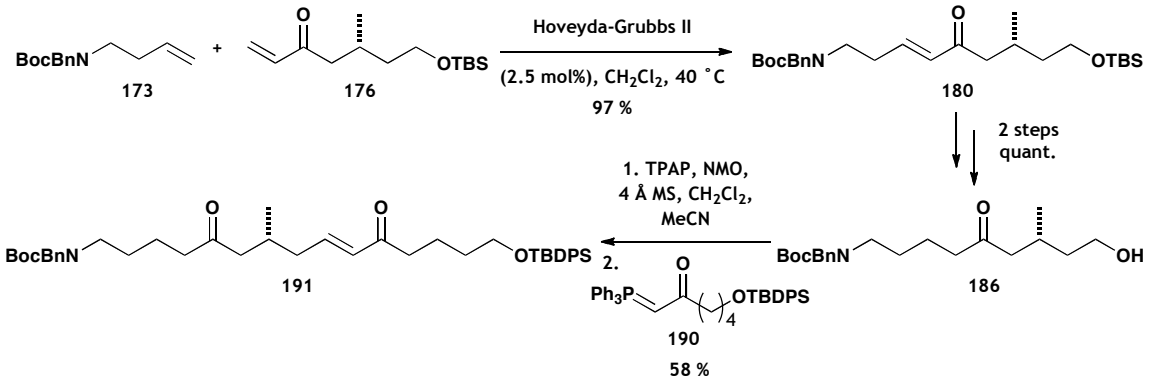
However, if our stereochemical assignment for system **348** is correct then we have succeeded in forming a skeleton with the correct stereochemistry for cermizine B. This would obviously be an excellent result, however we need to confirm this by removal of the benzyl group and comparison with the spectra of the natural product. Unfortunately a shortage of material prevented us from carrying this out but we are confident that it would be possible.

4 Conclusions and Future Work

4.1 Conclusions

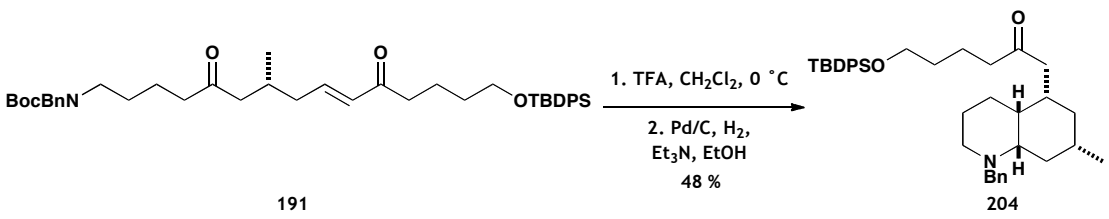
4.1.1 A linear precursor for lycopodine

We have developed a practical and scalable synthetic route to a linear precursor with the correct carbon skeleton for approaches to lycopodine (**191**, Scheme **134**). The linear precursor was prepared from three fragments: a homoallyl amine **173**, an α,β-unsaturated ketone **176** and an ylid **190**. The homoallyl amine **173** could be assembled in two steps, the α,β-unsaturated ketone **176** could be assembled in four steps, and the ylid **190** was assembled in two steps in one pot. Fragment coupling was achieved *via* two key reactions: a high yielding cross metathesis using Hoveyda-Grubbs II as catalyst and an oxidation-Wittig sequence which was optimized for this system.



Scheme 137

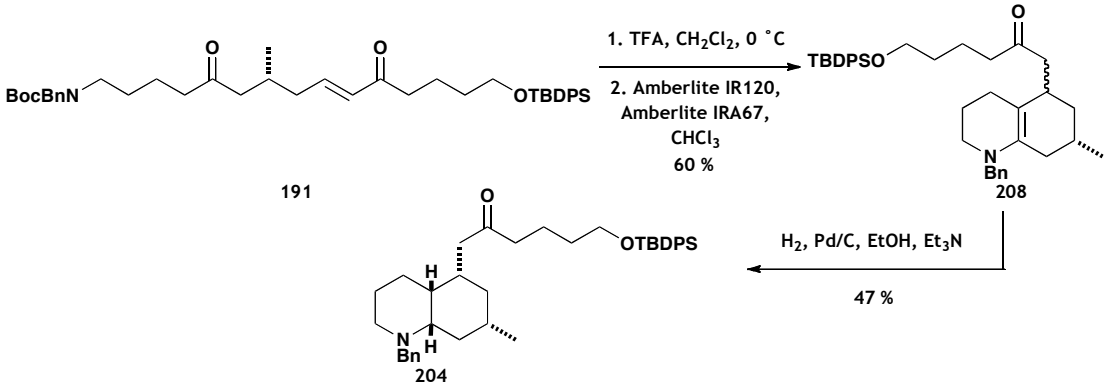
We found that sequential treatment of this linear precursor **191** with TFA to remove the *N*-Boc group and hydrogenation, in the presence of triethylamine, lead to the formation of decahydroquinoline **204** as a single diastereoisomer in good yield (Scheme **135**).



Scheme 138

We were able to fully characterize this decahydroquinoline **204** with the assistance of 2D NMR spectroscopy and the relative stereochemistry was determined by NOESY correlations.

We also found that treatment of our linear precursor with TFA followed by the addition of solid-supported acid and base (Scheme **136**) resulted in the formation of a bicyclic octahydroquinoline enamine system **208**. Subjecting this system to hydrogenation conditions as used in the previous case led to formation of decahydroquinoline **204**.

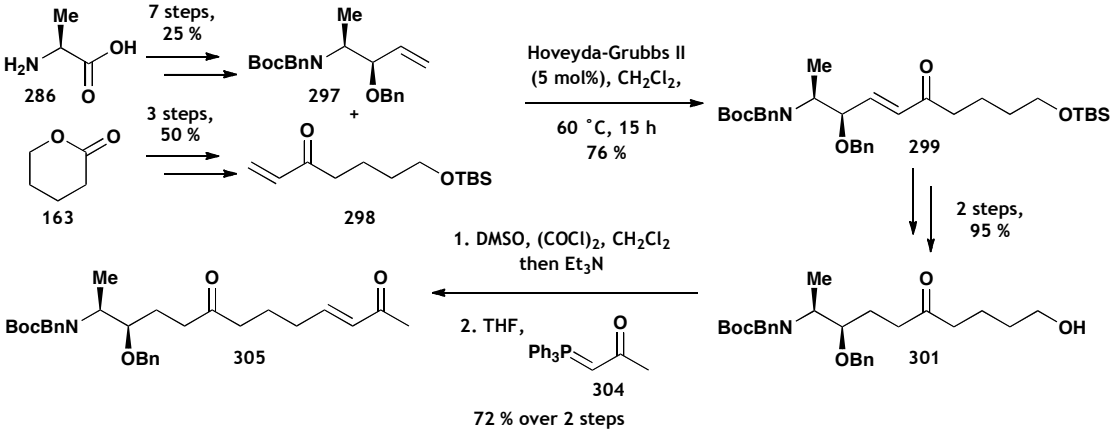


Scheme 139

4.1.2 A linear precursor for the lepadins

We have shown that our methodology for the formation of a linear precursor could also be extended to the synthesis of a linear precursor to allow access to lepadins D, E and H. We are confident that optimization of the cascade reaction would allow access to all eight known lepadins using this and related systems.

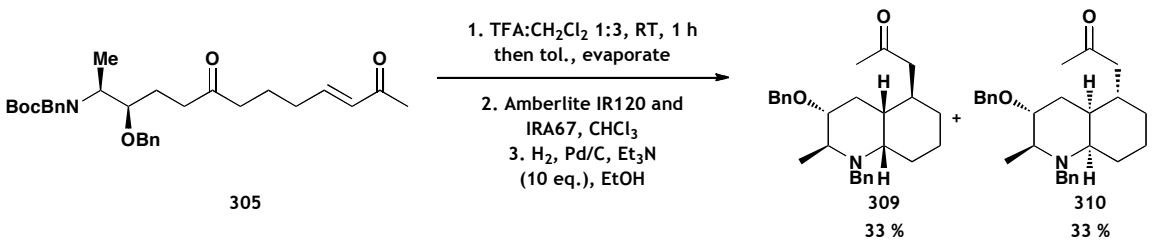
In this system the linear precursor was prepared from three similarly-sized fragments (Scheme **137**). The homoallyl amine **297** fragment was more complex in this system as it contained two stereocentres but we found that it could be prepared in seven steps from L-alanine **286**. The α,β-unsaturated ketone was synthesized in three steps from δ-valerolactone **163** and the ylid **304** was formed in a single step from chloroacetone.



Scheme 140

We found that the cross metathesis reaction had to be carried out at a higher temperature in this system, with higher catalyst loading, and that the yield was slightly lower. This could be attributed to the greater steric crowding in our electron-rich alkene precursor **297** compared with that in the lycopodium alkaloid systems, which slows the cross metathesis process down. However after optimization we found that the cross metathesis proceeded in a pleasing yield of 76 % to give alkene **299**. This olefin **299** could be transformed to alcohol **301** in two steps and we were able to carry out a very similar oxidation-Wittig process to the one used in our lycopodine system. We found that a Swern oxidation was the best protocol for this step and a subsequent Wittig reaction with ylid **304** delivered linear precursor **305** in an excellent yield.

We found that the best procedure for accessing the decahydroquinoline skeleton from this linear precursor involved a three step process (Scheme **138**).



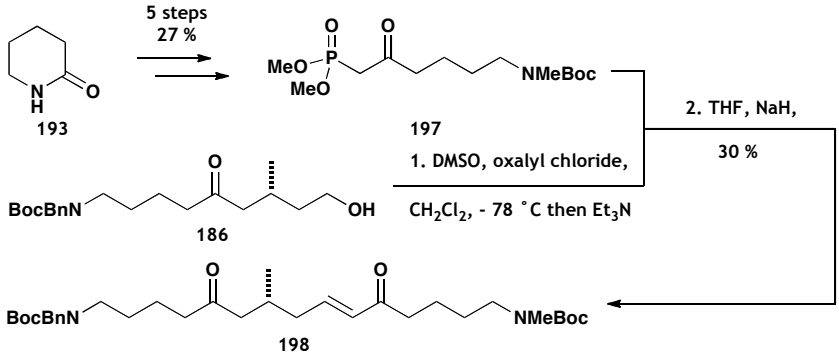
Scheme 141

Treatment of the linear precursor **305** with TFA to remove the *N*-Boc group was followed by the addition of solid-supported acid and base to encourage cyclization. Finally hydrogenation in the presence of triethylamine as a catalyst poison delivered decahydroquinolines **309** and **310** in excellent combined yield as a 1:1 mixture of separable diastereoisomers. We confirmed the formation of the two decahydroquinolines by 2D NMR spectroscopy in each case. We were also able to crystallize derivatives of the two diastereoisomers and confirmed the stereochemistry of each decahydroquinoline by X-ray diffraction.

We observed that in this system there was no selectivity in the Michael addition. Once the bicycle had formed we found that hydrogenation was highly selective, with the hydrogen being delivered from the same face as the ketone side-chain in each case.

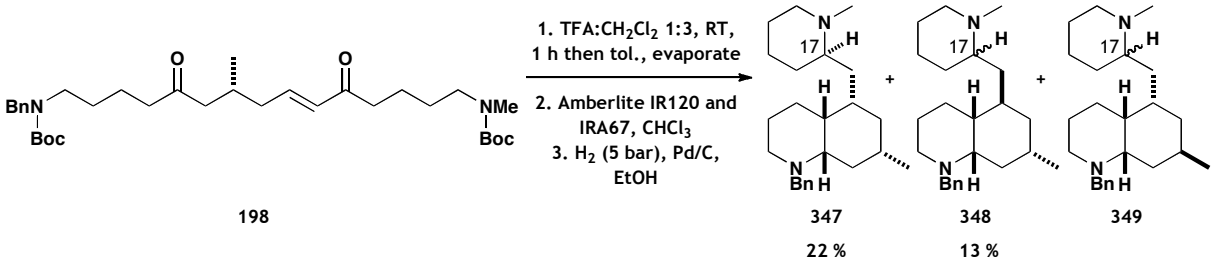
4.1.3 A linear precursor for cermizine B

We have extended our methodology to form a linear precursor for the synthesis of cermizine B. Use of the alcohol **186** from the lycopodine system allowed the linear precursor to be formed *via* a Horner-Wadsworth-Emmons olefination. Switching from a Wittig reaction was necessary to allow for a straightforward synthesis of the third fragment **197** (Scheme **139**). Phosphonate **197** could be synthesized in five steps from lactam **193** in moderate yield. Treatment of phosphonate **197** with sodium hydride and addition of the aldehyde derived from the oxidation of alcohol **186** resulted in olefination to yield the linear precursor **198** in a poor but unoptimized yield.



Scheme 142

We found that the three-step cyclization process we had developed in the lepadin system also worked well in this system (Scheme **140**).

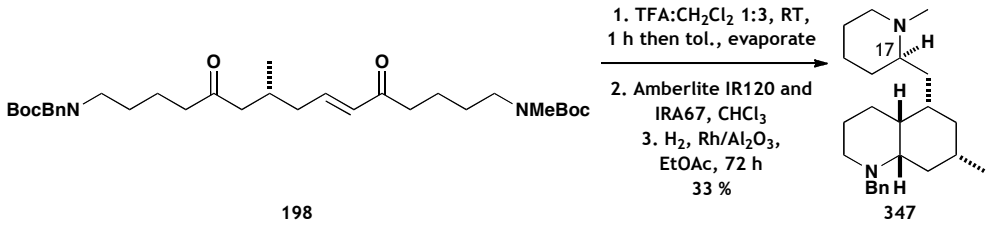


Scheme 143

Treatment of diketone **198** with TFA to remove the two *N*-Boc groups was again followed by the addition of solid-supported acid and base to promote cyclization. Finally we found that hydrogenation at a pressure of 5 bar in the presence of a palladium on carbon catalyst furnished tricycles **347**, **348** and **349** as a 2:1:1 partially separable mixture of diastereoisomers, with each separable major diastereoisomer also containing a minor component of the epimer at carbon 17. We confirmed the formation of tricycles **347** and **348** by 2D NMR spectroscopy and were able to assign the stereochemistry by observing the NOESY correlations.

We believe that tricycle **348** possesses the correct stereochemistry for cermizine B. Unfortunately we were unable to confirm this by removal of the *N*-benzyl group due to a lack of material but this would be the first step to take in any more work on this system.

We examined different conditions for hydrogenation in this system and found that we were able to select for a single decahydroquinoline diastereoisomer (3:1 dr, the minor component being its carbon 17 epimer) (Scheme **141**).



198 347

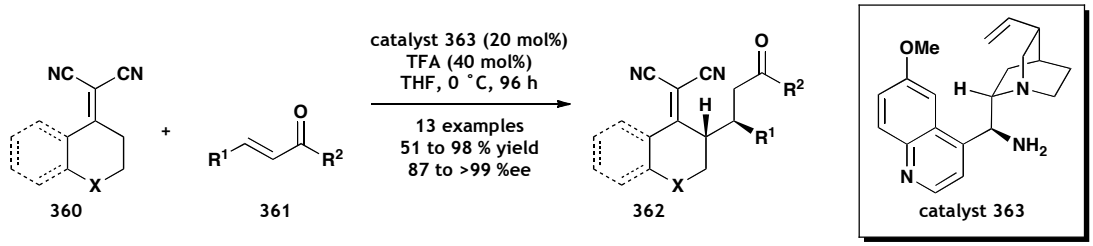
Scheme 144

By changing the hydrogenation conditions from 5 bar pressure with a palladium on carbon catalyst overnight to atmospheric pressure with a rhodium on alumina catalyst over three days we saw hydrogenation of the bicyclic enamine occur exclusively from the opposite face to the methyl and methylene-piperidine side-chains to give tricycle **347**.

4.2 Future Work

4.2.1 Future work towards lycopodine

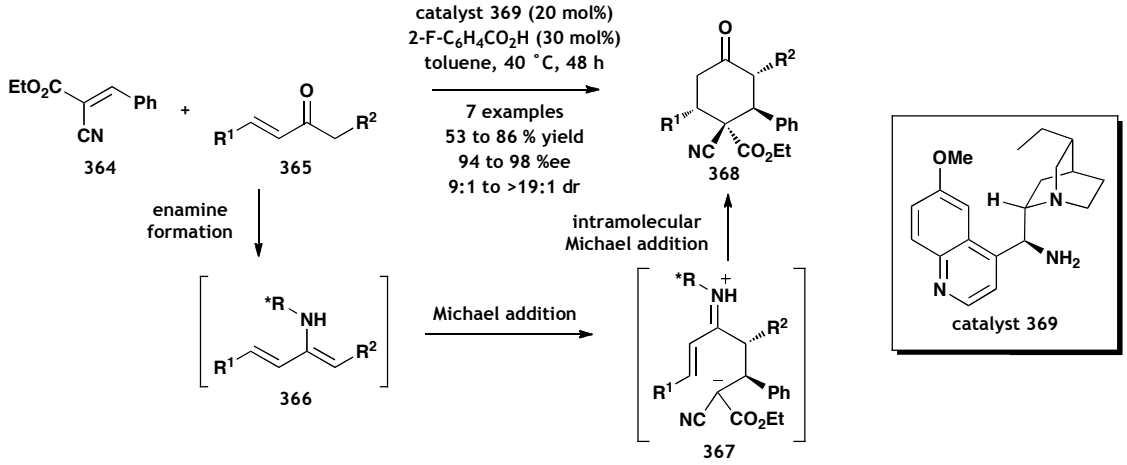
In our lycopodine system, we need to form three rings in a single cascade process in order to access the natural product. For this to occur with the correct stereochemistry we need to encourage the Michael addition to occur on the opposite face of the bicycle to the one we observe. One approach to this involves using iminium catalysis to direct the facial selectivity of the Michael addition. Cinchona-derived primary amines such as **363** have been shown to be useful as catalysts for the Michael addition of α,α-dicyanoalkene nucleophiles into α,β-unsaturated ketones (Scheme **142**).[91]



Scheme 145

Treatment of a range of electrophiles **361** with various nucleophiles **360** resulted in good to excellent yields and enantiomeric excesses of the Michael addition products **362**.

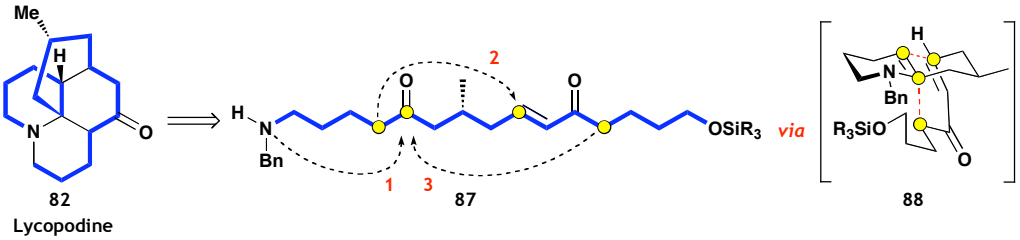
A very similar catalyst **369** has also been used in the formation of highly substituted cyclohexanones *via* a cascade process using both enamine and iminium activation of the substrates (Scheme **143**).[92]



Scheme 146

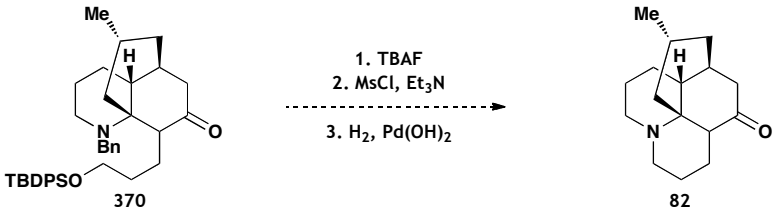
The catalyst **369** initially condenses with enone **365** to form an enamine **366**, which can then carry out a Michael addition into electron-poor alkene **364** to give adduct **367**. The anion generated from this Michael addition can then effect a second conjugate addition into the activated iminium species to give, upon hydrolysis, cyclohexanone products **368**, again with good to excellent yields and enantiomeric excesses. This enamine/iminium cascade exemplifies the reactivity we need to exploit in our system, in order to form the desired tricycle for lycopodine (Scheme **144**). Investigations to determine whether these

catalysts could induce asymmetry during step 2, the Michael addition, should prove invaluable.



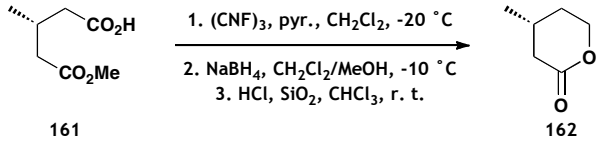
Scheme 147

If we could develop a Michael addition step with the desired stereochemistry we would expect to be able to complete the synthesis of lycopodine. The final steps would involve deprotection and activation of the primary alcohol, deprotection of the amine and displacement to form the fourth and final ring (Scheme **145**).



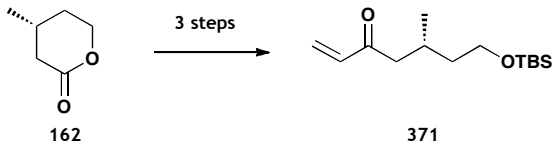
Scheme 148

Once the racemic synthesis of lycopodine has been completed we would expect to be able to render the synthesis asymmetric by the synthesis of our enone cross metathesis partner as a single diastereoisomer (Scheme **146**), as in A. B. Smith III's system.[49]



Scheme 149

With the enantiopure lactone **162** in hand it should be straightforward to transform this to our desired *α,β*-unsaturated ketone **371** by Weinreb amide formation, alcohol protection and vinyl addition (Scheme **147**).



162 371

Scheme 150

With the methyl stereocentre installed asymmetrically we would hope that the rest of the synthesis would proceed as outlined in the racemic system.

4.2.2 Future work towards the lepadins

There are a number of different avenues to explore with respect to forming the correct decahydroquinoline skeletons in order to access some or all of the lepadins. Initially we would like to find a way to direct the facial selectivity of the Michael addition to occur on one face or the other. We are interested in structures with the side-chain from the Michael addition on either face, as the side-chain needs to be on the opposite face to the methyl group in lepadins A-C and on the same face as the methyl group in lepadins D, E and H (Figure **18**). For lepadins F and G we would need to start from the opposite enantiomer of alanine so we will initially focus on the other six lepadins.

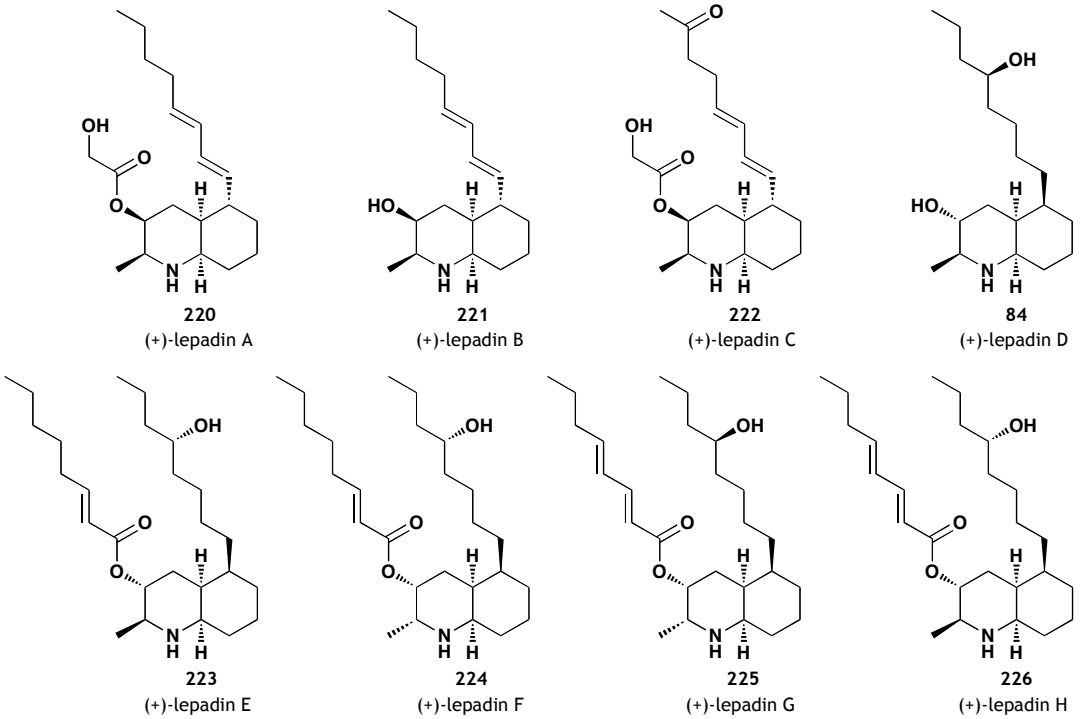
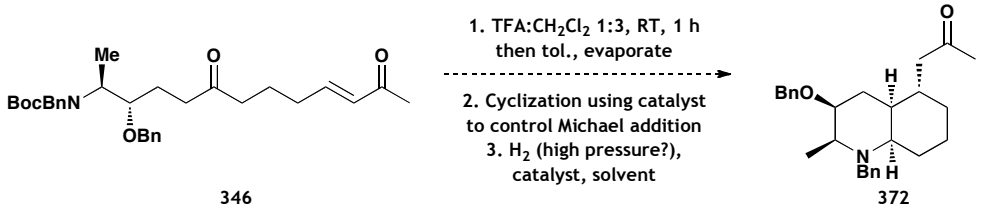


Figure 18

We would hope to control the Michael addition using iminium catalysis as described for our lycopodine system in section **4.2.1.**

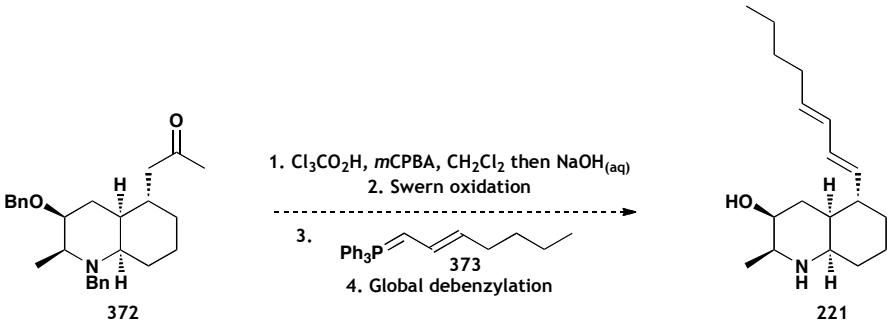
We would also need to examine the selectivity of the hydrogenation step. Lepadins A-C require the selectivity we have already observed in our system, however we would have to optimize conditions for this hydrogenation as we would be using the linear precursor with the alcohol on the opposite face to our successful system, for which we observed no hydrogenation in our preliminary cascade attempts (Scheme **148**).



Scheme 151

We are confident that we would be able to develop a set of conditions that would allow us to access decahydroquinoline **372**, which possesses the correct stereochemistry for access to

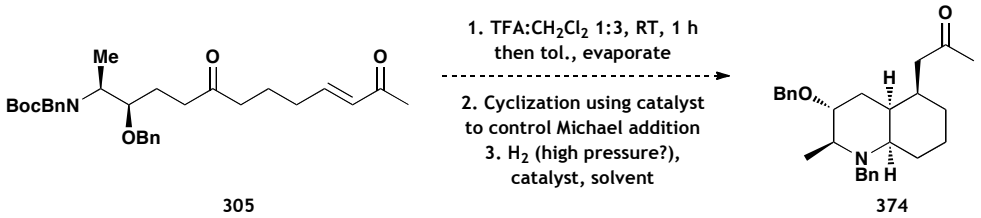
lepadins A-C. With the stereochemistry of the desired decahydroquinoline established, we must next consider how to elaborate this structure to the natural products. The most straightforward approach here would involve transformation of the ketone side-chain into the desired side-chain. Considering lepadin B as an example, as it differs from lepadin A only in the presence of an ester, and lepadin C in the presence of an ester and a remote ketone, we can suggest conditions for this end-game (Scheme **149**).



Scheme 152

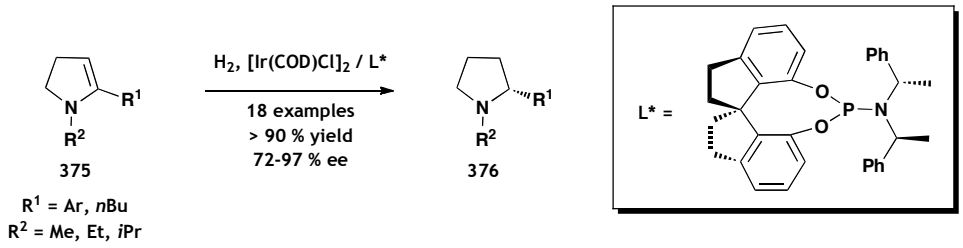
If we treat amino-ketone **372** with *m*CPBA under acidic conditions to protect the amine by protonation,[93] we can carry out a Baeyer-Villiger reaction to replace the ketone with a primary alcohol after hydrolysis. Oxidation to the aldehyde followed by Wittig reaction with the semi-stabilized ylid **373** should install the desired side-chain. Finally hydrogenolysis of the benzyl groups should yield lepadin B.

Turning our attention to lepadins D, E and H, once we had established conditions for selectivity in the Michael addition we would again need to consider selectivity in the hydrogenation step. Here we would require the opposite to our observed selectivity, with the hydrogen being delivered anti to the ketone side-chain (Scheme **150**).



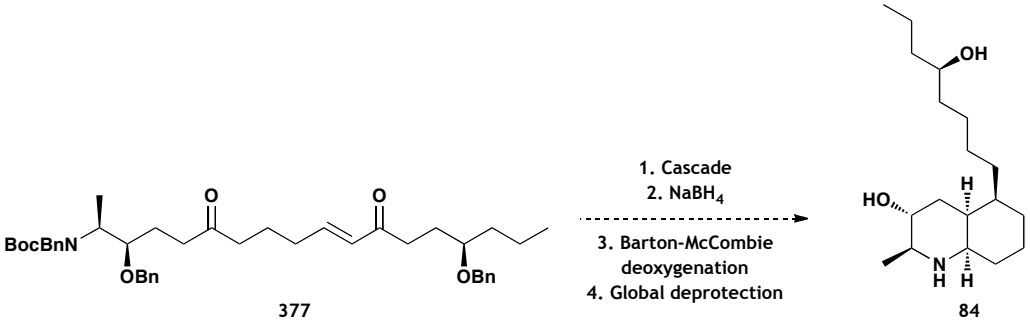
Scheme 153

We would initially hope to achieve this selectivity by varying solvent and catalyst conditions but if this was unsuccessful we might need to consider some asymmetric hydrogenation catalysts, such as the iridium system developed by Zhou *et al*. for the asymmetric hydrogenation of cyclic enamines (Scheme **151**).[94]



Scheme 154

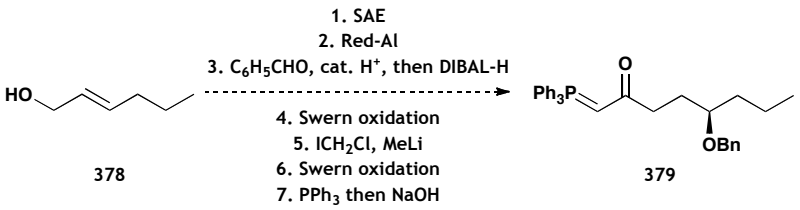
With the stereochemistry of the desired decahydroquinoline established, we must next consider how to elaborate this structure to the natural products. We have two possible routes to the final structures at this stage. One approach involves remaking our linear precursor with the correct side chain present, for example **377** (Scheme **152**). After completion of the cascade removal of the ketone and hydrogenolysis of the benzyl groups would give the natural product.



Scheme 155

If we could synthesize a linear precursor **377**, we could carry out our decahydroquinoline forming cascade, followed by reduction of the ketone. A Barton-McCombie deoxygenation is a gentle method for removing the unwanted alcohol, and finally hydrogenolysis of the benzyl protecting groups would furnish (+)-lepadin D **84**.

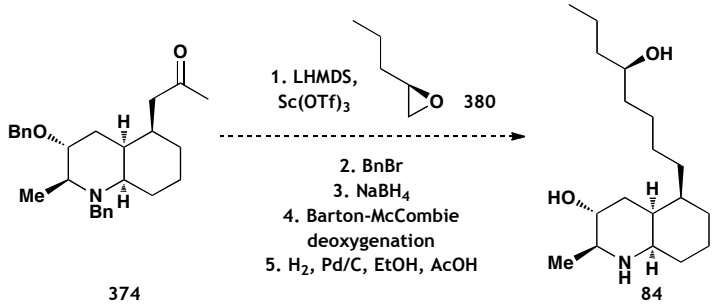
Forming this linear precursor would involve synthesis of a modified fragment C **379**, the ylid fragment for the Wittig reaction that installs the enone (Scheme **153**).



Scheme 156

Using a modified literature procedure[95] commercially available allylic alcohol **378** could be treated with (-)-DET in a Sharpless asymmetric epoxidation, followed by reduction of the epoxide with Red-Al to give the desired diol (in the literature example 93 % desired, 2 % undesired). Benzyl protection could be achieved by a regioselective ring opening of the *O,O*-benzylidene derivative with DIBAL-H. Swern oxidation of the primary alcohol to the aldehyde, followed by addition of the lithiated methylene chloride would set the stage for ylid formation. Finally, another oxidation followed by treatment with triphenylphosphine to displace the chloride would result in phosphonium salt formation, which could be deprotonated to give desired ylid **379**.

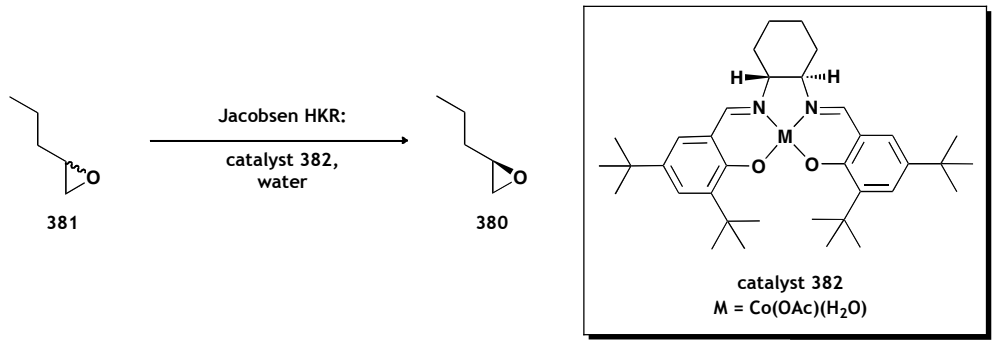
Alternatively, the decahydroquinoline containing the methyl ketone side-chain could be elaborated directly to the natural product (Scheme **154**).



Scheme 157

Treatment of ketone **374** with a strong base should result in kinetic enolate formation which could open epoxide **380** in the presence of a Lewis acid.[96] Benzyl protection of the resulting alcohol could be followed by reduction of the ketone and a Barton-McCombie

deoxygenation. Finally, global debenzylation should again yield (+)-lepadin D **84**. This route relies on the use of epoxide **380** which can be obtained by resolution of the racemic epoxide (Scheme **155**).

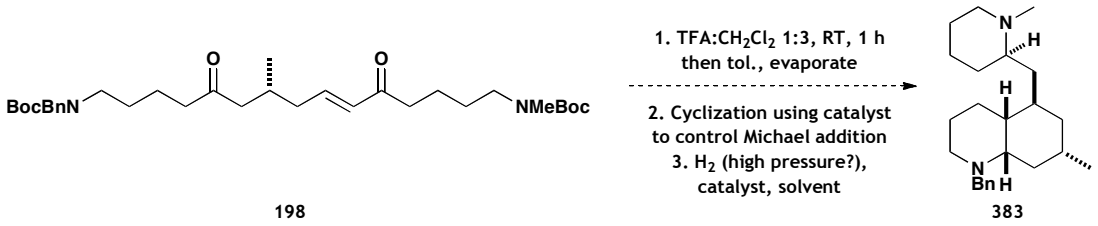


Scheme 158

Commercially available epoxide **381** can be subjected to Jacobsen hydrolytic kinetic resolution conditions[97] using the (*R,R*)-catalyst **382** to give the correct isomer of the epoxide **380**. This route seems the most promising as it involves fewer steps and starts from the decahydroquinoline system that we are more familiar with.

4.2.3 Future work towards cermizine B

In order to improve our synthesis of cermizine B we need to alter the selectivity of the cascade. We would initially need to control the diastereoselectivity of the Michael addition in order to select for addition on the opposite face to the methyl group. We would hope to achieve this using iminium catalysis such as that described in section **4.2.1**. We would then need to control hydrogen delivery onto the same face as the piperidine side-chain, as well as encouraging the formation of and controlling the hydrogenation of the piperidine ring. We would again hope to accomplish this by screening a series of catalyst and solvent conditions but again might need to consider asymmetric conditions as described in section **4.2.2** (Scheme **156**).



Scheme 159

Finally, once the racemic synthesis of cermizine B has been optimized we would hope to make it asymmetric by synthesizing our linear precursor as a single enantiomer using the methods described for the lycopodine sytem in section **4.2.1**.

5 Experimental

5.1 General Experimental Procedures

5.1.1 Solvents and Reagents

THF, CH_2Cl_2, toluene and acetonitrile were purified by filtration through activated alumina columns, employing the method of Grubbs *et al*,[98] or: THF was distilled under an atmosphere of dry nitrogen from lithium aluminium hydride and calcium hydride in the presence of triphenylmethane or sodium metal in the presence of benzophenone; CH_2Cl_2 was distilled from calcium hydride; toluene was distilled from sodium under an atmosphere of dry nitrogen. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. pH 7 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. Non-aqueous reactions were carried out under an atmosphere of argon unless otherwise indicated. All water used experimentally was distilled. Brine refers to a saturated solution of sodium chloride in water. Rochelle's salt refers to a saturated aqueous solution of sodium potassium tartrate.

5.1.2 Chromatography

Thin layer chromatography (TLC) was performed on glass or aluminium plates coated with Merck 60 F_{254} silica and visualization was achieved by UV light or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was carried out using Merck Kieselgel (230-400 mesh) or silica gel 60 (0.043-0.063 mm, VWR).

5.1.3 Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker AV700 (^{1}H: 700 MHz), DRX500 (^{1}H: 500 MHz and ^{13}C: 125 MHz), AVC500 (^{1}H: 500 MHz and ^{13}C: 125 MHz), DPX400 (^{1}H: 400 MHz and ^{13}C: 100 MHz) or Avance 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz). Chemical shifts are quoted in ppm and are referenced to the residual non-deuterated solvent peak, and are reported (based on appearance rather than interpretation) 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; qn, quintet; m, multiplet].

5.1.4 Infrared Spectroscopy

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer fitted with an attenuated total reflectance attachment with internal referencing or as thin films on NaCl plates on a Bruker Tensor 27 FTIR with internal calibration.

5.1.5 Mass Spectrometry

Low resolution mass spectra were recorded on a Micro Mass LCT Premier spectrometer under conditions of electrospray ionization (ESI). Accurate mass measurements were performed on a Finnigan MAT 900 XLT (ES+) at the EPSRC National Mass Spectrometry Service Centre at Swansea or on a Bruker microTOF spectrometer under conditions of electrospray ionization (ESI).

5.1.6 Polarimetry

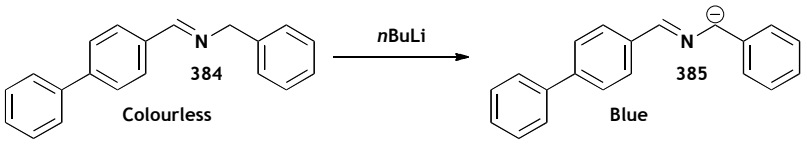
Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm and are quoted in deg $dm^{-1}cm^{3}$ g^{-1}.

5.1.7 Melting point

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

5.1.8 Indicators

The indicator used in the titration of *n*-butyllithium was either 1,10-phenanthroline (upon deprotonation the colour changed from yellow to brown) or **384** shown below (Scheme **157**); upon deprotonation the colour changed from colourless to blue.



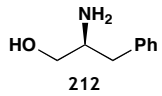
Scheme 160

5.1.9 Naming and numbering of compounds

Compounds are named according to IUPAC guidelines and the numbers within names refer to the IUPAC system of numbering. In assigning the NMR spectra of more complicated structures a separate numbering system was used which is shown on the structures where relevant.

5.2 Experimental

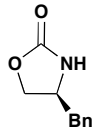
(*S*)-2-Amino-3-phenylpropan-1-ol (L-phenylalaninol) (212)



212

By a modification of the method of Abiko,[46] L-phenylalanine (60 g, 370 mmol) was added to a mechanically stirred suspension of sodium borohydride (35 g, 925 mmol) in dry THF (500 mL) under an atmosphere of dry nitrogen and the resulting mixture was cooled to 0 ˚C. A solution of conc. sulphuric acid (25 mL, 465 mmol) in dry ether (50 mL) was added dropwise over 2.5 h and the resulting mixture was allowed to attain room temperature and stirred overnight. Methanol (38 mL) was carefully added followed by aqueous sodium hydroxide solution (5.0 M, 375 mL). The bulk of the organic solvents was removed by distillation and the remaining solution was heated at reflux overnight at 98 ˚C. Dichloromethane (250 mL) was added then the solution was filtered through Celite™. The filtrate was washed with water (4 x 250 mL) and the combined aqueous layers were washed with 3:1 *iso*-propyl alcohol:chloroform (4 x 250 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The product was recrystallised from ethyl acetate to yield L-phenylalaninol **212** (21.58 g, 39 %) as colourless needles: mp 82-86 ˚C (lit. 88.5-91.0 ˚C); δ_H (400 MHz, $CDCl_3$) 7.33-7.29 (2H, m, Ar-C*H*), 7.27-7.18 (3H, m, Ar-C*H*), 3.64 (1H, dd, *J* 10.5, 4.0, C*H*HOH), 3.38 (1H, dd, *J* 10.5, 7.0, CH*H*OH), 3.14-3.10 (1H, m, C*H*N), 2.80 (1H, dd, *J* 13.5, 5.3, C*H*HPh), 2.53 (1H, dd, *J* 13.5, 8.5, CH*H*Ph); δ_C (100 MHz, $CDCl_3$) 138.4 (Ar-*C*), 129.0 (Ar-*C*H), 128.4 (Ar-*C*H), 126.2 (Ar-*C*H), 66.3 (*C*H_2OH), 53.9 (*C*HN), 40.9 (*C*H_2); $[\alpha]_D^{25}$ –19.0 (c 0.18, $CHCl_3$). The spectroscopic data are consistent with the literature.[47]

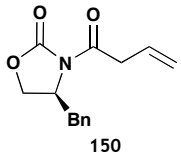
(*S*)-(-)-4-(Phenylmethyl)oxazolidin-2-one (148)



148

By the method of Evans,[47] potassium carbonate (9.14 g, 132 mmol) was added to a stirred mixture of L-phenylalaninol **212** (20.0 g, 132 mmol) and diethylcarbonate (8.0 mL, 132 mmol) under an atmosphere of dry nitrogen and the mixture was heated at reflux at 130 ˚C for 0.5 h then ethanol (~30 mL) was distilled as it formed and the mixture maintained at reflux until no more ethanol was produced. The mixture was diluted with ethyl acetate (50 mL) and dichloromethane (32 mL) and washed with water (64 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to yield oxazolidinone **148** (6.86 g, 29 %) as a colourless solid: mp 79-82 ˚C (lit. 84.5-86.5 ˚C); δ_H (400 MHz, $CDCl_3$) 7.41-7.35 (2H, m, Ar-C*H*), 7.32-7.29 (1H, m, Ar-C*H*), 7.21-7.16 (2H, m, Ar-C*H*), 5.17 (1H, br s, N*H*), 4.50 (1H, t, *J* 8.2, C*H*HO), 4.18 (1H, dd, *J* 8.2, 5.6, CH*H*O), 4.14-4.06 (1H, m, C*H*N), 2.94-2.84 (2H, m, CH_2Ph); δ_C (100 MHz, $CDCl_3$) 158.8 (*C*=O), 135.7 (Ar-*C*), 128.8 (Ar-CH), 128.7 (Ar-*C*H), 127.1 (Ar-CH), 69.5 (*C*H_2O), 50.7 (*C*HN), 41.3 (*C*H_2); $[\alpha]_D^{25}$ –60.0 (c 0.12, $CHCl_3$). The spectroscopic data are consistent with the literature.[47]

(*S*)-4-Benzyl-3-but-3-enoyloxazolidin-2-one (150)

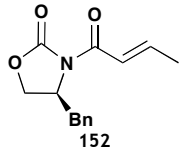


150

Dicyclohexylcarbodiimide (927 mg, 4.5 mmol) was added to a stirred solution of vinyl acetic acid (0.77 mL, 9.0 mmol) in dry dichloromethane (25 mL) and stirred overnight. The resulting mixture was filtered, and ether added. The mixture was filtered and the solvents removed *in vacuo* to provide vinyl acetic anhydride (693 mg, quantitative) which was used without further purification. *n*-Butyllithium (1.68 M in hexanes, 1.96 mL, 3.3 mmol) was added to a stirred solution of the oxazolidinone **148** (532 mg, 3.0 mmol) in dry THF (10 mL)

at -78 ˚C for 0.5 h. A precooled (-78 ˚C) solution of vinyl acetic anhydride (693 mg, 4.5 mmol) in dry THF (5 mL) was added to the solution and stirred for 1 h at -78 ˚C then warmed to ambient temperature and stirred for 4 h. Ammonium chloride solution (10 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (dichloromethane) to yield oxazolidinone **150** (636 mg, 86 %) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (2H, m, Ar-C*H*), 7.32-7.28 (1H, m, Ar-C*H*), 7.24-7.21 (2H, m, Ar-C*H*), 6.10-6.00 (1H, m, *H*C=CH_2), 5.33-5.25 (2H, m, HC=CH_2), 4.73-4.67 (1H, m, C*H*N), 4.27-4.19 (2H, m, CH_2O), 3.83-3.70 (2H, m, CH_2Ph), 3.34 (1H, dd, *J* 13.6, 3.6, O=CC*H*H), 2.80 (1H, dd, *J* 13.2, 9.6, O=CCH*H*); δ_C (100 MHz, $CDCl_3$) 171.0 (N*C*=O), 153.1 (O*C*=O), 135.0 (Ar-*C*), 129.5 (*C*H=CH_2), 129.2 (Ar-*C*H), 128.8 (Ar-*C*H), 127.2 (Ar-*C*H), 119.0 (CH=*C*H_2), 66.0 (*C*H_2OH), 40.0 (*C*HN), 37.6 (*C*H_2); $[\alpha]_D^{25}$ +61.0 (c 0.48, $CHCl_3$). The spectroscopic data are consistent with the literature.[99]

(*S*)-*E*-4-Benzyl-3-but-2-enoyloxazolidin-2-one (152)

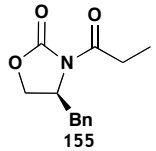


152

n-Butyllithium (1.6 M in hexanes, 3.9 mL, 6.2 mmol) was added to a stirred solution of the oxazolidinone **148** (1.00 g, 5.6 mmol) in dry THF (20 mL) at -78 ˚C for 0.5 h. Precooled (-78 ˚C) crotonyl chloride (0.8 mL, 8.5 mmol) was added and the solution was stirred for 1 h at -78 ˚C then warmed to ambient temperature and stirred for 4 h. Saturated ammonium chloride solution (20 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (2 x 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (dichloromethane) to yield oxazolidinone **152** (1.27 g, 92 %) as an off-white solid: m.p. 86-90 ˚C, (lit. 85.0-86.0 ˚C); δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (2H, m, Ar-C*H*), 7.33-7.25 (3H, m, Ar-C*H*), 7.23-7.20 (2H, m, O=CC*H*C*H*), 4.78-4.73 (1H, m,

C*H*N), 4.26-4.18 (2H, m, CH_2O), 3.36 (1H, dd, *J* 13.2, 3.2, C*H*HPh), 2.82 (1H, dd, *J* 13.2, 9.2, CH*H*Ph), 2.01 (3H, d, *J* 5.2, CH_3); δ_C (100 MHz, $CDCl_3$) 164.7 (N*C*=O), 153.2 (O*C*=O), 146.7 (*C*H=CHC=O), 135.2 (Ar-*C*), 129.2 (Ar-*C*H), 128.7 (Ar-*C*H), 127.1 (Ar-*C*H), 121.7 (*C*HC=O), 65.9 (*C*H_2OH), 55.1 (*C*HN), 37.7 (*C*H_2), 18.3 (*C*H_3); $[\alpha]_D^{25}$ +74.8 (c 0.44, $CHCl_3$). The spectroscopic data are consistent with the literature.[100]

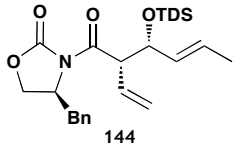
(*S*)-4-Benzyl-3-propanoyloxazolidin-2-one (155)



155

n-Butyllithium (1.57 M in hexanes, 1.97 mL, 3.1 mmol) was added to a stirred solution of the oxazolidinone **148** (500 mg, 2.8 mmol) in dry THF (10 mL) at -78 ˚C for 0.5 h. Precooled (-78 ˚C) propionyl chloride (370 μL, 4.2 mmol) was added and the solution was stirred for 1 h at -78 ˚C then warmed to ambient temperature and stirred for 4 h. Saturated ammonium chloride solution (10 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (dichloromethane) to yield oxazolidinone **155** (647 mg, 98 %) as an off-white solid: m.p. 43-47 ˚C, (lit. 44.0-46.0 ˚C); δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (2H, m, Ar-C*H*), 7.32-7.28 (1H, m, Ar-C*H*), 7.25-7.22 (2H, m, Ar-C*H*), 4.73-4.67 (1H, m, C*H*N), 4.25-4.18 (2H, m, CH_2O), 3.33 (1H, dd, *J* 13.2, 3.2, C*H*HPh), 3.07-2.90 (2H, m, O=CCH_2), 2.80 (1H, dd, *J* 13.2, 9.6, CH*H*Ph), 1.23 (3H, t, *J* 7.6, CH_3); δ_C (100 MHz, $CDCl_3$) 173.9 (N*C*=O), 156.8 (O*C*=O), 135.1 (Ar-*C*), 129.2 (Ar-*C*H), 128.7 (Ar-*C*H), 127.1 (Ar-*C*H), 66.0 (*C*H_2OH), 43.4 (*C*HN), 37.7 (*C*H_2C=O), 29.0 (*C*H_2Ph), 8.1 (*C*H_3); $[\alpha]_D^{25}$ +51.0 (c 0.10, $CHCl_3$). The spectroscopic data are consistent with the literature.[101]

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-((2,3-dimethylbutan-2-yl)dimethylsilyloxy)-2-vinylhex-4-enoyl)oxazolidin-2-one (144)

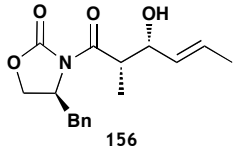


144

According to the method of Schneider,[42] dibutylboron triflate in dichloromethane (1.0 M, 0.13 mL, 0.13 mmol) followed by triethylamine (21 μL, 0.15 mmol) were added to a stirred solution of (*S*)-4-benzyl-3-but-3-enoyloxazolidin-2-one **150** (30 mg, 0.12 mmol) in dry dichloromethane (2.5 mL) at -78 ˚C and a bright yellow solution formed. The solution was stirred at -78 ˚C for 0.75 h then warmed to 0 ˚C and stirred for 0.25 h. The solution was cooled to -78 ˚C and freshly distilled crotonaldehyde (15 μL, 0.18 mmol) was added. Stirring was continued at -78 ˚C for 2 h then at 0 ˚C for 2 h. pH 7 buffer (0.5 mL), methanol (1.0 mL) and hydrogen peroxide (1.6 mL, 20 % in 1:1 methanol:water) were added while the solution was maintained at 0 ˚C and stirred vigorously for 0.5 h. The two-phase mixture was concentrated, dissolved in ether (3 mL) and water (3 mL) and the phases separated. The aqueous layer was extracted with ether (2 x 3 mL) and the combined organic layers were dried (K_2CO_3), filtered and evaporated. 2,6-Lutidine (17 μL, 0.15 mmol) followed by thexyldimethylsilyl triflate (30 mL, 0.12 mmol) were added to a stirred solution of the residue in dichloromethane (1.0 mL) at 0 ˚C. The solution was stirred for 1 h at 0 ˚C then the solvent removed *in vacuo*. The residue was purified by flash column chromatography (2:1 PE 40-60:EtOAc) to yield the protected aldol adduct **144** (43 mg, 78 %, d.r 10:1 *syn*:*anti*) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.31-7.28 (2H, m, Ar-C*H*), 7.26-7.23 (1H, m, Ar-C*H*), 7.19-7.17 (2H, m, Ar-C*H*), 5.98-5.91 (1H, m, *H*C=CH_2), 5.58-5.53 (1H, m, C*H*CH_3), 5.50-5.46 (1H, m, *H*C=CHCH_3), 5.24-5.21 (2H, m, HC=CH_2), 4.64 (1H, dd, *J* 7.6, 5.2, O=CC*H*), 4.60-4.57 (1H, m, C*H*N), 4.34 (1H, t, *J* 5.6, *H*COSi), 4.14-4.08 (2H, m, CH_2O), 3.23 (1H, dd, *J* 10.8, 2.8, C*H*HPh), 2.73 (1H, dd, *J* 10.8, 8.0, CH*H*Ph), 1.64 (3H, dd, *J* 4.8, 0.8, H_3CC=C), 1.60-1.53 (1H, m, C*H*$(CH_3)_2$), 0.83 (6H, dd, *J* 4.0, 1.6, SiC(CH_3)$_2$), 0.78 (6H, dd, *J* 6.0, 3.2, CH(CH_3)$_2$), 0.05 (3H, d, *J* 0.8, SiCH_3); δ_C (100 MHz, $CDCl_3$) 171.9 (N*C*=O), 152.8 (O*C*=O), 135.1 (Ar-*C*), 133.4 (H*C*=CH_2), 131.7 (H*C*CHOSi), 129.3 (Ar-*C*H), 128.7 (*C*HCH_3),

127.3 (Ar-*C*H), 127.1 (Ar-*C*H), 119.1 (HC=*C*H_2), 75.2 (H*C*OSi), 65.6 (*C*H_2OH), 55.3 (*C*HN), 54.5 (H*C*C=O), 37.4 (*C*H_2Ph), 33.8 (*C*H(CH_3)$_2$), 24.7 (*C*(CH_3)$_2$), 20.0 (CH(*C*H_3)$_2$), 18.3 (C(*C*H_3)$_2$), 17.4 (*C*H_3), -2.3 (Si(*C*H_3)$_2$); $[\alpha]_D^{25}$ +28.0 (c 0.22, $CHCl_3$). The spectroscopic data are consistent with the literature.[42]

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-3-hydroxy-2-methylhex-4-enoyl)oxazolidin-2-one (156)

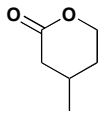


156

Triflic acid (0.21 mL, 2.4 mmol) was added dropwise to a stirred solution of tributylborane (0.57 mL, 2.4 mmol) in dichloromethane (2.4 mL) at 0 ˚C and the solution was stirred at 0 ˚C for 20 min then warmed to room temperature and stirred for 20 min. The newly formed dibutylboron triflate was added dropwise *via* cannula followed by addition of triethylamine (0.40 mL, 2.9 mmol) to a stirred solution of (*S*)-4-benzyl-3-propanoyloxazolidin-2-one **155** (500 mg, 2.1 mmol) in dry dichloromethane (2.6 mL) at 0 ˚C and the solution was stirred at 0 ˚C for 10 mins. The solution was then cooled to -78 ˚C and precooled (-78 ˚C) freshly distilled crotonaldehyde (0.27 mL, 3.2 mmol) was added. The resulting solution was stirred at -78 ˚C for 2 h followed by warming to 0 ˚C and stirring at this temperature for a further 2 h. A 1:2:1 mixture of pH 7 buffer:methanol:hydrogen peroxide (5 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography to yield the aldol adduct **156** (573 mg, 83 %, d.r 41:1 *syn*:*anti*) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (2H, m, Ar-C*H*), 7.33-7.30 (1H, m, Ar-C*H*), 7.24-7.22 (2H, m, Ar-C*H*), 5.79 (1H, dqd, *J* 15.4, 6.8, 1.2, HC=C*H*CH_3), 5.54 (1H, dddd, *J* 15.4, 6.4, 3.2, 1.6, *H*C=CHCH_3), 4.73 (1H, dddd, *J* 13.2, 7.2, 3.6, 1.2, C*H*N), 4.46-4.44 (1H, m, C*H*HO), 4.27-4.19 (2H, m, C*H*OH and CO*H*), 3.89 (1H, ddd, *J* 14.0, 7.2, 4.0, CH*H*O), 3.28 (1H, dd, *J* 13.5, 3.6, C*H*HPh), 2.78 (1H, d, *J* 13.5, CH*H*Ph), 2.77 (1H, d, *J* 13.4, O=CC*H*), 1.73 (3H, d, *J* 6.4, HC=CHC*H*$_3$), 1.27 (3H, d, *J* 6.0, O=CCHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 173.8 (NC=O), 151.9 (OC=O), 134.8 (Ar-*C*), 129.8 (HC=*C*HCHOH),

129.2 (Ar-*C*H), 128.8 (Ar-*C*H), 128.2 (HC=*C*HCH$_3$), 127.2 (Ar-*C*H), 72.6 (*C*HOH), 66.0 (*C*H$_2$OH), 55.0 (*C*HN), 42.6 (*C*H$_2$Ph), 37.6 (HC*C*=O), 17.6 (HC=*C*HCH$_3$), 11.0 (HC*C*H$_3$); $[\alpha]_D^{25}$ +48.0 (c 0.12, $CHCl_3$). The spectroscopic data are consistent with the literature.[102]

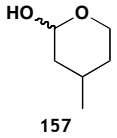
4-Methyltetrahydro-pyran-2-one (160)



160

According to a literature procedure,[103] a precooled (0 ˚C) solution of 3-methyl glutaric anhydride (3.00 g, 23.4 mmol) in dry THF (25 mL) was added to a suspension of sodium borohydride (1.01 g, 26.7 mmol) in dry THF (4.8 mL) at 0 ˚C. The resulting mixture was warmed to room temperature and stirred for 1 h. The mixture was cooled to 0 ˚C and ethanol (6 mL) was added carefully. The mixture was then acidified with 3 N HCl until it was pH 1 then heated to 50 ˚C for 1 h. 3 N HCl was added to the stirred solution until any remaining solid in the flask had dissolved and the aqueous layer remained at pH 1. The aqueous layers were extracted with chloroform (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (19:1 dichloromethane:ethyl acetate) to yield the lactone **160** (2.13 g, 79 %) as an off-white solid: δ_H (400 MHz, $CDCl_3$) 4.41 (1H, ddd, *J* 11.4, 4.9, 4.0, C*H*HO), 4.26 (1H, ddd, *J* 11.4, 10.7, 3.8, CH*H*O), 2.68 (1H, m, O=CC*H*H), 2.19-2.05 (2H, m, O=CCH*H* and C*H*CH$_3$), 1.92 (1H, dqd, *J* 13.8, 4.0, 1.5, C*H*HCHCH$_3$), 1.59-1.51 (1H, m, CH*H*CHCH$_3$), 1.07 (3H, d, *J* 6.3, C*H*$_3$);); δ_C (100 MHz, $CDCl_3$) 171.1 (*C*=O), 68.4 (*C*H$_2$O), 38.1 (*C*H$_2$C=O), 30.5 (*C*H), 26.4 (*C*H$_2$CH$_2$O), 21.3 (*C*H$_3$). LRMS (ES$^-$) calcd for $C_6H_9O_2^-$ 113.06, found 113.00. The spectroscopic data are consistent with that reported in the literature.[103]

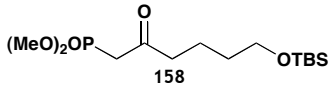
4-Methyltetrahydro-pyran-2-ol (157)



157

According to a literature procedure,[103] DIBAL-H (1.0 M in hexanes, 10.5 mL, 10.5 mmol) was added to a stirred solution of lactone **160** (1.00 g, 8.0 mmol) in dry toluene (38 mL) at -78 ˚C. The resulting solution was stirred for 2 h at -78 ˚C. Aqueous Rochelle's salt (10 mL) was added followed by warming to ambient temperature and stirring for 2 h, until the layers separated. Aqueous sodium bicarbonate (10 mL) was added then the organic layer was separated and the aqueous layer washed with diethyl ether (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield lactol **157** (850 mg, 91 %) as a pale yellow oil (1:1 mixture of diastereomers A and B) which was used without further purification: δ_H (400 MHz, $CDCl_3$) 5.28 (1H, s, C*H*OH, A), 4.67-4.63 (1H, m, C*H*OH, B), 4.03-3.96 (2H, m, C*H*HO, B and C*H*HO, A), 3.62 (1H, ddd, *J* 11.2, 4.6, 2.1, CH*H*O, A), 3.48 (1H, td, *J* 11.9, 2.3, CH*H*O, B), 3.39 (1H, br d, *J* 3.5, O*H*, B), 2.83 (1H, br s, O*H*, A), 2.05-1.95 (1H, m, C*H*CH_3, A), 1.92 (1H, ddt, *J* 12.6, 3.8, 2.0, C*H*HCHOH, B), 1.76-1.71 (1H, m, C*H*HCHOH, A), 1.69-1.61 (1H, m, *CH*CH_3, B) 1.59-1.56 (1H, m, C*H*HCHCH_3, A), 1.49 (1H, dtd, *J* 13.3, 3.8, 1.9, C*H*HCHCH_3, B), 1.33-1.22 (2H, m, CH*H*CHOH and CH*H*CHCH_3, A), 1.17 (1H, m, CH*H*CHCH_3, B), 1.10-1.02 (1H, m, CH*H*CHOH, B), 0.97 (3H, d, *J* 6.6, CH_3, B), 0.91 (3H, d, *J* 6.6, CH_3, A);); δ_C (100 MHz, $CDCl_3$) 95.9 (*C*HOH, B), 91.4 (*C*HOH, A), 65.4 (*C*H_2O, B), 59.5 (*C*H_2O, A), 50.5 (*C*H_2CHOH, B), 41.4 (*C*H_2CHOH, A), 38.4 (*C*H_2*C*H_2O, B), 33.8 (*C*H*C*H_3, B), 33.3 (*C*H_2*C*H_2O, A), 29.2 (*C*H*C*H_3, A), 23.3 (*C*H_3, B), 21.6 (*C*H_3, A). LRMS (ES^+) calcd for $C_6H_{12}NaO_2^+$ 139.07, found 139.08. The spectroscopic data are consistent with the literature.[103]

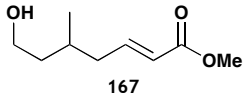
Dimethyl 6-9*tert*-butyldimethylsilyloxy)-2-oxohexylphosphonate (158)



158

According to a literature procedure,[51] *n*-butyllithium (1.6 M in hexanes, 4.5 mL, 7.2 mmol) was added to a solution of dimethyl methylphosphonate (910 mg, 7.1 mmol) in dry THF (20 mL) at -78 ˚C and the reaction was stirred for 0.5 h. A precooled (-78 ˚C) solution of δ-valerolactone **163** (474 mg, 4.7 mmol) in dry THF (7.5 mL) was added *via* cannula and the reaction was stirred for 1 h. A precooled (-78 ˚C) solution of *tert*-butyldimethylsilyl chloride (1.79 g, 11.9 mmol) in tetrahydrofuran (1 mL) was added *via* cannula and the reaction was allowed to warm to ambient temperature overnight. NH_4Cl:H_2O:MeOH (3:6:1, 20 mL) was added and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography (Et_2O:EtOAc 9:1) to yield phosphonate **158** (1.37 g, 86 %) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 3.78 (6H, d, *J* 11.2, $(CH_3O)_2P$), 3.61 (2H, t, *J* 6.3, CH_2O), 3.08 (2H, d, *J* 22.7, CH_2P), 2.64 (2H, t, *J* 7.2, $O{=}CCH_2$), 1.54-1.47 (4H, m, CH_2CH_2), 0.89 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 201.6 (*C*=O), 62.5 (CH_2O), 52.9 (CH_3O), 43.7 ($CH_2C{=}O$), 40.4 (PCH_2), 31.7 (CH_2CH_2O), 25.7 ($C(CH_3)_3$), 19.7 ($CH_2CH_2C{=}O$), 18.1 ($C(CH_3)_3$), -5.5 ($Si(CH_3)_2$). LRMS (ES^+) calcd for $C_{14}H_{31}NaO_5PSi^+$ 361.16, found 361.17. The spectroscopic data are consistent with the literature.[104]

(*E*)-Methyl 7-hydroxy-5-methylhept-2-enoate (167)

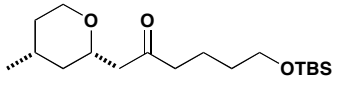


167

Methyl (triphenylphosphoranylidene) acetate (189 mg, 0.57 mmol) was added to a solution of lactol **157** (56 mg, 0.50 mmol) in acetonitrile (0.8 mL) and the reaction was stirred overnight. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (diethyl ether) to yield the α,β-unsaturated ester **167** (59 mg, 69 %) as a

pale yellow oil: δ_H (400 MHz, $CDCl_3$) 6.94 (1H, dt, *J* 15.5, 7.5, *H*C=CHC=O), 5.84 (1H, dt, *J* 15.5, 1.4, *H*CC=O), 3.73 (3H, s, OC*H*$_3$), 3.71-3.67 (2H, m, C*H*$_2$OH), 2.28-2.06 (2H, m, C*H*$_2$CH=C), 1.82 (1H, dq, *J* 13.6, 6.9, C*H*CH$_3$), 1.63 (1H, dtd, *J* 12.7, 7.1, 5.6, C*H*HCH$_2$OH), 1.47-1.38 (1H, m, CH*H*CH$_2$OH), 1.21 (1H, t, *J* 5.0, O*H*), 0.94 (3H, d, *J* 6.7, HCC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 166.8 (*C*=O), 147.7 (H*C*=CHC=O), 122.1 (H*C*C=O), 60.6 (*C*H$_2$OH), 51.2 (*C*H$_3$O), 39.5 (*C*H$_2$CH$_2$OH), 39.1 (*C*H), 29.0 (*C*H$_2$), 19.3 (*C*H$_3$); ν_{max} (film)/cm^{-1} 3423 (br, OH), 2955, 1725 (C=O), 1656 (C=C), 1437, 1273, 1170, 1045; HRMS (ES$^+$) calcd for $C_9H_{16}O_3^+$ 173.1172, found 173.1171.

6-(*tert*-Butyldimethylsilyloxy)-1-(4-methyltetrahydro-pyran-2-yl)hexan-2-one (165)

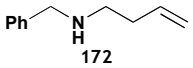


165

A precooled (0 ˚C) solution of *t*BuOK (37 mg, 0.33 mmol) in dry THF (1 mL) was slowly added *via* cannula to a solution of phosphonate **158** (100 mg, 0.30 mmol) in dry THF (3.3 mL) at 0 ˚C. The reaction was stirred at 0 °C for 1 h then cooled to -78 ˚C and a precooled (-78 ˚C) solution of lactol **157** (17 mg, 0.15 mmol) in dry THF (0.3 mL) was added *via* cannula and washed through with dry THF (0.3 mL). The reaction was stirred for 2 h at -78 ˚C then put in an ice bath and allowed to warm to room temperature overnight. Brine (2.5 mL) was added then the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (diethyl ether) to yield the tetrahydropyran **165** (23 mg, 47 %, d.r 2.5:1, *syn*:*anti*) as a colourless oil; mixture of diastereomers, major diastereomer tentatively assigned as shown above: δ_H (400 MHz, $CDCl_3$) 4.13-4.07 (1H, m, C*H*O), 3.93 (1H, ddd, *J* 11.4, 4.6, 1.5, C*H*O minor) 3.77-3.70 (1H, m, C*H*HO minor), 3.69-3.66 (2H, m, C*H*$_2$O), 3.60 (2H, t, *J* 6.3, C*H*$_2$OSi and minor), 3.40 (1H, ddd, *J* 12.5, 11.5, 2.2, CH*H*O minor), 2.69 (1H, dd, *J* 15.4, 8.0, HCC*H*HC=O), 2.64 (1H, dd, *J* 15.6, 7.6, HCC*H*HC=O minor), 2.47 (2H, t, *J* 7.2, C*H*$_2$C=O and minor), 2.38 (1H, dd, *J* 15.7, 4.9, HCCH*H*C=O minor), 2.35 (1H, dd, *J* 15.5, 5.0, HCCH*H*C=O), 2.05-1.98 (1H, m, C*H*CH$_3$), 1.76 (1H, dddd, *J* 13.7, 8.8, 6.1, 4.8 C*H*H), 1.66-

1.58 (2H, m, CH_2 and minor), 1.55-1.46 (3H, m, CH_2 and minor and CH*H* and minor and C*H*H minor), 1.39 (1H, dddd, *J* 13.3, 4.5, 3.1,1.4, CH*H*), 1.29-1.20 (1H, m, C*H*H and minor), 1.19-1.12 (1H, m, CH*H* minor) 1.07 (3H, d, *J* 7.1, *C*H_3), 0.92 (3H, d, *J* 6.3, CH_3 minor), 0.88 (9H, s, C(CH_3)$_3$ and minor), 0.04 (6H, s, Si(CH_3)$_2$ and minor); δ_C (100 MHz, $CDCl_3$) 209.2 (*C*=O), 68.5 (*C*HO), 62.6 (*C*H_2OSi), 62.4 (*C*H_2O), 49.1 (*C*H_2C=O, minor), 48.1 (*C*H_2C=O), 43.4 (*C*H_2C=O, minor), 43.3 (*C*H_2C=O), 37.2 (*C*H_2CHO), 32.0 (*C*H_2CH$_2$O), 31.7 (*C*H_2CH$_2$OSi), 25.7 (C(*C*H_3)$_3$), 24.6 (*C*HCH$_3$), 22.0 (*C*H_2CH$_2$C=O), 19.7 (*C*H_3), 18.3 (*C*(CH$_3$)$_3$ minor), 18.1 (*C*(CH$_3$)$_3$), -5.5 (Si(*C*H_3)$_2$); ν_{max} (film)/cm^{-1} 1715 (C=O); HRMS (ES$^+$) calcd for $C_{18}H_{36}O_3Si^+$ 329.2506, found 329.2511.

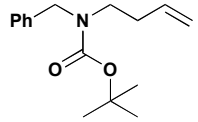
_N_-Benzylbut-3-en-1-amine (172)



172

According to a literature procedure,[105] sodium iodide (220 mg, 1.47 mmol) was added to a deoxygenated solution of benzylamine (21.0 mL, 195 mmol) and 4-bromo-1-butene (4.0 mL, 39 mmol) in ethanol (55 mL). The reaction mixture was heated to 75 ˚C with vigorous stirring for 16 h, and partitioned between CH_2Cl_2 (550 mL) and potassium hydroxide solution (1 M, 550 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic extracts dried with anhydrous potassium carbonate. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (19:1 Et_2O:MeOH) to yield the secondary amine **172** (4.92 g, 81 %) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.37-7.33 (4H, m, Ph), 7.33-7.25 (1H, m, Ph), 5.85-5.77 (1H, ddd, *J* 17.0, 10.0, 7.0, C*H*CH$_2$), 5.14-5.09 (1H, d, *J* 17.0, CHC*H*^{1}H), 5.07-5.05 (1H, d, *J* 10.0, CHCH*H*^{2}), 3.82 (2H, s, PhC*H*), 2.74-2.72 (2H, t, *J* 6.5, NHCH_2), 2.33-2.29 (2H, dt, *J* 7.0, 6.5, NHCH$_2$CH_2), 1.54-1.45 (1H, br, N*H*); δ_C (100 MHz, $CDCl_3$) 139.0 (Ph *ipso*-C), 135.3 (*C*H=CH$_2$), 127.2 (Ph *meta*-C), 127.0 (Ph *ortho*-C), 125.7 (Ph *para*-C), 115.2 (CH=*C*H$_2$), 52.7 (PhCH$_2$), 47.1 (BnNCH$_2$), 33.1 (*C*H$_2$CH=CH$_2$); ν_{max} (film) / cm^{-1} ~3400-3200 (broad, NH) 1640 (C=C), 1605 (Ph C=C); LCMS (ES$^+$) calcd for $C_{11}H_{16}N^+$ 162.13, found 162.11. These data are consistent with those reported in the literature.[105]

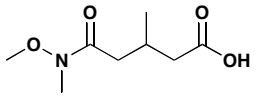
***tert*-Butyl benzyl(but-3-enyl)carbamate (173)**



173

A solution of amine **172** (4.88 g, 31 mmol), DMAP (368 mg, 3.9 mmol) and triethylamine (4.8 mL, 35 mmol) was prepared in CH_2Cl_2 (76 mL) at 0 ˚C. Di-*tert*-butyl dicarbonate (7.44 g, 35 mmol) was added slowly and the resulting mixture allowed to warm to room temperature and stirred for 48 h. pH 7 buffer (50 mL) was added, and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the tertiary amide **173** (7.33 g, 90 %) as a pale yellow oil: δ_H (500 MHz, $CDCl_3$) 7.36-7.32 (2H, m, Ph), 7.28-7.26 (3H, m, Ph), 5.76 (1H, br, C*H*CH_2), 5.07 (1H, br, CHCH_1H), 5.03-5.01 (1H, dt, *J* 10.0, 1.0, CHCHH_2), 4.48-4.44 (2H, br, PhCH_2), 3.31-3.20 (2H, br, BnBocNCH_2), 2.25 (2H, br, BnBocNCH$_2$CH_2), 1.59-1.46 (9H, m, O^{t}Bu**);** δ_C (125 MHz, $CDCl_3$) 155.4 (*C*=O), 137.6 (CH_2*C*HCH_2), 135.5 (Ph *ipso*-C), 128.4 (Ph *meta*-C), 127.8 (Ph *meta*-H), 127.1 (Ph *para*-H), 116.5 (CH*C*H_2), 79.6 (*C*(CH_3)$_3$), 50.6 (Ph*C*H_2), 46.2 (BnN*C*H_2), 32.5 (BnNCH$_2$*C*H_2), 28.4 (C(*C*H_3)$_3$); ν_{max} (film)/cm^{-1} 1689 (C=O), 1642 (C=C), 1606 (Ph C=C). LCMS (ES$^+$) calcd for $C_{11}H_{15}N^+$ (loss of Boc$^-$) 161.12, found 161.09. These data are consistent with the literature.[106]

5-(Methoxy(methyl)amino)-3-methyl-5-oxopentanoic acid (177)

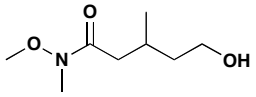


177

According to a literature procedure,[107] pyridine (7.5 mL, 92 mmol) was added dropwise to a stirred solution of 3-methylglutaric anhydride (5.40 g, 42 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (4.52 g, 46 mmol) in CH_2Cl_2 at 0 ˚C. The mixture was stirred for 10 min then warmed to room temperature and stirred for a further 7 h. The

solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2:Et_2O (1:1, 25 mL) and brine (38 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to yield acid **177** (7.91 g, 99 %) as a pale yellow oil which was used without further purification: δ_H (500 MHz, $CDCl_3$) 3.67 (3H, s, OC*H*$_3$), 3.17 (3H, s, NC*H*$_3$), 2.52-2.40 (4H, m, NC=OC*H*$_2$ and HOC=OC*H*$_2$), 2.27 (1H, dd, *J* 15.0, 6.5, C*H*Me), 1.04 (3H, d, *J* 6.5, C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 177.4 (HO*C*=O), 173.4 (N*C*=O), 61.2 (OCH_3), 40.8 (HOC=OCH_2), 38.1 (NC=OCH_2), 32.1 (NCH_3), 27.0 (*C*HMe), 20.1 (*C*H_3); ν_{max} (film)/cm^{-1} 3100 (br, OH), 2967, 1729 (C=O acid), 1625 (C=O amide) 1390, 1176, 1002; LRMS (ES$^+$) calcd for $C_8H_{15}NNaO_4^+$ 212.09, found 212.10. These data are consistent with the literature.[107]

5-Hydroxy-*N*-methoxy-*N*,3-dimethylpentanamide (178)

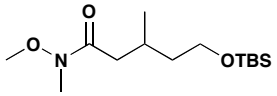


178

Triethylamine (6.1 mL, 44 mmol) was added dropwise to a stirred solution of acid **177** (7.80 g, 40 mmol) in THF (170 mL) at 0 ˚C. Ethyl chloroformate (4.2 mL, 44 mmol) was added dropwise and the mixture was stirred at 0 ˚C for 20 min during which time a white precipitate formed. The solution was filtered and the filtrate was added to a stirred solution of sodium borohydride (2.23 g, 61 mmol) in water (164 mL) at 0 ˚C then warmed to RT and stirred for 16 h. Aqueous potassium hydrogen sulfate (1 M, 80 mL) was added and the aqueous layer extracted with $CHCl_3$:*i*PrOH (3:1, 5 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (19:1 Et_2O:MeOH) to yield the alcohol **178** (5.28 g, 74 %) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 3.65 (3H, s, OC*H*$_3$), 3.60 (2H, t, *J* 7.0, C*H*$_2$OH), 3.15 (3H, s, NC*H*$_3$), 2.93 (1H, br, O*H*), 2.39 (1H, dd, *J* 15.8, 7.5, C*H*HC=O), 2.29 (1H, dd, *J* 15.8, 5.3, CH*H*C=O), 2.19 (1H, qd, *J* 13.4, 6.7, C*H*Me), 1.50 (2H, dtd, *J* 18.0, 6.9, 6.3, C*H*$_2$$CH_2$OH), 0.95 (3H, d, *J* 6.8, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 174.3 (*C*=O), 61.1 (OCH_3), 60.3 (*C*H_2OH), 40.0 (*C*H_2C=O), 38.8 (*C*$H_2$$CH_2$OH), 32.1 (N$CH_3$), 26.1 (*C*HMe), 20.8 (*C*H_3); ν_{max} (film)/cm^{-1} 3424

(br, OH), 2934, 1731 (C=O), 1643 (C=O), 1461, 1386, 1178, 1057, 1004; LRMS (ES^+) calcd for $C_8H_{17}NNaO_3^+$ 198.11, found 198.10. These data are consistent with the literature.[108]

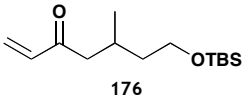
5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*,3-dimethylpentanamide (179)



179

Tert-butyldimethylchloro silane (8.14 g, 54 mmol) was added to a stirred solution of alcohol **178** (4.73 g, 27 mmol), imidazole (5.49 g, 81 mmol) and DMAP (316 mg, 2.7 mmol) in DMF (19 mL) at 0 ˚C. The reaction mixture was warmed to RT and stirred for 12 h. pH 7 buffer was added (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the silyl ether **179** (7.81 g, quant.) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 3.72-3.58 (2H, m, CH_2OSi), 3.66 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 2.42 (1H, dd, *J* 14.9, 5.5, C*H*HC=O), 2.27 (1H, dd, *J* 14.2, 8.2, CH*H*C=O), 2.15 (1H, sextet, *J* 6.6, C*H*Me), 1.59 (1H, sextet, *J* 6.6, C*H*HCH$_2$OSi), 1.42 (1H, sextet, *J* 6.9, CH*H*CH$_2$OSi), 0.95 (3H, d, *J* 6.6, CH_3), 0.87 (9H, s, SiC(CH_3)$_3$), 0.03 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 174.0 (*C*=O), 61.3 (*C*H$_2$OSi), 61.1 (O*C*H$_3$), 39.8 (*C*H$_2$CH$_2$OSi), 39.2 (*C*H$_2$C=O), 32.1 (N*C*H$_3$), 26.9 (*C*HMe), 25.9 (SiC(*C*H$_3$)$_3$), 20.0 (*C*H$_3$), 18.3 (Si*C*(CH$_3$)$_3$), -5.4 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 2931, 1669 (C=O), 1463, 1385, 1255, 1096, 1006, 837, 776; HRMS (ES^+) calcd for $C_{14}H_{32}NO_3Si^+$ 290.2146, found 290.2146. These data are consistent with the literature.[108]

7-((tert-Butyldimethylsilyl)oxy)-5-methylhept-1-en-3-one (176)

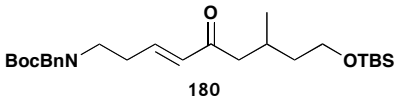


176

Vinylmagnesium bromide (1.0 M in THF, 66 mL, 66 mmol) was added *via* syringe pump over a period of 1 h to a stirred solution of Weinreb amide **179** (6.86 g, 24 mmol) in THF

(69 mL) at -78 ˚C. The mixture was allowed to warm to room temperature over a period of 12 h before being poured into cooled (-78 ˚C) CH_2Cl_2 (1.0 L) followed by addition of aqueous NH_4Cl (700 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 500 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1 PE 40-60:Et_2O) to yield the ketone **176** (4.60 g, 75 %) as a colourless oil: δ_H (500 MHz, $CDCl_3$) 6.35 (1H, dd, *J* 17.9, 11.2, C*H*C=O), 6.21 (1H, d, *J* 17.9, *trans*-C*H*HCH), 5.80 (1H, d, *J* 10.4, *cis*-CH*H*CH), 3.71-3.60 (2H, m, CH_2OSi), 2.64 (1H, dd, *J* 15.4, 5.5, C*H*HC=O), 2.40 (1H, dd, *J* 15.4, 8.2, CH*H*C=O), 2.20 (1H, sextet, *J* 6.6, C*H*Me), 1.55 (1H, sextet, *J* 6.7, C*H*HCH$_2$OSi), 1.44 (1H, sextet, *J* 6.7, CH*H*CH$_2$OSi), 0.93 (3H, d, *J* 6.7, CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$); δ_C (125 MHz, $CDCl_3$) 200.7 (*C*=O), 136.9 (*C*HC=O), 128.0 (*C*H$_2$CHC=O), 61.1 (*C*H$_2$OSi), 47.1 (*C*H$_2$C=O), 39.7 (*C*H$_2$CH$_2$OSi), 26.7 (*C*HMe), 26.0 (SiC(*C*H$_3$)$_3$), 20.0 (*C*H$_3$), 18.3 (Si*C*(CH$_3$)$_3$), -5.3 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 2930, 1683 (C=O), 1598 (w, C=C), 1401, 1255, 1098, 836, 775; HRMS (ES$^+$) calcd for $C_{14}H_{28}NaO_2Si^+$ 279.1751, found 279.1746.

(E)-tert-Butyl benzyl(9-((tert-butyldimethylsilyl)oxy)-7-methyl-5-oxonon-3-en-1-yl) carbamate (180)

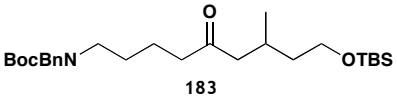


180

Hoveyda-Grubbs II catalyst **182** (132 mg, 0.21 mmol) was added to a stirred solution of amine **173** (1.57 g, 6.0 mmol) and α,β-unsaturated ketone **176** (2.31 g, 9.0 mmol) in CH_2Cl_2 (30 mL) and the mixture was heated to 40 ˚C for 16 h. The mixture was cooled and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1 PE 40-60:Et_2O) to yield the α,β-unsaturated ketone **180** (2.89 g, 97 %) as a brown oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.34 (2H, t, *J* 7.3, Ar-C*H*), 7.27 (3H, t, *J* 7.1, Ar-C*H*), 6.72 (1H, dt, *J* 15.9, 7.3, C*H*=CHC=O), 6.06 (1H, d, *J* 15.9, CH=C*H*C=O), 4.41 (1H, s, NCH_2Ph), 3.69-3.59 (2H, m, CH_2OSi), 3.34 (2H, t, *J* 6.7, CH_2N), 2.53 (1H, dd, *J* 15.5, 5.6, C*H*HC=O), 2.45-2.37 (2H, m, CH_2CH$_2$N), 2.35 (1H, dd, *J* 15.7, 7.7, CH*H*C=O), 2.08 (1H, sextet, *J* 6.5, C*H*Me), 1.52 (1H, sextet, *J* 6.5, C*H*HCH$_2$OSi), 1.43 (9H, s, OC(CH_3)$_3$), 1.38 (1H, sextet, *J* 6.5, CH*H*CH$_2$OSi), 0.89

(12H, br s, SiC(CH_3)$_3$ and CH_3), 0.05 (6H, s, Si(CH_3)$_2$); δ_C (125 MHz, (CD_3)$_2$SO, 363 K) 199.9 (*C*=O), 155.8 (N*C*=O), 144.4 (*C*HCHC=O), 139.5 (*ipso*-Ar-*C*), 132.7 (*C*HC=O), 129.2 (2 x *meta*-Ar-*C*H), 128.2 (2 x *ortho*-Ar-*C*H), 127.8 (*para*-Ar-*C*H), 79.9 (O*C*(CH_3)$_3$), 61.6 (*C*H$_2$OSi), 51.0 (NCH$_2$Ph), 47.8 (*C*H$_2$C=O), 46.4 (*C*H$_2$N), 40.2 (*C*H$_3$CH$_2$OSi), 31.8 (*C*H$_2$CH$_2$N), 28.9 (OC(*C*H$_3$)$_3$), 27.2 (*C*HMe), 26.6 (SiC(*C*H$_3$)$_3$), 20.6 (*C*H$_3$), 18.7 (Si*C*(CH$_3$)$_3$), -4.5 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 2930, 1696 (C=O), 1627 (C=C), 1414, 1366, 1250, 1167, 1097, 836, 775; HRMS (ES$^+$) calcd for $C_{28}H_{48}NO_4Si^+$ 490.3347, found 490.3350.

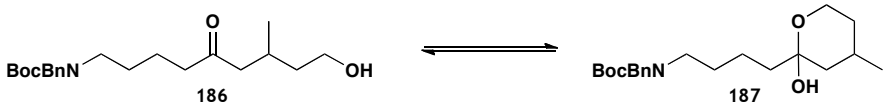
tert-Butyl benzyl(9-((tert-butyldimethylsilyl)oxy)-7-methyl-5-oxononyl)carbamate (183)



183

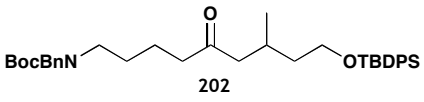
Palladium on carbon (510 mg, 10 wt% Pd) and triethylamine (14.3 mL, 103 mmol) were added to a stirred solution of alkene **180** (5.10 g, 10.3 mmol) in EtOH (70 mL) and the resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the ketone **183** (5.06 g, quant.) as a colourless oil: δ_H (500 MHz, (CD_3)$_2$SO, 363 K) 7.33 (2H, t, *J* 7.3, Ar-C*H*), 7.25 (3H, t, *J* 9.1, Ar-C*H*), 4.38 (2H, s, NC*H*$_2$Ph), 3.68-3.58 (2H, m, C*H*$_2$OSi), 3.15 (2H, t, *J* 6.1, C*H*$_2$N), 2.41 (1H, dd, *J* 16.1, 5.7, CHC*H*HC=O), 2.36 (2H, t, *J* 6.5, CH$_2$C*H*$_2$C=O), 2.23 (1H, dd, *J* 15.7, 7.6, CHCH*H*C=O), 2.06 (1H, sextet, *J* 6.7, C*H*Me), 1.53-1.26 (6H, m, C*H*$_2$CH$_2$OSi, C*H*$_2$CH$_2$N, C*H*$_2$CH$_2$C=O), 1.43 (9H, s, OC(C*H*$_3$)$_3$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.88 (3H, d, *J* 6.7, C*H*$_3$), 0.05 (6H, s, Si(C*H*$_3$)$_2$); δ_C (125 MHz, (CD_3)$_2$SO, 363 K) 210.4 (*C*=O), 155.9 (N*C*=O), 139.7 (*ipso*-Ar-*C*), 129.2 (2 x *meta*-Ar-*C*H), 128.1 (2 x *ortho*-Ar-*C*H), 127.8 (*para*-Ar-*C*H), 79.7 (O*C*(CH_3)$_3$), 61.6 (*C*H$_2$OSi), 50.7 (NCH$_2$Ph), 50.3 (CHCH$_2$C=O), 47.1 (*C*H$_2$N), 42.9 (CH$_2$CH$_2$C=O), 40.1 (*C*H$_2$CH$_2$OSi), 28.9 (OC(*C*H$_3$)$_3$), 28.2 (CH$_2$CH$_2$N), 26.7 (*C*HMe), 26.7 (SiC(*C*H$_3$)$_3$), 21.5 (*C*H$_2$CH$_2$C=O), 20.6 (*C*H$_3$), 18.7 (Si*C*(CH$_3$)$_3$), -4.5 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 2930, 1695 (C=O), 1416, 1252, 1169, 836, 775; HRMS (ES$^+$) calcd for $C_{28}H_{49}NNaO_4Si^+$ 514.3323, found 514.3307.

tert-Butyl benzyl(9-hydroxy-7-methyl-5-oxononyl)carbamate (186)



TBAF (1.0 M solution in THF, 10.6 mL, 10.6 mmol) was added dropwise to a stirred solution of silyl ether **183** (4.79 g, 9.7 mmol) in THF (100 mL) at 0 ˚C. The reaction mixture was allowed to warm to room temperature slowly and stirred for 16 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (1:1 PE 40-60:Et_2O) to yield the alcohol **186** (3.66 g, quant.) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.34 (2H, t, *J* 7.3, Ar-C*H*), 7.26 (3H, t, *J* 7.6, Ar-C*H*), 4.39 (2H, s, NCH_2Ph), 3.54-3.40 (2H, m, CH_2OH), 3.16 (2H, br s, CH_2N), 2.41 (1H, dd, *J* 15.9, 5.7, CHC*H*HC=O), 2.37 (2H, t, *J* 6.7, CH_2CH_2C=O), 2.22 (1H, dd, *J* 15.9, 7.9, CHCH*H*C=O), 2.05 (1H, sextet, *J* 6.6, C*H*Me), 1.53-1.38 (4H, m, C*H*HCH_2OH, CH_2CH_2N, C*H*HCH_2C=O), 1.43 (9H, s, OC(CH_3)$_3$), 1.38-1.26 (2H, CH*H*CH_2OH, CH*H*CH_2C=O), 0.87 (3H, d, *J* 6.7, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 155.9 (NC=O), 139.7 (*ipso*-Ar-*C*), 129.1 (2 x *meta*-Ar-CH), 128.1 (2 x *ortho*-Ar-CH), 127.7 (*para*-Ar-CH), 96.4 (OCOH), 79.6 (O*C*(CH_3)$_3$), 59.7 (*C*H_2OH), 50.7 (NCH_2Ph), 50.4 (CH*C*H_2C(O)OH), 47.1 (*C*H_2N), 42.9 (CH_2*C*H_2C(O)OH), 40.4 (*C*H_2CH_2OH), 29.0 (OC(*C*H_3)$_3$), 28.2 (*C*H_2CH_2N), 26.8 (*C*HMe), 21.5 (*C*H_2CH_2C(O)OH), 20.7 (*C*H_3); ν_{max} (film)/cm^{-1} 3444 (br, OH), 2949, 1693 (C=O), 1455, 1417, 1366, 1245, 1169, 1092, 987, 878, 771, 734, 700; HRMS (ES$^+$) calcd for $C_{22}H_{35}NNaO_4^+$ 400.2458, found 400.2463.

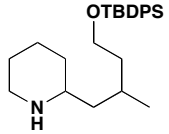
tert-Butyl benzyl(9-((tert-butyldiphenylsilyl)oxy)-7-methyl-5-oxononyl)carbamate (202)



Tert-butyldiphenylchloro silane (0.39 mL, 1.50 mmol) was added to a stirred solution of alcohol **186** (252 mg, 0.76 mmol), imidazole (154 mg, 2.26 mmol) and DMAP (10 mg, 0.08 mmol) in DMF (0.8 mL) at 0 ˚C. The reaction mixture was warmed to RT and stirred for 12 h. pH 7 buffer was added (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30

mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the silyl ether **202** (316 mg, 68 %) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.64 (4H, dd, *J* 6.1, 1.2, SiAr-C*H*), 7.50-7.37 (6H, m, SiAr-C*H*), 7.32 (2H, t, *J* 7.4, Ar-C*H*), 7.24 (3H, t, *J* 7.1, Ar-C*H*), 4.38 (2H, s, NCH_2Ph), 3.72 (2H, td, *J* 6.4, 2.0, CH_2OSi), 3.15 (2H, t, *J* 6.4, CH_2N), 2.37 (1H, dd, *J* 15.8, 5.7, CHC*H*HC=O), 2.33 (2H, t, *J* 6.5, CH_2CH_2C=O), 2.22 (1H, dd, *J* 15.9, 7.6, CHCH*H*C=O), 2.12 (1H, sextet, *J* 6.5, C*H*Me), 1.57 (1H, sextet, C*H*HCH_2OSi), 1.51-1.35 (5H, m, CH_2CH_2N, CH_2CH_2C=O, CH*H*CH_2OSi), 1.42 (9H, s, OC(CH_3)$_3$), 1.04 (9H, s, SiC(CH_3)$_3$), 0.84 (3H, d, *J* 6.6, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.1 (*C*=O), 156.0 (N*C*=O), 139.7 (*ipso*-Ar-*C*), 135.9 (*ortho*-SiAr-*C*H), 134.6 (*ipso*-SiAr-*C*), 130.5 (*para*-SiAr-*C*H), 129.1 (*meta*-Ar-*C*H), 128.5 (*meta*-SiAr-*C*H), 128.1 (*ortho*-Ar-*C*H), 127.7 (*para*-Ar-*C*H), 79.6 (O*C*(CH$_3$)$_3$), 62.7 (*C*H$_2$OSi), 50.8 (NCH$_2$Ph), 50.3 ($CHCH_2$C=O), 47.1 (*C*H$_2$N), 42.9 (CH_2CH_2C=O), 39.9 (*C*H$_2$CH$_2$OSi), 29.0 (OC(*C*H$_3$)$_3$), 28.2 (*C*H$_2$CH$_2$N), 27.6 (SiC(*C*H$_3$)$_3$), 26.6 (*C*HMe), 21.5 (CH_2CH_2C=O), 20.5 (*C*H$_3$), 19.6 (Si*C*(CH$_3$)$_3$); ν_{max} (film)/cm^{-1} 2931, 1693 (C=O), 1455, 1416, 1365, 1245, 1168, 1111, 823, 738, 702; HRMS (ES$^+$) calcd for $C_{38}H_{53}NNaO_4Si^+$ 638.3636, found 638.3646.

2-(4-((tert-Butyldiphenylsilyl)oxy)-2-methylbutyl)piperidine (203)

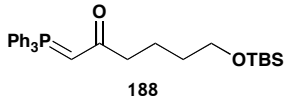


203

TFA (0.5 mL) was added dropwise to a stirred solution of amine **202** (50 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) at 0 ˚C. The resulting solution was stirred for 5 min before being warmed to RT and stirred for a further 10 min. The solvent was removed *in vacuo* and the residue was redissolved in EtOH (1 mL). Palladium on carbon (5 mg, 10 wt% Pd) and triethylamine (0.11 mL, 0.81 mmol) were added and the resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™

using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (Et_2O) to yield the piperidine **203** (19 mg, 58 %) as a pale yellow oil: δ_H (500 MHz, $CDCl_3$) 7.68 (4H, dd,, *J* 7.9, 1.4, SiAr-C*H*), 7.46-7.38 (6H, m, SiAr-C*H*), 3.76-3.67 (2H, m, CH_2OSi), 3.11 (1H, br d, *J* 10.5, C*H*N), 2.69-2.56 (2H, m, CH_2N), 1.85-1.56 (9H, m, N*H*, CH_2CH$_2$N, CH_2CH$_2$CH$_2$N, C*H*HCHN, C*H*Me, CH_2CH$_2$OSi), 1.43-1.25 (3H, m, CH*H*CHN, NCHCH_2CHMe), 1.07 (9H, s, SiC(CH_3)$_3$), 0.85 (3H, d, *J* 6.6, CH_3); δ_C (125 MHz, $CDCl_3$) 135.6 (*ortho*-SiArCH), 134.1 (*ipso*-SiAr*C*), 129.6 (*para*-SiArCH), 127.6 (*meta*-SiArCH), 61.9 (*C*H$_2$OSi), 54.5 (*C*HN), 46.7 (*C*H$_2$N), 39.6 (NCH*C*H$_2$CHMe), 34.3 (*C*H$_2$CH$_2$OSi), 30.4 (*C*H$_2$CHN), 29.7 (*C*H$_2$CH$_2$N), 26.9 (SiC(*C*H$_3$)$_3$), 25.8 (*C*HMe), 25.6 (*C*H$_2$CH$_2$CH$_2$N), 20.0 (Si*C*(CH$_3$)$_3$), 19.2 (*C*H$_3$); ν_{max} (film)/cm^{-1} 3400 (br, w, NH), 2930, 1111, 823, 738, 703; HRMS (ES^+) calcd for $C_{26}H_{40}NOSi^+$ 410.2874, found 410.2872.

6-((*tert*-Butyldimethylsilyl)oxy)-1-(triphenylphosphoranylidene)hexan-2-one (188)

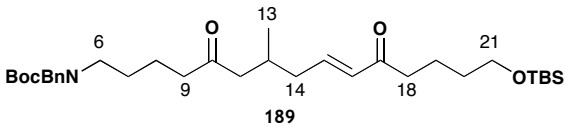


188

n-BuLi (1.6 M in hexanes, 0.59 mL, 0.95 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (339 mg, 0.95 mmol) in THF (5 mL) at 0 ˚C and the resulting solution was stirred for 5 min before being warmed to room temperature and stirred for a further 4 h. The solution was cooled to -78 ˚C and *δ*-valerolactone (44 *μ*L, 0.48 mmol) was added, forming a yellow precipitate. The mixture was warmed to room temperature and stirred for 1 h before the solvent was removed *in vacuo*. The residue was redissolved in DMF (5 mL) and cooled to -5 ˚C before the addition of imidazole (97 mg, 1.43 mmol) and TBSCl (143 mg, 0.95 mmol). The mixture was allowed to warm slowly to room temperature and stirred for 12 h. Et_2O (5 mL) and water (5 mL) were added and the organic layer was washed with water (3 x 2.5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL) then the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield ylid **188** (235 mg, quant.) as a yellow oil which was used without further purification: δ_H (400 MHz, $CDCl_3$) 7.75-7.58 (6H, m, PAr-C*H*), 7.56-

7.40 (9H, m, PAr-C*H*), 3.58 (2H, t, *J* 6.1, CH_2OSi), 2.89 (1H, d, $J_{H\text{-}P}$ 25.9, C*H*P), 2.38 (2H, t, *J* 7.1, CH_2C=O), 1.80-1.66 (2H, m, CH_2CH$_2$C=O), 1.65-1.53 (2H, m, CH_2CH$_2$OSi), 0.88 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 193.8 (*C*=O), 133.0 (d, $J_{C\text{-}P}$ 9.1, PAr-*C*H), 132.1 (d, $J_{C\text{-}P}$ 3.0, PAr-*C*H), 132.0 (PAr-*C*H), 131.8 (d, $J_{C\text{-}P}$ 3.0, PAr-*C*H), 130.5 (d, $J_{C\text{-}P}$ 10.4, PAr-*C*H), 128.9 (d, $J_{C\text{-}P}$ 13.4, PAr-*C*), 128. 8 (PAr-*C*H), 128.7 (PAr-*C*H), 128.6 (PAr-*C*H), 125.3 (PAr-*C*H), 61.6 (*C*H$_2$OSi), 40.4 (*C*H$_2$C=O), 36.5 (*C*HP), 32.5 (*C*H$_2$CH$_2$OSi), 25.8 (SiC(*C*H$_3$)$_3$), 22.5 (*C*H$_2$CH$_2$C=O), 18.1 (Si*C*(CH$_3$)$_3$), -3.5 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 3350 (br), 3057, 2929, 2856, 1518, 1438, 1406, 1314, 1254, 1184, 1108, 884, 835, 745, 717, 694; HRMS (ES$^+$) calcd for $C_{30}H_{40}O_2PSi^+$ 491.2530, found 491.2533.

(E)-tert-Butyl benzyl(15-((tert-butyldimethylsilyl)oxy)-7-methyl-5,11-dioxopentadec-9-en-1-yl)carbamate (189)

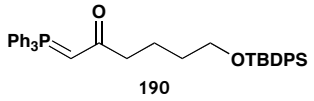


189

Oxalyl chloride (79 μL, 0.9 mmol) was added dropwise to a stirred solution of DMSO (128 μL, 1.8 mmol) in CH_2Cl_2 (1.5 mL) at -78 ˚C and the resulting solution was stirred at -78 ˚C for 0.5 h. A cooled (-78 ˚C) solution of alcohol **186** (100 mg, 0.3 mmol) in CH_2Cl_2 (1.5 mL) was added and the resulting mixture stirred at -78 ˚C for a further 0.5 h. Triethylamine (0.84 mL, 6.0 mmol) was added and the mixture stirred for 5 min before warming to room temperature. Water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was redissolved in Et_2O and filtered before the solvent was removed *in vacuo*. The residue was redissolved in THF (2.5 mL) and a solution of the ylid **188** (235 mg, 0.48 mmol) in THF (2.5 mL) was added *via* cannula. The resulting mixture was stirred for 16 h before the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the diketone **189** (82 mg, 46 %) as a colourless oil: δ_H (400 MHz, $(CD_3)_2SO$)

7.32 (2H, t, *J* 7.1, Ar-C*H*), 7.23 (3H, dd, *J* 16.0, 6.3, Ar-C*H*), 6.75 (1H, dt, *J* 15.9, 6.8, H^{15}), 6.03 (1H, d, *J* 16.0, H^{16}), 4.35 (2H, s, NCH_2Ph), 3.56 (2H, t, *J* 6.1, CH_2OSi), 3.09 (2H, br d, *J* 18.1, CH_2N), 2.56 (2H, t, *J* 7.3, 2 x H^{18}), 2.42-2.31 (3H, m, H^{11}, 2 x H^{9}), 2.25 (1H, dd, *J* 16.4, 6.4, H^{11}), 2.18-2.00 (3H, m, H^{12}, 2 x H^{14}), 1.52 (2H, qn, *J* 7.1, 2 x H^{19}), 1.47-1.29 (15H, m, 2 x H^{7}, 2 x H^{8}, 2 x H^{20}, OC(CH_3)$_3$), 0.84 (9H, s, SiC(CH_3)$_3$), 0.83 (3H, d, *J* 6.1, CH_3), 0.01 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $(CD_3)_2SO$) 210.4 (C^{10}), 200.5 (C^{17}), 156.0 (N*C*=O), 146.1 (C^{15}), 139.5 (C^{4}), 132.5 (C^{16}), 129.2 (Ar-*C*H), 128.1 (Ar-*C*H), 127.8 (Ar-*C*H), 79.5 (O*C*(CH$_3$)$_3$), 63.1 (C^{21}), 50.0 (C^{5}), 49.3 (C^{11}), 46.8 (C^{6}), 42.8 (C^{9}), 39.7 (C^{18}), 39.5 (C^{14}), 32.6 (C^{20}), 28.8 (OC(*C*H$_3$)$_3$), 28.8 (C^{7}), 28.8 (C^{12}), 26.6 (SiC(*C*H$_3$)$_3$), 21.1 (C^{19}), 21.1 (C^{8}), 20.4 (C^{13}), 18.7 (Si*C*(CH$_3$)$_3$), -4.5 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 2930, 1694 (C=O), 1607 (C=C), 1455, 1416, 1366, 1251, 1170, 1101, 837, 776, 700; HRMS (ES$^+$) calcd for $C_{34}H_{58}NO_5Si^+$ 588.4079, found 588.4068.

6-((tert-Butyldiphenylsilyl)oxy)-1-(triphenylphosphoranylidene)hexan-2-one (190)

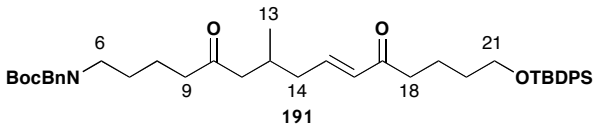


190

n-BuLi (1.6 M in hexanes, 3.3 mL, 5.1 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (1.83 g, 5.1 mmol) in THF (27 mL) at 0 ˚C and the resulting solution was stirred for 5 min before being warmed to RT and stirred for a further 4 h. The solution was cooled to -78 ˚C and *δ*-valerolactone (234 *μ*L, 2.6 mmol) was added, forming a yellow precipitate. The mixture was warmed to room temperature and stirred for 1 h before the solvent was removed *in vacuo*. The residue was redissolved in DMF (10 mL) and cooled to -5 ˚C before the addition of imidazole (522 mg, 7.70 mmol) and TBDPSCl (1.33 mL, 5.11 mmol). The mixture was allowed to warm slowly to RT and stirred for 12 h. Et_2O (27 mL) and water (27 mL) were added and the organic layer was washed with water (3 x 14 mL). The combined aqueous layers were extracted with EtOAc (3 x 27 mL) then the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield ylid **190** (1.598 g, quant.) as a yellow oil which was used without further

purification: δ_H (400 MHz, $CDCl_3$) 7.83-7.61 (10H, m, Ar-C*H*), 7.57-7.33 (9H, m, PAr-C*H*), 3.70 (2H, t, *J* 6.4, CH_2OSi), 2.90 (1H, d, $J_{H\text{-}P}$ 21.0, C*H*P), 2.38 (2H, s, CH_2C=O), 1.65-1.54 (2H, m, CH_2CH$_2$C=O), 1.42 (2H, sextet, *J* 7.5, CH_2CH$_2$OSi), 1.08 (9H, s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 192.7 (*C*=O), 135.9 (Ar-*C*H), 135.6 (Ar-*C*H), 134.9 (Ar-*C*H), 134.2 (Ar-*C*H), 133.0 (d, $J_{C\text{-}P}$ 11.4, PAr-*C*H), 132.1 (d, $J_{C\text{-}P}$ 10.4, PAr-*C*H), 131.8 (PAr-*C*H), 130.5 (d, $J_{C\text{-}P}$ 10.4, PAr-*C*H), 129.5 (Ar-*C*), 129.4 (Ar-*C*H), 129.1 (PAr-*C*H), 128.9 (d, $J_{C\text{-}P}$ 4.2, PAr-*C*H), 128.8 (d, $J_{C\text{-}P}$ 4.2, PAr-*C*H), 128.7 (d, $J_{C\text{-}P}$ 11.4, PAr-*C*H), 128.2 (Ar-*C*H), 127.6 (Ar-*C*H), 63.7 (*C*H$_2$OSi), 40.6 (*C*H$_2$C=O), 36.5 (*C*HP), 34.8 (*C*H$_2$CH$_2$OSi), 26.7 (SiC(*C*H$_3$)$_3$), 21.5 (*C*H$_2$CH$_2$C=O), 19.1 (Si*C*(CH$_3$)$_3$); ν_{max} (film)/cm^{-1} 3150 (br), 3070, 2931, 2856, 1668, 1473, 1428, 1184, 1111, 884, 822, 742, 703, 607; HRMS (ES$^+$) calcd for $C_{40}H_{44}O_2PSi^+$ 615.2843, found 615.2844.

(E)-tert-Butyl benzyl(15-((tert-butyldiphenylsilyl)oxy)-7-methyl-5,11-dioxopentadec-9-en-1-yl)carbamate (191)

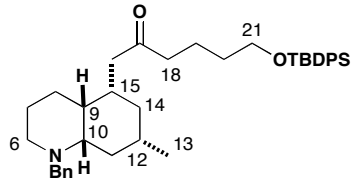


191

N-Methyl-morpholine-*N*-oxide (297 mg, 2.43 mmol) and activated powdered 4 Å MS (810 mg) were added to a stirred solution of alcohol **186** (611 mg, 1.62 mmol) in CH_2Cl_2 (12.2 mL) and MeCN (1.35 mL). The mixture was stirred for 15 min before TPAP (27 mg, 0.081 mmol) was added in one portion. The mixture was stirred for 14 h before the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2, filtered through a pad of silica and the solvent removed *in vacuo*. The residue was redissolved in THF (13.5 mL) and a solution of the ylid **190** (1.60 g, 2.61 mmol) in THF (13.5 mL) was added *via* cannula. The resulting mixture was stirred for 16 h before the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the diketone **191** (668 mg, 58 %) as a pale yellow oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.67-7.62 (4H, m, SiAr-C*H*), 7.48-7.40 (6H, m, SiAr-C*H*), 7.33 (2H, t, *J* 7.4, Ar-C*H*), 7.25 (3H, t, *J* 7.2, Ar-C*H*), 6.73 (1H, dt, *J* 15.8, 7.3, H^{15}), 6.06 (1H, d, *J* 15.7, H^{16}), 4.38 (2H, s, NCH_2Ph), 3.71 (2H, t, *J* 6.2,

CH_2OSi), 3.15 (2H, br t, *J* 6.2, CH_2N), 2.54 (2H, t, *J* 7.1, 2 x H^{18}), 2.43-2.34 (3H, m, H^{11}, 2 x H^{9}), 2.27 (1H, dd, *J* 16.3, 7.0, H^{11}), 2.23-2.05 (3H, m, H^{12}, 2 x H^{14}), 1.67-1.54 (4H, m, 2 x H^{19}, 2 x H^{20}), 1.48-1.39 (4H, m, 2 x H^{7}, 2 x H^{8}), 1.42 (9H, s, OC(CH_3)$_3$), 1.04 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, d, *J* 6.4, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.1 (C^{10}), 200.1 (C^{17}), 155.9 (N*C*=O), 145.4 (C^{15}), 139.7 (C^{4}), 135.9 (*ortho*-SiAr-*C*H), 134.6 (*ipso*-SiAr-*C*), 132.5 (C^{16}), 130.5 (*para*-SiAr-*C*H), 129.1 (*meta*-Ar-CH), 128.5 (*meta*-SiAr-CH), 128.1 (*ortho*-Ar-*C*H), 127.7 (*para*-Ar-*C*H), 79.6 (O*C*(CH$_3$)$_3$), 64.3 (C^{21}), 50.7 (C^{5}), 49.5 (C^{11}), 47.1 (C^{6}), 43.0 (C^{9}), 39.8 (C^{18}), 39.7 (C^{14}), 32.5 (C^{20}), 29.1 (C^{12}), 29.0 (OC(*C*H$_3$)$_3$), 28.2 (C^{7}), 27.7 (SiC(*C*H$_3$)$_3$), 21.5 (C^{19}), 21.2 (C^{8}), 20.4 (C^{13}), 19.7 (Si*C*(CH$_3$)$_3$); ν_{max} (film)/cm^{-1} 2932, 1692 (C=O), 1604 (C=C), 1415, 1365, 1169, 1111, 703; HRMS (ES$^+$) calcd for $C_{44}H_{61}NNaO_5Si^+$ 734.4211, found 734.4213.

1-((4aR,5S,7S,8aS)-1-Benzyl-7-methyldecahydroquinolin-5-yl)-6-((tert-butyldiphenylsilyl)oxy)hexan-2-one (204)



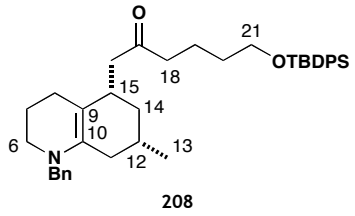
204

Method 1: TFA (0.8 mL) was added dropwise to a stirred solution of diketone **191** (80 mg, 0.12 mmol) in CH_2Cl_2 (0.8 mL) at 0 ˚C. The resulting solution was stirred for 5 min before being warmed to room temperature and stirred for a further 10 min. Dry toluene (12 mL) was added and the solvent was removed *in vacuo*. The residue was redissolved in EtOH (1.6 mL) and palladium on carbon (8 mg, 10 wt% Pd) and triethylamine (152 μL, 1.2 mmol) were added. The resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was redissolved in CH_2Cl_2 (10 mL), washed with pH 7 buffer (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo*. The

residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the decahydroquinoline **204** (35 mg, 48 %) as a pale yellow oil: δ_H (500 MHz, $CDCl_3$) 7.69-7.66 (4H, m, SiAr-C*H*), 7.45-7.21 (11H, m, SiAr-C*H*, Ar-C*H*), 4.11 (1H, d, *J* 13.2, NC*H*HPh), 3.68 (2H, t, *J* 6.3, CH_2OSi), 2.86 (1H, d, *J* 12.9, NCH*H*Ph), 2.84-2.72 (2H, m, H^6, H^{15}), 2.53 (1H, dd, *J* 15.5, 4.3, H^{16}), 2.48-2.36 (H^{10}, 2 x H^{18}), 2.18 (1H, br d, *J* 13.5, H^{11}), 2.05 (1H, dd, *J* 15.2, 9.2, H^{16}), 1.93 (1H, br s, H^{12}), 1.85-1.79 (1H, m, H^6), 1.79-1.71 (2H, m, H^8, H^{14}), 1.71-1.64 (3H, m, H^7, 2 x H^{19}), 1.59 (2H, dt, *J* 14.0, 6.6, 2 x H^{20}), 1.38-1.30 (2H, m, H^8, H^9), 1.28-1.22 (1H, m, H^7), 1.06 (9H, s, SiC(CH_3)$_3$), 1.04-0.97 (1H, m, H^{11}), 0.80 (3H, d, *J* 6.5, CH_3), 0.71 (1H, q, *J* 11.9, H^{14}); δ_C (125 MHz, $CDCl_3$) 211.6 (C^{18}), 140.4 (*ipso*-Ar-*C*), 135.6 (*ortho*-SiAr-*C*H), 134.0 (*ipso*-SiAr-*C*), 129.5 (*para*-SiAr-*C*H), 128.7 (*meta*-Ar-*C*H), 128.1 (*ortho*-Ar-*C*H), 127.6 (*meta*-SiAr-*C*H), 126.5 (*para*-Ar-*C*H), 63.6 (C^{21}), 62.3 (C^{10}), 57.1 (NCH_2Ph), 54.1 (C^6), 47.6 (C^{16}), 43.2 (C^{18}), 42.4 (C^9), 42.3 (C^{14}), 38.9 (C^{11}), 32.0 (C^{20}), 30.2 (C^{15}), 27.4 (C^8), 26.9 (SiC(*C*H_3)$_3$), 25.8 (C^{12}), 22.5 (*C*H_3), 21.2 (C^7), 20.3 (C^{19}), 19.2 (Si*C*(CH$_3$)$_3$); ν_{max} (film)/cm^{-1} 2931, 2862, 1712 (C=O), 1454, 1428, 1362, 1111, 823, 738, 702; HRMS (ES$^+$) calcd for $C_{39}H_{54}NO_2Si^+$ 596.3918, found 596.3916.

Method 2: Enamine **208** (30 mg, 0.05 mmol) was dissolved in EtOH (0.6 mL) and palladium on carbon (3 mg, 10 wt% Pd) and triethylamine (73 μL, 0.5 mmol) were added. The resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the decahydroquinoline **204** (14 mg, 47 %) as a pale yellow oil: The data was consistent with that given in *method 1*.

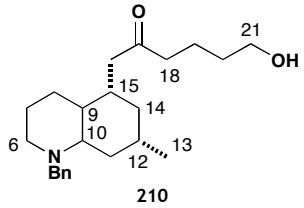
1-((5S,7S)-1-Benzyl-7-methyl-1,2,3,4,5,6,7,8-octahydroquinolin-5-yl)-6-((tert-butyldiphenylsilyl)oxy)hexan-2-one (208)



208

TFA (1.0 mL) was added dropwise to a stirred solution of diketone **191** (100 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) at 0 ˚C. The resulting solution was stirred for 5 min before being warmed to room temperature and stirred for a further 10 min. Dry toluene (15 mL) was added and the solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (2 mL), Amberlite™ IR 120 (35 mg, 0.15 mmol eq) and Amberlite™ IRA 67 (25 mg, 0.15 mmol eq) were added and the resulting mixture was stirred for 12 h. The mixture was filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1:0.01 PE 40-60:Et_2O:Et_3N) to yield the enamine **208** (25 mg, 28 %) as a yellow oil: δ_H (500 MHz, C_6D_6, major resonances) 7.92-7.89 (5H, m, SiAr-C*H*), 7.39-7.30 (10H, m, SiAr-C*H*, Ar-C*H*), 4.19 (1H, d, *J* 15.7, NC*H*HPh), 3.85 (1H, d, *J* 15.7, NCH*H*Ph), 3.76 (2H, t, *J* 6.2, 2 x H^{21}), 3.01-2.85 (2H, m, H^{16}, H^{15}), 2.75 (1H, td, *J* 11.6, 2.4, H^{16}), 2.63 (1H, dd, *J* 15.6, 4.0, H^{18}), 2.27-2.21 (3H, m, H^{11}, 2 x H^6), 2.08 (2H, m, H^{18}, H^8), 2.01-1.96 (1H, m, H^{14}), 1.85-1.77 (4H, m, H^7, H^{11}, 2 x H^{19}), 1.77-1.72 (1H, m, H^{12}), 1.71-1.60 (4H, m, H^8, H^7, 2 x H^{20}), 1.30 (9H, s, SiC(CH_3)$_3$), 0.94 (3H, d, *J* 6.4, CH_3), 0.90 (1H, q, *J* 11.6, H^{14}); δ_C (100 MHz, C_6D_6, major resonances) 209.4 (*C*=O), 141.0 (C^{10}), 137.6 (*ipso*-Ar-*C*), 135.3 (*ortho*-SiAr-*C*H), 134.0 (*ipso*-SiAr-*C*), 130.0 (*para*-SiAr-*C*H), 128.7 (*meta*-Ar-*C*H), 128.1 (*ortho*-Ar-*C*H), 127.9 (*meta*-SiAr-*C*H), 127.0 (*para*-Ar-*C*H), 106.9 (C^9), 64.0 (C^{21}), 54.3 (NCH_2Ph), 48.7 (C^{16}), 48.4 (C^{18}), 43.2 (C^6), 39.2 (C^{14}), 37.6 (C^{15}), 36.4 (C^{11}), 32.4 (C^{20}), 29.5 (C^{12}), 27.2 (SiC(CH_3)$_3$), 26.9 (C^8), 22.4 (C^{13}), 22.3 (C^7), 20.6 (C^{19}), 19.5 (Si*C*(CH_3)$_3$); ν_{max} (film)/cm^{-1} 3485 (br), 3070, 2929, 1711 (C=O), 1644 (C=C enamine), 1495, 1453, 1428, 1361, 1261, 1186, 1111, 823, 732, 702, 613; HRMS (ES$^+$) calcd for $C_{39}H_{52}NO_2Si^+$ 594.3762, found 594.3762.

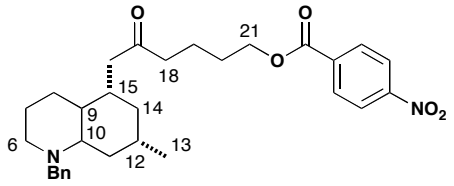
1-((5S,7S)-1-Benzyl-7-methyldecahydroquinolin-5-yl)-6-hydroxyhexan-2-one (210)



210

TBAF (1.0 M in THF, 98 mL, 0.098 mmol) was added dropwise to a stirred solution of decahydroquinoline **204** (53 mg, 0.086 mmol) in THF (0.95 mL) at 0 ˚C and the resulting mixture was allowed to warm to room temperature slowly and stirred for 14 h. The reaction was diluted with CH_2Cl_2 (10 mL) and pH 7 buffer (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (1:1 PE 40-60:Et_2O) to yield the alcohol **210** (31 mg, quant.) as a colourless oil: δ_H (500 MHz, C_6D_6) 7.34-7.20 (5H, m, Ar-C*H*), 4.15 (1H, d, *J* 13.3, NC*H*HPh), 3.54 (2H, t, *J* 6.1, 2 x H^{21}), 3.15-3.10 (2H, m, H^6), 3.07-2.98 (2H, m, H^{15}, H^{16}), 2.85 (1H, d, *J* 13.3, NCH*H*Ph), 2.38-2.33 (2H, m, H^{10}, H^{11}), 2.30-2.21 (2H, m, H^{18}), 2.15-2.07 (1H, m, H^{12}), 2.01-1.96 (1H, m, H^{14}), 1.94 (1H, dd, *J* 15.8, 8.9, H^{11}), 1.85-1.80 (2H, m, H^{16}, H^8), 1.77-1.71 (2H, m, 2 x H^{19}), 1.55-1.43 (4H, m, 2 x H^{20}, 2 x H^7), 1.31-1.27 (1H, m, H^9), 1.23-1.19 (1H, m, H^8), 0.90 (3H, d, *J* 6.4, CH_3), 0.77 (1H, q, *J* 11.8, H^{14}); δ_C (125 MHz, C_6D_6) 209.6 (*C*=O), 140.8 (*ipso*-Ar-*C*), 129.0 (*meta*-Ar-CH), 128.3 (*ortho*-Ar-CH), 126.9 (*para*-Ar-CH), 62.9 (C^{10}), 62.1 (C^{21}), 58.6 (C^6), 57.8 (C^5), 54.6 (C^{16}), 47.5 (C^{11}), 43.2 (C^{18}), 42.8 (C^{14}), 42.6 (C^9), 30.4 (C^{15}), 26.3 (C^{12}), 24.2 (C^{20}), 22.8 (CH_3), 21.6 (C^8), 20.3 (C^{19}), 20.0 (C^7); ν_{max} (film)/cm^{-1} 3407 (br), 2943, 1710 (C=O), 1453, 1067, 738, 700; HRMS (ES^+) calcd for $C_{23}H_{36}NO_2^+$ 358.2741, found 358.2740.

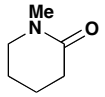
6-((5S,7S)-1-Benzyl-7-methyldecahydroquinolin-5-yl)-5-oxohexyl 4-nitrobenzoate (211)



211

Triethylamine (33 μL, 0.23 mmol) followed by 4-nitrobenzoyl chloride (23 mg, 0.12 mmol) were added to a stirred solution of alcohol **210** (36 mg, 0.077 mmol) in CH_2Cl_2 (1.3 mL) at 0 ˚C. The mixture was allowed to warm to room temperature and stirred for 14 h. The reaction was diluted with CH_2Cl_2 (10 mL) and pH 7 buffer (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Et_2O) to yield the ester **211** (36 mg, 92 %) as a yellow oil: δ_H (500 MHz, C_6D_6) 7.89 (2H, d, *J* 8.7, *ortho* NO_2-Ar-C*H*), 7.80 (2H, d, *J* 8.9, *meta*-NO_2-Ar-C*H*), 7.46 (2H, d, *J* 7.4, *ortho*-Ar-C*H*), 7.30 (2H, t, *J* 7.3, *meta*-Ar-C*H*), 7.22 (1H, t, *J* 7.3, *para*-Ar-C*H*), 4.19 (2H, t, *J* 6.5, CH_2O), 4.14 (1H, d, *J* 13.2, NC*H*HPh), 3.07-2.97 (2H, m, H^{15}, H^{6}), 2.85 (1H, d, *J* 13.2, NCH*H*Ph), 2.37-2.33 (2H, m, H^{16}, H^{10}), 2.23-2.08 (4H, m, H^{11}, 2 x H^{18}, H^{12}), 1.97 (1H, ddd, *J* 12.6, 5.6, 3.5, H^{14}), 1.92 (1H, dd, *J* 15.7, 8.9, H^{16}), 1.83 (1H, td, *J* 12.6, 2.3, H^{6}), 1.78 (1H, dt, *J* 12.6, 3.3, H^{7}), 1.73 (1H, dd, *J* 14.1, 2.3, H^{8}), 1.69-1.61 (2H, m, 2 x H^{19}), 1.60-1.52 (2H, m, 2 x H^{20}), 1.36 (1H, dt, *J* 13.6, 4.1, H^{8}, 1.29 (1H, br dt, *J* 13.6, 2.5, H^{9}), 1.24-1.19 (1H, m, H^{7}), 1.01-0.94 (1H, m, H^{11}), 0.89 (3H, d, *J* 6.6, CH_3), 0.78 (1H, q, *J* 11.9, H^{14}); δ_C (125 MHz, C_6D_6) 208.6 (*C*=O), 164.5 (O*C*=O), 150.6 (*ipso*-NO_2-Ar*C*), 140.6 (*ipso*-Ar-*C*), 135.5 (*para*-NO_2-Ar-*C*), 130.5 (*meta*-NO_2-Ar-*C*H), 129.0 (*ortho*-Ar-*C*H), 128.6 (*meta*-Ar-*C*H), 127.0 (*para*-Ar-*C*H), 123.5 (*ortho*-NO_2-Ar-*C*H), 65.4 (CH_2O), 62.8 (C^{10}), 57.7 (NCH_2Ph), 54.5 (C^{6}), 47.6 (C^{16}), 42.8 (C^{14}), 42.6 (C^{9}), 42.5 (C^{18}), 39.1 (C^{11}), 30.5 (C^{15}), 28.3 (C^{20}), 27.8 (C^{8}), 26.2 (C^{12}), 22.7 (CH_3), 21.6 (C^{7}), 20.2 (C^{19}); ν_{max} (film)/cm^{-1} 2945, 1726 (C=O), 1607 (C=O), 1528, 1453, 1349, 1276, 1103, 1015, 874, 720, 701; HRMS (ES^+) calcd for $C_{30}H_{39}N_2O_5^+$ 507.2853, found 507.2853.

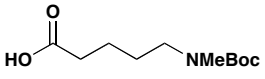
1-Methylpiperidin-2-one (194)



194

NaH (60 % suspension in mineral oil, 378 mg, 9.45 mmol) was added slowly to a solution of *δ*-valerolactam (891 mg, 9.00 mmol) in THF (42 mL) at 0 ˚C and the resulting mixture was stirred for 30 min. Methyl iodide (0.59 mL, 9.45 mmol) was added and the reaction was allowed to warm to room temperature and stirred vigorously for 5 h. Methanol was added (6 mL) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (19:1 Et_2O:MeOH) to yield lactam **194** (714 mg, 70 %) as a pale yellow volatile oil: δ_H (400 MHz, $CDCl_3$) 3.24 (2H, t, *J* 5.8, CH_2N), 2.90 (3H, s, CH_3N), 2.33 (2H, t, *J* 6.2, CH_2C=O), 1.82-1.71 (4H, m, CH_2CH$_2$N, CH_2CH$_2$C=O); δ_C (100 MHz, $CDCl_3$) 169.9 (*C*=O), 50.0 (*C*H$_2$N), 34.6 (*C*H$_3$N), 32.2 (*C*H$_2$C=O), 23.1 (*C*H$_2$CH$_2$C=O), 21.4 (*C*H$_2$CH$_2$N); ν_{max} (film)/cm^{-1} 3474 (br), 2945, 1633 (C=O), 1508, 1449, 1402, 1355, 1332, 1244, 1172, 1042, 968; LRMS (ES$^+$) calcd for $C_6H_{12}NO^+$ 114.09, found 114.08. These data are consistent with the literature.[109]

5-((tert-Butoxycarbonyl)(methyl)amino)pentanoic acid (195)

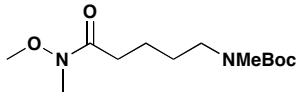


195

Concentrated sulfuric acid (0.7 mL), was added to a solution of lactam **194** (1.15 g, 10.1 mmol) in water (11.5 mL) and the resulting mixture was heated to 100 ˚C for 16 h. After cooling to room temperature, solid barium hydroxide was added until the solution reached pH 10. The mixture was filtered and solid CO_2 was added to the filtrate until it reached pH 6. The mixture was filtered through Celite™ and the solvent removed *in vacuo*. The residue was redissolved in dioxane:water (2:1, 30.3 mL) and NaOH (1 M in water, 20.2 mL) was added. The solution was cooled to 0 ˚C, di-*tert*-butyldicarbonate (2.42 g, 11.2 mmol) was

added and the resulting mixture was allowed to warm to RT and stirred for 14 h. EtOAc was added to cover the aqueous layer and $KHSO_4$ (1 M in water) was added until the solution reached pH 2. The aqueous phase was extracted with EtOAc (6 x 20 mL) and the combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to yield acid **195** (1.38 g, 59 %) as a pale yellow oil which was used without further purification: δ_H (400 MHz, $CDCl_3$) 9.13 (1H, br, O*H*), 3.20 (2H, br s, CH_2N), 2.81 (3H, s, CH_3N), 2.35 (2H, t, *J* 7.0, CH_2C=O), 1.66-1.48 (4H, m, CH_2CH$_2$N, CH_2CH$_2$C=O), 1.42 (9H, s, OC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 178.5 (O*C*=O), 155.9 (N*C*=O), 79.5 (O*C*(CH$_3$)$_3$), 50.0 (*C*H$_2$N), 34.1 (*C*H$_3$N), 33.6 (*C*H$_2$C=O), 28.4 (OC(*C*H$_3$)$_3$), 27.4 (*C*H$_2$CH$_2$C=O), 21.7 (*C*H$_2$CH$_2$N); ν_{max} (film)/cm^{-1} 3100 (br, OH), 2977, 1710 (C=O), 1695 (C=O), 1399, 1368, 1166, 1071, 877, 773; HRMS (ES$^+$) calcd for $C_{11}H_{21}NNaO_4^+$ 254.1363, found 254.1370.

tert-Butyl (5-(methoxy(methyl)amino)-5-oxopentyl)(methyl)carbamate (196)

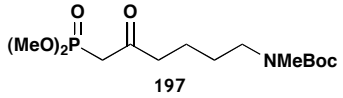


196

iso-Butyl chloroformate (1.1 mL, 8.3 mmol) was added dropwise to a stirred solution of acid **195** (1.64 g, 7.0 mmol) and *N*-methyl morpholine (0.92 mL, 8.3 mmol) in CH_2Cl_2 (16 mL) at -15 ˚C and the resulting solution was stirred for 45 min. *N*,*O*-dimethylhydroxylamine hydrochloride (1.72 g, 17.7 mmol) was added and the resulting mixture was stirred for a further 3 h at -15 ˚C. Aqueous sodium bicarbonate (16 mL) was added slowly and the aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (Et_2O) to yield the Weinreb amide **196** (1.44 g, 75 %) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 3.64 (3H, s, OCH_3), 3.18 (2H, br s, CH_2N), 3.13 (3H, s, ONCH_3), 2.79 (3H, s, CH_3N), 2.41 (2H, t, *J* 6.6, CH_2C=O), 1.62-1.47 (4H, m, CH_2CH$_2$C=O, CH_2CH$_2$N), 1.41 (9H, s, OC(CH_3)$_3$): δ_C (100 MHz, $CDCl_3$) 174.2

(NC=O), 155.7 (OC=O), 79.1 (OC(CH$_3$)$_3$), 61.1 (OCH$_3$), 48.3 (CH$_2$N), 34.0 (CH$_3$N), 32.1 (ONCH$_3$), 31.2 (CH$_2$C=O), 28.4 (OC(CH$_3$)$_3$), 27.4 (CH$_2$CH$_2$C=O), 21.6 (CH$_2$CH$_2$N); ν_{max} (film)/cm^{-1} 2937, 1694 (C=O), 1393, 1366, 1254, 1169, 999, 878, 772; HRMS (ES$^+$) calcd for $C_{13}H_{26}N_2NaO_4^+$ 297.1785, found 297.1787.

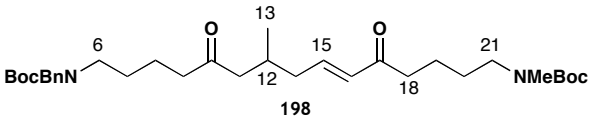
tert-Butyl (6-(dimethoxyphosphoryl)-5-oxohexyl)(methyl)carbamate (197)



197

A solution of dimethyl methyl phosphonate (1.9 mL, 17.9 mmol) in THF (9.5 mL) was added slowly to *n*BuLi (1.6 M in hexanes, 10.1 mL, 16.2 mmol) at -78 ˚C and the resulting solution was stirred for 30 min. A cooled (-78 ˚C) solution of Weinreb amide **196** (900 mg, 3.3 mmol) in THF (4.8 mL) was added and the resulting mixture was stirred for 1 h at -78 ˚C before the cold bath was removed and phosphoric acid (2 M in water, 9.5 mL) was added. The reaction was partitioned between Et$_2$O (12.3 mL) and phosphoric acid (2 M in water, 9.5 mL) and the aqueous layer was extracted with Et$_2$O (8.2 mL). The combined organic extracts were washed with brine (8.0 mL), dried (MgSO$_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (1:99 MeOH:Et$_2$O) to yield phosphonate **197** (970 mg, 88 %) as a pale yellow oil: δ_H (400 MHz, CDCl$_3$) 3.74 (6H, d, $J_{P\text{-}H}$ 11.0, (CH$_3$O)$_2$OP), 3.15 (2H, br s, CH$_2$N), 3.04 (2H, d, $J_{P\text{-}H}$ 22.9, CH$_2$P), 2.77 (3H, s, CH$_3$N), 2.61 (2H, t, *J* 6.7, CH$_2$C=O), 1.57-1.42 (4H, m, CH$_2$CH$_2$N, CH$_2$CH$_2$C=O), 1.40 (9H, s, OC(CH$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 201.4 (C=O), 155.7 (NC=O), 79.2 (OC(CH$_3$)$_3$), 53.0 (d, $J_{C\text{-}P}$ 6.3, (CH$_3$O)$_2$P), 48.1 (d, $J_{C\text{-}P}$ 81.2, CH$_2$C=O), 43.6 (CH$_2$N), 41.2 (d, $J_{C\text{-}P}$ 128.5, CH$_2$P), 34.0 (CH$_3$N), 28.4 (OC(CH$_3$)$_3$), 26.9 (d, $J_{C\text{-}P}$ 51.4, CH$_2$CH$_2$C=O), 20.3 (CH$_2$CH$_2$N); ν_{max} (film)/cm^{-1} 3490, 2957, 1694 (C=O), 1456, 1397, 1362, 1258, 1167, 1032, 879, 812; HRMS (ES$^+$) calcd for $C_{14}H_{28}NNaO_6P^+$ 360.1546, found 360.1544.

(E)-tert-Butyl (15-(benzyl(tert-butoxycarbonyl)amino)-9-methyl-5,11-dioxopentadec-6-en-1-yl)(methyl)carbamate (198)

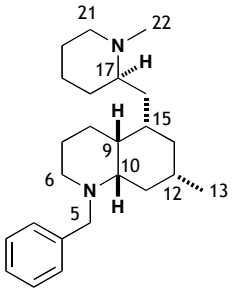


198

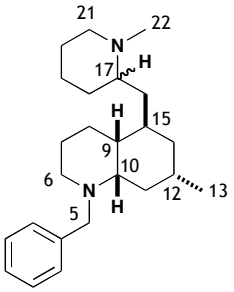
Oxalyl chloride (160 μL, 1.86 mmol) was added dropwise to a stirred solution of DMSO (270 μL, 3.72 mmol) in CH_2Cl_2 (3.1 mL) at -78 ˚C and the resulting solution was stirred at -78 ˚C for 0.5 h. A cooled (-78 ˚C) solution of alcohol **186** (207 mg, 0.62 mmol) in CH_2Cl_2 (3.1 mL) was added and the resulting mixture stirred at -78 ˚C for a further 0.5 h. Triethylamine (1.7 mL, 12.40 mmol) was added and the mixture stirred for 5 min before warming to room temperature. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 12 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was redissolved in Et_2O and filtered before the solvent was removed *in vacuo* to yield crude aldehyde. Sodium hydride (60 wt% dispersion in mineral oil, 30 mg, 0.76 mmol) was added to a solution of phosphonate **197** (262 mg, 0.76 mmol) in THF (7 mL) at 0 ˚C and the resulting mixture was stirred for 20 min before being cooled to -78 ˚C and stirred for a further 30 min. Crude aldehyde in THF (7 mL) was added *via* cannula and the resulting mixture was allowed to warm to RT and stirred for 16 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Et_2O) to yield diketone **198** (134 mg, 37 %) as a pale yellow oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.33 (2H, t, *J* 7.3, Ar-C*H*), 7.25 (3H, t, *J* 8.5, Ar-C*H*), 6.76 (1H, dt, *J* 15.9, 7.1, H^{15}), 6.08 (1H, d, *J* 15.9, H^{16}), 4.39 (2H, s, NCH_2Ph), 3.21-3.12 (4H, m, 2 x H^6, 2 x H^{21}), 2.77 (3H, s, CH_3N), 2.57 (2H, t, *J* 6.7, 2 x H^{18}), 2.41 (1H, dd, *J* 16.5, 5.6, H^{11}), 2.37 (2H, t, *J* 6.6, 2 x H^9), 2.28 (1H, dd, *J* 16.5, 7.1, H^{11}), 2.24-2.17 (1H, m, H^{14}), 2.17-2.07 (2H, m, H^{12}, H^{14}), 1.56-1.47 (2H, m, 2 x H^{20}), 1.47-1.44 (2H, m, 2 x H^8), 1.44-1.40 (4H, m, 2 x H^7, 2 x H^{19}), 1.42 (9H, s, OC(CH_3)$_3$), 1.41 (9H, s, OC(CH_3)$_3$), 0.89 (3H, d, *J* 6.3, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.2 (C^{10}), 200.2 (C^{17}), 155.9 (N*C*=O), 155.8 (N*C*=O), 145.5 (C^{15}), 139.7 (*ipso*-Ar*C*), 132.6 (C^{16}), 129.2 (*meta*-Ar-C*H*), 128.1 (*ortho*-Ar-CH),

127.7 (*para*-Ar-CH), 79.6 ($OC(CH_3)_3$), 79.1 ($OC(CH_3)_3$), 50.8 (NCH_2Ph), 49.5 (C^{11}), 48.6 (C^{21}),47.1 (C^6), 43.0 (C^9), 39.8 (C^{18}), 39.7 (C^{14}), 34.5 (CH_3N), 29.1 (C^{12}), 29.0 ($OC(CH_3)_3$), 29.0 ($OC(CH_3)_3$), 28.2 (C^{20}), 27.8 (C^7), 21.9 (C^8), 21.5 (C^{19}), 20.4 (CH_3); ν_{max} (film)/cm^{-1} 2932, 1692 (C=O), 1366, 1166; HRMS (ES^+) calcd for $C_{34}H_{55}N_2O_6^+$ 587.4055, found 587.4056.

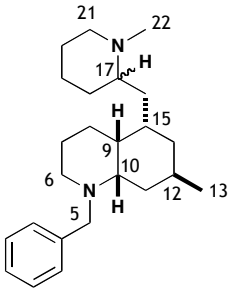
(4aR,5S,7S,8aS)-1-Benzyl-7-methyl-5-(((R)-1-methylpiperidin-2-yl)methyl)decahydroquinoline, (4aR,5R,7S,8aS)-1-benzyl-7-methyl-5-((1-methylpiperidin-2-yl)methyl)decahydroquinoline (347) and ***(4aR,5S,7R,8aS)-1-benzyl-7-methyl-5-((1-methylpiperidin-2-yl)methyl)decahydroquinoline (348)***



347



348



349

Method 1: TFA (0.25 mL) was added dropwise to a stirred solution of diketone **198** (50 mg, 0.09 mmol) in CH_2Cl_2 (0.75 mL) at RT. The resulting solution was stirred for 1 h before toluene (7.5 mL) was added and the solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (1.0 mL), Amberlite™ IR 120 (18 mg, 0.09 mmol eq) and Amberlite™ IRA 67 (16 mg, 0.09 mmol eq) were added and the resulting mixture was stirred for 12 h. The mixture was filtered and the solvent removed *in vacuo*. The residue was redissolved in EtOH (1.0 mL) and palladium on carbon (5 mg, 10 wt% Pd) was added. The resulting mixture was flushed five times with hydrogen and placed under an atmosphere of hydrogen at a pressure of 5 bar. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (10:1 CH_2Cl_2:NH_3) to yield the tricycles **347** (7 mg, 22 %), **348** (4 mg, 13 %) and **349** (unable to isolate and characterize) as colourless oils:

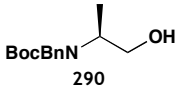
347: δ_H (700 MHz, $CDCl_3$) 7.36-7.7.29 (4H, m, Ar-*H*), 7.24 (1H, t, *J* 6.4, Ar-*H*), 4.09 (1H, d, *J* 13.4, NC*H*HPh), 2.91 (1H, d, *J* 13.4, NCH*H*Ph), 2.85 (1H, br d, *J* 11.8, H^{21}), 2.79 (1H, br d, *J* 10.6, H^6), 2.37 (1H, br d, *J* 1.9, H^{10}), 2.31 (3H, s, NCH_3), 2.18 (1H, br dd, *J* 14.3, 1.9, H^{11}), 2.16-2.10 (2H, m, H^9, H^{21}), 2.02-1.93 (3H, m, H^8, H^{16}, H^{17}), 1.93-1.87 (2H, m, H^{12}, H^{14}), 1.82 (1H, br td, *J* 12.1, 1.6, H^6), 1.79-1.69 (2H, m, H^{18}, H^{19}), 1.64-1.55 (3H, m, H^7, 2 x H^{20}), 1.36-1.30 (3H, m, H^{19}, H^8, H^{18}), 1.30-1.24 (2H, m, H^7, H^{15}), 1.00 (1H, qn, *J* 13.2, H^{11}), 0.84 (3H, d, *J* 6.3, 3 x H^{13}), 0.79 (1H, qn, *J* 7.8, H^{16}), 0.65 (1H, q, *J* 11.8, H^{14}); δ_C (175 MHz, $CDCl_3$) 140.5 (*ipso*-Ar-*C*), 128.8 (*ortho*-Ar-*C*H), 128.1 (*meta*-Ar-*C*H), 126.5 (*para*-Ar-*C*H), 62.7 (C^{17}), 62.4 (C^{10}), 57.2 (NCH_2Ph), 56.9 (C^{21}), 54.2 (C^6), 43.6 (C^{14}), 43.5 (C^{15}), 42.9 (NCH_3), 38.8 (C^{11}, C^{16}), 33.3 (C^{18}), 32.1 (C^9), 27.3 (C^8), 26.0 (C^{12}), 25.6 (C^{20}), 24.5 (C^{19}), 22.8 (C^{13}), 21.9 (C^7); ν_{max} (film)/cm^{-1} 2929, 2863, 2782, 1454, 1360, 1152, 734, 699; HRMS (ES^+) calcd for $C_{24}H_{39}N_2^+$ 355.3108, found 355.3103.

348: δ_H (700 MHz, $CDCl_3$) 7.37-7.34 (2H, m, Ar-*H*), 7.32-7.29 (2H, m, Ar-*H*), 7.23 (1H, t, *J* 7.4, Ar-*H*), 3.73 (1H, d, *J* 13.5, NC*H*HPh), 3.61 (1H, d, *J* 13.5, NCH*H*Ph), 2.95 (1H, dt, *J* 12.7, 4.1, H^{10}), 2.84 (1H, br d, *J* 9.3, H^6), 2.49 (2H, dd, *J* 8.8, 3.0, 2 x H^{21}), 2.20 (3H, s, NCH_3), 2.13 (1H, br t, *J* 10.2, H^6), 1.90 (1H, br s, H^{17}), 1.85 (1H, qnd, *J* 11.4, 2.6, H^{14}), 1.78 (1H, br d, *J* 12.3, H^9), 1.75-1.69 (2H, m, H^{16}, H^8), 1.61-1.55 (2H, m, H^7, H^{15}), 1.54 (3H, m, 2 x H^{20}, H^{12}), 1.36-1.18 (9H, m, H^{11}, 2 x H^{19}, H^7, H^8, 2 x H^{18}, H^{11}, H^{16}), 1.11-1.05 (1H, m, H^{14}), 0.92 (3H, d, *J* 6.3, 3 x H^{13}); δ_C (175 MHz, $CDCl_3$) 140.2 (*ipso*-Ar-*C*), 128.6 (*ortho*-Ar-*C*H), 128.1 (*meta*-Ar-*C*H), 126.6 (*para*-Ar-*C*H), 62.7 (C^{17}), 58.9 (NCH_2Ph), 56.9 (C^6), 55.2 (C^{10}), 45.9 (C^{21}), 42.9 (NCH_3), 38.5 (C^9), 37.0 (C^{15}), 36.2 (C^{11}), 35.9 (C^{14}), 33.7 (C^{18}), 31.3 (C^{16}), 26.9 (C^{12}), 26.5 (C^{20}), 25.7 (C^7), 24.2 (C^8), 23.1 (C^{13}), 22.8 (C^{19}); ν_{max} (film)/cm^{-1} 2924, 2854, 1455, 1373, 1261, 1103, 1027, 803, 735; HRMS (ES^+) calcd for $C_{24}H_{39}N_2^+$ 355.3108, found 355.3107.

347: *Method 2*: TFA (0.25 mL) was added dropwise to a stirred solution of diketone **198** (50 mg, 0.085 mmol) in CH_2Cl_2 (0.75 mL) at RT. The resulting solution was stirred for 1 h before toluene (7.5 mL) was added and the solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (1.0 mL), Amberlite™ IR 120 (18 mg, 0.085 mmol eq) and Amberlite™ IRA 67 (16 mg, 0.085 mmol eq) were added and the resulting mixture was stirred for 12 h. The mixture was filtered and the solvent removed *in vacuo*. The residue

was redissolved in EtOAc (1.0 mL) and rhodium on alumina (10 mg, 5 wt% Rh) was added. The resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 72 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (10:1 CH_2Cl_2:NH_3) to yield the tricycle **347** (10 mg, 33 %) as a colourless oil: The data was consistent with that given in *method 1*.

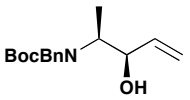
(S)-tert-Butyl benzyl(1-hydroxypropan-2-yl)carbamate (290)



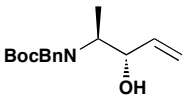
290

Lithium borohydride (2.0 M in THF, 42 mL, 84 mmol) and MeOH (46 mL) were added to a solution of ester **287** (12.39 g, 42 mmol) in THF (350 mL) at 0 ˚C and the resulting solution was allowed to warm to room temperature and stirred for 1 h. Water (1.0 L) was carefully added and the aqueous layer was extracted with CH_2Cl_2 (3 x 600 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Et_2O) to yield alcohol **290** (11.47 g, quant.) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.31 (2H, t, *J* 7.4, *meta*-Ar-C*H*), 7.27 (2H, d, *J* 7.3, *ortho*-Ar-C*H*), 7.22 (1H, t, *J* 7.2, *para*-Ar-C*H*), 4.38 (2H, s, NCH_2Ph), 4.35 (1H, br, O*H*), 3.90 (1H, q, *J* 6.2, C*H*N), 3.49 (1H, dd, *J* 10.3, 6.5, C*H*HOH), 3.38 (1H, dd, *J* 10.3, 6.5, CH*H*OH), 1.39 (9H, s, OC(CH_3)$_3$), 1.06 (3H, d, *J* 6.9, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 155.3 (*C*=O), 134.0 (*ipso*-Ar-*C*), 128.9 (*meta*-Ar-*C*H), 127.7 (*ortho*-Ar-*C*H), 127.3 (*para*-Ar-CH), 79.6 (O*C*(CH$_3$)$_3$), 64.5 (*C*H$_2$), 55.2 (NCH$_2$Ph), 48.8 (*C*HN), 29.0 (OC(*C*H$_3$)$_3$), 16.2 (*C*H$_3$); ν_{max} (film)/cm^{-1} 3400 (br, OH), 2976, 1689 (C=O), 1410, 1366, 1168; HRMS (ES$^+$) calcd for $C_{15}H_{23}NNaO_3^+$ 288.1570, found 288.1567; $[\alpha]_D^{25.3}$ -8.1 (c 1.1, $CHCl_3$).

tert-Butyl benzyl((2S,3R)-3-hydroxypent-4-en-2-yl)carbamate (288) and ***tert-butyl benzyl((2S,3S)-3-hydroxypent-4-en-2-yl)carbamate (289)***



288



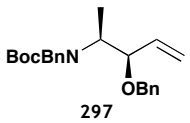
289

N-Methyl-morpholine-*N*-oxide (7.62 g, 63 mmol) and activated powdered 4 Å MS (20.78 g) were added to a stirred solution of alcohol **290** (11.472 g, 42 mmol) in CH_2Cl_2 (312 mL) and MeCN (35 mL). The mixture was stirred for 15 min before TPAP (664 mg, 2.1 mmol) was added in one portion. The mixture was stirred for 14 h before the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2, filtered through a pad of silica and the solvent removed *in vacuo*. The residue was redissolved in THF (286 mL) and cooled to -78 ˚C before vinylmagnesium bromide (1.0 M in THF, 143 mL, 143 mmol) was added dropwise. The resulting mixture was allowed to warm to RT slowly and stirred for 14 h. Aqueous NH_4Cl (350 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1 PE 40-60:Et_2O) to yield the secondary alcohols **288** (5.42 g, 51 %) and **289** (2.17 g, 21 %) both as colourless oils:

288: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.31 (2H, t, *J* 7.4, *meta*-Ar-C*H*), 7.28-7.19 (3H, m, Ar-C*H*), 5.80 (1H, ddd, *J* 17.2, 10.4, 6.2, CH_2CH), 5.18 (1H, d, *J* 17.3, *trans*-C*H*H), 5.04 (1H, d, *J* 10.5, *cis*-CH*H*), 4.71 (1H, br s, O*H*), 4.41 (1H, d, *J* 15.9, NC*H*HPh), 4.35 (1H, d, *J* 16.1, NCH*H*Ph), 4.14 (1H, br t, *J* 6.6, C*H*OH), 3.73 (1H, br s, C*H*N), 1.38 (9H, s, $OC(CH_3)_3$), 1.12 (3H, d, *J* 6.8, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 156.0 (*C*=O), 141.2 (*C*H), 141.0 (*ipso*-Ar-*C*), 128.8 (*meta*-Ar-*C*H), 127.9 (*ortho*-Ar-*C*H), 127.3 (*para*-Ar-CH), 115.4 (CH_2), 79.7 ($OC(CH_3)_3$), 74.9 (*C*HOH), 58.0 (*C*HN), 49.8 (NCH_2Ph), 29.0 ($OC(CH_3)_3$), 15.1 (CH_3); ν_{max} (film)/cm^{-1} 3431 (br, OH), 2978, 1668 (C=O), 1454, 1408, 1367, 1250, 1167, 1014, 923, 873, 700; HRMS (ES^+) calcd for $C_{17}H_{25}NNaO_3^+$ 314.1727, found 314.1722; $[\alpha]_D^{25.1}$ +3.0 (c 1.00, $CHCl_3$).

289: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.36-7.23 (4H, m, Ar-C*H*), 7.21 (1H, t, *J* 7.0, *para*-Ar-C*H*), 5.85 (1H, ddd, *J* 17.2, 10.4, 6.0, CH_2CH), 5.25 (1H, d, *J* 17.1, *trans*-C*H*H), 5.10 (1H, d, *J* 10.4), 4.63 (1H, br s, O*H*), 4.47 (1H, d, *J* 16.1, NC*H*HPh), 4.39 (1H, d, *J* 16.1, NCH*H*Ph), 4.14 (2H, t, *J* 6.5, C*H*OH), 3.87 (2H, br t, *J* 5.6, C*H*N), 1.37 (9H, s, $OC(CH_3)_3$), 1.05 (3H, d, *J* 7.0, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 156.2 (*C*=O), 141.3 (*ipso*-Ar-*C*), 140.8 (*C*H), 128.8 (*meta*-Ar-*C*H), 127.7 (*ortho*-Ar-*C*H), 127.1 (*para*-Ar-*C*H), 115.9 (CH_2), 79.5 ($OC(CH_3)_3$), 74.7 (*C*HOH), 57.6 (*C*HN), 49.6 (NCH_2Ph), 29.0 ($OC(CH_3)_3$), 16.3 (CH_3); ν_{max} (film)/cm^{-1} 3425 (br, OH), 2978, 1669 (C=O), 1454, 1366, 1248, 1167, 699; HRMS (ES^+) calcd for $C_{17}H_{25}NNaO_3^+$ 314.1727, found 314.1736; $[\alpha]_D^{25.0}$ +0.7 (c 0.95, $CHCl_3$).

tert-Butyl benzyl((2S,3R)-3-(benzyloxy)pent-4-en-2-yl)carbamate (297)

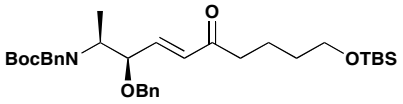


297

Sodium hydride (60 wt% dispersion in mineral oil, 758 mg, 18.9 mmol) was added to a solution of alcohol **288** (4.43 g, 15.1 mmol), benzyl bromide (5.43 mL, 45.3 mmol) and TBAI (505 mg, 1.5 mmol) in THF (44 mL) at -78 ˚C and the resulting mixture was allowed to warm slowly to room temperature and stirred for 14 h. Aqueous NH_4Cl (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (19:1 PE 40-60:Et_2O) to yield benzyl ether **297** (5.83 g, quant.) as a pale yellow oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.37-7.15 (10H, m, Ar-C*H*), 5.75-5.64 (1H, m, CH_2CH), 5.29-5.19 (2H, m, CH_2), 4.53 (1H, d, *J* 11.7, OC*H*HPh), 4.39 (1H, d, *J* 15.6, NC*H*HPh), 4.32 (1H, d, *J* 15.6, NCH*H*Ph), 4.31 (1H, d, *J* 11.7, OCH*H*Ph), 4.02 (1H, br t, *J* 6.8, C*H*OBn), 3.82 (1H, br s, C*H*N), 1.36 (9H, s, $OC(CH_3)_3$), 1.16 (3H, d, *J* 6.7, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 155.4 (*C*=O), 140.3 (*ipso*-OCH_2-Ar-*C*), 139.0 (*ipso*-NCH_2-Ar-*C*), 137.2 (*C*H), 128.6 (*meta*-OCH_2-Ar-*C*H), 128.5 (*meta*-NCH_2-Ar-*C*H), 128.0 (*ortho*-NCH_2-Ar-*C*H), 127.7 (*para*-OCH_2-Ar-*C*H), 127.5 (*ortho*-OCH_2-Ar-*C*H), 127.0 (*para*-

NCH_2-Ar-CH), 118.7 (CH_2), 83.1 (CHOBn), 79.5 ($OC(CH_3)_3$), 70.6 (OCH_2Ph), 56.4 (CHN), 49.6 (NCH_2Ph), 28.6 ($OC(CH_3)_3$), 15.3 (CH_3); ν_{max} (film)/cm^{-1} 2971, 1691 (C=O), 1455, 1406, 1361, 1324, 1230, 1167, 1041, 730, 690; HRMS (ES^+) calcd for $C_{24}H_{31}NNaO_3^+$ 404.2196, found 404.2197; $[\alpha]_D^{25.1}$ -25.9 (c 1.25, $CHCl_3$).

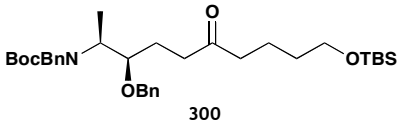
tert-Butyl benzyl((2S,3R,E)-3-(benzyloxy)-10-((tert-butyldimethylsilyl)oxy)-6-oxodec-4-en-2-yl)carbamate (299)



299

Hoveyda-Grubbs II catalyst **182** (79 mg, 0.13 mmol) was added to a stirred solution of amine **297** (798 mg, 2.06 mmol) and α,β-unsaturated ketone **298** (677 mg, 2.75 mmol) in CH_2Cl_2 (31 mL) and the mixture was heated to 60 ˚C for 16 h. The mixture was cooled and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1 PE 40-60:Et_2O) to yield the α,β-unsaturated ketone **299** (943 mg, 76 %) as a brown oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.35 (2H, t, *J* 7.3, Ar-C*H*), 7.32-7.27 (5H, m, Ar-C*H*), 7.23 (3H, t, *J* 7.1, Ar-C*H*), 6.53 (1H, dd, *J* 16.1, 7.3, C*H*CHC=O), 6.14 (1H, d, *J* 16.1, C*H*C=O), 4.51 (1H, d, *J* 11.9, OC*H*HPh), 4.36 (1H, d, *J* 11.9, OCH*H*Ph), 4.34 (2H, s, NCH_2Ph), 4.22 (2H, t, *J* 7.4, C*H*OBn), 3.86 (2H, br s, C*H*N), 3.62 (2H, t, *J* 6.3, CH_2OSi), 2.55-2.49 (2H, m, CH_2C=O), 1.58 (2H, qn, *J* 7.6, CH_2CH_2OSi), 1.50 (2H, qn, *J* 7.0, CH_2CH_2C=O), 1.35 (9H, s, $OC(CH_3)_3$), 1.19 (3H, d, *J* 6.9, CH_3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 200.0 (C=O), 155.6 (NC=O), 143.9 (CHCHC=O), 140.3 (*ipso*-OCH_2-Ar-C), 138.9 (*ipso*-NCH_2-Ar-C), 132.7 (CHC=O), 129.0 (*meta*-OCH_2-Ar-CH), 128.9 (*meta*-NCH_2-Ar-CH), 128.6 (*ortho*-NCH_2-Ar-CH), 128.3 (*para*-OCH_2-Ar-CH), 128.0 (*ortho*-OCH_2-Ar-CH), 127.5 (*para*-NCH_2-Ar-CH), 81.9 (CHOBn), 80.2 ($OC(CH_3)_3$), 71.9 (OCH_2Ph), 63.2 (CH_2OSi), 56.8 (CHN), 50.0 (NCH_2Ph), 40.1 (CH_2C=O), 32.7 (CH_2CH_2OSi), 28.9 ($OC(CH_3)_3$), 26.7 ($SiC(CH_3)_3$), 21.1 (CH_2CH_2C=O), 18.7 ($SiC(CH_3)$, 15.8 (CH_3), -4.5 ($Si(CH_3)_2$); ν_{max} (film)/cm^{-1} 2931, 1694 (C=O), 1366, 1253, 1167, 1101, 837, 776, 690; HRMS (ES^+) calcd for $C_{35}H_{53}NNaO_5Si^+$ 618.3585, found 618.3584; $[\alpha]_D^{18.4}$ -16.5 (c 1.00, $CHCl_3$).

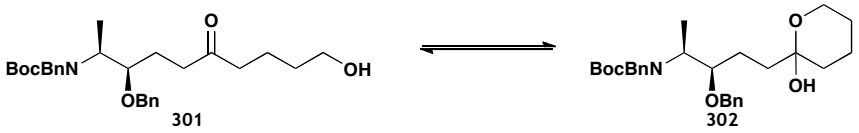
tert-Butyl benzyl((2S,3R)-3-(benzyloxy)-10-((tert-butyldimethylsilyl)oxy)-6-oxodecan-2-yl)carbamate (300)



300

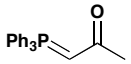
Palladium on carbon (94 mg, 10 wt% Pd) and triethylamine (2.1 mL, 15.7 mmol) were added to a stirred solution of alkene **299** (943 mg, 1.57 mmol) in EtOH (23 mL) and the resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the ketone **300** (920 mg, 98 %) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.36-7.21 (10H, m, Ar-C*H*), 4.51 (1H, d, *J* 11.6, OC*H*HPh), 4.43 (1H, d, *J* 11.6, OCH*H*Ph), 4.37 (2H, s, NCH_2Ph), 3.86 (1H, br s, C*H*N), 3.62 (1H, q, *J* 6.4, C*H*OBn), 3.59 (2H, t, *J* 6.1, CH_2OSi), 2.39 (2H, t, *J* 7.7, CHCH_2CH_2C=O), 2.37 (2H, t, *J* 7.4, $CH_2CH_2CH_2$C=O), 1.79 (1H, sextet, *J* 7.4, CHC*H*HCH_2C=O), 1.60 (1H, sextet, *J* 7.2, CHCH*H*CH_2C=O), 1.52 (2H, qn, *J* 7.4, $CH_2CH_2CH_2$C=O), 1.46 (2H, q, *J* 6.4, CH_2CH_2OSi), 1.38 (9H, s, OC(CH_3)$_3$), 1.14 (3H, d, *J* 7.0, CH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.3 (*C*=O), 155.8 (N*C*=O), 140.7 (*ipso*-OCH_2-Ar-*C*), 139.5 (*ipso*-NCH_2-Ar-*C*), 129.0 (*meta*-OCH_2-Ar-*C*H), 128.9 (*meta*-NCH_2-Ar-*C*H), 128.5 (*ortho*-NCH_2-Ar-*C*H), 128.2 (*para*-OCH_2-Ar-*C*H), 127.9 (*ortho*-OCH_2-Ar-*C*H), 127.4 (*para*-NCH_2-Ar-*C*H), 81.5 (*C*HOBn), 80.1 (O*C*(CH_3)$_3$), 72.5 (OCH_2Ph), 63.3 (*C*H_2OSi), 55.7 (*C*HN), 49.4 (NCH_2Ph), 42.6 ($CH_2CH_2CH_2$C=O), 38.3 (CHCH_2CH_2C=O), 32.8 (*C*H_2CH_2OSi), 28.9 (OC(*C*H_3)$_3$), 26.7 (SiC(*C*H_3)$_3$), 25.6 (CHCH_2CH_2C=O), 20.8 (*C*H_2CH_2CH_2OSi), 18.8 (Si*C*(CH_3)$_3$), 15.6 (*C*H_3), -4.5 (Si(*C*H_3)$_2$); ν_{max} (film)/cm^{-1} 2930, 1690 (C=O), 1459, 1410, 1377, 1262, 1166, 1107, 844, 762, 701; HRMS (ES$^+$) calcd for $C_{35}H_{55}NNaO_5Si^+$ 620.3742, found 620.3741; $[\alpha]_D^{20.3}$ -15.3 (c 1.15, $CHCl_3$).

tert-Butyl benzyl((2S,3R)-3-(benzyloxy)-10-hydroxy-6-oxodecan-2-yl)carbamate (301)



TBAF (1.0 M solution in THF, 1.3 mL, 1.30 mmol) was added dropwise to a stirred solution of silyl ether **300** (854 mg, 1.17 mmol) in THF (18 mL) at 0 ˚C. The reaction mixture was allowed to warm to room temperature slowly and stirred for 16 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (1:1 PE 40-60:Et_2O) to yield the alcohol **301** (566 mg, quant.) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.38-7.27 (6H, m, Ar-C*H*), 7.27-7.19 (4H, m, Ar-C*H*), 4.52 (1H, d, *J* 11.4, OC*H*HPh), 4.44 (1H, d, *J* 11.5, OCH*H*Ph), 4.38 (2H, s, NCH_2Ph), 3.87 (1H, br s, C*H*N), 3.63 (1H, qn, *J* 5.7, C*H*OBn), 3.41 (2H, t, *J* 6.5, CH_2OSi), 3.08 (1H, br s, O*H*), 2.39 (2H, t, *J* 7.6, CHCH_2CH_2C=O), 2.36 (2H, t, *J* 7.4, $CH_2CH_2CH_2$C=O), 1.79 (1H, sextet, *J* 7.1, CHC*H*HCH_2C=O), 1.60 (1H, sextet, *J* 6.3, CHCH*H*CH_2C=O), 1.52 (2H, qn, *J* 7.3, C$H_2CH_2CH_2$OSi), 1.42 (2H, qn, *J* 6.2, CH_2CH_2OSi), 1.39 (9H, s, OC(CH_3)$_3$), 1.14 (3H, d, *J* 6.7, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 155.9 (NC=O), 140.8 (*ipso*-OCH_2-Ar-*C*), 139.6 (*ipso*-NCH_2-Ar-*C*), 129.0 (*meta*-OCH_2-Ar-*C*H), 128.9 (*meta*-NCH_2-Ar-*C*H), 128.5 (*ortho*-NCH_2-Ar-*C*H), 128.2 (*para*-OCH_2-Ar-*C*H), 127.9 (*ortho*-OCH_2-Ar-*C*H), 127.4 (*para*-NCH_2-Ar-CH), 95.7 (O*C*OH), 81.5 (*C*HOBn), 80.0 (O*C*$(CH_3)_3$), 72.5 (OCH_2Ph), 61.5 (CH_2OH), 55.6 (*C*HN), 49.3 (NCH_2Ph), 42.7 ($CH_2CH_2CH_2$C(O)OH), 38.3 (CHCH_2CH_2C(O)OH), 32.9 (*C*H_2CH_2OH), 28.9 (OC(*C*H_3)$_3$), 25.6 (CH*C*H_2CH_2C(O)OH), 21.0 (*C*$H_2CH_2CH_2$OH), 15.6 (*C*H_3); ν_{max} (film)/cm^{-1} 3463 (br, OH), 2943, 1688 (C=O), 1455, 1410, 1365, 1074, 754, 709; HRMS (ES^+) calcd for $C_{29}H_{41}NNaO_5^+$ 506.2877, found 506.2878; $[\alpha]_D^{25.0}$ -18.3 (c 0.95, $CHCl_3$).

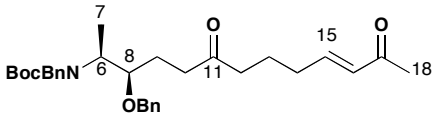
1-(Triphenylphosphoranylidene)propan-2-one (304)



304

Chloroacetone (2.4 mL, 30 mmol) and triphenylphosphine (8.43 g, 30 mmol) were mixed in toluene (36 mL) and heated to 80 ˚C for 1 h. The mixture was cooled and filtered to yield the solid triphenylphosphonium chloride salt. The salt was dissolved in water (600 mL) and NaOH (3 N in water, 30 mL) was added whereupon a white precipitate formed. The solid was filtered, dissolved in $CHCl_3$ (50 mL) and the solvent removed *in vacuo* to yield the ylid **304** (8.514 g, 89 %) as a white solid: mp 185-188 ˚C; δ_H (400 MHz, $CDCl_3$) 7.66 (6H, dd, *J* 12.5, 7.3, Ar-C*H*), 7.53 (3H, td, *J* 7.7, 1.5, Ar-C*H*), 7.45 (6H, td, *J* 7.7, 2.4, Ar-C*H*), 3.70 (1H, br d, $J_{P\text{-}H}$ 23.6, C*H*P), 2.10 (3H, d, $J_{P\text{-}H}$ 1.3, CH_3); δ_C (100 MHz, $CDCl_3$) 190.9 (d, $J_{C\text{-}P}$ 1.7, *C*=O), 133.0 (d, $J_{C\text{-}P}$ 10.2, *meta*-Ar-*C*H), 131.9 (d, $J_{C\text{-}P}$ 2.8, *para*-Ar-*C*H), 128.8 (d, $J_{C\text{-}P}$ 12.2, *ortho*-Ar-*C*H), 127.3 (d, $J_{C\text{-}P}$ 90.5, *ipso*-Ar-*C*H), 51.6 (d, $J_{C\text{-}P}$ 107.2, *C*HP), 28.5 (d, $J_{C\text{-}P}$ 15.6, *C*H_3); ν_{max} (film)/cm^{-1} 3042, 1539 (C=O), 1479, 1436, 1387, 1106, 869, 751, 717, 695; HRMS (ES^+) calcd for $C_{21}H_{20}OP^+$ 319.1246, found 319.1246.

tert-Butyl benzyl((2S,3R,E)-3-(benzyloxy)-6,12-dioxotridec-10-en-2-yl)carbamate (305)

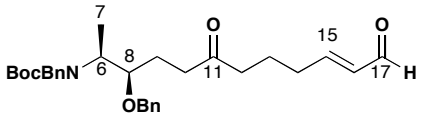


305

Oxalyl chloride (430 μL, 4.95 mmol) was added dropwise to a stirred solution of DMSO (0.70 mL, 9.86 mmol) in CH_2Cl_2 (8 mL) at -78 ˚C and the resulting solution was stirred at -78 ˚C for 0.5 h. A cooled (-78 ˚C) solution of alcohol **301** (795 mg, 1.65 mmol) in CH_2Cl_2 (8 mL) was added and the resulting mixture stirred at -78 ˚C for a further 0.5 h. Triethylamine (4.5 mL, 33 mmol) was added and the mixture stirred for 5 min before warming to room temperature. Water (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was redissolved in Et_2O and filtered before the solvent was removed *in vacuo*. The residue was redissolved

in MeCN (24 mL) and the ylid **304** (780 mg, 2.45 mmol) was added. The resulting mixture was heated to 50 ˚C for 16 h before the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the diketone **305** (621 mg, 72 %) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.38-7.20 (10H, m, Ar-C*H*), 6.79 (1H, dt, *J* 16.0, 6.7, H^{15}), 6.03 (1H, d, *J* 15.9, H^{16}), 4.51 (1H, d, *J* 11.6, OC*H*HPh), 4.44 (1H, d, *J* 11.4, OCH*H*Ph), 4.38 (2H, s, NCH_2Ph), 3.87 (1H, br s, C*H*N), 3.63 (1H, q, *J* 5.6, C*H*OBn), 2.40 (4H, br t, *J* 7.1, 2 x H^{10}, 2 x H^{12}), 2.22-2.15 (2H, m, 2 x H^{14}), 2.19 (3H, s, 3 x H^{18}), 1.80 (1H, sextet, *J* 5.3, H^9), 1.70-1.56 (3H, m, 2 x H^{13}, H^9), 1.39 (9H, s, OC(CH_3)$_3$), 1.15 (3H, d, *J* 6.8, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.2 (C^{11}), 198.3 (C^{17}), 155.9 (NC=O), 148.0 (C^{15}), 140.8 (*ipso*-OCH_2-Ar-*C*), 139.6 (*ipso*-NCH_2-Ar-*C*), 132.2 (C^{16}), 129.0 (*meta*-OCH_2-Ar-*C*H), 128.9 (*meta*-NCH_2-Ar-*C*H), 128.5 (*ortho*-NCH_2-Ar-*C*H), 128.2 (*para*-OCH_2-Ar-*C*H), 127.9 (*ortho*-OCH_2-Ar-*C*H), 127.4 (*para*-NCH_2-Ar-*C*H), 81.5 (*C*HOBn), 80.1 (O*C*$(CH_3)_3$), 72.5 (OCH_2Ph), 55.6 (*C*HN), 49.4 (NCH_2Ph), 42.0 (C^{10}), 38.4 (C^{12}), 32.0 (C^{14}), 28.9 (OC(*C*H_3)$_3$), 27.5 (C^{18}), 25.5 (C^9), 22.7 (C^{13}), 15.6 (CH_3); ν_{max} (film)/cm^{-1} 2975, 1683 (C=O), 1365, 1253, 1167, 700; HRMS (ES^+) calcd for $C_{32}H_{43}NNaO_5^+$ 544.3033, found 544.3033; $[\alpha]_D^{25.0}$ -14.2 (c 1.00, $CHCl_3$).

tert-Butyl benzyl((2S,3R,E)-3-(benzyloxy)-6,12-dioxododec-10-en-2-yl)carbamate (338)

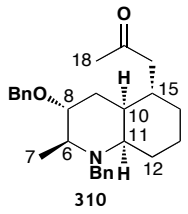


338

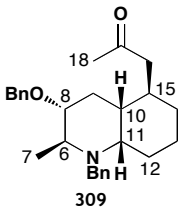
Oxalyl chloride (81 μL, 0.93 mmol) was added dropwise to a stirred solution of DMSO (132 μL, 1.86 mmol) in CH_2Cl_2 (1.5 mL) at -78 ˚C and the resulting solution was stirred at -78 ˚C for 0.5 h. A cooled (-78 ˚C) solution of alcohol **301** (150 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL) was added and the resulting mixture stirred at -78 ˚C for a further 0.5 h. Triethylamine (0.85 mL, 6.21 mmol) was added and the mixture stirred for 5 min before warming to room temperature. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was redissolved in Et_2O and filtered before the solvent was removed *in vacuo*. The residue was redissolved in MeCN:toluene (1:1, 8.7 mL) and (triphenylphosphoranylidene)acetaldehyde (135 mg,

0.45 mmol) was added. The resulting mixture was heated to 100 ˚C for 16 h before the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (3:1 PE 40-60:Et_2O) to yield the keto-aldehyde **338** (96 mg, 62 %) as an orange oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 9.50 (1H, d, *J* 7.4, *H*C=O), 7.37-7.20 (10H, m, Ar-C*H*), 6.96 (1H, dt, *J* 15.7, 6.7, H^{15}), 6.08 (1H, ddt, *J* 15.8, 7.5, 1.6, H^{16}), 4.51 (1H, d, *J* 11.5, OC*H*HPh), 4.44 (1H, d, *J* 11.7, OCH*H*Ph), 4.38 (2H, s, NCH_2Ph), 3.87 (1H, br s, C*H*N), 3.63 (1H, q, *J* 5.6, C*H*OBn), 2.44-2.35 (4H, m, 2 x H^{10}, 2 x H^{12}), 2.30 (2H, qd, *J* 7.2, 1.5, 2 x H^{14}), 1.80 (1H, sextet d, *J* 7.5, 1.7, H^9), 1.68 (2H, t, *J* 7.3, 2 x H^{13}), 1.61 (1H, sextet, *J* 6.0, H^9), 1.38 (9H, s, OC(CH_3)$_3$), 1.14 (3H, d, *J* 6.8, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.2 (C^{11}), 194.7 (C^{17}), 158.8 (C^{15}), 155.9 (NC=O), 140.8 (*ipso*-OCH_2-Ar-*C*), 139.5 (*ipso*-NCH_2-Ar-*C*), 133.6 (C^{16}), 129.0 (*meta*-OCH_2-Ar-*C*), 128.9 (*meta*-NCH_2-Ar-*C*), 128.5 (*ortho*-NCH_2-Ar-*C*H), 128.2 (*para*-OCH_2-Ar-*C*H), 127.9 (*ortho*-OCH_2-Ar-CH), 127.4 (*para*-NCH_2-Ar-CH), 81.5 (*C*HOBn), 80.1 (O*C*(CH$_3$)$_3$), 72.5 (OCH_2Ph), 55.6 (*C*HN), 49.4 (NCH_2Ph), 42.0 (C^{10}), 38.5 (C^{12}), 32.3 (C^{14}), 29.0 (OC(*C*H$_3$)$_3$), 25.5 (C^9), 22.6 (C^{13}), 15.6 (*C*H$_3$); ν_{max} (film)/cm^{-1} 2934, 1689 (C=O), 1453, 1366, 1166, 700; HRMS (ES^+) calcd for $C_{31}H_{41}NNaO_5^+$ 530.2877, found 530.2882; $[\alpha]_D^{20.2}$ -13.5 (c 1.15, $CHCl_3$).

1-((2S,3R,4aS,5R,8aR)-1-Benzyl-3-(benzyloxy)-2-methyldecahydroquinolin-5-yl)propan-2-one (310) and ***1-((2S,3R,4aR,5R,8aS)-1-benzyl-3-(benzyloxy)-2-methyldecahydroquinolin-5-yl)propan-2-one (309)***



310



309

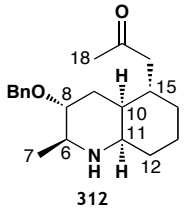
TFA (0.6 mL) was added dropwise to a stirred solution of diketone **305** (120 mg, 0.22 mmol) in CH_2Cl_2 (1.8 mL) at RT. The resulting solution was stirred for 1 h before toluene (18 mL) was added and the solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (2.4 mL), Amberlite™ IR 120 (50 mg, 0.22 mmol eq) and Amberlite™ IRA 67 (42 mg, 0.22 mmol eq) were added and the resulting mixture was stirred for 12 h. The mixture was filtered and the solvent removed *in vacuo*. The residue was redissolved in EtOH (2.4 mL)

and palladium on carbon (12 mg, 10 wt% Pd) and triethylamine (0.32 mL, 2.28 mmol) were added. The resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1 PE 40-60:Et_2O) to yield the decahydroquinolines **310** (29 mg, 33 %) and **309** (29 mg, 33 %) as colourless oils:

310: δ_H (500 MHz, $CDCl_3$) 7.42-7.25 (9H, m, Ar-C*H*), 7.20 (1H, t, *J* 7.2, Ar-C*H*), 4.51 (2H, s, OCH_2Ph), 3.83 (2H, s, NCH_2Ph), 3.31 (1H, ddd, *J* 13.1, 7.2, 3.9, C*H*OBn), 2.73 (1H, br s, H^{11}), 2.61 (1H, br t, *J* 5.8, H^6), 2.42 (1H, dd, *J* 15.5, 4.4, H^{16}), 2.38-2.30 (1H, m, H^{15}), 2.18 (1H, dd, *J* 15.4, 8.3, H^{16}), 2.13 (3H, s, 3 x H^{18}), 2.06 (1H, dt, *J* 13.2, 4.5, H^9), 1.97-1.86 (1H, m, H^{12}), 1.74-1.59 (2H, m, H^{14}, H^{10}), 1.51-1.34 (3H, m, H^{13}, H^{12}, H^9), 1.24 (3H, d, *J* 6.1, CH_3), 1.21-1.14 (1H, m, H^{13}), 1.01 (1H, q, *J* 9.9, H^{14}); δ_C (125 MHz, $CDCl_3$) 209.0 (C^{17}), 141.2 (*ipso*-NCH_2-Ar-*C*), 138.9 (*ipso*-OCH_2-Ar-*C*), 128.3 (*ortho*-NCH_2-Ar-*C*H), 128.0 (*meta*-OCH_2-Ar-*C*H), 128.0 (*meta*-NCH_2-Ar-*C*H), 127.9 (*para*-OCH_2-Ar-*C*H), 127.5 (*ortho*-OCH_2-Ar-*C*H), 126.2 (*para*-NCH_2-Ar-*C*H), 77.0 (C^8), 71.1 (OCH_2Ph), 60.7 (C^6), 59.8 (C^{11}), 54.8 (NCH_2Ph), 48.2 (C^{16}), 40.6 (C^{10}), 31.8 (C^{15}), 31.4 (C^{14}), 31.1 (C^9), 30.6 (C^{18}), 29.5 (C^{12}), 20.7 (C^{13}), 17.8 (CH_3); ν_{max} (film)/cm^{-1} 2928, 2964, 1714 (C=O), 1487, 1441, 1352, 1073, 737, 695; HRMS (ES^+) calcd for $C_{27}H_{36}NO_2^+$ 406.2741, found 406.2746; $[\alpha]_D^{20.2}$ -3.6 (c 1.15, $CHCl_3$).

309: δ_H (500 MHz, $CDCl_3$) 7.45-7.18 (10H, m, Ar-C*H*), 4.65 (1H, d, *J* 11.3, OC*H*HPh), 4.46 (1H, d, *J* 11.0, OCH*H*Ph), 3.89 (1H, d, *J* 14.4, NC*H*HPh), 3.62 (1H, d, *J* 14.4, NCH*H*Ph), 3.16 (1H, dt, *J* 12.8, 4.4, C*H*OBn), 2.84 (1h, br qn, *J* 6.4, H^6), 2.66 (1H, br d, *J* 11.2, H^{11}), 2.42 (1H, dd, *J* 16.1, 6.3, H^{16}), 2.30 (1H, dd, *J* 16.4, 6.8, H^{16}), 2.24-2.15 (1H, m, H^{15}), 2.05 (3H, s, 3 x H^{18}), 1.96 (1H, br d, *J* 11.2, H^9), 1.86-1.66 (3H, m, H^9, H^{10}, H^{12}), 1.65-1.51 (3H, m, H^{14}, H^{13}, H^{12}), 1.19 (3H, d, *J* 5.2, CH_3), 1.17-1.08 (2H, m, H^{14}, H^{13}); δ_C (125 MHz, $CDCl_3$) 208.8 (C^{17}), 141.4 (*ipso*-NCH_2-Ar-*C*), 138.7 (*ipso*-OCH_2-Ar-*C*), 128.4 (*ortho*-NCH_2-Ar-CH), 128.1 (*meta*-OCH_2-Ar-*C*H), 127.9 (*meta*-NCH_2-Ar-CH), 127.8 (*para*-OCH_2-Ar-*C*H), 127.5 (*ortho*-OCH_2-Ar-CH), 126.4 (*para*-NCH_2-Ar-CH), 80.7 (C^8), 71.2 (OCH_2Ph), 54.5 (C^6), 53.2 (C^{11}), 52.1 (NCH_2Ph), 47.0 (C^{16}), 37.5 (C^{10}), 35.0 (C^{15}), 31.2 (C^9), 30.7 (C^{18}), 25.4 (C^{14}), 20.7 (C^{13}), 19.2 (C^{12}), 16.9 (CH_3); ν_{max} (film)/cm^{-1} 2929, 1715 (C=O), 1458, 1369, 1102, 1076, 750, 699; HRMS (ES^+) calcd for $C_{27}H_{36}NO_2^+$ 406.2741, found 406.2740; $[\alpha]_D^{20.2}$ -31.2 (c 0.75, $CHCl_3$).

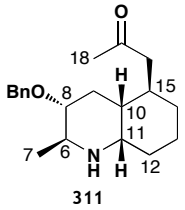
1-((2S,3R,4aS,5R,8aR)-3-(Benzyloxy)-2-methyldecahydroquinolin-5-yl)propan-2-one (312)



312

Palladium on carbon (3 mg, 10 wt% Pd) and acetic acid (1 drop) were added to a stirred solution of benzyl decahydroquinoline **310** (29 mg, 0.073 mmol) in EtOH (0.6 mL) and the resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (Et_2O) to yield the amine **312** (23 mg, quant.) as pale orange needles: δ_H (500 MHz, $CDCl_3$) 7.39-7.24 (5H, m, Ar-C*H*), 4.53 (1H, d, *J* 11.6, OC*H*HPh), 4.49 (1H, d, *J* 11.6, OCH*H*Ph), 3.11 (1H, ddd, *J* 11.1, 9.4, 4.1, C*H*OBn), 2.96 (1H, q, *J* 2.4, H^{11}), 2.68 (1H, dq, *J* 8.9, 6.2, H^{11}), 2.44 (1H, dd, *J* 16.0, 4.6, H^{16}), 2.30-2.21 (1H, m, H^{15}), 2.12 (3H, s, CH_3^{18}), 2.07 (1H, dd, *J* 16.0, 8.1, H^{16}), 2.03 (1H, ddd, *J* 13.4, 3.5, 2.6, H^9), 1.70-1.63 (2H, m, H^{12}, H^{14}), 1.59 (1H, tt, *J* 12.8, 3.1, H^{13}), 1.52 (1H, tt, *J* 13.0 3.8, H^{12}), 1.45-1.36 (2H, m, H^{13}, H^{10}), 1.31 (1H, ddd, *J* 13.0, 11.8, 4.8, H^9), 1.22 (3H, d, *J* 6.2, CH_3), 0.92 (1H, qd, *J* 12.4, 3.7, H^{14}); δ_C (125 MHz, $CDCl_3$) 208.9 (C^{17}), 138.8 (*ipso*-Ar-*C*), 128.3 (*meta*-Ar-*C*H), 128.0 (*ortho*-Ar-*C*H), 127.5 (*para*-Ar-*C*H), 77.0 (C^8), 71.4 (OCH_2Ph), 58.1 (C^6), 55.2 (C^{11}), 49.0 (C^{16}), 42.3 (C^{10}), 33.4 (C^{14}), 32.9 (C^9), 32.1 (C^{12}), 30.4 (C^{18}), 30.1 (C^{15}), 20.7 (C^{13}), 19.2 (CH_3); ν_{max} (film)/cm^{-1} 2925, 2847, 1714 (C=O), 1441, 1347, 1085, 1059, 708; HRMS (ES^+) calcd for $C_{20}H_{30}NO_2^+$ 316.2271, found 316.2272; $[\alpha]_D^{20.6}$ -15.8 (c 0.75, $CHCl_3$).

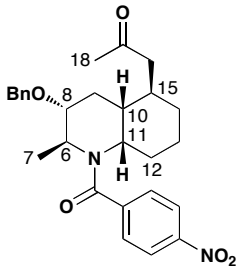
1-((2S,3R,4aR,5R,8aS)-3-(Benzyloxy)-2-methyldecahydroquinolin-5-yl)propan-2-one (311)



311

Palladium on carbon (2 mg, 10 wt% Pd) and acetic acid (1 drop) were added to a stirred solution of benzyl decahydroquinoline **309** (23 mg, 0.058 mmol) in EtOH (0.5 mL) and the resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (Et_2O) to yield the amine **311** (19 mg, quant.) as a yellow oil: δ_H (500 MHz, $CDCl_3$) 7.35 (4H, d, *J* 4.3, Ar-C*H*), 7.32-7.28 (1H, m, Ar-C*H*), 4.66 (1H, d, *J* 11.5, OC*H*HPh), 4.47 (1H, d, *J* 11.5, OCH*H*Ph), 3.03-2.94 (2H, m, H^8, H^{11}), 2.89 (1H, dq, *J* 8.5, 6.0, H^6), 2.59 (1H, dd, *J* 16.8, 7.0, H^{16}), 2.51 (1H, dd, *J* 16.6, 7.3, H^{16}), 2.26-2.20 (1H, m, H^{15}), 2.13 (3H, s, CH_3^{18}), 1.96 (1H, dd, *J* 9.0, 4.9, H^9), 1.90 (1H, qd, *J* 12.3, 3.6, H^{12}), 1.78-1.70 (2H, m, H^{10}, H^9), 1.60 (1H, td, *J* 9.7, 3.7, H^{13}), 1.57 (1H, dt, *J* 13.6, 4.2, H^{14}), 1.46-1.37 (2H, m, H^{12}, H^{13}), 1.23-1.20 (1H, m, H^{14}), 1.17 (3H, d, *J* 6.1, CH_3); δ_C (125 MHz, $CDCl_3$) 208.2 (C^{17}), 138.6 (*ipso*-Ar-*C*), 128.3 (*meta*-Ar-CH), 127.7 (*ortho*-Ar-CH), 127.6 (*para*-Ar-CH), 81.6 (C^8), 71.0 (OCH_2Ph), 50.2 (C^{11}), 49.7 (C^6), 47.1 (C^{16}), 39.5 (C^{10}), 34.6 (C^{15}), 31.1 (C^9), 30.5 (C^{18}), 26.3 (C^{12}), 24.9 (C^{14}), 20.7 (C^{13}), 19.2 (CH_3); ν_{max} (film)/cm^{-1} 2927, 2860, 1714 (C=O), 1458, 1360, 1059, 716, 678; HRMS (ES^+) calcd for $C_{20}H_{30}NO_2^+$ 316.2271, found 316.2272; $[\alpha]_D^{20.7}$ -32.3 (c 0.60, $CHCl_3$).

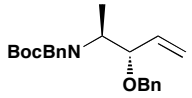
1-((2S,3R,4aR,5R,8aS)-3-(Benzyloxy)-2-methyl-1-(4-nitrobenzoyl)decahydroquinolin-5-yl)propan-2-one (313)



313

Triethylamine (25 μL, 0.174 mmol) followed by 4-nitrobenzoyl chloride (17 mg, 0.087 mmol) were added to a stirred solution of amine **311** (19 mg, 0.058 mmol) in CH_2Cl_2 (0.5 mL) at 0 ˚C. The mixture was allowed to warm to room temperature and stirred for 14 h. The reaction was diluted with CH_2Cl_2 (10 mL) and pH 7 buffer (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (19:1 Et_2O:MeOH) to yield the ester **313** (20 mg, 74 %) as a yellow needles: mp 131-137 ˚C; δ_H (500 MHz, $CDCl_3$) 8.25 (2H, d, *J* 8.5, *ortho*-NO_2-Ar-C*H*), 7.52 (2H, d, *J* 8.5, *meta*-NO_2-Ar-C*H*), 7.40-7.26 (5H, m, Ar-C*H*), 4.59 (1H, d, *J* 11.9, OC*H*HPh), 4.49 (1H, d, *J* 11.8, OCH*H*Ph), 4.09 (1H, br s, H^{11}), 3.86 (1H, qd, *J* 7.0, 4.5, H^6), 3.60 (1H, dt, *J* 7.3, 4.0, H^8), 2.52 (2H, br d, *J* 4.6, CH_2^{16}), 2.21 (1H, br q, *J* 4.7, H^{15}), 2.13 (3H, s, CH_3^{18}), 2.10 (1H, dd, *J* 13.4, 7.0, H^9), 2.06-1.99 (1H, m, H^{10}), 1.97 (1H, dd, *J* 5.7, 4.0, H^{12}), 1.92 (1H, dd, *J* 12.8, 3.4, H^9), 1.88-1.78 (1H, m, H^{12}), 1.69 (1H, tt, *J* 13.8, 4.0, H^{14}), 1.57 (1H, dt, *J* 14.0, 2.8, H^{13}), 1.42-1.31 (1H, m, H^{13}), 1.30-1.18 (4H, m, CH_3, H^{14}); δ_C (125 MHz, $CDCl_3$) 207.6 (C^{17}), 170.4 (NC=O), 148.0 (*ipso*-NO_2-Ar-*C*), 144.2 (*para*-NO_2-Ar-*C*), 138.1 (*ipso*-OCH_2-Ar-*C*), 128.5 (*meta*-NO_2-Ar-*C*H), 127.7 (*para*-OCH_2-Ar-CH), 127.5 (*meta*-OCH_2-Ar-*C*H), 127.3 (*ortho*-OCH_2-Ar-CH), 123.9 (*ortho*-NO_2-Ar-*C*H), 76.7 (C^8), 71.0 (OCH_2Ph), 52.4 (C^6), 51.8 C^{11}), 46.6 (C^{16}), 34.7 (C^{10}), 33.3 (C^{15}), 30.6 (C^{18}), 28.8 (C^9), 25.3 (C^{12}), 24.3 (C^{14}), 20.3 (C^{13}), 20.0 (CH_3); ν_{max} (film)/cm^{-1} 2928, 1714 (C=O), 1626 (C=O), 1522, 1419, 1348; HRMS (ES^+) calcd for $C_{27}H_{32}N_2NaO_5^+$ 487.2203, found 487.2210; $[\alpha]_D^{18.0}$ -35.2 (c 0.50, $CHCl_3$).

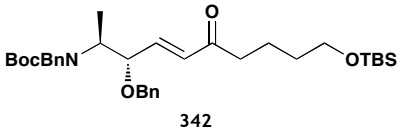
tert-Butyl benzyl((2S,3S)-3-(benzyloxy)pent-4-en-2-yl)carbamate (340)



340

Sodium hydride (60 wt% dispersion in mineral oil, 101 mg, 2.5 mmol) was added to a solution of alcohol **289** (587 mg, 2.0 mmol), benzyl bromide (0.72 mL, 6.0 mmol) and TBAI (67 mg, 0.2 mmol) in THF (4 mL) at -78 ˚C and the resulting mixture was allowed to warm slowly to room temperature and stirred for 14 h. Saturated NH_4Cl solution (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (19:1 PE 40-60:Et_2O) to yield benzyl ether **340** (338 mg, 44 %) as a pale yellow oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.40-7.16 (10H, m, Ar-C*H*), 5.81-5.71 (1H, m, CH_2CH), 5.39-5.30 (2H, m, CH_2), 4.52 (1H, d, *J* 11.9, OC*H*HPh), 4.43 (1H, d, *J* 16.2, NC*H*HPh), 4.33 (1H, d, *J* 16.2, NCH*H*Ph), 4.27 (1H, d, *J* 12.1, OCH*H*Ph), 4.01 (2H, br s, C*H*OBn, C*H*N), 1.35 (9H, s, $OC(CH_3)_3$), 1.07 (3H, d, *J* 6.4, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 156.0 (*C*=O), 141.0 (*ipso*-OCH_2-Ar-*C*), 139.6 (*ipso*-NCH_2-Ar-*C*), 137.6 (CH_2CH), 128.9 (*meta*-OCH_2-Ar-*C*H), 128.8 (*meta*-NCH_2-Ar-*C*H), 128.2 (*ortho*-NCH_2-Ar-*C*H), 128.0 (*para*-OCH_2-Ar-*C*H), 127.7 (*ortho*-OCH_2-Ar-*C*H), 127.2 (*para*-NCH_2-Ar-*C*H), 119.6 (CH_2), 83.1 (*C*HOBn), 79.6 ($OC(CH_3)_3$), 70.8 (OCH_2Ph), 56.5 (*C*HN), 49.6 (NCH_2Ph), 28.9 ($OC(CH_3)_3$), 16.4 (CH_3); ν_{max} (film)/cm^{-1} 2977, 1692 (C=O), 1452, 1365, 1229, 1059, 763; HRMS (ES^+) calcd for $C_{24}H_{31}NNaO_3^+$ 404.2196, found 404.2198; $[\alpha]_D^{17.9}$ +9.8 (c 1.35, $CHCl_3$).

tert-Butyl benzyl((2S,3S,E)-3-(benzyloxy)-10-((tert-butyldimethylsilyl)oxy)-6-oxodec-4-en-2-yl)carbamate (342)

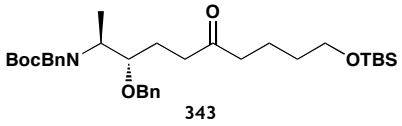


342

Hoveyda-Grubbs II catalyst **182** (20 mg, 0.033 mmol) was added to a stirred solution of amine **340** (202 mg, 0.52 mmol) and α,β-unsaturated ketone **298** (171 mg, 0.70 mmol) in

CH_2Cl_2 (7.8 mL) and the mixture was heated in an oil bath at 60 ˚C for 16 h. The mixture was cooled and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (9:1 PE 40-60:Et_2O) to yield the α,β-unsaturated ketone **342** (152 mg, 49 %) as a brown oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.38-7.18 (10H, m, Ar-C*H*), 6.65 (1H, dd, *J* 16.1, 6.6, C*H*CHC=O), 6.27 (1H, d, *J* 16.1, C*H*C=O), 4.51 (1H, d, *J* 12.0, OC*H*HPh), 4.46 (1H, d, *J* 16.2, NC*H*HPh), 4.35 (1H, d, *J* 16.2, NCH*H*Ph), 4.33 (1H, d, *J* 12.0, OCH*H*Ph), 4.25 (1H, t, *J* 6.8, C*H*OBn), 4.13 (1H, br t, *J* 6.3, C*H*N), 3.61 (2H, t, *J* 6.2, CH_2OSi), 2.60 (2H, t, *J* 7.5, CH_2C=O), 1.59 (2H, qn, *J* 7.3, CH_2CH_2C=O), 1.50 (2H, qn, *J* 6.5, CH_2CH_2OSi), 1.34 (9H, s, OC(CH_3)$_3$), 1.10 (3H, d, *J* 7.0, CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 200.2 (*C*=O), 156.0 (N*C*=O), 143.9 (*C*HCHC=O), 140.9 (*ipso*-OCH_2-Ar-*C*), 139.2 (*ipso*-NCH_2-Ar-*C*), 132.6 (*C*HC=O), 129.0 (*meta*-OCH_2-Ar-*C*H), 128.8 (*meta*-NCH_2-Ar-*C*H), 128.3 (*ortho*-NCH_2-Ar-*C*H), 128.2 (*para*-OCH_2-Ar-*C*H), 127.7 (*ortho*-OCH_2-Ar-*C*H), 127.2 (*para*-NCH_2-Ar-*C*H), 81.7 (*C*HOBn), 79.9 (O*C*(CH$_3$)$_3$), 71.9 (O*C*H$_2$Ph), 63.2 (*C*H$_2$OSi), 56.3 (*C*HN), 49.5 (NCH$_2$Ph), 40.2 (*C*H$_2$C=O), 32.7 (*C*H$_2$CH$_2$OSi), 28.9 (OC(*C*H$_3$)$_3$), 26.7 (SiC(*C*H$_3$)$_3$), 21.2 (*C*H$_2$CH$_2$C=O), 18.7 (Si*C*(CH$_3$)$_3$), 16.4 (*C*H$_3$), -4.5 (Si(*C*H$_3$)$_2$); ν_{max} (film)/cm^{-1} 2958, 2930, 2853, 1692 (C=O), 1466, 1357, 1251, 1168, 1101, 790, 706; HRMS (ES$^+$) calcd for $C_{35}H_{53}NNaO_5Si^+$ 618.3585, found 618.3588; $[\alpha]_D^{17.6}$ +15.8 (c 1.15, $CHCl_3$).

tert-Butyl benzyl((2S,3S)-3-(benzyloxy)-10-((tert-butyldimethylsilyl)oxy)-6-oxodecan-2-yl)carbamate (343)

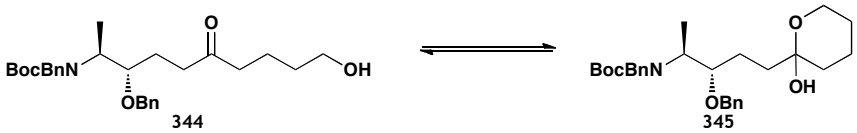


343

Palladium on carbon (19 mg, 10 wt% Pd) and triethylamine (0.43 mL, 3.2 mmol) were added to a stirred solution of alkene **342** (193 mg, 0.32 mmol) in EtOH (4.6 mL) and the resulting mixture was degassed three times with hydrogen using a pump-flood procedure and placed under an atmosphere of hydrogen. The reaction was stirred for 16 h and then filtered over Celite™ using CH_2Cl_2 to elute and the solvent removed *in vacuo*. The residue

was purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the ketone **343** (165 mg, 71 %) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.37-7.16 (10H, m, Ar-C*H*), 4.52 (1H, d, *J* 11.6, OC*H*HPh), 4.47 (1H, d, *J* 16.7, NC*H*HPh), 4.44 (1H, d, *J* 11.8, OCH*H*Ph), 4.36 (1H, d, *J* 16.0, NCH*H*Ph), 4.03 (1H, br t, *J* 5.9, C*H*N), 3.65 (1H, q, *J* 5.3, C*H*OBn), 3.58 (2H, t, *J* 6.1, CH_2OSi), 2.47 (2H, dd, *J* 14.9, 7.8, CHCH_2CH_2C=O), 2.40 (2H, t, *J* 7.1, $CH_2CH_2CH_2$C=O), 1.84 (1H, sextet, *J* 6.0, CHC*H*HCH_2C=O), 1.66 (1H, sextet, *J* 6.6, CHCH*H*CH_2C=O), 1.52 (2H, qn, *J* 7.2, $CH_2CH_2CH_2$C=O), 1.45 (2H, qn, *J* 6.9, CH_2CH_2OSi), 1.36 (9H, s, OC(CH_3)$_3$), 1.10 (3H, d, *J* 6.9, CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.3 (*C*=O), 156.1 (N*C*=O), 141.1 (*ipso*-OCH_2-Ar-*C*), 139.7 (*ipso*-NCH_2-Ar-*C*), 128.9 (*meta*-OCH_2-Ar-*C*H), 128.8 (*meta*-NCH_2-Ar-*C*H), 128.3 (*ortho*-NCH_2-Ar-*C*H), 128.1 (*para*-OCH_2-Ar-*C*H), 127.7 (*ortho*-OCH_2-Ar-*C*H), 127.2 (*para*-NCH_2-Ar-*C*H), 81.1 (*C*HOBn), 79.7 (O*C*(CH$_3$)$_3$), 72.5 (OCH_2Ph), 63.2 (*C*H_2OSi), 55.5 (*C*HN), 49.6 (NCH_2Ph), 42.6 ($CH_2CH_2CH_2$C=O), 38.2 (CHCH_2CH_2C=O), 32.7 (*C*H_2CH_2OSi), 29.0 (OC(*C*H$_3$)$_3$), 26.7 (SiC(*C*H$_3$)$_3$), 25.6 (CHCH_2CH_2C=O), 20.8 ($CH_2CH_2CH_2$C=O), 18.7 (Si*C*(CH$_3$)$_3$), 16.6 (*C*H$_3$), -4.5 (Si(*C*H$_3$)$_2$; ν_{max} (film)/cm^{-1} 2930, 1689 (C=O), 1369, 1254, 1157, 869, 788, 699; HRMS (ES$^+$) calcd for $C_{35}H_{55}NNaO_5Si^+$ 620.3742, found 620.3742; $[\alpha]_D^{21.5}$ -4.0 (c 0.95, $CHCl_3$).

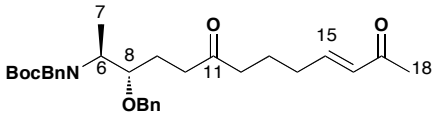
tert-Butyl benzyl((2S,3S)-3-(benzyloxy)-10-hydroxy-6-oxodecan-2-yl)carbamate (344)



TBAF (1.0 M solution in THF, 0.26 mL, 0.26 mmol) was added dropwise to a stirred solution of silyl ether **343** (165 mg, 0.23 mmol) in THF (3.4 mL) at 0 ˚C. The reaction mixture was allowed to warm to room temperature slowly and stirred for 16 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (1:1 PE 40-60:Et_2O) to yield the alcohol **344** (126 mg, quant.) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.38 (10H, m, Ar-C*H*), 4.52 (1H, d, *J* 11.8, OC*H*HPh), 4.47 (1H, d, *J* 16.0, NC*H*HPh), 4.44 (1H, d, *J* 11.8, OCH*H*Ph), 4.36 (1H, d, *J* 16.0, NCH*H*Ph), 4.02 (1H, br t, *J* 4.9,

C*H*N), 3.65 (1H, td, *J* 6.4, 5.0, C*H*OBn), 3.40 (2H, dd, *J* 10.7, 5.7, C*H*$_2$OH), 2.47 (2H, dd, *J* 14.6, 6.7, CHCH$_2$C*H*$_2$C=O), 2.39 (2H, t, 7.1, CH$_2$CH$_2$C*H*$_2$C=O), 1.88-1.80 (1H, m, CHC*H*HCH$_2$C=O), 1.65 (1H, qt, *J* 8.2, 6.3, CHCH*H*CH$_2$C=O), 1.52 (2H, dq, *J* 7.8, 6.9, C*H*$_2$CH$_2$CH$_2$OH), 1.41 (2H, dq, *J* 9.4, 6.3, C*H*$_2$CH$_2$OH), 1.36 (9H, s, OC(C*H*$_3$)$_3$), 1.10 (3H, d, *J* 6.9, C*H*$_3$); δ_C (125 MHz, (CD$_3$)$_2$SO, 363 K) 156.1 (N*C*=O), 141.1 (*ipso*-OCH$_2$-Ar-*C*), 139.8 (*ipso*-NCH$_2$-Ar-*C*), 128.9 (*meta*-OCH$_2$-Ar-*C*H), 128.8 (*meta*-NCH$_2$-Ar-*C*H), 128.3 (*ortho*-NCH$_2$-Ar-*C*H), 128.1 (*para*-OCH$_2$-Ar-*C*H), 127.7 (*ortho*-OCH$_2$-Ar-*C*H), 127.2 (*para*-NCH$_2$-Ar-*C*H), 95.9 (O*C*OH), 81.1 (*C*HOBn), 79.7 (O*C*(CH$_3$)$_3$), 72.5 (OCH$_2$Ph), 61.4 (*C*H$_2$OH), 55.5 (*C*HN), 49.6 (NCH$_2$Ph), 42.7 (CH$_2$CH$_2$CH$_2$C(O)OH), 38.2 (CHCH$_2$CH$_2$C(O)OH), 32.9 (*C*H$_2$CH$_2$OH), 28.9 (OC(*C*H$_3$)$_3$), 25.6 (CHCH$_2$CH$_2$C(O)OH), 21.0 (*C*H$_2$CH$_2$CH$_2$OH), 16.6 (*C*H$_3$); ν_{max} (film)/cm^{-1} 3453 (br, OH), 2933, 1687 (C=O), 1462, 1374, 1181, 718; HRMS (ES$^+$) calcd for $C_{29}H_{41}NNaO_5^+$ 506.2877, found 506.2877; $[\alpha]_D^{25.0}$ -5.0 (c 0.5, CHCl$_3$).

tert-Butyl benzyl((2S,3S,E)-3-(benzyloxy)-6,12-dioxotridec-10-en-2-yl)carbamate (346)



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Oxalyl chloride (62 μL, 0.71 mmol) was added dropwise to a stirred solution of DMSO (102 μL, 1.40 mmol) in CH$_2$Cl$_2$ (1.15 mL) at -78 ˚C and the resulting solution was stirred at -78 ˚C for 0.5 h. A cooled (-78 ˚C) solution of alcohol **344** (126 mg, 0.23 mmol) in CH$_2$Cl$_2$ (1.15 mL) was added and the resulting mixture stirred at -78 ˚C for a further 0.5 h. Triethylamine (0.66 mL, 4.67 mmol) was added and the mixture stirred for 5 min before warming to room temperature. Water (6 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL), dried (Na$_2$SO$_4$) and the solvent removed *in vacuo*. The residue was redissolved in Et$_2$O and filtered before the solvent was removed *in vacuo*. The residue was redissolved in MeCN (3.3 mL) and the ylid **304** (108 mg, 0.35 mmol) was added. The resulting mixture was heated to 50 ˚C for 16 h before the solvent was removed *in vacuo*. The residue was

purified by flash column chromatography (4:1 PE 40-60:Et_2O) to yield the diketone **346** (38 mg, 30 %) as a colourless oil: δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.38-7.18 (10H, m, Ar-C*H*), 6.77 (1H, dt, *J* 16.0, 6.8, *H*^{15}), 6.03 (1H, d, *J* 16.0, *H*^{16}), 4.52 (1H, d, *J* 11.5, OC*H*HPh), 4.47 (1H, d, *J* 16.1, NC*H*HPh), 4.44 (1H, d, *J* 11.5, OCH*H*Ph), 4.36 (1H, d, *J* 16.1, NCH*H*Ph), 4.04 (1H, br t, *J* 5.4, *H*^{6}), 3.65 (1H, q, *J* 6.0, *H*^{8}), 2.48 (2H, dd, *J* 14.6, 7.6, 2 x *H*^{10}), 2.43 (2H, t, *J* 7.3, 2 x *H*^{12}), 2.23-2.15 (5H, m, CH_3^{18}, *H*^{14}), 1.85 (1H, sextet, *J* 7.1, *H*^{9}), 1.70-1.60 (3H, m, *H*^{9}, 2 x *H*^{13}), 1.36 (9H, s, OC(CH_3)$_3$), 1.10 (3H, d, *J* 7.0, CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 363 K) 210.4 (*C*^{11}), 198.3 (*C*^{17}), 156.1 (NC=O), 148.1 (*C*^{15}), 141.1 (*ipso*-OCH_2-Ar-*C*), 139.8 (*ipso*-NCH_2-Ar-*C*), 132.2 (*C*^{16}), 128.9 (*meta*-OCH_2-Ar-*C*H), 128.8 (*meta*-NCH_2-Ar-*C*H), 128.3 (*ortho*-NCH_2-Ar-*C*H), 128.1 (*para*-OCH_2-Ar-*C*H), 127.7 (*ortho*-OCH_2-Ar-*C*H), 127.2 (*para*-NCH_2-Ar-CH), 81.1 (*C*^{8}), 79.7 (O*C*$(CH_3)_3$), 72.4 (O*C*H_2Ph), 55.5 (*C*^{6}), 49.7 (N*C*H_2Ph), 42.1 (*C*^{12}), 38.3 (*C*^{10}), 32.0 (*C*^{14}), 28.9 (OC(*C*H_3)$_3$), 27.5 (*C*^{18}), 25.6 (*C*^{9}), 22.7 (*C*^{13}), 16.6 (*C*H_3); ν_{max} (film)/cm^{-1} 2987, 2936, 1684 (C=O), 1470, 1373, 1254, 1174, 725; HRMS (ES$^+$) calcd for $C_{32}H_{43}NNaO_5^+$ 544.3033, found 544.3035; $[\alpha]_D^{25.0}$ -7.1 (c 0.35, $CHCl_3$).

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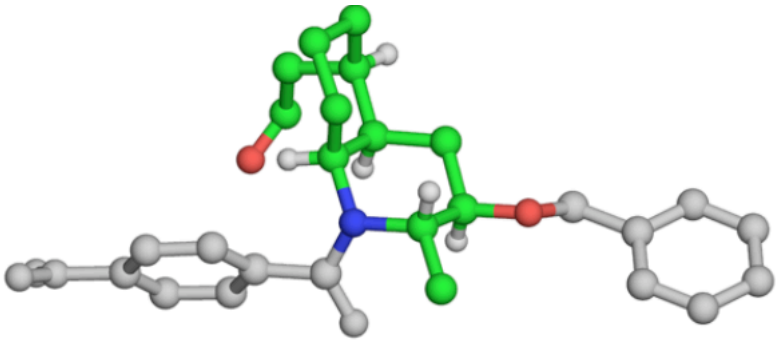
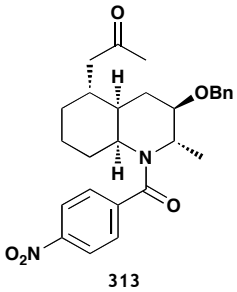
7 Appendix

7.1 X-ray crystallography data

Further data may be found on the attached CD for both DIA0002 and DIA0088. Key data and refinement for each structure are presented here.

1-((2S,3R,4aR,5R,8aS)-3-(benzyloxy)-2-methyl-1-(4-nitrobenzoyl)decahydroquinolin-5-yl)propan-2-one (313)





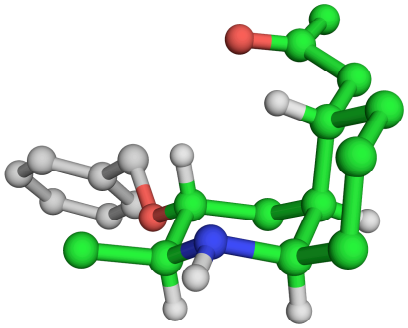
313

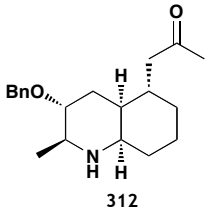
Key data and refinement for the crystal structure of 313/DIA0002

Identification code	DIA0002	
Empirical Formula	$C_{27}H_{32}N_2O_5$	
Formula Weight	464.56	
Temperature	150 K	
Wavelength	0.68890 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.527(3) Å	α = 90°
	b = 9.950(3) Å	β = 90°
	c = 28.889(9) Å	γ = 90°
Volume	2451.0(14) $Å^3$	
Z	4	
Density (calculated)	1.259 Mgm^{-3}	
Absorption coefficient	0.087 mm^{-1}	

F (000)	992
Crystal size	0.040 x 0.015 x 0.010 mm^3
Theta range for data collection	1.366 to 31.540˚
Index ranges	-12≤h≤12, -10≤k≤14, -43≤l≤42
Reflections collected	31828
Independent reflections	4722 [R(int) = 0.0580]
Completeness to theta = 26.178 ˚	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.55
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4704/0/307
Goodness-of-fit on F^2	0.9158
Final R indices [I>2sigma(I)]	R1 = 0.0466, wR2 = 0.1175
R indices (all data)	R1 = 0.0528, wR2 = 0.1283
Largest diff. peak and hole	0.37 and -0.27 e.$Å^{-3}$

1-((2S,3R,4aS,5S,8aR)-3-(benzyloxy)-2-methyldecahydroquinolin-5-yl)propan-2-one (312)





312

Key data and refinement for the crystal structure of 312

Identification code	DIA0088	
Empirical Formula	$C_{20}H_{29}NO_2$	
Formula Weight	315.46	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.701(8) Å	α = 90°
	b = 9.868(8) Å	β = 111.941(8)°
	c = 10.066(9) Å	γ = 90°
Volume	893.8(13) Å^3	
Z	2	
Density (calculated)	1.172 Mgm^{-3}	
Absorption coefficient	0.074 mm^{-1}	
F (000)	344	
Crystal size	0.050 x 0.050 x 0.030 mm^3	
Theta range for data collection	2.114 to 29.677°	
Index ranges	-13≤h≤13, -13≤k≤12, -14≤l≤14	
Reflections collected	10003	
Independent reflections	2804 [R(int) = 0.043]	

Completeness to theta = 25.225˚	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.78
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2798/1/208
Goodness-of-fit on F^2	0.8907
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.0964
R indices (all data)	R1 = 0.0516, wR2 = 0.0983
Largest diff. peak and hole	0.27 and -0.21 e.$Å^{-3}$