The synthesis and applications of methyleneaziridines

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The Synthesis and Applications of Methyleneaziridines

by

Tracey M. Ross

A Doctoral Thesis

Submitted in partial fulfilment of the requirements

for the award of

Doctor of Philosophy of Loughborough University

September 1998

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Abstract

This thesis discusses the synthesis of novel methyleneaziridines based on current methods of syntheses, attempts to develop new methods of synthesis and applications of these novel compounds in organic chemistry.

Chapter One discusses the properties of these unusual compounds and reviews the literature relating to the synthesis and chemistry of methyleneaziridines.

Chapter Two describes attempts to prepare a variety of novel methyleneaziridines using sodium amide induced ring closure of 2-bromoallylamines. A variety of enantiopure methyleneaziridines derived from enantiopure amines and β-amino alcohols were successfully prepared using this method.

Chapter Three describes NMR studies to investigate the free energy barrier for nitrogen inversion in such methyleneaziridines.

Chapter Four describes some preliminary studies relating to addition reactions to the methyleneaziridine double bond. In particular, [2+2] cycloaddition reactions with tetracyanoethylene were explored. The stereochemical influence of the chiral nitrogen substituents on the outcome of these reactions was evaluated. Attempts to effect intermolecular radical additions to the methyleneaziridine double bond are also described.

Chapter Five describes attempts to provide alternative, more generally applicable routes to methyleneaziridines by using selenoxide eliminations and fluoride induced eliminations to introduce the exocyclic double bond.

Chapter Six describes full details of the experimental work undertaken in this thesis.
Acknowledgements

I am indebted to Dr. Michael Shipman for giving me this research project and providing me with a great deal of support and enthusiasm throughout, especially during the times when I needed it the most. I would also like to thank Dr. Russ Bowman for his help and advice over this last year and Dr. Tim Hodgkinson, for his valuable input during the writing up period.

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This wouldn't be complete without thanking the people that kept me afloat at times when all I wanted to do was sink, so thank you Vics (wake-up Hun!), Tim (blood pressure!), John Rudd (Lab Secretary), Kershaw, Lesley and Gabs for your friendship and Sandra also yours, but more importantly, your help with the crossword. Also Lou and Simon, with whom it was quite a good laugh down our end of the lab. The Lab Boys: Craig, Justin, Andy and Graham for their intellectual contributions to chemistry and their not so intellectual contributions to football, for which I am none the wiser (on the later point, obviously). Lastly, all the past inhabitants of F0001 for a truly unforgettable experience.

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To Mum and Dad
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<th>Full Form</th>
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<tr>
<td>Ac</td>
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<tr>
<td>Ad</td>
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<tr>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<tr>
<td>DMF</td>
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<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
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<td>E.I.</td>
<td>electron impact</td>
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<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<tr>
<td>IR</td>
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</tr>
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<td>Pr</td>
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### Abbreviations

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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
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<td>tetracyanoethylene</td>
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<tr>
<td>THF</td>
<td>tetrahydofuran</td>
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<td>TLC</td>
<td>thin layer chromatography</td>
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<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulphonyl</td>
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CHAPTER ONE

Introduction to Methyleneaziridine Chemistry
1.1 Introduction

In 1951, the first methyleneaziridine, N-ethyl methyleneaziridine 1 was prepared inadvertently and unknowingly by Pollard and Parcell, whilst they were attempting to make N-ethylallylideneamine 2 (Figure 1.1). Methyleneaziridines contain the elements of an aziridine, enamine and double bond. However, the chemistry of these compounds is not really understood simply by considering these elements separately, and the interplay of the functional groups generates some unusual reactivity patterns. This chapter reviews the methods available for the preparation of methyleneaziridines as well as their chemistry, laying the groundwork for our own studies in this field.

Figure 1.1

1.2 Structure and Bonding in Methyleneaziridines

1.2.1 Bonding and Ring Strain

Like other three-membered rings, methyleneaziridines display large distortions from natural bond angles. These distortions result from changes in the bond hybridisation to relieve the strain brought about by the unusually small bond angles. The ring σ bonds are not pure $sp^3$ hybrids, but contain more $p$ character. This allows for more effective overlap of orbitals which occurs outside the axis joining the nuclei of the ring atoms. As the $p$ character of the ring bond increases, the natural interorbital angle is reduced from its $sp^3$ value of about 109°, to nearer 90° and the ring bonds become 'bent' or 'banana-shaped' (Figure 1.2).\textsuperscript{2,3}
The electron distribution in the aziridine ring can be regarded as being constructed from the interaction of \( \pi \) and \( \pi^* \) orbitals of an ethylene fragment with empty and filled orbitals on the nitrogen atom. There are two types of interaction, the first (a), involves the transfer of the electron density to the nitrogen atom, the second (b), involves the back donation of the electron density to the ethylene fragment (Figure 1.3).³

(a) Interaction of ethylene \( \pi \)-orbital with unfilled orbital on nitrogen.
(b) Interaction of \( \pi^* \)-orbital with filled orbital on nitrogen.

The rehybridisation on nitrogen that occurs to accommodate the three membered ring results in the increase in \( s \) character on the lone pair. As a result, there is a decrease in the basicity of the aziridine compared with secondary aliphatic amines.³ The lone pair also interacts less efficiently than other amines with conjugated substituents, such as a phenyl attached to the nitrogen. The bonds attaching substituents to the aziridine ring also possess more \( s \) character. They are approximately \( sp^2 \) hybrids. All these changes in hybridisation can be detected by the \( ^{13}C-{^1}H \) coupling constants in NMR spectra. Increases in \( s \) character are accompanied by an increase in the magnitude of the coupling constant.⁴ Methyleneaziridines, while displaying all the above characteristics, have in comparison, a further increase in ring strain, due the presence of the exocyclic double bond.
1.2.2 Nitrogen Inversion Studies

The obvious bonding constraints in the aziridine ring have the effect of retarding the rate of inversion at nitrogen. This can be measured using inversion coalescence temperatures obtained from variable temperature NMR spectroscopy.\(^5\) 1-Ethyl-2-methyleneaziridine 1 has been studied by Bottini and Roberts (Figure 1.4).\(^6,7\) Their report states that only one resonance for the ring methylene is observed at room temperature. However at -80°C, two signals are detected, the temperature of coalescence being estimated at between -60 and -70°C, where the mean lifetime for the \(N\)-invertomers of 1 is about 0.03 seconds between these temperatures. Comparison with aziridine 3, the estimated mean lifetime of the two invertomers is 0.04 seconds at 110°C. Thus the rate of inversion for 1 is significantly faster.\(^6\)

![Figure 1.4](image)

This result would be expected if the conjugation between nitrogen and the double bond is considered (Figure 1.5). The effect of such delocalisation is thought to decrease the transition state energy barrier by aiding the attainment of the planar inversion transition state.

![Figure 1.5](image)

Interestingly, the solvent affects the rate of nitrogen inversion in these systems.\(^8\) Hydroxylic solvents such as 0.01 N methanolic sodium hydroxide, have been found to decrease the rate of inversion of 1-ethyl-2-methyleneaziridine 1. This is thought to be as a result of stabilisation of the ground state through hydrogen bonding. Neat 1-ethyl-2-methyleneaziridine has an inversion rate constant of approximately 67 sec\(^{-1}\) at -65 ± 10°C. In 0.01 N methanolic sodium hydroxide, this rate of inversion is not reached until the temperature is raised to -25°C ± 10°C.

Evidence suggests that the more readily an aziridine is able to delocalise the nitrogen lone pair, the lower the energy barrier and hence faster the rate of inversion. The inversion rates and activation energies for many aziridines have been determined and can give dramatically
different rates of nitrogen inversion. For example, ester 4, which can delocalize the nitrogen lone pair onto the carbonyl group, possesses a low barrier. In contrast, chloro substituted aziridine 5, has one of the highest inversion barriers (Figure 1.6).

![Figure 1.6](image.png)

The energy barrier of 1-chloro-2-methyleneaziridine 5 is so large that the invertomers 5a and 5b (Figure 1.7) have been separated by GLC and their individual $^1$H NMR spectra recorded. 

![Figure 1.7](image.png)

1.2.3 Spectroscopic Properties

Proof of the incorrect assignment made by Pollard and Parcell was supplied by Infrared and $^1$H NMR data (see section 1.1). Methyleneaziridines show an intense infrared band at 1770 cm$^{-1}$, a unique feature of the double bond. $^1$H NMR identifies the aziridine hydrogens which display chemical shifts of between 1.9 and 2.1 ppm, depending on the nature of the nitrogen substituent. The hydrogens attached to the double bond typically resonate at 4-5.5 ppm.
1.3 Synthesis of Methyleneaziridines and Related Structures

1.3.1 Cyclisation of N-Bromoallylamines

1.3.1.1 Synthetic Scope

The very first methyleneaziridine 1 was prepared by Pollard and Parcell by reaction of N-(2-bromoallyl)-ethylamine 6 with 1.15 molar equivalents of sodium amide in liquid ammonia for a period of 12 hours.\(^1\) However, it was several years later before Bottini and Roberts correctly established the structure of the product of this reaction.\(^10\)

Bottini and Oslen, subsequently modified this procedure by significantly reducing the amount of liquid ammonia and the reaction time.\(^11\) This is essentially the method widely used today, although Quast and Risler obtained higher yields of products using increased amounts of sodium amide (15 equivalents).\(^12\)

![Scheme 1.1](image)

The synthesis of the requisite bromoallylamines 7 is relatively straightforward. Bottini and Oslen achieved this via N-alkylation of 2,3-dibromopropene 8 in water stirred with the appropriate amine 9 (3 equivalents), many of which are commercially available, at room temperature (Scheme 1.2). The yields they report are high, generally around 80%.\(^13\)

![Scheme 1.2](image)

At the start of this project, only a limited range of methyleneaziridines had been synthesised using this method (Scheme 1.3). Most of the examples reported relate to the preparation of methyleneaziridines possessing just simple alkyl groups with little other functionality.
Chapter 1: Introduction to Methyleneaziridine Chemistry

Methyleneaziridines are reasonably stable at room temperature. Pure samples have been stored at 0°C for well over a year with no significant deterioration. The best method of purification of low molecular weight methyleneaziridines is by distillation as many of these derivatives have only limited stability to column chromatography. Although this sodium amide cyclisation reaction produces predominately the desired methyleneaziridine, the corresponding N-substituted acetylene 9 is often produced as a side product (Scheme 1.4).17

Other amide bases have also been used. Lithium, sodium and potassium amides can all be used in this cyclisation reaction (Scheme 1.4).12 It has been shown using a 1:2 amine : amide ratio that no significant differences in the yields or composition are observed by switching counter ion.

In exactly the same way, the Pollard and Parcell method can be used to make methyleneaziridines bearing substituents on the double bond by cyclisation of the corresponding 3,3-disubstituted N-alkyl-(2-bromo-2-allyl)amines. For example, Quast and Risler made dimethyl substituted methyleneaziridine in 60% yield using this chemistry (Scheme 1.5).11

Scheme 1.3

Scheme 1.4
Steinberg and co-workers showed that such cyclisations can be facilitated using butyllithium (2 equivalents), in THF/hexane at temperatures between -60 and -70°C (Scheme 1.6). The authors maintain that this method is more convenient than the use of sodium amide in liquid ammonia as it does not give rise to a mixture of isomeric products. However, this methodology cannot be used to prepare 2-methyleneaziridines (Vide Infra).

R = i-C₃H₇, cyclopropyl, n-C₄H₉, CH₂C(CH₃)₃, C₂H₅, 1-adamantyl.
1.3.1.2 Mechanistic Studies

Several mechanisms for the formation of methyleneaziridines from \( N-(2\text{-bromoallyl}) \)-amines have been proposed.\(^{19,20}\) Bottini and Oslen investigated the plausibility of these mechanisms using \( N \)-propylbromoallyl amine \( 11 \), and tritium-labelled ammonia instead of ammonia, produced by equilibrating ammonia with a small quantity of tritium oxide. They were able to establish that methyleneaziridines were primarily formed via an allene intermediate \( 12 \) involving an elimination-addition reaction (Scheme 1.7).\(^{13}\)

\[
\begin{align*}
\text{H}_2\text{C} &\equiv\text{C} \equiv\text{C} - \text{N-Pr} \\
\text{H} &\quad \text{H} \\
\text{Br} &\quad \text{H} \\
\text{N-Pr} &\quad \text{N-Pr} \\
\hline
\text{H}_2\text{C} &\equiv\text{C} \equiv\text{C} - \text{N-Pr} \\
\text{H} &\quad \text{H} \\
\text{N-Pr} &\quad \text{N-Pr} \\
\hline
\text{11} &\quad \text{12} &\quad \text{13}
\end{align*}
\]

Scheme 1.7

Treatment of \( 11 \) with sodium amide and tritiated liquid ammonia gave the aziridine \( 15 \) in 39\% yield along with a small amount of the corresponding acetylene which was removed by distillation from lithium aluminium hydride at reduced pressure.

The resultant purified aziridine \( 15 \) possessed a specific radioactivity which was in agreement with that of the starting labelled ammonia. They further demonstrated that the protons of \( 11 \) and \( 15 \) did not exchange readily with those of the solvent under the reaction conditions. Treatment of \( 11 \) with sodium amide in tritium-labelled liquid ammonia, and treatment of radioactive \( 15 \) with sodium amide in ordinary liquid ammonia caused no significant change in the specific activity of either compound. Therefore, the proton must be donated by ammonia during the course of the cyclisation reaction.
Chapter 1: Introduction to Methyleneaziridine Chemistry

Radioactive methyleneaziridine 15 was converted to propanal 16, which still showed radioactivity (Scheme 1.8). Subsequent oxidation to propanoic acid 17, resulted in loss of the activity. This experiment provided proof that carbon atom 1 must be the site of tritium incorporation. These findings are consistent with the mechanism presented in Scheme 1.7. These results do not establish that this is the sole route to methyleneaziridine formation, but it is perhaps the most feasible route.13

![Chemical structure of 15, 16, and 17](image)

Scheme 1.8

1.3.1.3 Acetylene Formation

Interestingly, the amount of acetylene formation has been show to vary according to the nature of the halogen (X) contained within the amine precursor.14 Bottini and Oslen report moderate yields of methyleneaziridine when X is bromine with the corresponding acetylene being generated in very small quantities. However, when bromine is replaced with a chlorine atom, the acetylene is predominately formed. In some cases, acetylene formation is greater than 99% compared with aziridine formation at less than 1% of the product mixture.

The authors suggest a possible dehydrohalogenation occurring in direct competition with aziridine formation (Scheme 1.9).

![Chemical structure of Scheme 1.9](image)

Scheme 1.9
Chapter 1: Introduction to Methyleneaziridine Chemistry

1.3.2 Nitrene Addition to Allenes

Using an intrinsically different approach to methyleneaziridines, Bingham and Gilbert were able to show that methoxycarbonyl, generated by the base catalysed decomposition of 18, gives 1-ethyl-2-methyleneaziridine 20a in the presence of excess allene 19a (Scheme 1.10). A similar reaction was performed using 1,1-dimethylallene 19b which yielded 2-isopropylidene-N-carboxyaziridine 20b. Unfortunately, the very low yields of these reactions (6-8%) do not make them synthetically very useful.

\[
\begin{align*}
\text{Et}_3\text{N} \quad \xrightarrow{\text{R}^1=\text{R}^2=\text{H}} \quad \text{CO}_2\text{Me} \\
\text{Et}_3\text{N} \quad \xrightarrow{\text{R}^1=\text{R}^2=\text{Me}} \quad \text{CO}_2\text{Me}
\end{align*}
\]

Scheme 1.10

In somewhat related work, Atkinson and Malpass reacted methyl 2-methyl-2,3-dienoate 21 with what was then thought to be phthalimidonitrene 23 (Scheme 1.11).

Diazaspiropentane 23 was isolated in 14% yield, which one can speculate is derived from the intermediate methyleneaziridine 24 although this was not isolated from the reaction mixture (Figure 1.8).

\[
\begin{align*}
\text{N-N} \\
\text{N-N}
\end{align*}
\]

Scheme 1.11

Figure 1.8
1.3.3 Dehydrobromination of 2-(Bromomethyl)aziridines

De Kimpe and co-workers have recently published a relatively mild method for the preparation of 2-methyleneaziridines. This method involves base induced 1,2-dehydrobromination of 2-(bromomethyl)aziridines $^{25,24,25}$ to give the corresponding methyleneaziridine $^{26,26}$ using potassium tert-butoxide as the base. They report the yields to range from 40-48% after purification using high vacuum distillation. The reaction also produces the corresponding 2-(tert-butyloxymethyl)aziridines $^{27a-d}$ in approximately equal amounts (Scheme 1.12).

\[
\text{R} \quad \text{Br} \quad \text{1.5 equiv. KOtBu} \quad \text{THF, rt, 24 hours} \quad \text{1.5 equiv. KOtBu} \quad \text{THF, rt, 24 hours} \\
\text{25a-d} \quad \text{26a-d} \quad \text{27a-d}
\]

a: R = Ph
b: R = 4-MePh
c: R = 4-ClPh
d: R = CMe$_2$CH$_2$Ph

Scheme 1.12
1.4 Reactions of Methyleneaziridines

1.4.1 Addition Reactions

1.4.1.1 Reactions with Organic Azides

It has been shown that methyleneaziridine 29 reacts slowly (4 days at 90°C) with phenylazide to give triazole 30 as the major product (Scheme 1.13). The formation of 30 is modelled on the exclusive mode of addition of azides to enamines.27 The terminal nitrogen atom of the azide attacks the exocyclic carbon of 29 as the resultant species is the most likely to stabilise a positive charge. The triazoline 31 on formation, is highly unstable, and subsequently isomerizes to triazole 30, thereby providing relief of the ring-strain of the aziridine ring.28

![Scheme 1.13](image)

Lactamimide 32 was isolated as a minor product in this reaction. The formation of this product is presumed to involve ring opening of triazoline 31 to 33, followed by rearrangement involving loss of molecular nitrogen. Zwitterion formation is favoured by the presence of strongly electron withdrawing groups on the azide resulting in the predominance of amidine products (Scheme 1.14).29

![Scheme 1.14](image)

It was not surprising therefore, that p-toluenesulphonyl azide, on reaction with methyleneaziridine 29 gave lactamimidine 34 as the sole product. Similarly, tert-butoxycarbonyl azide and ethyl azidoformate gave lactamimides 35 and 36, respectively (Fig. 1.9).
1.4.1.2 Reactions with Tetracyanoethylene

1-Ethyl-2-methyleneaziridine 1 undergoes double bond addition to tetracyanoethylene in refluxing acetone to give the 1:1 adduct, 1-azaspiro[2,3]hexane 37, the structure for which was supported by \(^1\text{H}\) NMR spectroscopy (Scheme 1.15).\(^{30}\) The ethyl group methylene hydrogens of 1 appear as a quartet, but in 37 they appeared as a multiplet of sixteen peaks, which suggests two magnetically different protons.

1.4.1.3 Reaction with Dimethyl Acetylenedicarboxylate

Methyleneaziridine 1 has been found to react with excess dimethyl acetylenedicarboxylate in acetone at room temperature (Scheme 1.16). After stirring for 2 hours, adduct 38 was produced in 31% yield.\(^{30}\) Cookson and co-workers suggested that 38 is formed by an initial addition reaction to give 39, followed by ring-opening to give 40, which further isomerises to 41. Finally, addition of a third carboxylate took place to give 38 although the mechanism of this final interconversion was not detailed (Scheme 1.16).
1.4.1.4 Reactions with Butadiene

Methyleneaziridine 44 can be co-oligomerized with two equivalents of butadiene by nickel catalysts (Scheme 1.17). Four products can be isolated, the product distribution depends on the nature of the additional ligand in the catalyst and on the nickel-ligand ratio. For example, when L⁰ is used, the major product is bicyclic structure 43. When L² is used, the distribution of the products 43, 44 and 45/46 is more evenly spread. When only nickel is used the major product is 45/46.
1.4.1.5 Reaction with Carbon Monoxide

Metal catalysed carbonyl insertion are known to occur into various strained ring systems including aziridines and \(\alpha\)-lactams. Alper has shown that methyleneaziridine undergoes similar carbon monoxide insertion reactions to give the corresponding \(\alpha\)-methylene-\(\beta\)-lactam, in moderate yields (Scheme 1.18). The reaction proceeds regiospecifically due to the ability of the double bond to \(\pi\) complex to the metal.

The metal may also co-ordinate to the nitrogen atom by means of its lone pair of electrons allowing carbon monoxide insertion to take place into the unsaturated carbon-nitrogen bond. This chemistry provides a useful route to \(\beta\)-lactams which are of course, an important class of compounds.
Chapter 1: Introduction to Methyleneaziridine Chemistry

\[
\begin{align*}
\text{R} & \quad \text{CO} & \quad \text{Pd catalyst} & \quad \text{10-38\%} & \quad 48_{a-e} \\
47_{a-e} & \\
\end{align*}
\]

a: \( R = n-C_4H_9 \)
b: \( R = n-C_6H_{13} \)
c: \( R = 1\text{-adamantyl} \)
d: \( R = CH_2CH_2CH_2OCH_3 \)
e: \( R = CH_2CH(OCH_3)_2 \)

**Scheme 1.18**

1.4.1.6 Reactions with Singlet Oxygen

Photo-oxygenation of 2-adamantylideneaziridine 49 in deuteriochloroform at 15°C using methylene blue as sensitizer, led to the formation of adamantane 50, obtained as the sole isolated product (Scheme 1.19).\(^3\) The proof that singlet oxygen is the oxidising species is shown by the fact that aziridine 49 was stable under the given reaction conditions in the absence of light and the sensitizer. A singlet oxygen quencher was also found to inhibit the reaction.\(^3\) The presence of dioxetane 51 was confirmed by \(^1\)H and \(^13\)C NMR studies at -78°C. Interestingly, on warming to -50°C, a decrease of the dioxetane peaks were observed along with an increase in signals assigned to \(\alpha\)-lactam 52. Attempts to isolate the inherently explosive dioxetane 51 using flash distillation resulted in decomposition to 50 and 52.

\[
\begin{align*}
\text{C(CH}_3\text{)}_3 & \quad \text{50} & \quad \text{52} & \quad \text{51} \\
49 & \quad & & \quad \\
\end{align*}
\]

**Scheme 1.19**

\(\alpha\)-Lactam 52, could not be trapped by methanol, but was successfully converted to the oxaziridine 53, in 27% yield by oxidation with \(m\)-CPBA in the presence of sodium carbonate (Scheme 1.20).\(^3\)
1.4.2 Substitution Reactions

Quast and Vélez showed that 1-tert-butyl-2-methyleneaziridine 54, could be lithiated using n-butyllithium / TMEDA at -78°C to give 2-lithio-1-tert-butyl-3-methyleneaziridine 55 which is reported to be stable up to about 50°C (Scheme 1.21). 39

When 55 was treated with various electrophilic reagents (MeOD, MeI, SiMe₃Cl), the ring substituted methyleneaziridines 56a-c were formed with yields ranging from 30-69%, along with significant amounts (31-70%) of unreacted starting material 54 (Scheme 1.21).

The authors did find, however, by using sec-butyllithium / TMEDA, at -78°C, the anion was formed completely in a shorter period of time, resulting in much higher yields. 56c was also prepared in optically active form (12.4% ee) by lithiation of methyleneaziridine 54 using sec-butyllithium in pentane at -125°C, in the presence of the chiral additive, (S, S)-(+) -1,4-bis-(dimethylamino)-2,3-dimethyloxybutane [(+) -DDB]. 40

4.3.1 Protonation and Methylation of Methyleneaziridines

It has been shown that using strong acids, methyleneaziridines can be protonated on nitrogen without noticeable attack on the double bond and without rupture of the ring. De Boer and co-workers accomplished this by extracting methyleneaziridines 57a and 57b from solutions of pentane with cold (-78°C) solutions of HFSO₃/SbF₅ in SO₂ to give the methyleneaziridinium ions 58 (Scheme 1.22). 41 The products were studied and characterised by ¹H NMR and IR spectroscopy.
Methylation of 57a was achieved by extraction of a pentane solution of 57a with a solution of a dimethylchloronium salt (CH$_3$)$_2$Cl+$\text{SbF}_5\text{Cl}^-$, dissolved in liquid sulphur dioxide at -78°C, yielding methyleneaziridinium ion 59 (Scheme 1.23). Interestingly, the authors report that compounds 58a, 58b and 59 show remarkable thermal stability and when SO$_2$ was replaced by FS$_2$O$_3$H as the solvent, no changes in their measured NMR spectra were observed up to +50°C. Attempts to use other methylating agents such as methyl fluorosulphate led to the formation of a water soluble polymer.

### 1.4.4 Thermal Reorganisation of Methyleneaziridines

Quast and Velez have shown that methyleneaziridinium undergo thermal rearrangement reactions when heated at temperatures above 140°C (Scheme 1.24). Cyclopropanimines 61a-c were always the primary products which slowly converted to ethene and isonitrides 62a-c.
Steinberg and co-workers have also shown that methyleneaziridine ions undergo rearrangement. When a solution of 1,1-dimethyl-2-methyleneaziridinium ion 59 in \( \text{FSO}_3\text{H} / \text{SbF}_5 \) is heated to 115°C, NMR shows that iminium ion 63 is rapidly formed (Scheme 1.25). This rearrangement takes place at a lower temperature (115°C) than that of the corresponding methyleneaziridine (150°C-190°C). They further demonstrated that the iminium ion 63 is stable up to 150°C, then starts to slowly decompose to uncharacterised ring-opened products.

![Scheme 1.25](image)

1.4.5 Ring-Opening Reactions

1.4.5.1 Hydrogenation

Bottini and co-workers found it necessary to hydrogenate methyleneaziridine 64 to amino alcohol 65, in order to relate the configuration of an optically active form of methyleneaziridine 64 to amino alcohol 65, synthesised by another method. This was achieved using 30-35 p.s.i of hydrogen over Adams' catalyst giving amino alcohol 65 in 50% yield (Scheme 1.26).

![Scheme 1.26](image)

1.4.5.2 Reaction with Phenol

Crandall and co-workers found on reaction of methyleneaziridine 66 with phenylazide, diphenyl ketal 67 was formed as a minor product. It was deduced that phenol was present as an impurity in the phenyl azide. When the reaction was repeated using purified phenyl azide, ketal 67 was not isolated. Formation of the diphenyl ketal was reproduced on reaction of 66 with excess phenol at 25°C. The authors propose the reaction probably proceeds via Markovnikov addition of phenol to the exocyclic double bond to give 68 which subsequently
undergoes ring opening and addition of a second molecule of phenol to give 67 (Scheme 1.27).²⁸

\[ \begin{array}{c}
\text{66} \\
\rightarrow \\
\text{68} \\
\rightarrow \\
\text{67}
\end{array} \]

Scheme 1.27

1.4.5.3 Reactions with Chloroformates and Acid Chlorides

Recent results from our laboratories have demonstrated that methyleneaziridines 69 can undergo ring-opening reactions using chloroformates or acid chlorides under relatively mild conditions to give the corresponding enamides 70 in yields ranging from 50-85% (Scheme 1.28).⁴³ These reactions are believed to proceed via the N-acyl aziridinium ion 71 which is subsequently ring opened by chloride anion via an SN2 reaction.

\[ \begin{array}{c}
\text{MeOCCl, rt, 24 hr} \\
\text{69a-d} \\
\rightarrow \\
\text{71} \\
\rightarrow \\
\text{70a-d}
\end{array} \]

Scheme 1.28

a: \( R^1 = \text{Ph}, R^2 = \text{CH}_3 \)
b: \( R^1 = \text{CH}_2\text{OBn}, R^2 = \text{Ph} \)
c: \( R^1 = \text{CH}_2\text{OBn}, R^2 = \text{CH}(\text{CH}_3)\_2 \)
d: \( R^1 \text{ and } R^2 = -\text{CH}_2(\text{CH}_2)_3\text{CH}_2^- \)
1.5 Methyleneaziridines as Transient Intermediates

Deyrup and Greenwald were able to show that cis-chloro-3-methyl-1,2-diphenylaziridine 72, when heated under reflux for 90 minutes with an excess of a hindered base (potassium tert-butoxide) in tert-butanol, gave amide 73 in 23-46\% isolated yield (Scheme 1.29).44

\[ \text{Scheme 1.29} \]

The authors believe this rearrangement is initiated by base induced elimination to methyleneaziridine 74 (cf Scheme 1.12), which undergoes thermal isomerisation to imine 75. tert-Butoxide intercepts imine 75, yielding 76 which undergoes ring opening to the observed amide 73 (Scheme 1.30). In support of this mechanism, methyleneaziridine 74 has been detected and isolated from the reaction mixtures.

\[ \text{Scheme 1.30} \]
1.5 Biological Activity of Methyleneaziridines

Methyleneaziridines do not occur in nature, although many aziridine containing natural products such as Mitomycin are known. Often, aziridine-containing molecules exhibit biological activity principally because of their ability to act as powerful electrophiles.

In view of the strained nature of the methyleneaziridine ring system, one may anticipate that methyleneaziridines may possess some interesting biological activity. Surprisingly, very little work in this area has been undertaken. Bottini and Dev were interested to discover if 1-(2-methylene-1-aziridinyl)-3-butene-2-ol 77 would serve as a potent analogue of the anti-neoplastic drug Tetramin 78. However, it was found that methyleneaziridine 77 showed little potency. It was proposed that the greater bulk of the exocyclic double bond distorted the alignment of methyleneaziridine 77 within the biological active site.

In conclusion, the above introduction summarises methyleneaziridine research over the last forty years which might still be considered to be in its infancy. As has been seen, there is no single general method for the synthesis of methyleneaziridines and their potential as intermediates in organic synthesis still remains largely untapped.
CHAPTER TWO

Synthesis of Methyleneaziridines Using Cyclisation Reactions
Chapter 2: Synthesis of Methyleneaziridines using Cyclisation Reactions

2.1 Introduction

The method developed by Pollard and Parcell\textsuperscript{1} provided an ideal starting point for our studies in the synthesis of novel, homochiral methyleneaziridines. A straightforward \(N\)-alkylation of readily available chiral amines and their subsequent aziridination, using applications of the method developed by Quast and Riser\textsuperscript{12} was envisaged. Initial studies were focused on the synthesis of chiral, nonracemic methyleneaziridines of types 79-81 (Figure 2.1).

The decision to synthesis homochiral 1-(1-phenylethyl)-2-methyleneaziridine 79 was made on the basis of the known stability of the \(N\)-benzyl group to a wide range of reaction conditions and the ease with which the benzylic C-N bond can be cleaved by hydrogenation.\textsuperscript{47} Thus we imagined that a single enantiomer of methyleneaziridine 79 might prove to be useful as an intermediate for asymmetric synthesis.

In addition, we chose to prepare a range of ether containing methyleneaziridines such as 80 and 81 to examine whether the additional oxygen substituent may exert some influence on the stereochemical outcome of the subsequent reactions. We believed that these might be made from the corresponding commercially available, enantiomerically pure, \(\beta\)-amino alcohols.

\begin{center}
\begin{tabular}{ccc}
\textbf{79} & \textbf{80} & \textbf{81} \\
\end{tabular}
\end{center}

\textbf{Figure 2.1}

2.2 Preliminary Investigations

2.2.1 Synthesis of \(N\)-(1-Phenylethyl)-2-bromoallylamine

Using the method developed by Steinberg and co-workers,\textsuperscript{18} reaction of racemic \(\alpha\)-methylbenzylamine (2 equivalents) with 2,3-dibromopropene (1 equivalent) gave the \(N\)-alkylated product 82 in 49% yield after silica gel chromatography. Although a seemingly simple reaction, it was important to optimise the conditions for this reaction as we anticipated the use of expensive chiral amines in subsequent variants of this reaction. The results of attempts to optimise this reaction are summarised in Table 2.1.
Chapter 2: Synthesis of Methyleneaziridines using Cyclisation Reactions

\[
\begin{align*}
\text{Br} & \quad \text{Ph} \\
\text{Br} & \quad \text{H}_2\text{N} & \quad \text{Me}
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{Br} & \quad \text{H} & \quad \text{Ph} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[82\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine : Alkyl halide : Base</th>
<th>Reaction conditions</th>
<th>% Yield$^\text{§}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 : 1 : 0</td>
<td>80°C, 60 minutes</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>2 : 1 : 0</td>
<td>rt, 24 hours, acetonitrile</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>1 : 1 : 0</td>
<td>rt, 24 hours, acetonitrile</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1 : 1 : 1</td>
<td>rt, 24 hours, acetonitrile, K$_2$CO$_3$</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>2 : 1 : 1</td>
<td>rt, 24 hours, acetonitrile, K$_2$CO$_3$</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>1 : 1 : 0</td>
<td>rt, 24 hours, diethyl ether</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>2 : 1 : 1</td>
<td>rt, 24 hours, diethyl ether, K$_2$CO$_3$</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>2 : 1 : 1</td>
<td>rt, 48 hours, diethyl ether, K$_2$CO$_3$</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>2 : 1 : 1</td>
<td>reflux, 24 hours, THF, K$_2$CO$_3$</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>1.5 : 1 : 1</td>
<td>rt, 24 hours, diethyl ether, K$_2$CO$_3$</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 2.1. $^\text{§}$Isolated yields after column chromatography.

The best yields were obtained (Entries 7-9) when acetonitrile was replaced with a less polar solvent, diethyl ether or THF. The use of potassium carbonate enhanced the yield, presumably because it helps remove HBr from the mixture inhibiting quaternisation of the amine. When the reaction mixture was heated at 80°C, only 31% of product was isolated and none of the initial amine was recovered (Entry 1). Unfortunately, decreasing the molar ratio of the amine, even in the presence of potassium carbonate, resulted in a decrease in product yield (Entry 3 and 6). Eventually, we settled for performing such alkylations employing a two fold excess of the amine in refluxing ether solvent (THF or diethyl ether) in the presence of 1 equivalent of potassium carbonate.
2.2.2 Attempted Cyclisation Using Butyllithium

Initially, we attempted to effect ring closure of bromoallyl amine 82 to methyleneaziridine 79 using butyllithium in THF. However, this method proved unsuccessful, a 46% yield of the corresponding acetylene 83 was exclusively obtained (Scheme 2.1). The presence of the acetylene proton was readily established by $^1$H NMR indicated by a multiplet at 2.02 ppm, and by two distinct infrared bands (3300, 2131 cm$^{-1}$).

![Scheme 2.1](image)

In some respects, we were not surprised by the failure of this reaction. In the original paper on butyllithium-mediated cyclisation reactions to methyleneaziridines, only the formation of iso-propylideneaziridines was described.$^{18}$ In contrast to sodium amide in ammonia, $n$-butyllithium (in THF) is a very powerful, irreversible base.

On the addition of the first equivalent of base to substrate, deprotonation of the amine presumably occurs. The second equivalent of butyllithium deprotonates the most acidic proton, $H_a$, leading to the formation of the acetylene product. When $H_a$ is not present, i.e. replaced by a methyl group, deprotonation can occur at $H_b$. The resultant allene product is believed to be an intermeadiate en route to the methyleneaziridine product (Scheme 2.2).

![Scheme 2.2](image)
To try and substantiate these ideas further, we considered preparing bromoallylamine 84 and examining its cyclisation with n-butyllithium. However, the preparation of this precursor proved problematic. Addition of dibromocarbene to 2-methylpropene, gave dibromo substituted cyclopropane 85 in 70% yield. Unfortunately, attempts to ring-open the cyclopropane met with little success.\textsuperscript{16}

Heating cyclopropane 85 under reflux with \(\alpha\)-methylbenzylamine in 1,2-dichlorobenzene (b.p. 180°C) resulted mainly in the decomposition of the amine. Heating cyclopropane 85 alone, neat at 220°C for periods of up to 4 hours in an attempt to isomerise it to the dibromide also failed (Scheme 2.3).
Chapter 2: Synthesis of Methyleneaziridines using Cyclisation Reactions

2.2.3 Cyclisation Using Sodium Amide

Using an adaptation of the method of Quast and Risler,\(^\text{12}\) (±)-82 was reacted with 15 equivalents of sodium amide in refluxing liquid ammonia for a period of 45 minutes. Methyleneaziridine 79 was identified as the major product (Scheme 2.4). Acetophenone 86 was also present as a minor side product, the molar quantities ranging from 10% to 40% of the reaction mixture.

The corresponding acetylene 83 was not observed under these conditions. However, the purification of methyleneaziridine 79 initially proved very difficult. Bulb to bulb distillation (85°C / 3-5 mmHg) failed to improve the purity of the product. Column chromatography, even using silica pre-treated with triethylamine resulted in rapid product decomposition. Fluorosil™ and alumina were also ineffective for chromatography.

The following proposals for acetophenone formation are merely speculative. The possibility that acetophenone is present as an impurity in the starting material has been eliminated. The most obvious routes to acetophenone formation are either by elimination and subsequent hydrolysis of bromoallylamine 82, or further reactions of the methyleneaziridine product 79.

It is worth noting that when the reaction time is severely reduced to 5 minutes (\textit{Vide Infra}) acetophenone is not formed. This suggests the more likely source of acetophenone is from the methyleneaziridine, showing its precarious stability to longer reaction times. One possible route for the formation of acetophenone from the methyleneaziridine is outlined below. It requires deprotonation at the benzylic carbon, ring cleavage and subsequent hydrolysis on addition of water (Scheme 2.5). Enamine 87 was not isolated, but presumably would be hydrolysed to acetone on work up.

\[
\begin{align*}
82 & \xrightarrow{\text{NaNH}_2, \text{NH}_3, -33^\circ\text{C}} 45 \text{minutes} \quad 79 & + \quad 86 \\
\text{Me} \quad \text{Ph} & \quad \text{Me} \quad \text{Ph} & \quad \text{O} \quad \text{Me} \quad \text{Ph}
\end{align*}
\]

Scheme 2.4

The following proposals for acetophenone formation are merely speculative. The possibility that acetophenone is present as an impurity in the starting material has been eliminated. The most obvious routes to acetophenone formation are either by elimination and subsequent hydrolysis of bromoallylamine 82, or further reactions of the methyleneaziridine product 79.

It is worth noting that when the reaction time is severely reduced to 5 minutes (\textit{Vide Infra}) acetophenone is not formed. This suggests the more likely source of acetophenone is from the methyleneaziridine, showing its precarious stability to longer reaction times. One possible route for the formation of acetophenone from the methyleneaziridine is outlined below. It requires deprotonation at the benzylic carbon, ring cleavage and subsequent hydrolysis on addition of water (Scheme 2.5). Enamine 87 was not isolated, but presumably would be hydrolysed to acetone on work up.
2.2.4 Synthesis of a Known Methyleneaziridine

In light of the results obtained, we decided to synthesise a methyleneaziridine of similar structure to 79, e.g. phenylethylmethyleneaziridine 88, in which no side products have been reported. It would be interesting to observe, if under the same reaction conditions as used above, deprotonation at the benzylic carbon was occurring.

Standard N-alkylation using phenylethylamine (2 equivalents) with 2,3-dibromopropene (1 equivalent) gave the monosubstituted amine 89 in 50% yield (Scheme 2.6).

\[
\text{Scheme 2.6}
\]

Reaction of amine 89 with 15 equivalents of sodium amide, gave methyleneaziridine 88. The product mixture showed acetylene 90 and styrene 91 to be also present (Scheme 2.7). The ratio of methyleneaziridine : acetylene : styrene was 80 : 15 : 5 as determined by \(^1\)H NMR spectroscopy.

Again, problems were encountered in purifying the methyleneaziridine product. Simple bulb-to-bulb distillation failed to separate the three components. However, the stability of methyleneaziridine 88 to silica (pre-treated with triethylamine) was slightly better compared with methyleneaziridine 79, enabling its isolation in 31% yield.
Chapter 2: Synthesis of Methyleneaziridines using Cyclisation Reactions

Styrene formation is envisaged to result from deprotonation of the β-carbon atom of the vinyl bromide 89 or methyleneaziridine 88 followed by subsequent β-elimination (Scheme 2.8). The identification of styrene from the reaction mixture lends support to the idea that benzylic deprotonation is occurring under these reaction conditions. In terms of preparing chiral material, this observation has significant implications as deprotonation / reprotonation may result in the racemisation at the benzylic centres.

2.2.5 Synthesis of (S)-1-(1-Phenylethyl)-2-methyleneaziridine

Returning to the synthesis of methyleneaziridine 79, we examined a variety of methods for improving the cyclisation conditions. Eventually, we discovered that by reducing the reaction time to just 5 minutes, much cleaner cyclisation reactions could be accomplished. Using homochiral bromoallylamine 82, prepared from (S)-α-methylbenzylamine, cyclisation to (S)-79, could be readily accomplished.
Chapter 2: Synthesis of Methyleneaziridines using Cyclisation Reactions

Under these modified conditions, the reaction proved extremely clean and a simple bulb-to-bulb distillation furnished the pure methyleneaziridine (S)-79 in 76% isolated yield (the (R)-enantiomer of methyleneaziridine 79 can be prepared in an identical fashion).

\[
\text{MeHPh} \xrightarrow{i} \text{MeHPh} \quad \text{NH} \quad \xrightarrow{ii} \text{MeHPh} \quad \text{N} \\
\text{76%} \quad \text{76%} \\
82 \quad (S)-79 \quad \geq 95\% \text{ ee}
\]

Reagents and conditions: i) 2,3-dibromopropene, K$_2$CO$_3$, THF, rt, 2 days. ii) NaNH$_2$ (15 eq), NH$_3$, -33°C, 5 minutes.

Scheme 2.9

In the presence of the chiral shift reagent, tris[3-(heptafluoropropyldioxymethylene)-(+)camphorato], europium(III) derivative, the methyl doublet for the racemic material resolved into two sets of signals, (see Appendix 1). Repeating this analysis using (S)-79 produced only one set of signals. From this study we conclude that with short reaction times, no detectable racemisation is occurring.
2.3 Preparation of Methyleneaziridines Derived from β-Amino Alcohols

Our target was to synthesise a wide range of methyleneaziridines using the methodology devised by Pollard and Parcell. Their method involves ring closure of corresponding bromoallyl amines with sodium amide in liquid ammonia. These cyclisation precursors could in turn, be derived from the corresponding chiral β-amino alcohols, thus providing access to a large range of methyleneaziridines for subsequent evaluation as chiral building blocks for asymmetric synthesis (Scheme 2.10).

Initially, we focused our attention on preparing a range of methyleneaziridines derived from β-amino alcohols in which the alcohol grouping was protected as the corresponding benzyl ether.

2.3.1 Synthesis of O-Benzyl Protected Methyleneaziridines

Using the methodology recently developed by Hu and Cassady, O-benzylation was successfully accomplished on a range of chiral, nonracemic amino alcohols. The method, employing sodium hydride for anion formation, and subsequent reaction with benzyl chloride gave selectively O-benzylation in moderate to good yields (Table 2.2). Further purification was not required beyond an extractive work-up and no competitive N-benzylation was observed under these conditions.
Chapter 2: Methyleneaziridines using Cyclisation reactions

\[
\begin{array}{c}
\text{NaH, BnCl, THF} \\
\Delta \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R))-92\textsuperscript{51,52}</td>
<td>CH(_3)</td>
<td>H</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>((\pm))-93\textsuperscript{53}</td>
<td>CH(CH(_3))(_2)</td>
<td>H</td>
<td>91%</td>
</tr>
<tr>
<td>3</td>
<td>((S))-94</td>
<td>CH(_2)CH(CH(_3))(_2)</td>
<td>H</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>46%</td>
</tr>
</tbody>
</table>

Table 2.2

Subsequent N-alkylation of the resultant O-benzylated amines 92-95, proceeded smoothly. Reaction of these amines with 2,3-dibromopropene in THF at reflux for periods of between 12 and 14 hours resulted in the formation of the secondary amines 96-99 in reasonable yields (Table 2.3). Similar results could be obtained by stirring the reactants in diethyl ether for periods in excess of 48 hours at room temperature.

\[
\begin{array}{c}
\text{2,3-dibromopropene, K}_2\text{CO}_3, \text{THF} \\
\Delta \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Yield$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R))-96</td>
<td>CH(_3)</td>
<td>H</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td>((\pm))-97</td>
<td>CH(CH(_3))(_2)</td>
<td>H</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>((S))-98</td>
<td>CH(_2)CH(CH(_3))(_2)</td>
<td>H</td>
<td>51%</td>
</tr>
<tr>
<td>4</td>
<td>99</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>83%</td>
</tr>
</tbody>
</table>

Table 2.3 $\text{Isolated yield after column chromatography.}$
An initial attempt at ring closure using (R)-2-bromoallyl amine 96 with sodium amide in liquid ammonia for 45 minutes resulted in the formation of methyleneaziridine 101 and the corresponding acetylene 100 in a 2:1 ratio (Scheme 2.11).

On purification, methyleneaziridine 101 was obtained in 35% yield. However, reducing the reaction time to 30 minutes and subsequent purification by column chromatography using silica (not pre-treated with triethylamine) gave methyleneaziridine 101 in a much improved 73% yield. The corresponding acetylene was not observed under these conditions. Similar yields were obtained using allyl amines 102 (10 minutes cyclisation time) and 103 (5 minutes cyclisation time) (Table 2.4).

Methyleneaziridines 101-103 showed remarkable stability with respect to chromatography. Gradually increasing the size of the R1 substituent proved not to hinder cyclisation.
Furthermore, no racemisation occurred at the stereogenic centre. Enantiomeric excesses of \( \geq 95\% \) were determined for \textit{101} and \textit{103} (Appendices 2 and 3).

In contrast, allyl bromide \textit{99} failed to give the desired methyleneaziridine. Instead, acetylene \textit{105} was obtained in 55\% yield on purification using column chromatography (Scheme 2.12). No obvious explanation for the failure of this cyclisation is apparent.

Previous results have shown acetylene formation to be highly favoured when an electron withdrawing group such as tosyl or \textit{tert}-butoxycarbonyl group is attached to the nitrogen atom (Scheme 2.13).\textsuperscript{55} Such electron withdrawing groups attached to the nitrogen atom increase the acidity of the remaining hydrogen on nitrogen. As a consequence, deprotonation of nitrogen NH is more favourable than deprotonation at the \( \alpha \)-carbon and the nitrogen anion is formed presumably rapidly and essentially irreversibly. It is supposed that once the nitrogen anion is formed, a second deprotonation at the adjacent carbon, necessary for allene formation, is disfavoured due to electrostatic repulsion between the approaching base and the nitrogen anion.

The presence of a \textit{gem}-dimethyl group, as in the case of allylamine \textit{99}, is likely to increase the electron density on nitrogen through the inductive effect and so decrease the acidity of the hydrogen atom on nitrogen. Consequently, a similar argument cannot be employed in this instance.
Chapter 2: Methyleneaziridines using Cyclisation reactions

An explanation on the grounds of steric factors proves unrealistic since the syntheses of 1-tert-butylmethyleneaziridine, 1-adamantylmethyleneaziridine and N-(triphenylmethyl)-2-methyleneaziridine have all successfully been accomplished (Figure 2.2). All three are considered to possess large, sterically bulky groups adjacent to nitrogen, but methyleneaziridine formation was not inhibited and acetylene formation did not compete significantly.

![Figure 2.2](image)

With the intention of further expanding the class of chiral, non-racemic compounds for which the Pollard and Parcell method of synthesis could be applied, we aimed to produce O-methylated amino alcohol derived methyleneaziridines such as 106 (Figure 2.3).

![Figure 2.3](image)

Using commercially available (±)-2-aminomethoxypropane, N-alkylation proceeded smoothly to give vinyl bromide 107 in reasonable yield (63%). Subsequent ring closure, appeared, by $^1$H NMR spectroscopy, to give the desired methyleneaziridine 108 and acetylene 109, in a 1:5 ratio, in a crude yield of 45% (Scheme 2.14).

![Scheme 2.14](image)
Attempts to purify methyleneaziridine 108 using silica gel column chromatography (pretreated with triethylamine), resulted in extensive decomposition. Only 10% of the crude mixture was recovered from the column. Purification by bulb to bulb distillation also resulted in decomposition of the product. Attempts to remove the acetylene 109 by washing the crude mixture dissolved in diethyl ether with a 0.1% aqueous solution of acetic acid, were unsuccessful. Subsequent attempts to repeat this reaction reactions proved very difficult and un reproducible results were obtained with this substrate.

2.3.2 The role of the Ether Substituent

In order to establish any role the ether substituent may play in the above cyclisation reactions, related derivatives devoid of the ether oxygen atom, (e.g. \( X = \text{CH}_2 \)) such as 110-112 were required (Figure 2.4). In addition, we envisaged that subsequent organometallic reactions of the methyleneaziridines may be influenced by these ether oxygens and such substrates would be useful for comparative studies.

![Figure 2.4](image)

The amine starting material required for the preparation of methyleneaziridine 110 with the phenylpropyl linkage is not commercially available. The phenylethyl chain in 112 provides a possible alternative. For both 111 and 112, the corresponding amines required for their synthesis were commercially available.

Synthesis of methyleneaziridine 111 was achieved first by reaction of (\( R \))-1-cyclohexylethylamine with 2,3-dibromopropene in 58% yield. Attempted ring closure using sodium amide in liquid ammonia for 30 minutes resulted only in recovery of the allylamine 113. After five hours the allylamine 113 was totally consumed but resulted only in a 11% yield of methyleneaziridine 111 (Scheme 2.15).
Methyleneaziridine 111 was stable to column chromatography. A significant quantity of polymeric material was however, recovered from the reaction mixture, which was not identifiable. The low yield obtained on ring closure dissuaded us from undertaking further studies with this compound.

N-alkylation of 4-phenyl-2-butylamine was achieved in a moderate yield (50%) under standard conditions. Subsequent ring closure of 114 gave the desired methyleneaziridine 112 (35%) after subjection to a long reaction time (Scheme 2.16).

Although reaction times of greater and less than seven hours were examined for 112, 35% was the best yield obtained. $^1$H NMR spectroscopy studies showed the crude product to be reasonably clean, but on attempting to purify methyleneaziridine 112, using silica column chromatography, it completely decomposed. Purification using bulb to bulb distillation also resulted in decomposition.
2.3.3 Synthesis of Methyleneaziridines Containing Silyl Ethers

Due to the success of ring closure using \( O \)-benzylated allylamines, it was thought the methodology could be extended further to \( O \)-silyl protected allylamines such as 115 (Figure 2.5).

The synthesis of allylamines 116-119 was achieved in a two step process from the corresponding \( \beta \)-amino alcohols. \( N \)-alkylation with 2,3-dibromopropene gave the corresponding allylamines in reasonable yields (Table 2.5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Yield$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>116</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>(±)-117</td>
<td>CH(_3)</td>
<td>H</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>(±)-118</td>
<td>CH(CH(_3))(_2)</td>
<td>H</td>
<td>57%</td>
</tr>
<tr>
<td>4</td>
<td>(±)-119</td>
<td>CH(_2)CH(CH(_3))(_2)</td>
<td>H</td>
<td>59%</td>
</tr>
</tbody>
</table>

Table 2.5. $Isolated yield after column chromatography.

\( O \)-Silylation of allyl amines 116-119 with tert-butyldiphenylsilyl chloride was achieved in high yield. No further purification beyond a standard aqueous work up was required (Table 2.6).
Chapter 2: Methyleneaziridines using Cyclisation reactions

\[
\begin{align*}
R^1 & \quad R^2 & \quad OH \\
\text{triethylamine, DMAP, } & BuPh_2 SiCl \\
\downarrow & \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
\text{rt, 24 hrs} & \quad \text{rt, 24 hrs} & \quad \text{rt, 24 hrs}
\end{align*}
\]

Table 2.6.

Subsequent ring closure with sodium amide in liquid ammonia was successful using precursors 122 and 123. Methyleneaziridines 124 and 125 (both 30 minutes reaction time) were obtained under these optimised conditions in yields of 75% and 21% respectively. Acetylene formation was not observed in either case. These results demonstrate that silyl ethers survive these cyclisation conditions (Scheme 2.16).

\[
\begin{align*}
R^1 & \quad R^2 & \quad OH \\
\text{triethylamine, DMAP, } & BuPh_2 SiCl \\
\downarrow & \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
& \quad \downarrow & \quad \downarrow \\
\text{rt, 24 hrs} & \quad \text{rt, 24 hrs} & \quad \text{rt, 24 hrs}
\end{align*}
\]

Scheme 2.16

Gem-dimethyl substituted allylamine 120 showed a similar pattern of reactivity to its benzyloxy counterpart 104 in that acetylene 126 was the only observed product, formed in 35% yield (Scheme 2.17).

39
A reasonable explanation for acetylene formation in these examples remains elusive. Precursor 121 gave the most surprising result, in that it was recovered, along with a small amount of decomposed material using the standard 15 equivalents of sodium amide in refluxing ammonia for a period of 2 hours. When the reaction time was gradually increased, a decrease in recovered allylamine was observed although none of the desired methyleneaziridine was observed.

2.3.4 Conclusions

We have had some success in synthesising methyleneaziridines possessing chiral nitrogen substituents. The synthesis of \( \alpha \)-methylbenzyl substituted methyleneaziridines 101 and 103 in both enantiomerically forms without racemisation was particularly gratifying. However, the method developed by Pollard and Parcell can not be regarded as a general one. Variation in the reaction time has proven useful in facilitating ring closure, but certain substrates have failed to produce methyleneaziridines even after modifications in the reaction conditions have been applied. Reduction in the quantity of sodium amide was not attempted and may be worthy of investigation for the synthesis of the methyleneaziridines derived from allylamines 114 and 107 (Figure 2.6).

The exceptionally high yields obtained for methyleneaziridines such as 102 and 103 suggest possible involvement of the ether oxygen in the \( N \)-substituent. The reason for the failure of gem-dimethyl substituted allyl amines 104 to give the corresponding methyleneaziridines
remains unresolved. It is particularly surprising in light of the fact that the synthesis is extremely successful when only one methyl group is present. Clearly, predictions concerning the outcome of these cyclisation reactions are not always possible and there remains a large element of "try it and see" to these reactions.
CHAPTER THREE

Nitrogen Inversion Studies
3 Nitrogen Inversion Studies

The chirality of our methyleneaziridines arises from the substitution on the nitrogen atom. However, as early as 1939, several groups of workers postulated that suitably substituted aziridines could be resolved and a considerable amount of research has been undertaken in this area.

Previous studies using N-ethyl methyleneaziridine have established that the free energy barrier for nitrogen in this system is 81 KJmol\(^{-1}\) at -65±5°C (See Chapter 1). In our systems, N-inversion results in the formation of the alternate diastereomeric invertomer. We decided to study the activation barrier and populations of the two diastereomeric isomers in methyleneaziridines (R)-79 and (R)-101 using Variable Temperature NMR experiments (Figure 3.1).

![Figure 3.1: Methyleneaziridine (R)-79 invertomers.](image)

For methyleneaziridine (R)-79 temperature dependent (dynamic) \(^1\)H NMR studies were instigated at 25°C (acetone-d\(_6\)). At this temperature, the methyl group appeared as a sharp doublet at 1.01 ppm. When the temperature was successively decreased by 5-10°C intervals, a significant change was noted at -30°C. Below this temperature, the signal became increasingly broad. Upon further cooling to -55°C, two doublets were observed and no further change was observed below this temperature (Appendix 4). From these studies we were able to establish the coalescence temperature to be approximately -45°C (T\(_c\)).

It should be noted that the two sets of doublets at -55°C were not of exactly equal intensity. This indicates that unequal amounts of the two diastereomeric invertomers were produced (1:1.2 ratio) (Figure 3.2). This observation would suggest that one of the invertomers is thermodynamically more stable than the other, although the energy gap must be small.

![Figure 3.2: Methyleneaziridine (R)-79 invertomers.](image)
Chapter 3: Nitrogen Inversion Studies

To apply a simplified analysis, we have assumed that the populations of these two isomers are the same. Under these conditions, equation (1) may be employed to afford the rate constant \(k_r\) at the coalescence temperature of -45°C.

\[
k_r = \frac{(\nu_A - \nu_B)}{\sqrt{2}} = \frac{\Pi \Delta \nu}{\sqrt{2}} = 2.22 \Delta \nu
\]

\(\Delta \nu\) is the full width at half the maximum height of the signal at the coalescence point, -45°C. This corresponds to the difference in chemical shift \((\nu_A - \nu_B)\), observed during slow inversion. From our results for (R)-79, the difference in chemical shift is 16.25 Hz. Using equation (1), the frequency of the rate constant \(k_r\) is calculated to be \(\approx 35.8\) at 228K (-45°C).

According to the Erying equation (2), \(K_r\) decreases exponentially with the free molar energy \(\Delta G\).

\[
k_r = \frac{K T_c}{\hbar} e^{-\Delta G/RT_c}
\]

\(R =\) Gas Constant \(\approx 8.31\) kJmol\(^{-1}\)

\(k =\) Boltzmann constant \(\approx 1.38 \times 10^{-32}\) JK\(^{-1}\)

\(\hbar =\) Plank's constant \(\approx 4 \times 10^{-34}\) kJmol\(^{-1}\)

\(T_c =\) coalescence temperature

Assuming a first order process, equations (1) and (2) on rearrangement can be given in terms of the Gibbs Free Energy. Subsequent substitution of the constant values gives equation (3).

\[
\Delta G = 19.1 T_c [10.32 + \log(T_c/k_r)] \times 10^{-3} \text{kJmol}^{-1}
\]

Substituting values for \(T_c\) and \(k_r\), \(\Delta G\), the energy barrier at 228K for nitrogen inversion of methyleneaziridine (R)-79 is calculated to be approximately 49.5 kJmol\(^{-1}\).

Similarly, \(^1\)H NMR spectra were obtained for methyleneaziridine (R)-101 at a range of temperatures between 25°C and -80°C. The sharp methyl doublet seen at 25°C, begins to broaden at -35°C, reaching a maximum width at -50°C. This is the temperature of coalescence (see Appendix 5). Two doublets are seen to emerge below -55°C, and no final change was observed below -60°C. Using equation (1) the rate constant, \(k_r\), was calculated to be 16.5 Hz. At the temperature of coalescence (223K). Substituting \(T_c\) and \(k_r\) into equation (3) estimates the inversion barrier \(\Delta G\) for inversion of (R)-101, for the process described in Figure 3.4, to be approximately 50.2 kJmol\(^{-1}\).
Chapter 3: Nitrogen Inversion Studies

Figure 3.4: Methyleneaziridine (R)-101 invertomers

The results indicate little difference between methyleneaziridines (R)-79 and (R)-101 but significantly differs from the result of 81 kJmol\(^{-1}\) obtained for 1-ethylmethyleneaziridine.\(^2\) The lower values obtained may be attributed to an assumption of equal population, possibly the use of a different solvent or the steric bulk of the nitrogen substituent.

These studies do establish that in subsequent reactions involving chiral methyleneaziridines, two diastereomeric invertomers need to be considered in analysing the stereochemical outcome of the reactions.
CHAPTER FOUR

Addition Reactions to Methyleneaziridines
Chapter 4: Addition Reactions to Methyleneaziridines

4.1 Reactions of Methyleneaziridines with Tetracyanoethylene

4.1.1 Introduction

Tetracyanoethylene (TCNE) is one of the simplest of percyanoalkenes which has been used for many addition and cycloaddition reactions. The presence of the strongly electron withdrawing cyano groups, results in the vinyl double bond being highly electron deficient, and as a result, TCNE acts as a strong electrophilic reagent or cycloaddition component. Additionally, the cyano groups are small and present no serious steric problems in adduct formation. The addition reactions of TCNE have been studied in great detail.

TCNE is not only a potent dienophile in Diels-Alder reactions, but [2+2] cycloadditions are also favourable. For example, methyl vinyl ether and even p-methoxystyrene (but not styrene) are sufficiently electron rich to yield cyclobutane derivatives upon reaction with TCNE at room temperature.

Mechanistic studies relating to the [2+2] addition reactions of TCNE with electron rich alkenes have established that the reactions are non-concerted and ionic. Simple alkenes, and the double bond of acrylic esters are inert to such reactions. This observation, together with solvent effects, suggest the involvement of a zwitterion intermediate as opposed to a biradical intermediate (Scheme 4.1).

Evidence for the presence and involvement of a zwitterion of the type 127 has been provided by Huisgen. Studies have shown that TCNE on reaction with geometrically defined vinyl ethers, favours retention of configuration in non-polar solvents, but becomes less specific in polar solvents. The change is attributed to the effect of the solvent on the lifetime of the zwitterion intermediate. Solvation of the intermediate would be provided by more polar solvents. This increase in lifetime is thought to allow more C-C bond rotation to occur, thereby leading to a loss of stereospecificity.
Chapter 4: Addition Reactions to Methyleneaziridines

One of the most convincing pieces of evidence for the involvement of the zwitterion intermediate comes from trapping experiments. The reaction of ethyl vinyl ether 126 with TCNE in acetone proceeds to the corresponding cyclobutane. However, in methanol, the acetal 129 is formed (Scheme 4.2).^69,70,71

\[ \text{OEt} \quad \text{TCNE} \quad \text{MeOH} \]

\[ \text{126} \quad \text{129} \]

Scheme 4.2

4.1.2 TCNE Addition Reactions Involving Benzylether Substituted Methyleneaziridines

As discussed in Chapter 1, Cookson and co-workers have shown that \( N \)-ethyl methyleneaziridine 1 reacts with TCNE to give the cycloadduct product.\(^{28}\) In order to gain some insight into the stereochemical influence of the nitrogen substituent in new bond forming reactions, leading to the production of stereogenic centres, we decided to re-examine this TCNE chemistry using our homochiral methyleneaziridines. Cycloadducts of methyleneaziridines 101-103, and 130 were prepared based on the method developed by Cookson and co-workers. The best yields were obtained when the methyleneaziridine was reacted on a small scale (100 mg) using 1 molar equivalent of TCNE in acetone, at reflux for one hour. The results are summarised in Table 4.1.
Chapter 4: Addition Reactions to Methyleneaziridines

Addition Reaction:

\[
\begin{align*}
\text{R}^1 \quad \text{H} \quad \text{Ph} \\
\text{TCNE, acetone} \quad \text{reflux, 1 hour} \\
\text{N} \quad \text{•} \quad \text{N} \\
\text{O} /'\text{--Al} \quad \text{Rr} /'\text{--O} /'\text{--Al} \\
\end{align*}
\]

Entry | Methyleneaziridine | Cycloadducts | \( R^1 \) | Yield\( ^\dagger \) | ratio\( ^\ddagger \)
---|---|---|---|---|---
1 | (R)-101 | (R, S)-131a, (R, R)-131b | CH\(_3\) | 82\% | 5:1
2 | (+)-102 | (R\(^*\), S\(^*\))-132a, (R\(^*\), R\(^*\))-132b | CH(CH\(_3\))\(_2\) | 48\% | 4:1
3 | (S)-103 | (S, R)-133a, (S, S)-133b | CH\(_2\)CH(CH\(_3\))\(_2\) | 79\% | 6:1
4 \(^\dagger\) | (R)-130 | (R, S)-134a, (R, R)-134b | Ph | 81\% | 2:3

Table 4.1. \(^\dagger\)Isolated yield of purified diastereomeric mixture after column chromatography. \(^\ddagger\)Determined by \(^1\)H NMR analysis of the purified mixture.

All products (Entries 1-4) showed good stability to column chromatography. Studies showed partial decomposition of the products occurred on standing at room temperature. In the worst case, 134 underwent extensive decomposition over just 2 days.

Attempts to separate the resulting diastereoisomers using silica gel chromatography were only partially successful. Isolation of the major adduct was accomplished for diastereomeric mixtures 132-134 (Entries 2-4), but the minor isomers were not isolated in their pure form.

The exception was cyclobutane 131 (Entry 1). The major diastereoisomer was isolated using a diethyl ether/petroleum column solvent system. Attempts to grow suitable crystals of this diastereoisomer for X-ray crystallography so that the relative configuration could be established, were unsuccessful. In an attempt to isolate the minor diastereoisomer from this TCNE reaction, the cycloaddition was repeated on a 1g scale.

Although the yield was significantly reduced (45\%), the minor isomer was isolated by column chromatography using a 20\% ethyl acetate / hexane column solvent system. Fortunately, suitable crystals for X-ray Crystallography were obtained from this minor cycloadduct. The X-ray structure was solved (Figure 4.1) and it was determined that this minor isomer possesses the \( S \)-configuration at the new stereogenic centre.

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For other cycloaddition reactions (Entries 2-4) we have not been able to obtain conclusive proof of the configuration of the major cycloadduct. However, the results do show that changing the nature of the R group had little effect on stereoselectivity. This led us to wonder whether the major diastereoisomers were produced as a result thermodynamic or kinetic control.
4.1.3 Effect of Solvent and Temperature on TCNE Cycloaddition Reactions of Methyleneaziridines.

In order to establish the energetic processes influencing the cycloaddition reaction the effect of different solvents and temperature needed to be established. Before trying to provide plausible explanations for the stereochemistry observed for these reactions, it was important to know whether the major product was produced as a result of thermodynamic or kinetic control.

Research conducted by Huisgen has shown that the more polar the solvent, the greater the loss of stereoselectivity with regard to alkene geometry. This is due to stabilisation of the zwitterion intermediate (on the assumption the reaction pathway proceeds through this intermediate). The more stable the intermediate, the greater the amount of time available for rotation of the zwitterion intermediate. The effect of solvent in the reaction of methyleneaziridine 131 with TCNE at room temperature was examined (Table 4.3).

![Chemical structures](image)

| Entry | Solvent       | Time  | Yield $|$ | Diastereomer Ratio |
|-------|---------------|-------|----------|--------------------|
| 1     | toluene       | 1 hour| 33%      | 1:1                |
| 2     | dichloromethane | 1 hour | 30%      | 1:1                |
| 3     | acetone       | 1 hour | 41%      | 1:1                |
| 4     | 2-butanone    | 1 hour | 38%      | 1:1                |
| 4     | acetonitrile  | 1 hour | -        | -                  |
| 5     | methanol      | 1 hour | -        | -                  |

Table 4.3. Isolated yield of diastereomeric mixture

These results (Table 4.3) show that diastereomeric ratio is not affected by solvent polarity and no stereocontrol was observed at room temperature. Reaction of TCNE using methanol gave undetermined products, which is perhaps unsurprising, given the reports of methanol...
Chapter 4: Addition Reactions to Methyleneaziridines

reacting with intermediate zwitterions (*Vide Supra*). Acetonitrile is also known to react with the zwitterion to give undetermined products.

Using methyleneaziridine 131, reactions with TCNE were conducted at different temperatures (Table 4.4). The results show that the diastereomeric ratio does vary with temperature. When the reaction was conducted using acetone under reflux (56°C) over a period of one hour, a 5:1 ratio of cycloadducts was observed. Longer reaction times at this temperature were shown not to improve the diastereomeric ratio and reduced the isolated yields. At room temperature and below, no selectivity was observed. In an attempt to further improve the stereoselectivity, the reaction was performed at 80°C in toluene for 1 hour. However, under these conditions a mixture of products was obtained but none could be identified by 1H NMR.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield§</th>
<th>Diastereomeric Ratio§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>acetone</td>
<td>1 hour</td>
<td>31%</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>acetone</td>
<td>1 hour</td>
<td>41%</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>acetone</td>
<td>1 hour</td>
<td>82%</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>toluene</td>
<td>1 hour</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4.4 §Isolated yield of diastereotopic mixture.

These results strongly suggest that the stereoselectivity of these reactions is simply the result of cycloadduct equilibration. In order to confirm that such a thermodynamic equilibration was occurring, it was necessary to demonstrate interconversion of the two diastereoisomers. A 1:1 diastereomeric mixture was refluxed in acetone for a period of one hour. While some decomposition of the product occurred, the cycloadducts were reisolated in a 5:1 ratio (82%).

This result can be explained by interconversion between the two diastereoisomers or, by selective decomposition of one diastereoisomer on heating. More conclusive proof came when minor diastereoisomer (R, S)-131 was refluxed in acetone for 1 hour. Although decomposition again occurred, there was no doubt that interconversion had taken place. The cyclobutane recovered was predominately the other diastereoisomer (5:1 ratio).
Clearly, at equilibrium, in refluxing acetone (R, R)-131 is the thermodynamically more stable adduct and hence is produced as the major product. The proposed mechanism for the formation of cycloadduct (R, R)-131 from methyleneaziridine (R)-101 based on Huisgen's reports is shown in Scheme 4.3.71

\[
\begin{align*}
&(R, R)-131 \\
&\text{Me.} \quad \text{OBn} \\
&\text{N} \quad \text{NC} \quad \text{CN} \quad \text{CN} \\
&\text{Me.} \quad \text{OBn} \\
&\text{N} \quad \text{NC} \quad \text{CN} \quad \text{CN} \\
&(R, R)-131 \\
&\text{TCNE} \\
&(R)-101 \\
\end{align*}
\]

Scheme 4.3

4.1.4 TCNE Cycloaddition Reactions of Methyleneaziridines Containing Silyl Ethers

Reaction of silyl protected methyleneaziridines 124 and 125 with TCNE in refluxing acetone, gave a 1:1 mixture of diastereoisomers 135 and 136 respectively. The yields for the formation of 135 and 136 were 54% and 42% respectively (Scheme 4.4).

\[
\begin{align*}
&(\pm)-124 \quad R=\text{CH(CH}_3)_2 \\
&(R^*, R^*)-135a \quad R=\text{CH(CH}_3)_2 \\
&(R^*, S^*)-135b \quad R=\text{CH(CH}_3)_2 \\
&(\pm)-125 \quad R=\text{CH}_2\text{CH(CH}_3)_2 \\
&(R^*, R^*)-136a \quad R=\text{CH}_2\text{CH(CH}_3)_2 \\
&(R^*, S^*)-136b \quad R=\text{CH}_2\text{CH(CH}_3)_2 \\
\end{align*}
\]

Scheme 4.4

While no stereocontrol was observed in these reactions, we were still interested in determining the relative stereochemistry within each of the two sets of adducts obtained.
Since the structures of the cycloadducts were somewhat different to the benzylether compounds previously prepared, direct NMR comparisons were not envisaged to be reliable. Instead, we decided to try and correlate the stereostructures of 135 and 136 by converting them into benzylether protected methyleneaziridines by de-silylation and subsequent O-benzylation (Scheme 4.5).

Silyl protected cycloadduct 124, as a 1:1 mixture of stereomers, was treated with TBAF in THF at 0°C then allowed to warm to room temperature over a period of 4 hours. On work up and subsequent column chromatography, it was determined that deprotection had taken place because tert-butyldiphenylhydroxysilane was isolated. However, no other identifiable products were obtained. $^1$H NMR and IR spectra showed the crude product mixture contained no methylenaziridine related products. Similar results were obtained using the cycloadduct 125.
Applying a method developed Shekhani and co-workers, deprotection of 125 was attempted using sodium hydride in DMPU.\textsuperscript{72} Again, isolation of the protecting group was achieved but no other identifiable products were isolated. If indeed alcohol 138 is being generated, initially as the corresponding alkoxide, it appears to be highly unstable under these reaction conditions.

In a final attempt benzyl chloride was added to a stirred solution of cycloadduct 136 in the presence of sodium hydride in DMPU at 0°C. Under these conditions, we hoped to effect deprotection and etherification in a one pot process. Unfortunately, the reaction was unsuccessful.

### 4.2 Attempts to Effect Radical Additions to Methyleneaziridines

In view of the strained nature and hence high reactivity of the exocyclic double bond of a methyleneaziridine, we wished to establish if they might participate in intermolecular radical addition reactions. If successful, this might provide a novel route to functionalised aziridines.

A standard method for the generation of an "electrophilic" or "nucleophilic" radical in the presence of methyleneaziridine \textsuperscript{79,73} Free radical addition of diethylbromomalonate to methyleneaziridine 79, in the presence of tri-butyltin hydride and radical initiator AMBN, failed to give the desired product (Scheme 4.6). Instead, an unidentifiable mixture of products were produced. Decomposition of methyleneaziridine on refluxing in toluene for 90 minutes during the initial degassing process was not observed. Therefore, failure of the reaction could not be attributed to methyleneaziridine instability (all of the methyleneaziridine had been completely consumed during the reaction). Methyleneaziridine 101 gave a similar unsuccessful result.

Because of the problems associated with separating products from the tin residues, we chose to look at a second type of radical addition reaction which did not require the use of tin based
reagents. We examined the addition of thiols, which, in the presence of a free radical initiator, have been shown to add to a variety of double bonds. However, in our case, both methyleneaziridines 79 and 101 failed to give the desired product on reaction with thiophenol in the presence of AMBN. In both cases, at least six possible products were identified by TLC, none of which could be successfully isolated and characterised. Again, the methyleneaziridine starting material had in both cases, been completely consumed (Scheme 4.7).

![Scheme 4.7](image)

**4.3 Conclusions**

The results show that methyleneaziridines readily undergo [2+2] cycloadditions with TCNE in refluxing acetone. The stereochemical outcome of such reactions appear to be the result of equilibration of the cycloadducts to the most thermodynamically favoured product. Despite the tremendous strain in these spirocyclic systems, these structures are surprisingly stable. Disappointingly, our initial attempts to persuade methyleneaziridines 79 and 101 to undergo free radical addition to the exocyclic double bond have been unsuccessful.
CHAPTER FIVE

Attempted Synthesis of Methyleneaziridines from Functionalised Aziridines
5.1 Introduction

Although the methods developed by Quast and Risler\(^1\) proved adequate for the preparation of selected methyleneaziridines, this method is by no means general (Vide Supra). Clearly, the reaction conditions prove too harsh for some substrates and in others the reaction is further complicated by the formation of acetylene by-products (among others). It was desirable, therefore, to develop a new, milder method, eliminating the 'problem' side-reactions and providing access to a more diverse range of methyleneaziridines.

In this chapter, two new routes to methyleneaziridines have been explored. In these strategies, we hoped to introduce the exocyclic double bond into the target structures as the last synthetic step. The basic strategy is depicted below in Scheme 5.1. Such approaches have been shown to be useful for the preparation of highly reactive allene oxides.\(^8\),\(^5\)

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{Y} \\
\text{Y}
\end{array}
\xrightarrow{-\text{XY}}
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{Y}
\end{array}
\]

**Scheme 5.1**

5.2 Approaches Towards Methyleneaziridines using Selenoxide Eliminations

Our first approach to addressing this problem, was based on a route developed by Krief and Halazy,\(^7\) which takes advantage of selenoxide generation and subsequent elimination.\(^7\),\(^6\),\(^7\) For example, using this chemistry selenium substituted cyclopropane 139, on reaction with ozone, gives selenoxide 140. Elimination takes place in the presence of a base and, at relatively high temperature, yields alkylidenecyclopropane 141 (Scheme 5.2). This example demonstrates that the formation of highly strained ring systems using this method can be achieved.

\[
\begin{array}{c}
\text{SePh} \\
\text{CH}_2\text{C}_9\text{H}_{19}
\end{array}
\xrightarrow{\text{O}_3/\text{CH}_2\text{Cl}_2}
\begin{array}{c}
\text{SePh} \\
\text{O}^- \\
\text{CH}_2\text{C}_9\text{H}_{19}
\end{array}
\xrightarrow{\text{toluene/NEt}_3/110^\circ\text{C}}
\begin{array}{c}
\text{H} \\
\text{C}_9\text{H}_{19}
\end{array}
\]

**Scheme 5.2**

Applying a similar approach using aziridine 142, with substitution on the exocyclic carbon, with an aryl selenium derivative, subsequent oxidation and elimination might be expected to give the required methyleneaziridine 143 (Scheme 5.3).
5.2.1 Attempted Synthesis of Aziridinyl Alcohol 144

The first objective was to synthesize an aziridine with a suitable functional group to allow the introduction of the aryl selenide group. Grieco and co-workers have used alcohols to prepare alkenes by conversion to the corresponding selenide using aryl selenocyanates and subsequent oxidative elimination (Scheme 5.4).78

\[
\begin{array}{c}
RCH_2OH \\ \text{THF or pyridine} \\ \text{ArSeCN/}Bu_3P \\ \rightarrow \\
RCH_2SeAr
\end{array}
\]

Scheme 5.4

Using a benzyl protecting group for the aziridine nitrogen, we hoped to prepare alcohol 144 from the aziridine ester 145, (the preparation of which is reported by Stolberg and co-workers79), which we envisaged was a suitable compound from which to start our studies (Scheme 5.5).

\[
\begin{array}{c}
\text{144} \\
\text{145}
\end{array}
\]

Scheme 5.5

Treatment of 2,3-dibromopropanoic acid with oxalyl chloride, gave acid chloride 146 in high yield (99%). This acid chloride reacted cleanly with methanol to give the methyl ester 147 in
Chapter 5: Methyleneaziridines from Aziridines

90% crude yield. Aziridinyl ester 148 was subsequently formed in 65% yield by heating 147 with benzylamine in toluene in the presence of triethylamine (Scheme 5.6).

Attempts to reduce the aziridinyl ester 148 with common reducing agents such as DIBAL and lithium aluminium hydride failed to give any of the desired product as judged by \(^1\)H NMR spectroscopy.

![Scheme 5.6]

Similar problems arose when attempting to reduce the \(\alpha\)-methylbenzylamine substituted aziridine ester 149 (Scheme 5.7), prepared in an identical fashion from dibromo ester 147.

![Scheme 5.7]

In view of these problems, we examined an alternative approach to the selenide precursors. Sharpless and co-workers have shown that aryl selenides can be made by alkylation of alkyl bromides by \(S_N2\) displacement with an aryl selenide anion.\(^{80}\) Consequently, we envisaged that bromoaziridine 150 might serve as an alternative precursor. Using benzaldehyde as the starting material, 2-(bromomethyl)phenylethyl-aziridine 150 was prepared according to the sequence below in accordance with a literature method (Scheme 5.8).\(^{82}\)
Reaction of benzaldehyde with allylamine gave imine 151 in 96% yield. The $^1$H NMR spectrum showed small quantities (ca. 8%) of unreacted benzaldehyde to be present. We could not establish if this was due to incomplete reaction or hydrolysis of the imine product 151 by traces of water. Direct reaction of the crude imine 151, with bromine gave the desired bromoimine 152 in 91% crude yield. Reaction of 152 with excess sodium borohydride in refluxing methanol gave the bromoaziridine 150 in a modest 33% yield.

For the next step we needed to transform the halogen into the corresponding selenide. We planned to achieve this by substitution with arylselenide anion. Two different selenides were investigated in this substitution reaction. $O$-Nitrophenylselenocyanate 153, (Figure 5.1) which we planned to convert to the corresponding anion, is not commercially available and so had to be synthesised.

The $o$-nitro group within this selenide is strategically important. The electron-withdrawing properties of the nitro group through the inductive effect, increases the positive charge in any derived selenoxide making it more reactive.

Figure 5.1
Reaction of bromoaziridine 150 with o-nitrophenyl selenocyanate, and sodium borohydride gave the desired aziridinyl selenide 154 in 50% yield after column chromatography (Scheme 5.9).

Surprisingly, reaction of the bromoaziridine 150 with diphenyl diselenide gave the related aziridinyl selenide 155 in just 5% yield (Scheme 5.10).

In view of this disappointing yield, we decided to check the procedure by repeating a literature reaction. Using identical conditions, 1-bromoheptane was converted to phenylselenide 156 in 97% yield (Scheme 5.11).

Oxidation of selenides has been well documented. Many of the oxidants used are inorganic such as hydrogen peroxide, ozone, or sodium periodate. Organic acids such as m-CBPA or p-nitrophenyloxaziridine may provide milder conditions. Oxidation of 154 was achieved using m-CPBA to give the diastereomeric mixture of selenoxides 157 in 43% yield after chromatography (Scheme 5.12).
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Scheme 5.12

The reaction was found to work equally well using <i>p</i>-nitrophenyloxaziridine as oxidant. However, attempts to form the selenoxide using other oxidants such as hydrogen peroxide and sodium meta-periodate resulted in decomposition of the substrate.

Selenoxide elimination has in many cases, been reported to proceed smoothly at room temperature or at slightly elevated temperatures. In some instances, oxidation and elimination proceed in a one-pot process. However, our attempts at eliminating selenoxide from 157 to yield methyleneaziridine 158 have proved disappointing. A number of conditions were tried, which are summarised in Table 5.1. In some cases, heterogeneous bases were added in an attempt to sequester ArSeOH from the solution. On heating, with or without base, complete decomposition was observed or recovered starting material was unchanged.
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The aziridinyl selenoxide 157 is surprisingly stable and conditions for elimination remain elusive. Interestingly, a sample of this selenoxide 157 stored at about 3°C for a period of 2 years has shown virtually no decomposition as judged by $^1$H NMR Spectroscopy.
5.3 Methyleneaziridines via Silicon Containing Aziridines

Chan and co-workers, have shown that allene oxides such as 159 can be made by use of a fluoride ion triggered \( \beta \)-elimination of silyl substituted epoxides such as 160 (Scheme 5.13).\(^{85}\)

Elimination is normally achieved using caesium fluoride, although other fluoride sources can be employed. Recent studies have shown that similar types of elimination can also be facilitated by alkoxide ions.\(^{86}\)

![Scheme 5.13](image)

Applying this methodology to our own work (Scheme 5.14), a new route was anticipated for methyleneaziridine formation.

\[
\begin{align*}
R & \quad \text{leaving group} \\
\end{align*}
\]

\[\text{Scheme 5.14}\]

\(\alpha\)-Silyl substituted aziridines have been prepared by the addition of a nitrene to the double bond of a vinylsilane. For example, Lukevics and co-workers have shown that ethoxycarbonylnitrene, (:NCOOEt), generated under phase transfer conditions, will add to vinylsilane 161 to give the corresponding aziridine 162 (Scheme 5.15).\(^{87}\)

![Scheme 5.15](image)

Thus, by combining these two pieces of chemistry, we hoped to develop a novel method to methyleneaziridines according to the synthetic pathway illustrated below (Scheme 5.16).
5.3.1 *Synthesis of Vinyl Silane 163*

Vinylsilane 163 is a known compound and was prepared using standard methods.\(^{88}\) Bromination of vinyltrimethylsilane gave trimethylsilane 164 in 75\% yield after bulb-to-bulb distillation. Reaction of 164 with magnesium filings and subsequent reaction with gaseous formaldehyde gave the desired alcohol 163 in 46\% yield (Scheme 5.17).\(^{89}\) The use of the related organolithium species, prepared using tert-butylithium, gave less satisfactory results in this reaction (10-15\% yield).

Conversion of the alcohol group into an appropriate leaving group such as a chlorine atom can, in theory, be achieved by numerous methods. We initially chose to attempt this conversion using thionyl chloride (Scheme 5.19).\(^{90}\) Heating 163 with thionyl chloride at elevated temperatures gave some evidence for the formation of desired product 165 in just trace quantities.

Other reagents for the conversion of the hydroxyl group into a leaving group were tried. These included tribromophosphine\(^{89}\) and triphenylphosphine in carbon tetrachloride, but little success was achieved.\(^{91}\) To circumvent these problems, we elected to convert the alcohol into an ester, which we anticipated would act as a reasonable leaving group under appropriate conditions. Reaction of allylic alcohol 163 with acetic anhydride, furnished allyl acetate 166 in 51\% yield (Scheme 5.19).
Chapter 5: Methyleneaziridines from Aziridines

**Scheme 5.19**

5.3.2 Aziridination of Vinyl Silane 166

Using the method developed by Lukevics and co-workers, ethoxycarbonylnitrene was generated from water soluble ethyl-N-(p-nitrobenzenesulphonyloxy)carbamate and reacted with ester 166 under phase transfer conditions. The desired trimethylsilyl substituted aziridine 167 could be obtained in 48% yield (Scheme 5.20).

**Scheme 5.20**

Nitrene addition to vinyl alcohol 163 was attempted under identical conditions but it should be noted that this reaction proved unsuccessful.

With small quantities of the precursor in hand, we examined fluoride induced elimination to the N-ethoxycarbonylmethyleneaziridine 168. Various attempts were made to install the double bond, including the use of caesium fluoride in accordance to the method described by Chan and co-workers, but only aziridine starting material was recovered. Similar results were obtained using TBAF as the fluoride source (Scheme 5.21).

**Scheme 5.21**

Further studies to explore this approach to methyleneaziridines were not undertaken. While this chemistry might ultimately have provided fruitful, problems in obtaining adequate
supplies of 167 using the aziridine methodology deterred us from exploring this chemistry further.

5.4 Conclusions

The synthesis of methyleneaziridines via aziridine selenoxides such as 157 proved unsuccessful, largely as a result of the extraordinary stability of selenoxide 157. Interestingly, after completion our work, DeKimpe and co-workers published a method rather similar to our own ideas. Base induced elimination of HBr from bromoaziridine 150 has been shown to provide methyleneaziridines along with tert-butylether products. This work provides confirmation that, despite ring strain, the introduction of the exocyclic double bond can be achieved under relatively mild conditions using elimination reactions.
CHAPTER SIX

Experimental
6.1 General Information

Commercially available solvents were used throughout without further purification except for those detailed below.

Petroleum ether (which refers to the fraction boiling at 40-60°C) and ethyl acetate were distilled from calcium chloride prior to use. Dichloromethane and toluene were distilled from phosphorous pentoxide. Acetonitrile was distilled from calcium hydride and kept over 4Å sieves. Diethyl ether was distilled from sodium benzenophene ketel under nitrogen, prior to use, as was tetrahydrofuran, or alternatively, purchased from Aldrich in Sure/Seal™ bottles.

Sodium hydride was purchased as a 60% dispersion in mineral oil, which was removed by repeated washing with petroleum ether, then dried under reduced pressure and stored under nitrogen. All reactions were carried out using oven dried glassware under a nitrogen atmosphere unless otherwise stated.

Analytical thin layer chromatography was carried out using coated aluminium or plastic-backed silica plates coated with Merck Kieselgel 60 F254. Visualisation was achieved using ultra-violet light, permanganate stain, Dragendorff’s reagent or ammonium molybdate (IV) (with heating).

Preparative chromatography was carried out using Fisons Matrex 60 (30-70 mm) flash silica. Samples were applied as a saturated solution in an appropriate solvent.

$^1$H and $^{13}$C NMR spectra were recorded at 250 MHz and 62.9 MHz respectively on a Bruker AC-250 instrument or at 400 MHz and 100 MHz respectively on a Bruker DPX-400 instrument. All samples were recorded in deuterochloroform using tetramethylsilane as the internal standard.

Signals in $^1$H NMR are described as singlets (s), doublets (d), triplets (t), quartets (q), quintets (q) and multiplets (m). Signals in $^{13}$C spectra are also described whenever possible using DEPT 135 experiments and are assigned as singlets (s), doublets (d), triplets (t) and quartets (q).

Infra-red spectra were recorded in the range 4000 - 600 cm$^{-1}$ using a Nicolet FT 205 spectrometer. Spectra were recorded as solutions in dichloromethane, thin films, or as Nujol® mulls.
Experimental

High and low resolution mass spectra were obtained on a Kratos 80 mass spectrometer, under E.I.+ or by the EPSRC Mass Spectrometry Centre, Swansea, under E.I.+ or C.I. (thermospray). All mass spectra were obtained under E.I+ unless otherwise stated. All Melting points were measured on a Electrothermal digital melting point apparatus. Boiling points refer to the oven temperature for bulb to bulb distillation. Optical rotations were measured on an PolAAr 2001 digital polarimeter. X-ray crystal data was measured on a Rigaku AFC75 diffractometer with Cu-Kα radiation (graphic monochromator) using ω-scans.
6.2 EXPERIMENTAL FOR CHAPTER TWO

(±)-$N$-(2-Bromoallyl)-1-phenylethylamine (82).

To a stirred solution of (±)-1-phenylethylamine (10.0 g, 82.5 mmol), and potassium carbonate (5.70 g, 41.25 mmol) in THF (100 ml), was added 2,3-dibromopropene (8.20 g, 41.25 mmol) and the reaction mixture stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 75 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Subsequent column chromatography (25% diethyl ether / petroleum ether) gave (±)-$N$-(2-bromoallyl)-1-phenylethylamine 82 (8.00 g, 79%) as a pale yellow oil. Spectroscopic data for this compound are identical with those described for the (S)-enantiomer.

(S)-$N$-(2-Bromoallyl)-1-phenylethylamine (82).

To a stirred solution of (S)-1-phenylethylamine (10.0 g, 82.5 mmol) and potassium carbonate (5.70 g, 41.25 mmol) in THF (100 ml), was added 2,3-dibromopropene (8.20 g, 41.25 mmol) and the reaction mixture was stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 75 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Subsequent column chromatography (25% diethyl ether / petroleum ether) gave (S)-$N$-(2-bromoallyl)-1-phenylethylamine 82 (7.50 g, 76%) as a pale yellow oil. [α]_D[^{20}]= -30.8 (c 1.0, CHCl₃); ν_max(film) 3316, 3085, 2825, 1603, 699, 659 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.98-7.19 (5H, m, Ph), 5.65 (1H, d, 1.5 Hz, =CH), 5.54 (1H, d, 1.5 Hz, =CH), 3.85 (1H, q, 7.5 Hz, NHCH), 3.29
Experimental

(2H, m, NCH₂), 1.78 (1H, s, NH), 1.39 (3H, d, 7.5 Hz, CH₃); δ_C (62.9 MHz; CDCl₃) 144.8 (s), 133.8 (s), 128.4 (d), 127.0 (d), 126.7 (d), 117.7 (t), 55.5 (d), 55.0 (t), 24.2 (q); m/z: 242 / 240, 224, 160, 144, 120, 105; Observed (MH⁺): 240.0388; C₁₁H₁₅NBr requires 240.0388.

(R)-N-(2-Bromoallyl)-1-phenylethylamine (82).

\[
\begin{align*}
\text{Me}_2\text{CH} & \quad \text{Ph} \\
\text{NH}_2 & \quad \text{NH} \\
\text{Br} &
\end{align*}
\]

(R)-82

To a stirred solution of (R)-1-phenylethylamine (5.00 g, 41.2 mmol) and potassium carbonate (2.85 g, 20.6 mmol) in THF (50 ml) was added 2,3-dibromopropene (12 g, 20.6 mmol) and the reaction mixture stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 30 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Subsequent column chromatography (25% diethyl ether / petroleum ether) gave (R)-N-(2-bromoallyl)-1-phenylethylamine 82 (3.50 g, 71%) as a pale yellow oil. [α]_D^{20} = +31.9 (c 1.0, CHCl₃). Spectroscopic data for this compound are identical with those described for the (S)-enantiomer.
**Experimental**

**General Method A: Preparation of Methyleneaziridines.**

To a three-necked flask fitted with a dry ice condenser and gas inlet tube was added sodium amide (15 equivalents) and the system flushed with nitrogen, then ammonia. A dry ice / acetone mixture was added to the condenser and ammonia was condensed into the flask. The vinyl bromide was added to this mixture in a small volume of diethyl ether and the resultant solution was stirred for the stated period of time. The stirring reaction mixture was diluted with diethyl ether (20 ml) and quenched by the dropwise addition of water (10 ml / mmol) (CAUTION: exothermic). After the ammonia had evaporated, water (10 ml / mmol) and diethyl ether (10 ml / mmol) were added and stirring was continued for a few minutes. The organic phase was separated and the aqueous layer extracted with diethyl ether (x 3). The combined organic extracts were washed with 10% sodium hydroxide, then water, dried over MgSO₄ and the solvent removed under reduced pressure to give the crude product, which was purified by column chromatography using the specified solvent system.

(±)-1-(1-Phenylethyl)-2-methyleneaziridine (79).

Reaction of (±)-82 (1.0 g, 4.16 mmol) with sodium amide (2.43 g, 62.7 mmol) in liquid ammonia (10 ml) for 5 minutes as described in General Method A and subsequent purification by bulb to bulb distillation (ca 95°C / 5 mmHg) gave (±)-1-(1-phenylethyl)-2-methyleneaziridine 79 (0.49 g, 74%) as a colourless oil. Spectroscopic data are consistent with those of the (S)-enantiomer.
Experimental

(S)-1-(1-phenylethyl)-2-methyleneaziridine (79).

Reaction of (S)-82 (5.0 g, 20.7 mmol) with sodium amide (11.6 g, 310.9 mmol) in liquid ammonia (50 ml) for 5 minutes as described in General Method A and subsequent purification by bulb to bulb distillation (ca 95°C, 5 mmHg) gave (S)-1-(1-phenylethyl)-2-methyleneaziridine 79 (2.50 g, 76%) as a colourless oil. \([\alpha]_D^{20} = -101.9 \text{ (c 1.0, CHCl}_3\);
\(\nu_{\max (\text{film})} \text{ 3076, 1749, 1599, 1449, 699 cm}^{-1};\)
\(\delta_H \text{ (250 MHz; CDCl}_3\) 7.38-7.25 (5H, m, Ph), 4.64-4.62 (2H, m, =CH\_2), 2.93 (1H, q, 6.6 Hz, NCH), 2.05 (1H, d, 2.5 Hz, aziridine CH), 1.87 (1H, d, 2.5 Hz, aziridine CH), 1.01 (3H, d, 6.5 Hz, CH\_3); \(\delta_C \text{ (62.9 MHz; CDCl}_3\) 143.7 (s), 132.9 (s), 128.0 (d), 127.2 (d), 126.7 (d), 82.9 (t), 68.4 (d), 39.8 (t), 23.5 (q); \(m/z \text{ 159 (M}^+\)), 118, 105; Observed (M\(^+\)): 159.1048; \(\text{C}\_11\_H\_13\_N \text{ requires 159.1048.}

Chirality analysis of (S)-1-(1-phenylethyl)-2-methyleneaziridine (79).

\(^1\text{H NMR analysis at 400 MHz of (±)-79 (3.0 mg, 18.8 \mu mol) in the presence of (+)-[Eu(hfc)] (0.35 molar equivalents) in d-chloroform produced two overlapping doublets due to the methyl group at }\delta_H 1.59 \text{ (d, 6.6 Hz) and 1.58 (d, 6.6 Hz). Repetition of the procedure using (S)-79 indicated the presence of only one enantiomer, shown by the presence of one methyl group at }\delta_H 1.59 \text{ (d, 6.6 Hz). Addition of (±)-79 to this sample resulted in the appearance of the second set of resonances, where the methyl group at 1.58 for the second enantiomer was present.}
Experimental

**(R)-N-(1-Phenylethyl)-2-methyleneaziridine (79).**

![Reaction Scheme](image)

Reaction of (R)-82 (5.0 g, 20.8 mmol) with sodium amide (11.5 g, 295 mmol) in liquid ammonia (100 ml) for 5 minutes as described in General Method A and subsequent purification by bulb-to-bulb distillation (ca 95°C, 5 mmHg) gave (R)-N-(1-phenylethyl)-2-methyleneaziridine 79 (2.7 g, 82%) as a clear oil. [α]D20 = +99.8 (c 1.0, CHCl3); Spectroscopic data for this compound are identical with the (S)-enantiomer.

**Chirality analysis of (R)-N-(1-phenylethyl)-2-methyleneaziridine (79).**

1H NMR analysis at 400 MHz of (±)-79 (3.0 mg, 18.8 μmol) in the presence of (+)-[Eu(hfc)]3 (0.35 molar equivalents) in d-chloroform produced two overlapping doublets due to the methyl group at δH 1.63 (d, 6.6 Hz) and 1.62 (d, 6.6 Hz). Repetition of the procedure using (R)-79 indicated the presence of one enantiomer, where the methyl group was present at 1.62 ppm. Addition of (±)-79 to this sample resulted in the appearance of the second set of resonances for the (S)-enantiomer.

*N-(2-Bromoallyl)-2-phenylethylamine (89).*

![Reaction Scheme](image)

To a stirred solution of 2-phenylethylamine (4.00 g, 33.0 mmol) and potassium carbonate (2.20 g, 15.9 mmol) in diethyl ether (40 ml), was added 2,3-dibromopropene (3.25 g, 16.3 mmol) and the reaction stirred at room temperature for 2 days. The mixture was filtered, and washed with 10% sodium hydroxide solution. The organic phase was dried over MgSO4 and concentrated under reduced pressure to give the crude product. Subsequent column chromatography (20% diethyl ether / petroleum ether) gave N-(2-bromoallyl)-2-phenylethylamine 89 (1.96 g, 50%) as a yellow oil. νmax(film) 3326, 3085, 3026, 2923, 2832, 749 cm⁻¹; δH (250 MHz; CDCl3) 7.31-7.19 (5H, m, Ph), 5.61 (1H, d, 1.3 Hz, =CH), 5.57
Experimental

(1H, d, 1.3 Hz, =CH), 3.44 (2H, s, CH$_2$NH), 2.80 (4H, m, 2 x CH$_2$), 1.48 (1H, s, NH); δ$_C$
(62.9 MHz; CDCl$_3$) 139.7 (s), 133.4 (d), 128.6 (s), 128.4 (d), 126.2 (d), 117.4 (t), 57.3 (t),
48.9 (t), 36.3 (t); m/z 239 / 241 (M$^+$); Observed (M-H$^+$): 238.0225; C$_{11}$H$_{13}$BrN requires
238.0232.

1-(2-Phenylethyl)-2-methyleneaziridine (88).

![89 88]

Reactions of 89 (3.00 g, 12.5 mmol) with sodium amide (7.31 g, 187 mmol) in liquid
ammonia (40 ml) for 45 minutes as described in General Method A and subsequent column
chromatography (1% triethylamine / dichloromethane) gave 1-(2-phenylethyl)-2-
methyleneaziridine 88 (500 mg, 31%) as a pale brown oil. ν$_{\text{max}}$(film) 2988, 2850, 1759,
1462, 1649, 720 cm$^{-1}$; δ$_H$ (250 MHz; CDCl$_3$) 7.33-7.20 (5H, m, Ph), 4.66-4.62 (2H, m,=
=CH$_2$), 2.90 (2H, t, 6.6 Hz, CH$_2$), 2.70 (2H, t, 6.3 Hz, CH$_2$) 2.05-2.03 (2H, bs, aziridine
CH$_2$); δ$_C$ (62.9 MHz; CDCl$_3$) 138.2 (s), 135.0 (s), 128.5 (d), 128.2 (d), 127.7 (d), 85.7 (t),
64.1 (t), 63.9 (t), 36.5 (t); m/z 159 (M$^+$), 158, 106; Observed (M$^+$): 159.1046; C$_{11}$H$_{13}$N
requires 159.1048.

General Method B: Preparation of 1-(benzyloxy)-2-amines.

![R1 R2 NH2 O Ph]

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.9 molar
equivalents) in THF (0.8 ml / mmol of amino alcohol) at 0°C, was added the appropriate
amino alcohol (1.0 molar equivalents) dropwise. The resultant suspension was heated under
reflux for 30 minutes. Benzyl chloride (0.9 molar equivalents) was added dropwise and the
reaction mixture was refluxed for a further 14 hours then allowed to cool to room
temperature. Water (1 ml / 1.3 molar equivalents) was added then the solvents removed
under reduced pressure. The residue was redissolved in dichloromethane (1 ml / 0.5 molar
equivalents) and the product extracted into the aqueous phase by washing with 1M HCl (3 x
75 ml). The aqueous phase was basified with 10% sodium hydroxide and the product re-
Experimental

extracted into dichloromethane. The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure to give the crude product.

(2R)-1-(Benzyloxy)-2-propylamine (92).

Reaction of (R)-2-amino-1-propanol (5.00 g, 66.5 mmol) using sodium hydride (60% dispersion in mineral oil, 2.00 g, 51.0 mmol) and benzyl chloride (7.50 g, 59.1 mmol) as described in General Method B. In this case, the reflux times used were 90 minutes and 14 hours respectively, giving (R)-1-(benzyloxy)-2-propylamine (7.20 g, 73%) as a yellow oil which was used without further purification. \([\alpha]_D^{20} = -17.8 \text{ (c 1.0, CHCl}_3)\), lit\(^{51}\)[\([\alpha]_D = +16.4 \text{ (c 0.85, MeOH)}\) for (S)-enantiomer). \(v_{max}\) (film) 3362, 3030, 2969, 1453, 1369, 1098, 738, 699 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 7.33-7.26 (5H, m, Ph), 4.51 (2H, s, OCH\(_2\)Ph), 3.39-3.33 (1H, m, CH\(_2\)OBn), 3.21-3.15 (2H, m, NCH and CHOBN), 1.37 (2H, s, NH\(_2\)), 1.03 (3H, d, 5.9 Hz, CH\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 138.3 (s), 128.6 (d), 127.5 (d), 127.5 (d), 77.1 (t), 73.1 (t), 46.4 (d), 19.7 (q); \(m/z\) 166 (MH\(^+\)), 165 (M\(^+\)), 134, 91; Observed (M\(^+\)): 165.1144; C\(_{10}\)H\(_{15}\)NO requires 165.1154. Data in agreement with the literature values.\(^{51}\)

(±)-1-(Benzyloxy)-3-methyl-2-butyramine (93).

Reaction of (±)-valinol (5.00 g, 48.5 mmol) using sodium hydride (60% dispersion in mineral oil, 2.10 g, 52.5 mmol) and benzyl chloride (5.50 g, 43.6 mmol) as described in General Method B, gave (±)-1-(benzyloxy)-3-methyl-2-butyramine (7.60 g, 91%) as a yellow oil which was used without further purification. \(\delta_H\) (250 MHz; CDCl\(_3\)) 7.41-7.22 (5H, m, Ph), 4.48 (2H, s, CH\(_2\)Ph), 3.47 (1H, dd, 9.0, 3.8 Hz, CHOBn), 3.30 (1H, dd, 9.0, 8.1 Hz, CHOBn), 2.87-2.73 (1H, m, NCH), 1.62-1.57 (1H, m, CH(CH\(_3\))\(_2\)), 1.34 (2H, s, NH\(_2\)), 0.92 (3H, d, 6.7 Hz, CH\(_3\)), 0.90 (3H, d, 6.7 Hz, CH\(_3\)). Data is in agreement with literature values.\(^{54}\)
Experimental

(2S)-1-(Benzyloxy)-4-methyl-2-pentylamine (94).

Reaction of (S)-leucinol (5.00 g, 42.7 mmol) using sodium hydride (60% dispersion in mineral oil, 2.00 g, 52.2 mmol) and benzyl chloride (4.90 g, 38.7 mmol) as described in General Method B. In this case, the reflux times used were 90 minutes and 14 hours respectively, and gave (2S)-1-(benzyloxy)-4-methyl-2-pentylamine 94 (4.80 g, 60%) as a yellow oil which was used without further purification. \( [\alpha]_D^{20} = +5.0 \) (c 1.3, CHCl3); \( \nu_{\text{max}} \) (film) 3372, 3030, 2954, 2867, 698 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl3) 7.32-7.29 (5H, m, Ph), 4.51 (2H, s, CH2Ph), 3.44 (1H, dd, 8.9, 3.6 Hz, CHOBN), 3.20 (1H, dd, 8.9 Hz, 8.0 Hz, CHOBN), 3.10-3.03 (1H, m, NCH), 1.76-1.66 (1H, m, CH(CH3)$_2$), 1.4 (2H, bs, NH$_2$), 1.25-1.14 (2H, m, CH$_2$), 0.91 (3H, d, 6.5 Hz, CH$_3$), 0.89 (3H, d, 6.6 Hz, CH$_3$); \( \delta_C \) (62.9 MHz; CDCl3) 138.0 (s), 128.3 (d), 127.6 (d) 127.5 (d), 76.9 (t), 73.1 (t), 48.7 (d), 43.3 (t), 24.5 (d), 23.4 (q), 21.9 (q); \( m/z \) 208 (MH$^+$), 178, 91, Observed (MH$^+$): 208.1700; C$_{13}$H$_{22}$NO requires 208.1701.

1-(Benzyloxy)-2-methyl-2-propylamine (95).

Reaction of 2-amino-2-methyl-1-propanol (10.00 g, 112 mmol) using sodium hydride (60% dispersion in mineral oil, 5.00 g, 135 mmol) and benzyl chloride (12.70 g, 101 mmol) as described in General Method B. In this case the reflux times used were 30 minutes and 14 hours respectively, and gave 1-(benzyloxy)-2-methyl-2-propylamine 95 (14.80 g, 82%) as a yellow oil which was used without further purification. \( \nu_{\text{max}} \) (film) 3360, 2964, 2928, 2867, 1101, 736 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl3) 7.37-7.22 (5H, m, Ph), 4.53 (2H, m, CH$_2$Ph), 3.20 (2H, s, CH$_2$OBn), 1.25 (2H, s, NH$_2$). 1.18 (6H, s, 2 x CH$_3$); \( \delta_C \) (62.9 MHz; CDCl3) 138.5 (s), 128.2 (d), 127.4 (d), 127.3 (d), 80.5 (t), 73.2 (t), 49.9 (s), 27.4 (q); \( m/z \) 180 (MH$^+$), 148, 91; Observed (MH$^+$): 180.1388; C$_{11}$H$_{18}$NO requires 180.1388.
(2R)-N-(2-Bromoallyl)-1-(benzyloxy)-2-propylamine (96).

![Chemical structure of 96]

To a stirred solution of 92 (12.0 g, 72.6 mmol) and potassium carbonate (5.0 g, 36.2 mmol) in diethyl ether (100 ml) was added 2,3-dibromopropene (7.20 g, 36.3 mmol) and the reaction stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 75 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave (2R)-N-(2-bromoallyl)-1-(benzyloxy)-2-propylamine 96 (7.00 g, 68%) as a yellow oil. [α]D²⁰ = +19.3 (c 1.0, CHCl₃); νmax (film) 3328, 2858, 1635, 1099, 698 cm⁻¹; δH (250 MHz; CDCl₃) 7.34-7.25 (5H, m, Ph), 5.81 (1H, d, 1.4 Hz, =CH) 5.55 (1H, d, 1.7 Hz, =CH), 4.55 (1H, d, 12.0 Hz, A of AB, CH₂Ph), 4.52 (1H, d, 12.0 Hz, B of AB, CH₂Ph), 3.56-3.46 (2H, m, NHCH₂), 3.43 (1H, dd, 9.4, 4.4 Hz, CHOBn), 3.53 (1H, dd, 9.4, 7.6 Hz, CHOBn), 3.03-2.95 (1H, m, NCH), 2.36 (1H, bs, NH), 1.02 (3H, d, 6.4 Hz, CH₃); δC (62.9 MHz; CDCl₃) 138.0 (s), 133.3 (d), 128.3 (s) 127.52 (d), 127.50 (d), 117.5 (t), 74.6 (t), 73.0 (t), 54.7 (t), 50.3 (d) 16.7 (q); m/z 286 / 284 (M⁺), 285 / 283 (M⁺), 191; Observed (M⁺): 283.0580; C₁₃H₁₈BrNO requires 283.0571.

N-(2-Bromoallyl)-1-(benzyloxy)-3-methyl-2-butylamine (97).

![Chemical structure of 97]

To a stirred solution of (±)-93 (5.00 g, 25.8 mmol) and potassium carbonate (1.80 g, 12.9 mmol) in THF (50 ml), was added 2,3-dibromopropene (2.60 g, 12.9 mmol) and the mixture stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 30 ml). The organic phase was dried over MgSO₄
and concentrated under reduced pressure. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave N-(2-bromoallyl)-1-(benzyloxy)-3-methyl-2-butylamine 97 (3.0 g, 74%) as a yellow oil. δH (250 MHz; CDCl3) 7.34-7.29 (5H, m, Ph), 5.80 (1H, m, =CH), 5.51 (1H, d, 2.0 Hz, =CH), 4.56 (2H, s, CH2Ph), 3.54 (1H, dd, 9.6, 4.0 Hz, COBn), 3.48 (2H, s, CH2NH), 3.39 (1H, dd, 9.6, 6.7 Hz, CHOBn), 2.61-2.59 (1H, m, NHCH), 1.89 (1H, m, CH(CH3)2), 1.75 (1H, s, NH), 0.93 (3H, d, 6.6 Hz, CH3), 0.89 (3H, d, 6.6 Hz, CH3). Data are in agreement with literature values.54

(1S)-N-(2-Bromoallyl)-1-(benzyloxy)-4-methyl-2-pentylamine (98).

To a stirred solution of (1S)-94 (8.50 g, 41.0 mmol), and potassium carbonate (2.83 g, 20.5 mmol) in THF (85 ml) was added 2,3-dibromopropene (4.10 g, 20.5 mmol) and the reaction stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 30 ml). The organic phase was dried over MgSO4 and concentrated under reduced pressure. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave (1S)-N-(2-bromoallyl)-1-(benzyloxy)-4-methyl-2-pentylamine 98 (3.40 g, 51%) as a pale yellow oil. [α]D 20 = +1.3 (c 1.0, CHCl3); νmax (film) 3030, 2955, 1454, 1366, 1101, 698 cm⁻¹; δH (250 MHz; CDCl3) 7.34-7.29 (5H, m, Ph), 5.81 (1H, d, 1.0 Hz, =CH), 5.54 (1H, d, 1.0 Hz, =CH), 4.55 (H, d, 12.0 Hz, A of AB, CH2Ph), 4.51 (1H, d, 12.0 Hz, B of AB, CH2Ph), 3.55-3.47 (3H, m, NHCH2 and CHOBn), 3.36 (1H, dd, 9.6 Hz, 6.8 Hz, CHOBn), 2.90-2.84 (1H, m, NCH), 2.60 (1H, bs, NH), 1.65 (1H, m, CH(CH3)2), 1.36-1.23 (2H, m, CH2), 0.89 (3H, d, 6.5 Hz, CH3), 0.85 (3H, d, 6.2 Hz, CH3). δC (62.9 MHz; CDCl3) 138.0 (s), 134.0 (s), 128.5 (d) 128.0 (d), 127.5 (d), 117.9 (t), 73.1 (t), 72.9 (t), 54.9 (t), 53.2 (d), 41.2 (t), 24.9 (d), 23.0 (q), 22.8 (q); m/z 328 / 326 (MH⁺), 206, 204, 91; Observed (MH⁺): 326.1120; C16H25BrNO requires 326.1119.
Experimental

**N-[(2-Bromoallyl)-1-(benzyloxy)-2-methyl-2-propylamine (99).**

To a stirred solution of 95 (15.00 g, 83.7 mmol), and potassium carbonate (5.90 g, 42.5 mmol) in THF (150 ml) was added 2,3-dibromopropene (8.33 g, 41.85 mmol) and the reaction stirred at room temperature for 2 days. The mixture was filtered, and then washed with 10% aqueous sodium hydroxide solution (2 x 75 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave N-[(2-bromoallyl)-1-(benzyloxy)-2-methyl-2-propylamine 99 (10.5 g, 85%) as a pale yellow oil. ν_max(film) 3301, 2951, 2847, 1668, 1073 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.37-7.35 (5H, m, Ph), 5.88 (1H, d, 1.0 Hz, =CH), 5.51 (1H, d, 1.0 Hz, =CH), 4.55 (2H, s, CH₂Ph), 3.38 (2H, s, CH₂OBn), 3.27 (2H, s, CH₂), 1.98-1.91 (1H, bs, NH), 1.11 (6H, s, 2 x CH₃); δ_C (62.9 MHz; CDCl₃) 138.0 (s), 134.5 (s), 128.3 (d), 127.4 (d), 124.3 (d), 116.3 (t), 77.0 (t), 73.2 (t), 51.0 (t), 40.1 (s), 24.3 (q); m/z 298 / 296 (M⁺), 176, 91; Observed (M⁺): 297.0723, C₁₄H₂₀BrNO requires 297.0729.

(R)-1-[2-(1-benzyloxy)propyl]-2-methyleneaziridine (101).

Reaction of 96 (6.30 g, 22.2 mmol) with sodium amide (12.8 g, 32.8 mmol) in liquid ammonia (120 ml) for 30 minutes as described in General Method A and subsequent column chromatography (30% diethyl ether / petroleum ether) gave (R)-1-[2-(1-benzyloxy)propyl]-2-methyleneaziridine 101 (3.30 g, 73%) as a colourless oil. [α]_D²⁰ = -17.6 (c 1.0, CHCl₃) ν_max(film) 2970, 2857, 1768, 1190, 1101, 689 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.41-7.23 (5H, m, Ph), 4.75 (1H, d, 1.2 Hz, =CH), 4.66 (1H, d, 1.2 Hz, =CH), 4.55 (2H, s, OCH₂Ph), 3.59 (1H, dd, 9.5, 6.4 Hz, CHOBN ), 3.48 (1H, dd, 9.5, 5.3 Hz, CHOBN), 2.11-2.10 (3H, m,
aziridine CH₂, NCH), 1.20 (3H, d, 6.5 Hz, CH₃); δC (62.9 MHz; CDCl₃) 138.3 (s), 136.1 (s), 128.0 (d), 127.5 (d), 127.5 (d), 83.2 (t), 74.6 (t), 73.2 (t), 62.9 (d), 29.6 (t), 17.1 (q); m/z 203 (M⁺), 174, 91; Observed (M⁺): 203.1302; C₁₃H₁₇N requires 203.1310.

**Enantiomeric purity of (R)-1-[2-(1-benzyloxy)propyl]-2-methyleneaziridine (101).**

Enantiomeric purity of (R)-101 was determined to be ≥95% by ¹H NMR analysis (400 MHz, CDCl₃, using 101 (1.9 mg, 0.9 µmol) in the presence of (S)-(+)/-2,2,2-trifluoro-1-(9-anthryl)ethanol (1.1 molar equivalents). The following methyl resonances were resolved in the presence of chiral shift reagent for the racemic compound: 1.17 (1.5H, d, 6.5 Hz, (5) CH₃), 1.16 (1.5H, d, 6.5 Hz, (R)-CH₃).

**(±)-[2-(3-Methyl-1-benzyloxy)butyl]-2-methyleneaziridine (102).**

Reaction of 97 (3.00 g, 9.61 mmol) with sodium amide (5.63 g, 144 mmol) in liquid ammonia (100 ml) for 10 minutes as described in General Method A gave (±)-2-(3-methyl-1-benzyloxy)butyl]-2-methyleneaziridine 102 (2.00 g, 90%) as a clear oil. νmax(film) 2971, 2875, 1759, 1186, 1100, 698 cm⁻¹; δH (250 MHz; CDCl₃) 7.31-7.13 (5H, m, Ph), 4.78 (1H, d, 1.4 Hz, =CH), 4.65 (1H, d, 1.4 Hz, =CH), 4.34 (2H, s, OCH₂Ph), 3.65 (1H, dd, 9.4 Hz, 6.3 Hz, CHOBn), 3.48 (1H, dd, 9.4, 5.0 Hz, CHOBn), 1.99 (1H, s, aziridine CH), 2.00-1.95 (2H, m, CH(CH₃)₂ and NCH), 1.89 (1H, s, aziridine CH), 1.03 (3H, d, 6.6 Hz, CH₃), 0.95 (3H, d, 6.6 Hz, CH₃). Data are consistent with literature values.⁵⁴
(S)-1-[2-(1-benzyloxy)-4-methylpentyl]-2-methyleneaziridine (103).

Reaction of 98 (2.0 g, 6.13 mmol) with sodium amide (3.60 g, 92.3 mmol) in liquid ammonia (40 ml) for 5 minutes as described in General Method A and subsequent column chromatography (20% diethyl ether / petroleum ether) gave (S)-1-[2-(1-benzyloxy)-4-methylpentyl]-2-methyleneaziridine 103 (1.40 g, 93%) as a colourless oil. [α]_D^{20} = -10.6 (c 1.0, CHCl_3); ν_{max}(film) 3090, 3031, 2956, 2868, 1765, 1453, 1366, 1182, 1111, 736, 697 cm^{-1}; δ_H (400 MHz; CDCl_3) 7.37-7.26 (5H, m, Ph), 4.73 (1H, d, 1.0 Hz, =CH), 4.67 (1H, d, 1.0 Hz, =CH), 4.58 (1H, d, 12.5 Hz, A of AB, CH_2Ph), 4.55 (1H, d, 12.5 Hz, B of AB, CH_2Ph), 3.57 (2H, m, CH_2OBN)), 2.17 (1H, s, aziridine CH), 2.15-2.10 (1H, m, NCH), 2.10 (1H, s, aziridine CH), 1.74-1.64 (1H, m, CH(CH_3)_2), 1.49-1.42 (2H, m, CH_2CH(CH_3)_2), 0.92 (3H, d, 6.5 Hz, CH_3), 0.88 (3H, d, 6.5 Hz, CH_3); δ_C (62.9 MHz; CDCl_3) 136.0 (s) 135.0 (s), 128.3 (d), 127.5 (d), 127.4 (d), 83.1 (t), 73.2 (t), 72.9 (t), 65.1 (d), 41.2 (t), 29.5 (t) 24.7 (d), 23.3 (q), 22.6 (q); m/z 246 (MH^+), 189; Observed (MH^+): 246.1858; C_{16}H_{24}NO requires 246.1858.

Enantiomeric purity of (S)-1-[2-(1-benzyloxy)-4-methylpentyl]-2-methyleneaziridine (103).

The enantiomeric purity of 103 was determined to be >95% ee by chiral HPLC analysis using a Chiralcel OD column (1% iPrOH in hexanes; 0.5 ml min^{-1}; (R)-minor: 13.8 min, (S)-major: 15 min). The racemate was used for comparison purposes in this analysis.
Experimental

Attempted synthesis of 1-[1-benzyloxy)-2-methyl-2-propyl]-2-methyleneaziridine (104).

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Reaction of 99 (2.00 g, 6.71 mmol) with sodium amide (3.94 g, 101 mmol) in liquid ammonia (40 ml) for 2 hours as described in General Method A and subsequent chromatography (0.5% methanol / diethyl ether) gave N-[1-(benzyloxy)-2-methyl-2-propyl]-propargylamine 105 (800 mg, 55%). \(\nu_{\text{max}}\) (film) 3299, 2931, 2857, 1496, 1028, 738 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 7.34-7.22 (5H, m, Ph), 4.53 (2H, s, CH\(_2\)Ph), 3.34 (2H, s, CH\(_2\)O), 3.28 (2H, s, NHCH\(_2\)), 2.16 (1H, t, acetylene CH), 1.75 (1H, bs, NH), 1.09 (6H, s, 2 x CH\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 138.0 (s), 128.2 (d), 127.5 (d), 127.4 (d), 83.8 (d), 76.8 (t), 73.1 (t), 70.5 (s), 53.4 (s), 31.7 (t), 24.0 (q); \(m/z\) 218 (MH\(^+\)), 217 (M\(^+\)); Observed (M\(^+\)): 217.1460; C\(_{14}\)H\(_{19}\)NO requires 217.1467.

(±)-N-(2-Bromoallyl)-1-methoxy-2-propylamine (107).

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To a stirred solution of (±)-2-amino-1-methoxypropane (10.0 g, 112 mmol) and potassium carbonate (7.70 g, 55.7 mmol) in diethyl ether (100 ml) was added 2,3-dibromopropene (11.2 g, 56.0 mmol) and the reaction mixture stirred at room temperature for 2 days. The mixture was filtered then washed with 10% sodium hydroxide solution. The organic phase was dried
over MgSO₄ and concentrated under reduced pressure to give the crude product. Subsequent column chromatography (50% diethyl ether / petroleum ether) gave (±)-N-(2-bromoallyl)-1-methoxy-2-propylamine 107 (7.35 g, 63%) as a pale yellow oil. \( \nu_{\text{max}} \) (film) 3330, 2925, 2877, 2828, 1452, 1364, 1108 cm⁻¹; \( \delta_H \) (250 MHz; CDCl₃) 5.81 (1H, d, 1.4 Hz, =CH), 5.54 (1H, d, 1.4 Hz, =CH), 3.98 (2H, s, NHCH₂), 3.30 (3H, s, OCH₃), 3.26-3.20 (2H, m, CH₂OCH₃), 3.00-2.88 (1H, m, NCH), 2.20 (1H, bs, NH), 1.03 (3H, d, 6.4 Hz, CH₃); \( \delta_C \) (62.9 MHz; CDCl₃) 133.5 (s), 117.1 (t), 77.2 (t), 58.7 (d), 54.7 (t), 49.9 (q), 16.7 (q); \( m/z \) 209 / 207 (M⁺), 180, 58, 45; Observed (M⁺, CI): 207.0287; C₇H₁₄BrNO requires 207.0259.

(±)-N-(2-Bromoallyl)-1-cyclohexylethylamine (113).

To a stirred solution of (±)-1-cyclohexylethylamine (10.00 g, 78.6 mmol) and potassium carbonate (5.43 g, 39.3 mmol) in diethyl ether (100 ml) was added 2,3-dibromopropene (7.82 g, 39.3 mmol) and the reaction mixture stirred at room temperature for 2 days. The mixture was filtered, then washed with 10% aqueous sodium hydroxide solution (2 x 75 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave (±)-N-(2-Bromoallyl)-1-cyclohexylethylamine 113 (5.60 g, 58%) as a brown oil. \( \nu_{\text{max}} \) (film) 3319, 1635, 1448, 890 cm⁻¹; \( \delta_H \) (250 MHz; CDCl₃) 5.78 (1H, d, 1.4 Hz, =CH), 5.53 (1H, d, 1.4 Hz, =CH), 3.45 (2H, d, 2.5 Hz, NCH₂), 2.49-2.40 (1H, m, NHCH), 1.79-1.68 (7H, m, 6 x CH and NH), 1.30-1.10 (5H, m, 5 x CH), 0.97 (3H, d, 6.5 Hz, CH₃); \( \delta_C \) (62.9 MHz; CDCl₃) 133.8 (s), 117.3 (t), 55.3 (d), 54.9 (t), 42.9 (d), 29.6 (t), 28.1 (t), 26.6 (t), 16.3 (q); \( m/z \) 247 / 245 (M⁺); Observed (M⁺): 245.0788; C₁₁H₂₀BrN requires 245.0780.
Experimental

(+)-1-(1-Cyclohexylethyl)-2-methyleneaziridine (111).

Reaction of 113 (2.00 g, 8.12 mmol) with sodium amide (4.75 g, 122 mmol) in liquid ammonia (50 ml) for 5 hours as described in General Method A and subsequent chromatography (49% diethyl ether / 1% triethylamine / 50% petroleum ether) gave (+)-1-(1-cyclohexylethyl)-2-methyleneaziridine 111 (150 mg, 11%) as a pale yellow oil. $\nu_{\text{max}}$(film) 2924, 2852, 1766, 1449, 1375, 1183 cm$^{-1}$; $\delta$$_H$ (250 MHz; CDCl$_3$) 4.70 (1H, d, 1.4 Hz, $=\text{CH}$), 4.61 (1H, d, 1.4 Hz, $=\text{CH}$), 2.09 (1H, s, aziridine CH), 1.95 (1H, s, aziridine CH), 1.84-1.67 (5H, m, 5 x CH), 1.51-1.49 (1H, m, NCH), 1.29-1.21 (6H, m, 6 x CH), 1.16 (3H, d, 6.5 Hz, CH$_3$); $\delta$$_C$ (62.9 MHz; CDCl$_3$) 137.2 (s), 117.6 (t), 68.9 (d), 55.5 (t), 44.1 (d), 30.4 (t), 30.2 (t), 28.6 (t), 27.1 (t), 26.9 (t) 16.3 (q); m/z 165 (M$^+$); Observed (M$^+$): 165.1505; C$_{11}$H$_{19}$N requires 165.1517.

N-(2-Bromoallyl)-4-phenyl-2-butylamine (114).

To a stirred solution of 4-phenyl-2-butylamine (10.0 g, 67.0 mmol) and potassium carbonate (4.60 g, 33.3 mmol) in diethyl ether (100 ml) was added 2,3-dibromopropene (6.70 g, 33.5 mmol) and the reaction mixture stirred at room temperature for 30 hours. The mixture was filtered, then washed with 10% sodium hydroxide solution. The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure to give the crude product. Subsequent column chromatography (20% diethyl ether / petroleum ether) gave N-(2-bromoallyl)-4-phenyl-2-butylamine 114 (7.00 g, 78%) as a yellow oil. $\nu_{\text{max}}$(film) 3300, 2961, 2858, 1632, 1453, 839, 747, 698 cm$^{-1}$; $\delta$$_H$ (250 MHz; CDCl$_3$) 7.30-7.17 (5H, m, Ph), 5.73 (1H, d, 1.0 Hz, $=\text{CH}$), 5.51 (1H, d, 1.0 Hz, $=\text{CH}$), 3.46 (2H, s, CH$_2$NH), 2.74-2.62 (3H, m, NHCH, CH$_2$Ph), 83
1.77-1.64 (2H, m, CH₂CH₂Bn), 1.61 (1H, bs, NH) 1.08 (3H, d, 6.2 Hz, CH₃); δₜ (62.9 MHz; CDCl₃) 142.0 (s), 134.6 (s), 128.3 (d), 128.2 (d), 125.7 (d), 117.3 (t), 54.8 (t), 38.5 (t), 23.1 (t), 20.0 (q); m/z 269 / 267 (M⁺). Observed (M⁺): 267.0633; C₁₃H₁₈BrN requires 267.0623.

1-(1-Phenyl-3-butyl)-2-methyleneaziridine (112).

Reaction of 114 (2.00 g, 7.46 mmol) with sodium amide (3.16 g, 81.0 mmol) in liquid ammonia (50 ml) for 7 hours as described in General Method A gave 1-(1-phenyl-3-butyl)-2-methyleneaziridine 112 (480 mg, 35% crude) which could not be further purified due to it's instability with respect to silica gel chromatography or bulb to bulb distillation (50°C / 3 mmHg). νₘₐₓ(film) 2967, 2930, 2859, 1765, 1495, 1179, 699 cm⁻¹; δₜ (250 MHz; CDCl₃) 7.32-7.15 (5H, m, Ph), 4.75 (1H, d, 0.8 Hz, =CH), 4.65 (1H, d, 0.8 Hz, =CH), 2.75-2.66 (2H, m, CH₂Ph), 2.18 (1H, s, aziridine CH), 2.13-2.10 (1H, m, NCH), 2.07 (1H, s, aziridine CH), 1.99-1.87 (2H, m, CH₂), 1.40 (3H, d, 6.2 Hz, CH₃).

2-[N-(2-bromoallyl)amino]-2-methyl-1-propanol (116).

To a stirred solution of 2-amino-2-methyl-1-propanol (10.0 g, 112 mmol) and potassium carbonate (7.70 g, 56 mmol) in THF (100 ml) was added 2,3-dibromopropene (11.12 g, 56 mmol) dropwise and the mixture refluxed for 21 hours. On cooling, the mixture was filtered, concentrated under reduced pressure, redissolved in dichloromethane (200 ml) and washed with 10% aqueous sodium hydroxide solution (2 x 100 ml). The organic phase was dried over MgSO₄, and concentrated under reduced pressure to give the crude product. Subsequent
column chromatography (30% diethyl ether / petroleum ether) gave 2-\([N-(2\text{-bromoallyl})\text{amino}]\)-2-methyl-1-propanol 116 (5.20 g, 45%) as a brown oil. \(v_{\text{max}}\)(film) 3356, 2966, 1635, 1052, 839 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 5.82 (1H, d, 1.5 Hz, =CH), 5.47 (1H, d, 1.5 Hz, =CH), 3.35 (2H, s, CH\(_2\)OH), 3.27 (2H, s, CH\(_2\)NH), 2.41-1.75 (2H, bs, OH and NH), 1.05 (6H, s, 2 x CH\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 135.5 (s), 116.8 (t), 68.3 (t), 53.8 (s), 50.7 (t), 23.9 (q); \(m/z\) 209 / 207 (M\(^+\)), 176, 97; Observed (M\(^+\)): 207.0254; \(C_7H_{14}NO\) requires 207.0259.

2-\([N-(2\text{-Bromoallyl})\text{amino}]\)-1-propanol (117).

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{NH}_2 & \quad \rightarrow \\
\text{Br} & \quad \text{NH} \\
\text{117} & \quad \text{OH}
\end{align*}
\]

To a stirred solution of 2-amino-1-propanol (10.0 g, 133 mmol), and potassium carbonate (9.20 g, 66.5 mmol) in THF (100 ml) was added 2,3-dibromopropene (3.20 g, 66.5 mmol) and the reaction mixture refluxed for 21 hours. On cooling, the mixture was filtered, concentrated under reduced pressure, redissolved in dichloromethane (200 ml) and washed with 10% aqueous sodium hydroxide solution (2 x 100 ml). The organic phase was dried over MgSO\(_4\) and concentrated under reduced pressure to give the crude product. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave 2-\([N-(2\text{-bromoallyl})\text{amino}]\)-1-propanol 117 (6.30 g, 50%) as a brown oil. \(v_{\text{max}}\)(film) 3299, 2966, 2926, 2873, 1454, 1049, 859 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 5.81 (1H, d, 1.5 Hz, =CH), 5.56 (1H, d, 1.5 Hz, =CH), 3.61-3.49 (4H, m, 2 x CH\(_2\)), 2.84-2.70 (1H, m, NH\(_2\)), 2.25 (2H, bs, NH and OH), 1.05 (3H, d, 6.4 Hz, CH\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 133.2 (s), 117.6 (t), 65.4 (t), 54.7 (t), 52.3 (d), 16.8 (q); \(m/z\) 196 / 194 (M\(^+\)), 164, 121, 83; Observed (M\(^+\)): 194.0180; \(C_6H_{13}NOBr\) requires 194.0180.
Experimental

2-[N-(2-Bromoallyl)amino]-3-methyl-1-butanol (118).

To a stirred solution of (±)-valinol (10.0 g, 96.9 mmol) and potassium carbonate (6.68 g, 48.5 mmol) in THF (100 ml) was added 2,3-dibromopropene (9.70 g, 48.5 mmol) dropwise and the reaction mixture refluxed for 21 hours. On cooling, the reaction mixture was filtered, concentrated under reduced pressure, redissolved in dichloromethane (200 ml) and washed with 10% aqueous sodium hydroxide solution (2 x 100 ml). The organic phase was dried over MgSO₄ and concentrated under reduced pressure to give the crude product. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave 2-[N-(2-bromoallyl)amino]-3-methyl-1-butanol 118 (6.10 g, 57%) as a brown oil. \( \delta_H \) (250 MHz; CDCl₃) 5.80 (1 H, d, 1.4 Hz, =CH), 5.54 (1 H, d, 1.4 Hz, =CH), 3.60 (1 H, dd, 10.8, 4.0 Hz, CHOH), 3.49 (2H, s, NHCH₂), 3.39 (1H, dd, 10.8, 6.4 Hz, CH OH), 2.44-2.29 (1H, m, NHCH), 2.28-2.11 (2H, bs, NH and OH), 1.90-1.71 (1H, m, CH(CH₃)₂), 1.10 (3H, d, 6.7 Hz, CH₃), 1.03 (3H, d, 6.7 Hz, CH₃). Data in agreement with literature values.\(^5\)

(±)-2-Amino-4-methyl-1-pentanol.

To a stirred solution of sodium borohydride (13.3 g, 35.1 mmol), and (±)-leucine (20.0 g, 152 mmol) at room temperature was added iodine (38.7 g, 152 mmol) in THF (150 ml) dropwise over a period of 30 minutes (CAUTION: hydrogen vigorously evolved). After the reaction subsided, the mixture was refluxed for 18 hours. On cooling, methanol was added dropwise until the solution became clear. After stirring for 30 minutes the solvent was removed under reduced pressure. The remaining solids were dissolved in 20% potassium hydroxide solution (300 ml) and stirred for 4 hours. The aqueous phase was extracted with dichloromethane (3 x 150 ml), the combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give (±)-2-amino-4-methyl-1-pentanol (8.20 g, 46%) as a colourless oil. \( \delta_H \) (250 MHz; CDCl₃) 3.54 (1H, dd, 10.6 Hz, 3.7 Hz, CH₂OH), 3.23 (1H, dd, 10.6, 7.9 Hz,
Experimental

CH\textsubscript{3}OH), 2.90 (1H, m, CH\textsubscript{2}NH\textsubscript{2}), 2.00-1.91 (3H, bs, NH\textsubscript{2} and OH), 1.73-1.65 (1H, m, CH(CH\textsubscript{3})\textsubscript{2}), 1.18 (2H, t, 7.1 Hz, CH\textsubscript{2}CH(CH\textsubscript{3})\textsubscript{2}), 0.93 (3H, d, 6.4 Hz, CH\textsubscript{3}), 0.89 (3H, d, 6.4 Hz, CH\textsubscript{3}).

2-[N-(2-Bromoallyl)amino]-4-methyl-1-pentanol (119).

To a stirred solution of (±)-2-amino-4-methyl-1-pentanol (10.0 g, 85.4 mmol), and potassium carbonate (5.90 g, 42.7 mmol) in THF (100 ml) was added 2,3-dibromopropene (8.50 g, 43.0 mmol) dropwise and the mixture refluxed for 21 hours. On cooling, the mixture was filtered, concentrated under reduced pressure, redissolved in dichloromethane (200 ml) and washed with 10% aqueous sodium hydroxide solution (2 x 100 ml). The organic phase was dried over MgSO\textsubscript{4}, and concentrated under reduced pressure to give the crude product. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave 2-[N-(2-bromoallyl)amino]-4-methyl-1-pentanol 119 (6.0 g, 59%) as a brown oil. 

\begin{align*}
\nu\textsubscript{max} & (\text{film}) 3347, 2955, 2926, 2870, 1633, 1467, 1050, 894 \text{ cm}^{-1}; \\
\delta & (250 \text{ MHz; CDCl}_3) 5.68 (1H, d, 1.5 Hz, =CH), 5.43 (1H, d, 1.5 Hz, =CH), 3.51 (1H, dd, 10.8 Hz, 3.8 Hz, CH\textsubscript{2}OH), 3.24 (2H, d, 8.2 Hz, NHCH\textsubscript{2}), 3.17 (1H, dd, 10.8 Hz, 5.6 Hz, CH\textsubscript{2}OH), 2.60-2.57 (1H, m, NHCH), 1.56-1.50 (1H, m, CH(CH\textsubscript{3})\textsubscript{2}), 1.20-1.11 (2H, m, CH\textsubscript{2}CH(CH\textsubscript{3})\textsubscript{2}), 0.90 (3H, d, 6.4 Hz, CH\textsubscript{3}), 0.81 (3H, d, 6.3 Hz, CH\textsubscript{3}), (OH and NH signals were not identified); \\
\delta & (62.9 \text{ MHz; CDCl}_3) 133.4 (s), 117.7 (t), 63.1 (t), 54.7 (t), 54.5 (d), 41.1 (t), 24.8 (d), 22.9 (q), 22.6 (q); \\
m/z & 237 / 235 (M^+), 204, 147; \text{Observed (M^+)}: 235.0568; \text{C}_{9}\text{H}_{18}\text{BrNO} \text{requires} 235.0572.
\end{align*}
$N$-(2-Bromoallyl)-1-[(tert-butylidiphenylsilyl)oxy]-2-methyl-2-propylamine (120).

To a stirred solution of 116 (4.00 g, 19.2 mmol), and triethylamine (8 ml, 58.0 mmol) in dichloromethane (80 ml), was added tert-butylidiphenylsilyl chloride (5.80 g, 21.1 mmol) and a catalytic amount of DMAP (10.0 mg, 0.08 mmol). The reaction mixture was stirred at room temperature for 24 hours, then diluted with dichloromethane (30 ml), washed with saturated ammonium chloride solution (3 x 20 ml), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude product 120 (8.00 g, 93%) as a orange oil which was used without further purification. $\nu_{\text{max}}$(film) 3323, 2961, 2930, 2869, 1634, 1427, 1111, 823, 702 cm$^{-1}$; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 7.71-7.67 (4H, m, Ph), 7.44-7.40 (6H, m, Ph). 5.94 (1H, d, 1.1 Hz, =CH), 5.56 (1H, d, 1.1 Hz, =CH), 3.40 (2H, s, CH$_2$O), 3.44 (2H, s, NHCH$_2$), 1.11 (6H, s, 2 x CH$_3$), 2.3-2.0 (1H, bs, NH), 1.00 (9H, s, tBu): $\delta_{\text{C}}$ (62.9 MHz; CDCl$_3$) 135.6 (d), 134.8 (d), 133.2 (s), 133.0 (s), 129.6 (d), 117.2 (t), 70.1 (t), 55.0 (t), 53.9 (s), 26.9 (q), 19.3 (s), 17.0 (q); m/z 447 / 445 (M$^+$); Observed (MH$^+$): 446.1508; C$_{23}$H$_{33}$BrNOSi requires 446.1512.

$(\pm)$-$N$-(2-Bromoallyl)-1-[(tert-butylidiphenylsilyl)oxy]-2-propylamine (121).

To a stirred solution of 117 (5.00 g, 26.0 mmol) and triethylamine (11 ml, 78.9 mmol) in dichloromethane (10 ml), was added tert-butylidiphenylsilyl chloride (8.00 g, 29.0 mmol) and a catalytic amount of DMAP (10.0 mg, 0.08 mmol). The reaction mixture was stirred at room temperature for 24 hours, then diluted with dichloromethane (50 ml), washed with saturated ammonium chloride solution (3 x 30 ml), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude product, 121 (9.90 g, 89%) as a yellow oil which
Experimental

was used without further purification. $\nu_{\text{max}}$(film) 3296, 2890, 2856, 1626, 1567, 1111, 759 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 7.69-7.66 (4H, m, Ph), 7.40-7.31 (6H, m, Ph), 5.79 (1H, d, 1.4 Hz, =CH), 5.52 (1H, d, 1.4 Hz, =CH), 3.46-3.34 (4H, m, 2 x CH$_2$), 2.50 (1H, m, NHCH), 2.47-2.40 (1H, bs, NH), 1.06 (9H, s, tBu), 0.93 (3H, d, 6.7 Hz, CH$_3$); $\delta_C$ (62.9 MHz; CDCl$_3$) 135.5 (d), 134.9 (d), 133.9 (s), 132.7 (s), 129.6 (d), 117.3 (t), 68.1 (t), 54.6 (t), 52.1 (d), 26.6 (q), 19.2 (s), 16.3 (q); $m/z$ 431 / 433 (M$^+$); Observed (M$^+$): 431.1275; C$_{22}$H$_{30}$BrNOSi requires 431.1280.

($\pm$)-N-(2-Bromoallyl)-1-[(tert-butyldiphenylsilyl)oxy]-3-methyl-2-butylamine (122).

![Chemical structure](image)

To a stirred solution of 118 (4.00 g, 18.0 mmol) and triethylamine (7.5 ml, 54.0 mmol) in dichloromethane (8 ml), was added tert-butyldiphenylsilyl chloride (5.44 g, 19.8 mmol) and a catalytic amount of DMAP (10.0 mg, 0.08 mmol). The reaction mixture was stirred at room temperature for 24 hours, then diluted with dichloromethane (30 ml), washed with saturated ammonium chloride solution (3 x 20 ml), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude product 122 (6.71 g, 81%) as a yellow oil. $\delta_H$ (250 MHz; CDCl$_3$) 7.66-7.65 (4H, m, Ph), 7.40-7.37 (6H, m, Ph), 5.76 (1H, d, 1.1 Hz, =CH), 5.52 (1H, d, 1.1 Hz, =CH), 3.58 (1H, dd, 10.2, 6.6 Hz, CHOSi), 3.50 (1H, dd, 10.2 Hz, 6.7 Hz, CHOSi), 3.43 (2H, s, NHCH$_2$), 2.77-2.67 (1H, m, NHCH), 2.10 (1H, bs, NH), 1.63-1.47 (1H, m, CH(CH$_3$)$_2$), 1.06 (9H, s, tBu), 0.83 (3H, d, 6.8 Hz, CH$_3$), 0.61 (3H, d, 6.8 Hz, CH$_3$); $\delta_C$ (62.9 MHz; CDCl$_3$) 135.5 (d), 134.8 (s), 133.8 (s), 129.6 (d), 128.0 (d), 117.2 (t), 63.2 (t), 62.0 (d), 55.1 (t), 28.8 (d), 26.5 (q), 19.2 (s), 18.4 (q), 18.0 (q). Data in agreement with the literature values.$^{54}$

89
Experimental

(±)-N-(2-Bromoallyl)-1-[(tert-butyldiphenylsilyl)oxy]-2-pentylamine (123).

To a stirred solution of 119 (5.00 g, 21.2 mmol) and triethylamine (6.40 g, 63.2 mmol) in dichloromethane (5 ml), was added tert-butyldiphenylsilyl chloride (6.40 g, 23.3 mmol) and a catalytic amount of DMAP (10 mg, 0.08 mmol). The reaction mixture was stirred at room temperature for 24 hours, then diluted with dichloromethane (30 ml), washed with saturated ammonium chloride solution (3 x 20 ml), dried over Na₂SO₄ and concentrated under reduced pressure to give the crude product 123 (7.30 g, 73%) as a yellow oil. ν_{max} (film) 3049, 2956, 2858, 1635, 1471, 1112, 823, 740, 702 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.73-7.24 (4H, m, Ph), 7.45-7.21 (6H, m, Ph), 5.79 (1H, d, 1.4 Hz, =CH), 5.52 (1H, d, 1.4 Hz, =CH), 3.65-3.59 (2H, m, CH₂O), 3.43 (2H, s, CH₂N), 2.77-2.67 (1H, m, NHCH), 2.54-2.45 (1H, bs, NH), 1.60-1.46 (1H, m, CH(CH₃)₂), 1.24-1.19 (2H, m, CH₂), 1.06 (9H, s, 'Bu), 0.93 (3H, d, 6.7 Hz, CH₃), 0.90 (3H, d, 6.7 Hz, CH₃); δ_{C} (62.9 MHz; CDCl₃) 135.5 (d), 134.8 (d), 129.6 (s), 129.5 (s), 127.6 (d), 117.2 (t), 66.2 (t), 55.1 (d), 54.9 (t), 40.8 (t), 26.6 (q), 24.6 (d), 23.1 (q) 19.2 (q); m/z 476 / 474 (MH⁺), 206 / 204; Observed (MH⁺): 474.1828; C₂₅H₃₇BrNOSi requires 474.1828.

(±)-1-[2-[1-(tert-Butyldiphenylsilyloxy)-3-methyl]butyl]-2-methyleneaziridine (124).

Reaction of 122 (5.00 g, 10.6 mmol) with sodium amide (6.33 g, 162 mmol) in liquid ammonia (110 ml) for 30 minutes as described in General Method A and subsequent chromatography (50% diethyl ether / petroleum ether) gave (±)-1-[2-[1-(tert-butyldiphenylsilyloxy)-3-methyl]butyl]-2-methyleneaziridine 124 (2.00 g, 48%) as a pale yellow oil. δ_{H} (250 MHz; CDCl₃) 7.71-7.66 (4H, m, Ph), 7.40-7.35 (6H, m, Ph), 4.60 (2H,
Experimental

m, =CH), 3.79 (1H, dd, 10.8, 5.4 Hz, CHOSi), 3.76 (1H, dd, 10.0, 4.0 Hz, CHOSi), 2.17 (1H, s, aziridine CH), 2.15 (1H, bs, aziridine CH), 2.13-2.03 (1H, m, CH(CH3)2), 1.85 (1H, m, NCH), 1.02 (9H, s, 'Bu), 0.97 (3H, d, 5.6 Hz, CH3), 0.94 (3H, d, 5.6 Hz, CH3). Data are in agreement with the literature values.54

1-[2-[1-(tert-Butyldiphenylsilyloxy]-4-methylpenty]-2-methyleneaziridine (125).

Reaction of 123 (4.00 g, 8.43 mmol) with sodium amide (4.93 g, 126 mmol) in liquid ammonia (100 ml) for 30 minutes as described in General Method A and subsequent chromatography (40% diethyl ether / petroleum ether) gave 1-[2-[1-(tert-butyldiphenylsilyloxy]-4-methylpenty]-2-methyleneaziridine 125 (700 mg, 21%) as a yellow oil. v max(film) 2956, 2931, 2858, 1765, 1471, 1428, 1112, 822, 702 cm⁻¹; δ H (250 MHz; CDCl3) 7.70-7.69 (4H, m, Ph), 7.40-7.37 (6H, m, Ph), 4.67 (1H, d, 0.7 Hz, =CH), 4.62 (1H, d, 0.7 Hz, =CH), 3.75-3.70 (2H, m, CH2O), 2.16 (1H, s, aziridine CH), 2.11 (1H, s, aziridine CH), 2.05-1.98 (1H, m, NCH), 1.75-1.60 (2H, m, CH₂CH(CH₃)₂), 1.51-1.39 (1H, m, CH₂CH(CH₃)₂), 1.06 (9H, s, 'Bu), 0.89 (3H, d, 6.7 Hz, CH₃), 0.85 (3H, d, 6.7 Hz, CH₃); δ C (62.9 MHz; CDCl3) 135.6 (d), 134.0 (s), 129.6 (d), 127.6 (d), 82.8 (t), 67.0 (s), 66.7 (t), 60.1 (d), 41.2 (t), 29.9 (t), 26.7 (q), 23.3 (q), 20.9 (q), 19.2 (s), 14.8 (d); m/z 393 (M⁺); Observed (MH⁺) 393.2485; C₂₅H₃₅NOSi requires 393.2488.
Experimental

Attempted synthesis of 1-[2-[1-(tert-butyldiphenylsilyl)oxy]-2-methylpropyl]-2-methyleneaziridine.

Reaction of 120 (1.50 g, 3.36 mmol) with sodium amide (1.30 g, 33.3 mmol) in liquid ammonia (30 ml) for 2 hours as described in General Method A and subsequent chromatography (0.5% methanol / diethyl ether) gave N-2-[1-(tert-butyldiphenylsilyl)oxy]-2-methylpropyl propargylamine 126 (200 mg, 16%). $\nu_{max}$(film) 3333, 2878, 1461, 1385, 1601, 1112, 735 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 7.68-7.64 (4H, m, Ph), 7.41-7.35 (6H, m, Ph), 3.42 (2H, s, CH$_2$O), 3.31 (2H, d, 2.4 Hz, CH$_2$N), 2.16-2.15 (1H, m, acetylene CH), 2.70-2.45 (1H, bs, NH), 1.08 (6H, s, 2 x CH$_3$), 1.06 (9H, s, 'Bu); $\delta_C$ (62.9 MHz; CDCl$_3$) 135.9 (d), 133.8 (s), 130.0 (d), 129.7 (d), 83.3 (s), 70.7 (d), 69.9 (t), 54.4 (s), 31.8 (t), 26.8 (q), 23.4 (q), 19.5 (s); m/z 366 (M$^+$); Observed (MH$^+$) 366.2233; C$_{23}$H$_{32}$NOSi requires 366.2253.
6.3 EXPERIMENTAL FOR CHAPTER FOUR

\((1R, 3R)-1\text{-[2-(1-Benzylxoy)propyl]-1-azaspiro[2,3]hexane-4,4,5,5,-tetracarbonitrile (131a)}\) and \((1R, 3S)-1\text{-[2-(1-benzyloxy)propyl]-1-azaspiro[2,3]hexane-4,4,5,5,-tetracarbonitrile (131b)}\).

\((R)-101 \rightarrow \begin{array}{c} \text{Me} \text{H} \text{O} \text{Ph} \\ \text{N} \text{C} \text{I} \text{CN} \text{NE} \text{CN} \text{NE} \text{CN} \\ \text{Me} \text{H} \text{O} \text{Ph} \end{array} \)

\((1R, 3S)-131a \quad + \quad (1R, 3R)-131b\)

To a stirred solution of \((R)-101\) (100 mg, 0.49 mmol) in acetone (2.5 ml) was added TCNE (63.0 mg, 0.49 mmol) and the resultant mixture refluxed for 1 hour. On cooling, the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (50% diethyl ether / petroleum ether) gave 131a and 131b (133 mg, 82%) as a white solid and as a 1:5 mixture of diastereomers; m.p. 108-109°C; \(\nu_{max}\) (film) 3028, 2360, 2341, 1095, 782 cm\(^{-1}\); \(m/z\) 331 (M\(^+\)), 331, 254, 210, 91; Observed (M\(^+\)): 331.1433; C\(_{19}\)H\(_{17}\)N\(_{5}\)O requires 331.1433. Further purification by column chromatography (10-20% diethyl ether / petroleum ether) resulted in the isolation (63 mg, 39%) of the least polar (major) diastereomer of 131a (63 mg, 39%), for which the following data were obtained: \(\delta_H\) (250 MHz; CDCl\(_3\)) 7.37-7.25 (5H, m, Ph), 4.86 (1H, d, 11.6 Hz, A of AB, CH\(_2\)Ph), 4.39 (1H, d, 11.6 Hz, B of AB, CH\(_2\)Ph), 3.41 (1H, d, 13.1 Hz, A of AB, CH\(_2\)(CN)\(_2\)), 3.60-3.50 (2H, m, CH\(_2\)OBn), 3.13 (1H, d, 13.1 Hz, B of AB, CH\(_2\)(CN)\(_2\)), 2.76 (1H, s, aziridine CH), 2.66 (1H, s, aziridine CH), 2.10-2.08 (1H, m, NCH), 1.08 (3H, d, 6.5 Hz, CH\(_3\)). Repurification of the remaining mixture by column chromatography (10-20% ethyl acetate / petroleum ether) resulted in the isolation (20 mg, 12%) of the more polar (minor) diastereomer 131b (20 mg, 12%) (see Appendix 3), which crystallised on standing in the column eluent. The following data were obtained: \(\delta_H\) (250 MHz; CDCl\(_3\)) 7.37-7.26 (5H, m, Ph), 4.51 (2H, s, CH\(_2\)Ph), 3.65 (1H, d, 13.2 Hz, A of AB, CH\(_2\)(CN)\(_2\)), 3.58-3.47 (2H, m, CH\(_2\)OBn), 3.28 (1H, d, 13.2 Hz, B of AB, CH\(_2\)(CN)\(_2\)), 2.69 (1H, s, aziridine CH), 2.20 (1H, s, aziridine CH), 2.11-1.99 (1H, m, NCH), 1.27 (3H, d, 6.4 Hz, CH\(_3\)).
Equilibration of (1R, 3S)-1-[2-(1-(benzyloxy)propyl)-1-azaspiro[2,3]hexane-4,4,5,5-tetra-carbonitrile (131b).

A stirred solution of 131b (10 mg) in acetone (10 ml) was heated under reflux for one hour. On cooling, the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (10-20% ethyl acetate / petroleum ether) gave a 5:1 mixture of (1R, 3R) 131a and (1R, 3S) 1-[2-(1-(Benzyloxy)propyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetra-carbonitrile 131b (3 mg, 33%) respectively. Data as previously described.
Experimental


To a solution of $(±)$-102 (200 mg, 0.87 mmol) in acetone (5 ml) was added TCNE (111 mg, 0.87 mmol) and the resultant mixture refluxed for 1 hour. On cooling, the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (20% ethyl acetate / petroleum ether) gave $(1R^*, 3R^*)$-132a and $(1R^*, 3S^*)$-132b (150 mg, 48%) as a white solid and as a 1:4 mixture of diastereomers; m.p. 126-128°C. 

$\nu_{\text{max}}$ (film) 2966, 2254, 1466, 1373, 1094, 733 cm$^{-1}$; Further purification by column chromatography (10-20% ethyl acetate / petroleum ether) resulted in the isolation of the least polar (major) diastereomer (40 mg, 13%), for which the following data were obtained: $\delta$H (250 MHz; CDCl$_3$) 7.36-7.25 (5H, m, Ph), 4.81 (1H, d, 11.3 Hz, A of AB, CH$_2$Ph), 4.40 (1H, d, 11.3 Hz, B of AB, CH$_2$Ph), 4.36 (1H, d, 13.0 Hz, A of AB, CH$_2$C(CN)$_2$), 3.67-3.62 (2H, m, CH$_2$OBn), 3.07 (1H, d, 13.0 Hz, B of AB, CH$_2$C(CN)$_2$), 2.54 (1H, bs, aziridine CH), 1.89-1.83 (1H, m, NCH), 1.81-1.72 (1H, m, CH(CH$_3$)$_2$), 1.74 (1H, bs, aziridine CH), 1.01 (3H, d, 6.8 Hz, CH$_3$), 0.96 (3H, d, 6.8 Hz, CH$_3$); $\delta$C (62.9 MHz; CDCl$_3$) 139.0 (s), 129.0 (d), 128.4 (d), 128.0 (d), 112.0 (s), 111.3 (s), 110.7 (s), 108.2 (s), 73.8 (t), 70.9 (t), 67.2 (d), 52.1 (s), 46.4 (s), 39.7 (t), 36.6 (t), 31.4 (s), 30.9 (d), 19.3 (q), 17.0 (q); m/z 359 (M$^+$), 282; 91; Observed (M$^+$): 359.1751; C$_{21}$H$_{21}$N$_5$O requires 359.1746. The minor diastereomer could not be isolated from the mixture in pure form, but observable signals were present at $\delta$ 3.11 (1H, d, 13.5 Hz, CH$_3$H(CN)$_2$), 2.34 (1H, s, aziridine CH), 1.07 (3H, d, 6.8 Hz, CH$_3$) in the crude reaction product.
Experimental

((S, 3R)-1-[2-[(1-Benzylxylo)-4-methyl]pentyl]-1-azaspiro[2,3]hexane-4,4,5,5,-tetra-
carbonitrile (133a) and ((S, 3S)-1-[2-[(1-benzyloxy)-4-methyl]pentyl]-1-azaspiro-
[2,3]hexane-4,4,5,5,-tetracarbonitrile (133b).

\[
\begin{align*}
(\text{S})-103 & \quad \text{\rightarrow} \quad (\text{S, 3S})-133\text{a} + (\text{S, 3R})-133\text{b}
\end{align*}
\]

To a stirred solution of (S)-103 (100 mg, 0.41 mmol) in acetone (2.5 ml) was added TCNE (52.0 mg, 0.41 mmol) and the resultant mixture refluxed for 1 hour. Purification by column chromatography (50% diethyl ether / petroleum ether) gave ((S, 3R)-133a and ((S, 3S*)-133b (120 mg, 79%) as a white solid and as a 6:1 mixture of diastereomers; m.p. 124-
126°C; \( \nu_{max} \) (film) 2963, 2306, 1654, 1265, 896, 739 cm\(^{-1}\); Further purification by column chromatography (30-50% diethyl ether / petroleum ether) resulted in the isolation of the least polar (major) diastereomer (40 mg, 26%), for which the following data were obtained: \( \delta \text{H} \) (250 MHz; CDCl\(_3\)) 7.38-7.25 (5H, m, Ph), 4.84 (1H, d, 11.6 Hz, A of AB, CH\(_2\)Ph), 4.40 (1H, d, 11.6 Hz, B of AB, CH\(_2\)Ph), 4.34 (1H, d, 13.1 Hz, A of AB, CH\(_2\)C(CN)\(_2\)), 3.58-3.52 (2H, m, CH\(_2\)OBN), 3.11 (1H, d, 13.1 Hz, B of AB, CH\(_2\)C(CN)\(_2\)), 2.54 (1H, bs, aziridine CH), 2.04-1.94 (1H, m, NCH), 1.71 (1H, bs, aziridine CH), 1.60-1.53 (1H, m, CH(CH\(_3\))\(_2\)), 1.46-
1.36 (1H, m, CH\(_2\)CH(CH\(_3\))\(_2\)), 1.31-1.27 (1H, m, CH\(_2\)CH(CH\(_3\))\(_2\)), 0.90 (3H, d, 6.5 Hz, CH\(_3\)), 0.84 (3H, d, 6.5 Hz, CH\(_3\)); \( \delta \text{C} \) (62.9 MHz; CDCl\(_3\)) 137.1 (s), 128.5 (d), 128.4 (d), 128.0 (d), 111.2 (s), 108.8 (s), 108.6 (s), 108.5 (s), 73.7 (t), 72.2 (t), 60.9 (d), 60.0 (s), 46.5 (s), 40.8 (t), 38.6 (t), 36.5 (t), 32.0 (s), 24.7 (d), 23.3 (q), 22.3 (q); \( m/e \) 373 (M\(^+\)), 296; 91; Observed (M\(^+\)): 373.1900; C\(_{22}\)H\(_{23}\)N\(_3\)O requires 373.1902. The minor diastereomer could not be isolated from the mixture in pure form, but observable signals were present at \( \delta \) 3.26 (1H, d, 13.2 Hz, CH\(_2\)H(CN)\(_2\)), 2.62 (1H, bs, aziridine CH), 1.99 (1H, bs, aziridine CH) in the crude reaction product.
(1R, 3R)-1-[-2-(Benzylol)-1-phenylethyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetracarbonitrile (134a) and (1R, 3S)-1-[-2-(benzyloxy)-1-phenylethyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetracarbonitrile (134b).

To a stirred solution of (R)-130 (100 mg, 0.38 mmol) in acetone (2.5 ml) was added TCNE (49.0 mg, 0.38 mmol) and the resultant mixture was refluxed for 1 hour. On cooling, the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (20% ethyl acetate / petroleum ether) gave (1R, 3R)-134a and (1R, 3S)-134b (120 mg, 81%) as a white solid and as a 2:3 mixture of diastereomers; m.p. 125-127°C; ν_{max} (film) 2900, 2234, 1526, 1439, 1392, 740 cm^{-1}. Further purification by column chromatography (30-50% diethyl ether / petroleum ether) resulted in the isolation of the least polar (major) diastereomer (21 mg, 14%), for which the following data were obtained: δ_{H} (250 MHz; CDCl_3) 7.51-7.25 (10H, m, Ph), 4.90 (1H, d, 11.6 Hz, A of AB, CH_2Ph), 4.42 (1H, d, 11.6 Hz, B of AB, CH_2Ph), 4.40 (1H, d, 13.2 Hz, A of AB, CH_2C(CN)\_2), 3.62 (1H, m, CH_2OBn), 3.60 (1H, m, CH_2OBn), 3.23 (1H, d, 13.2 Hz, B of AB, CH_2C(CN)\_2), 3.00 (1H, t, 9.6 Hz, NCH), 2.46 (1H, s, aziridine CH), 1.63 (1H, s, aziridine CH); δ_{C} (62.9 MHz; CDCl_3) 137.1 (s), 137.0 (s), 128.7 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.1 (d), 127.2 (d), 111.1 (s), 109.9 (s), 109.5 (s), 109.1 (s), 75.4 (t), 73.8 (t), 67.4 (d), 47.5 (s), 39.3 (t), 36.7 (t), 31.4 (s), 29.0 (s); m/z 393 (M^+); 316, 91; Observed (M^+): 393.1584; C_{24}H_{19}N_{3}O requires 393.1589. The minor diastereomer could not be isolated from the mixture in pure form, but observable signals were present at δ 2.30 (1H, s, aziridine CH), 1.56 (1H, s, aziridine CH) in the crude reaction product.
Experimental

(1S*, 3R*)-1-[2-[(1-(tert-Butyldiphenylsilyl)oxy)-3-methyl]butyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetracarbonitrile (135a) and (1S*, 3S*)-1-[2-[(1-(tert-Butyldiphenylsilyl)oxy]-3-methyl]butyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetracarbonitrile (135b).

To a stirred solution of (±)-124 (1.00 g, 2.63 mmol) in acetone (15 ml) was added TCNE (337 mg, 2.63 mmol) and the resultant mixture refluxed for 1 hour. On cooling, the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (10% ethyl acetate / petroleum ether) gave (1S*, 3R*)-135a and (1S*, 3S*)-135b (720 mg, 54%) as a white solid and as a 1:1 mixture of diastereomers; mp 110°C (dec.); $\nu_{\text{max}}$ (film) 2961, 2932, 2859, 2252, 1471, 1113, 909, 735 cm$^{-1}$; $\delta$H (250 MHz; CDCl$_3$) 7.71-7.58 (4H, m, Ph), 7.44-7.37 (6H, m, Ph), 3.84 (1H, d, 4.7 Hz, CH$_2$OSi), 3.75 (1H, d, 4.7 Hz, CH$_2$OSi), 3.57 (0.5H, d, 13.5 Hz, C$_2$H$_2$(CN)$_2$), 3.28 (0.5 H, d, 13.5 Hz, C$_2$H$_2$(CN)$_2$), 3.00 (0.5 H, 11.3 Hz, C$_2$H$_2$(CN)$_2$), 2.58 (0.5 H, 11.3 Hz, C$_2$H$_2$(CN)$_2$), 2.28 (0.5H, bs, aziridine CH), 2.04 (1H, bs, aziridine CH), 1.92-1.86 (1H, m, NCH), 1.87 (0.5H, bs, aziridine CH), 1.69-1.64 (1H, m, CH(CH$_3$)$_2$), 1.56 (0.5H, bs, aziridine CH), 1.09 (4.5H, s, 'Bu), 1.06 (4.5H, s, 'Bu), 0.99 (1.5H, d, 6.3 Hz, CH$_3$), 0.90 (1.5H, d, 6.3 Hz, CH$_3$), 0.88 (1.5H, d, 7.0 Hz, CH$_3$), 0.77 (1.5H, d, 7.0 Hz, CH$_3$); $\delta$C (62.9 MHz; CDCl$_3$) 135.7 (d), 135.5 (s), 135.0 (s), 133.2 (s), 130.1 (d), 112.8 (s), 110.2 (s), 109.5 (s), 108.3 (s), 70.4 (d), 64.7 (t), 47.1 (s), 45.0 (s), 37.8 (t), 37.3 (t), 27.0 (q), 26.6 (d), 19.1 (s), 17.3 (q); m/z 507 (M$^+$), 353, 91; Observed (M$^+$): 507.2461; C$_{30}$H$_{33}$N$_3$OSi requires 507.2454.
Experimental

(1R*, 3R*)-1-[2-[1-(tert-Butyldiphenylsilyl)oxy]-4-methylpentyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetracarbonitrile (136a) and (1R*, 3S*)-1-[2-[1-(tert-Butyldiphenylsilyl)oxy]-4-methylpentyl]-1-azaspiro[2,3]hexane-4,4,5,5-tetracarbonitrile (136b).

![Chemical structure](image)

(±)-125

To a stirred solution of (±)-125 (400 mg, 1.02 mmol) in acetone (5 ml) was added TCNE (130 mg, 1.01 mmol) and the resultant mixture refluxed for 1 hour. On cooling, the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (30% ethyl acetate / petroleum ether) gave (1R*, 3R*)-136a and (1R*, 3S*)-136b (220 mg, 42%) as a white solid and as a 1:1 ratio of diastereomers; m.p. 115 °C (dec.); \( \nu_{\text{max}} \) (film) 2959, 2928, 2858, 2254, 1467, 1112, 908, 735 cm\(^{-1}\). Further purification by column chromatography (30-50% diethyl ether / petroleum ether) resulted in the isolation of the least polar diastereomer (21 mg, 14%), for which the following data were obtained: \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.72-7.61 (4H, m, Ph), 7.47-7.39 (6H, m, Ph), 3.76-3.73 (2H, m, CH\(_2\)OSi), 3.57 (1H, d, 13.2 Hz, A of AB, CH\(_2\)C(CN)\(_2\)), 3.28 (1H, d, 13.2 Hz, B of AB, CH\(_2\)C(CN)\(_2\)), 2.59 (1H, bs, aziridine CH), 2.19 (1H, bs, aziridine CH), 1.91-1.83 (1H, m, NCH), 1.71-1.70 (1H, m, CH(CH\(_3\))\(_2\)), 1.33-1.29 (2H, m, CH\(_2\)CH(CH\(_3\))\(_2\)), 1.09 (9H, s, 'Bu), 0.89 (3H, d, 6.4 Hz, CH\(_3\)), 0.83 (3H, d, 6.4 Hz, CH\(_3\)); \( \delta_C \) (62.9 MHz; CDCl\(_3\)) 137.7 (d), 137.5 (d), 134.7 (s), 132.1 (s), 130.0 (d), 129.9 (d), 129.8 (d), 129.5 (d), 110.5 (s), 110.4 (s), 109.9 (s), 109.7 (s), 69.8 (d), 68.2 (t), 65.7 (t), 43.4 (s), 43.2 (s), 40.3 (t), 39.1 (t), 33.4 (s), 28.9 (d), 26.9 (q), 26.3 (q), 24.1 (q), 21.7 (s); m/z 521 (M\(^+\)), 444, 373, 91; Observed (M\(^+\)): 521.2613; C\(_{31}\)H\(_{35}\)N\(_5\)OSi requires 521.2611. The minor diastereomer could not be isolated from the mixture in pure form, but observable signals were present at \( \delta \) 0.84 (3H, d, 6.5 Hz, CH\(_3\)), 0.76 (3H, d, 6.5 Hz, CH\(_3\)), 1.77 (1H, bs, aziridine CH), 1.43 (1H, bs, aziridine CH) in the crude reaction product.
6.4 EXPERIMENTAL FOR CHAPTER FIVE

Methyl 1-(phenylmethyl)-2-aziridinecarboxylate (148).

To 2,3-dibromopropanoic acid (42.0 g, 181 mmol) in dichloromethane (200 ml) at 0°C was added oxalyl chloride (46.0 g, 362 mmol) followed by DMF (4 drops). The resulting mixture (effervescence) was warmed to room temperature and stirred overnight. Concentration under reduced pressure gave acid chloride 146 (45.0 g) as a yellow oil. A portion of this acid chloride 146 (22.0 g, 100 mmol), was added dropwise to a stirred solution of methanol (100 ml) at 0°C (CAUTION: exothermic). The reaction mixture was allowed to stir for 10 minutes then heated under reflux for 2 hours. On cooling, the mixture was concentrated under reduced pressure, then redissolved in dichloromethane (50 ml), washed with 10% aqueous NaOH, dried over MgSO4 and concentrated under reduced pressure to give ester 147 (19.50 g, 79%) as a brown oil. A portion of this crude ester 147 (15.0 g) was dissolved in toluene (30 ml) and cooled to -5°C. A mixture of benzylamine (6.54 g, 61 mmol) and triethylamine (12.35 g, 122 mmol) were added in several syringed portions. The reaction mixture was refluxed for 3 hours, cooled and the precipitate removed by filtration. The filtrate was washed with water, dried over MgSO4 and concentrated under reduced pressure. Purification by column chromatography (1% triethylamine / 2% methanol / 97% dichloromethane) gave methyl 1-(phenylmethyl)-2-aziridinecarboxylate 148 (7.40 g, 57%) as a slightly opaque oil. v max (film) 3003, 2838, 1732, 1659, 1079, 698 cm⁻¹; δ H (250 MHz; CDCl3) 7.30-7.21 (5H, m, Ph), 3.65 (3H, s, CH), 3.48 (2H, s, CH2), 2.22-2.15 (2H, m, CH2), 1.70 (1H, d, 6.4 Hz, CH); δ C (62.9 MHz; CDCl3) 172.1 (s), 137.6 (s), 128.5 (d), 127.9 (d), 127.0 (d), 63.7 (t), 52.0 (q), 37.2 (t), 34.4 (d); m/z 191 (M+), 190, 189, 146, 91; Observed (M+): 191.0953; C11H13NO2 requires 191.0946. Data consistent with literature values.79
**Experimental**

Methyl 1-(1-phenylethyl)-2-aziridinecarboxylate (149).

\[\text{Me} \cdot \text{Ph} - \text{NH}_2 + \text{Br} \cdot \text{COOMe} \rightarrow \text{Me} \cdot \text{Ph} \cdot \text{NCH} \cdot \text{CH}_2 \cdot \text{COOMe} \]

Dibromide 147 (1.00 g, 4.00 mmol) was dissolved in toluene (10 ml) and cooled to -5°C. A mixture of (R)-1-methylbenzylamine (480 mg, 4.00 mmol) and triethylamine (810 mg, 8.00 mmol) were added in several portions, via syringe. After the addition was complete, the mixture was heated to 75°C for 1 hour. On cooling, the resultant mixture was filtered, washed with water, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (dichloromethane) gave methyl 1-(1-phenylethyl)-2-aziridinecarboxylate 149 (517 mg, 63%) as a pale yellow oil and as a 1:1 mixture of diastereomers. \(\nu_{\text{max}}\) (film) 2958, 2839, 1720, 1594, 1321, 1370, 749, 721 cm⁻¹; \(\delta_{\text{H}}\) (250 MHz; CDCl₃) 7.39-7.20 (10H, m, 2 x Ph), 3.73 (3H, s, OCH₃), 3.64 (1H, s, OCH₃), 2.54-2.51 (2H, m, 2 x NCH), 2.31-2.27 (1H, m, aziridine CH), 2.21-2.18 (1H, m, aziridine CHH), 2.12-2.11 (1H, m, aziridine CH), 2.08-2.05 (1H, m, aziridine CHH), 1.77-1.75 (1H, m, aziridine CHH), 1.59-1.57 (1H, m, aziridine CHH), 1.50 (3H, d, 6.4 Hz, CH₃), 1.46 (3H, d, 6.4, CH₃); \(m/z\) 206 (MH⁺), 205 (M⁺), 128, 105; Observed (M⁺): 205.1087; C₁₂H₁₅NO₂ requires 205.1103.

1-Benzyl-2-(bromomethyl)aziridine (150).

\[\begin{align*}
&\text{Ph} \cdot \text{H} \\
\rightarrow &\text{Ph} \cdot \text{H} \\
\rightarrow &\text{Ph} \cdot \text{H} \\
\rightarrow &\text{Ph} \cdot \text{H} \\
\end{align*}\]

To a stirred suspension of benzaldehyde (10.0 g, 94.2 mmol) and powdered 4Å molecular sieves (10.0 g) in dichloromethane (50 ml) was added allylamine (6.50 g, 114 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The resultant mixture was filtered and concentrated under reduced pressure to give imine 151 (12.0 g). A portion of this imine 151 (11.00 g, 76.0 mmol) was dissolved in dichloromethane (25 ml) cooled to 0°C and bromine (12.80 g, 80.1 mmol) dissolved in dichloromethane (25 ml) was added dropwise. The reaction mixture was allowed to stir overnight at room temperature and
then concentrated under reduced pressure to give crude 152 (21.00 g). A portion of crude 152 (16.4 g) was dissolved in methanol (80 ml) and cooled to 0°C. Portions of sodium borohydride (6.12 g, 162 mmol) were then added over a period of 30 minutes (caution). The reaction mixture was then heated to reflux for 2 hours. On cooling, the mixture was filtered, then washed with saturated sodium bicarbonate solution, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (30% ethyl acetate / hexane) gave 1-benzyl-2-(bromomethyl)aziridine 150 (6.40 g, 53%) as a brown oil. 

$$\nu_{\text{max}}(\text{film}) \, 2832, \, 1495, \, 734, \, 698, \, 674 \, \text{cm}^{-1}; \delta_H (250 \, \text{MHz; CDCl}_3) \, 7.36-7.25 \, (5H, \, m, \, Ph), \, 3.58 \, (1H, \, d, \, 13.2 \, Hz, \, CH\text{Br}), \, 3.40 \, (1H, \, d, \, 13.2 \, Hz, \, CH\text{Br}), \, 3.30 \, (2H, \, m, \, CH\text{Ph}), \, 1.97-1.92 \, (1H, \, m, \, azidine), \, 1.81 \, (H, \, s, \, azidine \, CHH), \, 1.64-1.62 \, (1H, \, s, \, azidine \, CHH); \delta_C (62.9 \, MHz; \, CDCl_3) \, 138.1 \, (s), \, 128.4 \, (d), \, 128.3 \, (d), \, 127.1 \, (d), \, 63.9 \, (t), \, 39.8 \, (d), \, 35.0 \, (t), \, 34.6 \, (t); \, m/z \, 227/225 \, (M^+), \, 146, \, 117, \, 108, \, 91, \, 79; \, \text{Observed} \, (M^+): \, 227.0160 / \, 225.0154; \, C_{10}H_{12}NBr \, \text{requires} \, 227.0134 / \, 225.0154.$$

1-Benzyl-2-[(2-nitrophenyl)selenomethyl]aziridine (154).

To a solution of (2-nitrophenyl)selenocyanate⁸⁰.⁸¹ (640 mg, 2.82 mmol) in ethanol (5 ml) was added sodium borohydride (64 mg, 1.7 mmol). A dark red solution was obtained to which a solution of 1-benzyl-2-bromomethylaziridine 150 (316 mg, 1.40 mmol) in ethanol (5 ml) was added dropwise. The yellow solution which formed was heated to reflux for 24 hours. On cooling, the mixture was diluted with ethyl acetate (20 ml) and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (30% ethyl acetate / hexanes) gave 1-benzyl-2-[(2-nitrophenyl)selenomethyl]aziridine 154 (200 mg, 41%) as a brown oil. 

$$\nu_{\text{max}}(\text{film}) \, 2971, \, 2895, \, 1590, \, 1566, \, 1505, \, 1330, \, 784, \, 730, \, 727 \, \text{cm}^{-1}; \delta_H (250 \, \text{MHz; CDCl}_3) \, 8.25 \, (1H, \, dd, \, 8.2, \, 1.5 \, Hz, \, Ar), \, 7.60 \, (1H, \, dd, \, 8.0, \, 1.0 \, Hz, \, Ar), \, 7.54-7.40 \, (1H, \, m, \, Ar), \, 7.43-7.42 \, (1H, \, m, \, Ar), \, 7.31-7.24 \, (5H, \, m, \, Ar), \, 3.46 \, (1H, \, d, \, 13 \, Hz, \, CH\text{HPh}), \, 3.38 \, (1H, \, d, \, 13 \, Hz, \, CH\text{HPh}), \, 2.96-2.91 \, (2H, \, m, \, CH\text{Se}), \, 1.87-1.84 \, (2H, \, m, \, 2 \times \, CH), \, 1.60-1.58 \, (1H, \, m, \, CH): \delta_C (62.9 \, MHz; \, CDCl_3) \, 138.5 \, (s), \, 138.4 \, (d), \, 129.6 \, (d), \, 129.4 \, (d).$$
Experimental

Experimental

(d), 129.3 (d), 128.3 (s), 128.2 (s), 127.3 (d), 126.3 (d), 125.3 (d), 64.5 (t), 37.8 (d), 35.4 (t),
29.4 (t); m/z  350 / 348 / 346 / 345 / 344 (M+), 251, 186, 146, 91; Observed (M+): 348.0374;
C_{16}H_{16}N_{2}O_{2}Se requires 348.0377.

1-Benzyl-2-(phenylselenomethyl)aziridine (155).

To a solution of diphenyl diselenide (1.70 g, 5.45 mmol) in ethanol (10 ml), was added sodium borohydride (400 mg, 10.6 mmol) followed by a solution of 1-benzyl-2-bromomethyl aziridine 150 (2.00 g, 8.85 mmol) in ethanol (10 ml) dropwise. The reaction mixture was heated to 80°C for 90 minutes, and on cooling, ethyl acetate (30 ml) was added. The resultant mixture was washed with sodium bicarbonate solution, dried over MgSO4 and concentrated under reduced pressure. Purification by column chromatography (30% ethyl acetate / hexane) gave 1-benzyl-2-(phenylselenomethyl)aziridine 155 (70.0 mg, 3%) as a yellow oil. v_{max} (film) 3059, 3028, 1578, 696 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 7.57-7.52 (2H, m, Ph), 7.39-7.24 (8H, m, Ph), 3.51 (1H, d, 13.2 Hz, NCH), 3.34 (1H, d, 13.2 Hz, NCH), 3.08-2.80 (2H, m, CH₂Se), 1.84 (1H, m, CH) 1.68-1.48 (2H, m, CH₂); δ_{C} (62.9 MHz; CDCl₃) 138.0 (s), 133.0 (s), 132.9 (d), 129.0 (d), 128.5 (d), 128.1 (d), 127.1 (d), 126.9 (d), 64.4 (t),
39.5 (d), 35.3 (t), 30.1 (t); m/z (El) 305, 303, 301, 300, 299 (M⁺), 222, 196, 146, 91.

1-(Phenylselenyl)heptane (156).

To diphenyl diselenide (1.00 g, 3.2 mmol) in ethanol (5 ml), was added sodium borohydride (250 mg, 6.61 mmol) followed by 1-bromohexane (1.00 g, 5.58 mmol) in ethanol (5 ml), dropwise. The resultant mixture was stirred at room temperature for 16 hours, concentrated under reduced pressure, then redissolved in dichloromethane (30 ml), washed with 10% NaOH solution (3 x 15 ml), dried over MgSO4 and concentrated under reduced pressure. Purification by column chromatography (hexanes) gave 1-(phenylselenyl)heptane 156 (1.3 g, 97%) as a yellow oil. v_{max}(film) 3058, 2927, 2870, 2854, 1654, 1466, 690 cm⁻¹; δ_{H} (250
Experimental

MHz; CDCl₃) 7.52-7.25 (2H, m, Ph), 7.29-7.25 (3H, m, Ph), 2.96-2.90 (2H, t, 7.5 Hz, SeCH₂), 1.72 (2H, pseudo q, 14.4 Hz, CH₂), 1.46-1.29 (8H, m, 4 x CH₂), 0.89 (3H, t, 5.0 Hz, CH₃); δ(C (62.9 MHz; CDCl₃) 132.4 (d), 132.3 (s), 128.9 (d), 126.5 (d), 31.6 (t), 30.1 (t), 29.7 (t), 28.7 (t), 27.4 (t), 22.5 (t), 14.0 (q); m/z 258, 256, 254, 253, 252 (M⁺); Observed (M⁺): 256.0723; C₁₃H₂₀Se requires 256.0730. Data in agreement with the literature values.⁸⁰


To a stirred suspension of 155 (200 mg, 0.58 mmol) and potassium carbonate (500 mg) in dichloromethane (10 ml) at 0°C, was added dropwise m-chloroperbenzoic acid (57%) (175 mg, 1.01 mmol) dissolved in dichloromethane (10 ml). The reaction was allowed to stir for 30 minutes, then washed with water (5 x 5 ml), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (100% ethyl acetate) gave 157 (90.0 mg, 43%) as a yellow solid. Further purification using column chromatography (90% ethyl acetate/ 10% hexanes) resulted in the isolation of the more polar diastereomer, for which the following data were obtained; m.p. 135-137°C; νmax(CDCl₃) 2254, 1529, 1467, 1340, 1096, 745; δ(1H (250 MHz; CDCl₃) 8.49 (1H, dd, 7.8, 1.4 Hz, Ar), 8.36 (1H, dd, 9.1, 1.4 Hz, Ar), 7.98-7.95 (1H, m, Ar), 7.76-7.72 (1H, m, Ar), 7.38-7.26 (5H, m, Ph), 3.67 (1H, d, 13.1 Hz, CH₂Ph), 3.52 (1H, d, 13.1 Hz, CH₂Ph), 3.25-3.14 (1H, m, CH₂Se), 2.90-2.82 (1H, m, CH₂Se), 2.19-2.11 (1H, m, aziridine CH), 1.82-1.73 (1H, m, aziridine CH₂), 1.73-1.53 (1H, m, aziridine CH₂); δ(C (62.9 MHz; CDCl₃) 146.1 (s), 138.0 (s), 135.6 (d), 135.5 (d), 131.8 (d), 131.7 (d), 128.5 (s). 128.2 (d), 127.9 (d), 124.9(d), 63.9 (t), 55.7 (t), 34.3 (t), 33.1 (d); m/z 366, 364, 362, 361, 360 (M⁺), 106, 91; Observed (M⁺): 364.0325; C₁₆H₁₆N₂O₃Se requires 364.0326.
Experimental

Attempted Elimination Reaction using Selenoxide (157).

\[
\begin{align*}
\text{CH}_2\text{Ph} & \quad \text{O}^- \\
\text{Se} & \quad \text{O}_2\text{N} \\
\text{N} & \end{align*}
\]

\[
\text{CH}_2\text{Ph}
\]

157

To a stirred solution of the diastereomeric selenoxide mixture 157 (51 mg, 0.14 mmol) in THF (5 ml), was added DBU (21 mg, 0.14 mmol). The reaction mixture was allowed to stir at room temperature for 4 days, then washed with water, dried over MgSO\(_4\), and concentrated under reduced pressure to give unreacted starting material 157 (45 mg, 88% recovery).

(1-Bromovinyl)trimethylsilane (164).

\[
\begin{align*}
\text{Si(CH}_3\text{)_3} & \quad \text{Br} \\
\text{Br} & \end{align*}
\]

164

To a stirred solution of vinyltrimethylsilane (20.0 g, 200 mmol) at -78°C was added bromine (38.0 g, 238 mmol). After addition was complete, the red viscous mixture was allowed to warm to 0°C and diethylamine (134 ml, 1.30 mol) was added dropwise (CAUTION: exothermic). The reaction mixture was warmed to room temperature then heated under reflux for 14 hours. On cooling, diethyl ether (150 ml) was added. The ethereal solution was washed with 10% hydrochloric acid (4 x 100 ml), followed by water (3 x 100 ml) and saturated ammonium chloride solution (2 x 100 ml). The organic phase was dried over MgSO\(_4\) and the solvent removed under reduced pressure to give (1-bromovinyl)trimethylsilane 164 (27.0 g, 75%) as a pale yellow oil which was used without further purification. 


\[\begin{align*}
\nu_{max}(\text{film}) & \quad \text{2758, 1648, 1269, 769, 739 cm}^{-1}; \\
\delta_H(250 \text{ MHz; CDCl}_3) & \quad 6.20 (1H, d, 1.9 Hz, =CH), 6.11 (1H, d, 1.9 Hz, =CH), 0.00 (9H, s, Si(CH}_3\text{)_3}); \\
\delta_C(62.9 \text{ MHz; CDCl}_3) & \quad 141.0 (s), 131.5 (t), 0.0 (q); \\
m/z & \quad 180 / 178 (M^+), 165 / 163; \\
\text{Observed (M}^+) & \quad 177.9824; \\
\text{C}_{5}\text{H}_{11}\text{SiBr requires 177.9814. Data are in agreement with literature values.}^89
\end{align*}\]
Experimental

2-(Trimethylsilyl)-2-propen-1-ol (163).

\[ 
\text{Si(CH}_3\text{)}_3 \quad \text{Br} \quad \rightarrow \quad \text{Si(CH}_3\text{)}_3 \quad \text{OH}
\]

To a slurry of magnesium filings (1.20 g, 49.4 mmol) in anhydrous THF (15 ml), was added a solution of 164 (9.00 g, 50.2 mmol) in THF (15 ml) dropwise, over a period of 15 minutes. The resultant mixture was heated to reflux for 1 hour, then cooled to 0°C. Gaseous formaldehyde, generated by heating p-formaldehyde (2.25 g, 75.0 mmol) at 160°C, was bubbled through the reaction mixture. On completion of the addition, the reaction mixture was allowed to stir for a further 10 hours at room temperature. On addition of water (4 ml), the solvent was decanted and the aqueous layer extracted with diethyl ether (3 x 30 ml). The combined organic phases were then washed sequentially with water (3 x 50 ml) and saturated sodium chloride solution (2 x 50 ml), dried over MgSO\(_4\) and concentrated under reduced pressure. Purification by column chromatography (30% diethyl ether / petroleum ether) gave 2-(trimethylsilyl)-2-propen-1-ol 163 (3.00 g, 46%) as a colourless oil. \(\nu_{\text{max}}\) (film) 3359, 2945, 1439, 2981, 2963, 1300, 1265, 716 cm\(^{-1}\): \(\delta\)\(_{\text{H}}\) (250 MHz; CDCl\(_3\)) 5.75 (1H, d, 1.4 Hz, =CH), 5.31 (1H, d, 1.4 Hz, =CH), 4.41 (2H, s, CH\(_2\)OH), 1.50 (1H, bs, OH), 0.00 (9H, s, Si(CH\(_3\))\(_3\)); \(\delta\)\(_{\text{C}}\) (62.9 MHz; CDCl\(_3\)) 140.5 (s), 124.3 (t), 66.0 (t), 0.00 (q); \text{m/z} 130 (M\(^{+}\)), 115, 113; Observed (M\(^{+}\)): 130.0814 requires C\(_6\)H\(_{14}\)O\(_3\)Si requires 130.0813. Data in agreement with literature values.\(^{89}\)

1-Acetoxy-2-trimethylsilyl-2-propene (166).

\[ 
\text{Si(CH}_3\text{)}_3 \quad \text{OH} \quad \rightarrow \quad \text{Si(CH}_3\text{)}_3 \quad \text{CO}_2\text{H}
\]

To a stirred solution of 163 (5.0 g, 38.4 mmol), acetic anhydride (5.90 g, 57.8 mmol) and DMAP (5.00 mg, 0.04 mmol) in dichloromethane (50 ml) was added triethylamine (8.0 ml, 57.8 mmol) dropwise. The reaction mixture was allowed to stir for 2 hours then washed with water (3 x 30 ml), dried over MgSO\(_4\) and concentrated under reduced pressure. Subsequent column chromatography (30% diethyl ether / petroleum ether) gave 1-acetoxy-2-trimethylsilyl-2-propene 166 (3.40 g, 51%) as a pale cream oil. \(\nu_{\text{max}}\) (film) 2991, 2889, 1749,
Experimental

1641, 1269, 1255, 801, 725 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 5.64 (1H, d, 1.4 Hz, =CH) 5.32 (1H, d, 1.4 Hz, =CH), 4.56 (2H, s, CH\(_2\)O), 1.95 (3H, s, CH\(_3\)), 0.00 (9H, s, Si(CH\(_3\))\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 154.0 (s), 139.7 (s), 129.6 (t), 79.5 (t), 18.4 (q), 0.0 (q); \(m/z\) 172 (M\(^+\)), 157, 109; Observed (M\(^+\)): 172.0926; C\(_8\)H\(_{16}\)O\(_2\)Si requires 172.0920.

1-(2-Acetoxymethyl-2-trimethylsilyl)aziridinylethylocarbamate (167).

\[
\begin{array}{c}
\text{Si(}CH_3\text{)} \\
\text{O} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{COOCH}_2\text{CH}_3 \\
\text{N} \\
\text{Si(}CH_3\text{)}
\end{array}
\]

To a stirred solution of 166 (3.00 g, 17.4 mmol) in dichloromethane (30 ml) was added \(p\)-nitro-benzenesulfonyloxyethylcarbamate (2.00 g, 6.89 mmol), benzyl triethylammonium chloride monohydrate (430 mg, 1.74 mmol) and 1 M sodium bicarbonate (20 ml). The resultant mixture was allowed to stir at room temperature for 4 hours, then washed with water (3 x 30 ml) and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate) gave 167 (860 mg, 48%) as a pale brown oil. \(\nu_{max}\) (film) 2980, 2958, 2903, 1746, 1231, 845, 794 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 4.20-4.15 (2H, m, CH\(_2\)), 4.03-4.3.97 (2H, m, CH\(_2\)), 2.16 (1H, s, aziridine CH), 2.10 (1H, s, aziridine CH), 1.94 (3H, s, CH\(_3\)) 1.16 (3H, t, 7.1 Hz, CH\(_3\)), 0.00 (9H, s, Si(CH\(_3\))\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 182.0 (s), 174.0 (s), 69.8 (t), 68.6 (t), 48.3 (s), 33.7 (t), 23.8 (q), 17.6 (q), 0.00 (q); \(m/z\) 260 (MH\(^+\)), 244, 113, 43; Observed (MH\(^+\)): 260.1318; C\(_{11}\)H\(_{22}\)NO\(_4\)Si requires 260.1317.
References
References

18 Wijndberg, J. B. P. A.; Weiring, P. J.; Steinberg, H. Synthesis 1981, 901.
References

33 Alper, H.; Roberto, D. Organometallics 1984, 3, 1767.
49 Ager, D. J.; Prakash, I.; Schaad, D. R. Chem Rev. 1995, 95, 907.
References

References

$^1$H NMR spectra for the enantomeric excess determination of (S)-1-(1-phenylethyl)-2-methyleneaziridine (79) in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato], europium(III) derivative.

![Chemical structures](image)

- (±)-79
- (S)-79
- (±)-79 (1 mg) and (S)-79 (2 mg)
$^1$H NMR spectra for the enantiomeric excess determination of (R)-1-[2-(1-benzyloxy)propyl]-2-methyleneaziridine (101) in the presence of (S)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

(R)-101 ≥95% ee

1:2 mixture of (R)-101:(±)-101

2:98 mixture of (R)-101:(±)-101
HPLC traces of the enantiomeric excess determination of (S)-1-[2-(1-benzyloxy)-4-methylpentyl]-2-methyleneaziridine (103).

(S)-103

(±)-103 (R)-103 (95% ee) (±)-103:(R)-103 (1:1)
$^1$H NMR spectra of (R)-1-(1-phenylethyl)-2-methyleneaziridine (79) showing methyl doublet at the temperatures indicated.
$^1$H NMR spectra of (S)-1-[2-(1-benzyloxy)propyl]-2-methyleneaziridine (101) showing methyl doublet at the temperatures indicated.

(S)-101
**EXPERIMENTAL DETAILS**

### A. Crystal Data

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### B. Intensity Measurements

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Appendix 6

Attenuator
Take-off Angle
Detector Aperture
Crystal to Detector Distance
Temperature
Scan Type
Scan Rate
Scan Width
2θmax
No. of Reflections Measured
Corrections

graphite monochromated
Ni foil (factor = 9.42)
6.0°
9.0 mm horizontal
13.0 mm vertical
400 mm
20.0°C
ω
16.0°/min (in ω) (up to 4 scans)
(1.00 + 0.35 tan θ)°
120.2°
Total: 1614

Lorentz-polarization
Absorption
(trans. factors: 0.8845 - 1.0000)
Decay (0.02% decline)
Secondary Extinction
(coefficient: 2.16927e-05)

C. Structure Solution and Refinement

Structure Solution
Refinement
Function Minimized
Least Squares Weights
p-factor
Anomalous Dispersion
No. Observations (I>2.00σ(I))
No. Variables
Reflection/Parameter Ratio
Residuals: R; Rw

Direct Methods (SIR92)
Full-matrix least-squares
Σw(|Fo| - |Fe|)²
\frac{1}{\sigma^2(Fo)} = \frac{4F_o^2}{\sigma^2(F_o^2)}
0.0010

All non-hydrogen atoms
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227
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0.030 ; 0.025
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### Table 1. Atomic coordinates and $B_{ee}/B_{ii}$

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$$B_{eq} = \frac{8}{3} \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha)$$
Table 3. Bond Lengths (Å)

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### Table 4. Bond Lengths (Å)

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exeunt