CHIRAL ALDEHYDES IN THE SYNTHESIS OF
TETRAHYDROFURANS

by

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, University of Natal.

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February 1994.
DECLARATION

I hereby certify that this research is the result of my own investigation which has not been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed: ........................................
O.L. NJAMELA

I hereby certify that this statement is correct.

Signed: ........................................
PROFESSOR S.E. DREWES
SUPERVISOR

Department of Chemistry
University of Natal
Pietermaritzburg
## CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Acknowledgements</strong></td>
<td>i</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Abbreviations</strong></td>
<td>ii</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Summary</strong></td>
<td>iv</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Publications</strong></td>
<td>viii</td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td><strong>INTRODUCTION</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.1.</td>
<td>The terminology of asymmetric synthesis</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1.2.</td>
<td>Stereocchemical models</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1.3.</td>
<td>Nucleophilic addition reactions of chiral aldehydes</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1.3.1.</td>
<td>Metalloorganic addition reactions</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1.3.1.1.</td>
<td>Chelation control</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1.3.1.2.</td>
<td>Non-chelation control</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1.3.2.</td>
<td>Addition of metal enolates to chiral aldehydes - The aldol reaction</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>1.3.3.</td>
<td>Addition of crotylmetal compounds to chiral aldehydes</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1.3.4.</td>
<td>The Baylis-Hillman reaction</td>
<td>28</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td><strong>DISCUSSION</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1.</td>
<td>Use of salicylaldehyde</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>2.2.</td>
<td>Synthesis of chiral aldehydes</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>2.3.</td>
<td>The Baylis-Hillman reaction</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>2.3.1.</td>
<td>The Baylis-Hillman reaction of methyl acrylate with chiral aldehydes</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>2.3.1.1.</td>
<td>Determination of diastereoselectivity ratios</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>2.3.1.2.</td>
<td>Stereostructural assignment</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>2.3.1.3.</td>
<td>The reactivity of the aldehydes</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>2.3.1.4.</td>
<td>Rationalisation of the stereochemical outcome of the Baylis-Hillman reaction</td>
<td>72</td>
</tr>
</tbody>
</table>
2.4. Substituted tetrahydrofurans
2.4.1. Electrophile-induced cyclisations
2.4.2. Halocyclisation reactions
2.4.2.1. Thermodynamically controlled cyclisation
2.4.2.2. Kinetically controlled cyclisation
2.4.3. The iodocyclisation of γ-alkoxy-α-hydroxy acrylates
2.4.3.1. Reactivity of isopropylidene acrylates
2.4.3.2. Reactivity of γ-alkoxy-α-hydroxyacrylates
2.4.3.3. Assignment of stereochemistry
2.4.3.4. Rationalisation of stereochemical outcome
2.4.3.5. Conclusions

3. EXPERIMENTAL

4. REFERENCES

5. APPENDIX
Selected $^1$H and $^{13}$C nuclear magnetic resonance spectra
I would like to thank Professor S.E. Drewes for his encouragement, guidance and interest throughout this investigation.

I also thank Dr G.H.P. Roos, Dr N.D. Emslie for helpful discussions and my colleagues for their assistance in the preparation of this thesis.

Thanks are also due to Mr M. Watson for NMR and useful discussions, Ms Z. Hall for NMR and MS, Professor J.S. Field and Ms N. Ramesar for the X-ray structural analyses, Mr M. Somaru and Mr H. Desai for elemental analyses, Mr P. Forder for glassblowing, Mr D. Crawley and Mr C. Morewood and their staff for technical assistance.

I also thank my mother for her patience, love and understanding.

I gratefully acknowledge the financial assistance of the FRD and the University of Natal.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>AZT</td>
<td>3’azido-3’deoxythymidine</td>
</tr>
<tr>
<td>BINAP</td>
<td>bis(diphenyrophosphino)-1,1-binaphthyl</td>
</tr>
<tr>
<td>BMS</td>
<td>Borane-methyl sulphide</td>
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<tr>
<td>b.p.</td>
<td>boiling point</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>Boc</td>
<td>‘butyloxy carbonyl</td>
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<tr>
<td>br</td>
<td>broad</td>
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<tr>
<td>Bu</td>
<td>butyl</td>
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<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
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<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Eu(hfc)₃</td>
<td>tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
<td>LMPT</td>
<td>lithium 2,2,6,6-tetramethylpiperidine</td>
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<tr>
<td>m</td>
<td>multiplet</td>
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<tr>
<td>MA</td>
<td>methyl acrylate</td>
</tr>
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<td>Me</td>
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<tr>
<td>MOM</td>
<td>methoxymethyl</td>
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<td>m.p.</td>
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<tr>
<td>NMR</td>
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<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
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<tr>
<td>OTFA</td>
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<td>Oxdn</td>
<td>Oxidation</td>
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<td>PAMP</td>
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<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<tr>
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<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TAI</td>
<td>trichloroacetyl isocyanate</td>
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<tr>
<td>TBCO</td>
<td>2,4,6-tetrabromo-2,5-cyclohexadienone</td>
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<tr>
<td>TBDMS</td>
<td>1-‘butyldimethylsilyl</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyryanl</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>p-toluenesulphonic acid</td>
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Iodine-induced cyclisation of \( \gamma \)-benzyloxy-\( \alpha \)-alkylacrylates to form tetrahydrofurans has been investigated. The \( \gamma \)-benzyloxy-\( \alpha \)-alkylacrylates were prepared by the Baylis-Hillman reaction of \( \beta \)-benzyloxy aldehydes with methyl acrylate.

Initially, salicylaldehyde was used as a model system to study various ways in which \( \beta \)-hydroxy aldehydes can be used in the Baylis-Hillman reaction. From a study of the intramolecular Baylis-Hillman reaction utilising the acrylate of salicylaldehyde (i), the quarternary coumarin salt (ii) was isolated. The events that lead to the formation of the salt (ii) prove for the first time that the elusive Michael adduct, postulated by all researchers in this area, but hitherto not isolated, does exist.

An alternative use of \( \beta \)-hydroxy aldehydes involves protection of the hydroxyl group. Thus, benzyl protected salicylaldehyde (iii) reacted with methyl acrylate to form (iv) in good yield. Addition of primary amines in a Michael type fashion, followed by debenzylation, led to the formation of variously substituted coumarin derivatives (v) and provides a general entry into this class of compounds.

In the second phase of this study, \( \beta \)-chiral \( \beta \)-benzyloxy aldehydes (vi) and (vii) were prepared in a number of transformations starting from baker's yeast and asymmetric hydrogenation of ethyl acetoacetate respectively. The \( \beta \)-benzyloxy-\( \alpha \)-methylaldehydes (viii) and (ix) were prepared by similar procedures starting from the corresponding commercially available esters. (3S,4)-O-Isopropylidene butyraldehyde (x) was accessible from (S)-malic acid. (2R)-Dibenzylxyglyceraldehyde (xi) was prepared from (S,S)-tartaric acid in a series of known transformations but an overall new synthetic route. This synthetic route was
adapted for ascorbic acid to produce isopropylidene aldehydes (xii) and (xiii) and (2S)-dibenzyloxyglyceraldehyde (xiv).

The Baylis-Hillman reaction of the aldehydes (vi) - (xiv) has been studied. In general the reactions of chiral aldehydes with methyl acrylate show little or reasonable diastereoselective formation of acrylates (xv).

α-Unsubstituted β-chiral aldehydes (vi) and (vii) reacted stereorandomly while α-chiral aldehydes (viii) and (ix) gave reasonable stereoselectivity (65:35). Isopropylidene butyraldehyde (x) and glyceraldehyde (xiii) showed high diastereofacial selection with the former showing exceptionally high (75:25) diastereoselectivity. α-Unsubstituted aldehydes (vi) and (vii) and α-methyl aldehydes (vii) and (ix) were syn-selective while α-alkoxy aldehydes (xi) - (xiv) were anti-selective. In contrast, isopropylidene aldehyde (x) showed high preference for anti selectivity. The relative configurations were established by derivatisation using TAI and by cyclisation to tetrahydofurans. The results obtained in this study have been formulated into a mechanistic rationale involving open transition states as postulated by Felkin and Anh.

Intramolecular iodoetherification of the substituted alkyl acrylates was strictly 5-exo-trig and proceeded with high stereochemical control.

The isopropylidene acrylates, produced from the reaction of (x), (xii) and (xiii), did not undergo cyclisation. On the other hand, γ-benzyloxyacrylates represented by general structure (xvi) showed a marked difference in reactivity. The reactivity was found to be strongly influenced by the relative configuration of the allylic hydroxyl group to the homoallylic substituent R₁ or in the absence of the latter, on the benzyloxy group. In the former, only the 1,2-anti substrates cyclised while 1,3-syn substrates cyclised in the latter case. In general, the iodocyclisation provided
cis-2-iodomethyl-3-hydroxy tetrahydrofurans (xvii) in high yield. The stereochemistry was assigned by NOE for all the tetrahydrofurans and in the case of (xvii) where $R_1 = \text{CH}_3$ and $R_2 = \text{H}$ corroborated by X-ray analysis. A mechanistic pathway to rationalise these results is proposed.
1. INTRODUCTION

The synthesis of structurally and substitutionary complex molecules continues to be an important area of research. In particular, the diastereoselective process has become a powerful tool and a contributory factor in the synthesis and understanding of interactions of a variety of optically active compounds.1,2,3 Many of the optically active compounds possess biological activity, the specific activity being assigned only to one stereoisomer, the other being either less effective, ineffective or, at worst, detrimental.4 For example muscarine (1) - an alkaloid isolated from the red fly agaric mushroom *Amanita muscaria* - is known for its ability to reproduce faithfully some of the responses to stimulation of the autonomous nervous system.5 When the hydroxyl group is *cis* to either or both the methyl and the trimethylaminomethyl groups *e.g.* 2, there is an enormous decrease in muscarinic activity.6 Epimuscarine, 2, is then described as a partial agonist since it does not provoke a full response.3

In the past, it was acceptable to leave isolation of the correct isomer (enantiomer or diastereomer) to the last step. However, in recent years, the challenge has been to produce the desired stereochemistry at the earliest possible
step in the sequence and then use the stereochemistry of that centre to control the stereochemistry of subsequent reactions. This constitutes asymmetric synthesis, a term that has been in use for over eighty years. Morrison and Mosher have defined asymmetric synthesis as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that he stereomeric products (enantiomeric or diastereomeric) are produced in unequal amounts."

An ideal asymmetric synthesis can be characterised by the following features:

a) in addition to high chemical yield, the desired isomer is produced in high stereomeric yield.

b) the chiral auxiliary is readily available, inexpensive and recoverable in good yield and undiminished purity.

c) the chiral product is easily separated from the chiral auxiliary.

d) it is possible to synthesise both enantiomers or diastereomers selectively.

With these features as guidelines, two principal synthetic strategies can be used. Firstly, homochirality in the synthesis of a target molecule can be introduced by the use of an external chiral auxiliary reagent. Secondly, a chiral fragment of known absolute configuration can be used. In both respects, nature's "chiral pool" and the use of enzymes play an important role.

Introduction of homochirality using external chiral auxiliary has been employed with great success by Meyers, Enders, Evans, Oppolzer and Schöllkopf. For example, Evans' chiral auxiliary 4 plays an important role for the preparation of the key intermediate 5 in the
synthesis of tetronasin, 6 - an acetotronic acid ionophore antibiotic (Scheme 1).\textsuperscript{20} The intermediate 5 is prepared by alkylation of 3 and the chiral auxiliary is prepared from norephedrine.\textsuperscript{21}

Scheme 1.

The second approach, \textit{i.e.}, incorporation of chiral fragments of known configuration is exemplified by the total synthesis of monensin (7) - a naturally occurring ionophore antibiotic (Scheme 2).\textsuperscript{22}

The key fragment 8 is prepared from the two structural building blocks 9 and 10 (Scheme 2), whose absolute configuration is known. The former, 9, is obtainable from enzymatic reduction\textsuperscript{23} and the latter from naturally occurring citronellol.
Asymmetric synthesis using these strategies remains the major contributor in the synthesis of homochiral natural products. In particular, asymmetric C-C bond formation is a crucial tool in all syntheses. In a large number of the syntheses, aldehydes have been used as electrophilic counterparts. In recent years, there has been a growing interest in the use of chiral non-racemic aldehydes because of the development of effective methods for controlling stereochemistry of several basic reactions. This chapter will focus on the reactions of chiral aldehydes. Because chiral aldehydes are widely used in organic synthesis, this introduction presents selected examples to highlight certain
facts and is not exhaustive.

1.1. THE TERMINOLOGY OF ASYMMETRIC SYNTHESIS

The two carbonyl faces on a chiral aldehyde are diastereotopic; addition of C-nucleophiles such as Grignard reagents or enolates creates a new chiral centre and is therefore diastereogenic (an example is illustrated in Scheme 3).

Scheme 3.

In reactions such as the one depicted in Scheme 3, the approaching nucleophile will in principle, exhibit varying degrees of preference from one face to the other. The degree of preference, as reflected on the products, is defined as diastereofacial selectivity. In reactions in which differentiation of faces is influenced by simultaneous action of chiral aldehydes and chiral nucleophiles, the addition process is termed double stereodifferentiation. In such circumstances, the two reactants may reinforce one
another (consonant double stereodifferentiation) or oppose one another (dissonant double diastereoselection).\textsuperscript{27, 28}

In regard to the addition products, several groups have addressed their stereo-nomenclature.\textsuperscript{29}

Research groups concerned with aldol additions, notably the group of Heathcock, predominantly use the terms \textit{threo} for 12\textit{a} and \textit{erythro} for 12\textit{b}.\textsuperscript{30}

The terms \textit{syn} and \textit{anti} first proposed by Masamune\textsuperscript{31} have been adopted by several authors including Heathcock, Evans, Mukaiyama, Hoffmann, Reetz and Braun. Consequently this stereostructural notation will be used here. Thus, 12\textit{a} would be \textit{anti} and 12\textit{b} \textit{syn} correspondingly as depicted in Scheme 3.

1.2. STEREOCHEMICAL MODELS

In addition reactions such as the one described above (Scheme 3), the electronic and steric factors of the chiral aldehyde and the attacking nucleophile play an important role to determine the stereochemical outcome (\textit{anti}/\textit{syn}) of the reaction. Several authors\textsuperscript{32-33} have formulated models on empirical basis to predict the qualitative diastereofacial preference of chiral aldehydes. In the interests of relevance to this work, only Cram’s model,\textsuperscript{32} Cram’s cyclic model\textsuperscript{33} and Felkin’s model\textsuperscript{34} will be considered in brief.

In \textit{Cram’s model}\textsuperscript{32} 13, an \(\alpha\)-chiral aldehyde such as 14 is assumed to adopt a conformation in which the largest of the three \(\alpha\)-substituents is antiperiplanar to the carbonyl function, nucleophilic attack then occurs from the sterically less hindered side to give about 66:34 (\textit{anti}:\textit{syn})
mixture of products depending on the nucleophile and the α-substituent (Figure 1).

Figure 1.

Cram's "cyclic" model\textsuperscript{33} 15 was proposed for carbonyl compounds which contain an α-substituent (OR, NR\textsubscript{2}) that is capable of co-ordinating the cationic counterpart of the nucleophile. Due to co-ordination, the α-substituent is then eclipsed with the double bond. The result, attack of the nucleophile at the less encumbered side, leads to preferential formation of syn products 16 (Figure 2).
In Felkin's model,\textsuperscript{34} 17a (Figure 3), co-ordination is neglected and intermediates are assumed to be more reactant-like rather than product-like. In this context, conformations in which the bond to the largest substituent (e.g. OR, NR\textsubscript{2} etc.) is perpendicular to the carbonyl bond are suggested for the transition state. This model has been refined by Anh 17b, who postulated nonperpendicular attack (Bürgi-Dunitz trajectory as shown in Figure 3) on the basis of molecular orbital considerations.\textsuperscript{37} An in-depth discussion on the Felkin-Anh model will be covered in the DISCUSSION.

\textbf{Figure 2.}

\textbf{Figure 3.}
1.3. NUCLEOPHILIC ADDITION REACTIONS OF CHIRAL ALDEHYDES

1.3.1. METALLO-ORGANIC ADDITION REACTIONS

Addition reactions of organometallic compounds to chiral aldehydes are of considerable interest in the context of understanding acyclic stereocontrol and of significant importance in stereoselective synthesis of natural products, e.g., ionophores, pheromones and carbohydrates.38-40

The stereochemical outcome of organometallic addition to chiral α, β-N or O-substituted aldehydes can be controlled by (i) use of Lewis acidic reagents which form intermediate chelates resulting in nucleophilic attack on the sterically less hindered side (Chelation control) or (ii) use of reagents incapable of chelation in which the electronic and steric factors of the aldehyde and nucleophile are the sole determinants of the stereoselectivity (Non-chelation).41 The two methods are generally complementary, i.e., they lead to opposite sense of diastereoselectivity.

1.3.1.1 CHELATION CONTROL

In the pioneering work, Cram et al.32,33 and Stocker42 studied the addition of Grignard and RLi to alkoxy (or hydroxy) compounds and asymmetric induction was rationalised on the basis of Cram's rule. The stereochemical outcome ranged between stereorandom (55:45) and high (96:4).

Ever since this treatise by Cram, organometallic additions have received growing attention as evidenced by reports and excellent reviews covering this subject.41-45

Reetz46 reported that the choice of reaction conditions, type of protecting group and Grignard reagent strongly
influence the extent (and in some cases, the sense) of diastereoselectivity.

![Chemical Structure](image)

The benzyloxymethyl protected aldehyde 18 for example, reacted with \( \text{CH}_3\text{MgBr} \) to give a diastereomeric ratio of 9:91 (\( \text{anti}/\text{syn} \)) products 20 - whereas the benzyl protected analogue 19 reacts with the same reagent fairly unselectively to produce 21 (\( \text{anti}/\text{syn} = 40:60 \)) (Scheme 4). The results were explained on the basis of five-membered chelate in accordance with Cram's cyclic model.

Generally, nucleophilic additions with organolithium and organomagnesium reagents give low diastereoselectivities. In contrast, use of lithium cuprates dramatically improves the diastereoselectivity.\(^{47,48} \) For instance, the
α-substituted aldehydes 22a - 22c react with CH₃MgX or RLi to produce a nearly equal mixture of diastereomers 23a/b while diastereoselectivity ratios of up to 97:3 were obtained with (CH₃)₂CuLi (Scheme 5). The benzyloxy protected aldehyde 22b again reacted less selectively. Furthermore, diastereoselection was not observed for the bulky protecting group in 22c. It is unclear why cuprates but not RMgX and RLi lead to efficient β-chelation. Use of reagents with pronounced Lewis acidity and chelating ability e.g., TiCl₄, SnCl₄ and MgBr₂ dramatically improved the selectivity. This was observed when CH₃TiCl₃ was used to methylate 24.
Scheme 6.

The mixture of diastereomer 26a/b was produced via the intermediate chelate 25 in high diastereoselectivity 8:92 (anti:syn). Complexation of 24 with TiCl₄ prior the addition of soft nucleophiles such as (CH₃)₂Zn also gave the same result.⁴⁶

Addition of metallo-organic compounds to polyoxygenated aldehyde functions that occur in carbohydrates has been studied by several groups.⁴¹-⁴³,⁴⁹-⁵¹

The isopropylidene glyceraldehyde 27 or its enantiomer and related aldehydes have been allowed to react with a large number of organometallic compounds. For example, Mulzer and Angermann⁵² reported on the structure of the nucleophile and the stereoselectivity of addition to the aldehydes 27 (Scheme 7).
Scheme 7.

All reagents generally favoured formation of the anti isomer 28a over the syn isomer except phenyltriisopropoxytitanium which afforded the syn isomer 28b with high selectivity. The high preference for anti selectivity has been explained by the Felkin model 29 in which there is no complexation to the α- or β-oxygen. β-Chelation as in 30 has also been postulated and leads to reinforcement of anti selectivity. The data can also be explained by adopting Conforth model 31.34
Reverse selectivity in chelation controlled addition of organometallic compounds to aldehydes has also been reported by Sato and coworkers. Moderate to good diastereoselectivity ratios were observed in nucleophilic additions to the epoxy trimethylsilyl aldehyde 32 (Scheme 8).

\[
\begin{align*}
\text{TMS} & \quad \text{CHO} \\
\text{32} & \\
\text{RM} & \\
\hline
\text{n-BuLi} & 79:29 \\
\text{BuMgBr} & 74:26
\end{align*}
\]

Scheme 8.

Stereocontrol in the addition of metalloorganic reagents to \(\beta\)-alkoxy aldehydes is not possible using ordinary organometallic compounds such as RMgX, RLi or \(R_2CuLi\). Reetz was able to achieve high levels of stereoselectivity by employing Lewis acids that have high affinity for complexation. In this context, addition of TiCl\(_4\) or SnCl\(_4\) followed by the nucleophile or direct addition of organotitanium reagents to aldehydes led to unprecedented levels of asymmetric induction. For example, 32 is converted via 33 to 34a with high diastereofacial selectivity (Scheme 9).
Scheme 9.

Stereocontrolled addition of Grignard reagents to chiral α-amino aldehydes under chelation control has been reported by several research groups\textsuperscript{56,58} to give poor to good diastereoselectivity. Addition of SnCl\textsubscript{4} and TiCl\textsubscript{4} improves the level of diastereoselection to greater than 8:92 in favour of syn product.\textsuperscript{59,60} The effect of the two Lewis acids was reported to be diminished as a result of weak N-Ti and N-Sn coordination resulting in formation of noncyclic chelates.

Available data also show that use of less sterically demanding protecting groups results in efficient chelation control. For example, a change from the dibenzyl protecting group - which gives 1:1 ratio of anti:syn - to protecting groups such as in 35, results in chelation controlled reaction even with (CH\textsubscript{3})\textsubscript{2}CuLi leading to preferential formation of syn 35a (Scheme 10).
1.3.1.2. NON-CHELATION CONTROL

Stereochemical controlled addition of Grignard reagents and a variety of other organometallic compounds can also be directed solely by the electronic and steric nature of the aldehyde and the reagent. In this regard, Cram's acyclic model\textsuperscript{32} or one of Conforth\textsuperscript{34} or Felkin-Anh\textsuperscript{36} model may be used to explain the diastereoselection.

Non-chelation control is generally difficult to accomplish because there is no general way to reduce the number of degrees of freedom of non-complexed molecules.\textsuperscript{41} However, the groups of Reetz,\textsuperscript{46} Kishi\textsuperscript{61} and Mulzer\textsuperscript{62} have been able to effect non-chelation controlled additions to chiral aldehydes.

Reetz et al.\textsuperscript{46} demonstrated that chelation and non-chelation control can be made complementary processes to give either anti or syn depending on the ligands on titanium. For example, addition of CH$_3$TiCl$_3$ to 24 gave 8:92 ratio of anti:syn products 26 (a and b) (Scheme 6 vide supra). On the other hand, non-chelation controlled addition using CH$_3$Ti(OCHMe$_2$)$_3$ afforded the anti isomer 26a.
as the major product (anti/syn 92:8). Herold and Procter and coworkers have also studied the complementary nature of these process. Herold reported additions, under different conditions, to Garner's aldehyde. Numerous addition reactions of various organometallic reagents to the aldehyde have been well documented but many of them report selective formation of anti adducts only.

In studies directed towards the synthesis of sphingosine derivatives, Herold demonstrated that silylalkyne metals add to to give either anti or syn depending on the reaction conditions. Thus, the anti isomer was formed (ratio 97:3) by addition of lithium pentadacyn in THF/HMPT whereas the corresponding syn isomer was produced (ratio 3:97 syn) in the presence of ZnBr₂ in Et₂O.
1.3.2. **THE ADDITION OF METAL ENOLATES TO CHIRAL ALDEHYDES - THE ALDOL REACTION**

In the last two decades, the aldol reaction has been revolutionised by the ability to study stereoselectivity by modern methods, advances in Lewis acid catalysts and advances in calculations. The impetus for this revival is the discovery that its stereochemistry can be controlled through the use of preformed enolates.\(^{30a,74}\) This aspect of the aldol reaction has since been extensively studied by Heathcock,\(^{29,30a}\) Evans,\(^{17,74}\) Masamune,\(^{75}\) Mukaiyama\(^{76,77}\) and others.

In the aldol reaction of achiral aldehydes with enolates, Heathcock *et al.*\(^ {78}\) found that there is a correlation between
the enolate geometry and the stereochemistry of the resultant aldol. Generally, Z-enolates give syn aldols and E-enolates give anti aldols provided the group attached to the oxygen-bearing carbon of the enolate is bulky. Since either the Z- or E-enolate can be selectively formed under kinetic conditions, stereochemical control can be manipulated to give either isomer.

Hence, under kinetic conditions, the Z-enolate proceeds as depicted in Scheme 12 to give the syn aldol 40. On the other hand, formation of the anti isomer 42 is favoured when the starting enolate has the E-configuration 41.

Scheme 12.
Under thermodynamic conditions (i.e., equilibrium conditions), the anti isomer becomes the major product since the more stable chairlike conformer of the intermediate chelate has the maximum number of equatorial substituents and hence thermodynamically stable.

Use of chiral aldehydes gives a different perspective to the stereochemical pathway of the aldol reaction because the faces of the carbonyl group are diastereotopic. For addition of lithium enolates to chiral aldehydes in which the stereogenic centre is adjacent to the carbonyl group, the intrinsic diastereofacial preference is usually low.\(^7\),\(^9\),\(^8\)

High diastereoface selectivity has been reported by Heathcock and coworkers\(^8\) to be accessible by addition of Lewis acids. For example, the aldol reaction of the enol silanes \(43\) and \(44\) and \(O\)-benzylacetalddehyde (45) proceeds
TABLE 1. Diastereomer ratios in the reactions of chiral enol silanes with aldehydes 45 given as anti:syn (Scheme 14).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enol silane</th>
<th>Lewis acid</th>
<th>Isomer Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43a</td>
<td>BF₃·OEt₂</td>
<td>40:60</td>
</tr>
<tr>
<td>2</td>
<td>43b</td>
<td>SnCl₄</td>
<td>35:65</td>
</tr>
<tr>
<td>3</td>
<td>44c</td>
<td>SnCl₄</td>
<td>1:99</td>
</tr>
<tr>
<td>4</td>
<td>44d</td>
<td>SnCl₄</td>
<td>1:99</td>
</tr>
<tr>
<td>5</td>
<td>44d</td>
<td>TiCl₄</td>
<td>1:99</td>
</tr>
</tbody>
</table>

with high diastereoselection to give syn aldols 46 and 47 (Scheme 14, Table 1). For achiral ketene acetal 43a and 43b, low diastereoselectivity ratios were observed (entries 1 and 2). Enol silanes 44c and 44d gave virtually syn aldols as the sole products with SnCl₄ and TiCl₄. The authors invoked formation of a five-membered metal chelate 48 by
SnCl₄ and TiCl₄. This results in nucleophilic addition to the less encumbered face i.e., Cram's cyclic model. This is unlikely to form in the case of BF₃ since it cannot expand its ligancy beyond four.

Several other incidences of chelation controlled aldol reactions have been reported recently by Reetz⁸¹,⁸² and Kita and coworkers⁸³ using LiClO₄⁸⁴ and Casiraghi et al.⁸⁵ using conventional Lewis acids.

The phenomenon of double stereodifferentiation has been widely used in aldol condensations and is becoming more successful as demonstrated by Evans in the synthesis of rutamycins.⁸⁶,⁸⁷

1.3.3. ADDITION OF CROTYLMETAL COMPOUNDS TO CHIRAL ALDEHYDES

The Lewis acid mediated condensation reaction of allyl- or crotylmetal reagents is a widely recognised method for the stereoselective synthesis of homoallylic compounds.⁸⁸-⁹⁰

The addition of crotylmetal reagents to aldehydes is structurally and, probably also, mechanistically analogous to the aldol addition.
Clearly, the configuration of the double bond (E or Z) which depends on the reaction conditions, plays an important role in stereochemical control of the reaction (Scheme 15).\textsuperscript{91} Stereocontrolled addition of crotylmetals to chiral aldehydes has been studied by several groups notably those of Hoffmann,\textsuperscript{92} Roush,\textsuperscript{93} and Reetz\textsuperscript{94} to name a few.

Hoffmann \textit{et al.}\textsuperscript{91a} reported that the chirality of an aldehyde is not the sole determinant in stereocontrolled addition reactions; the configuration of the double bond plays a crucial role. In this respect, addition of \textit{E}-crotyl...
boronates 49 -51 to α-substituted β-alkoxy aldehydes 52a, b and 53 resulted in predominant formation of syn adducts (Table 2, entry 1 and 2). On addition of Z-crotylboronates to the same aldehyde, the anti products are preferentially formed (Table 2, column 3).

![Structures](image)

Table 2. Diastereoselectivity on addition of allylboronates to α-chiral aldehydes: given as syn:anti).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl</th>
<th>E-Crotyl</th>
<th>Z-Crotyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49:50</td>
<td>95:5</td>
<td>9:91</td>
</tr>
<tr>
<td>2</td>
<td>61:39</td>
<td>89:11</td>
<td>22:78</td>
</tr>
<tr>
<td>3</td>
<td>79:21</td>
<td>98:2</td>
<td>40:60</td>
</tr>
</tbody>
</table>

52a R = TBDMS  
b R = MOM
It is also discernible from the table that change in the protecting group in the aldehyde (entry 1, 2) has a minor effect on the diastereoselectivity. Moreover, the relative configuration on the β-alkoxy group in the aldehyde does not have a major influence. Furthermore, use of the allylboronate 49 results, generally in syn selectivity. Use of the E-crotylboronate 50 reinforces syn selectivity.

Syn selectivity was also reported by Reetz et al.46 and others95,95 to be accessible by chelation controlled addition of crotylstannanes using TiCl₄ as a Lewis acid. Addition of the mono-coordinating BF₃.OEt₂ results in preferential formation of anti adduct. The reagent control for stereoselection using chelation or non-chelation procedure can be applied using various other crotylmetal reagents.97,98 The intramolecular allylstannane additions to chiral silyloxy aldehydes 54 in the presence of TiCl₄ (Scheme 16) provides yet another approach to these adducts 56.99,100

Scheme 16.
Recently, Kiyooka et al.\textsuperscript{101} reported that the diastereoselectivity of chelation controlled addition of allylsilane to $\alpha$-N-carbobenzyloxyamino aldehyde 57 is strongly influenced by the quantity of TiCl$_4$ in the reaction. For example, high \textit{anti} stereoselectivity (20:1) was observed when one equivalent of TiCl$_4$ was used whereas the use of 0.5 equiv. of TiCl$_4$ produced a good \textit{syn} selectively (8:1).\textsuperscript{102} The \textit{anti} selectivity rapidly decreases as the quantity of TiCl$_4$ is increased over 1 equiv. This trend is interpreted in terms of two differently derived species: aldehyde-TiCl$_4$ 1:1 58 and 2:1 complexes 59 which can proceed to their respective transition states.

In crotylmetal additions, as in the aldol reaction, double
asymmetric synthesis using chiral reagents is often necessary to achieve synthetically useful levels of aldehyde stereoselectivity. Several chiral allylboron reagents 60 - 63 have been developed by the groups of Roush - 60,103 Hoffmann - 61,104 Brown - 62,105 and Corey - 63.106 These reagents have, in several cases, enhanced the diastereoselectivity of crotylmetal additions to aldehydes.

\[ \text{Baylis-Hillman Reaction} \]

Which of the methods described above is suitable for effective direct addition of acrylate unit 64a to chiral aldehydes?
The aldol reaction? The direct coupling of electrophiles with carbanions requires proficient choice of reagents and extremely mild conditions. For example, Feit et al.\textsuperscript{107} demonstrated that direct generation of vinyl carbanions from \(\alpha\)-unsubstituted acrylate using bases such as LDA or LTMP suffers from severe limitation due to facile anionic polymerisation.

Organometallic addition? By adeptly choosing lithium vinyl cuprates as addition reagent, Marino et al.\textsuperscript{108} were able to successfully couple aldehydes with vinyl cuprates to form the desired \(\alpha\)-hydroxyalkylacrylates. However, the cuprate reagent required very low temperatures for very long periods (-78°C for 16-18 h) and gave moderate yields.

The difficulties associated with the introduction of carbanion character can be solved by using the Baylis-Hillman reaction.\textsuperscript{109} The Baylis-Hillman reaction is the nucleophilic addition of an acrylic system to an aldehyde (or ketone) in the presence of a tertiary amine catalyst to form an \(\alpha\)-(hydroxyalkyl)acrylic product (Scheme 18).
There has been growing interest in asymmetric synthesis using the Baylis-Hillman reaction\textsuperscript{110-114} and coupling with chiral aldehydes has been investigated by the groups of Drewes and Roos.

Drewes, Roos et al.\textsuperscript{115} studied the reactivity and stereochemical control in the Baylis-Hillman reaction of chiral aldehydes with a variety of acrylate systems. The \( \alpha \)-alkoxy aldehydes 65 (Scheme 19) were found to be fairly reactive giving chemical yields and diastereoselectivities that are in the synthetically useful range.

\textbf{Scheme 18.}

In all cases studied, formation of the \textit{anti} isomer 66a was
favoured over the *syn* isomer 66b (Scheme 19). The methoxymethyl protecting group was found to exhibit higher levels of diastereoselectivity than the benzyl and the benzyloxyethyl protecting groups. The nature of the catalyst had a minor effect on the stereochemical outcome of the reaction.\(^{116}\) The results were rationalised on the basis of Felkin's model.

In a projected extension of this approach, Manickum and Roos\(^{117}\) investigated the reactivity and stereocontrol of variously α-protected α-*N*-amino aldehydes.

![Scheme 20](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Anti:Syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBn(_2)</td>
<td>72:28</td>
</tr>
<tr>
<td>2</td>
<td>NBn(_2)</td>
<td>67:33 subst. CH(_3) for Ph</td>
</tr>
<tr>
<td>3</td>
<td>HN(_5)Boc</td>
<td>29:71</td>
</tr>
<tr>
<td>4</td>
<td>NPht</td>
<td>46:54</td>
</tr>
<tr>
<td>5</td>
<td>HNTs</td>
<td>44:56</td>
</tr>
</tbody>
</table>

In this series of aldehydes the stereochemical outcome was found to be dependent on the type of protecting group. For doubly protected amino aldehydes (entries 1, 2 and ref 116 for other examples) *anti* selectivity was favoured whereas amines bearing a hydrogen atom proceeded with *syn* stereofacial selectivity. For the latter the authors invoked Cram's cyclic model to rationalise their results.
A variation of this method involves use of α-cyclic amino aldehydes and has been explored by Drewes et al.\textsuperscript{118} In studies directed towards the synthesis of sphingosine analogues, Garner's aldehyde 37 was coupled with methyl acrylate to produce the anti isomer 71 as the major product (\textit{anti:syn} = 75:25).

This result and others represent admirable asymmetric induction achieved \textit{via} the Baylis-Hillman reaction.
2. DISCUSSION

Aldehydes play a significant role in organic synthesis because of their reactivity towards a variety of reagents. Of special interest is the versatility of this class of compounds in C-C bond-forming reactions, in particular, towards the synthesis of α-hydroxyalkylacrylates 64.

Apart from the fact that the acrylate unit occurs in many naturally occurring compounds of biological interest e.g., tulipalin (72) and conocandin (73) - a fungistatic antibiotic - it contains versatile functional groups and consequently it is a valuable intermediate for further elaboration.

Several methods have been used for the synthesis of systems such as 64 including α-methylenation of esters, condensation of masked acrylates or vinyl cuprates with aldehydes. These methods however, suffer from lack of generality and drastic conditions under which some of the reagents are used.

The Baylis-Hillman reaction is clearly the most general and useful coupling reaction that leads to the multifunctional
α-hydroxyalkylacrylates in a single step. Other important features of the Baylis-Hillman reaction are ease of implementation, mild conditions and obviated need for masking which avoid the anxieties of low temperature metal-enolates.

Various aldehydes have been used in the Baylis-Hillman reaction specially, aromatic aldehydes. They have featured in several studies including kinetic, mechanism and stereoselective studies. Surprisingly, the commercially available aromatic aldehyde, salicylaldehyde has rarely been used in the Baylis-Hillman reaction despite the fact that it offers three options in which it may be used, viz.,

i) it may be used directly without modification (this method has been carried out vide infra)

ii) the hydroxyl group may be used to make an acrylic ester of salicylaldehyde which may be used to gain insight into the feasibility of intramolecular Baylis-Hillman reaction and possibly to cast more light on its mechanism alternatively,

iii) protection of the hydroxyl group and use of the resulting alkoxy aldehyde in the Baylis-Hillman reaction.

It is interesting to note that salicylaldehyde is a β-hydroxy aldehyde. Consequently it can be used as a model to study various ways in which chiral β-hydroxy aldehydes may be used in the Baylis-Hillman reaction.

α-Chiral aldehydes have played a significant role in stereochemical control particularly, in understanding 1,2-asymmetric induction in the Baylis-Hillman reaction. A logical extension of this approach is to study the 1,3-asymmetric induction that results from use of chiral β-alkoxy aldehydes.
α-Hydroxyalkylacrylates, prepared by the Baylis-Hillman reaction, have repeatedly served as synthetic intermediates towards the synthesis of more complex molecules.\textsuperscript{129-132} Among other transformations, the Baylis-Hillman reaction has gained entry in the synthesis of α-methylene lactones,\textsuperscript{133} indolizines\textsuperscript{134} and pyrazolidinones.\textsuperscript{135} However, despite the conciseness and the elegance of these transformations in exploitation of the versatile functional groups provided by the α-hydroxyakylacrylates \textsuperscript{64}, use of functionalised chiral aldehydes followed by further elaboration has not been explored.

Use of chiral β-alkoxy aldehydes in particular, would produce γ,δ-unsaturated alkyl/benzyl ethers - substrates that are suitably substituted for electrophile-induced cyclofunctionalisation to multifunctionalised tetrahydrofurans.

With this background information, the initial aims of this investigation were set out as follows:

a) To study the use of various derivatives of salicylaldehyde in the Baylis-Hillman reaction as a model for β-hydroxy aldehydes.

b) To prepare functionalised chiral β-alkoxy aldehydes and investigate their reactivity and stereochemical control in the Baylis-Hillman reaction and

c) To investigate stereocontrol in iodocyclisation of the resultant α-hydroxy-(δ'-alkoxy)alkylacrylates to substituted tetrahydrofurans.
2.1. **USE OF SALICYLALDEHYDE IN THE BAYLIS-HILLMAN REACTION**

In order to expand the scope of the Baylis-Hillman reaction, a system that accommodates an intramolecular Baylis-Hillman reaction was designed. Such a system requires an electrophile-bearing α-unsubstituted acrylate 74. This would allow expedient preparation of derivatives of the type 75 directly from acrylate systems 74.

![Chemical Structures](image)

An intramolecular variant of the Baylis-Hillman has been reported only once previously by Fráter and coworkers.\textsuperscript{136} Their substrate, an α,β-unsaturated-ε-keto ester 76, was treated with various (tertiary amine and tertiary phosphine) catalysts to effect cyclisation (Scheme 22).

![Chemical Structures](image)

*Catalyst: DABCO, (-)-PAMP, (-)-CAMP*

**Scheme 22.**

Unlike tertiary amines - which were completely ineffective - tertiary phosphines such as (-)-PAMP and (-)-CAMP effected the condensation, giving the cyclic product 77 in 30-70%
yields.

Application of this methodology to α,β-unsaturated-ζ-keto ester 78, with a view to make six-membered adduct 79, gave mediocre results (Scheme 23).

\[
\begin{align*}
\text{Catalyst: DABCO, (-)-PAMP, (-)-CAMP}
\end{align*}
\]

Scheme 23.

Use of acrylate systems 76 and 78 in the Baylis-Hillman reaction has two drawbacks. Firstly, it involves the rather less reactive ketone group (relative to an aldehyde) as an internal electrophile. Secondly, assuming initial nucleophilic attack of the acrylate by the catalyst as the first step in the mechanism (vide infra), β-substitution of the acrylate as in 76 and 78 obviously diminishes the reactivity of the acrylate. This could be due to steric and electronic effects.

In this investigation, the acrylate ester of salicylaldehyde 80 was chosen as a model to study the intricacies of an intramolecular Baylis-Hillman reaction.

\[
\begin{align*}
\text{The acrylate 80 is easily accessible from base-catalysed esterification}^{137} \text{ of salicylaldehyde with acryloyl chloride.}
\end{align*}
\]
When the acrylate \(80\) was treated with DABCO in \(\text{CH}_2\text{Cl}_2\) at 0°C (exothermic reaction!), a bright yellow precipitate which was expected to be 4-hydroxy-3-methylenebenzopyranone, \(81\), formed immediately (Scheme 24).

\[
\begin{align*}
\text{Catalyst: DABCO, QDL} \\
\text{Scheme 24.}
\end{align*}
\]

Formation of the precipitate was solvent dependent; precipitation occurred in \(\text{CH}_2\text{Cl}_2\) and \(\text{CHCl}_3\) only. The precipitate was unreactive to alkoxy and phenoxy anions and several carbanions. The yellow powder was soluble in polar solvents such as water, methanol and dimethyl sulfoxide, suggesting that it was ionic in nature. Also, it was clear from MS and spectral data that the product was not the benzopyranone \(81\).

Examination of the GC-MS showed two peaks: \(m/z = 112\) and 194. This information, which suggests presence of a DABCO (\(M^+ 112\)) fragment, was at first bewildering. Further elucidation by NMR confirmed the presence of N-substituted DABCO. The DABCO methylene groups which usually resonate as a singlet appeared as two beautifully split multiplets (Figure 4).
With all this information, evidence pointed towards the coumarin ammonium cation 82 (Scheme 25).

Scheme 25.

The final task was to establish the identity of the counter ion. Perusal of the MS and high resolution MS indicated the four isotopes of chlorine with their respective natural abundance. Furthermore, counter anion exchange with AgPF₆ in methanol gave a white precipitate which tested positive for AgCl. Finally, the structure was confirmed by X-ray analysis (Figure 5), which confirmed that the counter ion was indeed Cl⁻.
A mechanistic pathway for the formation of the novel coumarin salt 82 is proposed in Scheme 26. The reaction is initiated by nucleophilic attack of DABCO on the acrylate to form resonance stabilised intermediate 84. This is followed by intramolecular nucleophilic addition to the aldehyde group to form 86. With DABCO still intact, proton migration and hydroxide elimination to form the conjugated system 87 ensues. Finally, interaction between the hydroxide 87 and the solvent (CH$_2$Cl$_2$ or CHCl$_3$) produces the chloride ion.

An intriguing inference can be drawn from this finding; it proves, for the first time, that the elusive Michael adduct postulated by all researchers in this area but hitherto not isolated does exist. The trapping of the intermediate rather than the usual elimination which ensues after reaction with aldehyde, is positively influenced by the stability of the product.

Under these reaction conditions, some elimination occurred but this was a minor pathway and afforded the coumarin 88 via allylic rearrangement of 81.
Scheme 26.
Previously, Bode and Kaye\textsuperscript{139} attempted to use unmodified salicylaldehyde in the Baylis-Hillman reaction but were only able to isolate 89 in 9.7\% yield.

Alternative use of salicylaldehyde involves protection of the hydroxyl group and use of the resulting aldehyde in the Baylis-Hillman reaction. Thus, the benzyl ether of salicylaldehyde 90, prepared by a base-catalysed reaction\textsuperscript{140} of salicylaldehyde with benzyl bromide, was subjected to the usual coupling conditions to afford the acrylate 91 (Scheme 27).
Scheme 27.

In an attempt to exploit the synthetic utility of this reaction, it was envisaged that masking the acrylate followed by deprotection-transesterification would afford the benzopyranone 92 which on unmasking would afford 3-methylene benzopyranone 81 (Scheme 28).

Scheme 28.
In the event, the acrylate 91 was masked\textsuperscript{122} giving 93 without incident, but debenzylation\textsuperscript{141} afforded the 3-substituted coumarin 94 in 86\% overall yield (Scheme 29).

![Scheme 29](image)

Scheme 29.

The use of salicylaldehyde in the Baylis-Hillman reaction has introduced a new entry; synthesis of coumarins. Coumarins are well known for their anthelmintic, hypnotic, insecticidal and antifungal properties as well as their anticoagulant effect on blood.\textsuperscript{142}

Compounds such as 94a, 94b and further analogues, which are currently receiving attention in these laboratories, are of particular interest because of their similarity to warfarin (95) and chromonar, 96. Warfarin is an approved anticoagulant and a widely used rodenticide\textsuperscript{143} while chromonar finds use as a coronary vasodilator.\textsuperscript{144}
2.2. SYNTHESIS OF CHIRAL ALDEHYDES

Optically active β-hydroxy esters are attractive starting materials for the synthesis of β-hydroxy or β-alkoxy aldehydes.

β-Hydroxy esters and acids were prepared by enzymatic reduction, asymmetric hydrogenation and some from naturally occurring acids - "chiral pool". The crucial operation in these syntheses was introduction of chirality in the first step.

Initial studies involved reduction of β-keto esters. The reduction of β-keto esters by baker’s yeast is probably the most extensively studied microbial transformation that leads to the β-hydroxy esters. Baker’s yeast has been widely used for this transformation because it is inexpensive, its growth does not require the assistance of a microbiologist and most significantly the reduction is highly enantioselective. Consequently, baker’s yeast was employed for enantioselective reduction of ethyl acetoacetate.
Scheme 29.

Indeed, compound 97 was obtained with high optical purity and reasonable chemical yield (Scheme 29). The enantiomeric excess was determined using chiral shift reagent (Eu(fod)$_3$) and by comparison with authentic samples. The optical yields were not reproducible and the reaction workup was physically demanding, tedious and resulted in low recovery of product. Nevertheless the result was sufficient for initial studies.

Inspired by this result, the synthesis of the enantiomer of 97 was considered.

Immobilisation of baker's yeast with magnesium alginate and other inorganic salts has been reported to reverse the selectivity of the reduction of some substrates. Unfortunately, application of this method on ethyl acetoacetate leads to an increase in enantioselectivity.$^{148}$

Seebach and Züger$^{149}$ have prepared the enantiomer of 97 by depolymerisation of naturally occurring polyhydroxybutyrate.

Noyori and coworkers$^{150,151}$ have demonstrated that β-hydroxy esters are accessible by asymmetric hydrogenation of β-keto esters catalysed by Ru-BINAP complexes (BINAP = (R)- or (S)-bis(diphenylphosphino)-1,1-binaphthyl). Either isomer can be synthesised selectively and in high enantioselectivity by the judicious choice of BINAP configuration. Thus (S)-BINAP converts acetoacetic esters to β-hydroxy esters that
have the (S) configuration while (R)-3-hydroxy esters are available using (R)-BINAP.\textsuperscript{150,151}

The latter method was adopted for the synthesis of the enantiomer of 97. The hydrogenation of ethyl acetoacetate in ethanol gave the desired ester in a low yield even after prolonged periods. When the hydrogenation was performed in methanol, complete hydrogenation of the keto group occurred but unfortunately the ethyl ester was accompanied by a transesterification product. Ultimately, the desired hydroxy compound 99 was synthesised by hydrogenation of methyl acetoacetate (98) which was prepared by transesterification of ethyl acetoacetate using a catalytic amount of \textit{in situ} prepared NaOMe (Scheme 30).

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\text{CO}_2\text{Et}};
\node (b) at (2,0) {\text{CO}_2\text{Me}};
\node (c) at (0,-1) {\text{CO}_2\text{Me}};

\draw[->] (a) -- node[above] {i)} (b);
\draw[->] (b) -- node[above] {ii)} (c);
\end{tikzpicture}
\end{center}

\textit{\textsuperscript{i) Na, MeOH}}

\textit{\textsuperscript{ii) Ru(O\text{OCOCH}_3)_2\{(R)-BINAP, MeOH, H}_2\text{}}}

\textbf{Scheme 30.}

Compound 99 was produced in high enantioselectivity and nearly quantitative yield. The preparation of the catalyst was time consuming and the whole method is potentially unsafe.

The second pair of enantiomeric \(\beta\)-hydroxy esters 100 and 101 are commercially available and were used without
purification in the next step.

The next step was to convert the hydroxy esters 97, 99, 100 and 101 to the required aldehydes. Preliminary studies\textsuperscript{152} had shown that the hydroxy group required protection prior to conversion of these substrates to aldehydes. In the same study, the methoxymethyl protecting group and the benzyl protecting group were found to be the most convenient protecting groups. In this study only the latter will be used.

Incorporation of the benzyl protecting group, bearing in mind that the optical integrity of the substrate must remain unaltered, is not a simple task. This operation was carried out in nonionic conditions using freshly prepared silver oxide and benzyl bromide (Scheme 31, method A). However,

\begin{equation}
\begin{array}{c}
\text{Method A}: \text{Ag}_2\text{O}, \text{BnBr}, \text{Et}_2\text{O} \\
\text{Method B}: \text{BnOC(OH)CCl}_3
\end{array}
\end{equation}

Scheme 31.

the yields were low and the unreacted starting material racemised during separation. Attempts to improve the chemical yields by using sonication\textsuperscript{153} resulted in a slight improvement.
An alternative mild method for the incorporation of the benzyl group involved the use of benzyl chloroacetimidate\textsuperscript{154,155} (Scheme 31, method B). This method uses a large excess of the benzylating reagent and yields again were low in the order of 40 - 50%. In the absence of a quantitative benzylating method, both methods (Scheme 31), albeit with low yields, were used to prepare \( \beta \)-benzyloxy esters 102 - 105.

\[
\begin{align*}
\text{OBn} & \quad \text{CO}_2\text{Et} \\
102 & \\
\text{OBn} & \quad \text{CO}_2\text{Et} \\
103 & \\
\text{OBn} & \quad \text{CO}_2\text{Me} \\
\text{CH}_3 & \\
104 & \\
\text{OBn} & \quad \text{CO}_2\text{Me} \\
\text{CH}_3 & \\
105 &
\end{align*}
\]

The next step was to convert the esters to aldehydes. DIBAL reduces esters at low temperature directly to the aldehydes. However, the aldehyde is often accompanied by the overreduction product \( i.e. \), the alcohol.\textsuperscript{156} An alternative approach is to reduce the esters to the corresponding alcohols followed by oxidation to aldehydes. The first step posed no problems and was readily accomplished by lithium aluminium hydride reduction.\textsuperscript{157} The following alcohols were thus obtained in 90% average yield.
Finally, to execute the last transformation, there were several oxidising methods\textsuperscript{158} to choose from. These include the Jones oxidation, Collins, Dess-Martin, PDC, PCC and Swern oxidation. The Swern oxidation\textsuperscript{159} was the most convenient and consequently was used for the preparation of the following aldehydes.

The aldehydes 110 to 113 were produced with an average yield of 70\% based on the alcohol and an overall yield of a low 35\%.

The chiral pool also provides a reliable source of
chiral β-hydroxy acids that can be transformed to aldehydes. The second series of aldehydes were prepared from malic acid, tartaric acid and ascorbic acid.

(s)-Malic acid was esterified to the known dimethyl ester 114\(^{160}\) to facilitate reduction with lithium aluminium hydride. The triol 115 thus obtained upon reduction (50% yield) was converted to its acetonide (90% yield) which according to NMR consisted only of the five-membered species 116. Swern oxidation of the alcohol 116 afforded the aldehyde\(^{160}\) in good yield.

Unfortunately, the use of the above approach is impeded by difficulties in the recovery of the triol. An alternative procedure would be to selectively reduce the ester group adjacent to the hydroxyl group followed by protection. In fact, regioselective reduction of the ester 114 was carried out using BMS complex and NaBH\(_4\) afforded the 1,2-diol in 80% yield.\(^{162}\) The diol 118 was protected as the acetonide 119 (Scheme 33) which was ready for reduction to the acetonide alcohol 116. The overall yield of the aldehyde 117 via this approach was improved by 17%.
Scheme 33.

Another source of aldehydes was the isomer of naturally occurring tartaric acid. The methyl ester of tartaric acid 120 was protected as the benzylidene acetal 121 and reductively cleaved to form the tetrol 122 according to Seebach's procedure. Oxidative cleavage of the 3,4-diol fragment with sodium periodate produced benzyl glyceraldehyde 123 (Scheme 34).
To further exploit tartaric acid as a source of chiral aldehydes, a system that produces dibenzyloxyglyceraldehyde was designed. Thus benzyl tetrol 122 was protected as the acetonide 124 in order to effect the protection of the terminal hydroxyl group in 124. Incorporation of the benzyl group was effected by sodium hydride and benzyl bromide giving 125 in high yield. The acetonide group was removed to give dibenzyl tetrol 125 which was cleaved oxidatively to afford dibenzyloxyglyceraldehyde 127 (Scheme 35).
Finally, the last series of aldehydes were produced from ascorbic acid by adaptation of chemical transformations as published by Abushanab et al. Ascorbic acid was first converted to the protected trihydroxy ester 128 in three steps (Scheme 36).

Scheme 35.

Scheme 36.

Synthesis of the first aldehyde commenced by hydroxyl
protection of the ester 128. This was achieved by treatment of 128 with freshly prepared silver oxide\textsuperscript{167} and benzyl bromide to give 129 in high yield. Reduction of the ester with lithium aluminium hydride produced 130 in quantitative yield. Oxidation of the alcohol 130 using Swern oxidation afforded the aldehyde 131 (Scheme 37).

\begin{center}
\includegraphics[width=\textwidth]{scheme37.png}
\end{center}

Scheme 37.

In another procedure, the ester 128 was reduced with lithium aluminium hydride, without protecting the free hydroxyl group, to produce 132. Oxidative cleavage of the tetrol 132 produced isopropylidenglyceraldehyde 133 in good yield (Scheme 38).
Scheme 38.

Several methods for the preparation of isopropylidene-glyceraldehydes (R and S) have been reported in the literature. Only once previously has the aldehyde 133 been prepared from ascorbic acid and the method is tedious.

The last aldehyde was prepared using 132 as the substrate. Treatment of 132 with 2 equivalents of benzyl bromide in the presence of sodium hydride furnished the dibenzyl derivative 134. Acid hydrolysis of the isopropylidene function on 134 led to the tetrol 135 which was converted to the aldehyde 136 via Swern oxidation (Scheme 39).
Previously, the dibenzzyloxyglyceraldehydes 127 and 136 have been prepared from D-mannitol in six steps \([\alpha]_D = +52^\circ \text{ (c 2.0 benzene)}\). The optical rotation obtained in this investigation \((\alpha)_D = +20^\circ \text{ (c 2.173 CHCl}_3\)) was relatively low probably due to racemisation by silica gel.

2.3. THE BAYLIS-HILLMAN REACTION

According to the salicylaldehyde model study

i) A \(\beta\)-hydroxy aldehyde can be protected as an acrylic ester and converted via intramolecular Baylis-Hillman reaction to cyclic adducts, or

ii) It can be protected as a benzyl ether and coupled with
The first approach cannot be applied to aldehydes 110, 111, 112, 113, 117, 127, 131, 133 and 136, since it would require deprotection which has been found resulting in decomposition of the aldehydes. Also, the hydroxyl groups of aldehyde 123 could not be protected as the acrylic ester since it forms acetals within minutes of its isolation and therefore this route was abandoned.

Since the aldehydes contain a β-alkoxy group with lone pairs of electrons, some organometallic compounds can in principle form intermediate chelates (see introduction) result in attack of the electrophilic carbon from the less encumbered face to afford a chelation-controlled product - generally, syn.

In the absence of chelation, free rotation around the C-C bond pertains and brings about a different scenario. In such circumstances prediction of the stereochemical outcome is generally difficult. One possibility is the application of the Felkin-Anh model which predicts formation of non-chelation controlled adducts which may have the syn or the anti relationship. The Baylis-Hillman reaction falls in this category i.e., absence of chelating metal.

In the Baylis-Hillman reaction, the vinyl carbanion 137 generated by the Michael-type addition of a tertiary amine base to the acrylate (see section 2.1), adds to chiral aldehydes (Scheme 40). Usually a catalytic amount of base is used. The acrylate plays a dual role; that of a reagent as well as the solvent. The reaction is generally slow (c.a. 7 days) and the reaction profile is monitored by the disappearance of the aldehyde peak and change of the vinyl region in the NMR spectrum of the reaction mixture.
Several tertiary amine bases have been used as catalysts.\textsuperscript{110} Especially, DABCO and QDL have been widely used because they are structurally simple and consequently it is easier to monitor the reaction profile. Although QDL has been found to enhance the reaction rate, DABCO enjoys frequent use because of its simplicity (single resonance peak in the NMR spectrum), clean reaction and ease of removal for the isolation of the product. Catalytic amounts of DABCO were used even though it is fairly obvious that an increase in catalyst concentration would enhance the reaction rate.\textsuperscript{111,117} The reason for this will be discussed in detail later.

Concerning the acrylate; a variety of acrylic systems\textsuperscript{110,171,172} have been used and the choice of acrylate, among other factors, has a profound effect on reaction rate.\textsuperscript{110,124,173,174} In this study methyl acrylate
2.3.1. THE BAYLIS-HILLMAN REACTION OF METHYL ACRYLATE WITH CHIRAL ALDEHYDES

The first experiment involved the reaction of the aldehyde 110 with the DABCO-generated zwitterionic intermediate 137 (Scheme 41).

A mixture of diastereomers 138a/b was obtained. In order to fully assess the reactivity and stereocontrol of chiral aldehydes in the Baylis-Hillman reaction, this system was extended to the enantiomer 111 and the $\alpha$-substituted aldehydes 112, 113, 117, 127, 131, 133 and 136 (Scheme 42). The results are shown in Table 3.
anti and syn products

110 \( R_1 R_2 R_4 = H, R_3 = CH_3, R_5 = OBn \) \[138\]
111 \( R_1 R_2 R_5 = H, R_3 = CH_3, R_4 = OBn \) \[139\]
112 \( R_1 = CH_3, R_2 R_3 R_4 = H, R_5 = OBn \) \[140\]
113 \( R_2 = CH_3, R_1 R_3 R_4 = H, R_5 = OBn \) \[141\]
117 \( R_1 R_2 R_5 = H, R_3 R_4 = \)

\[142\]
123 \( R_1 = OBn, R_2 R_3 R_4 = H, R_5 = OH \) \[143\]
127 \( R_1 = OBn, R_2 R_3 R_4 = H, R_5 = OBn \) \[144\]
131 \( R_2 = OBn, R_1 R_4 = H, R_3 R_5 = \)

\[145\]
133 \( R_2 R_3 = O, R_1 R_4 R_5 = H \) \[146\]
136 \( R_2 = OBn, R_1 R_2 R_4 = H, R_5 = OBn \) \[147\]

Scheme 42.
TABLE 2.: Diastereomer ratios in the Baylis-Hillman reaction of chiral aldehydes with MA (Scheme 42).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Reaction Time /d</th>
<th>Products</th>
<th>Yield</th>
<th>Isomer Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>110</td>
<td>5</td>
<td>138a:138b</td>
<td>68</td>
<td>49:51</td>
</tr>
<tr>
<td>2</td>
<td>111</td>
<td>5</td>
<td>139a:139b</td>
<td>69</td>
<td>49:51</td>
</tr>
<tr>
<td>3</td>
<td>112</td>
<td>6</td>
<td>140a:140b</td>
<td>65</td>
<td>33:67</td>
</tr>
<tr>
<td>4</td>
<td>113</td>
<td>6</td>
<td>141a:141b</td>
<td>66</td>
<td>34:66</td>
</tr>
<tr>
<td>5</td>
<td>117</td>
<td>12</td>
<td>142a:142b</td>
<td>60</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>123</td>
<td>8</td>
<td>143</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>127</td>
<td>7</td>
<td>144a:144b</td>
<td>65</td>
<td>66:34</td>
</tr>
<tr>
<td>8</td>
<td>131</td>
<td>12</td>
<td>145a:145b</td>
<td>48</td>
<td>66:34</td>
</tr>
<tr>
<td>9</td>
<td>133</td>
<td>15</td>
<td>146a:146b</td>
<td>60</td>
<td>69:31</td>
</tr>
<tr>
<td>10</td>
<td>136</td>
<td>7</td>
<td>147a:147b</td>
<td>65</td>
<td>66:34</td>
</tr>
</tbody>
</table>

An important practical aspect of the reactions summarised in Scheme 42 is relevant at this point. This concerns the order of addition of reagents. In a typical reaction, DABCO is added to a four-fold excess of methyl acrylate (MA) (i.e., with respect to the aldehyde) and allowed to stir at room temperature for 20 min. The aldehyde is then added in one portion. If the reagents are added in any sequence other than the one described, a yellow deposit forms at the bottom of the flask and little or no conversion occurs. The formation of the precipitate is partially eliminated by dissolving DABCO prior to the addition of the aldehyde.

2.3.1.1. DETERMINATION OF DIASTEREOSELECTIVITY RATIOS

The reaction of chiral aldehydes with the zwitterionic intermediate 137 resulted in a mixture of diastereomers.
The determination of the extent of such intrinsic diastereofacial selectivity has been addressed by a number of authors. Unlike determination of enantiomeric ratio, which requires derivatisation with a chiral substance, the diastereomeric ratio can be determined directly by GC-MS, HPLC or NMR spectroscopy on the mixture. The diastereomeric ratio can also be determined by use of these techniques on achiral derivatives such as silyl ether, acetyl, benzoyl or trifluoroacetyl (19FNMR) derivatives of the diastereomers.

Recently, Roos and Watson have reported on a rapid in situ determination of diastereomeric ratios of alcohols by 1HNMR spectroscopy. The method involves derivatisation of the alcohol with trichloroacytylisocyanate (TAI) resulting in the appearance of the carbamate NH singlets in the usual uncluttered 8.5 - 100 ppm region of the spectrum.

In this investigation the de ratios were determined by GC-MS, 1HNMR on unpurified mixture of isomers and by 1HNMR of TAI derivatives of the same mixture. Results are shown in Table 3. To illustrate this point, selected examples are discussed below.

Case 1: Use of 1HNMR.

Figure 6 shows the resonance signals of the vinyl protons of compounds 144a and 144b (mixture of diastercomers).
The two pseudo triplets around 6.30 ppm are due to one of these protons, (say H_b), of both isomers. The relative concentration of 144a : 144b in the mixture can thus be derived from integration of these peaks. This gives a ratio of [anti:syn] 66:34. The major peak is due to the anti isomer (See Stereostructural Assignment page 65).

Case II: Use of TAI.

Figure 7 shows the NMR spectrum of the mixture of diastereomers 142a and 142b.

![Diastereomers 142a and 142b](image)

The derivatisation of the mixture with TAI in an NMR tube forms the carbamates 148a/b (Scheme 43) whose spectrum is shown in Figure 8. This figure shows clearly the ratio of the isomers, as derived from the integration of the carbamate NH peaks.

![Scheme 43](image)

Interestingly, the two methods were corroborative e.g., determination of the de of 144a/b by the TAI protocol (insert in Figure 6) gave virtually the same de ratio. The
results also compared reasonably with GC-MS data. Application of these techniques on other mixtures gave the results as shown in Table 3.

2.3.1.2 STEREOSTRUCTURAL ASSIGNMENT

The relative configuration (anti/syn) of aldol-type products is generally determined by $^1$HNMR and $^{13}$CNMR. This task is generally easy for aldols in which the α- and β-carbons bear a hydrogen atom as in 149, since the coupling constant $J_{AB}$ has proven to be a reliable diagnostic tool in this regard.\(^{177}\)

In system such as 149, $J_{AB}$ is usually in the range 2 - 6 Hz for the syn isomer (as a result of gauche relationship) and $J_{AB} = 7 - 10$ Hz for the anti isomer. Intramolecular hydrogen bonding was shown to have a profound effect on these coupling constants.\(^{29}\)

Clearly, the two systems 149 and 150 are structurally different and therefore this method of assignment cannot be used as a reliable precedent in this study.

Apart from the difference in structure - which has been reported to give non uniform $J_{AB}$ values\(^{29}\) - the relevant resonance signals were in most cases not clearly resolved or were masked by other signals.

Poor resolution of the protons in question in the $^1$HNMR
spectra is not uncommon. To circumvent this problem, Heathcock\textsuperscript{178} reported a versatile technique that employs \textsuperscript{13}CNMR spectroscopy as a diagnostic tool for stereostructural assignment. However, this method could not be applied without some uncertainty in the present study due to fundamental structural differences between compounds 149 and the system 150.

At this stage the only stereostructural diagnostic tool that was available for the compounds 138 - 147 was the use of TAI. Roos and co-workers\textsuperscript{179} had reported that the TAI protocol for de determination could be extended to include assignment of relative configuration. They assigned the relative configurations on empirical basis as \textit{anti/syn} by observing $\delta_{\text{NH}}$ differences in the NMR spectrum of compounds 152 which were derived from 151 by simply adding TAI (Scheme 44).

The operative relationship was $\delta_{\text{NH}}(\text{syn}) > \delta_{\text{NH}}(\text{anti})$ in all cases studied.
This technique appeared fairly simple and consequently was applied for stereostructural assignments (Figure 6 and 8 inserts). The results are shown in Table 3.

Relative configurations have also been solved in the past by conversion of the aldol products or related systems to cyclic compounds. The relative configuration is then determined by comparison with authentic samples or alternatively derived by using the notion of vicinal coupling constants as well as $^{13}$C-NMR chemical shifts.

In this investigation, coupling products were converted to tetrahydrofuran derivatives (covered in detail in Section 2.4) and this proved to be a useful diagnostic tool for stereostructural assignments.

Consider compounds 139a/b (page 60). When this compound is subjected to iodocyclisation conditions, only one isomer undergoes cyclisation. Figure 9 shows the $^1$H-NMR spectrum of the mixture of products 139a/b before cyclisation and Figure 10 is the spectrum of the unreactive substrate - isolated from the reaction mixture when the cyclisation had attained >90% completion. Clearly, it is discernible from the two figures that the minor isomer has cyclised.

In the cyclic product, whose stereochemistry was deduced by NOE, coupling constants and unambiguously by X-ray analysis, the relative configuration of the hydroxyl group to the methyl group is cis. Since there is no inversion of configuration at any stage during the cyclisation, this product can only arise from 139a which has the anti relative configuration.
These results obtained from the cyclic products fully corroborated the earlier assignments based on the TAI protocol. Similar deductions were made for other compounds and some assignments were deduced by analogy.

2.3.1.3. THE REACTIVITY OF ALDEHYDES

The Baylis-Hillman reaction of aldehydes with methyl acrylate is generally slow. Data from Table 3 show the difference in reactivity of chiral aldehydes. α-Unsubstituted aldehydes 110 and 111 reacted relatively faster than the α-methyl aldehydes 112 - 113 and the α-0-benzyl aldehydes 127, 131 and 136 reacted even more sluggishly.

This observation is however, not unexpected and can readily be rationalised by assuming that both steric and inductive effects operate.

For the α-unsubstituted aldehydes 110 and 111 the aldehyde function is relatively less hindered and inductive effect is minimal.

In the case of the α-methyl substituted aldehydes 112/113 the methyl group brings about steric hindrance thereby inhibiting nucleophilic attack by the approaching nucleophile. This results in a lowered rate of the reaction. Furthermore, since the methyl group is electron donating, inductive effects cannot be ignored.

For the α-0-benzyl series 127, 131 and 137, it is assumed that the strong electron donor capability of this group in addition to some steric effect has a profound effect on the reactivity of these aldehydes.
The yields of the reactions of 110 - 113, 127 131 and 137 were in the synthetically useful range.

Anomalies were observed in the reaction of the acetonide aldehydes 117, 131 and 133. These aldehydes reacted sluggishly, giving low yields and generally resulted in a mixture of products. Cleavage of the isopropylidene group cannot be ruled out especially in view of earlier finding that protecting groups with good leaving group ability are eliminated via proton abstraction by DABCO. For example, when the aldehyde 153 is reacted with DABCO, evidence shows production of methacrolein 154 in situ which then reacts with methyl acrylate to form the diene 155 (Scheme 46). The proposed mechanism for the formation of 154 involves abstraction of the α-proton of the aldehyde followed by elimination of the hydroxyl protecting group.

\[
\begin{align*}
\text{OMOM} & \quad \text{CHO} \\
\text{CH}_3 & \\
153 & \\
\end{align*}
\]

\[
\begin{align*}
\text{OMOM} & \quad \text{CHO} \\
\text{CH}_3 & \quad \text{CHO} \\
\text{OMOM} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CHO} \\
\text{CO}_2\text{Me} & \quad \text{OH} \\
\text{155} & \\
\end{align*}
\]

\[
\begin{align*}
\text{DABCO} & \\
\text{MA} & \\
154 & \\
\end{align*}
\]

Scheme 46.
In view of this, it is also not surprising that all the \(\alpha\)-substituted aldehydes gave virtually racemic aldol-type products. DABCO presumably abstracts the \(\alpha\)-proton of the aldehyde - yellow precipitate during mixing - in an equilibrium reaction that results in racemisation (Scheme 47).

\[
\begin{align*}
R_1 & \quad R_2  \\
\text{CHO} & \quad \text{CHO} \\
\xrightarrow{\text{DABCO}} & \\
\end{align*}
\]

\text{Scheme 47.}

Therefore it was essential to use a minimum amount of DABCO (catalytic) so as to minimise racemisation of the aldehyde. Unfortunately, this was met with little success in the case of \(\alpha\)-substituted aldehydes.

The Baylis-Hillman reaction of aldehyde 123 gave a host of unidentifiable products which were of no relevance to the present study.
2.3.1.4. **RATIONALISATION OF THE STEREOCHEMICAL OUTCOME OF THE BAYLIS-HILLMAN REACTION**

Since the Baylis-Hillman reaction involves nucleophilic addition to aldehydes in the absence of a chelating metal reagent, stereofacial selectivity is governed solely by steric and electronic factors *i.e.*, non-chelation control. Under these circumstances, a logical prediction would be overall *anti* selectivity as predicted by Cram's model. However, examination of the results in Table 3 shows:

a) **Syn** selectivity for *α*-unsubstituted aldehydes 110 and 111 (entries 1 and 2). As might be expected, the intrinsic 1,3-asymmetric induction is virtually stereorandom. This is in agreement with addition of organometallic reagents,48 enolates41 and crotylemetal reagents,41,88 to β-chiral *α*-unsubstituted aldehydes (see INTRODUCTION).

b) **Syn** selectivity for *α*-methyl substituted aldehydes 112 and 113 (entries 3 and 4). The diastereofacial selectivity is relatively enhanced by the *α*-methyl substituent compared to the *α*-unsubstituted aldehydes 110 and 111 (entries 1 and 2). This suggests that steric effects do indeed contribute in this addition reaction. A similar trend was observed by Reetz 's group in both chelation and non-chelation controlled additions.41

c) That the diastereoselectivity in the case of *α*-0-benzyl aldehydes 127, 131 and 136 (entries 7, 8 and 10) is principally of the same degree as in (b) above but reversed, *i.e.*, *anti* selectivity is preferred in the case of *α*-0-benzyl aldehydes (entries 7, 8 and 10). This appears to imply that not only steric factors operate in
both cases but electronic factors play a crucial role.

d) That the isopropylidene aldehydes 117 and 133 give higher levels of diastereofacial selectivity (entries 5 and 9) with the former giving exceptionally high results. In comparison, the similar system 131 (entry 8) gives standard results suggesting that the α-substituent has a major directing effect. The preferred diastereoselectivity in the addition reaction to the acetonide 133 (entry 9) is anti and is in line with the other α-alkoxy substituted aldehydes (entries 7, 8 and 10). The increase in stereoselectivity (entry 9) could be due to the steric bulk provided by the acetonide group as well as the rigidity of this group. Also electronic effects cannot be ruled out.

The observed anti selectivity in the case of aldehyde 117 (entry 5) is opposite that of α-unsubstituted aldehydes and is exceptionally high. This was initially surprising and indeed confusing. However, consideration of the chain length and rationalisation of the stereochemical outcome by employing stereochemical models (vide infra) shed some light on this problem.

To rationalise the stereochemical outcome of the Baylis-Hillman reaction of methyl acrylate with chiral aldehydes, Felkin's model later modified by Anh and Einstein operates (Figure 3 page 8).

To recapitulate, the model by Felkin and his co-workers was initially designed for symmetrical ketones (such as cyclohexanone). These workers proposed that, unlike in Cram or Karabatsos models, the dominant interaction is that between incoming nucleophile and the largest group attached to the stereogenic centre; that is that the nucleophile
attacks antiperiplanar to the large group (Figure 3 page 8).

Anh and Einstein evaluated the Cram, Karabatsos and Felkin models by \textit{ab initio} calculation of hypothetical transition state structures.\cite{181} The Felkin conformers were found to be significantly lower in energy than either the Cram or Karabatsos conformers. In addition the authors postulated that if the two carbonyl ligands are the same (as in symmetrical ketones or formaldehyde) then the attacking nucleophile will approach along the Burgi-Dunitz trajectory in the plane that bisects the compound. This is essentially the normal plane as was earlier pointed out by Felkin (Figure 3 page 8). However, if the two carbonyl ligands are not the same, the nucleophile will follow a trajectory that keeps it further away from the larger of the two carbonyl ligands as shown below.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure11.png}
\caption{Figure 11.}
\end{figure}

The amount of distortion away from the normal plane will be related to the difference in steric bulk on the two sides of the normal plane.

Incorporation of the Burgi-Dunitz trajectory to the energetically favoured Felkin model as shown in 156 and 157 simplifies the problem of rationalisation of stereochemical outcome.
Here, the assumptions relating to the magnitudes of $0 \leftrightarrow M$ and $M \leftrightarrow H$ interactions are completely irrelevant. That is, it is implicitly assumed that conformations 156 and 157 are of comparable intrinsic energy and that stereodifferentiation arises from differential interactions of the attacking nucleophile with the small and medium ligands. Furthermore it was proposed on the basis of frontier molecular orbital arguments that the ligand with the lowest lying orbital, rather than the sterically most demanding group is perpendicular to the carbonyl plane and anti to the attacking nucleophile. What this means is that in the case of alkyl and O-alkyl groups, the latter will assume perpendicular arrangement to the carbonyl group in all cases as in 158.

To explain the stereochemical outcome in addition reaction to aldehydes 110 and 111, consider the Newman projections 159. The view in 159 is along $C_1-C_2$ and all ligands at quarternary centres are assumed to be staggered.
Since there are two groups of equal size (both small), addition to the aldehydes 110 and 111 would be expected to be stereorandom. Indeed, it is (Table 3). The slight discrepancy (51:49) is assumed to be due to electronic repulsion between the incoming carbanion and the oxygen of the protecting group (OBn, Ho is syn to this group) thereby favouring attack as illustrated in 159b. This results in a slight preference for the syn isomer 138b and 139b (Table 3, entries 1 and 2).

In view of this, it would not be surprising to see an increase in intrinsic diastereofacial selectivity when one of the hydrogen atoms is replaced by an alkyl group (medium group). In fact, this is the case with aldehydes 112 and 113 (Table 3, entries 2 and 3). Of the two Felkin-Anh conformers 160a and 160b preferential attack of the latter predominates at the expense of the former. In 160a, interaction between the methyl group and the incoming nucleophile pushes the attacking species further away until an arrangement as in 160b is achieved. This results in preferential formation of the syn isomer. Electronic repulsions as mentioned above might also play a role.
Application of the Felkin-Anh theory also explains the stereochemical outcome of the α-alkoxy aldehydes. Consider the Newman projections 161 of aldehydes 127, 131, 133 and 136 (Table 3, entries 7 - 10). The operating Felkin/Anh conformers for these aldehydes are shown below. The alkoxy group OBn assumes perpendicular alignment to the carbonyl double bond as required by Anh-Einstein hypothesis. Attack of conformer 161a is favoured because the incoming species experiences less steric interaction as well as electronic repulsion. Consequently the anti isomer predominates (Table 3, entries 7 - 10). These results are in accordance with recent observations by Roos and Manickum117 and Drewes et al.115,118 The preferred syn selectivity by α-unsubstituted aldehydes 110, 111, 112 and 113 (Table 3, entries 1 - 4) and the predominance of anti products with aldehydes 127, 131, 133, 136 (entries 7 - 10) can also be explained by invoking Karabatsos model.
A surprisingly high degree of diastereoface selection and anti selectivity was observed in the addition reaction of aldehyde 117 (entry 5). The reasons for this bewildering anomaly are not fully understood but the stereochemical outcome can be partially reconciled by considering Newman projections 117a, 117b and 117c in which the molecule is viewed along C2-C3 axis with all ligands in staggered fashion. The first of these representations 117a can be ruled out on the basis of electronic repulsions between the carbonyl group and the oxygen atoms of the isopropylidene group.

The Felkin-Anh conformers of 117b and 117c (not shown) suggest that attack of the carbonyl along H₀ (which leads to syn products) is disfavoured on the basis of electronic repulsion between the in-coming nucleophile and the oxygen atoms of the isopropylidene group. The steric bulk of the protecting group enforces the electronic effect by effectively shielding one face of the aldehyde.
2.4. SUBSTITUTED TETRAHYDROFURANS

The tetrahydrofuran unit features in a large number of naturally occurring polyfunctionalised molecules such as polyether\(^{182}\) and macrolide\(^{183}\) antibiotics.

Polyether antibiotics are a large group of naturally occurring monocarboxylic acid ionophores. Their ability to transport metal ions across lipid bilayers\(^{182}\), act as antimicrobial agents\(^{184}\), cause growth promotion in ruminants\(^{184}\) or produce cardiovascular responses\(^{185}\) has made them challenging synthetic targets. An example of a polyether antibiotic, Lasalocid A is given below.

![Lasalocid A](image)

The tetrahydrofuran unit, other than carbohydrate derivatives, also features in a new class of nucleoside analogues that show potent anti-HIV activity\(^ {186}\). For example isoddA (162) possesses good anti-HIV activity that can make it a reliable substitute for the rather toxic AZT
The latter is one of the major drugs approved for the treatment of AIDS.

Polyether antibiotics contain a plethora of asymmetric centres and functional groups dominated by substituted tetrahydrofurans. In this regard, regio- and stereochemical control in simultaneous creation of contiguous stereogenic centres have become particularly important in the construction of these ring systems. Several approaches towards achievement of this goal have received growing interest evidenced by the number of reports and excellent reviews written on this subject.188-190

2.4.1. ELECTROPHILE-INDUCED CYCLISATIONS

The functionalisation of the double bond, promoted by an electrophile is a common reaction in the construction of five-membered O-heterocycles. In principle, construction of tetrahydrofuran ring systems by electrophile-induced cyclisation involves addition of an electrophile to an alkene containing a suitably situated internal nucleophile, followed by intramolecular ring closure in which a carbon of the double bond becomes attached to a group specifically chosen to allow further modification. This is summarised in Equation 1.
A large number of intramolecular ring closure reactions conform to this general principle termed cyclofunctionalisation.$^{191}$

Although rings of all sizes are present in naturally occurring compounds, of special interest are the more common tetrahydrofurans. The chemoselectivity and the regiospecificity of ring-forming processes is governed by the size of the carbon skeleton of the substrate and electronic properties of the internal nucleophile. Baldwin$^{192}$ has formulated some rules on an empirical bases to predict the relative facility of ring-forming reactions. The rules are based on the trajectory of the reagent that attacks the electrophile-activated carbon centre leading to the ring closure reaction.

A number of electrophilic reagents have been employed in order to effect ring closure and the nature of the electrophile plays an important role in regio- and stereochemical control.

Mercuric acetates such as Hg(OAc)$_2$ and Hg(OTFA)$_2$ are generally employed to promote mercurycyclisation.$^{193-195}$ These reagents effect the cyclisation of $\gamma,\delta$-unsaturated alcohols to give trans-2,5-disubstituted tetrahydrofurans as major products. For example, cyclisation of $\beta$-fluoro-$\gamma$-hydroxy alkenes $^{164}$, carried out by using Hg(OTFA)$_2$ has been reported by Bravo et al.$^{195}$ to give
preferential formation of trans-2,5-disubstituted tetrahydrofurans 165 (Scheme 48).

Scheme 48.

Cyclisation of suitably substituted alkenes has also been effected by selenium-based electrophiles such as phenylselenium chloride, N-phenylselenophthalimide (NPSP) and phenylselenium triflate. Phenylselenoetherification (Scheme 49) is endocyclic and occurs at low temperature (-78°C) to give tetrahydrofurans in which the stereochemistry of the phenylseleno group is always trans to that of oxygen. The mechanism that rationalises this stereochemical outcome is outlined in Scheme 49.
It involves activation of the double bond of the homoallylic alcohol substrate 166 by phenylselenium cation to form intermediate 167. Subsequent intramolecular nucleophilic attack produces the tetrahydrofuran 168. Recent findings by Mihelich and Hite show that the overall stereochemical outcome of the reactions is influenced by the relative stereochemistry (anti/syn) of the allylic and homoallylic substituents and also by the configuration of the double bond.

Substitution pattern across the double bond also plays a role in the synthesis of tetrahydrofurans via ring contraction of tetrahydropyrans. The most commonly used electrophiles for this process are 2,4,4,6-tetra-bromo-2,5-cyclohexadienone (TBCO) and thallium salts. Michael et al. reported that 2,5-trans-disubstituted tetrahydrofurans 171 are conveniently prepared by Tl⁺-induced cyclisation via ring
contraction of organothallium intermediates 170. They found that regio- and stereocontrol was high in the case of terminally disubstituted olefinic substrates 169. (Scheme 50).

Scheme 50.

The authors proposed a mechanistic pathway that involves formation (in situ) of the organothallium cyclic ether 170a. The organothallium intermediate 170a then undergoes spontaneous decomposition via bridged oxonium ion 170b assisted by nucleophilic attack, resulting in the formation of β-alkoxy tetrahydrofurans 171 (Nu = OR Scheme 50).

Halogenes constitute the most widely used class of electrophiles by far. Since this method was used for cyclisations, it will be dealt with in greater detail.
2.4.2. **HALOCYCLISATION REACTIONS**

Halogen-induced cyclisation of \( \gamma,\delta \)-unsaturated alcohols and corresponding ethers provides an interesting route to the synthesis of substituted tetrahydrofuran derivatives.\(^{188-190}\) Application of this elegant method, first developed by Bartlett,\(^{204}\) can be manipulated to give either *cis* or *trans* substituted tetrahydrofurans. In fact, cyclisation of \( \gamma,\delta \)-unsaturated alcohols under kinetic conditions preferentially gives *cis*-2,5-disubstituted tetrahydrofurans while the corresponding *trans*-2,5-disubstituted products predominate under thermodynamic conditions.

**2.4.2.1. THERMODYNAMICALLY CONTROLLED CYCLISATION**

Thermodynamically controlled cyclisation is carried out by allowing the olefinic substrate, a \( \gamma,\delta \)-unsaturated benzyl or alkyl ether such as \(172\), to stir in a solvent (\( \text{CH}_3\text{CN} \)) in the presence of an electrophile (\( \text{I}_2 \)). Due to the nature of the substrate - which is usually an alkyl ether, the cyclisation attains equilibrium and is forced to the right because of the stability of products \(174\) and \(176\) (Scheme 51).

The stereochemical outcome of thermodynamically controlled cyclisation is rationalised on the basis of the mechanistic pathway outlined in Scheme 51.
According to pathway A, intermediates $173a$ and $173b$ are in equilibrium with the starting substrate $172$. In each of the two intermediates there exists strain due to steric hindrance of the ethereal group $R$. Intermediate $173a$ suffers from 1,5-strain while intermediate $173b$ suffers
from 1,2-strain. Consequently little conversion of the starting material to the trans substituted product is observed. On the other hand, both steric strains are easily avoided in pathway B (Scheme 51). This results in preferential formation of the cis isomer 176.

In accordance with this mechanism, it may be assumed that the bulkier the ether $I_2$ group the better the diastereoselection. Indeed, as has been reported by Marek et al., use of the bulky butyl group in the cyclisation of 177 dramatically increased the stereoselectivity to give 178 as the sole product (Scheme 52).

Scheme 52.

Electrofugal capability of the hydroxyl protecting group (R$^2$ in 172) also influences the stereoselectivity of the cyclisation. For example, 2,6-dichlorobenzyl ether provides higher yields of cis products compared to benzyl ether since it has the most steric and electronic properties.

2.4.2.2. KINETICALLY CONTROLLED CYCLISATION

The cyclisation of free hydroxy $\gamma,\delta$-unsaturated alcohols promoted by an electrophile usually in the presence of base
in aqueous medium is considered to be kinetic controlled conditions. Several electrophiles including I$_2$/NaHCO$_3$/THF, I$_2$/CHCl$_3$, NIS/CHCl$_3$, I$_2$/THF/py, are all considered kinetic conditions and have been used with great success. 

Regio- and stereochemical outcome of halocyclisation under kinetic conditions appear to be directed by a number of factors notably, allylic hydroxyl group of the substrate, relative stereochemistry of the nucleophilic carbinol group to allylic substituent, and the configuration (E or Z) of the double bond.

Chamberlin et al. have developed a model for the attack under kinetic control of an electrophile to an olefin containing an internal nucleophile, based on the relative affinity of the diastereotopic faces of the double bond towards a proton. The proposed mechanism involves intramolecular attack on a complex. In the presence of an allylic hydroxyl group, preferential attack of an electrophile on the OH-in-plane conformer occurs from the face of the double bond syn to the allylic hydrogen (Equation 2).

\[
\text{Equation 2.}
\]

When $R_1 = R_2 = H$ the cis diastereomer 180 is formed as the major product. This stereochemical outcome is also observed with substrates that have the trans configuration across the double bond. For example Iodocyclisation of the diol 181
affords the 1,2-cis tetrahydrofuran 182 (Scheme 53). 

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \quad \text{OH} \\
\text{I}_{2}/\text{NaHCO}_3 & \quad 79\% \\
\text{181} & \quad \rightarrow \quad \text{I} \quad \text{OH} \\
\text{182} & \quad \quad \text{Ph} \quad \text{CH}_3 \\
& \quad 93:7
\end{align*}
\]

Scheme 53.

On the other hand, substrates with cis substituents on the double bond (relative to the stereogenic allylic centre), which destabilise the OH-in-plane conformer, react on the opposite face (Scheme 54).

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \quad \text{OH} \\
\text{I}_{2}/\text{NaHCO}_3 & \quad 80:20 \\
\text{181} & \quad \rightarrow \quad \text{I} \quad \text{OH} \\
\text{182} & \quad \quad \text{Ph} \quad \text{CH}_3 \\
& \quad 80:20
\end{align*}
\]

Scheme 54.

The reversal of stereochemistry (Scheme 53 vs 54) has been rationalised on the basis of destabilisation of the OH-in-plane conformer with the H-in-plane conformer energetically more accessible in the latter (Scheme 54).

The regio- and stereochemical outcome of kinetically controlled iodosyclisation reactions is also strongly influenced by the relative configuration (syn:anti) of the allylic substituents to the nucleophilic carbinol. For example, iodocyclisation of 1,3-syn dihydroxy olefin 181 proceeds with exclusive 5-exo-trig ring closure to form 1,2-cis tetrahydrofuran 182 as the major product (Scheme 53 above). On the other hand, 6-endo-trig ring closure
leading to formation of tetrahydropyran 184 is predominantly favoured by the 1,3-anti substrate 183 (Scheme 55).

![Chemical structure](image)

Scheme 55.

The tetrahydropyran 184 is accompanied by a small percentage of 5-exo-trig product 185.

Geometric arrangement and substitutionary pattern across the double bond have been found to have similar effects on the regio- and stereochemical outcome of the reaction. For example, iodocyclisation of Z-olefinic substrate 185 gives 5-exo-trig ring closure with a diastereoselectivity ratio of 60:40 (2,5-cis 186a:2,5 trans 186b) (Scheme 56).
Scheme 57.

On the other hand cyclisation of the corresponding E-isomer 187 gives 188 as the sole product. Clearly, 188 is formed via 6-endo-trig ring closure (Scheme 57).

Scheme 57.

The above examples highlight advances in kinetically controlled iodocyclisation reactions. From these examples, it is clear that regio- and stereochemical control in kinetically controlled iodocyclisation has been extensively studies. In contrast, apart from the influence of ethereal groups, little is known of the factors that affect regio- and stereochemical control in thermodynamically controlled iodocyclisation.
2.4.3. **THE IODOCYCLISATION OF γ-ALKOXY-α-HYDROXYACRYLATES**

A series of γ-alkoxy-α-hydroxy acrylates 138 - 147 were prepared by the Baylis-Hillman reaction. Separation of the mixture of the diastereomers was very difficult by chromatography and in some of the cases the diastereomers were inseparable. Nevertheless small quantities of diastereomers 138a and 138b were obtained in pure form by careful collection of the first and the last fraction.

The first iodocyclisation experiment was performed on pure 138a and 138b separately. The substrate 138a or 138b was allowed to stir with a two fold excess of iodine in dry acetonitrile overnight. The diastereomer 138a was unreactive even for prolonged periods. On the other hand 138b reacted cleanly to produce tetrahydrofuran 190 within 18 hours (Scheme 58). Interestingly, no other diastereomer of 190 was detected by GC and NMR.

![Scheme 58.](image)

At this point, two tentative inferences were made; that only one diastereomer undergoes iodocyclisation at room temperature and the reaction proceeds with high diastereofacial selectivity.

Subsequently, the mixtures of diastereomers 138, 140 - 142 and 144 - 147 (entries 1, 3-5, and 7-10 Table 3) were subjected to the iodocyclisation conditions without prior
separation. The cyclisation product from 139 (Table 3, entry 2) was only detected by GC-MS and not isolated. Hence, it will not be discussed. The isopropylidene acrylates 131, 133 and 142 did not undergo cyclisation. In all the other cases, the reaction was generally clean and three spots ascribable to benzyl iodide (by-product), the tetrahydrofuran and the unreacted substrate were observed on tlc. The results are summarised in Table 4. The yields refer to the product isolated by means of flash column chromatography and in all cases complete conversion of the reactive isomer occurred within 18 hours.
TABLE 4.: Iodocyclisation of γ-bezyloxy-α-hydroxyalkyl-acrylates.

<table>
<thead>
<tr>
<th>Substrate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reactive Substrate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;c&lt;/sup&gt;</th>
<th>de Ratio</th>
</tr>
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<tr>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Reactive Substrate 1" /></td>
<td><img src="image3" alt="Product 1" /></td>
<td>100:0</td>
</tr>
<tr>
<td><img src="image4" alt="Substrate 2" /></td>
<td><img src="image5" alt="Reactive Substrate 2" /></td>
<td><img src="image6" alt="Product 2" /></td>
<td>100:0</td>
</tr>
<tr>
<td><img src="image7" alt="Substrate 3" /></td>
<td><img src="image8" alt="Reactive Substrate 3" /></td>
<td><img src="image9" alt="Product 3" /></td>
<td>100:0</td>
</tr>
<tr>
<td><img src="image10" alt="Substrate 4" /></td>
<td><img src="image11" alt="Reactive Substrate 4" /></td>
<td><img src="image12" alt="Product 4" /></td>
<td>&gt;95:5</td>
</tr>
<tr>
<td><img src="image13" alt="Substrate 5" /></td>
<td><img src="image14" alt="Reactive Substrate 5" /></td>
<td><img src="image15" alt="Product 5" /></td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Refers to a mixture of diastereomers.  
<sup>b</sup> The unreacted isomer was quantitatively recovered.  
<sup>c</sup> Percentage yield given in brackets. Refers to yield isolated by chromatography based on the reactive isomer.

The diastereomeric excess was determined by <sup>1</sup>HNMR, and GC-MS. It is interesting to note that...
γ-benzyloxy-α-hydroxyalkylacrylates (Table 4, first - third entry) gave single diastereomers of the tetrahydrofurans. The analogous α-benzyloxy substituted substrates (fourth and fifth entries) were also highly selective (>95:5). As is apparent from Table 4 concerning iodocyclisation substrates, irrespective of the substitution pattern, the reaction gave 1,2-cis selectivity i.e., the configuration of the hydroxyl group relative to the iodomethyl group is cis.

2.4.3.1. REACTIVITY OF ISOPROPYLIDENE ACRYLATES

Regarding the reactivity, isopropylidene acrylates 142, 145 and 146 did not undergo cyclisation under the present conditions.

Attempts were made to cyclise 142a at elevated temperatures but a tarry mixture with no identifiable product was obtained. A further attempt involved deprotection of the isopropylidene protecting group followed by iodocyclisation. This was achieved by treatment of 142 to form the triol 195 (Scheme 59). The triol was subjected to iodocyclisation under kinetic control (I$_2$/NaHCO$_3$, Et$_2$O-H$_2$O, Scheme 59). This procedure also gave a complex mixture of unrecognisable products. A considerable amount of the triol 195 was
recovered unchanged.

\[
\begin{align*}
142a & \xrightarrow{\text{H}^+/\text{EtOH}} \text{Amberlite CG 120} \\
& \text{195}
\end{align*}
\]

Scheme 59.

The reason for the lack of reactivity in the isopropylidene series 131, 133 and 134, is not entirely understood but the nature of the isopropylidene group probably contributes. The isopropylidene group apparently does not have the requisite electrophilic properties consequently it does not cleave or the cleavage is slow. Similar reactivity was observed for methyl ethers. Bartlett and Rychnovsky reported that due to poor electrophilic property of the methyl group, cleavage of the other C-O bond ensues and only 15% conversion to tetrahydrofuran occurs.

The lack of reactivity of the triol 195 under kinetically controlled conditions might be due to the relative configuration (i.e., \textit{anti:syn} relationship) of the allylic hydroxyl group to the \(\gamma\)-hydroxyl group (\(\gamma\), relative to acrylate). This anomaly is not uncommon and has been observed by Yoshida and co-workers. They reported that under similar conditions, the \textit{syn} diol 196 is selectively consumed to form a tetrahydrofuran while the \textit{anti} isomer 197 is recovered unchanged.
The authors proposed formation of transition state to explain the lack of reactivity of 197. This transition state is characterised by (i) an intramolecular hydrogen bonding, forming a six-membered ring, (ii) a nearly eclipsed conformation of the C₂ hydroxyl group in the C₄-C₅ double bond plane and (iii) a more or less concerted iodocyclisation, which proceeds in a trans fashion.

The syn substrate easily forms the proposed transition state 198a. However, the anti derivative is energetically most unfavourable to form a bicyclic structure in an analogous transition state 198b owing to an increase of nonbonding interactions and hence the low reactivity. Similarly, steric interaction between the axial groups (CH₂OH and CO₂Me) in the anti triol 195 disallow formation of the proposed intermediate state 198a hence show the observed lack of reactivity.
2.4.3.2. **Reactivity of \( \gamma \)-Alkoxy-\( \alpha \)-Hydroxyacrylates**

As for the reactivity of \( \gamma \)-alkoxy-\( \alpha \)-hydroxyalkylacrylates, data from Table 4 show a fascinating difference in the reactivity of *syn/anti* diastereomers. The *syn* isomer 138b reacted at room temperature within 18 h to form the tetrahydrofuran 190 while the *anti* isomer 138a was completely unreactive under the same conditions. A similar reactivity pattern was observed in the iodocyclisation of \( \gamma \)-benzyloxy-\( \beta \)-methyl-\( \alpha \)-hydroxyalkylacrylates 140 and 141 (Table 4, second and third entry). Interestingly, it was the *anti* isomer that cyclised in this series to give exclusive formation of tetrahydrofurans 191 and 192. In comparison, the \( \beta \)-benzyloxyacrylates 144 and 147 gave relatively less diastereoselection (>95:5) in the formation of tetrahydrofurans 193 and 194. Nevertheless, the observed diastereoselectivity is synthetically valuable.

In all these cases, the cyclisation occurred with firm regio-selective control *i.e.*, no formation of six-membered ethers was observed. The cyclisation proceeded according to Baldwin's rules\(^{192}\) *i.e.*, only the favoured 5-*exo-trig* ring closure occurred. Also, the possible but disfavoured 5-*endo-trig* ring closure in the dibenzyloxy series (entries 1 and 2) did not occur (Scheme 60).
2.4.3.3. ASSIGNMENT OF THE STEREOCHEMISTRY

Stereochemical assignments of tetrahydrofurans containing an iodomethyl group is usually determined by comparison of the iodomethyl carbons. The iodomethyl carbon of the cis isomer resonates at higher field (by ca. 5 ppm) relative to the trans isomer due to shielding in the $^{13}$CNMR. Also the iodomethyl protons in the cis isomers resonate far down field compared with those of corresponding trans isomers.

Clearly, for the two diagnostic features to operate, a mixture of diastereomers is necessary. Consequently, this method is not applicable in the reactions in which single isomers of tetrahydrofurans were obtained (entries 1 - 3). For tetrahydrofuran 193 and 194, the minor isomer did not appear on $^{13}$CNMR but the iodomethyl protons were clearly visible in the $^1$HNMR spectrum, without use of chiral shift reagent, at a relatively high field shift compared with the 1,2-cis isomer. Consequently it was concluded that the relative configuration of the hydroxyl group to the
iodomethyl group of the tetrahydrofurans 193 and 194 is cis.

In order to confirm the above conclusion and to further establish the stereochemistry at other centres in the molecule, NOE experiments were performed on all compounds. To illustrate this, NOE studies on tetrahydrofuran 191 will be discussed.

Figure 11 shows spectra for NOE experiments on 191.

(a) is the control spectrum obtained without irradiation.

(b) irradiation of the high field methyl group enhances the C₄-H proton as might be expected. This experiment also leads to enhancement of C₅-Hₐ and the CH₂I and gives a negative effect on C₅-Hₐ, a proton which is a geminal partner of C₅-Hₐ. This experiment clearly assigns the relative configuration at the three centres as

Irradiation of methyl group.

irradiation of the C₅-Hₐ proton (not shown) gives enhancement to its geminal partner and also of the methyl group and CH₂I.
Figure 11.

Figure 12.
(c) Irradiation of C4-H gives some enhancement to the methyl group (expected) and significant enhancement to Hb and also C3-H. From this experiment the relative configuration at the three centres is as follows:

Further irradiation at other centres also supported these assignments and no further information could be extracted from them. Nevertheless, the two experiments sufficed and the structure was assigned as shown in Table 4.

This structural assignment was confirmed by a single structure X-ray analysis as shown in Figure 12.

NOE experiments were also performed on tetrahydrofurans 192 - 194 and the results are shown in Table 4. Unfortunately, the absolute configuration of tetrahydrofuran 190 could not be determined directly by NOE without some uncertainty. During studies directed towards the synthesis of the nucleoside analogue 200 (comprehensive studies will be done in the future), the services of a good leaving group at C3 were required and the mesylate group was chosen for
this purpose. Incorporation of the mesyl group (Scheme 61) gave 199 (78% yield) and all the signals in the NMR spectrum of this compound were clearly resolved. The NOE experiments on 199 shown in Figure 13 confirmed the assigned configuration. The first experiment, (a), identifies the C₄ proton (C₄-H₈) that is cis to CH₃. This is achieved by irradiation of the high field methyl group. Irradiation on this signal i.e., C₄H₈ signal, shown in (b), gives enhancement of its geminal partner (expected) and importantly, enhancement of the C₃-H signal. The reverse experiment shown in (c) gives some enhancement on CH₃ resonance signals and a huge enhancement of C₄-H₈. From these experiments, it was concluded that the CH₃ group is on the same side as C₃-H i.e., trans to OMs. The last experiments e.g., (d) and others that are not shown, confirmed this assignment. Consequently, the absolute configuration of tetrahydrofuran 190 was concluded to be (2S, 3R, 5S), since the configuration at C₅ was known from the starting material.
Figure 13.
The reasons for the observed stereochemical outcome are not entirely understood but the observations seem to conform to a pattern that can be rationalised by assuming conformers 201 - 203 operate for substrates 138b 140a and 141a respectively.

The conformers 202 and 203 also apply to compounds 144a and 136a. These conformers are characterised by the following features.

(i) A chair conformation in which the double bond is an integral part of the framework.

(ii) The hydroxyl group is always eclipsed with the double bond i.e., OH-in-plane conformer.

(iii) Absence of 1,3-diaxial nonbonding interaction, particularly between the ester functional group and the methyl or benzyl substituents. In all the conformers the methyl or benzyl substituents assume an equatorial position. In this manner, 1,3-diaxial
interactions are avoided.

The latter is invoked to explain the lack of reactivity of the opposite isomers of these substrates. For example, 203 represents the reactive conformer for anti isomer of 141a. The corresponding syn isomer cannot assume a similar conformation since it is energetically unfavourable due to increased 1,3-diaxial strain e.g., 204.

Characteristic features (i) and (ii) are invoked to explain the common 1,2-syn relative configuration between CH₂I and the OH group. In all three conformers 201 - 203, conformational preference to position the hydroxyl group syn to the halogen presumably arises because of stabilising interactions between the developing charge and the oxygen lone pairs as shown. This is in accord with the observation of Chamberlin et al.²¹³ and the results by Yoshida's group.²¹¹ It is believed that the most stable conformation sets up the stage for thermodynamically controlled cyclisation. In accord with thermodynamic control, the relative stereochemical outcome at C₂ and C₅ is such that the more bulky groups are on the same side of the ring as in the oxonium intermediate 205 (Scheme 62).
The term 2,5-\textit{cis} used in the earlier literature\textsuperscript{204} will be inappropriate in this case since the priorities at C\textsubscript{2} are in fact in reversed order relative to C\textsubscript{5}. Moreover, this notation was used as a relative term to compare bulky groups in which the other functional group was always H.

As it is apparent from the data in Table 4, the substituents at C\textsubscript{2} and C\textsubscript{4} appear to influence the degree of diastereofacial selection (cf. entries 2 and 3 with 4 and 5).

It is not clear whether this influence is a result of steric or electronic effects.

In summary, the results show that the stereochemical outcome is directed by the energetically favourable conformation as well as steric interactions in an intermediate cyclic oxonium ion. The results are in agreement with recent findings by Reitz \textit{et al.}\textsuperscript{208} In their systems the stereochemical outcome
is directed by an allylic benzyloxy group. A similar
directing influence by an allylic hydroxy group has also
been reported by Williams et al.\textsuperscript{210}

2.4.3.5. CONCLUSIONS

This study has shown that the Baylis-Hillman reaction does
indeed involve a Michael-type addition. The resulting
Michael adduct adds to α and β-chiral β-benzyloxy aldehydes
with reasonable diastereofacial selection and the results
are in agreement with Felkin-Anh model. Iodocyclisation of
the resulting δ-benzyloxyalkylacrylates proceeds with strict
regiochemical control and high diastereoselection to form
1,2-cis-tetrahydrofurans. The mechanism of asymmetric
transfer is explained by an OH-in-plane conformer.
The 1,2-cis relative configuration and the multifunctional
nature of the tetrahydrofurans will be useful in synthesis
of polyether antibiotics.
3. EXPERIMENTAL

3.1 INSTRUMENTATION AND CHEMICALS

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were determined using Perkin-Elmer 240B and 2400 elemental analysers. NMR spectra ($^1$H 200 MHz and $^{13}$C 50 MHz) were recorded on a Gemini 200 instrument, and unless specified to the contrary, CDCl$_3$ was used as a solvent and TMS as internal standard. Mass spectra were recorded on a Hewlett-Packard gas chromatographic-mass spectrometer (HP5988A) and a Varian high-resolution spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Infra-red were recorded on a Perkin-Elmer 1420 spectrophotometer. Kieselgel 60 F$_{254}$ Merck plastic sheets were used for thin layer chromatography. Preparative column chromatography was performed using the technique of Still et al. on Merck silica gel 60 (230-400 mesh). Solvents were dried using standard techniques and were distilled before use. Low temperatures were maintained using CO$_2$-solvent baths according to the procedure of Phipps and Hume. Diastereomeric excesses were determined either by NMR spectroscopy or gas chromatographic-mass spectrometry while enantiomeric excesses were determined by $^1$H NMR using Eu(hfc)$_3$ shift reagent. Chemical shifts for NMR spectroscopy denote those of the major diastereomers. Where applicable, shifts of the minor diastereoisomer are denoted in square brackets.
2-Formylphenyl acrylate (80)

To a mixture of salicylaldehyde (10 g, 0.082 mol) and potassium carbonate (22 g, 0.160 mol) at 0°C was added acryloyl chloride (7.5 g, 0.083 mol) dropwise. The mixture was allowed to stir at 0°C for 1 h. The suspended potassium salts were filtered and the filtrate washed with brine. Evaporation of the solvent afforded the acrylate 80 (13.5 g, 92%). This product polymerised on standing. Consequently, it was used without isolation from the mother liquor, δH 6.03 – 6.71 ppm (3H, m, CH2=CHCO), 7.19 – 7.90 (4H, m, Ar H’s) and 10.12 (1H, s, CHO); δC 123.7, 126.8, 127.4, 130.7 and 135.7 ppm (5d, Ar C’s and vinyl CH), 134.1 (t, CH2) and 189.0 (d, CHO); m/z (EI) (%) 176 (M+, 3), 121 (100), 104 (6), 93(18),

3-N(1,4-diazabicyclo-2,2,2-octyl)methyl coumarin chloride (82)

A solution of o-formylphenyl acrylate (80), (8.8 g, 0.05 mol) in anhydrous dichloromethane (100 ml) was treated with DABCO (5.6 g, 0.05 mol) at -10°C. After 2.5 h, a yellow precipitate had formed. The precipitate was filtered off, washed with dichloromethane and recrystallised from methanol/dichloromethane to afford 82 as colourless needles (11.9 g, 78%). [Found: M+-HCl, 270.1349. C16H18N2O2 requires
270.1368]; m.p. 250°C (decomp); δ_H (CD_3OD) 3.22 - 3.35 ppm (6H, m, (CH_2)_3N^+), 3.56 - 3.64 (6H, m, (CH_2)_3N, 4.54 (2H, s, -CH_2N^+), 7.40 - 7.50 and 7.71 - 7.85 (4H, 2m, Ar H's) and 8.52 (1H, s, 4-H); δ_C (CD_3OD) 46.5 (t, NCH_2CH_2N^+), 54.1 (t, +NCH_2CH_2N), 64.1 (t, CCH_2N), 117.9, 126.6, 131.0, 135.4, 153.07 (d, Ar CH's and 4-C), 116.8, 120.3 (s, 2 x Ar C and 3-C) 163.3 (s, C=O); m/z (EI)(%) 270 (M^+-HCl, 40), 194(50) and 159 (100).

3-Methanolcoumarin 88

![Structure](image)

The filtrate from the above experiment was washed successively with dilute HCl, dilute NaHCO_3 and brine. Evaporation of solvent under reduced pressure afforded 88 (0.88 g, 10%); (Found C 68.16, H 4.49. C_{10}H_{10}O_3 requires C 68.18, H 4.58); m.p. 285°C; δ_H (CD_3COCD_3) 4.96 ppm (2H, s, CH_2O), 6.83 - 7.32 (4H, m, Ar H's) and 7.5 (1H, s, CH=C); δ_C 65.1 ppm (t, CH_2), 116.7 (d, CH=), 122.6, 129.9, 132.7, and 133.8 (d, Ar CH's), 121.9 (s, C=CH), 123.9 and 156.0 (s, Ar C's), 165.8 (s, C=O); m/z (EI) (%) 176 (M^+, 28), 131 (100), 103 (14), 77 (25) 51 (16).
o-Benzyl oxybenzaldehyde (90)

\[
\begin{align*}
\text{OCH}_2\text{Ph} & \quad \text{MF} \quad \text{C}_{14}\text{H}_{12}\text{O}_2 \\
\text{CHO} & \quad \text{MW} \quad 212
\end{align*}
\]

A mixture of salicylaldehyde (5 g, 0.041 mol), benzyl bromide (7 g, 0.041 mol) and 2 equivalents of potassium carbonate were stirred at room temperature for 1 h. The mixture was filtered and washed with dilute HCl and brine. Evaporation of the solvent followed by chromatography afforded 90 as white powder (7.9, 90%); m.p. 36°C; \( \delta_H 5.14 \) ppm (2H, s, \( \text{CH}_2\text{Ph} \)), 6.95 - 7.86 (9H, m, \( \text{Ar H's} \)) and 10.54 (1H, s, \( \text{CHO} \)); \( \delta_C 70.55 \) ppm (t, \( \text{CH}_2\text{Ph} \)), 113.3, 121.3, 127.6, 128.6, 128.7, 129.1 and 136.3 (d, \( \text{Ar CH's} \)) and 190.2 (d, \( \text{CHO} \)); \( m/z(\text{EI}) (\%) \) 212 (\( M^+ \), 4), 183 (6), 121 (12%) and 91 (100).

Methyl 3-(2-benzyl oxyphenyl)-3-hydroxy-2-methylene propanoate (91)

\[
\begin{align*}
\text{OCH}_2\text{Ph} & \quad \text{MF} \quad \text{C}_{16}\text{H}_{18}\text{O}_4 \\
\text{CO}_2\text{Me} & \quad \text{MW} \quad 298
\end{align*}
\]

Ortho-benzyl oxybenzaldehyde (90) (2.0 g, 9.43 mmol) was added to a solution of DABCO (0.75 g, 6.7 mmol) in methyl acrylate (0.69 g, 8.0 mmol). After 12 days the mixture was diluted with \( \text{CH}_2\text{Cl}_2 \) and washed successively with dilute HCl and aqueous \( \text{NaHCO}_3 \). Removal of the solvent afforded 91 (1.89 g) 90%, as a yellow oil. It was further purified on silica gel using ethyl acetate/hexane (1:9); \( \delta_H 3.66 \) ppm (1H, br s, \( \text{OH} \)), 3.67 (3H, s, \( \text{OCH}_3 \)), 5.04 (2H, s, \( \text{OCH}_2\text{Ph} \)), 5.68 and
6.26 (2H, m, =CH₂), 5.93 (1H, s, CHOH), 6.88 - 6.99, 7.18 - 7.41 (10H, m, Ar H's); δc 52.0 ppm (t, OCH₃), 68.4 (d, CHOH), 70.3 (t, OCH₂Ph), 126.2 (t, =CH₂), 111.8, 120.9, 127.3, 127.7, 128.1, 128.4, 129, and 129.2 (d, Ar CH's), 136.7, 141.4, 155.7 (d, Ar H's), 167.0 (s, C=O); m/z (EI) (%): 298 (M⁺, 0.5), 175 (30), 131 (20) and 91 (100).

*Methyl 3-(2-Benzylloxyphenyl)-3-hydroxy-2-N,N-dimethylaminomethylbutanoate (93a)*

A solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate (91) (1.5 g, 5.0 mmol) in ether (10 ml) was added to a cooled (0°C) solution of an excess dimethylamine (40%) in water, 6 mmol). After 12 h at room temperature the aqueous layer was separated, the organic layer dried and chromatographed (9:1 hexane:ethyl acetate) to give an oil (1.65 g) 96%; Found C, 69.8; H 7.6; N 4.0; C₂₀H₂₅NO₄ requires C, 69.9; H, 7.3; N, 4.1); δh 2.23 ppm (6H, s, 2 x CH₃), 2.66 (1Ha, dd, CH₃NMe₂), 2.91 (1H, dd, CH₂NMe₂), 3.19 (1H, dt, J 8.0 Hz, CHCH₂NMe), 3.42 (3H, s, OCH₃), 5.07 (2H, pseudo d, OCH₂Ph), 5.30 (1H, br s, OH), 5.35 (1H, d, J 7.69 Hz, CHOCH) and 6.88 - 7.49 (9H, m, Ar H's); δc 45.6 ppm (q, N(CH₃)₂), 48.5 (d, CHCH₂NMe₂), 51.6 (q, CH₃), 60.4 (t, CH₂N), 70.4 (t, OCH₂Ph), 73.0 (d, CHOCH), 111.9, 121.3 127.7, 128.2, 128.7, 128.8 and 129.1 (d, Ar CH's), 130.3, 137.0 and 155.8 (s, Ar C's), 172.8 (s, C=O).
3-N,N-dimethylaminomethyl coumarin (94a)

![Structure diagram]

A mixture of methyl 3-\((o\text{-benzyloxyphenyl})\)-3-hydroxy-2-N,N-dimethylbetanoate (93a) (2.5 g, 7.3 mmol) and a catalytic amount of pre-equilibrited palladium (19% on charcoal) in 95% ethanol (40 ml) was hydrogenated at room temperature and atmospheric pressure. Hydrogen absorption ceased after the uptake of 1 equivalent of hydrogen. The mixture was filtered and the filtrate evaporated at reduced pressure to afford 94a as a yellow oil (1.46 g, 99%); (Found: \(M^+\) 203.0946. C\(_{12}\)H\(_{13}\)NO\(_2\) requires 203.0932); \(\delta_H\) 2.4 ppm (6H, s, N(CH\(_3\))\(_2\)), 3.5 (2H, d, \(J\) 1.3 Hz, CH\(_2\)N), 7.3 - 7.6 (4H, m, Ar H's), 7.8 (1H, s, CH=C); \(\delta_C\) 45.5 (q, N(CH\(_3\))\(_2\)), 57.7 (t, CH\(_2\)N), 116.4, 124.4, 127.7 and 131.1 (d, Ar CH's), 140.7 (d, CH=C), 119.3 (s, =CCO), 125.9, 153.1 (s, Ar C's) 161.4 (s, C=O); \(m/z\) (EI) (%) 203 (\(M^+\), 13), 188 (\(M^+\)-15, 100), 159 (33), 131 (32), 115 (1), 77 (30).

**Yeast Reduction of Ethyl Acetoacetate**

\((S)-(+)\)-Ethyl 3-hydroxybutyrate (97)

![Structure diagram]

To a solution of sugar (300 g) in 1500 ml tap water, baker’s yeast (200 g) was added and the solution was left to stir at 30°C. After 1 h had elapsed, ethyl acetoacetate (20 g, 154 mmol) was added and stirring was continued for 24 h. A warm solution of sugar (200 g in 1000 ml tap water) was added.
After 1 h had elapsed a second portion of ethyl acetoacetate (20 g, 154 mmol) was added. The mixture was allowed to stir for seven days. The mixture was filtered under vacuum using celite. The filtrate was saturated with sodium chloride and extracted with ether. The ether extracts were dried with magnesium sulfate. The ether was removed by evaporation. Fractional distillation of the residue to afford the \( \beta \)-hydroxy ester 97 (30 g, 70%) as a colourless oil, b.p. 77 -78 °C/15-20 mm Hg (lit., \( \beta \)-71 - 73/12 mm Hg); [\( \alpha \)]\( \text{D} \)\( ^{25} \) 30.6° (c 1.003 CHCl\(_3 \)); \( \delta \)\( _H \) 1.15 ppm (3H, c, CHCH\(_3 \)), 1.28 (3H, t, CHCH\(_3 \)), 2.35 (2H, d, CHCH\(_2\)CO), 3.15 (1H, s, OH); 4.05 (2H, q, OCH\(_2\)CH\(_3\)) and 4.15 (1H, m, CHCH\(_3\)); \( \delta \)\( _C \) 14.23 ppm (q, OCH\(_2\)CH\(_3\)), 22.63 (q, CHCH\(_3\)), 43.20 (\( \tau \), CHCH\(_2\)CO), 60.86 (t, OCH\(_2\)CH\(_3\)), 64.52 (d, CHCH\(_3\)) and 173.36 (s, C-O); \( m/z \) (EI) (%): 131 (M\(^+\)-H, 3), 117 (76), 88 (100), 71 (69) and 45 (39).

**Transesterification of Ethyl Acetoacetate**

**Methyl Acetoacetate (98)**

\[
\begin{align*}
\text{CH}_3 & \quad \text{CO}_2\text{Me} \\
\text{98} & \quad \text{MF C}_5\text{H}_8\text{O}_3 \\
& \quad \text{MW 116}
\end{align*}
\]

Sodium hydride (0.74 g, 0.031 mol) was dissolved in dry methanol (200 ml) under nitrogen atmosphere at room temperature. The solution was cooled to 0°C and ethyl acetoacetate (40 g, 0.308 mol) was added dropwise and the solution refluxed for 1 h. It was then cooled to room temperature and treated with water (1 ml). The solvent was removed under vacuum and the residue taken up in ether. The ether solution was washed with dilute HCl, 5% NaHCO\(_3\), and brine. Removal of the solvent afforded 98 (34.5 g, 96%); \( \delta \)\( _H \) 2.28 ppm (3H, s, CH\(_3\)CO), 3.49 (2H, s, CH\(_2\)C) and 3.74 (3H, s, OCH\(_3\)); \( \delta \)\( _C \) 30.2 (q, CH\(_3\)CO), 49.8 (\( \tau \), CH\(_2\)), 52.33 (q, OCH\(_3\)), 167.7 (s, COOCH\(_3\)) and 200.7 (s, CH\(_3\)CO).
Hydrogenation of Methyl Acetoacetate

(R)-(−)-Methyl 3-hydroxybutyrate (99)

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{Me} \\
\text{CH}_3 & \quad 99
\end{align*}
\]

To a reddish solution of \(\text{Ru}((\text{OCOCH}_3)_2[(R)\text{-binap}]\) \{prepared by treatment of \([\text{Ru(cod)}\text{Cl}_2]_n\) with BINAP and triethylamine and the silver acetate\} (201 mg, 0.239 mmol) in degassed \(\text{CH}_2\text{Cl}_2\) (10 ml) was added 1.42N HCl in 90% methanol (0.35 ml, 0.5 mmol). After the resulting dark red solution was stirred at 23°C for 1 h, the solvent was removed under reduced pressure to give \(\text{RuCl}_2[(R)\text{-binap}]\) (160 mg) as a reddish brown catalyst.

A solution of 98 (20 g, 0.172 mol) in degassed anhydrous methanol (30 ml) was degassed by 3-freeze-thaw cycles and placed in a stainless steel autoclave containing a solution of the \(\text{RU-BINAP}\) catalyst (80 mg) in degassed methanol (30 ml). Hydrogen was pressurised to 70 atm and the solution was stirred at 30 - 50°C for 36 h. The solvent was removed under reduced pressure and the residue distilled to give 99 (19.5 g, 96%); b.p. 40°C (2 mmHg) \([\alpha]_D\text{-21.65° (neat)}\) \{lit.,15°\([\alpha]_D\text{-23° (neat)}\)\}; \(\delta_H\) 1.23 ppm (3H, d, \(J\,6.3\ Hz\), \(CH_3\text{CH}\)), 2.45 - 2.49 (2H, m, \(CH_2\text{CO}\)), 3.38 (1H, s, OH), 3.71 (3H, s, \(OCH_3\)) and 4.16 - 4.26 (1H, m, \(CH_3\text{CH}\)); \(\delta_C\) 22.6 ppm (q, \(CH_3\text{CH}\)), 42.9 (t, \(CH_2\text{CO}\)), 51.7 (q, \(OCH_3\)), 64.3 (d, \(CHO\)) and 173.2 (s, \(C=O\)). \(m/z(\text{EI})\) (%) 118 \((M^+, 0.3), 117 (40), 88 (49), 71 (50), 59 (48) and 43 (100).
General Procedure 1.

Benzyl protection of β-hydroxy esters

To a solution of the β-hydroxy ester (112 mmol) and benzyl bromide (20.9 g, 122 mmol) in anhydrous ether (100 ml), portions of freshly prepared silver oxide (34.0 g, 0.147 mol) were added so as to maintain gentle reflux. When the addition was complete, the mixture was refluxed for a further 30 min. The solid material was removed by filtration and washed with ether. The ether was evaporated and the residue purified by chromatography (hexane:EtOAc, 9:1) to give the benzyl ethers.

Ethyl (S)-3-benzyloxybutyrate (102)

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{Bn} \\
\text{CO}_2\text{Et} & \\
\text{102}
\end{align*}
\]

Yield (13.4 g, 54%); δH 1.19 ppm (3H, t, J 7.1 Hz, OCH₂CH₃); 1.85 (3H, d, J 7.1 Hz, CHCH₃), 3.68 (2H, s, CH₂Ph), 4.12 (3H and 1H, q and m, J 7.1 Hz for q, OCH₂CH₃ and CHCH₃ overlap) and 7.2 (5H, m, Ar H’s). According to the ¹H NMR spectra, the product was contaminated with 5 - 7% dibenzyl ether. Nevertheless the product was used without further purification in the next step.
Methyl (R)-benzyloxybutyrate (103)

Yield 11.6 g (56%); [α]D -63.69° (c 1.127 CDCl3); δH 1.25 ppm (3H, d, J 6.2 Hz, CH3CH), 2.42 (1H, dd, J 5.7 and 16 Hz, CHaCO), 2.65 (1H, dd, J 7.2 and 16 Hz, CHbCO), 3.66 (3H, s, OCH3), 3.95 - 4.05 (1H, q, CHCH3), 4.52 (2H, 2 x pseudo d, OCH2Ph) and 7.24 - 7.43 (5H, m, Ar H's); δH 19.8 ppm (q, CH3CH), 41.8 (t, CH2CO), 51.6 (q, OCH3), 70.8 (t, OCH2Ph), 71.9 (d, CHCH3), 127.6, 127.6, and 128.30 (3 x d, Ar H's), 138.43 (s, Ar quarternary C) and 171.9 (s, C=O). m/z (EI) (%) 208 (M+, 3), 177 (37), 149 (65), 91 (100) and 59 (39); No satisfactory analysis was obtained.

Methyl (R)-2-benzyloxy-3-methylpropionate (104)

Yield 18.6 g (80%); b.p. 110°C/0.5 mm Hg; [α]D -15° (c 1.36 CHCl3) δH 1.17 ppm (3H, d, J 7.1 Hz, CHCH3), 2.73 - 2.83 (1H, m, CHCH3), 3.48 (1H, dd, J 5.7/9.1 Hz, CHaOCH2Ph), 3.65 (1H, dd, J 7.3 and 9.1 Hz, CHbOCH2Ph), 3.67 (3H, s, OCH3), 4.55 (2H, s, OCH2Ph) and 7.25 - 7.37 (5H, m, Ar H's); δC 14.00 ppm (q, CHCH3), 40.27 (d, CHCH3), 51.83 (q, OCH3), 72.13 (t, OCH2Ph), 72.26 (t, CH2OCH2Ph), 127.91, 128.12 and 128.70 (d, Ar CH's), 138.66 (s, Ar quarternary C); m/z (EI) (%) 208 (0.6), 177 (16), 149 (23), 117 (33), 91 (100), 59 (30) and 44 (55). No satisfactory elemental analysis was obtained.
Methyl (S)-3-benzyloxy-2-methylpropionate (105)

\[
\text{\begin{tikzpicture}
  \node (a) at (0,0) {\text{CO}_2\text{Me}};
  \node (b) at (1,0) {\text{CH}_3};
  \node (c) at (2,0) {105};
  \node (d) at (3,0) {\text{BnO}};
  \draw (a) -- (b);
  \draw (b) -- (c);
  \draw (c) -- (d);
\end{tikzpicture}}
\]

MF C\textsubscript{12}H\textsubscript{16}O\textsubscript{3}

MW 208

Yield 20.0 g (86%) (pure by \textsuperscript{1}H NMR and GC/MS); \([\alpha]_D^{25} +11.3^\circ \) (c 1.54 CHCl\textsubscript{3}); \(\delta_H\) 1.17 ppm (3H, d, J 7 Hz, CHCH\textsubscript{3}), 2.73 - 2.83 (1H, m, CHCH\textsubscript{3}), 3.48 (1H, dd, J 5.8/9.0 Hz, CH\textsuperscript{a}OCH\textsubscript{2}Ph), 3.64 (1H, dd, J 7.4/9.1 Hz, CH\textsuperscript{b}OCH\textsubscript{2}Ph), 3.67 (3H, s, OCH\textsubscript{3}), 4.51 (2H, s, OCH\textsubscript{2}Ph) and 7.25 - 7.34 (5H, m, Ar H's); \(\delta_C\) 13.96 ppm (q, CHCH\textsubscript{3}), 40.16 (d, CHCH\textsubscript{3}), 51.68 (q, OCH\textsubscript{3}), 71.93 (t, CH\textsubscript{2}OBn), 73.06 (t, PhCH\textsubscript{2}C), 127.55, 127.58 and 128.33 (d, Ar CH's), 138.15 (s, Ar quarternary C) and 175.25 (s, CO\textsubscript{2}Me); \(m/z\) (EI) (%): 208 (0.6), 177 (16), (23), 117 (33), 91 (100), 59 (30) and 44 (55). No satisfactory elemental analysis was obtained.

General Procedure 2.

Reduction of \(\beta\)-benzyloxy esters

To a stirred suspension of LiAlH\textsubscript{4} (1.2 g, 32.4mmol) in anhydrous ether (40 ml), a concentrated ethereal solution of the ester was added dropwise to maintain gentle reflux. When the addition was complete, the mixture was refluxed for 45 min. Water (1.2 ml), 12% NaOH (1.2 ml) and water (1.3 ml) were added successively at 0°C. The reaction mixture turned white. The lithium salts were filtered, dried and dissolved in a minimum volume of 2N H\textsubscript{2}SO\textsubscript{4}. The solution was extracted with ether and washed with brine. The ether extract was dried (MgSO\textsubscript{4}) and evaporated to dryness. The alcohols were purified by distillation or chromatography.
(S)-3-Benzylxybutanol (106)

Prepared as described in GP 2 to give (4.5 g, 90%); b.p. 99 - 101°C/0.3 mm Hg; [α]D 25°+57.5° (c 1.304 CHCl₃); δH 1.25 ppm (3H, d, CH₃), 1.71 - 1.81 (2H, dd, CH₂CH₂CH₂), 2.83 (1H, s, OH), 3.70 - 3.82 (1H and 2H, m and t, CH₃CH₃ and CH₂OH overlap), 4.52 (2H, 2 x pseudo d, CH₂Ph), and 7.28 - 7.36 (5H, m, Ar H's); δC 19.44 ppm (q, CH₃CH₃), 38.94 (t, CH₃CH₂CH₂), 60.54 (d, CH₃CH₃), 70.62 (t, CH₂OH), 74.61 (t, CH₂Ph), 128.02, 128.08 and 128.82 (3 x d, Ar CH's) and 138.82 (s, Ar quarternary C); m/z (EI) (%) 180 (M⁺, 4), 162 (13), 107 (56) and 91 (100).

(R)-3-Benzylxybutanol (107)

Prepared as described in GP 2. Yield 94% (purified by chromatography to obtain a colourless oil); [α] -63° (c 1.24 CHCl₃) δH 1.24 ppm (3H, d, J 6.1 Hz, CH₃CH), 1.71 - 1.81 (2H, m, CH₃CH₂CH₂), 2.74 (1H, br s, OH), 3.70 - 3.82 (2H, m, CH₂OH), 4.52 (2H, 2 x pseudo d, OCH₂Ph) and 7.28 - 7.36 (5H, m, Ar H's); δH 19.4 ppm (q, CH₃CH₃), 38.8 (t, CH₂CH₂CH₂), 60.7 (t, CH₂OH), 70.4 (t, OCH₂Ph), 74.5 (d, CH₂OBn), 127.7, 127.7 and 128.5 (3 x d, Ar H's) and 138.4 (s, Ar quarternary C). m/z (EI) (%) 180 (M⁺, 1), 118 (1), 107 (39), 91 (100), 79 (12), 65 (15) and 43 (9).
(S)-3-Benzyl oxy-2-methylpropanol (108)

Prepared as described in GP 2. Yield 92% (as colourless oil); \([\alpha]_D^{25} -17.06^\circ (c 3.247) \delta H 0.87 ppm (3H, d, J 6.8 Hz, CHCH₃), 2.00 (1H, m, CHCH₃), 3.00 (1H, br. s, OH), 3.36 - 3.52 (2H, m, OCH₂CH₂), 3.55 (2H, d, J 6.0 Hz, CHCH₂OH), 4.48 (2H, s, PhCH₂O) and 7.22 - 7.34 (5H, m, Ar H's); \(\delta_c\) 13.55 ppm (q, CHCH₃), 67.10 (t, CH₂OH), 73.25 (t, OCH₂CH₂), 74.86 (t, CH₂Ph), 127.54 and 127.63 (3 x d, Ar CH's) and 138.09 (s, Ar quarternary C); m/z(EI) (%) 180 (M⁺, 0.01), 118 (2), 107 (39), 91 (100), 79 (12), 65 (15) and 43 (9).

(R)-3-Benzyl oxy-2-methylpropanol (109)

Following GP 2, the title compound was obtained as a colourless oil. Yield 95%; \([\alpha]_D^{25} +11.06^\circ (c 1.54 \text{ CHCl}_3); \delta H 0.88 ppm (3H, d, J 7.0 Hz, CHCH₃), 1.99 - 2.08 (1H, m, CHCH₃), 2.93 (1H, br. s, OH), 3.36 - 3.49 (2H, m, CH₂OBn), 3.49 - 3.59 (2H, m, CH₂OH), 4.49 (2H, s, CH₂Ph) and 7.23 - 7.35 (5H, m, Ar CH's); \(\delta_c\) 13.59 (q, CHCH₃), 35.75 (d, CHCH₃), 67.41 (d, CNOH), 73.49 (t, CH₂Ph), 75.17 (t, CH₂OBn), 127.94, 128.02 and 128.78 (3 x d, Ar CH's) and 138.50 (s, Ar quarternary C); m/z(EI) (%) 180 (M⁺, 5), 161 (4), 120 (4), 107 (67), 91 (100), 77 (20) and 65 (31). No satisfactory elemental analysis was obtained.
General Procedure 3

Oxidation of alcohols

Oxidation of alcohols was effected by the method of Swern. Thus a solution of oxalyl chloride (2.37 g, 18.7 mmol, 1.1 equiv) in \( \text{CH}_2\text{Cl}_2 \) (30 ml) was stirred mechanically and cooled to -62°C in a dry ice-acetone bath. Dimethyl sulfoxide (2.92 g, 37.4 mmol, 2.2 equiv) in \( \text{CH}_2\text{Cl}_2 \) (6 ml) was added dropwise. After 4 minutes, the solution of the alcohol (16.7 mmol) in \( \text{CH}_2\text{Cl}_2 \) (10 ml) was added dropwise. After 40 minutes triethylamine (7.91 g, 78.7 mmol, 4.6 equiv) was added dropwise. The solution was allowed to warm to room temperature and diluted with distilled water (30 ml). The organic layer was washed with 5% aqueous HCl (50 ml) and saturated NaHCO\(_3\) (50 ml), dried and filtered. Evaporation of the solvent gave the crude aldehyde as a residual oil. No satisfactory elemental analyses were obtained for all the aldehydes.

\((S)-3\text{-benzyloxybutyraldehyde (110)}\)

Oxidation of 106 (3.01 g, 16.7 mmol) as described in GP 3 afforded 110 (2.68 g, 90%), \([\alpha]_D^{25} +33.5^\circ\) (c 1.643 CHCl\(_3\)); \(\delta^c\) 1.27 ppm (3H, d, CHCH\(_3\)), 2.57 (2H, dd, J 1.8/14.6 Hz, CH\(_2\)CHO), 4.04 (1H, m, CHCH\(_3\)), 4.52 (2H, 2 pseudo d, OCH\(_2\)), 7.35 (5H, m, Ar CH's) and 9.70 (1H, t, J 1.8 Hz, CHO); \(\delta^c\) 19.81 (q, CHCH\(_3\)), 50.59 (t, CH\(_2\)CO), 70.41 (d, CHCH\(_3\)), 70.75 (t, CH\(_2\)Ph), 128.02 and 128.76 (3 x d, Ar CH's), 138.63 (s,
Ar quarternary C) and 201.97 (d, CHO); m/z(EI) (%) 178 (M⁺, 3), 107 (74), 91 (100) and 79 (26).

(R)-Benzylloxybutyraldehyde (111)

Prepared as described in GP 3. The alcohol 107 (3.01 g, 16.7 mmol) afforded 2.4 g of 111 (80%) as a light yellow oil, [α]D²⁵ -18.8°(c 2.987 CHCl₃); δH 1.30 ppm (3H, d, J 6.2 Hz, CH₃CH), 2.43 - 2.77 (2H, m, CH₂CHO), 4.04 - 4.13 (1H, m, CHCH₃), 4.54 (2H, 2 x d pseudo d, CCH₂Ph), 7.26 - 7.36 (5H, m, Ar H's), 9.79 (1H, t, J 2.5 Hz, CHO); δC 19.8 (q, CH₃), 50.5 (t, CH₂CHO), 70.2 (d, CHCH₃), 70.6 (t, OCH₂Ph), 127.7, 128.4 (2 x d, Ar CH's) and 201.5 (d, CHO). m/z (EI) (%) 178 (M⁺, 0.1), 108 (14), 91 (100) and 79 (36).

(R)-Benzylloxy-2-methylproprionaldehyde (112)

Prepared as described in GP 3. Thus 108 (3.01 g, 16.7 mmol), afforded 112 2.02 g (68%) as a colourless oil, [α]D²⁵ -21.1° (c 1.888 CHCl₃); δH 1.11 ppm (3H, d, J 7.1 Hz, CHCH₃), 2.59 - 2.69 (1H, m, CHCH₃), 3.57 - 3.68 (2H, m, CH₂OBn), 4.51 (2H, s, OCH₂Ph), 7.24 - 7.38 (5H, m, Ar CH's) and 9.71 (1H, d, J 1.6 Hz, CHO); δC 10.69 (q, CHCH₃), 46.88 (d, CHCH₃), 70.24 (t, OCH₂Ph), 73.44 (t, CH₂OBn), 127.94, 128.07 and 128.77 (3 x d, Ar CH's) and 204.43 (d, CHO); m/z(EI) (%) 178 (M⁺,
0.1), 107 (50), 91 (100), 87 (22).

\[(S)-\text{Benzyloxy-2-methylproprionaldehyde (113)}\]

Prepared as described in GP 3. Thus 109 (3.01 g, 16.7 mmol) gave 2.08 g (70%) of 113 as a colourless oil, \([\alpha]_D^{25} +23.9^\circ\) (c 3.61 CHCl₃); δH 1.10 ppm (3H, d, J 7.0 Hz, CHCH₃), 2.58 - 2.69 (1H, m, CHCH₃), 3.64 (2H, dd, J 1.2/5.9 Hz, OCH₂CH), 4.50 (2H, s, CH₂Ph), 7.24 - 7.37 (5H, m, Ar CH's) and 9.70 (1H, d, J 1.6 Hz, CHCHO); δC 10.66 (q, CHCH₃), 46.75 (d, CHCH₃), 70.04 (t, CH₂OBn), 73.21 (t, CH₂Ph), 127.55, 127.68 and 128.38 (3 x d, Ar CH's), 137.90 (s, Ar quarternary C) and 206.01 (d, CHO); m/z(EI) (%) 178 \((M^+, 0.1), 107 (50), 91 (100), 87 (22)\).

**General Procedure 4**

**Esterification of acids**

A mixture of acid (0.746 mol) and Dowex 50 W-X8 H⁺-ion exchange resin (7 g) in MeOH (110 ml) and CHCl₃ (160 ml) was heated under reflux through a Soxhlet thimble containing MgSO₄ (80 g). The drying agent was replaced twice during the reflux period of 14 h. The solution was filtered, the solvents were removed and the residue was distilled to give a colourless oily liquid.
Dimethyl (S)-malate (114)

Prepared as in GP 4. Thus, malic acid (50 g, 0.37 mol) was converted to 114 in 90% yield (54 g), $[\alpha]_D^{25} -26^\circ$ (neat) (Lit., $-29^\circ$ (neat)); $\delta$H 2.81 - 2.86 ppm (2H, m, CH$_2$CO$_2$Me), 3.58 (1H, s, OH), 3.72 (3H, s, OCH$_3$), 3.81 (3H, s OCH$_3$) and 4.54 (1H, m, CHO); $\delta$C 38.7 ppm (t, CH$_2$CO), 52.2 (q, OCH$_3$), 52.9 (q, OCH$_3$), 67.5 (d, CHO), 171.7 and 174.3 (2 x s, 2 x OCH$_3$); m/z (EI) 162 (M$^+$, 0.03), 159 (52), 101 (22), 99 (100) and 85 (38).

(S)-1,2,4-Butanetriol (115)

(S)-(−)-Dimethyl malate (25.9 g, 0.154 mol), dissolved in dry THF (30 ml), was added dropwise to a suspension of LiAlH$_4$ (21.0 g, 0.55 mol) in dry THF (1000 ml) and refluxed overnight. Addition of water (160 ml) gave a white precipitate, which was filtered and washed with four 130 ml portions of dry EtOH. The combined solution was evaporated to near dryness in vacuo. The inorganic material contained in the residual oil was removed by short column chromatography over 50 g of silica gel [elution with 560 ml (3:1 v/v) and 670 ml (2:1 v/v) of CHCl$_3$-EtOH]. Removal of solvent gave about 12 g (74%) of a yellow oil, indicated to be slightly impure by $^1$HNMR. This oil was submitted to fractional distillation to give a colourless oil (7.8 g, 48%
- 50%); (lit.,\textsuperscript{161} b.p. 145 -148 °C (1.4 mm Hg); δ\textsubscript{H}(C\textsubscript{5}D\textsubscript{5}N) 0.66 - 0.85 ppm (2H, m, CH\textsubscript{2}CH\textsubscript{2}OH), 2.60 (2H, d, J 5.5, OHCH\textsubscript{2}CH), 2.74 - 2.83 (2H, m, CH\textsubscript{2}CH\textsubscript{2}OH), 2.96 - 3.08 (1H, m, CHO\textsubscript{H}) and 4.87 (3H, s, 3 x CH); δ\textsubscript{C}(C\textsubscript{5}D\textsubscript{5}N) 37.9 (t, CH\textsubscript{2}CH\textsubscript{2}OH), 60.1 (t, CH\textsubscript{2}CH\textsubscript{2}OH), 67.9 (t, CHCH\textsubscript{2}OH) and 71.1 (d, CH\textsubscript{2}CHCH\textsubscript{2}). m/z(EI) (%) 88 (M\textsuperscript{+}-18, 1), 76 (5), 75 (100), 61 (5), 57 (29) and (9).

Regioselective reduction of (S)-malic acid

Methyl (S)-3,4-dihydroxybutyrate (118)

To a solution of (S)-(\textsuperscript{-})-dimethyl malate (114) (19.4 g, .12 mol) in dry THF (250 ml) was added BMS (12.2 ml, 0.122 mol) and the mixture was stirred at 20°C for 0.5 h. Then, NaBH\textsubscript{4} (0.2 g, 6.0 mmol) was thrown into the mixture and the resulting mixture was stirred for an additional 0.5 h, followed by the addition of dry MeOH (77 ml), stirring being continued for 0.5 h. The solvent was removed by using rotary evaporator to give a colourless oil which was purified by means of column chromatography on silica gel (EtOAc), affording 118 in 88% yield (14.1 g), b.p. 105°C (0.3 mmHg) [α]\textsubscript{D}\textsuperscript{25} -22.6°(c 3.025 CHCl\textsubscript{3}); δ\textsubscript{H} 2.53 ppm (2H, d, J 5.6 Hz, CH\textsubscript{2}CO), 3.50 - 4.18 (5H, m, CH\textsubscript{2}OH, 2 x OH, CHO\textsubscript{H}) and 3.70 (3H, s, OH); δ\textsubscript{C} 37.9 ppm (t, CH\textsubscript{2}CO), 51.9 (q, OCH\textsubscript{3}), 65.7 (t, CH\textsubscript{2}OH), 68.7 (d, CHO\textsubscript{H}) and 172.7 (s, C=O); m/z(EI) (%) 134 (M\textsuperscript{+}, 0.07%), 131 (100), 101 (12) 85 (12), 71 (74) and 43 (34).
Methyl (S)-1,2-O-Isopropylidenebutyrate (119)

\[
\text{MF } \text{C}_8\text{H}_{14}\text{O}_4 \\
\text{MW 174}
\]

A mixture of methyl 3,4-dihydroxybutyrate (10.0 g, 74.6 mmol) and dimethoxypropane (8.3 g, 80.0 mmol) in acetone (100 ml) was stirred with p-toluenesulphonic acid at room temperature for 1.5 h, \( \text{NaHCO}_3 \) was suspended in the solution, and the stirring was continued for an additional 10 min. The acetone was evaporated to dryness; the residue was taken up in EtOAc and washed with aqueous solutions of \( \text{NaHCO}_3 \) and \( \text{NaCl} \) and dried over \( \text{MgSO}_4 \). After removal of the solvent, distillation of the residue gave 12.0 g (92%) of a colourless oil; b.p. 43 - 45°C (0.4 mm Hg); \( [\alpha]_D +17.4^\circ \) (c 1.68 CHCl₃); \( \delta_H \) 1.36 and 1.42 ppm (6H, 2 x s, C(CH₃)₂), 2.53 (1H, dd, J 7 and 14 Hz, \( \text{CH}^a\text{CO} \)), 2.73 (1H, dd, J 6 and 16 Hz, \( \text{CH}^b\text{CO} \)), 3.66 (1H, dd, J 6.3 and 10 Hz, \( \text{CHCH}^a\text{OCC} \)), 3.70 (3H, s, \( \text{OCH}_3 \)), 4.16 (1H, dd, J 8.3 and 6 Hz, \( \text{CHCH}^b\text{OCC} \)) and 4.14 - 4.54 (1H, m, \( \text{CH}_2\text{CH}_2 \)); \( \delta_C \) 25.5 and 26.9 ppm (2 x q, C(CH₃)₂), 38.8 (t, \( \text{CH}_2\text{COO} \)), 52.0 (q, \( \text{OCH}_3 \)), 69.3 (t, \( \text{CHCH}_2\text{O} \)), 72.3 (d, \( \text{CH}_2\text{CHO} \)) 171.1 (s, quarternary C). \( m/z(\text{EI}) \) (%) 131 (100), 101 (14), 85 (14), 71 (78), 59 (18) and 43 (41)
(S)-1,2-O-Isopropylidenebutane-1,2,4-triol (116)

(S)-1,2,4-Butanetriol (9 g, 0.085 mol) was stirred in acetone (500 ml) with p-toluenesulphonic acid at room temperature for 1.5 h, NaHCO₃ was suspended in the solution, and the stirring was continued for an additional 10 min. The acetone was evaporated to dryness; the residue was taken up in EtOAc and washed with aqueous solutions of NaHCO₃ and NaCl and dried over MgSO₄. After removal of the solvent, distillation of the residue gave 11.6 g (93%) of a colourless oil; b.p. 50°C (5 mm Hg) [lit.,¹⁶¹ b.p. 87 °C (22 mm Hg)]; [α]D +10.87° (c 1.39 CHCl₃); δH 1.37 and 1.43 ppm (6H, 2 x s, C(CH₃)₂), 1.78 - 1.87 (2H, m, CH₂CH₂OH), 2.68 (1H, br s, OH), 3.59 (1H, dd, J 7.3 and 8 Hz, CHCH₃O), 3.78 (2H, m, CH₂OH), 4.10 (1H, dd, J 8 and 6 Hz, CHCH₂O) and 4.13 - 4.31 (1H, m, CH₂CHCH₂); δC 25.7 and 26.9 ppm (2 x q, C(CH₃)₂), 35.7 (t, CH₂CH₂OH), 60.3 (t, CH₂OH), 69.5 (t, CHCH₂O), 74.9 (d, CH₂CHCH₂) and 109.0 (s, CCH₃).

(S)-O-Isopropylidenebutane-3,4-diol-1-al (117)

Swern oxidation of 116 (3 g, 0.021 mol), as described in GP 3, afforded 117 (1.87 g, 61%); b.p. 27°C (0.4 mm Hg); [α]D +15.0° (c 2.226 CHCl₃); δH 1.36 and 1.42 ppm (6H, 2 x s,
C(CH$_3$)$_2$), 2.62 -2.91 (2H, 2 x d, all spectral lines are doubled, CH$_2$CHO), 3.59 (1H, dd, J 6.7 and 8 Hz, CHCH$^4$O), 4.18 (1H, dd, J 8.3 and 6.8 Hz, CHCH$^6$O), 4.47 - 4.60 (1H, m, CH$_2$CHCH$_2$) and 9.80 (1H, t, J 1.6 Hz, CHO); $\delta_c$ 25.5 and 26.8 ppm (2 x q, C(CH$_3$)$_2$), 47.8 (t, CH$_2$CHO), 69.1 (t, CHCH$_2$O), 70.7 (d, CH$_2$CHCH$_2$), 109.2 (s, C(CH$_3$)$_2$) and 200.0 (CHO); m/z (EI) (%) 129 (70), 101 (7), 85 (12), 72(13) and 69 (100).

(S,S)-Dimethyl tartrate (120)

![Diagram of dimethyl tartrate](image)

Prepared as outlined in GP 4. Thus, esterification of tartaric acid (100 g, 0.562 mol) afforded dimethyl tartrate (120) (118.0 g, 100%), $\delta_h$ 3.83 ppm (2H, br. s, exchanges with D$_2$O, 2 x OH), 3.83 (6H, s, 2 x OCH$_3$) and 4.59 (2H, s, 2 x CHO); $\delta_c$ 53.06 (q, OCH$_3$), 72.27 (d, CHOH) and 172.05 (s, CO$_2$Me); m/z(EI) (%) 179 (M$^+$+1, 2), 147 (1), 119 (29) and 90 (100)

Dimethyl (2S,3S)-O-benzylidenebutyrate (121)

![Diagram of dimethyl (2S,3S)-O-benzylidenebutyrate](image)

A mixture of dimethyl tartrate (111.17 g, 0.62 mol), benzaldehyde (52.8 g, 0.50 mol) and a catalytic amount of p-TsOH in C$_6$H$_6$ was refluxed overnight with the removal of
water (Dean and Stark). \([\alpha]_b^{24} +26.8^\circ(c 1.786)\); m.p. 65 -66 8H 3.72 ppm (3H, s, CO$_2$CH$_3$), 3.75 (3H, s, COCH$_3$), 4.84 (1H, d, J 3.9 Hz, CHOC), 4.97 (1H, d, J 3.9 Hz, CHOC), 6.12 (1H, s, CHPh) and 7.34 - 7.59 (5H, m, Ar CH's); 8c 52.74 (q, OCH$_3$), 77.09 and 77.44 (2 x d, 2 x CH$_2$CO$_2$Me), 106.64 (d, CHPh), 127.27, 128.36 and 129.98 (3 x d, Ar CH's), 169.58 and 170.02 (2 x s, 2 x CO$_2$CH$_3$); m/z(EI) (%) 265 (M$^+$-1, 1), 207 (13), 145 (9), 105 (100), 91 (56) and 77 (26).

\[(2S,3S)-2\text{-Benzyloxy-1,3,4-butanetriol (122)}\]

LiAlH$_4$ (30.4 g, 800 mmol) was suspended in dry ether (600 ml) at -40°C under nitrogen. To the stirred mixture was added dropwise a solution of AlCl$_3$ (106.7 g, 800 mmol) in ether (360 ml) at -5 to -10°C. After the addition of CH$_2$Cl$_2$ (100 ml), a solution of dimethyl 2,3-benzylidenebutyrate (53.2 g, 0.2 mol) in CH$_2$Cl$_2$ (600 ml) was added dropwise during 45 min. to the ice cooled reaction mixture. After stirring for 1 h at room temperature the reaction mixture was refluxed for 3 h. The reaction mixture was quenched cautiously with H$_2$O (57.5 ml) and a solution of KOH (134 g) in water (224 ml) at -20°C. The acetone-dry ice bath was removed and the reaction mixture was stirred for a further period of 2 h at 30°C, until the colour of the reaction mixture is white. After filtration over celite, the filter cake was suspended in CH$_2$Cl$_2$ (500 ml), refluxed for 45 min. and filtered again. The combined filtrates were concentrated in vacuo to give 122 (27 g, 64%) as white crystals. The yield was improved to about 90% by washing the
filter cake with CH₂Cl₂ (200 ml) in a Soxhlet over 3 days. Recrystallisation from CH₂Cl₂ give an analytically pure sample, m.p. 74 - 75 °C (lit., 164 75.5 - 76.5 °C); [α]D -13.5° (c 1.147 EtOH); (Found C, 61.70, H, 7.98. C₁₁H₁₆O₄ requires C, 61.89, H, 8.09); δH (CD₃COCD₃) 3.57 ppm (9H, m, 2 x CH₂OH, CHOH, CHOBn and 3 x OH), 4.69 (2H, 2 x pseudo d, CH₂Ph), and 7.26 - 7.43 (5H, m, Ar CH's); δC 62.1 ppm (t, CH₂OH), 64.1 (t, CH₂OH), 73.4 (t, OCH₂Ph), 73.4 (d, CHOBn), 81.57 (d, CHOH), 128.6, 128.9 and 129.5 (d, Ar CH's) and 140.1 (s, Ar quarternary C); m/z (EI) (%) 212 (M⁺, 4%), 181 (4), 91 (100) and 65 (9).

3-O-Benzyl-1,2-0-isopropylidenebutane-1,2,3,4-tetrol (124)

A mixture of 2-benzyloxy-1,2,4-butane-triol (3.0 g, 0.014 mol) and dimethoxy propane (3.68 g, 0.035 mol) in acetone (100 ml) was stirred with p-toluene sulphonic acid at room temperature for 1.5 h, NaHCO₃ was suspended in the solution, and the stirring was continued for an additional 10 min. The acetone was evaporated to dryness; the residue was taken up in EtOAc and washed with aqueous solutions of NaHCO₃ and NaCl and dried over MgSO₄. After removal of the solvent, 124 3.5 g (98%) was obtained as a colourless oil; [Found C, 66.69, H, 7.47. C₁₄H₂₀O₄ requires C, 66.65, H, 7.99]; [α] D⁺⁺⁺ +15.5° (c 1.713 CHCl₃); δH 1.34 ppm (3H, s, CCH₃), 1.41 (3H, s, CCH₃), 2.89 (1H, br s, OH), 3.44 - 3.67 (3H, m, CH₂OH and CHOBn), 3.73 (1H, dd, J 8.0 and 7.2 Hz, CH₂OCCH₃), 3.95 (1H, dd, J 8.0 and 6.6 Hz, CH₂OCCH₃), 4.21 - 4.30 (1H, m, CHOCCH₃), 4.69 (2H, 2 x pseudo d, J 11.9 Hz, OCH₂Ph) and 7.22 - 7.36 (5H, m, Ar CH's); δC 25.3 and 26.4 ppm (2 x q, 2
x CH₃), 61.8 (t, CH₂OH), 65.8 (t, CH₂OCCH₃), 72.9 (t, CH₂OBn), 76.8 (d, CHOBN), 79.7 (d, CHOCCCH₃), 109.2 (s, C(CH₃)₂), 127.7, 127.8 and 128.3 (d, Ar CH's) and 138.3 (s, Ar quarternary C); m/z(EI) (%) 253 (M⁺-1, 0.4%), 227 (3), 194 (12), 163 (3), 101 (69) and 91 (100).

3,4-Di-O-benzyl-1,2-O-isopropylidenebutane-1,2,3,4-diol (125)

To a mechanically stirred suspension of NaH (1.1 g, 0.048 mol; previously washed three times with THF) in dry DMF (50 ml) was added dropwise a solution of 124 (4.93 g, 0.019 mol) in DMF (15 ml). The reaction was stirred for 10 min. and then BnBr (3.34 g, 0.019 mol) was added dropwise. Excess NaH was decomposed by addition of water. The product was extracted with CHCl₃ and dried over anhydrous MgSO₄. Evaporation of the solvent gave 6.1 g (91%) of a light yellow oil (pure by NMR). An analytical sample of 125 was obtained by chromatography eluting with hexane-EtOAc (9:1): [Found C, 73.48, H, 7.55. C₂₁H₂₆O₄ requires C, 73.66, H, 7.65]; [α]D²⁰ +2.4° (c 1.796 EtOH); δH 1.35 ppm (3H, s, OCCH₃), 1.39 (3H, s, OCCH₃), 3.56 - 3.63 (3H, m, CH₂OBn and CHOBN), 3.74 (1H, dd, J 7.4/8 Hz, CHαOCCH₃), 3.97 (1H, dd, J 6.5/10 Hz, CHβOCCH₃), 4.24 - 4.27 (1H, m, CHOCCCH₃), 4.49 (2H, 2 x pseudo d, CH₂OCH₂Ph), 4.74 (2H, 2 x pseudo d, CHOCH₂Ph) and 1.23 - 7.37 (10H, m, Ar CH's); δC 25.4 and 26.4 ppm (2 x q, 2 x CH₃), 65.8 (t, CH₂OCCH₃), 70.2 (t, CH₂OBn), 72.8 (t, OCH₂Ph), 73.4 (t, OCH₂Ph-terminal), 76.8 (d, CHOBN), 78.2 (d, CHOCCCH₃), 109.0 (s, C(CH₃)₂), 127.5, 127.6, 127.7, 127.8, 128.2 and 128.3 (10 x d, Ar CH's), 137.96 and 138.5
(2 x s, Ar quarternary C's); m/z (EI) (%) 344 (M+, 2), 284 (2), 251 (13), 193 (38) and 91 (100).

1,2-Di-O-benzylbutane-1,2,3,4-tetrol 126

Compound 125 (7 g, 0.02 mol) was dissolved in 95% EtOH (40 ml) to which water (5 ml), concentrated HCl (0.2 ml) and acid activated Amberlite CG-120 resin (6 g) were added. The reaction was stirred at room temperature and was monitored by tlc until the disappearance of 125. After filtration of the resin, the remaining acid was neutralised with a saturated solution of NaHCO₃. The reaction mixture was concentrated, the product was extracted with CH₂Cl₂ and dried over anhydrous MgSO₄. Evaporation of the solvent gave 6.14 g (87%) of 126. Analytically pure 126 was obtained by silica gel column chromatography using hexane-EtOAc (9:1) and then absolute EtOH as eluant. The product was isolated in the EtOH fraction: [Found C, 71.48, H, 7.40. C₁₈H₂₂O₄ requires C, 71.51, H, 7.33]; [α]D²² = -31.3° (c 1.977 CHCl₃) δH 2.80 ppm (1H, br s, OH), 3.08 (1H, br. s, OH), 3.60 - 3.70 (5H, m, CH₂OH, CH₂OBn and CHOBr), 3.76 - 3.77 (1H, m, CHOH), 4.52 (2H, 2 x pseudo d, OCH₂Ph terminal), 4.62 (2H, 2 x pseudo d, OCH₂Ph) and 7.22 - 7.35 (10H, m, Ar CH's); δC 63.5 ppm (t, CH₂OH), 69.4 (t, CH₂OPh), 72.0 (d, CHOH), 72.7 (t, OCH₂Ph), 73.5 (t, OCH₂Ph terminal), 78.2 (d, CHOBr), 127.7, 127.8, 127.9, 128.0 and 128.4 (10 x d, Ar CH's), 137.7 and 137.9 (2 x s, Ar quarternary C's); m/z (EI) (%) 267 (1), 212 (6), 181 (5), 107 (56), 91 (100) and 65 (20).
General Procedure 5

Oxidative Cleavage of 1,2-diols

1,2-Di-O-benzylbutane-1,2,3,4-tetroli (2.77 g, 9.17 mmol) was dissolved in CH$_2$Cl$_2$ (25 ml) and the flask was placed in a water bath at 25°C. NaIO$_4$ (3.83 g, 18.3 mmol) was added with vigorous mechanical stirring, followed by distilled water (1 ml). The reaction temperature gradually rose to about 30°C and the stirring was continued until the reaction was judged to be complete by tlc. Powdered anhydrous MgSO$_4$ (3 g) was added and stirring continued for 15 min. The reaction mixture was filtered and the cake washed with CH$_2$Cl$_2$ (2 x 10 ml). Evaporation of the solvent gave the corresponding aldehyde.

(R)-1,2-Di-O-benzylglyceraldehyde (127)

Prepared as in GP 5. Thus evaporation of the solvent gave 1.84 g (75%) of 127: [Found C, 75.61, H, 6.74. C$_{17}$H$_{18}$O$_3$ requires C, 75.51, H, 6.71]; [α]$_D$ -20° (c 2.173 CHCl$_3$) (lit.,$^{169}$+52° (c 2.0 C$_6$H$_6$); δ$_H$ 3.74 - 3.77 ppm (2H, m, CH$_2$OBn), 3.94 - 3.99 (1H, m, CHOBN), 4.53 (2H, 2 x pseudo d, OCH$_2$Ph terminal), 4.69 (2H, 2 x pseudo d, OCH$_2$Ph), 7.21 - 7.36 (10H, m, Ar CH's) and 9.70 (1H, d, J 1.2 Hz, CHO); δ$_C$ 69.1 ppm (t, CH$_2$OBn), 72.7 (t, OCH$_2$Ph), 73.4 (t, OCH$_2$Ph terminal), 82.6 (d, CHOCH$_2$Ph), 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5 and 128.6 (10 x d, Ar CH's), 137.1 and 137.5 (2 x s, Ar quarternary C's) and 202.1 (d,
CHO); \( m/z (\text{EI}) \) (%) 242 (M\(^+\)-28, 1), 181 (4), 179 (5), 164 (2), 146 (20), 107 (1), 91 (100) and 65 (17).

_Ethyl (2R,3R)-3,4-o-isopropylidene-2,3,4-trihydroxybutanoate (128)_

\[
\begin{align*}
\text{OH} & \\
\text{CO}_2\text{Et} & \\
\text{O} & \\
\text{O} & \\
\text{128}
\end{align*}
\]

MW \( \text{C}_9\text{H}_{16}\text{O}_5 \)

MW 204

A mechanically stirred solution of \( \beta \)-isoascorbic acid (200 g, 1.14 mol) in acetone (4.5 L) was treated with anhydrous CuSO\(_4\) (300 g). After the reaction was stirred at room temperature for 24 h, a second portion of CuSO\(_4\) (300 g) was added, and stirring was continued for an additional 24 h. The reaction was then filtered and concentrated, giving a near-quantitative yield of 3,4-o-isopropylidene-\( \beta \)-isoascorbic acid. The isopropylidene derivative was then dissolved in water (1.2 L) containing K\(_2\)CO\(_3\) (312 g). This solution was chilled in an ice bath and stirred while 30% H\(_2\)O\(_2\) (249 ml) was slowly added. During the addition the temperature was maintained below 28°C. The solution was stirred over night and then concentrated _in vacuo_. The moist solute was extracted with boiling absolute ethanol (6 x 500 ml). After filtration and evaporation, the salt was dried under vacuum to provide 230 g of material. Treatment of a mechanically stirred suspension of the salt with EtI (241 g) in CH\(_3\)CN (1.5 L) at reflux for 24 h gave, after concentration and removal of the inorganic salt, 200 g of the crude ester. Distillation under reduced pressure gave pure 128: Yield 184.7 g (79%); \([\alpha]_D^{+18.3^\circ\text{C}}\) (c 1.597 MeOH); \( \delta_H\) 1.32 ppm (3H, t, J 7.2 Hz, CH\(_3\)CH\(_2\)), 1.36 and 1.43 (6H, 2 x s, C(CH\(_3\))\(_2\)), 3.31 (1H, d, J 7.8 Hz, OH), 3.97 - 4.44 (6H, m, CH\(_2\)CH\(_3\), CHOH, CH\(_2\)CHCH, CHCH\(_2\)O); \( \delta_C\) 13.9 ppm (q, CH\(_3\)CH\(_2\)), 25.1, 25.9 (2 x q, C(CH\(_3\))\(_2\)), 61.8 (t, CH\(_3\)CH\(_2\)), 65.5(t, CHCH\(_2\)O), 70.3 (d, CHOH), 76.4 (d, CHOCCCH\(_3\)), 109.9 (s,
C(CH₃)₂) and 172.4 (s, C=O).

Ethyl (2R,3R)-2-O-benzyl-3-4-isopropylidenebutyrate (129)

Prepared as in GP1. Thus 129 was produced in 80% (26 g) yield. (128 is the only substrate that gave nearly complete conversion to the benzyl ether). [α]D²⁵+51.7 (c 1.460); δH 1.28 ppm (3H, t, J 7 Hz, CH₃CH₂), 1.34 and 1.39 (6H, 2 x s, C(CH₃)₂), 3.91 - 4.04 (3H, m, CH₂CHCH, CH₂CHCH), 4.21 (2H, q, J 7 Hz, CH₂CH₃), 4.35 - 4.44 (1H, m, CHOBn), 4.64 (2H, 2 x pseudo d, OCH₂Ph) and 7.23 - 7.39 (5H, m, AR H's); δC 14.3 (q, CH₃CH₂), 25.4 and 26.3 (2 x q, C(CH₃)₂), 61.3 (t, CH₃CH₂O), 65.6 (t, CHCH₂O), 72.9 (t, OCH₂Ph), 76.1 (d, CHOCC₃), 78.7 (d, CHOBn), 110 (s, CCH₃), 128.3, 128.5 and 128.8 (d, Ar CH's), 137 (s, Ar quarternary C) and 170.5 (s, C=O).

3-O-Benzyl-1,2-0-isopropylidenebutane-1,2,3,4-tetrol (130)

Prepared in 92% yield from LiAlH₄ reduction of 129 following general procedure 2; δH 1.35 ppm (3H, s, CCH₃), 1.42 (3H, s, CCH₃), 2.77 (1H, br s, OH), 3.47 - 3.72 (3H, m, CH₂OH and CHOBn), 3.73 (1H, dd, J 8.0 and 7.2 Hz, CH₄OCCH₃), 3.95 (1H,
dd, J 8.0 and 6.6 Hz, $CH^bOCCH_3$, 4.21 - 4.30 (1H, m, CHOCCH$_3$), 4.69 (2H, 2 x pseudo d, J 11.9 Hz, OCH$_2$Ph) and 7.24 - 7.38 (5H, m, Ar CH's); $\delta$C 25.4 and 26.4 ppm (2 x q, 2 x CH$_3$), 61.8 (t, CH$_2$OH), 65.8 (t, CH$_2$OCCH$_3$), 72.9 (t, CH$_2$OBn), 76.8 (d, CHOObn), 79.6 (d, CHOCCH$_3$), 109.7 (s, C(CH$_3$)$_2$), 128.2, 128.3 and 128.8 (d, Ar CH's) and 138.6 (s, Ar quarternary C); m/z(EI) (%) 253 ($M^+ - 1$, 0.4%), 227 (3), 194 (12), 163 (3), 101 (69) and 91 (100).

(2R,3S)-1,2-0-isopropylidenebutane-1,2,3,4-tetrol (132)

![Diagram](image)

Prepared by LiAlH$_4$ reduction (GP1) in 94% yield. Purified by chromatography (EtOAc:Hex 2:8); [$\alpha$]$^0_{D} = 3.89$° (c 4.81 EtOH) [Lit.,$^{166}$ +7.82° (c 4.18 EtOH)]; $\delta$H 1.37 and 1.44 ppm (6H, 2 x s, C(CH$_3$)$_2$), 3.61 - 3.69 (3H, m, CH$_2$OC and OH, exchanges with D$_2$O), 3.75 - 3.79 (3H, m, CH$_2$OH and OH), 4.01 - 4.08 (1H, m, CHOC) and 4.11 - 4.20 (1H, m, CHOH); $\delta$C 25.3 and 26.4 (2 x q, C(CH$_3$)$_2$), 63.8 (t, CH$_2$OC), 65.7 (t, CH$_2$OH), 72.3 (d, CHO), 76.5 (d, CHOH) and 109.5 (s, C(CH$_3$)$_2$); m/z(EI) (%) 147 (47), 132 ($M^+ - 31$, 0.6), 101 (100), 87 (27) and 60 (25).
(S)-2,3-O-Isopropylidene glyceraldehyde (133)

Prepared according to GP5. Thus, 132 (1.36 g, 10.3 mmol) was oxidised to give 133; b.p. 55 - 58°C/20 mm Hg (Lit., 60 - 62°C/20 mm Hg); [α]D25 +36° (c 1.734 C6H6) [Lit.,16° [α]D+64.9° (c 8.28 C6H6); δH 1.40 and 1.47 (6H, 2 x s, C(CH3)2), 3.93 4.23 (2H, m, CHCH2), 4.33 (1H, m, CH2CH), 9.57 (1H, d, CHO), δC 25.2 and 26.3 (2 x q, C(CH3)2), 65.5 (t, CH2CH), 79.9 (d, CHCH2), 111.2 (s, OCCH3) and 201.7 (d, CHO); m/z (EI) (%) 130 (M+, 0.2), 115 (85), 101 (100), 86 (2), 85 (35).

(2R,3S)-3,4-Di-O-isopropylidenebutane-1,2,3,4-tetrol (134)

Prepared following the same procedure as for 127. Thus, 132 (2 g, 0.012 mol) gave 134 (3.77, 92%) as a light yellow oil after chromatography. [α]D25-1.89° (c 1.76 EtOH); δH 1.34 and 1.38 ppm (6H, 2 x s, C(CH3)2), 3.54 - 3.64 (3H, m, CH2OBn overlaps with CHOBn), 3.73 (1H, dd, J 7.3 and 8 Hz, CH4OC), 3.93 (1H, dd, J 6.5 and 8 Hz, CH4OC), 4.19 - 4.29 (1H, m, CHOC), 4.47 (2H, 2 x pseudo d, CH3OCH2Ph), 4.72 (2H, 2 x pseudo d, CHOCH2Ph) and 7.17 - 7.37 (10H, m, Ar 's); δC 25.5 and 26.4 ppm (2 x q, C(CH3)2), 65.8 (t, CH2CO), 72.8 (t, CHOCH2Ph), 73.4 (t, CH2OCH2Ph), 76.8 (d, CHOBn), 78.2
(d, CHCO), 109.0 (s, C(CH₃)₂, 127.5, 127.6, 127.8, 128.2 and 128.3 (5 x d, Ar CH's), 138.5 and 137.9 (5 x s, Ar quarternary C); m/z(EI) (%) 342 (0.06), 327 (0.2), 251 (4), 160 (6), 115 (3), 107 (19), 101 (52) and 91 (100).

(2S,3R)-1,2-O-Dibenzylbutane-1,2,3,4-triol (135)

\[
\text{OBn} \\
\text{HO} \\
\text{OH} \\
\text{135}
\]

Removal of the isopropylidene group was carried out using HCl and Amberlite CG 120 as described in the preparation of 126 to afford 135 (85%); δH 1.26 ppm (1H, br s, D₂O exchangeable OH), 3.09 (1H, br s, D₂O exchangeable OH), 3.53 - 3.58 (5H, m, CH₂OH and CH₂OBn overlap with CHOBN), 3.61 - 3.73 (1H, m, CHO), 4.45 (2H, s, CH₂OCH₂Ph), 4.56 (2H, 2 x pseudo d, CHOCH₂Ph) and 7.16 - 7.29 (10H, m, Ar CH's); δC 62.9 and 68.9 (2 x t, CH₂OH and CH₂CBn), 72.2 and 73.0 (2 x t, CH₂OCH₂Ph and CHOCH₂Ph), 71.5 and 77.6 (2 x d, CHO and CHOBN), 127.3 127.4, 127.5, 127.6 and 128.1 (5 x d, Ar CH's) and 137.7 and 137.9 (2 x s, Ar quarternary C's); m/z(EI) (%) 267 (0.08), 211 (5), 105 (6), 91 (100), 77 (4), 65 (11).

(S)-1,2-Di-O-benzylglyceraldehyde (136)

\[
\text{OBn}
\]

Prepared by oxidative cleavage of 135 (1 g, 3.31 mmol) following GP5 to give 0.58 g of 136 (65%). Chromatography
using hexane:ethyl acetate as eluant (9:1) gave pure 136 (61%). [Found C, 75.52, H, 6.71. C_{17}H_{18}O_{3} requires C, 75.54, H, 6.71]; [\alpha]_D^{26} -9.8^\circ \text{ (c } 2.0 \text{ CHCl}_3); \delta_H \text{ 3.71 ppm (2H, d, J 1.3 Hz, CHCH}_2); 3.90 - 3.95 (1H, m, CHOCH}_2); 4.49 (2H, s, CH}_2OCH}_2Ph), 4.66 (2H, 2 pseudo d, CHOCH}_2Ph), 7.23 - 7.35 (10H, m, Ar CH's) and 9.66 (1H, d, J 1.1, CHO), \delta_C \text{ 69.0 (t, CHCH}_2), 72.6 (t, CH}_2OCH}_2Ph), 73.5 (e, CHOCH}_2Ph), 82.6 (d, CHOCH}_2), 127.6, 127.7, 127.8, 127.9 and 128.0 (5 x d, Ar CH's), 137.2 and 137.5 (2 x s, Ar qarternary C's) and 202.0 (d, CHO); m/z(EI) (%) 242 (0.04), 193 (2), 179 (9), 107 (6), 91 (100), 77 (15), 65 (33).

General Procedure 6

The coupling of aldehydes with methyl acrylate

The aldehyde (1 equivalent) was added to a solution of DABCO (0.1 equivalent) in an excess of methyl acrylate. The mixture was allowed to stir until $^1$H NMR indicated complete consumption of the aldehyde. The mixture was taken up in CH$_2$Cl$_2$, washed successively with dilute HCl, 5% NaHCO$_3$ and brine. The CH$_2$Cl$_2$ solution was dried (MgSO$_4$), filtered and concentrated in vacuo to afford a mixture of diastereomers.

**Methyl 5-benzyl oxy-3-hydroxy-2-methylenehexanoate (138b)**

![Structure of 138b](image)

(Prepared as in GP6). Yield of the diastereomeric mixture 68%; [\alpha]_D^{26} +22.87^\circ \text{ (c } 1.29 \text{ CHCl}_3).
The mixture was separated partially by chromatography to give the major diastereomer of 138b; \([\alpha]_D^0 = +35.10\) (c 1.56 CHCl3); (Found: C, 68.1; H 7.6. C15H20O4 requires C, 68.2, H 7.6); \(\delta_H 1.22\) ppm (3H, d, J 6 Hz, CHCH3), 1.63 - 1.92 (2H, m, CHCH2CH), 3.69 (3H, s, OCH3), 3.81 - 3.95 (1H, m, CHCH3), 3.94 (1H, s, OH), 4.39 and 4.61 (2H, 2 pseudo d, OCH2Ph), 4.68 (1H, t, J 1.3, CH2CHOH), 5.94 and 6.23 (2H, 2 x m, CH2=C) and 7.24 - 7.33 (5H, m, Ar H's); \(\delta_C 19.56\) ppm (CHCH3), 43.91 (OCHCH2CH), 51.78 (CCH3), 70.08 (CHCH3), 70.56 (CH2Ph), 75.75 (CH3CHOH), 125.01 (C=CH2), 128.13, 128.20, 128.86 (Ar CH's), 138.4 (Ar quarternary C's), 142.88 (C=CH2) and 167.03 (C=O); m/z (EI) (%) 205 (2) (M'-CO2Me), 140 (17), 125 (22), and 91 (100).

The minor diastereomer 138a was characterised after cyclisation of the major isomer \([\alpha]_D^0+36^\circ\) (c 1.56 CHCl3); (Found: 246.1229. C15H16O3 (M'-18) requires 246.1256); \(\delta_H 1.26\) ppm (3H, d, J 6.2, CHCH3), 1.83 - 1.90 (2H, m, CHCH2CH), 3.37 (1H, br. s, OH), 3.73 (3H, s, OCH3), 3.71 - 3.88 (1H, m, CHCH3), 4.39 - 4.61 (2H, 2 pseudo d, OCH2Ph), 4.72 - 4.78 (1H, m, CH2CHOH), 5.87 and 6.26 (2H, 2 x m, CH2=C) and 7.23 - 7.34 (5H, m, Ar H's); \(\delta_C 19.1\) ppm (CHCH3), 41.8 (CHCH2CH), 51.7 (OCH3), 68.3 (CH2CHOBn), 70.5 (OCH2Ph), 72.9 (CCHOH), 125.0 (C=CH2), 127.7, 127.8 (Ar CH's), 138.2 (Ar quarternary C), 142.6 (C=CH2) and 166.8 (C=O); m/z (EI) (%) 233 (M'-31), 205 (1), 143 (3), 115 (11), 91 (100) and 83 (17).
Methyl 5-benzylxylo-3-hydroxy-2-methylenehexanoate (139)

(Prepared as in GP6). Yield of the diastereomeric mixture 68%; [α]D -31.3° (c 1.09 CHCl₃). Spectral data were similar to those of 138. The mixture was not separated.

Methyl (3,4)-syn-5-benzylxylo-3-hydroxy-4-methyl-2-methylenepentanoate (140b)

(Prepared as in GP6). Yield of diastereomeric mixture 65%; 140b was characterised after cyclisation; (Found: 264.1364. C₁₅H₂₀O₄ requires 264.1362); δH 0.90 ppm (3H, d, J 7.2 Hz, CHCH₃), 2.17 - 2.37 (1H, m, CHCH₃), 3.52 - 3.69 (2H, m, CH₂OBn), 3.73 (3H, s, OCH₃), 4.51 (2H, s, OCH₂Ph), 4.69 - 4.74 (1H, m, CHOH), 5.90 and 6.32 (2H, 2 x m, CH₂=C) and 7.26 - 7.38 (5H, m, Ar H's); δC 11.6[11.3] ppm (CHCH₃), 36.3[36.6] (CHCH₃), 52.1[52.0] (OCH₃), 71.4 (CH₂OBn), 71.0 (OCH₂Ph), 72.0 (CHOH), 126.0 (CH₂=C), 127.9, 128.0 and 128.1 (Ar CH's), 138.3 (Ar quarternary C) and 162.0 (C=O); m/z(EI) (%) 246 (M⁺-18, 0.4), 233 (0.1), 205 (3), 187 (1), 155 (1), 125 (13), 115 (18), 91 (100) and 55 (12). Acrylate 141b had similar analytical and NMR data.
Methyl 3-hydroxy-5,6-isopropyledene-2-methylenehexanoate (142)

(Prepared as described in GP6). Yield 65%; (Found 212.1049. C_{11}H_{16}O_{4}(M^+-18) requires 212.1049); [α]_D^{21}+11.1° (c 1.367 CHCl₃); δ_H 1.37 ppm and 1.43 (6H, 2 x s, C(CH₃)₂), 1.60 - 1.97 (2H, m, CHCH₂CH), 3.77 (3H, s, OCH₃), 3.59 - 3.77 (1H, dd, CH^{*}OC(CH₃)₂ overlaps with OCH₃), 4.11 (1H, dd, J 3.7 Hz and 9, CH^{*}OC(CH₃)₂), 4.24 - 4.38 (1H, m, CH₂CHCH₂), 4.67 (1H, m, CHO₃), 5.94 and 6.30 (2H, AB system, CH₂=CH); δ_C 25.8 ppm (CCH₃), 27.0 (CCH₃), 39.2 (CHCH₂CH), 52.0 (COCH₃), 68.4 (CHO₃)(CH₃)₂), 69.5 (CH₂OC(CH₃)₂), 73.8 (CHOH), 108.9 [109.4] (s, CCH₃), 125.2[125.5] (CH₂=CH), 142.3[141.8] (C=CH₂) and 166.6 (C=O); m/z(EI) (%) 215 (M^+-15, 37), 155 (17), 141 (54), 123 (100), 95 (40), 83 (62) and 59 (29).

Methyl (3,4)-syn-4,5-dibenzyloxy-3-hydroxy-2-methylenepentenoate (144b)

(Prepared as described in GP6). Yield 65%; 144b isolated after cyclisation of the mixture; (Found: M⁺ 356.1618. C_{21}H_{24}O₅ requires 356.1625); δ_H 3.67 ppm (3H, s, OCH₃), 3.66- 3.78 (1H, m, CHOObn), 4.49 and 4.68 (2H, 2
pseudo d, CHOCH₂Ph), 4.67 (2H, s, CH₂OCH₂Ph), 4.74 - 4.77 (1H, m, CHO₃H), 5.95 and 6.32 (2H, 2 x m, C=CH₂) and 7.24 - 7.37 (10H, m, Ar H's); δc 51.9 ppm (OCH₃), 69.7 (CH₂OBn), 71.6 (CHOCH₂Ph), 72.3 (OCH₂Ph), 73.6 (OCH₂Ph), 79.4 (CHOH), 127.0 (CH₂=C), 128.0, 128.1, 128.2, 128.3, 128.4 and 128.7 (AR CH's), 137.9 and 138.1 (AR quarternary C's), 139.9 (C=CH₂) and 166.6 (C=O); m/z (EI) (%): 338 (M⁺-18, 0.3), 247 (0.9), 217 (4), 181 (16), 159 (5), 115 (2) and 91 (100).

Methyl 3-hydroxy-4,5-isopropylidenedioxy-2-methylenepentanoate (146)

Prepared as described in GP6 to give 146 (54%) as a mixture of diastereomers which were separated by chromatography using hexane-ethyl acetate (70:30) as eluant. The major isomer was found to be anti (146a): [Found C 55.54, H 7.59. Calculated for C₁₀H₁₆O₅ (216.24) C 55.55, H 7.46], δH 1.35 and 1.44 ppm (6H, 2 x s, C(CH₃)₂), 3.12 (1H, d, J 4.9, OH), 3.79 (3H, s, OCH₃), 3.93 (2H, d, J 6.3, OCHCH₂O), 4.35 (1H, m, CH₂CHO), 4.55 (1H, m, CHOH), 6.01 (1H, t, J 1.3, CH²=C), 6.37 (1H, t, J 1.0, CH⁻²=C); δc 25.2 and 26.1 ppm (2 x q, C(CH₃)₂), 52.2 (q, OCH₃), 65.3 (t, OCH₂CHO), 71.2 (d, CHOH), 76.8 (d, OCH₂CHO), 110.1 (s, C(CH₃)₂), 127.9 (t, CH₂=C), 138.5 (s, C=CH₂), 167.1 (s, C=O).

For the minor isomer 146b: δH 1.36 and 1.46 ppm (2 x s, C(CH₃)₂), 2.96 (1H, d, J 7.0, OH), 3.79 (3H, s, OCH₃), 3.89 (2H, d, J 6.50, OCH₂CHO), 4.01 (1H, m, OCHCH₂), 4.50 (1H, m, CHOH), 6.00 (1H, t, J 1.2, CH²=C), 6.39 (1H, t, CH⁻²=C); δc 25.2 and 26.5 ppm (2 x s, C(CH₃)₂), 52.4 (q, OCH₃), 66.4 (t, OCH₂CHO), 70.9 (d, CHOH), 77.8 (d, OCH₂CHO), 110.1 (s,
C(CH$_3$)$_2$, 127.6 (t, CH$_2$=C), 139.9 (s, C=CH$_2$) and 167.0 (s, C=O); m/z(EI) (%) 201 (M$^+$-15, 11), 141 (5), 127 (7), 115 (3), 101 (100), 85 (8).

Methyl 4,5-dibenzyl oxy-3-hydroxy-2-methylene pentanoate (147b)

![Diagram](image)

(Prepared as described in GP6). Yield 65%; 147b was characterised after cyclisation. (Found: 338.1504. C$_{21}$H$_{22}$O$_4$(M$^+$-18) requires 338.1508); $\delta_H$ 3.20 ppm (1H, br. s, OH), 3.62 (3H, s, OCH$_3$), 6.62 - 3.80 (2H, m, CH$_2$OPh overlaps with OCH$_3$), 3.81 - 3.87 (1H, m, CHO$\text{OBn}$), 4.45 and 4.64 (2H, 2 pseudo d, CHO$\text{CH}_2$Ph), 4.67 (2H, s, OCH$_2$Ph), 4.73 - 4.76 (1H, m, CHOH), 5.93 and 6.29 (2H, 2 x m, CH$_2$=C) and 7.20 - 7.34 (10H, m, Ar H's); $\delta_C$ 51.9 ppm (OCH$_3$), 69.7 (CH$_2$OBn), 71.4 (CHO$\text{OBn}$), 72.3 and 73.6 (2 x OCH$_2$Ph), 79.3 (CHOH), 126.9 (CH$_2$=C), 128.0, 128.1, 128.3 and 128.7 (Ar CH's), 137.9 and 139.3 (Ar quaternary C's), 140.0 (C=CH$_2$) and 166.6 (C=O); m/z(EI) (%) 247 (0.3), 217 (1), 181 (1), 159 (3), 127 (1), 115 (18), 91 (100), 83 (9) and 65 (7).
Methyl 3-benzyloxy-4,5-epoxy-3-hydroxy-2-methylenepentanoate (143)

(Prepared as described in GP6). Yield 60%; (found C, 63.4%; H, 6.3. C_{14}H_{16}O_{5} requires C, 63.6%; H, 6.1); δH 3.29 ppm (1H, d, J 7.2 Hz, OH), 3.73 (3H, s, OCH₃), 4.20 and 4.39 (2H, 2 pseudo d, CH₂O), 4.77 (2H, s, OCH₂Ph), 4.99 (1H, d, J 7.1 Hz, CHOH), 5.92 and 6.31 (2H, AB system, CH₂=C), and 7.25 -7.35 (5H, m, Ar H's); δC 51.9 ppm (OCH₃), 69.6 (OCH₂Ph), 71.7 (CHOH), 131.9 (C'O) 126.6 (CH₂=C), 128.2, 128.9, 128.9 (Ar CH's), 13.6 Ar quaternary C), 139.7 (C=CH₂), 161.1 (COBn) and 166.6 (C=O); m/z(EI) 189 (0.2%), 143 (4), 133 (1), 115 (11), 91 (100) and 83 (9).

General Procedure 7

Iodoetherification of α-(δ'-benzyloxyalkyl)acrylates

To a solution of the α-methylene-β-hydroxy-δ-benzyloxy esters in anhydrous acetonitrile was added a solution of iodine (2 equiv) in anhydrous acetonitrile. The mixture was stirred at room temperature away from light for ca. 12 h. A saturated solution was added and the mixture turned pale yellow. The mixture was extracted with ether (3 times). The combined ether extracts were dried (MgSO₄) and concentrated to give a viscous material. The mixture was purified by chromatography to give the tetrahydrofuran derivatives 190 - 194 (Table 4).
Methyl cis,trans-3-hydroxy-2-iodomethyl-5-methyltetrahydrofuran-2-carboxylate (190)

The white powder was recrystallised from CH$_2$Cl$_2$/petroleum ether to give colourless needles. Yield 68%; m.p. 91 - 92°C; (Found C, 32.04, H, 4.16. C$_8$H$_{13}$IO$_4$ requires C, 32.02; H, 4.37); $[\alpha]_D$ +46.18° (c 0.94 CHCl$_3$); $\nu$ 1149.5 cm$^{-1}$ (C-O-C) and 1746.5 (C=O); $\delta_H$ 1.30 ppm (3H, d, J 6 Hz, CHCH$_3$), 1.89 (1H, ddd, J 5.2, 10.0, and 13.3 Hz, C$_4$H$_4$CHMe), 2.18 (1H, ddd, J 2.0, 5.4 and 13.2 Hz, C$_4$H$_4$CHMe), 2.49 (1H, d, J 4.2 Hz, OH), 3.51 (2H, dd, J 9.8 and 12.8 Hz, CH$_2$I), 3.80 (3H, s, OCH$_3$) and 4.51 (1H, poorly resolved t, CH$_2$CHOH); $\delta_C$ 5.33 ppm (CH$_2$I), 21.14 (CHCH$_3$), 42.39 (CH$_2$CHOH), 59.99 (OCH$_3$), 76.63 (CHCH$_3$), 76.45 (CH$_2$CHOH), 89.08 (OCCH$_2$I), and 172.64 (C=O); $m/z$(EI) (%) 241 (M$^+$-CO$_2$CH$_3$, 100), 169 (35), 141 (13), and 114 (52).

Methyl cis,cis-3-hydroxy-2-iodomethyl-4-methyltetrahydrofuran-2-carboxylate (191)

(For preparation see GP7). Yield 68%; m.p. 114 - 115°
Methyl cis,cis-3-hydroxy-2-iodomethyl-4-methyltetrahydrofuran-2-carboxylate (192)

\[
\begin{align*}
\text{MF} & : \text{C}_9\text{H}_{13}\text{IO}_4 \\
\text{MW} & : 300
\end{align*}
\]

(For preparation see GP7). Yield 70%; m.p. 114-115°C (recrystallised from EtOAc/petroleum ether); (Found C, 32.1; H, 4.4. C\textsubscript{8}H\textsubscript{13}IO\textsubscript{4} requires C, 32.0; H, 4.4); ν 1157 cm\textsuperscript{-1} (C-O-C), and 1739 (C=O); δ\textsubscript{H} 1.06 ppm (3H, d, J 6.8 Hz, CHCH\textsubscript{3}), 2.05 (1H, d, J 5.8 Hz, OH), 2.43 - 2.54 (1H, m, CHCH\textsubscript{3}), 3.50 and 3.58 (2H, 2 pseudo d, CH\textsubscript{2}I), 3.72 (1H, dd, J 8.0 Hz and 10.6, OCH\textsuperscript{4}CHMe), 3.80 (3H, s, OCH\textsubscript{3}), 4.19 (1H, dd, J 8.1 and 8.2 Hz, OCH\textsuperscript{5}CHMe), and 4.45 ((1H, d, J 5.8 Hz, CHO), δ\textsubscript{C} 5.53 ppm (CH\textsubscript{2}I), 10.29 (CHCH\textsubscript{3}), 38.95 (CHCH\textsubscript{3}), 53.15 (OCH\textsubscript{3}), 74.08 (CHCH\textsubscript{2}O), 76.47 (CHOH), 90.16 (OCCH\textsubscript{2}I), and 172.34 (C=O); m/z(EI) (%) 199 (6), 169 (35), 141 (18), 114 (69), 103 (95), 71 (100) and 55 (32).
Methyl cis,cis-4-benzyloxy-3-hydroxy-2-iodomethyltetrahydrofuran-2-carboxylate (193)

For preparation see GP7). Yield 65%; (Found 392.0151. C\textsubscript{14}H\textsubscript{17}IO\textsubscript{5} requires 392.0123); \(\nu\) 3382 cm\(^{-1}\), 1751 (C=O) and 1154 (C-O-C); \(\delta\text{H} 3.10\) ppm (1H, br. s, OH), 3.46 and 3.65 (2H, pseudo d, CH\textsubscript{2}I), 3.78 (3H, s, OCH\textsubscript{3}), 3.99 (1H, dd, J 4.6 and 10 Hz, CH\textsuperscript{a}OC), 4.02 - 4.20 (1H, m, CHO), 4.25 (1H, dd, J 4.0 and 5.0 Hz, CH\textsuperscript{b}OC), 4.38 - 4.44 (1H, d, J 5 Hz, CHOH), 4.56 and 4.62 (2H, 2 pseudo d, OCH\textsubscript{2}Ph), and 7.27 - 7.39 (5H, m, Ar H's); \(\delta\text{C} 5.62\) ppm (CH\textsubscript{2}I), 53.04 (OCH\textsubscript{3}), 70.08 (CH\textsubscript{3}CHCH\textsubscript{2}OC), 72.80 (OCH\textsubscript{2}Ph), 74.05 (CHOH), 78.49 (CHOBn), 87.55 (CH\textsubscript{2}OCCH\textsubscript{2}I), 128.28, 128.71 and 129.03 (Ar CH's), 136.58 (Ar quarternary C) and 171.73 (C=O); \(m/z\) (EI) (%) 392 (M\textsuperscript{+}, 0.1), 333(1), 265 (0.1), 241 (0.6), 205 (5), 175 (6), 115 (5), 91 (100), 83 (6) and 65 (10).

Methyl cis,cis-4-benzyloxy-3-hydroxy-2-iodomethyltetrahydrofuran-2-carboxylate (194)

(For preparation see GP7). Yield 67%; m.p. 107-109°C; (Found 392.0145. C\textsubscript{14}H\textsubscript{17}IO\textsubscript{5} requires 392.0123); \(\nu\) 3382 cm\(^{-1}\),
cis,trans-2-Iodomethyl-2-methoxycarbonyl-5-methyltetrahydrofuran-5-yl methanesulfonate (199)

\[
\begin{align*}
\text{MW} & \quad \text{C}_9\text{H}_{15}\text{IO}_6\text{S} \\
\text{MW} & \quad 378
\end{align*}
\]

To a solution of 190 (0.06 g, 0.2 mmol) and triethylamine (0.024 g, 0.24 mmol) in CH$_2$Cl$_2$ (10 ml) at 0°C was added mesyl chloride (0.024 g, 0.21 mmol) with continuous stirring. After 30 min had elapsed, water was added and the aqueous phase extracted twice with diethyl ether. The organic extracts were dried with MgSO$_4$ and the ether was evaporated. The residue was subjected to column chromatography (hexane:ethyl acetate 8:2) to afford 199 (0.059 g, 78%) as a colourles oil; [Found 378.1509 required for C$_9$H$_{15}$IO$_6$S 378.1511]; $[\alpha]_{D}^{23}$ +65.6° (c 0.564 CHCl$_3$); δ 1.33 ppm (3H, d, J 6.1 Hz, CH$_3$CH), 2.00 (1H, ddd, J 4.5, 12 Hz, C$_4$H$^a$), 2.55 (1H, m, C$_4$H$^b$), 3.18 (3H, s, CH$_3$SO$_2$), 3.48 (2H, 2 pseudo d, CH$_2$I), 3.83 (3H, s, OCH$_3$), 4.53 (1H, m, CHCH$_3$), 5.52 (1H, d, J 3.6 Hz, CHOS); δ$_C$ 3.15 ppm (t, CH$_2$I), 4.14 ppm (1H, d, J 6.4 Hz, OH), 3.46 and 3.65 (2H, 2 pseudo d, CH$_2$I), 3.78 (3H, s, OCH$_3$), 3.99 (1H, dd, J 4.5 and 10.7 Hz, CH$^a$OC), 4.06 - 4.20 (1H, m, CH$_2$CHOBn), 4.26 (1H, dd, J 4.5 and 6.0 Hz, CH$^b$OC), 4.38 - 4.44 (1H, dd, J 5.2 and 6.0 Hz, CHOH), 4.55 and 4.63 (2H, 2 pseudo d, OCH$_2$PH) and 7.27 and 7.39 (5H, m, Ar CH's); δ$_C$ 5.53 ppm (CH$_2$I), 52.88 (OCH$_3$), 69.89 (CH$_3$CHCH$_2$OC), 72.63 (OCH$_2$Ph), 73.79 (CHOH), 78.27 (CHOBn), 87.6 (CH$_2$OCCH$_2$I), 127.7, 127.9 and 128.3 (Ar CH's), 136.6 (Ar quarternary C) and 171.7 (C=O); m/z (EI) (%) 392 (M$^+$, 0.5), 334 (1), 240 (3), 208 (12) and 91 (100).
20.8 (q, CH$_3$CH), 38.9 (q, SCH$_3$), 41.4 (t, CHCH$_2$CH), 53.4 (q, OCH$_3$), 76.7 and 83.1 (2 x d, CHCH$_3$ and CHCH), and 170.0 (s, COCH); m/z (EI) (%) 378 (0.6), 319 (38), 223 (100), 169 (67), 141 (25), 96 (72), and 79 (68).
3. REFERENCES

17. a) D.A. Evans, M.D. Ennis and T. Le, *J. Am. Chem.*


75. See ref 27
b) See also ref 39.


     b) W.R. Roush, L.K. Hoong, M.A.J. Palmer and J.C.


162

Perkin Trans., 1985, 2247.


185. P.W. Reed and G.M. Bokoch Ref 184, Ch 9.


APPENDIX

Selected $^1$H and $^{13}$C nuclear magnetic resonance spectra
Molecular Formula: C_{11}H_{16}O_{2}

Molecular Weight: 180

Chemical Structure:

- Benzyl (BnO)
- Methoxy (CH_{2}OH)
- CH_{3}

Note: The diagram shows a chemical shift spectrum with peaks at different ppm values.
$\text{MF } \text{C}_{11}\text{H}_{14}\text{O}_{2}$

$\text{MW } 178$
\[ \text{MF} \quad C_{14}H_{20}O_4 \]

\[ \text{MW} \quad 252 \]
MF $C_{14}H_{17}O_5$

MW 392
Bn

OH

CO₂Me

CH₂I

MF: C₁₄H₁₇I₂O₅

MW: 392