STUDIES TOWARDS THE SYNTHESIS OF THE

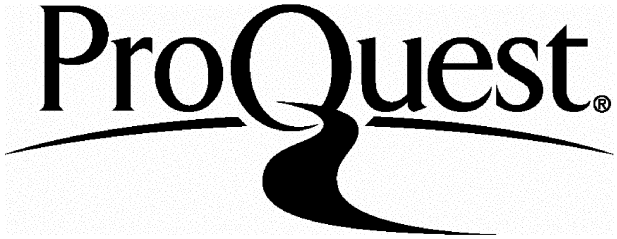
~~Synthetic Studies Towards the~~ Core Structure of Sarains A, B and C

A Thesis Presented to the University of London
in Partial Fulfilment of the Requirements for
the Degree of Doctor of Philosophy

Gurdeep Singh Nandra

September 2004

Christopher Ingold Laboratories
Department of Chemistry
University College London
London WC1H 0AJ



Abstract

Sarains A-C are marine alkaloids produced by the sponge *Reniera sarai*, which exhibit antitumor, antibacterial, and insecticidal activities. Sarains A-C have a complex structure, which comprises of a 1,5-diazatetracyclo[6.2.1.1^{3,9}.0^{4,11}]dodecane tricyclic core surrounded by two macrocycles. To date four groups have communicated the construction of the tricyclic core, however the total synthesis of sarains A-C has yet to be reported.

This thesis describes the work undertaken towards the synthesis of a tricycle that contains the core structure of sarains A-C, by the use of a novel carbene mediated ylide rearrangement reaction. The initial objective was to construct the precursor for this rearrangement, a *cis*-fused octahydropyrrolo[2,3-*b*]pyrrole ring system bearing an *endo* acetic acid substituent in the three position.

A number of strategies towards the construction of the desired octahydropyrrolo[2,3-*b*]pyrrole ring system were investigated, these included:

- The electrophilic azidation of a *cis*-fused hexahydro-isoindole.
- The cyclisation of α-amino-β-iodopyrrolidines.
- The formation of cyclic amidines.
- The Diels-Alder reaction between 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene and an *N*-protected-pyrrolin-2-one dienophile.

However, these approaches were unsuccessful. Following this, two closely related strategies were pursued, which gave promising results. A non-stereoselective strategy to the bicyclic system by the ring opening of butadiene monoxide with a

lactam enolate was investigated. A *cis*-fused octahydropyrrolo[2,3-*b*]pyrrole ring system was formed using a model system based on an azido-lactam synthesised in this strategy.

Finally, the use of a [3,3]-sigmatropic rearrangement provided a stereoselective method for construction of the required octahydropyrrolo[2,3-*b*]pyrrole ring system.

Waheguru Ji ka Khalsa, Waheguru Ji ki Fateh

(To God does the pure belong, To God do all victories belong)

This thesis is dedicated to my family for their endless love, support, encouragement and enduring patience.

Acknowledgements

There are many people to thank for their support and encouragement, without which this thesis would not have been possible.

First and foremost, I would like to thank my supervisor Dr. Mike Porter, his unquenchable curiosity and love for the subject are probably the most valuable lessons I have learned from this PhD. Dr Mike Porter's continual support has kept me going over the last three or so years and I could not have imagined having a better advisor and mentor for my PhD. I would also like to thank EPSRC for their generous financial support of this project.

Thank you to my CASE supervisor Dr Jason Elliott from Merck Sharp & Dohme Research Laboratories, you have been so encouraging and generous in your time that I will always be grateful. I would also like to gratefully thank Merck Sharp & Dohme for their financial input into this project.

I would like to thank all the members of the Porter group, especially to Fabienne, Nicola and Salma for their fellowship, support and company. I could not have wished for better work colleagues and will always remember the Friday afternoon muffin breaks.

Thanks also to Marcus, Shahid and Linos, for their companionship and for always being there through the ups and downs of my research.

Next there's all the friends I've made, the list is too long to mention but their friendship has helped to make my stay at UCL a really happy one,

I would like to thank my parents, the rest of my family and Gursharan for their support and encouragement, without which I would not have been able to complete my PhD studies.

Thanks also go to the UCL chemistry technical staff, especially Dr. Abil E. Aliev and John Hill. Finally I would also like to thank Novartis for use of their microwave oven.

Abbreviations

Ac	Acetyl
acac	Acetylacetonyl
AIBN	2,2'-azobis(isobutyronitrile)
Aq.	Aqueous
Ar	Aromatic
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
cat.	Catalyst/catalytic
Cbz	Benzyloxycarbonyl
Cy	Cyclohexyl
DA	Diels-Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMPU	*N*,*N*'-Dimethyl-N,N'-propyleneurea
DMSO	Dimethyl sulfoxide
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
EDG	Electron donating group

EWG	Electron withdrawing group
IC	Inhibitory concentration
KHMDS	Potassium hexamethyldisilazide
LD	Lethal Dose
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
Me	Methyl
MIC	Minimum inhibitory concentration
Ms	Methanesulfonyl
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NOE	Nuclear Ovenhauser Effect
Ns	Nitrobenzenesulfonyl
o-DCB	*ortho*-Dichlorobenzene
Ph	Phenyl
PMB	*para*-Methoxybenzyl
^{i}Pr	Isopropyl
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
rt	Room Temperature
TBAC	Tetra-*N*-butylammonium chloride
TBAF	Tetra-*N*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl

t-Bu	*tert*-Butyl
TES	Triethylsilyl
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetra-*N*-propylammonium perruthenate
Tf	Trifluoromethanesulfonyl
Trisyl	2,4,6-Triisopropylbenzenesulfonyl
Ts	*para*-Toluenesulfonyl

Table of Contents

Chapter One

INTRODUCTION

1.1 Marine Natural Products

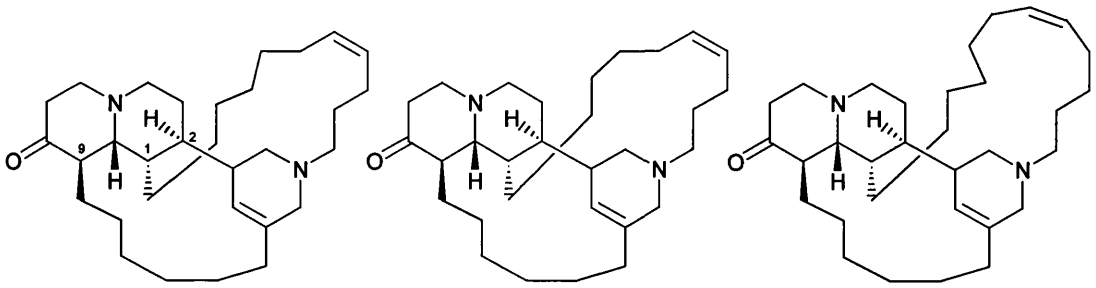
The marine environment has given rise to a unique ecosystem that is very different to that of land-based life. Over the last 25 years it has been possible to study nitrogenous substances (referred to as marine alkaloids) isolated from marine species. Many marine alkaloids have biological properties that may prove to be of value for mankind in the future.[1] Marine invertebrates such as sponges, soft corals, molluscs, coelenterates, and ascidians produce secondary metabolites, some of which can have extraordinary structures. These marine products often possess potent biological activities, which may include antitumour, antifungal, antimicrobial, immunosuppressant and enzyme inhibitory activities.[2] However, the full biological evaluation of these marine alkaloids can often not be performed as a consequence of limiting quantities of the active species. It is extremely difficult and ecologically undesirable to harvest large quantities of marine creatures and in most cases virtually impossible to grow them outside their natural habitat.

This is where chemical synthesis can be applied to produce substantial quantities of these interesting alkaloids with the added advantage of synthesising analogues and broadening the biological screening of the active species.

1.2 Alkaloids Isolated from *Reniera Sarai*

The Mediterranean sponge *Reniera sarai*, Pulitzeri-Finali, 1969 (Demospongiae: Haplosclerida: Renieridae) found in the Bay of Naples contains some interesting and complex nitrogenous metabolites. Cimino and co-workers[3]

have isolated several unprecedented polycyclic alkaloids from this sponge; these alkaloids have two distinct skeletons, although they have somewhat ambiguously been given the same name. Sarains 1-3 (**1-3**) contain a *trans*-fused quinolizidone moiety linked to an unsaturated piperidine ring both directly and by two linear alkyl chains (Figure 1).[4]



Sarain 1 (1) **Sarain 2 (2)** **Sarain 3 (3)**

Figure 1

Sarains A, B and C belong to the second family of alkaloids isolated from the sponge *Reniera sarai* and form a homologous series of alkaloids. The structure of sarain A (**4**) has been assigned by a combination of an X-ray study on the acetyl derivative of sarain A (**5**) and detailed spectral studies on sarain A itself. The structures of the superior homologues sarains B (**6**) and C (**7**) have been suggested by careful examination of their ^{1}H and ^{13}C NMR spectra and by comparison with the NMR spectra of sarain A (Figure 2).[5]

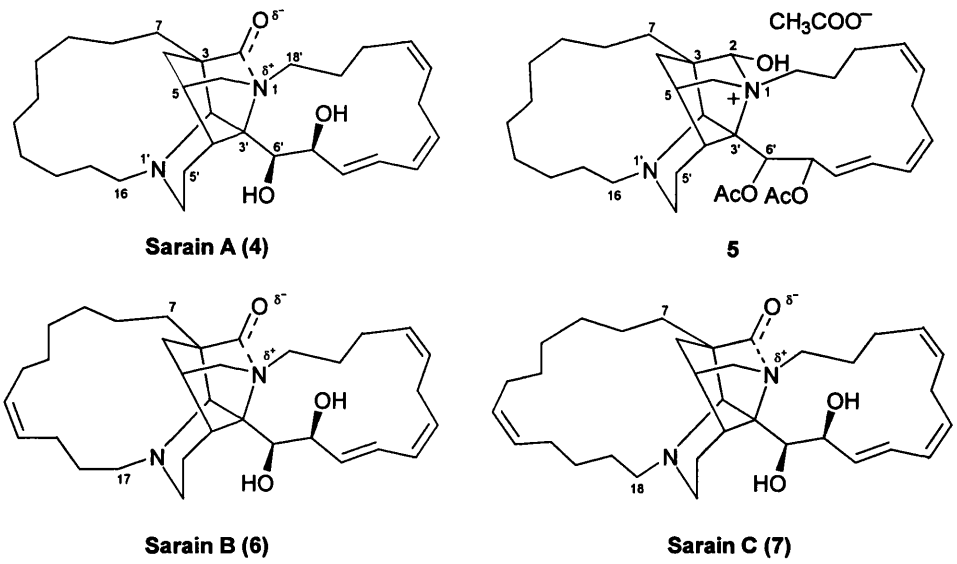
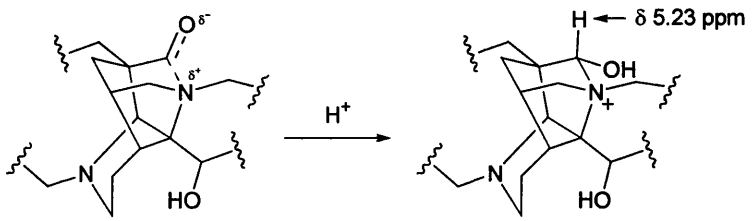


Figure 2

Sarains A-C share an unusual 1,5-diazatetracyclo[6.2.1.1^{3,9}.0^{4,11}]dodecane tricyclic core, incorporating a peculiar "proximity" interaction between the aldehyde group at C-3 and a tertiary amine group at N-1. Surrounding the central core are two macrocycles; one (which is common to sarains A-C), consists of a 14-membered ring containing three double bonds (two (*Z*) and one (*E*)) and a vicinal diol. The second macrocycle differs in size among the three sarains (a 13-, 14-, or 15-membered ring) and can contain a (*Z*)-olefin moiety (Figure 2).

Sarains A-C show some interesting spectral features.[3,6] The ^{1}H NMR chemical shift of the aldehyde proton in sarains A, B and C occurs as a broad signal at δ 8.50 ppm, δ 8.56 ppm and δ 8.63 ppm, respectively (500 MHz, neutral $CDCl_3$). The carbonyl IR maximum for sarains A-C (1650-1660 cm^{-1}) is shifted lower than the normal carbonyl frequency and disappears upon treatment with acid (HCl). Cimino and co-workers suggested that acidic conditions favour the formation of an N-C transannular bond and a hydroxy group in sarains A-C (Scheme 1). ^{1}H and ^{13}C NMR studies on sarain A using CD_3COOD showed the presence of some new

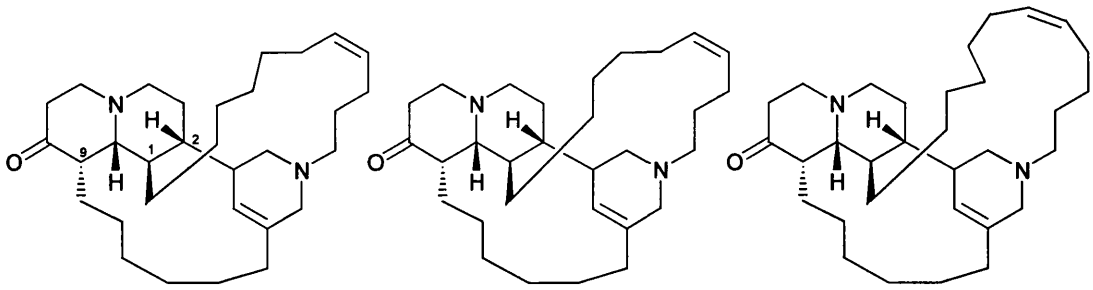
signals (compared to the ^{1}H NMR spectrum obtained in neutral $CDCl_3$). In particular a sharp singlet at δ 5.23 ppm, which correlated to a ^{13}C resonance at δ 98.0 ppm was observed. This signal was assigned as the methine between N-1 and the hydroxy group in the charged pseudobase **9** (Scheme 1).[3]



8 **9**

Scheme 1

Some minor alkaloids present in the sponge have also been isolated, isosarains 1-3 (**10-12**) are stereoisomers of sarains 1-3 and are characterised by having inverted stereochemistry at chiral centres 1, 2 and 9 (Figure 3).[7]



Isosarain 1 (10) **Isosarain 2 (11)** **Isosarain 3 (12)**

Figure 3

1.3 Biological Activity of Sarain Alkaloids

The sarain alkaloids isolated from *Reniera sarai* have interesting properties; they strongly retain inorganic salts and have catalytic properties similar to that of crown ethers.[8] The alkaloids appear to offer protection to the parent sponge and act

by preventing epibionts (a fouling organism often found on shells) from attaching to the surface tissues of the sponge.[9] Cimino and co-workers have conducted a preliminary screening of sarains A-C and sarains 1-3 for biological activity.[8] The alkaloids were tested for their activities in the following biological assays:

1. Cytotoxicity to *Artemia salina* (Brine shrimp).
2. Antibacterial activity on *Staphylococcus aureus*, a Gram-positive spherical bacterium.
3. Insecticidal/acaricidal activity on *Macrosiphum euphorbiae* (potato aphid), *Aedes aegypti* (yellow-fever mosquito) and *Tetranychus urticae* (two-spotted spider mite).
4. Antitumour effects on the potato disc infected by *Agrobacterium tumefaciens* (a Gram-negative, non-sporing, motile rod-shaped bacterium).
5. Growth inhibition of fertilised sea urchin eggs.

The reported activities of the sarains are summarised in Tables 1 and 2. Both sarain families exhibit encouraging activities, with sarains 1-3 being generally most active. The activities were found to be well below that of the crude *n*-butanol extract of *Reniera sarai*, suggesting that there may be a synergistic effect of the combined sarains, or that there may be a minor co-occurring metabolite which has yet to be isolated that may show dominant activity.

Table 1. Bioassay results

Compound	Brine shrimp *Artemia salina* (LD_{50} μg/mL)	Potato disc infected with *A. tumefaciens* (% Inhibition)	Fertilised sea urchin eggs development (IC μg/mL)	Antibacterial activity *Staphylococcus aureus* (MIC μg/mL)
Sarain A (**4**)	46.7	35	3.12	12.5
Sarain B (**6**)	6.8	30	3.12	25.0
Sarain C (**7**)	4.5	40	1.56	25.0
Sarain 1 (**1**)	3.3	51	6.25	No activity†
Sarain 2 (**2**)	6.4	16	>50.0	50.0
Sarain 3 (**3**)	2.5	55	3.12	6.25
Penicillin G Na	-	-	-	0.04

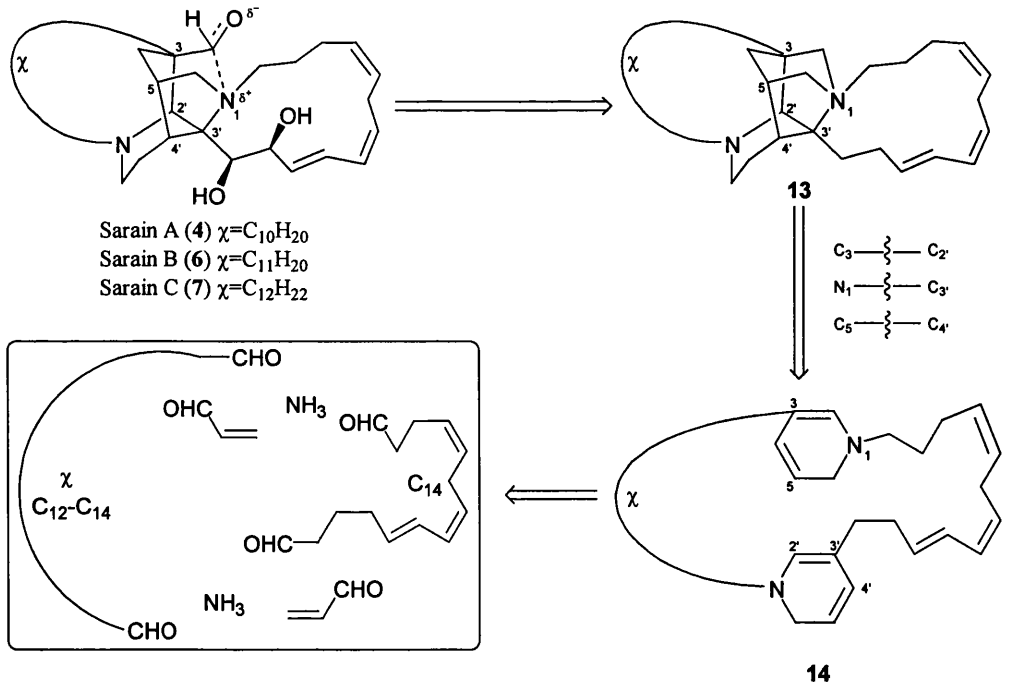
LD_{50} is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals. Inhibitory concentration (IC) is the concentration of a substance that causes a defined inhibition of a given system: IC_{50} is the median concentration that causes 50% inhibition. †More than 100 μg/mL.

Table 2. Insecticidal/acaricidal potency

Compound	*M. euphorbiae* (Potato aphid) spray at 100 ppm (% Mortality)	*Aedes aegypti* (Yellow-fever mosquito) Dipping in 0.2 ppm (% Mortality)	*Tetranychus uticae* (Two-spotted spider mite) spray at 100 ppm		
			Adults (% Mortality)	Eggs (% Mortality)	Juvenile forms (% Mortality)
Sarain A (**4**)	20	24	20	13	17
Sarain B (**6**)	29	0	19	12	8
Sarain C (**7**)	37	0	23	10	12
Sarain 1 (**1**)	68	20	40	2	79
Sarain 2 (**2**)	63	18	32	3	66
Sarain 3 (**3**)	29	46	9	14	11

1.4 Macrocyclic Marine Alkaloids and their Possible Derivation from Dihydropyridines

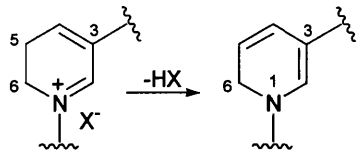
Although no studies have been carried out to elucidate the biosynthesis of sarains A-C, a biogenetic pathway has been proposed by Cimino and co-workers.[4] The retro-biosynthesis of sarains A-C proceeds through a *bis*-3-alkyl-dihydropyridine macrocycle (**14**), containing twelve carbons in an alkyl chain and 10, 11, or 12 carbons in another alkyl chain (χ) (Scheme 2). This bis-3-alkyldihydropyridine macrocylce can be derived from ammonia, a C_3 unit, a C_{14} dialdehyde and another dialdehyde which can comprise of twelve to fourteen carbons.



Scheme 2

Dihydropyridinium salts (**15**) and dihydropyridine (**16**) have been proposed as starting precursors to a number of complex macrocyclic alkaloids isolated from

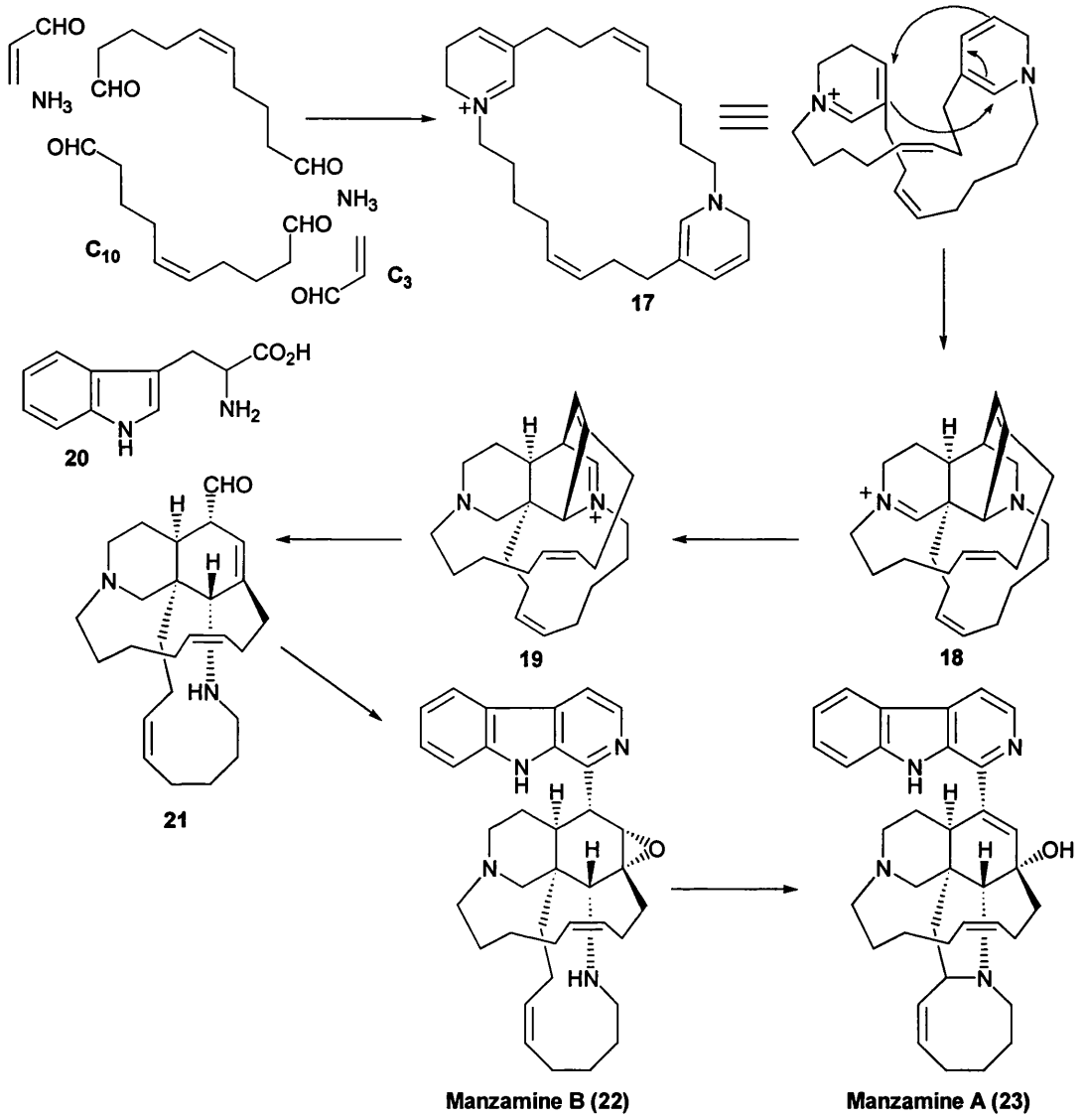
marine species, which include the manzamine, sarain, halicyclamine and ircinal families of alkaloids (Scheme 3).[10]



15 **16**

Scheme 3

In 1992 Baldwin and Whitehead proposed a fascinating biogenetic pathway for manzamine A (**23**) and manzamine B (**22**) (Scheme 4).[11] It was proposed that a *bis*-3-alkyldihydropyridine macrocycle (**17**), which could be derived from ammonia, a C_3 unit and a C_{10} unit, was the starting point for the pathway. This macrocycle could be converted to the pentacyclic intermediate **19** *via* a Diels-Alder-type [4+2] intramolecular cycloaddition followed by a hydride transfer. This, after hydrolysis and condensation with tryptophan (**20**), would lead to manzamines A (**23**) and B (**22**). However, their proposal lacked any experimental backing, until in 1992 Kobayashi and co-workers isolated two novel alkaloids ircinals A (**24**) and B (**25**) from the sponge *Ircinia*,[12] which appeared to be very close in structure to intermediate **21** (Figure 4).



Scheme 4

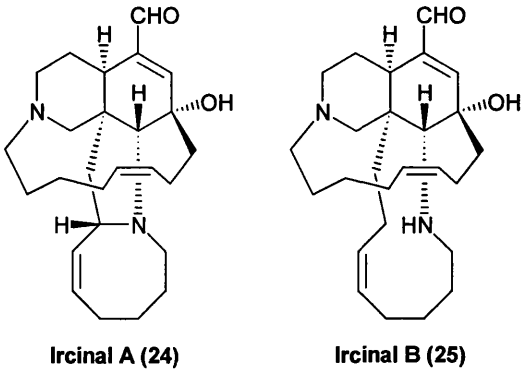


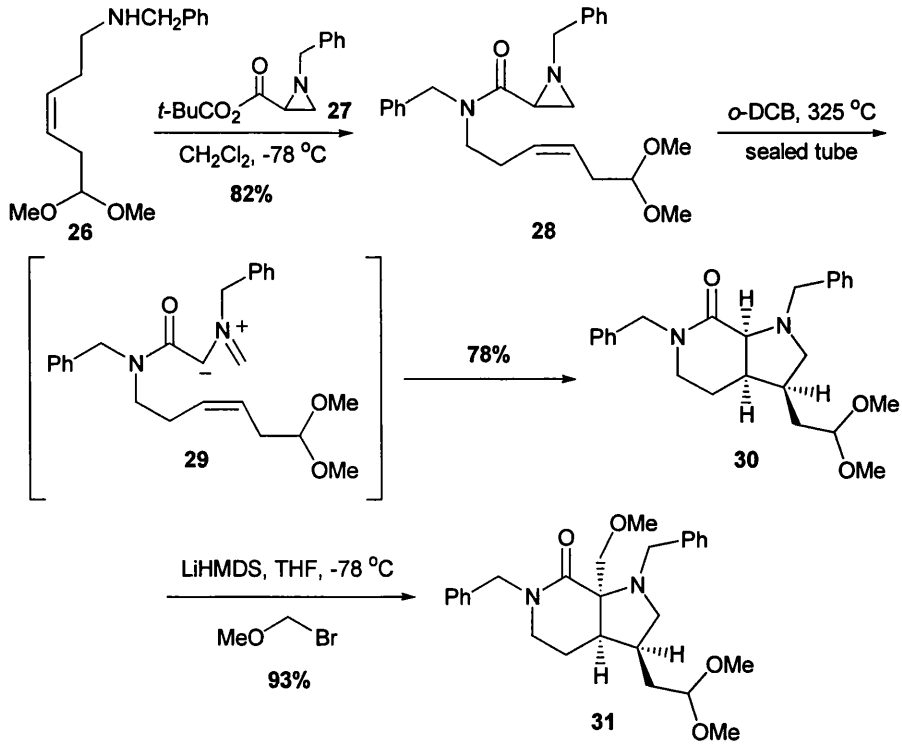
Figure 4

1.5 Previous Syntheses of the Sarain Core

The total synthesis of sarains A-C has yet to be reported, however, four groups have communicated the construction of the tricyclic core.

1.5.1 Weinreb's Synthesis of the Sarain Core

Weinreb and co-workers were first to report the assembly of the tricyclic core of sarains A-C in 1991.[13] This strategy has been improved over several years and in 1999 an optimised route was published.[14] The revised synthesis began by condensation of the *N*-benzyl protected amine **26** with the aziridine mixed anhydride **27** (Scheme 5).

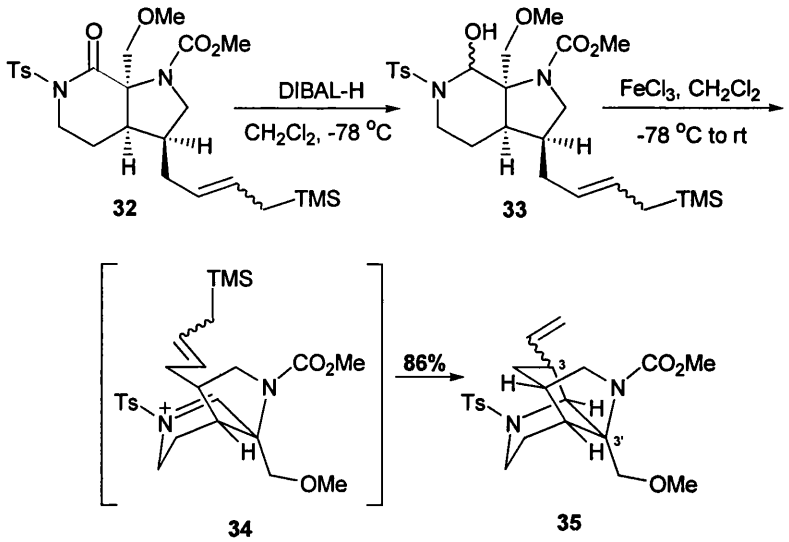


Scheme 5

The resulting adduct **28** was subjected to thermolysis at 325 °C in a sealed tube using degassed *o*-dichlorobenzene. This initiated an azomethine ylide / olefin

[3+2]-dipolar cycloaddition to give the *cis*-fused bicycle **30**. Following this, lactam **30** was deprotonated with lithium hexamethyldisilazide (LHMDS) and alkylated with bromomethyl methyl ether, to give the methyl ether side chain in the *cis*-fused bicycle **31**.

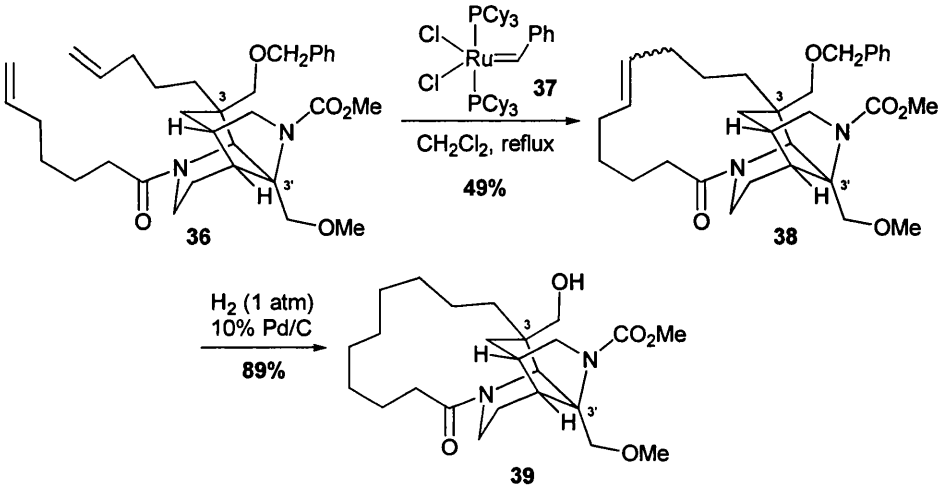
Bicycle **31** was further transformed to **32**. Reduction of the amide carbonyl in **32** with DIBAL-H gave the α-hydroxysulfonamide **33**, which was treated with anhydrous ferric chloride to afford the tricyclic nucleus **33** (Scheme 6). Weinreb and co-workers rationalised that the cyclisation occurred *via* an *N*-sulfonyliminium intermediate (**34**), where the allylsilane group was in a quasi-equatorial position.[15] The allylsilane / *N*-sulfonyliminium ion cyclisation yielded the tricyclic core **35** in 86% yield, as a 3:2 mixture of diastereomers at C-3.



Scheme 6

Tricycle **35** was further transformed to **36** which contained functional handles at the C-3 and C-3' positions for attachment of the eastern and western macrocycles. The 'western' macrocycle in **38** was successfully assembled *via* a ring-closing

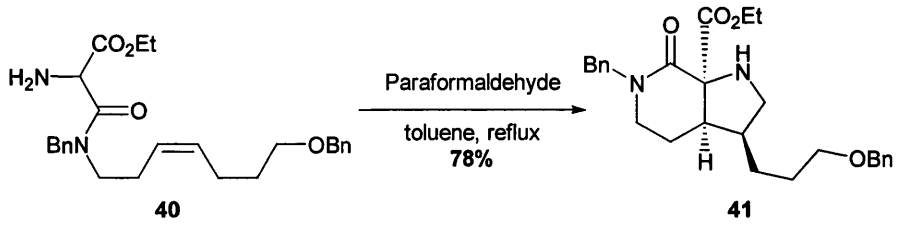
metathesis strategy using Grubbs' ruthenium catalyst (**37**) (Scheme 7).[13] Macrocycle **38** was produced as a mixture of (*Z*) and (*E*) isomers (49%), along with recovered starting material (7%) and a macrocyclic dimer (39%). Finally hydrogenation of **38** gave macrolactam alcohol **39** in an 89% yield.



Scheme 7

1.5.2 Heathcock's Synthesis of the Sarain Core

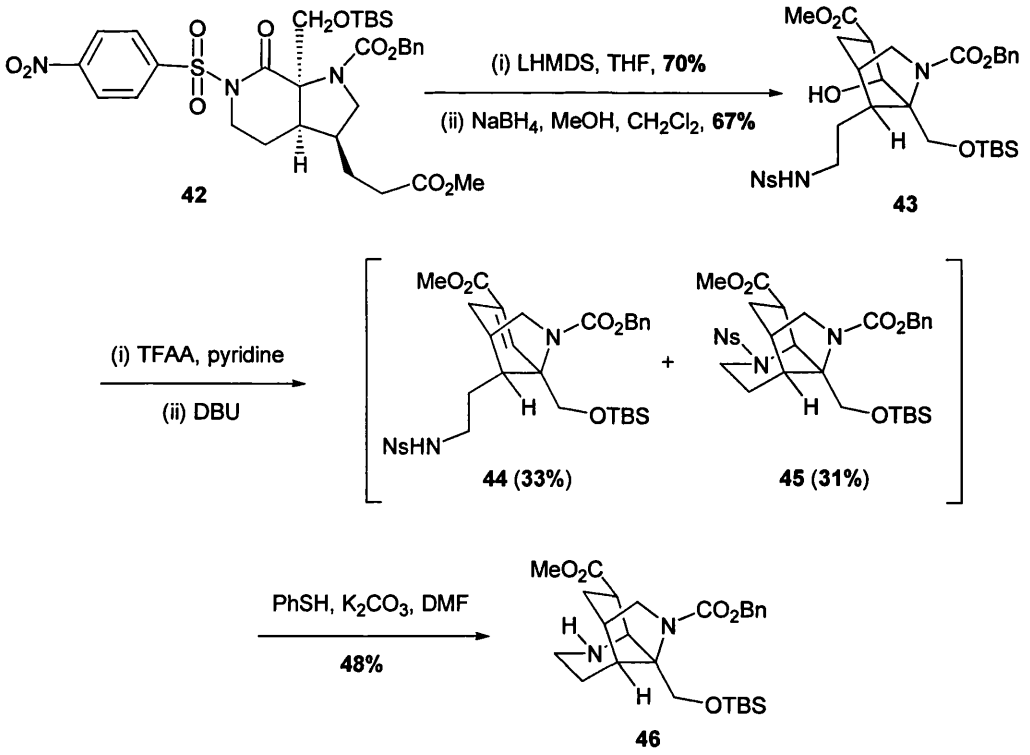
Heathcock *et al.*[16] started their synthesis in a similar method to the Weinreb group by using an intramolecular azomethine ylide cyclisation to construct bicycle **41**. However, it was discovered that higher yields of bicycle **41** could be achieved when the azomethine ylide was generated by the condensation of amine **40** with paraformaldehyde in toluene under reflux, rather than using an aziridine precursor (Scheme 8).



Scheme 8

The *cis*-fused bicycle **41** was then transformed to bicycle **42**. Enolisation of the methyl ester in **42** with LHMDS induced cyclisation with the amide carbonyl (Scheme 9). Reduction of the ketonic carbonyl with sodium borohydride gave **43** in 67% yield. The secondary alcohol in **43** was converted to the trifluoroacetate and eliminated by treatment with DBU. The reaction resulted in an approximately equal mixture of the α,β-unsaturated ester **44** and the desired cyclisation product **45**.

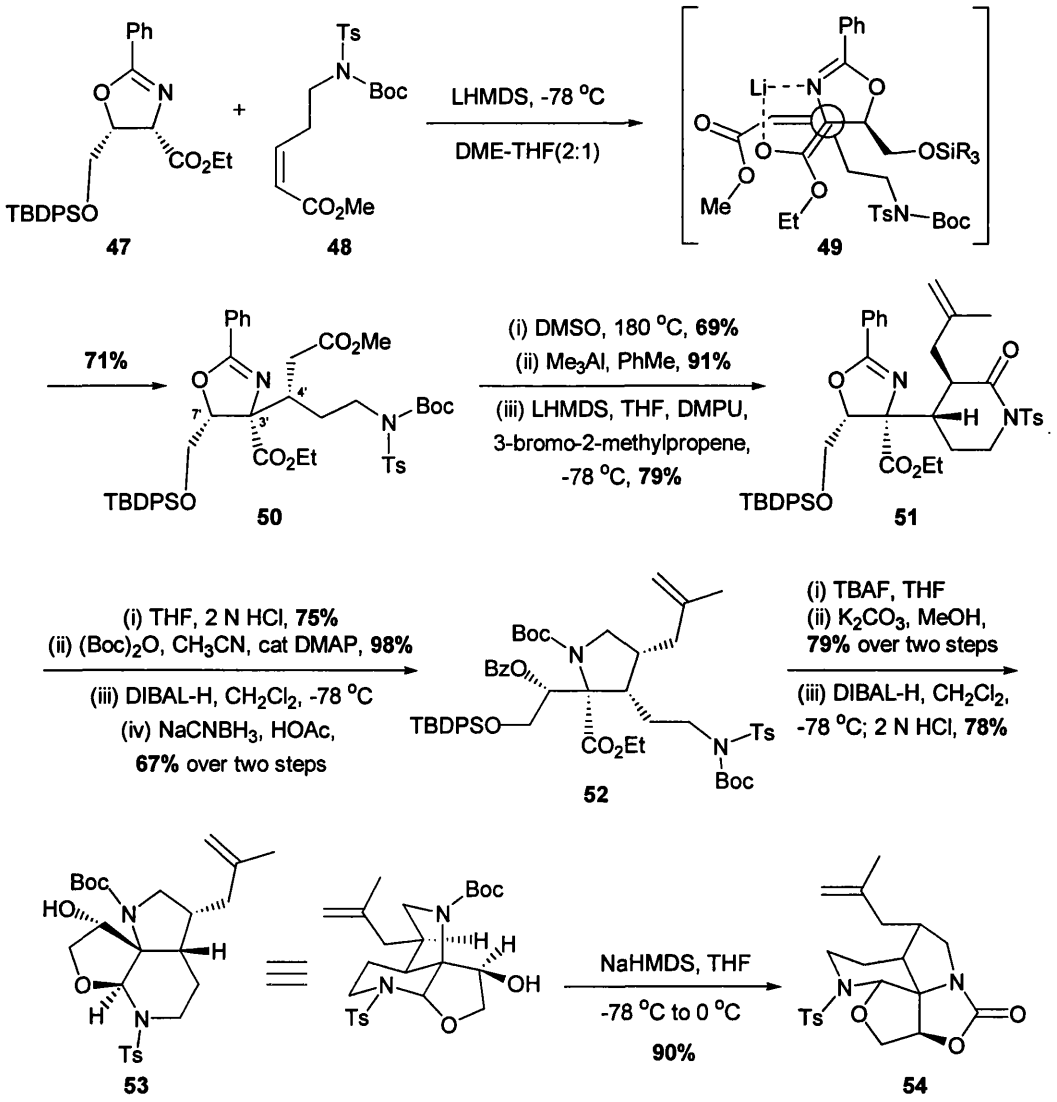
Exposure of the mixture of products **44** and **45** to thiophenol and potassium carbonate in DMF removed the nosyl group and gave tricycle **46** in 48% yield. This strategy to the sarain core suffered from a considerable amount of protecting group manipulation and led to a lengthy synthesis (22 steps, 1.4% overall yield).



Scheme 9

1.5.3 Overman's Synthesis of the Sarain Core

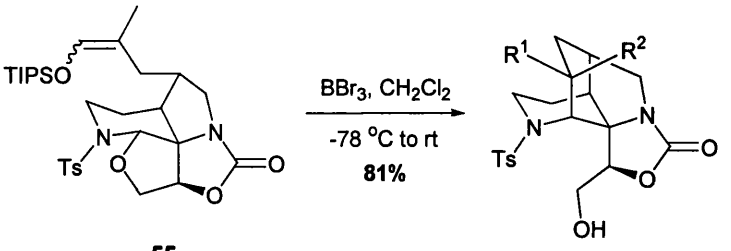
Overman and co-workers[17] developed the first asymmetric synthesis of the tricyclic core of sarains A-C. Their synthesis began with an intermolecular Michael reaction between the tartrate-derived oxazoline **47** and (*Z*)-enoate **48**. This effectively set the C4'-C3'-C7' stereocentres in adduct **50** (Scheme 10). Thermal cleavage of the *tert*-butoxycarbonyl group (Boc) in **50** followed by cyclisation of the resulting amino group with the methyl ester using trimethylaluminium generated a six membered lactam.



Scheme 10

Deprotonation of the lactam with LHMDS and alkylation with 3-bromo-2-methylpropene gave oxazoline **51** as a single stereoisomer. Exposure of **51** to 2N aqueous hydrochloric acid removed the oxazoline ring and promoted translactamization. Protection of the nitrogen atoms of the product from this reaction with Boc groups followed by reduction with DIBAL-H and $NaCNBH_3$ generated pyrrolidine **52** in 67% yield over two steps. Removal of the silyl protecting group with TBAF released the primary alcohol, treatment of the intermediate from this reaction with K_2CO_3 in methanol cleaved the benzoate and sulfonamide Boc protecting groups and effected lactonisation. Reduction of the lactone with DIBAL-H followed by an acidic work-up generated tricycle **53**. Cyclisation of **53** was achieved using NaHMDS and gave tetracycle **54** in 90% yield.

Tetracycle **54** was then transformed to **55**, which was set up for an intramolecular *N*-tosyliminium ion-enoxysilane cyclisation. Exposure of **55** to 3.5 equivalents of boron tribromide in dichloromethane gave a mixture of diazatricycloundecanes **56** and **57** in a 3:1 ratio and 81% combined yield (Scheme 11).



55

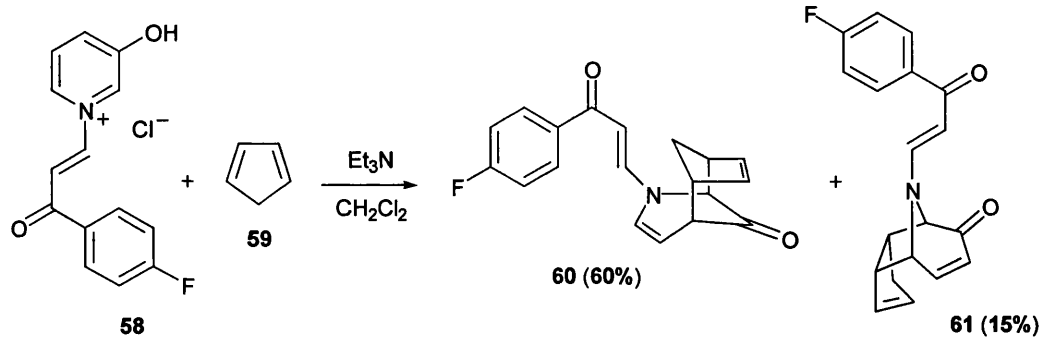
56 R^1 = CHO, R^2 = Me
57 R^1 = Me, R^2 = CHO

Scheme 11

1.5.4 Cha's Synthesis of the Sarain Core

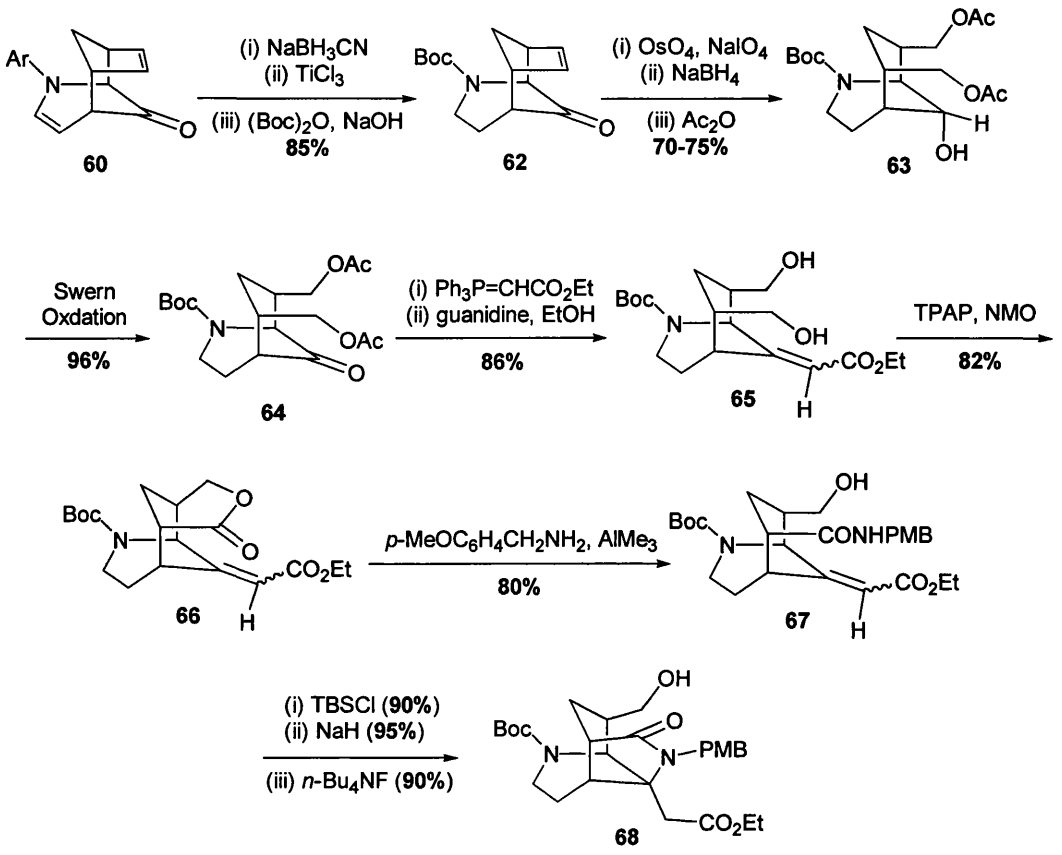
Cha and co-workers[18,19] have recently reported improvements to their previously published 10-step synthesis of the sarain core.

Their synthesis began by the construction of tricycle **60** by a [4+3]-cycloaddition reaction between the 3-oxidopyridinium betaine of 3-hydroxypyridium salt **58** and cyclopentadiene (**59**) (Scheme 12).



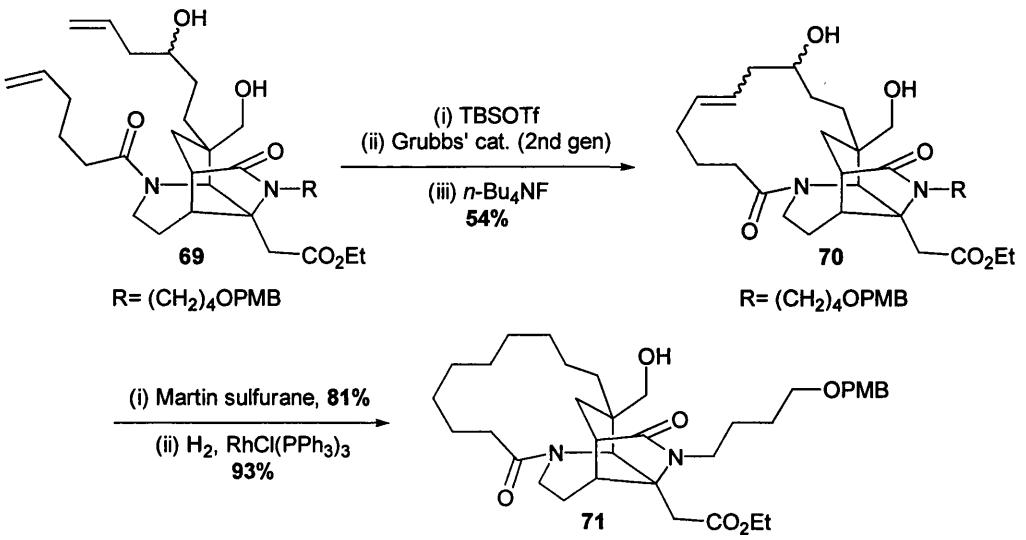
Scheme 12

Reduction of enamine **60** followed by replacement of the β-aroylvinyl nitrogen protecting group with a Boc group gave carbamate **62** (Scheme 13). Oxidative cleavage of the double bond in **62** followed by reduction and protection of the primary alcohols with acetate groups gave alcohol **63** in 70-75% yield. Oxidation of the secondary alcohol in **63**, followed by Wittig olefination and deprotection of the acetate protecting groups generated diol **65**. TPAP oxidation of **65** gave lactone **66**, which was then converted to the *N*-*p*-methoxybenzyl amide **67**. Protection of the free alcohol in **67** and deprotonation of the nitrogen with sodium hydride induced an intramolecular conjugate addition on the nearby α,β-unsaturated ester to give, after removal of the silyl protecting group, tricycle **68** in excellent yield.



Scheme 13

Cha and co-workers have also begun work on the synthesis of the two macrocycles surrounding the sarain core. The construction of the western macrocycle of sarain A using a ring closing metathesis strategy has been reported (Scheme 14). In addition the N_1 position in **71** was also functionalised for the future attachment of the eastern macrocycle.[20]



Scheme 14

1.6 Project Objective

The aim of this project was to synthesise tricycle **72**, containing the core structure of sarains A-C, by the use of a novel carbene mediated ylide rearrangement reaction (Figure 5).

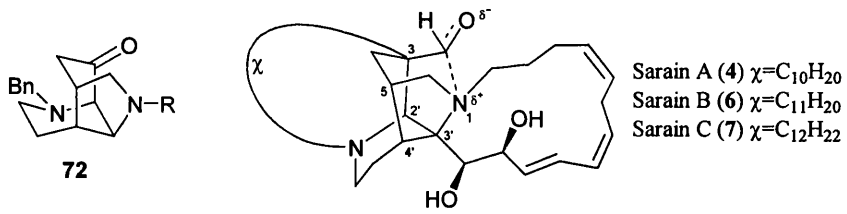


Figure 5

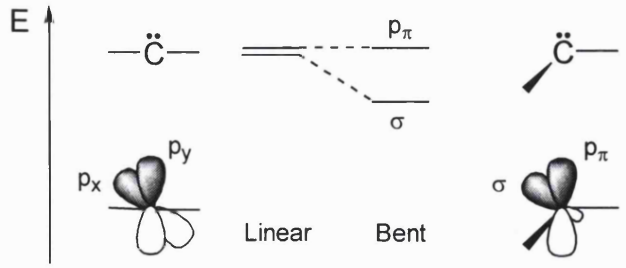
1.7 The Chemistry of Carbenes

Since the pioneering work of Buchner and Curtius[21] and Staudinger and Kupfer,[22] carbenes have played a prominent role as transient intermediates. Carbenes were first introduced into organic chemistry by Doering and Hoffman[23] in the 1950s. The organometallic chemistry of carbenes was initiated with the synthesis of stable

carbene complexes by Fischer and Maasböl[24] in the 1960s. Recent advances in the stabilisation of carbenes have made it possible to isolate these extremely reactive species.[25]

1.7.1 Structure and Stability of Carbenes

A carbene is a divalent species in which a carbon atom is linked to two adjacent groups by covalent bonds and possesses two non-bonded electrons, giving a total of six valence electrons. Considering a standard carbene –C̈–, the carbon atom can either be linear or bent; each geometry can be described by the level of hybridisation. The linear geometry implicates a carbon centre with two non-bonding degenerate orbitals (p_x and p_y) (Figure 6). The degeneracy of the orbitals is broken by bending the molecule and the carbon atom adopts an sp^2-type hybridisation. The p_y orbital is almost unchanged by this process (termed p_π), while the p_x orbital is stabilised as a consequence of acquiring some s character (termed σ). Most carbenes are bent and their frontier orbitals are referred to as σ and p_π.[26]

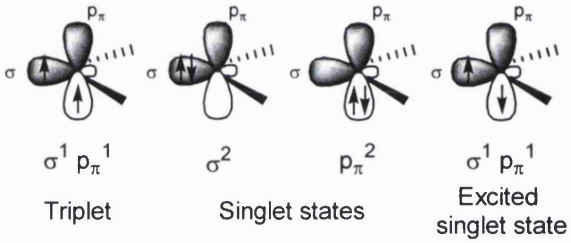


Relationship between the carbon bond angle and the nature of the frontier orbitals.

Figure 6

Four electronic configurations are available for carbenes (Figure 7).[26] In the triplet state the two non bonding electrons can be in two different orbitals with

parallel spins; described by the $\sigma^1 p_\pi^1$ configuration. In singlet carbenes the two non bonding electrons can be paired in the same σ or p_π orbitals, where the σ^2 configuration is generally more stable than the p_π^2. Lastly there is an excited singlet state which has the configuration $\sigma^1 p_\pi^1$, however this is not observed for ground state species.

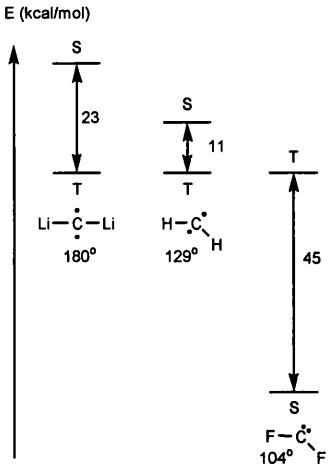


Electronic configurations of carbenes

Figure 7

The ground state spin multiplicity dictates the reactivity of carbenes and is related to the relative energy of the σ and p_π orbitals. The relative stability of the singlet and triplet state depends on the energy difference between the p_π and σ orbitals.[25] The stability of the p_π and σ orbitals is determined by the nature of the substituents adjacent to the carbenic centre. Interestingly the steric and electronic effects of substituents can be used to control the ground state of a carbene.

Methylene ($:CH_2$) is the parent carbene and has a triplet ground state (Figure 8). Molecular orbital calculations and experimental determination show that the difference in energies between singlet and triplet methylene is around 8-10 kcal mol^{-1} or 33-42 kJ mol^{-1}.[27,28]



Ground state carbene spin multiplicities of various carbenes

Figure 8

Carbenes are electron deficient and due to the carbon atom having only six electrons, are inherently electrophilic. Substituents can have a marked effect on the nature of the carbene. Carbenes bearing electron-withdrawing groups have electrophilic character while carbenes bearing electron-donating groups have less electrophilic character (these often have the effect of reducing the reactivity of the carbene). An example is dichlorocarbene (Cl_2C:) which is less reactive to nucleophiles than methylene.[29] Substituents with unshared electron pairs are able to stabilise singlet carbenes more than triplet carbenes.[30] The term 'carbenoid' refers to intermediates that display reactions that are similar to those of free carbenes without the presence (observation) of free divalent carbon species.

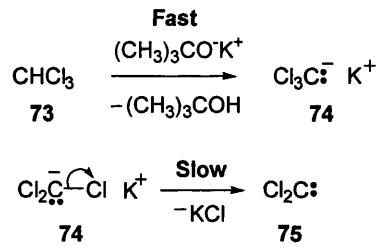
1.8 The Generation of Free Carbenes

Carbenes are short-lived species and must be generated *in situ* in the presence of the co-reactant. The common methods for carbene formation involve elimination

or fragmentation reactions *via* the breakage of relatively weak bonds. Two of the most commonly used methods for carbene generation are summarised below.

1.8.1 From α-Elimination Reactions

Historically the most important route to carbenes was the generation of halocarbenes by α-elimination of organic poly-halides under basic conditions. The polyhalides chosen were required not to contain any hydrogen atoms attached to the β-carbon since these were able to undergo β-elimination reactions. Dichlorocarbene (**75**) can be generated by proton abstraction of chloroform by a base, forming a stabilised trichloromethyl anion **74**. The anion can undergo α-elimination of a chloride ion to form dichlorocarbene (Scheme 15).[23]

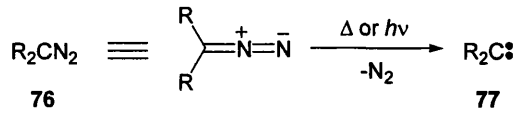


Scheme 15

An analogous reaction can also be observed when using other halomethanes and is a general route to dihalocarbenes. The ease of elimination follows the usual order: I > Br > Cl >> F.

1.8.2 From Diazoalkanes and α-Diazocarbonyl Compounds

Elimination of nitrogen from diazoalkanes has been known for over 50 years.[31] Thermolysis or photolysis of a diazo compound generates nitrogen and a carbene (Scheme 16).

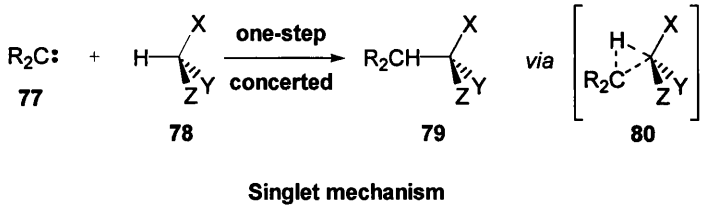


Scheme 16

1.9 Reactions of Free Carbenes

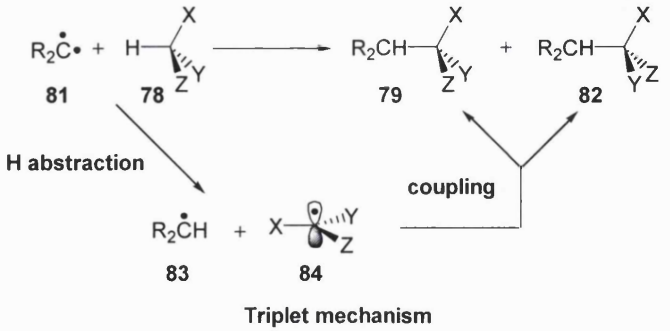
1.9.1 Insertion into C-H Bonds

The insertion of a carbene into a C-H bond is a useful reaction as it leads to the formation of a new carbon-carbon bond. There are two plausible mechanisms for this reaction, depending on whether a singlet or triplet carbene is involved.[32] The singlet carbene mechanism is a direct concerted reaction, where the insertion occurs with retention of configuration (Scheme 17).



Scheme 17

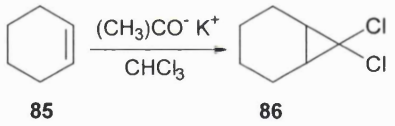
Triplet carbenes undergo a hydrogen abstraction-recombination reaction *via* a diradical; here insertion leads to some loss of stereochemical purity (Scheme 18).



Scheme 18

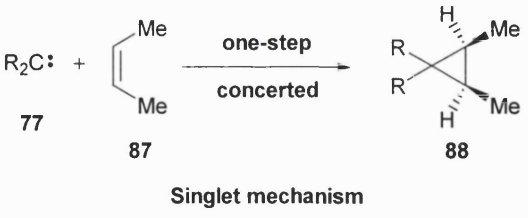
1.9.2 Cycloaddition to Alkenes

Doering and Hoffman demonstrated the earliest example of a [2+1]-cycloaddition reaction in 1954, where dichlorocarbene was reported to add to alkenes to form cyclopropane rings (Scheme 19).[23]



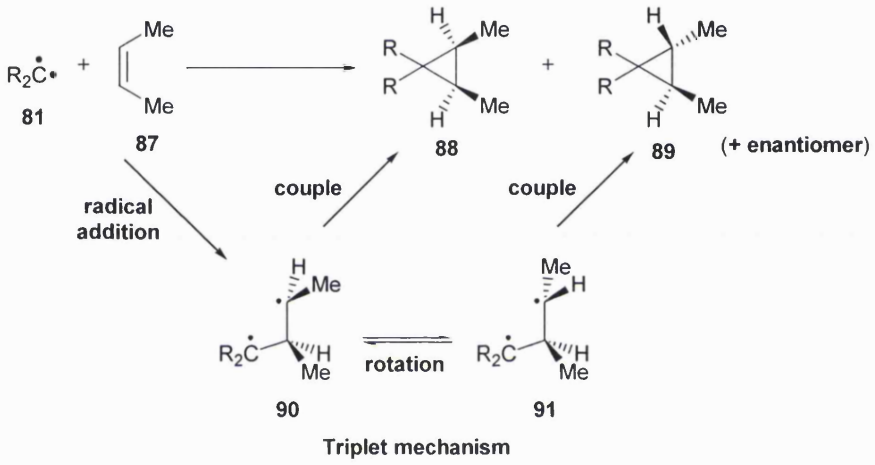
Scheme 19

The stereochemistry of the addition to the alkene is dependent on the type of carbene used. Singlet carbenes usually add stereospecifically to alkenes to form cyclopropanes that retain the geometry of the original alkene (Scheme 20).[33]



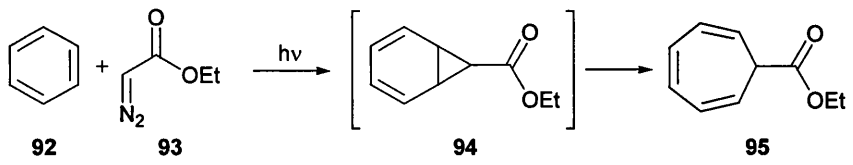
Scheme 20

The reaction of triplet carbenes tends to occur non-stereospecifically. The addition proceeds *via* a two-step mechanism, where the initial product is radical **90**. There is sufficient time for rotation of radical **90** to give **91** before undergoing intersystem crossing (or spin inversion) to singlets which have paired spins. The loss of stereospecificity arises when intersystem crossing is slower than bond rotation (Scheme 21).[34]



Scheme 21

This addition process is not restricted to double bonds of alkenes. The addition of carbenes to triple bonds is also observed and is a useful route to cyclopropenes. Carbenes are even able to react with the double bonds of aromatic rings. The photolytic reaction between benzene and ethyl diazoacetate gives the bicyclic intermediate **94**, which undergoes ring expansion to give cycloheptatriene **95** (Scheme 22).[35]



Scheme 22

1.10 The Chemistry of Metal Carbenes

Thermal decomposition of diazocompounds can be catalysed by the addition of transition metal salts.[36] Copper powder and copper(II) salts were originally used for this purpose. However, more effective catalysts such as rhodium(II) carboxylates have replaced these. The carbenes generated by this method are not 'free' carbenes; they are termed carbenoids or metal carbenes. The metal carbene is still electron deficient and undergoes the same reactions as a free carbene.[37] They can be represented as $L_nM{=}CRR'$ where L is a ligand and M is a metal. The vast array of different metals and ligands available for catalyst generation has greatly improved the selectivity and reactivity of metal carbenes.

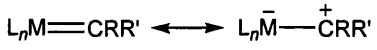
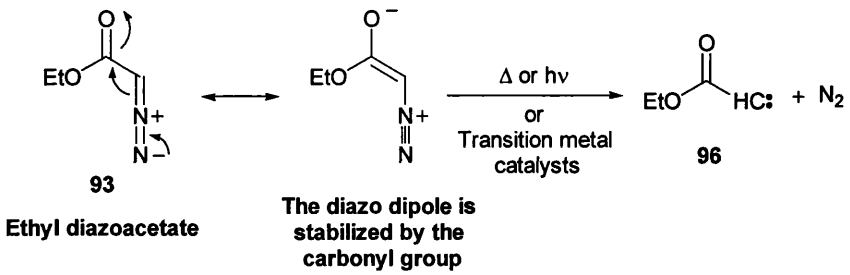


Figure 9

Diazo compounds are the most widely used precursors for forming metal stabilised carbenes. Loss of nitrogen from diazo compounds by action of transition metal catalysts results in the generation of metal carbenes. The stability of the diazo compounds used is dependent on the attached groups. Unsubstituted or simple diazocompounds such as diazomethane are relatively unstable which limit their use

in synthesis. α-Diazocarbonyl compounds offer resonance stabilisation to the 1,3-dipole of the diazo group, thereby making them less reactive (Scheme 23).[38]



Scheme 23

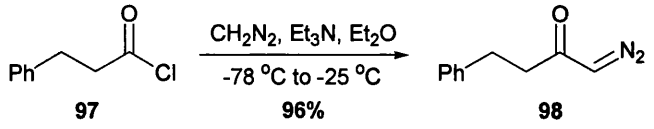
1.11 Synthesis of Diazo Compounds

1.11.1 Acylation of Diazoalkanes

The first reported synthesis of an α-diazocarbonyl compound was by Curtius during his work on the diazotization of natural α-amino acids. He also described the first synthesis of ethyl diazoacetate (probably the most widely used carbene precursor) in 1883 from glycine.[39] It was not until the late 1920s following the work of Arndt and Eistert[40] that simple diazocarbonyl compounds were easily obtained. Arndt and Eistert showed that diazoketones could be obtained by the reaction of acyl chlorides with diazomethane at low temperatures. Chain elongation was subsequently carried out by treatment of the diazoketone with water and silver oxide (or silver benzoate and triethylamine); this initiated the Wolff rearrangement *via* the formation of a carbene (the Arndt-Eistert homologation).

It was discovered that a second equivalent of diazomethane was required to sequester the hydrogen chloride liberated by the reaction and to prevent its addition

to the diazoketone. The use of excess diazomethane can be avoided by using an equivalent of a base such as triethylamine (Scheme 24).

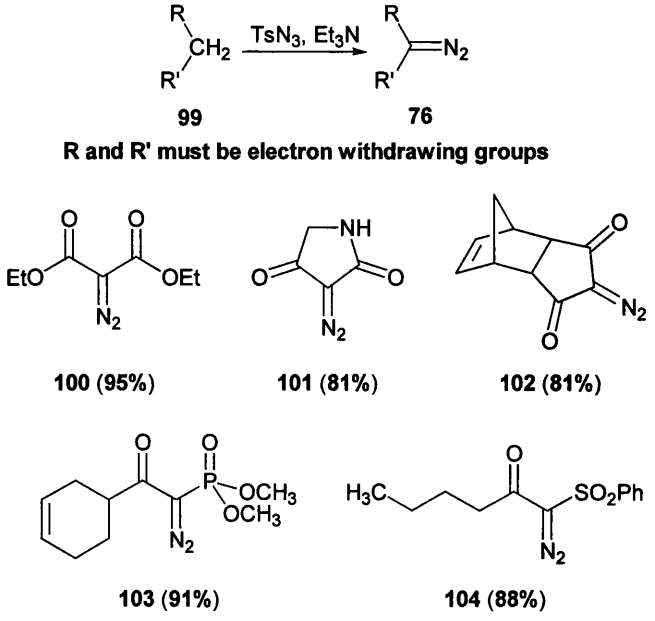


Scheme 24

1.11.2 Diazo Transfer reactions

The diazo transfer reaction is a convenient method for forming α-diazocarbonyl compounds and, unlike acylation methods, it is not restricted to the synthesis of acyclic α-diazoketones. Regitz and co-workers were the first to establish the complete transfer of a diazo group from a donor to an acceptor.[41]

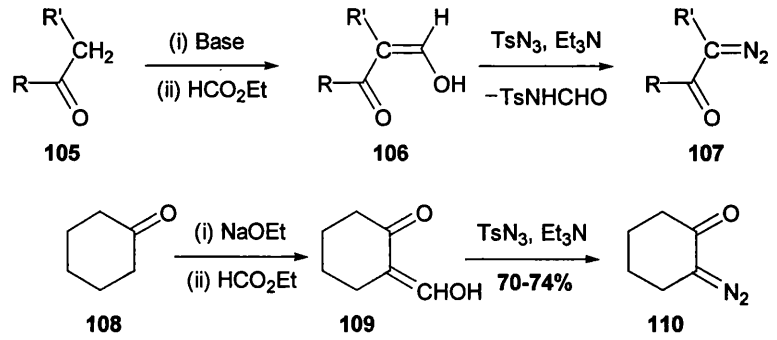
In the simplest sense the reaction involves the treatment of an activated CH_2 group with an arenesulfonyl azide in the presence of a base (Scheme 25).[42]



Scheme 25

Activated substrates for forming α-diazocarbonyl compounds are malonic esters, β-ketoesters, β-ketoamides, β-diketones, β-ketophosphonates and β-ketosulfones; these are easily converted to diazo compounds by exposure to tosyl azide in dry acetonitrile or ethanol using triethylamine as the base. In this way diazoester **100**, diazoamide **101**, diazoketone **102**, diazoketophosphonate **103** and diazoketosulfone **104** can be prepared.

When the methylene group is only activated by one carbonyl group, a deformylating strategy may be used for the generation of the diazocarbonyl compound. Here the methylene group is activated by a Claisen condensation of the ketone with ethyl formate, thereby introducing the strongly activating formyl group (Scheme 26). The metal salt of the condensation product or the neutral formyl compound can be used as the activated intermediate.[42]

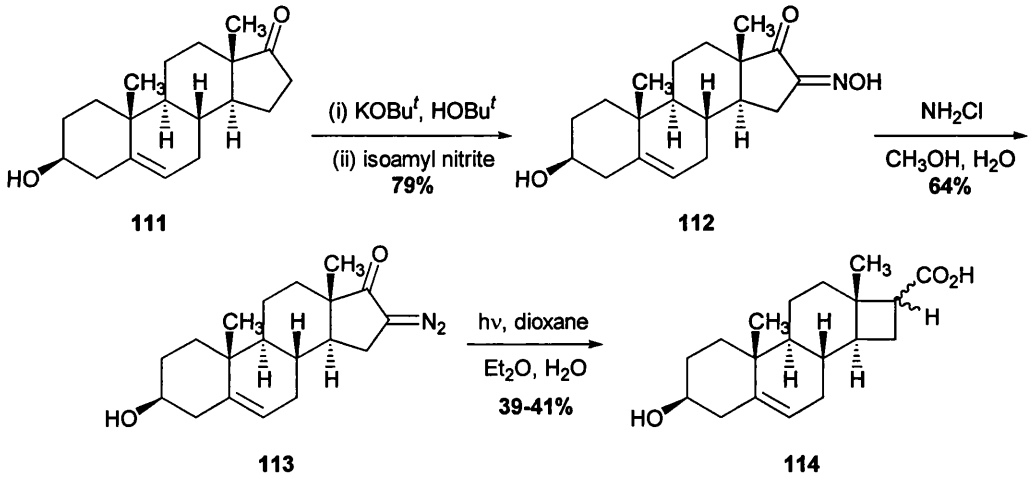


Scheme 26

1.11.3 Other Methods for Forming α-Diazocarbonyl Compounds

The Forster reaction[43] is characterised by the formation of an oxime at the α-methylene position of a ketone followed by the reaction with chloramine. Its use has been primarily in the preparation of α-diazoketones from derivatives of indanone and steroidal ketones. Meinwald and co-workers[44] used the Forster reaction to

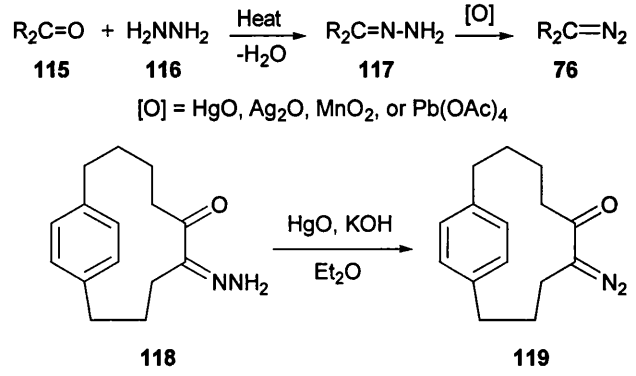
generate diazocarbonyl **113**, which underwent a photochemical Wolff rearrangement to give carboxylic acid **114** (Scheme 27).



111 **112** **113** **114**

Scheme 27

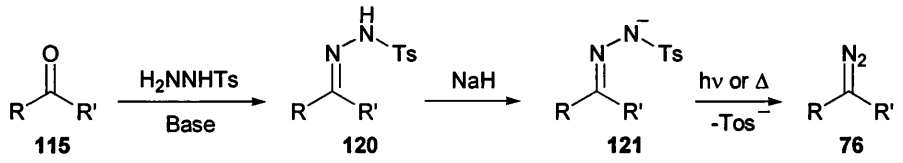
Another method for forming α-diazocarbonyl compounds is by the oxidation of hydrazones (formed by the reaction of α-ketocarbonyls with hydrazine). A number of different oxidising agents can be used; a representative example of this reaction is shown in Scheme 28.[45] The difficulty in the regioselective formation of the required hydrazone is a limiting factor for its use in making α-diazocarbonyl compounds.



118 **119**

Scheme 28

A related method to the oxidation of hydrazones for forming α-diazocarbonyl compounds is the Bamford-Stevens reaction.[46] Here oxidation of the hydrazone is avoided by making the corresponding tosylhydrazone (formed by the reaction of a ketone with tosylhydrazine) (Scheme 29).



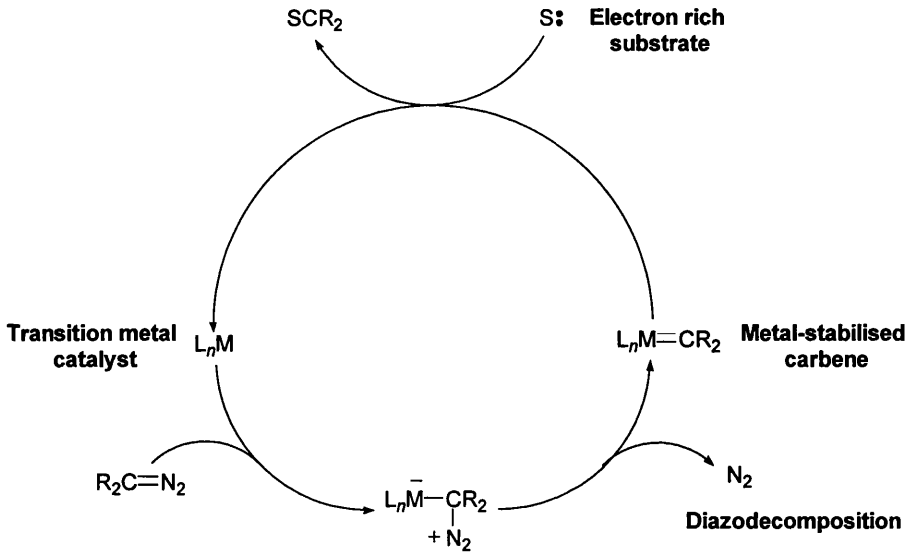
Bamford-Stevens method via tosylhydrazones

Scheme 29

Deprotonation of the tosylhydrazone with a base (such as sodium hydride) gives the corresponding tosylhydrazone salt, which is isolable. Upon heating or irradiation the salt undergoes decomposition to form the corresponding diazo compound.

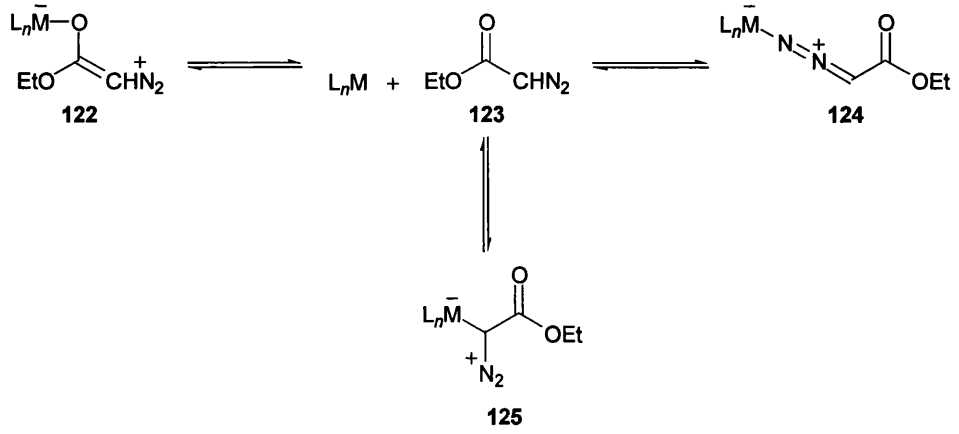
1.12 Mechanism of Catalytic Diazodecomposition

The overall catalytic process of metal carbene formation and its subsequent reaction is shown in Scheme 30.[47] Electrophilic addition of the transition metal catalyst to the diazocarbonyl compound results in nitrogen expulsion liberating a metal-stabilised carbene. The metal carbene is then able to transfer the carbene moiety to an electron rich substrate (S:) regenerating the transition metal catalyst (L_nM) and completing the cycle.[48]



Scheme 30

Transition metal catalysts can effectively co-ordinate with diazocarbonyl compounds at three basic sites (Scheme 31). Here only structure **125** contains a metal-carbon bond and leads to the formation of the metal carbene; the other two structures **122** and **124** serve as inhibitors to metal carbene generation. The rate of diazodecomposition is dependent on the relative amounts of **122** and **124** formed and the inherent stability of the diazo compound.[47]



Scheme 31

1.13 Transition Metal Catalysts for Diazodecomposition

The effective catalysts for the formation of transition metal complexes by diazodecomposition are Lewis acids.[47] Their catalytic activity depends on coordinative unsaturation at the metal centre, which allows them to react as electrophiles with diazo compounds.

Copper, rhodium, cobalt, palladium, and platinum-derived catalysts have been developed for diazodecomposition and metal carbene generation. However the versatility of catalysts derived from copper and rhodium have made them popular choices for diazodecomposition reactions.[47]

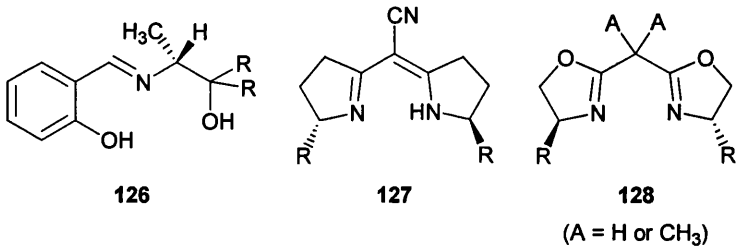
1.13.1 Copper Catalysts

The oldest copper catalysts used for diazo decomposition were copper bronze and copper(II) sulfate.[48] Both are insoluble in organic solvents and neither is regarded as the active form of the catalyst. The development of homogeneous catalysts in the 1960s led to the use of copper(I) chloride (as trialkyl or triaryl phosphite complexes) and copper(II) acetylacetonate catalysts.[49]

The introduction of copper(I) triflate, (CuOTf) by Kochi and Salomon as a catalyst for cyclopropanation reactions, led to an important discovery about the active form of copper catalyst.[50] They observed that diazo compounds reduced copper(II) chloride to copper(I) chloride and copper(II) triflate to copper(I) triflate, which led to the agreement that copper(I) is the active form of copper in diazodecomposition reactions.[50]

The greater air stability of copper(II) complexes compared to copper(I) catalysts, together with the fact that diazo compounds readily reduce copper(II) to copper(I) means that copper(II) catalysts are generally more practical

Modern copper(II) catalysts for diazodecomposition have bidentate ligands for example $Cu(acac)_2$ has two acetylacetonate ligands. It is believed that one of these ligands dissociates from copper during reduction; this belief is based on the observation of ligand dissociation of copper(II) complexes of chiral salicylaldimine (**126**), [51] semicorrin (**127**)[52] and bis-oxazoline (**128**)[53] ligands (Figure 10). Only one of the ligands remains bound to the active copper(I) catalyst during diazo decomposition.



126 **127** **128**

(A = H or CH_3)

Figure 10

Achiral copper catalysts which have been used for diazo decomposition include (trialkyl and triaryl)phosphite copper(I) chloride (**129**), bis(acetylacetonato)copper(II) (**130**) and its trifluoro and hexafluoro analogs, copper(I) triflate (**131**), and the *N-tert*-butyl-*N*-benzysalicyclaldimine complex of copper(II) (**132**) (Figure 11).[47]

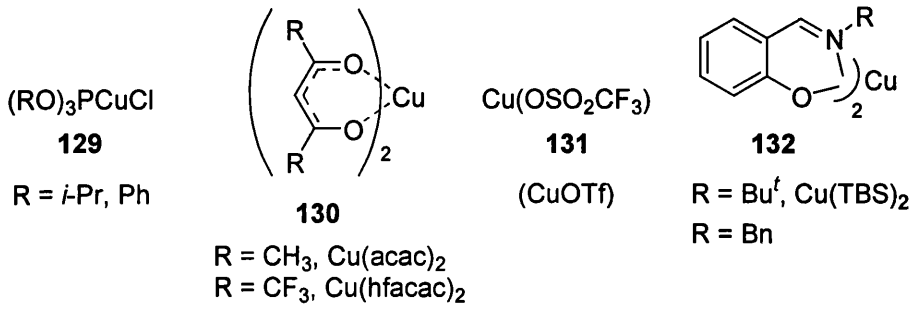


Figure 11

Information on the effect of ligand substituents on the selectivity and reactivity of copper catalysts is quite limited. However, the copper(II) acetylacetonate series does provide some useful insight. It appears that increasing fluorine substitution increases reactivity and decreases selectivity in metal carbene transformations, but additional data are required to confirm the generality of this observation.[54]

1.13.2 Rhodium Catalysts

Dirhodium(II) catalysts are effective catalysts for diazodecomposition and are the only catalysts which show general applicability for diazo decomposition reactions.[47] The range of different bridging carboxylate or carboxamide ligands available makes it possible to control reactivity and selectivity in decomposition reactions.

Dirhodium(II) tetraacetate ($Rh_2(OAc)_4$) (**134**) was first introduced by Teyssie and co-workers[55] in 1973 and has been used successfully in insertion cyclopropanation and aromatic cycloaddition reactions (Figure 12).[56] Dirhodium(II) tetraacetate possesses D_{4h} symmetry; the overall 'octahedral' geometry is due to the four bridging acetate ligands, which leave one vacant coordination site per rhodium atom available.[57]

A number of similar dirhodium(II) catalysts have been developed by replacement of the acetate ligands with carboxylate or carboxamide ligands. Replacement of the acetate ligands with perfluorobutyrate ligands gives dirhodium(II) perfluorobutyrate ($Rh_2(pfb)_4$) (**135**). Dirhodium(II) carboxamidates include dirhodium(II) acetamidate ($Rh_2(acam)_4$) (**133**) and dirhodium(II) caprolactamate ($Rh_2(cap)_4$). The ligands in dirhodium(II) acetamidate are arranged

so that each rhodium atom is attached to two nitrogen atoms *cis* to each other and two oxygen atoms *cis* to each other, this arrangement is termed '*cis*-2,2'. Other ligand arrangements are theoretically possible but have not been observed.[47]

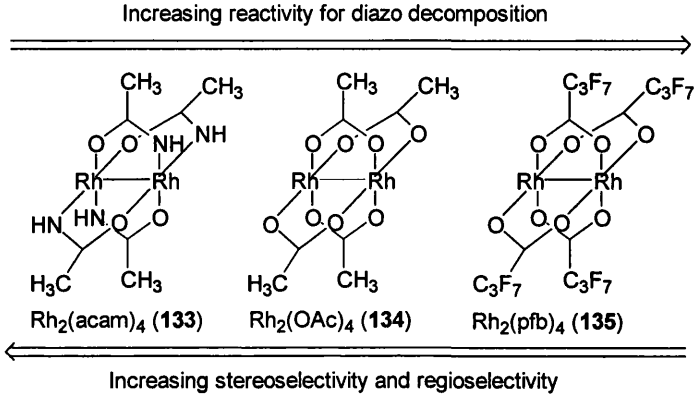
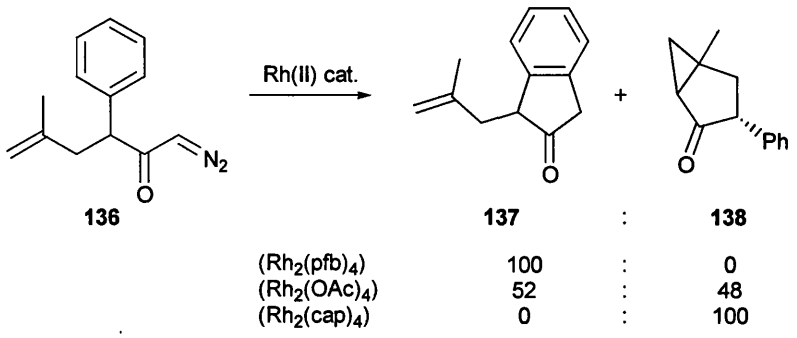


Figure 12

There is considerable evidence that the selectivity in metal carbene transformations is affected by the electronic properties of the bridging dirhodium(II) ligands. Electronegative ligands such as in dirhodium(II) perfluorobutyrate increase the reactivity towards diazo decomposition, but give low stereo- and regiocontrol in metal carbene reactions. Contrastingly, dirhodium(II) carboxamidates display lower reactivities and higher selectivities.[26,47] Padwa and co-workers[58] examined the competition between olefin cyclopropanation and aryl C-H insertion on diazoketone **136** with the catalysts: dirhodium(II) caprolactamate, dirhodium(II) tetraacetate and dirhodium(II) perfluorobutyrate (Scheme 32). They observed a complete reversal in reactivity between $Rh_2(pfb)_4$ and $Rh_2(cap)_4$. The highly electophilic dirhodium(II) perfluorobutyrate promoted C-H insertion, while the more electron rich dirhodium(II) caprolactamate advanced cyclopropanation to give **138**. When

dirhodium(II) tetraacetate was used a 1:1 mixture of products **137** and **138** was observed



136

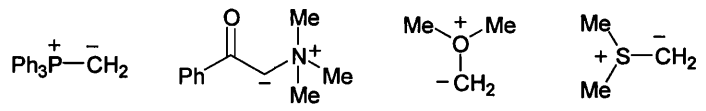
	137	:	**138**
$(Rh_2(pfb)_4)$	100	:	0
$(Rh_2(OAc)_4)$	52	:	48
$(Rh_2(cap)_4)$	0	:	100

Scheme 32

Doyle and co-workers have developed dirhodium(II) carboxamidate catalysts containing chiral amide ligands. These offer an effective route to enantioselective metal carbene reactions.[59,60]

1.14 The Chemistry of Nitrogen Ylides

Ylides are compounds in which a carbanionic carbon is immediately adjacent to an atom bearing a positive centre.[38] Phosphorus, nitrogen, oxygen and sulfur can form highly reactive ylides; they have an extremely rich chemistry that can be used for the construction of complex functionalised compounds from relatively simple starting materials (Figure 13). The advances made in discovering mild methods for generating nitrogen, oxygen and sulfur ylides has made it possible to use these highly reactive species in the total synthesis of complex molecules. The chemistry of nitrogen ylides, also referred to as ammonium ylides, is less well known than that of sulfur analogues.



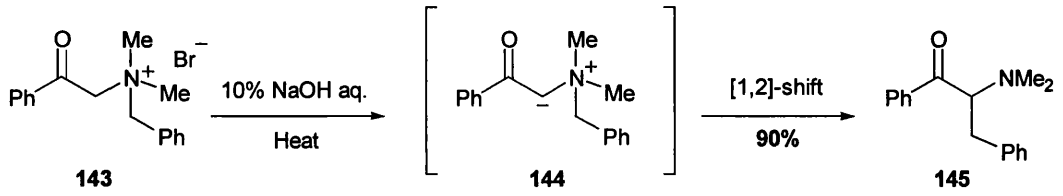
139 140 141 142

Examples of phosphorus, nitrogen, oxygen and sulfur ylides

Figure 13

1.15 The History of Nitrogen Ylides: Classical vs. Modern

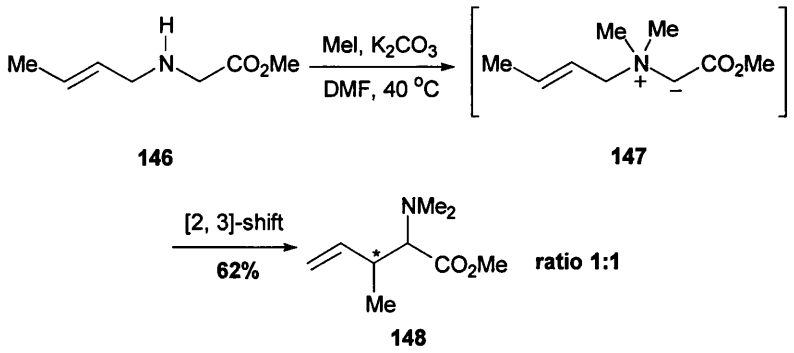
The classical method for generating nitrogen ylides is by the deprotonation of ammonium salts. Stevens and co-workers[61] in 1928 reported the deprotonation of phenacylbenzyldimethylammonium bromide (**143**) by treatment with aqueous sodium hydroxide. The ylide intermediate **144** from this reaction underwent a [1,2]-rearrangement (benzyl shift) upon heating to give the substituted amino ketone **145** (Scheme 33).



143 144 145

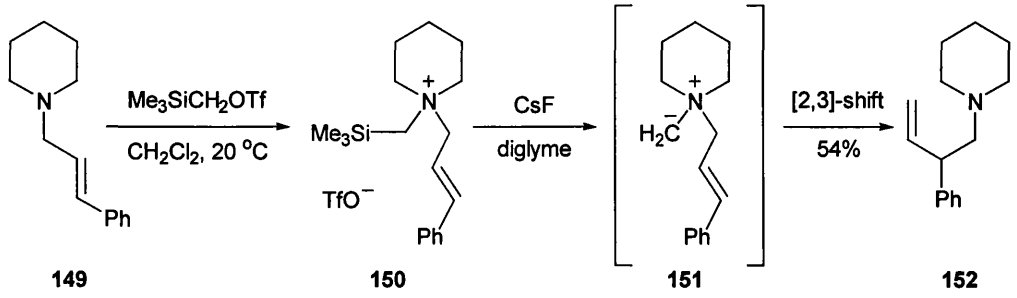
Scheme 33

Other related protocols for the generation of ammonium ylides have been developed. Coldham and co-workers reported that *N*-allyl-α-amino esters undergo [2,3]-rearrangements when warmed with methyl iodide and potassium carbonate in dimethylformamide in a one pot procedure (Scheme 34).[62]



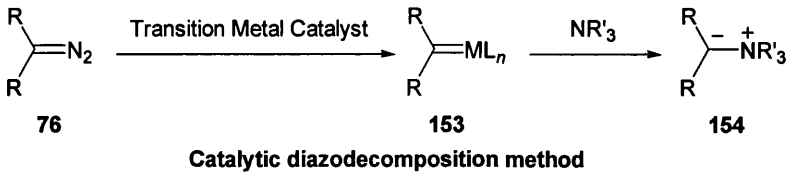
Scheme 34

There can be some problems associated with generating ammonium ylides by deprotonation of ammonium salts. Complications can occur when the ylide generated is unstable or when there is more than one possible site for deprotonation of the ammonium salt. Following this, milder and more specific methods for nitrogen ylide formation were developed. Desilylation of α-silyl ammonium salts is a method that avoids the problems associated with deprotonation and regioselectivity. Vedejs and co-workers established that exposure of α-silyl ammonium salts to cesium fluoride was an efficient method for generating nitrogen ylides. Desilylation of salt **150** generated ylide intermediate **151**, which underwent a [2,3]-rearrangement to form the homoallylic amine **152** (Scheme 35).[63]



Scheme 35

A modern alternative to conventional deprotonation or desilylation methodologies uses metal stabilised carbenes. The catalytic diazodecomposition of a diazocarbonyl compound by a transition metal catalyst generates a metal stabilised carbene, which can react with an amine to form a nitrogen ylide (Scheme 36).[47] The wide choice of catalysts and the extremely mild conditions of the reaction has made this a versatile method for the formation of ylides.



Scheme 36

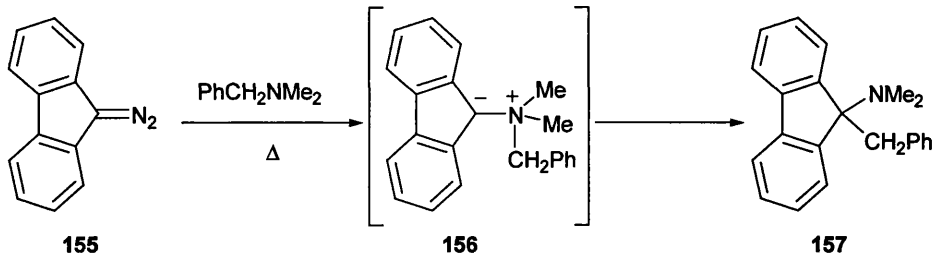
1.16 Reactions of Nitrogen Ylides

Nitrogen ylides undergo a number of different reactions and rearrangements, which include the [1,2]-Stevens rearrangement, the [2,3]-sigmatropic rearrangement, fragmentation (elimination) reactions and N-H insertion reactions.

1.16.1 The Stevens Rearrangement

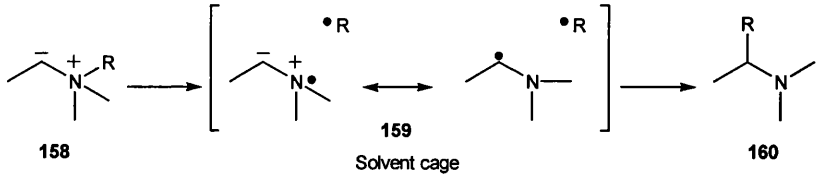
Bamford and Stevens generated the ammonium ylide **156** from the reaction of diazofluorene (**155**) with benzyldimethylamine (Scheme 37).[46] The ylide intermediate underwent a 1,2-benzyl shift to give the rearrangement product **157**. This rearrangement is now referred to as the Stevens rearrangement and is characterised by the nitrogen ylide undergoing a facile 1,2 shift of the best migrating group from nitrogen to carbon. The Stevens rearrangement is often described as a

stereoelectronically disfavoured transformation, since concerted 1,2-shifts are forbidden processes according to the Woodward-Hoffmann rules.[64]



Scheme 37

The mechanism of the Stevens rearrangement has been studied. Chemically Induced Dynamic Nuclear Polarisation (CIDNP) is a commonly utilised technique to discovery the presence of a radical pair intermediate produced during a chemical reaction; it has been used to investigate the mechanism of the Stevens rearrangement. CIDNP experiments performed on ylide rearrangements suggested that the products of the rearrangement are formed directly from a radical pair precursor, where the radicals are localised in the solvent cage and do not drift apart (Scheme 38).[65]

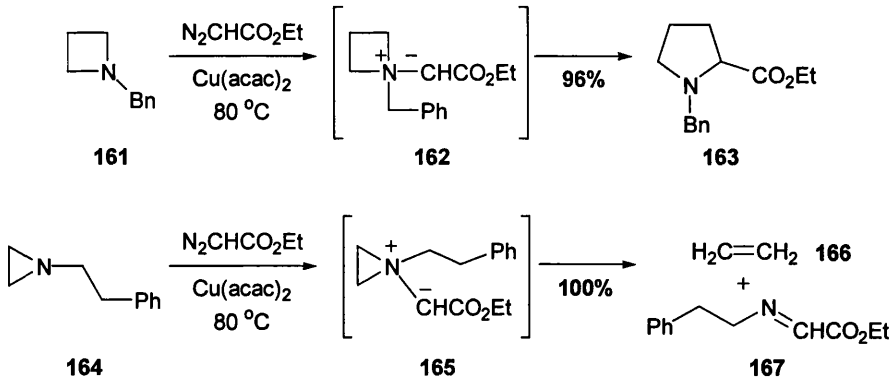


Scheme 38

However, Sato and co-workers[66] have speculated that the Stevens rearrangement of ammonium ylides may occur through either a [1,2]-radical shift

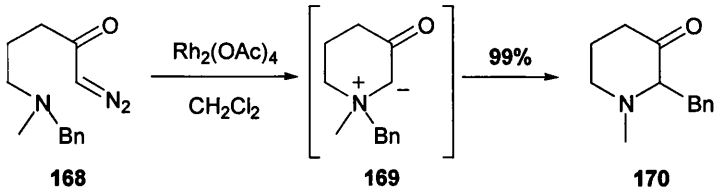
when the radical of the migrating group is stabilised by an adjacent group (such as oxygen, cyano or phenyl) or *via* a [1,2]-ionic shift when the migrating group has no adjacent stabilising groups. In cases where the migrating carbon is a stereogenic centre, the configuration is retained.

Another example of the Stevens rearrangement is shown by the reaction of ethyl diazoacetate and copper(II) acetylacetonate with 1-benzylazetidine (**161**); the resulting ammonium ylide **162** undergoes a ring expansion as a consequence of the Stevens rearrangement to generate pyrrolidine **163** (Scheme 39).[67] The analogous reaction with 1-phenethylaziridine (**164**), results in the fragmentation products **166** and **167**.[68] This difference has been attributed to the amount of ring strain energy released during the reaction and the heat of formation of the ethylene π-bond.



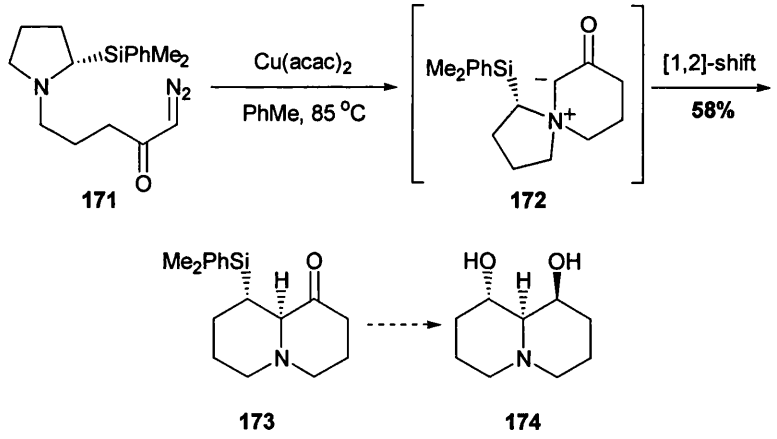
Scheme 39

Examples of intramolecular nitrogen ylide generation, and subsequent reactions have been reported. These have frequently been used to generate cyclic amines.[68] A typical example is the catalytic diazodecomposition of diazoketone **168**, which undergoes a [1,2]-shift to give the substituted piperidine **170** *via* ylide **169** (Scheme 40).



Scheme 40

West *et al.*[69] used a novel silyl-directed Stevens rearrangement for the stereoselective construction of hydroxylated quinolizidines. Treatment of diazoketone **171** with 10 mol% $Cu(acac)_2$ in toluene at reflux gave quinolizidine **173** as a single diastereoisomer in 58% yield (Scheme 41).



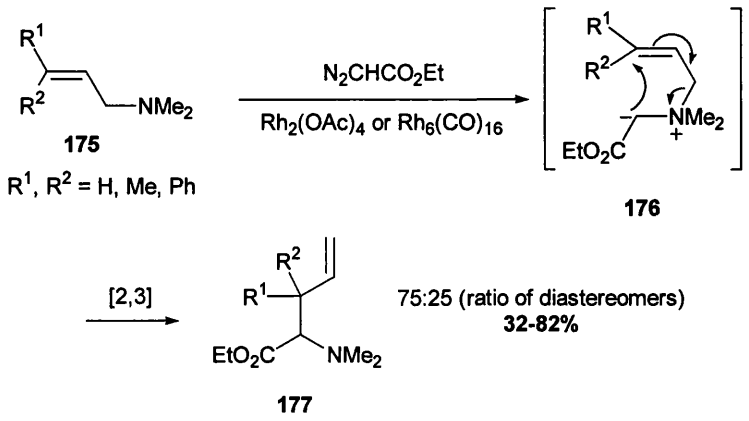
Scheme 41

1.16.2 [2,3]-Sigmatropic Rearrangement

Another common reaction of catalytically generated ylides is the [2,3]-sigmatropic rearrangement of allyl-substituted ylide intermediates. The [2,3]-sigmatropic rearrangement is a concerted, symmetry-allowed process.

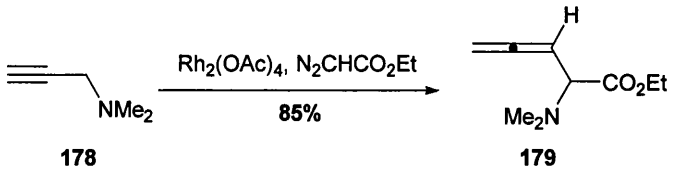
Doyle and co-workers have investigated the [2,3]-sigmatropic rearrangement of ammonium ylides. They reported that allylic amines could react with rhodium

carbenoids of ethyl diazoacetate to give homoallylic α-amino acid esters in modest yields (Scheme 42).[70]



Scheme 42

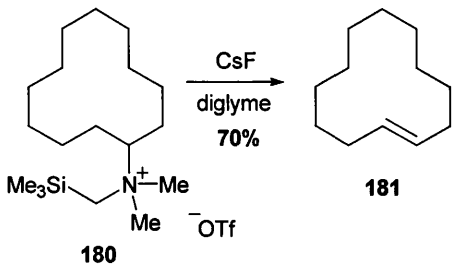
In addition propargyldimethylamine (**178**) was also discovered to undergo a [2,3]-sigmatropic rearrangement to form allene **179**, when treated with ethyl diazoacetate and $Rh_2(OAc)_4$ catalyst (Scheme 43).[71]



Scheme 43

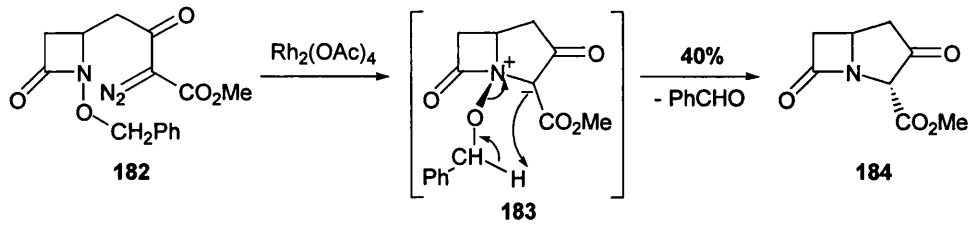
1.16.3 Fragmentation/Elimination Reactions

The desilylation of salt **180** with cesium fluoride gave an ammonium ylide, which underwent a Hofmann elimination to give *E*-cyclododecene (**181**) (Scheme 43).[64]



Scheme 44

Miller and Williams[72] have reported that the exposure of azetidinone **182** to $Rh_2(OAc)_4$ generates the ylide intermediate **183**. Intermediate **183** underwent a proton transfer from the benzylic position to the carbanionic centre followed by cleavage of the N-O bond liberating benzaldehyde and carbapenam **184** (Scheme 45).

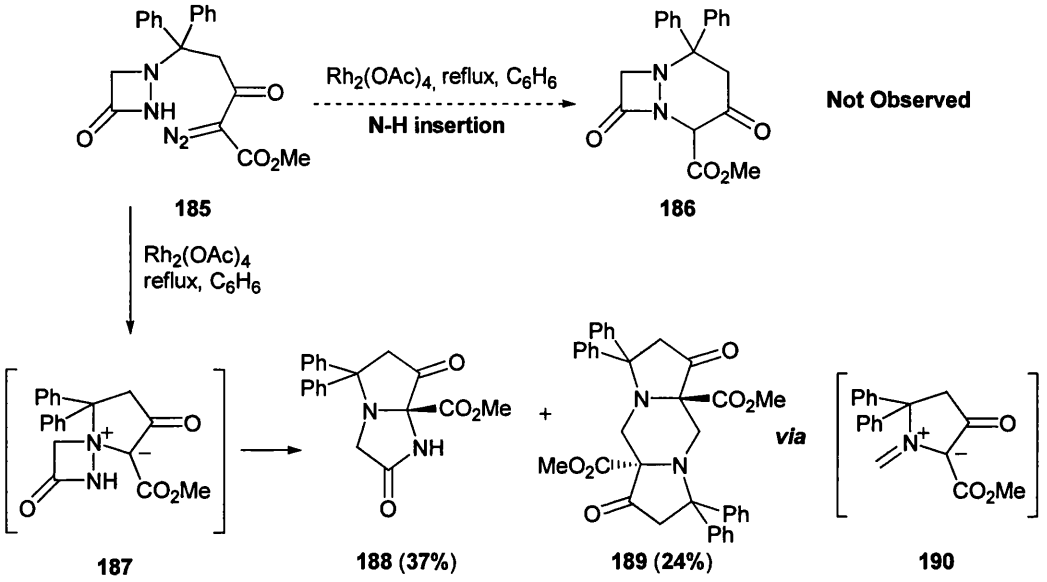


Scheme 45

1.16.4 Other Rearrangements of Ylides

Taylor and co-workers[73] have reported the synthesis of α-diazoketone **185**, which was used for the construction of an aza analogue of β-lactam antibiotics. They had envisaged that **185**, on exposure to dirhodium(II) tetraacetate, would undergo an N-H insertion reaction to give **186** (Scheme 46). However, the reaction gave two unexpected products **188** and **189**. These products arose as a consequence of the metal carbene being captured by the more nucleophilic nitrogen atom in **185**, thus

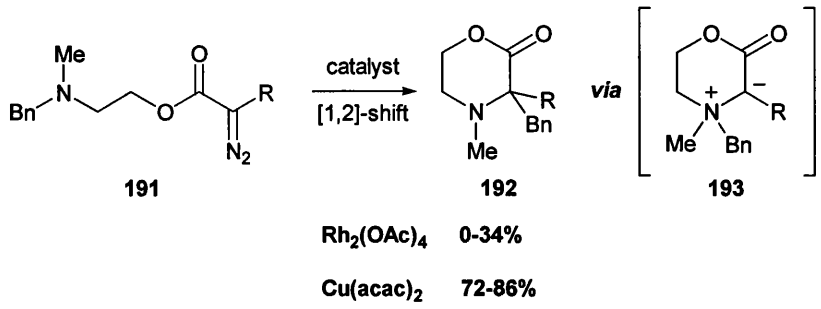
generating the quaternary nitrogen ylide **187**. The major bicyclic product **188** was formed by an intramolecular attack at the other nitrogen with fission of the N-N bond. The minor product **189** was formed by fragmentation of the ylide by loss of HNCO, generating an azomethine ylide (**190**), which underwent dimerisation.



Scheme 46

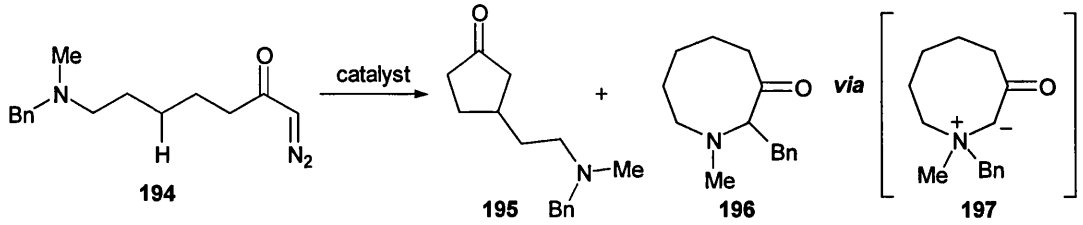
1.17 Catalyst Selectivity in Ylide Reactions

The choice of catalyst is an important factor in the generation and reactivity of carbenoid-derived ylides. West and co-workers have reported that dirhodium(II) tetraacetate is a poor catalyst for the inter- and intramolecular addition of diazocarbonyl compounds to tertiary amines.[74,75] An example is shown in Scheme 47, the rearrangement of diazo ester **191** using $Rh_2(OAc)_4$ as the catalyst gave amine **192** in less than 35% yield. The poor selectivity of the catalyst was attributed to the saturation of empty sites on the Rh-Rh dimer by excess amine in the reaction.



Scheme 47

It was also reported that copper(II) catalysts are superior to rhodium catalysts for ylide generation in these systems. Studies performed on the formation of cyclic amines with ring sizes greater then six also identified the problem of C-H insertion associated with rhodium carbenoids. C-H insertion was observed when diazoketone **194** was exposed to $Rh_2(OAc)_4$, giving cyclopentanone **195** as the major product (Scheme 48). The C-H insertion pathway was avoided by using a copper(II) catalyst. The efficiency and selectivity of the copper carbenoids towards the amine can be seen by the exclusive formation of azocinone **196** in 58% yield.



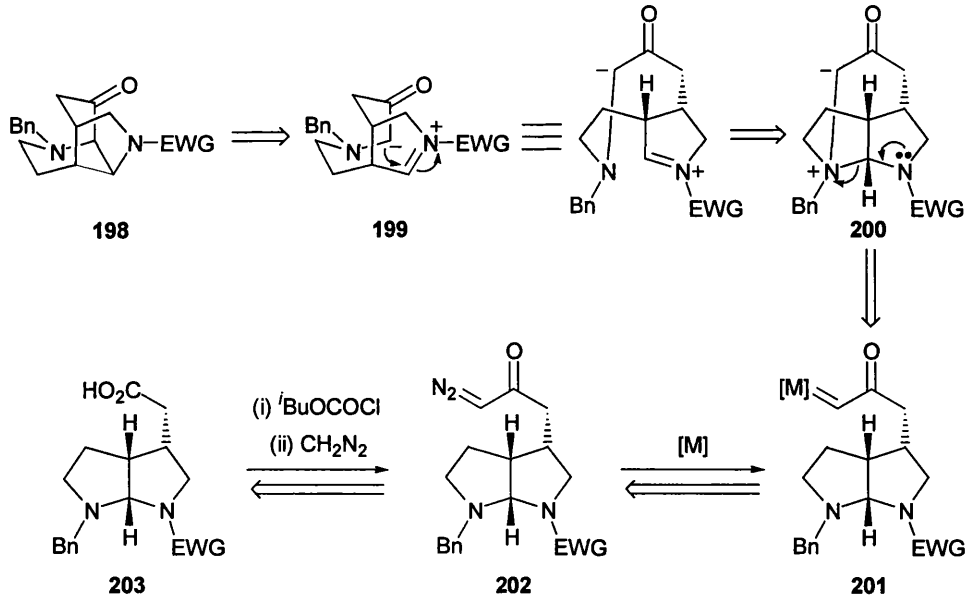
Scheme 48

Chapter Two

Results and Discussion

2.1 The Core Structure of Sarains A-C – A Retrosynthetic Analysis

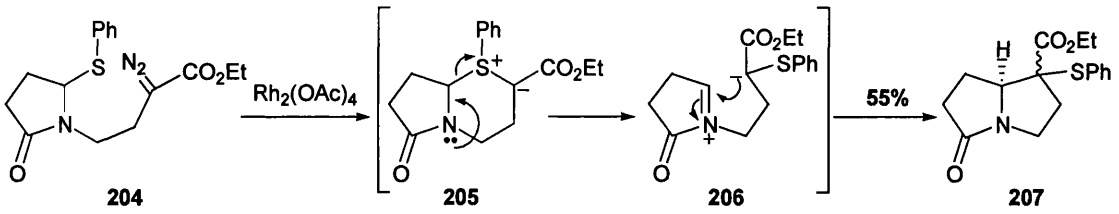
Retrosynthetically, the tricycle **198** can be obtained by a novel rearrangement of the ammonium ylide **200** *via* the Mannich-type intermediate **199**. The ammonium ylide would be generated from diazoketone **202** *via* an intramolecular reaction of the corresponding metal carbene with the more nucleophilic nitrogen atom in the aminal (which is protected by a benzyl group). Diazoketone **202** would be prepared from the corresponding carboxylic acid **203** (Scheme 49).



Scheme 49

Our initial objective was to construct bicycle **203**; a *cis*-fused octahydropyrrolo[2,3-*b*]pyrrole ring system bearing an *endo* acetic acid substituent in the three position.

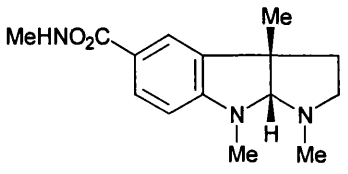
There is very little literature precedent for the rearrangement seen in Scheme 49. However, some similarities can be observed from the reaction of sulfur ylides. Kametani and co-workers[76] treated diazoketone **204** with a catalytic amount of rhodium(II) acetate in refluxing benzene, this generated a metal carbene which reacted with the nearby sulfur atom to produce a sulfonium ylide (**205**) (Scheme 50). Fragmentation of this ylide generated iminium ion **206**, which cyclised to give amide **207** in 55% yield.



Scheme 50

2.2 The Octahydropyrrolo[2,3-*b*]pyrrole Ring System

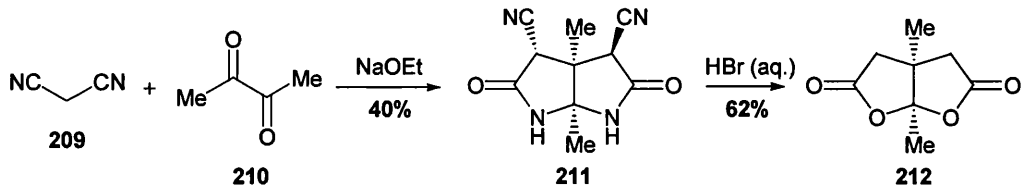
The octahydropyrrolo[2,3-*b*]pyrrole ring system is seen in (-)-physostigmine (**208**), an alkaloid isolated from the Calabar bean, which has received considerable interest due to its anti-cholinergic properties. The octahydropyrrolo[2,3-*b*]pyrrole ring system in **208** is fused to an aromatic ring (Figure 14).[77]



(-)-Physostigmine (208)

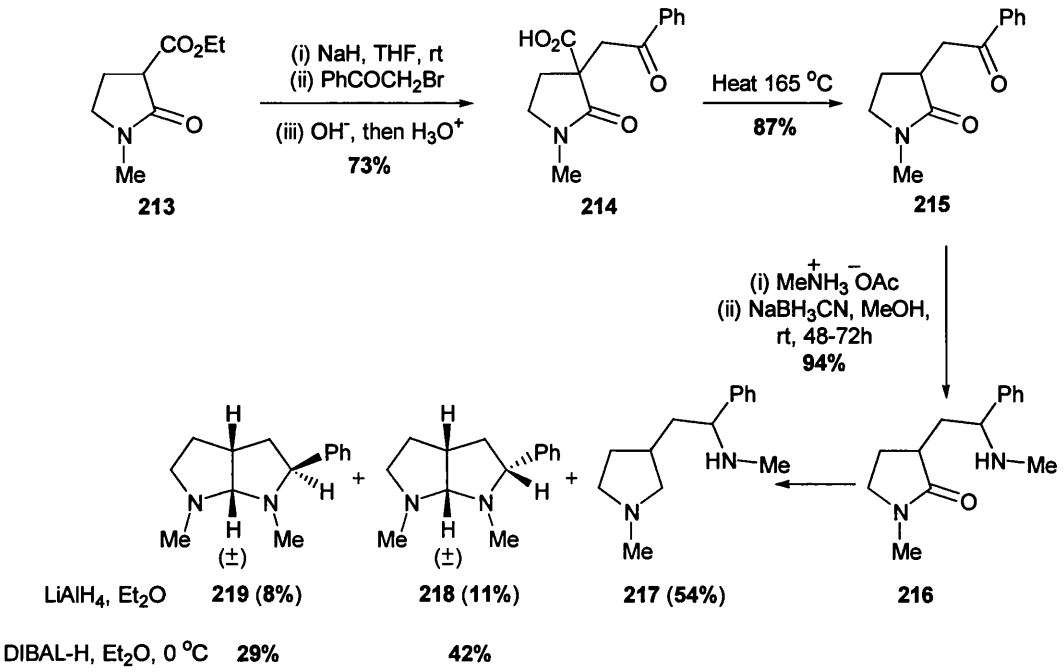
Figure 14

Hartke and co-workers[78] have reported the synthesis of a related bicyclic system in which both nitrogen atoms are present as amides. It was reported that malononitrile reacted with biacetyl in the presence of sodium ethoxide to give bicycle **211**. Bicycle **211** underwent hydrolysis upon exposure to hydrobromic acid to form a new bicycle **212** (Scheme 51).



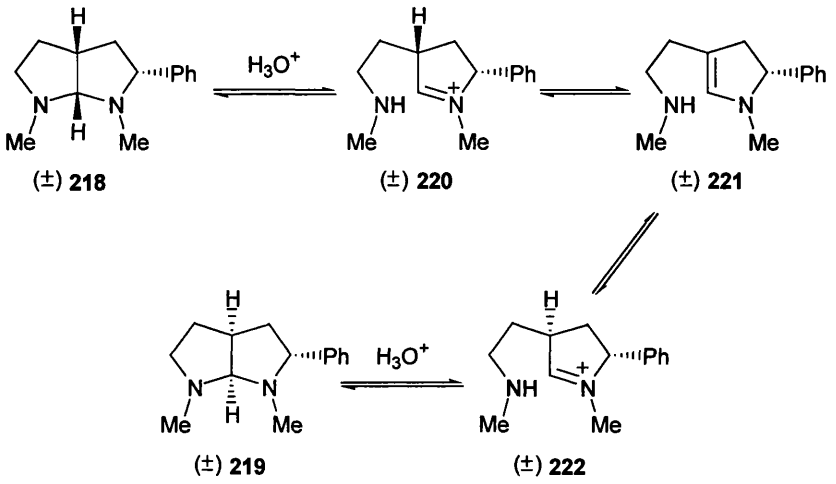
Scheme 51

The only reported synthesis of an octahydropyrrolo[2,3-*b*]pyrrole ring system in which both nitrogens are aliphatic amines was by Thorsett and co-workers[79] in 1978 (Scheme 52). Enolisation of lactam **213** followed by alkylation with phenacylbromide and hydrolysis afforded the substituted lactam **214**. Decarboxylation of **214** was accomplished by heating to 165 °C, which gave ketolactam **215**; this was reductively aminated by treatment with methylammonium acetate and sodium cyanoborohydride to afford amine **216**. Thorsett and co-workers anticipated that ring closure of **216** would occur by exposure to lithium aluminium hydride, a pathway which had been used for ring closure in the synthesis of physostigmine. They found, however that lithium aluminium hydride was too reactive for the cyclisation. The major product from this reaction was di-amine **217**, which was formed by the complete reduction of the amide carbonyl. The use of diisobutylaluminium hydride circumvented this problem, giving epimeric aminals **218** and **219** in good yields.



Scheme 52

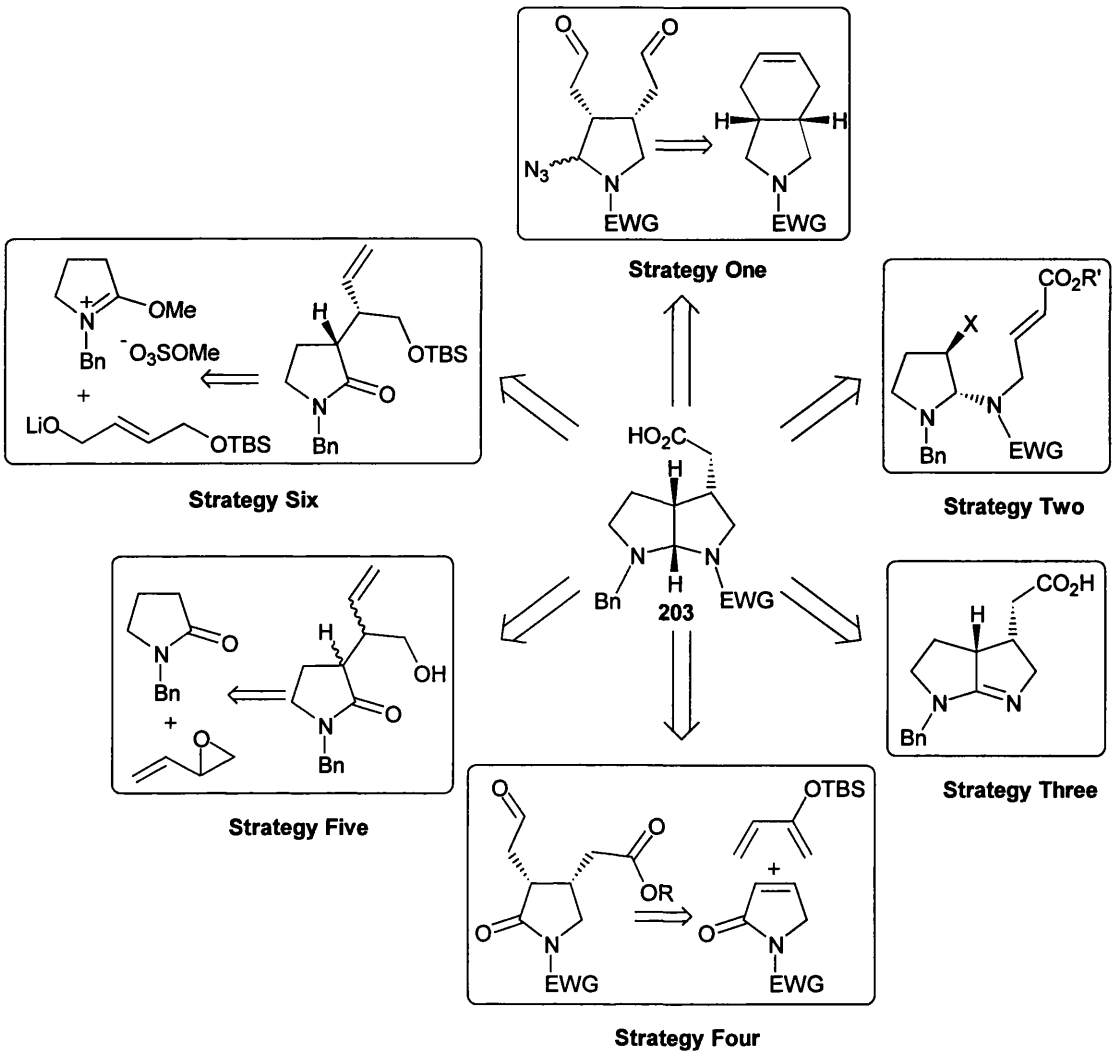
Epimers **218** and **219** were found to be stable to base, but were not stable to acid. Exposure of either epimer to acid and re-isolation gave the same mixture of epimers observed before chromatography (determined by ^{1}H NMR spectroscopy). It was also reported that under acidic conditions, ring opening of the aminal occurs, leading to formation of iminium species **220**, which is in equilibrium with enamine **221**. Since protonation of this enamine can occur from either face, there is the possibility of making iminium species **222**, which leads to the formation of bicycle **219** (the epimer of **218**) (Scheme 53).



Scheme 53

2.3 Summary of Routes Investigated

A number of routes to bicyclic acid **203** were investigated (Scheme 54). Strategy One involved the electrophilic azidation of a *cis*-fused hepxahydro-isoindole. In Strategy Two, the cyclisation of an α-amino-β-iodopyrrolidine was envisaged as a means of accessing the bicycle core. Strategy Three involved the generation of cyclic amidines, which upon reduction could lead to construction of bicycle **203**. Construction of **203** from a Diels-Alder reaction between 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene and an *N*-protected-pyrrolin-2-one dienophile was investigated in Strategy Four. Strategy Five was a (non-stereoselective) strategy involving the ring opening of butadiene monoxide with a lactam enolate. A model system was used to optimise the reductive cyclisation of an azido-lactam synthesised in this route. Strategy Six involved the use of a [3,3]-sigmatropic rearrangement in a stereoselective method for constructing bicycle **203**.



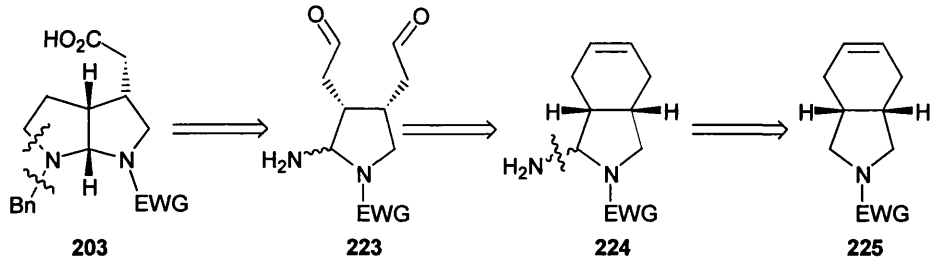
Scheme 54

2.4 Strategy One: Electrophilic Azidation

2.4.1 Retrosynthetic Analysis

This strategy was based on the supposition that the *cis*-fused bicycle in **203** could be constructed from an intramolecular reductive amination between the amine group and the closer aldehyde in **223** (Scheme 55). Protection of the secondary amine generated by this cyclisation with a benzyl group followed by oxidation of the unreacted aldehyde to the corresponding acid would lead to the formation of desired

bicyclic acid **203**. Dialdehyde **223** would be formed from ozonolysis of the ring olefin in **224**. The introduction of an amine functionality into the α-position of *cis*-fused hexahydro-isoindole **225** would lead to the formation of bicycle **224**.



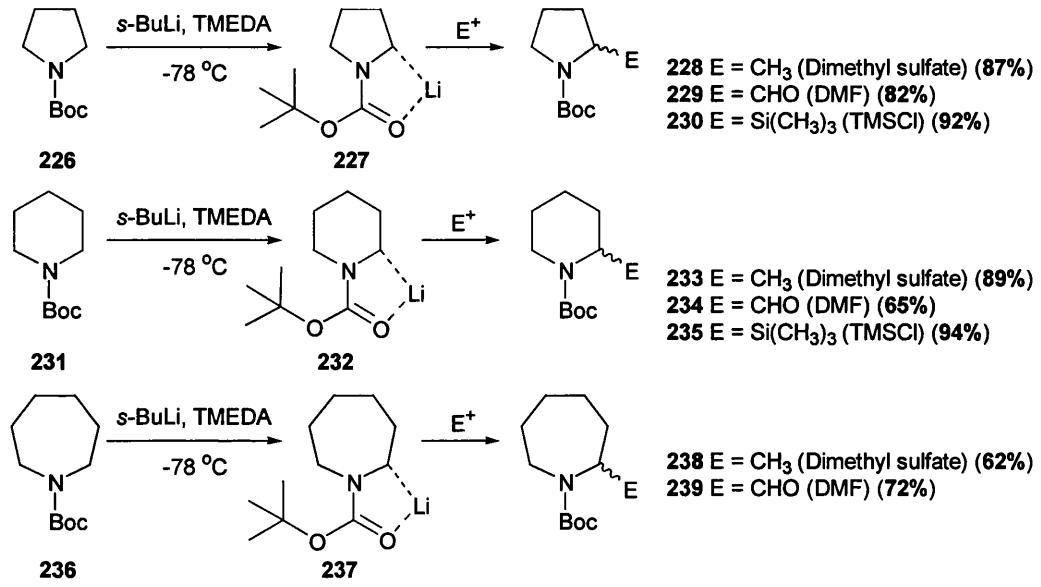
203 **223** **224** **225**

Scheme 55

A key feature of this synthesis is that by starting with commercially available *cis*-1,2,3,6-tetrahydrophthalimide we would be able to set the relative stereochemistry of two of the asymmetric centres from the start of the synthesis.

2.4.2 Background and Discussion

Beak and co-workers[80,81] have highlighted that protecting the nitrogen atom of pyrrolidine with a *tert*-butoxycarbonyl group (Boc) can be very effective in the activation of the α-position of the ring towards deprotonation by a strong base. It was reported that treatment of a THF solution of *N*-Boc-pyrrolidine with *sec*-butyllithium (*s*-BuLi) in the presence of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) at low temperatures brings about α-lithiation. The reaction generates a dipole-stabilised carbanion, which undergoes electrophilic substitution when treated with a reactive electrophile (Scheme 56).



Scheme 56

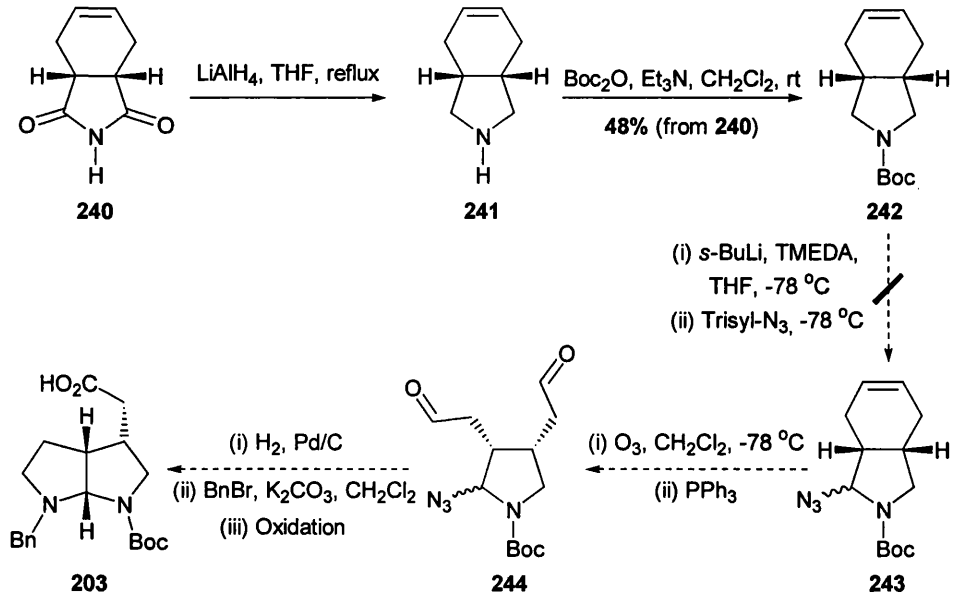
This methodology was explored on a range of cyclic amines including *N*-Boc-pyrrolidines, *N*-Boc-piperidines and *N*-Boc-perhydroazepines. In addition, 2-, 3-, 4- and 2,4-alkyl/aryl substituted *N*-Boc-piperidines were also shown to undergo substitution under the same conditions; yields were slightly lower than those from unsubstituted versions.

An unusual feature of organolithium bases is that they form aggregates in solution. Ethyllithium and *n*-butyllithium are hexameric in hexane, but tetrameric in either diethyl ether or THF. As a consequence of steric hindrance, the tendency for aggregation decreases as the steric bulk of the organolithium increases. More substituted alkyllithiums such as *i*-PrLi, *s*-BuLi and *t*-BuLi are not hexameric, but are tetrameric in hexane.[82]

The role of TMEDA in the lithiation of difficult substrates is well established. TMEDA has been shown to facilitate the breakdown of the organolithium polymers by chelation to the lithium anion, thus making the more reactive monomeric species available for the reaction. Therefore the combination of

sec-BuLi / TMEDA in the lithiation procedure reported by Beak and co-workers leads to an extremely strong base.

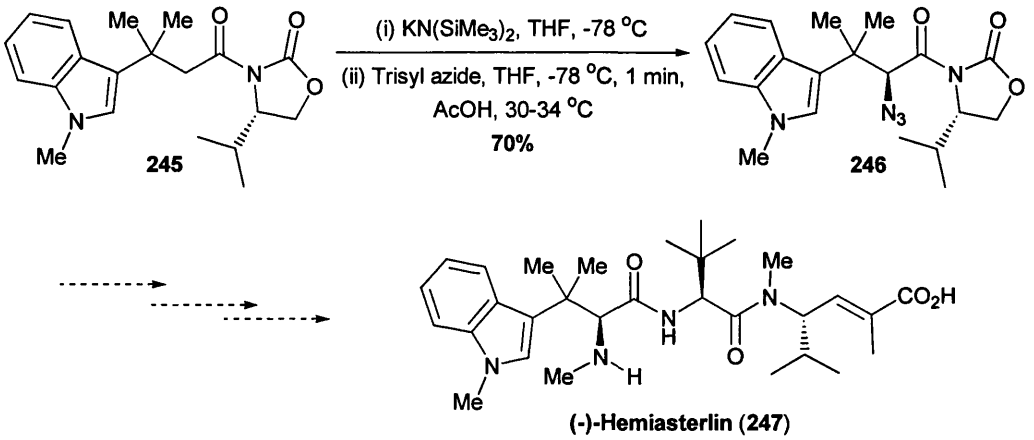
Our synthesis began with the reduction of *cis*-1,2,3,6-tetrahydrophthalimide with lithium aluminium hydride (Scheme 57).[83] This afforded the corresponding amine **241**, which was sufficiently pure to be used for the next step without purification. The secondary nitrogen in **241** was protected as the *tert*-butoxy carbamate to give **242** in a modest yield of 48% from **240**.



Scheme 57

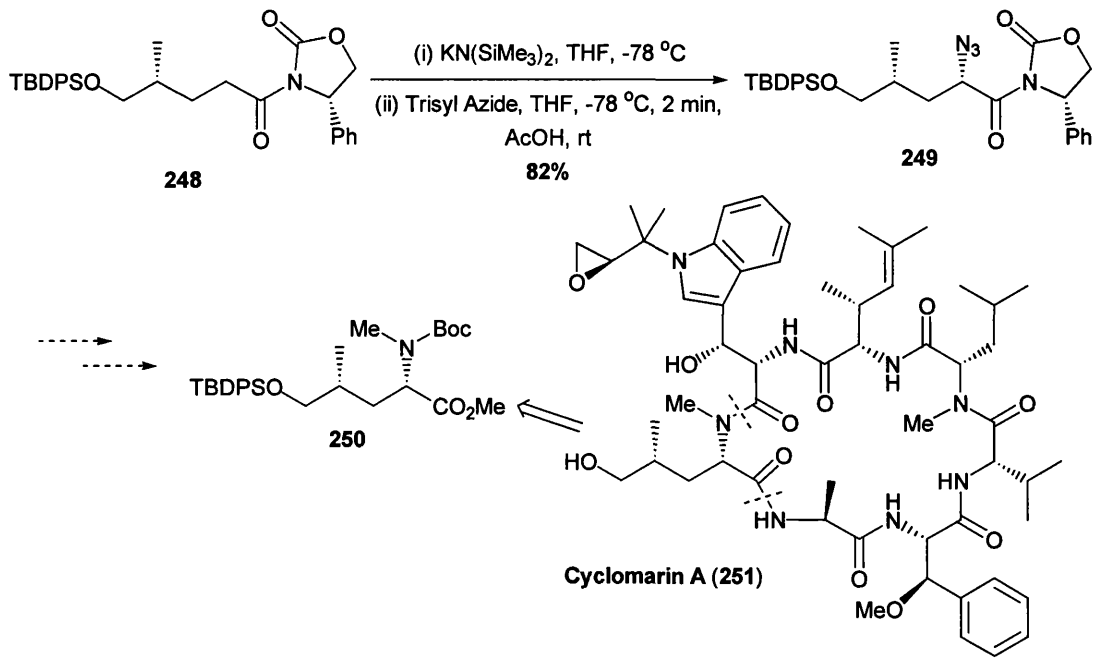
We decided to deprotonate **242** by using the Beak protocol and then to react the organolithium intermediate with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) in order to introduce an azide in to the α-position. The azide would serve as masked amine functionality and could be reduced to the primary amine at a later stage. We envisaged a short synthesis to aminal **203** once we had successfully introduced the amine functionality into carbamate **242**.

Trisyl azide is a convenient source of electrophilic azide; the aromatic group makes it more stable than aliphatic azides.[84] It has been used successfully in a number of syntheses. For example, Anderson *et al.*[85] asymmetrically introduced an azide group into oxazolidone **245**, by reaction of the potassium enolate with trisyl azide at low temperature (Scheme 58). The reaction proceeded with greater than 98% diastereoselectivity and **246** was subsequently converted to the cytotoxic tripeptide (-)- Hemiasterlin.



Scheme 58

Yokokawa *et al.*[86] used a similar method for making the azide derivative **249** (Scheme 59). This was converted into the *N*-methylhydroxyleucine precursor **250**, which was required for their ongoing synthesis of the cyclic peptide Cyclomarin A.



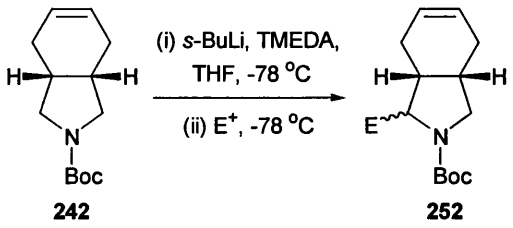
Scheme 59

There are several examples in the literature where trisyl azide has been reacted with potassium enolates, however there are no examples of reactions with organolithiums.

The Beak protocol for lithiation had not been investigated using bicyclic carbamate systems such as that in our synthesis. However, we believed that there was a good prospect that deprotonation could occur in bicycle **242** since it contained an *N*-Boc-pyrrolidine moiety and in theory should react in a similar fashion to an unsubstituted *N*-Boc-pyrrolidine.

A number of attempts were made to induce α-lithiation of carbamate **242**; some of the experiments conducted are summarised in Table 3. We followed the Beak procedure for lithiation by adding 1.2 equivalents of *s*-BuLi to an equimolar solution of carbamate **242** and TMEDA in diethyl ether at -78 °C. The reaction was then allowed to stir at –78 °C for a period of time (ranging from 30 minutes to 5 hours) before a dropwise solution of the electrophile in diethyl ether was added.

The resulting solution was then allowed to warm to room temperature before being worked up.



242 252

Table 3. Attempted lithiation and substitution of 252

Entry	Lithiation time (h)	Electrophile[a]	Reaction time (h)[b]	Yield (%)
1	0.5	Trisyl azide	0.5	0
2	0.5	D_2O	0.5	0
3	0.5	MeI	0.5	0
4	5.0	MeI	0.5	0

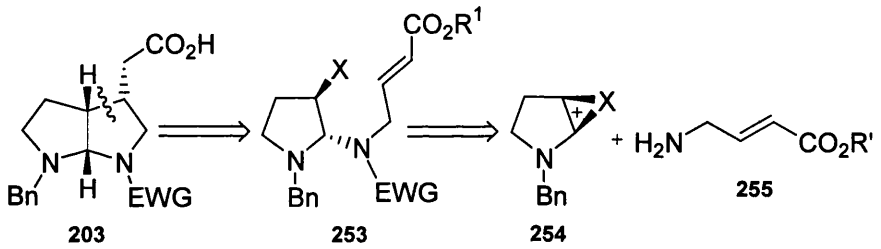
[a] 1.2 equivalents of electrophile was added; [b] time taken to warm to room temperature.

Our first attempt was performed using trisyl azide as the electrophile. The ^1H NMR of the crude reaction mixture showed no evidence that the reaction had occurred; the crude reaction mixture contained mainly unreacted starting material. Subsequently the lithiation was repeated and the mixture was quenched with more conventional electrophiles to confirm that lithiation was taking place. Quenching the reaction with either methyl iodide or deuterium oxide also gave no reaction. Unfortunately it became apparent that α-lithiation was not taking place using the conditions outlined by Beak and co-workers on our carbamate precursor. Consequently this approach for the construction of carboxylic acid **203** was abandoned.

2.5 Strategy Two: Cyclisation of α-amino-β-iodopyrrolidines

2.5.1 Retrosynthetic Analysis

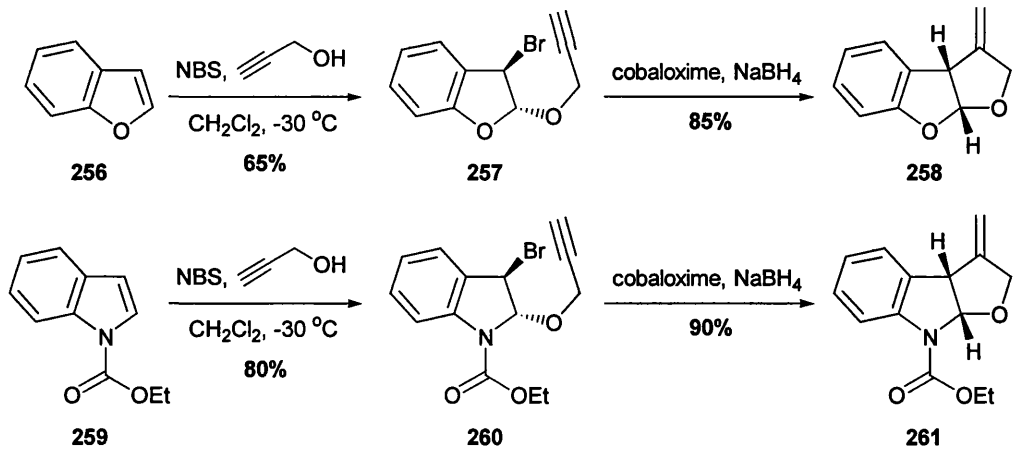
Retrosynthetically, bicyclic acid **203** could be formed by free radical cyclisation of α-amino-β-halopyrrolidine **253** followed by hydrolysis of the ester side chain (Scheme 60). This strategy was based on the assumption that the *trans*-substituted pyrrolidine **253** would be formed from the reaction of amine **255** with the halonium ion **254** (derived from the corresponding enamine), followed by protection of the secondary amine.



Scheme 60

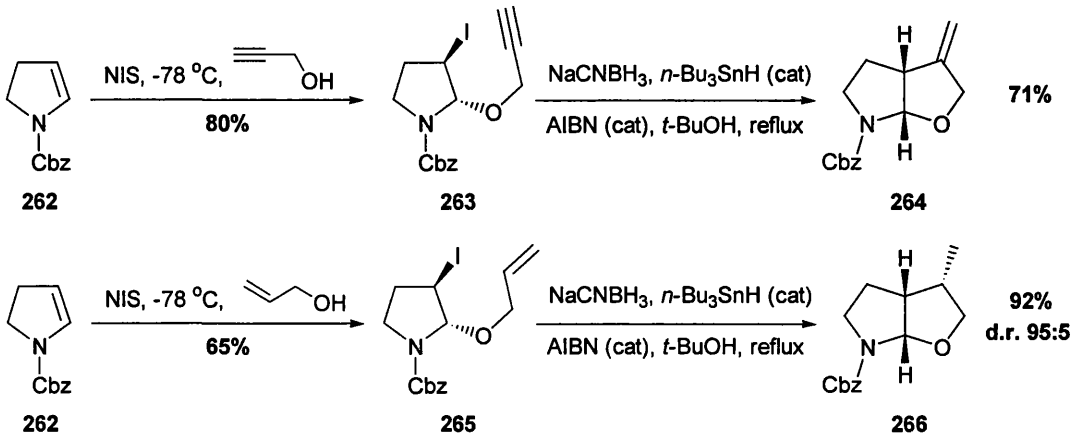
2.5.2 Background and Discussion

Hoffmann *et al.*[87] have reported that cyclic olefins can undergo bromopropargoxylation when treated with *N*-bromosuccinimide (NBS) and propargyl alcohol at low temperature. Heteroaromatic cyclic olefins such as benzofuran **256** and *N*-protected indole **259** also underwent this reaction and gave β-bromo-α-propargyl ethers **257** and **260** in high yield (Scheme 61). Adducts **257** and **260** were cyclised by treatment with sodium borohydride and catalytic cobaloxime to give products **258** and **261**. Cyclisation proceeded in 5-*exo-dig* fashion with *cis*-fusion at the ring junction of the newly generated five-membered ring.



Scheme 61

A similar method was reported by Batey *et al.*[88] for the synthesis of a number of functionalised bicyclic pyrrolidines (Scheme 62). The structure and relative stereochemistry of our aminal **203** closely resembles that of bicyclic **266,** only differing by having an *N-N cis*-fused bicycle rather than an *N-O* bicycle and an acid side chain. Batey and co-workers reported that *N*-acyl-2-pyrroline **262** could be converted into α-alkoxy-β-iodopyrrolidines **263** and **265** by an *N*-iodosuccinimide-promoted alcohol addition at low temperature. The substituted pyrrolidines **263** and **265** were formed in good yields and the substituents adopted a *trans* arrangement.

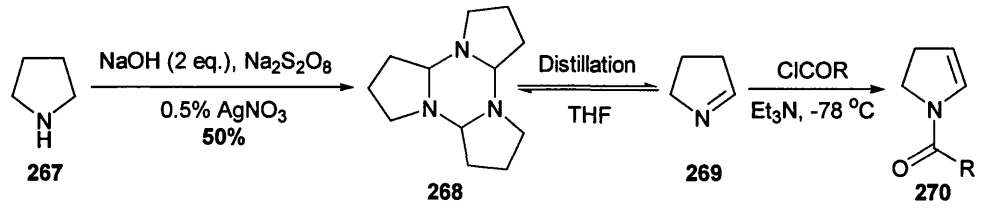


Scheme 62

The intermediates **263** and **265** were then subjected to free-radical cyclisation by treatment with a sodium cyanoborohydride-catalytic tributylstannane system. The cyclisations proceeded with high regioselectivity to give exclusively the *cis*-fused products **264** and **266** in good yields.

We decided to investigate the possibility of using a nitrogen nucleophile to make α-amino-β-iodopyrrolidine analogous to **266** based on the procedure reported by Batey *et al.*

The synthesis began by the generation of *N*-protected pyrrolines. Kraus *et al.*[89] described a procedure for forming *N*-acyl-2-pyrrolines from 1-pyrroline trimer. The trimer **268** was formed using a method originally described by Nomura and co-workers[90] who oxidised pyrrolidine with aqueous alkaline sodium persulfate and 0.5 mol% silver nitrate (Scheme 63). The trimer is reported to decompose to the 1-pyrroline monomer (**269**) at 50 °C. Kraus and co workers used an interesting method to obtain 1-pyrroline as the monomer, by distilling a solution of the trimer in THF into a flask pre-cooled at -78 °C. At this temperature trimerisation is slow, thus making this a convenient way of trapping the monomer intermediate. Treatment of the cooled 1-pyrroline monomer solution with triethylamine and an acyl chloride gave the corresponding 1-acyl-2,3-dihydro-1*H*-pyrrole. The results of the acylation experiments performed by Kraus *et al.* are summarised in Table 4.



Scheme 63

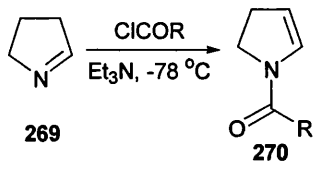
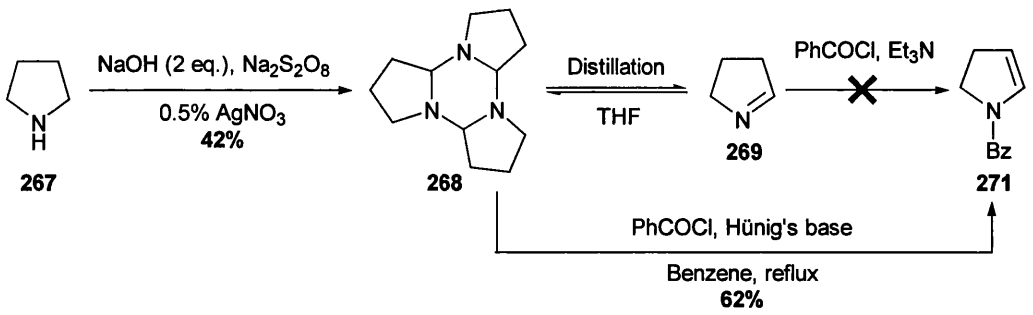


Table 4. Acylation of 1-pyrroline (269)

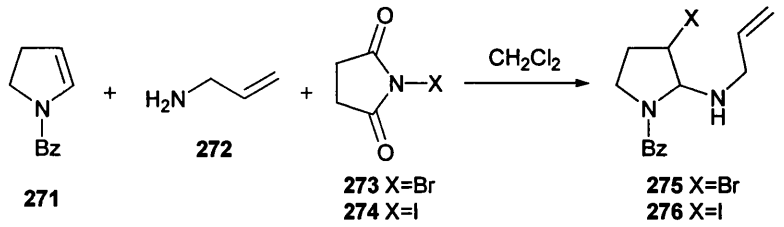
Entry	Acylating agent	Yield of product (%)
1	CH_3OCOCl	78
2	EtOCOCl	79
3	CH_3COCl	71
4	$PhCH_2OCOCl$	74
5	$ClCH_2OCOCl$	57
6	Cl_3CCH_2OCOCl	39

In our hands, oxidation of pyrrolidine using the method of Nomura proceeded in 42% yield (Scheme 64). When the reaction was attempted using benzoyl chloride as the acylating agent, very little formation of enamide **271** was observed. However, we discovered that the procedure by Holzapfel and co workers[91] in which the pyrroline trimer is heated with benzoyl chloride and *N,N*-diisopropylethylamine (Hünig's base) in benzene, gave much better yields of enamide **271**.



Scheme 64

Addition of allylamine to enamide **271** was attempted using both *N*-bromosuccinimide (NBS, **273**) and *N*-iodosuccinimide (NIS, **274**) as the electrophilic promoter (Scheme 65); some of the experiments that were conducted are summarised in Table 5.



271 **272** **273** X=Br **274** X=I **275** X=Br **276** X=I

Scheme 65

Table 5. NBS/NIS promoted amine addition to 271

Entry	Electrophile (eq.)	allylamine (eq.)	Temp.[a] (°C)	Time (min)	Yield (%)
1	NBS, 1.0	1.0	rt	40	0
2	NBS, 1.2	1.2	reflux	30	0
3	NIS, 1.2	1.2	-78	10	0
4	NIS, 1.2	9.6	-78	10	0

[a]All reactions were performed using dry CH_2Cl_2 as the solvent.

After work up of the reactions, ^{1}H NMR analysis of the crude reaction mixtures showed very little starting material; however, there was no evidence of any amine addition by the absence of any peaks corresponding to an allyl group. We concluded that we could not construct a functionalised α-amino-β-iodopyrrolidine using the modified Batey procedure.

After we had abandoned this route, Batey *et al.* released another communication describing their work on iodoamination of *N*-acyl-2-pyrrolines.[92] They reported that primary carbamates and primary sulfonamides underwent iodine-

promoted addition to the double bond of enecarbamate **262** at low temperatures. The reactions afforded *trans/cis* mixtures of functionalised 2-carbamato-3-iodopyrrolidines in good yields, as summarised in Table 6.

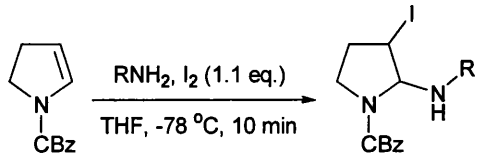


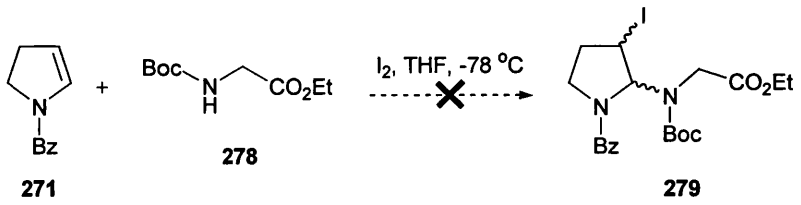
Table 6. Examples of iodocarbamation of 262

Entry	Nucleophile (eq.)	Product	Yield (%)[a]	d.r.[b]
1	$BocNH_2$, 1.0	R = Boc	74	72:28
2	$CbzNH_2$, 2.0	R = Cbz	71	77:23
3	$MeOCONH_2$, 2.0	R = CO_2Me	70	73:27
4	$TolSO_2NH_2$, 2.0	R = SO_2Tol	32[c]	69:31

[a] Yield of purified product (flash chromatography); [b] determined by ^1H NMR; [c] partial decomposition was observed within a few days at 4 °C.

The following amine nucleophiles failed to give stable addition products: primary amines (allylamine and propargylamine), dialkylamines (*N*-methyl allylamine and *N*-cyclohexylamine, arylamines (aniline, *N*-acetyl aniline) and amides (acrylamide and trifluoroacetamide). Batey and co workers had initially attempted some reactions using NIS as the promoter, but discovered that the succinimide anion was more nucleophilic than any of the amines added and instead added preferentially to give 2-succinimido-3-iodopyrrolidines.

Following this we decided to try to extend Batey's results by incorporation of the secondary carbamate nucleophile **278** into enamide **271** using Batey's revised conditions (Scheme 66).



271 278 279

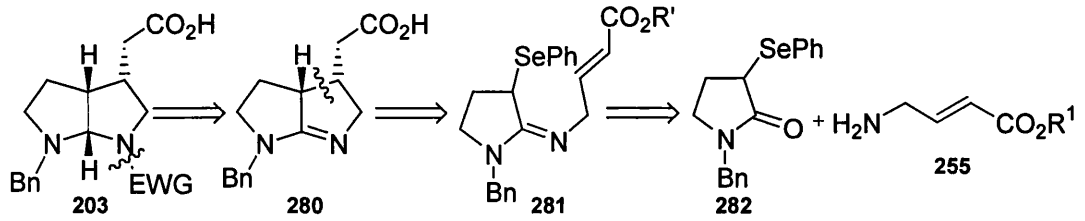
Scheme 66

Unfortunately, the reaction of *N*-Boc glycine ethyl ester with *N*-benzoyl-2-pyrroline gave no addition products (confirmed by the ^{1}H NMR after work-up). We decided not to pursue this strategy any further.

2.6 Strategy Three: Formation of a Bicyclic Amidine

2.6.1 Retrosynthetic Analysis

Retrosynthetically, we decided to investigate the possibility of constructing bicycle **280** at the amidine oxidation state before reducing it to an aminal. Carboxylic acid **203** could be constructed by reduction[93] of bicyclic amidine **280** from the less hindered top face followed by hydrolysis of the ester side chain and protection of the secondary amine (Scheme 67). Amidine **280** could be formed by free radical cyclisation of **281**; substituted amidine **281** would be constructed by the reaction of lactam **282** with functionalised amine **255**.

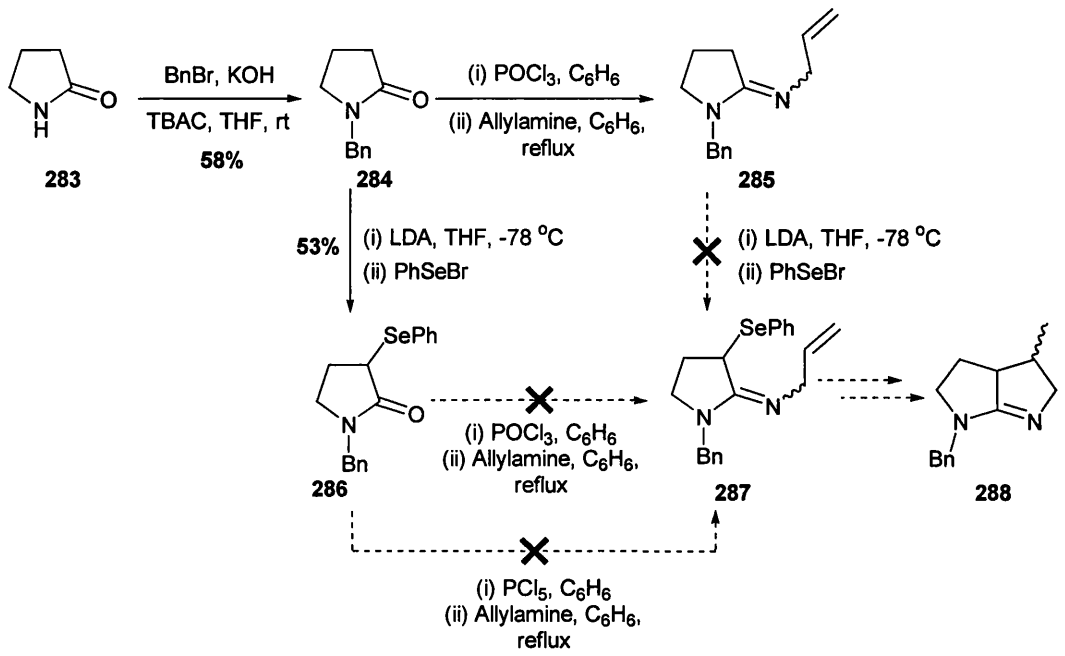


203 280 281 282 255

Scheme 67

2.6.2 Background and Discussion

For the initial studies allylamine rather than amine **255** was used. The synthesis began by protection of pyrrolidin-2-one with a benzyl group by treatment with benzyl bromide, potassium hydroxide and tetrabutylammonium chloride to afford *N*-benzylpyrrolidin-2-one (**284**) (Scheme 68).



Scheme 68

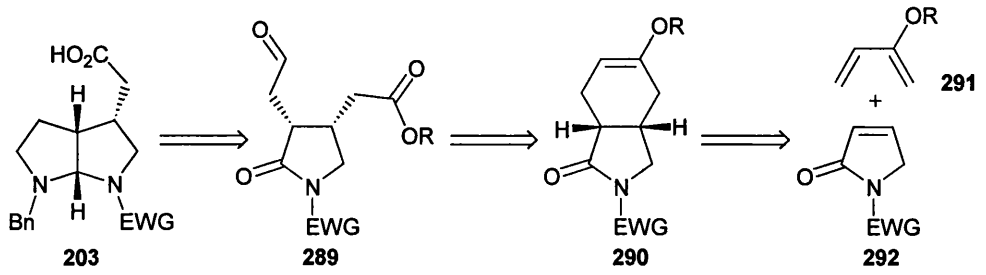
Treatment of **284** with phosphorus oxychloride was presumed to give a chloroiminium ion intermediate, which upon treatment with allylamine in benzene under reflux gave amidine **285** as the only product.[94,95] In order for amidine **285** to undergo free radical cyclisation to form bicycle **288** we required a radical precursor group such as a halogen or phenylselanyl group in the 3-position of **285**. Deprotonation of amidine **285** followed by quenching with phenylselenenyl bromide was unsuccessful, therefore we decided to investigate the possibility of introducing a phenylselanyl group before formation of the amidine. Treatment of **284** with lithium

diisopropylamide and then phenylselenenyl bromide gave **286**. Unfortunately the conversion of **286** to the corresponding amidine **287** under the same conditions as before ($POCl_3$ and allylamine) did not occur, and only starting material was recovered. Repeating the reaction with the more reactive phosphorus pentachloride (PCl_5) was also ineffective and as a result this route was abandoned.

2.7 Strategy Four: The Diels-Alder Approach

2.7.1 Retrosynthetic Analysis

In another approach, we envisaged the use of a Diels-Alder strategy to bicyclic acid **203**. Bicycle **203** could be formed by reductive amination of the aldehyde in lactam **289** with benzylamine, followed by reductive cyclisation with the amide carbonyl (Scheme 69). Lactam **289** containing an ester and an aldehyde functionality would be formed from ring olefin cleavage of **290**. Bicycle **290** would be constructed by a Diels-Alder reaction of **291** with **292**, in a regio- and stereoselective manner.



Scheme 69

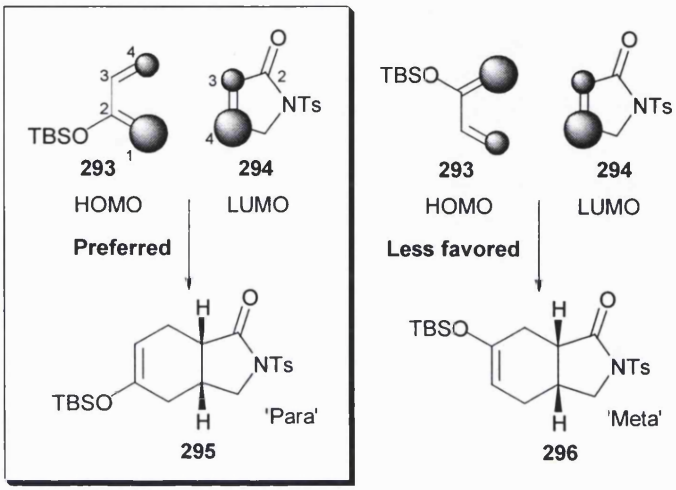
2.7.2 Background and Discussion

The Diels-Alder reaction is an extremely useful method for forming six membered carbocyles and heterocycles, with the added feature of being able to set up to four stereocentres in a single step. The large interest in this reaction has prompted significant advances in this field, which now include the use of chirally modified dienes,[96] dienophiles[97] and auxiliaries[12] in non-chiral and chiral Lewis acid catalysed cycloadditions.[98]

The possibility of using a Diels-Alder cycloaddition for the formation of bicycle **290** can be rationalised by examining the frontier molecular orbitals (FMOs) of the diene and dienophile.[99] Frontier molecular orbital theory involves the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other. The HOMO-LUMO energy separation of the diene and dienophile reactants governs the success of the Diels-Alder reaction. Having a low energy difference encourages mixing of orbitals, thus lowering the transition state energy of the reaction and ultimately increasing the rate of reaction.[100] In a normal DA reaction, the dienophile is required to have a low LUMO and the diene to have a high HOMO energy. Substituents have a marked effect on the energies of the FMOs; electron-withdrawing groups (EWG) lower HOMO/LUMO energy, while electron-donating groups (EDG) increase HOMO/LUMO energy.

The regioselectivity expected in our Diels-Alder reaction for the formation of adduct **290** can be rationalised by examining the FMOs of the diene and dienophile. The presence of an EWG on the dienophile **294** has the effect of making the LUMO coefficient of the C-4 carbon (terminal carbon furthest away from the EWG) larger than that of C-1 (terminal carbon closest to the EWG) (Scheme 68). For the diene

293, an electron-donating substituent in the 2-position contributes a higher HOMO coefficient to the 1-position, compared to the 4-position.[88]



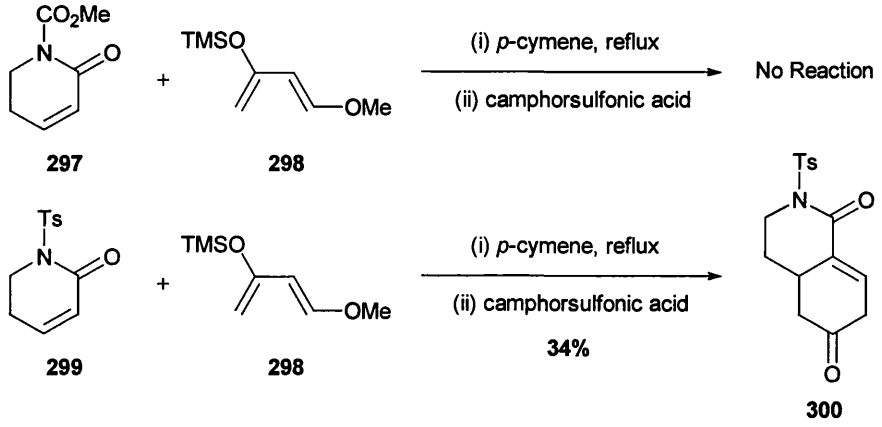
Scheme 70

When the Diels-Alder reaction is uncatalysed, and providing that there is a lack of strong solvent effects, the size of the coefficients on the individual atoms that are forming the new bonds are important in determining the regioselectivity of the cycloaddition. The new bonds are formed preferentially with 'large-large' and 'small-small' overlap (otherwise known as the Houk rule[101]). In our case this would give the more favourable 'pseudo-para' Diels-Alder adduct (**295**), which is the regioisomer we require for our synthesis.

2.7.2.1 Lactam Dienophiles

There is no evidence in the literature of a Diels-Alder reaction with our specific reactants. The closest related dienophiles in the literature are *N*-protected-5,6-dihydro-2-(1*H*)-pyridones and *N*-acetyl-5-isopropoxy-3-pyrrolin-2-ones. Casamitjana *et al.*[102] described a number of Diels-Alder reactions of 5,6-dihydro-2-

(1*H*)-pyridones with a variety of substituted buta-1,3-dienes under thermal and Lewis acid conditions, giving substituted isoquinolones in moderate yields. The choice of amide protecting group was very important; a strongly electron-withdrawing protecting group on nitrogen was found to be essential for their thermal DA reactions.

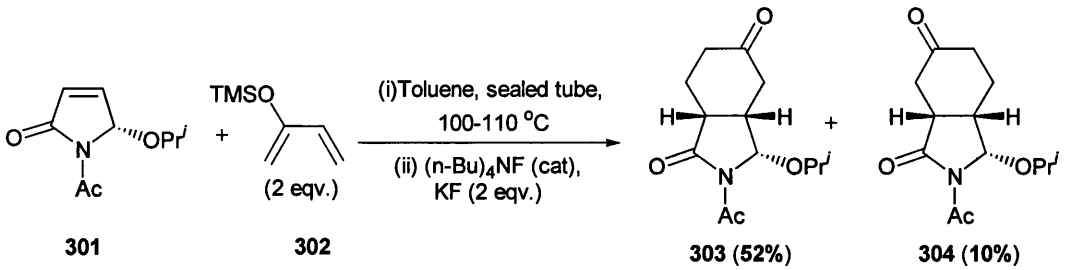


Scheme 71

N-tosyldihydropyridone **299** and the highly reactive Danishefsky's diene **298** underwent a Diels-Alder reaction in refluxing *p*-cymene (Scheme 71). After hydrolysis, the major product obtained from this reaction was **300** in a moderate yield of 34%. Interestingly, no reaction was observed when a carbamate-protecting group was employed; this can be rationalised by a smaller electronic perturbation of the LUMO of the double bond. Other groups have also reported the use of an *N*-tosyl protecting group to enhance the reactivity of an amide dienophile in Diels-Alder reactions.[103] On this basis, we decided to use *N*-tosyl-pyrroline-2-one as the dienophile for our Diels-Alder reaction.

A closely related Diels-Alder reaction has been reported by Koot *et al.*[104c] who performed a thermal Diels-Alder reaction using **301** and **302** (Scheme 72).

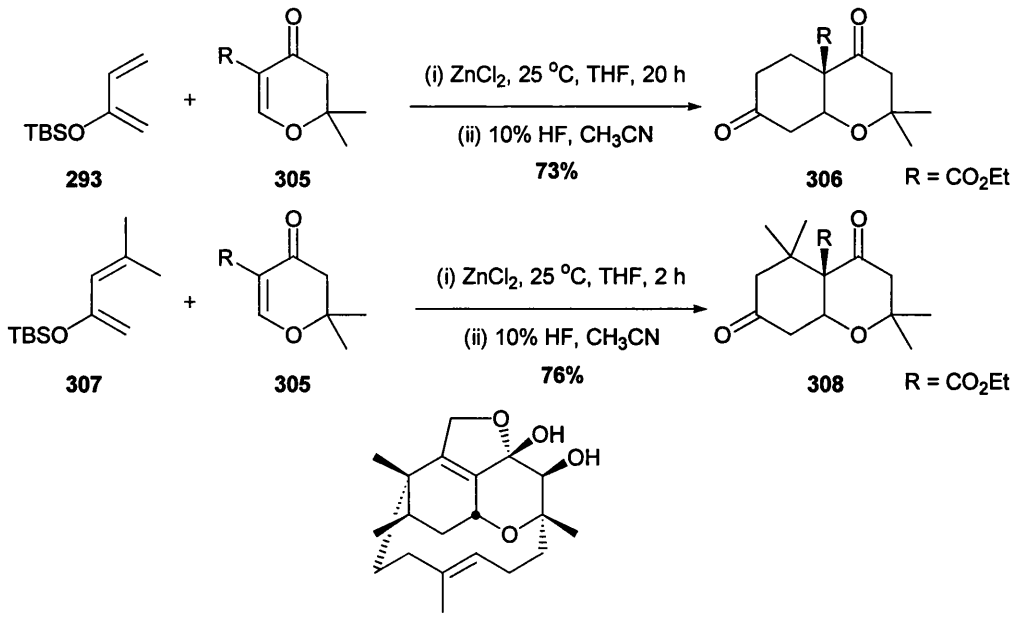
There was good selectivity for the reaction and the major product from this reaction was the 'pseudo-para' adduct **303**.



Scheme 72

2.7.2.2 Silyloxy Dienes

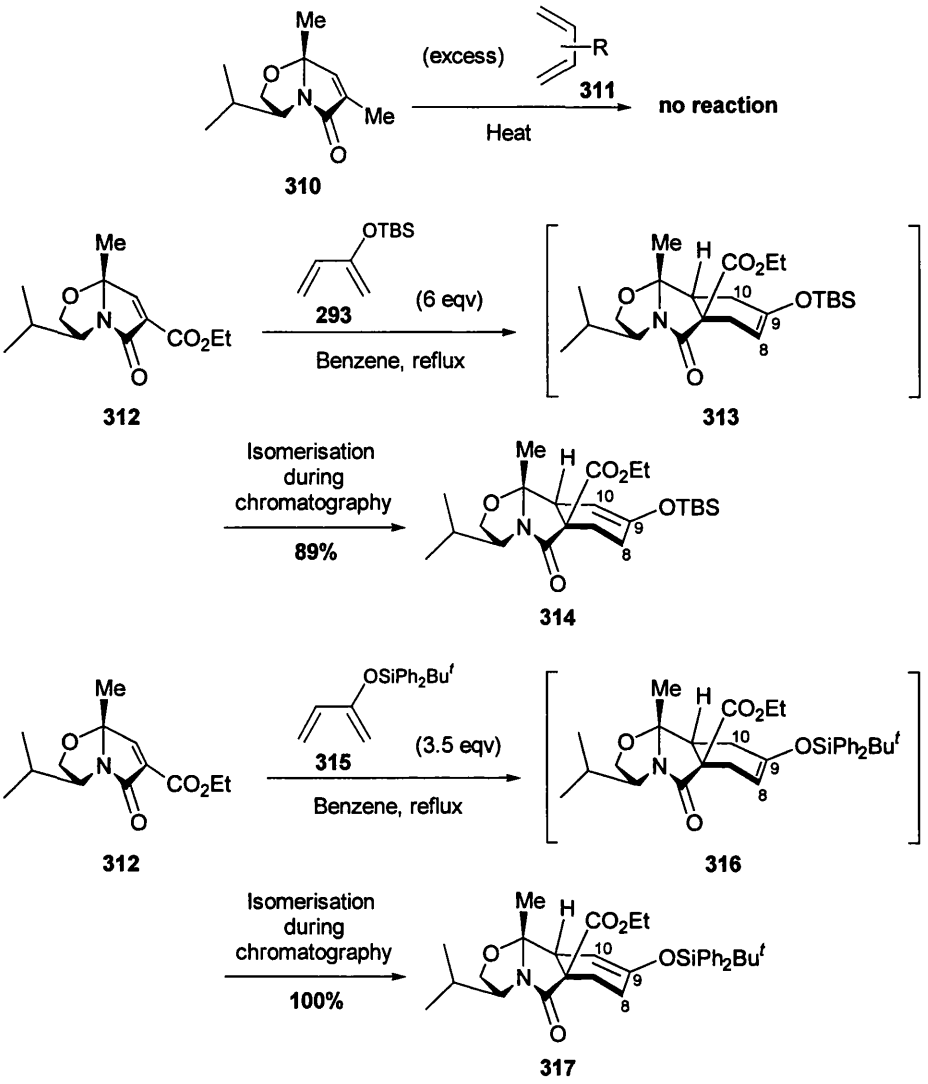
There are several examples of Diels-Alder reactions using 2-silyloxy-substituted dienes.[104] Most use a trimethylsilyl group, however there are a few examples where larger silyoxy groups have been used. Totah *et al.*[105] successfully demonstrated that *tert*-butyldimethylsilyoxy dienes **293** and **307** could undergo Lewis acid catalysed DA reaction with dihydropyrone **305** to give, after hydrolysis, products **306** and **308** in good yield (Scheme 73). These adducts contained a 1-oxadecalin unit which is observed in a number of natural products such as the platelet activating factor antagonist phomactin A (**309**).[106]



Phomactin A (309)

Scheme 73

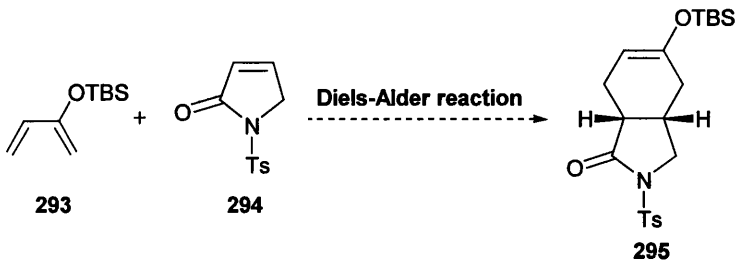
Meyers *et al.*[107] investigated some asymmetric thermal Diels-Alder reactions using bicyclic lactams. They reported that lactam **312** underwent Diels-Alder reactions with silyoxy dienes **293** and **315** (Scheme 74). The intermediates **313** and **316** from these reactions underwent complete double-bond isomerisation during chromatography from the initial $\Delta^{8,9}$ position to the $\Delta^{9,10}$ site. This gave tricyclic products **314** and **317** as single stereo- and regioisomers in excellent yields. Interestingly, the DA reaction of the sterically more bulky *tert*-butyldiphenylsilyoxy diene (**315**) proved to be higher yielding than that using the *tert*-butyldimethylsilyoxy diene (**293**).



Scheme 74

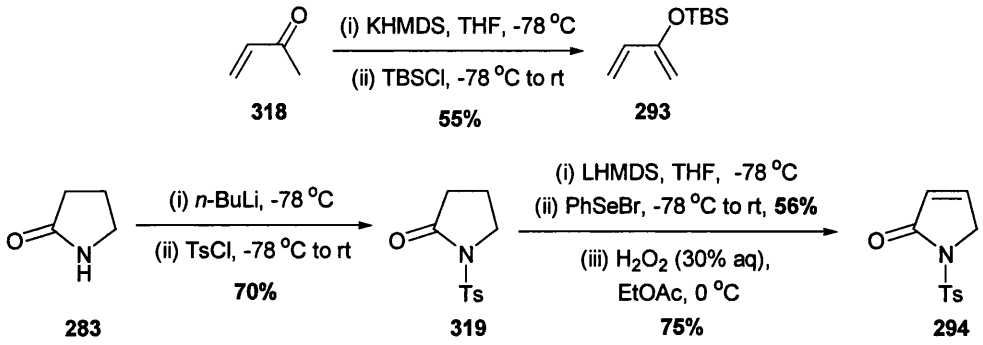
We chose to use a *tert*-butyldimethylsilyl group for the silyoxy substituted diene in our Diels-Alder reaction on the basis that it would be sufficiently stable to high temperature or Lewis acid catalysed conditions and the product from this reaction would be able to withstand the conditions for olefin cleavage.

It thus appeared that there was quite good reason on FMO grounds to expect that a DA reaction between a 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene and an *N*-tosyl-3-pyrrolin-2-one would give the desired adduct **295** (Scheme 75).



Scheme 75

Enolisation of methyl vinyl ketone using potassium hexamethyldisilazide followed by trapping with *tert*-butyldimethylsilyl chloride afforded 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene (**293**) (Scheme 76). Diene **293** could be purified by flash chromatography on neutral alumina. We did however observe some loss upon evaporation of the solvent after the column as a result of the high volatility of the diene. *N*-Tosyl protection of pyrrolidin-2-one was achieved by deprotonation with *n*-BuLi followed by treatment with *p*-toluenesulfonyl chloride (TsCl) under low temperature conditions. Introduction of the selenide group by deprotonation of **319** with lithium hexamethyldisilazide, followed by elimination of the selenoxide gave *N*-tosyl-pyrrolin-2-one (**294**) in good overall yield.



Scheme 76

A number of thermal Diels-Alder reactions were conducted, the results of which are summarised in Table 7. Conducting the Diels-Alder reaction in toluene under reflux gave no reaction; this was confirmed by the presence of unreacted diene and dienophile in the ^{1}H NMR spectrum of the crude reaction mixture. Performing the experiment in a sealed tube, raising the temperature of the experiment and the addition of molecular sieves were also ineffective. The Diels-Alder reaction was also carried out under pressure at even higher temperatures using microwave heating. However, no reaction was observed under these conditions.

Following this, a number of Lewis acid catalysed Diels-Alder reactions were conducted, the results of which are summarised in Table 8. There was no reaction observed when conducting the experiments at low temperatures (–78 °C or 0 °C) so reactions were performed at 0 °C and then warmed to room temperature. Decomposition of siloxy-substituted diene **293** was a possibility for the failure of these initial reactions (some decomposition was observed by TLC), so additives were included to counteract this problem. Molecular sieves were added to the reaction mixture to eliminate water from the reaction. Traces of acid were removed from the reaction by using 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP), a non-nucleophilic base. However, no reaction was observed under any of these conditions.

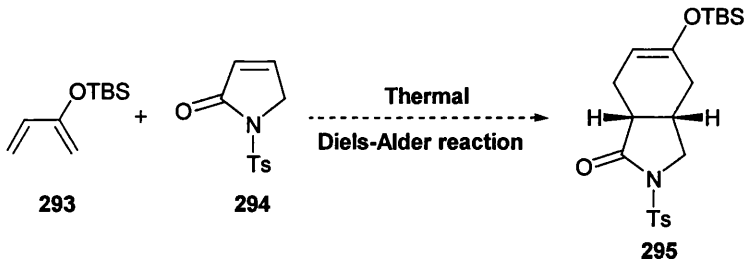
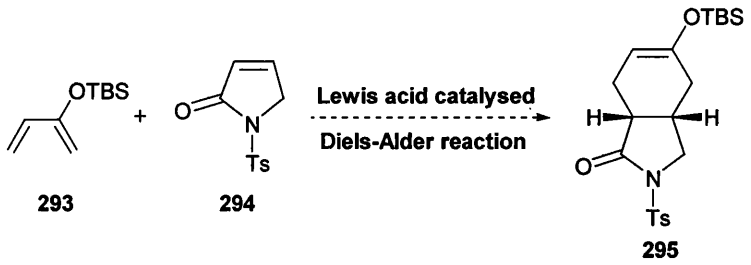


Table 7. Thermal Diels-Alder reactions of 293 with 294

Entry	**293** (eq.)	**Conditions**	Yield (%)[a]
1	1	Toluene, 72 h[b]	0
2	1	Toluene, 130 °C, 96 h[c]	0
3	2.1	Neat, 170 °C, 16 h	0
4	2.1	PhCN, 170 °C, 16 h[c]	0
5	5.2	*p*-cymene, 180 °C, 48 h[c]	0
6	4.5	Toluene, Mol sieves, 140 °C, 16 h[c]	0
7	2.3	Benzene/10% MeCN, 182 °C, 900 s, 11 bar[d]	0
8	2.3	Benzene/10% MeCN, 203 °C, 1200 s, 15 bar[d]	0
9	2.3	Benzene/10% MeCN, 223 °C, 600 s, 20 bar[d]	0

[a] Unreacted dienophile confirmed by ^{1}H NMR analysis; [b] heated to reflux; [c] heated in a sealed tube; [d] microwave reaction.



293 294 295

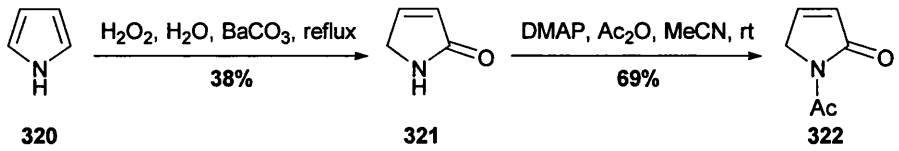
Table 8. Lewis acid catalysed reactions of 293 with 294

Entry	**293** (eq.)	Conditions[a,b]	Yield (%)[c]
1	2.1	Et_2AlCl, –78 °C, 1 h then 0 °C, 1 h	0
2	4.5	$ZnBr_2$, 0 °C, 4h	0
3	4.5	$ZnCl_2$, 0 °C, 4 h	0
4	4.5	$ZnBr_2$, 4 Å Mol sieves, 0 °C, 4h	0
5	4.5	Et_2AlCl, 4 Å Mol sieves,0 °C to rt, 16 h	0
6	4.5	$EtAlCl_2$, 4 Å Mol sieves, 0 °C to rt, 1 h	0
7	4.5	$BF_3.OEt_2$, 4 Å Mol sieves, 0 °C to rt, 16 h	0
8	4.5	$EtAlCl_2$, DTBMP, 0 °C to rt, 4 h	0
9	4.5	Et_2AlCl, DTBMP, 0 °C to rt, 4 h	0
10	4.5	$TiCl_4$, 4 Å Mol sieves, 0 °C to rt, 4 h	0
11	4.5	$ZrCl_4$, 4 Å Mol sieves, 0 °C to rt, 16 h	0
12	4.5	TMS-OTf, 4 Å Mol sieves, 0 °C to rt, 4 h	0

[a] All reactions were performed using dry CH_2Cl_2 as the solvent; [b] one equivalent of Lewis acid catalyst added to the reaction; [c] unreacted dienophile confirmed by ^1H NMR analysis.

We believe that the apparent lack of reactivity of the reactants may be due to steric effects; the bulky tosyl and TBS groups may prevent approach during the *endo*-transition state. Thus a dienophile containing a less bulky protecting group was anticipated to circumvent this problem.

Based on the work done by Koot *et al.*[104c] we decided to make the *N*-acetyl protected pyrrolin-2-one; this *N*-protecting group would be electron withdrawing whilst causing less steric hindrance than an *N*-tosyl protecting group. Dienophile **322** was made by oxidation of pyrrole[108] to 3-pyrrolin-2-one (**321**), followed by protection of the secondary nitrogen with an acetyl group (Scheme 77).



Scheme 77

Some thermal and Lewis acid catalysed reactions were performed using *N*-acetyl-3-pyrrolin-2-one with 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene; these are summarised in Table 9.

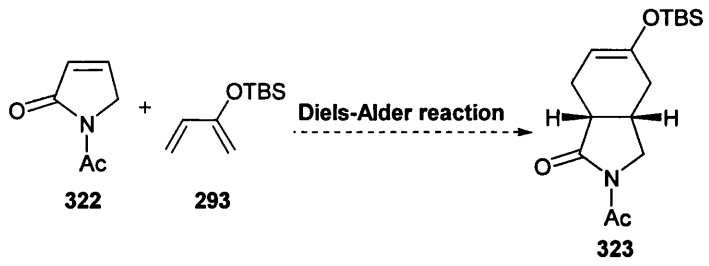


Table 9. Thermal and Lewis acid catalysed Diels-Alder reactions of 293 with 322

Entry	**293** (eq.)	Conditions	Yield (%)[c]
1	3	Toluene, 4 Å Mol sieves, 110 °C, 24 h[a]	0
2	3	Toluene, 4 Å Mol sieves, 130 °C, 16 h[a]	0
1	4.5	CH_2Cl_2, $ZnBr_2$,[b] 4 Å Mol sieves, 0 °C to rt, 4 h	0
2	4.5	CH_2Cl_2, $EtAlCl_2$,[b] 4 Å Mol sieves, 0 °C to rt, 4 h	0

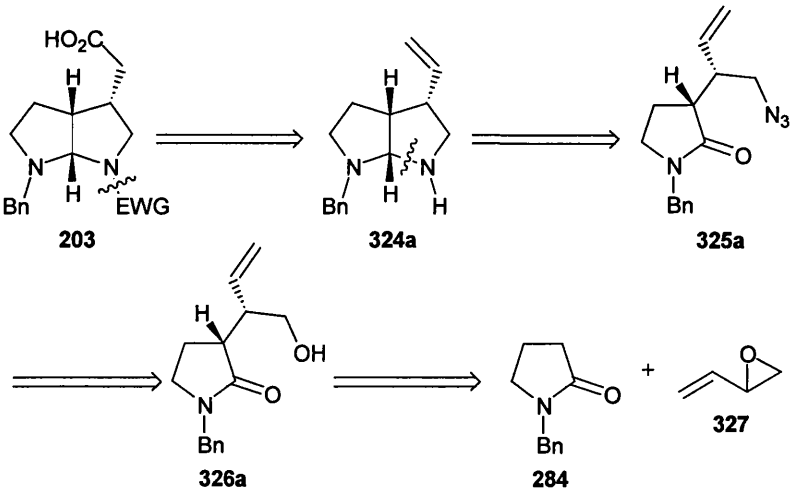
[a] Heated in a sealed tube; [b] one equivalent; [c] unreacted dienophile confirmed by ^1H NMR analysis.

Unfortunately, we were unable to initiate a thermal or Lewis acid catalysed Diels-Alder reaction using reactants **293** and **322** to form adduct **323**. We were unable to rationalise why this reaction did not occur and decided to undertake a different route to get to our desired bicyclic acid.

2.8 Strategy Five: The Opening of Butadiene Monoxide

2.8.1 Retrosynthetic Analysis

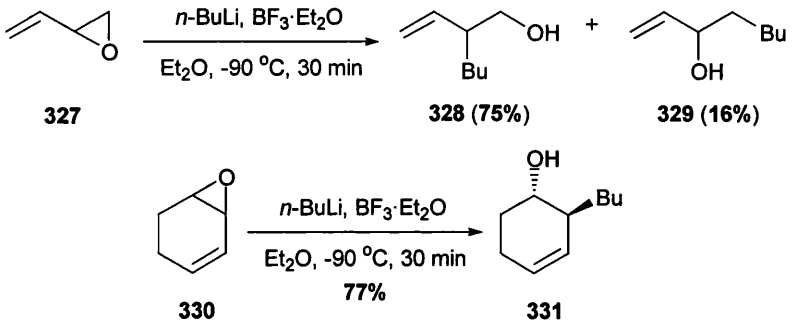
Retrosynthetically, carboxylic acid **203** could be formed by hydroboration and oxidation of the terminal olefin in bicycle **324a** followed by oxidation of the resulting primary alcohol to the corresponding acid and protection of the secondary nitrogen (Scheme 78). Bicyclic aminal **324a** could be constructed from azido-lactam **325a** by a reductive cyclisation reaction. Lactam **325a** would be formed by a functional group transformation of the primary alcohol in **326a** to an azide group. A Lewis-acid catalysed reaction of the amide enolate of **284** with epoxide **327** would give alcohol lactam **326a**.



Scheme 78

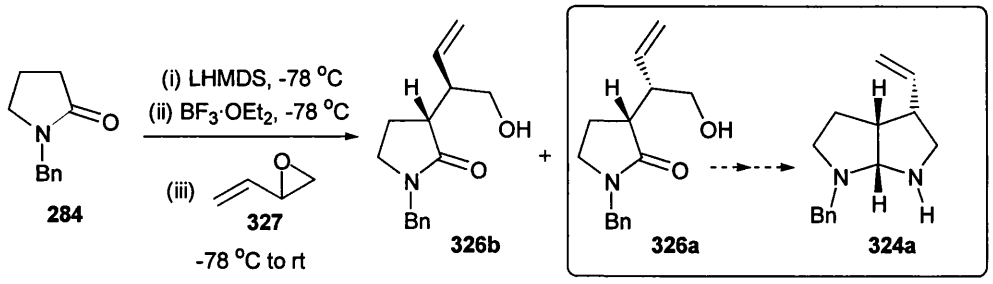
2.8.2 Background and Discussion

Alexakis *et al.*[109] have reported that regioselective attack by organolithium reagents at the allylic position of cyclic and acyclic α,β-ethylenic epoxides is promoted by boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) (Scheme 79). The Lewis acid promotes opening at the allylic position at the expense of the S_N2' and S_N2 pathways.



Scheme 79

We decided to investigate the possibility of opening butadiene monoxide by the enolate of *N*-benzylpyrrolidin-2-one based on this precedent. This reaction would lead to the formation of a mixture of two diastereomeric alcohol lactams **326a** and **326b**, one of which would contain the correct relative stereochemistry for conversion to bicycle **324a** (Scheme 80).



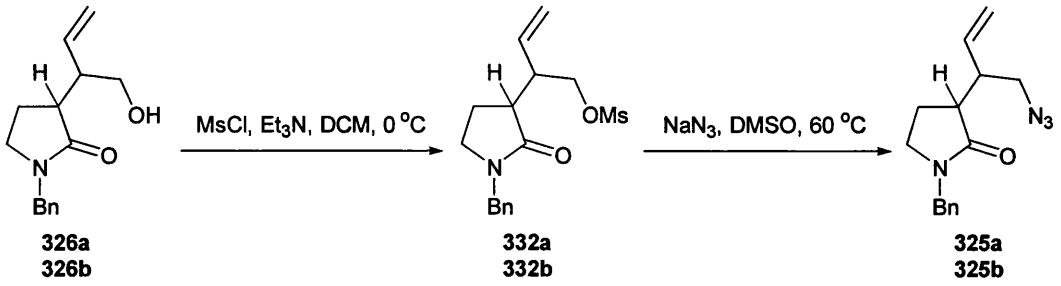
Scheme 80

The enolate of *N*-benzylpyrrolidin-2-one was generated by treatment with lithium hexamethyldisilazide at low temperature in THF (Scheme 80). Boron trifluoride diethyl etherate was then added, followed by butadiene monoxide. The products **326a** and **326b** were obtained as a mixture of diastereomers, which were difficult to separate from each other and from unreacted starting material.

After optimisation of the reaction (1.1 equivalents of $BF_3{\cdot}Et_2O$ and 1.1 equivalents of butadiene monoxide added at –78 °C) an estimated yield of 16% was obtained (after partial purification of the diastereomers), with a 2:1 ratio of diastereomers (based on the ^1H NMR spectrum of the crude reaction mixture). The use of other Lewis acids ($TiCl_4$, $ZnBr_2$, $MgBr_2$ and Et_2AlCl) gave no reaction.

A small sample of each diastereomer (**326a** and **326b**) was isolated; we were unable to identify the relative stereochemistry of the products by proton NMR. However, we thought that we would be able to obtain stereochemical information after cyclisation to the bicyclic aminal **324a** (Scheme 80).

After isolation of the alcohol diastereomers, some preliminary reactions were performed.



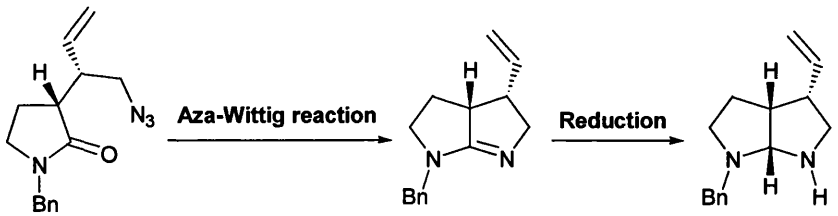
326a **326b** **332a** **332b** **325a** **325b**

Scheme 81

Each of the diastereomers **326a** and **326b** was converted separately to the corresponding mesylate **332a** and **332b** by treatment with mesyl chloride and

triethylamine (Scheme 81). These were subsequently converted to the azido-lactams **325a** and **325b** by treatment with sodium azide in DMSO. Only one of the diastereomeric azide products (**325a**, which we had tentatively assigned the configuration shown – see section 2.8.5) was used for the subsequent reactions

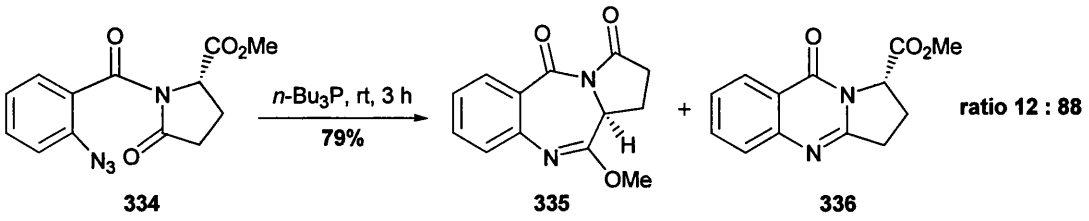
Our first strategy for cyclisation was to attempt an intramolecular aza-Wittig reaction; this would lead to the formation of amidine **333**, which could be reduced to the corresponding aminal **324a** (Scheme 82).



325a **333** **324a**

Scheme 82

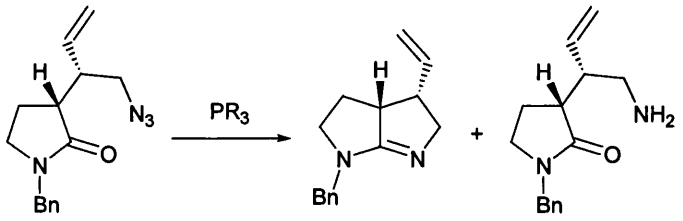
The criteria for reactivity in aza-Wittig reactions are however not as clear cut as for the Wittig olefination reaction. Ester carbonyl groups are generally unreactive in intermolecular aza-Wittig reactions, but can react in an intramolecular fashion to form rings.[110] The aza-Wittig reaction with an amide carbonyl has not been reported in the literature, however the aza-Wittig reaction of an imide carbonyl has been reported. Eguchi *et al.*[110] successfully cyclised ester **334** to give two compounds (**335** and **336**) each of which arose from an aza-Wittig reaction (Scheme 83). The iminophosphorane intermediate formed from **334** reacted either with the ester carbonyl to form [1,4]benzodiazepine **335** or with the imide carbonyl to form quinazoline **336**.



334 335 336

Scheme 83

The reactions performed on one of the diastereomers are summarised in Table 10.



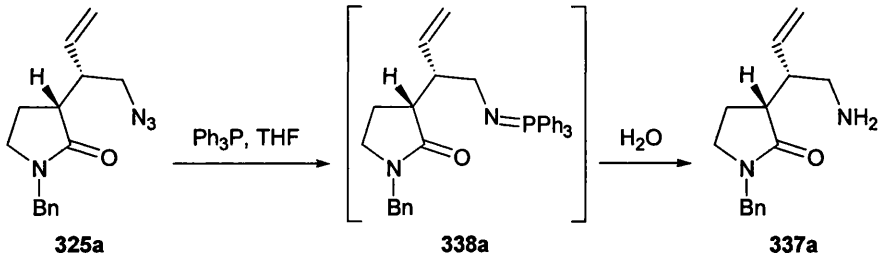
325a 333 337a

Table 30. Attempted aza-Wittig reactions performed on 325a

Entry	Phosphine R group (eq.)	Conditions	**333** Yield (%)
1	*n*-Bu_3P (2.0)	Toluene, rt 1 h then reflux 16 h	0[b]
2	PMe_3 (2.0)	Toluene, rt 1 h then reflux 16 h	0[b]
3	PMe_3 (5.0)	Toluene, rt 1 h then reflux 16 h	0[b]
4	PMe_3 (2.0)	MeCN, rt 1h then 190 °C 10 mins[a]	0[b]

[a] Reaction performed in a microwave oven; [b] ^1H NMR of the crude reaction mixture showed reduced azide compound (amine **337a**).

The reaction was initially attempted using tri-*n*-butylphosphine, but this gave the Staudinger reduction product **337a** and not the desired aza-Wittig product. A pure sample of this amine was obtained by reduction of azide **325a** with Ph_3P/water (Scheme 84) for ^1H NMR comparison.

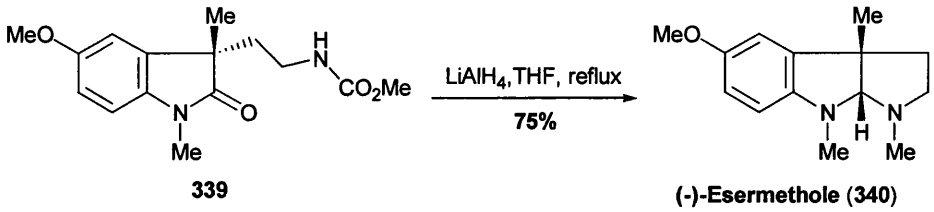


325a 338a 337a

Scheme 84

Experiments were conducted using trimethylphosphine, which was anticipated to increase the reactivity of the iminophoshorane intermediate in the aza-Wittig reaction. However, this gave no reaction and conducting the experiments under forcing conditions (microwave, 190 °C, 10 mins) was insufficient for promotion of this reaction. In all cases only amine **337a** was obtained. It appears that the amide carbonyl is less reactive than an imide carbonyl towards aza-Wittig reactions; consequently we chose to look for another method for cyclisation.

Wong *et al.*[111] described the synthesis of (-)-esermethole (**340**), a penultimate intermediate to (-)-physostigmine, an anticholinesterase agent, which is used for the treatment of glaucoma and myasthenia gravis. Cyclisation of oxindole **339** was achieved by refluxing with $LiAlH_4$ in THF and gave (-)-esermethole in a 75% yield (Scheme 85). The reaction presumably proceeds by reduction of the ring amide to the corresponding hemiaminal and reduction of the carbamate to the corresponding *N*-methyl aluminium amide, followed by cyclisation (possibly upon workup) to give the *cis*-fused tricycle.

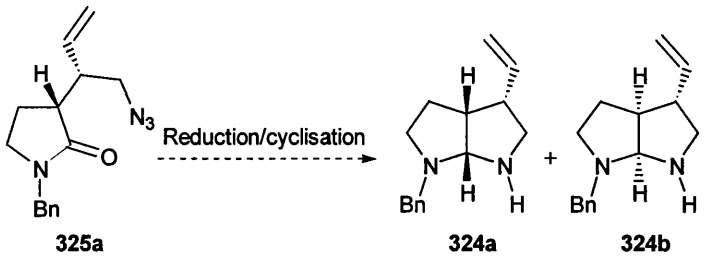


339 (-)-Esermethole (340)

Scheme 85

Red-Al[112] and sodium in ethanol[77] have also been used for cyclisation of an amine or amide side chain with an oxindole. Although there was no reference to a similar reaction occurring with an azide side-chain, we can envisage that the reaction should proceed in a similar fashion.

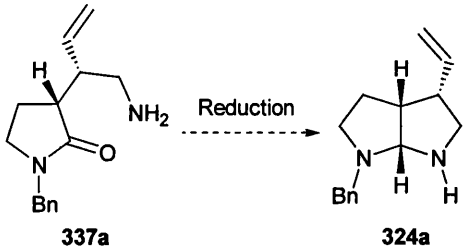
Our initial attempt at this reaction using a solution of $LiAlH_4$ in THF gave a mixture of compounds after workup with MeOH/Rochelle salt. The ^1H NMR spectrum of the crude reaction mixture (after work up) showed a mixture of two similar compounds, which were believed to be aminal **324a** and the diastereomer **324b**. Unfortunately, even after extensive experimentation, we were unable to obtain a clean sample of aminals **324a** or **324b**. Reduction using other reducing agents (DIBAL and Red-Al) also gave mixtures of compounds, which again were inseparable by chromatography.



325a 324a 324b

Scheme 86

Repeating the cyclisation using the reduced amino-lactam **337a** with a solution of $LiAlH_4$ in THF also gave a mixture of compounds that included aminals **324a** and **324b**, which again were inseparable by chromatography (Scheme 87).



337a **324a**

Scheme 87

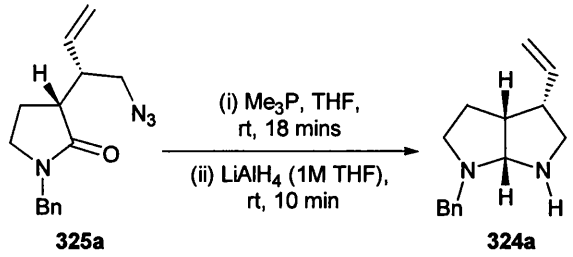
2.8.3 Reductive Cyclisation of an Iminophosphorane

After taking a closer look at the mechanism for the aza-Wittig reaction that was attempted earlier, we hypothesised that the reaction could occur if a better electrophile than an amide were involved. We decided to explore what would happen if a source of hydride was added to the iminophosphorane intermediate. This was expected to produce a hemiaminal that may in turn generate a more reactive electrophile - either an aldehyde or an iminium ion for the cyclisation by the attached iminophosphorane.

Treatment of a THF solution of azide **325a** with trimethylphosphine for a brief period at room temperature followed by the addition of a solution of $LiAlH_4$, gave a crude reaction mixture which by ^1H NMR did indeed show an improvement in the amount of the bicycle **324a** formed (Scheme 88).

The ^1H NMR of the crude reaction mixture was very clean with very few side products formed. Unfortunately we were unable to obtain a clean sample of aminal **324a** by chromatography as a consequence of difficulty in separation of **324a** from

trimethylphosphine oxide, a side product of the reaction. In addition, by probing the reductive cyclisation reactions we had exhausted our supply of azide **325a**.

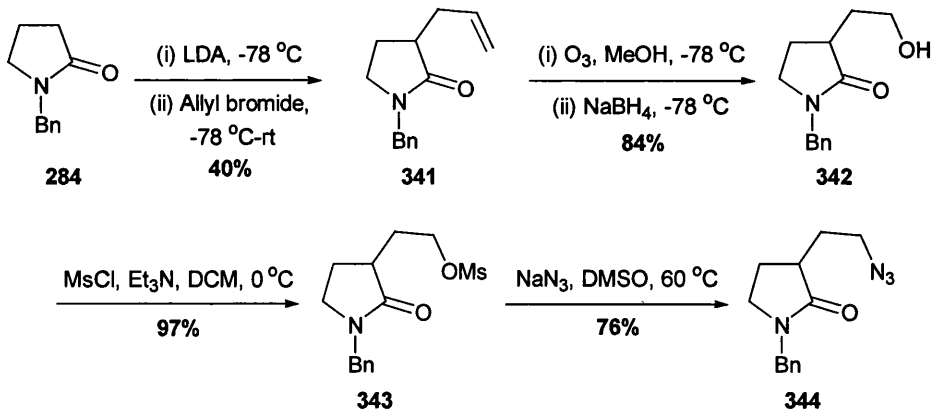


325a **324a**

Scheme 88

2.8.4 The Use of a Model System

At this point, due to problems in obtaining sufficient quantities of azides **325a** and **325b** for a thorough investigation of the reductive cyclisation we decided to employ a model system that lacked the vinyl side chain.



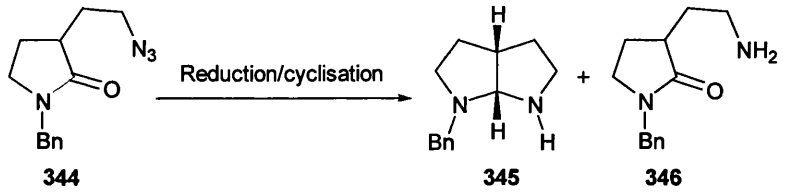
284 **341** **342**

343 **344**

Scheme 89

Thus, lactam **284** was deprotonated with LDA and alkylated with allyl bromide to give **341**. The yield for this step was quite low (40%) due to the formation of significant quantities (31%) of the diallylated product (Scheme 89).

Ozonolysis of the terminal olefin in **341** followed by a sodium borohydride workup yielded primary alcohol **342**, which was then converted to mesylate **343** by treatment with mesyl chloride. Substitution of the mesylate with sodium azide in DMSO at 60 °C gave azido-lactam **344** in good yield. A number of reactions were conducted using **344** to investigate the reduction/cyclisation reaction for the formation of bicyclic aminal **345** (Scheme 90). The results of these are summarised in Table 11.



344 **345** **346**

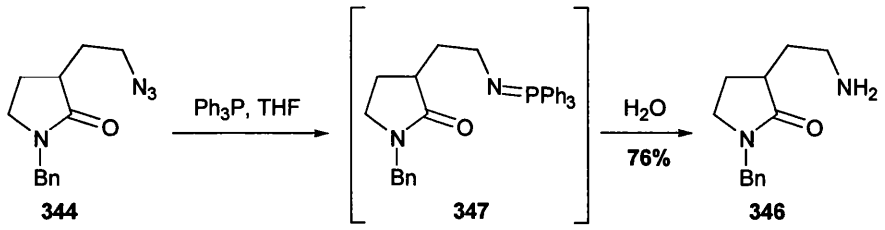
Scheme 90

Table 11. Cyclisation of azido-lactam 344

Entry	Conditions	**345** Yield (%)
1	1. $LiAlH_4$ (1M in THF, 1.2 eq.), THF, -78 °C, 10 min 2. MeOH/ Rochelle salt solution (1M) (2:1 ratio)	0[a]
2	1. $LiAlH_4$ (1M in THF, 1.2 eq.), THF, -78 °C, 30 min 2. MeOH/ Rochelle salt solution (1M) (2:1 ratio)	0[a]
3	1. $LiAlH_4$ (1M in THF, 1.2 eq.), THF, -78 °C, 1 h 2. MeOH/ Rochelle salt solution (1M) (2:1 ratio)	0[a]
4	1. $LiAlH_4$ (1M in THF, 1.2 eq.), THF, rt, 10 min 2. MeOH/ Rochelle salt solution (1M) (2:1 ratio)	0[b]
5	1. DIBAL-H (1.2M in toluene, 2.0 eq.), THF, rt, 30 min 2. MeOH/ Rochelle salt solution (1M) (2:1 ratio)	0[b]
6	1. Red-Al (3.5M in toluene, 2.0 eq.), THF, rt, 30 min 2. MeOH/ Rochelle salt solution (1M) (2:1 ratio)	0[b]
7	1. *n*-Bu_3P (1.2 eq.), THF, rt, 18-20 min 2. $LiAlH_4$ (1M in THF, 0.6 eq.), THF, rt, 1 h 3. Rochelle salt solution (1M)	54

[a] ^1H NMR of the crude reaction mixture showed amine **346** as the major product; [b] Mixture of inseparable compounds.

We discovered that lithium aluminium hydride was not reactive enough at –78 °C for cyclisation to aminal **344** (entries 1-3). The major product from these reactions was amine **346**, confirmed by obtaining a pure sample by reduction of azide **344** with Ph_3P/water (scheme 91).



Scheme 91

Repeating the reaction at room temperature (entry 4) gave a mixture of compounds that were inseparable by column chromatography, though we were able to identify aminal **345** and amine **346** from the ^{1}H NMR spectrum of the crude reaction mixture. Changing the reducing agent to DIBAL-H or Red-Al (entries 5 & 6) also gave a mixture of compounds, which again included **345** and **346**; these were difficult to separate by column chromatography.

We then tried to use the phosphine/hydride methodology we had developed for cyclisation of azide **325a**. Here we discovered that *n*-Bu_3P was sufficiently reactive and was preferable to the use of PMe_3 since it avoided the unwanted stench and extreme air sensitivity of the latter. The addition of the phosphine prior to $LiAlH_4$ addition had a marked effect on the cleanliness of the reaction; the ^{1}H NMR spectrum of the crude reaction mixture did not show any products apart from the cyclised material and tri-*n*-butylphosphine oxide.

We were very pleased to find that exposure of **344** to *n*-Bu_3P for 18-20 minutes, followed by a solution of $LiAlH_4$ in THF gave aminal **345** in 54% yield

(entry 7). The coupling constants of 7.0 Hz for the ring fusion proton at δ 4.10 ppm, which is a doublet, indicated that aminal **345** had a *cis*-fused ring junction (Figure 15)

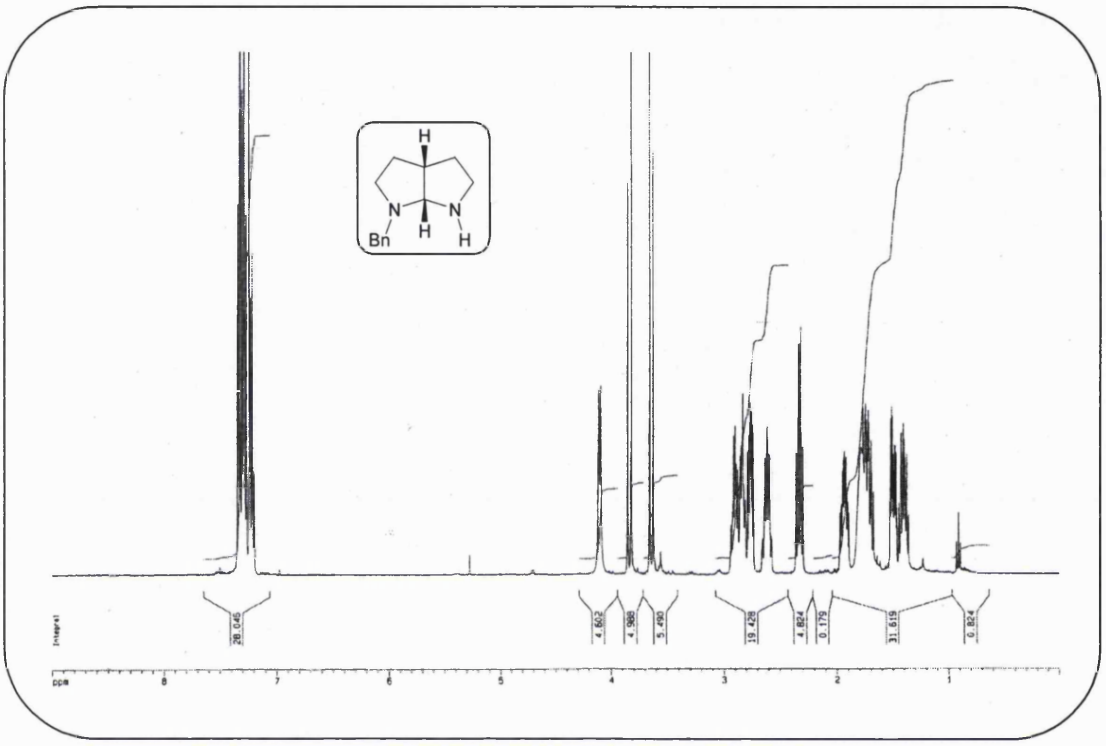
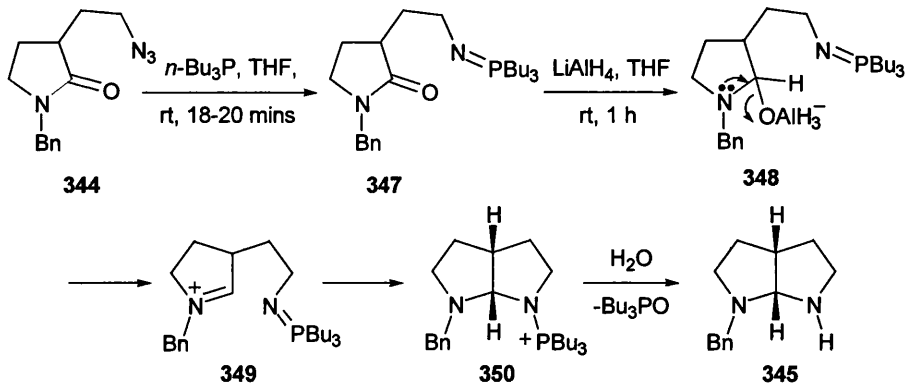


Figure 15. ^{1}H NMR of aminal **345** (500 MHz, $CDCl_3$)

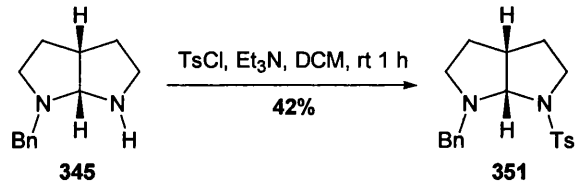
At this point we had succesfully constructed a bicycle containing a *cis*-fused octahydropyrrolo[2,3-*b*]pyrrole ring system. A possible mechanism for this cyclisation is shown in Scheme 92. Tri-*n*-butylphosphine reacts with the azide of **344** to generate iminophosphorane **347**. Subsequent addition of hydride to the lactam carbonyl, and expulsion of an aluminium alkoxide leads to iminium ion **349**. Cyclisation of the nucleophilic iminophosphorane nitrogen onto the iminium ion leads to bicycle **350**, and aqueous work-up cleaves the nitrogen-phosphorus bond to generate the observed product **345** and tri-*n*-butylphosphine oxide.



Scheme 92

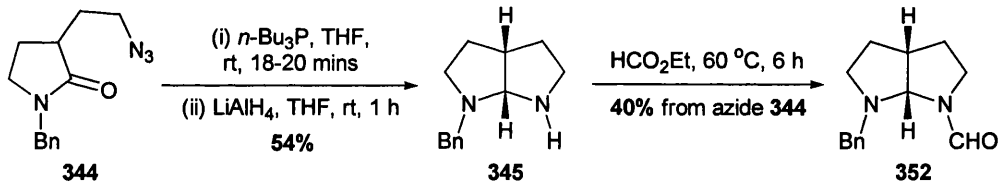
The yield of bicycle **345** was not as high as we anticipated, presumably as a consequence of the very low mobility of the aminal on silica, its adhesion to aluminium residues, and the difficulty of separating it from the tri-*n*-butylphosphine oxide by-product. We found that methanol was not actually required in the work-up and that a solution of Rochelle salt alone could facilitate the cyclisation (entry 7).

Protection of a sample of aminal **345** with a tosyl group did proceed cleanly, but the isolated yield of protected aminal **351** was low (Scheme 93). Despite the high R_f of the compound in a solvent system of petroleum ether: ethyl acetate 1:1, only a small amount of the compound could be recovered using this eluent; the remainder only eluted from the column when MeOH/EtOAc mixtures were used. We speculate that the unusual behaviour may be due to ring opening of the bicycle to a more polar compound on the column and then recyclisation upon exposure to methanol. Yields and ease of chromatography were improved by changing the column solvent system to 1-2% methanol/dichloromethane, which gave protected aminal **351** in a moderate yield of 42% from **345**.



Scheme 93

Aminal **345** was also protected as a formamide, which we believed would be more stable to chromatography (Scheme 94). Formamide protected aminal **352** was formed in a 40% yield from **344** and could be purified easily by chromatography in an eluent of petroleum ether: ethyl acetate (2:1).



Scheme 94

Aminal **352** was formed as pair of rotamers **352a** and **352b**, which were identified by NOE studies (Figure 16).

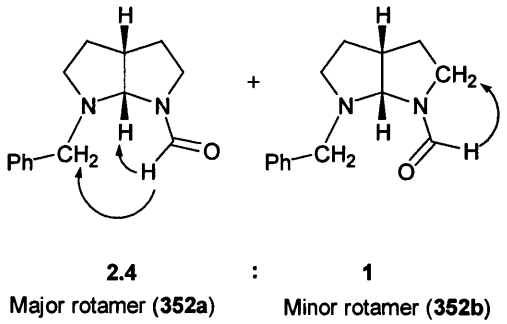


Figure 12. Selected nuclear Overhauser enhancements for **352a** and **352b**

The coupling constants of 6.7 Hz at δ 4.75 ppm for the major isomer and 7.2 Hz at δ 6.1 ppm for the minor isomer between the ring fusion protons indicated that both compounds had a *cis*-fused ring junction (Figure 17).

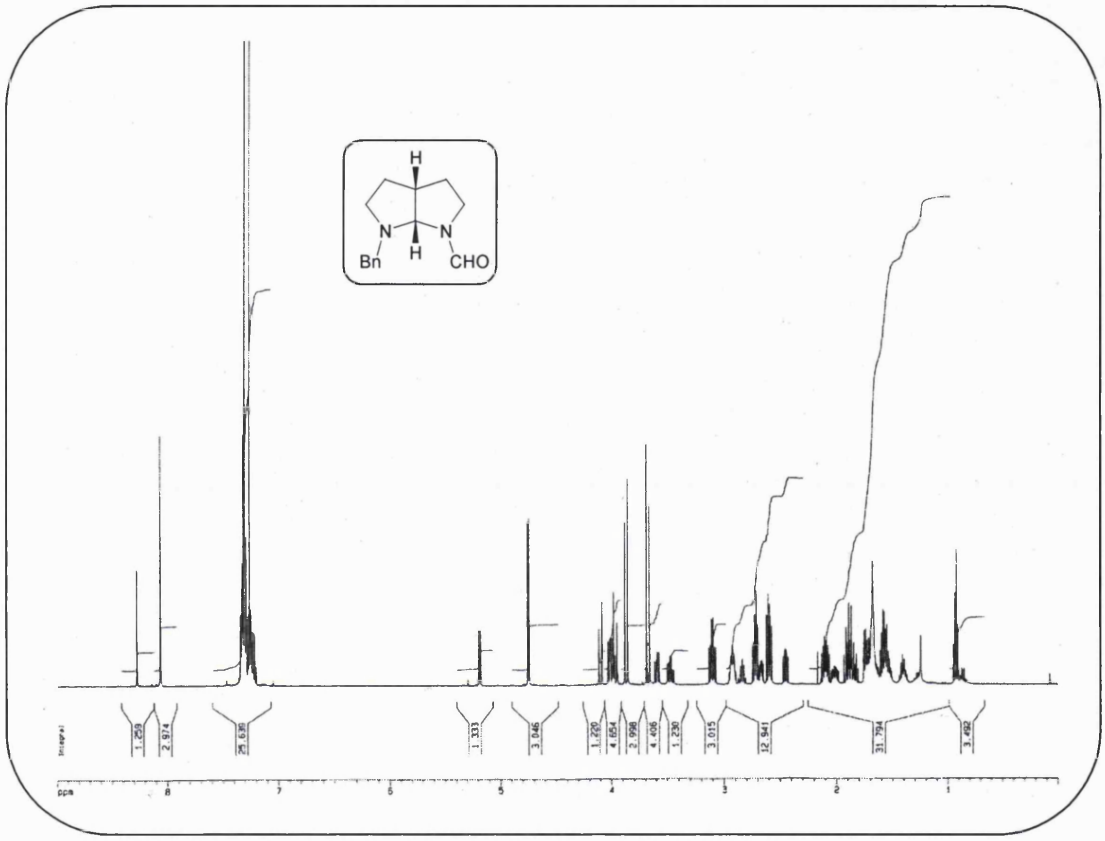
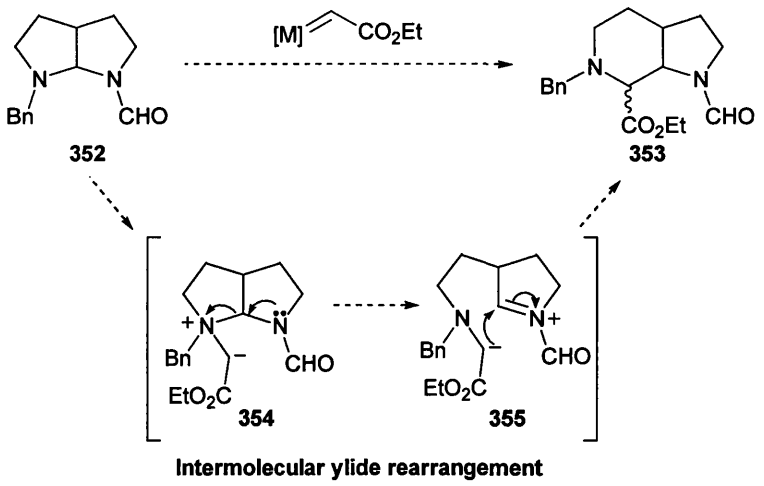


Figure 17. ^{1}H NMR of protected aminal **352a** and **352b** (500 MHz, CDCl3)

At this stage we had successfully made a *cis*-fused protected aminal, *via* an interesting *n*-$Bu_3P/LiAlH_4$ reduction/cyclisation. We decided to investigate the possibility of aminal **352** undergoing an intermolecular version of the ring expansion we had envisioned for the real system. We thought that exposure of aminal **352** to an electron-deficient metal carbene derived from ethyl diazoacetate would form ylide **354**, which it was anticipated would undergo ring expansion to give **353** *via* the pathway shown in Scheme 95.



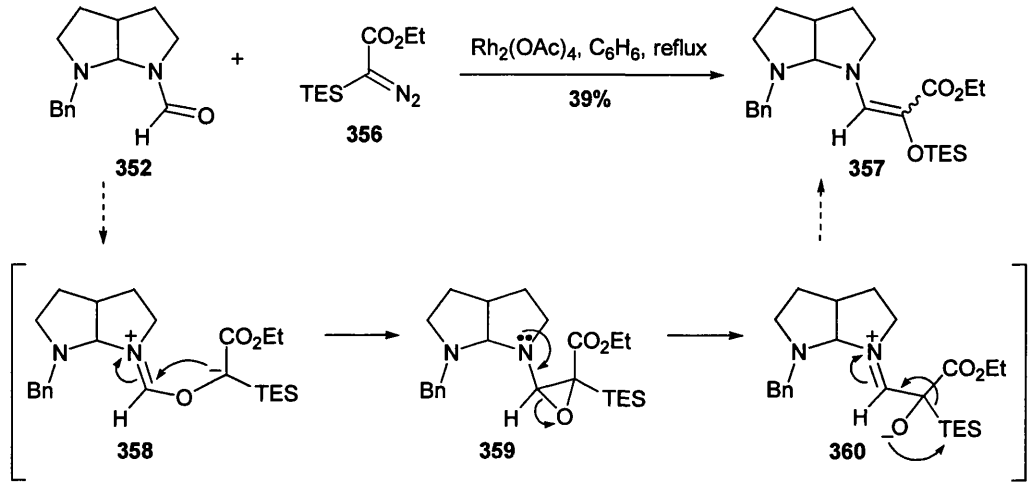
Scheme 95

Porter *et al.*[113] have performed several ring expansions on 1,3-oxathiolanes to give 1,4-oxathianes *via* sulfur ylide intermediates. Their work showed that in these reactions a diazo compound bearing both a silyl and an ester group was superior to ethyl diazoacetate. The presence of the silyl group suppresses the undesirable side reaction of dimerisation that is often observed with metal carbene reactions of ethyl diazoacetate. The undesired reaction of the oxathiane products with excess diazo compound is also suppressed. Therefore we began our ring expansion reactions using ethyl (triethylsilyl)diazoacetate.

No reaction of the bicycle was observed when using $Cu(acac)_2$ (10 mol%) and ethyl (triethylsilyl)diazoacetate (1.2 eq.), the conditions which had previously been found to be optimal with 1,3-oxathiolane substrates. However, consumption of the starting material was observed when the reaction was repeated using $Rh_2(OAc)_4$ as the catalyst. Through a combination of one dimensional ^1H NMR, COSY, and NOE experiments, the major product of this reaction was identified as bicycle **357**.

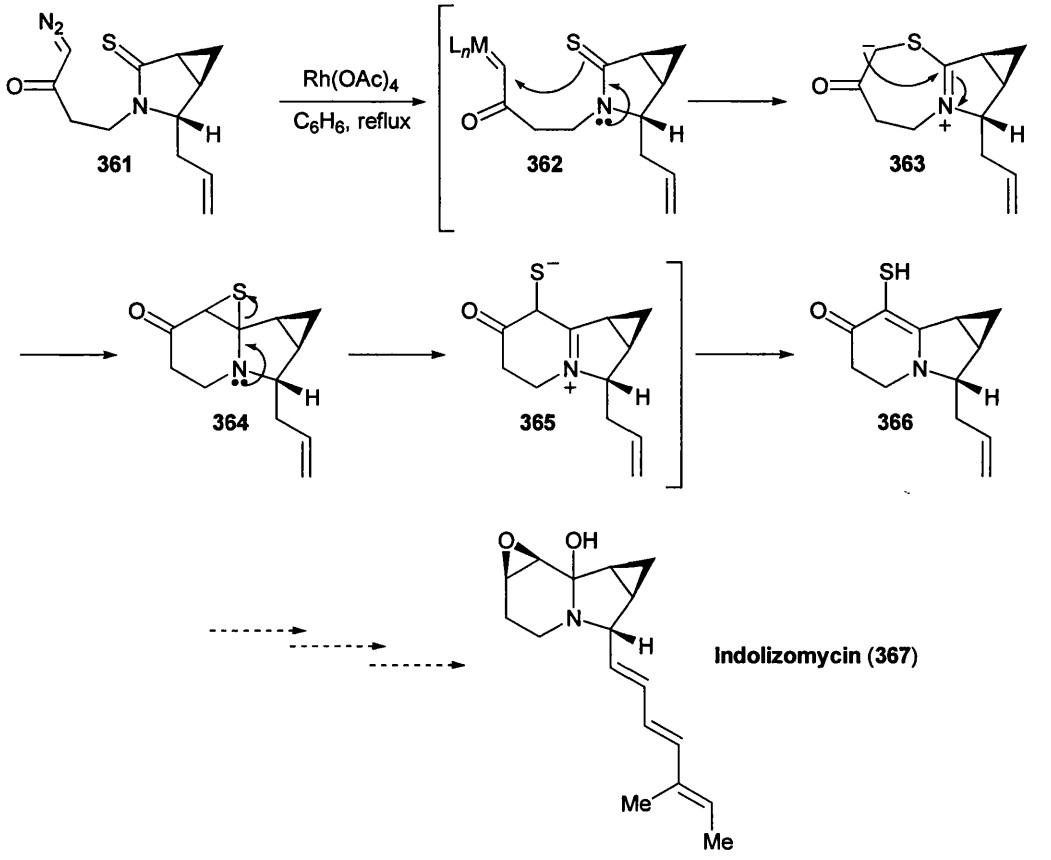
The mechanism of this reaction is presumed to involve the oxygen of the formamide group in aminal **352** reacting with the electron deficient carbene to

generate an oxygen ylide **358**. This ylide undergoes rearrangement *via* epoxide **359** to form silyl enol ether **360** a single geometric isomer (geometry of the double bond in **357** was not assigned) (Scheme 96).



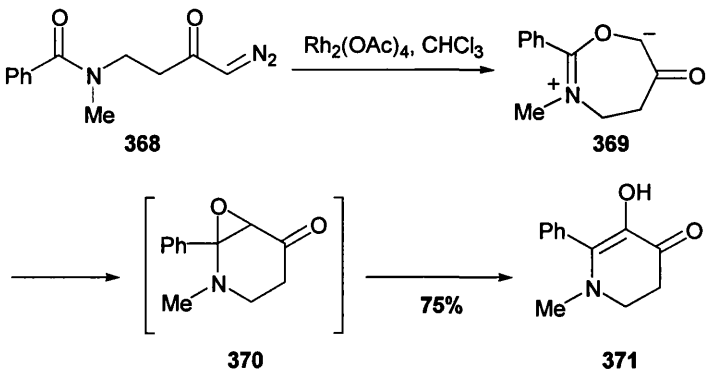
Scheme 96

To the best of our knowledge, this is the first example of an intermolecular reaction of this type. Such rearrangements are somewhat unusual. Danishefsky *et al.*[114] have reported a similar reaction of a thioamide in their synthesis of the antibiotic indolizomycin. Exposure of diazoketone **361** to rhodium(II) acetate led to the formation of the electron-deficient carbene **362**, which reacted with the nearby thiolactam sulfur atom. Ring contraction of the sulfur ylide *via* an episulfide intermediate led to the formation of vinylogous amide **366** (Scheme 97).



Scheme 97

Padwa *et al.*[115] have also reported a similar reaction during their study of acyclic diazo ketoamides prepared from *N*-benzoyl-*N*-alkylaminopropanoic acids. Treatment of **368** with a rhodium(II) catalyst afforded 5-hydroxydihydropyridone **371** in a 75% yield (Scheme 98). The carbonyl ylide **369** from this reaction was suggested to rearrange to form epoxide **370**, which isomerised to the more stable dihydropyridone tautomer **371**.

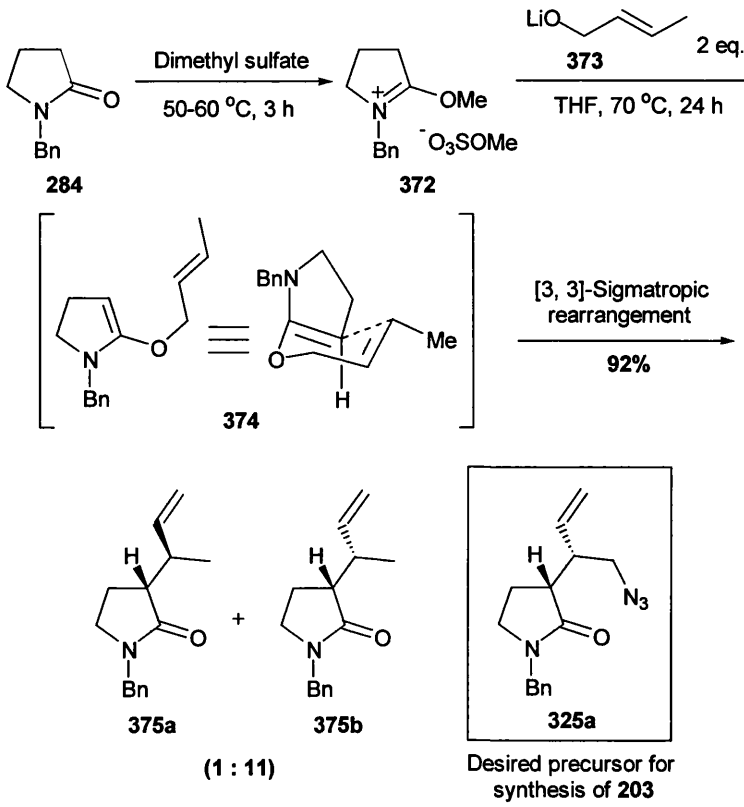


Scheme 98

2.9 Strategy Six: Sigmatropic Rearrangement

Having optimised the cyclisation and protection we decided to investigate a new stereoselective route to azido-lactam **325a**, which we hoped would not give a 2:1 mixture of diastereomers.

Stevenson *et al.*[116] reported an efficient synthesis of 3-substituted and 3,3-disubstituted lactams using a formal Meerwein-Eschenmoser [3,3]-sigmatropic rearrangement. They found that treating *N*-benzylpyrrolidin-2-one with a molar equivalent of dimethyl sulphate and heating to 50-60 °C for three hours generated the methoxymethyleniminium methyl sulfate salt **372** (Scheme 99). On heating with the lithium alkoxide of crotyl alcohol, the generated enamine **374,** underwent a [3,3]-sigmatropic rearrangement (*via* a chair transition state) to give substituted lactams **375a** and **375b** in a 92% yield, in an 11:1 ratio in favour of **375b**.



Scheme 99

Initially, we repeated the reaction reported by Stevenson and co-workers using the alkoxide of crotyl alcohol. The ^{1}H NMR of the crude reaction mixture after work-up showed the presence of both the major diastereomer **375b** and a significant amount of unreacted starting material (ratio of **375b** to *N*-benzyl pyrrolidin-2-one 2:1). Increasing the amount of dimethyl sulfate to 3.4 equivalents did slightly improve this ratio (major diastereomer **375b** to starting material, ratio 2.3:1)

The presence of unreacted starting material was thought to be due to incomplete formation of the iminium salt. Hydyrolysis prevented isolation of the iminium salt, but it was possible to monitor its formation by analysing the ^{1}H NMR of the crude reaction mixture (Figure 18).

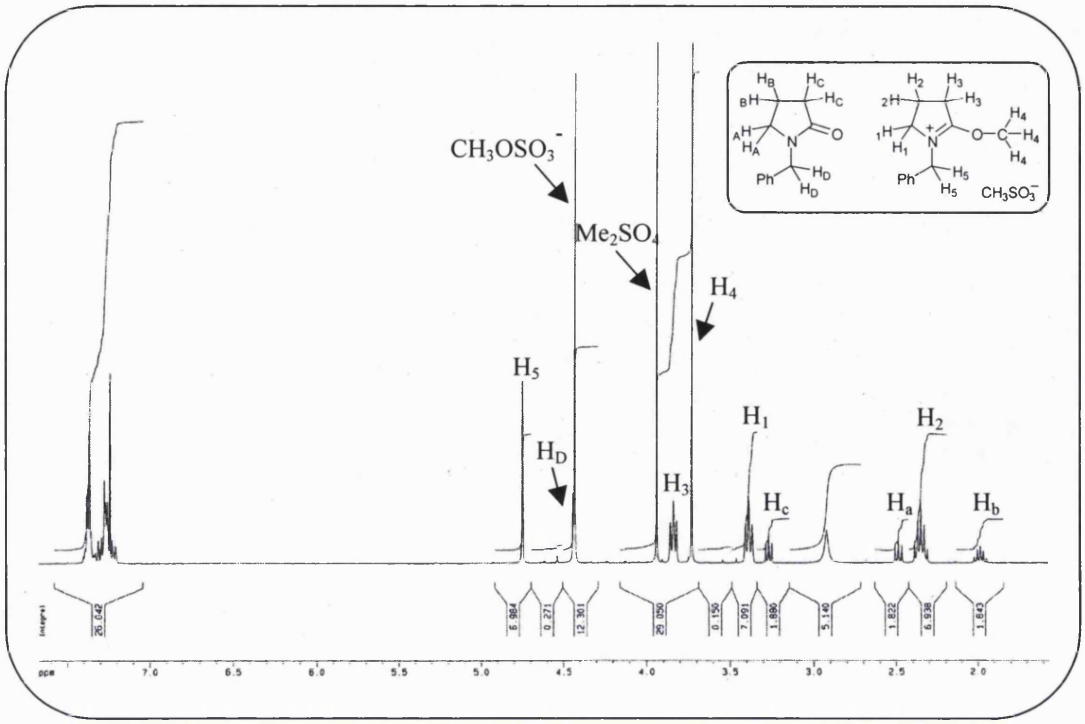
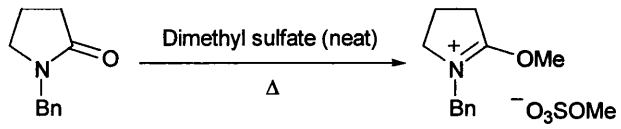


Figure 18. Determination of the ratio of iminium salt to *N*-benzylpyrrolidin-2-one by ^{1}H NMR (400MHz, $CDCl_3$)

The results of the optimisation reactions performed are summarised in Table 12. The addition of powdered molecular sieves to the reaction mixture increased the ratio of iminium salt (entries 5 and 6), while conducting the reaction at higher temperatures made ratios worse (entries 7 and 8). It also appeared that increasing the number of equivalents of dimethyl sulfate increased the ratio in favour of salt formation (entry 3). The optimum time for the reaction was approximately three hours. Taking into account this information, we performed the reaction with a sequential addition of two equivalents of dimethyl sulfate. This gave the best result, a 6:1 ratio of salt to starting material (Scheme 100).

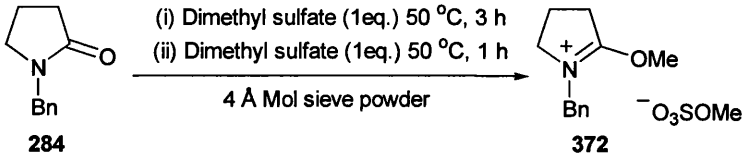


284 **372**

Table 14. Optimisation of salt formation

Entry	Dimethyl sulfate (eq.)[a]	Time (h)	Temperature (°C)	Additives	Ratio of salt to starting material[b]
1	1.2	3	50		2: 1
2	1.2	20	50		1.1: 1
3	2.2	3	50		3.4: 1
4	2.2	3	50		1.3: 1
5	1.2	1.5	50	4 Å Mol sieve powder	2.8: 1
6	1.2	3	50	4 Å Mol sieve powder	3.7: 1
7	1.2	1	90		1: 3.8
8	1.2	3	90		1: 2.2
9	1.0 1.0 (2nd eq.)	3 1	50 50	4 Å Mol sieve powder	6: 1

[a] Dry/distilled; [b] results obtained from ^{1}H NMR of the crude reaction mixture in dry $CDCl_3$



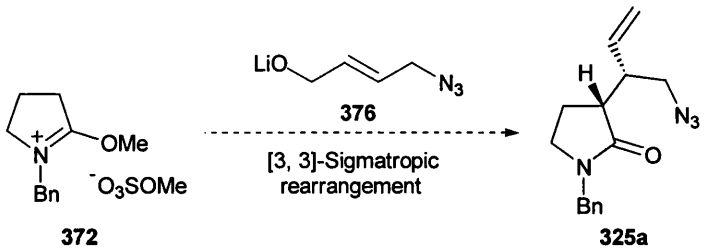
284 **372**

Ratio of salt to starting material 6: 1

Scheme 100

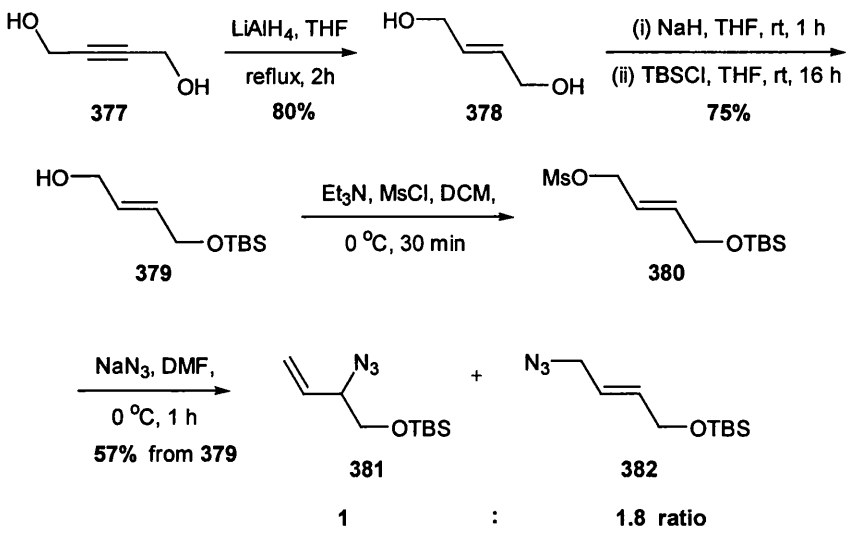
The alkylation of *N*-benzylpyrrolidin-2-one with oxonium salts (Me_3OBF_4/DCM, rt and Et_3OBF_4/DCM, rt) was also investigated, however, these were inferior to dimethyl sulfate for alkylation.

The relative stereochemistry of the major diastereomer **375b** from this reaction (Scheme 99) was identical to that required for our synthesis, while lacking any functionality for the introduction of the azide group. We were curious to see if a modified alkoxide containing an azide group would undergo the same sigmatropic rearrangement (Scheme 101). If successful this would give us azide **325a** in a very short sequence of steps.



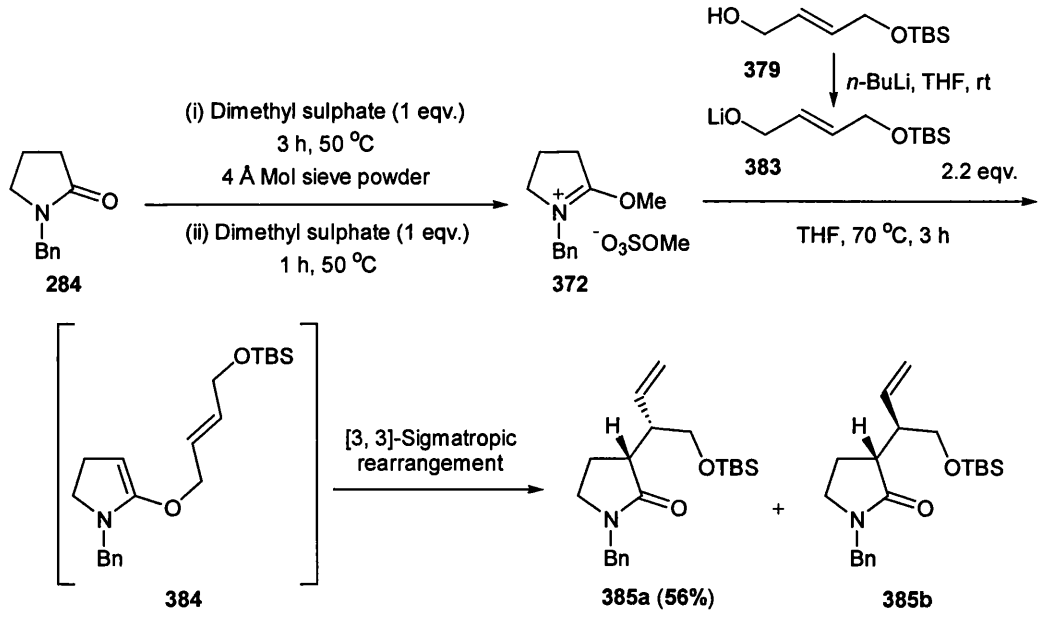
Scheme 101

The method we chose for making the desired alcohol **376** is shown in Scheme 102. Reduction of 2-butyn-1,4-diol with $LiAlH_4$ afforded diol **378**,[117] which was mono-silylated with a *tert*-butyldimethylsilyl group.[118] The remaining free alcohol group was mesylated to afford **380**, which was found to be unstable and had to be used immediately. The mesylation reaction had to be performed at 0 °C, as there was a strong tendency for elimination of the mesyl group to give 1-*tert*-butyldimethylsiloxy-buta-1,3-diene. Displacement of the crude mesylate by sodium azide gave a mixture of two compounds. ^1H NMR spectroscopy confirmed the presence of secondary azide **381** and the desired azide **382**. The origin of the two compounds could be a consequence of a mixture of S_N2 and S_N2' products or the primary azide **382** rearranging to the secondary azide **381**. It was decided to defer the introduction of the azide group until after the sigmatropic rearrangement step.



Scheme 102

Having optimised the salt formation step we performed the sigmatropic rearrangement with the lithium alkoxide of monosilylated alcohol **379** (Scheme 103).

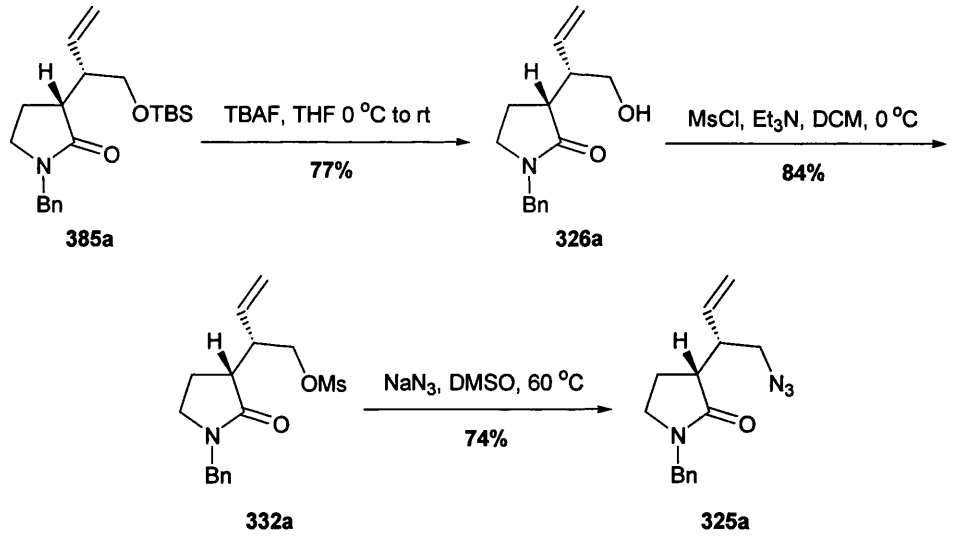


Scheme 103

This reaction gave two diastereomeric products **385a** and **385b**, with the major diastereomer **385a** obtained by flash chromatography in 56% yield. There was

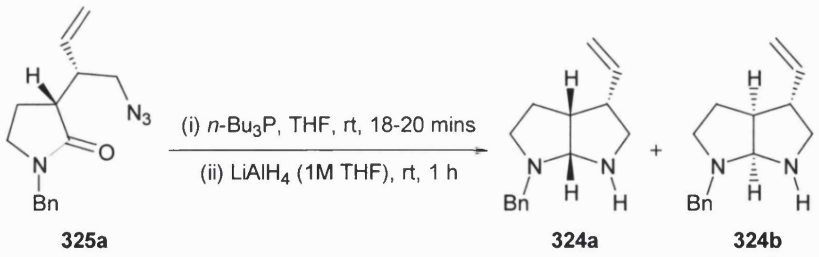
very little of the minor diastereomer formed and we were unable to obtain a clean sample by chromatography. We tentatively assigned the stereochemistry of the major diastereomer based on the results published by Stevenson and co-workers. Repeating this reaction with the lithium alkoxides of (*E*)-but-2-ene-1,4-diol, (*Z*)-but-2-ene-1,4-diol and (*Z*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol gave no reaction and only unreacted *N*-benzyl pyrrolidin-2-one was recovered.

Removal of the TBS group from **385a** by treatment with TBAF afforded alcohol **326a**, which was subsequently converted to mesylate **332a**. Substitution of the mesyl group with an azide gave functionalised lactam **325a** (Scheme 104).



Scheme 104

Azido-lactam **325a** was then cyclised using the conditions developed for the model system (Scheme 105).



Scheme 105

The ^{1}H NMR spectrum of the crude reaction mixture (after work up) showed a mixture of two similar compounds in a ratio of 2:1 (Figure 19). These were assigned as aminals **324a** and **324b**. The coupling constants of 6.3 Hz at δ 4.21 ppm for the major isomer and 6.8 Hz at δ 4.13 ppm for the minor isomer between the ring fusion protons indicated that both compounds had a *cis*-fused ring junction

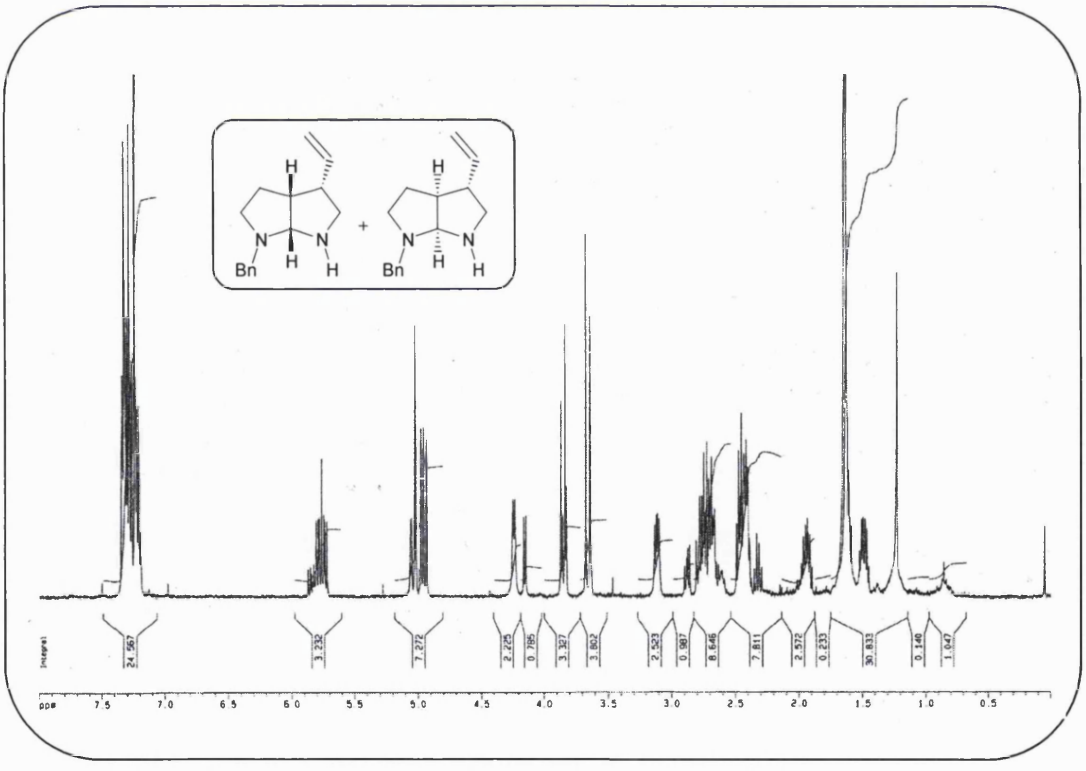
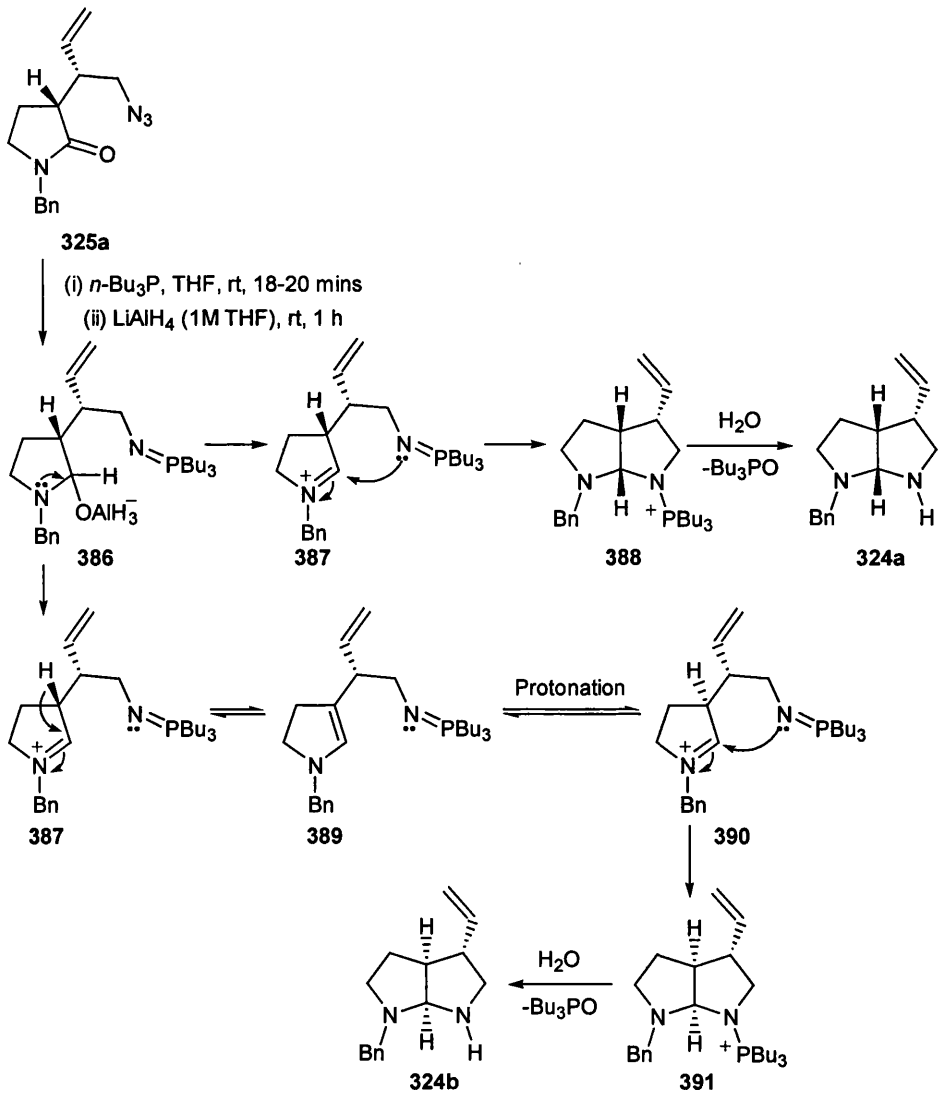


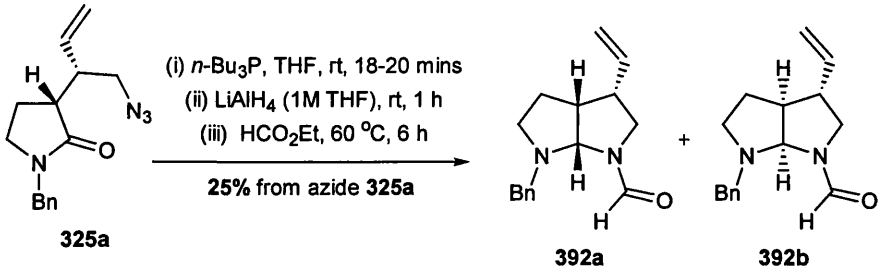
Figure 19. ^{1}H NMR of the mixture of aminals **324a** and **324b** (500 MHz, $CDCl_3$)

The formation of the second aminal was rationalised by the generation of an iminium intermediate **387** (Scheme 106). This can undergo proton loss to give an enamine **389**, which can re-protonate from the top face to regenerate **387** or from the bottom face to give **390**, this would lead to the undesired product **324b**. Alternatively, this equilibration process could take place after the formation of the bicyclic aminal product.



Scheme 106

Since it proved impossible to isolate a clean sample of aminal **324a** by flash chromatography, the crude mixture (containing aminals **324a** and **324b**) was treated with ethyl formate to protect the secondary nitrogen (Scheme 107).



Scheme 107

The proton NMR spectrum of the crude reaction mixture of the protected aminals (**392a** and **392b**) indicated that the ratio of bicycles had changed from 2:1 to 4:1 during the protection step. The mixture was purified by flash chromatography on alumina, but we were unable to separate the individual isomers **392a** and **392b**; the ^{1}H NMR spectrum is shown in Figure 20.

The coupling constants of 6.6 Hz at δ 4.83 ppm for the major isomer and 6.0 Hz at δ 4.71 ppm for the minor isomer between the ring fusion protons indicated that both compounds had a *cis*-fused ring junction. However, we were unable to ascertain the relative stereochemistry of any of the products obtained from the protection step by NMR experiments.

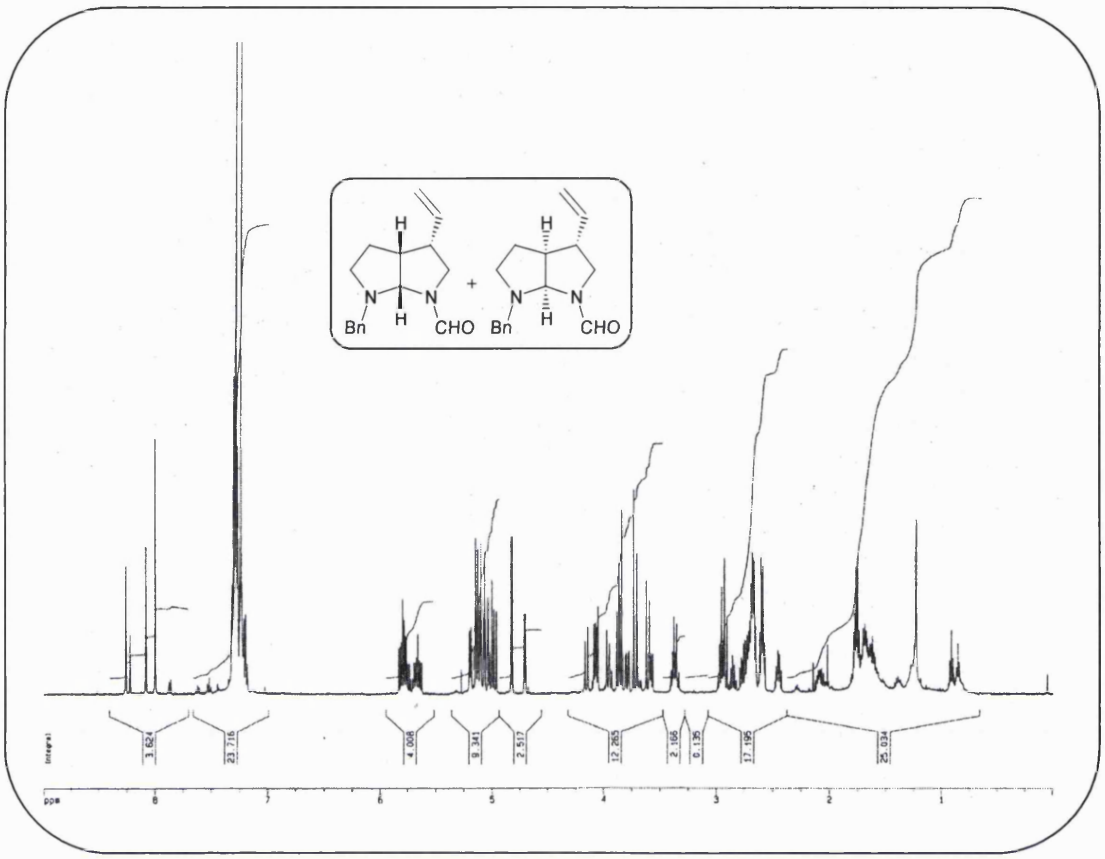


Figure 20. ^{1}H NMR of protected aminals **392a** and **392b** (500 MHz, $CDCl_3$)

At this point in our research, we have successfully managed to construct the target framework towards the synthesis of the sarain core. However, it seems likely that control of pH in the cyclisation and protection steps may be important in minimising loss of stereochemical integrity. This concluded our studies towards the core structure of sarains A-C.

Chapter Three

CONCLUSION

This project has been very challenging, the lack of literature on construction of octahydropyrrolo[2,3-*b*]pyrrole ring systems has also contributed to making this an extremely difficult project. As a consequence of this, several routes towards the construction of bicyclic acid **203** were investigated.

Initially we investigated the possibility of deprotonating *cis*-fused hexahydro-isoindole at the α-position and using trisyl azide as an electrophilic source of azide for introduction of an azide functionality. Unfortunately, it became apparent that in our system α-lithiation was not taking place and it was not possible to construct bicycle **203** by this strategy.

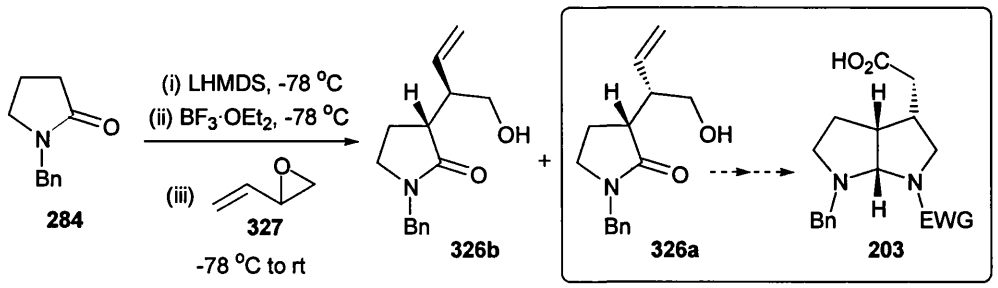
Next we investigated the possibility of forming α-amino-β-iodopyrrolidines *via* an *N*-iodosuccinimide-promoted amine addition to an enamide, using a procedure originally used for the formation of α-alkoxy-β-iodopyrrolidines. We had envisioned that the functionalised pyrrolidines from this reaction would undergo free radical cyclisation to afford an aminal, which could be transformed into bicycle **203**. Unfortunately, we were unable to induce amine addition using the literature conditions and had to pursue another route towards the construction of bicycle **203**.

Next we attempted to construct cyclic amidines. It was anticipated that these could at a later stage be reduced to form octahydropyrrolo[2,3-*b*]pyrrole ring systems. We were able to successfully make an acyclic amidine by reacting allylamine with *N*-benzylpyrrolidin-2-one using phosphorus oxychloride to generate the chloroiminium ion intermediate. However, we were unable to incorporate a free

radical group, such as a halogen or SePh group into the 3-position of the lactam ring for cyclisation, and so had to abandon this route.

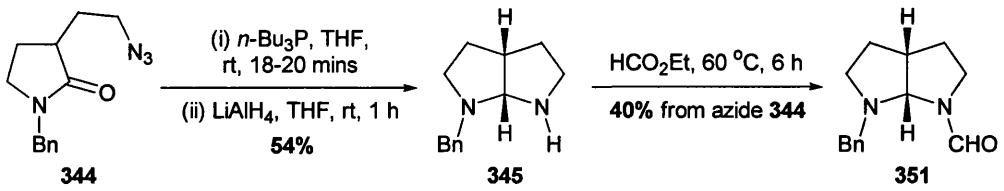
In the next strategy we investigated the Diels-Alder reaction between 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene and an *N*-protected-pyrrolin-2-one dienophile. We were unsuccessful in initiating a thermal or a Lewis acid catalysed Diels-Alder reaction using these reactants.

In the next route, the opening of butadiene monoxide by the enolate of *N*-benzylpyrrolidin-2-one gave a mixture of diastereomeric alcohols (**326a** and **326b**) (Scheme 108). One of these diastereomers contained the correct relative stereochemistry that could be further functionalised to give bicyclic acid **203**. Unfortunately the yield of the products from this reaction was very low and separation of the individual diastereomeric alcohols proved to be very difficult.



Scheme 108

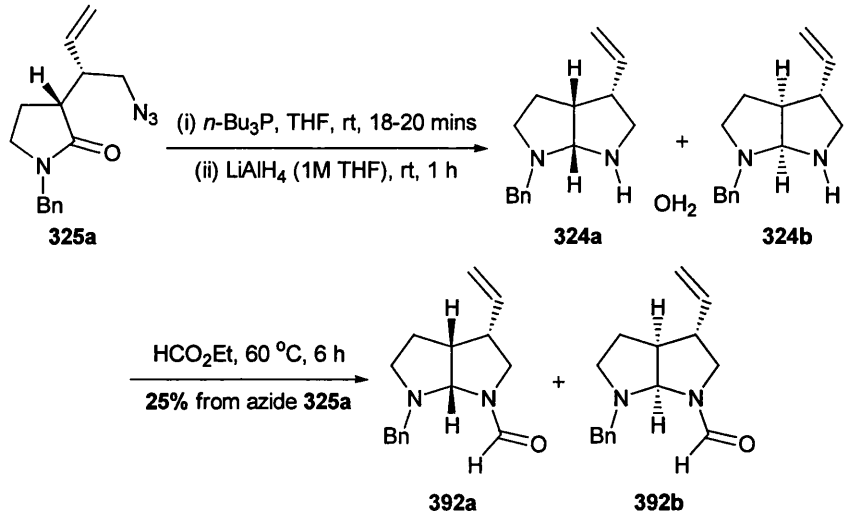
We decide to continue work using a model system approach. By removing the vinyl side chain in alcohols **326a** and **326b,** we would avoid the problems associated with separation of diastereoisomers. During work on this model system we successfully generated the azido-lactam **344**, which was used to probe the conditions required for reductive cyclisation of an azide side chain with an amide to form an aminal (Scheme 109).



Scheme 109

Several reducing agents were investigated for this reaction, but its was discovered that exposure of lactam **344** to *n*-Bu_3P and $LiAlH_4$ successfully gave *cis*-fused bicyclic aminal **345**, which contained the octahydropyrrolo[2,3-*b*]pyrrole ring system. Aminal **345** was produced in a 54% yield and protection of the secondary nitrogen in this aminal with a formamide-protecting group gave the fully protected aminal **351**.

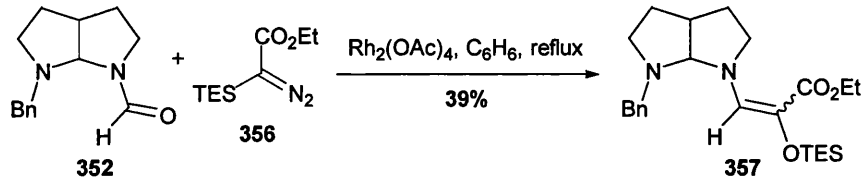
A moderately efficient route, which used a [3,3] -sigmatropic rearrangement for the construction of azido-lactam **325a**, was discovered. Lactam **325a** contained the correct relative stereochemistry required for the assembly of bicycle **203**.



Scheme 110

The application of the cyclisation conditions obtained from the model system on azido lactam **325a** led to a mixture of diastereomeric aminals **324a** and **324b**, these were protected to give aminals **392a** and **392b** (Scheme 110). We were unable to separate any of the diastereomeric aminals.

Aminal **351** obtained from the work on the model system, was used to probe an intermolecular version of the rearrangement intended for the construction of the sarain core (real system) (Scheme 111). Exposure to protected aminal **351** with ethyldiazo(triethylsilyl)acetate and a rhodium(II) catalyst in refluxing benzene gave unexpectedly, silyl enol ether **357** as the major product. We believe that the mechanism of this reaction is by rearrangement of a carbonyl ylide (instead of the intended nitrogen ylide), *via* reaction of the metal carbene with the carbonyl of the formamide protecting group.



Scheme 111

This unexpected rearrangement would not be possible in the intramolecular metal carbene reaction planned for the synthesis of bicycle **203**, as the orientation of the diazoketone side chain would only bring it in close proximity with the nucleophilic nitrogen in the aminal.

In conclusion, several routes towards the construction of the core structure of sarains A-C were attempted. We have developed a route to forming the octahydropyrrolo[2,3-*b*]pyrrole ring system by reductive cyclisation of an azide side chain with an amide carbonyl and applied it for the construction of two protected

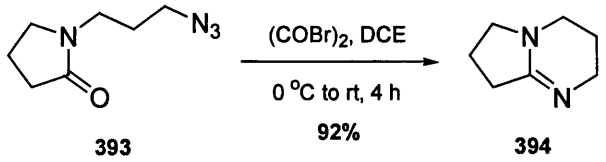
aminals (**352** and **392a**) The target framework needed to explore the cyclisation chemistry for construction of the sarain core has been constructed.

Chapter Four

FUTURE PERSPECTIVES

Future work would firstly involve the confirmation of the relative stereochemistry of azido-lactam **325a** by derivatisation. The optimised conditions for cyclisation of azido-lactam **325a** using the conditions obtained from the model system need to be adjusted to exclusively give a single aminal product. In particular, factors, which promote the formation of an iminium species, need to be investigated.

Other cyclisation protocols need to be examined. Shibasaki and co-workers[119] have recently reported an efficient synthesis of bicyclic amidines from tethered azido-lactams *via* an intramolecular cyclisation, a reaction that we had previously attempted in Strategy three. Shibasaki and co-workers screened various reagents for activation of the amide group in **393**; Ph_3P, Bu_3P, $POCl_3$ and PCl_5 gave very poor yields of **394** (Scheme 109). However, exposure of **393** to oxalyl bromide in 1,2-dichloroethane led to the clean formation of bicyclic amidine **378** (1,5-diazabicyclo[4.3.0]non-5-ene, DBN) in a 92% yield.

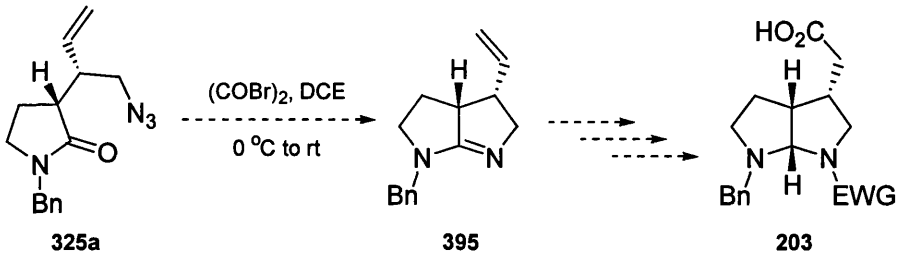


393 394

Scheme 112

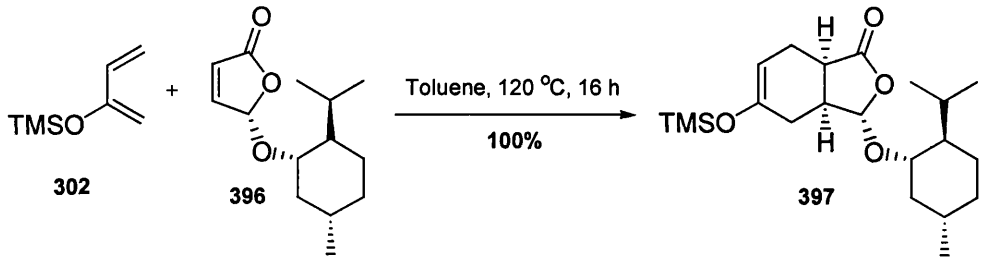
It would be very interesting to observe whether the conditions outlined by Shibasaki and co-workers would induce cyclisation of the azido-lactam **325a** to generate amidine **395** (Scheme 113). If successful the amidine formed from this

reaction could be transformed to the desired bicyclic acid **203** in a relatively short number of steps.



Scheme 113

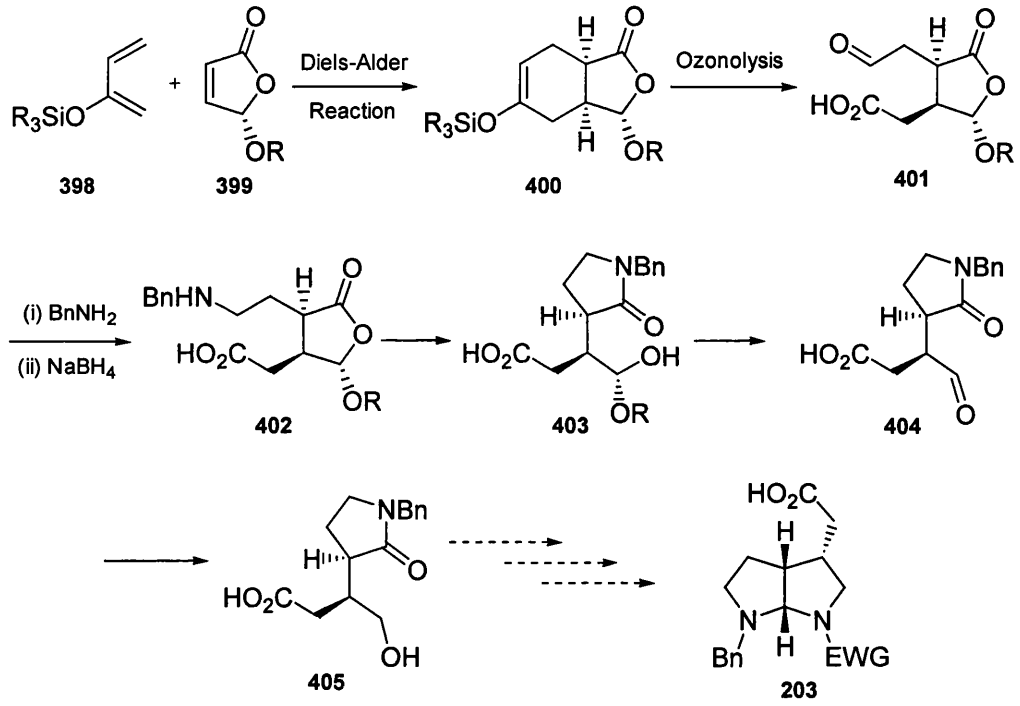
Finally further work on the Diels-Alder strategy to the sarain core is required. Feringa and co-workers[120] have reported the development of chiral dienophiles for use in thermal Diels-Alder reactions. Enantiomerically pure furanones bearing bulky alkoxy substituents in the C_5 position were generated. These groups were found to essentially shield one of the π-faces of the dienophile in the *endo* transition state, leading to high selectivity. Dienophile **396** bearing a menthyloxy substituent underwent a thermal Diels-Alder reaction with the silyloxy-substituted diene **302** to afford bicycle **397** as a single diastereomer (Scheme 114).



Scheme 114

Interestingly, a similar reactant to **396** could be used as a starting material for the synthesis of bicyclic acid **203**. Oxidative cleavage of the ring olefin in bicycle

400 would afford lactone **401** (Scheme 115). Reductive amination of **401** using benzylamine, followed by reduction with $NaBH_4$ would initiate cyclisation of the amine onto the lactone carbonyl to give lactam **403**. The hemiacetal in **403** would intern undergo reduction *via* aldehyde **404** to afford alcohol **405**. Alcohol **405** could then be converted to bicycle **203** in a similar manner as in Strategy five (mesylation, azide substitution followed by intramolecular cyclisation of an azide with an amide carbonyl).



Scheme 115

Chapter Five

EXPERIMENTAL

5.1 General Experimental Procedures

Melting points were obtained using a Reichert-Jung thermovar hot stage apparatus and are uncorrected.

Proton NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet and br, broad. Coupling constants are recorded in Hertz to the nearest 0.1 Hz.

Carbon-13 NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on a Bruker AMX400 spectrometer or 125 MHz on Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak.

NOE experiments were recorded on a Bruker AVANCE500 spectrometer.

Infrared spectra were recorded as $CDCl_3$ casts on a SHIMADZU FT-IR 8700 Fourier transform spectrometer. Major Features of each spectrum are reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

Low-resolution and high-resolution mass spectra were recorded by the University of London Intercollegiate Research Service and by John Hill (UCL chemistry department service). Low-resolution mass spectra were recorded on a Micromass 70-SE spectrometer and a Micromass ZAB-SE spectrometer using chemical ionisation (CI), electron impact (EI), fast atom bombardment (FAB) or

electrospray (esp). Mass spectra marked * were obtained using a Micromass ZAB-SE spectrometer at The University of London School of Pharmacy. Only molecular ions, fragments from molecular ions and major peaks are reported. High-resolution mass spectra were recorded on a Micromass 70-SE spectrometer.

Microanalyses were performed by Mrs. J. Maxwell, Christopher Ingold Laboratories on a Perkin Elmer 2400 CHN elemental analyser.

Flash chromatography was carried out on BDH silica gel (40-63 μm) or neutral aluminium oxide (deactivated with 6% wt% water (Grade III), 50-200 m). Thin layer chromatography was performed on pre-coated, aluminium-backed normal phase Merck gel 60 F_{254} silica plates. Components were visualised by the quenching of u.v. fluorescence (λmax 254 nm) as well as staining with iodine, vanillin, potassium permanganate or phosphomolybdic acid, all followed by heat.

Preparative thin layer chromatography was performed on pre-coated (glass), normal phase Merck gel 60 F_{254} (0.25mm layer thickness) silica plates.

All reactions in non-aqueous solution were performed under an inert atmosphere of nitrogen, using anhydrous solvents. All glassware was oven-dried (120 °C) and the glassware used for moisture sensitive reactions were flame dried and cooled under a nitrogen atmosphere prior to use.

All solvents were distilled before use. Anhydrous dichloromethane, benzene . *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and diisopropylamine were obtained by distillation from calcium hydride under a nitrogen atmosphere. Anhydrous diethyl ether and anhydrous THF were obtained by distillation from sodium/benzophenone ketyl under a nitrogen atmosphere. Anhydrous dimethyl sulfoxide, dimethyl sulfate and *N,N*-dimethyformamide were obtained by stirring over calcium hydride followed by distillation under reduced pressure. Anhydrous methyl vinyl ketone was obtained by distillation under reduced pressure (stored over

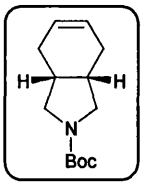
activated 4 Å molecular sieves). Petroleum ether 40-60 refers to the fraction of light petroleum ether boiling between 40-60 °C. Solvents were evaporated at 30 °C or below on a Büchi RE111 rotavapor. All other reagents were purified in accordance with the methods described in D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Pergamon Press, Third edition, 1988 or used as obtained from commercial sources.

Chemicals were purchased from Sigma-Aldrich Co. Ltd., Lancaster, Fluka, Acros and Avocado.

5.2 Experimental Procedures

5.2.1 Strategy One: Electrophilic Azidation

Synthesis of cis-*2*-tert-*butyloxycarbonyl-1,3,3a,4,7,7a-hexahydroisoindole* (**242**)[83,121]



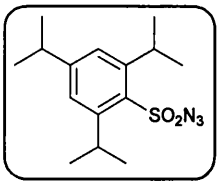
To a stirred slurry of lithium aluminium hydride (1.48 g, 39 mmol) in THF (15 mL), was added a solution of *cis*-1,2,3,6-tetrahydrophthalimide (3.93 g, 26 mmol) in THF (40 mL) dropwise, at such a rate that the solvent in the flask maintained a gentle reflux. After addition was complete the reaction mixture was heated to reflux for 35 hours. The mixture was cooled to room temperature and excess lithium aluminium hydride was decomposed by the dropwise addition of a solution of water (3 mL) in THF (10 mL). The grey mixture was diluted with diethyl ether (30 mL) and the precipitate was removed by filtration. The precipitate was washed with diethyl ether (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*, to afford cis-*2,3,3a,4,7,7a-hexahydro-(1*H*)-isoindole* (**241**, 2.60 g) as a orange oil. δ_H (300 MHz; $CDCl_3$) 1.82-1.94 (2H, m, 2 x CH_2CHCH_2), 2.14-2.20 (4H, m, $CH_2HC{=}CHCH_2$), 2.62-2.68 (2H, m, 2 of H_2CNCH_2), 2.98-3.04 (2H, m, 2 of H_2CNCH_2), 5.66 (2H, br s, *HC*=C*H*); δ_C (75 MHz; $CDCl_3$) 25.3 (2 x CH_2CHCH_2)), 30.8 ($CH_2HC{=}CHCH_2$), 52.3 (CH_2NCH_2), 126.4 (HC=CH).

Crude *cis*-2,3,3a,4,7,7a-hexahydro-(1*H*)-isoindole (2.60 g, 21 mmol) was stirred with di-*tert*-butyl dicarbonate (5.13 g, 24 mmol), 4-dimethylaminopyridine (0.61 g, 5 mmol) and triethylamine (2.95 mL, 21 mmol) in dichloromethane (75 mL) at room temperature for 50 hours. The reaction mixture was diluted with diethyl ether (120 mL), washed with hydrochloric acid (2M, 30 mL), saturated aqueous potassium carbonate (30 mL), and saturated aqueous sodium chloride (30 mL). The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash

chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:19) afforded cis-*2*-tert-*butyloxycarbonyl-1,3,3a,4,7,7a-hexahydroisoindole* (**242**, 2.78 g, 48% from *cis*-1,2,3,6-tetrahydrophthalimide) as a brown oil.

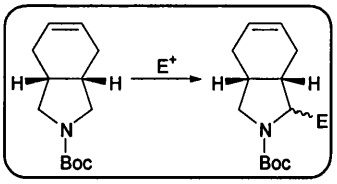
ν_{max} ($CDCl_3$ cast)/cm^{-1} 3024s (sp^2 C-H), 2884s (sp^3 C-H), 1680s (C=O), 1659m (C=C), 1475m, 1456m, 1334m; δ_H (400 MHz; $CDCl_3$) 1.42 (9H, s, $C(CH_3)_3$), 1.85-1.90 (2H, m, 2 x CH_2CHCH_2), 2.16-2.29 (4H, m, $CH_2HC{=}CHCH_2$), 3.04 (1H, dd, *J* 10.2, 6.2 Hz, 1 of H_2CNCH_2), 3.13 (1H, dd, *J* 10.4, 4.9 Hz, 1 of H_2CNCH_2), 3.33-3.69 (2H, m, 2 of H_2CNCH_2), 5.61 (2H, br s, *H*C=C*H*); δ_C (100 MHz; $CDCl_3$) 24.6 and 24.7 (2 x CH_2CHCH_2), 28.5 ($C(CH_3)_3$), 33.0 and 34.2 ($CH_2HC{=}CHCH_2$), 50.8 and 50.9 (CH_2NCH_2), 78.9 ($C(CH_3)_3$), 124.2 and 124.5 (HC=CH), 155.2 ($N\underline{C}O_2$); *m/z* (FAB) 224 (MH^+, 7%), 206 (7), 168 (MH^+ - ^{t}Bu, 100), 150 (10), 122 (12); HRMS calculated for $C_{13}H_{22}NO_2$ (MH^+) 224.1663, observed 224.1651.

Synthesis of 2,4,6-triisopropylbenzenesulfonyl azide (Trisyl Azide)[122]



2,4,6-Triisopropylbenzenesulfonyl chloride (2.04 g, 6.0 mmol) was added to a solution of sodium azide (1.46 g, 22 mmol) in 96 % aqueous ethanol (45 mL). The mixture was stirred at room temperature for 30 hours, then diluted with ice-cold water (20 mL) and extracted with diethyl ether (60 mL). The organic extract was washed with saturated aqueous sodium chloride (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallisation from methanol gave *2,4,6-triisopropylbenzenesulfonyl azide* (0.86 g, 42%) as white crystals.

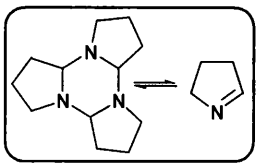
General procedure for lithiation and substitution of cis-*2*-tert-*butyloxycarbonyl-1,3,3a,4,7,7a-hexahydroisoindole*



A solution of *cis*-2-*tert*-butyloxy- carbonyl-1,3,3a,4,7,7a-hexahydroisoindole (**242**, 0.25 g, 1.1 mmol) in diethyl ether (2.3 mL) was cooled to –78 °C and treated with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (0.13 g, 1.1 mmol), followed by the dropwise addition of *sec*-butyllithium (1.3 M solution in cyclohexane, 1.1 mL, 1.4 mmol). The mixture was stirred for 30 minutes at –78 °C, and a solution of the electrophile (1.4 mmol) in diethyl ether (1 mL) was added dropwise. The resulting solution was then warmed to room temperature and stirred for 30 minutes. Water (6 mL) was added, followed by diethyl ether (10 mL) and the organic layer was separated. The aqueous layer was extracted further with diethyl ether (4 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

5.2.2 Strategy Two: Cyclisation of α-amino-β-iodopyrrolidines

Synthesis of 1-pyrroline (**269**)[123]



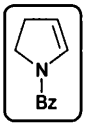
A solution of sodium persulfate (167.4 g, 0.7 mol) in water (500 mL) was added dropwise to a stirred mixture of pyrrolidine (50.0 g, 0.7 mol), sodium hydroxide (56.2 g, 1.4 mol) and silver nitrate (0.60 g, 4.0 mmol) in water (700 mL) at 0 °C and then stirred at room temperature for 2.5 hours. The mixture was then saturated with sodium chloride, extracted with dichloromethane (1.5 L). The extract was dried ($MgSO_4$), filtered and the filtrate was evaporated under reduced pressure at 0 °C.

Diethyl ether (75 mL) was added and the red/brown precipitate formed was removed by filtration. The solvent was evaporated under reduced pressure at 0 °C to give an orange oil. Elution of the product through a neutral alumina column with diethyl ether followed by evaporation of the solvent afforded *1-pyrroline* as a yellow oil (**269**, 20.2 g, 42%).

^{1}H NMR and ^{13}C NMR suggest that the major product formed from the reaction was the monomeric-1-pyrroline, with a small amount of the 1-pyrroline trimer being present (**268**). ν_{max} ($CHCl_3$ cast)/cm^{-1} 3364br, 2922s (sp^2 C-H), 2852m (sp^3 C-H), 1634w (C=N), 1461w; δ_H (300 MHz; $CDCl_3$) 1.68-1.78 (2H, m, NCH_2CH_2), 2.43-2.49 (2H, m, $N{=}CHCH_2$), 3.75-3.82 (2H, m, NCH_2), 7.55 (1H, s, N=C*H*); δ_C (75 MHz; $CDCl_3$) 20.5 (NCH_2CH_2), 36.6 ($N{=}CHCH_2$), 61.2 (NCH_2), 166.8 (N=*C*H); *m/z* (EI) 69 (MH^+, 100%), 68 (M^+, 40); HRMS calculated for C_4H_7N (MH^+) 69.0570, observed 69.0578.

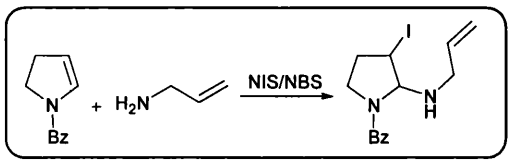
*Synthesis of 1-benzoyl-2,3-dihydro-(1*H*)-pyrrole* (**271**)

A solution of 1-pyrroline (**269**, 2.0 g, 9.6 mmol) in benzene (40 mL) was added dropwise to a solution of benzoyl chloride (3.4 mL, 29 mmol) and *N*-ethyldiisopropylamine (5.0 g, 29 mmol) in benzene (13 mL) and the mixture was heated to reflux. After 20 minutes the reaction mixture was allowed to cool to room temperature, diluted with dichloromethane (40 mL), washed with water (20 mL) and extracted with dichloromethane (40 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a purple liquid. Elution of the product through a neutral alumina column using ethyl acetate/petroleum ether 40-60 (1:4) afforded *1-benzoyl-2,3-dihydro-(1*H*)-pyrrole* as a yellow oil (**271**, 3.05 g, 61%).



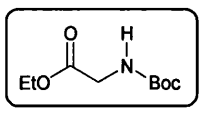
ν_{max} ($CHCl_3$ cast)/cm^{-1} 2951s (sp^2 C-H), 2883s (sp^3 C-H), 1640m (C=C), 1620m (C=O), 1582m, 1420m, 1377w; δ_H (300 MHz; $CDCl_3$) (major rotamer) 2.64-2.71 (2H, m, NCH_2CH_2), 3.99 (2H, t, *J* 8.7 Hz, NCH_2), 5.15 (1H, s, NCH=CH), 6.41 (1H, s, NCH=CH), 7.39-7.49 (5H, m, aromatic CH); δ_C (75 MHz; $CDCl_3$) 28.3 (NCH_2CH_2), 45.6 (NCH_2), 111.6 (NCH=CH), 128.2, 128.3 and 130.2 (aromatic CH), 130.6 (ipso C), 135.8 (NCH=CH), 166.9 (C=O); *m/z* (FAB) 174 (MH^+, 100%), 154 (21); HRMS calculated for $C_{11}H_{12}NO$ (MH^+) 174.0915, observed 174.0919.

General procedure for NBS/NIS promoted amine addition to 1-benzoyl-2,3-dihydro-(1H)-pyrrole



N-Iodosuccinimide or *N*-bromo-succinimide (0.7 mmol) was dissolved in dichloromethane (5 mL) and the solution was cooled to –78 °C. A solution of 1-benzoyl-2,3-dihydro-(1*H*)-pyrrole (**271**, 0.1 g, 0.6 mmol) in dichloromethane (1 mL) was added dropwise. A solution of allylamine (0.7 mmol) in dichloromethane (1 mL) was then added dropwise and the resulting mixture was stirred at –78 °C for 10 minutes. The solution was then poured into cold saturated aqueous sodium hydrogen carbonate (5 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Synthesis of N-tert-*butoxycarbonylglycine ethylester* (**278**)[124]



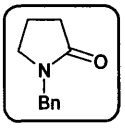
A solution of triethylamine (5.0 mL, 35.8 mmol) in *N,N*-dimethyformamide (40 mL) was added to glycine ethyl ester hydrochloride (2.0 g, 14.3 mmol) and the resulting slurry was heated to 60 °C. A

solution of di-*tert*-butyl dicarbonate (3.44 g, 15.8 mmol) in *N,N*-dimethyformamide (5 mL) was added dropwise and the resulting solution was stirred at 60 °C for 30 minutes and then allowed to cool to room temperature. The pale yellow solution was concentrated *in vacuo*. The solid residue was dissolved in water (50 mL) and extracted with dichloromethane (200 mL). The aqueous phase was extracted further with dichloromethane (3 x 80 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:4) afforded N-tert-*butoxycarbonylglycine ethylester* (**278**, 2.22 g, 76%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3369br (NH), 2980s (sp^3 C-H), 1738s (C=O), 1682s (NC=O), 1578m, 1367m, 1167m; δ_H (400 MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.43 (9H, s, $C(CH_3)_3$), 3.87 (2H, d, *J* 5.4 Hz, NCH_2CO_2), 4.19 (2H, q, 7.1 Hz, OCH_2CH_3), 4.97 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 28.2 ($C(CH_3)_3$), 42.4 (NCH_2CO_2), 61.2 (OCH_2CH_3), 79.8 ($C(CH_3)_3$), 155.7 (NCO_2), 170.3 ($CO_2CH_2CH_3$); *m/z* (FAB) 204 (MH^+, 100%), 195 (85); HRMS calculated for $C_9H_{18}NO_4$ (MH^+) 204.1227, observed 204.1236.

5.2.3 Strategy Three: Formation of a Bicyclic Amidine

Synthesis of 1-benzylpyrrolidin-2-one (**284**)[125]

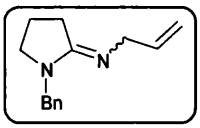


A solution of pulverised potassium hydroxide (5.9 g, 0.1 mol) and tetra-*N*-butylammonium chloride (4.3 g, 15.0 mmol) in THF (70 mL) was added to a 250 mL three-neck round bottom flask fitted with a mechanical stirrer and immersed in an ultrasonic bath. A solution of benzyl bromide (18.2 g, 0.1 mol) and pyrrolidin-2-one (9.0 g, 0.1 mol) in THF (70 mL) was added over 1 hour at room temperature. After the addition, the reaction mixture was stirred for 1 hour in an

ultrasonic bath at room temperature. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to leave an oil. Upon addition of diethyl ether the phase transfer catalyst crystallised out of the solution and was removed by filtration. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:1) afforded *1-benzylpyrrolidin-2-one* as a colourless oil (**284**, 10.8 g, 58%).

ν_{max} ($CDCl_3$ cast)/cm^{-1} 3030s (aromatic C-H), 2917m (sp^3 C-H), 1651s (C=O), 1604m, 1495m, 1464m; δ_H (300 MHz; $CDCl_3$) 1.94 (2H, quin, *J* 7.2 Hz, CH_2CH_2NBn), 2.39 (2H, t, *J* 7.2 Hz, $NCOCH_2$), 3.22 (2H, t, *J* 7.1 Hz, CH_2NBn), 4.41 (2H, s, NCH_2Ph), 7.20-7.33 (5H, m, aromatic CH); δ_C (75 MHz; $CDCl_3$) 17.5 (NCH_2CH_2), 30.7 ($NCOCH_2$), 46.5 (NCH_2CH_2), 46.5 (NCH_2Ph), 127.5, 127.9 and 128.4 (aromatic CH), 136.4 (ipso C), 174.6 (NC=O); *m/z* (FAB) 176 (MH^+ 100%); HRMS calculated for $C_{11}H_{14}NO$ (MH^+) 176.1070, observed 176.1075.

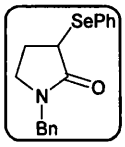
Synthesis of allyl[1-benzyl-pyrrolidin-2-ylidene]amine (**285**)[95]



A solution of 1-benzylpyrrolidin-2-one (**284**, 0.50 g, 2.9 mmol) in benzene (2 mL) was added dropwise to a solution of phosphorus oxychloride (0.24 mL, 2.6 mmol) in benzene (1 mL). The resulting solution was stirred at room temperature for 2 hours then left to stand overnight. Allylamine (0.15 g, 2.6 mmol) in benzene (1 mL) was added dropwise and then the solution was stirred at 60-75 °C for 8 hours. Water (2 mL) was added and the solution was extracted with benzene (5mL). The aqueous layer was made alkaline with aqueous sodium hydroxide (2M) and extracted further with benzene (5 mL). The combined benzene extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford *allyl[1-benzyl-pyrrolidin-2-ylidene]amine* as a brown oil (**285**, 0.734 g) which was used without further purification.

ν_{max} ($CDCl_3$ cast)/cm^{-1} 3420br, 3063m (sp^2 C-H), 2926m (sp^3 C-H), 1668br s (C=N, C=C), 1495w, 1107w; δ_H (300 MHz; $CDCl_3$) 1.88 (2H, quin, *J* 7.4 Hz, CH_2CH_2NBn), 2.48 (2H, t, *J* 8.0 Hz, $N{=}CCH_2$), 3.13 (2H, t, *J* 7.0 Hz, CH_2NBn), 3.85 (2H, dt, *J* 5.2, 1.5 Hz, $C{=}NCH_2$), 4.57 (2H, s, CH_2Ph), 4.99 (1H, dq, *J* 10.4, 1.8 Hz, 1 of $CH{=}CH_2$), 5.14 (1H, dq, *J*=17.1, 1.8 Hz, 1 of $CH{=}CH_2$), 5.91 (1H, ddt, *J*=17.2, 10.3, 5.2 Hz, $CH{=}CH_2$), 7.10-7.30 (5H, m, aromatic CH); δ_C (75 MHz; $CDCl_3$) 19.5 ($BnNCH_2CH_2$), 26.9 ($CH_2C{=}N$), 48.4, 48.9 and 52.5 (CH_2NCH_2Ph, $CH_2CH{=}CH_2$, and NCH_2Ph), 114.2 ($HC{=}CH_2$), 127.2, 128.2 and 128.5 (aromatic CH), 128.7 (ipso C), 137.3 ($HC{=}CH_2$), 164.5 ($C{=}N$); *m/z* (FAB) 215 (MH^+, 100%); HRMS calculated for $C_{14}H_{19}N_2$ (MH^+) 215.1560, observed 215.1548.

*Synthesis of (3*RS*)-1-benzyl-3-phenylselanylpyrrolidin-2-one* (**286**)[125]

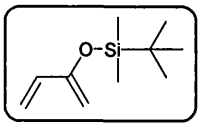


n-Butyllithium (1.6 M solution in hexane) (4.0 mL, 6.4 mmol) was added to a solution of diisopropylamine (0.66 g, 6.5 mmol) in THF (7 mL) at –78 °C. The mixture was stirred at –78 °C for 10 minutes and a solution of 1-benzylpyrrolidin-2-one (1.0 g, 5.7 mmol) in THF (11 mL) was added dropwise. The mixture was stirred at –78 °C for 10 minutes and then a solution of phenylselenenyl bromide (1.6 g, 6.9 mmol) in THF (8 mL) was added dropwise. The resulting mixture was stirred at –78 °C for a further 10 minutes and then warmed to room temperature. 10 % Aqueous ammonium chloride (8 mL) was added and the mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with water (10 mL) and saturated aqueous sodium chloride (10 mL). The combined aqueous extracts were extracted with ethyl acetate (20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:5) afforded *(3*RS*)-1-benzyl-3-phenylselanylpyrrolidin-2-one* (**286**, 0.58 g, 53%).

ν_{max} ($CDCl_3$ cast)/cm^{-1} 3027-2998br (aromatic C-H and sp^3 C-H), 1681s (C=O), 1418m 1284s, 1022m; δ_H (300 MHz; $CDCl_3$) 2.15-2.23 (1H, m, 1 of CH_2CH_2NBn), 2.52-2.59 (1H, m, 1 of CH_2CH_2NBn), 3.00-3.09 (1H, m, 1 of CH_2NBn), 3.13-3.20 (1H, m, 1 of CH_2NBn), 4.01 (1H, dd, *J* 8.9, 4.5 Hz, NCOC*H*), 4.42 (1H, d, *J* 14.7 Hz, 1 of $PhCH_2$), 4.49 (1H, d, *J* 14.7 Hz, 1 of $PhCH_2$), 7.21-7.76 (10H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 26.9 (NCH_2CH_2), 41.0 and 45.0 (CH_2NCH_2Ph and NCH_2Ph), 47.1 (*C*HCO), 127.4, 127.6, 128.13, 128.4, 128.6 and 129.0 (aromatic *C*H), 135.1 and 135.8 (ipso *C*), 173.0 (*C*=O); *m/z* (FAB) 332 (MH^+ 100%), 331 (M^+, 26), 175 (MH^+ -PhSe, 100); HRMS calculated for $C_{17}H_{18}NOSe$ (MH^+) 332.0563, observed 332.0557.

5.2.4 Strategy Four: The Diels-Alder Approach

*Synthesis of 2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene* (**293**)[126]

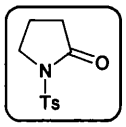


Potassium hexamethyldisilazide (0.5 M solution in toluene) (62.0 mL, 31.0 mmol) was diluted with THF (30mL) and cooled to -78 °C. To this a solution of methyl vinyl ketone (2.0 mL, 24.4 mmol) in THF (20 mL) was added dropwise and the resulting mixture was stirred at –78 °C for 1.5 hours. A solution of *tert*-butyldimethylsilyl chloride (4.66 g, 31.0 mmol) in THF (40 ml) was added dropwise. The resulting mixture was stirred at –78 °C for 1 hour, then warmed to room temperature and stirred for a further 1.5 hours. 10% Aqueous ammonium chloride (100 mL) was added and the solution was extracted with ethyl acetate (60 mL). The aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash

chromatography (Al_2O_3; petroleum ether) afforded 2-(tert-*butyldimethylsilyloxy)buta-1,3-diene* (**293**, 2.48 g, 55%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3357w, 2956s (sp^2 C-H), 2930s and 2858s (sp^3 C-H), 1682w, 1634m, 1585m (C=C), 1472m, 1304m, 1254s, 1060s; δ_H (300; MHz; $CDCl_3$) 0.12 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 4.24 (1H, s, 1 of CH_2CO), 4.26 (1H, s, 1 of CH_2CO), 5.00 (1H, br d, J_{cis} 10.5 Hz, 1 of CH_2CHCO), 5.43 (1H, dd, J_{trans} 16.9, J_{gem} 1.7 Hz, 1 of CH_2CHCO), 6.12 (1H, dd, J_{trans} 17.0, J_{cis} 10.5 Hz, CH_2CHCO); δ_C (75 MHz; $CDCl_3$) –4.7 ($Si(CH_3)_2$), –2.9 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 96.1 and 114.5 (H_2C=CH and H_2C=CH), 134.8 (OC=$\underline{C}H_2$), 157.8 (OC=CH_2).

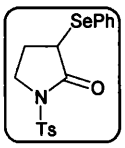
Synthesis of 1-(toluene-4-sulfonyl)pyrrolidin-2-one (**319**)[127]



n-Butyllithium (1.6 M solution in hexanes, 4.0 mL, 6.4 mmol) was dissolved in THF (5 mL) and cooled to –78 °C. To this a solution of pyrrolidin-2-one (0.50 g, 5.9 mmol) in THF (2.5 mL) pre-cooled to –78 °C, was added dropwise. After stirring at –78 °C for 2 hours, a solution of *p*-toluenesulfonyl chloride (1.23 g, 7.2 mmol) in THF (5 mL) was added dropwise. The resulting solution was stirred at –78 °C for 10 minutes and then warmed to room temperature. 10% Aqueous ammonium chloride solution (5 mL) was added and the mixture was extracted with ethyl acetate (40 mL). The organic layer was washed with water (5 mL) and saturated aqueous NaCl (5 mL). The aqueous layers were combined and extracted with ethyl acetate (2 x 40 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:5) afforded *1-(toluene-4-sulfonyl)-pyrrolidin-2-one* (**319**, 0.98 g, 70 %) as a white powder, Mp 148-149 °C (lit[128] 149 °C).

(Found C, 55.1; H, 5.6; N, 5.7 $C_{11}H_{13}NO_3S$ requires C, 55.2; H, 5.5; N, 5.9 %); ν_{max} ($CDCl_3$ cast)/cm^{-1} 2853s (sp^3 C-H), 1730s (C=O), 1456s, 1377s (S=O), 1171w, 1119w; δ_H (400 MHz; $CDCl_3$) 2.07 (2H, quin, *J* 7.8 Hz, C*H*$_2$CH$_2$N), 2.41 (2H, t, *J* 7.9 Hz, C*H*$_2$CO), 2.41 (3H, s, ArC*H*$_3$), 3.87 (2H, t, *J* 8.1 Hz, C*H*$_2$NBn), 7.31 (d, 2H, *J* 10.4 Hz, aromatic C*H*), 7.91 (d, 2H, *J* 10.4 Hz, aromatic C*H*); δ_C (100 MHz; $CDCl_3$) 18.1 (*C*H$_2$CH$_2$N), 21.7 (Ar*C*H$_3$), 32.2 and 47.2 (*C*H$_2$CO and *C*H$_2$N), 128.0 and 129.6 (aromatic *C*H), 135.1 (*C*Me), 145.1 (SO$_2$*C*), 173.3 (*C*=O); *m/z* (FAB) 240 (MH^+, 100%) 154 (37), 136 (38), 91 ($C_7H_7^+$, 69); HRMS calculated for $C_{11}H_{14}NO_3S$ (MH^+) 240.0687, observed 240.0694.

*Synthesis of (3*RS*)-3-phenylselanyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one*[125]



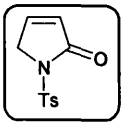
Lithium hexamethyldisilazide (1.06 M in THF, 0.83 mL, 0.88 mmol) was diluted in THF (3 mL) and cooled to –78 °C. A solution of 1-(toluene-4-sulfonyl)pyrrolidin-2-one (0.10 g, 0.42 mmol) in THF (3 mL) pre-cooled to –78 °C, was added dropwise. The resulting mixture was stirred at -78 °C for 2 hours. A solution of phenylselenenyl bromide (0.13 mg, 0.54 mmol) in THF (3 mL) pre-cooled to –78 °C, was added dropwise. The resulting mixture was stirred at –78 °C for 1 hour, then warmed to room temperature and stirred for 2 hours. 10% Aqueous ammonium chloride (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:4) afforded *(3*RS*)-3-phenylselanyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one* (93 mg, 57%).

ν_{max} ($CDCl_3$ cast)/cm^{-1} 3057s (aromatic C-H), 2923s (sp^3 C-H), 1718s (C=O) 1596w, 1477s, 1399s (S=O), 1353w, 1307w; δ_H (400 MHz; $CDCl_3$) 1.98-2.07 (1H, m, 1 of C*H*$_2$CH$_2$N), 2.44 (3H, s, ArC*H*$_3$), 2.44-2.52 (1H, m, 1 of C*H*$_2$CH$_2$N), 3.51-

3.51-3.60 (1H, m, C*H*CO), 3.76-3.82 (2H, m, CH_2N), 7.17 (2H, t, *J* 7.7 Hz, aromatic C*H*), 7.29-7.39 (5H, m, aromatic C*H*), 7.88 (2H, d, *J* 8.3 Hz, aromatic C*H*); δ_C (100 MHz; $CDCl_3$) 21.6 (Ar*C*H_3), 26.1 (*C*H_2CH_2N), 40.5 and 45.6 (*C*H_2CO and *C*H_2N), 125.9, 128.1, 128.9, 129.5 and 129.6 (aromatic *C*H), 134.6 (*C*Me) and 135.9 (ipso *C*), 145.2 (SO_2*C*), 171.5 (*C*=O); *m/z* (FAB) 396 (MH^+, 95%), 155 (46), 136 (50), 91 ($C_7H_7^+$, 100); HRMS calculated for $C_{17}H_{18}SeSNO_3$ (MH^+) 396.0180, observed 396.0173.

Synthesis of 1-(toluene-4-sulfonyl)-3-pyrrolin-2-one (**294**)[125]

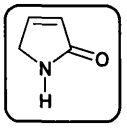
3-Phenylselanyl-1-(toluene-4-sulfonyl)pyrrolidin-2-one (**319**, 2.00 g, 5.0 mmol) was dissolved in ethyl acetate (12 mL) and cooled to 0 °C. Aqueous hydrogen peroxide (30% solution, 8.8 mL 7.8 mmol) was added dropwise, and the resulting solution was stirred at 0 °C for 30 minutes. Water (20 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic extract was washed with saturated aqueous sodium hydrogen carbonate (10 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:2) afforded *1-(toluene-4-sulfonyl)-3-pyrrolin-2-one* (**294**, 892 mg, 75%) as colourless crystals, Mp 159-160 °C.



(Found C, 55.4; H, 4.8; N, 5.7 $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.7; N, 5.9 %); ν_{max} (liq paraffin)/cm^{-1} 3010-2851br (aromatic C-H, sp^2 and sp^3 C-H), 1717s (C=O) 1456w (C=C), 1377s (S=O), 1169w, 1093w; δ_H (400 MHz; $CDCl_3$) 2.41 (3H, s, Ar*C*H_3), 4.47 (2H, t, *J* 2.0 Hz, *C*H_2N), 6.05, (1H, dt, *J* 6.1, 1.9 Hz, *C*H=CHCO), 7.22 (1H, dt, *J* 6.1, 2.0 Hz, CH=C*H*CO), 7.32 (d, 2H, *J* 8.1 Hz, aromatic C*H*), 7.94 (2H, d, *J* 8.3 Hz, aromatic C*H*); δ_C (100 MHz; $CDCl_3$) 21.7

(ArCH$_3$), 52.3 (CH$_2$N), 127.1 (CH$_2$C=C), 128.0 and 129.8 (aromatic C), 135.2 (CMe), 145.1 (SO$_2$C) and 146.5 (C=CHCO), 171.0 (C=O); *m/z* (FAB) 238 (MH$^+$, 100%), 91 (C$_7$H$_7^+$, 45); HRMS calculated for $C_{11}H_{12}NO_3S$ (MH$^+$) 238.0529, observed 238.0538.

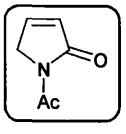
Synthesis of 3-pyrrolin-2-one (**321**)[108]



Pyrrole (10.4 mL, 0.15 mol), aqueous hydrogen peroxide (30% solution, 17.0 g, 0.5 mol) and barium carbonate (3.0 g, 15.2 mmol) were dissolved in water (900 mL) and the resulting solution was heated under reflux for 4 hours. The excess oxidant was removed by adding to the boiling solution lead(IV) oxide (1.0 g, 4.2 mmol) and the absence of peroxide was confirmed using starch-iodide paper. The solution was filtered then concentrated *in vacuo*. The orange oil was then treated with 1,4-dioxane (70 mL) and the mixture was filtered. The filtrate was dried (MgSO$_4$), filtered and concentrated *in vacuo* to afford *3-pyrrolin-2-one* (**321**, 3.87 g, 38%), which was used without further purification.

ν_{max} (CHCl$_3$ cast)/cm^{-1} 3264br (NH and sp^3 C-H), 1682s (C=O), 1421w, 1194m, 1057m; δ_H (400 MHz; CDCl$_3$) 4.05 (2H, t, *J* 1.8 Hz, CH$_2$N), 6.15 (1H, dt, *J* 5.8, *J* 1.9 Hz, CH=HCCO), 7.14 (1H, dt, *J* 5.8, 1.7 Hz, CH=CHCO), 7.35 (1H, br s, NH); δ_C (100 MHz; CDCl$_3$) 49.0 (CH$_2$N), 127.6 (HC=CHCO) 145.9 (HC=CHCO), 175.5 (C=O).

Synthesis of 1-acetyl-3-pyrrolin-2-one (**322**)[129]



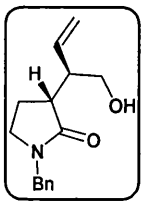
3-Pyrrolin-2-one (1.0 g, 14.5 mmol) and 4-(dimethylamino)pyridine (1.8 g, 14.5 mmol) were dissolved in acetonitrile (20 mL) and stirred at room temperature for 5 minutes. Acetic anhydride (1.6 mL, 21.8 mmol) was added dropwise and the resulting solution was stirred at

room temperature for 30 minutes. Aqueous hydrochloric acid (2M, 10 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (10 mL) and saturated aqueous sodium chloride (10 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford *1-acetyl-3-pyrrolin-2-one* (**322**, 1.1 g, 69%), which was used without further purification.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3587m, 2932br (sp^3 C-H and sp^2 C-H), 1697s (C=O) 1598m (C=C), 1445m, 1375m; δ_H (300 MHz; $CDCl_3$) 2.55 (3H, s, $COCH_3$), 4.38 (2H, t, *J* 2.0 Hz, CH_2N), 6.15 (1H, dt, *J* 6.1, *J*=2.0 Hz, *H*C=CHCO), 7.28 (1H, dt, *J* 6.2, *J* 2.1 Hz, HC=C*H*CO); δ_C (75 MHz; $CDCl_3$) 24.3 ($NCOCH_3$), 50.5 (CH_2N), 127.6 (HC=CHCO), 146.6 (HC=CHCO), 170.0 and 170.2 (CONCO); *m/z* (esp+) 148 (M^+Na, 100%); HRMS calculated for $C_6H_7NO_2$ (M^+) 125.0471, observed 125.0473.

5.2.5 Strategy Five: The Opening of Butadiene Monoxide

*Synthesis of (3*RS, *1'*SR*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* (**326a**) *and (3*RS, *1'*RS*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* (**326b**)



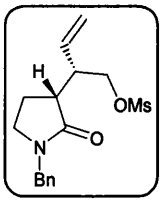
A solution of *N*-benzylpyrrolidin-2-one (6.0 g, 34.2 mmol) in THF (100 mL) was cooled to –78 °C. Lithium hexamethyldisilazide (1.06 M in THF, 35.5 mL, 37.6 mmol) was added dropwise and the resulting solution was stirred at –78 °C for 1 hour. Boron trifluoride etherate (4.8 mL, 37.6 mmol) was added dropwise and the resulting solution was stirred for 5 minutes at –78 °C. Butadiene monoxide (3.0 mL, 37.6 mmol) was added dropwise and the resulting solution was warmed to room temperature and stirred for 3 hours. Saturated aqueous sodium hydrogen carbonate (40 mL) and saturated aqueous

sodium chloride (40 mL) was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:3) afforded *(3*RS, *1'*SR*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* **(see section 2.5.6 for characterisation of this compound)** (**326a**, 0.40 g, 5%) and *(3*RS, *1'*RS*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* (**326b**, 0.71 g, 8%)

*(3*RS, *1'*RS*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* (**326b**) ν_{max} ($CHCl_3$ cast)/cm^{-1} 3400br (OH), 3028w (aromatic C-H), 2930s (sp^2 C-H), 2874s (sp^3 C-H), 1666s (C=O), 1495m, 1454m, 1263m; δ_H (400 MHz; $CDCl_3$) 1.80-1.88 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.04-2.11 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.45-2.58 (1H, m, C*H*CH$_2$OH), 2.67 (1H, q, *J* 8.8 Hz, C*H*C=O), 3.18-3.25 (2H, m, C*H*$_2$NBn), 3.74-3.76 (2H, m, C*H*$_2$OH), 4.42 (2H, d, *J* 14.6 Hz, NC*H*$_2$Ph), 4.49 (2H, d, *J* 14.6 Hz, NC*H*$_2$Ph), 5.10-5.16 (2H, m, CH=C*H*$_2$), 5.56-5.66 (1H, m, C*H*=CH$_2$), 7.22-7.36 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 22.6 (*C*H$_2$CH$_2$NBn), 45.1, 45.4, 47.0 and 48.4 (NCH$_2$Ph, *C*H$_2$NBn, *C*HC=O and *C*HCH$_2$OH), 66.0 (*C*H$_2$OH), 117.5 (HC=*C*H$_2$), 127.7, 128.1 and 128.7 (aromatic *C*H), 136.1 (ipso *C*), 136.6 (HC=CH$_2$), 176.4 (*C*=O); *m/z* (CI-methane) 246 (MH^+, 100%), 228 (82), 215 (15), 175 (45), 91 (50); HRMS calculated for $C_{15}H_{20}NO_2$ (MH^+) 246.1494, observed 246.1482.

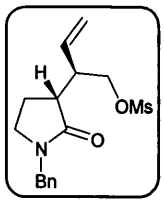
*Synthesis of (3*RS, *1'*SR*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one* (**332a**)

To a stirred solution (3*RS*, 1'*SR*)-1-benzyl-3-[1-(hydroxymethy)lally])pyrrolidin-2-one (0.40 g, 1.6 mmol) in



dichloromethane (8 mL) at 0 °C was added triethylamine (0.3 mL, 1.9 mmol) and 4-dimethylaminopyridine (19 mg, 0.1 mmol). Methanesulfonyl chloride (0.15 mL, 1.9 mmol) was added and the resulting solution was stirred at 0 °C for 3 hours. Water (3 mL) and saturated aqueous sodium chloride (3 mL) were added and the mixture was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:2) afforded *(3*RS, *1'*SR*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one* (**332a**, 0.31 g, 59 %) (**see section 2.5.6 for characterisation of this compound**)

*Synthesis of (3*RS, *1'*RS*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one* (**332b**)

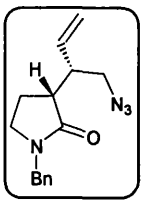


To a stirred solution (3*RS*, 1'*RS*)-1-benzyl-3-[1-(hydroxymethy)lally])pyrrolidin-2-one (0.58 g, 2.4 mmol) in dichloromethane (10 mL) at 0 °C was added triethylamine (0.4 mL, 2.9 mmol) and 4-dimethylaminopyridine (29 mg, 0.2 mmol). Methanesulfonyl chloride (0.22 mL, 2.9 mmol) was added and the resulting solution was stirred at 0 °C for 3 hours. Water (4 mL) and saturated aqueous sodium chloride (4 mL) were added and the mixture was extracted with dichloromethane (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:2) afforded *(3*RS, *1'*RS*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one* (**332b**, 0.17 g, 22 %).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3028w (aromatic C-H), 2936br (sp^2 C-H and sp^3 C-H), 1682s (C=O), 1494m, 1454m, 1435m, 1354s (S=O), 1175s; δ_H (400 MHz; $CDCl_3$) 1.78-1.84 (1H, m, 1 of CH_2CH$_2$NBn), 2.06-2.08 (1H, m, 1 of CH_2CH$_2$NBn), 2.72-

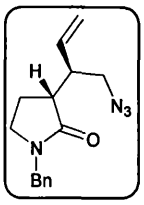
2.74 (2H, m, C*H*CH=CH_2), 2.99-3.04 (1H, m, C*H*C=O), 3.04 (3H, s, SO_2CH_3), 3.16-3.19 (2H, m, CH_2NBn), 4.37-4.52 (4H, m, CH_2OSO_2 and NCH_2Ph), 5.20-5.30 (2H, m, CH=CH_2), 5.64-5.73 (1H, m, C*H*=CH_2), 7.19-7.33 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 21.1 (CH_2CH_2NBn), 37.4 (*C*HCH=CH_2), 42.0, 43.4, 44.8 and 46.6 (NCH_2Ph, CH_2NBn, *C*HC=O, and SO_2CH_3), 70.4 ($CH_2OSO_2CH_3$), 119.5 (HC=CH_2), 127.6, 128.1 and 128.7 (aromatic *C*H), 133.7 (ipso *C*), 136.3 (H*C*=CH_2), 174.1 (*C*=O); *m/z* (FAB) 324 (MH^+, 30%) 246 (MH^+- SO_2CH_3, 100), 228 (12), 176 (52); HRMS calculated for $C_{16}H_{22}NO_4S$ (MH^+) 324.1270, observed 324.1269.

*Synthesis of (3*RS, *1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**325a**)



A solution of (3*RS*, 1'*SR*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one (0.31 g, 1.0 mmol) and sodium azide (0.19 g, 2.9 mmol) in dimethyl sulfoxide (5 mL) was stirred at 60 °C for 2 hours, then cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (50 mL). The aqueous layer was extracted further with ethyl acetate (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:3) afforded *(3*RS, *1'*RS*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**325a**, 0.11 g, 43%). (**see section 2.5.6 for characterisation of this compound**)

*Synthesis of (3*RS, *1'*RS*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**325b**)

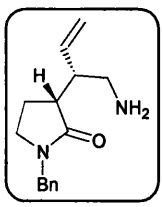


A solution of (3*RS*, 1'*RS*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one (0.42 g, 1.3 mmol) and sodium azide (0.51 g, 1.6 mmol) in dimethyl sulfoxide (5 mL) was stirred at 60 °C for 2 hours then cooled to room temperature. Water (10 mL) was

added and the mixture was extracted with ethyl acetate (80 mL). The aqueous layer was extracted further with ethyl acetate (3 x 80 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:3) afforded *(3*RS, *1'*RS*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**325b**, 0.30 g, 69%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3030w (aromatic C-H), 2918br (sp^2 C-H and sp^3 C-H), 2098s (N_3), 1682s (C=O), 1454w, 1435w, 1265m, 1194w; δ_H (400 MHz; $CDCl_3$) 1.74-1.83 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 1.97-2.06 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.65-2.71 (1H, m, C*H*C=O), 2.85-2.92 (1H, m, C*H*CH$_2$N$_3$), 3.12-3.20 (2H, m, C*H*$_2$NBn), 3.56 (2H, d, *J* 6.8 Hz, C*H*$_2$N$_3$), 4.38 (1H, d, *J* 14.6 Hz, 1 of C*H*$_2$Ph), 4.50 (1H, d, *J* 14.6 Hz, 1 of C*H*$_2$Ph), 5.19-5.23 (2H, m, CH=C*H*$_2$), 5.62-5.71 (1H, m, C*H*=CH$_2$), 7.20-7.35 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 20.8 (*C*H$_2$CH$_2$NBn), 43.0, 43.8, 44.8 and 46.8 (NCH$_2$Ph, *C*H$_2$NBn, *C*HC=O and *C*HCH$_2$N$_3$), 53.3 (*C*H$_2$N$_3$), 118.9 (HC=*C*H$_2$), 127.6, 128.1 and 128.7 (aromatic *C*H), 135.2 (ipso *C*), 136.4 (H*C*=CH$_2$), 174.6 (*C*=O); *m/z* (FAB) 271 (MH^+, 50%), 259 (100), 175 (10); HRMS calculated for $C_{15}H_{19}N_4O$ (MH^+) 271.1559, observed 271.1565.

*Synthesis of (3*RS, *1'*RS*)-3-[1-(aminomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**337a**)

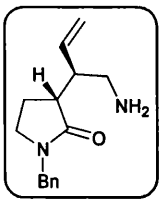


To a stirred solution (3*RS*, 1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one (20 mg, 70 μmol) in THF (1 mL) was added triphenylphosphine (39 mg, 0.15 mmol) and the resulting solution was stirred at room temperature for 30 minutes. Water (0.15 mL) was added dropwise and the resulting solution was stirred for 16 hours at room temperature. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Preparative thin layer chromatography (SiO_2; methanol: dichloromethane: NH_3 aq., 80%: 19%: 1%)

afforded *(3*RS, *1'*RS*)-3-[1-(aminomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**337a**, 12.1 mg, 67%).

δ_H (400 MHz; $CDCl_3$) 1.77-1.86 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.05-2.14 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.48-2.54 (1H, m, C*H*CH$_2$NH$_2$), 2.75 (1H, td, *J* 12.4, 3.52 Hz, C*H*CONBn), 3.02 (2H, br s, C*H*$_2$NH$_2$), 3.15-3.19 (4H, m, C*H*$_2$NBn and CH$_2$N*H*$_2$), 4.39 (1H, d, *J* 14.6 Hz, 1 of NC*H*$_2$Ph), 4.48 (1H, d, *J* 14.6 Hz, 1 of NC*H*$_2$Ph), 5.20-5.24 (2H, m, CH=C*H*$_2$), 5.65-5.75 (1H, m, C*H*=CH$_2$), 7.20-7.35 (5H, m, aromatic C*H*); δ_C (100 MHz; $CDCl_3$) 22.1 (*C*H$_2$CH$_2$NBn), 29.5 (*C*HCH$_2$NH$_2$), 43.1 (*C*H$_2$NH$_2$), 44.1 (*C*HC=O), 45.2 and 46.8 (N*C*H$_2$Ph and *C*H$_2$NBn), 119.3 (HC=*C*H$_2$), 127.6, 128.1 and 128.7 (aromatic *C*H), 136.3 (ipso *C* and H*C*=CH$_2$), 174.9 (*C*=O); *m/z* (esp+) 245 (MH^+, 100%), 228 (5).

*Synthesis of (3*RS, *1'*RS*)-3-[1-(aminomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**337b**)

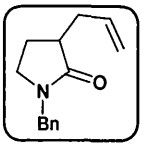


To a stirred solution of (3*RS*, 1'*RS*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one (20 mg, 0.07 mmol) in THF (1 mL) was added triphenylphosphine (39 mg, 0.15 mmol) and the resulting solution was stirred at room temperature for 30 minutes. Water (0.15 mL) was added dropwise and the resulting solution was stirred for 16 hours at room temperature. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Preparative thin layer chromatography (SiO_2; methanol: dichloromethane: NH_3 aq., 80%: 19%: 1%) afforded *(3*RS, *1'*RS*)-3-[1-(aminomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**337b**, 15 mg, 82%).

δ_H (500 MHz; $CDCl_3$) 1.76-1.83 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 1.99-2.05 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.64-2.71 (2H, m, C*H*CH$_2$NH$_2$ and C*H*CONBn), 2.84-2.88 (3H, m, 1 of C*H*$_2$NH$_2$ and CH$_2$N*H*$_2$), 2.95-2.99 (1H, m, 1 of C*H*$_2$NH$_2$), 3.14-3.17 (2H, m, C*H*$_2$NBn), 4.38 (1H, d, *J* 14.7 Hz, 1 of NC*H*$_2$Ph), 4.49 (1H, d, *J* 14.7

Hz, 1 of NCH_2Ph), 5.18-5.22 (2H, m, CH=CH_2), 5.59-5.66 (1H, m, CH=CH_2), 7.20-7.33 (5H, m, aromatic CH); δ_C (100 MHz; $CDCl_3$) 22.2 (CH_2CH_2NBn), 29.7 ($CHCH_2NH_2$), 43.9 (CH_2NH_2), 44.0 (CHC=O), 45.1 and 46.8 (NCH_2Ph and CH_2NBn), 118.8 (HC=CH_2), 127.6, 128.1 and 128.7 (aromatic CH), 136.3 (ipso C and HC=CH_2), 175.4 (C=O); *m/z* (esp+) 245 (MH^+, 100%).

*Synthesis of (3*RS*)-3-allyl-1-benzylpyrrolidin-2-one* (**341**)[130]



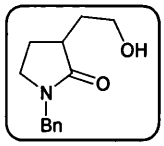
Diisopropylamine (1.7 mL, 12.2 mmol) was dissolved in THF (40 mL) and cooled to –78 °C. *n*-Butyllithium (1.6 M in hexanes) (8.0 mL, 12.8 mmol) was added dropwise and the resulting solution was stirred at –78 °C for 15 minutes. A solution of *N*-benzylpyrrolidin-2-one (2.0 g, 11.4 mmol) in THF (10 mL) was added dropwise and the resulting solution was stirred at –78 °C for 30 minutes. Allyl bromide (1.0 mL, 11.6 mmol) was added in one portion and the resulting mixture was allowed to warm to room temperature and stirred for 16 hours. Water (15 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:3) afforded *(3*RS*)-3-allyl-1-benzylpyrrolidin-2-one* (**341**, 0.99 g, 40%) and *3,3-diallyl-1-benzylpyrrolidin-2-one* (0.90 g, 31%).

*(3*RS*)-3-Allyl-1-benzylpyrrolidin-2-one* (**341**) ν_{max} ($CHCl_3$ cast)/cm^{-1} 3030m (aromatic C-H), 2874m (sp^3 C-H and sp^2 C-H), 1682s (C=O), 1641w (C=C), 1495w, 1429m, 1263m; δ_H (300 MHz; $CDCl_3$) 1.62-1.75 (1H, m, 1 of C$H_2$$CH_2$NBn), 2.02-2.24 (2H, m, 1 of C$H_2$$CH_2$NBn and 1 of C$H_2$HC=$CH_2$), 2.50-2.66 (2H, m, 1 of CH_2HC=CH_2 and CHC=O), 3.13-3.18 (2H, m, CH_2NBn), 4.41 (1H, d, *J* 14.7 Hz, 1of NCH_2Ph), 4.47 (1H, d, *J* 14.7 Hz, 1 of NCH_2Ph), 5.01-5.11 (2H, m, CH=CH_2), 5.78

(1H, ddt, *J* 17.0, 10.2, 6.8 Hz, C*H*=CH_2), 7.19-7.35 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 23.9 (*C*H_2CH_2NBn), 35.5 and 41.4 (*C*H_2CH=CH_2 and *C*HC=O), 44.8 and 46.7 (*C*H_2NBn and NCH_2Ph), 116.8 (CH=*C*H_2), 127.5, 128.1 and 128.6 (aromatic *C*H), 135.5 (*C*H=CH_2), 136.6 (ipso *C*), 175.9 (*C*=O); *m/z* (FAB) 216 (MH^+, 100%), 154 (80); HRMS calculated for $C_{14}H_{18}NO$ (MH^+) 216.1388, observed 216.1389.

3,3-Diallyl-1-benzylpyrrolidin-2-one ν_{max} ($CHCl_3$ cast)/cm^{-1} 3033w (aromatic C-H), 2922m (sp^2 C-H), 2854m (sp^3 C-H), 1688s (C=O), 1639m (C=C), 1495w, 1439m, 1261m; δ_H (300 MHz; $CDCl_3$) 1.88 (2H, t, *J* 7.1 Hz, C*H*$_2$CH_2NBn), 2.19 (2H, dd, *J* 13.7, 8.2 Hz, 2 x 1 of C*H*$_2$CH=CH_2), 2.37 (2H, dd, *J* 13.7, 6.5 Hz, 2 x 1 of C*H*$_2$CH=CH_2), 3.06 (2H, t, *J* 7.3 Hz, C*H*$_2$NBn), 4.42 (2H, s, NC*H*$_2$Ph), 5.02-5.11 (4H, m, 2 x CH=C*H*$_2$), 5.65-5.79 (2H, m, 2 x C*H*=CH_2), 7.19-7.35 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 26.7 (*C*H_2CH_2NBn), 41.6 (*C*H_2CH=CH_2), 43.8 (*C*C=O). 46.8 and 47.6 (*C*H_2NBn and NCH_2Ph), 118.4 (CH=*C*H_2), 127.5, 128.2 and 128.5 (aromatic *C*H), 133.9 (*C*H=CH_2), 136.6 (ipso *C*), 177.1 (*C*=O); *m/z* (CI-methane) 256 (MH^+, 100%), 213 (62), 91 ($C_7H_7^+$, 50), 41 (55); HRMS calculated for $C_{17}H_{22}NO$ (MH^+) 256.1701, observed 256.1703.

*Synthesis of (3*RS*)-1-benzyl-3-(2-hydroxyethyl)pyrrolidin-2-one* (**342**)[131]

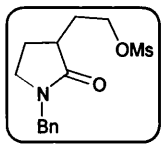


(3*RS*)-3-Allyl-1-benzylpyrrolidin-2-one (1.93 g, 8.96 mmol) was dissolved in methanol (50 mL) and cooled to –78 °C. Ozone was bubbled through the solution until a persistent blue colour was observed (approximately 1 hour) after which oxygen was bubbled for 15 minutes. Sodium borohydride (3.39 g, 89.6 mmol) was added in 10 portions at –78 °C and the resulting solution was warmed to room temperature and stirred for 1 hour. Water

(20 mL), aqueous hydrochloric acid (2M, 10 mL) were added and the mixture was extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; methanol: dichloromethane 1:49) afforded *(3RS)-1-benzyl-3-(2-hydroxyethyl)pyrrolidin-2-one* (**342**, 1.65 g, 84%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3406br (OH), 3032w (aromatic C-H), 2872m (sp^3 C-H), 1665s (C=O), 1495m, 1433m, 1261; δ_H (300 MHz; $CDCl_3$) 1.62-1.79 (2H, m, 1 of C*H*$_2$CH$_2$NBn and 1 of C*H*$_2$CH$_2$OH), 1.85-2.01 (1H, m, 1 of C*H*$_2$CH$_2$OH), 2.14-2.28 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.58-2.69 (1H, m, C*H*CON), 3.20-3.24 (2H, m, C*H*$_2$NBn), 3.71-3.87 (2H, m, C*H*$_2$OH), 4.25 (1H, m, CH$_2$O*H*), 4.42 (1H, d, *J* 14.9 Hz, 1 of C*H*$_2$Ph), 4.45 (1H, d, *J* 14.8 Hz, 1 of C*H*$_2$Ph), 7.19-7.38 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 25.9 (*C*H$_2$CH$_2$NBn), 34.7 (*C*H$_2$CH$_2$OH), 42.4, 45.4, and 47.0 (*C*HC=O, *C*H$_2$NBn, and NCH$_2$Ph) 62.0 (*C*OH), 127.6, 128.1 and 128.7 (aromatic *C*H), 136.2 (ipso *C*), 177.4 (*C*=O); *m/z* (CI-methane) 220 (MH^+, 100%), 175 (MH^+-C_2H_5O, 60), 91 ($C_7H_7^+$, 40); HRMS calculated for $C_{13}H_{17}NO_2$ (MH^+) 220.1338, observed 220.1338.

Synthesis of (3RS)-1-benzyl-3-(2-methanesulfonyloxyethyl)pyrrolidin-2-one (**343**)[132]



(3*RS*)-1-Benzyl-3-(2-hydroxyethyl)pyrrolidin-2-one (1.1 g, 5.0 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. Triethylamine (1.4 mL, 10 mmol) was added dropwise, followed by methanesulfonyl chloride (0.78 mL, 10 mmol) dropwise and the resulting solution was stirred at 0 °C for 3 hours. Water (20 mL) and saturated aqueous sodium chloride (10 mL) were added and the mixture was extracted with dichloromethane (4 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate:

petroleum ether 40-60 1:1) afforded *(3*RS*)-1-benzyl-3-(2-methanesulfonyloxyethyl)pyrrolidin-2-one* (**343**, 1.38 g, 97%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3030w (aromatic C-H), 2924br (sp^3 C-H), 1678s (C=O), 1433w, 1352w (S=O), 1173m; δ_H (300 MHz; $CDCl_3$) 1.65-1.73 (1H, m, 1 of CH_2CH_2NBn), 1.83-1.90 (1H, m, 1 of $CH_2CH_2OSO_2$), 2.24-2.33 (2H, m, 1 of CH_2CH_2NBn and 1 of $CH_2CH_2OSO_2$), 2.59-2.64 (1H, m, CHCON), 3.02 (3H, s, SO_2CH_3), 3.19-3.24 (2H, m, CH_2NBn), 4.40-4.50 (4H, m, NCH_2Ph and $CH_2OSO_2CH_3$), 7.20-7.34 (5H, m, aromatic CH); δ_C (75 MHz; $CDCl_3$) 25.3 (CH_2CH_2NBn), 31.2 (CH_2CH_2O), 37.3 (SO_2CH_3), 38.5, 44.8, and 46.8 (CH_2NBn, NCH_2Ph, and CHC=O), 68.3 (CH_2O) 127.6, 128.1 and 128.7 (aromatic CH), 136.3 (ipso C), 175.3 (C=O); *m/z* (CI-methane) 298 (MH^+, 20%), 202 (MH^+-MsOH, 25), 91 ($C_7H_7^+$, 25), 40 (100); HRMS calculated for $C_{14}H_{20}NO_4S$ (MH^+) 298.1113, observed 298.1115.

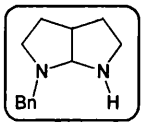
*Synthesis of (3*RS*)-3-(2-azidoethyl)-1-benzylpyrrolidin-2-one* (**344**)

(3*RS*)-1-Benzyl-3-(2-methanesulfonyloxyethyl)pyrrolidin-2-one (0.57 g, 2.0 mmol) and sodium azide (0.39 g, 6.0 mmol) were dissolved in dimethyl sulfoxide (5 mL) and stirred at 60 °C for 2 hours then cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:2) afforded *(3*RS*)-3-(2-azidoethyl)-1-benzylpyrrolidin-2-one* (**344**, 0.42 g, 86%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2932m (sp^3 C-H), 2097s (N_3), 1678s (C=O), 1427m, 1261m; δ_H (300 MHz; $CDCl_3$) 1.56-1.72 (2H, m, 1 of CH_2CH_2NBn and 1 of $CH_2CH_2N_3$), 2.11-2.27 (2H, m, 1 of CH_2CH_2NBn and 1 of $CH_2CH_2N_3$), 2.48-2.59

(1H, m, C*H*CONBn), 3.16-3.20 (2H, m, CH_2NBn), 3.40-3.53 (2H, m, CH_2N_3), 4.42 (1H, d, *J* 14.8 Hz, 1 of NCH_2Ph), 4.45 (1H, d, *J* 14.7 Hz, 1 of NCH_2Ph), 7.19-7.34 (5H, m aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 25.2 (*C*H_2CH_2NBn), 30.8 (*C*$H_2CH_2N_3$), 39.5, 44.7, 46.8, 46.6 (*C*H_2NBn, *C*HC=O, N*C*H_2Ph, and *C*H_2N_3), 127.6, 128.1 and 128.7 (aromatic *C*H), 136.5 (ipso *C*), 175.6 (*C*=O); *m/z* (CI-methane) 245 (MH^+, 50%), 217 (MH^+-N_2, 85), 189 (50), 91 ($C_7H_7^+$, 100); HRMS calculated for $C_{13}H_{17}N_4O$ (MH^+) 245.1402 observed 245.1399.

*Synthesis of (3a*RS, *6a*SR*)*-cis-*1-benzyloctahydropyrrolo[2,3-*b*]pyrrole* (**345**)

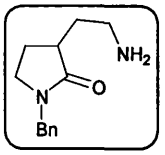


Tri-*n*-butylphosphine (1.0 mL, 4.1 mmol) was added to a solution of (3*RS*)-3-(2-azidoethyl)-1-benzylpyrrolidin-2-one (0.5 g, 0.2 mmol) in THF (25 mL) and the mixture was stirred at room temperature for 20 minutes. Lithium aluminium hydride (1M solution in THF, 1.2 mL, 1.2 mmol) was added dropwise and the resulting solution was stirred at room temperature for 1 hour. Aqueous potassium sodium tartrate tetrahydrate (1M solution, 20 mL) was added dropwise and the mixture was stirred at room temperature for 30 minutes. The mixture was then saturated with solid sodium chloride and extracted with ethyl acetate (2 x 400 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3; petroleum ether (neat), then ethyl acetate: petroleum ether 40-60 1:5) afforded *(3a*RS, *6a*SR*)*-cis-*1-benzyloctahydropyrrolo[2,3-*b*]pyrrole* (**345**, 0.22 g, 54%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2957m (sp^3 C-H), 2792w, 1484w, 1452m, 1101m; δ_H (400 MHz; $CDCl_3$) 1.38-1.45 (1H, m, 1 of CH_2CH_2NH), 1.47-1.53 (1H, m, 1 of CH_2CH_2NBn), 1.68-1.79 (2H, m, 1 of CH_2CH_2NBn and CH_2NH), 1.90-1.98 (1H, m, 1 of CH_2CH_2NH), 2.30-2.36 (m, 1 of CH_2NH), 2.58-2.65 (1H, m, C*H*CHNBn), 2.74-2.79 (1H, m, 1 of CH_2NH), 2.81-2.93 (2H, m, CH_2NBn), 3.64 (1H, d, *J* 13.0 Hz, 1 of

NC*H*$_2$Ph), 3.84 (1H, d, *J* 13.0 Hz, 1 of NC*H*$_2$Ph), 4.10 (1H, d, *J* 7.0 Hz, NCHN), 7.19-7.34 (5H, m aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 30.7 (*C*H$_2$CH$_2$NBn), 33.8 (*C*H$_2$CH$_2$NH), 41.6 (*C*HCHNBn), 45.1, 52.0 and 57.2 (*C*H$_2$NBn, NCH$_2$Ph, and *C*H$_2$NH), 83.2 (NCHN), 126.8, 128.2 and 128.9 (aromatic *C*H), 139.6 (ipso *C*); *m/z* (CI-methane) 203 (MH^+, 100%), 159 (30), 91 ($C_7H_7^+$, 25); HRMS calculated for $C_{13}H_{19}N_2$ (MH^+) 203.1548, observed 203.1545.

*Synthesis of (3*RS*)-3-(2-aminoethyl)-1-benzylpyrrolidin-2-one* (**346**)[133]

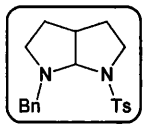


(3*RS*)-3-(2-Azidoethyl)-1-benzylpyrrolidin-2-one (0.20 g, 0.82 mmol) and triphenylphosphine (0.26 g, 0.98 mmol) were dissolved in THF (2 mL) and stirred at room temperature for 30 minutes. Water (0.5 mL) was added dropwise and the resulting solution was stirred for 16 hours at room temperature. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; methanol: dichloromethane 1:4) afforded *(3*RS*)-3-(2-aminoethyl)-1-benzylpyrrolidin-2-one* (**346**, 0.14 g, 76%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3358br (NH), 3030w (aromatic C-H), 2926m (sp^3 C-H), 2870w, 1674s (C=O), 1583w, 1495m, 1437m, 1304w; δ_H (300 MHz; $CDCl_3$) 1.42 (2H, br s, N*H*$_2$), 1.48-1.70 (2H, m, 1 of C*H*$_2$CH$_2$NBn and 1 of C*H*$_2$CH$_2$NH$_2$), 1.94-2.04 (1H, m, 1 of C*H*$_2$CH$_2$NH$_2$), 2.11-2.23 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.48-2.58 (1H, m, C*H*CONBn), 2.73-2.95 (2H, m, C*H*$_2$NH$_2$), 3.10-3.22 (2H, m, C*H*$_2$NBn), 4.42 (1H, d, *J* 14.7 Hz, 1 of NC*H*$_2$Ph), 4.45 (1H, d, *J* 14.7 Hz, 1 of C*H*$_2$Ph), 7.18-7.33 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 25.1 (*C*H$_2$CH$_2$NBn), 35.4 (*C*H$_2$CH$_2$NH$_2$), 39.8, 40.2, 44.9 and 46.8 (*C*H$_2$NBn, *C*HC=O, NCH$_2$Ph, *C*H$_2$NH$_2$), 127.5, 128.1 and 128.7 (aromatic *C*H), 136.6 (ipso *C*), 176.6 (*C*=O); *m/z* (CI-methane) 219 (MH^+, 100%), 202 (MH^+- NH_3, 75), 175 (MH^+- $CH_2CH_2NH_2$, 85),

91 ($C_7H_7^+$, 40); HRMS calculated for $C_{13}H_{19}N_2O$, 219.1497 (MH^+), observed 219.1494.

*Synthesis of (3a*RS, *6a*SR*)*-cis-*1-benzyl-6-(toluene-4-sulfonyl)-octahydropyrrolo[2,3-*b*]pyrrole* (**351**)[134]



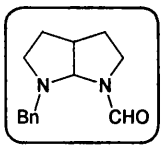
*(3a*RS, *6a*SR*)-cis*-1-Benzyloctahydropyrrolo[2,3-*b*]pyrrole (0.27 g, 1.3 mmol) was dissolved in dichloromethane (10 mL). Triethylamine (0.4 mL, 2.9 mmol) was added dropwise followed by *p*-toluenesulfonyl chloride (0.56 g, 2.9 mmol) and the resulting solution was stirred at room temperature for 1 hour. Water (10 mL) was added and the mixture was extracted with dichloromethane (100 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; methanol: dichloromethane 1:49) afforded *(3a*RS, *6a*SR*)*-cis-*1-benzyl-6-(toluene-4-sulfonyl)-octahydropyrrolo[2,3-*b*]pyrrole* (**351**, 0.30 g, 64%)

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3028w (aromatic C-H), 2963m (sp^3 C-H), 2872w, 2804w, 1452m, 1344s (S=O), 1303m, 1217m; δ_H (400 MHz; $CDCl_3$) 1.19-1.29 (1H, m, 1 of $CH_2CH_2NSO_2$), 1.36-1.45 (2H, m, 1 of $CH_2CH_2NSO_2$ and 1 of CH_2CH_2NBn), 1.86-1.95 (1H, m, 1 of CH_2CH_2NBn), 2.40 (3H, s, $ArCH_3$), 2.26-2.40 (1H, m, 1 of CH_2NBn), 2.56-2.65 (2H, m, CHCHNBn and 1 of CH_2NBn), 3.28 (1H, td, *J* 12.1, 5.6 Hz, 1 of CH_2NSO_2), 3.59 (1H, dd, *J* 12.3, 7.5 Hz, 1 of CH_2NSO_2), 3.98 (1H, d, *J* 13.8 Hz, 1 of NCH_2Ph), 4.03 (1H, d, *J* 13.8 Hz, 1 of NCH_2Ph), 5.03 (1H, d, *J* 6.8 Hz, NCHN), 7.19-7.32 (7H, m, aromatic CH), 7.73 (2H, d, *J*=8.2 Hz, aromatic CH); δ_C (75 MHz; $CDCl_3$) 21.5 ($ArCH_3$), 29.9 and 32.3 (CH_2CH_2NBn and CHCHNBn), 42.0, 48.0, 50.5 and 55.5, (CH_2NBn, NCH_2Ph, CH_2NSO_2 and $CH_2CH_2NSO_2$), 84.7 (NCHN), 126.7, 127.1, 128.1, 128.8 and 129.7 (aromatic CH), 137.4 (ipso C), 139.3 (CMe), 143.1 (CSO_2); *m/z* (CI-methane) 357 (MH^+, 100%),

201 (85), 91 ($C_7H_7^+$, 50); HRMS calculated for $C_{20}H_{25}N_2O_2S$ (MH^+) 357.1637, observed 357.1633.

*Synthesis of (3a*RS*, 6a*SR*)-3-(*cis*-6-benzyloctahydropyrrolo[2,3-*b*]pyrrole-1-carbaldehyde* (**352**)[135]

(3*RS*)-3-(2-Azidoethyl)-1-benzylpyrrolidin-2-one (0.50 g, 2.1 mmol) was converted to (3a*RS*, 6a*SR*)-*cis*-1-benzyloctahydropyrrolo[2,3-*b*]pyrrole as described before. The crude mixture was dissolved in ethyl formate (4 mL, 50 mmol) and the resulting mixture was heated to reflux for 6 hours then cooled to room temperature. The solution was concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3; ethyl acetate: petroleum ether 40-60 1:2) afforded *(3a*RS*, 6a*SR*)-3-(*cis*-6-benzyloctahydropyrrolo[2,3-b]pyrrole-1-carbaldehyde* (**352**, 0.18 g, 40% from (3*RS*)-3-(2-Azidoethyl)-1-benzylpyrrolidin-2-one).



ν_{max} ($CHCl_3$ cast)/cm^{-1} 3445br, 3061w, 3028w(aromatic C-H), 2939m (sp^3 C-H), 2872m, 2804w, 1674s (C=O), 1385m. Mixture of rotamers, ratio 1: 2.4.

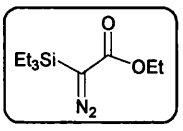
Major rotamer δ_H (500 MHz; $CDCl_3$) 1.54-1.61 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 1.71-1.76 (1H, m, C*H*$_2$CH$_2$NCHO), 1.85-1.91 (1H, m, 1 of C*H*$_2$CH$_2$NCHO) 2.08-2.12 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.58-2.63 (1H, m, 1 of C*H*$_2$NBn), 2.72 (1H, dt, *J* 9.3, 6.6 Hz, 1 of C*H*$_2$NBn), 2.90-2.96 (1H m, C*H*CHNBn), 3.10 (1H, td, *J* 11.5, 6.7 Hz, 1 of C*H*$_2$NCHO), 3.68 (1H, d, *J* 13.4 Hz, 1 of NC*H*$_2$Ph), 3.87 (1H, d, *J* 13.5 Hz, 1 of NC*H*$_2$Ph), 3.99-4.04 (1H, m, 1 of C*H*$_2$NCHO) 4.75 (1H, d, *J* 6.7 Hz, NC*H*N), 7.20-7.35 (5H, m, aromatic C*H*), 8.06 (1H, s, NC*H*O); δ_C (125 MHz; $CDCl_3$) 30.5 (*C*H$_2$CH$_2$NBn), 31.5 (*C*H$_2$CH$_2$NCHO), 41.2 (*C*HCHNBn), 42.4 (*C*H$_2$NCHO), 51.7 (*C*H$_2$NBn), 55.5 (N*C*H$_2$Ph), 80.9 (N*C*HN), 127.2, 128.4 and 128.9 (aromatic *C*H),

138.3 (ipso *C*), 161.2 (N*C*HO). Irradiation at δ 8.06 ppm gave a positive nuclear Overhauser enhancement at 3.68, 3.87 (NCH_2Ph) and 4.75 (NC*H*N).

Minor rotamer 1.51-1.54 (1H, m, 1 of CH_2CH$_2$NBn), 1.62-1.70 (1H, m, 1 of CH_2CH$_2$NCHO), 1.81-1.85 (1H, m, 1 of CH_2CH$_2$NCHO), 1.98-2.05 (1H, m, 1 of CH_2CH$_2$NBn), 2.43-2.48 (1H, m, 1 of CH_2NBn), 2.65-2.69 (1H, m, 1 of CH_2NBn), 2.84 (1H, quin, *J* 8.0 Hz, C*H*CHNBn), 3.47 (1H, dt, *J* 11.7, *J* 5.9 Hz, 1 of CH_2NCHO), 3.62 (1H, m, 1 of CH_2NCHO), 3.98 (1H, d, *J* 13.4 Hz, 1 of NCH_2Ph), 4.10 (1H, d, *J* 13.6 Hz, 1 of NCH_2Ph), 5.19 (1H, d, *J* 7.2 Hz, NC*H*N,), 7.20-7.35 (5H, m, aromatic C*H*), 8.27 (1H, s, NC*H*O); δ_C (125 MHz; $CDCl_3$) 30.4 (*C*H$_2$CH$_2$NBn), 31.4 (*C*H$_2$CH$_2$NCHO), 41.2 (*C*HCHNBn), 45.6 (*C*H$_2$NCHO), 51.4 (*C*H$_2$NBn), 56.5 (N*C*H$_2$Ph), 77.6 (N*C*HN), 126.7, 128.1 and 128.5 (aromatic *C*H), 139.1 (ipso *C*), 161.6 (N*C*HO). Irradiation at δ 8.27 ppm gave a positive nuclear Overhauser enhancement at 3.47 and 3.62 (CH_2NCHO).

m/z (EI) 230 (MH^+, 20%), 172 (22), 158 (50) 91 ($C_7H_7^+$, 100); HRMS calculated for $C_{14}H_{19}N_2O$ (MH^+) 230.1414, observed 230.1416.

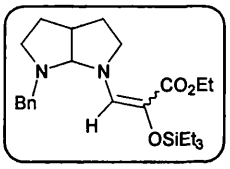
Synthesis of ethyl diazo(triethylsilyl)acetate (**356**)[136]



N-Ethyldiisopropylamine (3.96 mL, 17.5 mmol) was added to a solution of ethyl diazoacetate (1.84 mL, 17.5 mmol) in diethyl ether (100 mL) and the resulting solution was cooled to –78 °C. Triethylsilyl triflate (3.96 mL, 17.5 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 30 minutes, then warmed to room temperature and stirred for 16 hours. The yellow solution was filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; petroleum ether 40-60) afforded *ethyl diazo(triethylsilyl) acetate* as a yellow oil (**356**, 2.15 g, 54%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2957s, 2878s (sp^3 C-H), 2089s (C=N_2), 1693s (C=O), 1464w, 1366w, 1265s; δ_H (300 MHz; $CDCl_3$) 0.75 (6H, q, *J* 8.0 Hz, Si(CH_2CH_3)$_3$), 0.83 (9H, t, *J* 7.6 Hz, Si(CH_2CH_3)$_3$), 1.26 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 3.2 ($SiCH_2CH_3$), 7.0 ($SiCH_2CH_3$), 14.4 (OCH_2CH_3), 60.6 (OCH_2CH_3), 110.4 (*C*=N_2), 117.9 (C=O).

*Synthesis of ((3a*RS*, 6a*SR*)-3-(*cis*-6-benzyloctahydropyrrolo[2,3-b]pyrrol-1-yl)-2-triethylsilanyloxyacrylate* (**357**)



(3a*RS*, 6a*SR*)-3-(*cis*-6-benzyloctahydropyrrolo[2,3-*b*] pyrrole-1-carbaldehyde (94 mg, 0.4 mmol) and rhodium(II) acetate dimer (18 mg, 41 μmol) were dissolved in benzene (1 mL) and heated to reflux. A solution of ethyl diazo(triethylsilyl)acetate (112 mg, 0.5 mmol) in benzene (1 mL) was added dropwise to the refluxing solution and the mixture was stirred under reflux for 1 hour. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3; ethyl acetate: petroleum ether 40-60 1: 32) afforded *(3a*RS*, 6a*SR*)-3-(*cis*-6-benzyloctahydropyrrolo[2,3-b]pyrrol-1-yl)-2-triethylsilanyloxyacrylate* (**357**, 69 mg, 39%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3391br, 3063w, 3028w (aromatic C-H), 2953s (sp^2 C-H), 2910m, 2874s (sp^3 C-H), 2806w, 1693s (C=O), 1635s (C=C), 1366s (C-O), 1273, 1117; δ_H (500 MHz; $CDCl_3$) 0.76 (6H, q, *J* 7.7 Hz, $SiCH_2CH_3$), 1.01 (9H, t, *J* 7.8 Hz, $SiCH_2CH_3$), 1.26 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.48-1.53 (1H, m, 1 of CH_2CH_2NBn), 1.65-1.69 (1H, m, 1 of CH_2CH_2NCH=C), 1.86-1.91 (1H, m, 1 of CH_2CH_2NCH=C), 2.01-2.05 (1H, m, 1 of CH_2CH_2NBn), 2.51-2.56 (1H, m, 1 of CH_2NBn), 2.62-2.67 (1H, m, 1 of CH_2NBn), 2.77-2.84 (1H, m, CHCHNBn), 3.47 (1H, ddd, *J* 11.3, 10.6, 6.3 Hz, 1 of CH_2NCH=C), 3.71 (1H, d, 1 of *J* 13.3 Hz

NCH_2Ph,), 3.88 (1H, d, *J* 13.4 Hz, 1 of NCH_2Ph), 3.95, (1H, ddd, *J* 11.3, 8.1, 1.9 Hz, 1 of CH_2NCH=C), 4.14 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 4.50 (1H, d, *J* 6.6 Hz, NC*H*N), 6.87 (1H, s, NC*H*=C), 7.22-7.33 (5H, m, aromatic C*H*); δ_C (125 MHz; $CDCl_3$) 5.5 ($SiCH_2CH_3$), 7.0 ($SiCH_2CH_3$), 14.6 ($CO_2CH_2CH_3$), 30.2 (CH_2CH_2NBn), 32.6 ($CH_2CH_2NCH=C$), 40.6 (*C*HCHNBn), 48.4 ($CH_2NCH=C$), 51.3 (CH_2NBn), 55.8 (NCH_2Ph), 59.6 ($CO_2CH_2CH_3$), 87.3 (NCHN), 118.0 (CH=*C*), 126.9, 128.2, and 128.6 (aromatic *C*H), 132.0 (*C*H=C), 139.0 (ipso *C*), 167.2 (C=O); Irradiation at δ 6.87 ppm gave a positive nuclear Overhauser enhancement at 3.71, 3.88 (NCH_2Ph) and 4.50 (NC*H*N).

m/z (FAB) 431 (MH^+, 100%), 338 (55), 172 (40). HRMS calculated for $C_{24}H_{39}N_2O_3Si$ (MH^+) 431.2730, observed 431.2723.

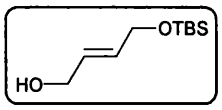
5.2.6 Strategy Six: Sigmatropic Rearrangement

*Synthesis of (*E*)-but-2-ene-1,4-diol* (**378**)[117]

Lithium aluminium hydride (7.76 g, 0.2 mol) was dissolved in THF (200 mL) and the resulting slurry was cooled to 0 °C. A solution of 2-butyn-1,4-diol (8.0 g, 93 mmol) in THF (200 mL) was added dropwise and the resulting solution was heated to reflux for 2 hours. The mixture was cooled to room temperature. Aqueous potassium sodium tartrate tetrahydrate (1M solution, 40 mL) was added and the mixture was stirred at room temperature for 30 minutes. The mixture was extracted with diethyl ether (4 x 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3; ethyl acetate: petroleum ether 40-60 3:1) afforded *(*E*)-but-2-ene-1,4-diol* (**378**, 6.56 g, 80%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3300br (OH), 2940m (sp^2 C-H), 2867m (sp^3 C-H), 1084m; δ_H (300 MHz; $CDCl_3$) 1.69 (2H, br s, O*H*), 4.14 (4H, br s, CH_2CH=CHCH_2), 5.86 (2H, br s, *H*C=C*H*); δ_C (75 MHz; $CDCl_3$) 62.8 (*C*H_2HC=CH*C*H_2), 130.5 (H*C*=*C*H).

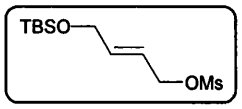
*Synthesis of (*E*)-4-(*tert*-butyldimethylsilanyloxy)but-2-en-1-ol* (**379**)[118]



Sodium hydride (60% dispersion in mineral oil, 1.36 g, 57 mmol) was washed with hexane (6 mL) and then suspended in THF (40 mL). A solution of (*E*)-but-2-ene-1,4-diol (3.00 g, 34 mmol) in THF (40 mL) was added dropwise and the resulting solution was stirred at room temperature for 1 hour. A solution of *tert*-butyldimethylsilyl chloride (5.00 g, 33 mmol) in THF (40 mL) was added dropwise and the resulting solution was stirred at room temperature for 16 hours. Diethyl ether (300 mL) was added and the solution was washed with saturated aqueous sodium bicarbonate solution (30 mL) and saturated aqueous sodium chloride solution (30 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:4) afforded *(*E*)-4-(*tert*-butyldimethylsilanyloxy)but-2-en-1-ol* (**379**, 5.1 g, 75%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3333br (OH), 2930s (sp^2 C-H), 2856 (sp^3 C-H), 1464m, 1362m, 1256m, 1096m; δ_H (300 MHz; $CDCl_3$) 0.06 (6H, s, Si(CH_3)$_2$), 0.90 (9H, s, C(CH_3)$_3$), 1.53 (1H, s, O*H*), 4.16 (4H, br s, CH_2HC=CHCH_2), 5.73-5.90 (2H, m, *H*C=C*H*); δ_C (75 MHz; $CDCl_3$) –5.25 (Si(*C*H$_3$)$_2$), 18.4 (*C*(CH$_3$)$_3$), 25.9 (C(*C*H$_3$)$_3$), 63.1 and 63.2 (*C*H_2HC=CH*C*H_2), 129.0 and 131.0 (H*C*=*C*H); *m/z* (EI) 203 (MH^+, 29%), 201 (66), 137 (100); HRMS calculated for $C_{10}H_{23}O_2Si$ (MH^+), 203.1467, observed 203.1467.

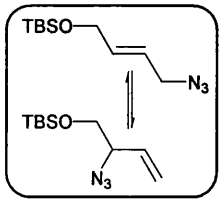
*Synthesis of (*E*)-1-(*tert*-butyldimethylsilanyloxy)-4-(methanesulfonyloxy)but-2-ene* (**380**)



(*E*)-4-(*tert*-butyldimethylsilanyloxy)but-2-en-1-ol (0.80 g, 4.0 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. Triethylamine (0.88 mL, 6.3 mmol) was added dropwise followed by methanesulfonyl chloride (0.61 mL, 7.9 mmol) dropwise and the resulting mixture was stirred at 0 °C for 30 minutes. The solution was washed with ice-cold water (8 mL) and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic extracts were washed with cold 10% aqueous hydrochloric acid (8 mL), saturated aqueous sodium bicarbonate solution (8 mL) and saturated aqueous sodium chloride solution (8 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*, to *(*E*)-1-(*tert*-butyldimethylsilanyloxy)-4-(methanesulfonyloxy)but-2-ene* (**380**, 1.26 g), which was used without further purification.

δ_H (300 MHz; $CDCl_3$) 0.00 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $C(CH_3)_3$), 3.64 (3H, s, SO_2CH_3), 4.18-4.19 (2H, m, CH_2OSi), 4.71 (2H, d, *J* 6.0 Hz, $HC{=}CHCH_2OMs$), 5.79-6.00 (2H, m, *H*C=C*H*); δ_C (75 MHz; $CDCl_3$) -5.38 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 38.2 (SO_2CH_3), 62.4 ($SiOCH_2$) 69.9 (CH_2OSO_2), 121.4 and 137.1 (HC=CH).

*Synthesis of 3-azido-4-(*tert*-butyldimethylsilanloxy)but-1-ene* (**381**) */ (*(*E*)-1-azido-4-(*tert*-butyldimethylsilanloxy)but-2-ene* (**382**)



(*E*)-4-(*tert*-butyldimethylsilanyloxy)but-2-en-1-ol (0.20 g, 1.0 mmol) was converted to (*E*)-1-(*tert*-butyldimethylsilanyloxy)-4-(methanesulfonyloxy)but-2-ene as described before. The crude mixture was dissolved in *N,N*-dimethyformamide (1 mL) and cooled to 0 °C. Sodium

azide (0.19 g, 3.0 mmol) was added and the resulting solution was stirred at 0 °C for 1 hour. The solution was washed with water (5 mL) and extracted with ethyl acetate (50 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:1) afforded a mixture of *3-azido-4-(*tert-*butyldimethylsilanloxy)but-1-ene* and *((*E*)-1-azido-4-(*tert-*butyldimethylsilanoxy)but-2-ene* (**381**:**382** ratio 1:1.8, respectively, 0.13 g, 57% over two steps).

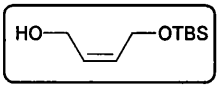
ν_{max} ($CHCl_3$ cast)/cm^{-1} 2927s (sp^2 C-H), 2856s (sp^3 C-H), 2100s (N_3).

*((*E*)-1-azido-4-(*tert-*butyldimethylsilanoxy)but-2-ene* δ_H (300 MHz; $CDCl_3$) 0.00 (6H, s, $Si(CH_3)_2$), 0.87 (9H, s, $C(CH_3)_3$), 3.72 (2H, d, *J* 5.7 Hz, N_3CH_2), 4.15-4.17 (2H, m, CH_2OSi), 5.64-5.85 (2H, m, *H*C=C*H*).

*3-azido-4-(*tert-*butyldimethylsilanloxy)but-1-ene* δ_H (300 MHz; $CDCl_3$) 0.00 (6H, s, $Si(CH_3)_2$), 0.87 (9H, s, $C(CH_3)_3$), 3.54-3.69 (2H, m, CH_2OSi), 3.86-3.92 (1H, m, CHN_3), 5.23-5.27 (2H, m, $CH=CH_2$), 5.64-5.85 (1H, m, *H*C=CH_2)

For both isomers δ_C (75 MHz; $CDCl_3$) -5.53 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 53.1, 63.5 66.4 and 66.9 ($CH_2HC=CH$, $CH_2HC=CHCH_2N_3$, $SiOCH_2CHN_3$ and $SiOCH_2CHN_3$), 119.6 and 133.6 ($N_3CHC=CH_2$), 121.4 and 134.8 ($SiOCH_2HC=CHCH_2N_3$).

*Synthesis of (Z)-4-(*tert-*butyldimethylsilanyloxy)but-2-en-1-ol*[118]

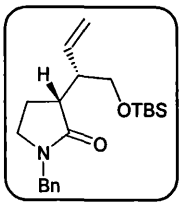


Sodium hydride (60% dispersion in mineral oil, 0.45 g, 19 mmol) was washed with hexane (2 x 2 mL) and then suspended in THF (20 mL). A solution of (*Z*)-but-2-ene-1,4-diol (1.0 g, 11 mmol) in

THF (20 mL) was added dropwise and the resulting solution was stirred at room temperature for 1 hour. A solution of *tert*-butyldimethylsilyl chloride (1.67 g, 11 mmol) in THF (20 mL) was added dropwise and the resulting solution was stirred at room temperature for 16 hours. Diethyl ether (200 mL) was added and the mixture was washed with saturated aqueous sodium bicarbonate solution (20 mL) and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:4) afforded *(Z)-4-(*tert-*butyldimethylsilanyloxy)but-2-en-1-ol* (1.73 g, 75%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3354br (OH), 2955s (sp^2 C-H), 2930s (sp^3 C-H), 2885m, 1472m, 1256m, 1088m, 1034m; δ_H (300 MHz; $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $C(CH_3)_3$), 2.00 (1H, s, O*H*), 4.18 (2H, d, *J* 4.8 Hz, CH_2OSi), 4.25 (2H, d, *J* 3.6 Hz, $HOCH_2$), 5.61-5.74 (2H, m, *H*C=C*H*); δ_C (75 MHz; $CDCl_3$) -5.27 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 25.9 $C(CH_3)_3$, 58.9 ($SiOCH_2$), 59.6 (CH_2OH), 130.1 and 131.4 (HC=CH); *m/z* (esp+) 225 (MNa^+, 100%), 203 (MH^+, 8); HRMS calculated for $C_{10}H_{22}O_2SiNa$ (MNa^+), 225.1281, observed 225.1287.

*Synthesis of (3*RS, *1'*RS*)-1-benzyl-3-[1-(*tert-*butyldimethylsilanyloxymethyl)allyl] pyrrolidin-2-one* (**385a**)

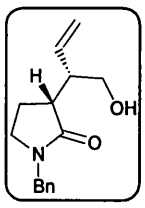


Dimethyl sulfate (0.27 mL, 2.85 mmol) was added dropwise to *N*-benzylpyrrolidin-2-one (0.50 g, 2.85 mmol) and the resulting mixture was stirred at 50 °C for 3 hours. A second equivalent of dimethyl sulfate (0.27 mL, 2.85 mmol) was added dropwise and the resulting mixture was stirred at 50 °C for 1 hour. In a separate flask, *n*-butyllithium (1.6M in hexanes, 4.9 mL, 6.3 mmol) was added dropwise to a solution of (*E*)-4-(*tert*-butyldimethylsilanyloxy)but-2-en-1-ol (**385a**, 1.15 g, 5.7 mmol) in THF (20 mL) and

the resulting solution was stirred at room temperature for 1 hour. The THF alkoxide solution was added in one portion to the pyrrolidinone-dimethyl sulfate mixture and the resulting solution was stirred at 70 °C for 3 hours. The orange mixture was cooled to room temperature, concentrated *in vacuo* and then dissolved in dichloromethane (50 mL). The solution was washed with saturated aqueous sodium hydrogen carbonate (5 mL) and saturated aqueous sodium chloride (5 mL) and then organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:9) afforded *(3*RS, *1'*RS*)-1-benzyl-3-[1-(*tert*-butyldimethylsilanyloxymethyl)allyl]pyrrolidin-2-one* (571 mg, 56%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3028w (aromatic C-H), 2960s (sp^2 C-H), 2880s (sp^3 C-H), 2341m, 1666s (C=O), 1435w, 1194s; δ_H (400 MHz; $CDCl_3$) 0.04 (6H, s, Si(CH_3)$_2$), 0.86 (9H, s, C(CH_3)$_3$), 1.82-1.92 (1H, m, 1 of CH_2CH_2NBn), 2.00-2.08 (1H, m, 1 of CH_2CH_2NBn), 2.48-2.54 (1H, m, CHCH$_2$OSi), 2.79 (1H, td, *J* 8.9, 3.5 Hz, CHC=O), 3.08-3.17 (2H, m, CH_2NBn), 3.73 (1H, dd, *J* 10.0, 6.3 Hz, 1 of CH_2OSi), 3.92 (1H, dd, *J* 9.9, *J* 7.0 Hz, 1 of CH_2OSi), 4.38 (1H, d, *J* 14.7 Hz, 1 of NCH_2Ph), 4.43 (1H, d, *J* 14.6 Hz, 1 of NCH_2Ph), 5.08-5.14 (2H, m, CH=CH_2), 5.70-5.79 (1H, m, CH=CH$_2$), 7.19-7.31 (5H, m, aromatic CH); δ_C (75 MHz; $CDCl_3$) –5.36 (Si(CH_3)$_2$), 18.3 (C(CH$_3$)$_3$), 22.2 (CH_2CH_2NBn), 25.9 (C(CH_3)$_3$), 42.0, 45.0, 46.6 and 48.3 (CH_2NBn, NCH_2Ph, CHC=O and $CHCH_2$OSi), 64.2 (CH_2OSi), 117.7 (HC=CH_2), 127.4, 128.2 and 128.6 (aromatic CH), 136.7 (ipso C), 136.9 (HC=CH$_2$), 175.1 (C=O); *m/z* (CI-methane) 360 (MH^+, 100%), 302 (55), 228 (20), 91 ($C_7H_7^+$, 20); HRMS calculated for $C_{21}H_{34}NO_2Si$ (MH^+) 360.2360, observed 360.2359.

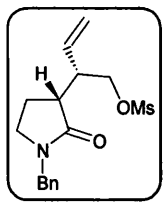
*Synthesis of (3*RS, *1'*SR*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* (**326a**)[137]



To a stirred solution of (3*RS*, 1'*RS*)-1-benzyl-3-[1-(*tert*-butyldimethylsilanyloxymethyl)allyl]pyrrolidin-2-one (302 mg, 0.84 mmol) in THF (1.5 mL) at 0 °C was added tetra-*N*-butylammonium fluoride (1M solution in THF, 1.0 mL, 1.0 mmol). The resulting solution was warmed to room temperature and stirred for 2 hours. The solution was concentrated *in vacuo*, diluted with ethyl acetate (20 mL) and washed with saturated aqueous sodium hydrogen carbonate (4 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:1) *(3*RS, *1'*SR*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one* (**326a**, 154 mg, 75%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3403br (OH), 3028w (aromatic C-H), 2928s (sp^2 C-H), 2856s (sp^3 C-H), 1686s (C=O), 1429m, 1258m, 1094m; δ_H (400 MHz; $CDCl_3$) 1.81-1.90 (1H, m, C*H*$_2$CH$_2$NBn), 2.02-2.13 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.43-2.48 (1H, m, C*H*CH$_2$OH), 2.85 (1H, td, *J* 9.0, 3.0 Hz, C*H*C=O), 3.17-3.24 (2H, m, C*H*$_2$NBn), 3.78 (1H, dd, *J* 11.1, 5.4 Hz, 1 of C*H*$_2$OH), 3.88 (1H, dd, *J* 11.1, 4.1 Hz, 1 of C*H*$_2$OH), 4.38 (1H, d, *J* 14.6 Hz, 1 of NC*H*$_2$Ph), 4.47 (1H, d, *J* 14.6 Hz, 1 of NC*H*$_2$Ph), 5.13-5.20 (2H, m, CH=C*H*$_2$), 5.84 (1H, dt, *J* 17.0, 10.1 Hz, C*H*=CH$_2$), 7.19-7.34 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 22.5 (*C*H$_2$CH$_2$NBn), 45.3, 45.6, 47.0 and 48.0 (NCH$_2$Ph, *C*H$_2$NBn, *C*HC=O and *C*HCH$_2$OH), 65.9 (*C*H$_2$OH), 118.9 (HC=*C*H$_2$), 127.7, 128.1 and 128.7 (aromatic *C*H), 135.3 (ipso *C*), 136.1 (H*C*=CH$_2$), 175.8 (*C*=O); *m/z* (esp+) 268 (MNa^+, 100%), 261 (8), 217 (9); HRMS calculated for $C_{15}H_{19}NO_2Na$ (MNa^+) 268.1308, observed 268.1306.

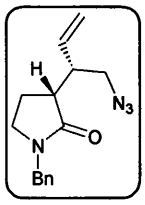
*Synthesis of (3*RS, *1'*SR*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one* (**332a**)



To a stirred solution of (3*RS*, 1'*SR*)-1-benzyl-3-[1-(hydroxymethy)lallyl]pyrrolidin-2-one (0.15 g, 0.6 mmol) in dichloromethane (2 mL) at 0 °C was added triethylamine (0.1 mL, 1.2 mmol) and methanesulfonyl chloride (0.17 mL, 1.2 mmol) and the resulting solution was stirred at 0 °C for 3 hours. Water (3 mL), saturated aqueous sodium chloride (3 mL) and dichloromethane (50 mL) were added and the organic layer was separated. The aqueous layer was extracted further with dichloromethane (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:2) afforded *of (3*RS, *1'*SR*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one* (**332a**, 0.16 g, 84%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 2924br (sp^2 C-H and sp^3 C-H), 1770m, 1676s (C=O), 1439w, 1354s (S=O), 1192m, 1177s; δ_H (400 MHz; $CDCl_3$) 1.76-1.86 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.05-2.13 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.73-2.86 (2H, m, C*H*CH=CH$_2$ and C*H*C=O), 3.03 (3H, s, SO_2CH_3), 3.13-3.21 (2H, m, C*H*$_2$NBn), 4.35-4.46 (3H, m, 1 of C*H*$_2$OSO$_2$, and NC*H*$_2$Ph), 4.65 (1H, dd, *J* 9.8, 8.1 Hz, 1 of C*H*$_2$OSO$_2$), 5.23-5.28 (2H, m, CH=C*H*$_2$), 5.63 (1H, dt, *J* 17.6, 9.4 Hz, C*H*=CH$_2$), 7.18-7.33 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 21.9 (*C*H$_2$CH$_2$NBn), 37.2 (*C*HCH$_2$OSO$_2$), 41.3, 45.1, 45.5 and 46.7 (NCH$_2$Ph, *C*H$_2$NBn, *C*HC=O, and SO_2CH_3), 70.6 (*C*H$_2$OSO$_2$), 120.7 (HC=*C*H$_2$), 127.6, 128.1 and 128.7 (aromatic *C*H), 133.3 (ipso *C*), 136.3 (H*C*=CH$_2$), 174.1 (*C*=O); *m/z* (esp+) 346 (MNa^+, 55%) 268 (MNa^+- SO_2CH_2, 100), 261 (12), 246 (15), 217 (10); HRMS calculated for $C_{16}H_{21}NO_4SNa$ (MNa^+) 346.1084, observed 346.1083.

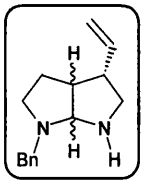
*Synthesis of (3*RS, *1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**325a**)



A solution of (3*RS*, 1'*SR*)-1-benzyl-3-[1-(methanesulfonyloxymethyl)lallyl]pyrrolidin-2-one (0.15 g, 0.47 mmol) and sodium azide (91 mg, 1.4 mmol) in dimethyl sulfoxide (1.5 mL) was stirred at 60 °C for 2 hours, then cooled to room temperature. Water (5 mL) was added, followed by ethyl acetate (25 mL) and the organic layer was separated. The aqueous layer was extracted further with ethyl acetate (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; ethyl acetate: petroleum ether 40-60 1:3) afforded *(3*RS, *1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one* (**325a**, 93.6 mg, 74%).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3030w (aromatic C-H), 2923br (sp^2 C-H and sp^3 C-H), 2097s (N_3), 1684s (C=O), 1495w, 1454m, 1431mw, 1262m, 1194m; δ_H (400 MHz; $CDCl_3$) 1.67-1.76 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 1.95-2.02 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 2.46-2.53 (1H, m, C*H*CH$_2$N$_3$), 2.67 (1H, td, *J* 9.1, 3.3 Hz, C*H*C=O), 3.04-3.11 (2H, m, C*H*$_2$NBn), 3.52 (1H, dd, *J* 12.2, 7.9 Hz, 1 of C*H*$_2$N$_3$), 3.61 (1H, dd, *J* 12.2, 7.0 Hz, 1 of C*H*$_2$N$_3$), 4.29 (1H, d, *J* 14.6 Hz, 1 of NC*H*$_2$Ph), 4.39 (1H, d, *J* 14.6 Hz, 1 of NC*H*$_2$Ph), 5.12-5.17 (2H, m, CH=C*H*$_2$), 5.62 (1H, dt, *J* 17.1, 9.3 Hz, C*H*=CH$_2$), 7.11-7.26 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 22.0 (*C*H$_2$CH$_2$NBn), 42.7 (*C*HCH$_2$N$_3$), 45.0, 45.8 and 46.7 (NCH$_2$Ph, *C*H$_2$NBn and *C*HC=O), 53.0 (*C*H$_2$N$_3$), 119.4 (HC=*C*H$_2$), 127.6, 128.2 and 128.7 (aromatic *C*H), 135.6 (ipso *C*), 136.4 (H*C*=CH$_2$), 174.2 (*C*=O); *m/z* (FAB) 271 (MH^+, 100%), 228 (10), 215 (15), 175 (10); HRMS calculated for $C_{15}H_{19}N_4O$ (MH^+) 271.1559, observed 271.1568.

*Sythesis of (3a*RS, *4*SR, *6a*RS*)*-cis-*1-benzyl-4-vinyloctahydropyrrolo[2,3-*b*]pyrrole and (3a*RS, *4*RS, *6a*RS*)*-cis-*1-benzyl-4-vinyloctahydropyrrolo[2,3-*b*]pyrrole* (**324**)



Tri-*n*-butylphosphine (0.09 mL, 0.37 mmol) was added dropwise to a solution of (3*RS*, 1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one (82.8 mg, 0.31 mmol) in THF and the resulting solution was stirred for 20 minutes. Lithium aluminium hydride (1M solution in THF,0.18 mL, 0.18 mmol) was added dropwise and the resulting solution was stirred at room temperature for 1 hour. Aqueous potassium sodium tartrate tetrahydrate (1M solution, 3 mL) was added and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was then saturated with solid sodium chloride and extracted with ethyl acetate (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The NMR of the crude reaction mixture showed the presence of two similar compounds in a ratio of 2:1. Preparative thin layer chromatography (SiO_2; dichloromethane: methanol 9:1) afforded *(3a*RS, *4*RS, *6a*RS*)*-cis-*1-benzyl-4-vinyloctahydropyrrolo[2,3-*b*]pyrrole* and *(3a*SR, *4*RS, *6a*SR*)*-cis-*1-benzyl-4-vinyloctahydropyrrolo[2,3-*b*]pyrrole* (**324**, ratio of diastereomers 2: 1).

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3368w (N-H), 3030w (aromatic C-H), 2958br (sp^2 C-H and sp^3 C-H), 1674 (C=C), 1465w, 1456m, 1147m;

Major diastereomer; δ_H (400 MHz; $CDCl_3$) 1.42-1.46 (1H, m, 1 of C*H*$_2$CH$_2$NBn), 1.86-1.98 (2H, m, 1 of C*H*$_2$CH$_2$NBn and N*H*), 2.34-2.45 (2H, m, 1 of C*H*$_2$NBn and C*H*CHNBn), 2.62-2.77 (3H, m, 1 of C*H*$_2$NH, 1 of C*H*$_2$NBn and C*H*CH$_2$NH), 3.07 (1H, dd, *J* 10.2, 5.7 Hz, 1 of C*H*$_2$NH), 3.62 (1H, d, *J* 13.1 Hz, 1 of NC*H*$_2$Ph), 3.81 (1H, d, *J* 13.0 Hz, 1 of NC*H*$_2$Ph), 4.21 (1H, d, *J* 6.3 Hz, NC*H*N), 4.87-5.02 (2H, m, HC=C*H*$_2$), 5.60-5.77 (1H, m, *H*C=CH$_2$), 7.15-7.30 (5H, m, aromatic C*H*); δ_C (100 MHz; $CDCl_3$) 29.8 (*C*H$_2$CH$_2$NBn), 45.8 (*C*HCH$_2$NH), 47.8

(*C*HCHNBn), 50.5, 51.1, 56.0 (*C*H_2NBn, NCH_2Ph, and *C*H_2NH), 83.8 (NC*H*N), 113.9 (HC=*C*H_2), 126.9, 128.2 and 128.9 (aromatic *C*H), 139.4 (ipso *C*), 140.5 (H*C*=CH_2); *m/z* (esp+) 229 (MH^+, 100%), 228 (M^+, 12), 217 (46), 203 (25); HRMS calculated for $C_{15}H_{21}N_2$ (MH^+) 229.1699, observed 229.1696.

*Synthesis of (3*RS*, 3a*SR*, 6a*RS*)*-cis-*6-benzyloctahydropyrrolo[2,3-*b*]pyrrole-1-carbaldehyde and (3*RS*, 3a*RS*, 6a*SR*)*-cis-*6-benzyloctahydropyrrolo[2,3-*b*]pyrrole-1-carbaldehyde* (**392**)

(3*RS*, 1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one (**325a**) (0.40 g, 1.4 mmol) was converted *cis*-1-benzyl-4-vinyloctahydropyrrolo[2,3-b]pyrrole (**324**) as described before. The crude mixture was dissolved in ethyl formate (3.4 mL, 42 mmol) and the resulting mixture was heated to reflux for 2 hours. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (Al_2O_3; ethyl acetate: petroleum ether 40-60 1:5) *(3*RS*, 3a*SR*, 6a*RS*)*-cis-*6-benzyloctahydropyrrolo[2,3-*b*]pyrrole-1-carbaldehyde and (3*SR*, 3a*RS*, 6a*SR*)*-cis-*6-benzyloctahydropyrrolo[2,3-*b*]pyrrole-1-carbaldehyde* (**392**, 94 mg, 25% after two steps from (3*RS*, 1'*SR*)-3-[1-(azidomethyl)lallyl]-1-benzylpyrrolidin-2-one).

The ratio of diastereomers was 4:1, and the rotamer ratio for the major diastereomer was 1:2.

ν_{max} ($CHCl_3$ cast)/cm^{-1} 3029w (aromatic C-H), 2960br (sp^2 C-H and sp^3 C-H), 1679 (C=O and C=C), 1465m, 1266m, 1149m; major rotamer of the major diasteromer; δ_H (500 MHz; $CDCl_3$) 1.58-1.66 (1H, m, 1 of C$H_2$$CH_2$NBn), 2.02-2.12 (1H, m, 1 of C$H_2$$CH_2$NBn), 2.43-2.49 (1H, m, 1 of CH_2NBn), 2.57-2.61 (1H, m, 1 of CH_2NBn), 2.65-2.71 (1H, m, C*H*CH_2NCHO), 2.91-2.99 (1H, m, C*H*CHNBn), 3.57-3.61 (1H, m, 1 of CH_2NCHO), 3.72 (1H, d, *J* 13.4 Hz, 1 of NCH_2Ph), 3.85 (1H, d,

J 13.4 Hz, 1 of NC*H*$_2$Ph), 4.05-4.08 (1H, m, 1 of C*H*$_2$NCHO), 4.83 (1H, d, *J* 6.6 Hz, NC*H*N), 5.06-5.16 (2H, m, HC=C*H*$_2$), 5.73-5.83 (1H, m, *H*C=CH$_2$), 7.22-7.33 (5H, m, aromatic C*H*), 8.00 (1H, s, NC*H*O); δ_C (125 MHz; $CDCl_3$) 28.8 (*C*H$_2$CH$_2$NBn), 44.6 (*C*H$_2$NCHO), 45.4 (*C*HCHNBn), 47.6 (*C*H$_2$NBn), 48.9 (*C*HCH$_2$NCHO), 55.8 (NCH$_2$Ph), 81.2 (NCHN), 117.4 (HC=*C*H$_2$), 128.1, 128.4 and 128.9 (aromatic *C*H), 138.1 (ipso *C*), 134.9 (H*C*=CH$_2$), 161.5 (NCHO); *m/z* (CI-methane) 257 (MH^+, 100%), 247 (35), 219 (70), 158 (71); HRMS calculated for $C_{16}H_{21}N_2O$ (MH^+) 257.1654, observed 257.1651.

Bibliography

1) Huggett, R. J. *Global Ecol. Biogeogr.*, **1999**, *8*, 425-431.

2) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.*, **2003**, *20*, 1-48.

3) Cimino, G.; Destefano, S.; Scognamiglio, G.; Sodano, G.; Trivellone, E. *Bull. Soc. Chim. Belg.*, **1986**, *95*, 783-800.

4) Yuewei, G.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron*, **1996**, *52*, 14961-14974.

5) Yuewei, G.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron*, **1996**, *52*, 8341-8348.

6) (a) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron*, **1989**, *45*, 3863-3872; (b) Cimino, G.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Pure Appl. Chem.*, **1989**, *61*, 535-538; (c) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.*, **1990**, *53*, 1519-1525.

7) Yuewei, G.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron Lett.*, **1998**, *39*, 463-466.

8) Caprioli, V.; Cimino, G.; Degiulio, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Comp. Biochem. Physiol. B-Biochem. Mol. Biol.*, **1992**, *103*, 293-296.

9) Thompson, J. E.; Walker, R. P.; Faulkner, D. J. *Mar. Biol.*, **1985**, *88*, 11-21.

10) Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B. *Tetrahedron Lett.*, **1995**, *36*, 707-710.

11) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.*, **1992**, *33*, 2059-2062.

12) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.*, **1992**, *57*, 2480-2483.

13) Sisko, J.; Weinreb, S. M. *J. Org. Chem.*, **1991**, *56*, 3210-3211.

14) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.*, **1999**, *64*, 587-595.

15) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.*, **1993**, *58*, 4945-4951.

16) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.*, **1998**, *63*, 9616-9617.

17) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.*, **1998**, *63*, 8096-8097.

18) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.*, **1999**, *1*, 2017-2019.

19) Sung, M. J.; Lee, H. I.; Lee, H. B.; Cha, J. K. *Heterocycles*, **2004**, *62*, 407-422.

20) Sung, M. J.; Lee, H. I.; Lee, H. B.; Cha, J. K. *J. Org. Chem.*, **2003**, *68*, 2205-2208.

21) Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.*, **1885**, *8*, 2377-2377.

22) Staudinger, H.; Kupfer, O. *Ber. Dtsch. Chem. Ges.*, **1912**, *45*, 501-509.

23) Doering, W. E.; Hoffmann, A. K. *J. Am. Chem. Soc.*, **1954**, *76*, 6162-6165.

24) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.*, **1964**, *3*, 580-590.

25) (a) Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.*, **1999**, *121*, 10213-10214; (b) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.*, **1997**, *36*, 2163-2187.

26) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.*, **2000**, *100*, 39-91.

27) Richards Jr., C. A.; Kim, S-J.; Yamaguchi, Y.; Scharfer III, H. F. *J. Am. Chem. Soc.*, **1995**, *117*, 10104-10107.

28) (a) Roos, B. O.; Siegbahn, P. M. *J. Am. Chem. Soc.*, **1977**, *99*, 7716-7718; (b) Lengel, R. K.; Zare, R. N. *J. Am. Chem. Soc.*, **1978**, *100*, 7495-7499.

29) Kirmse, W. *Carbene Chemistry*, Academic Press, New York, **1964**.

30) Tomioka, H.; Watanabe, T.; Hirai, K.; Furukawa, K.; Takui, T.; Itoh, K. *J. Am. Chem. Soc.*, **1995**, *117*, 6376-6377.

31) Huisgen, R. *Angew. Chem.*, **1955**, *67*, 439-463.

32) Hoffmann, R. *J. Am. Chem. Soc.*, **1968**, *90*, 1475-1485.

33) Doering, W. von E.; La Flamme, P. *J. Am. Chem. Soc.*, **1956**, *78*, 5447-5448.

34) Baron, W. J.; DeCamp, M. R.; Hendrick, M. E.; Jones, M.; Levin, R. H.; Sohn, M. B. in *Carbenes*, vol. 1, Jones, Jr. M.; Moss, R. A., Eds. Wiley, New York, **1973**.

35) (a) Doering, W. von E.; Wiley, D. W. *Tetrahedron*, **1960**, *11*, 183-198; (b) Zimmerman, H. E.; Sousa, L. R. *J. Am. Chem. Soc.*, **1972**, *94*, 834-842.

36) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. *The Chemistry of Diazonium and Diazo Groups*, Patai, S., Ed.; Wiley, New York, **1978**.

37) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.*, **1991**, *91*, 263-309.

38) Doyle, M. P. *Chem. Rev.*, **1986**, *86*, 919-939.

39) (a) Curtius, T. *Chem. Ber.*, **1883**, *16*, 2230-2231; (b) Curtius, T. *J. Prakt. Chem.*, **1888**, *38*, 396-404.

40) (a) Arndt, F.; Eistert, B.; Partale, W. *Ber.*, **1927**, *60B*, 1364-1370; (b) Arndt, F.; Eistert, B. *Chem. Ber.*, **1935**, *68*, 200-204.

41) a) Regitz, M. *Angew. Chem., Int. Ed. Engl.*, **1967**, *6*, 733-749; (b) Regitz, M. *Synthesis*, **1972**, 351-373; (c) Regitz, M.; Maas, G. "Transfer of Diazo

Groups" in *Newer Methods of Preparative Organic Chemistry; Vol. 6.* Forest, W., Ed.; Academic Press, New York, **1971**.

42) Regitz, M.; Rüter, J.; Liedhegener, A. *Org. Synth.*, **1971**, *51*, 86-89.

43) Forster, M. O. *J. Chem. Soc.*, **1915**, 260-267.

44) Meinwald, J.; Wheeler, T. N. *Org. Synth.*, **1988**, *6*, 840-844.

45) Newton, M. G.; Walter, T. J.; Allinger, N. L. *J. Am. Chem. Soc.*, **1973**, *95*, 5652-5658.

46) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.*, **1952**, 4735-5740.

47) Doyle, M. P. "Metal Carbene Complexes in Organic Synthesis: Diazodecomposition, Insertion and Ylide Chemistry," in *Comprehensive Organometallic chemistry II*; *Vol. 12.* Hegedus, L. S. Ed.; Pergamon Press, New York, **1995**.

48) Dave, V.; Warnhoff, E. W. *Org. React.*, **1970**, *18*, 217-401.

49) (a) Moser, W. R. *J. Am. Chem. Soc.*, **1969**, *91*, 1135-1140; (b) Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R. *Tetrahedron Lett.*, **1966**, *7*, 59-63.

50) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.*, **1973**, *95*, 3300-3310.

51) Aratani, T. *Pure Appl. Chem.*, **1985**, *57*, 1839-1844.

52) Pfaltz, A. *Acc. Chem. Res.*, **1993**, *26*, 339-345.

53) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.*, **1990**, *31*, 6005-6008.

54) Alonso, M. E.; Fernández, R. *Tetrahedron*, **1989**, 45, 3313-3320.

55) Paulissenen, R.; Reimlinger, H.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.*, **1973**, 2233-2246.

56) Doyle, M. P. *Acc. Chem. Res.*, **1986**, *19*, 348-356.

57) Boyar, E. B.; Robinson, S. D. *Coord. Chem. Rev.*, **1983**, *50*, 109-208.

58) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.*, **1992**, *114*, 1874-1876.

59) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.*, **1993**, *115*, 9968-9978.

60) Timmons, D. J.; Doyle, M. P; *J. Organomet. Chem.*, **2001**, *617-618*, 98-104.

61) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.*, **1928**, 3193.

62) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2951-2952.

63) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.*, **1979**, *101*, 6452-6454.

64) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.*, **1965**, *87*, 2511-2513.

65) (a) Iwamura, H.; Iwamura, M.; Nishida, T.; Yoshida, M.; Nakayama, J. *Tettrahedron Lett.*, **1971**, 63-66; (b) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1009-1027.

66) Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1491-1493.

67) Hata, Y.; Watanabe, M. *Tetrahedron Lett.*, **1972**, 4659-4660.

68) (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.*, **1994**, *116*, 8420-8421; (b) Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Commun.*, **1994**, 2701-2702.

69) Vanecko, J. A.; West, F. G. *Org. Lett.*, **2002**, *4*, 2813-2916.

70) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.*, **1981**, *46*, 5094-5102.

71) Doyle, M. P.; Bagheri, V.; Claxton, E. E. *J. Chem. Soc., Chem. Commun.*, **1990**, 46-48.

72) Williams, M. A.; Miller, M. J. *Tetrahedron Lett.*, **1990**, *31*, 1807-1810.

73) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.*, **1984**, *49*, 113-116.

74) West. F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis*, **1993**, 977-980.

75) (a) West, F. G.; Naidu, B. N. *J. Org. Chem.*, **1994**, *59*, 6051-6056; (b) West. F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.*, **1994**, *59*, 6892-6894.

76) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Chem. Commun.*, **1986**, 651-652.

77) Julian, P.; Pikl, J. *J. Am. Chem. Soc.*, **1935**, *57*, 755-757.

78) Hartke, K.; Roeber, H.; Matusch, R. *Chem. Ber.*, **1975**, *108*, 3256-3261.

79) Thorsett, E. D.; Harris, E. E.; Patchett, A. A. *J. Org. Chem.*, **1978**, *43*, 4276-4279.

80) Beak, P.; Lee, W. K. *J. Org. Chem.*, **1993**, *58*, 1109-1117.

81) Beak, P.; Kerrick, S. T.; Wu, S. D.; Chu, J. X. *J. Am. Chem. Soc.*, **1994**, *116*, 3231-3239.

82) *Encyclopedia of Reagents for Organic Synthesis, Vol. 7.* Paquette, L. A. Ed, Wiley, Chichester, UK, **1995**.

83) Punniyamurthy, T.; Katsuki, T. *Tetrahedron*, **1999**, *55*, 9439-9454.

84) (a) Bollinger, F. W.; Tuma, L. D. *Synlett*, **1996**, 407-413; (b) Leffler, J. E.; Tsuno, Y. *J. Org. Chem.*, **1963**, *28*, 902-906.

85) Anderson, R. J.; Coleman, J. E.; Piers, E.; Wallace, D. J. *Tetrahedron Lett.*, **1997**, *38*, 317-320.

86) Sugiyama, H.; Shioiri, T.; Yokokawa, F. *Tetrahedron Lett.*, **2002**, *43*, 3489-3492.

87) Hoffmann, H. M. R.; Last, K. *Synthesis*, **1989**, 901-905.

88) Matos, M. R. P. N.; Afonso, C. A. M.; McGarvey, T.; Lee, P.; Batey, R. A. *Tetrahedron Lett.*, **1999**, *40*, 9189-9193.

89) Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.*, **1981**, *46*, 4791-4792.

90) Nomura, Y.; Ogawa, K.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.*, **1977**, 693-696.

91) Marais, W.; Holzapfel, C. W. *Synth. Commun.*, **1998**, *28*, 3681-3691.

92) Matos, M. R. P. N.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron Lett.*, **2001**, *42*, 7007-7010.

93) (a) Matsuyama, H.; Kobayashi, M.; Wasserman, H. H. *Heterocycles*, **1987**, *26*, 85-90; (b) Takase, S.; Ulchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron*, **1986**, *42*, 5879-5886; (c) Wasserman, H. H.; Matsuyama, H.; Robinson, R. P. *Tetrahedron*, **2002**, *58*, 7177-7190.

94) Vilsmeier, A.; Haack, A. *Chem. Ber.*, **1927**, *60*, 119-122.

95) Brederck, H.; Brederck, K. *Chem. Ber.*, **1961**, *94*, 2278-2295.

96) Enders, D.; Meyer, O. *Liebigs Ann.*, **1996**, 1023-1035.

97) Ruck-Braun, K.; Kunz, H. *Chiral Auxiliaries in Cycloadditions*, Wiley-VCH, New York, **1999**.

98) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994**.

99) Fukui, K. *Acc. Chem. Res.*, **1971**, *4*, 57-64.

100) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, New York, **1976.**

101) Houk, K. N. *J. Am. Chem. Soc.*, **1973**, *95*, 4092-4094.

102) Casamitjana, N.; Lopez, V.; Jorge, A.; Bosch, J.; Molins, F.; Roig, A. *Tetrahedron*, **2000**, *56*, 4027-4042.

103) (a) Torisawa, Y.; Hosaka, T.; Tanabe, K.; Suzuki, N.; Motohashi, Y.; Hino, T.; Nakagawa, M. *Tetrahedron*, **1996**, *52*, 10597-10608; (b) Torisawa, Y.;

Nakagawa, M.; Takami, H.; Nagata, T.; Ali, M. A.; Hino, T.; *Heterocycles*, **1994**, *39*, 277-292; (c) Oppolzer, W.; Chapuis, C.; Bernardinelli, G.; *Helv. Chim. Acta*, **1983**, *67*, 1397-1401.

104) (a) Baldwin, S. W.; Greenspan, P.; Alaimo, C.; McPhail, A. T. *Tetrahedron Lett.*, **1991**, *32*, 5877-5880; (b) Vedejs, E.; Campbell, J. B.; Gadwood, Jr. R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.*, **1982**, *47*, 1534-1546; (c) Koot, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.*, **1992**, *57*, 1059-1061.

105) Seth, P. P.; Totah, N. I. *J. Org. Chem.*, **1999**, *64*, 8750-8753.

106) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.*, **1991**, *113*, 5463-5464.

107) Busacca, C. A.; Meyers, A. I. *J. Chem. Soc. Perkin Trans 1*, **1991**, 2299-2316.

108) Bocchi, V.; Chierici, L.; Gardini, G. P. *Tetrahedron*, **1970**, *26*, 4073-4032.

109) Alexakis, A.; Vrancken, E.; Mangency, P.; Chemla, F. *J. Chem. Soc., Perkin Trans. 1*, **2000**, *20*, 3352-3353.

110) (a) Okawa, T.; Sugimori, T.; Eguchi, S.; Kakehi, A. *Chem. Lett.*, **1996**, 843-844; (b) Okawa, T.; Sugimori, T.; Eguchi, S.; Kakehi. A. *Heterocycles*, **1998**, *47*, 375-382; (c) Eguchi, S; Tekeuchi, H. *J. Chem. Soc., Chem. Commun.*, **1989**, 602-603.

111) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.*, **1991**, *56*, 872-875.

112) (a) Pei, X. F.; Bi, S. *Heterocycles*, **1994**, *39*, 357-360; (b) Yu, Q. S.; Pei, X. F.; Holloway, H. W.; Greig, N. H.; Brossi, A. *J. Med. Chem.*, **1997**, *40*, 2895-2901.

113) Ioannou, M.; Porter, M. J.; Saez, F. *J. Chem. Soc., Chem. Commun.*, **2002**, 346-347.

114) (a) Kim, G.; Chumoyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **1990**, *112*, 2003-2005; (b) Kim, G.; Chumoyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.*, **1993**, *115*, 30-39.

115) Padwa, A.; Hasegawa, T.; Zhang, Z. *J. Org. Chem.*, **2000**, *65*, 7124-7133.

116) Coates, B.; Montgomery, D. J.; Stevenson, P. J. *Tetrahedron*, **1994**, *50*, 4025-4036.

117) McDonald, W. S.; Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.*, **1997**, *62*, 1215-1222.

118) Abdel-Baky, S.; Giese, R. W. *J. Org. Chem.*, **1986**, *51*, 3390-3391.

119 Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.*, **2004**, *43*, 478-482.

120) De Jong, J. C.; Van Bolhuis, F.; Feringa, B. L. *Tetrahedron-Asymmetry*, **1991**, *2*, 1247-1262.

121) Dieter, R. K.; Li, S. J. *J. Org. Chem.*, **1997**, *62*, 7726-7735.

122) Stone, M. J.; Vandyk, M. S.; Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1629-1635.

123) Ogawa, K.; Nomura, Y.; Takeuchi, Y.; Tomoda, S. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 3031-3035.

124) McNulty, J.; Still, I. W. J. *Synth commun.*, **1992**, *22*, 979-985.

125) Li, B.; Smith, M. B. *Synth. Commun.*, **1995**, *25*, 1265-1275.

126) Jacobi, P. A.; Guolin, C. *Hetrocycles*, **1993**, *35*, 1103-1120.

127) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.*, **1996**, *37*, 8257-8260.

128) Reppe V. W. *Justus Liebigs Ann. Chem.*, **1955**, *596*, 1-224.

129) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis* (2nd Edition), John Wiley & Sons, New York, **1991**.

130) Daoust, B.; Lessard, J. *Tetrahedron*, **1999**, *55*, 3495-3514.

131) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.*, **1982**, *104*, 5521-5523.

132) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.*, **1998**, *120*, 1757-1771.

133) Arkel, B. A.; Van der Baan, J. L.; Balt, S.; Bickelhaupt, F.; De Bolster, M. W. G.; Klumpp, G. W. *Tetrahedron*, **1995**, *51*, 4161-4172.

134) Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron*, **1997**, *53*, 14355-14368.

135) Schmidhammer, H.; Brossi, A. *Can. J. Chem.*, **1982**, *60*, 3055-3060.

136) Allspach, T.; Gümbel, H.; Regitz, M. *J. Organomet. Chem.*, **1985**, *290*, 33-39.

137) Collington, E. W.; Finch, H.; Smith, I. *Tetrahedron Lett.*, **1985**, *26*, 681-684.