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The Development of the Asymmetric Anionic Amino-Cope Rearrangement

by

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A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy at Loughborough University

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Abstract

The Allin group has recognised that the amino-Cope rearrangement of suitably functionalised 3-amino-1,5-diene substrates (A) could potentially constitute a powerful tool for the stereoselective synthesis of highly functionalised δ,ε-unsaturated aldehyde products such as (B) - our ultimate goal being a one-pot asymmetric synthesis of such aldehydes containing up to three contiguous chiral centres via amino-Cope rearrangement (Step 1) and subsequent enamine derivatisation and hydrolysis (Step 2).

Our group has demonstrated the key steps of this protocol, including a successful tandem amino-Cope rearrangement/enamine derivatisation reaction. More recently, we have established that an anionic (charge accelerated) variant of the rearrangement and tandem imine anion derivatisation is also possible, with high asymmetric induction achieved during rearrangement of a diastereoisomerically pure substrate (C). Research has shown that the anionic amino-Cope rearrangement does not advance solely by a concerted pathway. The development of novel substrates with substituents at C-6 aims to further study in depth the mechanism by which rearrangement proceeds.

Our group has proposed a novel and versatile route to access linear fused ring systems that could allow entry to the tetracycline and other natural product systems. Our approach is based around an innovative iterative protocol of aromatic Claisen rearrangement/ring closing metathesis chemistries.
Acknowledgements

There have been many people who have contributed towards this thesis in some way or another. Firstly I would like to thank my supervisor Dr. Steven Allin. His inspiration, direction and support has developed me into the confident chemist I am today and his good humour has made my postgraduate studies an enjoyable experience. I would also like to offer my sincere gratitude to my industrial supervisor, Dr. David Hallett, for his invaluable discussion and advice. I would like to thank the academic and technical staff, especially Dr. Mark Edgar for his continual support with NMR analysis.

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I owe a great deal to my close friends and family who have continuously given me words of encouragement and showed a keen interest in my studies. A special heartfelt mention to Raju Kaka, who once said “If I can’t print my own son’s thesis, then who’s can I?”

To my one and only Alka – thank you for having the belief in me, when at times I questioned myself and above all, helping me achieve my dreams. Apart from the well-needed breaks, you gave me a shoulder to lean on when times were hard and someone to share those unforgettable moments with.

To Lina – thanks for all the timely checks on reality and much appreciated motivation throughout those long and stressful days; I couldn’t have asked for a better sister. Last, and most importantly, I wish to thank my parents who have always encouraged me to achieve my aspirations in life through their understanding, patience and love. It is to them I dedicate this thesis.
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Abbreviations

* = denotes chiral centre
Ac = acetate
Ar = aryl
Boc = t-butoxycarbonyl
Bn = benzyl
Bu = butyl
bp = boiling point
Cbz = benzyloxycarbonyl
CSA = camphorsulfonic acid
DCE = dichloroethane
DCM = dichloromethane
d.e. = diastereoisomeric excess
DFT = density functional theory
DIAD = diisopropylazodicarboxylate
DIBAL = diisobutylaluminium hydride
DMAP = 4-dimethylaminopyridine
DMF = N,N-dimethylformamide
DMP = Dess Martin periodinane
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO = dimethyl sulfoxide
E+ = denotes electrophile
e.e. = enantiomeric excess
eq. = equivalent(s)
Et = ethyl
HMPA = hexamethylphosphoramide
HPLC = high performance liquid chromatography
hr = hour
i- = iso-
IBX = 2-iodoxybenzoic acid
Im = imidazole
IR = infra-red
KHMDS = potassium hexamethyldisilazide
LC/MS = liquid chromatography/mass spectrometry
LDA = lithium diisopropylamide
LHMDS = lithium hexamethyldisilazide
Ln = lanthanide
min(s) = minute(s)
mp = melting point
Ms = methanesulfonyl
MS = mass spectrometry
m-CPBA = 4-chloroperbenzoic acid
n- = normal-
NHMDS = sodium hexamethyldisilazide
NMM = 4-methylmorpholine
NMR = nuclear magnetic resonance
nOe = nuclear Overhauser effect
NOESY = nuclear Overhauser effect spectroscopy
NPSP = N-(phenylseleno)phthalimide
[O] = denotes oxidation
OAc = acetyl
OTf = triflate
PCC = pyridinium chlorochromate
Ph = phenyl
Phth = phthalimide
ppm = parts per million
PPTS = pyridinium p-toluenesulfonate
Pr = propyl
PTSA = p-toluene sulfonic acid
Py = pyridine
RCM = ring closing metathesis
RT = room temperature
SCX = strong cation exchange
t- = tertiary-
TBAF = tetrabutylammonium fluoride
TBDMS = t-butyldimethylsilyl
TEA = triethylamine
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>$N,N,N',N'$-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane/tetramethylsilyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>total correlation spectroscopy</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>wrt</td>
<td>with respect to</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction
1.1. Sigmatropic Rearrangements

Sigmatropic rearrangements are recognised as molecular rearrangements in which a \( \sigma \)-bond, flanked by one or more \( \pi \)-electron systems, shifts to a new location with a corresponding reorganisation of the \( \pi \)-bonds. The total number of \( \sigma \)-bonds and \( \pi \)-bonds remain unchanged. The term "sigmatropic rearrangement" was given to such reactions by Woodward and Hoffmann since "sigmatropic" indicates the movement of a sigma bond.

Sigmatropic rearrangements belong to a class of reactions known as pericyclic reactions. A pericyclic reaction involves the concerted reorganisation of \( \pi \)-electrons throughout a fully conjugated cyclic array of continuously bonded atoms generating a product containing one or more new \( \sigma \)-bonds.

1.1.1. Classification of Sigmatropic Rearrangements

Conventionally, two numbers set in brackets describe these rearrangements, which refer to the relative distance (in atoms) that each end of the \( \sigma \)-bond has moved. An \([i,j]\) shift is one in which the \( \sigma \)-bond migrates across \( i \) atoms of one system and \( j \) atoms of another.

\[
\begin{array}{c}
\text{\[3,3\]}
\end{array}
\]

\[
\begin{array}{c}
\text{\[1,5\]}
\end{array}
\]

Figure 1
Figure 1 shows two examples of sigmatropic rearrangements. Each of the original termini is given the number 1. In the first example, each terminus of the σ-bond has migrated from C-1 to C-3 and thus is described as a [3,3] rearrangement. In the second example, the carbon terminus has moved from C-1 to C-5 but the hydrogen terminus has not moved at all and therefore termed as a [1,5] shift.

In addition, according to Woodward and Hoffmann, such rearrangements can be effected in two distinct ways, either suprafacial or antarafacial as shown in Figure 2. With the suprafacial process, the migrating atom forms the new bond on the same face of the π-system, whereas with the antarafacial process, it is formed on the opposite face.

1.1.2. [3,3] Sigmatropic Rearrangements

Although many sigmatropic shifts are well known and have been thoroughly studied, the [3,3] rearrangement, as illustrated in Scheme 1, is probably the most interesting as far as synthesis is concerned.
There is a continued interest in asymmetric variants of sigmatropic rearrangements since these protocols could potentially develop into an efficient approach to the stereoselective synthesis of products containing several contiguous chiral centres. A common feature of [3,3] sigmatropic rearrangements is that they proceed through highly ordered transition state geometries, which allow the prediction, and control, of both relative and absolute stereochemistry in the desired product. Although many [3,3] sigmatropic rearrangements are used in organic synthesis, the most commonly encountered ones are highlighted in this section.

1.2. The Cope Rearrangement

The most basic form of a [3,3] sigmatropic rearrangement is known as the Cope rearrangement. Discovered by Arthur Cope in 1940, it holds its prestige as one of the best examples of the Woodward-Hoffmann pericyclic rules. The Cope rearrangement is a reversible reaction, and at equilibrium the starting material and product interconvert through a cyclic transition state. The final equilibrium position depends strongly on a number of factors focusing on the stability difference between the starting material and the product:

- Alkyl substitution, in the absence of any conjugating substituents, generally causes the reaction to favour the side containing the more substituted double bonds.

- $\pi$-Substituents such as ketone, cyano or phenyl conjugated to one or both of the double bonds causes the conjugated isomer to dominate the equilibrium.

- Integration of one of the double bonds into an aromatic system is also highly favoured and drives the reaction to completion in most cases.

- The removal of ring strain in 3- and 4-membered ring dienes can also force the equilibrium in favour of the formation of less strained products.
• The rearrangement is included as a step in a cascade process leading to a stable product. 

The synthetic value of the Cope rearrangement and its remarkable degree of specificity are due to a number of characteristics:

• Thermal activation is possible thus accommodating acid/base sensitive groups.

• The location of the new single and double bonds is unambiguously and predictably fixed.

• The reaction is extremely stereospecific due to the highly ordered cyclic transition state.

• Development of new analogues has enabled the use of lower temperatures and allowed easier access to the diene substrate.

1.2.1. Stereochemistry in the Cope Rearrangement

The Cope rearrangement and its variants all exhibit high levels of stereocontrol and this is a consequence of the cyclic transition states involved. When considering only suprafacial-suprafacial geometries, there are two limiting conformations possible for the 6-membered transition state – these being the chair and boat conformations as shown in Figure 3.
Doering and Roth have extensively investigated the Cope rearrangement and were the first to show that the rearrangement mainly proceeded via a chair-like transition state.\textsuperscript{10} One such compound used in these studies was meso-3,4-dimethyl-1,5-hexadiene (1) and its racemic equivalent (2). The meso-starting material rearranged predominantly to the (E, Z)-isomer of the 2,6-octadiene (3) with only 0.3\% of the (E, E)-isomer (4) being formed, whilst the racemic starting material afforded 90\% of the (E, E)-octadiene and 10\% of the (Z, Z)-isomer (5) (Scheme 2).

Scheme 2
Not only did these findings show that the chair conformation was more favourable than the boat, but also the fact that substituents at sp³ carbons have a tendency to occupy equatorial rather than axial positions allowing for the racemic diene to rearrange primarily via the diequatorial chair conformation to give the major (E, E)-isomer (4). ⁹

An energy diagram of the Cope transition states, as illustrated in Figure 4, highlights the relative energy difference of 5.8 kcal mol⁻¹ between the chair and boat conformation. ¹¹

![Figure 4](image)

Kato and co-workers demonstrated that the boat conformation is still a viable alternative to the chair-like transition state as can be seen in Scheme 3, where the lactol ring forces the substrate (6) to rearrange in this manner. ¹²
Scheme 4 summarises the studies carried out by Hill and Gilman, which demonstrated that the chair transition state enables the transfer of chirality from a stereogenic centre in the substrate to a new centre in the product. The nearly quantitative transfer (>97%) to the newly developing asymmetric centre gives strong additional evidence for a concerted cyclic rearrangement.
1.2.2. Mechanistic Aspects of the Cope Rearrangement

The Cope rearrangement is by and large regarded as a concerted process and thought to proceed through a cyclic transition state consisting of two partially bonded 3-carbon units, such as that shown in Scheme 1. However, there have been a number of possible alternative transition states postulated in recent years.14-18 Doering was one of the first to challenge the classical mechanism, proposing an alternative route via a cyclohexan-1,4-dyil diradical intermediate (7) as shown in Scheme 5.14
Also suggested was a stepwise mechanism involving the cleavage to two allyl radicals (8) but was calculated to be energetically unfavourable (Scheme 6).

Subsequent theoretical studies concluded that the alternative transition states proposed by Doering were higher in energy than that of which is associated with the concerted process, and hence unfavourable in the rearrangement of unsubstituted 1,5-hexadienes. However, studies by Dewar and others have demonstrated that structural features, in particular, substituents on the diene moiety can bring into question the alternative mechanisms put forward by Doering. It has been shown that the position and type of substituent can alter the reaction rate, depending on whether they can stabilise the transition state or ground state more effectively.

After extensive computational examination of a large set of Cope-related reactions, Schreiner derived the following simple rule: biradical intermediates are involved along the reaction path if they are stabilized by allylic resonance or aromaticity. This was in good agreement with previous studies.
1.2.3. The Oxy-Cope Rearrangement

Although synthetically useful, the Cope rearrangement has limitations such as high temperature requirements and reversibility. The discovery of the oxy-Cope rearrangement by Berson and Jones in 1964 significantly reduced the limitations of the traditional Cope rearrangement.\(^{19}\) They pointed out that the substitution of a hydroxy group at the C-3 or C-4 position of the 1,5-hexadiene resulted in, after rearrangement, an enol (9) whose tautomerisation led to a \(\delta,\varepsilon\)-unsaturated carbonyl compound (10), rendering it irreversible (Scheme 7).

Another major advancement in the synthetic applications of the Cope rearrangement occurred in 1975, when Evans and Golob reported that rate enhancements of \(10^{10} - 10^{17}\) were achieved in the oxy-Cope rearrangement by producing the sodium or potassium alkoxide of the 1,5-hexadiene as a substrate (11).\(^{20}\) The anionic oxy-Cope rearrangements were further accelerated when 18-crown-6 was added to dissociate \(\text{Na}^+\) or \(\text{K}^+\) from the alkoxide (Scheme 8).

The oxy-Cope and more significantly, the anionic oxy-Cope rearrangements, have become very common throughout synthetic organic chemistry over recent years. The relative ease at which the 1,5-dien-ols can be prepared has hugely contributed to their
popularity. Another contributory factor to their broad appeal is their facile nature. With reactions proceeding at room temperature or lower, there is a tolerance to a variety of functional groups in the substrate. The carbonyl compound obtained after rearrangement has a major advantage in that it can be easily manipulated for further synthetic purposes.

1.2.4. The Amino-Cope Rearrangement

The amino-Cope rearrangement is analogous to the oxy-Cope rearrangement with a nitrogen atom in place of the oxygen. The amino-Cope rearrangement of the 3-amino-1,5-hexadienes (12a) and (12b) leads to enamines (13a) and (13b). Enamine (13a) can also be shown in its resonance form as iminium ion (14). Enamine (13b) is in tautomeric equilibrium with imine (15) respectively, making the product thermodynamically more favourable. These intermediates should readily undergo hydrolysis to give the carbonyl compound (16) shown in Scheme 9.

As shown in Scheme 9, the amino-Cope rearrangement can take place using tertiary amine (12a) and secondary amine (12b) substrates. The reaction can proceed thermally for both substrates and in addition, anionically for the secondary amine substrate (12b).
Compared to other [3,3] sigmatropic rearrangements, there is little information on the amino-Cope rearrangement since most of the work to date has concentrated on the effect of substituents on the reaction rate.\textsuperscript{34-36} Before our own contribution to the area, only one example of the rearrangement being used synthetically was known. In 1979, Wender used the ester (17) in the amino-Cope rearrangement in tandem with a Diels-Alder reaction to produce \textit{cis}-hydroisoquinoline (18) (Scheme 10).\textsuperscript{21}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Scheme10}
\caption{Scheme 10}
\end{figure}

A summary of the Allin group contribution to the amino-Cope rearrangement is given in Section 1.4.

1.3. The Claisen Rearrangement

Since its discovery in 1912 by Rainer Ludwig Claisen,\textsuperscript{22} the rearrangement of allyl vinyl ethers, which allows the preparation of \(\gamma,\delta\)-unsaturated carbonyl compounds has become one of the most powerful tools for stereoselective carbon-carbon bond formation.\textsuperscript{23} Closely related to the Cope rearrangement, the Claisen rearrangement substrate differs in the fact that there is a heteroatom in the C-3 position within the hexadiene framework. When the heteroatom is oxygen, the reaction is the classical Claisen or 'oxa-Cope' rearrangement. Other Claisen-type rearrangements include the aza-, thia- and phospho-Claisen rearrangement (\(X = N, S\) and \(P\) respectively, Scheme 11).
As with the Cope rearrangement, the mechanism of the Claisen rearrangement is usually referred to as being concerted although there have been a number of possible transition states postulated. Figure 5 features the possible transition states of the Claisen rearrangement.

\[
\begin{align*}
\text{Figure 5}
\end{align*}
\]

1.3.1. Variants of the Claisen Rearrangement

The popularity of the Claisen rearrangement has been achieved by the development of a great number of variants over the last few decades. The following section will discuss some of the well-known modifications.

1.3.1.1. The Carroll Rearrangement

The Carroll rearrangement, initially described in 1940, is a thermal rearrangement of allylic $\beta$-ketoesters (19) followed by decarboxylation to yield $\gamma,\delta$-unsaturated ketones (20). Kimel and Cope interpreted Carroll's results and, along with their own findings, devised the following mechanism (Scheme 12).
This reaction has not been widely developed due to the harsh conditions employed, with temperatures in excess of 130 °C. However, Wilson reported that dianions such as (21), generated on deprotonation with 2 equivalents of LDA, can rearrange under milder conditions to give β-ketoacids (22).28

1.3.1.2. The Eschenmoser Rearrangement

In 1964, Eschenmoser described the rearrangement of N,O-ketene acetals (24) to yield γ,δ-unsaturated amides (25). The reaction typically involves the reaction of an amide acetal (23) with an allylic alcohol and subsequent in situ sigmatropic rearrangement of the resultant mixed ketene acetal.29
1.3.1.3. The Johnson Orthoester Rearrangement

Closely related to the Eschenmoser rearrangement, Johnson in 1970 described the process of heating an allylic alcohol with an excess of orthoester (26) in the presence of a catalytic amount of acid to generate the ketene acetal (27), which in turn undergoes rearrangement to produce a γ,δ-unsaturated ester (28).

\[
\begin{align*}
\text{HO} & \rightarrow \text{OR} \\
\text{RO} & \rightarrow \text{OR} \\
\text{OR} & \rightarrow \text{OR} \\
\text{H}^+ , \Delta & \rightarrow \\
\text{(26)} & \rightarrow \text{(27)} \\
\text{(27)} & \rightarrow \text{(28)} \\
\end{align*}
\]

Scheme 15

1.3.1.4. The Ireland-Claisen Rearrangement

One of the most significant advances to the Claisen rearrangement appeared in 1972 when Ireland introduced his variant. Scheme 16 shows how rearrangement of allyl silyl ketene acetals (29), prepared by reaction of allylic ester enolates with TMSCl, yields γ,δ-unsaturated carboxylic acids (30).

\[
\begin{align*}
\text{O} & \rightarrow \text{OTMS} \\
\text{O} & \rightarrow \text{OTMS} \\
\text{O} & \rightarrow \text{OH} \\
\text{LDA} & \rightarrow \\
\text{TMSCI} & \rightarrow \\
\text{(i)} & \rightarrow \text{(ii)} \\
\text{(29)} & \rightarrow \text{(30)} \\
\end{align*}
\]

Scheme 16

The Ireland-Claisen rearrangement has found broad application in organic synthesis due to its versatility, relatively mild conditions and a highly reliable and predictable transfer of stereochemical information during the rearrangement through highly-ordered transition states.
1.3.1.5. The Reformatsky-Claisen Rearrangement

It has been seen that allylic ester enolates rearrange quite readily. However, [3,3] sigmatropic rearrangement of zinc enolates has also been reported. These zinc enolates (32), generated by Reformatsky reaction of an α-haloester (31) with zinc dust, rearrange to give γ,δ-unsaturated carboxylic acids (33) after hydrolysis, in good yield under either acidic or basic conditions.

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
\text{O} & \quad \text{Zn dust} \\
\text{O} & \quad \text{Zn dust} \\
\text{OH} & \\
\end{align*}
\]

Scheme 17

1.4. Studies on the Amino-Cope Rearrangement

This section gives an insight into the history of the amino-Cope rearrangement and the studies carried out on it by various research groups as well as past members of the Allin Group.

In 1980, Ollis published a series of papers looking at base catalysed rearrangements involving ylide intermediates. In Part 4 of this series, amongst other things, the [3,3] sigmatropic rearrangement of \(N,N\)-dimethyl-3-amino-1,5-hexadienes was studied. First studied was the substituent effect on the base catalysed Stevens rearrangement. Their findings encouraged them to look at similar substituent effects on other [3,3] rearrangements, at that time documented only for the related oxy-Cope rearrangement.

The required substrates (35a-c) were synthesised by the Stevens rearrangement of quaternary ammonium salts (34a-c), in good yield (Scheme 18).
Thermal amino-Cope rearrangements, monitored by NMR analysis were performed on all the substrates as shown in Scheme 19. The rearrangement of (35a) took place at a relatively low temperature (80 °C) to give enamine (36a) with trans-stereochemistry. The highly substituted diene (35b) rearranged at a slightly higher temperature of 100 °C to give the trans-enamine (36b). The less substituted diene (35c) required a higher temperature of 170 °C for the rearrangement to proceed, again giving the trans-enamine (36c).

Ollis proposed that the stereochemical integrity of the enamines formed was either as a consequence of the concerted rearrangement of the dienes, which were present as single diastereoisomers, or as a result of a thermal equilibrium between the diastereoisomeric enamines. As can be seen from the results, the substituents on C-4 had an influential role.
on the temperature at which the rearrangement occurred. The accelerating effects of 4-aryl substituents in Cope rearrangements has been noted by Doering\textsuperscript{14} and Dewar\textsuperscript{16} The effects are thought to result from the electron donating properties of C-4 substituents, although steric effects may also contribute to this phenomenon.

Ollis also examined other 3-hetero substituted 1,5-hexadienes and concluded that the effects for 3-NMe\textsubscript{2} substituents were more significant than those for a 3-OR and 3-SR group at lowering the energy of the Cope rearrangement transition state. This influence was thought to be a consequence of increased electron donating properties.

In 1982, Kirmse investigated the effect of single heteroatom substituents on the activation parameters of [3,3] sigmatropic rearrangements.\textsuperscript{35} In order to study the donor substituent effect on the rate of rearrangement and to gain an insight into the reaction mechanism, they prepared a series of heteroatom substituted 1,5-hexadienes. Amongst the heteroatom substituted 1,5-hexadienes prepared was \textit{N,N}-dimethyl-3-amino-1,5-hexadiene (38), which was made by a Stevens rearrangement of diallyldimethylammonium bromide (37) (Scheme 20).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme20}
\caption{Scheme 20}
\end{figure}

\textbf{Scheme 21} describes the successful amino-Cope rearrangement following thermolysis of substrate (38), which generated the desired enamine (39) with exclusive \textit{trans}-stereochemistry. The activation energy was found to be 1.4 kcal mol\textsuperscript{-1} lower than that of the unsubstituted 1,5-hexadiene. The effect of substituent stabilisation on the product was studied. It was observed that the considerable stabilisation effect of the product was found to have only a moderate effect on the activation energy of the Cope rearrangement. The greatest effect was observed with the 3-NMe\textsubscript{2} substituent.
From these studies they concluded that the alkoxy, alkylthio and dialkylamino groups in the C-3 position of the 1,5-hexadiene and C-2 position of 3,3-dimethyl-1,5-hexadienes have only small effects on the Cope rearrangement reaction rate. This substituent effect was more consistent with the diradical mechanism than the concerted sigmatropic mechanism.

In 1995, Hagen\textsuperscript{36} used Hine's $D$ values\textsuperscript{37} to predict the position of equilibrium in the Cope rearrangement of multiple substituted 1,5-hexadienes. Hine's $D$ value is a reflection of the double bond stabilizing ability which permits prediction of free energy changes of allylic isomerisation. Scheme 22 shows a series of heterosubstituted 1,5-hexadienes prepared, including oxygen, amino, carbamoyl and thioalkyl variants (40a-j).

\begin{align*}
\text{(40)} & \quad \text{(41)} \\
\text{a; } X = \text{OMe}, Y = R = H & \quad \text{f; } X = \text{N(Me)}_2, Y = \text{OMe}, R = H \\
\text{b; } X = \text{OMe}, Y = \text{Me}, R = H & \quad \text{g; } X = \text{N(Me)}(\text{CO}_2\text{Et}), Y = R = H \\
\text{c; } X = \text{OMe}, Y = \text{Me}, R = \text{Me} & \quad \text{h; } X = \text{N(Me)}(\text{CO}_2\text{Et}), Y = \text{Me}, R = H \\
\text{d; } X = \text{N(Me)}_2, Y = R = H & \quad \text{i; } X = \text{N(Me)}(\text{CO}_2\text{Et}), Y = \text{OMe}, R = H \\
\text{e; } X = \text{N(Me)}_2, Y = \text{Me}, R = H & \quad \text{j; } X = \text{SMe}, Y = R = H \\
\end{align*}

Scheme 22
Cope rearrangements were carried out on these heterosubstituted substrates in the gas phase and the extent of the reaction was estimated from the ratio of substrate (40a-j) to product (41a-j) in the resulting NMR spectra. The calculated Hine's $D$ values were said to compare directly with the resulting $K_{eq}$ values. It was concluded that a reduction of the $\pi$-donating character of nitrogen (dimethylamino vs. carbamoyl) alters its directing ability, giving an aggregate order for reaction rate of N(Me)$_2$ $>$ OMe $>$ Et$_2$CN(Me) $>$ Me $>$ H.

1.4.1. Synthetic Potential of the Amino-Cope Rearrangement

From these early reports the Allin group recognised that the amino-Cope rearrangement of suitably functionalised 3-amino-1,5-diene substrates (42) could potentially constitute a powerful tool for the stereoselective synthesis of highly functionalised product systems in a cascade-like sequence as illustrated in Scheme 23.

![Scheme 23](image)

Successful sigmatropic rearrangement of the 3-amino-1,5-diene substrate (42) would lead to the formation of the enamine (43). Substitution at the 1- or 6-position of the diene moiety in (42) would allow, during step 1, the creation of new asymmetric centres in the aldehyde product (44). Indeed, high stereoselectivities are known to be induced at the chiral centres that are created in related [3,3] sigmatropic rearrangements. If this synthesis can be extended with typical enamine derivatisation, as outlined in step 2, this would constitute the formation of a product with up to three new asymmetric centres in a one-pot reaction. An asymmetric centre within the amine component of the diene (42) could act as a chiral multiplier: producing and manipulating the stereochemical induction of the newly generated asymmetric centres.
1.4.2. The Thermal Amino-Cope Rearrangement

Initial studies by Allin and Button, began with the preparation of simple, unsubstituted tertiary 3-amino-1,5-diene substrates such as (46a-g). This was achieved by employing a Stevens rearrangement of appropriate quaternary ammonium salts (45a-g) as shown in Scheme 24.

$$R^1\text{N}^+\text{R}^2\text{H} \xrightarrow{\text{K}_2\text{CO}_3, \text{MeCN} / \Delta} R^1\text{N}^+\text{R}^2\text{N}^+\text{R}^2 \xrightarrow{\text{K'O}Bu, \text{MeCN}} R^1\text{N}^+\text{R}^2\text{N}^+\text{R}^2$$

Scheme 24

The salts (45a-g) were reacted with base in acetonitrile to furnish the desired tertiary 3-amino-1,5-dienes (46a-g) in reasonable to good yields (Table 1).

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>Et</td>
<td>46a</td>
<td>74</td>
</tr>
<tr>
<td>Pr</td>
<td>Pr</td>
<td>46b</td>
<td>72</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-Bu</td>
<td>46c</td>
<td>84</td>
</tr>
<tr>
<td>n-Bu</td>
<td>i-Bu</td>
<td>46d</td>
<td>80</td>
</tr>
<tr>
<td>i-Bu</td>
<td>i-Bu</td>
<td>46e</td>
<td>64</td>
</tr>
<tr>
<td>-(CH₂)₄-</td>
<td></td>
<td>46f</td>
<td>83</td>
</tr>
<tr>
<td>-(CH₂)₅-</td>
<td></td>
<td>46g</td>
<td>72</td>
</tr>
</tbody>
</table>

Table 1

Thermal rearrangements of the substrates (46a-g) were attempted initially in high boiling solvents such as toluene and decane. However it was shown that superior results were obtained when the substrates were heated neat in sealed tubes at temperatures between 170-250 ºC and variable times between 15 minutes and 2 hours (Table 2).
All enamines observed were formed exclusively as one geometrical isomer, the thermodynamically more favourable trans-enamine. This was supported by $^1$H NMR data which gives coupling constants of 13.9 Hz for the doublet signal corresponding to the enamine double bond proton adjacent to the nitrogen. This geometrical preference is consistent with the expected pseudo-chair transitions state in which the amino group occupies an equatorial orientation as shown in Figure 6.
It was noted, however, that under the thermodynamic conditions used (high temperature, long reaction times), the exclusive formation of the \textit{trans} enamine may simply be due to equilibration of any initially formed \textit{cis} enamine to the more favourable \textit{trans} isomer.

1.4.3. Tandem Amino-Cope Rearrangement/Enamine Derivatisation

Enamine hydrolysis to the corresponding aldehyde proved problematic due to the formation of aldol products. Therefore studies turned to the direct derivatisation of the enamine, a feat that at that time had yet to be reported, other than simple hydrolysis.

\begin{equation}
\begin{array}{c}
\text{R}^1 \text{R}^1 \\
\text{N} \text{N} \\
\text{R}^2 \text{N} \text{C} \\
\text{R}^2 \text{N} \text{C} \\
\end{array} \xrightarrow{\Delta} \quad \begin{array}{c}
\text{R}^1 \text{R}^1 \\
\text{N} \text{N} \\
\text{R}^2 \text{N} \text{C} \\
\text{R}^2 \text{N} \text{C} \\
\end{array} \xrightarrow{(i), (ii)} \begin{array}{c}
\text{H} \\
\text{O} \\
\text{C} \\
\text{H} \\
\end{array}
\end{equation}

(i) allyl bromide (1.2 eq), MeCN, $\Delta$, 3 hr, (ii) $\text{H}_2\text{O}^+$

\textit{Scheme 26}

\textit{Scheme 26} illustrates the first tandem amino-Cope rearrangement/enamine derivatisation which was carried out initially using allyl bromide as the electrophile.\textsuperscript{43}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$\text{R}^1$</th>
<th>$\text{R}^2$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46a</td>
<td>Et</td>
<td>Et</td>
<td>11</td>
</tr>
<tr>
<td>46b</td>
<td>Pr</td>
<td>Pr</td>
<td>31</td>
</tr>
<tr>
<td>46c</td>
<td>$n-$Bu</td>
<td>$n-$Bu</td>
<td>30</td>
</tr>
<tr>
<td>46d</td>
<td>$n-$Bu</td>
<td>$i-$Bu</td>
<td>45</td>
</tr>
<tr>
<td>46e</td>
<td>$i-$Bu</td>
<td>$i-$Bu</td>
<td>50</td>
</tr>
</tbody>
</table>

\textit{Table 3}

Side reactions such as \textit{N}-alkylation were to account for the low yields obtained and are characteristic of previously reported aldehyde enamine chemistry.\textsuperscript{41,42} Curphey suggested
that high yielding mono-alkylation of aldehyde-derived enamines can be achieved by increasing steric bulk of the amine component.\textsuperscript{42} This was indeed found to be the case as shown in Table 3.

Substrate (46d) was further investigated with a range of electrophiles as shown in Scheme 27. The results are summarised in Table 4.

\begin{equation}
\begin{aligned}
(46d) & \quad \Delta \quad \rightarrow \quad (49a-f) \\
(46d) & \quad \text{(i) } E^+ (1.2 \text{ eq}), \text{ MeCN, } \Delta, \text{ 3 hr; (ii) } \text{NaOAc/HOAc/H}_2\text{O, } \Delta \\
(46d) & \quad \text{(i) } E^+ (1.2 \text{ eq}), \text{ MeCN, } \Delta, \text{ 3 hr; (ii) } \text{NaOAc/HOAc/H}_2\text{O, } \Delta
\end{aligned}
\end{equation}

\begin{table}[h]
\begin{tabular}{|l|c|c|c|}
\hline
Electrophile & R\textsuperscript{3} & Product & Yield (%) \\
\hline
Methyl iodide & Me & 49a & 63 \\
Ethyl iodide & Et & 49b & 17 \\
Triethyloxonium tetrafluoroborate & Et & 49b & 56 \\
Benzyl bromide & CH\textsubscript{2}Ph & 49c & 69 \\
Methyl bromoacetate & -CH\textsubscript{2}CO\textsubscript{2}Me & 49d & 57 \\
Ethyl acrylate & -(CH\textsubscript{2})\textsubscript{2}CO\textsubscript{2}Et & 49e & 60 \\
Acrylonitrile & -(CH\textsubscript{2})\textsubscript{2}CN & 49f & 53 \\
\hline
\end{tabular}
\caption{Table 4}
\end{table}
1.4.4. The Anionic Amino-Cope Rearrangement

Until Allin’s contribution to the area, there had been only one report of an anionic (charge accelerated) amino-Cope rearrangement. In 1993, Macdonald and co-workers examined the thermal and charge accelerated rearrangements of 3-amino-1,5-diene substrates. It was anticipated that the charge accelerated [3,3] sigmatropic rearrangements of such substrates were considerably more facile than those of the corresponding 3-hydroxy-1,5-dienes (oxy-Cope rearrangement) due to the increased basicity of the nitrogen anion, in comparison with an alkoxide anion, and thus subsequently producing a greater rate acceleration in the anionic rearrangement.

To verify this hypothesis, and to evaluate the scope and limitations of the amino-Cope rearrangement, a series of acyclic and bicyclic amino-dienes were prepared. The thermal rearrangement of diene (50) was achieved at 150 °C and lead to aldehyde (51) following hydrolysis in 48% yield. The anionic variant of the rearrangement was shown to be successful by deprotonation with n-BuLi at -40 °C to give the aldehyde (51) after acid hydrolysis in 40% yield (Scheme 28).

Scheme 28
It was noteworthy that the anionic amino-Cope rearrangement of the lithium amide of substrate (50) took place at a temperature 65 °C lower than that required for the anionic oxy-Cope rearrangement of the potassium alkoxide of the corresponding alcohol.

### 1.4.5. Asymmetric Induction in the Anionic Amino-Cope Rearrangement

Allin and Button further developed the process first developed by Macdonald\(^4^4\) by reporting the first example of asymmetric induction in an anionic amino-Cope rearrangement.\(^4^5\) It was demonstrated that the incorporation of an enantiomerically pure amine substituent into a typical substrate for anionic amino-Cope rearrangement, would lead to formation of an enantiomerically enriched β-substituted aldehyde product.

![Scheme 29](image)

*Scheme 29*

Scheme 29 illustrates how suitable secondary amine substrates were prepared by addition of allyl magnesium bromide to the corresponding imines (52a-c) derived from *trans*-cinnamaldehyde and suitable primary amines to generate the desired diene substrates (53a-c) in good yields (Table 5).

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH(_2)-</td>
<td>52a</td>
<td>94</td>
<td>53a</td>
<td>95</td>
</tr>
<tr>
<td>cyclohexyl-</td>
<td>52b</td>
<td>87</td>
<td>53b</td>
<td>72</td>
</tr>
<tr>
<td>(±)-α-methylbenzyl-</td>
<td>52b</td>
<td>89</td>
<td>53b</td>
<td>82</td>
</tr>
</tbody>
</table>

*Table 5*
The racemic diene substrates (53a-c) successfully underwent anionic amino-Cope rearrangement as expected on employing n-BuLi as base as shown in Scheme 30. The intermediate lithiated imine anions (54a-c) were directly hydrolysed to provide the desired racemic aldehyde (55) in good yield (Table 6). Interestingly, no reaction was observed using potassium hydride as base or with a range of non-nucleophilic bases (LDA, LHMDS, KHMDS, NHMDS) in THF.

\[
\begin{align*}
\text{(53a-c)} & \xrightarrow{(i)} \text{[3.3]} \rightarrow \left[ \text{Li} \right] \rightarrow \text{(54a-c)} \rightarrow \text{(ii)} \rightarrow \text{(±)-(55)} \\
(i) & n\text{-BuLi} (1.5 \text{ eq}), \text{THF, } 25 \degree \text{C, 3hr}; (ii) \text{NaOAc/HOAc/H}_2\text{O} (1:1:2), \triangle, 2\text{hr}
\end{align*}
\]

Scheme 30

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53a</td>
<td>PhCH₂⁻</td>
<td>81</td>
</tr>
<tr>
<td>53b</td>
<td>cyclohexyl⁻</td>
<td>64</td>
</tr>
<tr>
<td>53b</td>
<td>(±)-α-methylbenzyl⁻</td>
<td>78</td>
</tr>
</tbody>
</table>

Table 6

To further study the scope of asymmetric induction in the anionic amino-Cope rearrangement, an enantiomerically pure amine substituent was incorporated into a typical rearrangement substrate. The non-racemic diene substrate (56) was prepared by the protocol outlined in Scheme 29 as a 1.3:1 mixture of diastereoisomers, which were separated by flash column chromatography. The minor diastereoisomer (R,S)-(56) was subjected to the rearrangement conditions in Scheme 31 to yield the target aldehyde (R)-(55).
The enantioselectivity of the reaction was determined by derivatisation of (55) with (1R, 2S)-(−)-ephedrine to form a diastereoisomeric oxazolidine product for ¹H NMR analysis as described by Agami.⁴⁶ This revealed an enantiomeric excess of 75% for the aldehyde and also confirmed the absolute stereochemistry at the β-position to be as expected from the proposed transition state models highlighted in Scheme 32.

Such models, if accurate, would allow us to predict the stereochemical outcome of the rearrangement, since it is believed that in a chair-like transition state the amine component would have a preference for a pseudo-equatorial orientation.⁴³ From these models it was predicted that the anionic amino-Cope rearrangement of substrate (R,S)-(56) would yield the (R)-enantiomer of aldehyde (55) and that (R,R)-(56) would yield the (S)-enantiomer. The corresponding asymmetric rearrangement of the major diastereoisomer (R,R)-(56) gave the expected product (S)-(55) but with a lower level of
enantioselectivity. The results indicate a possible type of matched/mis-matched diastereoisomer effect being involved in the stereochemical outcome of the product from its precursor diene substrate. Table 7 summarises the results of the preliminary asymmetric anionic amino-Cope rearrangements.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>Major enantiomer</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,R)-(56)</td>
<td>73</td>
<td>(S)</td>
<td>41</td>
</tr>
<tr>
<td>(R,S)-(56)</td>
<td>66</td>
<td>(R)</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 7

From these studies it has been demonstrated that in terms of asymmetric induction, the amino-Cope rearrangement has a significant advantage over the analogous anionic oxy-Cope rearrangement as highlighted in Scheme 33. Both variants of the anionic Cope rearrangement can yield the same aldehyde product, however the amino-Cope rearrangement has generated the product with a greater degree of enantioselectivity, up to 75% e.e.\(^{45}\) compared to only 30% e.e. by the oxy-Cope.\(^{47}\)

**Asymmetric Anionic Amino-Cope Rearrangement**

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Me} & \quad (i) \text{n-BuLi, THF, } \Delta \\
\text{Ph} & \quad (ii) \text{H}_3\text{O}^+ \\
\end{align*}
\]

75% e.e.

**Asymmetric Anionic Oxy-Cope Rearrangement**

\[
\begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{Ph} & \quad (i) \text{KH, 18-crown-6, THF, } \Delta \\
\text{Ph} & \quad (ii) \text{H}_3\text{O}^+ \\
\end{align*}
\]

30% e.e.

Scheme 33
1.4.6. Asymmetric Induction in the Anionic Amino-Cope Rearrangement Controlled by β-Aminoalcohol Auxiliaries

The methodology was advanced further by Allin, Button and Baird\textsuperscript{48} by employing enantiomerically pure β-aminoalcohols instead of secondary amines, as these auxiliaries are known to control a range of asymmetric transformations and are capable of forming a 5-membered chelate in the presence of a metal counter-ion.\textsuperscript{6}

As shown before, each diastereoisomer of the diene substrate is known to lead to the opposite enantiomer of the rearrangement product and therefore the diastereoselectivity obtained during preparation of the 3-amino-1,5-diene substrates is of key importance. Separation of the substrate diastereoisomers is an additional problem if one aims to achieve high enantioselectivity in the amino-Cope rearrangement. To address this problem, the use of β-aminoalcohol chiral auxiliaries has been employed with great effect. Results have shown that they have greatly improved the diastereoselectivity of the formation of 3-amino-1,5-diene substrates and hence significantly improving product enantioselectivity during the sigmatropic rearrangement.

Analogous to the procedure highlighted in Scheme 29, the 3-amino-1,5-diene substrates (59\textsubscript{a-e}) were synthesised in good yield following addition of allyl magnesium bromide to the corresponding imines (58\textsubscript{a-e}) as shown in Scheme 34. The results are summarised in Table 8.
<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>d.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Pr</td>
<td>58a</td>
<td>99</td>
<td>59a</td>
<td>78</td>
<td>97</td>
</tr>
<tr>
<td>t-Bu</td>
<td>58b</td>
<td>99</td>
<td>59b</td>
<td>77</td>
<td>94</td>
</tr>
<tr>
<td>i-Bu</td>
<td>58c</td>
<td>86</td>
<td>59c</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>Ph</td>
<td>58d</td>
<td>99</td>
<td>59d</td>
<td>64</td>
<td>96</td>
</tr>
<tr>
<td>PhCH₂</td>
<td>58e</td>
<td>99</td>
<td>59e</td>
<td>67</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 8

Amino-Cope rearrangement of the major diastereoisomers of diene substrates (59a-e) generated an oxazolidine (60), resulting from the ring closure of the intermediate imine anion on work-up (Scheme 35). Purification of the product by flash column chromatography hydrolysed (60) to yield aldehyde (55). The enantiomeric excesses and absolute configurations of the products were verified by derivatisation with (1R, 2S)-(-)-ephedrine and are summarised in Table 9.

(i) n-BuLi (2.5 eq), THF, -78 °C-RT, then Δ; (ii) NaOAc/HOAc/H₂O (1:1:2), Δ, 4hr

Scheme 35

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<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>59a</td>
<td>i-Pr</td>
<td>60</td>
<td>84</td>
</tr>
<tr>
<td>59b</td>
<td>t-Bu</td>
<td>53</td>
<td>88</td>
</tr>
<tr>
<td>59c</td>
<td>i-Bu</td>
<td>57</td>
<td>71</td>
</tr>
<tr>
<td>59d</td>
<td>Ph</td>
<td>61</td>
<td>83</td>
</tr>
<tr>
<td>59e</td>
<td>PhCH₂</td>
<td>65</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 9

The results showed that an increase in steric bulk of the amine auxiliary component lead to a corresponding increase in product enantioselectivity during amino-Cope rearrangement (Figure 7).

\[
R = \begin{array}{c}
\text{(59c)} & \text{(59d)} & \text{(59a)} & \text{(59b)} & \text{(59e)} \\
\text{e.e. (%)} &= 71 & 83 & 84 & 88 & 94 \\
\end{array}
\]

Increase in enantioselectivity

Figure 7

Figure 8 shows how an increase in steric bulk, possibly enhanced by intramolecular chelation in the amine component, would disfavour the competing chair transition state (B) leading to the opposite product enantiomer due to an increased possibility of unfavourable 1,3-diaxial interactions with the axial amine substituent.
1.4.7. Mechanistic Studies on the Anionic Amino-Cope Rearrangement

Being a variant of the Cope rearrangement, the amino-Cope rearrangement inherits the ambiguity of the mechanism by which it proceeds. This area of the amino-Cope rearrangement has received considerable interest in recent years.

Houk and Meyers$^{49}$ investigated the rearrangement of 3-amino-1,5-dienes using \textit{ab initio} calculations and compared them with those of the oxy-Cope rearrangement, which is widely considered to be concerted.$^{50}$

After comparing the bond dissociation energies of the anionic amino-Cope rearrangement with those of the anionic oxy-Cope rearrangement, Meyers and Houk proposed that, unlike the concerted oxy-Cope pathway, the amino-Cope mechanism was in fact stepwise, involving deallylation of the substrate \textit{via} an imine/allyl anion intermediate and subsequent conjugate addition of the anion at the double bond terminus.
Figure 9 shows the stationary points found in the anionic oxy-Cope rearrangement. This reaction proceeds *via* a concerted pathway, with an activation energy of 9.9 kcal mol\(^{-1}\) of energy and the overall reaction is exothermic generating 19.1 kcal mol\(^{-1}\) of energy. An intrinsic reaction co-ordinate calculation indicates no intermediates with the transition structure occurring quite early and is dissociative.

In contrast, the anionic amino-Cope substrate has an unexpectedly different energy surface, and is proposed to proceed *via* a stepwise mechanism. The initial barrier to the reaction is 7.4 kcal mol\(^{-1}\) of energy and leads to intermediate ion complex (61), consisting of an allyl anion and acrolein imine. The complex then recombines to form the rearrangement product in an exothermic reaction, liberating 21.1 kcal mol\(^{-1}\) of energy.
Recently, Houk in collaboration with Haeffner and Lee,\textsuperscript{51} extended his and Meyers' original work with the aid of DFT calculations. From these studies, it was concluded that [3,3] pericyclic rearrangements are promoted by heteroatoms such as sulfur and oxygen, which are not highly basic and are therefore relatively stable. In contrast, heteroatoms such as nitrogen and carbon, owing to considerably more basic character than sulfur and oxygen, promote cleavage/recombination. However it was also proposed that the presence of a lithium counter-ion on the deprotonated substrates could stabilise the negative charge on the heteroatom and promote a concerted rearrangement.

In 1999, Macdonald reported that the anionic rearrangement of 3-amino-1,5-hexadienes such as (62a) and (62b), could afford both [3,3] (63a-b) and [1,3] (64a-b) products (Scheme 36).\textsuperscript{52}
It was noted that with some substrates the regioselectivity of the reaction was strongly influenced by solvent polarity. Table 10 summarises the results obtained by Macdonald et al. The 3-amino-1,5-hexadiene substrate studied contained either a 4-SPh or a 4-OPh substituent.

<table>
<thead>
<tr>
<th>Y</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>[3,3]/[1,3]</th>
<th>Cis/Trans [3,3]</th>
<th>Yield (%)</th>
<th>[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>THF</td>
<td>-</td>
<td>-78</td>
<td>10</td>
<td>1:2</td>
<td>1:5</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMEDA</td>
<td>-70</td>
<td>30</td>
<td>1:2</td>
<td>1:9</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPA</td>
<td>-78</td>
<td>30</td>
<td>1:5</td>
<td>1:10</td>
<td>43</td>
<td>b</td>
</tr>
<tr>
<td>S</td>
<td>Toluene</td>
<td>-</td>
<td>-20</td>
<td>60</td>
<td>1:1</td>
<td>2:1</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMEDA</td>
<td>-78</td>
<td>30</td>
<td>8:1</td>
<td>3:1</td>
<td>49</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPA</td>
<td>-60</td>
<td>60</td>
<td>3:2</td>
<td>2:1</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Hexanes</td>
<td>-</td>
<td>-20</td>
<td>60</td>
<td>2:1</td>
<td>2:1</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>TMEDA</td>
<td>-78</td>
<td>30</td>
<td>10:1</td>
<td>4:1</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPA</td>
<td>-60</td>
<td>60</td>
<td>4:1</td>
<td>3:1</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>THF</td>
<td>TMEDA</td>
<td>25</td>
<td>45</td>
<td>3:1</td>
<td>1:2</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMPA</td>
<td>25</td>
<td>45</td>
<td>2:1</td>
<td>1:1</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Toluene</td>
<td>TMEDA</td>
<td>25</td>
<td>45</td>
<td>4:1</td>
<td>1:3</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

[a] no starting material or other products; [b] 6% yield of allyl phenylsulfide

Table 10
It was observed that when the 4-phenylsulfanyl-3-amino-1,5-hexadiene (62a) was treated with n-BuLi in a non-polar solvent, such as hexane, the [3,3] product (63a) is favoured. However, when a polar solvent such as THF is used, the [1,3] product (64a) is predominant.

The addition of co-ordinating additives such as HMPA or TMEDA resulted in a more facile reaction, particularly with a less or non-polar solvent. The co-ordinating additives also increased the solvent effect on the regioselectivity of the reactions; TMEDA increased the selectivity for the [3,3] product in the less or non-polar solvent while HMPA increased the selectivity for the [1,3] product in THF.

Exchanging the 4-PhS substituent to a 4-PhO substituent in the diene substrates yielded interesting results. When 4-phenyloxy-3-amino-1,5-hexadiene (62b) was subjected to anionic rearrangement conditions, the [3,3] pathway was predominant, even when THF was used as the solvent. In contrast, the PhS substituent had a significant directing effect on the course of the reaction, allowing the pathway and hence regioselectivity of the reaction to be strongly influenced by choice of solvent. It was also worth noting, that 4-PhO containing substrate (62b) reacts at a higher temperature (25 °C) than the corresponding 4-PhS containing substrate (62a), which reacts at −78 °C.

The ratio of the cis/trans [3,3] products was also found to be under the influence of choice of solvent. The non-polar solvents favoured the cis product while the polar solvent favoured the trans product. Macdonald concluded that polar solvents enhanced a fragmentation pathway and that a concerted pathway was favoured by non-polar solvents. The solvent effect on the cis/trans [3,3] product selectivity was thought to be attributed to the cis [3,3] product generated via a concerted mechanism whilst the of trans [3,3] product is formed by a fragmentation pathway.

These studies by other groups may contradict Allin’s findings, where high enantioselectivity was obtained on anionic rearrangement. One would expect high enantioselectivity as a result of a highly ordered concerted process, rather than a dissociative pathway, which could lead to loss of stereochemical information from within the diene unit.
Allin and Button prepared a suitable substrate that might allow more insight into whether
the anionic amino-Cope rearrangement was a concerted [3,3] sigmatropic process.\textsuperscript{53} It
was reasoned that the presence of a methyl "marker" at C-4 of the 3-amino-1,5-diene
substrate (65) might allow for detection of the involvement of alternative reaction
pathways during the rearrangement. A concerted [3,3] sigmatropic rearrangement of the
substrate would only lead to product (66), with the methyl "marker" located at the
terminal alkene position. However, if the rearrangement proceeded by a competing
mechanism, such as a dissociative pathway or a [1,3] alkyl shift, the possibility of
recombination to give alternative products (66) and (67) would be feasible.

\[ \begin{array}{c}
\text{HO} \quad \text{H} \\
\text{N} \quad \text{Ph} \\
\text{Me} \\
(65) \\
\end{array} \quad \xrightarrow{[3,3] \text{Concerted}} \\
\begin{array}{c}
\text{O} \quad \text{Ph} \\
\text{H} \\
\text{Me} \\
(66) \\
\end{array} \\
\text{i) } \text{n-BuLi/THF} \\
\text{ii) } \text{H}_2\text{O}^+ \\
\begin{array}{c}
[\text{RN} \quad \text{Ph}] \\
\text{Me} \\
\end{array} \quad \xrightarrow{\text{recombination}} \\
\begin{array}{c}
\text{Me} \\
(66) \\
\end{array} + \\
\begin{array}{c}
\text{H} \quad \text{Ph} \\
\text{Me} \\
(67) \\
\end{array} \\
\text{(then } \text{H}_2\text{O}^+) \\
\end{array} \\
\text{Scheme 37} \\
\]

Analysis of the product mixture by \textsuperscript{1}H NMR revealed a 1:1 mixture of the two possible
products. Aldehyde (66) was formed as a 4:1 mixture of geometrical isomers, with the
\textit{trans} isomer predominating. Aldehyde (67) was formed as an equal mixture of \textit{syn} and
\textit{anti} diastereoisomers. Recently, Essat performed the reaction shown in Scheme 37 using
hexanes and toluene as the solvent.\textsuperscript{54} In both cases of hexanes and toluene, a preference
towards the dissociative product (67) was observed, with ratios of 2:1 and 3:1 being
obtained respectively.

Introduction
In Scheme 37 it is indicated that dissociation leads to the imine/allyl anion intermediate as implied by Houk and Meyers. It is, of course, feasible that a diradical intermediate may be involved. Also, it was not discounted that a competing [1,3] alkyl shift under the appropriate reaction conditions could lead to product (67). In conclusion, it was shown that the anionic amino-Cope rearrangement of some 4-alkyl-3-amino-1,5-diene substrates in THF do not proceed solely by a concerted [3,3] sigmatropic rearrangement mechanism.

Recent work within the group has focussed on further investigating the mechanism of the amino-Cope rearrangement by studying the effect of varying substituents around the 3-amino-1,5-diene core and the influence of solvent choice and additives on the enantio- and regioselectivity of the process.

Thus far, only substrates bearing a phenyl substituent at the 1-position of the diene unit had been reported within the group. A range of novel substrates, with varying substituents at C-1 of the diene substrate, were prepared by Allin and Horro Pita. A series of α,β-unsaturated aldehydes were condensed with phenylalaninol and the resulting imine reacted with allyl magnesium bromide to furnish the novel diene substrates (Scheme 38).
Rearrangement of the 3-amino-1,5-diene substrates was performed on treatment with 2.5 equivalents n-BuLi in the appropriate solvent system at -78 °C, followed by warming, aqueous work-up and product isolation by flash column chromatography. The enantiomeric excess was determined by the procedure described by Agami.\(^\text{46}\) Table 11 summarises the results of the rearrangements of the novel diene substrates under varied solvent conditions. Due to the structure of the substrates, [1,3] and [3,3] rearrangement products are identical. Although an over-simplification, it was regarded that a higher e.e. may support the evidence of a concerted [3,3] process.
<table>
<thead>
<tr>
<th>Product</th>
<th>THF</th>
<th>Toluene</th>
<th>Hexanes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yield (%)</td>
<td>e.e. (%)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>(69a)</td>
<td>69</td>
<td>84</td>
<td>69</td>
</tr>
<tr>
<td>(69b)</td>
<td>53</td>
<td>67</td>
<td>32</td>
</tr>
<tr>
<td>(69c)</td>
<td>65</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>(69d)</td>
<td>35</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>(69e)</td>
<td>20</td>
<td>57</td>
<td>14</td>
</tr>
<tr>
<td>(69f)</td>
<td>54</td>
<td>70</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 11

Hanna$^{56}$ as well as Paquette$^{57}$ reported that oxy-Cope rearrangements are favoured by an additional unsaturation, conjugated to the double bond of the 3-hydroxy-1,5-diene. This effect was explained in terms of stabilisation of the concerted transition state by the additional unsaturation.

The aldehyde (69e), with a simple alkyl substituent was generated with the lowest yield in all cases. This substrate does not possess conjugation at the C-1 position and would therefore support Hanna’s and Paquette’s argument. In addition, substrates with phenyl substituents (68a & 68c) were generated with high yields and enantiomeric excess. This could be due to an enhanced stabilising effect of the phenyl substituent on the concerted transition state and hence an increase in enantioselectivity. This would also account for a decrease in overall yield and e.e. for the substrate bearing the furan group (68b) as it possess less aromatic character than a phenyl group and possibly provides less stabilisation on the concerted transition state.

It is thought that polar solvents such as THF are known to decrease association between the cation and the anion in anionic oxy-Cope rearrangements and therefore increase the reaction rate.$^{58}$ This would account for the higher yields observed when THF was employed as the solvent for the substrates.
When the rearrangements were performed in toluene and hexanes there was a decrease in yields and e.e.'s. This would suggest that a less or non-polar solvent system disfavours a [3,3] sigmatropic rearrangement and encourages participation of the stepwise mechanism. In addition, a [1,3] shift could be taking place with a poor recombination of the molecule after fragmentation, resulting in a decreased yield. In the case of substrate (68c), yields and enantiomeric excess remained relatively high in the less polar solvents. This is thought to be due to the highly electron donating presence of the dimethylamino substituent on the phenyl group, which could favour the concerted process over the stepwise mechanism.

These results contrast Macdonald's findings, where it is suggested that the concerted process is favoured in non-polar solvent systems. It is however important to stress the differences between the substrates generated by Allin and those of Macdonald, in particular a phenylsulfanyl in the C4 position of the core diene of Macdonald's substrates. Interestingly it is known, in anionic oxy-Cope chemistry, that the presence of a sulfur-based substituent in this position actually promotes the dissociative heterolytic cleavage pathway due to the strong stabilising effect of the divalent sulfur.

In addition, computational studies by Haeffner, in collaboration with Houk and Paquette, reported that substituents at position C-4 or C-6 of 3-hydroxy-1,5-hexadienes affects the rate and mechanism of the anionic oxy-Cope rearrangement. A substitution of a methoxy group at either C-4 or C-6 position on a 3-hydroxy-1,5-hexadiene substrate, causes the bond length between C-3 and C-4 to increase and the bond length between C-1 and C-6 to decrease. In addition, the activation energy is increased leading to a concerted transition state. On the other hand a thiomethoxy substituent at either C-4 or C-6 causes dramatic changes in the rearrangement. The activation energy is lowered with bond length between C-3 and C-4 reduced and bond length between C-1 and C-6 increased leading to a dissociative pathway.

As part of the study, and to compare with Macdonald's results, the addition of a co-solvent was investigated. It was decided to employ DMPU as the co-solvent due to its versatility, ability to alter reactivity and stereoselectivity of organolithium reactions, and its proven effectiveness as a replacement for the highly carcinogenic HMPA. THF was chosen as the main solvent since it provided the more superior yields and e.e.'s in the...
initial screen of solvents. Three substrates were chosen for the investigation; (68a) which was the original favoured model, the furan derivative (68b) since this gave the lowest e.e. amongst the aromatic substituents and (68d) which gave the lowest e.e. of all. The results are presented in Table 12.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(68a)</td>
<td>6</td>
<td>84</td>
<td>29</td>
<td>86</td>
<td>50</td>
<td>89</td>
<td>69</td>
<td>84</td>
</tr>
<tr>
<td>(68b)</td>
<td>11</td>
<td>74</td>
<td>32</td>
<td>82</td>
<td>41</td>
<td>82</td>
<td>53</td>
<td>67</td>
</tr>
<tr>
<td>(68d)</td>
<td>8</td>
<td>72</td>
<td>10</td>
<td>82</td>
<td>18</td>
<td>85</td>
<td>35</td>
<td>44</td>
</tr>
</tbody>
</table>

**Table 12**

Although the addition of DMPU gave a lowering of product yield in all cases, this was accompanied by significant increase in the e.e. of the aldehydes. The optimum conditions were found to be an equimolar amount of co-solvent relative to the amount of n-BuLi. The increase in the enantioselectivity of the anionic amino-Cope rearrangement with DMPU acting as a co-solvent or co-ordinating additive supports the theory of a rate enhancement of the [3,3] concerted mechanism due to an increase of the donor properties of the nitrogen atom.²⁵

Concurrently, Allin and Essat carried out studies on the anionic amino-Cope rearrangement of substrate (70) under various conditions.⁵⁴ This substrate was analogous to that utilised by Button for similar studies in which the substrate (65) was derived from valinol. A prominent feature of both substrates it that they both contain a methyl group at the C-4 position and thus enables the differentiation between a [3,3] and [1,3] pathway. As well as altering the solvent system, the use of additives was also examined. The results of the investigation is summarised in Table 13.
(i) n-BuLi (2.5 eq), solvent/additive (10 eq), -78 °C-RT, then Δ; (ii) H₂O; (iii) SiO₂

**Scheme 39**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Additive</th>
<th>[3,3]/[1,3]</th>
<th>Cis/Trans [3,3]</th>
<th>Syn/Anti [1,3]</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexanes</td>
<td>-</td>
<td>1:4</td>
<td>1:1.5</td>
<td>1.5:1</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>TMEDA</td>
<td>1.4:1</td>
<td>1:1</td>
<td>1:2.8</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Sparteine</td>
<td>1.8:1</td>
<td>1:1.6</td>
<td>1:2</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>4:1</td>
<td>2.5:1</td>
<td>1:1</td>
<td>37</td>
</tr>
<tr>
<td>Toluene</td>
<td>-</td>
<td>1:2</td>
<td>1:1</td>
<td>1:2</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>TMEDA</td>
<td>1:4</td>
<td>1:1</td>
<td>1:5</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Sparteine</td>
<td>1:3</td>
<td>1.4:1</td>
<td>1:3</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>3:1</td>
<td>4:1</td>
<td>1:1</td>
<td>47</td>
</tr>
<tr>
<td>Ether</td>
<td>-</td>
<td>1.2:1</td>
<td>1:1.2</td>
<td>1:1.4</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>TMEDA</td>
<td>1.2:1</td>
<td>1.1:1</td>
<td>1:2.4</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Sparteine</td>
<td>1.2:1</td>
<td>1:1.6</td>
<td>1:3</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>5.7:1</td>
<td>5.4:1</td>
<td>1:1.2</td>
<td>45</td>
</tr>
<tr>
<td>THF</td>
<td>2:1</td>
<td>5:1</td>
<td>1:1</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>TMEDA</td>
<td>2:1</td>
<td>5:1</td>
<td>1:1.4</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Sparteine</td>
<td>2.5:1</td>
<td>5.5:1</td>
<td>1:1.5</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>DMPU</td>
<td>9.3:1</td>
<td>5.3:1</td>
<td>2.7:1</td>
<td>49</td>
</tr>
</tbody>
</table>

**Table 13**

Introduction - 45 -
The products (66) and (67) were obtained as an inseparable mixture of geometric and diastereoisomeric isomers. As it can be seen from Table 13, polar solvents such as THF and diethyl ether favoured the [3,3] product (66), whilst non-polar solvents preferred the [1,3] product (67). Addition of TMEDA and sparteine to toluene increased the selectivity towards the [1,3] product but lessened the selectivity, and in fact slightly favoured selectivity towards the [3,3] product in hexanes. TMEDA and sparteine did not offer much effect on the polar solvents. However DMPU had significant directing effects on both polar and non-polar solvents during the course of the reaction. The [3,3] product predominated with DMPU in both polar and non-polar solvents, and increased the selectivity of the cis isomer in most cases. Although overall there was very little variation in the syn/anti ratio, TMEDA and sparteine had the greatest effect in any deviation.

The solvent of choice for the preparation of the [3,3] product from diene (70) was DMPU in THF, favouring the [3,3] product in the ratio of 9:1. Hexanes or toluene in TMEDA favoured the [1,3] product in a 4:1 ratio. In contrast, Macdonald\textsuperscript{52} revealed that TMEDA in hexanes favoured the [3,3] product in the ratio of 10:1 and THF in HMPA favoured the [1,3] product in a 5:1 ratio.

Again the disparity between the results and those that of Macdonald lie in the difference in the structure of 3-amino-1,5-diene substrate as mentioned previously. It has been postulated that a 1-thioalkylallyl anion, generated on cleavage of a Macdonald-type substrate is increasingly stabilised in polar solvents.\textsuperscript{59} However, in non-polar solvents, the weakly solvated metal cations will bind more strongly to the oxy anion favouring the formation of the concerted rearrangement product rather than dissociative product. This hypothesis endorses Macdonald’s findings. To determine whether this was applicable to the Allin-type substrate, it was decided to prepare a 3-amino-1,5-hexadiene substrate incorporating a PhS substituent.

The 4-phenylsulfanyl-3-amino-1,5-hexadienes (71\textsubscript{a} & 71\textsubscript{b}) were generated in a combined yield of 60% by applying a method developed by Yamamoto,\textsuperscript{66} who reported a stereoselective synthesis of olefinic \(\beta\)-hydroxy sulfides from the reaction of carbonyl compounds with [(alkylthio)allyl]titanium reagents, to an \(\alpha,\beta\)-unsaturated imine (58\textsubscript{e}) (Scheme 40).

Introduction
Dienes (71a & 71b) were isolated and successfully rearranged individually in three different solvent systems to yield mixtures of products generated via both [3,3] and [1,3] pathways as shown in Scheme 41. The systems used were: control conditions using THF alone without any additives, the optimum conditions for formation of the [3,3] product (THF and DMPU) and Macdonald's best conditions for the [3,3] product (hexanes and TMEDA).

Scheme 41 shows that the [3,3] and [1,3] product profile for substrate (71a) is the opposite for substrate (72b) due to the positioning of the phenylsulfanyl substituent.
The outcome of the study was in agreement with work carried out by Macdonald.52 The rearrangement of diene (71a) in a non-polar solvent favours the formation of the [3,3] product to a greater extent than in polar solvent. However, the preference towards the [3,3] product in the non-polar solvent (ratio of 4:1) is not as prominent as in the case with Macdonald’s substrate (10:1 in favour). The rearrangement in polar solvent with DMPU was surprisingly unsuccessful as it was thought that under these conditions, the formation of the [1,3] product would be most predominant.

The effects of the thioalkyl substituent at either C-4 or C-6 of 3-hydroxy-1,5-diene during the anionic oxy-Cope rearrangement are thought to be essentially the same, i.e. both substrates having preference for the dissociative pathway.59 The [3,3]/[1,3] ratio between the products observed for the rearrangement of diene (71a) with the phenylsulfanyl substituent at C-4 and diene (71b) with the phenylsulfanyl substituent at C-6 was very different, although they both followed the same pattern. Diene (71a) predominately favoured the [3,3] product in both polar and non-polar solvent, however, the ratio of the [3,3] product increased in non-polar solvent. On the other hand diene (71b) rearranged to give predominately the [1,3] product in polar solvent and addition of the DMPU further encouraged the reaction towards the [1,3] product.

It was expected that the [3,3] product would be most prominent in the non-polar solvent but unfortunately, this was not the case. However a decrease in [1,3] product selectivity was observed, generating both the [3,3] and [1,3] products in equal ratio.
The results gathered together by Allin, Essat and Horro Pita sustain the argument by others,\textsuperscript{67} that the pathway chosen by both the anionic amino-Cope and oxy-Cope rearrangement is strongly influenced by many factors including the type and position of substituents as well as the conditions under which the rearrangement is performed.

It has been determined that the nature of the substituent at C-1 may influence the stabilising capacity of a concerted transition state and hence affect reaction enantioselectivity. The findings also demonstrate that the anionic amino-Cope rearrangement of 3-amino-1,5-hexadiene substrates with substituents at either C-4 or C-6 does not proceed solely by a concerted [3,3] sigmatropic rearrangement. We are unable to rule out the possibility of a competing concerted [1,3] rearrangement nor are we able to distinguish the proposed concerted [1,3] rearrangement from a dissociative pathway. Nevertheless, it has been discovered that by careful choice of reaction conditions, the pathway of the anionic amino-Cope rearrangement can be controlled, leading to formation of [3,3] products almost exclusively.

\subsection*{1.4.8. Synthetic Applications of the Anionic Amino-Cope Rearrangement}

Through studies within the group, we have been able to demonstrate the synthetic utility of the asymmetric anionic amino-Cope rearrangement and highlight its potential for future application in natural product synthesis. Asymmetric synthetic routes to tetrahydropyran and lactone sub-units are of considerable interest since these heterocyclic components are found in many biologically active molecules and natural products.\textsuperscript{68}

The novel route developed delivers functionalised disubstituted tetrahydropyrans and lactones in high enantiomeric excess from readily available precursors. The key step in the synthetic protocol is the introduction of asymmetry by the recently developed asymmetric anionic amino-Cope methodology. To further demonstrate the potential of this chemistry the synthesis of a simple piperidine target from a product of an amino-Cope rearrangement has been achieved.
1.4.8.1. Tetrahydropyrans

One useful method for the formation of oxygen heterocycles involves the electrophile-induced cyclisation of an unsaturated alcohol precursor.\textsuperscript{69} Greeves recently published work on the tandem [2,3] Wittig/anionic oxy-Cope rearrangement, which leads to the synthesis of aldehydes, similar to those obtained after the amino-Cope rearrangement.\textsuperscript{70} Examples of the utility of these aldehydes are also reported.\textsuperscript{71} Following this methodology, Allin and Baird, by applying the aldehyde products of the amino-Cope rearrangement, have developed the synthesis of simple non-racemic 2,4-disubstitued tetrahydropyrans.\textsuperscript{72}

Anionic amino-Cope rearrangement product (55) was reduced by sodium borohydride to give alcohol (73) in good yield, whilst retaining the same level of enantiomeric excess as the aldehyde precursor. Iodine-induced electrophilic cyclisation was performed on alcohol (73) to generate the target iodo-THP (74) in a diastereoselectivity of 4:1 in favour of the cis-diastereoisomer (74a). The major diastereoisomer was shown to have lost no stereochemical integrity during cyclisation and had an enantiomeric excess of 92% (Scheme 42).
The cyclisation methodology was attempted once more to incorporate a phenylselenyl group. In this case however, a 1:1 diastereoisomeric ratio was observed for the cyclisation product (75). Analysis of the separated diastereoisomers showed that tetrahydropyran (75a) had an e.e. of 92%, again in good agreement with that of the starting alcohol (73).

A final class of tetrahydropyran was prepared through epoxidation of the double bond of (73) followed by treatment with catalytic CSA. The intermediate epoxides (2:1 mixture of (77a) and (77b)) were then treated with CSA (0.1 eq.) to afford the final product (77b).

Scheme 42
of diastereoisomers (76a & 76b)) were not separated, but directly cyclised with CSA to yield the target tetrahydropyran (77) as a 2:1 mixture of diastereoisomers.

1.4.8.2. δ-Lactones

Based on the success of the approach to tetrahydropyrans, a similar electrophile-induced cyclisation route to access δ-lactones was investigated, as described by others. Allin and Essat demonstrated the synthesis of enantiomerically enriched δ-lactones (79) and (80), as shown in Scheme 43, using the amino-Cope rearrangement as a key step. This synthesis was based on work carried out by Lutz and co-workers, who synthesised lactones from chiral amides.

![Scheme 43](attachment:image)

Carboxylic acid (78) was prepared by sodium chlorite oxidation from aldehyde (55). Iodine-induced cyclisation at low temperature gave the iodo-lactone (79) in a high 13:1 diastereoselectivity in favour of the cis-diastereoisomer (79a). Iodo-lactone (79a) was...
shown to have an e.e. of 86%, confirming minimal loss of stereochemical information during derivatisation and subsequent cyclisation of aldehyde (55).

As with the synthesis of the tetrahydropyran (75), cyclisation of acid (78) by employing phenylselenyl chloride as the source of electrophile was achieved to deliver the δ-lactone product (80) in a 3:1 diastereoisomeric ratio, again in favour of the cis-isomer (80a).

1.4.8.3. Piperidines

Having achieved the asymmetric synthesis of tetrahydropyran and lactone products the group’s attention turned to piperidine targets, and so were required to achieve a successful cyclisation of an aminated derivative of aldehyde (55). Secondary amine (81) was prepared by reductive amination of aldehyde (55) with benzylamine. Despite repeated attempts to access piperidine targets through application of known electrophile-induced cyclisation methods\(^7^6\) of the secondary amine derivative (81), it was evident that a direct cyclisation route would be ineffective.

Finally an oxidative cleavage-cyclisation route, described by Xue,\(^7^7\) was employed to furnish the 4-phenyl piperidine derivative (85).\(^5^5,\, 7^4\) Scheme 44 highlights the synthetic route in which protection of the secondary amine (81) as its Cbz-analogue (82), and treatment under ozonolysis conditions yielded the amino-aldehyde (83). One-pot removal of both protecting groups promoted in situ cyclisation of the primary amine product to generate the piperidine derivative (84) that was initially isolated as its TFA salt but then used as crude to access the Cbz-protected piperidine target (85).
Although this method generates an achiral piperidine in this case (due to the centre of symmetry in \(85\)), the importance of having discovered a suitable method to access the important piperidine nucleus from simple products of the amino-Cope rearrangement should not be overlooked.

In summary, it has been demonstrated that the preparation of various substituted tetrahydropyran, lactone and piperidine targets, with high enantiomeric excess in the asymmetric series, represents the first synthetic applications of the asymmetric anionic amino-Cope rearrangement.
From these early studies our group has demonstrated that the amino-Cope rearrangement could become a significant addition to asymmetric chemistry. Studies are continuing in realising the potential stereoselective synthesis of highly functionalised products such as (44) in Figure 11.

![Figure 11]
Chapter 2

Results & Discussion

Development of the Amino-Cope Rearrangement
2.1. Introduction

As described in Section 1.4., the development of the amino-Cope rearrangement has advanced a great deal in recent years, allowing it to become a useful tool in synthetic chemistry. Its application in the asymmetric synthesis of chiral heterocycles has highlighted its promising potential as an effective alternative to routes towards important chiral building blocks.

We wished to expand the scope of the methodology further, by investigating the stereocontrolled introduction of electrophilic species to the α-position of the aldehyde. If successful, this would constitute the formation of an aldehyde (88) with controlled α,β-asymmetric substitution (Scheme 45).

For this synthetic step to be realised, the imine anion intermediate (87), formed on amino-Cope rearrangement of a substrate, would be quenched with a range of suitable electrophiles. Although a tandem amino-Cope rearrangement/enamine derivatisation has been achieved previously by Allin and Button, it has not yet been attempted on the anionic variant of the rearrangement.
Organic chemists are well acquainted with the notion of asymmetric synthesis, which is traditionally defined as a process of forming an optically active compound through the reaction of a homochiral or enantiomerically pure substrate with an achiral reagent, or vice-versa. Double asymmetric synthesis concerns the interaction of two homochiral reactants; a substrate and a reagent. The objective of double asymmetric synthesis is not simply to prepare optically active compounds but to achieve a high diastereoselection as well. Although we aim to perform such a double asymmetric synthesis, our route differs to the classical defined practice by the fact that it is a tandem process, i.e. generation of a single stereogenic centre followed by controlled introduction of an achiral reagent to form the next asymmetric centre.

The following sections of this chapter discuss the results obtained in our studies towards the asymmetric tandem anionic amino-Cope rearrangement/imine anion derivatisation.

2.2. Preparation of Aminoalcohol Derived Diene Substrate

Our group has demonstrated that by employing enantiomerically pure β-aminoalcohols as auxiliaries in a typical diene substrate, high levels of asymmetric induction can be obtained. The diene substrate (86) in Scheme 45 has been, to date, the most effective in terms of chirality transfer yielding the aldehyde product (88) (E = H) with up to 94% e.e. on rearrangement, as previously discussed in Section 1.4.6.

With this in mind, work was initiated on the synthesis of diene substrate (86). The synthesis followed a protocol derived by a past group member, Dr. Robert Baird, and employed (S)-phenylalaninol (90) as the β-aminoalcohol component of the substrate. (S)-Phenylalaninol was synthesised by reduction of its corresponding amino acid, (S)-phenylalanine (89), following a procedure by Giannis. The method uses lithium borohydride/chlorotrimethylsilane in THF, where a borane-THF complex is proposed to be generated and acts as the reducing agent (Scheme 46).

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The product was obtained in near quantitative yield and could be used without further purification.

Imine (91) was prepared by a condensation between (S)-phenylalaninol (90) and an equimolar amount of trans-cinnamaldehyde in DCM as shown in Scheme 47. Anhydrous magnesium sulfate was added to remove the water formed and lead the reaction to completion. The product was obtained in 95% yield and could be used without further purification. Imine (91) afforded great stabilisation due to its conjugation with the aryl unit and allowed it to be handled without degradation during subsequent reactions.

It has been observed by others that similar imines derived from β-aminoalcohols may exist, in solution, as a mixture of imino alcohol (92) and oxazolidine (93) tautomers in a process known as ring-chain tautomerism. However in our hands, imines generated under essentially mild conditions, were observed only as the open chain tautomer (92) by 400 MHz 1H NMR in deuterated chloroform or DMSO.
Following a comprehensive literature search and initial studies, Allin and Button found that the most suitable method of introducing an allyl group for the preparation of the desired 3-amino-1,5-diene substrates was by the addition of an allyl Grignard reagent. The addition of organometallic species to imines derived from non-racemic β-aminoalcohols and their derivatives is known to be highly diastereoselective and has been proposed by others to proceed through a chelated transition state.

The absolute stereochemistry of the chiral auxiliary controls the stereochemical induction during the Grignard addition, allowing for accurate predictions to be made about the relative stereochemistry of the diene product. The high degree of stereocontrol in this reaction may be attributed to a highly ordered transition state resulting from chelation of the alcohol and imino nitrogen to the magnesium ion, giving a conformationally rigid structure. A further equivalent of allylmagnesium bromide is then encouraged to attack from the least hindered face of the C=N double bond (Scheme 48).
Imine (91) was dissolved in an anhydrous mixture of freshly distilled toluene/diethyl ether (4:1) and stirred with magnesium turnings and a catalytic amount of iodine under an inert atmosphere. The magnesium turnings were activated by washing with dilute HCl, water and acetone and left to dry in a preheated oven. Allyl bromide was added to the stirring suspension. This method of generating the Grignard reagent in situ is often referred to as a Barbier type reaction and its application was recently reported by Hou. The choice of this methodology over the conventional separate formation of the Grignard reagent was to avoid handling of such organometallic species, due to their toxicity in preparation and transfer. The diene substrate (86) was obtained in good yield and diastereoselectivity following recrystallisation.

Interestingly, Pridgen and Koga observed that the addition of Grignard reagents to β-aminoalcohol derived α,β-unsaturated imines results in a 1,4-addition. In contrast, organolithium, cerium and cuprate reagents have a strong preference to attack at the hard aminal/imino carbon, leading to 1,2-addition products.
However, our results are inconsistent with these findings, as no conjugate addition product was observed when performing the Grignard addition. We believe that the conflict in our results and those of Pridgen and Koga lie in the nature of the Grignard reagent. It was postulated that in the particular case of allyl Grignard, a unique six-membered transition state (94) may be in effect, with the magnesium coordinated with the imine nitrogen and allowing for addition in a 1,2-fashion. A 1,4-addition by similar means would require the transformation to proceed via an eight-membered transition state (95) as shown in Scheme 49.

![Scheme 49](image-url)
2.3. Anionic Amino-Cope Rearrangement/Hydrolysis of Aminoalcohol Derived Diene Substrate

Conditions for the anionic amino-Cope rearrangement of substrates containing β-aminoalcohol had previously been optimised by Allin, Button and Baird. A detailed survey was carried out using various strong bases, solvents and temperatures. The majority of successful rearrangements were observed when n-BuLi was used as the base. In contrast, the use of sodium hydride, potassium hydride, LDA, LHMDS, KHMDS and NHMDS were shown to be ineffective, with recovery of starting material a common feature. It was found that optimal conditions for the rearrangement for substrates such as (86) were to employ an excess of 2 equivalents of n-BuLi in anhydrous THF. A minimum of 2 equivalents of base were necessary since the first equivalent would deprotonate the hydroxy functionality before deprotonation of the secondary amine occurred.

Rearrangement of substrate (86) was effected by dissolving the substrate in anhydrous THF and cooling to −78 °C before dropwise addition of n-BuLi and reflux of the resulting mixture. Hydrolysis afforded the rearrangement product as the oxazolidine (96) resulting from the ring closure of the hydroxy group onto the intermediate imine anion (87). Purification of the crude product by flash column chromatography on silica hydrolysed the heterocycle allowing isolation of the aldehyde (55) in 44% yield (Scheme 50).
Measurement of enantiomeric excess was achieved by following a procedure described by Agami,\textsuperscript{46} which makes use of the stereoselective condensation of naturally occurring (1R, 2S)-(-)-ephedrine with aldehyde (55), leading to oxazolidines (97a-b) as shown in Scheme 51. Very mild conditions (DCM, molecular sieves, room temperature) are required for the reaction to proceed in good yield.

Analysis of $^1$H NMR spectra and by calculating the difference in integration of the peaks corresponding to both diastereoisomers provided the diastereoisomeric excess, which is directly related to the enantiomeric excess of the aldehyde. After calculation, the (R)-enantiomer of the aldehyde was determined to be the major enantiomer with an e.e. of 83%.
The employment of reflux to effect anionic amino-Cope rearrangement of the phenylalaninol derived diene substrate was briefly investigated. The method was developed by a previous group member, Dr. Robert Baird, and has been used since. It is questionable why it is necessary to employ reflux to take the reaction to completion as it is thought the charge-acceleration of the anion formed on deprotonation should be sufficient. Indeed, when using valinol and O-Bn valinol derived diene substrates, rearrangement proceeds at low temperatures.\cite{88}

Anionic amino-Cope rearrangement was carried out on the phenylalaninol derived diene substrate (86). The reaction was allowed to warm to room temperature overnight after deprotonation at $-78^\circ$C before being hydrolysed. $^1$H NMR analysis of the crude product showed that complete rearrangement had not proceeded, with only a trace amount of product observed and mostly starting material recovered. It is evident that reflux is required to afford complete rearrangement for the phenylalaninol derived diene substrate (86).
2.4. Tandem Anionic Amino-Cope Rearrangement/Imine Anion Derivatisation of Aminoalcohol Derived Diene Substrate

Studies were then directed towards the stereocontrolled introduction of electrophilic species to the \( \alpha \)-position of the aldehyde. Imine anions, also known as metallated enamines\(^9^9\) and metallated Schiff bases,\(^9^0\) are known to exhibit a high ratio of alkylation rate relative to proton transfer and therefore polyalkylation is minimal. Also these anions show an intrinsic low reactivity at the nitrogen atom, which can be rationalised as a steric shielding of nitrogen by the metal and its solvent shell.\(^9^1\)

Unless imine anions are generated by forms of rearrangement, as in our case, they are commonly prepared by typical imine formation followed by deprotonation of the most acidic proton on the imino carbon. Conversion of imines to lithiated anions appears to be universally accomplished by lithium diethyl or diisopropylamide as base at temperatures ranging from \(-78^\circ C\) to \(10^\circ C\).\(^9^2\) Formation of magnesium salts are achieved with either ethyl or isoproylmagnesium bromide.\(^9^3\) Magnesium as a counter ion has little to recommend it since higher reactivity of the imine anion requires elevated temperatures. On the other hand, lithiated imine anions are easily prepared and are fully reactive at \(-78^\circ C\).\(^9^4\)

Although imine anions are sometimes depicted as C-metallated, perhaps to emphasize the site of reactivity,\(^9^5\) most authors are inclined to draw them as N-metallated, which may represent a more preferable arrangement for the relatively hard lithium cation.\(^9^6\) A more subtle aspect of the structure of imine anions is the question of the hybridization at nitrogen, whether \(sp^2\) as in enamines with lone-pair-\(\pi\)-system overlap (98),\(^9^7\) or \(sp^3\) with lithium-nitrogen \(\sigma\)-pair-\(\pi\)-system overlap (99)\(^9^8\) as shown in Figure 13. The question is of importance as it relates to asymmetric induction in the derivatisation of chiral imines, but there is as yet no definitive experimental information available.
The first electrophile to be used in this investigation was a methyl group. The anionic amino-Cope rearrangement was carried out as previously described, again using the 3-amino-1,5-diene substrate (86). The imine anion intermediate generated on rearrangement was quenched with methyl iodide and stirred for 2 hours before being hydrolysed (Scheme 52).

The crude product, again an oxazolidine, was then subjected to flash column chromatography on silica. From the $^1$H NMR spectra of the purified product, two peaks corresponding to the methyl group having an approximate integration ratio of 1.5:1, indicated that a mixture of the major diastereoisomers of the aldehyde (100a) had formed in the reaction; these being the anti- and syn- isomers (Figure 14). However, the majority of the reaction product was shown to be unalkylated aldehyde (55). The mixture of aldehydes was inseparable by further flash column chromatography, which hindered the determination of the stereochemistry of aldehyde (100a) and hence we were unable to establish which stereoisomer corresponded to the major aldehyde product.
Further attempts were made at this reaction by applying different conditions to the rearrangement. The variables altered were the equivalents of methyl iodide used, the employment of reflux and the temperature at which the imine anion intermediate was quenched. The results are highlighted in Table 15.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents Mel</th>
<th>Reflux</th>
<th>Temperature Mel quench</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.6</td>
<td>Yes</td>
<td>RT</td>
<td>24% yield, mixture of diastereoisomers syn and anti ((100a)) (1.5:1 ratio) and unalkylated aldehyde ((55))</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>No</td>
<td>RT</td>
<td>Traces of target aldehyde, very impure</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>No</td>
<td>-78 °C</td>
<td>No reaction - Starting material obtained</td>
</tr>
<tr>
<td>4</td>
<td>2.6</td>
<td>Yes</td>
<td>RT</td>
<td>25% yield, mixture of diastereoisomers syn and anti ((100a)) (1.5:1 ratio) and unalkylated aldehyde ((55))</td>
</tr>
</tbody>
</table>

Table 15

It has been previously observed that a matched/mis-matched diastereoisomer effect may be involved on rearrangement.\(^{45}\) To verify the existence of this effect, the conditions for the reaction for Entry 4 were identical to those for Entry 1 except that the 3-amino-1,5-diene substrate was derived from the opposite enantiomer of the starting amino acid as shown in Scheme 53. We believed that a variation in the ratio of the relative
The stereochemistry of the aldehyde product (100a) would discount the theory of a matched/mis-matched diastereoisomer effect. As expected, this was shown not to be the case as no exchange in major isomer of aldehyde (100a) was observed with a similar ratio obtained as before.

\[
\begin{align*}
\text{Scheme 53}
\end{align*}
\]

The generation of the unalkylated aldehyde (55) as the major product may provide evidence of competing \(O\)-alkylation. Although this was a feasible possibility, the large excess of electrophile was thought to have compensated for this eventuality, leaving only the problem of polyalkylation. However, in all cases there was no evidence of this occurring.

\[
\begin{align*}
\text{Scheme 54}
\end{align*}
\]
The tandem anionic amino-Cope rearrangement/imine anion alkylation was carried out on the phenylalaninol derived diene substrate (86) using benzyl bromide as the electrophile as illustrated in Scheme 54. The product (100d) was obtained as a 2:1 mixture of diastereoisomers in 44% yield but as with the methyl derivatised product (100a), we were unable to assign the stereochemistry to the major diastereoisomer. There was no evidence of unalkylated aldehyde (55).

2.5. Preparation of O-Bn Aminoalcohol Derived Diene Substrate

Our interest was turned towards the preparation of the O-benzylated diene substrate (104), which we believed would lead to the target aldehyde (55) in a cleaner and better yielding reaction following anionic amino-Cope rearrangement (Scheme 55). By protecting the alcohol moiety, no deprotonation can occur on the oxygen atom therefore preventing the formation of an oxazolidine intermediate. This would in addition benefit the imine anion derivatisation step, as the competing O-derivatisation would be nullified. Furthermore, the need for an extra equivalent of base in the anionic amino-Cope rearrangement would be eliminated.

![Scheme 55](image)

Direct O-benzylation was attempted on the 3-amino-1,5-diene substrate (86) using sodium hydride and benzyl chloride. However, all attempts proved unsuccessful, with competing N-benzylation a major hindrance. Our failures to develop a reliable method for O-benzylation of diene (86) lead us to attempt O-benzylation on its precursor, imine (91).

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O-Benzylaion of imine (91) was attempted by employing 1.1 equivalents of sodium hydride and 1.1 equivalents of benzyl chloride (Scheme 56). $^1$H NMR analysis of the crude product appeared to show that the benzylation was successful. However, due to the instability of the imine during purification, this route was deemed not practical.

Concurrently, we set about applying a procedure of selectively $O$-benzylating valinol,\(^{88}\) to our $\beta$-aminoalcohol, (S)-phenylalaninol (90) as shown in Scheme 57. A former postdoctoral researcher, Dr. Roger Lins, developed this process by modification of the method described by Hu and Cassady.\(^{99}\) $O$-Benzyalted diene (104) would then be prepared from the $O$-Bn aminoalcohol (106) by the previously reported method of the formation of unprotected diene (86). Lins’ method required reflux for 30 minutes after the addition of the aminoalcohol and seemed essential to affect deprotonation. The use of benzyl chloride was also important as the bromide derivative reduced selectivity, forming $N$-Bn by-products. Analysis of the product confirmed that the benzylation was successful in our hands and was obtained in good yield following recrystallisation.

Formation of imine (105) was not as clean as the corresponding unprotected imine (91) and yielded a tarry solid. This was thought to be due to an increase in steric hindrance, which impeded the normally rapid condensation of the aminoalcohol and trans-
cinnamaldehyde. On recalling the instability of imines during purification, it was decided that the imine was adequate to be used without purification.

The Grignard reaction on the crude O-Bn imine (105) was performed under Barbier conditions as described previously, producing the desired O-Bn 3-amino-1,5-diene (104) in moderate yield as a single diastereoisomer after flash column chromatography.

\[ \text{Scheme 58} \]

2.6. Anionic Amino-Cope Rearrangement/Hydrolysis of O-Bn Aminoalcohol Derived Diene Substrate

Rearrangement of the O-Bn diene substrate (104) was achieved using the method described above with the exception of a reduced amount of base being employed. \(^1\)H NMR of the crude product showed that the typical oxazolidine had not formed. The aldehyde (55) was produced in relatively low yield following flash column chromatography (Scheme 59). Measurement of enantiomeric excess using the method described by Agami\(^{46}\) was shown to be 26%.
The next investigation was to perform a tandem anionic amino-Cope rearrangement/imine anion alkylation with the O-Bn 3-amino-1,5-diene substrate as described in Scheme 60. The intermediate generated on rearrangement was quenched with methyl iodide and hydrolysed. A 1:1 mixture of diastereoisomers of the alkylated aldehyde (100a) was isolated in 31% yield following flash column chromatography. As expected, it was also noted that there was only a trace amount of the unalkylated aldehyde (55) observed. This was in contrast to the product obtained under the same conditions using the corresponding unprotected diene substrate (86), where the unalkylated aldehyde (55) was the major product.

The results showed that O-benzylation of the aminoalcohol substituted diene substrate had significance in the improved formation of the alkylated product by preventing the O-alkylation of the dianion intermediate and hence favouring the imine anion alkylation. Although O-benzylation of the aminoalcohol substituted diene substrate leads to better conversion to the alkylated product, it has a disadvantage in that stereocontrol of the β-substituent is compromised as shown by the low enantioselectivity of the rearrangement/hydrolysis of substrate (104).
Studies previously carried out by Baird\textsuperscript{100} and Lins\textsuperscript{88} on a similar substrate (O-Bn valinol derived diene) have shown that protection of the hydroxy group in the β-aminoalcohol auxiliary can lead to the aldehyde (55) in much lower enantiomeric excess compared to the analogous unprotected species. However, it was found that the enantioselectivity could be increased to levels similar to those obtained from the unprotected species by carefully controlling the temperature after the addition of \( n \)-BuLi. Very slow warming is required until \(-30^\circ C\) at which point the reaction could be warmed to room temperature and quenched.

With this in mind, anionic amino-Cope rearrangement/imine anion hydrolysis was carried out on the O-Bn phenylalaninol derived diene substrate (104). The reaction was allowed to warm to room temperature overnight after deprotonation at \(-78^\circ C\) before being hydrolysed. \(^1\)H NMR analysis of the crude product showed the rearrangement had gone to completion and was subjected to flash column chromatography. The aldehyde product was obtained in moderate yield but disappointingly low enantiomeric excess of 38%. This value was an improvement on 26%, which was obtained when reflux was employed.

It was decided that tandem anionic amino-Cope rearrangement/imine anion derivatisation be tried out on the O-Bn valinol derived diene substrate (110) due to its previously reported high enantioselectivity. Work was initiated on the synthesis of the O-Bn valinol derived diene substrate, which followed the same protocol that was used in the synthesis of the O-Bn phenylalaninol derived diene substrate, using (S)-valinol (107) as the starting β-aminoalcohol (Scheme 61).
The O-Bn valinol derived diene substrate (110) was synthesised in an overall yield of 55%. Rearrangement/imine anion hydrolysis was performed as described by Lins\textsuperscript{88} (Scheme 62). Once the diene substrate had been deprotonated at \(-78^\circ\text{C}\), the reaction was allowed to slowly warm to room temperature over 1 hour and finally stirred at room temperature for 90 minutes before being quenched. Aldehyde (55) was formed in 32% yield following flash column chromatography, with enantiomeric excess of the aldehyde shown to be 74%. Although lower than the e.e. obtained by Lins (82%), the enantioselectivity achieved was much greater than when using the O-Bn phenylalaninol derived diene substrate (38%).
The tandem anionic amino-Cope rearrangement/imine anion derivatisation was carried out on the O-Bn valinol derived diene substrate (110). The reaction was repeated as described for the rearrangement/imine anion hydrolysis with the exception of re-cooling the reaction to -78 °C, quenching the reaction with methyl iodide and allowing the reaction to warm to room temperature overnight before hydrolysis as shown in Scheme 63.

\[
\begin{align*}
\text{OBn} & \quad \text{~YPh} \\
\text{(110)} & \quad \text{i) n-BuLi} \\
& \quad \text{ii) Mel} \\
& \quad \text{iii) SiO}_2 \\
\rightarrow & \quad \text{52%}
\end{align*}
\]

Scheme 63

\[\text{H Me} \]
\[\text{(100a)}\]

\(^1^H\) NMR analysis of the crude product showed that all of the starting material had been converted, however, there was minimal evidence of aldehyde. The crude product was subjected to flash column chromatography, which yielded a 1:1 mixture of diastereoisomers of the alkylated aldehyde (100a) in 52% yield. Again, as with the protected phenylalaninol diene (104), there was only trace amount of aldehyde (55) observed. As the final hydrolysis step of the reaction did not yield the aldehyde directly, the hydrolysed crude product must have been in the form of an imine or enamine. The formation of an oxazolidine ring could be ruled out since the hydroxy group of the aminoalcohol auxiliary would be unable to ring-close onto the intermediate imine anion due to its protection.

The tandem anionic amino-Cope rearrangement/imine anion derivatisation was repeated, this time applying low temperature acidic hydrolysis. It was thought that this method would provide a true representation of the diastereoselectivity of the reaction rather than obtaining a ratio after flash column chromatography. \(^1^H\) NMR analysis of the crude product showed evidence of the alkylated aldehyde. The aldehyde was however unable to be isolated following flash column chromatography, possibly due to decomposition.
The rearrangement was again repeated, with the exception of quenching the reaction with glacial acetic acid at $-78\,^\circ C$ one hour after adding the methyl electrophile. The reaction was allowed to slowly warm to room temperature overnight. $^1$H NMR analysis of the crude product showed that only a minimal amount of the unalkylated aldehyde (55) had formed. There was no evidence of the alkylated aldehyde (100a) and hence purification was not carried out.

Since acid hydrolysis of the reaction was not yielding the alkylated aldehyde in noticeable quantities, work was started on the tandem anionic amino-Cope rearrangement/imine anion derivatisation using other electrophiles. The electrophiles used introduced ethyl, allyl, benzyl and $i$-propyl substituents. The same conditions used for the methyl electrophile were employed for the new electrophiles. The results obtained are summarised in Table 16.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>$E^+$</th>
<th>Yield</th>
<th>Ratio of diastereoisomers</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100a</td>
<td>Me</td>
<td>52</td>
<td>1:1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>100b</td>
<td>Et</td>
<td>67</td>
<td>1:1</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>100c</td>
<td>Allyl</td>
<td>49</td>
<td>1.5:1</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>100d</td>
<td>PhCH$_2$</td>
<td>-</td>
<td>-</td>
<td>Evidence of dialkylation</td>
</tr>
<tr>
<td>5</td>
<td>100d</td>
<td>PhCH$_2$ (1.0 eq)</td>
<td>62</td>
<td>2:1</td>
<td>Complex $^1$H NMR spectra</td>
</tr>
<tr>
<td>6</td>
<td>100e</td>
<td>$i$-Pr</td>
<td>-</td>
<td>-</td>
<td>Majority unalkylated product (55)</td>
</tr>
</tbody>
</table>

$^a$ 1.5 eq. used unless otherwise stated. $^b$ ratio obtained after flash column chromatography

Table 16

Results & Discussion - 77 -
As can be seen in Table 16, an increase in size of the electrophile has a corresponding increase in product diastereoselectivity. This was expected due to the steric hindrance exerted by the phenyl substituent, which is alpha- to the incoming electrophile and also by the protected β-aminoalcohol auxiliary, which may be enhanced by possible intramolecular chelation of the ether oxygen and nitrogen with the metal counter ion.

When benzyl bromide was used as the electrophile, $^1$H NMR analysis of the purified product suggested dialkylation had taken place (Entry 4). This was possible due to the high reactivity of benzyl bromide. The reaction was successful when repeated using only 1 equivalents of the benzyl bromide (Entry 5). The product following hydrolysis and flash column chromatography when using i-propyl iodide as the electrophile consisted mainly of the unalkylated product, which suggests the extent of steric hindrance may be too great for the incoming large i-propyl electrophile.

2.7. Derivatisation of Aldehyde Generated on Amino-Cope Rearrangement

It is thought that the phenyl substituent alpha- to the incoming electrophile contributes to the diastereoselectivity of the tandem anionic amino-Cope rearrangement/imine anion alkylation. An attempt was made at alkylating the α-position of aldehyde (55) by derivatising its enolate, which was to be generated on deprotonation using LDA. The reasoning behind this was to investigate the degree of diastereoselectivity exerted by the β-substituent of the aldehyde compared to that exerted during alkylation of the imine.
anion, where the effect of the β-aminoalcohol auxiliary may also be playing a role in directing the incoming electrophile.

$^1$H NMR analysis of the product obtained on flash column chromatography showed no sign of either starting or product aldehyde. It is known that enolates of aldehydes are unstable and have a tendency to self condense or undergo rapid aldol reaction. This is by and large due to the high reactivity of the aldehyde carbonyl. A way to overcome this problem is to convert the aldehyde to a less reactive system such as an imine or enamine.

Enamine alkylations were first developed in 1954 and have a major advantage that strongly basic or acidic conditions are not required for formation and reaction.$^{101}$ It has been observed that primary and secondary alkyl halides do not perform well on enamine alkylation, mostly due to the added complication of $N$-alkylation, particularly in the case of enamines derived from aldehydes. However, enamines prepared from aldehydes and diisobutylamine can be alkylated by simple primary alkyl halides in good yields.$^{102}$ $N$-Alkylation in this case is presumably prevented by steric hindrance.

With this in mind, it was decided to attempt the derivatisation via the enamine formed on reaction of the aldehyde (55) with diisobutylamine as shown in Scheme 66.

![Scheme 66](https://example.com/scheme66.png)

Results & Discussion
Enamine (111) was formed under mild conditions and isolated in good yield. A procedure used by a previous group member, Dr. Martin Button, for the derivatisation of enamines formed on thermal amino-Cope rearrangement was followed. $^1$H NMR analysis of the crude products showed that both methyl and benzyl derivatisations had been successful, although the majority of the product consisted of the unalkylated aldehyde (55). The $^1$H NMR spectra of the crude methyl derivatised product showed two doublets of the aldehyde (100a) in a 1:1 ratio. The spectrum of the crude benzyl derivatised product however was not as straightforward to interpret since the triplet corresponding to the proton adjacent to the carbonyl of the unalkylated product overlaps one of the doublets associated with the carbonyl proton of the diastereoisomeric alkylated product. The crude benzyl derivatised product was subjected to flash column chromatography to separate the alkylated and unalkylated products. The alkylated product (100d) was isolated in a 1.5:1 ratio.

The results suggest that the $\beta$-substituent of the aldehyde, generated on amino-Cope rearrangement, exerts a certain level of diastereoselectivity upon derivatisation at the $\alpha$-position during the tandem anionic amino-Cope rearrangement/imine anion alkylation.

2.8. Tandem Anionic Amino-Cope Rearrangement/Imine Anion Transmetallation & Derivatisation of Aminoalcohol and $O$-Bn Aminoalcohol Derived Diene Substrates

The ability of $\beta$-aminoalcohol auxiliaries to form a 5-membered chelate in the presence of a lithium counter-ion has been discussed in Section 1.4.6. Studies were directed towards investigating whether the presence of an alternative counter-ion, would affect the stereocontrol and the reactivity towards an incoming electrophile. Anionic amino-Cope rearrangement/imine anion derivatisation was carried out on the $O$-Bn valinol derived diene substrate (110), as previously reported, with the exception of the addition of zinc chloride to the reaction prior to electrophile quench. The reaction was performed using methyl iodide and benzyl bromide as the electrophiles as shown in Scheme 67.
1H NMR analysis of the crude products of both reactions indicated that only the unalkylated product (55) had been formed. The imine anion transmetallations were carried out on the phenylalaninol-derived diene (86) for comparison (Scheme 68). Again, 1H NMR analysis confirmed that derivatisation of the α-position of the aldehyde had not occurred, with only unalkylated product (55) isolated.
The results confirmed that the transmetallation of the imine anion with zinc chloride has an adverse influence on electrophilic derivatisation, with the increase in size of the counter-ion possibly impeding the incoming electrophile.

2.9. Tandem Anionic Amino-Cope Rearrangement/Imine Anion Derivatisation/Reduction of O-Bn Aminoalcohol Derived Diene Substrates

The level of diastereoselectivity obtained in the imine anion derivatisation was considered to be disappointing with the best ratio of 2:1 obtained when using a benzyl electrophile. It was hypothesised that when the product is isolated as the aldehyde, there is a possibility of epimerisation of the centre α- to aldehyde. Also the fact that aldehydes are generally relatively unstable could account for the poor to moderate yields achieved. It was thought that if we could avoid isolating the product as an aldehyde, the true diastereoselectivity of the imine anion derivatisation step could be shown to be much higher than previously seen. Macdonald has shown that amino-Cope rearrangement products can be isolated as alcohols or amines in his studies\(^\text{103}\) and consequently it was decided that our work would benefit by employing a similar approach.

\[ 
\begin{align*}
\text{O} & \text{B} & \\
\text{N} & \text{H} & \text{Ph} \\
\text{Bn} & \text{Ph} & (112) \quad \text{i) \text{n-BuLi, THF} \quad \text{ii) BnBr} \quad \text{iii) Na(OAc)\text{BH, AcOH, MeOH}} \\
\text{O} & \text{B} & \\
\text{N} & \text{H} & \text{Ph} \\
\text{Bn} & \text{Ph} & (113)
\end{align*}
\]

Scheme 69

Anionic amino-Cope rearrangement/imine anion derivatisation was achieved on the O-Bn valinol derived diene substrate (112) as previously described. The reaction was re-cooled to \(-78^\circ\text{C}\), whereupon sodium triacetoxyborohydride, acetic acid and methanol were added and the reaction allowed to warm to room temperature. The reaction was followed by real-time chemical ionisation MS, which showed that the reduction was proceeding...
slowly. After further additions of the reagents and heating to drive the reaction to completion, the majority of the derivatised imine anion intermediate had been consumed.

TLC and \(^1\)H NMR of the crude product showed a mixture of products, which were later isolated by flash column chromatography. As well as the required product (113) and the unreduced product, there was evidence of a product with a mass corresponding to \(N\)-derivatised or bis-derivatised product. The reaction was repeated, with the intermediate after derivatisation divided into two portions. The reduction was attempted as before using sodium borohydride on one portion of the reaction mixture. The reduction was complete within 2 hours. On the other portion of the mixture, the formation of acetal (114) was attempted as shown in Scheme 70, using ethylene glycol and an acid catalyst in the form of PTSA. The reaction showed no evidence of \(O\)-Bn valinol cleavage product and therefore was heated to reflux in toluene. \(^1\)H NMR confirmed that the acetal formation was unsuccessful with the harsh conditions, causing decomposition.

![Scheme 70](image)

The crude reduction product was purified using a SCX acid resin cartridge and further purified by HPLC. The required amine product (113) was isolated as a mixture of two diastereoisomers. There were also traces of product relating to the unreduced imine/enamine and \(N\)-derivatised or bis-derivatised product. This was unusual as LC/MS analysis of the crude product showed no such product. However, LC/MS of the product after purification using the SCX acid resin cartridge showed a trace of product with mass corresponding to the \(N\)-derivatised or bis-derivatised product. It was thought that any unreacted benzyl bromide remaining after work-up could have possibly reacted with the product and thus generating the \(N\)-benzylated product. Although real-time chemical ionisation MS and LC/MS are generally sensitive forms of analysis, it is thought that the
detection of an imine would be slow relative to that of an amine and hence following the reaction by such methods could be misleading.

The reduction was repeated and acetic acid was added to aid the completion of the reaction. This method was thought to promote formation of the iminium ion. The crude reaction product was absorbed on to silica straight after work-up and purified by dry-flash chromatography to remove any unreacted benzyl bromide. $^1$H NMR analysis at this stage indicated a 2:1 mixture of diastereoisomers of the desired product (113). The reaction product was then further purified by preparatory TLC and amine (113) was isolated as a mixture of diastereoisomers in a ratio of 2:1 as determined by $^1$H NMR analysis and in a yield of 85%, which is greater than the 62% yield obtained for the corresponding aldehyde.

There is a possibility of four diastereoisomers being obtained after derivatisation of the rearrangement intermediate as it is known that in the anionic amino-Cope rearrangement, although highly stereocontrolled, complete transfer of chirality from the starting diene substrate is not achieved. This mixture of diastereoisomers is in turn subjected to conditions lacking notable stereocontrol when derivatising the imine anion. The reason why only two diastereoisomers are observed may be due to the minor products being produced in such small quantities, they would be difficult to detect by NMR. To determine whether the ratio of 2:1 obtained after derivatisation and reduction of the rearrangement intermediate was due to the lack of chiral transfer in the rearrangement or due to the derivatisation step, the anionic amino-Cope rearrangement was carried out on the $O$-Bn valinol derived diene substrate (112) followed by reduction of the imine anion intermediate, excluding the derivatisation step, as illustrated in Scheme 71.

![Scheme 71](image)

Results & Discussion
To ensure that the imine anion had been consumed, the reduction using sodium borohydride was left overnight in the presence of an excess of reagents. Amine (115) was isolated in 63% yield following flash column chromatography. $^1$H NMR analysis showed a mixture of two diastereoisomers had been formed in an approximate ratio of 7:1, which is in good agreement with the e.e. of 74% obtained for the corresponding aldehyde (55).

Simple conformational analysis of the derivatisation step was surveyed to determine the rationale behind the stereocontrol. Assuming that the rearrangement proceeds through a chair-like transition state, the derivatisation would occur as depicted in Figure 15.

From this, the possible staggered conformers shown in Figure 16 can be deduced. Of the six shown, the conformations (120) and (121) would be considered the most unfavourable, due to the enamine segment occupying a gauche arrangement to both the allyl and phenyl substituents. Of the remaining four, configurations (117) and (118) would result in the most stable products, having the incoming electrophile gauche to only one of the allyl or phenyl groups. These would lead to the two major diastereoisomers observed, with the two other diastereoisomers possible coming from the minor rearrangement product after following a similar means of derivatisation.
It would be difficult to specify which of the two conformers can be attributed to the higher yielding diastereoisomer, as there is little difference in the space they occupy. However, as there is free rotation of the allyl substituent, it would be likely to exert more steric hinderance to the incoming electrophile compared to the planar phenyl substituents, thus favouring conformer (118).

Results & Discussion
The low level of diastereoselectivity gained on the derivatisation step could potentially be attributed to the fact that if the imine anion intermediate is in equilibrium between the imine (122) and enamine (123) form, epimerisation could be possible at the newly derivatised centre hence nullifying any stereochemical integrity. To verify this hypothesis, it was decided to block the newly derivatised centre from epimerisation. This was achieved by generating diene substrate (127), which had a methyl substituent at the 2-position of the diene. The diene was formed in good yield with trace quantities of the minor diastereoisomer following the route shown in Scheme 73. The minor diastereoisomer was inseparable from the major by flash column chromatography. However, purification was achieved by formation and liberation of the oxalate salt of the major diastereoisomer.

\[
\begin{align*}
\text{Scheme 72} \\
\text{Results \& Discussion}
\end{align*}
\]
Following the anionic amino-Cope rearrangement/imine anion derivatisation of diene substrate (127), the reaction mixture was divided into two portions. As the occurrence of epimerisation had been obstructed by the presence of the methyl substituent, it was thought that isolating the product as the aldehyde (128), would be acceptable. But for comparison, half the imine anion intermediate was also reduced to yield the amine (129).

Aldehyde (128) was isolated as a mixture of diastereoisomers in a ratio of 2:1 and yield of 30%. Amine (129) was also isolated as a mixture of diastereoisomers, again in a ratio of 2:1 and yield of 73%. These results would confirm that there is no evidence to support the theory of epimerisation in either imine anion intermediate or aldehyde following derivatisation. The consistent 2:1 ratio of diastereoisomers obtained in amines (113) and (129) and aldehydes (100d) and (128) would substantiate the fact that the low diastereoselectivity observed is indeed due to the derivatisation of the imine anion.
2.10. Thermal Amino-Cope Rearrangement of Aminoalcohol and O-Bn Aminoalcohol Derived Diene Substrates

As mentioned above, Allin and Button had studied the thermal amino-Cope rearrangement on various tertiary amine substrates.\(^{39}\) However, the thermal rearrangements had not been performed on secondary amine substrates or any of the \(\beta\)-aminoalcohol substrates he constructed. We have seen that enantioselectivity as high as 94% \(e.e.\) can be achieved by the anionic variant of the amino-Cope rearrangement using \(\beta\)-aminoalcohol substrates. Studies were directed towards the thermal amino-Cope rearrangement of the \(\beta\)-aminoalcohol derived substrates to determine the degree of asymmetric induction they offer under thermolysis conditions.

Button performed the thermal rearrangements by heating the substrates neat in sealed pressure tubes at temperatures as high as 250 °C. He also attempted heating the substrates in high boiling solvents but found that rearrangement did not occur in toluene (bp 110 °C) and had difficulty in removing the reaction product away from decane (bp 173 °C). It was apparent that temperatures in excess of 170 °C had to be employed. It was suggested that Dowtherm® A, a high boiling (258 °C) eutectic mixture of diphenyl (26.5%) and diphenyl oxide (73.5%) be used to thermally rearrange the diene substrates. The solvent could also be removed from the product during flash column chromatography.

The solvent was heated to 180 °C before diene substrate (86) was added and left for 2 hours. No rearrangement product was observed by \(^1\)H NMR so the temperature was elevated to 200 °C and heated for an additional 2 hours. This time a rearrangement product as well as starting material was evident. The reaction was continued for a further 2 hours, this time at 220 °C, which was high enough to convert all of the starting diene substrate. Flash column chromatography of the reaction product gave aldehyde (55) in low yield. This was not entirely expected as we had envisaged an enamine product (130), which after purification would have been hydrolysed to aldehyde (55) as described in Scheme 75. Derivatisation with \((1R, 2S)-(-)\)-ephedrine confirmed the enantiomeric excess of the aldehyde to be 27%.
The reaction was repeated on the $O$-Bn phenylalaninol (104) and $O$-Bn valinol (110) derived diene substrates. The temperature of the solvent, set at 220 °C and a reaction time of 4 hours was sufficient to convert all of the starting material in both cases. Aldehyde (55) was obtained after flash column chromatography in 16% yield and 19% e.e. for the $O$-Bn phenylalaninol derived substrate (104) and 33% yield and 12% e.e. for the $O$-Bn valinol derived substrate (110).

It could be that the low extent of asymmetric induction observed in the product of the thermal rearrangement is due, or partly due, to potential dissociation involving deallylation/reallylation of the substrate as discussed in Section 1.4.7. This is a viable possibility due to the high temperatures employed. Another likelihood is that in the anionic amino-Cope rearrangement, the steric bulk of the amine auxiliary component, enhanced by intramolecular chelation, causes it to have a preference to lie in a pseudo-equatorial position (A) as shown in Figure 17. The high temperatures associated with the thermal variant of the rearrangement could possibly encourage the transformation to proceed through the competing chair transition state (B), in which the amine segment occupies a pseudo-axial orientation, leading to the opposite enantiomeric product.
Results & Discussion

Figure 17

\[
\begin{align*}
\text{(A)} & \quad \text{A} & \quad \text{B} \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
Chapter 3

Results & Discussion

Preparation of Novel Substrates for Amino-Cope Rearrangement Studies


3.1. Introduction

It has been seen that a range of substrates have been developed for amino-Cope rearrangement studies, with the majority of routes thus far exploiting the addition of Grignard reagents to an α,β-unsaturated imine. While this method is highly stereoselective, and generally robust, it has limitations in that it only applies to allyl Grignard reagents.

This limitation has a knock-on effect in that it hinders the formation of 6-substituted dienes. Indeed, this has been demonstrated before when attempting the construction of dienes (132a) and (132b). It was shown that treating imines (131) and (91) with crotyl magnesium bromide did not give the desired dienes (132a) and (132b) but their structural isomers (133a) and (133b). This was thought to have resulted through crotyl addition via mechanism 2 rather than mechanism 1 (Scheme 76). In fact studies have shown that crotyl Grignard reagents have a tendency to react on the internal carbon of the allylic system rather than on the terminal carbon to which the magnesium is bonded.

Exploring introducing functionality at the C-6 position of the diene moiety, which to date has had limited application within the group, would provide us the opportunity to further study in depth the mechanism by which the amino-Cope rearrangement proceeds as well as accessing aldehydes with γ-substitution.
Results & Discussion

Scheme 76

(131); $R = \text{CH(Me)}_2$

(91); $R = \text{CH}_2\text{Ph}$

(132a); $R = \text{CH(Me)}_2$

(132b); $R = \text{CH}_2\text{Ph}$

(133a); $R = \text{CH(Me)}_2$

(133b); $R = \text{CH}_2\text{Ph}$
3.2. Synthesis and Amino-Cope Rearrangement of Acyclic Vinyl Sulfides

Our interests turned to the preparation and anionic amino-Cope rearrangement of 5-alkylsulfanyl-3-amino-1,5-dienes (134). The compounds (135) generated on rearrangement would have a useful combination of a nucleophilic vinyl sulfide and an electrophilic aldehyde in a 1,5 relationship (Scheme 77).

Previous work in anionic oxy-Cope chemistry has shown that sulfur-based substituents at either the C-4 or C-6 position on a 3-amino-1,5-dienes substrate can stabilise an allyl anion therefore favouring a stepwise mechanism for the reaction. In addition, these substituents are also known to have increased the rate of rearrangement. However, there is only one example in the literature of anionic oxy-Cope rearrangement of 3-hydroxy-1,5-dienes with an alkylsulfanyl group at C-5.

Unlike 4- and 6-alkylsulfanyl groups, a 5-alkylsulfanyl group would not be expected to promote a stepwise mechanism that could reduce stereocontrol. Furthermore, it could control orientation of the imino-anion in the transition state of the rearrangement. The spontaneous cyclisation of the vinyl sulfide (135) is expected to be slow relative to cyclisation of the more nucleophilic analogous enol ethers. Consequently, it may be possible to manipulate the two functional groups independently, without the complication of an intramolecular aldol reaction.
Hartley and co-workers have shown the hydroxy variant of similar substrates can undergo anionic oxy-Cope rearrangement to yield aldehyde products as described. Their studies confirmed that the 5-alkylsulfanyl group assists stereocontrol in the anionic oxy-Cope rearrangement of 3,4-anti vinyl sulfides by discouraging a pseudo axial oxyanion.

3.2.1. Preparation of 5-Alkylsulfanyl-3-Amino-1,5-Diene

The procedure illustrated in Scheme 78, parallel to that developed by Hartley for the synthesis of 5-alkylsulfanyl-3-hydroxy-1,5-dienes, has been initially outlined to generate the 5-alkylsulfanyl-3-amino-1,5-dienes. It was anticipated that imino-aldol reaction of ethyl thioacetate and imine (136), synthesised by simple condensation of benzylamine and trans-cinnamaldehyde, would give β-amino thioester (137). Takai alkylidation of (137) would be expected to yield diene substrate (138), from which anionic amino-Cope rearrangements could be studied.

\[
\begin{align*}
\text{EtS}^+ & \xrightarrow{i) LDA/THF} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \\
& \quad \text{Ph} \quad \text{Et} \quad \text{Ph} \\
(136) & \xrightarrow{\text{Ph} \quad \text{N} \quad \text{Ph}} \quad \text{Ph} \quad \text{O} \\
& \quad \text{Ph} \quad \text{NH}_2 \\
\text{Ph} \quad \text{N} \quad \text{Ph} & \xrightarrow{\text{TiCl}_4, \text{TMEDA}, \text{Zn}, \text{CH}_2\text{Br}_2, \text{THF/DCM}} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \\
& \quad \text{Ph} \quad \text{Et} \\
(137) & \xrightarrow{\text{Ph} \quad \text{NH}_2} \quad (138)
\end{align*}
\]

Scheme 78
3.2.2. Iminio-Aldol Reaction via Lithium Enolate

Imine (136) was synthesised readily from benzylamine and trans-cinnamaldehyde using standard conditions. The results of the imino-aldol reaction are summarised in Table 17. The first attempt at the reaction, which employed an excess of LDA, generated a mixture of unknown products. The use of excess base may have lead to the enolate formation of the required product and may have reacted further with other species in the reaction mixture to generate polymerisation and breakdown products.

![Scheme 79](image)

Table 17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Excess LDA / One-pot imino-aldol</td>
<td>Mixture of unknown products – Possible polymerisation</td>
</tr>
<tr>
<td>2</td>
<td>LDA limiting / Enolate added to imine</td>
<td>Unsuccessful – Starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td>Excess cerium enolate / One-pot imino-aldol</td>
<td>Unsuccessful – Starting material recovered</td>
</tr>
</tbody>
</table>

The reaction was repeated with the base as the limiting reagent. This however proved unsuccessful with mostly starting material being recovered. A final attempt was made using the cerium enolate of the thioacetate.

Organocerium reagents have been widely used to facilitate nucleophilic addition to carbonyl compounds\(^{106}\) and \(\alpha,\beta\)-unsaturated compounds\(^{107}\) and in the case of the latter, it
has been well documented that these reagents greatly enhance 1,2-addition versus 1,4-addition by activation of the relatively electron-rich carbonyl centre. While the structure and reaction mechanism of organocerium reagents have not been fully clarified, it is certain that their chemical behaviour relates to strong coordination of cerium(III) with oxygen and nitrogen.\textsuperscript{108}

Although imines are much less reactive than their carbonyl counterparts, we envisaged that the introduction of cerium(III) would promote electrophilicity of the imine centre. The cerium enolate was generated by adding the lithium enolate of ethyl thioacetate to a CeCl\textsubscript{3}-THF slurry at -78°C, to which the imine was added after a short period of time. The reaction was deemed unsuccessful, with starting material again being recovered.

Problems associated with reactions of α,β-unsaturated imines which contain hydrogens α- to nitrogen with common organometallic reagents generally fail to give acceptable yields of product by simple addition because of the relatively poor electrophilicity of the imine carbon and competing loss of the α-proton.\textsuperscript{109}

### 3.2.3. Imino-Aldol Reaction via Silyl Enolate

The preparation of the diene substrate (138) would give a good indication of the yield and stereochemical impact on the amino-Cope rearrangement having an alkylsulfanyl group attached in the 5-position. However, it would be beneficial in the long-term scope of this study and for comparison with previous work to introduce the use of β-aminoalcohol auxiliaries. This would ensure that substrates generated would have similar diastereoisomeric purity as those employed in earlier work. For this to be realised, it is essential that the auxiliary be introduced in the first stage of Scheme 78. This was not encouraging, as it has been shown in our hands that the imino-aldol is not a straightforward transformation.

A comprehensive literature search showed that the Lewis acid-catalysed reactions of imines with silyl enolates are one of the most efficient methods for the preparation of β-amino esters.\textsuperscript{110} Of many Lewis acids to be used in this field and of other carbon-carbon
bond forming reactions, the use of rare earth metal triflates such as ytterbium and scandium triflates has recently received substantial interest.\textsuperscript{111} These triflates are stable in water and can be recovered after the reactions are completed and reused. In addition, only a catalytic amount of the triflate is required to complete the reactions.\textsuperscript{112}

Kobayashi and co-workers\textsuperscript{113} have shown that silyl enolates derived from thioesters (139) can be successfully added to unactivated imines (140) in the presence of 5 mol\% \text{Yb(OTf)}\textsubscript{3} and \text{Sc(OTf)}\textsubscript{3} to give the desired \(\beta\)-amino thioester (141) as shown in Scheme 80.

![Scheme 80](image)

We decided to attempt the imino-aldol reaction using \text{Yb(OTf)}\textsubscript{3} as the Lewis acid catalyst on our \text{O-Bn} valinol derived imine (142) as described in Scheme 81.

![Scheme 81](image)

The formation of the silyl enolate (140) was challenging, with a number of attempts being made.\textsuperscript{114} It was eventually obtained in good yield by quenching the lithium enolate of the thioester with TMSCI at \(-78\) °C.\textsuperscript{115} Purification was achieved by short-path vacuum distillation (Scheme 82).

Results & Discussion
The first attempt at the imino-aldol reaction outlined in Scheme 81 was carried out using 5 mol% Yb(OTf)$_3$. After stirring at 0°C for 5 hours, the reaction mixture was analysed by real-time chemical ionisation MS, which showed a trace of material with mass corresponding to the required product (143) although this could also be attributed to the 1,4-addition product. Further additions of catalyst and silyl enolate had no influence and the reaction was deemed unsuccessful.

The reaction performed by Kobayashi, highlighted in Scheme 80, was carried out to see whether the chemistry would be successful in our hands. Although all of the starting material had not been consumed, even after further addition of catalyst and silyl enolate, the expected product (141) was isolated after flash column chromatography in similar yield to that reported.

As the reported chemistry was shown to be reproducible, thoughts were turned to the reactivity of our imine substrate. There are two apparent features of the O-Bn valinol derived imine substrate that may reduce reactivity; one being the conjugated double bond and the other being the aminoalcohol portion of the imine. It was thought that there could be possible chelation of the ytterbium with not only the imine nitrogen but also the O-Bn ether oxygen, which would reduce the function of the catalyst as shown in Figure 18.

Results & Discussion
This theory was discounted as Cozzi and Umani-Ronchi\textsuperscript{116} showed that the synthesis of β-amino esters can be accomplished by a one-pot procedure starting from an aldehyde, (S)-valine methyl ester and a silyl enolates using \(\text{Yb(OTf)}_3\) as a catalyst at room temperature. The silyl enolate was shown to have preference to add diastereoselectively to the imine formed \textit{in situ} due to the chelation of the catalyst and the nitrogen of the imine and carbonyl of the ester (Figure 19).

The imino-aldol reaction on our imine substrate (142) was repeated using a stoichiometric catalytic quantity of \(\text{Yb(OTf)}_3\), again proving fruitless. This led us to believe that the \(\alpha,\beta\)-unsaturated nature of the imine was the major cause of the failure of the reaction. There is limited reporting of 1,2-additions to \(\alpha,\beta\)-unsaturated imines,\textsuperscript{109} with those reported utilising activated imines. Shimizu\textsuperscript{117} recently reported the high diastereoselective addition of silyl enolates to a range of imines catalysed by samarium(III) iodide, which is made \textit{in situ} from samarium(II) iodide. One such imine substrate used in the course of his studies was one derived from benzylamine and cinnamaldehyde (Scheme 83). Although the yield obtained was relatively low, the substrate exclusively gave the β-amino ester as the sole product with the best \textit{anti}-selectivity. The use of samarium(II) iodide as a precatalyst for a variety of Lewis acid-catalysed carbon-carbon bond-forming reactions has been widely employed.\textsuperscript{118}
The reaction illustrated in Scheme 80 was carried out using Sml₃ (10 mol%) as the catalyst. Sml₃ was prepared \textit{in situ} from Sml₂ and iodine and was cooled to -78 °C. To this was added a solution of imine (139) and the silyl enolate (140). The reaction was allowed to warm to room temperature and stirred for 20 hours. β-amino ester (141) was isolated after flash column chromatography in 62% yield.

The reaction was performed on the O-Bn valinol derived imine substrate (142) using the same conditions as described by Shimizu (Scheme 85). After 20 hours of stirring there was only a trace of material with mass corresponding to the product, as analysed by real-time chemical ionisation MS. The reaction mixture was then warmed to 60 °C and stirred for a further 20 hours. This had no effect on the conversion of starting material. The reaction was repeated using 50 mol% catalyst but again was unsuccessful.

Results & Discussion - 102 -
There is plenty of scope for the imino-aldol reaction of the O-Bn valinol derived imine substrate (142) with the screening of various catalysts being a possible option. It is known that various Lewis acids have different properties, which make them unique in their uses. It has also been shown that the efficiency of rare-earth metal catalysts, in particular triflates, varies from one to another depending on conditions.\textsuperscript{112}

3.2.4. Mitsunobu Reaction of 5-Alkylsulfanyl-3-Hydroxy-1,5-Diene

Due to the drawback of the unsuccessful imino-aldol reaction, the route described in Scheme 78 was modified to the one shown in Scheme 86. It follows the route developed by Hartley et al. for their synthesis of 5-alkylsulfanyl-3-hydroxy-1,5-dienes.\textsuperscript{105} To introduce the nitrogen moiety, we anticipated that 5-alkylsulfanyl-3-hydroxy-diene (146) would undergo Mitsunobu reaction to generate the phthalimide-protected diene (147). Hydrazinolysis and reductive amination would be expected to give diene substrate (138).
Hartley has demonstrated that the synthesis of his 5-alkylsulfanyl-3-hydroxy-1,5-dienes can be carried out diastereoselectively using Evans' oxazolidinone chiral auxiliary\textsuperscript{119} and also Heathcock's diastereoselective aldol reaction using 2,6-dimethylphenyl propionate.\textsuperscript{120} The use of diene substrate (138) for anionic amino-Cope rearrangement of novel substrates was considered to be adequate for our initial studies.

Results & Discussion
Work was initiated on the aldol reaction of ethyl thioacetate and trans-cinnamaldehyde (Scheme 87). Attempts made at the reaction are summarised in Table 18. The first attempt employed an excess of LDA, which may have lead to problems similar to those that arose when experimenting the imino-aldol using the same conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Excess LDA / One-pot aldol</td>
<td>Possible polymerisation</td>
</tr>
<tr>
<td>2</td>
<td>LDA limiting / Enolate added to ( \text{E}^+ )</td>
<td>Compound isolated -- Analysis indicates not required product</td>
</tr>
<tr>
<td>3</td>
<td>Hartley Method – Thioacetate limiting / One-pot aldol</td>
<td>Product obtained in 82 % yield (cf. 31% - Hartley(^{121}))</td>
</tr>
</tbody>
</table>

**Table 18**

The second entry in Table 18, shows that a compound was isolated, which was thought to be the correct product, but was later determined to be sulfino thioester (149) (Scheme 88).
The reaction was successful when the thioacetate was used as the limiting reagent. The product was isolated in 82% yield after flash column chromatography. At this point, before continuing with the synthesis of the 5-alkylsulfanyl-3-hydroxy-diene (146), it was decided to briefly investigate other possible routes using the aldol product (144), which would be less elaborate and time-consuming as the route shown in Scheme 86.

\[
\begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{Oxidation} & \\
\text{SEt} & \\
\text{(144)} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph} \\
\text{SEt} & \\
\text{(150)} & \\
\text{Reductive} & \text{amination} \\
\text{Ph} & \quad \text{N} \\
\text{SEt} & \\
\text{(138)} & \\
\end{align*}
\]

**Scheme 89**

**Scheme 89** describes the synthesis of diene substrate (138) via an oxidation/reductive amination pathway. The oxidation of aldol (144) was attempted using Dess-Martin Periodinane with conversion of starting material complete within 1 hour. $^1$H NMR of the reaction product suggested that enone (150) had possibly tautomerised to the enol (151), therefore the route was not further investigated.

\[
\begin{align*}
\text{O} & \quad \text{Ph} \\
\text{SEt} & \\
\text{(150)} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph} \\
\text{SEt} & \\
\text{(151)} & \\
\end{align*}
\]

**Scheme 90**

Another possible route to the formation of diene substrate (138) was investigated using a mesylation/displacement method as shown in **Scheme 91**. Aldol (144) was dissolved in DCM and stirred at 0 °C with triethylamine and methanesulfonyl chloride for 1 hour.
It was unclear by $^1$H NMR whether the mesylation had occurred, however the product was taken through to the attempted displacement using benzylamine. The reaction was analysed by real-time chemical ionisation MS after 1 hour, which showed no evidence of the required product (138). The reaction was heated to 70 °C for a further 1 hour and re-analysed but again there was no sign of product. This prompted us to think that the chloride could have been formed instead of the mesylate, so the mesylation was repeated at -10 °C. However the $^1$H NMR spectrum of the reaction product was identical to the previous attempt. It was also thought that the α,β-double bond could cause problems, if not in the mesylation then possibly in the displacement reaction, with the nucleophile adding at the double bond and displacing the mesylate. This route was also deemed unsuccessful and abandoned.

The next investigation was to carry out the Mitsunobu reaction$^{122}$ on the aldol product (144) to test the capability of the reaction. If successful, this would eliminate the alcohol protection step in preparation for the Takai alkylidenation, as the nitrogen moiety in the Mitsunobu product (153) would already be protected as the phthalimide. Aldol product (144) was stirred with triphenylphosphine, DIAD and phthalimide in THF for 4 hours at room temperature, given a suitable work-up and subjected to flash column chromatography. The required product (153) was isolated in a disappointingly low yield of 15%, with the majority of the reaction product being confirmed as the elimination product (154).
In retrospect, the protons alpha- to the carbonyl are expected to be more acidic and hence more susceptible to elimination than those alpha- to the alkenic functionality in the product after Takai alkylidenation. Although the ratio of required to elimination product could be altered by varying the experimental conditions, it was thought that the original route in Scheme 86 would be superior.

Hartley reported that protection of the hydroxy functionality in the aldol product prior to the alkylidenation step is vital to the success of the reaction.\textsuperscript{123} \textit{i}-Butyldimethylsilyl (TBDMS), triethylsilyl (TES) and trimethylsilyl (TMS) groups were all effective but TMS was the preferred option as it is the easiest to remove and there is no need to purify the intermediate before the Takai reaction. Following the reported procedure, which employed 2 equivalents of chlorotrimethylsilane and 3 equivalents of Hunig’s base in DMF, the TMS-protected product (145) was obtained in a poor 45% yield. The reaction was repeated using only a slight excess of the reagents, which lead to the product in an increased and almost quantitative yield of 98% (Scheme 93).

\textbf{Results & Discussion}

- 108.-
The preparation of enol ethers is usually limited to methods which use as starting materials either acetals\textsuperscript{124} or acetylenes.\textsuperscript{125} But these methods have limitations and the most promising direct approach to overcome these difficulties is the alkylideneation of ester carbonyl compounds. The Wittig reaction is an established method for construction of a carbon-carbon double bond from a carbonyl compound.\textsuperscript{126} However, alkylideneation of carboxylic acid derivatives does not transpire \textit{via} Wittig reagents due to their electron-rich carbonyl nucleus.\textsuperscript{127}

Hartley's selection of Takai's procedure\textsuperscript{128} was owing to the fact that similar methods developed by Tebbe\textsuperscript{129} and by Grubbs,\textsuperscript{130} that generated titanium alkylidene reagents, were limited to methylation. Furthermore, the Takai reagent exhibits good Z-selectivity when converting esters into enols and in the rare cases of thioesters into vinyl sulfides.\textsuperscript{131}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {i) TiCl\textsubscript{4}, TMEDA, Zn, CH\textsubscript{2}Br\textsubscript{2}, PbCl\textsubscript{2}, THF/DCM, ii) TBAF, THF \(\text{33\%}\)};
  \node (b) at (2,0) {\text{HO} - \text{Ph}};
  \node (c) at (0,-1) {\text{TMSO} - \text{Ph} - \text{Et}};
  \node (d) at (-1,-1) {\text{SEt}};
  \node (e) at (-2,-1) {\text{SEt}};
  \node (f) at (1.5,-1) {\text{SEt}};
  \node (g) at (2,-1) {\text{SEt}};
  \draw (a) -- (b);
  \draw (c) -- (d);
  \draw (d) -- (e);
  \draw (e) -- (f);
  \draw (f) -- (g);
\end{tikzpicture}
\end{center}

\textbf{Scheme 94}

For our preliminary studies, methylation of the thioester was considered sufficient. The Takai reagent was prepared by addition of 4 equivalents of a DCM solution of titanium(IV) chloride to THF, followed by 8 equivalents TMEDA, which turned the suspension from yellow to orange-brown. Addition of 9 equivalents of activated zinc powder lead to a dark green-blue suspension. After addition of 1 equivalent of the TMS-protected thioester (145) and 2.2 equivalents of dibromomethane the mixture turned black and after 3-4 hours stirring at room temperature the reaction was quenched with aqueous potassium carbonate. Following removal of titanium salt residues and an elaborate work-up, the reaction product was treated with a THF solution of TBAF. \(^1\)H NMR analysis confirmed that the alkylideneation was unsuccessful with the majority of the initial unprotected aldol recovered.
Takai had reported that the presence of trace amounts of lead(II) is essential to the accomplishment of the reaction. This is often present in commercially available zinc, but the quantity varies and therefore Takai suggested employing a catalytic amount (1-5 mol%) of lead(II) chloride to ensure the success of the reaction.

The reaction mechanism is not yet clear. In the absence of lead, dibromomethane is rapidly converted into zinc carbenoid (155), but is converted only very slowly to geminal dizinc (156) as shown in Scheme 95. It would appear that lead(II) chloride accelerates the formation of geminal dizinc (156). Takai proposed that transmetallation from zinc to lead gives rise to carbenoid (157), which is reduced by zinc to give lead-zinc compound (158). He suggested that lead carbenoid (157) is more easily reduced than the corresponding zinc carbenoid (155) as the Pb–C bond has greater covalent character. Transmetallation from lead to zinc then gives geminal dizinc (156).

![Scheme 95](image)

Takai proposed that in the presence of titanium(IV) salts, geminal dizinc (156) transmetallates to give a titanium-containing geminal dimetallic (159) or a titanium methylidene (160), which is the active methylenating agent (Scheme 96).
However, titanium complexes must be involved in the reduction of the dibromomethane, as the rate of conversion of dibromomethane into a geminal dizinc (156) in the absence of titanium salts was shown to be too slow to account for the alkylidenation reaction times. Furthermore, low valent titanium complexes are generated prior to the addition of dibromomethane. The identity of these low valent titanium complexes has not yet been established.

The reaction illustrated in Scheme 94 was repeated, this time using 4.5 mol% lead(II) chloride. The product (146) was isolated after deprotection and flash column chromatography in a disappointing 16% yield. However this yield was improved to 33% when carried out on a larger scale. The overall yield of the formation of the 3-hydroxy-diene (146) was 27%, which was an increase on Hartley’s reported 5%. It is clear that the greatest loss in yield of the sequence is observed in the Takai alkylidenation step.

The next step in the sequence, shown in Scheme 97, was the Mitsunobu reaction on the 3-hydroxy-diene (146) with phthalimide. The reaction conditions employed were identical to those used for the formation of phthalimide-protected thioester (153) and the reaction was completed within 4 hours. As expected there was no trace of elimination product as encountered in the corresponding reaction on aldol (144). The product (147) was however obtained in a low 25% yield following flash column chromatography.

Results & Discussion
Deprotection of the phthalimide group was attempted by stirring the phthalimide-protected diene (147) in a methanolic solution of hydrazine at room temperature. The reaction was followed by real-time chemical ionisation MS, which showed no evidence of the unprotected product (148). TLC analysis showed that the starting material had been consumed, however it was unclear if the product had been formed. \(^1\)H NMR could not confirm the presence of the unprotected diene (148). It was later shown that the phthalimide-protected diene (147) is very unstable and decomposes readily. This was exemplified by the difficulty in obtaining \(^{13}\)C NMR analysis. It was thought that the protected diene (147) could have decomposed before attempting the deprotection. Therefore, the deprotection was attempted again straight after isolation from the previous step, again proving fruitless. A final attempt was made on the deprotection using methyl hydrazine. This had no effect and gave rise to the same result.

The later stages of the synthesis towards diene (138) were shown to be challenging and thought to be too time consuming to pursue. The poor yields for the Takai and Mitsunobu steps made the preparation of diene (138) impractical.

### 3.3. Novel Route to 1,6-Disubstituted-3-Amino-1,5-Diene Substrates

Despite the setback in the preparation of 5-alkylsulfanyl-3-amino-1,5-diene (138), we were intent on generating substrates with substitution at C-6 due to its limited study within the group.
Scheme 99 shows a route that utilises the chemistry carried out during the synthesis of diene (138). It was thought that the formation of 3-hydroxy-1,5-diene (161) should be straightforward. However, we decided not to pursue this route as we thought we would encounter similar problems when performing the Mitsunobu/phthalimide deprotection chemistry.

Scheme 99

Scheme 100 shows a similar approach to that with which we have already been able to access our 3-amino-1,5-dienes via a 1,2-allyl Grignard addition to a conjugated imine. We envisaged that a masked aldehyde Grignard reagent (162) addition to the imine would later enable us to perform Wittig olefinations on aldehyde (163) to introduce functionality.
at the 6-position diene. However, the Grignard addition was unsuccessful with starting material being recovered. This was not totally unexpected due to the reactions partiality towards allyl Grignard as discussed in Sections 2.2. and 3.1.

![Scheme 100](image)

### 3.3.1. Preparation of Racemic 1,6-Disubstituted-3-Amino-1,5-Diene Substrates

Recent work by Knight and co-workers have utilised substrates such as (165) for studies on cyclisations of homoallylic sulfonamides as an approach to the formation of pyrrolidines. These precursors were readily obtained using Stork's procedure, in which the benzylidene derivative of glycine ethyl ester (164) was alkylated via its lithium enolate using various alkylating agents. It was thought that we could incorporate this chemistry to generate substrates such as (166) for amino-Cope rearrangement studies as illustrated in Scheme 101.
We felt that this route offered a lot in the way of flexibility in exchanging groups at C-1 and C-6. A range of commercially available alkylating agents is accessible in order to vary substituents at C-6, as are a variety of Wittig reagents, although these can also be generated quite easily. In addition, the dioxalane (167) is also readily available, which may allow Wittig chemistry to be performed at both ends of the diene (Scheme 102).
Glycine imine ester (164) was synthesised in almost quantitative yield by condensing glycine ethyl ester hydrochloride with benzaldehyde in the presence of triethylamine and was used without further purification. It was initially decided to introduce a methyl group to the 6-position of the diene moiety (Scheme 103).

![Scheme 103](image)

Alkylation of the derivatised glycine ester was achieved by Stork's procedure using crotyl bromide as the alkylating agent to give the derivatised imine ester (168) as shown in Scheme 104. Although crotyl bromide comes as an 85% assay with the remainder consisting of 3-bromo-1-butene, imine ester (168) was the exclusive mono-alkylated product. Flash column chromatography partially hydrolysed the imine and hence purification was unsuccessful.

![Scheme 104](image)

It was decided to take the crude product through to the imine reduction reaction without further purification. The first attempt at the reduction was carried out using sodium borohydride in methanol, which resulted in a mixture of unknown products, with possible reduction of the ester functionality. A milder, more specific reductive agent for imines was used in the second attempt in the form of sodium triacetoxyborohydride in the presence of acetic acid.
Sodium triacetoxyborohydride is especially suitable for reductive aminations. Since the reaction rate for the reduction of iminium ions is much faster than for esters, ketones or even aldehydes, the reductive amination can be carried out as a one-pot procedure by introducing the reducing agent into a mixture of the amine and carbonyl compound. The presence of a stoichiometric amount of acetic acid, which catalyzes the imine formation and provides the iminium ion, does not present any problems under these conditions. In comparison to mild reducing agents such as sodium cyanoborohydride and borane-pyridine, sodium triacetoxyborohydride gives consistently high yields and fewer side products. It is believed that the boron-hydrogen bond is stabilized by the steric and electron-withdrawing effects of the acetoxy groups, making the reagent a mild reducing agent.\(^{137}\)

\[
\text{Ph} = \text{NC} \quad \text{Me} \\
\text{Na(OAc)}_3\text{BH, AcOH, DCE} \\
\text{Ph} = \text{NC} \quad \text{Et} \\
\text{Me} \\
\text{78\%} \\
\text{Me} \\
\text{22\%} \\
\text{Me}
\]

**Scheme 105**

The reduction was successful and conversion was observed within 1 hour. The required product (169) was obtained in 78\% yield over two steps after flash column chromatography. On purification, a small amount of the dialkylated product (170) was also isolated.

\[
\text{Ph} = \text{NC} \quad \text{Me} \\
\text{DIBAL/THF} \\
\text{-78 \degree C} \\
\text{X} \\
\text{Ph} = \text{NC} \\
\text{Me} \\
\text{Me} \\
\text{22\%} \\
\text{Me} \\
\text{78\%} \\
\text{Me} \\
\text{22\%} \\
\text{Me}
\]

**Scheme 106**

The next step was to reduce ester (169) to the corresponding aldehyde (171) using DIBAL, as illustrated in **Scheme 106**. The substrate was dissolved in THF and cooled to
-78 °C where a 1M solution of DIBAL in THF was added dropwise whilst maintaining the reaction temperature below -65 °C, stirred for 2 hours and quenched with methanol at the same temperature. ¹H NMR analysis of the crude product showed that the reaction was unsuccessful with a mixture of starting material and fully reduced alcohol. It was decided that pursuing the aldehyde via the DIBAL reductive method would not be beneficial at this stage and complete reduction to the alcohol (172) and oxidation up to the aldehyde (171) would be more effective.

\[
\begin{align*}
\text{Ph} - \text{N} - \text{CH} - \text{CO}_2\text{Et} & \quad \xrightarrow{\text{DIBAL/THF} \quad -78 \degree\text{C} - \text{RT}} \quad \text{Ph} - \text{N} - \text{CH} - \text{OH} \\
(169) & \quad \xrightarrow{82\%} \quad (172)
\end{align*}
\]

**Scheme 107**

Reduction of ester (169) to alcohol (172) was effected by treating the substrate with DIBAL at -78 °C and warming to room temperature whereupon the reaction was quenched. The crude product was obtained in 82% yield and was used without further purification (Scheme 107).

\[
\begin{align*}
\text{Ph} - \text{N} - \text{CH} - \text{OH} & \quad \xrightarrow{\text{DMP/DCM}} \quad \text{Ph} - \text{N} - \text{CH} - \text{O} \\
(172) & \quad \xrightarrow{\times} \quad (171)
\end{align*}
\]

**Scheme 108**

Scheme 108 shows the attempted oxidation of alcohol (172) to aldehyde (171). The alcohol was stirred at room temperature with Dess-Martin periodinane for 24 hours and given a suitable work-up. TLC analysis confirmed the consumption of starting material although several products were observed. ¹H NMR analysis of the crude product showed that reaction was unsuccessful, with no trace of aldehyde.

Consumption of starting material suggested that the oxidant was functioning. It was hypothesised that side reactions could have occurred once the aldehyde had formed, Results & Discussion
possibly with the free secondary amine participating. Protection of the secondary amine would help avoid such complications. The reproducibility of the ester reduction step was also brought into question, as the reaction product was lost during work-up once scaled-up. It was thus thought that the protection step could be incorporated once the imine functionality had been reduced, using a t-butyl carbamate (Boc) group.

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

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

Scheme 109

The protection, highlighted in Scheme 109, was not routine and did not go to completion after 48 hours stirring at room temperature. Reflux was applied for 24 hours, which appeared to drive the reaction; however some starting material was recovered after flash column chromatography. The product (173) was obtained in 70% yield, but if the recovered starting material is taken into consideration the yield increases to around 87%.

The DIBAL reduction of the N-Boc ester (173) to the N-Boc aldehyde (174) was attempted as before. $^1$H NMR analysis of the crude product showed only starting material and no trace of either aldehyde or alcohol. Again a full reduction/oxidation approach to the aldehyde was thought to be the more suitable route at this point.

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

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

Scheme 110

Alcohol (175) was generated as previously described using DIBAL as the reducing agent. TLC analysis showed complete consumption of starting material, however with two
products observed. The required product was isolated in a poor 46% yield. It was thought that the by-product (more polar by TLC) could have been the deprotected product (169). Analysis confirmed that the by-product was N-methyl alcohol (176). A possible explanation and mechanism for formation of the by-product (176) is shown in Scheme 111.

![Scheme 111](image)

It was evident that the N-Boc protection was not as stable to DIBAL as first thought and a milder reducing agent was sought. Although ester reductions using sodium borohydride are not very common and proceed slowly, they are useful when the Lewis basicity of aluminium hydrides causes unwanted secondary effects.138

![Scheme 112](image)

The reaction shown in Scheme 112 was carried out using 4 equivalents of sodium borohydride in ethanol. Conversion of starting material was sluggish and so an extra 4

Results & Discussion
equivalents of sodium borohydride was added. This increased the rate of reaction and a final addition of a further 4 equivalents of sodium borohydride, pushed the reaction to completion. As expected, there was clean conversion of starting material without any by-products, with alcohol (175) being obtained in quantitative yield and used without further purification.

![Scheme 113](image)

Dess-Martin periodinane was again used to achieve oxidation of the N-Boc alcohol (175) to N-Boc aldehyde (174). Consumption of starting material was complete after 16 hours stirring, with TLC analysis showing formation of one major product. $^1$H NMR analysis of the crude product confirmed the product as being the required aldehyde (174) and was obtained in 96% yield after flash column chromatography. The oxidation was equally successful when IBX was used as the oxidant in DMSO.

![Scheme 114](image)

It has been shown that the Lewis acidity of DIBAL in solution increases when changing from THF to DCM and even more so when changing to toluene.\textsuperscript{140} The reduction of N-Boc ester (173) to the N-Boc aldehyde (174) was repeated using DCM as the solvent. N-Boc aldehyde (174) was obtained in 98% yield as was deemed suitable to be used without further purification (Scheme 114).
\( N\)-Boc diene (177) was synthesised by treating ethyltriphenylphosphonium bromide in THF with \( n\)-BuLi and adding aldehyde (174) to the *in situ* generated phosphonium ylide. The diene was isolated in 67% yield after flash column chromatography. Due to the complex nature of the \( ^1\text{H} \) NMR spectra, it was difficult to determine the *cis/trans* ratio of the new double bond. It was thought that this would be made easier once the Boc group was removed.

Diene (178) was made in similar fashion, using benzyltriphenylphosphonium bromide as the Wittig reagent, in an 82% yield after flash column chromatography. \( ^1\text{H} \) NMR indicated an inseparable 2:1 mixture of geometric isomers in the favour of the *trans* isomer.

The final stage of the generation of the amino-Cope rearrangement substrate was the deprotection of the \( N\)-Boc group. Deprotection of \( N\)-Boc diene (177) was achieved by stirring with 5 equivalents TFA in DCM for 24 hours to give 1,6-dimethyl diene (179) in almost quantitative yield (Scheme 117). The *cis/trans* ratio was still unfortunately unobtainable due to the complex \( ^1\text{H} \) NMR spectra.
These conditions were not suitable for deprotection of \( N \)-Boc diene (178), as an inseparable mixture of products, including the require diene (180), was found to be acquired. The reaction was repeated with varying concentrations and quantities of the TFA in DCM yet no change in outcome was observed. We were unsure as to what the by-products were and it was decided that milder conditions should be utilised.

Routier\(^{140}\) recently reported a mild and selective method for \( N \)-Boc deprotection using TBAF in refluxing THF. However, these conditions yielded only starting material when applied to \( N \)-Boc diene (178). It has been demonstrated by our group\(^{141}\) and others\(^{142}\) that formic acid induced deprotection of \( N \)-Boc compounds can be achieved without the complications associated with using stronger acids such as TFA and HCl.

Deprotection of \( N \)-Boc diene (178) was finally achieved in good yield by stirring in neat formic acid for 24 hours. \(^1\)H NMR suggested that the \textit{cis}/\textit{trans} ratio had reduced to only 11:9 in favour of the \textit{trans} isomer compared to 2:1 after the Wittig olefination. We were unsure if this was to be attributed to isomerisation under the acid conditions or whether a false ratio was obtained due to the \( N \)-Boc group having a restrictive effect on the diene structure.
It was decided that diene substrates (181) and (182) be made to compare with substrates (179) and (180) and to give a better understanding of substituent pattern effects on the mechanism of the anionic amino-Cope rearrangement.

\[
\begin{align*}
\text{(164)} & \quad \xrightarrow{(i)} \quad \text{(183)} \\
\text{(188); } R = \text{Me} & \quad \text{(189); } R = \text{Ph} \\
\text{(187)} & \quad \xrightarrow{(iv)} \quad \text{(186)} \\
\text{(i) LDA, BrCH}_2\text{CH}=\text{CHPh; (ii) Na(OAc)}_2\text{BH, AcOH, DCE; (iii) Boc}_2\text{O, TEA, DMAP, THF; (iv) DIBAL, DCM, } -78 \degree \text{C; (v) Ph}_3\text{PCH}_2\text{RBr, } n\text{-BuLi, THF; (vi) HCOOH}
\end{align*}
\]

Scheme 119

The route to the new substrates (181) and (182) was analogous to that which was developed for the synthesis of diene substrates (179) and (180) and is highlighted in Scheme 119. The alkylation step was carried out using cinnamyl bromide as the electrophile, which as with the crotyl variant gave the trans isomer of the product (183) as the exclusive product.
Imine ester (184) was obtained in a 65% yield over two steps. Again, a small quantity of dialkylated product (185) was also isolated.

Following N-Boc protection, reduction of the N-Boc ester (186) to N-Boc aldehyde (187) was achieved using DIBAL in DCM. The aldehyde (187) was obtained in an excellent 98% yield.
N-Boc diene (188) was generated as before using ethyltriphénylphosphonium bromide. The product was made in good yield, however, as with N-Boc diene (177), it was difficult to interpret the stereochemistry of the new C=C double bond. On the other hand, N-Boc diene (189) was obtained in a good yield as an inseparable approximate 2:1 mixture of trans:cis isomers (Scheme 123).

The anionic amino-Cope rearrangement substrates (181) and (182) were furnished by removal of the N-Boc group using formic acid (Scheme 124).

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Diene (181) was obtained in quantitative yield as an inseparable 4:1 mixture of geometric isomers. With the aid of $^1$H NMR homonuclear decoupling experiments, we were able to determine that the cis isomer corresponded to the major product. The 1,6-diphenyl diene (182) was isolated in 80% yield following flash column chromatography and in a 2.5:1 mixture of inseparable isomers in favour of the trans isomer. It would be fair to assume that as the ylide generated from ethyltriphenylphosphonium bromide is not stabilised, the major isomers of dienes (179) and (181) would be expected to be the cis isomer and in the case of the latter, this has been confirmed. This argument is strengthened as the ylide generated from benzyltriphenylphosphonium bromide, which is expected to be more stabilised, delivers the trans isomer as the major product.

The route to the diene substrates takes a minimum of 7 steps and has overall yields of 33%, 37%, 24% and 20% for dienes (179), (180), (181) and (182) respectively. Although somewhat longer, the methodology has a distinct advantage over other previous routes developed within the group, in that substituents at both C-1 and C-6 can be introduced quite easily.
3.3.2. Preparation of Non-Racemic 1,6-Disubstituted-3-Amino-1,5-Diene Substrates

The production of dienes (179-182) has now allowed us to further study the mechanism by which the amino-Cope rearrangement proceeds. To further enhance the application of these substrates it was decided to generate their optically active equivalents. This exercise would require modification of the route developed in Section 3.3.1. so as to incorporate enantiopure starting materials. Scheme 125 illustrates the course by which we aimed to synthesis our diastereoisomerically pure diene substrates (194) for anionic amino-Cope rearrangement studies.

Scheme 125
By altering the order of the original reaction sequence established in Section 3.3.1., it can be shown that non-racemic compounds such as (190) can be integrated without increasing the number of steps. Imine (192) can be readily made by condensing the enantiomeric primary amine (190) with commercially available ethyl glyoxalate (191). It is thought that following imine reduction and protection of the secondary amine, stereocontrolled introduction of the allylic electrophile can be achieved to generate (193). Diene (194) would then be prepared as before by ester reduction using DIBAL, Wittig olefination and deprotection. Initially we decided to employ (S)-α-methylbenzylamine (195) as the starting amine.

![Scheme 126](image)

Imine ester (196) was delivered in an excellent 94% yield following condensation between (S)-α-methylbenzylamine (195) and ethyl glyoxalate in DCM in the presence of activated 4Å molecular sieves. Although this reaction appeared routine, ethyl glyoxalate exists partly in the polymerized form and may have required harsher conditions to effect conversion. Since we found this reaction to proceeded efficiently, we decided to employ (R)-O-Bn valinol (197) to introduce this previously applied β-aminoalcohol auxiliary (Scheme 127).

![Scheme 127](image)

As expected, imine ester (198) was obtained in high yield. The next step was to reduce the imines (196) and (198) to the corresponding amines (199) and (200). In view of the

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fact that the imines were obtained without difficulty, we anticipated that amines (199) and (200) could be made directly from the starting primary amines by reductive amination. This would also reduce the number of stages in the preparation of the diene substrates.

![Scheme 128](image)

Amino esters (199) and (200) were furnished in 87% and 70% yields, respectively by the conditions shown in Scheme 128. Protection of the amines (199) and (200) was achieved in good yield by generating their N-Boc derivatives as shown in Scheme 129.

![Scheme 129](image)
The alkylation step was attempted using crotyl bromide as the electrophile on both N-Boc protected ester substrates (201) and (202). Crotyl derivative (203) was produced in good yield but as a disappointing 2.5:1 mixture of inseparable diastereoisomers.

![Scheme 130](image)

On the other hand, crotylation of (202) gave (204) as a mixture of inseparable isomers with a higher diastereoselectivity of 4:1, albeit in only a moderate yield of 54% as shown in Scheme 131.

![Scheme 131](image)

Although, in early stages of development, based on previous work within the group, it would be fair to say that an increase in steric bulk of the amine auxiliary component leads to a corresponding increase in diastereoselectivity of the alkylation step (Schemes 130 and 131). To confirm this, screening of other amine auxiliaries, in particular the β-aminoalcohol auxiliaries, which has been employed highly successfully, should be carried out.

Due to time constraints we were unable to determine the stereochemistry of the major diastereoisomers of the derivatised N-Boc esters (203) and (204). Furthermore, again due to lack of time, the synthesis towards the diene substrates for amino-Cope rearrangement studies was unfortunately not completed. However, previous work on the racemic route

Results & Discussion
towards the 1,6-disubstituted-3-amino-1,5-dienes, has laid precedent towards successful accomplishment of the asymmetric variants.

3.4. Anionic Amino-Cope Rearrangements of Novel 1,6-Disubstitued-3-Amino-1,5-Dienes

Section 1.4.7. summarises work by previous group members on the mechanistic studies on the anionic amino-Cope rearrangement. Due to our development of unprecedented 1,6-disubstituted-3-amino-1,5-diene substrates, we were in a position to probe this area of the rearrangement in more depth. Similar studies have been carried out with substituents in the 4-position of the diene core, by which rearrangement proceeded by a non-exclusive pathway resulting in mixtures of products.53-54

Rearrangement of diene substrate (166) could substantiate the involvement of an alternative mechanism by which it occurs. Scheme 132 highlights that a concerted [3,3] sigmatropic rearrangement of (166) would lead only to product (205), whereas the competing [1,3] rearrangement would give a mixture of products (205) and (206).

![Scheme 132](image)
Button\textsuperscript{39} performed anionic amino-Cope rearrangements on racemic substrates using various conditions. We initially decided to perform the rearrangements on our current substrates in THF and by deprotonating the substrates at $-78^\circ$C using $n$-BuLi.

\begin{align*}
\text{Ph} & \quad \text{H} \quad \text{Ph} \\
& \quad \text{n-BuLi/THF} \\
(179) & \quad \xrightarrow{\text{n-BuLi/THF}} \\
\text{Me} & \quad \text{Me} \\
& \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}

Scheme 133

Anionic amino-Cope rearrangement was attempted on 1,6-dimethyl diene substrate (179) by deprotonation at $-78^\circ$C using 1.5 equivalents $n$-BuLi and stirring at the same temperature for 1 hour before warming to room temperature. The reaction was analysed by TLC and $^1$H NMR, which showed the majority of the reaction contents to be starting material. The reaction was heated to reflux for 1 hour. However, this had no effect on the conversion of starting material.

The rearrangement was repeated using 3 equivalents $n$-BuLi with the reaction allowed to warm to room temperature from $-78^\circ$C overnight. Reflux was also applied, again proving fruitless. Attempts were also made on the rearrangement using additives in the form of DMPU in THF, and TMEDA in hexanes. However, starting material was the major product of each attempt. We were unsure as to why substrate (179) was unsuccessful on rearrangement and decided to try other substrates.

\begin{align*}
\text{Ph} & \quad \text{H} \quad \text{Ph} \\
& \quad \text{n-BuLi/THF} \\
(180) & \quad \xrightarrow{\text{n-BuLi/THF}} \\
\text{Me} & \quad \text{Me} \\
& \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}

Scheme 134

Results & Discussion
Rearrangement of (180) was achieved successfully by deprotonation with 2 equivalents of n-BuLi and with the reaction allowed to warm to room temperature from -78 °C overnight. Flash column chromatography of the crude product gave aldehyde (67) as the sole product in 47% yield. This would suggest that a concerted pathway was in operation for diene substrate (180). The product was obtained as an inseparable mixture of syn and anti diastereoisomers in a ratio 11:9 in favour of the syn isomer as determined by 1D NOESY and TOCSY. Irradiating the multiplet signal of the phenyl substituent generated a positive nOe with the signal corresponding to the proton adjacent to the methyl group of the minor isomer. This space interaction provided reliable evidence to support the fact that the minor isomer is indeed shown to be the anti diastereoisomer. This result is consistent with the 11:9 trans: cis ratio around C-1 which is seen in the preceding diene substrate (180).
Using previously employed chair transition states, in which the amine component occupies a pseudo-equatorial orientation, we can see our findings are as expected where the trans, trans isomer of (180) is anticipated to yield the syn isomer of (67) and the cis,
trans substrate to deliver the anti product as illustrated in Scheme 135. The fact that the stereochemistry of the product can be predicted by such models was highly encouraging.

\[ \text{Ph-} \text{H-} \text{Me} \xrightarrow{n-\text{BuLi/THF}} \text{O Me} \text{H-} \text{Ph} \]

Scheme 135

Diene substrate (181), was rearranged using the conditions employed for substrate (180) as shown in Scheme 136. In this event, an inseparable mixture of aldehydes (209) and (210) were obtained in a combined yield of 48% following flash column chromatography. The proportion of [3,3] to [1,3] products was shown to be marginally in favour of the [1,3] product (210), with a ratio of 4:5 calculated. The [1,3] product (210) was obtained exclusively as the trans isomer. The [3,3] product (209) was revealed to be in an almost 1:1 mixture of syn and anti diastereoisomers. This may suggest that, although designated as the [3,3] product, aldehyde (209) could also be formed by the dissociative mechanism resulting from re-combination of the allyl anion via the carbon adjacent to the substituent (C-6 in original diene) as shown in Scheme 132.

It would appear that having a phenyl substituent at C-6 encourages the transformation to proceed by a dissociative or [1,3] mechanism more so than the presence of a methyl substituent in the same position. Although aldehyde (209) may have been formed through the dissociative mechanism, we cannot rule out the activity of a [3,3] concerted pathway.

\[ \text{Ph-} \text{H-} \text{Me} \xrightarrow{n-\text{BuLi/THF}} \text{O Me} \text{H-} \text{Ph} \]

Scheme 137

Results & Discussion
Interestingly, rearrangement of (182) using the same conditions yielded only the trans [1,3] product (212). There was no evidence of the [3,3] product (211) in the crude $^1$H NMR and aldehyde (212) was isolated in a 51% yield following flash column chromatography. If the rearrangement proceeded solely by way of a dissociative pathway, as it appears in the case of diene (181), one would expect to observe both aldehydes (211) and (212) due to equal probability of recombination through C-4 or C-6 of the starting diene. However, this result may be attributed to unfavourable steric effects upon recombination of the intermediate imine with the stabilised phenyl substituted allyl anion in the formation of aldehyde (211). It would appear that the phenyl substituted allyl anion exhibits partiality to add via the carbon centre furthest away from the substituent in preference to the one adjacent to it, thus yielding aldehyde (212) as the exclusive product.

The results of the anionic amino-Cope rearrangement of substrates (179-182) are summarised in Table 19.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>[3,3]/[1,3]</th>
<th>Syn/Anti [3,3]</th>
<th>Cis/Trans [1,3]</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>176</td>
<td>Me</td>
<td>Me</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>177</td>
<td>Me</td>
<td>Ph</td>
<td>1:0</td>
<td>11:9</td>
<td>-</td>
<td>47</td>
</tr>
<tr>
<td>178</td>
<td>Ph</td>
<td>Me</td>
<td>4:5</td>
<td>1:1</td>
<td>0:1</td>
<td>48</td>
</tr>
<tr>
<td>179</td>
<td>Ph</td>
<td>Ph</td>
<td>0:1</td>
<td>-</td>
<td>0:1</td>
<td>51</td>
</tr>
</tbody>
</table>

**Table 19**

It was interesting to note that although rearrangement of (179) was shown to be unsuccessful under varied conditions, Essat had performed successful rearrangement on substrate (213), which had methyl substituents at C-1 and C-4.54
Also worth noting for comparison was rearrangement of diene substrate (70) as shown in Scheme 138. Whereas in our hands we observed only [3,3] product, Essat observed a 2:1 mixture of [3,3]:[1,3] products.

Although our substrates differ to those of Essat’s in the position of the methyl substituent, it has been previously suggested that C-4 and C-6 substituents have essentially the same stabilising effect on anionic oxy-Cope rearrangements, albeit substituents in this argument is directed to thioalkyl groups. Essat proposed that, in the particular case of diene substrates (213) and (70), the diene may have been forced to rearrange via the dissociative pathway as a consequence of steric interactions between the aminoalcohol segment and the adjacent methyl substituent.

Essat also showed that replacing phenyl with methyl at C-1 resulted in a much higher preference towards the [3,3] product in both polar and non-polar solvents compared to only a slight preference to the [3,3] product in polar solvents and a high preference towards the [1,3] product in non-polar solvent when C-1 is occupied by a phenyl substituent. It was proposed that the phenyl substituent at C-1, due to its aromatic nature,
introduces stability in the α,β-unsaturated imine component of the dissociated complex after fragmentation and hence facilitates the formation of the [1,3] product.

However, our findings when performing anionic amino-Cope rearrangement of diene substrate (180) contradicts this hypothesis as it was shown that the [3,3] product was the sole product. It cannot be ruled out that a very rapid fragmentation-recombination pathway may be occurring resulting in the [3,3] product.

3.5. Future Work

Due to shortage of time, we were unable to study further the anionic amino-Cope rearrangement of 1,6-disubstitued-3-amino-1,5-dienes. Investigations into varying solvents and additive additions would be advantageous. This would be in addition to the rearrangements of the non-racemic substrates discussed in Section 3.3.2., which would also provide information on the method of rearrangement of 3-amino-1,5-hexadiene substrates.

It would be beneficial for work to be carried out on optimising the Wittig olefination stage as we have observed that the stereoselectivity of the product after rearrangement may be predicted by the stereochemistry of the starting diene substrate. There have been modifications of the Wittig reaction over the years which can favour either cis or trans products and combined with the use of chiral auxiliaries, the prospect of generating highly defined stereochemical substrates is a promising aspiration.

With the research presented in Chapters 2 and 3, the Allin group is closer to realising the potential stereoselective synthesis of highly functionalised products such as (44) as shown in Figure 20 by successful application of the amino-Cope rearrangement of our novel 1,6-disubstitued-3-amino-1,5-dienes in tandem with the developed imine anion derivatisation chemistry.
Figure 20

(44)
Chapter 4

Results & Discussion

A New Route to the Tetracycline Antibiotics
4.1. Introduction

The art of total synthesis of elaborate organic natural products of biological interest has been a major challenge to chemists. Complex antibiotics based on natural products are almost invariably prepared by semi-synthesis or chemical transformation of the isolated natural products. This approach greatly limits the range of accessible structures that might be studied as new antibiotic candidates.144

The tetracycline antibiotics began to appear in the late 1940's and have since been widely used clinically in human and veterinary medicine.145 Because of their wide antimicrobial and clinical spectrum, they have proven highly effective in treating a wide range of bacterial infections and have assumed a major role in chemotherapy. However, decades of clinical use have led to the emergence of widespread bacterial resistance and, as a result, a need for the development of new antibiotics.146

The tetracycline class of antibiotics is characterized structurally by a carbon skeleton composed of four linearly fused six-membered carbon rings; a highly functionalized A-ring that is cis-fused to the B-ring, a C-ring containing a tetrasubstituted stereogenic centre and a D ring that is aromatic. This is exemplified by tetracycline147 (214) and is illustrated in Figure 21.

![Figure 21](image.png)

The tetracycline family of substituted hydronaphthacene compounds stem from distinct strains of Streptomyces bacteria. Aureomycin (215) (chlortetracycline) was the first member of this antibiotic family to be discovered by Duggar in 1948 from a culture of Streptomyces aureofaciens.148 Two years later, Finlay and co-workers reported the
isolation of terramycin (216) (oxytetracycline) from by *Streptomyces rimosus*\(^{149}\). The other known natural antibiotic in this series is demeclocycline (217) (demethylchlortetracycline)\(^{150}\).

Figure 22

Since the discovery of the natural tetracyclines, a number of second generation tetracyclines (those not available by purely microbiological techniques and are synthetically manipulated) have been introduced and have been employed clinically. These include, rolitetracycline (218) (pyrrolidinomethyltetracycline)\(^{151}\), lymecycline (219) (lysinomethyltetracycline)\(^{152}\), clomocycline (220) (chlormethylenecycline)\(^{153}\), methacycline (221) (6-methylenoxytetracycline)\(^{154}\), doxycycline (222) (6-deoxyoxytetracycline)\(^{155}\), and minocycline (223) (7-dimethylamino-6-demethyl-6-deoxytetracycline)\(^{156}\) (Figure 23).
Of those mentioned in Figure 23, the 6-deoxytetracyclines (222) and (223) are of particular recent interest, since it has been recognised that these compounds are considerably more resistant to degradation than their 6-hydroxy counterparts, and show equal or greater potencies in antibacterial assays. Unfortunately, the elaboration of natural tetracyclines is greatly limiting and general synthetic routes to diverse tetracyclines proves to be elusive.
4.2. Synthetic Approaches to the Tetracycline Antibiotics.

Synthetic approaches to the tetracyclines have varied little over that last 50 years with research largely restricted to semi-synthesis.\textsuperscript{158} The challenge of the tetracyclines has attracted many research groups and a substantial literature has built up on the subject, with the net result of all major tetracyclines being conquered. The magnitude of the accomplishment can be appreciated in the part of considering the number of contiguous asymmetric centres. Most approaches to the total synthesis of the tetracycline antibiotics have proceeded by stepwise assembly of the ABCD ring system, beginning with D or CD precursors and are typically low yielding.

The first synthesis of a tetracycline antibiotic was reported by Woodward and co-workers in 1968 with the synthesis of (±)-6-demethyl-6-deoxtetracycline (224).\textsuperscript{159} Although their route suffered from low yields (25 steps, \(\sim 0.002\%\) overall), this synthesis is of historical significance because it was the first preparation of a member of the tetracycline family (Scheme 139).
Since Woodward's contribution to the area, only a few other total syntheses have been achieved. The first total synthesis of a tetracycline natural product, (±)-12a-deoxy-5a,6-anhydrotetracycline (225), was achieved by Shemyakin et al. as shown in Scheme 140. The route utilised Diels-Alder chemistry to construct the B ring and Woodward's approach to ring A.
The Muxfeldt group achieved the total synthesis of (±)-terramycin (216) in 1979, utilizing a different approach that started from a CD ring precursor and building the A and B rings in a single step.\cite{161} The key step involved generation of thiazolone intermediate (226), which was then condensed with glutamate derivative (227) to give the tetracycline core (228). This low-yielding but elegant condensation created 3 new C-C bonds in one step with most of the positions having the appropriate substitution as the desired diastereoisomer readily crystallises (Scheme 141).
In 1996, a landmark synthesis carried out by Stork and co-workers produced (±)-12a-deoxytetracycline (232) (17 steps, 22% overall yield). The key step in this synthesis involved a double Claisen cyclisation to generate the A and B rings of the tetracycline nucleus as shown in Scheme 142. This involves generating ketal (230) from ketone (229), followed by deprotonation which initiates the cascade cyclisation. Considering the complexity of the cyclisation to generate (231), a yield of 59% was deemed very respectable. Unfortunately, hydroxylation at the C-12a position, which is known to be associated increased antimicrobial activity, could not be achieved.
4.3. Asymmetric Total Syntheses of the Tetracycline Antibiotics

Despite significant synthetic efforts, an asymmetric total synthesis of a tetracycline was not achieved until 2000 by Tatsuta when he prepared (−)-tetracycline (214) in a 34 step sequence from D-glucosamine in an 0.002% overall yield.164

Tatsuta’s group developed a novel approach; beginning from an A-ring precursor rather than with a D- or DC-ring precursor as seen in previous tetracycline syntheses. This enabled them to achieve the asymmetric synthesis by exploiting the carbohydrate chiral pool. The key step in this synthesis was the formation of the tetracycline skeleton (234) in 3 steps from α,β-unsaturated enone (233), culminating with a tandem Michael-Dieckmann reaction.
In 2005, Myers reported a new and convergent route to 6-deoxytetracycline (238) and structurally diverse analogues starting from benzoic acid. The Myers group chose to construct an AB-ring precursor enone (236) and stereospecifically coupled it to a D-ring precursor (237) via the Michael-Dieckmann reaction, generating the C-ring in the process. This approach allows for rapid access to analogues by structural modifications to the D-ring and also linear extensions to novel E-ring derivatives. In principle, this reaction could have yielded a mixture of four tetracycline diastereoisomers. Instead, the analogues are formed as largely one diastereoisomer with stereochemistry that matches that of the natural product.

The synthesis of 6-deoxytetracycline (238) is summarised in Scheme 144. The route was initiated by whole-cell microbial dihydroxylation of benzoic acid (which would become the B ring of the targeted 6-deoxytetracycline) using a mutant strain of *Alcaligenes eutrophus*, producing diol (235) with >95% enantiomeric excess and in 79% yield.
Compared to previous attempts to prepare members of this family, Myers’ strategy towards 6-deoxytetraycline is revolutionary, and with this convergent approach, derivatives that might be more potent can now be readily accessed. Myers and co-workers decided to apply a similar strategy towards the synthesis of (−)-tetracycline (214).166
Starting from an AB-ring precursor (239) previously employed in the synthesis of 6-deoxytetracycline analogues, a phenylsulfanyl substituent was added to the α-position of the enone to generate (240). *Endo*-selective Diels-Alder cycloaddition with benzocyclobutene (241) was achieved, giving the tetracycline nucleus (242). (-)-Tetracycline (214) was synthesised in a further 4 steps (Scheme 145).

The attraction of Myers' synthesis, when compared to Tatsuta's, is the remarkably quick access it provides to natural tetracycline (214) from simple starting materials.

Results & Discussion
4.4. A New Route to the Tetracycline Antibiotics

It can be seen that recent work towards the synthesis of the tetracycline antibiotics has greatly advanced the quest for accessing new candidates for combating the bacterial resistance towards existing tetracyclines.

Our group has proposed a novel and versatile route to access linear fused ring systems that could allow entry to the tetracycline and other natural product systems. Our approach is based around an innovative iterative protocol of aromatic Claisen rearrangement/ring closing metathesis chemistries.

![Scheme 146](image-url)
As outlined in Scheme 146, we envisage aromatic Claisen rearrangement on diallyl ether (243) to yield hydroquinone (244). Alcohol protection and ring closing metathesis is expected to give bicyclic linear fused adduct (245) of which sequential oxidation and rearomatisation would lead to 1,4-naphthalenediol (246). From this point, it is believed (246) can be fed back into the iterative process in order to add extra rings in a left-to-right fashion and finally furnish products such as (247).

Since alcohol protection is carried out following each Claisen rearrangement, it would be possible to use complementary protecting groups that would, at a later stage, enable selective deprotection of any pair of ring hydroxyl groups permit further functional manipulations of the tetracyclic core.

4.5. Initial Results

4.5.1. Formation of Bicyclic Linear-Fused Adduct

Scheme 147 depicts our successful route towards the bicyclic linear-fused adduct (252) and therefore establishing that the proposed Claisen/RCM approach to such systems is a viable synthetic protocol.
We were able to comfortably diallylate 2,3-dimethylhydroquinone (248) using conventional allylation conditions to give the Claisen-precursor (249) in good yield following flash column chromatography. Double aromatic Claisen rearrangement was successfully achieved by applying the method of Widenhoefer, which required heating bis-allyl ether (249) in refluxing mesitylene for 24 hours. The resulting hydroquinone (250) was obtained in good yield, however was shown to be unstable and was thus carried forward to the protection step promptly without further purification.

Thermal Claisen rearrangement on substrate (249) has been attempted elsewhere, although it is reported that the product obtained is the quinone (253) as shown in Scheme 148. However, we believe that this would require an oxidation to occur as well as rearrangement. Analysis of our Claisen product confirmed that hydroquinone (250) was obtained in our hands.
We choose to protect the alcohol moieties as their acetates using standard conditions to give diacetate (251). The final step involved ring closing metathesis of diacetate (251) using Grubbs 2nd generation catalyst and stirring in toluene for 24 hours. The bicyclic target (252) was obtained in good yield following flash column chromatography.

The two subsequent steps would require oxidation and rearomatisation to the 1,4-naphthalenediol (255). With this compound in hand, we felt we would be in an ideal position to perform the iterative process proposed in Scheme 156; a feat that we currently believe is unreported in the literature.

4.5.2. Oxidation of Bicyclic Linear-Fused Adduct

Many methods for oxygenation of unfunctionalized hydrocarbons have been developed over the years. The site to which we wished to introduce oxygen functionality was thought to be highly reactive. With it being benzylic as well as allylic we anticipated this would facilitate rapid oxidation. As a benzylic carbon is analogous to an allylic carbon in
its reactivity, oxidative methods are applicable to both systems and many general procedures are routinely utilised.\textsuperscript{171}

Rodriguez and co-workers reported the identical oxidative transformation that we wished to achieve using chromium(III) oxide in acetic acid.\textsuperscript{172} Unfortunately on each attempt of this reaction, even on altering conditions, naphthalene (256) was isolated as the major product as shown in Scheme 150.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme150.png}
\end{center}

\textbf{Scheme 150}

From this result it would appear that elimination through the double bond is occurring. We considered the conditions to be too harsh and decided to investigate alternative milder methods. Selenium dioxide is regarded as the most reliable and predictable reagent for the direct insertion of oxygen into an allylic C-H bond. Several studies of the stereochemistry and mechanism of these oxidations have been carried out over the years.\textsuperscript{173a} The general accepted mechanism is shown in Scheme 151.\textsuperscript{173b}
Although there are a number of ways of utilizing selenium methodology for allylic/benzylic oxidations, we choose to employ a widely exploited procedure developed by Sharpless in which a catalytic amount of selenium dioxide is used in the presence of t-buty1 hydroperoxide. This method has the advantage that reduced amounts of colloidal selenium residues and organoselenium by-products are observed. The purpose of the hydroperoxide is to re-oxidise reduced selenium species back to SeO₂. Regrettably, the reaction failed to give the desired product (254) under catalytic and also stoichiometric conditions. Again naphthalene (256) was shown to be the sole product.

Further attempts on the oxidation were attempted under different methods and are summarised in Table 20.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CrO₃/AcOH¹⁷²</td>
<td>(256)</td>
</tr>
<tr>
<td>2</td>
<td>SeO₂/t-BuOOH¹⁷⁴ (catalytic and stoichiometric)</td>
<td>(256)</td>
</tr>
<tr>
<td>3</td>
<td>SeO₂/EtOH¹⁷⁵</td>
<td>(256)</td>
</tr>
<tr>
<td>4</td>
<td>PCC¹⁷⁶</td>
<td>(256)</td>
</tr>
<tr>
<td>5</td>
<td>CrO₃/t-BuOOH¹⁷⁷</td>
<td>(256)</td>
</tr>
<tr>
<td>6</td>
<td>KMnO₄/Al₂O₃¹⁷⁸</td>
<td>(256)</td>
</tr>
</tbody>
</table>

Table 20
As can be seen, all attempts yielded the fully aromatised naphthalene (256). With (256) in hand we decided to try to employ Yamazaki's reported method of preparing quinones by chromium(III) oxide catalysed oxidation, with periodic acid as the terminal oxidant, to generate quinone (254). However, only starting material was recovered when applied to our substrate.

\[
\begin{align*}
\text{(256)} & \xrightarrow{\text{CrO}_3, \ H_2\text{IO}_6, \ MeCN} \times \xrightarrow{\text{(254)}} \\
\end{align*}
\]

Scheme 152

Due to the lack of progress in oxidising bicyclic adduct (251) to the required (254), we returned to the diacetate (251) to try the oxidation before the ring closing metathesis step. We were confident that this would be fruitful as the substrate still possessed its allylic/benzylic reactivity and the possibility of elimination was nullified.

\[
\begin{align*}
\text{(251)} & \xrightarrow{[O]} \text{(257)} \\
\end{align*}
\]

Scheme 153

We were disappointed at the failure when attempting the oxidation on diacetate (251). The conditions under entries 1, 2 and 5 in Table 20 were applied to diacetate (251), but only gave back starting material in all cases. With this setback, we re-thought our approach to introducing oxygenation to our RCM substrate.

Results & Discussion - 159 -
4.5.3. Fries Rearrangement Route

The Fries rearrangement of phenyl esters has been reported as the most efficient process in direct 2-acylation reactions of phenols in the preparation of hydroxyaryl ketones.\textsuperscript{180} The reaction usually requires stoichiometric amounts of strong Lewis acids such as aluminium(III) chloride,\textsuperscript{181} although milder catalysts like titanium(IV) chloride\textsuperscript{182} and lanthanide triflates\textsuperscript{183} have also been employed. The rearrangement can also be carried out with UV light in a reaction called the photo-Fries rearrangement.\textsuperscript{184}

We rationalised that double Fries rearrangement of (258) would provide us a plausible and direct route to (257) as proposed in Scheme 154. We were able to prepare bis-acrylate (258) from 2,3-dimethylhydroquinone (248) and acryloyl chloride in high yield after flash column chromatography as shown in Scheme 155.

Results & Discussion
Fries rearrangement using stoichiometric aluminium(III) chloride is generally not regioselective and the drastic conditions required for AlCl₃-mediated acylation can cause side reactions and deacylation. However, Vukičević found that the reaction can proceed in moderate yield by doubling the quantity of AlCl₃ and in diluted solutions at room temperature rather than the neat, high temperatures usually encountered.

Bis-acrylate (258) was stirred with aluminium(III) chloride in DCM for 24 hours at room temperature. ¹H NMR of the product confirmed that only starting material was obtained. The reaction was attempted again, this time using boron trifluoride diethyl etherate as the Lewis acid in benzene. Unfortunately, starting material was once again recovered.

We next attempted the Fries rearrangement using titanium(IV) chloride as catalyst and heating the mixture at 140 °C for 2 hours. Spectral analysis of the isolated product following flash column chromatography suggested formation of the undesired cleavage product (260) as shown in Scheme 156. Further reviewing of the literature disclosed the fact that double Fries rearrangement is not usually observed as the first rearrangement deactivates the ring by the presence of the electron-withdrawing group and thus makes the second rearrangement unfavourable. Our results would appear to support this argument.
4.5.4. Review of Original Route

We decided to return to our originally proposed route and deliberated on how to introduce the oxygen functionality other than by allylic/benzylic oxidation methods. It was apparent that the C=C of the second ring was the cause of the problems associated with elimination to the naphthalene (256). We therefore decided to remove the double bond and attempt oxidation on the saturated substrate (261), which would still process high benzylic reactivity.
Catalytic hydrogenation of the ring closed substrate (252) was achieved using Pd/C under an atmosphere of hydrogen, with stirring in ethanol at room temperature for 24 hours. Oxidation was then attempted using what we believed to be the most harsh and effective method; chromium(III) oxide in acetic acid. The reaction was stirred at room temperature for 20 hours. Initial TLC and \(^1\)H NMR spectral analysis was inconclusive. However, due to the loss in symmetry of the compound, \(^1^3\)C NMR analysis provided evidence of mono-oxidised product (263). Further analysis confirmed (263) to be the sole product of the reaction.

\[
\begin{align*}
\text{(261)} & \xrightarrow{\text{CrO}_3, \text{AcOH}} \text{(262)} \\
\text{(263)} & \xrightarrow{\text{CrO}_3, \text{AcOH}, \text{34\%}} \text{(262)}
\end{align*}
\]

Scheme 158

Unfortunately, due to time constraints, we were unable to further develop this route. It was encouraging that we capable of oxidising the linear fused bicyclic template, albeit only mono-oxidation being achieve as opposed to the required bis-oxidation product (262). However, we were confident that this transformation was possible and this was later found to be the case when a colleague effected bis-oxidation of substrate (261) by simple modification of the conditions shown in Scheme 158.\(^{187}\) The substrate was heated to 50 °C with chromium(III) oxide in acetic acid, which was sufficient to effect bis-oxidation to give (262). High yields, in excess of 80%, were obtained when the mixture was quenched with a minimum amount of ice water and kept in a freezer overnight.
With these promising results, we believe that we are in an exciting point in our research and that the Allin group is in an ideal position to pursue this novel synthetic strategy with a view to access a range of important and related biological natural products.

4.6. Future Work

With di-ketone (262) now in hand, rearomatisation would be expected to yield (255) from which we would be able to perform the iterative process as proposed (Scheme 159).

![Scheme 159](image)

This new protocol has great flexibility and versatility in the preparation of building blocks for the target synthesis of a range of natural products and is not just limited to the tetracycline family of antibiotics. From the one iterative cycle we have achieved, we now have an avenue to a potential building block for juglone and C-aryl glycoside chemistry, which would enable the synthesis of products such as *alkannin* (264) and *aquayamycin* (265) as shown in Scheme 160. These natural products show a wide spectrum of biological activities including antibacterial, anti-cancer, anti-thrombotic and enzyme inhibition activity.
Two iterative cycles presents us with a building block from which C-aryl glycoside and tetracycline templates could be accessed. In addition, anthracyclines such as adriamycin (267), which are known to be important anti-tumour drugs, can also be approached using the sequential aromatic Claisen rearrangement/RCM methodology.
The new and promising tetracycline antibiotic minocycline (223) is unusual in this series as it contains an amino-substituent on the terminal D-ring (Figure 24). This provides the opportunity to investigate the formation of a range of product types resulting from variation of the heteroatom in the initial substrate such as those shown in Figure 25.
Variation of the heteroatoms shown in Figure 25 would allow the preparation of compounds by applying mixed Claisen/aza-Claisen and Claisen/thia-Claisen chemistries.

![Figure 25](image)

It can be seen from these initial studies that this novel protocol has given great scope for further research and if successfully achieved, the access of numerous natural products is possible.
Chapter 5

Experimental
5.1. General Information

Solvents and Reagents

All solvents, where necessary, were dried, distilled and either used immediately or stored over 4Å molecular sieves prior to use.

Dichloromethane: distilled from phosphorus pentoxide
Diethyl ether: distilled from sodium and benzophenone
Ethyl acetate: distilled from calcium chloride
40-60 petroleum ether: distilled from calcium chloride
Tetrahydrofuran: distilled from sodium and benzophenone
Toluene: distilled from sodium

Unless otherwise stated, light petroleum refers to 40-60 petroleum ether. Chemicals used in this work were purchased from Acros (Fischer) Chemicals Ltd., Aldrich Chemical Co. Ltd. and Lancaster Synthesis Ltd., and where necessary, were purified before use.

Chromatographic Procedures

Analytical thin layer chromatography (TLC) was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) and/or stained with potassium permanganate, iodine or phosphomolybdic acid solution. Flash column chromatography was carried out using Merck Kieselgel 60 H silica. Samples were applied as saturated solutions in an appropriate solvent or pre-absorbed onto the minimum quantity of silica. Pressure was applied to the column by use of hand bellows or a pressurised flow of nitrogen.

HPLC separations were carried out on Hewlett Packard Series 1100. Column: Supelco, Supelcosil ABZ+PLUS column. 15 cm x 4.6 mm, 5 µm. Flow rate 1 ml/min, injection volume 2 µl.
Spectral Analysis

Infra-red (IR) spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Perkin Elmer Paragon 1000 FT-IR spectrometer, with internal calibration. Solid samples were run as Nujol\(^\circledR\) mulls or dissolved in an appropriate solvent and applied as a thin film or CaS thin film to the NaCl IR plates. Liquid samples were applied neat to the plates and run as thin films.

\(^1\)H and \(^{13}\)C Nuclear Magnetic Resonance (NMR) spectra were recorded using a Bruker AC250 or DPX400 spectrometer. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). All NMR samples were prepared in deuterated solvents using tetramethylsilane (TMS) as an internal standard (0 ppm). All values are quoted in ppm relative to TMS and coupling constants (J values) are reported when possible in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the \(^1\)H NMR spectrum.

Electron Impact (EI) and Fast Atom Bombardment (FAB) mass spectra were recorded on a Fisons VG Quattro II SQ instrument and accurate mass were recorded using a Kratos MS80 instrument. Real-time Chemical ionisation mass spectra were recorded on a Gilson Micromass ZMD.

LC/MS analysis was carried out on a Gilson Micromass ZQ. Detection method: Chemical ionisation. Column: Supelco, Supelcosil ABZ+PLUS column. 3.3cm x 4.6 mm, 3 \(\mu\)m. Flow rate 1 ml/min, injection volume 1 \(\mu\)l.

Other Data

Melting points were determined using an Electrothermal 9100 melting point instrument and are uncorrected. Optical rotations were performed where possible using an Optical Activity AA-10 automatic polarimeter and are reported in units of 10\(^{-1}\) deg cm\(^2\) g\(^{-1}\). All yields quoted are for isolated pure products unless stated otherwise.
5.2. Development of the Amino-Cope Rearrangement

5.2.1. Preparation of Aminoalcohol and O-Bn Aminoalcohol Derived Diene Substrates

5.2.1.1. Reduction of Amino Acids

General Method

Chlorotrimethylsilane (15.2 cm$^3$, 120.00 mmol) was added to suspension of lithium borohydride (1.31 g, 60.00 mmol) in anhydrous THF (85 cm$^3$) under an inert atmosphere of nitrogen over 5 minutes at room temperature. Amino acid (30.00 mmol) was then added over 5 minutes. The mixture was left to stir at room temperature for 24 hours then quenched with methanol until there was no effervescence visible. This was followed by removal of solvent under reduced pressure. The remaining residue was then treated with 20% aqueous potassium hydroxide solution and extracted with DCM (3 x 30 cm$^3$). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the required aminoalcohol.

1. (2S)-2-Amino-3-phenyl-propan-1-ol$^{80}$

Amino acid reduction of (S)-phenylalanine (5.00 g, 30.09 mmol) was carried out using the general method described. (S)-Phenylalaninol (90) was obtained as a pale yellow solid (4.30 g, 95%), which was used without further purification. mp 92-94 $^\circ$C (Lit. mp 92-94 $^\circ$C$^{188}$; [α]$^{25}_D$ -18.5 (c 1.08, DCM) (Lit. [α]$^{25}_D$ -22.8, c 1.2, 1N HCl)$^{188}$; ν$_{max}$ (film/cm$^{-1}$): 3080 (O-H), 3355 and 1578 (N-H); δ$_H$ (400MHz; CDCl$_3$): 2.50 (1H, dd, $J$
13.6 and 8.8, \(CH(H)CHNH_2\), 2.79 (1H, dd, \(J\) 13.6 and 5.2, \(CH(H)CHNH_2\), 3.08-3.13 (1H, m, \(NH_2CH\)), 3.39 (1H, dd, \(J\) 10.8 and 7.2, \(CH(H)OH\)), 3.62 (1H, dd, \(J\) 10.8 and 4.0, \(CH(H)OH\)) and 7.18-7.32 (5H, m, ArH); \(\delta_C\) (100MHz; CDCl\(_3\)): 41.09 (CH\(_2\)), 54.60 (CH), 66.50 (CH\(_2\)), 126.80 (CH), 128.97 (2 x CH), 129.60 (2 x CH) and 139.10 (q); m/z (FAB) 152 ((M + 1)\(^+\), 100%); Found: 152.1074; C\(_9\)H\(_{13}\)NO requires (M + 1)\(^+\), 152.1075.

2. (2R)-2-Amino-3-phenyl-propan-1-ol\(^{10}\)

\[
\begin{align*}
&\text{OH} \\
&\text{NH}_2 \\
&\text{Ph} \\
&(101)
\end{align*}
\]

Amino acid reduction of (R)-phenylalanine (5.00 g, 30.09 mmol) was carried out using the general method described. (R)-Phenylalaninol (101) was obtained as a pale yellow solid (4.30 g, 95%), which was used without further purification. mp 91-93 °C (Lit. mp 92-94 °C\(^{188}\)), \([\alpha]_D^{25}\) 21.6 (c 1.15, DCM) (Lit. \([\alpha]_D^{25}\) 23.0, c 1.2, 1N HCl\(^{188}\); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 3079 (O-H), 3355 and 1575 (N-H); \(\delta_H\) (250MHz; CDCl\(_3\)): 2.51 (1H, dd, \(J\) 13.4 and 8.8, \(CH(H)CHNH_2\)), 2.80 (1H, dd, \(J\) 13.4 and 5.1, \(CH(H)CHNH_2\)), 3.06-3.16 (1H, m, \(NH_2CH\)), 3.40 (1H, dd, \(J\) 10.6 and 7.2, \(CH(H)OH\)), 3.65 (1H, dd, \(J\) 10.9 and 3.9, \(CH(H)OH\)) and 7.18-7.35 (5H, m, ArH); \(\delta_C\) (100MHz; CDCl\(_3\)): 40.77 (CH\(_2\)), 54.18 (CH), 66.19 (CH\(_2\)), 126.41 (CH), 128.58 (2 x CH), 129.20 (2 x CH) and 138.68 (q); m/z (El) 152 ((M + 1)\(^+\), <1%); Found: 152.1078; C\(_9\)H\(_{13}\)NO requires (M + 1)\(^+\), 152.1075.
3. (2S)-2-Amino-3-methylbutan-1-ol\textsuperscript{80}

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

Amino acid reduction of (S)-valine (7.50 g, 64.02 mmol) was carried out using the general method described. (S)-Valinol (107) was obtained as a yellow oil (5.70 g, 86%), which was used without further purification. mp 31-33 °C (Lit. mp 30-32 °C)\textsuperscript{189}; [\alpha]_{D}^{25} = 25.2 (c 1.24, DCM) (Lit. [\alpha]_{D}^{25} = 10.0, c 10% in H\textsubscript{2}O)\textsuperscript{189}; \nu_{\text{max}} (\text{film/cm}^{-1}): 3354 (O-H), 2957 and 1577 (N-H); \delta_{H} (250MHz; CDCl\textsubscript{3}): 0.92 (6H, dd, J 6.9 and 2.5, CH(CH\textsubscript{3})\textsubscript{2}), 1.51-1.70 (1H, m, CH(CH\textsubscript{3})\textsubscript{2}), 2.57 (1H, ddd, J 10.1, 6.2 and 3.7, CHNH\textsubscript{2}), 3.32 (1H, dd, J 10.9 and 8.4, CH(H)OH) and 3.63 (1H, dd, J 10.6 and 3.7, CH(H)OH); \delta_{C} (100MHz; CDCl\textsubscript{3}): 18.43 (CH\textsubscript{2}), 19.34 (CH\textsubscript{2}), 31.20 (CH), 58.47 (CH) and 64.65 (CH\textsubscript{2}); m/z (FAB) 104 ((M + 1)^{+}, <1%).

4. (2R)-2-Amino-3-methylbutan-1-ol\textsuperscript{80}

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

Amino acid reduction of (R)-valine (5.00 g, 42.68 mmol) was carried out using the general method described. (R)-Valinol (124) was obtained as a yellow solid (3.46 g, 79%), which was used without further purification. mp 34-36 °C (Lit. mp 35-36 °C)\textsuperscript{189}; [\alpha]_{D}^{25} = -28.3 (c 1.20, DCM) (Lit. [\alpha]_{D}^{25} = -16.0, c 10% in EtOH)\textsuperscript{189}; \nu_{\text{max}} (\text{film/cm}^{-1}): 3353 (O-H), 2958 and 1588 (N-H); \delta_{H} (400MHz; CDCl\textsubscript{3}): 0.92 (6H, dd, J 6.8 and 5.6, CH(CH\textsubscript{3})\textsubscript{2}), 1.53-1.61 (1H, m, CH(CH\textsubscript{3})\textsubscript{2}), 2.56 (1H, ddd, J 8.8, 6.4 and 4.0, CHNH\textsubscript{2}), 3.29 (1H, dd, J 10.8 and 9.2, CH(H)OH) and 3.64 (1H, dd, J 10.4 and 4.0, CH(H)OH); \delta_{C} (100MHz; CDCl\textsubscript{3}): 18.42 (CH\textsubscript{2}), 19.32 (CH\textsubscript{2}), 31.62 (CH), 58.48 (CH) and 64.75 (CH\textsubscript{2}); m/z (FAB) 104 ((M + 1)^{+}, 2%); Found: 103.0996; C\textsubscript{6}H\textsubscript{13}NO requires (M + 1)^{+}, 103.0997.
5.2.1.2. Preparation of O-Bn Aminoalcohols

**General Method**

Anhydrous THF (10 cm³) was added to sodium hydride (60% dispersion in mineral oil, 0.39 g, 9.85 mmol) at 0 °C under an inert atmosphere of nitrogen. Whilst maintaining the temperature at 0 °C, aminoalcohol (8.95 mmol) in anhydrous THF (35 cm³) was added. The mixture was heated to reflux for 30 minutes before cooling to room temperature. Benzyl chloride (1.0 cm³, 8.06 mmol) was added and the resulting mixture heated to reflux for 2 hours. The reaction was allowed to cool to room temperature before being quenched with water. This was followed by removal of solvent under reduced pressure. The remaining residue was then treated with 1M aqueous hydrochloric acid solution and extracted with DCM. The aqueous phase was adjusted to pH>12 with 6M aqueous sodium hydroxide solution and extracted with DCM. The combined organic phases were then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product.

5. (2S)-1-(Benzyloxy)-3-phenylpropan-2-amine

O-Bn protection of (S)-phenylalaninol (90) (1.35 g, 8.95 mmol) was carried out using the general method described. Recrystallisation from DCM/hexane gave the (S)-O-Bn phenylalaninol (106) as a yellow crystalline solid (1.92 g, 89%). mp 158-160 °C; [α]²⁵_D 41.8 (c 1.13, DCM) (Lit. [α]²⁵_D 29.1, c 0.97, CHCl₃)¹⁰⁰; ν max (film/cm⁻¹): 1173 (O-C), 3372 and 1603 (N·H); liH (400MHz; CDCl₃): 2.97 (lH, dd, J 12.8 and 8.8, PhCH(H)CH), 3.18 (lH, dd, J 13.2 and 4.8, PhCH(H)CH), 3.47-3.59 (3H, m, CHNH₂ and CHCH₂OCH₂Ph), 4.50 (2H, dd, J 39.6 and 7.6, PhCH₂O) and 7.14-7.33 (10H, m, ArH); 8c (100MHz; CDCl₃): 36.44 (CH₂), 53.02 (CH), 68.64 (CH₂), 73.30 (CH₂), 126.97 (CH),
127.74 (CH), 127.79 (2 x CH), 128.39 (2 x CH), 128.69 (2 x CH), 129.32 (2 x CH), 136.11 (q) and 137.45 (q); m/z (El) 241 (M⁺, <1%); Found: 241.1461; C₁₆H₁₉NO requires M⁺, 241.1467.

6. (2S)-1-(Benzyloxy)-3-methylbutan-2-amine\(^{88}\)

\[
\begin{align*}
&\text{O-Bn protection of (S)-valinol (107) (5.00 g, 48.46 mmol) was carried out using the} \\
&\text{general method described. Dry flash column chromatography on silica, eluting initially} \\
&\text{with 2%/0.25% methanol/ammonia in DCM gave product (S)-O-Bn valinol (108) as a} \\
&\text{yellow oil (7.91 g, 84%). } \ \ \ \ [\alpha]^{25}_D 12.7 (c 1.07, \text{DCM}) \ (\text{Lit. } [\alpha]^{25}_D 16.4, c 1.48, \text{CHCl}_3)\text{;} \\
&\nu_{\text{max}} (\text{film/cm}^{-1}): 1098 (\text{O-C}), 3375 \text{ and } 1585 (\text{N-H}); \ \delta_1 (400MHz; \text{CDCl}_3): 0.91 (6H, dd,} \\
&J 6.8 \text{ and } 2.9, \text{ CH(}CH_3)\text{)}_2, 1.63-1.71 (1H, m, CH(CH_3)\text{)}_2, 2.79 (1H, ddd, J 9.7, 6.0 \text{ and} \\
&3.8, \text{ CH(}NH_2)\text{)}, 3.31 (1H, dd, J 9.1 \text{ and } 8.1, \text{ CH(}H\text{)OCH}_2\text{Ph}), 3.54 (1H, dd, J 9.1 \text{ and } 3.8,} \\
&\text{CH(}H\text{)OH}_2\text{Ph}), 4.53 (2H, s, PhCH}_2\text{O) and } 7.27-7.37 (5H, m, \text{Ar}H); \ \delta_\text{C} (100MHz;} \\
&\text{CDCl}_3): 18.17 (\text{CH}_3), 19.41 (\text{CH}_3), 30.84 (\text{CH}), 56.39 (\text{CH}), 73.27 (\text{CH}_2), 73.81 (\text{CH}_2),} \\
&127.61 (\text{CH}), 127.66 (2 \text{ x CH}), 128.40 (2 \text{ x CH}) \text{ and } 138.40 (q); \ m/z (\text{El}) 194 ((M + 1)^+; \ <1%); \text{Found: 193.1468; C}_{12}H_{19}NO \text{ requires M}^+, 193.1467.}
\end{align*}
\]

7. (2R)-1-(Benzyloxy)-3-methylbutan-2-amine\(^{88}\)

\[
\begin{align*}
&\text{O-Bn protection of (R)-valinol (124) (5.00 g, 48.46 mmol) was carried out using the} \\
&\text{general method described. Dry flash column chromatography on silica, eluting initially} \\
&\text{...}
\end{align*}
\]

Experimental - 175 -
with 2%/0.25% methanol/ammonia in DCM gave product (R)-O-Bn valinol (125) as a yellow oil (6.68 g, 71%). $[\alpha]^{25}_D = -15.8$ (c 1.09, DCM) (Lit. $[\alpha]^{25}_D = -14.2$, c 1.58, CHCl$_3$)\(^{192}\); $v_{\text{max}}$ (film/cm$^{-1}$): 1099 (O-C), 3378 and 1585 (N-H); $\delta_H$ (400MHz; CDCl$_3$): 0.91 (6H, dd, $J$ 6.8 and 1.6, CH(CH$_3$)$_2$), 1.61-1.70 (1H, m, CH(CH$_3$)$_2$), 2.78 (1H, ddd, $J$ 8.4, 6.0 and 4.0, CH$_2$NH$_2$), 3.30 (1H, dd, $J$ 9.2 and 8.0, CH(H)OCH$_2$Ph), 3.53 (1H, dd, $J$ 9.2 and 4.0, CH(H)OCH$_2$Ph), 4.53 (2H, s, PhCH$_2$O) and 7.27-7.37 (5H, m, ArH); $\delta_C$ (100MHz; CDCl$_3$): 18.13 (CH$_3$), 19.43 (CH$_3$), 30.90 (CH), 56.33 (CH), 73.24 (CH$_2$), 73.98 (CH$_2$), 127.60 (CH), 127.65 (2 x CH), 128.39 (2 x CH) and 138.38 (q); m/z (FAB) 194 ((M + 1)$^+$, 100%); Found: 194.1546; C$_{12}$H$_{19}$NO requires (M + 1)$^+$ 194.1545.

5.2.1.3. Preparation of Imines

8. (2S)-3-Phenyl-2-(3-phenylallylideneamino)-propan-1-ol\(^{100}\)

\[
\begin{align*}
\text{O} & \\
\text{H} & \\
\text{N} & \\
\text{Ph} & \\
\text{Ph} & \\
(91)
\end{align*}
\]

trans-Cinnamaldehyde (3.4 cm$^3$, 26.98 mmol) in DCM (40 cm$^3$) was added to a stirred solution of (S)-phenylalaninol (90) (4.08 g, 26.98 mmol) in DCM (100 cm$^3$) at room temperature and stirred for 30 minutes. Anhydrous magnesium sulfate (4 g) was added and the reaction stirred for a further 15 minutes. Filtration and removal of solvent under reduced pressure yielded imine (91) as a yellow solid (6.80 g, 95%), which was used without further purification. mp 113-115 $^\circ$C (Lit. mp 115.7-116.7 $^\circ$C\(^{100}\); $[\alpha]^{25}_D = -163.8$ (c 1.16, DCM) (Lit. $[\alpha]^{25}_D = -9.8$)\(^{100}\); $v_{\text{max}}$ (film/cm$^{-1}$): 3383 (O-H), 3025 (C=C) and 1635 (C=N); $\delta_H$ (400MHz; CDCl$_3$): 2.77 (1H, dd, $J$ 13.6 and 8.4, PhCH(H)), 2.92 (1H, dd, $J$ 13.6 and 4.8, PhCH(H)), 3.40-3.44 (1H, m, CHCH$_2$OH), 3.78 (1H, dd, $J$ 10.8 and 2.8, CH(H)OH), 3.86 (1H, dd, $J$ 11.6 and 8.0, CH(H)OH), 6.69 (1H, d, $J$ 16.2, CH=CHPh), 6.82 (1H, dd, $J$ 16.2 and 8.3, CH=CHPh), 7.11-7.33 (10H, m, ArH) and 7.61 (1H, d, $J$ 8.4, CH=N); $\delta_C$ (100MHz; CDCl$_3$): 39.36 (CH$_2$), 66.20 (CH$_2$), 74.85 (CH), 126.60 (CH), 127.54 (CH), 127.70 (2 x CH), 128.69 (2 x CH), 129.16 (2 x CH), 129.69 (CH), 130.02 (2
9. (2R)-3-Phenyl-2-(3-phenylallylideneamino)-propan-1-ol

\[
\text{OH} \\
\text{Ph}
\]

(102)

trans-Cinnamaldehyde (3.4 cm\(^3\), 27.30 mmol) in DCM (40 cm\(^3\)) was added dropwise to a stirred solution of (R)-phenylalaninol (101) (4.13 g, 27.30 mmol) in DCM (100 cm\(^3\)) at room temperature and stirred for 30 minutes. Anhydrous magnesium sulfate (4 g) was added and the reaction stirred for a further 15 minutes. Filtration and removal of solvent under reduced pressure yielded imine (102) as a yellow solid (7.20 g, 99%), which was used without further purification. mp 113-115 °C; [\(\alpha\)]\(^{25}\)_D 166.4 (c 1.06, DCM); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 3384 (O-H), 3025 (C=C) and 1635 (C=N); \(\delta_{\text{H}}\) (250MHz; CDCl\(_3\)): 2.79 (1H, dd, \(J\) 13.4 and 8.1, PhCH(H)), 2.94 (1H, dd, \(J\) 13.6 and 5.3, PhCH(H)), 3.37-3.49 (1H, m, CHCH\(_2\)OH), 3.78 (1H, dd, \(J\) 10.8 and 2.8, CH(H)OH), 3.86 (1H, dd, \(J\) 11.6 and 8.0, CH(H)OH), 6.75 (1H, d, \(J\) 15.7, CH=CHPh), 6.85 (1H, dd, \(J\) 15.0 and 7.6, CH=CHPh), 7.13-7.61 (10H, m, Arf) and 7.71 (1H, d, \(J\) 7.6, CH=N); \(\delta_{\text{C}}\) (100MHz; CDCl\(_3\)): 38.94 (CH\(_2\)), 65.82 (CH\(_2\)), 74.43 (CH), 126.18 (CH), 127.15 (CH), 127.27 (2 x CH), 128.27 (2 x CH), 128.74 (2 x CH), 129.27 (CH), 129.60 (2 x CH), 135.41 (q), 138.42 (q), 142.52 (CH) and 164.09 (CH); \(m/z\) (EI) 265 (M\(^+\), 6%); Found: 265.1468; C\(_{18}\)H\(_{19}\)NO requires M\(^+\), 265.1467.
10. (2S)-1-(Benzyloxy)-3-phenyl-N-(3-phenylallylidene)-propan-2-amine

\[ \text{trans-Cinnamaldehyde (1.2 cm}^3, 9.75 \text{ mmol) in DCM (20 cm}^3) \text{ was added to a stirred solution of (S)-O-Bn phenylalaninol (106) (2.35 g, 9.75 mmol) in DCM (50 cm}^3) \text{ at 0 }^\circ\text{C and stirred for 1 hour at room temperature. Anhydrous magnesium sulfate (4 g) was added and the reaction stirred for a further 30 minutes. Filtration and removal of solvent under reduced pressure yielded imine (105) as a solid (3.46 g, 99%), which was used without further purification. v} \text{ max (film/cm}^{-1}): 1099 (O-C), 3025 (C=\text{C}) \text{ and } 1635 (C=\text{N}); \delta\text{ H (250MHz; CDCl}_3): 2.83 (1H, dd, J 8.1 and 4.2, PhCH(\text{H})), 2.94 (1H, dd, J 13.4 and 5.1, PhCH(\text{H})), 3.49-3.58 (1H, m, (CH}_2\text{)CHN}), 3.64 (1H, dd, J 9.0 and 4.6, CHCH(\text{H})OCH}_2\text{Ph}), 3.77 (1H, dd, J 6.9 and 4.2, CHCH(\text{H})OCH}_2\text{Ph), 4.57 (2H, d, J 12.2, PhCH}_2\text{O}), 6.78 (1H, d, J 17.3, CH=CHPh), 6.89 (1H, dd, J 15.9 and 8.6, CH=CHPh), 7.13-7.46 (15H, m, Ar\text{H}) \text{ and } 7.72 (1H, dd, J 7.2 and 3.7, N=CH); \delta\text{ C (100MHz; CDCl}_3): 39.33 (\text{CH}_2), 72.15 (\text{CH}), 73.27 (\text{CH}_2), 73.40 (\text{CH}_2), 126.12 (\text{CH}), 127.25 (2 \times \text{CH}), 127.55 (\text{CH}), 127.68 (2 \times \text{CH}), 127.82 (\text{CH}), 128.21 (2 \times \text{CH}), 128.34 (2 \times \text{CH}), 128.79 (2 \times \text{CH}), 129.15 (\text{CH}), 129.64 (2 \times \text{CH}), 135.69 (\text{q}), 138.29 (\text{q}), 138.64 (\text{q}), 141.98 (\text{CH}) \text{ and } 163.42 (\text{CH}).

11. (2S)-1-(Benzyloxy)-3-methyl-N-(3-phenylallylidene)-butan-2-amine

\[ \text{trans-Cinnamaldehyde (4.9 cm}^3, 38.86 \text{ mmol) in DCM (20 cm}^3) \text{ was added to a stirred solution of (S)-O-Bn valinol (108) (7.91 g, 40.91 mmol) in DCM (50 cm}^3) \text{ at 0 }^\circ\text{C and stirred for 1 hour at room temperature. Anhydrous magnesium sulfate (4 g) was added} \]
and the reaction stirred for a further 30 minutes. Filtration and removal of solvent under reduced pressure yielded imine (109) as a yellow oil (12.54 g, 99%), which was used without further purification. $[\alpha]^{25}_{D}$ 9.4 (c 1.15, DCM); $\nu_{\text{max}}$ (film/cm$^{-1}$): 1103 (O-C), 3027 (C=C) and 1633 (C=N); $\delta_{\text{H}}$ (250MHz; CDCl$_3$): 0.91 (6H, dd, $J$ 6.9 and 4.0, CH(CH$_3$)$_2$), 1.84-2.02 (1H, m, CH(CH$_3$)$_2$), 3.04 (1H, ddd, $J$ 9.7, 5.9 and 3.9, CHN=CH), 3.56 (1H, dd, $J$ 9.6 and 8.1, CH(H)OCH$_2$Ph), 3.73 (1H, dd, $J$ 9.6 and 3.9, CH(H)OCH$_2$Ph), 4.52 (2H, d, $J$ 0.8, PhCH$_2$O), 6.96-6.98 (2H, m, CH=CH), 7.21-7.46 (8H, m, ArH), 7.49 (2H, dd, $J$ 8.2 and 1.9, ArH) and 8.01 (1H, dd, $J$ 5.7 and 3.0, N=CH); $\delta_{\text{C}}$ (100MHz; CDCl$_3$): 18.40 (CH$_3$), 19.86 (CH$_3$), 30.34 (CH), 72.32 (CH$_2$), 73.19 (CH$_2$), 76.61 (CH), 127.22 (2 x CH), 127.46 (CH), 127.59 (2 x CH), 128.31 (CH), 128.36 (2 x CH), 128.81 (2 x CH), 129.05 (CH), 135.90 (q), 138.50 (q), 141.63 (CH) and 163.03 (CH); m/z (FAB) 308 ((M + 1)$^+$, 40%); Found: 308.2013; C$_{21}$H$_{25}$NO requires (M + 1)$^+$, 308.2014.

12. (2R)-1-(Benzyloxy)-3-methyl-N-(3-phenylallylidene)-butan-2-amine

$$\text{O}$$
$$\text{O}$$

trans-Cinnamaldehyde (4.4 cm$^3$, 34.56 mmol) in DCM (20 cm$^3$) was added to a stirred solution of (R)-O-Bn valinol (125) (6.68 g, 34.56 mmol) in DCM (50 cm$^3$) at 0 °C and stirred for 1 hour at room temperature. Anhydrous magnesiu sulfate (4 g) was added and the reaction stirred for a further 30 minutes. Filtration and removal of solvent under reduced pressure yielded imine (142) as a yellow oil (9.66 g, 91%), which was used without further purification. $[\alpha]^{25}_{D}$ -15.1 (c 1.03, DCM); $\nu_{\text{max}}$ (film/cm$^{-1}$): 1103 (O-C), 3026 (C=C) and 1633 (C=N); $\delta_{\text{H}}$ (400MHz; CDCl$_3$): 0.91 (6H, t, $J$ 6.4, CH(CH$_3$)$_2$), 1.87-1.99 (1H, m, CH(CH$_3$)$_2$), 3.04 (1H, ddd, $J$ 8.0, 6.0 and 3.6, CHN=CH), 3.56 (1H, dd, $J$ 9.6 and 8.0, CH(H)OCH$_2$Ph), 3.73 (1H, dd, $J$ 9.6 and 3.6, CH(H)OCH$_2$Ph), 4.52 (2H, d, $J$ 2.4, PhCH$_2$O), 6.96-6.97 (2H, m, CH=CH), 7.23-7.39 (8H, m, ArH), 7.49 (2H, dd, $J$ 8.8 and 1.6, ArH) and 8.01 (1H, dd, $J$ 5.6 and 2.8, N=CH); $\delta_{\text{C}}$ (100MHz; CDCl$_3$): 18.80 (CH$_3$), 19.86 (CH$_3$), 30.34 (CH), 72.32 (CH$_2$), 73.19 (CH$_2$), 76.61 (CH), 127.22 (2 x CH), 127.46 (CH), 127.59 (2 x CH), 128.31 (CH), 128.36 (2 x CH), 128.81 (2 x CH), 129.05 (CH), 135.90 (q), 138.50 (q), 141.63 (CH) and 163.03 (CH); m/z (FAB) 308 ((M + 1)$^+$, 40%); Found: 308.2013; C$_{21}$H$_{25}$NO requires (M + 1)$^+$, 308.2014.
19.88 (CH₃), 30.36 (CH), 72.35 (CH₂), 73.21 (CH₂), 76.64 (CH), 127.23 (2 x CH), 127.47 (CH), 127.61 (2 x CH), 128.26 (CH), 128.32 (2 x CH), 128.82 (2 x CH), 129.05 (CH), 135.93 (q), 138.52 (q), 141.59 (CH) and 163.01 (CH); m/z (EI) 307 (M⁺, 1%); Found: 307.1943; C₂₁H₂₉NO requires M⁺, 307.1936.

13. *(2R)-1-(Benzyloxy)-3-methyl-N-(2·methyl-3-phenylallylidene)-butan-2-amine*

![Structure](image)

α-Methyl-trans-cinnamaldehyde (1.3 cm³, 9.45 mmol) in DCM (20 cm³) was added to a stirred solution of *(R)-O-Bn valinol (125)* (2.03 g, 10.50 mmol) in DCM (50 cm³) at 0 °C and stirred for 1 hour at room temperature. Anhydrous magnesium sulfate (4 g) was added and the reaction stirred for a further 30 minutes. Filtration and removal of solvent under reduced pressure yielded imine (126) as a yellow oil (2.98 g, 98%), which was used without further purification. [α]D²⁵ -31.6 (c 1.10, DCM); ν max (film/cm⁻¹): 1104 (O-C), 3026 (C=C) and 1627 (C=N); ν max (film/cm⁻¹): 1104 (O-C), 3026 (C=C) and 1627 (C=N); δH (400MHz; D₆-DMSO): 0.85 (6H, dd, J 7.0 and 1.6, CH(CH₃)₂), 1.79-1.92 (1H, m, CH(CH₃)₂), 2.08 (3H, s, PhCH=C(C(H₃)), 3.10-3.14 (1H, m, CHN=CH), 3.44 (1H, dd, J 9.4 and 7.8, CH(H)OCH₂Ph), 3.64 (1H, dd, J 9.8 and 4.3, CH(H)OCH₂Ph), 4.47 (2H, q, J 12.5, PhCH₂O), 6.92 (1H, s, PhCH=C(CH₃)), 7.26-7.49 (10H, m, ArH) and 8.00 (1H, s, N=CH); δC (100MHz; D₆-DMSO): 135.52 (CH₃), 18.66 (CH₃), 20.23 (CH₃), 30.29 (CH), 72.24 (CH₂), 72.32 (CH₂), 75.22 (CH), 127.72 (CH), 127.75 (2 x CH), 128.16 (CH), 128.61 (2 x CH), 128.89 (2 x CH), 129.70 (2 x CH), 136.78 (q), 136.86 (q), 138.72 (CH), 139.07 (q) and 165.73 (CH). m/z (FAB) 322 ((M + 1)⁺, 29%); Found: 322.2173; C₂₂H₂₇NO requires (M + 1)⁺, 322.2171.
5.2.1.4. Preparation of Dienes

14. (2S)-2-((3S)-1-Phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol

Imine (91) (6.48 g, 24.42 mmol) was dissolved in anhydrous toluene/diethyl ether (4:1, 100 cm³) and stirred at room temperature with magnesium turnings (1.96 g, 80.59 mmol) and a catalytic amount of iodine under an inert atmosphere of nitrogen. Allyl bromide (7.0 cm³, 80.59 mmol) was added dropwise to the imine solution and the mixture was left to stir overnight under an inert atmosphere of nitrogen. The reaction was then quenched with water until a gelatinous precipitate was formed. The organic layer was decanted and the remaining gelatinous residue washed with diethyl ether (2 x 100 cm³). The combined organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a brown solid. Recrystallisation from diethyl ether/hexane gave diene (86) as a yellow solid (4.30 g, 57%). mp 92-94 °C (Lit. mp 91.3-92.3)¹⁰⁰, [α]²⁵D -16.6 (c 1.23, DCM) (Lit. [α]²⁵D -18.7)¹⁰⁰, ν max (film/cm⁻¹): 3416 (O-H), 3024 (C=C), 1494 and 1198 (N-H); δH (400MHz; CDCl₃): 2.23 (2H, t, J 7.2, CH₂CH=CH₂), 2.68-2.84 (2H, m, PhCH₂), 2.98-3.07 (1H, m, CHCH₂OH), 3.25 (1H, q, J 6.7, NCHCH=CH), 3.34 (1H, dd, J 10.8 and 3.2, CH(H)OH), 3.63 (1H, dd, J 10.8 and 4.0, CH(CH=CH₂)OH), 5.02-5.11 (2H, m, CH=CH₂) 5.64-5.77 (2H, m, CH₂CH=CH₂ and CH=CHPh), 6.25 (1H, d, J 16.0, CH=CHPh) and 7.13-7.31 (10H, m, ArH); δC (100MHz; CDCl₃): 39.28 (CH₂), 41.31 (CH₂), 56.87 (CH), 58.18 (CH), 62.50 (CH₂), 117.90 (CH₂), 126.71 (2 x CH), 126.86 (CH), 127.87 (CH), 128.95 (4 x CH), 129.68 (2 x CH), 131.19 (CH), 132.44 (CH), 135.27 (CH), 137.12 (q) and 139.00 (q); m/z (FAB) 308 [(M + 1)+, 38%]; Found: 308.2008; C₂₁H₂₅NO requires (M + 1)+, 308.2014.
15. \((2R)-2-((3R)-1\text{-Phenylhexa-1,5-dien-3-ylamino})-3\text{-phenylpropan-1-ol}\)

\[\text{Imine (102)} \ (7.00 \text{ g, } 26.38 \text{ mmol}) \text{ was dissolved in anhydrous toluene/diethyl ether (4:1, } 100 \text{ cm}^3\) \text{ and stirred at room temperature with magnesium turnings (2.12 g, 87.05 mmol) and a catalytic amount of iodine under an inert atmosphere of nitrogen. Allyl bromide (7.5 cm}^3, 87.05 \text{ mmol}) \text{ was added dropwise to the imine solution and the mixture was left to stir overnight under an inert atmosphere of nitrogen. The reaction was then quenched with water until a gelatinous precipitate was formed. The organic layer was decanted and the remaining gelatinous residue washed with diethyl ether (2 x 100cm}^3\). The combined organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a brown solid. Recrystallisation from diethyl ether/hexane gave diene (103) as a yellow solid (3.70 g, 46%). mp 90-92°C; \([\alpha]^{25}_D\) 21.8 (c 1.10, DCM); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 3420 (O-H), 3024 (C=C), 1490 and 1117 (N-H); \(\delta_{\text{H}}\) (250MHz; CDCl\(_3\)): 2.24 (2H, t, J 7.2, CH\(_2\)CH=CH\(_2\)), 2.68-2.83 (2H, m, PhCH\(_2\)), 2.97-3.06 (1H, m, CHCH\(_2\)OH), 3.25 (1H, q, J 6.5, CHCH=CH), 3.34 (1H, dd, J 10.9 and 3.5, CH(H)OH), 3.64 (1H, dd, J 10.6 and 3.7, CH(H)OH), 5.01-5.12 (2H, m, CH=CH\(_2\)), 5.63-5.85 (2H, m, CH\(_2\)CH=CH\(_2\) and CH=CHPh), 6.26 (1H, d, J 16.0, CH=CHPh) and 7.13-7.35 (10H, m, ArH); \(\delta_{\text{C}}\) (100MHz; CDCl\(_3\)): 38.90 (CH\(_2\)), 40.94 (CH\(_2\)), 56.46 (CH), 57.79 (CH), 62.10 (CH\(_2\)), 117.53 (CH\(_2\)), 126.33 (2 x CH), 126.49 (CH), 127.50 (CH), 128.57 (4 x CH), 129.30 (2 x CH), 130.81 (CH), 132.04 (CH), 134.89 (CH), 136.73 (q) and 138.61 (q); \(m/z\) (EI) 307 (M\(^+\), <1%); Found: 307.1943; C\(_{21}\)H\(_{25}\)NO requires M\(^+\), 307.1936.\]
16. (3S)-N-((2S)-1-(Benzyloxy)-3-phenylpropan-2-yl)-1-phenylhexa-1,5-dien-3-amine

Imine (105) (9.05 g, 25.45 mmol) was dissolved in anhydrous toluene/diethyl ether (4:1, 150 cm³) and stirred at room temperature with magnesium turnings (2.04 g, 83.97 mmol) and a catalytic amount of iodine under an inert atmosphere of nitrogen. Allyl bromide (7.3 cm³, 83.97 mmol) was added dropwise to the imine solution and the mixture was left to stir overnight under an inert atmosphere of nitrogen. The reaction was then quenched with water until a gelatinous precipitate was formed. The organic layer was decanted and the remaining gelatinous residue washed with diethyl ether (2 x 100 cm³). The combined organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a brown solid. Flash column chromatography on silica, eluting with light petroleum-ethyl acetate (5:1) yielded diene (104) as a yellow oil (4.09 g, 40%).

Experimental - 183 -
Allyl bromide (5.3 cm³, 61.20 mmol) was added dropwise, with vigorous stirring at 0 °C, to a mixture of magnesium turnings (1.98 g, 81.60 mmol) and a catalytic amount of iodine in anhydrous THF (40 cm³) under an inert atmosphere of nitrogen. The mixture was stirred vigorously at room temperature until decolourisation occurred. The reaction was cooled to 0 °C before a solution of imine (109) (12.54 g, 40.80 mmol) in anhydrous THF (60 cm³) was added dropwise. The mixture was stirred at 0 °C for 1 hour before being quenched with water until a gelatinous precipitate was formed. The organic layer was decanted and the remaining gelatinous residue washed with diethyl ether (3 x 50 cm³). The combined organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a brown oil. Flash column chromatography on silica, eluting with light petroleum-ethyl acetate (10:1) yielded diene (110) as a yellow oil (2.64 g, 65%). "Experimental - 184 -"
A 2M solution of allylmagnesium chloride in THF (30.3 cm³, 60.68 mmol) was added dropwise to a stirred solution of imine (142) (8.48 g, 27.58 mmol) in anhydrous THF (100 cm³) at 0 °C under an inert atmosphere of nitrogen. The mixture was stirred at room temperature for 3 hours before being quenched with water until a gelatinous precipitate was formed. The organic layer was decanted and the remaining gelatinous residue washed with diethyl ether (3 x 100 cm³). The combined organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield diene (112) as a yellow oil (8.17 g, 85%), which was used without further purification. [α]²⁵ D 70.3 (c 1.29, DCM); ν max (film/cm⁻¹): 1101 (O-C), 3025 (C=C) and 1180 (N-H); δH (400MHz; CDCl₃): 0.90 (6H, t, J 6.8, CH(CH₃)₂), 1.77-1.87 (1H, m, CH(CH₃)₂), 2.21-2.32 (2H, m, CH₂CH=CH₂), 2.54 (1H, q, J 4.9, NCH₂OCH₂Ph), 3.33 (1H, q, J 7.0, NCHCH=CH), 3.42 (1H, dd, J 9.6 and 4.5, CH(H)OCH₂Ph), 3.51 (1H, dd, J 9.5 and 4.6, CH(H)OCH₂Ph), 4.48 (2H, d, J 2.2, PhCH₂O), 5.01-5.12 (2H, m, CH=CH₂), 5.71-5.82 (1H, m, CH=CH₂), 6.01 (1H, dd, J 15.8 and 8.3, CH=CHPh), 6.43 (1H, d, J 15.8, CH=CHPh) and 7.15-7.35 (10H, m, ArH); δC (100MHz; CDCl₃): 19.31 (CH₃), 19.54 (CH₃), 30.46 (CH), 41.49 (CH₂), 58.94 (CH), 59.99 (CH), 70.27 (CH₂), 73.55 (CH₂), 117.84 (CH₂), 126.65 (2 x CH), 127.68 (CH), 127.88 (CH), 127.95 (2 x CH), 128.73 (2 x CH), 128.86 (2 x CH), 130.92 (CH), 134.31 (CH), 135.73 (CH), 137.67 (q) and 139.08 (q). m/z (EI) 349 (M⁺, 3%); Found: 349.2409; C₂₄H₃₁NO requires M⁺, 349.2406.
A 2M solution of allylmagnesium chloride in THF (10.2 cm$^3$, 20.38 mmol) was added dropwise to a stirred solution of imine (126) (2.98 g, 9.26 mmol) in anhydrous THF (40 cm$^3$) at 0 °C under an inert atmosphere of nitrogen. The mixture was stirred at room temperature for 3 hours before being quenched with water until a gelatinous precipitate was formed. The organic layer was decanted and the remaining gelatinous residue washed with diethyl ether (3 x 50 cm$^3$). The combined organic phase was washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a clear oil (2.95 g, assumed 8.12 mmol). The crude product was then redissolved in ethanol (12 cm$^3$) and heated to 80 °C. To the mixture was added a pre-heated solution of oxalic acid (0.77 g, 8.53 mmol) in ethanol (8 cm$^3$). The mixture was allowed to cool to room temperature during which time a precipitate had formed. The oxalate salt (2.40 g, assumed 5.29 mmol) was filtered and washed with cold ethanol and then heated to 60 °C in water (60 cm$^3$) whereupon a 4M aqueous sodium hydroxide solution (2.7 cm$^3$, 10.57 mmol) was added. The mixture was stirred at 60 °C for 1 hour before cooling to room temperature. The mixture was extracted with diethyl ether (100 cm$^3$) and the resulting organic layer washed with 1M aqueous hydrochloric acid solution (100 cm$^3$). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield diene (127) as a clear oil (1.52 g, 45%). [α]$^{25}$D 52.3 (c 1.43, DCM); ν$_{max}$ (film/cm$^{-1}$): 1101 (O-C), 2955 (C=C) and 1466 (N-H); δ$_{H}$ (400MHz; CDCl$_3$): 0.89 (6H, dd, J 8.6 and 6.7, CH(CH$_3$)$_2$), 1.77-1.85 (1H, m, CH(CH$_3$)$_2$), 1.81 (3H, s, PhCH=C(CH$_3$)), 2.17-2.32 (2H, m, CH$_2$CH=CH$_2$), 2.40 (1H, q, J 4.3, NCHCH$_2$OCH$_2$Ph), 3.27 (1H, t, J 7.4, NCHC(CH$_3$)), 3.44 (1H, dd, J 9.4 and 3.9, CH(H)OCH$_2$Ph), 3.52 (1H, dd, J 9.4 and 4.7, CH(H)OCH$_2$Ph), 4.52 (2H, q, J 12.2, PhCH$_2$O), 5.00-5.11 (2H, m, CH=CH$_2$), 5.67-
5.78 (1H, m, CH=CH₂), 6.35 (1H, s, PhCH═C(CH₃)) and 7.16-7.35 (10H, m, ArH); δC (100MHz; CDCl₃): 13.10 (CH₃), 18.91 (CH₃), 19.59 (CH₃), 30.04 (CH), 39.46 (CH₂), 59.63 (CH), 64.12 (CH), 69.13 (CH₂), 73.18 (CH₂), 116.74 (CH₂), 126.04 (CH), 126.95 (CH), 127.47 (CH), 127.55 (2 x CH), 128.00 (2 x CH), 128.28 (2 x CH), 128.93 (2 x CH), 135.88 (CH), 138.17 (q), 138.69 (q) and 140.17 (q); m/z (FAB) 364 ((M + 1)⁺, 8%); Found: 364.2646; C₂₄H₃₁NO requires (M + 1)⁺, 364.2640.

5.2.2. Anionic Amino-Cope Rearrangements

5.2.2.1. Anionic Amino-Cope Rearrangement/Imine Anion Hydrolysis

20. (3R)-3-Phenylhex-5-enal from (2S)-2-((3S)-1-phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol (86)³⁹

\[ \text{Ph} \quad \text{H} \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad \begin{array}{c} \text{H} \\ \text{CH₂} \end{array} \]

\( (R)-(55) \)

Diene (86) (0.52 g, 1.69 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (15 cm³) under an inert atmosphere of nitrogen and cooled to -78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (1.8 cm³, 4.38 mmol) was added dropwise and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was heated to reflux for 1 hour then quenched with water (1 cm³), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude oxazolidine as an orange oil. Flash column chromatography on silica, eluting with light petroleum-diethyl ether (10:1) hydrolysed the oxazolidine giving aldehyde \((R)-(55)\) as a light yellow oil (0.13 g, 44%) with an e.e. of 83% (e.e. measured by derivatisation with \((1R, 2S)-(−)-\)ephedrine – Experimental Entry 40). \([\alpha]_D^{25} -20.5 (c 1.33, \text{CHCl}_3)\) (Lit. \([\alpha]_D^{25} -21.3, c 1.70, \text{CHCl}_3)\); ν max (film/cm⁻¹): 2838, 2723 (CHO), 1723 (C=O) and 3027 (C=C); δH
(250MHz; CDCl₃): 2.36-2.44 (2H, m, CH₂CH=CH₂), 2.73-2.78 (2H, m, CH=CH₂), 3.24-3.36 (1H, m, PhCH), 4.97-5.06 (2H, m, CH=CH₂), 5.58-5.74 (1H, m, CH=CH₂), 7.17-7.34 (5H, m, ArH) and 9.67 (1H, t, J 2.0, CH=O). δc (100MHz; CDCl₃): 40.12 (CH), 41.34 (CH₂), 49.73 (CH₂), 117.59 (CH₂), 126.61 (CH), 127.09 (2 x CH), 129.03 (2 x CH), 136.13 (CH), 143.76 (q) and 202.11 (CH); m/z (El) 174 (M⁺, 3%); Found: 174.1041; C₁₂H₁₄O requires M⁺, 174.1045.

21. (3R)-3-Phenylhex-5-enal from (3S)-N-(2S)-1-(benzyloxy)-3-phenylpropan-2-yl)-1-phenylhexa-1,5-dien-3-amine (104)

Diene (104) (1.15 g, 2.90 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (30 cm³) under an inert atmosphere of nitrogen and cooled to −78°C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (1.7 cm³, 4.34 mmol) was added dropwise and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was heated to reflux for 1 hour then quenched with water (1 cm³), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude oxazolidine as an orange oil. Flash column chromatography on silica, eluting with light petroleum-diethyl ether (10:1) yielded aldehyde (R)-(55) as a light yellow oil (0.17 g, 34%) with an e.e. of 26% (e.e. measured by derivatisation with (1R, 2S)-(−)-ephedrine – Experimental Entry 40). Spectral analysis consistent with Experimental Entry 20.
22. (3R)-3-Phenyhex-5-enal from (3S)-N-((2S)-1-(benzyloxy)-3-methylbutan-2-yl)-1-phenylhexa-1,5-dien-3-amine (110)

Diene (110) (0.37 g, 1.07 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (10 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (0.6 cm³, 1.61 mmol) was added dropwise and the resulting mixture stirred for 30 minutes at −78 °C. The dry ice/acetone slush bath was removed and the reaction warmed to room temperature over 30 minutes. The reaction was stirred for a further 90 minutes at room temperature before being quenched with water (0.5 cm³), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude product as a yellow oil. Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave aldehyde (R)-(55) as a light yellow oil (59 mg, 32%) with an e.e. of 74% (e.e. measured by derivatisation with (1R, 2S)-(-)-ephedrine – Experimental Entry 40). Spectral analysis consistent with Experimental Entry 20.

5.2.2.2. Tandem Anionic Amino-Cope Rearrangement/Imine

Anion Derivatisation

General Method 1

Diene (1.80 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (15 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (1.9 cm³, 4.68 mmol) was added dropwise and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was heated to reflux for 1 hour before electrophile (2.70 mmol) was added. The mixture was stirred for a further 2 hours and quenched with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate,
filtered through a pad of celite and concentrated under reduced pressure to give the crude oxazolidine as a yellow oil.

**General Method 2**

Diene (0.70 mmol) was dried *in vacuo* for 1 hour then dissolved in anhydrous THF (10 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath. A 2.5M solution of *n*-butyllithium in hexanes (0.4 cm³, 1.05 mmol) was added dropwise and the resulting mixture stirred for 30 minutes at −78 °C. The dry ice/acetone slush bath was removed and the reaction warmed to room temperature over 30 minutes. The reaction was stirred for a further 90 minutes at room temperature before being re-cooled to −78 °C. Electrophile (1.05 mmol) was added to the reaction, which was then allowed to slowly warm to room temperature overnight within the dry ice/acetone slush bath. The reaction was finally quenched with water (0.5 cm³), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude product as a yellow oil.

23. Attempted synthesis of (3R)-2-methyl-3-phenylhex-5-enal from (2S)-2-((3S)-1-phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol (86)

![Chemical Structure](image)

(100a)

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (86) (0.55 g, 1.80 mmol) was carried out using general method 1 with methyl iodide (0.17 cm³, 2.70 mmol). Flash column chromatography on silica, eluting with light petroleum-diethyl ether (20:1) hydrolysed the oxazolidine yielding a mixture of aldehydes (55) and (100a) as a light yellow oil (73 mg, 24%). Spectral analysis consistent with Experimental Entry 25.
24. (3R)-2-Methyl-3-phenylhex-5-enal from (3S)-N-((2S)-1-(benzyloxy)-3-methylpropan-2-yl)-1-phenylhexa-1,5-dien-3-amine (104)

![Chemical structure](100a)

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (104) (0.20 g, 0.51 mmol) was carried out using general method 1 with methyl iodide (0.05 cm³, 0.77 mmol). Flash column chromatography on silica, eluting with light petroleum-diethyl ether (10:1) gave a 1:1 mixture of diastereoisomers of aldehyde (100a) as a light yellow oil (30 mg, 31%). Spectral analysis consistent with Experimental Entry 25.

25. (3R)-2-Methyl-3-phenylhex-5-enal from (3S)-N-((2S)-1-(benzyloxy)-3-methylbutan-2-yl)-1-phenylhexa-1,5-dien-3-amine (110)

![Chemical structure](100a)

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (110) (0.24 g, 0.70 mmol) was carried out using general method 2 with methyl iodide (0.07 cm³, 1.05 mmol). Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave a 1:1 mixture of diastereoisomers of aldehyde (100a) as a light yellow oil (68 mg, 52%). ν max (film/cm⁻¹): 2872, 2708 (CHO), 1724 (C=O) and 3027 (C=C); δH (250MHz; CDCl₃, both isomers): 0.88 & 1.13 (3H, d, J 6.9, CH₃CH & 3H, d, J 7.0, CH₃CH), 2.42-2.55 (4H, m, 2 x CH₂CH=CH₂), 2.59-2.78 (2H, m, 2 x CH₃CH), 3.00-3.10 (2H, m, 2 x PhCH), 4.91-5.04 (4H, m, 2 x CH=CH₂), 5.51-5.69 (2H, m, 2 x CH=CH₂), 7.11-7.33 (10H, m, 2 x ArH), and 9.58 & 9.70 (1H, d, J 2.1, CH=O & 1H, d, J 2.8, CH=O); δC (100MHz; CDCl₃, both isomers): 11.23 & 11.68 (CH₃), 36.16 & 38.31 (CH₂), 46.16 & 46.67 (CH), 51.14 (CH), 116.89 & 116.98 (CH₂), 126.76 (CH), 128.30 &
26. (3R)-2-Ethyl-3-phenylhex-5-enal

\[ \text{H} \quad \text{O} \quad \Phi \quad \text{Ph} \]

\[ (100b) \]

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (110) (0.14 g, 0.39 mmol) was carried out using general method 2 with ethyl iodide (0.05 cm\(^3\), 0.58 mmol). Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave a 1:1 mixture of diastereoisomers of aldehyde (100b) as a light yellow oil (53 mg, 67%). \( \nu_{\text{max}} \) (film/cm\(^{-1}\)): 2868, 2713 (CHO), 1722 (C=O) and 3026 (C=C); \( \delta_{\text{H}} \) (250MHz; CDCl\(_3\), both isomers): 0.77 & 0.91 (3H, t, \( J = 7.6 \), CH\(_2\)CH\(_3\) & 3H, t, \( J = 7.4 \), CH\(_2\)CH\(_3\)), 1.25-1.46 & 1.60-1.72 (2H, m, CH\(_2\)CH\(_3\) & 2H, m, CH\(_2\)CH\(_3\)), 2.35-2.61 (6H, m, 2 x CH\(_2\)CH=CH\(_2\) and 2 x CHCH\(_2\)CH\(_3\)), 2.92-3.04 (2H, m, 2 x PhCH), 4.86-5.04 (4H, m, 2 x CH=CH\(_2\)H), 5.45-5.69 (2H, m, 2 x CH=CH\(_2\)H), 7.11-7.35 (10H, m, 2 x ArH) and 9.47 & 9.63 (1H, d, \( J = 3.7 \), CH=O & 1H, d, \( J = 4.2 \), CH=O); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\), both isomers): 11.47 & 11.76 (CH\(_3\)), 20.33 & 20.51 (CH\(_2\)), 37.18 & 38.80 (CH\(_2\)), 45.61 & 46.14 (CH), 57.65 & 58.65 (CH), 116.80 & 116.93 (CH\(_2\)), 126.73 & 126.79 (CH), 128.36 & 128.45 (2 x CH), 128.48 & 128.49 (2 x CH), 135.76 & 135.81 (CH), 141.16 & 141.24 (q) and 205.13 & 205.27 (CH).
27. (3R)-2-Allyl-3-phenylhex-5-enal

\[
\begin{align*}
\text{O} & \quad \text{H} \\
& \quad \text{Ph} \\
& \quad \text{(100c)}
\end{align*}
\]

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (110) (0.18 g, 0.53 mmol) was carried out using general method 2 with allyl bromide (0.07 cm³, 0.79 mmol). Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave a 1.5:1 mixture of diastereoisomers of aldehyde (100c) as a light yellow oil (55 mg, 49%). \( \nu_{\text{max}} \) (film/cm\(^{-1}\)): 2874, 2717 (CHO), 1723 (C=O) and 3027 (C=C); \( \delta_H \) (250MHz; CDCl3, both isomers): 2.02-2.22 (2H, m, 2 x CH(H)CH=CH₂), 2.30-2.45 (4H, m, 2 x CH(H)CH=CH₂ and 2 x PhCHCH(H)), 2.49-2.60 (2H, m, 2 x PhCHCH(H)), 2.62-2.74 (2H, m, 2 x PhCHCH(CH₂), 3.00-3.08 (2H, m, 2 x PhCH), 4.89-5.10 (4H, m, 2 x CH=CH₂), 5.46-5.81 (2H, m, 2 x CH=CH₂), 7.13-7.35 (10H, m, 2 x ArH), 9.53 (1H, d, J 3.2, CH=O minor isomer) and 9.66 (1H, d, J 3.7, CH=O major isomer); \( \delta_C \) (100MHz; CDCl₃, both isomers): 31.52 & 31.91 (CH₂), 37.16 & 38.36 (CH₂), 45.39 & 45.75 (CH), 55.16 & 56.25 (CH), 116.93 & 117.05 (CH₂), 117.28 & 117.39 (CH₂), 126.88 & 126.91 (CH), 128.41 & 128.49 (2 x CH), 128.54 & 128.58 (2 x CH), 135.69 & 135.72 (CH), 140.82 & 140.91 (q) and 204.48 & 204.68 (CH).

28. (3R)-2-Benzyl-3-phenylhex-5-enal from (2S)-2-[(3S)-1-phenylhexa-1,5-dien-3-ylamino]-3-phenylpropan-1-ol (86)

\[
\begin{align*}
\text{O} & \quad \text{H} \\
& \quad \text{Ph} \\
& \quad \text{Ph} \\
& \quad \text{(100d)}
\end{align*}
\]

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (86) (0.30 g, 0.97 mmol) was carried out using general method 1 with benzyl bromide (0.30...
cm³, 2.52 mmol). Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave a 2:1 mixture of diastereoisomers of aldehyde (100d) as a light yellow oil (0.11 g, 44%). Spectral analysis consistent with Experimental Entry 29.

29. (3R)-2-Benzyl-3-phenylhex-5-enal from (3S)-N-((2S)-1-(benzyloxy)-3-methylbutan-2-yl)-1-phenylhexa-1,5-dien-3-amine (110)

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (110) (0.37 g, 1.06 mmol) was carried out using general method 2 with benzyl bromide (0.13 cm³, 1.06 mmol). Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave a 2:1 mixture of diastereoisomers of aldehyde (100d) as a light yellow oil (0.17 g, 62%). v max (film/cm⁻¹): 2875, 2717 (CHO), 1725 (C=O) and 3027 (C=C); δH (400MHz; CDCl₃, both isomers): 2.43-2.48 (2H, m, CH₂CH=CH₂ major isomer), 2.54-2.99 (8H, br m, CH₂CH=CH₂ minor isomer, 2 x CH₂Ph and 2 x PhCH), 3.05-3.09 (2H, m, 2 x CHCH₂Ph), 4.91-5.07 (4H, m, 2 x CH=CH₂), 5.51-5.68 (2H, m, 2 x CH=CH₂), 6.96-7.42 (20H, m, 2 x ArH), 9.59 (1H, d, J 2.5, CH=O minor isomer) and 9.66 (1H, d, J 3.4, CH=O major isomer); δC (100MHz; CDCl₃, both isomers): 33.12 & 33.78 (CH₂), 37.11 & 38.03 (CH₂), 45.85 & 46.24 (CH), 57.29 & 58.37 (CH), 117.03 & 117.19 (CH₂), 126.36 (CH), 126.95 (CH), 128.41 & 128.49 (2 x CH), 128.52 & 128.55 (2 x CH), 128.56 & 128.64 (2 x CH), 128.81 & 128.93 (2 x CH), 135.66 & 135.67 (CH), 138.70 & 138.90 (q), 140.67 & 140.96 (q) and 204.29 & 204.63 (CH).
30. (3R)-2-Benzyl-2-methyl-3-phenylhex-5-enal

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

(128)

Tandem anionic amino-Cope rearrangement/imine anion derivatisation of diene (127) (0.72 g, 1.98 mmol) was carried out using general method 1 with benzyl bromide (0.24 cm³, 1.98 mmol). Flash column chromatography on silica, eluting with 1% diethyl ether in petrol yielded a 2:1 mixture of diastereoisomers of aldehyde (128) as a yellow oil (0.17 g, 30%). \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 2873, 2714 (CHO), 1721 (C=O) and 3027 (C=C); \(\delta_{\text{H}}\) (400MHz; CDCl\(_3\), both isomers): 0.98 (3H, s, CH\(_3\)CCH=O minor isomer), 0.99 (3H, s, CH\(_3\)CCH=O major isomer), 2.29-2.36 (2H, m, PhCH\(_2\)C minor isomer), 2.33 (1H, d, \(J\) 13.7, CH(H)CH=CH\(_2\) major isomer), 2.51-2.66 (2H, m, PhCH\(_2\)C major isomer), 2.73 (1H, d, \(J\) 13.7, CH(H)CH=CH\(_2\) minor isomer), 2.96-3.03 (2H, m, 2 x PhCH\(_2\)H), 3.03 (1H, d, \(J\) 13.3, CH(H)CH=CH\(_2\) major isomer), 3.18 (1H, d, \(J\) 13.7, CH(H)CH=CH\(_2\) minor isomer), 4.83-4.99 (4H, m, 2 x CH=CH\(_2\)H), 5.42-5.55 (2H, m, 2 x CH=CH\(_2\)H), 6.91-7.36 (20H, m, 2 x ArH), 9.61 (1H, s, CH=O minor isomer) and 9.70 (1H, s, CH=O major isomer); \(\delta_{\text{C}}\) (100MHz; CDCl\(_3\), both isomers): 14.45 & 16.93 (CH\(_3\)), 33.70 & 35.02 (CH\(_2\)), 40.53 & 42.20 (CH\(_2\)), 51.24 & 51.89 (CH), 53.23 & 54.01 (q), 116.40 (CH\(_2\)), 126.50 & 127.05 (CH), 128.08 & 128.16 (2 x CH), 128.20 & 128.24 (2 x CH), 129.71 & 129.90 (2 x CH), 130.21 & 130.39 (2 x CH), 136.23 & 136.29 (CH), 136.55 & 136.98 (q), 138.95 & 139.11 (q) and 206.00 & 207.00 (CH); \(m/z\) (El) 278 (M\(^+\), <1%); Found: 278.1675; C\(_{20}\)H\(_{22}\)O requires M\(^+\), 278.1671.

Experimental - 195 -
5.2.2.3. Tandem Anionic Amino-Cope Rearrangement/Imine
Anion Derivatisation/Reduction

31. \(N-((2R)-1-(\text{Benzyloxy})-3\text{methylbutan-2-yl})-3\text{phenylhex-5-en-1-amine}\)

\[
\text{Diene (112) (2.57 g, 7.35 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (40 cm}^3\text{) under an inert atmosphere of nitrogen and cooled to -78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (3.5 cm}^3, 8.82 mmol) was added dropwise and the resulting mixture stirred for 30 minutes at -78 °C. The dry ice/acetone slush bath was removed and the reaction warmed to room temperature over 30 minutes. The reaction was stirred for a further 90 minutes before sodium borohydride (0.61 g, 16.18 mmol) and glacial acetic acid (0.8 cm}^3, 14.70 mmol) were added at room temperature. Methanol (4 cm}^3\text{) was added dropwise and the resulting mixture stirred for 24 hours at room temperature before quenching the reaction with saturated aqueous sodium hydrogen carbonate solution (50 cm}^3\text{). The mixture was extracted with ethyl acetate (50 cm}^3\text{) and the resulting organic layer washed with saturated aqueous sodium hydrogen carbonate solution (100 cm}^3\text{). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in hexanes with 0.5% triethylamine yielded a mixture of diastereoisomers of amine (115) as a yellow oil (1.63 g, 63%). \(\nu\) (film/cm\(^{-1}\)): 1100 (O-C), 1452 (N-H) and 3026 (C=C); \(\delta_H\) (400MHz; CDCl\(_3\), both isomers): 0.84 (6H, dd, \(J\) 9.8 and 6.6, \(CH(CH_3)_2\) major isomer), 0.85 (6H, dd, \(J\) 10.2 and 7.0, \(CH(CH_3)_2\) minor isomer), 1.66-1.79 (4H, m, 2 x \(CH(CH_3)_2\) and 2 x NCH\(_2\)CH(H)), 1.81-1.91 (2H, m, 2 x NCH\(_2\)CH(H)), 2.35 (4H, t, \(J\) 6.6, 2 x CH\(_2\)CH=CH\(_2\)), 2.39-2.46 (6H, m, 2 x NCH\(_2\)CH\(_3\)O and 2 x NCH\(_2\)CH\(_2\)), 2.66-2.76 (2H, m, 2 x PhCH\(_3\)), 3.31 (2H, dd, \(J\) 9.4 and 6.6, 2 x NCH\(_2\)CH\(_2\)O), 4.46 (4H, s, 2 x OCH\(_2\)Ph), 4.89-4.97 (4H, m, 2 x CH=CH\(_2\)), 5.59-5.70 (2H, m, 2 x CH=CH\(_2\)) and 7.12-7.35 (20H, m, 2 x ArH); \(\delta_C\) (100MHz; CDCl\(_3\), Experimental).}
both isomers): 18.21 & 18.33 (CH₃), 18.93 (CH₃), 28.83 & 29.00 (CH), 36.59 & 36.63 (CH₂), 41.47 & 41.57 (CH₂), 43.76 (CH), 45.90 & 45.98 (CH₂), 62.57 & 62.68 (CH), 70.33 & 70.38 (CH₂), 73.18 (CH₂), 115.91 (CH₂), 126.05 (CH), 127.50 (CH), 127.59 (2 x CH), 127.63 (2 x CH), 128.26 (2 x CH), 128.32 (2 x CH), 136.92 (CH), 138.53 (q) and 144.90 (q); m/z (EI) 351 (M⁺, 2%); Found: 351.2554; C₂₄H₃₃NO requires M⁺, 351.2562.

32. 2-Benzyl-N-((2R)-1-(benzyloxy)-3-methylbutan-2-yl)-3-phenylhex-5-en-1-amine

![Chemical Structure](image)

Diene (112) (4.02 g, 11.51 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (50 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (5.5 cm³, 13.81 mmol) was added dropwise and the resulting mixture stirred for 30 minutes at −78 °C. The dry ice/acetone slush bath was removed and the reaction warmed to room temperature over 30 minutes. The reaction was stirred for a further 90 minutes at room temperature before being re-cooled to −78 °C. Benzyl bromide (1.4 cm³, 11.51 mmol) was added to the reaction, which was then allowed to slowly warm to room temperature overnight within the dry ice/acetone slush bath. To the stirred reaction mixture was added sodium borohydride (0.96 g, 25.32 mmol) and glacial acetic acid (1.3 cm³, 23.02 mmol) at room temperature. Methanol (5 cm³) was added dropwise and the resulting mixture stirred for 24 hours at room temperature before quenching the reaction with saturated aqueous sodium hydrogen carbonate solution (50 cm³). The mixture was extracted with ethyl acetate (50 cm³) and the resulting organic layer washed with saturated aqueous sodium hydrogen carbonate solution (100 cm³). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Dry flash column chromatography on silica, eluting initially with 2%/0.5% ethyl acetate/triethylamine in hexanes followed by flash column chromatography on
silica, eluting with 5% ethyl acetate in hexanes with 0.5% triethylamine gave a 2:1 mixture of diastereoisomers of amine (113) as a yellow oil (4.31 g, 85%). $\nu_{\text{max}}$ (film/cm$^{-1}$): 1099 (O-C), 1452 (N-H) and 3024 (C=C); $\delta_H$ (400MHz; CDCl$_3$, both isomers): 0.78 (6H, dd, $J$ 16.4 and 7.9, CH(CH$_3$)$_2$ minor isomer), 0.85 (6H, dd, $J$ 9.4 and 6.7, CH(CH$_3$)$_2$ major isomer), 1.62-1.80 (2H, m, 2 x CH(CH$_3$)$_2$), 1.99-2.02 (2H, m, 2 x PhCH$_2$CH$_2$), 2.24-2.76 (14H, br m, 2 x CH$_2$CH=CH$_2$, 2 x NCH$_2$CH$_2$O and 2 x NCH$_2$CHCH$_2$Ph), 2.84-2.89 (1H, m, PhCH minor isomer), 2.94-2.99 (1H, m, PhCH major isomer), 3.21 (1H, dd, $J$ 9.4 and 6.2, NCHCH(H)O minor isomer), 3.31 (1H, dd, $J$ 9.4 and 6.3, NCHCH(H)O major isomer), 3.36 (1H, dd, $J$ 9.8 and 4.5, NCHCH(H)O minor isomer), 3.41 (1H, dd, $J$ 9.8 and 4.3, NCHCH(H)O major isomer), 4.42-4.45 (4H, m, 2 x OCH$_2$Ph), 4.86-4.98 (4H, m, 2 x CH=CH$_2$), 5.53-5.67 (2H, m, 2 x CH=CH$_2$) and 7.05-7.35 (30H, m, 2 x ArH); $\delta_C$ (100MHz; CDCl$_3$, both isomers): 18.57 & 18.84 (CH$_3$), 19.00 & 19.09 (CH$_3$), 29.02 & 29.14 (CH), 35.87 & 36.10 (CH$_2$), 36.83 & 37.00 (CH$_2$), 45.76 & 45.80 (CH), 46.36 & 46.55 (CH), 47.10 & 47.76 (CH$_2$), 62.94 & 63.05 (CH), 70.05 & 70.13 (CH$_2$), 73.09 & 73.17 (CH$_2$), 115.72 & 115.77 (CH$_2$), 125.63 & 125.69 (CH), 126.03 & 126.06 (CH), 127.45 & 127.49 (CH), 127.55 (2 x CH), 128.02 & 128.07 (2 x CH), 128.14 & 128.20 (2 x CH), 128.32 (2 x CH), 128.77 & 128.83 (2 x CH), 129.01 & 129.15 (2 x CH), 137.31 & 137.44 (CH), 138.58 (q), 141.48 (q) and 143.24 (q); m/z (FAB) 442 ((M + 1)$^+$, 92%); Found: 442.3119; C$_{31}$H$_{39}$NO requires (M + 1)$^+$, 442.3109.

33. 2-Benzyl-2-methyl-$N$-((2R)-1-(benzyloxy)-3-methylbutan-2-yl)-3-phenylhex-5-en-1-amine

![Chemical Structure](129)

Diene (127) (0.72 g, 1.98 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (12 cm$^3$) under an inert atmosphere of nitrogen and cooled to $-78^\circ$C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (1.0 cm$^3$, 2.38 mmol) was added dropwise and the resulting mixture stirred for 30 minutes at $-78^\circ$C.
The dry ice/acetone slush bath was removed and the reaction warmed to room temperature over 30 minutes. The reaction was stirred for a further 90 minutes before being re-cooled to -78 °C. Benzyl bromide (0.24 cm³, 1.98 mmol) was added to the reaction, which was then allowed to slowly warm to room temperature overnight within the dry ice/acetone slush bath. To the stirred reaction mixture was added sodium borohydride (0.16 g, 4.35 mmol) and glacial acetic acid (0.2 cm³, 3.95 mmol) at room temperature. Methanol (3 cm³) was added dropwise and the resulting mixture stirred for 24 hours at room temperature before quenching the reaction with saturated aqueous sodium hydrogen carbonate solution (25 cm³). The mixture was extracted with ethyl acetate (25 cm³) and the resulting organic layer washed with saturated aqueous sodium hydrogen carbonate solution (50 cm³). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Dry flash column chromatography on silica, eluting initially with 1%/0.5% ethyl acetate/triethylamine in hexanes followed by flash column chromatography on silica, eluting with 5% ethyl acetate in hexanes with 0.5% triethylamine gave a 2:1 mixture of diastereoisomers of amine (129) as a yellow oil (0.66 g, 73%). $\nu_{\text{max}}$ (film/cm⁻¹): 1102 (O-C), 1455 (N-H) and 3024 (C=C); $\delta_{\text{H}}$ (250MHz; CDCl₃, major isomer): 0.74 (3H, s, CH₃CCH₂N), 0.95 (6H, dd, $J$ 12.9 and 6.9, CH(CH₃)₂), 1.87-1.97 (1H, m, CH(CH₃)₂), 2.21 (1H, d, $J$ 13.6, NCH(H)C), 2.30 (2H, d, $J$ 9.4, PhCH₂C), 2.37-2.43 (1H, m, NCHCH₂O), 2.46-2.61 (2H, m, CH₂CH=CH₂), 2.67 (1H, d, $J$ 13.3, NCH(H)C), 3.04 (1H, dd, $J$ 11.4 and 4.0, PhCH), 3.44 (1H, dd, $J$ 9.4 and 6.2, NCHCH(H)O), 3.55 (1H, dd, $J$ 9.4 and 3.9, NCHCH(H)O), 4.56 (2H, q, $J$ 11.9, OCH₂Ph), 4.75-4.94 (2H, m, CH=CH₂), 5.41-5.58 (1H, m, CH=CH₂) and 7.01-7.39 (15H, m, ArH); $\delta_{C}$ (100MHz; CDCl₃, major isomer): 18.47 (CH₃), 19.39 (CH₃), 19.94 (CH₃), 29.05 (CH), 33.53 (CH₂), 41.11 (q), 42.75 (CH₂), 51.34 (CH), 52.35 (CH₂), 63.94 (CH), 69.74 (CH₂), 73.28 (CH₂), 115.17 (CH₂), 125.73 (CH), 126.05 (CH), 127.54 (CH), 127.57 (2 x CH), 127.60 (4 x CH), 128.39 (2 x CH), 130.71 (4 x CH), 138.21 (CH), 138.63 (q), 138.79 (q) and 141.71 (q); m/z (FAB) 456 ((M + 1)^+), 60%; Found: 456.3266; C₃₂H₄₁NO requires (M + 1)^+, 456.3266.
5.2.3. Thermal Amino-Cope Rearrangements

General Method

Dowtherm® A (5 cm³) was added to a round bottomed flask containing anti-bumping granules and heated to 220 °C with the aid of a heating mantle. Once the temperature was stable, diene was added and the reaction was continued at 220 °C for a further 4 hours. The reaction was cooled to room temperature before being loaded onto a chromatography column containing silica. Flash column chromatography, eluting initially with light petroleum to remove the Dowtherm® A and increasing polarity of the eluent to light petroleum-ethyl acetate (10:1) isolated aldehyde (R)-(55).

34. (3R)-3-Phenylhex-5-enal from (2S)-2-((3S)-1-phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol (86)

Thermal amino-Cope rearrangement and subsequent purification on diene (86) (0.50 g, 1.64 mmol) was carried out using the general method described. Aldehyde (R)-(55) was isolated as a light yellow oil (56 mg, 20%) with an e.e. of 27% (e.e. measured by derivatisation with (1R, 2S)-(−)-ephedrine – Experimental Entry 40). Spectral analysis consistent with Experimental Entry 20.
35. (3R)-3-Phenylhex-5-enal from (3S)-N-((2S)-1-(benzyloxy)-3-phenylpropan-2-yl)-1-phenylhexa-1,5-dien-3-amine (104)

Thermal amino-Cope rearrangement and subsequent purification on diene (104) (0.26 g, 0.64 mmol) was carried out using the general method described. Aldehyde (R)-(55) was isolated as a light yellow oil (19 mg, 17%) with an e.e. of 19% (e.e. measured by derivatisation with (1R, 2S)-(−)-ephedrine – Experimental Entry 40). Spectral analysis consistent with Experimental Entry 20.

36. (3R)-3-Phenylhex-5-enal from (3S)-N-((2S)-1-(benzyloxy)-3-methylbutan-2-yl)-1-phenylhexa-1,5-dien-3-amine (110)

Thermal amino-Cope rearrangement and subsequent purification on diene (110) (0.26 g, 0.73 mmol) was carried out using the general method described. Aldehyde (R)-(55) was isolated as a light yellow oil (42 mg, 33%) with an e.e. of 12% (e.e. measured by derivatisation with (1R, 2S)-(−)-ephedrine – Experimental Entry 40). Spectral analysis consistent with Experimental Entry 20.
5.2.4. Derivatisation of Aldehyde Generated on Amino-Cope Rearrangement

5.2.4.1. Preparation of Enamine

37. *N,N*-Diisobutyl-(3R)-phenylhexa-1,5-dien-1-amine

![Structure](image)

Diisobutylamine (0.3 cm³, 1.73 mmol) was added dropwise to a stirred solution of aldehyde *(R)-(55)* (0.30 g, 1.72 mmol) and 4Å molecular sieves in anhydrous DCM (20 cm³) at 0 °C and stirred overnight at room temperature. The reaction mixture was dried over anhydrous sodium sulfate followed by filtration and removal of solvent under reduced pressure to yield enamine (111) as a yellow oil (0.39 g, 80%), which was used without further purification. \([\alpha]^{25}_D -29.1\) (c 1.27, DCM); \(\nu_{\text{max}}\) (film/cm⁻¹): 1673 (N=C=C) and 3025 (C=C); \(\delta_H\) (250MHz; CDCl₃): 0.83 (6H, dd, \(J\) 6.7 and 2.7, \(CH(CH_3)_2\)), 0.90 (6H, d, \(J\) 6.7, \(CH(CH_3)_2\)), 1.65-1.98 (2H, m, 2 \(x\) \(CH(CH_3)_2\)), 2.39 (4H, d, \(J\) 6.9, \(N(CH_2)_2\)), 2.69 (2H, d, \(J\) 7.2, \(CH_2CH=CH_2\)), 3.22 (1H, q, \(J\) 7.7, PhCH), 4.11 (1H, dd, \(J\) 13.7 and 7.9, NCH=CH), 4.89-5.06 (2H, m, CH=CH₂), 5.66-5.83 (1H, m, CH=CH₂), 5.87 (1H, dd, \(J\) 11.4 and 0.9, NCH=CH)), and 7.17-7.37 (5H, m, ArH). \(\delta_C\) (100MHz; CDCl₃): 20.68 (4 \(x\) CH₃), 27.08 (CH), 28.13 (CH), 40.96 (CH₂), 47.23 (CH), 60.46 (2 \(x\) CH₂), 97.89 (CH), 115.26 (CH₂), 127.85 (2 \(x\) CH), 128.10 (2 \(x\) CH), 128.63 (CH), 135.74 (CH), 138.86 (CH) and 147.31 (q).
5.2.4.2. Enamine Derivatisations

38. 2-Methyl-(3R)-3-phenylhex-5-enal from N,N-diisobutyl-(3R)-phenylhexa-1,5-dien-1-amine (111)

Methyl iodide (0.03 cm$^3$, 0.47 mmol) was added to a stirred solution of enamine (111) (0.13 g, 0.47 mmol) in anhydrous acetonitrile (10 cm$^3$) under an inert atmosphere of nitrogen and heated to reflux for 3 hours. The reaction mixture was then hydrolysed using 1 cm$^3$ of a 1:1:2 mixture of NaOAc/AcOH/H$_2$O and heated to reflux for a further 2 hours. Water (30 cm$^3$) was added to the mixture before the product was extracted with diethyl ether (3 x 10 cm$^3$). The combined organic phases were then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the crude aldehyde product (100a) as a yellow oil. Spectral analysis consistent with Experimental Entry 25.

39. 2-Benzyl-(3R)-3-phenylhex-5-enal from N,N-diisobutyl-(3R)-phenylhexa-1,5-dien-1-amine (111)

Benzyl bromide (0.36 cm$^3$, 3.02 mmol) was added to a stirred solution of enamine (111) (0.53 g, 2.52 mmol) in anhydrous acetonitrile (10 cm$^3$) under an inert atmosphere of nitrogen and heated to reflux for 3 hours. The reaction mixture was then hydrolysed using 1 cm$^3$ of a 1:1:2 mixture of NaOAc/AcOH/H$_2$O and heated to reflux for a further 2 hours. Water (30 cm$^3$) was added to the mixture before the product was extracted with
diethyl ether (3 x 10 cm³). The combined organic phases were then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product as a yellow oil. Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave a 1.5:1 mixture of diastereoisomers of aldehyde (100d) as a light yellow oil (14 mg, 8%). Spectral analysis consistent with Experimental Entry 29.

5.2.5. Determination of Absolute Configuration and Enantioselectivity of Aldehyde Products

40. (2S, 4S, 5R)-3,4-dimethyl-5-phenyl-2-[(2R)-2-phenylpent-4-enyl]-oxazolidine and (2S, 4S, 5R)-3,4-dimethyl-5-phenyl-2-[(2S)-2-phenylpent-4-enyl]-oxazolidine

Aldehyde (55) (37 mg, 0.20 mmol)) was dissolved in DCM (5 cm³) and stirred with activated 4Å molecular sieves. (1R, 2S)-(−)-ephedrine (32 mg, 0.20 mmol) was added and the mixture stirred at room temperature overnight. The resulting suspension was filtered through a small pad of celite and solvent was removed under reduced pressure to yield the mixture of derivatised oxazolidines (97a and 97b) as a light yellow oil. ¹H NMR analysis of the diastereoisomeric mixture enabled measurement of the d.e., which could be directly related to the e.e. of the starting aldehyde.

Oxazolidine data from derivatising (3R)-3-phenylhex-5-enal (from Experimental Entry 20) (e.e. 83%). δH (400MHz; CDCl₃, both isomers): 0.62 (3H, d, J 8.0, CH₃CH R-isomer), 0.65 (3H, d, J 8.0, CH₃CH S-isomer), 2.04-2.13 (4H, m, 2 x CH₂CH₂), 2.11 (3H, s, NCH₃ R-isomer), 2.25 (3H, s, NCH₃ S-isomer), 2.36-2.48 (4H, m, 2 x CH₂CH=CH₂), 2.59-2.66 (1H, m, CH₃CH R-isomer), 2.75-2.82 (1H, m, CH₃CH S-isomer), 3.03-3.11 (2H, m, 2 x CHPH), 3.50-3.52 (1H, m, OCH₃ R-isomer), 3.94-3.96

Experimental - 204 -
(1H, m, OCHN S-isomer), 4.92-5.00 (6H, m, 2 x PhCHO and 2 x CH=CH2), 5.62-5.73
(2H, m, 2 x CH=CH2) and 7.19-7.34 (20H, m, 2 x ArH).

5.3. Preparation of Novel Substrates for Amino-Cope Rearrangement Studies

5.3.1. Synthesis of Acyclic Vinyl Sulfides

5.3.1.1. Imino-Aldol Route

41. \textit{N-}(3-Phenylallylidene)-benzylamine

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \equiv \quad \equiv \quad \text{Ph} \\
\text{(136)}
\end{align*}
\]

trans-Cinnamaldehyde (2.4 cm\textsuperscript{3}, 18.66 mmol) was added to a stirred solution of benzylamine (2.0 cm\textsuperscript{3}, 18.66 mmol) in DCM (50 cm\textsuperscript{3}) containing activated 4Å molecular sieves at 0°C and stirred for 1 hour at room temperature. Anhydrous magnesium sulfate (4 g) was added and the reaction stirred for a further 15 minutes. Filtration and removal of solvent under reduced pressure yielded imine (136) as a yellow oil (4.05 g, 98%), which was used without further purification. \(\nu_{\text{max}}\) (film/cm\textsuperscript{-1}): 1634 (C=N) and 3025 (C=C); \(\delta_{\text{H}}\) (400MHz; CDCl\textsubscript{3}): 4.72 (2H, s, PhCH\textsubscript{2}N), 6.97-6.99 (2H, m, CH=CHPh), 7.24-7.58 (10H, m, ArH) and 8.13-8.16 (1H, m, CH=N); \(\delta_{\text{C}}\) (100MHz; CDCl\textsubscript{3}): 65.26 (CH\textsubscript{2}), 127.05 (CH), 127.26 (2 x CH), 128.08 (2 x CH), 128.17 (CH), 128.57 (2 x CH), 128.83 (2 x CH), 129.20 (CH), 135.68 (q), 139.14 (q), 142.05 (CH) and 163.48 (CH); \textit{m/z} (EI) 221 (M\textsuperscript{+}, 27%); Found: 221.1204; C\textsubscript{16}H\textsubscript{15}N requires M\textsuperscript{+}, 221.1204.
42. \( N,N\)-(Benzyldiene)-benzylamine

\[
\begin{align*}
\text{Ph} & \rightleftharpoons \text{N} & \text{Ph} \\
(139)
\end{align*}
\]

Benzaldehyde (2.1 cm\(^3\), 20.77 mmol) was added to a stirred solution of benzylamine (2.3 cm\(^3\), 20.77 mmol) in DCM (50 cm\(^3\)) containing activated 4Å molecular sieves at 0 °C and stirred for 1 hour at room temperature. Anhydrous magnesium sulfate (4 g) was added and the reaction stirred for a further 15 minutes. Filtration and removal of solvent under reduced pressure yielded imine (139) as a pale yellow oil (4.05 g, 99%), which was used without further purification. v \(_{\text{max}}\) (film/cm\(^{-1}\)): 1643 (C=N); \(\delta\)\(_{\text{H}}\) (400MHz; D\(_6\)-DMSO): 4.78 (2H, s, PhCH\(_2\)N), 7.24-7.49 (8H, m, ArH), 7.77-7.81 (2H, m, ArH) and 8.50 (1H, s, CH=N); \(\delta\)\(_{\text{C}}\) (100MHz; D\(_6\)-DMSO): 64.41 (CH\(_2\)), 127.21 (CH), 128.33 (2 x CH), 128.40 (2 x CH), 128.79 (2 x CH), 129.11 (2 x CH), 131.18 (CH), 136.50 (q), 140.05 (q) and 162.18 (CH); \(m/z\) (FAB) 196 (M\(^+\), 100%); Found: 196.1126; C\(_{14}\)H\(_{13}\)N requires M\(^+\), 196.1126.

43. (1-(Ethylthio)vinlyloxy)-trimethylsilane\(^{115}\)

\[
\begin{align*}
\text{OTMS} & \rightarrow \text{SEt} \\
(140)
\end{align*}
\]

A 2.5M solution of \(n\)-butyllithium in hexanes (29.0 cm\(^3\), 72.43 mmol) was added dropwise to a solution of diisopropylamine (11.2 cm\(^3\), 79.02 mmol) in anhydrous THF (100 cm\(^3\)) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 5 minutes at 0 °C then cooled to −78 °C in a dry ice/acetone slush bath before S-ethyl thioacetate (7.0 cm\(^3\), 65.84 mmol) was added. The solution was stirred for 30 minutes at −78 °C before chlorotrimethylsilane (10.9 cm\(^3\), 85.60 mmol) was added and the resulting mixture stirred for 30 minutes at −78 °C before warming to room temperature and stirred for 3 hours by which time a colourless precipitate formed. The solvent was removed under reduced pressure (30-40 mmHg, room temperature). The remaining residue was
then suspended in cooled hexane and washed quickly with cooled saturated aqueous sodium hydrogen carbonate solution (2 x 100 cm³), cooled water (2 x 100 cm³) and cooled saturated aqueous sodium chloride solution (100 cm³). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure (50-100 mmHg, room temperature). The residue was distilled under reduced pressure (35 mmHg, 80 °C) to afford the silyl enolate (140) as a colourless oil (10.34 g, 89%). ν max (film/cm⁻¹): 1253 (Si-C), 1008 (Si-O) and 1599 (OC=C); δH (400MHz; D6-DMSO): 0.21 (9H, s, (CH₃)₂SiO), 1.20 (3H, t, J 7.4, CH₃CH₂S), 2.66 (2H, q, J 7.3, CH₃CH₂S), 4.47 (1H, d, J 2.0, C=CH(H)) and 4.56 (1H, d, J 2.0, C=CH(H)); δC (100MHz; D6-DMSO): 2.11 (3 x CH₃), 14.86 (CH₃), 22.98 (CH₂), 92.53 (CH₂) and 195.80 (q); m/z (El) 176 (M⁺, 16%); Found: 176.0695; C₇H₁₆OSSi requires M⁺, 176.0691.

44. S-Ethyl-3-(benzylamino)-3-phenylpropanethioate¹¹³

\[ Ph\begin{array}{c}
\text{N} \\
\text{Ph}
\end{array}CH=CH(\text{H}) \text{S}\]

(141)

**Method 1**

To a stirred suspension of ytterbium triflate (0.32 g, 0.51 mmol) in anhydrous DCM (8 cm³) was added a solution of imine (139) (1.00 g, 5.12 mmol) and silyl enolate (140) (0.99 g, 5.63 mmol) in anhydrous DCM (16 cm³) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirring for 5 hours at 0 °C after which the reaction mixture was partitioned between water (50 cm³) and DCM (50 cm³). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in hexanes yielded the β-amino thioester (141) as a yellow oil (0.88 g, 57%). δH (400MHz; CDCl₃): 1.21 (3H, t, J 7.4, CH₃CH₂S), 2.80-2.97 (4H, m, CH₂C=O and CH₃CH₂S), 3.59 (2H, dd, J 44.2 and 13.3, NHCH₂Ph), 4.16 (1H, q, J 4.7, PhCH(CH₂)NH) and 7.22-7.35 (10H, m, ArH); δC (100MHz; CDCl₃): 14.64 (CH₃), 23.40

*Experimental - 207 -
(CH₂), 51.33 (CH₂), 52.19 (CH₂), 59.41 (CH), 126.87 (CH), 127.17 (2 x CH), 127.51 (CH), 128.08 (2 x CH), 128.32 (2 x CH), 128.59 129.59 (2 x CH), 140.20 (q), 142.28 (q) and 197.89 (q).

Method 2

To a stirred suspension of iodine (12.7 mg, 0.05 mmol) in propionitrile (1 cm³) was added a 0.1M solution of samarium diiodide in THF (1.0 cm³, 0.10 mmol) at room temperature under an inert atmosphere of nitrogen. The resulting solution was cooled to -78 °C and stirred for 15 minutes before a solution of imine (139) (0.20 g, 1.00 mmol) and silyl enolate (140) (0.26 g, 1.50 mmol) in propionitrile (3 cm³) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours before partitioning the reaction mixture between saturated aqueous sodium chloride solution (20 cm³) and ethyl acetate (20 cm³) and the aqueous layer was extracted with ethyl acetate (2 x 20 cm³). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in hexanes yielded the β-amino thioester (141) as a yellow oil (0.19 g, 62%). Spectral analysis consistent with Experimental Entry 44.

5.3.1.2. Mitsunobu Route

45. S-Ethyl-3-(ethylthio)-5-phenylpent-4-enethioate

![Chemical Structure](image)

A 2.5M solution of n-butyllithium in hexanes (5.5 cm³, 13.64 mmol) was added dropwise to a solution of diisopropylamine (1.9 cm³, 13.64 mmol) in anhydrous THF (5 cm³) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 10 minutes at 0 °C then cooled to -78 °C in a dry ice/acetone slush bath before S-ethyl thioacetate (1.7 cm³,
16.37 mmol) was added. The solution was stirred for 30 minutes at -78 °C before trans-
cinnamaldehyde (2.0 cm³, 16.37 mmol) was added. The reaction was allowed to slowly
warm to room temperature overnight within the dry ice/acetone slush bath before being
quenched with saturated aqueous ammonium chloride solution. The mixture was
extracted with ethyl acetate (50 cm³), washed with water (50 cm³) and saturated aqueous
sodium chloride solution (50 cm³). The organic phase was dried over anhydrous
magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil.
Flash column chromatography on silica, eluting with 10% ethyl acetate in light petroleum
did not yield the desired aldol product but (149) as a yellow oil (2.84 g, 62%). $\nu_{\text{max}}$
(film/cm⁻¹): 1682 (SC=O) and 3025 (C=C); $\delta_{\text{H}}$ (250MHz; CDCl₃): 1.21 (3H, t, $J = 7.4,$
CH₃CH₂SC=O), 1.23 (3H, t, $J = 7.4,$ CH₃CH₂SCH), 2.40-2.61 (2H, m, CH₃CH₂SCH), 2.83-
2.92 (4H, m, CH₃CH₂SC=O and CH₂C=O), 3.86-3.96 (1H, m, CH₃CH₂SCH), 6.01 (1H,
dd, $J = 15.6$ and 9.2, CH=CHPh), 6.41 (1H, d, $J = 15.8$, CH=CHPh) and 7.19-7.39 (5H, m,
ArH); $\delta_{C}$ (100MHz; CDCl₃): 14.58 (CH₃), 14.63 (CH₃), 23.56 (CH₂), 24.81 (CH₂), 43.80
(CH), 48.62 (CH), 126.48 (2 x CH), 127.70 (CH), 128.86 (2 x CH), 129.21 (CH), 131.15
(CH), 136.43 (q) and 196.38 (q); m/z (El) 280 (M⁺, 4%).

46. $S$-Ethyl-3-hydroxy-5-phenylpent-4-enethioate$^{121}$

\[
\begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{CH=CH} & \quad \text{O} \\
\text{S Et} & \\
\end{align*}
\]

(144)

A 2.5M solution of $n$-butyllithium in hexanes (15.9 cm³, 39.72 mmol) was added
dropwise to a solution of diisopropylamine (5.6 cm³, 39.72 mmol) in anhydrous THF (60
cm³) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 40
minutes at 0 °C then cooled to -78 °C in a dry ice/acetone slush bath before $S$-ethyl
thioacetate (4.0 cm³, 37.74 mmol) was added. The solution was stirred for 40 minutes at
-78 °C before trans-cinnamaldehyde (5.0 cm³, 39.72 mmol) was added and the resulting
mixture left to stir for 2 hours at -78 °C. The reaction was quenched at -78 °C with
saturated aqueous sodium hydrogen carbonate solution and allowed to warm to room
temperature whereupon the mixture was extracted with diethyl ether (50 cm³) and the
resulting aqueous layer further extracted with diethyl ether (2 x 50 cm³). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 20% ethyl acetate in light petroleum yielded aldol (144) as a yellow oil (7.28 g, 82%). $\nu$ max (film/cm$^{-1}$): 1682 (SC=O) and 3443 (O-H); $\delta$ H (250MHz; CDCl$_3$): 1.26 (3H, t, J 7.5, CH$_3$CH$_2$S), 2.87 (2H, d, J 6.0, CH(OH)CH$_2$), 2.93 (2H, q, J 7.4, CH$_3$CH$_2$S), 4.73-4.81 (1H, m, CHOH), 6.20 (1H, dd, J 15.9 and 6.0, CH=CHPh), 6.65 (1H, d, J 15.9, CH=CHPh) and 7.20-7.39 (5H, m, ArH); $\delta$ C (100MHz; CDCl$_3$): 14.59 (CH$_3$), 23.50 (CH$_2$), 50.64 (CH$_2$), 69.49 (CH), 126.57 (2 x CH), 127.85 (CH), 128.59 (2 x CH), 129.74 (CH), 130.91 (CH), 136.39 (q) and 198.71 (q); m/z (EI) 236 (M$^+$, 8%); Found: 236.0870; C$_{13}$H$_{16}$O$_2$S requires M$^+$, 236.0871.

47. S-Ethyl-3-(1,3-dioxoisindolin-2-yl)-5-phenylpent-4-enethioate and S-ethyl-5-phenylpenta-2,4-dienethioate

To a stirred solution of aldol (144) (0.37 g, 1.55 mmol), triphenylphosphine (0.73 g, 2.79 mmol) and phthalimide (0.36 g, 2.48 mmol) in anhydrous THF (10 cm³) was added diisopropylazodicarboxylate (0.6 cm³, 2.79 mmol) dropwise at room temperature. The reaction was stirred at room temperature for 4 hours before solvent extraction under reduced pressure. The remaining residue was then suspended in diethyl ether, washed with water, saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in hexanes yielded the required product (153) as a yellow oil (86 mg, 15%) and elimination product (154) as a yellow oil (0.23 g, 68%).
Analysis for (153)

\( \nu_{\text{max}} \) (film/cm\(^{-1}\)): 1685 (SC=O), 1773 and 1714 (OC-N-CO); \( \delta_\text{H} \) (400MHz; CDCl\(_3\)): 1.15 (3H, t, \( J = 7.4 \), CH\(_3\)CH\(_2\)S), 2.82 (2H, q, \( J = 7.4 \), CH\(_3\)CH\(_2\)S), 3.20 (1H, dd, \( J = 15.2 \) and 5.9, NPhth-CHCH(H)), 3.57 (1H, dd, \( J = 15.3 \) and 9.4, NPhth-CHCH(H)), 5.40-5.46 (1H, m, NPhth-CHCH\(_2\)), 6.53 (1H, dd, \( J = 15.6 \) and 7.8, CH=CHPh), 6.66 (1H, d, \( J = 15.6 \), CH=CHPh), 7.21-7.37 (5H, m, ArH), 7.71 (2H, dd, \( J = 5.5 \) and 3.2, Phth-ArH) and 7.84 (2H, dd, \( J = 5.5 \) and 2.8, Phth-ArH); \( \delta_\text{C} \) (100MHz; CDCl\(_3\)): 14.50 (CH\(_3\)), 23.43 (CH\(_2\)), 45.83 (CH\(_2\)), 50.05 (CH), 123.34 (2 x CH), 124.95 (CH), 126.89 (2 x CH), 128.12 (CH), 128.54 (2 x CH), 131.87 (2 x q), 133.70 (CH), 133.99 (2 x CH), 135.92 (q), 167.50 (2 x q) and 196.09 (q); \( m/z \) (El) 365 (M\(^+\), 2%); Found: 365.1079; C\(_{21}\)H\(_{19}\)NO\(_3\)S requires M\(^+\), 365.1086.

Analysis for (154)

\( \nu_{\text{max}} \) (film/cm\(^{-1}\)): 1684 (SC=O) and 3027 (C=C); \( \delta_\text{H} \) (400MHz; CDCl\(_3\)): 1.31 (3H, t, \( J = 7.4 \), CH\(_3\)CH\(_2\)S), 2.99 (2H, q, \( J = 7.4 \), CH\(_3\)CH\(_2\)S), 6.27 (1H, d, \( J = 15.2 \), CH=CHC=O), 6.83 (1H, dd, \( J = 15.7 \) and 11.0, CH=CHPh), 6.96 (1H, d, \( J = 15.2 \), CH=CHPh) and 7.22-7.42 (6H, m, CH=CHC=O and ArH); \( \delta_\text{C} \) (100MHz; CDCl\(_3\)): 14.79 (CH\(_3\)), 23.24 (CH\(_2\)), 126.09 (CH), 127.21 (2 x CH), 128.26 (CH), 128.81 (2 x CH), 129.17 (CH), 136.02 (q), 140.29 (CH), 141.67 (CH) and 198.73 (q); \( m/z \) (El) 218 (M\(^+\), 7%); Found: 218.0769; C\(_{13}\)H\(_{14}\)OS requires M\(^+\), 218.0765.

48. \textit{S-}Ethyl-3-(trimethyl-silanyloxy)-5-phenylpent-4-enethioate\textsuperscript{[21]}

\textbf{(145)}

Chlorotrimethylsilane (1.2 cm\(^3\), 9.39 mmol) was added to a solution of aldol (144) (2.11 g, 8.94 mmol) and diisopropylethylamine (1.7 cm\(^3\), 9.84 mmol) in anhydrous DMF (30 cm\(^3\)) at 0 °C under an inert atmosphere of nitrogen. The reaction mixture was warmed to
room temperature and left to stir for 16 hours before quenching with saturated aqueous sodium hydrogen carbonate solution (200 cm$^3$). The mixture was extracted with diethyl ether (30 cm$^3$) and the resulting aqueous layer further extracted with diethyl ether (2 x 30 cm$^3$). The combined organic phase was washed with 0.5N citric acid (100 cm$^3$) and water (100 cm$^3$), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the TMS-protected aldol (145) as an orange oil (2.71 g, 98%), which was used without further purification. $\nu_{\text{max}}$ (film/cm$^{-1}$): 1686 (SC=O), 1250 (Si-C) and 1062 (Si-O); $\delta_H$ (400MHz; D$_6$-DMSO): 0.08 (9H, s, (CH$_3$)$_3$SiO), 1.17 (3H, t, J 7.4, CH$_3$CH$_2$S), 2.75-2.87 (4H, m, CH(OTMS)CH$_2$ and CH$_3$CH$_2$S), 4.73-4.78 (1H, m, CHOTMS), 6.29 (1H, dd, J 15.6 and 6.3, CH=CHPh), 6.57 (1H, d, J 15.6, CH=CHPh) and 7.22-7.42 (5H, m, ArH); $\delta_C$ (100MHz; D$_6$-DMSO): 0.61 (3 x CH$_3$), 15.20 (CH$_3$), 23.21 (CH$_2$), 52.32 (CH$_2$), 70.71 (CH), 126.81 (2 x CH), 128.09 (CH), 129.07 (2 x CH), 129.70 (CH), 131.85 (CH), 136.72 (q) and 197.00 (q); $m/z$ (El) 308 (M$^+$, 4%); Found: 308.1267; C$_{16}$H$_{24}$O$_2$SiS requires M$^+$, 308.1266.

49. 5-(Ethylthio)-1-phenylhexa-1,5-dien-3-ol$^{12}$

![Structure of 5-(Ethylthio)-1-phenylhexa-1,5-dien-3-ol](image)

A 1M solution of titanium tetrachloride in DCM (27.3 cm$^3$, 27.31 mmol) was added slowly to anhydrous THF (25 cm$^3$) at 0 °C under an inert atmosphere of nitrogen. To the suspension was added TMEDA (8.2 cm$^3$, 54.61 mmol) dropwise. The resulting suspension was stirred for 30 minutes at 0 °C before zinc powder (activated by sequential washing with 1M aqueous hydrochloric acid solution, water, acetone and ether and dried by vacuum) (4.02 g, 61.44 mmol) and lead(II) chloride (85 mg, 0.31 mmol) was added. The reaction flask was flushed with nitrogen and left to stir for 50 minutes at room temperature. To the resulting deep blue mixture was added a solution of TMS-aldol (145) (2.11 g, 6.83 mmol) and dibromomethane (1.1 cm$^3$, 15.02 mmol) in anhydrous THF (5 cm$^3$) over 10 minutes. The reaction mixture was stirred for 4 hours, gradually turning black, cooled to 0 °C and then quenched by slowly adding saturated aqueous potassium
carbonate solution until a black precipitate formed. The suspension was stirred at room temperature for 20 minutes before ethyl acetate (50 cm³) was added and the mixture vigorously stirred for 15 minutes. The reaction mixture was then filtered rapidly through a thin pad of neutral alumina (6% H₂O) before solvent extraction of the filtrate under reduced pressure to give an orange oil and a white precipitate. The oil was dissolved in ethyl acetate and filtered through a thin pad of neutral alumina (6% H₂O). The filtrate was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield an orange oil. A 1M solution of TBAF in THF (8.3 cm³, 8.29 mmol) was added to the orange oil (1.69 g, assumed 5.53 mmol) and stirred for 90 minutes at room temperature under an inert atmosphere of nitrogen. The resulting mixture was quenched with saturated aqueous sodium hydrogen carbonate solution (20 cm³). The mixture was extracted with diethyl ether (25 cm³) and the resulting aqueous layer further extracted with diethyl ether (2 x 25 cm³). The combined organic phase dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a red oil. Flash column chromatography on silica, eluting with 10% ethyl acetate in hexanes yielded diene (146) as a yellow oil (0.53 g, 33% over 2 steps). \( \nu_{\text{max}} \) (film/cm⁻¹): 3396 (O-H) and 3024 (C=C); \( \delta_{\text{H}} \) (400MHz; CDCl₃): 1.32 (3H, t, J 7.4, CH₃CH₂S), 2.47-2.57 (2H, m, CH(OH)CH₂), 2.77 (2H, q, J 7.4, CH₃CH₂S), 4.51-4.57 (1H, m, CHOH), 4.87 (1H, s, C=CH(H)), 5.17 (1H, s, C=CH(H)), 6.23 (1H, dd, J 15.6 and 6.3, CH=CH(Ph)), 6.65 (1H, d, J 15.6, CH=CH(Ph)) and 7.21-7.40 (5H, m, ArH); \( \delta_{\text{C}} \) (100MHz; CDCl₃): 13.16 (CH₃), 25.47 (CH₂), 45.97 (CH₂), 70.94 (CH), 108.66 (CH₂), 126.48 (2 x CH), 127.59 (CH), 128.52 (2 x CH), 130.33 (CH), 130.97 (CH), 136.73 (q) and 141.55 (q); \( m/z \) (EI) 234 (M⁺, 20%); Found: 234.1080; C₁₄H₁₈OS requires M⁺, 234.1078.
50. 2-(5-(Ethylthio)-1-phenylhexa-1,5-dien-3-yl)-isoindoline-1,3-dione

![Chemical Structure](image)

(147)

To a stirred solution of diene (146) (0.58 g, 2.46 mmol), triphenylphosphine (1.16 g, 4.43 mmol) and phthalimide (0.58 g, 3.93 mmol) in THF (15 cm³) was added diisopropylazodicarboxylate (0.9 cm³, 4.43 mmol) dropwise at room temperature. The reaction was stirred at room temperature for 4 hours before solvent extraction under reduced pressure. The remaining residue was then suspended in diethyl ether, washed with water, saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in hexanes yielded the product (147) as a yellow oil (0.23 g, 25%). \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 1710 (OC-N-CO) and 3025 (C=C); \(\delta_H\) (400MHz; CDCl\(_3\)): 1.21 (3H, t, \(J = 7.2\), CH\(_3\)CH\(_2\))S), 2.67 (2H, q, \(J = 7.6\), CH\(_2\)CH\(_2\)), 2.74-2.79 (1H, m, NPhth-CHCH(H)), 3.22 (1H, dd, \(J = 14.0\) and 10.0, NPhth-CHCH(H)), 4.72 (1H, s, C=CH(H)), 5.09 (1H, s, C=CH(H)), 5.23-5.28 (1H, m, NPhth-CHCH\(_2\)), 6.39-6.46 (1H, m, CH=CHPh), 6.61-6.64 (1H, m, CH=CHPh), 7.21-7.45 (5H, m, ArH), 7.68-7.72 (2H, m, Phth-ArH) and 7.83 (2H, dd, \(J = 5.6\) and 2.8, Phth-ArH); \(m/z\) (EI) 363 (M\(^+\), 2%); Found: 363.1287; C\(_{22}\)H\(_{21}\)NO\(_2\)S requires M\(^+\), 363.1293.

Experimental
5.3.2. Novel Route to 1,6-disubstituted-3-amino-1,5-diene substrates

5.3.2.1. Preparation of Racemic 1,6-Disubstituted-3-Amino-1,5-Diene Substrates

51. Ethyl-2-(benzylideneamino)-acetate

\[
\begin{align*}
\text{Ph} & \xrightarrow{N} \text{CO}_2\text{Et} \\
& (164)
\end{align*}
\]

A solution of glycine ethyl ester hydrochloride (10.00 g, 71.64 mmol), triethylamine (20.0 cm\(^3\), 143.29 mmol) and anhydrous magnesium sulfate in DCM (150 cm\(^3\)) was treated with benzaldehyde (6.9 cm\(^3\), 68.06 mmol) at room temperature. The mixture was stirred at room temperature for 30 hours before filtration and removal of solvent. The residue was dissolved in diethyl ether (150 cm\(^3\)) and washed with water (150 cm\(^3\)) and saturated aqueous sodium chloride solution (150 cm\(^3\)). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the imine ester (164) as a yellow oil (12.35 g, 95%), which was used without further purification. \(\nu_{max}\) (film/cm\(^{-1}\)): 1745 (O=C-O) and 1650 (C=N); \(\delta_H\) (250MHz; D\(_6\)-DMSO): 1.21 (3H, t, J 7.1, CO\(_2\)CH\(_2\)CH\(_3\)), 4.13 (2H, q, J 7.0, CO\(_2\)CH\(_2\)CH\(_3\)), 4.41 (2H, s, NCH\(_2\)CO\(_2\)), 7.43-7.50 (3H, m, ArH), 7.75-7.80 (2H, m, ArH) and 8.37 (1H, s, PhCH=N); \(\delta_C\) (100MHz; D\(_6\)-DMSO): 14.07 (CH\(_3\)), 60.33 (CH\(_2\)), 60.87 (CH\(_2\)), 128.06 (2 x CH), 128.71 (2 x CH), 131.11 (CH), 135.61 (q), 165.15 (CH) and 169.84 (q); \(m/z\) (EI) 192 ((M + 1)\(^+\), 33%); Found: 192.1028; C\(_{11}H_{12}NO_2\) requires (M + 1)\(^+\), 192.1025.
A 2.5M solution of n-butyllithium in hexanes (2.4 cm$^3$, 6.11 mmol) was added dropwise to a solution of diisopropylamine (0.9 cm$^3$, 6.43 mmol) in anhydrous THF (10 cm$^3$) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 5 minutes at 0 °C then cooled to -78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. DMPU (0.8 cm$^3$, 6.43 mmol) was added dropwise and the reaction stirred for 10 minutes before imine ester (164) (1.23 g, 6.43 mmol) in anhydrous THF (15 cm$^3$) was added dropwise. The reaction was stirred for 30 minutes at -78 °C before crotyl bromide (0.8 cm$^3$, 6.43 mmol) was added and the reaction stirred for a further 1 hour at the same temperature. The reaction was stirred at room temperature for a further 3 hours before being quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (50 cm$^3$) and the resulting aqueous layer further extracted with diethyl ether (2 x 50 cm$^3$). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield (168) as an orange oil (1.81 g). The crude product was carried forward without purification. $\delta_H$ (250MHz; CDCl$_3$): 1.28 (3H, t, $J$ 7.2, CO$_2$CH$_2$CH$_3$), 1.63 (3H, dd, $J$ 6.2 and 1.2, CH$_2$CH=CHCH$_3$), 2.46-2.77 (2H, m, CH$_2$CH=CHCH$_3$), 3.98 (1H, t, $J$ 7.5, NCHCO$_2$CH$_2$CH$_3$), 4.17-4.26 (2H, m, CO$_2$CH$_2$CH$_3$), 5.30-5.61 (2H, m, CH$_2$CH=CHCH$_3$), 7.37-7.45 (3H, m, ArH), 7.74-7.81 (2H, m, ArH) and 8.25 (1H, s, PhCH=PhH); $\delta_C$ (100MHz; CDCl$_3$): 14.24 (CH$_3$), 18.11 (CH$_3$), 36.88 (CH$_2$), 60.90 (CH$_2$), 73.68 (CH), 126.06 (CH), 128.53 (2 x CH), 128.55 (2 x CH), 128.96 (CH), 131.04 (CH), 135.72 (q), 163.29 (CH) and 171.89 (q).
53. Ethyl-2-(benzylideneamino)-5-phenylpent-4-enoate\textsuperscript{136}

\[ \text{Ph} \xrightarrow{N} \text{CO}_2\text{Et} \]

(183)

A 2.5M solution of \(n\)-butyllithium in hexanes (64.0 cm\(^3\), 160.09 mmol) was added dropwise to a solution of diisopropylamine (23.8 cm\(^3\), 168.53 mmol) in anhydrous THF (100 cm\(^3\)) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 5 minutes at 0 °C then cooled to −78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. DMPU (20.4 cm\(^3\), 168.53 mmol) was added dropwise and the reaction stirred for 10 minutes before imine ester (164) (32.23 g, 168.53 mmol) in anhydrous THF (100 cm\(^3\)) was added dropwise. The reaction was stirred for 30 minutes at −78 °C before cinnamyl bromide (33.21 g, 168.53 mmol) in anhydrous THF (30 cm\(^3\)) was added dropwise and the reaction stirred for a further 1 hour at the same temperature. The reaction was stirred at room temperature for a further 3 hours before being quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (50 cm\(^3\)) and the resulting aqueous layer further extracted with diethyl ether (2 x 50 cm\(^3\)). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield (183) as an orange oil (53.4 g). The crude product was carried forward without purification. \(\delta_H\) (400MHz; CDCl\(_3\)): 1.27 (3H, t, \(J\) 6.8, CO\(_2\)CH\(_2\)CH\(_3\)), 2.74-2.98 (2H, m, CH\(_2\)CH=CHCH\(_3\)), 4.01 (1H, t, \(J\) 6.0, NCHCO\(_2\)CH\(_2\)CH\(_3\)), 4.18-4.26 (2H, m, CO\(_2\)CH\(_2\)CH\(_3\)), 6.09-6.19 (1H, m, CH\(_2\)CH=CHPh), 6.48 (1H, d, \(J\) 14.8, CH\(_2\)CH=CHPh), 7.18-7.47 (6H, m, ArH), 7.77-7.80 (4H, m, ArH) and 8.29 (1H, s, PhCH=N); \(\delta_C\) (100MHz; CDCl\(_3\)): 14.25 (CH\(_3\)), 37.18 (CH\(_2\)), 61.14 (CH\(_2\)), 73.42 (CH), 125.42 (CH), 126.15 (2 x CH), 127.26 (CH), 128.47 (2 x CH), 128.59 (4 x CH), 131.15 (CH), 133.27 (CH), 135.65 (q), 137.25 (q), 163.68 (CH) and 171.55 (q).
54. Ethyl-2-(benzlamino)-hex-4-enoate and Ethyl-2-(benzlamino)-2-(but-2-enyl)-hex-4-enoate

\[
\text{Ph-NC} \quad \rightarrow \quad \text{Ph-NC} + \text{Ph-((:t}
\]

Sodium triacetoxyborohydride (2.61 g, 12.31 mmol) was added to a solution of imine ester (168) (2.01 g, 8.21 mmol) in DCE (30 cm³) at room temperature. Glacial acetic acid (0.7 cm³, 12.31 mmol) was added to the resulting suspension at room temperature and stirred for 1 hour. The reaction was quenched by the slow addition of water until effervescence had subsided. DCM (50 cm³) was added and the resulting mixture washed with saturated aqueous sodium hydrogen carbonate solution (2 x 50 cm³). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a red oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in light petroleum with 0.5% triethylamine yielded the required amino ester (169) as an orange oil (1.37 g, 78% over two steps) and the dialkylated by-product (170) as a yellow oil (0.48 g, 22% over two steps).

Analysis for (169)

\[\nu_{\text{max}} \text{ (film/cm}^{-1}) : 1730 \text{ (O-C-O)}, 3026 \text{ (C=C) and 1181 (N-H)}; \delta_H (250MHz; \text{CDCl}_3) : 1.27 \text{ (3H, t, J 7.0, CO}_2\text{CH}_2\text{CH}_3), 1.65 \text{ (3H, dd, J 6.1 and 1.2, CH}_2\text{CH=CHCH}_3), 2.33-2.47 \text{ (2H, m, CH}_2\text{CH=CHCH}_3), 3.30 \text{ (1H, t, J 7.5, NCHCO}_2\text{CH}_2\text{CH}_3), 3.65 \text{ (1H, d, J 12.9, PhCH(H)NH), 3.83 \text{ (1H, d, J 12.9, PhCH(H)N), 4.09-4.27 (2H, m, CO}_2\text{CH}_2\text{CH}_3), 5.28-5.65 \text{ (2H, m, CH}_2\text{CH=CHCH}_3) \text{ and 7.20-7.34 (5H, m, ArH)}; \delta_C (100MHz; \text{CDCl}_3) : 14.38 \text{ (CH}_3), 18.00 \text{ (CH}_3), 36.58 \text{ (CH}_2), 51.96 \text{ (CH}_2), 60.53 \text{ (CH}_2), 60.55 \text{ (CH), 125.85 (CH), 127.06 (CH), 128.22 (4 x CH), 128.74 (CH), 139.75 (q) and 174.71 (q); m/z (EI) 247 (M}^+, 1\%); \text{Found: 247.1577; } \text{C}_{15}\text{H}_{21}\text{NO}_2 \text{ requires M}^+, 247.1572.\]
Analysis for (170)

δ_H (250MHz; CDCl_3): 1.29 (3H, t, J 7.1, CO_2CH_2CH_3), 1.67 (6H, dd, J 5.9 and 0.9, 2 x CH_2CH=CHCH_3), 2.32-2.52 (4H, m, 2 x CH_2CH=CHCH_3), 3.63 (2H, s, PhCH_2N), 4.19 (2H, q, J 7.2, CO_2CH_2CH_3), 5.34-5.67 (4H, m, 2 x CH_2CH=CHCH_3) and 7.20-7.39 (5H, m, ArH); δ_C (100MHz; CDCl_3): 14.48 (CH_3), 18.16 (2 x CH_3), 37.90 (2 x CH_2), 47.81 (CH_2), 60.61 (CH_2), 65.07 (q), 125.19 (2 x CH), 127.02 (CH), 128.41 (2 x CH), 128.46 (2 x CH), 129.09 (2 x CH), 140.30 (q) and 175.28 (q).

55. Ethyl-2-(benzylamino)-5-phenylpent-4-enoate and Ethyl-2-(benzylamino)-2-cinnamyl-5-phenylpent-4-enoate

Sodium triacetoxyborohydride (55.23 g, 260.57 mmol) was added to a solution of imine ester (183) (53.4 g, 173.72 mmol) in DCE (500 cm^3) at room temperature. Glacial acetic acid (14.9 cm^3, 260.57 mmol) was added to the resulting suspension at room temperature and stirred for 2 hours. The reaction was quenched by the slow addition of water until effervescence had subsided. DCM (500 cm^3) was added and the resulting mixture washed with saturated aqueous sodium hydrogen carbonate solution (2 x 500 cm^3). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a red oil. Flash column chromatography on silica, eluting with 10% ethyl acetate in light petroleum yielded the required amino ester (184) as a pale yellow oil (33.78 g, 65% over two steps) and the dialkylated by-product (185) as a yellow oil (8.68 g, 12% over two steps).
Analysis for (184)

ν_{max} (film/cm^{-1}): 1731 (O=C=O), 3026 (C=C) and 1184 (N-H); δ_{H} (400MHz; CDCl3): 1.26 (3H, t, J 7.2, CO2CH2CH3), 2.57-2.60 (2H, m, CH2CH=CHPh), 3.42 (1H, t, J 6.4, NCH2CO2CH2CH3), 3.69 (1H, d, J 13.2, PhCH(N)H), 3.86 (1H, d, J 13.2, PhCH(H)), 4.15-4.23 (2H, m, CO2CH2CH3), 6.15 (1H, dt, J 15.6 and 7.2, CH2CH=CHPh), 6.45 (1H, d, J 16.0, CH2CH=CHPh) and 7.19-7.35 (10H, m, ArH); δ_{C} (100MHz; CDCl3): 14.30 (CH3), 37.04 (CH2), 60.51 (CH), 60.73 (CH2), 125.26 (CH), 126.16 (2 x CH), 127.12 (CH), 127.27 (CH), 128.32 (2 x CH), 128.41 (2 x CH), 128.49 (2 x CH), 132.94 (CH), 137.20 (q), 139.64 (q) and 174.57 (q); m/z (FAB) 310 ((M + 1)^{+}, 46%); Found: 310.1812; C20H13N02 requires (M + 1)^{+}, 310.1807.

Analysis for (185)

δ_{H} (400MHz; CDCl3): 1.31 (3H, t, J 7.2, CO2CH2CH3), 2.63-2.78 (4H, m, 2 x CH2CH=CHPh), 3.75 (2H, s, PhCH2N), 4.24 (2H, q, J 7.2, CO2CH2CH3), 6.19-6.26 (2H, m, 2 x CH2CH=CHPh), 6.49 (2H, d, J 15.6, 2 x CH2CH=CHPh) and 7.19-7.39 (15H, m, ArH); δ_{C} (100MHz; CDCl3): 14.53 (CH3), 38.57 (2 x CH2), 48.02 (CH2), 60.94 (CH2), 65.44 (q), 124.51 (2 x CH), 126.18 (4 x CH), 127.14 (CH), 127.26 (2 x CH), 128.41 (2 x CH), 128.48 (2 x CH), 128.51 (4 x CH), 133.65 (2 x CH), 137.34 (2 x q), 140.00 (q) and 174.95 (q).

56. 2-(Benzylationino)-hex-4-en-l-ol

![Structural formula](172)

Ester (169) (1.07 g, 4.33 mmol) was dissolved in anhydrous THF (20 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. A 1M solution of DIBAL in THF (13.0 cm³, 12.99 mmol) was added dropwise and the reaction was stirred at −78 °C for 30 minutes before warming to room temperature for another 30 minutes.
temperature and stirred overnight. The reaction was quenched by the slow addition of methanol until effervescence had subsided. The mixture was then poured into saturated aqueous potassium sodium tartrate solution (100 cm³) and vigorously stirred for 5 minutes before being extracted with ethyl acetate (50 cm³) and the resulting aqueous layer further extracted with diethyl ether (2 x 50 cm³). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (100 cm³), saturated aqueous sodium chloride solution (100 cm³), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield alcohol (172) as a yellow oil (0.73 g, 82%), which was used without further purification. ν max (film/cm⁻¹): 3312 (O-H), 3024 (C=C) and 1495 (N-H); δ H (400MHz; CDCl₃): 1.66 (3H, dq, J 6.4 and 1.2, CH₂CH=CHCH₃), 2.14-2.25 (2H, m, CH₂CH=CHCH₃), 2.71-2.76 (1H, m, NCHCH₂OH), 3.35 (1H, dd, J 10.8 and 6.0, NCHCH(H)OH), 3.64 (1H, dd, J 11.2 and 4.0, NCHCH(H)OH), 3.81 (2H, dd, J 22.8 and 12.8, PhCH₂N), 5.28-5.38 (1H, m, CH₂CH=CHCH₃), 5.47-5.57 (1H, m, CH₂CH=CHCH₃) and 7.23-7.36 (5H, m, ArH); δ C (100MHz; CDCl₃): 18.01 (CH₃), 34.36 (CH₂), 50.92 (CH₂), 57.85 (CH), 62.44 (CH₂), 126.72 (CH), 127.40 (CH), 128.32 (2 x CH), 128.57 (2 x CH), 128.86 (CH) and 139.03 (q).

57. t-Butyl-1-(ethoxycarbonyl)-pent-3-enylbenzylcarbamate

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{CO₂Et} & \quad \text{Me}
\end{align*}
\]

(173)

Triethylamine (8.4 cm³, 60.28 mmol), DMAP (0.74 g, 6.03 mmol) and di-tert-butyl dicarbonate (13.16 g, 60.28 mmol) were successively added to a solution of ester (169) (7.45 g, 30.14 mmol) in anhydrous THF (100 cm³) and stirred at reflux for 48 hours. Volatiles were removed under reduced pressure and the resulting residue was dissolved in ethyl acetate (100 cm³), washed with saturated aqueous ammonium chloride solution (2 x 100 cm³), saturated aqueous sodium hydrogen carbonate solution (100 cm³) and saturated aqueous sodium chloride solution (100 cm³). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield alcohol (172) as a yellow oil (0.73 g, 82%), which was used without further purification.
pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in light petroleum yielded N-Boc ester (173) as a pale yellow oil (7.33 g, 70%). $\nu_{\text{max}}$ (film/cm$^{-1}$): 1737 (O=C–O), 3027 (C=C) and 1697 (O-CO-N); $\delta_{\text{H}}$ (400MHz; D$_6$-DMSO, 100 °C): 1.16 (3H, t, $J$ 7.1, CO$_2$CH$_2$CH$_2$H), 1.39 (9H, s, (CH$_3$)$_3$CO), 1.56 (3H, dd, $J$ 6.2 and 1.2, CH$_3$CH=CHCH$_3$), 2.41-2.63 (2H, m, CH$_2$CH=CHCH$_3$), 3.98-4.10 (2H, m, CO$_2$CH$_2$CH$_3$), 4.17 (1H, t, $J$ 6.6, NCH/CO$_2$CH$_2$CH$_3$), 4.42 (2H, dd, $J$ 29.4 and 15.7, PhCH$_2$N), 5.23-5.42 (2H, m, CH$_2$CH=CHCH$_3$) and 7.21-7.34 (5H, m, ArH); $\delta_{\text{C}}$ (100MHz; D$_6$-DMSO, 100 °C): 13.21 (CH$_3$), 16.75 (CH$_3$), 27.43 (3 x CH$_3$), 32.32 (CH$_2$), 50.35 (CH$_2$), 59.56 (CH), 59.74 (CH$_2$), 79.13 (q), 125.89 (CH), 126.16 (CH), 126.54 (CH), 126.72 (CH), 127.19 (CH), 127.31 (2 x CH), 138.12 (q), 154.32 (q) and 169.95 (q); m/z (El) 347 (M$^+$, 1%); Found: 347.2102; C$_{28}$H$_{29}$N$_2$O$_4$ requires M$^+$, 347.2097.

58. $\beta$-Butyl-1-(ethoxycarbonyl)-4-phenylbut-3-enylbenzyl carbamate

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
& \quad \text{CO}_2\text{Et} \\
& \quad \text{Ph} \\
\end{align*}
\]

(186)

Triethylamine (60.1 cm$^3$, 430.95 mmol), DMAP (6.58 g, 53.87 mmol) and di-tert-butyldicarbonate (58.78 g, 269.34 mmol) were successively added to a solution of ester (184) (33.34 g, 107.74 mmol) in anhydrous THF (215 cm$^3$) and stirred at reflux for 48 hours. Volatiles were removed under reduced pressure and the resulting residue was dissolved in ethyl acetate (500 cm$^3$), washed with saturated aqueous ammonium chloride solution (2 x 500 cm$^3$), saturated aqueous sodium hydrogen carbonate solution (500 cm$^3$) and saturated aqueous sodium chloride solution (500 cm$^3$). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a brown oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded N-Boc ester (186) as a pale yellow oil (24.37 g, 55%). $\nu_{\text{max}}$ (film/cm$^{-1}$): 1733 (O=C–O), 3028 (C=C) and 1699 (O-CO-N); $\delta_{\text{H}}$ (400MHz; D$_6$-DMSO, 100 °C): 1.18 (3H, t, $J$ 7.2, CO$_2$CH$_2$CH$_2$H), 1.39 (9H, s, (CH$_3$)$_3$CO), 2.66-2.84 (2H, m, CH$_2$CH=CHPh), 4.03-4.13 (2H, m, CO$_2$CH$_2$CH$_3$), 4.32 (1H, t, $J$ 7.6, NCH/CO$_2$CH$_2$CH$_3$), 4.46 (2H, q, $J$ 15.6, PhCH$_2$N), 6.03-6.10 (1H, m, CH$_2$CH=CHPh), 7.13-7.34 (5H, m, ArH); $\delta_{\text{C}}$ (100MHz; D$_6$-DMSO, 100 °C): 13.21 (CH$_3$), 16.75 (CH$_3$), 27.43 (3 x CH$_3$), 32.32 (CH$_2$), 50.35 (CH$_2$), 59.56 (CH), 59.74 (CH$_2$), 79.13 (q), 125.89 (CH), 126.16 (CH), 126.54 (CH), 126.72 (CH), 127.19 (CH), 127.31 (2 x CH), 138.12 (q), 154.32 (q) and 169.95 (q); m/z (El) 347 (M$^+$, 1%); Found: 347.2102; C$_{28}$H$_{29}$N$_2$O$_4$ requires M$^+$, 347.2097.
6.36 (1H, d, J 15.6, CH₂CH=CHPh) and 7.19-7.34 (10H, m, ArH); δc (100MHz; D₆-DMSO, 100 °C): 13.18 (CH₃), 27.39 (3 x CH₃), 32.74 (CH₂), 50.51 (CH₂), 59.50 (CH), 59.82 (CH₂), 79.23 (q), 125.29 (2 x CH), 126.06 (CH), 126.16 (CH), 126.38 (CH), 127.17 (2 x CH), 127.32 (2 x CH), 127.75 (2 x CH), 131.39 (CH), 136.70 (q), 138.00 (q), 154.28 (q) and 169.80 (q); m/z (FAB) 410 ([M + 1]⁺, 6%); Found: 410.2328; C₂₉H₃₁N₂O₄ requires (M + 1)⁺, 410.2331.

59. t-Butyl benzyl-1-hydroxyhex-4-en-2-ylcarbamate

Sodium borohydride (4.68 g, 123.72 mmol) was added to a solution of N-Boc ester (173) (4.30 g, 12.37 mmol) in absolute ethanol (70 cm³) and stirred at room temperature for 24 hours. The reaction was quenched by the slow addition of concentrated hydrochloric acid until effervescence had subsided, whereupon water (20 cm³) was added. Solvent was removed under reduced pressure and the resulting residue was dissolved in ethyl acetate (100 cm³), washed with saturated aqueous sodium hydrogen carbonate solution (100 cm³) and saturated aqueous sodium chloride solution (100 cm³). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield N-Boc alcohol (175) as a viscous clear oil (3.78 g, 99%), which was used without further purification. v max (film/cm⁻¹): 3425 (OH) and 1681 (O-CO-N); δH (400MHz; D₆-DMSO, 100 °C): 1.38 (9H, s, (CH₃)₃CO), 1.57 (3H, dd, J 6.0 and 1.2, CH₂CH=CHCH₃), 2.18-2.22 (2H, m, CH₂CH=CHCH₃), 3.41-3.55 (2H, m, CHCH₂OH), 3.76-3.83 (1H, m, CHCH₂OH), 4.24 (1H, t, J 5.2, CHCH₂OH), 4.35 (2H, dd, J 31.9 and 15.9, PhCH₂N), 5.23-5.49 (2H, m, CH₂CH=CHCH₃), 7.18-7.23 (1H, m, ArH) and 7.26-7.31 (4H, m, ArH); δc (100MHz; D₆-DMSO, 100 °C): 16.79 (CH₃), 27.57 (3 x CH₃), 32.23 (CH₂), 48.21 (CH₂), 59.08 (CH), 61.86 (CH₂), 78.13 (q), 125.45 (CH), 125.81 (CH), 126.70 (2 x CH), 127.27 (2 x CH), 127.80 (CH), 139.54 (q) and 154.88 (q); m/z (El) 306 ([M + 1]⁺, 5%).
60. 2-(N-Benzyl-N-methylamino)-hex-4-en-1-ol

\[ \text{Me} \]
\[ \text{Ph} \]
\[ \text{N} \]
\[ \text{OH} \]
\[ \text{Me} \]
\[ (176) \]

\( N\)-Boc Ester (173) (1.02 g, 2.92 mmol) was dissolved in anhydrous THF (20 cm\(^3\)) under an inert atmosphere of nitrogen and cooled to \(-78^\circ\text{C}\) in a dry ice/acetone slush bath and stirred for 15 minutes. A 1M solution of DIBAL in THF (8.8 cm\(^3\), 8.77 mmol) was added dropwise and the reaction was stirred at \(-78^\circ\text{C}\) for 30 minutes before warming to room temperature and stirred overnight. The reaction was quenched by the slow addition of methanol until effervescence had subsided. The mixture was then poured into saturated aqueous potassium sodium tartrate solution (100 cm\(^3\)) and vigorously stirred for 5 minutes before being extracted with ethyl acetate (50 cm\(^3\)) and the resulting aqueous layer further extracted with diethyl ether (2 x 50 cm\(^3\)). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (100 cm\(^3\)), saturated aqueous sodium chloride solution (100 cm\(^3\)), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Flash column chromatography on silica, eluting with 20% ethyl acetate in light petroleum with 0.5% triethylamine yielded the desired \( N\)-Boc alcohol (175) as a yellow oil (0.52 g, 58%) and by-product (176) as a yellow oil.

**Analysis for (176)**

\( \nu_{\text{max}} \) (film/cm\(^{-1}\)): 3441 (O-H) and 3034 (C=C); \( \delta_{\text{H}} \) (250MHz; CDCl\(_3\)): 1.66 (3H, dd, \( J \) 6.1 and 1.0, CH\(_2\)CH=CHCH\(_3\)), 1.78-1.94 (1H, m, CH(H)CH=CHCH\(_3\)), 2.19 (3H, s, NCH\(_3\)), 2.32-2.42 (1H, m, CH(H)CH=CHCH\(_3\)), 2.77-2.91 (1H, m, NCHCH\(_2\)OH), 3.33 (1H, t, \( J \) 10.4, NCHCH(H)OH), 3.49-3.57 (2H, m, NCHCH(H)OH and PhCH(H)N), 3.74 (1H, d, \( J \) 12.9, PhCH(H)N), 5.28-5.60 (2H, m, CH\(_2\)CH=CHCH\(_3\)) and 7.22-7.38 (5H, m, ArH); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)): 17.99 (CH\(_3\)), 28.24 (CH\(_2\)), 35.78 (CH\(_3\)), 58.14 (CH\(_2\)), 60.81 (CH\(_2\)), 63.84 (CH), 127.18 (CH), 127.45 (CH), 127.85 (CH) 128.41 (2 x CH), 128.84 (2 x CH) and 139.04 (q); \( m/z \) (EI) 219 (M\(^+\), 4%).
**61. t-Butyl benzyl-1-formylpent-3-enylcarbamate**

![Chemical Structure](attachment:image.png)

**Method 1**

Dess-Martin periodinane (1.09 g, 2.56 mmol) in anhydrous DCM (10 cm³) was cooled to 0 °C and stirred for 15 minutes before a solution of N-Boc alcohol (175) (0.52 g, 1.71 mmol) in anhydrous DCM (10 cm³) was added dropwise. The reaction was warmed to room temperature and stirred for 16 hours before diluting the mixture with diethyl ether (100 cm³). The mixture was poured into a 50:50 saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium thiosulfate solution (100 cm³) and stirred vigorously for 5 minutes. The phases were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (100 cm³), water (100 cm³), saturated aqueous sodium chloride solution (100 cm³), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 10% ethyl acetate in light petroleum yielded N-Boc aldehyde (174) as a yellow oil (0.50 g, 96%).

\[ \text{v}_{\text{max}} \text{(film/cm}^{-1}) : 2813, 2724 \text{ (CHO), 1737 (C=O), 3028 (C=C) and 1693 (O-CO-N); } \delta_{\text{H}} \text{(400MHz; D}_6\text{-DMSO, 120 °C): 1.40 (9H, s, } (\text{CH}_3)_3\text{CO), 1.59 (3H, dd, } J = 5.9 \text{ and 1.1, } \text{CH}_2\text{CH}=\text{CHCH}_3\text{), 2.35-2.42 (1H, m, CH(H)CH=CHCH}_3\text{), 2.55-2.63 (1H, m, CH(H)CH=CHCH}_3\text{), 3.82 (1H, dd, } J = 8.1 \text{ and 5.8, NCHCH}=\text{O), 4.35 (1H, d, } J = 15.4, \text{PhCH(H)N), 4.58 (1H, d, } J = 15.4, \text{PhCH(H)N), 5.28-5.47 (2H, m, CH}_2\text{CH}=\text{CHCH}_3\text{), 7.26-7.34 (5H, m, ArH) and 9.46 (1H, s, NCHCH}=\text{O); } \delta_{\text{C}} \text{(100MHz; D}_6\text{-DMSO, 120 °C): 16.51 (CH}_3\text{), 27.27 (3 x CH}_3\text{), 30.10 (CH}_2\text{), 51.07 (CH}_2\text{), 65.61 (CH), 79.73 (q), 125.50 (CH), 126.39 (CH), 126.50 (CH), 127.10 (2 x CH), 127.58 (2 x CH), 137.74 (q), 154.17 (q) and 198.00 (CH); } m/z \text{(FAB) 304 ((M + 1))}, 2\%; \text{Found: 304.1918; } \text{C}_{18}\text{H}_{23}\text{NO}_3 \text{requires (M + 1))}, 304.1913.\]
Method 2

N-Boc Ester (173) (4.05 g, 11.65 mmol) was dissolved in anhydrous DCM (50 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. A 1M solution of DIBAL in DCM (23.3 cm³, 23.30 mmol) was added dropwise at a rate that kept the internal temperature below −65 °C. The reaction was stirred at −78 °C for a further 2 hours before slowly quenching with methanol (4 cm³), again at a rate whilst maintaining an internal temperature below −65 °C. The resulting white emulsion was poured into saturated aqueous potassium sodium tartrate solution (100 cm³) and vigorously stirred for 5 minutes before being extracted with DCM (50 cm³) and the resulting aqueous layer further extracted with DCM (2 x 50 cm³). The combined organic phase was washed with water (100 cm³), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield N-Boc aldehyde (174) (3.45 g, 98%) as a yellow oil, which was used without further purification. Spectral analysis consistent with Experimental Entry 61.

62. t-Butyl benzyl-1-formyl-4-phenylbut-3-enylcarbamate

\[
\text{Ph} \quad \text{N} \quad \text{O} \\
\text{Ph} \quad \text{Boc}
\]

(187)

N-Boc Ester (186) (8.07 g, 19.69 mmol) was dissolved in anhydrous DCM (100 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. A 1M solution of DIBAL in DCM (39.4 cm³, 39.40 mmol) was added dropwise at a rate that kept the internal temperature below −65 °C. The reaction was stirred at −78 °C for a further 2 hours before slowly quenching with methanol (8 cm³), again at a rate whilst maintaining an internal temperature below −65 °C. The resulting white emulsion was poured into saturated aqueous potassium sodium tartrate solution (200 cm³) and vigorously stirred for 5 minutes before being extracted with DCM (100 cm³) and the resulting aqueous layer further extracted with DCM (2 x 100 cm³). The combined organic phase was washed with water (200 cm³), dried over
anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield \( \text{N-Boc aldehyde (187)} \) (7.08 g, 98%) as a yellow oil, which was used without further purification. \( \nu_{\text{max}} \) (film/cm\( ^{-1} \)): 2813, 2720 (CHO), 1734 (C=O), 3025 (C=C) and 1684 (O-CO-N); \( \delta_H \) (400MHz; D\textsubscript{6}-DMSO, 100 °C): 1.42 (9H, s, (CH\textsubscript{3})\textsubscript{3}CO), 2.60-2.67 (1H, m, CH(H)CH=CHPh), 2.80-2.86 (1H, m, CH(H)CH=CHPh), 3.98-4.02 (1H, m, NCHCH=O), 4.40 (1H, d, J 15.6, PhCH(H)N), 4.63 (1H, d, J 15.2, PhCH(H)N), 6.11-6.19 (1H, m, CH\textsubscript{2}CH=CHPh), 6.40 (1H, d, J 15.6, CH\textsubscript{2}CH=CHPh), 7.15-7.39 (10H, m, ArH) and 9.52 (1H, s, NCHCH=O); \( \delta_C \) (100MHz; D\textsubscript{6}-DMSO, 100 °C): 27.34 (3 x CH\textsubscript{3}), 30.73 (CH\textsubscript{2}), 51.28 (CH\textsubscript{2}), 65.62 (CH), 79.85 (q), 125.32 (2 x CH), 125.90 (CH), 126.38 (CH), 126.55 (CH), 127.21 (2 x CH), 127.70 (2 x CH), 127.74 (2 x CH), 131.52 (CH), 136.70 (q), 137.80 (q), 154.27 (q) and 197.94 (CH); \( m/z \) (FAB) 366 ((M + 1)\textsuperscript{+}, 2%); Found: 366.2062; C\textsubscript{23}H\textsubscript{27}N\textsubscript{3}O\textsubscript{3} requires (M + 1)\textsuperscript{+}, 366.2069.

63. \( \text{t-Butyl benzyl-octa-2,6-dien-4-ylcarbamate} \)

\[ \text{Ph} \quad \text{N} \quad \text{Me} \]
\[ \text{Me} \]
\[ \text{Boc} \]
\[ (177) \]

Ethyltriphenylphosphonium bromide (4.11 g, 18.95 mmol) in anhydrous THF (30 cm\textsuperscript{3}) was treated with a 2.5M solution of \( n \)-butyllithium in hexanes (7.5 cm\textsuperscript{3}, 16.25 mmol) at 0 °C under an inert atmosphere of nitrogen. The mixture was warmed to room temperature and stirred for 30 minutes before a solution of \( \text{N-Boc aldehyde (174)} \) (4.11 g, 13.54 mmol) in anhydrous THF (30 cm\textsuperscript{3}) was added dropwise. The reaction was stirred for 4 hours at room temperature, quenched with water (50 cm\textsuperscript{3}) and extracted with diethyl ether (100 cm\textsuperscript{3}). The organic phase was washed with saturated aqueous sodium chloride solution (100 cm\textsuperscript{3}), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded an inseparable mixture of geometric isomers of \( N \)-Boc diene (177) as a yellow oil (2.87 g, 67%). \( \nu_{\text{max}} \) (film/cm\( ^{-1} \)): 3024 (C=C) and 1690 (O-CO-N); \( \delta_H \) (400MHz; D\textsubscript{6}-DMSO, 100 °C, both isomers): 1.38 (9H, s, (CH\textsubscript{3})\textsubscript{3}CO), 1.54-1.58 (6H, m, CH\textsubscript{2}CH=CHCH\textsubscript{3} and NCHCH=CHCH\textsubscript{3}), 2.11-2.34
(2H, m, CH₂CH=CHCH₃), 4.29-4.35 (2H, m, PhCH₂N), 4.64 (1H, q, J 6.8, NCHCH=CHCH₃), 5.23-5.51 (4H, m, CH₂CH=CHCH₃ and NCHCH=CHCH₃) and 7.17-7.37 (5H, m, ArH); δc (100MHz; D₆-DMSO, 100 °C, both isomers): 13.24 (CH₃), 17.79 (CH₃), 28.57 (3 x CH₃), 37.23 (CH₂), 48.38 (CH₂), 54.01 (CH), 79.30 (q), 126.83 (CH), 127.00 (CH), 127.59 (2 x CH), 128.10 (CH), 128.26 (2 x CH), 130.31 (2 x CH), 140.40 (q) and 155.40 (q); m/z (FAB) 316 ((M + 1)⁺, 12%); Found: 316.2279; C₂₀H₂₉N⁰₂ requires (M + 1)⁺, 316.2277.

64. t-Butyl benzyl-1-phenylhepta-1,5-dien-3-ylcarbamate

Benzyltriphenylphosphonium bromide (9.55 g, 22.04 mmol) in anhydrous THF (30 cm³) was treated with a 2.5M solution of n-butyllithium in hexanes (7.8 cm³, 19.45 mmol) at 0 °C under an inert atmosphere of nitrogen. The mixture was warmed to room temperature and stirred for 30 minutes before a solution of N-Boc aldehyde (174) (3.93 g, 12.97 mmol) in anhydrous THF (30 cm³) was added dropwise. The reaction was stirred for 4 hours at room temperature, quenched with water (50 cm³) and extracted with diethyl ether (100 cm³). The organic phase was washed with saturated aqueous sodium chloride solution (100 cm³), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded an inseparable 2:1 mixture of geometric isomers in the favour of the trans isomer of N-Boc diene (178) as a yellow oil (4.02 g, 82%). v max (film/cm⁻¹): 3025 (C=C) and 1693 (O-CO-N); δH (400MHz; D₆-DMSO, 100 °C, both isomers): 1.38 (9H, s, (CH₃)₃CO cis isomer), 1.42 (9H, s, (CH₃)₃CO trans isomer), 1.56 (3H, d, J 7.6, CH₂CH=CHCH₃ cis isomer), 1.60 (3H, d, J 6.0, CH₂CH=CHCH₃ trans isomer), 2.13-2.27 (1H, m, CH(H)CH=CHCH₃ cis isomer), 2.36-2.50 (3H, m, CH(H)CH=CHCH₃ cis isomer and CH₂CH=CHCH₃ trans isomer), 4.41-4.50 (5H, m, NCHCH=CHPh trans isomer and 2 x PhCH₂N), 4.87 (1H, q, J 7.2, NCHCH=CHPh cis isomer), 5.17-5.54 (4H, m, 2 x CH₂CH=CHCH₃), 5.71-5.82 (1H, m, Experimental - 228 -
NCHCH=CHPh *cis* isomer), 6.19-6.25 (1H, m, NCHCH=CHPh *trans* isomer), 6.43 (1H, d, J 16.0, NCHCH=CHPh *trans* isomer), 6.50 (1H, d, J 11.6, NCHCH=CHPh *cis* isomer) and 7.21-7.36 (20H, m, 2 x ArH); δC (100MHz; D₆-DMSO, 100 °C, both isomers): 17.80 & 17.84 (CH₃), 28.53 & 28.62 (3 x CH₃), 36.24 & 37.54 (CH₂), 48.94 & 49.14 (CH₂), 54.69 & 59.38 (CH), 79.50 & 79.54 (q), 126.59-128.87 (Ar CH), 126.95 & 127.19 (CH), 127.50 & 127.64 (CH), 130.04 & 131.02 (CH), 131.34 & 131.48 (CH), 137.01 & 137.40 (q), 140.25 & 140.29 (q) and 155.25 & 155.54 (q); m/z (FAB) 378 ((M + 1)+, 6%); Found: 378.2438; C₂₅H₃₁N0₂ requires (M + 1)+, 378.2433.

65. *t*-Butyl benzyl-1-phenylhepta-1,5-dien-4-ylcarbamate

![Structure of 65](image)

Ethyltriphenylphosphonium bromide (4.91 g, 13.21 mmol) in anhydrous THF (30 cm³) was treated with a 2.5M solution of *n*-butyllithium in hexanes (4.5 cm³, 11.33 mmol) at 0 °C under an inert atmosphere of nitrogen. The mixture was warmed to room temperature and stirred for 30 minutes before a solution of N-Boc aldehyde (187) (3.45 g, 9.44 mmol) in anhydrous THF (30 cm³) was added dropwise. The reaction was stirred for 4 hours at room temperature, quenched with water (50 cm³) and extracted with diethyl ether (100 cm³). The organic phase was washed with saturated aqueous sodium chloride solution (100 cm³), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded an inseparable mixture of geometric isomers of N-Boc diene (188) as a yellow oil (2.59 g, 73%). νₓₓₓ (film/cm⁻¹): 3025 (C=C) and 1682 (O-CO-N); δₓₓ (400MHz; D₆-DMSO, 100 °C, both isomers): 1.38 (9H, s, (CH₃)₂CO), 1.59 (3H, d, J 5.6, NCHCH=CHCH₃), 2.35-2.42 (1H, m, CH(H)CH=CHPh), 2.53-2.60 (1H, m, CH(H)CH=CHPh), 4.39 (2H, s, PhCH₂N), 4.80 (1H, q, J 7.6, NCHCH=CHCH₃), 5.51-5.60 (2H, m, NCHCH=CHCH₃), 6.02-6.11 (1H, m, CH₂CH=CHPh), 6.37 (1H, d, J 15.6, CH₂CH=CHPh) and 7.18-7.30 (10H, m, ArH); δC (100MHz; D₆-DMSO, 100 °C, both isomers): 12.21 (CH₃), 27.48 (3 x CH₃), 36.52 (CH₂),...
47.39 (CH₂), 52.91 (CH), 78.37 (q), 125.19 (2 × CH), 125.81 (CH), 125.96 (CH), 126.25 (CH), 126.39 (CH), 126.54 (2 × CH), 127.24 (2 × CH), 127.71 (2 × CH), 129.05 (CH), 131.04 (CH), 136.88 (q), 139.25 (q) and 154.34 (q); m/z (El) 377 (M⁺, 3%); Found: 377.2355; C₂₅H₃₁N₂O₂ requires M⁺, 377.2355.

66. t-Butyl benzyl-1,6-diphenylhexa-1,5-dien-3-ylcarbamate

Benzyltriphenylphosphonium bromide (6.02 g, 13.90 mmol) in anhydrous THF (30 cm³) was treated with a 2.5M solution of n-butyllithium in hexanes (4.8 cm³, 11.91 mmol) at 0 °C under an inert atmosphere of nitrogen. The mixture was warmed to room temperature and stirred for 30 minutes before a solution of N-Boc aldehyde (187) (3.63 g, 9.93 mmol) in anhydrous THF (30 cm³) was added dropwise. The reaction was stirred for 4 hours at room temperature, quenched with water (50 cm³) and extracted with diethyl ether (100 cm³). The organic phase was washed with saturated aqueous sodium chloride solution (100 cm³), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded an inseparable 2:1 mixture of geometric isomers in the favour of the trans isomer of N-Boc diene (189) as a yellow oil (3.24 g, 74%). \( \nu_{\text{max}} \) (film/cm⁻¹): 3025 (C=C) and 1681 (O-CO-N); H (400MHz; D₆-DMSO, 100 °C, both isomers): 1.35 (9H, s, (CH₃)₂CO cis isomer), 1.41 (9H, s, (CH₃)₂CO trans isomer), 2.40-2.47 (1H, m, CH(H)CH=CHPh cis isomer), 2.58-2.75 (3H, m, CH(H)CH=CHPh cis isomer and CH₂CH=CHPh trans isomer), 4.42 (2H, q, \( J = 15.6 \) Hz, PhCH₂N cis isomer), 4.47 (2H, s, PhCH₂N trans isomer), 4.66 (1H, q, \( J = 7.2 \) Hz, NCHCH=CHPh trans isomer), 5.02 (1H, q, \( J = 7.6 \) Hz, NCHCH=CHPh cis isomer), 5.84 (1H, t, \( J = 10.4 \) Hz, NCHCH=CHPh cis isomer), 5.97-6.04 (1H, m, CH₂CH=CHPh cis isomer), 6.09-6.17 (1H, m, CH₂CH=CHPh trans isomer), 6.27-6.33 (1H, m, NCHCH=CHPh trans isomer), 6.34 (1H, d, \( J = 14.8 \) Hz, CH₂CH=CHPh cis isomer), 6.43 (1H, d, \( J = 15.6 \) Hz, CH₂CH=CHPh trans isomer), 6.50 (1H, d, \( J = 16.0 \) Hz, NCHCH=CHPh trans isomer), 6.54
(1H, d, J 11.6, NCHCH=CHPh cis isomer) and 7.17-7.36 (30H, m, 2 x ArH); δc (100MHz; D6-DMSO, 100 °C, both isomers): 27.42 & 27.52 (3 x CH3), 35.56 & 36.87 (CH2), 47.09 & 47.96 (CH2), 53.55 & 58.25 (CH), 78.57 & 78.59 (q), 125.22-127.80 (Ar CH), 125.87 & 125.92 (CH), 126.48 & 126.52 (CH), 128.80 (CH), 129.74 (CH), 130.47 & 130.63 (CH), 131.16 & 131.18 (CH), 135.86 & 136.27 (q), 136.76 & 136.86 (q), 139.12 & 139.15 (q) and 154.22 & 154.48 (q); m/z (FAB) 440 ((M + 1)\(^+\), <1%); Found: 440.2597; C30H33N02 requires (M + 1)\(^+\), 440.2590.

67. N-Benzylota-2,6-dien-4-amine

\[
\begin{align*}
\text{Ph} & \quad \text{CH} \quad \text{CH} \quad \text{CH} \\
\text{CH} & \quad \text{CH} \quad \text{CH} \quad \text{CH} \\
\text{Me} & \quad \text{Me} \\
\hline
\end{align*}
\]

N-Boc diene (177) (1.07 g, 3.40 mmol) in DCM (50 cm\(^3\)) was stirred with TFA (1.3 cm\(^3\), 17.01 mmol) at room temperature for 24 hours. The reaction was quenched by the slow addition of saturated aqueous sodium hydrogen carbonate solution until effervescence had subsided. The mixture was extracted with DCM (50 cm\(^3\)) and the resulting aqueous layer further extracted with DCM (2 x 50 cm\(^3\)). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield an inseparable mixture of geometric isomers of diene (179) as a yellow oil (0.72 g, 98%), which was used without further purification. \(v_{\text{max}}\) (film/cm\(^{-1}\)): 1494 (N-H) and 3022 (C=C); δ\(_{H}\) (400MHz; CDCl\(_3\)): 1.58 (3H, dd, J 6.8 and 2.0, NCHCH=CHCH\(_3\)), 1.65 (3H, dq, J 6.0 and 1.2, CH\(_2\)CH=CHCH\(_3\)), 2.07-2.20 (2H, m, CH\(_2\)CH=CHCH\(_3\)), 3.41-3.47 (1H, m, NCHCH=CHCH\(_3\)), 3.63 (1H, d, J 13.6, PhCH(H)N), 3.82 (1H, d, J 13.2, PhCH(H)N), 5.23-5.40 (2H, m, CH\(_2\)CH=CHCH\(_3\) and NCHCH=CHCH\(_3\)), 5.46-5.67 (2H, m, CH\(_2\)CH=CHCH\(_3\) and NCHCH=CHCH\(_3\)) and 7.17-7.37 (5H, m, ArH); δ\(_{c}\) (100MHz; CDCl\(_3\)): 13.43 (CH\(_3\)), 18.06 (CH\(_3\)), 39.12 (CH\(_2\)), 51.29 (CH\(_2\)), 53.43 (CH), 125.89 (CH), 126.77 (CH), 127.59 (CH), 127.90 (CH), 128.17 (2 x CH), 128.33 (2 x CH), 133.61 (CH) and 140.66 (q); m/z (EI) 216 ((M + 1)\(^+\), 78%); Found: 216.1751; C\(_{15}\)H\(_{21}\)N requires (M + 1)\(^+\), 216.1752.

Experimental - 231 -
N-Benzyl-1-phenylhepta-1,5-dien-3-amine (180)

N-Boc diene (178) (3.89 g, 10.30 mmol) was stirred with formic acid (38.9 cm³, 1.03 mol) at room temperature for 24 hours. The reaction was quenched by the slow addition of saturated aqueous sodium hydrogen carbonate solution until effervescence had subsided. The mixture was extracted with DCM (100 cm³) and the resulting aqueous layer further extracted with DCM (2 x 50 cm³). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Flash column chromatography on silica, eluting with 20% ethyl acetate in light petroleum yielded an inseparable 11:9 mixture of geometric isomers in the favour of the trans isomer of diene (180) as a yellow oil (2.53 g, 88%). ν max (film/cm⁻¹): 1491 (N-H) and 3023 (C=C); δH (400MHz; CDCl₃, both isomers): 1.62-1.68 (6H, m, 2 x CH₂CH=CHCH₃), 2.20-2.33 (4H, m, 2 x CH₂CH=CHCH₃), 3.23 (1H, q, J 7.2, NCHCH=CHPh trans isomer), 3.50 (1H, d, J 13.2, PhCH(H)N cis isomer), 3.67-3.72 (1H, m, NCHCH=CHPh cis isomer), 3.68 (1H, d, J 13.6, PhCH(H)N trans isomer), 3.77 (1H, d, J 12.8, PhCH(H)N cis isomer), 3.87 (1H, d, J 13.6, PhCH(H)N trans isomer), 5.35-5.44 (2H, m, 2 x CH₂CH=CHCH₃), 5.50-5.62 (3H, m, 2 x CH₂CH=CHCH₃ and NCHCH=CHPh cis isomer), 6.09 (1H, dd, J 16.0 and 8.0, NCHCH=CHPh trans isomer), 6.49 (1H, d, J 16.0, NCHCH=CHPh trans isomer), 6.62 (1H, d, J 11.6, NCHCH=CHPh cis isomer) and 7.10-7.41 (20H, m, 2 x ArH); δC (100MHz; CDCl₃, both isomers): 18.09 & 18.11 (CH₃), 38.97 & 39.49 (CH₂), 51.38 & 51.41 (CH₂), 53.82 & 59.95 (CH), 126.35-128.43 (Ar CH), 126.74 & 126.78 (CH), 127.34 & 127.37 (CH), 128.59 & 128.72 (CH), 130.86 & 131.14 (CH), 132.93 (CH), 135.91 (CH), 137.16 & 137.35 (q) and 140.50 & 140.63 (q); m/z (FAB) 278 ((M + 1)+, 47%); Found: 278.1906; C₂₀H₂₃N requires (M + 1)+, 278.1909.
69. *N*-Benzyl-1-phenylhepta-1,5-dien-4-amine

\[
\text{Ph} - \text{CH} = \text{CH} - \text{CH} = \text{N} - \text{Ph}
\]

(*181*)

*N*-Boc diene (*188*) (2.17 g, 5.75 mmol) was stirred with formic acid (21.7 cm\(^3\), 575.23 mmol) at room temperature for 24 hours. The reaction was quenched by the slow addition of saturated aqueous sodium hydrogen carbonate solution until effervescence had subsided. The mixture was extracted with DCM (100 cm\(^3\)) and the resulting aqueous layer further extracted with DCM (2 x 50 cm\(^3\)). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Flash column chromatography on silica, eluting with 20% ethyl acetate in light petroleum yielded an inseparable 4:1 mixture of geometric isomers in the favour of the *cis* isomer of diene (*181*) as a yellow oil (1.59 g, 99%). 

\[\text{v}_{\text{max}}(\text{film/cm}^{-1}): 1490 (\text{N}-\text{H}) \text{ and } 3022 (\text{C}=\text{C}); \delta_{\text{H}} (400\text{MHz}; \text{CDCl}_3, \text{both isomers}): 1.60 (3\text{H, dd, } J = 6.8 \text{ and } 1.6, \text{NCHCH=CHCH}_3 \text{ cis isomer}), 1.73 (3\text{H, dd, } J = 6.4 \text{ and } 1.6, \text{NCHCH=CHCH}_3 \text{ trans isomer}), 2.30-2.44 (4\text{H, m, } 2 \times \text{CH}_2\text{CH=CHPh}), 3.14 (1\text{H, q, } J = 6.8, \text{NCH/CH=CHCH}_3 \text{ trans isomer}), 3.54-3.60 (1\text{H, m, NCHCH=CHCH}_3 \text{ cis isomer}), 3.65 (1\text{H, d, } J = 13.6, \text{PhCH(H)N trans isomer}), 3.66 (1\text{H, d, } J = 13.6, \text{PhCH(H)N cis isomer}), 3.84 (1\text{H, d, } J = 13.2, \text{PhCH(H)N cis isomer}), 3.85 (1\text{H, d, } J = 13.2, \text{PhCH(H)N cis isomer}), 5.28-5.38 (2\text{H, m, } 2 \times \text{NCHCH=CHCH}_3), 5.57-5.70 (2\text{H, m, } 2 \times \text{NCHCH=CHCH}_3), 6.10-6.20 (2\text{H, m, } 2 \times \text{CH}_2\text{CH=CHPh}), 6.43 (1\text{H, d, } J = 16.0, \text{CH}_2\text{CH=CHPh trans isomer}), 6.44 (1\text{H, d, } J = 16.0, \text{CH}_2\text{CH=CHPh cis isomer}) \text{ and } 7.18-7.34 (20\text{H, m, } 2 \times \text{ArH}); \delta_{\text{C}} (100\text{MHz}; \text{CDCl}_3, \text{both isomers}): 13.51 \& 17.84 (\text{CH}), 39.63 \& 39.84 (\text{CH}_2), 51.12 \& 51.27 (\text{CH}_2), 53.43 \& 59.61 (\text{CH}), 126.04 (2 \times \text{CH}), 126.28 (\text{CH}), 126.78 \& 126.83 (\text{CH}), 127.00 \& 127.19 (\text{CH}), 127.06 \& 127.32 (\text{CH}), 128.16 \& 128.20 (2 \times \text{CH}), 128.36 (2 \times \text{CH}), 128.49 (2 \times \text{CH}), 132.28 (\text{CH}), 133.36 \& 133.63 (\text{CH}), 137.51 (q) \text{ and } 140.57 (q); m/z (\text{FAB}) 278 ((M + 1)^+, 74\%); \text{Found: } 278.1905; \text{C}_{20}\text{H}_{23}\text{N} \text{ requires } (\text{M} + 1)^+, 278.1909.
N-Benzyl-1,6-diphenylhexa-1,5-dien-3-amine

N-Boc diene (189) (2.71 g, 6.17 mmol) was stirred with formic acid (23.3 cm$^3$, 616.94 mmol) at room temperature for 24 hours. The reaction was quenched by the slow addition of saturated aqueous sodium hydrogen carbonate solution until effervescence had subsided. The mixture was extracted with DCM (100 cm$^3$) and the resulting aqueous layer further extracted with DCM (2 x 50 cm$^3$). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Flash column chromatography on silica, eluting with 20% ethyl acetate in light petroleum yielded an inseparable 2.5:1 mixture of geometric isomers in the favour of the trans isomer of diene (182) as a yellow oil (1.67 g, 80%).

$\text{v}_{\text{max}}$ (film/cm$^{-1}$): 1492 (N-H) and 3023 (C=C); $\delta_{\text{H}}$ (400MHz; CDCl$_3$, both isomers): 2.43-2.56 (4H, m, 2 x CH$_2$CH=CHPh), 3.34-3.40 (1H, m, NCHCH=CHPh trans isomer), 3.55 (1H, d, J 13.2, PhCH(H)N cis isomer), 3.72 (1H, d, J 13.2, PhCH(H)N trans isomer), 3.80-3.86 (1H, m, NCHCH=CHPh cis isomer), 3.80 (1H, d, J 13.2, PhCH(H)N cis isomer), 3.89 (1H, d, J 13.6, PhCH(H)N trans isomer), 5.60 (1H, dd, J 12.0 and 10.0, NCHCH=CHPh cis isomer), 6.11-6.22 (3H, m, NCHCH=CHPh trans isomer and 2 x CH$_2$CH=CHPh), 6.44-6.50 (2H, m, 2 x CH$_2$CH=CHPh), 6.54 (1H, d, J 16.0, NCHCH=CHPh trans isomer), 6.66 (1H, d, J 12.0, NCHCH=CHPh cis isomer) and 7.09-7.42 (30H, m, 2 x ArH); $\delta_{\text{C}}$ (100MHz; CDCl$_3$, both isomers): 39.47 & 39.91 (CH$_2$), 51.31 (CH$_2$), 53.71 & 59.83 (CH), 126.10-128.66 (Ar CH), 126.56 & 126.64 (CH), 126.84 & 126.88 (CH), 127.15 & 127.18 (CH), 131.21 & 131.44 (CH), 132.53 & 132.64 (CH), 132.74 (CH), 135.52 (CH), 136.99 (q), 137.21 & 137.34 (q) and 140.33 & 140.46 (q); m/z (FAB) 340 ((M + 1)$^+$, 26%); Found: 340.2062; C$_{25}$H$_{25}$N requires (M + 1)$^+$, 340.2065.
5.3.2.2. Preparation of Non-Racemic 1,6-Disubstituted-3-Amino-1,5-Diene Substrates

71. Ethyl-2-((1S)-1-phenylethylimino)-acetate

\[
\text{Ph} \quad \text{N} \quad \text{CO}_2 \text{Et}
\]

(196)

A 50% solution of ethyl glyoxalate in toluene (1.4 cm³, 6.98 mmol) was added to a stirred solution of (S)-α-methylbenzylamine (1.0 cm³, 7.76 mmol) in DCM (1 cm³) containing activated 4Å molecular sieves at 0 °C and stirred for 24 hours at room temperature. Anhydrous magnesium sulfate (0.5 g) was added and the reaction stirred for a further 15 minutes. Filtration and removal of solvent under reduced pressure yielded imine ester (196) as a yellow oil (1.35 g, 94%), which was used without further purification. \([\alpha]_D^{25} = -47.3 (c 1.04, \text{DCM})\); \(\nu_{\text{max}}\) (film/cm⁻¹): 1748 (O=C−O) and 1720 (C=N); \(\delta_H\) (400MHz; D₆-DMSO): 1.24 (3H, t, \(J = 7.2\), CO₂CH₂CH₃), 1.46 (3H, d, \(J = 6.8\), PhCH(CH₃)N), 4.22 (2H, q, \(J = 7.2\), CO₂CH₂CH₃), 4.64 (1H, q, \(J = 6.4\), PhCHH(CH₃)N), 7.32-7.37 (5H, m, ArH) and 7.88 (1H, d, \(J = 0.8\), N=CHCO₂CH₂CH₃); \(\delta_C\) (100MHz; D₆-DMSO): 14.85 (CH₃), 24.49 (CH₃), 61.91 (CH₂), 69.12 (CH), 127.61 (2 x CH), 128.09 (CH), 129.35 (2 x CH), 144.09 (q), 153.62 (CH) and 173.38 (q); \(m/z\) (FAB) 206 ((M + 1)⁺, 13%); Found: 206.1185; C₁₂H₁₅NO₂ requires (M + 1)⁺, 206.1181.

72. Ethyl-2-((1S)-1-phenylethlamino)-acetate

A solution of (S)-α-methylbenzylamine (6.0 cm³, 46.55 mmol), acetic acid (6.7 cm³, 116.35 mmol) and sodium triacetoxyborohydride (24.66 g, 116.35 mmol) in DCE (240 cm³) was treated with a 50% solution of ethyl glyoxalate in toluene (13.8 cm³, 69.92
mmol) at room temperature. The resulting mixture was stirred for 18 hours before partitioning the mixture between DCM (200 cm³) and saturated aqueous sodium hydrogen carbonate solution (500 cm³). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 10% ethyl acetate in light petroleum yielded the amino ester (199) as a yellow oil (8.43 g, 87%). \([\alpha]_{D}^{25} \approx -72.2 \text{ (c 1.02, DCM)}; \nu_{\text{max}} (\text{film/cm}^{-1}) : 1735 (\text{O=C-O}) \text{ and } 1194 (\text{N-H}); \delta_{\text{H}} (400\text{MHz; CDCl}_3) : 1.24 (3\text{H, t, } J 7.2, \text{CO}_2\text{CH}_2\text{CH}_3), 1.39 (3\text{H, d, } J 6.4, \text{PhCH(CH}_3\text{)}\text{N}), 3.26 (2\text{H, q, } J 17.6, \text{NCH}_2\text{CO}_2\text{CH}_2\text{CH}_3), 3.79 (1\text{H, q, } J 6.8, \text{PhCH(_CH}_3\text{)}\text{N}), 4.16 (2\text{H, q, } J 7.2, \text{CO}_2\text{CH}_2\text{CH}_3) \text{ and } 7.22-7.35 (5\text{H, m, ArH}); \delta_{\text{C}} (100\text{MHz; CDCl}_3) : 14.21 (\text{CH}_3), 24.23 (\text{CH}_3), 48.88 (\text{CH}_2), 57.75 (\text{CH}), 60.72 (\text{CH}_2), 126.77 (2 \times \text{CH}), 127.18 (\text{CH}), 128.53 (2 \times \text{CH}), 144.62 (\text{q}) \text{ and } 172.61 (\text{q}); \text{m/z (FAB) } 208 ([\text{M + 1}^+]\text{, 100%}); \text{Found: } 208.1334; \text{C}_{12}\text{H}_{17}\text{NO}_2 \text{ requires (M + 1)}^+. \text{208.1338.}

73. \text{t-Butyl-(ethoxycarbonyl)-methyl-(1S)-1-phenylethylcarbamate}

![Structural formula](image)

Triethylamine (22.4 cm³, 161.02 mmol), DMAP (2.46 g, 20.13 mmol) and di-tert-butyldicarbonate (21.96 g, 100.64 mmol) were successively added to a solution of ester (199) (8.34 g, 40.25 mmol) in anhydrous THF (80 cm³) and stirred at reflux for 48 hours. Volatiles were removed under reduced pressure and the resulting residue was dissolved in ethyl acetate (150 cm³), washed with saturated aqueous ammonium chloride solution (2 x 150 cm³), saturated aqueous sodium hydrogen carbonate solution (150 cm³) and saturated aqueous sodium chloride solution (150 cm³). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded \(N\)-Boc ester (201) as a pale yellow oil (9.33 g, 75%). \([\alpha]_{D}^{25} \approx -51.7 \text{ (c 1.27, DCM)}; \nu_{\text{max}} (\text{film/cm}^{-1}) : 1755 (\text{O=C-O}) \text{ and } 1698 (\text{O-CO-N}); \delta_{\text{H}} (400\text{MHz; D}_6\text{- DMSO, 100 °C}): 1.18 (3\text{H, t, } J 6.8, \text{CO}_2\text{CH}_2\text{CH}_3), 1.40 (9\text{H, s, (CH}_3\text{)}_3\text{CO}), 1.50 (3\text{H, d, } J...
6.8, PhCH(CH2)N), 3.74 (2H, q, \( J = 17.6 \), NCH2CO2CH2CH3), 4.04-4.10 (1H, m, PhCH(CH2)N), 5.29 (2H, q, \( J = 7.2 \), CO2CH2CH3) and 7.22-7.36 (5H, m, ArH); \( \delta_c \) (100MHz; D6-DMSO, 100 °C): 13.27 (CH3), 16.66 (CH3), 27.41 (3 x CH3), 44.92 (CH2), 53.31 (CH), 59.54 (CH2), 78.93 (q), 126.21 (2 x CH), 126.34 (CH), 127.55 (2 x CH), 141.16 (q), 154.02 (q) and 169.05 (q); \( m/z \) (FAB) 308 ((M + 1)+, 12%); Found: 308.1866; C17H25NO4 requires (M + 1)+, 308.1862.

74. \( t \)-Butyl-1-(ethoxycarbonyl)-pent-3-enyl-(1S)-1-phenylethylcarbamate\(^{136}\)

![Image of molecule](image)

A 2.5M solution of \( n \)-butyllithium in hexanes (11.4 cm\(^3\), 28.55 mmol) was added dropwise to a solution of diisopropylamine (4.3 cm\(^3\), 30.05 mmol) in anhydrous THF (50 cm\(^3\)) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 5 minutes at 0 °C then cooled to -78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. DMPU (3.6 cm\(^3\), 30.05 mmol) was added dropwise and the reaction stirred for 10 minutes before \( N \)-Boc ester (201) (9.24 g, 30.05 mmol) in anhydrous THF (70 cm\(^3\)) was added dropwise. The reaction was stirred for 30 minutes at -78 °C before crotyl bromide (3.1 cm\(^3\), 30.05 mmol) was added and the reaction stirred for a further 1 hour at the same temperature. The reaction was stirred at room temperature for a further 3 hours before being quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (100 cm\(^3\)) and the resulting aqueous layer further extracted with diethyl ether (2 x 100 cm\(^3\)). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in light petroleum yielded an inseparable 2.5:1 mixture of diastereoisomers of \( N \)-Boc ester (203) as a yellow oil (7.75 g, 71%). \( \nu_{\text{max}} \) (film/cm\(^{-1}\)): 1741 (O=C–O), 2977 (C=C) and 1693 (O-CO-N); \( \delta_H \) (400MHz; D6-DMSO, 100 °C, both isomers): 1.04 (3H, t, \( J = 7.2 \), CO2CH2CH3 minor isomer), 1.23 (3H, t, \( J = 7.2 \), CO2CH2CH3 major isomer), 1.37 (9H, s, (CH3)3CO minor isomer), 1.40 (9H, s, (CH3)3CO major isomer), 1.43 (3H, d, \( J = 6.4 \),
CH₂CH=CHCH₃ major isomer), 1.53 (3H, d, J 7.2, PhCH(CH₃)N minor isomer), 1.54 (3H, d, J 6.8, PhCH(CH₃)N major isomer), 1.64 (3H, d, J 4.8, CH₂CH=CHCH₃ minor isomer), 2.00-2.10 (1H, m, CH(H)CH=CHCH₃ major isomer), 2.44-2.59 (2H, m, CH(H)CH=CHCH₃ major isomer and CH(H)CH=CHCH₃ minor isomer), 2.71-2.80 (1H, m, CH(H)CH=CHCH₃ minor isomer), 3.70 (1H, t, J 6.8, NCHCO₂CH₂CH₃ major isomer), 3.80 (1H, t, J 6.8, NCHCO₂CH₂CH₃ minor isomer), 3.89 (2H, q, J 7.2, CO₂CH₂CH₃ minor isomer), 4.12 (2H, q, J 7.2, CO₂CH₂CH₃ major isomer), 4.84-4.95 (1H, m, CH₂CH=CHCH₃ major isomer), 5.00-5.10 (1H, m, CH₂CH=CHCH₃ major isomer), 5.16 (1H, q, J 7.2, PhCH(CH₃)N minor isomer), 5.26-5.34 (1H, m, PhCH(CH₃)N major isomer), 5.42-5.55 (2H, m, CH₂CH=CHCH₃ minor isomer) and 7.20-7.39 (10H, m, 2 x ArH); δ_C (100MHz; D₆-DMSO, 100 °C, both isomers): 12.95 & 13.17 (CH₃), 16.09 & 17.73 (CH₃), 16.56 & 16.63 (CH₃), 27.39 & 27.42 (3 x CH₃), 33.57 & 33.63 (CH₂), 53.91 & 54.45 (CH), 56.57 & 57.35 (CH), 59.36 & 59.64 (CH₂), 78.88 & 78.90 (q), 125.43 & 126.90 (CH), 126.88 & 127.70 (CH), 126.12 & 125.45 (CH), 126.99 & 127.15 (2 x CH), 127.36 & 127.38 (2 x CH), 140.86 & 141.00 (q), 153.37 (q) and 169.81 & 170.37 (q); m/z (FAB) 362 ((M + 1)⁺, 9%); Found: 362.2328; C₂₁H₃₁NO₄ requires (M + 1)⁺, 362.2331.

75. Ethyl-2-((2R)-1-(benzyloxy)-3-methylbutan-2-ylimino)-acetate

![Chemical Structure](195)

A 50% solution of ethyl glyoxalate in toluene (0.2 cm³, 1.18 mmol) was added to a stirred solution of (R)-O-Bn valinol (125) (0.25 g, 1.31 mmol) in DCM (1 cm³) containing activated 4Å molecular sieves at 0 °C and stirred for 24 hours at room temperature. Anhydrous magnesium sulfate (0.5 g) was added and the reaction stirred for a further 15 minutes. Filtration and removal of solvent under reduced pressure yielded imine ester (198) as a yellow oil (0.30 g, 90%), which was used without further purification. [α]²⁵_D 4.5 (c 1.16, DCM); v_max (film/cm⁻¹): 1748 (O=C–O), 1721 (C=N) and 1105 (O-C); δ_H (400MHz; D₆-DMSO): 0.83 (6H, dd, J 14.8 and 6.8, CH(CH₃)₂), 1.26 (3H, t, J 7.2, CO₂CH₂CH₃), 1.83-1.92 (1H, m, CH(CH₃)₂), 3.22-3.26 (1H, m, NCHCH(CH₃)₂), 3.50...
(1H, dd, J 9.6 and 8.4, CH(H)OCH2Ph), 3.65 (1H, dd, J 12.0 and 3.6, CH(H)OCH2Ph),
4.25 (2H, q, J 7.2, CO2CH2CH3), 4.45 (2H, q, J 12.4, PhCH2O), 7.25-7.36 (5H, m, ArH)
and 7.72 (1H, s, N=CH/CO2CH2CH3); δC (100MHz; D6-DMSO): 13.95 (CH3), 18.30
(CH3), 19.30 (CH3), 29.40 (CH), 60.93 (CH2), 70.59 (CH2), 71.81 (CH2), 74.85 (CH),
127.31 (2 x CH), 127.34 (CH), 128.16 (2 x CH), 138.31 (q), 153.84 (CH) and 162.54 (q);
m/z (FAB) 278 ([M + 1]+, 35%); Found: 278.1756; C16H23N03 requires (M + 1)+,
278.1756.

76. Ethyl-2-[(2R)-1-(benzyloxy)-3-methylbutan-2-ylamino]-acetate

\[
\text{(200)}
\]

A solution of (R)-O-Bn valinol (125) (1.99 g, 10.31 mmol), acetic acid (1.5 cm³, 25.78
mmol) and sodium triacetoxyborohydride (5.46 g, 25.78 mmol) in DCE (50 cm³) was
treated with a 50% solution of ethyl glyoxalate in toluene (3.1 cm³, 15.47 mmol) at room
temperature. The resulting mixture was stirred for 18 hours before partitioning the
mixture between DCM (50 cm³) and saturated aqueous sodium hydrogen carbonate
solution (100 cm³). The organic phase was dried over anhydrous magnesium sulfate,
filtered and concentrated under reduced pressure to yield a yellow oil. Flash column
chromatography on silica, eluting with 10% ethyl acetate in light petroleum yielded the
amino ester (200) as a yellow oil (2.01 g, 70%). [α]²⁵_D 2.5 (c 1.27, DCM); ν_max (film/cm⁻¹
1): 1738 (O=C=O), 1099 (O-C) and 1200 (N-H); δH (400MHz; CDCl₃): 0.92 (6H, t, J 7.2,
CH(CH₃)₂), 1.25 (3H, t, J 7.2, CO₂CH₂CH₃), 1.81-1.89 (1H, m, CH(CH₃)₂), 2.60 (1H,
ddd, J 6.8, 4.8 and 4.0, NCHCH(CH₃)₂), 3.41 (1H, dd, J 9.6 and 7.2, CH(H)OCH₂Ph),
3.47 (2H, q, J 17.6, NCH₂CO₂CH₂CH₃), 3.52 (1H, dd, J 9.6 and 3.6, CH(H)OCH₂Ph),
4.25 (2H, q, J 6.8, CO₂CH₂CH₃), 4.51 (2H, s, PhCH₂O) and 7.27-7.35 (5H, m, ArH); δC
(100MHz; CDCl₃): 14.22 (CH₃), 18.36 (CH₃), 18.79 (CH₃), 29.35 (CH), 49.61 (CH₂),
60.66 (CH₂), 62.36 (CH), 71.08 (CH₂), 73.22 (CH₂), 127.54 (CH), 127.59 (2 x CH),
128.36 (2 x CH), 138.38 (q) and 172.76 (q); m/z (FAB) 280 ([M + 1]+, 97%); Found:
280.1916; C₁₆H₂₅N₃O₃ requires (M + 1)+, 280.1913.
77. *t*-Butyl-(ethoxycarbonyl)-methyl-(2R)-1-(benzyloxy)-3-methylbutan-2-ylcarbamate

\[
\text{OBn} \quad \text{Boc} \quad \text{CO}_2\text{Et}
\]

(202)

Triethylamine (3.9 cm\(^3\), 27.67 mmol), DMAP (0.42 g, 3.46 mmol) and di-tert-butyldicarbonate (3.77 g, 17.29 mmol) were successively added to a solution of ester (200) (1.93 g, 6.92 mmol) in anhydrous THF (15 cm\(^3\)) and stirred at reflux for 48 hours. Volatiles were removed under reduced pressure and the resulting residue was dissolved in ethyl acetate (50 cm\(^3\)), washed with saturated aqueous ammonium chloride solution (2 x 50 cm\(^3\)), saturated aqueous sodium hydrogen carbonate solution (150 cm\(^3\)) and saturated aqueous sodium chloride solution (50 cm\(^3\)). The organic phase was then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 5% ethyl acetate in light petroleum yielded *N*-Boc ester (202) as a pale yellow oil (1.93 g, 74%). \(\lbrack \alpha \rbrack_{\text{D}}^{25} = 44.5\) (c 1.32, DCM); \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 1754 (O=C-O), 1698 (O-CO-N) and 1113 (O-C); \(\delta_H\) (400MHz; D\(_6\)-DMSO, 100 °C): 0.92 (6H, dd, \(J\) 12.8 and 6.8, CH(CH\(_3\))\(_2\)), 1.19 (3H, t, \(J\) 7.2, CO\(_2\)CH\(_2\)CH\(_3\)), 1.40 (9H, s, (CH\(_3\))\(_3\)CO), 1.90-2.00 (1H, m, CH(CH\(_3\))\(_2\)), 3.62-3.71 (3H, m, NCHCH\(_2\)OCH\(_2\)Ph), 3.87 (2H, q, \(J\) 17.2, NCH\(_2\)CO\(_2\)CH\(_2\)CH\(_3\)), 4.02-4.18 (2H, m, CO\(_2\)CH\(_2\)CH\(_3\)), 4.43 (2H, q, \(J\) 12.0, PhCH\(_2\)O) and 7.22-7.36 (5H, m, ArH); \(\delta_C\) (100MHz; D\(_6\)-DMSO, 100 °C): 13.30 (CH\(_3\)), 18.93 (CH\(_3\)), 19.16 (CH\(_3\)), 27.40 (3 x CH\(_3\)), 29.55 (CH), 45.96 (CH\(_2\)), 59.38 (CH\(_2\)), 61.96 (CH), 69.61 (CH\(_2\)), 71.78 (CH\(_2\)), 78.56 (q), 126.60 (2 x CH), 126.63 (CH), 127.46 (2 x CH), 137.89 (q), 154.46 (q) and 169.15 (q); \(m/z\) (FAB) 380 ((M + 1)+, 6%); Found: 380.2433; C\(_{21}\)H\(_{33}\)NO\(_3\) requires (M + 1)+, 380.2437.
A 2.5M solution of n-butyllithium in hexanes (1.9 cm$^3$, 4.63 mmol) was added dropwise to a solution of diisopropylamine (0.7 cm$^3$, 4.88 mmol) in anhydrous THF (5 cm$^3$) at 0 °C under an inert atmosphere of nitrogen. The reaction was stirred for 5 minutes at 0 °C then cooled to −78 °C in a dry ice/acetone slush bath and stirred for 15 minutes. DMPU (0.6 cm$^3$, 4.88 mmol) was added dropwise and the reaction stirred for 10 minutes before N-Boc ester (202) (1.85 g, 4.88 mmol) in anhydrous THF (15 cm$^3$) was added dropwise. The reaction was stirred for 30 minutes at −78 °C before crotyl bromide (0.5 cm$^3$, 4.88 mmol) was added and the reaction stirred for a further 1 hour at the same temperature. The reaction was stirred at room temperature for a further 3 hours before being quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (50 cm$^3$) and the resulting aqueous layer further extracted with diethyl ether (2 x 50 cm$^3$). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a yellow oil. Flash column chromatography on silica, eluting with 2% ethyl acetate in light petroleum yielded an inseparable 4:1 mixture of diastereoisomers of N-Boc ester (204) as a yellow oil (1.14 g, 54%).

Experimental
(CH₃), 17.74 (CH₃), 20.02 & 20.09 (CH₃), 20.84 & 20.95 (CH₃), 28.49 (3 x CH₃), 29.29 (CH), 35.03 (CH₂), 58.75 (CH), 60.58 (CH₂), 62.64 (CH), 71.06 & 71.53 (CH₂), 72.76 & 73.03 (CH₂), 79.79 & 79.86 (q), 126.56 & 126.62 (CH), 127.71 & 127.73 (CH), 127.79 & 127.82 (2 x CH), 128.51 & 128.52 (2 x CH), 129.23 & 129.38 (CH), 138.81 & 138.87 (q), 154.75 & 154.83 (q), and 171.24 & 171.46 (q); m/z (FAB) 434 ((M + 1)⁺, 3%); Found: 434.2909; C₂₅H₃⁹NO₅ requires (M + 1)⁺, 434.2907.

5.3.3. Anionic Amino-Cope Rearrangements

79. 4-Methyl-3-phenylhex-5-enal

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

(67)

Diene (180) (0.32 g, 1.17 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (10 cm³) under an inert atmosphere of nitrogen and cooled to -78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (0.9 cm³, 2.33 mmol) was added dropwise and the resulting mixture was then allowed to slowly warm to room temperature overnight within the dry ice/acetone slush bath. The reaction was finally quenched with water (0.5 cm³), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude product as a yellow oil. Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave aldehyde (67) as a yellow oil (0.10 g, 47%). ν max (film/cm⁻¹): 2858, 2719 (CHO), 1722 (C=O), 3025 and 968 (C=C); δH (400MHz; CDCl₃, both isomers): 0.82 (3H, d, J 6.4, CH₃CH anti isomer), 0.96 (3H, d, J 6.8, CH₃CH syn isomer), 2.31-2.38 (1H, m, CH₃CH anti isomer), 2.42-2.48 (1H, m, CH₃CH syn isomer), 2.67 (1H, ddd, J 16.8, 8.0 and 2.4, CH(H)CH=O anti isomer), 2.79 (2H, ddd, J 7.2 and 2.0, CH₂CH=O syn isomer), 2.85 (1H, ddd, J 16.8, 4.8 and 1.2, CH(H)CH=O anti isomer), 2.97-3.03 (1H, m, PhCHH anti isomer), 3.20-3.25 (1H, m, PhCH syn isomer), 4.92-5.09 (4H, m, 2 x CHCH=CH₂), 5.54-5.70 (2H, m, 2 x CHCH=CH₂), 7.12-7.31 (10H, m, 2 x ArH), 9.57
Diene (181) (0.32 g, 1.15 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (10 cm$^3$) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (0.9 cm$^3$, 2.30 mmol) was added dropwise and the resulting mixture was then allowed to slowly warm to room temperature overnight within the dry ice/acetone slush bath. The reaction was finally quenched with water (0.5 cm$^3$), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude product as a yellow oil. Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave an inseparable mixture of aldehydes (209) and (210) as a yellow oil (0.10 g, 48%). 

OH (400MHz; CDCl$_3$; both isomers): 0.80 (3H, d, $J$ 6.4, CH$_3$CH major [3,3] isomer), 1.00 (3H, d, $J$ 6.4, CH$_3$CH minor [3,3] isomer), 1.01 (3H, d, $J$ 5.6, CH$_3$CH [1,3] isomer), 2.10 (1H, ddd, $J$ 16.8, 9.2 and 2.8, CH(H)CH=O minor [3,3] isomer), 2.17-2.28 (SH, m, CH(H)CH=O [1,3] isomer, CH$_3$CH major [3,3] isomer and CH$_3$CH minor [3,3] isomer), 2.63-2.69 (1H, m CH(H)CH=O major [3,3] isomer), 3.02 (1H, t, $J$ 9.2, PhCHCH=CH$_2$ major [3,3] isomer), 3.05 (1H, t, $J$ 9.2, PhCHCH=CH$_2$ minor [3,3] isomer), 5.05-5.10 (4H, m, PhCHCH=CH$_2$ major [3,3] isomer and PhCHCH=CH$_2$ minor [3,3] isomer), 5.88-
6.02 (2H, m, PhCH=CH₂ major [3,3] isomer and PhCH=CH₂ minor [3,3] isomer), 6.15 (1H, dt, J 15.6 and 7.2, CH=CHPh [1,3] isomer), 6.38 (1H, d, J 16.0, CH=CHPh [1,3] isomer), 7.14-7.35 (15H, m, 3 x ArH), 9.57 (1H, dd, J 2.8 and 1.6, CH=O minor [3,3] isomer) and 9.73-9.75 (2H, m, CH=O major [3,3] isomer and CH=O [1,3] isomer); δC (100MHz; CDCl₃): 18.11 & 18.49 (CH₃) [3,3], 20.05 (CH₃) [1,3], 28.52 (CH) [1,3], 32.69 & 32.81 (CH) [3,3], 40.30 (CH₂) [1,3], 49.04 & 49.21 (CH₂) [3,3], 50.39 (CH₂) [1,3], 56.34 & 56.88 (CH) [3,3], 116.30 (CH₂) [3,3], 126.07 (2 x CH) [1,3], 126.52 & 126.63 (2 x CH) [3,3], 127.20 (CH) [1,3], 127.88 & 127.89 (CH) [3,3], 128.04 (CH) [1,3], 128.59 (2 x CH) [1,3], 128.65 & 128.75 (2 x CH) [3,3], 132.19 (CH) [1,3], 137.43 (q) [1,3], 139.59 & 140.38 (CH) [3,3], 142.77 & 143.06 (q) [3,3], 202.27 & 202.59 (CH) [3,3], and 202.65 (CH) [1,3]; m/z (EI) 188 (M⁺, 3%); Found: 188.1199; C₁₃H₁₆O requires M⁺, 188.1201.

81. 3,6-Diphenylhex-5-enal

![Chemical structure](image)

Diene (182) (0.34 g, 1.00 mmol) was dried in vacuo for 1 hour then dissolved in anhydrous THF (10 cm³) under an inert atmosphere of nitrogen and cooled to −78 °C in a dry ice/acetone slush bath. A 2.5M solution of n-butyllithium in hexanes (0.8 cm³, 2.01 mmol) was added dropwise and the resulting mixture was then allowed to slowly warm to room temperature overnight within the dry ice/acetone slush bath. The reaction was finally quenched with water (0.5 cm³), dried over anhydrous sodium sulfate, filtered through a pad of celite and concentrated under reduced pressure to give the crude product as a yellow oil. Flash column chromatography on silica, eluting with 3% diethyl ether in light petroleum gave aldehyde (212) as a yellow oil (0.13 g, 51%). ν max (film/cm⁻¹): 2824, 2713 (CHO), 1720 (C=O), 3024 and 966 (C=C); δH (400MHz; CDCl₃): 2.48-2.62 (2H, m, CH₂CH=CHPh), 2.74-2.87 (2H, m, CH₂CH=O), 3.35-3.42 (1H, m, PhCH(CH₂)₂), 6.01-6.09 (1H, m, CH₂CH=CHPh), 6.38 (1H, dt, J 15.6 and 1.2, CH₂CH=CHPh), 7.17-7.35 (10H, m, ArH) and 9.69 (1H, t, J 2.0, CH=O); δC (100MHz; CDCl₃): 40.14 (CH),

Experimental
40.26 (CH₂), 49.30 (CH₂), 126.08 (2 x CH), 126.79 (CH), 127.24 (CH), 127.44 (CH),
127.46 (2 x CH), 128.53 (2 x CH), 128.73 (2 x CH), 132.14 (CH), 137.28 (q), 143.36 (q)
and 201.74 (CH).

5.4. A New Route to the Tetracycline Antibiotics

5.4.1. Claisen Rearrangement/RCM Route

82. 1,4-Bis(allyloxy)-2,3-dimethylbenzene \(^{167}\)

\[
\text{\textcopyright} 20\text{\textcopyright} \text{image}
\]

A suspension of 2,3-dimethylhydroquinone (2.50 g, 18.09 mmol), allyl bromide (3.8 cm\(^3\),
45.23 mmol) and anhydrous potassium carbonate (6.25 g, 45.23 mmol) in acetone (15
\text{cm}^3\) was heated to reflux for 24 hours. The reaction was allowed to cool to room
temperature before water (50 \text{cm}^3\) and diethyl ether (50 \text{cm}^3\) were added. The layers
were separated and the aqueous layer extracted with diethyl ether (4 x 50 \text{cm}^3\). The
combined organic phase was washed with IM aqueous sodium hydroxide solution (3 x
100 \text{cm}^3\) and water (100 \text{cm}^3\), dried over anhydrous magnesium sulfate, filtered and
concentrated under reduced pressure to give the crude product as a brown oil. Flash
column chromatography on silica, eluting with 10% ethyl acetate in petroleum ether,
yielded bis-allyl ether (249) as a green oil (3.53 g, 89%). \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 3080 (C=C)
and 1101 (C-O); \(\delta_H\) (400MHz; CDCl\(_3\)): 2.20 (6H, s, 2 x ArCH\(_3\)), 4.47 (4H, dt, \(J = 4.8\) and
1.6, 2 x OCH\(_2\)CH=CH\(_2\)), 5.25 (2H, dq, \(J = 10.4\) and 1.6, 2 x OCH\(_2\)CH=CH(H)), 5.41 (2H,
dq, \(J = 17.2\) and 1.6, 2 x OCH\(_2\)CH=CH(H)), 6.02-6.12 (2H, m, OCH\(_2\)CH=CH\(_2\)) and 6.63
(2H, s, ArH); \(\delta_C\) (100MHz; CDCl\(_3\)): 12.25 (2 x CH\(_3\)), 69.77 (2 x CH\(_2\)), 109.58 (2 x CH),
83. 2,3-Dimethyl-5,6-diallylhydroquinone$^{167}$

\[
\text{OH} \\
| \text{OH} \\
\text{OH}
\]

(250)

Bis-allyl ether (249) (3.51 g, 16.27 mmol) was heated to reflux in mesitylene (20 cm$^3$) for 24 hours. The solvent was removed under reduced pressure to yield a tarry brown solid. Hexane (50 cm$^3$) was added and removed under reduced pressure to azeotrope any residual mesitylene. The resulting solid was filter-washed with cold hexane (50 cm$^3$) to yield the hydroquinone (250) as a brown solid (2.39 g, 68%). $\nu_{\text{max}}$ (film/cm$^{-1}$): 3314 (O-H) and 3075 (C=C); $\delta_{\text{H}}$ (400MHz; D$_6$-DMSO): 2.06 (6H, s, 2 x ArCH$_3$), 3.31 (4H, dt, $J$ 6.0 and 1.6, 2 x CH$_2$CH=CH$_2$), 4.85-4.92 (4H, m, 2 x CH$_2$CH=CH$_2$), 5.80-5.90 (2H, m, 2 x CH$_2$CH=CH$_2$) and 7.40 (2H, s, 2 x ArOH); $\delta_{\text{C}}$ (100MHz; D$_6$-DMSO): 13.04 (2 x CH$_3$), 30.49 (2 x CH$_2$), 114.07 (2 x CH$_2$), 122.36 (2 x q), 123.41 (2 x q), 137.48 (2 x CH) and 145.71 (2 x q).

84. 2,3-Dimethyl-5,6-diallylhydroquinone diacetate$^{167}$

\[
\text{OAc} \\
| \text{OAc} \\
\text{OAc}
\]

(251)

Acetic anhydride (2.7 cm$^3$, 28.40 mmol) was added slowly to a solution of hydroquinone (250) (2.38 g, 10.92 mmol) and DMAP (0.40 g, 3.28 mmol) in triethylamine (1.6 cm$^3$) at
0 °C and the resulting mixture stirred at room temperature for 20 hours. Methanol (10 cm³) and diethyl ether (50 cm³) were added and the solution washed with 1M aqueous hydrochloric acid solution (50 cm³) and saturated aqueous sodium hydrogen carbonate solution (100 cm³). The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a brown solid. Flash column chromatography on silica, eluting with 10% ethyl acetate in petrol, yielded diacetate (251) as a white solid (2.84 g, 86%). mp 96-99 °C; νmax (film/cm⁻¹): 1762, 1189 (O=C–O) and 3077 (C=C); δH (400MHz; CDCl₃): 2.04 (6H, s, 2 x ArCH₃), 2.31 (6H, s, 2 x OCOCH₃), 3.10-3.50 (4H, br, 2 x CH₂CH=CH₂), 4.92-5.01 (4H, m, 2 x CH₂CH=CH₂) and 5.75-5.85 (2H, m, 2 x CH₂CH=CH₂); δC (100MHz; CDCl₃): 13.41 (2 x CH₃), 20.71 (2 x CH₃), 31.51 (2 x CH₂), 115.60 (2 x CH₂), 128.66 (2 x q), 128.80 (2 x q), 135.62 (2 x CH), 145.98 (2 x q) and 169.06 (2 x q); m/z (FAB) 303 [(M + 1)+, 37%]; Found: 303.1594; C₁₈H₂₂O₄ requires (M + 1)+, 303.1596.

85. 2,3-Dimethyl-5,8-dihydro-1,4-naphthalendiol diacetate

\[
\begin{align*}
\text{OAc} & \\
\text{OAc} & \\
\end{align*}
\]

A catalytic amount of Grubbs 2nd generation catalyst was added to a solution of diacetate (251) (0.54 g, 1.79 mmol) in anhydrous toluene under an inert atmosphere of nitrogen. The completion of the reaction was monitored by TLC analysis and additional catalyst was added if required. After 24 hours stirring the reaction mixture was absorbed on to silica following removal of the reaction solvent and loaded on to a chromatographic column. Flash column chromatography on silica, eluting with 5% ethyl acetate in petrol, yielded the ring-closed product (252) as a white solid (0.44 g, 89%). mp 186-189 °C (Lit. mp 186 °C)¹⁷²; νmax (film/cm⁻¹): 1746, 1198 (O=C–O) and 3028 (C=C); δH (400MHz; CDCl₃): 2.06 (6H, s, 2 x ArCH₃), 2.34 (6H, s, 2 x OCOCH₃), 2.91-3.36 (4H, br, 2 x CH₂CH=CH₂) and 5.82 (2H, t, J 1.2, CH=CH); δC (100MHz; CDCl₃): 12.93 (2 x CH₃), 20.71 (2 x CH₃), 31.51 (2 x CH₂), 115.60 (2 x CH₂), 128.66 (2 x q), 128.80 (2 x q), 135.62 (2 x CH), 145.98 (2 x q) and 169.06 (2 x q); m/z (FAB) 303 [(M + 1)+, 37%]; Found: 303.1594; C₁₈H₂₂O₄ requires (M + 1)+, 303.1596.
20.52 (2 x CH₃), 24.34 (2 x CH₂), 123.00 (2 x CH), 125.04 (2 x q), 127.45 (2 x q), 144.95 (2 x q) and 169.15 (2 x q); m/z (FAB) 275 ((M + 1)^+, 43%); Found: 275.1287; C₁₆H₁₈O₄ requires (M + 1)^+, 275.1283.

86. 2,3-Dimethyl-1,4-naphthalendiol diacetate

![Diagram](image)

To a saturated solution of chromium(III) oxide (0.79 g, 7.92 mmol) in 80% acetic acid (25 cm³) was added a solution of diacetate adduct (252) (0.43 g, 1.58 mmol) in glacial acetic acid (15 cm³) whilst maintaining the temperature below 5 °C. The reaction was then stirred for 24 hours at room temperature before being added to ice water (250 cm³) with continuous stirring, forming a precipitate in the process. The mixture was then filtered through a pad of celite and washed with ice water. The filter cake was suspended in diethyl ether and filtered through a pad of anhydrous magnesium sulfate. The organic phase was concentrated under reduced pressure to yield a yellow solid. °H NMR spectral analysis confirmed that the required product (254) was not generated, with the undesired naphthalene (256) shown to be isolated. mp 188-190 °C (Lit. mp 189-189.5 °C); νmax (film/cm⁻¹): 1749, 1177 (O=C–O) and 1601 (ArH); δH (400MHz; CDCl₃): 2.24 (6H, s, 2 x ArCH₃), 2.47 (6H, s, 2 x OCOCH₃), 7.45 (2H, dd, J 6.4 and 3.2, ArH) and 7.71 (2H, dd, J 6.4 and 3.2, ArH); δC (100MHz; CDCl₃): 13.59 (2 x CH₃), 20.62 (2 x CH₃), 121.13 (2 x CH), 126.02 (2 x q), 126.25 (2 x CH), 126.93 (2 x q), 142.16 (2 x q) and 169.14 (2 x q);
87. 2,3-Dimethyl-5,6,7,8-tetrahydro-1,4-naphthalendiol diacetate

\[
\text{OAc} \\
\text{OAc}
\]

\((261)\)

Pd/C (0.10 g, 10% w/w) was added to a solution of diacetate adduct (252) (1.01 g, 3.66 mmol) in absolute ethanol (30 cm³). The resulting suspension was stirred at atmospheric pressure under hydrogen at room temperature for 24 hours. The solution was filtered through Celite and the filtrate rinsed with ethyl acetate (50 cm³). The solvent was removed under reduced pressure, to yield the product (261) as a white solid (0.81 g, 81%). 

\[\nu_{\text{max}} \text{(film/cm}^{-1}\text{)}: \quad 1745 \text{ and } 1192 (\text{O=C-O}); \delta_{\text{H}} (400\text{MHz; CDCl}_3): \quad 1.54-1.87 (4\text{H, br, CH}_2\text{CH}_2\text{CH}_2\text{CH}_2), \quad 2.04 (6\text{H, s, 2 x ArCH}_3), \quad 2.33 (6\text{H, s, 2 x OCOCH}_3) \text{ and } 2.51-2.77 (4\text{H, br, CH}_2\text{CH}_2\text{CH}_2\text{CH}_2); \quad \delta_{\text{C}} (100\text{MHz; CDCl}_3): \quad 12.90 (2 \times \text{CH}_3), \quad 20.54 (2 \times \text{CH}_3), \quad 21.98 (2 \times \text{CH}_2), \quad 23.54 (2 \times \text{CH}_2), \quad 126.81 (2 \times \text{q}), \quad 127.95 (2 \times \text{q}), \quad 145.32 (2 \times \text{q}) \text{ and } 169.16 (2 \times \text{q}); \quad m/z \text{ (El)} \quad 276 (M^+, 7\%); \quad \text{Found: } 276.1364; \quad \text{C}_{16}\text{H}_{20}\text{O}_4 \text{ requires } M^+, 276.1362.

\[m/z \text{ (FAB) } 272 ((M + 1)^+, 55\%); \quad \text{Found: } 272.1044; \quad \text{C}_{16}\text{H}_{16}\text{O}_4 \text{ requires } (M + 1)^+, 272.1049.\]
88. 2,3-Dimethyl-8-oxo-5,6,7,8-tetrahydro-1,4-naphthalendiol diacetate

\[
\text{\begin{align*}
&\text{\begin{array}{c}
\text{CH}_3c \\
\text{O} \\
\text{CH}_3a \\
\text{O} \\
\text{CH}_3b \\
\text{O} \\
\text{CH}_3d \\
\end{array}} \\
&\end{align*}}
\]

(263)

To a saturated solution of chromium(III) oxide (0.46 g, 4.62 mmol) in 80% acetic acid (5 cm\(^3\)) was added a solution of diacetate (261) (0.26 g, 0.92 mmol) in glacial acetic acid whilst maintaining the temperature below 5 °C. The reaction was stirred for 20 hours at room temperature before being added to ice water (300 cm\(^3\)) with continuous stirring, forming a precipitate in the process. The mixture was then filtered through a pad of celite and washed with ice water. The filter cake was suspended in ethyl acetate and filtered through a pad of anhydrous magnesium sulfate. The organic phase was concentrated under reduced pressure to yield the mono-oxidised product (263) as a light yellow solid (91 mg, 34%). \(\nu_{\text{max}}\) (film/cm\(^{-1}\)): 1755 (O=C–O) and 1683 (C=O); \(\delta_{\text{H}}\) (400MHz; CDCl\(_3\)): 1.99-2.10 (2H, br, O=CH\(_2\)CH\(_2\)CH\(_2\)), 2.11 (3H, s, ArCH\(_3\)\(_a\)/ArCH\(_3\)\(_b\)), 2.13 (3H, s, ArCH\(_3\)\(_a\)/ArCH\(_3\)\(_b\)), 2.36 (3H, s, OCOCH\(_3\)\(_c\)/ OCOCH\(_3\)\(_d\)), 2.40 (3H, s, OCOCH\(_3\)\(_c\)/ OCOCH\(_3\)\(_d\)), 2.56 (2H, t, \(J\) 6.4, O=CH\(_2\)CH\(_2\)CH\(_2\)) and 2.60-2.92 (2H, br, O=CH\(_2\)CH\(_2\)CH\(_2\)); \(\delta_{\text{C}}\) (100MHz; CDCl\(_3\)): 12.40 (CH\(_3\)), 13.93 (CH\(_3\)), 20.39 (CH\(_3\)), 21.02 (CH\(_3\)), 21.98 (CH\(_2\)), 24.01 (CH\(_2\)), 39.99 (CH\(_2\)), 122.81 (q), 129.93 (q), 135.30 (q), 136.59 (q), 144.36 (q), 146.08 (q), 168.62 (q), 169.70 (q) and 195.20 (q); \(m/z\) (EI) 290 (M\(^+\), 5%); Found: 290.1148; C\(_{16}\)H\(_{18}\)O\(_5\) requires M\(^+\), 290.1154.
5.4.2. Fries Rearrangement Route

89. 1,4-Bis(acrylate)-2,3-dimethylbenzene

To a suspension of 2,3-dimethylhydroquinone (1.00 g, 7.24 mmol) and anhydrous potassium carbonate (2.50 g, 18.11 mmol) in acetone (20 cm³) was added acryloyl chloride (1.5 cm³, 18.11 mmol) dropwise. The mixture was stirred at room temperature for 24 hours. The reaction was allowed to cool to room temperature before water (20 cm³) and ethyl acetate (20 cm³) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (4 x 25 cm³). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (25 cm³) and water (25 cm³), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product as a brown solid. Flash column chromatography on silica, eluting with 10% ethyl acetate in petroleum ether, yielded bis-acrylate (258) as a white solid (1.28 g, 92%). mp 108-110 °C; νmax (film/cm⁻¹): 1732 and 1168 (O=O); δH (400MHz; CDCl3): 2.11 (6H, s, 2 x ArCH₃), 6.04 (2H, dd, J 10.4 and 1.2, 2 x OCOCH=CH(H)), 6.36 (2H, dd, J 17.2 and 10.4, 2 x OCOCH=CH₂), 6.63 (2H, dd, J 17.2 and 1.2, 2 x OCOCH=CH(H)) and 6.94 (2H, s, ArH); δC (100MHz; CDCl3): 13.05 (2 x CH₃), 119.86 (2 x CH), 127.68 (2 x CH), 130.52 (2 x q), 132.73 (2 x CH₂), 146.66 (2 x q) and 164.41 (2 x q); m/z (FAB) 246 (M⁺, 92%); Found: 246.0891; C₁₄H₁₄O₄ requires M⁺, 246.0892.
90. 4-Hydroxy-2,3-dimethylphenyl acrylate

A mixture of bis-acrylate (258) (0.49 g, 2.55 mmol) and titanium(IV) chloride (3.0 cm$^3$, 27.36 mmol) were stirred at 140 °C for 2 hours. The reaction mixture was slowly diluted with DCM (50 cm$^3$) and slowly quenched with water (50 cm$^3$). The complex was hydrolyzed with 4M aqueous hydrochloric acid solution (15 cm$^3$), washed with saturated aqueous sodium hydrogen carbonate solution (20 cm$^3$), water (20 cm$^3$), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield an white solid. $^1$H NMR spectral analysis confirmed that the required product (259) was not generated, with the undesired cleavage product (260) shown to be isolated. $\nu_{\text{max}}$ (film/cm$^{-1}$): 3417 (O-H), 1709 and 1156 (O=C-O); $\delta_H$ (400MHz; CDCl$_3$): 2.03 (3H, s, ArCH$_3$a), 2.09 (3H, s, ArCH$_3$b), 6.02 (1H, dd, $J$ 10.4 and 1.2, OCOCH=CH(H)), 6.09 (1H, br s, OH), 6.34 (1H, dd, $J$ 17.2 and 10.4, OCOCH=CH$_2$), 6.42 (1H, d, $J$ 8.8, ArHc), 6.62 (1H, dd, $J$ 17.2 and 1.2, OCOCH=CH(H)) and 6.65 (1H, d, $J$ 8.4, ArHd); $\delta_C$ (100MHz; CDCl$_3$): 12.10 (CH$_3$), 12.92 (CH$_3$), 113.12 (CH), 119.01 (CH), 124.56 (q), 127.75 (CH), 129.66 (q), 133.00 (CH$_2$), 142.22 (q), 151.87 (q) and 165.90 (q); $m/z$ (FAB) 192 (M$^+$, 95%).
Chapter 6

References


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