Synthesis of a new class of homochiral amines and novel bio-active tropanes

Tavasli, Mustafa

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Synthesis of a New Class of Homochiral Amines and Novel Bio-active Tropanes

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Mustafa Tavasli, B.Ed. (Hons), M.Sc.

Ph.D. Thesis

University of Durham, Department of Chemistry

September 1999
To my family...
Declaration

The work contained in the thesis was carried out in the Department of Chemistry at the University of Durham between October 1996 and September 1999. All the work is the author's individual contribution, unless otherwise indicated and it has not previously been submitted for a degree either in this or any other university.

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Abstract

Synthesis of a New Class of Homochiral Amines and Novel Bio-active Tropanes

Mustafa Tavasli, B.Ed. (Hon), M.Sc.

This thesis describes two main programmes: the synthesis of a new class of homochiral amines and the synthesis of ketone analogues of 3α-esterified tropane alkaloids.

In chapter one, a scaled-up synthesis of \((S)-\alpha-(\text{diphenylmethyl})\text{pyrrolidine} 1\) is described. The key hydrogenation step of the oxazolidinone intermediate 2 was extended to the synthesis of the other chiral amines 70, 73, 76, 79 and 82. Hydrogenation of the oxazolidinones proceeded in good yields (71 - 87%) and was not susceptible to racemisation. Thus, a convenient route from amino acid ester hydrochlorides \((S)\)-valine 65, \((S)\)-phenylalanine 66, \((S)\)-alanine 67, \((iS)\)-isoleucine 68 and \((S)\)-leucine 69 allowed a range of novel chiral amines to be prepared.

In chapters two and three, a new route to ketone analogues of tropane esters is described. In chapter two, results of an attempt to prepare ketone 110 are outlined. Ketone 110 is an analogue of the tropane alkaloid littorine 101, where the bridging ester O atom is replaced by a CH₂ group. The first approach to ketone 110 involved the Wittig reaction of acetylbenzylphosphorane 118 and the Homer-Wadsworth-Emmons reaction of diethylbenzoylmethanephosphonate 122 with tropinone 116. Tropinone 116 was found to be particularly unreactive in both cases. The second approach to ketone 110 involved the coupling reactions of both N-troc-3α-tosyloxymethyltropane 170 and N-troc-3α-iodomethyltropane 185 with 2-phenylacetyl-1,3-dithiane 147 and 1,3-dithiane 142. These were also unreactive and as a result the synthesis of ketone 110 remains unresolved.

In chapter three, the synthesis of other ketone analogues of naturally occurring 3α-esterified tropane alkaloids is described. A six-step route to the ketones was devised and in this route the Grignard reactions of tropan-3-yl-acetaldehyde 227 emerged as the key to the success of the strategy. Three ketone analogues 218, 219 and 220 of tropate esters were successfully prepared. Ketone 220, the analogue of apoatropine 201, was found to be a muscarinic acetylcholine receptor antagonist \((EC_{50} 1.9 \times 10^{-7} \text{M})\) in guinea-pig ileum, showing a 500-fold less activity than atropine 202. However the activity is still within the clinical range.
I would like to thank my supervisor, Prof. David O'Hagan, for his unlimited support, encouragement and help throughout this work.

I would also like to thank Dr. Robert F. Halliwell, not only allowing us to do the biological testing in his lab, but also making them a priority. In this respect, Graham R. Foxon deserves a special thank you, both for setting up the required apparatus to a working condition from scratch and for bringing me up to the standard to run the biological tests myself.

I also wish to thank my colleagues in the GC50, especially to those individuals who were brave enough to stand up to the smell of dimethyl sulphide. A big thank you goes to Dr. Alan Kenwright for his effort to sort out the problems associated with endo and exo isomers.

Finally thanks to my sponsor Kocatepe University of Afyon, Turkiye, for the YOK scholarship.
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<th>Definition</th>
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<tr>
<td>CSA</td>
<td>Chiral solvating agent</td>
</tr>
<tr>
<td>CDA</td>
<td>Chiral derivatizing agent</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Xe</td>
<td>Chiral auxiliary</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>$E^+$</td>
<td>Electrophile</td>
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<tr>
<td>SAMP</td>
<td>(S)-1-Amino-2-(methoxymethyl)pyrrolidine</td>
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<tr>
<td>RAMP</td>
<td>(R)-1-Amino-2-(methoxymethyl)pyrrolidine</td>
</tr>
<tr>
<td>MOMO</td>
<td>Methoxymethoxy</td>
</tr>
<tr>
<td>HAL</td>
<td>Homochiral amine ligand</td>
</tr>
<tr>
<td>HLAB</td>
<td>Homochiral lithiumamide base</td>
</tr>
<tr>
<td>CLSR</td>
<td>Chiral lanthanide shift reagent</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoric triamide</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-Butoxycarbonyl</td>
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<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-Dimethoxyethane</td>
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<tr>
<td>Trisyl azide</td>
<td>2,4,6-Triisopropylbenzenesulfonyl azide</td>
</tr>
<tr>
<td>atm.</td>
<td>Atmosphere</td>
</tr>
<tr>
<td>p.s.i</td>
<td>Pounds per square inches</td>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>HETCOR</td>
<td>Heteronuclear correlated</td>
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<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarisation transfer</td>
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<tr>
<td>HMBC</td>
<td>Heteronuclear multiple bond correlation</td>
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<tr>
<td>D</td>
<td>Deuterium</td>
</tr>
<tr>
<td>T</td>
<td>Tritium</td>
</tr>
<tr>
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<td>Horner-Wadswoth-Emmons</td>
</tr>
<tr>
<td>THF</td>
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</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
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<tr>
<td>Ts</td>
<td>Tosyl</td>
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<tr>
<td>THP</td>
<td>Tetrahydropyryl</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium $p$-toluenesulfonate</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>Sia₂BH</td>
<td>Disiamylborane</td>
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<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
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<tr>
<td>TrocCl</td>
<td>2,2,2-Trichloroethyl chloroformate</td>
</tr>
<tr>
<td>LiAlH₄</td>
<td>Lithium aluminium hydride</td>
</tr>
<tr>
<td>BMS</td>
<td>Borane-methyl sulfide</td>
</tr>
<tr>
<td>t.l.c.</td>
<td>Thin layer chromatography</td>
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<td>DNA</td>
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<td>DIBAL-H</td>
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<td>PCC</td>
<td>Pyridinium chlorochromate</td>
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<td>PDC</td>
<td>Pyridinium dichromate</td>
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<tr>
<td>NOESY</td>
<td>Nuclear overhauser enhancement spectrum</td>
</tr>
<tr>
<td>mAChR</td>
<td>Muscarinic acetylcholine receptor</td>
</tr>
<tr>
<td>ACh</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>Inhibition concentration required for half maximal response</td>
</tr>
<tr>
<td>EC₅₀</td>
<td>Effective concentration required for half maximal response</td>
</tr>
<tr>
<td>μM</td>
<td>Micromolar</td>
</tr>
<tr>
<td>nM</td>
<td>Nanomolar</td>
</tr>
<tr>
<td>τ</td>
<td>Torsion angle</td>
</tr>
<tr>
<td>CSD</td>
<td>Cambridge Crystallographic database</td>
</tr>
<tr>
<td>vmax</td>
<td>Maximum absorption</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionisation</td>
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<tr>
<td>CI</td>
<td>Chemical ionisation</td>
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CHAPTER ONE

Synthesis of a New Class of Homochiral Amines
CHAPTER ONE

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1.1.2 Amines as chiral ligands

1.1.3 Amines as chiral bases

1.1.4 Amines as chiral resolving agents

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1.3.3 Enantiomeric excess of (S)-α-(diphenylmethyl)-α-alkyl-methylamines 3

1.3.4 Discussion
CHAPTER ONE

1.1 General introduction

The development of enantioselective carbon-carbon (C-C) bond forming reactions is an important activity for many leading researchers in academia, and the pharmaceutical and chemical industries. As a result of this interest many enantiomerically enriched compounds have been produced. In this respect, a great deal of enantioselective C-C bond forming reactions was carried out by using homochiral amine auxiliaries, ligands and bases. The use of homochiral amines has not been limited to these areas, however they have also found applications as chiral resolving agents in the determination of enantiomeric excess (e.e) of the end products, as well as in the combinatorial synthesis.

In this research programme, the scaled synthesis of (S)-α-(diphenylmethyl)pyrrolidine 1 is demonstrated and the key step, hydrogenation of oxazolidinone 2, is extended to the syntheses of more general (S)-α-(diphenylmethyl)-α-alkyl-methylamines 3. Homochiral amines such as 3 will open access to a series of chiral amines. At the outset, it is appropriate to review briefly the current status of homochiral amines in asymmetric synthesis.

1.1.1 Amines as chiral auxiliaries

Chirality transfer with chiral auxiliaries usually occurs in cases where achiral substrates are covalently bond to chiral auxiliaries. In the case of chiral amine auxiliaries (X_c-NH_2 or X_c-NH), this covalent bond could be generated via a formation of imines 5 from achiral aldehydes 4 (or ketones) (Scheme 1a), or via a formation of amides 7 from a carboxylic acid derivatives, such as acid chloride 6 (Scheme 1b).
The carbanions 9 and 10 then generated from 5 and 7 with lithium amide bases such as lithium diisopropyl amide (LDA) can react with one of the following electrophiles (E⁺): alkyl halides, carboxylic acid derivatives, and aldehydes (or ketones). These reactions, depending on the electrophile used, are known as alkylations, acylations and aldol reactions and generate diastereoisomers 8 and 11. Chiral primary and secondary amine auxiliaries (X^-NH₂ and X^-NH) are finally removed from the system, affording enantiomerically enriched chiral products 12 and 13. The set of chemical operations discussed above is depicted in Scheme 2.
Transformation of achiral aldehydes (or ketones) into their corresponding chiral derivatives are widely achieved by chiral hydrazine auxiliaries\(^2\) \((X_C^-\text{NH-NH}_2^-)\), such as \((S)\)- or \((R)\)-1-amino-2-(methoxymethyl)pyrrolidine \(^{14}\). These auxiliaries were developed by Enders\(^2\) from \((S)\)- or \((R)\)-2-methoxymethylpyrrolidine \(^{15}\), and are known as SAMP-14 or RAMP-14.

\[
\begin{align*}
\text{SAMP-14} & \quad \overset{\text{OMe}}{\text{NH}_2} \quad \overset{\text{Me}}{\text{O}} \\
\text{RAMP-14} & \quad \overset{\text{OMe}}{\text{NH}_2} \quad \overset{\text{Me}}{\text{O}} \\
\text{SAMP-14} & \quad \overset{\text{O}}{\text{N}} \quad \overset{\text{Me}}{\text{O}} \\
\text{RAMP-14} & \quad \overset{\text{O}}{\text{N}} \quad \overset{\text{Me}}{\text{O}}
\end{align*}
\]

A more recent application\(^{12}\) of SAMP-14 was reported in the total synthesis of epothilone A, where propionaldehyde \(^{16}\), after coupling with SAMP-14, was transformed into one of the building blocks \(^{17}\). In this transformation, alkylation of the SAMP derivative \(^{18}\) with 4-iodo-1-benzylxybutane was the key step, and proceeded in good yield \((92 \%)\) and in excellent e.e. \((98 \%)\) to give \(^{19}\). Ozonolysis of \(^{19}\) finally produced the target molecule \(^{17}\).

\[
\begin{align*}
16 & \quad \overset{\text{Ph}}{\text{O}} \\
17 & \quad \overset{\text{OMe}}{\text{N}} \\
18 & \quad \overset{\text{OMe}}{\text{N}} \\
19 & \quad \overset{\text{OMe}}{\text{N}}
\end{align*}
\]

On the other hand, transformation of achiral carboxylic acid derivatives are accessible using C2-symmetric amines\(^3\), such as \((2R,5R)-2,5\text{-bis-(methoxymethoxymethyl)pyrrolidine}\)^{13} \(^{20}\), where MOMO is acronym for methoxymethoxy.

\[
\begin{align*}
\text{MOMO} & \quad \overset{\text{OMe}}{\text{N}} \quad \overset{\text{OMe}}{\text{OMe}}
\end{align*}
\]

Such a transformation is illustrated in the synthesis\(^{14}\) of \((2R,5S)-2\text{-methyl-5-hexanolide} \(^{25}\), a sex pheromone of the carpenter bee. In this synthesis, propionyl chloride \(^{21}\) was
first coupled with 20 to give the corresponding amide 22 (Step 1), which was then lithiated under standard conditions (LDA, THF, -78 °C) (Step 2). Treatment of the lithiated amide 23 with the iodide 24 (Step 3), followed by acid-catalysed hydrolysis (Step 4), generated the target molecule 25, as shown in Scheme 3.

![Scheme 3]

**1.1.2 Amines as chiral ligands**

Chiral ligands have played a key role in the development of asymmetric bond forming reactions\(^\text{15}\). In this respect, chiral amines, in particular chiral diamines\(^\text{5}\), such as 27, 29 and 28 feature prominently. The chiral environment is usually introduced via coordination to metals via N atom\(^\text{16}\). Metal complexes of homochiral amine ligands (HALs) such as organometallics\(^\text{17}\) (RM), Grignard reagents\(^\text{18}\) (RMgX) and osmium tetraoxide\(^\text{19}\) (OsO\(_4\)) are well studied.
For instance, the use of 27 was reported by Nakajima et al. in the enantioselective 1,2-addition reaction of phenylmagnesium bromide to isobutanal (Scheme 4a). Ligand 28 was reported by Asami and Inoue for the enantioselective 1,2-addition of diethylzinc to benzaldehyde (Scheme 4b) and 29 was reported by Hanessian et al. in enantioselective OsO₄-mediated cis-dihydroxylation of alkenes (Scheme 4c). These reactions clearly illustrate the value of HALs. However, in order to maximise enantioselectivity, structural tuning is still a challenge in the design and synthesis of new chiral ligands.

\[
\begin{align*}
\text{a) } & \text{PhMgBr} \xrightarrow{1. \text{HAL}} \text{Ph} \quad 68\% \quad 47\% \text{ e.e.} \\
\text{b) } & \text{Et₂Zn} \xrightarrow{1. \text{HAL}} \text{Et} \quad 82\% \quad 80\% \text{ e.e.} \\
\text{c) } & \text{OsO₄} \xrightarrow{1. \text{HAL}} \text{CO₂Me} \quad 80\% \quad 99\% \text{ e.e.}
\end{align*}
\]

Scheme 4

1.1.3 Amines as chiral bases

Lithium amide bases such as lithium diisopropylamide (LDA) have established an important position in organic synthesis, and are widely used as strong bases with low nucleophilicity. With the discovery of lithium di[(S)-1-phenylethyl]amide (S,S)-30 or its antipode (R,R)-30 by Whitesell and Felman, the use of homochiral lithium amide bases (HLAB), such as 31, (S)-32 has attracted considerable attention in connection with recent progress in asymmetric synthesis.
Interests in this area have focused primarily on two asymmetric reactions: the enantioselective deprotonation of cyclic ketones (Scheme 6a) and the enantioselective rearrangement of epoxides to allylic alcohols (Scheme 6b).

More recent studies have however shifted towards asymmetric aromatic and benzylic functionalisation of tricarbonyl(η⁶-arene)chromium complexes, as depicted in Scheme 6a and Scheme 6b respectively.

1.1.4 Amines as chiral resolving agents

Asymmetric synthesis is not complete without analysing the end product, in where enantiomeric excess (e.e.) of the isomer and the configuration of new stereogenic centre has to be determined. To date, NMR spectroscopy is one of the most straightforward methods used. It relies on the fact that diastereotopic nuclei are, in principle, anisochronous and should have a different chemical shifts and different coupling constants. Conversion of enantiomers into a diastereoisomeric mixture / complex is
therefore necessary, and this is usually achieved by one of the following methods\textsuperscript{26}: chiral lanthanide shift reagents (CLSRs), chiral derivatizing agents (CDAs) and chiral sovating agents (CSAs). The use of CSAs\textsuperscript{27}, which make \textit{in situ} NMR analysis possible by inducing anisochrony either through the formation of ion pairing or hydrogen bonding, emerges as an efficient method for the determination of the e.e. of the isomer and the configuration of new stereogenic centre. In this respect, the most widely employed CSAs are ($R$)-amines\textsuperscript{28,29} \textit{33} and \textit{34} (or their antipodes ($S$)-\textit{33} and ($S$)-\textit{34}). Other amines, such as\textsuperscript{30,31} ($R,R$)-\textit{35} are also known. Although the use of amines as CSAs has had wide applications, they are mainly dedicated to the analysis\textsuperscript{27} of asymmetric carboxylic acids and alcohols.

\[
\begin{align*}
(R)-33 \\
(R)-34 \\
(R,R)-35
\end{align*}
\]

\textbf{1.1.5 Amines in combinatorial synthesis}

In drug discovery, various amines ($R,R,NH$) have been used to develop a range of quinolones\textsuperscript{32}, such as \textit{36}, a potent antibacterial agent. Amines ($R,R,NH$) have been employed to mimic transition states or intermediates of enzyme catalysed reactions\textsuperscript{33}, such as peptide isosteres \textit{37} and \textit{38}. In both cases, the type of amines used was however not disclosed.

\[
\begin{align*}
36 \\
37 \\
38
\end{align*}
\]
1.2  \( (S)-\alpha-(\text{Diphenylmethyl})\text{pyrrolidine} \) - Scale up

1.2.1  Introduction

A new and straightforward route to \( (S)-\alpha-(\text{diphenylmethyl})\text{pyrrolidine} \) 1 was developed in Durham as part of my MSc\textsuperscript{34} programme. This improved significantly on a previous synthesis\textsuperscript{35}. Amine 1 was used in Durham to prepare\textsuperscript{36} the diamines 39 and 40, as potential bidentate ligands for asymmetric chemistry.

![](image)

The chemistry of 1 and its applications were explored in a preliminary way\textsuperscript{34}. In particular, 1 was investigated as a chiral auxiliary in asymmetric alklylation reactions and as a chiral solvating agent (CSA) for \(^1\)H NMR analysis of the enantiomeric purity of chiral carboxylic acids and alcohols. Asymmetric alkylations were carried on N-phenylacetamide 41 and N-propionamide 42 under standard deprotonation conditions (LDA, THF, -78 °C) with benzylbromide (PhCH\textsubscript{2}Br) and methyl iodide (CH\textsubscript{3}I), in the presence and absence of HMPA. The results are summarised in Table 1. From these results, it was concluded that 1 is not a good chiral auxiliary.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Alkyl halide</th>
<th>Additive</th>
<th>Diastereoisomer ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="img1.png" alt="Image" /></td>
<td>CH₃I</td>
<td>None</td>
<td>1.1 : 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH₃I</td>
<td>HMPA</td>
<td>1.5 : 1.0</td>
</tr>
<tr>
<td>2</td>
<td><img src="img2.png" alt="Image" /></td>
<td>PhCH₂Br</td>
<td>None</td>
<td>1.1 : 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PhCH₂Br</td>
<td>HMPA</td>
<td>2.1 : 1.0</td>
</tr>
</tbody>
</table>

Table 1: Asymmetric alkylation of amide derivatives 41 and 42 in the presence and absence of HMPA.

Although 1 did not emerge as a good chiral auxiliary, it proved to be an excellent CSA for $^1$H NMR analysis of the enantiomeric purity of chiral carboxylic acids. To promote the application of 1 and make it available to the wider-research community, it became necessary to scale up the preparation of 1. At the outset, the objective was to prepare a 60 g batch of 1, a three fold increase in scale. This required the preparation of amide ester 44 in large quantities as the first step in the synthesis of 1.

1.2.2 Synthesis of (S)-α-(diphenylmethyl)pyrrolidine 1

Following the literature method described by Kanth and Periasamy, and with our previous experience, amide ester 44 was readily prepared by the reaction of (S)-proline 43 with ethyl chloroformate in the presence of K₂CO₃ and MeOH, as depicted in Scheme 7. This reaction began with 90 grams of (S)-proline 43 and gave 157 grams of the amide ester 44 as a clear oil. The conversion was essentially 100 %, which made for an excellent first step in the synthesis of 1.
The second step involved the Grignard reaction of the amide ester 44 with phenylmagnesium bromide. Cyclisation to oxazolidinone 2 occurred in situ, as illustrated in Scheme 8. Contemporaneously, this cyclisation was also reported by Deleunay and Le Corre. This provided 133 grams of oxazolidinone 2 as a white solid. The compound 2 was purified by re-crystallisation from ethyl acetate in a moderate (62 %) yield.

The final step in the synthesis of 1 was the hydrogenation of oxazolidinone 2 with palladium on activated carbon in MeOH, as shown in Scheme 9. This process successfully generated pyrrolidine 1, by formally removing the elements of CO₂ from oxazolidinone 2. Pyrrolidine 1 is an oil, but distillation gave an impure product. However, re-crystallisation of its HCl salt from isopropyl alcohol proved an excellent method for purification and gave a nice white crystalline solid. After basification and extraction into dichloromethane, 50 grams of pyrrolidine 1 was obtained as an oil in moderate yield (44 %). This material was pure by ¹H and ¹³C NMR, GC and elemental analysis.
1.2.3 Discussion

By following the three-step route, a 50 g batch of pyrrolidine 1 was successfully prepared. This was made available to the Aldrich Chemical Company (Cat. No: 46,718-9) and pyrrolidine 1 is now commercially available to the wider research community. We hope that many research groups world-wide will now start to explore the chemistry of 1.

1.3 Homochiral primary amines from amino acids

1.3.1 Introduction

New chiral building blocks, especially enantiomerically pure are required by pharmaceutical and agrochemical industries, in particular to service the recent growth in combinatorial chemistry, which is now dominating drug discovery. In this respect, the conversion of amino acids into chiral amines such as (5)-α-(diphenylmethyl)-α-alkylmethylamines 3, provide an interesting range of novel compounds. Amines with the general structure 3 are potentially available by extending the chemistry of (5)-proline / (S)-α-(diphenylmethyl)pyrrolidine and starting from a more general range of α-amino acids.

Increasingly attention has been focused on the synthesis of (R)- or (S)-α-(diphenylmethyl)glycine\textsuperscript{39,40,41,42,43} 45, which fulfil general structure 3 and have
found applications in the preparation of bioactive peptides.\textsuperscript{44,45} Another example is the preparation of (S)-\(\alpha\)-(diphenylmethyl)-\(\alpha\)-(2-hydroxyethy)-methylamine\textsuperscript{46} 46, which also fulfil general structure 3 and has found application in the preparation of 47\textsuperscript{47}, a potential receptor for carboxylic acids and reagent/catalyst.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=\textwidth]{structures.png}
\end{tabular}
\end{center}

The syntheses of 45 and 46 involved either the modification of enantiomerically pure amino acids or the use of asymmetric reactions. With the former approach, the synthesis of (R)-45 began with the preparation of the fully protected oxazolidine ester\textsuperscript{49} 49 from (S)-serine 48. This was then followed by the Grignard addition to the ester moiety and catalytic dehydroxylation (Pd(OH)\textsubscript{2}-C, HCO\textsubscript{2}H; NaOH, MeOH-H\textsubscript{2}O) to give amino alcohol\textsuperscript{50} 50. This generated the required diphenylmethyl group. Then BOC protection of the amino group, Jones oxidation (CrO\textsubscript{3}, H\textsubscript{2}SO\textsubscript{4}, acetone) of the alcohol to the corresponding carboxylic acid and then removal of the BOC group finally yielded (R)-45 in enantiomerically pure form.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=\textwidth]{structures.png}
\end{tabular}
\end{center}

The synthesis of (S)-46 began by transforming (S)-methionine 51, into 52. This was followed by a Grignard reaction to give amino-diol 53, where the primary OH and NH\textsubscript{2} groups were protected as N-Ac (acyetyl) and O-Ac, respectively. The Ac-protected 53 was then subjected to a range of hydrogenolysis conditions, but only application of Ram and Spicer's catalytic transfer method\textsuperscript{49} (10 % Pd-C, NH\textsubscript{4}+HCO\textsubscript{3}-, AcOH) successfully gave 54, generating the required diphenylmethyl group. Removal of the N-Ac and O-Ac protecting groups from 54 finally yielded (S)-46 in enantiomerically pure form.
With later approaches, chiral auxiliaries were employed, where either stereoselective introduction of the diphenylmethyl group or the amino group was achieved. As enolate alkylation of Schiff bases derived from glycine is well defined and frequently used in the synthesis of a variety of optically active amino acids, the same approach was adopted in the synthesis of 45, to introduce the required diphenylmethyl group either in (S) or (R) form. The following two examples are illustrative.

Alkylation of the sultam-derived N-(diphenylmethylene)glycine amide 55 with bromodiphenylmethane (Ph₂CHBr) provided the desired diphenylmethyl group in good yield (68 %) and in excellent diastereoisomeric excess (d.e.) (> 95 %). Subsequent hydrolysis of the ketimine and cleavage of the sultam group finally yielded (S)-45. Alkylation of the nickel (II) complex-derived glycine 56 with Ph₂CHBr generated the desired diphenylmethyl group in good yield (68 %) and in excellent d.e. (90 %). Subsequent decomposition of the complex and separation of Ni (II) ions yielded (S)-45, when the (S)-proline containing complex was used.
In addition to the enolate alkylation of Schiff bases derived from glycine, a Schmidt rearrangement was also deployed in the synthesis of 45. The requisite β-ketocarboximide substrate, (4R,2'R)-57 was prepared from the alkylation\(^\text{42}\) of the (4R)-acetoacetimide 58 with Ph\(_2\)CHBr. In this reaction, the desired diphenylmethyl group was generated in the (R) form, but in low yield (41%) and in modest d.e. (64%). The Schmidt rearrangement (NaN\(_3\), H\(_2\)SO\(_4\), DME) proceeded then with retention of configuration providing (4R,2'R)-acetamide 59 in good yield (85%). Subsequent cleavage of the oxazolidinone group and hydrolysis of the acetamide group yielded (R)-45. However, alkylation of (4S)-58 provided (S)-45.

\[\begin{align*}
\text{(4R,2'R)-57} & \quad \text{(4R)-58} & \quad \text{(4R,2'R)-59}
\end{align*}\]

The three examples reported above involve the stereoselective introduction of the diphenylmethyl group via alkylation of chiral enolates. A conceptually different approach was also reported for the synthesis of (R)- and (S)-45. This involved the stereoselective introduction of the amino group via a direct azidation\(^\text{40}\) of (4R,5S)-diphenylpropionimide 60 with trisyl azide. The azidation proceeded in excellent yield (94%) and in complete stereocontrol to give a single diastereoisomer. Subsequent cleavage produced (R)-azido acid 61. Hydrogenation of 61 furnished the final product, (R)-45. By the azidation of (4S,5R)-60, (S)-azido acid 61 was also produced in enantiomerically pure form.

\[\begin{align*}
\text{(4R,5S)-60} & \quad \text{(R)-61} & \quad \text{(R)-45}
\end{align*}\]

There was no standard procedure available to transform the amino acid carboxylate into the corresponding diphenylmethyl group. However, following the success of the
synthesis of pyrrolidine 1 from (S)-proline 43, it was decided to explore a similar strategy for the synthesis of other chiral amines from primary amino acids. Catalytic hydrogenation of a range of 5,5-diphenyl-2-oxazolidinones represented by 64 had the potential to deliver the new series of amines 3. For this purpose, the route outlined in Scheme 10 was proposed, and addressed.

![Scheme 10](image)

The first step in the syntheses of (S)-α-(diphenylmethyl)alkyl amines 3 required the preparation of amino alcohols 63, by straightforward Grignard reaction of the corresponding amino acid ester hydrochlorides 62 with phenylmagnesium bromide. Of course, the presence of the ammonium chloride demands at least 5 equivalents of Grignard reagent. If the amino alcohols 63 are then converted to the oxazolidinones 64, hydrogenation would generate the required amines 3. For simplicity, (S)-amino acid ester hydrochlorides without extra functional groups on their side chains were chosen as starting materials in these reactions. The amino acid ester hydrochlorides 65-69 of (S)-valine, (S)-phenylalanine, (S)-alanine, (S)-isoleucine and (S)-leucine were therefore chosen and are depicted in Figure 1.
Preparation of the amino alcohols 63 from 65-69 and their cyclisation to the oxazolidinones 64 is well known and has already been described in the literature. The only exception was the oxazolidinone derived from (S)-isoleucine 68. It was anticipated that the hydrogenation would be straightforward following our previous experience in the synthesis of pyrrolidine 1, however that remained to be tested.

1.3.2 Synthesis of (S)-α-(diphenylmethyl)-α-alkyl-methylamine 3

(S)-Valine methyl ester hydrochloride 65 was chosen as the first starting material among the five amino acid ester hydrochlorides. This transformation would generate amine 70. The first step in this transformation began with the preparation of the corresponding amino alcohol 71.

Amino alcohol 71 has been prepared by Itsuno et al. from the reaction of (S)-valine methyl ester hydrochloride 65 with an 8-fold excess of phenylmagnesium bromide (PhMgBr) in 56% yield, and by Gawley and Zhang with a 5-fold excess of PhMgBr in 44% yield. Very recently, a free amine of (S)-valine methyl ester rather than its hydrochloride salt was employed by Hintermann and Seebach, thus reducing the
excess of PhMgBr to only 3-fold. The yield was 50 %. In our case, amino alcohol 71 was prepared by the addition of (S)-valine methyl ester hydrochloride 65 to a 10-fold excess of PhMgBr in THF, as depicted in Scheme 11.

\[
\begin{array}{c}
\text{65} \\
\text{PhMgBr (10 equiv.), THF, 0 °C; reflux, 20h.}
\end{array}
\rightarrow
\begin{array}{c}
\text{71} \\
\text{36 %}
\end{array}
\]

Scheme 11

After work-up, amino alcohol 71 was found to be contaminated with a large amount of biphenyl as an impurity. By dissolving the HCl salt of amino alcohol 71 in methanol, the majority of this impurity was immediately precipitated out as a white solid. Further purification by column chromatography gave amino alcohol 71 as a white solid in moderate yield (36 %). Following the method described by Akiba et al., reaction of this amino alcohol 71 with diphosgene (Cl\textsubscript{3}COCOCl), in the presence of triethylamine (Et\textsubscript{3}N) gave then the corresponding oxazolidinone 72 as a white solid in good yield (86 %). This is summarised in Scheme 12.

\[
\begin{array}{c}
\text{71} \\
\text{1. Et\textsubscript{3}N (2.1 equiv.), Cl\textsubscript{3}COCOCl (1.1 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 2h.}
\end{array}
\rightarrow
\begin{array}{c}
\text{72} \\
\text{86 %}
\end{array}
\]

Scheme 12

As an alternative to diphosgene, the following reagents were also reported: tri-phosgene [(Cl\textsubscript{3}CO)\textsubscript{2}CO] by Gibson et al., ethyl chloroformate (EtOCOCl) by Hintermann and Seebach and phosgene (Cl\textsubscript{2}CO) by Gawley and Zhang. Cyclisation of amino alcohol 71 with these reagents proceeded in 73 %, 91 % and 95 % yields, respectively. Oxazolidinone 72 was then subjected to hydrogenation with a catalytic amount of palladium on activated carbon, in a mixture of AcOH and MeOH, as illustrated in Scheme 13.
As anticipated, the hydrogenation was successful and gave the first amine 70 of the series as a white crystalline solid, in good yield (72 %). The amine 70 was recrystallised from petroleum ether. $^1$H NMR analysis of 70 indicated a doublet of doublets (3.46 ppm, J= 10.5 and 2.4 Hz) for the proton at the stereogenic centre and a doublet (3.70 ppm, J= 10.5 Hz) for the CH of the diphenylmethyl group. The Heteronuclear Correlated (HETCOR) spectrum of 70 proved necessary for the assignment of the $^{13}$C NMR signals. Thus, the peak at 58.1 ppm was assigned to the CH of the diphenylmethyl group and the peak at 58.9 ppm assigned to the carbon atom at the stereogenic centre. In the event, (S)-valine methyl ester 65 was successfully transformed into novel amine 70.

(S)-Phenylalanine ethyl ester hydrochloride 66 was chosen as the next amino acid to be studied, to generate amine 73. Again the first step in this transformation commenced with the synthesis of the corresponding amino alcohol 74.

Amino alcohol 74 was prepared by the portionwise addition of (S)-phenylalanine ethyl ester hydrochloride 66 to PhMgBr, as depicted in Scheme 14. However, this time an 8-fold excess of Grignard reagent was used following the literature method reported by Itsuno et al.
Biphenyl was again a significant by-product, however since biphenyl is a neutral impurity, the basicity of the amino alcohols was exploited in its purification. The reaction mixture was therefore treated with hydrochloric acid. Upon work-up, amino alcohol 74 was isolated as a single product, but in low yield (9 %). However, this can clearly be improved and the reaction has been reported by Itsuno et al. in a 53 % yield. Further purification, if required, was possible by re-crystallisation of the free amine from a mixture of ethyl acetate and diethyl ether, which gave a white crystalline solid. Surprisingly, two disparate yields (26 and 63 %) were reported by Weber et al. and Dammast and Reißig for this reaction, carried out under the same conditions (diethyl ether and 5-fold excess of PhMgBr). A moderate yield (50 %) was also reported by Hintermann and Seebach, in which the free base of 66 was subjected to the Grignard reaction with a 3-fold excess of PhMgBr. Improvement of the yield in our hands was not pursued as our focus was on the final hydrogenation step. Amino alcohol 74 was then submitted to the cyclisation reaction with diphosgene (Cl₃COCOCl) in the presence of triethylamine (Et₃N), as shown in Scheme 15.

Scheme 15

This generated oxazolidinone 75 as a white solid in excellent yield (97 %). The cyclisation procedure described by Akiba et al. this time proved superior to the one used by Hintermann and Seebach. For the final step, oxazolidinone 75 was subjected to the hydrogenation reaction with a catalytic amount of palladium on activated carbon.
in a mixture of AcOH and MeOH, as illustrated in **Scheme 16**.

![Scheme 16](image)

This successfully generated the second amine 73, which was purified by column chromatography and obtained as a light-brown solid in good yield (71%). The $^1$H NMR spectrum of 73 displayed a doublet (3.71 ppm, $J=9.9$ Hz) for the CH of the diphenylmethyl group and a doublet of doublets of doublets (3.81 ppm, $J=9.9, 9.6, 2.7$ Hz) for the proton at the stereogenic centre. The HETCOR spectrum of 73 proved necessary for the assignment of the $^{13}$C NMR signals. From this, the peak at 59.7 ppm was assigned to the CH of the diphenylmethyl group and the peak at 55.7 ppm assigned to the carbon atom at the stereogenic centre.

It emerged at this stage that a limitation of the route is the syntheses of the amino alcohols 71 and 74, which suffer from moderate to poor yields. This appears to be due to biphenyl formation, and the separation of this by-product in an effective way is an important issue. None-the-less, the synthesis of the third amine 76 was pursued, which began with the preparation of amino alcohol 77.

![Amino alcohol 77](image)

Amino alcohol 77 has already been prepared in 40-60% yield by Itsuno$^{51}$ et al., in 57% yield by Weber$^{57}$ et al. and in 45% yield by Dammast and Reißig$^{58}$ from (S)-alanine methyl ester hydrochloride 67. In these reactions, 8-fold$^{51}$ and 5-fold$^{57,58}$ excesses of phenylmagnesium bromides were used. In our case, the amino alcohol was also
prepared from 67, after reacting with a 6-fold excess of PhMgBr, as depicted in Scheme 17.

\[
\begin{array}{c}
\text{O} \\
\text{NH}_3\text{Cl} \\
\text{PhMe} \\
\text{Me} \\
\text{NH}_2 \\
\text{77}
\end{array}
\begin{array}{c}
\text{1. PhMgBr (6 equiv.), THF, 0 °C/r.t., 21 h.} \\
\text{52 %}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{NH}_2 \\
\text{OH}
\end{array}
\]

Scheme 17

Upon work-up, amino alcohol 77 was recovered but, as expected, was contaminated with biphenyl. However, this time, purification by dry-flash column chromatography proved relatively straightforward and was more successful in comparison to the previous methods investigated so far. This gave amino alcohol 77 as a white solid in a yield of 52 %, which was satisfactory and competitive with previous reports. With amino alcohol 77 in hand, it was subjected to cyclisation with diphosgene (Cl\(_2\)COCOCl) in the presence of triethylamine (Et\(_3\)N), as shown in Scheme 18. The same transformation, but with the \textit{racemic}-amino alcohol 77 has been reported by Hassner\(^{59}\) and Reuss. However, in that case phosgene (Cl\(_2\)CO) was employed in the cyclisation step, according to the method described by Newman\(^{60}\) and Kutner. The yield was not reported.

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{NH}_2 \\
\text{OH}
\end{array}
\begin{array}{c}
\text{1. Et}_3\text{N (2.1 equiv.), CH}_2\text{Cl}_2, \text{Cl}_2\text{COCOCl (1.1 equiv.),} \\
\text{CH}_2\text{Cl}_2, 0 \degree \text{C}, 5\text{h.} \\
\text{76 %}
\end{array}
\begin{array}{c}
\text{HN} \\
\text{O}
\end{array}
\]

Scheme 18

Upon work-up, the corresponding oxazolidinone 78 was recovered as a white solid in good yield (76 %). Finally, oxazolidinone 78 was subjected to hydrogenation with a catalytic amount of palladium on activated carbon as before (Scheme 19).
This generated amine 76, which was purified over dry-flash column chromatography and obtained as a white solid in moderate yield (65%). The $^1$H NMR spectrum of 76 illustrated a doublet (3.55 ppm, $J$= 9.0 Hz) for the CH of the diphenylmethyl group and a doublet of quartets (3.73 ppm, $J$= 9.0 Hz) for the proton at the stereogenic centre. The HETCOR spectrum of 76 proved diagnostic for the assignment of the $^{13}$C NMR signals. As a result, the peak at 50.3 ppm was assigned to the CH of the diphenylmethyl group and the peak at 62.4 ppm was assigned to the carbon atom at the stereogenic centre.

With the syntheses of three chiral amines 70, 73 and 76, the consistency of the new method has been established. To extend the range of amines further, it was anticipated that conversion of two other amino acid esters, namely (S)-isoleucine and (S)-leucine methyl ester hydrochlorides 68 and 69, would be amenable to the method, as they have no complicating functional groups in their side chains. Thus the synthesis of amino alcohol 80 was addressed as the first step towards amine 79.

Amino alcohol 80 has already been prepared by Itsuno et al. from (S)-isoleucine methyl ester hydrochloride 68 in 40-60 % yield. In this reaction, direct addition of 68 to the Grignard was used. In our case, amino alcohol 80 was prepared by inverse addition and with a 5-fold excess of phenylmagnesium bromide, as depicted in Scheme 20.
After usual work-up, biphenyl as a neutral impurity was readily separated from the amino alcohol 80 by treatment of the crude product with concentrated HCl. After basification and extraction into ethyl acetate, 80 was isolated, but was contaminated with the unreacted amino ester from the starting material 68. The crude product was however used directly for the next step without further purification. Only a small amount of this product was purified by dry-flash column chromatography and amino alcohol 80 was obtained as a white solid in low yield (25 %). The application of inverse addition in the synthesis of other amino alcohols, such as 71 by Delair et al. resulted also in poor yields (~17 %).

Despite the fact that the 40 % impurity was present, the cyclisation proceeded without any complications. Upon work-up, the impurity was readily separated from
oxazolidinone 81, as the solubility of the oxazolidinones was poor in common organic solvents. Thus, oxazolidinone 81 was obtained as a light-brown solid in good yield (83%). This novel compound was a single diastereoisomer as judged by \(^1\)H and \(^{13}\)C NMR analysis. Oxazolidinone 81 was finally subjected to hydrogenation under the standard conditions, as illustrated in Scheme 22.

Scheme 22

Amine 79 was obtained as a white solid in good yield (71%), after purification by dry-flash column chromatography. The \(^1\)H NMR spectrum of 79 displayed a doublet of doublets (3.50 ppm, \(J = 10.5\) and 2.4 Hz) for the proton at the stereogenic centre and a doublet (3.87 ppm, \(J = 10.5\) Hz) for the CH of the diphenylmethyl group. In order to assign the rest of the \(^1\)H NMR signals, a Distortionless Enhancement by Polarization Transfer (DEPT) spectrum of 79, where methine (CH), methylene (CH\(_2\)) and methyl (CH\(_3\)) carbons are distinguished, proved necessary. From this, it became clear that the multiplets at 1.00-1.20 and 1.50-1.70 ppm were due to the protons of the CH\(_2\) group, hence the multiplet at 1.28-1.44 ppm was assigned to the proton of the CH next to the methyl group. With the DEPT analysis of 79 in hand, the \(^{13}\)C NMR signals were also readily assigned. For example, the peak at 56.4 ppm was assigned to the CH of the diphenylmethyl group and the peak at 58.4 ppm assigned to the carbon at the C-N stereogenic centre.

The final transformation of the series started with (S)-leucine methyl ester hydrochloride 69, to generate the corresponding amine 82. The first step in this transformation began with the synthesis of amino alcohol 83.
Preparation of 83 was first reported by Itsuno\textsuperscript{51} et al. by the direct addition of (S)-leucine methyl ester hydrochloride 69 to an 8-fold excess of phenylmagnesium bromide. In our case, inverse addition, but with a 5-fold excess of Grignard reagent, was used.

After usual work-up, treatment of the crude product with concentrated HCl allowed separation of biphenyl from the amino alcohol 83. After basification and extraction into ethyl acetate, a crude product was obtained as a pale-yellow solid, but was contaminated with the amino ester derived from the starting material 69. None-the-less, the crude product was used directly for the next step without further purification. Only a small amount of this product was purified by dry-flash column chromatography and amino alcohol 83 was isolated as a white solid in low yield (31 %). With amino alcohol 83 (65 %) in hand, it was submitted to cyclisation with diphosgene (Cl\textsubscript{3}COCOCl) in the presence of triethylamine (Et\textsubscript{3}N), as shown in Scheme 24.
The cyclisation again proceeded without any complications and upon work-up, the impurity was readily separated from oxazolidinone 84. Thus, the corresponding oxazolidinone 84 was obtained as a white solid and in excellent yield (90 %). Oxazolidinone 84 was then subjected to hydrogenation, as illustrated in Scheme 25.

Upon work-up, this generated our final amine 82 of the series as a white solid and in good yield (87 %). The $^1$H NMR spectrum of 82 was readily assigned, but in contrast to the previous examples, the proton at the stereogenic centre and the CH of the diphenylmethyl group overlapped at 3.6 ppm to give a multiplet. The DEPT and the Heteronuclear Multiple Bond Correlation (HMBC) spectra of 82 proved necessary for the assignment of the $^{13}$C NMR signals. With the DEPT analysis of 82, it became clear that the CH$_2$ group unexpectedly shifted to higher frequency giving a signal at 45.2 ppm, whereas the CH of the isobutyl group shifted to lower frequency at 25.2 ppm. Assignment of the carbon signals at 52.1 and 61.2 ppm was possible on the basis of the HMBC spectrum, which shows correlation between two- or three-bond distant proton and carbon atoms. Since the carbon signal at 61.2 ppm shows correlation to the aromatic (Ph) protons, this must be the diphenylmethyl (Ph$_2$CH) carbon, and therefore the carbon signal at 52.1 ppm must be the carbon atom at the stereogenic centre (CHNH$_2$). The HMBC spectrum of 82 is depicted in Figure 2.
1.3.3 Enantiomeric excess of (S)-α-(diphenylmethyl)-α-alkyl-methylamines 3

Determination of the enantiomeric purity of the novel chiral amines became necessary to demonstrate that the stereogenic centre had not racemised to any extent during the three-step synthesis. This therefore required a synthesis of one of the amines as a racemate, to provide a control. For this purpose, (SR)-alanine ethyl ester hydrochloride 85 was chosen as a starting material. Following the previously established route, (SR)-85 was converted to the (SR)-α-(diphenylmethyl)-α-methyl-methylamine 76.
The non-equivalence of the CF₃ group in diastereoisomers of α-methoxy-α-trifluoromethylphenylacetyl (Mosher) derivatives is often observable by ¹⁹F-NMR, and such esters and amides are widely employed for enantiomeric excess (e.e.) determinations. Therefore, the racemic amine 76 was converted to the corresponding diastereoisomeric (SR)- and (RR)-amides 87 with one equivalent of (S)-Mosher’s acid chloride 86, as depicted in Scheme 26, by a modification of the published procedure. As a result of this reaction, the stereogenic centre of 86 is inverted from (S) to (R) by replacement of the Cl atom with the amide N atom.

The reaction was monitored by ¹⁹F NMR spectroscopy and after 5h, the fluorine peak at -72.4 ppm had disappeared, suggesting that all of the Mosher’s acid chloride (S)-86 was consumed. After purification by chromatography, both ¹⁹F and ¹¹H NMR analysis of (SR)- and (RR)-87 displayed two separate signals (Table 2, Entry 1) for the diastereotopic CF₃ (-69.3 and -70.0 ppm) and OCH₃ (3.02 and 2.84 ppm) groups. The chemical shift differences (Δδ) between the diastereoisomers for these groups were measured at 0.2 and 0.19 ppm, respectively. Such differences give base-line separations and allow precise integration of the fluorine and proton signals. The diastereoisomeric ratio of (SR)-87 / (RR)-87 was determined as 1.1:1. This small deviation from the expected 1:1 ratio probably arises from isomer separation on purification. The pure amine, (S)-76 was then converted to the diastereoisomeric amide, (SR)-87, as illustrated in Scheme 27. In view of the small kinetic bias observed with the racemate, the (S)-76 was reacted with a 1.4 equivalent of Mosher’s acid chloride (S)-86, to ensure a complete conversion.
Scheme 27

The reaction was monitored by $^{19}$F and $^1$H NMR and the peak at -70.0 ppm was assigned to the CF$_3$ group in the resulting amide (SR)-87, whereas the peak at -71.9 ppm was assigned to the product of some hydrolysis (Mosher's acid). Comparison of both the $^1$H- and $^{19}$F-NMR spectra (Table 2) of the racemate- and (S)-amine- derived Mosher's amides 87 shows very clearly that in the latter case a single diastereoisomer is formed, and by implication that the starting amine 76 was optically pure.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>$\delta_H$ of OCH$_3$ (ppm)</th>
<th>$\delta_F$ of CF$_3$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(SR) and (RR)-87</td>
<td>3.02 ppm, 2.84 ppm</td>
<td>-69.3 ppm, -70.0 ppm</td>
</tr>
<tr>
<td>2</td>
<td>(SR)-87</td>
<td>3.02 ppm</td>
<td>-70.0 ppm</td>
</tr>
</tbody>
</table>

Table 2: Selected regions of the $^1$H-NMR (OCH$_3$: 3.10, 2.70 ppm) and $^{19}$F-NMR (CF$_3$: -68, -73 ppm) spectra of the (R)-Mosher's amide 87, prepared either from racemic (SR)-76 or pure (S)-76.
All of the remaining amines, (S)-3 (R= isopropyl 70, benzyl 73, sec-butyl 79 and isobutyl 82) were also converted to their respective Mosher's amide derivatives 88-91, as shown in Scheme 28. In all cases the resulting amides (SR)-88-91 were subjected to $^1$H and $^{19}$F NMR analyses, and the spectra indicated that all were single diastereoisomers, consistent with their origin from enantiomerically pure amines. The relevant sections of the $^1$H and $^{19}$F NMR spectra are shown in Table 3.

Scheme 28
<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>$\delta_H$ of OCH$_3$ (ppm)</th>
<th>$\delta_F$ of CF$_3$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(SR)-88</td>
<td>2.98 ppm</td>
<td>-69.6 ppm</td>
</tr>
<tr>
<td>2</td>
<td>(SR)-89</td>
<td>2.84 ppm</td>
<td>-69.5 ppm</td>
</tr>
<tr>
<td>3</td>
<td>(SR)-90</td>
<td>2.97 ppm</td>
<td>-69.6 ppm</td>
</tr>
<tr>
<td>4</td>
<td>(SR)-91</td>
<td>2.98 ppm</td>
<td>-69.7 ppm</td>
</tr>
</tbody>
</table>

Table 3: Selected regions of the $^1$H-NMR (OCH$_3$: 3.10, 2.70 ppm) and $^{19}$F-NMR (CF$_3$: -68, -73 ppm) spectra of the (R)-Mosher's amides 88-91, prepared from the (S)-3.
1.3.4 Discussion

A three-step route, as depicted in Scheme 29, has been developed to transform amino acid esters 62 into the novel chiral amines 3. This transformation is amenable to some variety and potentially allows one to choose different starting amino acid esters 62 to generate different amines 3.

The first step in the route involved preparation of amino alcohols 63 either by direct or inverse addition of the corresponding amino acid ester hydrochlorides 62 to the Grignard reagent. A summary of the conditions for all of the amino alcohols prepared is shown in Table 4. The yields for the Grignard reactions varied between (9 %) and (52 %), according to the addition, hydrolysis and purification methods. Hydrolysis with HCl gave the lowest yield (9 %). The two lowest yields (25 % and 31 %) were obtained from the inverse addition of the amino acid esters. Recrystallisation of amino alcohol as an HCl salt was partially successful in the separation of the biphenyl impurity, but further purification by chromatography was still required. This gave the second best recovery, but still in low yield (36 %). Hydrolysis with saturated NH₄Cl and purification with dry-flash column chromatography led to a better recovery (52 %). Excess of Grignard reagents at more than 6-fold seemed to have little effect on the conversion, and purification became more difficult due to increased biphenyl formation. From these
observations, it can be concluded that a 6-fold excess of Grignard reagent, direct addition of amino acid esters, hydrolysis with saturated NH₄Cl and purification by dry-flash chromatography are key elements in the successful amino alcohol synthesis.

<table>
<thead>
<tr>
<th>Amino alcohol</th>
<th>PhMgBr (equiv.)</th>
<th>Addition</th>
<th>Hydrolysis</th>
<th>Purification</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>10</td>
<td>direct</td>
<td>NH₄Cl</td>
<td>recrystallisation and chromatography</td>
<td>36</td>
</tr>
<tr>
<td>74</td>
<td>8</td>
<td>direct</td>
<td>HCl</td>
<td>recrystallisation</td>
<td>9</td>
</tr>
<tr>
<td>77</td>
<td>6</td>
<td>direct</td>
<td>NH₄Cl</td>
<td>chromatography</td>
<td>52</td>
</tr>
<tr>
<td>80</td>
<td>5</td>
<td>inverse</td>
<td>NH₄Cl</td>
<td>chromatography</td>
<td>31</td>
</tr>
<tr>
<td>83</td>
<td>5</td>
<td>inverse</td>
<td>NH₄Cl</td>
<td>chromatography</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 4: Synthesis of the amino alcohols 71, 74, 77, 80 and 83 under different conditions.

The second step in the route required the preparation of the oxazolidinones 72, 75, 78, 81 and 84, with the general structure 64 (see Figure 3). This was readily achieved by cyclisation of the amino alcohols 63 with diphosgene, in the presence of triethylamine.
in good to excellent yields (76 - 97 %). The solubility of the oxazolidinones 64 was poor in common organic solvents and this assisted their purification. It was observed that the solubility improved with the larger alkyl groups on the 4 position. For instance, 81 and 84 were soluble in dichloromethane or chloroform, whereas with 72, 75 and 78 were insoluble, except in dimethyl sulphoxide (DMSO).

![Chemical Structures]

(Yield: 86 %)  (Yield: 97 %)  (Yield: 76 %)

(Yield: 83 %)  (Yield: 90 %)

**Figure 3:** The oxazolidinones 72, 75, 78, 81 and 84 prepared in this transformation and their general structure 64.

The final step in the route was hydrogenation of the oxazolidinones 64 over palladium on activated carbon. In this hydrogenation, a mixture of acetic acid and methanol was used as a solvent, where the oxazolidinones 64 formed either a solution or a suspension. The hydrogenation was carried out at 4-5 atm by using a Parr hydrogenator. Upon concentration, the crude amines were treated with hydrochloric acid, to disassociate amine-acetate salts formed during the hydrogenation, followed by basification and extraction into dichloromethane. Purification of the amines was achieved by one of the following:

i) Re-crystallisation, as was the case for amine 70.

ii) Column chromatography, as was the case for amines 73 and 76.

iii) Washing the acidic solution with diethyl ether, as was the case for amines 79 and 82.
The yields varied between 65% and 87%. The resultant amines 70, 73, 76, 79 and 82, represented by the general structure 3 are depicted in Figure 4.

![Chemical structures of amines 70, 73, 76, 79, and 82](image)

Figure 4: The novel homochiral amines 70, 73, 76, 79, and 82 prepared from the three-step route and their general structure 3.

The presence of a single stereoisomer for the resultant amines in each case was demonstrated by the reaction of (S)-Mosher’s acid chloride with the (S)-amines 3. In all cases $^1$H and $^{19}$F NMR analysis of the resultant stereoisomers indicated that the synthetic sequence followed for the preparation of the novel amines is not susceptible to racemisation, certainly not at a detectable level.
CHAPTER TWO

Towards the Synthesis of Ketone Analogue of Littorine
CHAPTER TWO

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CHAPTER TWO

2.1 General introduction

2.1.1 Biosynthesis of tropane alkaloids hyoscyamine and scopolamine

Hyoscyamine 92 and its epoxidised derivative scopolamine 93 are secondary metabolites of the Solenaceae family of plants and have been widely used in the clinic. They are esters of tropine 94 and (S)-tropic acid 95. The biosynthetic origin of the tropine moiety 94 and (S)-tropic acid 95 have been the focus of much interest for many years.

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{O} & \quad \text{N} & \quad \text{CH}_2\text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Ph} \\
\text{O} & \quad \text{OH} & \quad \text{CH}_2\text{OH} \\
\end{align*}
\]

The biosynthesis of tropine 94 has been substantially settled as is shown Scheme 30. It has been confirmed that the amino acid ornithine 96 is incorporated into N-methylpyrrolidium 97. However, points of detail on the condensation of two acetyl groups with 97 remain to be resolved.

\[
\begin{align*}
\text{COOH} & \quad \text{2x} & \quad \text{O} & \quad \text{CO}_2 \\
\text{COOH} & \quad \text{NH}_2 & \quad \text{NH}_2 \\
\end{align*}
\]

Scheme 30

2.1.2 Biosynthetic origin of (S)-tropic acid 95

The biosynthetic origin of the (S)-tropic acid 95 is still a subject of discussion and investigations. In the 60s, Leete suggested that (S)-phenylalanine 98 was a direct
precursor of (S)-tropic acid 95. In a definitive experiment fifteen years later Leete demonstrated in Datura innoxia plants that (RS)-phenyl[1,3-\textsuperscript{13}C\textsubscript{2}]alanine 98 was incorporated into the tropate moiety of hyoscyamine 92, in where the two \textsuperscript{13}C isotopes became contiguous by an intramolecular rearrangement, as shown in Scheme 31.

![Scheme 31](image)

Although (S)-phenylalanine 98 is a good precursor of (S)-tropic acid 95, the true substrate for the rearrangement and the stereochemical course to (S)-tropic acid 95 has recently been re-evaluated. Feeding experiments with \textsuperscript{14}C-labelled phenylpyruvate 99 and phenyllactate 100 indicated that the two compounds become similarly incorporated into the tropic acid moiety of the alkaloids. This observation can be explained if phenylalanine 98, phenylpyruvate 99 and phenyllactate 100 interconvert in vivo, as depicted in Scheme 32.

![Scheme 32](image)

The importance of phenyllactate 100 as a precursor to (S)-tropic acid 95 was shown by two different research groups after feeding (RS)-phenyl[1,3-\textsuperscript{13}C\textsubscript{2}]lactate 100 to transformed root cultures of Datura stramonium. The observed spin-spin coupling of the two \textsuperscript{13}C nuclei in the extracted hyosyamine 92 and scoplamine 93 confirmed the intramolecular rearrangement shown by Leete. It remained to be confirmed however which was the most direct precursor of the three. Therefore, a series of feeding experiments was carried out in Durham by supplementing Datura stramonium root
cultures with the following labelled compounds: racemic, and resolved (R)- and (S)-phenyl[2-$^{13}$C,$^2$H]alanines 98 and racemic phenyl[2-$^{13}$C,$^2$H]lactate 100. All of the feeding experiments with racemic phenyl[2-$^{13}$C,$^2$H]alanine 98, the (R)-isomer, and racemic phenyl[2-$^{13}$C,$^2$H]lactate 100 resulted in a substantial retention of $^2$H (D, deuteruim) and $^{13}$C isotopes, at C3' of hyoscyamine 92 (Scheme 33). On the other hand feeding with the (S)-phenyl[2-$^{13}$C,$^2$H]alanine 98 resulted in a complete lost of D isotope, at C3' of hyoscyamine 92 (Scheme 34). These results clearly indicate that (R)-phenyllactate 100 is the stereosiomer used during the biosynthesis.
2.1.3 Stereochemistry of the rearrangement

During the rearrangement of phenyllactate 100 to hyoscyamine 92, two bonds (C1-C2 and C3-H3) of 100 are broken, and C1 migrated to C3 to form a new bond of the tropate moiety (C1'-C2') of 92. However, H6 of 100 is removed and the origin of the new C3'-H bond of the tropate moiety is unknown. Feeding experiments with radiolabelled phenyl[2-^H]lactate 100 showed that the tritium (T) isotope was retained at the 3'-pro-S position (H°) in the resultant hyoscyamine 92, whereas feeding 75 (2R,3R)- and (2R,3S)-[3-^H]phenyllactates 100 only the deuterium (D) isotope at the 3S position (C3-H3) of 100 retained. This hydrogen becomes configurationally inverted in the resultant hyoscyamine 92 (C2'-H3). These experiments clearly demonstrate that inversion of configuration occurred at both bond-breaking and -forming centres. The overall stereochemical course of the rearrangement is summarised in Scheme 35.
2.1.4 Littorine 101 is a direct precursor to hyoscyamine 92

In tropane alkaloid forming plants, littorine 101, the tropine ester of (R)-phenyllactate 100, was also co-produced with hyoscyamine 92 and scopolamine 93. Therefore, it appeared reasonable that (R)-phenyllactate 100 can couple to tropine 94 in *Datura stramonium* to give littorine 101. This then is the true substrate for the putative isomerase enzyme. The role of littorine 101 as a direct precursor of hyoscyamine 92 was established in an experiment using isotopically labelled littorine 101, where three $^2$H (D) nuclei incorporated into N-CH$_3$ of the tropine moiety and two $^{13}$C nuclei incorporated into C1 and C3 position of phenyllactoyl moiety. A high level of $^{13}$C spin-spin coupling, observed by NMR, unequivocally demonstrated that littorine 101 can rearrange in vivo to hyoscynamine 92, as shown in Scheme 36.

2.1.5 Mechanistic hypothesis

It is interesting to note that a considerable number of biosynthetic rearrangement reactions are reasonably explained as cytochrome P$_{450}$-mediated reactions, such as...
formation of 2,7,4'-trihydroxyisoflavanone 104 from flavanone 102, as depicted in Scheme 37. In P₄O₇-mediated reactions, the initially formed Fe(III)-O-O' species is converted into Fe(III)-O-OH and then heterolysis of the oxygen-oxygen bond gives the oxo-derivative for which a number of structures are possible; for example Fe(IV)=O, (+-)Fe(IV)=O and Fe(IV)-O'. For example, in the case of 2,7,4'-trihydroxyisoflavanone 104 formation, one of these species, e.g. iron-oxo [Fe(V)=O], appears to initiate the abstraction of hydrogen to generate a substrate radical 103. Rearrangement to a product radical 105, followed by oxygen rebound, where the rearranged radical is quenched by an hydroxyl radical from Fe(IV)-OH, gave 2,7,4'-trihydroxyisoflavanone 104. This intermediate was isolable and the new hydroxyl group was labelled from ¹⁸O. A dehydratase then acts to produce the final product, daidzein 106.

Scheme 37
The recent stereochemical conclusions, and in particular the absence of a vicinal interchange process (i.e. the proton (H₃) at C3 of phenyllactate 100 was lost and not relocated at the 3'-pro-R site of hyoscyamine 92, see Scheme 35, p. 44) have led to the suggestion that a haem-thiolate enzyme, cytochrome P₄₅₀ may be responsible for the rearrangement. This hypothesis has gained support by the observation that the P₄₅₀ inhibitor, chlortrimazole inhibited the conversion of littorine 101 to hyoscyamine 92 in roots of *Datura stramonium*. The possibility of an oxygen-rebound was also investigated by a feeding experiment, where racemic (R,S)-phenyl[2-²H,₁⁸O]lactate was supplemented to transformed root cultures of *Datura stramonium*, as illustrated in Scheme 38. It was shown that both ¹⁸O and ²H (D, deuterium) isotopes were incorporated into littorine 101. However during the rearrangement of littorine 101 to hyoscyamine 92, 25-29 % of the ¹⁸O isotope was lost.

![Scheme 38](image)

The high retention of the ¹⁸O isotope (71-75 %) can be rationalised if a diol hydrate 108, formed by oxygen-rebound from product radical 107, collapses to an aldehyde 109 in a stereospecific manner (Scheme 39a) or disproportionation of the Fe(IV)-OH and the product radical 107 occurs to give an aldehyde 109 directly (Scheme 39b).
2.1.6 **Aim and objectives**

In this research programme, 110 became a target molecule. This is an analogue of littorine 101, where the bridging O atom has been replaced by a CH₂ group. If prepared and fed to cell free extracts of *Datura stramonium*, it may give a shunt product, which might reveal some detail of the process. For example, if an oxygen rebound process is operating, then diol 111 may be generated.

More interesting, of course, would be to observe a rearrangement of ketone 110 to 112, as depicted in **Scheme 40**, however this would require a considerable flexibility of the enzyme and this was not anticipated as a realistic outcome.
2.2 Wittig and HWE reactions of tropinone

2.2.1 Introduction

In order to prepare the required target we initiated the synthetic route to ketone 110 as shown in Scheme 41. The first step in this route involved preparation of β-ketophosphonate 115, as analogues compounds have commonly been used for the preparation of α,β-unsaturated ketones via the Horner-Wadsworth-Emmons (HWE) reactions. It was anticipated that the desired β-ketophosphonate 115 could be prepared from the reaction of the lithium salt of diethyl methylphosphonate 114 with carboxylic acid ester 113. We envisaged that the HWE reaction of tropinone 116 with 115 would be the key step in this route, leading to the formation of α,β-unsaturated ketone 117. Finally double bond reduction was anticipated to afford the *endo* isomer as the predominant product.

\[
\text{Ph} \quad \text{O} \quad \text{Bn}
\]

\[
\text{113}
\]

\[
\text{O} \quad \text{Et}
\]

\[
\text{114}
\]

\[
\text{n-BuLi}
\]

\[
\text{Ph} \quad \text{O} \quad \text{Bn}
\]

\[
\text{115}
\]

\[
+ \quad \text{NaH}
\]

\[
\text{116}
\]

\[
\text{H}_2 / \text{Pd}
\]

\[
\text{110}
\]

\[
\text{117}
\]

Scheme 41
2.2.2 Attempted synthesis of (tropane-3-ylidene) ketones 119 and 123

It was judged appropriate to establish the protocol on a model system. Therefore, acetylmethylene phosphorane\(^{118}\) was chosen as a model reagent. This was attractive, as hydrogenation of 119 would give ketone 120, the CH\(_2\) analogue of the tropane alkaloid acetoxytropane\(^{121}\).

Phosphorane 118 was subjected to the Wittig reaction with tropinone 116 under two sets of conditions, as summarised in Scheme 42. The \(^{31}\)P NMR analysis of the reaction mixture in THF (reflux, 7 days) did not show any traces of triphenylphosphine oxide, however the reaction mixture in DMF (reflux, 6 days) displayed the characteristic peak at 24 ppm in the \(^{31}\)P NMR spectrum. This suggested a conversion of almost 50 %, however, neither the desired product 119 nor the starting material 116 could be recovered from the reaction.

In view of the failed Wittig reaction between tropinone 116 and phosphorane 118, diethyl benzoylmethanephosphonate 122 was considered as an alternative model compound. This HWE reaction, if followed by hydrogenation, would generate ketone 123, the CH\(_2\) analogue of the tropane alkaloid benzoyloxytropane\(^{125}\).
Phosphonate 122 was prepared from the reaction of acetophenone 126 with diethyl chlorophosphite 127, following a literature method\(^{86}\), as depicted in Scheme 43. This required the formation of the lithium enolate of acetophenone 126 at -78 °C, followed by addition of diethyl chlorophosphite 127. Upon work-up, the resulting product was subjected to air oxidation and gave the desired phosphonate 122, in moderate yield (66 %).

An alternative approach to phosphonate 122 was investigated in parallel and followed the method described by Dawson\(^{87}\) and Burger, in which bromoacetophenone 128 and triethyl phosphite 129 are heated together, as shown in Scheme 44.

Although this proved to be a straightforward route, a side product (probably unavoidable Perkow product 130) was also generated, which made purification difficult.
Only after three subsequent distillations and column chromatography (eluting with a 1:1 mixture of ethyl acetate and hexane), a fairly pure sample of phosphonate 122 was obtained in 54 % yield.

Phophonate 122 was treated with tropinone 116 under various conditions and these are summarised in Scheme 45 and Table 5. In the end this reaction was unsuccessful.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>THF</td>
<td>r.t., 3d</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>THF</td>
<td>r.t., 4d</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>Et₂O</td>
<td>r.t., 22h; reflux, 6d</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>KOtBu</td>
<td>DMF</td>
<td>r.t., 25h; reflux, 7d</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi</td>
<td>DME</td>
<td>-78 °C to r.t., 1h; reflux, 8d</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>LDA</td>
<td>THF</td>
<td>-78 °C, 2h; r.t., 16h; reflux, 4d</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 5: The attempted HWE reaction of tropinone 116 with phophonate 122 under different conditions.

2.2.3 Discussion

Starting from either acetophenone 126 or bromoacetophenone 128, model β-ketophosphonate 122 was readily prepared in good (66 %) to moderate (54 %) yields respectively, as depicted in Scheme 46.
Preparation of phosphonate 122 from 128 represents a classical Arbuzov reaction and proved a straightforward route to β-ketophosphonate 122. However, it is known that this route quite commonly suffers from an un-avoidable Perkow reaction, which generates vinyl phosphate 130 via the nucleophilic attack of the carbonyl oxygen on to the phosphorus atom, as shown in Figure 5.

Figure 5: Formation of vinyl phosphate 130 by an avoidable Perkow reaction.

Formation of phosphonate 122 by an Arbuzov reaction occurs via the elimination of ethyl bromide as illustrated in Figure 6 and is dependant upon the halide used and the reaction temperature. High temperatures and less electronegative halogens usually favour phosphonate formation. From our experience, column chromatography is a reasonable method for the separation of the Arbuzov product 122 from the Perkow product 130.
Figure 6: Formation of phosphonate 122 by an Arbuzov reaction.

Tropinone 116 was found to be particularly unreactive both for the Wittig reaction of acetylmethylenephosphorane 118 and for the HWE reaction of diethyl benzoylmethane-phosphonate 122. This is perhaps due to a combination of steric effects associated with nucleophilic approach to the ketone of the tropinone ring, and the relative decrease in the nucleophilicity of phosphorane 118 and phosphonate 122, when compared to triethyl phosphonoacetate 131. Unlike phosphorane 118 and phosphonate 122, the anion derived from phosphonate ester 131 is more strongly nucleophilic and was reported to react with tropinone 116 to give both \(\alpha,\beta\)-unsaturated ester 132 and \(\beta,\gamma\)-unsaturated ester 133, as depicted in Scheme 47.

![Scheme 47](image-url)

This failure has led us to develop another potential route to ketone 110, and this is discussed in the following section.
2.3 Coupling reactions: thioacetal and tropane precursors

2.3.1 Introduction

It is well known that lithiated 1,3-dithiane species show high nucleophilicity towards alkyl halides and arene sulfonates derived from primary alcohols. The following example is illustrative: (2S)-N-(t-Butoxycarbonyl)-O-tosylprolinol reacted smoothly with the 2-(3,4-dimethoxyphenyl)-1,3-dithiane, in spite of this relatively hindered primary centre to generate the substituted product in good yield (76 %), as shown in Scheme 48.

\[ \text{134} + \text{135} \rightarrow \text{136} \]

Scheme 48

In order to prepare ketone 110, we proposed a coupling reaction between 3\(\alpha\)-tosyloxymethyltropane 137 and thioacetal 138 to generate thioacetal 139. The final step in the synthesis would only require the removal of the protecting groups from 139 as illustrated in Scheme 49. The synthesis of tropane 137 and thioacetal 138 are discussed in the following sections.
2.3.2 Thioacetal precursor synthesis

2.3.2.1 Introduction

Starting from phenylacetaldehyde 140, it was anticipated that the synthesis of thioacetal 138 would be straightforward. The first step in the synthesis of 138 required the preparation of 141. Such compounds have already been reported in the literature and are successfully prepared by the reaction of aldehydes with 2-lithio-1,3-dithianes. Protection of the hydroxyl group with THP was expected to give thioacetal 138, as depicted in Scheme 50.
2.3.2.2 Synthesis of thioacetal 138

In the event, compound 141 was readily prepared by the reaction of phenylacetaldehyde 140 with the anion of 1,3-dithiane 142 at -78 °C, as depicted in Scheme 51. According to the method described by Corey and Seebach\(^\text{102}\), the anion was generated with n-butyllithium between -20 and -40 °C in THF. Compound 141 was purified over silica gel and obtained as a light-brown liquid in moderate yield (44%). The reverse addition of the dithiane anion was also explored in the hope of improving the yield. However, this offered no improvement (42%).

![Scheme 51](image)

Protection of the hydroxyl group of 141 as a tetrahydropyranyl (THP) ether followed the method described by Miyashita\(^\text{103}\) et al. (1977). Thus treatment of 141 with 3,4-dihydro-2H-pyran 143 in pyridinium p-toluenesulfonate (PPTS) was carried out, as shown in Scheme 52. Thioacetal 138 was, as expected, a mixture of two diastereoisomers and was purified over silica gel. However, presence of some starting material (as an almost 1:1 mixture) could be still detected by \(^1\)H and \(^{13}\)C NMR, and GC-MS. This may be a disadvantage of the silica gel purification.

![Scheme 52](image)
2.3.2.3 Potential problem of thioacetal 138, and its replacement by thioacetal 147

It was anticipated that thioacetal 138, when treated with a base, might generate the corresponding 2-phenylethylidene-1,3-dithiane 144, following the mechanism shown in Scheme 53. It has already been reported that 2-(tetrahydrofuran-2-yl)-1,3-dithiane 145 gave the corresponding unsaturated alcohol 146, when treated with a strong base such as n-BuLi or LDA, as depicted in Figure 7.

Therefore it became necessary to design an alternative thioacetal compound, in which the following criteria are met:

i) Stabilisation of anion when treated with a base

ii) Generation of an hydroxyl group after the coupling reaction.

It was judged that 2-phenylacetyl-1,3-dithiane 147 would be ideal for this purpose.
Addition of 2-lithio-1,3-dithianes to aldehydes, followed by Swern oxidation is reported as a general method for the preparation of 2-acyl-1,3-dithianes. Alternatively, N-methoxy-N-methyl amides proved to be efficient in the acylation of 2-lithio-1,3-dithianes and gave the corresponding 2-acyl-1,3-dithianes in high yields ranging from 80 to 95%. However, acylation of 2-lithio-1,3-dithianes with esters and acid chlorides commonly resulted in double alkylations and deprotonations. Therefore, it was anticipated that the target molecule 147 could be readily prepared either by the Swern oxidation of 141 or by the reaction of 2-lithio-1,3-dithianes with N-methoxy-N-methyl amide 148, as illustrated in Scheme 54. Preparation of amide 148 has already been described in the literature in good to excellent yields (69-100%).

Scheme 54

2.3.2.4 Synthesis of alternative thioacetal 147

With 141 in hand, Swern oxidation was initially investigated. The Swern oxidation required the activation of dimethylsulfoxide (DMSO) by oxalyl chloride [(COCl)₂] at low temperature (-78 °C), followed by the addition of 141 and triethylamine (Et₃N), as shown in Scheme 55. The target thioacetal compound 147 was purified over silica gel and obtained as a white solid in low yield (7%).

Scheme 55
This conversion was unsatisfactory and therefore an alternative method was explored, beginning with the synthesis of amide \(148\). Following the method described by Sibous and Tipping, amide \(148\) was readily prepared from the reaction of phenylacetyl chloride \(149\) with \(N\)-methoxy-\(N\)-methylamine hydrochloride \(150\) in the presence of pyridine, as depicted in Scheme 56. Amide \(148\) was purified by distillation and obtained in good yield (74%), an improvement on the previous synthesis.

\[ \text{Scheme 56} \]

Amide \(148\) was then subjected to the condensation reaction with the anion derived from \(1,3\)-dithiane \(142\), as depicted in Scheme 57. The resultant thioacetal \(147\) was this time purified over neutral alumina and isolated as a white solid in fairly low yield (19%). However, with the use of excess of amide \(148\), compound \(147\) could be recovered in 38% yield.

\[ \text{Scheme 57} \]

2.3.2.5 Discussion

Thioacetal \(138\), required for the coupling reaction, was prepared starting from phenylacetaldehyde \(140\), as depicted in Scheme 58.
The moderate yield (44 %) for the first step may be explained by the mechanism shown below. If the dithiane anion abstracts one of the α-protons from aldehyde 140 (path a), this anion would attack another aldehyde 140 (path b), leading to the formation of the aldol product 151. Dehydration of 151 would then give the α,β-unsaturated aldehyde 152, which is also liable to Michael attack (path c). These are shown in Scheme 59.
If the dithiane anion attack occurs as depicted in Scheme 60 (path d), then compound 141 could be generated from aldehyde 140. Inverse addition\textsuperscript{105}, which keeps the concentration of highly reactive dithiane anion low with respect to the aldehyde\textsuperscript{113}, is generally known to increase the yield by circumventing side-product formations. However, this did not have a demonstrable effect in our hands. A chiral centre in a molecule makes prochiral centres throughout the molecule non-equivalent\textsuperscript{114}. Therefore, carbons adjacent to the sulphur atom in 141 became resolved, but could not be assigned unambiguously in the $^{13}$C NMR spectra.

The THP oxygen undergoes an $\alpha$-cleavage in mass spectroscopy, as illustrated in Figure 8. This is an important process in identifying the presence of a THP ether and produces a peak at 85 amu, which often dominates the spectrum\textsuperscript{115}. In our case the peak at 85 amu was therefore attributed to the formation of 138. The preparation of this compound however still requires optimisation.
**Figure 8:** An α-cleavage of THP oxygen of 138 in mass spectroscopy and the corresponding ion at 85 amu.

Thioacetal 147, an alternative substrate to THP protected thioacetal 138, was also prepared successfully either from 141 or starting from phenylacetylchloride 149, as illustrated in Scheme 61.

![Scheme 61](image)

The Swern oxidation of 141 gave a disappointingly low yield (7 %), despite other successful Swern oxidations of e.g. 2-(1'-hydroxyalkyl)-2-alkyl-1,3-dithianes\(^{116}\) 153 to 2-acyl-2-alkyl-1,3-dithiane 154 in high yields (62-93 %), as depicted in Scheme 62.
It became apparent from the above reaction that the low yield (7 %) was due to the presence of the acidic proton at the C2 position of thioacetal 141. On addition of triethylamine (Et₃N), this proton (path a) was probably abstracted faster than the proton of the sulfoxonium salt (path b) and thus led to the formation of 2-phenylethylidene-1,3-dithiane 144 in an elimination reaction, as depicted in Scheme 63.

Amide 148 was readily prepared from phenylacetyl chloride 149 in good yield (74 %) and then was indeed successfully employed in the synthesis of thioacetal 147, however the yield was still low (38 %). This improvement was possibly due to the methoxyl oxygen, which is capable of coordinating to Li metal, as shown in Scheme 64. This may suppress carbonyl formation until aqueous work-up, and prevent any side product formation and thus furnish thioacetal 147 as suggested by Seebach and Corey.
2.3.3 Functionalised tropane precursor synthesis

2.3.3.1 Introduction

Starting from tropinone 116, it was anticipated that 3α-tosyloxymethyltropane 137 could be prepared, following the route described by Murr et al. This route, in the first instance, requires the preparation of 3-methylenetropane 155 by Wittig reaction of 116. Hydroboration of 155 with disiamylborane (Sia₂BH), followed by oxidation with alkaline hydrogen peroxide was expected to give 3α-hydroxymethyltropane 156. Treatment of 156 with n-butyllithium and the addition of p-toluenesulfonyl chloride would then generate the tosyl compound 137, as depicted in Scheme 65.

Scheme 64

Scheme 65
2.3.3.2 Attempted synthesis of 3α-tosyloxymethyltropane 137

In the event, 3-methylenetropane 155 was readily prepared, following the method described by Murr et al. This required the addition of tropinone 116 to a solution of methylenetriphenylphosphine, which was generated from a mixture of methyltriphenylphosphonium bromide 157 and potassium tert-butoxide in THF (Scheme 66). Compound 155 was purified by distillation and isolated as oil in good yield (87%).

\[
\text{N} \quad \text{O} \\
\text{116} \quad \text{157} \\
\text{1. KO}^\text{Bu} (1.3 \text{ equiv.}), \quad \text{THF, 0 °C, 4h.} \\
\text{87 %} \\
\text{155}
\]

Scheme 66

The next step required hydroboration and it was necessary to establish the hydroboration protocol on a model system. Therefore, styrene 158 was selected and subjected to hydroboration with disiamylborane (Sia₂BH) 159 and 9-borabicyclo[3.3.1]nonane (9-BBN) 160.

\[
\begin{align*}
\text{158} & \quad \text{Sia}_2\text{BH 159} & \quad \text{9-BBN 160}
\end{align*}
\]

When Sia₂BH 159 was used, no reaction was observed at all. Fortunately, the use of 9-BBN 160 successfully generated 2-phenylethyl alcohol 161, as depicted in Scheme 67. The various conditions are summarised in Table 6.
1. THF, r.t., 4h.
2. EtOH, NaOH, H₂O₂, r.t., 15h.

158 + \[ \text{Sia}_2^\text{BH} \] \[ \rightarrow \] 161

(1.1 equiv.)

Scheme 67

<table>
<thead>
<tr>
<th>Entry</th>
<th>olefin</th>
<th>hydroborating agent</th>
<th>NaOH</th>
<th>H₂O₂</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>158</td>
<td>Sia₂BH 159</td>
<td>5 ml, 3 M</td>
<td>5 ml, 27.5 %</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10.00 mmol)</td>
<td>(12.00 mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>158</td>
<td>Sia₂BH 159</td>
<td>1 ml, 6 M</td>
<td>2 ml, 27.5 %</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.00 mmol)</td>
<td>(3.38 mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>158</td>
<td>9-BBN 160</td>
<td>2 ml, 6 M</td>
<td>5 ml, 27.5 %</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.73 mmol)</td>
<td>(9.60 mmol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Hydroboration and oxidation of styrene 158 under different conditions.

After the modest but promising result of the hydroboration of styrene 158, 3-methylenetropane 155 was then subjected to hydroboration with 9-BBN 160 and Sia₂BH 159. No reaction could be achieved with Sia₂BH 159 under a variety of different conditions. Some success was achieved however, when compound 155 was treated with a four-fold excess of 9-BBN 160, as shown in Scheme 68.
In the event, neither 155 nor 156 could be isolated. Attempted distillation of the reaction mixture almost certainly lead to loss of the desired alcohol 156, leaving only the cis-1,5-cyclooctanediol, an alcohol generated from the oxidation of 9-BBN 160. This reaction needs further investigation. In addition, compound 155 was also subjected to hydroboration with BH$_3$.THF, following the method described by Lyle$^{11}$ et al. However, despite some effort no reaction was observed. The various conditions are summarised in Table 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>olefin</th>
<th>hydroborating agent</th>
<th>NaOH</th>
<th>H$_2$O$_2$</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>155</td>
<td>Sia$_2$BH 159</td>
<td>2 ml, 3 M</td>
<td>2 ml, 27.5 %</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.24 mmol) (1.24 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>9-BBN 160</td>
<td>2 ml, 3 M</td>
<td>2 ml, 27.5 %</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.00 mmol) (2.00 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>155</td>
<td>Sia$_2$BH 159</td>
<td>4 ml, 3 M</td>
<td>8 ml, 27.5 %</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.00 mmol) (4.00 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>155</td>
<td>9-BBN 160</td>
<td>2 ml, 6 M</td>
<td>5 ml, 27.5 %</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.00 mmol) (4.00 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>155</td>
<td>BH$_3$.THF</td>
<td>1 ml, 9M</td>
<td>3 ml, 27.5 %</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.00 mmol) (1.80 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Hydroboration and oxidation of 3-methylenetropane 155 under different conditions.

In order to proceed with the synthesis of the target electrophile 137, hydroboration of 3-methylenetropane 155 was re-investigated under two different sets of conditions.
In the first case, 155 was subjected to hydroboration by \textit{in situ} preparation of \textit{Sia}$_2$BH 159 following the literature method described by Brown$^{119}$ and Zweifel, as shown in Scheme 69. The reaction generated a product, which emerged to be a 1:1 mixture of stereoisomers, as determined from the $^1$H NMR spectrum, showing a set of doublets at δ 3.63 and 3.58 ppm for the methylene protons of CH$_2$OH moiety for each stereoisomer. The $^{13}$C NMR spectrum, shown in Figure 9, also indicated that the stereoisomers were present in a 1:1 ratio. One of the isomer was later revealed to be the \textit{endo} BH$_2$-N complex 162 (see Figure 11, p. 62). The product mixture was purified by chromatography and isolated as viscous oil. The yield of this reaction was however disappointingly low (10%).

$$\text{Scheme 69}$$
Another isomer, present as a 1:1 mixture with endo-162 can have two potential origins: either it is an exo isomer 162 as a result of the hydroboration or it is a diastereomeric endo BH₃ complex 162 with a different BH₃ configuration at nitrogen, as depicted in Figure 10.

When Sia,BH 159 (4.6 equiv.) was used, the yield did not significantly increase (12 %). In an attempt to improve the yield, reverse addition of the reagents was explored, with Sia,BH 159 (5.0 equiv.). However, no hydroboration was observed at all in this case. To optimise the reaction conditions and to increase the isomer ratio, 3-methylenetropane 155 was also submitted to hydroboration by in situ preparation of 9-BBN 160, under three different sets of conditions (Table 8). However, in each case no hydroboration product was observed.
Table 8: Optimised hydroboration and oxidation conditions of 3-methylenetropane 155.

With N-borane-3α-hydroxymethyltropane 162 in hand, the compound 162 was subjected to tosylation, following the method described by Murr et al. (1991). The method first requires generation of the alkoxide with n-butyllithium in the presence of a catalytic amount of triphenylmethane (Ph₃CH), and then addition of tosyl chloride 163, as shown in Scheme 70. The reaction generated a tosyl compound 164 was also a 1:1 mixture of two stereoisomers.

One isomer was successfully purified by chromatography and isolated as a white solid. A suitable crystal of this isomer was obtained by re-crystallisation from petroleum ether and was submitted for X-ray analysis. Surprisingly, at the time, the isomer was revealed to be a BH⁻-N complex and its tosyloxymethyl group was indeed had the \textit{endo} configuration, as required for the target stereoisomer. The X-ray structure of the isomer is illustrated in Figure 11. It was concluded in retrospect that one of the mixtures in the
product alcohol 162 obtained from the hydroboration reaction was also a BH$_3$-N complex with an *endo* hydroxymethyl configuration.

**Figure 11:** The X-ray crystal structure of the *endo* BH$_3$-N complex 164.

### 2.3.3.3 Synthesis of N-Troc-3α-tosyloxymethyltropane 137

The preparation of 3α-tosyloxymethyltropane 137 was unsuccessful in our hands due to complex 164, which formed between diborane and the nitrogen of the tropane ring.

To succeed it became necessary to deactivate the N-methyl group. This can be achieved by urethane formation by reaction with ethyl chloroformate 165, benzyl chloroformate 166 or 2,2,2-trichloroethyl chloroformate (TrocCl) 167. This strategy has been known
for some time in the alkaloid field and among these urethanes TrocCl 167 is reported to be a valuable protecting group for tropane nitrogen.

\[ \text{H}_3\text{C} \overset{\text{O}}{\text{O}} \text{Cl} \quad \text{Ph} \overset{\text{O}}{\text{O}} \text{Cl} \quad \text{TrocCl} \]

165 166 167

It was anticipated that either the N-methyl group of tropinone 116 or 3-methylenetropane 155 could be deactivated in this way, as depicted in Scheme 27, to generate 168 or 169. Such a reaction of 116 with TrocCl 167 has already been described by Montzka et al.

\[
\begin{align*}
\text{N-Demethylation} & \quad \text{Troc} \quad \text{N} \\
\text{Wittig reaction} & \\
\text{N-Demethylation} & \quad \text{Troc} \\
\end{align*}
\]

Scheme 71

The required urethane electrophile, in this case, N-Troc-3α-tosyloxymethyltropane 170 should be readily prepared, following the same route described for 3α-tosyloxymethyltropane 137. After hydroboration-oxidation, re-conversion of Troc into the necessary N-methyl group should be readily achieved by a LiAlH₄ reduction. During the synthesis of scopine, pseudoscopine and epoxytropanes, a similar conversion by Justice and Malpass has already been reported.
First, N-demethylation of tropinone 116 was carried out following the method described by Montzka et al. This involved the reaction of 116 with 20% excess of TrocCl 167 in refluxing benzene with a catalytic amount of $K_2CO_3$, as shown in Scheme 72. Compound 168 was purified by column chromatography and isolated as a white amorphous solid in a moderate yield (52%).

\[
\begin{align*}
\text{1. } & K_2CO_3 \text{ (3 %), benzene,} \\
& \text{reflux, 39h. } \text{TrocCl} \rightarrow \text{TrocCl} \\
\end{align*}
\]

Scheme 72

Next, N-demethylation of 3-methylenetropane 155 with TrocCl 167 was explored. The reaction was carried out in refluxing toluene, following the method described by He and Brossi, as shown in Scheme 73. The absence of a catalytic amount of $K_2CO_3$ differs from the previous method. Again compound 169 was purified by column chromatography and was isolated as clear oil in good yield (79%). This compound solidified on standing.

\[
\begin{align*}
\text{1. } & \text{Toluene, reflux, 40h.} \\
& \text{TrocCl} \rightarrow \text{TrocCl} \\
\end{align*}
\]

Scheme 73

Compound 169 was then submitted to hydroboration by in situ preparation of 9-BBN 160 following the literature methods, as shown in Scheme 74. The resultant alcohol
Compound 171 was purified by chromatography and isolated as viscous oil in excellent yield (100%). However, compound 171 was a mixture of two isomers with an endo/exo ratio of ~3:1, as determined from $^1$H NMR spectrum.

The $^{13}$C NMR spectrum of 171 showed a peak at $\delta$ 67.4 ppm for the endo and $\delta$ 67.6 ppm for the exo carbon resonances of -CH$_2$OH moiety. In an attempt to increase the isomer ratio in the favour of the endo product, compound 169 was also subjected to hydroboration by in situ preparation of more bulky Sia$_2$BH$_{119}$ 159, as depicted in Scheme 75, using a variety of different conditions (see Table 9, p. 66).

The resultant compound 171 was purified by chromatography and isolated as oil in up to 81% yield. Compound 171 was also a mixture of two isomers, and this time the endo/exo isomer ratio, which was determined by $^1$H NMR analysis, increased substantially, varying from 18:1 to 73:1 in different experiments in favour of the endo isomer. These experiments are summarised in Table 9.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroborating agent (equiv.)</th>
<th>Quenching agent (ml)</th>
<th>6M NaOH (ml)</th>
<th>28 % H₂O₂ (ml)</th>
<th>Yield (%)</th>
<th>Isomer ratio (endo/exo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sia₂BH^a (1.5)</td>
<td>H₂O (0.5)</td>
<td>3</td>
<td>6</td>
<td>30</td>
<td>18:1</td>
</tr>
<tr>
<td>2</td>
<td>Sia₂BH^a (3.0)</td>
<td>H₂O (1.0)</td>
<td>4</td>
<td>8</td>
<td>38</td>
<td>21:1</td>
</tr>
<tr>
<td>3</td>
<td>Sia₂BH^a (3.5)</td>
<td>H₂O (0.5)</td>
<td>4</td>
<td>8</td>
<td>68</td>
<td>43:1</td>
</tr>
<tr>
<td>4</td>
<td>Sia₂BH^a (5.3)</td>
<td>H₂O (2.0)</td>
<td>2</td>
<td>2</td>
<td>81</td>
<td>73:1</td>
</tr>
</tbody>
</table>

a) prepared readily by treating a mixture of 2-methyl-2-butene and sodium borohydride either in THF or diglyme (entry 4) with boron trifluoride diethyl etherate at -10 to 0 °C.

Table 9: Optimised conditions of hydroboration and oxidation of N-Troc-3-methylenetropane 169.

Compound 169 was finally subjected to hydroboration with Sia₂BH 159 (8.0 equiv.), a reagent which was prepared from borane-THF complex (1.0 M solution in THF) and 2-methyl-2-butane (2.0M solution in THF) using a kit supplied by the Aldrich Chemical Company. However, no hydroboration reaction was observed at all.

Thus, it was demonstrated that the more bulky alkyl groups on the Sia₂BH 159, when compared to the 9-BBN 160, increase the isomer ratio substantially. A typical set of ^1H NMR spectra for 171, showing the endo (δ 3.65 ppm) and exo (δ 3.43 ppm) methylene resonances of -CH₂OH moiety, are shown in Figure 12 for 9-BBN and Sia₂BH.
9-BBN (as Scheme 74, p. 65)  
Sia₂BH (entry 1, Table 9, p. 66)

Figure 12: Typical $^1$H NMR spectra for 171, showing the endo and exo methylene resonances of the CH₂OH moiety.

Reduction of the Troc group was required now to reconver the protecting group into an N-methyl group and provide the required 3α-hydroxymethyltropane 156. Therefore compound 171 was subjected to reduction by LiAlH₄ in refluxing THF following the method described by Justice and Malpass, as illustrated in Scheme 76. The $^1$H NMR analysis of the crude material did not indicate the presence of the carbamate moiety (4.50-5.00 ppm) and were now two methyl singlets at 2.22 and 2.23 ppm. Although the $^1$H NMR analysis was encouraging, t.l.c. analysis of the crude material indicated a complex mixture.
In view of this, N-Troc-3α-tosyloxymethyltropane 170 emerged as an alternative electrophile to 3α-tosyloxymethyltropane 137 for the coupling reaction. It was anticipated that synthesis of 170 should be straightforward, following the tosylation method described by Murr et al.

To develop this strategy, compound 171 was treated with p-toluenesulfonyl chloride 163, in the presence of n-BuLi and a catalytic amount of triphenylmethane (Ph₃CH), as depicted in Scheme 77. After purification over silica gel, tosylate 170 was isolated in low yield (14 %), but N-tosylamide 172 was also isolated as a by-product in low yield (4 %).

Scheme 76
This low yield (14 %) was disappointing and therefore the method described by Prisbe\textsuperscript{128} et al. was explored, as shown in Scheme 78. This required treatment of 171 with tosyl chloride 163 in the presence of the much milder base, pyridine. Following the work-up described by Furniss\textsuperscript{129} et al. involving purification over neutral alumina, tosylate 170 was this time isolated as a white solid and in excellent yield (90%).

2.3.3.4 Discussion

Tosyloxy methyl tropane, required for the coupling reaction, could only be prepared as its BH\textsubscript{3} complex 164, as shown in Scheme 79.
The first step involved the preparation of 3-methylenetropane 155 from tropinone 116 in excellent yield (87%), but the next step, hydroboration of 155 proved to be very difficult and generated 162 as a 1:1 mixture in a disappointingly low yield (12%). The final step was the tosylation of 162, which proceeded in only moderate yield (51%) to give the final product 164. The X-ray crystal structure analysis of 164 offered a method not only for assigning the stereochemistry of 164, but also for assigning the stereochemistry of the alcohol 162. Clearly as compound 164 had the tosyloxymethyl group in the endo configuration, this tells us retrospectively that alcohol 162 must also have possessed the endo configuration.

A review of the literature reveals that unsaturated amines, such as 2,4-dihydropyrroline 173 and 1,2,3,6-tetrahydro-pyridine 175, on treatment with an excess of borane-methyl sulfide (BMS) or disiamylborane (Sia,BH), gave BH₃-N complexes 174 and 176, leaving the double bond intact, as depicted in Scheme 80.
On the other hand, N-alkyl-1,2,3,6-tetrahydropyridine\textsuperscript{130,121} and 2-tropidine\textsuperscript{179} behaved differently and not only formed BH\textsubscript{3}-N complexes, but also underwent hydroboration with an excess of diborane. Upon oxidation, the corresponding amino alcohols\textsuperscript{178} and\textsuperscript{180} were obtained as BH\textsubscript{3}-N complexes in moderate to good yields, as shown in Scheme 81. Formation of BH\textsubscript{3}-N complex\textsuperscript{162} was therefore consistent with these results during BH\textsubscript{3} and \textit{in situ} prepared Sia\textsubscript{2}BH reactions.

All of the tropanes\textsuperscript{155,162} and\textsuperscript{164}, which have been examined by mass spectroscopy, exhibit a metastable peak at 82 amu. This is almost a characteristic peak for tropane alkaloids and can be rationalised in the following manner\textsuperscript{131}. First, removal of one of the non-bonding electrons from nitrogen forms the molecular ion (f), which is then cleaved homolytically between CI and C2. Initial generation of radical ion (g) involves hydrogen transfer from C-6, affording (h), which on decomposition generates metastable ion (i), as illustrated in Figure 13.
Figure 13: Formation of the characteristic metastable peak at 82 amu for the tropane alkaloids 155, 162 and 164.

N-Troc-3α-tosyloxyethyltropane 170 has been developed as an alternative substrate to the N-BH₃ complex 164 and was readily prepared starting from 3-methylenetropane 155, as depicted in Scheme 82.

The first step involved demethylation of 155 and proceeded in good yield (79 %) to give 169. This was followed by hydroboration of 169 and the alcohol 171 was successfully generated as an almost single endo isomer and also in excellent yield (81 %). The final step was the tosylation of 171, which yielded the required tosyl product 170 in excellent yield (90 %).

In hydroboration reactions, the availability of the double bond and the size of the alkyl group on the borane generally influence the stereoselectivity. The endo-face of the
double bond in 169 is less available than the exo-face, due to transannular interactions with the hydrogen atoms attached to C6 and C7. Sia₂BH 159 is a bulkier reagent than 9-BBN 160, as shown in Figure 14. Therefore, hydroboration of 169 with Sia₂BH 159 took place exclusively from the exo-face of the double bond giving the required endo isomer, as a major product. However, hydroboration of 169 with 9-BBN 160 was less selective and gave only a 3:1 mixture in favour of the endo isomer.

Figure 14: The 3D molecular modelling of N-Troc-3-methylenetropane 169, 9-BBN 160 and Sia₂BH 159.

When n-BuLi rather than pyridine was used as a base in the tosylation of 171, the yield was disappointingly low (14%). This may be due to a competing radical process, where n-BuLi initiates the formation of pseudotropane 181 and then its ultimate conversion to N-tosylamide 172, as illustrated in Scheme 83. Isolation of N-tosylamide 172 as a by-product may support the hypothesis suggested above.

Scheme 83
2.3.4 Coupling reactions

2.3.4.1 Introduction

N-Troc-3α-Tosyloxymethyltropane 170 is a potential substrate now for the coupling reaction with 2-phenylacyl-1,3-dithiane 147 and offers a route for the synthesis of ketone 110, as outlined in Scheme 84. It was envisaged that the key step in this route would involve the synthesis of 182. The final steps would then require reduction of the Troc group to an N-methyl tropane and reduction of the carbonyl group to a hydroxyl group. Removal of 1,3-dithiane would finally generate the target molecule 110.

![Scheme 84](image)

2.3.4.2 Attempted synthesis of key intermediate 182 via tosylate 170

Following the literature method, compound 170 was subjected to a coupling reaction with the carbanion derived from thioacetal 147. The reaction was carried out in the presence of hexamethylphosphoric triamide (HMPA) under two different sets of conditions, as illustrated in Scheme 85. In the first instance, the carbanion was generated at -78 °C by in situ preparation of LDA and was then stirred for 2.5 h at
-30 °C, prior to the addition of 170. In the second case, the carbanion was generated using commercially available LDA and then stirred for 30 min at -30 °C, prior to the addition of 170. In both reactions an excess of 170 was added to the carbanion at -78 °C and then the reaction mixture was left to stir overnight (17 h) or 41 h. However, in both cases no reaction was observed.

![Chemical structures](image)

**Scheme 85**

In order to ensure that the lithiation of thioacetal 147 had taken place, a deuterium exchange reactions was carried out as suggested by Seebach and Corey. This required generation of the anion from thioacetal 147, followed by the addition of an excess of D<sub>2</sub>O, as illustrated in **Scheme 86**. Upon work-up, the <sup>1</sup>H NMR analysis of the crude material revealed that not only had the thioacetal proton (a) become labelled with isotope, but that one of the methylene protons (b) adjacent to the carbonyl group was also substantially exchanged. The level of deuterium incorporation into both sites (a and b) in 183 was determined by the integration of the <sup>1</sup>H NMR signals for the thioacetal methine (a) and the methylene protons (b) relative to the methylene protons adjacent to the sulphur atom. The reaction conditions and the incorporation results are summarised in **Table 10**.

![Chemical structures](image)

**Scheme 86**
<table>
<thead>
<tr>
<th>entry</th>
<th>Base (equiv.)</th>
<th>Reaction temp., time</th>
<th>Deuterated 183 at a (%)</th>
<th>Deuterated 183 at b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA(^a) (1.1)</td>
<td>-78/0 °C, 3h</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>LDA(^b) (1.1)</td>
<td>-30 °C, 0.5h</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>NaH (2.7)</td>
<td>r.t., 15 min.</td>
<td>94</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^a\) In situ Prepared by the addition of n-BuLi (1.6 M solution in hexanes) into the solution of diisopropylamine in THF at -78 °C \(^b\) Commercially available

Table 10: Generation of the deuterated thioacetal 183 by deuterium exchange reaction of thioacetal 147 under different conditions.

After this failure, the coupling reaction of 170 with 1,3-dithiane 142 was also investigated. Following the method described by Page et al., dithiane 142 was first lithiated with lithium diisopropylamine (LDA) in THF between -30 and -20 °C. The anion was then reacted with 170 between -78 °C and r.t., as shown in Scheme 87. The reaction was monitored by t.l.c. (3:7 AcOEt/Petrol) and a single new spot was observed. Purification over silica gel (1:4 ethyl acetate/petrol) gave a milk-white amorphous solid. However, characterisation of this product by the \(^1\)H NMR analysis was inconsistent with the desired product 184.

\[ \text{Troc} \quad 170 \quad + \quad \text{OTs} \quad 142 \quad \rightarrow \quad \text{Troc} \quad 184 \]

Scheme 87

2.3.4.3 Synthesis of N-Troc-3α-iodomethyltropane 185

In view of the failed reactions of N-Troc-3α-tosyloxyethyltropane 170 with 2-phenylacetyl-1,3-dithiane 147 and 1,3-dithiane 142, and also in view of the fact that primary iodides are reported to react readily with 1,3-dithiane 142, N-Troc-3α-iodomethyltropane 185 was considered as an alternative electrophile. It was anticipated that this could be achieved either by nucleophilic substitution of tosylate 170 with NaI.
or by hydroboration / iodination of 169, as depicted in **Scheme 88**.

![Scheme 88]

Nucleophilic displacement of tosylate 170 with NaI was investigated in the first instance. Following the literature method described by Byon\textsuperscript{134} et al., tosylate 170 was treated with NaI in refluxing acetone, as shown in **Scheme 89**. When wet acetone was used, hydroxide (OH\textsuperscript{-}) displacement occurred and gave predominantly N-Troc-3α-hydroxymethylnorropane 171. However, in freshly distilled and dry acetone, this reaction was suppressed and only iodide (I\textsuperscript{-}) displacement took place, generating the required product 185, which was purified by chromatography and isolated as an oil in good yield (79\%).

![Scheme 89]

Since organoboranes give very rapid reactions with iodine under the influence of NaOH\textsuperscript{135} or NaOMe\textsuperscript{136}, this has emerged as a straightforward method for the transformation of terminal olefins into primary iodides\textsuperscript{135}. Accordingly the hydroboration-iodination of N-Troc-3-methylenetropane 169 was also investigated. This required hydroboration of 169 with Si\textsubscript{2}BH\textsubscript{159}, followed by iodination under two sets of conditions, as illustrated in **Scheme 90**. The \textsuperscript{1}H NMR analysis of the crude material did not indicate any residual double bond. However, the title compound could never be isolated. The conditions are summarised in **Table 11**.
1. THF, r.t., 4 - 18h.
2. MeOH, I₂, NaOMe (3 - 5 equiv.)

**Scheme 90**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroborating agent (equiv.)</th>
<th>Quenching agent (ml)</th>
<th>3M NaOH in MeOH, ml</th>
<th>I₂ (equiv.)</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sia₂BH⁻¹ 159 (3)</td>
<td>MeOH 3</td>
<td>3</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Sia₂BH⁻¹ 159 (5)</td>
<td>MeOH 6</td>
<td>5</td>
<td>5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

a) *In situ* prepared by treating a mixture of 2-methyl-2-butene and NaBH₄ in THF with BF₃.OEt₂ at -10 to 0 °C.

**Table 11:** Hydroboration and iodination of N-Troc-3-methylenetropane 169 under different conditions.

### 2.3.4.4 Attempted synthesis of key intermediate 182 via iodide 185

With N-Troc-3α-iodomethyltropane 185 in hand, it was subjected to a coupling reaction with the anion generated from 1,3-dithiane 142 and LDA, following the method described by Page et al., as shown in **Scheme 91**. The reaction was monitored by t.l.c. (2:8 Petrol / CH₂Cl₂) and two new spots were observed. However, purification by column chromatography over silica gel (0.5:9 ethyl acetate/petrol) did not afford the desired compound 184.
1. LDA (1.2 equiv.), THF, -20 °C, 1.5h; -78 °C to r.t., 33h.

Scheme 91

2.3.4.5 Discussion

N-Troc-3α-Tosyloxymethyltropane 170 failed to react with 2-lithiated-2-phenylacetyl-1,3-dithiane. More surprisingly, both N-Troc-3α-tosyloxymethyltropane 170 and N-Troc-3α-iodomethyltropane 185 also failed to react with 2-lithiated-1,3-dithiane, as depicted in Scheme 92.

The most reasonable explanation as to why the coupling reactions of N-Troc-3α-tosyloxy- and iodo- methyltropanes 170 and 185 were unsuccessful in our hands is the steric hindrance due to C6 and C7 of the tropane ring, and consequently a lack of susceptibility of the tosyl group of 170 and iodo group of 185 to nucleophilic attack.
A review of the literature indicates that coupling reactions of 2-acyl-1,3-dithianes with alkyl iodides are adversely influenced by the increased size of substituents at the 2-position of 1,3-dithianes, consistent with our observations. For instance, the iodide 186 reacted with the acyldithiane 187 [R: CH₂CH₂CH=C(CH₃)₂] within 96 h and gave 188 in low yield (25 %). However, the iodide 186 reacted with the 2-acetyl-1,3-dithiane 189 [R: CH₃] within 3 h and gave 190 in moderate yield (50 %), as depicted Scheme 93.

\[
\begin{align*}
186 & \quad \text{OTHP} + \text{R}^n \text{SSn}^o \quad 1. \text{DME, NaH} \quad 25-50 \% \\
187 & \quad 188 \quad \text{R}: \text{CH}_2\text{CH}_2\text{CH}=\text{C(CH}_3)_2 \\
189 & \quad 190 \quad \text{R}: \text{CH}_3 \\
\end{align*}
\]

Scheme 93

It is not clear at present that why N-Troc-3α-iodomethyltropane 185, obtained by a hydroboration-I₂ reaction, could not be isolated, apart from suggesting that the use of NaOMe as a base led to the conversion of the two sec-siamyl groups of borane 192, in preference to the primary group, into the corresponding iodide 191 (Scheme 94). As suggested by Brown et al., the choice of base, such as NaOH, may circumvent the formation of 191, by producing only the desired iodide 185, since the primary group will react in preference to the sec-siamyl groups in the borane 192 (Scheme 94).

\[
\begin{align*}
\text{I}_2, \text{NaOMe} & \quad \text{191} \quad \text{I}_2, \text{NaOH} \quad \text{Troc}^N \quad \text{192} \\
\text{191} & \quad \text{192} \quad \text{185} \\
\end{align*}
\]

Scheme 94
CHAPTER THREE

Ketone Analogues of 3α-Esterified

Tropane Alkaloids
CHAPTER THREE 92

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CHAPTER THREE

3.1 General introduction

3.1.1 3α-Esterified tropane alkaloids

The tropane alkaloids have a common bridged heterocyclic system containing the 8-methyl-8-aza-bicyclo[3.2.1]octane ring as shown below. These alkaloids are not only found in the plant family Solanaceae, but also in other plant families, such as Convolvulaceae, Erythroxylaceae, Proteaceae and Rhizophoraceae. In addition, the presence of tropane alkaloids has occasionally been identified in the plant families Brassicaceae (Cruciferae), Euphorbiaceae and Olacaceae. This class of natural products displays interesting and diverse pharmacological activities, such as parasympatholitic, anaesthetic and anticholinergic effects.

![tropane alkaloid structure](image)

The largest group of tropanes are the 3α-monosubstituted tropane alkaloids, which are derived by esterification of the alcohol tropine (3α-hydroxytropane) with a carboxylic acid. The carboxylic acid moiety of these naturally occurring alkaloids can be quite diverse and range from aliphatic to aromatic acids. Some of the naturally occurring ones are summarised in Table 12.
Table 12: Some of the known carboxylic acid moieties of the naturally occurring tropane alkaloids 200, 125 and 203-204.

Among these acids, the (RS)- and (S)-tropic acid esters 202 and hyoscyamine 92, respectively are widely occurring tropane alkaloids found in the plant family Solanaceae, especially in Hyoscyamus niger, Atropa belladonna and Datura stramonium. These alkaloids were the first of the parasympatholytics 63 to be identified, i.e. muscarinic receptor antagonists.
The benzoic acid ester 125, benzoyloxytropane is found in the plant families Rhizophoraceae and Erythroxylaceae and inhibits 5-hydroxytryptamine (5-HT₃)-induced bradycardia in urethane-anesthetized rats. 5-Hydroxytryptamine is a neurotransmitter, which operates within the central and peripheral nervous systems and its deficiency is associated with depression. Benzoyloxytropane 125 has approximately 100-fold less affinity to the 5-HT₃ receptors than those well-known 5-HT₃ receptor ligands, such as tropisetron 205, a synthetic 3α-monosubstituted tropane alkaloid. The synthetic tropane alkaloid, MDL-72222 206 has also been developed. This compound is amongst the most commonly used 5-HT₃ receptor ligands in the treatment of depression.

3.1.2 CH₂ for O replacement

In this programme analogues of tropane alkaloids have been prepared where the O atom is replaced by a CH₂ group. This follows other successes of this strategy, for example phosphonic acids 207 can function as analogues of natural phosphates 208 and renders them stable to phosphatase activity.

Vidarabine (9-β-D-arabinofuranosyladenine) 209 is an antitumour agent and shows a broad-spectrum activity against DNA viruses. As a result, it is clinically used for the treatment of herpes encephalitis and herpes keratitis. However, it suffers from rapid
in vivo deamination to the corresponding 9-β-D-arabinofuranosylhypoxanthine 210 by adenosine deaminase. In order to suppress this problem, compound 211, known as cyclaridine was prepared, in which the ring ether oxygen of 209 was replaced by a CH₂ group. This was reported to be resistant to adenosine deaminase and displays substantial anti herpes activity.

Benztropine 212, a tropane ether is a parasympatholytic agent used clinically as an anti-Parkinson's disease drug. When the bridging ether oxygen was replaced by a CH₂ moiety, the corresponding 2-(tropan-3-yl)-1,1-diphenylethane 213 was found to be more active than atropine 202 and as active as benztropine 212 in the in vitro assays. This is the only example of such a modification in tropane alkaloids analogue synthesis.

Tropane alkane 213 was prepared from ethyl (tropan-3-yl)acetate 214 in three steps, as shown in Scheme 95. The first step involved reaction of tropane ester 214 with phenyl lithium to give the corresponding 2-(tropane-3-yl)-1,1-diphenylethanol 215 in good yield (76%). Alcohol 215 was then heated in a mixture of HCl and AcOH to give the corresponding olefin 2-(tropane-3-yl)-1,1-diphenylethene 216 in quantitative yield (100%). Hydrogenation of tropane alkene 216 under strenuous conditions (Raney Ni / 60 °C / 35 kg/cm² H₂) finally generated tropane alkane 213, however, the yield was not
reported for the final step.

\[
\begin{align*}
\text{1. PhLi (3-5 equiv.), Et}_2\text{O, 2-5h.} & \quad 76\% \\
\text{214} & \quad \text{N} \\
\text{215} & \quad \text{216} \\
\text{1. AcOH/HCl (3:1),} & \quad 100\% \\
\text{100 \degree C, 30 min.} & \quad \text{100 \degree C, 60 \degree C.}
\end{align*}
\]

Scheme 95

3.2 Ketone analogues of 3α-esterified tropane alkaloids

Ketone 124 is a CH₂ analogue of benzoyloxytropane 125 and was first prepared by Zirkle\textsuperscript{150} \textit{et al.} in 1962 as an intermediate in the synthesis of 3-substituted tropane derivatives, mainly with the general structure 217. More recently, it was reported that ketone 124 was as good inhibitor of 5-HT\textsubscript{3} receptor as benzoyloxytropane 125.

\[
\begin{align*}
\text{124} & \quad \text{125} \\
\text{217}
\end{align*}
\]

A literature survey has shown that ketone 124 is the only known CH₂ analogue of the naturally occurring 3α-substituted tropane alkaloids and it was decided to devise a route
that would allow the synthesis of more such analogues of tropane ester natural products. At the outset, the ketones 218, 219 and 220 were selected as target compounds for this study. In each case the corresponding esters 195, 198 and 201 have all been identified in various plants.

Since ketone 124 was prepared from the Grignard reaction of ester 214 with phenylmagnesium bromide, as depicted in Scheme 96 and isolated as a major product in good yield (75 %), it was envisaged that an analogous strategy would provide an appropriate route for the synthesis of ketones 218-220.

Scheme 96

Preparation of the key starting ester, ethyl (tropan-3-yl)acetate 214 by two different methods 151,88 has been reported, both starting from tropinone 116. The method of
Zirkle et al. began with a Knoevenagel condensation of tropinone 116 with malononitrile 221 to generate the corresponding (tropan-3-ylidine)malononitrile 222 as an HCl salt in excellent yield (100 %). Acid-catalysed hydrolysis of 222, followed by decarboxylation and esterification gave ethyl (tropan-3-ylidine)acetate 132 in good yield (76 %). An alternative method reported by Calvert and Hobson differs only in the synthesis of 132. This route used a Horner-Emmons reaction between tropinone 116 and triethyl phosphonoacetate 131 to generate 132 in moderate yield (63 %). These approaches to 132 are shown in Scheme 97.

The final step to ester 214, as illustrated in Scheme 98, involved the catalytic hydrogenation of 132. Raney nickel was used as a catalyst and the hydrogenation was carried out under 5 atm. or 60 p.s.i pressure to generate 214 in excellent yield (89 %), but as a mixture of stereoisomers. The endo (α) form was the predominant isomer of the hydrogenation reaction, and was isolated as a single isomer, after recrystallisation of its picrate salt.
A modification of Calvert's and Hobson's method to 214 has recently been reported by Kato et al. The Horner-Emmons reaction of tropinone 116 was carried out in THF rather than in 1,2-dimethoxyethane (DME) and the hydrogenation used palladium on activated carbon under 14 atm. pressure. The yield of Horner-Emmons reaction was improved slightly, however hydrogenation yield was reported to be only 60%.

3.2.1 Attempted synthesis of ketone analogues from ester 214

At the outset a Grignard reaction of ester 214 was chosen as a method to the ketone analogues 218-220, as outlined in Scheme 99. Thus the programme began with the synthesis of ester 214.
Calvert and Hobson's method was chosen to prepare 214. The first step in this route, as discussed before, involved the Horner-Emmons reaction of tropinone 116 with triethyl phosphonoacetate. Deprotonation of triethyl phosphonoacetate 131 was mediated at -78 °C with NaH, followed by the addition of tropinone 116, as shown in Scheme 100.

After distillation, the α,β-unsaturated ester 132 was obtained as an oil in 77 % yield, an improvement on the reported yields (63 % and 66 %). As expected, ester 132 was contaminated with the β,γ-unsaturated ester 133 about 11 % (8:1 ratio). This was clearly evident by 13C NMR analysis of ester 132. Separation of the two isomers was not necessary, as ester 132 was used directly as a mixture with 133 for hydrogenation.

Under three sets of conditions i) 1 atm - 23 h, ii) 3-4 atm - 96 h and iii) 20 atm - 21 h, hydrogenation over palladium on activated carbon failed to give 214, and only the starting esters 132 and 133 were recovered, after filtration of the catalyst. This was unexpected, since hydrogenation of conjugated double bonds under these conditions is common. For instance, it was reported that ethyl (4-piperidine-3-ylidene)acetate 223 in ethanol was successfully hydrogenated over palladium on activated carbon to the corresponding ethyl (4-piperidine-3-yl)acetate 224 in excellent yield (90 %).
Since the core structure of 223 is present in 132, the focus turned towards purification of the starting ester 132 (+11% of 133). Ester 132 (+11% of 133) was treated with HCl and then the aqueous layer was washed with diethyl ether, made basic with NaOH and extracted back into diethyl ether. Hydrogenation then proceeded smoothly over palladium on activated carbon even under 4-5 atm., and the reaction was complete within 22h, as depicted in Scheme 101. Thus it is concluded that the initial reaction product contained an impurity which rendered catalytic hydrogenation problematic.

This hydrogenation was carried out under 14 atm. pressure of hydrogen for 14h by Kato et al. and from this, ester 214 was obtained as a mixture of stereoisomers, but the ratio was not reported. The endo form was the predominant isomer of the hydrogenation reaction and isolated as a single stereoisomer in moderate yield (60%), after purification over neutral alumina. In our case, ester 214 was also a mixture of stereoisomers and obtained as clear oil in excellent yield (87%), after distillation. The endo/exo isomer ratio was determined to be 5:1 from the $^{13}$C NMR spectrum.

With ester 214 in hand, albeit as a mixture of stereoisomers, it was first subjected to a Grignard reaction with 1.1 equivalents of isopropylmagnesium chloride 225 in THF, as depicted in Scheme 102. In contrast to the method described by Zirkle et al., in where 2.5-4 equivalents of Grignard reagent was reported, only a slight excess of the Grignard reagent was used in order to prevent the overaddition to the product ketone 218. The $^1$H
NMR analysis of the crude material indicated that ketone 218 had formed, but approximately 50 % of the starting material 214 still remained. We did not attempt to separate the two compounds, since the conversion was about 50 %.

![Chemical structure of compounds](image1)

Scheme 102

Further investigation was pursued by submitting compound 214 to the Grignard reaction again with 1.1 equivalents of 4-methoxyphenylmagnesium bromide 226 in refluxing diethyl ether, as illustrated in Scheme 103. Following the literature methods, the Grignard reagent 226 was readily prepared in diethyl ether from the reaction of 4-bromoanisole with magnesium turnings in the presence of iodine crystals. Ketone 219 was generated, but $^1$H NMR again indicated an approximate 50 % conversion of 214.

![Chemical structure of compounds](image2)

Scheme 103

3.2.2 Ketone analogues from aldehyde 227

The low levels of conversion of the Grignard reactions with tropane ester 214, under even prolonged reaction conditions, prompted an alternative substrate to be explored in order to develop a satisfactory route. An ideal replacement for this was judged to be tropane aldehyde 227.

102
It was anticipated that aldehyde 227 could be prepared by the DIBAL-H reduction of ester 214, following the method described by Baasov\textsuperscript{157} and Sheves. This would then be amenable to Grignard reaction to generate a secondary alcohol 228, which could be oxidised to ketone 229, as shown in Scheme 104.

Accordingly, ester 214 was subjected to DIBAL-H reduction in dichloromethane (Scheme 105), under different conditions (Table 13, p. 95). The reaction temperature was varied from -78 °C to room temperature (25 °C) and in each case (Entry 1-4) was monitored by \textsuperscript{1}H NMR spectroscopy. However, the formation of aldehyde 227 was observed only between -60 °C to -40 °C (Entry 2 and 3). The same reaction was again carried out at almost identical temperatures (Entry 5 and 6), but with 2 equivalents of DIBAL-H. This time the reaction was much more successful generating aldehyde 227 at -35 °C and in a 71 % conversion (Entry 6).
N 1. DIBAL-H (2 equiv.), CH₂H₂, -35 °C, 47h.

214 (5:1 endo / exo) → 227 (5:1 endo / exo)

Scheme 105

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>DIBAL-H (equiv.)</th>
<th>Aldehyde (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>-78</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>-60</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
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<td>-40</td>
<td>3</td>
<td>50</td>
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<td>14</td>
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<td>2</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>-35</td>
<td>2</td>
<td>71</td>
</tr>
</tbody>
</table>

Table 13: The DIBAL-H reduction of ester 214 under different conditions.

Although the conversion was good (71%), aldehyde 227 could not be purified, as it decomposed on silica gel and activated neutral aluminium oxide. Therefore, an alternative route to aldehyde 227 was investigated. This required oxidation of tropane alcohol 230, as depicted in Scheme 106. Since many methods are available for the oxidation¹⁵ of primary alcohols to aldehydes, it was anticipated that this should be straightforward. Alcohol 230 could be directly prepared either by LiAlH₄ reduction of saturated ester 214 or reduction of the unsaturated ester 132.
The LiAlH₄ reduction of 132 was explored in the first instance. This was carried out by reacting ester 132 with LiAlH₄ in refluxing THF, as illustrated in Scheme 107. In contrast to the method described by Dutta et al., ester 132 was added to the slurry of LiAlH₄ at -60 °C and allowed to warm to room temperature prior to reflux.

After a tedious work-up, due to the gelatinous nature of the reaction mixture after the addition of NaOH solution, distillation afforded allylic alcohol 231 as a white solid in moderate yield (49%). Allylic alcohol 231 was contaminated with about 11 % of the endo-cyclic unsaturated alcohol 232 (8:1 ratio), as anticipated.
Since LiAlH₄ reductions of α-β-unsaturated carbonyl compounds are accompanied, to an appreciable extent, by carbon-carbon double bond reductions, isolation of allylic alcohol 231 was however a surprise. For instance, it was reported that LiAlH₄ reduction of ethyl (N-benzyl-piperidine-3-ylidine)acetate 233 gave the corresponding saturated alcohol, (N-benzyl-piperidine-3-ylidine)ethanol 234 in excellent yield (91 %), as depicted in Scheme 108.

Therefore the reaction was conducted by the addition of ester 132 to the slurry of LiAlH₄ at 0 °C and then followed by reflux (24 h). This time, some of the allylic alcohol 231 was further reduced to give the saturated alcohol 230. So the product mixture containing allylic alcohol 231 was eventually contaminated with the saturated endo and exo alcohol 230, as well as with the endo-cyclic unsaturated alcohol 232. These contaminants are shown in Figure 15 and it was clearly evident from the ¹H NMR spectrum that the contamination was about 50 % of the product mixture.
Following the literature methods previously described by Zirkle et al. and Kato et al., allylic alcohol 231 (with 11% of 232) was then subjected to hydrogenation with a catalytic amount of palladium on activated carbon, but under 1 atm. pressure of hydrogen. This resulted in a reaction product of 230, as shown in Scheme 109. The optimal conditions for this hydrogenation was 3-4 atm. pressure and the double bond was efficiently reduced to the saturated alcohol 230. Alcohol 230 was purified by distillation and obtained as a clear oil in excellent yield (84%). The $^{13}$C NMR revealed that alcohol 230 was a mixture of endo (88%) and exo (12%) isomers, in the ratio of 7:1.

With saturated ester 214 in hand, its LiAlH$_4$ reduction to the corresponding alcohol 230 was also explored. The LiAlH$_4$ reduction of 214 was carried out in refluxing diethyl ether, as illustrated in Scheme 110. In the event this proved straightforward and upon work-up by the hydrolysis method described by Micolovic and Mihailovic, alcohol 230 was obtained as a clear oil and in good yield (85%). In comparison to the LiAlH$_4$ reduction of unsaturated ester 132, the LiAlH$_4$ reduction of saturated ester 214 progressed much more smoothly.
With alcohol 230 (5:1 endo / exo) in hand, it was subjected to various oxidation protocols with pyridinium chlorochromate\(^{162}\) (PCC) and pyridinium dichromate\(^{163}\) (PDC), however all failed to give the necessary aldehyde 227. However, following the method described by Gilligan\(^{164}\) et al., the Swern oxidation of 230 proved very successful and gave aldehyde 227 in excellent yield (93 %). As described by Mancuso\(^{165}\) et al., the reaction first involves the activation of dimethyl sulfoxide (DMSO) by the addition of oxalyl chloride [(COCl)\(_2\)] at low temperature (-78 °C to -60 °C). This is followed by the addition of alcohol 230 and triethylamine (Et\(_3\)N), as depicted in Scheme 111.

Longer reaction times (e.g. 24h or 45h) led to the formation of some unidentified side products. However, short reaction times (max 30 min.), upon work-up, gave aldehyde 227 as a light-brown oil in excellent yield (93 %) and in this case aldehyde 227 was sufficiently clean to be used directly in the next step. It is noteworthy that when the aqueous layer was at pH 9-10, aldehyde 227 was always isolated as its HCl salt and in low yields. However, with the aqueous layer at pH 10-11, aldehyde 227 was isolated as...
a free amine and in excellent yield (93%). The isomer ratio was calculated to be 5:1 from the integration of aldehydic protons in the $^1$H NMR spectrum. This ratio was consistent with the isomer ratio of the starting material.

With aldehyde 227 in hand, a series of Grignard reactions were explored. These involved reactions with isopropylmagnesium chloride 225, 4-methoxyphenylmagnesium bromide 226 and α-phenylvinylmagnesium bromide 235. In all of the three Grignard reactions studied, the literature method described by Gilligan $^{164}$ et al. was followed, with only slight modifications to optimise the reactions conditions.

Aldehyde 227 was first reacted $^{164}$ with the commercially available Grignard reagent 225, as depicted in Scheme 112, under different conditions (see Table 14, p. 102). At the outset, the reaction was carried out in THF and at low to high temperature for 14 hours (Table 14: Entry 1). In the event, alcohol 236 was obtained as a mixture of endo and exo isomers in good yield (67%). This was clearly evident by the $^{13}$C NMR spectrum of alcohol 236, in which two sets of signals were displayed in a 5:1 ratio for each carbon, as illustrated in Figure 16. This ratio reflects the ratio of the starting aldehyde 227. The reaction was then repeated in THF and at room temperature for a longer time period (Table 14: Entry 2). On work-up, the extraction was carried out with the aqueous layer at pH 9-10, instead of pH at 10-11, and alcohol 236 was obtained as its HCl salt, but in low yield (12%).
Figure 16: The $^{13}$C NMR spectrum of alcohol 236 obtained from the Grignard reaction of aldehyde 227 with isopropylmagnesium chloride 225 at room temperature, showing a 5:1 isomer ratio.

The reaction was finally conducted in diethyl ether and at low temperature for a short time (Table 14: Entry 3). After the usual work-up, alcohol 236 was isolated as a clear oil, but was contaminated with the unreacted aldehyde 227. Alcohol 236 was readily separated from residual unreacted aldehyde 227 during work-up with the aqueous layer at pH 9-10 and extraction into dichloromethane. From this, alcohol 236 was obtained as an almost endo isomer, but in low yield (16 %). This was evident by the $^{13}$C NMR spectrum shown in Figure 17.
Table 14: The Grignard reaction of aldehyde 227 with isopropylmagnesium chloride 225 under different conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Excess of Grignard (equiv.)</th>
<th>Solvent</th>
<th>Reaction temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>THF</td>
<td>-78/r.t.</td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>THF</td>
<td>r.t.</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>Et₂O</td>
<td>-70/-10</td>
<td>1.5</td>
<td>16</td>
</tr>
</tbody>
</table>

Figure 17: The $^{13}$C NMR spectrum of alcohol 236 obtained from the Grignard reaction of aldehyde 227 with isopropylmagnesium chloride 225 at low temperature, showing a predominant endo isomer.

Aldehyde 227 was next subjected to a Grignard reaction with 4-methoxyphenylmagnesium bromide 226, as illustrated in Scheme 113. At the outset, the reaction was carried out in a 2:1 mixture of THF / diethyl ether, and at low (-78 °C) to high temperature (r.t.), for an extended time period (21 h). From this, alcohol 237 was obtained as a mixture of endo and exo isomers again in the ratio of 5:1 and in good yield (64 %). The reaction was then conducted in diethyl ether at low temperature (-70 °C to -20 °C) for a shorter time (1.5 h) and this gave alcohol 237 as an almost endo isomer, but in low yield (13 %).
It emerges that product alcohols can be obtained as predominantly single endo isomers at low temperatures with short reaction times, where conversions are also low. This indicates some level of kinetic discrimination during the reaction. To explore this further, α-phenylvinylmagnesium bromide 235, the last Grignard reagent studied in this series, was first prepared in diethyl ether from the reaction of α-bromostyrene and magnesium turnings, according to the method of Normant156, where a trace of iodine was used. Following the method described by Gilligan164 et al., 1.5 equivalents of the Grignard reagent 235 was then reacted with aldehyde 227, as shown in Scheme 114, with different reaction times (see Table 15, p. 104).

With a short reaction time (Table 15, Entry 1) again only an endo isomer of alcohol 238 was obtained in a low yield (19 %). As the reaction time was increased (Table 15, Entry 2), the yield increased and the isomer ratio was now 11.5:1.0, indicating some reaction of the minor exo isomer. Extending the reaction time to 4.5h (Entry 3) resulted in complete reaction to give the alcohol 238 in excellent yield (79 %), and now in a ratio of 5:1, which reflects that of the starting aldehyde 227.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reaction temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>Isomer ratio (endo / exo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>-60/0</td>
<td>1.5</td>
<td>19</td>
<td>endo</td>
</tr>
<tr>
<td>2</td>
<td>THF/Et₂O (2:1)</td>
<td>-78/-60</td>
<td>3</td>
<td>38</td>
<td>11.5/1.0</td>
</tr>
<tr>
<td>3</td>
<td>THF/Et₂O (1:2)</td>
<td>-78/-10</td>
<td>4.5</td>
<td>79</td>
<td>5.1/1.0</td>
</tr>
</tbody>
</table>

Table 15: The Grignard reaction of aldehyde 227 with α-phenylvinylmagnesium bromide 235 under different conditions.

In order to complete the synthesis of the target ketone analogues, it became necessary to oxidise the corresponding alcohols 236, 237 and 238, either as a mixture of endo and exo isomers or as an endo isomer. Alcohol 236 was chosen as the first substrate and following the method described by Gilligan et al., it was subjected to the Swern oxidation, as a mixture of endo and exo isomers. During the Swern oxidation, dimethyl sulfoxide (DMSO) was activated first by the addition of oxalyl chloride \([\text{COCI}_2]\) at -60 / -70 °C, and was then followed by subsequent reaction with alcohol 236 and triethylamine (Et₃N), as depicted in Scheme 115.

![Scheme 115](image)

Although the Swern oxidation was very successful in generating ketone 218 (5:1 endo/exo), there was a general drawback due to the unpleasant smell of dimethyl sulphide. Therefore oxidation of alcohol 236 to the corresponding ketone 218 was also explored using the pyrridinium chlorochromate (PCC) adsorbed on to alumina. This method was described by Cheng et al. and proved straightforward, as it only required stirring alcohol 236 and PCC in dichloromethane. The reaction is depicted in Scheme 116.
The PCC adsorbed on alumina clearly prevented the black-tar formation, found in the unsupported reaction and thus aided the separation of the majority of PCC from the medium by filtration. However, isolation of ketone 218 from the traces of PCC still required further work-up. From this, the first ketone analogue 218 was obtained as a pale-yellow oil, as a mixture of endo / exo isomers (5:1). The reaction was conducted with an endo isomer of alcohol 236, obtained after low conversion in the Grignard reaction and from this product ketone 218 was obtained as an endo isomer. The 2D $^1$H NMR Nuclear Overhauser Enhancement Spectrum (NOESY) of product ketone 218, obtained from this experiment, showed a strong interaction between the C9 protons and those attached to the endo-C6,7 protons. There are weak interactions as well between the C9 protons and eq-C2,4 and the C9 protons and the C-3 proton. From this it is concluded that the ketone 218 was indeed the endo isomer, and in retrospect, alcohol 236 must also be the endo isomer as well. The NOESY spectrum of ketone 218 and the relevant proton interactions are illustrated in Figure 18.
Since manganese dioxide (MnO₂) is a well known and mild oxidising agent\textsuperscript{167}, particularly for the oxidation of allylic and benzylic alcohols, it was anticipated that oxidation of alcohols 237 and 238 to the corresponding ketones 220 and 219 would be

\textbf{Figure 18:} The NOESY spectrum of ketone 218 and the relevant proton interactions.
readily achieved with MnO₂. In this respect, benzylic alcohol 237 (5:1 endo/exo) was subjected to oxidation with activated MnO₂ in dichloromethane, as shown in Scheme 117. In this reaction, the MnO₂ supported on activated carbon was used, and its activity was further increased, following the method described by Carpino. This required heating at 80 °C for a few days in an oven.

![Scheme 117](image)

After filtration of the MnO₂, ketone 219 was obtained as a light-brown oil in moderate yield (51 %) with an isomer ratio of 5:1. The reaction was also conducted for the single endo isomer of alcohol 237, and from this reaction ketone 219 was obtained as a single isomer. Ketone 219, as its HCl salt was re-crystallised from a mixture of diethyl ether and ethanol. This allowed us to obtain an X-ray structure of ketone 219 from a suitable crystal. The resultant X-ray structure is depicted in Figure 19 and clearly shows that ketone 219 is an endo isomer.

![Figure 19](image)

**Figure 19:** The X-ray structure of the endo ketone 219.
Allylic alcohol 238 was then submitted to a similar oxidation with activated MnO₂ in dichloromethane, as shown in Scheme 118. After filtration, this gave the final ketone 220 of the series, as a light-brown oil again in moderate yield (55 %). These reactions could be followed conveniently by ¹H NMR spectroscopy. If the MnO₂ was used without activation, the reaction was generally incomplete, even when the reaction time was increased.

Scheme 118

3.2.3 Biological testing

To assess the potential biological effects of the structural changes imposed by the CH₂ replacement, the muscarinic acetylcholine receptor (mAChR) antagonist activity of the ketone analogues 219 and 220 were determined using a in vitro guinea-pig ileum preparation. The results were compared with the mAChR antagonist atropine 202. Biological tests were carried out in the laboratory of Dr. Robert F. Halliwell by Graham R. Foxon and myself at the Department of Biological Sciences in the University of Durham. The isolated guinea-pig ileum contains heterogeneous populations of muscarinic receptors¹⁶⁹, and is a well established pharmaceutical assay for the investigation of mAChR acting drugs¹⁷⁰.
Addition of ACh (3 nM-10 μM) evoked a concentration-dependant contraction of the quinea-pig ileum, as depicted in Figure 20a. The EC_{50} value for ACh from Figure 20b was determined to be 1.15x10^{-7} ± 0.0086 M (n=6). After a concentration response curve (CRC) was correlated, addition of 0.1 μM ACh yielded reproducible responses.

![Chart recorder traces](a)

**Figure 20:** a) The actual chart recorder traces of ACh-evoked responses from one of the 6 experiments; b) The concentration-response data plotted from an average of 6 experiments. The EC_{50} value for ACh was found to be 1.15x10^{-7} ± 0.0086 M (n=6).

Atropine 202 (0.1 nM-0.1 μM) concentration-dependently inhibited the control ACh (0.1 μM) response, as illustrated in Figure 21a, demonstrating antagonist activity. The IC_{50} value for atropine from Figure 21c was determined to be 3.15x10^{-9} ± 0.085 M (n=3), which was very close to those of the IC_{50} values (2 nM) reported by other research groups. Ketone 220 similarly inhibited the control ACh (0.1 μM) response in a concentration dependant manner, as shown in Figure 21b. The IC_{50} value for ketone 220 from Figure 21c was determined to be 1.9x10^{-6} ± 0.235 M (n=4). The inhibitory effects of atropine 202 and ketone 220 were reversible upon washing, but the reversibility of ketone 220 was much quicker than atropine 202, suggesting less strong binding. A preliminary test with ketone 219 showed no inhibition of the control ACh (0.1 μM) response.
Figure 21: The actual chart recorder traces of ACh (0.1 μM)-evoked responses in the absence and presence of atropine 202 (a) and ketone 220 (b); c) The concentration-inhibition data plotted from an average of 3 and 4 experiments for atropine 202 and ketone 220, respectively. The EC$_{50}$ values for atropine 202 and ketone 220 were 3.15x10$^{-9}$ ± 0.085 M (n= 3) and 1.9x10$^{-6}$ ± 0.235 M (n=4), respectively.

3.2.4 Conformation of ketones versus esters

The three-dimensional structure of the muscarinic receptors is yet to be determined. Information on how muscarinic antagonists interact with these receptors comes from a comparison of the X-ray structures of both highly active and less active individual antagonists$^{172}$. In this respect, the X-ray structure of atropine$^{173}$ 202 has played a crucial role in the correlation of the structural features of other known antagonists, such as azaprophen$^{174}$ 239. In our case, the X-ray structure of ketone 219 was compared with those$^{174}$ of atropine 202 and azaprophen 239.
It was revealed that the replacement of the bridging ester O atom by a CH$_2$ group did not have a significant effect on:

i) the distance between the N atom and the carbonyl O atom. For 219 this was calculated to be 5.45 Å. The same N-O distance was 5.29 Å for atropine 202 and 5.41 Å for azaprophen 239.

ii) the torsion angle (τ) between the secondary alcohol C(3)-H bond and the carbonyl C=O bond. For 219 this was calculated to be -34°. The same τ was 33° for atropine 202 and 30° for azaprophen 239.

To gain a more informed conclusion on whether such tropane ketones can be convincing analogues of tropane esters for biological studies, it became desirable to get a wider picture on how the carbonyl C=O bond and the secondary alcohol C-H bond orientate in X-ray structures of other esters and ketones. The relationship between the C=O bond and the C-H bond is described by the torsion angle H-C---C=O (τ), as depicted in Figure 22.

![Figure 22](image)

For this purpose, a survey of the current (April 1999) release of the Cambridge Crystallographic Database (CSD) was carried out by Dr. Andrei S. Batsanov (Durham University), for related structures and the τ values determined. The results, which are
summarised in Table Table 16, clearly show that the conformation of ketone 219 (\(\tau = -34^\circ\)) is similar to the mean value for fragments in both Entry 2 and Entry 3. This study is really very revealing, and indicates that the replacement of O by a CH\(_2\) group in going from tropane esters to ketones does not introduce a dramatic conformational change. Thus the ketones are anticipated to produce good biological mimics of these tropane esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Type of fragment</th>
<th>Number of compounds</th>
<th>Torsion angle ((\tau) extremes)</th>
<th>Mean value of ((\tau))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>221</td>
<td>1-56</td>
<td>30-32</td>
</tr>
<tr>
<td></td>
<td>![Diagram 1]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(18-42, 82 %)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>12</td>
<td>20-48</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>![Diagram 2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>14</td>
<td>34-49</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>![Diagram 3]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 16:** Torsion angles H-C\(\cdots\)C=O (\(\tau\)) in esters of secondary alcohols (Entry 1), tropane esters (Entry 2) and ketones (Entry 3).
3.2.5 Discussion

In this research programme a six-step route has been developed from tropinone 116 to ketones 229, as depicted in Scheme 119.

![Scheme 119](image-url)
For the first step, the HWE reaction of tropinone 116 with triethyl phosphonoacetate 131 proceeded smoothly and generated the α,β-unsaturated ester 132 as the major product. The yield was good (77%), however this was contaminated with the β,γ-unsaturated ester 133 as a minor product. Similar observations were also noted in other literature reactions of cyclic ketones with triethyl phosphonoacetate 131. For instance, the reaction of dihydrotestosterone 241 with triethyl phosphonoacetate 131 in the presence of 2 equivalents of NaH at 80 °C (method a) was reported to give the β,γ-unsaturated ester 240 in quantitative yield. However, the same reaction, in the presence of 1 equivalent of NaH (method b), gave exclusively the α,β-unsaturated ester 242 as the trans isomer, as illustrated in Scheme 120.

![Scheme 120](image)

For the second step, successful hydrogenation of the α,β-unsaturated ester 132 was only achieved after the esters 132 and 133 was treated with HCl and the aqueous layer was washed with diethyl ether. Thus hydrogenation gave the saturated ester 214 in excellent yield (87%). The Grignard reactions of ester 214 with isopropylmagnesium chloride and 4-methoxyphenyl-magnesium bromide proved unsatisfactory, as the conversion was only about 50%. Unsatisfactory results were also reported by Zirkle et al. in the Grignard reaction of ester 214 with cyclohexymagnesium bromide 243 (2.5-4 equivalents). For instance, when the reaction was carried out at room temperature, the corresponding ketone 244 was obtained in an optimised yield of 35%, as shown in Scheme 121.
For the third step, LiAlH₄ reduction of the saturated ester 214 was successful in generating alcohol 230 in good yield (85%). The attempted synthesis of alcohol 230 by LiAlH₄ reduction of the α,β-unsaturated ester 132 resulted in generating either allylic alcohol 231 or a 1:1 mixture of allylic and saturated alcohols 231 and 230. However, when the α,β-unsaturated ester 132 was added to the slurry of LiAlH₄ at -60 °C, allylic alcohol 231 was the only product isolated. This proved to be a very subtle reaction. At 0 °C, partial addition of the hydride to the C=C double bond also occurred to generate alcohol 230, as depicted in Scheme 122.

For the fourth step, aldehyde 227 was obtained by Swern oxidation of alcohol 230 in excellent yield (93%). As depicted in Scheme 123, attempted synthesis of aldehyde 227 from the direct DIBAL-H reduction of saturated ester 214 was unsuccessful. The conversion was about 71 %, but the separation of aldehyde 227 from ester 214 could not be achieved, as it decomposed on silica and on neutral alumina.
For the fifth step, Grignard reactions of aldehyde 227 generated secondary alcohols 236, 237 and 238, with the general structure 228, in good yields (64-79 %). At low temperature and with short reaction time, the alcohols 228 were isolated as predominantly endo isomers. However, the yields were low (13-19 %).

For the final step, oxidation of alcohols 228 either by MnO₂ or PCC gave the corresponding ketones 218, 219 and 220, with the general structure 229, in moderate yields (44-55 %). It was concluded both from NOE spectrum of 218 and X-ray structure of 219 that ketones were predominantly endo isomers and it follows that the alcohols must also be the endo isomers.

It was shown that ketone 220 is a novel muscarinic acetylcholine receptor (mACrR) antagonist, which is 500-fold less potent than atropine, but 33-fold more potent than pirenzepine in the inhibition of the ACh-induced contraction of guinea-pig ileum. Pirenzepine is a mAChR antagonist, which reduces gastric acid and pepsin secretion and was once popular for the treatment of peptic ulcers.
CHAPTER FOUR

Experimental
CHAPTER FOUR

4.1 General experimental

4.2 Experimental for chapter one

4.2.1 (S)-N-Ethoxycarbonyl-2-(methoxycarbonyl)pyrrolidine 44
4.2.2 (S)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane 2
4.2.3 (S)-α-(Diphenylmethyl)pyrrolidine 1
4.2.4 (S)-2-Amino-1,1-diphenyl-3-methylbutan-1-ol 71
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4.2.6 (S)-α-(Diphenylmethyl)-α-isopropyl-methylamine 70
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4.2.9 (S)-α-(Diphenylmethyl)-α-benzyl-methylamine 73
4.2.10 (S)-2-Amino-1,1-diphenylpropan-1-ol 77
4.2.11 (S)-4-Methyl-5,5-diphenyl-2-oxazolidinone 78
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4.2.14 (S)-4-[(R)-1-Methylpropyl]-5,5-diphenyl-2-oxazolidinone 81
4.2.15 (S)-α-(Diphenylmethyl)-α-[(R)-1-methylpropyl]-methylamine 79
4.2.16 (S)-2-Amino-1,1-diphenyl-4-methylpentan-1-ol 83
4.2.17 (4S)-4-Isobutyl-5,5-diphenyl-2-oxazolidinone 84
4.2.18 (S)-α-(Diphenylmethyl)-α-isobutyl-methylamine 82
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4.3.10 N-(2', 2', 2''-Trichloroethoxycarbonyl)-3α/β-hydroxymethyltropane 171
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4.4 Experimental for chapter three

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4.4.2 Ethyl (tropan-3'-yl)acetate 214
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4.4.4 2-(Tropan-3'-yl)ethanol 230
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CHAPTER FOUR

4.1 General experimental

$^1$H-, $^{13}$C-, $^{19}$F- and $^{31}$P-NMR spectra were recorded on the following spectrometers: A Varian Gemini-200, operating at 199.977 MHz for the proton and at 50 MHz for the carbon. A Bruker AC-250, operating at 250.133 MHz for the proton and 62.257 MHz for the carbon. A Varian VXR-400 (S), operating at 399.952 MHz for the proton and 100.577 MHz for the carbon. The chemical shifts are $\delta$ (ppm) units and quoted relative to tetramethylsilane (TMS) in chloroform-$d$ (CDCl$_3$), followed by the number of hydrogens, multiplicity, and assignment. Infrared (ir) spectra were recorded on a Perkin-Elmer F. T. 170X spectrometer. Band positions are recorded as their wavenumber (cm$^{-1}$) and given as maximum absorption ($\nu_{\text{max}}$). Mass spectra (ms) were recorded on a VG Analytical 7070E organic mass spectrometer, operating at 70eV. Peaks are reported as m/e ratios, followed by relative intensities in parentheses. All melting points (m.p.) were determined in Pyrex capillaries, using a digital Gallenkamp melting point apparatus and are uncorrected. Optical rotations, $[\alpha]_D^{25}$ were measured on an Optical Activity Ltd. AA-10 Automatic Polarimeter and are recorded in units of 10$^{-1}$deg.cm$^2$g$^{-1}$. Flash Chromatography was carried out using Fluka silica gel-60 (35-70 $\mu$m), or Beckman activated neutral aluminium oxide. X-Ray crystal data was collected on a Siemens R3m/v diffractometer. All solvents were dried and distilled prior to use unless otherwise stated. Solvents were dried from the following reagents under a nitrogen atmosphere: Tetrahydrofuran (THF) and diethyl ether were dried first by standing over sodium wire and then heated at reflux over sodium and benzophenone until the mixture develops the deep purple colour of the sodium benzophenone ketyl. Dichloromethane (DCM), chloroform (wash with water to remove EtOH, dry over KCO$_3$) and toluene distilled first to discard wet forerun and then heated at reflux over calcium hydride. Methanol (MeOH) and ethanol (EtOH) were heated under reflux over magnesium alkoxide. Acetone was dried first over MgSO$_4$, and then heated under reflux over phosphorus pentoxide. Petrol refers to petroleum ether (40-60 °C) and ether refers to diethyl ether. Non-aqueous reactions were carried out under a nitrogen atmosphere. In general chemicals were used as received from suppliers (Aldrich, Sigma and Jannsen).
4.2 Experimental for chapter one

4.2.1 (S)-N-Ethoxycarbonyl-2-(methoxycarbonyl)pyrrolidine

Ethyl chloroformate (178 g, 1.6 mol) was added dropwise to a suspension of (S)-proline (90 g, 0.78 mol) and Na₂CO₃ (87 g, 0.82 mol) in MeOH (800 ml) at 0 °C. After addition was complete, the solution was stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue partitioned between water and CHCl₃. Organic products were extracted into CHCl₃ (8x100 ml) and the combined extracts were washed with brine (3x100 ml) and the combined extracts were washed with brine (3x100 ml) and dried over MgSO₄. Concentration gave the title compound 44 (157 g, 100%) as a clear oil. δH 1.00-1.25 (2H, m, C4), 1.70-2.00 (2H, m, C3), 2.00-2.30 (3H, m, CH₃CH₂O), 3.25-3.50 (2H, m, C5), 3.60 (3H, s, CH₃O), 3.95-4.15 (H, m, CH), 4.15-4.35 (2H, q, CH₃CH₂O). δC 14.6 (CH₃CH₂O), 23.4 and 24.3 (C4), 29.8 and 30.8 (C3), 46.2 and 46.6 (C5), 52.0 and 52.1 (OCH₃), 58.7 and 58.9 (C2), 61.1 and 61.2 (OCH₂CH₃), 154.5 and 155.0 (N-C=O), 173.2 and 173.3 (C=O).

C₉H₁₅NO₄. Calculated C 53.70, H 7.52, N 6.96; Found C 53.41, H 7.50, N 7.61. νmax (cm⁻¹): 2981, 2956, 2882, 1749 and 1703 (C=O), 1419, 1382, 1349, 1201, 1174, 1121, 1090. m/z (EI) 201 (M⁺, 5 %), 142 (100 %), 70 (91 %), 41 (46 %).

4.2.2 (S)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane

A solution of (S)-N-ethoxycarbonyl-2-(methoxycarbonyl)pyrrolidine 44 (157 g, 0.78 mol) in THF (300 ml) was added dropwise to a 1 M solution of PhMgBr (284 g, 1.6 mol) in THF at 0 °C. The reaction mixture was heated under reflux for 48 h, and then...
an ice-cold saturated solution of NH₄Cl (2000 ml) was added. Organic products were extracted into ethyl acetate (20x100 ml) and the combined extracts were dried over MgSO₄. Concentration gave a crude product as a pale-yellow solid, which was re-crystallised from ethyl acetate. This gave the title compound 2 (133 g, 61 %) as a white amorphous solid. m.p. 148.3-148.5 °C (lit 148-149 °C). [α]D²⁵ = -271° (c, 1.00 in CH₂Cl₂) (lit²⁸: -241.6 (c, 0.002, MeOH). δH 1.00-1.25 (1H, p, C4), 1.65-2.05 (3H, m, C3 and C4), 3.15-3.35 (1H, m, C5), 3.65-3.80 (1H, m, C5), 4.50-4.65 (1H, dd, CH), 7.20-7.45 (8H, m, Ar-H), 7.45-7.60 (2H, d, Ar-H). δC 24.9 (C4), 29.0 (C3), 46.0 (C5), 69.2 (CH), 85.8 (C), 125.4, 125.9, 127.7, 128.3, 128.5, 140.2, 143.3 (Ar), 160.4 (N-C=O). C₁₈H₁₇NO₃. Calculated C 77.38, H 6.14, N 5.02; Found C 77.25, H 6.16, N 4.94. v max (cm⁻¹): 2979, 2905, 1751 (C=O), 1447, 1387, 1345, 1248, 1227, 1056, 1005. m/z (EI) 279 (M⁺, 13 %), 182 (45 %), 105 (100 %), 77 (32 %); (CI) 280 (MH⁺, 9 %), 236 (16 %), 70 (2 %).

4.2.3 (S)-α-(Diphenylmethyl)pyrrolidine 1

A 20 g of palladium (10 %) on activated carbon was added to a solution of (5S)-[3.3.0]-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane 2 (133 g, 0.48 mol) in MeOH (900 ml) at room temperature. The mixture was stirred until the hydrogenation was complete, as judged by the consumption of hydrogen gas by volume. Filtration of the catalyst and removal of the solvent gave a residue, which was re-crystallised from isopropyl alcohol as an HCl salt. After basification with NaOH and extraction into ethyl acetate (6x100 ml), concentration yielded the title compound 1 (50 g, 44 %) as an oil. [α]D²⁵ = -7.8° (c, 2.05 in CHCl₃) (lit²⁵: -7.8 (c, 2.11 in CHCl₃). δH 1.51-1.62 (1H, m, C4), 1.83-2.00 (3H, m, C3 and C4), 2.28 (1H, s, NH), 2.92-2.98 (1H, m, C5), 3.10-3.19 (1H, m, C5), 3.82-4.01 (2H, m, CH). δC 24.8 (C4), 30.6 (C3), 46.2 (C5), 58.5 (CHPh₂), 62.3 (CH), 126.4, 128.3, 128.7, 143.7 (Ar). C₁₇H₂₆NCl (HCl salt). Calculated C 74.69, H 7.38, N 5.13, Cl 12.80; Found C 74.65, H 7.62, N 4.98, Cl 12.71. v max (cm⁻¹): 3405 (NH). m/z (EI) 237 (M⁺, 0.3 %), 167 (35 %), 70 (100 %); (CI) 238 (MH⁺, 100 %), 70 (22 %).
(S)-Valine methyl ester hydrochloride 65 (9.9 g, 59.1 mmol) was added portionwise to a 1 M solution of phenylmagnesium bromide (108.8 g, 0.6 mol) in THF at 0 °C and heated at reflux for 20h. After quenching with an ice-cold saturated solution of NH₄Cl, the organic layer was separated, washed with brine and concentrated. The resulting solid was treated with HCl (2 M, 100 ml) and then evaporated to dryness. A large amount of biphenyl impurity precipitated out as a white solid when the amine-hydrochloride salt was dissolved in hot MeOH and allowed to cool to room temperature. After filtration, the filtrate was made basic with KOH (1 M) and the organics were extracted into diethyl ether (4x100 ml). Combined extracts were dried over MgSO₄ and concentrated to obtain a crude product as a light brown solid. Purification over silica gel, eluting with a 1:4 and 1:1 mixture of ethyl acetate and petrol gave the title compound 71 (5.4 g, 36 %) as a white amorphous solid. m.p. 90-92 °C (lit⁵¹-⁵² 94-95 °C). [α]_D²⁵ = - 107.9° (c, 4.24 in CHCl₃) (lit⁵¹: - 127.7° (c, 0.64 in CHCl₃). δ_H 0.83 (6H, dd, J= 6.9 and 7.2 Hz, CH₃), 1.58-1.76 (1H, m, CH-Me), 0.40-2.80 (3H, NH₂ and OH), 3.76 (1H, s, CH-NH₂), 7.04-7.58 (10H, m, Ar). δ_C 16.3, 23.2 (CH₃), 28.1 (CH-Me₂), 60.4 (CH-NH₂), 79.9 (C), 125.7, 126.1, 126.5, 126.8, 128.2, 128.6, 145.1, 148.2 (Ar). C₁₇H₃₁NO. Calculated C 79.96, H 8.29, N 5.48; Found C 79.80, H 8.15, N 5.39. ν_max (cm⁻¹): 3383 (N-H), 3338 (O-H), 3021 (Ar C-H), 2962, 2926, 2873 (methyl C-H), 1594, 1490, 1447 (Ar C=C), 1382, 1366 (methyl C-H). m/e (CI) 256 (MH⁺, 14 %), 72 (100 %).
4.2.5 (S)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone\textsuperscript{52,53,55} 72

![Chemical Structure]

Trichloromethyl chloroformate (2.7 g, 13.7 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-3-methylbutan-1-ol 71 (3.2 g, 12.4 mmol) and triethylamine (2.7 g, 26.5 mmol) in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C. The reaction mixture was stirred for 2h at the same temperature and then poured into a brine solution (250 ml). The aqueous layer was made basic with NaOH pellets and the organics were extracted into AcOEt (5x200 ml). Combined organic extracts were dried over MgSO\textsubscript{4} and concentrated. The resulting crude product was washed with diethyl ether to obtain the title compound 72 (3.0 g, 86 %) as a white amorphous solid. m.p. 250-251 °C (lit\textsuperscript{72} 250-251 °C; lit\textsuperscript{72} 250-252 °C). 

\[ \alpha \text{D} = -201.6° \quad \text{(c, 2.52 in DMSO)} \]

\[ \delta_{\text{H}} \text{(DMSO-}d_6\text{)}: 0.51 \text{ (3H, d, J= 6.6 Hz, CH}_3\text{)}, 0.92 \text{ (3H, d, J= 7.2 Hz, CH}_3\text{)}, 1.76-1.94 \text{ (1H, m, CH-Me\textsuperscript{1})}, 4.46 \text{ (1H, s, CH-NHCO)}, 7.24-7.72 \text{ (10H, m, Ar-H)}, 8.14 \text{ (1H, s, NH)}. \]

\[ \delta_{\text{C}} \text{(DMSO-}d_6\text{)}: 15.2, 20.9 \text{ (CH}_3\text{)}, 29.8 \text{ (CH-Me\textsuperscript{1})}, 64.9 \text{ (CH-NH)}, 88.4 \text{ (C)}, 125.8, 126.2, 127.9, 128.4, 128.8, 129.1, 140.5, 146.1 \quad \text{(Ar)}, 158.1 \text{ (C=O)}. \]

Accurate mass (CI): Found 282.149210; Calculated for (MH\textsuperscript{+}) C\textsubscript{18}H\textsubscript{20}NO\textsubscript{2} 282.149404 (0.7 ppm). \( \nu_{\text{max}} \text{(cm}^{-1}) \): 3295 (N-H), 2956, 2927, 2867 (methyl C-H), 1765, 1746 (C=O), 1596, 1490, 1451 (Ar C=C), 1251 (C-O).

m/e (CI) 299 (MNH\textsuperscript{4+}, 8 %), 282 (MH\textsuperscript{+}, 25 %), 238 (96 %), 223 (100 %), 72 (100 %).

4.2.6 (S)-α-(Diphenylmethyl)-α-isopropyl-methylamine\textsuperscript{70}

![Chemical Structure]

A solution of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone 72 (2.9 g, 10.3 mmol) in MeOH/AcOH and a 10 % Pd (435 mg, 4.1 mmol) on activated carbon was shaken for 68h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was
treated with HCl (2 M, 50 ml), stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K$_2$CO$_3$ and NaCl. Organic compounds were then extracted into AcOEt (3x 100 ml), dried over MgSO$_4$/K$_2$CO$_3$ and concentrated to obtain a crude product. Re-crystallisation from petroleum ether gave the title compound 70 (1.8 g, 72 %) as a light-brown crystals. **m.p. 71-72 °C.** $[\alpha]_{D}^{25} = -4.2^\circ$ (c, 10.98 in CHCl$_3$). $\delta_{H}$ 0.78 (3H, d, J= 6.6 Hz, CH$_3$), 0.91 (3H, d, J= 7.2 Hz, CH$_3$), 1.26 (2H, broad s, NH$_2$), 1.54-1.72 (1H, m, CHMe$_2$), 3.45 (1H, dd, J= 10.5 and 2.4 Hz, CH-NH$_2$), 3.70 (1H, d, J= 10.5 Hz, CH-Ph$_2$), 7.00-7.40 (10H, m, Ar-H). $\delta_{C}$ 14.2, 21.5 (CH$_3$), 28.9 (CHMe$_2$), 58.1 (CH-Ph$_2$), 58.9 (CH-NH$_2$), 126.5, 126.7, 128.2, 128.5, 128.8, 129.0, 143.5 (Ar). C$_{17}$H$_{21}$N. Calculated C 85.30, H 8.84, N 5.85; Found C 85.12, H 8.91, N 5.96. $\nu_{max}$ (cm$^{-1}$): 3361 (N-H), 3065, 3022 (Ar C-H), 2956, 2926, 2867 (methyl C-H), 1596, 1493, 1450 (Ar C=C). m/e (Cl) 240 (MH$^+$, 8 %), 72 (100 %).

**4.2.7 (S)-2-Amino-1,1,3-triphenylpropan-1-ol** 74

(S)-Phenylalanine ethyl ester hydrochloride 66 (9.9 g, 43.1 mmol) was added portionwise to a 1 M solution of phenylmagnesium bromide (63.5 g, 0.35 mol) in THF at 0 °C and stirred for 20h at room temperature. After quenching with ice-cold concentrated HCl, the aqueous layer was separated and evaporated to dryness. The resulting solid was washed with diethyl ether and AcOEt to obtain an amine-HCl salt as a white gummy solid. Upon basification with 1 M NaOH, organic products were extracted into diethyl ether and AcOEt, dried over MgSO$_4$, and concentrated to obtain a crude product. Re-crystallisation from a mixture of AcOEt and diethyl ether gave the title compound 74 (1.2 g, 9 %) as a white crystals. **m.p. 141-142 °C (lit$^{51}$ 144-145 °C; lit$^{52}$ 143-144 °C).** $[\alpha]_{D}^{25} = -88.4^\circ$ (c, 1.81 in CHCl$_3$) (lit$^{51}$: -88.5° (c, 0.604 in CHCl$_3$); lit$^{52}$: -94.3° (c, 2.30 in CHCl$_3$). $\delta_{H}$ 1.00-1.80 (3H, broad s, NH$_2$ and OH), 2.38 (1H, dd, J= 10.8 and 13.8 Hz, CH$_2$), 2.58 (1H, dd, J= 2.4 and 13.8 Hz, CH$_2$), 4.11 (1H, dd, J= 2.4 and 10.8 Hz, CH), 7.06-7.62 (15H, m, Ar-H). $\delta_{C}$ 36.9 (CH$_2$), 58.4 (CH), 78.7 (C), 125.6, 126.0, 126.6, 126.7, 126.9, 128.4, 128.7, 128.8, 129.3, 139.5, 144.5, 147.0 (Ar).
Accurate mass (CI): Found 304.171134; Calculated for (MH\(^+\)) \(C_{21}H_{22}NO\) 304.170140 (-3.3 ppm). \(\nu_{\max} (\text{cm}^{-1})\): 3365 (N-H), 3320 (O-H), 3058, 3020 (Ar C-H), 2966, 2936 (methylene C-H), 1599, 1493, 1451(Ar C=C). \(m/e (CI)\) 304 (MH\(^+\), 30 %), 271 (100 %).

4.2.8 (S)-4-Benzyl-5,5-diphenyl-2-oxazolidine

Trichloromethyl chloroformate (718 mg, 3.6 mmol) was added to a mixture of (S)-2-amino-1,1,3-triphenylpropan-1-ol 74 (1.0 g, 3.3 mmol) and triethylamine (710 mg, 7.0 mmol) in CH\(_2\)Cl\(_2\) at 0 °C. The reaction mixture was stirred for 5h at the same temperature and then poured into a brine solution (150 ml). The aqueous layer was made basic with powdered \(K_2CO_3\) and organic products were extracted into CH\(_2\)Cl\(_2\) (3x50 ml). Combined extracts were dried over MgSO\(_4\)/K\(_2\)CO\(_3\) and concentrated. The resulting crude product was washed with diethyl ether to obtain the title compound 75 (1.1 g, 97 %) as a white amorphous solid. \(m.p.\) 259-261 °C (lit\(^5\) 255-257 °C). \([\alpha]_b^{25} = -241.9^\circ\) (c, 2.11 in DMSO) (lit\(^3\) -281.5 ° (c, 0.63 in CHCl\(_3\)). \(\delta_\text{H} (CD_3COOD)\) 2.18 (1H, dd, J= 10.8 and 13.8 Hz, CH\(_3\)), 2.52 (1H, dd, J= 3.6 and 13.8 Hz, CH\(_2\)), 4.67 (1H, dd, J= 3.6 and 10.8 Hz, CH), 6.90-7.60 (15H, m, Ar-H). \(\delta_\text{C} (CD_3COOD)\) 44.2 (CH\(_3\)), 50.5 (CH), 94.1 (C), 130.5, 130.9, 131.5, 132.6, 132.8, 133.0, 133.1, 133.3, 133.4, 141.1, 143.4, 146.5 (Ar), 163.7 (C=O). Accurate mass (CI): Found 330.147890; Calculated for (MH\(^+\)) \(C_{22}H_{20}NO_2\) 330.149404 (4.6 ppm). \(\nu_{\max} (\text{cm}^{-1})\): 3248, 3174 (N-H), 3062, 3028 (Ar C-H), 2938, 2905 (methylene C-H), 1760, 1725 (C=O), 1493, 1448 (Ar C=C), 1243 (C-O). \(m/e (CI)\) 330 (MH\(^+\), 5 %), 347 (MNH\(_4^+\), 6 %), 196 (100 %).
4.2.9 (S)-α-(Diphenylmethyl)-α-benzyl-methylamine 73

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

A solution of (S)-4-benzyl-5,5-diphenyl-2-oxazolidinone 75 (940 mg, 2.8 mmol) in MeOH/AcOH and a 10 % Pd (121 mg, 1.1 mmol) on activated carbon was shaken for 43h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl, stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K$_2$CO$_3$ and NaCl. Organics were then extracted into CH$_2$Cl$_2$ (4x 50 ml), dried over MgSO$_4$/$K_2$CO$_3$ and concentrated to obtain a crude product. Purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petroleum ether, gave the title compound 73 (584 mg, 71 %) as a light-brown amorphous solid, m.p. 71-72 °C. $[\alpha]_D^{25} = -8.0^o$ (c, 10.46 in CHCl$_3$). δ$_H$ 1.21 (2H, broad s, NH$_2$), 2.29 (1H, dd, J= 9.6 and 13.5 Hz, CH$_2$), 2.79 (1H, d, J= 13.2 Hz, CH$_2$), 3.71 (1H, d, J= 9.9 Hz, CH-Ph$_2$), 3.81 (1H, dt, J= 2.7, 9.6 Hz, CH-NH$_2$), 7.06-7.33 (15H, m, Ar-H). δ$_C$ 41.9 (CH$_2$), 55.7 (CH-NH$_2$), 59.7 (CH-Ph$_2$), 126.3, 126.5, 126.6, 128.1, 128.2, 128.4, 128.7, 128.8, 129.1, 139.7, 142.6, 143.1 (Ar). Accurate mass (CI): Found 288.175856; Calculated for (MH$^+$) C$_{16}$H$_{22}$N 288.175225 (-2.2 ppm). ν$_{max}$ (cm$^{-1}$): 3383 (N-H), 3082, 3059, 3025 (Ar C-H), 2936, 2912 (methylene C-H), 1595, 1493, 1450 (Ar C=C). m/e (CI) 288 (MH$^+$, 100 %).

4.2.10 (S)-2-Amino-1,1-diphenylpropan-1-ol$^{51,57,58}$ 77

(S)-Alanine methyl ester hydrochloride 67 (9.9 g, 70.9 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (78.0 g, 0.4mol) in THF at 0 °C and then heated under reflux for 21h. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH$_4$Cl, and stirred for 1h. After filtration, the organic
layer was separated and the aqueous layer was extracted with AcOEt (3x100 ml). Combined extracts were dried over K$_2$CO$_3$/MgSO$_4$ and concentrated to obtain a crude product. Purification over silica gel by means of dry-flash column chromatography (eluting first with CH$_2$Cl$_2$ and then with a mixture of AcOEt and petrol, increasing from 20 % up to 100 %) gave the title compound 77 (8.5 g, 52 %) as a white amorphous solid. **m.p.** 100-101 °C (lit$^{51,57}$ 100-102 °C). [$\alpha$]$^D_{	ext{p}}$ = - 85.6° (c, 3.62 in CHCl$_3$) (lit$^{51}$: - 82.4° (c, 0.814 in CHCl$_3$; lit$^{57}$: - 85.9° (c, 2.77 in CHCl$_3$). $\delta_h$ 0.94 (3H, d, J= 6.3 Hz, CH$_3$), 1.00-1.50 (2H, broad s, NH$_2$), 4.15 (1H, q, J= 6.3 Hz, CH), 4.18-4.36 (1H, broad s, OH), 7.10-7.66 (1OH, m, Ar-H). $\delta_c$ 17.4 (CH$_3$), 52.1 (CH), 78.7 (C), 125.7, 126.1, 126.6, 126.9, 128.2, 128.7, 145.0, 147.2 (Ar). C$_{15}$H$_{14}$NO. Calculated C 79.26, H 7.54, N 6.16; Found C 79.30, H 7.66, N 6.27. $\nu_{\text{max}}$ (cm$^{-1}$): 3432 (O-H), 3389, 3324 (N-H), 3025 (Ar C-H), 2987, 2902 (methyl C-H), 1593, 1487, 1447 (Ar C=C). **m/e (Cl)** 228 (MH$^+$, 100 %).

4.2.11 (S)-4-Methyl-5,5-diphenyl-2-oxazolidinone 78

![Structure](image)

Trichloromethyl chloroformate (6.4 g, 32.2 mmol) was added to a mixture of (S)-2-amino-1,1-diphenylpropan-1-ol 77 (6.6 g, 29.3 mmol) and triethylamine (6.3 g, 62.3 mmol) in CH$_2$Cl$_2$ at 0 °C. The reaction mixture was stirred for 5h at the same temperature, poured into a brine solution (150 ml), and diluted with more CH$_2$Cl$_2$. After filtration, the organic layer was separated and the aqueous layer was extracted once with a 1:1 mixture of CH$_2$Cl$_2$ and AcOEt. The combined organic extracts were dried over MgSO$_4$/K$_2$CO$_3$ and concentrated. The resulting crude product was washed with diethyl ether, water, AcOEt and diethyl ether again, to obtain the title compound 78 (5.7 g, 76 %) as a white amorphous solid. **m.p.** 264-266 °C. [$\alpha$]$^D_{	ext{p}}$ = -279.7° (c, 4.14 in DMSO). $\delta_h$ 0.82 (3H, d, J= 6.3 Hz, CH$_3$), 4.65 (1H, q, J= 6.0 Hz, CH), 7.10-7.70 (10H, m, Ar-H), 7.93 (1H, broad s, NH). $\delta_c$ 19.6 (CH$_3$), 55.9 (CH), 85.6 (C), 126.3, 126.4, 128.1, 128.6, 128.8, 129.1, 140.6, 144.2 (Ar), 157.6 (C=O). **Accurate mass (Cl):** Found 254.116639; Calculated for (MH$^+$) C$_{16}$H$_{16}$NO$_2$ 254.118104 (5.8 ppm). $\nu_{\text{max}}$ (cm$^{-1}$): 3255, 3152 (N-H), 137.
3059, 3027 (Ar C-H), 2987, 2970, 2905 (methyl C-H), 1745, 1726 (C=O), 1493, 1447 (Ar C=C), 1243 (C-O).

**m/e (CI)** 254 (MH+, 9%), 271 (MNH4+, 55%), 52 (100%).

### 4.2.12 (S)-α-(Diphenylmethyl)-α-methyl-methylamine 76

![Chemical Structure](image)

A suspension of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone 78 (3.5 g, 13.9 mmol) in MeOH/AcOH and a 10% Pd (148 mg, 1.4 mmol) on activated carbon was shaken for 45h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl (2 M, 100 ml), stirred overnight at room temperature, made basic with NaOH pellets, and saturated with K2CO3. Organic compounds were then extracted into diethyl ether (3x 100 ml), dried over MgSO4/K2CO3 and concentrated to obtain a crude product. Purification over silica gel by means of dry-flash column chromatography (eluting first with AcOEt and then with a mixture of MeOH and AcOEt, ranging from 5% up to 30%) gave the title compound 76 (1.9 g, 65%) as a white amorphous solid.

**m.p.** 76-77 °C. [α]D 25 = -19.3 (c, 10.76 in CHCl3). δm 1.04 (3H, d, J= 6.3 Hz, CH3), 1.31 (2H, s, NH2), 3.55 (1H, d, J= 9.9 Hz, CH-Ph), 3.66-3.80 (1H, m, CH-NH), 7.10-7.40 (10H, m, Ar-H). δC 22.4 (CH3), 50.3 (CH-NH2), 62.4 (CH-Ph), 126.5, 126.8, 128.2, 128.5, 129.0, 143.3, 143.7 (α-Ar). **C15H17N.** Calculated C 85.26, H 8.11, N 6.63; Found C 85.10, H 8.08, N 6.36. νmax (cm⁻¹): 3344 (N-H), 3083, 3027 (Ar C-H), 2976, 2958 (methylene C-H), 1597, 1493, 1449 (Ar C=C). **m/e (CI)** 212 (MH+, 100%).

### 4.2.13 (2S,3R)-2-Amino-1,1-diphenyl-3-methylpentan-1-ol 80

![Chemical Structure](image)

A 1 M solution of phenylmagnesium bromide (49.0 g, 0.27 mol) in THF was added dropwise to (S)-isoleucine methyl ester hydrochloride 68 (9.8 g, 54.0 mmol) at 0 °C and
then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH₄Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x50 ml), dried over MgSO₄/K₂CO₃ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (150 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight, diluted with water until partition occured. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x75 ml) and dried over MgSO₄/K₂CO₃. Concentration gave a crude product (6.1 g, 42 %) as a pale yellow solid. This contaminated with the amino ester derived from the starting material, however was used for the next step without further purification. A small amount of the crude product (1.1 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH₂Cl₂, then with a mixture of AcOEt and petrol, increasing from 40 % up to 80 %. From this, a pure amino alcohol 80 (654 mg, 60 %) was obtained as a white amorphous solid. m.p. 128-129 °C (lit 135-136 °C). [α]D = - 128.17° (c, 4.26 in CHCl₃) (lit: - 124.1° (c, 1.23 in CHCl₃)). δH 0.72 (3H, t, J= 7.2 Hz, CH₃), 0.94 (3H, d, J= 6.9 Hz, CH₃), 0.80-1.10 (1H, m, CH₂), 1.40-1.60 (1H, m, CH), 1.76-1.94 (1H, m, CH₂), 0.60-2.10 (3H, OH and NH₂), 3.85 (1H, d, J= 1.5 Hz, CH-NH₂), 7.10-7.70 (10H, m, Ar-H). δC 12.1 (CH₃-CH₂), 18.7 (CH₃-CH), 34.8 (CH-Me), 60.9 (CH-NH₂), 79.6 (C), 125.5, 125.9, 126.1, 126.5, 127.8, 128.2, 144.9, 147.9 (Ar). vₚₚₚ (cm⁻¹): 3343, 3279 (N-H and O-H), 3085, 3023 (Ar C-H), 2959, 2926, 2873 (methyl and methylene C-H), 1589, 1491, 1447 (Ar C=C). m/e 270 (MH⁺, 4 %), 252 (20 %), 86 (100 %).

4.2.14 (S)-4-[(R)-1-Methylpropyl]-5,5-diphenyl-2-oxazolidinone 81

![Chemical Structure](image)

Trichloromethyl chloroformate (5.4 g, 27.3 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-3-methylpentan-1-ol 80 (4.97 g of 60 %, 11.1 mmol) and
triethylamine (5.3 g, 52.0 mmol) in CH₂Cl₂ at 0 °C. The reaction mixture was stirred for 3h at 0 °C, then allowed to warm to room temperature for 18h. The mixture was then washed with HCl (3x100 ml) and water (2x100 ml) and dried over MgSO₄. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound 81 (2.7 g, 83 %) as a white amorphous solid. m.p. 221-223 °C. [α]₀^25 = -243.9° (c, 4.33 in CHCl₃). δₜ 0.41 (3H, t, J= 7.2 Hz, CH₃), 0.80 (3H, d, J= 6.9 Hz, CH₃), 0.80-0.96 (1H, m, CH₂), 1.18-1.32 (1H, m, CH-Me), 1.34-1.50 (1H, m, CH₂), 4.27 (1H, d, J= 3.6 Hz, CH-NH), 6.98 (1H, s, NH), 7.10-7.50 (10H, m, Ar-H). δₚ 11.3 (CH₃-CH₂), 17.2 (CH₃-CH), 22.7 (CH₂), 36.3 (CH-Me), 66.1 (CH-NH), 89.5 (C), 125.9, 126.5, 127.7, 128.0, 128.3, 128.6, 139.3, 144.0 (Ar), 159.1 (C=O). ν max (cm⁻¹): 3281, 3162 (N-H), 3058 (Ar C-H), 2980, 2960, 2933, 2877 (methyl and methylene C-H), 1760, 1725 (C=O), 1493, 1448 (Ar C=C), 1243 (C-O). m/e 313 (MNH₄⁺, 6 %), 296 (MH⁺, 8 %), 237 (100 %).

4.2.15 (S)-α-(Diphenylmethyl)-α-[(R)-1-methylpropyl]-methylamine 79

A suspension of (S)-4-i'^c-butyl-5,5-diphenyl-2-oxazolidinone 81 (2.3 g, 7.9 mmol) in MeOH/AcOH and a 10 % Pd (100 mg, 0.9 mmol) on activated carbon was shaken for 47h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and solvents were evaporated. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (2x100 ml) and the aqueous layer was made basic with NaOH pellets. Organic compounds were then extracted into CH₂Cl₂ (5x100 ml) and the combined extracts were dried over MgSO₄. Concentration gave a crude product, which was purified over silica gel by means of dry-flash column chromatography, eluting first with CH₂Cl₂, then with a mixture of AcOEt and petrol, ranging from 50 % up to 70 %. This afforded the title compound 79 (1.4 g, 71 %) as a white amorphous solid. m.p. 59-61 °C. [α]₀^25 = -13.7° (c, 4.80 in CHCl₃). δₜ 0.76 (3H, t, J= 7.5 Hz, CH₃), 0.96 (3H, d, J= 6.9 Hz, CH₃), 1.00-1.18 (3H, broad s and m, NH₂ and
CH₂), 1.28-1.42 (1H, m, CH-Me), 1.50-1.70 (1H, m, CH₂), 3.50 (1H, dd, J= 10.5 and 2.40 Hz, CH-NH₂), 3.87 (1H, d, J= 10.5 Hz, CH-Ph₂), 7.10-7.40 (10H, m, Ar-H). δc
11.2 (CH₃-CH₂), 16.7 (CH₃-CH), 20.4 (CH₂), 34.8 (CH-Me), 56.4 (CH-Ph₂), 58.4 (CH-NH₂), 125.2, 125.4, 127.0, 127.4, 127.5, 127.7 (Ar). **Accurate mass (CI):** Found 254.189998; Calculated for (MH⁺) C₉H₁₈N₂ 254.190875 (3.4 ppm). νmax (cm⁻¹): 3355 (N-H), 3082, 3065, 3024 (Ar C-H), 2959, 2931, 2872 (methyl and methylene C-H), 1598, 1494, 1450 (Ar C=C). m/e (CI) 254 (MH⁺, 100 %).

4.2.16  **(S)-2-Amino-1,1-diphenyl-4-methylpentan-1-ol**

A 1 M solution of phenylmagnesium bromide (96.1 g, 0.53 mol) in THF was added dropwise at 0 °C to (S)-leucine methyl ester hydrochloride 69 (19.3 g, 0.11 mol) and then stirred for 17h at room temperature. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH₄Cl and then diluted with AcOEt and water until partition occurred. Organic products were extracted into AcOEt (3x100 ml), dried over MgSO₄/K₂CO₃ and concentrated to obtain a crude product. The crude product was dissolved in diethyl ether (400 ml), treated with concentrated HCl until all of the amine was converted to its HCl salt. The amine-HCl salt was stirred overnight and then diluted with water until partition occurred. The non-basic organics were extracted into diethyl ether (5x100 ml) and then the aqueous layer was made basic with NaOH pellets. After stirring for 4h, organic products were extracted into AcOEt (4x200 ml) and dried over MgSO₄/K₂CO₃. Concentration gave a crude product (13.7 g, 48 %) as a pale yellow solid. This contaminated with the amino ester of the unreacted starting material, however was used directly for the next step without further purification. A small amount of the crude product (1.31 g) was purified over silica gel by means of dry-flash column chromatography, eluting first with CH₂Cl₂, then a mixture of AcOEt and petrol, increasing from 30 % up to 55 %. From this, a pure amino alcohol 83 (852 mg, 65 %) was obtained as a white amorphous solid. **m.p.** 131-132 °C (lit 132-134 °C).  
[α]D²⁵ = -101.0 ° (c, 5.38 in CHCl₃) (lit²⁵: -95.1 ° (c, 1.01 in CHCl₃)). δn 0.79 (6H, dd, J= 7.20 and 7.80 Hz, CH₃), 0.86-1.80 (6H), 3.89 (1H, J= 9.6 Hz, CH-NH₂), 7.00-7.70
(10H, m, Ar-H). δ C 21.1, 23.8, 25.1, 39.2, 54.3, 78.9, 125.4, 125.6, 126.1, 126.4, 127.8, 128.2, 144.3, 147.0 (Ar). ν max (cm⁻¹): 3337, 3268 (N-H and O-H), 3025 (N-H), 2954, 2935, 2866 (methyl and methylene C-H), 1597, 1491, 1448 (Ar C=C). m/e 270 (MH⁺, 5%), 252 (M-OH, 11%), 86 (100%).

4.2.17 (4S)-4-Isobutyl-5,5-diphenyl-2-oxazolidinone 84

![Chemical structure of 84](image)

Trichloromethyl chloroformate (13.0 g, 65.8 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-4-methylpentan-1-ol 83 (12.4 g of 65%, 29.9 mmol) and triethylamine (12.7 g, 125.5 mmol) in CH₂Cl₂ at 0 °C. The reaction mixture was stirred for 15 h, allowing to warm to room temperature. The mixture was then washed with HCl (3x200 ml) and water (2x200 ml), and dried over MgSO₄. Concentration gave a crude product, which was washed with diethyl ether to afford the title compound 84 (7.9 g, 90%) as a white solid. m.p. 212-214 °C. [α]D²⁵ = -286.1° (c, 4.32 in CHCl₃). δ H 0.85 (3H, d, J= 6.6 Hz, CH₃), 0.91 (3H, d, J= 6.6 Hz, CH₃), 0.96-1.08 (2H, m, CH₂), 1.53-1.73 (1H, m, CH-Me), 4.57 (1H, dd, J= 10.5 and 3.60 Hz, CH-NH), 7.05 (1H, s, NH), 7.16-7.50 (10H, m, Ar-H). δ C 20.8, 23.7, 24.9, 41.8, 58.8, 89.1, 125.9, 126.3, 127.6, 127.8, 128.1, 128.3, 139.3, 142.5 (Ar), 158.8 (C=O). ν max (cm⁻¹): 3261, 3160 (N-H), 2955, 2869 (methyl and methylene C-H), 1752, 17235 (C=O), 1495, 1447 (Ar C=C), 1251 (C-O). m/e 313 (MNH⁺, 12%), 296 (MH⁺, 15%), 237 (100%).

4.2.18 (S)-α-(Diphenylmethyl)-α-isobutyl-methylamine 82

![Chemical structure of 82](image)

A suspension of (S)-4-isobutyl-5,5-diphenyl-2-oxazolidinone 84 (7.6 g, 25.6 mmol) in MeOH/AcOH and a 10% Pd (282 mg, 2.6 mmol) on activated carbon was shaken for 93 h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered
off over Hyflo Super Cell and solvents were evaporated under reduced pressure. The resulting residue was treated with HCl until all of the amine was converted to its HCl salt, stirred overnight at room temperature and diluted with water until partitioned occurred. The non-basic organics were extracted into diethyl ether (2x100 ml) and then the aqueous layer was made basic with NaOH pellets. Organics were then extracted into CH₂Cl₂ (5x 100 ml) and the combined extracts were dried over MgSO₄. Concentration gave the title product 82 (5.7 g, 87 %) as a white amorphous solid. m.p. 46-48 °C. [α]ᵣ 25 = -31.6° (c, 4.12 in CHCl₃). δₓ 0.86 (6H, dt, J= 6.60 and 2.10 Hz, CH₃), 1.00-1.50 (4H, m and broad s, CH₂ and NH₂), 1.66-1.86 (1H, m, CH), 3.61 (2H, broad s, CH-NH₂ and CH-Ph₂), 7.10-7.40 (10H, m, Ar-H). δₓ 21.8 and 24.7 (CH₃), 25.5 (CH), 45.6 (CH₂), 52.4 (CH-NH₂), 61.6 (CH-Ph₂), 126.9, 127.1, 128.8, 129.0, 129.2, 129.4, 143.8, 144.0 (Ar). Accurate mass (CI): Found 254.190200; Calculated for (MH⁺) C₁₈H₂₄N₂ 254.190875 (2.7 ppm). uₓ (cm⁻¹): 3368 (N-H), 3057, 3027 (Ar C-H), 2951, 2932, 2909, 2867 (methyl and methylene C-H), 1595, 1494, 1450 (Ar C=C). m/e (CI) 254 (MH⁺, 100 %).

4.2.19 N-[(SR)-α,α-Diphenylmethylethyl](R)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide 87

A solution of pyridine-d₅ (56 mg, 0.70 mmol)) and (S)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride 86 (48 mg, 0.19 mmol) in CH₂Cl₂ (8 ml) was sequentially added to a solution of (SR)-α-(diphenylmethyl)-α-methyl-methylamine 76 (40 mg, 0.19 mmol) in CH₂Cl₂ (8 ml). The reaction mixture was stirred for 18h at room temperature and then washed with a 10 % HCl (2x15 ml) and water (3x15 ml). The organic layer was dried over MgSO₄ and was then concentrated to give a crude product. Purification over silica gel, eluting with CH₂Cl₂ gave the title compound 87 as a mixture of diastereomers. The product was only characterised, sufficiently to determine the stereochemical analysis. δₓ -70.0 (CF₃), -69.3 (CF₃). δₓ 2.84 (OCH₃), 3.02 (OCH₃).
4.2.20  N-[(S)-α,α-Diphenylmethylalkyl](R)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide

A solution of pyridine-d$_5$ (4 equiv.) and (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride 86 (1.4 equiv.) in CDCl$_3$ (1.0 ml) was sequentially added via syringe into the sample bottle fitted with rubber septum and charged with the (S)-α-(diphenylmethyl)-α-alkyl-methylamine 3 (10 mg). The reaction mixture was then stirred for 24h at room temperature and analysed by both $^1$H and $^{19}$F NMR spectroscopy. The products were only characterised, sufficiently to determine the stereochemical analysis. (SR)-87 (R= Me): δ$_f$ -70.0 (CF$_3$). δ$_h$ 3.02 (OCH$_3$). (SR)-88 (R= i-Pr): δ$_f$ -69.6 (CF$_3$). δ$_h$ 2.99 (OCH$_3$). (SR)-89 (R= Bn): δ$_f$ -69.5 (CF$_3$). δ$_h$ 2.84 (OCH$_3$). (SR)-90 (R= sec-Bu): δ$_f$ -69.6 (CF$_3$). δ$_h$ 2.97 (OCH$_3$). (SR)-91 (R= isobutyl): δ$_f$ -69.7 (CF$_3$). δ$_h$ 2.98 (OCH$_3$).
4.3 Experimental for chapter two

4.3.1 Diethyl benzoylmethanephosphonate 122

![Chemical structure](image)

**a) Via an Arbusov\(^{87}\)**

A mixture of bromoacetophenone 128 (6.0 g, 30.1 mmol) and triethyl phosphite 129 (5.0 g, 30.1 mmol) was heated under reflux at 165 °C for 16 h. Purification by three sequential distillations (68-72 °C, 0.1-0.01 mm-Hg) and over silica gel (1:1 ethyl acetate/hexane) gave the title compound 122 (4.2 g, 54 %) as a clear oil. This product was contaminated, probably with 130 (1 %). δ\(^p\) 23.1. δ\(^n\) 1.27 (3H, dt, J= 7.2 and 0.4 Hz, 2xCH\(_3\)CH\(_2\)O), 3.62 (2H, d, J= 22.8 Hz, CH\(_2\)P), 4.13 (2H, dq, J= 7.2 and 0.8 Hz, 2xCH\(_3\)CH\(_2\)O), 7.47 (2H, t, J= 6.7 Hz, Ar-H), 7.58 (1H, t, J= 6.7 Hz, Ar-H), 8.00 (2H, d, J= 6.7 Hz, Ar-H). δ\(^c\) 16.1 (CH\(_3\)CH\(_2\)O), 38.3 (d, J=130 Hz, CH\(_2\)P), 62.5 (CH\(_2\)CH\(_2\)O), 128.5, 128.9, 133.5 and 136.4 (Ar), 191.79 (C=O). \(\nu_{\text{max}}\) (cm\(^{-1}\)): 1681 (C=O), 1276 and 1254 (P=O), 1055 and 1026 (PO\(_2\)). m/e (EI) 256 (M\(^+\), 3 %), 105 (100 %).

**b) Using LDA\(^{86}\)**

Diisopropylamine (0.9 g, 9.2 mmol) was added dropwise to a solution of n-butyllithium (0.6 g, 10.1 mmol) in hexanes at room temperature and was then diluted with diethyl ether (15 ml). The LDA solution was cooled to -78 °C, and then a solution of acetophenone 126 (1.0 g, 8.3 mmol) in diethyl ether (1 ml) was added and the mixture stirred for 1 h at this temperature. Diethyl chlorophosphite 127 (1.4 g, 9.2 mmol) was added at -78 °C and then the entire mixture was allowed to warm to room temperature over 5 h. The reaction was quenched with acetic acid (10 mmol) in diethyl ether (10 ml) and the mixture filtered through a Hyflo super cel. After concentration under reduced pressure, the residue was magnetically stirred for 33 h open to the air. Purification over silica gel (radial chromatography, 1:1 ethyl acetate/hexane) gave the title product 122 (1.4 g, 66 %) as clear oil. The spectral data are consistent with those of obtained by method a.
4.3.2 2-(1'-Hydroxy-2'-phenylethyl)-1,3-dithiane$^{141}$

A 1.6 M solution of n-butyllithium (0.5 g, 7.8 mmol) in hexane was added dropwise to a 0.375 M solution of 1,3-dithiane $^{142}$ (0.9 g, 7.5 mmol) in THF. The mixture was stirred for 2 h at -40 to -10 °C, and then a solution of phenylacetaldehyde $^{140}$ (0.9 g, 7.5 mmol) in THF was added at -78 °C. The reaction was stirred for 12 h at -78 °C to room temperature and then diluted with water (100 ml). Organic compounds were extracted into pentane (4x40 ml), and then the organics were washed with water (3x50 ml), 7 % aqueous KOH (3x70 ml), and again water (3x50 ml). The organic extracts were dried over K$_2$CO$_3$, concentrated under reduced pressure, and then purified over silica gel, eluting with a 1:9 mixture of ethyl acetate and petrol. The title compound $^{141}$ (0.8 g, 44 %) was recovered as a light-brown liquid. $\delta$$_{n}$ 1.80-2.00 (1H, complex, CH$_2$), 2.00-2.20 (1H, complex, CH$_2$), 2.60-3.00 (6H, complex, CH$_2$Ph + CH$_2$-S + OH), 3.17 (1H, dd, J= 4.0 Hz, J=13.6 Hz, CH$_2$Ph), 3.88 (1H, d, J= 6.0 Hz, S-CH-S), 4.09 (1H, m, J= 4.4, 6.2, and 7.9 Hz, CH-OH), 7.20-7.40 (5H, complex, Ar-H). $\delta$$_{c}$ 25.5 (CH$_2$), 27.8 and 28.3 (S-CH-S), 39.9 (CH$_2$Ph), 51.2 (CH-OH), 73.2 (S-CH-S), 126.3, 128.2, 129.4 and 137.7 (Ar). Accurate mass (EI): Found 240.0643; calculated for (M+) C$_{12}$H$_{10}$O$_2$S$_2$ 240.0643 (-0.2 ppm). $\nu_{max}$ (cm$^{-1}$): 3443 (OH). m/e (EI) 240 (M+, 7 %), 119 (100%).

4.3.3 N-Methyl-N-methoxyphenylacetylamide$^{149}$

Neat phenylacetyl chloride $^{149}$ (5.0 g, 32.3 mmol) was added to a solution of N,O-dimethylhydroxylamine hydrochloride $^{150}$ (3.5 g, 35.5 mmol) in chloroform (70 ml). The mixture was cooled to 0 °C and pyridine (5.6 g, 71.0 mmol) was added dropwise.
The entire mixture was stirred for 16 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in a 1:1 mixture of ether (50 ml) and CH$_2$Cl$_2$ (50 ml) and then washed with saturated NH$_4$Cl (5x60 ml) and water (3x100 ml). The organic layer was dried over MgSO$_4$ and concentrated. Purification by distillation (b.p. 58-62 °C, 0.1-0.01 mm-Hg) gave the title compound 148 (4.3 g, 74 %) as a clear oil. δ$_r$ 3.19 (3H, s, N-CH$_3$), 3.59 (3H, s, O-CH$_3$), 3.77 (2H, s, CH$_2$), 7.20-7.34 (5H, m, Ar). δ$_c$ 32.1 (N-CH$_3$), 39.3 (O-CH$_3$), 61.1 (CH$_2$), 126.6, 128.4, 129.2, 134.8 (Ar), 172.3 (C=O). $v_{max}$ (cm$^{-1}$): 1663 (C=O). m/e (EI) 179 (M$^+$, 8 %), 91 (100 %).

4.3.4 2-Phenylacetyl-1,3-dithiane 147

A 1.6 M solution of n-butyllithium (0.5 g, 7.3 mmol) in hexane was added dropwise at -60 °C to a solution of 1,3-dithiane 142 (0.8 g, 7.0 mmol) in THF (25 ml). The mixture was stirred for 2.5 h at -20 °C, and then a solution of N-methyl-N-methoxyphenylacetylamide 148 (1.5 g, 8.4 mmol) in THF (5 ml) added at -60 °C. The reaction was stirred for 18 h at -60 °C to room temperature and was then quenched with water (100 ml). Organic products were extracted into CH$_2$Cl$_2$ (4x50 ml) and the organic extract was washed with 1M HCl (4x70 ml), saturated NaHCO$_3$ and water (4x100 ml). Drying over MgSO$_4$ and concentration under reduced pressure gave a crude product as a pale-yellow solid. Purification over alumina (3:7 ethyl acetate/petrol) gave the title compound 147 (0.6 g, 38 %) as a white solid. m.p. 89-91 °C (Lit$^{107}$ 79-81 °C). δ$_r$ 1.90-2.20 (2H, m), 2.50-2.60 (2H, m), 3.20-3.30 (2H, m), 3.96 (2H, s, CH$_2$Ph), 4.26 (1H, s, S-CH-S), 7.22-7.38 (5H, m, Ar). δ$_c$ 25.1 (CH$_2$), 25.9 (CH$_2$S), 45.3 and 46.8 (CH$_2$Ph and S-CH-S), 127.2, 128.7, 129.5 and 133.7 (Ar), 199.9 (C=O). C$_{12}$H$_{14}$O$_2$S$_2$. Calculated C, 60.47; H, 5.92; S, 26.90. Found: C, 60.03; H, 5.89. $v_{max}$ (cm$^{-1}$): 1709. m/e (Cl) 256 (M+NH$_4^+$, 11 %), 239 (M+H$^+$, 2 %), 152 (100 %).
b) From Swern\textsuperscript{111} oxidation of 141

A solution of methyl sulfoxide (1.3 g, 16.6 mmol) and 141 (1.8 g, 7.5 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (15 ml) were added dropwise at -78 °C to a solution of oxalyl chloride (1.1 g, 8.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (20 ml) every 15 min. After stirring for 15 min., Et\textsubscript{3}N (3.8 g, 37.6 mmol) was added. The entire mixture was stirred for 20 h at -78 °C to room temperature and then quenched with distilled water (100 ml). Organic products were extracted into CH\textsubscript{2}Cl\textsubscript{2} (1x50 ml) and the combined extracts were washed with diluted HCl (6x70 ml), saturated NaHCO\textsubscript{3} (2x100 ml) and distilled water (2x150 ml). Drying over MgSO\textsubscript{4} and concentration under reduced pressure gave a crude product. Purification over silica gel (1:6 AcOEt/petrol) afforded the title compound (0.1 g, 7 %) as a white solid, m.p. 89-91 °C (Lit\textsuperscript{107} 79-81 °C). Spectroscopic data were identical to that in part (a).

4.3.5 3-Methylenetropone \textsuperscript{118} 155

A mixture of methyltriphenylphosphonium bromide 157 (3.4 g, 9.4 mmol) and potassium tert-butoxide (1.0 g, 9.1 mmol) in THF (20 ml) was stirred for 1 h at 0 °C, and then a solution of tropinone 116 (1.0 g, 7.2 mmol) in THF (5 ml) was added. The entire mixture was stirred for 3 h at 0 °C, quenched with 1M HCl solution and then THF was removed under reduced pressure. The mixture was diluted with water and the resultant triphenylphosphine oxide extracted into toluene (4x40 ml). The aqueous solution was then basified with 3M NaOH solution, and the desired product extracted into pentane (5x30 ml). Concentration of the combined organic extracts, after drying over MgSO\textsubscript{4}, gave a crude product. Distillation (25 °C, 0.1-0.01 mm-Hg) gave the title compound 155 (0.7 g, 72 %) as a clear oil. \( \delta \)\textsubscript{H} 1.46 (2H, d, J= 8.1 Hz, endo-C6,7), 1.80-1.90 (2H, complex, exo-C6,7), 1.93 (2H, d, J=14.8 Hz, C2,4 ), 2.30 (3H, s, C8), 2.46 (2H, d, J=14.0 Hz, C2,4), 3.14 (2H, broad s, C1,5), 4.70 (2H, t, J= 2.2 Hz, C9). \( \delta \)\textsubscript{C} 26.3 (C6,7), 39.4 (C2,4), 40.1 (C8), 61.4, (C1,5), 111.6 (=CH\textsubscript{2}), 143.1 (C3). \( \nu \)\textsubscript{max} (cm\textsuperscript{-1}): 3069 (=CH\textsubscript{2}), 2792 (N-Me), 1644 (C=C). m/e (EI) 137 (M\textsuperscript{+}, 10 %), 82 (100 %).
Neat BF$_3$OEt$_2$ (3.8 g, 26.7 mmol) was added dropwise to a mixture of NaBH$_4$ (0.8 mg, 20.0 mmol) and 2-methyl-2-butene (3.7 g, 53.4 mmol) in THF (10 ml) at -20 °C/ 0 °C. The reaction mixture was stirred at this temperature for an additional hour, and then a solution of 3-methylenetropane 155 (0.6 g, 4.5 mmol) in THF (5 ml) was added to this mixture. The entire reaction was further stirred for 16h at room temperature, and then oxidised at 0 °C with the subsequent addition of EtOH (2 ml), NaOH (5 ml, 6 M,) and H$_2$O$_2$ (8 ml, 30 %). The whole reaction was stirred for 4h at room temperature and then heated to 60 °C. After being diluted with water and ether, the mixture was filtered. The aqueous layer was saturated with solid K$_2$CO$_3$, and the organic products were extracted into ether (5x40 ml), combined and dried over MgSO$_4$. Concentration under reduced pressure and purification over silica gel (100 % ethyl acetate) gave the title compound 162 (70 mg, 10 %) as a pale yellow oil. This product was a 1:1 mixture of two stereoisomers. 

**endo-isomer:** $\delta$$_H$ 1.55 (2H, d, C6,7), 1.60 (2H, d, ax-C2,4), 1.90-2.10 (1H, complex, C3), 2.20-2.30 (2H, complex, C6,7), 2.60-2.65 (2H, complex, eq-C2,4), 2.70 (3H, s, N-CH$_3$), 3.30 (2H, broad s, C1,5), 3.63 (2H, d, J= 8.4 Hz, CH$_2$OH). $\delta_c$ 26.6 (C6,7), 27.6 (C2,4), 30.92 (C3), 42.4 (N-CH$_3$), 63.1 (C1,5), 68.2 (CH$_2$OH). 

**exo-isomer:** $\delta$$_H$ 1.45 (2H, d, ax-C2,4), 1.76 (2H, d, C6,7), 1.90-2.10 (1H, complex, C3), 2.20-2.30 (2H, complex, C6,7), 2.60 (3H, s, N-CH$_3$), 2.60-2.64 (2H, m, exo-6,7 of CH$_2$), 2.85 (2H, dt, eq-C2,4), 3.17 (2H, broad s, C1,5), 3.58 (2H, d, J= 8.9 Hz, CH$_2$OH). $\delta_c$ 28.5 (C6,7), 30.3 (C2,4), 30.3 (C3), 49.4 (N-CH$_3$), 64.9 (C1,5), 68.5 (CH$_2$OH). 

**Accurate mass (EI):**

Found 155.1312; calculated for (M$^+$) C$_8$H$_{13}$NO 155.1310 (- 1.4 ppm). $\nu_{max}$ (cm$^{-1}$): 3375 (OH). m/e (EI) 169 (M$^+$, 1 %), 155 (M-BH$_4$, 28 %), 82 (100 %).
4.3.7 N-Trihydroborate-3α/β-tosyloxymethyltropane\textsuperscript{118} 164

A 1.6M solution of n-BuLi (11 mg, 2.8 mmol) in hexane was added dropwise at 0 °C to a mixture of 3α/β-hydroxymethyltropane 162 (0.4 g, 2.6 mmol) and Ph$_2$CH (2 mg) in THF (10 ml). The reaction, which was slightly pink in colour, was stirred for 15 min., and then a solution of tosyl chloride 163 (0.5 g, 2.6 mmol) in THF (5.0 ml) was added. The entire mixture was stirred for 3.5 h at 0 °C, diluted with diethyl ether (80 ml), and was then washed with brine (4x50 ml). The organic layer was dried over MgSO$_4$, and concentrated under reduced pressure to give the product as a white solid. Purification over silica gel, eluting with ethyl acetate : petrol (5:15), gave some of the \textit{endo}-isomer 164 (55 mg, 8 %) as a white amorphous solid, which was re-crystallised from petroleum ether. m.p. 113.8-116.5 °C. δ$_H$ 1.30-1.50 (4H, m, $\alpha$-C$_2$,4 and \textit{endo}-C$_6$,7), 2.10-2.30 (3H, complex, C3 and \textit{exo}-C$_6$,7), 2.45 (3H, s, $p$-CH$_3$-Ar), 2.50-2.60 (2H, complex, $\textit{eq}$-C$_2$,4), 2.65 (3H, s, N-CH$_3$), 3.25 (H, broad s, Cl,5), 3.98 (H, d, J= 8.0 Hz, CH$_2$OH), 7.37 (2H, d, J= 8.0 Hz, Ar), 7.79 (2H, d, J= 8.0 Hz, Ar). δ$_C$ 21.7 ($p$-CH$_3$-Ar), 24.3 (C3), 27.1 (C6,7), 27.3 (C2,4), 42.4 (N-CH$_3$), 62.7 (C1,5), 74.0 (CH$_2$OH), 127.8, 130.0, 132.7, 145.2 and 151.0 (Ar). \textbf{Accurate mass (EI)}: Found 309.1398; calculated for (M$^+$) C$_{16}$H$_{23}$NO$_3$S 309.1399 (0.2 ppm). m/e (EI) 323 (M$^+$, 2 %), 309 (M-BH$_3$, 12 %), 82 (100 %). See X-ray structure in \textbf{Figure 11} (p. 71).
4.3.8 N-(2', 2', 2'-Trichloroethoxycarbonyl)tropinone 168

2,2,2-Trichloroethyl chloroformate 167 (2.5 g, 12.0 mmol) was added to a mixture of potassium carbonate (42 mg, 0.3 mmol) and tropinone 116 (1.4 g, 10.0 mmol) in benzene (20 ml). The reaction mixture was heated at reflux for 38 h, and then the organic solvent was removed under reduced pressure. The residue was taken into ether (70 ml) and then the precipitate was filtered off. The whole was washed with a 3M HCl (2x40 ml) and water (2x40 ml), and then dried over MgSO₄. Concentration under reduced pressure gave oil, which was solidified on standing. Purification over silica gel (1:9 ethyl acetate/petrol) gave the title compound 168 (1.6 g, 52 %) as a milky-white solid, m.p. 78.8-80.1 °C (lit 79-80 °C). δH 1.60-1.80 (2H, m, endo-C6,7), 2.00-2.20 (2H, m, exo-C6,7), 2.41 (2H, d, J= 16.0 Hz, αx-C2,4), 2.73 (2H, d, J= 16.4 Hz, eq-C2,4), 4.64 (2H, m, C1,5), 4.69 (1H, d, J= 12.0 Hz, CH₂O), 4.91 (1H, d, J= 12.0 Hz, CH₂O). δC 28.4 and 29.4 (C6,7), 48.6 and 49.2 (C2,4), 53.4 (C1,5), 74.72 (CH₂O), 95.6 (CCl₃), 151.6 (N-C=O), 207.23 (C=O). C₁₉H₁₅Cl₃N0₃. Calculated C, 39.96; H, 4.02; Cl, 35.39; N, 4.66. Found: C, 39.49; H, 3.98; N, 4.35. νmax (cm⁻¹): 1706 (C=O). m/e (CI) 300 and 302 (MH⁺, 8 and 8 %), 126 (100 %).

4.3.9 N-(2', 2', 2'-Trichloroethoxycarbonyl)-3-methylenetropane 169

2,2,2-Trichloroethyl chloroformate 167 (1.4 g, 6.8 mmol) was added to a solution of 3-methylenetropane 155 (0.4 g, 3.1 mmol) in toluene (20 ml) at room temperature. The reaction mixture was heated under refluxed for 40h. Concentration under reduced pressure and then purification over silica gel (1:19 ethyl acetate/petrol) gave the title
compound 169 (0.7 g, 79 %) as a clear oil, which solidified on standing. m.p. 42-44 °C. δH 1.50-1.70 (2H, m, endo-C6,7), 1.80-2.00 (2H, m, exo-C6,7), 2.14 (2H, d, J=14.0 Hz, ax-C2,4), 2.52 (2H, d, J=14.0 Hz, eq-C2,4), 4.40 (2H, broad d, J=17.2 Hz, C1,5), 4.66 (1H, d, J=11.6 Hz, CH2O), 4.80-5.00 (3H, m, CH2O + =CH2). δC 27.6 and 28.5 (C6,7), 40.6 and 41.3 (C2,4), 54.6 (C1,5), 74.6 (CH2O), 95.9 (CCl4), 114.2 (=CH2), 141.3 (C3), 151.6 (NC=O). Accurate mass (EI): Found 297.0090; calculated for (M+) C11H14NO2Cl3 297.0090 (0.2 ppm). νmax (cm⁻¹): 3073 (=CH2), 1719 (C=O), 1646 (C=C). m/e (EI) 297, 299 and 301 (M⁺, 28, 28 and 11 %), 68 (100 %).

4.3.10 N-(2', 2', 2'-Trichloroethoxycarbonyl)-3α/β-hydroxymethyltropane 171

![Structure of 171](image.jpg)

a) Method using 9-BBN

A 0.50 M solution of 169 (149 mg, 0.5 mmol) in THF (1.0 ml) was added dropwise to an in situ prepared 0.55 M solution of 9-BBN 160 (203 mg, 1.7 mmol) in THF (3 ml) at room temperature. The reaction mixture was stirred for 23 h, and then oxidised at 0 °C with the subsequent additions of MeOH (2 ml), 6.0 M NaOH (1 ml) and 30 % H2O2 (2 ml). The reaction mixture was further stirred for 2 h at r.t., and then heated under reflux for 30 min. The aqueous layer was saturated with solid K2CO3 and organic products were extracted into ether (5x15 ml). Drying over MgSO4 and concentration under reduced pressure gave a crude product. Purification over silica gel (1:4 and 2:3 ethyl acetate/petrol) yielded the title compound 171 (158 mg, 100 %) as a clear oil. This product was a 3:1 mixture of two stereoisomers. δH 1.40-1.60 (4H, complex, ax-C2,4), 1.60-1.80 (4H, complex, endo-C6,7), 1.80-2.30 (10H, complex, C3, exo-C6,7 and eq-C2,4), 3.43 (2H, d, J=6.4.0 Hz, exo-C11), 3.65 (2H, d, J=8.0 Hz, endo-CH2OH), 4.20-4.50 (4H, broad dd, C1,5), 4.60-4.70 (2H, m, CH2O), 4.80-4.90 (2H, m, CH2O). endo-isomer: δC 28.6 and 29.3 (C6,7), 31.3 and 32.0 (C2,4), 31.7 (C3), 52.8 and 53.0 (C1,5), 67.4 (CH2OH), 74.5 (CH2O), 95.9 (CCl4), 151.5 (NC=O). exo-isomer: δC 27.7 and 28.5 (C6,7), 31.2 (C3), 33.9 and 34.6 (C2,4), 53.7 and 53.8 (C1,5), 67.6 (CH2OH), 74.5
(CH₂O), 95.9 (CCl₃), 151.5 (NC=O). **Accurate mass (EI):** Found 315.0172; calculated for (M⁺) C₁₅H₁₆NO₃Cl₃ 315.0196 (7.5 ppm). νₘₙₙ (cm⁻¹): 3433 (OH), 1702 (C=O). m/e (EI) 315, 317 and 319 (M⁺, 20, 19 and 7 %), 244 (100 %).

**b) Method using disiamylborane**

Neat BF₃.OEt₂ (560 mg, 3.9 mmol) was added dropwise at -10 °C to a mixture of NaBH₄ (103 mg, 2.7 mmol) and 2-methyl-2-butene (516 mg, 7.3 mmol) in diglyme (4 ml). The semi-solid reaction mixture was stirred at this temperature for an additional hour, and then a solution of 169 (225 mg, 0.7 mmol) in diglyme (1 ml) was added. The reaction was further stirred for 12 h at r.t., and was then oxidised at 0 °C with the subsequent additions of water (2 ml), NaOH (2 ml, 6 M), and H₂O₂ (2 ml, 30 %). The reaction was stirred for an additional 2h at r.t. and heated to 60 °C. After being diluted with water and ether, the mixture was filtered. The aqueous layer was saturated with solid K₂CO₃, and then the organic products were extracted into diethyl ether (5x20 ml). The organic layer was washed with brine (7x20 ml) to remove excess diglyme. Drying over MgSO₄ and concentration under reduced pressure gave a residue, which was purified over silica gel (1:1 ethyl acetate/petrol) to give the product 171 (194 mg, 81 %) as a pale yellow oil. This product was a 77:1 mixture of two stereoisomers. **endo-isomer:** δₜ 1.40-1.60 (2H, m, α-C2,4), 1.60-1.80 (2H, m, endo-C6,7), 1.80-2.10 (3H, complex, C3 and exo-C6,7), 2.10-2.30 (2H, m, eq-C2,4), 3.64 (2H, d, J= 8.0 Hz, CH₂OH), 4.30 (2H, broad d, C1,5), 4.66 (1H, d, J= 12.0 Hz, CH₂O), 4.82 (1H, d, J= 12.0 Hz, CH₂O). δₜ 28.6 and 29.3 (C6,7), 31.3 and 32.0 (C2,4), 31.7 (C3), 52.8 and 53.0 (C1,5), 67.39 (CH₂OH), 74.5 (CH₂O), 95.9 (CCl₃), 151.5 (NC=O). The **exo-isomer** cannot be assigned due to its low concentration in the mixture. The rest of the spectroscopic data were identical to that obtained by method a.
4.3.11 N-(2',2',2'-Trichloroethoxycarbonyl)-3α/β-tosyloxymethyltropane 170.

\[
\text{Cl}_3\text{C} - \text{O} - \text{N} - \text{O} - \text{S} - \text{O}
\]

170

**a) Method using n-butylithium**

A 1.6 M solution of n-BuLi (154 mg, 2.4 mmol) in hexanes was added dropwise at 0 °C to a mixture 171 (604 mg, 1.9 mmol) and triphenylmethane (2 mg) in THF (8 ml). The reaction was stirred for 30 min., and then a solution of p-toluene-sulfonyl chloride 163 (364 mg, 1.9 mmol) in THF (6 ml) was added. The entire mixture was stirred for 18 h at 0 °C to r.t., diluted with ether (50 ml), and was then washed with brine (10x10 ml). The organic layer was dried over MgSO₄, and concentrated under reduced pressure to obtain a crude product. Purification over silica gel (1:4 and 1:1 ethyl acetate/petrol) gave a product, which was a mixture of two compounds. Further purification over silica gel afforded the title product 170 (123 mg, 14 %) as a liquid, which solidified on long standing. **m.p.** 80-81 °C. δₜ 1.40-1.60 (4H, complex, C6,7), 1.90-2.20 (5H, complex, C3 and C2,4), 2.45 (3H, s, p-CH₃-Ar), 4.03 (2H, d, J= 7.6 Hz, CH₂-OTs), 4.29 (2H, broad d, J= 20.8 Hz, Cl,5), 4.64 (1H, d, J= 12.0 Hz, CH₂-O), 4.82 (1H, d, J= 12.4 Hz, CH₂-O), 7.35 (1H, d, J= 8.0 Hz, Ar), 7.78 (1H, d, J= 8.4 Hz, Ar). δC 21.7 (p-CH₃-Ar), 28.3 and 28.4 (C6,7), 29.1 (C3), 30.9 and 31.6 (C2,4), 52.5 and 52.6 (Cl,5), 73.8 (CH₂-OTs), 74.5 (CH₂-O), 95.8 (CCl₃), 127.8, 129.9, 132.9 and 145.0 (Ar), 151.4 (NC=O). C₁₈H₂₄Cl₂NO₅S. Calculated C 45.92; H 4.71; N 2.97; Cl 22.59; S 6.81. **Found:** C 45.73; H 4.66; N 3.08. ν₅₅₅ (cm⁻¹): 2966, 1713 (C=O), 1597, 1500 and 1417 (C=C), 1361, 1188 and 1176 (O=S=O). m/e (EI) 469, 471 and 473 (M⁺, 11, 12 and 4 %), 91 (100 %).

**b) Method using pyridine**

A solution of 171 (675 mg, 2.1 mmol) and p-toluenesulfonyl chloride 163 (650 mg, 3.4 mmol) in pyridine (15 ml) was stirred for 64 h at r.t. The reaction was poured into a mixture of crushed ice and CH₂Cl₂ and then organic product was extracted into CH₂Cl₂.
(4x50 ml). The organic extracts were combined and washed with 3M HCl (3x50 ml), saturated NaHCO₃ (3x75 ml) and water (3x100 ml). Drying over MgSO₄ and concentration gave a golden yellow liquid. Purification over aluminium oxide (1:4 ethyl acetate/petrol) gave the title product 170 (0.9 g, 90 %) as a liquid, which was solidified on standing. The spectroscopic data were identical to that obtained by method a.

4.3.12  \(\text{N-(2',2',2'-Trichloroethoxycarbonyl)-3\alpha/\beta-iodomethyltropane 185}\)

A solution of 170 (1.13 g, 2.39 mmol) and NaI (2.87 g, 19.13 mmol) in acetone (60 ml) was heated under reflux for 9h. After evaporation of the solvent, the residue was stirred with a 1:1 mixture of \(\text{CH}_2\text{Cl}_2\) and petrol (250 ml). Purification over aluminum oxide (1:1 \(\text{CH}_2\text{Cl}_2/petrol\)) gave the title compound 185 (783 mg, 79 %) as a pale-yellow liquid.

\[\begin{align*}
\text{Cl}_3\text{C} & \quad \text{O} \\
\text{N} & \quad \text{I} \\
185
\end{align*}\]

\(\delta_h\) 1.40-1.80 (4H, complex, C6,7), 1.90-2.20 (5H, complex, C3 and C2,4), 4.03 (2H, d, J= 7.6 Hz, CH₂I), 3.36 (2H, d, J= 8 Hz, CH₂I), 4.30-4.50 (2H, broad d, C1,5), 4.62 (d, J= 12.4 Hz, CH₂O), 4.82 (1H, d, J= 12.4 Hz, CH₂O). \(\delta_c\) 15.4 (CH₂I), 29.1 and 29.7 (C6,7), 31.8 (C3), 35.7 and 36.4 (C2,4), 52.5 and 52.6 (C1,5), 74.6 (CH₂O), 95.9 (CCl₃), 151.6 (C8). \textbf{Accurate mass (EI)}: Found 424.9228; calculated for (M⁺) \(\text{C}_1\text{H}_{13}\text{NO}_2\text{ClI}\) 424.9213 (- 3.5 ppm). \(\nu_{\text{max}}\) (cm⁻¹): 2958, 1717 (C=O), 1419, 1119. \(\text{m/e (EI)}\) 425, 427 and 429 (M⁺, 8, 7 and 3 %), 298 (100 %).
4.4 Experimental for chapter three

4.4.1 Ethyl (tropan-3'-ylidine)acetate \(^{88,152}\) 132

![Chemical Structure](image)

Neat triethyl phosphonoacetate 131 (27.1 g, 0.121 mol) was added dropwise to a slurry of NaH (3.0 g, 0.125 mol) in THF (150 ml) at -30 °C. The mixture was stirred for 1 h and then a solution of tropinone 116 (15.0 g, 0.108 mol) in THF (100 ml) was added. The entire mixture was allowed to warm to room temperature for 2 h and was then heated under reflux for 35 h. The reaction mixture was quenched with water (50 ml) and concentrated to give a residue. The residue was partitioned between water (300 ml) and Et₂O (100 ml) and the organics were extracted into Et₂O (4 x 100 ml). The combined organic layers were treated with a 2 M HCl (150 ml) and were then washed with Et₂O (2 x 300 ml). Upon basification with a 2.5 M NaOH (130 ml), the title compound was extracted into Et₂O (4 x 100 ml), dried over MgSO₄ and concentrated to give the title compound 132 (17.4 g, 77 %) as a pale-yellow oil. The product was contaminated with 11 % of β,γ-unsaturated ester 133. This was used directly for the next step without purification. δ \(\text{H} \) 1.23 (3H, t, J = 7.2 Hz, CH₃CH₂O), 1.46 (2H, broad dd, J = 8.8 and 2.4 Hz, endo-C6',7'), 1.88-1.98 (3H, m, exo-C6',7' and α-C4'), 2.33 (3H, s, NCH₃), 2.30-2.40 (1H, broad d, eq-C2'), 2.65 (1H, broad d, J = 14.0 Hz, eq-C4'), 3.21 (2H, broad s, C1',5'), 3.46 (1H, broad d, J = 14.8 Hz, α-C2'), 4.10 (2H, q, J = 7.2 Hz, CH₃CH₂O), 5.65 (1H, s, C=CH). δ \(\text{C} \) 14.2 (CH₃CH₂O), 26.7 and 26.9 (C6',7'), 38.8 (NCH₃), 35.0 and 41.6 (C2',4'), 59.5 (CH₃CH₂O), 61.0 and 61.4 (C1',5'), 117.7 (=CH), 157.9 (C3'), 166.6 (C=O). ν \(\text{max} \) (cm⁻¹): 2940, 2874, 2846, 2795 (N-Me), 1714 (C=O), 1643 (C=C), 1199, 1153, 1041. m/z (CI) 210 (M+H⁺).
A solution of ethyl (tropan-3'-ylidene)acetate 132 (16.4 g, 78.4 mmol) in MeOH (400 ml) and a 10 % palladium (834 mg, 7.8 mmol) on activated carbon was shaken for 51h under 4-5 atm. pressure of hydrogen at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate was concentrated to give a crude product. Purification by distillation (66 °C; 0.1-0.01 mm-Hg) gave the title compound 214 (15.3 g, 87 %) as a clear oil. The product was a mixture (5:1 endo/exo) and used directly for the next step.

**endo-isomer:** \( \delta_h \) 1.12 (3H, t, J= 6.9 Hz, CH\(_3\)CH\(_2\)O), 1.17 (2H, broad d, J= 14.7 Hz, eq-C2',4'), 1.50 (2H, broad d, J= 8.4 Hz, endo-C6',7'), 1.88-1.96 (2H, m, exo-C6',7'), 1.97-2.09 (2H, m, ax-C2',4'), 2.10-2.20 (1H, m, C3'), 2.12 (3H, s, N-CH\(_3\)), 2.32 (2H, d, J= 8.1 Hz, CH\(_2\)C=O), 2.96 (2H, broad s, C1',5'), 3.99 (2H, q, J= 6.9 Hz, CH\(_3\)CH\(_2\)O).

**endo-isomer:** \( \delta_c \) 14.4 (CH\(_3\)CH\(_2\)O), 24.7 (C3'), 26.5 (C6',7'), 35.3 (C2',4'), 40.2 (N-CH\(_3\)), 43.2 (CH\(_2\)C=O and CH\(_3\)CH\(_2\)O), 60.4 (C1',5'), 173.2 (C=O).

**exo-isomer:** \( \delta_h \) 1.11 (3H, t, J= 6.9 Hz, CH\(_3\)CH\(_2\)O), 1.08-1.56 (4H), 1.84-2.20 (5H), 2.12 (3H, s, N-CH\(_3\)), 2.34 (2H, d, J= 8.1 Hz, CH\(_3\)CH\(_2\)O), 2.92-3.02 (2H, broad s, C1',5'), 3.97 (2H, q, J= 6.9 Hz, CH\(_3\)CH\(_2\)O).

**exo-isomer:** \( \delta_c \) 14.4 (CH\(_3\)CH\(_2\)O), 24.7 (C3'), 25.6 and 26.2 (C6',7'), 37.9 and 41.5 (C2',4'), 40.4 (N-CH\(_3\)), 42.9 (CH\(_2\)C=O and CH\(_3\)CH\(_2\)O), 60.3 and 61.3 (C1',5'), 172.8 (C=O). \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2932, 2796 (N-Me), 1735 (C=O), 1478, 1450, 1368, 1342, 1307, 1169, 1149, 1063, 1033. m/z (EI) 211 (M\(^+\), 28 % ), 124 (55 %), 96 (79 %), 82 (100 %), 42 (65 %).
A solution of ethyl (tropan-3'-ylidine)acetate 132 (5.2 g, 24.9 mmol) in THF (55 ml) was added dropwise to a suspension of LiAlH₄ (4.7 g, 0.124 mol) in THF (75 ml) at -60 °C. The reaction mixture was allowed to warm to room temperature and then heated under reflux for 41 h. The reaction mixture was quenched with a 2.5 M NaOH (10 ml), diluted with Et₂O (50 ml) and then filtered through a sintered funnel. The filtrate was concentrated to give a residue, which was partitioned between brine and Et₂O. The organics were then extracted into Et₂O (6x50 ml). Combined extracts were dried over MgSO₄ and concentrated to give a crude material. This was purified by distillation (b.p. 68-72 °C; 0.1-0.01 mm-Hg) to yield the title compound 231 (2.0 g, 48 %) as a white crystalline solid. The product was contaminated with 11 % of endo-cyclic alcohol 232. 

**m.p.** 55.5-57.5 °C. δₙ 1.36 (1H, broad d, J= 8.4 Hz, endo-C6',7'), 1.44 (1H, broad s, J= 9.3 Hz, endo-C6',7'), 1.80-1.90 (3H, m, exo-C6',7' and ax-C2',4'), 2.16-2.23 (2H, m, (ax + eq)-C2',4'), 2.28 (3H, s, N-CH₃), 2.49 (1H, broad s, J= 15.3 Hz, eq-C2',4'), 3.10 (2H, broad s, C1',5'), 3.64 (1H, broad s, OH), 4.08 (2H, d, J= 6.6 Hz, CH₂OH), 5.44 (1H, t, J= 6.9 Hz, C=CH). δc 26.5 and 26.8 (C6',7'), 39.9 (N-CH₃), 34.6 and 41.6 (C2',4'), 58.4 (CH₂OH), 61.4 and 61.8 (C1',5'), 126.4 (=CH), 136.6 (C3'). C₁₀H₁₇NO. Calculated C, 71.82; H, 10.25; N, 8.37. Found: C, 71.79; H, 10.31; N, 8.45. v max (cm⁻¹): 3161 (OH), 2940, 2797 (N-Me), 1669 and 1654 (C=CH). m/z (EI) 167 (M⁺,17 %), 82 (100 %).
4.4.4 2-(Tropan-3'-yl)ethanol 230

a-) From the hydrogenation of 2-(tropan-3-ylidine)ethanol 231

A solution of 2-(tropan-3-ylidine)ethanol 231 (6.2 g, 36.9 mmol) in EtOH (150 ml) and a 10 % palladium (300 mg, 2.8 mmol) on activated carbon was shaken for 45h under 3-4 atm. pressure of hydrogen at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate was concentrated to give a crude product. Purification by distillation (76-78 °C; 0.1-0.01 mm-Hg) gave the title compound 230 (5.2 g, 84 %) as a clear oil and as a 7:1 endo / exo mixture. **(endo+exo)-isomer:** δ_H 1.29 (2H, broad d, J= 14.1 Hz, eq-C2',4'), 1.34-1.86 (7H), 1.61 (2H, broad d, J= 8.1 Hz, endo-C6',7'), 1.72 (2H, t, J= 6.6 Hz, CH2CH2OH), 1.66-1.86 (1H, m, C3'), 1.90-2.04 (2H, m, exo-C6',7'), 2.04-2.16 (2H, m, ax-C2',4'), 2.21 (3H, s, N-CH3), 2.78 (1H, broad s, OH), 3.06 (2H, broad s, C1',5'), 3.59 (2H, t, J= 6.6 Hz, CH2OH). **endo-isomer:** δ_C 24.1 (C3'), 26.6 (C6',7'), 35.9 (C2',4'), 40.4 (N-CH3), 41.7 (CH2CH2OH), 60.7 (C1',5'), 61.7 (CH2OH). **exo-isomer:** δ_C 24.5 (C3'), 26.3 (C6',7'), 38.5 (C2',4'), 40.0 (N-CH3), 40.7 (CH2CH2OH), 60.5 (CH2OH), 61.5 (C1',5'). ν_max (cm⁻¹): 3201, 3161 (OH), 2967, 2927, 2886, 2851, 2797 (N-CH3), 1473, 1342, 1026, 1011. **Accurate mass (EI):** Found 169.1470; Calculated for (M⁺) C10H14NO 169.1467 (-1.8 ppm). m/z (EI) 169 (M⁺, 21 % ), 96 (83 %), 82 (100 %).

b-) From the LiAlH₄ reduction of ethyl (tropan-3'-yl)acetate

A solution of ethyl (tropan-3'-yl)acetate 214 (12.4 g, 58.9 mmol) in Et₂O (50 ml) was added dropwise to a suspension of LiAlH₄ (4.5 g, 0.118 mol) in Et₂O (250 ml) at -60 °C. The reaction mixture was allowed to warm to room temperature and was then heated under reflux for 24h. The reaction mixture was sequentially quenched with water (4.8 ml), a 15 % NaOH (4.8 ml) and water (15 ml) to give a granular precipitate. The precipitate was filtered off through a sintered funnel and was then washed with Et₂O (2x50 ml). The combined filtrate was dried over MgSO₄ and concentrated to give the
title compound (8.5 g, 86 %) as a clear oil and as a 5:1 endo/exo mixture. The spectral data are consistent with those of obtained by method a.

4.4.5 (Tropan-3'-yl)acetaldehyde 227

![Structure of 227](image)

A solution of dimethyl sulfoxide (3.2g, 41.3 mmol) in CH₂Cl₂ was added dropwise to a solution of oxalyl chloride (2.7 g, 21.2 mmol) in CH₂Cl₂ at -78 °C. After stirring for 15 min., a solution of 2-(tropan-3'-yl)ethanol 230 (2.0 g, 11.8 mmol) in CH₂Cl₂ was added. The mixture was stirred for 2h at -78 °C and was then quenched with triethylamine (6.6 g, 64.9 mmol). After stirring for 15 min at room temperature, 10 % NaOH solution was added to make the reaction mixture strongly basic. Organics were then extracted into CH₂Cl₂ (4x80 ml) and then the combined extracts were dried over MgSO₄ and concentrated to give the title compound 227 (1.84 g, 93 %) as a light-brown liquid and as a 5:1 endo/exo mixture. **endo-isomer:** δH 1.17 (2H, broad d, J= 14.4 Hz, eq-C2',4'), 1.52 (2H, broad d, J= 8.4 Hz, endo-C6',7'), 1.90-2.02 (2H, m, exo-C6',7'), 2.08-2.16 (2H, m, ax-C2',4'), 2.18 (3H, s, N-CH₃), 2.24-2.38 (1H, m, C3'), 2.48 (2H, dd, J= 7.8 and 2.0 Hz, CH₂CHO), 3.06 (2H, broad s, C1',5'), 9.54 (1H, t, J= 1.8 Hz, CHO). **exo-isomer:** δC 20.5 (C3'), 25.2 (C6',7'), 34.2 (C2',4'), 38.9 (N-CH₃), 51.4 (CH₂CHO), 59.4 (C1',5'), 201.6 (CHO). **exo-isomer:** δH 1.08-1.62 (4H), 1.90-2.38 (5H), 2.22 (3H, s, N-CH₃), 2.45-2.52 (2H, CH₂CHO), 3.14 (2H, broad s, C1',5'), 9.60 (1H, t, J= 1.8 Hz, CHO). **exo-isomer:** δC 21.7 (C3'), 24.8 (C6',7'), 36.4 (C2',4'), 39.1 (N-CH₃), 49.3 (CH₂CHO), 60.6 (C1',5'), 200.4 (CHO). νmax (cm⁻¹): 2930, 2795 (N-CH₃), 1723 (C=O), 1450, 1339, 1231, 1129. **Accurate mass (EI):** Found 167.1311; Calculated for (M⁺) C₁₀H₁₇NO 167.1310 (-0.5 ppm). m/z (EI) 167 (M⁺, 9 %), 124 (58 %), 96 (49 %), 83 (67 %), 82 (100 %), 42 (59 %).
A 2 M solution of isopropylmagnesium chloride (492 mg, 4.78 mmol) was added to a
solution of (tropan-3'-yl)acetaldehyde 227 (400 mg, 2.39 mmol) in THF (30 ml) at -78
°C. The reaction mixture was allowed to warm to room temperature for 14 h and was
then concentrated under reduced pressure. The residue was diluted with saturated NH₄Cl
and impurities were extracted into Et₂O (3x 30 ml). After the aqueous layer was made
basic (pH 10-11) with NaOH pellets, organics were then extracted into CH₂Cl₂ (5x 40
ml). The combined extracts were washed once with 2.5 M NaOH solution, dried over
MgSO₄ and concentrated to give the title compound 236 (337 mg, 67 %) as a clear oil
and as a 5:1 endo/exo mixture. δH 0.86 (6H, dd, J= 4.5 Hz, CH₃), 1.20-1.40 (3H, m),
1.50-1.70 (4H, m), 180-2.30 (6H, m), 2.22 (3H, s, NCH₃), 3.10 (2H, broad s, C1',5'),
3.40 (1H, m, CHOH). endo-isomer: δC 17.5 and 19.0 (CH₂), 24.1 (C3'), 26.5 and 26.7
(C6',7'), 34.2 and 37.4 (C2',4'), 40.3 (N-CH₃), 42.8 (CH₃CHOH + CHCHOH), 60.8
(C1',5'), 74.9 (CHOH). exo-isomer: δC 17.3 and 18.9 (CH₂), 24.3 (C6',7'), 26.2 (C2',4'),
34.3, 37.4, 41.3 (N-CH₃), 42.8 (CH₂CHOH + CHCHOH), 61.7 and 61.9 (C1',5'), 73.7
(CHOH). Accurate mass (EI): Found 211.1936; Calculated for (M⁺) C₁₅H₂₅NO
211.1936 (0.07 ppm). νmax (cm⁻¹): 3373 (O-H), 2958, 2928, 2797 (N-CH₃), 1470, 1451,
1338, 1230, 1131, 1063. m/z (EI) 211 (M⁺, 3 %), 168 (3 %), 96 (64 %), 82 (100 %), 42
(74 %).
A solution of 4-bromoanisole (673 mg, 3.60 mmol) in Et₂O (15 ml) was added dropwise to a suspension of magnesium turnings (96 mg, 3.96 mmol) and iodine crystals in Et₂O (5 ml) at room temperature. After addition was complete, the mixture was heated under reflux for 15 min and then cooled to ambient temperature. This Grignard reagent was added to a solution of (tropan-3'-yl)acetaldehyde 227 (200 mg, 1.20 mmol) in THF (20 ml) at -78 °C. The reaction mixture was allowed to warm to room temperature for 21h and then concentrated. The residue was diluted with saturated NH₄Cl and impurities were extracted into Et₂O (3x30 ml). After the aqueous layer was made basic (pH 10-11) with NaOH pellets, organics were then extracted into CH₂Cl₂ (5x40 ml). The combined extracts were washed once with 2.5 M NaOH solution, dried over MgSO₄ and concentrated to give the title compound 237 (210 mg, 64 %) as a pale-yellow viscous oil and as a 5:1 endo/exo mixture. δH 1.20-1.50, 1.60-2.30, 2.18 (3H, s, NCH₃), 3.10 (2H, broad s, C1',5') 3.74 (3H, s, OCH₃), 4.50 (1H, t, CHOH), 6.80 (2H, d, J= 8.7 Hz, Ar), 7.18 (2H, d, J= 8.7 Hz, Ar). endo-isomer: δc 24.1 (C3'), 26.5 and 26.6 (C6',7'), 34.7 and 36.0 (C2',4'), 39.6 (N-CH₃), 48.4 (CH₂CHOH), 55.4 (OCH₃), 60.5 (C1',5'), 72.3 (CHOH), 113.9, 127.3, 138.2 and 159.0 (Ar). exo-isomer: δc 24.5 (C3'), 26.3 (C6',7'), 37.7 and 38.5 (C2',4'), 39.6 (N-CH₃), 46.7 (CH₂CHOH), 53.6 (OCH₃), 61.4 and 61.5 (C1',5'), 71.0 (CHOH), 113.9, 127.1, 138.3 and 159.0 (Ar). Accurate mass (EI): Found 275.1882; Calculated for (M⁺) C₁₁H₂₃N O₂ 275.1885 (1.2 ppm). νmax (cm⁻¹): 3355 (O-H), 2931, 2836, 2801 (N-CH₃), 1610, 1585, 1510, 1451, 1338, 1245, 1075, 1037. m/z (EI) 275 (M, 23 %), 257 (8 %), 138 (78 %), 96 (73 %), 82 (100 %).
A solution of α-bromostyrene (657 mg, 3.59 mmol) in Et₂O (10 ml) was added dropwise to a suspension of magnesium turnings (96 mg, 3.95 mmol) and iodine crystals in Et₂O (5 ml) at room temperature. After addition was complete, the mixture was heated under reflux for 15 min and was then cooled to ambient temperature. This Grignard reagent was added to a solution of (tropan-3'-yl)acetaldehyde 227 (400 mg, 2.39 mmol) in THF (30 ml) at -78 °C. The reaction mixture was diluted with Et₂O (45 ml) and then stirred for 4.5 h between -78 °C and -10 °C. The reaction mixture was concentrated, the residue was diluted with saturated NH₄Cl and impurities were extracted into AcOEt (3x 40 ml). After the aqueous layer was made basic (pH 10-11) with NaOH pellets, organics were then extracted into CH₂Cl₂ (4x 50 ml). The combined extracts were washed once with 2.5 M NaOH solution, dried over MgSO₄ and concentrated to give the title compound 238 (514 mg, 79 %) as a pale-yellow viscous oil and as a 5:1 endo/exo mixture. The δ values are given in ppm: δH 1.10-1.50 (4H), 1.60-2.20 (7H), 2.09 (3H, s, NCH₃), 2.93 (2H, broad s, C1',5'), 3.95 (1H, broad s, OH), 4.46-4.58 (1H, m, CHOH), 5.18 (1H, s, =CH₂), 5.30 (1H, s, =CH₂), 7.14-7.34 (5H, m, Ar). 

**endo-isomer:** δC 24.3 (C3'), 26.3 and 26.4 (C6',7'), 34.3 and 37.0 (C2',4'), 40.2 (N-CH₃), 45.3 (CH₂CHOH), 60.6 (C1',5'), 72.3 (CHOH), 112.3 (=CH₂), 127.1, 127.8, 128.6 and 140.3 (Ar), 153.0 (C=). 

**exo-isomer:** δC 24.5 (C3'), 26.3 (C6',7'), 28.0 and 30.3 (C2',4'), 40.6 (N-CH₃), 43.9 (CH₂CHOH), 61.5 and 61.6 (C1',5'), 71.1 (CHOH), 112.3 (=CH₂), 127.0, 127.8, 128.6 and 140.2 (Ar), 153.2 (C=). 

**Accurate mass (EI):** Found 271.1936; Calculated for (M⁺) C₁₈H₂₃NO 271.1936 (0.05 ppm). 

**ν_{max} (cm⁻¹):** 3343 (O-H), 3079, 3055, 3028, 2923, 2855, 2800 (N-CH₃), 1627, 1597, 1492, 1450, 1338, 1122, 1071. 

**m/z (EI):** 271 (M⁺, 13 %), 254 (61 %), 138 (41 %), 96 (93 %), 82 (100 %).
A mixture of PCC (604 mg, 2.80 mmol) adsorbed on alumina and 1-(tropan-3'-yl)-3-methyl-2-butanol \(\text{236}\) (295 mg, 1.40 mmol) in \(\text{CH}_2\text{Cl}_2\) (30 ml) was stirred for 24 h. The reaction was then diluted with ether (30 ml) and filtered through Hyflo Super Cell. Alumina was washed twice with a mixture of ether and \(\text{CH}_2\text{Cl}_2\) (1:1) and the solution was concentrated to give a residue, which was made basic with 2.5 M NaOH solution. Organic were then extracted into AcOEt (3x 30 ml) and the combined extracts were dried over MgSO\(_4\) and concentrated to give the title compound \(\text{218}\) (130 mg, 44 %) as a light-brown liquid and as a 5:1 endo/exo mixture. **endo-isomer:** \(\delta^H\) 1.07 (3H, d, J= 6.9 Hz, \((\text{CH}_3)_2\)), 1.20 (2H, broad d, J= 14.1 Hz, \(eq\)-C2',4'), 1.61 (2H, broad d, J= 8.1 Hz, \(endo\)-C6',7'), 1.98-2.10 (2H, m, \(exo\)-C6',7'), 2.10-2.24 (2H, m, \(ax\)-C2',4'), 2.26 (3H, s, NCH\(_3\)), 2.28-2.42 (1H, m, C3'), 2.56 (1H, septet, J= 6.9 Hz, CHC=O), 2.62 (2H, d, J= 7.8 Hz, CH\(_2\)C=O), 3.10 (2H, broad s, C1',5'). **endo-isomer:** \(\delta^C\) 17.2 (CH\(_3\)), 21.6 (C3'), 25.3 (C6',7'), 34.2 (C2',4'), 39.6 (N-CH\(_3\)), 48.2 (CH\(_2\)C=O and CHC=O), 59.3 (C1',5'), 213.1 (C=O). **exo-isomer:** \(\delta^H\) 1.04 (6H, d, J= 6.9 Hz, CH\(_3\)), 1.13-1.70 (4H), 1.94-2.40 (5H), 2.26 (3H, s, NCH\(_3\)), 2.45-2.65 (2H), 3.06-3.16 (2H, broad s, C1',5'). **exo-isomer:** \(\delta^C\) 17.0 (CH\(_3\)), 22.8 (C3'), 24.8 (C6',7'), 36.6 (C2',4'), 38.8 (N-CH\(_3\)), 45.9 (CH\(_2\)C=O and CHC=O), 60.5 (C1',5'), 213.1 (C=O). **Accurate mass (EI):** Found 209.1773; Calculated for \((\text{M}^+)\) \(C_{13}H_{23}NO\) 209.1780 (3.1 ppm). \(\nu_{max}\ (\text{cm}^{-1})\): 2960, 2930, 2795 (N-CH\(_3\)), 1710 (C=O), 1467, 1382, 1128, 1079, 1039. \(m/z\ (\text{EI})\) 209 (M\(^+\), 15 %), 138 (41 %), 124 (52 %), 96 (68 %), 82 (100 %).
Activated manganese dioxide (4.3 g, 49.4 mmol) was added to a solution of 2-(tropan-3'-yl)-1-para-methoxyphenyl-1-ethanol 237 (358 mg, 1.30 mmol) in CH₂Cl₂ (40 ml) and the mixture was stirred for 22h at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate concentrated to give the title compound 219 (181 mg, 51 %) as a light-brown liquid and as a 5:1 endo/exo mixture. **endo-isomer:** \( \delta \), 1.27 (2H, broad d, J= 14.4 Hz, eq-C2',4'), 1.64 (2H, broad d, J= 8.4 Hz, endo-C6',7'), 1.90-2.06 (2H, m, exo-C6',7'), 2.08-2.18 (2H, m, ax-C2',4'), 2.19 (3H, s, NCH₃), 2.32-2.46 (1H, m, C3'), 3.00 (2H, d, J= 7.8 Hz, CH₂C=O), 3.05 (2H, broad s, C1',5'), 3.80 (3H, s, OCH₃), 6.86 (2H, d, J= 9.0 Hz, Ar), 7.84 (2H, d, J= 9.0 Hz, Ar). **endo-isomer:** \( \delta \), 23.7 (C3'), 26.4 (C6',7'), 35.4 (C2',4'), 40.0 (N-CH₃), 46.6 (CH₂C=O), 55.4 (OCH₃), 60.3 (C1',5'), 113.6, 130.2, 130.4 and 163.3 (Ar), 198.5 (C=O). **exo-isomer:** \( \delta \), 1.36-1.70 (4H), 1.90-2.30 (5H), 2.20 (3H, s, NCH₃), 2.71 (2H, d, J= 6.6 Hz, CH₂C=O), 2.92 (2H, broad s, C1',5'), 3.80 (3H, s, OCH₃), 6.80-6.90 (2H, Ar), 7.80-7.90 (2H, Ar). **exo-isomer:** \( \delta \), 24.8 (C3'), 25.8 (C6',7'), 38.1 (C2',4'), 40.3 (N-CH₃), 44.6 (CH₂C=O), 55.3 (OCH₃), 61.4 (C1',5'), 113.6, 130.1, 130.5 and 163.3 (Ar), 198.3 (C=O). **Accurate mass (EI):** Found 273.1732; Calculated for (M⁺) C₁₇H₂₃NO₂ 273.1729 (-1.1 ppm). **ν max (cm⁻¹):** 2959, 2931, 2844, 2795 (N-CH₃), 1671 (C=O), 1599, 1575, 1509, 1260, 1169, 1029. **m/z (EI):** 273 (M⁺, 11 %), 138 (77 %), 124 (100 %), 96 (70 %), 82 (82 %). See X-ray structure in **Figure 19** (p. 116).
Activated manganese dioxide (8.0 g, 92.0 mmol) was added to a solution of 4-(tropan-3'-yl)-2-phenyl-2-buten-3-ol 238 (657 mg, 2.4 mmol) in CH₂Cl₂ (25 ml) and the mixture was stirred for 24h at room temperature. The catalyst was filtered off through Hyflo Super Cell and the filtrate concentrated to give the title compound 220 (360 mg, 55 %) as a light-brown liquid and as a 5:1 endo / exo mixture. **endo-isomer:** δH 1.19 (2H, broad d, J= 14.4 Hz, eq-C2',4'), 1.51 (2H, broad d, J= 8.1 Hz, endo-C6',7'), 1.86-2.02 (2H, m, exo-C6',7'), 2.04-2.22 (2H, m, ax-C2',4'), 2.17 (3H, s, N-CH₃), 2.24-2.38 (1H, m, C3'), 2.81 (2H, d, J= 7.8 Hz, CH₂C=O), 3.02 (2H, broad s, C1',5'), 5.80 (1H, s, =CH₂), 5.97 (1H, s, =CH₃), 7.16-7.34 (5H, m, Ar). **endo-isomer:** δC 23.7 (C3'), 26.4 (C6',7'), 35.3 (C2',4'), 39.9 (N-CH₃), 48.1 (CH₂C=O), 60.2 (C1',5'), 123.8 (=CH₂), 127.2, 128.2, 128.3 and 137.1 (Ar), 149.6 (C=), 202.0 (C=O). **exo-isomer:** δH 1.12-1.66 (4H), 1.86-2.40 (5H), 2.16 (3H, s, N-CH₃), 2.52 (2H, d, J= 6.9 Hz, CH₂C=O), 2.96-3.10 (2H, broad s, C1',5'), 5.80 (1H, s, =CH₂), 5.99 (1H, s, =CH₃), 7.16-7.34 (5H, m, Ar). **exo-isomer:** δC 24.8 (C3'), 25.9 and 26.9 (C6',7'), 34.1 and 38.0 (C2',4'), 40.4 (N-CH₃), 46.2 (CH₂C=O), 59.7 and 61.2 (C1,5), 123.8 (=CH₂), 128.0, 128.1, 128.5 and 137.1 (Ar), 149.8 (C=), 201.6 (C=O). **Accurate mass (EI):** Found 269.1782; Calculated for (M⁺) C₁₈H₂₃NO 269.1780 (-1.0 ppm). νmax (cm⁻¹): 2955, 2930, 2846, 2794 (N-CH₃), 1685 (C=O), 1493, 1446, 1130. m/z (EI) 269 (M⁺, 6 %), 96 (85 %), 82 (100 %).
4.4.12 Biological testing

4.4.12.1 Drugs and solutions

Acetylcholine (ACh) chloride and atropine sulphate were purchased from Sigma and prepared daily as a 1 mM and 10 mM aqueous stock solutions, respectively. Ketone was dissolved in 1.0 M HCl and then diluted with distilled water to prepare a 1 mM final stock solution. In these assays, the tissue was maintained in four 50 ml organ baths. Each organ bath was filled with a modified Tyrode solution, continuously oxygenated and maintained at 32 °C. The composition of modified Tyrode solution was as follows (mM): 136 NaCl, 2.62 KCl, 1.8 MgCl₂·6H₂O, 1.8 CaCl₂·2H₂O, 0.42 NaH₂PO₄, 11.9 NaHCO₃ and 5.5 glucose.

4.4.12.2 Tissue preparation

Dunkin Hartley guinea-pigs (200-300 g) were rapidly killed by cervical dislocation. The abdomen was opened, a length of ileum was removed and kept in oxygenated Tyrode solution at room temperature. Small pieces of ileum (1.0-1.5 cm) were dissected and mounted longitudinally in an organ bath chamber, as shown in Figure 1. An initial load of 1 g was applied to each preparation and the ileum was allowed to equilibrate for at least 15 min before testing. After the equilibrium period, contractions of the muscle were induced by addition of ACh (3 nM-10 μM).

4.4.12.3 Determination of acetylcholine potency (EC₅₀)

A non-cumulative concentration-response curve (CRC) for ACh was obtained with eight different concentrations of ACh, ranging from 3 nM to 10 μM (n=6; n= number of preparations involved in the experiment). ACh was added to the organ bath for 30 s and then the tissues were washed with fresh Tyrode solution. This was then repeated in a 4 min time cycle. The tissue responses were measured as changes in isometric tension displayed on a pen chart recorder (see Figure 20a). The responses were then calculated as a percentage of the maximum response obtained to ACh and plotted against the logarithm of the ACh concentration (see Figure 20b). The ACh potency was expressed as the 50 % effective concentration value (EC₅₀).

4.4.12.4 Determination of antagonist potency (IC₅₀)

The tissues were incubated with antagonists for 3 min at increasing concentrations, ranging from 0.1 nM to 0.1 μM for atropine and from 10 nM to 30 μM for ketone.
Each incubation was followed by addition of 0.1 µM ACh for 30 s and then the tissues were washed with fresh Tyrode solution at least twice during the 4 min time cycle. The tissue responses to Ach in the presence of the drugs (see Figure 21a for atropine 202 and Figure 21b for ketone 220) were measured and calculated as a percentage of the control response obtained to ACh in the absence of the antagonists. These data were plotted against the logarithm of the antagonist concentration (see Figure 21c). The antagonist potency was expressed as the 50% inhibitory concentration value (IC₅₀).
REFERENCES


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APPENDIXES
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APPENDIX

A.1 Publications, conferences and seminars

A.1.1 Papers published


A.1.2 Research conferences attended

1996

December 16 The Royal Society of Chemistry, One-Day Postgraduate Symposium in Bioorganic Chemistry, University of Liverpool (Poster presentation).

1997

May 7 21st Century Heterocyclic Chemistry, University of Sunderland.

December 17 The Royal Society of Chemistry, Perkin Division, 26th Scottish Regional Meeting for the Reading of Original Papers, University of Strathclyde.

1998

April 6-9 The Royal Society of Chemistry, National Congress and Young Researchers Meeting, University of Durham.

1999

January 6 The Royal Society of Chemistry, Perkin Division, Bioorganic Group One-Day Postgraduate Symposium, University of Leicester.

May 5 The 2nd Sunderland Pre-grasmere Conference, Heterocycles as Synthetic Reagents: a Review Symposium, University of Sunderland.
August 1-6 17th International Congress of Heterocyclic chemistry, Institute of Organic Chemistry, Vienna University of Technology, Vienna, Austria (Poster presentation).

A.1.3 Colloquia, lectures and seminars from invited speakers

1996

October 14* Prof. A. R. Katritzky, University of Gainesville, University of Florida, USA: Recent Advances in Benzotriazole Mediated Synthetic Methodology.

October 16* Prof. Ojima, Guggenheim Fellow, State University of New York at Stony Brook: Silylformylation and Silylcarbocyclisations in Organic Synthesis.

October 22 Prof. B. J. Tighe, Department of Molecular Sciences and Chemistry, University of Aston: Making Polymers for Biomedical Application - can we meet Nature's Challenge?

October 29* Prof. D. M. Knight, Department of Philosophy, University of Durham: The Purpose of Experiment - A Look at Davy and Faraday.


November 18* Prof. G. A. Olah, University of Southern California, USA: Crossing Conventional Lines in my Chemistry of the Elements.

November 27 Dr. Richard Templer, Imperial College, London: Molecular Tubes and Sponges.

December 4 Prof. K. Muller-Dethlefs, York University: Chemical Applications of Very High Resolution ZEKE Photoelectron Spectroscopy.

December 11 Dr. Chris Richards, Cardiff University: Stereocchemical Games with Metalloccenes.
January 15*  Dr. V. K. Aggarwal, University of Sheffield: Sulfur Mediated Asymmetric Synthesis.

January 16  Dr. Sally Brooker, University of Otago, NZ: Macrocycles - Exciting yet Controlled Thiolate Coordination Chemistry.

January 21  Mr. D. Rudge, Zeneca Pharmaceuticals: High Speed Automation of Chemical Reactions.


January 29  Dr. Julian Clarke, UMIST: What can we learn about polymers and biopolymers from computer-generated nanosecond movie-clips?

February 4  Dr. A. J. Banister, University of Durham: From Runways to Non-metallic Metals - A New Chemistry Based on Sulphur.

February 5  Dr. A. Haynes, University of Sheffield: Mechanism in Homogeneous Catalytic Carbonylation.

February 12 Dr. Geert-Jan Boons, University of Birmingham: New Developments in Carbohydrate Chemistry.

February 18 Prof. Sir James Black, Foundation/King's College London: My Dialogues with Medicinal Chemists.


February 26* Dr. Tony Ryan, UMIST: Making Hairpins from Rings and Chains.

March 4*  Prof. C. W. Rees, Imperial College: Some Very Heterocyclic Chemistry.

March 5  Dr. J. Staunton FRS, Cambridge University: Tinkering with biosynthesis - towards a new generation of antibiotics.
October 8* Prof. E. Atkins, Department of Physics, University of Bristol: *Advances in the control of architecture for polyamides: fromnylons to genetically engineered silks to monodisperse oligoamides.*

October 15* Dr. R. M. Ormerod, Department of Chemistry, Keele University: *Studying catalysts in action.*


October 22 Prof. R. J. Puddephatt, University of Western Ontario: *Organoplatinum chemistry and catalysis.*


October 29 Prof. R. Peacock, University of Glasgow: *Probing chirality with circular dichroism.*

November 5 Dr. M. Hii, Oxford University: *Studies of the Heck reaction.*

November 11 Prof. V. Gibson, Imperial College, London: *Metalloocene polymerisation.*

November 19 Dr. G. Morris, Department of Chemistry, Manchester Univ.: *Pulsed field gradient NMR techniques: Good news for the Lazy and DOSY.*

November 20 Dr. L. Spiccia, Monash University, Melbourne, Australia: *Polynuclear metal complexes.*

November 26 Prof. R. W. Richards, University of Durham, Inaugural Lecture: *A random walk in polymer science.*

December 3 Prof. A. P. Davis, Department of Chemistry, Trinity College Dublin: *Steroid-based frameworks for supramolecular chemistry.*

December 10* Prof. M. Page, Department of Chemistry, University of Huddersfield: *The mechanism and inhibition of beta-lactamases.*

January 27*  Prof. R. Jordan, Dept. of Chemistry, Univ. of Iowa, USA: Cationic transition metal and main group metal alkyl complexes in olefin polymerisation.

January 28  Dr. S. Rannard, Courtaulds Coatings, Coventry: The synthesis of dendrimers using highly selective chemical reactions.

February 3*  Dr. J. Beacham, ICI Technology: The chemical industry in the 21st century.

February 24  Prof. R. Ramage, University of Edinburgh: The synthesis and folding of proteins.

February 25  Dr. C. Jones, Swansea University: Low coordination arsenic and antimony chemistry.

March 4  Prof. T. C. B. McLeish, IRC of Polymer Science Technology, Leeds University: The polymer physics of pyjama bottoms (or the novel rheological characterisation of long branching in entangled macromolecules).

March 11  Prof. M. J. Cook, Dept of Chemistry, UEA: How to make phthalocyanine films and what to do with them.

March 17  Prof. V. Rotello, University of Massachusetts, Amherst: The interplay of recognition & redox processes - from flavoenzymes to devices.

March 18  Dr. J. Evans, Oxford University: Materials, which contract on heating (from shrinking ceramics to bullet proof vests).

October 7  Dr. S. Rimmer, Ctr Polymer, University of Lancaster: New Polymer Colloids.

October 23  Prof. J. C. Scaiano (RSC Endowed Lecture), Department of Chemistry, University of Ottawa, Canada: In Search of Hypervalent Free Radicals.
October 26  Dr. W. Peirs, University of Calgary, Alberta, Canada: *Reactions of the Highly Electrophilic Boranes HB(C6F5)2 and B(C6F5)3 with Zirconium and Tantalum Based Metallocenes.*

October 28  Prof. J. P. S. Badyal, Department of Chemistry, Inaugural Lecture, University of Durham: *Tailoring Solid Surfaces.*

November 10  Dr. J. S. O. Evans, Chemistry Department, University of Durham: *Shrinking Materials.*

November 11*  Dr. M. Wills, Department of Chemistry, University of Warwick: *New Methodology for the Asymmetric Transfer Hydrogen of Ketones.*

November 12  Prof. S. Loeb, University of Windsor, Ontario, Canada: *From Macrocycles to Metallo-Supramolecular Chemistry.*

November 18*  Dr. R. Cameron, Department of Materials Science & Metallurgy, Cambridge University: *Biodegradable Polymers.*

November 24  Dr. B. G. Davis, Department of Chemistry, University of Durham: *Sugars and Enzymes.*

December 2*  Dr. M. Jaspers, Department of Chemistry, University of Aberdeen: *Bioactive Compounds Isolated from Marine Invertebrates and Cyanobacteria.*

1999

January 19  Dr. J. Mann, University of Reading: *The Elusive Magic Bullet and Attempts to find it?*

January 27*  Prof. K. Wade, Department of Chemistry, University of Durham: *Foresight or Hindsight? Some Borane Lessons and Loose Ends.*

February 3  Dr. C. Schofield, University of Oxford: *Studies on the Stereoelectronics of Enzyme Catalysis.*

February 17  Dr. B. Horrocks, Department of Chemistry, Newcastle University: *Microelectrode techniques for the Study of Enzymes and Nucleic Acids at Interfaces.*
February 24* Dr. A-K Duhme, University of York: Bioinorganic Aspects of Molybdenum Transport in Nitrogen-Fixing Bacteria.

March 3 Prof. B. Gilbert, Department of Chemistry, University of York: Biomolecular Damage by Free Radicals: New Insights through ESR Spectroscopy.

March 9 Dr. Michael Warhurst, Chemical Policy issues, Friends of the Earth: Is the Chemical Industry Sustainable?

March 17* Dr. J. Robertson, University of Oxford: Recent Developments in the Synthesis of Heterocyclic Natural Products.
A.2 Crystal structure data

A.2.1 N-Trihydroborate-3α-tosyloxymethyltropane 164
Table 1: Crystal data and structure refinement for N-trihydroborate-3α-tosyloxymethyltropane.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tr>
<td>Identification code</td>
<td>97srv171</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C16H26BN03S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>323.25</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
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<td>Crystal system</td>
<td>Orthorhombic</td>
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<tr>
<td>Space group</td>
<td>Pna2,</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 21.443(2) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 7.9590(10) Å, β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 10.224(2) Å, γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>1744.9(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
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<tr>
<td>Density (calculated)</td>
<td>1.230 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>1.731 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>696</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.28 × 0.22 × 0.11 mm³</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>4.12 to 75.00°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-16 ≤ h ≤ 26, -6 ≤ k ≤ 9, -8 ≤ l ≤ 12</td>
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<tr>
<td>Reflections collected</td>
<td>2243</td>
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<tr>
<td>Independent reflections</td>
<td>2157 [R(int) = 0.0197]</td>
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<tr>
<td>Reflections with I&gt;2σ(I)</td>
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<tr>
<td>Absorption correction</td>
<td>Analytical</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.837 and 0.726</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Largest final shift/e.s.d. ratio</td>
<td>-0.001</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.045</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>R₁ = 0.0431, wR₂ = 0.1026</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R₁ = 0.0657, wR₂ = 0.1154</td>
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<tr>
<td>Absolute structure parameter</td>
<td>0.35(3)</td>
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<tr>
<td>Extinction coefficient</td>
<td>0.00081(14)</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>.206 and -.168 e.Å⁻³</td>
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Table 2: Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for 97srv171. \(\text{U}(\text{eq})\) is defined as one third of the trace of the orthogonalized \(\text{U}_{ij}\) tensor.

<table>
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<tr>
<th></th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(\text{U}(\text{eq}))</th>
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<td>4096(1)</td>
<td>4911(1)</td>
<td>52(1)</td>
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<td>3808(4)</td>
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<td>3152(5)</td>
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<td>3904(5)</td>
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<td>9258(6)</td>
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<td>55(1)</td>
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<td>3959(6)</td>
<td>76(2)</td>
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<td>5163(6)</td>
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<td>C(15)</td>
<td>6919(2)</td>
<td>8745(7)</td>
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<tr>
<td>B</td>
<td>3812(3)</td>
<td>11297(9)</td>
<td>5579(8)</td>
<td>75(2)</td>
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Table 3: Bond lengths [Å] and angles [°] for 97srv171.

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<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
</tr>
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<tbody>
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<td>S-O(2)</td>
<td>1.424(4)</td>
<td>C(8)-N-C(1) 113.3(4)</td>
</tr>
<tr>
<td>S-O(3)</td>
<td>1.432(4)</td>
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</tr>
<tr>
<td>S-O(1)</td>
<td>1.573(3)</td>
<td>C(1)-N-C(5) 99.7(3)</td>
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<tr>
<td>S-C(11)</td>
<td>1.745(5)</td>
<td>C(8)-N-B 106.0(4)</td>
</tr>
<tr>
<td>O(1)-C(9)</td>
<td>1.467(5)</td>
<td>C(1)-N-B 113.1(4)</td>
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<tr>
<td>N-C(8)</td>
<td>1.497(7)</td>
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<td>N-C(1)</td>
<td>1.502(6)</td>
<td>N-C(1)-C(2) 111.9(4)</td>
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<tr>
<td>N-C(5)</td>
<td>1.518(6)</td>
<td>N-C(1)-C(7) 101.9(4)</td>
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<tr>
<td>N-B</td>
<td>1.649(8)</td>
<td>C(2)-C(1)-C(7) 112.3(4)</td>
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<td>C(1)-C(2)</td>
<td>1.522(6)</td>
<td>C(1)-C(2)-C(3) 115.0(4)</td>
</tr>
<tr>
<td>C(1)-C(7)</td>
<td>1.523(7)</td>
<td>C(9)-C(3)-C(4) 113.6(4)</td>
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<tr>
<td>C(2)-C(3)</td>
<td>1.545(6)</td>
<td>C(9)-C(3)-C(2) 110.0(4)</td>
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<td>C(3)-C(9)</td>
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<td>C(3)-C(4)</td>
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<td>O(3)-S-O(1)</td>
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<td>C(13)-C(14)-C(10) 120.4(6)</td>
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<td>O(2)-S-C(11)</td>
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<td>O(3)-S-C(11)</td>
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<td>O(1)-S-C(11)</td>
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<tr>
<td>C(9)-O(1)-S</td>
<td>117.5(3)</td>
<td></td>
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Table 4: Anisotropic displacement parameters ($\AA^2 \times 10^3$) for 97srv171. The anisotropic displacement factor exponent takes the form: 

$$-2 \pi^2 [ h^2 a^* 2 U_{11} + ... + 2 h k a^* b^* U_{12} ] .$$

<table>
<thead>
<tr>
<th></th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{12}$</th>
<th>$U_{13}$</th>
<th>$U_{23}$</th>
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<td>53(1)</td>
<td>53(1)</td>
<td>-6(1)</td>
<td>-2(1)</td>
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<td>72(3)</td>
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<td>47(3)</td>
<td>2(2)</td>
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<tr>
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<td>58(3)</td>
<td>41(3)</td>
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<td>48(4)</td>
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<td>41(3)</td>
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<td>50(4)</td>
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<td>C(6)</td>
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Table 5: Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for 97srv171.

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A.2.2 2-(Tropan-3'-yl)-1-para-methoxyphenyl-1-ethanone 219
Table 1: Crystal data and structure refinement for 2-(Tropan-3-yl)-1-para-methoxyphenyl-1-ethanone.

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<tr>
<td></td>
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<td></td>
<td>(c = 21.415(4) \text{ Å} \quad \gamma = 90°)</td>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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Table 2: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 99srv170. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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Table 3: Bond lengths [Å] and angles [°] for 99srv170.

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201
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Table 4: Anisotropic displacement parameters (Å² × 10⁴) for 99srv170. The anisotropic displacement factor exponent takes the form: $-2\pi^2 \left[ h^2 a^* a^* U_{11} + \ldots + 2 h k a^* b^* U_{12} \right]$

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Table 5: Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($\AA^2 \times 10^3$) for 99srv170.

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<td>C(3)-C(9)-C(10)-O(1)</td>
<td>5.2(3)</td>
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<td>C(3)-C(9)-C(10)-C(11)</td>
<td>-173.72(16)</td>
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<td>C(9)-C(3)-C(4)-C(5)</td>
<td>-90.7(2)</td>
<td>O(1)-C(10)-C(11)-C(16)</td>
<td>175.05(19)</td>
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<td>C(9)-C(10)-C(11)-C(16)</td>
<td>-6.1(3)</td>
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<tr>
<td>C(8)-N-C(5)-C(4)</td>
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<td>O(1)-C(10)-C(11)-C(12)</td>
<td>-6.9(3)</td>
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<td>75.07(18)</td>
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<td>172.00(17)</td>
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<td>77.3(2)</td>
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<td>-176.15(17)</td>
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<td>C(17)-O(2)-C(14)-C(15)</td>
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<td>C(17)-O(2)-C(14)-C(13)</td>
<td>177.70(18)</td>
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<td>53.7(2)</td>
<td>C(12)-C(13)-C(14)-O(2)</td>
<td>177.83(17)</td>
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<td>N-C(5)-C(6)-C(7)</td>
<td>27.11(18)</td>
<td>O(2)-C(14)-C(15)-C(16)</td>
<td>-177.19(17)</td>
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### Table 7: Hydrogen bonds for 99srv170 [Å and °].

<table>
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<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-H(1N)..&lt;Cl</td>
<td>1.02(3)</td>
<td>2.05(3)</td>
<td>3.0481(18)</td>
<td>164.2(18)</td>
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</tbody>
</table>