Studies Towards the Synthesis of the Core of Sarains A, B & C

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I, Pui Shan Pang, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Sarains A-C are alkaloids isolated from the Mediterranean sponge *Reniera sarai*, which possess moderate antibacterial, insecticidal and antitumour properties. These alkaloids are popular targets for total synthesis, thanks to their rather unusual and challenging structure, which consists of a central diazatricyclic cage attached to two peripheral macrocycles. Arguably the most challenging aspect of their synthesis is that of the tricyclic core, and our approach involves a novel rearrangement of a simpler bicyclic aminal system. This thesis describes various attempts to synthesise *cis*-fused octahydropyrrolo[2,3-*b*]pyrrole ring systems that bear an *endo* acetaldehyde-derived substituent in the 3-position.

The research into the synthesis of this ring system began with enantioselective approaches, utilising asymmetric Diels-Alder reactions to establish the stereochemistry required for subsequent transformations into the bicyclic aminal. Progress from these reactions was troublesome.

In racemic approaches, the use of a Michael reaction was unsuccessful, but successful installation of the required stereochemistry was achieved by use of a thio-Claisen rearrangement. Using this method, the aforementioned functionalised acetaldehyde was produced in good yield in ten steps from simple starting materials. This provided a branching point for the exploration of four different, but related routes to the sarain core involving the generation of diazoketones, a bromoketone and hydroxy-aldehydes. Substrates to test our proposed rearrangement reaction were synthesised, but transformations into the sarain core proved unfruitful. However, a different tricyclic compound has been produced from a hydroxy-aldehyde approach.

In a separate investigation instigated by a result from previous research into synthesis of the sarain core, it was found that treatment of tertiary formamides with a silylated diazoester in the presence of rhodium acetate leads to formation of 3-amino-2-silyloxyacrylates in good yields. The scope and limitations of this novel reaction were investigated.

To my mum

ACKNOWLEDGEMENTS

Finally, I have to thank my family and friends for their love and support throughout my education. Thank you for keeping me sane and for helping me through thick and thin – this thesis would never have been completed without your encouragement and understanding over the last few months, and for that, I am eternally grateful.

ABBREVIATIONS

2,4-DNP	2,4-Dinitrophenol
9-BBN	9-Borabicyclo[3.3.1]nonane
*p*ABSA	*para*-Acetamidobenzenesulfonyl azide
Ac	Acetyl
acac	Acetylacetonate
aq.	Aqueous
Ar	Aryl
b.p.	Boiling point
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
calcd	Calculated
CDI	Carbonyl diimidazole
CI	Chemical ionisation
COSY	Correlation spectroscopy
*m*CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
d	Day
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
*o*DCB	*ortho*-Dichlorobenzene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarisation transfer
DIBAH	Diisobutylaluminium hydride
DIPEA	Ethyl diisopropylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethyl formamide
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio

EDG	Electron donating group
ee	Enantiomeric excess
EI	Electron ionisation
eq.	Equivalent
er	Enantiomeric ratio
ESI	Electrospray ionisation
EWG	Electron withdrawing group
FAB	Fast atom bombardment
FMO	Frontier molecular orbital
h	Hour
hfacac	Hexafluoroacetylacetonate
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherence
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectroscopy
IR	Infrared
LDA	Lithium diisopropylamine
LiHMDS	Lithium hexamethyldisilazide
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m.p.	Melting point
m/z	Mass to charge ratio
min	Minute
MOM	Methoxymethyl
MS	Molecular sieves
Ms	Methanesulfonyl
MVK	Methyl vinyl ketone
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	4-Nitrobenzenesulfonyl

OMen	Menthyloxy
PCC	Pyridinium chlorochromate
pfb	Perfluorobutyrate
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PMB	*p*-Methoxylbenzyl
PS	Petroleum ether (40-60°C)
py	Pyridine
rt	Room temperature
SM	Starting material
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Temp.	Temperature
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammonium perruthenate (VII)
Ts	4-Toluenesulfonyl
UCL	University College London

CONTENTS

1. INTRODUCTION

The ocean is home to many organisms that produce a diverse range of natural products, which can be very different to those found in land-based life. Many of these natural products are structurally novel, and possess biological activities that may be useful in the treatment of diverse diseases. Thus the marine environment has attracted great interest from synthetic chemists and biologists alike.

In 1986, a fascinating group of such structurally unusual alkaloids were found in extracts from the Mediterranean sponge *Reniera sarai* by Cimino and co-workers.[1] The main metabolites were classified into two groups, each containing alkaloids with distinct polycyclic skeletons. Sarains 1-3 consist of a *trans*-fused quinolizidone system linked to an unsaturated piperidine ring, both directly and by two hydrocarbon chains (Figure 1). Some minor co-occurring alkaloids, isosarains 1-3, were also isolated, which are stereoisomers of sarains 1-3, with inverted stereocentres at C1, C2 and C9.[1-4]
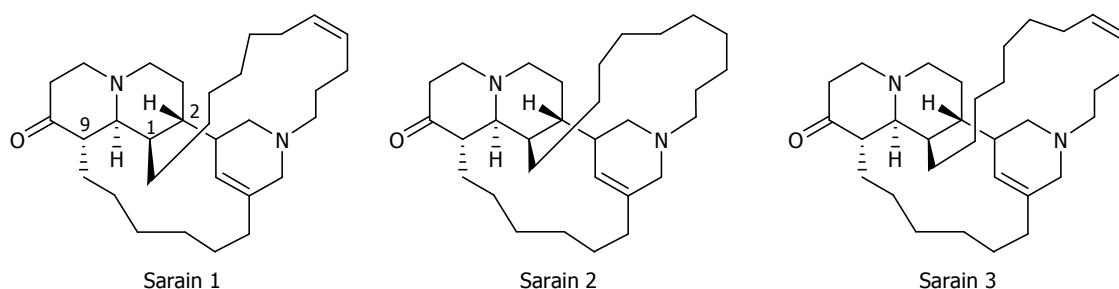
Figure 1: Sarains 1-3

The second major group of metabolites isolated from the sponge is sarains A-C[5,6] (**1-3**, Figure 2). Their unusual and challenging structure was elucidated by a combination of spectral studies and an X-ray crystal structure determination of the sarain A diacetate derivative **4**.[5] They were found to share a fused central core containing a diazatricycloundecane cage flanked by two peripheral macrocycles, the eastern of which is a 14-membered ring containing a vicinal diol and a skipped triene (with two *cis* and one *trans* double bond). With the structure of sarain A elucidated, the structures of sarains B and C were deciphered on the basis of extensive NMR studies. The three sarains were found to differ in the size and level of unsaturation of the western macrocycle; sarains A, B and C contain a 13-, 14- or 15-membered ring respectively, and there is an extra double bond in sarains B and C.[6]
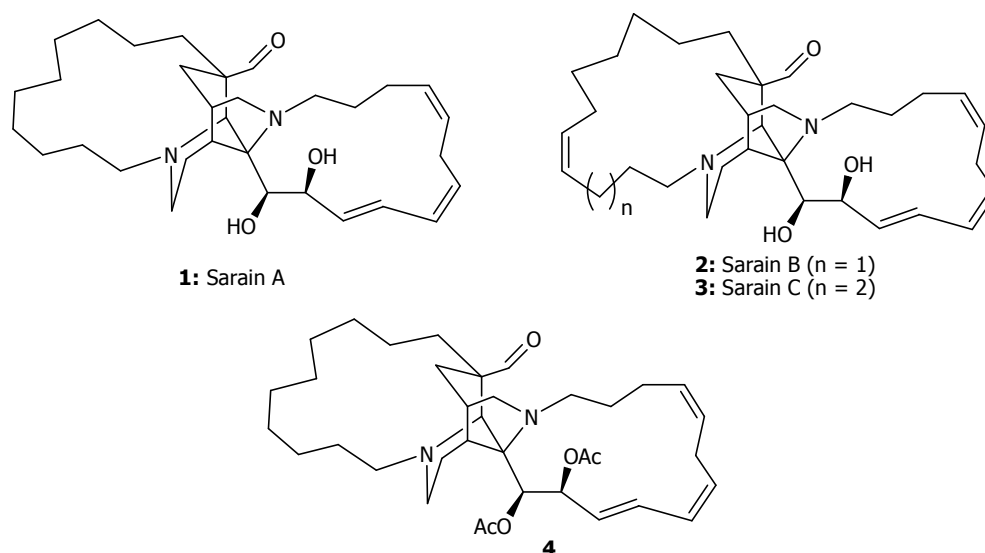
Figure 2: Sarains A-C and diacetate derivative 4

Another intriguing structural feature of sarains A-C is their zwitterionic property, whereby in the common tricyclic core there is a strong 'proximity interaction' between the tertiary amine at N1 and the carbonyl at C2 (Figure 3). This was found to be sensitive to pH and solvent environment, as treatment with acid causes the characteristic aldehyde peaks in NMR and IR spectra to disappear.[5-7] In addition, by running the ^{1}H and ^{13}C NMR in the presence of CD_3COOD, signals were observed at δ 5.25 and δ 97.1 respectively. These were assigned to the methine moiety between the quaternary nitrogen atom and the hydroxy group, shown in bold.
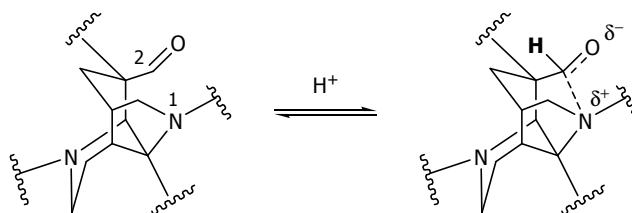
Figure 3: Proximity interaction displayed by sarains A-C

1.1. Properties of the sarains

The sarains were found to strongly retain inorganic salts, giving them catalytic properties comparable to those of crown ethers.[1] They are able to dissolve compounds such as potassium acetate in organic solvents, enhancing the nucleophilic properties of the anion.[1] With regard to biological properties, the absence of epibionts on the surface of the sponge suggested that sarains display a protective role against these fouling

organisms. Preliminary screenings on the biological activities of sarains demonstrated moderate antibacterial, insecticidal and antitumour properties.[8] Sarains 1-3 were generally more active than sarains A-C when studied individually, but both were less active than the crude extract from the sponge. This increased activity may either be due to a synergistic effect of the sarains, or due to strong activity from minor co-occurring metabolites. It should be noted however, that the activity of sarains A-C could be influenced by pH, as the tricyclic core can adopt two conformations (see Figure 3).

1.2. Proposed biosynthetic pathway

Despite the obvious differences in structural skeleton, the sarains are believed to have the same biogenetic origin as some other alkaloids including keramaphidin B and the manzamines (Figure 4).[9,10] These products are thought to arise from intramolecular cyclisations of bis(dihydropyridine) macrocylic intermediates, which are derived from condensation of acrolein and long chain aminoaldehydes.[9]

1: Sarain A

Keramaphidin B

Manzamine A
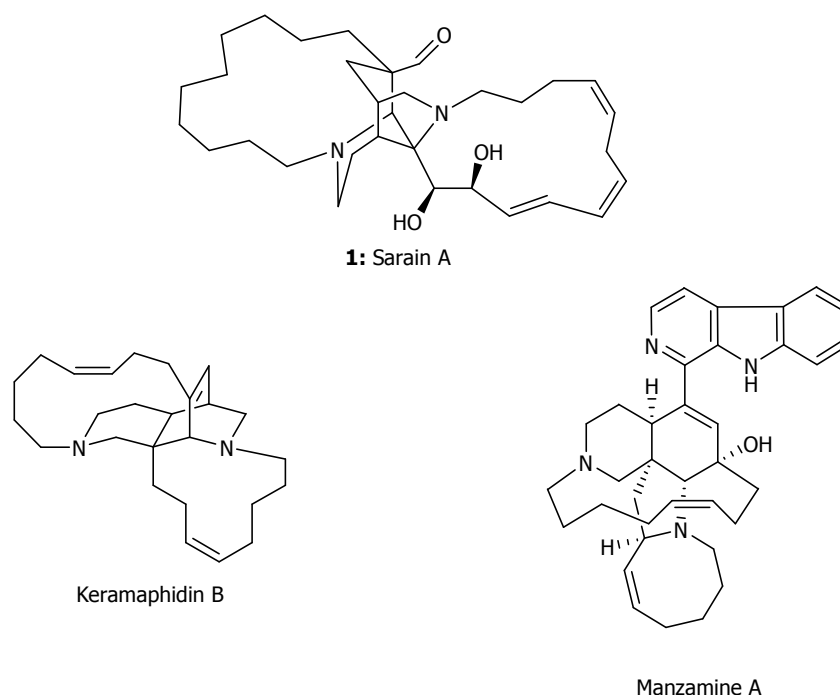
Figure 4

A proposed mechanism for the cyclisation of these species to form sarains A-C was put forward by Marazano (Scheme 1).[11] A protonation of enamine **5** to iminium species **6**, followed by an intramolecular cyclisation leads to **7**. Subsequent reduction of the α,β-unsaturated iminium ion affords **8**, and its reaction with an electrophile, such as Br$^+$

provides **9**. A further cyclisation generates tricyclic iminium species **10**, which is trapped with water to give hemiaminal **11**, and a final cyclisation completes the biosynthesis of sarains A-C, with tetracycle **12** displaying the proximity interactions shown in Figure 3.
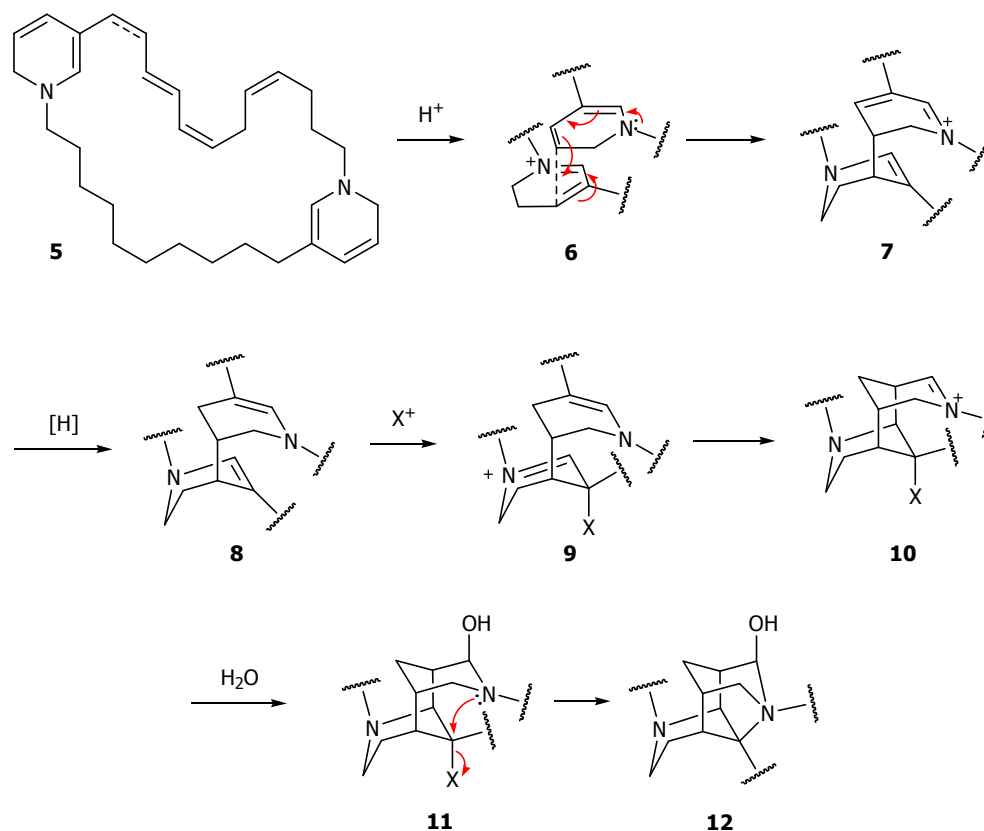
Scheme 1: Biosynthesis of sarain core

Sarains A-C and sarains 1-3 are derived from the same sponge but the two groups of alkaloids have completely different skeletons. Cimino has noted that the skeletons of sarain A (**13**) and that of sarain 2 (**15**) show a common 10-membered alkyl chain skeleton, as highlighted in Figure 5.[7] Based on these similarities, he suggested a related biogenetic origin, as bond disconnection of the two sarains leads to piperidine derivatives **14** and **16**. It can be envisaged that coupling of the same precursor (the highlighted region) with a 3-alkyl piperidine containing 10 and 12 carbons in the alkyl chain would lead to sarain A and sarain 2 respectively.
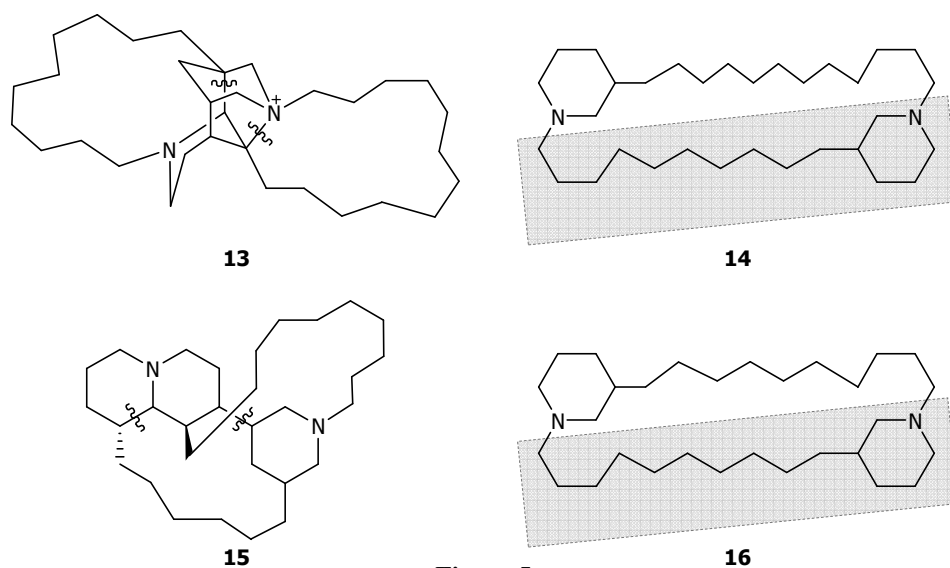
Figure 5

A second biosynthetic pathway that does not involve the formation of bis(dihydropyridines) has also been proposed by Marazano (Scheme 2).[12] A retro-Mannich disconnection leads to iminium ion **17**, which could result from condensation of the corresponding amino-aldehyde **18**. This in turn can be derived from a reductive amination, with reduction of the carboxylic acid and of two double bonds in **19**.
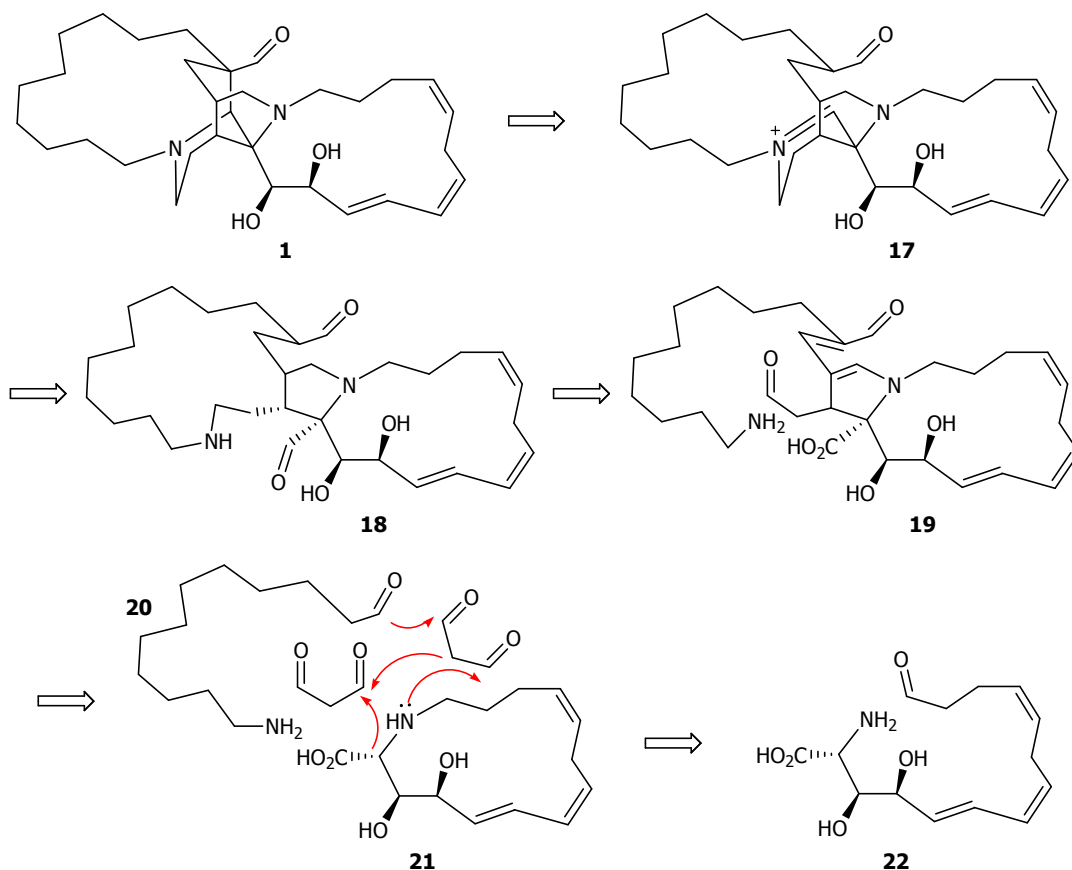
Scheme 2: Alternative biosynthesis of sarain A

It is anticipated that intermediate **19** is the result of multiple condensations between amino-aldehyde **20**, two malondialdehyde units and macrocycle **21**, which results from an intramolecular reductive amination of sphingolipid derivative **22**. Thus it is proposed that the biosynthesis of sarain A is closely related to the polyketide pathway, and includes intermediates which may be derived from secondary metabolites of the spingolipid family.

1.3. Synthetic background

Although sarains A-C display some biological activity, what interests most chemists in this fascinating class of compounds are their rather unusual structure, which have attracted a number of groups to embark on the challenge of its synthesis. Arguably the most difficult component of the synthesis is that of the tricyclic core; this has been accomplished by five groups, with the first by Weinreb in 1991.[13] A review of the various successful approaches is described, starting from the route by Overman,[14] who was the first to complete the total synthesis of sarain A in 2006.

1.3.1. Overman's total synthesis of sarain A

In 1998, Overman reported the first asymmetric route to the sarain core,[15] beginning the synthesis by converting L-diethyl tartrate to oxazoline **23** in 5 steps (Scheme 3). A key intermolecular Michael reaction under optimised conditions provided oxazoline **24** in good diastereoselectivity, and subsequent *N*-Boc deprotection, cyclisation and alkylation afforded lactam **25**, which translactamised to pyrrolidinone **26** upon cleavage of the oxazoline ring. Elaboration to lactone **27** was followed by partial reduction and deprotonation to give tetracycle **28**.
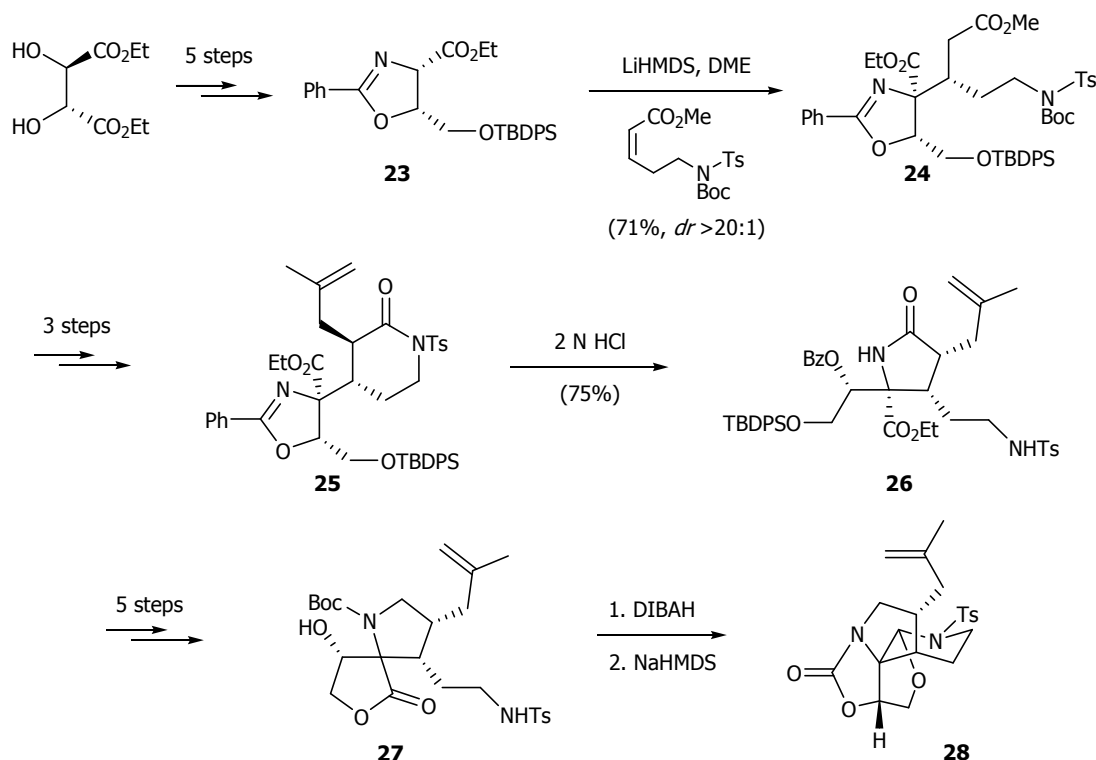
Scheme 3: Synthesis of oxazolidinone 28

To complete the synthesis of the sarain core, olefin **28** was converted to silyl enol ether **29**, which upon treatment with BBr₃, underwent an intramolecular enoxysilane-*N*-sulfonyliminium ion cyclisation to furnish the diazatricycloundecanes **30** and **31** (desired diastereoisomer) in a 3:1 ratio.
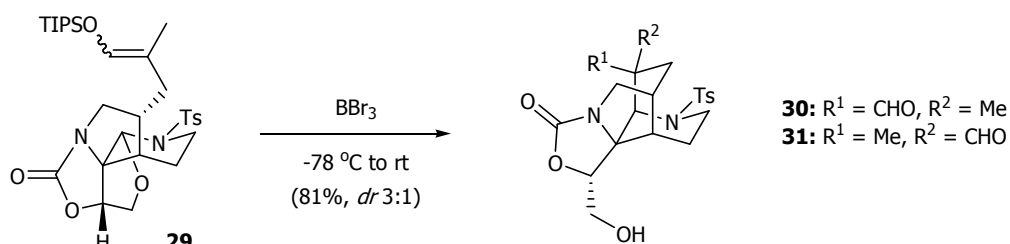
Scheme 4: Completion of Overman's first generation synthesis of the sarain core

Overman has since improved the diastereoselectivity of the final cyclisation.[16] It was postulated that replacing the methyl group with a larger side chain at the alkene would not only provide a handle to synthesise the western macrocycle, but would also serve to sterically promote cyclisation to the desired diastereoisomer (Scheme 5). In addition, he postulated that it is likely that the cyclisation mechanism proceeded through the (*E*)-OTIPS enol ether rather than a boron enolate or enol.[16] Thus optimised reaction conditions that converted **32** into sarain core derivative **33** in excellent yield and diastereoselectivity involved the use of a pyridine buffer to prevent premature O-Si

bond cleavage, and at higher temperatures to promote double bond isomerisation to the *E*-alkene.
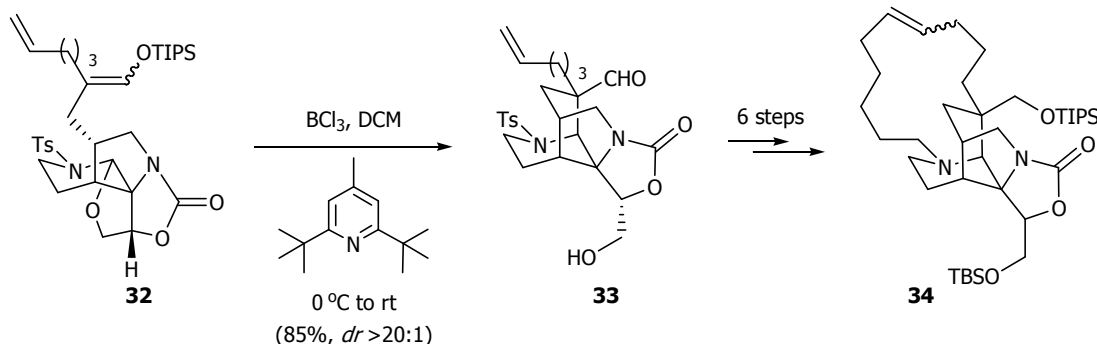
Scheme 5: Towards the synthesis of western macrocycle

After several protecting group manipulations, including removal of the *N*-tosyl group, the newly liberated amine was treated with 6-hepten-1-al, and a subsequent ring-closing metathesis then provided unsaturated macrocycle **34** in 75-85% yield.[14,16,17]

The final macrocycle was installed by an intramolecular Stille coupling of stannane iodide **35**. Subsequent reduction of the hemiaminal moiety to **36**, followed by a buffered oxidation of the resulting primary alcohol, and removal of both protecting groups completed the total synthesis of (−)-sarain A.
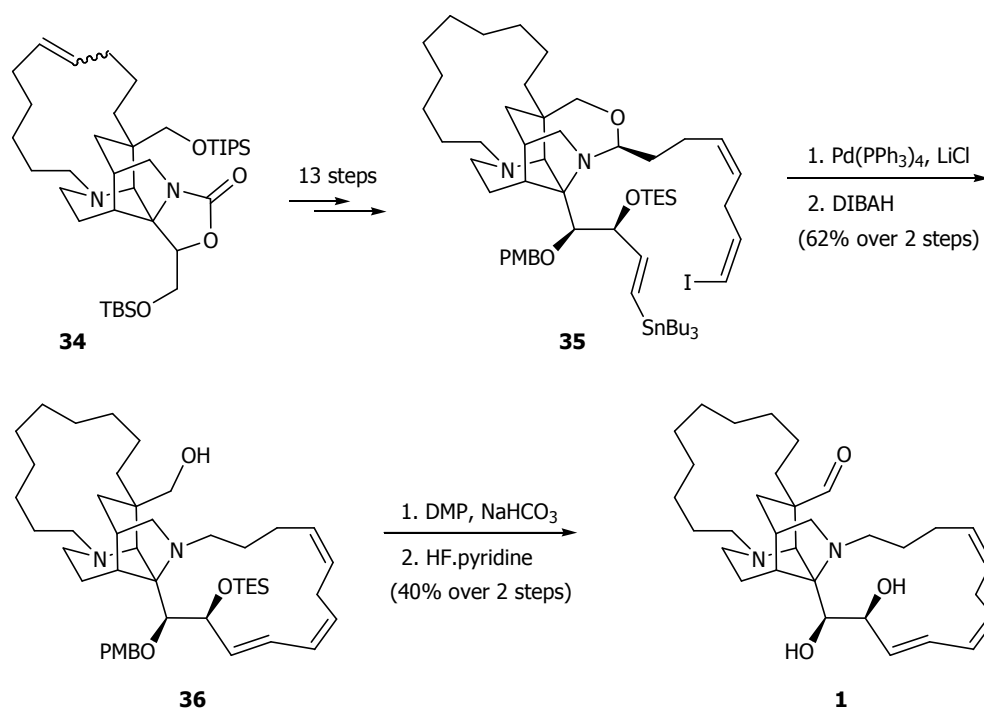
Scheme 6: Completion of total synthesis of (−)-sarain A

1.3.2. Weinreb's progress towards the synthesis of sarain A

Weinreb's first publication of a strategy to the sarain core was made in 1991.[13] Since then, the sequence of steps has been refined, with functional handles provided in his target molecule for the attachment of the two macrocycles (Scheme 7).[18-20] The key strategic steps include the stereospecific [3+2]-azomethine ylide/olefin cycloaddition that, *via* dipolar intermediate **37**, forms the bicyclic system in **38**. Subsequent protecting group manipulations and functionalisation at C3' provided alcohol **39**. This was converted to a mixture of acetates **40** which was treated with the Fleming silyl cuprate reagent to give allyl silane **41** as a mixture of geometric isomers. The sulfonamide lactam was then partially reduced and the resulting hemiaminal underwent an allylsilane/*N*-sulfonyliminium ion cyclisation upon treatment with FeCl$_3$ to give core fragment **42** as a mixture of epimers.
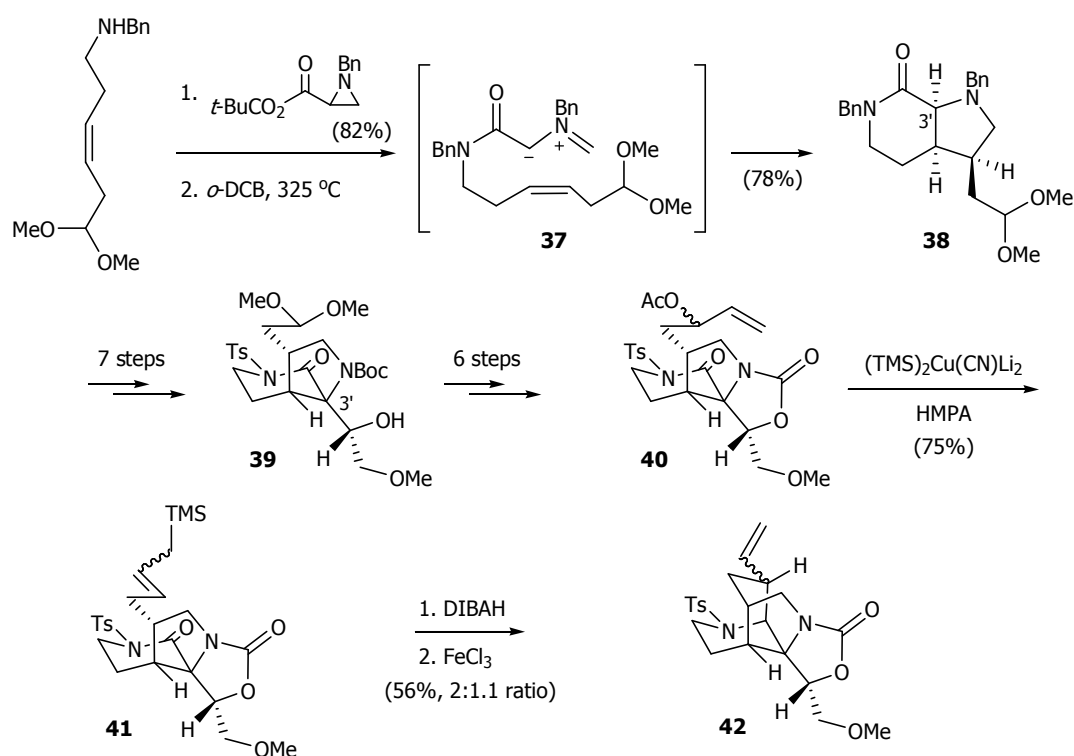
Scheme 7: Weinreb's latest synthesis of sarain core

Weinreb's strategy towards the installation of the western macrocycle began by conversion of olefin **42** to nitrile **43** in five steps.[20] The formation of epimers in the final stage of the core assembly had no overall significance to the total synthesis, as deprotonation of nitrile **43** led to an anion which underwent a stereoselective alkylation

with the mesylate of 4-penten-1-ol, from the least hindered equatorial direction. Reductions followed by protecting group manipulations, and acylation at the piperidine nitrogen provided the second handle for a ring closing metathesis to form macrocycle **44** (Scheme 8).
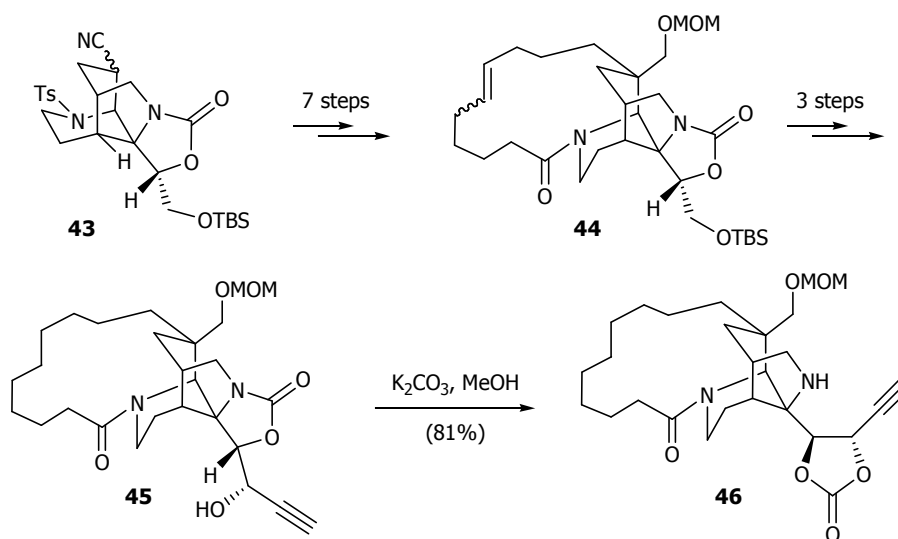
Scheme 8: Weinreb's progress towards total synthesis of sarain A

After reduction of the newly formed olefin in **44**, the silyl ether was cleaved and the resulting alcohol oxidised to the aldehyde. A stereoselective chelation controlled addition of ethynylmagnesium bromide to the aldehyde then produced oxazolidinone **45**, thereby establishing the remaining stereocentre *en route* to the eastern macrocycle. Under mildly basic conditions, this oxazolidinone rearranged to cyclic carbonate **46**, simultaneously protecting the diol and freeing the nitrogen for further investigations into completing the eastern ring, and ultimately the total synthesis.[20]

1.3.3. Heathcock's progress towards the synthesis of sarain A

Like Weinreb, Heathcock's approach to the sarain core involved an intramolecular azomethine ylide cyclisation. In this route, the azomethine ylide was originally generated by flash vacuum pyrolysis of an aziridine activated by ester and amide carbonyl groups.[21-23] Limitations in the scale-up capabilities of that route led to pursuance of an alternative, and the azomethine ylide was eventually generated by condensation of amine **47** with paraformaldehyde, forming bicycle **48** in good yields (Scheme 9).[24]
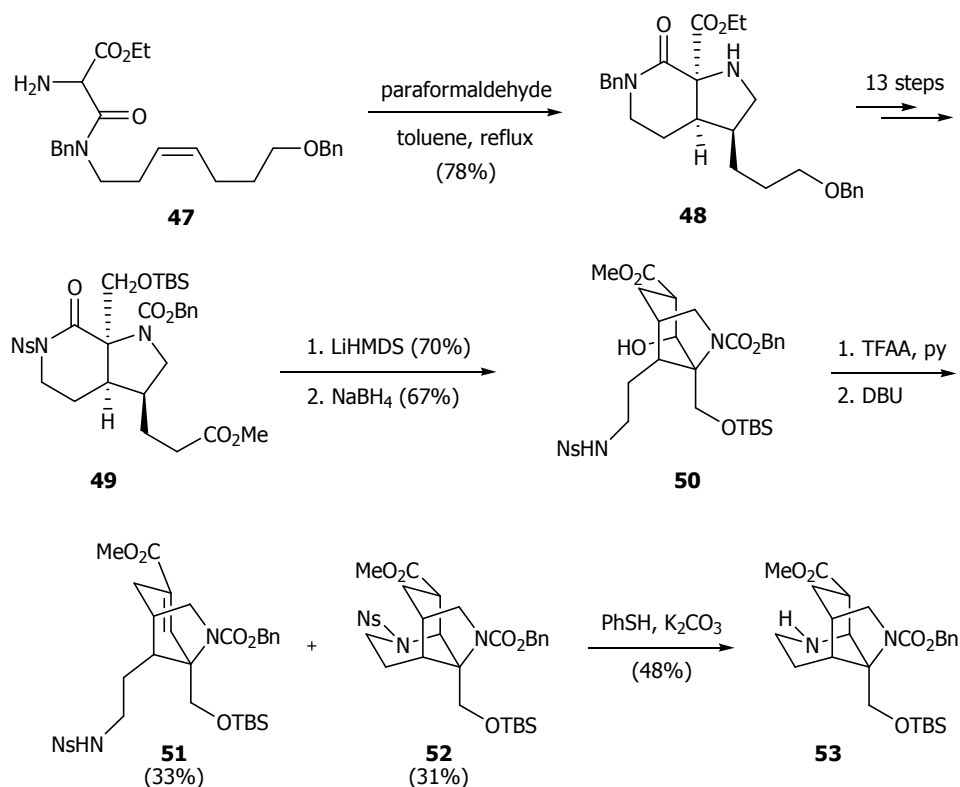
Scheme 9: Heathcock's synthesis of sarain core

Further functionalisation of bicycle **48**, including extensive protecting group manipulations afforded ester **49**, which underwent isomerisation *via* a base promoted Dieckmann reaction to give a β-keto ester that was reduced to alcohol **50**. Exposure of the derived trifluoroacetate to DBU produced a mixture of unreacted starting material, α,β-unsaturated ester **51** in 33% yield, and the desired tricyclic nucleus **52** in 31% yield. Finally, removal of the nosyl group from a mixture of the latter two compounds released the amines, thus promoting 1,4-addition in the uncyclised material, and furnished the sarain core derivative **53** in 48% yield.

While other synthetic groups were focusing their attention on the synthesis of the western macrocycle, Heathcock was the first to synthesise a model of the eastern macrocycle (Scheme 10).[23] The two stereocentres in the model system were installed early, achieved by a catalytic dihydroxylation to give diol **54**. Elaboration to (*E*)-vinyl iodide **55** and acylation with acid chloride **56** gave amide **57**. A palladium catalysed cyclisation gave yne-diene **58**, which was subjected to hydrozirconation followed by hydrolysis of the vinylzirconium intermediate with silica gel to complete the synthesis of the triene unit within **59**.
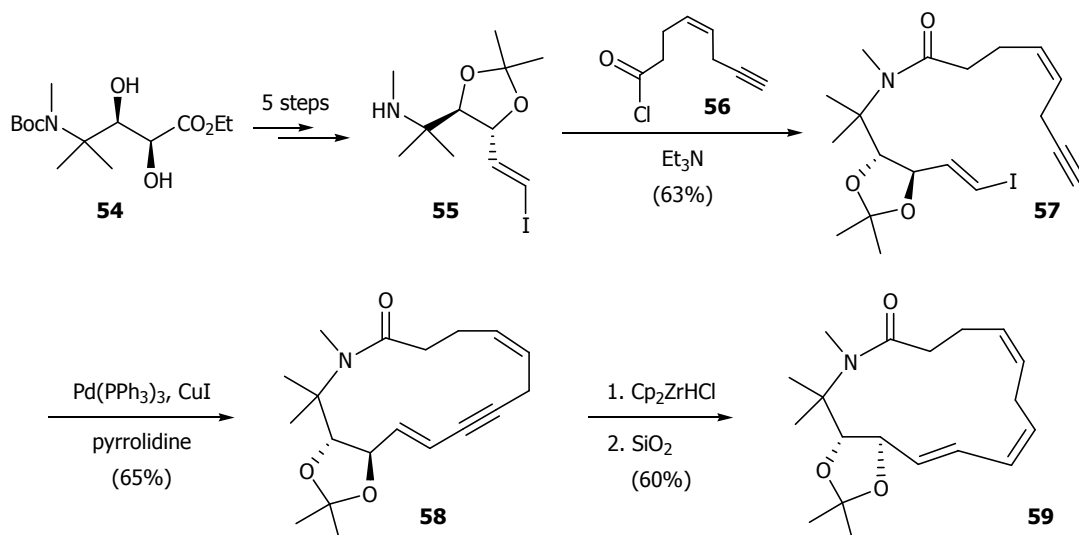
Scheme 10: Heathcock's synthesis of a model eastern macrocycle

1.3.4. Cha's progress towards the synthesis of sarain A

Cha's synthesis of the sarain core is the shortest to date, employing a [4+3]-cycloaddition between a 3-oxidopyridinium betaine and cyclopentadiene (Scheme 11). Complications involving the use of 5-nitro-2-pyridine-substituted compounds in the initial route[25] led to a second generation synthesis using an *E*-β-(4'-fluorobenzoyl)vinyl derivative in **60**.[26] This not only modestly improved the yield of the key cyclisation to **61**, but more importantly, eased the subsequent removal of the protecting group. A series of steps involving the cleavage of the olefin in **61** ultimately provided diol **62**, which was oxidised with TPAP to furnish lactone **63** as the major product, with only a small amount (5%) of the other regioisomer. The rationale proposed for this surprising selectivity is the difference in steric environment experienced by the two hydroxymethyl substituents of **62**, due to the presence of the *Z*-double bond and the carbamate group.[26] The opening of the lactone ring followed by protection of the primary alcohol in **64**, then treatment with NaH to promote Michael addition, provided the final ring of the desired tricyclic core in **65** in high yield.
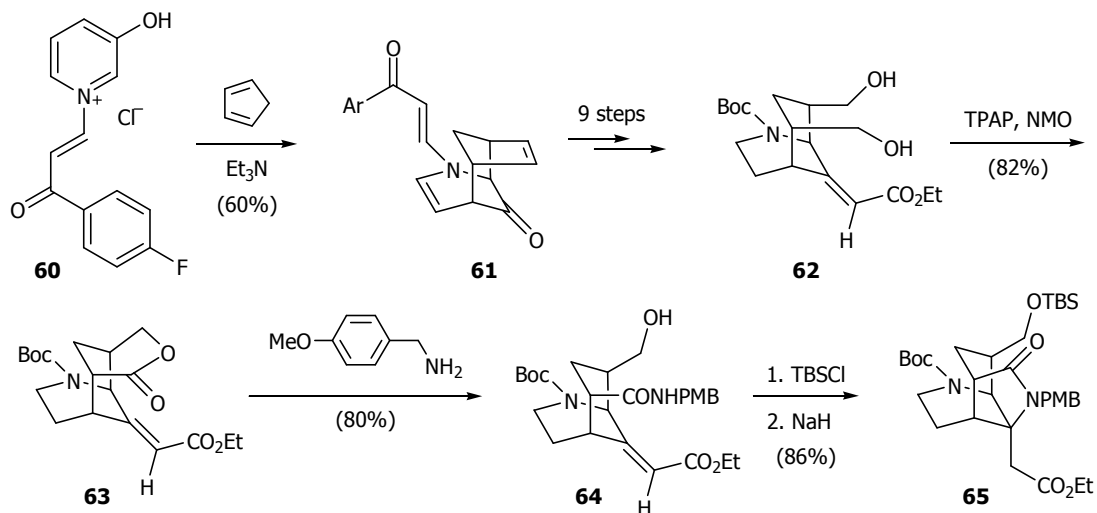
Scheme 11: Cha's synthesis of the sarain core

Conversion of the protected primary alcohol **65** into aldehyde **66** followed by an aldol condensation-Tischenko reaction provided alcohol **67** (Scheme 12). A series of steps including an intramolecular Horner-Wadsworth-Emmons reaction then produced lactone **68**, which was converted into a substrate for a ring-closing metathesis with second generation Grubbs' catalyst to furnish the 13-membered macrocycle **69**, and then transformed into **70**. In addition, Cha has also brought a second compound through the synthetic route, where the 5-membered lactam is protected with a $(CH_2)_4OPMB$ instead of the PMB group, with the purpose of providing a handle for future attachment of the eastern macrocycle.[26]
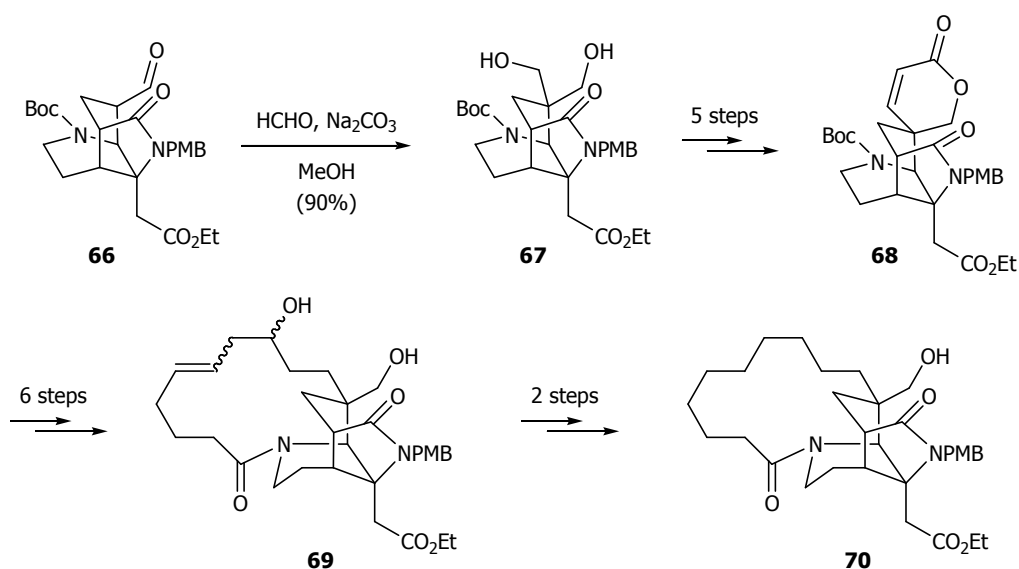
Scheme 12: Cha's synthesis of 70

1.3.5. Marazano's synthesis of the sarain core

The strategy adopted by Marazano is based upon their proposed biomimetic route to the sarain core, in which multiple condensations of amino-aldehyde and malondialdehyde units lead to a key intermediate **71** (*cf*. **19** in Scheme 2).[12,27]
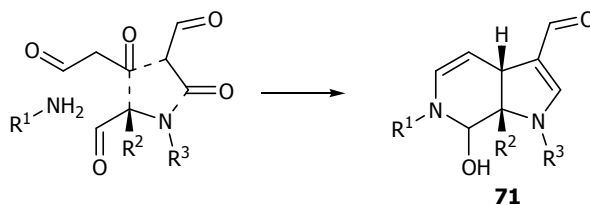
Scheme 13

Thus Marazano's synthesis began by carrying out multi-component couplings, which first involved deprotonation of imine **72** and reaction with a bromoacrylamide derivative, followed by imine hydrolysis, to give amine salt **73** (Scheme 14). This was treated with malonaldehyde sodium salt to form intermediate **74**, which was deprotonated to drive its cyclisation, and then methylated to provide the functionalised diazabicyclo[4.3.0]nonane **75**, with a *cis*-fused ring junction. Reduction of the enaminal functionality by hydrogenation in the presence of catalytic quantities of PtO_2 and $SnCl_2$ provided alcohol **76** with only modest diastereoselectivity. Reduction of this material with DIBAH provided two distinct, separable compounds, **77** and **78**, with the major product being tricycle **77** that possesses the correct relative stereochemistry.
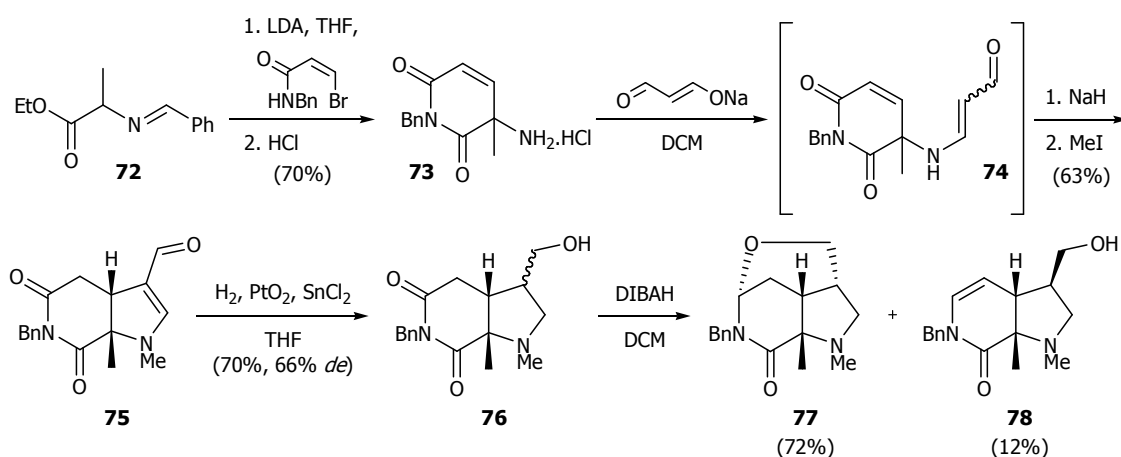
Scheme 14

A Lewis acid mediated rearrangement of **77** gave enamine **79**, and this was converted into aldehyde **80** in 5 steps *via* a nitrile intermediate. The closing stages of Marazano's route involved conversion of aldehyde **80** into allylsilane **81** for a ferric chloride

cyclisation to the tricyclic core analogue **82**, a method akin to that previously utilised by Weinreb in the final step of his synthesis of the sarain core.[13]
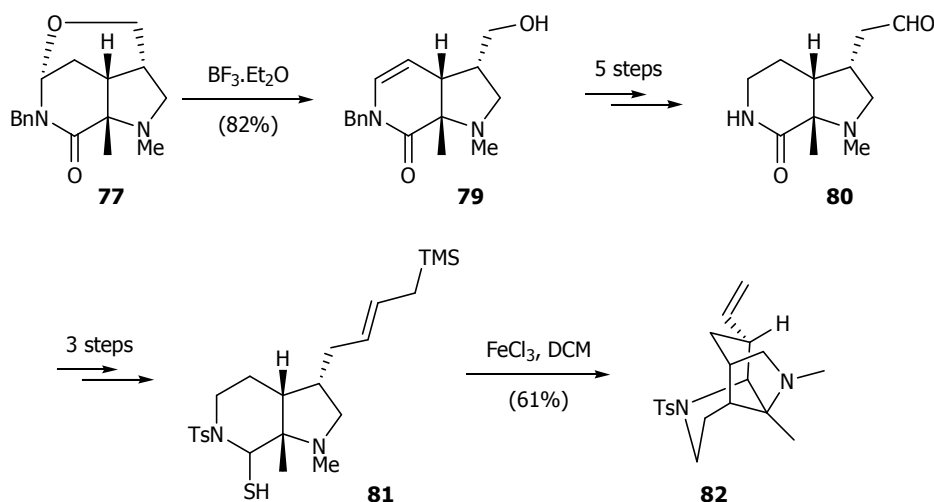
Scheme 15: Completion of Marazano's synthesis of the sarain core

1.3.6. Our synthetic approach

As a key intermediate in the total synthesis of sarain A, a synthesis of tricycle **83** is proposed. It contains the tricyclic framework of the sarain core, but with a keto-substituent in place of the formyl group (Figure 6).
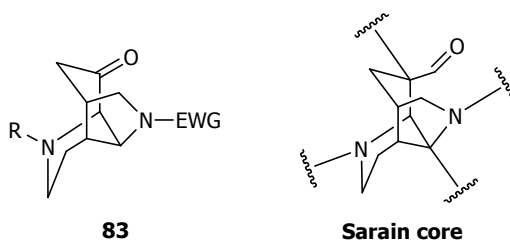
Figure 6: Synthetic target

It is anticipated that treatment of diazoketone **84** with a metal catalyst will lead to metallocarbene formation, followed by cyclisation from the more nucleophilic nitrogen to provide ammonium ylide **85** (Scheme 16). Subsequent C-N bond cleavage by ring opening from the neighbouring nitrogen, and an internal Mannich cyclisation of the enolate moiety onto the iminium ion in **86** provides target **83**. In summary, this route involves a novel carbene-derived ammonium ylide rearrangement, so that in just one transformation, the relatively simple bicyclic compound **84** can be converted to the complex tricyclic target **83**.

Scheme 16: Our synthetic strategy
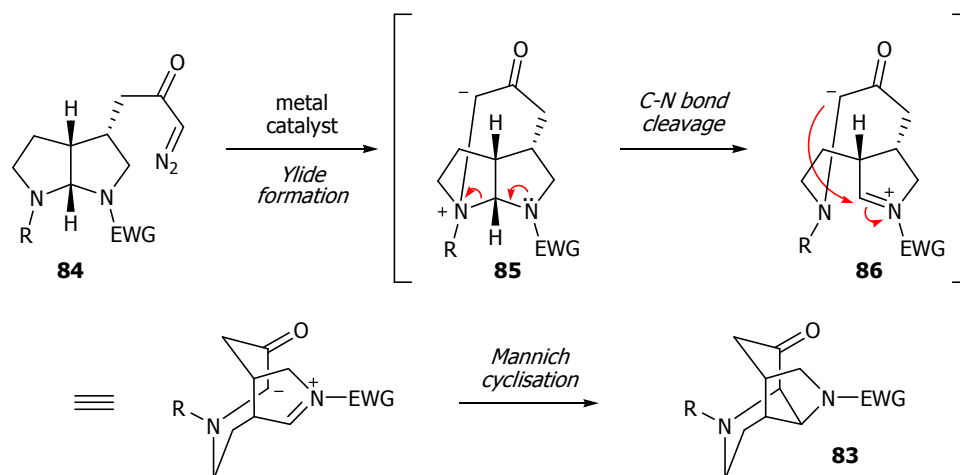
There is little literature precedent for the rearrangement proposed in Scheme 16. However, similarities can be drawn with the use of sulfur ylides by Kametani and co-workers in their work towards the synthesis of pyrrolizidine alkaloids.[28] The diazodecomposition of **87** followed by intramolecular trapping from the sulfur atom generated sulfur ylide **88**, which underwent a ring opening/ring closure rearrangement to form bicycle **89** (Scheme 17).

Scheme 17
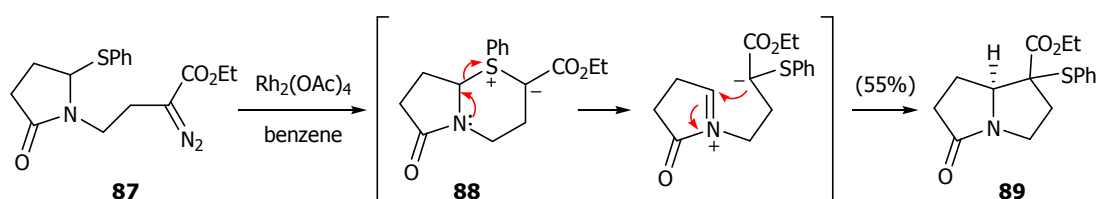
An intermolecular variant of this rearrangement that promotes ring expansions of 1,3-oxathiolanes into 1,4-oxathianes has also been developed by our group (*vide infra*).

1.3.6.1. *Previous work within the Porter group*

A number of different strategies to synthesise bicyclic aminal **84** had previously been investigated by the group.[29] However, all these syntheses were lengthy, low yielding, gave racemic products and moreover, were incomplete. In one approach to investigate the formation of the 5,5-bicyclic aminal system, *N*-benzylpyrrolidin-2-one was treated with LDA, then alkylated with allyl bromide to provide a terminal alkene. The alkene was subsequently cleaved by reductive ozonolysis to give primary alcohol **90** (Scheme 18). Mesylation and then azide displacement to give **91**, followed by a reductive

cyclisation protocol developed within the group,[30] produced the bicyclic aminal **92**. This was converted into formamide **93**, an analogue of target **84** that lacks the key side chain at C3.
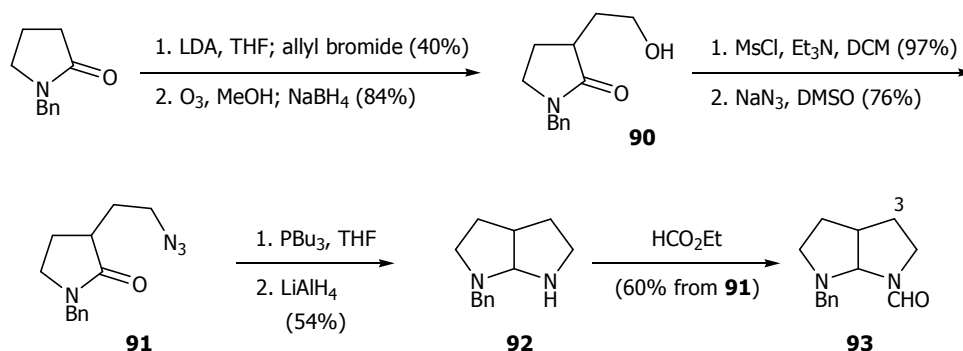
Scheme 18: Preparation of bicyclic aminal 93

A proposed mechanism for the reductive cyclisation is detailed in Scheme 19; it begins with a Staudinger reaction of azide **91** to produce iminophosphorane **94**. Subsequent hydride addition to effect partial reduction of the amide, followed by cyclisation of the nucleophilic iminophosphorane onto the iminium ion leads to bicycle **95**. Finally, a loss of tributylphosphine oxide during aqueous workup provides the desired aminal **92**.
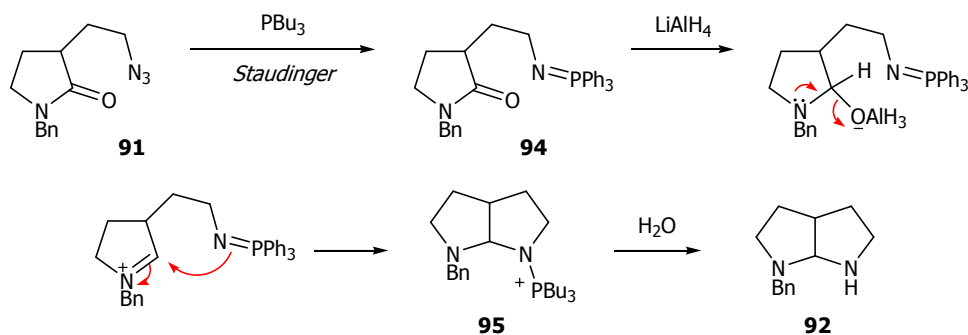
Scheme 19: Proposed mechanism of reductive cyclisation

The simple bicyclic aminal **93** was treated with a silylated diazoester in the presence of a catalytic $Rh_2(OAc)_4$ to ascertain whether it would undergo an intermolecular variant of the intramolecular ring expansion reaction featured in our proposed route to the sarain core (see Scheme 16). However, rather than being the envisaged piperidine **96**, the isolated product **97** was in fact the result of an unexpected olefination of the amide carbonyl (Scheme 20).
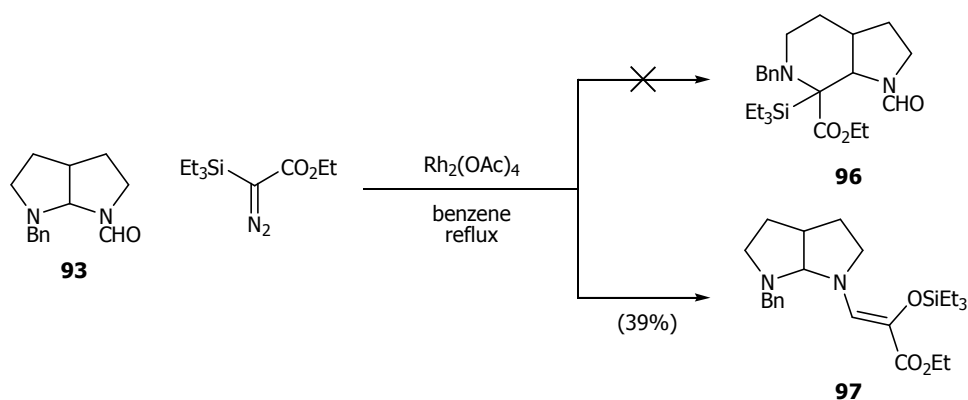
Scheme 20: Unexpected olefination of the formamide group

1.4. Aims

The aims of this research are:

- To develop a route to functionalised bicyclic aminal **84**

- To investigate a carbene-derived ammonium ylide rearrangement as a route to tricycle **83**, which bears the tricyclic framework of the sarain core

- To investigate the scope and limitations of the unexpected olefination reaction.

This research has been largely based around the aims listed above, the results of which will be discussed in turn. However, as the overall transformation in the conversion of ylide **85** to the tricycle **83** is essentially a Stevens rearrangement, albeit unusual in that it involves a neighbouring heteroatom, the next section will begin by introducing this reaction. The synthetic applications of the Stevens rearrangement of ammonium ylides will also be reviewed.

2. SYNTHETIC APPLICATIONS OF THE STEVENS REARRANGEMENT OF AMMONIUM YLIDES

Ammonium ylides are important intermediates in organic synthesis, as they are capable of rearrangements under mild conditions to generate a variety of nitrogen containing compounds in a stereoselective manner. The first example of an [1,2]-rearrangement of an ammonium ylide was published by Stevens in 1928. Under basic conditions, ammonium salt **98** was converted into product **100**, a result of an [1,2]-benzyl shift in the intermediate ylide **99** (Scheme 21).[31] This [1,2]-shift of a migrating group from a heteroatom to carbon is known as the Stevens rearrangement.
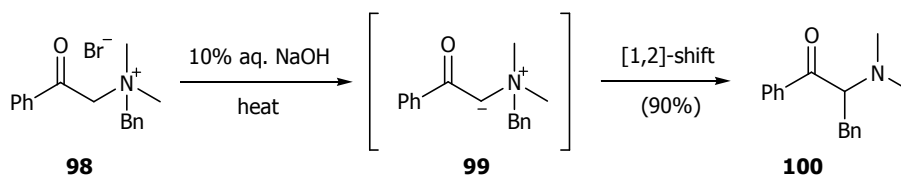
Scheme 21

The Stevens rearrangement is unlikely to proceed through a concerted [1,2]-shift, as it is a thermally forbidden process according to the Woodward-Hoffmann rules.[32] Most evidence instead suggests that the shift proceeds *via* a radical pair mechanism. This involves homolytic cleavage of the C-N bond in ylide **99**, generating a pair of radicals that are localised in a solvent cage. Rapid recombination to the more stable carbon radical centre then gives the rearranged product **100** (Scheme 22).[33-35] This mechanistic pathway also accounts for the high stereoselectivity observed in the rearrangements, which proceed with retention of configuration of the migrating group.[36]
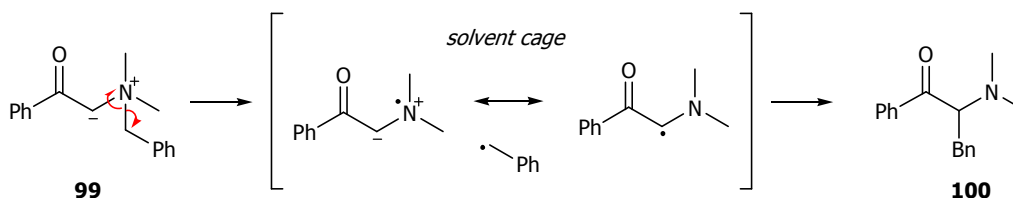
Scheme 22

2.1. Formation of ammonium ylides

Ammonium ylides[37] were classically generated by base-promoted deprotonation of ammonium salts, but there are disadvantages to their preparation in this way. These include the requirement for a two step synthesis, involving initial formation of the quaternary salt, followed by deprotonation; the latter may occur unspecifically if there is more than one acidic site. In addition, Hoffmann elimination of the ammonium salts can also compete with the Stevens rearrangement (Scheme 23).
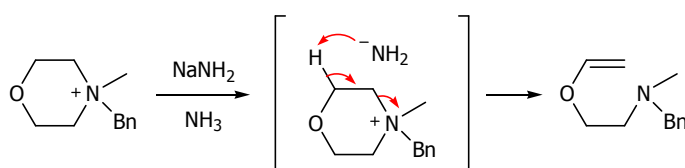
Scheme 23

Generation of ammonium ylides from the reaction of tertiary amines and carbenes is a useful alternative; it was first introduced by Stevens in 1952, whereby treatment of diazofluorene **101** with *N,N*-dimethylbenzylamine at elevated temperatures led to rearrangement product **102**.[38]
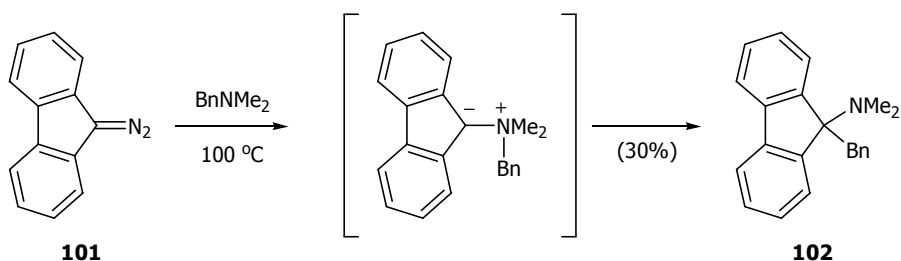
Scheme 24

2.1.1. Carbenes and carbenoids

Carbenes are neutral divalent species containing a carbon with six electrons in its valence shell, generally denoted **:**CR_2. The classic way to generate carbenes is the α-elimination of hydrogen halides from haloforms by treatment with base to produce dihalogenocarbenes. They can also be generated from the thermolysis or photolysis of diazo compounds, liberating nitrogen and forming a carbene.

Free carbenes are highly energetic species exhibiting a (largely) electrophilic centre, and are thus able to react with relatively unreactive moieties in a number of different ways. For example, carbenes are able to react with benzene, breaking its aromaticity to form the unstable norcaradiene intermediate **103**, which then undergoes an electrocyclic ring expansion to cycloheptatriene **104** (Scheme 25).[39] Due to this reactivity, carbenes were first thought to be of limited value in organic synthesis, as the reactions are unspecific and difficult to control.
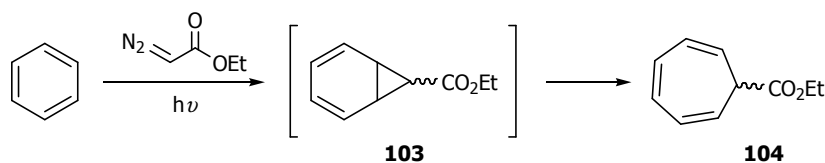
Scheme 25

Decomposition of diazo carbonyl compounds can be catalysed by the addition of transition metal catalysts, typically based around copper (*e.g.* $Cu(acac)_2$) and rhodium (*e.g.* $Rh_2(OAc)_4$), to form metal carbenes. The metallocarbene thus formed reacts in a similar manner to the free carbene, but its greater degree of stabilisation offers better control of reactivity. Carbenes can react with unactivated C-H bonds to form new bonds at unfunctionalised centres; the reaction proceeds in a concerted fashion, so that if the C-H moiety is at a stereogenic centre the stereochemistry is retained. This chemistry was utilised by Cane to generate **105** in the total synthesis of pentalenolactone (Scheme 26),[40] demonstrating the high selectivity that can be achieved with metallocarbenes.
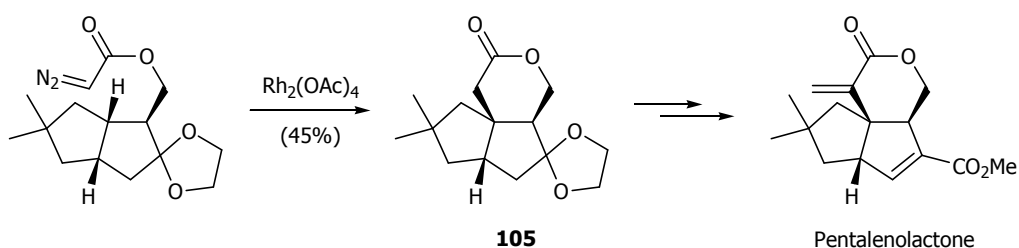
Scheme 26

2.1.2. Formation of ylides from diazo carbonyl compounds

Metallocarbenes are generally highly electrophilic intermediates and so react readily with lone pairs of heteroatoms to give the corresponding ylides. Scheme 27 illustrates this catalytic cycle, whereby reaction of a diazo compound with an appropriate metal

catalyst eliminates nitrogen and generates the highly electrophilic carbenoid intermediate **106**. Nucleophilic attack from a heteroatom (in this case, nitrogen) lone pair then generates **107**, and dissociation of this intermediate to ammonium ylide **108** releases the metal back into the catalytic cycle.
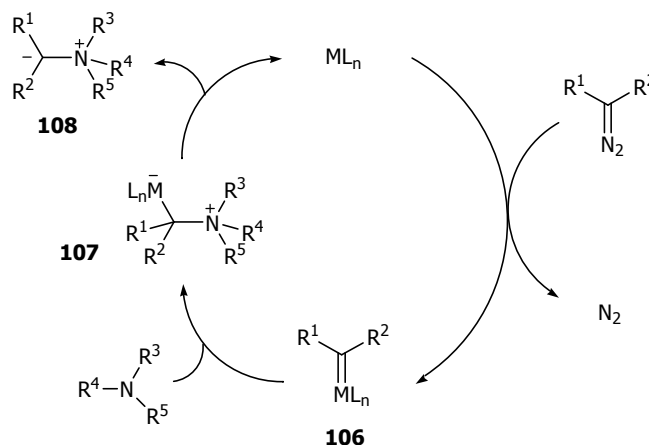
Scheme 27: Ammonium ylide generation by metal catalysed diazodecomposition

2.2. Some competing reactions to the Stevens rearrangement

Even though the emphasis of this section is placed on the Stevens [1,2]-rearrangement, it is noteworthy that other than the desired rearrangement, ammonium ylides can undergo several other competing reactions, which increases the potential for side products. These include [2,3]-sigmatropic rearrangements,[41] and a reaction of this type is the Sommelet-Hauser rearrangement.[42] This chemistry was utilised in the synthesis of the benzo-fused azonane product **111**, by treatment of ammonium salt **109** with base, then a ring expansion of the subsequent ammonium ylide **110** (Scheme 28).[43] The [2,3]-shift of ammonium ylides was also used by Clark to synthesise azalactone **113** from diazoester **112** in good yield.[44]
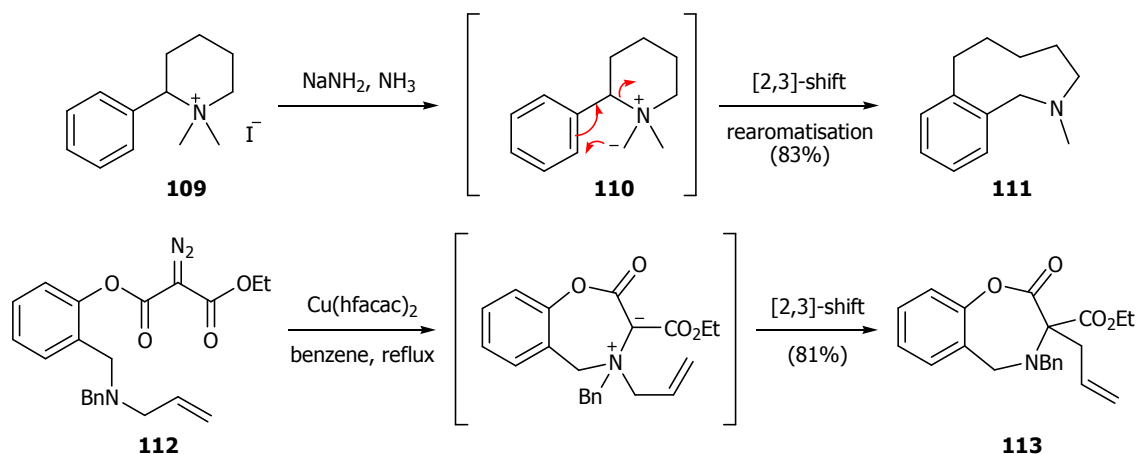
Scheme 28

In addition to the [2,3]-rearrangement, other reactions in competition with a Stevens rearrangement include fragmentation reactions, as was observed from treatment of azetidinone **114** with $Rh_2(OAc)_4$; formation of ylide **115** led to a proton abstraction from the benzylic carbon and cleavage of the N-O bond, losing benzaldehyde and forming carbapenam **116**.[45]
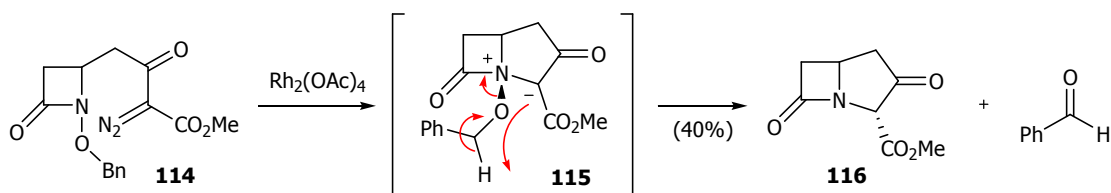
Scheme 29

Additionally, if the ylide is prepared from a carbene, formation of the ylide is in competition with cyclopropanation and C-H insertion reactions. Although it is important to be aware of the potential for these competing side reactions, they are normally avoidable by selecting the correct substrate and catalyst, and thus the Stevens rearrangement has been an important tool in the generation of many nitrogen containing compounds. There have been many developments in this area in the last decade, which are reviewed in the next section.

2.3. New methodologies employing the Stevens rearrangement

2.3.1. Silyl-directed Stevens rearrangement of ammonium ylides

West and Vanecko have developed a silyl-directed Stevens rearrangement for the stereoselective synthesis of hydroxylated quinolizidines.[46] This strategy began by preparing chiral silane **117** by asymmetric lithiation and silylation of the corresponding pyrrolidine. Conversion of silane **117** into the diazoketone **118**, followed by treatment with Cu(acac)$_2$ promoted a Stevens rearrangement of the intermediate ylide, and furnished the desired quinolizidine **119** as a single diastereoisomer in 58% yield and 77% *ee* (Scheme 30). The silyl group proved to be a suitable 'surrogate' to a hydroxyl group, as quinolizidine **119** was stereoselectively converted to quinolizidinediol **120** in excellent yields.
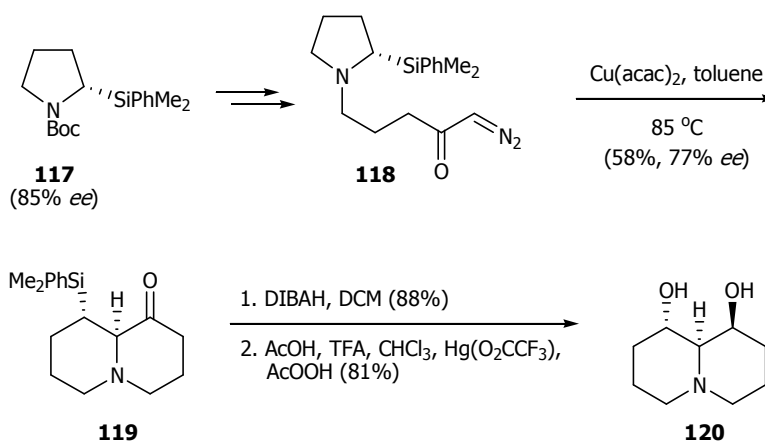
Scheme 30

2.3.2. Synthesis of *N*-fused tricyclic indoles

Iwasawa and co-workers have developed an efficient method for the construction of *N*-fused tricyclic indole derivatives that proceeds *via* a Stevens rearrangement.[47] Treatment of an irradiated solution of *o*-alkynylphenyl pyrrolidine derivatives **121** with W(CO)$_6$, or the corresponding piperidine or morpholine derivatives **123** with ReBr(CO)$_5$, provided indole products **122** and **124** respectively, both in good yields (Scheme 31).
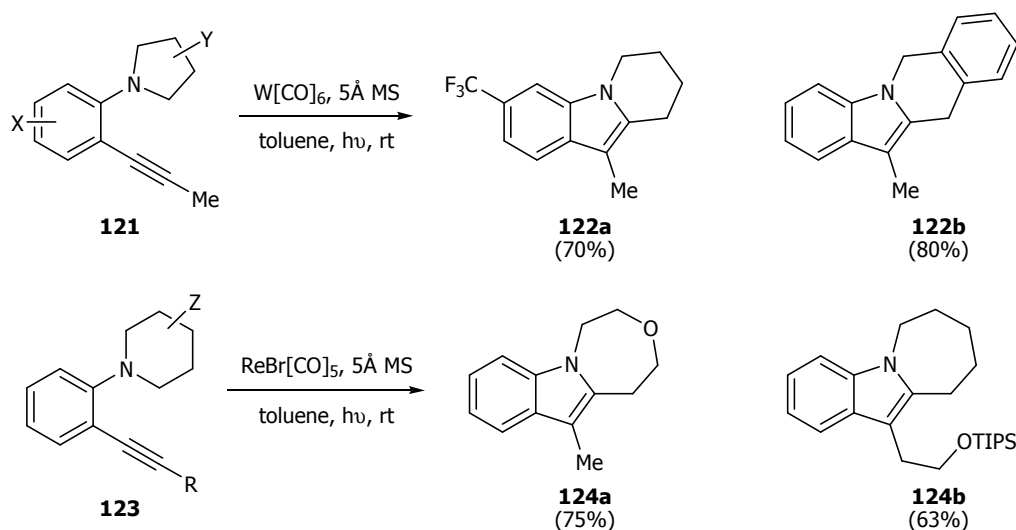
Scheme 31

A proposed mechanism for this transformation involves the initial generation of the electrophilically activated alkyne complex **125** (Scheme 32). Nucleophilic attack from the amine then gives the metallated ammonium ylide **126**, and a tandem Stevens rearrangement/1,2-alkyl shift completes the construction of indole products **122** and **124**.
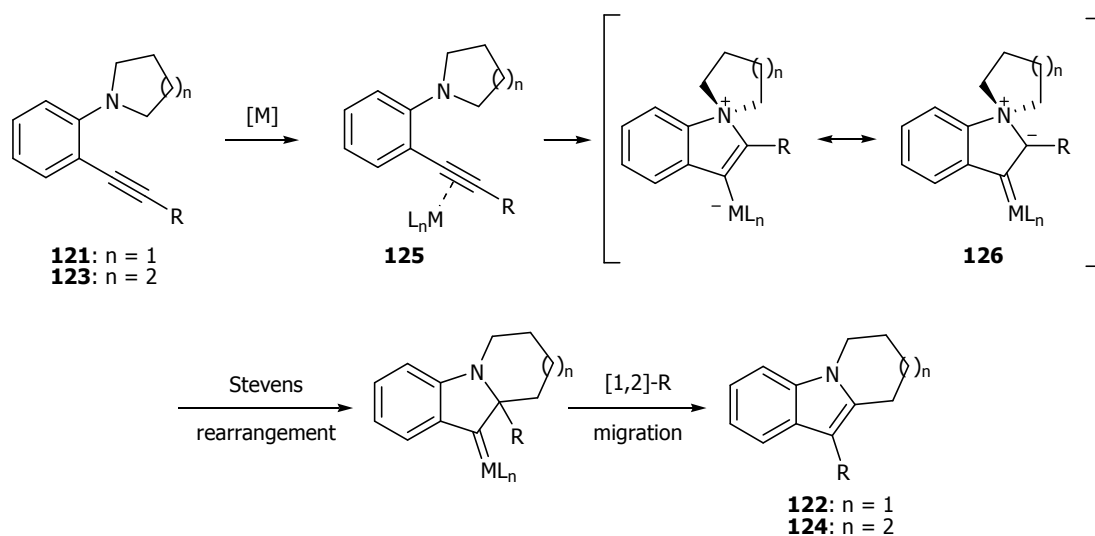
Scheme 32

2.3.3. Lewis acid mediated Stevens rearrangement of ammonium ylides

Somfai and co-workers have previously reported that glycine-derived *N*-allyl-*N*-benzylamines can be converted into the corresponding homoallylic amines by sequential

treatment with BBr$_3$ and base,[48] as the result of a [2,3]-sigmatropic rearrangement. It had also been reported that when there are unfavourable steric interactions in the substrate for a [2,3]-shift, or when elevated reaction temperatures are used, the [1,2]-rearrangement becomes a significant competing pathway to the [2,3]-rearrangement.[49,50] Based on this work, Somfai and Tuzina embarked on an investigation to prepare [1,2]-shift products in a similar way, using substrates that are less likely to undergo [2,3]-shifts. As predicted, treatment of glycine-derivative **127** with BBr$_3$ resulted in the formation of oxazaborolidine **128**, which upon deprotonation gave ylide **129** and then rearrangement product **130** after hydrolysis (Scheme 33).[51] This represents the first example of a Lewis acid mediated [1,2]-rearrangement of glycine derivatives. Optimal conditions involve the use of 1.2 equivalents of BBr$_3$ and 5 equivalents of Et$_3$N in DCM under microwave heating, and were successful for a number of glycine derivatives.

R^1	R^2	Yield / %
H	H	60
t-Bu	H	46
F	H	51
H	F	60
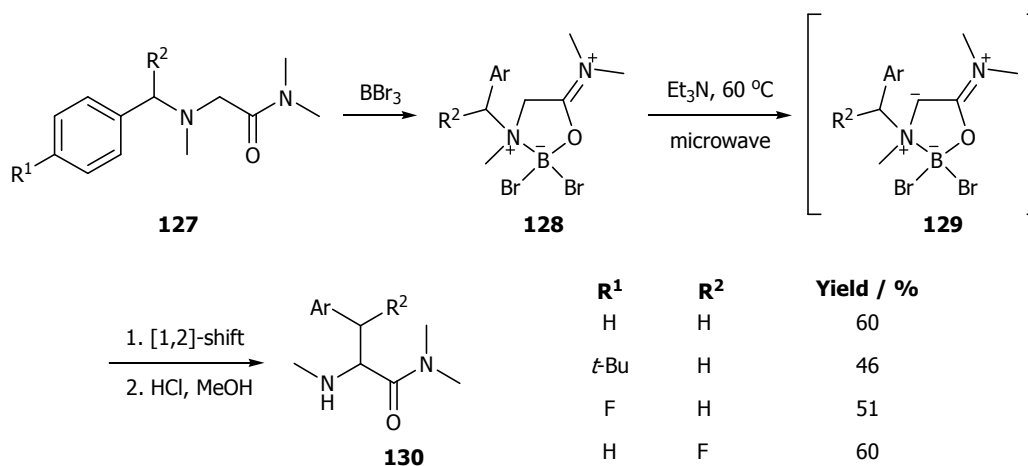
Scheme 33

2.3.4. A diastereoselective approach to chiral α-amino ketones

In 2004, Tomooka and co-workers described a novel Stevens rearrangement of cyclic hemiacetals as a diastereoselective approach to chiral α-amino ketones.[52] Treatment of racemic hemiacetal (±)-**131** with KO^{t}Bu in EtOH at room temperature furnished the hydroxy-ketone **132** in 35% yield and hemiacetal **133** in 40% yield, both as single diastereoisomers (Scheme 34). It was also observed that the hydroxy-ketone **132** easily cyclised to hemiacetal **133** on silica gel.

Scheme 34
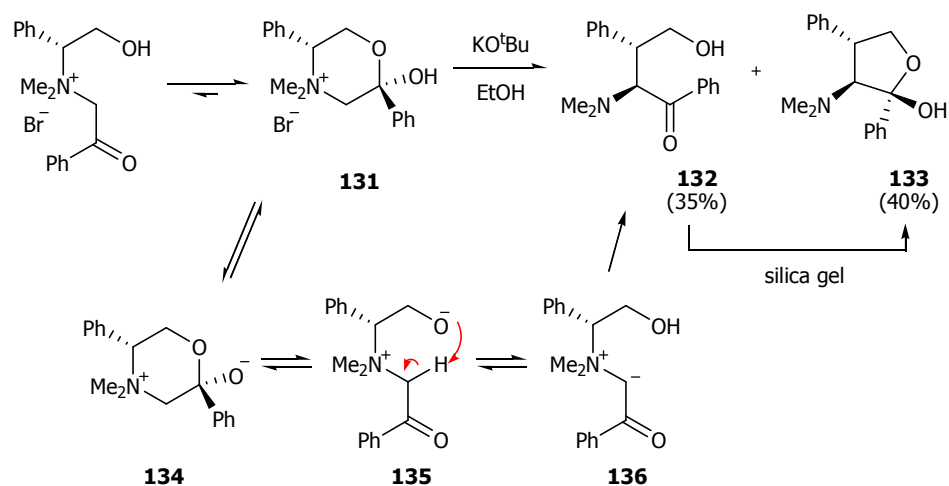
The mechanism proposed for this rearrangement process is shown above; deprotonation of hemiacetal **131** gives alkoxide **134**, which isomerises to acyclic form **135**, and the alkoxide moiety acts as the intramolecular base to generate ammonium ylide **136** for rearrangement into **132**. An asymmetric variant using chiral hemiacetal (*R*)-**131** was also described, and under optimised conditions (NaOH in H$_2$O at 60 °C), provided the products **132** and **133** in 86% combined yield and 72% *ee*.

2.3.5. Chirality transfer from nitrogen to carbon

West and Glaeske have described a stereoselective route to α-quaternary amino acid derivatives through a novel chirality transfer approach.[53] This involved initial formation of optically active quaternary ammonium salts **137** from proline, and **139** from threonine, and then their subjection to KO^{t}Bu in THF. This led to the generation of ammonium ylides, which underwent a facially selective migration of one of the substituents on nitrogen to furnish the rearrangement products: **138a** and **140a** from [1,2]- and **138b** and **140b** from [2,3]-rearrangement (Scheme 35).
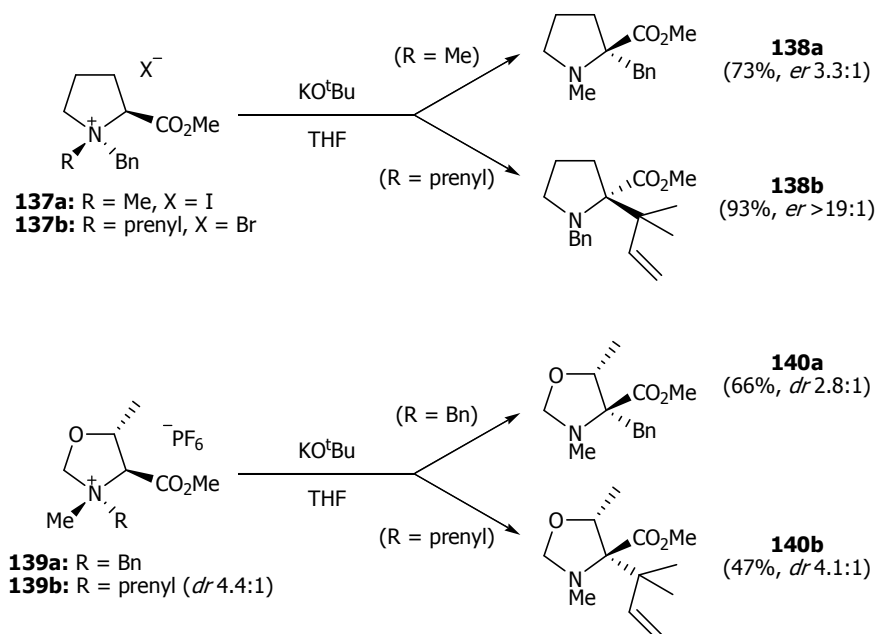
Scheme 35

If the mechanistic pathway for the rearrangement of the ammonium ylide (*cf.* **141**, Scheme 36) was *via* a fast radical recombination process, a migration with retention of stereochemistry should provide [1,2]-benzyl shift products **138a** and **140a** as single diastereoisomers. However, **138a** was obtained with an enantiomeric ratio of 3.3:1, and **140a** with a diastereoisomeric ratio of 2.8:1. This suggests that radical pair recombination from the same face is competitive with that of diffusion to the opposite face or out of the solvent cage entirely. In contrast, the [2,3]-shift products **138b** and **140b** were obtained as a single enantiomer; this is because the rearrangement is a concerted process, thereby making the rearrangement enantiospecific.
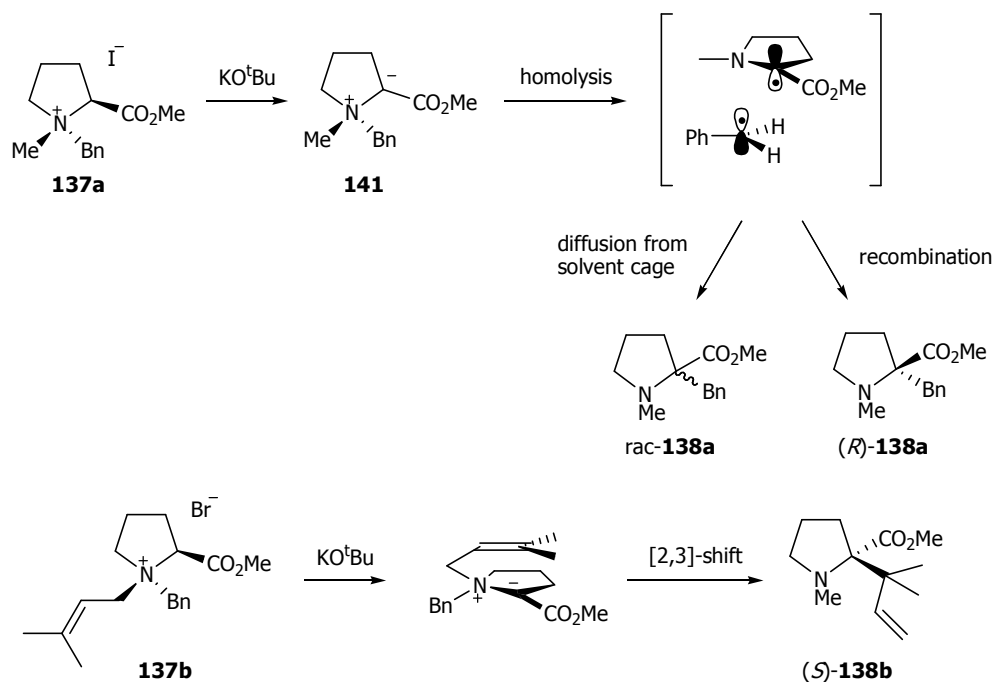
Scheme 36

2.3.6. Synthesis of pyrrolidines and azepanes

Couty and co-workers have recently carried out a number of ring expansions of 2-alkenylazetidium salts to produce either 3-alkenylpyrrolidines **143** from [1,2]-shifts, or 4,5-dehydroazepanes **144** from [2,3]-shifts.[54,55] These studies showed that preference for the formation of either product is determined by the relative stereochemistry between the substituent bearing the negative charge in the ammonium ylide and the adjacent alkene. When they are in a *trans* relationship, *i.e.* **142a**, the two reacting centres that would lead to a [2,3]-shift product are too far apart, and deprotonation occurs at the benzylic position to produce the [1,2]-shift pyrrolidine product **143** exclusively (Scheme 37). Conversely, a [2,3]-shift takes place when the ylide and alkene are in a *cis* relationship; for example, deprotonation next to the ester moiety in **142b** produces azepane **144** in excellent yields.

R	Yield / %	*de* / %
Ph	39	8
Me	94	72
H	83	6
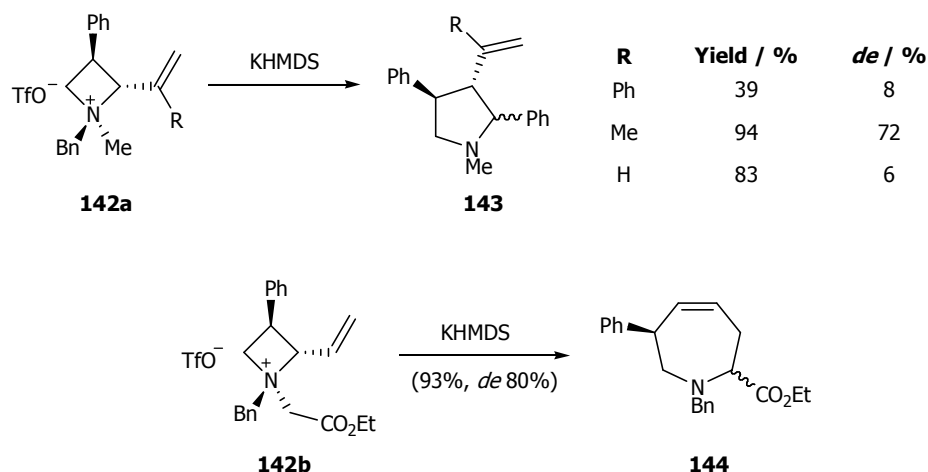
Scheme 37

2.4. Stevens rearrangements in natural product synthesis

2.4.1. Pyrrolizidine and indolizidine alkaloids

2.4.1.1. Pyrrolizidine alkaloids

West and co-workers demonstrated that the synthesis of turneforcidine **150** and platynecine **151**, both pyrrolizidine alkaloids, could be quickly achieved through a ring expansion methodology.[56] Azetidinecarboxylate **145** was efficiently converted into diazoketone **146** and as had been anticipated, treatment with Cu(acac)$_2$ generated the spirocyclic ylide **147**, which led to the [1,2]-shift products **148a** and **148b** in good yields and modest diastereoselectivity (Scheme 38). Subjection of this mixture to hydrogenation conditions led to a separable mixture of alcohol **149a** and lactone **149b**, which were then individually treated with LiAlH$_4$ to provide the natural products **150** and **151** respectively, both in excellent yields.
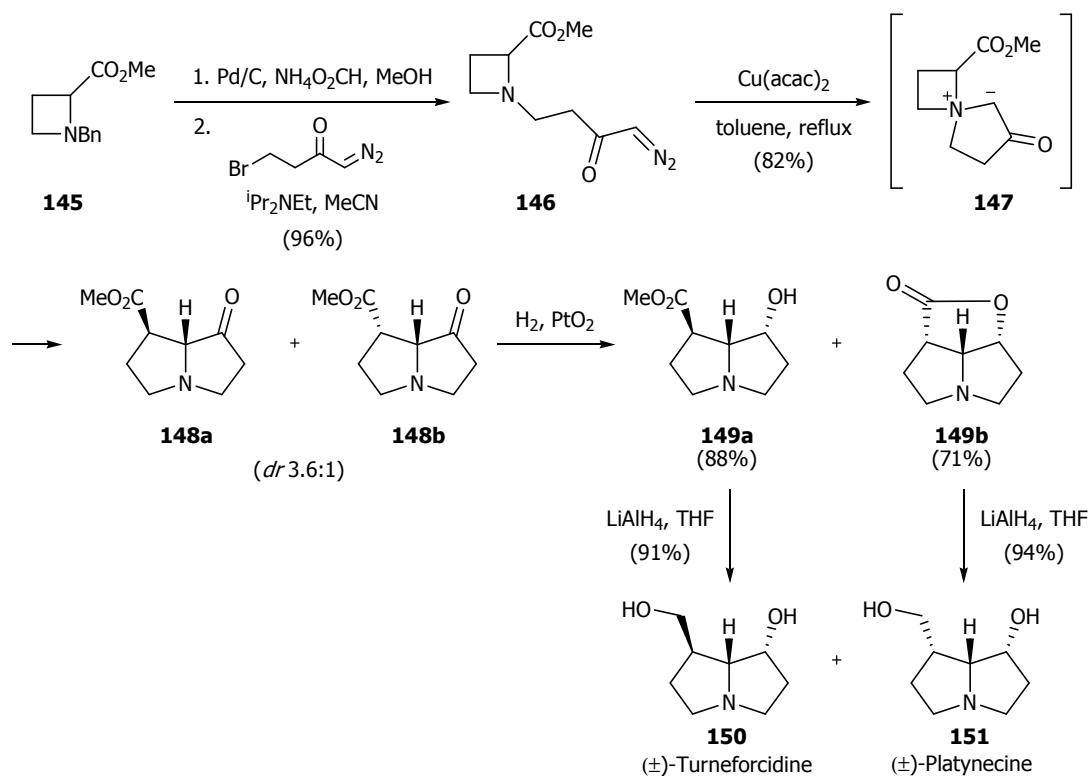
Scheme 38

2.4.1.2. Indolizidine alkaloids

In an attempt to synthesise the related indolizidine alkaloids, which contain 6,5-fused rather than 5,5-fused bicycles, West and co-workers applied the same conditions, using $Cu(acac)_2$, to the pyrrolidino diazoketone **152**.[56] However, under these conditions, only trace amounts of the indolizidine products **153a** and **153b** were obtained. Greater success was achieved by lowering the reaction temperature, with use of $Rh_2(OAc)_4$ in refluxing benzene being optimal (Scheme 39).
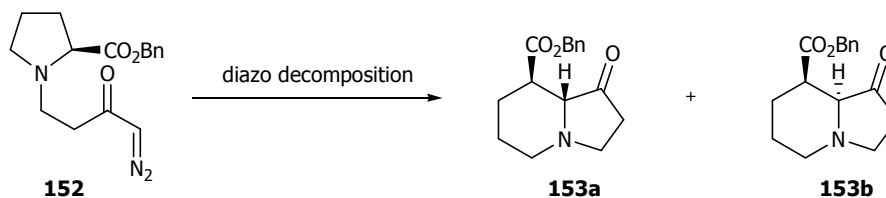
Condition	Yield (153a and 153b)
$Cu(acac)_2$, toluene, reflux	trace
$Cu(acac)_2$, benzene or DCM, reflux	50-62%
$Rh_2(OAc)_4$, benzene, reflux	73% ($dr \sim$1:1)

Scheme 39

In studies towards the preparation of analogues of swansoamine, a potential anticancer agent, Saba and co-workers reported a similar approach to the synthesis of chiral indolizidines **156a** and **156b**, which differs from **153a** and **153b** by the presence of an ethyl ester at the bridgehead carbon (Scheme 40).[57] Starting from chiral diazoester **154**, high yields and enantioselectivity and good diastereoselectivity were observed. Formation of the indolizidines was found to proceed *via* the [5,5]-spirocyclic ylides **155a** and **155b**; the authors rationalised that the presence of the ester substituent on the ylide carbon improved the enantioselectivity in the rearrangement step, by the increased steric interaction with the approaching chiral migrating group.

Catalyst	Yield (156a:156b)	*ee*
$Cu(acac)_2$	90% (65:35)	90%
$Rh_2(OAc)_4$	85% (72:28)	84%
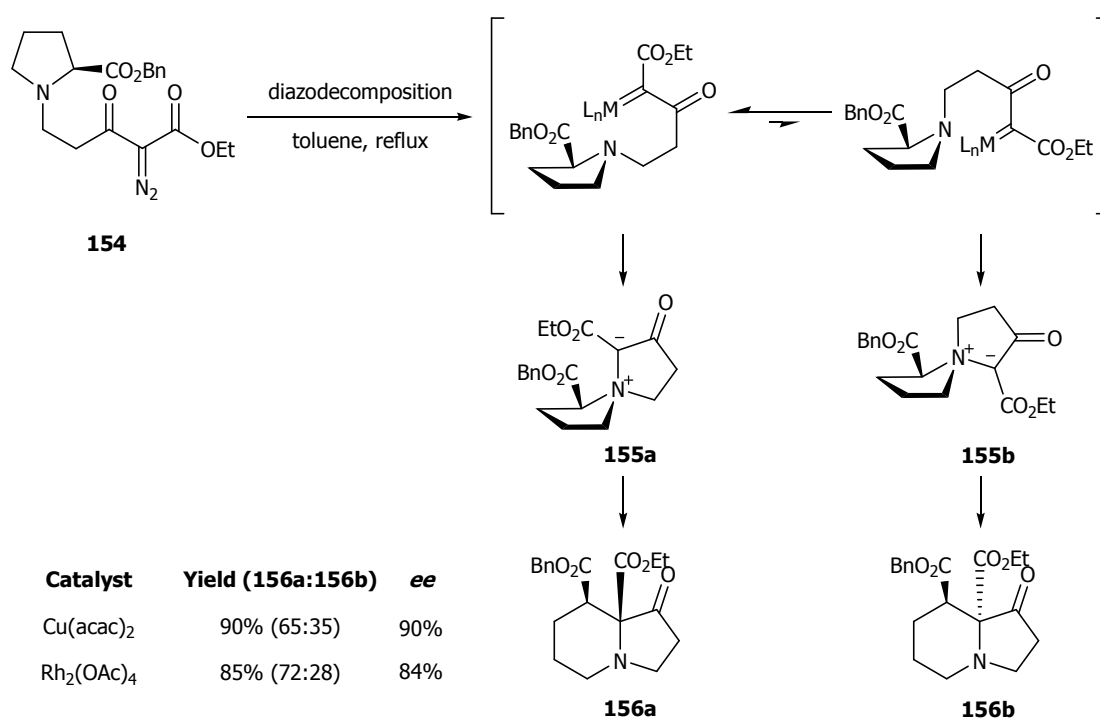
Scheme 40

In addition, it was found that by decreasing the reaction temperature using a refluxing solution of DCM, and using $Rh_2(OAc)_4$ as catalyst, ylides **155a** and **155b** were produced in 90% yield and 7:3 *dr*. Separation of the ylides and heating a solution of **155a** or **155b** in toluene in the absence of catalyst gave the rearrangement product **156a** and **156b** as single diastereoisomers in 83% and 85% yield respectively, both with 100% *de* and 95% *ee*.

2.4.2. (−)-Epilupinine

A related ring-expansion approach was utilised by West in an enantioselective synthesis of (−)-epilupinine **161**.[58,59] Treatment of diazoketone **157** with a range of catalysts led to bicyclic [1,2]-rearrangement products **160a** and **160b** in excellent yields and good diastereoselectivity (Scheme 41). Conversion of **160b** into a dithiolane intermediate, and subsequent reduction completed the synthesis of (−)-epilupinine **161**.

Conditions	Yield (160a:160b)	*ee*
Rh$_2$(OAc)$_4$, DCM, rt	74% (25:75)	40-55%
Cu(acac)$_2$, toluene, reflux	84% (5:95)	65-75%
Cu, toluene, reflux	87% (7:93)	

1. HSCH$_2$CH$_2$SH, BF$_3$.OEt$_2$ (64%)
2. LiAlH$_4$, THF (94%)
3, Na, N$_2$H$_4$, DME, 90 °C (76%)
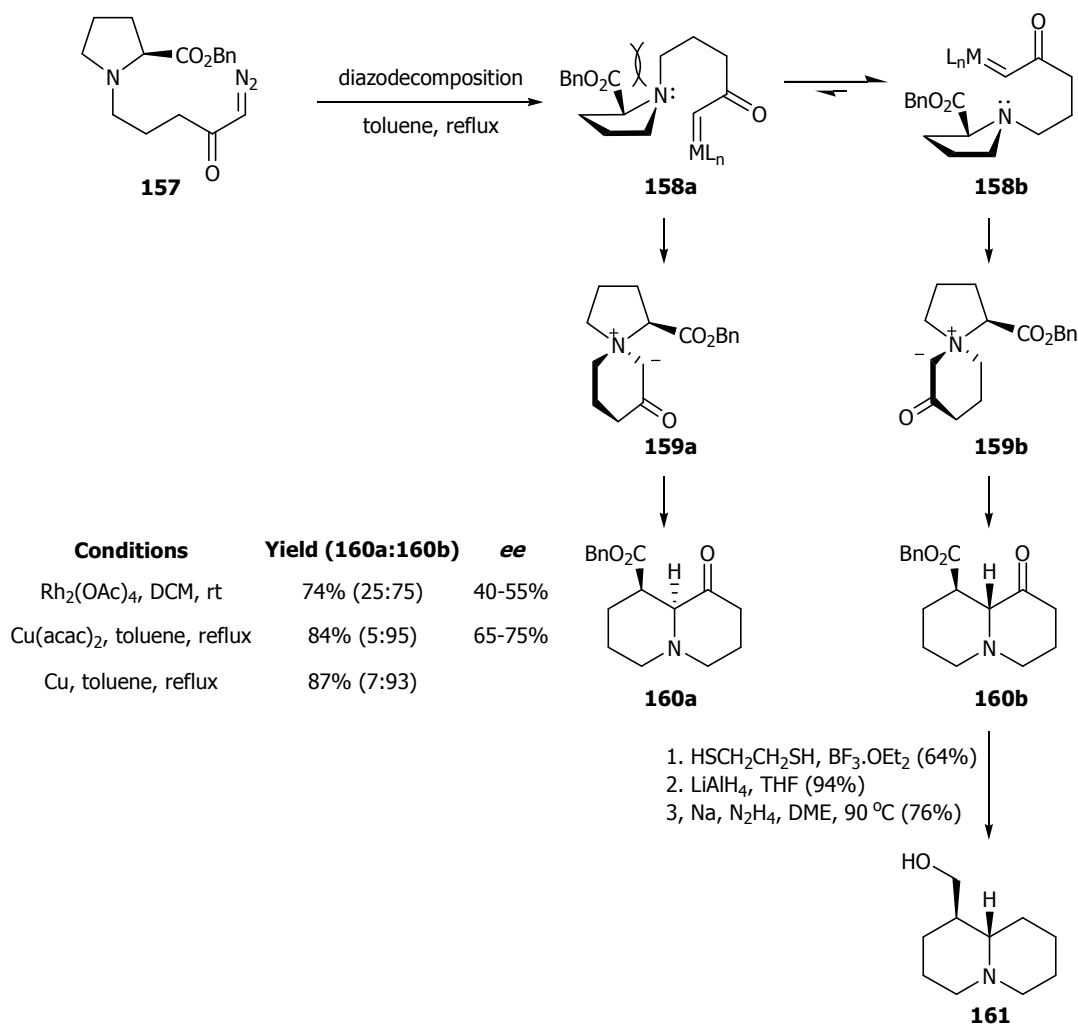
Scheme 41

The selectivity in the rearrangement step was assumed to be mainly determined from which of the two rapidly interconverting pyramidal forms (**158a** and **158b**) the ring nitrogen preferentially adopts. The major product **160b** would require the preference for the formation of ammonium ylide diastereoisomer **159b**, formed if the side chain of the carbenoid is in a *trans* relationship to the vicinal ester group (*i.e.* **158b**), thereby minimising unfavourable steric interactions.

Whilst a rearrangement of ylide **159b** with retention would have provided the bicycle **160b** as an optically pure compound, NMR analysis using a chiral shift reagent indicated that that it was formed in only 65-75% *ee* at best. The authors agreed that the mechanism of rearrangement is likely to take place by the widely accepted mechanism, of initial homolysis of the C-N bond followed by a rapid radical recombination, but suggested that if the rate of migration is comparable to bond rotation, persistence of biradical **162** would decrease optical purity (Scheme 42). However, the high diastereoselectivity (up to 95:5 *dr*) in the reaction implies that stereoselective recombination of biradical **162** is also possible. This was rationalised by two possible rotamers of **162** that can be adopted prior to bond formation, in which the planar ester-substituted radical approaches the piperidone ring with either the larger ester, or the smaller hydrogen under the ring. Rotamer **162a** requires unfavourable steric interactions between the ester and the ring, which are avoided with rotamer **162b**.
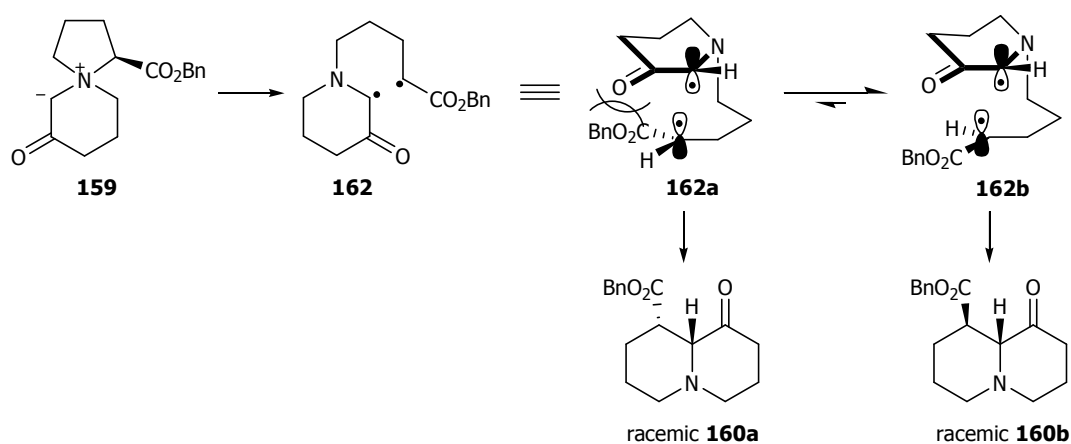
Scheme 42

2.4.3. Approaches to the morphine core and morphinomimetics

2.4.3.1. (±)-Desoxycodeine-D

In his work towards the total synthesis of morphine, Cheng reported a novel route to (±)-desoxycodeine-D (**165**), a compound which incorporates the morphine skeleton.[60] Polycyclic amine **163** was generated through a series of palladium-catalysed couplings, and upon treatment with MeI then PhLi, the resulting ammonium ylide **164** underwent

the anticipated Stevens rearrangement to provide (±)-desoxycodeine-D (**165**) in 83% yield over the two steps (Scheme 43).

Scheme 43
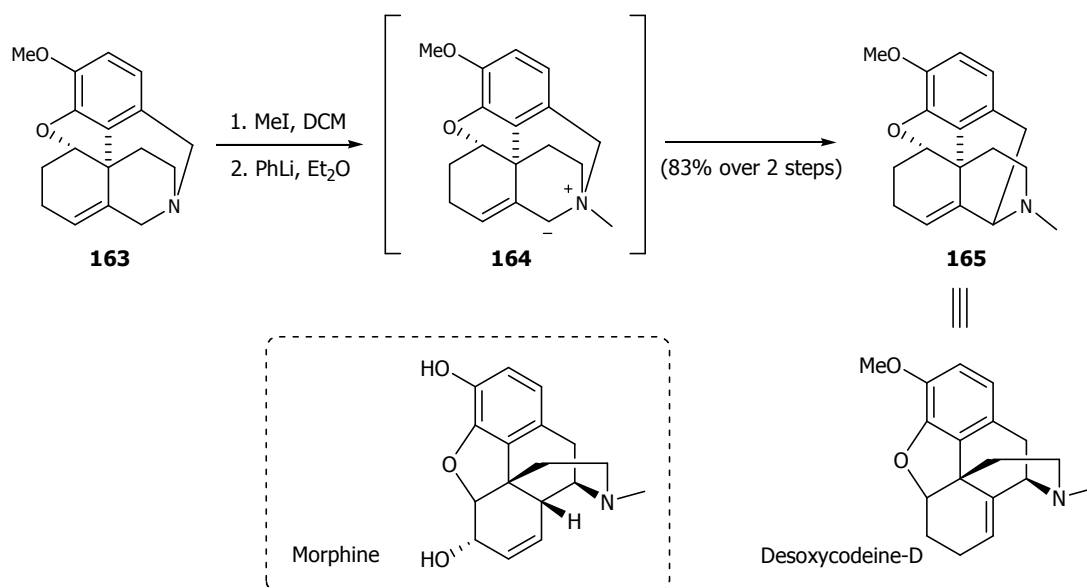
2.4.3.2. *Functionalised isopavines as morpholinomimetics*

Hanessian utilised a highly stereocontrolled, diastereoselective Stevens rearrangement to synthesise a number of isopavines.[61] After conversion of aldehyde **166** into bridged amine **167**, sequential treatment of **167** with MeI and KO^{t}Bu furnished isopavine **168** in good yields (Scheme 44).
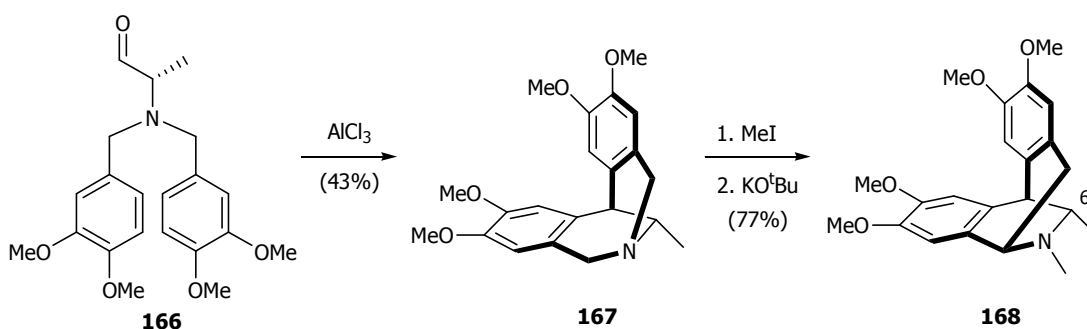
Scheme 44

This reaction can theoretically proceed through two different pathways, one of which generates the observed isopavine **168**, and the other giving the isomeric product (*cf.* **172b**, Scheme 45). In this reaction, as well as in analogous reactions on related amines with variations at C6, isopavine product **172a** was obtained as a single regioisomer,

with none of **172b** detected. An ionic mechanism was proposed by the authors to explain this phenomenon; deprotonation of a benzylic proton at C7 in the ammonium salt **169** leads to ylide **170a**, which fragments into the iminium anion **171a** (or its diradical equivalent). This is in a favourable alignment for an intramolecular attack (or recombination) by the benzylic anion to generate **172a**. Alternatively, deprotonation could be from the C5 benzylic proton, generating ylide **170b**, but leading to anion **171b** (or diradical) that is destabilised by allylic 1,2-strain, and will ring-flip to a conformation that cannot cyclise.
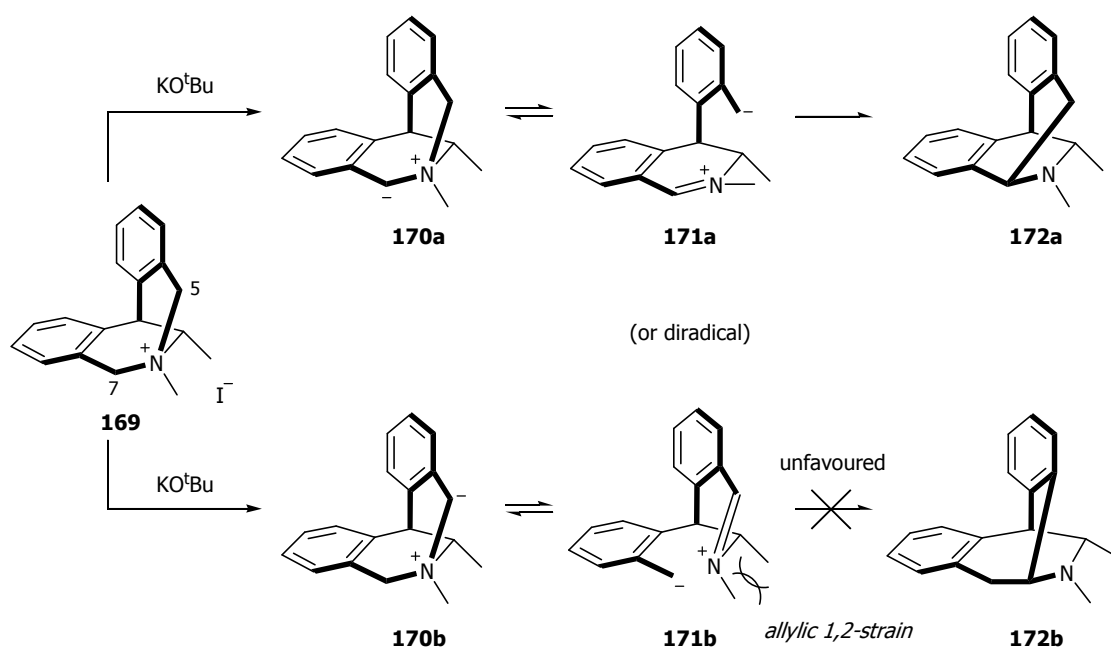
Scheme 45

In contrast, the isomeric structures (*i.e.* **172b**) could be synthesised with tetracyclic compounds, and due to the skeletal similarities with the morphine backbone, Hanessian synthesised a number of tetracyclic analogues (*e.g.* **173**, Scheme 46) as morphinomimetics. The results from preliminary biological testing of these compounds against the opiod receptors are encouraging.[61]
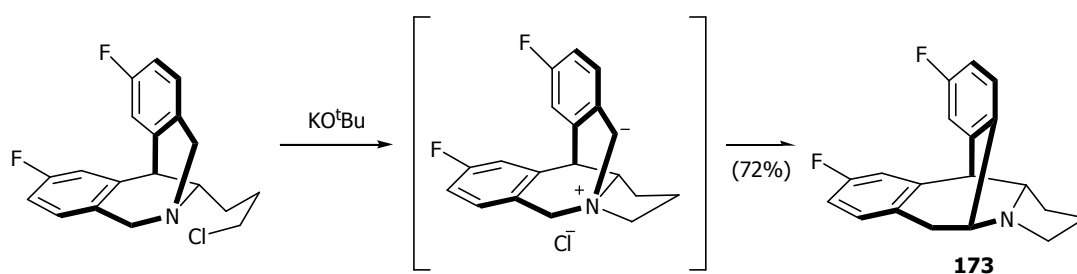
Scheme 46

2.4.4. Synthesis of benzodiazepinone and benzazepine alkaloids

Saba and co-workers utilised a Stevens rearrangement to generate a number of pyrrolo[1,2-*a*][1,4]benzodiazepinones.[62] Treatment of tetrahydroquinazolidines **174** with either $Rh_2(OAc)_4$ or $Cu(acac)_2$ led to diazodecomposition, then generation of spiro-[6,5]-ammonium ylide **175**, which rearranged to products **176a** and **176b**. These products were obtained as single diastereoisomers, with the substituents at C3 and C4 being *trans* disposed (Scheme 47). Better yields were obtained when $Rh_2(OAc)_4$ was employed, exceeding the yields from reactions with $Cu(acac)_2$ by 10-30%.

				Combined yield of 176a and 176b / %	
R¹	**R²**	**R³**	**R⁴**	$Rh_2(OAc)_4$	$Cu(acac)_2$
CO_2Et	H	H	Et	65	54
CO_2Et	H	H	(-)-menthyl	71	62
Ph	H	H	(-)-menthyl	83	53
CO_2Et	Cl	Cl	Et	70	58
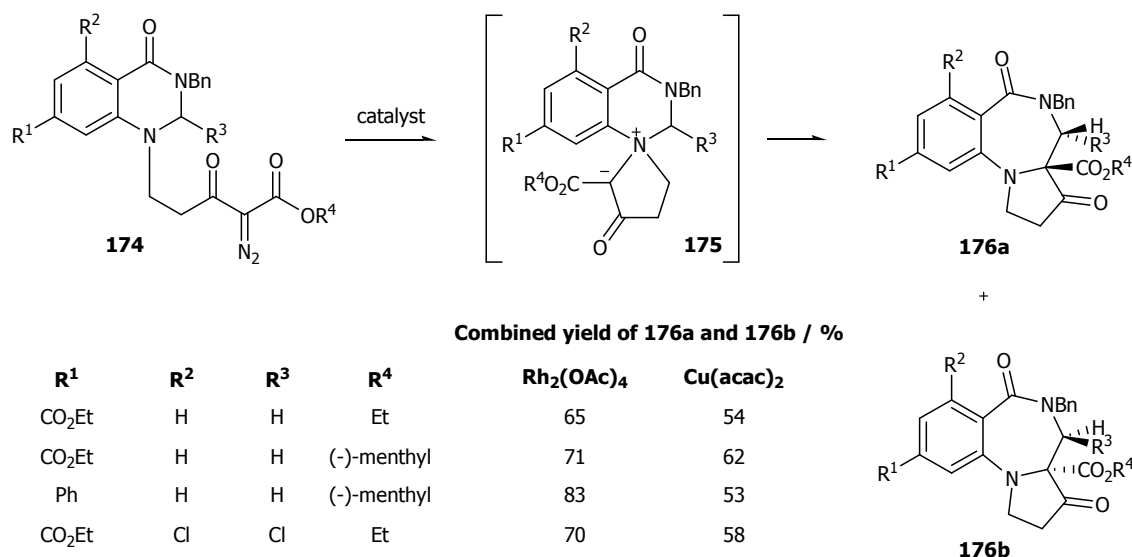
Scheme 47

In their work directed towards the total synthesis of lennoxamine (**180**), Padwa and co-workers proposed the use of a Stevens rearrangement to generate the skeletal framework of the natural product, which is based upon an isoindolobenzazepine ring system.[63] Attempts to convert ester **177a** into the rearrangement precursor **178a** by diazo transfer were unsuccessful, which the authors attributed to the lowered acidity of the benzylic protons, due to the presence of the group at C5 (Scheme 48). In agreement with this explanation, **177b**, which lacks this methoxy group, was converted into **178b** in excellent yields. Treatment of **178b** with $Rh_2(OAc)_4$ furnished isoindolobenzazepine **179** in good yields. Although this method was unsuccessful in synthesising lennoxamine (**180**), a number of indolobenzazepines were prepared in this way.
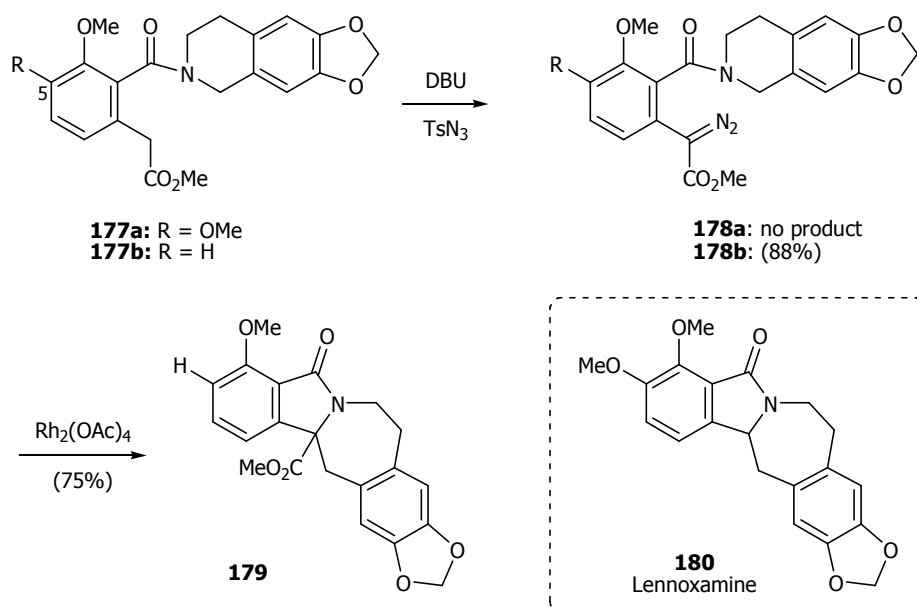
Scheme 48

In addition, Padwa and co-workers envisaged a similar approach toward the preparation of (−)-cephalotaxine (**184**).[63] In a model system, a number of spirocyclic ylides, such as **182**, derived from treatment of the corresponding diazoacetoacetates **181** with Cu(acac)$_2$, were successfully converted into the Stevens rearrangement benzazepine products **183** (Scheme 49). Notably, the reaction was slowed upon replacing the catalyst with Rh$_2$(OAc)$_4$, and provided a complex mixture of products.
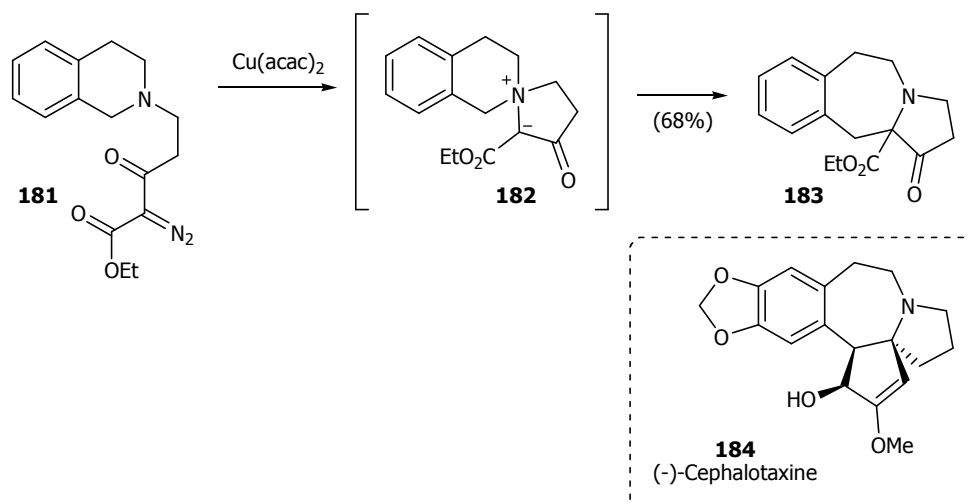
Scheme 49

A related ring expansion method to give fused quinoxalinones **185** by Stevens rearrangement of a spiro-quinoxaline derived ammonium ylide was also reported by Arán and co-workers (Scheme 50).[64] Additionally, the separable enantiomerically pure 1-phenyl-4,9-dioxohexahydropyrrolo[1,2-*d*][1,4]oxazepine-9a(7*H*)-carboxylates **187**

have been obtained in this way from Cu(acac)$_2$-catalysed decomposition of an diazocarbonyl moiety tethered to a chiral morpholinone (**186**, Scheme 51).[65]
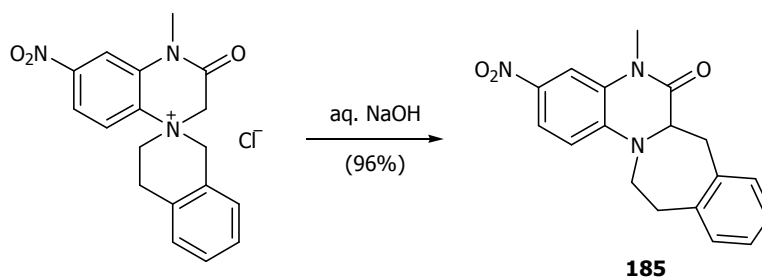
Scheme 50
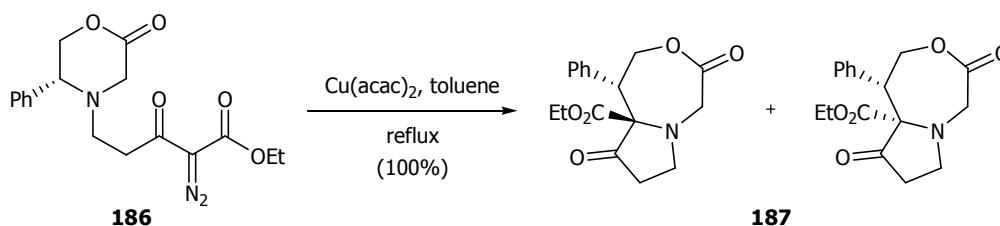
Scheme 51

In conclusion, this section has shown that a variety of important alkaloid skeletons can be accessed in high yields using [1,2]-shifts of ammonium ylides. In particular, a number of ring expansion strategies have proven to be effective in the synthesis of natural products, and sets good precedent for the novel ylide generation-rearrangement process employed in our approach to the synthesis of the sarain core.

3. RESULTS AND DISCUSSION

As described in section 1.3.6, our group's approach to **83**, which bears the tricyclic framework of the sarain core, involves a novel carbene-derived ammonium ylide rearrangement of diazoketone **84** (Scheme 52). As diazoketones are typically prepared from carboxylic acid derivatives, the construction of **188**, a *cis*-fused octahydropyrrolo[2,3-*b*]pyrrole ring system bearing an *endo* acetic acid substituent at C3, was targeted.
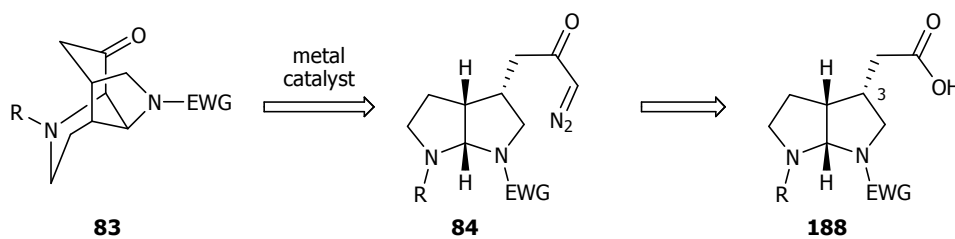
Scheme 52

A number of different strategies were investigated, the results from which will be discussed in turn.

3.1. Strategy one – Diels-Alder reaction involving a chiral dienophile

Retrosynthetic analysis suggested that bicyclic aminal **189** could be produced from lactam **190**, which itself could be derived from aldehyde **191** (Scheme 53). In the forward sense, it was expected that a reductive amination of this aldehyde would initiate a cascade of reactions: namely a cyclisation of amine **193** onto the lactone carbonyl, then ring opening to lactam **194**, followed by collapse of the hemiacetal moiety to aldehyde **195**. In the presence of the excess reducing agent remaining in the reaction, the aldehyde was expected to be reduced to the desired alcohol **190**.

Aldehyde **191** could be derived from an oxidative cleavage of the double bond in **192**, hence an enantioselective synthesis of this bicycle would provide all the required stereochemical information prior to transformation into the desired lactam material **190**. A powerful method of creating such systems is *via* an asymmetric Diels-Alder reaction.

Scheme 53

3.1.1. Dienes and Dienophiles

The Diels-Alder reaction is an extremely useful tool in organic synthesis and has been integral to the synthesis of many complex molecules.[66] Through a [4+2]-cycloaddition between a diene and an alkene, the reaction generates six-membered ring systems, creating up to four stereocentres in the cyclohexene ring in a single step. Since its discovery 80 years ago, significant developments have made it possible to achieve asymmetric induction in this reaction, usually by the use of chiral Lewis acid catalysts, or with chiral auxiliaries attached to either the diene or dienophile.

To generate the bicyclic system in **192**, the dienophile component would need to be based upon furanone derivative **194** with an auxiliary attached at R' (Figure 7). An auxiliary which has proven to be effective in achieving high diastereoselectivity is the menthyloxy group developed by Feringa.[67] As with most chiral auxiliaries, the face selectivity of this reaction is governed sterically, where the large menthyloxy group at the C5 position of the dienophile effectively shields one of the π-faces from approach by the diene.

Figure 7: Face selective addition of diene to chiral dienophile

It is well documented that there is a preference for the formation of *endo*-adducts in Diels-Alder reactions.[68] Feringa used extensive COSY and NOESY NMR analysis of the product derived from the reaction of this dienophile with cyclopentadiene to confirm that *endo*-addition took place with >96% *de*.[67] In addition, Feringa has also shown that reactions of the menthyloxy dienophile with 2-methylbutadiene, 2,3-dimethylbutadiene, 1,3-cyclohexadiene, butadiene and 2-trimethylsilyloxy-1,3-butadiene all took place with excellent diastereoselectivity and enantioselectivity.[67] These results would therefore suggest that, combined with the correct enantiomer of menthol, the dienophile should proceed to react with the selected butadiene to provide our desired bicycle **192** in good diastereoselectivity.

High levels of regiocontrol can also be expected by the use of a 2-alkoxy-1,3-butadiene. This regioselectivity can be explained using frontier molecular orbital (FMO) theory. A pericyclic reaction involves the interaction of the highest occupied molecular orbital (HOMO) of one component, and the lowest unoccupied molecular orbital (LUMO) of the other. A successful reaction is based upon the successful overlap of these orbitals. A small difference in energy between the HOMO and LUMO lowers the activation energy, and ultimately increases the rate of reaction. In this Diels-Alder reaction, the overlap of the LUMO of the electron poor dienophile with the HOMO of the electron rich diene is the more important interaction. The presence of an electron withdrawing group (EWG) on the dienophile makes the LUMO coefficient at C4 larger than that of C3, and an electron donating group (EDG) at C2 of the diene contributes to a higher HOMO coefficient in C1 in comparison to C4 (Figure 8). This difference in size of the coefficients is important in the regioselectivity of the cycloaddition, as the new bonds are formed preferentially with a 'large-large' and 'small-small' overlap. Therefore a Diels-Alder reaction between menthyloxy-furanone **194** (R' = menthyloxy) and 2-

alkoxy-1,3-butadiene **193** is expected to take place regioselectively, and diastereoselectively, to give the desired "pseudo-*para*" adduct **192**.
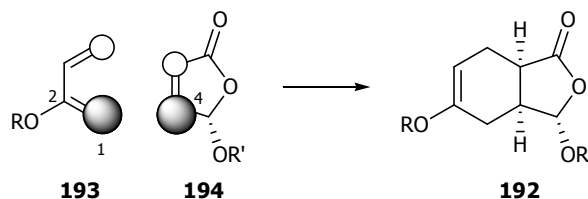
Figure 8

3.1.2. Results and Discussion

Preparation of the dienophile started with the reaction of furfural with singlet oxygen (Scheme 54).[69] In the presence of rose bengal, dioxygen is excited to the singlet state, and then undergoes a Diels-Alder reaction with furfural to give a transient bicyclic intermediate. A nucleophilic attack by methanol at the aldehyde moiety then leads to elimination of methyl formate to break the weak O-O bond and give furanone **195**.
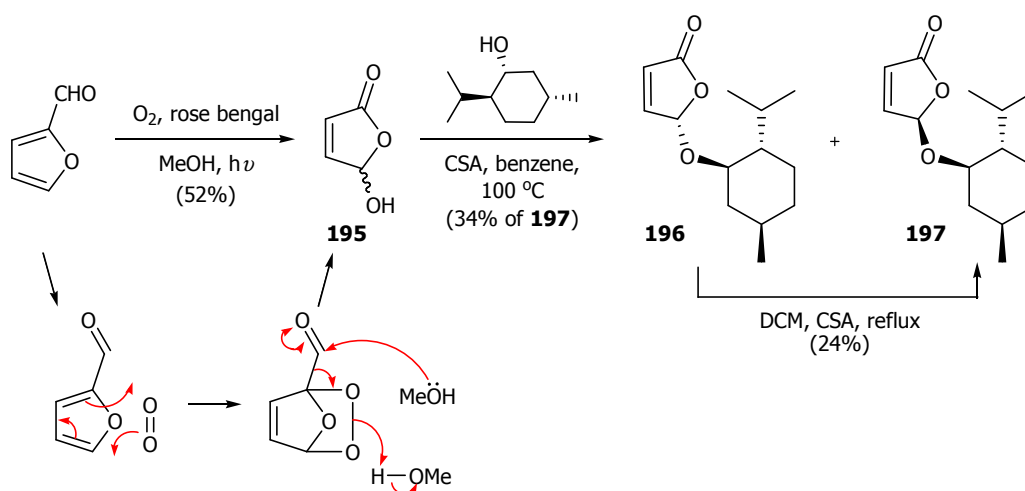
Scheme 54: Preparation of chiral dienophile 197

To establish chirality within the dienophile, alcohol **195** was treated with L-menthol[*] and catalytic CSA under Dean-Stark conditions to give a quantitative yield of furanones **196** and **197** as an approximately 1:1 mixture of diastereoisomers.[69] Following chromatography to remove rose bengal, the diastereoisomers were separated by three

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[*]The less expensive (1*R*,2*S*,5*R*)-enantiomer of menthol was used; consequently the absolute stereochemistry of the Diels-Alder adduct and its subsequent products will be opposite to those depicted in Scheme 53, and would ultimately lead to the synthesis of (+)-sarain A.

recrystallisations from petroleum ether, providing **197** in 34% yield and >95% *de*. The unwanted diastereoisomer **196** was recycled by epimerisation with CSA in DCM, with subsequent recrystallisations providing a further crop of **197** in 24% yield.

In the original strategy, the diene of choice was 2-trimethylsilyloxy-1,3-butadiene (**198**). This diene was successfully utilised by Feringa and co-workers in a Diels-Alder reaction with dienophile **197**, but the resulting adduct was immediately deprotected in the next step.[67] In our hands, reproduction of this Diels-Alder reaction took place smoothly, but the purification of the resulting labile trimethylsilyl enol ether adduct **199** was difficult.[70] Subjecting impure material to the oxidative cleavage reaction to aldehyde-acid **200** was unsuccessful (Scheme 55).
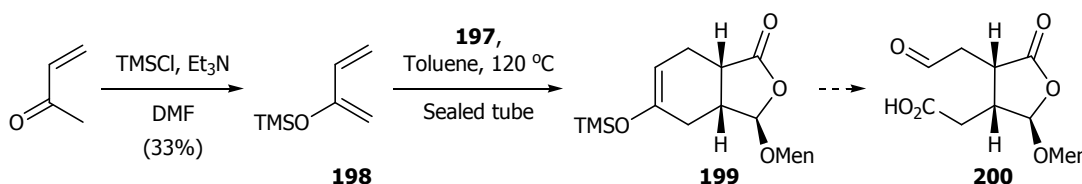
Scheme 55

Unfortunately, the use of bulkier, and hence more stable, *tert*-butyldimethylsilyloxy and triisopropylsilyloxy protecting groups only led to a vast decrease in the rate of the Diels-Alder reaction. After a search for dienes that were successful in both reactions, 2-methoxy-1,3-butadiene was identified to be the best substrate.[70]

In contrast to the one step procedures used to make silyloxy-substituted dienes, the preparation of 2-methoxy-1,3-butadiene necessitated two steps (Scheme 56).[71] Treatment of methyl vinyl ketone with MeOH in the presence of TsOH and trimethyl orthoformate promoted conjugate addition and acetal formation to generate 1,3,3-trimethoxybutane (**201**) in good yield. Subsequent treatment with KHSO$_4$ at elevated temperature led to elimination of methanol and furnished diene **202** in 34% yield.
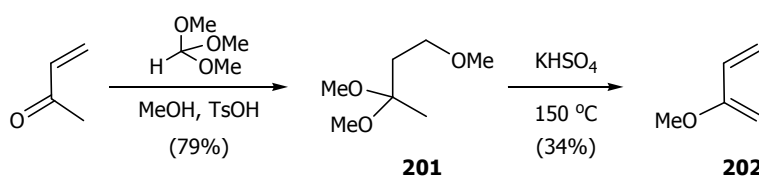
Scheme 56: Preparation of 2-methoxy-1,3-butadiene

The Diels-Alder reaction was carried out using two different methods of heating (Table 1); the results are directly comparable in terms of scale of reaction (1.5 g of dienophile) and volume of solvent used. The first was performed in a sealed tube heated at 120 °C (entry 1), and the reaction was still incomplete even after prolonged heating. The use of microwave radiation at a higher temperature clearly provided better results (entry 2), with a markedly increased rate of reaction and also an improved yield.
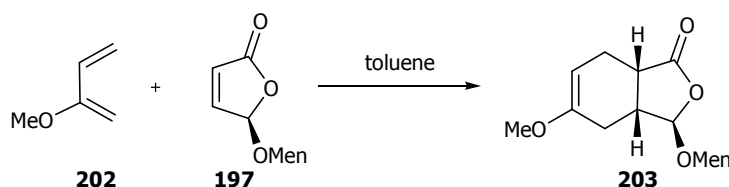
Table 1: Diels-Alder reaction of chiral dienophile with methoxy-butadiene

Entry	Method	Temperature / °C	Time / h	Yield / %
1	Thermal sealed tube	120	168	53
2	Microwave sealed tube	180	2	70

3.1.3. Oxidative cleavage of Diels-Alder adduct

The oxidative cleavage reaction to convert methyl enol ether **203** into aldehyde-ester **204** proved capricious. Early examinations suggested that the optimum conditions were to carry out the ozonolysis in a mixture of MeOH/DCM, with a PPh$_3$ reductive workup.[70] However, only a very small amount of the desired product (~2%) was isolated when the same conditions were repeated. Consequently, reproducible conditions for the oxidative cleavage step were sought (Table 2).

The substrate was treated with ozone under different solvent and reductive workup conditions, with varying degrees of success. Initially, the disappointing yield from the previously mentioned reaction with PPh$_3$ workup (entry 1) was attributed to the difficulty in separating the product from triphenylphosphine oxide. As a result, the reaction was repeated, substituting PPh$_3$ with PBu$_3$, as tributylphosphine oxide is more water soluble, and therefore more easily removed. However, only a small amount of material was recovered after flash chromatography, containing only trace amounts of the desired product.
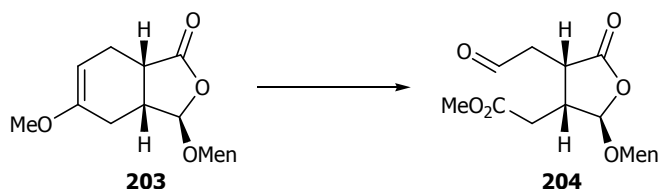
Table 2: Oxidative cleavage of Diels-Alder adduct

Entry	Reagents	Solvent	Yield	Notes
1	O_3; PPh_3	MeOH, DCM	2%	-
2	O_3; PBu_3	MeOH, DCM	Trace	-
3	O_3; DMS	MeOH, DCM	Trace	a
4	O_3, $NaHCO_3$; DMS	MeOH, DCM	Trace	a
5	O_3; DMS	DCM	Trace	a
6	O_3; PPh_3	DCM	<18-30%	b, c
7	O_3; DMS	DCM	<20-39%	b, c
8	O_3, Sudan Red; DMS	DCM	27-30%	b
9	$RuCl_3.2H_2O$, $NaIO_4$	DCE, H_2O	Trace	-

[a] peak in ^{1}H NMR spectrum corresponding to acetal proton observed predominantly at 5.8 ppm (see text); [b] anhydrous conditions; [c] impure – inseparable mixture

Closer inspection of the ^{1}H NMR spectra of the crude and partially purified products from entries 3-5 revealed they had a signal at ~5.8 ppm for the acetal OCHO proton, rather than at the expected ~5.5 ppm observed from previously prepared authentic samples. In addition, the two protons at ~3 ppm (corresponding to one proton α- to the aldehyde, and another β- to the aldehyde) were absent. Although this undesired product was neither isolated nor definitely identified, the results from preliminary and tentative 2D NMR (COSY, HMQC, HMBC) analysis of the impure material are in agreement with a structure that has the acetal proton in the β-position to the aldehyde moiety, leading to the proposed structure **205** (Scheme 57).
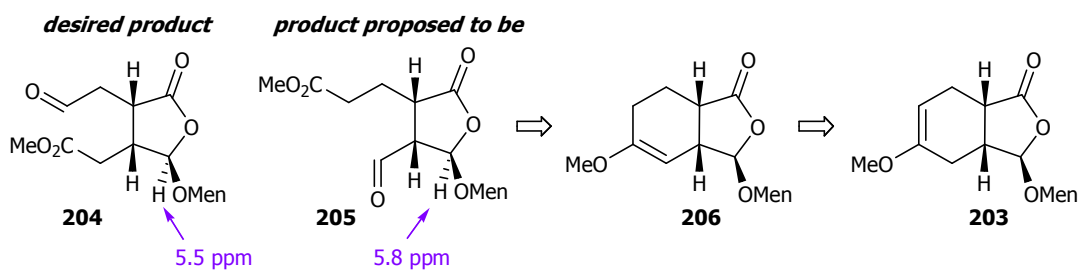
Scheme 57: Isomerisation of Diels-Alder adduct before ozonolysis

This compound is assumed to arise from double bond isomerisation of Diels-Alder adduct **203** to **206** before the reaction with ozone. Isomerisation of an oxy-substituted double bond of a 5,6-fused ring system is not without precedent; Meyers[72] carried out a Diels-Alder reaction of chiral bicycle **207** with 2-(*tert*-butyldimethylsilyloxy)-1,3-butadiene in excellent yield, but the double bond of their adduct isomerised from the initial C8-C9 to the C9-C10 position upon purification (Scheme 58). This isomerisation was only observed in adducts possessing an oxygen substituent at C9, and was attributed to be the result of the greater thermodynamic stability of the enol ethers at the C9-C10 position.[72]
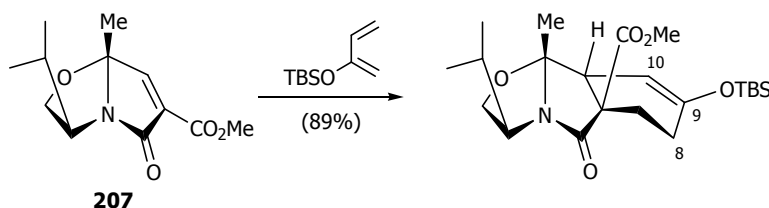
Scheme 58

This isomerisation is assumed to be acid catalysed, *via* protonation of the double bond, followed by deprotonation at the alternative site, so with the aim of preventing this, ozonolysis was carried out in the presence of NaHCO$_3$ (entry 4), but the acetal proton peak at ~5.8 ppm still predominated in the ^{1}H NMR spectrum of the product. When the ozonolysis was repeated in DCM alone under anhydrous conditions, the desired product was produced within an inseparable mixture of impurities, albeit in low yields. The best yields were obtained using anhydrous conditions with the addition of a Sudan Red indicator. When this solution became decolourised, signifying an excess of ozone, the reaction was immediately purged with argon and then DMS was added. Under these conditions, the desired product **204** was attained in low, but consistent yields.

An attempt to cleave the alkene with a high valent ruthenium species failed to provide the desired product **204**.

3.1.4. Use of isoprene

Due to the isomerisation behaviour of the methyl enol ether, an analogous simple methyl alkene adduct was prepared by a Diels-Alder reaction of the chiral dienophile with isoprene. Adducts **208a** and **208b** were obtained in excellent yields but as a mixture of regioisomers (1:1 by ^{1}H NMR spectroscopy, Scheme 59). Their separation was possible, but required multiple recrystallisations from hexanes.
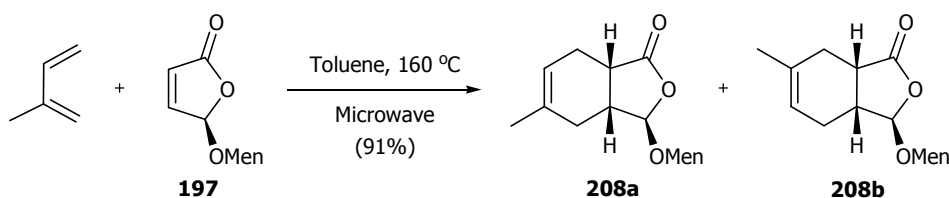
Scheme 59: Diels-Alder reaction with isoprene

Attempts to improve the regioselectivity of the reaction by addition of AlCl$_3$[73] led to a complex mixture of products.

It was hoped that the two isomers would be easier to separate at a later stage, and thus the synthesis was progressed using the regioisomeric mixture. However, subsequent reactions, either ozonolysis to **209** or acetal exchange to **210**, resulted only in a low yield of inseparable regioisomers (Scheme 60).
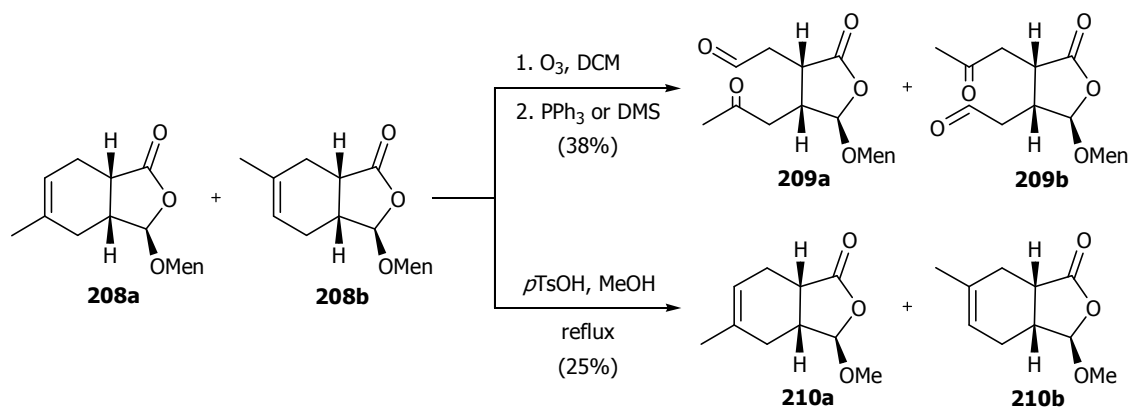
Scheme 60

3.1.5. Reductive amination-cyclisation cascade

Returning to aldehyde-ester **204**, studies into the proposed reductive amination-cyclisation-reduction cascade to lactam **213** were carried out (Scheme 61). Upon treatment of aldehyde **204** with benzylamine, formation of the imine was straightforward, as evident from carrying out the reaction in CD_3OD, and monitoring by NMR spectroscopy. However, reduction of this imine and the subsequent cascade were rather more difficult.

Scheme 61
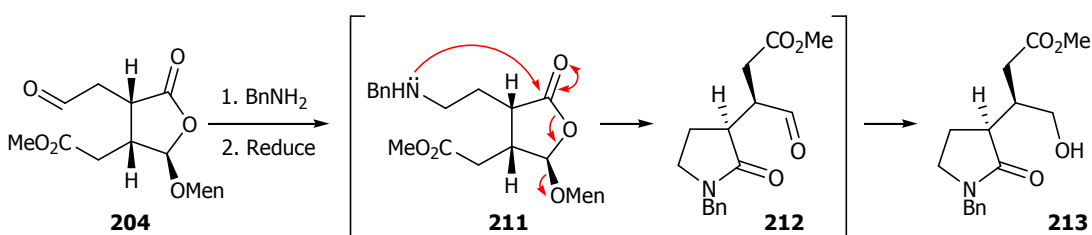
An investigation into various reductive amination conditions was carried out and encouragingly, loss of menthol was observed for almost all of the reaction conditions, but unfortunately none of the correct product **213** was isolated. However, there were indications that the cascading reaction had at least progressed somewhat – the tentatively assigned ^{1}H NMR spectra of the partially purified products from reduction with $NaBH_4$ in MeOH showed an impure mixture of diastereoisomers **212** and **212a** (Scheme 62).

Scheme 62
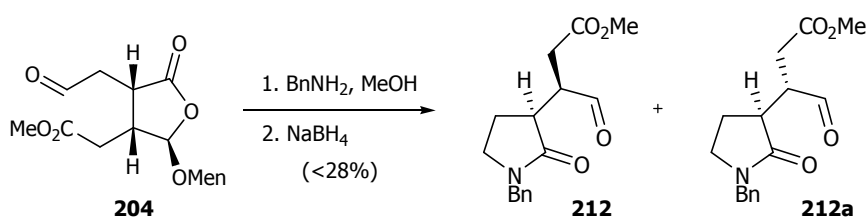
It is possible that this result arose because the reduction of the imine to amine **211** is fast, but the cyclisation of the amine onto the lactone and subsequent steps are slow. During this time the excess $NaBH_4$ may have been hydrolysed in MeOH, and consequently unable to reduce the aldehyde to the alcohol. This would therefore render the chiral centre next to the aldehyde susceptible to epimerisation, and give rise to diastereoisomers **212** and **212a**.

With the intention of reducing the susceptibility of NaBH₄ to premature alcoholysis, the reductive aminations were carried out with varying amounts of NaBH₄ and in a number of alcoholic solvents: MeOH, EtOH and ⁱPrOH. In the instances when MeOH was used, a small amount of the impure diastereoisomeric aldehydes **212** and **212a** were formed, even when the reactions were carried out in a greater excess of NaBH₄, and also when more reagent was introduced portionwise over a period of time. Increasing the steric bulk of the solvent to EtOH or ⁱPrOH gave a complicated and intractable mixture of compounds, and the ¹H NMR spectra of the partially purified fractions all contained menthol-like peaks, which suggests that the menthyloxy moiety is retained in the product(s), and that the cyclisation or the elimination of menthol did not take place.

It was also difficult to identify products derived from reactions with NaBH(OAc)₃ or from NaBH₃CN with ZnCl₂. However, in almost all cases, the ¹H NMR spectra of the partially purified products showed the presence of more benzyl peaks than expected, and also the absence of the methyl ester peak. This could be the result of a displacement of the methyl ester by benzylamine to form a benzylamide. Carrying out the reaction in ⁱPrOH and reduction with NaBH₃CN and ZnCl₂ led to the isolation of *N*-benzyl-3-(*N*-benzyl-5-oxopyrrolidin-3-yl)pyrrolidin-2-one (**215**).
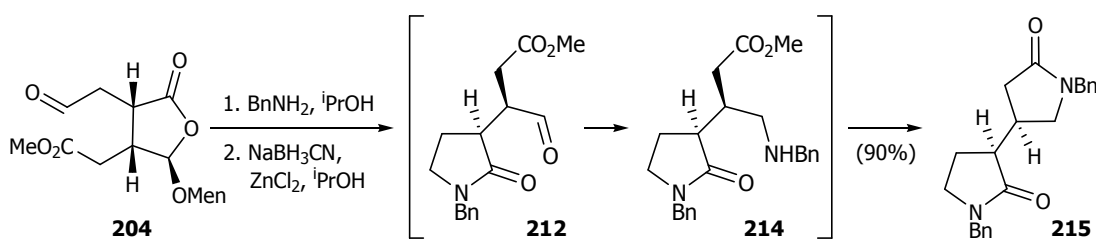
Scheme 63: Double reductive amination-cyclisation cascade

Its formation is thought to be *via* a double reductive amination-cyclisation mechanism, whereby aldehyde **212** undergoes a second reductive amination with benzylamine to form amine **214**, which can then cyclise onto the methyl ester and form the second pyrrolidinone ring in **215** (Scheme 63). The presence of ZnCl₂ in the reaction mixture was thought to assist the displacement of the methyl ester, but removing it from the reaction only led to a much more complicated set of products.

It was felt that if a clean sample of aldehyde **212** could be obtained, the problem of epimerisation of the chiral centre could be resolved later. Thus reducing agents that have been used in reductive amination reactions, but do not generally reduce aldehydes to alcohols were also investigated. Use of formic acid with Pd/C catalyst,[74] or use of H_2 gas over Pd/C, provided a complex mixture of compounds. Hantzsch's base **216** was easily prepared in high yield (Scheme 64);[75] however, no product was identified from the attempted reductive amination reaction with this reagent.
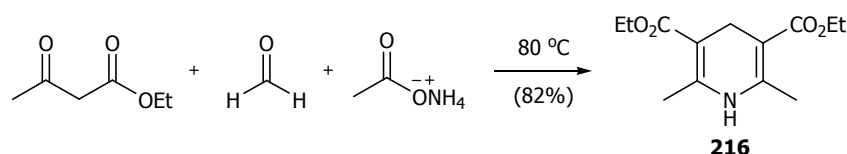
Scheme 64: Preparation of Hantzsch's base

Whilst these reaction conditions were unsuccessful in producing lactam **213**, it was promising that menthol was produced from the reactions, and in one case, pyrrolidinone **215** was also isolated. This suggests that the amine derived from the reductive amination reaction is capable of cyclising onto the lactone carbonyl, and subsequently eliminating menthol. The problems in attaining the desired lactam may have been contributed to by the difficulty in getting pure starting material **204**, and hence not being able to accurately introduce only one equivalent of benzylamine into the reaction mixture. The difficulties in the identification of side products from the ozonolysis and the subsequent reductive amination-cyclisation reactions were also exacerbated by the presence of menthol in the structure. This bulky leaving group may also have an effect on the ease of cyclisation, as reductive amination with $NaBH_4$/EtOH (entry 2) provided a set of products that all still contained the menthol moiety. Attention therefore turned to removing the menthol moiety prior to oxidative cleavage.

3.1.6. Removal of the menthol moiety

3.1.6.1. Acetal exchange

Feringa[67] has demonstrated the possibility of methanolysis of a menthyloxy group after the Diels-Alder reaction, by heating the adduct derived from reaction with

cyclopentadiene with *p*TsOH in MeOH. However, when the same conditions were applied to enol ether **203**, dimethyl acetal **217** was produced (Scheme 65).
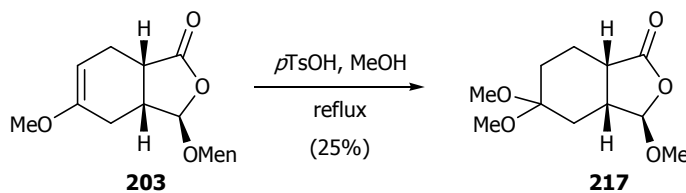
Scheme 65: Methanolysis of menthol moiety

In an attempt to produce the methoxy-derivative of menthyloxy adduct **203** directly, 5-methoxy-2-(5*H*)-furanone (**218**) was prepared from the corresponding hydroxyfuranone **195** (Scheme 66). Although aware that this would result in a lack of face selectivity in the Diels-Alder reaction, it would provide an insight into whether it was menthol that was limiting the progress in subsequent transformations. Disappointingly, Diels-Alder adduct **219** was produced in only moderate yields, and the subsequent ozonolysis to **220** occurred in very poor yield.
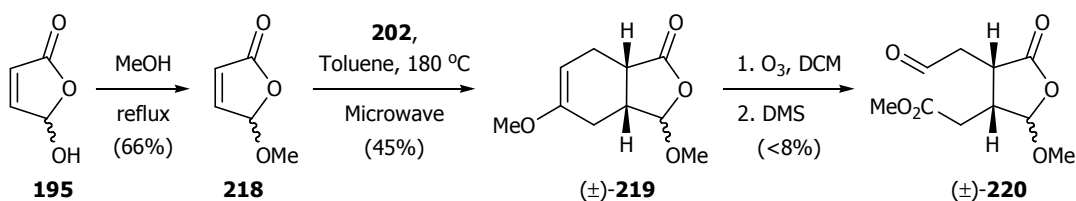
Scheme 66: Preparation and reaction of 5-methoxy-2-(5*H*)-furanone

3.1.6.2. Complete removal of the alkoxy group

A search in the literature showed that removal of the menthyloxy group from 5-menthyloxy-γ-lactones can be achieved by addition of KOH and NaBH$_4$, and has been used by Pelter and Ward[76] in their synthesis of lignans and by the Pete group[77] in their total syntheses of (−)-isoretronecanol and (+)-laburnine. It is believed that base-induced ring opening of the lactone to hemiacetal **221**, followed by elimination of menthol, reduction of the resulting aldehyde, and cyclisation of the alcohol onto the carboxylic acid provides the dementhylated lactone **223** (Scheme 67).
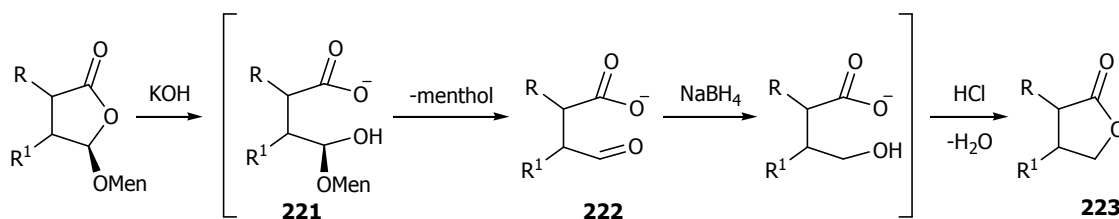
Scheme 67: Mechanism for the removal of menthyloxy group

Completely removing the alkoxy group would also remove the problem of a second reductive amination in the subsequent steps (*cf.* Scheme 63), as cyclisation onto the lactone carbonyl would lead directly to an alcohol, without the need to go through a hemiacetal/aldehyde intermediate.

Investigations into the removal of the menthyloxy group from Diels-Alder adduct **203** are presented in Table 3. Due to the acidic proton at the chiral centre α- to the aldehyde in intermediate **222**, the reactions were carried out by a dropwise addition of the base into the stirred solution of the substrate and $NaBH_4$ at 0 °C, so that upon formation, the aldehyde could be quickly reduced and epimerisation of this chiral centre avoided. To our knowledge, demethylation in the literature was almost always carried out using metal hydroxides as base, but when this method was applied on substrate **203**, only a complex mixture of products was obtained (entries 1 and 2). However, on one occasion when 1 M ethanolic solution of KOH was used, the diethyl acetal derivative of the desired enol ether **224**, (3a*R*,7a*S*)-5,5-diethoxyhexahydroisobenzofuran-1(3*H*)-one (**225**) was isolated in 39% yield (entry 3).
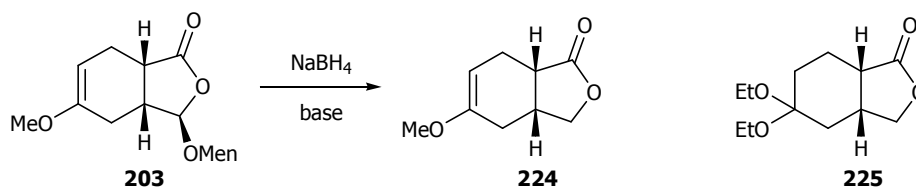
Table 3: Removal of menthyloxy moiety from Diels-Alder adduct 203[a,b]

Entry	Eq. of $NaBH_4$	Base	Solvent	pH at workup	Yield / %
1	2.6[c]	20% aq. KOH	MeOH	3[d]	0
2	25[e]	2 M NaOH	MeOH, THF	1[d]	0

Entry	Eq. of NaBH$_4$	Base	Solvent	pH at workup	Yield / %
3	6.5	1 M ethanolic KOH	EtOH	3[d,f]	0[g]
4	1.3	NaOMe	MeOH	-	0
5	1.3	NaOMe	MeOH	7[h]	see text
6	10	NaOMe	MeOH	7[h]	see text

[a] Typical procedure involves addition of NaBH$_4$ then base, followed by aqueous workup; [b] menthol always isolated; [c] 1.3 eq. then extra 1.3 eq. after 6 h; [d] acidified with 2 M HCl; [e] 20 eq. initially then extra 5 eq. after addition of base; [f] organic extract from acidic workup stirred for 62 h; [g] (3a*R*,7a*S*)-5,5-diethoxyhexahydroisobenzofuran-1(3*H*)-one (**225**, 39%) isolated; [h] neutralised with pH 7 KH$_2$PO$_4$/KOH buffer

If the proposed mechanism of dementhylation is correct, then changing the base to NaOMe should have no effect on the net result. The advantage of using NaOMe is that the intermediates contain an ester functionality rather than a carboxylate, and will not require an acidic workup. Thus when NaOMe was used, the reaction mixture was neutralised to pH 7 before concentration. The crude product was partially purified into three main fractions; the ^{1}H NMR spectra of these fractions all confirmed the presence of a lactone CH$_2$ group, and from the remaining peaks, the compounds were tentatively assigned to be the desired product **224**, **226** from methanolysis, and **227** from hydrolysis of the enol ether (Scheme 68).
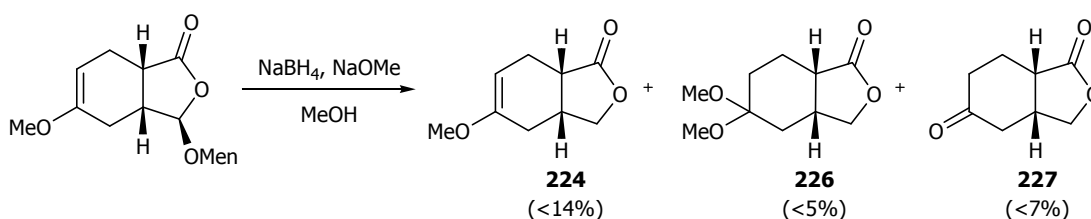
Scheme 68: Tentatively assigned products of dementhylation reactions with NaOMe

3.1.6.2.1 A model substrate

To ascertain whether the problems of dementhylation were due to the procedure or the substrate, it was decided to test this reaction on a simple model, 5-menthyloxy-2-(5*H*)-furanone **197**, which does not contain the labile enol ether (Table 4).

Although menthol was isolated upon treatment of acetal **197** with NaBH$_4$ and either with KOH or NaOMe as base, no other product was identified when using KOH. With NaOMe, it appeared that the double bond was also reduced to form γ-butyrolactone. Although the method of using NaOMe in MeOH is shown to be successful in removal of the menthyloxy group in both substrates **197** and **203**, it became clear that pursuance of this route would be challenging due to problems with the labile methyl enol ether in Diels-Alder adduct **203**.
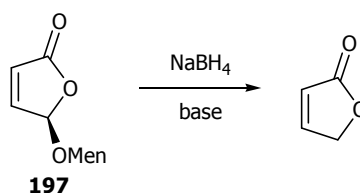
Table 4: Demethylation with NaBH$_4$ (2.0 eq.) and base

Entry	Base	Solvent	pH during workup	Yield / %
1	KOH	MeOH	7.0	0
2	NaOMe	MeOH	7.0	0[a]

[a] γ-butyrolactone (55%) isolated

3.1.6.3. Diels-Alder reaction with 2-(5H)-furanone

To circumvent the observed problems in the removal of the menthyloxy moiety, the Diels-Alder reaction was carried out with a simple unsubstituted furanone. Following the procedure of Näsman,[78] a Baeyer-Villiger reaction of furfural followed by fragmentation of the resulting formate provided 2-(5*H*)-furanone (**228**). However, the Diels-Alder reaction provided **229** in low yields, possibly due to the absence of an oxygen substituent at the C5 position of the furanone, rendering it a weaker dienophile. Unfortunately low yields continued to prevail upon transformation of **229** into **230**.
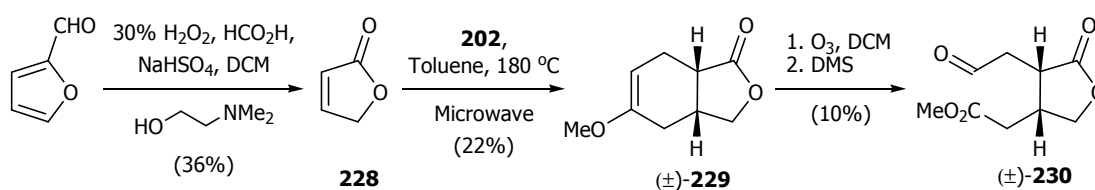
Scheme 69: Preparation and reaction of 2-(5*H*)-furanone

3.1.7. Nitrosation of Diels-Alder adducts

The search for further manipulations of the Diels-Alder adducts revealed that the cleavage of 1,2-dione monooximes with $SOCl_2$ can provide the corresponding ester-nitrile functionalities (Scheme 70).[79] Successful application of this chemistry on a substrate such as oxime **231** would therefore provide **232**, whereupon a reduction of the nitrile moiety would provide the free amine **233** for our reductive amination-cyclisation protocol.
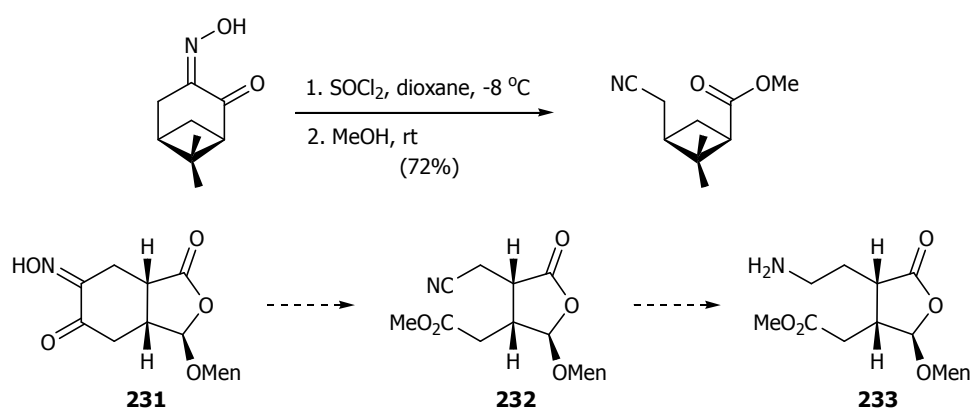
Scheme 70: Cleavage of 1,2-dione monooxime with $SOCl_2$

Hassner[80] showed that nitrosation of carbonyl compounds can be carried out by addition of nitrosyl chloride to trimethylsilyl enol ethers (Scheme 71). In addition, the work of Nagendrappa[81] showed that is possible to effect α-oximation of ketones to 1,2-dione monooximes **234** in high yields by generating nitrosyl chloride *in situ* using a combination of trimethylsilyl chloride and isoamyl nitrite.
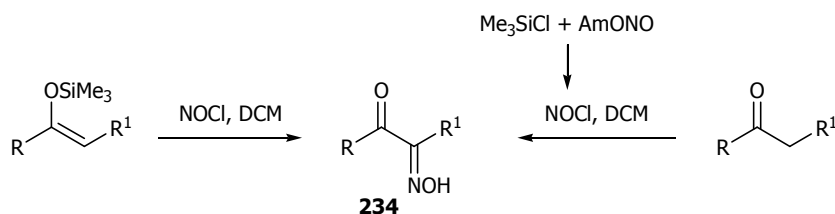
Scheme 71: Preparations of 1,2-dione monooximes

To prepare a substrate for the investigation of nitrosation reaction conditions, a Diels-Alder reaction between chiral butenolide **197** and 2-trimethylsilyloxy-1,3-butadiene was carried out to provide the required adduct **199**, for further transformation into oxime **231** (Scheme 72).
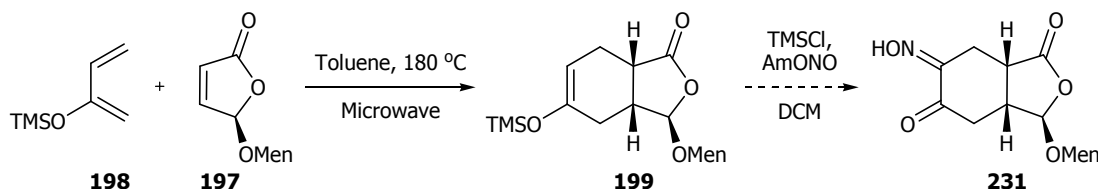
Scheme 72: Preparation of trimethylsilyloxy enol ether adduct

Due to the labile nature of the TMS enol ether, purification was avoided and the crude reaction mixture was subjected to Nagendrappa's conditions to generate NOCl *in situ*. Treatment with isoamyl nitrite and catalytic or stoichiometric quantities of TMSCl only gave an unidentified mixture of products.

Leeper[82] was successful in utilising Tanimoto's Lewis acid promoted nitrosation reaction[83] to convert silyl enol ether **235** into an α-keto oxime in their synthesis of chiral polycyclic thiazolium salts (Scheme 73). However, when analogous conditions[83] were applied on our substrate, using AmONO rather than BuONO, no product was isolated, but the menthyl group appeared to have been exchanged for an isoamyl group, probably facilitated by the Lewis acid.
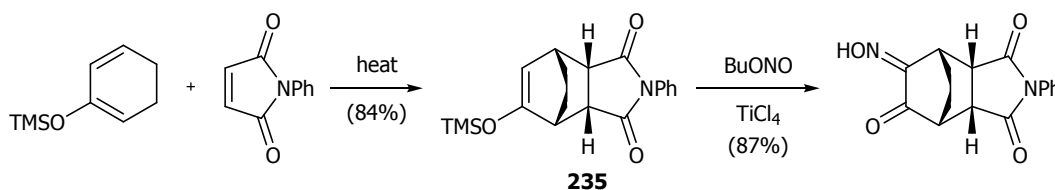
Scheme 73

As a result of the difficulties with nitrosation of the TMS enol ether, the target substrate was changed to ketone **236**, anticipating that nitrosation would take place at the desired, more accessible position. As well as being a readily purified starting material, this ketone had the added advantage that it could be treated to the dementhylation conditions without the problems associated with the alcoholysis or hydrolysis of the labile enol ethers.

Removal of the TMS protecting group in **199** with TBAF was low yielding (entry 1, Table 5), while an improvement was attained by changing the fluoride source to NH$_4$F. With the intent of either purifying or deprotecting the crude silyl enol ether **199**, it was passed through chromatography column on silica gel, and the desired ketone product

236 was obtained in 70% yield (entry 4). However, it was observed that a small amount of what is assumed to be impure silyl enol ether **199** was also collected. With this in mind, the crude enol ether was initially treated with silica before the column (entries 5 and 6), but provided the ketone product in lower yields than for simply loading directly onto the column. This suggests that ketone **236** has limited stability to acidic conditions.
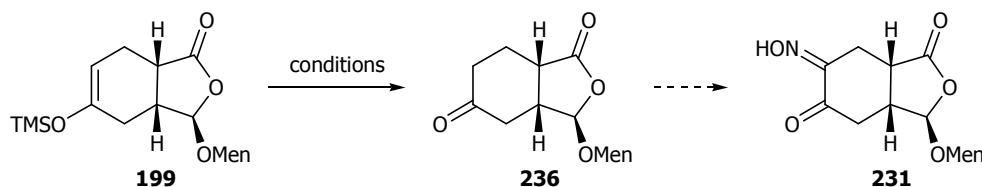
Table 5: Deprotection of OTMS enol ether

Entry	Conditions	Yield / %
1	TBAF, THF	20
2	NH$_4$F, MeOH	56
3	3 M HCl, DCM	3
4	Column on silica gel support	70
5	Adsorb onto silica, leave overnight then column	43
6	Stir in silica in 50% MeOH/DCM overnight then column	33

Unfortunately, the nitrosation reaction to give **231** continued to be problematic, and although the reaction of ketone **236** was significantly cleaner than that of the silyl enol ether, none of the desired product was isolated. To minimise the possibility that the lack of success in this reaction was due to the purity of the reagents, isoamyl nitrite was prepared using a procedure described by Maskill.[84] Treatment of isoamyl alcohol with sodium nitrite and concentrated sulfuric acid in the absence of organic solvent provided isoamyl nitrite in not entirely pure form, but it was cleaner by ^{1}H NMR spectroscopy than the commercial material (Scheme 74). When used in the nitrosation reaction, again the reaction was cleaner, but again no product was isolated.
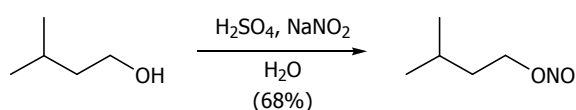
Scheme 74: Preparation of isoamyl nitrite

After a laborious and unsuccessful investigation into the possibility of using the Diels-Alder reaction of butenolides in our synthesis of the sarain core, this route was abandoned.

3.2. Strategy two: *N*-tosyl-1*H*-pyrrol-2(5*H*)-one as dienophile

In another Diels-Alder approach, an asymmetric catalyst rather than a chiral auxiliary was employed to induce enantioselectivity. Corey and co-workers have published several papers detailing the protonation of oxazaborolidines with either triflic acid[85,86] or triflimide[87,88] to generate chiral boron Lewis acids that are highly effective in catalysing the reactions between a wide variety of dienes and dienophiles (Scheme 75). Dienophiles used include dimethyl fumarate, 2-substituted acroleins, cyclic α,β-enones and quinones.[88]
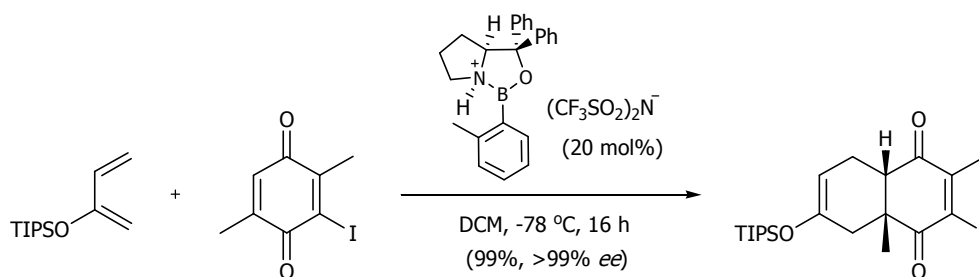
Scheme 75

Corey proposed that the face selectivity of the reaction is governed by the co-ordination of the Lewis acid catalyst to the dienophile, which forces the diene to approach from the convex face of the bicyclic catalyst, away from the two bulky aromatic rings (Figure 9). As shown, the predicted selectivity depends on the nature of the dienophile, where α,β-unsaturated enals are proposed to coordinate through the carbonyl oxygen and the aldehyde hydrogen, whereas α,β-unsaturated esters adopt a different geometry, coordinating through the hydrogen α- to the ester functionality.
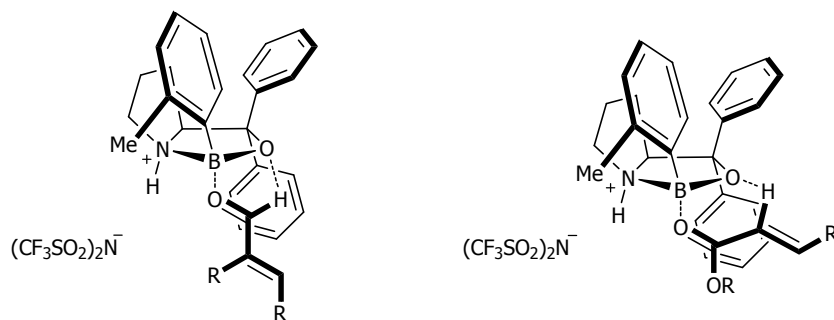
Figure 9

Retrosynthetic analysis suggested that bicyclic aminal **189** could be derived from **237**, produced as a result of cleavage of the Diels-Alder adduct **238** (Scheme 76). An advantage to this Diels-Alder approach is that use of a pyrrol-2(5*H*)-one would avoid the problems encountered with the reductive amination-cyclisation-fragmentation approach employed in the previous study with furanones.
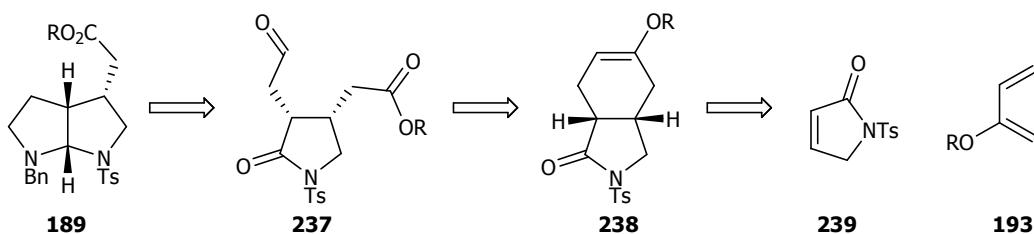
Scheme 76: Retrosynthetic route using *N*-tosyl-1*H*-pyrrol-2(5*H*)-one as dienophile

Previous work in our group involved an investigation into the reaction of *N*-tosyl-1*H*-pyrrol-2(5*H*)-one (**239**) with 2-(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**193**, R = TBS) in a number of solvents, reaction temperature and reaction media, with and without Lewis acids catalysis including *inter alia* Et_2AlCl, $TiCl_4$ and $BF_3.OEt_2$. However all reactions were unsuccessful and the lactam starting material was recovered. The lack of reactivity was attributed to steric effects of the bulky tosyl and TBS groups; thus a series of reactions involving *N*-acetyl-1*H*-pyrrol-2(5*H*)-one and the same diene were tested, but were also unsuccessful and the route was abandoned.[29]

From the studies of the reaction of various dienes with menthyloxy-furanone **197**,[70] it was evident that the steric bulk of 2-(*tert*-butyldimethylsilyloxy)-1,3-butadiene greatly hindered the reaction, even with a dienophile which is more activated than *N*-tosyl-1*H*-pyrrol-2(5*H*)-one (**239**). It was envisaged that use of a less sterically demanding diene

would be able to increase the reactivity and provide the required Diels-Alder adduct **238**.

3.2.1. Preparation of <u>N</u>-tosyl-1<u>H</u>-pyrrol-2(5<u>H</u>)-one

Work began using the procedure outlined by Nandra[29] to produce the pyrrol-(5H)-one **241** from pyrrolidinone **240**. Initial *N*-tosyl protection occurred in good yields with purification by flash chromatography (86%), and was optimised for larger scale preparations by using only recrystallisation from ethyl acetate to remove excess *p*TsCl and provide the pure product in 83% yield (Scheme 77). Nandra reported a modest 57% yield to generate **242** by selenylation α- to the carbonyl with LiHMDS followed by PhSeBr.[29] Modifying this procedure, by quenching with 1 M HCl, rather than saturated NH$_4$Cl, effected selenylation with a vastly improved yield of 98%. Subsequent oxidation with H$_2$O$_2$ furnished the elimination product **239** in 83% yield. It was also possible to carry out the oxidation without purification of the intermediate selenyl product with no appreciable change in the overall yield.
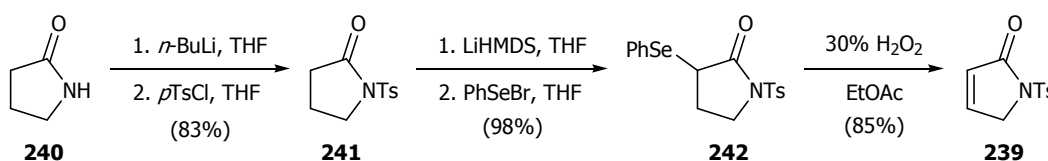
Scheme 77: Preparation of *N*-tosyl-1*H*-pyrrol-2(5*H*)-one

As PhSeBr is rather expensive (£92 for 25 g, Alfa Aesar) and the selenide is only a transient functionality in this route, an alternative cheaper route was sought. Bromination with NBS, followed by dehydrobromination to the elimination product would result in the same overall transformation. A number of procedures was used for the initial bromination step, and are listed in Table 6.

With a procedure based upon that employed by Otaka,[89] the protected lactam **241** was treated with LiHMDS and 1.2 equivalents of NBS, followed by workup with 1 M NaHSO$_3$ to provide bromide **243** in 63% yield (entry 1). Use of LDA rather than LiHMDS led to incomplete reaction, and extended reaction times led to significant decomposition. Changing the quenching reagent to sodium sulfite led to greatly

decreased yields (entry 3), whereas the use of ammonium chloride gave the desired product in 82% yield.
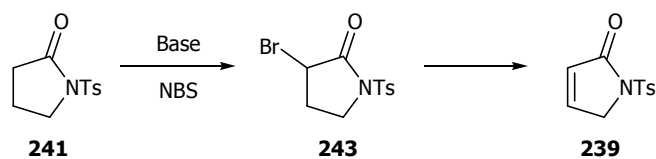
Table 6: α-Bromination of *N*-tosyl-pyrrolidinone with NBS (1.2 eq.) to give 243

Entry	Base	Eq.	Workup	Yield / %
1	LiHMDS, THF	2.0	1 M NaHSO$_3$	63
2	LDA, THF	2.0	1 M Na$_2$SO$_3$	20
3	LiHMDS, THF	2.0	1 M Na$_2$SO$_3$	2-25
4	LiHMDS, THF	2.0	Saturated NH$_4$Cl	82
5	LiHMDS, THF	1.1	Saturated NH$_4$Cl	65[a]
6	Amberlyst-15, EtOAc	0.75 g / mmol	Saturated Na$_2$CO$_3$	0[b]

[a] 3,3-Dibromo-*N*-tosyl-pyrrolidin-2-one isolated (7%); [b] starting material recovered

The reactions were carried out using two equivalents of base with the assumption that the reaction would be otherwise incomplete, as the remaining α-hydrogen to the carbonyl in product **243** is more acidic than those in starting material **241**, and would hence be more favourably deprotonated. To verify this, 1.1 equivalents of LiHMDS was used and as expected, the reaction remained incomplete and provided only 65% of the desired product (entry 5). Surprisingly, a small amount of the dibrominated product was also isolated, a result that was not observed with two equivalents of base.

Meshram has recently developed a facile method to effect 2-halogenation of 1,3-ketoesters and cyclic ketones using *N*-halosuccinimides and Amberlyst-15®,[90] but these conditions were unsuccessful with our substrate, presumably because the amide is less readily enolisable (entry 6).

A variety of methods were investigated for dehydrobromination of **243** to give **239**, with little success. The best results were obtained with either a combination of LiBr and

Li_2CO_3,[91] or with $CaCO_3$,[92] both in DMF at reflux, but a yield of no greater than 33% was obtained in either case.

At this point, as the selenylation route had been optimised, further work on bromination-dehydrobromination was ceased.

3.2.2. Uncatalysed Diels-Alder reactions

Preliminary investigations into the Diels-Alder reaction of enamide **239** were carried out under microwave irradiation without Corey's catalyst and the results are summarised in Table 7. It was initially pleasing to find that reaction between *N*-tosyl-1*H*-pyrrol-2(5*H*)-one **239** and methoxy diene **202** occurred without catalysis under microwave irradiation, albeit slowly and remaining largely incomplete at 150 °C (entry 1). With this in mind, the temperature was raised to 180 °C (entries 2 and 3) and indeed after 2 h, no starting material remained. However, near total isomerisation of the double bond occurred, producing an inseparable mixture of the desired product **244** and its regioisomer **245**, with yields not much higher than when carrying out the reaction at a lower temperature. Variation of reaction temperature, concentration and duration was carried out (entries 4-7). As is evident from the table, the yields and ratio of products were very inconsistent, and lowering the reaction temperature and reacting for prolonged periods did not necessarily improve the results.
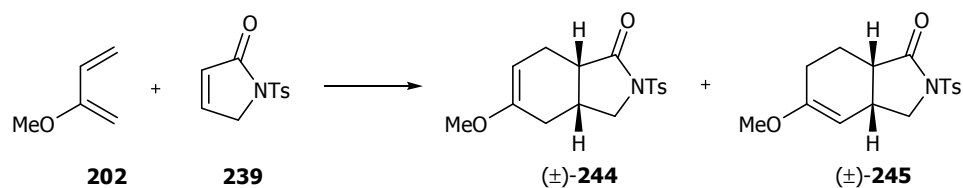
Table 7: Diels-Alder reactions with 2-methoxy-1,3-butadiene (3 eq.)

Entry	Conditions[a, b]	Conc^n / M	Temp. / °C	Time / h	Ratio of 244:245	Combined yield / %
1	Toluene	0.4	150	2	14:1	30
2	Toluene	1.1	180	2	1:9	45
3	Toluene	1.4	180	2	0:1	35

Entry	Conditions[a, b]	Conc^n / M	Temp. / °C	Time / h	Ratio of 244:245	Combined yield / %
4	Toluene	1.1	140	2	1:5	33
5	Toluene	0.4	140	2	3:1	20
6	Toluene	0.8	125	4	1:0	14
7	Toluene	0.8	125	8	2:1	49
8	Toluene, basic alumina	0.4	160	2	3:1	19
9	2 M KOH wash, toluene, basic alumina	0.4	180	2	1:4	8
10	Toluene, NaHCO$_3$	0.4	150	8	-	0
11	Toluene, NaHCO$_3$	0.8	140	8	-	0
12	(Me$_3$Si)$_2$NH wash, toluene, basic alumina	0.8	140	8	1:1	19
13	(Me$_3$Si)$_2$NH wash, toluene	0.2	125	7	5:1	4[c]
14	Toluene	0.2	125	7	3:1	5[c]
15	Toluene, sealed tube, no microwave	0.1	120	168	1:10	7
16	DCM	0.2	80	2	-	0[d]

[a] Unless otherwise stated, reactions were carried out under microwave irradiation; [b] 'wash' indicates washing the reaction vessel with the stated reagent followed by rinsing with acetone and thoroughly drying before use; [c] purified by flash chromatography using basic alumina (grade III); [d] no reaction took place, starting material recovered

In an attempt to suppress the isomerisation, the reaction glassware was washed with base and/or base was added to the reaction mixture (entries 8-13). Unfortunately, the yields were significantly reduced and moreover, little effect was observed on the ratio of products. To minimise the risk of isomerisation during purification by chromatography on silica gel, basic alumina was used; although the results suggest that this improved the regioisomeric ratio (entries 13-14), the yield was significantly lower, possibly due to the decrease in concentration of the reaction. Carrying out the reaction in a non-microwave

irradiated sealed tube also produced poor results (entry 15), as did changing to a more volatile solvent, where no reaction took place (entry 16).

3.2.3. Oxidative cleavage of Diels-Alder adduct

Even though the reproducibility in the synthesis of desired Diels-Alder adduct **244** was difficult, it was desirable to ascertain whether there were going to be problems at the oxidative cleavage step as previously discussed. The two regioisomers **244** and **245**, obtained from reactions where only a single regioisomer was produced (entries 3 and 6), were separately treated with ozone followed by workup with DMS (Scheme 78). In contrast to the results for the corresponding furanone substrates, the crude products of these ozonolyses were often very clean. However, the desired aldehyde product **246** appeared to decompose or was retained on silica as it was isolated in only a 38% yield. Aldehyde **247** was obtained from the isomerised enol ether **245** in 60% yield. As the oxidative cleavage step did not pose a big problem, it was felt that if the Diels-Alder reaction could be optimised, the ozonolysed products could be separated by flash chromatography at the next step.
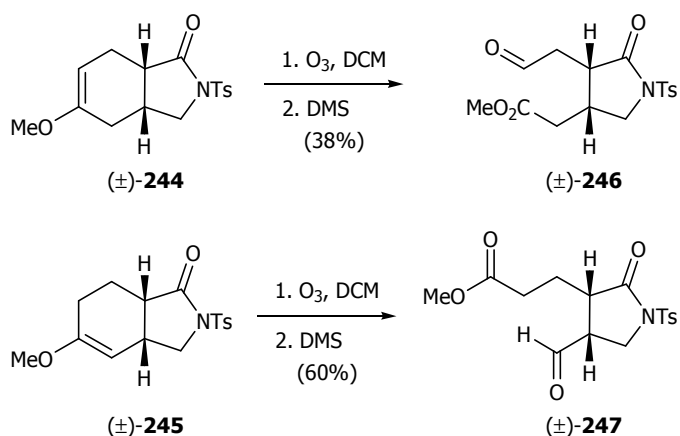
Scheme 78: Oxidative cleavage of Diels-Alder adducts

To ascertain whether the problems with isomerisation of the Diels-Alder adducts could be made irrelevant by nitrosation of the equivalent ketone substrate, the trimethylsilyloxy enol ether adduct **248** was prepared and was then desilylated by purification by flash chromatography on silica gel to provide ketone **249** (Scheme 79). Treatment of **248** or the ketone variant, **249**, with AmONO and TMSCl unfortunately led to incomplete reaction and produced a complex mixture of products.
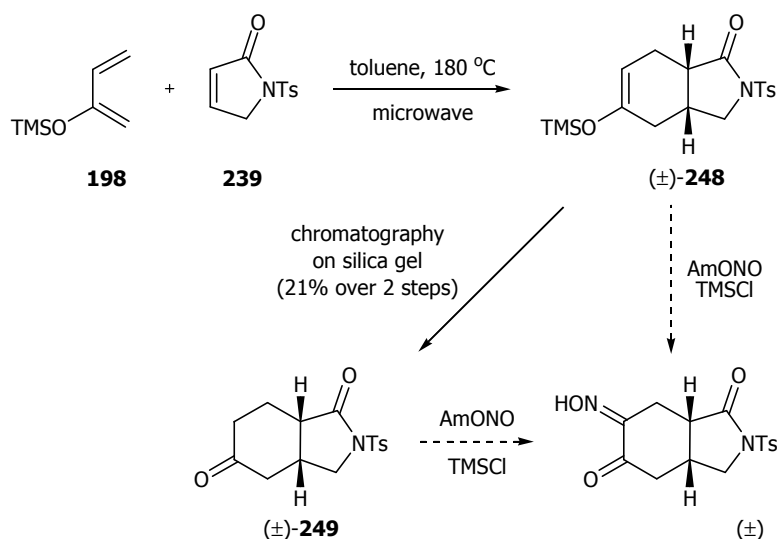
Scheme 79

3.2.4. Asymmetric Diels-Alder reaction with Corey's catalyst

Despite the isomerisation troubles encountered with the uncatalysed Diels-Alder reactions, it was thought that the problem might be overcome when the reaction was carried out in the presence of the aforementioned Corey oxazaborolidine catalysts, as lower temperatures would be used.

3.2.4.1. *Preparation of the oxazaborolidine catalyst*

The oxazaborolidine derived from (*S*)-α,α-di(3,5-dimethylphenyl)-2-pyrrolidinemethanol (**253**) was selected to be used as the catalyst in this Diels-Alder reaction, as published results showed that it generally gave better yields and enantioselectivity than the diphenyl equivalent.[85-88] The (*S*)-catalyst was selected due to its lower cost, even though it would provide the adduct with the wrong stereochemistry for the total synthesis.

Using a procedure of Mathre,[93,94] (*S*)-proline was treated with triphosgene followed by base to initiate cyclisation to form anhydride **250**, which was immediately treated with Grignard reagent **251**, prepared from 5-bromo-*m*-xylene (Scheme 80). The Grignard reagent could theoretically attack either carbonyl of the anhydride and thus the major by-products of this reaction are (*S*)-*N*-(3,5-dimethylbenzoyl)proline, 3,3',5,5'-

tetramethylbenzophenone and tri(3,5-dimethylphenyl)methanol. Mathre developed a very convenient workup procedure for removal of these impurities by formation of the prolinol sulfate salt then simply washing with water and ethyl acetate to afford pure **252** in 55% yield. Treatment with NaOH provided the free prolinol **253** in quantitative yield which was further purified by recrystallisation.
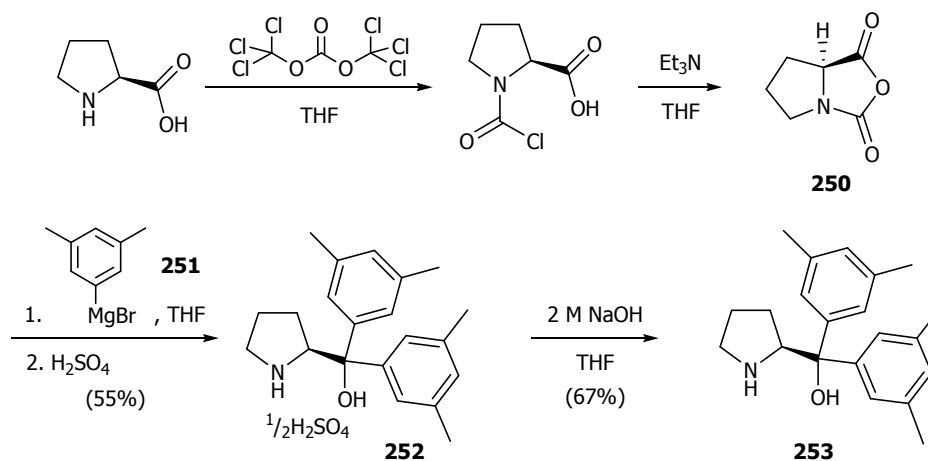
Scheme 80: Preparation of prolinol 253

To synthesise the boroxine component, benzene was distilled from *o*-tolylboronic acid to furnish the dehydrated boroxine **254** in quantitative yield (Scheme 81).[85] Completion of the oxazaborolidine synthesis involved refluxing a solution of boroxine **254** and prolinol **253** in toluene over molecular sieves to furnish **255**. This product was used immediately in the Diels-Alder reactions.
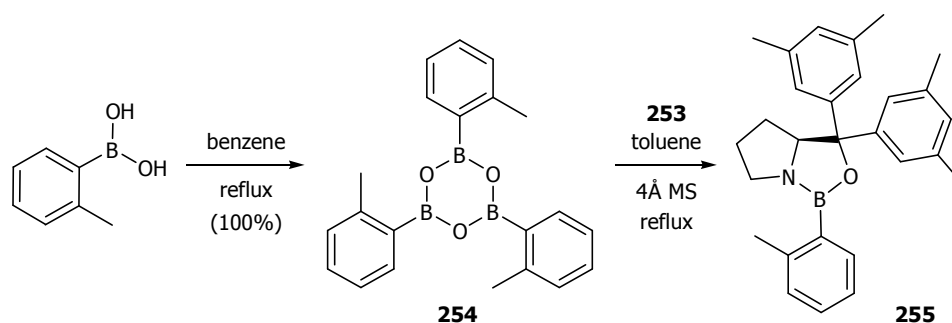
Scheme 81: Synthesis of oxazaborolidine 255

3.2.4.2. Catalysed Diels-Alder reaction

Corey reported that the use of the oxazaborolidine **255** with triflic acid in the Diels-Alder reaction required the temperature of the reaction to be kept below 0 °C, otherwise the Lewis acid suffered from decomposition.[87] Unfortunately the lactam dienophile **239**

was insoluble in DCM at low temperatures and therefore the reactions had to be carried out at high dilutions. It was difficult to sustain the solubility of **239** during the reaction and it often precipitated out. Reactions with the methoxy- and trimethylsilyloxy dienes, starting at −95 °C and gradually warming up to −10 °C over a number of days were unsuccessful, and the lactam dienophile was recovered (Scheme 82). The lack of reaction was attributed to the low temperature of the reaction.
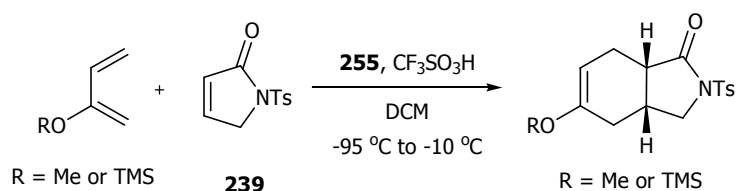
Scheme 82: Diels-Alder reaction with oxazaborolidine and triflic acid

Corey has discovered that it was possible to warm the reaction to room temperature if triflic acid was replaced with triflimide, with the added advantage of successfully catalysing reactions between a number of substrates that failed when using triflic acid.[87] Repeating these conditions with our substrates began at −78 °C, then warming to room temperature, stirring for several days. Although the substrates were soluble, no reaction took place with the methoxy-diene, and with the trimethylsilyloxy-diene there appeared to be only a trace signal in the region of the ^{1}H NMR spectra compatible with the Diels-Alder adducts.

In addition, the simple furanone **228**, a dienophile which was used in Corey's studies, was treated with the methoxy-diene in the presence of Corey's catalyst and triflimide. Although the furanone starting material was consumed within a few hours, the reaction yielded a complex mixture of products, and comparison of its crude ^{1}H NMR spectrum to that of the authentic product (**229**) from the uncatalysed reaction (section 3.1.6.3) showed absence of the desired product.

3.2.5. Isoprene as diene

To conclude the investigation into using *N*-tosyl-1*H*-pyrrol-2(5*H*)-one as dienophile, it was reacted with isoprene and various Lewis acids (Table 8). Low conversion was achieved with absence of Lewis acid, but a favourable ratio of the desired "pseudo-

para" regioisomer **256a** over **256b** was obtained with AlCl$_3$[73] in refluxing DCM. Unfortunately ozonolysis of these adducts led to an inseparable mixture of cleaved products in moderate yields.

239   (±)-**256a**   (±)-**256b**
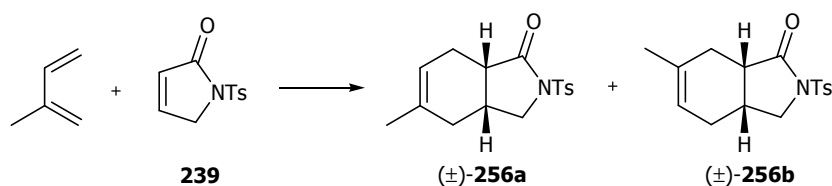
Table 8: Diels-Alder reaction with isoprene (10 eq.)

Entry	Conditions	Yield / %
1	Microwave, toluene, 130 °C, 2 h	20[a,b]
2	Microwave, AlCl$_3$, toluene, 130 °C, 1 h	43[b]
3	AlCl$_3$, DCM, 50 °C	78[c]
4	EtAlCl$_2$, ZnCl$_2$, DCM, rt	0[d]

[a] 30% conversion; [b] ratio of isomers not determined; [c] ratio of **256a**:**256b** 3:1; [d] starting material recovered

Due to the unpredictability of the reaction rates and problems of isomerisation, development with this Diels-Alder route was ceased.

3.3. Strategy three – Michael addition of *N*-benzylpyrrolidin-2-one

Heathcock and co-workers have published a report detailing studies into the regio- and diastereoselectivity of the addition of amide and thioamide enolates to α,β-unsaturated ketones; these reactions were found to be affected by the nature of enone, enolate, enolate counterion and solvent.[95] The selective formation of either the *syn* or *anti* addition products by varying solvents and counterion was also demonstrated. As part of these studies, the enolate of *N*-methylpyrrolidin-2-one was treated with a variety of α,β-unsaturated ketones. In the example shown in Scheme 83, *syn* adduct **257a** was produced in preference to *anti* adduct **257b** in a ratio of 9:1; the reaction was also selective for 1,4-addition over 1,2-addition by 97:3.
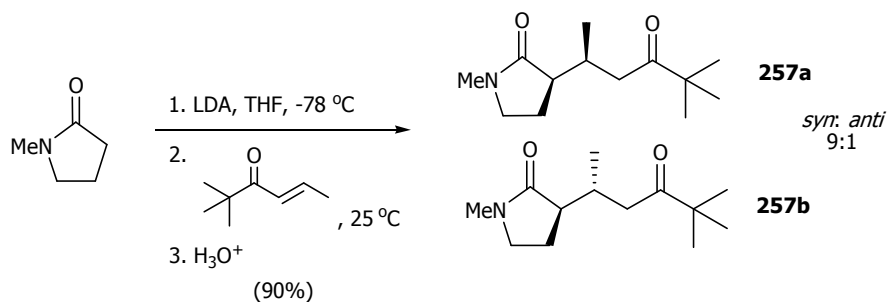
Scheme 83: Michael addition of *N*-methylpyrrolidin-2-one

The synthesis of **258**, a key intermediate in our synthesis of the sarain core, was next investigated *via* such a Michael addition. *N*-Benzylpyrrolidin-2-one and protected (*E*)-5-hydroxypent-3-en-2-one **259** were selected as suitable starting materials (Scheme 84); however, there were no examples of Michael additions onto γ-oxygenated-α,β-unsaturated ketones within Heathcock's report.
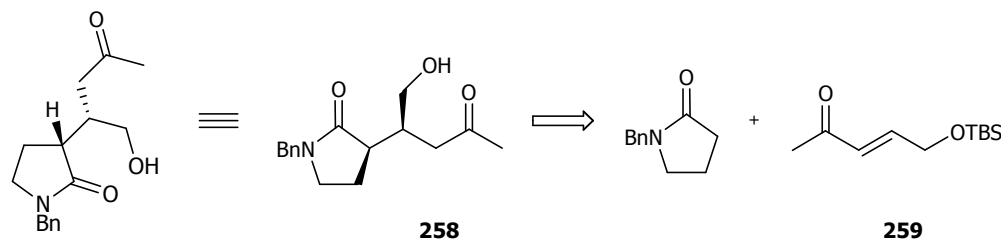
Scheme 84: Retrosynthetic route to lactam 258 *via* Michael addition

3.3.1. Preparation of Michael acceptor

A preparation of the alcohol corresponding to **259** has been reported in the literature,[96] but purification is known to be difficult and moreover, the compound is unstable to basic conditions. Under such conditions, it undergoes an oxa-Michael/Michael dimerisation to tetrahydrofuran **260**, followed by an intramolecular aldol condensation to fused bicycle **261** (Scheme 85). The protection of the hydroxy group was therefore carried out early in the synthesis.
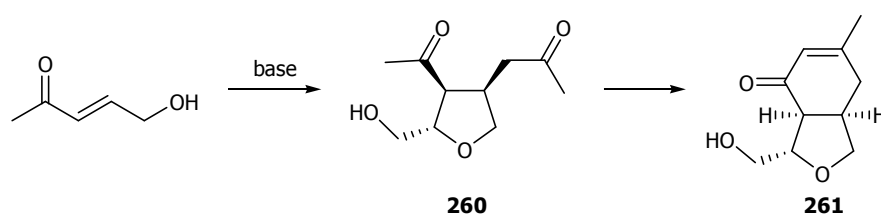
Scheme 85: Reactions of (*E*)-5-hydroxypent-3-en-2-one with base

A literature procedure for the preparation of the Michael acceptor **259** involves a Horner-Wadsworth-Emmons reaction of phosphonate **262** and aldehyde **263** (Scheme 86);[97] our investigation into the Michael addition strategy began with the synthesis of these two fragments.
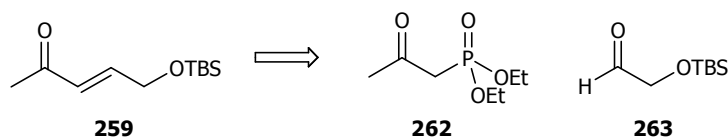
Scheme 86: Preparation of Michael acceptor 259

Phosphonate **262** was prepared in moderate yields by an Arbuzov reaction of chloroacetone with triethyl phosphite (Scheme 87).[98] The preparation of the aldehyde fragment from allyl alcohol was more problematic due to the volatility of the intermediate allyl *tert*-butyldimethylsilyl ether (**264**). The problems associated with this method led to the development of another route to the enone.
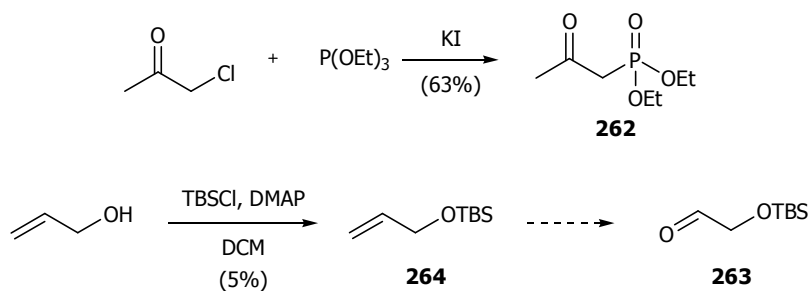
Scheme 87: Synthesis of fragments for Horner-Wadsworth-Emmons reaction

Monoprotection of (*Z*)-butene-1,4-diol with *tert*-butyldimethylsilyl chloride afforded alcohol **266** in good yield, but although a large excess of the diol was used, a small amount of the doubly protected alcohol **265** was also isolated (Scheme 88). Turning this to our advantage, it was anticipated that treatment of this by-product with ozone would create two equivalent of the aldehyde **263** for the Horner-Wadsworth-Emmons route. But instead, a compound with NMR and mass spectrometric properties which were consistent with the aldehyde in its trimeric form (**267**) was produced.
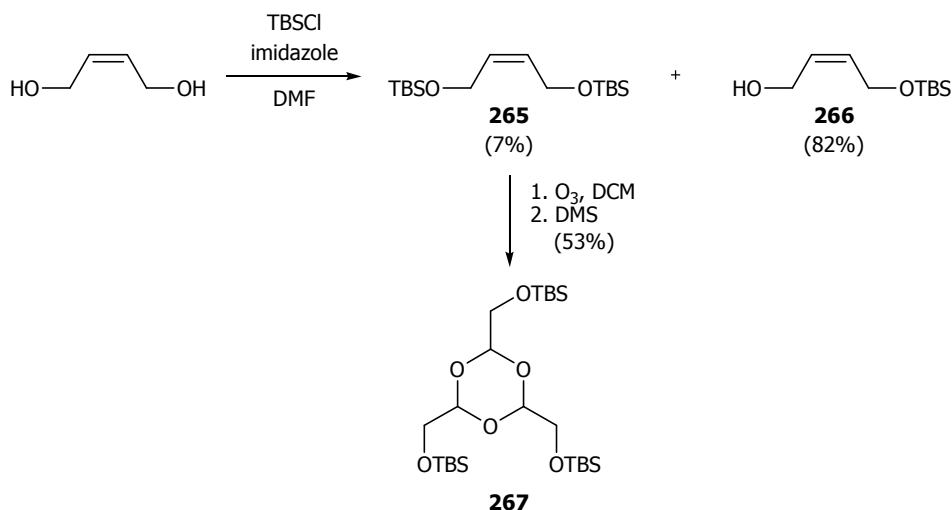
Scheme 88

Reverting to the previous route, the mono-protected alcohol **266** was treated with PCC to effect both oxidation and isomerisation of the double bond to provide the desired (*E*)-α,β-enal **268**, which following addition of methyllithium and subsequent oxidation furnished the desired methyl ketone **259** in moderate yields (Scheme 89). Only a small amount of impurities was observed in the crude products, and it is assumed that the low isolated yields were due to the decomposition of the allylic silyl ethers during purification by silica gel chromatography. The sequence from monoprotected alcohol **266** to methyl ketone **259** was therefore repeated without purification of any intermediates, and furnished the product in an improved 29% overall yield.
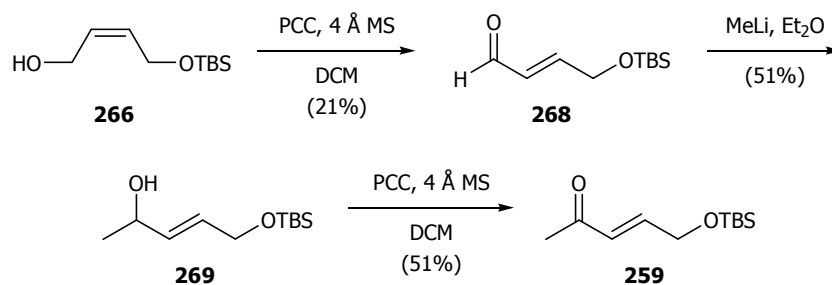
Scheme 89: Multistep preparation of Michael acceptor

Although the yields for this route were far from ideal, sufficient quantities of (*E*)-5-(*tert*-butyldimethylsilyloxy)-pent-3-en-2-one (**259**) were generated for a preliminary investigation into the efficiency of the Michael reaction to produce desired adduct (*cf.* **258**).

3.3.2. Michael addition

N-Benzylpyrrolidin-2-one was treated sequentially with LDA then the enone at −78 °C, followed by warming to room temperature. The addition reaction appeared very slow and therefore this mixture was subsequently heated to 60 °C. The partially purified major product from this reaction was only isolated in very small quantities and the ^{1}H NMR spectrum of this material contained a large number of peaks in the alkene region which did not appear to correspond to the enone or the 1,2-Michael product. Heathcock's paper suggested that the use of thioamide rather than oxoamide enolates increases the likelihood of 1,4-conjugate addition as the enethiolate is a softer nucleophile. Analogous conditions were therefore applied to *N*-benzylpyrrolidin-2-thione but unfortunately the reaction was again very slow, and heating the reaction mixture for prolonged periods led to decomposition of the enone, while the thioamide was recovered unreacted (Scheme 90).
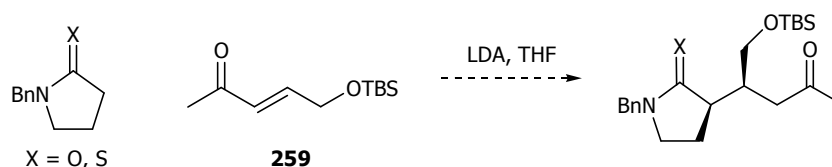
Scheme 90

These poor results together with the difficulties in the preparation of the enone, and the uncertainty as to whether good regio- or diastereoselectivity would be achieved led to abandonment of this route.

3.4. Strategy four: Thio-Claisen rearrangement

3.4.1. Previous work

One of the more promising routes previously developed within the group to synthesise bicyclic aminals involves a Claisen rearrangement. Reaction of *N*-benzylpyrrolidin-2-one with dimethyl sulfate generated a methoxymethyleniminium methyl sulfate salt. Heating this salt with the lithium alkoxide of alcohol **270** led to formation of a *N,O*-ketene acetal,[99] which underwent a [3,3]-sigmatropic rearrangement to give **271** in a somewhat modest yield of 33-56% (Scheme 91).[30]
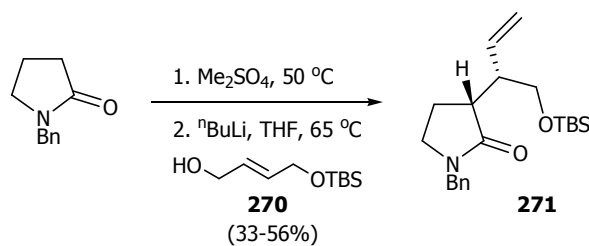
Scheme 91

The success of the Claisen rearrangement in generating **271** was promising despite the modest yield, and led to examination of alternative processes, including thio-Claisen rearrangement. This is advantageous as the nucleophilicity of the sulfur allows direct alkylation with an allylic bromide, without the prior need for formation of the iminium salt. Thus lactam **272** was first converted into the corresponding thiolactam **273** in good yield by treatment with P_4S_{10} (Scheme 92). Conditions were developed for the thio-Claisen rearrangement to take place with excellent diastereoselectivity, which consisted of first stirring a concentrated solution of the thiolactam with bromide **274** in MeCN to form the salt **275**, followed by dilution with further MeCN, heating to 40 °C, and then addition of Et_3N.[100] This produced the desired product **276** in >50:1 diastereoselectivity, and an X-ray structural analysis of the *p*-nitrobenzoate derivative of the alcohol confirmed the relative stereochemistry of the compound to be as drawn in **276**, which is consistent with the reaction proceeding *via* a chair transition state.[100]
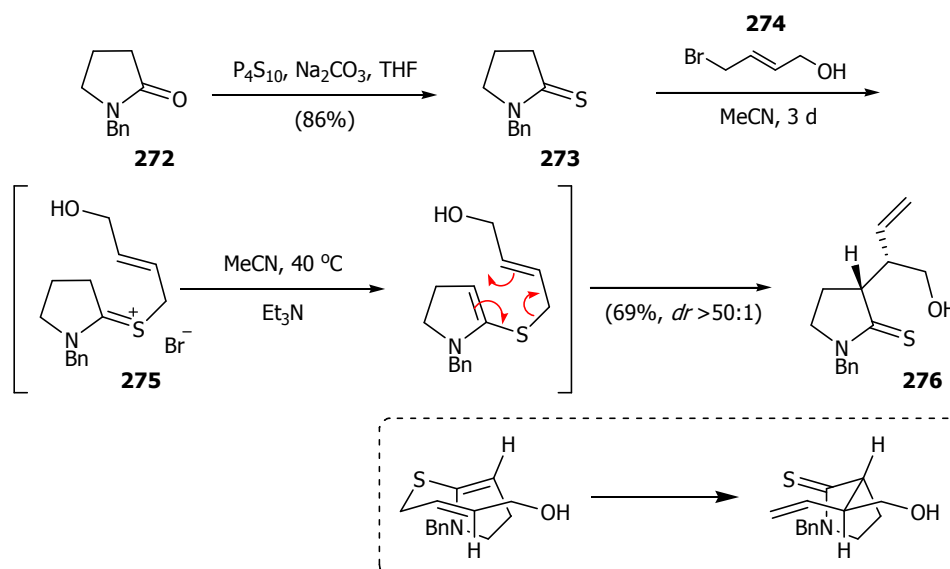
Scheme 92

Thiolactam **276** was then hydrolysed to the corresponding lactam, and mesylation of the alcohol followed by its displacement provided azide **277**, which was converted to

bicycle **278**, through the reductive cyclisation protocol described in section 1.3.6.1 (Scheme 93).
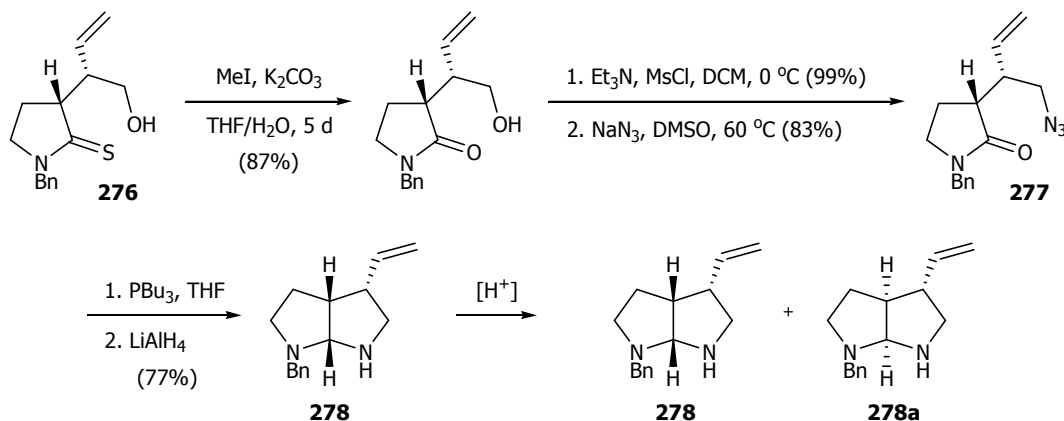
Scheme 93

Unfortunately, exposure of the bicyclic aminal **278** to even mildly acidic conditions, such as silica gel, caused isomerisation to give a mixture of isomers **278** and **278a**. Whilst purification of aminal **278** was possible by chromatography on alumina, retaining stereochemical purity whilst introducing further functionalisation was difficult.

It is believed that the mechanism of the isomerisation follows the pathway depicted in Scheme 94. Protonation of either amine could cause ring opening of the bicyclic aminal, and subsequent loss of a proton would lead to enamine **279**. This species could reprotonate from either face, and therefore leads to a mixture of stereoisomers **278** and **278a**.[101]
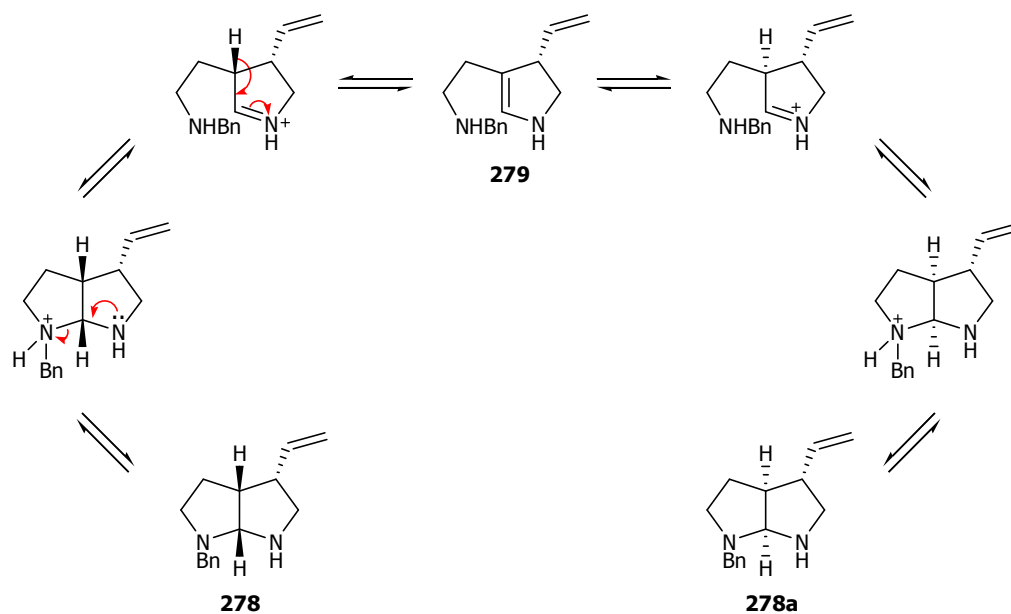
Scheme 94: Proposed mechanism of ring isomerisation

3.4.2. Synthesis of a bicyclic aminal bearing a methyl group

It was decided that the successful preliminary work described above could be continued by replacing the hydrogen at the ring junction with a 'blocking group' so that enamine formation, and hence the stereoisomerisation process, is prevented. An ideal blocking group would be one that can be removed at the end of the synthesis, but a simple methyl group was chosen to provide a simple 'proof of concept' model.

The methyl group was incorporated into the substrate at the start of the synthesis. Alkylation of *N*-benzylpyrrolidinone by treatment with *n*-BuLi followed by MeI provided the desired product **280** in excellent yields. Unfortunately, the subsequent synthesis of the bicyclic aminal was not as straightforward as hoped. Although the sequence of reactions was essentially the same as before, several of the procedures previously developed needed to be modified for the methylated substrates.
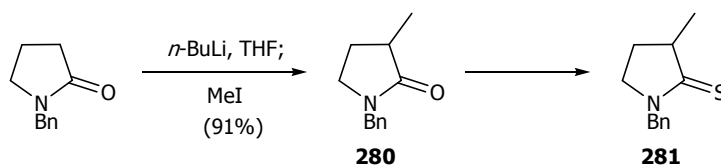
Scheme 95

Thionation of lactam **280** under the previously used conditions of P_4S_{10} with Na_2CO_3[102] in THF at ambient temperature resulted in an incomplete reaction even after a prolonged period of time, with 28% starting material being recovered, and the product being isolated in only 55% yield (Table 9, entry 1). Although better yields were obtained with P_4S_{10} at higher temperatures, they were inferior to those obtained with Lawesson's reagent,[103] which furnished thiolactam **281** in excellent yield.

Table 9: Thionation of *N*-benzyl-3-methyl-pyrrolidin-2-one

Entry	Conditions	Time / h	Yield / %
1	P_4S_{10}, Na_2CO_3, THF, rt	40	55
2	P_4S_{10}, THF, 40 °C	5	70
3	P_4S_{10}, DCM, 50 °C	20	86
4	Lawesson's reagent, THF, 40 °C	2	91

Bromide **274** was freshly prepared by DIBAH reduction of methyl 4-bromocrotonate (Scheme 96).[104] However, if bromide **274** was used crude (as was the case for the non-methylated route) the thio-Claisen rearrangement took place in highly inconsistent and low yields, with decomposition of starting material. In addition, when the salt formation step was carried out at a concentration of 0.5 M in MeCN, thiolactam **281** remained largely unreacted. The optimal conditions were to perform the salt formation at a concentration of ~6 M, using purified bromide **274**; following dilution to 0.2 M and treatment with Et_3N, this routinely provided the desired product **282** in 75% yield, with 3% recovered starting material. There was no evidence of formation of the undesired stereoisomer.
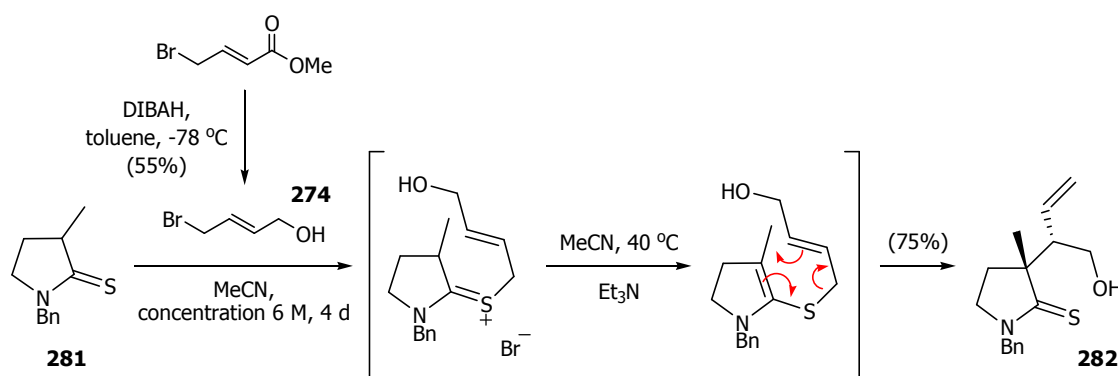
Scheme 96

Hydrolysis of the thiolactam **282** by treatment with MeI and K_2CO_3 in a THF/H_2O mix[105] was very slow and inconsistent. The best result was obtained after 14 days of reaction, with incomplete conversion, providing the product **283** in 72% yield, and also 14% of iodide product **284** (Scheme 97).
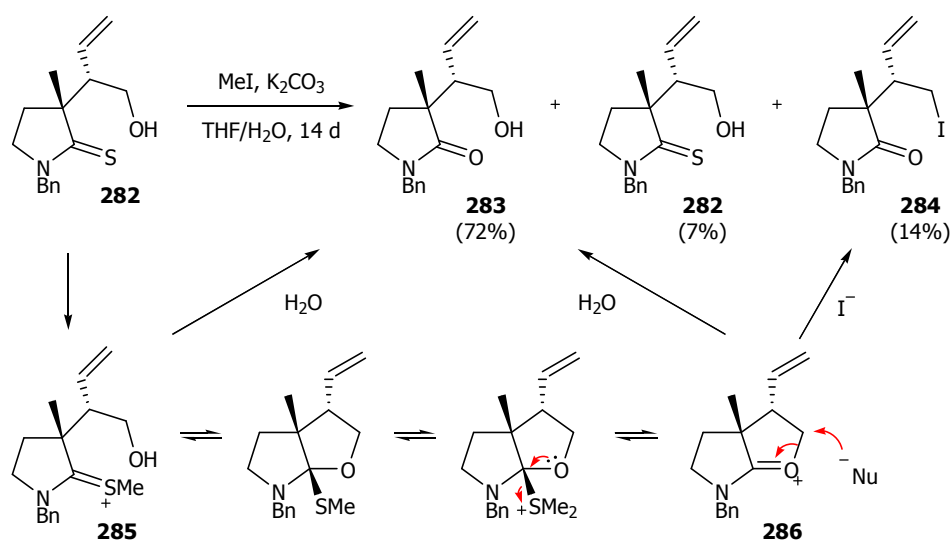
Scheme 97

The mechanism of this hydrolysis is assumed to begin with methylation of the thiolactam; the resulting salt **285** could be attacked by H_2O to give product **283**, or by the internal hydroxyl group, leading to formation of oxocarbenium ion **286** (Scheme 97). A nucleophilic attack by water would form the desired product **283**, but attack from iodide would yield product **284**. It was thought that iodoalkane **284** could be useful in that the iodide could be directly displaced with NaN_3 (rather than requiring activation, like alcohol **283**). When the reaction was carried out, it afforded an inseparable mixture of the olefinic elimination product **287** and desired azide **288**, with the undesired olefin **287** present as the major component (Scheme 98).
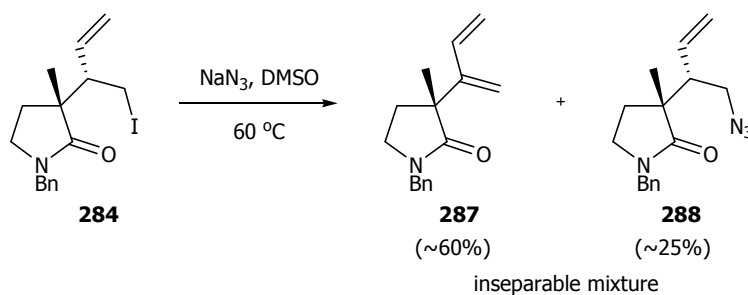
Scheme 98

Other methods for the hydrolysis of thiolactam **282** were tried, including reaction with dimethyldioxirane, generated *in situ* by use of oxone and NaHCO$_3$,[106] but this gave **283** in only 17% yield, with decomposition of starting material. The best method involved treatment with *m*CPBA in DCM,[107] which in 2 h provided the desired product **283** in 93% yield (Scheme 99). Slow, portionwise addition of the reagent was required to prevent any oxidation of the double bond.

Mesylation of alcohol **283** and subsequent azide displacement took place uneventfully; mesylate **289** could be isolated in 94% yield, but was routinely used without purification in the next reaction to provide azide **288** in 87% yield over 2 steps. Initial attempts at carrying out the reductive cyclisation step using published conditions of 1.2 equivalents of PBu$_3$ and 0.6 equivalents of LiAlH$_4$[30] often returned the simple azide reduction material **290** as the major product (50%, with 25% desired product **291**). Attempts to convert this simple amide into the desired product by addition of LiAlH$_4$ in a subsequent step were unsuccessful, returning a polar compound, thought to be the pyrrolidine derived from reduction of the pyrrolidinone moiety. Optimal conditions for the reductive cyclisation procedure consisted of using 1.8 equivalents of PBu$_3$ followed by two equivalents of LiAlH$_4$ in two batches, one hour apart. Under these conditions, bicyclic aminal **291** was routinely obtained in yields of >70%. As predicted, the additional methyl group proved to be effective in preventing the stereoisomerisation process, and it was possible to purify this and subsequent bicyclic aminal products by chromatography on silica gel.
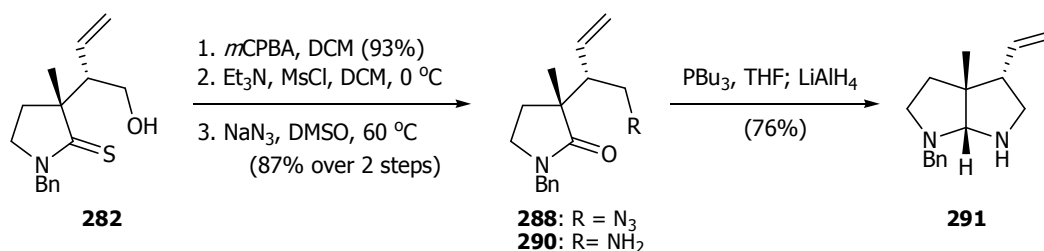
Scheme 99

The next step was to protect the secondary amine in **291** with an electron withdrawing group. A sulfonamide was chosen and a number of protection conditions were explored (Table 10).

291   **292**
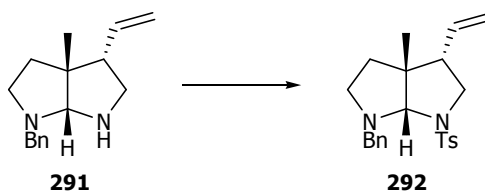
Table 10: Tosylation of amine

Entry	Reagents	Time	Yield / %
1	TsCl, DIPEA, DCM	5 d	62
2	TsCl, DIPEA, DMAP, DCM	4 d	65
3	^{n}BuLi, TsCl, THF	2 h	47
4	TsCl, pyridine	16 h	87

On using DIPEA, the reaction was slow in the absence or presence of catalytic DMAP (Table 10), while the use of ^{n}BuLi as base gave only moderate yields. The best conditions were to use pyridine as the solvent in the reaction, which furnished the sulfonamide **292** in 87% yield.

3.4.3. Functionalisation of the olefin into a carboxylic acid

With the bicyclic aminal finally synthesised, the next task in hand was to convert the terminal olefin in **292** into a carboxylic acid, for transformation into a diazoketone. For such, a hydroboration-oxidation strategy to synthesise the primary alcohol was adopted. Whilst use of BH$_3$.THF and 9-BBN failed, hydroboration with pinacolborane in the presence of Wilkinson's catalyst[108] in THF was successful (Table 11).

Table 11: Hydroboration of olefin product 292

Entry	Conditions	Result
1	9-BBN	No reaction
2	BH$_3$.THF	Decomposition
3	Pinacolborane, Wilkinson's catalyst, DCM, 5 d	3%, 43% SM
4	Pinacolborane, Wilkinson's catalyst, THF, 24 h	72%
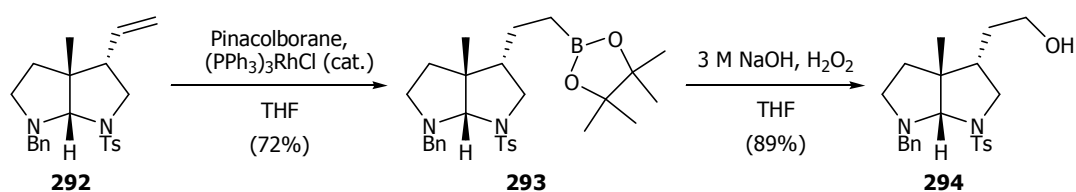
Scheme 100

The boronate **293** could be isolated first before oxidation to give the desired alcohol product **294** (Scheme 100), but it was more convenient to carry out the oxidation in the same pot by addition of NaOH and H_2O_2 after consumption of starting material. However, with the Wilkinson's catalyst remaining in the reaction mixture, the H_2O_2 was partially decomposed into O_2 and it was difficult to prevent sudden foaming of the reaction mixture. Despite these problems, alcohol **294** was isolated in 70% overall yield. The decomposition of H_2O_2 could be circumvented by use of the milder water/sodium perborate[109] combination for the oxidative step.
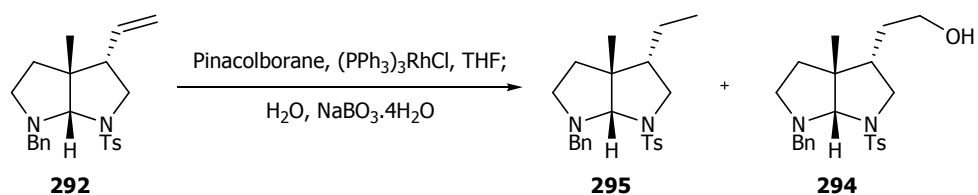
Scheme 101

When the reaction was carried out on a larger scale, a significant amount of a side product was consistently produced from the hydroboration step, and this material was inert to the oxidative agents. This was identified to be the simple reduction product **295** and was isolated in yields of up to 27% (Scheme 101). This observation is in keeping with a detailed study into the analogous reactions of catecholborane with Wilkinson's catalyst, in which reaction with 2-ethylbut-1-ene resulted in not only formation of the desired boronate ester **296** in 85% yield, but also 3-methylpentane as the hydrogenation product in 15% yield.[110]
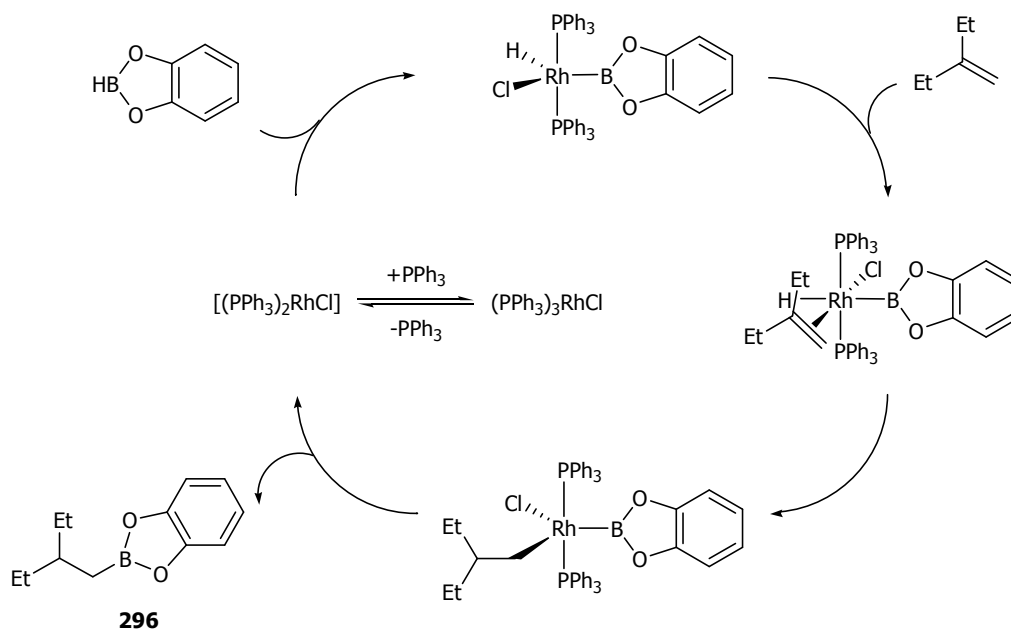
Scheme 102

The mechanism proposed for the hydroboration of alkenes mediated by Wilkinson's catalyst involves oxidative addition of the B-H bond to Rh, followed by alkene insertion and reductive elimination to furnish the observed product **296** (Scheme 102).[110] In the absence of the alkene substrate, there was appreciable degradation of catecholborane from reaction with the catalyst to give a number of different products (Scheme 103).[110] A by-product of particular relevance is dihydride complex **297**, a catalyst precursor for hydrogenation reactions, and as hydrogen is also a degradation product, this could explain the formation of simple alkene reduction products.
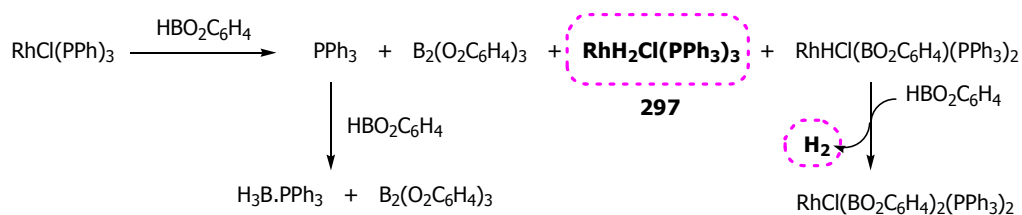
Scheme 103

In addition, RhCl(PPh$_3$)$_3$ is susceptible to oxidation, especially when the catalyst is in solution. Significantly, this oxidised catalyst is reported to be a more active catalyst for alkene hydrogenation.[111] In light of this, hydroboration of alkene **292** was carried out by first thoroughly degassing the reaction mixture, before maintaining the reaction strictly under an inert atmosphere of argon. This, in combination with use of sodium perborate as the oxidant, led to isolation of the desired product **294** in 86% yield, and the reduced product **295** in only 7% yield.

Attempts to oxidise the primary alcohol **294** to a carboxylic acid directly proved ineffective with either oxone/2-iodobenzoic acid[112] or a NaOCl/TEMPO[113] combination. Use of the strong ruthenium tetroxide oxidant[114] (from either RuCl$_3$ or RuO$_2$ with NaIO$_4$) was unselective, as it not only oxidised the primary alcohol, but also led to the disappearance of the BnNC*H$_2$* proton signals in the ^{1}H NMR spectrum, suggesting that this activated position adjacent to the amine was also simultaneously oxidised to give a lactam.

A two step oxidation protocol, *via* aldehyde **298**, was thus adopted. Subjecting alcohol **294** to Swern oxidation conditions led to recovery of starting material **294**, whilst variable and modest yields were obtained using TPAP/NMO (Table 12).[115,116] Initially, similar results were obtained with Dess-Martin Periodinane, but more reliable reactions and greater yields were obtained by carrying out the oxidation using freshly prepared Dess-Martin Periodinane[117] in the presence of pyridine.
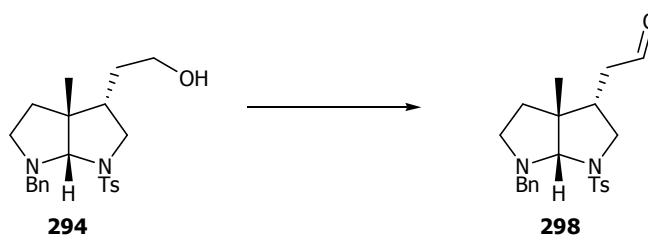
Table 12: Oxidation of alcohol to aldehyde

Entry	Conditions	Yield
1	(COCl)$_2$, DMSO, Et$_3$N, DCM	No reaction
2	TPAP, NMO, DCM	28-42%
3	TPAP, NMO, MeCN	35-60%
4	DMP, pyridine, DCM	80%

Aldehyde **298** was subsequently oxidised to carboxylic acid **299** using Pinnick's conditions (Scheme 104).[118] The product was isolated in good yields by carrying out the workup at pH 6, and this could be exploited to further purify the compound by a simple acid/base wash.
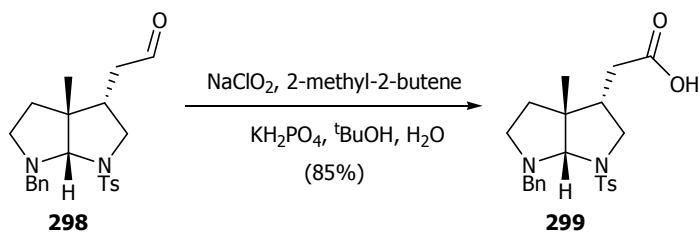
Scheme 104

The synthesis of carboxylic acid **299** represents the accomplishment of a major milestone in our studies. With this in hand, attention turned to converting it into a diazoketone to test the novel carbene ammonium ylide rearrangement strategy as a viable route towards the sarain core.

3.5. Synthesis of diazo compounds

3.5.1. Conversion of carboxylic acid into a diazoketone

The transformation of carboxylic acid **299** to diazoketone **300** was expected to be relatively straightforward, involving first activation of carboxylic acid **299**, then treatment with a diazomethane derivative, such as TMSCHN$_2$ (Scheme 105).[119]
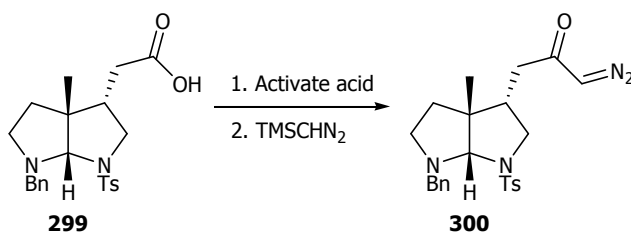
Scheme 105

Diazoketones are typically synthesised from carboxylic acids by activation to an acid chloride or a mixed anhydride intermediate. However, the use of (COCl)$_2$/DMF, ^{i}BuOCOCl/Et$_3$N or EtOCOCl/Et$_3$N on carboxylic acid **299** consistently led to the starting material being consumed to give a polar compound which was unreactive to TMSCHN$_2$. Using extensive NMR spectroscopy, this compound was subsequently identified as lactam **301**, which was produced in yields of up to 62% (Scheme 106). One rationale for its formation is that the HCl produced on activation of the acid protonates the more nucleophilic benzylamine (**302**), leading to ring opening to provide secondary amine **303**, which cyclises onto the activated carbonyl group to give the seven-

membered lactam. Hydration of the tosyliminium ion then completes the generation of observed product **301**.
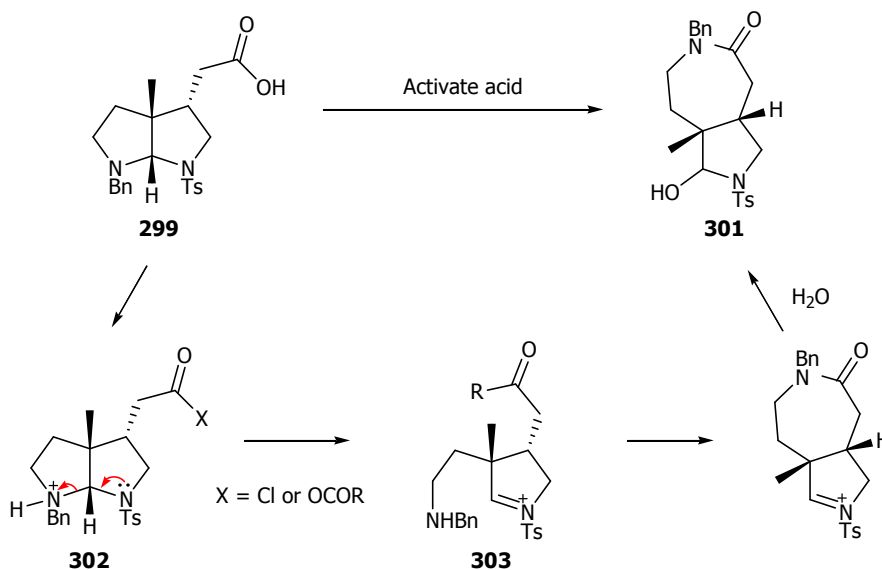
Scheme 106

In this proposed mechanism, the initial step involves protonation of the benzylamine nitrogen (*i.e.* **302**). This is assumed to be favoured over direct acylation of the tertiary amine, as the resulting tricycle would be under considerable ring strain. Had protonation taken place at the sulfonamide, with subsequent cleavage of the C-NTs bond, then it is conceivable that an alternative lactam adduct, **301a**, could be produced. The ^{1}H and ^{13}C NMR spectra of **301** and **301a** should be very similar, but evidence for formation of the former was observed in the HMBC spectra, where there is clearly a long range coupling between the carbonyl carbon and the benzylic protons, which is only possible in product **301** (Scheme 107).

Although the formation of **301** is an undesired result, it was encouraging to see that the bicyclic ring system is capable of undergoing a facile ring-opening-cyclisation sequence. Similarities can be drawn with our proposed strategy, in which the X group in **302** would be a metal carbene, and would be expected to first form an ammonium ylide with the benzylamine before ring opening to the tosyliminium ion (*cf.* **303**). An intramolecular Mannich cyclisation of the enolate onto the iminium ion, rather than the hydration leading to product **301** would then give the desired sarain tricyclic core.
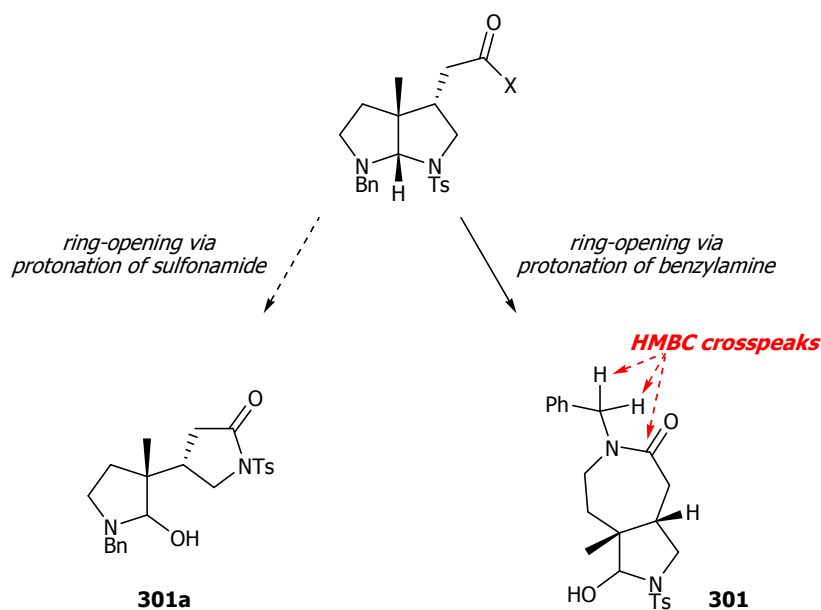
Scheme 107

On the grounds that the acidity of the reaction may be a problem in the synthesis of diazoketone **300**, basic additives were incorporated into the reaction: NaH was first used to pre-form the sodium salt of the carboxylic acid before addition of ^{i}BuOCOCl so the by-product would be NaCl instead of HCl; in another reaction, NaHCO$_3$ and molecular sieves were also added, but again lactam **301** was formed. Conversely, addition of HCl in the activation stage was also investigated, as this could lead to complete protonation of the secondary amine **303**, thus preventing cyclisation onto the activated acid. Unfortunately this led to decomposition of materials with the formation of a small amount of the undesired lactam **301**.

Other reagents which do not produce acidic by-products were also investigated. Ghosez has reported the synthesis of acyl halides in excellent yields using 1-chloro-*N*,*N*,2-trimethylpropenylamine as the activating agent.[120] He described that acids are almost instantaneously transformed into the acid chlorides; the by-product being the relatively inert *N*,*N*-dimethylisobutyramide and not HCl. As such, this method presents a synthesis of acyl halides under very mild conditions. However, the carboxylic acid starting material **299** remained largely unreacted when treated with Ghosez's reagent.

Other activating strategies that have also been used in the synthesis of diazoketones include formation of pentafluorophenyl- or *N*-hydroxysuccinimido- esters by DCC

coupling with pentafluorophenol[121,122] or *N*-hydroxysuccinimide.[123] Unfortunately, these protocols also produced lactam **301**, a result which was attributed to the relative low pK_a values of 5.2 and 5.9 respectively for both reagents. Rannard[124] has reported that imidazolides, synthesised from the reaction of carboxylic acids with carbonyl diimidazole (CDI), react with primary amines preferentially, even exclusively in some cases, in the presence of secondary and tertiary amine functionalities. Although there are no reports of reaction of imidazolides to form diazoketones, similarities in their reaction properties can be drawn from its successful reaction with nitromethane in the presence of KO^{t}Bu.[125] The use of imidazolides was expected to suppress lactam formation, but when acid **299** was treated with CDI, the rearranged product **301** once again prevailed. This may have occurred before the formation of the imidazolide, using the initially formed electrophilic anhydride as an intermediate.

Markó has reported that acid bromides can be prepared directly from aldehydes from treatment with NBS and AIBN,[126] but when this protocol was applied to aldehyde **298**, only a complex mixture of products was obtained.

There were occasions when carboxylic acid **299** was not completely consumed in the activation stage, and thus upon addition of TMSCHN$_2$, methyl ester **304** was produced, in yields of up to 50%. There have been reports of successful ring opening of lactones[127] and lactams,[128] and also displacement of esters[129] to form the corresponding diazoketones by treatment with LiTMSCN$_2$, but when the procedure was applied to ester **304**, only the starting material was recovered (Scheme 108).
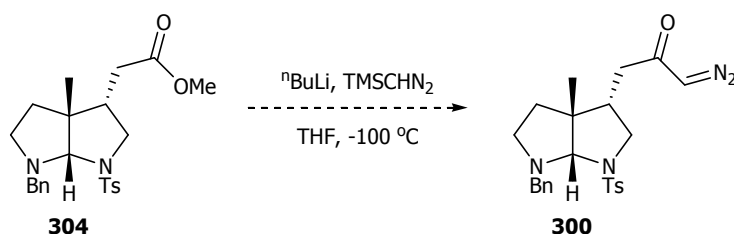
Scheme 108

A search for alternative approaches to diazoketones returned a methodology developed by Aller and Molina,[130] where aliphatic, aromatic and α,β-unsaturated acid chlorides can be converted to diazoketones by treatment with *N*-isocyanotriphenyliminophosphorane

(**305**), followed by Et_3N and catalytic *p*TsCl. The mechanistic pathway proposed by Aller and co-workers involves a chemoselective acylation at the isocyano group to provide intermediate **306**, which after hydrolysis gives the isolable α-ketohydrazidoyl chloride **307**. Reaction with Et_3N and catalytic *p*TsCl results in tosylation of the terminal nitrogen, and elimination of *p*TsCl gives intermediate **308**, and hence the diazoketone after hydrogen migration (Scheme 109).
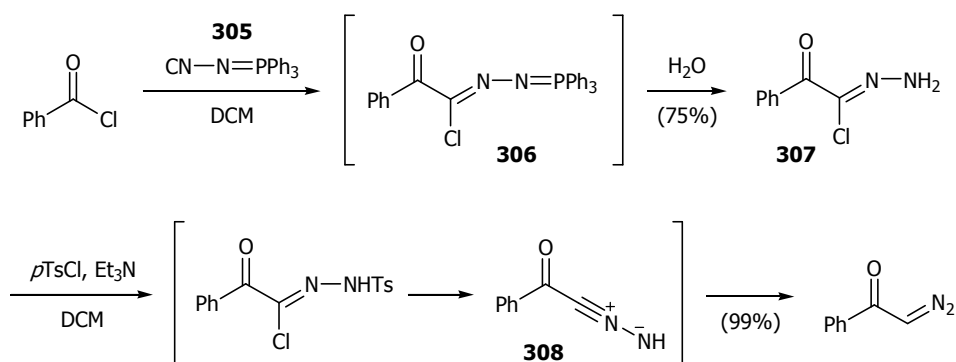
Scheme 109

This reaction is described as a convenient synthesis of diazoketones as it uses a thermally stable, solid reagent, and has general applicability and chemoselectivity.[130] It has also been shown to be successful in converting phenylacetyl chloride to the corresponding diazoketone in 99% yield, whereas the diazomethane method resulted in poor yields (<10%).

It was thought that this method of synthesising diazoketones may be useful in relieving the problems of persistent formation of lactam **301** during activation of carboxylic acid **299**. Our initial choice of reagent, $TMSCHN_2$, could not be added at the beginning of the reaction, as the acid would no doubt react with $TMSCHN_2$ to form the methyl ester **304**. In contrast, the acid should be inert to *N*-isocyanotriphenyliminophosphorane **305**, and consequently it could be included in the initial reaction mixture. The iminophosphorane **305** was thus prepared by treatment of formylhydrazine with PPh_3 and DBU (Scheme 110).[131] Unfortunately, inclusion of reagent **305** in the activation of carboxylic acid **299** by CDI, resulted in recovery of starting material **299**, while its inclusion in the reaction of acid **299** with isobutyl chloroformate in the presence of Et_3N gave an intractable mixture of products.
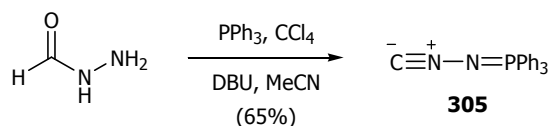
Scheme 110

3.5.2. Synthesis of a methyl ketone as a precursor to the diazoketone

There is another approach to diazoketones that does not start from a carboxylic acid, but rather from a methyl ketone. The ketone is first converted to a β-diketone, which is then subjected to diazo transfer. Deacylation, either concomitant with or subsequent to diazo transfer gives the desired diazomethyl ketone. In the approach developed by Danheiser,[132] the methyl ketone is first converted to a trifluoroacetyl derivative, and diazo transfer occurs with concomitant fragmentation, generating the diazoketone (Scheme 111).
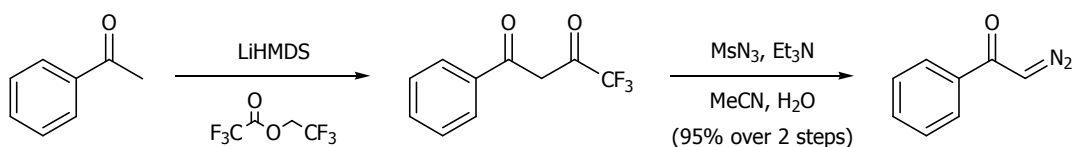
Scheme 111

Applying this methodology to the preparation of diazoketone **300**, methyl ketone substrate **310** was prepared by a Grignard reaction with aldehyde **298** to give secondary alcohol **309** as a mixture of diastereoisomers, followed by an oxidation with DMP to afford the methyl ketone **310** (Scheme 112). Disappointingly, treatment with LiHMDS and trifluoroethyl trifluoroacetate resulted in the recovery of a large amount of starting material, with no evidence for formation of the desired product **311**.
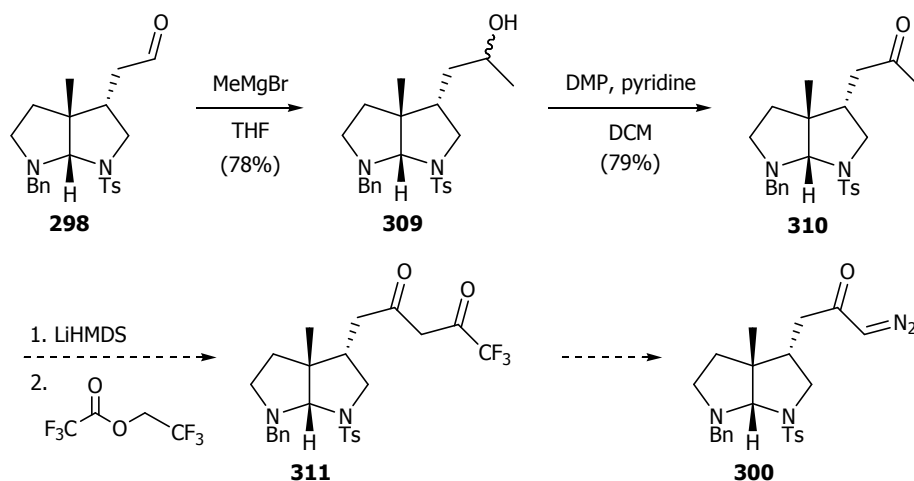
Scheme 112

3.5.3. A second diazoketone substrate

Due to problems in the synthesis of diazomethyl ketone **300**, attention turned to synthesising an alternative diazoketone substrate, α-diazo-β-keto-ester **314**, which could be used to test the cascade proposal, but would ultimately lead to the sarain core with an additional ester functionality (**315**). Roskamp reported that it is possible to transform an aldehyde into a β-ketoester directly with ethyl diazoacetate in the presence of catalytic SnCl₂,[133] but when this was tried on aldehyde **298**, only resulted in decomposition. The transformation was therefore carried out in two steps, by treatment of aldehyde **298** with ethyl diazoacetate in the presence of catalytic DBU to afford a mixture of diastereoisomeric alcohols **312**,[134] which was treated with Rh₂(OAc)₄ to provide β-keto-ester **313** in excellent yield.[135]
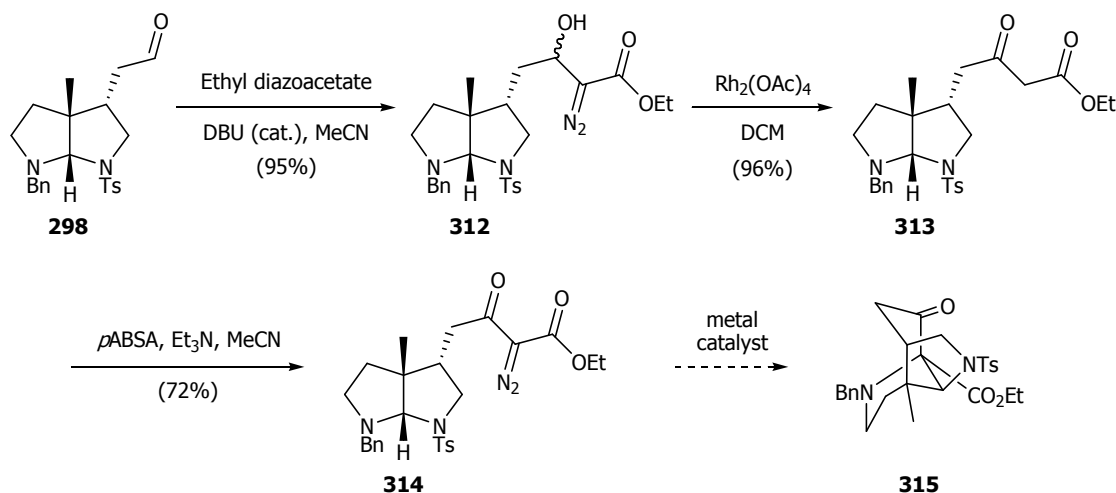
Scheme 113

Diazo transfer with *para*-acetamidobenzenesulfonylazide[135] successfully generated diazoketone substrate **314**. A number of catalysts were then screened to initiate the ammonium ylide rearrangement cascade. The most popular catalysts for diazo-decomposition are based on copper and rhodium and so these were selected for this reaction. It is well known that metal carbenes can undergo a number of reactions, namely cyclopropanation, C-H insertion and the formation of ylides with heteroatoms.[37] Our understanding of the effect of the metal catalyst, and its associated ligands, on the selectivity and reactivity of the metal carbene is quite limited, and so selection was largely based on literature precedent.

As discussed in Scheme 17, Kametani[28] has successfully used $Rh_2(OAc)_4$ in refluxing benzene to prepare a sulfur ylide, which subsequently underwent a thermal 1,2-rearrangement. West has also demonstrated that diazoketone **316** can be converted to hydrazulene **317** through a similar rearrangement using $Cu(hfacac)_2$ in refluxing DCM (Scheme 114).[136]
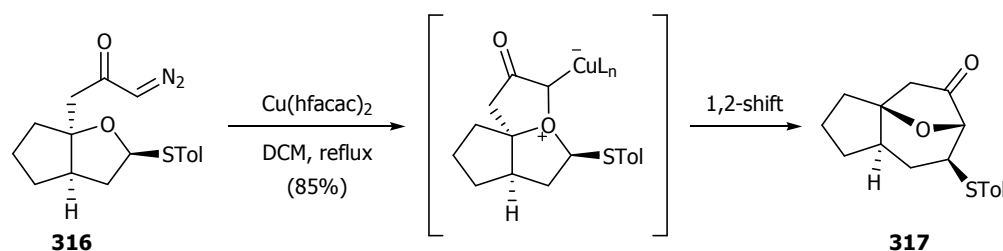
Scheme 114

Diazoketone **314** was treated with a range of catalysts in various solvents, either at room temperature or at reflux. These conditions include $Cu(acac)_2$/benzene, $Cu(hfacac)_2$/DCM, CuOTf/benzene, $Cu(MeCN)_4PF_6$/benzene, $Rh_2(OAc)_4$/benzene, $Rh_2(OAc)_4$/DCM and $Rh_2(pfb)_4$/benzene. Unfortunately, the starting material **314** was consumed to give acomplex mixture of products from each of these reactions, with no evidence for the formation of desired tricyclic product **315**.

3.6. Synthesis of an ammonium ylide *via* an α-bromoketone

Whilst the original plan was to synthesise ammonium ylide **319** *via* a diazoketone, it was envisaged that **319** could also be prepared by a nucleophilic attack of the benzylic

nitrogen onto an appropriate electrophile, such as α-bromoketone **321**, to form ammonium salt **320**, followed by deprotonation to provide ylide **319** (Scheme 115). Hence bromoketone **321** could also serve as a precursor to the ammonium ylide intermediate in the synthesis of the sarain core.
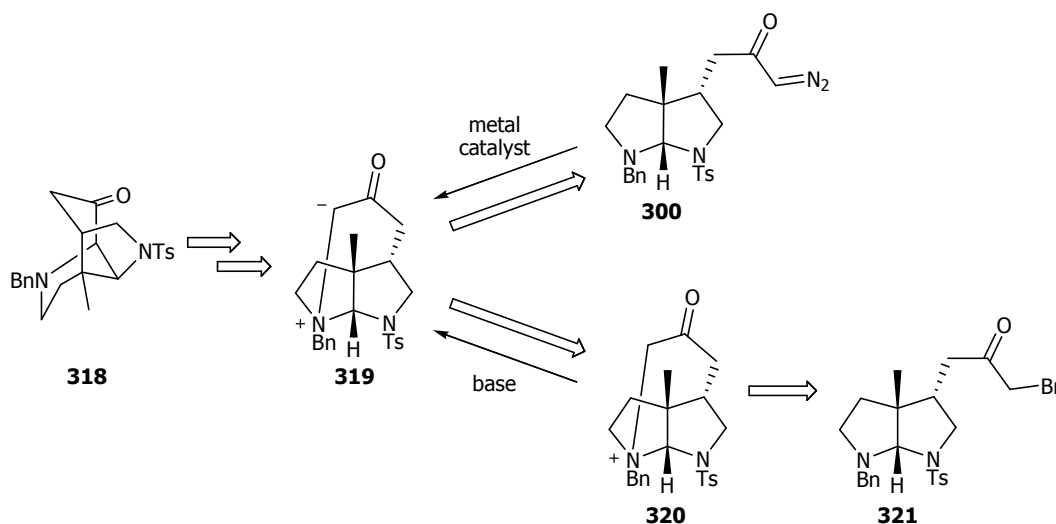
Scheme 115

Treatment of methyl ketone **310** with bromine was expected to provide bromoketone **321**; whilst starting material **310** was consumed, a complex mixture of products was returned after aqueous sodium thiosulfate was used to quench the excess bromine. This was partly attributed to the aqueous solubility of an intermediate or product, possibly resulting from formation of the desired ammonium salt **320**, or of an equivalent ring-opened product. To avoid aqueous workup conditions, 2-methyl-2-butene was used to scavenge any excess bromine before concentration, but again, no product was identified. It was then decided to add Et$_3$N to the reaction mixture prior to concentration, to establish whether the bromination-intramolecular cyclisation-deprotonation protocol could be carried out *in situ*. While mass spectrometry indicated the presence of some material with the correct formula for tricycle **318**, we were unable to isolate the compound responsible for these signals. Unfortunately at this point, the supply of the methyl ketone starting material **310** had been exhausted.

Another attempt to synthesise bromoketone **321** started from a Wittig reaction on aldehyde **298**, and although it provided terminal alkene **322** in low yields, it was sufficient to probe a possible bromohydration, followed by oxidation to the desired

bromoketone. Unfortunately, upon treatment of **322** with NBS followed by oxidation with CrO_3, a complex mixture of products prevailed (Scheme 116).
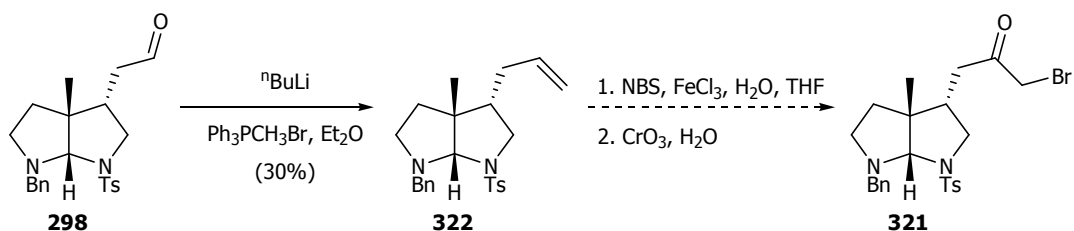
Scheme 116

An alternative route to bromoketone **321** was designed in which the final step would be hydration of a bromoalkyne (Scheme 117). Hence aldehyde **298** was converted into terminal alkyne **324**; for this purpose the Ohira-Bestmann reagent[137] **323** was slightly higher yielding than the Gilbert-Seyferth reagent.[138] Notably, the Ohira-Bestmann reagent was prepared by diazo transfer onto the corresponding β-ketophosphonate **262**, and if the phosphonate was used in excess, reagent **323** could be isolated in 95% yield by simple trituration. This compares well with the 72% yield obtained when using excess *p*ABSA, in which case column chromatography was required. Treatment of alkyne **324** with NBS and $AgNO_3$[139] was expected to provide the terminal bromide **325** to be further hydrated, but instead starting material **324** was recovered.
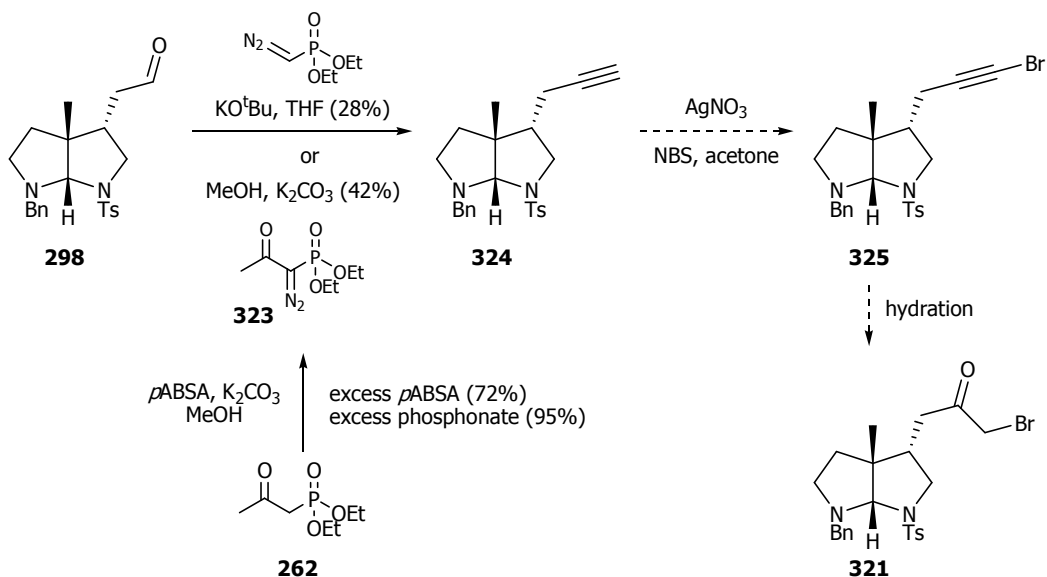
Scheme 117

3.7. An alternative approach to the sarain core

As the previously discussed problems associated with the synthesis of the ylide precursors arose, a related but different route to the sarain core was recognised. Our original strategy involved a Mannich-like disconnection to enolate **326**, but rather than enolates, it is enols that are usually the partners in Mannich cyclisations. Thus an alternative approach would involve the preparation of **327** (Scheme 118). In addition to being part of an enol, the olefin moiety of **327** is part of an enamine functionality. Intermediate **327** could therefore be the product of an intramolecular condensation of **328**, which bears an aldehyde and a secondary amine moiety. The tosyliminium ion **328** could be the product of acid-catalysed ring opening of the bicyclic aminal **329**, as previously observed in the formation of lactam **301**, and thus hydroxy-aldehyde **329** presents a new target in this alternative approach to the synthesis of the sarain core.

Scheme 118
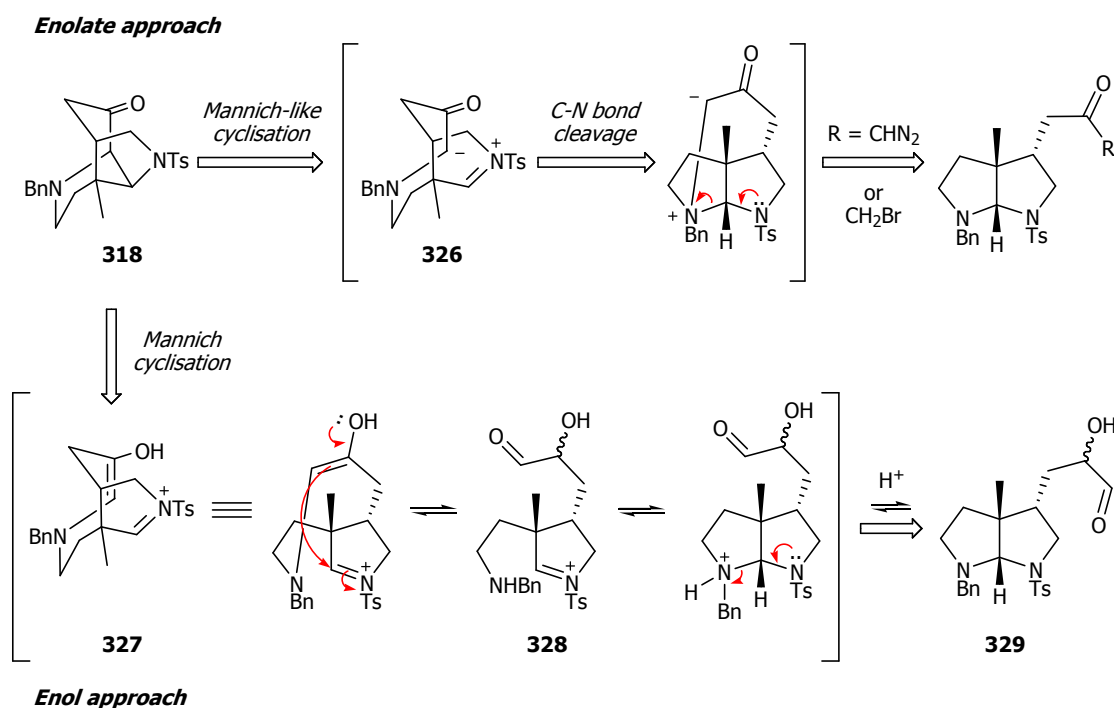
Whilst it is understood that the α-hydroxy-ketone **330**, a tautomer of **329**, is likely to be more thermodynamically stable, the intramolecular condensation onto the aldehyde group is expected to be significantly faster than onto the ketone. Should condensation onto the ketone take place, the subsequent steps are predicted to be reversible, so with the whole system being in equilibrium, it was predicted that material could be drawn into the desired Mannich cyclisation step (Scheme 119).
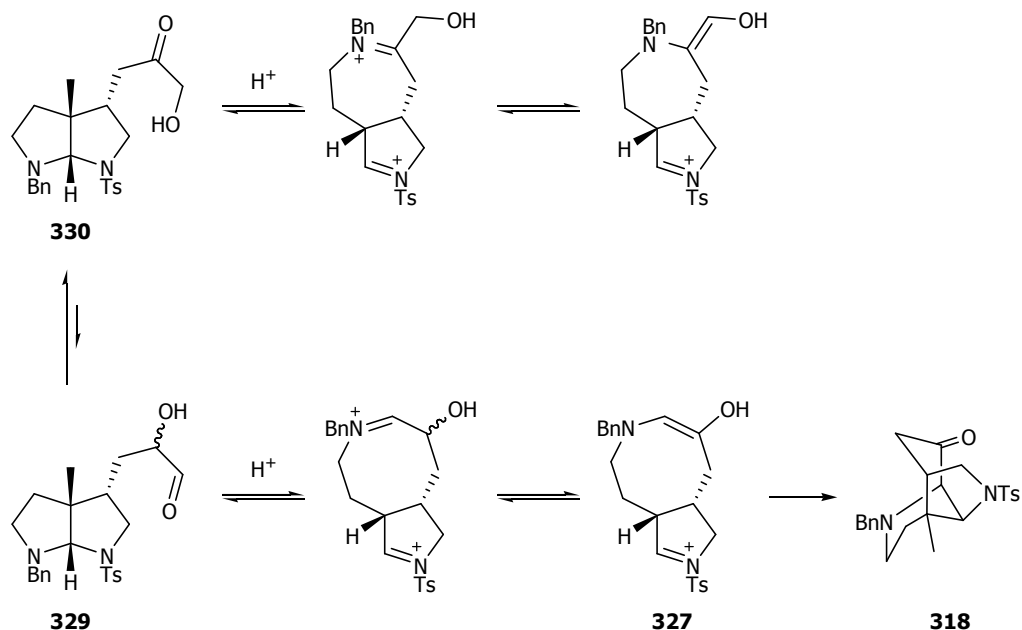
Scheme 119

In addition, there are examples in the literature where α-hydroxy-ketones have been converted into α-amino-ketones, one such being the transformation of 3-hydroxycamphor **331** into ketoamine **332** upon treatment with *tert*-butyl glycinate and BF₃. This was presumed to arise through tautomerisation to **333** then imine formation, before re-tautomerisation back to the camphor form (Scheme 120).[140] Therefore should the position of equilibrium between hydroxy-ketone **330** and hydroxy-aldehyde **329** favour the former, there is still precedent for the formation of enamine **327** through a sequence of reactions similar to those observed in the hydroxycamphor. Furthermore, such considerations also suggested hydroxy-ketone **330** to be a viable target.
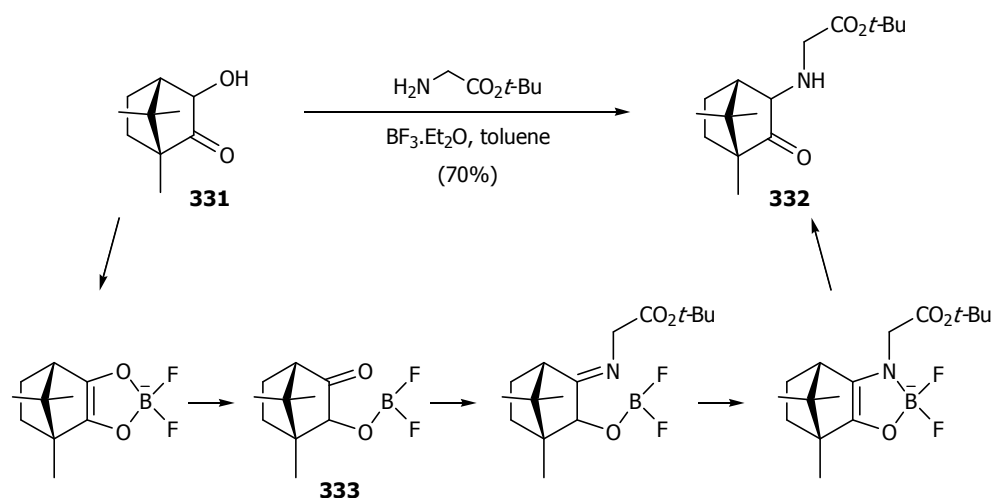
Scheme 120

3.7.1. Synthesis of a hydroxy-aldehyde

A number of approaches to hydroxy-aldehyde **329** were envisaged, the most direct being the addition of a lithiated dithiane to aldehyde **298**, followed by reduction to unmask the corresponding aldehyde. Using this route, Rieger was able to generate the aldehyde **334**, which was not isolated, but used immediately in a reductive amination to give **335** in good overall yields (Scheme 121).[141] The fact that it is possible to manipulate a hydroxy-aldehyde without conversion into the keto-alcohol sets a promising precedent for our chemistry. Unfortunately, treating aldehyde **298** with a lithiated dithiane failed to produce the desired product.
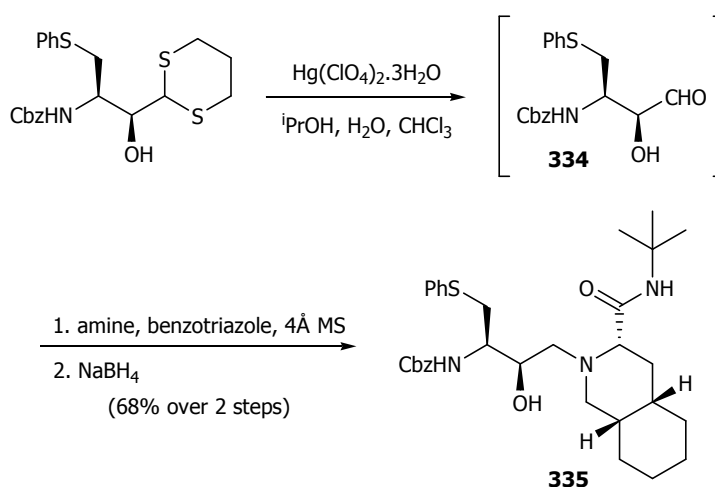
Scheme 121

Another strategy involved a proposed oxidation of alkyne **324** using [bis(trifluoroacetoxy)iodo]benzene (PIFA)[142] to give either hydroxy-ketone **330**, or hydroxy-aldehyde **329** (Scheme 122). When the reaction was carried out, a complex mixture of unidentifiable products and unreacted starting material was recovered.
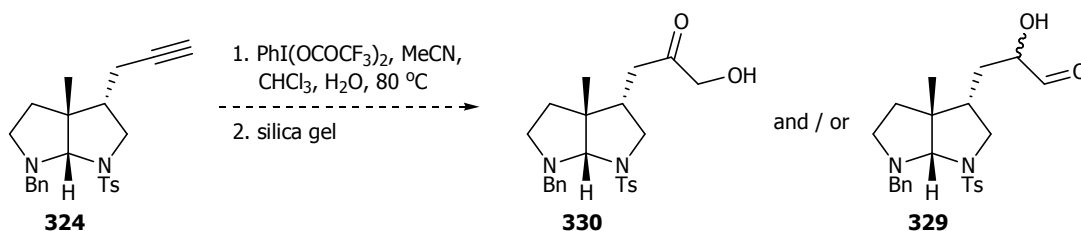
Scheme 122

In an alternative route, reaction of vinyl magnesium bromide with aldehyde **298** provided allylic alcohol **336** in excellent yields (Scheme 123). Ozonolysis of **336** in the presence of Sudan Red led to a complex mixture of products and so it was decided to

first protect the alcohol functionality. Treatment of **336** with TBSOTf and 2,6-lutidine in DCM provided the protected allylic alcohol **337** in good yields. However, ozonolysis of the alkene in **337** proved unsuccessful, although a two step cleavage protocol, *via* diol **338** did provide the desired product **339** in poor yields.
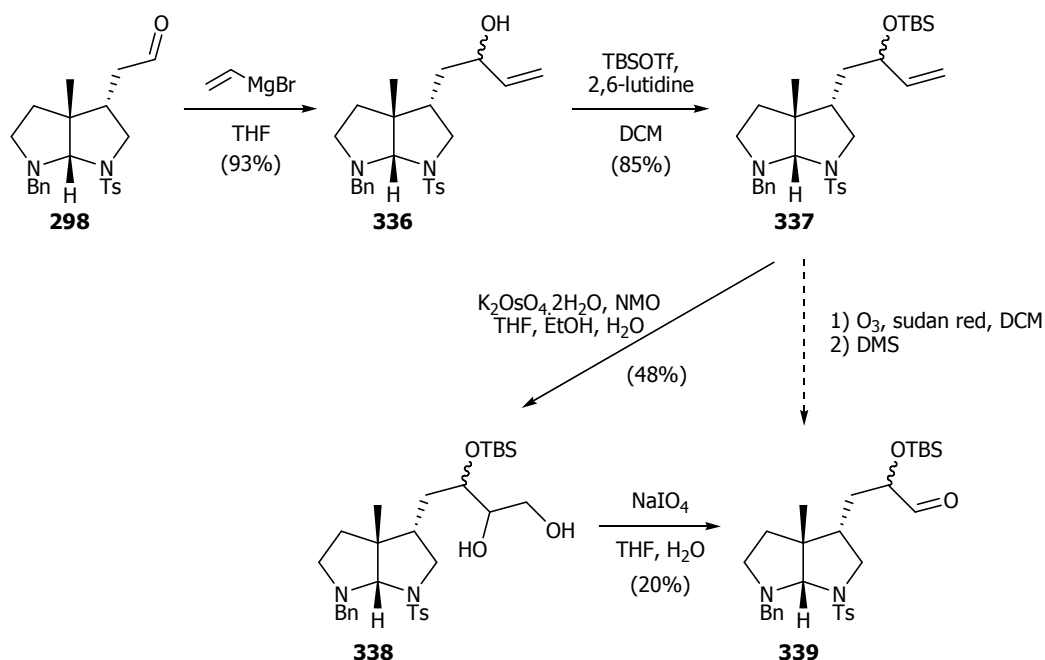
Scheme 123

A fourth route investigated to produce α-hydroxy-aldehyde **329** was the cyanosilylation of aldehyde **298**, followed by a partial reduction of the cyano group to the terminal aldehyde. The cyanosilylation was carried out by treatment of aldehyde **298** with excess TMSCN and catalytic LiCl in an almost solvent free reaction medium (LiCl was added as a solution in THF), and furnished the desired product **340** in good yields, which was used without purification (Scheme 124).[143] The reduction to aldehyde **341** was attempted using DIBAH, with a number of methods being employed to remove the aluminium salts. Due to uncertainty over the stability of the product, and the potential for rearrangements, an aqueous workup procedure was approached with caution. In one method, water, aqueous NaOH and MgSO$_4$ were added sequentially and then the insoluble salts were filtered off before concentration. In another, AcOH was used to quench the reaction, and then the salts were filtered off and washed with copious amounts of acetone. The latter method was thought to be advantageous as the acidic conditions should favour the desired cyclisation process, if it had not already been initiated, but neither aldehyde **341** nor the desired tricyclic products were isolated under any conditions investigated.
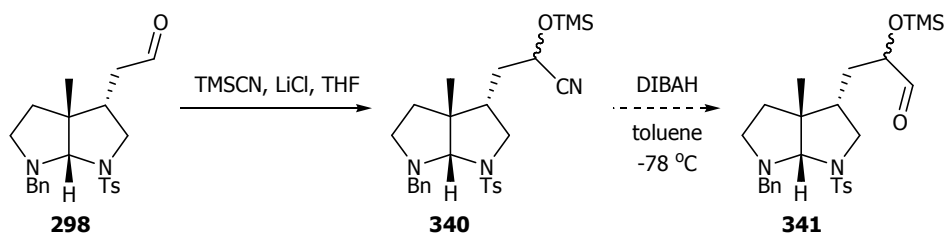
Scheme 124

Although the crude reaction from the cyanosilylation reaction was almost pure by ^{1}H NMR, it was thought that purification of the product **340** may facilitate the subsequent DIBAH reduction. Purification by column chromatography on Florisil® returned the trimethylsilyloxy product **340** in 58% yield, with 25% of the unprotected cyanohydrin also isolated. Unfortunately the major product from a DIBAH reduction of this purified cyanohydrin **340** was the corresponding primary amine **342**, from full reduction of the cyano group (Scheme 125).
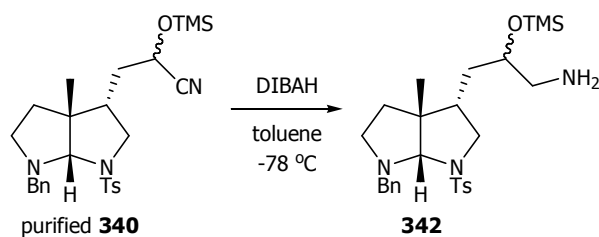
Scheme 125

Uncertain of whether the problems in the DIBAH reduction were due to the labile nature of the trimethylsilyl protecting group, attention turned to synthesising the equivalent *tert*-butyldimethylsilyl analogue. Cava[144] reported high yields for the conversion of aldehydes to TBS protected cyanohydrins, but application of the published conditions of TBSCl, KCN and catalytic ZnI$_2$ to substrate **298** instead afforded the unprotected cyanohydrin **343** and the starting material **298** as an inseparable mixture in ~50% and ~10% yield respectively (Scheme 126). Treatment of this material with DIBAH resulted in a complex mixture of products.
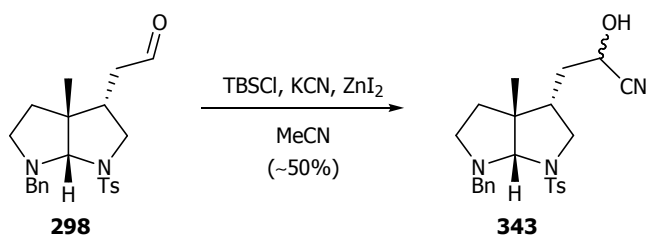
Scheme 126

Adapting the previously utilised method of TMSCN and LiCl, by direct replacement of TMSCN with TBSCN was not straightforward, as neither the substrate nor reagents are in liquid form at room temperature, and adding the minimum amount of THF to dissolve the reactants gave very low yields (<20%). Similar yields were obtained when THF was substituted with toluene, but replacing it with DCM provided the TBS protected cyanohydrin **344** in a vastly improved yield of 88%, after purification by silica gel chromatography (Scheme 127).
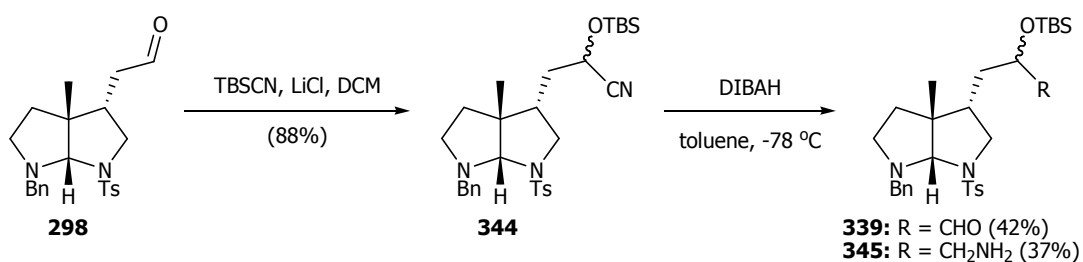
Scheme 127

DIBAH reduction of *tert*-butyldimethylsilyl protected cyanohydrin **344** gave a mixture of the desired aldehyde **339** and the fully reduced amine product **345** in variable proportions; the best yields being 42% and 37% respectively. It is not understood why there was a significant quantity of amine **345** produced from this reaction, as there is ample literature precedent for the reduction of silylated cyanohydrins to aldehydes under the same conditions, often with a greater excess of DIBAH than that employed in this reaction. Changing the number of equivalents of DIBAH, or the solvent of the reaction, failed to improve yields. Therefore while formation of aldehyde **339** was possible using this method, the variable ratio of amine and aldehyde produced presented a frustrating drawback to the supply of material for subsequent research.

3.7.2. Rearrangement of a hydroxy-aldehyde derivative

As the aldehyde **339** did not spontaneously undergo the rearrangement cascade to **318** (Scheme 118), it was treated with a range of acids to promote this process (Table 13).
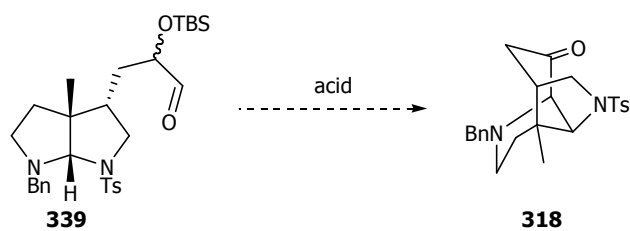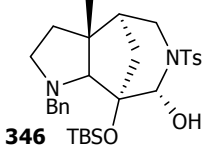
Table 13

Entry	Conditions	Result
1	AcOH, NaOAc, MeOH	Starting material recovered
2	AcOH, MeOH	Starting material recovered
3	AcOH, MeOH, 65 °C	<47%[a]
4	*p*TsOH, 4Å MS, DCM	SM, **346** and decomposition
5	TfOH, 1,4-dioxane	Decomposition
6	Stir with 2 M HCl then basify	Decomposition
7	Extract into HCl, remove DCM layer, then neutralise	Decomposition
8	TBAF, THF	Decomposition
9	NH₄F, MeOH	20% SM and decomposition
10	Amberlyst®-15, DCM	Starting material recovered
11	Dowex®-50	Decomposition

[a] This was isolated with a small amount of impurities. In addition, the moderate yield of this reaction can be partly attributed to the small scale of the reaction, as the crude material consisted almost entirely of this product.

Treatment of aldehyde **339** with AcOH in MeOH at room temperature, with or without NaOAc buffer, led to no reaction, with starting material **339** being recovered. However, when the unbuffered reaction was warmed to 65 °C for 3 d, a new compound was produced (entry 3). This compound was identified as tricycle **346** (*vide infra*).

A mechanism for the formation of the tricyclic product is proposed in Scheme 128; ring opening of the bicyclic aminal by cleavage of the C-NTs bond leads to sulfonamide **347**, which can undergo an intramolecular condensation with the aldehyde to form enesulfonamide **348**; subsequent cyclisation onto the benzyliminium ion provides tricycle **349**, which after hydration will furnish the observed product **346**. Another viable route is for the aldehyde in **347** to act as a nucleophile in its enol form, **350**, and cyclise onto the benzyliminium ion to form bicycle **351**; hemiaminal formation between the aldehyde and sulfonamide will then provide tricycle **346**.
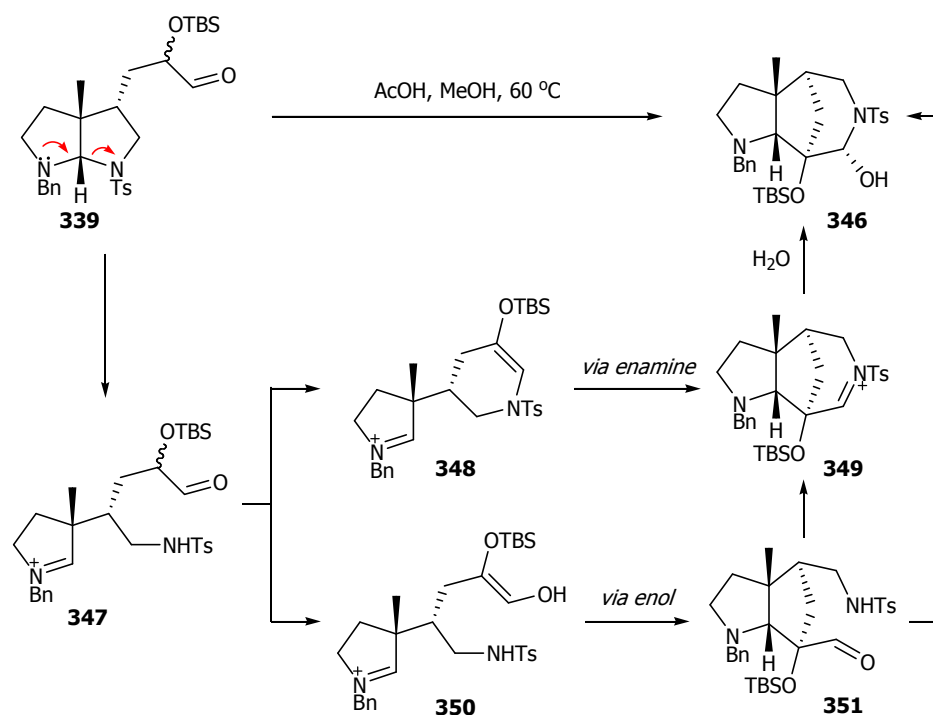
Scheme 128

The structure of the isolated product was deciphered through extensive NMR spectroscopic work; based on the ^{1}H and ^{13}C NMR chemical shifts, the product could correspond to either **346** or **346a**, with the latter resulting from a similar mechanism as proposed above, but with inital cleavage of the C-NBn bond rather than the C-NTs bond (Scheme 129). However, HMBC and NOESY experiments identified the isolated product to be **346**, as there are clear couplings between the benzylic protons and the bridging tertiary carbon, and also between the proton on the carbon bearing the alcohol and the secondary carbon adjacent to the sulfonamide, as indicated in the scheme.
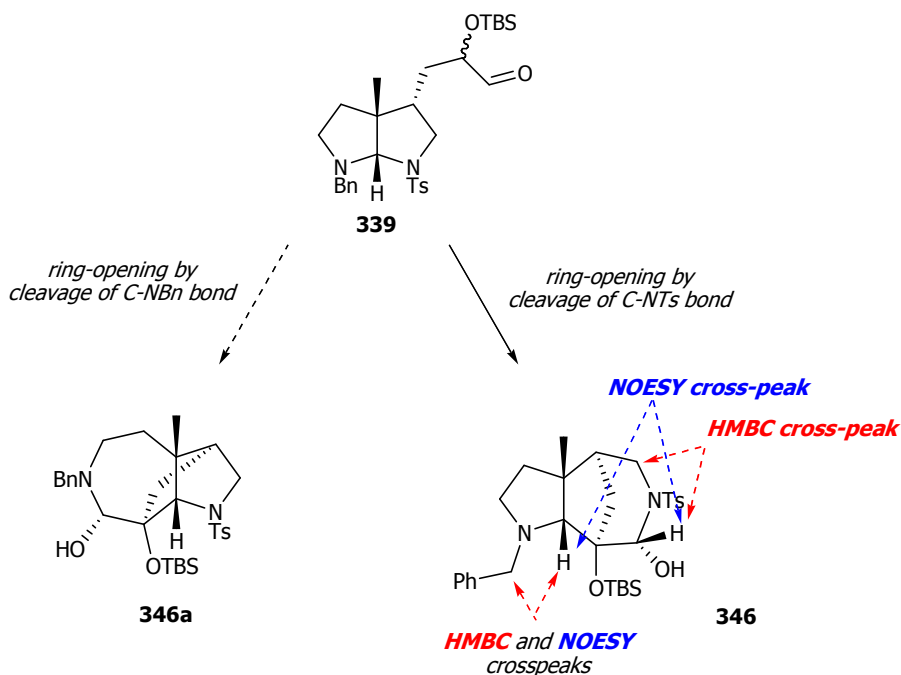
Scheme 129

The production and isolation of tricycle **346** presents two problems: first, the ring opening of the bicyclic aminal proceeded in the wrong direction – with cleavage of the C-NTs rather than the C-NBn bond; secondly, should the mechanism of formation progress *via* compound **348**, then the cyclisation onto the benzyliminium ion took place from the enamine functionality, rather than from the enol as desired.

The mode of aminal opening can be rationalised by the fact that the benzylamine is more electron-releasing, and the sulfonamide is more electron-withdrawing, so indeed the formation of iminion ion **347** is entirely normal. But if the benzylamine group were protonated, the ring opening process was expected to proceed in the opposite direction, as was the case in the formation of lactam **301** in section 3.5.1. It was hoped that this difference in outcome could be governed by the nature of the acid used, and therefore stronger acids were screened for this reaction. Use of *p*TsOH and 4Å MS resulted in partial conversion of aldehyde **339** to tricycle **346**, while TfOH led to decomposition (entries 4 and 5). Addition of HCl to aldehyde **339** was expected to mimic the process that led the correct direction of ring opening to form lactam **301**, but here only resulted in a complex mixture of products (entries 6 and 7). This was also the case when silyl deprotecting reagents TBAF and NH$_4$F were employed (entries 8 and 9). The use of solid supported acidic resins Amberlyst®-15 and Dowex®-50 also failed to provide the desired cyclisation material (entries 10-11).

The second problem in the formation of tricycle **346** *via* **348** is that it occurred through the enamine rather than the *tert*-butyldimethylsilyl enol ether; this may have been contributed by the presence of the bulky protecting group. In contrast, the DIBAH reduction of the unprotected cyanohydrin **343** generated a complex mixture of products. The employment of a different protecting group, which allows for isolation of the protected hydroxy-aldehyde prior to the rearrangement step (*cf.* **353**), may be useful in circumventing this problem. Synthesis of these compounds was approached by the protection of allylic alcohol **336**. The sterically demanding but acid labile trityl group was chosen for this investigation, but unfortunately, treatment of allylic alcohol **336** with trityl chloride failed to provide **352** (Scheme 130).
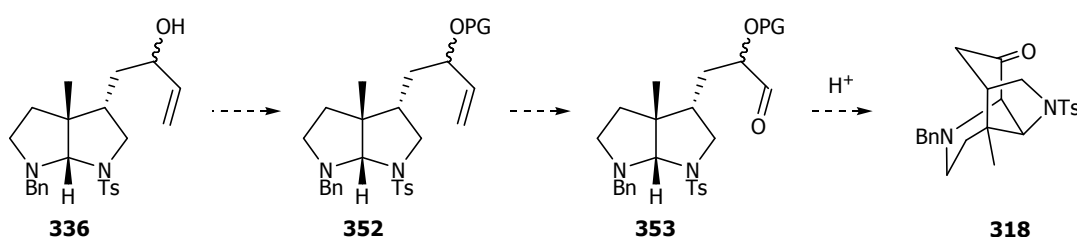
Scheme 130

Another idea was to synthesise epoxy-acetal **354**, which upon treatment with acid would undergo ring-opening of the acetal, generating hydroxy-oxonium ion **355** (Scheme 131). This would thus create a more electrophilic moiety than an aldehyde, aiding ring cyclisation/condensation.
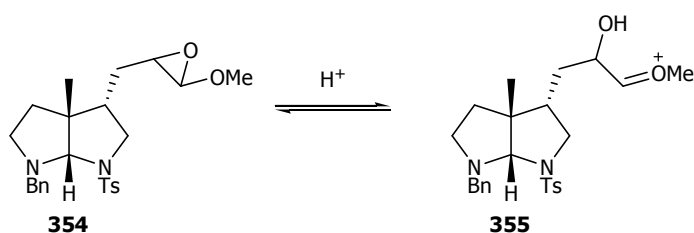
Scheme 131

The synthesis of epoxide **354** began by a Wittig olefination of aldehyde **298** with methoxymethyltriphenylphosphonium chloride,[145] forming methoxy enol ether **356** as a 3:2 *E:Z* mixture of geometrical isomers in moderate yield. Attempted epoxidation of olefin **356** with *m*CPBA instead resulted in oxidation of the benzylamine to form *N*-oxide **357** in an almost quantitative yield (Scheme 132). In another attempt, reaction with singlet oxygen[146] resulted in both the recovery of starting material, in an increased

E:Z ratio of >10:1, and also the formation of α,β-unsaturated aldehyde **358**. This product presumably results from ene reaction of the enol ether **356** with singlet oxygen, which after reduction with DMS, gives a hemiacetal that then collapses to give the isolated aldehyde. The change in the ratio of the geometric isomers between the starting material and product can be attributed to the higher rate of ene reaction for the *Z*- compared to the *E*-isomer of enol ether **356**.[147,148]
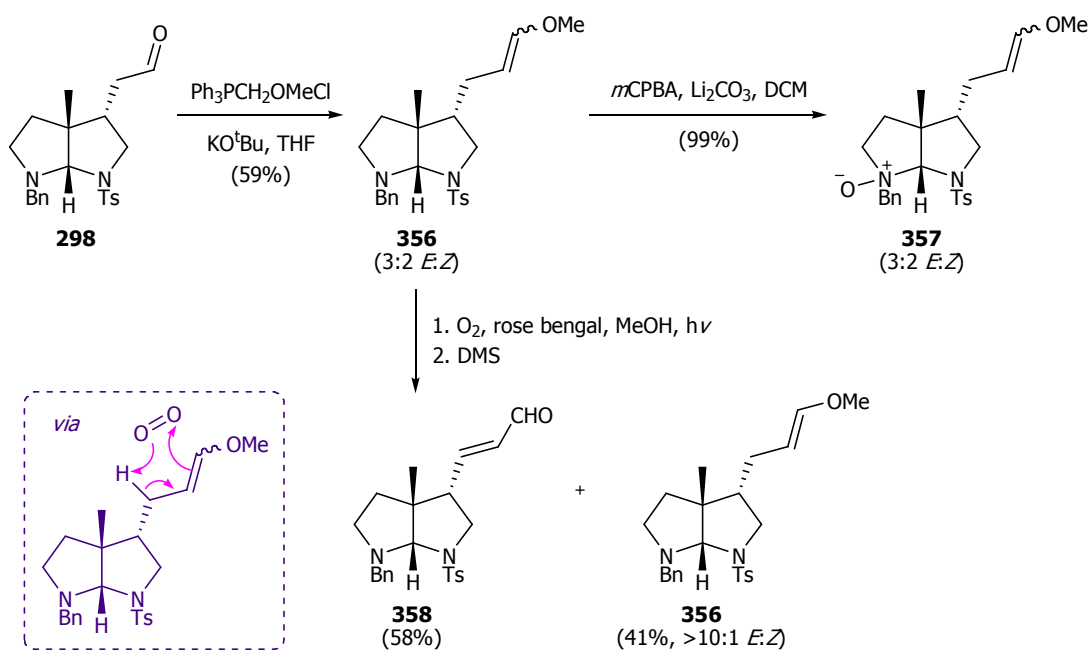
Scheme 132

At this stage, time constraints and exhausted supply of material prevented further investigation into the rearrangement of protected hydroxy-aldehyde **339**, and similar derivatives, into the tricyclic sarain core.

4. SYNTHESIS OF 3-AMINO-2-SILYLOXYACRYLATES BY OLEFINATION OF FORMAMIDES

In addition to the work towards the synthesis of the sarain core, a study into an unusual olefination of formamides was carried out and is reported herein.

4.1. Background

Previous work within the Porter group investigated the feasibility of the proposed intramolecular rearrangement of an ammonium ylide as a route to the sarain core by mimicking it in an intermolecular fashion. To do this, simple bicyclic aminal **93**, which lacks the side chain, was treated with a silylated diazoacetate in the presence of a metal catalyst. This was anticipated to result in ammonium ylide formation from the more nucleophilic nitrogen, ring opening followed by ring closure to give **96**, a ring-expansion product (Scheme 133).
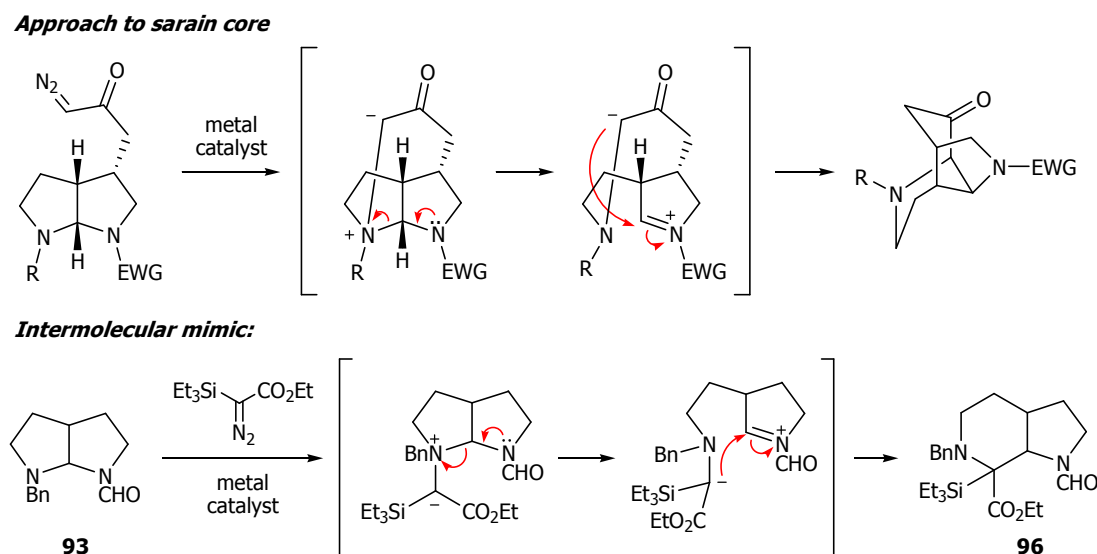
Scheme 133

Prior to this, our group had successfully developed conditions to perform ring expansions of 1,3-oxathiolanes, where treatment with ethyl (triethylsilyl)diazoacetate (**359**) in the presence of Rh$_2$(OAc)$_4$ or Cu(acac)$_2$ led to rearrangement of the sulfur ylide intermediate to provide the corresponding 1,4-oxathianes in moderate yields (Scheme 134).[149,150] The presence of the silyl group in the diazoacetate was found to be important as it suppresses the undesirable carbene dimerisation observed when using ethyl

diazoacetate, as well as any further reaction of the oxathiane products with excess diazo reagent.
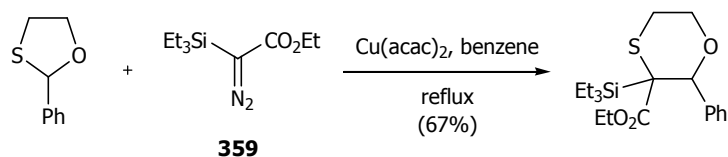
Scheme 134: Ring-expansion of 1,3-oxathiolanes

When bicyclic aminal **93** was treated with diazoester **359** in the presence of $Rh_2(OAc)_4$, rather than undergoing a ring-expansion, the formamide underwent an unexpected olefination to provide **97** in 39% yield. A rationale for the formation of this product could be that instead of reacting with the amine to form an ammonium ylide, the metal carbene reacted at the formamide oxygen to provide carbonyl ylide **360** (Scheme 135). Formation of epoxide **361** followed by ring opening, and then migration of the silyl group to the alkoxide in **362** would furnish the observed olefination product **97**.
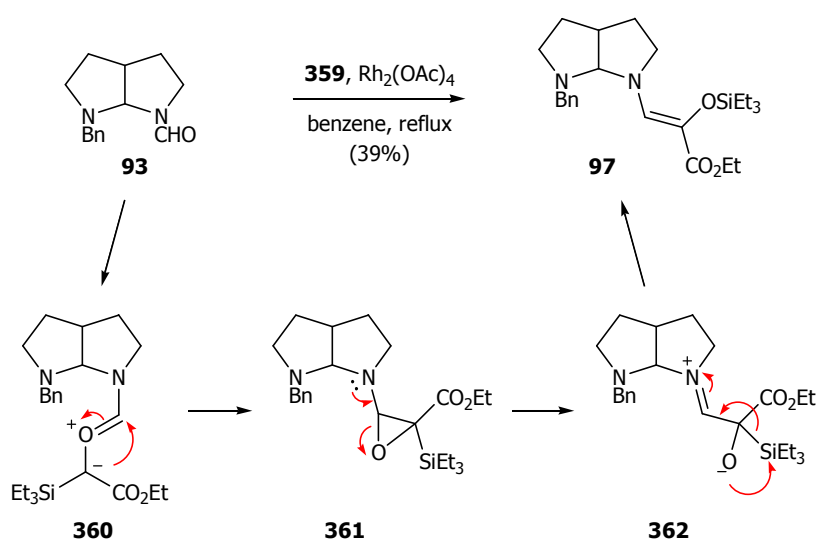
Scheme 135: Proposed mechanism for the olefination of formamide carbonyl group

The mechanism to this reaction bears similarities to that proposed by Padwa for the cyclisation of amido diazo carbonyl compounds, where treatment of diazoketone **363** with $Rh_2(OAc)_4$ led to formation of dihydropyridone **366** in good yields (Scheme 136).[151] The metal carbene reacted at the amido oxygen to give oxonium ylide **364**, and then epoxide **365**, which isomerised to the observed product.
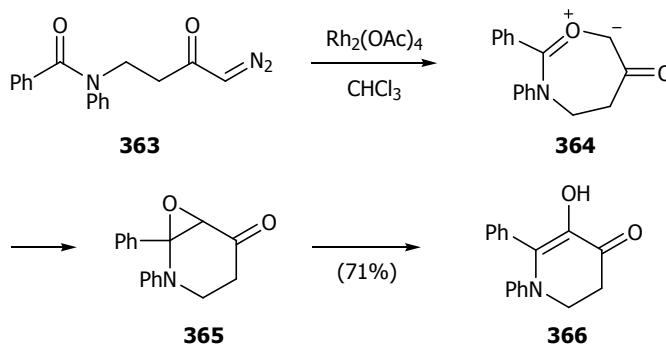
Scheme 136

In addition, related intramolecular reactions between diazo carbonyl compounds and thiolactams have been reported, where the metal carbene forms a thiocarbonyl ylide. This chemistry was utilised by Danishefsky in the syntheses of iso-A58365A[152] and indolizomycin;[153] in one intermolecular example, thiolactam **367** was treated with ethyl diazoacetate and $Rh_2(OAc)_4$ to give vinylogous urethane **368** in moderate yields (Scheme 137).[153]
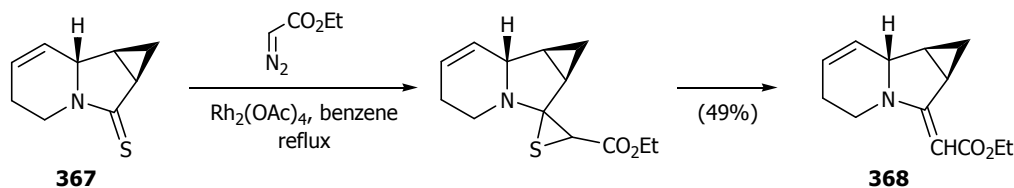
Scheme 137

4.2. *N*-Formylpyrrolidine as a test substrate

Investigative efforts into the scope and limitations of this reaction began using *N*-formylpyrrolidine (**369a**) as a test substrate. This was prepared in excellent yields by heating pyrrolidine in excess ethyl formate under reflux. As with the bicyclic aminal, treatment of *N*-formylpyrrolidine (**369a**) with ethyl (triethylsilyl)diazoacetate (**359**) in the presence of $Rh_2(OAc)_4$ provided the vinylogous carbamate **370a**. Upon optimisation, it was found that only 0.4 mol% of $Rh_2(OAc)_4$ was required to catalyse the reaction. Interestingly the acrylate **370a** was obtained as a single geometric isomer. This was established to have the *Z*-geometry by observation of a nuclear Overhauser enhancement in the ^{1}H NMR spectrum between the α-protons on the pyrrolidine ring and the methylene protons of the triethylsilyl moiety (Scheme 138).
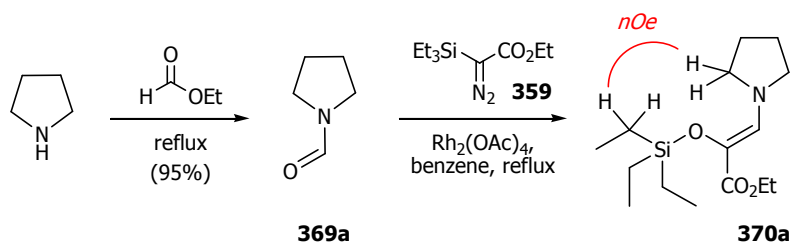
Scheme 138

Purification of vinylogous carbamate **370a** by chromatography on alumina gave a better yield (80%) than on silica gel (50%), presumably due to hydrolysis of the triethylsilyl group on the acidic support. The reaction was found to be complete within 90 min and prolonging the reaction time to 16 h produced similar yields (89%), with no observed decomposition of the product.

In addition, a series of control experiments was carried out, which confirmed that no reaction took place in the absence of the catalyst, with both starting materials **359** and **369a** recovered unchanged. If ethyl diazoacetate was used in place of the silylated analogue, the starting amide **369a** remained unreacted, but ethyl diazoacetate was consumed in a dimerisation reaction to form a mixture of diethyl fumarate and diethyl maleate.

4.3. Tertiary formamides as substrates

A number of tertiary formamides (**369a**-**369l**) were prepared to investigate the scope of this reaction (Figure 10), and with the exception of dimethyl formamide, **369h**, were obtained by treatment of the corresponding secondary amines with ethyl formate. *N*-Benzylallylamine was synthesised from the reaction of allylamine and benzyl bromide;[154] all other amines were obtained from commercial sources.
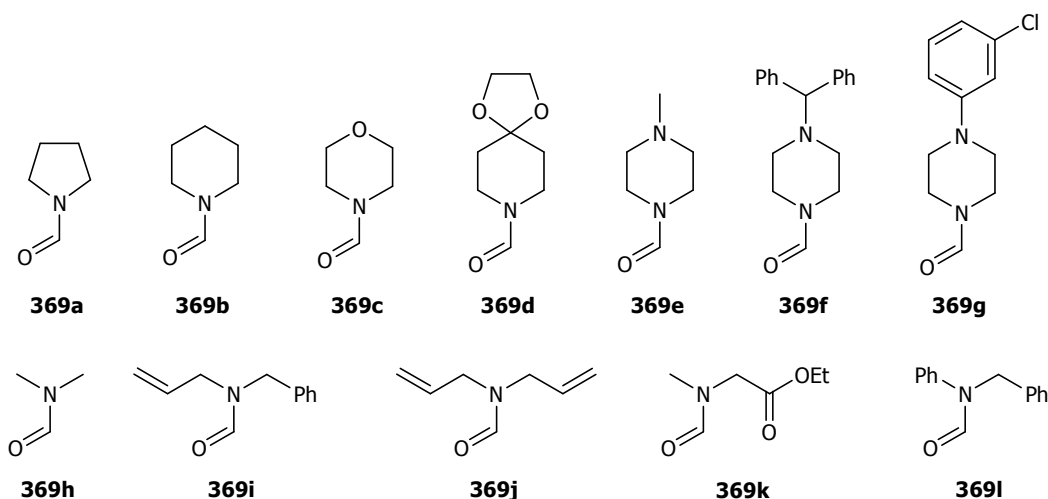
Figure 10: Formamide substrates for olefination reaction

These formamides (**369b**-**369l**) were exposed to the conditions developed for *N*-formylpyrrolidine **369a**, and all successfully reacted to provide the corresponding vinylogous carbamates (**370b**-**370l**, Table 14).[155] Several reactions were repeated to confirm no significant difference between the yields obtained for reactions of 90 min duration and those for 16 h (entries 1-3, 8-10). The reactions were generally very efficient, producing the olefin products in greater than 80% yield, but substrates **369e**-**369g**, which contain a tertiary amine (entries 5-7), consistently gave lower yields. Monitoring the reaction of 1-formyl-4-methylpiperazine (**369e**) by ^{1}H NMR spectroscopy showed that it took place very slowly, although a respectable yield of 63% was obtained by addition of extra catalyst and diazoacetate in combination with extended reaction time. This reduced reactivity is thought to be due to competitive complexation of its tertiary amine to the rhodium catalyst. With the intention of overcoming this problem, the same reaction was carried out with 4 mol % catalyst, but this only provided **370e** in 55% yield after 63 h. Complete conversion of benzhydrylpiperazine **369f** to **370f** took almost 3 h, and the 3-chlorophenyl piperazine (**369g**) gave moderately decreased yields in the olefination, but nevertheless, still furnished the desired products in comparatively short times. The higher rate of these reactions (compared to that of **369e**) was attributed to the steric bulk around the nitrogen in **369f**, and its decreased basicity in **369g**, reducing the unwanted complexation to the catalyst.
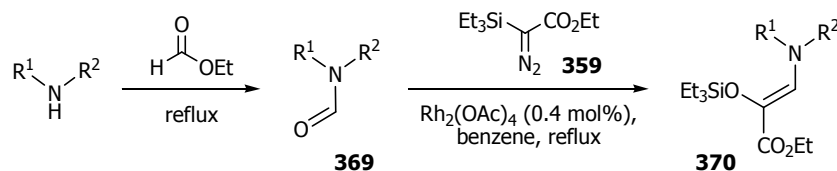
Table 14: Conversion of formamides to vinylogous carbamates

Entry	Formamide 369		Vinylogous carbamate 370		
	Substrate	Yield / %	Time	Yield / %	After 16 h / %
1	**a**	95	90 min	80	89
2	**b**	95	90 min	83	92
3	**c**	91	90 min	87	89
4	**d**	99	45 min	90	-
5	**e**	93	240 h[a]	63	-
6	**f**	99	165 min	87	-
7	**g**	99	45 min	64	
8	**h**	-	90 min	90	89
9	**i**	96	90 min	85	81
10	**j**	88	90 min	97	96
11	**k**	100	90 min	69	-
12	**l**	80	180 min	50[b]	-

[a] Extra portion of catalyst and ethyl diazo(triethylsilyl)acetate added after 144 h;

[b] 3:2 ratio of *Z* and *E* isomers

A number of symmetrical and unsymmetrical acyclic formamides (**369h**-**369l**) were also converted to the corresponding vinylogous carbamates (**370h**-**370l**), with varying degrees of success (entries 8-12). The use of rhodium carbenes in the cyclopropanation of alkenes is well documented,[37] and it is interesting to note that there was no evidence of such a competitive reaction from substrates containing isolated alkene moieties (**369i** and **369j**).

For substrates **369a-369k**, olefin products **370a**-**370k** were produced exclusively as the *Z*-isomer; it is not clear why the reaction is so stereoselective. Interconversion of the product isomers is expected to be relatively easy due to the decreased double bond character of such systems (Scheme 139) and hence the observed stereoselectivity may simply reflect the greater thermodynamic stability of the *Z*-isomers.[156,157]
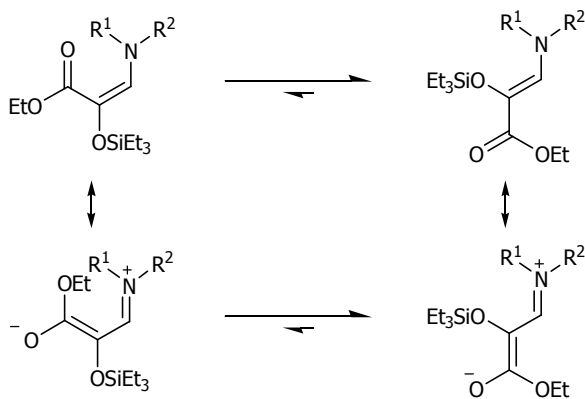
Scheme 139

Only upon reaction of formanilide **369l** was the product **370l** obtained as a mixture of geometric isomers (entry 12). This was thought to be due to the lesser extent of electron release from the nitrogen, hence suppressing this equilibration. There was no sign of any isomerisation to the *E*-isomer when a solution of *Z*-olefin **370l** was heated in benzene at reflux overnight.
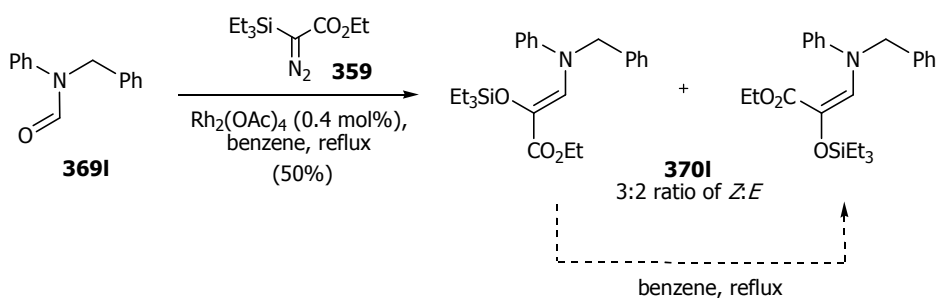
Scheme 140

4.4. Trapping the intermediate 1,3-dipole

In the mechanism proposed in Scheme 135 for the olefination reaction, a 1,3-dipole system is created in intermediate **360**. To confirm the mechanism, and expand the utility of the reaction, attempts to trap this dipole were explored. Addition of dimethyl acetylenedicarboxylate was expected to provide a competing pathway for an

intermolecular interception of the dipole, but there was no evidence for the formation of substituted dihydrofuran **371**. Instead vinylogous carbamate **370g** was isolated in a lowered yield of 38%, compared to the 64% that was isolated in the absence of the acetylene.
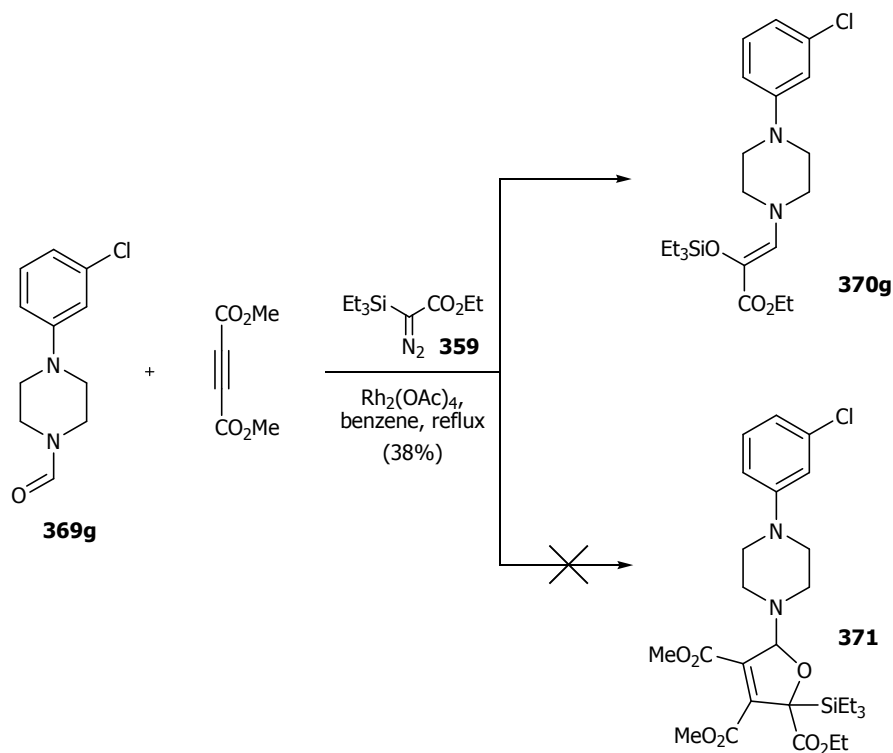
Scheme 141: Attempted intermolecular interception of 1,3-dipole

N-Benzyl-*N*-(but-3-enyl)formamide (**369m**) was also prepared in an attempt to trap the dipole intramolecularly. It was thought that the γ,δ-unsaturated formamide could give rise to the bicyclic hemiaminal **372** as a competing product, but instead gave the usual vinylogous carbamate **370m** in an excellent yield (Scheme 142).
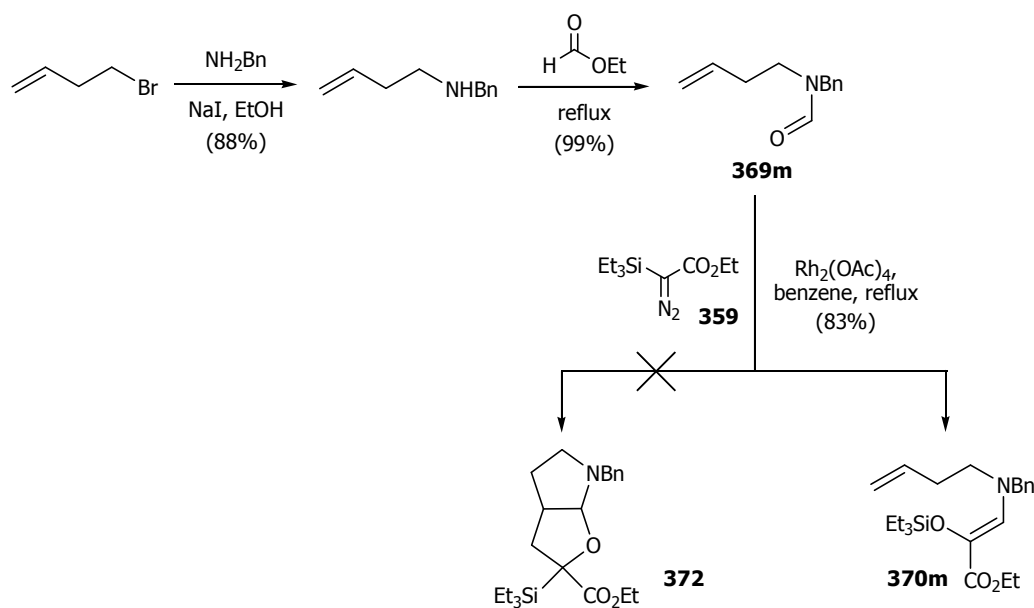
Scheme 142: Attempted intramolecular interception of 1,3-dipole

4.5. Other substrates

To briefly examine the possibility of utilising other amide substrates in the olefination reaction, a secondary formamide (*N*-methylformamide) and a tertiary acetamide (*N,N*-dimethylacetamide) were subjected to the same conditions. Unfortunately purification of the products from these reactions was difficult, and there was no conclusive evidence to suggest that either had undergone the desired olefination.

4.6. Deprotection of silyl enol ether

To explore the possibility of further functionalisation of the 3-amino-2-silyloxyacrylates, they were exposed to a number of different deprotection protocols (Table 15). Use of TBAF or aqueous HCl was unsuccessful, with low mass recovery after aqueous workup (entries 1-3). Low yields were obtained from using NH_4F, but again with low mass recovery (entry 4). The considerable aqueous solubility of enol products **373** may help to explain why only a small amount of materials was recovered after aqueous workup. Other substrates were therefore treated with NH_4F, but to reduce solubility problems, brine rather than water was used in the workup. This greatly

increased the recovery of products, but rather unexpectedly, the production of formamide **369** was also observed.
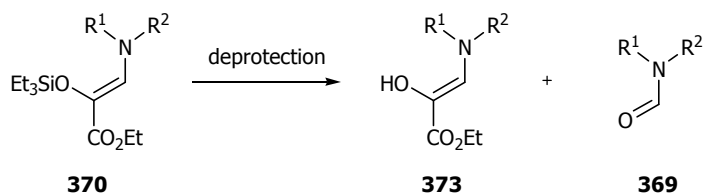
Table 15: Deprotection of silyl enol ether

Entry	Substrate	Reagents	Product	Yield / %
1	**370c**	TBAF, THF	**373c**	0
2	**370a**	TBAF, THF	**373a**	0
3	**370f**	10% HCl, MeOH, THF	**373f**	0
4	**370j**	NH$_4$F, MeOH	**373j**	<5
5	**370d**	NH$_4$F, MeOH	**373d**	<30
6	**370f**	NH$_4$F, MeOH, THF	**373f**	<44

The crude deprotection product from ketal substrate **370d** contained a small amount of the corresponding formamide **369d**, but when this was exposed to silica gel purification, the proportion of the formamide greatly increased. Likewise, it was possible to separate the benzhydryl deprotection product **373f** from the corresponding formamide **369f** temporarily, but upon standing at room temperature, the material became contaminated once again with formamide **369f**. A mechanism for this hydrolysis is proposed whereby addition of water to iminium ion **374** leads to olefin **375** which upon tautomerisation to **376**, can undergo a retro-aldol pathway to provide the formamide (Scheme 143). However, ethyl glycolate **377** was not observed as a by-product in this reaction.
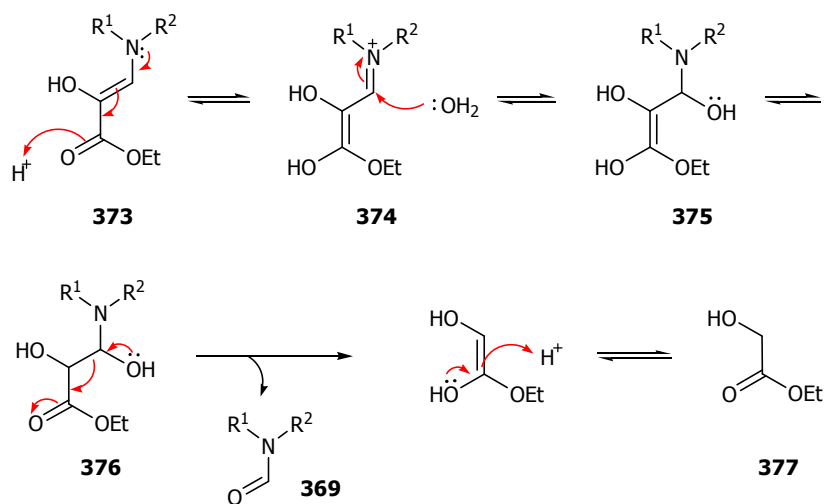
Scheme 143: Proposed mechanism for the formation of the formamide

In conclusion, a new and general method for the conversion of tertiary formamides to 3-amino-2-silyloxyacrylates has been discovered. Future work in this area would include investigations into the reactivity and further functionalisation of this novel class of compounds.

5. CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis describes a proposal for a novel carbene-derived ammonium ylide rearrangement as an approach to target **318**, which contains the tricyclic framework of the sarain core (Scheme 144). To provide a substrate for this rearrangement, the main aim of the research was to develop a route to functionalised bicyclic aminal **300**.
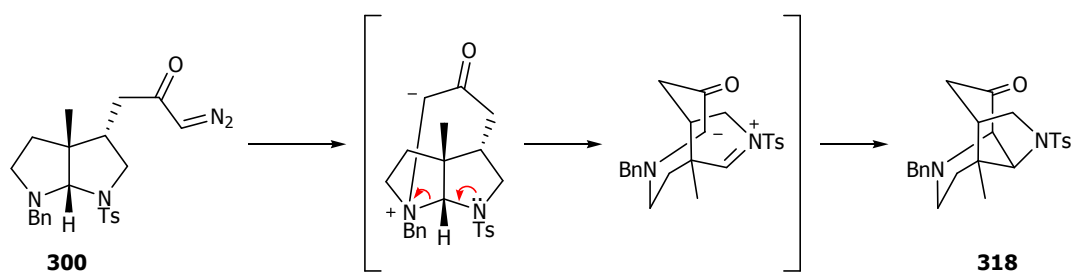
Scheme 144

A number of strategies to synthesise **300** were investigated; the initial approach involved a Diels-Alder reaction using a chiral dienophile to provide an enantioselective synthesis of **203** (Scheme 145). This reaction proceeded with excellent regio- and diastereoselectivity, but transformation into **213** proved troublesome. In another asymmetric Diels-Alder approach, use of Corey's oxazaborolidine catalyst in reactions with dienophile **239** to give **244** was unsuccessful due to the low reactivity and solubility of **239**. Uncatalysed reactions required high temperatures for the dienophile to react, resulting in significant double bond isomerisation in adduct **244**, from the desired C1-C2 to the C2-C3 position.

Asymmetric Diels-Alder reaction using a chiral dienophile
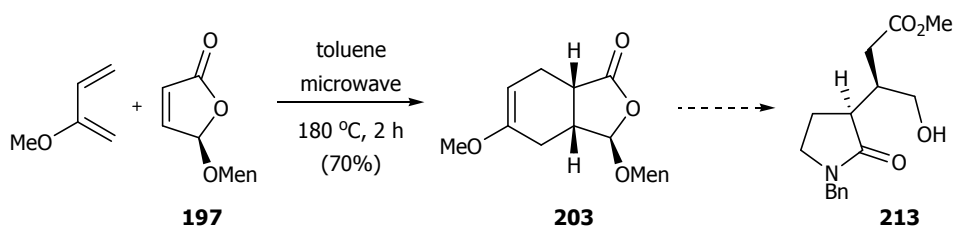
Asymmetric Diels-Alder reaction using a chiral catalyst
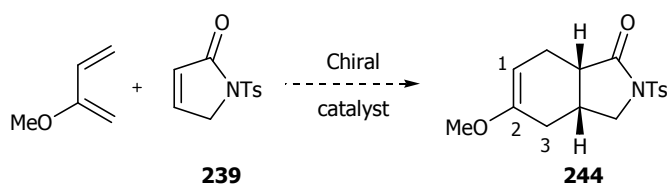
Scheme 145

In racemic approaches, the use of a Michael reaction was unsuccessful, but successful installation of the required stereochemistry was achieved by use of a thio-Claisen rearrangement. Under optimised conditions, the simple thiolactam substrate **281** was converted into **282** in good yield and excellent diastereoselectivity (Scheme 146). Bicyclic aminal **292** was prepared using an optimised reductive cyclisation methodology, and incorporation of a methyl group at C3a (**292**) prevented the problems of ring isomerisation in substrates that were unfunctionalised at that position. Further transformations provided carboxylic acid **299**, but conversion into the desired diazoketone **300** was unsuccessful, instead generating lactam **301**.
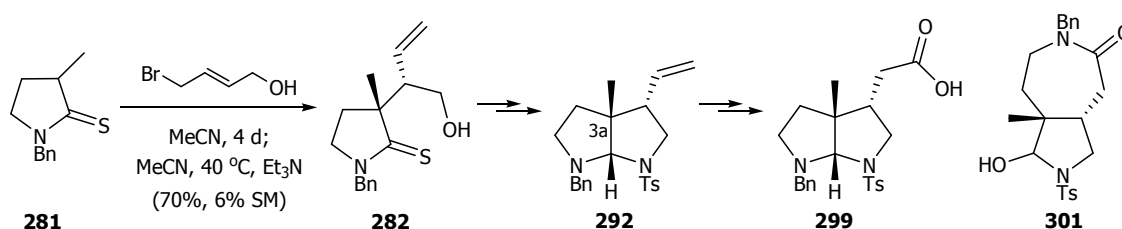
Scheme 146

Over the course of this research, a further three different, but related routes to the sarain core were investigated, including the synthesis of diazoester **314**, bromoketone **321** and hydroxy-aldehyde **339** (Scheme 147). Substrates to test the proposed rearrangement reactions were synthesised, using aldehyde **298** as the common branching point.
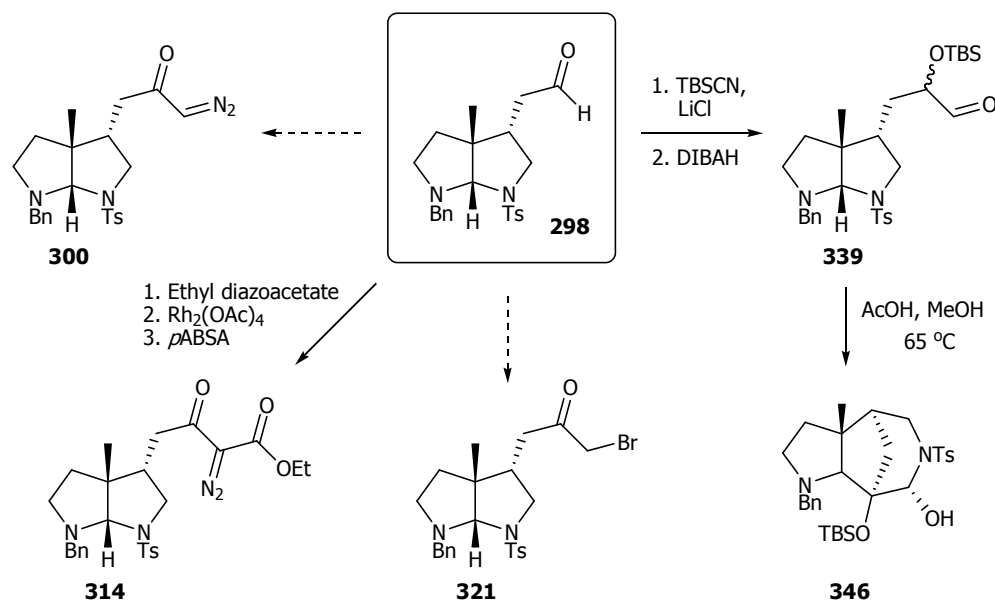
Scheme 147

Diazoester **314** was prepared starting from reaction of aldehyde **298** with ethyl diazoacetate followed by treatment with Rh$_2$(OAc)$_4$, and then a diazo transfer reaction. Unfortunately, exposure of **314** to a number of metal catalysts failed to provide the ethyl ester derivative of the sarain core. However, the options of metal catalysts or solvent systems that can be used to promote this rearrangement have not been exhausted. In addition, a photochemical, rather than a thermal process could be employed to generate the metallocarbene, and thus the ylide; in work towards the synthesis of the Tagetitoxin, our group recently utilised a photo-Stevens rearrangement to generate **380** from diazoester **378** (Scheme 148).[158] Upon treatment with Rh$_2$(OAc)$_4$ in refluxing benzene, ylide **379** was isolated, and found to be stable under thermal conditions, in various solvents and also to microwave heating. However, upon photolysis of **379**, the desired compound **380** was obtained in 69% yield. Applications of similar system to diazoester **314** to generate the sarain core **315** could be investigated.
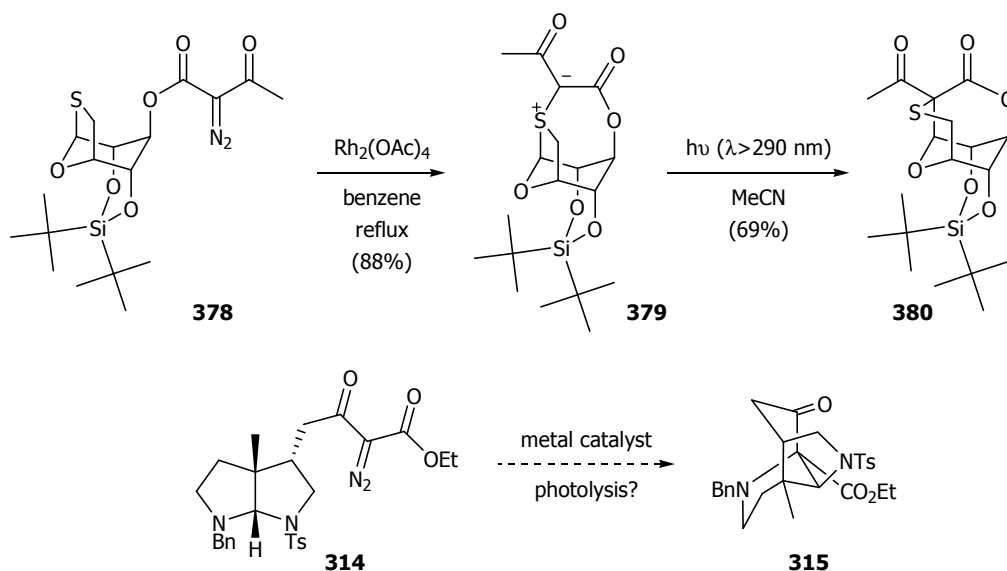
Scheme 148

Synthesis of an α-bromoketone as a viable route towards the synthesis of **318** was also investigated, using a variety of approaches. Although most were fruitless, the results from one attempt, involving first treatment of the corresponding methyl ketone with bromine followed by addition of triethylamine, were promising. The mass spectra of the products indicated the presence of some material with the correct formula for tricycle **318**, and thus warrant further investigation into this reaction.

In the final approach, protected hydroxy-aldehyde **339** was prepared from a cyanosilylation reaction. Whilst treatment with a number of acids to promote rearrangement failed to provide desired tricycle **318**, a different tricyclic compound **346** was produced. Future work in this area would involve the continued investigation into using this acid catalysed rearrangement of hydroxy-aldehyde **339**. A relatively small selection of acids was used in our studies, with the potential for many more – using acids of different strengths, including Lewis acids. One of the limiting factors in this investigation was the difficulties in preparing reliable quantities of the *tert*-butyldimethylsilyl protected hydroxy-aldehyde **339**, so a more efficient preparation of this material would be favoured. In addition, changing the protecting groups on the bicyclic aminals may be useful in promoting the ring opening process to occur in the desired direction.

All four approaches to the sarain core employ a methylated substrate that would ultimately lead to a methylated derivative of (±)-sarain A. The purpose of the additional methyl group was to prevent the ring isomerisation of the bicyclic aminal. Ideally, the methyl group should be replaced with a more labile group so that it can be removed at the end of the synthesis. An asymmetric thio-Claisen replacement would also allow for an enantioselective route to the sarain core.

Finally, in a separate investigation, it was found that treatment of tertiary formamides with a silylated diazoester in the presence of $Rh_2(OAc)_4$ leads to formation of 3-amino-2-silyloxyacrylates in good yields (Scheme 149). Future work in this area would involve investigations into the reactivity and further functionalisation of this novel class of compounds.
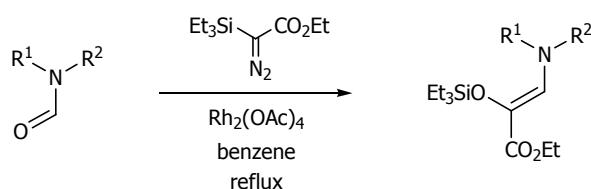
Scheme 149

6. EXPERIMENTAL

General

All reactions carried out in non-aqueous conditions were performed under argon, using flame-dried flasks.

Reagents

Chemicals were purchased from Aldrich, Alfa Aesar, Acros, Fluka, Fisher, BDH or STREM, and unless otherwise stated, were used without further purification.

- NH_2Bn, Et_3N, DIPEA and 2,6-lutidine were distilled from CaH_2 and stored over KOH.

- Pyridine and MVK were distilled from CaH_2 and stored over 4Å MS.

- Isobutyl chloroformate and furfural were distilled and stored over 4Å MS.

- Methyl-4-bromocrotonate was purified by flash chromatography (SiO_2; Et_2O:PS 2:3).

- TMSCl was distilled from CaH_2.

- LiCl was flame dried under vacuum before use.

- TsCl and NBS were recrystallised according to procedures described in "Purification of Laboratory Materials".[159]

- Lawesson's reagent was prepared using a procedure described by Clausen *et al*,[160] and Dess-Martin Periodinane using a procedure described by Boeckman *et al*.[117]

A saturated solution refers to a saturated aqueous solution.

Solvents

- DCM, Et_2O, MeCN, THF and toluene were obtained from the UCL Chemistry Department's Anhydrous Solvent System (dried by passage through activated alumina columns under a nitrogen atmosphere).

- DMF and acetone were distilled from, and stored over 4Å MS.

- DMSO, benzene and ^{i}PrOH were distilled from CaH_2 and stored over 4Å MS.

PS refers to petroleum ether that boils in the range 40-60 °C.

Chromatography

Flash chromatography was carried out on Merck silica gel 60 (40-60 μm), Florisil$^®$ (100-200 mesh), or either neutral, or basic, aluminium oxide (deactivated to grade III with 6% w/v water, 40-60 μm). Preparative thin layer chromatography was performed on glass plated pre-coated with normal phase Merck silica gel 60 F_{254} (0.25mm layer thickness). TLC was performed on Merck Kieselgel 60 F_{254} aluminium sheets, visualised with short wavelength ultraviolet light (254 nm) and through staining with potassium permanganate, iodine, vanillin, anisaldehyde, or 2,4-DNP.

Spectroscopy/spectrometry

Infrared (IR) spectra were recorded on a SHIMADZU FT-IR 8700 spectrometer using potassium bromide (KBr) disks.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz or 500 MHz on Bruker AMX-300, AMX-400 and AMX-500 spectrometers respectively. ^{13}C NMR spectra were recorded on the same instruments at 75 MHz, 100 MHz or 125 MHz. Chemical shifts (δ) are recorded in parts per million (ppm), and reported with reference to the solvent peak. The signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets, ddd = doublet of doublets of doublets, ddt = doublet of doublets of triplets, dddd = doublet of doublets of doublets of doublets, m = multiplet and br = broad. Coupling constants (*J*), reported in hertz, are calculated from observed chemical shifts, and can have an accuracy margin of ±0.3 Hz. COSY, DEPT, HMQC and HMBC were routinely used to aid assignment of spectra. Nuclear Overhauser enhancement experiments were performed by Dr Abil Aliev, Department of Chemistry, UCL.

Low resolution and high resolution mass spectra were measured by Mr John Hill or Dr Lisa Harris, both from Department of Chemistry, UCL. The instruments used were VG70-SE (CI+, EI+, FAB+) or Thermo MAT 900 (ESI+, ESP+).

Elemental analyses were carried out by Mrs Jill Maxwell, Department of Chemistry, UCL, and were recorded on a Perkin Elmer 2400 CHN elemental analyser.

Other

Melting points were determined with an Electrothermal 9100 instrument.

Microwave oven experiments were carried out in a CEM Discover instrument, with a maximum power of 250 W.

Lamp used was an IQ Premier Floodlight 500W tungsten halogen lamp.

6.1. Studies towards the synthesis of the core of sarains A, B & C

5-Hydroxy-2-(5*H*)-furanone (195)[69]
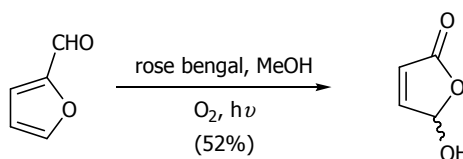
Through a solution of distilled furfural (110 g, 1.15 mol) and rose bengal (1.36 g, 1.34 mmol) in MeOH (600 mL) was slowly bubbled oxygen, while the solution was irradiated with a 500 W tungsten filament lamp. The reaction temperature was maintained below 33 °C at all times by external cooling. After 55 h, the solvent was removed *in vacuo*. The brown solid that formed overnight was filtered, washed twice with cold CHCl₃ (80 mL, −78 °C) and dried under high vacuum to afford furanone **195**[67] (44.5 g, 39%) as a pale orange solid. Addition of a seed crystal to a stirring solution of the combined mother liquors in chloroform (−78 °C) followed by filtration of the resulting crystals provided an extra 15.3 g of the furanone (total yield 59.2 g, 52%); m.p. 57-59 °C [lit.[67] 57.3-59.2 °C]; δ_H (300 MHz, CDCl₃) 7.31 (1H, dd, *J* 5.7, 1.2, HC=C*H*CH), 6.24 (1H, s, O=CC*H*), 6.21 (1H, dd, *J* 5.7, 1.3, C*H*OH), 5.24 (1H, br s, OH); δ_C (75 MHz, CDCl₃) 171.4 (O=C), 152.0 (HC=*C*HCH), 124.7 (O=C*C*H), 98.8 (*C*H(OH)).

(5*R*)-5-(ʟ-Menthyloxy)-2-(5*H*)-furanone (197)[67,69]
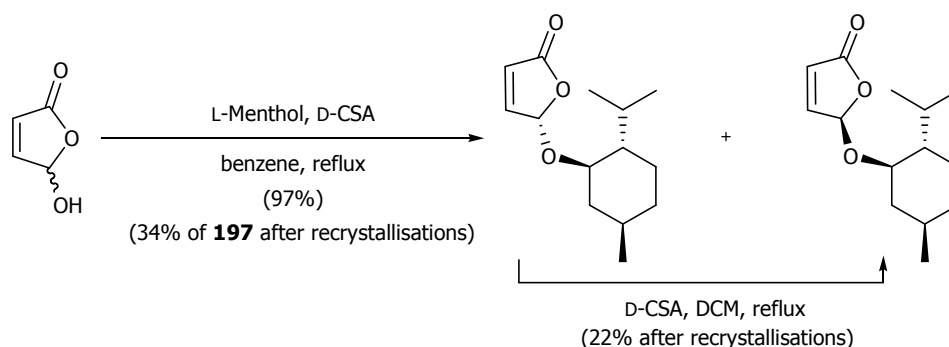
A 250 mL round bottomed flask equipped with a 10 mL Dean-Stark trap was charged with 5-hydroxy-2-(5*H*)-furanone (25.1 g, 251 mmol), ʟ-menthol (35.0 g, 224 mmol) and benzene (125 mL). ᴅ-(+)-Camphorsulfonic acid (2.67 g, 11.5 mmol) was added and the stirring mixture heated at reflux for 7 h. After cooling to 0 °C, saturated NaHCO₃

(125 mL) was added and the resulting suspension stirred for 3 h as it warmed to room temperature. DCM (250 mL) was added to the mixture and the organic layer was removed, washed with brine (3 × 200 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; DCM) gave a pale yellow oil, which solidified overnight to afford a 1:1 diastereoisomeric mixture of the menthyloxybutenolides (51.8 g, 97%). Three recrystallisations from PS (40-60 °C) furnished desired diastereoisomer **197** (17.1 g, 34%) as white needles.

Acid catalysed epimerisation[69]

The combined mother liquors from the recrystallisations (i.e. predominantly diastereoisomer **196**) were concentrated to dryness, dissolved in benzene (40 mL) and concentrated again. The resulting solid (51.3 g, 215 mmol) and D-(+)-camphorsulfonic acid (2.00 g, 8.6 mmol) in DCM (150 mL) were heated at reflux for 16 h. The reaction mixture was cooled to 0 °C, added saturated NaHCO$_3$ (40 mL), then stirred for 3 h while warming to room temperature. The organic phase was separated and washed with H$_2$O (50 mL), brine (3 × 150 mL), dried (MgSO$_4$), and then concentrated to afford a yellow oil which solidified overnight. Two recrystallisations from PS (40-60 °C) provided additional diastereoisomer **197** (11.3g, 24%); m.p. 80-81 °C [lit.[69] 79-80 °C]; $[\alpha]_D^{20}$ −139.2 (CHCl$_3$, c 8.2) [lit.[69] $[\alpha]_D^{20}$ −135.1 (CHCl$_3$, c 8.2)]; δ$_H$ (300 MHz, CDCl$_3$) 7.15 (1H, dd, *J* 5.7, 1.2, HC=C*H*CH), 6.19 (1H, dd, *J* 5.7, 1.2, OC*H*O), 6.08-6.07 (1H, m, O=CC*H*), 3.65 (1H, td, *J* 10.8, 4.4, OC*H*CH$_2$), 2.20-2.02 (2H, m, OCHC*H*H and C*H*Me$_2$), 1.74-1.60 (2H, m, CH(Me)C*H*HC*H*H), 1.50-1.31 (1H, m, CH$_2$C*H*Me), 1.31-1.19 (1H, m, C*H*^{i}Pr), 1.12-0.80 (3H, m, OCHCH*H*, CH(Me)CH*H*CH*H*), 0.94 (3H, d, *J* 6.6, CH$_2$CH(C*H$_3$*)), 0.87 (3H, d, *J* 7.1) and 0.80 (3H, d, *J* 7.0, CH(C*H$_3$*)$_2$); δ$_C$ (75 MHz, CDCl$_3$) 170.8 (C=O), 150.9 (C=CHCH), 124.8 (O=C*C*H), 100.5 (OCHO), 79.1 (O*C*HCH$_2$), 47.7 (*C*H^{i}Pr), 40.3 (OCH*C*H$_2$), 34.2 (CH(Me)*C*H$_2$CH$_2$), 31.5 (*C*HMe$_2$), 25.3 (CH$_2$*C*HMe), 23.1 (^{i}PrCH*C*H$_2$), 22.2, 20.9 (CH(*C*H$_3$)$_2$), 15.6 (CH$_2$CH(*C*H$_3$)).

Procedure for removal of menthyl 3-formylacrylate when it was produced as major side product in the reaction:

The crude oil was dissolved in ether and washed with saturated sodium hydrogensulfite. Organic materials from the aqueous phase were extracted with ether, and the combined organic layers were washed with brine and dried (MgSO$_4$) to give a yellow oil which solidified overnight. A hot filtration in PS (40-60 °C), followed by concentration

afforded a 1:1 diastereoisomeric mixture of the menthyloxybutenolides as an orange solid which could be separated by recrystallisations from PS.

2-Trimethylsilyloxy-1,3-butadiene (198)[161]
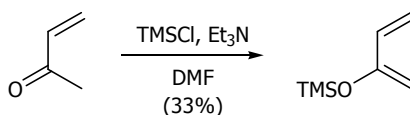
A 3-necked flask equipped with 2 addition funnels and a reflux condenser was charged with Et$_3$N (24.1 mL, 173 mmol) and DMF (80 mL), and heated to 90 °C. MVK (12 mL, 147 mmol) in DMF (10 mL) and TMSCl (21.7 mL, 171 mmol) in DMF (10 mL) were added simultaneously to the reaction over 30 min. The suspension was stirred at 90 °C for 16 h, then cooled to room temperature and filtered. The filtrate was diluted with pentane (120 mL) and washed with cold 5% aqueous NaHCO$_3$ (400 mL). The organic materials were extracted from the aqueous layer with pentane (2 × 120 mL) and the combined organic extracts were washed with cold H$_2$O (80 mL) and then dried (Na$_2$SO$_4$). Pentane and other volatiles were removed by fractional distillation at atmospheric pressure before the product was distilled through a 10 cm Vigreux column to afford the title diene **198**[161] (6.86 g, 33%) as a colourless liquid; b.p. 40-43 °C/40 mmHg [lit.[161] 50-55 °C/50 mmHg]; δ_H (300 MHz, CDCl$_3$) 6.19 (1H, dd, *J* 17.0, 10.5, H$_2$C=C*H*), 5.47 (1H, br d, *J* 17.0) and 5.08 (1H, br d, *J* 10.5, HC=C*H*$_2$), 4.35 (1H, s) and 4.34 (1H, s, (TMSO)C=C*H*$_2$), 0.23 (9H, s, Si(C*H*$_3$)$_3$); δ_C (75 MHz, CDCl$_3$) 154.9 ((TMSO)*C*), 134.7 (H$_2$C=*C*H), 114.5 (H$_2$*C*=CH), 96.3 ((TMSO)C=*C*H$_2$), 0.0 (Si(*C*H$_3$)$_3$).

1,3,3-Trimethoxybutane (201)[71]
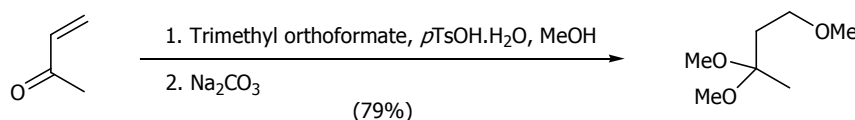
To methyl vinyl ketone (200 mL, 2.44 mol) in MeOH (300 mL, 7.33 mol) were added trimethyl orthoformate (446 mL, 4.08 mol), followed by *p*-toluenesulfonic acid monohydrate (270 mg, 1.4 mmol). Over the next 5 min the reaction became exothermic and dark brown in colour. The reaction mixture was allowed to stand at room temperature for 12 d. Na$_2$CO$_3$ (4.92 g, 46.4 mmol) was added and the resulting deep red

coloured solution was stirred for 3 d. The solids were filtered and excess methanol and other volatiles were removed by distillation at atmospheric pressure (maintaining the head temperature below 70 °C). The resulting mixture was filtered and purified by distillation under reduced pressure to afford 1,3,3-trimethoxybutane (285 g, 79%) as a colourless liquid; b.p. 59-60 °C/18 mmHg [lit.[71] 57-58 °C/18 mmHg]; δ_H (300 MHz, CDCl$_3$) 3.40 (2H, t, *J* 7.2, C*H$_2$*OMe), 3.30 (3H, s, CH$_2$OC*H$_3$*), 3.15 (6H, s, C(OC*H$_3$*)$_2$), 1.91 (2H, t, *J* 7.2, C(OMe)$_2$C*H$_2$*), 1.24 (3H, s, C(OMe)$_2$CH$_3$); δ_C (75 MHz, CDCl$_3$) 100.5 (*C*(OMe)$_2$), 68.9 (*C*H$_2$OMe), 58.6 (CH$_2$OC*H$_3$*), 48.0 (C(OC*H$_3$*)$_2$,), 36.3 (C(OMe)$_2$*C*H$_2$), 21.5 (C(OMe)$_2$*C*H$_3$).

2-Methoxy-1,3-butadiene (202)[71]
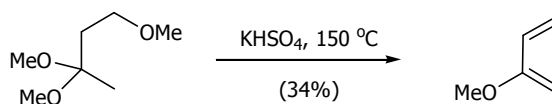
To a 100 mL 3-necked flask equipped with a pressure equalising dropping funnel, a 10 cm Vigreux column fitted with a distillation apparatus, and a glass stopper was added KHSO$_4$ (61 mg, 0.5 mmol) and approximately 25 mL of 1,3,3-trimethoxybutane. The flask was lowered into an oil bath preheated to 150 °C, and the remaining 1,3,3-trimethoxybutane (total amount 70.0 mL, 444 mmol) was added dropwise at a rate to maintain approximately 25 mL material in the reaction flask. The distilled products were collected in a flask cooled to −78 °C, and when the rate of distillation appeared to slow down (when head temperature decreased from 63 °C to 55 °C), additional KHSO$_4$ (61 mg, 0.5 mmol) was added. On completion of the distillation, the colourless distillate was warmed to room temperature and washed with H$_2$O (3 × 20 mL), taking care not to shake the mixture. The organic layer was dried (Na$_2$SO$_4$) and stored over 4Å molecular sieves overnight at 4 °C. A small amount of hydroquinone was added and the product was distilled through a 10 cm Vigreux column to afford diene **202** (12.6 g, 34%) as a colourless liquid; b.p. 76-77 °C [lit.[71] 75 °C]; δ_H (300 MHz, CDCl$_3$) 6.17 (1H, dd, *J* 17.3, 10.9, H$_2$C=C*H*), 5.56 (1H, br d, *J* 17.3) and 5.09 (1H, br d, *J* 10.8, HC=C*H$_2$*), 4.16 (1H, s) and 4.13 (1H, s, (OMe)C=C*H$_2$*), 3.63 (3H, s, OC*H$_3$*); δ_C (75 MHz, CDCl$_3$) 159.1 (MeO*C*), 133.2 (CH$_2$*C*H), 114.2 (*C*H$_2$CH), 86.5 (*C*H$_2$COMe), 54.7 (O*C*H$_3$).

(3*R*,3a*R*,7a*S*)-3-(L-Menthyloxy)-5-methoxy-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (203)
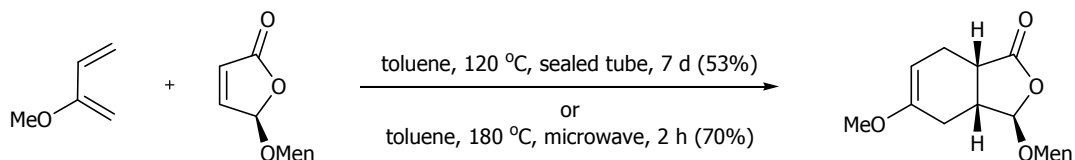
Thermal sealed tube:

A stirring solution of furanone **197** (1.50 g, 6.3 mmol) and diene **202** (1.32 g, 15.7 mmol) in toluene (2 mL) was heated in a sealed tube for 7 d at 120 °C. Concentration and purification by flash chromatography (SiO$_2$; PS→EtOAc:PS 1:19) afforded adduct **203** (1.07 g, 53%) as a white solid.

Microwave sealed tube:

A stirring solution of furanone (1.50 g, 6.3 mmol) and diene (1.32 g, 15.7 mmol) in toluene (2 mL) was treated with microwave radiation while heated in a sealed tube at 180 °C for 2h. Concentration and purification by flash chromatography (SiO$_2$; PS→EtOAc:PS 1:19) afforded adduct **203**[70] (1.41 g, 70%) as a white solid; m.p. 115-116 °C [lit.[70] 129.5-130.5 °C]; $[\alpha]_D^{20}$ −130.4 (CHCl$_3$, c 1.0); δ$_H$ (300 MHz, CDCl$_3$) 5.28 (1H, s, OC*H*O), 4.51 (1H, br s, (MeO)C=C*H*), 3.58-3.46 (1H, m, OC*H*CH$_2$), 3.50 (3H, s, OC*H*$_3$), 3.09-2.96 (2H, m, OCH(OMen)C*H* and O=CC*H*), 2.28-2.05 (3H, m, O=CCHC*H*$_2$ and OCHC*H*H), 2.05-1.88 (2H, m, C*H*Me$_2$ and (MeO)CC*H*H), 1.87-1.72 (1H, m, (MeO)CCH*H*), 1.72-1.57 (2H, m, CH(Me)C*H*HC*H*H), 1.47-1.29 (1H, m, CH$_2$C*H*Me), 1.29-1.14 (1H, m, C*H*^{i}Pr), 1.10-0.81 (3H, m, OCHCH*H*, CH(Me)CH*H*CH*H*), 0.93 (3H, d, *J* 6.6, CH$_2$CH(C*H*$_3$)), 0.86 (3H, d, *J* 7.0) and 0.76 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$); δ$_C$ (75 MHz, CDCl$_3$) 178.2 (*C*=O), 158.2 ((MeO)*C*=CH), 103.9 (O*C*HO), 90.0 ((MeO)C=*C*H), 76.2 (O*C*HCH$_2$), 54.1 (O*C*H$_3$), 47.8 (*C*H^{i}Pr), 41.8 (OCH(OMen)*C*H), 39.8 (OCH*C*H$_2$), 36.7 (O=C*C*H), 34.3 (CH(Me)*C*H$_2$CH$_2$), 31.4 (*C*HMe$_2$), 25.6 (*C*H$_2$CHMe), 23.9 ((MeO)C*C*H$_2$), 23.1 (^{i}PrCH*C*H$_2$), 22.3 and 20.9 (CH(*C*H$_3$)$_2$), 20.1 (O=CCH*C*H$_2$), 15.6 (CH(*C*H$_3$)).

Methyl [(2*R*,3*R*,4*S*)-2-(L-menthyloxy)-5-oxo-4-(2-oxoethyl)tetrahydrofuran-3-yl]-acetate (204)
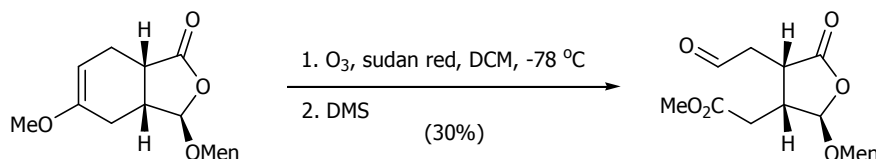
Through a stirring solution of methoxy-alkene **203** (0.30 g, 0.93 mmol) and Sudan Red (0.01% in MeOH w/v, 0.1 mL) in DCM (10 mL) was bubbled ozone in O_2 at −78 °C. When the solution was decolourised, argon was flushed through the system for 20 min. DMS (0.43 mL, 5.9 mmol) was added and the solution stirred for 18 h under argon, gradually warming up to room temperature. DCM and excess DMS were removed *in vacuo*, and to the remaining oil was added EtOAc (20 mL). The resulting solution was washed with H_2O (3 × 20 mL), brine (3 × 20 mL) and dried ($MgSO_4$). Filtration, concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:9→3:17) afforded cleaved product **204** (0.10 g, 30%) as a white solid; m.p. 101-103 °C; $[\alpha]_D^{20}$ −63.7 (CHCl₃, c 1.0); v_{max}/cm⁻¹ (KBr) 2953, 2868 (CH), 1772, 1730 (C=O); δ_H (500 MHz, CDCl₃) 9.80 (1H, s, CHO), 5.48 (1H, s, OCHO), 3.67 (3H, s, CO₂CH₃), 3.59-3.48 (1H, m, OCH(OMen)C*H*), 3.47-3.44 (1H, m, OC*H*CH₂), 3.02 (1H, dd, *J* 19.1, 4.9, OHCC*H*H), 2.98-2.94 (1H, m, O=CCH), 2.61 (1H, ddd, *J* 19.0, 9.6, 0.8, OHCCH*H*), 2.26 (1H, dd, *J* 16.5, 5.9) and 2.20 (1H, dd, *J* 16.5, 9.4, MeO₂CC*H₂*), 2.06-2.03 (1H, m, OCHC*H*H), 2.03-1.99 (1H, m, C*H*Me₂), 1.65-1.60 (2H, m, CH(Me)C*H*HC*H*H), 1.39-1.30 (1H, m, CH₂C*H*Me), 1.28-1.19 (1H, m, C*H*ⁱPr), 0.98-0.95 (1H, m, OCHCH*H*), 0.91 (3H, d, *J* 6.6, CH₂CH(C*H₃*)), 0.91-0.80 (2H, m, CH(Me)CH*H*CH*H*), 0.85 (3H, d, *J* 7.1) and 0.73 (3H, d, *J* 7.0, CH(C*H₃*)₂); δ_C (125 MHz, CDCl₃) 198.7 (CHO), 176.9 (O=*C*OCH), 171.2 (*C*O₂Me), 102.8 (OCHO), 77.0 (O*C*HCH₂), 52.1 (CO₂*C*H₃), 47.6 (*C*HⁱPr), 40.9 (O=C*C*H), 39.7 (OHC*C*H₂), 39.6 (OCH*C*H₂), 36.1 (OCH(OMen)*C*H), 34.2 (CH(Me)*C*H₂CH₂), 31.7 (MeO₂C*C*H₂), 31.3 (*C*HMe₂), 25.5 (CH₂*C*HMe), 22.9 (ⁱPrCH*C*H₂), 22.2 and 20.9 (CH(*C*H₃)₂), 15.4 (CH(*C*H₃)); *m/z* (CI+) 355 (MH⁺, 5%), 217 (32), 199 (100), 181 (22), 153 (24), 139 (59), 83 (57); HRMS (CI+) calcd for $C_{19}H_{31}O_6$ (MH⁺) 355.2121, found 355.2123.

(3*R*,3a*R*,7a*S*)-3-(L-Menthyloxy)-5-methyl-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (208a) and (3*R*,3a*R*,7a*S*)-3-(L-Menthyloxy)-6-methyl-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (208b)
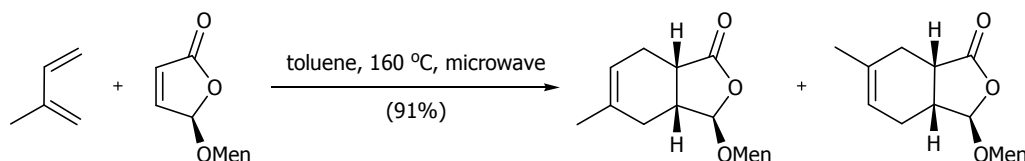
A stirring solution of furanone **197** (1.00 g, 8.8 mmol) and isoprene (2.1 mL, 210 mmol) in toluene (2 mL) was treated with microwave radiation at 160 °C for 2 h. Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19) afforded an inseparable 1:1 mixture of the olefin regioisomers **208a** and **208b** (1.17 g, 91%) as a white solid; m.p. 65-69 °C [lit.[67] 68-74 °C]; δ$_H$ (300 MHz, CDCl$_3$) 5.46-5.40 (0.5H, m) and 5.40-5.34 (0.5H, m, MeC=C*H*), 5.32-5.25 (1H, m, OCHO), 3.51 (0.5H, dt, *J* 10.6, 1.6) and 3.50 (0.5H, dt, *J* 10.6, 1.6, OC*H*CH$_2$), 3.10 (0.5H, dt, *J* 7.9, 2.1) and 3.02 (1H, *J* 7.9, 2.1, OCH(OMen)C*H*), 2.58-2.31 (2H, m, O=CCH and O=CCHC*H*H), 2.31-2.17 (1H, m, O=CCHCH*H*), 2.17-1.92 (3H, m, OCHC*H*H, C*H*Me$_2$ and OCH(OMen)CHC*H*H), 1.90-1.74 (1H, m, OCH(OMen)CHCH*H*), 1.69 (1.5H, s) and 1.66 (1.5H, s, HC=CC*H$_3$*), 1.63-1.52 (2H, m, CH(Me)C*H*HC*H*H), 1.47-1.29 (1H, m, CH$_2$C*H*Me), 1.29-1.15 (1H, m, C*H*^{i}Pr), 1.08-0.79 (3H, m, OCHCH*H*, CH(Me)CH*H*CH*H*), 0.93 (3H, d, *J* 6.6, CH$_2$CH(C*H$_3$*)), 0.87 (3H, d, *J* 7.0) and 0.76 (3H, d, *J* 7.0, CH(C*H$_3$*)$_2$); δ$_C$ (75 MHz, CDCl$_3$) 178.8 (O=C), 132.9, 131.4 (HC=*C*Me), 119.2, 118.2 (MeC=*C*H), 103.6 (OCHO), 76.4 (O*C*HCH$_2$), 47.8 (*C*H^{i}Pr), 39.8 (OCH*C*H$_2$), 38.8, 37.8 (O=C*C*H), 36.5, 35.4 (OCH(OMen)*C*H), 34.3 (CH(Me)*C*H$_2$CH$_2$), 31.4 (*C*HMe$_2$), 28.2, 26.4 (OCH(OMen)CH*C*H$_2$), 25.5 (CH$_2$*C*HMe), 23.8, 23.4 (C=C*C*H$_3$), 22.7, 22.1 (O=CCH*C*H$_2$), 23.0 (^{i}PrCH*C*H$_2$), 22.3, 21.0 (CH(*C*H$_3$)$_2$), 15.5 (CH$_2$CH(*C*H$_3$)).

2-[(3*S*,4*R*,5*R*)-5-(L-Menthyloxy)-2-oxo-4-(2-oxopropyl)tetrahydrofuran-3-yl]acetaldehyde (209a) and 2-[(3*S*,4*R*,5*R*)-5-(L-Menthyloxy)-2-oxo-3-(2-oxopropyl)tetrahydrofuran-3-yl]acetaldehyde (209b)
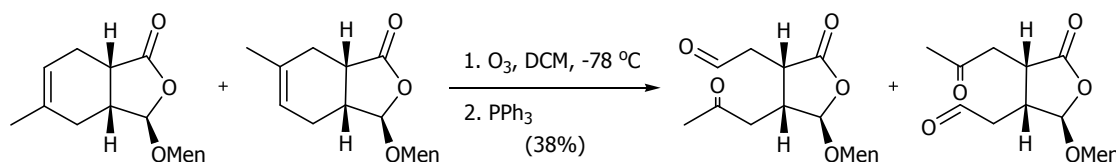
Through a stirring solution of olefins **208** (0.30 g, 0.98 mmol) in DCM (10 mL) was bubbled ozone in O_2 at −78 °C. When the solution became blue, oxygen was bubbled through the solution until it was colourless. PPh_3 (0.51 g, 2.0 mmol) was added and the solution stirred overnight under argon, slowing warming up to room temperature. Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 2:3) afforded an inseparable 7:3 mixture of the two regioisomers **209a** and **209b** (0.13 g, 38%) as a colourless oil; v_{max}/cm^{-1} (film) 2924, 2870 (CH), 1770, 1717 (C=O); δ_H (300 MHz, $CDCl_3$) 9.78 (0.3H, s) and 9.72 (0.7H, s, CH_2CHO), 5.36 (1H, s, OCHO), 3.52-3.39 (2H, m, OCH(OMen)C*H* and OC*H*CH$_2$), 3.11-3.03 (1H, m, O=CC*H*), 3.00 (1H, dd, *J* 18.8, 4.5) and 2.51 (1H, dd, *J* 18.7, 9.8, OHCCC*H$_2$*), 2.41-2.38 (2H, m, MeOCC*H$_2$*), 2.19 (2.1H, s) and 2.16 (0.9H, s, COC*H$_3$*), 2.12-1.93 (2H, m, OCHC*H*H and C*H*Me$_2$), 1.75-1.55 (2H, m, CH(Me)C*H*HCH$_2$ and ^{i}PrCHC*H*H), 1.45-1.30 (1H, m, CH$_2$C*H*Me), 1.30-1.15 (1H, m, C*H*^{i}Pr), 1.05-0.76 (3H, m, OCHCH*H*, CH(Me)CH*H*CH$_2$ and ^{i}PrCHCH*H*), 0.92 (3H, d, *J* 6.6, CH$_2$CH(C*H$_3$*)), 0.86 (3H, d, *J* 7.1) and 0.72 (3H, d, *J* 7.1, CH(C*H$_3$*)$_2$); δ_C (75 MHz, $CDCl_3$) 205.5, 205.4 (CH$_2$*C*HO), 199.0, 198.2 (*C*OMe), 177.3, 171.1 (O=*C*OCH), 103.1, 102.9 (OCHO), 77.3, 76.6 (O*C*HCH$_2$), 47.6 (*C*H^{i}Pr), 41.5, 40.6 (O=C*C*H), 40.0, 39.6, 39.5, 38.9 (2 × O=C*C*H$_2$), 39.8 (OCH*C*H$_2$), 37.2, 36.0 (OCH(OMen)*C*H), 34.3 (CH(Me)*C*H$_2$CH$_2$), 31.4 (*C*HMe$_2$), 30.1, 29.9 (CO*C*H$_3$), 25.5 (CH$_2$*C*HMe), 23.0 (^{i}PrCH*C*H$_2$), 22.2, 20.9 (CH(*C*H$_3$)$_2$), 15.5 (H$_2$CCH(*C*H$_3$)); *m/z* (CI+) 339 (MH$^+$, 5%), 201 (15), 183 (100), 165 (47), 139 (32); HRMS (CI+) calcd for $C_{19}H_{31}O_5$ (MH$^+$) 339.2171, found 339.2174.

(3*R*,3a*R*,7a*S*)-3-Methoxy-5-methyl-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (210a) and **(3*R*,3a*R*,7a*S*)-3-Methoxy-6-methyl-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (210b)**[67]
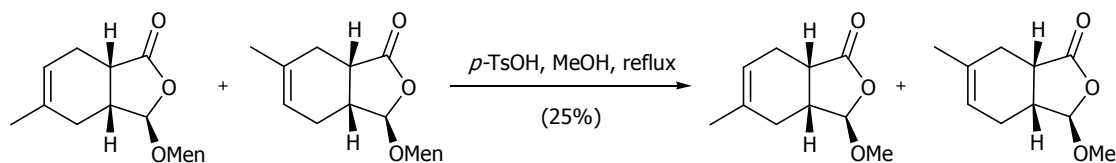
A stirring solution of menthyloxy-furanones **208** (0.20 g, 0.65 mmol) and *p*-TsOH (6 mg, 30 μmol) in MeOH (28 mL) was heated at reflux for 3 h. MeOH was removed *in vacuo* and the remaining residue was diluted with EtOAc (30 mL). The solution was washed with saturated NaHCO$_3$ (2 × 30 mL), H$_2$O (2 × 30 mL), brine (2 × 30 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO_2;

DCM→MeOH:DCM 1:49) afforded an inseparable 1:1 mixture of the two methoxy-furanone regioisomers **210a** and **210b** (0.03 g, 25%) as a colourless oil; v_{max}/cm^{-1} (film) 2919, 2845 (CH), 1770 (C=O); δ_H (300 MHz, CDCl$_3$) 5.46-5.40 (0.5H, m) and 5.40-5.34 (0.5H, m, MeC=C*H*), 4.99 (1H, s, OC*H*O), 3.48 (1.5 H, s) and 3.47 (1.5H, s, OC*H$_3$*), 3.07 (0.5H, td, *J* 8.0, 2.1) and 2.99 (0.5H, td, *J* 8.0, 2.1, OCH(OMe)C*H*), 2.65-2.48 (1H, m, O=CC*H*), 2.44 (1H, t *J* 8.0, O=CCHC*H*H), 2.39-2.14 (2H, m, O=CCHCH*H* and OCH(OMe)CHC*H*H), 1.91-1.71 (1H, m, OCH(OMe)CHCH*H*), 1.68 (1.5 H, s) and 1.66 (1.5H, s, HC=C(C*H$_3$*)); δ_C (75 MHz, CDCl$_3$) 178.8 (C=O), 133.2, 131.6 (HC=*C*Me), 119.3, 118.2 (MeC=*C*H), 108.6 (O*C*HO), 56.7 (O*C*H$_3$), 38.6, 37.7 (O=C*C*H), 36.3, 35.2 (OCH(OMe)*C*H), 28.3, 26.4 (OCH(OMe)CH*C*H$_2$), 23.9, 22.1 (O=CCH*C*H$_2$), 23.7, 23.4 (HC=C*C*H$_3$); *m/z* (CI+) 183 (MH$^+$, 28%), 168 (10), 151 (40), 137 (10), 122 (31), 105 (54), 93 (100); HRMS (CI+) calcd for C$_{10}$H$_{15}$O$_3$ (MH$^+$) 183.1021, found 183.1022.

(3*S*,3'*R*)-1-Benzyl-3-(1-benzyl-5-oxopyrrolidin-3-yl)pyrrolidin-2-one (215)
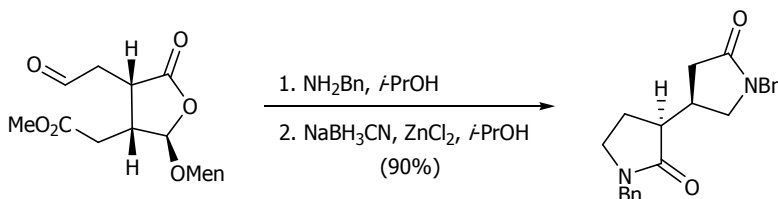
NH$_2$Bn (apparently 0.01 mL, 0.09 mmol) was added dropwise to a solution of aldehyde **204** (0.030 g, 0.08 mmol) in isopropanol (1.5 mL) and stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and was added a solution of NaBH$_3$CN (0.021 g, 0.34 mmol) and ZnCl$_2$ (0.023 g, 0.17 mmol) in isopropanol (0.5 mL). The stirring reaction was maintained at 0 °C, and then allowed to stand for 19 h while warming to room temperature. The suspension was then stirred for a further 2 h and the solvent removed *in vacuo*. The remaining material was dissolved in EtOAc (10 mL) and washed with saturated NaHCO$_3$ (2 × 10 mL), brine (2 × 10 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; DCM→MeOH:DCM 1:49) afforded lactam **215** (0.026 g, 90%) as a white solid; m.p. 72-74 °C; v_{max}/cm^{-1} (CDCl$_3$ cast) 2361 (CH), 1665 (C=O); δ_H (500 MHz, CDCl$_3$) 7.29-7.13 (10H, m, 10 × Ar*H*), 4.50-4.31 (4H, m, 2 × C*H$_2$*Ph), 3.33 (1H, dd, *J* 10.0, 8.3, NC*H*HCH), 3.10 (1H, dt, *J* 9.8, 8.2, NC*H*HCH$_2$), 3.01 (1H, dt, *J* 9.1, 2.7) and 3.03-2.99 (1H, m, NCH$_2$CH$_2$C*H* and NCH*H*CH), 2.76-2.70 (2H, m, NCH$_2$C*H*C*H*H), 2.57 (1H, dt, *J* 9.2, 6.0,

NCH*H*CH$_2$), 2.41-2.34 (1H, m, NCH$_2$CHCH*H*), 2.05-1.98 (1H, m) and 1.54-1.43 (1H, m, NCH$_2$C*H$_2$*); δ$_C$ (125 MHz, CDCl$_3$) 174.2, 173.8 (2 × C=O), 136.3, 136.2 (2 × aromatic C), 128.7, 128.3, 128.0, 127.6 (10 × aromatic CH), 49.0 (NCH$_2$CH), 46.7, 46.5 (2 × *C*H$_2$Ph), 44.7 (NCH$_2$CH$_2$*C*H), 44.4 (NCH$_2$*C*H$_2$), 35.3 (NCH$_2$CH*C*H$_2$), 31.8 (NCH$_2$*C*H), 21.5 (NCH$_2$*C*H$_2$); *m/z* (CI+) 349 (MH$^+$, 100%), 216 (10), 175 (44), 137 (13), 97 (19), 81 (11); HRMS (CI+) calcd for C$_{22}$H$_{25}$N$_2$O$_2$ (MH$^+$) 349.1916, found 349.1918.

Diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (216)[162]
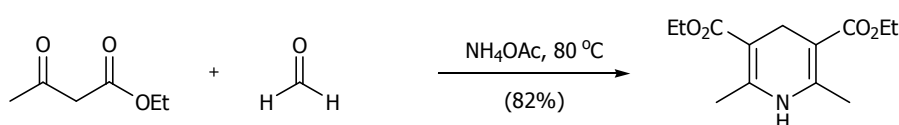
A stirring mixture of formaldehyde (37% in solution, 2.00 g, 49 mmol), ethyl acetoacetate (6.40 g, 67 mmol) and ammonium acetate (2.85 g, 37 mmol) were heated at 80 °C for 45 min. The bright yellow suspension was cooled to 0 °C and filtered, washing with H$_2$O (4 × 10 mL) and dried under vacuum on the filter. The collected solids were dissolved in hot EtOAc and dried (Na$_2$SO$_4$). A hot filtration followed by recrystallisation from EtOAc afforded Hantzsch's base **216**[163] (5.12 g, 82%) as yellow needles; m.p. 176-179 °C [lit.[163] 176-178 °C]; δ$_H$ (300 MHz, CDCl$_3$) 5.11 (1H, br s, NH), 4.15 (4H, q, *J* 7.1, 2 × OCH$_2$), 3.25 (2H, s, C=CCH$_2$), 2.18 (6H, s, 2 × C=CCH$_3$), 1.27 (6H, t, *J* 7.1, 2 × OCH$_2$C*H$_3$*); δ$_C$ (75 MHz, CDCl$_3$) 168.1 (2 × C=O), 144.9 (2 × *C*CO$_2$Et), 99.5 (2 × NH*C*), 59.7 (2 × OCH$_2$), 24.8 (C=C*C*H$_2$), 19.2 (2 × C=C*C*H$_3$), 14.5 (2 × OCH$_2$*C*H$_3$).

(3*R*,3a*R*,7a*S*)-Hexahydro-3,5,5-trimethoxyisobenzofuran-1(3*H*)-one (217)[67]
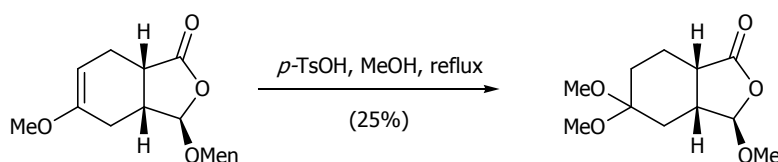
A stirring mixture of menthyloxy-furanone **203** (0.10 g, 0.31 mmol) and *p*-TsOH (3 mg, 16 μmol) in MeOH (14 mL) were heated at reflux for 2 h. MeOH was removed *in vacuo* and the remaining residue was dissolved in EtOAc (20 mL). The solution was washed with saturated NaHCO$_3$ (3 × 20 mL), H$_2$O (2 × 20 mL) and brine (2 × 20 mL), and then

dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; PS→EtOAc:PS 1:4) afforded dimethyl acetal **217** (0.02 g, 25%) as a colourless oil; v_{max}/cm^{-1} (film) 2951 (CH), 1780 (C=O); δ_H (300 MHz, CDCl$_3$) 4.96 (1H, s, OC*H*O), 3.45 (3H, s, OCHOC*H$_3$*), 3.18 (3H, s) and 3.15 (3H, s, C(OC*H$_3$*)$_2$), 2.88 (1H, br t, *J* 6.4, OCH(OMe)C*H*), 2.53 (1H, dt, *J* 12.4, 6.5, O=CC*H*), 2.21-2.06 (2H, m, (MeO)$_2$CC*H$_2$*CH$_2$), 1.95-1.84 (1H, m) and 1.83-1.69 (1H, m, (MeO)$_2$CC*H$_2$*CH), 1.25 (1H, dt, *J* 13.7, 4.5) and 1.12 (1H, t, *J* 12.9, O=CCHC*H$_2$*); δ_C (75 MHz, CDCl$_3$) 177.9 (C=O), 107.0 (OCHO), 98.7 (*C*(OMe)$_2$), 56.6 (OCHO*C*H$_3$), 47.8, 47.6 (C(O*C*H$_3$)$_2$), 40.0 (O=C*C*H), 36.7 (OCH(OMe)*C*H), 31.7 ((MeO)$_2$C*C*H$_2$CH$_2$), 28.6 ((MeO)$_2$C*C*H$_2$CH), 19.5 (O=CCH*C*H$_2$); *m/z* (CI+) 231 (MH$^+$, 21%), 213 (33), 199 (100), 181 (82), 142 (85), 123 (71), 101 (53); HRMS (CI+) calcd for C$_{11}$H$_{19}$O$_5$ (MH$^+$) 231.1232, found 231.1220.

5-Methoxy-2-(5*H*)-furanone (218)[67]
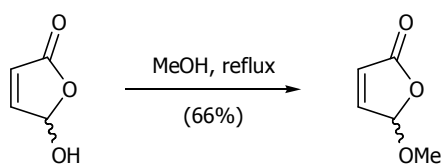
A stirring solution of furanone **195** (5.00 g, 50.0 mmol) in MeOH (20.0 mL, 500 mmol) was heated at reflux for 7 d. Excess MeOH was removed *in vacuo* and the product purified by distillation to afford methoxy-furanone **218**[67] (3.76 g, 66%) as a pale yellow liquid; b.p. 54-56 °C/2 mmHg [lit.[67] 70-72 °C/2 mmHg]; δ_H (300 MHz, CDCl$_3$) 7.20 (1H, dd, *J* 5.7, 1.1, C=C*H*CH), 6.22 (1H, dd, *J* 5.7, 1.2, O=CC*H*), 5.85 (1H, d, *J* 1.2, OC*H*O), 3.56 (3H, s, OC*H$_3$*); δ_C (75 MHz, CDCl$_3$) 170.4 (C=O), 150.2 (C=*C*HCH), 125.2 (O=C*C*H), 104.1 (OCHO), 57.1 (O*C*H$_3$).

## 3,5-Dimethoxy-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (219)
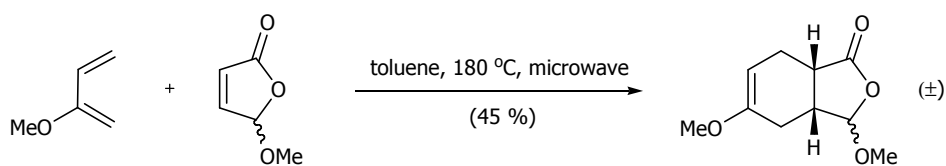
A stirring solution of furanone **218** (1.00 g, 8.8 mmol) and diene **202** (1.51 g, 17.5 mmol) in toluene (2 mL) was treated with microwave radiation at 180 °C for 1 h.

Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:9) afforded adduct **219** (0.78 g, 45%) as a colourless oil; ν_{max}/cm^{-1} (film) 2919, 2848 (CH), 1722 (C=O), 1661 (C=C); δ_H (400 MHz, $CDCl_3$) 4.99 (1H, s, OC*H*O), 4.50 (1H, dd, *J* 3.1, 2.0, (MeO)C=C*H*), 3.50 (3H, s, HC=C(OC*H₃*)), 3.47 (3H, s, OCHOC*H₃*), 3.06-3.02 (1H, m, OCH(OMe)C*H*), 3.00-2.96 (1H, m, O=CC*H*), 2.23-2.14 (1H, m) and 2.13-2.05 (1H, m, (MeO)C=CHC*H₂*), 1.94 (1H, dd, *J* 16.9, 5.8) and 1.82-1.73 (1H, m, (MeO)CC*H₂*); δ_C (75 MHz, $CDCl_3$) 178.1 (C=O), 158.3 (HC=*C*(OMe)), 108.9 (O*C*HO), 89.8 ((MeO)C=*C*H), 56.6 (OCH(O*C*H₃)), 54.1 (HC=C(O*C*H₃)), 41.5 (O=C*C*H), 36.4 (OCH(OMe)*C*H), 23.8 ((OMe)C*C*H₂), 20.1 (C=CH*C*H₂); *m/z* (CI+) 200 (MH⁺, 9%), 167 (10), 153 (14), 123 (13), 85 (100); HRMS (CI+) calcd for $C_{10}H_{15}O_4$ (MH⁺) requires 199.0970, found 199.0971.

Methyl [2-Methoxy-5-oxo-4-(2-oxoethyl)tetrahydrofuran-3-yl]acetate (220)
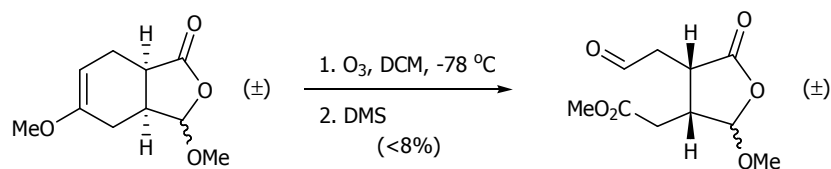
Through a stirring solution of enol ether **219** (0.34 g, 1.72 mmol) in DCM (10 mL) was bubbled ozone in O_2 at -78 °C. When the solution became blue, oxygen was passed through the solution until it was colourless. DMS (0.25 mL, 3.4 mmol) was added and the mixture stirred for 16 h under argon, gradually warming up to room temperature. The volatiles were removed *in vacuo*, and to the remaining oil was added EtOAc (10 mL). The solution was washed with H_2O (3 × 10 mL), brine (3 × 10 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 2:3) afforded a 1:3 diastereoisomeric mixture of impure ester **220** (0.03 g, <8%) as a colourless oil; diagnostic peaks are quoted: δ_H (300 MHz, $CDCl_3$) 9.81 (0.75H, s) and 9.78 (0.25H, s, CH₂C*H*O), 5.21 (0.75H, s) and 5.09 (0.25H, s, OC*H*O), 3.71 (0.75H, s) and 3.70 (2.25H, s, CO₂C*H₃*), 3.58-3.41 (1H, m, OCH(OMe)C*H*), 3.49 (3H, s, OCH(OC*H₃*)), 3.07-2.96 (2H, m, OHCC*H*H and O=CC*H*), 2.70-2.53 (1H, m, OHCCH*H*), 2.33-2.15 (2H, m, MeO₂CC*H₂*); δ_C (75 MHz, $CDCl_3$) 198.6, 198.5 (CH₂*C*HO), 176.8 (O=*C*OCH), 171.2 (*C*O₂Me), 107.2, 107.1 (O*C*HO), 56.8 (OCH(O*C*H₃)), 52.2 (CO₂*C*H₃), 40.7 (O=C*C*H), 39.6, 37.7 (OHC*C*H₂), 37.7, 35.7 (OCH(OMe)*C*H), 31.7, 30.2 (MeO₂C*C*H₂); *m/z* (EI) 215 (M⁺−Me, 8%), 197 (28), 184 (63), 169 (34), 156 (68), 140 (30), 126 (55), 111 (55), 97 (100).

(3a*R*,7a*S*)-5,5-Diethoxyhexahydroisobenzofuran-1(3*H*)-one (225)[76]

To a stirring solution of menthyloxy-furanone **203** (0.15 g, 0.47 mmol) in EtOH (10 mL) at 0 °C was added NaBH$_4$ (0.12 g, 3.0 mmol) slowly, followed by the dropwise addition of an ethanolic solution of KOH (1 M, 0.8 mL, 0.8 mmol). The temperature was maintained at 0 °C for 3 h then the reaction was warmed to room temperature and acidified to pH 3 with 2 M HCl. Dilution with H$_2$O (10 mL) was followed by extractions with DCM (3 × 20 mL), and the combined organic extracts were stirred at room temperature for 60 h. After concentration, the crude product was dissolved in DCM (50 mL), washed with brine (3 × 40 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→3:17) afforded diethyl acetal **225** (0.04 g, 39%) as a colourless oil; δ_H (300 MHz, CDCl$_3$) 4.22 (1H, dd, *J* 8.9, 4.6) and 3.97 (1H, d, *J* 8.9, OC*H$_2$*CH), 3.48 (2H, q, *J* 7.2) and 3.41 (2H, q, *J* 7.2, C(OC*H$_2$*Me)$_2$), 2.73-2.58 (2H, m, O=CC*H* and OCH$_2$C*H*CH$_2$), 2.20-2.05 (2H, m, O=CCHCH$_2$C*H$_2$*), 1.95-1.84 (1H, m) and 1.84-1.73 (1H, m, OCH$_2$CHC*H$_2$*), 1.33 (1H, dt, *J* 13.9, 3.5) and 1.30-1.23 (1H, m, O=CCHC*H$_2$*), 1.18 (3H, t, *J* 7.2) and 1.15 (3H, t, *J* 7.2, C(OCH$_2$C*H$_3$*)$_2$); δ_C (75 MHz, CDCl$_3$) 177.9 (C=O), 98.9 (*C*(OEt)$_2$), 71.2 (O*C*H$_2$CH), 55.3, 55.2 (C(O*C*H$_2$Me)$_2$), 39.0 (O=C*C*H), 34.4 (O*C*H$_2$CH), 34.2 (O=CCHCH$_2$*C*H$_2$), 29.4 (OCH$_2$CH*C*H$_2$), 19.9 (O=CCH*C*H$_2$), 15.5, 15.4 ((OCH$_2$*C*H$_3$)$_2$); *m/z* (CI+) 228 (MH$^+$, 0.4%), 183 (47), 155 (43), 85 (100).

Treatment of menthyloxy-furanone 203 with NaOMe and NaBH$_4$:
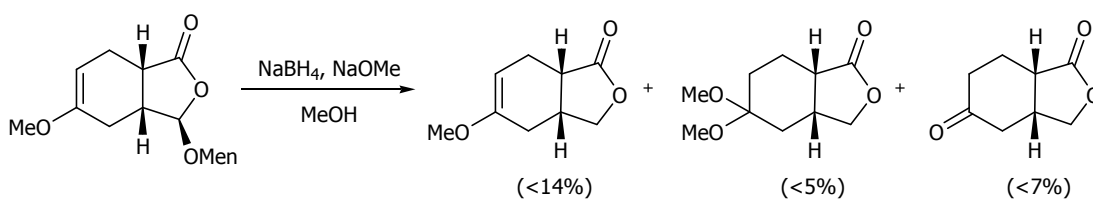
To a stirring solution of menthyloxy-furanone **203** (0.20 g, 0.62 mmol) in MeOH (12 mL) at 0 °C was added NaBH$_4$ (0.031 g, 0.81 mmol) slowly, followed by the dropwise addition of a solution of NaOMe [prepared by addition of Na (0.02 g, 0.8 mmol) to

MeOH (5 mL)]. The temperature was maintained at 0 °C for 10 min then the reaction was allowed to warm to room temperature, and stirred for 80 min before neutralisation with pH 7 KH_2PO_4/KOH buffer. After removal of the organic volatiles, EtOAc (25 mL) was added to the mixture and the organic phase was separated. Following two further extractions with EtOAc (2 × 25 mL), the combined organic extracts were dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:9→1:4) afforded impure dementhylated furanone **224** (0.02 g, <14%), dimethyl acetal **226** (0.006 g, <5%) and ketone **227** (0.007 g, <7%) as colourless oils.

5-Methoxy-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one

See below (**229**) for characterisation.

(3a*R*,7a*S*)-Hexahydro-5,5-dimethoxyisobenzofuran-1(3*H*)-one (226)

δ_H (300 MHz, $CDCl_3$) 4.23 (1H, dd, *J* 8.8, 4.6) and 3.98 (1H, d, *J* 8.9, OC*H*$_2$CH), 3.19 (3H, s) and 3.16 (3H, s, C(OC*H*$_3$)$_2$), 2.72-2.56 (2H, m, O=CC*H* and OCH$_2$C*H*), 2.20-2.13 (1H, m) and 2.13-2.07 (1H, m, (MeO)$_2$CC*H*$_2$CH$_2$), 1.95-1.84 (1H, m) and 1.84-1.71 (1H, m, OCH$_2$CHC*H*$_2$), 1.37-1.29 (2H, m, O=CCHC*H*$_2$); δ_C (75 MHz, $CDCl_3$) 177.9 (C=O), 99.0 (*C*(OMe)$_2$), 71.2 (O*C*H$_2$CH), 47.8, 47.6 (C(O*C*H$_3$)$_2$), 38.0 (O=C*C*H), 34.3 (OCH$_2$*C*H), 33.2 ((MeO)$_2$C*C*H$_2$CH$_2$), 28.4 (OCH$_2$CH*C*H$_2$), 19.8 (O=CCH*C*H$_2$); *m/z* (CI+) 200 (MH$^+$, 2%), 169 (17), 85 (100).

(3a*R*,7a*S*)-Tetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione (227)

δ_H (300 MHz, $CDCl_3$) 4.42 (1H, dd, *J* 9.6, 5.9) and 4.01 (1H, dd, *J* 9.6, 2.7, OC*H*$_2$), 3.11-2.98 (1H, m) and 2.97-2.87 (1H, m, O=CC*H* and OCH$_2$C*H*), 2.57 (1H, dd, *J* 15.3, 6.2, OCH$_2$CHC*H*H), 2.46-2.29 (4H, m, O=CCHC*H*HC*H*$_2$ and OCH$_2$CHC*H*H), 2.25-2.11 (1H, m, O=CCHC*H*H); δ_C (75 MHz, $CDCl_3$) 208.8 (O=*C*CH$_2$), 177.9 (O*C*=O), 71.6 (O*C*H$_2$), 41.2 (O=C*C*H), 38.2 (OCH$_2$CH*C*H$_2$), 37.3 (O=CCHCH$_2$*C*H$_2$), 35.8 (OCH$_2$*C*H), 22.8 (O=CCH*C*H$_2$); *m/z* (CI+) 155 (MH$^+$, 64%), 127 (9), 85 (100).

Furan-2(5*H*)-one (228)[78]
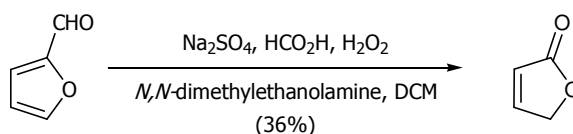
A 500 mL 3-necked flask equipped with a glass stopper, reflux condenser and a pressure equalising dropping funnel was successively charged with furfural (20.7 mL, 0.25 mol), DCM (100 mL), Na_2SO_4 (10.0 g, 70 mmol) and *N,N*-dimethylethanolamine (8.5 mL, 86 mmol). Subsequent addition of HCO_2H (18.9 mL, 0.50 mol) dropwise, followed by addition of H_2O_2 (30% aqueous, 5 mL, 0.05 mmol) in one portion led to an exothermic refluxing reaction within 5 min. The suspension was vigorously stirred and stayed exothermic while the remaining H_2O_2 (30% aqueous, 40.1 mL, 0.39 mol) was added at a rate of 10 mL/h *via* a syringe pump. After 16 h, the organic phase was separated and the aqueous phase extracted with DCM (2 × 10 mL). The combined organic extracts were washed with saturated sodium sulfite (3 × 10 mL) and after a negative H_2O_2 test, was dried ($MgSO_4$). Concentration and distillation of the crude material through a 10 cm Vigreux column afforded the furanone (9.83 g) as a pale yellow oil; b.p. 56-58 °C/2 mmHg [lit.[78] 85 °C/13 mmHg]. Redistillation removed the remaining traces of high boiling impurities to afford the pure furanone **228** (7.58 g, 36%) as a colourless oil; b.p. 64-65 °C/2 mmHg [lit.[78] 79-81 °C/9mmHg]; v_{max}/cm^{-1} (film) 1776 (C=O), 1742; δ_H (300 MHz, CDCl$_3$) 7.58 (1H, dt, *J* 5.9, 1.6, OCH$_2$C*H*), 6.16 (1H, dt, *J* 5.6, 2.1, O=CCH), 4.92-4.88 (2H, m, OCH$_2$); δ_C (75 MHz, CDCl$_3$) 173.7 (C=O), 152.8 (OCH$_2$CH), 121.6 (O=C*C*H), 72.1 (OCH$_2$); *m/z* (CI+) 85 (MH$^+$, 100%); HRMS (CI+) calcd for $C_4H_5O_2$ (MH$^+$) 85.0290, found 85.0289.

### *Cis*-5-methoxy-3a,4,7,7a-tetrahydro-(3*H*)-isobenzofuran-1-one (229)

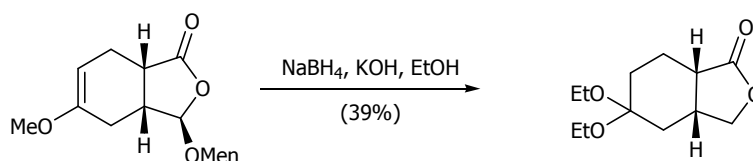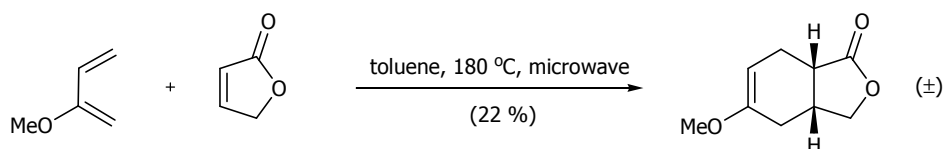

A stirring solution of furanone **228** (0.20 g, 2.4 mmol) and diene **202** (0.40 g, 4.8 mmol) in toluene (1 mL) was treated with microwave radiation at 180 °C for 1 h. Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→3:17) provided adduct **229** (0.09 g, 22%) as a colourless oil; v_{max}/cm^{-1} (film) 2908, 2850 (CH), 1754 (O=C), 1672 (C=C); δ_H (400 MHz, CDCl$_3$) 4.59 (1H, br s, C=CH), 4.32-4.28 (1H, m) and 4.01-3.96 (1H, m, OCH$_2$), 3.46 (3H, s, OCH$_3$), 2.78-2.70 (2H, m, O=CCH and OCH$_2$C*H*), 2.58-2.50 (1H, m) and 2.42-2.30 (1H, m, (MeO)C=CHC*H*$_2$), 2.23 (1H, dd, *J* 16.6, 7.4) and 1.94 (1H, dd, *J* 15.6, 5.7, (MeO)CC*H*$_2$); δ_C (75 MHz, CDCl$_3$) 179.1 (C=O), 153.5 ((MeO)C=*C*H), 90.7 ((MeO)*C*=CH), 72.5 (OCH$_2$), 54.1

(OCH_3), 37.6 (O=CCH), 33.4 (OCH$_2$$C$H), 28.1 ((MeO)C$CH_2$), 21.5 ((MeO)C=CH$CH_2$); *m/z* (CI+) 169 (MH$^+$, 53%), 91 (100), 85 (18); HRMS (CI+) calcd for C$_9$H$_{13}$O$_3$ (MH$^+$) 169.0865, found 169.0863.

Methyl-*cis*-5-oxo-4-(2-oxoethyl)tetrahydrofuran-3-yl-acetate (230)
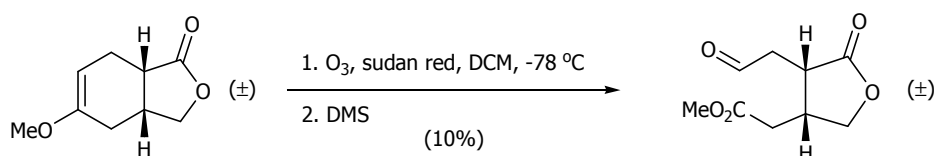
Through a solution of enol ether **229** (0.05 g, 0.30 mmol) and Sudan Red (0.01% in MeOH w/v, 0.05 mL) in DCM (2 mL) was bubbled ozone in O$_2$ at −78 °C. When the solution was decolourised, argon was flushed through the system for 2 min. DMS (0.04 mL, 0.6 mmol) was added and the mixture maintained at −78 °C for 90 min, before warming to room temperature. After 16 h, DCM and other volatiles were removed *in vacuo*, and to the remaining oil was added EtOAc (5 mL). The solution was washed with H$_2$O (3 × 5 mL), brine (3 × 5 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→3:7) afforded cleaved product **230** (0.06 g, 10%) as a colourless oil; δ$_H$ (400 MHz, CDCl$_3$) 9.84 (1H, s, CHO), 4.42 (1H, dd, *J* 9.6, 5.7) and 4.21 (1H, dd, *J* 9.7, 1.8, OCH_2CH), 3.70 (3H, s, OCH$_3$), 3.29-3.16 (2H, m, OCH$_2$CH and O=CCH), 3.04 (1H, dd, *J* 19.3, 4.7) and 2.68 (1H, dd, *J* 19.2, 9.1, OHCCH_2), 2.32-2.24 (2H, m, MeO$_2$CCH_2); *m/z* (EI) 199 (MH$^+$, 3%), 185 (10), 140 (16), 126 (19), 112 (20), 99 (100).

(3*R*,3a*R*,7a*S*)-4-(L-Menthoxy)-tetrahydroisobenzofuran-1,5(3*H*,6*H*)-dione (236)
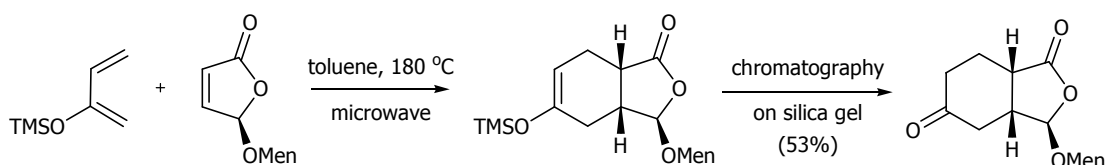
A stirring solution of furanone **197** (0.15 g, 0.63 mmol) and diene **198** (0.18 g, 1.3 mmol) in dry toluene (1 mL) was treated with microwave radiation while heated at 180 °C for 2 h. Concentration gave the crude adduct **199** (0.32 g) as a pale yellow viscous oil. Purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→3:17) provided a 17:3 mixture of ketone **236** and its C3-epimer (0.10 g, 53%), as a white solid; m.p. 90-92°C

[lit.[67] 93.2-93.4 °C]; $[\alpha]_D^{20}$ −127.8 (CHCl$_3$, c 1.0); v_{max}/cm^{-1} (KBr) 2955, 2926 (CH), 1773, 1724 (C=O); δ_H (300 MHz, CDCl$_3$) 5.27 (0.85H, s) and 5.15 (0.15H, s, OC*H*O), 3.49 (0.85H, td, 10.7, 4.0) and 3.27 (0.15H, td, *J* 10.4, 4.0, OC*H*CH$_2$), 3.19-3.06 (1H, m, OCH(OMen)C*H*), 2.89-2.73 (1H, m, O=CC*H*), 2.54 (1H, dd, *J* 15.5, 7.0, OCH(OMen)CHC*H*H), 2.42-1.89 (7H, m, O=CCHC*H$_2$*C*H$_2$*, OCH(OMen)CHCH*H*, OCHC*H*H and C*H*Me$_2$), 1.70-1.55 (2H, m, CH(Me)C*H*HCH$_2$ and ^{i}PrCHC*H*H), 1.45-1.26 (1H, m, CH$_2$C*H*Me), 1.26-1.10 (1H, m, C*H*^{i}Pr), 1.04-0.77 (3H, m, OCHCH*H*, CH(Me)CH*H*CH$_2$ and ^{i}PrCHCH*H*), 0.90 (3H, d, *J* 6.4, CH$_2$CH(C*H$_3$*)), 0.83 (3H, d, *J* 7.0) and 0.73 (3H, d, *J* 7.0, CH(C*H$_3$*)$_2$); δ_C (75 MHz, CDCl$_3$) 208.4 (O=*C*CH$_2$), 177.1 (O=*C*CH), 108.0, 102.7 (O*C*HO), 82.3, 76.9 (O*C*HCH$_2$), 48.2, 47.7 (*C*H^{i}Pr), 42.6 (OCH(OMen)*C*H), 39.6 (OCH*C*H$_2$), 39.5 (CH(OMen)CH*C*H$_2$), 37.4 (O=CCHCH$_2$*C*H$_2$), 37.0 (O=C*C*H), 34.2, 34.1 (CH(Me)*C*H$_2$CH$_2$), 31.6, 31.3 (*C*HMe$_2$), 25.8, 25.5 (CH$_2$*C*HMe), 23.2, 23.0 (^{i}PrCH*C*H$_2$), 22.4 (O=CCH*C*H$_2$), 22.2, 20.9 (CH(*C*H$_3$)$_2$), 16.2, 15.5 (CH$_2$CH(*C*H$_3$)); *m/z* (CI+) 309 (MH$^+$, 9%), 171 (43), 153 (100), 138 (95), 125 (41), 96 (73); HRMS (CI+) calcd for C$_{18}$H$_{29}$O$_4$ (MH$^+$) 309.2066, found 309.2057.

1-(4-Toluenesulfonyl)pyrrolidin-2-one (241)
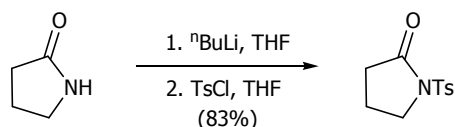
2-Pyrrolidinone (9.0 mL, 118 mmol) in THF (60 mL) was added slowly to a solution of ^{n}BuLi (1.6 M in hexanes, 79.3 mL, 127 mmol) in THF (30 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 90 min then a solution of TsCl (27.3 g, 143 mmol) in THF (60 mL) was added *via* cannula, and the temperature was maintained at −78 °C for a further 30 min before warming to room temperature. After 16 h, the reaction was quenched by addition of saturated NH$_4$Cl (300 mL) and the product was extracted with EtOAc (3 × 300 mL), washed with brine (2 × 500 mL) and dried (MgSO$_4$). Concentration and recrystallisation from EtOAc afforded sulfonamide **241** (23.3 g, 83%) as peach coloured needles; m.p. 145-147 °C [lit.[164] 149 °C]; v_{max}/cm^{-1} (KBr) 2914 (CH), 1730 (C=O), 1593 (C=C), 1356, 1169 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.90 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.32-7.29 (2H, m, 2 × S-*m*CH), 3.86 (2H, t, *J* 7.1, NCH$_2$), 2.42-2.38 (2H, m, O=CCH$_2$), 2.41 (CH$_3$), 2.08-2.01 (2H, m, NCH$_2$C*H$_2$*); δ_C (75 MHz, CDCl$_3$)

173.4 (C=O), 145.2, 135.2 (2 × aromatic C), 129.7, 128.1 (4 × aromatic CH), 47.3 (N*C*H$_2$), 32.2 (O=C*C*H$_2$), 21.7 (CH$_3$), 18.2 (NCH$_2$*C*H$_2$); *m/z* (CI+) 240 (MH$^+$, 100%); HRMS (CI+) calcd for C$_{11}$H$_{14}$NO$_3$S (MH$^+$) 240.0689, found 240.0678; Elemental analysis: calcd for C$_{11}$H$_{13}$NO$_3$S (MH$^+$) C: 55.2, H: 5.5, N: 5.9. Found C: 55.1, H: 5.4, N: 5.7.

3-(Phenylselenyl)-1-(4-toluenesulfonyl)pyrrolidin-2-one (242)
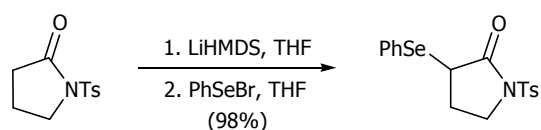
A solution of 1-(4-toluenesulfonyl)pyrrolidin-2-one (5.00 g, 21 mmol) in THF (50 mL) was treated with LiHMDS (20% in hexanes, 40 mL, 42 mmol) and the mixture was stirred at −78 °C for 1 h. A solution of PhSeBr (6.51 g, 28 mmol) in THF (50 mL) was added *via* cannula, and the reaction mixture was maintained at −78 °C for a further 30 min, and then warmed to room temperature. After 2.5 h the reaction was quenched by addition of 1 M HCl (100 mL) and the product was extracted with EtOAc (3 × 100 mL), washed with saturated NaHCO$_3$ (100 mL), brine (100 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 3:7→2:3) afforded the title compound **242**[29] (8.11 g, 98%) as a viscous pale brown oil; δ$_H$ (300 MHz, CDCl$_3$) 7.90 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.46-7.37 (2H, m), 7.37-7.25 (3H, m) and 7.24-7.12 (2H, m, 7 × ArH), 3.88-3.74 (2H, m, C*H*SePh and NC*H*H), 3.63-3.48 (1H, m, NCH*H*), 2.57-2.40 (1H, m) and 2.11-1.96 (1H, m, NCH$_2$C*H*$_2$), 2.45 (3H, s, CH$_3$); δ$_C$ (75 MHz, CDCl$_3$) 171.6 (C=O), 145.3 (aromatic C), 136.1 (2 × aromatic CH), 134.7 (aromatic C), 129.7, 129.3, 129.1, 128.3 (7 × aromatic CH), 126.0 (aromatic C), 45.7 (NCH$_2$), 40.7 (*C*HSePh), 26.3 (NCH$_2$*C*H$_2$), 21.7 (CH$_3$); *m/z* (CI+) 396 (MH$^+$, 100%), 240 (31); HRMS (CI+) calcd for C$_{17}$H$_{18}$NO$_3$SSe (MH$^+$) 396.0173, found 396.0173.

3-Bromo-1-(4-toluenesulfonyl)pyrrolidin-2-one (243)
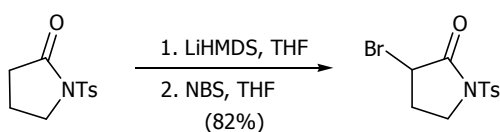
To a stirring solution of 1-(4-toluenesulfonyl)pyrrolidin-2-one (5.00 g, 21 mmol) in THF (100 mL) at −78 °C was added LiHMDS (20% in hexanes, 39.4 mL, 42 mmol). After 1 h, a pre-cooled (−78 °C) solution of NBS (4.46 g, 25 mmol) in THF (10 mL) was added *via* cannula, and the suspension was stirred for 3 h at the same temperature. Saturated NH_4Cl (100 mL) was added and the reaction was warmed to room temperature. After dilution with brine (100 mL), the product was extracted with EtOAc (3 × 100 mL), washed with brine (2 × 200 mL), and then dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 3:7) furnished the monobrominated product **243** (5.45 g, 82%) as a white powder; m.p. 119.5-120 °C; v_{max}/cm^{-1} (KBr) 2907 (CH), 1738 (C=O), 1593 (C=C), 1358, 1173 (SO_2); δ_H (300 MHz, CDCl$_3$) 7.91 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.34 (2H, d, *J* 8.3, 2 × S-*m*CH), 4.33 (1H, dd, *J* 6.7, 2.7, CHBr), 4.04-3.83 (2H, m, NCH$_2$), 2.60 (1H, td, *J* 8.0, 6.7) and 2.28 (1H, ddt, *J* 14.4, 6.2, 2.7, NCH$_2$C*H$_2$*), 2.44 (3H, s, CH$_3$); δ_C (75 MHz, CDCl$_3$) 168.5 (C=O), 145.7, 133.9 (2 × aromatic C), 129.8, 128.2 (4 × aromatic CH), 45.4 (NCH$_2$), 43.4 (CHBr), 29.8 (NCH$_2$C*H$_2$*), 21.8 (CH$_3$); *m/z* (CI+) 320, 318 (MH$^+$, 33/31%), 240 (100), 155 (41), 125 (27), 107 (17); HRMS (CI+) calcd for C$_{11}$H$_{13}$BrNO$_3$S 317.9800, found 317.9788; Elemental analysis: calcd for C$_{11}$H$_{12}$^{79}BrNO$_3$S C: 41.5, H: 3.8, N: 4.4. Found C: 41.6, H: 3.8, N: 4.2.

3,3-Dibromo-1-(4-toluenesulfonyl)-pyrrolidin-2-one

Dibrominated product isolated in 7% yield when 1.1 eq of LiHMDS was used; m.p. 188-189 °C; v_{max}/cm^{-1} (KBr) 1734 (C=O), 1593 (C=C); δ_H (300 MHz, CDCl$_3$) 7.91 (2H, d, *J* 8.0, 2 × S-*o*CH), 7.36 (2H, d, *J* 8.0, 2 × S-*m*CH), 3.85 (2H, t, *J* 6.0, NCH$_2$), 3.00 (2H, t, *J* 6.0, NCH$_2$C*H$_2$*), 2.45 (3H, s, CH$_3$); δ_C (75 MHz, CDCl$_3$) 164.7 (C=O), 146.2, 133.0 (2 × aromatic C), 129.9, 128.3 (4 × aromatic CH), 53.6 (CBr$_2$), 44.7 (NCH$_2$), 42.8 (NCH$_2$*CH$_2$*), 21.8 (CH$_3$) *m/z* (CI+) 400, 398, 396 (MH$^+$, 19/39/19%), 320, 318 (84/85), 240 (100), 155 (86). 123 (31); HRMS (CI+) calcd for C$_{11}$H$_{12}$^{79}Br$_2$NO$_3$S (MH$^+$) 395.8905, found 395.8895; Elemental analysis: calcd for C$_{11}$H$_{11}$Br$_2$NO$_3$S C: 33.3, H: 2.8, N: 3.5. Found C: 33.3, H: 2.8, N: 3.3.
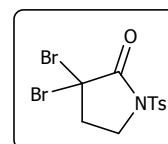
1-(4-Toluenesulfonyl)-1*H*-pyrrol-2(5*H*)-one (239)
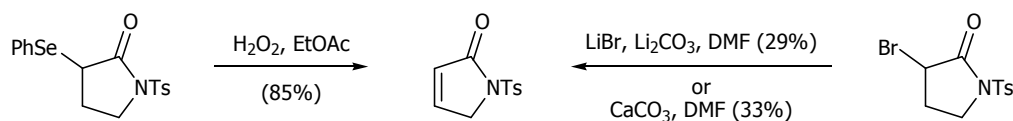
From oxidation of 3-(phenylselenyl)-1-(4-toluenesulfonyl)pyrrolidin-2-one:

H_2O_2 (30% aqueous, 5.8 mL, 51 mmol) was added to a solution of 3-(phenylselenyl)-1-(4-toluenesulfonyl)pyrrolidin-2-one (8.04 g, 20 mmol) in EtOAc (100 mL) at 0 °C. After 90 min, the reaction was warmed to room temperature and diluted with EtOAc (100 mL), washed with H_2O (100 mL), saturated $NaHCO_3$ (2 × 250 mL) and brine (250 mL), and then dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 2:3) produced the desired product **239** (4.10 g, 85%) as a white solid.

From dehydrobromination of 3-bromo-1-(4-toluenesulfonyl)pyrrolidin-2-one with LiBr, Li_2CO_3:

A stirring mixture of 3-bromo-1-(4-toluenesulfonyl)pyrrolidin-2-one (1.06 g, 3.3 mmol), LiBr (0.35 g, 4.0 mmol) and Li_2CO_3 (0.29 g, 4.0 mmol) in DMF (25 mL) was heated at reflux for 3 h. The mixture was cooled to room temperature and after addition of H_2O (350 mL), was extracted with EtOAc (3 × 90 mL), which was washed with brine (2 × 90 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:9→3:7) furnished the dehydrobrominated product **239** (0.24 g, 29%) as a white solid.

From dehydrobromination of 3-bromo-1-(4-toluenesulfonyl)pyrrolidin-2-one with $CaCO_3$:

A stirring mixture of 3-bromo-1-(4-toluenesulfonyl)-pyrrolidin-2-one (0.50 g, 1.6 mmol) and $CaCO_3$ (1.10 g, 11.0 mmol) in DMF (9 mL) was heated at reflux for 20 h. The mixture was cooled to room temperature and after addition of H_2O (30 mL), was extracted with EtOAc (4 × 10 mL), which was washed with brine (2 × 20 mL) and dried ($MgSO_4$). Subsequent concentration and purification by flash chromatography (SiO_2; EtOAc:PS 2:3) furnished the dehydrobrominated product **239** (0.13 g, 33%) as a white solid.

m.p. 159-160 °C [lit.[29] 159-160 °C]; ν_{max}/cm^{-1} (KBr) 1717 (C=O), 1597 (C=C), 1354, 1175 (SO$_2$); δ_H (300 MHz, CDCl$_3$) 7.93 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.32 (2H, d, *J* 8.3, 2 × S-*m*CH), 7.24 (1H, dt, *J* 6.2, 1.9, NCH$_2$C*H*), 6.05 (1H, dt, *J* 6.2, 1.9, O=CCH), 4.48 (2H, t, *J* 1.9, NCH$_2$), 2.41 (3H, s, CH$_3$); δ_C (75 MHz, CDCl$_3$) 168.4 (C=O), 146.7 (NCH$_2$*C*H), 145.2, 135.3 (2 × aromatic C), 129.8, 128.0 (4 × aromatic CH), 127.1 (O=C*C*H), 52.4 (NCH$_2$), 21.7 (CH$_3$); *m/z* (CI+) 238 (MH$^+$, 100%), 173 (31), 155 (26), 107 (91), 91 (26), 87 (69); HRMS (CI+) calcd for C$_{11}$H$_{12}$NO$_3$S (MH$^+$) requires 238.0538, found 238.0540.

Typical procedure for microwave preparations of 5-methoxy-2-(4-toluenesulfonyl)isoindol-1-ones:
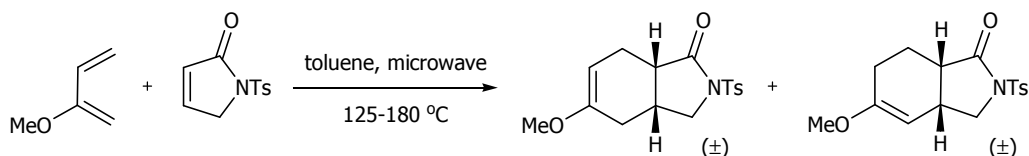
5-Methoxy-2-(4-toluenesulfonyl)-3a,4,7,7a-tetrahydro-(3*H*)-isoindol-1-one (244)

A solution of 1-(4-toluenesulfonyl)-1*H*-pyrrol-2(5*H*)-one (0.20 g, 0.84 mmol) and 2-methoxy-1,3,butadiene (0.21 g, 2.5 mmol) in toluene (1 mL) was treated with microwave radiation at 125 °C for 4 h. Concentration and purification by silica chromatography (SiO$_2$; EtOAc:PS 1:19→1:4) afforded the lactam starting material (0.07 g, 35%) and the desired adduct **244** (0.04g, 14%) as a colourless oil; ν_{max}/cm^{-1} (film) 2915, 2848 (CH), 1740 (C=O), 1677 (C=C), 1362, 1152 (SO$_2$); δ_H (300 MHz, CDCl$_3$) 7.88 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.31 (2H, d, *J* 8.3, 2 × S-*m*CH), 4.49 (1H, br t, *J* 3.5, C=CH), 3.89 (1H, dd, *J* 10.2, 5.1) and 3.59 (1H, d, *J* 10.2, NCH$_2$), 3.41 (3H, s, OCH$_3$), 2.71-2.56 (2H, m, NCH$_2$C*H* and O=CCH), 2.51-2.34 (1H, m, O=CCHC*H*H), 2.41 (3H, s, ArCH$_3$), 2.32-2.09 (2H, m, O=CCHCH*H* and (MeO)CC*H*H), 1.85-1.64 (1H, m, (MeO)CCH*H*); δ_C (75 MHz, CDCl$_3$) 174.5 (C=O), 152.9 (HC=*C*(OMe)), 145.1, 135.2 (2 × aromatic C), 129.7, 127.9 (4 × aromatic CH), 90.6 (C=*C*H), 54.0 (OCH$_3$), 51.9 (NCH$_2$), 41.2 (O=C*C*H), 30.1 (NCH$_2$*C*H), 28.1 ((OMe)C*C*H$_2$), 21.7 (ArCH$_3$), 20.7 (O=CCH*C*H$_2$); *m/z* (CI+) 322 (MH$^+$, 100%), 166 (30); HRMS (CI+) calcd for C$_{16}$H$_{20}$NO$_4$S (MH$^+$) 322.1113, found 322.1107.

5-Methoxy-2-(4-toluenesulfonyl)-3a,6,7,7a-tetrahydro-(3*H*)-isoindol-1-one (245)

1-(4-Toluenesulfonyl)-1*H*-pyrrol-2(5*H*)-one (1.0 g, 4.2 mmol) and 2-methoxy-1,3-butadiene (0.71 g, 8.4 mmol) at 180 °C for 2 h provided isomerised adduct **245** (0.47 g, 35%) as a white solid; m.p. 120-125 °C; v_{max}/cm^{-1} (KBr) 2930, 2907 (CH), 1740 (C=O), 1665, 1597 (C=C) 1362, 1165 (SO$_2$); δ_H (300 MHz, CDCl$_3$) 7.85 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.29 (2H, d, *J* 8.3, 2 × S-*m*CH), 4.36 (1H, br d, *J* 2.7, C=CH), 3.94 (1H, dd, *J* 9.9, 6.4) and 3.60 (1H, dd, *J* 9.9, 2.4, NCH$_2$), 3.41 (3H, s, OCH$_3$), 3.07-2.96 (1H, m, NCH$_2$C*H*), 2.66 (1H, dt, *J* 4.8, 2.4, O=CCH), 2.41 (3H, s, ArCH$_3$), 2.05-1.93 (1H, m) and 1.73-1.58 (1H, m, O=CCHC*H*$_2$), 1.93-1.84 (2H, m, (MeO)CC*H*$_2$); δ_C (75 MHz, CDCl$_3$) 174.2 (C=O), 158.2 (*C*(OMe)), 145.0, 135.3 (2 × aromatic C), 129.5, 127.8 (4 × aromatic CH), 92.4 (C=*C*H), 54.0 (OCH$_3$), 53.1 (NCH$_2$), 41.8 (O=C*C*H), 31.8 (NCH$_2$*C*H), 23.8 ((MeO)C*C*H$_2$), 21.7 (ArCH$_3$), 20.2 (O=CCH*C*H$_2$); *m/z* (CI+) 322 (MH$^+$, 69%), 307 (20), 289 (11), 219 (15), 199 (35), 166 (28), 154 (100); HRMS (CI+) calcd for C$_{16}$H$_{20}$NO$_4$S (MH$^+$) 322.1113, found 322.1106.

Typical procedure for ozonolysis of 5-methoxy-2-(4-toluenesulfonyl)isoindol-1-ones:

Methyl *cis*-[5-oxo-4-(2-oxoethyl)-1-(4-toluenesulfonyl)pyrrolidin-3-yl]-acetate (246)
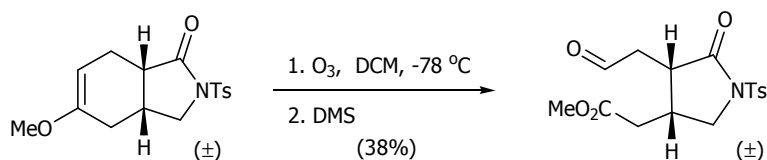
Through a solution of methoxy-alkene **244** (0.04 g, 0.12 mmol) in DCM (3 mL) was bubbled ozone in O$_2$ at −78 °C. When the solution became blue, oxygen was passed through the mixture until it was colourless. DMS (0.02 mL, 0.3 mmol) was added and the solution stirred for 16 h under argon, gradually warming up to room temperature. The volatiles were removed *in vacuo*, and the remaining oil was diluted with EtOAc (5 mL). The solution was washed with H$_2$O (2 × 5 mL), brine (2 × 5 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:4→2:3) afforded ozonolysed product **246** (0.016 g, 38%) as a colourless oil; δ_H (300 MHz, CDCl$_3$) 9.72 (1H, s, CHO), 7.88 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.33 (2H, d, *J* 8.3, 2 × S-*m*CH), 3.93 (1H, dd, *J* 10.4, 6.2) and 3.80 (1H, dd, *J* 10.4, 2.1, NCH$_2$), 3.67 (3H, s, OCH$_3$), 3.16 (1H, td, *J* 8.5, 4.8, O=CCH), 3.06-2.94 (1H, m, NCH$_2$C*H*), 2.88 (1H, dd, *J* 19.0, 4.8) and 2.55 (1H, dd, *J* 19.0, 8.5, OHCC*H*$_2$), 2.43 (3H, s, ArCH$_3$), 2.23 (1H, dd, *J*

16.3, 5.6) and 2.12 (1H, dd, *J* 16.3, 9.1, MeO$_2$CC*H$_2$*); δ_C (75 MHz, CDCl$_3$) 198.6 (CHO), 172.9 (NC=O), 171.4 (*C*O$_2$Me), 145.5, 134.7 (2 × aromatic C), 129.8, 128.1 (4 × aromatic CH), 52.1 (CO$_2$*C*H$_3$), 50.8 (NCH$_2$), 41.1 (O=C*C*H), 39.7 (OHC*C*H$_2$), 33.1 (MeO$_2$C*C*H$_2$), 31.3 (NCH$_2$*C*H), 21.7 (Ar*C*H$_3$); *m/z* (ESI+) 376 (MNa$^+$, 100%); HRMS (ESI+) calcd for C$_{16}$H$_{19}$NO$_6$SNa (MH$^+$) 376.0831, found 376.0837

Methyl 3-(4-formyl-2-oxo-1-(4-toluenesulfonyl)-pyrrolidin-3-yl)propanoate (247)

Methoxy-diene **245** (0.47 g, 1.4 mmol) provided cleaved product **247** (0.31 g, 60%) as a pale yellow oil; v_{max}/cm^{-1} (KBr) 2955 (CH), 1730 (C=O), 1597, 1358, 1168 (SO$_2$); δ_H (300 MHz, CDCl$_3$) 9.72 (1H, s, CHO), 7.90 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.34 (2H, d, *J* 8.3, 2 × S-*m*CH), 4.22 (1H, dd, *J* 10.8, 2.7) and 3.86 (1H, dd, *J* 10.8, 6.4, NCH$_2$), 3.64 (3H, s, OCH$_3$), 3.35-3.26 (1H, m, NCH$_2$C*H*), 2.96 (1H, dd, *J* 15.5, 8.0, NC(=O)CH), 2.52-2.45 (2H, m, MeO$_2$CC*H$_2$*), 2.43 (3H, s, ArCH$_3$), 1.99-1.75 (2H, m, MeO$_2$CCH$_2$C*H$_2$*); δ_C (75 MHz, CDCl$_3$) 198.4 (CHO), 172.9 (NC=O), 172.0 (*C*O$_2$Me), 145.6, 134.8 (2 × aromatic C), 129.8, 128.1 (4 × aromatic CH), 51.8 (OCH$_3$), 46.3 (NCH$_2$*C*H), 44.6 (NCH$_2$), 43.9 (NC(=O)*C*H), 31.0 (MeO$_2$C*C*H$_2$), 21.7 (Ar*C*H$_3$), 21.3 (MeO$_2$CC*H$_2$*); *m/z* (CI+) 354 (MH$^+$, 12%), 322 (13), 200 (12), 168 (100), 141 (16), 125 (79), 93 (43); HRMS (CI+) calcd for C$_{16}$H$_{20}$NO$_6$S (MH$^+$) 354.1011, found 354.1017.
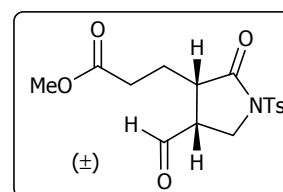
Tetrahydro-2-(4-toluenesulfonyl)-6-isoindole-1,5(*3*H,6*H*)-dione (249)
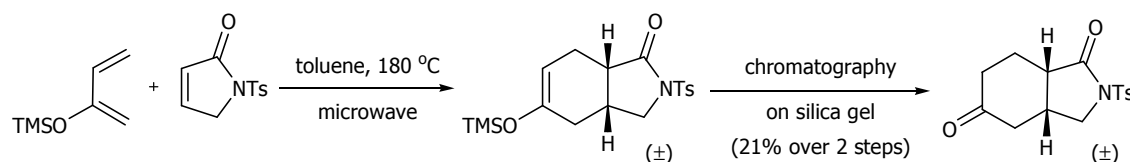
A solution of 1-(4-toluenesulfonyl)-1*H*-pyrrol-2(5*H*)-one (0.50 g, 2.1 mmol) and 2-trimethylsilyloxy-1,3-butadiene (0.60 g, 4.2 mmol) in toluene (2 mL) was treated with microwave radiation at 180 °C for 2 h. Concentration provided the crude trimethylsilyloxy-2-(4-toluenesulfonyl)-isoindol-1-one (1.07 g) as a dark brown oil. Purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→3:7) provided the desilylated analogue **249** (0.13 g, 21%) as a yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2957 (CH), 1722 (C=O), 1360, 1169 (SO$_2$); δ_H (300 MHz, CDCl$_3$) 7.91 (2H, d, *J* 8.3, 2 × S-

*o*CH), 7.35 (2H, d, *J* 8.3, 2 × S-*m*CH), 3.96 (1H, dd, *J* 10.4, 6.2) and 3.58 (1H, dd, *J* 10.4, 2.3, NCH$_2$), 2.94-2.84 (1H, m, NCH$_2$C*H*), 2.84-2.74 (1H, m, O=CCH), 2.55-2.48 (1H, m, NCH$_2$CHC*H*H), 2.44 (3H, s, CH$_3$), 2.31-2.07 (4H, m, O=CCHCH$_2$C*H*$_2$, NCH$_2$CHC*H*H and O=CCHC*H*H), 2.07-1.92 (1H, m, O=CCHCH*H*); δ$_C$ (75 MHz, CDCl$_3$) 208.8 (CH$_2$C=O), 173.3 (NC=O), 145.6, 134.8 (2 × aromatic C), 129.9, 127.9 (4 × aromatic CH), 51.2 (NCH$_2$), 41.8 (O=C*C*H), 41.5 (NCH$_2$CH*C*H$_2$), 37.2 (O=CCH *C*H$_2$CH$_2$), 32.6 (NCH$_2$*C*H), 22.6 (O=CCH*C*H$_2$), 21.7 (*C*H$_3$); *m/z* (CI+) 308 (MH$^+$, 84%), 238 (46), 193 (19), 168 (100), 154 (54), 136 (17); HRMS (CI+) calcd for C$_{15}$H$_{18}$NO$_4$S (MH$^+$) 308.0957, found 308.0962.

(*S*)-1,1-Bis(3,5-dimethylphenyl)prolinol sulfate salt (252)[93,94]
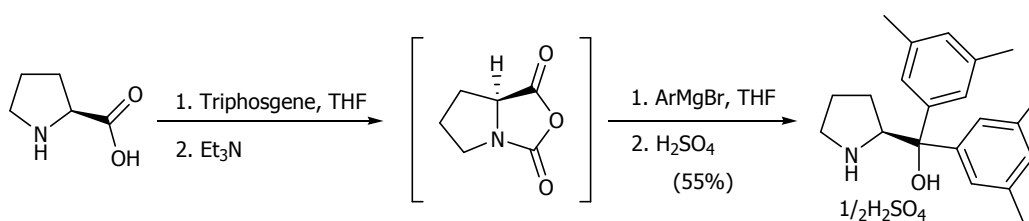
An 100 mL 3-necked flask equipped with a reflux condenser, low temperature thermometer probe and a septum was charged with (*S*)-proline (1.50 g, 13.0 mmol) and THF (15 mL). The mixture was cooled to 15-20 °C and a solution of triphosgene (1.54 g, 5.2 mmol) in THF (3 mL) was added slowly, maintaining the internal temperature below 20 °C. The septum was then quickly replaced with a glass stopper and the suspension heated to 44 °C, where the reaction became homogenous after 15 min. After heating for an additional 30 min, the reaction mixture was concentrated, re-dissolved in THF (15 mL) then cooled to 0 °C. Et$_3$N (1.8 mL, 13.0 mmol) was added over 7 min *via* syringe pump, maintaining the internal temperature below 5 °C. After 30 min, the reaction was warmed to room temperature then filtered under a flow of argon. The cake was washed with THF (5 × 5 mL) to provide a solution of the carboxyanhydride that was used immediately in the next reaction.

A 250 mL 3-necked flask fitted with a reflux condenser, pressure-equalising addition funnel and a stopper was charged with Mg turnings (1.30 g, 54 mmol) and 10 mL of a solution of 5-bromo-*m*-xylene (5.5 mL, 41 mmol) in THF (20 mL). The suspension was vigorously stirred and when it became exothermic and brown in colour, the remaining bromide was added dropwise, and then stirred for 1 h at room temperature. The glass

stopper was quickly replaced with a low temperature thermometer probe and ~1 mL of the carboxyanhydride solution was added, then the mixture was cooled to −15 °C. The remaining solution of carboxyanhydride was added dropwise at a rate that maintained the internal temperature below −10 °C. When the addition was complete, the mixture was stirred for 3 h at −15 °C, 2 h at 0 °C then at room temperature for 16 h. The reaction was quenched by its dropwise addition into a flask of 2M H_2SO_4 (26.3 mL, 53 mmol) cooled at 0 °C, maintaining the internal temperature below 20 °C. The resulting suspension was stirred at 0 °C for 1 h then filtered, washing the cake with THF (3 × 15 mL). The filtrate was concentrated, cooled at 0 °C for 1 h, and then filtered. The cake was washed with cold H_2O (2 × 3 mL) and EtOAc (3 × 4 mL) then dried to afford the prolinol sulfate salt **252** (2.58 g, 55%) as a white solid; m.p. = 251-252 °C; v_{max}/cm^{-1} (KBr) 3277 (br, OH), 1602 (C=C), 1539; δ_H (300 MHz, MeOH) 7.20 (2H, s), 7.10 (2H, s), 6.89 (2H, s, 6 × ArCH), 4.87 (3H, m, OH and NH_2^+), 4.81-4.73 (1H, m, NCH), 3.28-3.13 (2H, m, NCH_2), 2.28 (12H, s, 4 × CH_3), 2.20-1.91 (4H, m, $NCH_2CH_2CH_2$); δ_C (75 MHz, CDCl$_3$) 145.8, 145.6, 139.5, 139.2 (6 × aromatic C), 130.1, 129.9, 124.6, 124.4 (6 × aromatic CH), 78.2 (C(OH)), 68.2 (NCH$_2$), 48.7 (NCH), 27.1, 25.5 (NCH$_2$CH$_2$CH$_2$), 21.6, 21.5 (4 × CH$_3$);

(*S*)-1,1-Bis(3,5-dimethylphenyl)prolinol (253)[93,94]
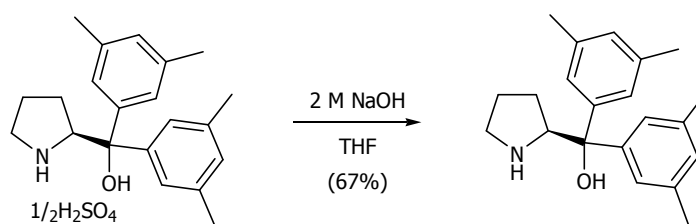
A mixture of the prolinol sulfate salt **252** (1.00 g, 2.80 mmol) and 2 M NaOH (2.8 mL, 5.6 mmol) in THF (6 mL) was vigorously stirred for 30 min then toluene (11 mL) was added and the mixture stirred for an additional 30 min. The aqueous phase was removed and the organic phase was washed with H_2O (3 mL), concentrated, re-dissolved in toluene (10 mL) then concentrated to afford a pale brown oil which crystallised at room temperature. Recrystallisation from hexane afforded the free prolinol **253** (0.58 g, 67%) as a peach coloured solid; m.p. 99-100 °C [lit.[93] 97.5-98 °C]; $[\alpha]_D^{20}$ −55.6 (MeOH, c 0.322), [lit.[93] −63.0 (MeOH, c 0.318)]; v_{max}/cm^{-1} (KBr) 3368 (br, OH), 2980 (NH), 2912, 2862 (CH), 1601 (C=C), 1454, 1387; δ_H (300 MHz, CDCl$_3$) 7.18 (2H, s), 7.12

(2H, s), 6.81 (2H, s, $6 \times$ ArCH), 4.60 (1H, br s, OH), 4.22 (1H, t, J 7.5, NCH), 3.09-2.99 (1H, m) and 2.99-2.88 (1H, m, NCH$_2$), 2.30 (6H, s) and 2.29 (6H, s, $4 \times$ CH$_3$), 1.9 (1H, br s, NH), 1.81-1.67 (2H, m) and 1.67-1.53 (2H, m, NCH$_2$C*H*$_2$C*H*$_2$); δ_C (75 MHz, CDCl$_3$) 148.3, 145.4, 137.5, 137.2 ($6 \times$ aromatic C), 128.1, 128.0 123.6, 123.3 ($6 \times$ aromatic CH), 76.9 (C(OH)), 64.5 (NCH$_2$), 46.8 (NCH), 26.3 25.6 (NCH$_2$*C*H$_2$*C*H$_2$), 21.6 ($4 \times$ CH$_3$); *m/z* (CI+) 310 (MH$^+$, 8%), 292 (52), 239 (100), 133 (45), 107 (54), 95 (24); HRMS (CI+) calcd for C$_{21}$H$_{28}$NO (MH$^+$) 310.2171, found 310.2168; Elemental analysis: calcd for C$_{21}$H$_{27}$NO C: 81.5, H: 8.8, N: 4.5. Found C: 81.1, H: 8.6, N: 4.5.

Tri-*o*-tolyboroxine (254)[85]
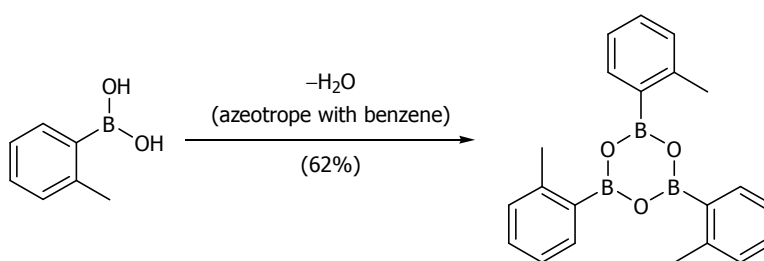
A 25 mL round bottomed flask fitted with a short path distillation kit was charged with *o*-tolylboronic acid (0.50 g, 3.7 mmol). Distillations of benzene (3 x 10 mL) from the acid afforded the crude boroxine product (0.44 g, 100%). Recrystallisation from a benzene-hexane mixture provided the pure boroxine **254** (0.27 g, 62%) as a white solid; m.p. 171-172 °C [lit.[85] 165-166 °C]; ν_{max}/cm^{-1} (KBr) 1599, 1443, 1342, 1298; δ_H (400 MHz, CDCl$_3$) 8.22 (3H, dd, J 7.5, 1.7, $3 \times$ B-*o*CH), 7.45 (3H, td, J 7.5, 1.7, $3 \times$ B-*p*CH), 7.31 (3H, td, 7.4, 1.3, $3 \times$ Me-*p*C*H*), 7.27 (3H, d, J 7.6, $3 \times$ Me-*o*C*H*), 2.82 (9H, s, $3 \times$ CH$_3$); δ_C (75 MHz, CDCl$_3$) 146.3 ($3 \times$ *C*Me), 137.2, 132.2, 130.6 ($9 \times$ aromatic CH), 130.4 ($3 \times$ BC), 125.2 ($3 \times$ aromatic CH), 23.1 ($3 \times$ CH$_3$); *m/z* (CI+) 383 (M+C$_2$H$_5$, 17%), 355 (MH$^+$, 100), 119 (15), 93 (94); HRMS (CI+) calcd for C$_{21}$H$_{22}$B$_3$O$_3$ (MH$^+$) 355.1848, found 355.1852; Elemental analysis: calcd for C$_{21}$H$_{21}$B$_3$O$_3$ C: 71.3, H: 6.0. Found C: 71.4, H: 6.0.

5-Methyl-2-(4-toluenesulfonyl)-3a,4,7,7a-tetrahydro-(3*H*)-isoindol-1-one (256a) and
6-Methyl-2-(4-toluenesulfonyl)-3a,4,7,7a-tetrahydro-(3*H*)-isoindol-1-one (256b)[73]
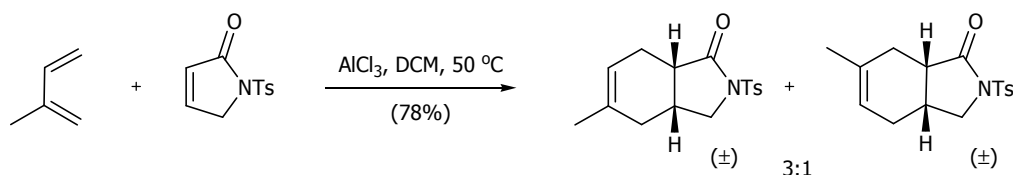
A mixture of 1-(4-toluenesulfonyl)-1*H*-pyrrol-2(5*H*)-one (0.10 g, 0.4 mmol), isoprene (0.97 mL, 9.7 mmol) and AlCl$_3$ (0.02 g, 0.1 mmol) in DCM (3 mL) was heated at 50 °C for 24 h. The reaction was cooled to 0 °C and was quenched by addition of saturated NaHCO$_3$ (5 mL). The product was then extracted with DCM (10 mL), and washed with saturated NaHCO$_3$ (5 mL), brine (2 × 5 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) provided a 3:1 regioisomeric mixture of the adducts **256a:256b** (0.10 g, 78%) as a colourless oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2912 (CH), 1737 (C=O), 1362, 1167 (SO$_2$); δ_H (300 MHz, CDCl$_3$) 7.89 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.32 (2H, d, *J* 8.3, 2 × S-*m*CH), 5.35-5.26 (1H, m, (H$_3$C)C=C*H*), 3.86 (1H, dd, *J* 9.6, 5.4) and 3.50 (1H, dd, *J* 9.6, 2.1, NCH$_2$), 2.70 (0.25H, td, *J* 7.5, 2.9) and 2.60 (0.75H, td, *J* 7.5, 2.9, NCH$_2$C*H*), 2.56-2.47 (1H, m, O=CCH), 2.42 (3H, s, ArCH$_3$), 2.35 (0.25H, br s) and 2.28 (0.75H, br s, O=CCHC*H*H), 2.24-2.09 (2H, m, O=CCHCH*H* and NCH$_2$CHC*H*H), 2.03 (1H, dd, *J* 17.4, 7.5, NCH$_2$CHCH*H*), 1.57 (3H, H$_2$CC(CH$_3$)); δ_C (75 MHz, CDCl$_3$) 174.8 (C=O), 145.0, 135.2 (2 × aromatic C), 131.7 (H$_2$CC=*C*Me), 129.7, 127.9 (4 × aromatic CH), 118.7 (H$_2$CC=*C*H), 52.2 (NCH$_2$), 41.8, 40.7 (O=C*C*H), 29.9 (NCH$_2$*C*H), 29.5, 28.3 (NCH$_2$CH*C*H$_2$), 23.7, 21.8 (O=CCH*C*H$_2$), 21.7 (ArCH$_3$); *m/z* (CI+) 306 (MH$^+$, 100%), 150 (74), 107 (36), 93 (60); HRMS (CI+) calcd for C$_{16}$H$_{20}$NO$_3$S (MH$^+$) 306.1164, found 306.1160.

Diethyl phosphonoacetone (262)[98]
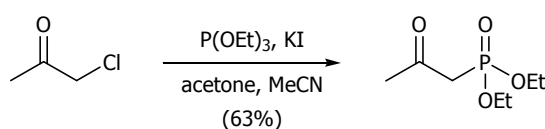
To a solution of chloroacetone (5.00 g, 54 mmol) in acetone (16.5 mL) and acetonitrile (14 mL) were added KI (8.97 g, 54 mmol) and triethyl phosphite (8.98 g, 54 mmol). The resulting suspension was stirred for 6 h at room temperature, then at 50 °C for 16 h.

Filtration, removal of solvents and subsequent distillation provided phosphonoacetone **262**[165] (6.64 g, 63%) as a colourless liquid; b.p. 101-102 °C/2 mmHg [lit.[98] 100-101 °C/2 mmHg]; δ_H (300 MHz, CDCl$_3$) 4.17 (4H, m, 2 × OCH_2), 3.06 (2H, d, J 22.9, CH_2P), 2.30 (3H, s, C(=O)CH_3), 1.85-1.29 (6H, m, 2 × OCH$_2$CH_3); δ_C (75 MHz, CDCl$_3$) 199.9 (d, J 5.9, C=O), 62.5 (d, J 6.5, 2 × OCH$_2$), 43.4 (d, J 126.2, CH$_2$P), 31.3 (s, C(=O)CH$_3$), 16.3 (d, J 6.2, 2 × OCH$_2$$CH_3$).

Allyl (*tert*-butyldimethyl)silyl ether (264)[166]

To a solution of allyl alcohol (0.50 g, 8.6 mmol) in DCM (5 mL) was added DMAP (0.11 g, 0.86 mmol), followed by the dropwise addition of TBSCl (1.56, 10.3 mmol) in DCM (2 mL). After 16 h, the reaction mixture was washed with saturated NaHCO$_3$ (3 × 10 mL), brine (3 × 10 mL), and then dried (Na$_2$SO$_4$). Concentration and purification by flash chromatography (Al$_2$O$_3$; PS) afforded protected alcohol **264**[166] (0.08 g, 5%) as a colourless liquid; δ_H (300 MHz, CDCl$_3$) 5.92 (1H, ddt, J 17.1, 10.4, 4.6, H$_2$C=CH), 5.26 (1H, dq, J 17.1, 1.9) and 5.08 (1H, dq, J 10.4, 1.7, H_2C=CH), 4.17 (2H, dt, J 4.6, 1.9, CH_2OTBS), 0.92 (9H, s, C(CH$_3$)$_3$), 0.07 (6H, s, Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 137.5 (H$_2$C=CH), 113.9 (H$_2$$C$=CH), 64.1 (CH$_2$), 25.9 (C($CH_3$)$_3$), 18.4 ($CMe_3$), −5.3 (Si(CH$_3$)$_2$).
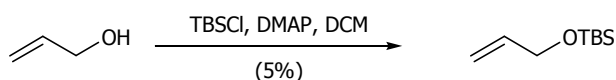
(*Z*)-1,4-Bis-(*tert*-butyldimethylsilyloxy)-2-butene (265) and (*Z*)-4-(*tert*-Butyldimethylsilyloxy)-2-buten-1-ol (266) [167]
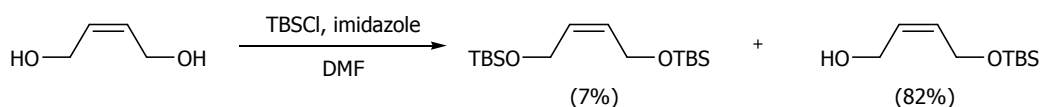
To a solution of *cis*-butene-1,4-diol (8.8 g, 100 mmol) in DMF (20 mL) at −10 °C were added imidazole (1.4 g, 20.9 mmol) and TBSCl (3.0 g, 20 mmol). The reaction was stirred at −10 °C for 30 min then at room temperature for 3 d, and then poured into H$_2$O (150 mL). The product was extracted with Et$_2$O (3 × 150 mL), washed with H$_2$O (100 mL), brine (100 mL) and then dried (Na$_2$SO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) afforded doubly protected diol **265**[168] (0.47 g, 7%) as a colourless liquid; δ_H (300 MHz, CDCl$_3$) 5.54 (2H, br t, J 3.5, HC=CH), 4.17

(4H, br d, J 3.8, 2 × CH$_2$), 0.90 (18H, s, 2 × C(CH$_3$)$_3$), 0.06 (12H, s, 2 × Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 130.2 (C=C), 59.6 (2 × CH$_2$), 25.9 (2 × C(CH$_3$)$_3$), 18.3 (2 × CMe$_3$), −5.2 (2 × Si(CH$_3$)$_2$).

Further elution provided monoprotected diol **266**[169] (3.29 g, 82%) as a colourless liquid; δ_H (300 MHz, CDCl$_3$) 5.69-5.56 (2H, m, HC=CH), 4.25 (2H, d, J 3.6, CH_2OTBS), 4.21 (2H, d, J 4.5, CH_2OH), 2.83 (1H, br s, OH), 0.87 (9H, s, C(CH$_3$)$_3$), 0.05 (6H, s, Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 131.1 and 130.1 (C=C), 59.5 and 58.6 (2 × CH$_2$), 25.9 (C(CH$_3$)$_3$), 18.3 (CMe$_3$), −5.3 (Si(CH$_3$)$_2$).

2,4,6-Tris-(*tert*-butyldimethylsilyloxymethyl)-1,3,5-trioxane (267)
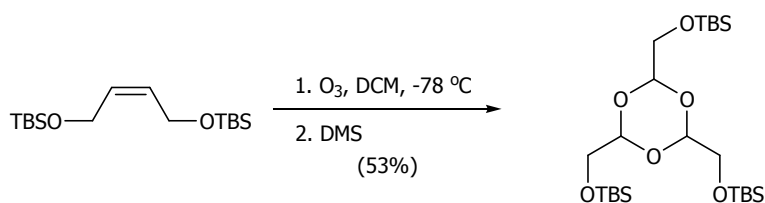
Through a solution of protected diol **265** (0.40 g, 1.3 mmol) in DCM (13 mL) was bubbled ozone in O$_2$ at −78 °C. When the solution became blue, oxygen was passed through the solution until it became colourless. Following the addition of DMS (0.19 mL, 2.5 mmol), the reaction mixture was slowly warmed to room temperature. After 16 h, the mixture was concentrated and the crude product was dissolved in DCM (20 mL). The solution was washed with H$_2$O (2 × 20 mL) and brine (2 × 20 mL), and then dried (Na$_2$SO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9) afforded the trimeric product **267** (0.23 g, 53%) as a colourless liquid; δ_H (300 MHz, CDCl$_3$) 5.27 (3H, t, J 4.6, 3 × OCHO), 3.62 (6H, d, J 4.6, 3 × OCH$_2$), 0.89 (27H, s, 3 × C(CH$_3$)$_3$), 0.08 (18H, s, 3 × Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 103.2 (3 × OCHO), 62.2 (3 × OCH$_2$), 25.8 (3 × C(CH$_3$)$_3$), 18.3 (3 × CMe$_3$), −5.3 (3 × Si(CH$_3$)$_2$); *m/z* (CI+) 522 (MH$^+$, 0.01%), 174 (22), 159 (68), 117 (66), 85 (100).

(*E*)-4-(*tert*-Butyldimethylsilyloxy)-2-butenal (268)[170]
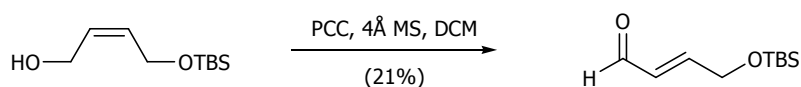
Powdered 4Å molecular sieves (0.52 g) and PCC (0.55 g, 2.6 mmol) were successively added to a solution of alcohol **266** (0.50 g, 2.5 mmol) in DCM (6 mL) at 0 °C. The temperature was maintained at 0 °C for 10 min then at room temperature for 15 h. After concentration, Et$_2$O (20 mL) was added and the resulting suspension filtered through Celite®, washing with Et$_2$O (30 mL). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:9) afforded the title aldehyde[171] (0.11 g, 21%) as a colourless liquid; δ_H (400 MHz, CDCl$_3$) 9.60 (1H, d, *J* 8.1, CHO), 6.88 (1H, dt, *J* 15.4, 3.3, C*H*CH$_2$), 6.39 (1H, ddt, *J* 15.4, 8.1, 2.1, OHCC*H*), 4.45 (2H, dd, *J* 3.2, 2.2, CH$_2$), 0.92 (9H, s, C(CH$_3$)$_3$), 0.09 (6H, s, Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 193.4 (CHO), 156.5 (*C*HCH$_2$), 130.6 (OHC*C*H), 62.3 (CH$_2$), 25.8 (C(*C*H$_3$)$_3$), 18.3 (*C*Me$_3$), −5.5 (Si(CH$_3$)$_2$).

(*E*)-5-(*tert*-Butyldimethylsilyloxy)-pent-3-en-2-ol (269)
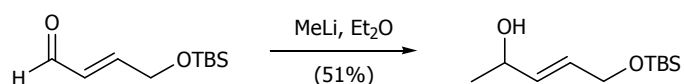
MeLi (1.6M in Et$_2$O, 0.4 mL, 0.7 mmol) was added to a solution of aldehyde **268** (0.10 g, 0.50 mmol) in Et$_2$O (2 mL) at −10 °C. Stirring was continued at −10 °C for 30 min, then at room temperature for 3 h. Following the addition of H$_2$O (10 mL), the product was extracted with Et$_2$O (3 × 10 mL), then washed with brine (20 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; PS→EtOAc:PS 3:7) afforded alcohol **269**[97] (0.06 g, 51%) as a colourless liquid; δ_H (400 MHz, CDCl$_3$) 5.78-5.72 (2H, m, HC=CH), 4.39-4.28 (1H, m, C*H*(OH)), 4.17 (2H, br s, CH$_2$), 1.58 (1H, br d, *J* 17.7, OH), 1.27 (3H, d, *J* 6.3, CHC*H$_3$*), 0.91 (9H, s, C(CH$_3$)$_3$), 0.07 (6H, s, Si(CH$_3$)$_2$); δ_C (75 MHz, CDCl$_3$) 133.9 (C=*C*CH$_2$), 129.2 (CH*C*=C), 68.2 (CH(OH)), 63.0 (CH$_2$), 25.8 (C(*C*H$_3$)$_3$), 23.1 (CH*C*H$_3$), 18.3 (*C*Me$_3$), −5.3 (Si(CH$_3$)$_2$).

(*E*)-5-(*tert*-Butyldimethylsilyloxy)-pent-3-en-2-one (259)[170]
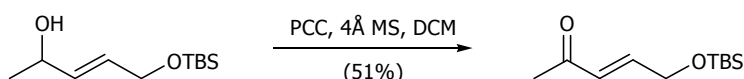
Powdered 4Å molecular sieves (0.51 g) and PCC (0.54 g, 2.5 mmol) were successively added to a stirring solution of alcohol **269** (0.53 g, 2.4 mmol) in DCM (6 mL) at 0 °C. The reaction temperature was maintained at 0 °C for 10 min then at room temperature

for 16 h. After concentration, Et_2O (20 mL) was added and the resulting suspension filtered through Celite®, washing with Et_2O (30 mL). Concentration and purification by flash chromatography (SiO_2; PS→EtOAc:PS 1:9) afforded methyl ketone **259**[97] (0.26 g, 51%) as a colourless liquid; δ_H (300 MHz, $CDCl_3$) 6.83 (1H, dt, *J* 15.8, 3.5, C*H*CH$_2$), 6.34 (1H, dt, *J* 15.8, 2.1, *H*C=CHCH$_2$), 4.36 (2H, dd, *J* 3.5, 2.1, CH$_2$), 2.27 (3H, s, COCH$_3$), 0.92 (9H, s, C(CH$_3$)$_3$), 0.08 (6H, s, Si(CH$_3$)$_2$); δ_C (75 MHz, $CDCl_3$) 198.4 (C=O), 146.2 (*C*HCH$_2$), 128.8 (H*C*=CHCH$_2$), 62.2 (CH$_2$), 27.3 (CO*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 18.4 (*C*Me$_3$), −5.4 (Si(*C*H$_3$)$_2$).

(*E*)-4-Bromobut-2-en-1-ol (274)[104]
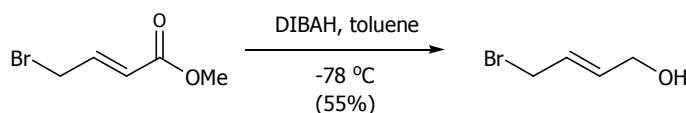
To a stirring solution of methyl-4-bromocrotonate (20.0 mL, 170 mmol) in toluene (90 mL) at −78 °C was slowly added DIBAH (20% in toluene, 305 mL, 366 mmol). After maintaining the temperature at −78 °C for 30 min, the reaction was quenched with 50% aqueous AcOH (43 mL, 375 mmol) then warmed to room temperature. Filtration over Celite®, washing with acetone (5 x 90 mL) followed by concentration and purification by flash chromatography (SiO_2; Et_2O:PS 1:4→2:3) gave alcohol **274**[104] (14.1 g, 55%) as a pale yellow oil; δ_H (500 MHz, $CDCl_3$) 5.98-5.85 (2H, m, HC=CH), 4.17-4.15 (2H, m, C*H$_2$*OH), 3.96-3.94 (2H, m, CH$_2$Br), 1.74 (1H, br s, OH); δ_C (125 MHz, $CDCl_3$) 134.1 (*C*HCH$_2$OH), 127.3 (*C*HCH$_2$Br), 62.4 (CH$_2$OH), 32.0 (CH$_2$Br).

1-Benzyl-3-methylpyrrolidin-2-one (280)
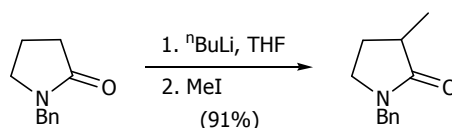
To a stirring solution of 1-benzylpyrrolidin-2-one (18.5 mL, 116 mmol) in THF (250 mL) at −78 °C was added ^{n}BuLi (1.6 M in hexanes, 87 mL, 139 mmol) and the mixture stirred for 30 min. MeI (14.4 mL, 231 mmol) was added slowly and after 30 min at −78 °C, the mixture was allowed to warm to room temperature and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl (250 mL) then extracted with EtOAc (3 × 250 mL). The organic extracts were washed with brine

$(2 \times 250$ mL), dried (MgSO$_4$), concentrated and purified by flash chromatography (SiO$_2$; EtOAc:PS 1:4→2:3) to provide the methylated product **280** (19.9 g, 91%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2968, 2931, 2874 (CH), 1683 (C=O), 1429; δ_H (400 MHz, CDCl$_3$) 7.34-7.19 (5H, m, 5 × ArH), 4.46 (1H, d, J 14.7) and 4.42 (1H, d, J 14.7, NC*H*$_2$Ph), 3.19-3.13 (2H, m, BnNC*H*$_2$), 2.56-2.45 (1H, m, C*H*Me), 2.25-2.15 (1H, m) and 1.65-1.54 (1H, m, BnNCH$_2$C*H*$_2$), 1.23 (3H, d, J 7.1, CH$_3$); δ_C (100 MHz, CDCl$_3$) 177.3 (C=O), 136.6 (aromatic C), 128.5, 128.0, 127.4 (5 × aromatic CH), 46.6 (N*C*H$_2$Ph), 44.5 (BnN*C*H$_2$), 36.6 (*C*HMe), 27.0 (BnNCH$_2$*C*H$_2$), 16.3 (CH$_3$); m/z (CI+) 190 (MH$^+$, 100), 175 (18); HRMS (CI+) calcd for C$_{12}$H$_{16}$NO (MH$^+$) 190.1232, found 190.1228.

1-Benzyl-3-methylpyrrolidine-2-thione (281)
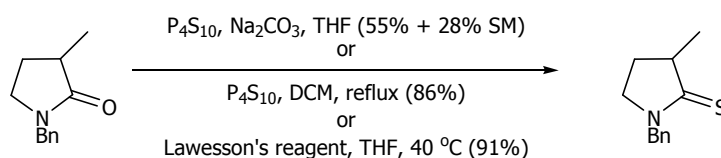
From P$_4$S$_{10}$ and Na$_2$CO$_3$:[102]

A solution of P$_4$S$_{10}$ (16.2 g, 36.4 mmol) and Na$_2$CO$_3$ (3.86 g, 36.4 mmol) in THF (350 mL) was stirred vigorously for 15 min, followed by addition of lactam **280** (4.59 g, 24.3 mmol) in THF (20 mL). After 40 h, 10% aqueous Na$_3$PO$_4$ (200 mL) was slowly added, and the mixture stirred for 10 min. The product was then extracted with EtOAc (3 × 100 mL), washed with brine (2 × 200 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:9 then 2:3 to recover starting material) afforded the amide starting material (1.31 g, 28%) and thiolactam **281** (2.18 g, 55%) as a pale yellow oil.

From heating with P$_4$S$_{10}$:

A solution of lactam **280** (9.74 g, 51.5 mmol) and P$_4$S$_{10}$ (12.6 g, 28.3 mmol) in DCM (250 mL) was heated at reflux for 20 h. After cooling to room temperature, the reaction was quenched with H$_2$O (200 mL) and stirred for 10 min. The product was extracted with DCM (3 × 200 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:9) afforded thiolactam **281** (9.09 g, 86%) as a pale yellow oil.

From Lawesson's reagent[103]:

A solution of lactam **280** (16.2 g, 85.6 mmol) and Lawesson's reagent (20.8 g, 51.4 mmol) in THF (400 mL) was heated at 40 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (250 mL), then stirred for 10 min. The organic products were extracted with EtOAc (3 × 200 mL), washed with brine (250 mL) and dried ($MgSO_4$). Concentration followed by filtration through a short plug of silica gel, eluting with EtOAc:PS 2:3, removed the polar impurities. Further purification by flash chromatography (SiO_2; EtOAc:PS 1:19→1:9) provided thiolactam **281** (16.0 g, 91%) as a pale yellow oil.

v_{max}/cm^{-1} (film) 2966, 2927, 2872 (CH), 1452, 1232 (C=S); δ_H (400 MHz, CDCl$_3$) 7.38-7.24 (5H, m, 5 × ArH), 5.04 (1H, d, *J* 14.5) and 4.95 (1H, d, *J* 14.5, NC*H*$_2$Ph), 3.55-3.40 (2H, m, BnNC*H*$_2$), 3.02-2.88 (1H, m, C*H*Me), 2.33-2.21 (1H, m) and 1.69-1.55 (1H, m, BnNCH$_2$C*H*$_2$), 1.39 (3H, d, *J* 7.0, CH$_3$); δ_C (75 MHz, CDCl$_3$) 206.7 (C=S), 135.2 (aromatic C), 128.8, 128.2, 128.0 (5 × aromatic CH), 51.9 and 51.8 (Ph*C*H$_2$N*C*H$_2$), 48.9 (*C*HMe), 28.3 (BnNCH$_2$*C*H$_2$), 19.5 (CH$_3$); *m/z* (CI+) 234 (M(C$_2$H$_5$)$^+$, 23%), 206 (MH$^+$, 100); HRMS (CI+) calcd for C$_{12}$H$_{16}$NS (MH$^+$) 206.1003, found 206.1005.

(3*RS*,2'*SR*)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)-3-methylpyrrolidine-2-thione (282)
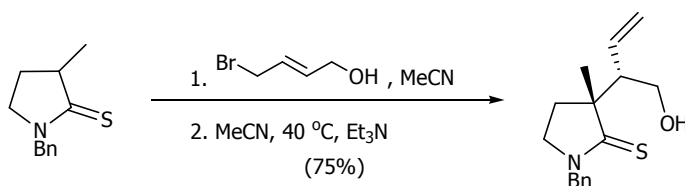
A solution of thiolactam **281** (13.6 g, 66.4 mmol) and allylic bromide **274** (11.2 g, 74.3 mmol) in MeCN (10 mL) was stirred at room temperature for 4 d. After dilution with further MeCN (350 mL) the mixture was heated to 40 °C then Et$_3$N (10.2 mL, 73.1 mmol) was added. After 6 h, the mixture was cooled to room temperature, diluted with DCM (750 mL) and washed with 10% aqueous citric acid (2 × 150 mL), brine (150 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:9→3:7) afforded thiolactam starting material (0.41 g, 3%) and the desired product **282** (13.7 g, 75%) as a pale yellow solid; m.p. = 49-50 °C; v_{max}/cm^{-1} (KBr) 3337 (br, OH), 2872 (CH), 1504, 1448, 1232 (C=S); δ_H (400 MHz, CDCl$_3$) 7.37-7.27

(5H, m, 5 × ArH), 5.64 (1H, dt, *J* 17.0, 10.0, *H*C=CH$_2$), 5.32-5.24 (2H, m, HC=C*H*$_2$), 5.03 (1H, d, *J* 14.4) and 4.99 (1H, d, *J* 14.3, NC*H*$_2$Ph), 3.70-3.55 (2H, m, C*H*$_2$OH), 3.53-3.40 (2H, m, BnNC*H*$_2$), 2.93 (1H, dt, *J* 9.7, 6.6, C*H*CH$_2$OH), 2.16 (1H, ddd, *J* 12.8, 9.1, 8.0, BnNCH$_2$C*H*H), 1.90 (1H, br dd, *J* 6.6, 3.8, OH), 1.74 (1H, ddd, *J* 12.8, 8.0, 4.7, BnNCH$_2$CH*H*), 1.23 (3H, s, CH$_3$); δ$_C$ (100 MHz, CDCl$_3$) 208.6 (C=S), 135.5 (H*C*=CH$_2$), 135.1 (aromatic C), 128.9, 128.2, 128.1 (5 × aromatic CH), 120.1 (HC=*C*H$_2$), 63.1 (CH$_2$OH), 56.6 (*C*Me), 54.5 (*C*HCH$_2$OH), 52.0 and 51.1 (Ph*C*H$_2$N*C*H$_2$), 28.6 (BnNCH$_2$*C*H$_2$), 27.1 (CH$_3$); *m/z* (CI+) 304 (M+C$_2$H$_5$, 20%), 276 (MH$^+$, 100), 258 (16), 205 (19); HRMS (CI+) calcd for C$_{16}$H$_{22}$NOS (MH$^+$) 276.1422, found 276.1424; Elemental analysis: calcd for C$_{16}$H$_{21}$NOS C: 69.8, H: 7.7, N: 5.1. Found C: 69.6, H: 7.9, N: 5.0.

(3*RS*,2'*SR*)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)-3-methylpyrrolidin-2-one (283)
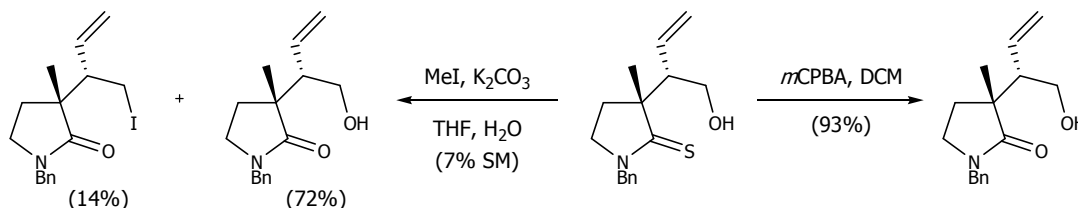
From oxidation with m*CPBA:*[107]

To a stirring solution of thiolactam **282** (13.7 g, 50.0 mmol) in DCM (600 mL) at 0 °C was added *m*CPBA (70% by weight, 27.7 g, 112 mmol) in 0.25 eq. portions (3.1 g) every 10 min. After a further 1 h at 0 °C, the reaction was warmed to room temperature, poured into saturated NaHCO$_3$ (400 mL) and the organic layer removed. Further extraction with DCM (2 × 400 mL) followed by drying (MgSO$_4$), concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 2:3→4:1) afforded lactam **283** (12.0 g, 93%) as a white solid; m.p. = 53-55 °C; ν$_{max}$/cm^{-1} (KBr) 3371 (br, OH), 2862 (CH), 1676 (C=O), 1496, 1450; δ$_H$ (500 MHz, CDCl$_3$) 7.35-7.16 (5H, m, 5 × ArH), 5.78 (1H, dt, *J* 17.0, 10.0, *H*C=CH$_2$), 5.21-5.14 (2H, m, HC=C*H*$_2$), 4.45 (1H, d, *J* 14.7) and 4.40 (1H, d, *J* 14.7, NC*H*$_2$Ph), 3.97 (1H, br s, OH), 3.90 (1H, ddd, *J* 11.3, 4.4, 1.6) and 3.62 (1H, dd, *J* 11.3, 4.4, C*H*$_2$OH), 3.23-3.10 (2H, m, BnNC*H*$_2$), 2.26 (1H, dt, *J* 9.9, 4.4, C*H*CH$_2$OH), 2.13 (1H, dt, *J* 12.8, 8.5) and 1.62 (1H, ddd, *J* 12.8, 7.9, 3.5, BnNCH$_2$C*H*$_2$), 1.23 (3H, s, CH$_3$); δ$_C$ (75 MHz, CDCl$_3$) 178.8 (C=O), 136.2 (H*C*=CH$_2$), 136.1 (aromatic C), 128.7, 128.1, 127.7 (5 × aromatic CH), 119.2 (HC=*C*H$_2$), 63.0

(CH$_2$OH), 53.1 (CHCH$_2$OH), 47.0 (NCH$_2$Ph), 46.8 (CMe), 44.1 (BnNCH$_2$), 29.7 (BnNCH$_2$CH$_2$), 22.8 (CH$_3$); *m/z* (CI+) 260 (MH$^+$, 100%), 242 (32), 229 (17), 190 (45), 91 (28); HRMS (CI+) calcd for C$_{16}$H$_{22}$NO$_2$ (MH$^+$) 260.1645, found 260.1640; Elemental analysis: calcd for C$_{16}$H$_{21}$NO$_2$ C: 74.1, H: 8.2, N: 5.4. Found C: 74.0, H: 8.2, N: 5.3.

From methylation with MeI under aqueous conditions:[105]

A solution of thiolactam **282** (0.20 g, 0.73 mmol), MeI (0.23 mL, 3.6 mmol) and K$_2$CO$_3$ (0.20 g, 1.5 mmol) in THF (8 mL) and H$_2$O (2 mL) was stirred at room temperature for 8 d. Additional MeI (0.45 mL, 7.2 mmol), THF (8 mL) and H$_2$O (2 mL) were added and the mixture stirred for a further 6 d. The products were then extracted with DCM (2 × 50 mL), washed with brine (50 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:1) afforded thiolactam starting material (0.01 g, 7%), the desired product **283** (0.14 g, 72%), and the 1-iodobut-3-en-2-yl analogue **284** (0.04 g, 14%) as a white solid.

N-Benzyl-3-(1-iodobut-3-en-2-yl)-3-methylpyrrolidin-2-one (284)

Iodide product (0.04 g, 14%) as a white solid; m.p. = 108-109 °C; ν_{max}/cm^{-1} (KBr) 2880 (CH), 1680 (C=O), 1495, 1427, 1360, 1184 (SO$_2$); δ_H (400 MHz, CDCl$_3$) 7.31-7.18 (5H, m, 5 × ArH), 5.40 (1H, dt, *J* 17.0, 10.0, *H*C=CH$_2$), 5.26 (1H, dd, *J* 10.2, 1.3) and 5.14 (1H, d, *J* 16.9, HC=C*H*$_2$), 4.41 (2H, s, NC*H*$_2$Ph), 3.40 (1H, dd, *J* 9.5, 2.6, C*H*HI), 3.16-3.05 (3H, m, CH*H*I and BnNC*H*$_2$), 2.63 (1H, td, *J* 10.5, 2.6, C*H*CH$_2$I), 2.03 (1H, ddd, *J* 13.2, 9.0, 8.0) and 1.59 (1H, ddd, *J* 13.2, 8.0, 3.9 BnNCH$_2$C*H*$_2$), 1.18 (3H, s, CH$_3$); δ_C (125 MHz, CDCl$_3$) 177.0 (C=O), 136.3 (aromatic C), 136.0 (*H*C=CH$_2$), 128.7, 128.1, 127.7 (5 × aromatic CH), 120.4 (HC=*C*H$_2$), 53.4 (CHCH$_2$I), 47.7 (CMe), 46.8 (NCH$_2$Ph), 43.4 (BnNCH$_2$), 27.8 (BnNCH$_2$CH$_2$), 23.7 (CH$_3$), 7.3 (CH$_2$I); *m/z* (CI+) 271 (MH$^+$, 16%), 270 (100), 244 (27), 242 (63), 189 (14), 125 (14); HRMS (CI+) calcd for C$_{16}$H$_{21}$NOI (MH$^+$) 370.0662, found 370.0649; Elemental analysis: calcd for C$_{16}$H$_{20}$NOI C: 52.0, H: 5.5, N: 3.8. Found C: 52.2, H: 5.6, N: 3.6.

1-Benzyl-3-(buta-1,3-dien-2-yl)-3-methylpyrrolidin-2-one (287)
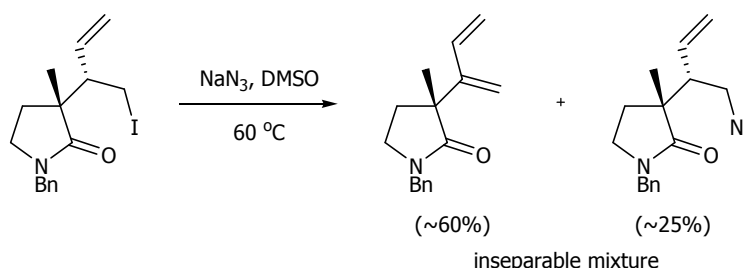
A stirring solution of iodide **284** (0.20 g, 0.5 mmol) and NaN$_3$ (0.11 g, 1.6 mmol) in DMSO (2 mL) was heated at 60 °C for 20 h. The reaction mixture was cooled to room temperature then diluted with H$_2$O (50 mL) and extracted with EtOAc (3 × 10 mL), which was subsequently washed with brine (10 mL) and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:4) provided an inseparable mixture of the title diene product **287** and azide **288** (*vide infra*) (0.12 g, ~85% combined yield) as a colourless oil; diagnostic peaks excluding those corresponding to azide **288** are quoted: δ$_H$ (500 MHz, CDCl$_3$) 7.33-7.18 (5H, m, 5 × ArH), 6.25 (1H, ddd, *J* 17.4, 11.0, 0.6, *H*C=CH$_2$), 5.33 (1H, dd, *J* 17.4, 1.5, HC=C*H*H), 5.28-5.25 (1H, m, MeCC=C*H*H), 5.06 (1H, dd, *J* 11.0, 1.5, HC=CH*H*), 5.01 (1H, s, MeCC=CH*H*), 4.50-4.40 (2H, m, NC*H$_2$*Ph), 3.17-3.06 (2H, m, BnNC*H$_2$*), 2.23 (1H, ddd, *J* 13.2, 7.3, 5.9) and 1.76 (1H, ddd, *J* 13.0, 7.5, 6.4, BnNCH$_2$C*H$_2$*), 1.34 (3H, s, CH$_3$); δ$_C$ (125 MHz, CDCl$_3$) 176.9 (C=O), 148.1 (MeC*C*=CH$_2$), 136.5 (aromatic C), 136.0 (H*C*=CH$_2$), 128.6, 128.1, 127.5 (5 × aromatic CH), 115.8 (HC=*C*H$_2$), 112.8 (MeCC=*C*H$_2$), 48.6 (*C*Me), 46.9 (N*C*H$_2$Ph), 43.3 (BnN*C*H$_2$), 32.2 (BnNCH$_2$*C*H$_2$), 22.6 (CH$_3$); *m/z* (ESI+) 285 (azide **288**, 19%), 264 (MNa$^+$, 13), 242 (MH$^+$, 100); HRMS (ESI+) calcd for C$_{16}$H$_{20}$NO (MH$^+$) 242.1539, found 242.1546.

(3*RS*,2'*SR*)-1-Benzyl-3-(1-methanesulfonyloxybut-3-en-2-yl)-3-methylpyrrolidin-2-one (289)
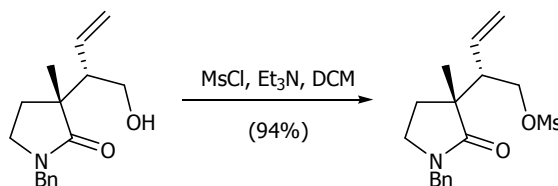
To a stirring solution of alcohol **283** (0.29 g, 1.1 mmol) in DCM (12 mL) at 0 °C was added Et$_3$N (0.31 mL, 2.3 mmol) and MsCl (0.17 mL, 2.3 mmol). After 1 h, the reaction

was warmed to room temperature, diluted with DCM (30 mL), washed successively with H_2O (2 × 10 mL) and brine (2 × 10 mL), and then dried ($MgSO_4$). Concentration provided the mesylate **289** as a colourless oil, which can be used without further purification. If desired, the oil can be purified by flash chromatography (SiO_2; EtOAc:PS 1:4→2:3) to provide the mesylate (0.36 g, 94%) as a white solid; m.p. = 69-70 °C; v_{max}/cm^{-1} ($CHCl_3$ cast) 2966, 2928, 2876 (CH), 1680 (C=O), 1501, 1435, 1340, 1180 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.36-7.14 (5H, m, 5 x ArH), 5.65-5.55 (1H, m, HC=CH$_2$), 5.29-5.20 (2H, m, HC=CH_2), 4.47 (1H, d, J 14.6, NCHHPh), 4.38-4.27 (3H, m, NCHHPh and CH_2OMs), 3.17-3.09 (2H, m, BnNCH_2), 2.93 (3H, s, SO_2CH_3), 2.66 (1H, ddd, J 13.3, 8.3, 5.0, CHCH$_2$OMs), 2.12-2.03 (1H, m) and 1.63 (1H, ddd, J 13.0, 7.4, 4.5, BnNCH$_2$CH_2), 1.17 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 177.0 (C=O), 136.3 (aromatic C), 133.9 (HC=CH$_2$), 128.8, 128.1, 127.7 (5 × aromatic CH), 120.8 (HC=CH$_2$), 70.0 (CH$_2$OMs), 49.8 (CHCH$_2$OMs), 46.8 (NCH$_2$Ph), 45.6 (CMe), 43.5 (BnNCH$_2$), 37.3 (SO_2CH_3), 28.5 (BnNCH$_2$$CH_2$), 23.2 (C$CH_3$); m/z (CI+) 338 (MH$^+$, 9%), 324 (15), 278 (30), 242 (100), 190 (70), 91 (42); HRMS (CI+) calcd for $C_{17}H_{24}NO_4S$ (MH$^+$) 338.1426, found 338.1416; Elemental analysis: calcd for $C_{17}H_{23}NO_4S$ C: 60.5, H: 6.9, N: 4.2. Found C: 60.3, H: 6.7, N: 4.1.

(3*RS*,2'*SR*)-3-(1-Azidobut-3-en-2-yl)-1-benzyl-3-methylpyrrolidin-2-one (288)

Using the procedure previously described, alcohol **283** (11.9 g, 45.9 mmol) provided 17.7 g of crude mesylate **289**. This was treated with NaN_3 (8.9 g, 138 mmol) in DMSO (50 mL) and stirred at 60 °C for 21 h. The reaction mixture was cooled to room temperature, then diluted with H_2O (400 mL) and the organic material extracted with EtOAc (4 × 50 mL). Subsequent washing with brine (50 mL) and drying ($MgSO_4$), followed by concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:9→1:4) provided azide **288** (11.3 g, 87%) as white crystals; m.p. = 40-42 °C; v_{max}/cm^{-1} (KBr) 2968, 2893 (CH), 2085 (N_3), 1680 (C=O), 1497, 1433 (C=C); δ_H (500 MHz, $CDCl_3$) 7.34-7.14 (5H, m, 5 × ArH), 5.57 (1H, dt, J 17.4, 9.8, HC=CH$_2$), 5.28-5.23 (2H, m, HC=CH_2), 4.43 (1H, d, J 14.7) and 4.40 (1H, d, J 14.7, NCH_2Ph), 3.44

(1H, dd, *J* 12.2, 4.3) and 3.30 (1H, dd, *J* 12.2, 9.7, CH_2N$_3$), 3.16-3.06 (2H, m, BnNCH_2), 2.53 (1H, td, *J* 9.6, 4.3, CHCH$_2$N$_3$), 2.03 (1H, ddd, *J* 13.1, 8.7, 7.8) and 1.60 (1H, ddd, *J* 13.1, 7.8, 3.9, BnNCH$_2$CH_2), 1.14 (3H, s, CH_3); δ_C (125 MHz, CDCl$_3$) 177.1 (C=O), 136.3 (aromatic C), 135.2 (H*C*=CH$_2$), 128.7, 128.1, 127.6 (5 × aromatic CH), 120.2 (HC=*C*H$_2$), 51.6 (*C*H$_2$N$_3$), 50.2 (*C*HCH$_2$N$_3$), 46.8 (N*C*H$_2$Ph), 45.7 (*C*Me), 43.3 (BnN*C*H$_2$), 28.1 (BnNCH$_2$*C*H$_2$), 23.2 (*C*H$_3$); *m/z* (CI+) 285 (MH$^+$, 43%), 257 (67), 242 (100), 228 (35), 188 (18), 152 (22), 117 (21); HRMS (CI+) calcd for C$_{16}$H$_{21}$N$_4$O (MH$^+$) 285.1710, found 285.1706; Elemental analysis: calcd for C$_{16}$H$_{20}$N$_4$O C: 67.6, H: 7.1, N: 19.7. Found C: 67.5, H: 7.2, N: 19.4.

(3a*RS*,4*SR*,6a*RS*)-1-Benzyl-3a-methyl-4-vinyloctahydropyrrolo[2,3-*b*]pyrrole (291)

A solution of azide **288** (2.00 g, 7.0 mmol) and PBu$_3$ (3.2 mL, 12.7 mmol) in THF (60 mL) was stirred at room temperature for 1 h then LiAlH$_4$ (0.27 g, 7.0 mmol) was slowly added. After 1 h, another portion of LiAlH$_4$ (0.27 g, 7.0 mmol) was added and stirring was continued for a further 1 h. After quenching by addition of 0.5 M aqueous sodium potassium tartrate (60 mL) the mixture was stirred for 30 min. The product was then extracted with EtOAc (3 × 60 mL), washed with H$_2$O (2 × 60 mL) and brine (2 × 60 mL), then dried (MgSO$_4$) and concentrated. The O=PBu$_3$ by-product was subsequently removed by dilution with DCM (20 mL) and extracting the amine material with 2 M HCl (3 × 20 mL). Basification to pH 11 with 3 M NaOH, cooling with an ice bath, was followed by extraction of the materials into EtOAc (3 × 50 mL), which was washed with brine (50 mL) and dried (MgSO$_4$). Further purification by flash chromatography (SiO$_2$; MeOH:DCM 1:49→1:9) provided the bicycle **291** (1.27 g, 76%) as a pale yellow oil; δ_H (400 MHz, CDCl$_3$) 7.37-7.20 (5H, m, 5 × ArH), 5.74 (1H, ddd, *J* 17.1, 10.7, 7.4, *H*C=CH$_2$), 5.10-5.02 (2H, m, HC=CH_2), 3.92 (1H, d, *J* 12.9, NCHHPh), 3.79 (1H, s, NCHN), 3.68 (1H, d, *J* 13.0, NCHHPh), 3.03-2.93 (2H, m, BnNCH_2), 2.87-2.80 (1H, m) and 2.51-2.43 (1H, m, HNCH_2), 2.31 (1H, dt, *J* 10.4, 7.4, HNCH$_2$CH), 1.82 (1H, ddd, *J* 12.3, 10.4, 7.1) and 1.21 (1H, ddd, *J* 12.3, 5.5, 2.0, BnNCH$_2$CH_2), 1.15 (3H, s, CH_3); δ_C (100 MHz, CDCl$_3$) 139.1 (aromatic C), 135.1 (H*C*=CH$_2$), 128.8, 128.2, 126.9

(5 × aromatic CH), 116.9 (HC=CH$_2$), 90.1 (NCHN), 57.7 (NCH$_2$Ph), 54.4 (HNCH$_2$$C$H), 51.9 ($C$Me), 51.3 (HN$CH_2$), 49.3 (BnN$CH_2$), 32.0 (BnNCH$_2$$CH_2$), 25.1 (CH$_3$); *m/z* (CI+) 243 (MH$^+$, 100%), 214 (34), 173 (27); HRMS (CI+) calcd for C$_{16}$H$_{23}$N$_2$ (MH$^+$) 243.1856, found 243.1854.

(3*RS*,2'*SR*)-3-(1-Aminobut-3-en-2-yl)-1-benzyl-3-methylpyrrolidin-2-one (290)

Amine **290** produced as a pale yellow oil when one crop of 1 eq. of LiAlH$_4$ was used; Pale yellow oil; ν_{max}/cm^{-1} (film) 3438, 3080, 3032 (NH$_2$ and OH), 2925, 2873 (CH), 1672 (C=O) 1369, 1161 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.30-7.14 (5H, m, 5 × ArH), 5.47 (1H, dt, *J* 17.0, 10.1, HC=CH$_2$), 5.22 (1H, dd, *J* 10.3, 2.1) and 5.16 (1H, dd, *J* 17.0, 2.1, HC=CH_2$), 4.42 (1H, d, *J* 14.7) and 4.36 (1H, d, *J* 14.7, NCH_2$Ph), 3.14-3.02 (2H, m, BnNCH_2$), 2.70 (1H, dd, *J* 12.4, 3.0) and 2.50 (1H, dd, *J* 12.3, 10.3, CH_2NH_2$), 2.22 (1H, td, *J* 10.0, 3.0, CHCH$_2$NH$_2$), 1.98 (1H, ddd, *J* 13.0, 8.8, 7.5) and 1.55 (1H, ddd, *J* 12.3, 8.1, 4.0, BnNCH$_2$CH_2$), 1.42 (2H, br s, NH$_2$), 1.09 (3H, s, CH$_3$); δ_C (125 MHz, CDCl$_3$) 178.0 (C=O), 136.5 (aromatic C), 136.4 (HC=CH$_2$), 128.7, 128.1, 127.5 (5 × aromatic CH), 119.9 (HC=CH$_2$), 54.9 (CHCH$_2$NH$_2$), 46.7 (NCH$_2$Ph), 46.0 (CMe), 43.4 (BnNCH$_2$), 41.8 (CHCH$_2$NH$_2$), 27.8 (BnNCH$_2$$CH_2$), 23.4 (CH$_3$); *m/z* (CI+) 259 (MH$^+$, 64%), 242 (75), 230 (31), 190 (100), 91 (65); HRMS (CI+) calcd for C$_{16}$H$_{23}$N$_2$O (MH$^+$) 259.1810, found 259.1813.
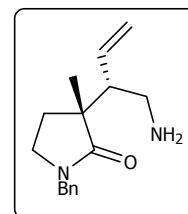
(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)-3-vinyloctahydropyrrolo[2,3-*b*]pyrrole (292)
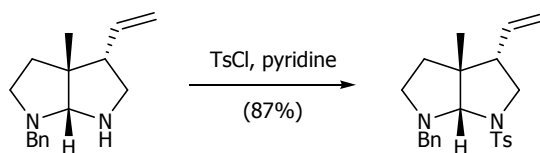
TsCl (2.00 g, 10.5 mmol) was added to a stirring solution of amine **291** (1.27 g, 5.6 mmol) in pyridine (8.5 mL, 105 mmol) at 0 °C. The reaction was slowly warmed to room temperature, and stirred for 16 h. The mixture was diluted with EtOAc (50 mL) then successively washed with H$_2$O (20 mL) and saturated CuSO$_4$ (3 × 20 mL). The aqueous washes were re-extracted with EtOAc (3 × 30 mL), and the combined organic extracts washed with brine (2 × 10 mL) then dried (MgSO$_4$). Concentration and

purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) afforded sulfonamide **292** (1.81 g, 87%) as a pale yellow solid; v_{max}/cm^{-1} (CHCl$_3$ cast) 2923, 2878 (CH), 1599, 1448 (C=C), 1348, 1157 (SO$_2$); δ$_H$ (400 MHz, CDCl$_3$) 7.77 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.36-7.20 (7H, m, 7 × ArH), 5.57 (1H, ddd, *J* 17.4, 10.5, 7.1, *H*C=CH$_2$), 5.06 (1H, d, *J* 10.5) and 4.91 (1H, d, *J* 17.4, HC=C*H*$_2$), 4.68 (1H, s, NCHN), 4.05 (2H, s, NC*H*$_2$Ph), 3.66 (1H, dd, *J* 12.1, 7.1) and 3.23 (1H, t, *J* 12.0, TsNC*H*$_2$), 2.72-2.58 (2H, m, BnNC*H*$_2$), 2.43 (3H, s, aromatic CH$_3$), 1.88-1.75 (2H, m, TsNCH$_2$C*H* and BnNCH$_2$C*H*H), 1.20 (1H, ddd, *J* 12.8, 6.4, 5.1, BnNCH$_2$CH*H*), 0.96 (3H, s, NCHCC*H*$_3$); δ$_C$ (100 MHz, CDCl$_3$) 143.3, 139.2, 137.2 (3 × aromatic C), 133.8 (H*C*=CH$_2$), 129.7, 128.7, 128.1, 127.2, 126.7 (9 × aromatic CH), 118.0 (HC=*C*H$_2$), 90.7 (NCHN), 55.6 (N*C*H$_2$Ph), 52.9 (NCH*C*Me), 52.0 (TsN*C*H$_2$), 51.7 (TsNCH$_2$*C*H), 50.4 (BnN*C*H$_2$), 31.1 (BnNCH$_2$*C*H$_2$), 24.8 (NCHC*C*H$_3$), 21.6 (Ar*C*H$_3$); *m/z* (CI+) 425 (M+C$_2$H$_5$, 21%), 397 (MH$^+$, 100), 241 (16), 213 (21), 172 (16), 125 (52), 93 (44); HRMS (CI+) calcd for C$_{23}$H$_{29}$N$_2$O$_2$S (MH$^+$) 397.1941, found 397.1950; Elemental analysis: calcd for C$_{23}$H$_{28}$N$_2$O$_2$S C: 69.7, H: 7.1, N: 7.1. Found C: 69.4, H: 7.1, N: 7.0.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-octahydro-3a-methyl-3-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-1-(4-toluenesulfonyl)pyrrolo[2,3-*b*]pyrrole (293)
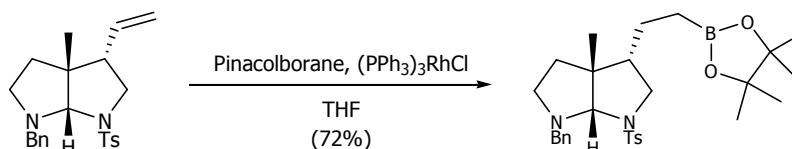
Pinacolborane (0.12 mL, 0.79 mmol) was added to a solution of olefin **292** (0.10 g, 0.26 mmol) and (PPh$_3$)$_3$RhCl (7 mg, 8 µmol) in THF (2 mL). After 3 h, additional catalyst (7 mg, 8 µmol) was added. After a further 20 h, the reaction mixture was diluted with Et$_2$O (20 mL) and successively washed with H$_2$O (3 × 15 mL), brine (2 × 15 mL) and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:4) afforded the hydroboration product **293** (0.10 g, 72%) as a white solid; δ$_H$ (500 MHz, CDCl$_3$) 7.72 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.32-7.16 (7H, m, 7 × ArH), 4.58 (1H, s, NCHN), 4.05 (1H, d, *J* 14.0) and 4.01 (1H, d, *J* 14.0, NC*H*$_2$Ph), 3.68 (1H, dd, *J* 12.0, 6.9) and 2.92 (1H, t, *J* 12.0, TsNC*H*$_2$), 2.67-2.61 (1H, m) and 2.61-2.54 (1H, m, BnNC*H*$_2$), 2.39 (3H, s, aromatic CH$_3$), 1.76 (1H, dt, *J* 12.6, 7.5) and 1.38-1.28 (1H, m, BnNCH$_2$C*H*$_2$), 1.25-1.10 (2H, m, BCH$_2$C*H*$_2$), 1.19 (6H, s) and 1.18 (6H, s,

B(OC(CH_3)$_2$)$_2$), 1.08-0.97 (1H, m, TsNCH$_2$CH), 0.89 (3H, s, NCHCCH_3), 0.61 (1H, ddd, *J* 15.8, 11.0, 5.8) and 0.50 (1H, ddd, *J* 15.8, 10.3, 5.8, BCH_2); δ_C (125 MHz, CDCl$_3$) 143.0, 139.2, 137.4 (3 × aromatic C), 129.5, 128.8, 128.0, 127.2, 126.6 (9 × aromatic CH), 91.4 (NCHN), 83.1 (B(OCMe$_2$)$_2$), 55.6 (NCH$_2$Ph), 52.8 (NCHCMe), 52.5 (TsNCH$_2$), 50.5 (BnNCH$_2$), 50.4 (TsNCH$_2$$C$H), 30.5 (BnNCH$_2$$CH_2$), 24.8 and 24.7 (B(OC(C$H_3$)$_2$)$_2$ and NCHCCH$_3$), 21.5 (ArCH$_3$), 21.3 (BCH$_2$$CH_2$), 10.2 (br, B$CH_2$); *m/z* (CI+) 525 (MH$^+$, 69%), 371 (16), 171 (31), 125 (100), 93 (88); HRMS (CI+) calcd for C$_{29}$H$_{42}$BN$_2$O$_4$S (MH$^+$) 525.2958, found 525.2945; Elemental analysis: calcd for C$_{29}$H$_{41}$BN$_2$O$_4$S C: 66.4, H: 7.9, N: 5.3. Found C: 66.3, H: 7.9, N: 5.3.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3-ethyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (295) and **(3*RS*,3a*SR*,6a*RS*)-6-benzyl-octahydro-3-(2-hydroxyethyl)-3a-methyl-1-(4-toluenesulfonyl)pyrrolo[2,3-*b*]pyrrole (294)**

THF (40 mL) was added to alkene **292** (1.75 g, 4.4 mmol) and Wilkinson's catalyst (0.12 g, 0.13 mmol), and the flask immediately degassed by Ar/vacuum flushes (× 3). Pinacolborane (1.9 mL, 13.2 mmol) was added slowly and the flask degassed again (× 3), then stirred under an Ar atmosphere for 20 h. The reaction was cooled to 0 °C and treated successively with H$_2$O (40 mL) and NaBO$_3$.4H$_2$O (2.42 g, 13.2 mmol), then warmed to room temperature after 15 min. After 5 h, the product was extracted with EtOAc (3 × 40 mL) then washed with H$_2$O (2 × 40 mL), brine (2 × 40 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:4) afforded reduced product **295** (0.12 g, 7%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2930, 2874 (CH), 1599, 1454, 1334, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.75 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.36-7.18 (7H, m, 7 × ArH), 4.60 (1H, s, NCHN), 4.08 (1H, d, *J* 13.8) and 4.00 (1H, d, *J* 13.8, NCH_2Ph), 3.70 (1H, dd, *J* 11.8, 6.3) and 2.92 (1H, t, *J* 11.7, TsNCH_2), 2.67 (1H, ddd, *J* 11.7, 7.3, 4.4) and 2.62-2.55 (1H, m, BnNCH_2), 2.40 (3H, s, ArCH_3), 1.75 (1H, dt, *J* 12.6, 7.6, BnNCH$_2$CHH), 1.32-1.21 (1H, m, CHHCH$_3$), 1.21-1.11(1H, m, BnNCH$_2$CHH), 1.11-1.00 (2H, m, CHHCH$_3$ and TsNCH$_2$CH), 0.90

(3H, s, NCHCC*H₃*), 0.76 (3H, t, *J* 7.1, CH₂C*H₃*); δ_C (125 MHz, CDCl₃) 143.2, 139.1, 137.5 (3 × aromatic C), 129.6, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 91.3 (NCHN), 55.7 (N*C*H₂Ph), 52.7 (TsN*C*H₂), 52.5 (NCH*C*Me), 50.5 (BnN*C*H₂), 49.8 (TsNCH₂*C*H), 30.5 (BnNCH₂*C*H₂), 24.7 (NCHC*C*H₃), 21.5 (Ar*C*H₃), 20.1 (*C*H₂CH₃), 13.0 (CH₂*C*H₃); *m/z* (ESI+) 421 (MNa⁺, 100%); HRMS (ESI+) calcd for C₂₃H₃₁N₂O₂SNa (MNa⁺) 421.1926, found 421.1919.

Further elution (EtOAc:PS 1:4→3:2) provided alcohol **294** (1.51 g, 86%) as a pale yellow oil; v_{max}/cm⁻¹ (CHCl₃ cast) 3449 (br, OH), 2930, 2876 (CH), 1334, 1155 (SO₂); δ_H (500 MHz, CDCl₃) 7.75 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.32-7.18 (7H, m, 7 × ArH), 4.60 (1H, s, NCHN), 4.07 (1H, d, *J* 13.9) and 3.99 (1H, d, *J* 13.9, NC*H₂*Ph), 3.74 (1H, dd, *J* 12.0, 6.7, TsNC*H*H), 3.55-3.44 (2H, m, C*H₂*OH), 2.99 (1H, t, *J* 12.0, TsNCH*H*), 2.67 (1H, ddd, *J* 9.0, 7.4, 4.3) and 2.59 (1H, ddd, *J* 8.9, 7.6, 6.5, BnNC*H₂*), 2.40 (3H, s, ArCH₃), 1.75 (1H, dt, *J* 12.6, 7.7, BnNCH₂C*H*H), 1.58 (1H, br s, OH), 1.54-1.47 (1H, m, C*H*HCH₂OH), 1.35-1.16 (3H, m, CH*H*CH₂OH, TsNCH₂C*H*, and BnNCH₂CH*H*), 0.92 (3H, s, NCHCC*H₃*); δ_C (125 MHz, CDCl₃) 143.2, 139.1, 137.5 (3 × aromatic C), 129.6, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 90.7 (NCHN), 61.7 (O*C*H₂), 55.8 (N*C*H₂Ph), 52.8 (NCH*C*Me), 52.7 (TsN*C*H₂), 50.4 (BnN*C*H₂), 45.2 (TsNCH₂*C*H), 30.7 (BnNCH₂*C*H₂), 30.2 (*C*H₂CH₂OH), 24.5 (NCHC*C*H₃), 21.5 (Ar*C*H₃); *m/z* (ESI+) 453 (M+K, 14%), 437 (MNa⁺, 14), 415 (MH⁺, 100); HRMS (ESI+) calcd for C₂₃H₃₁N₂O₃S (MH⁺) 415.2051, found 415.2050.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-3-(2-oxoethyl)-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (298)

To a solution of alcohol **294** (1.48 g, 3.6 mmol) in DCM (50 mL) at 0 °C was added pyridine (2.9 mL, 36 mmol), followed by DMP (3.8 g, 8.9 mmol). The reaction mixture was warmed to room temperature, and after 16 h, was quenched by addition of saturated Na₂S₂O₃ (40 mL) and saturated NaHCO₃ (40 mL). After vigorously stirring for 1 h, the organic materials were extracted with DCM (2 × 50 mL), washed with saturated CuSO₄

$(3 \times 40$ mL), brine (40 mL) and then dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 3:7) afforded aldehyde **298** (1.18 g, 80%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2928, 2822 (CH), 1724 (C=O), 1599, 1454, 1334, 1155 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 9.64 (1H, s, CHO), 7.78 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.33-7.19 (7H, m, 7 × ArH), 4.57 (1H, s, NCHN), 4.08 (1H, d, *J* 14.0) and 4.00 (1H, d, *J* 13.8, NC*H*$_2$Ph), 3.87 (1H, dd, *J* 12.3, 6.9) and 2.95 (1H, t, *J* 12.1, TsNC*H*$_2$), 2.71-2.65 (1H, m) and 2.63-2.56 (1H, m, BnNC*H*$_2$), 2.42-2.36 (1H, m, C*H*HCHO), 2.41 (3H, s, ArCH$_3$), 2.22 (1H, ddd, *J* 17.8, 10.1, 1.0, CH*H*CHO), 1.74-1.54 (2H, m, BnNCH$_2$C*H*H and TsNCH$_2$C*H*), 1.20 (1H, ddd, *J* 11.0, 6.5, 4.6, BnNCH$_2$CH*H*), 0.87 (3H, s, NCHCC*H$_3$*); δ_C (125 MHz, CDCl$_3$) 199.9 (C=O), 143.4, 138.8, 137.1 (3 × aromatic C), 129.7, 128.8, 128.1, 127.3, 126.8 (9 × aromatic CH), 90.1 (NCHN), 55.4 (N*C*H$_2$Ph), 52.4 (NCH*C*Me), 52.2 (TsN*C*H$_2$), 50.1 (BnN*C*H$_2$), 41.9 (TsNCH$_2$*C*H), 41.5 (*C*H$_2$CHO), 30.9 (BnNCH$_2$*C*H$_2$), 24.4 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$); *m/z* (CI+) 413 (MH$^+$, 100%), 257 (17), 229 (20), 157 (27), 91 (67); HRMS (CI+) calcd for C$_{23}$H$_{29}$N$_2$O$_3$S (MH$^+$) 413.1899, found 413.1895.

((3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)acetic acid (299)

To aldehyde **298** (0.62 g, 1.5 mmol) in ^{t}BuOH (10 mL) and H$_2$O (6 mL) at 0 °C was added 2-methyl-2-butene (1.9 mL, 18.1 mmol), followed by a solution of NaClO$_2$ (0.68 g, 7.6 mmol) and KH$_2$PO$_4$ (1.0 g, 7.6 mmol) in H$_2$O (14 mL). The mixture was stirred at 0 °C for 3 h then warmed to room temperature. The reaction was quenched by the addition of 5% aqueous Na$_2$S$_2$O$_3$ (16 mL), and then the mixture was acidified to pH 6.0 with 1% aqueous HCl. The organic material was extracted with EtOAc (3 × 20 mL) and then dried (MgSO$_4$) to afford acid the (0.66 g, quantitative) as a brown solid. This was further purified by dilution with EtOAc (20 mL), then extractions into 0.1 M NaOH (3 × 20 mL) and subsequent acidification to pH 6.0 with 1% aqueous HCl, before extraction into EtOAc (3 × 50 mL) and drying (MgSO$_4$) to provide acid **299** (0.55 g, 85%) as a peach coloured foamy solid; v_{max}/cm^{-1} (CHCl$_3$ cast) 3412 (br, OH), 2928, 2878 (CH),

1719 (C=O), 1597, 1452, 1346, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.76 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.68 (1H, br s, CO$_2$H), 7.35-7.19 (7H, m, 7 × ArH), 4.58 (1H, s, NCHN), 4.09 (1H, d, *J* 13.8) and 4.03 (1H, d, *J* 13.8, NC*H*$_2$Ph), 3.93 (1H, dd, *J* 12.2, 6.9) and 3.06 (1H, t, *J* 12.2, TsNC*H*$_2$), 2.75 (1H, ddd, *J* 9.1, 7.3, 3.9) and 2.65-2.59 (1H, m, BnNC*H*$_2$), 2.39 (3H, s, ArCH$_3$), 2.27 (1H, dd, *J* 16.3, 3.6) and 2.11 (1H, dd, *J* 16.4, 10.7, C*H*$_2$CO$_2$H), 1.73 (1H, dt, *J* 12.7, 7.7, BnNCH$_2$C*H*H), 1.60-1.52 (1H, m, TsNCH$_2$C*H*), 1.20 (1H, ddd, *J* 12.4, 6.2, 4.0, BnNCH$_2$CH*H*), 0.84 (3H, s, NCHCC*H*$_3$); δ_C (125 MHz, CDCl$_3$) 177.0 (C=O), 143.5, 138.0, 136.9 (3 × aromatic C), 129.8, 129.2, 128.2, 127.3, 127.0 (9 × aromatic CH), 89.9 (NCHN), 55.3 (N*C*H$_2$Ph), 52.6 (TsN*C*H$_2$), 52.2 (NCH*C*Me), 50.1 (BnN*C*H$_2$), 43.7 (TsNCH$_2$*C*H), 32.7 (*C*H$_2$CO$_2$H), 30.6 (BnNCH$_2$*C*H$_2$), 24.0 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$); *m/z* (CI+) 429 (MH$^+$, 100%), 273 (24), 186 (39); HRMS (CI+) calcd for C$_{23}$H$_{29}$N$_2$O$_4$S (MH$^+$) 429.1848, found 429.1841.

Failed transformation of carboxylic acid into diazoketone:

(3a*RS*,8a*SR*)-6-Benzyl-octahydro-1-hydroxy-8a-methyl-2-(4-toluenesulfonyl)pyrrolo[3,4-d]azepin-5(1*H*)-one (301)

Produced from attempts to produce diazoketone, by activation of carboxylic acid for treatment with TMSCHN$_2$:

To a stirring solution of acid **299** (0.11 g, 0.25 mmol) in THF (2 mL) at −10 °C was added Et$_3$N (0.046 mL, 0.33 mmol) and ^{i}BuOCOCl (0.043 mL, 0.33 mmol). After 1 h, TMSCHN$_2$ (2 M in Et$_2$O, 0.25 mL, 0.50 mmol) was added, and after an additional 2 h, further TMSCHN$_2$ (2M in Et$_2$O, 0.25 mL, 0.50 mmol) was added before warming the mixture to room temperature. After 16 h, the mixture was concentrated and purified by flash chromatography (SiO$_2$; EtOAc:PS 1:4→3:2) to afford impure lactam **301** (0.066 g, <62%) as a white solid; v_{max}/cm^{-1} (KBr) 3350 (br, OH), 2927, 2881 (CH), 1630 (C=O), 1342, 1169 (SO$_2$); diagnostic peaks are quoted: δ_H (500 MHz, CDCl$_3$) 7.74 (2H, d, *J* 8.1, 2 × S-*o*CH), 7.35-7.10 (7H, m, 7 × ArH), 4.86 (1H, d, *J* 14.7, NC*H*HPh), 4.80 (1H, s, NC*H*(OH)), 3.77 (1H, d, *J* 14.7, NCH*H*Ph), 3.64-3.55 (1H, m, TsNC*H*H), 3.38 (1H,

br s, OH), 3.32 (1H, dd, *J* 15.6, 11.3, BnNC*H*H), 2.95-2.86 (1H, m, TsNCH*H*), 2.82 (1H, dd, *J* 15.6, 6.1, BnNCH*H*), 2.77 (1H, d, *J* 14.7) and 2.50 (1H, dd, *J* 14.8, 7.2, O=CCH₂), 2.44 (3H, s, ArCH₃), 2.42-2.35 (1H, m, TsNCH₂C*H*), 1.10 (1H, dd, *J* 14.3, 6.3, BnNCH₂C*H*H), 1.04 (3H, s, TsNCH(OH)CC*H*₃), 0.83 (1H, dd, *J* 14.0, 11.7, BnNCH₂CH*H*); δ_C (125 MHz, CDCl₃) 172.1 (C=O), 143.7, 136.9, 135.5 (3 × aromatic C), 129.8, 128.7, 128.0, 127.6, 127.3 (9 × aromatic CH), 90.0 (NCH(OH)), 50.4 (N*C*H₂Ph), 49.0 (TsN*C*H₂), 46.5 (TsN*C*HCMe), 42.7 (BnN*C*H₂), 38.6 (TsNCH₂*C*H), 33.1 (O=C*C*H₂), 32.6 (BnNCH₂*C*H₂), 21.6 (Ar*C*H₃), 18.5 (TsNCHC*C*H₃); *m/z* (FAB+) 429 (MH⁺, 5%), 307 (44), 289 (14), 154 (100); HRMS (FAB+) calcd for C₂₃H₂₉N₂O₄S (MH⁺) 429.1848, found 429.1846.

Methyl-((3*RS*,3a*SR*,6a*RS*)-6-benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)acetate (304)

Isolated when TMSCHN₂ was added to unreacted carboxylic acid 299 that was not activated in the reaction mixture:

To a stirring solution of acid **299** (0.07 g, 0.16 mmol) in DCM (1 mL) at −45 °C was slowly added (COCl)₂ (0.017 mL, 0.20 mmol) and DMF (~0.001 mL). After 15 min, the mixture was warmed to −10 °C and was treated with additional DMF (~0.001 mL), and after 3 h, further (COCl)₂ (0.017 mL, 0.20 mmol) and DMF (~0.001 mL) were added. After 1 h, TMSCHN₂ (2 M in Et₂O, 0.5 mL, 1.0 mmol) was added, and after an additional 1 h, the mixture was warmed to room temperature. Concentration followed by purification by flash chromatography (SiO₂; EtOAc:PS 1:4) afforded methyl ester **304** (0.036 g, 50%) as a colourless oil; ν_max/cm⁻¹ (CHCl₃ cast) 2955, 2926 (CH), 1738 (C=O), 1599, 1447, 1344, 1159 (SO₂); δ_H (500 MHz, CDCl₃) 7.76 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.33-7.18 (7H, m, 7 × ArH), 4.56 (1H, s, NCHN), 4.09 (1H, d, *J* 13.8) and 3.99 (1H, d, *J* 13.8, NC*H*₂Ph), 3.86 (1H, dd, *J* 12.2, 6.9, TsNC*H*H), 3.62 (3H, s, OCH₃), 3.02 (1H, t, *J* 12.2, TsNCH*H*), 2.68 (1H, ddd, *J* 11.8, 7.5, 4.3) and 2.62-2.56 (1H, m, BnNC*H*₂), 2.41 (3H, s, ArCH₃), 2.23 (1H, dd, *J* 15.9, 3.9) and 2.06 (1H, dd, *J* 15.9, 10.6, C*H*₂CO₂Me), 1.68 (1H, dt, *J* 12.5, 7.5, BnNCH₂C*H*H), 1.60-1.51 (1H, m, TsNCH₂C*H*), 1.18 (1H, ddd, *J* 12.4, 6.5, 4.5, BnNCH₂CH*H*), 0.87 (3H, s, NCHCC*H*₃); δ_C (125 MHz, CDCl₃) 172.3 (C=O), 143.3, 139.0, 137.2 (3 × aromatic C), 129.7, 128.8, 128.1, 127.3, 126.7 (9 × aromatic CH), 90.5 (NCHN), 55.5 (N*C*H₂Ph), 52.7 (TsN*C*H₂), 52.2 (N*C*HCMe), 51.8 (O*C*H₃), 50.2 (BnN*C*H₂), 43.8 (TsNCH₂*C*H), 32.2 (*C*H₂CO₂Me),

30.7 (BnNCH$_2$$CH_2$), 24.2 (NCHC$CH_3$), 21.5 (Ar$CH_3$); *m/z* (FAB+) 465 (MNa$^+$, 22%), 199 (33), 173 (100); HRMS (FAB+) calcd for C$_{24}$H$_{30}$N$_2$O$_4$SNa (MNa$^+$) 465.1834, found 465.1809.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3-(2-hydroxypropyl)-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (309)
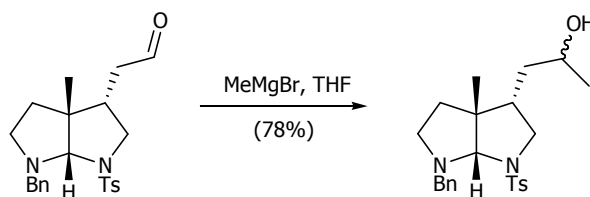
To a stirring solution of aldehyde **298** (0.63 g, 1.5 mmol) in THF (18 mL) at 0 °C was added MeMgBr (1.0 M in THF, 3.1 mL, 3.1 mmol). The temperature was maintained at 0 °C for 15 min then the flask was stirred at room temperature for 3 h and quenched by addition of saturated NH$_4$Cl (20 mL). The product was extracted into EtOAc (3 × 20 mL), washed with brine (20 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 3:7→2:3) afforded a 2:3 mixture of diastereoisomeric alcohols **309** (0.51 g, 78%) as a pale yellow oil; v_{max}/cm^{-1} (film) 3449 (br, OH), 2982, 2877 (CH), 1454, 1336, 1157 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.76 (0.8 H, d, *J* 8.3) and 7.75 (1.2H, d, *J* 8.3, 2 × S-*o*CH), 7.32-7.18 (7H, m, 7 × ArH), 4.59 (1H, s, NC*H*N), 4.09-3.98 (2H, m, NC*H$_2$*Ph), 3.79 (0.6H, dd, *J* 12.2, 6.7) and 3.76 (0.4H, dd, *J* 12.2, 6.7, TsNC*H*H), 3.67-3.61 (0.4H, m) and 3.58 (0.6H, q, *J* 6.2, C*H*(OH)), 3.00 (0.6H, t, *J* 12.1) and 2.96 (0.4H, t, *J* 12.1, TsNCH*H*), 2.69-2.63 (1H, m) and 2.62-2.56 (1H, m, BnNC*H$_2$*), 2.40 (3H, s, Ar*CH$_3$*), 1.77-1.68 (1H, m, BnNCH$_2$C*H*H), 1.65 (1H, br s, OH), 1.38-1.20 (2H, m, C*H$_2$*CH(OH)), 1.20-1.10 (2H, m, BnNCH$_2$CH*H* and TsNCH$_2$C*H*), 1.08 (1.2H, d, *J* 6.2) and 1.04 (1.8H, d, *J* 6.2, CH(OH)C*H$_3$*), 0.91 (1.8H, s) and 0.89 (1.2H, s, NCHC*CH$_3$*); δ_C (125 MHz, CDCl$_3$) 143.2, 143.1, 139.1, 137.5, 137.4 (3 × aromatic C), 129.6, 128.8, 128.1, 127.3, 127.2, 127.0, 126.7 (9 × aromatic CH), 90.7, 90.3 (NCHN), 67.6, 66.2 (CH(OH)), 55.6 (NCH$_2$Ph), 53.2, 52.7 (TsNCH$_2$), 52.8, 52.5 (NCHCMe), 50.4, 50.3 (BnNCH$_2$), 46.0, 43.8 (TsNCH$_2$$C$H), 36.7, 36.3 ($CH_2$CH(OH)), 30.7 (BnNCH$_2$$CH_2$), 24.6, 24.3 (NCHC$CH_3$), 24.0, 23.9 (CH(OH)$CH_3$), 21.5 (Ar$CH_3$); *m/z* (ESI+) 451 (MNa$^+$, 100%), 429 (83), 258 (56); HRMS (ESI+) calcd for C$_{24}$H$_{32}$N$_2$O$_3$SNa (MNa$^+$) 451.2031, found 451.2036.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-3-(2-oxopropyl)-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (310)
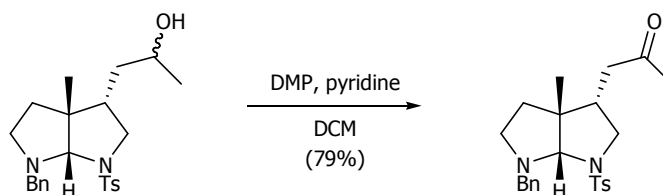
To a solution of alcohol **309** (0.46 g, 1.1 mmol) in DCM (25 mL) at 0 °C was added pyridine (0.44 mL, 5.4 mmol), followed by DMP (1.1 g, 2.7 mmol). The reaction mixture was allowed to warm to room temperature, and after 5 h was quenched by addition of saturated $Na_2S_2O_3$ (25 mL) and saturated $NaHCO_3$ (25 mL). After vigorously stirring for 30 min, the organic materials were extracted with DCM (3 × 30 mL), washed with brine (30 mL), and then dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 3:7→2:3) afforded methyl ketone **310** (0.36 g, 79%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2926, 2880 (CH), 1715 (C=O), 1599, 1448, 1348, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.78 (2H, d, *J* 8.2, 2 × S-*o*CH), 7.35-7.18 (7H, m, 7 × ArH), 4.50 (1H, s, NC*H*N), 4.08 (1H, d, *J* 13.8) and 4.00 (1H, d, *J* 13.8, NC*H₂*Ph), 3.88 (1H, dd, *J* 12.3, 6.9) and 2.89 (1H, t, *J* 12.1, TsNC*H₂*), 2.65 (1H, ddd, *J* 9.0, 7.5, 4.6) and 2.61-2.54 (1H, m, BnNC*H₂*), 2.39 (3H, s, ArCH$_3$), 2.34 (1H, dd, *J* 17.6, 3.2) and 2.11 (1H, dd, *J* 17.6, 10.5, C*H₂*COMe), 2.03 (COC*H₃*), 1.66 (1H, dt, *J* 12.5, 7.5, BnNCH₂C*H*H), 1.54-1.46 (1H, m, TsNCH₂C*H*), 1.17 (1H, ddd, *J* 12.5, 6.5, 4.6, BnNCH₂CH*H*), 0.82 (3H, s, NCHCC*H₃*); δ_C (125 MHz, CDCl$_3$) 206.5 (C=O), 143.3, 139.0, 137.0 (3 × aromatic C), 129.7, 128.8, 128.1, 127.4, 126.7 (9 × aromatic CH), 90.2 (N*C*HN), 55.3 (N*C*H₂Ph), 52.6 (TsN*C*H₂), 52.1 (NCH*C*Me), 50.1 (BnN*C*H₂), 42.7 (TsNCH₂*C*H), 41.4 (*C*H₂COMe), 31.0 (BnNCH₂*C*H₂), 30.1 (O=C*C*H₃), 24.4 (NCHC*C*H₃), 21.5 (Ar*C*H₃); *m/z* (ESI+) 449 (MNa⁺, 45%), 427 (MH⁺, 100), 242 (39); HRMS (ESI+) calcd for $C_{24}H_{31}N_2O_3S$ (MH⁺) 427.2055, found 427.2047.

Ethyl 4-((3*RS*,3a*SR*,6a*SR*)-6-benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-b]pyrrol-3-yl)-2-diazo-3-hydroxybutanoate (312)[135]
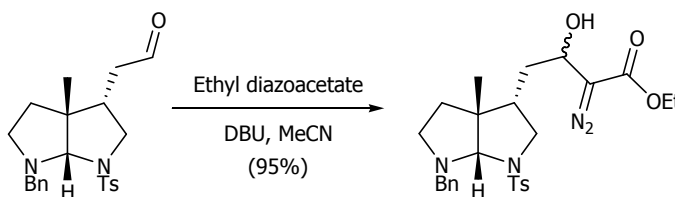
Ethyl diazoacetate (0.11 mL, 1.1 mmol) and DBU (0.03 mL, 0.2 mmol) were added to a solution of aldehyde **298** (0.22 g, 0.53 mmol) in MeCN (5 mL). After stirring for 16 h, the reaction mixture was concentrated and purified by flash chromatography (SiO$_2$; EtOAc:PS 1:9→3:7) to afford diastereoisomeric alcohols **312** (0.14 g and 0.09 g isolated, 0.04 g as mixture of diastereoisomers, total 0.27 g, 95%) as a yellow oil;

Less polar diastereoisomeric alcohol (0.14 g); v_{max}/cm^{-1} (CHCl$_3$ cast) 3416 (br, OH), 2927 (CH), 2095 (CN$_2$), 1688 (C=O), 1339, 1159 (SO$_2$); δ$_H$ (500 MHz, CDCl$_3$) 7.74 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.33-7.18 (7H, m, 7 × ArH), 4.96 (1H, br s, OH), 4.56 (1H, s, NCHN), 4.49-4.45 (1H, m, C*H*(OH)), 4.23 (2H, q, *J* 7.2, OCH$_2$), 4.08 (1H, d, *J* 13.9) and 3.99 (1H, d, *J* 13.9, NC*H$_2$*Ph), 3.80 (1H, dd, *J* 11.9, 6.3) and 3.02 (1H, t, *J* 11.8, TsNC*H$_2$*), 2.68 (1H, ddd, *J* 9.0, 7.4, 4.3) and 2.59 (1H, ddd, *J* 9.0, 7.2, 6.7, BnNC*H$_2$*), 2.39 (3H, s, ArCH$_3$), 1.71 (1H, dt, *J* 12.6, 7.5, BnNCH$_2$C*H*H), 1.60 (1H, dd, *J* 10.2, 9.3, C*H*HCH(OH)), 1.44-1.34 (2H, m, CH*H*CH(OH) and TsNCH$_2$C*H*), 1.27 (3H, t, *J* 7.2, OCH$_2$C*H$_3$*), 1.22-1.15 (1H, m, BnNCH$_2$CH*H*), 0.88 (3H, s, NCHCC*H$_3$*); δ$_C$ (125 MHz, CDCl$_3$) 166.2 (C=O), 143.3, 139.0, 137.2 (3 × aromatic C), 129.7, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 90.6 (NCHN), 64.9 (CH(OH)), 61.2 (OCH$_2$), 55.6 (N*C*H$_2$Ph), 52.5 (NCH*C*Me), 52.3 (TsN*C*H$_2$), 50.3 (BnN*C*H$_2$), 43.7 (TsNCH$_2$*C*H), 31.7 (*C*H$_2$CH(OH)), 30.8 (BnNCH$_2$*C*H$_2$), 24.3 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 14.5 (OCH$_2$*C*H$_3$), CN$_2$ too weak to be observed; *m/z* (FAB+) 527 (MH$^+$, 4%), 307 (35), 154 (100); HRMS (CI+) calcd for C$_{27}$H$_{35}$N$_4$O$_5$S (MH$^+$) 527.2328, found 527.2315.

More polar diastereoisomeric alcohol (0.09 g); v_{max}/cm^{-1} (CHCl$_3$ cast) 3416 (br, OH), 2931 (CH), 2095 (CN$_2$), 1688 (C=O), 1339, 1159 (SO$_2$); δ$_H$ (500 MHz, CDCl$_3$) 7.72 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.34-7.18 (7H, m, 7 × ArH), 4.56 (1H, s, NCHN), 4.47 (1H, t, *J* 7.2, C*H*(OH)), 4.27-4.24 (2H, m, OCH$_2$), 4.06 (1H, d, *J* 13.8) and 4.00 (1H, d, *J* 13.8,

NCH_2Ph), 3.81 (1H, dd, J 12.4, 6.8) and 3.05 (1H, t, J 12.2, TsNCH_2), 2.67 (1H, ddd, J 8.9, 7.3, 4.4) and 2.58 (1H, ddd, J 8.9, 7.5, 6.7, BnNCH_2), 2.40 (3H, s, ArCH$_3$), 1.74 (1H, dt, J 12.6, 7.5, BnNCH$_2$CHH), 1.70 (1H, br s, OH), 1.53-1.48 (2H, m, CH_2CH(OH)), 1.30 (3H, t, J 7.2, OCH$_2$CH_3), 1.18 (1H, ddd, J 12.5, 6.4, 4.6, BnNCH$_2$CHH), 1.10-1.00 (1H, m, TsNCH$_2$CH), 0.87 (3H, s, NCHCCH_3); δ_C (125 MHz, CDCl$_3$) 166.1 (C=O), 143.3, 139.0, 137.3 (3 × aromatic C), 129.6, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 90.2 (NCHN), 66.2 (CH(OH)), 61.3 (OCH$_2$), 55.4 (NCH$_2$Ph), 53.0 (NCHCMe), 52.7 (TsNCH$_2$), 50.2 (BnNCH$_2$), 45.5 (TsNCH$_2$$C$H), 31.6 ($CH_2$CH(OH)), 30.7 (BnNCH$_2$$CH_2$), 24.5 (NCHC$CH_3$), 21.5 (ArCH$_3$), 14.5 (OCH$_2$$CH_3$), CN$_2$ too weak to be observed; m/z (FAB+) 527 (MH$^+$, 5%), 371 (29), 279 (19), 154 (100); HRMS (FAB+) calcd for C$_{27}$H$_{35}$N$_4$O$_5$S (MH$^+$) 527.2328, found 527.2319.

Ethyl 4-((3*RS*,3a*SR*,6a*RS*)-6-benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)-3-oxobutanoate (313)[135]
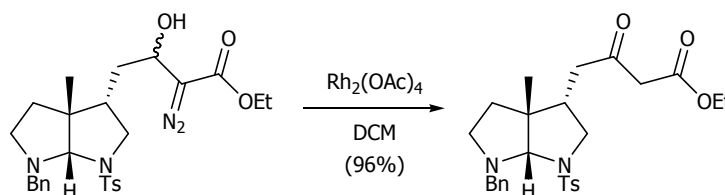

To a stirring solution of alcohols **312** (0.26 g, 0.49 mmol) in DCM (5 mL) was added Rh$_2$(OAc)$_4$ (2 mg, 5 μmol) and the mixture stirred for 3 h. Concentration and filtration through a short plug of silica gel (EtOAc:PS 1:1) afforded β-keto ester **313** (0.24 g, 96%) as a yellow oil; $\delta_H^\dagger$ (500 MHz, CDCl$_3$) 7.78 (2H, d, J 8.3, 2 × S-*o*CH), 7.35-7.18 (7H, m, 7 × ArH), 4.50 (1H, s, NCHN), 4.15 (2H, q, J 7.2, OCH$_2$), 4.08 (1H, d, J 13.9) and 3.99 (1H, d, J 13.9, NCH_2Ph), 3.91 (1H, dd, J 12.4, 6.9, TsNCHH), 3.34 (1H, d, J 15.7) and 3.32 (1H, d, J 15.7, CH_2CO$_2$Et), 2.92 (1H, t, J 12.1, TsNCHH), 2.67 (1H, ddd, J 9.0, 7.5, 4.5) and 2.61-2.55 (1H, m, BnNCH_2), 2.47 (1H, dd, J 18.1, 3.2, CHHC(=O)CH$_2$CO$_2$Et), 2.40 (3H, s, ArCH$_3$), 2.31 (1H, dd, J 18.1, 10.3, CHHC(=O)CH$_2$CO$_2$Et), 1.66 (1H, dt, J 12.5, 7.3, BnNCH$_2$CHH), 1.60-1.51 (1H, m, TsNCH$_2$CH), 1.24 (3H, t, J 7.2, OCH$_2$CH_3), 1.18 (1H, ddd, J 12.2, 6.5, 4.7, BnNCH$_2$CHH), 0.82 (3H, s, NCHCCH_3); δ_C (125 MHz, CDCl$_3$) 200.8

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† The ^{1}H NMR spectrum suggests that ~22% of the β-keto ester exists in the enol form in CDCl$_3$ at r.t.: 12.01, (0.18H, s), 4.58 (0.22H, s), 3.90 (0.23H, dd, J 6.9, 12.2)

(O=*C*CH$_2$CO$_2$Et), 166.9 (*C*O$_2$Et), 143.3, 139.0, 137.0 (3 × aromatic C), 129.7, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 90.2 (N*C*HN), 61.5 (O*C*H$_2$), 55.3 (N*C*H$_2$Ph), 52.5 (TsN*C*H$_2$), 52.1 (NCHC*C*Me), 50.1 (BnN*C*H$_2$), 49.2 (*C*H$_2$CO$_2$Et), 42.4 (TsNCH$_2$*C*H), 40.8 (*C*H$_2$C(=O)CH$_2$CO$_2$Et), 31.1 (BnNCH$_2$*C*H$_2$), 24.3 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 14.1 (OCH$_2$*C*H$_3$); *m/z* (ESI+) 521 (MNa$^+$, 91%), 499 (MH$^+$, 48), 475 (39), 453 (92), 393 (30), 348 (100); HRMS (ESI+) calcd for C$_{27}$H$_{34}$N$_2$O$_5$SNa (MNa$^+$) 521.2086, found 521.2071.

Ethyl 4-((3*RS*,3a*SR*,6a*RS*)-6-benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)-2-diazo-3-oxobutanoate (314)[135]

To a stirring solution of β-keto ester **313** (0.24 g, 0.48 mmol) in MeCN (5 mL) at 0 °C was added Et$_3$N (0.20 mL, 1.4 mmol) and *p*ABSA (0.17 g, 0.72 mmol). After 3 d, H$_2$O (5 mL) was added and the organic materials were extracted with EtOAc (3 × 5 mL), washed with H$_2$O (5 mL) and brine (5 mL), then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9) afforded diazo ester **314** (0.18 g, 72 %) as a yellow oil; v_{max}/cm^{-1} (film) 2930, 2878 (CH), 2137 (CN$_2$), 1714, 1651 (C=O), 1454, 1356, 1159 (SO$_2$); δ$_H$ (500 MHz, CDCl$_3$) 7.78 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.32-7.18 (7H, m, 7 × ArH), 4.54 (1H, s, NCHN), 4.24 (2H, q, *J* 7.1, OCH$_2$), 4.09 (1H, d, *J* 13.9) and 3.99 (1H, d, *J* 13.9, NC*H*$_2$Ph), 3.87 (1H, dd, *J* 12.2, 6.9) and 2.99 (1H, t, *J* 12.1, TsNC*H*$_2$), 2.81 (1H, dd, *J* 16.7, 3.4, O=CC*H*H), 2.68 (1H, ddd, *J* 9.0, 7.4, 4.3, BnNC*H*H), 2.64-2.60 (1H, m, O=CCH*H*), 2.62-2.59 (1H, m, BnNCH*H*), 2.40 (3H, s, ArCH$_3$), 1.76 (1H, dt, *J* 12.6, 7.5, BnNCH$_2$C*H*H), 1.69-1.62 (1H, m, TsNCH$_2$C*H*), 1.29 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.24 (1H, ddd, *J* 12.5, 6.5, 4.4, BnNCH$_2$CH*H*), 0.88 (3H, s, NCHC*C*H$_3$); δ$_C$ (125 MHz, CDCl$_3$) 190.8 (O=*C*C(=N$_2$)CO$_2$Et), 161.2 (*C*O$_2$Et), 143.1, 139.1, 137.3 (3 × aromatic C), 129.6, 128.8, 128.1, 127.3, 126.7 (9 × aromatic CH), 90.3 (N*C*HN), 75.9 (*C*=N$_2$), 61.5 (O*C*H$_2$), 55.5 (N*C*H$_2$Ph), 52.4 (NCHC*C*Me), 52.3 (TsN*C*H$_2$), 50.2 (BnN*C*H$_2$), 43.2 (TsNCH$_2$*C*H), 38.0 (O=C*C*H$_2$), 31.0 (BnNCH$_2$*C*H$_2$), 24.2 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$); *m/z* (ESI+) 547 (MNa$^+$, 100%), 525

(MH$^+$, 12), 519 (63), 499 (38); HRMS (ESI+) calcd for $C_{27}H_{32}N_4O_5SNa$ (MNa$^+$) 547.1991, found 547.1975.

(3RS,3aSR,6aRS)-3-Allyl-6-benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-b]pyrrole (322)[172]

To a stirring suspension of Ph$_3$PCH$_3$Br (0.047 g, 0.13 mmol) in THF (3 mL) at 0 °C was added ^{n}BuLi (1.6 M in hexanes, 0.08 mL, 0.13 mmol) and the mixture was warmed to room temperature. After 1 h, the reaction mixture was cooled to −78 °C and aldehyde **298** (0.050 g, 0.12 mmol) in THF (1 mL and 2 × 0.5 mL washes) was added *via* cannula. After 10 min, the reaction was warmed to room temperature and after a further 4 h, H$_2$O (5 mL) was added. The organic materials were extracted with EtOAc (3 × 5 mL), washed with brine (2 × 5 mL) and dried (MgSO$_4$), then concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:9) provided olefin **322** (0.015 g, 30%) as a pale yellow oil; δ_H (500 MHz, CDCl$_3$) 7.74 (2H, d, J 8.3, 2 × S-*o*CH), 7.36-7.19 (7H, m, 7 × ArH), 5.55 (1H, dddd, J 16.5, 10.6, 7.5, 6.3, HC=CH$_2$), 4.94-4.89 (2H, m, HC=CH_2), 4.61 (1H, s, NCHN), 4.08 (1H, d, J 13.9) and 3.98 (1H, d, J 13.9, NCH_2Ph), 3.60 (1H, dd, J 12.1, 6.9) and 2.94 (1H, t, J 12.1, TsNCH_2), 2.69 (1H, ddd, J 9.0, 7.4, 4.3) and 2.62-2.56 (1H, m, BnNCH_2), 2.41 (3H, s, ArCH$_3$), 2.04-1.98 (1H, m, BnNCH$_2$CHH), 1.84-1.74 (2H, m, H_2CCH=CH$_2$), 1.28-1.16 (2H, m, TsNCH$_2$CH and BnNCH$_2$CHH), 0.92 (3H, s, NCHCCH_3); δ_C (125 MHz, CDCl$_3$) 143.1, 139.1, 137.5 (3 × aromatic C), 136.2 (HC=CH$_2$), 129.6, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 116.1 (HC=CH$_2$), 91.2 (NCHN), 55.7 (NCH$_2$Ph), 52.6 (TsNCH$_2$), 52.3 (NCHCMe), 50.4 (BnNCH$_2$), 47.3 (TsNCH$_2$$C$H), 31.6 (H$_2$$C$CH=CH$_2$), 30.6 (BnNCH$_2$$CH_2$), 24.6 (NCHC$CH_3$), 21.5 (Ar$CH_3$); m/z (CI+) 411 (MH$^+$, 51%), 125 (36), 93 (100); HRMS (CI+) calcd for $C_{24}H_{31}N_2O_2S$ (MH$^+$) 411.2106, found 411.2112.

Diethyl (1-diazo-2-oxopropyl)phosphonate (323)
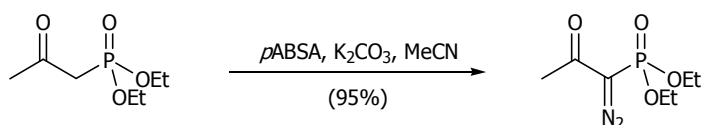
To a stirring solution of *p*ABSA (0.26 g, 1.1 mmol) in MeCN (15 mL) was added K_2CO_3 (0.43 g, 3.1 mmol) and phosphonate **262** (0.20 g, 1.0 mmol). After 20 h, the suspension was filtered, washing with DCM (40 mL). After concentration, the white solid was partially re-dissolved in DCM (10 mL) and filtered. Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 3:7→2:3) provided diazo phosphonate **323** (0.22 g, 95%) as a yellow oil; v_{max}/cm^{-1} (film) 2988, (CH), 2124 (CN$_2$), 1661 (C=O), 1369, 1267, 1020; δ_H (500 MHz, CDCl$_3$) 4.26-4.10 (4H, m, 2 × OCH$_2$), 2.25 (3H, d, *J* 1.6, O=CCH$_3$), 1.38-1.34 (6H, m, 2 × OCH$_2$C*H*$_3$); δ_C (125 MHz, CDCl$_3$) 190.2 (*J* 13.7, C=O), 63.4 (*J* 5.5, OCH$_2$), 27.2 (O=C*C*H$_3$), 16.1 (*J* 6.9, OCH$_2$*C*H$_3$), C=N$_2$ too weak to be observed; *m/z* (ESI+) 243 (MNa$^+$, 100%), 221 (MH$^+$, 84); HRMS (ESI+) calcd for C$_7$H$_{13}$N$_2$O$_4$PNa (MNa$^+$) 243.0511, found 243.0506.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-3-(prop-2-ynyl)-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (324)
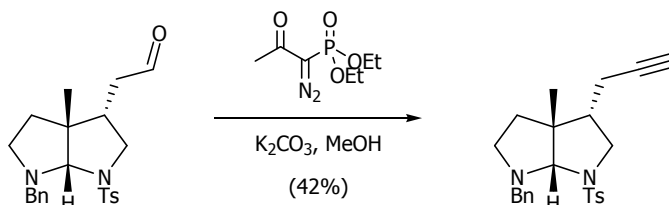
To a stirring solution of aldehyde **298** (0.27 g, 0.65 mmol) in MeOH (3 mL) was added K_2CO_3 (0.23 g, 1.6 mmol) and phosphonate **323** (0.22 g, 0.98 mmol). After 20 h, the mixture was concentrated, then diluted with Et$_2$O (10 mL), washed with H$_2$O (10 mL), brine (10 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) provided alkyne **324** (0.11 g, 42%) as a pale yellow oil; δ_H (500 MHz, CDCl$_3$) 7.75 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.31-7.19 (7H, m, 7 × ArH), 4.60 (1H, s, NCHN), 4.10 (1H, d, *J* 13.9) and 3.96 (1H, d, *J* 13.9, NC*H*$_2$Ph), 3.82 (1H, dd, *J* 12.1, 6.9) and 3.05 (1H, t, *J* 12.1, TsNC*H*$_2$), 2.70 (1H, ddd, *J* 9.0, 7.3, 4.2) and 2.62-2.55 (1H, m, BnNC*H*$_2$), 2.41 (3H, s, ArCH$_3$), 2.10 (1H, ddd, *J* 17.0, 5.8, 2.8) and 1.99 (1H, ddd, *J* 17.0, 9.3, 2.7, C*H*$_2$C≡CH), 1.92 (1H, t, *J* 2.7,

C≡CH), 1.74 (1H, dt, *J* 12.6, 7.7, BnNCH$_2$C*H*H), 1.48-1.40 (1H, m, TsCH$_2$C*H*), 1.26-1.18 (1H, m, BnNCH$_2$CH*H*), 0.94 (3H, s, NCHCC*H$_3$*); δ_C (125 MHz, CDCl$_3$) 143.3, 139.0, 137.3 (3 × aromatic C), 129.7, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 91.3 (N*C*HN), 81.7 (*C*≡CH), 69.6 (C≡*C*H), 55.6 (N*C*H$_2$Ph), 52.5 (TsN*C*H$_2$), 52.1 (NCH*C*Me), 50.3 (BnN*C*H$_2$), 46.5 (TsNCH$_2$*C*H), 30.3 (BnNCH$_2$*C*H$_2$), 24.6 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 16.5 (*C*H$_2$C≡CH); *m/z* (CI+) 409 (MH$^+$, 21%), 93 (100); HRMS (CI+) calcd for C$_{24}$H$_{29}$N$_2$O$_2$S (MH$^+$) 409.1950, found 409.1939.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3-(2-hydroxybut-3-enyl)-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (336)
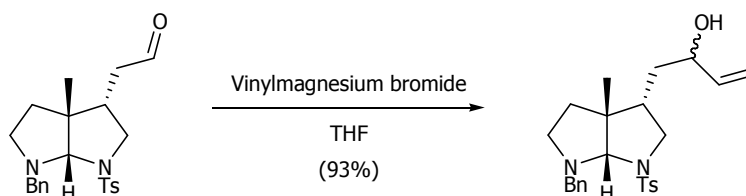
To a stirring solution of aldehyde **298** (0.20 g, 0.49 mmol) in THF (5 mL) at 0 °C was added vinylmagnesium bromide (0.7 M in THF, 1.04 mL, 0.73 mmol). After 1 h, saturated NH$_4$Cl (5 mL) was added and the mixture warmed to room temperature, then extracted with EtOAc (3 × 5 mL), washed with H$_2$O (5 mL), brine (5 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 3:7) afforded a 2:3 mixture of diastereoisomeric alcohols **336** (0.20 g, 93%) as a colourless oil; v_{max}/cm^{-1} (film) 3491 (br, OH), 2928, 2876 (CH), 1597, 1452, 1337, 1157 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.73 (0.8H, d, *J* 8.1) and 7.72 (1.2H, d, *J* 8.1, 2 × S-*o*CH), 7.33-7.18 (7H, m, 7 × ArH), 5.72-5.59 (1H, m, *H*C=CH$_2$), 5.15-4.99 (2H, m, HC=C*H$_2$*), 4.56 (0.6H, s) and 4.55 (0.4H, s, N*C*HN), 4.09-3.98 (2H, m, NC*H$_2$*Ph), 3.98-3.03 (0.4H, m, C*H$_{(minor)}$*(OH), 3.87-3.76 (1.6H, m, C*H$_{(major)}$*(OH) and TsNC*H*H), 3.02 (0.4H, t, *J* 12.2) and 2.98 (0.6H, t, *J* 11.8, TsNCH*H*), 2.66 (1H, ddd, *J* 8.9, 7.7, 4.5) and 2.61-2.55 (1H, m, BnNC*H$_2$*), 2.39 (3H, s, Ar*C*H$_3$), 1.90 (1H, br s, OH), 1.77-1.69 (1H, m, BnNCH$_2$C*H*H), 1.45-1.22 (2.4H, m, C*H$_2$*CH(OH) and TsNCH$_2$C*H$_{(minor)}$*), 1.22-1.05 (1.6H, m, BnNCH$_2$CH*H* and TsNCH$_2$C*H$_{(major)}$*), 0.87 (1.8H, s) and 0.86 (1.2H, s, NCHCC*H$_3$*); δ_C (125 MHz, CDCl$_3$) 143.2, 143.1 (aromatic C), 140.7, 140.5 (H*C*=CH$_2$), 139.1, 137.4, 137.3 (2 × aromatic C), 129.6, 128.8, 128.1, 127.3, 127.0, 126.7 (9 × aromatic CH), 115.5, 115.1 (HC=*C*H$_2$), 90.5, 90.3 (N*C*HN), 72.7, 71.4 (*C*H(OH)), 55.5 (N*C*H$_2$Ph), 53.1, 52.9 (TsN*C*H$_2$), 52.8, 52.7 (NCH*C*Me), 50.3 (BnN*C*H$_2$), 45.2, 43.5

(TsNCH$_2$*C*H), 34.5, 34.3 (*C*H$_2$CH(OH)), 30.8 (BnNCH$_2$*C*H$_2$), 24.4, 24.3 (NCHC*C*H$_3$), 21.6 (Ar*C*H$_3$); *m/z* (ESI+) 463 (MNa$^+$, 100%), 441 (MH$^+$, 30), 270 (55), 172 (23); HRMS (ESI+) calcd for C$_{25}$H$_{32}$N$_2$O$_3$SNa (MH$^+$) 463.2031, found 463.2029.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3-(2-(*tert*-butyldimethylsilyloxy)but-3-enyl)-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (337)[173]
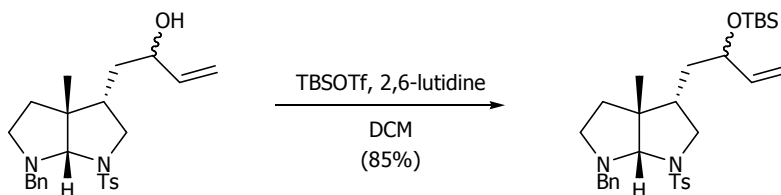
To a stirring solution of alcohols **336** (0.10 g, 0.23 mmol) in DCM (5 mL) at 0 °C was added 2,6-lutidine (0.11 mL, 0.91 mmol) and TBSOTf (0.10 mL, 0.45 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 16 h. Saturated NaHCO$_3$ (5 mL) was added, then the organic materials were extracted with EtOAc (2 × 5 mL), washed with H$_2$O (5 mL), brine (5 mL), and then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:9) afforded a 2:3 mixture of diastereoisomeric products **337** (0.11 g, 85%) as a pale yellow oil; v_{max}/cm^{-1} (film) 2933 (CH), 1597, 1456, 1344, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.72 (0.8H, d, *J* 8.1) and 7.71 (1.2H, d, *J* 8.1, 2 × S-*o*CH), 7.34-7.18 (7H, m, 7 × ArH), 5.59-5.48 (1H, m, *H*C=CH$_2$), 5.05-4.90 (2H, m, HC=C*H$_2$*), 4.58 (0.4H, s) and 4.54 (0.6H, s, NCHN), 4.13-3.95 (3H, m, NC*H$_2$*Ph and C*H*(OTBS)), 3.80 (0.4H, dd, *J* 12.0, 6.6) and 3.73 (0.6H, dd, *J* 12.2, 6.8, TsNC*H*H), 2.96 (0.4H, t, *J* 12.0) and 2.95 (0.6H, t, *J* 12.0, TsNCH*H*), 2.70-2.63 (1H, m) and 2.62-2.55 (1H, m, BnNC*H$_2$*), 2.40 (3H, s, Ar*C*H$_3$), 1.77-1.68 (1H, m, BnNCH$_2$C*H*H), 1.46-1.37 (1H, m, C*H*HCH(OTBS)), 1.36-1.20 (2H, m, CH*H*CH(OTBS) and TsNCH$_2$C*H*), 1.19-1.10 (1H, m, BnNCH$_2$CH*H*), 0.88, 0.86, 0.83 (12H, s, NCHCC*H$_3$* and C(CH$_3$)$_3$), 0.00, −0.01, −0.02, −0.03 (6H, s, Si(CH$_3$)$_2$); δ_C (125 MHz, CDCl$_3$) 143.0, 142.9 (aromatic C), 140.7, 140.2 (H*C*=CH$_2$), 139.2, 137.5, 137.4 (2 × aromatic C), 129.6, 128.8, 128.1, 127.4, 127.3, 126.7, 126.6 (9 × aromatic CH), 114.6, 114.4 (HC=*C*H$_2$), 90.2, 90.1 (NCHN), 72.3, 72.1 (*C*H(OTBS)), 55.6, 55.5 (N*C*H$_2$Ph), 53.8, 53.4 (TsN*C*H$_2$), 53.0, 52.9 (NCH*C*Me), 50.3, 50.2 (BnN*C*H$_2$), 43.1, 43.0 (TsNCH$_2$*C*H), 35.9, 35.3 (*C*H$_2$CH(OTBS)), 30.9, 30.8 (BnNCH$_2$*C*H$_2$), 25.9, 25.8 (C(*C*H$_3$)$_3$), 24.5, 24.4 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 18.1 (*C*Me$_3$), −4.5, −4.5, −4.9, −5.0

(Si(CH$_3$)$_2$); *m/z* (FAB+) 577 (MNa$^+$, 26%), 555 (MH$^+$, 100), 399 (22), 172 (22); HRMS (FAB+) calcd for C$_{31}$H$_{47}$N$_2$O$_3$SSi (MH$^+$) 555.3077, found 555.3083.

4-((3RS,3aSR,6aRS)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)pyrrolo[2,3-b]octahydropyrrol-3-yl)-3-(*tert*-butyldimethylsilyloxy)butane-1,2-diol (338)
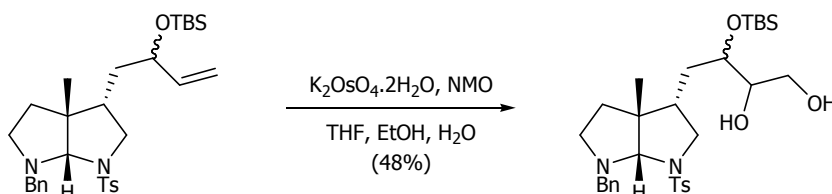
To a stirring solution of olefins **337** (0.08 g, 0.14 mmol) in THF (2 mL), EtOH (1 mL) and H$_2$O (1 mL) was added NMO (0.029 g, 0.22 mmol) and K$_2$OsO$_4$.2H$_2$O (0.01 g, 0.03 mmol). After 20 h and 3 d, further portions of NMO (0.029 g, 0.22 mmol) were added. After a total reaction time of 5 d, the mixture was filtered through Celite$^®$, washing with MeOH (10 mL). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 3:7→2:3) afforded a 2:3 mixture of diols **338** (0.04 g, 48%) as a pale yellow oil; v_{max}/cm^{-1} (film) 3447 (br s, OH), 2932, 2858 (CH), 1599, 1458, 1337, 1157 (SO$_2$); δ$_H$ (500 MHz, CDCl$_3$) 7.75 (2H, d, *J* 8.1, 2 × S-*o*CH), 7.32-7.18 (7H, m, 7 × ArH), 4.67 (0.4H, s) and 4.58 (0.6H, s, NCHN), 4.11-3.96 (2H, m, NC*H*$_2$Ph), 3.75 (0.4H, dd, *J* 12.3, 6.9) and 3.70 (0.6H, dd, *J* 12.0, 6.9, TsNC*H*H), 3.66-3.39 (3H, m, C*H*(OH)C*H*$_2$OH), 3.33-3.28 (0.4H, m) and 3.26-3.20 (1H, m, C*H*(OTBS)), 3.02 (0.6H, t, *J* 12.2) and 2.91 (0.4H, t, *J* 12.0, TsNCH*H*), 2.71-2.64 (1H, m) and 2.63-2.56 (1H, m, BnNC*H*$_2$), 2.39 (3H, s, ArCH$_3$), 2.38 (2H, br s, CH(O*H*)CH$_2$O*H*), 1.72 (1H, dt, *J* 12.7, 7.5, BnNCH$_2$C*H*H), 1.63-1.34 (2.4H, m, C*H*$_2$CH(OTBS) and TsNCH$_2$C*H*$_{(minor)}$), 1.31-1.08 (1.6H, m, BnNCH$_2$CH*H* and TsNCH$_2$C*H*$_{(major)}$), 0.97, 0.90, 0.86, 0.81 (12H, s, NCHCC*H$_3$* and C(CH$_3$)$_3$), 0.04, 0.03, 0.00, −0.02 (6H, s, Si(CH$_3$)$_2$); δ$_C$ (125 MHz, CDCl$_3$) 143.4, 143.2, 139.0, 137.6, 137.3 (3 × aromatic C), 129.7, 129.6, 128.8, 128.1, 127.3, 127.2, 126.7 (9 × aromatic CH), 90.3 (NCHN), 73.1, 72.4 (CH(OTBS)), 72.4, 71.6 (*C*H(OH)CH$_2$OH), 63.4, 63.2 (CH$_2$OH), 56.0, 55.5 (N*C*H$_2$Ph), 53.2 (TsN*C*H$_2$), 53.0, 52.9 (NCH*C*Me), 50.4, 50.2 (BnN*C*H$_2$), 43.4, 42.8 (TsNCH$_2$*C*H), 31.4, 30.9 (*C*H$_2$CH(OTBS)), 30.6 (BnNCH$_2$*C*H$_2$), 25.9, 25.7 (C(*C*H$_3$)$_3$), 24.5, 24.2 (NCHC*C*H$_3$), 21.5 (ArCH$_3$), 17.9, 17.8 (*C*Me$_3$), −4.2, −4.3, −4.8, −4.9 (Si(CH$_3$)$_2$); *m/z* (ESI+) 611 (MNa$^+$, 100%), 589 (MH$^+$, 32); HRMS (ESI+) calcd for C$_{31}$H$_{48}$N$_2$O$_5$SSiNa (MNa$^+$) 611.2951, found 611.2958.

3-((3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)-2-trimethylsilyloxypropanenitrile (340)[143]
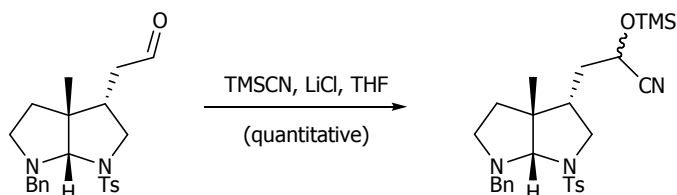
To a solution of aldehyde **298** (0.035 g, 0.08 mmol) and TMSCN (0.14 mL, 0.97 mmol) was added LiCl (0.3 M in THF (sonicated for 15 min) 3 μL, 0.9 μmol) and the mixture stirred for 16 h. Concentration provided a 1:1 mixture of diastereoisomeric silyl-protected cyanohydrins **340** (0.042g, quantitative) as a yellow oil, which was used without further purification; δ_H (500 MHz, CDCl$_3$) 7.74 (2H, d, *J* 8.0, 2 × S-*o*CH), 7.37-7.20 (7H, m, 7 × ArH), 4.58 (0.5H, s) and 4.57 (0.5H, s, NCHN), 4.38 (0.5H, t, *J* 4.9) and 4.21 (0.5H, t, *J* 6.5, C*H*(OTMS)), 4.08 (0.5H, d, *J* 14.0), 4.07 (0.5H, d, *J* 14.0), 2.99 (0.5H, d, *J* 14.0) and 3.98 (0.5H, d, *J* 14.0, NC*H*$_2$Ph), 3.87 (0.5H, dd, *J* 12.4, 7.0), 3.80 (0.5H, dd, *J* 12.4, 7.0), 3.03 (0.5H, t, *J* 12.2) and 3.02 (0.5H, t, *J* 12.2, TsNC*H*$_2$), 2.71-2.63 (1H, m) and 2.62-2.55 (1H, m, BnNC*H*$_2$), 2.40 (3H, s, ArCH$_3$), 1.78-1.49 (3H, m, BnNCH$_2$C*H*H and C*H*$_2$CH(OTMS)), 1.38-1.11 (2H, m, TsNCH$_2$C*H* and BnNCH$_2$CH*H*), 0.91 (3H, s, NCHCC*H*$_3$), 0.35, 0.19, 0.18, 0.05 (15H, m, (Si(CH$_3$)$_3$ and other TMS containing impurities); δ_C (125 MHz, CDCl$_3$) 143.6, 143.4, 139.1, 139.0, 137.2, 137.0 (3 × aromatic C), 129.9, 129.8, 128.7, 128.1, 127.2, 127.1, 126.8, 126.7 (9 × aromatic CH), 119.3, 119.1 (C≡N), 90.0, 89.9 (NCHN), 60.6 (CH(OTMS)), 55.5, 55.4 (N*C*H$_2$Ph), 53.2, 52.7 (TsN*C*H$_2$), 52.9, 52.7 (NCH*C*Me), 50.1 (BnN*C*H$_2$), 44.6, 44.0 (TsNCH$_2$*C*H), 34.6, 34.1 (*C*H$_2$CH(OTMS)), 30.9, 29.7 (BnNCH$_2$*C*H$_2$), 24.4 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 1.9, 1.3, 0.9, −0.4, −1.8 (Si(CH$_3$)$_3$ and other TMS containing impurities).

3-((3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)-2-hydroxypropanenitrile (343)
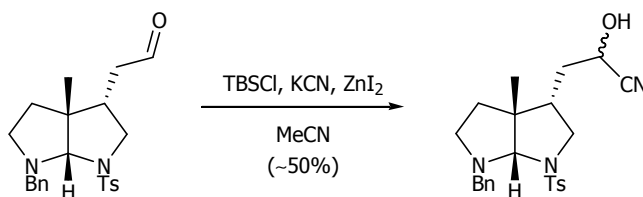

To a stirring solution of aldehyde **298** (0.03 g, 0.07 mmol) in MeCN (1 mL) was added KCN (0.047 g, 0.73 mmol), ZnI_2 (1 μg, 2 μmol) and TBSCl (0.013 g, 0.09 mmol). After 20 h, further ZnI_2 (4 μg, 8 μmol) was added and after an additional 5 h, the mixture was concentrated. The residue was diluted with EtOAc (30 mL) and filtered on Celite® and the filtrate was then washed with H_2O (5 mL), brine (10 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:4→3:7) provided a 3:2 mixture of diastereoisomeric alcohols **343** (0.017 g, ~50%) which contained ~10% aldehyde starting material; v_{max}/cm^{-1} (CHCl$_3$ cast) 3449 (OH), 2928 (CH), 2246 (C≡N), 1720 (C=O of aldehyde), 1596, 1454, 1339, 1157 (SO$_2$); peaks excluding those from aldehyde are quoted: δ_H (500 MHz, CDCl$_3$) 7.75 (0.8H, d, *J* 8.3) and 7.74 (1.2H, d, *J* 8.3, 2 × S-*o*CH), 7.32-7.20 (7H, m, 7 × ArH), 4.57 (0.6H, s) and 4.55 (0.4H, s, NCHN), 4.42 (0.6H, dd, *J* 6.3, 4.9) and 4.28 (0.4H, dd, *J* 7.6, 6.5, C*H*(OH)), 4.08 (0.6H, d, *J* 13.9), 4.06 (0.4H, d, *J* 13.9), 3.99 (0.4H, d, *J* 13.9) and 3.98 (0.6H, d, *J* 13.9, NC*H*$_2$Ph), 3.93 (0.4H, dd, *J* 6.7, 12.4) and 3.90-3.84 (0.6H, m, TsNC*H*H), 3.08 (0.4H, t, *J* 12.2) and 3.07 (0.6H, t, *J* 12.2, TsNCH*H*), 2.71 (1H, ddd, *J* 9.0, 7.3, 3.9) and 2.64-2.57 (1H, m, BnNC*H*$_2$), 2.40 (3H, s, ArCH$_3$), 1.81-1.54 (3H, m, BnNCH$_2$C*H*H and C*H*$_2$CH(OH)), 1.45-1.35 (0.6H, m, TsNCH$_2$C*H*$_{(major)}$), 1.34-1.14 (1.4H, m, TsNCH$_2$C*H*$_{(minor)}$ and BnNCH$_2$CH*H*), 0.90 (1.2H, s) and 0.88 (1.8H, s, NCHCC*H*$_3$); δ_C (125 MHz, CDCl$_3$) 143.7, 138.5, 137.0, 136.8 (3 × aromatic C), 129.9, 128.9, 128.2, 127.3, 127.1, 126.9, 126.8 (9 × aromatic CH), 119.4, 119.3 (C≡N), 90.0, 89.8 (NCHN), 60.6, 60.0 (CH(OH)), 55.5 (NCH$_2$Ph), 52.8, 52.74 (NCHCMe), 52.68, 52.6 (TsNCH$_2$), 50.2, 50.1 (BnNCH$_2$), 45.0, 43.8 (TsNCH$_2$CH), 33.3, 32.7 (CH$_2$CH(OH)), 30.9, 30.8 (BnNCH$_2$CH$_2$), 24.4, 24.2 (NCHCCH$_3$), 21.5 (ArCH$_3$); *m/z* (ESI+) 440 (MH$^+$, 84%), 413 (100); HRMS (ESI+) calcd for C$_{24}$H$_{30}$N$_3$O$_3$S (MH$^+$) 440.2008, found 440.2027.

3-((3RS,3aSR,6aRS)-6-Benzyl-3a-methyl-1-(4-

toluenesulfonyl)octahydropyrrolo[2,3-b]pyrrol-3-yl)-2-(tert-

butyldimethylsilyloxy)propanenitrile (344)
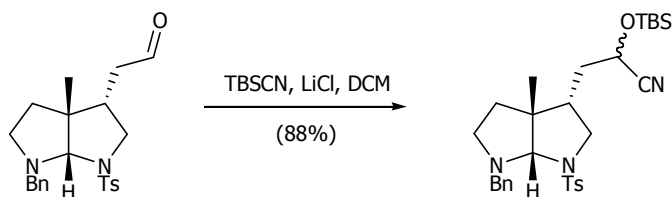
To a solution of aldehyde **298** (0.32 g, 0.78 mmol) and TBSCN (0.22 g, 1.6 mmol) in DCM (0.5 mL) was added LiCl (0.3 M in DCM (sonicated for 15 min) 0.026 mL, 7.8 μmol) and the mixture stirred for 2 d. The mixture was diluted with H_2O (5 mL) and the organic materials were extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), and dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc:PS 1:19→3:17) afforded a 2:3 mixture of the diastereoisomeric OTBS protected cyanohydrins **344** (0.37 g, 88%) as a pale yellow oil; v_{max}/cm^{-1} ($CHCl_3$ cast) 2933 (CH), 2332 (C≡N), 1599, 1458, 1348, 1159 (SO_2); δ_H (500 MHz, $CDCl_3$) 7.77-7.72 (2H, m, 2 × S-*o*CH), 7.34-7.19 (7H, m, 7 × ArH), 4.57 (0.4H, s) and 4.56 (0.6H, s, NCHN), 4.44 (0.4H, t, *J* 4.3) and 4.28 (0.6H, t, *J* 6.0, C*H*(OTBS)), 4.09 (0.4H, d, *J* 14.0), 4.08 (0.6H, d, *J* 14.0) and 4.04-3.98 (1H, m, NC*H₂*Ph), 3.93-3.85 (1H, m), 3.04 (0.6H, t, *J* 12.2) and 3.01 (0.4H, t, *J* 12.2, TsNC*H₂*), 2.71-2.64 (1H, m) and 2.62-2.55 (1H, m, BnNC*H₂*), 2.39 (3H, s, ArCH₃), 1.75-1.63 (2H, m, BnNCH₂C*H*H and C*H*HCH(OTBS)), 1.62-1.49 (1H, m, CH*H*CH(OTBS)), 1.42-1.32 (1H, m, TsNCH₂C*H*), 1.23-1.14 (1H, m, BnNCH₂CH*H*), 0.91, 0.90, 0.85 (12H, s, NCHCC*H₃* and C(CH₃)₃), 0.18, 0.15, 0.10 (6H, s, Si(CH₃)₂); δ_C (125 MHz, $CDCl_3$) 143.6, 143.4, 139.0, 137.1, 136.9 (3 × aromatic C), 129.9, 128.8, 128.1, 127.2, 127.1, 126.8, 126.7 (9 × aromatic CH), 119.4, 119.0 (C≡N), 89.9 (NCHN), 61.5, 61.0 (CH(OTBS)), 55.5, 55.4 (NCH₂Ph), 53.5, 52.7 (TsNCH₂), 53.0, 52.8 (NCHCMe), 50.1 (BnNCH₂), 44.2, 43.8 (TsNCH₂CH), 34.7, 34.1 (*C*H₂CH(OTBS)), 30.9 (BnNCH₂CH₂), 25.5 (C(*C*H₃)₃), 24.4 (NCHCCH₃), 21.5 (ArCH₃), 18.0, 17.9 (*C*Me₃), −5.2, −5.3, −5.5 (Si(CH₃)₂); *m/z* (FAB+) 576 (MNa⁺, 93%), 554 (MH⁺, 78), 381 (100), 176 (58); HRMS (FAB+) calcd for $C_{30}H_{43}N_3O_3SSiNa$ (MNa⁺) 576.2692, found 576.2702.

3-((3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)-2-(*tert*-butyldimethylsilyloxy)propanal (339) and 3-((3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)-2-(*tert*-butyldimethylsilyloxy)propylamine (345)
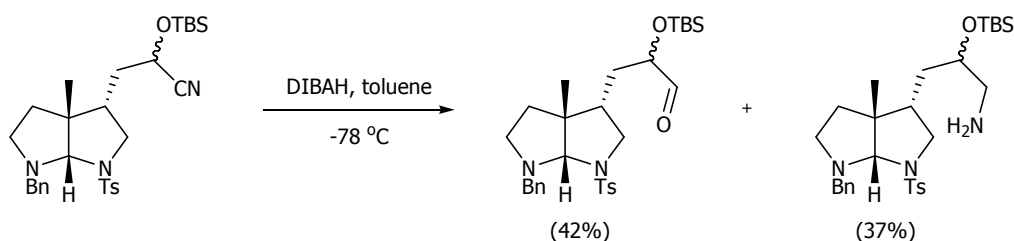

To a solution of nitrile **344** (0.28 g, 0.51 mmol) in toluene (5 mL) at −78 °C was added DIBAH (20% weight in toluene, 0.68 mL, 0.82 mmol) dropwise. After stirring for 1.5 h at −78 °C, 0.5 M sodium potassium tartrate (5 mL) was added and the stirring mixture warmed to room temperature. After 30 min, the organic materials were extracted with EtOAc (3 × 5 mL), washed with brine (5 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:19→1:9 then MeOH:DCM 1:9 to isolate amine) afforded a 2:3 mixture of the diastereoisomeric aldehydes **339** (0.12 g, 42%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2934 (CH), 1702 (C=O), 1597, 1460, 1339, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 9.46 (0.4H, d, *J* 1.8) and 9.41 (0.6H, s, CHO), 7.72 (0.8H, d, *J* 8.3) and 7.71 (1.2H, d, *J* 8.3, 2 × S-*o*CH), 7.34-7.17 (7H, m, 7 × ArH), 4.58 (0.6H, s) and 4.56 (0.4H, s, NCHN), 4.10 (0.4H, d, *J* 13.5), 4.07 (0.6H, d, *J* 13.5), 3.98 (0.6H, d, *J* 13.5) and 3.96 (0.4H, d, *J* 13.5, NC*H$_2$*Ph), 3.92-3.89 (0.6H, m, C*H$_{(major)}$*(OTBS)), 3.87-3.79 (0.8H, m, C*H$_{(minor)}$*(OTBS) and TsNC*H$_{(minor)}$*H), 3.67 (0.6H, dd, *J* 12.2, 6.9, TsNC*H$_{(major)}$*H), 2.97 (0.6H, t, *J* 12.0) and 2.96 (0.4H, t, *J* 12.0, TsNCH*H*), 2.71-2.64 (1H, m) and 2.61-2.54 (1H, m, BnNC*H$_2$*), 2.41 (3H, s, ArCH$_3$), 1.76-1.35 (3.6H, m, BnNCH$_2$C*H*H, C*H$_2$*CH(OTBS) and TsNCH$_2$C*H$_{(major)}$*), 1.21-1.09 (1.4H, m, TsNCH$_2$C*H$_{(minor)}$* and BnNCH$_2$CH*H*), 0.91, 0.89, 0.87 (12H, s, NCHCC*H$_3$* and C(CH$_3$)$_3$), 0.07 (2.4H, s) and 0.03 (3.6H, s, Si(CH$_3$)$_2$); δ_C (125 MHz, CDCl$_3$) 205.5, 204.6 (CHO), 143.2, 143.1, 139.0, 137.5, 137.3 (3 × aromatic C), 129.9, 129.8, 128.8, 128.1, 127.2, 127.1, 127.0, 126.7 (9 × aromatic CH), 90.0, 89.9 (NCHN), 76.6, 76.5 (CH(OTBS)), 55.7 (N*C*H$_2$Ph), 53.4, 53.1 (TsN*C*H$_2$), 53.0, 52.9 (NCH*C*Me), 50.3, 50.1 (BnN*C*H$_2$), 43.8, 43.5 (TsNCH$_2$*C*H), 30.9, 30.7, 30.5 (*C*H$_2$CH(OTBS) and BnNCH$_2$*C*H$_2$), 25.7 (C(*C*H$_3$)$_3$), 24.3, 24.2 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 18.1, 18.0 (*C*Me$_3$), −4.6, −4.7, −4.9, −5.0 (Si(*C*H$_3$)$_2$); *m/z* (FAB+) 557 (MH$^+$, 34%), 286 (23), 173

(100), 154 (93); HRMS (FAB+) calcd for $C_{30}H_{45}N_2O_4SSi$ (MH$^+$) 557.2870, found 557.2883.

Amine **345** isolated as a 1:1 mixture of diastereoisomers (0.09 g, 37%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 3385 (NH), 2931 (CH), 1599, 1458, 1344, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.75 (1H, d, J 8.2) and 7.74 (1H, d, J 8.2, 2 × S-*o*CH), 7.31-7.18 (7H, m, 7 × ArH), 4.65 (0.5H, s) and 4.59 (0.5H, s, NCHN), 4.09 (0.5H, d, J 14.0), 4.08 (0.5H, d, J 14.0), 3.98 (0.5H, d, J 14.0) and 3.97 (0.5H, d, J 14.0, NC*H*$_2$Ph), 3.72 (0.5H, dd, J 11.9, 6.9) and 3.68 (0.5H, dd, J 11.9, 6.9, TsNC*H*H), 3.58-3.38 (1H, m, C*H*(OTBS)), 2.97 (0.5H, t. J 11.9) and 2.92 (0.5H, t, J 11.9, TsNCH*H*), 2.71-2.65 (1H, m) and 2.62-2.55 (1H, m, BnNC*H*$_2$), 2.51-2.43 (1H, m, C*H*HNH$_2$), 2.40 (3H, s, ArCH$_3$), 2.40-2.34 (1H, m, CH*H*NH$_2$), 1.81-1.78 (1H, m, BnNCH$_2$C*H*H), 1.61-1.06 (6H, m, C*H*$_2$CH(OTBS), NH$_2$, TsNCH$_2$C*H* and BnNCH$_2$CH*H*), 0.86, 0.84, 0.83 (12H, s, NCHCC*H*$_3$ and C(CH$_3$)$_3$), 0.03, 0.02, 0.01, −0.02 (6H, s, Si(CH$_3$)$_2$); δ_C (125 MHz, CDCl$_3$) 143.2, 143.0, 139.2, 139.1, 137.8, 137.6 (3 × aromatic C), 129.6, 129.5, 128.8, 128.5, 128.2, 128.0, 127.3, 127.2, 127.0, 126.7 (9 × aromatic CH), 90.3 (NCHN), 72.7, 72.5 (CH(OTBS)), 56.0, 55.7 (N*C*H$_2$Ph), 53.2 (TsN*C*H$_2$), 53.0 (NCH*C*Me), 50.4, 50.3 (BnN*C*H$_2$), 47.3, 46.9 (*C*H$_2$NH$_2$), 44.1, 43.6 (TsNCH$_2$*C*H), 32.5 (*C*H$_2$CH(OTBS)), 30.7 (BnNCH$_2$*C*H$_2$), 25.9, 25.8 (C(*C*H$_3$)$_3$), 24.4, 24.3 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$), 18.0 (*C*Me$_3$), −4.4, −4.5, −4.9, −5.0 (Si(*C*H$_3$)$_2$); *m/z* (FAB+) 558 (MH$^+$, 31%), 307 (25), 154 (100); HRMS (FAB+) calcd for $C_{30}H_{48}N_3O_3SSi$ 558.3186, found 558.3196 .

(1*RS*,2*SR*,6*SR*,7*RS*,10*SR*)-3-Benzyl-1-(*tert*-butyldimethylsilyloxy)-6-methyl-9-(4-toluenesulfonyl)-3,9-diaza-tricyclo[5.3.1.0^{2,6}]undecan-10-ol (346)
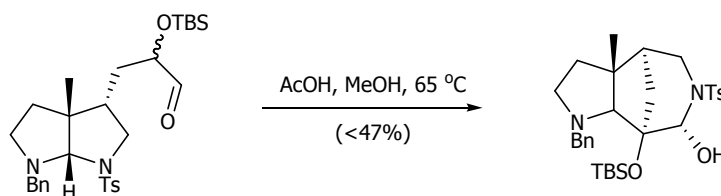
To a solution of aldehydes **339** (0.03 g, 0.05 mmol) in MeOH (0.5 mL) was added AcOH (0.012 mL, 0.22 mmol) and the mixture stirred at room temperature for 16 h, then at 65 °C for a further 30 h. After cooling to room temperature, the mixture was concentrated, diluted with EtOAc (5 mL) and washed with saturated NaHCO$_3$ (5 mL).

The organic materials were extracted from the aqueous layer with EtOAc (2 × 5 mL), and the combined organic extracts were washed with brine (5 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) afforded impure tricycle **346** (0.017 g, <47%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 3412 (OH), 2926 (CH), 1599, 1456, 1336, 1159 (SO$_2$); diagnostic peaks are quoted: δ_H (500 MHz, CDCl$_3$) 7.79 (2H, d, *J* 8.3, 2 × S-*o*CH), 7.37-7.20 (7H, m, 7 × ArH), 5.30 (1H, s, NC*H*(OH)), 4.04 (1H, d, *J* 13.1) and 3.47 (1H, d, *J* 13.1, NC*H*$_2$Ph), 3.24-3.18 (1H, m) and 3.03 (1H, dd, *J* 11.3, 1.5, TsNC*H*H), 2.90 (1H, dd, *J* 9.0, 7.3) and 2.46-2.39 (1H, m, BnNC*H*$_2$), 2.42 (ArCH$_3$), 2.33 (1H, s, BnNC*H*CMe), 2.11 (1H, d, *J* 11.8, C*H*HC(OTBS)), 1.75-1.50 (4H, BnNCH$_2$C*H*H, TsNCH$_2$C*H*, CH*H*C(OTBS) and OH), 1.46 (1H, dd, *J* 12.5, 5.8, BnNCH$_2$CH*H*), 0.88 (3H, s, NCHCC*H*$_3$), 0.86 (9H, s, C(CH$_3$)$_3$), 0.15, 0.11 (6H, s, Si(CH$_3$)$_2$); δ_C (125 MHz, CDCl$_3$) 143.3, 139.0, 136.7 (3 × aromatic C), 129.4, 128.6, 128.4, 127.9, 127.2 (9 × aromatic CH), 84.2 (NCH(OH)), 79.3 (*C*(OTBS)), 76.4 (BnNCHCMe), 62.3 (NCH$_2$Ph), 52.8 (BnNCH$_2$), 49.3 (NCHCMe), 44.0 (TsNCH$_2$), 41.1 (TsNCH$_2$*C*H), 39.4 (BnNCH$_2$*C*H$_2$), 33.7 (*C*H$_2$C(OTBS)), 26.1 (C(*C*H$_3$)$_3$), 21.5 (ArCH$_3$), 21.4 (NCHC*C*H$_3$), 18.5 (*C*Me$_3$), −3.9, −4.3 (Si(CH$_3$)$_2$); *m/z* (EI+) 556 (M$^+$, 2%), 499 (67), 269 (86), 95 (100); HRMS (EI+) calcd for C$_{30}$H$_{44}$N$_2$O$_4$SSi (M$^+$) 556.2786, found 556.2781.

(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3-(3-methoxyallyl)-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole (356)[145]
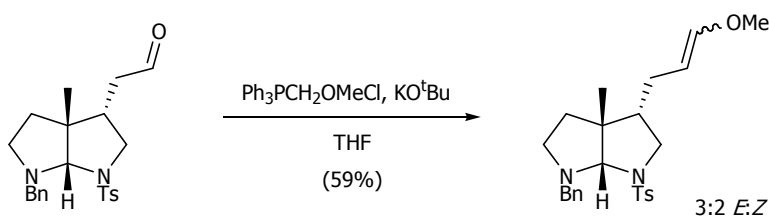
To a suspension of (methoxymethyl)triphenylphosphonium chloride (0.20 g, 0.58 mmol) in THF (2 mL) at −10 °C was added KO^{t}Bu (0.065 g, 0.58 mmol). The brightly orange coloured suspension was stirred at −10 °C for 30 min then a solution of aldehyde **298** (0.060 g, 0.15 mmol) in THF (1 mL and 2 × 0.5 mL washes) was added *via* cannula. The temperature was maintained at 0 °C for 30 min and then warmed to room temperature. H$_2$O (5 mL) was added, and then the organic materials were extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), and dried (MgSO$_4$). Concentration and

purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) afforded a 3:2 *E:Z* mixture of olefins **356** (0.038 g, 59%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2930 (CH), 1720, 1660, 1599, 1454, 1344, 1157 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 7.74 (1.2H, d, *J* 8.3) and 7.73 (0.8H, d, *J* 8.3, 2 × S-*o*CH), 7.35-7.18 (7H, m, 7 × ArH), 6.17 (0.6H, d, *J* 12.5) and 5.83 (0.4H, dt, *J* 6.2, 1.3, C*H*(OMe)), 4.62 (0.6H, s) and 4.59 (0.4H, s, NCHN), 4.44 (0.6H, ddd, *J* 12.6, 8.0, 6.9, *H*$_{(major)}$C=CH(OMe)), 4.11-4.05 (1.4H, m, *H*$_{(minor)}$C=CH(OMe) and NC*H*HPh), 3.98 (0.6H, d, *J* 13.8) and 3.97 (0.4H, d, *J* 13.8, NCH*H*Ph), 3.69-3.62 (1H, m, TsNC*H*H), 3.52 (1.2H, s) and 3.45 (1.8H, s, OCH$_3$), 2.98 (0.4H, t, *J* 12.0) and 2.92 (0.6H, t, *J* 12.0, TsNCH*H*), 2.72-2.65 (1H, m) and 2.61-2.55 (1H, m, BnNC*H*$_2$), 2.40 (3H, s, ArCH$_3$), 1.94-1.84 (1H, m, C*H*HCH=CH), 1.84-1.73 (1H, m, BnNCH$_2$C*H*H), 1.71-1.63 (1H, m, CH*H*CH=CH), 1.25-1.15 (2H, m, TsNCH$_2$C*H* and BnNCH$_2$CH*H*), 0.93 (1.8H, s) and 0.92 (1.2H, s, NCHCC*H*$_3$); δ_C (125 MHz, CDCl$_3$) 147.8, 147.2 (*C*H(OMe)), 143.1, 143.0, 139.2, 139.1, 137.6 (3 × aromatic C), 129.6, 129.5, 128.8, 128.1, 128.0, 127.2, 126.7, 126.6 (9 × aromatic CH), 103.8, 100.4 (H*C*=CH(OMe)), 91.4 (NCHN), 59.5, 56.0 (OCH$_3$), 55.8 (N*C*H$_2$Ph), 52.9, 52.7 (TsN*C*H$_2$), 52.4, 52.3 (NCH*C*Me), 50.5 (BnN*C*H$_2$), 48.8, 48.1 (TsNCH$_2$*C*H), 30.5 (BnNCH$_2$*C*H$_2$), 25.5 (*C*H$_2$CH=CH), 24.7 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$); *m/z* (FAB+) 441 (MH$^+$, 4%), 307 (32), 154 (100); HRMS (FAB+) calcd for C$_{25}$H$_{33}$N$_2$O$_3$S (MH$^+$) 441.2212, found 441.2217.
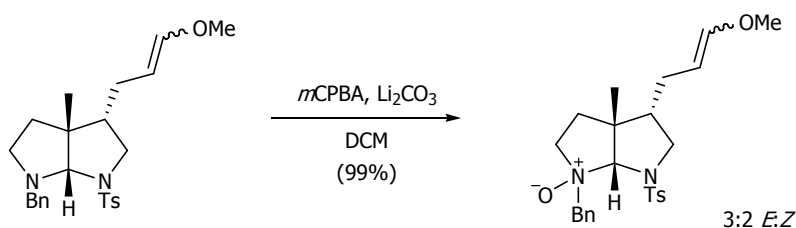
(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-3-(3-methoxyallyl)-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrole 6-oxide (357)[174]

*m*CPBA (0.025 g, 0.10 mmol) and Li$_2$CO$_3$ (0.05 g, 0.68 mmol) in DCM (7.5 mL) were stirred at room temperature for 45 min and then cooled to −78 °C, and methoxy-alkene **356** (0.03 g, 0.07 mmol) was added. After 2 h at −78 °C, Na$_2$S$_2$O$_3$.5H$_2$O (0.42 g, 1.7 mmol) was added and the mixture was stirred at −78 °C for 10 min before warming to room temperature. The organic phase was removed, and the remaining material was extracted from the aqueous phase with DCM (3 × 5 mL). The combined organic extracts

were washed with H_2O (5 mL), brine (5 mL), and then dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; MeOH:DCM 1:49→1:9) afforded *N*-oxide **357** (0.31 g, 99%) as a pale yellow oil as a 3:2 *E*:*Z* mixture; v_{max}/cm^{-1} (CHCl$_3$ cast) 3412 (br), 2955 (CH), 1665, 1599, 1454, 1350, 1159 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 8.01-7.95 (2H, m), 7.64-7.58 (2H, m) and 7.40-7.30 (3H, m, 7 × ArH), 6.18 (0.6H, d, *J* 12.5) and 5.80 (0.4H, dt, *J* 6.2, 1.2, C*H*(OMe)), 5.14 (0.6H, s) and 5.13 (0.4H, s, NCHN), 4.58 (0.4H, d, *J* 12.8) and 4.57 (0.6H, d, *J* 12.8, NC*H*HPh), 4.52-4.42 (1.6H, *H*$_{(major)}$C=CH(OMe) and NCH*H*Ph), 4.11-4.06 (0.4H, m, *H*$_{(minor)}$C=CH(OMe)), 3.76-3.70 (1H, m) and 3.54 (1H, t, *J* 11.6, TsNC*H*$_2$), 3.47 (1.2H, s) and 3.42 (1.8H, s, OCH$_3$), 3.39-2.25 (1H, m) and 3.21-3.11 (1H, m BnNC*H*$_2$), 2.65-2.56 (1H, m, BnNCH$_2$C*H*H), 2.40 (3H, s, ArCH$_3$), 2.03-1.97 (1H, m) and 1.96-1.82 (1H, m, C*H*$_2$CH=CH), 1.56-1.47 (1H, m, TsNCH$_2$C*H*), 1.24-1.16 (1H, m, BnNCH$_2$CH*H*), 0.89 (1.8H, s) and 0.86 (1.2H, s, NCHCC*H*$_3$); δ_C (125 MHz, CDCl$_3$) 148.3, 147.4 (*C*H(OMe)), 144.1, 144.0, 139.2, 139.1 (2 × aromatic C), 132.5, 132.4 (aromatic CH), 130.8 (aromatic C), 129.9, 129.8, 129.4, 128.6, 128.1, 127.7, 127.5 (8 × aromatic CH), 103.2, 100.0 (H*C*=CH(OMe)), 97.6, 97.5 (NCHN), 70.2 (N*C*H$_2$Ph), 62.8, 62.7 (BnN*C*H$_2$), 59.5, 56.1 (O*C*H$_3$), 55.9, 55.8 (TsN*C*H$_2$), 51.5, 51.4 (NCH*C*Me), 50.2, 49.4 (TsNCH$_2$*C*H), 29.6, 29.5 (BnNCH$_2$*C*H$_2$), 26.3 (NCHC*C*H$_3$), 25.9, 25.7 (*C*H$_2$CH=CH), 21.6 (Ar*C*H$_3$); *m/z* (ESI+) 479 (MNa$^+$, 42%), 457 (MH$^+$, 100), 429 (27), 397 (33), 155 (21); HRMS (ESI+) calcd for $C_{25}H_{33}N_2O_4S$ (MH$^+$) 457.2161, found 457.2166.

(*E*)-3-((3a*RS*,3a*SR*,6a*RS*)-6-Benzyl-3a-methyl-1-(4-toluenesulfonyl)octahydropyrrolo[2,3-*b*]pyrrol-3-yl)propenal   **(358)**   and **(3*RS*,3a*SR*,6a*RS*)-6-Benzyl-octahydro-3-((*E*)-3-methoxyallyl)-3a-methyl-1-(4-toluenesulfonyl)pyrrolo[2,3-*b*]pyrrole (356)**


(58%)   (41%, >10:1 *E*:*Z*)
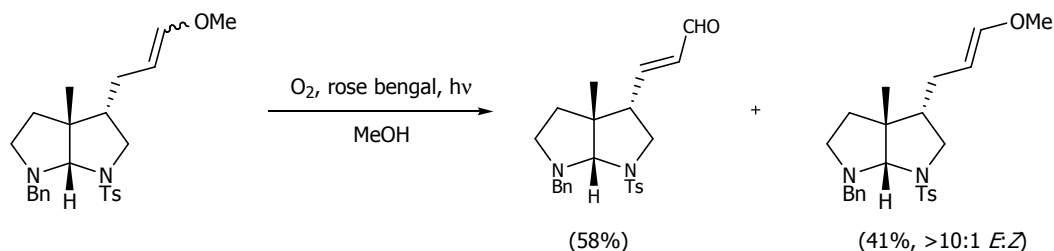
Through a solution of methoxy-alkene **356** (0.033 g, 0.07 mmol) and rose bengal (1 μg, 10 μmol) in MeOH (0.9 mL) at −78 °C was slowly bubbled oxygen, while irradiating with a 500 W tungsten filament light bulb. The reaction temperature was maintained at

−78 °C for 6 h, then DMS (0.11 mL, 0.15 mmol) was added and the reaction slowly warmed to room temperature. After 16 h, the mixture was concentrated and purified by flash chromatography (SiO$_2$; EtOAc:PS 1:9→1:4) to afford aldehyde **358** (0.018 g, 58%) as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2928, 2820 (CH), 1690 (C=O), 1456, 1344, 1157 (SO$_2$); δ_H (500 MHz, CDCl$_3$) 9.44 (1H, d, *J* 7.7, CHO), 7.76, (2H, d, *J* 8.3, 2 × S-*o*CH), 7.32-7.20 (7H, m, 7 × ArH), 6.55 (1H, dd, *J* 15.8, 7.2, *H*C=CHCHO), 5.95 (1H, ddd, *J* 15.8, 7.7, 1.3, C*H*CHO), 4.73 (1H, s, NCHN), 4.04 (1H, d, *J* 13.8) and 4.00 (1H, d, *J* 13.9, NC*H$_2$*Ph), 3.73 (1H, dd, *J* 12.2, 6.9) and 3.31 (1H, t, *J* 11.9, TsNC*H$_2$*), 2.70 (1H, ddd, *J* 9.1, 7.4, 4.7) and 2.66-2.59 (1H, m, BnNC*H$_2$*), 2.43 (3H, s, ArCH$_3$), 2.15-2.08 (1H, m, TsNCH$_2$C*H*), 1.75 (1H, dt, *J* 12.7, 7.3, BnNCH$_2$C*H*H), 1.27 (1H, ddd, *J* 12.6, 6.7, 4.8, BnNCH$_2$CH*H*), 1.01 (3H, s, NCHCC*H$_3$*); δ_C (125 MHz, CDCl$_3$) 192.9 (C=O), 152.0 (H*C*=CHCHO), 143.7, 138.8, 137.0 (3 × aromatic C), 129.8, 128.7, 128.2, 127.2, 126.9 (9 × aromatic CH), 134.8 (HC=*C*HCHO), 90.6 (NCHN), 55.4 (N*C*H$_2$Ph), 53.5 (NCH*C*Me), 51.5 (TsNCH$_2$*C*H), 51.1 (TsN*C*H$_2$), 50.2 (BnN*C*H$_2$), 31.4 (BnNCH$_2$*C*H$_2$), 24.8 (NCHC*C*H$_3$), 21.6 (Ar*C*H$_3$); *m/z* (ESI+) 447 (MNa$^+$, 100%), 417 (16); HRMS (ESI+) calcd for C$_{24}$H$_{28}$N$_2$O$_3$SNa (MNa$^+$) 447.1718, found 447.1722.

Olefin starting material **356** (0.014 g, 41%) in a >10:1 *E*:*Z* ratio as a pale yellow oil; v_{max}/cm^{-1} (CHCl$_3$ cast) 2930 (CH), 1720, 1660, 1597, 1454, 1344, 1157 (SO$_2$); peaks corresponding to *E* alkene are quoted: δ_H (500 MHz, CDCl$_3$) 7.74, (2H, d, *J* 8.3, 2 × S-*o*CH), 7.33-7.18 (7H, m, 7 × ArH), 6.17 (1H, d, *J* 12.5, C*H*(OMe)), 4.62 (1H, s, NCHN), 4.45 (1H, ddd, *J* 12.6, 8.0, 6.9, *H*C=CH(OMe)), 4.09 (1H, d, *J* 13.9) and 3.97 (1H, d, *J* 13.8, NC*H$_2$*Ph), 3.66 (1H, dd, *J* 12.1, 6.9, TsNC*H*H), 3.46 (3H, s, OCH$_3$), 2.92 (1H, t, *J* 12.1, TsNCH*H*), 2.69 (1H, ddd, *J* 9.0, 7.5, 4.1) and 2.59 (1H, ddd, *J* 9.0, 8.2, 6.5, BnNC*H$_2$*), 2.41 (3H, s, ArCH$_3$), 1.93-1.86 (1H, m, C*H*HCH=CH), 1.77 (1H, dt, *J* 12.6, 7.7, BnNCH$_2$C*H*H), 1.71-1.63 (1H, m, CH*H*CH=CH), 1.25-1.16 (2H, m, TsNCH$_2$C*H* and BnNCH$_2$CH*H*), 0.93 (3H, s, NCHCC*H$_3$*); δ_C (125 MHz, CDCl$_3$) 147.8 (*C*H(OMe)), 143.1, 139.1, 137.6 (3 × aromatic C), 129.6, 128.8, 128.1, 127.2, 126.7 (9 × aromatic CH), 100.4 (H*C*=CH(OMe)), 91.4 (NCHN), 56.0 (OCH$_3$), 55.8 (N*C*H$_2$Ph), 52.8 (TsN*C*H$_2$), 52.3 (NCH*C*Me), 50.5 (BnN*C*H$_2$), 48.8 (TsNCH$_2$*C*H), 30.5 (BnNCH$_2$*C*H$_2$), 25.5 (*C*H$_2$CH=CH), 24.7 (NCHC*C*H$_3$), 21.5 (Ar*C*H$_3$); *m/z* (ESI+) 463 (MNa$^+$, 100%), 441 (MH$^+$, 95); HRMS (ESI+) calcd for C$_{25}$H$_{32}$N$_2$O$_3$SNa (MNa$^+$) 463.2031, found 463.2034.

## 6.2. Synthesis of 3-amino-2-silyloxyacrylates

Ethyl diazo(triethylsilyl)acetate (359)[175]
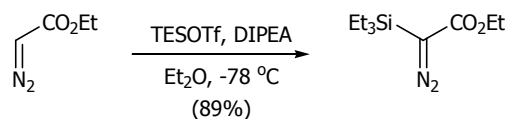
A stirring solution of ethyl diazoacetate (4.0 mL, 38 mmol) and ethyldiisopropylamine (6.6 mL, 38 mmol) in Et_2O (170 mL) was cooled to -78 °C. Triethylsilyl trifluoromethanesulfonate (8.6 mL, 38 mmol) was added dropwise and the resulting suspension stirred at -78 °C for 30 min, then at room temperature for 17 h. Filtration, concentration and purification by flash chromatography (SiO_2; PS→EtOAc:PS 1:49) provided silylated product **359**[149] (7.7 g, 89%) as a yellow liquid; δ_H (300 MHz, $CDCl_3$) 4.17 (2H, q, *J* 7.1, OCH_2), 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 0.97 (9H, t, *J* 7.8, $Si(CH_2CH_3)_3$), 0.72 (6H, q, *J* 7.8, $Si(CH_2Me)_3$); δ_C (75 MHz, $CDCl_3$) 169.7 (O=C), 85.9 ($C=N_2$), 60.6 (CO_2CH_2), 14.4 ($CO_2CH_2CH_3$), 7.0 ($Si(CH_2CH_3)_3$), 3.2 ($Si(CH_2CH_3)_3$).

Typical procedure for preparation of formamides:

1-Formylpyrrolidine (369a)
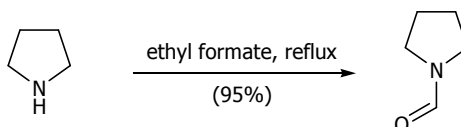
A stirring mixture of pyrrolidine (1.0 mL, 12 mmol) and ethyl formate (10.0 mL, 124 mmol) were heated at reflux for 16 h. Excess ethyl formate and ethanol were removed *in vacuo* to afford 1-formylpyrrolidine **369a** (1.25 g, 95%) as a brown oil; δ_H (300 MHz, $CDCl_3$) 8.22 (1H, s, CHO), 3.48-3.44 (2H, m) and 3.43-3.39 (2H, m, $N(CH_2)_2$), 1.91-1.87 (4H, m, $N(CH_2CH_2)_2$); δ_C (75 MHz, $CDCl_3$) 160.1 (CHO), 46.0, 43.1 ($N(CH_2)_2$), 24.9, 24.2 ($N(CH_2CH_2)_2$).

1-Formylpiperidine (369b)

Piperidine (0.56 mL, 5.6 mmol) afforded formamide **369b**[176] (0.60 g, 95%) as a pale brown oil; δ_H (300 MHz, $CDCl_3$) 7.90 (1H, s, CHO), 3.39-3.35 (2H, m) and 3.23-3.19 (2H, m, $N(CH_2)_2$), 1.62-1.50 (2H, m) and 1.49-1.39
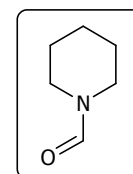
(4H, m, and N(CH$_2$C*H$_2$*)$_2$C*H$_2$*); δ$_C$ (75 MHz, CDCl$_3$) 160.8 (C*H*O), 46.8, 40.5 (N(CH$_2$)-$_2$), 26.5, 25.0 (N(CH$_2$C*H$_2$*)$_2$), 24.6 (NCH$_2$CH$_2$C*H$_2$*).

4-Formylmorpholine (369c)

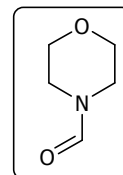Morpholine (0.56 mL, 6.3 mmol) afforded formamide **369c**[176] (0.66 g, 91%) as a colourless oil; δ$_H$ (300 MHz, CDCl$_3$) 8.04 (1H, s, CHO), 3.71-3.66 (4H, m, O(CH$_2$)$_2$), 3.59-3.56 (2H, m) and 3.41-3.38 (2H, m, N(CH$_2$)$_2$); δ$_C$ (75 MHz, CDCl$_3$) 160.9 (CHO), 67.2, 66.4 (O(CH$_2$)$_2$), 45.8, 40.6 (N(CH$_2$)$_2$).

8-Formyl-1,4-dioxa-8-azaspiro[4.5]decane (369d)

1,4-Dioxa-8-azaspiro[4.5]decane (0.50 g, 3.5 mmol) provided formamide **369d** (0.60 g, 99%) as a pale brown oil; ν$_{max}$/cm^{-1} (film) 2880 (CH), 1674 (C=O); δ$_H$ (300 MHz, CDCl$_3$) 8.03 (1H, s, CHO), 3.98 (4H, s, OCH$_2$CH$_2$O), 3.64-3.60 (2H, m) and 3.47-3.43 (2H, m, N(CH$_2$)$_2$), 1.74-1.66 (4H, m, N(CH$_2$C*H$_2$*)$_2$; δ$_C$ (75 MHz, CDCl$_3$) 160.8 (CHO), 107.2 (*C*(OCH$_2$)$_2$), 64.6 (OCH$_2$CH$_2$O), 43.8, 37.5 (N(CH$_2$)$_2$), 35.7, 34.3 (N(CH$_2$C*H$_2$*)$_2$); *m/z* (CI+) 172 (MH$^+$, 100%), 121 (28); HMRS (CI+) calcd for C$_8$H$_{14}$NO$_3$ (MH$^+$) 172.0974, found 172.0980.
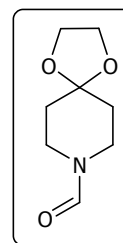
1-Formyl-4-methyl-piperazine (369e)

1-Methylpiperazine (0.50 mL, 4.5 mmol) afforded formamide **369e**[177] (0.53 g, 93%) as a pale brown oil; δ$_H$ (300 MHz, CDCl$_3$) 8.08 (1H, s, CHO), 3.55-3.52 (2H, m) and 3.38-3.35 (2H, m, OHCN(C*H$_2$*)$_2$), 2.40-2.33 (4H, m, MeN(C*H$_2$*)$_2$), 2.29 (3H, s, CH$_3$); δ$_C$ (75 MHz, CDCl$_3$) 160.7 (CHO), 55.3, 54.2 (OHCN(*CH$_2$*)$_2$), 46.1, 45.4 (MeN(*CH$_2$*)$_2$), 39.8 (CH$_3$).
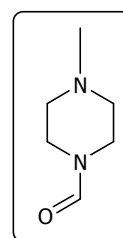
1-Benzhydryl-4-formylpiperazine (369f)

1-Benzhydrylpiperazine (0.50 g, 2.0 mmol) afforded formamide **369f** (0.55 g, 99%) as a pink solid; m.p. = 106-107 °C; ν$_{max}$/cm^{-1} (KBr) 2953 (CH), 1688, 1632; δ$_H$ (300 MHz, CDCl$_3$) 7.99 (1H, s, CHO), 7.43-7.40 (4H, m), 7.31-7.26 (4H, m) and 7.23-7.17 (2H, m, 10 × ArH), 4.27 (1H, s,
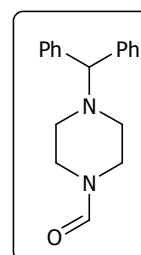
NCHPh$_2$), 3.57-3.54 (2H, m) and 3.37-3.34 (2H, m, OHCN(CH_2)$_2$), 2.41-2.36 (4H, m, Ph$_2$CHN(CH_2)$_2$); δ_C (75 MHz, CDCl$_3$) 160.8 (CHO), 142.0 (2 x aromatic C), 128.7, 127.8, 127.3 (10 × aromatic CH), 75.9 (NCHPh$_2$), 52.3, 51.1 (OHCN(CH$_2$)$_2$), 45.9, 40.2 (Ph$_2$CHN(CH$_2$)$_2$); m/z (CI+) 281 (MH$^+$, 12%), 280 (23), 167 (100); HRMS (CI+) calcd for C$_{18}$H$_{21}$N$_2$O (MH$^+$) 281.1654, found 281.1647; Elemental analysis: calcd for C$_{18}$H$_{20}$N$_2$O C: 77.1, H: 7.2, N: 10.0. Found C: 77.2, H: 7.3, N: 9.9.

1-(3-Chlorophenyl)-4-formylpiperazine (369g)

1-(3-Chlorophenyl)piperazine (0.50 g, 2.5 mmol) afforded formamide **369g** (0.57 g, 99%) as a pale brown oil; v_{max}/cm^{-1} (film) 2829 (CH), 1649 (C=O); δ_H (300 MHz, CDCl$_3$) 8.10 (1H, s, CHO), 7.22-7.16 (1H, m), 6.89-6.86 (2H, m) and 6.81-6.78 (1H, m, 4 × ArH), 3.71-3.68 (2H, m) and 3.54-3.51 (2H, m, OHCN(CH_2)$_2$), 3.21-3.11 (4H, m, ArN(CH$_2$)$_2$); δ_C (75 MHz, CDCl$_3$) 160.8 (CHO), 152.0 (NC=C), 135.1 (CCl), 130.2, 120.6, 116.9, 115.0 (4 × aromatic CH), 50.0, 49.0 (OHCN(CH$_2$)$_2$), 45.4, 39.8 (ArN(CH$_2$)$_2$); m/z (CI+) 225 (MH$^+$, 100%), 197 (44), 166 (31); HRMS (CI+) calcd for C$_{11}$H$_{14}$ClN$_2$O (MH$^+$) 225.0795, found 225.0796.
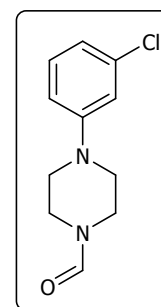
N-Allyl-*N*-benzylformamide (369i)
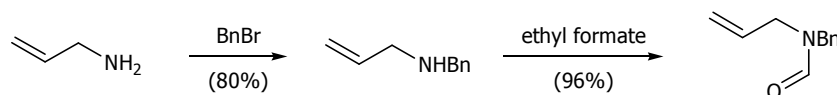
Benzyl bromide (2.00 g, 11.7 mmol) was added dropwise to allylamine (4.01 g, 70.2 mmol) at 0 °C. Stirring was maintained at this temperature for 30 min then for 16 h at room temperature before it was quenched with saturated NaHCO$_3$ (10 mL). The product was extracted with ether (3 × 10 mL), washed with brine (3 × 10 mL) then dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc:PS 1:9→3:7) provided *N*-benzylallylamine[154] (1.37 g, 80%) as a colourless oil; δ_H (300 MHz, CDCl$_3$) 7.34-7.25 (5H, m, 5 × ArH), 5.99-5.90 (1H, m, H$_2$C=CH), 5.22-5.10 (2H, m, H_2C=CH), 3.80 (2H, s, PhCH_2), 3.29 (2H, d, J 6.0, H$_2$C=CHCH_2), 1.48 (1H, br s, NH); δ_C (75 MHz, CDCl$_3$) 140.3 (aromatic C), 136.8 (H$_2$C=CH), 128.4, 128.2, 127.0 (5 × aromatic CH), 116.0 (H$_2$C=CH), 53.3 (PhCH$_2$), 51.8 (H$_2$C=CHCH$_2$).

N-Benzylallylamine (0.50 g, 3.4 mmol) afforded formamide **369i**[178] (0.57 g, 96%) as a pale brown oil; ratio of rotamers 1:1 in CDCl$_3$ at room temperature; δ_H (300 MHz, CDCl$_3$) 8.32, 8.22 (1H, s, CHO), 7.36-7.18 (5H, m, 5 × ArH), 5.78-5.60 (1H, m, H$_2$C=C*H*), 5.27-5.08 (2H, m, *H$_2$*C=CH), 4.52, 4.37 (2H, s, PhC*H$_2$*), 3.84, 3.72 (2H, d, *J* 5.9, H$_2$C=CHC*H$_2$*); δ_C (75 MHz, CDCl$_3$) 162.9, 162.6 (CHO), 136.2, 135.9 (aromatic C), 132.9, 131.9 (H$_2$C=*C*H), 128.9, 128.7, 128.4, 128.1, 127.6 (5 × aromatic CH), 118.9, 118.4 (H$_2$*C*=CH), 50.5, 49.1 (Ph*C*H$_2$) 45.0, 44.0 (H$_2$C=CH*C*H$_2$).

N,N-Diallylformamide (369j)

Diallylamine (0.50 g, 5.2 mmol) afforded formamide **369j**[179] (0.57 g, 88%) as a pale brown oil; δ_H (300 MHz, CDCl$_3$) 8.11 (1H, s, CHO), 5.79-5.63 (2H, m, 2 × H$_2$C=C*H*), 5.25-5.18 (4H, m, 2 × *H$_2$*C=CH), 3.92 (2H, d, *J* 5.7) and 3.80 (2H, d, *J* 5.7, 2 × NCH$_2$); δ_C (75 MHz, CDCl$_3$) 162.6 (CHO), 133.1, 132.1 (2 × H$_2$C=*C*H), 118.6, 118.1 (2 × H$_2$*C*=CH), 49.3, 44.3 (2 × NCH$_2$).
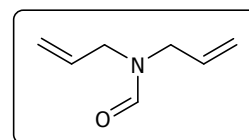
N-Formylsarcosine ethyl ester (369k)
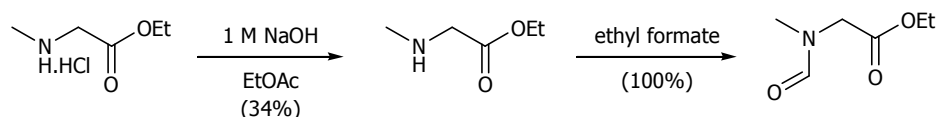
1 M NaOH was added to a stirring suspension of sarcosine ethyl ester hydrochloride (2.00 g, 13.0 mmol) in EtOAc (10 mL) until the solids were dissolved. The organic layer was separated, washed with brine (3 × 10 mL) and dried (MgSO$_4$). Concentration afforded the free amine[180] (0.52 g, 34%) as a colourless oil; δ_H (300 MHz, CDCl$_3$) 4.18 (2H, q, *J* 7.2, OCH$_2$), 3.35 (2H, s, NCH$_2$), 2.43 (3H, s, NCH$_3$), 1.60 (1H, s, NH), 1.27 (3H, t, *J* 7.2, OCH$_2$C*H$_3$*); δ_C (75 MHz, CDCl$_3$) 172.4 (C=O), 60.7 (OCH$_2$), 52.7 (NCH$_2$), 36.2 (NCH$_3$), 14.3 (OCH$_2$*C*H$_3$).

Sarcosine ethyl ester (0.48 g, 4.10 mmol) afforded formamide **369k**[181] (0.59 g, 100%) as a colourless oil; ratio of rotamers in CDCl$_3$ at room temperature 2:1; δ_H (300 MHz, CDCl$_3$) 8.08, 8.01 (1H, s, CHO), 4.23-4.14 (2H, m, OCH$_2$), 4.05, 3.95 (2H, s, NCH$_2$),

3.01, 2.90 (3H, s, NCH$_3$), 1.29-1.22 (3H, m, OCH$_2$CH_3); δ_C (75 MHz, CDCl$_3$) 168.7, 168.3 (C=O), 163.2, 163.0 (CHO), 61.7, 61.4 (OCH$_2$), 50.9, 45.6 (NCH$_2$), 35.3, 30.8 (NCH$_3$), 14.1 (OCH$_2$$CH_3$).

N-Benzylformanilide (369l)

N-Benzylaniline (0.50 g, 2.7 mmol) was heated to reflux in ethyl formate (5.0 mL, 62 mmol) for 8 d. Concentration and purification by flas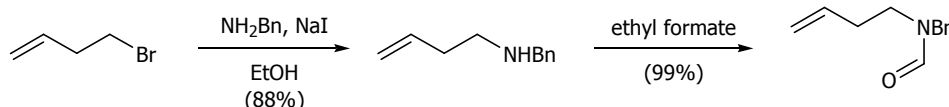h chromatography (SiO$_2$; EtOAc:PS 1:4) provided formanilide **369l**[182] (0.46 g, 80%) as a pale yellow solid; δ_H (300 MHz, CDCl$_3$) 8.58 (1H, s, CHO), 7.36-7.24 and 7.11-7.08 (10H, m, 10 × ArH), 4.87 (2H, s, CH$_2$); δ_C (75 MHz, CDCl$_3$) 162.4 (CHO), 141.0, 136.7 (2 x aromatic C), 129.6, 128.6, 127.9, 127.5, 126.9, 124.1 (10 × aromatic CH), 48.9 (CH$_2$).

N-Benzyl-*N*-(but-3-enyl)formamide (369m)

To a stirring solution of 4-bromo-1-butene (1.00 g, 7.4 mmol) in EtOH (10 mL) was added NH$_2$Bn (4.0 mL, 37 mmol) dropwise, followed by NaI (0.04 g, 0.27 mmol). The resulting mixture was heated at reflux for 4 h, and the solvent removed *in vacuo*. The product was diluted with DCM (100 mL) and washed with 1 M KOH (100 mL), H$_2$O (2 × 100 mL), brine (2 × 100 mL) and dried (K$_2$CO$_3$). Concentration and purification by flash chromatography (SiO$_2$; MeOH:DCM 1:19→1:9) afforded *N*-benzyl-3-buten-1-ylamine[183] (1.05 g, 88%) as a pale brown oil; δ_H (300 MHz, CDCl$_3$) 7.36-7.24 (5H, m, 5 × ArH), 5.83-5.74 (1H, m, H$_2$C=CH), 5.13-5.05 (2H, m, H_2C=CH), 3.80 (2H, s, CH_2Ph), 2.71 (2H, t, *J* 6.8, NCH_2CH$_2$), 2.34-2.24 (2H, m, NCH$_2$CH_2), 1.50 (1H, br s, NH); δ_C (75 MHz, CDCl$_3$) 140.4 (aromatic C), 136.5 (H$_2$C=CH), 128.4, 128.1, 127.0 (5 × aromatic CH), 116.4 (H$_2$$C$=CH), 53.9 ($CH_2$Ph), 48.3 (N$CH_2CH_2$), 34.3 (NCH$_2$$CH_2$).
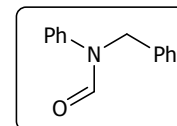
N-Benzyl-3-buten-1-ylamine (0.50 g, 3.1 mmol) afforded formamide **369m**[184] (0.58 g, 99%) as a brown oil; ratio of rotamers 1:1 in CDCl$_3$ at room temperature; δ_H (300 MHz, CDCl$_3$) 8.27, 8.18 (1H, s, CHO), 7.37-7.21 (5H, m, 5 × ArH), 5.86-5.60 (1H, m,

$H_2C=CH$), 5.10-5.01 (2H, m, $H_2C=CH$), 4.54, 4.39 (2H, s, CH_2Ph), 3.33-3.28, 3.23-3.18 (2H, m, NCH_2CH_2), 2.28-2.21 (2H, m, NCH_2CH_2); δ_C (75 MHz, CDCl$_3$) 163.0, 162.9 (CHO), 136.4, 136.1 (aromatic C), 135.0, 133.9 ($H_2C=CH$), 128.9, 128.7, 128.2, 128.1, 127.6, 127.5 (5 × aromatic CH), 118.1, 117.0 ($H_2C=CH$), 51.5, 41.4 (CH_2Ph), 46.4, 45.4 (NCH_2CH_2), 32.7, 31.5 (NCH_2CH_2).

### *Typical procedure for preparation of vinylogous carbamates:*

Ethyl (*Z*)-3-(pyrrolidin-1-yl)-2-(triethylsilyloxy)acrylate (370a)
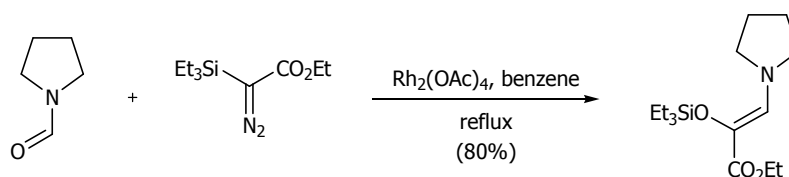
Ethyl diazo(triethylsilyl)acetate (0.29 g, 1.3 mmol) in benzene (3 mL) was added to a refluxing solution of 1-formylpyrrolidine (0.10 g, 1.0 mmol) and Rh$_2$(OAc)$_4$ (2 mg, 4.0 µmol) in benzene (3 mL). After 90 min the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (Al$_2$O$_3$; PS→EtOAc:PS 3:97) to afford acrylate **370a** (0.24 g, 80%) as a colourless oil; ν_{max}/cm^{-1} (film) 2953, 2876 (CH), 1693, 1639; δ_H (300 MHz, CDCl$_3$) 6.86 (1H, s, NCH=C), 4.13 (2H, q, *J* 7.1, OCH$_2$), 3.48-3.43 (4H, m, N(CH$_2$)$_2$), 1.84-1.80 (4H, m, N(CH$_2$CH_2)$_2$), 1.26 (3H, t, *J* 7.1, OCH$_2$CH_3), 0.96 (9H, t, *J* 7.8, Si(CH$_2$CH_3)$_3$), 0.71 (6H, q, *J* 7.8, Si(CH_2Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.2 (O=C), 131.7 (NCH=C), 117.8 (NCH=C), 59.5 (OCH$_2$), 50.6 (N(CH$_2$)$_2$), 25.4 (N(CH$_2$CH$_2$)$_2$), 14.6 (OCH$_2$CH$_3$), 7.0 (Si(CH$_2$CH$_3$)$_3$), 5.3 (Si(CH$_2$Me)$_3$); *m/z* (CI+) 300 (MH$^+$, 36%), 270 (100); HRMS (CI+) calcd for C$_{15}$H$_{30}$NO$_3$Si (MH$^+$) 300.1995, found 300.1984; Elemental analysis: calcd for C$_{15}$H$_{29}$NO$_3$Si C: 60.2, H: 9.8, N: 4.7. Found C: 60.0, H: 9.9, N: 5.0.

Ethyl (*Z*)-3-(piperidin-1-yl)-2-(triethylsilyloxy)acrylate (370b)

Formamide **369b** (0.10 g, 0.88 mmol) afforded acrylate **370b** (0.23 g, 83%) as a colourless oil; ν_{max}/cm^{-1} (film) 2937, 2876 (CH), 1693, 1639; δ_H (300 MHz, CDCl$_3$) 6.61 (1H, s, NCH=C), 4.14 (2H, q, *J* 7.1, OCH$_2$), 3.41-3.40 (4H, m, N(CH$_2$)$_2$), 1.62-1.58 (6H, m, (N(CH$_2$CH_2)$_2$CH_2), 1.25 (3H, t, *J* 7.1, OCH$_2$CH_3), 0.97 (9H, t, *J* 7.8,
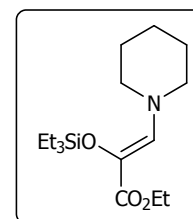
Si(CH$_2$CH_3)$_3$), 0.71 (6H, q, *J* 7.8, Si(CH_2Me)$_3$); δ$_C$ (75 MHz, CDCl$_3$) 167.4 (O=C), 133.3 (NCH=C), 117.3 (NCH=C), 59.7 (OCH$_2$), 51.1 (N(CH$_2$)$_2$), 26.2 (N(CH$_2$CH$_2$)$_2$), 24.4 (N(CH$_2$CH$_2$)$_2$CH$_2$) 14.6 (OCH$_2$CH$_3$), 6.9 (Si(CH$_2$CH$_3$)$_3$), 5.3 (Si(CH$_2$Me)$_3$); *m/z* (CI+) 314 (MH$^+$, 84%), 284 (100), 268 (50), 256 (27); HRMS (CI+) calcd for C$_{16}$H$_{32}$NO$_3$Si (MH$^+$) 314.2151, found 314.2137; Elemental analysis: calcd for C$_{16}$H$_{31}$NO$_3$Si C: 61.3, H: 10.0, N: 4.5. Found C: 61.2, H: 10.2, N: 4.1.

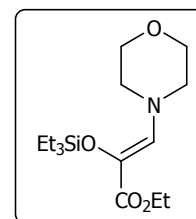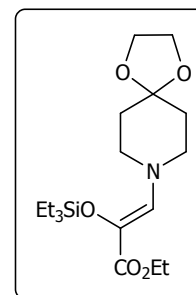### Ethyl (*Z*)-3-(morpholin-4-yl)-2-(triethylsilyloxy)acrylate (370c)

Formamide **369c** (0.10 g, 0.87 mmol) afforded acrylate **370c** (0.24 g, 87%) as a colourless oil; ν$_{max}$/cm^{-1} (film) 2957, 2876 (CH), 1699, 1643; δ$_H$ (300 MHz, CDCl$_3$) 6.54 (1H, s, NCH=C), 4.15 (2H, q, *J* 7.1, CO$_2$CH$_2$), 3.69-3.66 (4H, m, O(CH$_2$)$_2$), 3.43-3.40 (4H, m, N(CH$_2$)$_2$), 1.27 (3H, t, *J* 7.1, CO$_2$CH$_2$CH_3), 0.96 (9H, t, *J* 7.9, Si(CH$_2$CH_3)$_3$), 0.71 (6H, q, *J* 7.9, Si(CH_2Me)$_3$); δ$_C$ (75 MHz, CDCl$_3$) 166.9 (O=C), 132.2 (NCH=C), 119.6 (NCH=C), 66.8 (O(CH$_2$)$_2$), 60.0 (CO$_2$CH$_2$), 50.2 (N(CH$_2$)$_2$), 14.6 (CO$_2$CH$_2$CH$_3$), 6.9 (Si(CH$_2$CH$_3$)$_3$), 5.3 (Si(CH$_2$Me)$_3$); *m/z* (CI+) 316 (MH$^+$, 86%), 286 (100), 88 (25); HRMS (CI+) calcd for C$_{15}$H$_{30}$NO$_4$Si (MH$^+$) 316.1944, found 316.1940.

Ethyl (*Z*)-3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-(triethylsilyloxy)acrylate (370d)

Formamide **369d** (0.10 g, 0.58 mmol) provided acrylate **370d** (0.20 g, 90%) as a colourless oil; ν$_{max}$/cm^{-1} (film) 2953, 2876 (CH), 1693, 1639; δ$_H$ (300 MHz, CDCl$_3$) 6.60 (1H, s, NCH=C), 4.14 (2H, q, *J* 7.1, CO$_2$CH$_2$), 3.97 (4H, s, OCH$_2$CH$_2$O), 3.54-3.50 (4H, m, N(CH$_2$)$_2$), 1.72-1.69 (4H, m, N(CH$_2$CH_2)$_2$), 1.25 (3H, t, *J* 7.1, CO$_2$CH$_2$CH_3), 0.96 (9H, t, *J* 7.9, Si(CH$_2$CH_3)$_3$), 0.70 (6H, q, *J* 7.9, Si(CH_2Me)$_3$); δ$_C$ (75 MHz, CDCl$_3$) 167.1 (O=C), 132.3 (NCH=C), 118.4 (NCH=C), 106.8 (C(OCH$_2$)$_2$), 64.4 (OCH$_2$CH$_2$O), 59.8 (CO$_2$CH$_2$), 48.1 (N(CH$_2$)$_2$), 35.3 (N(CH$_2$CH$_2$)$_2$), 14.6 (CO$_2$CH$_2$CH$_3$), 6.9 (Si(CH$_2$CH$_3$)$_3$), 5.3 (Si(CH$_2$Me)$_3$); *m/z* (CI+) 372 (MH$^+$, 33%), 342 (41), 172 (100), 144 (39), 127 (21), 85 (21); HRMS (CI+) calcd for C$_{18}$H$_{34}$NO$_5$Si (MH$^+$) 372.2206, found 372.2194; Elemental analysis: calcd for C$_{18}$H$_{33}$NO$_5$Si C: 58.2, H: 9.0, N: 3.8. Found C: 57.9, H: 9.1, N: 3.7.

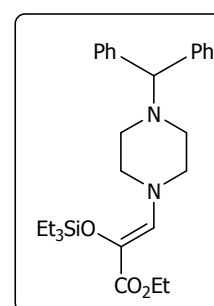**Ethyl (*Z*)-3-(4-methylpiperazin-1-yl)-2-(triethylsilyloxy)acrylate (370e)**

Ethyl diazo(triethylsilyl)acetate (0.22 g, 0.96 mmol) in benzene (3 mL) was added to a refluxing solution of 1-formyl-4-methyl-piperazine (0.10 g, 0.78 mmol) and $Rh_2(OAc)_4$ (1.3 mg, 3.1 µmol) in benzene (3 mL). After 6 d, an extra portion of ethyl diazo(triethylsilyl)acetate (0.22 g, 0.96 mmol) in benzene (3 mL) and $Rh_2(OAc)_4$ (1.3 mg, 3.1 µmol) was added to the reaction mixture.
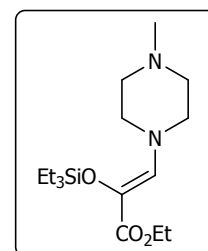
After a total reaction time of 10 d, the reaction mixture was concentrated and purified by flash chromatography (Al_2O_3; DCM→MeOH:DCM 1:9) to afford acrylate **370e** (0.16 g, 63%) as a colourless oil; v_{max}/cm^{-1} (film) 2953, 2876 (CH), 1693, 1643; δ_H (300 MHz, CDCl$_3$) 6.57 (1H, s, NCH=C), 4.13 (2H, q, *J* 7.1, OCH$_2$), 3.45 (4H, t, *J* 5.0, C=CHN(C*H$_2$*)$_2$), 2.39 (4H, t, *J* 5.0, MeN(C*H$_2$*)$_2$), 2.28 (3H, s, NCH$_3$), 1.26 (3H, t, *J* 7.1, OCH$_2$C*H$_3$*), 0.96 (9H, t, *J* 7.9, Si(CH$_2$C*H$_3$*)$_3$), 0.70 (6H, q, *J* 7.9, Si(C*H$_2$*Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.1 (O=C), 132.4 (NCH=*C*), 118.7 (N*C*H=C), 59.9 (OCH$_2$), 55.0 (MeN(*C*H$_2$)$_2$), 50.6 (C=CHN(CH$_2$)$_2$), 46.2 (NCH$_3$), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 329 (MH$^+$, 100%), 299 (100), 283 (34), 103 (24); HRMS (CI+) calcd for C$_{16}$H$_{33}$N$_2$O$_3$Si (MH$^+$) 329.2260, found 329.2249.

Ethyl (*Z*)-3-(4-benzhydrylpiperazin-1-yl)-2-(triethylsilyloxy)acrylate (370f)
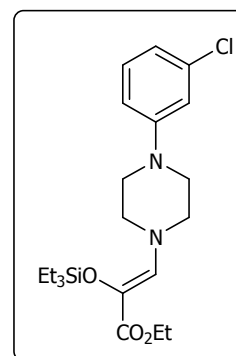
Formamide **369f** (0.60 g, 2.1 mmol) afforded acrylate **370f** (0.90 g, 87%) as a white solid; m.p. = 64-66 °C; v_{max}/cm^{-1} (KBr) 2953 (CH), 1688, 1632; δ_H (300 MHz, CDCl$_3$) 7.41 (4H, d, *J* 7.1), 7.30-7.26 (4H, m) and 7.21-7.16 (2H, m, 10 × ArH), 6.57 (1H, s, NCH=C), 4.22 (1H, s, NCHPh$_2$), 4.14 (2H, q, *J* 7.1, OCH$_2$), 3.46-3.43 (4H, m, C=CHN(C*H$_2$*)$_2$), 2.40-2.37 (4H, m, Ph$_2$CHN(C*H$_2$*)$_2$), 1.26 (3H, t, *J* 7.1, OCH$_2$C*H$_3$*), 0.94 (9H, t, *J* 8.0, Si(CH$_2$C*H$_3$*)$_3$), 0.67 (6H, q, *J* 8.0, Si(C*H$_2$*Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.1 (O=C), 142.4 (2 × aromatic C), 132.6 (NCH=*C*), 128.6, 127.9, 127.1 (10 × aromatic CH), 118.5 (N*C*H=C), 77.5 (NCHPh$_2$), 59.8 (OCH$_2$), 52.0 (C=CHN(CH$_2$)$_2$), 50.1 (Ph$_2$CHN(*C*H$_2$)$_2$), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.2 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 481 (MH$^+$, 68%), 451 (100), 167 (64); HRMS (CI+) calcd for C$_{28}$H$_{41}$N$_2$O$_3$Si (MH$^+$) 481.2886, found 481.2898; Elemental analysis: calcd for C$_{28}$H$_{40}$N$_2$O$_3$Si C: 70.0, H: 8.4, N: 5.8. Found C: 69.8, H: 8.6, N: 5.5.

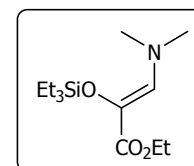### Ethyl (*Z*)-3-[4-(3-chlorophenyl)piperazin-1-yl]-2-(triethylsilyloxy)acrylate (370g)

Formamide **369g** (0.10 g, 0.45 mmol) afforded acrylate **370g** (0.12 g, 64%) as a colourless oil; v_{max}/cm^{-1} (film) 2953, 2876 (CH), 1643, 1593; δ_H (300 MHz, CDCl$_3$) 7.17 (1H, t, *J* 8.1) and 6.91-6.77 (3H, m, 4 × Ar*H*), 6.61 (1H, s, NC*H*=C), 4.16 (2H, q, *J* 7.1, OC*H$_2$*), 3.59-3.56 (4H, m, C=CHN(C*H$_2$*)$_2$), 3.18-3.15 (4H, m, ArN(C*H$_2$*)$_2$), 1.28 (3H, t, *J* 7.1, OCH$_2$C*H$_3$*), 0.99 (9H, t, *J* 7.9, Si(CH$_2$C*H$_3$*)$_3$), 0.74 (6H, q, *J* 7.9, Si(C*H$_2$*Me)$_3$); δ_C (75 MHz, CDCl$_3$) 166.9 (O=C), 152.3, 135.0 (2 × aromatic C), 131.9 (NCH=*C*), 130.1, 120.0 (2 × aromatic CH), 120.0 (N*C*H=C), 116.3, 114.4 (2 × aromatic CH), 60.0 (OCH$_2$), 49.6 (C=CHN(*C*H$_2$)$_2$), 49.1 (ArN(*C*H$_2$)$_2$), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 425 (MH$^+$, 85%), 395 (100), 345 (52), 225 (29), 197 (39), 161 (31), 115 (45), 87 (51); HRMS (CI+) calcd for C$_{21}$H$_{32}$ClN$_2$O$_3$Si (MH$^+$) 425.2027, found 425.2045.

Ethyl (*Z*)-3-dimethylamino-2-(triethylsilyloxy)acrylate (370h)

Dimethylformamide (0.10 g, 1.4 mmol) afforded acrylate **370h** (0.34 g, 90%) as a colourless oil; v_{max}/cm^{-1} (film) 2953, 2876 (CH), 1699, 1643; δ_H (300 MHz, CDCl$_3$) 6.61 (1H, s, NC*H*=C), 4.13 (2H, q, *J* 7.1, OC*H$_2$*), 2.97 (6H, s, N(C*H$_3$*)$_2$), 1.25 (3H, t, *J* 7.1, OCH$_2$C*H$_3$*), 0.96 (9H, t, *J* 7.8, Si(CH$_2$C*H$_3$*)$_3$), 0.70 (6H, q, *J* 7.8, Si(C*H$_2$*Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.3 (O=C), 134.3 (NCH=*C*), 117.7 (N*C*H=C), 59.7 (OCH$_2$), 42.0 (N(*C*H$_3$)$_2$), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 (Si(*C*H$_2$CH$_3$)$_3$); *m/z* (CI+) 274 (MH$^+$, 82%), 244 (100), 228 (67), 119 (21), 91 (43), 74 (23); HRMS (CI+) calcd for C$_{13}$H$_{28}$NO$_3$Si (MH$^+$) 274.1842, found 274.1842.

Ethyl (*Z*)-3-(*N*-allyl-*N*-benzylamino)-2-(triethylsilyloxy)acrylate (370i)

Formamide **369i** (0.10 g, 0.57 mmol) afforded acrylate **370i** (0.18 g, 85%) as a colourless oil; v_{max}/cm^{-1} (film) 2953, 2876 (CH), 1699, 1634; δ_H (400 MHz, CDCl$_3$) 7.35-7.23 (5H, m, 5 × Ar*H*), 6.80 (1H, s, NC*H*=C), 5.78 (1H, ddt, *J* 16.8, 10.5, 6.0, H$_2$C=C*H*), 5.23-5.07 (2H, m, *H$_2$*C=CH), 4.51 (2H, s, PhC*H$_2$*), 4.16 (2H, q, *J* 7.1, OC*H$_2$*), 3.79 (2H, d, *J* 5.8, H$_2$C=CHC*H$_2$*), 1.28 (3H, t, *J* 7.1, OCH$_2$C*H$_3$*), 0.93 (9H, t, *J* 7.9, Si(CH$_2$C*H$_3$*)$_3$), 0.68

(6H, q, *J* 7.9, Si(C*H*$_2$Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.2 (O=C), 138.1 (aromatic C), 134.0 (H$_2$C=*C*H) 132.5 (NCH=*C*), 128.5, 127.8, 127.3 (5 × aromatic C), 117.9 (N*C*H=C), 117.6 (H$_2$*C*=CH), 59.8 (O*C*H$_2$), 54.2 (Ph*C*H$_2$), 53.7 (N*C*H$_2$CH), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.4 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 376 (MH$^+$, 57%), 346 (57), 330 (34), 91 (63), 59 (35), 41 (100); HRMS (CI+) calcd for C$_{21}$H$_{34}$NO$_3$Si (MH$^+$) 376.2308, found 376.2302.

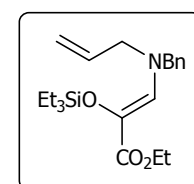### Ethyl (*Z*)-3-(*N*,*N*-diallylamino)-2-(triethylsilyloxy)acrylate (370j)

N,*N*-Diallylformamide (0.10 g, 0.80 mmol) afforded acrylate **370j** (0.25 g, 97%) as a colourless oil; v_{max}/cm^{-1} (film) 2955, 2876 (CH), 1693, 1636; δ_H (400 MHz, CDCl$_3$) 6.66 (1H, s, NCH=C), 5.78 (2H, ddt, *J* 16.6, 10.7, 5.9, 2 × H$_2$C=C*H*), 5.17-5.12 (4H, m, 2 × *H$_2$*C=CH), 4.14 (2H, q, *J* 7.1, OCH$_2$), 3.86 (4H, d, *J* 5.8, 2 × NCH$_2$), 1.27 (3H, t, *J* 7.1, OCH$_2$C*H$_3$*), 0.95 (9H, t, *J* 7.9, Si(CH$_2$C*H$_3$*)$_3$), 0.71 (6H, q, *J* 7.9, Si(C*H$_2$*Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.2 (O=C), 134.3 (H$_2$C=*C*H), 132.1 (NCH=*C*), 118.0 (N*C*H=C), 117.2 (H$_2$*C*=CH), 59.8 (O*C*H$_2$), 53.7 (N*C*H$_2$), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.4 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 326 (MH$^+$, 42%), 296 (100); HRMS (CI+) calcd for C$_{17}$H$_{32}$NO$_3$Si (MH$^+$) 326.2151, found 326.2141.
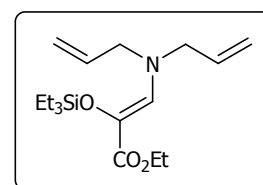
Ethyl (*Z*)-3-(*N*-ethoxycarbonylmethyl-*N*-methylamino)-2-(triethylsilyloxy)acrylate (370k)

N-Formylsarcosine ethyl ester (0.10 g, 0.69 mmol) afforded acrylate **370k** (0.17 g, 69%) as a colourless oil; v_{max}/cm^{-1} (film) 2955, 2876 (CH), 1749 (C=O), 1697, 1651; δ_H (300 MHz, CDCl$_3$) 6.64 (1H, s, NCH=C), 4.22-4.09 (6H, m, NCH$_2$ and 2 × OCH$_2$), 3.00 (3H, s, NCH$_3$), 1.29-1.23 (6H, m, 2 × OCH$_2$C*H$_3$*), 0.95 (9H, t, *J* 7.9, Si(CH$_2$C*H$_3$*)$_3$), 0.70 (6H, q, *J* 7.9, Si(C*H$_2$*Me)$_3$); δ_C (75 MHz, CDCl$_3$) 169.8 (NCH$_2$*C*=O), 166.9 (NCH=C*C*=O), 132.5 (NCH=*C*), 119.2 (N*C*H=C), 61.0, 60.0 (2 × OCH$_2$) 54.4 (N*C*H$_2$), 42.1 (N*C*H$_3$), 14.6, 14.2 (2 × OCH$_2$*C*H$_3$) 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 346 (MH$^+$, 49%), 316 (100), 300 (15), 121 (25); HRMS (CI+) calcd for C$_{16}$H$_{32}$NO$_5$Si (MH$^+$) 346.2050, found 346.2032; Elemental analysis: calcd for C$_{16}$H$_{31}$NO$_5$Si C: 55.7, H: 9.0, N: 4.1. Found C: 55.8, H: 9.2, N: 4.1.
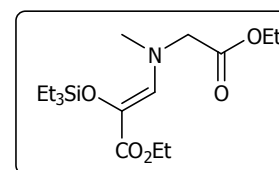
Ethyl (*Z*)-3-(*N*-benzyl-*N*-phenylamino)-2-(triethylsilyloxy)acrylate (370l)

Ethyl diazo(triethylsilyl)acetate (0.15 g, 0.59 mmol) in benzene (3 mL) was added to a refluxing solution of *N*-benzylformanilide (0.10 g, 0.47 mmol) and $Rh_2(OAc)_4$ (0.9 mg, 1.9 µmol) in benzene (3 mL). After 3 h, the reaction mixture was concentrated *in vacuo* to provide a 3:2 mixture of *Z*:*E* geometric isomers. Purification by flash chromatography (Al_2O_3; PS) afforded pure *Z*-isomer **370l** (0.05 g, 28%) and a mixture of *Z*:*E*-isomers (total yield 0.09 g, 50%) as a colourless oil; v_{max}/cm^{-1} (film) 2953, 2876 (CH), 1703, 1643; δ_H (300 MHz, CDCl$_3$) 7.33-7.20 (8H, m) and 6.98-6.93 (3H, m, 10 × ArH and NCH=C), 5.18 (2H, s, NCH$_2$), 4.22 (2H, q, *J* 7.1, OCH$_2$), 1.32 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 0.87 (9H, t, *J* 7.9, Si(CH$_2$C*H*$_3$)$_3$), 0.60 (6H, q, *J* 7.9, Si(C*H*$_2$Me)$_3$); δ_C (75 MHz, CDCl$_3$) 166.5 (O=C), 146.3 (NCH=*C*), 138.6 (aromatic C), 128.9, 128.6, (4 × aromatic CH), 126.9 (aromatic C), 126.3, 126.2, 125.2 (4 × aromatic CH), 121.7 (N*C*H=C), 118.0 (2 × aromatic CH), 60.5 (OCH$_2$), 52.9 (NCH$_2$), 14.5 (OCH$_2$*C*H$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 412 (MH$^+$, 67%), 382 (100), 91 (39); HRMS (CI+) calcd for C$_{34}$H$_{34}$NO$_3$Si (MH$^+$) 412.2308, found 412.2309.
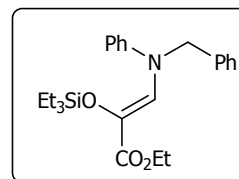
Ethyl (*Z*)-3-(*N*-benzyl-*N*-but-3-enylamino)-2-(triethylsilyloxy)acrylate (370m)

*N*-Benzyl-*N*-(but-3-enyl)formamide (0.10 g, 0.53 mmol) afforded acrylate **370m** (0.17 g, 83%) as a colourless oil; v_{max}/cm^{-1} (film) 2952, 2875 (CH), 1694, 1634; δ_H (400 MHz, CDCl$_3$) 7.35-7.24 (5H, m, 5 × ArH), 6.78 (1H, s, NC*H*=C), 5.73 (1H, ddt, *J* 17.1, 10.2, 6.9, H$_2$C=C*H*), 5.08-5.01 (2H, m, *H*$_2$C=CH), 4.56 (2H, s, C*H*$_2$Ph), 4.16 (2H, q, *J* 7.1, OCH$_2$), 3.24 (2H, t, *J* 7.4, NCH$_2$CH$_2$), 2.28 (2H, q, *J* 7.2, NCH$_2$C*H*$_2$), 1.28 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 0.93 (9H, t, *J* 7.8, Si(CH$_2$C*H*$_3$)$_3$), 0.68 (6H, q, *J* 7.8, Si(C*H*$_2$Me)$_3$); δ_C (75 MHz, CDCl$_3$) 167.3 (CHO), 138.4 (NCH=*C*), 135.2 (H$_2$C=*C*H), 132.6 (N*C*H=C), 128.5, 127.6, 127.3 (5 × aromatic CH), 117.6 (aromatic C), 116.9 (*H*$_2$C=CH), 59.8 (OCH$_2$), 55.0 (*C*H$_2$Ph), 51.3 (N*C*H$_2$CH$_2$), 33.2 (NCH$_2$*C*H$_2$), 14.6 (OCH$_2$*C*H$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 5.4 (Si(*C*H$_2$Me)$_3$); *m/z* (CI+) 390 (MH$^+$, 46%), 389 (66), 360 (100), 349 (57), 290 (13), 91 (72); HRMS (CI+) calcd for C$_{22}$H$_{36}$NO$_3$Si (MH$^+$) 390.2464, found 390.2458.
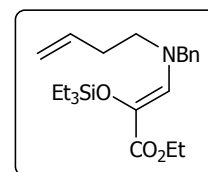
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