CHIRAL LITHIUM AMIDES

IN

ASYMMETRIC SYNTHESIS

A thesis submitted to the University of Surrey
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by

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Abstract

This thesis describes the use of chiral lithium amides as enantiotopic deprotonating agents and as nucleophiles in asymmetric synthesis.

The chiral lithium amides were prepared from their corresponding secondary amines by reaction with butyl lithium. The syntheses of the secondary amines are described; in general (R) or (S)-1-phenylethylamine was condensed with an aldehyde or ketone and the subsequent imine was reduced. Two new secondary amines (1R,2R,3S,4R)-2-hydroxy-3-(N-(S)-1-phenylethylamine)-2,6,6-trimethylbicyclo[3.1.1]heptane (126b) and (1R,2R,3R,4R)-2-hydroxy-3-(N-(R)-1-phenylethylamine)-2,6,6-trimethylbicyclo[3.1.1]heptane (126a) were synthesised and the absolute stereochemistry of 126b was determined from an X-ray crystal structure. A simple method was developed for the condensation of camphor with hindered primary amines; (R)-N-(1-phenylethyl)bomanimine (113a) and (S)-N-(1-phenylethyl)bomanimine (113b) were produced in high yield. Subsequent reduction of the C=N bond occurred diastereoselectively to give exo-(1R)-N-(1-phenylethyl)bomanimine (119a) and endo-(1S)-N-(1-phenylethyl)bomanimine (119b); the absolute stereochemistry of 119b was confirmed from an X-ray crystallographic analysis.

The enantiotopic deprotonation of 4-\text{-}t\text{-}butylthiane-1,1-dioxide (pentamethylene sulphone) and subsequent reaction of the carbanion with methyl iodide and trimethylsilyl chloride was investigated. Lithium (R)-N-benzyl-1-phenylethylamide, lithium (R)-N-(1-phenylethyl)-\alpha\text{-}methylbenzylamide, and lithium exo-(1R)-N-(1-phenylethyl)bomanamide failed to differentiate between the enantiotopic protons to the SO\text{2} function. However the lithium amide bases derived from 3-hydroxyamines showed some selectivity; deprotonation using the dianion of (1R,2S)-ephedrine or the dianion of 226b, and subsequent reaction with methyl iodide or trimethylsilyl chloride gave 2-methyl-4-t-butylthiane-1,1-dioxide or 2-trimethylsilyl-4-t-butylthiane-1,1-dioxide in 15-24\% e.e..

The Michael addition of lithium (R)-N-benzyl-1-phenylethylamide (30a) and lithium bis [(R)-N-(1-phenylethyl)]amide (17a) to a variety \(\alpha,\beta\)-unsaturated aldehydes, ketones, imines, nitriles, esters and carboxamides was investigated. The Michael addition of 30a to cinnamoyl and crotonoyl amides was found to be highly face selective (d.e. 85-96\%). Addition of 30a to cinnamoyl amides followed by reaction with methyl iodide lead to two new chiral centres (72-91\% d.e.) while reaction with benzaldehyde produced three new chiral centres with high diastereoselectivity (85-90\% d.e.). The stereochemistry of the Michael adducts was confirmed by X-ray crystallography.

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Finally, I would like to thank my parents for their support and encouragement throughout my studies.
List of Abbreviations

b.p. Boiling point
BnBr Benzyl bromide
BuLi Butyl lithium
CLSR Chiral lanthanide shift reagent
COSY Correlated Spectroscopy
d.e. Diastereomeric excess
DEPT Distortionless Enhancement by Polarisation Transfer
DIBAl-H Diisobutylaluminium hydride
DMPU 1,3-Dimethyl-3,4,5,6-tetrahydro-2-(H)-pyrimidinone
e.e. Enantiomeric excess
FTIR Fourier Transform Infra-red (spectroscopy)
HMPA Hexamethylphosphoramide
LDA Lithium diisopropylamide
o.p. Optical purity
m.p. Melting point
NMR Nuclear Magnetic Resonance (spectroscopy)
n.O.e. Nuclear Overhauser enhancement
TEA Triethylamine
THF Tetrahydrofuran
Tlc Thin layer chromatography
TMEDA N,N,N',N'-Tetramethylene diamine
TMS Trimethylsilyl-[(CH₃)₃Si]
TMSCl Trimethylsilyl chloride [(CH₃)₃SiCl]
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INTRODUCTION

CHAPTER 1

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This thesis deals with the application of chiral lithium amides to asymmetric synthesis.

The introduction has been divided into the following sections:

i) A brief introduction to asymmetric synthesis
ii) An introduction to chiral lithium amides
iii) An introduction to asymmetric Michael additions
iv) The aim of this work

1.1 ASYMMETRIC SYNTHESIS

Asymmetric synthesis has been defined as 'a reaction in which an achiral unit of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts. This is to say an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result.'\(^1\) (The reactant can be a reagent, solvent, catalyst or a physical force such as circularly polarised light.). Strictly speaking this definition only covers reagent controlled synthesis but the definition of asymmetric synthesis is generally widened to describe any synthetic operation that produces a new chiral centre in an enantiomerically enriched form.

1.1.1 METHODS OF ASYMMETRIC SYNTHESIS

A new stereogenic centre is formed in the substrate under the influence of a chiral group ultimately derived from a naturally occurring, enantiomerically pure compound. The main methods of asymmetric induction are grouped according to how this influence is exerted.

Substrate controlled asymmetric induction

A new stereogenic centre is introduced into a chiral substrate. The configuration of the new chiral centre is established in a relative relationship to the pre-existing chiral centre(s). The existing stereogenic centres are said to 'direct' the formation of the new centre by causing the achiral reactant to approach the reaction site from one trajectory in preference. The original stereogenic centre remains connected throughout the sequence and is an integral part of the final product. In the lithium aluminium hydride reduction of (1) ketone (Scheme 1.1), lithium aluminium hydride attacks from the less hindered side, opposite the large phenyl substituent.\(^2\)
**Scheme 1.1:** Example of substrate-control; LiAlH₄ reduction of ketone (1) to diastereomeric alcohols 2a and 2b (50:1)

**Auxiliary controlled asymmetric induction**

A chiral auxiliary is attached to an achiral substrate in order to direct the subsequent reaction with an achiral reagent. The transition states leading to the two possible diastereomers are diastereomeric and therefore different in energy. The factor directing attack of the reagent is normally steric but can be chelation, hydrogen bonding, electrostatic etc. If the selectivity of induction is poor, the resultant diastereomers may be separated by chromatography or crystallisation, giving rise to a pure enantiomeric product after removal of the chiral auxiliary. Auxiliary controlled asymmetric induction is illustrated in the following reaction sequence (Scheme 1.2); a chiral auxiliary (3) derived from norephedrine was attached to a carboxylic acid (4) and directed the subsequent alkylation of enolate (5) to give one major diastereomer (6) which was cleaved to yield the enantiomerically pure α-substituted carboxylic acid (S)-7.

**Scheme 1.2:** Example of auxiliary control; asymmetric synthesis of an α-substituted carboxylic acid (S)-7.
Reagent controlled asymmetric induction
In this method the control is intermolecular, unlike substrate and auxiliary controlled methods where the control is intramolecular. The chiral information is brought transiently into the reacting system by the chiral reagent. The choice of starting material is much wider because it does not have to come from the chiral pool and there is no need for two extra steps to attach and remove a chiral auxiliary. Unfortunately, effective chiral reagents have only been found for a small number of reactions,\(^5\) for example, the hydroboration of \textit{cis}-2-butene (8) with \(-\)-\textit{Icp\textsubscript{2}}BH (9) to yield the allylic alcohol (10) in 87\% e.e. (Scheme 1.3).\(^6\)\(^7\)\(^8\)

![Scheme 1.3: Example of reagent controlled synthesis; hydroboration of \textit{cis}-2-butene (8) with \(-\)-\textit{Icp\textsubscript{2}}BH (9) to yield the allylic alcohol (10) in 87\% e.e.](image)

Catalyst controlled asymmetric induction
Here the chiral reagent is replaced by an achiral reagent and a chiral catalyst which directs the conversion of an achiral substrate into a chiral product with an achiral reagent. A representative reaction is depicted in Scheme 1.4.\(^9\)

![Scheme 1.4: Example of catalyst controlled asymmetric induction; Sharpless epoxidation of the alkene (11) to yield the epoxide (12) in 96\% e.e.](image)
Kinetic resolution

Kinetic resolution involves the reaction of a racemic chiral compound or an achiral compound containing equivalent enantiotopic groups with a chiral reagent. The two enantiomers or enantiotopic groups undergo reaction at different rates and ideally one is converted into the product while the other is unchanged. Many kinetic resolutions involve enzymes; an example is the hydrolysis of (±)-N-acetylphenylalanine methyl ester (13) with α-chymotrypsin to give (S)-14 and unchanged (R)-13 (Scheme 1.5).

\[
\text{PhCH}_2\text{H} \quad \text{H}_2\text{O} \quad \text{cat. } \alpha-\text{chymotrypsin} \quad \text{PhCH}_2\text{H} + \text{PhCH}_2\text{CO}_2\text{Me} \\
\text{AcNH} \quad \text{CO}_2\text{Me} \quad \text{racamic 13} \quad 14 \quad (R)-13
\]

Scheme 1.5: Kinetic resolution of (±)-N-acetylphenylalanine methyl ester (13).

1.2 INTRODUCTION TO CHIRAL LITHIUM AMIDES

Chiral lithium amide bases are used to transfer chirality intermolecularly (reagent controlled synthesis) in two ways:

i) The chiral lithium amide base differentiates between enantiotopic protons in a kinetically controlled deprotonation of prochiral and achiral substrates.

ii) The chiral lithium amide first acts as a strong base to generate a prochiral carbanion from the substrate and complexes with the carbanion. This complex then directs the stereochemical outcome of the subsequent reaction.

The other main use of chiral lithium amides are as nucleophiles in asymmetric Michael addition reactions.

1.2.1 ASYMMETRIC DEPROTONATION REACTIONS

The chiral lithium amide base selects between enantiotopic protons in kinetically controlled deprotonations of prochiral or achiral substrates. These substrates normally have two reaction sites and a plane of symmetry, and the chiral base preferentially removes one of the two enantiotopic hydrogens. The two transition states are diastereomeric and their energy difference determines the relative rates of the two competing deprotonation reactions, and thereby the ratio of the enantiomers produced.
Asymmetric deprotonation of epoxides

The first reported enantioselective deprotonation using a chiral lithium amide base came from Whitesell and Felman who described the rearrangement of cyclohexene oxide (15) to non-racemic 2-cyclohexene-1-ol (16) using a variety of bases (Scheme 1.6); the highest e.e. (31%) was obtained with base (17b) (Table 1.1 entry 1). In later work Asami used (S)-2-(disubstituted aminomethyl)-pyrrolidines prepared from (S)-proline and obtained optically active 16 (e.e. 45-92 %). It was found that small modifications in the structure of the bases could lead to the formation of the product with the opposite configuration. (Table 1.1 entries 2-4). These proline derived bases have been successfully applied to several other cyclic and acyclic epoxides (Table 1.1 entries 6-13). Bases derived from aminoacids such as (S)-N-phenylglycine gave also been used (Table 1.1, entry 5). This information has been summarised in Table 1.1 and Scheme 1.6.

Scheme 1.6: Rearrangement of cyclohexene oxide to 2-cyclohexene-1-ol by deprotonation with chiral lithium amide bases.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Base</th>
<th>Conditions</th>
<th>% Yield</th>
<th>e.e. % allylic alcohol (R/S)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclohexene oxide</td>
<td>17b</td>
<td>THF. reflux, 2h</td>
<td>65</td>
<td>31 (R)</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexene oxide</td>
<td>18</td>
<td>THF, 0°C,</td>
<td>77</td>
<td>92 (S)</td>
<td>14,14</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexene oxide</td>
<td>19</td>
<td>THF, rt., overnight, 1.65 eq. HMPA</td>
<td>80</td>
<td>78 (S)</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexene oxide</td>
<td>20</td>
<td>THF, rt., overnight, 1.65 eq. HMPA</td>
<td>77</td>
<td>62 (S)</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexene oxide</td>
<td>21</td>
<td>THF, 0°C to rt., 16h</td>
<td>70</td>
<td>92 (R)</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>cyclopentene oxide</td>
<td>18</td>
<td>THF, rt., overnight, 1.65 eq. DBU</td>
<td>49</td>
<td>31 (S)</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>cyclopentene oxide</td>
<td>20</td>
<td>THF, rt., overnight, 1.65 eq. HMPA</td>
<td>48</td>
<td>15 (R)</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>cyclooctene oxide</td>
<td>18</td>
<td>THF, rt., overnight, 1.65 eq. DBU</td>
<td>45</td>
<td>58 (S)</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>cyclooctene oxide</td>
<td>20</td>
<td>THF, rt., overnight, 1.65 eq. HMPA</td>
<td>56</td>
<td>42 (R)</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>(Z)-2-buten oxide</td>
<td>18</td>
<td>THF, rt., overnight, 1.65 eq. DBU</td>
<td>60</td>
<td>70 (S)</td>
<td>16</td>
</tr>
<tr>
<td>11</td>
<td>(Z)-2-buten oxide</td>
<td>20</td>
<td>THF, rt., overnight, 1.65 eq. HMPA</td>
<td>58</td>
<td>62 (R)</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>(Z)-4-octene oxide</td>
<td>18</td>
<td>THF, rt., overnight, 1.65 eq. DBU</td>
<td>66</td>
<td>60 (S)</td>
<td>16</td>
</tr>
<tr>
<td>13</td>
<td>(Z)-4-octene oxide</td>
<td>20</td>
<td>THF, rt., overnight, 1.65 eq. HMPA</td>
<td>66</td>
<td>59 (R)</td>
<td>16</td>
</tr>
</tbody>
</table>

* Corrected for optical purity of the base

Table 1.1: Rearrangement of cyclohexene oxide to 2-cyclohexene-1-ol by deprotonation with chiral lithium amide bases, yield and e.e. of the resultant allylic alcohols (refer to scheme 1.6).

The rearrangement of cyclic epoxides to allylic alcohols is known to involve removal of a proton that occupies a pseudo axial orientation \( \text{syn} \) to the oxygen.\(^\text{18}\) A 6-membered ring transition state with N-H, N-Li and O-Li interactions was suggested for the reaction of cyclohexene oxide with base 18 (Scheme 1.7). Transition state A is favoured because there is no steric repulsion between the cyclohexene ring and the diamine; the alcohol having the (S)-configuration is obtained (Table 1.1, entry 2).\(^\text{14}\)

Scheme 1.7: Rearrangement of cyclohexene oxide to 2-cyclohexene-1-ol by deprotonation with base (18); proposed transition state leading to (S)-16.
Meso-spiro-epoxides such as 22 have been rearranged to allylic alcohols using this methodology (Scheme 1.8, Table 1.2).

![Scheme 1.8: The rearrangement of the meso-spiro-epoxide (22) to allylic alcohol (23)](image)

Base | Solvent | Yield of 23 (%) | e.e. (%) | (±)
--- | --- | --- | --- | ---
17a | THF | 50 | 76 | +
17a | Et₂O | 56 | 23 | +
17a | Benzene | 40 | 21 | +
18 | THF | 58 | 21 | +
18 | Et₂O | 50 | 23 | +
18 | Benzene | 35 | 45 | -

*The yields were low because only the exo-isomer reacted.

Table 1.2: Reaction of two chiral lithium amide bases with epoxide 22 (3:2 endo:exo); yield and e.e. of the allylic alcohol obtained (refer to scheme 1.8).

These results demonstrate many of the complexities when using chiral lithium amide bases. Base 17a gave the best enantiomeric induction with 22 while the proline derived base 18 gave low e.e.'s (Table 1.2). In contrast, base 18 gave better induction with simple cyclic and acyclic epoxides than base 17a (Table 1.1). Also, the choice of solvent is critical with lithium amide base reactions; base 17a was more enantioselective in THF while base 18 was more selective in benzene (Table 1.2). Base 17a is monobasic and solvents which can coordinate to the lithium in the transition state are thought to be superior while base 18 has an internal coordination site and solvents which do not coordinate are preferred. To further complicate matters base 18 showed reversal of selectivity when used in benzene rather than THF or ether; this again may be due to coordination of the solvent in the transition state.

The rearrangement of protected cis-4-hydroxycyclopentene oxides and trans-4-hydroxycyclopentene oxides has received considerable attention with the resulting allylic alcohols being used as intermediates for prostaglandins and other cyclopentanoids. In the initial reports 24 was rearranged using base 18 in benzene and give (S)-25 in 90% e.e. or 76% e.e. (the discrepancy in results possibly due to the different techniques used to measure
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the e.e.) (Scheme 1.9). Chiral amines required to prepare bases such as 18 are difficult to synthesise and recently readily available aminoalcohols such as ephedrine, norephedrine and pseudoephedrine have been used. The dilithium salts of (1R,2S) norephedrine (26) effected the rearrangement of epoxide 27 in 86% e.e. (Scheme 1.9).

![Scheme 1.9: Rearrangement of 4-hydroxycyclopentene oxides with amino-alcohol derived bases](image)

The ultimate aim of reagent controlled asymmetric induction is to use the chiral reagent catalytically. Catalytic enantioselective deprotonation of meso-epoxides has recently been achieved using chiral lithium amide base 18 and excess lithium diisopropylamine in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. This catalytic reaction proceeded without significant loss in selectivity or yield (Scheme 1.10, Table 1.3).

![Scheme 1.10: Catalytic enantioselective deprotonation of meso-epoxides](image)
Chapter 1: Introduction

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Catalytic reaction</th>
<th>Stoichiometric reaction&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reaction</td>
<td>% e.e. (% yield) of allylic alcohol</td>
</tr>
<tr>
<td></td>
<td>conditions</td>
<td></td>
</tr>
<tr>
<td>cyclohexene</td>
<td>rt. 12h</td>
<td>75 (71)</td>
</tr>
<tr>
<td>(Z)-4-octene oxide</td>
<td>rt. 3 days</td>
<td>60 (54)</td>
</tr>
<tr>
<td>cyclooctene oxide</td>
<td>rt. 3 days (refl. 7h)</td>
<td>45 (86)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1.5 eq. of chiral lithium amide base, 1.65 eq. DBU

Table 1.3: Catalytic and stoichiometric deprotonation of meso-epoxides with base 18; yields and e.e. of allylic alcohols obtained (refer to scheme 1.10).<sup>25</sup>

Deprotonation of pro-chiral ketones

In this process, one of a pair of enantiotopic protons are removed by the chiral lithium amide base (axial protons are removed in preference to the equatorial protons in cyclohexanone) to give a chiral intermediate enolate that is then reacted further with a suitable electrophile.

The first experiment in this area involved the deprotonation of cis-2,6-dimethylcyclohexanone (29) with lithium amide (30) followed by direct alkylation with allyl bromide to give 31 (Scheme 1.11).<sup>26,27</sup>

![Scheme 1.11: Deprotonation of cis-2,6-dimethylcyclohexanone, using a chiral lithium amide base](image)

The e.e. of 31 was quite low but subsequent changes in method and electrophilic quench led to a marked improvement in the asymmetric induction.

Deprotonation of cis-2,6-dimethylcyclohexanone (29) by the chiral lithium amide bases shown in Scheme 1.12, followed by trapping of the intermediate enolate with acetic anhydride or trimethylsilyl chloride yielded the enol-ethers (32 and 33) in good enantiomeric purity (Table 1.4, entries 1-5, method i, Scheme 1.12).<sup>26,27,31,28</sup> Higher enantiomeric purity was observed when TMSCl was present at the time of deprotonation and the enolate was trapped...
in situ as it formed (Table 1.4, entry 6, method ii, Scheme 1.12). This internal quench method (method ii) was subsequently used for all the studies on cyclohexanones.27,33,35

Scheme 1.12: Enantioselective deprotonation of substituted cyclohexanones

The degree of asymmetric induction produced by the chiral lithium amide base is substrate specific, for example, the camphor derived bases (36) and (37) gave good induction with 2,6-dimethylcyclohexanone (29), but were disappointing with the 4-tert-butylcyclohexanone (34) (Table 1.4, entries 4 and 5 vs entries 8 and 9). Base 17 showed good enantioselectivity with 4-tert-butylcyclohexanone (34) (Table 1.4, entries 11 and 12). This base has been recently crystallised as a bis-THF-solvated cyclic dimer which adopted a conformation that maximised the Me-Li contacts. No obvious explanations for the observed sense of enantioselectivity could be deduced from this arrangement of atoms.29,30
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<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Base</th>
<th>Method/ type of quench</th>
<th>Quenching agent</th>
<th>Temp. (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>e.e.(^1) or S or R</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>30a</td>
<td>i) external</td>
<td>Ac₂O</td>
<td>-78</td>
<td>32</td>
<td>75</td>
<td>29 R</td>
<td>26,27</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>36</td>
<td>i) external</td>
<td>Ac₂O</td>
<td>-78</td>
<td>32</td>
<td>65</td>
<td>65 S</td>
<td>26,27</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>37</td>
<td>i) external</td>
<td>Ac₂O</td>
<td>-78</td>
<td>32</td>
<td>68</td>
<td>74 R</td>
<td>26,27</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>36</td>
<td>i) external</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>33</td>
<td>76</td>
<td>66(^b) S</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>37</td>
<td>i) external</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>33</td>
<td>-</td>
<td>~70(^b) R</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>39</td>
<td>ii) internal</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>33</td>
<td>30</td>
<td>83(^a) S</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>30</td>
<td>ii) internal</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>35</td>
<td>71</td>
<td>51 S</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>36</td>
<td>ii) internal</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>35</td>
<td>80</td>
<td>21 S</td>
<td>27</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>37</td>
<td>ii) internal</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>35</td>
<td>75</td>
<td>31 S</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>17</td>
<td>ii) internal</td>
<td>Me₃SiCl</td>
<td>-78</td>
<td>35</td>
<td>73</td>
<td>70 S</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>34</td>
<td>17</td>
<td>ii) internal</td>
<td>Me₃SiCl</td>
<td>-90</td>
<td>35</td>
<td>66</td>
<td>88 S</td>
<td>27</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>38</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-78</td>
<td>35</td>
<td>86</td>
<td>84 S</td>
<td>32</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>39</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-78</td>
<td>35</td>
<td>87</td>
<td>84 R</td>
<td>33</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>39</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-105</td>
<td>35</td>
<td>51</td>
<td>97 R</td>
<td>33</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>40</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-78</td>
<td>35</td>
<td>67</td>
<td>84 R</td>
<td>33</td>
</tr>
<tr>
<td>16</td>
<td>34</td>
<td>41</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-78</td>
<td>35</td>
<td>93</td>
<td>78 R</td>
<td>34</td>
</tr>
<tr>
<td>17</td>
<td>34</td>
<td>42</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-78</td>
<td>35</td>
<td>74</td>
<td>87 R</td>
<td>34</td>
</tr>
<tr>
<td>18</td>
<td>34</td>
<td>42</td>
<td>ii) internal</td>
<td>Me₃SiCl(^c)</td>
<td>-100</td>
<td>35</td>
<td>88</td>
<td>93 R</td>
<td>34</td>
</tr>
</tbody>
</table>

**Method (i):** Incorporates an external quench. A solution of the ketone was added to the lithiated base in THF (temperature given in Table), stirred 3h; reaction quenched with acetic anhydride or TMSCl

**Method (ii):** Lithiated amine in THF; cooled (temperature given in Table); TMSCl added, followed by a solution of the ketone in THF; reaction quenched with TEA/ NaHCO₃

\(^a\) There is some disagreement about the exact extent of the e.e. determined from optical rotation results.\(^3\)\(^5\)

\(^b\) Silyl-enol ether was reacted directly with mCPBA to give a α-hydroxyketone. The e.e. of the hydroxy ketone was measured and it was assumed that the e.e. of the silyl enol ether was the same.

\(^c\) HMPA added to base before TMSCl

**Table 1.4:** Ketones, bases, reaction conditions and quenches used in enantioselective deprotonation reaction of cyclic ketones; yields and e.e. of the enol-ethers (refer to Scheme 1.12).

Bases 38-42 showed similar enantioselectivity with 2,6-dimethylcyclohexanone (29) and 4-tert-butylcyclohexanone (34) (Table 1.4, entries 12-18, Scheme 1.12).\(^3\)\(^2\).\(^3\)\(^3\) These bases exist in a conformationally restrained, five membered chelate type structure with the bulky alkyl group on the nitrogen trans to the bulky phenyl group on the chiral carbon for steric reasons and the lone pair on the amide nitrogen cis to the phenyl group (confirmed by X-ray crystal structure
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of lithiated base 38 and by $^6$Li and $^{15}$N NMR). It is thought that for deprotonation to occur by synchronous proton and lithium ion transfer the carbonyl group will coordinate to lithium from the same side as the lone pair. (Figure 1.1) The aggregation state of the base in solution was controlled by the addition of an external ligand such as HMPA to satisfy the coordination of lithium. $^6$Li and $^{15}$N NMR studies of the base (38) in THF showed that it was present as a monomer, but in toluene and ether-toluene (4:1) it existed as a dimer. Addition of 2 eq of HMPA caused the base to exist as a chelated monomer in all the solvents used and it was concluded that the monomeric form gave higher enantioselectivity than the dimeric form.

![Figure 1.1 Conformational arrangement of bases 38-42 (see Scheme 1.12)](image)

When these bases had fluorine in the alkyl chain, eg base 42, higher induction was observed than with the corresponding alkyl bases for deprotonation of 4-t-butylcyclohexanone (Table 1.4, entry 16 vs entry 17). An electrostatic interaction between the partial negative charge on the fluorine and a partial positive charge on the lithium which fixes the conformation of the base was suggested as a reason for the greater asymmetric induction; bulkiness of the alkyl chain or fluorine working as an internal ligation site were ruled out.

One notable observation was that the asymmetric induction was much higher when an internal quench (IQ) was used (TMSCl mixed with base before addition of ketone) in place of an external quench (EQ) (ketone deprotonated then enolate quenched with TMSCl). In the internal quench, as the enolate reacts with TMSCl. The LiCl which is produced as the enolate reacts with TMSCl is thought to be incorporated into the mixed aggregate species. If however LiCl is added to the reaction mixture before the external quench, substantial improvements in e.e. are seen. This is illustrated in Table 1.5, where the e.e. on deprotonation of ketones 34, 43 and 44 using an internal quench, external quench and external + LiCl (EQ + LiCl) quench are listed (Scheme 1.13). In these systems, high e.e.
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were obtained from the external quench with 0.1-1.5 eq. LiCl and there was no significant drop when >1 eq. of LiCl was used.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{Li} \\
\text{17a} & \quad \rightarrow \quad \text{silyl enol ether}
\end{align*}
\]

**Scheme 1.13:** Deprotonation of substituted ketones in the presence of LiCl, followed by reaction with TMSCl

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Yields (%) of silyl enol ether</th>
<th>IQ e.e. (%)</th>
<th>EQ e.e. (%)</th>
<th>EQ + LiCl (0.5 eq)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>73-85</td>
<td>69</td>
<td>23</td>
<td>83</td>
<td>36</td>
</tr>
<tr>
<td>43</td>
<td>83-98</td>
<td>70</td>
<td>27</td>
<td>58</td>
<td>38</td>
</tr>
<tr>
<td>44</td>
<td>75-81</td>
<td>82</td>
<td>33</td>
<td>84</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 1.5: Deprotonation of substituted ketones in the presence and absence of LiCl, followed by reaction with TMSCl; yields and e.e. of products given (refer to scheme 1.13).

In another example, when cyclohexanone (45) was deprotonated by base 46, and the enolate was treated with benzyl bromide, much higher induction was achieved in the presence of LiBr (Scheme 1.14).

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{45} & \quad \rightarrow \quad \text{CH}_2\text{Ph} \\
1) & \quad \text{(LiBr), toluene} \\
2) & \quad \text{PhCH}_2\text{Br}, 18h
\end{align*}
\]

*No added LiBr: 58% e.e.
62% yield

*1.1 eq LiBr: 92% e.e.
62% yield

**Scheme 1.14:** Enantioselective deprotonation of cyclohexanone and subsequent benzylation

Lithium amides are known to exist as monomers, dimers, trimers, tetramers or higher order oligomers in solution, and form mixed aggregates with the solvent, additives, the resultant lithium enolate/carbanion and contaminant amine that is freed in deprotonation reactions.\(^{40}\).
The enantioselective deprotonation of a range of protected 4-hydroxycyclohexanones was examined and found to be generally less successful than the enantioselective deprotonation of 4-t-butylcyclohexanone, because alkoxy groups provide much less conformational bias than alkyl groups (Scheme 1.15, Table 1.6). The highest e.e. obtained in the study was 74%, with most in the range 30-50%. Again, the presence of LiCl increased the e.e..

Enantioselective deprotonation using chiral lithium amide bases has been used in synthetic routes aimed at producing natural products or intermediates in the synthesis of biologically active material. (+)-Brasilenol, (5S, 6S)-aeginetolide, (5S)-dihydroactinidiolide, (+)-monomorine cocaine analogues, and precursors to carbacyclin and Corynanthé alkaloids and cis-2,6-disubstituted piperidines prepared using this methodology have been detailed in a review therefore more recent examples of natural products synthesised using chiral lithium amide bases are described here.
Compound 51 which is a known intermediate for C-nucleoside synthesis was prepared in >98% e.e. from 50. The key step involved enantiotopic deprotonation of 49 using base 17a to yield 50 in 85% e.e. (Scheme 1.16).60,61

Scheme 1.16: Enantioselective deprotonation of 49 as the key step in the synthesis of 51

The dipeptide chlorotetaine (52) was also synthesised using enantioselective deprotonation as a key step (Scheme 1.17).62

Scheme 1.17: Important step in the synthesis of 52

The synthesis of unnatural enantiomers of the tropane alkaloids darlingine, chalcostrobamine and isobellendine (54) has been described from the enantioselective deprotonation of tropinone (53); enantioselectivity was increased in the presence of LiCl.63,64 The synthesis of isobellendine (54) is outlined in Scheme 1.18.

Scheme 1.18: Enantioselective deprotonation of tropinone
Chiral, substituted γ-butyrolactones such as 57 were easily accessed by enantioselective deprotonation of cyclobutanone derivatives (55) followed by oxidative bond cleavage of the resulting silyl enol ether (56).65

\[
\begin{align*}
55 & \xrightarrow{\text{Ph, Me, Me, Li } 17b, \text{TESCl, THF, } -100^\circ C} 56 \\
& \xrightarrow{1) O_3, 2) \text{NaBH}_4, 3) 2N \text{HCl}} 57 \quad 92\% \text{ e.e.}, 70\% \text{ yield}
\end{align*}
\]

Scheme 1.19: Enantioselective deprotonation of a cyclobutanone

The lignan lactones (-)-hinokinin, (-)-deoxypodophorhizone, (-)-isohibalactone (58) and (-)-savinin were then synthesised by means of enantioselective deprotonation strategy; the significant step in the synthesis of (-)-isohibalactone (58) is illustrated in Scheme 1.20.66

\[
\begin{align*}
& \xrightarrow{\text{Ph, Me, Me, Li } 17b, \text{THF, } -100^\circ C, \text{Et}_3\text{SiCl}} \xrightarrow{\text{several steps}} 58 \quad 63\% \text{ yield} \\
& \quad \frac{\text{80\% o.p.}}{} \quad \frac{\text{75\% yield.}}{}
\end{align*}
\]

Scheme 1.20: Asymmetric induction in the synthesis of (-)-isohibalactone (58).

Enantioselective deprotonation of 4-phenyl-4-methyl-cyclohexanone (59) led to the construction of a chiral quaternary centre (Scheme 1.21).67

\[
\begin{align*}
& \xrightarrow{\text{Ph, Me, Me, Li } 17b, \text{TMSCl, THF, } -100^\circ C} \xrightarrow{\text{Pd(OAc)}_2, \text{MeCN}} 59 \\
& \quad \frac{\text{oSiMe}_3}{} \xrightarrow{\text{71\% e.e.}} \frac{\text{70\% yield}}{}
\end{align*}
\]

Scheme 1.21: Formation of a chiral quaternary centre, using chiral lithium amide base methodology.
This methodology was used for the synthesis of (+)-α-cuparenone (60) (Scheme 1.22).\textsuperscript{67}

![Scheme 1.22: The key step in the synthesis of (+)-α-cuparenone](image)

**Enantioselective deprotonation of thiane-oxide systems**

Cyclic and acyclic sulphoxides have been enantioselectively deprotonated with chiral lithium amide bases.\textsuperscript{68} When sulphoxide 61 was treated with base 36, then methylated, an optically active sulphoxide 62 was obtained; the base differentiated between the equatorial protons alpha to sulphur. When 61 was reacted with base 36, and then TMSCl was added, 63 was formed in 60% e.e.,\textsuperscript{69,70} but when base 17a was used under the same conditions, racemic 63 was formed. However, when TMSCl was added to the base, before 61 (internal quench), a mixture of (-)-63 (10% yield, 69% e.e.) and (-)-64 (40% yield) was isolated. It was shown that under the internal quench, racemic 63 was formed, but this underwent a kinetic resolution where (+)-63 was converted into (-)-64 via a TMSCl-mediated Pummerer-type reaction (Scheme 1.23).

![Scheme 1.23: Reaction of chiral lithium amide bases with sulphoxides](image)
**Kinetic resolution by chiral lithium amide bases.**

Optically active material has been generated from racemic epoxides\textsuperscript{71} and ketones\textsuperscript{72,73} by treatment with chiral lithium amide bases in kinetic resolution process. In principle, half an equivalent of base is employed in order to convert the more rapidly reacting enantiomer into the product by deprotonation, the slower reacting enantiomer is unchanged. As the base approaches the racemic substrate it experiences two distinct enantiomeric environments and can remove a hydrogen from one of the enantiomers more easily; this leads to kinetic resolution.

When the *cis* disubstituted epoxide 65 was kinetically resolved, the yield and e.e. of the 'products' depended on the ratio of substrate to base used (Scheme 1.24, Table 1.7).\textsuperscript{71}

![Scheme 1.24: Kinetic resolution of epoxide 65](image)

<table>
<thead>
<tr>
<th>ratio of base (18) to epoxide (65)</th>
<th>(-)-65 yield %</th>
<th>e.e. %</th>
<th>(+)-66 yield %</th>
<th>e.e. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:4</td>
<td>31</td>
<td>&gt;95</td>
<td>31</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2:3</td>
<td>37</td>
<td>89</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>1:2</td>
<td>52</td>
<td>62</td>
<td>38</td>
<td>70</td>
</tr>
<tr>
<td>1:3</td>
<td>67</td>
<td>30</td>
<td>21</td>
<td>72</td>
</tr>
</tbody>
</table>

*Table 1.7: Kinetic resolution of 65 (refer to scheme 1.24)*\textsuperscript{71}
Substituted cyclohexanones such as 67 were also found to undergo kinetic resolution (Scheme 1.25).[^1]  

![Scheme 1.25: Kinetic resolution of racemic cyclohexanone 67](image)

The kinetic resolution of a chiral imidazolidinone (68) and a β-lactam (70) using the chiral lithium amide base method have also been examined. Treatment of imidazolidinone 68 with base 17a resulted in removal of the hydrogen anti to the t-butyl substituent. The level of conversion to the product (69) and e.e. of the unreacted substrate were controlled by the amount of base used (Scheme 1.26). A selectivity factor of about 4:1 was obtained (Table 1.8).

![Scheme 1.26: Kinetic resolution of a racemic imidazolidinone](image)

<table>
<thead>
<tr>
<th>Conversion to 69 (%)</th>
<th>14</th>
<th>25</th>
<th>44</th>
<th>56</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>o.p. (%) of recovered (R)-68</td>
<td>9</td>
<td>28</td>
<td>45</td>
<td>53</td>
<td>80</td>
</tr>
</tbody>
</table>

**Table 1.8: Kinetic resolution of 68, % conversion to 69 and % o.p. of unreacted 68 (refer to Scheme 1.26)**
When the racemic β-lactam 70 was subjected to such a kinetic resolution, a selectivity factor of about 7:1 was achieved (Scheme 1.27, Table 1.9).75

\[
\begin{align*}
\text{racemic 70} & \quad \text{Me} \quad \text{Me} \\
& \quad \text{Me}_3\text{SiCl} \\
& \quad \text{Et}_3\text{SiCl} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{SPh} & \quad \text{O} \\
\text{NTBS} & \quad \text{Me}_3\text{Si} \\
\end{align*}
\]

\[
\begin{align*}
\text{(3R,4S)-71} & \quad \text{(R)-70} \\
\text{(major enantiomer)} & \quad \text{(major enantiomer)} \\
\end{align*}
\]

**Scheme 1.27:** Kinetic resolution of a racemic β-lactam

<table>
<thead>
<tr>
<th>Conversion to 71 (%)</th>
<th>19</th>
<th>36</th>
<th>45</th>
<th>52</th>
<th>57</th>
<th>59</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.e. 71 (%)</td>
<td>72</td>
<td>64</td>
<td>61</td>
<td>55</td>
<td>50</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>e.e. 70 (%)</td>
<td>16</td>
<td>36</td>
<td>51</td>
<td>68</td>
<td>70</td>
<td>69</td>
<td>88</td>
</tr>
</tbody>
</table>

**Table 1.9:** Kinetic resolution of 70: % conversion to 71, and e.e. of 71 and unreacted 70 (refer to Scheme 1.27)

**Enantioselective Dehydrohalogenation**

Chiral lithium amide bases have been used for the deracemisation of 4-substituted cyclohexylidene acetic acid (72) via the hydrohalogenated intermediate (73) (Scheme 1.28, Table 1.20).76

\[
\begin{align*}
\text{R}_1 & \quad \text{HCl} \\
\text{CO}_2\text{H} & \quad \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{Ph} \quad \text{Li} \\
\text{CO}_2\text{H} & \quad \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{Ph} \quad \text{N} \quad \text{R}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{2.5 eq. THF, -72°C} & \quad \text{2.5 eq. THF, -72°C} \\
\text{73} & \quad \text{74} \\
\end{align*}
\]

**Scheme 1.28:** Enantioselective dehydrohalogenation of 73
Table 1.20: Yields and optical purities of 74 obtained by enantioselective
dehydrohalogenation of 73 (refer to Scheme 1.28)\textsuperscript{76}

<table>
<thead>
<tr>
<th>R\textsubscript{1} (cis:trans)</th>
<th>R\textsubscript{2}</th>
<th>o.p. of 74</th>
<th>( \alpha S ) or ( R )</th>
<th>Yield of 74 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me (100:0)</td>
<td>( \text{tBu} )</td>
<td>52</td>
<td>( S )</td>
<td>73</td>
</tr>
<tr>
<td>Me (46:54)</td>
<td>( \text{tBu} )</td>
<td>14</td>
<td>( R )</td>
<td>64</td>
</tr>
<tr>
<td>Me (100:0)</td>
<td>1-adamantyl</td>
<td>80</td>
<td>( S )</td>
<td>75</td>
</tr>
<tr>
<td>tBu (100:0)</td>
<td>( \text{tBu} )</td>
<td>54</td>
<td>( S )</td>
<td>88</td>
</tr>
<tr>
<td>tBu (100:0)</td>
<td>1-adamantyl</td>
<td>82</td>
<td>( S )</td>
<td>84</td>
</tr>
</tbody>
</table>

The intermediate 73 can exist as the \textit{cis} and \textit{trans} isomers and it was discovered that the
chiral base selected the same enantiotopic hydrogen in each isomer, thus leading to opposite
configurations; this demonstrated that the dehydrohalogenation step was under kinetic control
(thermodynamic control would lead to the same configuration).\textsuperscript{77} Two or more equivalents of
base were required to give the product so dehydrohalogenation occurred on the carboxylate
salt co-ordinated to the free amine and/or the lithium amide. Duhamel has proposed a
transition state to account for these findings\textsuperscript{78} and has recently used other metal bases for the
same reaction.\textsuperscript{79,80}

**[2,3]-Wittig rearrangement**

The Wittig rearrangement of large ring allylic propargylic ethers initiated by a chiral lithium
amide base has been extensively studied. For example, the Wittig rearrangement of the 13
membered ring (75) proceeded rapidly to give 76 in 82\% yield and 70 \% e.e.\textsuperscript{81}

\[
\begin{array}{c}
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{N} \quad \text{Ph} \\
\text{Li}
\end{array}
\]

\[
\text{THF, -70 to -15°C, 45 min.}
\]

\[
\begin{array}{c}
75 \\
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{N} \quad \text{Ph} \\
\text{Li}
\end{array}
\]

\[
\text{76 (+)-aristolactone}
\]

Scheme 1.29: The Wittig rearrangement of the 13-membered ring allylic propargylic ether,
initiated by a chiral lithium amide base.

The 13 membered ring is flexible enough to allow the reacting centres to come together
whilst still being able to constrain the \textit{relsi} orientation of the carbanion with the allylic double
bond. The 17 membered homologue gave the corresponding propargylic alcohol in only 30\%
e.e. and it is thought that the larger rings are too flexible to constrain the orientation in this way.\textsuperscript{82} The acyclic propargylic ether 77 underwent chiral base initiated [2,3]-rearrangement to the allenyl alcohol 78 in 33% e.e. (Scheme 1.30).\textsuperscript{83}

\begin{center}
\textbf{Scheme 1.30:} The Wittig rearrangement of the acyclic allylic propargylic ether, initiated by a chiral lithium amide base
\end{center}

\textbf{Planar chiral tricarbonylchromium complexes}
Chiral lithium amide bases have been used to differentiate between enantiotopic hydrogens in prochiral (arene)\textit{Cr(CO)}\textsubscript{3} complexes such as 79.\textsuperscript{84,85}

\begin{center}
\textbf{Scheme 1.31:} Enantiotopic deprotonation of a prochiral (arene)\textit{Cr(CO)}\textsubscript{3} complex
\end{center}

Two groups independently achieved similar results where 80 was produced in 48% yield, (81\% e.e.)\textsuperscript{84} and 36\% yield, (84\% e.e.)\textsuperscript{85}, with 81 as the other product (Scheme 1.31).

\textbf{Regioselective deprotonation of optically active 3-keto steroids}
Regioselective deprotonation does not fit into the category of enantiotopic deprotonations, because the base is not used to distinguish between enantiotopic protons. However, it has been included in this review to demonstrate how chiral lithium amide bases have been used to bring about regioselective enolisation of steroidal ketones. Regioselectivity of enolisation of 82 was increased or reversed from that seen with achiral bases by changing the configuration of the chiral lithium amide base used (Scheme 1.32, Table 2.1).\textsuperscript{86,87}
Scheme 1.32: Regioselective deprotonation of a steroidal ketone by deprotonation with chiral lithium amide bases

<table>
<thead>
<tr>
<th>Conditions/ base</th>
<th>Yield %</th>
<th>Ratio 83:84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermodynamic/ HN(TMS),</td>
<td>88</td>
<td>20:80</td>
</tr>
<tr>
<td>Kinetic/ LDA</td>
<td>96</td>
<td>27:73</td>
</tr>
<tr>
<td>Kinetic (R-39)</td>
<td>92</td>
<td>89:11</td>
</tr>
<tr>
<td>Kinetic (S-39)</td>
<td>95</td>
<td>&lt;2:98</td>
</tr>
</tbody>
</table>

Table 2.1: Yields and ratio of products obtained by the enolisation of 82 with different bases (refer to Scheme 1.32).

1.2.2 NON-COVALENTLY BONDED AUXILLARIES

In this type of reaction the chiral lithium amide base initially deprotonates the substrate to give a prochiral enolate anion and a loosely bound enolate-amine complex is formed. The reaction of this anion is then influenced by the chirality of the complex since the asymmetric induction is generated in the subsequent electrophilic quench, rather than in the initial deprotonation reaction. Reactions involving an achiral lithiated base followed by the addition of a chiral ligand are outside the scope of this introduction.
Enantioselective protonation

Enantioselective protonation\(^9\) may be illustrated by the reaction of \(85\) with a 6 fold excess of base \(17b\), and subsequent protonation of the enolate-amide complex with water, to yield the optically active ketone (Scheme 1.31).\(^8\)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{N} \\
\text{Li} & \quad 17b \\
\end{align*}
\]

\[
\text{THF/n-hexane 6:1}
\]

\[
\begin{align*}
\text{1) 6 eq.} & \quad \text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{N} \\
\text{Li} & \quad 17b \\
\end{align*}
\]

\[
\text{2) H}_2\text{O}
\]

\[
\begin{align*}
\text{racemic 85} & \quad \text{O} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{85} & \quad 48\% \text{ e.e.}
\end{align*}
\]

Scheme 1.33: Deprotonation of \(85\), followed by enantioselective protonation

Enantioselective alkylation

Low e.e's were obtained (< 31% e.e.) when \(86\) was deprotonated by a range of chiral lithium amides and then methylated and derivatised to give (S)-N-acetyl-\(\alpha\)-methylphenylalanine (87) (Scheme 1.34).\(^9\)

\[
\begin{align*}
\text{Ph-CH=N} & \quad \text{CO}_2\text{CH}_3 \\
\text{86} & \quad \text{1)} & \quad \text{Li} \\
\text{-78°C} & \quad \text{88} \\
\text{2)} & \quad \text{MeI} & \quad \text{3)} & \quad \text{OH}^- & \quad \text{4)} & \quad \text{acetylation}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CH}_2\text{Ph} \\
\text{HN} & \quad \text{CO}_2\text{CH}_3 \\
\text{87} & \quad \text{COMe}
\end{align*}
\]

Scheme 1.34: Synthesis of derivatised optically active amino-acids

Enantioselective carboxylation

Complete enolisation of \(89\) occurred at 0°C when it was treated with base \(17b\). Addition of \(\text{CO}_2\) to the frozen enolate (90) at -196°C, followed by methylation gave ester 91 (Scheme 1.35). The asymmetric induction observed for this reaction has been attributed to a complex between the enolate, the lithium amide, the corresponding amine and \(\text{CO}_2\), because the enolate was prochiral and two equivalents of base were required to achieve this induction.
Scheme 1.35: Enantioselective carboxylation of 89

Two equivalents of chiral lithium amide base were required to give good asymmetric induction when \(N\)-benzylidene benzylamine (92) was deprotonated by a chiral lithium amide and the resultingazaallyllithium anion was reacted with a carboxylating agent. This again was taken as an indication that both the secondary amine liberated after deprotonation and the excess lithium amide participated in an aggregated transition state.92

Scheme 1.36: Enantioselective carboxylation of 92.

Aldol-type reactions
Enantioselective aldol-type reactions of achiral enolates in the presence of chiral lithium amides have been widely examined.93,94,95,96,97,98,99 The enantioselective aldol reaction of 2,2-dimethyl-3-pentanone (93) with benzaldehyde using several chiral lithium amide bases has been chosen to illustrate the principles of this reaction (Scheme 1.37, Table 1.22).94,95,96
Scheme 1.37: Enantioselective aldol reaction of 2,2-dimethyl-3-pentanone and an aldehyde using several chiral lithium amide bases

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>Yield</th>
<th>% e.e.</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(CH₃)₂</td>
<td>CH(CH₃)₂</td>
<td>H</td>
<td>OMe</td>
<td>92</td>
<td>68</td>
<td>SS</td>
</tr>
<tr>
<td>CH(CH₃)₂</td>
<td>H</td>
<td>Ph</td>
<td>OMe</td>
<td>92</td>
<td>68</td>
<td>RR</td>
</tr>
<tr>
<td>PhCH₂</td>
<td>CH(CH₃)₂</td>
<td>H</td>
<td>OMe</td>
<td>80</td>
<td>66</td>
<td>RR</td>
</tr>
</tbody>
</table>

Table 1.22: Yields, e.e. and configurations of the aldol products, from 93 and PhCHO (refer to scheme 1.37).

The structure of the base was important to the degree of induction obtained; it was found that the best induction was observed when R¹ = iPr, R² = H or R¹ = H, R² = Ph and the R group was bulky. Solvent was found to play a part in these reactions; the enantioselectivity was reversed in ether/HMPA compared to THF, although the erythro diastereomer still predominated. Similar enantiomeric excesses were obtained using three different experimental methods:
i) the ketone was treated with a mixture of one equivalent of LDA and one equivalent of chiral lithium amide base;
ii) the ketone was treated with two equivalents of chiral lithium amide base;
iii) the ketone was treated with one equivalent of the chiral lithium amide base and then one equivalent of BuLi was added to the mixture.

From this it was deduced that a complex is formed between the chiral lithium amide and the enolate which directs the stereochemistry of the subsequent reaction with benzaldehyde, and that the amine released on formation of the enolate does not play a part in chiral recognition. In a separate study, addition of cyclic lithium enolates to benzaldehyde gave the highest selectivities when the reaction was carried out in the presence of three equivalents of chiral lithium amide, and one further equivalent of base to make the enolate; this indicated the participation of tetrameric aggregates as the reactive species.
1.3 INTRODUCTION TO CONJUGATE ADDITION

The addition of a nucleophile to the β position of an α,β-unsaturated substrate of the form \( \text{C} = \text{C} - \text{Z} \) where \( \text{Z} = \text{CHO}, \text{COR}, \text{CO}_2 \text{R}, \text{CONR}_2, \text{CN}, \text{NO}_2, \text{SOR}, \text{SO}_2 \text{R} \) etc. is known as Michael addition when carbanionic reagents are used; the name is now applied to such processes regardless of the nature of the nucleophile. It is one of the most useful bond forming processes.\(^{100}\) This process is shown schematically for α,β-unsaturated ketones (\( \text{Nu}^- = \) nucleophile, \( \text{E}^+ = \) electrophile) (Scheme 1.38).

![Scheme 1.38: Generalised Michael addition](image)

In a typical conjugate acceptor, the electron deficiency is greater at the C=O carbon than at the β carbon. However, frontier molecular orbital (FMO) analysis shows that the coefficient of the LUMO is larger at the β position, therefore, soft nucleophiles eg. enolates, stabilised carbanions, copper based reagents, enamines, and heteronucleophiles add to the β carbon.\(^{101}\)

Addition of \( \text{Nu}^- \) to the β-position converts the sp\(^2\) carbon to an sp\(^3\) carbon. When \( \text{Nu}^- \cong \text{R}^1 \cong \text{R}^2 \) a chiral centre is created and this transformation may be carried out stereoselectively. Asymmetric conjugate addition can be achieved in three ways:

i) Reaction of an achiral reagent with a α,β-unsaturated substrate which contains a chiral centre.

ii) Reaction of an achiral substrate with a complex reagent containing a non-transferable chiral ligand and a transferable achiral ligand.

iii) Reaction of an achiral substrate with a chiral nucleophile.
1.3.1 METHODS FOR ASYMMETRIC CONJUGATE ADDITION

Reaction of an achiral reagent with a chiral $\alpha,\beta$-unsaturated substrate (i)

The asymmetric centre in the $\alpha,\beta$-unsaturated substrate directs the achiral nucleophile to one face; normally through steric hinderance of one face\textsuperscript{102} or via chelation\textsuperscript{103}. For example $\alpha,\beta$-unsaturated acids have been reacted with several chiral alcohols and amines (chiral auxiliaries) and the chirality in the resultant ester or amide moiety has been used to direct the attack of achiral organometallic reagents.\textsuperscript{104} The chiral alcohols used include 8-phenylmenthol, 1,1'-binaphthol\textsuperscript{105} and camphor derived alcohols\textsuperscript{106} and the chiral amines used include ephedrine\textsuperscript{107}, norephedrine\textsuperscript{108}, proline\textsuperscript{109} and camphor derived sultams.\textsuperscript{110} Organocopper, Grignard reagents and organolithiums are the most common sources of nucleophiles.\textsuperscript{104} This may be illustrated by the reaction of EtMgBr with $\alpha,\beta$-unsaturated amide (94) derived from $l$-ephedrine to yield the optically active $\alpha$-substituted carboxylic acid 95 (Scheme 1.39).\textsuperscript{107}

Initial deprotonation of the alcohol by the Grignard reagent forms an intermediate chelating magnesium complex which is believed to direct the approach of the subsequent Grignard reagent to the relatively unencumbered side of the complex.

\[ \text{Scheme 1.39: Stereocontrolled addition of EtMgBr to a chiral } \alpha,\beta\text{-unsaturated amide} \]

Reaction of an achiral substrate with a complex reagent containing a non-transferable chiral ligand and a transferable achiral ligand (ii)

Method (ii) involves the reaction of an achiral $\alpha,\beta$-unsaturated substrate with a complex organometallic reagent that contains a non-transferable chiral ligand which distinguishes between the two enantiomeric faces of the double bond (the two transition states are diastereomeric and are therefore of different energy) and directs attack of the transferable achiral ligand during the reaction. The most developed chiral reagents are the lithium organocuprates [R(Z*)CuM] with M = metal, often Li; R = alkyl or phenyl and Z* as a chiral alkoxide or amido ligand\textsuperscript{111} which may contain more than one chelating group.\textsuperscript{104,112} For example, (\textit{R})-muscone (98) was prepared in 89% e.e. by treatment of 96 with a complex organo-copper reagent made from MeLi, CuI and aminoalcohol (97) (Scheme 1.40).\textsuperscript{113}
Reaction of an achiral substrate with a chiral nucleophile (iii)
In this procedure, an achiral $\alpha,\beta$-unsaturated substrate is treated with a chiral nucleophile; the resultant transition states are diastereomeric so attack of one face of the C=C bond by the nucleophile is favoured. There are many examples of the asymmetric addition of chiral nucleophiles such as chiral enamines$^{114}$, imines$^{115}$ and sulphoxides$^{116}$ to achiral $\alpha,\beta$-unsaturated substrates in the literature.$^{112}$ This method may be illustrated by the addition of a chiral $\alpha$-lithiated sulphoxide (99) to cyclopentenone (100) with good asymmetric induction (Scheme 1.41).$^{117}$

Scheme 1.40: Preparation of 98 via a Michael addition with a chiral reagent

Scheme 1.41: Face selective addition of a chiral nucleophile (99) to an $\alpha,\beta$-unsaturated substrate (100)
Chapter 1: Introduction

1.3.2 Conjugate addition of chiral amines and lithium amides to achiral α,β-unsaturated substrates

Introduction

The formation of a C-N bond may be achieved by the addition of an amine\textsuperscript{118,119,120,121,122} or metal amide\textsuperscript{123,124,125,126} to an α,β-unsaturated compound.\textsuperscript{127} An amine is a 'soft' nucleophile and will attack an α,β-unsaturated substrate, for example an α,β-unsaturated ester, at the β-position. In contrast, treatment of an α,β-unsaturated ester with a metal amide derived from a secondary amine can give a mixture of products due to conjugate addition, deprotonation at the γ-position and attack at the C=O function leading to carboxamide formation. Recently, amides such as lithium N-benzyl-N-(trimethylsilyl)amide have been found to give exclusive 1,4-conjugate addition,\textsuperscript{124,125,126}

Addition of chiral amines to conjugate acceptors

The addition of amines to α,β-unsaturated compounds is difficult to achieve and poor yields are encountered unless forcing conditions such as high pressure are used.\textsuperscript{121} When the amine is chiral, the absolute stereochemistry of the newly created chiral centre at the β position, can, in principle, be controlled.\textsuperscript{118,128,129} The addition of (R) or (S)-1-phenylethylamine to methyl crotonate (101) has been investigated by several groups (Scheme 1.42).\textsuperscript{118,130,131,132} The results are difficult to interpret because in some cases the d.e. is given for the addition product (102) and in other cases, for the β-aminocarboxylic acid (103).

Scheme 1.42: Face selective addition of (R) or (S)-1-phenylethylamine to 101
Table 1.23: Yields and d.e. of 102 and 103 under different reaction conditions (refer to Scheme 1.42).\textsuperscript{132}

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield % [d.e. (configuration of major diastereomer)]</th>
<th>Yield % [o.p. (configuration of major enantiomer)]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>methanol, reflux, 4d, reagents heated together 80-90°C, 10h</td>
<td>74% [22% d.e. (R,S)]</td>
<td>not reported</td>
<td>130, 131</td>
</tr>
<tr>
<td>ethanol, reflux</td>
<td>35% [&lt;4% d.e. (R,S)]</td>
<td>not synthesised</td>
<td>132</td>
</tr>
</tbody>
</table>

Low face selectivity has also been observed for the addition of (R) or (S)-1-phenylethylamine to crotonitrile (8-10\% o.p.), ethyl cinnamate (17-19\% o.p.), and methacrylonitrile (11-12\% o.p.).\textsuperscript{118} In contrast, addition of the related hydroxylamines (R) or (S)-1-phenylethyl hydroxylamine to various α,β-unsaturated esters resulted in the formation of lactones (formed by initial conjugate addition followed by lactonization) in high yield and much higher d.e.\textsuperscript{133}

Scheme 1.43: Addition of (R)-1-phenylethyl hydroxylamine to various α,β-unsaturated esters.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield %</th>
<th>ratio lactones [(R,R):(R,S)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>91</td>
<td>80:20</td>
</tr>
<tr>
<td>n-Pr</td>
<td>80</td>
<td>82:18</td>
</tr>
<tr>
<td>i-Pr</td>
<td>74</td>
<td>80:20</td>
</tr>
</tbody>
</table>

Table 1.12: Ratio of lactones formed by reaction of α,β-unsaturated esters with (R)-1-phenylethyl hydroxylamine (refer to Scheme 1.43)
Hawkins,\textsuperscript{134} has shown that treatment of a large excess of methyl crotonate with $\pm$-3,5-dihydro-$4H$-dinaphth[2,1-$c'$:1',2'-$e$]azepine (104) at reflux yielded the amine ester 105 as a mixture of diastereomers (scheme 1.44). The ratio of diastereomers (105a:105b) was initially 4:1 which decreased to 1:1 with time (250 h). This behaviour was consistent with an initial kinetically controlled addition, followed by equilibration to the thermodynamic mixture of products.\textsuperscript{134}

\begin{center}
\begin{tikzpicture}[scale=0.8]

\node (a) at (0,0) {104};
\node (b) at (3,0) {105a};
\node (c) at (6,0) {105b};
\node (d) at (0,-2) {101};
\node (e) at (0,-4) {THF};

\draw[->] (a) -- (b);
\draw[->] (a) -- (c);
\draw[->] (a) -- (d);
\draw[->] (d) -- (e);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.44: Addition of 104 to 101}

\textbf{Addition of chiral lithium amides}

Chiral lithium amides have been shown to differentiate between two faces of an $\alpha,\beta$-unsaturated substrate in asymmetric Michael additions.\textsuperscript{134,132} Higher yields and d.e.'s are obtained, than with the corresponding amines.

Treatment of methyl crotonate with the (S)-lithium amide (106) in THF at $-78^\circ$C was found to yield the amino-esters (105a:105b) as a 1:61 mixture of diastereomers (Scheme 1.45).\textsuperscript{134}

\begin{center}
\begin{tikzpicture}[scale=0.8]

\node (a) at (0,0) {(S)-106};
\node (b) at (3,0) {105a};
\node (c) at (6,0) {105b};
\node (d) at (0,-2) {101};
\node (e) at (0,-4) {THF};

\draw[->] (a) -- (b);
\draw[->] (a) -- (c);
\draw[->] (a) -- (d);
\draw[->] (d) -- (e);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.45: Addition of 106 to 101}

Significantly, the face selectivity of the amine reaction and that of the lithium amide reaction were opposite. Force-field modelling of the two reactions gave rise to a model that rationalises these experimental results.\textsuperscript{135} It was also shown that when racemic 106 was used,
a 1:94 mixture of diastereomers (105a:105b) was formed; this high diastereoselectivity with both racemic and optically pure lithium amide is consistent with the chirality of the incoming nucleophile controlling the diastereoselectivity rather than it being due to aggregated molecules of chiral lithium amide.

Table 1.25 shows some results in a study of the formation of diastereomers of 107 in which steric effects are seen when the OR' group is increased in size, but not when the R substituent is altered (Scheme 1.46). The one (Z)-ester examined showed the same face selectivity (and therefore reverse diastereoselectivity) (Table 1.25, entry 2). This reversed diastereoselectivity is consistent with a closed cyclic transition state where the chiral lithium amide determines the facial approach and opposite placements of R and H give opposite diastereomers.136

![Scheme 1.46: Addition of 106 to various α,β-unsaturated esters](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>107a:107b (Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(E)-Hept</td>
<td>tBu</td>
<td>1:53 (80)</td>
</tr>
<tr>
<td>2</td>
<td>(Z)-Hept</td>
<td>tBu</td>
<td>8:1 (39)</td>
</tr>
<tr>
<td>3</td>
<td>(E)-Hept</td>
<td>Me</td>
<td>1:22 (32)</td>
</tr>
<tr>
<td>4</td>
<td>(E)-iPr</td>
<td>tBu</td>
<td>1:34 (69)</td>
</tr>
<tr>
<td>5</td>
<td>(E)-iBu</td>
<td>tBu</td>
<td>1:69 (74)</td>
</tr>
</tbody>
</table>

Table 1.25: Ratio of diastereomers 107a:107b produced by reaction of (S)-106 with a range of α,β-unsaturated esters (refer to Scheme 1.46).136

Davies has investigated the Michael addition of three chiral lithium amides to a series of crotonate esters and obtained high d.e. (95-99%) of 109 in each case.132 Hydrogenolysis of the benzylic groups followed by hydrolysis of the ester groups gave the β-amino-acid (103) in high enantiomeric purity. The absolute configuration of 103 was assigned by comparison of
the optical data with that from an authentic sample and so the face selectivity of the lithium amides 30a, 108 and 17a on the crotonate esters was known (pro-\(R\) face).

\[
\begin{align*}
\text{crotonate esters} & \overset{\text{Base}}{\underset{\text{THF, -78°C}}{\longrightarrow}} \text{Me} \quad & \overset{\text{1) Pd/C/H}_2, \text{acetic acid}}{\underset{\text{2) HCl}}{\longrightarrow}} \text{NH}_3^+ \\
(R,R)-109 & & (R)-103
\end{align*}
\]

Bases:

\[
\begin{align*}
30a & : \text{Me} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{Li} \\
108 & : \text{Me} \quad \text{Me} \quad \text{Ph} \quad \text{N} \quad \text{Li} \\
17a & : \text{Ph} \quad \text{N} \quad \text{Li}
\end{align*}
\]

**Scheme 1.47:** Addition of a range of lithium amides to crotonate esters

<table>
<thead>
<tr>
<th>(R^1)</th>
<th>Base 30a</th>
<th>Base 108</th>
<th>Base 17a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% e.e. (% yield)</td>
<td>% e.e. (% yield)</td>
<td>% e.e. (% yield)</td>
</tr>
<tr>
<td>Me</td>
<td>95 (85)</td>
<td>95 (68)</td>
<td>99 (57)</td>
</tr>
<tr>
<td>(\text{CH}_2\text{Ph})</td>
<td>95 (88)</td>
<td>96 (74)</td>
<td>98 (23)</td>
</tr>
<tr>
<td>(t\text{Bu})</td>
<td>99 (82)</td>
<td>99 (83)</td>
<td>99 (27)</td>
</tr>
</tbody>
</table>

Table 1.26: Table showing the chiral lithium amide base used, and the yield and e.e. of the addition product 109 (refer to Scheme 1.47).\(^{132}\)

1.4 **AIMS AND OBJECTIVES OF THE WORK INCLUDED IN THIS THESIS**

The first objective was to investigate both the deprotonation of cyclic sulphones with achiral lithium amide bases and the reaction of the resultant carbanions with electrophilic reagents. Subsequently, chiral lithium amides were to be used as enantioselective bases in these reactions; this was expected to lead to enantiomerically enriched 2-substituted sulphones.

The second objective was to use chiral lithium amides as nucleophiles in the Michael addition to a number of conjugate acceptors and to examine the diastereoselectivity of both the addition reaction and the subsequent electrophilic quenches.
CHAPTER 2

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Chiral lithium amide bases were required as i) enantioselective deprotonating agents for the enantiotopic deprotonation of cyclic sulphones and ii) nucleophiles for asymmetric Michael addition to conjugate acceptors.

The syntheses of selected chiral secondary amines are described in this chapter. These secondary amines were prepared by condensation of an aldehyde or ketone with a chiral primary amine, then reduction of the resultant imine to a secondary amine. The stereochemistry of some of these reductions has been examined in detail.

When compounds are synthesised from an (R)-amine, they are denoted as (a), and when synthesised from an (S)-amine they are denoted as (b). If a compound is synthesised from a racemic amine, (a/b) is used.

2.1 N-BENZYL-1-PHENYLETHYLAMINE

Lithium (R) and (S)-N-benzyl-1-phenylethylamine (30a and 30b) have been successfully used as an enantiotopic deprotonating agents. The literature method for the synthesis of (R)-N-benzyl-1-phenylethylamine (110a) involved treatment of (R)-1-phenylethylamine and benzaldehyde in methanol (pH 6-7) with sodium cyanoborohydride. Seebach has recently expressed concern about this procedure because of the careful control of the pH needed to prevent extensive racemisation and described an alternative preparation of 110a where (R)-1-phenylethylamine and benzyl bromide were heated in DMPU for 1.5 h at 100°C in the presence of 2 equivalents of sodium carbonate, from which 110a was obtained in 95% yield after flash chromatography.

A simpler method in which (R) or (S)-1-phenylethylamine and benzaldehyde were mixed together and then treated with sodium borohydride in methanol to give 110a or 110b in 92-94% yield and > 99% o.p. was developed (Scheme 2.1).

\[ \text{PhCHO} \rightarrow \text{PhNMe} \]

\[ \text{NaBH}_4 \rightarrow \text{PhNMe} \]

\[ (R)-1\text{-phenylethylamine} \quad (R) \quad 110a \quad 92\% \text{ yield} \quad [\alpha]_D^{\circ}+53.9 \ (c \ 9.9, \text{ ethanol}) \]

\[ (S)-1\text{-phenylethylamine} \quad (S) \quad 110b \quad 94\% \text{ yield} \quad [\alpha]_D^{\circ}-54.2 \ (c \ 8.1, \text{ ethanol}) \]

**Scheme 2.1: Preparation of 110a and 110b**
2.2 BIS [(R)-N-(1-PHENYLETHYL)]AMINE

Acetophenone and (R)-1-phenylethylamine were condensed together under Dean and Stark conditions with camphor sulphonic acid as the catalyst (Scheme 2.2) to give (R)-N-(1-phenylethyl)-α-methylbenzylamine (112a). In the original method, the materials were refluxed in benzene for 48h. Toluene was used in place of benzene but side products were produced when the reaction time was 48h; no side products were formed when the reaction time was shortened to 16h. A mixture of the E and Z imines of 111a were formed in the ratio 6:1; a doublet due to the Me group was observed at δ 1.53 (E-isomer) and δ 1.30 (Z-isomer).

\[
\begin{align*}
\text{(R)-1-phenylethylamine} & \quad \text{111a (R)} & \quad 83\% \text{ yield} \\
\text{(S)-1-phenylethylamine} & \quad \text{111b (S)} & \quad 86\% \text{ yield}
\end{align*}
\]

Scheme 2.2: Preparation of 112a and 112b

Imine 111a was dissolved in THF and stirred at room temperature for 4 h with 5% Pd/C (5% by weight) (Scheme 2.2). A mixture of diastereomers ca 9:1 was found, the ratio being determined from comparison of the integrals of the 1H NMR signals due to the Me groups at δ 1.26 (major): δ 1.34 (minor). The major diastereomer of 111a had the (R,R)- configuration, the minor diastereomer had the (S,R)- configuration (meso isomer) and they were readily separated by fractional recrystallisation of the hydrochlorides from water.

Imine 111b and amine 112b were prepared similarly. A mechanism explaining the stereochemistry of reduction has been proposed for this system by Harada et al. (Figure 2.1)
Anti-imine is favoured over the syn imine for steric reasons.

Most favourable conformations of anti and syn 111 occurred with the hydrogen that is attached to the chiral carbon atom of the α-methylbenzyl moiety, in the plane of the Ph-C=N moiety.

The diastereoselectivity can then be explained by hydrogenation occurring from the less hindered side, that is, from the side of the methyl groups.

The major diastereomer has the (R,R)-configuration (112a) and the minor diastereomer has the (S,R)-configuration (meso isomer).

Figure 2.1: Harada's mechanism of the stereochemistry of reduction

2.3 SECONDARY AMINES DERIVED FROM CAMPHOR
Chiral lithium amide 36a, derived from the (R)-(+)camphor-amine 119a has been shown to be a good enantiotopic deprotonating agent for cyclic ketones and sulphoxides.26,27,29,31,69,70

2.3.1 THE SYNTHESIS OF 'CAMPHOR IMINES'
Condensation of a ketone with a primary amine to give an imine is brought about using TiCl₄, BF₃.etherate, camphor sulphonic acid and molecular sieves etc.140 In the case of hindered imines, such as those derived from camphor, this condensation is difficult to achieve and a number of different routes to the 'camphor imine' have been developed. Conversion of camphor into its thione before reaction with an amine141,142 is one method that has been used. For example, thiocamphor was found to react very quickly with primary benzylic amines when heated at 170°C for 1-5 min. or refluxed in xylene for 15 minutes; unfortunately these conditions failed for primary aromatic amines and secondary benzylic amines.141 The sulphine, obtained by oxidation of thiocamphor, has also been reacted with primary aliphatic amines at room temperature without a catalyst to give the corresponding imines in high yield with the elimination of [HSOH].143
The preparation of \( N\)-(1-phenylethyl)bornanimine (113a/b) was originally attempted using a procedure described by Simpkins et al.\(^2\)\(^7\). \((R)\)-(+)\)-Camphor and racemic 1-phenylethylamine were heated together at 120 °C for 5 days in the presence of a catalytic amount of \( p\)-toluene sulphonnic acid and 4Å molecular sieves. Several products were obtained including the imine (20% yield compared to 45% quoted in the reference\(^2\)\(^7\)).

The reaction of \((\pm)\)-1-phenylethylamine and \((R)\)-(+)\)-camphor under Dean and Stark conditions using i) benzene or ii) toluene as the solvent and a) \( \text{ZnCl}_2 \), b) 4Å molecular sieves, c) camphor sulphonic acid or d) \( \text{BF}_3\).etherate as catalyst, and with reaction times ranging from 12 h - 5 days, failed to yield the imine.

However, when \((R)\)-(+)\)-camphor and \((R)\)-1-phenylethylamine were refluxed for 48 h in xylene under Dean and Stark conditions in the presence of 10 mol% \( \text{ZnCl}_2 \) as a Lewis acid catalyst, the corresponding imine (113a) was formed in 77% yield (Scheme 2.3). This reaction was clean, and only a small amount of unreacted amine remained at the end of the reaction (the corresponding amount of \((R)\)-(+)\)-camphor had sublimed out of the reaction flask).

\[
\begin{align*}
\text{(R)-1-phenylethylamine} & + \quad \text{xylene, 48h, reflux} \quad \text{ZnCl}_2 \text{ (cat)} \\
\text{(R)-1-phenylethylamine} & \quad \text{77% yield}
\end{align*}
\]

**Scheme 2.3: Preparation of 113a**

This method was repeated using \((S)\)-1-phenylethylamine to give 113b in 85% yield (Scheme 2.4).

\[
\begin{align*}
\text{(S)-1-phenylmethylamine} & + \quad \text{xylene, 48h, reflux} \quad \text{ZnCl}_2 \text{ (cat)} \\
\text{(S)-1-phenylmethylamine} & \quad \text{85% yield}
\end{align*}
\]

**Scheme 2.4: Preparation of 113b**
Chapter 2: Synthesis of chiral amines

The preparation of hindered (R)-(+)–camphor imines of similar structures was investigated. Firstly the primary amines (±)-1-phenylpropylamine (114a/b), (±)-1-phenyl-2-methylpropylamine (115a/b) and (±)-1-phenyl-2,2-dimethylpropylamine (116a/b) were synthesised as shown in Scheme 2.5.

(±)-1-Phenylpropylamine (114a/b; R = Et) reacted with (R)-(+)–camphor when refluxed for 72 h in xylene, in the presence of ZnCl₂ (10%), to give a mixture of two diastereomers (117a and 117b) (Scheme 2.6). (±)-1-Phenyl-2-methylpropylamine (115a/b; R = iPr) failed to react with (R)-(+)–camphor in xylene but when these reagents were refluxed in mesitylene for 72 h, a mixture of diastereomers 118a and 118b was obtained (Scheme 2.6). (±)-1-Phenyl-2,2-dimethylpropylamine (116a/b; R = tBu) failed to react with (R)-(+)–camphor in toluene, xylene or mesitylene. These results suggest that the activation energy required for the condensation reaction increases as the steric bulk of the primary amine increases. Therefore a higher reaction temperature is required, necessitating the use of a higher boiling solvent. 1-Phenyl-2,2-dimethylpropylamine (116a/b) was too sterically hindered for condensation to occur.
Imines 117a, 117b, 118a and 118b were identified by comparison of their NMR spectra with imines 113a and 113b. The presence of a doublet of triplets due to the H$_{3\text{exo}}$ proton and a signal due to the H$_{\alpha}$ proton were particularly characteristic of the imines (Table 2.1).

![Scheme 2.6: Preparation of imines 117a/b and 118a/b](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>Chirality of primary amine</th>
<th>R</th>
<th>$^1H$ NMR H$_{3\text{exo}}$</th>
<th>$^1H$ NMR H$_{\alpha}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>113a</td>
<td>$R$</td>
<td>Me</td>
<td>$\delta$ 2.24, $q$ (J 16.9, 4.5)</td>
<td>$\delta$ 4.45, $d$ (J 6.6)</td>
</tr>
<tr>
<td>113b</td>
<td>$S$</td>
<td>Me</td>
<td>$\delta$ 2.44, $q$ (J 16.6, 4.7)</td>
<td>$\delta$ 4.45, $d$ (J 6.6)</td>
</tr>
<tr>
<td>117a$^a$</td>
<td>$R$</td>
<td>Et</td>
<td>$\delta$ 2.18, $q$ (J 16.6, 4.5)</td>
<td>$\delta$ 4.13, $d$ (J 6.8)</td>
</tr>
<tr>
<td>117b$^a$</td>
<td>$S$</td>
<td>Et</td>
<td>$\delta$ 2.45, $q$ (J 16.6, 4.7)</td>
<td>$\delta$ 4.14, $d$ (J 6.8)</td>
</tr>
<tr>
<td>118a$^b$</td>
<td>$R$</td>
<td>$i$Pr</td>
<td>signal overlapping with other peaks</td>
<td>$\delta$ 3.85, $d$ (J 7.6)</td>
</tr>
<tr>
<td>118b$^b$</td>
<td>$S$</td>
<td>$i$Pr</td>
<td>$\delta$ 2.42, $d$ (J 16.6, 4.7)</td>
<td>$\delta$ 3.82, $d$ (J 7.6)</td>
</tr>
</tbody>
</table>

$^a$ Imines 117a and 117b were not separated. $^b$ Imines 118a and 118b were not separated.

**Table 2.1:** Summary of characteristic NMR signals of (R)-(+)camphor derived imines.
Recently a procedure describing the synthesis of 113a in 78% yield with tetraethyl orthosilicate as the dehydrating agent appeared in the literature.\textsuperscript{144} The procedure described above is comparable.

**Determination of the configuration about the C=N bond of 113a and 113b**

\[ \text{113a: Irradiation of the quartet at 4.45 ppm assigned to } H_\alpha \text{ gave a 2\% n.O.e. enhancement of the signal corresponding to } H_{3_{\text{exo}}} \text{ at 2.24 ppm and a 3\% n.O.e effect on the signal corresponding to } H_{3_{\text{endo}}} \text{ at 1.91 ppm. There was also a 2\% enhancement of the signal at 1.42 ppm, corresponding to the methyl group adjacent to } H_\alpha. \text{ No enhancement of the singlet at 0.90 ppm corresponding to the protons on } C_{10} \text{ was observed. Irradiation of the doublet of triplets at 2.24 ppm, due to } H_{3_{\text{exo}}} \text{ gave a 2\% n.O.e effect on the signal corresponding to } H_\alpha \text{ at 4.45 ppm and a 2\% n.O.e effect on the signal corresponding to } H_{3_{\text{endo}}} \text{ at 1.91 ppm. Irradiation of the doublet at 1.91 ppm, due to } H_{3_{\text{endo}}} \text{ gave a 2\% n.O.e. enhancement of the signal corresponding to } H_\alpha \text{ at 4.45 ppm and a 2\% n.O.e. effect on the signal corresponding to } H_{3_{\text{exo}}} \text{ at 2.24 ppm.} \]

\[ \text{113b: Irradiation of the quartet at 4.45 ppm due to } H_\alpha \text{ gave a 2\% n.O.e. enhancement of the signal corresponding to } H_{3_{\text{exo}}} \text{ at 2.44 ppm and a 3\% n.O.e effect on the signal corresponding to } H_{3_{\text{endo}}} \text{ at 1.80 ppm. There was also a 2\% enhancement of the signal at 1.41 ppm, corresponding to the methyl group adjacent to } H_\alpha. \text{ No enhancement of the singlet at 0.93 ppm corresponding to the protons on } C_{10} \text{ was observed. Irradiation of the doublet of triplets at 2.44 ppm, due to } H_{3_{\text{exo}}} \text{ gave a 2\% n.O.e effect on the signal corresponding to } H_\alpha \text{ at 4.45 ppm and a 2\% n.O.e effect on the signal corresponding to } H_{3_{\text{endo}}} \text{ at 1.80 ppm. Irradiation of the doublet at 1.80 ppm, due to } H_{3_{\text{endo}}} \text{ gave a 2\% n.O.e. enhancement of the signal corresponding to } H_\alpha \text{ at 4.45 ppm and a 2\% n.O.e. effect on the signal corresponding to } H_{3_{\text{exo}}} \text{ at 2.44 ppm.} \]

\( \text{Figure 2.2: Configuration of imines 113a and 113b; n.O.e enhancements} \)
corresponding to H_\alpha at 4.45 ppm and a 2% n.O.e. effect on the signal corresponding to H_{3exo} at 2.44 ppm.

Consequently, the arrangement around the C=N bond must be E to bring H_\alpha, H_{3exo} and H_{3endo} into close proximity. Correspondingly, the absence of an enhancement of the signal from the protons of the C_{10} methyl group upon irradiating the signal of H_\alpha ruled out the Z configuration. This is consistent with the structures of other (R)-(+-)camphor imines.\textsuperscript{145}

2.3.2 THE SYNTHESIS OF 'CAMPHOR AMINES'

Secondary 'camphor amines' were prepared via reduction of the corresponding imines. Catalytic reduction of N-(1-phenylethyl)bornanimine (113) with Pd/C/H_2 in THF was unsuccessful; steric hindrance around the C=N bond possibly making alignment with the catalyst surface difficult. Reduction did not occur when the imine was treated with LiAlH_4; difficulties in reducing hindered imines with LiAlH_4 have also been encountered by other workers.\textsuperscript{146} Reduction of the C=N bond was achieved using NaBH_4 in methanol at -78°C (Scheme 2.7 and 2.8).

**Stereochemistry of reduction about the C=N bond**

Reduction of the C=N bond of imine 113a to give amine 119 could in theory occur from both faces, giving a mixture of two diastereomers. Only one diastereomer was evident in the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of the product. This indicated that reduction had occurred stereoselectivity. A doublet of doublets at \( \delta \) 2.46 (J 5.9, 7.8) was present in the \textsuperscript{1}H NMR spectrum. This was in the correct region for H_{2endo} and showed expected coupling to H_{3endo} (J 7.8) and H_{3exo} (J 5.9).\textsuperscript{147,148} Therefore reduction occurred at the endo (bottom) face i.e. the face opposite the C_8 bridge (Scheme 2.7); if reduction had occurred at the exo (top) face a doublet of doublets of doublets would have been present due to H_{2exo}. This direction of reduction was expected because the gem-dimethyl bridge is known to hinder attack at the top face and the reducing reagent would attack at the bottom face.\textsuperscript{148}

\[ \text{NaBH}_4 \text{ methanol} \rightarrow \text{H}_{2\text{endo}} \rightarrow \text{H}_{3\text{endo}} \rightarrow \text{H}_{3\text{exo}} \rightarrow \text{H}_{2\text{exo}} \]

**Scheme 2.7: Stereoselective reduction of 113a with NaBH_4**
Similarly, 113b gave 119b specifically (Scheme 2.8). In the $^1$H NMR spectrum of 119b, a doublet of doublets of doublets at $\delta$ 2.84 ($J$ 10.3, 4.3, 2.0) was in the expected region for H$_{2\text{exo}}$. This signal was at lower field than the signal due to H$_{2\text{endo}}$ in 119a (an exo proton is normally found downfield from an endo proton in norbornane type structures)\textsuperscript{147} and showed coupling to H$_{3\text{endo}}$ ($J$ 2.0), H$_{3\text{exo}}$ ($J$ 10.2) and w-coupling to H$_{6\text{exo}}$ ($J$ 4.3).\textsuperscript{147,148} The presence of w-coupling indicated that H$_2$ was in the exo, not the endo position. Therefore reduction occurred from the exo-face i.e. from the same face as the gem-dimethyl bridge; this was unexpected because it requires the hydride to approach the C=N bond from the area of the gem-dimethyl bridge.\textsuperscript{149} Reduction at the exo-face of 113b, by NaBH$_3$CN had been reported previously by other workers\textsuperscript{27} who assigned the stereochemistry on the basis of w-coupling.

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node at (0,0) {$113b$};
\node at (2,0) {$119b$};
\node at (-2,0) {$\text{NaBH}_4$};
\node at (-2,-0.5) {methanol};
\node at (2,1) {90\% yield};
\draw[->] (-2,0) -- (-2,-0.5);
\draw[->] (2,0) -- (2,1);
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.8: Stereoselective reduction of 113b with NaBH$_4$}

The stereochemistry about the C$_2$-N bond of 119b was unequivocally confirmed from an X-ray crystal structure of 119b.HCl. (Figure 2.3)
119b.HCl crystallised in the orthorhombic space group \( P2_12_12_1 \), \( a = 7.369 \) Å, \( b = 12.947 \) Å, \( c = 18.355 \) Å; 4 molecules were present in the unit cell. The hydrogens attached to nitrogen were located in the Fourier map and isotropically refined. The nitrogen had two hydrogen atoms \( H_n \) and \( H_n' \) attached to it, each hydrogen atom was hydrogen bonded to a chlorine atom. The chlorine atoms were symmetry related with \( Cl \) at position \( x,y,z \) and \( Cl' \) at \( (\frac{1}{2} + x), (\frac{1}{2} - y), (1 - z) \). Each \( Cl \) atom was hydrogen bonded to two hydrogens in different molecules. \( H_n \) was 2.392 Å from \( Cl \), corresponding to a \( N-Cl \) distance of 3.258 Å and \( H_n' \) was 2.303 Å from \( Cl' \), corresponding to a \( N-Cl' \) distance of 3.138 Å.

**Figure 2.3:** X-ray crystal structure of 119b.HCl
Like imine 113, imine 117 was reduced with NaBH₄ in methanol, but conditions could not be found for the reduction of imine 118. Imine 117 was a mixture of the two diastereomers 117a and 117b; if there had been no face selectivity in reduction of the C=N bond four diastereomeric amines would have resulted. In practice only two diastereomeric amines were produced (120a/b) (Scheme 2.9).

**Scheme 2.9:** Stereoselective reduction of 117a/b with NaBH₄

Comparison of the ¹H NMR signals and coupling constants of 120a/b with those obtained for 119a/b (Table 2.2) indicated that one diastereomer had a H₂endo proton and the other diastereomer had a H₂exo proton. The orientation of reduction of 113a and 113b has been shown to depend on the chirality of the α-methylbenzylamine. It is reasonable to assume that reduction of imines 117a/b has the same relationship. Therefore reduction of 117a (derived from (R)-1-phenylpropylamine) is thought to have occurred at the endo-face to give 120a and reduction of 117b (derived from (S)-1-phenylpropylamine) at the exo-face to give 120b.

<table>
<thead>
<tr>
<th>Amine</th>
<th>Chirality</th>
<th>¹H NMR: H₂</th>
<th>¹H NMR: Hα</th>
</tr>
</thead>
<tbody>
<tr>
<td>119a</td>
<td>R</td>
<td>H₂endo δ 2.46, dd (J 7.8, 5.9)</td>
<td>δ 3.75, q (J 6.6)</td>
</tr>
<tr>
<td>119b</td>
<td>S</td>
<td>H₂exo δ 2.84, ddd (J 10.3, 4.3, 2.0)</td>
<td>δ 3.80, q (J 6.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>characteristic w-coupling H₂exo-H₆exo</td>
<td></td>
</tr>
<tr>
<td>120a</td>
<td>R</td>
<td>H₂endo δ 2.41, t (J 6.7)</td>
<td>δ 3.47, t (J 6.8)</td>
</tr>
<tr>
<td>120b</td>
<td>S</td>
<td>H₂exo δ 2.78 ppm, ddd (J 10.3, 4.3, 2.0)</td>
<td>δ 3.49, q (J 6.8)</td>
</tr>
</tbody>
</table>

**Table 2.2:** Characteristic ¹H NMR signals of camphor amines
Relationship between the face of reduction and the configuration of the α-alkylbenzyl entity

When 121 (derived from benzylamine) was reduced with NaBH$_4$ in methanol at -78°C, a 4:1 mixture of diastereomers 122a and 122b were produced where reduction had occurred at the endo-face in preference, but had also occurred at the exo-face (Scheme 2.30). This is consistent with the C$_7$ methyl group on the gem-dimethyl bridge hindering attack of the exo-face far more than the U-shaped cavity hinders approach of the hydride to the endo-face and is in agreement with the selective endo-face attack of organometallics and metal hydride reagents on the C=O function of camphor itself.$^{150,151}$

![Scheme 2.30: Reduction of 117 with NaBH$_4$ to yield diastereomeric amines 119a and 119b (4:1)](image)

However, experimental results obtained from the reduction of imines 113a, 113b, 117a and 117b suggest that the (R)-(+-)camphor entity is not the overriding factor in determining the face of reduction for these imines and that the absolute configuration of the α-alkylbenzylamine entity determines the direction of reduction of imines; in the reduction of 113b and 117b, the steric bulk of the methyl group attached to C$_7$ can not be the controlling factor in directing the hydride reagent to one face in preference. Also, the differences in face of attack are not due to the diastereomeric imines having different configurations about their C=N bonds because n.O.e experiments showed that 113a and 113b both have the E configuration.

Modelling studies of the imines 113a and 113b, and the possible reduction products were carried out (see Appendix 1). In each case, the torsion angle (a-b-c-d) was rotated in 10° increments to obtain the lowest energy minima. Energy vs dihedral angle (a-b-c-d, Figure 2.4) energy plots were obtained.
The energy vs dihedral angle (a-b-c-d, Figure 2.4) energy plots obtained for imine 113a and imine 113b were almost 'mirror images' (Figures 2.5, 2.7). The Ph group was on the same side as the gem-dimethyl bridge in 113a-1 (113a-1 is the lowest energy conformer of 113a) (Figure 2.6) and on the opposite side to the gem-dimethyl bridge in 113b-1 (113b-1 is the lowest energy conformer of 113b) (Figure 2.8); H_a was on the opposite side to the N lone pair in each case.

Reduction of each imine could theoretically lead to two diastereomeric amines. Because of the constraints of the molecular modelling package, the N atom was taken to be chiral, and each diastereomer was minimised with the nitrogen atom in both possible configurations (Figure 2.9, 2.10). The difference in energy between the two consequent minimum-energy configurations was small. Reduction of imine 113a is known to give amine 119a and none of amine 119c but molecular modelling studies indicated that amine 119a was of higher energy than amine 119c (Figure 2.9). Reduction of imine 113b is known to give 119b and none of 119d, but again, amine 119b was found to be of higher energy than 119d (Figure 2.10). Therefore, the high degree of stereocontrol in the reduction of the camphor imines with NaBH_4 is thought to stem from the configuration of the starting material rather than the stability of the product.
Figure 2.5: Energy vs dihedral angle plot for imine 113a

Exo-face is hindered by Ph group and gem-dimethyl bridge

Endo-face is more open to attack

Figure 2.6: Conformation 113a-1 at lowest energy minima.
Chapter 2: Synthesis of chiral amines

Figure 2.7: Energy vs dihedral angle plot for imine 113b

**Exo-face is more open to attack**

Approach to the *endo* face is hindered by the Ph group

Figure 2.8: Conformation of 113b-1 at lowest energy minima.
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Figure 2.9: Minimum energy conformations of amines 119a and 119c
Chapter 2: Synthesis of chiral amines

Amine 119b
(synthesised in practice)

168.66 KJ/mol 166.28 KJ/mol

reduction on exo face

imine 113b-1

reduction on endo face

Amine 119d
(not formed in practice)

168.63 KJ/mol 163.13 KJ/mol

Figure 2.10: Minimum energy conformations of amines 119b and 119d
It is envisaged that reducing agent (NaBH₄) attacks the C=N from the side away from the large phenyl group of the α-methylbenzyl moiety; this is consistent with the stereochemistry of the amines produced experimentally.

Table 2.3 contains details of the reduction of imines 113 and 117 using a variety of conditions. Imines 117a/b reacted with NaBH₄ more slowly than imines 113a/113b (Table 2.3, entry 9 compared with entry 4) while imines 118a/b were not reduced under the conditions quoted in the table. This is further evidence that the hydride approaches from the side of the alkyl group and Hₓ, away from the phenyl group; as the alkyl group gets larger, reduction becomes more difficult.

When a mixture of 113a/b was reduced with excess NaBH₄ in methanol using the conditions stated in Table 2.3 (entries 1-5), a greater proportion of 113a was reduced compared to 113b (Table 2.3, entries 1-7). The relative rates of reduction can be explained by steric arguments; the endo-face is relatively more open to attack by the reagent than the exo-face which is protected by the gem-dimethyl group. Imines 113a/b were reduced by NaBH₄ more slowly in ethanol than in methanol and there was greater selectivity in reduction of the diastereomers;¹⁵² these imines were not reduced in isopropanol.

The relative amount of 117a reduced compared to 117b was larger than the relative amount of 113a reduced compared to 113b under similar conditions (Table 2.3, entry 9 compared to entry 4). This may be similarly explained by attack on the exo-face (which is hindered by both the gem-dimethyl bridge and the alkyl substituent) becoming more difficult, relative to attack on the endo face (which is hindered only by the alkyl group) as the alkyl group increases in size.
Chapter 2: Synthesis of chiral amines

Table 2.3: Relative amounts of the diastereomeric imines reduced.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Solvent</th>
<th>Reaction conditions</th>
<th>% (R)-imine$^{a,c}$ reduced</th>
<th>% (S)-imine$^{b,c}$ reduced</th>
<th>Ratio $R : S^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>113a(R)/b(S) methanol 28 h, reflux</td>
<td>90</td>
<td>75</td>
<td>1.2 : 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>113a(R)/b(S) methanol 12 h, rt.</td>
<td>87</td>
<td>72</td>
<td>1.2 : 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>76</td>
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<tr>
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<td>8</td>
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<td>0</td>
<td>0</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>117a(R)/b(S) methanol 2 h, -78°C</td>
<td>39</td>
<td>14</td>
<td>2.8 : 1</td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>117a(R)/b(S) methanol 12 h, rt.</td>
<td>78</td>
<td>32</td>
<td>2.6 : 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>117a(R)/b(S) methanol 24 h, rt.</td>
<td>100</td>
<td>50</td>
<td>2.0 : 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reduction occurs solely from the bottom face.

$^b$ Reduction occurs solely from the top face.

$^c$ Ratio and % of imines reduced were calculated from the $^1$H NMR spectra.

2.4 SECONDARY AMINES DERIVED FROM PINANE

Chiral lithium amide 123 has recently been used as a chiral lithium amide base in an enantiotopic deprotonation reaction.$^5$3

![Lithium amide (123)](image)

An amine with the general structure shown below (Figure 2.12) seemed to possess several features that are needed to make a good chiral base: i) bulky group to confer chirality, ii) self-contained alkoxide; such a system in lithiated norephedrine was associated with unusually high enantioselective deprotonation of epoxide.$^2$4 This amine may be synthesised by condensation of ketone 124 with a chiral primary amine and then stereoselective reduction of the imine.
2.4.1 SYNTHESIS OF 'PINANE IMINES'

(+)-2-Hydroxypinan-3-one 124 was obtained by KMnO₄ oxidation of (1S)-(−)-α-pinene.¹⁵³ A shorter reaction time (5 h instead of 34 h) gave a cleaner product. Comparison of the observed optical rotation with that given in the literature indicated that 124 was > 93% optically pure.¹⁵³ The absolute stereochemistry of 124 is known, with the C₁₀ methyl group being cis to the gem-dimethyl bridge.¹⁵⁴ 124 was condensed with (R) and (S)-1-phenylethylamine to give oils 125a and 125b respectively (Scheme 2.31).

```
  Me
        |
   HO    |
        |
   Me    |

  (R)-1-phenylethylamine

  Me
        |
   HO    |
        |
   Me    |

  (S)-1-phenylethylamine
```

**Scheme 2.31: Synthesis of 125a and 125b**

2.4.2 SYNTHESIS OF 'PINANE AMINES'

Reduction of the resultant imines was achieved with NaBH₄ in methanol.

**Stereochemistry of reduction about the C=N bond**

When imine 125b was reduced a 4:1 mixture of two diastereomers (126b:126c) were produced, from which the pure major diastereomer readily precipitated as large plate-like crystals when the oil was treated with hexane (Scheme 2.32). An X-ray crystal structure proved that the major isomer had the NH group cis to the OH group and was therefore 126b; consequently reduction had occurred from the face of the gem-dimethyl group (exo face).
125b crystallised in the orthorhombic space group $P2_12_12_1$. $a = 7.335 \, \text{Å}$; $b = 10.708 \, \text{Å}$, $c = 21.074 \, \text{Å}$; (4 molecules were present in the unit cell). The hydrogen ($H_n$) attached to nitrogen and the hydrogen ($H_o$) attached to oxygen were located in the Fourier map and isotropically refined. $H_o$ was pointing towards $N$ giving an internal hydrogen bond of $1.85\, \text{Å}$. There was no intermolecular hydrogen bonding. The atoms $C_1$, $C_2$, $C_3$, $C_5$, and $C_6$ were approximately in a plane ($\pm 0.004\, \text{Å}$ out of the plane), with $C_4$ and $C_7$ sitting $1.0 \, \text{Å}$ below and above the plane.

Figure 2.13: X-ray crystal data of 126b
The X-ray crystal structure of 126b showed that reduction had occurred at the exo-face. This was not expected; reduction of 2-hydroxypinan-3-one itself with NaBH₄ in methanol is known to occur mainly at the endo-face due to the steric hindrance produced by the gem-dimethyl bridge.¹⁵³ Reduction at the exo-face is normally only seen when the reduction is carried out using LiAlH₄ in ether; LiAlH₄ reacts with the OH group and blocks the access from the endo-face of the molecule so that the H⁺ group attacks the exo-face.¹⁵⁵ For example, LiAlH₄ reduction of racemic 127 (Scheme 2.33) was reported to give 128; an X-ray structure the HCl salt showed that the OH and NH groups were cis with one of the 6-membered rings in the half chair conformation and the other 6-membered ring in the boat conformation.¹⁵⁵

\[ \text{LiAlH₄, rt THF} \]

**Scheme 2.33: Reduction of 127 to 128**

In contrast, reduction of 125b was carried out with NaBH₄ in methanol. Because of the hydroxylic nature of the solvent, complexation of NaBH₄ to the OH group is unlikely to have occurred so reduction was expected at the endo-face, however, as established by the X-ray structure, it occurred at the more hindered exo-face.

The ¹H NMR spectrum of 126b was examined in detail. A COSY experiment and an XHOCORRD experiment, taken together allowed assignment of the individual protons in the ¹H NMR spectra of 126b, and confirmation was obtained by homonuclear decoupling experiments. The vicinal coupling constants and long range coupling constants were calculated from the ¹H NMR spectrum and from the ¹H homonuclear decoupled spectra. The coupling constants were correlated with the dihedral angles determined by X-ray (Karplus-Conroy curve) (Tables 2.4 and 2.5). W-coupling was seen between H₁ and H₆ (J 5.8) and also between Hᵢ and Hⱼ (J ~ 2.5). H₁ does not couple with protons H₁ and H₆ because the dihedral angles are close to 90° (Karplus-Conroy curve).
**Figure 2.14:** Hydrogen numbering of 126b used in the $^1H$ NMR assignment

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<tr>
<th>$H$</th>
<th>$\delta$</th>
<th>multiplicity</th>
</tr>
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<tr>
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<td>0.78</td>
<td>s</td>
</tr>
<tr>
<td>b</td>
<td>1.20</td>
<td>s</td>
</tr>
<tr>
<td>c</td>
<td>1.21</td>
<td>s</td>
</tr>
<tr>
<td>d</td>
<td>1.37</td>
<td>d</td>
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<tr>
<td>e</td>
<td>3.82</td>
<td>q</td>
</tr>
<tr>
<td>f</td>
<td>1.96</td>
<td>t</td>
</tr>
<tr>
<td>g</td>
<td>1.79</td>
<td>m</td>
</tr>
<tr>
<td>h</td>
<td>2.11</td>
<td>m</td>
</tr>
<tr>
<td>i</td>
<td>1.25</td>
<td>d</td>
</tr>
<tr>
<td>j</td>
<td>2.24</td>
<td>m</td>
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<tr>
<td>k</td>
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<td>l</td>
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<td>dd</td>
</tr>
<tr>
<td>OH/NH</td>
<td>5.6</td>
<td>bs</td>
</tr>
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</table>

**Table 2.4:** Chemical shifts and multiplicity of the protons in 126b

**Table 2.5:** J-couplings, W-couplings and geminal-couplings of the protons in 126b and the corresponding dihedral angles
When imine 125a was reduced with NaBH₄ only one diastereomer (126a) was produced and therefore reduction was completely stereoselective (Scheme 2.34). Attempts to crystallise 126a and its salts failed, so an X-ray crystal structure could not be obtained. Also the ¹H NMR spectrum of 126a was less informative than that of 126b because some of the protons showed equivalent chemical shifts and so the stereochemistry of reduction could not be confirmed.

Reduction of 125a gave only one diastereomer 126a which showed a triplet at 2.94 ppm (J 9.2) due to Hᵢ. In comparison, reduction of 125b gave a 4:1 mixture of diastereomers 126b and 126c as described previously; the major diastereomer 126b whose OH and NH groups were cis showed a doublet of doublets at 2.79 ppm (J 9.9, 5.9) due to Hᵢ. The minor diastereomer 126c, whose OH and NH groups were trans, showed a triplet at 2.90 ppm (J 8.9) due to Hᵢ. Tentatively, the chemical shift and splitting pattern of the Hᵢ signal in 126a [triplet at 2.94 ppm (J 9.2)] suggests that the configuration around C₁ of 126a is the same as that around C₁ of 126c.

Other evidence for the stereochemistry around C₁ came from n.O.e. experiments. Irradiation of the singlet due to Meₐ at 0.73 ppm produced a 5% n.O.e. effect on the signal at 2.79 ppm corresponding to proton Hᵢ in compound 126b, indicating that Hᵢ was on the same face of the ring as Meₐ (Figure 2.14). In contrast, irradiation of the singlet due to Meₐ at 0.78 ppm produced no observed n.O.e. effect on the signal at 2.94 ppm corresponding to proton Hᵢ in compound 126a, suggesting that Hᵢ was on the opposite face of the ring to Meₐ (Figure 2.15).
Relationship between the face of reduction and the configuration of the α-alkylbenzyl moiety

The evidence presented above suggests that reduction of 125a occurred at the endo-face as opposed to reduction of 125b which occurred at the exo-face. The differences in face of attack are not due to the diastereomeric imines having different configurations about their C=N bonds because they both have the E configuration. As with the camphor imines it seems that the absolute configuration of the α-methyllbenzylamine group of 125a and 125b determines the direction of reduction.

The observed stereochemistry of reduction is consistent with the predicted stereochemistry if a conformation similar to that seen in the camphor imines (Section 2.3.2.2) is applied to the pinene imines. In compound 125a it is thought that the Ph group hinders approach to the exo-face, so attack occurs on the endo-face (Scheme 2.35).

![Scheme 2.35: Attack of H⁻ on 125a](image)
In compound 125b it is thought that the Ph group hinders approach to the endo-face, so attack occurs on the exo-face, but the bridgehead methyl groups counteract this effect to some extent and 20% of the reduction occurs on the endo-face.

![Scheme 2.36: Attack of H⁻ on 125b](image)

2.5 SUMMARY

(R) and (S)-N-benzyl-1-phenylethylamine (110a and 110b) and (R) and (S)-Bis [N-(1-phenylethyl)]amine (112a and 112b) were prepared in > 98% e.e.. The camphor derived amines (119a) and (119b) were prepared as single diastereomers in overall yields of 74% and 77% which compared well to the literature yield of 30%. The pinene derived amines (126a) and (126b) were isolated as pure diastereomers in overall yields of 68% and 50% respectively. The absolute stereochemistries of 119b and 126b were determined from X-ray crystallographic analysis. These amines were converted into lithium amide bases when required by treatment with BuLi.
# DEPROTONATION OF SULPHONES

## CHAPTER 3

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Chapter 3: Deprotonation of sulphones

The deprotonation of cyclic sulphones with lithium amide bases are discussed in this chapter. Firstly, deprotonation was achieved using achiral bases and subsequent reaction of the carbanion was examined. Secondly, chiral lithium amide bases were used in an attempt to differentiate between the enantiotopic protons of the sulphone.

3.1 INTRODUCTION TO SULPHONYL CARBANIONS

The sulphone group has been widely used in organic synthesis;\textsuperscript{157,158} the ease of formation of carbanions \(\alpha\)- to the \(\text{SO}_2\) group (deprotonation of attached alkyl and alkenyl groups is possible), while the sulphone group itself is relatively inert to nucleophilic attack, enables C-C bond formation \textit{via} alkylation, acylation, aldol-type and Michael addition processes.

The sulphone group is known to stabilise carbanions. This ability has been traditionally attributed to planar \(\pi\)(p-d) bonding, but there is considerable evidence for non-planar carbanions (see below) and this stabilisation has also been ascribed to polarisation effects, with a build-up of electron density on the sulphur.\textsuperscript{159}

The structure of sulphonyl carbanions has been subject to intense study but the results have been contradictory, allowing very few generalisations. Much of the early information about the configuration at \(C_\alpha\) (\(C_\alpha = \) carbon adjacent to \(\text{SO}_2\) group, \(H_\alpha = \) hydrogen attached to \(C_\alpha\)), came from hydrogen-deuterium exchange experiments. It was shown that some optically active acyclic sulphones \textit{e.g.} \textbf{127}, undergo H-D exchange faster than racemisation (\(k_{\text{exchange}}/k_{\text{racemise}} > 1\)) (Scheme 3.1).\textsuperscript{160-162}

\[
\begin{align*}
\text{H}_3\text{C}_6\text{H}_3 & \quad \text{alkoxide, D}_2\text{O} & \quad \text{D}_3\text{C}_6\text{H}_3 \\
\text{Me} & \quad \text{SO}_2\text{Ar} & \quad \text{Me} & \quad \text{SO}_2\text{Ar}
\end{align*}
\]

\textbf{127}

\textbf{Scheme 3.1:} H-D exchange with retention of configuration

Decarboxylation of some \(\alpha\)-sulphonyl carboxylic acids \textit{e.g.} \textbf{128} also occurred with retention of configuration (Scheme 3.2).\textsuperscript{163,164,165}

\[
\begin{align*}
\text{Ph} & \quad \text{Me} & \quad 0.01\% \text{NaOH, dioxane} / \text{H}_2\text{O (4:3), 65}\degree\text{C} & \quad \text{Ph} & \quad \text{Me} \\
\text{CO}_2\text{H} & \quad \text{SO}_2\text{Ph} & \quad \text{-CO}_2 & \quad \text{H} & \quad \text{SO}_2\text{Ph}
\end{align*}
\]

\textbf{128}

\textbf{Scheme 3.2:} Decarboxylation of \textbf{128} with retention of configuration
Several possible structures of the carbanionic centre which lead to retention of configuration have been proposed but overall the results suggest a chiral intermediate carbanion. Both a pyramidal sp\(^3\) structure (a) or a planar sp\(^2\) structure (b) would provide this but achiral structures such as (c) (a rotomer of (b)) are ruled out (Figure 3.1).

![Possible configurations of the carbanion](image)

Retention of configuration can then be explained by invoking an energy barrier to inversion in (a) or to rotation about the α C-S bond in (b).

Whereas acyclic sulphonyl carbanions may be inherently chiral, cyclic sulphonyl carbanions in small rings become optically inactive on attainment of planarity, because they are constrained to adopt the achiral configuration (c) (Figure 3.1).\(^{168}\) This is supported by the observation that deprotonation or decarboxylation of 129 is accompanied by racemisation (Scheme 3.3).\(^{166,167,168}\)

![Scheme 3.3: Racemisation of 129 on deprotonation](image)

There are a number of arguments supporting the planar\(^ {167,168}\) and the pyramidal structures\(^ {165}\) and configurations in between,\(^ {165}\) but recent NMR and X-ray results indicate that the configuration of the sulphonyl carbanionic centre is dependent on the structure of the sulphone concerned. Coupling constants (\(J_{\text{C-H}}\)) for \(C_x\) may be used to determine the hybridisation state; in benzyl-lithiums (PhSO\(_2\)CPhLi, CH\(_3\)SO\(_2\)CPhLi, \(^t\)BuSO\(_2\)CPhLi) the coupling constants were found to be large and in agreement with a nearly planar
configuration at Cα while in the non-benzylic anions (BuSO₂CHLi, PhSO₂CHLi) the change in coupling constants relative to the corresponding sulphones were considerably smaller so that hybridisation somewhere between sp² and sp³ and therefore a non-planar Cα atom was proposed.¹⁶⁹,¹⁷⁰

The structures of several lithiosulphones have been determined by X-ray crystallography (Table 3.1); each occurred as a dimer linked in an 8-membered ring with lithium atoms bridging the two SO₂ groups; no bond was formed between the Li atom and Cα, the Cα-S was considerably shorter than the corresponding bond length in the sulphones and the S-O bond was slightly lengthened. In Table 3.1 the sum of the angles |α| + |β| is a measure of the pyramidalisation of Cα, while γ expresses the divergence of the unshared electron pair on Cα from the ideal gauche conformation (Figure 3.2).

![Figure 3.2: Arrangement of atoms in X-ray crystal structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lithiosulphone in the form [RSO₂ABL]</th>
<th></th>
<th></th>
<th></th>
<th>Conformation of Cα</th>
<th>Ref</th>
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<td>130</td>
<td>[PhSO₂CHPhLi.TMEDA]₂</td>
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<td>131</td>
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<tr>
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<td>174</td>
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<td></td>
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<td>175</td>
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<td>136</td>
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<td>182</td>
<td>18</td>
<td></td>
<td>planar</td>
<td>174</td>
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</table>

Table 3.1: Configuration at Cα in a number of lithiated sulphones; determined by X-ray crystallography

Only the Cα carbon of the phenyl substituted compounds 135 and 136, (probably due to partial stabilisation of the negative charge by (p-p) interactions with the phenyl ring) and the Me₃Si substituted compound 133 were largely planar; 130, 131, 132 and 134 showed considerable pyramidal character. All the structures had an approximately gauche arrangement of the carbanion lone pair with respect to the sulphone oxygens (Figure 3.2). This had been predicted by modelling studies which also indicate that the energy difference between a planar and pyramidised Cα atom is not large.¹⁷⁶
Although H-D exchange of acyclic sulphones can be carried out with a high degree of retention of configuration under protic conditions where the carbanion is very rapidly deuteriated, it is not possible to use strong bases in aprotic solvents at low temperature to generate the configurationally stable sulphonyl carbanion, as rapid racemisation occurs.\textsuperscript{177} The only way in which an optically active compound may be prepared is if the carbanion is quenched as it is formed. This was illustrated when racemic 138 was formed in the reaction of sulphone 137 with LDA followed by immediate quenching with TMSCl, while when the sulphone was added to a mixture of LDA and TMSCl (internal quench procedure)\textsuperscript{178} optically active 138 was formed (Scheme 3.4).\textsuperscript{158}

\begin{center}
\begin{tikzcd}
\text{Me} & \text{H} \\
\text{SO}_2\text{Ph} & \\
\arrow[r, shift right=1, shift left=1, start anchor=center, end anchor=center] & \text{Me} & \text{SiMe}_3 \\
\text{LDA, TMSCl} & \\
\text{THF, -78°C} & \\

137 & 138 \\
\end{tikzcd}
\end{center}

\textbf{Scheme 3.4: Deprotonation of 137 with LDA; internal and external quench with TMSCl gave different results}

On this account, chiral sulphones have not found widespread use in organic synthesis.

\section*{3.2 AIMS OF THIS WORK}

Following Simpkins' observations of enantiotopic deprotonation of cyclohexanones and sulphoxides with chiral lithium amide bases (described in Chapter 1) we began a study of the analogous processes in sulphones. There is one mention in the literature\textsuperscript{11} of the attempted enantiotopic deprotonation of an acyclic sulphone (139) (Scheme 3.5) and of a cyclic sulphone (141) (Scheme 3.6). Bases 36a and 37 gave enantiocomplementary results with sulphone 139\textsuperscript{11}, whereas they gave opposite enantiomers in enantiotopic deprotonations of ketones\textsuperscript{27} It was suggested that a different mechanism was operating, presumably involving a transient carbanion-chiral amine complex. In both cases, an external quench gave the racemic product and it was concluded that the induced asymmetry at the \(\alpha\)-carbanion was transient.
Chapter 3: Deprotonation of sulphones

![Diagram of sulphone deprotonation](image)

**Scheme 3.5**: Enantiotopic deprotonation of 139 with bases 36a and 37; internal quench with TMSCl gave optically active material

In this present work, the deprotonation of the conformationally locked cyclic sulphone \( \text{179} \) 4-\( t \)-butylpentamethylene sulphone (143) with a range of chiral lithium amide bases was investigated, with the expectation that higher e.e.'s would be obtained.

The literature indicated that in constrained sulphone systems, the equatorial proton \( \alpha \)- to the SO\(_2\) group is removed in preference to the axial proton by a lithiated base\(^{180,181}\) and the new substituent always goes into the equatorial position.\(^{182,183}\) Consequently, as described pictorially in Scheme 3.7, it was expected that the chiral lithium amide base would distinguish between the enantiotopic equatorial protons adjacent to the SO\(_2\) group in 4-\( t \)-butylpentamethylene sulphone and that reaction of the carbanion with an electrophilic reagent \( \text{e.g.} \text{MeI, } \) would lead to the new substituent being introduced into the equatorial position. The
symmetry of the molecule would be broken, and if the base was completely selective, one enantiomer would be produced.

![Diagram of pro-R and pro-S equatorial hydrogens]

**Scheme 3.7:** Generalised reaction scheme describing the enantiotopic deprotonation of 143 with a chiral base and subsequent alkylation.

### 3.3 PREPARATION OF SULPHONES

Oxidation of the corresponding sulphides is the most universally applied method for the preparation of sulphones; a very large number of reagents are available e.g. peracetic acid (generated *in situ* from 30% H₂O₂ in glacial acetic acid),¹⁸⁴,¹⁸⁵ potassium permanganate ¹⁸⁶,¹⁸⁷,¹⁸⁸ and MCPBA ¹⁸⁹,¹⁹⁰ Oxidation of the sulphide to the sulphoxide is normally very rapid, with subsequent oxidation to the sulphone being slower and often requiring an excess of the oxidising reagent, prolonged reaction times and/or heating. 'Oxone' (2KHSO₅·KH₂SO₄·K₂SO₄) is a safe commercially available oxidant and has been widely used for the oxidation of sulphides to sulphones,¹⁹¹,¹⁹²,¹⁹³,¹⁹⁴ especially when high chemoselectivity is required.¹⁹⁵,¹⁹⁶
3.1.1 SYNTHESIS OF PENTAMETHYLENE SULPHONE AND THIOPYRAN-1,1-DIOXIDE

Pentamethylene sulphone (Thiane-1,1-dioxide) (145) and 4-thiopyran-4,4-dioxide (146) were prepared by oxidation of the corresponding sulphides with Oxone (Scheme 3.8 and Scheme 3.9).

$$\text{S}
\begin{array}{c}
\text{KHSO}_5, \text{H}_2\text{O} \\
\text{CH}_3\text{OH, 4h, rt}
\end{array}
\rightarrow
\text{O}
\begin{array}{c}
\text{S} \equiv \text{O}
\end{array}
_{145}
$$

96% yield

Scheme 3.8: Preparation of 145

$$\text{S}
\begin{array}{c}
\text{KHSO}_5 \\
\text{CH}_3\text{OH, 4h, rt}
\end{array}
\rightarrow
\text{O}
\begin{array}{c}
\text{S} \equiv \text{O}
\end{array}
_{146}
$$

65% yield

Scheme 3.9: Preparation of 146

3.1.2 PREPARATION OF 4-\textit{t}-BUTYL-PENTAMETHYLENE SULPHONE

The preparation of 4-\textit{t}-butylthiane (153) described in the literature uses 4-\textit{t}-butylpyridine which, via benzylation and hydrogenation (PtO$_2$ or Rh/C) provides 1-benzoyl-4-\textit{t}-butylpiperidine. Ring opening to the 1,5-dibromopentane derivative and subsequent ring closure (Na$_2$S) gives the desired sulphide in 26% overall yield. The costly starting material and the extensive poisoning of the precious metal catalyst encouraged a less expensive synthesis based on 4-\textit{t}-butylcyclohexanone (147) (Scheme 3.10). Nitrosation (BuONO-HCl) gave the dioxime (148) which was dehydrated (Ac$_2$O-KOH) to the dinitrile (149). Hydrolysis (aq. H$_2$SO$_4$, 24h), reduction (LiAlH$_4$) and treatment with PBr$_3$ gave 152. which cyclised with Na$_2$S to give 153 in 52% overall yield. 153 was oxidised to 4-\textit{t}-butylpentamethylene sulphone (143) in 94% yield with hydrogen peroxide in acetic acid.
Scheme 3.10: Steps in the synthesis of 4-t-butylpentamethylene sulphone
3.4 DEPROTONATION OF CYCLIC SULPHONES USING LDA

Three six-membered ring sulphones were deprotonated with LDA and the carbanions were quenched with methyl iodide, benzyl bromide and trimethylsilyl chloride.

3.4.1 DEPROTONATION OF PENTAMETHYLENE SULPHONE

The deprotonation - electrophilic quench reactions were first carried out on pentamethylene sulphone (this being readily synthesised from the commercially available sulphide) to set up conditions.

Reactions with methyl iodide

\[
\begin{align*}
1) & \text{LDA, THF, } -78^\circ\text{C, 3h} \\
2) & \text{MeI, 4h}
\end{align*}
\]

Scheme 3.11: Deprotonation of 145 with LDA; reaction with MeI

Pentamethylene sulphone was deprotonated with LDA and the carbanion was quenched with MeI (Scheme 3.11). The \(^1\text{H}\) NMR spectrum of the crude product indicated that 75\% of the monomethylated material (145) and 15\% of the dimethylated material (154) had been produced; some unreacted pentamethylene sulphone (ca. 10\%) also remained. In the \(^1\text{H}\) NMR spectrum of 154, a doublet at 1.35 ppm was assigned to the methyl protons and in the \(^1\text{H}\) NMR spectrum of 155, the doublet at 1.36 was assigned to the both sets of methyl protons.

It is known that methylcyclohexane exists about 95\% of the time with the methyl group equatorial and 5\% of the time with the methyl group axial at 25\(^\circ\)C,\(^{198}\) and the inversion barrier in pentamethylene sulphone is very similar to that in cyclohexane.\(^{199}\) Therefore it is likely that the rate of inversion of 2-methylpentamethylene sulphone is similar to that of methylcyclohexane and that the methyl group 154 spends most of its time in the equatorial position. The NMR chemical shifts and coupling constants are weighted averages of the two conformers, but with the methyl group predominately in the equatorial position, the chemical shifts and coupling constants are close to those of the equatorially substituted sulphone.

The signal at lowest chemical shift in \(^1\text{H}\) NMR spectrum of 154 was a distorted doublet of triplets at 3.1 ppm. This was assigned to \(\text{H}_{\text{eqp}}\) geminal coupling was observed to \(\text{H}_{\text{ax}}\) (J
13.9), and vicinal coupling to \( \text{H}_{5\text{ax}} (J \sim 3) \) and \( \text{H}_{5\text{eq}} (J \sim 3) \). This distorted doublet of triplets is very characteristic of a mono-2-substituted pentamethylene sulphones. The signal from \( \text{H}_{6\text{ax}} \) was seen at 2.8-2.9 ppm; this was, as expected, at lower chemical shift than the signal corresponding \( \text{H}_{6\text{eq}} \) at 3.0-3.2 ppm. Irradiation of the doublet due to \( \text{CH}_3 \) at 1.35 ppm simplified the signal corresponding to \( \text{H}_2 \) to a doublet of doublets (\( J \sim 11.4, 3.7 \) Hz). These coupling constants were characteristic of ax-ax coupling and ax-eq coupling in a six membered ring chair conformation, and indicated that \( \text{H}_2 \) was in the axial position and therefore the methyl group was in the equatorial position.

**Reaction with benzyl bromide**

![Chemical structure](attachment:structure.png)

**Scheme 3.12**: Deprotonation of 145 with LDA; reaction with BnBr

Sulphone 145 was treated with LDA and then benzyl bromide. The \(^1\text{H NMR}\) spectrum of the crude product indicated that 74\% of the monobenzylated sulphone (156) and 16\% of the dibenzylated sulphone (157) was present. In the \(^1\text{H NMR}\) spectrum of 156 the characteristic doublet of triplets due to \( \text{H}_{6\text{eq}} \) appeared at 3.15 ppm (\( J \sim 14.0, 3.9 \)). This doublet of triplets was also split by ca. 1 Hz, due to \( w \)-coupling to \( \text{H}_{4\text{eq}} \) (\( J \sim 1 \)). A pair of doublets of doublets at 2.66 (\( J \sim 13.5, 11.2 \)) and 3.53 (\( J \sim 13.5, 3.1 \)) were assigned to the methylene protons of the benzyl moiety. The \(^{13}\text{C NMR}\) spectrum of 157 verified that the molecule was symmetrical with one signal due to \( \text{C}_3 \) and \( \text{C}_5 \) at 29.15 ppm and one signal due to \( \text{H}_2 \) and \( \text{H}_6 \) at 63.70 ppm. In the \(^1\text{H NMR}\) spectrum of 157 a doublet of doublets at 2.70 ppm (\( J \sim 13.5, 11.0 \)) and 3.58 ppm (\( J \sim 13.5, 3.9 \)) were assigned to the inequivalent methylene protons of the benzyl moiety. The triplet of triplets at 3.00 ppm was due to \( \text{H}_{2\text{ax}} / \text{H}_{6\text{ax}} \) (\( J \sim 11.0, 3.9 \)); these coupling constants were consistent with \( \text{H}_2/\text{H}_6 \) being in the axial position and so the benzyl substituents were both equatorial. There was also some evidence for a small amount of \( \text{trans-2,6-dibenzylpentamethylene sulphone} \) in the mixture; a multiplet at 3.2 ppm in the crude \(^1\text{H NMR}\) spectrum was possibly due to \( \text{H}_2 \) and \( \text{H}_6 \) while a pair of doublets of doublets at 2.80 and 2.60 ppm were assigned to the inequivalent \( \text{CH}_2\text{Ph} \) protons; this compound was not isolated.
**Monoalkylated vs dialkylated sulphones**

Some dialkylation was observed in both the methylation and the benzylation reactions although equivalent quantities of sulphone and base were used. The formation of dialkylated sulphone in the presence of 1 equivalent of base and an alkylation agent has been reported in the literature\(^{200}\) when methyl phenyl sulphone (158) was treated with 1eq. of base significant quantities of dialkylated methyl phenyl sulphone (161) where observed (Scheme 3.13 and Table 3.2).

![Scheme 3.13: Multiple alkylation of methyl phenyl sulphone](image)

**Table 3.2:** Relative amounts of mono-, di- and tri- alkylated methyl phenyl sulphone obtained by treatment of methyl phenyl sulphone with 1 eq. of base (refer to Scheme 3.13).\(^{200}\)

<table>
<thead>
<tr>
<th>RX</th>
<th>160 monoalkylated</th>
<th>161 dialkylated</th>
<th>162 trialkylated</th>
<th>158 PhSO(_2)Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)CH(_2)CH(_2)Br</td>
<td>71</td>
<td>19</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>CH(_2)CH(_2)CH(_2)Br</td>
<td>66</td>
<td>19</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>CH(_2)=CHCH(_2)Br</td>
<td>63</td>
<td>18</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>CH(_2)=CHCH(_2)Br</td>
<td>40</td>
<td>25</td>
<td>2.5</td>
<td>33</td>
</tr>
<tr>
<td>PhCH(_2)Br</td>
<td>36</td>
<td>43</td>
<td>0</td>
<td>21</td>
</tr>
</tbody>
</table>

This finding was ascribed to an equilibrium between the initially formed sulphone stabilised carbanion (159) and 160, followed by alkylation of 163 to give 161. (Scheme 3.14).\(^{200}\)

![Scheme 3.14: Proposed mechanism of dialkylation](image)

It is also recognised that the sulphone group allows multiple proton extraction \(\alpha\)- to SO\(_2\) to give a range of polyanionic species and that these will undergo two-fold reaction with electrophiles rather than the single reaction observed with most dianionic substrates.\(^{201}\) When
possible, it is known that 1,3-dianion formation is preferred over 1,1-dianion formation.\textsuperscript{202,203,204} This is illustrated in Scheme 3.15.

![Scheme 3.15: 1,3-dianion formation](image)

Thus, the formation of 2,6-dialkylated pentamethylene sulphone, along with monoalkylated pentamethylene sulphone may be attributed to either one or both of the following processes: i) as the concentration of the mono-lithiated sulphone increases on addition of the base, a second deprotonation occurs due to relative ratios of unreacted and mono-lithiated sulphone (if there was no preference for mono over dilithiated sulphone a statistical distribution would be formed), and ii) an equilibrium process occurs between the initially formed sulphone stabilised carbanion and the alkylated product, followed by alkylation of the new stabilised sulphone; this is illustrated in Scheme 3.16 for the benzylolation of pentamethylene sulphone.

![Scheme 3.16: Mechanism of dibenzylolation of 145](image)

**Reaction with TMSCl (external quench)**

Pentamethylene sulphone was deprotonated with LDA and then the carbanion was quenched with TMSCl. This reaction sequence is known as an external quench because the carbanion was formed before the quenching agent was introduced.

![Scheme 3.17: Reaction of 145 with LDA; external TMSCl quench](image)
The $^1$H NMR spectrum of the crude product mixture indicated that the ratio of monosilylated (164), disilylated (165) and unreacted sulphone was produced in the ratio 78:9:13. Again the monosubstituted sulphone (164) showed the characteristic doublet of triplets at 3.02 ppm ($J_{10.3, 3.6}$) due to $H_{eq}$, indicating the substituent was in the equatorial position. A doublets of doublets assigned to $H_{ax}$ was present at 2.42 ppm ($J_{12.2, 3.9}$). The $^{13}$C NMR spectrum of the disilylated material (165) indicated that the molecule was symmetrical with one signal due to C$_2$ and C$_6$ at 55.47 ppm; this suggested that the 2- and 6-trimethylsilyl groups were cis (diequatorial).

**Reaction with TMSCI (internal quench)**

![Scheme 3.18: Reaction of 145 with LDA; internal TMSCI quench](image)

When TMSCI was mixed with LDA at -78°C and pentamethylene sulphone was added to this mixture, then the mixture was stirred for 2h, and quenched with TEA (method a, Scheme 3.18); the $^1$H NMR of the crude product indicated that none of the expected monosilylated sulphone (164) had been produced. Instead 50% of the pentamethylene sulphone had been converted to 2,6-disilylpentamethylene sulphone and 50% remained unreacted. The order of addition of the reagents was changed and a solution of LDA was added dropwise to a mixture of the sulphone and TMSCI in THF at -78°C (method b, Scheme 3.18). The $^1$H NMR spectrum of the crude product indicated that 30% of 164 and 30% of 165 had been produced with ca. 40% of 145 remaining.

When TMSCI was used in an external quench the ratio of products was similar to those obtained when MeI or BnBr were used. It was therefore surprising that when TMSCI was used in an internal quench, much more disubstitution was observed. These results suggest that the first introduced trimethylsilyl group has made $H_6$ of the monosilylated sulphone (164) more acidic than $H_2$ of pentamethylene sulphone (145), so competitive deprotonation of the monosilylated sulphone has occurred. The ability of silicon to make the proton attached to the carbon bearing silicon more acidic is well known and is due to stabilisation of the resultant $\alpha$-carbanion.205 This ability to stabilise the carbanion has been attributed to several factors
including overlap of the α-carbon-metal bond with a silicon $d$ orbital and overlap of the α-carbon metal bond with the $\sigma^*$ orbital of an adjacent silicon-carbon bond.\(^{205}\) It is not obvious why the trimethylsilyl group attached to $C_2$ should cause $H_6$ of 164 to be removed by LDA more easily than $H_2$ of 145.

**Reaction with benzaldehyde**

The reaction of tetramethylene sulphone (141) with BuLi followed by benzaldehyde has been reported to give a 65:35 mixture of the diastereomers 166a and 166b, the stereochemistry of each was identified from the observed H-H coupling constants.\(^{206}\)

![Scheme 3.19: Synthesis of 166a and 166b](image)

When pentamethylene sulphone was treated with LDA then quenched with benzaldehyde, diastereomers 167a and 167b were formed (3:1 mixture) (Scheme 3.20). The major diastereomer (167a) had a broad singlet at 5.83 ppm due to $H_7$, and an OH signal at 3.19 ppm. The minor diastereomer (167b) had a doublet at 5.20 ppm due to $H_7$ and an OH signal at 3.87 ppm. The relative stereochemistry of 167a and 167b was not determined absolutely but comparison of the coupling constants for $H_2$ and $H_7$ with those obtained for the tetramethylene system suggested that the major diastereomer has the $R^*R^*$ relationship and the minor one has the $R^*S^*$ relationship (Figure 3.3).

![Scheme 3.20: Reaction of 145 with LDA; benzaldehyde quench to give 167a and 167b.](image)
3.4.2 Deprotonation of 4-\(t\)-butylpentamethylene sulphone

A \(4-t\)-butyl group was used as a 'holding group' to keep the ring in one predominant conformation. 4-\(t\)-Butylpentamethylene sulphone (143) was deprotonated with LDA and the carbanion was quenched with a number of electrophilic reagents.

**Reaction with methyl iodide**

4-\(t\)-Butylpentamethylene sulphone (143) was deprotonated with one equivalent of base and methylated to give 144, 168, 169 and unreacted 143, in the ratio 72:5:3:20 (Scheme 3.21). The doublet assigned to the methyl group of 144 occurred at 1.34 ppm and was partially overlapping with the doublet assigned to the methyl groups at 1.37 ppm of 168. The doublet due to one of the methyl groups of 169 occurred at 1.40 ppm.

**Scheme 3.21: Reaction of 143 with LDA and then Mel**

Evidence for the relative stereochemistry of compound 144 (\(t\)-butyl and methyl groups *cis*) was obtained from the \(^1\)H NMR spectrum and DQF COSY analysis. It was assumed that the ring was conformationally locked by the \(t\)-butyl and the methyl group, so that the coupling
constants and chemical shifts were a good indication of the major conformer. The triplet of triplets at 1.2-1.4 ppm due to H₄ (J 13.4, 2.8) indicated that H₄ was axial; therefore the t-butyl group was equatorial. The signal due to H₃ax occurred at 1.55-1.7 ppm and was a distorted quartet, because the geminal coupling constant to H₃seq and the vicinal coupling constants to H₄axx and H₂ were all of the same order of magnitude (ca. J 13 Hz). This indicated that H₂ was in the axial position and therefore the methyl group was equatorial. H₃seq occurred at 1.95-2.05 ppm as a distorted doublet of quartets; due to the geminal coupling (ca. J 13) to H₃ax and small couplings of similar magnitude (ca. J 3) to H₄ax, H₂ax and w-coupling to H₅seq (observed in COSY spectrum). Also characteristic of an equatorial substituent in the 2-position was the doublet of triplets at 3.05-3.15 ppm due to H₆seq (ca. J 14, 3). The identity of 168 and 169 were confirmed by deprotonation of 143 with two equivalents of base, followed by methylation to give 168 and 169 in a ratio of approximately 3:2. The mixture was separated by flash chromatography. After recrystallisation, 168 was obtained in a pure form, but 169 was contaminated with some of 168 and the spectrum NMR of 169 was assigned after subtraction of the contaminant signals. The ¹³C NMR spectrum of 168 indicated that dimethylation had occurred and the molecule was symmetrical with the methyl signals coincident at 11.1 ppm. In the ¹H NMR a distorted quartet at 1.55-1.70 ppm was due to H₃ax/5ax with vicinal coupling to H₂ax/H₆ax and H₄ (ca. J 12) indicating that both these protons were axial and therefore the substituents were equatorial. The ¹³C NMR of 169 indicated that dimethylation had occurred, but the molecule was unsymmetrical with methyl signals at 10.9 and 14.3 ppm. Two doublets at 1.33 ppm (J 6.8) and 1.46 ppm (J 7.4) were seen in the ¹H NMR spectrum due to the two methyl groups with a trans relationship.

**Reaction with benzyl bromide**

4-t-Butylpentamethylene sulphone was deprotonated with one equivalent of base and alkylated with benzyl bromide (Scheme 3.22).

![Scheme 3.22: Reaction of 143 with LDA and then benzyl bromide](image_url)
The $^1$H NMR spectrum of the crude mixture indicated that a mixture of compounds 170 (60%), 171 (10%), 172 (6%), 143 (24%) had been formed. These were separated by chromatography and then recrystallised. Evidence for the relative stereochemistry of 170 came from the NMR spectra, using a similar argument as that set out for compound 144. The characteristic signals included a doublet of triplets at 3.16 ppm ($J_{14,3}$) from $H_{6\text{eq}}$ and a triplet of triplets at 1.15 ($J_{9,2}$) from $H_{4\text{ax}}$. The doublets of doublets assigned to the inequivalent methylene protons of the benzyl group occurred at 2.62 ppm ($J_{13.6,10.8}$) and 3.52 ppm ($J_{13.7,3.1}$). Evidence that the $t$-butyl group, and both benzyl substituents were cis in compound 171 came from the $^{13}$C NMR and $^1$H NMR spectra; the $^{13}$C NMR spectrum indicated the molecule was symmetrical and disubstituted with one signal at 62.46 ppm due to the methine $C_2$ and $C_6$ carbons. A triplet of triplets at 1.0-1.1 ppm with vicinal coupling of 12Hz and 3Hz was consistent with $H_4$ being in the axial position. The distorted quartet, assigned to $H_{3\text{ax}/5\text{ax}}$ showed vicinal coupling of 12Hz to $H_{2/6}$, therefore $H_{2/6}$ were in the axial position and the dibenzyl groups were equatorial. Compound 172 is thought to have one of the benzyl groups equatorial and the other axial; the $^{13}$C NMR contained signals due to two phenyl groups in the region 126-137 ppm, and signals due to the methine carbons $C_2$ and $C_6$ at 58.2 and 61.4 ppm (if both substituents were axial, the $^{13}$C NMR would have been simplified).

**Reaction with TMSCl (internal quench)**

4-$t$-Butylpentamethylene sulphone was treated with a mixture of LDA and TMSCl (internal quench procedure) (Scheme 3.23). As with pentamethylene sulphone, half was disilylated and half did not react.

A mixture of disilylated sulphones 173 and 174 (ca. 22:3) were produced. 173 had all the substituents cis, as evidenced by the symmetrical nature of the $^{13}$C NMR spectrum, with one signal at -1.62 ppm due to both -Si(CH$_3$)$_3$ groups and one signal at 55.24 ppm due to the methine carbons $C_2$ and $C_6$. In the $^1$H NMR spectrum of 173 the doublet of doublets at 2.35-2.45 ppm was assigned to $H_{2\text{ax}/6\text{ax}}$ and showed vicinal coupling of 13 Hz to $H_{3\text{ax}/5\text{ax}}$ and 2 Hz to $H_{3\text{eq}/5\text{eq}}$. The $^{13}$C NMR spectrum of 174 was consistent with the silyl substituents trans; the two methine carbon signals at 52.0 and 52.9 ppm were assigned to $C_2$ and $C_6$. 

---

**Scheme 3.23:** Reaction of 143 with LDA; internal quench with TMSCl
Reaction with TMSCI (external quench)

4-t-Butylpentamethylenesulphone was first deprotonated with LDA, then the carbanion was quenched with trimethylsilyl chloride (external quench) (Scheme 3.24).

![Scheme 3.24: Reaction of 143 with LDA; external quench with TMSCI]

A mixture of two monosilylated compounds 175 and 176 (2:1) were isolated (76% in total), as well as the disubstituted sulphones 173 and 174 (7% in total) and unreacted 143 (15%).

Repeated recrystallisation of the mixture from hexanes gave pure 175. The $^1$H NMR spectrum indicated that the t-butyl group and trimethylsilyl group were cis. The doublet of doublets at 2.40 ppm ($J_{13.2, 2.7}$) was assigned to $H_2$; coupling constants verified that $H_2$ was axial, therefore the silyl substituent was equatorial. The distorted triplet of triplets at 1.18 ppm was due to $H_4$ ($J_{12.0, 2.8}$); coupling constants were consistent with $H_4$ in the axial position, therefore the t-butyl group was in the equatorial position.

The identity of 176 was puzzling at first, but microanalysis suggested the unknown compound had the same formula as 175. It is thought that the 4-t-butyl group and 2-trimethylsilyl groups are trans. The signal assigned to $H_4$ occurred at 1.27 ppm, and showed vicinal coupling of $ca.$ 12 and 4 Hz. These coupling constants were consistent with ax-ax coupling and ax-eq coupling, indicating that $H_4$ was in the axial position, therefore the t-butyl group was in the equatorial position. The doublet of doublets at 2.61 ppm was assigned to $H_2$, but coupleings of 7.7 and 4.2 Hz were less informative as they were ambiguous (ax-ax coupling is normally 6-14 Hz and ax-eq and eq-eq coupling is normally 0-5 Hz in 6-membered cyclic systems—chair conformation). Nevertheless, the trans relationship of substituents requires $H_2$ to be equatorial. It is likely that the chair conformation is distorted to relieve steric interactions, because, although there is evidence that a trimethylsilyl group is less stERICALLY DEMANDING THAN...
Chapter 3: Deprotonation of sulphones

a t-butyl group (ascribed to the increased distance between the silicon atom and its point of attachment to the molecule in question),\textsuperscript{205} they are still both relatively large.

**Stereochemistry of formation and quenching of sulphonyl carbanions**

The formation of trans-2-trimethylsilyl-4-t-butylpentamethylene sulphone was surprising, because the literature had lead us to believe that, in constrained systems, $H_{\text{eq}}$ was removed in preference to $H_{\text{ax}}$ by a lithiated base and that the substituent always went into the equatorial position.\textsuperscript{180,181} For example, studies of the relative rates of H-D exchange of diastereotopic hydrogens in conformationally constrained cyclic sulphones have shown that the exchange of an equatorial hydrogen for deuterium is significantly faster than exchange of the axial hydrogen (Scheme 3.25 and Table 3.3).\textsuperscript{180,181} Deprotonation involves removal of an $\alpha$-hydrogen which lies along the internal bisector of the O-S-O angle.

$$
\text{deprotonation} \rightarrow \text{NaOMe, D}_2\text{O}
$$

**Scheme 3.25: Removal of an equatorial hydrogen**

<table>
<thead>
<tr>
<th>Sulphone</th>
<th>$k_{\text{eq}}/k_{\text{ax}}$</th>
<th>$k_{\text{eq}}/k_{\text{ax}}$</th>
<th>$k_{\text{eq}}/k_{\text{ax}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H→D exchange</td>
<td>1.6:1</td>
<td>90:1</td>
<td>200:1</td>
</tr>
<tr>
<td>Ref</td>
<td>181</td>
<td>180</td>
<td>180</td>
</tr>
</tbody>
</table>

**Table 3.3: Ratio of $k_{\text{eq}}/k_{\text{ax}}$ protons exchanged for D$_2$O**

Also, when cyclic sulphones are deprotonated $\alpha$- to the sulphone group and quenched with electrophiles; the new substituents are introduced solely into the equatorial position (Scheme 3.26).\textsuperscript{182,183}

$$
\begin{align*}
\text{BuLi, THF, -78°C} & \quad \text{Me, acetone or D}_2\text{O} \\
\end{align*}
$$

**Scheme 3.26: Sole equatorial substitution**
Retention/Inversion of configuration

The 2:1 mixture of monosilylated sulphones $175/176$ was treated at $-78^\circ$C with 2 eq. of BuLi and then the lithiated carbanion was warmed up to room temperature. Water was added to quench the carbanion at room temperature. All of the substrate was converted into $176$ (Scheme 3.27).

Scheme 3.27: Conversion of the equatorial silyl group of $175$ into an axial silyl group

This change in stereochemistry at the 2-position was not seen when $144$ and $170$ were treated with 2 eq. of BuLi and quenched either at $-78^\circ$C or at $0^\circ$C (Scheme 3.28).

Scheme 3.28: No inversion of configuration the substituent substituted carbon in $144$ or $170$

This was at variance with literature reports\cite{182} which state that if there is a substituent in the equatorial position, it appears in the axial position after deprotonation and electrophilic quenching. For example, complete conversion was reported for compound $177$, $179$ and $181$ to $178$, $180$ and $182$ respectively (Scheme 3.29). For the group to end up in the axial position, axial deprotonation or a change in conformation to the chair-boat form followed by equatorial deprotonation, must occur. This has been attributed to the preference of lithium for the equatorial position and/or a strong preference for an equatorial carbanion.
In contrast to the retention of configuration that we saw with cis-2-methyl-4-t-butylpentamethylene sulphone (144) and cis-2-benzyl-4-t-butylpentamethylene sulphone (170), complete inversion of one of the substituents was noted when the cis-2,6-dimethyl-4-t-butylpentamethylene sulphone (168) and cis-2,6-dibenzyl-4-t-butylpentamethylene sulphone (171) were treated with 2 eq. of LDA or BuLi and quenched at either -78°C or 0°C (Scheme 3.30).

There does not seem to be any straightforward reason for our results; possibly it is a steric effect and as the 2- and 6-substituents increase in size, one substituent prefers to be axial to minimise steric interactions; this is illustrated in Figure 3.4.

![Steric crowding around SO2 group](image)

**Figure 3.4: Steric crowding around SO2 group**
3.4.3 DEPROTONATION OF 4-THIOPYRAN-4,4-DIOXIDE

Compound 146 was added to a mixture of 1 equivalent of lithiated base and trimethylsilyl chloride (internal quench). 50% reacted to give 183 while 50% remained unreacted (Scheme 3.31). The $^{13}$C NMR spectrum contained only 3 signals at -1.56, 56.97 and 66.60 due to the methyl carbons of the trimethylsilyl group, $C_{3/5}$ and $C_{2/6}$. Coupling constants for $H_{2/6}$ of 12.6 and 3.5 Hz were consistent with the hydrogens being in the axial positions.

![Scheme 3.31: Treatment of 146 with LDA and an internal TMSCl quench](image)

When 146 was treated with LDA, and the resultant carbanion was quenched with trimethylsilyl chloride, benzyl bromide or methyl iodide (external quench), the expected products were not isolated and the $^1$H NMR spectrum, although showing the loss of 146, was unstructured and did not allow the identification of any of the species. It is possible, that the base has ring-opened the substrate and polymerisation has occurred (Scheme 3.32).

![Scheme 3.32: Fate of 146 when treated by a base in aprotic conditions](image)
Chapter 3: Deprotonation of sulphones

3.5 DEPROTONATION USING CHIRAL LITHIUM AMIDE BASES.
The aim of this work was to use chiral lithium amide bases to enantiotopically deprotonate a constrained cyclic sulphone such as 4-t-butylpentamethylene sulphone and thereby create an enantomerically enriched/pure product (See Section 3.2, Scheme 3.7).

3.5.1 DETERMINATION OF ENANTIOMERIC EXCESS
The optical rotations of enantiomerically pure 2-substituted-4-t-butylpentamethylene sulphones are unknown, therefore the optical purity of the products described in this section could not be determined from optical rotation measurements. The enantiomeric purity of the products was estimated from their 1H NMR spectra in the presence of chiral lanthanide shift reagents (CLSR). The accuracy of the enantiomeric excess determined by CLSR is reportedly ±2% with enantiomeric excesses in the region 0-60 %, but this falls to ± 10% for enantiomeric excesses ≥ 90%.207

Three chiral lanthanide shift reagents were tested (Figure 3.5). Compounds 144, 175/176 and 170 (10 mg) were dissolved in deuterated chloroform and 0.1 mg portions of the chiral lanthanide shift reagents were added.

Figure 5: Structures of the chiral lanthanide shift reagents used and the compounds they were tested on.
Pr (III) is generally significantly better than Eu (III) in its resolving powers\textsuperscript{207} and shifts peaks to higher field whereas Eu causes downfield shifts. Upfield shifts are advantageous when observing methyl groups because the methyl signals are moved out of the region of overlap with other peaks. When CLSR-184 used with racemic 144, extensive line broadening with no separation of the enantiomeric methyl signals was observed. CLSR-184 did not separate the enantiomeric signals in compounds 170 or 175/176 either. With CLSR-185 all the signals from 144 were shifted down field; a large amount of the reagent had to be added to achieve any separation of the enantiomeric signals and, unfortunately, extensive line broadening was seen before complete separation of the methyl doublets occurred. Similarly, CLSR-185 did not resolve the enantiomeric signals in compound 170 or 175/176.

CLSR-186 successfully separated the enantiomeric methyl doublets of compound 144 (by \( \sim 0.1 \) Hz); the methyl signals were shifted to \( \sim 2.1 \) ppm where they were not coincident with any other signals. Both the enantiomeric \( \text{-butyl} \) singlets and the trimethylsilyl singlets of compounds 175/176 were separated by this CLSR but the enantiomeric signals in 170 were not.

3.5.2 Formation of the Chiral Lithium Amide Base

Hindered lithium amide bases have been widely used, but conditions for their preparation by reaction of BuLi on the corresponding amine differ greatly.\textsuperscript{208} \textsuperscript{13}C NMR has been used to evaluate the formation of lithium amide bases at low temperature and it was reported that lithium diisopropylamide, lithium bis(trimethylsilyl)amide and lithium 2,2,6,6-tetramethylpiperidine were completely formed in THF at -73°C after 3 minutes.\textsuperscript{208} These amines were relatively hindered and it was thought likely that the reaction of the hindered chiral amines (shown in Scheme 3.33) with BuLi would also occur speedily. The chiral lithium amide bases described in Scheme 3.33 were prepared by treatment of the corresponding amines with BuLi at 0°C to -20°C over 15-30 minutes, under a nitrogen atmosphere. Amines 110a, 112a, 119a, and 119b were treated with one equivalent of lithium amide base, but amines 187, 189, 126b and 126a were treated with two equivalents (one to remove the OH proton, the other to remove an NH proton).


It was important to check that the lithium amide was fully formed under those conditions, because unreacted BuLi would give the same product as the chiral lithium amide base, but without asymmetric induction. A series of standard reactions were carried out in which 1.1 equivalents of the chiral amine was treated with 1 equivalent of BuLi at 0°C in THF and stirred for 15 minutes, then benzaldehyde was added (Scheme 3.34). Alcohol 192 was not seen in any run, except when excess BuLi was added as a control, and so complete conversion to the lithium amide under those conditions had been achieved.

Scheme 3.34: Test to determine if the chiral lithium amide base had completely formed.
3.5.3 Deprotonation of 4-7-Butylpentamethylene Sulphone and Reaction with MeI

4-7-Butylpentamethylene sulphone was deprotonated with a range of chiral lithium amide bases and the resultant carbanion was reacted with MeI. The lithium amide bases and reaction conditions used (including the reaction times $t_1$ and $t_2$); the ratio of products and the e.e. of 144 are detailed in Table 3.4.

Scheme 3.35: Enantiotopic deprotonation of 143, and methylation to give 144 as a mixture of enantiomers 144a and 144b in varying amounts depending on the chiral lithium amide base used.

In the $^1$H NMR spectrum of the crude product, the doublet assigned to the methyl group of 144 occurred at 1.34 ppm and was partially overlapping with the doublet assigned to the methyl groups at 1.37 ppm of 168. The doublet due to one of the methyl groups of 169 occurred at 1.40 ppm. The ratio of products was calculated by comparison of the integrals of the relevant methyl doublets. As these doublets were very close and in one case overlapping, it must be stated that the ratios are only approximate and no definite distinction can be made between reactions that give similar ratios of products. Even so, it was noticeable that relatively less dimethylated product (168 and 169) was isolated when bases 30a and 17a were used, while bases 188, 190, 191b and 191b, which are dilithated, gave larger amounts.

Compound 144 was isolated as a mixture of two enantiomers; the enantiomeric signals were separated by the addition of CLSR-186 (see Figure 3.7). The ratio of the enantiomers...
differed, depending on which chiral lithium amide base was used. The absolute configuration of the major enantiomer was not established.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>LiCl added</th>
<th>$T_1$ / $T_2$</th>
<th>Ratio $^b$</th>
<th>Yield $^c$ (%) of 144 after purification</th>
<th>Ratio of enantiomers $^d$</th>
<th>% e.e.$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36a</td>
<td>X</td>
<td>18h</td>
<td>8:1:1</td>
<td>42</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>36a</td>
<td>X</td>
<td>3h min.</td>
<td>7:1:1</td>
<td>57</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>36a</td>
<td>X</td>
<td>15 min.</td>
<td>7:1:1</td>
<td>49</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>36a</td>
<td>√</td>
<td>15 min.</td>
<td>81:1</td>
<td>51</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>36b</td>
<td>X</td>
<td>30 min.</td>
<td>No reaction</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>36b</td>
<td>X</td>
<td>5h.</td>
<td>No reaction</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>30a</td>
<td>X</td>
<td>15 min.</td>
<td>15:1:1</td>
<td>59</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>30a</td>
<td>√</td>
<td>15 min.</td>
<td>18:1:1</td>
<td>48</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>17a</td>
<td>X</td>
<td>15 min.</td>
<td>25:2:1</td>
<td>54</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>17a</td>
<td>√</td>
<td>30 min.</td>
<td>25:1:1</td>
<td>56</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
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<td>15 min.</td>
<td>5:1:1</td>
<td>32</td>
<td>60:40</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
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<td>X</td>
<td>15 min.</td>
<td>5:1:1</td>
<td>60</td>
<td>38:62</td>
<td>22</td>
</tr>
<tr>
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<td>√</td>
<td>15 min.</td>
<td>5:1:1</td>
<td>59</td>
<td>60:40</td>
<td>20</td>
</tr>
<tr>
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<td>√</td>
<td>15 min.</td>
<td>4:2:1</td>
<td>42</td>
<td>40:60</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>190</td>
<td>X</td>
<td>30 min.</td>
<td>10:2:1</td>
<td>51</td>
<td>55:45</td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>190</td>
<td>√</td>
<td>15 min.</td>
<td>10:2:1</td>
<td>39</td>
<td>55:45</td>
<td>10</td>
</tr>
<tr>
<td>17</td>
<td>191b</td>
<td>X</td>
<td>15 min.</td>
<td>5:1:1</td>
<td>58</td>
<td>62:38</td>
<td>22</td>
</tr>
<tr>
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<td>√</td>
<td>15 min.</td>
<td>4:1:1</td>
<td>55</td>
<td>60:40</td>
<td>20</td>
</tr>
<tr>
<td>19</td>
<td>191a</td>
<td>X</td>
<td>15 min.</td>
<td>5:1:1</td>
<td>51</td>
<td>55:44</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>191a</td>
<td>√</td>
<td>15 min.</td>
<td>5:1:1</td>
<td>58</td>
<td>56:44</td>
<td>12</td>
</tr>
</tbody>
</table>

$^a$ For $T_1$ and $T_2$ refer to Scheme 3.35. $^b$ Ratio of products calculated from the $^1$H NMR spectrum of the crude material. $^c$ Approximate yield of 144 after purification of the mixture by flash chromatography (still contained small amount of the other products). $^d$ Ratio of enantiomers 144a and 144b and e.e. calculated from the ratio of intensities of the separated enantiomeric signals of 144a and 144b in the presence of CLSR-186

Table 3.4: Summary of results obtained when 143 was treated with one mol. eq. of chiral lithium amide base, followed by methyl iodide.
The camphor derived base 36a was the first chiral lithium amide base used to deprotonate 4-\textit{t}-butylpentamethylene sulphone (143). Initially, the method reported for the deprotonation of 2,6-dimethylcyclohexanone was followed; amine 119a was treated with BuLi at -10°C and stirred for 30 minutes. The solution was cooled to -78°C and 143 was added, then the mixture was stirred overnight ($t_1$) at -78°C before quenching with MeI. The mixture was stirred for a further 5 hours ($t_2$) before work-up (Table 4, entry 1). This method presented certain practical difficulties in keeping the mixture at -78°C for so long but as it was found to be fully deprotonated after 15 minutes (Table 4, entries 3 and 4) shorter reaction times were then used for the deprotonation of 4-\textit{t}-butylpentamethylene with the other bases.

The camphor derived base 36b did not deprotonate 4-\textit{t}-butylpentamethylene sulphone (Table 4, entries 5 and 6); it has been reported previously that although this base gave good results with 2,6-dimethycyclohexanone, it would not deprotonate 4-\textit{t}-butylcyclohexanone.

Racemic 144 was obtained when bases, 30a, 17a and 36a were used (Table 4, entries 1, 2, 3, 7 and 9). Only the bases containing both a lithium amide and a lithium alkoxide function showed some enantiotopic selection. Base 188a (derived from (1R,2S)-(\textit{\textendash})-ephedrine) was the first base of this series used to deprotonate 4-\textit{t}-butylpentamethylene sulphone; subsequent methylation of the carbanion gave 2-methylpentamethylene sulphone (144a) in 20% e.e. (Table 4, entry 11). Base 188b (derived from (1S,2R)-(\textit{\textendash})-ephedrine) gave the opposite enantiomer (144b) also in ~20% e.e. (Table 4, entry 12).

Base 190 (derived from (1R,2S)-norephedrine) which has a free NH proton as well as NLi and OLi groups, showed less selectivity and 2-methylpentamethylene sulphone (144a) was produced in 12% e.e. (Table 4 entry 15).

Because of the relative success of the ephedrine bases 188, two new chiral lithium amide bases (191a and 191b) were designed, with a similar 1-hydroxy-3-amino relationship, but with a more constrained structure. 144a was obtained in 22% e.e. with base 191b (Table 4, entry 17) while base 191a was less selective and gave 144 in 10% e.e. (Table 4, entry 19). This suggests that the 'cis' arrangement of NLi and OLi in bases 191a and 191b is important in the asymmetric induction. Bases 188a, 190, 191a and 191b all gave the same major enantiomer.

![Figure 3.6: Chiral lithium amide bases with the LiO-C-C-NLi arrangement of atoms](image-url)
The addition of lithium chloride to deprotonation reactions with chiral lithium amide bases has been shown to increase the e.e. of the products\textsuperscript{36,37,38,39} (described in Chapter 1, Section 1.2.1.2); the amount of lithium chloride added was not critical, with 0.5 mol. eq. per mole of base being the most common. This effect is thought to be due to the formation of an aggregate of base and LiCl which is more selective than the lithium amide alone. When the deprotonation-methylation reaction of 4-t-butylpentamethylene sulphone (143) with base 191b was carried out in the presence of 0.5 eq. of LiCl, there was no change in e.e. (20% e.e; same major enantiomer) (Table 4, entry 18 vs entry 17). Likewise, there was no significant change in e.e. when bases 191a and 190 were used in the presence of LiCl (Table 4, entries 20 vs 19 and 16 vs. 15). When the ephedrine derived base 188a was used in the presence of LiCl, the results were not reproducible. The reaction was carried out six times, with apparently identical conditions. In four cases, the same major enantiomer (144a) was produced in 20\% ± 4\% e.e. (Table 4, entry 13). In the other two instances, the opposite enantiomer (144b) (identified from comparison of \textsuperscript{1}H NMR signals in the presence of CLSR) was produced, also in 20\% e.e.; it was also noted that relatively more dimethylated product had been produced in these later two experiments (Table 4, entry 14). The reason for this change in the major enantiomer and for the greater extent of dimethylation is unknown. Perhaps the rate of addition of the reagents or the rate of stirring are significant; perhaps a kinetic resolution of 144 has occurred \textit{in situ} (i.e. one of the enantiomers of 144 reacted faster with another mole of base leaving an excess of this other enantiomer), although the analogous reaction of racemic 2-methylpentamethylene sulphone (144) with 0.5 eq. of base 188a in the presence of LiCl gave equal amounts of racemic 144 and dimethylated material.
Figure 3.7: The gradual separation of the enantiomeric methyl doublets from a non-racemic mixture of 144 in CDCl₃ by the successive addition of portions of CLSR-186.
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20\% e.e. of 144a (Table 3.4, entry 11)
(Chiral lithium amide base 188a was used)

22\% e.e. of 144b (Table 3.4, entry 12)
(Chiral lithium base 188b was used)

Figure 3.8: A sample of the $^1$H NMR spectra obtained from non-racemic mixtures of 144 in the presence of CLSR-186. The e.e's obtained from these spectra are detailed in Table 3.4
3.5.4 DEPROTONATION OF 4-t-BUTYLPENTAMETHYLENE SULPHONE AND REACTION WITH TMSCl

An internal quench with TMSCl has been shown to give better asymmetric induction in the enantiotopic deprotonation reactions of cyclic ketones and sulfoxides. However an internal quench was not suitable in this case because of the large amount of disubstituted rather than monosubstituted sulphone that is generated (described in sections 3.4.1.5 and 3.4.2.3). Therefore 4-t-Butylpentamethylene sulphone (143) was deprotonated with a range of chiral lithium amide bases and the resultant carbanion was reacted with TMSCl in an external quench.

\[ \text{LITHIUM AMIDE BASE} \]
\[ \text{143} \]
\[ \text{stirred for } t_1, -78^\circ\text{C, THF} \]
\[ \rightarrow \]
\[ \text{2) TMSCl added} \]
\[ \text{stirred for } t_2, -78^\circ\text{C} \]
\[ 3) 3\text{M HCl added} \]

175a and 175b represent the two enantiomeric products. The relative amounts of each change, depending on the base used, but the absolute configuration of each is unknown

176a and 176b represent the two enantiomeric products. The relative amounts of each change, depending on the base used, but the absolute configuration of each is unknown

Scheme 3.36: Enantiotopic deprotonation of 143, and reaction with TMSCl to give 175 as a mixture of enantiomers 175a and 175b in varying amounts and 176 as a mixture of enantiomers 176a and 176b in varying amounts, depending on the chiral lithium amide base used.
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As with the achiral bases, the silyl group went into both the equatorial and axial positions to give the diastereomeric sulphones 175 and 176; the characteristic singlets in the $^1$H NMR from Si(CH$_3$)$_3$ occurring at 0.25 ppm and 0.27 ppm respectively. Each compound was present as a mixture of two enantiomers; the ratio of which differed depending on which chiral lithium amide base had been used. The ratio of enantiomers was determined from the $^1$H NMR spectrum by comparison of the relative areas of the enantiomeric t-Bu and of the enantiomeric Si(CH$_3$)$_3$ signals which both separated on addition of CLSR-186. The enantiomeric signals in 175 separated first, while several more portions of CLSR were required to separate the enantiomeric signals of 176. In both cases, the Si(CH$_3$)$_3$ signals moved more quickly downfield than the t-butyl signals and eventually were observed at lower field than the t-butyl signals (Figure 3.9). The absolute configuration of the major enantiomer in each case was not established.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>LiCl added$^a$</th>
<th>$T_1 / T_2^a$</th>
<th>Ratio of 175:176$^b$</th>
<th>Yield of 175/176 (%)$^c$</th>
<th>Ratio of enantiomers 175a:175b$^d$</th>
<th>e.e.$^d$</th>
<th>Ratio of enantiomers 176a:176b$^d$</th>
<th>e.e.$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36a</td>
<td>X</td>
<td>10 min. 10 min.</td>
<td>3:1</td>
<td>63</td>
<td>50:50</td>
<td>0</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>36a</td>
<td>✓</td>
<td>10 min. 30 min.</td>
<td>5:1</td>
<td>56</td>
<td>50:50</td>
<td>0</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>17a</td>
<td>X</td>
<td>10 min. 30 min.</td>
<td>5:1</td>
<td>49</td>
<td>50:50</td>
<td>0</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>17a</td>
<td>✓</td>
<td>10 min. 30 min.</td>
<td>4:1</td>
<td>56</td>
<td>50:50</td>
<td>0</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>188a</td>
<td>X</td>
<td>10 min. 30 min.</td>
<td>2:1</td>
<td>47</td>
<td>57:43</td>
<td>14</td>
<td>58:42</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>188a</td>
<td>✓</td>
<td>5 min. 5 min.</td>
<td>2:1</td>
<td>48</td>
<td>59:41</td>
<td>18</td>
<td>59:41</td>
<td>18</td>
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<tr>
<td>7</td>
<td>190</td>
<td>X</td>
<td>10 min. 30 min.</td>
<td>3:1</td>
<td>57</td>
<td>53:47</td>
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</tr>
<tr>
<td>8</td>
<td>190</td>
<td>✓</td>
<td>10 min. 30 min.</td>
<td>3:1</td>
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<td>54:46</td>
<td>8</td>
<td>53:47</td>
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<td>3:1</td>
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<td>56:44</td>
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<td>2:1</td>
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<td>54:46</td>
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<tr>
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<td>56</td>
<td>54:46</td>
<td>8</td>
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</table>

$^a$ For $t_1$ and $t_2$ refer to Scheme 3.36. $^b$ Ratio of products calculated from the $^1$H NMR spectrum of the crude material. $^c$ Approximate yield of the diastereomeric mixture 175/176 after purification of the crude material by flash chromatography. $^d$ Ratio of enantiomers and e.e. are calculated from the ratio of intensities of the separated enantiomeric signals of the compounds in the presence of CLSR-186

Table 3.5: Summary of results obtained when 143 was treated with one mol. eq. of chiral lithium amide base, followed by TMSCl
When 143 was treated with a chiral base and the subsequent carbanion was reacted with TMSCl, asymmetric induction was slightly less than that obtained when the carbanion was quenched with Mel. Bases 36a and 17a failed to produce any induction (Table 3.5, entries 1-4), while bases 188a and 191b gave the best induction (14-18 % e.e.) (Table 3.5, entries 5,6, 9 and 10). The presence of LiCl did not have any significant effect on the level of e.e.. The axially substituted diastereomer (176) and equatorially substituted diastereomer (177) showed the same enantiomeric ratios in all cases.

### 3.5.5 Effect of solvent, temperature and other additives

Briefly, the effect of temperature, a change in solvent and the addition of DMPU on the enantioselective reaction of a chiral lithium amide base with 4-tert-butylpentamethylene sulphone and subsequent methylation was examined. The results are summarised in Table 3.6. When base 188a was used, the e.e. of 144 increased slightly when the reaction was carried out at -110°C compared to -78°C, and decreased as the temperature was increased; no e.e. was obtained when the reaction temperature was 0°C, yields of 144 were similar (ca. 60%). (Table 3.6, entries 1-4). Changing the solvent to ether or toluene did not increase the enantioselectivity of base 118a; only 10 % e.e. was seen in ether (Table 3.6, entry 5) and <5 % e.e in toluene (Table 3.6, entry 7). The presence of DMPU in the reaction lowered the yield and no e.e. was observed (Table 3.6, entry 9). No e.e. was generated when base 30a was used in toluene, ether and THF with or without DMPU (Table 3.6, entries 6, 8 and 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp. °C</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Ratio of enantiomers</th>
<th>e.e. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>-78</td>
<td>THF</td>
<td>X</td>
<td>60</td>
<td>60:40</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>10a</td>
<td>ca. -110</td>
<td>THF</td>
<td>X</td>
<td>60</td>
<td>62:38</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>10a</td>
<td>ca. -50</td>
<td>THF</td>
<td>X</td>
<td>60</td>
<td>53:47</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>10a</td>
<td>0</td>
<td>THF</td>
<td>X</td>
<td>60</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>10a</td>
<td>-78</td>
<td>Etherb</td>
<td>X</td>
<td>55</td>
<td>55:45</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>10a</td>
<td>-78</td>
<td>Etherb</td>
<td>X</td>
<td>55</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10a</td>
<td>-78</td>
<td>Toluene</td>
<td>X</td>
<td>40</td>
<td>50:50</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>10a</td>
<td>-78</td>
<td>Toluene</td>
<td>X</td>
<td>45</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>10a</td>
<td>-78</td>
<td>THF</td>
<td>DMPUc</td>
<td>35</td>
<td>50:50</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>-78</td>
<td>THF</td>
<td>DMPUc</td>
<td>40</td>
<td>50:50</td>
<td>0</td>
</tr>
</tbody>
</table>

\(a\) Yield calculated from \(^1\)H NMR spectrum of crude product containing monosubstituted, disubstituted and unreacted sulphone.

\(b\) The sulphone was practically insoluble in ether at -78°C

\(c\) 1 mol. eq. of DMPU added

**Table 3.6:** Effect of temperature, solvent and the presence of DMPU on the asymmetric induction
Figure 3.9a: Separation of the enantiomeric tBu and Si(Me)₃ signals in compounds 175 and 176 using CLSR-186 (continued on next page).
Chapter 3: Deprotonation of sulphones

Addition of more CLSR-186

Figure 3.9b: Separation of the enantiomeric tBu and Si(Me)$_3$ signals in compounds 175 and 176 using CLSR-186.
3.6 SUMMARY

2-Substituted-4-t-butylpentamethylene sulphones were prepared by deprotonation of the cyclic sulphone followed by reaction with an electrophilic reagent such as MeI or TMSCl. The group in the 2-position could be either cis or trans to the 4-t-butyl group depending on the electrophilic reagent, the base and reaction conditions used. When the chiral lithium amides bases 30a, 17a and 36a, which are known to be excellent enantiotopic deprotonating agents for ketones, sulphoxides and epoxides,\textsuperscript{11,27} were used, no enantiotopic selection was observed. However, when the bases 188, 190, 191a and 191b, which have a 1-hydroxy-3-amino arrangement of atoms were used, some enantioselectivity was observed and 2-methyl-4-t-butylpentamethylene sulphone and 2-trimethyl-4-t-butylpentamethylene sulphone were produced in 10-24% e.e. This enantioselectivity is still very low and these reactions were not pursued.
MICHAEL ADDITION OF CHIRAL LITHIUM AMIDES TO α,β-UNSATURATED SUBSTRATES

CHAPTER 4

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Chapter 4: Michael additions using chiral lithium amides

4.1 INTRODUCTION

Chapter 1 summarises the literature concerning the 1,4-conjugate addition of chiral amines and chiral lithium amides to achiral \( \alpha,\beta \)-unsaturated substrates. This chapter deals with the conjugate addition of chiral lithium amides to several Michael acceptors under the following headings:

i) Addition of a chiral lithium amide to several Michael acceptors.

ii) Addition of a chiral lithium amide to an \( \alpha,\beta \)-unsaturated ester followed by an electrophilic quench.

iii) Addition of a chiral lithium amide to a series of \( \alpha,\beta \)-unsaturated amides.

There are two components to any conjugate acceptor; the unsaturated system and the activating substituent (\( Z \)). The two common conjugated acceptors are the activated alkene and alkyne (Figure 4.1).

\[
\begin{align*}
\text{where } Z &= \text{H, R, OR, S-R, S-OR, S-NR}_2, \text{ etc.} \\
\end{align*}
\]

**Figure 4.1:** A list of common activating groups for \( \alpha,\beta \)-unsaturated substrates

The relative activating power of these groups can be roughly correlated with their ability to stabilise an adjacent carbanion (\( \text{NO}_2 > \text{RCO} > \text{CO}_2\text{R} > \text{SO}_2\text{R} > \text{CN} \sim \text{CONR}_2 \)). In general, the reactivity of acceptors towards various stabilised carbanions follows \( \alpha,\beta \)-unsaturated aldehydes \( \gg \alpha,\beta \)-unsaturated ketones \( > \alpha,\beta \)-unsaturated nitriles \( > \alpha,\beta \)-unsaturated esters \( > \alpha,\beta \)-unsaturated amides.
### 4.2 INVESTIGATION OF SEVERAL MICHAEL ACCEPTORS

In the present studies, the chiral lithium amide bases 17a and 30a were investigated as reagents to several Michael acceptors (Figure 4.2). Table 4.1 summarises the reaction conditions and results.

![Structure of chiral lithium amides 17a and 30a](image)

**Figure 4.2:** Structure of chiral lithium amides 17a and 30a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate No.</th>
<th>Lithium amide (quench)</th>
<th>Temp. (°C)</th>
<th>Time (min.)</th>
<th>Colour change on addition of substrate to soln. of base</th>
<th>Result - crude 1H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>17a (H₂O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour lost but reappeared after 5 min.</td>
<td>No addition. Starting materials recovered</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>17a (H₂O)</td>
<td>0</td>
<td>15</td>
<td>Pink colour lost but reappeared after 5 min.</td>
<td>No addition. Starting materials recovered</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>17a (H₂O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour lost but reappeared faintly after 5 min.</td>
<td>No addition. Amine recovered (substrate evaporated off)</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>17a (H₂O)</td>
<td>0</td>
<td>15</td>
<td>Pink colour lost but reappeared after 5 min.</td>
<td>No addition. Amine recovered (substrate evaporated off)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>30a (D₂O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour disappeared immediately and did not reappear</td>
<td>No addition. Deuterium incorporation into substrate</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>17a (D₂O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour disappeared immediately and did not reappear</td>
<td>No addition. Deuterium incorporation into substrate</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>30a (D₂O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour disappeared immediately and did not reappear</td>
<td>No addition. Deuterium incorporation into substrate</td>
</tr>
</tbody>
</table>

Table 4.1: (Continued on next page) Results obtained on the addition of chiral lithium amides 17a or 30a to various α,β-unsaturated substrates
## Chapter 4: Michael additions using chiral lithium amides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Lithium amide (quench)</th>
<th>Temp. (°C)</th>
<th>Time (min.)</th>
<th>Colour change&lt;sup&gt;a&lt;/sup&gt; on addition of substrate to soln. of base</th>
<th>Result- crude&lt;sup&gt;b&lt;/sup&gt; 1&lt;sup&gt;1&lt;/sup&gt;H NMR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>![PhNPh]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour did not disappear</td>
<td>No addition. Starting materials recovered</td>
</tr>
<tr>
<td>9</td>
<td>![PhNPh]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>0</td>
<td>15</td>
<td>Pink colour did not disappear</td>
<td>No addition. Starting materials recovered</td>
</tr>
<tr>
<td>10</td>
<td>![PhNPh]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>15</td>
<td>Solution turned dark red immediately</td>
<td>No addition. Starting materials recovered</td>
</tr>
<tr>
<td>11</td>
<td>![PhNO]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>15</td>
<td>Solution turned black immediately</td>
<td>Amine was recovered but no substrate. Possible polymerisation</td>
</tr>
<tr>
<td>12</td>
<td>![OOMe]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>30</td>
<td>Solution turned black immediately</td>
<td>Amine was recovered but no substrate. Possible polymerisation</td>
</tr>
<tr>
<td>13</td>
<td>![PhOMe]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour disappeared immediately and did not reappear</td>
<td>The Michael addition product was isolated quantitatively</td>
</tr>
<tr>
<td>14</td>
<td>![OON]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>30</td>
<td>Solution immediately turned green and brown ppt formed</td>
<td>Amine was recovered but no substrate. Possible polymerisation</td>
</tr>
<tr>
<td>15</td>
<td>![PhO]</td>
<td>30a (H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>-78</td>
<td>15</td>
<td>Pink colour disappeared but returned after 1 min.</td>
<td>The Michael addition product was isolated quantitatively</td>
</tr>
</tbody>
</table>

<sup>a</sup> The chiral lithium amides were prepared by reaction of the corresponding amine with BuLi at 0°C. These lithium amide solutions were bright pink and a change in colour on addition of a solution of the substrate in THF was an indication that some reaction had occurred. The reaction mixtures were stirred for 15-30 minutes, then H<sub>2</sub>O or D<sub>2</sub>O was added.

<sup>b</sup> Crude product mixtures were analysed by 1<sup>1</sup>H NMR.

<sup>c</sup> Substrate and Mel were added together to the solution of lithium amide.

Table 4.1: Results obtained on the addition of chiral lithium amides 17a or 30a to various α,β-unsaturated substrates.
Chapter 4: Michael additions using chiral lithium amides

α,β-Unsaturated aldehydes
The Michael addition of pyrrolidine to crotonaldehyde (THF containing 1 mol% of DBU at -15°C) has been reported in the literature; it was found that while 3-methyl-3-(pyrrolidin-1-yl)-propanal was formed quantitatively in solution, removal of the solvent lead to immediate polymerisation (Scheme 3.1).211

The Michael additions of lithium amide 17a to cinnamaldehyde (193) (Table 4.1, entries 1 and 2) and crotonaldehyde (194) (Table 4.1, entries 3 and 4) were attempted. The pink colour of the lithium amide solution disappeared on addition of the α,β-unsaturated aldehyde solution, but returned after a few minutes. No addition products or polymerised material were isolated and the starting materials were recovered. This absence of polymerisation suggested that the Michael addition product had not formed in the first place.211

α,β-Unsaturated aldehydes are the most reactive of the acceptors but addition of organolithiums or organomagnesium halides to α,β-unsaturated aldehydes normally gives exclusive 1,2-addition to yield allylic alcohols. The lithium cation is a hard acid and with α,β-unsaturated aldehydes the C₁ carbon (C=O) is a harder base than the C₃ carbon so reaction is preferred at the hard C₁ site.212 1,2-Addition of lithium amide 17a to 193 and 194 may have occurred but in these examples the 1-amino alcohol adduct is expected to be unstable with respect to decomposition to the starting materials (Scheme 4.2).

Scheme 4.1: Addition of pyrrolidine to crotonaldehyde211

Scheme 4.2: Possible 1,2-addition of lithium amide 17a to 193
\(\alpha,\beta\)-Unsaturated ketones

The next substrates investigated were 3-methylcyclohex-2-enone (195) (Table 4.1, entry 5) and 4-phenylbut-3-en-2-one (196) (Table 4.1, entries 6 and 7). No addition products were isolated and starting materials were recovered. The pink colour attributed to the lithium amide disappeared on addition of the \(\alpha,\beta\)-unsaturated ketones. Deuterium incorporation was seen \(\alpha\)- to the carbonyl function in both cases when the reactions were quenched with D\(_2\)O (Scheme 4.3) to give 205 and 204 respectively, suggesting formation of the enolate. Therefore the lithium amide was acting as a base rather than a nucleophile towards these substrates.

\[
\begin{align*}
1) & \quad \text{Ph} \quad \text{CH}_3 \quad \text{THF} \\
2) & \quad \text{D}_2\text{O} \\
\end{align*}
\]

Scheme 4.3: Deuterium incorporation into the \(\alpha,\beta\)-unsaturated ketones

\(\alpha,\beta\)-Unsaturated imines and nitriles and nitro compounds

\(\alpha,\beta\)-Unsaturated imines\(^{213,214}\) and \(\alpha,\beta\)-unsaturated nitriles\(^{215}\) have been shown to undergo 1,4-addition with carbon nucleophiles, but no reaction was observed when 197 (Table 4.1, entries 8 and 9) or 198 (Table 4.1, entry 10) were treated with the lithium amide 30a. Nitroolefins are also known to make excellent Michael acceptors due to a low propensity for 1,2-addition and strong anion stability of the nitro group\(^{216}\). For example, the addition of ammonia to 1-nitrocyclohexene is achieved simply by treating with ammonia in THF at 45°C for 24 hours\(^{217}\). When nitrostyrene (199) (Table 4.1, entry 11) was added to a solution of the lithium amide, polymerisation occurred rapidly. Therefore MeI was added with the substrate in an attempt to quench the intermediate enolate immediately it formed. This was unsuccessful and polymerisation occurred rapidly.
\( \alpha, \beta \)-Unsaturated esters and amides

When dimethyl maleate (200) (Table 4.1, entry 12) and N-phenylmaleimide (202) (Table 4.1, entry 14) were added to solutions of the lithium amide 30a, polymerisation occurred rapidly, due to the reactive nature of these substrates. In contrast, lithium amide 30a reacted smoothly with the less activated methyl cinnamate (201) (Table 4.1, entry 13) and N-cinnamoyl amide (203) (Table 4.1, entry 15) to give the corresponding Michael addition products (Scheme 4.4); these reactions have been investigated in detail and the findings are described in Section 4.3 and Section 4.5 respectively.

4.3 \( \alpha, \beta \)-UNSATURATED ESTERS: TANDEM ADDITION-ALKYLATION

4.3.1 INTRODUCTION

An initial Michael-type addition of a nucleophile (NuM) to a \( \alpha, \beta \)-unsaturated substrate transforms both the \( \beta \) and \( \alpha \) carbons. The \( \beta \)-carbon becomes further substituted and the \( \alpha \)-carbon takes on nucleophilic character. The conjugate enolate ion can, subsequently be trapped \textit{in situ} with an appropriate electrophile (EX). When \( E^+ \neq H^+ \) a new chiral centre is formed in the \( \alpha \)-position (Scheme 4.5).

![Scheme 4.5: Generalised Michael addition reaction](image-url)
It was known from the literature\textsuperscript{132} that lithium amide 30a will add to methyl crotonate (101) face selectively to give the Michael adduct 208 in 95\% d.e. (Scheme 4.6).

\[
\begin{array}{c}
\text{Me} \\
\text{J}
\end{array}
\text{L}
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph}
\end{array}
30a
\xrightarrow{\text{THF, -78°C}}
\begin{array}{c}
\text{Me} \\
\text{J}
\end{array}
\text{L}
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph}
\end{array}
208
\]

Scheme 4.6: Addition of lithium amide 30a to methyl crotonate

Initially we wanted to examine the diastereoselectivity of electrophilic quenches at the α-position in such systems.

\textbf{4.3.2 ADDED添加ITION OF LITHIUM AMIDE 30A TO METHYL CINNAMATE}

Addition of lithium amide 30a to methyl cinnamate followed by a proton quench was carried out to check the diastereoselectivity of the initial addition on a cinnamate ester (Scheme 4.7). Lithium amide 30a in THF was treated with a solution of methyl cinnamate in THF at -78°C. After 15 minutes the intermediate enolate was quenched with a saturated solution of NH\textsubscript{4}Cl.

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{Me}
\end{array}
\xrightarrow{\text{THF, -78°C}}
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{Me}
\end{array}
\]

Scheme 4.7: Addition of lithium amide 30a to methyl cinnamate

The \textsuperscript{1}H NMR spectrum of the crude material indicated that a 16:1 mixture of diastereomers (206a and 206b) had been produced (88\% d.e.). This ratio was determined by comparison of the relative areas of a pair of doublet of doublets at 2.5-2.7 ppm and a pair of doublet of doublets at 2.9-3.1 ppm due to the methylene protons attached to C\textsubscript{2} for the major diastereomer and minor diastereomer respectively. When the reaction was carried out at 0°C there was no change in the observed diastereoselectivity. The relative stereochemistry of the new chiral centre was tentatively assigned by comparison to the results obtained by Davies for
Chapter 4: Michael additions using chiral lithium amides

his crotonate ester series. It was believed that the lithium amide would show the same face selectivity with the cinnamate esters as with crotonate esters.\textsuperscript{132} Subsequently, several papers have been published in this area, confirming the stereochemical assignment.\textsuperscript{218,219}

In a second reaction, the intermediate enolate was quenched with MeI at -78°C. (Scheme 4.8). Methyl iodide was chosen as the electrophile; it is the most common alkyl halide used for this purpose and is more reactive than primary alkyl halides and allylic alcohol halides.\textsuperscript{220,221}

![Scheme 4.8: Addition of lithium amide 30a to methyl cinnamate, MeI quench](image)

The \(^1\text{H} \) NMR of crude 209 indicated that a 25:2:1 mixture of diastereomers (209a: others) had been produced (78% d.e.). This ratio was determined by comparison of the relative areas of a doublet at 0.74 ppm, a doublet at 0.65 ppm and a doublet at 0.60 ppm assigned to the methyl protons of the major diastereomer and two minor diastereomers respectively. It was thought that the nucleophile entity would hinder one face so MeI would attack from the opposite side, giving the relative configuration as drawn for the major diastereomer. In a parallel investigation, this compound was prepared using similar conditions in 85% d.e.\textsuperscript{218} and the stereochemistry was confirmed.

In the above reaction the intermediate enolate was quenched sequentially with MeI (Scheme 3.8). It was hoped that if the alkylating agent was in the reaction mixture at the time of Michael addition, the intermediate enolate would be quenched immediately and that this would give a higher d.e.. MeI was added to 201 before addition of chiral lithium amide 1. 209 was produced in 60% yield but there was no improvement in diastereoselectivity (74% d.e.). Other alkylating agents including methyl mesylate, methyl tosylate and bromobutane failed to react with the intermediate enolate.
4.3.3 Attempted Intramolecular Electrophilic Quench

When an α,β-unsaturated substrate contains a suitable leaving group such as a halide, intramolecular substitution is sometimes observed. The alkyl halide may originate as part of the substrate or more commonly as part of the nucleophile.

In an attempt to prepare the lactone via a tandem Michael addition-intramolecular substitution, chiral lithium amide (1 eq.) was added dropwise to a solution of (2-iodoethyl)cinnamate (210) (Scheme 4.9).

![Scheme 4.9: Attempted Tandem Michael addition - intramolecular substitution](image)

The $^1$H spectrum of the crude product mixture indicated that none of the cyclised product had formed but 20% of 212, 20% 213 and 10% 214 and 50% (2-iodoethyl)cinnamate were isolated; the mixture was partially separated by preparative tlc. The chiral lithium amide 30a added in a Michael fashion to 210 to give 212 which was identified on the basis of $^1$H and $^{13}$C NMR. No olefinic signals were present, indicating that Michael addition had occurred and the doublet of doublets at 4.47 ppm in the $^1$H NMR spectrum was characteristic of the methine proton attached to C₃. The upfield signal at -0.006 ppm in the $^{13}$C NMR spectrum was due to the carbon of the CH₂I function; its presence verified that HI had not been eliminated. The lithium amide 30a also acted as a base on 210 to give 213 by elimination of HI in an E2 type reaction. Compound 213 contained two double bonds as evidenced by the pair of doublets of doublets at 4.46 and 5.00 ppm which were assigned to the two CH₂=C protons and the doublets at 6.48 and 7.75 which were assigned to the PhCH=CH protons. Compound 214 was formed from 210 by 30a acting both as a nucleophile and a base; Michael addition and
elimination of HI had occurred. The $^1$H NMR spectrum of 214 contained a pair of doublets of doublets at 4.48 ppm and 4.73 ppm due to the two CH$_2$=C protons, a doublet of doublets at 7.13 ppm due to the OCH=CC proton and a pair of doublets of doublets at 2.62 and 2.75 ppm due to the magnetically inequivalent methylene protons attached to C$_2$. As there was no evidence for the intramolecularly cyclised product, this line of investigation was not pursued.

### 4.3.4 Recent Publications Concerning the Addition of Chiral Lithium Amides to $\alpha,\beta$-Unsaturated Esters (1993 & 1994)

The Michael addition of chiral lithium amides to $\alpha,\beta$-unsaturated esters has recently received considerable attention and a summary of the relevant literature is given here.

The synthesis of (-)-(1R, 2S)-cispentacin (215), an anti fungal antibiotic, was achieved in 98% e.e. using this methodology (Scheme 4.10).$^{227,228}$

\[ \text{Scheme 4.10: Synthesis of (-)-(1R, 2S)-cispentacin} \]

A number of $\alpha,\beta$-unsaturated esters were reacted with lithium amide 30a, and the intermediate enolate was reacted in situ with an alkylating agent (tandem alkylation) (Scheme 4.11 and Table 4.2).$^{218}$ With the exception of the tandem methylation of methyl cinnamate, only a small preference was found for the anti diastereomer. A stepwise approach, in which the proton quenched conjugate adducts were isolated before subsequent redeprotonation and alkylation was found to give much higher selectivity at the $\alpha$-centre due to the different enolate geometries (Scheme 4.11 and Table 4.2).$^{218}$
Chapter 4: Michael additions using chiral lithium amides

**Tandem alkylation**

\[
\begin{align*}
\text{R}^1\text{C} = \text{O} & \rightarrow \text{R}^1\text{C} = \text{O}_\text{R}^2 \\
1) & \text{Li} \text{R}^- \text{N} \text{Ph} \text{Ph} \text{N} \text{Li} \\
\text{THF, } -78^\circ\text{C} & \\
2) & \text{R}^3\text{X} \\
& -78^\circ\text{C} \text{ to rt overnight}
\end{align*}
\]

**Stepwise alkylation**

\[
\begin{align*}
\text{R}^1\text{C} = \text{O} & \rightarrow \text{R}^1\text{C} = \text{O}_\text{R}^2 \\
1) & \text{LDA} \text{ Ph} \% \text{ N} \text{Ph} \\
\text{THF, } -78^\circ\text{C} & \\
2) & \text{R}^3\text{X} \\
& -78^\circ\text{C} \text{ to rt overnight}
\end{align*}
\]

**Scheme 4.11:** Tandem and stepwise approaches to alkylation at the α-positon

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R³</th>
<th><strong>Tandem alkylation</strong></th>
<th></th>
<th><strong>Stepwise alkylation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yield %</td>
<td>ratio anti : syn</td>
<td>Yield %</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>50</td>
<td>1.2:1</td>
<td>89</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Bn</td>
<td>54</td>
<td>3:1</td>
<td>52</td>
</tr>
<tr>
<td>Me</td>
<td>tBu</td>
<td>Me</td>
<td>60</td>
<td>1.36:1</td>
<td>69</td>
</tr>
<tr>
<td>Me</td>
<td>tBu</td>
<td>Bn</td>
<td>42</td>
<td>1:1</td>
<td>83</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>61</td>
<td>≥ 13:1</td>
<td>76</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Bu</td>
<td>55</td>
<td>3:1</td>
<td>80</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>allyl</td>
<td>79</td>
<td>3:1</td>
<td>70</td>
</tr>
<tr>
<td>Ph</td>
<td>tBu</td>
<td>Me</td>
<td>78</td>
<td>1.36:1</td>
<td>70</td>
</tr>
<tr>
<td>Ph</td>
<td>tBu</td>
<td>Bn</td>
<td>46</td>
<td>2.5:1</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 4.2:** The yield and ratio of diastereomers obtained in the tandem and stepwise alkylations at the α-positon of crotonate and cinnamate esters (refer to Scheme 4.11).
Syn-α-methyl-β-amino esters have been prepared from (E)-2-methyl-α,β-unsaturated esters. Protonation was found to share the same diastereofacial preference as the corresponding alkylations (Scheme 4.12, Table 4.3). The low yields were attributed to γ-deprotonation and 1,2-addition.

![Scheme 4.12: Addition of lithium amide 30a to (E)-2-methyl-α,β-unsaturated esters]

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Solvent</th>
<th>Proton source</th>
<th>Yield %</th>
<th>ratio syn : anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>THF</td>
<td>pH 7 buffer</td>
<td>21</td>
<td>10:1</td>
</tr>
<tr>
<td>Me</td>
<td>Bn</td>
<td>Me</td>
<td>THF</td>
<td>pH 7 buffer</td>
<td>11</td>
<td>&gt;10:1</td>
</tr>
<tr>
<td>Me</td>
<td>tBu</td>
<td>Me</td>
<td>THF</td>
<td>pH 7 buffer</td>
<td>43</td>
<td>15:1</td>
</tr>
<tr>
<td>Me</td>
<td>tBu</td>
<td>Me</td>
<td>toluene-THF</td>
<td>pH 7 buffer</td>
<td>43</td>
<td>15:1</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>THF</td>
<td>pH 7 buffer</td>
<td>38</td>
<td>15:1</td>
</tr>
<tr>
<td>Ph</td>
<td>tBu</td>
<td>Me</td>
<td>toluene-THF</td>
<td>2,6-di-t-butylphenol</td>
<td>45</td>
<td>50:1</td>
</tr>
<tr>
<td>Et</td>
<td>tBu</td>
<td>Me</td>
<td>toluene-THF</td>
<td>2,6-di-t-butylphenol</td>
<td>65</td>
<td>99:1</td>
</tr>
</tbody>
</table>

Table 4.3 Addition of lithium amide 30a to (E)-2-methyl-α,β-unsaturated esters (Refer to Scheme 4.12)²²⁹

In a complementary study, t-butyl crotonate and t-butyl tiglate were treated with (S)-106 (Scheme 4.13), then Mel; good diastereoselectivity was obtained in both cases to give 216 in 86% d.e. and 217 in 67% d.e. respectively.²³⁰

The synthesis of several anti-α-alkyl-β-amino acids²¹⁸,²¹⁹,²³⁰ and syn-α-alkyl-β-amino acids²²⁹,²³⁰,²³¹ has been achieved by debenzylation and hydrolysis of the above products.
Chapter 4: Michael additions using chiral lithium amides

\[
\text{(S)-106}
\]

Scheme 4.13: Addition of (S)-106 to t-butyl crotonate and t-butyl tiglate

Unlike tandem alkylation, hydroxylation of the intermediate enolates with (+)-(camphorsulphonyl)oxaziridine was reported to show high selectivity and this methodology has been used in the synthesis of the taxol side chain\textsuperscript{232,233}, allophenylnorstatine\textsuperscript{234,235} and (2S,3R)-3-amino-2-hydroxydecanoic acid\textsuperscript{236}. The general method that was used is illustrated in Scheme 4.14 by the synthesis of the unnatural enantiomer (218) of the taxol side chain\textsuperscript{232}

Scheme 4.14: Synthesis of the taxol side chain
4.4 αβ-UNSATURATED AMIDES: TANDEM MICHAEL ADDITIONS - ELECTROPHILIC QUENCHES

4.4.1 INTRODUCTION

α,β-Unsaturated amides undergo conjugate addition with a variety of nucleophiles.\textsuperscript{237,238,239,240,241,242,243,244} Michael addition is normally seen in preference to 1,2-addition, especially when the substituents attached to nitrogen are large.\textsuperscript{238,244} It has been shown that alkyl and aryl lithium reagents, LDA, lithium enolates, lithiated dithiane and Grignard reagents undergo rapid Michael addition to tertiary crotonamides and that the resulting amide enolates can be quenched with alkyl and acyl halides, chloroformates and aromatic aldehydes to give α,β-disubstituted products in high yield (Table 4.4, entries 1-10).\textsuperscript{239} Secondary crotonamides reacted with the hard alkyl lithium nucleophiles only (Table 4.4, entries 11, 12).\textsuperscript{239}

\[
\begin{align*}
\text{Me} & \quad \text{Nu}^- \\
\text{N} & \quad \text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{E}^+ &
\end{align*}
\]

Amide 219, 220 or 221

Scheme 4.15: Reported tandem addition of nucleophiles to α,β-unsaturated amides followed by electrophilic quenchs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Nu⁺</th>
<th>E⁺</th>
<th>Yield %\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>219</td>
<td>t-BuLi</td>
<td>n-PrBr</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>219</td>
<td>n-BuLi</td>
<td>Mel</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>220</td>
<td>n-BuLi</td>
<td>Cl</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>n-BuLi</td>
<td>Me</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>220</td>
<td>n-BuLi</td>
<td>ClCO₂Et</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>220</td>
<td>n-BuLi</td>
<td>ClCO₂Et</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>220</td>
<td>PhMgBr</td>
<td>H⁺</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>220</td>
<td>PhMgBr</td>
<td>H⁺</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>220</td>
<td>n-BuLi</td>
<td>Me</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>220</td>
<td>LDA</td>
<td>Mel</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>221</td>
<td>n-BuLi</td>
<td>H⁺</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>221</td>
<td>n-BuLi</td>
<td>Mel</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{a} isolated as mixtures of diastereomers when E⁺ ≠ H⁺

Table 4.4: Tandem Michael addition-electrophilic quench products of 219, 220 and 221.\textsuperscript{239}
In a parallel and complementary investigation to Davies's additions of chiral lithium amides to \( \alpha,\beta \)-unsaturated esters we have studied the use of \( \alpha,\beta \)-unsaturated amides as Michael acceptors towards lithium amides.

### 4.4.2 Synthesis of \( \alpha,\beta \)-Unsaturated Amides

\( N,N \)-Disubstituted amides were required for use as Michael acceptors. These amides were prepared by treatment of an \( \alpha,\beta \)-unsaturated acid chloride with a secondary amine.\(^{245}\)

\[ \text{R-CH=CH-OH} \overset{\text{SOCl}_2}{\rightarrow} \text{R-CH=CH-Cl} \overset{\text{ether, TEA, XH}}{\rightarrow} \text{R-CH=CH-X} \]

\( \alpha,\beta \)-unsaturated amide

**Scheme 4.16: Synthesis of \( \alpha,\beta \)-unsaturated amides**

<table>
<thead>
<tr>
<th>( \alpha,\beta )-Unsaturated amide</th>
<th>R</th>
<th>R(^1)</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>203</td>
<td>Ph</td>
<td>H</td>
<td>N</td>
<td>O</td>
</tr>
<tr>
<td>222</td>
<td>Ph</td>
<td>H</td>
<td>N</td>
<td>Ph</td>
</tr>
<tr>
<td>223</td>
<td>Ph</td>
<td>H</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>224</td>
<td>Ph</td>
<td>H</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>225</td>
<td>Me</td>
<td>H</td>
<td>N</td>
<td>O</td>
</tr>
<tr>
<td>226</td>
<td>Me</td>
<td>H</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>227</td>
<td>Et</td>
<td>H</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>228</td>
<td>Ph</td>
<td>Me</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Extensive polymerisation occurred when crotonyl chloride and 2-pentenoyl chloride were reacted with \( N,N \)-dimethylamine, leading to low yields of 226 and 227 respectively.

**Table 4.5:** Table showing the R, R\(^1\) and X group and the yield of each of \( \alpha,\beta \)-unsaturated amide.
**4.4.3 ADDITION OF LITHIUM AMIDE 30A TO α,β-UNSATURATED AMIDES**

The Michael addition of lithium amide 30a to the series of α,β-unsaturated amides was examined, in which the resulting amide enolates were quenched with water, methyl iodide, benzyl bromide, benzaldehyde and acetaldehyde. In a typical experiment the α,β-unsaturated amide in tetrahydrofuran was added to a solution of the chiral lithium amide 30a at -78°C. After 15 minutes the electrophilic reagent was added and mixture was stirred for a further 15 minutes before the reaction was worked-up under standard conditions.

In the following sections two sets of results are discussed. In the first, the evidence for Michael addition and a subsequent electrophilic quench is provided; in the second the evidence supporting diastereomeric excess of one isomer and the absolute configurations of the chiral centres is presented. The orientation of the addition and of the electrophilic quench was proved by X-ray crystallographic examination of addition product 247 an 249. The results are discussed on pages 129-131 and they provided unequivocal evidence of the absolute stereochemistry.

**Michael addition - proton quench**

Lithium amide 30a was reacted with the α,β-unsaturated amides in THF at -78°C and the intermediate enolate was quenched with a proton source (aq. NH₄Cl) at -78°C (Scheme 4.17).

![Scheme 4.17: Addition of 30a to an α,β-unsaturated amide followed by a proton quench](image-url)
Michael addition of lithium amide 30a to the α,β-unsaturated amides was detected by the loss of the olefinic signals in the $^1$H NMR and the appearance of a pair of doublets of doublets arising from the inequivalent protons attached to C$_2$ which couple to each other and the proton at C$_3$ and a doublet of doublets (when R= Ph) or a more complex signal (when R= Me or Et) due to the proton at C$_3$. This $^1$H NMR data is summarised in Table 4.6 for the major diastereomer (a) in each reaction. The methylene protons at C$_4$ were inequivalent and each proton was seen as a doublet; this data has also been included in Table 4.6.

The $^1$H NMR spectrum of the crude material indicated that the Michael addition product had been formed quantitatively in each case. The excess amine that was used in the reaction was removed by flash chromatography and the yields of the purified material are given in Table 4.16. The 1,2-addition product was not observed in any of the reactions.

A new chiral centre at C$_3$ was created in this reaction, giving rise to the possibility of two diastereomers. In each case, the addition was highly diastereoselective and one major diastereomer (a) was isolated. The ratio of diastereomers produced in the reaction was determined by comparison of the relative areas of distinctive proton signals assigned to each diastereomer in the $^1$H NMR spectrum of the crude material. The proton signals that were chosen for comparison, the ratio of diastereomers in the crude product and the ratio of diastereomers after purification are given in Table 4.7. The assignment of the absolute stereochemistry of these addition products is explained in section 4.4.4.
Chapter 4: Michael additions using chiral lithium amides

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>R</th>
<th>Yield(^a)</th>
<th>(^1)H NMR of the major diastereomer (a)</th>
<th>(^1)H NMR of the major diastereomer (a)</th>
<th>(^1)H NMR of the major diastereomer (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(H_2)</td>
<td>(H_3)</td>
<td>(H_4)</td>
</tr>
<tr>
<td>207</td>
<td></td>
<td>Ph</td>
<td>79%</td>
<td>2H, m, (\delta 2.4-2.5)</td>
<td>1H, t, (\delta 4.51) ((J 6.3))</td>
<td>1H, d, (\delta 3.67) ((J 15.0))</td>
</tr>
<tr>
<td>228</td>
<td></td>
<td>Ph</td>
<td>69%</td>
<td>1H, dd, (\delta 2.48) ((J 15.1, 4.0))</td>
<td>1H, dd, (\delta 4.70) ((J 11.4, 4.0))</td>
<td>1H, signal overlapping</td>
</tr>
<tr>
<td>229</td>
<td></td>
<td>Ph</td>
<td>68%</td>
<td>1H, dd, (\delta 2.44) ((J 15.0, 3.0))</td>
<td>1H, dd, (\delta 4.55) ((J 8.1, 5.0))</td>
<td>1H, d, (\delta 3.68) ((J 14.9))</td>
</tr>
<tr>
<td>230</td>
<td></td>
<td>Ph</td>
<td>85%</td>
<td>2H, m, (\delta 2.4-2.5)</td>
<td>1H, t, (\delta 4.58) ((J ~7))</td>
<td>1H, d, (\delta 3.67) ((J 15.0))</td>
</tr>
<tr>
<td>231</td>
<td></td>
<td>Me</td>
<td>68%</td>
<td>1H, dd, (\delta 2.17) ((J 13.5, 10.0))</td>
<td>1H, signal overlapping with other signals</td>
<td>2H, s, (\delta 3.74)</td>
</tr>
<tr>
<td>232</td>
<td></td>
<td>Me</td>
<td>76%</td>
<td>1H, dd, (\delta 2.13) ((J 14.2, 9.2))</td>
<td>1H, m, (\delta 3.42)</td>
<td>1H, d, (\delta 3.72) ((J 14.6))</td>
</tr>
<tr>
<td>233</td>
<td></td>
<td>Et</td>
<td>65%</td>
<td>1H, dd, (\delta 1.82) ((J 15.3, 4.3))</td>
<td>1H, m, (\delta 3.39)</td>
<td>1H, d, (\delta 3.58) ((J 14.8))</td>
</tr>
</tbody>
</table>

\(^a\) yield after chromatography,  
\(^b\) ratio of diastereomers in the crude product mixture

Table 4.6: Yields of Michael adducts and characteristic \(^1\)H NMR signals of the major diastereomer (refer to Scheme 4.17)

<table>
<thead>
<tr>
<th>Product</th>
<th>207</th>
<th>228</th>
<th>229</th>
<th>230</th>
<th>231</th>
<th>232</th>
<th>233</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton observed</td>
<td>(H_2)</td>
<td>(H_3)</td>
<td>(H_4)</td>
<td>(H_5)</td>
<td>(H_6)</td>
<td>(H_7)</td>
<td>(H_8)</td>
</tr>
<tr>
<td>Multiplicity</td>
<td>dd</td>
<td>d</td>
<td>dd</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>t</td>
</tr>
<tr>
<td>(\delta) values/(ppm)</td>
<td>4.51</td>
<td>1.37</td>
<td>4.55</td>
<td>1.32</td>
<td>0.94</td>
<td>1.36</td>
<td>1.05</td>
</tr>
<tr>
<td>(\delta) values/(ppm)</td>
<td>4.38</td>
<td>1.27</td>
<td>4.30</td>
<td>1.26</td>
<td>1.16</td>
<td>1.60</td>
<td>0.73</td>
</tr>
<tr>
<td>(\delta) values/(ppm)</td>
<td>16:1 (88)</td>
<td>19:1 (90)</td>
<td>16:1 (88)</td>
<td>(\geq 49:1) (96)</td>
<td>12:1 (85)</td>
<td>(\geq 49:1) (96)</td>
<td>(\geq 49:1) (96)</td>
</tr>
<tr>
<td>Ratio of diastereomers in crude product d.e. (%)(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified product d.e. (%)</td>
<td>90</td>
<td>90</td>
<td>88</td>
<td>(\geq 96)</td>
<td>85</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
</tbody>
</table>

\(^a\) ratio of diastereomers is calculated from the ratio of signals in the crude \(^1\)H NMR spectrum

Table 4.7: Ratio of diastereomers; details of the \(^1\)H NMR signals from which the ratios were calculated (refer to Scheme 4.17).
Chapter 4: Michael additions using chiral lithium amides

The high face selectivity attained on the addition of lithium amide 30a to the α,β-unsaturated amides was encouraging but, surprisingly, the analogous reaction of compound 228 with 30a failed to yield the Michael addition product (235). This is possibly because the intermediate enolate can not attain the stable s-cis conformation (234) due to allylic strain between the C2 methyl group and the N-methyl group anti to the carbonyl group (Scheme 4.18).

![Scheme 4.18: Attempted formation of the syn-diastereomer (235)](image)

**Michael addition - quench with alkylating agent**

In this series of experiments, the lithium amide 30a was added to the series of α,β-unsaturated amides and the intermediate enolates were quenched with Mel. The tandem Michael addition-alkylation products 236-242 were isolated in high yield.

![Scheme 4.19: Michael addition of 30a to various α,β-unsaturated amides and subsequent quench with Mel](image)
Michael addition was shown by the loss of olefinic signals and the subsequent alkylation by the presence of signals from the entran alkyl substituent in the $^1$H and $^{13}$C NMR spectra of the products. Other characteristic proton signals were a multiplet arising from the proton at C$_2$ and a doublet (when R= Ph) or a more complicated splitting pattern (when R= Me or Et) due to the proton at C$_3$. This $^1$H NMR data is recorded in Table 4.8 for the major diastereomer (a) of products 236-240 and 242.

New chiral centres at C$_3$ and C$_2$ were created in the Michael addition-methylation reaction, giving rise to the possibility of four diastereomers. The ratio of diastereomers was determined by comparison of the relative areas of the proton signals assigned to each diastereomer. The protons chosen for this comparison and the ratios of diastereomers in each product are detailed in Table 4.9.

Both the addition of the lithium amide 30a to $\alpha,\beta$-unsaturated amides 203, 223 and 224 and the subsequent alkylation reactions occurred with high diastereoselectivity to give one major diastereomer (a) and two minor diastereomers in each case. The diastereoselectivity of the methylation reaction was much lower when $\alpha,\beta$-unsaturated amides 222 and 227 were used and in the case of both 225 and 226, methylation at C$_2$ showed no selectivity and 1:1 mixtures of two major diastereomers, along with small amounts of other minor diastereomers were isolated.

The individual diastereomers in products 241 and 242 (from $\alpha,\beta$-unsaturated amides 225 and 226 respectively) were not separated; therefore the signals in their $^1$H NMR spectra were not assigned to the individual diastereomers and have not been included in Table 4.8. Evidence that the Michael addition product 241 had been isolated came from the presence of six methyl doublets in the region $\delta$ 0.8-1.3 (three for each diastereomer) and a multiplet at $\delta$ 2.30 and 2.50 arising from the proton at C$_2$ of each diastereomer. Similar evidence (six methyl doublets in the region $\delta$ 0.8-1.5 and the C$_2$ proton at $\delta$ 2.45 and $\delta$ 3.15) suggested that the Michael addition product 242 had been formed.
Table 4.8: Yields of Michael addition-tandem alkylation products and their characteristic ¹H NMR signals

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>R</th>
<th>R²X</th>
<th>Product (yield)*</th>
<th>¹H NMR of major diastereomer (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H₇, H₄, H₅</td>
</tr>
<tr>
<td>236</td>
<td></td>
<td>Ph</td>
<td>MeI</td>
<td>67%</td>
<td>1H, signal overlapping with others</td>
</tr>
<tr>
<td>237</td>
<td></td>
<td>Ph</td>
<td>MeI</td>
<td>69%</td>
<td>1H, dq, δ 3.32 (J 10.6, 6.8)</td>
</tr>
<tr>
<td>238</td>
<td></td>
<td>Ph</td>
<td>MeI</td>
<td>60%</td>
<td>1H, signal overlapping with others</td>
</tr>
<tr>
<td>239</td>
<td></td>
<td>Ph</td>
<td>MeI</td>
<td>82%</td>
<td>1H, dq, δ 3.24 (J 10.4, 6.8)</td>
</tr>
<tr>
<td>240</td>
<td></td>
<td>Ph</td>
<td>BnBr</td>
<td>82%</td>
<td>1H, m, δ 3.6-3.7</td>
</tr>
<tr>
<td>241</td>
<td></td>
<td>Me</td>
<td>MeI</td>
<td>74%</td>
<td>see text</td>
</tr>
<tr>
<td>242</td>
<td></td>
<td>Me</td>
<td>MeI</td>
<td>60%</td>
<td>see text</td>
</tr>
<tr>
<td>243</td>
<td></td>
<td>Et</td>
<td>MeI</td>
<td>54%</td>
<td>1H, m, δ 2.3-2.4</td>
</tr>
</tbody>
</table>

*yield after chromatography

Table 4.9: Ratio of diastereomers from Michael addition-tandem alkylation reaction and details of the ¹H NMR signals from which the ratios were calculated (refer to Scheme 4.19).
**Chapter 4: Michael additions using chiral lithium amides**

Michael addition - quench with PhCHO

As the formation of the second chiral centre at C₂ occurred with high diastereoselectivity when αˌβ-unsaturated amides 203, 223 and 224 were treated with lithium amide 30a and the intermediate enolates were quenched with Mel, we decided to examine the generation and diastereoselectivity of three new chiral centres by quenching the intermediate enolates with benzaldehyde (Scheme 4.20).

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H} \\
\text{Ph} & \quad \text{N} \\
\text{Li} & \quad \text{X} \\
\end{align*}
\]

1) R\[\longrightarrow\]X

\[
\begin{align*}
\text{THF, } -78^\circ\text{C}, 15 \text{ min} & \quad \text{2) PhCHO, } -78^\circ\text{C}, 10 \text{ min.} \\
\end{align*}
\]

\[
\begin{align*}
\text{diastereomer (a)} \\
\text{diastereomer (b)} \\
\end{align*}
\]

\[
\begin{align*}
\text{αˌβ-Unsaturated} & \quad \text{Product} \\
\text{amide} & \quad \text{R} \\
\text{X} & \quad \text{N} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>αˌβ-Unsaturated amide</th>
<th>Product</th>
<th>R</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>203</td>
<td>244</td>
<td>Ph</td>
<td>N</td>
</tr>
<tr>
<td>222</td>
<td>245</td>
<td>Ph</td>
<td>N</td>
</tr>
<tr>
<td>223</td>
<td>246</td>
<td>Ph</td>
<td>N</td>
</tr>
<tr>
<td>224</td>
<td>247</td>
<td>Ph</td>
<td>N</td>
</tr>
<tr>
<td>225</td>
<td>248</td>
<td>Me</td>
<td>N</td>
</tr>
<tr>
<td>227</td>
<td>249</td>
<td>Et</td>
<td>N</td>
</tr>
</tbody>
</table>

**Scheme 4.20:** Tandem Michael addition-pseudo aldol reaction with PhCHO

The tandem Michael addition-pseudo aldol products 244-249 were isolated in good yields. (Table 4.10). Evidence that the tandem addition-aldol type reaction had succeeded came from the presence of an OH signal which was verified by exchange with D₂O, a doublet of doublets arising from the proton at C₇ which couples to the proton at C₃ and the hydroxy proton, a doublet of doublets arising from the proton at C₂ which couples to the proton at C₃ and the proton at C₇ and a doublet (when R=Ph) or a more complicated splitting pattern (when R=Me or Et), due to the proton at C₃, in the ¹H NMR spectra of these products. This NMR data is summarised in Table 4.10 for the major diastereomer (a) of products 244-247 and 249.

Eight diastereomeric products were theoretically possible from this reaction, but three were isolated in most cases. The three new chiral centres at C₃, C₂ and C₇ in the products were formed with excellent diastereoselectivity when αˌβ-unsaturated amides 203, 223 and 224 were used; the respective tandem Michael addition-aldol products 244, 246, and 247 contained one major diastereomer (a) and two minor diastereomers. The formation of the C₂ chiral centre occurred with less diastereoselectivity when αˌβ-unsaturated amides 222 and 227 were used; the tandem Michael addition pseudo-aldol products 245 and 249 were isolated as 2:1 and 3:1 mixtures of diastereomers (a and b). When 225 was used, there was
no selectivity and product 248 was isolated as a 1:1 mixture of two major diastereomers and other minor diastereomers; these diastereomers were not separated but comparison of the $^{13}$C NMR spectrum of the mixture with that of similar compounds indicated that Michael addition-tandem aldol reaction had occurred. Signals at 73.03, 70.80 and 73.84 ppm were assigned to C$_7$ for diastereomers a and b of 248.

<table>
<thead>
<tr>
<th>Product</th>
<th>X=</th>
<th>R</th>
<th>Yield$^a$</th>
<th>$^1$H NMR of major diastereomer</th>
<th>$^1$H NMR of major diastereomer</th>
<th>$^1$H NMR of major diastereomer</th>
<th>$^1$H NMR of major diastereomer</th>
<th>$^1$H NMR of major diastereomer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>244</td>
<td>N</td>
<td>O</td>
<td>Ph</td>
<td>80%</td>
<td>1H, dd, $\delta$ 3.70 (J 11.2, 2.2)</td>
<td>1H, d, $\delta$ 4.72 (J 11.2)</td>
<td>1H, dd, $\delta$ 4.32 (J 9.0, 2.2)</td>
<td>d, $\delta$ 5.34 (J 9.0)</td>
</tr>
<tr>
<td>245</td>
<td>N</td>
<td>Ph</td>
<td>Ph</td>
<td>75%</td>
<td>1H, dd, $\delta$ 3.82 (J 11.2, 1.7)</td>
<td>1H, d, $\delta$ 4.87 (J 11.2)</td>
<td>1H, dd, $\delta$ 4.46 (J 9.0, 1.7)</td>
<td>d, $\delta$ 5.95 (J 9.0)</td>
</tr>
<tr>
<td>246</td>
<td>N</td>
<td>Ph</td>
<td>Ph</td>
<td>84%</td>
<td>1H, signal overlapping with others</td>
<td>1H, d, $\delta$ 4.69 (J 11.2)</td>
<td>1H, signal overlapping with others</td>
<td>d, $\delta$ 5.75 (J 9.5)</td>
</tr>
<tr>
<td>247</td>
<td>N</td>
<td>Ph</td>
<td>Ph</td>
<td>72%</td>
<td>1H, signal overlapping with others</td>
<td>1H, d, $\delta$ 4.68 (J 11.3)</td>
<td>1H, dd, $\delta$ 4.29 (J 9.4, 2.0)</td>
<td>d, $\delta$ 5.38 (J 9.4)</td>
</tr>
<tr>
<td>248</td>
<td>N</td>
<td>O</td>
<td>Me</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>249</td>
<td>N</td>
<td></td>
<td>Et</td>
<td>52%</td>
<td>1H, dd, $\delta$ 2.93 (J 9.3, 2.2)</td>
<td>1H, m, $\delta$ 3.5</td>
<td>1H, dd, $\delta$ 4.87 (J 9.0, 1.9)</td>
<td>d, $\delta$ 5.58 (J 9.0)</td>
</tr>
</tbody>
</table>

$^a$ yield after chromatography

Table 4.10: Yields of the Michael addition-pseudo-aldol (PhCHO) products and their characteristic $^1$H NMR signals.

<table>
<thead>
<tr>
<th>Product</th>
<th>244</th>
<th>245</th>
<th>246</th>
<th>247</th>
<th>248</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton observed</td>
<td>H$_6$</td>
<td>H$_4$</td>
<td>H$_3$</td>
<td>NCH$_3$</td>
<td>OH</td>
<td>H$_9$</td>
</tr>
<tr>
<td>Multiplicity</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>s</td>
<td>d</td>
<td>t</td>
</tr>
<tr>
<td>$\delta$ values/ppm</td>
<td>4.71</td>
<td>0.92</td>
<td>4.69</td>
<td>2.66</td>
<td>5.42</td>
<td>1.10</td>
</tr>
<tr>
<td>4.82</td>
<td>1.10</td>
<td>4.83</td>
<td>2.33</td>
<td>5.15</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>4.72</td>
<td>1.20</td>
<td>4.85</td>
<td>2.77</td>
<td>5.08</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Ratio of diastereomers in crude material (d.e. %)$^a$</td>
<td>25:1:1 (85)</td>
<td>12:2:1$^b$ (60)</td>
<td>24:1:1 (85)</td>
<td>40:1:1 (90)</td>
<td>2:2:1$^b$ (0)</td>
<td>12:4:1$^b$ (33)</td>
</tr>
<tr>
<td>Ratio of diastereomers in purified material (d.e. %)</td>
<td>45:1:0 (96)</td>
<td>23:2:0 (84)</td>
<td>99:1:0 (98)</td>
<td>99:1:0 (98)</td>
<td>1:1 (0)</td>
<td>99:1:0 (98)</td>
</tr>
</tbody>
</table>

$^a$d.e. was determined from the $^1$H NMR spectrum of the crude product mixtures.

Table 4.11: Ratio of diastereomers obtained from the tandem Michael addition-pseudoaldol reactions and details of the $^1$H NMR signals from which the ratios were calculated (refer to Scheme 4.20).
Michael addition - quench with MeCHO

The Michael addition intermediate enolates were also treated with acetaldehyde.

The Michael addition intermediate enolates were also treated with acetaldehyde.

\[ \text{THF, -78}^\circ\text{C, 15 min} \]

\[ \text{MeCHO, -78}^\circ\text{C, 10 min.} \]

\[ \text{diastereomer (a)} \]

\[ \text{diastereomer (b)} \]

\[ \text{Scheme 4.21: Tandem Michael addition -pseudo-aldol reaction (MeCHO)} \]

The \(^1\)H NMR and \(^13\)C NMR spectra of the crude mixtures obtained from this reaction contained signals that could not be assigned to the expected Michael addition product. In the \(^1\)H NMR spectrum there were 6 doublets in the region 0.9-1.5 ppm, a quartet at 4.85 ppm, and multiplets at 4.95 and 5.4 ppm. The \(^13\)C NMR spectrum showed CH\(_3\) signals at 20.6, 20.7, 21.1 and 22.8 ppm, CH\(_2\) signals at 25.4, 37.0, 39.9, 40.0 and 67.8 ppm and CH signals at 67.3, 70.9, 90.3, 90.4, 94.4, 95.7 and 95.8 ppm. These signals were from 'self addition products' of acetaldehyde in the highly basic medium; this was confirmed by the addition of acetaldehyde to a solution of lithium amide; the resultant products showed identical NMR signals.

The 'self addition products' of acetaldehyde were removed by flash chromatography, leaving the tandem Michael addition-pseudo-aldol products 250-255 in good yield. The tandem Michael addition-pseudo-aldol products were identified by the presence of an OH group (verified by exchange with D\(_2\)O); a multiplet arising form the proton at C\(_7\) which had vicinal coupling to the proton at C\(_3\), the hydroxy proton and the methyl protons; a doublet of doublets arising from the proton at C\(_2\) which coupled to the proton at C\(_3\) and the proton at C\(_7\) and a doublet (when R=Ph) or a more complicated splitting pattern (when R=Me and Et) arising from the proton at C\(_3\). This \(^1\)H NMR data and the isolated yields are summarised in Table 4.12 for the major diastereomer (a) of products 250-253.
The presence of the 'self condensation products of acetaldehyde' made it very difficult to calculate the d.e. from the $^1$H NMR spectrum of the crude product mixture alone so the d.e. was calculated on the basis of the relative intensities of signals in the $^{13}$C NMR and $^1$H NMR spectra, although the $^{13}$C NMR ratios were less accurate due to n.O.e. effects..

As with benzaldehyde, the product had three new chiral centres at C$_3$, C$_2$, and C$_7$. These chiral centres were formed with excellent diastereoselectivity when $\alpha,\beta$-unsaturated amides 203, 223 and 224 were used, to give products 250, 252 and 253 respectively (Table 4.13) but C$_2$ was formed with less selectivity with 222, 225 and 227. Compound 254 (from 225) was isolated as a 1:1 mixture of two major diastereomers (a and b) and compound 255 (from 227) was isolated as a 4:3 mixture of two diastereomers (a and b). In both cases the two diastereomers were not separated by flash chromatography and the signals in the mixtures were not individually assigned to each diastereomer. Evidence that the required products had formed came from the $^1$H NMR spectra of the mixtures by comparison of distinctive signals with those from similar compounds. In the $^1$H NMR spectrum of 254, a doublet of doublets at 2.05 ppm and 2.45 ppm was assigned to the proton at C$_2$ for each diastereomer. Similarly the $^1$H NMR of product 255 showed doublets of doublets at 2.12 and 2.65 ppm assigned to the proton attached to C$_2$, doublets at 4.60 and 4.66 ppm due to the OH groups, and multiplets at 3.30 and 3.50 ppm due to the proton at C$_7$ for each diastereomer.

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>R</th>
<th>Product (yield)$^a$</th>
<th>$^1$H NMR of major diastereomer (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$H_2$</td>
</tr>
<tr>
<td>250</td>
<td>N</td>
<td>Ph</td>
<td>68%</td>
<td>1H, d, $\delta$ 4.61 (J 11.0)</td>
</tr>
<tr>
<td>251</td>
<td>N</td>
<td>Ph</td>
<td>71%</td>
<td>1H, d, $\delta$ 4.69 (J 10.7)</td>
</tr>
<tr>
<td>252</td>
<td>N</td>
<td>Ph</td>
<td>63%</td>
<td>1H, dd, $\delta$ 3.48 (J 9.3, 1.9)</td>
</tr>
<tr>
<td>253</td>
<td>N</td>
<td>Ph</td>
<td>57%</td>
<td>1H, dd, $\delta$ 3.48 (J 11.3, 2.2)</td>
</tr>
<tr>
<td>254</td>
<td>N</td>
<td>Me</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>255</td>
<td>N</td>
<td>Et</td>
<td>55%</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ yield after chromatography

Table 4.12: Yields of the Michael addition-pseudo-aldol (MeCHO) products and their characteristic $^1$H NMR signals.
Table 4.13: Ratio of diastereomers obtained from the tandem Michael addition-pseudo-aldol reactions and details of the ¹H NMR signals from which the ratios were calculated (refer to Scheme 4.21).

4.4.4 DETERMINATION OF THE RELATIVE AND ABSOLUTE STEREOCHEMISTRY OF THE MICHAEL ADDITION PRODUCTS

Although the ratio of diastereomers produced in these Michael addition reactions could be determined from the NMR spectra of the crude products, there was no evidence for the relative stereochemistry of the new chiral centres formed.

Three new chiral centres were formed in the addition of lithium amide 30a to α,β-unsaturated amide 224, followed by reaction of the intermediate enolate with benzaldehyde (Scheme 4.22).

Scheme 4.22: Diastereoselective formation of three new chiral centres in 247
The relative stereochemistry of these new chiral centres was determined from the coupling constants (Table 4.14) and nuclear Overhauser effects of compound 257. Compound 257 was prepared from 247 by debenzylation to 256 and subsequent cyclocondensation with CDI.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

**Scheme 4.23: Preparation of 257**

**1H NMR analysis of 257 to determine relative stereochemistry**

<table>
<thead>
<tr>
<th>Proton</th>
<th>(\delta) (CDCl\textsubscript{3})</th>
<th>(J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H_2) (CHCO)</td>
<td>3.53 ppm</td>
<td>4.9, 2.8</td>
</tr>
<tr>
<td>(H_1) (CHNH\textsubscript{2})</td>
<td>5.19 ppm</td>
<td>4.9</td>
</tr>
<tr>
<td>(H_2) (CHOH)</td>
<td>5.72 ppm</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**Table 4.14: Important vicinal coupling constants in the 1H NMR spectrum of 257**

**n.O.e. enhancements observed in compound 257:** Irradiation of the doublet at 5.19 ppm (\(H_3\)) produced a 2.5% enhancement of the doublet at 5.72 (\(H_2\)). Also seen was a 1% enhancement of the double doublet at 3.53 ppm (\(H_2\)) and a 1% enhancement of the multiplet at 7.43 (corresponding to the ortho-phenyl protons). Irradiation of the doublet at 5.72 ppm (\(H_2\)) produced a 2.5% enhancement of the doublet at 5.19 (\(H_3\)). A 1% enhancement of the doublet of doublets at 3.53 ppm (\(H_2\)) and a 1% enhancement of the multiplet at 7.44 (corresponding to the ortho-phenyl protons) was observed.

It was assumed that the 6-membered ring of 257 was in a chair conformation with the N(CO)O end flattened out due to the sp\textsuperscript{2} carbon. The n.O.e enhancements suggested that the protons \(H_3\) and \(H_2\) were close in space which would only happen if they were both in axial positions. The coupling constants between \(H_7\) and \(H_2\) and between \(H_3\) and \(H_2\) were consistent with either ax-eq coupling or eq-eq coupling but not ax-ax coupling. To satisfy this criteria, \(H_2\) would have to be in the equatorial position. Therefore the relative configuration of the three chiral centres was \(R*S*S*\) (Figure 4.3) and so the relative stereochemistry of the three new chiral centres in 247 was \(R*S*S*\).
Although the relative stereochemistry of the three new chiral centres in 247 was determined with the above analysis, the absolute stereochemistry could not be derived because the α-methylbenzyl group of known configuration was removed.

X-ray crystallographic analysis

After several attempts, crystals of compound 247 were isolated and proved suitable for X-ray crystallographic analysis (Figure 4.5). The results showed conclusively that when the α-methylbenzyl centre had the (R)-configuration, the configuration was (S) at C3, (S) at C2 and (R) at C7 (Figure 4.5).

The coupling constants of H2, H3 and H6 have been correlated with the dihedral angles determined by X-ray crystallography and are in agreement with the Karplus curve.

<table>
<thead>
<tr>
<th>Atoms involved</th>
<th>Vicinal coupling (Hz)</th>
<th>Dihedral angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2-C3-C2-H2</td>
<td>11.3</td>
<td>174.97</td>
</tr>
<tr>
<td>H2-C7-C7-H7</td>
<td>2.0</td>
<td>72.24</td>
</tr>
</tbody>
</table>

Table 4.15: Correlation of the important vicinal couplings and dihedral angles of 247
Compound 247 crystallised in the orthorhombic space group $P2_12_12_1$ (4 molecule in the unit cell), $a = 13.782$ Å, $b = 12.197$ Å, $c = 17.386$ Å. The hydrogen (H$_0$) of the OH group attached to C$_7$ was located in the Fourier map and was refined isotropically; there was a hydrogen bond of 2.027 Å between H$_0$ and O$_1$. The angle O$_2$-H$_0$-O$_1$ was 149.22°. The atoms O$_1$, N$_1$, C$_8$ and C$_9$ were nearly in a plane (Chi squared = 233). One notable feature of this structure was the partial occupancy of positions C$_6$ and C$_{6A}$. Partial occupancy factors of 0.66 and 0.33 for C$_6$ and C$_{6A}$ respectively gave the lowest R value. This means that 66% of the material has crystallised with the methyl group in position C$_6$ and 33% has crystallised with the methyl group in C$_{6A}$ (the chirality around both carbons is (R)). The carbons in the C$_{41}$ and C$_{51}$ phenyl rings are well defined and so the packing constraints in the unit cell allow the PhCH(CH$_3$)NCH$_2$Ph to be in two orientations, with the Ph groups in identical positions but the C$_6$ methyl group in one of two positions.

Figure 4.5: X-ray crystal structure of 247
A single crystal of the major diastereomer of compound \textbf{249} was also subjected to X-ray analysis and the same topicity was seen (the priority of the groups have changed relative to those of compound \textbf{247}). The important $^3J$ couplings were correlated with the dihedral angles obtained from the X-ray crystal structure (Table 4.16) and are in agreement with the Karplus curve.

<table>
<thead>
<tr>
<th>Atoms involved</th>
<th>Vicinal coupling (Hz)</th>
<th>Dihedral angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_3$-C$_7$-C$_7$-H$_2$</td>
<td>9.3</td>
<td>178.3</td>
</tr>
<tr>
<td>$H_2$-C$_7$-C$_7$-H$_7$</td>
<td>1.9</td>
<td>66.3</td>
</tr>
</tbody>
</table>

\textbf{Table 4.16:} Correlation of the important vicinal couplings and dihedral angles of \textbf{249}

\begin{center}
\includegraphics[width=\textwidth]{figure46}
\end{center}

\textbf{Figure 4.6:} Absolute stereochemistry of \textbf{249}

Compound \textbf{249} crystallised in the monoclinic space group P2$_1$, a = 6.180 Å, b = 19.204 Å, c = 10.587 Å, $\beta$ = 95.43° (2 molecules in unit cell). H$_O$ (of the OH group attached to C$_7$) was found in the Fourier map and was refined isotropically. There was an internal hydrogen bond between H$_O$ and O$_1$ of 1.89 Å.

\begin{center}
\includegraphics[width=\textwidth]{figure47}
\end{center}

\textbf{Figure 4.7:} X-ray crystal structure of \textbf{249}
Diastereoselectivity at each new chiral centre
The identical stereochemistry of the three newly formed chiral centres in 247 and 249 shows a commonality of approach by the nucleophilic addend and the electrophilic quench in both systems. The $^1$H and $^{13}$C NMR spectra of compounds 247 and 249 were compared with the spectra of the other Michael adducts and similar vicinal coupling constants between $H_2$ and $H_3$ and, where applicable, $H_2$ and $H_7$ were found (Tables 4.6, 4.8, 4.10 and 4.12). Consequently, it is assumed that the stereochemistry of both the addition of the nucleophile and the electrophilic quench is general throughout the range of substrates and quenches used.

The absolute configurations of the major diastereomers produced in the Michael addition-tandem electrophilic quench reactions are therefore assigned relative to the known configurations of compounds 247 and 249.

The formation of the new chiral centre at C$_3$ by the addition of lithium amide 30a to the $\alpha,\beta$-unsaturated amides occurred with a high degree of stereoselectivity (Summarised in Table 4.17). Changing the R group from Ph to Et to Me did not affect the face selectivity of the addition reaction ($\geq 49:1$ d.e.). Changing the X group effected the diastereoselectivity slightly; the highest diastereoselectivities were obtained with the $N,N$-dimethyl amides, while the $N$-morpholine and $N$-piperidine amides showed slightly lower selectivity. Conjugate addition of lithium amides to $\alpha,\beta$-unsaturated esters is believed to proceed through the $s$-cis form$^{246}$ and the same is presumed to hold true for $\alpha,\beta$-unsaturated amides.

![](image)

**Scheme 4.24**: Face selective addition of 30a to various $\alpha,\beta$-unsaturated amides

<table>
<thead>
<tr>
<th>Product</th>
<th>207</th>
<th>228</th>
<th>229</th>
<th>230</th>
<th>231</th>
<th>232</th>
<th>233</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
</tr>
<tr>
<td>X</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ratio of diastereomers</td>
<td>16:1</td>
<td>19:1</td>
<td>16:1</td>
<td>$\geq 49:1$</td>
<td>12:1</td>
<td>$\geq 49:1$</td>
<td>$\geq 49:1$</td>
</tr>
</tbody>
</table>

**Table 4.17**: Ratio of diastereomers of the Michael addition-proton quench products (see also Table 4.7)
Very recently, a molecular modelling study on the transition state geometries of the analogous addition of amide 30a to t-butyl cinnamate was reported.\textsuperscript{247}

It was found that the amide (30) approaches the \( \alpha,\beta \)-unsaturated ester 3-si-face, in a butterfly conformation. When (\( R \))-30a was placed 2\( \AA \) from the ester, the minimum energy conformation was lower in energy than when (\( S \))-30b was placed there. Also, when (\( R \))-30a was present, the lowest energy conformation had the lone pair of electrons on the nitrogen pointing towards the ester C=O function (necessary for Li chelation), while when (\( S \))-30b was substituted, the lone pair of electrons on the nitrogen was pointing away from the ester C=O function.

This corresponds to (\( R \))-30a attacking the 3-si-face in preference (figure 4.8), while (\( S \))-30b adds to the 3-re-face and is consistent with the experimental findings.\textsuperscript{247} It is thought that the preference that lithium amide 30a shows for the 3-si-face of the \( \alpha,\beta \)-unsaturated amides can be explained similarly.

Two new chiral centres were formed when lithium amide 30a was added to an \( \alpha,\beta \)-unsaturated amide and the intermediate enolate was quenched with an alkyl halide. Four diastereomers were theoretically possible but three were isolated in varying amounts (Scheme 4.19). The chiral centre at C\textsubscript{3} was formed with good stereocontrol as demonstrated above.

\begin{itemize}
  \item Methyl iodide quenches the enolate derived from the conjugate addition of 30a to the cinnamoyl amides 203, 223 and 224 with excellent \textit{anti} diastereoselectivity; the greatest
\end{itemize}
stereocontrol was obtained when X= dimethylamine (67:2:1 ratio of diastereomers a:b:other), but the larger the X group, the lower the stereoselectivity of the alkylation (Table 4.18, Table 4.9). When X= dibenzylamine, the stereoselectivity was decreased to 3:2 (a:b); it is believed that an increase in size of the X-group makes the approach of the alkylating agent to either face more difficult, but the difference between the ease of approach to each face becomes less as well. The diastereoselectivity of the electrophilic quench decreases in the order R= Ph > Et > Me since it is based on the crowding of one face of the enolate specifically. It is believed that a 6-membered transition state with Li chelation is involved. When R= Ph, this group hinders attack of one face of the enolate, so methylation occurs on the opposite face (Scheme 4.25).

![Scheme 4.25: Diastereoselectivity of alkylation at the C2 position when R = Ph](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>236</th>
<th>237</th>
<th>239</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio</td>
<td>25:3:1</td>
<td>3:2</td>
<td>45:3:1</td>
<td>67:2:1</td>
</tr>
<tr>
<td>diastereomers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.18: Ratio of diastereomers of the Michael addition-Mel quench products when R=Ph (see also Table 4.9)
When \( R = \text{Me} \), the enolate was not quenched diastereoselectively and 1:1 mixtures of diastereomers (a:b) were formed. It is believed that the Me group is not large enough to direct attack to one face of the enolate in preference. The larger Et group gave a 3:1 (a:b) ratio of diastereomers (Table 4.19, Table 4.9).

Scheme 4.26: Less stereocontrol of alkylation at the \( C_2 \) position when \( R = \text{Me} \) and Et

<table>
<thead>
<tr>
<th>Product</th>
<th>241</th>
<th>242</th>
<th>243</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R )</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
</tr>
<tr>
<td>( X )</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ratio of diastereomers [(a) (anti) : (b) (syn)]</td>
<td>1:1</td>
<td>1:1</td>
<td>3:1</td>
</tr>
</tbody>
</table>

Table 4.19: Ratio of diastereomers of the Michael addition-MeI quench products when \( R = \text{Et} \) and Me (see also Table 4.9).
The magnitude of stereocontrol at C2 was greater with cinnamoyl amides than with that reported for cinnamate esters,²¹⁸ but the same lack of selectivity at C2 was seen with crotonyl amides and crotonate esters (Table 4.20).²¹⁸

<table>
<thead>
<tr>
<th>α,β-unsaturated amide</th>
<th>Ratio anti : syn diastereomers</th>
<th>α,β-unsaturated ester</th>
<th>Ratio anti : syn diastereomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-cinnamoylpiperidine</td>
<td>15:1</td>
<td>t-butyl cinnamate</td>
<td>1.3:1</td>
</tr>
<tr>
<td>N-cinnamoyldimethylamine</td>
<td>44:1</td>
<td>methyl cinnamate</td>
<td>13:1</td>
</tr>
<tr>
<td>N-crotonoylmorpholine</td>
<td>1:1</td>
<td>t-butyl cinnamate</td>
<td>1.2:1</td>
</tr>
<tr>
<td>N-crotonoyldimethylamine</td>
<td>1:1</td>
<td>methyl cinnamate</td>
<td>1.3:1</td>
</tr>
</tbody>
</table>

Table 4.20: Comparison of the ratio of diastereomers obtained on methylation of the enolates derived from the addition of 30a to α,β-unsaturated amides and α,β-unsaturated esters.

Three new chiral centres were created when lithium amide 30a was added to an α,β-unsaturated amide and the intermediate enolate was quenched with benzaldehyde.

Scheme 4.20: Tandem Michael addition-pseudo aldol reaction with PhCHO (repeated from section 4.4.3.3)

When R=Ph only one major (a) and two minor diastereomers were observed out of the possible eight diastereomers. The absolute stereochemistry of the major diastereomer 247a and 249a were known from X-ray crystallographic studies; to achieve this stereochemistry, benzaldehyde is thought to approach the 'top face' of the enolates with the Ph group over the X-group (Scheme 4.27) and reaction occurs at the pro-R face of benzaldehyde in preference. The diastereoselectivity achieved over the formation of three new chiral centres was unusually high when the α,β-unsaturated amides 203, 223 and 224 were used, especially in the case of 224 which gave 247 as a 40:1:1 mixture of diastereomers (a: others) (Table 4.11 and Table 4.21). Again the degree of stereocontrol is thought to be due to steric factors with it decreasing in the order R = Ph > Et > Me.
Attack occurs from the upper face in preference.

\[
\text{where } NR''R'' = \text{Ph}^\prime\text{N}^\prime\text{Ph} \text{ in the enolate}
\]

\[
\text{Intermediate enolate}
\]

\[
\text{Attack from lower face is hindered by the large phenyl group below the plane}
\]

\[
\text{major diastereomer (a)}
\]

Scheme 4.27: Good stereocontrol over the formation of C₂ and C₇ when the enolate is quenched with PhCHO

<table>
<thead>
<tr>
<th>Product (R=Ph)</th>
<th>244</th>
<th>245</th>
<th>246</th>
<th>247</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of diastereomers (a: others)</td>
<td>25:1:1</td>
<td>12:2:1</td>
<td>24:1:1</td>
<td>40:1:1</td>
</tr>
<tr>
<td></td>
<td>(85)</td>
<td>(60)</td>
<td>(85)</td>
<td>(90)</td>
</tr>
</tbody>
</table>

Table 4.21: Ratio of diastereomers of the Michael addition-PhCHO quench products when R= Ph (see also Table 4.11).

When R= Me, two major diastereomers (1:1 mixture) and other minor diastereomers were isolated; the 1:1 ratio indicated that only one centre was formed without any stereocontrol (Table 4.22, also see Table 4.11). It was known from methylation that the C₂ centre was formed with no stereoselectivity when R=Me, therefore it is reasonable to assume that it is the C₂ centre which has been formed without stereocontrol while the C₇ chiral centre in each diastereomer has formed diastereoselectively. Although benzaldehyde approached the intermediate enolate from both faces, the enolate attacked one face of the benzaldehyde...
molecule specifically (Scheme 4.28). When R= Et there was more stereocontrol at C₂ and a 3:1 mixture of two major diastereomers (a:b) was obtained (Table 4.22, Table 4.11).

![Diagram of Michael additions using chiral lithium amides]

Scheme 4.28: Low stereocontrol over the formation of C₂ when the enolate is quenched with PhCHO if R= Me or Et, but the C₇ centre is formed diastereoselectively.

<table>
<thead>
<tr>
<th>Product</th>
<th>248</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Et</td>
<td>Me</td>
</tr>
<tr>
<td>X</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ratio of diastereomers (a:b)</td>
<td>4:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Table 4.22: Ratio of diastereomers of the Michael addition-PhCHO quench products when R= Me and Et (see also Table 4.11).
When the intermediate enolate was quenched with acetaldehyde instead of benzaldehyde, very similar ratio of diastereomers were produced in each case (Table 4.13). The same face selectivity is expected for both benzaldehyde and acetaldehyde.

Whereas, three new chiral centres could be created stereoselectively by these Michael addition-pseudo aldol reactions on cinnamoyl amides, the analogous reactions with cinnamate esters showed poor stereocontrol at C₂ and C₇. When the lithium amide 30a was added to methyl cinnamate and the intermediate enolate was quenched with benzaldehyde, a mixture of diastereomers of 258 were isolated (4:2:1:1) plus other minor, unidentified products. This lack of diastereoselectivity has also been noted for other esters.²⁴⁸,²⁴⁹

\[
\text{Scheme 4.29: Addition of lithium amide 30a to 201 and quenching of the intermediate enolate with PhCHO}
\]

4.4.5 Effect of temperature and solvent on the Michael addition reactions

Effect of temperature

The difference in activation energies between two diastereomeric transition states determines the selectivity of a reaction under kinetic control, for a given value of ΔE, lowering the temperature should lead to greater selectivity. The effect of temperature on the face selectivity of addition of lithium amide 30a to 224 was examined. When low temperatures (-40 to -120°C) were used the diastereomeric excess of 230 was between 92-96% d.e.. When higher temperatures were used (0°C and 18°C) there was no face selectivity and a 1:1 mixture of both diastereomers of 230a and 230b were produced along with another product. This was identified as 259; it would seem that the intermediate enolate reacts with another mol of 224 then the original nucleophilic addend is eliminated (Scheme 4.30).
Chapter 4: Michael additions using chiral lithium amides

At higher reaction temperature, this product is also isolated.

**Scheme 4.30:** Effect of temperature on the Michael addition reaction of 30a to 224

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>Yield (%) of 230</th>
<th>Ratio of 230a:230b:259</th>
</tr>
</thead>
<tbody>
<tr>
<td>-120 to -110</td>
<td>82%</td>
<td>49:1:0</td>
</tr>
<tr>
<td>-78</td>
<td>85%</td>
<td>49:1:0</td>
</tr>
<tr>
<td>-45 to -40</td>
<td>87%</td>
<td>24:1:0</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>1:1:1</td>
</tr>
<tr>
<td>18 (rt)</td>
<td>-</td>
<td>1:1:2</td>
</tr>
</tbody>
</table>

**Table 4.23:** Ratio of products obtained from the Michael addition reaction of 30a to 224 as the temperature is increased.
Effect of solvent
THF is the most common solvent used in the Michael addition of chiral lithium amides to \(\alpha,\beta\)-unsaturated esters, but toluene and DME have also been employed. DME was found to give better selectivity than THF in addition of 106 to \(\alpha,\beta\)-unsaturated esters.\textsuperscript{136} It has recently been reported that toluene is a superior solvent to THF for the addition of 30a to \((E)\)-2-methylbut-2-enoate acceptors, because there is less 1,2-attack and \(\gamma\)-deprotonation, but this is mirrored by a deterioration in the protonation selectivity.\textsuperscript{228}

The effect of the solvents tetrahydrofuran, toluene and ether on the Michael addition of 30a to \(\alpha,\beta\)-unsaturated amide 224 followed by a proton quench was examined (Scheme 4.17). When THF was used the Michael addition product 230 was produced quantitively (judged from \(\textsuperscript{1}H\) NMR). 230a and 230b were produced in the ratio 49:1 (96% d.e.). When toluene was employed, 230 (23:2 ratio of 230a and 230b) was produced cleanly in 70% yield. The \(\alpha,\beta\)-unsaturated amides were nearly insoluble in ether and only 50% of 224 had reacted after 5 hours at -78°C to give 230a and 230b (4:1).

The effect of THF and toluene on the tandem Michael addition-methylation reaction on 224 was examined (Scheme 4.19). Methylation occurred far more rapidly in THF than in toluene since the more polar solvent promotes the development of the dipolar transition state but, also the degree of stereocontrol at C\(_{2}\) was greater in THF, possibly due to greater chelation in the transition state. In THF, 239 was isolated as one major diastereomer (239a) (67:2:1, 91% d.e.) after 15 minutes. In contrast, only 50% of the intermediate enolate had reacted with Mel after 3 hours in toluene at -78°C. The major diastereomer (239a) and several minor diastereomers of the tandem addition-methylation reaction were isolated (~ 60% d.e.) along with 230 (formed when the intermediate enolate was quenched with water).
4.4.6 Modification of the Michael addition products

Considerable effort has been directed towards the synthesis of β-amino compounds because of their wide occurrence in natural products, derivatives and mimics of amino acids, β-lactams, and peptides etc. and chiral ligands, chiral auxiliaries and chiral building blocks. (250, 251, and ref. therein).

In this section, conversion of the Michael addition products into free β-amino-amides and 1,3-amino compounds is described.

Debenzylation of the Michael adducts with Pd/C or Pd(OH)$_2$/C

Cleavage of the benzylic bonds as shown below would yield a compound with a primary amine in the β-position.

\[
\text{H}_3\text{C} \quad \text{H} \quad \text{Ph} \\
\text{Ph} \quad \text{N} \quad \text{O} \\
\begin{array}{c}
\text{Ph} \\
\text{Y} \\
\text{X}
\end{array}
\xrightarrow{\text{debenzylation}}
\begin{array}{c}
\text{NH}_2 \\
\text{O} \\
\text{Y} \\
\text{X}
\end{array}
\]

Scheme 4.31: Debenzylation of a Michael adduct

The hydrogenolysis of the benzyl-nitrogen bonds of 244 was attempted first (Scheme 4.32).

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{H} \quad \text{Ph} \\
\text{Ph} \quad \text{N} \quad \text{O} \\
\begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{Ph}
\end{array}
\xrightarrow{5\% \text{ Pd/C}, \text{H}_2(g), \text{acetic acid}}
\begin{array}{c}
\text{H}_3\text{C} \quad \text{H} \\
\text{Ph} \\
\text{N} \quad \text{O} \\
\begin{array}{c}
\text{Ph} \\
\text{3} \\
\text{1}
\end{array}
\xrightarrow{65-70\,\text{psi}, 4\,\text{h}}
\begin{array}{c}
\text{H}_3\text{C} \quad \text{H} \\
\text{Ph} \\
\text{N} \quad \text{O} \\
\begin{array}{c}
\text{Ph} \\
\text{2} \\
\text{7}
\end{array}
\end{array}
\]

Scheme 4.32: Partial hydrogenolysis of 244

$^1$H NMR of the crude product indicated that only partial hydrogenolysis had occurred; a 1:1 mixture of compounds 260 and 261 was isolated. It had been expected that hydrogenolysis of the N-CH$_2$Ph bond would proceed more rapidly than hydrogenolysis of the N-CH(CH$_3$)Ph bond, but the presence of an equal amount of 260 and 261 indicated that neither reaction was favoured. When the reaction time was increased to 24 h (conditions i), the fully debenzylated material 262 was produced (Scheme 4.33).
Chapter 4: Michael additions using chiral lithium amides

Palladium hydroxide on carbon (Pearlman's catalyst) is normally the catalyst of choice for hydrogenolysis of benzyl-nitrogen bonds and this catalyst has been used to debenzylate N-benzyl-N-α-methylbenzyl-β-amino esters. Therefore Pd(OH)$_2$/C was used in the above reaction [conditions (ii)]. It was found that both Pd/C and Pd(OH)$_2$/C gave similar results (Table 4.24, Scheme 4.33).

It was also found that the hydrogenation of 244 to give 262 could be readily performed in an ultrasound bath at low pressure (the pressure of hydrogen in a normal balloon), removing the need for a high-pressure reaction setup.[conditions (iii)]. 262 was isolated in 82% yield after 7h, compared to 15h required for the reaction under 60 psi of H$_2$(g).

To confirm that the nature of the carboxamide X group did not affect the debenzylation, compounds 245, 246 and 247 were debenzylated. The conditions used and characteristic $^1$H NMR signals of the products are summarised in Table 4.24. The chiral centres were not racemised under the conditions stated.

**Scheme 4.33: Hydrogenolysis of 244 to give 262**

**Scheme 4.34: General scheme showing debenzylation of the Michael adducts which differ in their X groups**
### Table 4.24: Debenzylation of Michael adducts which differ in their X group

The effect of the substituent in the α-position of the Michael adducts on the debenzylation reaction was examined. The \(N,N\)-dimethyl series of compounds was used and debenzylation occurred readily in each case (Scheme 4.35). The yields and significant peaks in the \(^1\)H NMR spectrum of compounds 265 and 266 which indicate that debenzylation has occurred are given in Table 4.25. The chiral centres were not racemised under the conditions used.
Scheme 4.35: Debenzylation of Michael adducts which differ in their α-functionalities

Table 4.25: Debenzylation of Michael adducts which differ in their Y group

Unfortunately, when substrates which did not have an α-substituent were subjected to the normal hydrogenolysis conditions a major side reaction occurred simultaneously. As well as cleaving the required C-N bonds (i) and (ii), the reductive conditions cleaved the third C-N bond (iii) of 230 as indicated in Scheme 4.36. No reaction conditions were found which fully removed the required benzylic groups without some cleavage of the N-C3 bond. When a short reaction time (8-16 h) or low pressure (30 psi) were used, not all the material was debenzylated, but even then, some material was cleaved at (iii). When longer reaction times (24-48 h) or higher pressures (60-80 psi) were used, cleavage of bond (iii) became more pronounced.

The identity of compound 270 was initially puzzling because the $^{13}$C NMR of the *product mixtures* seemed to lack the required C3 methylene carbon. This CH$_2$ carbon was found by off resonance decoupling of the $^{13}$C NMR spectrum of the mixture. A triplet due to this CH$_2$ in compound 270 was found at 35.27 ppm, and a quartet due to the N(CH$_3$) signal of compound 269 also occurred at 35.27 ppm. The coincidence of these two signals explained why a DEPT experiment did not show up the CH$_2$ signal.
Chapter 4: Michael additions using chiral lithium amides

The debenzylation of 209 was also attempted, but again cleavage of the N-C₃ bond occurred.

Reduction of the carbonyl function of the Michael adducts with DIBAl-H

Tertiary amides may be reduced with hydride reagents to aldehydes, alcohols and amines; the nature of the product depends on the hydride reagent and reaction conditions used (Scheme 4.38).
Chapter 4: Michael additions using chiral lithium amides

Firstly, the reduction of the C=O group in series of Michael adducts which differ in their \( \alpha \)-functionality was examined; the carbonyl groups of the Michael addition products 230, 239, 247 and 253 were easily reduced to methylene groups using DIBAL-H in toluene under the conditions described in Table 4.26, Scheme 4.39. Secondly the reduction of the C=O group in a series of Michael addition products which differ in their X group was examined. The nature of the carboxamide group did not effect the reduction; the carbonyl groups of compounds 244, 245, 246 (and 247) were reduced cleanly (Scheme 4.39). When the Michael adduct contained an OH group, excess DIBAL-H had to be added to ensure complete reduction (more than was required to reduce the C=O group and react with the OH group). The lose of a carbonyl carbon and the appearence of a \( \text{CH}_2 \) group in the \( ^{13} \text{C} \) NMR spectrum was taken as proof that reduction had occurred, also, reduction of the C=O group removed the magnetic inequivalence of the groups attached to N(C=O) (Table 4.26). The chiral centres in the products were not racemised with the same ratio of diastereomers in the product as in the initial Michael adduct.
### Table 4.26: Reduction products obtained by treatment of the Michael adducts with DIBAL-H

When the reactions of 244 or 245 with DIBAL-H were carried out in an US bath, reduction occurred more quickly in both cases (No systematic study was undertaken to show if this rate increase is general for other DIBAL-H reductions).

The reduced products could also be debenzylated to give the free primary amine, for example, reduction of 224 followed by hydrogenolysis gave 281 (Scheme 4.40).
Hydrolysis of amide function
The Michael addition products may, in principle, provide β-amino-carboxylic acid derivatives after amide hydrolysis however we were unable to find conditions that would bring about this hydrolysis. Neither TFA or 13M HCl hydrolysed the amide function while basic conditions caused a retro-Michael addition and the original α,β-unsaturated amide was reformed.

4.5 SUMMARY
α,β-Unsaturated amides proved suitable Michael acceptors for the chiral lithium amide 30a; very high face selectivity was seen. When the intermediate enolate formed on addition of 30a to N-cinnamoyldimethylamine was quenched with MeI, the new chiral centre at C2 was formed with a high degree of stereocontrol (67:2:1 mixture of diastereomers). Unusually high stereocontrol over the formation of three new chiral centres was observed in the Michael addition reaction of 30a to N-cinnamoyldimethylamine followed by reaction with benzaldehyde (40:1:1 mixture of diastereomers). The diastereoselectivity at C2 decreased as the β-substituent was changed (Ph > Et > Me). The absolute stereochemistry of the three new chiral centres of compounds 247 and 249 were determined and from that, the stereochemistry of the other Michael adducts was assigned.
CHAPTER 5

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5.1 GENERAL EXPERIMENTAL DETAILS

Solvents and reagents

*Diethyl ether* was dried over lithium aluminium hydride and was freshly distilled under nitrogen.

*Tetrahydrofuran* was dried over potassium benzophenone ketyl and was freshly distilled under nitrogen.

*Toluene* was dried over sodium and was freshly distilled under nitrogen.

*Diisopropylamine* was dried over sodium hydroxide pellets, distilled under nitrogen and stored over molecular sieves under a nitrogen atmosphere.

*Trimethylsilyl chloride* was distilled from calcium hydride under nitrogen and was stored over molecular sieves under a nitrogen atmosphere.

*BuLi* in hexanes was standardised against diphenylacetic acid in THF, under nitrogen.

All starting materials were used as supplied unless purification is quoted.

Chromatography

All flash chromatography quoted in this thesis was performed on silica gel (0.035-0.07 nm, pore diameter *ca.* 6 nm). Thin layer chromatography was performed on precoated silica gel 60 plates with fluorescent indicator. Preparative chromatography was performed on Merck Art. 5717 (silica gel 60 F_{254}), 2 mm thick plates.

Melting points

Melting points were measured on a Kofler hot stage micromelting point apparatus and are uncorrected.

Elemental analysis

Elemental analyses was performed by Mrs. N. J. Walker at the University of Surrey, Chemistry Department on a Leeman Laboratory 444 Elemental Analyser.

Infra-red analysis

Infra-red spectra were recorded on a Perkin-Elmer System 2000 Fourier transform infra-red instrument, as liquid films, nujol mulls or KBr discs.

Nuclear Magnetic Resonance

Spectra were recorded on a Brüker AC300 machine with an Oxford Instruments 7.04T magnet. Proton spectra were recorded at 300 MHz. Carbon-13 spectra were recorded at 75.5 MHz with composite pulse broad band decoupling. Deuterium spectra were recorded at
46.07 MHz. DEPT-135 (polarisation transfer from $^1$H to $^{13}$C), COSY (homonuclear shift correlated 2-D NMR), NOESY (homonuclear dipolar correlated 2-D NMR) and XHCorrd (heteronuclear shift correlated 2-D NMR) were run with standard Bruker software. All chemical shifts are quoted in ppm relative to tetramethylsilane internal standard.

5.2 EXPERIMENTAL DETAILS FOR THE WORK DESCRIBED IN CHAPTER 2

5.2.1 PREPARATION OF N-BENZYL-1-PHENYLETHYLAMINE (110)

1-Phenylethylamine (14.00 g, 0.115 mol) and benzaldehyde (12.26 g, 0.115 mol) were stirred together for 1 h, then methanol (50 ml) was added. The solution was cooled in an ice bath and NaBH₄ (5.22 g, 0.138 mol) was added carefully over 10 minutes. The reaction mixture was stirred for 4 h then concentrated in vacuo. Water (50 ml) was added and the product was extracted into ether (3x 50 ml). The combined organic layers were washed with brine (10 ml), dried over MgSO₄ and filtered. The solvent was removed under reduced pressure and the yellow oil purified via Kugelrohr distillation.

Preparation of (R)-N-1-phenylethylamine (110a)
The general method described in above was followed with (R)-1-phenylethylamine (14.00 g, 0.115 mol). The crude product was distilled via Kugelrohr distillation to give 110a as a colourless oil (22.45 g, 92%); bp 125 °C/ 0.1 mmHg; (Found: C, 85.3; H, 8.1; N, 6.6. C₁₄H₁₇N requires C, 85.3; H, 8.; N, 6.6 %); ν max/cm⁻¹ 3846 (NH sharp); $^1$H NMR (CDCl₃): δ 1.36 (3H, d, J 6.6, CH₃), 3.54 (1H, d, J 13.1, CH), 3.65 (1H, d, J 13.1, CH), 3.80 (1H, q, J 7.6, CH), 1.2-1.6 (10H, m, 2x Ph); $^{13}$C NMR (CDCl₃): δ 25.24 (CH₃), 51.53 (CH*), 57.36 (CH), 126.58, 126.72, 126.81, 128.01, 128.24, 128.34, 140.51, 145.45 (2x Ph); [α]D$^{18}$ +53.9° (c 9.9 EtOH), Lit [α]D$^{21}$ +54.5° (c 0.5 EtOH),27 [α]D$^{21}$ +54.4° (c 3.86 EtOH)$^{253}$.

Preparation of (S)-N-1-phenylethylamine (110b)
The general method described above was followed using (S)-1-phenylethylamine (14.00 g, 0.115 mol). 110b was isolated as a colourless oil (94%); spectral data was identical to that obtained for 110a; [α]D$^{18}$ = -54.2° (c 8.1, EtOH).
Chapter 5: Experimental details

5.2.2 Preparation of 111

1-Phenylethylamine (30.00 g, 0.246 mol), acetophenone (29.54 g, 0.246 mol) and p-toluenesulphonic acid (0.46 g, 24.6 mmol, 10% cat.) were dissolved in toluene (100 ml) and refluxed (Dean and Stark trap), for 16 h. Toluene was removed and the mixture was dissolved in ether and then filtered. The ether layer was washed with water (20 ml) and brine (10 ml), dried over MgSO₄ and filtered. The solvent was removed under reduced pressure to yield the crude product. When a longer reaction time (48h) was used, unidentified side products were isolated.

Preparation of 111a

The general method given above was followed with (R)-1-phenylethylamine (30.00 g, 0.246 mol). Kugelrohr distillation of the crude product gave 111a as a colourless oil (46.03 g, 83%); bp 120°C/ 0.1 mmHg; (Found: C, 86.2; H, 7.6; N, 6.3. C₁₆H₁₇N requires C, 86.1; H, 7.6; N, 6.3%). A mixture of E and Z imines were formed in a ratio of 6:1. E imine ¹H NMR (CDCl₃): δ 1.53 (3H, d, J=6.1, CH₃), 2.25 (3H, s, CH₃), 4.83 (1H, q, J=6.1, CH), 7-8 (10 H, m, Ph).

Preparation of 111b

Using the general method described above, 111b was prepared using (S)-1-phenylethylamine (30.00 g, 0.246 mol). 111b was isolated as a colourless oil (86%); the spectra data was identical to that from 111a.

5.2.3 Preparation of Bis[(A)-l-phenylethyl]amine (112)

Imine 111 (46.00 g, 0.206 mol) was dissolved in THF (100 ml) and 5% Pd/C (2.3 g, 5% by weight) was added. Hydrogenation at r.t and atmospheric pressure took 4 h. The catalyst was removed by filtration through Celite and the solvent was evaporated off. The product was dissolved in ether and filtered again to remove the last traces of catalyst. The solvent evaporated under reduced pressure and the oil was distilled affording the crude product.

Preparation of (+)-Bis[(R)-A-(1-phenylethyl)]amine [R,R] (112a)

Using the method described above, 112a was prepared from imine 111a. The crude product was distilled via Kugelrohr distillation to yield 112a as a colourless oil (34.81 g, 80%), bp 130°C/ 0.4 mmHg; (¹H NMR data described below). 10% of the meso-compound was also seen: ¹H NMR (CDCl₃): δ 1.35 (6H, d, J=6.1, CH₂), 1.70 (1H, bs, NH), 3.70 (2H, q, J=6.1, CH₂), 7.0-7.5 (10H, m).

Ether (50 ml) and HCl (3M, 4 ml) were added to 112a. The amine salt precipitated out and the mixture was evaporated to dryness. The salt was recrystallised from boiling water (500 ml) containing HCl (13M, 10 ml), to give large needle shaped crystals which were slightly
pink (112a.HCl) (36.37 g, 72%); m.p. >300°C; (Found: C, 73.4; H, 7.8; N, 5.5; C_{16}H_{17}N requires C, 73.4; H, 7.8; N, 5.5%); [α]_{D}^{18} +85.38° (c 3.0 EtOH), reported for the (S,S)-amine [α]_{D}^{18} -84.1° (c 3, EtOH).^{254} { }^{1} H NMR (CDCl_{3}; δ 1.26 (6H, d, J 6.8, 2x CH_{3}), 1.58 (1H, bs, NH), 3.49 (2H, q, J 6.8, CH), 7.2-7.4 (10H, m, 2x Ph). 112a.HCl (36.00 g, 0.148 mol) was dissolved in water (100 ml), solid KOH (16 g, 0.285 mol) and ether (100 ml) were added and the mixture was stirred for 2 h. The ether layer was removed and the aq. layer was extracted with ether (2x 20 ml). The combined organic layer was washed with brine, dried over MgSO_{4}, filtered and concentrated in vacuo. The oil was subjected to Kugelrohr distillation to yield 112a (30.35 g, 91%); 90°C/ 0.05 mmHg; (Found: C, 85.2; H, 8.6; N, 6.3. C_{16}H_{19}N requires C, 85.3; H, 8.5; N, 6.2%); [α]_{D}^{18} +195.4° (c 5.0, CHCl_{3}), Lit [α]_{D}^{20} +167.6° (c 1.1, CHCl_{3});^{138} ν_{max}/cm^{-1} (film) 3327 (NH); { }^{1} H NMR (CDCl_{3}): δ 1.26 (6H, d, J 6.5, 2x CH_{3}), 1.57 (1H, bs, NH), 3.49 (2H, q, J 6.5, 2x CH), 7.2-7.4 (10 H, m, 2x Ph); { }^{13} C NMR (CDCl_{3}): δ 24.7 (CH_{3}), 54.6 (CH), 126.3, 126.5, 128.0, 145.6 (Ph).

Preparation of (−)-Bis[(S)-N-(1-phenylethyl)]amine [S,S] (112b)

The same general method was used to obtain 112b from imine 111b. 111b was isolated as a colourless oil (89%) and was converted to its HCl salt by treatment with hydrochloric acid (3M, 4 ml) in ether (50 ml). The HCl salt was recrystallised from boiling water (500 ml) containing HCl (13M, 15 ml) to give 112b.HCl (75%); m.p. >300°C; (Found: C, 73.5; H, 7.8; N, 5.5; C_{16}H_{17}N requires C, 73.4; H, 7.8; N, 5.5%); [α]_{D}^{18} -84.7° (c 2.8 EtOH), Lit. [α]_{D}^{18} -84.1° (c 3, EtOH);^{138} the spectra data was identical to that from 112a. 112b was converted back into the free amine when required, using the procedure described for 112a. The free amine was distilled via Kugelrohr distillation to yield 112b (82%) [α]_{D}^{18} -190.2° (c 5.1, CHCl_{3}).

5.2.4 Preparation of hindered primary amines

Preparation of ±-1-phenylpropylamine (114a/b)

Racemic 114a/b was prepared by the Leuckart method; a procedure for the synthesis of 1-phenylethylamine was followed. A rbf was equipped with a a short fractionating column, Claisen still head and condenser set for downward distillation. Propiophenone (10 g, 0.175 mol) and ammonium formate (15.66 g, 0.248 mol) were heated together. As the temperature increased the mixture became homogeneous (150°C). Heating was continued until the temperature reached about 185°C, at which time acetophenone, water and ammonium carbonate distilled. After 2 h, more propiophenone (10 g, 0.175 mol) was added and the mixture was heated at 185°C for 3 h. The mixture was cooled and dissolved in toluene (40 ml), then washed with water (2x 75 ml) to remove formamide and ammonium formate. The toluene was removed in vacuo and HCl (13M, 10 ml) was added. The mixture was refluxed
for 40 minutes, washed with toluene to remove unreacted propiophenone, then basified by the addition of KOH pellets. The product was extracted into toluene (3x 20 ml), washed with water (50 ml) and brine (20 ml), then concentrated in vacuo. The crude product was distilled under vacuum (125°C/15 mmHg) to yield **114a/b** as a colourless oil (12.30 g, 52%); (Found: C, 80.0; H, 9.8; N, 10.3. C_{12}H_{13}N requires C, 80.0; H, 9.7; N, 10.4%); ^1^H NMR (CDCl_3): δ 0.87 (3H, t, J 7.1, CH3), 1.58 (2H, s, NH^2_), 1.69 (2H, q, J 6.9, CH2), 3.80 (1H, t, J 7.0, CH), 7.1-7.4 (5H, m, Ph).

**Preparation of ±1-phenyl-2-methylpropylamine (115a/b)**

A 3-necked rbf was charged with magnesium turnings (7.30 g, 0.30 mmol) and ether (150 ml); nitrogen was bubbled through. One iodine crystal was added, followed by bromobenzene (2 ml). After the reaction had started the rest of the bromobenzene (31.5 ml, 0.30 mmol in total) was added dropwise to maintain a gentle reflux. The mixture was refluxed for 30 minutes, the cooled to r.t.. Isobutroynitrile (23 ml, 0.25 mmol) in ether (100 ml) was added slowly, the mixture was refluxed for 4 h then methanol (100 ml) was added and the mixture was filtered. NaBH₄ (10.0 g, 0.26 mmol) was added and the mixture was stirred at r.t. overnight. Methanol was removed in vacuo and water was added to dissolve the residue. The product was extracted into ether (2x 40 ml). The ether layer was shaken with HCl (3M, 5x 40 ml) to extract the product (a white solid precipitated which was not soluble in either the organic or aqueous layer and was removed by filtration). The aqueous acidic layer was evaporated to dryness and the white solid was recrystallised four times from ethanol/ether.

The HCl salt was treated with KOH (2M, 50 ml) and extracted into ether (3x 40 ml). The combined organic layer was washed with brine (10 ml) and dried over MgSO₄. After filtration the solvent was removed under vacuum, leaving a colourless oil, (±1-phenyl-2-methylpropylamine (115a/b)) (13.0 g, 35%); ^1^H NMR (CDCl_3): δ 0.79 (3H, d, J 6.6, CH3), 0.95 (3H, d, J 6.6, CH3), 1.39 (2H, bs, NH2), 1.78 (1H, m, CH(CH3)2), 3.55 (1H, d, J 7.7, CHPh), 7.0-7.3 (5H, m, Ph); (Found: C, 80.5; H, 10.0; N, 9.4. C_{10}H_{15}N requires C, 80.5; H, 10.1; N, 9.4%).

**Preparation of ±1-phenyl-2,2-dimethylpropylamine (116a/b)**

PhLi (1.8M in cyclohexanes, 25 ml) was added to trimethylacetonitrile (5 ml, 45 mmol) in dry THF (40 ml) at -78°C, immediately the solution turned bright orange. The reaction was allowed to warm to -40°C over 4h, then was quenched with methanol (10 ml) and the solvent was removed under reduced pressure. The residue was dissolved in ether (50 ml), insoluble impurities were filtered off and the material was concentrated to give two isomeric imines (2:6:1) (6.76 g, 93%); (Found: C, 80.9; H, 10.6; N, 8.6. C_{11}H_{17}N requires C, 80.9; H, 10.5; N, 8.6 %). **Major product:** ^1^H NMR (CDCl_3): δ 1.19 (9H, s, (CH₃)C), 7.0-7.4 (5H, m, Ph), 9.05 (1H, s, NH); ^1^C NMR (CDCl_3): δ 29.30 (CH₃), 39.84 (C), 126.77, 127.94, 129.11,
142.49 (Ph), 190.16 (C=NH). Minor product: $^1$H NMR (CDCl$_3$): $\delta$ 1.15 (9H, s, (CH$_3$)$_3$C), 7.0-7.4 (5H, m, Ph), 9.75 (1H, s, NH); $^{13}$C NMR (CDCl$_3$): $\delta$ 27.86 (CH$_3$), 40.29 (C), 126.85, 127.96, 128.99, 140.49 (Ph), 188.77 (C=NH). The imines (1.00 g, 6.20 mmol) were reduced with NaBH$_4$ in methanol under standard conditions to give 1-phenyl-2,2-dimethylpropanamine (116a/b) (0.91 g, 89%), (Found: C, 80.4; H, 11.2; N, 8.6. C$_{11}$H$_{18}$N requires C, 80.4; H, 11.0; N, 8.5 %); $^1$H NMR (CDCl$_3$): $\delta$ 0.93 (9H, s, (CH$_3$)$_3$C), 1.47 (2H, bs, NH$_2$), 3.69 (1H, s, CH), 7.2-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 28.27 (CH$_3$), 34.70 (C), 65.01 (CH), 126.42, 127.19, 127.95, 143.48 (Ph).

5.2.5 Condensation of (R)-(+) -camphor with 1-phenylalkylamine
Camphor (50 mmol) and a primary amine of the general formula 1-phenylalkylamine (50 mmol) was dissolved in a specified solvent and the mixture was refluxed with ZnCl$_2$ (10 mol. %) under Dean and Stark conditions until the correct amount of water had azeotroped off. The solvent was removed by rotary evaporation and the residue was mixed with ether (50 ml). Insoluble ZnCl$_2$-amine complex was filtered out (otherwise it caused an emulsion during extraction). The ether layer was washed with water (20 ml) and brine (10 ml), dried over MgSO$_4$ and filtered. Evaporation of the solvent under reduced pressure left the crude product.

Preparation of (R)-N-(1-phenylethyl)boranminine (113a)
Using the procedure described above, camphor (7.00 g, 46.00 mmol) was dissolved in xylene (75 ml) and (R)-phenylethylamine (5.57 g, 46.00 mmol) and ZnCl$_2$ (0.06 g, 10 mol%) were added. The mixture was refluxed under Dean-Stark conditions for 48 h. The solvent was removed by rotary evaporation and the residue was mixed with ether (50 ml). Insoluble ZnCl$_2$-amine complex was filtered out. The ether layer was washed with water (20 ml) and brine (10 ml), dried over MgSO$_4$ and filtered. Evaporation of the solvent under reduced pressure then Kugelrohr distillation yielded 113a as a colourless oil (9.52 g, 81%); bp 120°C/0.2 mmHg; (Found: C, 84.7; H, 9.9; N, 5.5. C$_{19}$H$_{32}$N requires C, 84.7; H, 9.9; N, 5.5%); $\nu_{\text{max}}$/cm$^{-1}$ 1682 (C=N); $^1$H NMR (CDCl$_3$): $\delta$ 0.63 (3H, s, Me$_8$), 0.90 (3H, s, Me$_{10}$), 1.03 (3H, s, Me$_9$), 1.15-1.45 (2H, m, H$_{\text{endo}}$ H$_{\text{endo}}$), 1.42 (3H, d, J 6.6, CH$_3$CH), 1.60-2.00 (3H, m, H$_{\text{exo}}$ H$_{\text{exo}}$ H$_2$), 1.91 (1H, d, J 16.9, H$_{\text{endo}}$), 2.24 (1H, dt, J 16.9, 4.5, H$_{\text{exo}}$), 4.45 (1H, q, J 6.6, NCH$_2$CH$_3$), 7.1-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 11.52 (10-CH$_3$), 19.17 (9-CH$_3$), 19.54 (8-CH$_3$), 24.6 (CH$_3$CH), 27.61 (6-CH$_2$), 32.25 (5-CH$_2$), 35.51 (3-CH$_2$), 43.96 (4-CH), 47.00 (C), 53.60 (C), 59.71 (CH$_3$CH), 126.28, 126.47, 128.13, 146.2 (Ph), 180.5 (C=N).

Preparation of (S)-N-(1-phenylethyl)boranminine (113b)
Using the procedure described above, 113b was prepared from camphor (7.00 g, 46.00 mmol) and (S)-phenylethylamine (5.64 g, 46.59 mmol) in xylene (50 ml). 113b was isolated
as a colourless oil (10.11 g, 86%); bp 120°C/ 0.2 mmHg; (Found: C, 84.7; H, 9.9; N, 5.5.
C_{18}H_{25}N requires C, 84.7; H, 9.9; N, 5.5%); ν max/cm⁻¹ 1680 (C=N); ¹H NMR (CDCl₃): δ 0.80 (3H, s, Me₈), 0.93 (3H, s, Me₉), 1.03 (3H, s, Me₁₀), 1.10 (1H, m, H₆end), 1.32 (1H, m, H₆end), 1.41 (3H, d, J 6.6, CH₂), 1.63 (1H, m, H₅exo), 1.80 (1H, d, J 16.6, H₆end), 1.83 (1H, m, H₈exo), 1.90 (1H, t, J 4.4, H₂), 2.44 (1H, dt, J 16.6, 4.7, H₆exo), 4.45 (1H, q, J 6.6, CHCH₃), 7.1-7.4 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 11.17 (10-CH₃), 18.90 (9-CH₃), 19.41 (8-CH₃), 24.43 (CH₃CH), 27.33 (6-CH₂), 31.94 (5-CH₂), 35.17 (3-CH₂), 43.77 (4-CH₃), 46.73 (C), 53.37 (C), 59.53 (CH₃CH), 126.07, 126.32, 128.02, 146.21 (Ph), 179.74 (C=N)

Preparation of (±)-N-(1-phenylpropyl)boranimine (117a/b)

Following the procedure above, 117a/b was prepared by refluxing camphor (3.00 g, 19.71 mmol) and ±1-phenylpropylamine (114a/b) (3.17 g, 23.65 mmol) in xylene for 72 h in the presence of ZnCl₂ (10 mol. %) under Dean and Stark conditions. The crude imine was distilled via Kugelrohr distillation to give a colourless oil which was a 1:1 mixture of two diastereomers 117a and 117b (3.72 g, 70%); bp 125°C/ 0.2 mmHg; (Found: C, 84.9; H, 10.0; N, 5.3. C_{19}H_{27}N requires C, 84.7; H, 10.1; N, 5.2%); ν max/cm⁻¹ 1686 (C=N). The diastereomers were not separated therefore the NMR spectra contained signals for both diastereomers and was only generally assigned. 117a, ¹H NMR (CDCl₃): δ 0.55 (3H, s, CH₃), 0.89 (3H, s, CH₃), 1.02 (3H, s, CH₃), 0.7-0.9 (3H, CH₂CH₂), 1.1-2.0 (8H, m), 1.98 (1H, dt, J 16.6, 4.7, H₃exo), 4.13 (1H, t, J 6.8, CH₂CH₂), 7.1-7.4 (5H, Ph). 117b ¹H NMR (CDCl₃): δ 0.81 (3H, s, CH₃), 0.92 (3H, s, CH₃), 1.04 (3H, s, CH₃), 0.7-0.9 (3H, CH₂CH₂), 1.1-2.0 (8H, m, CH₂CH₂, H₃end, H₄, H₅exo, H₅end, H₆exo, H₆end), 2.45 (1H, dt, J 16.6, 4.7, H₃end), 4.14 (1H, t, J 6.8, CH₂CH₂), 7.1-7.4 (5H, Ph). 117a/b ¹³C NMR (CDCl₃): δ [11.54, 11.54] (CH₃), [27.29, 27.55] (CH₂), [32.01, 32.16, 32.19, 32.42, 35.68, 35.95] (CH₂), [43.89, 43.84] (CH), [46.53, 46.88, 53.55, 53.65] (C), [68.38 x2] (CH), [126.12 x2, 126.83, 126.87, 127.88, 127.96, 145.14, 145.24] (Ph), [180.35, 180.68] (C=N)

Preparation of (±)-N-(1-phenyl-2-methylpropyl)boranimine (118a/b)

Camphor (3.00 g, 19.71 mmol), ±1-phenyl-2-methylpropylamine (3.53 g, 23.65 mmol), and zinc chloride (0.05 g) were refluxed under Dean and Stark conditions in mesitylene (50 ml) for 72 h. The workup procedure was the same as described in the general procedure in 5.2.6. The crude imine was distilled by Kugelrohr distillation to give a colourless oil (3.34 g, 60%); (Found: C, 84.8; H, 10.3; N, 5.2. C₂₀H₂₈N requires C, 85.0; H, 10.0; N, 5.0%); Two diastereomers 118a:118b were formed in the ratio 3:2. 118a/b ν max/cm⁻¹ 1686 (C=N). Distinctive signals in the ¹H NMR spectrum of the diastereomeric mixture: 118a ¹H NMR (CDCl₃): δ 0.45 (3H, s, CH₃), 3.85 (1H, d, J 7.6, CHN). 118b ¹H NMR (CDCl₃): δ 2.42 (1H, dt, J 16.6, 4.7, H₃exo), 3.82 (1H, d, J 7.6, CHN). 118a/b ¹³C NMR (CDCl₃): δ [11.54
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x2, 18.96, 18.98, 19.03, 19.13, 19.31, 19.63, 19.74, 19.87] (CH₃), [27.28, 27.60] (CH),
[31.86, 32.36] (CH₂), [35.50 x2] (CH), [35.57, 35.89] (CH₂), [43.88, 43.94] (CH), [46.49,
46.93, 53.51, 53.71] (C), [71.72 x2] (CH), [126.08-128.56 (signals overlapping), 144.07,
144.20] (Ph), [179.71, 180.07] (C=N)

Attempted condensation of (±)-1-phenyl-2,2-dimethylpropylamine (116a/b) with
camphor.
Camphor (3.00 g, 19.71 mmol), ±1-phenyl-2,2-dimethylpropylamine (3.53 g, 23.65 mmol),
and zinc chloride(0.05 g) were refluxed under Dean and Stark conditions in mesitylene (50
ml) for 120 h. The work up detailed in 5.2.6 was followed. The ¹H NMR spectrum of the
 crude material indicated that no reaction had taken place.

Preparation of N-(1-phenylmethyl)boranamine (121)
Camphor (7.00 g, 46.00 mmol), benzylamine (4.91g, 46.00 mmol) and ZnCl₂ (0.20
g, 1.47 mmol) were refluxed in toluene for 4 h. The work-up described in 5.2.6 was followed and the
yellow oil was distilled via Kugelrohr distillation to give 121 (8.76 g, 79%); bp 110°C/ 0.2
mmHg; (Found: C, 84.7; H, 9.6; N, 5.8. C₁₇H₂₃N requires C, 84.5; H, 9.5; N, 5.8%); ν
max/cm⁻¹ 1685 (C=N); ¹H NMR (CDCl₃): δ 0.76 (3H, s, Me₈), 0.94 (3H, s, Me₁₀), 1.04 (3H, s,
Me₉), 1.20 (1H, m, H₅ endo), 1.42 (1H, m, H₆ endo), 1.70 (1H, m, H₆exo), 1.8-2.0 (3H, H₅ exo,
H₄, H₃ endo), 2.38 (1H, dt, J 16.9, 4.5, H₃ exo), 4.41 (1H, d, J 15.0, NCHH), 4.49 (1H, d, J 15.0,
NCHH), 7.1-7.4 (5H, m, Ph)

5.2.6 REDUCTION OF THE 'CAMPHOR IMINES' WITH NaBH₄
The camphor imine (35.0 mmol) was dissolved in methanol (100 ml) and the solution was
cooled to -78°C. NaBH₄ (2.66 g, 70.3 mmol) was added slowly. The mixture was stirred
overnight while the reaction was allowed to warm up to r.t. Methanol was removed on a
rotary evaporator and water was added to dissolve the solid. The product was extracted into
ether (3x 50 ml). The combined organic layers were washed with brine (10 ml), then dried
over MgSO₄, filtered and further dried over NaOH pellets. The solvent was removed under
reduced pressure to yield the crude product.

Preparation of (exo)-(1R)-N-(1-phenylethyl)boranamine (119a) from 113a
Amine 119a was prepared using the procedure described above with 113a (9.0 g, 35.2
mmol). The crude product was distilled via Kugelrohr distillation to yield a colourless oil
(119a) (8.38 g, 93%); bp 120°C/ 0.2 mmHg, which solidified when left at 4°C. (Found: C,
83.9; H, 10.7; N, 5.4. C₁₈H₂₅N requires C, 84.0; H, 10.6; N, 5.4%); ν max/cm⁻¹ (film) 3460
(NH); ¹H NMR (CDCl₃): δ 0.78 (3H, s, Me₈), 0.93 (3H, s, Me₁₀), 0.99 (3H, s, Me₉), 0.98-
1.10 (2H, m, H$_{endo}$, H$_{endo}$), 1.2 (1H, bs, NH), 1.27 (3H, d, J 6.6, CH$_3$CH), 1.3-1.7 (5H, m, H$_{exoo}$, H$_{endo}$, H$_{exo}$, H$_{exo}$, H$_4$), 2.46 (1H, dd, J 7.8, 5.9, H$_{endo}$), 3.75 (1H, q, J 6.6, CH$_2$CH), 7.1-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): δ 12.25 (10-CH$_3$), 20.47 (9-CH$_3$), 20.54 (8-CH$_3$), 24.54 (CH$_3$CH), 27.21 (6-CH$_2$), 36.83 (5-CH$_2$), 40.43 (3-CH$_2$), 45.24 (4-CH), 46.76 (C), 48.62 (C), 58.15 (CH$_3$CH), 65.01 (2-CH), 126.41, 126.76, 128.11, 147.31 (Ph); [α]$_D^{18}$ -10.2° (c 3.80 CHC$_3$), Lit [α]$_D^{21}$ -10.6° (c 3.23 CHC$_3$) .

Preparation of (endo)-(1S)-N-(1-phenylethyl)boranamine (119b) from 113b

119b was prepared from 113b (10.0g, 39.15 mmol) using the procedure described above. 119b was isolated in 90% yield. 119b was dissolved in ether and HCl gas (generated from NaCl/ conc. H$_2$SO$_4$) was passed through until the ether layer was saturated and a white ppt had formed. 119b.HCl was filtered off and recrystallised from hot ethanol to give needle shaped crystals which were submitted for X-ray analysis. (82%) (Found: C, 73.4; H, 9.8; N, 4.8. C$_{18}$H$_{28}$NCI requires C, 73.6; H, 9.6; N, 4.8%); $^1$H NMR (D$_2$O): δ 0.57 (3H, s, CH$_3$), 0.82 (3H, s, CH$_3$), 0.89 (3H, s, CH$_3$), 0.80 (1H, m), 1.20 (1H, m), 1.50 (2H, m), 1.60 (1H, t, J 4.4), 1.71 (1H, d, J 6.6), 1.7-1.9 (2H, m), 3.32 (1H, m), 4.51 (1H, q, J 6.6, CH$_3$CH), 7.4-7.6 (5H, m, Ph). 119b.HCl was treated with aqueous NaOH (2M, 20 ml) and extracted into ether (50 ml). The dried (NaOH pellets) ether extract was evaporated off under reduced pressure and the oil was distilled via Kugelrohr distillation to yield 119b (7.1 g, 70%); bp 120°C/ 0.2 mmHg; (Found: C, 84.0; H, 10.6; N, 5.4. C$_{18}$H$_{28}$N requires C, 84.0; H, 10.6; N, 5.4%); ν$_{max}$/cm$^{-1}$ (film) 3457 (NH); $^1$H NMR (CDCl$_3$): δ 0.62 (1H, dd, J 12.4, 4.3, H$_{exo}$), 0.78 (3H, s, Me$_8$), 0.82 (3H, s, Me$_{10}$), 0.85 (3H, s, Me$_9$), 1.0-1.3 (3H, m, NH, H$_{endo}$, H$_{endo}$), 1.31 (3H, d, J 6.6, CH$_2$CH), 1.50 (1H, t, J 4.5, H$_2$), 1.6-2.0 (3H, m, H$_{exo}$, H$_{endo}$, H$_{exo}$), 2.84 (1H, ddd, J 10.3, 4.3, 2.0, H$_{exo}$), 3.80 (1H, q, J 6.6, CH$_2$CH), 7.1-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): δ 14.28 (10-CH$_3$), 18.60 (9-CH$_3$), 19.89 (8-CH$_3$), 24.09 (CH$_3$CH), 27.38 (6-CH$_2$), 28.45 (5-CH$_2$), 39.07 (3-CH$_2$), 45.05 (4-CH), 48.03 (C), 48.99 (C), 57.57 (CH$_2$CH), 60.98 (2-CH), 126.53, 126.67, 128.15, 147.14 (Ph); [α]$_D^{18}$ +13.9° (c 0.50 CHCl$_3$), Lit [α]$_D^{21}$ +14.7° (c 0.43 CHCl$_3$). 27

Reduction of 117a/b with NaBH$_4$ to give 120a/b

Using the general method described above, 120a/b was prepared from 117a/b (1.00 g, 3.71 mmol). The imine was dissolved in methanol, NaBH$_4$ was added and the mixture was stirred for 24 h at r.t. The $^1$H NMR spectrum of the crude product indicated that 100% of 120a had been formed and 50% of 120b had been formed (with 50% of 117b remaining). 117b was removed by flash chromatography (ether/hexane 1:1), leaving a mixture of 120a (ca. 66%) and 120b (ca. 33%) (overall yield 50%). Distinctive signals in $^1$H NMR were: 120a δ 2.41 (1H, t, J 6.7, H$_{endo}$), 3.49 (1H, t, J 6.8, CH/CH$_2$CH$_3$); 120b δ 0.56 (1H, dd, J 12.8, 4.3, H$_{exo}$), 2.78 (1H, ddd, J 10.3, 4.3, 2.0, H$_{exo}$), 3.49 (1H, t, J 6.8, CH/CH$_2$CH$_3$); 120a/b $^{13}$C
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NMR (CDCl₃): δ [10.82, 10.97, 12.42, 14.44, 18.61, 19.62, 20.36, 20.52] (CH₃), [27.16, 27.33, 28.46, 30.93, 31.63, 36.72, 39.26, 40.77] (CH₂), [45.08, 45.21] (CH), [46.72, 48.04, 48.82, 49.18] (C), [61.28, 64.86, 65.06, 66.43] (CH), [126.38, 126.51, 127.53 x2, 127.94, 128.01, 145.81, 146.08] (Ph)

Reduction of 121 with NaBH₄ to give 122a and 122b

121 (1.00 g, 4.14 mmol) was reduced with NaBH₄ using the method described above. A mixture of two diastereomeric amines was isolated (122a and 122b, 4:1) (79% in total); 122a (Found: C, 84.1; H, 10.2; N, 5.6. C₁₇H₂₂N requires C, 84.0; H, 10.4; N, 5.6%); v_max/cm⁻¹ (film) 3463 (NH); ¹H NMR (CDCl₃): δ 0.81 (3H, s, Me₈), 0.88 (3H, s, Me₁₀), 1.09 (3H, s, Me₉), 0.98-1.10 (2H, m, H₆endo H₅endo), 1.2 (1H, bs, NH), 1.3-1.6 (5H, m, H₆exo H₃endo H₃exo H₅exo H₄), 2.60 (1H, dd, J 7.8, 5.9, H₆endo H₂endo), 3.58 (1H, d, J 13.3, CH₂Ph), 3.76 (1H, d, J 13.3, CH₂Ph), 7.1-7.4 (5H, m, Ph). 122b (Found: C, 84.0; H, 10.1; N, 5.6. C₁₇H₂₂N requires C, 84.0; H, 10.4; N, 5.6%); v_max/cm⁻¹ (film) 3465 (NH); ¹H NMR (CDCl₃): δ 0.85 (3H, s, Me₈), 1.03 (3H, s, Me₁₀), 1.06 (3H, s, Me₉), 0.98-1.10 (2H, m, H₆endo H₂endo), 1.2 (1H, bs, NH), 1.3-1.6 (5H, m, H₆exo H₃endo H₃exo H₅exo H₄), 2.85 (1H, m, H₂endo), 3.70 (1H, d, J 13.3, CH₂Ph), 3.88 (1H, d, J 13.3, CH₂Ph), 7.1-7.4 (5H, m, Ph).

Attempted reduction of imines 118a/b with NaBH₄ in methanol

Initially 118a/b (1.00 g, 3.54 mmol) was treated with NaBH₄ (0.28 g, 7.42 mmol) using the general procedure given above (-78°C to r.t. overnight). The ¹H NMR spectrum of the crude product mixture indicated that no reduction had occurred. The reaction was repeated both at r.t. for 48 h and in refluxing methanol for 120 h, but no reduction products were isolated.

Reduction of 113a/b with NaBH₄ to give 119a/b under varying reaction conditions

The diastereomeric mixture of imines 119a/b was reduced with sodium borohydride using various experimental conditions. These are summarised in Table 2.3. The work up procedure is given in the general method. The product mixtures were analysed by ¹H NMR spectroscopy and the results are detailed in Table 2.3.

5.2.7 ATTEMPTED REDUCTION OF THE 'CAMPHOR IMINES' WITH OTHER REDUCING AGENTS

Attempted reduction of the C=N bond of 113a/b by catalytic reduction

113a/b (0.25 g, 0.98 mmol) was dissolved in THF (30 ml). 5% Pd/C/ (0.05 g) was added and the mixture was stirred under hydrogen at 1 atm. for 24 h. The mixture was filtered and the
solvent was evaporated off to give a yellow oil. $^1$H NMR indicated that no reduction had occurred, and that 113a/b was recovered. The same result was obtained when the experiment was repeated using i) ethanol, 5 % Pd/C/H$_2$, 24 h and ii) ethanol, Pd/C/H$_2$, 48 h.

**Attempted reduction of the C=N bond of 113a/b with lithium aluminium hydride**

113a/b (0.25 g, 0.98 mmol) was dissolved in ether (30 ml) and the solution was cooled to 0°C. LiAlH$_4$ (0.11g, 2.89 mmol) was added and the mixture was stirred under nitrogen for 24 h. Saturated sodium sulphate solution was added and the mixture was filtered. The ether layer was set to one side and the aqueous layer was extracted with ether (2x 20 ml). The combined organic layers were washed with brine (10 ml) and dried over MgSO$_4$. Evaporation left a yellow oil. $^1$H NMR indicated that no reduction had taken place and 113a/b had been recovered. The same result was obtained when the experiment was repeated using i) ether, reflux, 24h ii) THF, reflux, 24 h.

### 5.2.8 Preparation of (1R,2R,5R)-(+)−2-hydroxypinan-3-one (124)

(1S)-(−)-α-Pinene [Aldrich 97% ee [α]$_D$ $^{20}$−45°] (8.00 g, 58.7 mmol) was dissolved in 90% aqueous acetone (50 ml) and the solution was cooled to -10°C in an ice-salt bath. Powdered KMnO$_4$ (16.0 g, 101.2 mmol) was added slowly over 3 h so that the temperature was maintained < 0°C. The mixture was stirred for a further 2 h at -10°C, then filtered under suction to remove most of the MnO$_2$ then was filtered under gravity. Acetone was removed on a rotary evaporator and the product was extracted into ether (3x 20 ml), washed with brine (10 ml), dried over MgSO$_4$, filtered and concentrated. A colourless oil (4.25 g, 43%) was formed. The oil distilled at 88-90°C/4 mmHg, then recrystallised from pentane at low temperature (oil was dissolved in pentane at r.t., then cooled to -80°C whereupon crystals precipitated and the mother liquor was pipetted off). White crystals of (1R,2R,5R)-(+)−2-hydroxypinan-3-one were isolated (124) (3.10 g, 32%), m.p. 34-35°C; [α]$_D$ $^{20}$ +37.5° (c 2.64 CHCl$_3$) indicates >93% op, Lit.$^{256}$ for other enantiomer [α]$_D$ $^{20}$−40° (c 2.65 CHCl$_3$); $\nu_{\max}$/cm$^{-1}$ (nujol) 3419 (bs), 1722 (C=O); $^1$H NMR (CDCl$_3$): δ 0.89 (3H, s, CH$_3$), 1.37 (3H, s, CH$_3$), 1.39 (3H, s, CH$_3$), 1.69-2.15 (4H, m, CH$_2$, CH, CH), 2.30 (1H, bs -OH), 2.62 (2H, t, CH$_2$C≡N).

### 5.2.9 Condensation of 124 with 1-phenylethylamine

A 50 ml rbf was fitted with a reflux condenser and nitrogen inlet tube. 124 (1.20 g, 7.76 mmol) and 1-phenylethylamine (0.94 g, 7.76 mmol) were placed in the flask with dry toluene (20 ml). Molecular sieve (4Å) and BF$_3$-etherate (1 drop) were added and the mixture was refluxed for 4 h [When carried out on a larger scale, a Dean and Stark apparatus was used]
instead of molecular sieves, giving identical results]. The mixture was filtered and concentrated in vacuo.

Condensation of 124 with (R)-1-phenylethylamine to give 125a
The method described above was followed with (R)-1-phenylethylamine (0.94 g, 7.76 mmol). The crude product was distilled via Kugelrohr distillation 100°C/0.07 mmHg to give 125a as a colourless oil (1.98 g, 94%); (Found: C, 79.5; H, 9.3; N, 5.0. C_{18}H_{22}NO requires C, 79.7; H, 9.3; N, 5.2%); ν\text{max/cm}^{-1} 3413 (OH), 1648 (C=N); ^1H NMR (CDCl₃): δ 0.68 (3H, s, Meₐ), 1.28 (3H, s, Meₐ), 1.44 (3H, d, J 6.5 CH₂CH), 1.56 (1H, d, J 10.5, Hₗ), 2.00 (1H, m, Hₗ), 2.08 (1H, t, J 5.8, Hₗ), 2.35 (1H, m, J 10.5, Hₗ), 2.40 (1H, dt, J 17.8, 2.5, Hₗ), 2.66 (1H, dd, J 17.8, 3.0, Hₗ), 4.66 (1H, q, J 6.8, CH₂CH), 7.2-7.4 (5H, m, Ph), OH unassigned; ^13C NMR (CDCl₃): δ 22.63 (CH₃), 24.71 (CH₃), 27.24 (CH₃), 27.98 (4-CH₃), 28.36 (CH₃), 33.02 (6-CH₂), 38.22 (7-C), 38.29 (5-CH), 50.18 (3-CH), 58.01 (CH₂CH), 76.40 (2-C), 126.31, 145.48 (Ph), 174.12 (C=N)

Condensation of 124 with (S)-1-phenylethylamine to give 125b
125b was prepared by condensing 124a (1.20 g, 7.78 mmol) with (S)-1-phenylethylamine (0.94 g, 7.78 mmol) as described above. 125b was isolated as a pale yellow oil after Kugelrohr distillation at 100°C/0.07 mmHg, (2.01 g, 95%); (Found: C, 79.6; H, 9.3; N, 5.1. C_{18}H_{22}NO requires C, 79.7; H, 9.3; N, 5.2%); ν\text{max/cm}^{-1} 3413 (OH), 1648 (C=N); ^1H NMR (CDCl₃): δ 0.91 (3H, s, Meₐ), 1.31 (3H, s, Meₐ), 1.42 (3H, d, J 6.5, CH₂CH) 1.50 (1H, d, J 12.0, Hₗ), 1.52 (3H, s, Meₐ), 1.98 (1H, m, Hₗ), 2.07 (1H, t, J 5.9, Hₗ), 2.28 (1H, m, J 12.0, Hₗ), 2.40 (1H, bs, OH), 2.53 (1H, dd, J 17.8, 3.0, Hₗ), 2.63 (1H, dt, J 17.8, 2.2, Hₗ), 4.67 (1H, q, J 6.5, CH₂CH), 7.1-7.5 (5H, m, Ph); ^13C NMR (CDCl₃): δ 22.63 (CH₃), 23.99 (CH₃), 27.25 (CH₃), 27.91 (4-CH₂), 28.41 (CH₃), 32.67 (6-CH₂), 38.20 (7-C), 38.27 (5-CH), 50.05 (7-CH), 57.94 (CH₂CH), 76.35 (2-C), 126.38, 126.46, 128.23, 145.21 (Ph), 173.54 (C=N)

5.2.10 Reduction of 125 with NaBH₄ in methanol
Imine (125) (0.70 mmol) was dissolved in methanol (10 ml) and the solution was cooled to -78°C. NaBH₄ (0.06 g, 1.59 mmol) was added and the mixture was stirred for 24 h while the temperature was allowed to warm up slowly to r.t.. The material was concentrated in vacuo and the product was extracted into ether (3x 20 ml). The combined organic layer was washed with brine (5 ml), dried over MgSO₄, filtered and evaporated to leave the crude product.

Reduction of 125a with NaBH₄ to give 126a
Using the procedure described above, 125a (0.20 g, 0.74 mmol) was reduced with NaBH₄ (0.06 g, 1.59 mmol) to give crude 126a as a yellow oil. This was distilled under vacuum (100°C/0.05 mmHg) to give pure 126a as a colourless oil, (0.16 g, 79%); ν\text{max/cm}^{-1} (film)
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3430 (bs OH); The numbering scheme for the NMR assignment of 126a is the same as that for 126b and is given in Figure 2.13 and Figure 2.14. $^1$H NMR (CDCl$_3$): $\delta$ 0.87 (3H, s, Me$_2$), 1.21 (3H, s, CH$_3$), 1.32 (2H, m, J 6.7, Me$_2$), 1.39 (1H, d, J 10.0, H$_2$), 1.40 (3H, s, CH$_3$), 1.60 (1H, bs, OH), 1.80-1.86 (2H, m, J 5.5, H$_6$, H$_8$), 2.0-2.15 (2H, m, H$_6$, H$_7$), 2.94 (1H, t, 9.2, H$_2$), 4.04 (1H, q, J 6.7), 7.2-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 23.11 (Me$_2$), 24.40 (CH$_3$), 24.46 (4-CH$_2$), 24.52 (CH$_3$), 27.63 (CH$_3$), 33.62 (6-CH$_3$), 39.13 (7-C), 40.24 (5-CH), 55.83 (3-CH), 56.39 (CHCH$_3$), 57.72 (1-CH), 78.43 (2-C), 126.65, 128.28, 146.63 (Ph). The oil did not crystallise when dissolved in pentane. In an attempt to prepare the HCl salt of 126a, 126a was dissolved in ether, cooled to 0°C and HCl (g) [NaCl/H$_2$SO$_4$] was blown through the solution. An oil dropped out. Evaporation of the solvent left an oil which would not crystallise from ether, ether/hexane, ethanol, ethanol/ether, ethanol/hexane or CHCl$_3$.

Reduction of 125b with NaBH$_4$ to give 126b and 126c

A mixture of two diastereomers 126b and 126c (4:1) were prepared by reduction of 125b (0.20 g, 0.74 mmol) with NaBH$_4$ in methanol using the procedure given above. A colourless oil containing 126b and 126c was dissolved in pentane and immediately large crystals of 126b precipitated (0.10 g, 52%); m.p. 126°C (Found: C, 79.1; H, 10.2; N, 5.1. C$_{18}$H$_{27}$NO requires C, 79.1; H, 10.0; N, 5.1%); $\nu_{max}/\text{cm}^{-1}$ 3861 (vs, NH), 3320 (bs, OH), The numbering scheme for the NMR assignment of 126b is given in Figure 2.13 and Figure 2.14. $^1$H NMR (CDCl$_3$): $\delta$ 0.78 (3H, s, Me$_2$), 1.17 (1H, ddd, J 10.4, 5.9, 2.6, H$_k$), 1.20 (3H, s, CH$_3$), 1.21 (3H, s, CH$_3$), 1.25 (1H, d, J 10.2, H$_j$), 1.37 (3H, d, J 6.7, Me$_2$), 1.79 (1H, m, H$_g$), 1.96 (1H, t, J 5.7, H$_j$), 2.11 (1H, dddd, J 10.4, 5.7, 2.5, 2.0, H$_b$), 2.24 (1H, dddd, J 10.4, 9.9, 2.5, 2.0, H$_j$), 2.73 (1H, dd, J 9.9, 5.9, H$_j$), 3.82 (1H, q, J 6.7, H$_z$), 5.55 (1H, bs, OH), 7.2-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 24.02 (Me$_2$), 24.57 (Me$_2$), 27.87 (Me$_b$), 28.14 (4-CH$_2$), 31.34 (Me$_2$), 38.25 (7-C), 38.89 (6-CH$_2$), 40.42 (5-CH), 54.08 (3-CH), 54.12 (1-CH), 58.07 (CHCH$_3$), 71.28 (2-C), 126.19, 127.08, 128.60, 145.16 (Ph).

5.3 EXPERIMENTAL DETAILS FOR THE WORK DESCRIBED IN CHAPTER 3

5.3.1 PREPARATION OF PENTAMETHYLENE SULPHONE (145)

Pentamethylene sulphide (0.26 ml, 2.50 mmol) was dissolved in methanol (10 ml) and the flask was cooled in an ice-bath. Oxone (2.31 g, containing KHSO$_5$, 7.50 mmol) was dissolved in water (10 ml) and added slowly. The mixture was stirred at r.t. for 4 h, then diluted with water (10 ml) and extracted into CHCl$_3$ (3x 20 ml). The combined organic layer was washed with brine (5 ml) and dried over MgSO$_4$. The solvent was evaporated off leaving a white solid.
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(146) (0.32 g, 96%) analytical data was in agreement with published data;\textsuperscript{257} m.p. 96-98 °C, (Found: C, 44.7; H, 7.5. \( \text{C}_9\text{H}_{10}\text{SO}_2 \) requires C, 44.8; H, 7.5%); \( ^1\text{H} \text{NMR (CDCl}_3 \): \( \delta \) 1.65 (2H, m, 2x H4 ), 2.10 (4H, m, 2x H3 , 2x H5 ), 2.99 (4H, m, 2x H2 , 2x H6 ); \( ^{13}\text{C} \text{NMR (CDCl}_3 \): \( \delta \) 23.80 (4-CH\text{3}), 24.19 (3-0\text{1}*) , 52.10 (2-CH\text{2})\textsuperscript{258}; EI 70 eV 134 (M+'), 69 (C\text{5}H\text{5}+, 100%).

5.3.2 PREPARATION OF 4-THIOPYRAN-4,4-DIOXIDE (146)
4-Thiopyran (2.0 ml, 21.39 mmol) was dissolved in methanol (60 ml) and cooled to 0°C. Oxone (39.50 g, containing KHSO\textsubscript{5} 21.39 mmol) was added slowly then the mixture was stirred at r.t. for 24 h. The methanol was removed on a rotary evaporator and solid was stirred with CHCl\textsubscript{3} (3 x 40 ml) to extract the product. The combined organic layer was washed with water (10 ml) and brine (10 ml), then dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo, leaving 146 as a white solid (2.06 g, 65%); the analytical data was in agreement with the published data;\textsuperscript{259,260} m.p. 132-133 °C, (Lit m.p. 130°C);\textsuperscript{259} (Found: C, 35.3; H, 5.9. \( \text{C}_9\text{H}_{18}\text{SO}_3 \) requires C, 35.3; H, 5.9%); \( ^1\text{H} \text{NMR (CDCl}_3 \): \( \delta \) 3.11 (4H, m, CH\text{2}SO\text{2}CH\text{2}), 4.14 (4H, m, CH\text{2}OCH\text{2}); \( ^{13}\text{C} \text{NMR (CDCl}_3 \): \( \delta \) 52.8 (CH\text{2}S), 66.0 (CH\text{2}O).

5.3.3 PREPARATION OF 4-\textit{t}-BUTYLPENTAMETHYLENE SULPHONE (143)
4-t-Butylpentamethylene sulphone was synthesised in 7 steps from 4-t-butylcyclohexanone.

Preparation of oxime (148)
4-t-Butylcyclohexanone (28.76 g, 0.186 mol) was dissolved in ether (150 ml). Hydrochloric acid (13M, 7.3 ml) was added and the mixture was cooled in an ice-salt bath. \textit{n}-Butylnitrite (freshly prepared, 40.0 g, 0.388 mol) was added slowly and the temperature of the mixture was kept < 15°C. A yellow solid precipitated after 50% of the \textit{n}-butyl nitrite had been added. After addition, the mixture was stirred for a further 3 h. The yellow solid was filtered and washed with ether (10 x 50 ml) to give 148 (34.0 g, 85%); m.p. >300°C, \( \nu_{\text{max/cm}^{-1}} \) (nujol) 3584 (bs, OH), 1705 (C=O); \( ^1\text{H} \text{NMR (d}_6\text{-acetone): \( \delta \) 1.02 (9H, s, C(CH\text{3})\text{3}), 1.64 (1H, ttt J 7.4, 3.7, 3.7, CH\text{C(CH\text{3})\text{3}}), 2.25 (2H, m, 2x CH\text{H}), 2.84 (2H, bs, -OH), 3.35 (2H, m, 2x CH\text{H}); mass spectrum (DCI, ammonia gas) 230 (M+1 + NH\text{3}), 168 (M-C\text{NOH}^+).\n
\( \beta\text{-t}-\text{Butylglutaronitrile (149)}
\text{Oxime 148} (30.0 g, 0.141 mmol) was dissolved in aq. KOH (2.2 M, 60.0 ml), and the mixture was cooled in an ice-bath. Acetic anhydride (26.6 ml, 28.2 mmol) was added slowly, the temperature was kept < 15°C and the pH was kept > 10 by the addition of several portions of KOH (2.2 M). The mixture was then stirred for a further 2 h. The crude material was extracted into CHCl\textsubscript{3} (6x 20 ml); the combined organic layer was washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated. A dark brown oil was isolated and used without
further purification (149) (18.85 g, 89%); (Found: C, 80.0; H, 10.4; N 10.3. C\textsubscript{9}H\textsubscript{14}N requires C, 79.4; H, 10.3; N, 10.3%); ν\textsubscript{max}/cm\textsuperscript{-1} 2248 (CN); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 1.03 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.95 (1H, m, CHC(CH\textsubscript{3})\textsubscript{3}), 2.54 (2H, dd, J 17.3, 7.3, 2x CHH), 2.68 (2H, dd, J 17.3, 5.0, 2x CHH).

β-\textit{t}-Butylglutaric acid (150)
The nitrile (149) (18.0 g, 0.12 mmol) was refluxed in aq. sulphuric acid (50% conc sulphuric acid, 50 % water by weight, 225 g) for 24 h. The mixture was cooled and saturated with ammonium sulphate, then extracted into ether (6x 20 ml). The combined organic layer was washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated to yield 150 as white needle shaped crystals (21.02 g, 93%); m.p. 145-147°C (with decomposition); (Found: C, 57.3; H, 8.5. C\textsubscript{9}H\textsubscript{16}O\textsubscript{4} requires C, 57.4; H, 8.6%); 3800-2000 (bs COOH), 1723 (C=O); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 0.94 (9H, s, (CH\textsubscript{3})\textsubscript{3}), 2.1-2.3 (3H, m, CHC(CH\textsubscript{3})\textsubscript{3}, 2x CHH), 2.63 (2H, dd, J 14.0, 1.5, 2x CHH), 11.5-12.5 (2H, bs, 2x COOH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 27.29 (CH\textsubscript{3}), 33.06 (C), 36.05 (CH\textsubscript{2}), 42.35 (CH), 180.94 (COOH).

3-\textit{t}-Butylpentan-1,5-diol (151)
A 250 ml rbf was fitted with a reflux condenser, nitrogen inlet tube and powder funnel. The flask was charged with LiAlH\textsubscript{4} (28.0 g, 0.75 mmol) and ether (100 ml) and cooled in an ice-bath. 150 (21.0 g, 112 mmol) was added slowly to maintain a gentle reflux and then the mixture was refluxed for 16 h. Excess LiAlH\textsubscript{4} was decomposed by the slow addition of a saturated solution of sodium sulphate. The white precipitate was filtered off and washed well with ether (100 ml). The ether layer was washed with NaOH (2M, 50 ml) and dried over MgSO\textsubscript{4}. Evaporation of the solvent left a colourless oil (151) (16.63 g, 93%); (Found: C, 67.5; H, 12.7. C\textsubscript{9}H\textsubscript{20}O\textsubscript{2} requires C, 67.5; H, 12.6%); ν\textsubscript{max}/cm\textsuperscript{-1} 3420 (OH); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 0.88 (9H, s, (CH\textsubscript{3})\textsubscript{3}), 1.2-1.4 (3H, m, CHC(CH\textsubscript{3})\textsubscript{3}, 2x CHH), 1.7-1.9 (2H, m, 2x CHH), 3.00 (2H, s, 2x OH), 3.55-3.8 (4H, m, 2x CH\textsubscript{2}OH).

1,5-Dibromo-3-\textit{t}-butylpentane (152)
151 (13.00 g, 81.1 mmol) was placed in a rbf and cooled in an ice-bath. PBr\textsubscript{3} (10.7 ml, 112 mmol) was added and the mixture was heated to 160°C for 5 h. The mixture was cooled and water (20 ml) was added then the mixture was filtered through sinter-glass to remove the orange solid. The solid was washed with CH\textsubscript{2}Cl\textsubscript{2} (20 ml). The aqueous layer was further extracted with CH\textsubscript{2}Cl\textsubscript{2} (2x 20 ml) and the combined organic layer was washed with brine (10 ml) dried over MgSO\textsubscript{4} and filtered. The material was concentrated in vacuo leaving 152 as a colourless oil (20.8 g, 90%); bp. 87-88°C (0.7 mmHg); (Found: C, 37.6; H, 6.0. C\textsubscript{9}H\textsubscript{18}Br\textsubscript{2} requires C, 37.8; H, 6.3%); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 0.90 (9H, s, (CH\textsubscript{3})\textsubscript{3}), 1.24 (1H, m,
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CHC(CH$_3$)$_3$), 1.5-1.7 (2H, m, 2x CHH), 2.0-2.2 (2H, m, 2x CHH), 3.3-3.6 (4H, m, 2x CH$_2$Br).

4-t-Butylpentamethylene sulphide (153)

A rbf was fitted with a reflux condenser and pressure equalising dropping funnel. Na$_2$S.9H$_2$O (15.10 g, 62.9 mmol) was dissolved in ethanol (100 ml) and heated to reflux. The dibromide (152) (18.0 g, 62.9 mmol) in ethanol (100 ml) was added dropwise over 1 h then the mixture was refluxed for 5 h. The flask was fitted with a still head and the ethanol was distilled off. Ether (50 ml) was added to the residue and the mixture was filtered. The filtrate was concentrated on a rotary evaporator at 0°C, then distilled bp 50°C/ 1 mmHg to give 153; (8.86 g, 89%); (analytical data in agreement with that given in the literature); $^1$H NMR (CDCl$_3$): δ 0.85 (9H, s, (CH$_3$)$_3$), 1.40 (2H, m, 2x CHHCH), 2.10 (2H, m, 2x CHH), 2.60 (4H, m, CH$_2$SO$_2$CH$_2$). It was converted to 4-t-butylpentamethylene sulphone immediately.

4-t-Butylpentamethylene sulphone (143)

The sulphide (153) (7.96 g, 50.3 mmol) was dissolved in 50% acetic acid (30 ml) and was treated with H$_2$O$_2$ (30% wt, 15 ml). The mixture was refluxed for 18 h, cooled and extracted into CH$_2$Cl$_2$ (3x 20 ml), dried over MgSO$_4$ and filtered. Evaporation of the solvent left a white solid (9.09 g, 94%); m.p. 130 °C (sublimes from 110 °C onwards); (Found: C, 56.5; H, 9.7. C$_9$H$_{18}$SO$_2$ requires C, 56.8; H, 9.5%); $^1$H NMR (CDCl$_3$): δ 0.93 (9H, s, (CH$_3$)$_3$), 1.20 (1H, tt, J 12.1, 2.6, CHC(CH$_3$)$_3$), 1.80-2.00 (2H, m, 2x CHHCH), 2.10-2.20 (2H, m, 2x CHHCH), 2.80-3.20 (4H, m, CH$_2$SO$_2$CH$_2$); $^{13}$C NMR (CDCl$_3$): δ 25.28 (CH$_3$), 27.46 (CH$_2$CH), 32.52 (C), 46.18 (CH$_2$SO$_2$), 51.56 (CH)

5.3.4 DEPROTONATION OF 145 WITH LDA FOLLOWED BY REACTION OF THE CARBANION WITH AN ELECTROPHILE

All the glassware was oven-dried. Each flask was fitted with a rubber septum and evacuated using a needle attached to a vacuum pump. The flask was then filled with nitrogen from a balloon containing nitrogen gas. This procedure was repeated three times.

Deprotonation of 145 and reaction with MeI

THF (2 ml) and diisopropylamine (0.12 ml, 0.86 mmol) were added to a flask via a syringe, and the mixture was cooled to ca. -45 °C. BuLi (1.6M in hexanes, 0.55 ml, 0.88 mmol) was added dropwise and the mixture was stirred for 30 minutes.; the temperature was then decreased to -78°C and pentamethylene sulphone (0.10 g, 0.74 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 3 h, and then MeI (0.25 ml, 4.02 mmol) was
added and the mixture was stirred for a further 4 h at -78°C. Hydrochloric acid (3M, 20 ml) was added and the mixture was warmed to r.t. and then extracted into ether (30 ml). The ether layer was washed with brine, dried over MgSO₄, filtered and evaporated. Only a trace of product was isolated. The aqueous layer was further extracted with CHCl₃ (2x 30 ml) and the combined CHCl₃ layer was washed with brine (10 ml), dried over MgSO₄, filtered and concentrated to give a white solid. ¹H NMR spectrum of the crude material showed a mixture ca. 75% 154, 15% 155 and 10% of 145 remaining. The mixture was flash chromatographed through silica (CHCl₃) and the white crystals were recrystallised from CHCl₃/hexane to yield 154 (72 mg, 65%); m.p. 62-63°C (Lit. 2 6 1 m.p. 65-66°C); (Found: C, 48.4; H, 8.2. C₆H₁₂SO₂ requires C, 48.6; H, 8.2%). The NMR spectra were assigned from a COSY and XHCCORRD experiment. ¹H NMR (CDCl₃): δ 1.36 (3H, d, J 6.8, CH₃), 1.35-1.60 (1H, m, H₄ax), 1.65-1.95 (2H, m, H₄eq H₃ax), 1.95-2.15 (3H, m, H₃eq H₅ax H₅eq), 2.80-2.90 (1H, m, H₆ax), 2.90-3.00 (1H, ddd, J 11.4, 6.8, 3.7, H₂ax), 3.0-3.2 (1H, dt, J 13.9, 3.4, H₆eq); ¹³C NMR (CDCl₃): δ 11.10 (CH₃), 24.02 (4-CH₂), 24.46 (5-CH₂), 32.18 (3-CH₂), 51.47 (6-CH₂), 57.04 (2-CH); El (70eV) 148 (M⁺ 25%), 83 (C₆H₇ + ).

Deprotonation of 145 and reaction with BnBr
THF (2 ml) and diisopropylamine (0.12 ml, 0.86 mmol) were added to a flask via a syringe, and the mixture was cooled to ca. -45 °C. BuLi (1.6M in hexanes, 0.55 ml, 0.88 mmol) was added dropwise and the mixture was stirred for 30 minutes; the temperature was then decreased to -78°C and pentamethylene sulphone (0.10 g, 0.74 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 3 h, then benzyl bromide (0.30 ml, 2.52 mmol) was added to quench the carbanion. The product was extracted into ether (3× 20 ml) and the combined organic layer was washed with brine and dried over MgSO₄. The mixture was filtered and the solvent was removed to yield the crude oil. The crude material was heated at 80°C/1 mmHg for 2 h to remove excess benzyl bromide. ¹H NMR spectrum of the crude material showed the presence of 156, 157 and unreacted 145 (ca. 76:16:10). Tlc (CHCl₃) indicated 2 products; Rₜ 0.25 and Rₜ 0.43 which were separated by flash chromatography (CHCl₃) then recrystallised from CHCl₃/hexane. (Yields given are for the purified material, fractions which contained mixtures of the two compounds were discounted). 2-Benzylpentamethylene sulphone (156) Rₜ 0.25; 44 mg, 26%; m.p. 114°C; (Found: C, 64.3; H, 7.3. C₁₂H₁₆SO₂ requires C, 64.3; H, 7.2%). The NMR spectra were assigned from a COSY and an XHCCORRD experiment. ¹H NMR (CDCl₃): δ 1.2-1.4 (1H, bm, H₄ax), 1.65-2.0 (3H, m, H₄eq H₃ax H₃eq), 2.0-2.1 (2H, m, H₅ax H₅eq), 2.66 (1H, dd, J 13.5, 11.2, PhCHH), 2.8-3.1 (2H, m, H₆ax H₂ax), 3.15 (1H, dt, J 14.0, 3.5, H₆eq), 3.53 (1H, dd, J 13.5, 3.1, PhCHH), 7.1-7.4 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 23.97 (4-CH₂), 24.34 (5-CH₂), 28.65 (3-CH₂), 30.90 (CH₂Ph), 51.97 (6-CH₂), 63.14 (2-CH), 126.93, 128.74, 129.39, 136.58 (Ph); El (160°C) 224 (M⁺, 32%), 91 (C₇H₇⁺, 100%). 2,6-Dibenzylpentamethylene sulphone (157) Rₜ 0.43;
(16 mg), m.p. 177-179°C; (Found: C, 72.5; H, 7.1. C_{19}H_{22}SO_2 requires C, 72.1; H, 7.1%); ¹H NMR (CDCl₃): δ 1.1-1.3 (1H, m, H₄ax), 1.6-2.0 (5H, m, H₄eq, H₃ax, H₃eq, H₅ax, H₅eq), 2.70 (2H, dd, J 13.5, 11.0, 2x PhCH/H), 3.00 (2H, ttt, J 11.0, 3.9, 3.9, H₂ax, H₆ax), 3.58 (2H, dd, J 13.5, 3.9, 2x PhCH/H), 7.1-7.4 (10H, m, 2x Ph); ¹³C NMR (CDCl₃): δ 24.51 (4-CH₂), 29.15 (3/5-CH₂), 31.01 (2x CH₂Ph), 63.70 (2/6-CH), 126.92, 128.73, 129.40, 136.69 (Ph); EI (70eV) 314 (M⁺, 25%), 91 (C₇H₇⁺, 100%).

Deprotonation of 145 and reaction with PhCHO
THF (6 ml) and diisopropylamine (0.50 ml, 3.57 mmol) were added via a syringe, and the flask was cooled to ca. -45°C. BuLi (1.6M in hexanes, 2.20 ml, 3.52 mmol) was added dropwise and the mixture was stirred for 30 minutes. The temperature was decreased to -78°C and 145 (0.40 g, 2.98 mmol) in THF (4 ml) was added dropwise. The mixture was stirred for 3 h, then benzaldehyde (0.60 ml, 5.90 mmol) was added and the mixture was stirred for a further 4 h at -78°C. Hydrochloric acid (3M, 20 ml) was added and the mixture was warmed to r.t. then extracted with CHCl₃ (2x 30 ml) and the combined CHCl₃ layer was washed with brine (10 ml), dried over MgSO₄, filtered and concentrated to give a white solid. This was heated at 100°C/1 mmHg for 10 minutes. to remove excess benzaldehyde. The ¹H NMR spectrum of the crude material indicated a mixture of two diastereomers 167a and 167b (ca. 3:1). The crude material was subjected to flash chromatography (CHCl₃-ethyl acetate 1:1) and the two diastereomers were separated. 167a (0.38 g, 53%); m.p. 161-162°C; R₇ 0.5; (Found: C, 59.8; H, 7.1. C_{12}H_{16}SO₃ requires C, 60.0; H, 6.7%); The NMR signals were assigned from a COSY and an XHCONRD experiment; ¹H NMR (CDCl₃): δ 1.2-1.4 (1H, m, H₄ax), 1.8-2.3 (5H, m, H₄eq, H₃ax, H₃eq, H₅ax, H₅eq), 2.9-3.0 (2H, m, H₂ax, H₆ax), 3.19 (1H, s, OH), 3.20 (1H, dt, J 14.4, 2.4, H₆eq), 5.83 (1H, s, CHO), 7.2-7.4 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 22.05 (5 -0 CH), 23.66 (4-CH₂), 24.24 (3-CH₂), 52.99 (6-CH₂), 67.06 (2-CH), 67.56 (CHOH), 125.76, 127.75, 128.45, 139.57 (Ph); EI 240 (M⁺, 15%), 107 (Ph(CH)OH⁺, 100%). 167b (63 mg, 9%); m.p. 183-187°C; R₇ 0.42, (Found: C, 60.0; H, 7.1. C_{12}H_{16}SO₃ requires C, 60.0; H, 6.7%); The NMR spectra were assigned from a COSY and a XHCONRD experiment. ¹H NMR (CDCl₃): δ 1.2-1.8 (4H, m, H₄ax, H₄eq, H₃ax, H₃eq), 2.0-2.1 (2H, m, H₅ax, H₅eq, 2.9-3.3 (3H, m, H₆ax, H₆eq, H₂ax), 3.87 (1H, s, OH), 5.20 (1H, d, J 9.1, CHO), 7.3-7.4 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 23.45 (4-CH₂), 24.04 (5-CH₂), 27.59 (3-CH₂), 52.30 (6-CH₂), 67.60 (2-CH), 72.23 (CHOH), 127.12, 128.72 x2, 138.82 (Ph); EI (70 eV) 240 (M⁺, 10%), 107 (Ph(CH)OH⁺, 100%).

Deprotonation of 145 and reaction with TMSCl in an external quench
THF (2 ml) and diisopropylamine (0.25 ml, 1.79 mmol) were added via a syringe to a flask maintained under a nitrogen atmosphere, and the mixture was cooled to ca. -45°C. BuLi (1.6M in hexanes, 1.10 ml, 1.79 mmol) was added dropwise and the mixture was stirred for
30 minutes. The temperature was decreased to -78 °C and 145 (0.20 g, 1.49 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 3 h, then a mixture of TMSCl (0.40 ml, 3.15 mmol) and TEA (0.40 ml, 2.86 mmol) in THF (2 ml) was added and the mixture was stirred for a further 3 h at -78°C. The mixture was diluted with ether (30 ml) and washed with NaHCO₃ (saturated; 20 ml) and then brine (20 ml). The solvent was dried over MgSO₄, filtered and concentrated. An orange oil was produced. The ¹H NMR of the crude material contained a mixture of 164, 165 and unreacted 145 (ca. 78:9:13). The oil was purified by flash chromatography on silica (ether-hexane 1:1) to yield 164 (0.20 g, 64 %); m.p. 46-47°C; (Found: C, 46.5; H, 9.1. C₈H₁₈SiSO₂ requires C, 46.6; H, 8.8%); ¹H NMR (CDCl₃): δ 0.25 (9H, s, (CH₃)₃), 1.36 (1H, m, H₄ax), 1.8-2.2 (5H, m, H₅ax, H₅eq, H₃ax, H₃eq), 2.42 (1H, dd, J 12.2, 3.9, H₂axCSi), 2.8-3.0 (2H, m, H₆ax), 3.02 (1H, dt, J 10.3, 3.6, H₆eq); ¹³C NMR (CDCl₃): δ -1.65 (CH₃Si), 24.52 (4-CH₂), 25.32 (5-CH₂), 26.43 (3-CH₂), 53.50 (2-CHSi), 53.84 (6-CH₂SO₂). 165 was isolated (3 mg) and its ¹H NMR spectrum was consistent with the expected structure (see following section).

This reaction was repeated but TMSCl (without TEA) was added to quench the carbanion, the reaction mixture was stirred for 3 h and then TEA was added. 164 was isolated in 66% yield after chromatography.

The order of reagents was changed; diisopropylamine (0.25 ml, 1.79 mmol) was dissolved in THF (2 ml) and cooled to -10°C. BuLi (1.6 M in hexanes, 1.10 ml, 1.79 mmol) was added and the mixture was stirred for 15 minutes and then cooled to -78°C. This was cannulated into a mixture of 145 (0.20 g, 1.49 mmol) and TMSCl (0.40 ml, 3.15 mmol) and then the mixture was left at -70°C for 10 minutes. A standard work-up (described above) was used. 164, 165 and unreacted 145 (ca. 3:3:4 in the ¹H NMR spectrum) were isolated.

**Deprotonation of 145 and reaction with TMSCl in an internal quench**

The flask was evacuated of filled with nitrogen. THF (40 ml) and diisopropylamine (0.36 ml, 2.57 mmol) were added via a syringe, and the flask was cooled to ca. -45°C. BuLi (2.56 M in hexanes, 0.90 ml, 2.30 mmol) was added dropwise and the mixture was stirred for 30 minutes. The temperature was decreased to -78°C and TMSCl (1.3 ml, 10.2 mmol) was added. Two minutes later pentamethylene sulphone (0.27 g, 2.00 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 2 h, then TEA (4.0 ml, 28.54 mmol) was added. The mixture was diluted with ether (30 ml) and washed with NaHCO₃ (saturated; 20 ml) and brine (20 ml). The solvent was dried over MgSO₄, filtered and concentrated. Evaporation left a white solid. The silylated product (165) was soluble in the ether layer, but most of the unreacted pentamethylene sulphone remained in the aqueous layer and was recovered by extraction into CHCl₃. A small amount of unreacted pentamethylene contaminated 165 so this...
the mixture was treated with hexane (5 ml) and the insoluble starting material (145) was filtered out. Evaporation of the hexane left white crystals which were identified as 2,6-dimethylsilylpentamethylene sulphone 165 (instead of the expected mono-silylated product) (95% assuming only half of the initial sulphone would have undergone reaction). Recrystallisation from hexane gave 165 (0.22 g, 80%) (assuming that only half of the sulphone present would have undergone reaction); m.p. 87-88°C; (Found: C, 47.5; H, 9.7. C_{11}H_{26}Si_{2}SO_{2} requires C, 47.4; H, 9.4%); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.23 (18H, s, 2x(CH\(_3\))\(_3\)Si), 1.2-1.4 (1H, m, H\(_{4ax}\)), 1.9-2.1 (5H, m, H\(_{3ax}\), H\(_{5ax}\), H\(_{5eq}\), H\(_{3eq}\)), 2.41 (2H, m, H\(_{2ax}\), H\(_{6ax}\)); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) -1.61 ((CH\(_3\))\(_3\)Si), 26.73, (3/5-CH\(_2\)), 26.94 (4-CH\(_2\)), 55.74 (2/6-CH).

5.3.5 DEPROTONATION OF 146 WITH LDA FOLLOWED BY REACTION OF THE CARBANION WITH AN ELECTROPHILE

Deprotonation of 146 and reaction with TMSCl in an internal quench

THF (40 ml) and diisopropylamine (0.36 ml, 2.57 mmol) were added via a syringe to a nitrogen filled flask, and the flask was cooled to ca. -45 °C. BuLi (2.56 M in hexanes, 0.85 ml, 2.20 mmol) was added dropwise and the mixture was stirred for 30 minutes. The temperature was decreased to -78 °C and TMSCl (1.3 ml, 10.2 mmol) was added. Two minutes later 146 (0.27 g, 1.99 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 2 h, then TEA (4.0 ml, 28.54 mmol) was added. The mixture was diluted with ether (30 ml) and washed with NaHCO\(_3\) (saturated solution; 20 ml) and brine (20 ml). The solvent was dried over MgSO\(_4\), filtered and concentrated. Evaporation left a white solid which was flash chromatographed (ether-hexane 3:7) to give white crystals of 183 (0.24 g, 84%; assuming that it was only possible for 50% of the sulphone to react because the disubstituted material was formed); m.p. 96°C; (Found: C, 42.6; H, 8.9. C\(_{10}\)H\(_{24}\)Si\(_2\)SO\(_3\) requires C, 42.8; H, 8.6%); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.25 (18H, s, 2x(CH\(_3\))\(_3\)Si), 2.79 (2H, dd, J 12.1, 3.7, 2x SiCH), 3.98 (2H, t, J 12.3, H\(_{3ax/5ax}\)), 4.19 (2H, dd, J 12.6, 3.5 H\(_{3ax/5ax}\)); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) -1.56 ((CH\(_3\))\(_3\)Si), 56.97 (CHSO\(_2\)), 66.60 (CH\(_2\)O).

Deprotonation of 146 and reaction with TMSCl in an external quench

Diisopropylamine (0.36 ml, 2.6 mmol) was dissolved in THF (15 ml) and cooled to -10°C. BuLi (2.56M, 0.85 ml, 2.2 mmol) was added and the mixture was stirred for 15 minutes and then cooled to -78°C. 146 (0.27 g, 1.99 mmol) in THF (20 ml) was added dropwise. Immediately a yellow gelatinous precipitate formed and the whole mixture became immobile. After 1 minute, TMSCl (0.25 ml) was added and the mixture was left at -70°C for 10 minutes. TEA (4.0 ml, 28.54 mmol) was added and the mixture was diluted with ether (30 ml) and washed with NaHCO\(_3\) (saturated soln.; 20 ml) then brine (20 ml). The solvent was
dried over MgSO$_4$, filtered and concentrated to give a yellow oil. The product was not identified.

When benzyl bromide or MeI were used in place of TMSCl, about 50% of 146 did not react, and the other products were not identified; the $^1$H NMR spectrum was unstructured.

The order of addition of the reagents was changed; diisopropylamine (0.36 ml, 2.6 mmol) was dissolved in THF (15 ml) and cooled to -10°C. BuLi (2.56M, 0.85 ml, 2.2 mmol) was added and the mixture was stirred for 15 minutes and then cooled to -78°C. 146 (0.27 g, 1.99 mmol) and TMSCl (0.25 ml) in THF (10 ml) was added dropwise and the mixture was left at -70°C for 10 minutes. A standard work-up (described above) was used to give 183 in 68% yield. No 3-trimethylsilyl-4-thiopyran-4,4-dioxide was isolated.

The order of addition of the reagents was changed. Diisopropylamine (0.36 ml, 2.6 mmol) was dissolved in THF (15 ml) and cooled to -10°C. BuLi (2.56M, 0.85 ml, 2.2 mmol) was added and the mixture was stirred for 15 minutes and then cooled to -78°C. This was cannulated into a mixture of 146 (0.27 g, 2.0 mmol) and TMSCl (0.25 ml) in THF (10 ml) and then the mixture was left at -70°C for 10 minutes. A standard work-up (described above) was used to give mainly 183 with ca. 10% of 3-trimethylsilyl-4-thiopyran-4,4-dioxide.

The order of addition of the reagents was changed. Diisopropylamine (0.36 ml, 2.6 mmol) was dissolved in THF (15 ml) and cooled to -10°C. BuLi (2.56M, 0.85 ml, 2.2 mmol) was added and the mixture was stirred for 15 minutes and cooled to -78°C then TMSCl (0.25 ml) was added. This mixture was cannulated into 146 (0.27 g, 2.0 mmol) in THF (10 ml) and then the mixture was left at -70°C for 10 minutes. A standard work-up (described above) was used to give mainly 183 with ca. 10% of 3-trimethylsilyl-4-thiopyran-4,4-dioxide.

5.3.6 DEPROTONATION OF 143 WITH LDA FOLLOWED BY REACTION OF THE CARBANION WITH AN ELECTROPHILE

Deprotonation of 143 and reaction with MeI

The flask was evacuated and filled with nitrogen. BuLi (1.6M, 0.35 ml, 0.56 mmol) was added to a solution of diisopropylamine (0.08 ml, 0.57 mmol) in THF (5 ml) at -10°C. This was stirred for 10 minutes and then the temperature was decreased to -78°C. 143 (0.10 g, 0.53 mmol) in THF (5 ml) was added via a cannula and the mixture was stirred for 15 minutes. MeI (0.10 ml, 1.60 mmol) was added and the mixture was stirred for 1 h. HCl (3M, 5 ml) was added and the product was extracted into ether (3x 10 ml). The combined ether
layers were washed with brine (10 ml), dried over MgSO₄ and filtered. Removal of the solvent left a crude oil; ¹H NMR analysis indicated it contained 144, 168, 169 and unreacted 143 (ca. 72:5:3:20). Flash chromatography (ether-hexane 1:1) and subsequent recrystallisation from hexane gave 144 (54 mg, 51%) m.p. 74-75°C; (Found: C, 58.7; H, 9.9. C₁₉H₂₀SO₂ requires C, 58.8; H, 9.9%); ¹H NMR (CDCl₃): δ 0.92 (9H, s, (CH₃)₃), 1.2-1.4 (1H, tt, J ~13, ~3, H₄₅), 1.34 (3H, d, J 6.7, CH₃), 1.55-1.70 (1H, distorted q, J ~13, H₃₅), 1.75-1.95 (1H, distorted qd, J ~13, ~3, H₅₆), 1.95-2.05 (1H, distorted dq, J ~13, ~3, H₃₆), 2.05-2.20 (1H, m, H₅₆), 2.83-3.00 (2H, m, H₆₇, H₄₆); ¹³C NMR (CDCl₃): δ 10.91 (CH₃ CH), 25.45 (C₁₉ CH), 32.48 (C), 33.64 (3-CH₂), 46.71 (4-CH), 51.18 (6-CH₂), 56.22 (2-CH).

Deprotonation of 143 with 2 equivalents of LDA and reaction with Mel

The identity of 168 was confirmed by addition of 143 (0.10 g, 0.52 mmol) in THF (5 ml) to a solution of LDA (1.12 mmol) using the procedure described above. Mel (0.2 ml, 3.2 mmol) was added to quench the carbanion and a standard workup was used. A mixture of 168 and 169 were isolated (ca. 3:2). Flash chromatography (ether-hexane 1:1) and recrystallisation from hexane gave 168 (54 mg, 45%); m.p. 141°C (sublimes from about 80°C onwards); (Found: C, 60.5; H, 10.1 C₁₉H₂₂SO₂ requires C, 60.5; H, 10.2% NMR (CDCl₃): δ 0.91 (9H, s, (CH₃)₃), 1.3-1.4 (1H, m, H₄₅), 1.37 (6H, d, J 6.8, CH₃), 1.55-1.7 (2H, distorted q, J ~12, H₃₅₆), 1.93-2.03 (2H, m, H₅₆₇), 2.85-2.95 (2H, m H₆₇₈); ¹³C NMR (CDCl₃): δ 11.06 (CH₃ CH), 27.53 ((CH₃)C), 32.54 (C), 33.90 (3/5-CH₂), 46.76 (4-CH), 56.12 (2/6-CH). The fractions from the column containing 169 as the major compound were evaporated and recrystallised to give 169 contaminated with about 20% of 168. This was not purified further. 169 (ca. 20% yield); ¹H NMR (CDCl₃): δ 0.90 (9H, s, (CH₃)₃), 1.33 (3H, d, J 6.8, CH₃), 1.46 (3H, d, J 7.4, CH₃), 1.3-1.4 (1H, m, H₃), 1.85-2.20 (4H, m, 2xH₃, 2xH₅), 3.0-3.2 (2H, m, H₂, H₃); ¹³C NMR (CDCl₃): δ 10.88 (CH₃ CH), 14.29 (CH₃ CH), 27.49 ((CH₃)C), 31.32 (CH₂), 32.52 (C), 33.85 (CH₂), 40.04 (CH), 50.83 (CH), 54.68 (CH).

Deprotonation of 143 and reaction with benzyl bromide

The flask was evacuated and filled with nitrogen. THF (10 ml) and diisopropylamine (0.30 ml, 2.14 mmol) were added via a syringe, and the flask was cooled to ca. -45°C. BuLi (1.58 M in hexanes, 1.00 ml, 1.58 mmol) was added dropwise and the mixture was stirred for 30 minutes. The temperature was decreased to -78°C and 4-2-butyldipentamethylene sulphone (0.30 g, 1.58 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 20 minutes then benzyl bromide (0.37 ml, 3.11 mmol) was added and the mixture was stirred for a further 1 h at -78°C. Hydrochloric acid (3M, 20 ml) was added and the mixture was warmed to r.t. then extracted into ether (30 ml). The ether layer was washed with brine (10 ml), dried over MgSO₄, filtered and evaporated. Excess benzyl bromide was removed under
vacuum overnight. $^1$H NMR of the crude material indicated a mixture of 170, 171, 172 and unreacted 143 (ca. 60:10:7:24). The crude material was subjected to flash chromatography (CHCl$_3$-ether 1:1). 170 was isolated as a white solid (0.16g, 41%) which was recrystallised from ether/ hexane to give needles; m.p. 122°C (15%); (Found: C, 68.4; H, 8.8. C$_{16}$H$_{24}$SO$_2$ requires C, 68.5; H, 8.6%); $^1$H NMR (CDCl$_3$): $\delta$ 0.82 (9H, s, (CH$_3$)$_3$C), 1.15 (1H, tt, J $\sim$9, $\sim$2, H$_{4a}$), 1.45-1.65 (1H, distorted q, J $\sim$12, H$_{3a}$), 1.80-2.05 (2H, m, H$_{3eq}$, H$_{5a}$), 2.05-2.20 (1H, m, H$_{5eq}$), 2.62 (1H, dd, J 13.6, 10.8, PhCH/H), 2.8-3.1 (2H, m, H$_{6a}$, H$_{2a}$), 3.16 (1H, dt, J $\sim$14, $\sim$3, H$_{6a}$), 3.52 (1H, dd, J 13.7, 3.1, PhCH/H), 7.1-7.4 (5H, m, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 25.37 (5-CH$_2$), 27.37 (C(CH$_3$)$_3$), 30.19 (3-CH$_2$), 30.90 (PhCH$_2$), 32.61 (C), 46.48 (4-CH), 51.58 (6-CH$_2$), 62.69 (2-CH), 126.65, 128.65, 129.22, 136.54 (Ph)

**Deprotonation of 143 with 2 equivalents of LDA and reaction with benzyl bromide**

The identity of 171 and 172 were confirmed by deprotonation of 143 (0.10 g, 0.52 mmol) with two equivalents of LDA using the method described above for the synthesis of 168 and 169; except benzyl bromide was added to quench the carbanion. A crude white solid was isolated and the $^1$H NMR spectrum indicated it contained 171 and 172 (ca. 3:2). These were partially separated by flash chromatography (CHCl$_3$) and material containing one major product was recrystallised. 171 was isolated as white needle shaped crystals after recrystallisation from ethanol (29%), m.p. 194°C; (Found: C, 74.2; H, 8.2. C$_{23}$H$_{30}$SO$_2$ requires C, 74.5; H, 8.2%); NMR (CDCl$_3$): $\delta$ 0.72 (9H, s, (CH$_3$)$_3$C), 1.00-1.13 (1H, tt, J $\sim$12, $\sim$3, H$_{4a}$), 1.45-1.65 (2H, distorted q, J $\sim$12, H$_{3a}$/5a), 1.90-2.00 (2H, d, J 11.8, H$_{3eq}$/5eq), 2.68 (2H, dd, J 13.6, 10.6, 2xPhCH/H), 2.95-3.05 (2H, m, H$_{2a}$/6a), 3.57 (2H, dd, J 13.6, 3.1, 2xPhCH/H), 7.1-7.4 (10H, m, 2x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 27.30 (C(CH$_3$)$_3$), 30.28 (3/5-CH$_2$), 30.10 (PhCH$_2$), 32.61 (C), 46.48 (4-CH), 62.46 (2/6-CH), 126.88, 128.67, 129.25, 136.81 (Ph). 172 was isolated as a white solid after recrystallisation from ethanol (15%) m.p. 223°C; $^1$H NMR (CDCl$_3$): $\delta$ 0.74 (9H, s, (CH$_3$)$_3$C), 1.2-2.2 (5H, m), 2.69 (1H, dd, J 13.5, 10.8), 2.85 (1H, t, 13.5), 3.12 (1H, m), 3.25 (1H, m), 3.45-3.55 (2H, m), 7.1-7.4 (10H, 2xPh) $^{13}$C NMR (CDCl$_3$): $\delta$ 26.49 (CH$_2$), 27.33 (C(CH$_3$)$_3$), 30.25 (CH$_2$), 30.35 (CH$_2$), 31.00 (CH$_2$), 32.61 (C), 33.28 (CH$_2$), 39.60 (CH), 58.24 (CH), 61.44 (CH), 126.97, 127.12, 128.75, 128.88, 129.04, 129.27, 136.75, 136.87 (2x Ph).

**Deprotonation of 143 and reaction with TMSCl (internal quench)**

The flask was evacuated and filled with nitrogen. THF (15 ml) and diisopropylamine (0.36 ml, 2.60 mmol) were added via a syringe, and the flask was cooled to ca. -10°C. BuLi (1.58 M in hexanes, 0.90 ml, 1.42 mmol) was added dropwise and the mixture was stirred for 15 minutes. The temperature was decreased to -78°C and TMSCl (1.3 ml) was added followed by 4-t-butylpentamethylene sulphone (0.135 g, 0.71 mmol) in THF (10 ml) two minutes later. The mixture was stirred for 10 minutes, then TEA (4.0 ml, 28.54 mmol) and NaHCO$_3$ (sat.;
10 ml) was added and the mixture was diluted with ether (30 ml) and washed with NaHCO₃ (sat. 20 ml) and then brine (20 ml). The solvent was dried over MgSO₄, filtered and removed in vacuo. A mixture of diastereomers 173 and 174 were isolated in the ratio ca. 7:1. The material was flash chromatographed (ether-hexane 3:7) to give a white solid 173 (0.18 g, 77%), m.p. 151-151.5°C (sublimes from 110°C onwards and dissappears on melting); (Found: C, 53.6; H, 10.6. C₁₅H₃₄Si₂SO₂ requires C, 53.8; H, 10.2%); ¹H NMR (CDCl₃): δ 0.24 (18H, s, 2x(CH₃)₃Si), 0.93 (9H, s, (CH₃)₃C), 1.07-1.20 (1H, tt, J ~12, ~3, H₄a), 1.70-1.90 (2H, distorted q, J ~13, H₃a/5a), 2.00-2.10 (2H, d, J ~13, H₃e/5e), 2.35-2.45 (2H, distorted dd, J ~13, ~2, H₂a/6a); ¹³C NMR (CDCl₃): δ -1.62 ((CH₃)₃Si), 27.55 ((CH₃)₂C), 27.61 (3/5-CH₂), 32.80 (C), 49.01 (4-CH), 55.24 (2/6-CH₂). 174 was not isolated in its pure form. Its ¹³C NMR was assigned after removal of the signals due to 173; ¹³C NMR (CDCl₃): δ -1.8 ((CH₃)₃Si), -0.9 ((CH₃)₂Si), 26.3 (CH₂), 27.3 ((CH₃)₂C), 27.6 (CH₂), 32.2 (C), 44.3 (CH), 52.0 (CH), 52.9 (CH).

Deprotoonation of 143 and reaction with TMSCl (external quench)
The flask was evacuated and filled with nitrogen. THF (15 ml) and diisopropylamine (0.36 ml, 2.60 mmol) were added via a syringe, and the flask was cooled to ca. -45°C. BuLi (2.56 M in hexanes, 0.90 ml, 2.40 mmol) was added dropwise and the mixture was stirred for 20 minutes. The temperature was decreased to -78°C and 4-/ butylpentamethylene sulphone (0.35 g, 2.00 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 5 minutes, then TMSCl (0.50 ml, 3.94 mmol) was added. After 30 minutes TEA (4.0 ml, 28.54 mmol) was added and the mixture was diluted with ether (30 ml) and washed with NaHCO₃ (sat.; 20 ml) then brine (20 ml). The solvent was dried over MgSO₄, filtered and removed in vacuo. A white solid was isolated. ¹H NMR indicated a mixture of 175 and 176 (75% in total), 173 (about 7%) and unreacted 143 (15%). Flash chromatography (ether-hexane 1:1) gave an oil which slowly solidified (0.21 g, 45 %); the ¹H NMR spectrum indicated a mixture of 175 : 176 (7:1) Repeated recrystallisation from hexanes gave 175 (21%) m.p. 72-73°C (Found: C, 52.7; H, 10.6. C₁₁H₂₆SiSO₂ requires C, 52.6; H, 10.5%); ¹H NMR (CDCl₃): δ 0.26 (9H, s, (CH₃)₃Si), 0.92 (9H, s, (CH₃)₂C), 1.18 (1H, tt, J 12.0, 2.8, H₄a), 1.70-1.85 (1H, distorted q, J ~13.5 H₃a), 1.85-2.00 (1H, m, H₄a), 2.00-2.20 (2H, m, H₃e/5e), 2.40 (1H, dd, J 13.2, 2.7, H₂a), 2.90 (1H, ddd, J 13.7, 13.5, 3.5 H₆a), 3.05 (1H, dt, J 13.8, 3.7, H₆a); ¹³C NMR (CDCl₃): δ -1.68 ((CH₃)₃Si), 25.57 (3-CH₂), 27.39 (5-CH₂), 27.50 ((CH₃)₂C), 32.65 (C), 47.61 (4-CH), 52.65 (2-CH), 53.67 (6-CH₂). (The analytical data for 176 is provided in the next section).
5.3.7 DEPROTONATION OF THE SUBSTITUTED SULPHONES WITH BuLi AND QUENCHING WITH WATER (INVERSION OR RETENTION OF CONFIGURATION)

Deprotonation of 175/176 (2:1) followed by reaction with water to give 176
A mixture of 175 and 176 (2:1) (0.21 g, 0.82 mmol) was placed in a flask which was the evacuated and filled with nitrogen. The flask was cooled to -78°C and BuLi (1.23 ml, 2.04 mmol, 2.5 eq.) was added. The mixture was allowed to warm up to r.t over 10 minutes. Water (10 ml) was added to quench the reaction and the material was extracted into ether (3x 10 ml). The combined organic layer was washed with brine (5 ml) and dried over MgSO4, filtered and evaporated to give white crystals of 176 (0.20 g, 95 %) (no 175 was isolated) Recrystallisation from hexane gave 176 as white needle shaped crystals (78%); (m.p. 92-93°C; sublimes before melting into small droplets which crystallise again) (Found: C, 52.7; H, 10.7. C11H26SiS02 requires C, 52.6; H, 10.5%); 1H NMR (CDCl3): δ 0.28 (9H, s, (CH3)3Si), 0.92 (9H, s, (CH3)3C), 1.27 (1H, tt, J 12, ~3.5, H4a), 1.80-1.97 (1H, distorted dq J 12, ~4, H5a), 1.95-2.2 (3H, m, H3a, H3e, H5e), 2.61 (1H, dd, J 7.7, 4.2, H2e), 2.85-3.10 (2H, m, H6a, H6e); 13C NMR (CDCl3): δ -0.67 ((CH3)3Si), 25.10 (3-CH2), 27.25 (5-CH2), 27.42 ((CH3)3C), 32.87 (C), 43.38 (4-CH), 51.32 (2-CH), 52.33 (6-CH2).

This procedure was repeated but the reaction was maintained at -78°C; water was added to the flask and then the mixture was warmed up to r.t. Complete conversion of 175 to 176 was seen. In another experiment, the same method was followed but with LDA instead of BuLi. Again complete conversion of 175 into 176 was observed.

Deprotonation of 144 followed by reaction with water.
Compound 144 (0.10 g, 0.48 mmol) was dissolved in THF (2 ml) and cooled to -78°C. BuLi (1.58M, 1.58 ml, 1.00 mmol) was added and the mixture was stirred for ten minutes. Water was added to quench the reaction and the product was extracted into ether using the work-up procedure described above. The 1H NMR spectrum of the isolated material indicated that only 144 (85 mg) was present.

Deprotonation of 170 followed by reaction with water.
Compound 170 (0.10 g, 0.36 mmol) was dissolved in THF (2 ml) and cooled to -78°C. BuLi (1.58M, 0.55 ml, 0.87 mmol) was added and the mixture was stirred for ten minutes. Water was added to quench the reaction and the product was extracted into ether using the work-up procedure described above. The 1H NMR spectrum of the isolated material indicated that only 170 (72 mg) was present.
Deprotonation of 168 followed by reaction with water to give 169.
Compound 168 (0.10 g, 0.46 mmol) was dissolved in THF (2 ml) and cooled to -78°C. BuLi (1.58M, 0.6 ml, 0.95 mmol) was added and the mixture was stirred for ten minutes. Water was added to quench the reaction and the product was extracted into ether using the work-up procedure described above. The $^1$H NMR spectrum of the isolated material indicated that 90% of 168 had been converted into 169 (87 mg); (See section 5.3.6.2. for analytical data on this compound).

Deprotonation of 171 followed by reaction with water to give 172.
Compound 171 (0.10 g, 0.36 mmol) was dissolved in THF (2 ml) and cooled to -78°C. BuLi (1.58M, 0.5 ml, 0.79 mmol) was added and the mixture was stirred for ten minutes. Water was added to quench the reaction and the product was extracted into ether using the work-up procedure described above. The $^1$H NMR spectrum of the isolated material indicated that 100% of 171 had been converted into 172 (80 mg); (See section 5.3.6.4. for analytical data on this compound).

5.3.8 PREPARATION OF CHIRAL LITHIUM AMIDE BASES (GENERAL METHOD)
Amine (0.58 mmol) was placed in a dry flask which was evacuated and filled with nitrogen. THF (5 ml) was added and the solution was cooled to 0°C. When amines 110a, 112a, 119a or 119b were used, BuLi (1.56 M, 0.35 ml, 0.55 mmol) was added and the mixture was stirred for 15 minutes at 0°C. When amines 187, 189, 126a or 126b were used, BuLi (1.56, 0.65 ml, 1.04 mmol) was added and the mixture was stirred at 0°C for 15 minutes.

5.3.9 DEPROTONATION OF 4-T-BUTYL-PENTAMETHYLENE SULPHONE USING A CHIRAL LITHIUM AMIDE BASE AND REACTION OF THE CARBANION WITH MeI

Without LiCl
The chiral lithium amide bases used and the reaction times are listed in Table 3.4. A solution of the chiral lithium amide base (0.55 mmol) in THF was prepared as described in Section 5.3.8. and cooled to -78°C. A solution of 4-t-butylpentamethylene sulphone (0.10g, 0.52 mmol) in THF (5 ml) was added dropwise, via a cannula. The mixture was stirred for time $t_1$, then MeI (0.1 ml, 1.6 mmol) was added and the reaction mixture was stirred for a further time $t_2$. 3M HCl was added and the material was extracted into ether (1x 10 ml) then CHCl$_3$ (2x 10 ml). Each organic layer was washed with 3M HCl (10ml) and brine (10 ml), dried over MgSO$_4$ and filtered. Evaporation of the combined layers gave the crude material. Amines 110a, 112a, 187 and 189 were removed in the work-up but the hydrochloride salts of amines
119a, 119b, 126a and 126b were extracted into the organic layer and had to be removed by flash chromatography. The ratio of products 144, 168 and 169 in the crude material was calculated from the $^1$H NMR spectrum and is given in Table 3.4 for each reaction. The crude products were chromatographed (ether-hexane 1:1) to give mainly 144, but a small amount of other components did not affect the studies with chiral lanthanide chiral shift reagents.

With LiCl
The general procedure described above was used but LiCl (0.01 g, 0.24 mmol) was added to neat amine before addition of THF.

Effect of temperature, solvents and additives
The general procedure described above was used. Modifications to the procedure, and the results obtained are detailed in Table 3.6.

5.3.10 DEPROTONATION OF 4-T-BUTYL-PENTAMETHYLENE SULPHONE USING A CHIRAL LITHIUM AMIDE BASE AND REACTION OF THE CARBANION WITH TMSCL

Without LiCl
The chiral lithium amide bases used and the reaction times are listed in Table 3.5. A solution of the chiral lithium amide base in THF was prepared as described in Section 5.3.8. and cooled to -78°C. A solution of 4-t-butylpentamethylene sulphone (0.10g, 0.52 mmol) in THF (5 ml) was added dropwise, via a cannula. The mixture was stirred for time $t_1$, then TMSCl (0.15 ml, 1.18 mmol) was added and the reaction mixture was stirred for a further time $t_2$. TEA (2 ml) and NaHCO$_3$ (10 ml) were added and the material was extracted into ether (3x 10 ml). The combined organic layer was washed with NaHCO$_3$ (10ml) and brine (10 ml), dried over MgSO$_4$ and filtered. Evaporation of the combined layers gave the crude product. The crude products were purified by flash chromatography to give a mixture of 175 and 176.

With LiCl
The general procedure described above was used but LiCl (0.01 g, 0.24 mmol) was added to neat amine before addition of THF.
5.3.11 DETERMINATION OF ENANTIOMERIC EXCESSES USING CHIRAL LANTHANIDE SHIFT REAGENTS

The chiral lanthanide shift reagent was dried in vacuo overnight and placed under nitrogen. CDCl₃ was dried over molecular sieves before use. The material under investigation (144 or 175/176) (ca. 20 mg) was dissolved in CDCl₃ and portions of CLSR (ca. 10 mg) were added until the enantiomeric signals were separated. The ratio of the integrals was taken as a measure of the enantiomeric excess.

5.4 EXPERIMENTAL DETAILS FOR THE WORK DESCRIBED IN CHAPTER 4

5.4.1 ATTEMPTED ADDITION OF CHIRAL LITHIUM AMIDES TO α,β-UNSATURATED SUBSTRATES (GENERAL METHOD)

All the glassware was oven-dried. Round bottom flasks were fitted with rubber septa and were evacuated then filled with nitrogen gas from a balloon; this procedure was repeated three times to ensure complete removal of oxygen. Solvents and reagents were added via syringes.

Preparation of chiral lithium amide 17a

(+)-(R)-Bis[(R)-1-phenylethyl]amine [R,R] (112a) (0.45g, 2.00 mmol) was dissolved in THF (5 ml) at 0°C and BuLi (1.52M, 0.76 ml, 2.00 mmol) was added. The resultant red solution was stirred for 15 minutes at 0°C.

Preparation of chiral lithium amide 30a

(R)-N-(1-phenylethyl)benzylamine (110a) (0.42g, 2.00 mmol) was dissolved in THF (5 ml) at 0°C and BuLi (1.52M, 0.76 ml, 2.00 mmol) was added. The resultant pink solution was stirred for 15 minutes.

General procedure for attempted Michael addition reaction (see Table 4.1)

The chiral lithium lithium amide solution was prepared as described above and was cooled to -78°C or 0°C (temperature given in Table 4.1) and the α,β-unsaturated substrate (1.50 mmol) in THF (5 ml) was added. After 15 minutes H₂O or D₂O (1 ml) was added and the mixture was warmed up to r.t.. The material was extracted into ether (2x 10 ml) and the combined organic layer was washed with brine (10 ml), dried over MgSO₄, filtered and concentrated in vacuo. The material was analysed by ¹H NMR spectroscopy.
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With cinnamaldehyde (193)
Chiral lithium amide 17a (2.00 mmol) in THF (5 ml) (preparation described above) was cooled to -78°C and cinnamaldehyde (193) (0.20 g, 1.52 mmol) in THF (5 ml) was added via a cannula; immediately the pink colour of the solution was lost but this reappeared after a few minutes. The reaction was quenched with water at -78°C and the work-up procedure described above was followed. The starting materials (193 and 112a) were recovered (0.61 g in total) (there was no indication of any other compounds in the 1H NMR spectrum). This reaction was repeated at 0°C; again no compounds other than than 193 and 122a were formed.

With crotonaldehyde (194)
Chiral lithium amide 17a (2.00 mmol) in THF (5 ml) (preparation described above) was cooled to -78°C and crotonaldehyde (194) (0.10 g, 1.50 mmol) in THF (5 ml) was added via a cannula; immediately the pink colour of the solution was lost but this reappeared after a few minutes. The reaction was quenched with water at -78°C and the work-up procedure described above was followed. The original amine (112a) was recovered (0.40 g), but 194 was volatile and was lost during work-up; there was no indication of any other products in the 1H NMR spectrum of the crude material. The same result was obtained when the reaction was carried out at 0°C.

With 3-methylcyclohex-2-enone (195)
Chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was cooled to -78°C and 3-methylcyclohex-2-enone (195) (0.17 g, 1.87 mmol) in THF (5 ml) was added via a cannula; immediately the solution turned yellow. The reaction was quenched with D2O at -78°C and the work-up procedure described above was followed. The 1H NMR spectrum of the crude material showed the original amine (110a) and 3-methylcyclohex-2-enone (0.55 g in total); the 2H NMR spectrum had a broad peak at 2.4 ppm corresponding to deuterium incorporation at the 6-position (205).

With 4-phenylbut-3-en-2-one (196)
Chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was cooled to -78°C and 4-phenylbut-3-en-2-one (196) (0.22 g, 1.50 mmol) in THF (5 ml) was added via a cannula; immediately the solution turned yellow. The reaction was quenched with D2O at -78°C and the work-up procedure described above was followed. The 1H NMR spectrum of the crude material showed the original amine (110a) and 4-phenylbut-3-ene-2-one (196) (0.59 g in total); the 2H NMR spectrum had a broad peak at 2.4 ppm corresponding to deuterium incorporation into at the 1-position of 196 to give (204).
With 197
Chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was treated with (197) (0.28 g, 1.50 mmol) in THF (5 ml), both at -78°C and at 0°C; there was no colour change. The reaction was quenched with water after 15 minutes and the work-up procedure described above was followed. The $^1$H NMR spectrum of the crude material showed the original amine (110a) and 197 (0.66 g in total); there was no evidence of any other components.

With 198
Chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was treated with (198) (0.19 g, 1.50 mmol) in THF (5 ml), both at -78°C; the solution immediately turned bright red. The reaction was quenched with water after 15 minutes and the work-up procedure described above was followed. The $^1$H NMR spectrum of the crude material showed the original amine (110a) and 198 (0.56 g in total); there was no evidence of any other components.

With nitrostyrene (199)
When chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was treated with (199) (0.22 g, 1.50 mmol) in THF (5 ml) at -78°C the solution immediately turned black. The reaction was quenched with water after 15 minutes and the material was extracted into ether as described above. The $^1$H NMR spectrum of the crude material showed the original amine (110a) only (0.18 g); no unreacted 199 or any other compound was recovered. No compounds were isolated when the aqueous layer from the above work-up was re-extracted into CHCl$_3$ (3 x 20 ml) and the combined organic layers were washed with brine (10 ml); dried over MgSO$_4$, filtered and removed in vacuo.

With diethyl maleate (200)
When chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was treated with (200) (0.22 g, 1.50 mmol) in THF (5 ml) at -78°C the solution immediately turned black. The reaction was quenched with water after 30 minutes and the material was extracted into ether as described above. The $^1$H NMR spectrum of the black oil showed the original amine (110a) only (0.20 g); no unreacted 200 or any other compound was isolated.

With N-phenylmaleimide (202)
When chiral lithium amide 30a (2.00 mmol) in THF (5 ml) (preparation described above) was treated with (202) (0.26 g, 1.50 mmol) in THF (5 ml) at -78°C the solution immediately turned dark green and the reaction was quenched with water after 30 minutes. A purple solid precipitated out. On addition of ether (10 ml) this solid moved to the interface. The solid
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(0.18 g) was removed by filtration through a sintered glass filter and the ether layer was washed with brine (10ml), dried over MgSO4 and filtered. Evaporation of the solvent left 110a (0.40 g). The 1H NMR spectrum of the solid (d6-acetone) was unstructured.

5.4.2 Michael addition of 30a to 201

As normal, this reaction was carried out under nitrogen. Amine 110a (0.21 g, 1.00 mmol) was dissolved in THF (2 ml) and BuLi (1.53M, 0.65 ml, 1.00 mmol) was added to generate 30a. This was stirred for 15 minutes in an ice bath then the red solution was cooled to -78°C and methyl cinnamate (0.08 g, 0.50 mmol) in THF (2 ml) was added dropwise; immediately the solution went yellow. Over 15 minutes the solution turned orange and the reaction was quenched with saturated NH4Cl solution (2 ml). The mixture was diluted with brine and extracted into ether (3x 10 ml). The combined organic layers were washed with brine (5 ml), dried over MgSO4, filtered and concentrated. The 1H NMR spectrum of the crude material indicated a mixture of two diastereomers 206a and 206b were present (16:1). Flash chromatography on silica (CHCl3-hexane 4:1) gave an orange oil, 206a, 96% d.e. (0.125 g, 65%); (Found C, 80.3; H, 7.3; N, 3.8. C25H27NO2 requires C, 80.4; H, 2.3; N, 3.8%); ν max/cm-1 (nujol) 1737 (C=O); 1H NMR (CDCl3): δ 1.21 (3H, d, J 6.9, CH3), 2.56 (1H, dd, J 9.2, 14.9, CHHCO2), 2.68 (1H, dd, J 5.8, 14.9, CHHCO2), 3.45 (3H, s, CH3CH), 3.66 (1H, d, J 14.8, CHPhH), 3.75 (1H, d, J 14.8, CHHPh), 4.00 (1H, q, J 6.9, CH3CH), 4.43 (1H, dd, J 5.8, 9.1, CH2CHN), 7.1-7.4 (15H, m, 3xPh); 13C NMR (CDCl3): δ 15.74 (CH3), 37.47 (CH2CO2), 50.70 (CH2Ph), 51.42 (CH3O), 56.64 (CH3CH), 59.22 (CH2CHN), 126.60, 126.81, 127.22, 127.62, 127.99, 128.09, 128.13, 128.27, 141.33, 141.70, 145.00 (3x Ph), 172.17 (C=O).

5.4.3 Michael addition of 30a to 201 and subsequent reaction with MeI

Amine 110a (0.21 g, 1.00 mmol) was dissolved in THF (2 ml) and BuLi (1.53M, 0.65 ml, 1.00 mmol) was added. The mixture was stirred for 15 minutes in an ice bath then the red solution was cooled to -78°C and methyl cinnamate (0.08 g, 0.50 mmol) in THF (2 ml) was added dropwise. After 15 minutes the intermediate enolate was quenched with MeI (0.20 ml, 3.20 mmol); stirring was continued for a further 15 minutes and then the reaction was quenched with sat. NH4Cl solution. The work up procedure described in Section 5.4.2 was used. A mixture of 206 (15%), and 209 85% was obtained. 209 consisted as a mixture of 3 diastereomers (ca. 25:2:1). Compound 209a was purified by flash chromatography (CHCl3-hexane 4:1) (62%); ν max/cm-1 1725 (C=O); 1H NMR (CDCl3): δ 0.74 (3H, d, J 6.8, CH3CHCO), 0.92 (3H, d, J 6.8, CH3CHN), 3.25 (1H, m, CH3CHCO), 3.55 (3H, s, CH3O), 3.61 (1H, d, J 13.8, CHHPh), 3.96 (1H, d, J 13.8, CHHPh), 4.15 (2H, m, CH2CHN and
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CH₃CHN) 7.1-7.5 (15H, m, 3x Ph); ¹³C NMR (CDCl₃): δ 13.96 (CH₃CHCO), 15.79 (CH₃CHN), 42.99 (CHCO), 50.67 (CH₂), 51.38 (PhCHCH₃), 55.46 (PhCHCH), 64.47 (CH₂O), 126.44, 126.79, 127.35, 127.72, 128.05, 128.09, 128.13, 128.30, 129.01, 129.17, 138.86, 140.02, 144.10 (3x Ph), 175.62 (C=O).

5.4.4 Attempted Intramolecular Electrophilic Quench

Preparation of (2-iodoethyl)cinnamate (210)

Cinnamoyl chloride (12.8 mmol) was prepared as described in section 5.4.5. Ether (50 ml) and TEA (5 ml) were added followed by (2-iodoethyl)cinnamate (1.00 ml, 12.8 mmol). The mixture was stirred for 3 h at r.t. then extracted into ether (2x 10 ml), washed with sat. NaHCO₃ solution (10 ml), dried over MgSO₄, filtered and evaporated. The crude material was subjected to flash chromatography on silica (ether-hexane 1:4). A waxy yellow solid (2-iodoethyl)cinnamate (3.15 g, 81%), m.p. 45°C; (Found: C, 44.0; H, 3.6. C₁₁H₁₇O₂I requires C, 43.7; H, 3.8%); ν<sub>max</sub>/cm⁻¹ 1724 (C=O); ¹H NMR (CDCl₃): 3.36 (2H, t, J 6.8, CF₃I), 4.46 (2H, t, J 6.8, CH₂O), 6.44 (1H, d, J 14.8, PhCH=CH₂), 7.2-7.5 (5H, m, Ph), 7.75 (1H, d, J 14.8, PhCH=CH₂).

Reaction of (2-iodoethyl)cinnamate (210) with 30a

210 (0.20 g, 0.66 mmol) was dissolved in THF (5 ml) and cooled to -78°C. Amine 110a (0.15 g, 0.70 mmol) was dissolved in THF (5 ml) at 0°C and BuLi (1.53M, 0.46 ml, 0.70 mmol) was added to generate 30a. This solution of 30a was added to the ester solution. The mixture was stirred for 15 minutes. The work-up procedure described in section 5.4.2 was followed. The ¹H spectrum of the crude product mixture showed three compounds: 212, 213 and 214 had been formed (2:2:1) along with unreacted 210. These components were separated by flash chromatography (ether-hexane 3:7) and approximately 50% of the original (2-iodoethyl)cinnamate (210) was recovered. 212 (10 mg) (R<sub>f</sub> 0.6); ν<sub>max</sub>/cm⁻¹ 1732 (C=O); ¹H NMR (CDCl₃): δ 1.23 (3H, d, J 7, CH₃), 2.65 (2H, m, CH₂CO), 2.98 (2H, t, J 7, CH₂I), 3.68 (1H, d, J 14, PhCH/H), 3.75 (1H, d, J 14, PhCH/H), 4.00 (1H, q, J 7, CH₃CH), 4.10 (2H, t, J 7, CH₂O), 4.47 (1H, m, CHCH₂), 7.1-7.5 (15H, 3x Ph); ¹³C NMR (CDCl₃): δ -0.006 (CH₂I), 15.96 (CH₃), 37.31 (CH₂CO), 50.73 (CH₂Ph), 56.70 (CH₃CH), 59.27 (PhCHCH₂), 64.39 (CH₂O), 126-144 [aromatic region; signals overlapping], 171.07 (C=O). 213 (5 mg, but contaminated with traces of 212) (R<sub>f</sub> 0.3) ¹H NMR (CDCl₃): δ 4.46 (1H, dd, J 6, 1, CHH=), 5.00 (1H, dd, J 14, 1 CHH=), 6.48 (1H, d, J 16, =CHCO), 7.30 (1H, dd, J 14, 6, OCH=), 7.1-7.6 (5H, m, Ph), 7.75 (1H, d, J 16, PhCH=). 214 (14 mg) (R<sub>f</sub> 0.8); ν<sub>max</sub>/cm⁻¹ 1754 (C=O); ¹H NMR (CDCl₃): δ 1.22 (3H, d, J 6.9, CH₃), 2.62 (1H, dd, J 15.1, 9.1, CHHCO), 2.75 (1H, dd, J 15.1, 5.8, CH/HCO), 3.65 (1H, d, J 14.6, PhCHH), 3.75 (1H, d, J
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14.6, Ph(CHH), 4.00 (1H, q, J 6.9, CH3(CH), 4.45-4.55 (2H, m, PhCHCH2 and CHH=), 4.73 (1H, dd, J 13.4, 1.5, CHH=), 7.13 (1H, dd, J 13.4, 5.5, OCH=), 7.1-7.6 (15H, m, 3xPh); 13C NMR (CDCl3): δ 15.91 (CH3), 37.21 (CH2CO), 50.70 (O^Ph), 56.74 (CH3CH), 58.93 (PhCHCH2), 97.55 (CH2=), 126.68, 126.89, 127.36, 127.94, 127.97, 128.10, 128.17, 128.25, 128.34, 141.10, 141.30, 143.61 (3x Ph), 168.81 (C=O).

5.4.5 Preparation of α,β-unsaturated amides

N-Cinnamoyl chloride
Cinnamic acid (10.00g, 67.49 mmol) was placed in a flask and thionyl chloride (6.00 ml, 82.26 mmol) was added dropwise. The mixture was warmed until a solution formed and then refluxed at 100°C for 30 minutes. Evaporation of the excess thionyl chloride left N-cinnamoyl chloride (67.49 mmol) as a brown solid.

N-Cinnamoylmorpholine (203)
N-Cinnamoyl chloride (67.49 mmol) was cooled in an ice bath and TEA (12.00 ml, 86.10 mmol) and then morpholine (17.00 ml, 206.18 mmol) were added. The mixture was refluxed for 2 h. Toluene (50 ml) was added and the precipitate (TEA.HCl) was filtered off. Evaporation of the filtrate left a thick black oil which was dissolved in a small amount of toluene and was treated with ether to precipitate the product. An off white solid was collected and washed with several portions of ether (10x 50 ml) giving 203 (11.63 g, 79%), m.p. 92°C; (Found: C, 71.8; H, 7.0; N, 6.3. C13H15NO2 requires C, 71.9; H, 7.0; N, 6.4%); νmax/cm⁻¹ (nujol) 1646 (C=O); 1H NMR (CDCl3): δ 3.5-4.0 (8H, m, 4x Ctf2-ring), 6.84 (1H, d, J 13.3, PhCH=CH), 7.1-7.5 (5H, m, Ph), 7.69 (1H, d, J 13.3, PhCH=CH); 13C NMR (CDCl3): δ 66.67 (4x CH2-ring), 116.45 (PhCH=CH), 127.62, 128.66, 129.58, 134.97 (Ph), 142.98 (PhCH=CH), 165.39 (C=O)

N-cinnamoyldibenzyamine (222)
Cinnamoyl chloride (10.0 g, 67.49 mmol) was treated with ether (50 ml) and TEA (10.00 ml, 71.74 mmol). Dibenzyamine (15.60 ml, 80.99 mmol) was added and the mixture was stirred at r.t. overnight. Water (100 ml) was added to dissolve the precipitate and ether was removed in vacuo. The product was extracted into CHCl3 (4x 50 ml) and the combined organic layers were washed with brine, dried over MgSO4 and filtered. Evaporation of the solvent left an orange oil which was stirred with ether. The white precipitate of 222 was isolated by filtration (16.19 g, 73%), m.p. 132-133°C; (Found: C, 84.3; H, 6.4; N, 4.3. C32H21NO requires C, 84.37; H, 6.46; N, 4.28%); νmax/cm⁻¹ (nujol) 1643 (C=O); 1H NMR (CDCl3): δ 4.61 (2H, s, CH2Ph), 4.71 (2H, s, CH2Ph), 6.90 (1H, d, J 15.5, PhCH=CH), 7.2-7.5 (15 H, m, 3x Ph),
7.87 (1H, d, J 15.5, PhCH=CH); $^{13}$C NMR (CDCl$_3$): δ 48.79 (CH$_2$), 50.04 (CH$_2$), 117.22 (=CHCO), 126.57, 127.44, 127.72, 127.87, 128.38, 128.62, 128.76, 128.99, 129.69, 135.17, 136.70, 137.33 (3x Ph), 143.83 (PhCH=), 167.18 (C=O).

**N-Cinnamoylpiperidine (223)**

Cinnamoyl chloride (15.0 g, 101.24 mmol) was treated with ether (50 ml) and TEA (28.0 ml, 200.89 mmol) and the mixture was cooled to 0°C. Piperidine (10.32 g, 121.19 mmol) was added and the mixture was stirred for 6 h at r.t.. A similar work-up to that described for the preparation of 222 was used. Evaporation of the solvent left a crude brown solid which recrystallised from boiling toluene, to give a white solid (232) (18.63 g, 82%), m.p. 120-121°C, (Found: C, 78.1; H, 8.0; N, 6.6. C$_{14}$H$_{17}$NO requires C, 78.1; H, 8.0; N, 6.5%); $\nu$ max/cm$^{-1}$ (nujol) 1644 (C=O); $^1$H NMR (CDCl$_3$): δ 1.5-1.8 (6H, m, CH$_2$CH$_2$CH$_2$-ring), 3.63 (4H, m, CH$_2$NCH$_2$-ring), 6.90 (1H, d, J 13.5, PhCH=CH), 7.3-7.5 (5H, m, Ph), 7.65 (1H, d, J 13.5, PhCH=CH); $^{13}$C NMR (CDCl$_3$): δ 24.61 (NCH$_2$CH$_2$-ring), 25.56 (NCH$_2$CH$_2$-ring), 26.72 (NCH$_2$CH$_2$-ring), 43.27 (NCH$_2$-ring), 46.97 (NCH$_2$-ring), 111.74 (PhCH=CH), 127.62, 128.69, 129.33, 135.46 (Ph), 142.04 (PhCH=CH), 165.28 (C=O)

**N-Cinnamoyldimethylamine (224)**

Cinnamoyl chloride (5.00 g, 33.75 mmol) was treated with ether (50 ml) and a large excess of TEA (28.00 ml, 200.89 mmol) and the mixture was cooled to 0°C. Dimethylamine.HCl (2.75 g, 33.75 mmol) was added and the mixture was stirred at r.t. for 6 h. A similar work-up to that described for the preparation of 222 was used. The crude red solid was dissolved in boiling toluene and 224 was precipitated out of the cold solvent with ether. Gold coloured crystals were sublimed under vacuum (0.5 mmHg/ 50°C) to give white needle shaped crystals (224) (7.27 g, 81%), m.p. 98°C. (Found: C, 75.2; H, 7.6; N, 8.0. C$_{11}$H$_{13}$NO requires C, 75.4; H, 7.5; N 8.0%); $\nu$ max/cm$^{-1}$ (nujol) 1651 (C=O); $^1$H NMR (CDCl$_3$): δ 3.07 (3H, s CH$_3$), 3.17 (3H, s, CH$_3$), 6.90 (1H, d, J 13, PhCH=CH), 7.3-7.5 (5H, m, Ph), 7.62 (1H, d, J 13, PhCH=CH); $^{13}$C NMR (CDCl$_3$): δ 35.89 (CH$_3$), 37.39 (CH$_3$), 117.36 (PhCH=CH), 127.74, 128.74, 129.49, 135.32 (Ph), 142.28 (PhCH=CH), 166.63 (C=O)

**N-Crotonylmorpholine (225)**

Crotonyl chloride (15 ml, 15.6 mmol) was added to an ice-cooled solution of morpholine (13.64 g, 15.6 mmol) and TEA (40 ml) in ether (50 ml). The mixture was stirred for 6 h then water was added to dissolve the precipitate. The product was extracted into ether (3x 20 ml) and the combined organic layers were washed with brine (10 ml), dried over MgSO$_4$ and evaporated. The orange oil was distilled under vacuum to give a colourless oil which solidified on cooling (225) (2.42 g, 70%), 120°C/0.3 mmHg; m.p. 55°C (Found: C, 70.0; H, 8.3; N, 9.1. C$_8$H$_{13}$NO$_2$ requires C, 61.9; H, 8.5; N 9.0%); $\nu$ max/cm$^{-1}$ 1667 (C=O); $^1$H NMR
(CDCl₃): δ 1.89 (3H, dd, J 6.7, 1.5, CH₃), 3.4-3.8 (8H, m, 4x CH₂-ring), 6.23 (1H, dd, J 15, 1.5, CH₃CH=CH), 6.91 (1H, m, CH₃CH=CH); ¹³C NMR (CDCl₃): δ 18.22 (CH₃), 66.78 (CH₂), 120.94 (CH=CH), 142.11 (CH=CH), 165.60 (C=O).

N-Crotonyldimethylamine (226)
N,N-Dimethylamine.HCl (3.53 g, 43.29 mmol) was added to an ice-cooled solution of crotonyl chloride (90%, 4.61 ml, 43.29 mmol) and TEA (40 ml) in ether (50 ml). The mixture was stirred for 6 h. The same work-up procedure as that described for 225 was used. The product was isolated from the crude mixture by Kugelrohr distillation to give 226, bp ca. 120°C/0.4 mmHg, (1.15 g, 23%); (Found: C, 63.5; H, 9.4; N, 12.1. C₆H₁₁NO requires C, 63.8; H, 9.8; N 12.3%); νmax/cm⁻¹ 1660 (C=O); ¹H NMR (CDCl₃): δ 1.87 (3H, dd, J 6.8, 1.6, CH₃CH=), 2.99 (3H, s, NCH₃), 3.07 (3H, s, NCH₃), 6.27 (1H, dd, J 15.0, 1.6, CH₃CH=CH), 6.88 (1H, m, CH₃CH=CH); ¹³C NMR (CDCl₃): δ 18.17 (CH₃), 121.70 (CH=CH), 141.22 (CH=CH), 166.87 (C=O).

N-2-Pentenoyldimethylamine (227)
2-Pentenoyl chloride (7.00g, 69.92 mmol) (prepared from 2-penteneoic acid by reaction with thionyl chloride) was treated with ether (50 ml) and TEA (40.00 ml). Dimethylamine.HCl (5.70 g, 69.92 mmol) was added and the mixture was stirred at r.t. for 6 h. The work-up procedure described for 222 was used. The crude product was distilled via Kugelrohr distillation bp ca. 120°C/0.4 mmHg, to give 227 (2.09 g, 23%); νmax/cm⁻¹ (film) 1643 (C=O); ¹H NMR (CDCl₃): δ 1.03 (3H, t, J7.4, CH₃), 2.23 (2H, m, CH₂), 3.00 (3H, s, CH₃N), 3.07 (3H, s, CH₃N), 6.23 (1H, dt, J 1.47, 15.1, CH=CHCO), 6.91 (1H, dt, J 15.1, 6.45, CH=CHCO); ¹³C NMR (CDCl₃): δ 12.61 (CH₃), 25.54 (CH₂), 35.66 (NCH₃), 37.32 (NCH₃), 119.23 (CH=CH), 147.58 (CH=CH), 167.04 (C=O).

5.4.6 General procedure for the Michael addition of 30a to α,β-unsaturated amides, with a subsequent proton quench
(R)-(+)N-(1-phenylethyl)benzylamine (0.50 g, 2.37 mmol, 1.5 mol. eq.) in THF (5.00 ml) was treated at 0°C with BuLi (1.6M, 1.50 ml, 2.37 mmol, 1.5 eq). The bright reddish pink solution was held at 0°C for 15 minutes then the temperature was lowered to -78°C. The α,β-unsaturated amide (1.83 mmol, 1 eq) in THF (5.00 ml) was added via a cannula. Immediately the solution turned a pale orange colour. Stirring was continued for 15 minutes and the pink colour reappeared. The mixture was quenched at -78°C with a saturated solution of ammonium chloride (2ml) and warmed up to r.t.. After separating the THF layer and washing it with brine, the aqueous layer was extracted with CH₂Cl₂ (2x 15 ml), and again the organic
phase was washed with brine (5 ml). The combined organic layer was dried over MgSO4, filtered and evaporated to give the crude product.

**Preparation of 207**

The general method was followed using α,β-unsaturated amide 203 (0.40 g, 1.83 mmol). The crude material contained diastereomers 207a and 207b in the ratio 16:1 (88% d.e.). The material was flash chromatographed twice on silica (ether-hexane 1:1; ether-CHCl3 1:1) to yield a mixture of diastereomers 207a and 207b in the ratio 18:1 (90% d.e), as a colourless glassy oil (0.62 g, 79%); (Found: C, 78.3; H, 7.6; N, 6.5. C28H32N2O2 requires C, 78.5; H, 7.5; N, 6.5%); νmax/cm\(^{-1}\) (film) 1640 (C=O); 207a: \(^1\)H NMR (CDCl3): δ 1.31 (3H, d, J 6.8 CH3), 2.4-2.5 (2H, m, CH2CO), 2.8-3.6 (6H, m, 2xCH2N-ring and 2x CH2-O ring), 3.67 (1H, J 15.0, CHPh), 3.81 (1H, d, J 15.0, CHPh), 4.00 (1H, q, J 6.8, CH3CH), 4.51 (1H, dd, J 15, 3, NCHCH2), 7.1-7.6 (15 H, m, 3x Ph); 13C NMR (CDCl3): δ 13.11 (CH3), 37.69 (CH2CO), 41.62 (CH2N-ring), 45.64 (CH2N-ring), 50.66 (CH2Ph), 56.29 (PhCHCH2), 60.94 (PhCHCH2), 66.07 (OCH2-ring), 66.53 (OCH2-ring), 126.41, 126.62, 127.21, 127.27, 127.72, 127.93, 127.98, 128.06, 128.32, 142.12, 142.69, 144.00 (3x Ph), 169.51 (C=O).

**Preparation of 228**

The general method given above was followed using α,β-unsaturated amide 222 (0.31 g, 0.94 mmol). The crude material contained diastereomers 228a and 228b in the ratio 19:1 (90% d.e.). The crude oil was flash chromatographed twice (ether-CHCl3 1:24 and then ether-hexane 1:1) to give a mixture containing the same ratio of diastereomers without the excess amine (110a) as a yellow oil (0.35 g, 69%); νmax/cm\(^{-1}\) (film) 1639 (C=O); 228a: \(^1\)H NMR (CDCl3): δ 1.37 (3H, d, J 6.8 CH3), 2.48 (1H, dd, J 15.0, 4.0, CHHCO), 2.66 (1H, dd, J 15.0, 10.4 CHHCO), 3.6-3.9 (3H, m, PhCHHNCO and PhCH2NCH), 3.95 (1H, q, J 6.8, CH3CH), 4.25 (1H, d, J 15.0, PhCHHNCO), 4.51 (1H, d, J 15.0, PhCHHNCO), 4.70 (1H, dd, J 10.4, 4.0, PhCHN), 6.8-7.4 (25H, m, 5x Ph); 13C NMR (CDCl3): δ 13.74 (CH3), 37.65 (CH2CO), 47.66 (CH2Ph), 49.65 (CH2Ph), 51.61 (CH2Ph), 56.43 (PhCHCH2), 61.33 (PhCHCH2), 126.26, 126.36, 126.47, 126.62, 127.07, 127.36, 127.60, 127.68, 127.77, 127.95, 128.04, 128.13, 128.22, 128.34, 128.66, 136.33, 137.10, 142.16, 142.60, 144.07 (5x Ph), 171.36 (C=O); m/z (FAB; thioglycerol) 540 (M+2•95%), 196, 91(C7H7•, 100%)

**Preparation of 229**

The general procedure given above was followed using α,β-unsaturated amide 223 (0.34 g, 1.58 mmol). The crude material contained diastereomers 229a and 229b in the ratio 16:1 (88% d.e.). The crude oil was flash chromatographed (ether-hexane 1:1.7) to give a colourless oil which contained the two diastereomers in the ratio 17:1 (89% d.e.), (0.45 g, 68%); (Found: C, 81.4; H, 8.2; N, 6.5. C29H34N2O requires C, 81.7; H, 8.0; N, 6.6%); νmax/cm\(^{-1}\)
(film) 1640 (C=O); $^1$H NMR (CDCl$_3$): $\delta$ 0.95-1.5 (6H, m, CH$_2$CH$_2$CH$_2$-ring), 1.30 (3H, d, J 6.8, CH$_3$), 2.44 (1H, dd, J 14.9, 5.0 CHCH$_2$CO), 2.54 (1H, dd, J 14.9, 8.1, CHCH$_2$CO), 2.8-3.4 (4H, m, 2xNCH$_2$-ring), 3.68 (1H, d, J 15.0, PhCH$_2$), 3.79 (1H, d, J 15.0, PhCH$_2$), 4.02 (1H, q, J 6.8, CH$_3$), 4.55 (1H, dd, J 8.1, 5.0, PhCH$_2$CH$_2$), 7.0-7.4 (15H, m, 3x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 13.76 (CH$_3$), 24.17 (NCH$_3$-ring), 25.20 (NO$_2$-ring), 25.81 (NCH$_2$-ring), 37.27 (CH$_2$CO), 42.31 (NCH$_2$-ring), 50.53 (CH$_2$Ph), 56.28 (PhCH$\equiv$CH$_2$), 60.31 (PhC$\equiv$CH$_2$), 126.25, 126.47, 126.64, 127.69, 127.76, 127.82, 127.83, 127.94, 128.10, 142.12, 142.94, 144.01 (3x Ph), 168.96 (C=O).

Preparation of 230

The general procedure given above was followed using $\alpha,\beta$-unsaturated amide 224 (0.30g, 1.71 mmol). The crude material contained diastereomers 230a and 230b in the ratio 49:1 (96% d.e.). The red oil was flash chromatographed (ether-CHCl$_3$ 1:17) to give a colourless oil (230a) (98% d.e.), (0.56 g, 85%); (Found: C, 80.5; H, 7.7; N, 7.2. C$_{26}$H$_{30}$N$_2$O requires C, 80.8; H, 7.8; N, 7.3%); v $\nu$ cm$^{-1}$ (KBr) 1646 (C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.32 (3H, d, J 6.9, CH$_3$CH), 2.40 (3H, s, NCH$_3$), 2.48 (2H, m, CH$_2$CO), 2.74 (3H, s, NCH$_3$), 3.67 (1H, d, J 15.0, PhCH$_2$), 3.80 (1H, d, J 15.0, PhCH$_2$), 3.99 (1H, q, J 6.8, CH$_3$CH), 4.58 (1H, t, J 7.0, PhCHCH$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 13.54 (CH$_3$), 35.13 (NCH$_3$), 36.66 (NCH$_3$), 37.78 (CH$_2$CO), 50.48 (PhCH$_2$), 56.44 (CH$_3$CHN), 60.22 (PhCHCH$_2$), 126.29, 126.53, 126.90, 137.73, 127.84, 127.94, 128.02, 128.10, 128.17, 142.26, 143.312, 144.10 (3x Ph), 170.82 (C=O); m/z (FAB; thioglycerol) 387 (M+1$^+$, 90%), 105 (PhCH$_2$N$^+$, 100%)

This reaction was repeated in toluene; a mixture of 230a and 230b (23:2) were isolated (70% in total). When repeated using ether it was found that 224 was nearly insoluble and only 50% of 224 had reacted after 5 h to give 230a and 230b (4:1).

Preparation of 231

The general procedure given above was followed using $\alpha,\beta$-unsaturated amide 225 (0.18 g, 1.18 mmol). The crude material contained diastereomers 231a and 231b in the ratio 12:1 (85% d.e.). The crude material was subjected to flash chromatography on silica (ether) to give a colourless oil (231a) (98% d.e.), (0.36 g, 68%); (Found: C, 75.2; H, 8.0; N, 7.5. C$_{23}$H$_{30}$N$_2$O$_2$ requires C, 75.4; H, 8.3; N, 7.6%); v $\nu$ cm$^{-1}$ (film) 1643 (C=O); $^1$H NMR assigned using a COSY experiment) $^1$H NMR (CDCl$_3$): $\delta$ 1.16 (3H, d, J 6.6, CH$_3$CHCH$_2$), 1.30 (3H, d, J 6.8, CH$_3$CHN), 2.17 (1H, dd, J 13.5, 10.0, CHCH$_2$), 2.33 (1H, dd, J 13.5, 4.0, CHCHCO), 2.7-3.7 (9H, m, CH$_2$CH$_2$NCH$_2$CH$_2$-ring and CH$_3$CHCH$_2$), 3.74 (2H, s, CH$_2$Ph); 3.89 (1H, q, J 6.8, PhCH$_2$), 7.1-7.5 (10 H, m, 2x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 16.58 (CH$_3$CHCH$_2$), 17.86 (PhCH$_2$), 39.59 (CH$_2$CO), 41.56 (NCH$_2$-ring), 45.63 (NCH$_2$-ring), 49.03 (CH$_3$CH), 49.51 (CH$_2$Ph), 57.06 (PhCH), 66.38 (OCH$_2$-ring), 66.63 (OCH$_2$-ring), 125.56, 126.80, 130.84, 131.26, 131.48, 132.81, 137.02, 142.17, 144.99 (3x Ph), 170.96 (C=O).
126.54, 126.57, 127.67, 127.93, 128.08, 128.29, 141.48, 144.45 (2x Ph), 170.11 (C=O); m/z (FAB; thioglycerol) 367 (M+1+, 45%), 261 (M - N(CO)C₆H₄O⁺), 105 (NCH₂Ph⁺, 100%)

**Preparation of 232**

The general procedure given above was followed using α,β-unsaturated amide 226 (0.20 g, 1.77 mmol). The crude material contained diastereomers 232a and 232b in the ratio 49:1 (96% d.e.). This was subjected to flash chromatography on silica (ether) to give a colourless oil, 232a (96% d.e.) (0.25 g, 76%); (Found: C, 77.5; H, 8.9; N, 8.4. C₂₃H₂₈N₂O requires C, 77.7; H, 8.7; N, 8.6%; ν_max/cm⁻¹ (film) 1645 (C=O); ¹H NMR (CDCl₃): δ 1.15 (3H, d, J 6.6, CH₃CHCH₂), 1.36 (3H, d, J 7.0, CH₃CHPh), 2.13 (1H, dd, J 14.2, 9.2, CHHCO), 2.32 (1H, dd, J 14.2, 4.7, CHHCO), 2.50 (3H, s, NCH₃), 2.80 (3H, s, NCH₃), 3.42 (1H, m, CH₃CHCH₂), 3.72 (1H, d, J 14.6, PhCHH), 3.78 (1H, d, J, 14.6, PhCHH), 3.90 (1H, q, CH₃CHPh), 7.1-7.5 (10H, m, 2x Ph); ¹³C NMR (CDCl₃): δ 17.28 (O(CHCH₃)), 18.13 (CH₃CH₂), 35.04 (NCH₃), 36.72 (NCH₃), 39.24 (CH₂CO), 49.11 (CH₃CHCH₂), 49.53 (PhCH₂), 57.45 (CH₃CHPh), 126.40, 126.50, 127.62, 127.81, 127.93, 128.20, 141.77, 144.45 (2x Ph), 171.40 (C=O).

**Preparation of 233**

The general procedure given above was followed using α,β-unsaturated amide 227 (0.30 g, 2.35 mmol). The crude material contained diastereomers 233a and 233b in the ratio 49:1 (96% d.e.). The oil was subjected to flash chromatography on silica (ether-CH₂Cl₂ 1:4) to give a colourless oil (233a) (98% d.e.) (0.52g, 65%); (Found: C, 78.0; H, 8.9; N, 8.4. C₂₂H₃₀N₂O requires C, 78.1; H, 8.9; N, 8.3%); ν_max/cm⁻¹ (film) 1644 (C=O); ¹H NMR (CDCl₃): 1.04 (3H, t, J 7.2, CH₂CH₂), 1.37 (3H, d, J 7.0, CH₂CH), 1.3-1.5 (2H, m, CH₃CHH₂), 1.82 (1H, dd, J 15.3, 4.3, CHHCO), 1.94 (1H, dd, J 15.3, 8.7, CHHCO), 2.56 (3H, s, NCH₃), 2.84 (3H, s, NCH₃), 3.39 (1H, m, CH₃CH₂CH), 3.58 (1H, d, J 14.8, PhCHH), 3.7-3.9 (2H, m, CH₃CH, PhCHH), 7.1-7.5 (10H, m, 2x Ph); ¹³C NMR (CDCl₃): δ 11.90 (CH₃), 19.19 (CH₃), 26.53 (CH₂CH₂), 35.02 (NCH₃), 35.06 (CH₂CO), 36.64 (NCH₃), 49.63 (PhCH₂), 54.36 (CH₃CH₂CH), 56.97 (CH₃CH), 126.47, 127.74, 127.75, 127.90, 128.06, 128.14, 141.56, 142.63 (2x Ph), 171.70 (C=O).

**Attempted addition of 30a to 228**

The general procedure given above was followed using α,β-unsaturated amide 228 (0.30 g, 1.58 mmol). A black colour appeared immediately when 228 was added, but disappeared when the reaction was quenched with ammonium chloride. An orange oil was produced. ¹H NMR indicated that only the two starting materials 110a and 228 were present, but instead of the initial ratio of 1.5:1, they were isolated in the ratio 6:1 (0.50 g).
5.4.7 General procedure for the Michael addition of 30A to α,β-unsaturated amides, followed by reaction with MeI or benzyl bromide

As normal, these reactions were carried out under nitrogen. (R)-(–)-N-(1-phenylethyl)benzylamine (0.50 g, 2.37 mmol, 1.5 mol. eq.) in THF (5.00 ml) was treated at 0°C with BuLi (1.6M, 1.50 ml, 2.37 mmol, 1.5 eq). The bright reddish pink solution was held at 0°C for 15 minutes, then the temperature was lowered to -78°C. The α,β-unsaturated amide (1.83 mmol, 1 eq) in THF (5.00 ml) was added via a cannula. Immediately the solution turned a pale orange colour. Stirring was continued for 15 minutes during which time the red colour reappeared. MeI (0.6 ml, 9.6 mmol) was added and immediately the solution turned yellow. The mixture was stirred for a further 30 minutes, then quenched with a saturated solution of ammonium chloride (2ml) and warmed up to r.t.. After separating the THF layer and washing it with brine (5 ml), the aqueous layer was extracted with CHjClj (2x 15 ml), and again the organic phase was washed with brine (10 ml). The combined organic layer was dried over MgS04, filtered and evaporated to give the crude product.

Preparation of 236

The method described above was followed using α,β-unsaturated amide 203 (0.37 g, 1.71 mmol). The crude material contained diastereomers 236a and 236b and another minor diastereomer in the ratio 25:3:1 (72% d.e.). The crude material was flash chromatographed (ether-CHCl3 1:20) to give a colourless oil (0.50 g, 67%) which contained a mixture of 236a and 236b in the ratio 47:3 (88% d.e.). (Found: C, 78.6; H, 7.8; N, 6.3. C29H34N2O2 requires C, 78.7; H, 7.7; N, 6.3%); 236a: δmax/cm−1 (film) 1643 (C=O) The NMR spectra were assigned using a COSY and an XHCORRD experiment. 1H NMR (CDCl3): δ 0.71 (3H, d, J 6.8, CH3CHCO), 1.18 (3H, d, J 6.8, CH3CHN), 2.9-3.7 (8H, m, CHCO and 7x C//H-ring), 3.63 (1H, d, J 13.4, PhCH), 3.82 (1H, d, J 13.4, PhCH), 3.98 (1H, m, CH2CH2), 4.16 (1H, q, J 6.8, CH3CH2), 4.42 (1H, d, J 10.4, PhCH2CH2), 7.15-7.4 (15H, m, 3x Ph); 13C NMR (CDCl3): δ 16.58 (CH3CH2), 16.89 (CH3CHN), 37.29 (CH2C), 41.87 (NCH2-ring), 45.48 (NCH2-ring), 50.28 (PhCH2), 57.27 (CH2CH2), 65.34 (NCH2), 66.41 (OCH2-ring), 66.69 (OCH2-ring), 126.40, 126.48, 127.11, 127.70, 127.75, 127.98, 128.10, 128.16, 129.33, 139.15, 141.17, 144.64, 173.68 (C=O).

Preparation of 237

The method described above was followed using α,β-unsaturated amide 222 (0.56 g, 1.71 mmol). The crude material contained diastereomers 237a and 237b in the ratio 3:2 and other minor diastereomers plus several unidentified products. The mixture was subjected to flash chromatography (silica) (ether-hexane 1:1) which partially separated the mixture of
diastereomers. The 1st fraction contained a 12:1 mixture of 237a and 237b and the second fraction contained a 1:1 mixture of 237a and 237b. (Combined yield 69%) 237a: $\nu_{\text{max}}$ cm$^{-1}$ (film) 1639 (C=O); $^1$H NMR (CDCl$_3$): $\delta$ 0.70 (3H, d, $J$ 6.8, CH$_3$CHCO), 1.16 (3H, d, $J$ 6.8, CH$_3$CHN), 3.32 (1H, dq, $J$ 10.6, 6.8, CH$_3$CHCO), 3.55 (1H, d, $J$ 14.9, PhCHHNCH), 3.75 (1H, d, $J$ 14.9, PhCHHNCH), 4.00 (1H, d, $J$ 17.3, aPhCHHNCO), 4.1-4.3 (2H, PhCHCH$_3$ and bPhCHHNCO), 4.28 (1H, d, $J$ 17.3, aPhCHHNCO), 4.47 (1H, d, $J$ 10.3, PhCHCH), 5.12 (1H, d, $J$ bPhCHHNCO), 7.0-7.5 (25 H, m, 5x Ph); m/z (FAB; thioglycerol) 554 (M+2$^+$, 70%), 196 (N^PhV; 100%), 105 (C$_{7}$/CHN), 91 (C$_{7}$/H$_{7}^+$).

Preparation of 238
The method described above was followed using $\alpha,\beta$-unsaturated amide 223 (0.37 g, 1.71 mmol). The crude material contained diastereomers 238a and 238b and another minor diastereomer in the ratio 45:3:1 (80% d.e.). The crude material also contained about 16% of compound 229 (when the same reaction was repeated and allowed to warm up to r.t after the addition of MeI, complete conversion of 223 to 238 was observed). The crude material was flash chromatographed (ether-CH$_2$Cl$_2$ 4:1) but compound 229 was not removed. The white solid was washed several times with hexane to give 238a (96% d.e.) (0.45 g, 60%); m.p. 113-114°C; (Found C, 81.8; H, 8.4; N, 6.4. C$_{30}$H$_{36}$N$_2$O requires C, 81.8; H, 8.2; N, 6.4%); $\nu_{\text{max}}$ cm$^{-1}$ (KBr) 1627 (C=O). The NMR spectra were assigned with the aid of a COSY and an XHCORRD experiment. $^1$H NMR (CDCl$_3$): $\delta$ 0.69 (3H, d, $J$ 6.8, CH$_3$CHCO), 1.16 (3H, d, $J$ 6.8, CH$_3$CHN), 1.3-1.7 (6H, m, NCH$_2$CH$_2$CH$_2$CH$_2$-ring), 2.77 (1H, m, N$^6$CHH-ring), 2.98 (1H, m, N$^6$CHH-ring), 3.3-3.5 (2H, m, CHCO and N$^6$CHH-ring), 3.63 (1H, d, $J$ 15.3, PhCHH), 3.82 (1H, d, $J$ 15.3, PhCHH), 4.16 (2H, m, CH$_3$CHN and N$^6$CHH-ring), 4.41 (1H, d, $J$ 10.3, NCHCH), 7.1-7.5 (15 H, m, 3x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 16.36 (CH$_3$CHN), 16.95 (CH$_3$CHCO), 24.62 (NCH$_2$CH$_2$CH$_2$-ring), 25.38 (NCH$_2$CH$_2$-ring), 26.57 (NCH$_2$CH$_2$-ring), 37.37 (CHCO), 42.73 (N$^6$CH$_2$-ring), 46.18 (N$^4$CH$_2$-ring), 50.31 (PhCH$_2$), 57.37 (CH$_3$CHN), 65.62 (NCHCH), 126.26, 126.31, 126.96, 127.62, 127.87, 127.88, 128.04, 128.25, 129.43, 139.79, 141.47, 144.66 (3x Ph), 173.33 (C=O); m/z 441 (M+1$^+$, 95%), 112 (C(O)NC$_5$H$_{10}^+$, 100%)

Preparation of 239
The method described above was followed using $\alpha,\beta$-unsaturated amide 224 (0.30 g, 1.71 mmol). The crude material contained diastereomers 239a and 239b and another minor diastereomer in the ratio 67:2:1 (91% d.e.). The crude material was flash chromatographed (ether: hexane 1:9) to yield a pale yellow glassy oil which solidified after a few weeks (239a) (0.56 g, 82%), (96% d.e.), m.p. 84-85°C (Found: C, 80.7; H, 8.2; N, 6.7. C$_{27}$H$_{32}$N$_2$O requires C, 81.0; H, 8.1; N, 7.0%); $\nu_{\text{max}}$ cm$^{-1}$ (KBr) 1645 (C=O). The NMR spectra were assigned with the aid of a COSY and an XHCORRD experiment. $^1$H NMR (CDCl$_3$): $\delta$ 0.67...
Chapter 5: Experimental details

(3H, d, J 6.8, CH₃CHCO), 1.23 (3H, d, J 6.8, CH₃CHN), 2.53 (3H, s, NCH₃), 2.92 (3H, s, NCH₃), 3.24 (1H, dq, J 6.8, 10.4, CHCO), 1.23 (3H, d, J 6.8, OT₃CH), 2.53 (3H, s, NCH₃), 2.92 (3H, s, NCH₃), 3.24 (1H, dq, J 6.8, 10.4, CHCO), 3.64 (1H, d, J 15.4, PhCH₃H), 3.79 (1H, d, J 15.4, PhCH₃H), 4.15 (1H, q, J 6.8, CH₃CHN), 4.42 (1H, d, J 10.4, NCHCH), 7.7-7.5 (15H, m, 3x Ph); ¹³C NMR (CDCl₃): δ 16.46 (OT₃CHCO and OT₃CHCH), 35.44 (CH₃N), 36.51 (CH₃N), 37.62 (CHCO), 49.77 (CH₂), 57.43 (CH₃CHN), 65.65 (NCHCH), 126.15, 126.20, 126.88, 127.52, 127.58, 127.67, 127.75, 127.94, 129.19, 139.32, 141.39, 144.64 (3x Ph), 174.79 (C=O). m/z (FAB; Thioglycerol) 401 (M+1⁺; 100%), 105 (PhCH₂), 91 (C₇H₇⁺).

When the reaction was carried out in toluene using the same procedure, only 50% of 239 (as a number of diastereomers) was isolated after 3 h, along with 50% of 230.

Preparation of 241

The method described above was followed using α,β-unsaturated amide 225 (0.30 g, 1.39 mmol). The crude material contained two major diastereomers 241a and 241b in the ratio 1:1 and another minor diastereomer. Flash chromatography (CHCl₃-ether 5:1) gave an orange oil (0.43 g, 74%) which contained 241a and 241b (1:1). Diastereomers 241a/b: ¹H NMR (CDCl₃): δ 0.86, 1.00, 1.03, 1.06, 1.37, 1.44 (3H, d, J 6.8, 3x CH₃ for each diastereomer), 2.30, 2.50 (1H, m, CHCO for each diastereomer), 3.7-4.0 (12H, ring protons, PhCH₂, PhCH₂, CH₃CHN for each diastereomer), 7.2-7.4 (5H, m, Ph for each diastereomer); ¹³C NMR (CDCl₃): δ 12.14, 12.53, 14.55, 14.82, 15.72, 15.93 (3x CH₃ for each diastereomer), 39.47, 41.38 (CH for both diastereomers), 41.47, 44.65, 45.61, 50.09 (2x CH₂ for each diastereomer), 53.17, 55.24, 57.89, 58.83 (2x CH for each diastereomer), 66.27, 66.38 x 2, 66.45 (2x CH₃ for each diastereomer), 126.14, 126.26, 126.39, 127.51, 127.55, 127.60, 127.71, 127.76, 127.91, 127.97, 128.11, 128.59, 140.98, 141.31, 143.62, 144.21 (2x Ph for each diastereomer), 173.45, 174.55 (C=O for each diastereomer).

Preparation of 242

The method described above was followed using α,β-unsaturated amide 226 (0.20 g, 1.77 mmol). The crude material contained two major diastereomers 242a and 242b in the ratio 1:1 and another minor diastereomer. An orange oil was isolated in 40% yield after flash chromatography, containing 242a and 242b (3:2); (Found: C, 79.3; H, 8.8; N, 8.2. C₂₂H₄₀N₂O requires C, 79.1; H, 8.9; N, 8.3%). 21a/b: v max/cm⁻¹ (film) 1644 (C=O); ¹H NMR (CDCl₃): δ 0.85, 0.96, 0.98, 1.00, 1.39, 1.42 (3H, d, J 6.8, 3x CH₃ for each diastereomer), 2.32, 2.79, 2.84 x 2 (3H, s, 2x CH₃N for each diastereomer), 2.30, 2.45, (1H, m, CHCO for each diastereomer), 3.15, 3.45 (1H, m, CH₃CH/CH for each diastereomer), 7.0-7.5 (10H, m, 2x Ph for each diastereomer); ¹³C NMR (CDCl₃): δ 12.49, 13.75, 14.59, 15.63, 15.89, 17.19 (3x CH₃ for each diastereomer), 35.19, 35.23, 36.12, 36.67 (2x CH₃N for each diastereomer), 40.18, 41.42 (CH for each diastereomer), 49.50, 50.30 (CH₂ for each
diastereomer), 54.97, 55.40, 58.65, 59.41 (2x CH for each diastereomer), 126-128 (aromatic region; signals overlapping), 141.17, 141.98, 144.07, 144.53 (2x Ph for each diastereomer), 175.27, 176.22 (C=O for each diastereomer).

Preparation of 243
The method described above was followed using $\alpha,\beta$-unsaturated amide 227 (0.30 g, 2.35 mmol). The crude material contained two major diastereomers 243a and 243b in the ratio 3:1. The crude material was flash chromatographed (ether:CH$_2$Cl$_2$ 1:4), to give a 4:1 mixture of 243a:243b. (54%) (Found: C, 80.4; H, 9.5; N, 7.6. C$_{23}$H$_{32}$N$_2$O requires C, 78.4; H, 9.2; N, 7.9%); $\nu_{\text{max}}$ cm$^{-1}$ (film) 1644 (C=O); 243a: 0.97 (3H, d, $J$ 7.2, CH$_3$), 1.01 (3H, t, $J$ 7.3, CH$_3$CH$_2$), 1.35 (3H, d, $J$ 7.0, CH$_3$), 1.3-1.5 (2H, m, CH$_2$CH$_3$), 2.3-2.4 (1H, m, CHCO), 2.33 (3H, s, CH$_3$N), 2.84 (3H, s, CH$_3$N), 3.32 (1H, m, CH$_3$CHN), 3.71 (1H, d, $J$ 14.7, PhCH/H), 3.85-3.95 (2H, m, PhCH/H and CH$_3$CHN), 7.2-7.4 (10H, m, 2x Ph), $^1$C NMR (CDCl$_3$): $\delta$ 12.59 (CH$_3$), 13.81 (CH$_3$), 18.75 (CH$_3$), 21.57 (CH$_2$), 35.31 (NCH$_3$), 36.52 (NCH$_3$), 38.44 (CHCO), 50.50 (CH$_3$), 57.72 (CH), 58.35 (CH), 118-128, 141.62, 143.78 (2x Ph), 175.95 (C=O). 243b: 0.87 (3H, t, $J$ 7.4, CH$_3$CH$_2$), 0.97 (3H, d, $J$ 7.2 CH$_3$), 1.43 (3H, d, $J$ 7.0, CH$_3$), 1.3-1.5 (2H, m, CH$_3$CH$_2$), 2.69 (3H, s, CH$_3$N), 2.82 (3H, s, CH$_3$N), 3.05 (1H, m, CHCO), 3.73 (1H, d, $J$ 14.7, PhCH/H), 3.85-4.10 (2H, m, PhCH/H and CH$_3$CHN), 7.2-7.4 (10H, m, 2x Ph).

Preparation of 240
The method described for the preparation of 239 was followed with the $\alpha,\beta$-unsaturated amide 224 (0.33 g, 1.71 mmol). The intermediate enolate was quenched with benzyl bromide (0.60 ml, 5.06 mmol) instead of Mel. The crude material contained diastereomers 240a and two minor diastereomers in the ratio 70:2:1 (92% d.e.). The crude material was flash chromatographed (CHC$_2$H$_2$) to give a colourless oil (0.67g, 82%). Crystals precipitated out of the oil when ether was added and were recrystallised from ether to give 240a, (0.47 g, 57%), (96% d.e.), m.p. 141°C, (Found: C, 82.8; H, 7.6; N, 5.9. C$_{33}$H$_{36}$N$_2$O requires C, 83.2; H, 7.6; N, 5.9%); $\nu_{\text{max}}$ cm$^{-1}$ (KBr) 1627 (C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.02 (3H, d, $J$ 6.8, CH$_3$CHCO), 1.99 (3H, s, CH$_3$N), 2.28 (1H, dd, $J$ 12.7, 2.7, PhCH/HCH), 2.55 (1H, t, $J$, 12.5. PhCH/HCH), 2.71 (3H, s, CH$_3$N), 3.5-3.7 (2H, m, CHCO, PhCH/HN), 3.90 (1H, d, $J$ 14.8, PhCH/HN), 4.24 (1H, q, $J$ CH$_2$CH), 4.34 (1H, d, J10.9, PhCHCH), 6.9-7.6 (15H, m, 3x Ph); $^1$C NMR (CDCl$_3$): 16.39 (CH$_3$), 35.27 (NCH$_3$), 36.27 (NCH$_3$), 37.73 (CH$_2$CH), 46.25 (CHCO), 50.81 (PhCH$_2$), 55.47 (CH$_3$CCHN), 64.27 (NCHCH),126.04, 126.20, 126.66, 127.28, 127.43, 127.57, 127.94, 128.00, 128.36, 128.59, 128.71, 129.15, 139.00, 139.79, 139.84, 144.25, 172.92 (C=O).
Attempts to quench the enolate of amide 203 with a range of alkylating agents
The general method was followed but a) n-C$_4$H$_9$Br (0.30 ml, 2.79 mmol); b) CH$_3$C$_6$H$_4$SO$_2$Me (0.30 ml, 2.82 mmol) or c) EtOSO$_2$Me (0.20 ml, 2.93 mmol) in THF (5.00 ml) was added in place of Mel. The mixture was stirred for a further 30 minutes, then quenched with a saturated solution of ammonium chloride (2ml) and warmed up to r.t.. After separating the THF layer and washing it with brine (5 ml), the aqueous layer was extracted with CH$_2$Cl$_2$ (2x 15 ml), and was washed with brine (5 ml). The combined organic layer was dried over MgSO$_4$, filtered and evaporated to the crude material. $^1$H NMR indicated that, in each case, the enolate had not reacted with the alkylating agent, but had been quenched with a proton to give 207.

Attempts to quench the enolate of amide 203 with a range of alkylating agents in situ.
The same general method was used but the alkylating agent a) n-C$_4$H$_9$Br (0.30 ml, 2.79 mmol); b) CH$_3$C$_6$H$_4$SO$_2$Me (0.30 ml, 2.82 mmol) or c) EtOSO$_2$Me (0.20 ml, 2.93 mmol) in THF (5.00 ml) and 203 were added together to the solution of 30a. The general work-up procedure was used and the $^1$H NMR spectrum of the crude material indicated that, in each case, the enolate had not reacted with the alkylating agent, but had been quenched with a proton to give 207.

5.4.8 General procedure for the Michael addition of 30a to $\alpha,\beta$-unsaturated amides, followed by reaction with benzaldehyde
(R)-(+)-N-(1-phenylethyl)benzylamine (0.50 g, 2.37 mmol, 1.3 mol. eq.) in THF (5.00 ml) was treated at 0°C with BuLi (1.6M, 1.50 ml, 2.37 mmol, 1.3 eq). The bright reddish pink solution was held at 0°C for 15 minutes. Then the temperature was lowered to -78°C. The $\alpha,\beta$-unsaturated amide (1.83 mmol, 1 eq) in THF (5.00 ml) was added via a cannula. Immediately the solution turned a pale orange colour. Stirring was continued for 15 minutes during which time the red colour reappeared. Benzaldehyde (0.50 ml, 4.7 mmol) was added and the mixture was stirred for a further 15 minutes. A saturated solution of ammonium chloride (2ml) was added and the reaction mixture was warmed up to r.t.. After separating the THF layer and washing it with brine (5 ml), the aqueous layer was extracted with CH$_2$Cl$_2$ (2x 15 ml), and this organic phase was washed with brine. The combined organic layer was dried over MgSO$_4$, filtered and evaporated to leave the crude product.

Preparation of 244
The general method was followed using $\alpha,\beta$-unsaturated amide 203 (0.37 g, 1.71 mmol). The crude material contained a major diastereomers 244a and other minor diastereomers in the ratio 25:1:1 (85% d.e.). The crude product was precipitated with ether and was washed with
several portions of ether to remove excess benzaldehyde. 244a was obtained as a white powder (0.73 g, 80%; 92% d.e.) and was recrystallised three times from ethanol to increase the d.e. (0.63 g, 69%; 96% d.e.); m.p. 151-152°C; (Found: C, 78.6; H, 7.2; N, 5.2. C$_{35}$H$_{38}$N$_2$O$_3$ requires C, 78.6; H, 7.2; N, 5.2%); $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3374, 3275 (OH, split into a doublet), 1599 (C=O). The NMR spectra were assigned in conjunction with a COSY and an XHCORRD experiment. $^1$H NMR (CDCl$_3$): $\delta$ 0.92 (3H, d, J 6.8, CH$_3$), 1.84 (1H, m, cCHHO-ring), 2.46 (1H, m, bCHH-ring), 2.6-3.1 (4H, m, 4x$^b$cdCHH-ring), 3.44 (1H, m dCHH-ring), 3.70 (1H, dd, J 11.2, 2.2, CHCO) 3.71 (1H, d, J 14.6, PhCHH ), 3.96 (1H, d, J 14.6, PhCHH), 4.07 (1H, m, aCHH-ring), 4.21 (1H, q, J 6.8, CH$_3$CH), 4.32 (1H, dd, J 9, J 2.2, CHOH), 4.72 (1H, d, J 11, NCHCH), 5.34 (1H, d, J 9.0, OH), 7-7.5 (20 H, m, 4x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 15.58 (CH$_3$), 41.63 ($^a$CH$_2$N-ring), 46.03 ($^b$CH$_2$N-ring), 48.78 (CHCO), 51.13 (PhCH$_2$), 54.82 (CH$_3$CH), 61.20 (NCHCH), 65.26 (CH=O-ring), 65.97 ($^a$CH$_2$O-ring), 71.59 (CHOH), 125.09, 126.52, 127.05, 127.17, 127.27, 127.76, 127.87, 128.03, 128.12, 128.32, 128.47,128.68, 138.26, 138.90, 143.73, 143.99 (4x Ph), 171.10 (C=O); m/z (FAB; thioglycerol) 535 (M+1$^-$, 10%), 105 (PhCH$_2$N$^+$, 100%), 91 (C$_7$H$_7^+$).

Preparation of 245
The general method was followed using $\alpha,\beta$-unsaturated amide 222 (0.20 g, 0.61 mmol). The crude material contained a mixture of diastereomers (245a:others) in the ratio 12:2:1. The crude material was flash chromatographed (ether-hexane 1:4) to give a yellow oil (0.29 g, 75%) containing 245a (86% d.e). An XHCORRD and a COSY experiment were used to allow assignment of the NMR spectra. $^1$H NMR (CDCl$_3$) of major diastereomer: $\delta$ 0.93 (3H, d, J 6.8, CH$_3$), 3.33 (1H, d, J 15.8, $^a$PhCHHNCO), 3.75 (1H, d, J 14.7, PhCHHNCH), 3.62 (1H, dd, J 11.2, 1.7, CHCO), 4.01 (1H, d, J 14.7, PhCHHNCH), 4.13 (1H, d, J 15.8 $^a$PhCHHNCO, ), 4.15 (1H, d, J 14.1, $^b$PhCHHNCO), 4.29 (1H, q, J 6.8, , 4.46 (2H, d, CHOH and $^b$PhCHHNCO), 4.87 (1H, d, J 11.2, NCHCHCH), 5.95 (1H, d, OH), 5.95-7.5 (30H, m, 6x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 15.88 (CH$_3$), 47.78 ($^b$PhCH$_2$NCO), 49.99 (CHCO), 50.25 ($^b$PhCH$_2$NCO), 51.67 (PhCH$_2$NCH), 55.89 (CH$_3$CH), 62.48 (NCHCH), 72.58 (CHOH), 125.70, 126.41, 126.91, 127.02, 127.21, 127.31, 127.63, 127.67, 127.85, 128.06, 128.18, 128.32, 128.43, 128.58, 128.61, 128.91, 129.31, 129.86, 134.77, 136.66, 138.31, 139.05, 143.86, 143.90 (Ph x 6), 174.13 (C=O); m/z (FAB; thioglycerol) 631 (M+1$^-$, 7%), 210 (CH$_2$N(PhCH)$_2$)$_2^+$, 100%).

Preparation of 246
The general method was followed using $\alpha,\beta$-unsaturated amide 223 (0.32 g, 1.50 mmol). The crude material contained a major diastereomer 246a other minor diastereomers in the ratio 24:1:1 (85% d.e.). The crude material was flash chromatographed (ether-CH$_2$Cl$_2$ 1:20) to give a colourless oil which solidified when heated to remove the excess benzaldehyde.
which had not been removed on the column. 246a was isolated as a white solid, (0.67 g, 84%) which was recrystallised from ethanol to increase the d.e. (54%, 96% d.e.), m.p. 170-171°C (Found; C, 81.1; H, 7.5; N, 5.2. C_{36}H_{40}N_{2}O_{2} requires C, 81.2; H, 7.6; N, 5.3%); ν_{max}/cm^{-1} (KBr) 3272 (OH), 1603 (C=O and Ph C=C). A COSY and an XHCORD experiment was used to assign the NMR spectra. \^1H NMR (CDCl$_3$): δ -0.40 (1H, bm, \textit{NCH}$_2$CH$_2$H-ring), 0.7-1.5 (5H, m, \textit{NCH}$_2$CH$_2$CHHCH$_2$-ring), 0.92 (3H, d, J 6.8, CH$_3$), 2.17 (1H, m, CHFHN-ring), 2.31 (1H, m, CHFHN-ring), 3.09 (1H, m, CHFHN-ring), 3.75 (2H, m, CHCO and PhCHH), 3.97 (1H, d, J 14.6, PhCHH), 4.19 (1H, q, J 6.8, CH$_3$CH), 4.30 (2H, m, CHOH and CHFHN-ring), 4.69 (1H, d, J 11.2, NCHCH), 5.75 (1H, d, J 9.5, OH), 7.0-7.5 (20 H, m, 4x Ph); \^13C NMR (CDCl$_3$): δ 15.28 (CH$_3$), 23.86 (NCH$_2$CH$_2$CH$_2$), 24.79 (NCH$_2$CH$_2$ ring x2), 42.43 (NCH$_2$-ring), 46.69 (NCH$_2$-ring), 48.47 (CHCO), 51.13 (CH$_2$), 54.61 (CH$_3$CH), 61.36 (NCHCH), 71.71 (CHOH), 125.25, 126.12, 126.80, 126.87, 127.39, 127.57, 127.70, 127.79, 128.10, 128.21, 128.50, 128.56, 138.66, 139.11, 143.74, 144.23 (4x Ph), 170.76 (C=O); m/z (FAB; thioglycerol) 534 (M+2+; 20%), 418 (M - CONC$_5$H$_{10}$)$_+$, 91 (C$_7$H$_{17}$; 100%).

Preparation of 247

The general method was followed using α,β-unsaturated amide 224 (0.30 g, 1.71 mmol). The crude material contained a major diastereomer 247a other minor diastereomers in the ratio 40:1:1 (90% d.e.). The crude material was flash chromatographed (ether-CH$_2$Cl$_2$ 1:17) to yield a white solid (0.60 g, 72%), which was recrystallised from ethanol to give 247a (0.5g, 59%), (96% d.e); m.p. 177°C, (Found; C, 80.4; H, 7.4; N, 5.7. C$_{33}$H$_{36}$N$_2$O$_2$ requires C, 80.5; H, 7.4; N, 5.7%); ν_{max}/cm^{-1} (KBr) 3304 (OH), 1611 (C=O and Ph C=C). A COSY and an XHCORD experiment were used to help assign the NMR spectra. \^1H NMR (CDCl$_3$): δ 0.99 (3H, d, J 6.8,CH$_3$CH), 1.98 (3H, s, \textit{NCH}$_3$), 2.66 (3H, s, \textit{NCH}$_3$), 3.69 (2H, m, PhCHH and CHCO), 3.98 (1H, d, J 14.5, PhCHH), 4.22 (1H, q, J 6.8, CH$_3$CH), 4.29 (1H, dd, J 9.4, 2, CHOH), 4.68 (1H, d, J 11.3, NCHCH), 5.38 (1H, d, J 9.4, OH), 7.0-7.5 (20H, m, 4x Ph); \^13C NMR (CDCl$_3$): δ 15.67 (CH$_3$), 35.01 (NCH$_3$), 36.63 (NCH$_3$), 49.56 (CHCO), 51.25 (CH$_2$), 55.27 (CH$_3$CH), 61.42 (NCHCH), 71.72 (CHOH), 124.89, 126.42, 126.94, 127.00, 127.47, 127.66, 127.71, 127.997, 128.24, 128.61, 128.64, 129.71, 138.38, 139.29, 143.79, 143.96 (4x Ph), 172.59 (C=O).

Preparation of 248

The general method was followed using α,β-unsaturated amide 225 (0.37 g, 2.37 mmol). The crude material contained a mixture of two major diastereomers plus another diastereomer (2:2:1); (Combined yield 70%). These diastereomers were partially separated on a silica column and although no fractions contained a single diastereomer it was possible to generally assign the spectra of each. Major diastereomer 1: ν_{max}/cm^{-1} (film) 3366 (OH), 1603 (C=O);
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\[ ^1H\text{ NMR (CDCl}_3\text{): } \delta 1.41 (3H, d, J 6.8 CH}_3\text{), 1.44 (3H, d, J 6.9 CH}_3\text{), 1.90-3.90 (12H, m, CHCO, 8x ring protons, PhCH}_2\text{, CH}_2\text{CHCH}) , 3.98 (1H, q, J 6.8, PhCHCH}_3\text{), 4.93 (1H, dd, J 9.8, 2.0, CHOH), 5.50 (1H, d, J 9.9, OH), 6.9-7.4 (15H, m, 3x Ph); ^13\text{C NMR (CDCl}_3\text{): } \delta 14.46 (CH}_3\text{), 15.52 (CH}_3\text{), 41.49 (CH}_2\text{), 45.79 (CH}_2\text{), 50.26 (CH}_2\text{), 51.39 (CH), 52.63 (CH), 56.48 (CH), 65.54 (CH), 66.02 (CH), 73.03 (CHOH), 125-130 (aromatic region; signals overlapping), 139.88, 143.79, 143.94, (3x Ph), 171.97 (C=O)\]

\text{**Major diastereomer 2:** } v_{\text{max}}/\text{cm}^{-1} (film) 3366 (OH), 1602 (C=O); ^1H\text{ NMR (CDCl}_3\text{): } \delta 0.85 (3H, d, J 6.8 CH}_3\text{), 1.64 (3H, d, J 6.9 CH}_3\text{), 2.1-3.6 (10H, m, 7x ring protons, CHCO, PhCH}_2\text{), 3.90 (1H, m, CH}_3\text{CHCH) 4.05 (1H, m, lx ring proton), 4.20 (1H, q, J 6.9, CH}_3\text{CH), 5.20 (1H, d, J 9.9, OH), 5.35 (1H, dd, J 9.0, 1.9, CHOH), 6.8-7.4 (15H, m, 3x Ph); ^13\text{C NMR (CDCl}_3\text{): } \delta 13.92 (CH}_3\text{), 20.28 (CH}_3\text{), 41.27 (CH}_2\text{), 45.79 (CH}_2\text{), 48.43 (CH}_2\text{), 51.47 (CH), 55.29 (CH), 56.23 (CH), 65.76 (CH), 66.19 (CH), 70.80 (CHOH), 125-130 (aromatic region; signals overlapping), 142.19, 143.22, 144.17, (3x Ph), 172.83 (C=O).\]

\text{**Minor diastereomer:** } v_{\text{max}}/\text{cm}^{-1} (film) 3366 (OH), 1603 (C=O); ^1H\text{ NMR (CDCl}_3\text{): } \delta 1.45 (3H, d, J 6.8 CH}_3\text{), 1.64 (3H, d, J 6.9 CH}_3\text{), 2.1-3.6 (11H, m, 7x ring protons, CHCO, PhCH}_2\text{, CH}_3\text{CHCH) 4.30 (1H, m, lx ring proton), 4.40 (1H, q, J 6.9, CH}_3\text{CH), 5.20 (1H, d, J 9.9, CHOH), 5.20 (1H, bs, OH), 6.8-7.4 (15H, m, 3x Ph); ^13\text{C NMR (CDCl}_3\text{): } \delta 11.16 (CH}_3\text{), 15.28 (CH}_3\text{), 41.71 (CH}_2\text{), 45.95 (CH}_2\text{), 50.72 (CH}_2\text{), 53.19 (CH), 56.14 (CH), 57.31 (CH), 66.17 (CH), 66.47 (CH), 73.84 (CHOH), 125-130 (aromatic region; signals overlapping), 140.66, 142.83, 144.02, (3x Ph), 170.30 (C=O).\]

\text{Preparation of 249}

The general method was followed using α,β-unsaturated amide 227 (0.20 g, 1.80 mmol). A 12:4:1 mixture of diastereomers was produced. The material was subjected to flash chromatography (ether) (64 %). The material was recrystallised from ethanol to give 249a (0.41g, 52%), m.p. 120°C: (Found; C, 78.4; H, 8.3; N, 6.3. C\text{\textsubscript{9}}H\text{\textsubscript{16}}NO\text{\textsubscript{2}} requires C, 78.3; H, 8.2; N, 6.3%); v_{\text{max}}/\text{cm}^{-1} (nujol) 3330 (C=O), 1606 (C=O); ^1H\text{ NMR (CDCl}_3\text{): } \delta 1.45 (3H, d, J 6.8 CH}_3\text{), 1.64 (3H, d, J 6.9 CH}_3\text{), 2.1-3.6 (11H, m, 7x ring protons, CHCO, PhCH}_2\text{, CH}_3\text{CHCH) 4.30 (1H, m, lx ring proton), 4.40 (1H, q, J 6.9, CH}_3\text{CH), 5.20 (1H, d, J 9.9, CHOH), 5.20 (1H, bs, OH), 6.8-7.4 (15H, m, 3x Ph); ^13\text{C NMR (CDCl}_3\text{): } \delta 11.16 (CH}_3\text{), 15.28 (CH}_3\text{), 41.71 (CH}_2\text{), 45.95 (CH}_2\text{), 50.72 (CH}_2\text{), 53.19 (CH), 56.14 (CH), 57.31 (CH), 66.17 (CH), 66.47 (CH), 73.84 (CHOH), 125-130 (aromatic region; signals overlapping), 140.66, 142.83, 144.02, (3x Ph), 170.30 (C=O).\]

\text{249b (80 mg, 10%) v}_{\text{max}}/\text{cm}^{-1} (nujol) 3328 (OH), 1603 (C=O); ^1H\text{ NMR (CDCl}_3\text{): } \delta 0.68 (3H, t, J 7.4 CH}_3\text{CH}_2\text{), 1.67 (3H, d, J 6.9 CH}_3\text{CH)_1, 1.0-1.3 (2H, m, CH}_3\text{CH}_2\text{), 2.02 (3H, s, NCH}_3\text{), 2.55 (3H, s, NCH}_3\text{), 2.58 (1H, dd, J 9.3, 2.2, CHCO), 3.70 (1H, m, CHN), 3.83 (1H, d, J 14.0, PhCHH), 4.20 (1H, d, J 14.0, PhCHH), 4.30 (1H, q, J 6.9, CH}_3\text{CH}, 5.10 (1H, m, CHOH), 5.46 (1H, m, CHOH), 7.20 (CH_3CH), 7.30 (CH_3CH), 7.40-7.80 (15H, m, 3x Ph); ^13\text{C NMR (CDCl}_3\text{): } \delta 12.81 (CH}_3\text{CH}_2\text{), 17.39 (CH}_3\text{CH), 23.11 (CH}_3\text{CH}_2\text{), 34.86 (NCH}_3\text{), 36.50 (NCH}_3\text{), 50.79 (PhCH}_2\text{), 51.45 (CHCO), 58.49 (CH}_3\text{CH), 58.85 (CHN), 72.02 (CHOH), 125.06, 126.54, 126.85, 127.69, 127.86, 127.93, 128.04, 128.29, 129.16, 140.90, 143.85, 144.44 (3x Ph), 173.54 (C=O).\]
d, J 9, OH), 7.0-7.4 (15H, m, 3x Ph); 13C NMR (CDCl3): δ 12.20 (CH3CH2), 21.94 (CH3CH), 23.40 (CH3CH2), 34.66 (NCH3), 36.77 (NCH3), 49.14 (PhCH2), 51.79 (CHCO), 60.36 (CHN), 63.21 (CH3CH), 71.06 (CHOH), 124.79, 125.24, 126.71, 127.53, 127.66, 127.83, 128.24, 128.51, 129.62, 142.50, 144.09, 146.41 (3x Ph), 175.04 (C=O).

5.4.9 General procedure for the Michael addition of 30a to α,β-unsaturated amides, followed by reaction with acetaldehyde

As normal, this reaction was carried out under nitrogen. (R)-(+-)-N-(1-phenylethyl)benzylamine (0.50 g, 2.37 mmol, 1.3 mol. eq.) in THF (5.00 ml) was treated at 0°C with BuLi (1.6M, 1.50 ml, 2.37 mmol, 1.3 eq). The bright reddish pink solution was held at 0°C for 15 minutes and then the temperature was lowered to -78°C. The α,β-unsaturated amide (1.83 mmol, 1 eq) in THF (5.00 ml) was added via a cannula. Immediately the solution turned a pale orange colour. Stirring was continued for 15 minutes during which time the red colour reappeared. Acetaldehyde (0.25 ml, 4.7 mmol) was added and the mixture was stirred for a further 15 minutes. A saturated solution of ammonium chloride (2ml) was added and the reaction mixture was warmed up to r.t.. After separating the THF layer and washing it with brine (5 ml), the aqueous layer was extracted with CH2Cl2 (2x 15 ml), this organic phase was washed with brine. The combined organic layer was dried over MgSO4, filtered and evaporated to leave the crude product.

Preparation of 250

The general method was followed using α,β-unsaturated amide 203 (0.37 g, 1.71 mmol). The 1H NMR spectrum of the crude material showed several self condensation products of acetaldehyde, which made determination of the d.e. difficult. 1H and 13C NMR results taken together indicated that there was a mixture of one major diastereomer 250a and other minor diastereomers in the ratio 35:1:1 (89% d.e.). White crystals were precipitated out from the crude material by the addition of ether, filtered and washed with ether to give 250a (0.55 g, 68 %); (Found; C, 76.1; H, 7.7; N, 5.9. C30H36N2O3 requires C, 76.2; H, 7.7; N, 5.9%). This solid was recrystallised from ethyl acetate to give 250a (0.41 g, 51%), (98% d.e), m.p. 172.5-173°C; νmax/cm-1 (KBr) 3299 (OH), 1603 (C=O). The NMR spectra were assigned using information from an XHCORRD and a COSY spectrum. 1H NMR (CDCl3): δ 0.94 (3H, d, J 6.8, CH3NCH), 1.00 (3H, d, J 6.5 CH3CHOH), 2.95 (1H, m, CHHN-ring), 3.05 (1H, m, CHHN-ring), 3.2-3.7 (8H, m, CHOH, CHCO, CH2OCH2-ring, CHHN-ring, PhCHH), 3.96 (1H, d, J 14.7, PhCHH), 4.08 (1H, d, J 10.2, OH), 4.21 (2H, m, CH3CHN and CHHN-ring), 4.61 (1H, d, J 11, NCHCH), 7.19-7.45 (15H, m); 13C NMR (CDCl3): δ 15.80 (CH3CHN), 23.05 (CH3CHOH), 41.80 (CH2N-ring), 46.48 (CH2N-ring), 47.05 (CHCO), 51.20 (CH2),
55.09 (CH$_3$CHN), 61.21 (N(CHCH), 65.69 (CHOH), 66.28 (OCH$_2$-ring), 66.76 (OCH$_2$-ring), 126.42, 127.00, 127.37, 127.51, 127.91, 128.31, 128.42, 128.46, 129.03, 138.55, 139.11, 143.86 (3x Ph), 172.19 (C=O).

Preparation of 251

The general method was followed using $\alpha,\beta$-unsaturated amide 222 (0.20 g, 0.61 mmol). The $^1$H NMR spectrum of the crude material showed several self condensation products of acetaldehyde, which made determination of the d.e. difficult. $^1$H and $^{13}$C NMR results taken together indicated that there was a mixture of one major diastereomer 251a and other minor diastereomers in the ratio 11:2:1 (60% d.e.). The bright orange oil was flash chromatographed (ether-CHCl$_3$ 1:19) to yield a yellow oil (0.25 g, 71%) which contained a mixture of 251a (80% d.e.) contaminated with other diastereomers and unknown products.

251a: $\nu_{\text{max/ cm}}^{-1}$ (film) 3410 (OH), 1614 (C=O); $^1$H NMR (CDCl$_3$): $\delta$ 0.86 (3H, d, $J$ 6.8, CH$_3$CHN), 0.91 (3H, d, $J$ 6.8, CH$_3$CHOH), 3.3-3.5 (2H, m, CHCO and CHOH), 3.67 (1H, d, $J$ 14.6 PhCHHNCH), 3.89 (1H, d, $J$ 16.7, PhCHHNCO), 3.98 (1H, d, $J$ 14.6, PhCHHNCH), 4.22 (1H, q, $J$ 6.8, CH$_3$CHN), 4.44 (1H, d, $J$ 9.2, OH), 4.46 (1H, d, $J$ 14.7, PhCHHNCO), 4.51 (1H, d, $J$ 16.5, PhCHHNCO), 4.69 (1H, d, $J$ 10.7, NCHCHCO), 4.81 (1H, d, $J$ 14.7, PhCHHNCO), 6.9-7.5 (25H, m, 5x Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 16.09 (CH$_3$CHN), 23.01 (CH$_3$CHOH), 48.44 (CHCO), 49.02 (PhCH$_2$NCO), 50.66 (PhCH$_2$NCO), 51.79 (PhCH$_2$NCH), 56.42 (CH$_3$CHN), 62.56 (PhCHCH), 66.73 (CHOH), 126.42, 126.79, 127.29, 127.49, 127.62, 127.73, 127.79, 128.06, 128.10, 128.26, 128.41, 128.55, 128.62, 129.34, 129.89, 135.86, 137.14, 138.32, 139.31, 143.75, 175.29; m/z (FAB; thioglycerol) 584 (M+2$^+$, 80%), 196 (N(CH$_2$Ph)$_2$+, 100%), 105 (NCH$_2$Ph$^+$, 100%).

Preparation of 252

The general method was followed using $\alpha,\beta$-unsaturated amide 223 (0.32 g, 1.50 mmol). The $^1$H NMR spectrum of the crude material showed several self condensation products of acetaldehyde, which made determination of the d.e. difficult. $^1$H and $^{13}$C NMR results taken together indicated that there was a mixture of one major diastereomer 252a and other minor diastereomers in the ratio 25:1:1 (85% d.e.). The crude oil was subjected to column chromatography (ether-CH$_2$Cl$_2$ 1:9). An off white solid was produced which was washed with several portions of hexane (0.44 g, 63%), (Found; C, 79.1; H, 8.2; N, 6.0. C$_{31}$H$_{38}$N$_2$O$_2$ requires C, 79.1; H, 8.1; N, 6.0%). The white solid was recrystallised from ethyl acetate to give 252a (0.40 g, 57%) (98% d.e.; m.p. 206 °C; $\nu_{\text{max/cm}}^{-1}$ (KBr) 3278 (OH), 1598 (C=O and Ph C=C). The NMR spectra were assigned using information from an XHCORRD and a COSY spectrum. $^1$H NMR (CDCl$_3$): $\delta$ 0.93 (3H, d, $J$ 6.8, CH$_3$CHN), 1.01 (3H, d, $J$ 6.4, CH$_3$CHOH), 1.2-1.8 (6H, m, 3x CH$_2$-ring), 2.55 (2H, m, CH$_2$-ring), 3.27 (1H, m, $J$ 6.8,
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CH(OH), 3.48 (1H, dd, J 9.3, 1.8, CHCO), 3.69 (1H, d, J 14.7, PhCHH), 3.77 (1H, m, CHHN-ring), 3.97 (1H, d, J 14.7, PhCHH), 4.19 (1H, q, J 6.8, CH$_3$CN), 4.42 (1H, d, J 10, OH), 4.53 (1H, m, CHHN-ring), 4.60 (1H, d, J 11.1, NCHCH), 7.0-7.5 (15H, m, 3x Ph); $^{13}$C NMR (CDCl$_3$): δ 15.54 (CH$_3$CHN), 23.22 (CH$_3$CHOH), 24.34 (NCH$_2$CH$_2$CH$_2$-ring), 25.60 (NCH$_2$CH$_2$-ring), 26.43 (NCH$_2$CH$_2$-ring), 42.57 (NCH$_2$-ring), 46.82 (CHCO), 47.03 (NCH$_2$-ring), 51.20 (CH$_2$), 55.23 (CH$_3$CHN), 61.32 (PhCHCH), 65.64 (CHOH), 126.29, 126.81, 127.33, 127.50, 127.72, 128.19, 128.32, 128.49, 129.05, 138.99, 139.37, 144.10 (3x Ph), 171.72 (C=O).

Preparation of 253

The general method was followed using $\alpha,\beta$-unsaturated amide 224 (0.30 g, 1.71 mmol). The $^1$H NMR spectrum of the crude material showed several self condensation products of acetaldehyde, which made determination of the d.e. difficult. $^1$H and $^{13}$C NMR results taken together indicated that there was a mixture of one major diastereomer 253a and other minor diastereomers in the ratio 50:1:1 (92% d.e.). The bright orange oil was subjected to flash chromatography (ether-CH$_2$Cl$_2$ 1:4) A yellow solid was produced which was washed with hexane (0.50 g, 68%), (Found; C, 78.1; H, 8.1; N, 6.5. C$_{28}$H$_{34}$N$_2$O$_2$ requires C, 78.1; H, 8.0; N, 6.5%). The solid was recrystallised from ethanol to give 253a (0.39 g, 50%), (98% d.e), m.p. 145.5-149.5°C; $\nu$ max/cm$^{-1}$ (KBr) 3370 (OH), 1614 (C=O). The NMR spectra were assigned using information from an XHCORRD and a COSY spectrum. $^1$H NMR (CDCl$_3$): δ 0.97 (3H, d, J 6.8, CH$_3$), 0.975 (3H, d, J 6.8, CH$_3$), 2.77 (3H, s, NCH$_3$), 2.93 (3H, s, NCH$_3$), 3.28 (1H, J 10, 11.3, 2, CCH), 3.48 (1H, dd, J 11.3, 2.2, CHCO), 3.67 (1H, d, J 14.7, PhCHH), 3.98 (1H, d, J 14.7, PhCHH), 4.25 (1H, q, J 6.8, CH$_3$CHN), 4.25 (1H, d, J 10, OH), 4.60 (1H, d, J 11.3, NCHCH), 7.1-7.5 (15H, m, 3x Ph); $^{13}$C NMR (CDCl$_3$): δ 13.65, 14.32, 14.48, 20.26, 21.73, 23.20 (CH$_3$), 13.65, 14.32, 14.48, 20.26, 21.73, 23.20 (CH$_3$),

Preparation of 254

The general method was followed using $\alpha,\beta$-unsaturated amide 225 (0.18 g, 1.18 mmol). The $^1$H NMR spectrum of the crude material showed several self condensation products of acetaldehyde, which made determination of the d.e. difficult. $^1$H and $^{13}$C NMR results taken together indicated that there was a mixture of two major diastereomers and other minor diastereomers in the ratio 1:1 plus other minor diastereomers. Major diastereomers: $\nu$ max/cm$^{-1}$ (film) 3419 (OH), 1615-1622 (C=O); $^1$H NMR (CDCl$_3$): δ 0.8-1.6 (6x 3H, d, 3x CH$_3$ for each diastereomer), 2.05 and 2.45 (2x 1H, dd, CHCO, for each diastereomer), 2.5-3.9 (complex overlapping signals), 3.95 and 4.10 (2x 1H, q, CH$_3$CHN for each diastereomer), 7.1-7.6 (aromatic region); $^{13}$C NMR (CDCl$_3$): δ 13.65, 14.32, 14.48, 20.26, 21.73, 23.20 (CH$_3$),
40.27x2, 41.55, 41.65, 48.52, 50.38, 66.28, 66.40, 66.50, 66.68 (CH₂), 49.03, 50.09, 52.28, 54.84, 56.32, 63.14, 65.10, 65.95 (CH), 126-129, 140.2, 141.9, 143.9, 144.1 (aromatic region), 173.0, 173.7 (C=O).

Preparation of 255
The general method was followed using α,β-unsaturated amide 227 (0.20 g, 1.80 mmol). The ¹H NMR spectrum of the crude material showed several self condensation products of acetaldehyde, which made determination of the d.e. difficult. ¹H and ¹³C NMR results taken together indicated that there was a mixture of two major diastereomers 255a and 255b and other minor diastereomers in the ratio 4:3 (Total 55%), (Found; C, 75.6; H, 8.8; N, 7.2. C₂₄H₃₄N₂O₂ requires C, 75.3; H, 9.0; N, 7.3%). Major diastereomers: νmax/cm⁻¹ (film) 3367, 1614 (C=O); ¹H NMR (CDCl₃): δ 0.65 (3H, t, J 7.4, CH₂CH₃), 0.80 (3H, d, J 6.6, CH₃CHN), 0.97 (3H, t, J 7.4, CH₂CH₂), 1.05 (3H, d, J 6.6, CH₃CHN), 1.35 (3H, d, J 6.8, CH₃CHOH), 1.59 (3H, d, J 6.8, CH₃COH), 1.1-1.8 (m, CH₃CH₂ for each diastereomer), 2.12 (1H, dd, J 10.0, 1.7, CHCO), 2.51 (3H, s, NCH₃), 2.55 (3H, s, NCH₃), 2.65 (1H, dd, J 10.0, 2.0), 2.85 (3H, s, NCH₃), 2.90 (3H, s, NCH₃), 3.0 (1H, m, OCHOH), 3.50 (1H, m, CH₂CH₂), 3.66 (1H, d, J 14.5, PhCH₃), 3.93 (2H, s, PhCH₂), 4.00 (2H, m, CH₃CH₂CH and CH₃CN), 4.12 (1H, d, J 14.5, PhCHH), 4.20 (1H, q, CH₃CHN), 4.30 (1H, m, CH₃CH₂CH), 4.60 (1H, d, J 9.8, OH), 4.66 (1H, d, J 9.8, OH), 7.2-7.4 (4x Ph); ¹³C NMR (CDCl₃): δ 12.15, 12.76, 17.13, 21.62, 21.71, 22.66 (CH₃), 22.71, 23.36 (CH₂), 34.82, 34.98, 37.20, 37.35 (NCH₃), 49.11, 50.61 (CH₂), 49.47, 49.62 (CH), 58.33, 58.81, 60.05, 63.07, 65.30, 65.94 (CH), 126.36, 126.47, 127.34, 127.60, 127.73, 127.81, 127.86, 127.90, 128.03, 128.07, 128.23, 128.72, 141.08, 142.26, 144.52, 146.18 (Ph), 174.55, 175.92 (C=O).

5.4.10 Effect of temperature on the Michael addition of 30a to 224
(R)-(+)-N-(1-phenylethyl)benzylamine (0.50 g, 2.37 mmol, 1.5 mol. eq.) in THF (5.00 ml) was treated at 0°C with BuLi (1.6M, 1.50 ml, 2.37 mmol, 1.5 eq). The bright reddish pink solution was held at 0°C for 15 minutes. The flask was cooled to the required temperature (-120°C; -78°C; -45°C; 0°C, r.t. See Table 4.23). The α,β-unsaturated amide (1.83 mmol, 1 eq) in THF (5.00 ml) was added via a cannula. Immediately the solution turned a pale orange colour. Stirring was continued for 15 minutes and the pink colour reappeared. The mixture was quenched at -78°C with a saturated solution of ammonium chloride (2ml). After separating the THF layer and washing it with brine (5 ml), the aqueous layer was extracted with CH₂Cl₂ (2x 15 ml), and then was washed with brine (5 ml). The combined organic layer was dried over MgSO₄, filtered and evaporated to give the crude product. The results are given in Table 4.3.2). At -45°C and below, only 230a and 230b were isolated (analytical data given in section 5.4.6). At 0°C and above, 259 was also isolated. This was purified by flash
chromatography (ether). Two isomers (differing configuration around the double bond) in the ratio of 259 were seen (4:1); m/z (FAB; MNOBA) 351 (M+1+, 100%), 306 (M-N(CH$_3$)$_2$+).

**Major isomer:** 1H NMR (CDCl$_3$): δ 1.95 (3H, s, NCH$_3$), 2.68 (3H, s, NCH$_3$), 2.87 (1H, dd, J , 12.2, 7.8, CHHCO), 2.89 (3H, s, NCH$_3$), 3.16 (3H, s, NCH$_3$), 3.56 (1H, dd, J 12.2, 8.2, CHHCO), 4.39 (1H, distorted dd, J 7.8, 8.2, PhCH), 6.63 (1H, CH=), 7.1-7.4 (10H, m, 2x Ph); 13C NMR (CDCl$_3$): δ 33.73 (CH$_3$), 35.52 (CH$_3$), 36.49 (CH$_3$), 37.50 (CH$_3$), 37.64 (CH$_3$), 49.94 (CH), 126.86 (CH=), 127.3, 127.98, 127.75, 127.80, 128.25, 128.28, 135.79, 137.85 (2x Ph), 140.66 (-C=), 169.93 (C=O), 171.33 (C=O).

**Minor isomer:** 1H NMR (CDCl$_3$): δ 2.46 (3H, s, NCH$_3$), 2.82 (3H, s, NCH$_3$), 2.84 (1H, m CHHCO), 2.98 (3H, s, NCH$_3$), 3.16 (3H, s, NCH$_3$), 3.48 (1H, m, PhCH), 4.39 (1H, m, PhCH), 6.28 (1H, CH=), 7.1-7.4 (10H, m, 2x Ph); 13C NMR (CDCl$_3$): δ 34.20 (CH$_3$), 35.44 (CH$_3$), 36.96 (CH$_2$), 37.17 (CH$_3$), 45.83 (CH), 126.70 (CH=), 127 - 128 (aromatic region; signals obscured by other isomer), 135.70 , 139.44 (2x Ph), 142.07 (-C=), 170.73 (C=O), 171.33 (C=O).

5.4.11 **HYDROGENOLYSIS OF 244: PREPARATION OF 260, 261 AND 262**

**With Pd/C**

A glass pressure vessel was charged with 244 (50.0 mg, 0.08 mmol), glacial acetic acid (40 ml) and catalyst [5% Pd/C] (0.15 g). The mixture was shaken in a Parr Hydrogenator for 4 h at 65-70 psi. The catalyst was removed by filtration through Celite and the acetic acid was evaporated off, leaving a brown oil. This was treated with saturated NaHCO$_3$ (20 ml) and the product was extracted into CH$_2$Cl$_2$ (3x 20 ml). The combined organic layer was washed with brine (10 ml), dried over MgSO$_4$, filtered and evaporated. 1H NMR indicated the presence of two products in the ratio ca. 1:1 which were separated by preparative chromatography on silica (ether-CH$_2$Cl$_2$ 1:1). 260: (R$_f$0.43); 1H NMR (CDCl$_3$): δ 1.27 (3H, d, J 6.5, CH$_3$), 2.90 (2H, m, ring), 3.0 (1H, m, ring), 3.15 (1H, dd, J 10.1, 3.2, PhCHCH), 3.15-3.5 (5H, m, ring), 3.55 (1H, q, J 6.5, CH$_3$CH), 4.43 (1H, d, J 10.1, CHNH$_2$), 4.84 (1H, d, J 3.2, CHOH), 7.2-7.4 (15H, m, 3x Ph), -OH and -NH protons were not assigned. 261: (R$_f$ 0.30); 1H NMR (CDCl$_3$): δ 2.5-2.7 (2H, m, ring), 2.83 (1H, m, ring), 3.00 (1H, m, ring), 3.15 (1H, dd, J 10.1, 2.8, PhCHCH), 3.23 (1H, m, ring), 3.3-3.5 (m, ring), 3.52 (1H, d, J 13.0, PhCH), 3.71 (1H, d, J 13.0, PhCHH), 4.10 (1H, d, J 10.1, CHNH$_2$), 4.80 (1H, d, J 2.8, CHOH), 7.2-7.4 (15H, m, 3x Ph), -OH and -NH protons are not assigned; m/z (FAB; thioglycerol), 341 (M+1+, 20%), 114 (NC$_3$H$_8$O$_2^+$, 80%), 131 (100%).

The experiment was repeated using longer reaction times. After 8 h, 1H NMR indicated 45% of the fully debenzylated material (262); after 24 h all the material had been fully debenzylated
giving 262 as a brown oil (84%). (Found; C, 69.8; H, 7.7; N, 8.2. C_{19}H_{24}N_{2}O_{3} requires C, 69.5; H, 7.4; N, 8.5%). The NMR spectra were assigned with the help of a COSY and an XHCONRD experiment. ^{1}H NMR (CDCl₃): δ 2.50 (1H, m, CHHO-ring), 2.85 (1H, m, CHHN-ring), 3.35 (6H, m, CHHO-ring x2, CHHO-ring x3 and PhCHCH), 3.60 (1H, m, CHHN-ring), 4.48 (1H, d, J 8.1, CHNH₂), 4.64 (1H, d, J 3.3, CHOH), 7.1-7.6 (10H, m, Ph x2); ^{13}C NMR (CDCl₃): δ 41.60 (CH₁N-ring), 46.13 (CH₂N-ring), 54.41 (PhCHCH), 56.41 (CHNH₂), 65.68 (CH₂O-ring), 66.14 (CH₂O-ring), 72.84 (CHOH), 125.13, 126.58, 127.16, 127.52, 128.09, 128.51, 143.01, 143.27 (Ph x2), 171.57 (C=O).

With Pd(OH)₂/C

A glass pressure vessel was charged with 244 (0.50 g, 0.94 mmol), glacial acetic acid (20 ml) and catalyst [10% Pd(OH)₂/C] (0.10 g, 20 % by weight). The mixture was shaken in a Parr Hydrogenator for 15 h at 50 psi. The catalyst was removed by filtration through Celite and the acetic acid was evaporated off, leaving a brown oil. This was treated with saturated NaHCO₃ solution (20 ml) and the product was extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine (10 ml), dried over MgSO₄, filtered and evaporated. 262 was isolated as a brown oil (82%). Analytical data as above.

With Pd(OH)₂/C in the presence of ultrasound

A 50 ml rbf was charged with 244 (0.20 g, 0.37 mmol), acetic acid (20 ml) and catalyst [5% Pd/C] (0.05 g). The flask was fitted with a three-way tap and a balloon containing hydrogen was fitted to one arm. The flask was evacuated via a water aspirator the filled with hydrogen. This was repeated three times to remove all the oxygen. The flask was then placed in an ultrasound bath for 7 h. The bath was initially at 20°C, but reached approximately 50°C over 7h. The catalyst was removed by filtration through Celite and the acetic acid was evaporated off, leaving a brown oil. This was treated with saturated NaHCO₃ solution (20 ml) and the product was extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine (10 ml) and dried over MgSO₄. After filtration, the solvent was removed in vacuo, leaving an orange oil which was subjected to flash chromatography on silica (ether-ethanol 1:1). An orange oil of 262 (0.11 g, 82%) was obtained. Analytical data as above.
5.4.12 HYDROGENOLYSIS OF 245: PREPARATION OF 263

With Pd/C.

β-Amino-amide 245 (0.20 g, 0.32 mmol), catalyst [5% Pd/C] (0.030 g) and glacial acetic acid (20 ml) were shaken in the Parr hydrogenator for 15 h at 50 psi hydrogen. The work-up described in section 5.4.10 was followed. 263 was produced as a brown oil, contaminated with 15% of unknown material. The crude product was subjected to flash chromatography on silica (ether-hexane 1:1 followed by methanol) but the impurity was not removed. Hydrochloric acid (2M, 10 ml) was added and the resultant oil was washed with ether (2x 10 ml), then basified with a saturated solution of NaHCO₃ (20 ml) and extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine (10 ml) and dried over MgSO₄. After filtration, the solvent was removed in vacuo to give 263 (90% pure): m/z (FAB; thioglycerol), 451 (M+1+, 20%), 91 (C₇H₇+, 100%); νmax/cm⁻¹ (film) 3360 (OH), 1622 (C=O);¹H NMR (CDCl₃): δ 3.22 (1H, dd, J 8.3, 2.7, CHCO), 3.78 (1H, d, J 17.0, PhCHH), 4.00 (1H, d, J 17.0, PhCHH), 4.37 (1H, d, J 16.5, PhCHH), 4.45 (1H, d, J 16.5, PhCHH), 4.63 (1H, d, J 8.3, CHN), 4.82 (1H, d, J 2.7, CHO), 7.1-7.5 (20H, m, 4x Ph); ¹³C NMR (CDCl₃): δ 47.90 (NCH₂Ph), 49.65 (NCH₂Ph), 55.14 (PhCHCH), 57.88 (CHNH₂), 75.74 (CHOH), 125-135 [signals overlapping], 135.44, 143.14, 143.93 (Ph x4), 174.23 (C=O).

With Pd(OH)₂/C in the presence of ultrasound.

β-Amino-amide 245 (0.20 g, 0.37 mmol), glacial acetic acid (20 ml) and Pd/C (0.03 g) were placed in a flask fitted with a hydrogen balloon. The reaction vessel was placed in an ultrasound cleaning bath for 7 h. After work-up (described in section 5.4.10) a brown oil was isolated and was identified as 263.

5.4.13 HYDROGENOLYSIS OF 247: PREPARATION OF 256

With Pd(OH)₂/C

β-Amino-amide 247 (3.60 g, 7.31 mmol), glacial acetic acid (40 ml) and catalyst [10% Pd(OH)₂/C] (0.47g, 13% by weight) were shaken in a Parr Hydrogenator for 20 h at 30 psi. Work-up (described in 5.4.10) gave a brown solid which was recrystallised from ether to give 256 (1.91 g, 87%), m.p. 129°C; (Found C, 72.6; H, 7.5; N, 9.2. C₁₈H₂₂N₂O₂ requires C, 72.5; H, 7.4; N, 9.4%); νmax/cm⁻¹ 3381, 3362, 3311 (NH₂ and OH), 1595 (C=O);¹H NMR (CDCl₃): δ 1.60 (3H, bs, NH₂ and OH), 2.42 (3H, s, CH₃), 2.80 (3H, s, CH₃), 3.18 (1H, dd, J 8.5, 2.4, CHCO), 4.45 (1H, d, J 2.4, CHO), 4.58 (1H, d, J 8.5, CHNH₂), 7.1-7.5 (10H, m, 2x Ph); ¹³C NMR (CDCl₃): δ 34.94 (CH₃), 37.00 (CH₃), 55.22 (CHCO), 56.43 (CHNH₂),
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With Pd(OH)$_2$/C in the presence of ultrasound

β-Amino-amide 247 (1.20 g, 2.44 mmol), glacial acetic acid (30 ml) and catalyst [10% Pd(OH)$_2$/C] (0.11 g) were added to a flask which was fitted with three way tap and a hydrogen balloon. The flask was evacuated and filled with hydrogen and then placed in an ultrasound bath for 6 h. The work-up procedure described in 5.4.11 was used. A brown solid was isolated and was recrystallised from ether to give 265 as a white solid (0.61 g, 89%) m.p. 128-129°C, analytical data given previously.

5.4.14 Hydrogenolysis of 246; 253; 239 with Pd(OH)$_2$/C

Hydrogenolysis of 246; preparation of 264

β-Amino-amide 246 (0.80 g, 1.50 mmol), [10% Pd(OH)$_2$/C] (0.15 g, 20% by weight) in acetic acid (30 ml) was shaken in the Parr hydrogenator for 15 h, with 40 psi hydrogen. After work-up (described in 5.4.11) a brown oil was isolated which solidified on standing. Ether was added to dissolve the solid and then pentane was added to re-precipitate it. A white solid (264) was produced (0.39 g, 79%), m.p. 108-109°C, (Found C, 74.5; H, 7.8; N, 8.2. C$_{21}$H$_{26}$N$_2$O$_2$ requires C, 74.5; H, 7.8; N, 8.3%); $\nu_{\text{max}}$/cm$^{-1}$ 3347 (OH, NH$_2$), 1575 (C=O); $^1$H NMR (CDCl$_3$): δ 0.45 (1H, m, NCH$_3$/CH$_2$/H-ring), 1.15 (2H, m, NCH$_3$/CH$_2$/H-ring x 2), 1.40 (3H, m, NCH$_3$/CH$_2$/CH$_2$/ring and NCH$_3$/CH$_2$/H-ring), 3.00 (4H, NCH$_3$/H-ring x 3 and PhCH$_2$/CH), 3.76 (1H, m, NCH/H-ring), 4.52 (1H, d, J 2.5, CHO/H), 4.60 (1H, d, J 8.9, CHNH$_2$), 7.1-7.6 (10H, m, 2x Ph); $^{13}$C NMR (CDCl$_3$): δ 24.10 (NCH$_3$/CH), 25.35 (NCH$_2$/CH$_2$/ring), 25.55 (NCH$_2$/CH$_2$/ring), 42.64 (NCH$_2$/ring), 47.14 (NCH$_2$/ring), 54.69 (PhCH$_2$/CH), 56.95 (CHNH$_2$), 72.89 (CHO/H), 125.27, 126.98, 127.02, 127.68, 128.10, 128.68, 143.57 x2 (2x Ph), 171.66 (C=O); m/z (FAB; thioglycerol), 339 (M+1$^+$, 100%), 91 (C$_7$H$_7^+$)

Hydrogenolysis of 253; preparation of 265

β-Amino-amide 253 (0.80 g, 1.86 mmol) and Pd(OH)$_2$/C (0.10 g) in glacial acetic acid (20 ml) were shaken in the Parr hydrogenator for 20 h at 50 psi of hydrogen. After work-up (5.4.11) the resultant brown oil was subjected to flash chromatography (ether:ethanol 1:1) and gave 265 as a white 'oily' solid (0.30 g, 69%), m.p. 72°C, (Found C, 66.0; H, 8.5; N, 11.9. C$_{13}$H$_{20}$N$_2$O$_2$ requires C, 66.1; H, 8.5; N, 11.9%); $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3371 (OH, NH$_2$), 1614 (C=O); $^1$H NMR (CDCl$_3$): δ 1.08 (3H, d, J 6.4, CH$_3$/CH), 2.68, (3H, bs, OH and NH$_2$),
2.91 (1H, dd, J 8.4, 3.3, PhCHCH), 2.99, (3H, s, NCH₃), 3.07 (3H, s, NCH₃), 3.65 (1H, dq, J 3.3, 6.4, CH₃CH), 4.50 (1H, d, J 8.4, CHOH), 7.2-7.5 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 22.05 (CH₃CH), 35.35 (CH₃N), 37.94 (CH₃N), 53.61 (PhCHCH), 56.52 (PhCH), 66.85 (CHOH), 126.69, 127.42, 128.41, 143.45 (Ph), 174.296 (C=O); m/z (FAB; thioglycerol) 237 (M+1⁺, 100%), 176 (PhCHCHCON(CH₃)₂H⁺)

Hydrogenolysis of 239; preparation of 266
β-Amino-amide 239 (0.80 g, 1.99 mmol) and Pd(OH)₂/C (0.10 g) in glacial acetic acid (20 ml) were shaken in the Parr hydrogenator for 20 h at 40 psi of hydrogen. After work-up the resulting brown oil was distilled ca. 100°C/0.8 mmHg to give a colourless oil which solidified as a white solid 266 (0.37 g, 91%), m.p. 79°C, (Found C, 70.0; H, 9.0; N, 13.6. C₂₁H₁₈N₂O requires C, 69.9; H, 8.8; N, 13.6%); v max/cm⁻¹ (KBr) 3500, 3374, 3303 (OH, NH₂), 1638 (C=O); ¹H NMR (CDCl₃): δ 0.89 (3H, d, J 7.0, CH₃CH), 1.83 (2H, bs, NH₂), 2.90 (1H, dq, J 7.0, 9.0, PhCHCH), 2.97 (3H, s, CH₃), 3.02 (3H, s, CH₃), 4.14 (1H, d, PhCHCH, J 9.0), 7.2-7.4 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 15.03 (CH₃), 35.27 (NCH₃), 36.99 (NCH₃), 43.96 (CH₃CH), 59.18 (PhCHCH), 127.14, 128.11, 143.43 (Ph), 175.18 (C=O); m/z (FAB; thioglycerol) 207 (M+1⁺, 100%), 106 (PhCHNH₃⁺)

5.4.15 Attempted hydrogenolysis of 230; isolation of 267, 268, 269, 270
230 (0.18 g, 0.47 mmol) was dissolved in glacial acetic acid (20 ml) and placed in a heavy-walled pressure vessel. 10% Pd(OH)₂/C (10%, 0.02g) was added and the vessel was evacuated then filled with hydrogen. This was repeated 3 times to ensure all the oxygen had been removed. The mixture was shaken for 16 h under hydrogen gas (30 psi). The catalyst was removed by filtration through Celite and the product was concentrated in vacuo. The brown oil was treated with saturated NaHCO₃ solution (10 ml) and extracted into CH₂Cl₂ (2x 20 ml). The combined organic layer was washed with brine (10 ml), dried over MgSO₄, filtered and concentrated in vacuo to give a brown oil. The crude mixture contained four compounds which were identified by ¹³C NMR as compounds 267, 268, 269 and 270, in the ratio 2:2:1:1. 267: ¹³C NMR (CDCl₃): δ 21.4 (CH₃), 35.1 (NCH₃), 36.8 (NCH₃), 41.9 (CH₂), 52.4 (CH), 56.7 (CH), 126-145 (aromatic region), 171.0 (C=O). 268: ¹³C NMR (CDCl₃): δ 35.1 (CH₃), 36.8 (CH₃), 41.5 (CH₂), 51.46 (CH₂), 52.4 (CH), 126-145 (aromatic region), 170.0 (C=O). 269: ¹³C NMR (CDCl₃): δ 35.27 (CH₃), 36.99 (CH₃), 43.07 (CH₂), 52.51 (CH), 126.41, 127.26, 128.39, 144.89 (Ph), 171.24 (C=O). 270: ¹³C NMR (CDCl₃): δ 31.31 (CH₂CO), 35.27 (CH₃), 35.37 (PhCH₂), 37.09 (CH₃), 126.02, 128.23, 128.36, 141.43 (Ph), 171.24 (C=O).
The reaction was repeated using different reaction times and pressures. The conditions and results are summarised in Table 5.1

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Ratio of products$^a$ 267 : 268 : 269 : 270</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), 30 psi., 16 h</td>
<td>2 : 2 : 1 : 1</td>
</tr>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), 60 psi., 8 h</td>
<td>3 : 3 : 2 : 1</td>
</tr>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), 60 psi., 16 h</td>
<td>0 : 0 : 2.5 : 1</td>
</tr>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), 60 psi., 24 h</td>
<td>0 : 0 : 2 : 1</td>
</tr>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), 80 psi., 24 h</td>
<td>0 : 0 : 2 : 1</td>
</tr>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), 80 psi., 48 h</td>
<td>0 : 0 : 1 : 2</td>
</tr>
<tr>
<td>5% Pd(OH)$_2$/C/H$_2$(g), ultrasound, 10h</td>
<td>1 : 0 : 1 : 1</td>
</tr>
</tbody>
</table>

$^a$ The ratios are only approximate because they were calculated from the $^{13}$C NMR spectra of the crude mixtures.

Table 5.1: Attempted hydrogenolysis of 230; reaction conditions and ratio of products.

5.4.16 Attempted hydrogenolysis of 209; isolation of 271; 272; 273

$\beta$-Amino-amide 209 (0.447 g) and 5% Pd/C (0.10 g) were mixed in acetic acid (20 ml). The flask was fitted with a three way tap and a balloon containing hydrogen. The flask was evacuated and filled with hydrogen. The reaction mixture was placed in an ultra-sound bath for 8 h. After workup the brown oil was found to contain a mixture of 271 and 272 (ca. 3:1). When the reaction time was increased to 16 h a mixture of compounds 272 and 273 were isolated ca. 1:1. 271: $^{13}$C NMR (CDCl$_3$): δ 21.62 (CH$_3$), 40.92 (CH$_2$-ring), 41.67 (CH$_2$-ring), 45.87 (CH$_2$), 54.48 (CH), 57.24 (CH), 66.20 (CH$_2$-ring), 66.34 (CH$_2$-ring), 126-146 [aromatic region], 169.62 (C=O). 272: $^{13}$C NMR (CDCl$_3$): δ 31.39 (CH$_2$-ring), 34.72 (CH$_2$-ring), 41.84 (CH$_2$), 45.67 (CH$_2$), 66.37 (CH$_2$-ring), 66.75 (CH$_2$-ring), 125-141 [aromatic region], 169.62 (C=O). 273: $^{13}$C NMR (CDCl$_3$): δ 41.74 (CH$_2$-ring), 42.78 (CH$_2$-ring), 45.88 (CH$_2$), 54.47 (CH), 66.36 (CH$_2$-ring), 66.75 (CH$_2$-ring), 125-141 [aromatic region], 170.78 (C=O)

5.4.17 Reduction of 244; preparation of 278

Attempted reduction with LiAlH$_4$

A 50 ml rbf was fitted with a condenser and nitrogen bubbler. 244 (0.10 g, 0.197 mmol) was dissolved in dry THF (5 ml) and nitrogen was blown slowly over the reaction. The flask was
placed in an ice-bath and LiAlH$_4$ (0.036 g, 0.95 mmol) was added. After 15 minutes, TLC (silica, CH$_2$Cl$_2$; ether 25:1) indicated that no reaction had occurred. The mixture was then stirred at r.t. for 3 h. Again no reaction was observed. The mixture was then refluxed for 30 minutes. Several new spots were seen in the TLC and $^{13}$C NMR showed the presence of several compounds. These were not identified.

**Reduction with DIBAH**

244 (0.69 g, 1.29 mmol) was placed in a flask which was fitted with a three-way tap. A balloon containing nitrogen was attached to one arm and the other arm was attached to a vacuum pump. The flask was evacuated and filled with nitrogen 3 times to ensure all the air had been removed. Toluene (30 ml) was added via a syringe and the mixture was cooled in an ice-bath. DIBAH (1.0M in toluene, 6.45 ml, 6.54 mmol) was added. The solution was stirred for 15 h over which time the temperature rose to r.t. A small sample was removed. The $^1$H NMR spectrum indicated that only 50% had reacted so DIBAH (4 ml, 4.0 mmol) was added. Full reduction then occurred within 1 h. Methanol (2 ml) was added to quench the reaction, followed by water (5 ml). A white gelatinous precipitate formed and was removed by filtration through a sinter-glass funnel. The precipitate was washed well with toluene. The toluene layer was set to one side and the aqueous layer was extracted into toluene (2 x 20 ml). The combined organic layer was washed with brine (10 ml); dried over MgSO$_4$, filtered and concentrated *in vacuo* to give a colourless oil. This was purified by flash chromatography, (CH$_2$Cl$_2$-ether 25:1) to give a colourless glassy oil (278) (0.62 g, 92%); $\nu_{max}$ cm$^{-1}$ (KBr) 3400 (OH), no C=O; $^1$H NMR (CDCl$_3$): $\delta$ 0.82 (3H, d, $J$ 7.0, CH$_3$), 2.05 (4H, m, CH$_2$N-ring x2), 2.60 (2H, m, PhCHCH, PhCHCHF/H), 2.75 (1H, dd, $J$ 12.4, 4.9, PhCHCHCH), 3.40 (4H, m, CH$_2$O-ring x2), 3.60 (1H, d, $J$ 13.9, NCHPh), 4.13 (4H, m, NCHPh, CH$_3$CH, NCH/CHCH$_2$ and possibly OH), 4.24 (1H, d, $J$ 2.4, CHO), 6.9-7.7 (20H, m, Ph x4); $^{13}$C NMR (CDCl$_3$): $\delta$ 13.89 (CH$_3$), 44.73 (PhCHCHCH$_2$), 51.23 (NCH$_2$Ph), 54.54 (NCH$_2$-ring x2), 56.15 (CH$_3$CH), 57.10 (PhCHCHCH$_2$), 62.04 (NCHCHCH$_2$), 66.84 (CH$_2$O-ring x2), 74.68 (CHOH), 125.31, 126.14, 126.86, 127.08, 127.79, 128.07, 128.14, 128.30, 128.46, 128.50, 128.96, 129.33, 140.19, 141.05, 143.61, 145.58 (Ph x4); m/z (FAB; thioglycerol) 522 (M+1$^+$, 20%), 415 (M-PhCHOH$^+$), 105 (PhCH$_2$N$^+$, 100%).

**With DIBAH in the presence of ultrasound**

244 (0.20 g, 0.374 mmol) was placed in a flask which was fitted with a three-way tap. A balloon containing nitrogen was attached to one arm and the other arm was attached to a vacuum pump. The flask was evacuated and filled with nitrogen 3 times to ensure all the air had been removed. Toluene (5 ml) was added via a syringe and the mixture was cooled in an ice-bath. DIBAH (1.0M in toluene, 1.5 ml, 1.5 mmol) was added. The reaction flask was placed in an ultrasound cleaning bath for 30 minutes. After 30 minutes, approximately 75%
had reacted. DIBAL-H (0.5 ml, 0.5 mmol) was added. After a further 15 minutes in the ultrasound bath, the reaction was quenched with methanol (2 ml). A white gelatinous precipitate formed and was removed by filtration through a sinter-glass funnel. The precipitate was washed well with toluene. The toluene layer was set to one side and the aqueous layer was extracted into toluene (2x 20 ml). The combined organic layer was washed with brine and dried over MgSO4, filtered and concentrated in vacuo to give a colourless oil. The crude material was purified by flash chromatography, (CH2Cl2: ether 25:1) to give 278 as a colourless glassy oil (0.16 g, 80%). Analytical data as given previously.

5.4.18 Reduction of 245; 246; 239; 249; 253; 247

Reduction of 245; preparation of 279
β-Amino-amide 245 (0.232 g, 0.360 mmol) was dissolved in toluene (4 ml) and DIBAL-H (1M, 1.80 ml, 1.80 mmol) was added. The reaction was subjected to ultrasound for 4 h. Tlc (silica, ether-hexane 1:1) indicated that most of the amide had been reduced. DIBAL-H (0.5 ml, 0.5 mmol) was added to complete the reaction. After a further 15 minutes, in the ultrasound bath, the reaction was quenched with methanol (2 ml) (work-up described in section 5.4.17). The crude material was purified by flash chromatography, (CH2Cl2-ether 25:1) to give 279 as a yellow oil (0.19 g, 83%); \( \nu_{\text{max}}/\text{cm}^{-1} \) (film) 3584 (OH), no C=O; \(^1\)H NMR (CDCl3): \( \delta \) 0.85 (3H, d, \( J = 6.8 \), CH3), 2.79 (2H, m, PhCHCHCHHN and PhCHCH), 3.02 (1H, m, PhCHCHCHHN), 3.20 (2H, m, CH2NCH2Ph), 3.65 (4H, m, CH2NCH2Ph, CNCHHPPh) and NCHCH), 4.10 (2H, m, CHNCHHPPh and CH3CH), 4.25 (1H, bs, CHOH), 6.4-7.8 (20H, m, Ph x4); \(^1\)^C NMR (CDCl3): \( \delta \) 13.65 (CH3), 43.58 (PhCHCH), 51.49, CHNCH2Ph, 55.41 (PhCHCHCH2N), 55.89 (CH3CH), 58.67 (CH2NCH2Ph x2), 63.39 (NCHCH2N), 77.00 (CHOH), 126.5-129.4 [unassigned overlapping signals] 136.03 x2, 140.03, 140.71, 143.67, 144.42 (Ph x6)

Reduction of 246; preparation of 280
β-Amino-amide 246 (0.40 g, 0.75 mmol) was dissolved in toluene (15 ml) and DIBAL-H (1.5M, 2.0 ml, 3.0 mmol) was added. The solution was stirred for 15 h, after which time another portion of DIBAL-H (2 ml, 3.0 mmol) was added. The solution was stirred for a further 2 h, then quenched with methanol. After work-up (described in section 5.4.17) the crude material was purified by flash chromatography (ether-CH2Cl2 1:1) to give 280 as a glassy colourless oil, (0.30 g, 96%); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3400 (OH) no C=O; \(^1\)H NMR (CDCl3): \( \delta \) 0.83 (3H, d, \( J = 7 \), CH3), 1.2-1.6 (6H, NCH2CH2CH2CH2-ring), 2.1-2.3 (4H, m, NCH2-ring x2), 3.69 (1H, d, \( J = 17.9 \), NCHHPH), 4.01 (1H, d, \( J = 9.6 \), PhCHCHCHOH), 4.12 (2H, m, NCHHPH and CH3CH), 4.23 (1H, d, \( J = 3.7 \), CHOH), 6.9-7.6 (20H, m, Ph x4), 7.65 (1H, bs, OH); \(^1\)^C NMR (CDCl3): \( \delta \) 14.08 (CH3), 23.55 (NCH2CH2CH2-ring), 26.00 (NCH2CH2-ring x2), 44.17
(PhCHCH), 51.30 (NCH₂Ph), 55.45 (NCH₂-ring x2), 56.15 (CH₃CH), 58.32 (PhCHCHCH₂N), 62.39 (NCHCH), 75.99 (CHOH), 125.76, 125.96, 126.70, 126.76, 126.93, 127.62, 127.05, 128.00, 128.35, 128.37, 128.89, 129.42, 140.30, 140.92, 143.68, 145.78 (Ph x4); m/z (FAB; thioglycerol), 519 (M+1⁺, 25%), 105 (PhCH₂N⁺, 100%)

Reduction of 247; preparation of 277

β-Amino-amide 247 (0.80 g, 1.62 mmol) was dissolved in toluene (10 ml) and Dibal-H (1.5M, 5.4 ml, 8.1 mmol) was added. The solution was stirred for 15 h, after which time a further portion of Dibal-H (2 ml, 3.0 mmol) was added. The solution was stirred for a further 2 h, then quenched with methanol. After work-up (described in section 5.4.17) the crude material was purified by flash chromatography (ether) but still contained traces of impurity. The oil was further flash chromatographed (ether-CH₂Cl₂ 1:24 initially to remove least polar impurity, then ether-CH₂Cl₂ 1:1 to flush the compound off the column). 277 was produced as a glassy colourless oil (0.52 g, 67%), ν_max/cm⁻¹ (film) 3364 (OH), no C=O; (Found C, 82.4; H, 8.4; N, 5.8. C₃₃H₃₈N₂O requires C, 82.8; H, 8.0; N, 5.9%); ¹H NMR (CDCl₃): δ 0.85 (3H, d, J 7.0, CH₃), 2.05 (6H, s, NCH₃), 1.6-1.8 (3H, m, PhCHCH₂ and PhCHCH), 3.63 (1H, d, J 14.0, PhCHCH₂ and PhCHCH), 3.63 (1H, d, J 14.0, PhCHHN), 3.90 (1H, d, J 9.4, NCHCH), 4.13 (2H, m, CH₃CH and PhCHHN), 4.23 (1H, d, J 4.5 CHOH), 6.7-7.5 (21H, Ph x4 and OH); ¹³C NMR (CDCl₃): δ 14.27 (CH₃), 44.09 (PhCHCH), 45.95 (NCH₃ x2), 51.32 (NCH₂Ph), 55.98 (CH₃CH), 59.85 (PhCHCHCH₂), 62.65 (NCHCH), 76.95 (CHOH), 126.63, 126.70, 126.90, 127.54, 127.84, 127.93, 127.98, 128.10, 128.32, 128.78, 128.91, 129.48, 140.19 x2, 140.21, 143.89 (Ph x 4); m/z (FAB; thioglycerol); 479 (M+1⁺, 85%), 300 (PhCHOHCHCH₂N-(CH₃)₂H⁺), 105 (PhCH₂N⁺, 100%), 91 (C₃H₇⁺)

Reduction of 230; preparation of 274

β-Amino-amide 230 (0.40 g, 1.03 mmol) was dissolved in toluene (15 ml) and Dibal-H (1.5M, 2.80 ml, 4.12 mmol) was added. The solution was stirred for 2 h, quenched with methanol and subjected to a normal work-up. The material was flash chromatographed (ether-hexane 3:7) to give a yellow oil. This was subjected to flash chromatography (ether-CH₂Cl₂ 4:1). A colourless glassy oil was produced (274) (0.29 g, 76%), ν_max/cm⁻¹ no C=O stretch present; (Found C, 83.8; H, 8.5; N, 7.5. C₂₆H₃₂N₂ requires C, 83.8; H, 8.7; N, 7.5%); ¹H NMR (CDCl₃): δ 1.10 (3H, d, J 6.8, CH₃), 1.7-2.1 (4H, m, PhCHCH₂CH₂), 3.64 (1H, d, J 14.7, PhCHHN), 3.78 (2H, m, PhCHHN, PhCHCH₂), 4.06 (1H, q, J 6.8, CH₃CH), 7.1-7.5 (15H, m, 3x Ph); ¹³C NMR (CDCl₃): δ 14.73 (CH₃CH), 30.59 (PhCHCHCH₂), 45.34 (CH₃N), 50.66 (CH₂Ph), 56.12 (CH₃CH), 57.40 (PhCHCHCH₂), 61.29 (PhCHCHCH₂), 126.24, 126.51, 126.88, 127.75, 127.96, 128.02, 128.08, 128.18, 128.42, 142.12, 142.42, 144.99 (3x Ph); m/z 373 (M+1⁺, 80%), 105 (PhCH₂N⁺, 100%)
Reduction of 239; preparation of 275

β-Amino-amide 239 (0.40 g, 0.99 mmol) was dissolved in toluene (15 ml) and DIBAL-H (1.5M, 2.60 ml, 3.99 mmol). The solution was stirred for 2 h, quenched with methanol and worked-up as normal. The material was subjected to flash chromatography (ether-hexane 3:7) to give a slightly yellow oil, 275 (0.26 g, 68%). (Found C, 83.9; H, 8.9; N, 7.2%); ν<sub>max/cm<sup>−1</sup></sub> 3403 (OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.43 (3H, d, J 6.5, CH<sub>3</sub>), 0.98 (3H, d, J 6.9, CH<sub>3</sub>), 1.65 (1H, dd, J 12.0, 9.5, PhCHCHCHHN), 2.10 (6H, s, NCH<sub>3</sub> x2), 2.30 (1H, m, PhCHCHCH<sub>2</sub>N), 2.52 (1H, dd, J 14.2, PhCHHN), 3.55 (1H, d, J 8, PhCHCHCH<sub>2</sub>N), 4.07 (1H, d, J 14.2, PhCHHN), 4.15 (1H, q, J 6.9, CH<sub>3</sub>CH), 7.2-7.5 (15H, m, Ph x3); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 12.66 (CH<sub>3</sub>), 15.70 (CH<sub>3</sub>), 32.51 (NCH<sub>3</sub>), 51.46 (PhCH<sub>2</sub>N), 55.52 (CH<sub>3</sub>CH), 64.64 (PhCHCHCH<sub>2</sub>), 67.35 (PhCHCHCH<sub>2</sub>), 126.42, 126.54, 126.73, 127.86, 128.08 x3, 128.65, 129.48, 140.30, 141.30, 144.74 (Ph x3); m/z (FAB; thioglycerol) 387 (M+1<sup>+</sup>; 100%), 105 (PhCH<sub>2</sub>N<sup>+</sup>), 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>)

Reduction of 253; preparation of 276

β-Amino-amide 253 (0.40 g, 0.93 mmol) was dissolved in toluene (10 ml) and DIBAL-H (1.5M, 2.50 ml, 3.75 mmol) was added. The solution was stirred for 15 h, after which DIBAL-H (2 ml, 3.0 mmol) was added. The solution was stirred for a further 2 h, then quenched with methanol. After work-up the crude material was purified by flash chromatography (ether-CH<sub>2</sub>Cl<sub>2</sub> 1:1) to give 276 as a colourless glassy oil, (0.36 g, 89%); ν<sub>max/cm<sup>−1</sup></sub> 3586 (OH), no C=O stretch; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.57 (3H, d, J 6.3, CH<sub>3</sub>), 0.93 (3H, d, J 6.9, CH<sub>3</sub>), 2.15 (6H, s, NCH<sub>3</sub> x2), 2.1-2.4 (2H, m, PhCHCHCHHN and PCHCHCHHN), 2.78 (1H, d, J 14.5, PhCHHN), 3.55 (1H, d, J 8.2 PhCHCHCH<sub>2</sub>N), 4.07 (1H, d, J 14.5, PhCHHN), 4.17 (1H, q, J 6.9, CH<sub>3</sub>CH), 5.65 (1H, bs, OH), 7.2-7.6 (15H, Ph x3); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 14.12 (CH<sub>3</sub>), 23.82 (CH<sub>3</sub>), 42.67 (PhCH<sub>3</sub>H), 45.49 (NCH<sub>3</sub>), 51.47 (PhCH<sub>2</sub>N), 55.64 (CH<sub>3</sub>CHN), 60.90 (PhCHCHCH<sub>2</sub>), 63.75 (PhCHCHCH<sub>2</sub>), 70.86 (CHOH), 126.55, 126.83, 127.18, 127.78, 128.02, 128.20, 128.36, 128.49, 129.29, 140.47, 140.64, 144.46 (Ph x3); m/z (FAB; thioglycerol) 417 (M+1<sup>+</sup>; 100%), 105 (PhCH<sub>2</sub>N<sup>+</sup>), 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>)

5.4.19 Hydrogenolysis of 262 with Pd/C to give 281

The method described for in section 5.4.13 with Pd(OH)<sub>2</sub>/C was followed, with 244 (87.0 mg, 0.17 mmol), glacial acetic acid (40 ml) and catalyst [5% Pd/C] (20.0 mg). The mixture was shaken in the Parr hydrogenator for 24 h under 70 psi hydrogen. After the standard work-up, evaporation of the solvent left a white powder (281) (38.0 mg, 73%); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 47.74 (PhCHCH), 53.75 (NCH<sub>2</sub>-ring), 54.48 (CHNH<sub>3</sub>), 57.22 (PhCHCHCH<sub>2</sub>), 66.77
Chapter 5: Experimental details

5.4.20 Preparation of 257

256 (0.20 g, 0.67 mmol) and TEA (0.33 g, 3.35 mmol) were dissolved in CH₂Cl₂ (10 ml). Carbonyldiimidazole (0.162 g, 1.00 mmol) was added and the colourless solution was stirred overnight at r.t. during which time a white precipitate formed. The organic layer was washed with sulphuric acid (0.05M, 2x 30 ml), NaHCO₃ solution (sat.; 2x 10ml) and brine (10 ml) then dried over MgSO₄. Evaporation of the solvent left a white solid 257 (98 mg, 45%), m.p. >290°C [all the material vapourised before melting], (Found C, 70.1; H, 6.3; N, 8.5. C₁₉H₂₀N₂O₃ requires C, 70.4; H, 6.2; N, 8.6%); ν max /cm⁻¹ 3408 (NH), 1691 (C=O lactone), 1638 (C=O amide); ¹H NMR (CDCl₃): δ 2.20 (3H, s, CH₃), 2.44 (3H, s, CH₃), 3.53 (1H, dd, J 4.9, 2.8, CHCO), 5.11 (1H, d, J 4.9, CHNH), 5.26 (1H, bs, NH), 5.72 (1H, d, J 2.8, CHOH), 7.2-7.5 (10H, m, Ph x2), ¹³C NMR (CDCl₃): δ 35.25 (CH₃), 37.49 (CH₃), 44.55 (CHCO), 54.29 (CHNH), 80.24 (CHOH), 127.00, 128.08, 129.35, 129.45, 129.50, 129.80, 138.70, 139.11 (Ph x2), 157.30 (COO), 169.38 (CON), m/z (FAB; thioglycerol) 324 (M+1⁺, 15%), 176 (PhCHCHCON(CH₃)₂H⁺ 100%)}

5.4.21 Attempted Hydrolysis of Some of the Michael Adducts

Attempted hydrolysis of 207 with TFA

Amide 207 (20 mg) was dissolved in TFA (2 ml) and refluxed for 15 h. TFA was removed in vacuo, then HCl (2M, 10 ml) was added and the mixture was extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine and dried over MgSO₄. Filtration and evaporation left the original amide, (as a salt). This was basified with sat. NaHCO₃ (10 ml) and extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine and dried over MgSO₄. Filtration and evaporation gave original 207 (15 mg).

Attempted hydrolysis of 207 with hydrochloric acid

Amide 207 (19 mg) was dissolved in HCl (50% conc: 50% water) and refluxed for 15 h. The mixture was cooled and extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine and dried over MgSO₄. Filtration and evaporation left the original amide, (as a salt). This was basified with sat. NaHCO₃ (10 ml) and extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine and dried over MgSO₄. Filtration and evaporation gave original 207 (13 mg).
Chapter 5: Experimental details

Attempted hydrolysis of 230 with TFA
Amide 230 (0.29 g, 0.74 mmol) was dissolved in THF (2 ml) and water (1 ml). LiOH (0.04 g, 0.92 mmol) was added and the mixture was stirred at r.t. for 15 h. The material was concentrated in vacuo, then acidified (pH 4.5) with NH₄Cl (aq) and 2 drops of acetic acid. The mixture was extracted into CH₂Cl₂, dried over MgSO₄, filtered and evaporated to leave a yellow oil. The ¹H NMR spectrum indicated that no hydrolysis had taken place.

Attempted hydrolysis of 247 with TFA
β-Amino-amide 247 (18 mg) was dissolved in TFA (2 ml) and refluxed for 15 h. TFA was removed in vacuo. The ¹H NMR spectrum indicated that no hydrolysis had occurred, only the amine salt was isolated. This was basified with sat. NaHCO₃ (10 ml) and extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine and dried over MgSO₄. Filtration and evaporation gave original 247 (15 mg).

Attempted hydrolysis of 207 with NaOH
NaOH (0.80 g) was dissolved in methanol (10 ml) [2M soln.]. Amide 207 (50 mg, 0.16 mmol) was added and the mixture was refluxed for 15 h. Methanol was removed and the material acidified (pH 2) with HCl (2M). The product was extracted into CH₂Cl₂ (3x 20 ml). The combined organic layer was washed with brine (5 ml) and dried over MgSO₄. Filtration and evaporation left a solid, which was shown by ¹H NMR to be 203 (18 mg, 85%); the corresponding α,β-unsaturated amide.
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Appendix A

A.1. X-ray crystallography ................................................................. 224
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A.2. Molecular modelling studies ................................................... 237
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A.1. X-RAY CRYSTALLOGRAPHY

The X-ray crystal structures given in this thesis were solved by Mr. G. Smith, Chemistry Department, University of Surrey.

A.1.1 BRIEF DESCRIPTION OF METHOD

The unit cell parameters were measured on a CAD4 diffractometer using 25 accurately centred reflections from a crystal of approximate dimensions 0.4 x 0.3 x 0.3 mm. The reflections were collected using the ω/2θ method out to a Bragg angle of 26°, with a standard reflection measured hourly. Analysis of the standard reflections showed negligible decay for each data set. Reflections having I ≥ 3σ(I) were used. Most of the structure was obtained by the Direct Methods program MULTAN and the remaining atoms were found from structure factor / Fourier calculation. The structure was refined isotropically and then anisotropically with full matrix least squares procedure. Hydrogen atoms were included in geometrically calculated positions (dH = 1.0 Å), but were not refined. The weighting scheme used in the anisotropic refinement was: \( \omega^{-1} = [\sigma(F)^2 + (0.05F)^2 + 5.0] \). Hydrogens associated with nitrogen or oxygen were found from difference Fourier maps and were refined isotropically.

The tables given here are:

i) Crystal data

ii) Bond lengths

iii) Fractional co-ordinates of the atoms (* Starred atoms were refined isotropically, the other atoms were refined anisotropically).

iv) Bond angles

Numbers in () are the estimated standard deviation in the least significant digits.
## A.1.2. COMPOUND 119b.HCl - C$_{19}$H$_{28}$NCl

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<td>c</td>
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**Table A.1**: Crystal data for compound 119b

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**Table A.2**: Bond lengths in 119b.HCl
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Table A.3: Positional parameters of atoms in 119a.HCl
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<td>H n</td>
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**Table A.4: Bond angles in 119a.HCl**
A.1.3. Compound 119b, C₁₂H₂₂NO

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<td>Space group</td>
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</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>V</td>
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</tr>
<tr>
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<tr>
<td>$\mu$ (Mo Kα)</td>
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<tr>
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Table A.5: Crystal data for compound 126b

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Table A.5: Bond lengths in compound 126b
## Table A.7: Positional parameters for atoms in compound 126b

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<th>z</th>
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<td>0.3012(1)</td>
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<tr>
<td>N</td>
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<td>0.1532(5)</td>
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**Table A.8: Bond angles for compound 126b**
A.1.4. COMPOUND 247 - C_{33}H_{36}N_{2}O_{2}

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Table A.9: Crystal data for compound 247

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Table A.10: Bond lengths in compound 247
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Table A.11: Positional parameters for atoms in compound 247
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Table A.12: Bond angles in compound 247
Appendix 1

A.1.5. COMPOUND 249 - C_{29}H_{36}N_{2}O_{2}

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Table A.13: Crystal data for compound 249

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<th>Atom 2</th>
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Table A.14: Bond lengths in compound 249
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Table A.15: Positional parameters of atoms in compound 249
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Table A.16: Bond angles in compound 249
A.2. MOLECULAR MODELLING STUDIES

The molecular modelling studies of the 'camphor imines' in Chapter 2 were carried out by Dr. G. Harden, University of Oulu, Finland.

A.2.1 BRIEF DESCRIPTION OF METHOD

Modelling studies were carried out using MacroModel 4.5 running on a Silicon Graphics Indy Workstation. Models were constructed and minimised using the MacroModel implementation of the MM2 Force Field with default charges. Chloroform was selected as the solvent and the minimisations were run to a conjugate gradient; the torsion angle (Figure 2.4) was rotated through 10° steps and each new conformation was relaxed.
MATERIAL REDACTED AT REQUEST OF UNIVERSITY