Stereoselective Tetrahydrofuran Synthesis

by

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DECLARATION

I hereby declare that the substance of this thesis has not been submitted nor is being concurrently presented for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and where the work of other researchers has been used, this has been fully acknowledged in the text.

D. E. SHAW

Director of Study

D. W. KNIGHT
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ABSTRACT

This thesis begins in Chapter One with a discussion of the role of electrophilic cyclisation in the synthesis of tetrahydrofurans. Chapter Two begins with a discussion of the synthesis of iodo-δ-lactones, by the iodolactonisation of β-silyloxy-δ-alkenoic acids (Scheme A). It will show how the potential of this chemistry has been expanded by proving the absolute stereochemistry at the iodine centre.

Scheme A

Chapter Two goes on to consider the stereospecific synthesis of 2,3,5-trisubstituted iodo-tetrahydrofurans by the related iodo-etherification of homoallylic alcohols (Scheme B). This is facilitated by the use of anhydrous conditions.

Scheme B

The synthesis of 2,3,5-trisubstituted iodo-tetrahydrofuranaenic
acid esters and 2,3,5-trisubstituted hydroxy-tetrahydrofuranacetic acid esters by the iodocyclisation of geometrically pure (E)- and (Z)-β-hydroxy-δ-alkenoates was then developed and the stereochemical outcome of the reactions was proven (Scheme C).

**Scheme C**

![Scheme C](image)

Targets were chosen which illustrated the utility of the key cyclisations of β-hydroxy-δ-alkenoates. Chapter Three discusses the synthesis of muscarine 93. It was chosen to synthesise muscarine from the cyclisation of the (Z)-β-hydroxy-δ-alkenoate 146. This synthesis is particularly versatile as it not only allows the preparation of muscarine itself, but also of various potentially highly biologically active analogues 146a.

![Chemical structures](image)

The second target selected was Goniofurfurone 170.
Approaches to this molecule will be discussed in Chapter Four. Model work in the synthesis of goniofufurone began with the cyclisation of the (E)-\(\beta\)-hydroxy-\(\delta\)-alkenoate 53b, which indeed, led to the facile synthesis of the iodolactone 204. However, early attempts to incorporate the natural side chain met with limited success.

Chapter Five discusses an approach to the 2-oxabicyclo-[2.2.1]-heptane ring system, which has been synthesised by the radical cyclisation of various \(\beta,\gamma\)-unsaturated tetrahydrofurans of the general form shown in Scheme D.
# CONTENTS

| CHAPTER ONE | Electrophilic Cyclisation in the Synthesis of Saturated Oxygen Heterocycles | 1 |
| CHAPTER TWO | New Stereoselective Routes to Tetrahydrofurans | 40 |
| CHAPTER THREE | The Total Synthesis of Muscarine | 82 |
| CHAPTER FOUR | Approaches to Goniofufurone | 113 |
| CHAPTER FIVE | Radical Reactions of Tetrahydrofurans | 139 |
| CHAPTER SIX | Experimental | 163 |
| REFERENCES | | 241 |
CHAPTER ONE

Electrophilic Cyclisation as a Route to Saturated Oxygen Heterocycles

(I) Introduction 1
(II) Electrophilic Cyclisation 3
   (A) Electrophilic Lactonisation 4
      (i) Phenylselenolactonisation 5
      (ii) Halolactonisation 7
   (B) 5-exo-trig Electrophilic Cycloetherification 12
      (i) Haloetherification 13
      (ii) Selenoetherification 20
      (iii) Sulphenyl Etherification 22
   (C) 5-endo-trig Electrophilic Etherification 24
      (i) Haloetherification 24
      (ii) Selenoetherification 28
      (iii) Sulphenyl Etherification 31
      (iv) Other Electrophiles 33
(III) Other Routes To Tetrahydrofurans 34
   (A) Michael Addition Approaches 34
   (B) Epoxide Opening Methods 35
   (C) Condensation of Diols 36
   (D) Lewis Acid Catalysed Rearrangements 37
   (E) Oxidative Cyclisation of 1,5-Dienes 38
Electrophilic Cyclisation as a Route to Saturated Oxygen Heterocycles

(I) Introduction

The stereocontrolled synthesis of saturated oxygen heterocycles is one of the key challenges of modern organic synthetic chemistry. The preparation of highly substituted tetrahydrofurans (THFs) and tetrahydropyrans (THPs), along with β-, γ- and δ- lactones, of defined stereochemistry, is of great importance, due to the vast array of biologically important natural products which contain this type of functionality.
The polyether antibiotics (e.g., Monensin 1) are extremely important because they have the ability to transport metal ions across biological membranes\(^1-2\) and consequently, the range of their possible biological activity is extensive.\(^3\) They are anti-microbial agents\(^4\) and are known to provoke cardiovascular responses.\(^5\) The key structural features of these molecules are THFs and THPs. Naturally there has been much synthetic interest in these natural products due to their biological and commercial importance and also due to the huge synthetic challenge which they present. Despite this, there have only been a few total syntheses reported.\(^6-11\) There are also a wide range of other natural products which contain THFs as important sub-units, including steroids, C-nucleosides and marine natural products such as the Halichondrins 2 and Eunicellin diterpenoids 3.

![结构式](image)

Lactones are also present in a wide range of natural products with various different roles in nature. Actinobolin 4 was isolated from Streptomyces cultures, whereas (+)-Nepetalactone 5 is a pheromone found in aphids.
(II) Electrophilic Cyclisation

One of the most important routes to saturated oxygen heterocycles of known stereochemistry is the electrophilic cyclisation of unsaturated molecules containing internal nucleophiles. There are many electrophiles which allow this reaction to take place and there are a huge variety of examples of this process in synthesis. This section will outline the main types of electrophilic cyclisation and will give an idea of their scope in terms of organic synthesis.

The electrophilic cyclisation reaction follows the general equation shown in Scheme 1. As with most cyclisation processes the reaction can either take an exo or endo pathway. In most cases, these processes will broadly follow the empirical rules laid down by Baldwin\textsuperscript{12} for the geometry of transition states and the balance of steric and electronic factors: ie 4-exo, 5-exo and 6-exo are favoured over 5-endo, 6-endo and 7-endo. In the cases of some of the reactions
which will be described, the transition state involved does not have even charge distribution and is therefore not equivalent to a normal double bond. This means that it will not be constrained by the stereoelectronic forces used by Baldwin when formulating his rules. In particular, in the cases of electrophiles which do not form standard “onium” complexes with the double bond, other factors can determine the mode of cyclisation.

\[
\text{Scheme 1}
\]

The cyclisation generally gives the opportunity to generate new stereocentres at sites \(b\) and \(c\) (Scheme 1). In most cases, the stereochemistry of centres \(b\) and \(c\) will be determined by the geometry of the double bond as there will normally be overall \textit{anti} addition of nucleophile and electrophile to the double bond. The extent to which the stereochemistry of the new stereocentres is determined by the cyclisation process, and also the extent to which the stereochemistry is induced by other substituents, allows the usefulness of the individual cyclisations to be assessed.

\textbf{(A) Electrophilic Lactonisation}

The electrophilic lactonisation of unsaturated acids to give functionalised lactones with generally excellant levels of stereocontrol
is, perhaps, the most important method of lactone synthesis available to organic chemists, beyond the simple intramolecular condensation of hydroxy-acids. This section will discuss some of the range of electrophiles available for such processes and the extent of their usefulness.

(i) Phenylselenolactonisation.\textsuperscript{13}

Selenium mediated cyclisation has become popular due to the usefulness of the phenylselenenyl (PhSe) group which is incorporated into the resulting lactones. The PhSe group is versatile and can be easily manipulated. It can be oxidatively (H\textsubscript{2}O\textsubscript{2}) or reductively (Bu\textsubscript{3}SnH) removed to give unsaturation and saturation respectively. The first reagent used in phenylselenolactonisation was phenylselenenyl chloride, and, in cyclic systems, this generally gives good stereocontrol. However, the rate of this reaction, even at -78°C, is usually so rapid that it probably does not allow thermodynamic control, so in the lactonisation of acyclic substrates, the stereocontrol is not high. The introduction of N-phenylselenophthalimide (NPSP)\textsuperscript{14} brought much more reversibility into the lactonisation reaction and allows much better stereocontrol. (Scheme 2).

Scheme 2
<table>
<thead>
<tr>
<th>R</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Yield</th>
<th>cis :trans</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>PhSeCl</td>
<td>ether 25°C</td>
<td>69%</td>
<td>1 : 1</td>
<td>15</td>
</tr>
<tr>
<td>Ph</td>
<td>PhSeCl</td>
<td>dcm -78°C</td>
<td>54%</td>
<td>2.7:1</td>
<td>16</td>
</tr>
<tr>
<td>Ph</td>
<td>NPSP</td>
<td>ether 25°C</td>
<td>75%</td>
<td>15:1</td>
<td>16</td>
</tr>
</tbody>
</table>

The mode of cyclisation in the phenylselenolactonisation reaction is not so much controlled by Baldwin's rules as by the ability of the two possible sites to stabilise a carbonium ion.

Scheme 3

![Scheme 3](image-url)
In general, the ring closure occurs at the carbon most able to stabilise a positive charge, although subsequent rearrangements are often possible. Empirical observations suggest that 5-membered lactones are preferred over the 4- and 6-membered alternatives. Some examples are shown in Scheme 3.

The oxidative removal of the PhSe group is particularly useful as the elimination proceeds selectively in a syn fashion and away from the oxygen atom. This directing effect is explained as the polar selenoxy function will tend to align anti-parallel to the oxygen lone pairs in order to minimise repulsion. Interestingly, selenolactonisation can be reversed using sodium in liquid ammonia to reductively remove the selenium function. This enhances the power of this reaction as it can potentially be used as a protection step.

(ii) Halolactonisation

Halolactonisation is by no means a new process. As early as 1908, Bougault investigated the process, but it is only recently that the full stereochemical and regiochemical subtleties have been studied. Early work suggested that only 5- and 6-membered lactones could be synthesised in this way, but this proved to be untrue. Indeed, according to Baldwin's rules and Markovnikov orientation, 4-exo lactonisation is the favoured process under kinetic conditions. The cyclisation shown in Scheme 4 illustrates the type of strained systems which can be constructed in this way.
Halolactonisation, unlike selenolactonisation, usually follows Baldwin's rules fairly closely.

Bartlett\textsuperscript{20} brought a new dimension to the halolactonisation reaction when he advocated the use of thermodynamic conditions ([I\textsubscript{2}, non-basic solvent (usually acetonitrile)], instead of kinetic conditions [presence of base, NaHCO\textsubscript{3}(aq)] or limiting the concentration of halonium ions (\textit{i.e.} N-iodosuccinimide, CHCl\textsubscript{3}) (Scheme 5).

The use of thermodynamic conditions allows the equilibration of the less thermodynamically stable \textit{cis} lactone \textit{via} protonation of the first lactone formed. This requires a certain amount of free
protons to be available. Iodine/ether/aqueous bicarbonate allows some equilibration (i.e. no 6-endo cyclisation products are seen but there is no equilibration of cis-lactones to trans-lactones). In the formation of δ-lactones under thermodynamic conditions, 1,2- and 1,3- asymmetric induction can be achieved because of the well-defined "chair-like" transition state involved, but 1,4-induction is not generally very good (Scheme 6).21

Scheme 6

The use of 2,4-disubstituted substrates ensures good
asymmetric induction and this was used by Bartlett in his synthesis of Multistriatin\textsuperscript{22} and Serricornin.\textsuperscript{21}

Chamberlain\textsuperscript{23} and Katzenellenbogen\textsuperscript{24} have also studied the effect of having a free hydroxyl function upon stereoselection in this reaction. In both cases, high selectivities for the cis-lactones were observed, this time in the case of γ-lactones (Scheme 7). In these examples, there is steric control over the cyclisation by the free hydroxyl group and only the isomers shown were isolated.

![Scheme 7](image)

Halolactonisation has been applied to a wide range of substrates. The spirolactonisation (Scheme 8) used by Wovkulich \textit{et al}\textsuperscript{25} in the approach work to a synthesis of Mevinolin illustrates this particularly well.

![Scheme 8](image)

Medium ring lactones can also be synthesised by
halolactonisation methods, as long as the substrate contains either hydroxyl or gem-dimethyl substituents. Such substituents restrict the rotation of the substrate and give a much greater chance of cyclisation (Scheme 9).

Nitrogen substituted unsaturated acids can also be halolactonised with good asymmetric induction (Scheme 10). The high stereoselection is rationalised by the possibility of nitrogen stabilising the transition state creating the kinetically more favourable transition state 6.

It is also possible to halolactonise unsaturated amides; indeed, this process is favoured over the alternative mode of cyclisation.
in which the nitrogen acts directly as the nucleophile (Scheme 11).28

Knapp29 has, however, demonstrated that upon protection of an amide with two equivalents of trimethylsilyl triflate, the N,O-bis-(trimethylsilyl)imidate can be induced to iodocyclise, via the nitrogen, to give the iodo-γ-lactam. (Scheme 12).

(B) 5-exo-trig Electrophilic Cycloetherification.

One of the key routes to the synthesis of THFs of controlled stereochemistry is the 5-exo-trig cycloetherification of γ,δ-unsaturated alcohols. This is by far the most common use of cycloetherification and it has therefore been studied extensively using a variety of different electrophiles. In this section the range of electrophiles and
the scope of the process will be discussed.

(i) Haloetherification

This approach was developed ten to fifteen years ago by Bartlett and his colleagues. He found that \(\gamma,\delta\)-unsaturated alcohols cyclised under thermodynamic conditions (iodine/acetonitrile) to give trans 2,5-disubstituted THFs with moderate selectivity (Scheme 13), whereas when the corresponding ethers were cyclised under the same conditions, cis 2,5-disubstituted THFs, the thermodynamically more stable isomers, were formed with moderate to good selectivity depending on the ether group used. The best stereoselectivity was obtained using sterically bulky ether groups, but some groups were found to be so bulky that they hindered cyclisation and led to much reduced yields.

Scheme 13

Bartlett found that the 2,6-dichlorobenzyl group (DCB) gave the best selectivities as it had the best balance of beneficial stereo- and electronic effects. More recently, Normant found that the use of
butyl ethers gave an even better stereoselection (28:1 cis:trans ratio); these ethers are also easier to form than the corresponding DCB ethers. The rationale for these selectivities is shown in Scheme 14.

Scheme 14

cis-2,5-Disubstituted THFs are the major products when the ether group is bulky because there is a transition state available where the steric interactions are minimised, whereas both possible transition states that would result in the corresponding trans-2,5-disubstituted THFs being formed have an unfavourable interaction between one of the substituents and the ether group. There are vast
numbers of examples of these reaction in synthesis; Bartlett\textsuperscript{32} has exemplified the process in the synthesis of Davanone 7 (Scheme 15).

Many other halogen sources have been used in this process. Kishi\textsuperscript{33} used an NBS mediated cyclisation as part of an approach to the right-hand half of Monensin 1 and obtained a stereochemically pure 2,5-\textit{trans} disubstituted THF (Scheme 16). This stereoselectivity is surprising in the context of Bartlett's work, but the effect of the 3-methyl substituent must be large.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{Scheme_16.png}};
\end{tikzpicture}
\end{center}

As early as 1970, Rhoads\textsuperscript{34} used NBS in refluxing carbon tetrachloride to effect the cyclisation of an unsaturated alcohol (Scheme 17) under thermodynamic conditions, although the stereochemical purity was low.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{Scheme_17.png}};
\end{tikzpicture}
\end{center}

Torr\textsuperscript{35} used 2,4,4,6-tetabromocyclohexa-2,5-dienone (TBCD) as a source of bromonium ions in the 5-\textit{exo} cycloetherification of a polyhydroxylated substrate with reasonable \textit{cis}-selectivity.
The use of bis-(sym-collidine)iodine(I) perchlorate, as devised by Schauble, allows the formation of cyclic ethers of ring size 3-7 with high regioselectivity (generally consistent with Baldwin's rules), and is consequently of great interest in the synthesis of epoxides and oxetanes of controlled stereochemistry.

Incorporation of an extra free hydroxyl function into the substrate, other than that which cyclises, was pioneered by Yoshida. It was found that 1,3-syn diols gave high stereoselectivity for 2,5-trans-THFs (95%), whereas 1,3-anti diols gave a poorer selectivity of 2:1 trans:cis (Scheme 19). This was rationalised by proposing the transition states shown (Scheme 20).
The transition state that gives the \textit{trans}-THF from the \textit{syn}-diol is favoured due to the lower steric hindrance, so the cyclisation is fast and selective, whereas the corresponding transition state from the \textit{anti}-diol has serious steric hindrance preventing one-step cyclisation to the \textit{cis}-THF. It therefore rotates to give the transition state 8 which cyclises to give the \textit{trans}-THF preferentially. This stereochemical outcome is also seen in the work of Williams\textsuperscript{38} where the benzyl ether 9 was cyclised with a similar stereochemical outcome (Scheme 21).

Another example of note in this field is the work of Reitz\textsuperscript{39} in which the glycoside derivative 10 was cyclised. It was shown that NBS in dimethylformamide (DMF) gave a slightly better selectivity for the \textit{trans}-THF than iodine/THF/sodium carbonate (Scheme 22).
Labelle\textsuperscript{40} investigated the mechanism of allylic control in stereoselection and found that the effect varied with the nature of the substituent (Scheme 23). It was shown that the effect was in the order $F > OH > Me$. The transition state 11 was postulated to be the most favourable and leads to a $2,3$-\textit{cis} relationship between the substituents. It should be noted that in all the favoured transition states, the allylic substituent is positioned pseudoaxially.

Where it is possible for both 5-\textit{exo} and 5-\textit{endo} iodoetherification to occur, the faster 5-\textit{exo} process occurs exclusively (Scheme 24).\textsuperscript{41}
5-exo-Trig iodoetherification has also been used by several groups to synthesise 2,3-dihydrofurans (Scheme 25).

The electron withdrawing group E is necessary, as these reactions involve the iodocyclisation of the corresponding enol. It is therefore important that a high proportion of the enol form is present in the reaction conditions.
Kurth showed that the difference in energy between halo-lactonisation and haloetherification is exceptionally small, by cyclising the stereoisomers 12 and 13; this illustrated that either process can occur exclusively at the expense of the other, on purely stereochemical grounds (Scheme 26).

(ii) Selenoetherification

Selenium mediated electrophilic etherification has been widely used in synthesis, and as mentioned earlier, the incorporation of the PhSe group is a great advantage in synthetic terms. It is, in many ways, complementary to the haloetherification reaction and the controlled elimination away from oxygen provides an excellent route to allylic ethers.

5-exo-Selenoetherification was first introduced by Clive in 1977, initially for the cyclisation of phenols and subsequently for more general cyclisations. Phenylselenenyl chloride induces phenylselenoetherification rapidly at -78°C. The methodology is therefore tolerant of a wide range of functionality (Scheme 27). Although in cyclic systems selenoetherification gives good stereocontrol, in the etherification of acyclic substrates, there is little stereoselectivity, although the addition of a mild base such as potassium carbonate can increase this in some cases.
The work of Ley in this area is also worth noting. His group has shown that hydroxy-ketones can be cyclised to give the spiroacetals shown, with moderate stereocontrol, using NPSP as the selenium ion source (Scheme 28). More recently, Ley has extended this idea to include a THF synthesis in which the enolic hydroxy group of a β-keto ester acts as a nucleophile in selenoetherifications leading to an ylidene THF (Scheme 29). Asymmetric induction from the allylic substituent was observed and a facile reduction furnished the corresponding 2,5-cis-THF exclusively.
(iii) Sulphenyl Etherification

Sulphur is not as commonly used in electrophilic cyclisations because it is less able to stabilise a positive charge and so the necessary sulphonium ion sources are less easily obtained. There are, however, a large number of sulphur reagents for 5-exo-trig electrophilic cyclisation now available.

In 1981, Capozzi used methyl bis(methylthio)sulphonium (MBMT) salts to cyclise ortho-allylic phenols, with some success, in the synthesis of α-thiomethylbenzofurans (Scheme 30).

Scheme 30
Cava$^{51}$ used dimethyl(methylthio)sulphonium tetrafluoroborate and base in acetonitrile to effect 5-exo-trig cyclisations of various $\gamma,\delta$-unsaturated alcohols. Although the stereochemistry of the products from acyclic substrates was not addressed, the stereocontrol in cyclic systems was good (Scheme 31).

Brownbridge$^{52}$ used N-(phenylthio)morpholine as a source of phenylsulphonium ions and carried out various 5-, 6- and 7-exo cyclisations. This reagent was also used to repeat the work of Capozzi in significantly improved yields. Again there was no attempt to effect stereocontrol or define stereochemistry.

Fallis$^{53}$ used phenylsulphenyl chloride and base to perform a number of sulphenyletherifications. It is interesting to note that when a homoallylic alcohol was subjected to the cyclisation conditions, an overall addition of phenylsulphenyl chloride was observed (Scheme 32). This illustrates the favourability of the 5-exo process over the 5-
endo process because the attack of chloride occurs preferentially to cyclisation.

Recently, Capozzi demonstrated that the cyclisation of acyclic γ,δ-unsaturated alcohols using MBMT salts proceeds with very little stereoselectivity, illustrating how much more development is needed before this process becomes viable in stereoselective synthesis.

(C) “5-endo-trig” Electrophilic Cycloetherification

The electrophilic cyclisation of homoallylic alcohols is a potentially attractive route to 2,3,5-trisubstituted THFs and higher homologues of defined stereochemistry, as a single stereocentre can be used to generate two more, and is therefore of potentially significant synthetic importance. In recent years, there have been a number of examples using a range of electrophiles. This section will deal with the various types of reaction known so far, and their scope. It will also tackle the stereochemical aspects of the cyclisation.

(i) Halocyclisation

In 1978, Bartlett made what was then an isolated
observation, that the α-hydroxy ester 13 cyclised in a 5-endo-trig fashion to give the iodo-THF 14 as the only product (Scheme 33). The stereochemistry of the product was not proven, but since only one product was isolated, it was assumed to be the most thermodynamically stable isomer. The iodocyclisation of the corresponding methyl ether gives 33% of the iodo-THF 14.

In 1984, Mechoulam introduced a novel source of presumably iodine(I) for electrophilic cyclisation, by reacting sodium iodide with m-chloroperbenzoic acid, although most of the regiochemical outcomes were similar to those in established iodoetherification reactions. (E)-3-Hexen-1-ol however was also successfully cyclised, effectively via a 5-endo-trig process (Scheme 34).

Scheme 34

\[
\text{mCPBA, NaI} \quad \text{18-Crown-6}
\]

Schauble also observed the same reaction when he treated (E)-3-hexen-1-ol with bis(sym-collidine)iodine(I) perchlorate, another source of anhydrous iodonium ions. He noted, however, that other homoallylic alcohols cyclised via the “4-exo-trig” pathway under these conditions to give iodomethyl-oxetanes.

Takano used a 5-endo-trig bromoetherification in his synthesis of intermediates from Mycinamycin (Scheme 35). This example is unique as it occurs in the presence of water where one might expect the intermediate bromonium ion to be opened.
intermolecularly by water. The authors make no comment as to the unusual nature of this cyclisation.

Scheme 35

In 1992, Lipshutz and Barton\textsuperscript{57} were the first to report detailed work on the stereochemical nature of the iodoetherification of homoallylic alcohols. As part of their investigations of an approach to the THF portion of Tetronasin 16, it was envisaged that such a cyclisation could be useful (Scheme 36).

Scheme 36

It was found that the stereochemistry of the products varied with the choice of electrophile. The results were also unusual in that there appears to be an overall \textit{syn} addition of the electrophile and the hydroxyl oxygen to the double bond (Scheme 37). This suggests that a complex mechanism may be involved. These results are difficult to explain in terms of a simple transition state and, as yet, the authors have offered no explanation. The results differ from others in the area in terms of the stereochemical outcome.\textsuperscript{58} One possible explanation is the presence of the \(\beta\)-methyl substituent. Interestingly, when NBS
was used for these cyclisations, the expected stereochemistry resulting from \textit{anti} addition to the double bond was obtained (Scheme 38).

Scheme 37

\[ \text{Scheme 38} \]

Recently Kang\textsuperscript{59} has also examined the 5-\textit{endo}-trig iodoetherification of homoallylic alcohols. The investigation was, however, restricted to substrates wherein the olefin is in conjugation with an aromatic system (\textit{i.e.} where a 5-\textit{endo}-trig cyclisation is favoured by the possibility of an allylic carbocation existing). It was found that treatment of the substrates in the presence of potassium carbonate at -78°C in diethyl ether with iodine led to up to a 65:1 ratio of 2,5-\textit{trans}: 2,5-\textit{cis} THFs under slow addition conditions (Scheme 39).
(ii) Selenoetherification

Nicolaou\(^{13}\) noted some time ago that selenium mediated cyclisations can be used to form five membered rings preferentially over four membered rings and also that the selenoetherification of homoallylic alcohols led to the formation of 2,3,5-substituted THFs by a “5-endo-trig” cyclisation (Scheme 40).

Mihailović\(^{60}\) also noted an isolated example of this reaction in acyclic homoallylic alcohols (Scheme 41) during studies of electrochemical selenoetherification.
Mihelich\textsuperscript{61} showed that 5-\textit{endo}-trig selenoetherification of acyclic substrates was an extremely viable process when he generated the selenodiols 17 by treating the epoxy alcohols 18 with sodium phenyl selenide.

The selenodiols were then induced to form selenonium ions by treatment with acid (HClO\textsubscript{4}, THF) and these intermediates underwent facile 5-\textit{endo}-trig cyclisation to give THFs (Scheme 42).

In the first three cases, the selectivity results from the formation of a single selenonium ion. The final result has been rationalised by suggesting that the intermediate generates an olefin by
elimination and then reforms the alternative selenonium ion intermediate. This suggests that the cyclisation must be highly stereoselective and that the cyclisation of the transition state which eliminates the selenium moiety must be highly disfavoured (Scheme 43).

Lipshutz and Barton\textsuperscript{57} found that phenylselenenyl chloride can be used to induce stereoselective 5-	extit{endo}-trig cyclisations of homoallylic alcohols (Scheme 44). The stereochemistry obtained from these was different from that obtained by iodocyclisation (\textit{vide supra}). It is interesting to note that when Lipshutz generated the transition state analogous to that found to be disfavoured by Mihelich (with the extra methyl group in the 2-position) smooth cyclisation was observed.
One possible explanation is the fact that Mihelich used acidic conditions for the cyclisations and therefore the rearrangements may have been acid catalysed.

Kang\textsuperscript{62} has also investigated 5-\textit{endo}-trig selenoetherification although his studies were limited to cases in which the olefin was in conjugation with an aromatic system. High stereoselection was obtained at -78°C under Lewis acid catalysis (Scheme 45). The cyclisation of the corresponding silyl ethers was also investigated\textsuperscript{63} (Scheme 46), and these were found to cyclise at 20°C in the absence of catalysis and in the presence of potassium carbonate to give even better stereoselection.

\begin{center}
\textbf{Scheme 45}
\end{center}

\begin{center}
\begin{align*}
\text{Ph} & \quad \text{PhSeCl, ZnBr, DME, -78°C} \\
\text{R} & \quad \text{Ph} \\
\text{OH} & \quad \text{PhSe} \\
\text{20:1} & \quad \text{R}
\end{align*}
\end{center}

\begin{center}
\textbf{Scheme 46}
\end{center}

\begin{center}
\begin{align*}
\text{Ph} & \quad \text{OSiR}_3 & \quad \text{PhSeCl, K}_2\text{CO}_3, \text{CH}_3\text{CN, 20°C} \\
\text{R} & \quad \text{Ph} \\
\text{20:1} & \quad \text{PhSe}
\end{align*}
\end{center}

(iii) Sulphenyl etherification

Williams\textsuperscript{64} developed a route to 2,3,4,5-tetrasubstituted THFs via the sulphur-mediated 5-\textit{endo}-trig cyclisation of 2-methyl-3-thiophenyl-1,4-diols. The process probably involves the formation of an
intermediate episulphonium ion, by the elimination of methanol, upon
treatment with dimethyl sulphate in dichloromethane at 0°C (Scheme
47).

This was carried out on both stabilised (α-phenyl) and
unstabilised sulphonium ions without any trace of 4-exo-trig
products. Good stereochemical purity was maintained throughout
and there were no anomalous results similar to those found by
Mihelich in the selenium-based work.

Warren\textsuperscript{65} found that this reaction could be extended to
tertiary thioethers, as long as the stereochemistry of the molecules
was favourable, and thus was able to construct spiro-THFs (Scheme
48).

Brownbridge\textsuperscript{52} observed an example of a 5-endo-trig
sulphenyletherification using N-(phenylthio)morpholine (Scheme 49);
Fallis\textsuperscript{53} did not observe a similar reaction, although the presence of chloride ions in the latter reaction may explain this.

\begin{align*}
\text{Scheme 49} \\
\text{\includegraphics[width=0.5\textwidth]{scheme49.png}}
\end{align*}

(iv) Other Electrophiles

Hu\textsuperscript{66} used aryltellurinyl acetates to effect 5-\textit{endo}-trig cyclisations of 3-alkenols (Scheme 50). Interestingly, iodoetherification of this molecule resulted in 4-\textit{exo}-trig cyclisation\textsuperscript{36}

\begin{align*}
\text{Scheme 50} \\
\text{\includegraphics[width=0.5\textwidth]{scheme50.png}}
\end{align*}

Thallium triacetate has also been used to mediate 5-\textit{endo}-trig cyclisations of alkenols by Ferraz\textsuperscript{67} with good stereochemical purity (Scheme 51).

\begin{align*}
\text{Scheme 51} \\
\text{\includegraphics[width=0.5\textwidth]{scheme51.png}}
\end{align*}
(III) Other Routes to 2,3,5-Trisubstituted Tetrahydrofurans

Although electrophilic etherification is an important route to substituted THFs, there are many other routes available; in this section, some of the major approaches will be briefly outlined. Comprehensive reviews of this topic have been published.\(^{68}\)

(A) Michael Addition Processes

Homoallylic alcohols possessing a sulphone group at the 3-position undergo cyclisation when treated with potassium hydride in THF at RT to afford a 2,2,4-trisubstituted THF, as shown by Normant\(^{69}\) (Scheme 52).

\[ \text{Scheme 52} \]

More recently, Craig\(^{70}\) has prepared 2,3,5-trisubstituted THFs by the same strategy, using potassium t-butoxide in t-butanol; the products have a 2,3-\textit{anti} configuration. The cyclisation leads to a moderate selectivity for 2,5-\textit{trans}-THFs over 2,5-\textit{cis}-THFs. The selectivity is much greater in the case of the (E)-isomers than in the case of the (Z)-isomers (Scheme 53).
Cha\textsuperscript{71} used a similar idea in the approach to Verrucosidin (Scheme 54).

\textbf{Scheme 54}

\begin{align*}
\text{HO} & \xrightarrow{\text{NaHCO}_3} \text{HO} \\
\text{MeOH} & \xrightarrow{\text{MeOH}} 90\% 
\end{align*}

\textbf{(B) Epoxide Opening Methods}

This route involves the acid catalysed 5-exo-tet opening of a \(\gamma,\delta\)-epoxide by an alcohol and it has increased in popularity due to the obvious compatibility with Sharpless\textsuperscript{72} epoxidation methodology. This approach is, in many ways, complementary to the use of electrophiles such as halogens because the stepwise cyclisation will lead to a different stereochemistry (Scheme 55). Kishi\textsuperscript{73} used this approach as
part of his work towards the Halichondrins (Scheme 56).

Scheme 55

\[
\begin{align*}
&\text{VO(acac)}_2 \\
&{^t}\text{BuOOH} \\
\rightarrow \\
&\text{I}_2, \text{NaHCO}_3, \text{MeCN}
\end{align*}
\]

(C) Condensation of Diols

Scheme 56

\[
\begin{align*}
(i) &\text{tBuOOH} \\
&\text{VO(acac)}_2 \\
&(+)^{\text{DET}} \\
&\text{Ti(OPr)}_4 \\
(ii) &\text{CSA}
\end{align*}
\]

Condensation of 1,4-diols under acidic conditions has been used extensively in the synthesis of substituted THFs (Scheme 57). Fleet\textsuperscript{74} has used the ring contraction of δ-lactones with leaving groups as α-substituents (ie 1,4-diols) extensively in carbohydrate chemistry, to generate highly substituted THFs (Scheme 58). Mulzer\textsuperscript{75} used a
similar approach when he cyclised benzyl ethers with $\gamma$-leaving groups to give 2,5-substituted THFs of defined stereochemistry (Scheme 59).

(D) Lewis Acid Catalysed Rearrangement
Overman\textsuperscript{76} has developed a concise route to 2,3,5-substituted THFs by the rearrangement of \textit{trans}-vinyllic-1,2-diol acetals (Scheme 60). He has used this approach in the synthesis of the Kumausalledes (\textit{eg} \textit{trans}-Kumausallene).

\begin{center}
\textbf{Scheme 60}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme60.png}
\end{center}

\textit{trans}-Kumausallene

\textbf{(E) Oxidative Cyclisation of 1,5 Dienes\textsuperscript{77}}

Potassium permanganate can be used under mildly alkaline conditions to generate 2,5-\textit{cis}-disubstituted THFs in which the stereochemistry at the positions \(\alpha\) to the THF ring is defined by the geometry of the starting diene (Scheme 61). These highly oxidative conditions can be a little too harsh to use in the course of synthesising complex multi-functional molecules, but they do give THFs of predictable stereochemistry. This was among the first routes to allow such stereocontrol.
Scheme 61
CHAPTER TWO

New Stereoselective Routes to Tetrahydrofurans

(I) Valerolactone Chemistry

(II) Tetrahydrofurans By Overall 5-endo-trig Cyclisations

(III) Generation of the Cyclisation Precursors

(A) (Z)-\(\beta\)-Hydroxy-\(\delta\)-alkenoates

(B) (E)- and (Z)-Homoallylic alcohols

(C) (E)-\(\beta\)-Hydroxy-\(\delta\)-alkenoates
New Stereoselective Routes to Tetrahydrofurans

(I) Valerolactone Chemistry

Work concerning electrophilic cyclisations began within our group as a part of the approach to analogues of the mevinic acids, Compactin 19 and Mevinolin 20 (Scheme 62), which are among the worlds best selling pharmaceuticals in their role as inhibitors of cholesterol biosynthesis in man.

Scheme 62

\[\text{HO}\]
\[\text{R}^{\text{Me}}\]
\[\text{R}^{\text{H}}\]

\((\pm\)-Compactin \(R=H\) (19) \(\pm\)-Mevinolin \(R=\text{Me}\) (20)

The active \(\delta\)-lactone portion in its open chain form acts as a mimic of mevalonic acid, a crucial intermediate in the terpenoid biosynthetic pathway leading to cholesterol. The mevinic acids act as
potent inhibitors of the pathway by blocking a major rate limiting step, the conversion of HMGCoA [3-hydroxy-3-methylglutaric acid co-enzyme A] into mevalonic acid. The mevinic acids block the action of HMGCoA reductase presumably by occupying the active site of the enzyme. One possible synthetic approach to the mevinic acids which has been studied at Nottingham is the electrophilic lactonisation of a β-hydroxy- or silyloxy-δ-alkenoic acid (Scheme 63).

Scheme 63

This led to the requirement of a chiral route to such molecules. Bennett\textsuperscript{78} used baker’s yeast reduction of the corresponding β-keto esters as a route to the hydroxy-acids 21. Bennett\textsuperscript{78} then used selenolactonisation of the hydroxy-acid 21 to prove the absolute stereochemistry produced by the enzymes in baker’s yeast (Scheme 64).

The non-stereoselective selenolactonisation gave the lactones 22 and 23. The selenium group was reductively removed to give a mixture of hydroxy-lactones which were then chromatographically separated and individually converted into the R- and S-enantiomers of natural para sorbic acid 24 and 25. From the optical purity of these isomers the optical purity and the absolute stereochemistry of the yeast reduction product was deduced.
Detailed analysis of the coupling constants in the lactones after the removal of the selenium function showed that the less polar isomer derived from 22 exhibited resonances at $\delta_H$ 4.38 (br quin, $J = 3.7$) and at 4.87 (ddq, $J = 11.3$, 6.4 and 3.1). Assigning these resonances by COSY experiments as the 4-H and 6-H respectively and assuming that the methyl group is likely to adopt the equatorial position, led to the conclusion that this was the trans isomer which exists in conformation 26 (Scheme 65). The more polar isomer derived from 23 exhibited the corresponding
resonances at $\delta_H$ 4.25 (ddddd, $J = 9.1, 7.6, 5.8$ and $5.6, 4$-H) and 4.37 (dqd, $J = 11.7, 6.2$ and $3.0, 6$-H). These data are consistent with the corresponding cis isomer which adopts conformation 27 in which both 4- and 6-protons are in axial positions.

As the absolute stereochemistry and optical purity of the 4-centre in the lactones is transferred to the 6-centre, the stereochemistry of the yeast product can be deduced. The trans lactone gave unnatural (R)-parasorbic acid 24. This implies that the yeast product must have had the S-configuration as shown above. From measurements of optical rotation an optical purity of lactones 24 and 25 78% was deduced for the initial product 21.

By contrast the corresponding silyl ethers of the hydroxy-acid 21 could be iodolactonised, with good stereoselectivities, to give predominantly trans-iodolactones. The stereoselectivity increased with increasing bulk of the silicon protecting group; indeed, a selectivity of 5.5:1 was achieved using the triisopropylsilyl group. In the case of the homologous acids with a cis stereochemistry at the double bond, even higher selectivities of up to 10.5:1 were observed (Scheme 66).
The selectivity of 10.5:1 observed in the cyclisation of (Z)-3-triisopropylsilyloxy-dec-5-enoic acid was seen to improve even further in the cyclisation of the corresponding (E)-isomer 28 in an isolated observation by a previous researcher. Cyclisation gave a single isomer of the valerolactone 29 which differed from the major product of the cyclisation of the corresponding (Z)-isomer only in the configuration at the iodine centre. However, when this reaction was repeated as part of this present project, selectivities of around 8:1 were observed (vide infra) (Scheme 67)
Elaboration of these *trans* iodo-Iactones provides an efficient route to mevinic acid analogues. The *trans* selectivity, although important in the synthesis of such compounds, was not the expected result from these iodolactonisations.

The stereoselectivity obtained is higher than that found by Bartlett\textsuperscript{21} in the iodocyclisation of acid 30 (Scheme 68) and, more remarkably, it gives predominantly the *trans*- and not the *cis*-iodolactone (*ie.* it is overriding the "normal" selectivity). The selectivity which Bartlett observed is consistent with the adoption of a 'chair-like' transition state in which the methyl group will be predominantly in an 'equatorial' position (Scheme 69).

This implies that the stereoselectivity in the cyclisation of β-hydroxy-δ-alkenoic acids is the result of iodolactonisation *via* a transition state 31 in which the silyloxy function is predominantly in the axial

\[ \text{Scheme 68} \]

\[ \text{Scheme 69} \]
The suggested reason for the predominance of transition state 31 is hydrogen bonding between the acid group and the oxygen of the silyloxy function. This provides stabilisation for the transition state 31 to such an extent that it becomes favourable to have the silicon group in the axial position.

This explanation is deficient in that it does not explain the increasing selectivity associated with the increasing bulk of the silicon protecting group, unless increasing electron density at silicon causes an increase in electron donation to the oxygen atom enabling it to hydrogen bond more efficiently. There are also only a few examples of the involvement of silyl ethers in hydrogen bonding of this sort. There have, however, been no alternative explanations proposed so far.

This project began with these results in hand. In order to enhance the utility of the iodolactones, it was necessary to determine the stereochemistry of the iodine centre in these lactones. Previous workers had generally removed the iodine reductively as a first step after iodocyclisation. However, it was envisaged that the iodine could be used to enable the introduction of additional functional groups with known stereochemistry into the side chain, as well as provide other synthetic opportunities.
The approach used in this project to determine the stereochemistry at the iodine centre was the synthesis of the (Z)- and (E)-β-hydroxy-δ-alkenoic acids 32 and 28 in such a way that pure geometrical isomers were obtained. The geometrical purity was required to ensure that the stereoselectivity with which the iodine centre was formed was a true reflection of the stereoselectivity of the reaction. These acids were investigated separately as it was anticipated that the geometry of the olefin would be important. It was envisaged that the stereochemistry at the iodine centre could be determined as follows: iodolactonisation of the acids 33 and treatment of the resulting lactones 34 with sodium carbonate in methanol was expected to give just, the epoxy methyl esters 35; by methanolysis of the lactone ring; base induced cyclisation of the resulting iodohydrin completes the sequence. It was anticipated that the stereochemistry of these epoxides could then be determined by NMR studies allowing the original stereochemistry at iodine to be deduced (Scheme 70).

The alkyne 36 was prepared by a method to be described later (p. 73) and silylated in good yield using triisopropylsilyl chloride and imidazole in dimethylformamide. The resulting silyl ether 37 was Lindlar reduced, using 5% palladium on barium sulphate, poisoned with
quinoline in ethyl acetate,\(^{82}\) to furnish the (Z)-ester 38, which was saponified to give the desired (Z)-acid 32, in high yield, as a single geometrical isomer (according to \(^{13}\)C NMR). The silyl ether 37 was itself saponified to give the acid 39 in good yield. Reduction of the acetylene function in the acid 39 using lithium in ammonia\(^{83}\) gave the desired (E)-acid 28 as a single geometrical isomer (by \(^{13}\)C NMR), in high yield (Scheme 71). Cyclisation of the (Z)-\(\beta\)-hydroxy-\(\delta\)-alkenoic acid 32 (in aqueous acetonitrile, at 0°C, using 3 equivalents of iodine and 3 equivalents of sodium bicarbonate, for 3 hours) led to the iodolactone 40, whereas cyclisation of the corresponding (E)-\(\beta\)-hydroxy-\(\delta\)-alkenoic acid 28 in the same way led to the iodolactones 41 and 42 in a ratio of 8:1.

Scheme 71
The relative stereochemistries of these lactones were determined primarily by consideration of coupling constants; the major lactone 41 exhibited a narrow resonance for the 4-H with couplings to the adjacent 3-H\textsubscript{ax} and 5-H\textsubscript{ax} which indicated it was in an equatorial position and therefore \textit{trans} to the clearly axially positioned 6-H. The minor lactone 42 showed data indicating that both 4-H and 6-H were axially positioned. All three iodolactones were converted into the corresponding epoxides 43, 44 and 45 as described above.

Analysis of the 400 MHz \textsuperscript{1}H NMR spectra of the three epoxides allowed the 5-H to 6-H (cross epoxide) coupling constant [\textit{J}_{5,6}] to be found
in each case, by determining which coupling was present in both the 5-H and 6-H resonances. In epoxide 43 derived from the (Z)-acid 32, $J_{5,6}$ was 4.6 Hz, whereas in the epoxides 44 and 45, derived from the (E)-acid 28, $J_{5,6}$ was 2.3 and 2.7 Hz respectively. These values correspond to literature values for such epoxide coupling constants; cis epoxides show cross epoxide coupling constants of 4-6 Hz whereas trans epoxides have corresponding values of 2-3 Hz. This demonstrates that the (E)-acids lead to trans epoxides and (Z)-acids lead to cis epoxides. This enables the assignment of the stereochemistry at the iodine centres to be deduced as shown (Scheme 72).

The stereochemistry proven to exist at the iodine centre is consistent with the transition state 31 and also shows that the expected overall anti addition of iodine to the olefin has occurred. This provides evidence for the transition states shown in Scheme 73 (vide supra).

(II) Tetrahydrofurans By Overall 5-endo-trig Cyclisations

During the course of his work on selenolactonisation, Bennett
used hydroxy-acids because the silicon protecting groups used in the iodolactonisations were incompatible with the use of selenium. In these reactions, he noted the occurrence of side products which were identified as the seleno-THFs 46. There was little stereoselection observed under the conditions used (Scheme 74).

Bennett also iodocyclised the hydroxy acid 47 and obtained the THF acids 48 and 49 exclusively. This can be explained by the fact that lactonisation would require a positive charge to be effectively generated β to the aryl system and is therefore disfavoured relative to overall “5-endo-trig” cyclisation via a stabilised positive charge in a benzylic position (Scheme 75).

Also, whilst working on the foregoing iodolactonisation reactions, Bennett \(^7\^8\) noted the occurrence of the THF acids 50 as trace by-products (less than 5%).
It was assumed that these compounds arose from loss of the silicon group and subsequent cyclisation of the hydroxyl function in a 5-endo trig fashion. It became obvious that to further investigate these reactions, β-hydroxy-δ-alkenoate esters needed to be synthesised. By blocking the lactonisation process and favouring the etherification process, it was thought that the “5-endo-trig” cyclisation process could be induced to occur to a greater or even exclusive extent. Unexpectedly, when the methyl (Z)-β-hydroxy-δ-alkenoate 51a was cyclised under the standard kinetic conditions developed by Bartlett, the hydroxy-THF 52a was obtained as a single diastereoisomer (Scheme 76). Bedford had carried out a small number of these reactions in aqueous acetonitrile and had obtained somewhat lower yields of the hydroxy-THFs. He also cyclised (Z)-β-hydroxy-δ-alkenoates under anhydrous conditions but obtained a mixture of hydroxy- and iodo-THFs.

Scheme 76

Bennett synthesised the benzoate ester of the hydroxy-THF product 52a and also of its epimer (synthesised by Mitsunobu inversion). The spectral data from these compounds were compared to the examples
given by Williams\textsuperscript{87} for similar systems and the stereochemical assignments thus derived were consistent with those derived from NOE irradiation data (Scheme 77).

Scheme 77

\[
\begin{align*}
\text{PhCOCl (52a)} & \quad \text{Mitsunobu} \\
\text{Ph} & \quad \text{Bu}
\end{align*}
\]

The situation was further complicated by the fact that upon treatment of the (E)-β-hydroxy-δ-alkenoate 53a in aqueous acetonitrile with 3 equivalents of iodine and 3 equivalents of sodium bicarbonate at 0°C, good yields of the iodo-THF ester 54a were obtained with very high stereoselectivity (Scheme 78).\textsuperscript{80}

Scheme 78

\[
\begin{align*}
\text{R}^{-}\text{C}=\text{O} & \quad \text{I}_2, \text{MeCN} \\
\text{R} & \quad \text{NaHCO}_3 \\
\text{H}_2\text{O} & \quad \text{R} = \text{Et}
\end{align*}
\]

With these results in hand, it was decided to investigate the generality of this process. Bedford\textsuperscript{80} had attempted to cyclise the homoallylic alcohols 55 and 56 under aqueous conditions and recovered regio- and stereoisomers of the iodohydrins resulting from the addition of water to the iodonium ion; significant regioselectivity was observed (Scheme 79).
It was against the background of these somewhat confusing results that the present project began. There were three primary objectives: (i) To establish a consistent pattern for the iodocyclisation of $\beta$-hydroxy-$\delta$-alkenoates and a mechanistic rationalisation, (ii) To attempt to extend this to give a pattern for homoallylic alcohols in general, and (iii) To devise efficient routes to the cyclisation precursors.

The observation of iodohydrin formation in the attempted cyclisation of homoallylic alcohols 55 and 56, presumably by the attack of water upon the iodonium ions, suggested that the removal of all the water from the reaction mixture would lead to interesting results. This was achieved using Aldrich HPLC grade acetonitrile, distilled under an atmosphere of nitrogen from $P_2O_5$ (Super dry acetonitrile), as the solvent. The use of molecular sieves or the addition of dried magnesium sulphate was considered, but it was decided to postpone these investigations, as it was felt that the use of such additives could complicate the results still further. It has been discovered that the cyclisation of (Z)-$\beta$-hydroxy-$\delta$-alkenoates to give a hydroxy-THF is an unusual and so far unique result.
which was in some ways misleading during the early stages of this work.

As the first part of this present project, it was established that the 5-endo-trig cyclisation of (E)-β-hydroxy-δ-alkenoates 53b is relatively insensitive to the presence of water. The ester 53b was obtained as a single geometrical isomer by a route to be described later (p. 76). A single sample of the ester 53b was divided into two equal portions and one was iodocyclised using anhydrous conditions as described above and the other was iodocyclised using acetonitrile containing 10% water. The iodo-THF 54b was obtained as a single diastereoisomer in high yield in both cases, although a slightly higher yield was obtained in the former case under anhydrous conditions (Scheme 80). This finding proved to be extremely significant.

The cyclisations of a variety of homoallylic alcohols in super dry acetonitrile have been investigated, and it was pleasing to find that generally good yields of a variety of iodo-THFs have been obtained. (E)-Hex-3-en-1-ol 57 underwent a facile cyclisation in less than 5 min at 0°C or in under 2 hours at -25°C to give the iodo-THF 58 in equally high yield in either case (Scheme 81). There was absolutely no trace of any other
products upon work up and a crude $^{13}$C NMR showed only resonances assignable to the iodo-THF 58 (Figure 1). The data obtained for this compound corresponded to those quoted by Schauble et al.\textsuperscript{36} Further investigation by NOE experiments proved the trans stereochemistry of the product obtained. (Z)-Hex-3-en-1-ol 59 cyclised only slowly at 0°C, but under the anhydrous conditions, and with periodic addition of iodine, reasonable yields of the iodo-THF 60 were eventually obtained, using either nucleophilic (NaHCO$_3$) or non-nucleophilic (MgO) bases. Detailed NMR studies of the product revealed that it was definitely a THF and not the corresponding iodomethyloxetane which would result from an overall “4-exo-trig” cyclisation. This was proven by the use of $^{13}$C-$^1$H correlation experiments which identified the proton resonance which was related to the easily identifiable carbon bonded to iodine (ie the resonance is shifted significantly upfield in the $^{13}$C spectrum); this was a methine QHI and comparison of its couplings in the $^1$H-$^1$H COSY spectrum showed that it was coupled to the resonances of the CH$_2$ protons in the ring and to the 2-CH$_2$O resonance. There was no coupling to the side chain proton resonances as would be observed in the case of an iodomethyloxetane. In compound 60, there is also a significant upfield shift of the resonance resulting from the 2-CH$_2$O, which is observed at $\delta_H = 2.80$. This phenomenon has yet to be fully explained but it could result from the strained configuration of the molecule. Cyclisation of 4-methylpent-4-en-1-ol 61 gave no THF products, probably because the expected educt, being a tertiary iodide, underwent rapid decomposition. The black oily nature of the crude reaction product and its $^1$H NMR spectrum suggested this had
occurred. The secondary alcohols 55 and 56, which Bedford used to produce iodohydrins, were cyclised under the present anhydrous conditions to give the iodo-THFs 62 and 63 respectively; the stereochemistries of which were proven by NOE experiments. The (E)-isomer again underwent a much smoother cyclisation, which was complete after 16 hours. In reality, the cyclisation was probably over in about 2 hours \((\text{cf cyclisation of primary homoallylic alcohols})\); crude \(^1\)H NMR showed a single product which was isolated in 80% yield after chromatography. In the case of the (Z)-isomer, cyclisation required a longer period of time but proceeded in a reasonable yield, after chromatography, of 70%.

The tertiary alcohol, (E)-2-methyl-hept-4-en-2-ol 64, was found to cyclise in equally high yield in less than 1 hour to give the 5,5-dimethyliodo-THF 65 which showed data appropriate to the structure shown. Comparison with the data for iodo-THFs 58 and 60 showed that the 2,3-trans relationship was obtained. Disubstituted double bonds could also be incorporated. For example, 4-methylpent-3-en-1-ol 66 was found to cyclise in less than 1 hour, and in high yield, to give the 2,2-dimethyliodo-THF 67 (Scheme 81). The determination of structure and stereochemistry for the iodo-THF systems involved analysis of 400 MHz \(^1\)H, \(^1\)C, \(^1\)H-\(^1\)H COSY, \(^1\)C-\(^1\)H COSY and NOE spectra. As an example, the structural and stereochemical information for the iodo-THF 62 is analysed (Figure 2 a-j) [the \(^1\)H spectrum of the iodo-THF 63 is included for comparison (Figure 3)] to illustrate how the structures of all the THFs synthesised during the course of this project were deduced.
Scheme 81

Conditions | Yield
--- | ---
I₂, MeCN, NaHCO₃ 5 min, 0°C | 90%
I₂, MeCN, NaHCO₃ 2h, -25°C | 90%
I₂, MeCN, MgO 72h, 0°C | 63%
I₂, MeCN, NaHCO₃ 16h, 0°C | 0%
I₂, MeCN, NaHCO₃ 72h, 0°C | 70%
I₂, MeCN, NaHCO₃ 16h, 0°C | 80%
I₂, MeCN, NaHCO₃ 1h, 0°C | 90%
I₂, MeCN, NaHCO₃ 1h, 0°C | 80%
Analysis of the $^{13}\text{C}\text{H}$ COSY spectrum (Figure 2e) allowed the resonances at $\delta_\text{C} = 32.35$ and $\delta_\text{H} = 4.40$ to be assigned as those corresponding to the 5-C and 5-H respectively; the large upfield shift in the resonance due to the carbon bonded to iodine means that it can easily be identified. Comparison with the $^1\text{H}\text{H}$ COSY spectrum (Figure 2d) showed that the 5-H resonance exhibited coupling to the resonances at $\delta_\text{H} = 2.76$ and 2.92. The fact that there is no coupling apparent to the side chain allows the isomeric oxetane product of the cyclisation to be discounted. The resonance at $\delta_\text{H} = 2.76$ was assigned as the 6-H because it was related to the $^{13}\text{C}$ signal in the $^{13}\text{C}\text{H}$ COSY at $\delta_\text{C} = 81.60$, and therefore it was known to be a methine $\text{CHOR}$; the coupling to the 5-H resonance proved that it was not the 3-H. The resonance at $\delta_\text{H} = 2.92$ was related to the $^{13}\text{C}$ signal in the $^{13}\text{C}\text{H}$ COSY at $\delta_\text{C} = 43.90$, and therefore it was known to be part of a methylene $\text{CH}_2$; the coupling to the 5-H resonance suggested that it was the 4-H$_A$ (ie the proton on the same face of the molecule as the 5-H). The 6-H resonance showed couplings to the side chain resonances at $\delta_\text{H} = 1.69$ and 1.83, as well as to the 5-H in the $^1\text{H}\text{H}$ COSY. Both of these side chain resonances were related to the $^{13}\text{C}$ peak at $\delta_\text{C} = 36.99$ and these signals were therefore
assigned as the 7-CH₂. The 4-H_A showed a strong geminal coupling to the resonance at δ_H = 2.31 in the ¹H-¹H COSY, suggesting that the latter was the 4-H_B. This was confirmed by the fact that both of these resonances were related to a single ¹³C signal at δ_C = 43.90. The remaining ¹H signal in the ¹³C spectrum was thought to be the 3-H and this was confirmed by the fact that the corresponding ¹H resonance at δ_H = 3.87 showed coupling to the 4-H_A and 4-H_B in the ¹H-¹H COSY. Having assigned the relevant ¹³C and ¹H resonances, the coupling constants (determined from the 400 MHz ¹H NMR), and subsequently the NOE data, were analysed.

<table>
<thead>
<tr>
<th>Resonance</th>
<th>δ_H</th>
<th>multiplicity</th>
<th>J values</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-H_B</td>
<td>2.31</td>
<td>ddd</td>
<td>14.6, 6.4 and 3.0</td>
</tr>
<tr>
<td>6-H</td>
<td>2.76</td>
<td>ddd</td>
<td>6.4, 6.4 and 4.0</td>
</tr>
<tr>
<td>4-H_A</td>
<td>2.92</td>
<td>ddd</td>
<td>14.6, 8.0 and 7.0</td>
</tr>
<tr>
<td>3-H</td>
<td>3.86</td>
<td>dddd</td>
<td>8.0, 6.4, 6.4 and 6.4</td>
</tr>
<tr>
<td>5-H</td>
<td>4.40</td>
<td>ddd</td>
<td>7.0, 4.0 and 3.0</td>
</tr>
</tbody>
</table>

These coupling constants give a great deal of information about the stereochemistry of the product. During these studies, it has been found that those systems in which the iodine has a cis relationship to the adjacent CHOR, the coupling constants observed for the adjacent CHOR are of the pattern J = -7, 4-7 and -3. Those systems in which the iodine has a trans relationship to the adjacent CHOR, the coupling constants for the adjacent CHOR are again of the pattern J = -7, 4-7 and -3. However, in the case of the cis example, the smallest coupling is between the CHI and the CHOR, whereas, in the case of the trans examples, the smallest
coupling is between the CHOR and one of the side chain protons closest to the iodine atom (Figure 4).

Figure 4

These coupling constants therefore suggested a *cis* relationship between the 6-H and 5-H, as the coupling constant was 4.0 Hz, whereas the couplings to the side chain were both 6.4 Hz. The 4-H<sub>A</sub> appears to be on the same face as both the 5-H and the 3-H, as it has large couplings to both of these resonances. NOE data (Figure 2f-j) confirmed this as shown, suggesting an all-*cis* stereochemistry for the iodo-THF 62. The strong enhancement of both the 3-H and the 5-H, by irradiation of the 4-H<sub>A</sub>, shows that these three protons share the same face of the molecule. The enhancement of 6-H, by irradiation of the 5-H, confirms an all-*cis*-stereochemistry.

<table>
<thead>
<tr>
<th></th>
<th>3</th>
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<th>4&lt;sub&gt;B&lt;/sub&gt;</th>
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The dithiane derivative 68 cyclised smoothly but in somewhat lower yield due to \textit{in situ} hydrolysis of the dithiane unit. This resulted in the formation of a significant proportion of the aldehyde 69 which was produced along with corresponding dithiane 70 in 49% overall yield (Scheme 82).

Further examples included various (E)-\(\beta\)-hydroxy-\(\delta\)-alkenoates which were synthesised as part of the work towards a general synthesis of the cyclisation precursors. These molecules underwent fast cyclisation to give the iodo-THF esters with at least as good stereocontrol as in the cyclisation of ester 53b. The \textsuperscript{t}butyldiphenylsilyloxy group was shown to survive the cyclisation conditions, although a \textsuperscript{t}butyldimethylsilyloxy group was cleaved. A THF containing a remote phenyl substituent 54c was also synthesised; the aryl function could be a potential synthetic equivalent of an acid moiety upon oxidation (Scheme 76).\textsuperscript{88} NOE data and comparison to the data from iodo-THF 54b was used to confirm the stereochemistries shown.
When (Z)-β-hydroxy-δ-alkenoates were cyclised by stirring under the standard iodoetherification conditions using anhydrous acetonitrile for 72 hours, hydroxy-THFs were obtained in high yields (Scheme 84). Bedford also cyclised (Z)-β-hydroxy-δ-alkenoates in dry conditions but obtained a mixture of hydroxy- and iodo-THFs. This result has since been attributed to impurities consisting of (E)-β-hydroxy-δ-alkenoates in the starting materials. Examples of the cyclisations were repeated as part of this present project using geometrically pure (Z)-methyl 3-hydroxy-dec-5-enoate (one isomer by $^{13}$C NMR) in 0%, 1%, 5%, 10% and 50% aqueous acetonitrile (Scheme 85) to give hydroxy-THF but no iodo-THF products. The reactions proceed with good stereoselectivities for the isomer shown over its 3-epimer of around 10:1. [An exception was the case of $R = \text{Me}$ where a stereoselection of around 8:1 was obtained in subsequent studies (see p 104).]

Various (Z)-methyl β-hydroxy-δ-alkenoates have been synthesised as part of this project and all the examples cyclise in high yields under these conditions [eg (Scheme 86)]. However, both the butyl and benzyl esters corresponding to the β-hydroxy-δ-alkenoate underwent cyclisation in much lower yields (Scheme 87). This result has not been explained; there were no signs of valerolactone products from ester cleavage in the case of the benzyl ester, but there were various impurities, apparently resulting primarily from iodoxydrin formation.

63
Scheme 85

\[
\begin{align*}
&\text{Bu} & \text{CO}_2\text{Me} & \text{I}_2, \text{NaHCO}_3 \\
&\text{OH} & & 72\text{h}, 0^\circ\text{C} \\
&(\text{71}) & & \text{MeCN/ X% H}_2\text{O} \\
&\xrightarrow{\text{I}_2, \text{NaHCO}_3} & & \text{HO-} \\
&\text{Bu} & \text{CO}_2\text{Me} & (\text{72}) \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>X% H\text{O}</th>
<th>Yield</th>
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<tr>
<td>0%</td>
<td>83%</td>
</tr>
<tr>
<td>1%</td>
<td>85%</td>
</tr>
<tr>
<td>5%</td>
<td>75%</td>
</tr>
<tr>
<td>10%</td>
<td>75%</td>
</tr>
<tr>
<td>50%</td>
<td>60%</td>
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Scheme 86

\[
\begin{align*}
&\text{Ph} & \text{CO}_2\text{Me} & \text{I}_2, \text{MeCN}, \text{NaHCO}_3 \\
&\text{OH} & & 72\text{h}, 0^\circ\text{C} \\
&(\text{51b}) & & \text{Ph} \\
&\xrightarrow{\text{I}_2, \text{MeCN}, \text{NaHCO}_3} & & \text{HO-} \\
&\text{Ph} & \text{CO}_2\text{Me} & (\text{52b}) \\
\end{align*}
\]

\[
\begin{align*}
&\text{Et} & \text{CO}_2\text{Me} & \text{I}_2, 50\% \text{MeCN}, \\
&\text{OH} & & 72\text{h}, 0^\circ\text{C} \\
&\text{Et} & & \text{Et} \\
&\xrightarrow{\text{I}_2, 50\% \text{MeCN},} & & \text{HO-} \\
&\text{Et} & \text{CO}_2\text{Me} & 70\%^{80} \\
\end{align*}
\]

Scheme 87

\[
\begin{align*}
&\text{Bu} & \text{CO}_2\text{Bu} & \text{I}_2, 70\% \text{MeCN}, \\
&\text{OH} & & 30\% \text{H}_2\text{O}, \text{NaHCO}_3 \\
&(\text{BuOH}) & & \text{Bu} \\
&\xrightarrow{\text{I}_2, 70\% \text{MeCN},} & & \text{HO-} \\
&\text{Bu} & \text{CO}_2\text{Bu} & 30\% \\
\end{align*}
\]

\[
\begin{align*}
&\text{Bu} & \text{CO}_2\text{Bz} & \text{I}_2, 70\% \text{MeCN}, \\
&\text{OH} & & 30\% \text{H}_2\text{O}, \text{NaHCO}_3 \\
&(\text{BuOH}) & & \text{Bu} \\
&\xrightarrow{\text{I}_2, 70\% \text{MeCN},} & & \text{HO-} \\
&\text{Bu} & \text{CO}_2\text{Bz} & 10\% \\
\end{align*}
\]
It is assumed that the cyclisation of (E)-β-hydroxy-δ-alkenoates proceeds through a ‘chair like’ transition state (Scheme 88). The reason that the cyclisations are insensitive to the presence of water could be that the hydroxyl function has increased nucleophilicity due to the fact that it is intramolecularly hydrogen bonded to the ester function. The electron donating effect of this hydrogen bonding, and the consequent weakening of the O-H bond, allows cyclisation to take preference over the attack of water upon the iodonium ion. This explanation is closely related to the explanation of the unusual stereochemical outcome of the iodo-lactonisation reactions (cf transition state 31) (Scheme 89).

The proposed transition states for the 5-endo-trig cyclisations of general homoallylic alcohols in anhydrous acetonitrile are postulated to be ‘chair like’, and are related to the foregoing transition state for the cyclisation of (E)-β-hydroxy-δ-alkenoates (Scheme 90). The transition state for (E)-homoallylic alcohols 73 is favoured as there are no large steric interactions, whereas the corresponding transition state 74 for (Z)-homoallylic alcohols has a great deal of steric hindrance. This is consistent with the observation that the cyclisation of the trans isomers is
much smoother than that of the cis isomers. In transition state 74 the approach of the hydroxyl to the iodonium ion is blocked by the substituent R\(^1\) and the transition state has a "boat" like eclipsed conformation. This would lead to a slow cyclisation, consistent with the observations made earlier. The stereochemistry of the substituents on the iodo-THF products are derived from the transition states as drawn and these also correspond to the products observed in these reactions. This provides good evidence for intermediacy of a "chair like" transition state.

![Scheme 90](image.png)

The hindered nature of transition state 74 also helps to explain perhaps the most unusual result in this field, namely the cyclisation of (Z)-\(\beta\)-hydroxy-\(\delta\)-alkenoates to give hydroxy-THFs.

At first, the more obvious mechanistic explanations for the formation of hydroxy-THFs from the iodocyclisation of (Z)-\(\beta\)-hydroxy-\(\delta\)-alkenoates were investigated, in two isolated studies by Bedford.\(^80\) The
possibility of hydroxy-THFs arising from an $S_N2$ substitution at an initially formed iodo-THF was discounted because when the all-cis-iodo-THF 75 was subjected to the reaction conditions, no substitution was observed (Scheme 91).

A second possible explanation is the *in situ* formation and ring opening of epoxides 76 to give hydroxy-THFs. This was discounted because when such an epoxide was subjected to the reaction conditions, no THF products were observed (Scheme 92).

These results led to the consideration of the possible involvement of the ester function at an early stage of the cyclisation. The hindered nature of transition state 74 causes direct cyclisation to be a slow process, but in the case of general (Z)-homoallylic alcohols there are no alternative pathways. In the case of (Z)-\(\beta\)-hydroxy-\(\delta\)-alkenoates, it is proposed that the
mechanism shown (Scheme 93) operates in preference to direct cyclisation due to the steric strain involved in transition state 74.

Scheme 93

Attack of the ester function upon the iodonium ion 75 in an 6-exo-fashion, would yield the stabilised carbocation 76. Attack of an external oxygen nucleophile (eg water) upon this carbocation would furnish the ortho-ester 77 which could then collapse, regenerating the methyl ester and giving rise to the iodo-diol 78, as a single isomer. The enhanced nucleophilicity of the hydroxyl function in β-hydroxy-δ-
alkenoates, which is a key feature of the insensitivity of the cyclisation of (E)-β-hydroxy-δ-alkenoates to the presence of water, allows displacement of the iodine intramolecularly to give the hydroxy-THF 72. When the cyclisation was stopped after 3 hours, an intermediate consistent by 1H and 13C NMR and IR with the iodo-diol 78, was isolated as the major product. This intermediate was converted quantitatively into the hydroxy-THF 72 upon treatment with sodium carbonate in acetonitrile proving that iodine was unnecessary for this final step. Although the final step of the process has now been proven to be a fairly slow displacement of iodine, the mechanism of the iodo-diol formation remains somewhat open to speculation, although the proposed route certainly does account for the observed stereochemistry.

The cationic nature of these processes means that they are only formally exceptions to Baldwin’s rules, which were not intended for use in cationic processes. An interesting test case was chosen as part of the initial work of this project. The gem-dimethyl-β-hydroxy-δ-alkenoate 80 was synthesised in order to see whether steric hindrance would make it behave like a (Z)-β-hydroxy-δ-alkenoate or whether the extra electron donation to the iodonium ion would stabilise a positive charge sufficiently to favour a direct cyclisation in a 5-endo-trig fashion. Unsaturated acid 81 was prepared by a literature procedure89 and was converted into its acyl imidazole derivative before being treated with the magnesium chelate Grignard reagent from methyl hydrogen malonate to give the β-keto ester 82. The ester was then reduced using borane-tbutylamine complex to give the hydroxy ester 80. To our surprise, this molecule underwent
iodocyclisation to give the iodo-THF 83 in good yield, despite the effects of steric hindrance. This serves to emphasise the pronounced effect that stabilisation of a cation can have upon the cyclisation of β-hydroxy-δ-alkenoates (Scheme 94).

Scheme 94

Prior to the beginning of this project, various different routes had been used by previous researchers in our group to synthesise the homoallylic alcohols required as cyclisation precursors; there was, however, no general or particularly efficient route available. The potential sensitivity of the β-hydroxy-δ-alkenoates to acid and base meant that a mild route for their preparation was required. It was decided to seek routes to these compounds which would not only yield pure geometrical isomers, to ensure the results of the cyclisations were clear
and to maximise the synthetic utility of the products, but which would also prove amenable to the incorporation of chirality into the system, which would be vital in later projected natural product target syntheses. An appropriate approach would therefore involve the generation of the chiral centre in the cyclisation precursor in a controlled way.

The use of methyl 3,4-epoxybutanoate 84 has allowed all of these goals to be achieved. Previous workers\textsuperscript{80} had found this molecule difficult to prepare in usable quantities due to its high volatility (bp = 110°C) and its extreme acid and base sensitivity (Scheme 95). As shown below, the acidity of the $\alpha$ protons is reasonably high and even treatment with carbonate will cause rearrangement to the unsaturated ester 85. Acid also triggers ring opening of the epoxide. However, it was found that with the use of low boiling solvents and mild conditions, the epoxide could be prepared in 90% overall yield in 2 steps, in quantities of up to 20 g. Vinyl acetic acid was esterified using the DCC/DMAP method\textsuperscript{90} in dichloromethane and the resulting ester epoxidised using buffered urea-hydrogen peroxide complex and trifluoroacetic anhydride (Scheme 96).\textsuperscript{91}

Scheme 95

\begin{align*}
\text{H}^+ & \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{Me} \\
\text{(84)} & \quad \text{acid or base} \quad \text{HO} \quad \text{HO} \quad \text{CO}_2\text{Me} \\
& \quad \text{(85)}
\end{align*}

Scheme 96

\begin{align*}
\text{HO} & \quad \text{O} \quad \text{DCM, 98%} \\
\text{DCC/DMAP} & \quad \text{MeO} \quad \text{DCM, 97%} \\
& \quad \text{UHP, TFAA} \\
\pm & \quad \text{(84)}
\end{align*}
The corresponding butyl ester was prepared as part of the early work of this present project, in order to reduce the volatility problems, but the failure of the (Z)-butyl β-hydroxy-δ-alkenoates formed to cyclise in high yield meant that this approach was not continued.

Treatment of the epoxide 84 with an appropriate nucleophile then leads to a convergent route to the required β-hydroxy esters. The use of (E)-vinyl anions would give the (E)-β-hydroxy-δ-alkenoates whilst treatment with acetylide anions, and subsequent Lindlar reduction would lead to the (Z)-β-hydroxy-δ-alkenoates (Scheme 97).

Scheme 97

Possible viable sources of non-basic vinyl anions appropriate for epoxide opening include vinyl alanate complexes and vinyl cuprates, whereas simple lithio acetylides can be used to open epoxides.

Chiral ethyl 3,4-epoxybutanoate has been synthesised in 5 steps from (S)-malic acid by Larchevêque who demonstrated that it was opened highly regioselectively by various nucleophiles, especially vinyl cuprates (Scheme 98).
The methyl ester has also been resolved using pig liver esterase. The general approach adopted to all the (Z)-β-hydroxy-δ-alkenoates synthesised in this project has been the coupling of acetylide anions, generated using butyl lithium, with the (±)-epoxy ester 84 in the presence of a stoichiometric amount of boron trifluoride etherate. The original procedure was developed by Yamaguchi. The approach used during this project was adapted because the excess acetylene used in the original procedure also attacked the ester function of the substrate at the carbonyl site to give the dialkynyl ketone 86 as a side product. The coupling was carried out for 15-20 minutes at -78°C which gave high yields of the β-hydroxy-δ-alkynoate 87 and minimal ketone formation (Scheme 99).
Lindlar reduction of these acetylenes was accomplished in high yield to give the (Z)-β-hydroxy-δ-alkenoates as single isomers according to $^{13}$C NMR spectroscopy. The commercially supplied Lindlar catalyst (Aldrich) proved unreliable and so the catalyst was prepared from 5% palladium on barium sulphate by poisoning with quinoline, prior to each reduction.\textsuperscript{82}

**(B) (E)- and (Z)- Homoallylic alcohols**

These molecules can generally be accessed by a coupling reaction of an acetylene and an epoxide under boron trifluoride catalysis, as described by Yamaguchi.\textsuperscript{96}

The acetylenes produced can be reduced specifically to give (E)- or (Z)-homoallylic alcohols as single geometric isomers. Lindlar reduction, as previously described, gave the (Z)-isomers in high yield, pure by $^{13}$C NMR spectroscopy, whereas reduction by refluxing with lithium aluminium hydride bis-tetrahydrofuran in toluene over 48 hours,
afforded the corresponding (E)-isomers in approximately 75% yield, again as single isomers according to $^{13}$C NMR spectroscopy (Scheme 100).

Scheme 100

Overall, this provides routes to homoallylic alcohols which are applicable to many systems and can be applied to asymmetric synthesis.

**(C) (E)-β-Hydroxy-δ-alkenoates**

The synthesis of (E)-β-hydroxy-δ-alkenoates has provided many more problems than the routes to the other homoallylic alcohols. The use of lithium aluminium hydride to reduce an acetylene is obviously not compatible with the ester function. The work of Alexakis$^{97}$ led to the consideration of the use of vinyl alanates as the source of vinyl anions. This work comprised the first use of vinyl alanates in the synthesis of β-hydroxy-esters. The (±)-epoxy-ester 84 was treated with the vinyl alanate complex derived from 1-hexyne [by treatment with diisobutylaluminium hydride in hexane at 50°C for 2 hours, and reaction of the resulting vinyl alane with methyl lithium] in the presence of boron trifluoride etherate, to give the (E)-β-hydroxy-δ-alkenoate 53b in high yield, as a single isomer,
according to $^{13}$C NMR spectroscopy (Scheme 101). This pure hydroxy-ester \( 53b \) proved extremely useful in the investigations of the iodocyclisations (Scheme 80).

Scheme 101

\[ \begin{align*}
\text{Al}^{\prime}(\text{Bu})_{2}\text{Me} & \quad \text{(i) BF$_3$:OEt$_2$ -78°C} & \quad \text{OH} \\
\text{Li}^+ & \quad \text{(ii) epoxide \ 84} & \quad \text{CO$_2$Me} \\
\end{align*} \]

However, when this new approach was extended to the alkylation of 4-phenylbutyne, smooth vinyl alane formation was not observed, except over 48 hours at 50°C in the presence of diisobutylaluminium hydride. Subsequent vinyl alanate formation in this system was not observed. Although this methodology is probably extendable to the coupling of enynes\(^98\) to the (±)-epoxy-ester \( 84 \), it is also limited in that smooth (E)-vinyl alane formation is not observed in the presence of heteroatoms.\(^99\) Other methods of coupling to the (±)-epoxyester \( 84 \) were therefore sought.

Vinyl cuprate chemistry proved very unreliable in the generation of vinyl anions and in the subsequent coupling reactions required. The results obtained by Larchevêque\(^94\) could not be repeated. (E)-1-Iodo-hexene was prepared\(^92\) and used in the formation of the corresponding vinyl lithium via halogen metal exchange. This vinyl lithium was used in the attempted cuprate formation with copper (I) iodide and with copper (I) cyanide and also in the formation of higher cuprates using lithium 2-thienylcyanocuprate.\(^100\) However, none of these reagents were found to couple with the epoxy-ester \( 84 \). One reason for this could be the extreme base sensitivity of the epoxide; the major product isolated from these
attempted couplings was the ester 85 (Scheme 102). This simply results from the potential nucleophile acting as a base rather than as a nucleophile. Further work on the use of vinyl cuprates is described later (p. 130).

Scheme 102

\[
\begin{align*}
\text{CuLi}_2 \quad \text{epoxide 84} \\
\xrightarrow{\text{HO-CO}_2\text{Me}} \\
(85)
\end{align*}
\]

Direct transformation of vinyl alanes into vinyl cuprates was advocated by Ireland\textsuperscript{101} but this method carries with it the restrictions which apply to the generation of vinyl alanates. At this point, it was decided that the adoption of less elegant routes to the (E)-β-hydroxy-δ-alkenoates was necessary. The first approach considered was the use of the aforementioned acid 28 (p. 48); this compound was treated with diazomethane to give the silyl ether 88 in good yield. Deprotection of this molecule with tetrabutyl-ammonium fluoride in tetrahydrofuran gave the (E)-β-hydroxy-δ-alkenoate 53\textsuperscript{b} (Scheme 103) which was easily identified by comparison to earlier samples. Although this method is fairly general, it is relatively lengthy and is also incompatible with aromatic functionality which would be reduced (Birch) during the lithium in ammonia step, which is used to generate the (E)-double bond.
It was necessary to find a functional group to act as an equivalent of the ester grouping. This group needed to be simply convertible into a methyl ester group, and also needed to be stable to lithium aluminium hydride reduction at high temperatures. The dithiane group was investigated with this in mind, because the epoxide 89 had been prepared in homochiral form by Bèneche. The racemic epoxide 89 was prepared by literature methods[^103] and was coupled in reasonable yield to 4-phenylbutyne under standard Yamaguchi conditions[^96] to give the dithianyl acetylene 90. This was reduced using lithium aluminium hydride bis-tetrahydrofuran in toluene to furnish the alkene 68, in high yield, as a single geometrical isomer by $^{13}$C NMR. This alkene was treated with excess methyl iodide in wet acetone, at reflux in the presence of sodium carbonate, to give the aldehyde 91 in good yield. Addition of further portions of methyl iodide to the mixture was necessary in order to obtain a good conversion. Hydrolysis of the dithiane group with N-chlorosuccinimide[^104] was attempted without success; the dithiane
appeared to be stable to these reaction conditions. The aldehyde 91 was oxidised directly to the methyl ester 92 using pyridinium dichromate in dimethylformamide in the presence of methanol (Scheme 104).105 This involves direct oxidation of the dimethyl acetal which occurs rapidly; the methanol solvent is only oxidised slowly under the reaction conditions and there was no oxidation of the secondary hydroxyl present in the substrate. The data for this pure geometrical isomer were compared to that of the pure (Z)-isomer (Scheme 86) and the two compounds were shown to be different.

Scheme 104

Oxidation of the aldehyde to the corresponding acid was also attempted using potassium permanganate in t-butanol106 and also with
silver(I) oxide, but with little success. The dithiane based approach proved to be fairly general but it is by no means ideal and other routes to accomplish the synthesis also need to be investigated.

In conclusion, the synthetic importance of these reactions makes it slightly surprising that the iodo cyclisation of homoallylic alcohols has not been explored before. The susceptibility of these systems to solvolysis of the iodonium ion, and the fact that the cyclisation is formally a 5-endo-trig process, goes some way to explaining this. The processes are, however, not strictly governed by Baldwin's rules due to their cationic nature, so the term 5-endo-trig is only an approximate description of the reactions.

The synthetic utility of the iodoetherification of homoallylic alcohols is extensive. However, the cyclisation of the (Z)-isomers needs further optimisation because the water which is generated during the course of the reaction causes some solvolysis to occur. This leads to the somewhat lower yields. Higher yields may well be obtained if the water produced can be removed, perhaps by the inclusion of molecular sieves.

The possibility that these processes occur via an initial 4-exo-trig cyclisation to give an iodomethyl oxetane and subsequent dyotropic rearrangement to give the tetrahydrofuran, has been considered (Scheme 105). These processes are known in lactone systems under Lewis acid catalysis; indeed Black has investigated them extensively. However, no evidence for the proposed oxetane intermediates has been seen, even when the reactions have been stopped after less than five minutes. Therefore, if these intermediates exist, their rearrangement must be almost
The cyclisation of (Z)-β-hydroxy-δ-alkenoates is also a very synthetically useful process. An overall stereospecific trans-dihydroxylation of a double bond, controlled by a remote hydroxyl group, is achieved. This is in many ways complementary to the chiral cis-dihydroxylations introduced by Sharpless and others.\textsuperscript{109} The limitation of this process to β-hydroxy-esters is still under investigation, but at this stage it does present a restriction of the synthetic utility of the process. The comparison of this technique to the Sharpless epoxidation of homoallylic alcohols is favourable, as only approximately 30\% enantiomeric excess is obtained from such an epoxidation.\textsuperscript{110}
CHAPTER THREE

The Total Synthesis of Muscarine

(I) Introduction 82

(II) Approaches to Muscarine 84

(III) (Z)-β-Hydroxy-δ-alkenoates in the Synthesis of Muscarine 98
The Total Synthesis of Muscarine

(1) Introduction

L-(+)-Muscarine 93 was the subject of intense interest long before its structure was first determined by X-ray crystallography in 1957. Indeed, the plot of a murder mystery novel, published in 1930, turned upon the difference between natural and synthetic muscarine.

Muscarine is the major toxic principle found in the well known mushroom *Amanita muscaria* (Fly agaric), a common, but dangerous feature of deciduous woodland in autumn. It is, however, not the only biologically active alkaloid isolated from this species. In fact, the related alkaloid muscimol 94 (Scheme 106) is responsible for the notorious hallucinogenic effects of the mushroom, which have led to its ritualistic use by the Shamen and medicine men of Siberian tribes, and to the cults of mushroom worship among South American indians. Muscarine has also been isolated from *Amanita phalloides* (death cap mushroom) and certain species of *Inocybe* and *Clitocybe*. 
The pharmacological action of muscarine upon smooth muscle so resembles that of acetyl choline that direct action on cholinergic receptors in the autonomic nervous system has come to be known as "muscarinic" action. Muscarine is a selective agonist of acetyl choline in the smooth muscles of the gastro-intestinal tract, eye, exocrine glands and heart. Recently, pharmacological investigations with selective antagonists evidenced distinct sub-types of muscarinic receptors. The receptors in the central nervous system and peripheral ganglia (M\textsubscript{1}), are distinguishable from the receptors of the cardiac cells (M\textsubscript{2}) and also from those of the smooth muscles and exocrine glands (M\textsubscript{3}). There is renewed interest in the muscarinic field because of the discovery of a relationship between cholinergic deficits in cortical and hippocampal areas and the pathology of Alzheimer's disease. Current activity in exploring compounds which may be specific agonists or antagonists of individual muscarinic receptors is intense. This means that a readily adaptable synthesis of muscarine and its analogues, particularly those where changes are made at C-2 (ie where the methyl group at C-2 is exchanged for another functional group) and which retain activity, would be of great synthetic value.

Muscarine isolated from natural sources is frequently
contaminated with *allo*-muscarine 95 and its purification is tedious and impractical. For this reason, pharmacological studies are generally carried out using synthetic material. This means that short and efficient syntheses of L-\((+)\)-muscarine are of utilitarian value.

(95)

(II) Approaches to Muscarine

There have been numerous asymmetric total syntheses of muscarine, some of which are genuinely asymmetric while others involve the separation of enantiomers. There have also been a number of achiral syntheses. A wide ranging review of the area was published in 1984.\textsuperscript{115} As part of this chapter, all the syntheses of muscarine published to date will be evaluated in terms of flexibility (ie ease of incorporation of new functional groups to the muscarine skeleton), practicality (ie number of synthetic operations involved and the scale upon which these operations can be carried out), overall yield and stereo/enantioselectivity. A new synthesis of muscarine utilising the iodoxyclisation of \((Z)\)-\(\beta\)-hydroxy-\(\delta\)-alkenoates carried out as part of this project will also be described.

L-\((+)\)-Muscarine was synthesised, and its absolute
configuration finally proven, in 1957, as the culmination of an extensive amount of work in the field by Hardeggar and his colleagues in a twelve step synthesis starting from L-arabinose. This pioneering synthesis used the diazotisation of glucose amino acid 96 to give the tetrahydrofuran 97, which was esterified and then converted into the amide 98. Amide 98 is a key intermediate, analogues of which have been used in a number of subsequent approaches to muscarine.

Scheme 107

Regiospecific tosylation followed by lithium aluminium
hydride (LAH) reduction gave the amine 99, which were then methylated to give muscarine 93 in a low overall yield (Scheme 107).

There is some scope for the synthesis of C-2 analogues of muscarine by this or by many of the subsequent carbohydrate-based approaches because the C-2 methyl group is obtained by degradation of a CH₂OH function in the original sugar. This functionality could be utilised to synthesise C-2 analogues, but this has not been attempted.

Since 1957, a variety of other carbohydrate-based syntheses have been developed: Pochet and Huynh-Dinh¹¹⁷ also synthesised one of the stereoisomers of the amine 99, this time in four steps from 2-deoxyribose. The key reaction was again the reduction of an amide, this time compound 100. Both enantiomers of muscarine and allo-muscarine were synthesised individually, but the number of steps required to synthesise 2-deoxyribose compromised the overall yield in each case (Scheme 108).

Scheme 108

\[
\begin{align*}
\text{HO}_3\text{TsO} & \quad \text{CONMe}_2 \\
\xrightarrow{\text{LAH}} & \quad \text{HO}_3\text{CH}_2\text{NMe}_2
\end{align*}
\]

(100)

Joullie et al.¹¹⁸ synthesised D-epi-allo-muscarine from D-glucose in thirteen steps with a reasonable overall yield. The carbohydrate derived epoxide 101 was ring opened using a moderately regioselective LAH reduction. After a number of steps, the amide 102
was synthesised, and another LAH reduction followed by methylation, furnished D-epi-
allo-muscarine (Scheme 109).

Scheme 109

Mubarek and Brown¹¹⁹ improved this approach by synthesising the epoxide 103 in seven steps from D-mannitol and effecting a regiospecific ring opening using Red-Al®. Monotosylation of the diol 104 thus produced, and treatment of the resulting tosylate with trimethylamine, gave muscarine in a good overall yield of 30% for the last seven steps of the synthesis (Scheme 110). The use of diol 104 to access muscarine as first seen here, has become a common feature of
many of the more recent approaches to muscarine.

Bandouzzi and Chapleur$^{120}$ also synthesised the diol 104, this time in nine steps from D-gluconolactone 105. This approach featured the homologation of lactones using hexamethylphosphoramide (HMPA) in carbon tetrachloride to give the dichloride 106 (Scheme 111) which was converted into the diol 104. The toxicity of these reagents precludes their use on larger scales and this synthesis is again not amenable to the production of C-2 analogues of muscarine.

The first non-carbohydrate based synthesis of D-(−)-allo-muscarnine was published by Fronza et al.$^{121}$ The fermentation of cinnamaldehyde with baker's yeast gave the chiral diol 107 which was converted into the amide 108 in ten steps with low overall yield. The
amide was then converted into muscarine as before (Scheme 112). Again this approach is not easily adaptable to the synthesis of C-2 analogues of muscarine because the methyl group originates from the ethanol produced by the fermentation process.

Scheme 112

Shapiro et al\textsuperscript{122} identified the problem that there were “no general syntheses of analogues of muscarine with the natural (S) stereochemistry at C-2” which is required for biological activity. The large scale synthesis of analogues of muscarine was then addressed. The piperidine \textbf{109} was cyclised in a 5-\textit{endo}-trig fashion using mercury(II) acetate to give the THF derivative \textbf{110}, which furnished the C-5 analogue of muscarine \textbf{111} after a Mitsunobu inversion (Scheme 113).

Scheme 113

These compounds are potentially highly biologically active because unlike muscarine itself, they have been shown to penetrate the blood/brain barrier. These authors did not however address the
synthesis of C-2 analogues.

Whiting et al\textsuperscript{123} developed a potentially flexible synthesis of L-(+) muscarine in 1972, \textit{via} the pig liver esterase resolution of the N-acyl amino acid 112 to give the chiral amino acid 113. Diazotisation of the amino acid 113 in the presence of methanol gave the methyl esters 114 which were converted to the corresponding amides 115. These were then separated and individually converted as before to give a moderate overall yield of L-(+) -muscarine and L-(+) -allo -muscarine (Scheme 114).

Micheli et al\textsuperscript{124} synthesised all 8 enantiomers of muscarine.
and *allo*-muscarnine by using a chemoenzymatic reduction to resolve the iodoketones 116. The iodoalcohols 117 produced were converted in two steps into muscarines (Scheme 115). The iodoketones were synthesised using an extended reaction sequence in which the C-2 methyl group was derived from methyl lactate. Obviously this substituent would be difficult to change without taking a higher homologue of lactate through the entire sequence.

Adams *et al*\textsuperscript{125} devised an elegant nine step route to the diol 104 using alanine as the starting material and utilising a rhodium carbenoid insertion. The diazoketone 118 was obtained in good yield over three steps from homochiral bromopropionic acid, derived from alanine. Rhodium catalysed insertion into the C-H bond gave the ketone 119 in good yield. Removal of the benzyl protecting group was followed by a highly stereoselective reduction of the ketone using sodium triacetoxy borohydride to invoke the directing effect of the 3-hydroxyl. This procedure gives muscarine in an acceptable 7.3% overall yield and it is theoretically extendable to the synthesis of C-2 analogues by using a different amino acid as the starting material.
A second, somewhat less flexible amino acid-based approach to muscarine, was developed by Chastrette et al.\textsuperscript{126} The epoxide 120 was synthesised in six steps from threonine and treated with vinyl magnesium bromide to give the homoallylic alcohol 121. Using the methodology for 5-exo-trig iodoetherification developed by Bartlett,\textsuperscript{30} the alcohol was cyclised to give the iodide 122 in a highly stereoselective fashion. This compound was used to alkylate trimethylamine in a single step to give muscarine iodide (Scheme 117).
The rather unsatisfactory synthesis of epoxide 120 gives a rather low overall yield and does not allow the incorporation of C-2 substituents other than methyl, except by the use of substituted threonines.

Scheme 117

Mulzer\textsuperscript{127} greatly improved this approach when he synthesised the epoxide 120 in five steps from (R)-2,3-\textsuperscript{\textregistered} isopropylidine glyceraldehyde 123, which allowed the molecule to be accessed routinely in quantities greater than 10 g. Consequently, muscarine iodide was obtained in multigram quantities. The C-2 substituent is incorporated using a stereoselective Grignard addition to the aldehyde 123 (Scheme 118) and therefore the incorporation of C-2 substituents is potentially easy. This is a comparatively long route to muscarines and the separation of stereoisomers at the early stages of the synthesis reduces the overall yield. It does however rate as one of the most
practical routes to muscarine to date.

Scheme 118

\[ \text{Scheme 118} \]

Achiral syntheses of muscarine have been used by several groups to illustrate the utility of their own methodology. Still et al\textsuperscript{128} [(a)] and Matsumoto et al\textsuperscript{129} [(b)] both synthesised the (±) amide \textsuperscript{108} by related cyclisations and converted it, as previously, into muscarine (Scheme 119). Although both of these syntheses illustrate new methodology, they represent relatively lengthy approaches to muscarine.

Scheme 119

\[ \text{Scheme 119} \]

\[ \text{Pirrung}^{130} \text{ synthesised (±)-muscarine using the ring expansion of cyclobutanones. The cycloaddition of a silyl enol ether} \]

94
with chloromethylketene followed by the removal of the halogen group, gave the cyclobutanones 124, which were separated. After a non-stereoselective ring expansion, and treatment with cyanotrimethylsilane, the mixture of THFs 125 was obtained. Separation and reduction gave the amine 126 which was methylated to give muscarine iodide using methyl iodide and 1,2,2,5,5-pentamethyl piperidine (PMP). The low yields and lack of stereospecificity rather tends to reduce this to an illustration of the use of ring expansion methodology (Scheme 120).

Scheme 120

```
OTBS

(i) Zn, Et₂O

(ii) Zn(Cu), MeOH, NH₄Cl

3:1

(124)

(i) hν, MeOH
(ii) TMSCN, BF₃.OEt₂

Steps

TBSO

1:1

(125)

(126)

MeI, PMP

N³Me₃

95
```
Overmann\textsuperscript{131} et al used the synthesis of L-\((+)-\)muscarine to illustrate the acid promoted rearrangement of allylic diols as a route to THFs. It was found that the lactate derived allylic diol \textsuperscript{127} rearranged to give the ketone \textsuperscript{128} stereospecifically. After cleavage of the benzyl ether, this ketone was oxidised using the Baeyer-Villiger reaction to give the corresponding acetate, which was cleaved to give the diol \textsuperscript{104} (Scheme 121). This compound was converted into muscarine as previously described. The overall yield for this synthesis was not high but its adaptability to allow the incorporation of a variety of functional groups makes this a potentially important route to THFs in general, and to the muscarines in particular.

\begin{center}
\textbf{Scheme 121}
\end{center}

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node[transform shape] (127) at (0,0) {\includegraphics[width=0.7\textwidth]{Scheme121}};
\node[transform shape] (128) at (1.5,0) {\includegraphics[width=0.3\textwidth]{Scheme121}};
\node[transform shape] (104) at (3,0) {\includegraphics[width=0.3\textwidth]{Scheme121}};
\end{scope}
\end{tikzpicture}
\end{center}

Fleet et al\textsuperscript{132} also synthesised the diol \textsuperscript{104} as part of an approach to L-\((+)-\)muscarine. This synthesis involved the ring contraction of lactones \textsuperscript{129} to give the diol \textsuperscript{104} stereospecifically. They achieved a total synthesis of L-\((+)-\)muscarine from L-rhamnose \textsuperscript{130} in nine steps and an overall yield of 10%; no protecting groups were used and remarkably 5.01 g of L-\((+)-\)muscarine tosylate was isolated (Scheme 122). Although this is most certainly one of the most
practical routes to muscarine, it does not allow for easy expansion into syntheses of C-2 analogues.

Scheme 122

Takano et al.\textsuperscript{133} devised a highly flexible route to muscarine starting from (R)-\textsuperscript{\$}-benzyl glycidol 131; overall, 8 steps were used to access the natural product. The homochiral acetylene 132 was cyclised using potassium \textsuperscript{t}butoxide in dimethyl sulphoxide to give the 2,3-dihydrofuran 133. Subsequent hydroboration and oxidative cleavage gave the alcohol 134, which was deprotected to give the known diol 104 (Scheme 123). This approach would allow the access of various C-2 analogues of muscarine but the overall yield is lower than the other comparable approaches.
(III) (Z)-β-hydroxy-δ-alkenoates in the Synthesis of Muscarine

Despite the extensive amounts of work in this field, a gap still exists. The asymmetric synthesis of C-2 analogues of muscarine by a short synthetic procedure in high overall yield remains an exceedingly desirable target. The availability of hydroxy-THFs of the desired stereochemistry from the iodocyclisation of (Z)-β-hydroxy-δ-alkenoates, as shown in Scheme 124, offers such a route. The efficiency with which these cyclisations occur has been demonstrated in Chapter Two. Multigram quantities of a variety of hydroxy-THF esters have been routinely obtained in a highly stereoselective manner. All of these facts pointed to the use of these hydroxy THFs to synthesise muscarine and its analogues. Such a synthesis would also be useful further proof of the structure and stereochemistry of the hydroxy-THFs formed in the cyclisation reaction, by what appears to be a
rather odd mechanism (p 68).

Scheme 124

\[
\begin{align*}
\text{\text{H}_2\text{O}} & \quad \text{I}_2, \text{MeCN} \\
\text{\text{H}_\text{2O}} & \quad \text{NaHCO}_3 \\
\end{align*}
\]

The conversion of the cyclisation products into muscarine requires a one carbon degradation of the methyl acetate side chain as shown in Scheme 125.

Scheme 125

Problems reported in the saponification of these ester groups by a previous researcher in this group at first led to the consideration of the use of (Z)-benzyl β-hydroxy-δ-alkenoates, which after cyclisation could be hydrogenolysed to give the corresponding THF-acids. These acids were considered to be vital intermediates in the approach to one carbon degradation. The outstandingly poor yields obtained from the attempted cyclisation of these benzyl esters caused this approach to be abandoned [see earlier (p. 64)]. A second approach also considered was reduction of the initial ester products to give the diol 135. Displacement of the primary alcohol with a selenocyanide function,\textsuperscript{134}
and subsequent elimination, should then result in the formation of the olefin 136. Ozonolysis with reductive (NaBH₄) work up would then furnish the known diol 104 (Scheme 126). This approach was abandoned because the displacement of the primary alcohol was not effected efficiently. Information obtained in a concurrent part of this project (p. 123), showed that the saponification of these THF acetic acid esters proceeded in good yield, without epimerisation.

Scheme 126

As the earlier results⁸⁰ turned out to be misleading, the way was left open to use the (Z)-methyl β-hydroxy-δ-alkenoates in the cyclisations. This allowed the high yielding reactions which were developed in the early part of this project to be utilised.

Model studies towards the synthesis of muscarine then began in earnest. The alkene 71 was available in geometrically pure form according to ¹³C NMR spectroscopy, via the Lindlar reduction of the corresponding acetylene 36, in turn obtained in high yield by the alkylation of the epoxy ester (±) 84. Large scale cyclisations of the
alkene proceeded in high yield, as in the earlier experiments. The hydroxy-THF 72 was obtained with very high stereoselectivity; less than 5% of what was assumed to be the 3-epimer 137 was obtained (Scheme 127).

When the hydroxy-THF produced was purified by column chromatography, consistently high losses were observed. For this reason and since all the spectroscopic data had been obtained, it became common practice to silicon protect the crude reaction mixture with tbutyldimethylsilyl chloride (TBS-Cl) and imidazole in DMF. Even when an extended reaction time of over 72 hours was used, the yield of the silyl ether 138 was generally low; typically around 55% (in this case 54%). However, chromatographical purification of the silyl ether 138 was facile. Disappearance of the (OH) stretch in the infrared spectrum was noted (Scheme 128).
Direct saponification was not attempted here for reasons described earlier. Instead, the silyl ether 138 was reduced using diisobutylaluminium hydride in hexanes,\textsuperscript{135} at -78°C, over 2 hours. The aldehyde 139 was obtained in a low yield of 38% after chromatography. This was the result of cleavage of the silicon-oxygen bond during the reaction. Not only did this reduce the reductant available, but it also caused the substrate to be effectively removed from the reaction, by the insolubility of the aluminium complex formed in hexane, and this caused both deprotected starting material and over reduced diol 140 to be formed (Scheme 129).
The aldehyde 139 was then oxidised using the urea-hydrogen peroxide/TFAA method,\textsuperscript{91} to give the acid 141 in a reasonable 66% yield in what amounts to a Baeyer-Villiger rearrangement in which the proton migrates. One carbon degradation of this acid was first approached using the Curtius rearrangement. Incorporation of nitrogen at this stage of the synthesis seemed to be a favourable route to approach muscarine, particularly considering the work of Pirrung\textsuperscript{130} who converted the amine 126 into muscarine. The acid 141 was treated with diphenylphosphoranyl azide\textsuperscript{136} to furnish the acyl azide which was heated in refluxing toluene to give the expected isocyanate. This intermediate was then hydrolysed by the addition of water to give the amine 142. Surprisingly, the reaction was found to proceed with concomitant desilylation. The loss of the silicon must occur at a late stage in the reaction because no products from the alcoholyis of the isocyanate by the free hydroxyl leading to the dimerisation product 143 were observed. Although the yield for the process was a moderate 38%, the effective accomplishment of two steps
in one offers some compensation for this shortcoming.

Scheme 130

The amino alcohol 142 was treated with methyl iodide and PMP according to the procedure of Pirrung\textsuperscript{130} but the separation of the muscarine analogue 144 formed from the hydrogen iodide salts of the quaternised base 145 did not prove possible; no details of how this could be achieved have been given by Pirrung (Scheme 130).

The studies then continued with incorporation of the methyl side chain required for the synthesis of muscarine; in addition, necessary improvements were incorporated into the route. Alkylation
of the (±) epoxide 84 using propynyl lithium was carried out using the Yamaguchi procedure.\textsuperscript{96} Certain modifications were made to the procedure to take into account the fact that propyne is a gas at ambient temperature. A large excess of propyne was condensed at -78°C and a measured amount of it was then distilled into cooled THF. Excess propyne was used to compensate for evaporative losses. A good yield of the acetylene 146 was obtained after chromatography. Lindlar reduction of this acetylene was carried out in the dark as \textsuperscript{13}C NMR analysis of samples hydrogenated using the normal procedure showed that greater than 50% isomerisation to the (E)-alkene had occurred. This has only been observed in the case of the methyl substituted alkene, so it may be that the energy barrier to isomerisation is lower in this case. However, excluding light during the reduction allowed the (Z)-alkene 147 to be isolated as a single geometrical isomer in excellent yield. Cyclisation of this alkene under the standard conditions led to an excellent 84% yield of the hydroxy-THF 148. The stereoselectivity however was somewhat reduced and 11% of another hydroxy-THF 149 were observed (Scheme 131), perhaps due to the smaller methyl substituent exerting less stereocontrol. The corresponding silyl ether 151 of this compound was proven to be the 3-epimer by NOE experiments, and was shown to differ as expected from the corresponding silyl ether 150 of the hydroxy-THF 148.

Silicon protection of the crude cyclisation product was achieved in high yield using triisopropylsilyl triflate and 2,6-lutidine in dichloromethane\textsuperscript{137} over 3 hours at 0°C. The silyl ethers 150 and 151
were readily separated by column chromatography. The triisopropylsilyl protecting group was chosen as it was thought likely that it would survive the Curtius rearrangement and lead to a higher yield from that step.

Scheme 131

Direct saponification, using potassium hydroxide in methanol, led to the acid 152 in high yield, contrary to the results of an earlier project. The loss of the methyl ester resonances in the $^1$H and $^{13}$C NMR and the change in the infra red spectrum confirmed this. There was no sign of any epimerisation by ring opening of the THF. Curtius rearrangement of this acid following the earlier procedure
yielded the amine 153 without loss of the silicon group; disappointingly though, there was little increase in yield (Scheme 132).

**Scheme 132**

The dimethylation of this amine using the Eschweiler-Clarke reaction with sodium cyanoborohydride and formaldehyde was unsuccessful despite the success of this reaction on the model compound tetrahydrofururylamine 154 (Scheme 133).

**Scheme 133**

The low yields obtained in this way led to the consideration of other methods to effect decarboxylation of the acid 152. It was then concluded that a Hunsdieker type decarboxylation was the most hopeful alternative. The traditional Hunsdieker reaction is
notoriously low yielding and inefficient; however, the modern approach features the use of the methodology for decarboxylation developed by Barton et al.\textsuperscript{139} The acid 155 concerned is converted to the corresponding thiohydroxamic acid ester 156 in the presence of a source of radicals. The decomposition of the ester formed leads to the carbon centered radical 157, which is trapped with the halogen radical to give the halide 158 (Scheme 134).

\textbf{Scheme 134}

\[ \text{RX} \quad \text{CYX}_3 \xrightarrow{\text{reaction}} \quad \text{CYX}_2 + X^+ \]

\[ \text{(155)} \]

\[ X = \text{Halogen} \]
\[ Y = \text{H or Halogen} \]

\[ \text{RX} \quad \text{CYX}_2 \xrightarrow{\text{reaction}} \quad \text{R}^+ + \text{CO}_2 \]

\[ \text{(157)} \]

The acid 152 was converted into the acid chloride 159 using oxalyl chloride in benzene in the presence of catalytic DMF and pyridine,\textsuperscript{140} without any of the expected acid catalysed ring opening. Treatment of this acid chloride with 2-mercaptopyridine-N-oxide, sodium salt and 4-dimethylaminopyridine (DMAP) in carbon tetrachloride at reflux, gave the chloride 160 in a good yield after
chromatographic isolation. Treatment of the chloride 160 with TBAF in THF for 24 hours then gave the chloro-alcohol 161 which showed a characteristic infra red stretch at 3450 cm\(^{-1}\), together with appropriate NMR data (Scheme 135).

![Scheme 135]

Treatment of the chloro-alcohol 161 with trimethylamine in methanol in a sealed tube at 90°C, 130°C and 150°C was unsuccessful in forming muscarine chloride. At temperatures of up to 130°C, no reaction was observed, and at 150°C the alcohol decomposed. This was disappointing, as trimethylamine had been successfully alkylated with tetrahydrofurfuryl chloride under the same conditions at 130°C (Scheme 136). The fact that the chloro-alcohol 161 is a \(\beta\)-chloro ether may explain its lack of reactivity. Alkylations using chlorides are known to occur under the conditions used in other circumstances.\(^{141}\) The chloro-alcohol 161 is much more prone to decomposition than tetrahydrofurfuryl chloride, as it can be dehydrated at higher
temperatures.

Scheme 136

The unreactivity of the chloride led to the consideration of the synthesis of the iodo-alcohol 163. This compound has been converted into muscarine by two previous groups.$^{126,127}$ Two approaches were available for the synthesis of the iodo-alcohol; firstly a Finkelstein$^{142}$ reaction of the chloro-alcohol 161 or alternatively, adaption of the Barton decarboxylation step to incorporate an iodine atom instead of a chlorine. The second option was thought to be preferable because it allowed the composition of the final product (i.e., muscarine iodide) to be certain; if some of the chloride was also converted into muscarine, the data for the final product would be confused. When the acid chloride 159 was refluxed in cyclohexene in the presence of DMAP, iodoform and 2-mercaptopyridine-N-oxide, sodium salt, the iodide 162 was formed in reasonable yield.$^{139}$ Iodoform is used in the reaction because it decomposes to give the important chain carrying diiodomethyl radical ($\text{CHI}_2^-$) and an iodine radical upon heating. Cyclohexene is used as solvent because it acts as a trap for the molecular iodine which is a major by-product of this radical process. The iodide was again smoothly desilylated by treatment with TBAF in THF to give the pure iodo-alcohol 163 after chromatography (Scheme 137).
The data found for the iodo-alcohol 163 corresponded exactly to that quoted by Mulzer.\textsuperscript{127} Treatment of the iodo-alcohol 163 with trimethylamine in ethanol, at 80°C, for 2 hours, according to the literature procedure\textsuperscript{127} gave (±) muscarine iodide 164, the data for which corresponded to that quoted in the literature.\textsuperscript{127} The final step as described by Chastrette \textit{et al}\textsuperscript{126} (ie treatment of the iodo-alcohol with trimethylamine in methanol for 16 hours at RT) however, could not be repeated (Scheme 138).

The sequence was then repeated using the (S)-epoxy ester 84
which was obtained in five steps from (S)-malic acid following the procedure of Larchèvèque et al.\textsuperscript{93,94} (S)-Malic acid \textbf{165} was monoesterified by conversion into the anhydride \textbf{166} followed by methanolysis to give the half-ester \textbf{167}.

Scheme 139

\begin{center}
\begin{tikzpicture}

\node at (0,0) {\textbf{165}};
\node at (2,0) {\textbf{166}};
\node at (0,-2) {\textbf{168}};
\node at (2,-2) {\textbf{167}};
\node at (0,-4) {\textbf{169}};
\node at (2,-4) {\textbf{84}};

\draw [->] (0,0) -- (2,0);
\draw [->] (0,0) -- (0,-2);
\draw [->] (2,0) -- (2,-2);
\draw [->] (0,-2) -- (2,-2);
\draw [->] (0,-4) -- (2,-4);
\draw [->] (2,-2) -- (2,-4);

\node at (1,0) {$\text{AcCl, } \Delta$};
\node at (1,0) {$\text{MeOH}$};
\node at (1,-2) {$(\text{i}) \text{NaBH}_4$};
\node at (1,-2) {$\text{tBuOH}$};
\node at (1,-4) {$(\text{ii}) \text{MeOH, } H^+$};
\node at (1,-4) {$\text{TMS-I}$};
\node at (1,-4) {$\text{MeOH}$};
\node at (1,-4) {$\text{Ag}_2O, \Delta$};
\node at (1,-4) {$\text{glyme}$};
\node at (1,-4) {$\text{glyme}$};
\end{tikzpicture}
\end{center}

This was reduced using sodium borohydride in t-butanol/methanol to give the (S)-lactone \textbf{168} which is now commercially available as either enantiomer. Ring opening of the lactone with iodonitrtrimethylsilylane and methanol gave the iodoxydrin \textbf{169} which, upon treatment with silver(I) oxide in glyme, at reflux, for 8 hours in the dark, ring closed to give the (S)-epoxide \textbf{84} (Scheme 139).

Extremely careful distillation afforded the epoxide free from
Extremely careful distillation afforded the epoxide free from the solvent, although losses were incurred during this process. The conversion of this epoxide into D-(-)-muscarine proceeded smoothly, exactly as described for the racemate above. The chiral iodo-alcohol 162 exhibited optical rotation close to that reported in the literature.\textsuperscript{127} The (S)-epoxide 84 from (S)-malic acid was synthesised rather than the (R)-epoxide 84 from (R)-malic acid simply on the grounds of cost, because the starting material (S)-malic acid is significantly cheaper. The synthesis of natural L-(+)-Muscarine from (R)-malic acid or the (R)-epoxide 84, obtained by enzymatic resolution, would be equally possible to achieve.

In summary, the route that has been developed provides the required flexible, and reasonably brief, 8 step route to muscarine, and possible C-2 analogues. The final product was isolated in a 14.3% overall yield from the (S)-epoxide 84. This route was found to be good in many respects, but the selectivity of the key cyclisation was disappointing, compared to the examples investigated in Chapter Two. This is probably due to the reduced steric influence of the methyl substituent with respect to the model reactions. A better overall yield could therefore be expected in the preparation of C-2 analogues of muscarine. The relatively low yield in the Barton decarboxylation step was also slightly disappointing, but further optimisation of this step has not been carried out. The easy incorporation of C-2 analogues makes this a useful synthesis of muscarines. Further improvement of this synthesis is still possible; for example, the use of a cheaper oxygen protecting group (eg benzyloxy) is under consideration.
CHAPTER FOUR

Approaches to Goniofufurone

(I) Introduction 113

(II) Synthetic Approaches to Goniofufurone 115

(III) Reterosynthetic Analysis of Goniofufurone 119

(IV) Model Reactions 121

(V) Incorporation of the Natural Side Chain 127
Approaches To Goniofufurone

(I) Introduction

In 1990, McLaughlin et al\textsuperscript{143} isolated three novel styryl lactones; (±)-goniofufurone 170, (±)-goniopypyrone 171 and (±)-8-acetyl goniotriol 172 (Scheme 140).

The lactones were isolated from ethanolic extracts of the stem bark of Goniothalamus giganteus (Hook. f., Thomas), a Taiwanese lily, and the X-ray structures of (±)-goniofufurone 170 and (±)-goniopypyrone 171 were determined. The three compounds exhibited activity against human tumor cell lines; (±)-goniopypyrone 171 was the most bioactive, showing $ED_{50}$ values
of about 0.67 µg/ml. These compounds form part of a family of styryl lactones isolated from the stem bark of this plant. It has been proposed\textsuperscript{143} that they all originate from a single parent molecule 173 derived \textit{in vivo} from a combination of shikimate and polyketide pathways (Scheme 141).
(II) Synthetic Approaches to Goniofufurone

(-)-Goniofufurone 174 was synthesised by two groups of researchers during early 1992. This enabled the configuration of the natural enantiomer to be established as that shown in Scheme 142.

\[ \text{Scheme 142} \]

Shing and Tsui\textsuperscript{144} synthesised the unsaturated lactone 175 in eleven steps from D-glycero-D-gulo-heptonolactone 176, and then converted it into (-)-goniofufurone 174 by a 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)-catalysed Michael-type cyclisation (Scheme 143).

\[ \text{Scheme 143} \]
By contrast, Jäger and Gracza\textsuperscript{145} took the tetrol mixture 177, available in five steps from monoacetone D-glucose, and converted it into a readily separable mixture of (-)-goniofufurone 174 and (-)-7-epi-goniofufurone 178, by a palladium(II)-catalysed cyclisation-carbonylation reaction (Scheme 144).

Scheme 144

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme144.png}
\end{center}

Four further approaches to goniofufurone have since been reported. The first of these was that developed by Prakash and Rao\textsuperscript{146} in which (+)-Goniofufurone was synthesised from D-glucose in eleven steps. The unsaturated lactone 179 was synthesised by a stereocontrolled Wittig addition to the lactol 180. This ester then cyclised spontaneously to give dibenzylgoniofufurone 181, which was deprotected by hydrogenation to give the natural product (Scheme 145).
Murphy and Dennison\textsuperscript{147} used a very similar approach, generating the lactone 182, also from D-glucose, and acylating to give the bromoacetate 183. Intramolecular Wittig reaction gave the unsaturated lactone 184,
hydrogenation of which furnished (+)-goniofurfurone 170 in thirteen steps overall from D-glucose (Scheme 146).

Scheme 147

Hanaoka et al.\textsuperscript{148} used the homochiral chromium complex 185 in an efficient route to (+)-goniofurfurone, the first non-carbohydrate based synthesis. The titanium enolate of thioester 186 was reacted with the complex 185 to give the aldol product 187. This was converted into the aldehyde 188 and reacted with trimethylsilyloxyfuran under chelation controlled conditions, to give the lactone 189 which, upon deprotection, cyclised spontaneously to give (+)-goniofurfurone 170 (Scheme 147).

Honda et al.\textsuperscript{149} have used the chiral lactonic aldehyde 190 to effect
elegant syntheses of (+)-goniofufurone (+)-goniopyrone, (+)-goniotriol, (+)-8-acetylgoniotriol and (+)-altholactone. The aldehyde 190 was treated with an equivalent of phenyl anion, under chelation control, to give the alcohol 191. This was deprotected with trifluoroacetic acid (TFA) to give the triol 192, which was cyclised, via an unexplained base initiated rearrangement, to give (+)-goniofufurone 193 (Scheme 148).

Scheme 148

![Scheme diagram](image)

(III) Retrosynthetic Analysis of Goniofufurone

Retrosynthetic analysis of goniofufurone, soon after its isolation in 1991, led to the consideration of a synthesis of this molecule using the methodology developed earlier in this project (see Chapter Two). At first
glance, the hydroxy-THF with an acetic acid ester side chain as the 2-
substituent present in the molecule, makes it look ideally set up for an 
approach using the cyclisation of (Z)-β-hydroxy-δ-alkenoates. However, the 
cyclisation of these molecules gives a high selectivity for the 2,5-cis-
stereochemistry. The natural product has a 2,5-trans-stereochemistry so an approach via this route is not a viable prospect. The cyclisation of (E)-β-
hydroxy-δ-alkenoates however, gives a very good selectivity for the 2,5-
trans-stereochemistry required. Thus an approach to goniofufurone was 
planned using the iodocyclisation of (E)-β-hydroxy-δ-alkenoates to give iodo-
THF acetic acid esters of the desired stereochemistry. This left open a 
number of routes to the natural product skeleton.

Scheme 149
It became clear that a dihydrofuran of the type 194 could be a key intermediate in such an approach (Scheme 149).

Simple lactonisation of the acid would allow the skeleton 195 to be assembled directly, and it would only remain to alter the functionality at the 5-position. Stereocontrolled oxidation of the acid to give the epoxide 196 would allow acid-catalysed cyclisation to give the target molecule 197. Stereoselective osmylation, on either face, would also allow elaboration to the target molecule. Osmylation on the same face of the acid moiety, to give the dihydroxy acid 198, would allow the specific lactonisation to give the alcohol 199, which could be inverted by a Mitsunobu reaction to give the target ring system 197. Alternatively, osmylation on the opposite face to the acid moiety, to give the dihydroxy acid 200, and subsequent formation of the bidentate sulphonate ester,150 would yield the target molecule, upon ring opening.

(IV) Model Reactions

Considering the potential usefulness of the unsaturated acid 194 in the approach to the natural product, model work began with the development of a route to these acids and then proceeded with investigations of the synthesis of the natural product skeleton.

The β-hydroxy ester 53b was readily available in large quantities from the vinyl-alanate chemistry described earlier (p 76). Iodocyclisation of this molecule was smooth and stereospecific following the earlier procedures,
and yielded large quantities of the iodo-THF 54b. Earlier experiments by Bedford\(^{80}\) suggested that when the iodo-THFs were heated at too high a temperature with sodium azide and 18-crown-6 in DMF, the olefin 201 was produced along with the expected azide 202 resulting from S\(_{N2}\) substitution. These results were unexplained, but nevertheless these findings were investigated as part of these model reactions. Pleasingly, a high yield of the olefin 201 was obtained when the iodo-THF 54b was heated with sodium azide in DMF at 110°C for 16 hours; only traces of the azide 202 were isolated. DBU was also used to initiate this elimination reaction, but the olefin was isolated in much lower yields; this was because ring opening elimination reactions competed with the 2,5-dihydrofuran formation (Scheme 150).

Scheme 150

2,5-Dihydrofurans of controlled stereochemistry are useful synthetic intermediates. For example, they have been used in [3+2]
cycloadditions to give tetrasubstituted THFs.\textsuperscript{151}

There appear to be two possible explanations for this unexpected elimination reaction. It is conceivable that sodium azide acts as a mild base, abstracting a proton to initiate the elimination. However, the regiospecificity of this process suggests that the cyclic decomposition of the azide is also a viable mechanism (Scheme 151).

![Scheme 151](image)

West\textsuperscript{152} has also observed a similar reaction using sodium azide. Unfortunately, further investigation of this process was prohibited by time considerations.

The olefinic ester 201 was saponified successfully using potassium hydroxide in methanol to give the acid 203 in high yield. This was a very pleasing result as epimerisation and ring opening had been observed in a similar system by a previous researcher.\textsuperscript{80} This result also had implications in the synthesis of muscarine (see p 99). Both the ester 201 and the acid 203 were treated with osmium(VIII) tetroxide, under standard conditions.\textsuperscript{153} It was hoped that face selective dihydroxylation might take place in the case of the ester 201 on steric grounds or, in the case of the acid 203, by co-ordination of the approaching osmium species. Disappointingly, there was little stereoselectivity observed in either case (Scheme 152).
Selective epoxidation of the acid 203 was considered, possibly by formation of the peracid at low temperature followed by intramolecular delivery of oxygen.\textsuperscript{154} However, selective delivery of the oxygen atom from below to give the epoxide (the epimer of the epoxide 196) would not allow easy elaboration to the natural product.

Lactonisation of the acid 203 was the next approach adopted. Mercury mediated lactonisation was considered, but as the replacement of the alkyl mercury function generated to give an alcohol is a radical process (Scheme 153), the stereocentre produced would be expected to be largely stereorandom, and therefore of little use in the context of this sequence.
Halolactonisation seemed the most reliable alternative, and indeed, smooth iodolactonisation of the acid 203 furnished the iodolactone 204 in excellent yield (Scheme 154).

![Scheme 154](image)

The iodolactone 204 showed considerable similarities to the natural product in the $^1$H and $^{13}$C NMR spectra. The resonances for the 1-H, 4-H, 5-H and 8-CH$_2$, for example, showed similar coupling patterns and chemical shifts to those reported by McLaughlin$^{143}$ for goniofufurone. The $^{13}$C NMR signals for the 1-CH, 3-CH, 5-CH, 7-C and 8-CH$_2$ were again consistent with the corresponding signals in the natural product.

Investigations of the possible introduction of oxygen functionality began with model reactions on the easily accessible iodo-THF 58. Cesium acetate at 100°C in DMF$^{155}$ was used to give the acetate 205 in moderate yield. Slightly better results were obtained using potassium superoxide and 18-crown-6 in DMF, at RT, to give the alcohol 206 (Scheme 155).

![Scheme 155](image)
Corey\textsuperscript{156} used this latter method in the presence of an ester group. The yields from these reactions are, of course, related to pure compounds after chromatography. In the case of these model reactions, the yields were possibly reduced by the volatility of the products.

Kocovsky\textsuperscript{157} used silver salts with non-nucleophilic counter anions to effect substitution of a bromine atom by an oxygen function with overall retention of configuration, in the presence of anchimeric assistance from a proximal oxygen atom (Scheme 156).

\textbf{Scheme 156}

\[
\begin{array}{c}
\text{Br} \quad \text{AgClO}_4 \\
\text{DME, H}_2\text{O} \\
\end{array}
\]

Bartlett\textsuperscript{158} observed the formation of formate esters, with retention of configuration, using silver tetrafluoroborate in DMF on a similar system to that used by Kocovsky (Scheme 157).

\textbf{Scheme 157}

\[
\begin{array}{c}
\text{AgBF}_4 \\
\text{DMF} \\
\end{array}
\]
Overall retention of configuration would be ideal in our system in that it would give the required configuration of the natural product directly. The examples which Bartlett used to perform this reaction were six-membered rings, but, in principle, the use of five-membered rings is not precluded. The iodolactone \textbf{204} was treated with both potassium superoxide/18-crown-6 in DMF, and with silver tetrafluoroborate in DMF. The results were promising in that there was good evidence for substitution in both cases (ie formation of a single, more polar spot by tlc). However, there was insufficient material to prove this conclusively.

(V) Incorporation of the Natural Side Chain

The first approach adopted to the synthesis of natural goniofufurone was the elaboration of mandelic acid \textbf{207}, the (R)- and (S)-enantiomers of which are both commercially available and relatively inexpensive. It was thought that mandelic acid could be an ideal starting material with which to attempt the homochiral synthesis of the \(\beta\)-hydroxyester \textbf{208}. This could be converted into (+)-goniofufurone by following the foregoing model work (Scheme 158).

\begin{center}
\textbf{Scheme 158}
\end{center}

\begin{center}
\includegraphics{scheme158.png}
\end{center}

\textbf{208} \hspace{2cm} \textbf{170}

Retrosynthetic analysis shows that two of the possible approaches
to the ester 208 are: (i) coupling of the vinyl anion 209 to a single enantiomer of the epoxy ester 84, and (ii) stereochemically controlled chiral aldol reaction of the aldehyde 210 with a chiral acetate enolate (Scheme 159).

Scheme 159

Natural (+)-goniofurfurone would arise from elaboration of the (3R,7R)-ester 208 (ie from the coupling of the (R)-mandelic acid derivative with the (R)-enantiomer of the epoxy ester 84). Bearing in mind that the (S)-enantiomer of the epoxy ester 84 had already been synthesised, and was derived from the cheaper (S)-enantiomer of malic acid, it was decided to begin work on the synthesis of (-)-goniofurfurone from the (3S,7S)-ester 208 (ie by the coupling of the (S)-mandelic acid derivative with the (S)-enantiomer of the epoxy ester 84 (Scheme 160).

Scheme 160

The first work in this area was the synthesis of the vinyl anion 209 (M = Li) by derivatisation of (S)-mandelic acid. (S)-Methyl mandelate,
prepared by literature methods\textsuperscript{159} was silylated using TIPS chloride, in dry DMF in the presence of imidazole, to give the silyl ether 211. Reduction of this silyl ether at -78°C with diisobutylaluminium hydride in hexane:ether\textsuperscript{160} gave the aldehyde 212 in high yield. This aldehyde was then homologated using the Takai procedure\textsuperscript{161} to give the (E)-vinyl iodide 213 exclusively. However, extensive modifications to the literature procedure were required as the aldehyde 212 reacts much less readily than the examples given by Takai, possibly due to the steric effect of the TIPS protecting group. A standard procedure, as used by Takai, involved stirring the given aldehyde with chromium(II) chloride and iodoform, at 0°C, in THF. However, homologation of the aldehyde 212 required 16 hours at 60°C. Interestingly, this slower reaction gave better stereoselection for the (E)-isomer than that quoted by Takai. Separation of the extremely non-polar vinyl iodide 213 from iodoform proved difficult, but after two separations eluting with cyclohexane, the pure iodide was obtained in 45% yield (Scheme 161).

Scheme 161

Extensive studies of the halogen-lithium exchange of this molecule
with two equivalents of t-butyl lithium showed that, although this process normally occurs at -78°C in less than 15 minutes, the lithium exchange of the vinyl-iodide 213 only occurs after warming to RT and stirring for 2 hours. Quenching of the reaction before this point resulted in recovery of starting material; in fact, the molecule did not react with t-butyl lithium at all at -78°C. It is essential that diethyl ether, and not THF, is used as solvent for this reaction as at 0°C t-butyl lithium and THF react together. Once the conditions for halogen-lithium exchange had been established, cuprate formation was attempted using lithium 2-thienyl-cyanocuprate\textsuperscript{162} and also using copper(I) iodide but in both cases, although it was not shown whether cuprate formation had occurred, the major product from the exposure of the resulting solutions to the (±)-epoxide 84 was the (±)-iodohydrin 169. It seems that the iodide anion is more nucleophilic than the anionic species generated by these procedures. The vinyl iodide was exclusively converted into the terminal olefin 214 (Scheme 162).

With these results in mind, the aldehyde 212 was converted by the Corey procedure\textsuperscript{163} into the dibromide 215, and subsequently the acetylene 216, in reasonable overall yield. Again, reaction times far in excess of those
used in the literature were required. Hydrostannylation of this acetylene proceeded in low yield to give exclusively the (E)-vinyl-stannane 217 which was purified by column chromatography (Scheme 163). The recently developed Hodgson route to (E)-vinyl-stannanes directly from aldehydes was not used, as the steric restraints of our system seemed likely to prevent this method from being appropriate.

Scheme 163

\[
\begin{align*}
\text{OTIPS} & \quad \text{Zn/CBr}_{4}/\text{PPh}_{3} \\
\text{CHO} & \quad 72\text{h} \ 70\% \\
\text{OTIPS} & \\
\end{align*}
\]

\[
\begin{align*}
(212) & \quad \text{BuLi} \\
& \quad -78^\circ\text{C}-0^\circ\text{C} \\
& \quad 8\text{h}, 75\% \\
\text{OTIPS} & \\
(215) & \\
\end{align*}
\]

\[
\begin{align*}
\text{OTIPS} & \quad \text{Bu}_{3}\text{SnH} \\
\text{SnBu}_{3} & \quad \text{AIBN} \\
& \quad \text{PhH}, 13\% \\
(217) & \quad (216) \\
\end{align*}
\]

The (E)-vinyl stannane 217 was treated with butyl lithium, for two hours at RT, to effect tin-lithium exchange. The vinyl lithium thus formed was reacted with copper(I) iodide at -40°C, and then treated with the (±)-epoxide 84. This time the products were the terminal olefin 214 and the ester 85 from the action of base upon the epoxy-ester (Scheme 164). This suggests that the required cuprate complex was not formed (ie the basic vinyl-organometallic extracted a proton from the (±)-epoxide 84).
With this discouraging result, investigation of the second disconnection of the hydroxyester 208 began. The required aldehyde 210 was thought to be accessible by following the work of Nakai et al., who used a [2,3]-sigmatropic rearrangement to give an unsaturated hydroxy-acid, which was cleaved with sodium periodate to give a \( \beta,\gamma \)-unsaturated aldehyde, as shown in Scheme 165.

The known aldehyde 220 was synthesised by a route which differed from that used by Corey. Although the route as described by Corey was also attempted, it yielded less of the desired compound than the route which is shown in Scheme 166.

The methoxymethoxy (MOM) ether 218 of (S)-methyl mandelate was formed in quantitative yield by treatment with chloromethyl methyl ether and ethyldiisopropylamine in dcm. The ester was then reduced to the
known diol derivative 219,\textsuperscript{167} using diisobutylaluminium hydride in toluene, in essentially quantitative yield. Swern oxidation\textsuperscript{168} of the unprotected primary alcohol gave the aldehyde 220 in reasonable yield.

Scheme 166

\[
\begin{align*}
\text{OH} \quad \text{CO}_2\text{Me} & \xrightarrow{\text{MOM-Cl}} \quad \text{OMOM} \\
\text{EtN}^+\text{Pr}_2 & \xrightarrow{\text{dcm 100\%}} \quad \text{EtN}^+\text{Pr}_2 \\
\text{OMOM} & \xrightarrow{\text{DIBAL-H}} \quad \text{OMOM} \\
\text{CHO} & \xrightarrow{(\text{COCl})_2} \quad \text{CH}_2\text{OH}
\end{align*}
\]

The aldehyde 220 was then treated with vinylmagnesium chloride to give the allylic alcohols 221, by a partially stereoselective addition reaction (approximately 3:1 ratio of isomers). Alkylation of the allylic alcohols 221, using sodium hydride in THF to form the alkoxide and treating the resulting solution with sodium iodoacetate, gave the acids 222 (Scheme 167).

Scheme 167

\[
\begin{align*}
\text{OMOM} & \xrightarrow{\text{Vinylmagnesium chloride, THF 75\%}} \quad \text{OMOM} \\
\text{CHO} & \xrightarrow{\text{(i) NaH}} \quad \text{OMOM} \\
\text{OH} & \xrightarrow{\text{(ii) Sodium iodoacetate 68\%}} \quad \text{OMOM}
\end{align*}
\]

These acids are precursors to the Wittig rearrangement, as described by Nakai;\textsuperscript{165} formation of an anion \( \alpha \) to the carboxylate function, at
-78°C, using two equivalents of lithium diisopropylamide, allows the thermal rearrangement to occur upon warming to room temperature. The hydroxy-acid 223 was obtained in reasonable yield (Scheme 168).

This hydroxy-acid was treated with sodium periodate but there was no aldehyde formation, and significant amounts of the starting material decomposed. Reduction of the hydroxy-acid to the diol 224 was then attempted, as it was thought that periodate cleavage of this would be more facile. However, attempted reduction using LAH gave only a 10% yield of the desired diol 224 and the majority of the product was the undesired hydroxy-THF 225 (Scheme 169). This hydroxy-THF is presumably formed by an S_N1' cyclisation as shown in Scheme 170. The reason for this cyclisation is the fact that the benzylic centre is now also allylic and this allows great stabilisation of a carbocation at this centre. Consequently, loss of the methoxymethoxy group is extremely facile under even mildly (Lewis) acidic conditions. The extra stability of a conjugated double bond relative to an isolated double bond also causes migration to be extremely facile, giving the cyclisation observed. Unfortunately, there is little stereoselectivity in this process, otherwise it would comprise an interesting new route to THFs.
This result gave cause for doubts about whether the iodocyclisation of the ester 208 would be a smooth reaction, or whether the same process as we observed here would occur under the attempted iodocyclisation conditions.

These problems led to the consideration of the use of another disconnection to access the natural product. It was anticipated that the addition of a phenyl anion to the aldehyde 226 would give potentially good chelation control (Scheme 171).
The synthesis of the aldehyde 226 then became a desirable target. It was envisaged that this could be approached using the successful model chemistry described earlier. The β-hydroxy ester 227 became the initial target because it was considered that the oxidation of the primary alcohol would allow the synthesis of the aldehyde 226.

The alcohol 228 was synthesised following the methods of Momose et al. and was subsequently oxidised to give the aldehyde 229 in a disappointing yield of 40% by the use of a Swern oxidation (Scheme 172).
Unfortunately, Moffat oxidation\(^{170}\) gave only the conjugated aldehyde 230, and other techniques failed to give any reaction (Scheme 173).

**Scheme 173**

\[
\begin{align*}
\text{MOMO} & \text{O} \\
(228) & \text{OH} \\
\text{Py.SO}_3 & \text{complex} \\
\rightarrow & \text{MOMO} \text{O} \\
(230) & \text{O}
\end{align*}
\]

Chiral aldol reaction of the aldehyde 229 was eventually effected using the methodology first described by Braun.\(^{171}\) The lithium enolate of (S)-1,1,2-triphenyl-1,2-ethandiol-2-acetate reacted with the aldehyde to give a moderate yield of the \(\beta\)-hydroxy ester 231 on a small scale. Subsequent hydrolysis of this ester and treatment with diazomethane\(^{172}\) furnished what appeared to be a small quantity of the desired \(\beta\)-hydroxy ester 227. Time restrictions have not allowed these reactions to be repeated on a larger scale to confirm these results (Scheme 174).

**Scheme 174**

\[
\begin{align*}
\text{MOMO} \text{O} \\
(229) & \text{O} \\
\text{Ph} \text{Ph} \text{Ph} & \text{Ph} \\
\rightarrow & \text{MOMO} \text{O} \\
(231) & \text{OH} \\
\text{Ph} & \text{Ph} \\
(i) & \text{KOH, MeOH} \\
(ii) & \text{Diazomethane} \\
\rightarrow & \text{MOMO} \text{O} \\
(227) & \text{CO}_2\text{Me} \\
\text{OH} & 
\end{align*}
\]
This synthesis may well be feasible if the phenyl group is introduced at a late stage as shown in Scheme 171, but otherwise the intermediates seem to be too sensitive to undergo the desired transformations.
CHAPTER FIVE

Radical Reactions of Tetrahydrofurans

(I) Introduction

(II) Radical Chemistry of 2,3,5-Trisubstituted Tetrahydrofurans
Radical Reactions of Tetrahydrofurans

(I) Introduction

As part of the ongoing investigation into methods for the elaboration of the initial products of the iodocyclisations described in Chapter Two, some aspects of the radical chemistry of these tetrahydrofurans were investigated. One of the important considerations in the design of homologation methods for these trisubstituted THF systems is the difficulty in the formation of $\beta$-anions. The anticipated facile $\beta$-elimination reaction (Scheme 175) which would be expected to occur, allows the stabilisation of the negative charge by transferring it from a carbon atom to an oxygen centre.

![Scheme 175](image)

This is a significant limitation in the chemistry of $\beta$-iodo-THF systems. Although there are examples of the generation of kinetically stable $\beta$-anions in THF systems at extremely low temperatures\textsuperscript{173} (Scheme 176), the usefulness of this process has so far been limited.
The generation of a β-radical, however, is a potentially extremely useful process, as the anticipated kinetic stability of carbon centered radicals, relative to oxygen centered species, means that the β-elimination process does not take place (Scheme 177).

With this knowledge, it was decided to exploit the products of the cyclisation reactions described in Chapter Two to attempt to generate 2,5-disubstituted β-radicals from these THF systems. It has proven possible to illustrate the synthetic potential of this type of intermediate in a new approach to the 2-oxabicyclo-[2.2.1]-heptane ring system 232.

During the last decade, much attention has been focused on
various physiological activities of cyclopentanoids and derivatives of related fused ring systems, especially those of prostacyclines and thromboxanes. Expectations of possible biological activity in this area are high. The 2-oxabicyclo-[2.2.1]-heptane ring system 232 has recently been brought to prominence by the isolation of two fatty acid derived oxylipin natural products, the Cymathere ethers A and B shown in scheme 178. These molecules were isolated from the Marine brown algae Cymathere triplicata and appear to be derived by oxidative cyclisation of fatty acids. There are only a very few isolated examples of ring systems of the 2-oxabicyclo-[2.2.1]-heptane type to be found in the chemical literature. The cyclisation of 1-hydroxy-methyl-3,4-epoxycyclopentanes has been used in two cases to generate the ring system (Scheme 179).

Scheme 179

Kakimuna177 used the electrophilic 5-exo-trig cyclisation of Plinol C by both halo- and selenoetherification procedures to obtain the substituted 2-oxabicyclo-[2.2.1]-heptanes shown in Scheme 180. The stereoselectivity of the thermodynamically controlled iodoetherification, is excellent, but the kinetically controlled selenoetherification shows little selectivity. The difficulty of obtaining other cyclopentanes suitable for
Renaud has used a radical addition to 7-oxabicyclo-[2.2.1]-heptane to generate this ring system in an isolated example (Scheme 181). 178

Elaboration of these systems was carried out, but only to a limited extent, and there appear to have been no examples of the generation of 3,5-disubstituted 2-oxabicyclo-[2.2.1]-heptane systems. The related lactone and hemi-acetal ring systems 233 and 234 are somewhat better known. The lactone 233 has been generated by the Baeyer-Villiger oxidation of the ketone 235 (Scheme 182).
By contrast the hemi-acetal 234 is derived from ring closure of the cis-cyclopentane aldehyde 236 (Scheme 183). 179

Bicyclic hemi-acetals of the type described above have also been generated by the cyclisation of the cyano-epoxide shown in Scheme 184. 180

An interesting radical cyclisation of carbohydrate derived iodo-hemi-acetals has been used by Fraser-Reid to generate bicyclic hemi-acetals, in a related ring system, as shown in Scheme 185. 181
With these exceptions, the ring system has not been approached by organic chemists.

(II) Radical Chemistry of 2,3,5-Trisubstituted THFs

It was anticipated that this ring system would be accessible from the cyclisation of the $\alpha$-alkenyl-THF radicals 237, available from the 2,3,5-trisubstituted THFs 238. These THFs would, in turn, be available from simple elaboration of the cyclisation products described in Chapter Two (Scheme 186).

Consequently, when the aldehyde 70 was isolated as a side product from the iodocyclisation of the dithiane 68, the opportunity to
investigate such cyclisations was presented. The aldehyde 70 was homologated using methyl triphenylphosphoranilideneacetate in dichloromethane to give the (E)-ester 239 in good yield (Scheme 187).

Scheme 187

When this ester was subsequently treated, on a small scale, with triphenyltin hydride and azo-bis-isobutyronitrile (AIBN) in benzene, at reflux, using the slow addition conditions recommended by Motherwell and Crich,\textsuperscript{182} the desired ring system 240 was isolated in a 70% yield as a 3:1 mixture of isomers, the stereochemistry of which was not proven (Scheme 188). No sign of reduced starting material 241 was observed. Slow addition conditions were used to ensure a low concentration of hydride radicals, therefore maximising the chance of cyclisation occurring. The final product of this reaction sequence was fully characterised, but insufficient data were obtained for the intermediates to allow their inclusion in the experimental section.
To investigate this encouraging preliminary result, a variety 2-alkenyl-4-iodo-THFs and 2-alkenyl-4-hydroxy-THFs were synthesised containing both conjugated and unconjugated double bonds. The cyclisation of the trans-2,5-disubstituted-THF radical 242 showed only moderate stereoselectivity. However, upon consideration of the transition state from this and from the cyclisation of the corresponding cis-2,5-disubstituted THF radical 243, it was postulated that the cyclisation of the cis-2,5-disubstituted THF radicals might be expected to proceed with greater stereoselectivity (Scheme 189), assuming the departed iodine atom does not influence these conformations.
The 2-substituent containing the radical acceptor is constrained to be in a pseudo-equatorial position so that it is able to cyclise. This means that in the case of the trans-2,5-disubstituted-THF radical, the 5-substituent is in a pseudo-equatorial position and therefore little steric effect is exerted upon the cyclisation. In contrast, in the case of the cis-2,5-disubstituted-THF radical, the 5-substituent is constrained to be in a pseudo-axial position for cyclisation to take place. This means that this substituent could exert a steric effect upon the cyclisation causing a higher stereoselectivity to be observed. The availability of both trans-2,5-disubstituted-THF radicals (from the iodo-THFs) and cis-2,5-disubstituted-THF (from the Barton deoxygenation of the hydroxy-THFs) allowed this theory to be investigated.

The iodotetrahydrofuran 54b was easily available in multigram quantities from the iodoetherification of the β-hydroxy-δ-alkenoate 53b. Treatment of this compound with diisobutylaluminium hydride in hexanes at -78°C over 2 hours gave the aldehyde 244 in good yield. This aldehyde was then homologated with various Wittig reagents. Methyl triphenylphosphoranylideneacetate in dichloromethane gave a 76% yield of the (E)-alkenoate ester 245. Ethyl triphenylphosphonium iodide was treated with butyl lithium at -78°C to generate the corresponding ylid, which reacted with the aldehyde 244 to give a 46% yield of the (Z)-alkene 246. Triphenyl-phosphoranylidine-2-propanone reacted with the aldehyde to give a 55% yield of the (E)-ketone 247 (Scheme 190).
The cyclisations of these molecules were carried out under similar conditions to those specified for the preliminary cyclisation of the ester 239. In the case of the cyclisation of the ester 245, the earlier conditions were closely followed. In the case of the cyclisation of the alkene 246, which was carried out on a larger scale, the addition of reagents was carried out using a syringe pump. To facilitate the removal of non-polar tin residues from the products, which are themselves non-polar, an aqueous potassium fluoride work up was used in the cyclisations of the alkene 246 and the ketone 247, to enable the isolation of the products in a pure form.\textsuperscript{182}
The cyclisation of the ester 245 furnished a 3:1 mixture of the two isomeric 2-oxabicyclo-[2.2.1]-heptyl esters 248 and 249 (Scheme 191), in a satisfying 77% combined yield.

![Scheme 191]

Comparative coupling constant data from norbornane systems were used to assign the stereochemistries of these products (Scheme 192).\textsuperscript{183}

\textsuperscript{1}H-\textsuperscript{1}H and \textsuperscript{1}H-\textsuperscript{13}C COSY NMR spectra allowed the assignment of the NMR resonances of both isomers. Both exhibited a broad triplet due to the 3'-H resonance (assigned by \textsuperscript{1}H-\textsuperscript{1}H COSY NMR spectrum) with $J = 6.5$ Hz (major isomer 248) and 6.2 Hz (minor isomer 249) due to coupling to the butyl side chain. In neither case was coupling to the 4'-H
observed. This suggested the assignment of a 3'-exo configuration of the butyl side chain in both isomers. In both isomers, the 1'-H occurred as a broad singlet in accordance to the literature precedent;\textsuperscript{174-176} the 4'-H was also a broad singlet at $\delta_H = -2$ in both isomers. Both the 7'-H resonances occurred separately between $\delta = 1.10-1.70$, as observed in previous examples.\textsuperscript{176}

Scheme 193

A coupling of 3.4 Hz is observed from the 5'-H to the 6'-H\textsubscript{A} in the major isomer; since a coupling of 2.8 Hz is also observed in the resonance for the 6'-H\textsubscript{A}, almost certainly to the 1'-H, this indicates that the 6'-H\textsubscript{A} is endo, the 1'-H fixed and the 5'-H also endo (ie the major isomer 248 has the 3'-exo, 5'-exo conformation). The relevant resonances for the 5'-H, 6'-H\textsubscript{A} and 6'-H\textsubscript{B} of the minor isomer 249 are obscured but as the 3'-exo conformation is suggested by the lack of coupling from the 3'-H to the 4'-H, the 3'-exo, 5'-endo conformation is the only likely possibility remaining (Scheme 193).
In the cyclisation of the alkene 246 under the same conditions three isomeric 2-oxabicyclo-[2.2.1]-heptanes 250, 251 and 252 were isolated (Scheme 194).

Scheme 194

![Chemical Structure](image)

A ratio of 6:2:1 was observed; careful chromatography allowed the minor third isomer 252 to be separated from the two others. Mass spectrometry confirmed that these were indeed isomers of the same molecular formula, whilst $^{13}$C NMR showed that the three isomers had discernable differences. Again, in the cases of isomers 250 and 251, $^1$H-$^1$H and $^1$H-$^{13}$C COSY NMR spectra allowed the assignment of the resonances for both isomers. The 3-H resonance in both cases was a broad triplet of coupling constant 6.5 Hz to the butyl side chain, with no coupling apparent to the 4-H, suggesting the assignment of a 3-exo configuration to both the isomers 250 and 251. The 4-H again appeared as a broad singlet at $\delta = -2$ in both isomers. As expected from the literature data of these systems, both the 7-H resonances occurred separately between $\delta_H = 1.20$-$1.50$. The resonances relating to the 5-H, 6-H$_A$ and 6-H$_B$ of both the isomers occur together and are therefore obscured. However, since the 3-H has been assigned to the endo
position, the 3-exo configuration for the butyl substituent has been demonstrated. This means that the isomers 250 and 251 represent the 3-exo, 5-exo and the 3-exo, 5-endo isomers respectively. By analogy to the similar cyclisation products, it seems reasonable that the major isomer 250 has the 3-exo, 5-exo configuration.

![Scheme 195](image)

The third isomer 252 exhibited a resonance at $\delta_H = 3.78$ for the 3-H which was a triplet of doublets containing couplings of 6.9 Hz to the butyl side chain and 2.1 Hz to the 4-H. This suggested that in the isomer 252, the butyl group has the 3-endo configuration. The other information derived from the $^1$H NMR spectrum did not allow a firm assignment of the 5-H stereochemistry of this single isomer; however, the
assumption is made that it is unlikely to be the 3-endo, 5-endo isomer due to the steric constraints involved in the cyclisation. The fact that this isomer is formed to the exclusion of the other possible isomer, suggests that this has the 3-endo, 5-exo configuration (Scheme 195).

The cyclisation of the ketone 247 under the earlier conditions led to the formation of the three isomeric ketones 253, 254, and 255 in a high combined yield (Scheme 196). A ratio of 3:1:1 was observed; separation of the third isomer 255 was achieved by careful chromatography.

The reduced stereoselectivity of this cyclisation may be due to the fact that the cyclisation is faster, as the conjugated ketone used is the best radical acceptor tried in this series. This may also explain the high overall yield. Mass spectrometry showed that these compounds had the same molecular formula, whilst $^{13}$C NMR was used to demonstrate that the three isomers had discernable differences. The 3-H resonance for the isomers 253 and 254, was a broad triplet of coupling constant 7.0 Hz to the butyl side chain, with no apparent coupling to the 4-H, in either case. This suggested the assignment of a 3-exo conformation for the butyl substituent in both the isomers 250 and 251. The 4-H again appeared as a broad singlet at $\delta = -2$ in both isomers. Both the 7-H
resonances occurred separately between $\delta_H = 1.50-1.60$, as in the literature examples. The resonances relating to the 5-H, 6-H\textsubscript{A} and 6-H\textsubscript{B} of both the isomers occur as overlapping multiplets and are therefore obscured. However, since the 3-H has been assigned to the endo position, the 3-exo configuration has been demonstrated.

![Scheme 197](image)

This means that the isomers 253 and 254 represent the 3-exo, 5-exo and the 3-exo, 5-endo isomers respectively. By analogy to the similar cyclisation products, it can be assumed that the major isomer 253 has the 3-exo, 5-exo configuration. The third isomer 255 exhibited a resonance at $\delta_H = 3.81$ for the 3-H which was a triplet of doublets containing couplings of 7.0 Hz to the butyl side chain and 2.5 Hz to the 4-
H, indicating that the isomer 255 had the 3-endo conformation. The other information derived from the $^1$H NMR spectrum did not allow a firm assignment of the 5-H stereochemistry of this single isomer; as before the assumption is made that it is unlikely to be the 3-endo, 5-endo isomer due to the steric constraints involved in the cyclisation. The formation of the isomer 255 without the formation of the other possible isomer suggests that this product has the 3-endo, 5-exo configuration (Scheme 197).

The hydroxy-THF 72 used in the earlier model work, is easily obtained in multigram quantities from the iodocyclisation of (Z)-methyl 3-hydroxydec-5-enoate 71. This hydroxy-THF was silylated in exactly the same manner as the corresponding 5'-methyl hydroxy-THF 148, (ie using TIPS triflate, and 2,6-lutidine in dichloromethane) to give the silyl ether 256. A somewhat lower yield was obtained, but as this was an isolated occurrence the reaction was not optimised further. The TIPS protecting group was used in preference to the corresponding TBS function as low yields were obtained in the reduction of the silyl ether 138, due to the cleavage of the silicon group. However, reduction of the silyl ether 256 with diisobutylaluminium hydride in hexane, at -78°C, proceeded without removal of the protecting group, to give the aldehyde 257, in an excellant yield of 85%. This aldehyde was then homologated with various Wittig reagents. Methyl triphenylphosphoranylideneacetate in dcm gave a 51% yield of the alkenoate ester 258 (Scheme 198).
Ethyl triphenylphosphonium iodide was treated with butyl lithium at -78°C to generate the corresponding ylid, which reacted with the aldehyde 257 to give only a 17% yield of the alkene 259. These yields are again unoptimised (from a single experiment) and consequently disappointing; however, if significantly improved they would offer a
comprehensive route to these cyclisation precursors.

Desilylation of these Wittig products proceeded in relatively good yields to give the hydroxy-THFs 260 and 261 (Scheme 199).

Scheme 199

The Barton deoxygenation of these alkenes gives the 2,5 cis-disubstituted-THF radicals which are the direct analogues of the 2,5 trans-disubstituted THF radicals generated from the iodo-THFs 245 and 246. This provides an opportunity to test the proposal made earlier in this chapter, ie that a better stereoselection would be obtained from the 2,5 cis-disubstituted THF radicals.

The thioimidazole esters 262 and 263 of the alcohols 260 and 261 were formed quantitatively using thiocarbonyldiimidazole in THF at reflux (Scheme 200).
Treatment of these derivatives with tributyltin hydride in refluxing toluene resulted in deoxygenation, forming the required radicals.\textsuperscript{184} The alkenoate ester \textsuperscript{260} cyclised to give the substituted 2-oxabicyclo-[2.2.1]-heptanyl ester \textsuperscript{264} as the only product in 77\% yield, whereas the alkene \textsuperscript{261} was simply deoxygenated to give the 2,5-cis-THF \textsuperscript{265} in 80\% yield (Scheme 201).
The cyclisation of the alkenoate ester 260 was stereospecific giving a single isomer. This result is especially pleasing as it provides
evidence that the reaction path follows that discussed earlier, as greater
selectivity was predicted on the basis of the transition states described in
Scheme 189. The substituted 2-oxabicyclo-[2.2.1]-heptyl ester 264
exhibited the broad singlet in the \(^1\)H NMR spectrum at \(\delta_H = 4.26\)
corresponding to the 1'-H. It also showed the characteristic broad singlet
at \(\delta_H = 2.04\) from the 4'-H. Mass spectrometry demonstrated that the
isomer had the same molecular formula and major fragmentation pattern
as the two isomeric products from the cyclisation of the corresponding
2,5-trans-THF radical from ester 245. The \(^{13}\)C NMR spectrum showed
that the isomers 248, 249 and 264 were similar but showed distinct
differences. Crucially, the 3'-H shows a resonance at \(\delta_H = 3.81\), which is a
triplet of doublets showing coupling constants of 7.4 Hz to the butyl side
chain and 2.6 Hz to the 4'-H.

By analogy to the earlier systems, this suggests a 3'-endo
configuration; although the rest of the coupling constants in this isomer

Scheme 202
are difficult to analyse, the 5'-exo configuration is thought to be more likely as the stereoselectivity is almost certain to arise from the steric strain involved in the formation of the 3'-endo, 5'-endo isomer (Scheme 202).

The deoxygenation of the alkene 261 could perhaps be avoided by the use of lower temperatures for the cyclisation process (ie allowing less collisions and favouring intramolecular reaction), or by further increasing dilution or slowing down the speed of addition of the tributyltin hydride. However, time constraints did not allow these trial reactions to be carried out.

Atom transfer cyclisation of the ester 245 was attempted using the procedure developed by Curran which consists of irradiation of the molecule with a 275 W sun lamp, in the presence of 0.1 mol% hexabutylditin in benzene. Cyclisation was not observed, but the iodine atom was epimerised to give a 1:1 mixture of the ester 245 and its 7-epimer 263 (Scheme 203).

I thank Dr J. A. Murphy and others for helpful discussion at this...
point, suggesting that there is a low driving force for the cyclisation, which can be considered to be an equilibrium process. It is possible that upon formation of a small concentration of THF radicals during this process, the tributyltin iodide which is also produced can trap the radical before it cyclises. This would regenerate the iodo-THF, but without stereoselectivity (ie epimerisation at the 7-position would be observed). Alternatively, this could occur by a simple Finkelstein exchange between the starting material and the tributyltin iodide generated under the reaction conditions.

In conclusion, it has been shown that the radical cyclisation of 2,5-disubstituted-THF radicals having alkenyl side chains provides an efficient and, in some cases, highly stereoselective route to the 2-oxabicyclo-[2.2.1]-heptane ring system. This could, therefore possibly, be developed into a viable approach to the Cymathere ethers A and B (Scheme 204). There is however a lot of development of the methodology required.
Similar radical cyclisations could be used to generate other interesting ring systems (Scheme 205). This would provide an interesting combination of ionic and radical processes in the preparation of bicyclic systems.

Scheme 202
CHAPTER SIX

Experimental
General Experimental

Melting Points were determined on a Kofler hot stage apparatus and are uncorrected. Infra red spectra were recorded on a Perkin Elmer 1720 FTIR as liquid films or as chloroform solutions. $^1$H NMR spectra were measured on Brüker WM 250 (250 MHz, PFT), Brüker AM 400 (400 MHz, PFT), and JEOL EX270 (270 MHz, PFT) instruments. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and dt; doublet of triplets, etc. $^{13}$C NMR spectra were recorded on Brüker AM 400 (101 MHz, PFT) [indicated by (400)] and JEOL EX270 (68 MHz, PFT) [indicated by (270)] instruments. Chemical shifts are reported in ppm from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 (CHCl$_3$) ppm for $^1$H NMR and 77.30 (CDCl$_3$) ppm for $^{13}$C NMR. Deuteriochloroform was used as solvent for NMR measurements unless otherwise stated. Where no clear resonances for the OH function of alcohols or acids were observed the values have not been quoted. Mass spectra and molecular weights were determined using a VG MM7070E or AEI MS 902 spectrometer. Molecular formulae quoted for molecular fragment ions are converted to ±3 mmu. Optical rotations ($\alpha_D$) were measured on a JASCO DIP 370 polarimeter. All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under atmospheres of argon or nitrogen. All solvents and reagents were purified according to procedures laid down in "Purification of Laboratory Chemicals" by D. D. Perrin and W. L. F. Armarego. All organic solutions were dried by brief exposure to anhydrous magnesium sulphate. Chromatography was performed using silica gel SORBASIL® C60-H (40-60 μm).
(±)-Methyl 3-hydroxydec-5-ynoate (36)

Hexyne (5.31 g, 64.7 mmol, 1.5 eq) was dissolved in dry tetrahydrofuran (80 ml) and treated exactly as in the preparation of compound 146 using the racemic epoxide 84 (2.5 g, 21 mmol, 1.0 eq), to give an oil (7.7 g) which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the alkyne 36 as a pale yellow oil (3.5 g, 70%), \(\nu_{\text{max}}\) 3448 (OH), 1738 (C=O), 1437, 1162 and 1058 cm\(^{-1}\); \(\delta_H\) (250) 0.91 (3H, t, \(J = 7.1\), 10-CH\(_3\)), 1.37-1.48 (4H, m, 8- and 9-CH\(_2\)), 2.14-2.19 (2H, m, 7-CH\(_2\)), 2.39-2.42 (2H, m, 4-CH\(_2\)), 2.52 (1H, dd, \(J = 16.3\) and 8.7, 2-CH\(_{\text{A}}\)H\(_{\text{B}}\)), 2.67 (1H, dd, \(J = 16.3\) and 3.8, 2-CH\(_{\text{A}}\)H\(_{\text{B}}\)), 3.78 (3H, s, OMe) and 4.05-4.20 (1H, m, 3-CH); \(\delta_C\) (270) 13.46 (10-Me), 18.23 (CH\(_2\)), 21.84 (CH\(_2\)), 26.70 (CH\(_2\)), 30.89 (4-CH\(_2\)), 40.73 (2-CH\(_2\)), 51.68 (OMe), 66.83 (3-CH), 75.06 (5-C), 83.36 (6-C) and 172.78 (C=O); m/z 180 (7%, M\(^+\)-H\(_2\)O), 103 (100), 81 (18), 71 (51) and 61 (23) [Found: M\(^+\)-H\(_2\)O, 180.1157. C\(_{11}\)H\(_{16}\)O\(_2\) requires M, 180.1350].

(±)-Methyl 3-hydroxy-8-phenyl-oct-5-ynoate (35b)

4-Phenylbutyne (0.70 ml, 5 mmol, 1.0 eq) was alkylated with the (±)-epoxide 84 (580 mg, 5 mmol, 1.0 eq) exactly as in the preparation of compound 146, to give a brown oil (2 g) which was
chromatographed on silica (eluting with 25% ethyl acetate in petrol) to give, as a colourless oil, the alkyne 36b (0.66 g, 56%), \( \nu_{\text{max}} \) 3515 (OH), 1738 (C=O), 1437, 1173 and 1058 cm\(^{-1}\); \( \delta_H \) (250), 2.38-2.42 (2H, m, 4-CH\(_2\)), 2.43-2.51 (1H, m, 7-CH\(_2\)), 2.67-2.86 (2H, m, 2-CH\(_2\)), 2.81 (2H, t, \( J = 10.0 \), 8-CH\(_2\)), 3.74 (3H, s, OMe), 4.06-4.12 (1H, m, 3-CH) and 7.19-7.32 (5H, m, Ph); \( \delta_C \) (270) 29.25 (CH\(_2\)), 34.03 (CH\(_2\)), 35.93 (CH\(_2\)), 41.05 (CH\(_2\)), 51.75 (OMe), 66.83 (3-CH), 76.43 (5-C), 82.10 (6-C), 125.43 (CH), 128.76 (CH), 128.83 (CH), 135.67 (C) and 173.29 (C=O); m/z 246 (5%, M\(^+\)), 228 (10%, M\(^+\)-H\(_2\)O), 154 (45), 144 (47) and 129 (100) [Found: M\(^+\), 246.3032. \( C_{15}H_{18}O_2 \) requires M, 246.1256].

\( \pm \)-Methyl 3-triisopropylsilyloxydec-5-ynoate (37)

![Diagram](attachment:image.png)

Triisopropylsilyl chloride (366 mg, 1.9 mmol, 1.5 eq) was added to a stirred solution of the alkyne 36 (238 mg, 1.2 mmol, 1.0 eq) and imidazole (211 mg, 3.1 mmol, 2.5 eq) in dimethylformamide (6 ml). The resulting solution was stirred at RT for 72h and water (100 ml) was added. The resulting mixture was extracted with ether (3 x 100 ml) and the combined organic layers dried and evaporated to give a yellow oil (600 mg), which was chromatographed on silica (eluting with 9% ethyl acetate in petrol) to give the silyl derivative 37 as a colourless oil (426 mg, 98%). \( \nu_{\text{max}} \) 1736 (C=O), 1465, 1109 and 1069 cm\(^{-1}\); \( \delta_H \) (250) 0.89 (3H, t, \( J = 7.1 \), 10-CH\(_2\)), 0.91-1.15 (21H, m, TIPS), 1.31-1.72 (4H, m, 8- and 9-CH\(_2\)),
2.10-2.21 (2H, m, 7-CH₂), 2.41-2.43 (2H, m, 4-CH₂), 2.60 (1H, dd, J = 15.0 and 6.3, 2-CH₃H₂B), 2.79 (1H, dd, J = 15.0 and 5.1, 2-CH₃H₂B), 3.74 (3H, s, OMe) and 4.10-4.30 (1H, m, 3-H); δC (270) 12.41 (3 x CH, TIPS), 13.58 (10-Me), 17.80 (6 x Me, TIPS), 18.42 (CH₂), 21.80 (CH₂), 28.01 (CH₂), 30.51 (CH₂), 40.01 (2-CH₂), 51.37 (OMe), 68.31 (3-CH), 75.60 (5-C), 84.10 (6-C) and 171.01 (C=O); m/z 311 (7%, M⁺·iPr), 131 (35), 103 (29), 71 (100) and 61 (30)

(±)-(Z)-Methyl 3-triisopropylsilyloxydec-5-enoate (38)

The silyl derivative 37 (420 mg, 1.2 mmol) was reduced exactly as in the preparation of compound 147, to give the alkene 38 as a pale yellow oil (400 mg, 94%), νMAX 1741 (C=O), 1465 and 1103 cm⁻¹; δH (250) 0.89 (3H, t, J = 7.1, 10-CH₃), 0.92-1.17 (21H, m, TIPS), 1.31-1.71 (4H, m, 8- and 9-CH₂), 2.10-2.13 (2H, m, 7-CH₂), 2.41-2.44 (2H, m, 4-CH₂), 2.60 (1H, dd, J = 15.0 and 6.7, 2-CH₃H₂B), 2.79 (1H, dd, J = 15.0 and 4.1, 2-CH₃H₂B), 3.74 (3H, s, OMe), 4.01-4.09 (1H, m, 3-H), 5.35-5.42 (1H, m, 5-H) and 5.55-5.60 (1H, m, 6-H); δC (270) 12.44 (3 x CH, TIPS), 13.91 (10-Me), 18.00 (6 x Me, TIPS), 22.43 (CH₂), 27.24 (CH₂), 31.86 (CH₂), 35.54 (CH₂), 42.08 (2-CH₂), 51.63 (OMe), 66.31 (3-CH), 124.35 (5-CH), 132.79 (6-CH) and 171.73 (C=O); m/z 313 (4%, M⁺·iPr), 131 (100), 71 (65), 61 (41) and 55 (47) [Found: M⁺·iPr, 313.2180. C₁₆H₃₁O₃Si requires M, 313.2199].
(±)-(Z)-3-Triisopropylsilyloxydec-5-enoic acid (32)

The alkene 38 (400 mg, 1.2 mmol) was saponified exactly as in the preparation of compound 352, to give the (Z)-acid 32 as a pale yellow oil (380 mg, 95%), ν\textsubscript{max} 3664 (OH), 1713 (C=O) and 1103 cm\(^{-1}\); δ\textsubscript{H} (250) 0.90 (3H, t, J = 7.1, 10-CH\(_3\)), 1.10-1.13 (21H, m, TIPS), 1.31-1.71 (4H, m, 8- and 9-CH\(_2\)), 1.93-2.25 (2H, m, 7-CH\(_2\)), 2.45-2.46 (2H, m, 4-CH\(_2\)), 2.60 (1H, dd, J = 15.3 and 8.0, 2-CH\(_{A\,H_B}\)), 2.65 (1H, dd, J = 15.3 and 5.9, 2-CH\(_{A\,H_B}\)), 4.01-4.09 (1H, m, 3-H), 5.35-5.42 (1H, m, 5-H) and 5.55-5.60 (1H, m, 6-H); δ\textsubscript{C} (270) 12.47 (3 x CH, TIPS), 13.98 (10-Me), 18.08 (6 x Me, TIPS), 22.39 (CH\(_2\)), 27.22 (CH\(_2\)), 31.79 (CH\(_2\)), 40.71 (CH\(_2\)), 41.51 (2-CH\(_2\)), 69.52 (3-CH), 124.13 (5-CH), 132.99 (6-CH) and 175.53 (C=O); m/z 299 (87%, M\(^+\)Pr), 201 (20), 157 (44), 131 (80) and 71 (30) [Found: M\(^+\)Pr, 299.2017. C\(_{16}\)H\(_{31}\)O\(_3\)Si requires M, 299.2041].

(±)-3-Triisopropylsilyloxydec-5-ynoic acid (39)

The silyl derivative 37 (0.52 g, 1.47 mmol, 1 eq) was saponified exactly as in the preparation of compound 352, to give the alkynoic acid 39 as a colourless oil (500 mg, 95%), ν\textsubscript{max} 3500 (OH), 1714 (C=O), 1465, 1109 and 1069 cm\(^{-1}\); δ\textsubscript{H} (250) 0.89 (3H, t, J = 7.0, 10-
CH$_3$), 1.05-1.10 (21H, m, TIPS), 1.31-1.47 (4H, m, 8- and 9-CH$_2$),
2.11-2.17 (2H, m, 7-CH$_2$), 2.43-2.46 (2H, m, 4-CH$_2$), 2.58 (1H, dd, $J =$
15.1 and 6.6, 2-CH$_A$H$_B$), 2.78 (1H, dd, $J =$ 15.1 and 5.0, 2-CH$_A$H$_B$)
and 4.26-4.30 (1H, m, 3-H); $\delta_C$ (270) 12.40 (3 x CH, TIPS), 13.53 (10-
Me), 17.95 (6 x Me, TIPS), 18.39 (CH$_2$), 21.89 (CH$_2$), 27.82 (7-CH$_2$),
30.91 (4-CH$_2$), 41.62 (2-CH$_2$), 68.56 (3-CH), 75.62 (5-C), 83.09 (6-C)
and 177.18 (C=O); m/z 297 (10%, M$^+$-Pr), 131 (65), 85 (45), 71 (100)
and 61 (37) [Found: M$^+$-Pr, 297.1902. C$_{16}$H$_{29}$O$_3$Si requires M,
297.1886].

$(\pm)$-(E)-3-Triisopropylsilyloxydec-5-enoic acid (28)

$^t$Butanol (120 mg, 1.47 mmol, 1 eq) was added to a suspension
of ammonium sulphate (1.94 g, 14.7 mmol, 10 eq) and the alkyenoic
acid 39 (420 mg, 1.2 mmol) in tetrahydrofuran (25 ml). Ammonia
(50 ml) was condensed into the solution at -78°C and the resulting
mixture was stirred at -40°C during the addition of lithium chips
(54 mg, 8.9 mmol, 6 eq). The reaction was stirred at this
temperature for 2h and then allowed to warm to RT over 16h.
Water (100 ml) was added and the resulting solution was extracted
with chloroform (3 x 50 ml) and the combined organic layers dried
and evaporated to give, as a colourless oil, the (E)-acid 28 (475 mg,
95%), $\nu_{\text{max}}$ 3500 (OH), 1713 (C=O), 1464 and 1106 cm$^{-1}$; $\delta_H$ (250) 0.89
(3H, t, $J =$ 7.1, 10-CH$_3$), 1.05-1.07 (21H, m, TIPS), 1.31-1.40 (4H, m, 8-
...
and 9-CH₂), 1.95-1.98 (2H, m, 7-CH₂), 2.20-2.29 (2H, m, 4-CH₂), 2.47 (1H, dd, J = 15.2 and 5.9, 2-CH₃H₃B), 2.57 (1H, dd, J = 15.2 and 4.1, 2-CH₃H₃B), 4.17-4.27 (1H, m, 3-H), 5.30-5.42 (1H, m, 5-H) and 5.55-5.60 (1H, m, 6-H); δₐ (270) 12.42 (3 x CH, TIPS), 13.89 (10-Me), 18.01 (6 x Me, TIPS), 22.19 (CH₂), 31.47 (CH₂), 32.33 (7-CH₂), 40.75 (4-CH₂), 41.48 (2-CH₂), 69.44 (3-CH), 124.64 (5-CH), 134.52 (6-CH) and 177.45 (C=O); m/z 299 (2%, M⁺-jPr), 131 (45), 89 (51), 85 (100) and 71 (52) [Found: M⁺-jPr, 299.2035. C₁₆H₃₁O₅Si requires M, 299.2041].

(3RS,4SR,6SR)-6-Iodo-3-triisopropylsilyloxydecan-5-olide (40)

![Structure of 6-Iodo-3-triisopropylsilyloxydecan-5-olide (40)](image)

The (Z)-acid 32 (130 mg, 0.38 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 54b, but using 3:1 actetonitrile:water as solvent, to give a yellow oil (140 mg), which, upon chromatography on silica (eluting with 15% ether in petrol), gave the lactone 40 as a colourless oil (100 mg, 57%), νₐₓₗₙ 1748 (C=O), 1464, 1342 and 1248 cm⁻¹; δₐ (250) 0.92 (3H, t, J = 6.7, 10-CH₃), 1.05-1.08 (21H, m, TIPS), 1.22-1.45 (4H, m, 8- and 9-CH₂), 1.50-1.65 (1H, m, 7-Hₐ), 1.87 (1H, ddd, J = 14.4, 9.9 and 4.9, 4-CH₃H₃B), 2.06 (1H, ddd, J = 14.4, 8.3 and 2.6, 4-CH₃H₃B), 2.09-2.13 (1H, m, 7-Hₐ), 2.61 (1H, dd, J = 17.5 and 3.7, 2-CH₃H₃B), 2.65 (1H, dd, J = 17.5 and 5.1, 2-CH₃H₃B), 4.12 (1H, ddd, J = 9.9, 4.7 and 2.6, 5-
H) and 4.39-4.50 (2H, m, 3- and 6-H); δ_C (270) 12.29 (3 x CH, TIPS), 13.93 (10-Me), 17.72 (6 x Me, TIPS), 21.89 (CH_2), 31.91 (CH_2), 35.88 (CH_2), 35.93 (CH_2), 38.96 (6-CH), 39.41 (2-CH_2), 63.59 (3-CH), 77.23 (5-CH) and 169.41 (C=O); m/z 425 (5%, M^+Pr), 297 (10), 157 (100), 99 (45) and 57 (40) [Found: M^+Pr, 425.0986. C_{16}H_{30}IO_3Si requires M, 425.1011].

(3RS,4SR,6RS)-6-Iodo-3-triisopropylsilyloxy-decan-5-olide (41) and (3RS,4RS,6SR)-6-iodo-3-triisopropylsilyloxy-decan-5-olide (42)

![Structural diagram of compounds 41 and 42]

The (E)-acid 28 (504 mg, 1.47 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 40, to give a yellow oil (900 mg), which, upon chromatography on silica (eluting with 15% ether in petrol), gave the trans-lactone 41 as a colourless oil (540 mg, 78%), ν_max 1748 (C=O), 1464, 1342 and 1248 cm^{-1}; δ_H (250) 0.92 (3H, t, J = 7.0, 10-CH_3), 1.05-1.07 (21H, m, TIPS), 1.13-1.42 (6H, m, 7-, 8- and 9-CH_2), 1.70-1.90 (2H, m, 4-CH_2), 2.67 (2H, app. dd, J = 17.5 and 5.1, 2-CH_2), 4.27-4.37 (2H, m, 6- and 3-H) and 4.48 (1H, ddd, J = 6.8, 6.8 and 3.5, 5-H); δ_C (270) 12.31 (3 x CH, TIPS), 14.14 (10-Me), 18.24 (6 x Me, TIPS), 22.12 (CH_2), 31.81 (CH_2), 35.65 (7-CH_2), 35.77 (4-CH_2), 39.66 (2-CH_2), 41.04 (6-CH), 63.83 (3-CH), 77.79 (5-H) and 169.34 (C=O); and, as a colourless oil, the cis-lactone 42 (50 mg,
8%), $\nu_{\text{max}}$ 1748 (C=O), 1464, 1342 and 1248 cm$^{-1}$; $\delta_H$ (250) 0.93 (3H, t, $J$ = 6.7, 10-CH$_3$), 1.05-1.10 (21H, m, TIPS), 1.26-1.36 (4H, m, 8- and 9-CH$_2$), 1.55-1.62 (2H, m, 4-CH$_A$), 1.72-1.87 (2H, m, 7-CH$_2$), 2.09 (2H, dd, $J$ = 17.3 and 8.3, 2-CH$_2$), 2.85 (1H, ddd, $J$ = 17.1, 5.2 and 1.2, 4-CH$_B$), 3.97 (1H, ddd, $J$ = 11.1, 6.0 and 3.0, 5-H), 4.29 (1H, td, $J$ = 6.2 and 3.0, 6-H) and 4.30 (1H, app. tt, $J$ = 8.6 and 5.2, 3-H); $\delta_C$ (270) 12.19 (3 x CH, TIPS), 13.97 (10-Me), 16.02 (6 x Me, TIPS), 21.91 (CH$_2$), 31.55 (CH$_2$), 35.04 (7-CH$_2$), 38.13 (4-CH$_2$), 39.11 (6-CH), 40.37 (2-CH$_2$), 64.25 (3-CH), 78.90 (5-CH) and 169.41 (C=O).

(3RS,5SR,6RS)-Methyl 5,6-epoxy-3-triisopropylsilyloxydec-anoate (43)

Sodium carbonate (16.1 mg, 0.16 mmol, 1.7 eq) was added to a stirred solution of the lactone 40 (45 mg, 0.09 mmol, 1 eq) in dry methanol (1.6 ml) and the resulting mixture was stirred for 16 h in the dark. The solvent was removed in vacuo and the residue partitioned between water (1 ml) and ether (3 ml). The organic phase was dried and evaporated to give, as a colourless oil, the epoxide 43 (18 mg, 76%), $\nu_{\text{max}}$ 1741 (C=O), 1463, 1381, 1170 and 1096 cm$^{-1}$; $\delta_H$ (250) 0.92 (3H, t, $J$ = 6.9, 10-CH$_3$), 1.10-1.27 (21H, m, TIPS), 1.35-1.60 (6H, m, 7-, 8- and 9-CH$_2$), 1.68 (1H, ddd, $J$ = 14.4, 7.8 and 4.1, 4-CH$_AH_B$), 1.94 (1H, ddd, $J$ = 14.4, 6.1 and 3.9, 4-CH$_AH_B$), 2.65
(2H, app. dd, $J = 6.4$ and 2.2, 2-CH$_2$), 2.92 (1H, ddd, $J = 7.8$, 4.1 and 3.9, 5-H), 3.13 (1H, td, $J = 7.9$ and 4.1, 6-H), 3.67 (3H, s, OMe) and 4.55 (1H, tdd, $J = 6.4$, 6.1 and 4.1, 3-H); $\delta$$_C$ (270) 12.45 (3 x CH, TIPS), 14.00 (10-Me), 18.06 (6 x Me, TIPS), 22.59 (CH$_2$), 27.35 (CH$_2$), 27.65 (7-CH$_2$), 35.31 (4-CH$_2$), 41.83 (2-CH$_2$), 51.50 (OMe), 53.05 (5-CH), 56.26 (6-CH), 67.78 (3-CH) and 171.59 (C=O); m/z 329 (90%, M$^+$-iPr), 227 (77), 131 (85), 131 (75) and 75 (100) [Found: M$^+$-iPr, 329.2916. C$_{17}$H$_{33}$O$_4$Si requires M, 329.2148].

(3RS,5SR,6SR)-Methyl 5,6-epoxy-3-triisopropylsilyloxydecanoate (44)

The trans-lactone 41 (400 mg, 0.85 mmol, 1 eq) was treated as in the preparation of compound 43, to give, as a colourless oil, the epoxide 44 (190 mg, 75%), <span class="mathjax">
\begin{align*}
\nu_{\text{MAX}} & 1741 (C=O), 1463, 1371, 1176 \text{ and } 1060 \\
\delta_H & (250) 0.91 (3H, t, J = 6.9, 10-CH$_3$), 1.05-1.07 (21H, m, TIPS), \\
& 1.36-1.44 (4H, m, 8- and 9-CH$_2$), 1.51-1.62 (2H, m, 7-CH$_2$), 1.68 (1H, \\
& ddd, $J = 14.3$, 7.1 and 3.8, 4-CH$_A$H$_B$), 1.94 (1H, ddd, $J = 14.3$, 6.4 and \\
& 4.3, 4-CH$_A$H$_B$), 2.58-2.71 (3H, m, 6-H and 2-CH$_2$), 2.86 (1H, ddd, $J = \\
& 7.1$, 4.3 and 2.2, 5-H), 3.66 (3H, s, OMe) and 4.47 (1H, dddd, $J = 6.4$, \\
& 6.4, 3.8 and 2.6, 3-H); $\delta_C$ (270) 12.71 (3 x CH, TIPS), 14.25 (10-Me), \\
& 18.33 (6 x Me, TIPS), 22.81 (CH$_2$), 28.39 (CH$_2$), 31.97 (7-CH$_2$), 39.97 \\
& (4-CH$_2$), 42.07 (2-CH$_2$), 51.79 (OMe), 55.10 (5-CH), 58.55 (6-CH), 67.80
\end{align*}
</span>
(3-CH) and 172.22 (C=O); m/z 329 (90%, M+ iPr), 227 (77), 131 (85), 131 (75) and 75 (100).

\((3RS,5RS,6RS)\)-Methyl 5,6-epoxy-3-triisopropyl-silyloxydecanoate (45)

The cis-lactone 42 (40 mg, 0.8 mmol, 1 eq) was treated exactly as in the preparation of compound 43 to give, as a colourless oil, the epoxide 45 (15 mg, 70%) \( \nu_{\text{max}} \) 1741 (C=O), 1463, 1371, 1174 and 1095 cm\(^{-1}\); \( \delta \) \( \text{H} \) (250) 0.92 (3H, t, \( J = 6.9, 10-\text{CH}_3 \)), 1.07-1.17 (21H, m, TIPS), 1.27-1.45 (6H, m, 7-, 8- and 9-\( \text{CH}_2 \)), 1.70-1.72 (1H, m, 4-\( \text{CH} \)), 1.82-1.85 (1H, m, 4-\( \text{CH} \)), 2.53 (2H, dd, \( J = 6.3 \) and 1.7, 2-\( \text{CH}_2 \)), 2.66 (1H, td, \( J = 5.3 \) and 2.2, 6-\( \text{H} \)), 2.79 (1H, ddd, \( J = 5.6, 4.1 \) and 2.2, 5-\( \text{H} \)), 3.67 (3H, s, OMe) and 4.54 (1H, m, 3-\( \text{H} \)); \( \delta \) \( \text{C} \) (270) 12.46 (3 x \( \text{CH} \), TIPS), 13.91 (10-\( \text{Me} \)), 18.05 (6 x \( \text{Me} \), TIPS), 22.48 (CH\(_2\)), 27.98 (CH\(_2\)), 31.63 (7-CH\(_2\)), 40.07 (4-CH\(_2\)), 42.70 (2-CH\(_2\)), 51.48 (OMe), 58.89 (5-\( \text{CH} \)), 56.26 (6-\( \text{CH} \)), 67.91 (3-\( \text{CH} \)) and 171.68 (C=O); m/z 329 (90%, M+ iPr), 227 (77), 131 (85), 131 (75) and 75 (100).

\((\pm)-(E)\)-Methyl 3-hydroxydec-5-enoate (53b)

Diisobutylaluminium hydride (27 ml of a 1M solution, 27
mmol, 1 eq) was added to 1-hexyne (3.1 ml, 27 mmol, 1 eq) in hexane (91 ml) at -78°C and the resulting solution was then heated at 50°C for 2 h, before cooling to -30°C. Methyl lithium (18.5 ml of a 1.4 M solution in ether, 26 mmol, 0.96 eq) and then ether (90 ml) were added. The resulting suspension was stirred at 0°C for 0.5 h and then cooled to -78°C. The (±)-epoxide 84 (3 g, 26 mmol, 0.96 eq) followed by boron trifluoride etherate (3.18 ml, 26 mmol, 0.96 eq) were added. The solution was stirred at -78°C for 0.75 h. Methanol (15 ml) was added and after 10 min, 1 M hydrochloric acid (60 ml). The resulting mixture was extracted with ethyl acetate (3 × 50 ml) and the combined organic phases were dried and evaporated to give a colourless oil (6.4 g). Chromatography on silica (eluting with 15% ethyl acetate in petrol gave alkene 5d as a colourless oil (3.28 g, 63%), ν<sub>max</sub> 3417 (OH) and 1732 (C=O) cm<sup>-1</sup>; δ<sub>H</sub> (250) 0.90 (3H, t, <i>J</i> = 6.4, 10-CH<sub>3</sub>), 1.20-1.40 (4H, m, 8- and 9-CH<sub>2</sub>), 2.01-2.05 (2H, m, 7-CH<sub>2</sub>), 2.10-2.14 (2H, m, 4-CH<sub>2</sub>), 2.45 (1H, dd, <i>J</i> = 15.7 and 9.8, 2-CH<sub>A</sub>H<sub>B</sub>), 2.52 (1H, dd, <i>J</i> = 15.7 and 3.8, 2-CH<sub>A</sub>H<sub>B</sub>), 3.71 (3H, s, OMe), 4.05-4.20 (1H, m, 3-CH), 5.35-5.45 (1H, m, 5-CH) and 5.55-5.65 (1H, m, 6-CH); δ<sub>C</sub> (270) 13.92 (10-Me), 22.22 (CH<sub>2</sub>), 31.55 (CH<sub>2</sub>), 32.32 (CH<sub>2</sub>), 39.91 (4-CH<sub>2</sub>), 40.44 (2-CH<sub>2</sub>), 51.80 (OMe), 67.75 (3-CH), 124.82 (5-C), 138.70 (6-C) and 173.26 (C=O); m/z [NH₄⁺Cl⁻] 218 (85%, M⁺ + NH₄), 201 (20%, MH⁺), 183 (100), 169 (5) and 151 (10); [Found: C, 65.4; H, 9.9. C₁₁H₂₀O₃ requires C, 66.0; H, 10.1%].
Sodium hydrogen carbonate (4.11 g, 48.9 mmol, 3 eq) was added to an ice-cold solution of the alkene 5a (3.26 g, 16.3 mmol, 1 eq) in dry acetonitrile (66 ml) and the suspension stirred for 5 mins. Iodine (12.42 g, 48.9 mmol, 3 eq) was added and the resulting mixture was stirred at 0-5°C in the dark for 16 h. Ether (100 ml) was added and the solution was washed with saturated aqueous sodium thiosulphate (120 ml). The separated aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried and evaporated to give the iotetrahydrofuran 5b as a colourless oil (3.98 g, 75%). $\nu_{\text{max}}$ 1732 (C=O) cm$^{-1}$; $\delta_\text{H}$ (250) 1.06 (3H, t, $J = 6.7$, CH$_3$), 1.38-1.90 (6H, m, 3 x CH$_2$), 2.05 (1H, ddd, $J = 12.6$, 5.6 and 3.7, 3'-CH), 2.39 (1H, dd, $J = 15.5$ and 6.5, 2-CH$_A$H$_B$), 2.45 (1H, ddd, $J = 12.6$, 6.7 and 6.4, 3'-CH), 2.70 (1H, dd, $J = 15.5$ and 7.0, 2-CH$_A$H$_B$), 3.49 (1H, ddd, $J = 6.7$, 3.7 and 3.5, 4'-CH), 3.51 (3H, s, OMe), 4.20 (1H, ddd, $J = 6.7$, 6.7 and 3.5, 5'-CH) and 4.39 (1H, dddd, $J = 7.0$, 6.5, 6.4 and 5.6, 2'-CH); $\delta_\text{C}$ (270, C$_6$D$_6$) 14.11 (Me), 22.50 (4'-CH), 22.94 (CH$_2$), 28.34 (CH$_2$), 32.27 (CH$_2$), 40.59 (3'-CH$_2$), 44.76 (2-CH$_2$), 51.06 (OMe), 74.47 (2'-CH), 86.75 (5'-CH) and 170.56 (C=O); m/z [NH$_4$•Cl] 327 (15%, MH$^+$), 281 (30), 221 (43), 207 (36) and 147
The alkyne 36b (600 mg, 2.4 mmol) was reduced exactly as in the preparation of compound 147 to give the alkene 51b as a pale yellow oil (510 mg, 85%), ν_max 3505 (OH), 1737 (C=O), 1437, 1201 and 1172 cm⁻¹; δ_h (250) 2.15-2.20 (2H, m, 4-CH₂), 2.30-2.40 (2H, m, 6-CH₂), 2.40-2.51 (2H, m, 2-CH₂), 2.57 (2H, t, J = 10.1, 8-CH₂), 3.70 (3H, s, OMe), 3.92-4.00 (1H, m, 3-CH), 5.38-5.45 (1H, m, 5-CH), 5.55-5.62 (1H, m, 6-CH) and 7.15-7.31 (5H, m, Ph); δ_c (270) 29.37 (CH₂), 34.31 (CH₂), 35.74 (CH₂), 40.38 (CH₂), 51.74 (OMe), 67.85 (3-CH), 125.37 (5-CH), 128.36 (CH), 128.39 (CH), 128.46 (CH), 133.80 (6-CH), 141.75 (C) and 173.25 (C=O); m/z [NH₄⁺Cl⁻] 266 (75%, M⁺+NH₄⁺), 249 (100%, MH⁺), 199 (23), 134 (27) and 91 (24). [Found: C, 72.3; H, 8.0. C₁₁H₁₂O₃ requires C, 72.6; H, 8.1%].
(2'SR,4'RS,5'SR) Methyl (4'-hydroxy-5'-phenylethyltetrahydrofuran-2'-yl) acetate (52b)

![Chemical Structure](image)

The alkene 51b (80 mg, 0.32 mmol, 1 eq) was treated exactly as in the preparation of the preparation 148, to give the hydroxytetrahydrofuran 52b as a colourless oil (60 mg, 70%), $\nu_{\text{MAX}}$ 3570 (OH), 1736 (C=O), 1157 and 1084 cm$^{-1}$; $\delta_H$ (250) 1.83 (1H, ddd, $J = 13.5, 9.6$ and 6.1, 3'-CH$_A$), 2.03 (1H, ddd, $J = 13.5, 5.6$ and 2.0, 3'-CH$_B$), 2.52 (1H, dd, $J = 15.6$ and 6.2, 2'-CH$_A$CH$_B$), 2.63 (1H, dd, $J = 15.6$ and 6.9, 2'-CH$_A$CH$_B$), 2.48-2.51 (2H, m, 7-CH$_2$), 2.78-2.80 (2H, m, 6-CH$_2$), 3.70 (3H, s, OMe), 3.75 (1H, ddd, $J = 6.1, 5.6$ and 3.1, 4'-CH), 4.10 (1H, td, $J = 6.3$ and 3.1, 5'-CH) and 4.50 (1H, dddd, $J = 9.6, 6.9$, 6.2 and 2.0, 2'-CH); $\delta_C$ (270) 32.14 (CH$_2$), 36.14 (CH$_2$), 40.72 (CH$_2$), 40.85 (CH$_2$), 51.74 (OMe), 74.16 (4'-CH), 76.57 (2'-CH), 86.43 (5'-CH), 128.51 (CH), 128.52 (CH), 128.54 (CH), 141.78 (C) and 172.71 (C=O); m/z 246 (25%, M$^+$-H$_2$O), 191 (37), 104 (65), 98 (95) and 91 (100)

[Found: M$^+$-H$_2$O, 246.1261. C$_{15}$H$_{18}$O$_3$ requires M, 246.1259].
(2'RS,4'SR,5'RS) Methyl (4'-iodo-5'-phenylethyltetrahydro-furan-2'-yl)-acetate (54c)

The methyl ester 92 (60 mg, 0.24 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 54b, to give an oil (100 mg) which was chromatographed on silica (eluting with 10% ethyl acetate in petrol) to give, as a colourless oil, the iodo-tetrahydrofuran 54c (170 mg, 69%), \( \nu_{\text{MAX}} \) 1736 (C=O), 1438, 1202 and 1030 cm\(^{-1}\); \( \delta_H \) (250) 1.71 (1H, ddd, \( J = 13.8, 4.7 \) and 3.5, 3'-CH), 2.05 (1H, m, 3'-CH), 2.48 (1H, dd, \( J = 15.5 \) and 6.4, 2-CH\(_A\)H\(_B\)), 2.60-2.85 (5H, m, 2-CH\(_A\)H\(_B\), 6- and 7-CH\(_2\)), 3.64 (3H, s, OMe), 3.70 (1H, ddd, \( J = 7.4, 3.5 \) and 3.4, 4'-H), 3.94 (1H, dt, \( J = 8.5 \) and 3.5, 5'-H), 4.35 (1H, dddd, \( J = 6.9, 6.4, 4.7 \) and 1.4, 2'-H) and 7.08-7.25 (5H, m, Ph); \( \delta_C \) (270) 21.52 (4'-CH), 32.18 (CH\(_2\)), 33.93 (CH\(_2\)), 40.67 (3'-CH\(_2\)), 44.52 (2-CH\(_2\)), 51.83 (OMe), 74.48 (2'-CH), 85.88 (5'-CH), 125.96 (CH), 128.44 (CH), 128.46 (CH), 134.45 (C), 141.63 (C=O) and 170.45 (C=O); m/z 246 (2%, M\(^+\)-HI), 186 (43), 160 (36), 91 (100) and 55 (100).

(2RS,3SR)-2-Ethyl-3-iodotetrahydrofuran (58)

(E)-3-Hexen-1-ol 57 (0.37 ml, 3 mmol, 1 eq) was iodocyclised
(over various times: 5-45 mins) exactly as in the preparation of compound 56b, to give the iodoseterahydrofuran 58 as a colourless oil (0.54 g, 80%), which showed data which was identical to literature values,36 $\nu_{\text{max}}$ 1462, 1384, 1164, 1069 and 1023 cm$^{-1}$; $\delta_H$ (250) 0.99 (3H, t, $J = 7.4$, CH$_3$), 1.49 (1H, ddd, $J = 13.9$ and 7.4, 7.4, 1'-H$_A$), 1.72 (1H, ddd, $J = 13.9$, 7.4 and 7.4, 1'-H$_B$), 2.23-2.27 (1H, m, 4-H$_A$), 2.46-2.50 (1H, m, 4-H$_B$), 3.79 (1H, ddd, $J = 6.9$, 5.9 and 4.2, 3-H), 3.89 (2H, dt, $J = 7.1$ and 1.2, 5-CH$_2$) and 3.97 (1H, td, $J = 7.4$ and 4.2, 2-H); $\delta_C$ (400) 10.23 (Me), 23.35 (3-CH), 25.91 (CH$_2$), 38.59 (4-CH$_2$), 66.92 (5-CH$_2$) and 89.48 (2-CH); m/z 198 (16%, M$^+$), 156 (37), 91 (61), 85 (100) and 57 (92).

(2SR,3SR)-2-Ethyl-3-iodotetrahydrofuran (60)

(Z)-3-Hexen-1-ol 59 (0.37 ml, 3 mmol, 1 eq) was iodocyclised over 72h in the same way as in the preparation of compound 56b to give the iodoseterahydrofuran 60 as a colourless oil (0.41 g, 60%), $\nu_{\text{max}}$ 1462, 1384, 1164 and 1023 cm$^{-1}$; $\delta_H$ (250) 0.93 (3H, t, $J = 7.5$, CH$_3$), 1.50 (1H, dqq, $J = 13.7$ and 7.5, 6.6, 1'-H$_A$), 1.76 (1H, dqq, $J = 13.9$, 7.5 and 6.5, 1'-H$_B$), 2.47 (1H, dddd, $J = 14.2$, 7.1, 2.9 and 1.4, 4-H$_A$), 2.73 (1H, dt, $J = 14.2$, 9.2 and 5.6, 4-H$_B$), 2.80 (1H, dt, $J = 6.5$ and 3.2, 2-H), 3.79 (1H, ddd, $J = 6.9$, 5.9 and 4.2, 3-H), 3.91 (1H, ddd, $J = 9.2$, 8.3 and 2.9, 5-CH$_A$), 4.14 (1H, ddd, $J = 9.2$, 8.3 and 7.2, 5-CH$_B$) and 4.48 (1H, ddd, $J = 5.6$, 3.2 and 1.4, 2-H); $\delta_C$ (270) 10.24
(Me), 30.46 (CH₂), 34.16 (3-CH), 39.10 (4-CH₂), 66.00 (5-CH) and 83.49 (2-CH); m/z 226 (10%, M⁺), 197 (15), 99 (100), 71 (28) and 57 (95).

(2SR,3SR,5RS) 2-Butyl-5-ethyl-3-iodotetrahydrofuran (62)

(Z)-Dec-5-en-3-ol (230 mg, 1.6 mmol, 1 eq) was iodocyclised exactly as in the preparation of 54b, to give the iodo-tetrahydrofuran 62 (270 mg, 60%) as a colourless oil which showed, \( \nu_{\text{max}} \) 1463 and 1168 cm⁻¹; \( \delta_H \) (250) 0.92 (3H, t, \( J = 7.1 \), CH₃), 0.95 (3H, t, \( J = 7.4 \), CH₃), 1.23-1.39 (4H, m, 2 x CH₂), 1.50-1.83 (4H, m, 2 x CH₂), 2.31 (1H, ddd, \( J = 14.6, 6.4 \) and 3.0, 4-H₄), 2.76 (1H, ddd, \( J = 6.4, 6.4 \) and 4.0, 2-H), 2.92 (1H, ddd, \( J = 14.6, 8.0 \) and 7.0, 4-H₅), 3.86 (1H, dddd, \( J = 8.0, 6.4, 6.4 \) and 6.4, 5-H) and (1H, ddd, \( J = 7.0, 4.0 \) and 3.0, 3-H); \( \delta_C \) (400) 10.63 (Me), 14.09 (Me), 22.72 (CH₂), 28.02 (CH₂), 29.32 (CH₂), 30.95 (CH₂), 32.35 (3-CH), 43.90 (4-CH₂), 81.38 (2-CH) and 81.60 (5-CH); m/z 253 (M⁺-Et, 4%), 225 (50), 155 (91), 85 (69) and 69 (100) [Found: M⁺-Et, 253.0172. C₈H₁₄IO requires M, 253.0089].

(2RS,3SR,5RS) 2-Butyl-5-ethyl-3-iodotetrahydrofuran (63)

(E)-Dec-5-en-3-ol (160 mg, 1.02 mmol, 1 eq) was iodocyclised exactly as in the preparation of 54b, to give the iodotetrahydro-furan 63 (250 mg, 90%) as a colourless oil which showed, \( \nu_{\text{max}} \) 1680, 1540
and 1403 cm$^{-1}$; $\delta_H$ (250) 0.92 (6H, app. t, $J = 7.5$, 2 x CH$_3$), 1.22-1.47 (4H, m, 2 x CH$_2$), 1.51-1.85 (4H, m, 2 x CH$_2$), 1.99 (1H, ddd, $J = 12.8$, 10.3 and 8.5, 4-H$_A$), 2.65 (1H, ddd, $J = 12.8$, 7.3 and 6.2, 4-H$_B$), 3.75 (1H, ddd, $J = 8.7$, 7.5 and 3.3, 2-H), 3.89 (1H, dddd, $J = 8.5$, 6.4, 6.4 and 6.2, 5-H) and (1H, ddd, $J = 10.3$, 7.3 and 3.3, 3-H); $\delta_C$ (400) 10.23 (Me), 14.28 (Me), 23.05 (CH$_2$), 23.35 (3-CH), 28.48 (CH$_2$), 29.22 (CH$_2$), 32.32 (CH$_2$), 44.78 (4-CH$_2$), 79.93 (2-CH) and 86.50 (5-CH); m/z 267 (1%, M$^+$/Me), 239 (5), 222 (15), 155 (10) and 125 (100).

(2SR,3RS)-5,5-Dimethyl-2-ethyl-3-iodotetrahydrofuran (65)

(E)-2-Methylhept-5-en-2-ol 64 (1 g, 7.8 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 54b, to give the iodotetrahydrofuran 65 (1.5 g, 76%) as a colourless oil which showed, $\nu_{\text{MAX}}$ 1453, 1367, 1182 and 1099 cm$^{-1}$; $\delta_H$ (250) 0.99 (3H, t, $J = 7.5$, CH$_3$), 1.23 (3H, s, CH$_3$), 1.33 (3H, s, CH$_3$), 1.42-1.58 (1H, m, CH$_A$H$_B$CH$_3$), 1.76-1.88 (1H, m, CH$_A$H$_B$CH$_3$), 2.18 (1H, dd, $J = 12.9$ and 9.9, 4-H$_A$), 2.39 (1H, dd, $J = 12.9$ and 6.9, 4-H$_B$), 3.79 (1H, ddd, $J = 9.9$, 6.9 and 3.4, 3-H) and 4.00 (1H, ddd, $J = 8.9$, 6.9 and 3.4, 2-H); $\delta_C$ (270) 9.76 (Me), 22.51 (4-CH), 24.91 (CH$_2$), 28.75 (Me), 29.46 (Me), 51.34 (3-CH$_2$) and 81.11 (2-CH); m/z 239 (7%, M$^+$/Me), 225 (59), 127 (33), 98 (100) and 69 (85) [Found: M$^+$/Me, 238.9940. C$_7$H$_{12}$IO requires M, 238.9933].
(±)-2,2-Dimethyl-3-iodotetrahydrofuran (67)

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\begin{array}{c}
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\text{O}
\end{array}
\]

5-Methylpent-4-en-1-ol 66 (1 g, 10 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 54b to give the iodo
tetrahydrofuran 67 (1.94 g, 85%) as a colourless oil, \( \nu_{\text{MAX}} \) 1455, 1384, 1370, 1246, 1126 and 1038 cm\(^{-1}\); \( \delta_H \) (250) 1.33 (3H, s, CH\(_3\)), 1.39 (3H, s, CH\(_3\)), 2.18-2.46 (1H, m, 4-H\(_A\)), 2.54-2.67 (1H, m, 4-H\(_B\)), 3.79-3.98 (3H, m, 4-H and 2-CH\(_2\)); \( \delta_C \) (270) 25.00 (Me), 26.36 (Me), 31.00 (4-CH), 37.65 (3-CH\(_2\)), 65.79 (2-CH) and 82.03 (5'-C); m/z 226 (8%, M\(^+\)), 211 (31), 99 (89), 84 (41) and 41 (100) [Found: M\(^+\), 225.9850. C\(_6\)H\(_{10}\)IO requires M, 225.9854].

(±)-(E)-2-(2'-Hydroxy-7'-phenylhept-4'-enyl)-1,3-dithiane (68)

\[
\begin{array}{c}
\text{OH} \\
\text{S} \end{array}
\]

Lithium aluminium hydride bis-tetrahydrofuran (37.7 ml of a 1M solution in toluene, 37.7 mmol, 2.6 eq) was added to a solution of the dithiane 90 (4.45 g, 14.5 mmol, 1 eq) in glyme (80 ml). The solution was heated at reflux for 16h and then cooled to RT. Water (25 ml) was added very cautiously and the resulting mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried and evaporated to give the alkene 68 as a
colourless oil (3.71 g, 83 %), $\nu_{\text{MAX}}$ 3430 (OH), 1313, 1147, 1052 and 1030 cm$^{-1}$; $\delta_H$ (250) 1.80-1.82 (2H, m, 5'-CH$_2$), 1.85-1.93 (2H, m, 1'-CH$_2$), 2.05-2.25 (2H, m, 3'-CH$_2$), 2.32-2.40 (2H, m, 6'-CH$_2$), 2.70 (2H, t, $J = 9.0$, 7'-CH$_2$), 2.80-2.97 (4H, m, 4 and 6-CH$_2$), 3.82-3.91 (1H, m, 2'-H), 4.27 (1H, t, $J = 8.0$, 2-H), 5.32-5.60 (2H, m, 3' and 4'-H) and 7.20-7.35 (5H, m, Ph); $\delta_C$ (270) 25.96 (CH$_2$), 30.02 (CH$_2$), 30.36 (CH$_2$), 34.40 (CH$_2$), 36.58 (CH$_2$), 40.69 (CH$_2$), 42.01 (CH$_2$), 44.18 (2-CH), 67.58 (2'-CH), 125.87 (4-CH), 125.87 (CH), 126.03 (CH), 128.32 (CH), 133.86 (3-CH) and 141.71 (C); m/z [NH$_4$-Cl] 326 (63%, M$^+$-NH$_4$), 309 (MH$^+$, 60), 291 (MH$^+$-H$_2$O, 40), 119 (100) and 91 (75) [Found: C, 66.1; H, 8.0. C$_{17}$H$_{24}$O$_2$S$_2$ requires C, 66.2, H, 7.8%].

(2RS,4RS,5RS)-2-(1,3-Dithiane-2-ylmethyl)-4-iodo-5-(2-phenylethyl)tetrahydrofuran (69) and (2'RS,4'RS,5'SR)-(4'-iodo-5'-phenylethyl-tetrahydrofuran-2'-yl)acetaldehyde (70)

![Structural diagram]

The alkene 68 (1.0 g, 3.24 mmol, 1 eq) was treated exactly as in the preparation of compound 59b, to give a brown oil (1.9 g) which was chromatographed on silica (eluting with 10% ethyl acetate in petrol) to give the iodontetrahydrofuran 69 as a colourless oil (270 mg, 34%), $\nu_{\text{MAX}}$ 1602, 1496, 1454, 1422, 1376, 1276, 1144, 1074 and 1031 cm$^{-1}$; $\delta_H$ (250) 1.70-1.80 (2H, m, 5'-CH$_2$), 1.82-2.05 (6H, m,
1-, 3- and 6-CH$_2$), 2.47-2.95 (6H, m, 4'-, 6'- and 7-CH$_2$), 3.72 (1H, ddd, $J = 6.2$, 4.0 and 3.0, 3-H), 3.95 (1H, td, $J = 7.0$ and 3.0, 5-H), 4.20 (1H, dd, $J = 12.0$ and 8.0, 2'-H), 4.32 (1H, m, 2-H) and 7.15-7.30 (5H, m, Ph); $\delta_C$ (270) 21.75 (CH$_2$), 29.98 (CH$_2$), 30.32 (CH$_2$), 31.93 (CH), 32.24 (CH$_2$), 33.67 (CH$_2$), 41.71 (CH$_2$), 44.05 (4-CH), 44.58 (CH$_2$), 66.39 (2'-CH), 74.57 (2-CH), 85.23 (5-CH), 125.80 (CH), 128.30 (CH), 128.36 (CH) and 141.60 (C); and also the aldehyde 70 (100 mg, 15%) as a colourless oil which showed, $\delta_H$ (250) 1.75 (1H, ddd, $J = 13.0$, 4.7 and 3.5, 3'-H), 2.05 (1H, ddd, $J = 13.0$, 6.0 and 2.1, 3-H), 2.70-2.90 (6H, m, 2'-, 6- and 7-CH$_2$), 3.73 (1H, ddd, $J = 6.2$, 4.0 and 3.0, 4'-H), 4.03 (1H, dd, $J = 7.0$ and 3.0, 5'-H), 4.42-4.52 (1H, m, 2'-H) and 7.15-7.30 (5H, m, Ph).

$(\pm)$-(Z)-Methyl 3-hydroxydec-5-enoate (71)

The alkyne 36 (430 mg, 2.1 mmol) was reduced exactly as in the preparation of compound 147, to give the alkene 71 as a pale yellow oil (410 mg, 97%), $\nu_{\text{MAX}}$ 3442 (OH), 1736 (C=O), 1438, 1163 and 1060 cm$^{-1}$; $\delta_H$ (250) 0.90 (3H, t, $J = 7.1$, 10-CH$_3$), 1.27-1.40 (m, 6H, 3 x CH$_2$), 2.0-2.1 (2H, m, 7-CH$_2$), 2.20-2.37 (2H, m, 4-CH$_2$), 2.45 (1H, dd, $J = 16.2$ and 8.7, 2-CH$_A$H$_B$), 2.76 (1H, dd, $J = 16.2$ and 3.8, 2-CH$_A$H$_B$), 3.25 (1H, br, OH), 3.71 (3H, s, OMe), 4.01-4.09 (1H, m, 3-CH), 5.35-5.42 (1H, m, 5-CH) and 5.55-5.60 (1H, m, 6-CH); $\delta_C$ (270)
14.23 (10-Me), 22.63 (CH₂), 27.41 (CH₂), 32.02 (CH₂), 34.65 (4-CH₂), 40.72 (2-CH₂), 52.01 (OMe), 68.25 (3-CH), 124.40 (5-CH), 133.80 (6-CH) and 173.55 (C=O); m/z 182 (6%, M⁺·H₂O), 103 (100), 71 (95), 61 (44) and 55 (95) [Found: M⁺·H₂O, 182.2469. C₁₁H₁₈O₂ requires M, 182.2469].

(2'SR,4'RS,5'SR) Methyl (5'-butyl-4'-hydroxytetrahydrofuran-2'-yl)acetate (72)

The alkene 71 (1.75g, 8.75 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 148, to give the hydroxytetrahydrofuran 72 as a colourless oil (1.80 g, 95%), νMAX 3500 (OH) and 1738 (C=O) cm⁻¹; δH (250) 0.90 (3H, t, J = 6.3, Me), 1.1-1.5 (6H, m, 3 x CH₂), 1.76 (1H, ddd, J = 12.7, 9.6 and 6.1, 3'-CH), 1.97 (1H, ddd, J = 12.7, 6.6 and 3.9, 3'-CH), 2.50 (1H, dd, J = 15.6 and 6.2, 2-CHₐCHₐ), 2.62 (1H, dd, J = 15.6 and 6.9, 2-CHₐCHₐ), 3.75 (3H, s, OMe), 3.85 (1H, td, J = 6.3 and 3.1, 5'-CH), 4.01 (1H, ddd, J = 6.6, 6.1 and 3.1, 4'-CH) and 4.49 (1H, dddd, J = 9.6, 6.9, 6.2 and 3.9, 2'-CH); δC (270) 13.99 (Me), 22.71 (CH₂), 27.96 (CH₂), 34.10 (CH₂), 40.78 (2-CH₂), 51.69 (OMe), 73.90 (2'-CH), 76.28 (4'-CH), 87.10 (5'-CH) and 171.62 (C=O); m/z 198 (2%, M⁺·H₂O), 130 (19), 117 (18), 98 (100) and 57 (61) [Found: M⁺·H₂O, 198.2640. C₁₁H₁₈O₃ requires M, 198.2643].
1,1'-Carbonyldiimidazole (4.36 g, 27 mmol, 1.01 eq) was added to a stirred solution of 4-methylpent-3-enoic acid 81 (3.0 g, 26 mmol, 1.0 eq), prepared following the procedure of Smith,88 in tetrahydrofuran (20 ml) and the resulting solution was stirred for 16h at RT. The resulting solution was then added dropwise to the magnesium chelate form of the methyl hydrogen malonate dianion (27 ml of a 1M solution in tetrahydrofuran, 27 mmol, 1eq). The resulting mixture was stirred for 24h and saturated aqueous ammonium chloride was added (50 ml). The resulting solution was extracted with ethyl acetate (3 x 100 ml) and the combined organic phases were washed with saturated aqueous sodium bicarbonate (50 ml) and brine (50 ml), dried and evaporated to give a brown oil (2 g) which was chromatographed on silica (eluting with 15% ethyl acetate in petrol), to give the keto-ester 80 as a colourless oil (1.05 g, 45%), which showed, $\nu_{\text{max}}$ 1750 (C=O), 1438, 1377 and 1108 cm$^{-1}$; $\delta$H (250) 1.38 (6H, d, $J = 9.0$, 2 x CH$_3$), 1.65-1.80 (2H, m, 4-CH$_2$), 2.41-2.60 (2H, m, 2-CH$_2$), 3.75 (3H, s, OMe) and 5.10-5.15 (1H, m, 5-H); $\delta$C (400) 25.61 (Me), 29.20 (Me), 30.71 (4-CH$_2$), 45.23 (2-CH$_2$), 51.54 (OMe), 125.39 (5-CH), 131.95 (6-C), 173.61 (C=O) and 200.91 (C=O); m/z 170 (2%, M$^+$), 143 (46), 101 (39), 97 (69) and 89
Butylamine-borane complex (502 mg, 10, mmol, 1.05 eq) was added to a stirred solution of the keto-ester 80 (1.7 g, 10 mmol, 1 eq) and 1M citric acid (7ml) in methanol (30 ml) and the resulting solution was stirred for 1h at RT. The solution was then diluted with water (30 ml) and extracted with ether (3 x 100 ml). The combined organic phases were dried and evaporated to give a brown oil (1.9 g), which was chromatographed on silica (eluting with 20% ethyl acetate in hexane) to give the hydroxy-ester 82 as a colourless oil (1.37 g, 80%), \( \nu_{\text{max}} 3490(\text{OH}), 1744(\text{C}=\text{O}) \) and 1643 cm\(^{-1}\); \( \delta_H \) (250) 1.64 (6H, d, \( J = 4.6 \), 2 x CH\(_3\)), 2.20-2.43 (2H, m, 4-CH\(_2\)), 2.46 (2H, dd, \( J = 15.1 \) and 8.7, 2-CH\(_A\)H\(_B\)), 2.51 (2H, dd, \( J = 15.1 \) and 6.3, 2-CH\(_A\)H\(_B\)), 3.72 (3H, s, OMe), 4.02-4.05 (1H, m, 3-H) and 5.23-5.24 (1H, m, 5-H); \( \delta_C \) (400) 25.64 (Me), 29.30 (Me), 31.57 (4-CH\(_2\)), 42.10 (2-CH\(_2\)), 51.59 (OMe), 63.91 (3-CH), 126.00 (5-CH), 131.49 (6-C) and 172.59 (C=O); \( m/z \) 172 (1%, M\(^+\)), 154 (30), 101 (100), 70 (64) and 55 (43).
(2'SR,4'SR) Methyl (5',5'-dimethyl-4'-iodotetrahydrofuran-2'-yl)acetate (83)

The hydroxy-ester 82 (150 mg, 0.9 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound 54b, to give the iodo-tetrahydrofuran 83 as a colourless oil (160 mg, 59%) which showed, $\nu_{\text{MAX}}$ 1462, 1384, 1164 and 1023 cm$^{-1}$; $\delta_H$ (250) 1.64 (3H, s, CH$_3$), 1.40 (3H, s, CH$_3$), 1.83-1.91 (1H, m, 3-H$_A$), 2.22 (1H, ddd, $J = 13.0$ and 10.8, 9.1, 3'-H$_B$), 2.53 (1H, dd, $J = 15.4$, and 6.7, 2-H$_A$), 2.65 (1H, dd, $J = 15.4$, and 6.5, 2-H$_B$), 3.69 (3H, s, OMe), 4.02 (1H, dd, $J = 10.8$ and 6.8, 4'-H$_B$) and 4.33 (1H, dddd, $J = 9.1$, 6.7, 6.7 and 6.5, 2'-H); $\delta_C$ (400) 25.66 (Me), 29.23 (Me), 29.96 (4'-CH), 41.58 (3'-CH$_2$), 43.66 (4-CH$_2$), 51.79 (OMe), 73.93 (2'-CH), 82.74 (5'-C) and 171.46 (6-C).

(±)-2-(2'-Hydroxy-7'-phenylhept-4'-ynyl)-1,3-dithiane (90)

A solution of 4-phenylbutyne (6.67 g, 0.05 mol, 1.5 eq) in tetrahydrofuran (60 ml) was alkylated exactly as in the preparation of
with 2-(2,3-epoxypropan-1-yl)-1,3-dithiane \( \text{90} \) (6.02 g, 0.033 mol, 1.0 eq), prepared by the method of Seebach\(^{103} \) to give a yellow oil (9 g), which was chromatographed on silica (eluting with 10% ethyl acetate in petrol), to give, as a pale yellow oil, the dithiane \( \text{90} \) (5.8 g, 55\%), \( \nu_{\text{max}} \) 3437 (OH), 1453, 1423, 1276, 1075 and 1030 cm\(^{-1} \); \( \delta_{\text{H}} \) (250) 1.85-1.95 (2H, m, 5-CH\(_2\)), 2.10-2.20 (2H, m, 1'-CH\(_2\)), 2.30 (1H, ddt, \( J = 14.7, 6.3 \) and 2.0, 3'-CH\(_A\)H\(_B\)), 2.40 (1H, ddt, \( J = 14.7, 4.0 \) and 2.0, 3'-CH\(_A\)H\(_B\)), 2.48 (2H, tt, \( J = 9.0 \) and 2.0, 6'-CH\(_2\)), 2.81 (2H, t, \( J = 9.0, 7'\)-CH\(_2\)), 3.95-4.03 (1H, m, 2'-H), 4.25 (1H, dd, \( J = 11.0 \) and 9.2, 2-H) and 7.20-7.35 (5H, m, Ph); \( \delta_{\text{C}} \) (270) 20.85 (CH\(_2\)), 25.89 (CH\(_2\)), 27.65 (CH\(_2\)), 29.84 (CH\(_2\)), 30.22 (CH\(_2\)), 35.14 (CH\(_2\)), 41.47 (CH\(_2\)), 43.86 (2'-CH), 66.75 (2-CH), 76.37 (4'-C), 82.70 (3'-C), 126.25 (CH), 128.36 (CH), 128.38 (CH) and 140.62 (C); m/z \([\text{NH}_4^+\text{Cl}]\) 324 (100\%, M\(^+\) + \text{NH}_4\), 307 (MH\(^+\), 90), 199 (87), 161 (65) and 119 (91), [Found: C, 66.3; H, 7.3; S, 20.5. \( \text{C}_{17}\text{H}_{22}\text{O}_2\text{S}_2 \) requires C, 66.6; H, 7.2; S, 20.9\%].

(±)-(E)-3-Hydroxy-8-phenyloct-5-enal (\( \text{91} \))

Methyl iodide (4.4 ml, 70.2 mmol, 8 eq) was added to a suspension of the alkene \( \text{68} \) (2.71 g, 8.8 mmol, 1 eq) and sodium hydrogencarbonate (5.9 g, 70.2 mmol, 8 eq) in acetone (300 ml) and
water (15 ml). The resulting suspension was refluxed for 5h. Further portions of methyl iodide were added, until the reaction was complete by tlc., water (500 ml) was added, and the cooled mixture extracted with ethyl acetate (3 x 300 ml). The combined organic phases were dried and evaporated to give an oil (1.6 g), which was chromatographed on silica (eluting with 40% ethyl acetate in petrol), to give the aldehyde 91 (1.6 g, 87%) $\nu_{\text{max}}$ 1721 (C=O) cm$^{-1}$; $\delta_{\text{H}}$ (250) 2.12-2.21 (2H, m, 4-CH$_2$), 2.30-2.41 (2H, m, 7-CH$_2$), 2.47-2.50 (2H, m, 2-CH$_2$), 2.62-2.73 (2H, m, 8-CH$_2$), 4.05-4.12 (1H, m, 3-H), 5.30-5.60 (2H, m, 5- and 6-H), 7.15-7.31 (5H, m, Ph) and 9.80 (1H, t, $J$ = 0.7, 1-H); $\delta_{\text{C}}$ (270) 34.42 (CH$_2$), 35.67 (CH$_2$), 40.33 (CH$_2$), 40.95 (CH$_2$), 68.04 (3-CH), 125.76 (5-CH), 128.45 (CH), 128.56 (CH), 128.95 (CH), 134.67 (6-CH), 141.54 (C) and 200.14 (C=O).

(±)-(E)-Methyl 3-hydroxy-8-phenyloct-5-enoate (92)

Pyridinium dichromate (2.27 g, 6 mmol, 6 eq) was added to a solution of the aldehyde 91 (218 mg, 1 mmol, 1 eq) in dimethylformamide (2 ml) and methanol (2.0 ml, 6 mmol, 6 eq). The resulting suspension was stirred for 16h before being diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined organic phases were dried and evaporated to give an oil (300 mg) which was chromatographed on silica (eluting with 40% ethyl
acetate in petrol) to give, as a colourless oil, the *methyl ester* 92 (170 mg, 69%) $v_{\text{MAX}}$ 1737 (C=O) cm$^{-1}$; $\delta_H$ (250) 2.14 (2H, t, $J = 6.5$, 7-CH$_2$), 2.31 (1H, dd, $J = 16.5$ and 8.0, 2-CH$_2$A$_B$), 2.35 (2H, m, 4-CH$_2$), 2.63 (2H, t, $J = 6.5$, 8-CH$_2$), 2.67 (1H, dd, $J = 16.5$ and 3.3, 2-CH$_2$A$_B$), 3.65 (3H, s, OMe), 3.91-3.93 (1H, m, 3-H), 5.27-5.55 (2H, m, 5- and 6-H) and 7.09-7.25 (5H, m, Ph); $\delta_C$ (270) 34.43 (CH$_2$), 35.79 (CH$_2$), 39.63 (CH$_2$), 40.44 (CH$_2$), 51.79 (OMe), 67.71 (3-CH), 125.89 (CH), 128.36 (CH), 128.53 (CH), 134.54 (C), 141.80 (CH) and 173.22 (C=O); m/z 230 (15%, M$^+$/H$_2$O), 199 (27), 146 (40) 134 (30) and 91 (100)

(2'SR,4'RS,5'SR) *Methyl (5'-butyl-4'-tbutyldimethylsilyloxytetrahydrofuran-2'-yl) acetate* (138)

![TBDMSO\_Bu\_O\_CO\_Me\_structure](image)

Imidazole (1.79 g, 26 mmol, 2.5 eq) was added to a stirred solution of the hydroxytetrahydrofuran 72 (2.22 g, 10.5 mmol, 1 eq) and $t$-butyldimethylsilyl chloride (3.95 g, 26 mmol, 2.5 eq) in dry dimethylformamide (12 ml). The resulting solution was stirred at RT for 72h. Water (200 ml) was added and the resulting solution was extracted with hexane (3 x 80 ml). The combined organic phases were dried and evaporated to give an oil (5 g), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *silyloxytetrahydrofuran* 138 as a colourless oil (4.2 g, 191
54%), $\nu_{\text{max}}$ 1738 (C=O); $\delta_H$ (250) 0.05 (6H, m, 2 x MeSi), 0.85 (9H, s, tBuSi), 0.9 (3H, t, $J = 6.4$, Me), 1.23-1.50 (6H, m, 3 x CH$_2$), 1.71 (1H, ddd, $J = 12.7$, 9.2 and 6.4, 3'-CH), 1.97 (1H, ddd, $J = 12.7$, 5.9 and 2.7, 3'-CH), 2.45 (1H, dd, $J = 15.2$ and 6.4, 2-CH$_A$CH$_B$), 2.60 (1H, dd, $J = 15.2$ and 6.6, 2-CH$_A$CH$_B$), 3.75 (3H, s, OMe), 3.6-3.7 (1H, td, $J = 6.4$ and 3.1, 5'-CH), 3.95 (1H, ddd, $J = 6.4$, 5.9 and 3.1, 4'-CH) and 4.42 (1H, dddd, $J = 9.2$, 6.6, 6.4 and 2.7, 2'-CH); $\delta_C$ (270) -4.58 (MeSi), -4.78 (MeSi), 13.95 (Me), 17.91 (Me$_3$Si), 22.70 (CH$_2$), 25.73 ($^t$Bu), 28.00 (CH$_2$), 33.77 (CH$_2$), 40.60 (3'-CH$_2$), 41.06 (2-CH$_2$), 51.57 (OMe), 73.84 (CH), 76.53 (CH), 86.88 (5'-CH) and 171.55 (C=O); m/z 261 (47%, M$^{+}$-tBu), 187 (37), 173 (87), 147 (100) and 89 (52)

$\text{(2'SR,4'RS,5'SR)}^{-5'}$-Butyl-4'-tbutyldimethylsilyloxytetrahydrofuran-2'-yl) acetaldehyde (139)

![Diagram of the compound](image)

Diisobutylaluminium hydride (3.7 ml of a 1.0 M solution in hexanes, 3.7 mmol, 1 eq) was added to a solution of the silyloxytetrahydrofuran 138 (1.17 g, 3.7 mmol, 1 eq) in hexane (2 ml) at -78°C, and the resulting solution was stirred at this temperature for 2h. Methanol (2 ml) was then added and after 10 min, 2M hydrochloric acid (20 ml). The resulting mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic
phases dried and evaporated. The resulting oil (1.1 g) was
chromato-graphed over silica (eluting with 5% ethyl acetate in
hexane) to give the aldehyde 139 as a colourless oil (400 mg, 38%),
\( \nu_{\text{max}} \) 1735 (C=O); \( \delta_H \) (250) 0.10 (6H, 2 x MeSi), 0.90 (12H, m, tBu), 1.2-
1.5 (6H, m, 3 x CH\(_2\)), 1.72 (1H, ddd, \( J = 12.7, 9.0 \) and 6.3, 3'-CH), 1.95
(1H, ddd, \( J = 12.7, 5.7 \) and 2.4, 3'-CH), 2.61 (1H, dd, \( J = 10.2 \) and 5.6,
2-CH\(_A\)CH\(_B\)), 2.63 (1H, dd, \( J = 10.2 \) and 3.4, 2-CH\(_A\)CH\(_B\)), 3.68 (1H, td,
\( J = 6.3 \) and 3.2, 5'-CH), 3.98 (1H, ddd, \( J = 6.3, 3.2 \) and 2.4, 4'-CH),
4.51 (1H, dddd, \( J = 9.0, 5.7, 5.6 \) and 3.4, 2'-CH) and 9.55 (1H, s,
CHO); \( \delta_C \) (270) -4.62 (MeSi), -4.81 (MeSi), 13.91 (Me), 17.90 (Me\(_3\)CSi),
22.63 (CH\(_2\)), 25.70 (tBu), 28.02 (CH\(_2\)), 33.73 (CH\(_2\)), 41.28 (3'-CH\(_2\)),
49.29 (2-CH\(_2\)), 72.62 (CH), 76.48 (CH), 87.05 (5'-CH) and 201.13
(C=O); m/z 286 (13%, M\(^+\)-Me), 216 (100), 173 (87), 99 (50) and 75 (52).

(2'SR,4'RS,5'SR)-5'-Butyl-4-t-butyldimethylsiloxytetrahydro-furan-
2'-yl) acetic acid (141)

\begin{center}
\includegraphics[width=0.3\textwidth]{image}
\end{center}

Trifluoroacetic anhydride (0.12 ml, 87 mmol, 2.5 eq) was
added dropwise to a stirred solution of urea-hydrogen peroxide\(^{91}\)
(0.325 g, 3.46 mmol, 10 eq), disodium hydrogen phosphate (0.368 g,
8.7 eq, 2.7 mmol) and the aldehyde 139 in dichloromethane (2.2 ml).
The resulting suspension was refluxed for 1 h and then poured into
saturated aqueous sodium carbonate (10 ml). The resulting mixture was then neutralised with 1M hydrochloric acid (5 ml) and extracted with dichloromethane (3 x 25 ml), and the combined organic phases were dried and evaporated. The acid 141 was obtained as a pale yellow oil (70 mg, 66%), \( \nu_{\text{MAX}} \) 3400 (OH) and 1712 (C=O); \( \delta_H \) (250) 0.02 (6H, 2 x MeSi), 0.82 (12H, s, \(^t\)Bu), 1.15-1.40 (6H, m, 3 x CH\(_2\)), 1.81 (1H, ddd, \( J = 12.8, 9.6 \) and \( 6.0, 3'\)-CH), 2.02 (1H, ddd, \( J = 12.8, 5.8 \) and \( 2.3, 3'\)-CH), 2.65 (2H, d, \( J = 5.6, 2\-\text{CH}_2\)), 3.91 (1H, td, \( J = 6.3 \) and \( 2.9, 5'\)-CH), 4.06 (1H, ddd, \( J = 6.0, 2.9 \) and \( 2.3, 4'\)-CH) and 4.48 (1H, dddd, \( J = 9.6, 5.8, 5.6 \) and \( 5.6, 2'\)-CH); \( \delta_C \) (270) -4.56 (MeSi), -4.78 (MeSi), 13.96 (Me), 17.95 (Me\(_3\)CSi), 22.70 (CH\(_2\)), 25.75 (\(^t\)Bu), 28.03 (CH\(_2\)), 33.78 (CH\(_2\)), 40.54 (2-CH\(_2\)), 41.04 (3'-CH\(_2\)), 73.80 (CH), 76.44 (CH), 87.24 (5'-CH) and 175.01 (C=O); m/z 259 (47%, M\(^+\)-\(^t\)Bu), 187 (100), 131 (60), 75 (60) and 57 (70) [Found: M\(^+\)-\(^t\)Bu, 259.1289. C\(_{12}\)H\(_{23}\)O\(_4\)Si requires M, 259.1366].

\( 2'\text{SR,4'RS,5'SR} \)-2-Aminomethyl-5-butyl-4-hydroxytetrahydrofuran (142)

\[
\begin{align*}
\text{HO}_m & \quad \text{NH}_2 \\
\text{Bu} & \quad \text{O}
\end{align*}
\]

Triethylamine (0.032 ml, 0.23 mmol, 1 eq) was added to a solution of the acid 141 (63 mg, 0.23 mmol, 1 eq) in dry toluene (5 ml) and diphenylphosphoranyl azide (0.049 ml, 0.23 mmol, 1 eq) was added. The resulting solution was slowly warmed to 80°C and
stirred at this temperature for 2h. The solution was then cooled to RT, water (5 ml) was added and the mixture was stirred for a further 16h at this temperature. The resulting mixture was extracted with chloroform (3 x 10 ml) and the combined organic phases were dried and evaporated to give a brown oil (70 mg). The oil was chromatographed on silica (eluting with 50% ethyl acetate in hexane) to give the amino-alcohol 142 as a pale yellow oil (16 mg, 38%), $\nu_{\text{max}}$ 3530 (NH$_2$/OH); $\delta_H$ (250) 0.85 (3H, t, $J = 6.6$, Me), 1.20-1.50 (6H, m, 3 x CH$_2$), 1.73 (1H, ddd, $J = 13.3$, 9.6 and 6.2, 3-CH), 1.82 (1H, ddd, $J = 13.3$, 6.2 and 2.7, 3-CH), 3.18 (1H, dd, $J = 14.0$, and 6.1 CH$_A$H$_B$NH$_2$), 3.49 (1H, dd, $J = 14.0$, and 6.2 CH$_A$H$_B$NH$_2$), 3.66 (1H, td, $J = 6.6$ and 3.1, 5-CH), 4.02 (1H, ddd, $J = 6.2$, 6.2 and 3.1, 4-CH) and 4.16 (1H, dddd, $J = 9.6$, 6.1, 6.2 and 2.7, 2-CH); $\delta_C$ (270) 13.98 (Me), 22.64 (CH$_2$), 28.02 (CH$_2$), 33.95 (CH$_2$), 37.68 (CH$_2$NH$_2$), 44.44 (3-CH$_2$), 76.13 (CH), 76.29 (CH) and 86.97 (5-CH); m/z 173 (5%, M$^+$), 143 (100), 99 (66), 81 (87) and 69 (58)
The epoxide 84 was obtained in quantities from 0.5-2.5g following exactly the methods of Larcheveque et al.\textsuperscript{93} for the preparation of the corresponding ethyl epoxy-ester from (S)-malic acid the epoxide 84 showed, $[\alpha]_D = -11.0$ [c, 1.3 (CH\textsubscript{2}Cl\textsubscript{2})]. (lit) $[\alpha]_D = +10.7$ [c, 1.8 (CHCl\textsubscript{3})].; the intermediate iodohydrin 116 showed, $\nu_{\text{MAX}}$ 3471 (OH), 1732, 1434 and 1372 cm\textsuperscript{-1}; $\delta_\text{H}$ (250) 2.54 (1H, dd, $J = 16.3$ and 7.9, 4-CH\textsubscript{A}H\textsubscript{B}I), 2.65 (1H, dd, $J = 16.3$ and 4.3, 4-CH\textsubscript{A}H\textsubscript{B}I), 3.24 (1H, dd, $J = 14.4$ and 10.3, 2-CH\textsubscript{A}H\textsubscript{B}), 3.24 (1H, dd, $J = 14.4$ and 5.7, 2-CH\textsubscript{A}H\textsubscript{B}), 3.67 (3H, s, OMe) and 3.9-4.1 (1H, m, 3-CH); $\delta_\text{C}$ (270) 12.20 (4-CH\textsubscript{2}), 40.83 (2-CH\textsubscript{2}), 51.30 (OMe), 67.49 (3-CH) and 171.79 (CH); m/z 226 (5%, M$^+$- H\textsubscript{2}O), 117 (100), 99 (18), 85 (25) and 71 (22) [Found: M$^+$-H\textsubscript{2}O, 225.9507. C\textsubscript{5}H\textsubscript{7}IO\textsubscript{2} requires M, 225.9490]; $[\alpha]_D = -9.6$ [c, 1.3 (CH\textsubscript{2}Cl\textsubscript{2})].
Propyne (~8 ml) was condensed under an atmosphere of nitrogen, dissolved in dry tetrahydrofuran (60 ml), and the solution cooled to -78°C before butyl lithium (21.5 ml of a 1.6M solution in hexanes, 34.4 mmol, 1.5 eq) was added. The resulting solution was stirred for 0.5 h at this temperature and then boron trifluoride etherate (2.83 ml, 23.0 mmol, 1.0 eq) was added. After a further 10 min at -78°C, (S)-methyl 3,4,-epoxybutanoate 84 (2.64 g, 23 mmol, 1.0 eq) was added. The mixture was stirred at this temperature for 4 h and then poured into saturated aqueous ammonium chloride (200 ml). The resulting mixture was extracted with ethyl acetate (3 x 50 ml), and the combined organic phases were dried and evaporated to give a pale yellow oil (4.4 g), which was chromatographed on silica (eluting with 15% ether in petrol) to give the alkyne 146 as a pale yellow oil (2.9 g, 80%), \( \nu_{\text{max}} \) 3452 (OH), 2221, 1736 (C=O), 1672, 1439, 1162 and 1059 cm\(^{-1}\); \( \delta_\text{H} \) (250) 1.79 (3H, t, \( J = 2.6 \), 7-CH\(_3\)), 2.38-2.40 (2H, m, 4-CH\(_2\)), 2.47 (1H, dd, \( J = 16.2 \) and 8.6, 2-CH\(_A\)H\(_B\)), 2.71 (1H, dd, \( J = 16.2 \) and 3.8, 2-CH\(_A\)H\(_B\)), 3.71 (3H, s, OMe) and 4.12-4.20 (1H, m, 3-CH); \( \delta_\text{C} \) (270) 3.22 (7-Me), 26.54 (4-CH\(_2\)), 39.91 (2-CH\(_2\)), 51.56 (OMe), 66.65 (3-CH), 74.31 (5-C), 78.35 (6-C) and 172.67 (C=O); m/z 138 (7%, M+\text{-H}_2\text{O}), 103 (100), 81 (15), 71 (56) and 61 (22) [Found: M+\text{-H}_2\text{O}, 138.0685. \( \text{C}_9\text{H}_{10}\text{O}_2 \) requires M, 138.0681]; [\( \alpha \)]\( _D \) = -13.16 [c, 7.1 (CH\(_2\)Cl\(_2\))] .
(R)-(Z)-Methyl 3-hydroxyhept-5-enoate (147)

5% Palladium on barium sulphate (63.2 mg) was suspended in dry ethyl acetate (2.1 ml) and quinoline (58 µl) was added. The suspension was stirred for 10 min before the acetylene 146 (329 mg, 2.1 mmol) in ethyl acetate (2.1 ml) was added. The mixture was stirred in the dark under an atmosphere of hydrogen until no more gas was absorbed (0.75 h) and then filtered through celite. The filtrate was washed with 1 M hydrochloric acid (10 ml), saturated aqueous sodium bicarbonate (10 ml) and brine (10 ml), before being dried and evaporated to give the alkene 147 as a pale yellow oil (290 mg, 87%). $\nu_{\text{MAX}}$ 3417 (OH), 1732 (C=O), 1438, 1371, 1259, 1202, 1163 and 1058 cm$^{-1}$; $\delta_H$ (250) 1.84 (3H, dd, $J = 7.3$ and 0.5, 7-CH$_3$), 2.40 (2H, m, 4-CH$_2$), 2.52 (1H, dd, $J = 16.2$ and 8.7, 2-CH$_A$H$_B$), 2.76 (1H, dd, $J = 16.2$ and 3.9, 2-CH$_A$H$_B$), 3.25 (1H, d, $J = 4.2$, OH), 3.73 (3H, s, OMe), 4.15 (1H, m, 3-CH), 5.43 (1H, m, 5-CH) and 5.64 (1H, m, 6-CH); $\delta_C$ (270) 12.99 (7-Me), 34.16 (4-CH$_2$), 40.70 (2-CH$_2$), 51.77 (OMe), 68.01 (3-CH), 125.41 (5-CH), 127.15 (6-CH) and 173.29 (C=O); m/z 140 (11%, M-H$_2$O), 103 (100), 81 (22), 71 (95) and 61 (41) [Found: M$^+$-H$_2$O, 140.0846. C$_8$H$_{12}$O$_2$ requires M, 140.0837; $[\alpha]_D$ = -22.70 [c, 2.7 (CH$_2$Cl$_2$)].
(2'R,4'S,5'R)-Methyl (5'-methyl-4'-hydroxytetrahydrofuran-2'-yl) acetate (148)

Sodium hydrogen carbonate (810 mg, 9.6 mmol, 3 eq) was added to an ice-cold solution of the alkene 147 (450 mg, 3.2 mmol, 1 eq) in dry acetonitrile (7 ml) and the suspension stirred for 5 mins. Iodine (2.44 g, 9.6 mmol, 3eq) was added and the resulting mixture was stirred at 0-5°C, in the dark, for 72 h. Ether (10 ml) was added and the solution was washed with saturated aqueous sodium thiosulphate (120 ml). The separated aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried and evaporated to give the hydroxytetrahydrofuran 148 as a colourless oil (350 mg, 63 %), $\nu_{\text{max}}$ 3402 (OH) and 1734 (C=O), 1653, 1440, 1371, 1163 and 1078 cm$^{-1}$; $\delta_H$ (250) 1.27 (3H, d, $J = 6.4$, 5'-CH$_3$), 1.87 (1H, ddd, $J = 13.2$, 9.4 and 6.4, 3'-CH), 2.02 (1H, ddd, $J = 13.2$, 6.0 and 2.6, 3'-CH), 2.52 (1H, dd, $J = 15.6$ and 6.2, 2-CH$_A$CH$_B$), 2.66 (1H, dd, $J = 15.6$ and 6.9, 2-CH$_A$CH$_B$), 3.69 (3H, s, OMe), 3.87 (1H, qd, $J = 6.4$ and 3.4, 5'-CH), 4.00-4.03 (1H, m, 2'-CH) and 4.47 (1H, ddd, $J = 9.4$, 6.0 and 3.4, 4'-CH); $\delta_C$ (270) 19.75 (5'-Me), 40.47 (3'-CH$_2$), 40.68 (2-CH$_2$), 51.74 (OMe), 73.99 (2'-CH), 77.21 (4'-CH), 82.08 (5'-CH) and 173.29 (C=O); m/z 156 (5%, M$^+$-H$_2$O), 101 (51), 98 (100), 74 (57) and 57 (61) [Found: M$^+$-H$_2$O, 156.0791. $C_8H_{12}O_3$ requires M, 156.0786]; $[\alpha]_D = +14.8$ [c, 0.4 (CH$_2$Cl$_2$)].
(2'R,4'S,5'R)-Methyl (5'-methyl-4'-triisopropylsilyloxy-tetrahydrofuran-2'-yl) acetate (150)

2,6-Lutidine (154 mg, 1.44 mmol, 2.5 eq) was added to a solution of the hydroxytetrahydrofuran 148 (100 mg, 0.57 mmol, 1 eq) in dry dichloromethane (0.63 ml) maintained at 0°C. Triisopropylsilyl trifluoromethanesulphonate (0.23 ml, 0.86 mmol, 1.5 eq) was added dropwise and the resulting mixture stirred at 0°C for 3 h. Brine (20 ml) was added and the resulting mixture extracted with dichloromethane (2 x 25 ml). The combined organic phases were dried and evaporated to give a colourless oil (360 mg) which was chromatographed on silica (eluting with 7% ethyl acetate in petrol) to give the silyloxytetrahydrofuran 150 as a clear oil (140 mg, 74%), $v_{\text{MAX}}$ 1729 (C=O), 1464, 1382, 1268, 1163, 1108 and 1040 cm$^{-1}$; $\delta_H$ (250) 1.09-1.11 (21H, m, TIPS) 1.27 (3H, d, $J = 6.4$, 5'-CH$_3$), 1.80 (1H, ddd, $J = 13.6$, 9.3 and 6.4, 3'-CH), 2.05 (1H, ddd, $J = 13.6$, 5.9 and 2.7, 3'-CH), 2.54 (1H, dd, $J = 15.3$ and 6.6, 2-CH$_A$CH$_B$), 2.65 (1H, dd, $J = 15.3$ and 6.4, 2-CH$_A$CH$_B$), 3.67 (3H, s, OMe), 3.85 (1H, qd, $J = 6.4$ and 3.1, 5'-CH), 4.05 (1H, ddd, $J = 6.4$, 3.1 and 2.7, 4'-CH) and 4.50 (1H, dddd, $J = 9.3$, 6.6, 6.4 and 5.9, 2'-CH); $\delta_C$ (270) 12.04 (6 x Me, TIPS), 17.92 (3 x CH, TIPS), 19.87 (5'-Me), 40.60 (3'-CH$_2$), 41.24 (2-CH$_2$), 51.63 (OMe), 74.11 (2'-CH), 78.17 (4'-CH), 83.36
(5'-CH) and 171.50 (C=O); m/z 287 (14%, M+Pr), 187 (100), 113 (21), 103 (31) and 75 (35) [Found: M+Pr, 287.1669. C_{14}H_{27}O_{4}Si requires M, 287.1679]; [\alpha]D = +16.2 [c, 1.6 (CH_{2}Cl_{2})].

\(2'R, 4'S, 5'R\)-(5'-Methyl-4'-triisopropylslyloxytetrahydrofuran-2'-yl)acetic acid (152)

Potassium hydroxide (2.04 g, 36.4 mmol, 8 eq) was added to a solution of the methyl ester 150 (1.5 g, 4.4 mmol, 1 eq) in methanol (18.2 ml). The resulting solution was stirred at room temperature for 16h. The solvent was removed under vacuum, the oil obtained was dissolved in water, and the solution washed with ether (25 ml). 2M Hydrochloric acid (16 ml) was added to the solution which was then extracted with chloroform (3 x 50 ml). The combined organic phases were dried and evaporated to give the acid 152 as a clear oil (1.40 g, 97%), \(\nu_{\text{MAX}}\) 3368 (OH), 1717 (C=O), 1507, 1419, 1163, 1109 and 1040 cm\(^{-1}\); \(\delta_{H}\) (250) 1.03-1.05 (21H, m, TIPS), 1.20 (3H, d, \(J = 6.2, 5'\text{-CH}_3\)), 1.80 (1H, ddd, J = 12.8, 9.6 and 6.0, 3'\text{-CH}), 2.02 (1H, ddd, J = 12.8, 5.8 and 2.3, 3'\text{-CH}), 2.65 (2H, d, J = 6.3, 2-CH\(_2\)), 3.91 (1H, qd, J = 6.2 and 2.9, 5'\text{-CH}), 4.06 (1H, ddd, J = 6.0, 2.9 and 2.3, 4'-CH) and 4.48 (1H, dddd, J = 9.6, 6.3, 6.3 and 5.8, 2'-CH); \(\delta_{C}\) (270) 12.51 (6 x CH\(_3\)-TIPS), 18.45 (3 x CH-TIPS), 20.38 (5'-Me), 40.90 (3'-CH\(_2\)), 41.69 (2-CH\(_2\)), 74.45 (2'-CH), 78.56 (4'-CH), 84.29 (5'-CH) and 201
175.97 (C=O); m/z 317 (11%, M⁺), 273 (24%, M⁺·iPr), 187 (100), 131 (58) and 75 (64) [Found: M⁺·iPr, 273.1517. C₁₃H₂₅O₄Si requires M, 273.1522]; [α]D = +17.1 [c, 1.0 (CH₂Cl₂)].

(2'SR,4'RS,5'SR)-2-Aminomethyl-5-methyl-4-triisopropylsilyl-oxytetrahydrofuran (153)

The acid 152 (130 mg, 0.41 mmol) was treated exactly as in the preparation of the amine 142, to give a brown oil (300 mg), which was chromatographed on silica (eluting with 30% ethyl acetate in hexane) to give the amine 153 as a pale yellow oil (106 mg, 90%), νMAX 3430 (NH₂); δH (250) 1.10 (21H, m, TIPS), 1.27 (3H, t, J = 6.4, 5-Me), 1.73 (1H, ddd, J = 13.1, 9.4 and 6.2, 3-CH), 1.82 (1H, ddd, J = 13.1, 6.1 and 2.7, 3-CH), 3.18 (1H, ddd, J = 14.0 and 6.1, CH₆H₅NH₂), 3.49 (1H, dd, J = 14.0 and 6.4, CH₆H₅NH₂), 3.66 (1H, td, J = 6.4 and 3.1, 5-CH), 4.02 (1H, ddd, J = 6.2, 6.1 and 3.1, 4-CH) and 4.16 (1H, dddd, J = 9.4, 6.4, 6.1 and 2.7, 2-CH); δC (270) 12.02 (5-Me), 17.90 (6x Me-TIPS), 19.84 (3x CH-TIPS), 37.95 (3-CH₂), 44.42 (CH₂NH₂), 76.52 (CH), 78.11 (CH) and 83.88 (5-CH); m/z 234 (5%, M⁺·iPr), 143 (100), 81 (93), 57 (70) and 49 (32).
The racemic acid 152 (100 mg, 0.32 mmol, 1 eq) was dissolved in dry benzene (5 ml) and the resulting solution was cooled to 0°C before pyridine (1 drop) and dimethylformamide (1 drop) were added. The resulting solution was stirred during the dropwise addition of oxalyl chloride (0.15 ml, 0.32 mmol, 1 eq) and stirring was continued for a further 3 h. The solvent was then removed in vacuo. The crude oil thus obtained was azeotroped with dry benzene (5 ml) before being dissolved in dry carbon tetrachloride (3 ml) and added to a refluxing suspension of 2-mercaptopyridine-N-oxide sodium salt (57 mg, 0.38 mmol, 1.2 eq) and catalytic 4-dimethylaminopyridine (2 mg) in carbon tetrachloride (15 ml). The resulting suspension was heated for 1.5 h before being cooled and filtered through celite. The filtrate was evaporated to give a brown oil (300 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the chloride 160 as a clear oil (72 mg, 73%), ν̇ (250) 1402, 1371, 1249, 1106 and 1058 cm⁻¹; δ (2H, m, TIPS), 1.20 (3H, d, J = 6.2, 5-CH₃), 1.93-1.96 (2H, m, 3-CH₂), 3.59 (2H, d, J = 4.8, CH₂Cl), 3.95 (1H, qd, J = 6.4 and 3.1, 5-CH), 4.07 (1H, ddd, J = 4.1, 3.6 and 3.1, 4-CH) and 4.39 (1H, tdd, J
= 6.2, 4.8 and 2.1, 2-CH); $\delta_C$ (270) 11.97 (6 x CH$_3$, TIPS), 17.94 (3 x CH, TIPS), 20.46 (5-Me), 38.83 (3-CH$_2$), 47.17 (CH$_2$Cl), 77.34 (CH), 77.92 (CH), 83.52 (5-CH); m/z 263 (29%, M$^{+}$-iPr), 187 (77), 131 (100), 97 (40) and 75 (33) [Found: M$^{+}$-iPr, 263.1198. C$_{12}$H$_{24}$ClO$_2$Si requires M, 263.1234].

(2SR,4RS,5SR) 2-Chloromethyl-4-hydroxy-5-methyltetrahydrofuran (161)

The chloride 160 (48 mg, 0.15 mmol, 1eq) was dissolved in dry tetrahydrofuran (1 ml) and tetrabutylammonium fluoride (0.3 ml of a 1M solution in tetrahydrofuran, 0.3 mmol, 2 eq) was added. The resulting solution was stirred at RT for 40h, before the solvent was removed in vacuo to give a viscous oil, which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the chloro-alcohol 161 as a clear oil (15 mg, 60%), $\nu_{\text{MAX}}$ 3430 (OH), 1645, 1444, and 1350 cm$^{-1}$; $\delta_H$ (250) 1.25 (3H, d, $J = 6.2$, 5-CH$_3$), 2.05 (2H, m, 3-CH$_2$), 3.59 (2H, d, $J = 5.0$, CH$_2$Cl), 4.02-4.05 (2H, m, 4- and 5-CH) and 4.39 (1H, tdd, $J = 5.0$, 2.8 and 2.0, 2-CH); $\delta_C$ (270) 19.52 (5-Me), 38.08 (3-CH$_2$), 46.99 (CH$_2$Cl), 77.21 (CH), 77.34 (CH) and 82.93 (5-CH); m/z 115 (17%, M$^{+}$-Cl), 101 (71), 71 (53), 70 (32) and 57 (100). [Found: M$^{+}$-Cl, 115.0078. C$_6$H$_{11}$O$_2$ requires M, 115.0759].
(2R,4S,5R)-2-Iodomethyl-5-methyl-4-triisopropylsilyloxytetrahydrofuran (162)

The acid 152 (20.5 mg, 0.065 mmol, 1 eq) was dissolved in dry benzene (1 ml) and the resulting solution was cooled to 0°C before pyridine (1 drop) and dimethylformamide (1 drop) were added. The resulting solution was stirred during the dropwise addition of oxalyl chloride (0.03 ml, 0.065 mmol, 1 eq) and stirring was continued for a further 3 h. The solvent was then removed in vacuo. The crude oil thus obtained was azeotroped with dry benzene (1 ml) before being dissolved in cyclohexene (2 ml) and added to a refluxing suspension of iodoform (28 mg, 0.07 mmol, 1.1 eq), 2-mercaptopyridine-N-oxide sodium salt (11 mg, 0.07 mmol, 1.1 eq) and catalytic 4-dimethylaminopyridine (1 mg) in cyclohexene (5 ml). The resulting suspension was heated for 15 h before being cooled and filtered through celite. The filtrate was evaporated to give a brown oil (60 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the iodide 163 as a clear oil (8.9 mg, 40%), \( \nu_{\text{max}} \) 1445, 1250, 1156 and 1071 cm\(^{-1}\); \( \delta_{\text{H}} \) (250) 1.00-1.02 (21H, m, TIPS), 1.25 (3H, d, \( J = 6.3, 5-\text{CH}_3 \)), 1.74 (1H, ddd, \( J = 12.7, 6.5 \text{ and } 2.9, 3-\text{CH} \)), 1.93 (1H,
ddd, $J = 12.7, 6.0$ and $2.9, 3$-CH), $3.22$ (2H, d, $J = 4.8$, CH$_2$I), $3.92$ (1H, qd, $J = 6.3$ and $3.2$, 5-CH), $4.02$ (1H, ddd, $J = 6.0$, 3.2 and $2.9$, 4-CH) and $4.39$ (1H, dtd, $J = 6.5$, 4.8 and $2.9$, 2-CH); $\delta_C$ (270) $11.04$ (CH$_2$I), $12.00$ (6 x CH$_3$-TIPS), $17.92$ (3 x CH-TIPS), $19.88$ (5-Me), $41.78$ (3-CH$_2$), $77.00$ (CH), $78.10$ (CH) and $83.86$ (5-CH); m/z $355$ (3%, $M^+$-Pr), $187$ (100), $141$ (35), $127$ (40) and $75$ (15) [Found: $M^+$-Pr. 355.0512. C$_{12}$H$_{24}$IO$_2$Si requires M, 355.0590]; $[\alpha]_D = +24.6$ [c, 8.7 (CH$_2$Cl$_2$)].

(2R,4S,5R) 4-Hydroxy-2-iodomethyl-5-methyltetrahydrofuran (163)

![Chemical Structure](image)

The iodide 162 (32 mg, 0.10 mmol, 1 eq) was dissolved in dry tetrahydrofuran (0.5 ml) and tetrabutylammonium fluoride (0.2 ml of a 1M solution in tetrahydrofuran, 0.2 mmol, 2 eq) was added. The resulting solution was stirred at RT for 40h, before the solvent was removed in vacuo to give a viscous oil, which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the iodo-alcohol 163 as a clear oil (10 mg, 60%), $\nu_{\text{max}}$ $3400$ (OH), $1447, 1353, 1061$ and $1028$ cm$^{-1}$; $\delta_H$ (250) $1.26$ (3H, d, $J = 6.4$, 5-CH$_3$), $1.91$ (1H, ddd, $J = 13.3, 8.6$ and $6.2$, 3-CH), $2.05$ (1H, ddd, $J = 13.3, 6.2$ and $3.0$, 3-CH), $3.34$ (1H, dd, $J = 10.2$ and $6.2$, CH$_A$H$_B$I), $3.31$ (1H, dd, $J = 10.2$ and $4.9$, CH$_A$H$_B$I), $3.97$ (1H, qd, $J = 6.4$ and $3.2$, 5-CH), $4.05$ (1H, ddd, $J = 8.6, 6.2$ and $3.2$, 4-CH) and $4.16$ (1H, dddd,
\[ J = 6.2, 6.2, 4.9 \text{ and } 3.0, 2-\text{CH}; \delta_\text{C} (270) 10.42 (\text{CH}_2\text{I}), \hspace{1mm} 19.79 (\text{5-Me}), \hspace{1mm} 41.06 (3-\text{CH}_2), \hspace{1mm} 77.17 (\text{CH}), \hspace{1mm} 77.59 (\text{CH}), \hspace{1mm} 83.34 (\text{5-CH}); \text{ m/z } 242 (2\%), \text{ M}^+), \hspace{1mm} 115 (31), \hspace{1mm} 101 (100), \hspace{1mm} 71 (70) \text{ and } \hspace{1mm} 57 (49); [\alpha]_D = +20.5 [c, \hspace{1mm} 2.0 (\text{CHCl}_3)]; \text{ (lit) } [\alpha]_D = +26.5 [c, \hspace{1mm} 1.8 (\text{CHCl}_3)] \text{ for the enantiomer.}

\[ (-J- \text{Muscarine iodide (164)} \]

Trimethylamine (0.05 ml) was added to a solution of the iodoalcohol 163 (10 mg, 0.04 mmol, 1 eq) in ethanol (0.2 ml) and the resulting solution was heated at 70°C in a sealed tube over 4h. Cooling was allowed over 16h. and the solvent was evaporated to give a solid residue (8 mg) which was crystallised from acetone to give muscarine iodide 164 (5 mg, 60%) which showed spectral data identical to the literature values: m.p. 135-137°C [lit127 m.p. 138-142°C; \( \delta_\text{H} (250) 1.23 (3\text{H}, d, J = 6.5, 5-\text{CH}_3), 2.04 (1\text{H}, \text{ddd}, J = 14.0, 10.0 \text{ and } 5.5, 3-\text{CH}), 2.17 (1\text{H}, \text{ddd}, J = 14.0, 6.0 \text{ and } 2.0, 3-\text{CH}) 3.29 (9\text{H}, s, \text{NMe}_3), 3.49 (1\text{H}, \text{dd}, J = 14.0 \text{ and } 9.2, \text{CH}_A\text{H}_B\text{N}), 3.63 (1\text{H}, \text{dd}, J = 14.0 \text{ and } 2.0, \text{CH}_A\text{H}_B\text{I}), 4.13 (1\text{H}, \text{qd}, J = 6.5 \text{ and } 2.5, 5-\text{CH}), 4.24 (1\text{H}, \text{ddd}, J = 5.5, 2.5 \text{ and } 2.0) \text{ and } 4.72 (1\text{H}, m, 2-\text{CH}).]
Sodium azide (1.32 g, 20.2 mmol, 2 eq) was added to a solution of the iodonitrofuran 5b (3.31 g, 10.1 mmol, 1 eq) in dry dimethylformamide (35 ml) and the solution was heated to 110°C for 16h and then cooled to RT before diluting with water (150 ml). The resulting mixture was extracted with ether (3 x 100 ml). The combined organic phases were dried and evaporated to give an oil (2 g) which was chromatographed on silica (eluting with 10% ethyl acetate in hexane) to give the dihydrofuran 201 as a colourless oil (0.93 g, 47%), \( \nu_{\text{MAX}} \) 1736 (C=O), 1437, 1163 and 1068 cm\(^{-1}\); \( \delta_H \) (250) 0.87 (3H, t, \( J = 6.8 \), CH\(_3\)), 1.20-1.60 (6H, m, 3 x CH\(_2\)), 2.47 (1H, dd, \( J = 15.3 \) and 6.2, 2-CH\(_A\)H\(_B\)), 2.59 (1H, dd, \( J = 15.3 \) and 7.0, 2-CH\(_A\)H\(_B\)), 3.68 (3H, s, OMe), 4.85 (1H, dt, \( J = 5.9 \) and 0.5, 5'-CH), 5.19 (1H, ddd, \( J = 7.0 \), 6.2 and 0.5, 2'-CH) and 5.80 (2H, m, 3'- and 4'-CH); \( \delta_C \) (270) 14.02 (Me), 22.77 (CH\(_2\)), 27.19 (CH\(_2\)), 35.55 (CH\(_2\)), 41.04 (2-CH\(_2\)), 51.65 (OMe), 81.76 (2'-CH), 85.85 (5'-CH), 128.75 (3'-CH), 131.05 (4'-CH) and 171.45 (C=O); m/z 198 (16%, M\(^+\)), 156 (37), 91 (61), 85 (100) and 57 (92) [Found: M\(^+\), 198.1236. C\(_{11}\)H\(_{18}\)O\(_3\) requires M, 198.1256].
The dihydrofuran 201 (500 mg, 2.52 mmol, 1 eq) was treated exactly as in the preparation of compound 152 to give the acid 203 as a colourless oil (400 mg, 86%), $\nu_{\text{max}}$ 3300 (OH), 1715 (C=O), 1424, 1259 and 1069 cm$^{-1}$; $\delta_H$ (250) 0.87 (3H, t, $J = 6.5$, CH$_3$), 1.30-1.70 (6H, m, 3 x CH$_2$), 2.60 (1H, d, $J = 7.0$, 2-CH$_2$), 4.85 (1H, dt, $J = 5.9$ and 0.7, 5'-CH), 5.20 (1H, dt, $J = 7.0$ and 0.7, 2'-CH) and 5.90 (2H, m, 3' and 4'-CH); $\delta_C$ (270) 14.02 (Me), 22.75 (CH$_2$), 27.19 (CH$_2$), 35.44 (CH$_2$), 40.77 (2-CH$_2$), 81.51 (2'-CH), 86.16 (5'-CH), 128.36 (3'-CH), 131.27 (4'-CH) and 176.10 (C=O); m/z 184 (10%, M$^+$), 139 (41), 127 (43), 81 (44) and 57 (57) [Found: M$^+$, 184.1509. C$_{10}$H$_{16}$O$_3$ requires M, 184.1099].

3-Butyl-4-iodo-2,6-dioxabicyclo-[3,3,0]-7-one (204)

The acid 203 (15 mg, 0.1 mmol, 1 eq) was treated exactly as in the preparation of compound 54b, to give the iodo-ester 204 as a colourless oil (21 mg, 75%), $\nu_{\text{max}}$ 1787 (C=O), 1467, 1185, 1148 and 1047 cm$^{-1}$; $\delta_H$ (250) 0.91 (3H, t, $J = 7.0$, CH$_3$), 1.20-1.80 (6H, m, 3 x CH$_2$), 2.73 (1H, dd, $J = 17.8$ and 8.4, 8-CH$_A$H$_B$), 2.59 (1H, dd, $J = 17.8$ and 6.2, 8-CH$_A$H$_B$), 3.18 (1H, dt, $J = 6.4$ and 3.0, 3-CH), 4.51 (1H, d,
\[ J = 3.0, 4-\text{CH}, 5.10 \ (1\text{H}, \text{ddd}, J = 8.4, 6.2 \text{ and } 4.4, 1\text{-CH}) \text{ and } 5.37 \ (1\text{H}, \text{d}, J = 4.4, 5\text{-CH}); \delta_{\text{C}} (270) \ 13.91 \ (\text{Me}), 22.52 \ (\text{CH}_2), 27.68 \ (\text{CH}_2), 34.77 \ (4\text{-CH}), 46.08 \ (8\text{-CH}_2), 75.68 \ (\text{CH}), 77.12 \ (\text{CH}), 90.60 \ (5\text{-CH}), \text{ and } 176.59 \ (\text{C=O}); \text{ m/z } 310 \ (3\%, M^+), 253 \ (100), 183 \ (99), 127 \ (30), 85 \ (31) \text{ and } 57 \ (73) \ [\text{Found: } M^+, 310.0146. \ C_{16}H_{15}I_3 \text{ requires } M, 310.0066]. \]

(2RS,3RS)-3-Acetoxy-2-ethyltetrahydrofuran (205)

![Diagram](image)

Cesium acetate (127 mg, 0.66 mmol, 1.5 eq) was added to a stirred solution of the iodotetrahydrofuran 58 (100 mg, 4.4 mmol, 1 eq) in dimethylformamide (0.5 ml). The resulting mixture was heated at 80°C for 14h and then water (25 ml) was added. The mixture was extracted with ether (3 x 20 ml) and the combined organic phases were dried and evaporated to give a brown oil (50 mg) which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give, as a colourless oil, the acetoxytetrahydrofuran 205 (20 mg, 35%), which showed data identical to literature values,\textsuperscript{186} \( v_{\text{max}} \) 1741 (C=O), 1242, 1106 and 1025 cm\(^{-1}\); \( \delta_{\text{H}} \) (250) 0.87 (3H, t, \( J = 7.6, \ \text{CH}_3\)), 1.40-1.55 (2H, m, 1'-CH\(_2\)), 1.85-2.03 (1H, m, 4-H\(_A\)), 2.17-2.29 (1H, m, 4-H\(_B\)), 3.57 (1H, td, \( J = 7.3 \text{ and } 3.7, 2\text{-H}\)), 3.72 (1H, td, \( J = 8.7 \text{ and } 5.3, 5\text{-H}\_A\)), 3.95 (1H, dt, \( J = 8.0 \text{ and } 7.6, 5\text{-H}\_B\)) and 5.23 (1H, ddd, \( J = 6.0, 4.3 \text{ and } 1.5, 3\text{-H}\)).
Potassium superoxide (344 mg, 4.8 mmol, 1.1 eq) was added to a stirred solution of the iodotetrahydrofuran 58 (1 g, 4.4 mmol, 1 eq) and 18-crown-6 (0.1 ml) in dimethylformamide (1 ml). The resulting mixture was stirred for 16h at RT and water (50 ml) was added. The mixture was extracted with ether (3 x 20 ml) and the combined organic phases were dried and evaporated to give a brown oil (500 mg), which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the hydroxytetrahydrofuran 206 as a colourless oil (104 mg, 25%), which showed data identical to literature values, 109 ν_MAX 3542 (OH), 1375, 1150 and 1023 cm⁻¹; δ_H (250) 0.94 (3H, t, J = 7.6, CH₃), 1.40-1.55 (2H, m, 1'-CH₂), 1.84-1.90 (1H, m, 4-H_A), 2.09-2.18 (1H, m, 4-H_B), 3.42 (1H, td, J = 6.8 and 3.1, 2-H), 3.79 (1H, td, J = 8.9 and 4.6, 5-H_A), 3.97 (1H, m, 5-H_B) and 4.16-4.17 (1H, m, 3-H).

(S)-Methyl 2-phenyl-2-(triisopropylsilyloxy)acetate (211)

Triisopropylsilyl chloride (10.6 ml, 50 mmol, 1.1 eq) was added dropwise to a stirred solution of (S)-methyl mandelate (7.5 g, 45.1 mmol, 1.0 eq) and imidazole (6.14 g, 90.2 mmol, 2 eq) in
dimethylformamide (25 ml) at RT. The resulting solution was stirred for 26h and then poured into water (300 ml). The resulting mixture was extracted with petrol (3 x 100 ml) and the combined organic phases dried and evaporated to give the silyl ether 211 as a colourless oil (14.95 g, 97%), \( \nu_{\text{MAX}} \) 1732 (C=O), 1465, 1206 and 1074 \( \text{cm}^{-1} \); \( \delta_{\text{H}} \) (250) 0.90-1.10 (21H, m, TIPS), 3.70 (3H, s, OMe), 5.32 (1H, s, 2-H) and 7.30-7.60 (5H, m, Ph); \( \delta_{\text{C}} \) (270) 11.88 (TIPS, 3 x CH), 17.54 (TIPS, 6 x CH\(_3\)), 51.67 (OMe), 74.36 (2-CH), 126.13 (CH), 127.89 (CH), 128.07 (CH), 139.27 (C) and 172.31 (C=O), m/z 279 (76%, M\(^+\)-Pr), 202 (15), 77 (100), 71 (56) and 51 (53); \([\alpha]_D^\circ = + 80.2 \) [c, 1.0 (CH\(_2\)Cl\(_2\))].

**(S)-Methyl 2-phenyl-2-(triisopropylsilyloxy)acetaldehyde** (212)

\[
\begin{align*}
\text{OTIPS} & \quad \text{CHO} \\
\text{Ph} & 
\end{align*}
\]

The silyl ether 211 (1.0 g, 3.1 mmol, 1 eq) was dissolved in dry hexane (10 ml) and dry ether (10 ml) and was reduced as in the preparation of compound 244 to give the aldehyde 212 as a colourless oil (0.57 g, 63%), \( \nu_{\text{MAX}} \) 1730 (C=O), 1464, 1291 and 1117 \( \text{cm}^{-1} \); \( \delta_{\text{H}} \) (250) 1.00-1.30 (21H, m, TIPS), 5.32 (1H, d, \( J = 1.0 \), 2-H), 7.30-7.60 (5H, m, Ph) and 9.55 (1H, d, \( J = 1.0 \), CHO); \( \delta_{\text{C}} \) (270) 12.04 (TIPS, 3 x CH), 17.81 (TIPS, 6 x CH\(_3\)), 80.09 (2-CH), 126.43 (CH), 128.07 (CH), 128.41 (CH), 132.85 (C) and 199.64 (C=O); \([\alpha]_D^\circ = + 11.5 \) [c, 1.1 (CH\(_2\)Cl\(_2\))].
To a suspension of chromium(II) chloride (5 g, 40.7 mmol, 6 eq) in dry tetrahydrofuran (100 ml) was added dropwise a solution of iodoform (5.34 g, 13.6 mmol, 2 eq) and aldehyde 212 (1.98 g, 6.78 mmol, 1 eq) in dry tetrahydrofuran (8 ml). The resulting solution was refluxed in the dark for 24h, under an atmosphere of argon, before being cooled and poured into water (250 ml). The resulting mixture was extracted with ether (3 x 200 ml), and the combined organic phases were dried and evaporated to give a purple oil, which was chromatographed twice on silica (eluting with cyclohexane) to give the vinyl iodide 213 as a colourless oil (1.10 g, 42%), ν_max 1600, 1463, 1197 and 1114 cm⁻¹; δ_H (250) 0.90-1.20 (21H, m, TIPS), 5.20 (1H, dd, J = 5.5 and 1.1, 3-H), 6.37 (1H, dd, J = 14.4 and 1.1, 1-H), 6.45 (1H, dd, J = 14.4 and 5.5, 2-H) and 7.30-7.60 (5H, m, Ph); δ_C (270) 12.11 (TIPS, 3 x CH), 17.85 (TIPS, 6 x CH₃), 75.65 (3-CH), 77.34 (1-CH), 125.89 (CH), 127.39 (CH), 128.27 (CH), 137.24 (C) and 148.95 (2-CH); m/z 416 (5%, M⁺), 373 (100%, M⁺-iPr), 245 (29), 213 (35) and 116 (57) [Found: M⁺-iPr, 373.0536. C₁₅H₂₂IOSi requires M, 373.0485]; [α]_D = -15.4 [c. 1.0 (CH₂Cl₂)].
Zinc dust (3.58 g, 55 mmol, 2 eq) was added to a stirred solution of carbon tetrabromide (18.17 g, 55 mmol, 2 eq) and triphenylphoshine (14.4 g, 55 mmol, 2 eq)\(^\text{163}\) in dry dichloromethane (200 ml) at RT, and the resulting solution was stirred for 24h. The aldehyde 212 (8 g, 27 mmol, 1 eq) was added and the resulting solution was stirred for 80h at RT and then poured into petrol (300 ml) and the mixture filtered. The filtrate was evaporated to give a clear oil, which was chromatographed on silica (eluting with 10% dichloromethane in petrol) to give the dibromide 215 as a colourless oil (9.2 g, 75%), \(\nu\text{MAX} 1630, 1464\text{ and } 1063\text{ cm}^{-1}, \delta_H (250) 1.00-1.40 (21H, m, TIPS), 5.40 (1H, d, } J = 14.0, 3\text{-H}), 6.55 (1H, d, } J = 14.0, 1\text{-H}), \text{ and } 7.20-7.60 (5H, m, Ph); \delta_C (270) 12.11 (3x \text{CH-TIPS}), 17.85 (3x \text{CH}_3\text{-TIPS}), 74.89 (3\text{-CH}), 88.62 (1\text{-C}), 128.25 (\text{CH}), 128.34 (\text{CH}), 128.41 (\text{CH}), 136.75 (\text{C}) \text{ and } 141.96 (2\text{-CH}); \[\alpha\]_D = - 62.3 [c, 1.0 (CH\text{CH}_2\text{Cl}_2)].

\textbf{(S)-3-Phenyl-3-triisopropylsilyloxypropyne (216)}

\textbf{Butyl lithium (7.4 ml of a 1.6 M solution in hexane, 11.9}
mmol, 2 eq) was added to a solution of the dibromide 215 (2.68 g, 5.95 mmol, 1 eq) in dry tetrahydrofuran (25 ml) at -78°C. The resulting solution was stirred at this temperature for 8h, and then allowed to warm to RT over 20h. Saturated aqueous ammonium chloride (10 ml) was added and the mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic phases were dried and evaporated to give a brown oil (2.7 g), which was chromatographed on silica (eluting with petrol) to give acetylene 216 as a colourless oil (900 mg, 53%), \( \nu_{\text{max}} \) 2200, 1630, 1464, and 1063 cm\(^{-1}\); \( \delta_H \) (250) 1.00-1.20 (21H, m, TIPS), 2.52 (1H, d, \( J = 2.3, 1-H \)), 5.55 (1H, d, \( J = 2.3, 3-H \)) and 7.26-7.60 (5H, m, Ph); \( \delta_C \) (270) 12.11 (3 x CH, TIPS), 17.85 (6 x Me, TIPS), 76.45 (2-C), 74.89 (3-CH), 88.62 (1-C), 128.25 (Ph-CH), 128.34 (Ph-CH), 128.41 (CH) and 136.75 (C); m/z 245 (100%, M\(^+\)-iPr), 220 (27), 131 (60), 71 (35) and 55 (100) [Found: M\(^+\)-iPr, 245.1367. C\(_{15}\)H\(_{21}\)OSi requires M, 245.1361].

\((3S,1E)-3\text{-Phenyl}-3\text{-triisopropylsilyloxy-1-tributyl-stannylprop-1-ene} (217)\)

A solution of azo-bis-isobutyronitrile (49.8 mg, 0.028 mmol, 0.28 eq) in dry benzene (3 ml) was added slowly to a refluxing solution of acetylene 216 (292 mg, 1.01 mmol, 1 eq) and tributyltin hydride (0.3 ml, 1.12 mmol, 1.1 eq) in dry benzene (15 ml). The resulting solution was refluxed in the dark for 15h, under an
atmosphere of argon, before the solvent was evaporated to give an oil, which was chromatographed on silica (eluting with petrol) to give the vinyl stannane 217 as a colourless oil (100 mg, 17%), \( \nu_{\text{max}} \) 1596, 1463, 1096 and 1067 cm\(^{-1}\); \( \delta_H \) (250) 0.70 (9H, t, \( J = 7.0 \), 3 x Me), 1.00-1.05 (21H, m, TIPS), 1.20-1.70 (18H, m, 9 x CH\(_2\)), 5.20 (1H, dd, \( J = 5.5 \) and 0.8, 3-H), 5.99 (1H, dd, \( J = 18.9 \) and 5.5, 2-H), 6.23 (1H, dd, \( J = 18.9 \) and 0.8, 1-H) and 7.20-7.40 (5H, m, Ph); \( \delta_C \) (270) 9.44 (3 x CH\(_2\)Sn), 13.70 (3 x CH, TIPS), 14.35 (3 x Me), 18.06 (6 x CH\(_3\), TIPS), 27.23 (3 x CH\(_2\)), 29.08 (3 x CH\(_2\)), 78.85 (3-CH), 77.34 (1-CH), 125.97 (CH), 126.34 (CH), 126.65 (CH), 127.96 (C) and 151.36 (2-C); m/z 523 (100%, M\(^+\)-Bu), 521 (75%, M\(^+\)-Bu), 117 (88), 115 (48) and 55 (59); \([\alpha]_D\) = - 7.1 [c, 0.7 (CH\(_2\)Cl\(_2\))].

(S)-Methyl 2-methoxymethoxyphenylacetate (218)

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

Chloromethyl methyl ether (6 ml, 78.9 mmol, 5 eq) was added dropwise to a stirred solution of (S)-methyl mandelate (2.62 g, 15.8 mmol, 1.0 eq) and ethyldiisopropylamine (4.12 ml, 23.7 mmol, 1.5 eq) in dichloromethane (10 ml) at RT. The resulting mixture was stirred for 19h and the poured into water (50 ml). The resulting solution was extracted with dichloromethane (3 x 30 ml) and the combined organic phases were dried and evaporated to give the ether 218 as a yellow oil (3.58 g, 100%), which showed data corresponding exactly to literature values,\(^{167}\) \( \nu_{\text{max}} \) 1735 (C=O) cm\(^{-1}\);
\[ \delta_H \ (250) \ 3.46 \ (3H, \ s, \ OMe), \ 3.79 \ (3H, \ s, \ CO_2Me), \ 4.80 \ (2H, \ s, \ OCH_2OMe), \ 5.26 \ (1H, \ s, \ 2-CH) \ and \ 7.40-7.60 \ (5H, \ m, \ Ph); \ \delta_C \ (270) \ 52.60 \ (MeO), \ 56.22 \ (Me \ ester), \ 76.89 \ (2-CH), \ 95.25 \ (OCH_2OMe), \ 127.71 \ (CH), \ 128.94 \ (CH), \ 129.03 \ (CH), \ 136.35 \ (C) \ and \ 171.50 \ (C=O). \]

\[ \text{(S)-2-Methoxymethoxy-2-phenylethanol (219)} \]

Diisobutylaluminium hydride (38.1 ml of a 1.5 M solution in toluene, 57 mmol, 4 eq) was added to a stirred solution of the ester 218 in dry toluene (10 ml) at -78°C and the resulting solution allowed to warm to RT over 1.75h. The resulting solution was cooled to 0°C during the cautious addition of 2M hydrochloric acid (15 ml). The resulting mixture was then extracted with ethyl acetate (3 x 25 ml) and the combined organic phases were dried and evaporated to give the pure alcohol 219 as a colourless oil (2.45 g, 94%), which showed data in accordance with literature values,\textsuperscript{167} \( \nu_{\text{max}} \ 3600 \ (OH) \ \text{cm}^{-1}; \ \delta_H \ (250) \ 2.80-3.05 \ (1H, \ br, \ OH), \ 3.38 \ (3H, \ s, \ OMe), \ 3.64 \ (1H, \ dd, \ J = 11.9 \ and \ 4.0, \ CH_2HB\text{OH}), \ 3.73 \ (1H, \ dd, \ J = 11.9 \ and \ 8.0, \ CH_2HB\text{OH}), \ 4.63 \ (2H, \ dd, \ J = 8.0 \ and \ 4.0, \ 2-H), \ 5.26 \ (1H, \ s, \ OCH_2OMe) \ and \ 7.20-7.40 \ (5H, \ m, \ Ph); \ \delta_C \ (270) \ 55.33 \ (OMe), \ 67.01 \ (CH_2OH), \ 79.93 \ (2-CH), \ 94.74 \ (OCH_2OMe), \ 126.83 \ (CH), \ 127.98 \ (CH), \ 128.35 \ (CH) \ and \ 138.26 \ (C); \ [\alpha]_D = +190 \ [c, \ 2.0 \ (CH_2Cl_2)]; \ (lit); +196 \ [c. \ 2.7 \ (CHCl_3)]. \]
(S)-2-Methoxymethoxyphenylacetaldehyde (220)

A solution of dimethyl sulphoxide (1.25 ml, 17.5 mmol, 2.5 eq) in dichloromethane (6 ml) was added dropwise to a solution of oxalyl chloride (0.8 ml, 8.7 mmol, 1.1 eq) in dichloromethane at -60°C at such a rate that the temperature was kept below -55°C. After 0.25h, the alcohol 219 (1.45 g, 8 mmol, 1 eq) was added and after a further 5 min, triethylamine (5.6 ml, 40 mmol, 5 eq) was added slowly and the resulting mixture allowed to warm to 10°C over 0.5h before water (12 ml) was added. The resulting mixture was extracted with dichloromethane (2 x 30 ml) and the combined organic phases were washed with brine (20 ml), 1M hydrochloric acid (3 x 30 ml) and brine (30 ml) and then dried and evaporated to give the aldehyde 220 as a yellow oil (1.02 g, 71%), which showed data in accordance to literature values,\(^{166}\) \(v_{\text{MAX}}\) 1730 (C=O) cm\(^{-1}\); \(\delta_{\text{H}}\) (250) 3.35 (3H, s, OMe), 4.65 (2H, s, OCH\(_2\)OMe), 5.26 (1H, d, \(J = 0.4, 2\)-H), 7.20-7.40 (5H, m, Ph) and 9.53 (1H, d, \(J = 0.4, 1\)-H); \(\delta_{\text{C}}\) (270) 56.01 (OMe), 73.16 (2-CH), 94.72 (OCH\(_2\)OMe), 127.61 (CH), 128.94 (CH), 129.03 (CH), 133.49 (C) and 195.88 (C=O); [\(\alpha\)]\(_D\) = +105 [c, 2.0 (CH\(_2\)Cl\(_2\))]; (lit) +112 [c, 1.0 (CHCl\(_3\))].
Vinylmagnesium chloride (10 ml of a 1.7 M solution in tetrahydrofuran, 17 mmol, 3 eq) was added to a solution of the aldehyde 220 (1.02 g, 5.6 mmol, 1 eq) in dry tetrahydrofuran (5 ml) at 0°C. The resulting solution was stirred at RT for 16h. Saturated aqueous ammonium chloride (10 ml) was added and the mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic phases were dried and evaporated to give a brown oil (1 g), which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the alcohols 221 as a yellow oil (1.02 g, 71%), $\nu_{\text{MAX}} 3300$ (OH) cm$^{-1}$; $\delta_{H} (250)$ 3.46 (3H, s, OMe), 4.37 (1H, dd, $J = 7.5$ and 6.6, 3-H), 4.51 (1H, d, $J = 7.5$, 4-H), 4.69 (2H, s, OCH$_2$OMe), 5.17 (1H, dd, $J = 10.5$ and 1.5, 1-H), 5.30 (1H, dd, $J = 17.2$ and 1.5, 1-H), 5.73 (1H, ddd, $J = 17.2$, 10.5 and 6.6, 2-H) and 7.30-7.42 (5H, m, Ph); $\delta_{C} (270)$ 55.41 (OMe), 75.60 (4-CH), 81.80 (3-CH), 94.56 (OCH$_2$OMe), 116.41 (1-CH$_2$), 127.51 (CH), 127.91 (CH), 128.01 (CH), 135.81 (2-CH) and 137.36 (C); and also the 3-epimer which showed, $\delta_{H} (250)$ 3.45 (3H, s, OMe) and 5.80 (1H, ddd, $J = 16.6$, 9.4 and 6.0, 2-CH) [other peaks obscured]; a ratio of ca. 3:1 between the two isomers was observed.
(4RS,5S)-4-Ethenyl-5-methoxymethoxy-5-phenyl-3-oxapentanoic acid (222)

Sodium hydride (249 mg of a 60% suspension in mineral oil, 6.5 mmol, 1.5 eq) was added to a solution of the alcohols 221 (900 mg, 4.3 mmol, 1 eq) in dry tetrahydrofuran (5 ml) at 0°C. The resulting solution was stirred at RT for 1h before solid sodium iodoacetate (1.87, 6.5 mmol, 1.5 eq) was added. The resulting suspension was refluxed for 16h. 2M Sodium hydroxide (30 ml) was added to the cooled mixture which was then washed with ethyl acetate (2 x 30 ml). The aqueous phase was acidified with 2M hydrochloric acid and extracted with chloroform (2 x 30 ml). The combined chloroform phases were dried and evaporated to give the acids 222 as a yellow oil (0.75 g, 68%), \( \nu_{\text{MAX}} \) 3450 (OH) and 1715 (C=O) cm\(^{-1}\), \( \delta_H \) (250) 3.41 (3H, s, OMe), 3.96 (1H, dd, \( J = 9.6 \) and 7.4, 4-H), 4.02 (1H, d, \( J = 17.4, 2-\text{CH}_A\text{H}_B \)), 4.30 (1H, d, \( J = 17.4, 2-\text{CH}_A\text{H}_B \)), 4.62 (2H, s, OCH\(_2\)OMe), 4.65 (1H, d, \( J = 9.6, 5-\text{H} \)), 5.05-5.15 (2H, m, 2'-CH\(_2\)), 5.45 (1H, ddd, \( J = 17.5, 10.0 \) and 6.6, 1'-H), and 7.20-7.42 (5H, m, Ph); \( \delta_C \) (270) 55.74 (OMe), 66.54 (4-CH), 79.91 (5-CH), 85.62 (2-CH\(_2\)), 93.80 (OCH\(_2\)OMe), 119.62 (2'-CH\(_2\)), 127.89 (CH), 128.36 (CH), 128.49 (CH), 132.49 (1'-CH), 136.32 (C) and 172.76; and also the 4-
epimer which showed, $\delta_H (250) 3.38 (3H, s, OMe), 5.20-5.25 (2H, m, 2'-CH$_2$) and 5.66 (1H, ddd, $J = 17.8, 10.4$ and $2.7, 1'$-H) [other peaks obscured].

(4E,2RS,6S)-2-Hydroxy-6-methoxymethoxy-6-phenylhex-4-enoic acid (223)

Butyl lithium (3.76 ml of a 1.6M solution in hexane, 6.02 mmol, 2.0 eq) was added to a solution of diisopropylamine (1.05 ml, 7.52 mmol, 3 eq) in dry tetrahydrofuran (5 ml) at -78°C. The resulting solution was stirred at -10°C for 0.5h before being cooled to -78°C. A solution of the acids 222 (800 mg, 3.01 mmol, 1 eq) in dry tetrahydrofuran (5 ml) was added. After 8h at -78°C, the mixture was allowed to warm to RT before adding saturated aqueous ammonium chloride (50 ml). The resulting mixture was extracted with chloroform (3 x 50 ml) and the combined organic phases were dried and evaporated to give, as a brown oil (460 mg, 58%), the hydroxy-acid 223 (460 mg, 58%), $\nu_{\text{max}}$ 3400 (OH) and 1709 cm$^{-1}$; $\delta_H (250) 2.41-2.43 (1H, m, 3-H_A), 4.30 (1H, m, 3-H_B), 3.29 (3H, s, OMe), 2.53-2.60 (1H, m, 2'-H), 4.70 (2H, s, OCH$_2$OMe), 5.20 (1H, d, $J = 6.0, 6$-H), 5.60-5.75 (2H, m, 4 and 5-H) and 7.20-7.52 (5H, m, Ph); $\delta_C (270) 36.50 (3$-CH$_2$), 54.50 (OMe), 69.75 (2-CH), 77.50 (6-CH), 93.50
(OCH₂OMe), 119.27 (5-CH), 126.76 (CH), 127.9 (CH), 128.34 (CH), 128.48 (C), 141.29 (4-CH) and 176.05 (C=O).

(4E,2RS,6S)-6-Methoxymethoxy-6-phenylhex-4-en-1,2-diol (224) and (2RS,4RS) and (2RS,4SR)-4-hydroxy-2-[(1EJ-2-styryl]-tetrahydrofuran (225)

![Chemical Structures]

Lithium aluminium hydride bis-tetrahydrofuran (0.97 ml of a 1.0M solution in toluene, 0.97 mmol, 2.6 eq) was added to a solution of the hydroxy-acid 223 (100 mg, 0.37 mmol, 1 eq) in dry toluene (1 ml) and the resulting solution stirred at RT for 1.5h. Saturated aqueous ammonium chloride (5 ml) was added and the resulting mixture was extracted with chloroform (3 x 60 ml). The combined organic phases were dried and evaporated to give a brown oil (120 mg) which was chromatographed on silica (eluting with 50% ethyl acetate in petrol) to give, as a colourless oil, the diol 224 (14 mg, 15%),ν_max 3455 (OH) cm⁻¹; δ_H (250) 2.40-2.46 (2H, m, 3-CH₂), 3.40 (3H, s, OMe), 3.55-3.60 (1H, m, 2-H), 3.70-3.73 (1H, m, CH₃OH), 3.80-3.82 (1H, m, CH₃HBOH), 4.68-4.70 (1H, m, 6-CH), 4.80 (2H, s, OCH₂OMe), 5.75-5.80 (2H, m, 4 and 5-H) and 7.15-7.30 (5H, m, Ph); and also, as a colourless oil, the
hydroxytetrahydrofurans \( \text{225} \) (87 mg, 74\%), \( \nu_{\text{max}} \) 3420 cm\(^{-1} \); \( \delta_{\text{H}} \) (250) 2.17 (1H, ddd, \( J = 13.3, 5.7 \) and 1.2, 3'-H\( _{A} \)), 2.48 (1H, ddd, \( J = 13.3, 6.2 \) and 1.9, 3'-H\( _{B} \)), 3.63 (1H, dddd, \( J = 6.2, 3.4, 2.2, 1.2, \) CH and 1.9, 4'-H), 3.93 (1H, dd, \( J = 8.4 \) and 1.6, 5'-H), 4.15 (1H, dd, \( J = 9.8 \) and 4.3, 5'-H), 6.21 (1H, dd, \( J = 16.0 \) and 6.9, 2-H), 6.63 (1H, d, \( J = 16.0, 1\)-H) and 7.20-7.50 (5H, m, Ph); \( \delta_{\text{C}} \) (270) 42.87 (3'-CH\( _{2} \)), 57.63 (2'-CH), 76.31 (5'-CH\( _{2} \)), 79.81 (4'-CH), 126.97 (2-CH), 128.16 (Ph-CH), 128.27 (Ph-CH), 129.00 (1-CH), 129.76 (Ph-CH), 131.75 (C) and 148.95 (2-C); m/z 190 (61\%, M\(^+\)), 151 (37), 104 (58), 91 (40) and 45 (100); [Found: M\(^+\), 190.1001. \( \text{C}_{12}\text{H}_{14}\text{O}_{2} \) requires M, 190.0993].

\( (2'SR,4'\text{RS},5'SR)-2-\text{(5'-Butyl-4'-iodotetrahydrofuran-2'-yl)} \text{acet-aldehyde} \) (244)

\[
\text{I} \quad \text{CH}_2 \quad \text{CH}_3 \quad \text{CHO} \\
\text{Bu} \quad \text{O} \\
\text{I} \\
\text{Bu}
\]

Diisobutylaluminium hydride (8.8 ml of a 1.0M solution in hexanes, 8.8 mmol, 1 eq) was added quickly to a solution of the iodotetrahydrofuran \( \text{54b} \) (2.88 g, 8.78 mmol, 1 eq) in petrol (10 ml) at -78°C and the resulting solution was stirred at this temperature for 3h. Methanol (3 ml) was added followed by 1M hydrochloric acid (8 ml) and the resulting mixture extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried and evaporated to give the \text{iodo-aldehyde} \( \text{244} \) as a colourless oil (2.15 g, 82\%), \( \nu_{\text{max}} \) 1725 (C=O), 1454, 1379 and 1068 cm\(^{-1} \); \( \delta_{\text{H}} \) (250) 0.81 (3H, t, \( J = 7.0, \) \( \text{CH}_3 \)),
1.19-1.43 (6H, m, 3 x CH₂), 1.91 (1H, m, 3'-Hₐ), 2.50-2.70 (3H, m, 2-CH₂ and 3'-Hₐ), 3.71-3.91 (1H, m, 4'-H), 4.02 (1H, td, J = 7.8 and 3.0, 5'-H), 4.30-4.42 (1H, m, 2'-H) and 9.30 (1H, br-s, 1-H); δ_C (270) 13.87 (CH₃), 21.49 (4'-CH), 22.59 (CH₂), 28.00 (CH₂), 31.93 (CH₂), 44.73 (3'-CH₂), 49.62, (2-CH₂), 72.83 (2'-CH), 86.23 (5'-CH) and 200.27 (C=O); m/z 239 (33%, M⁺-Bu), 125 (43), 84 (41), 68 (27) and 55 (100) [Found: M⁺-Bu, 238.9566. C₆H₈IO₂ requires M, 239.8569].

(5SR,7RS,8SR,2E)-Methyl 7-iodo-5,8-oxadodec-2-enoate (245)

Methyl triphenylphosphoranylidineacetate (271 mg, 0.8 mmol, 1.2 eq) was added to a solution of the iodo-aldehyde 244 (200 mg, 0.67 mmol, 1 eq) in dichloromethane (5 ml) at RT and the resulting solution stirred at this temperature for 16h. The solvent was removed in vacuo and the solid residue was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the iodo-alkene 245 as a colourless oil (180 mg, 76%), ν_max 1723 (C=O), 1659, 1436, 1326, 1274 and 1175 cm⁻¹; δ_H (250) 0.82 (3H, t, J = 7.0, 12-CH₃), 1.23-1.48 (6H, m, 9-, 10- and 11-CH₂), 1.99 (1H, ddd, J = 14.5, 3.0 and 1.0, 6-Hₐ), 2.30-2.52 (2H, m, 4-Hₐ and 6-H₈), 2.63 (1H, ddd, J = 14.0, 6.6, 1.3, 4-H₇), 3.69 (3H, s, OMe), 3.68-3.71 (1H, m, 7-H), 3.90-4.10 (2H, m, 5- and 8-H), 5.84 (1H, dt, J = 15.7 and 1.3, 2-H) and 6.88 (1H,
dt, \( J = 15.7 \) and \( 6.6 \) \( 3\)-H); \( \delta_c (270) \) 14.22 (12-Me), 22.19 (7-CH), 22.95 (CH\(_2\)), 28.32 (CH\(_2\)), 32.24 (CH\(_2\)), 38.82 (6-CH\(_2\)), 44.67 (4-CH\(_2\)), 51.72 (OMe), 76.78 (5-CH), 86.96 (8-CH), 123.68 (2-CH), 144.65 (3-CH) and 166.85 (C=O); \( \text{m/z} \) 239 \( (51\%) \), \( M^+\text{-CH}_2\text{CH=CHCO}_2\text{Me} \), 125 \( (45) \), 107 \( (18) \), 74 \( (64) \) and 55 \( (100) \) [Found: \( M^+\text{-CH}_2\text{CH=CHCO}_2\text{Me} \), 253.0106. \( \text{C}_{8}\text{H}_{14}\text{IO} \) requires \( M \), 253.0089].

\( (5SR,7RS,8SR,2Z)-7\)-Iodo\-5,8-oxadodec\-2\-ene (246)

Butyl lithium \( (5.03 \text{ ml of a } 1.6 \text{ M solution, } 8.14 \text{ mmol, } 1.2 \text{ eq}) \) was added to a solution of ethyltriphenylphosphonium iodide \( (3.36 \text{ g, } 8.1 \text{ mmol, } 1.2 \text{ eq}) \) in dry tetrahydrofuran \( (10 \text{ ml}) \) at -78°C and the resulting solution stirred at 0°C for 0.5h and then recooled to -78°C. A solution of the iodo-aldehyde 244 \( (2 \text{ g, } 6.7 \text{ mmol, } 1 \text{ eq}) \) in dry tetrahydrofuran \( (5 \text{ ml}) \) was added and the resulting solution was allowed to warm to RT over 16h. The solvent was removed \textit{in vacuo} and the solid residue obtained was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the \textit{iodo-alkene} 246 as a colourless oil \( (1.10 \text{ g, } 46\%) \), \( \nu_{\text{max}} \) 1436, 1377, 1264, 1149, 1057 and 1015 cm\(^{-1}\); \( \delta_h (250) \) 0.89 (3H, t, \( J = 6.8 \), CH\(_3\)), 1.21-1.47 (5H, m, 9-\( \text{H}_A \) and 10- and 11-CH\(_2\)), 1.61 (3H, d, \( J = 6.8 \), 1-CH\(_3\)), 1.72-1.98 (1H, m, 9-\( \text{H}_B \)), 2.01 (1H, ddd, \( J = 8.9 \), 2.6 and 1.9, 6-\( \text{H}_A \)), 2.11-2.44 (2H, m, 4-\( \text{H}_A \))
and 6-H$_B$), 2.60 (1H, m, 4-H$_B$), 3.68-3.72 (1H, m, 7-H), 3.90-4.15 (2H, m, 5- and 8-H), 5.25-5.41 (1H, m, 2-H) and 5.47-5.62 (1H, m, 3-H); $\delta$$_C$ (270) 12.99 (CH$_3$), 14.16 (1-CH$_3$), 23.06 (7-CH), 23.25 (CH$_2$), 28.18 (CH$_2$), 32.17 (CH$_2$), 33.48 (6-CH$_2$), 44.62 (4-CH$_2$), 77.93 (5-CH), 86.52 (8-CH), 125.57 (2-CH) and 126.77 (3-CH); m/z 308 (1%, M$^+$), 253 (100), 125 (47), 81 (50) and 69 (57) [Found: M$^+$, 308.0688. C$_{12}$H$_{21}$IO requires M, 308.0637]; and also 5% of the (E)-isomer which showed, $\delta$$_C$ (270) 125.51 (CH) and 128.21 (CH).

(6SR,8RS,9SR,3E)-8-Iodo-6,9-oxatridec-3-en-2-one (247)

Triphenylphosphoranylidine-2-propanone (152 mg, 0.47 mmol, 1.5 eq) was added to a solution of the iodo-aldehyde 244 (95 mg, 0.32 mmol, 1 eq) in dichloromethane (0.5 ml) at RT and the resulting solution was stirred at this temperature for 16h. The solvent was removed in vacuo and the solid obtained was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the ketone 247 as a colourless oil (53 mg, 55%), $\nu$$_{MAX}$ 1675 (C=O), 1629, 1455, 1360, 1254 and 1176 cm$^{-1}$; $\delta$$_H$ (250) 0.89 (3H, t, $J$ = 7.0, 13-CH$_3$), 1.23-1.43 (6H, m, 9-, 10- and 11-CH$_2$), 2.04 (1H, ddd, $J$ = 13.2, 9.8 and 1.5, 7-H$_A$), 2.16 (1H, ddd, $J$ = 13.2, 6.1 and 2.6, 7-H$_B$),
2.27 (3H, s, 1-CH₃), 2.29-2.74 (2H, m, 5-CH₂), 3.77 (1H, ddd, J = 11.2, 9.8 and 2.6, 8-H), 4.01-4.29 (2H, m, 6- and 9-H), 6.14 (1H, dt, J = 16.0 and 1.3, 3-H) and 6.78 (1H, dt, J = 16.0 and 7.2, 4-H); δC (270) 13.95 (CH₃), 21.87 (CH₂), 22.19 (8-CH), 26.96 (1-CH₃), 28.07 (CH₂), 31.95 (7-CH₂), 38.78 (CH₂), 44.39 (5-CH₂), 51.72 (OMe), 76.53 (6-CH), 86.81 (9-CH), 133.44 (3-CH), 144.23 (4-CH) and 199.72 (C=O); m/z 337 (1%, M⁺), 125 (100), 107 (36), 81 (64) and 55 (95) [Found: M⁺, 337.0625. C₁₃H₂₂IO₂ requires M, 337.0664].

(3'-exo,5'-exo)-Methyl 2-(3'-butyl-2'-oxabicyclo-[2.2.1]-heptan-5'-yl) acetate (248) and (3'-exo,5'-endo)-methyl 2-(3'-butyl-2'-oxabicyclo-[2.2.1]-heptan-5'-yl) acetate (249)

![Tertiary Butyl Acetate Structures](image)

Triphenyltin hydride (17 ml of a 0.02M solution in dry benzene, 0.34 mmol, 1.5 eq) and azo-bis-isobutyronitrile (11.3 ml of a 0.006M solution in dry benzene, 0.068 mmol, 0.3 eq) were added to a solution of the iodo-alkene 245 (80 mg, 0.23 mmol, 1 eq) in dry benzene (27 ml) at 80°C, over a period of 2h, under an atmosphere of argon. The resulting solution was heated for a further 2h and then cooled to RT before evaporating to give a clear oil (150 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in...
petrol) to give the esters 248 and 249 as a colourless oil (40 mg, 77%, as a 3:1 ratio), which showed \( \nu_{\text{max}} \) 1738 (C=O), 1434 and 1153 cm\(^{-1}\); m/z 226 (3%, \( \text{M}^+ \)), 169 (45), 137 (100), 125 (33) and 67 (41) [Found: \( \text{M}^+ \), 226.1549. \( \text{C}_{13}\text{H}_{22}\text{O}_3 \) requires \( \text{M} \), 226.1569]; for the isomer 248 \( \delta_H \) (250) 0.82 (3H, t, \( J = 6.8 \), \( \text{CH}_3 \)), 1.08 (1H, ddd, \( J = 13.8, 3.4 \) and 2.8, \( \text{6}'-\text{H}_A \)), 1.21-1.34 (7H, m, \( \text{7}'-\text{H}_A \) and 3 x \( \text{CH}_2 \)), 1.53 (1H, br s, \( \text{7}'-\text{H}_B \)), 1.92-2.01 (1H, m, \( \text{6}'-\text{H}_B \)), 2.01 (1H, br s, \( \text{4}'-\text{H} \)), 2.16 (1H, ddd, \( J = 8.4, 8.0 \) and 3.4, \( \text{5}'-\text{H} \)), 2.31 (1H, dd, \( J = 14.9 \) and 8.0, \( \text{2-H}_A \)), 2.46 (1H, dd, \( J = 14.9 \) and 8.4, \( \text{2-H}_B \)), 3.43 (1H, t, \( J = 6.5, \text{3}'-\text{H} \)), 3.61 (3H, s, OMe) and 4.22 (1H, br s, \( \text{1}'-\text{H} \)); \( \delta_C \) (270) 13.68 (\( \text{CH}_3 \)), 22.35 (\( \text{CH}_2 \)), 27.65 (\( \text{CH}_2 \)), 31.17 (\( \text{7}'-\text{CH}_2 \)), 34.91 (\( \text{CH}_2 \)), 39.59 (2-\( \text{CH}_2 \)), 44.72 (\( \text{4}'-\text{CH} \)), 51.19 (OMe), 75.91 (\( \text{1}'-\text{CH} \)), 83.27 (\( \text{3}'-\text{CH} \)) and 173.42 (C=O); for the isomer 249 \( \delta_H \) (250) 0.82 (3H, t, \( J = 6.8 \), \( \text{CH}_3 \)), 1.08 (1H, ddd, \( J = 13.8, 3.4 \) and 2.8, \( \text{6}'-\text{H}_A \)), 1.21-1.34 (7H, m, \( \text{7}'-\text{H}_A \) and 3 x \( \text{CH}_2 \)), 1.53 (1H, br s, \( \text{7}'-\text{H}_B \)), 1.92 (1H, m, \( \text{6}'-\text{H}_B \)), 2.01 (1H, br s, \( \text{4}'-\text{H} \)), 2.16 (1H, ddd, \( J = 8.4, 8.0 \) and 3.4, \( \text{5}'-\text{H} \)), 2.29 (1H, dd, \( J = 14.9 \) and 8.0, \( \text{2-H}_A \)), 2.45 (1H, dd, \( J = 14.9 \) and 8.4, \( \text{2-H}_B \)), 3.60 (3H, s, OMe), 3.68 (1H, t, \( J = 6.2, \text{3}'-\text{H} \)) and 4.18 (1H, br s, \( \text{1}'-\text{H} \)); \( \delta_C \) (270) 13.68 (\( \text{CH}_3 \)), 22.35 (\( \text{CH}_2 \)), 27.65 (\( \text{CH}_2 \)), 31.17 (7'-CH\(_2\)), 34.70 (5-CH\(_2\)), 34.98 (CH\(_2\)), 35.25 (6'-CH\(_2\)), 37.14 (2-CH\(_2\)), 44.05 (4'-CH), 51.19 (OMe), 75.57 (1'-CH), 76.58 (3'-CH) and 173.42 (C=O).
(3-exo,5-exo)-3-Butyl-5-ethyl-2-oxabicyclo-[2.2.1]-heptane \((250)\), (3-exo,5-endo)-3-butyl-5-ethyl-2-oxabicyclo-[2.2.1]-heptane \((251)\) and (3-endo,5-exo)-3-butyl-5-ethyl-2-oxabicyclo-[2.2.1]-heptane \((252)\)

Triphenyltin hydride (146 ml of a 0.02M solution in dry benzene, 2.93 mmol, 1.5 eq) and azo-bis-isobutyronitrile (97 ml of a 0.006M solution in dry benzene, 0.58 mmol, 0.3 eq) were added by syringe pump to a solution of the iodo-alkene \(246\) (600 mg, 1.95 mmol, 1 eq) in dry benzene (240 ml) at 80°C, under an atmosphere of argon, over a period of 2h. The resulting solution was heated for a further 2h and then cooled to RT. Carbon tetrachloride (100 ml) was added and the resulting solution was treated with iodine (~100 mg) until the colour just persisted. Evaporation gave a clear oil (400 mg) which was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous potassium fluoride until there was no further precipitation. The combined organic phases were dried and evaporated to give a colourless oil (200 mg), which was chromatographed on silica (eluting with 1% ethyl acetate in petrol) to give the alkanes \(250\) and \(251\) as a colourless oil (151 mg, 43%, as a 3:1 ratio) which showed \(\nu_{\text{MAX}}\) 1468, 1327 and 1063 cm\(^{-1}\); m/z 181 (8%, M\(^+\)), 155 (29), 77 (17), 69 (24) and 57 (23); for isomer \(250\), \(\delta_H\) (250) 0.83
(6H, t, J = 6.8, 2 x CH₃), 1.15-1.20 (1H, m, 6-Hᴬ), 1.21-1.34 (10H, m, 5-
H, 7-Hᴬ and 4 x CH₂), 1.52 (1H, br s, 7-Hᴮ), 1.79-1.82 (1H, m, 6-Hᴮ),
2.03 (1H, br s, 4-H), 3.41 (1H, t, J = 6.4, 3-H) and 4.25 (1H, br s, 1-H);
δ_C (270) 12.69 (CH₃), 14.28 (CH₃), 23.02 (CH₂), 28.39 (CH₂), 28.86
(CH₂), 31.74 (CH₂), 35.64 (7-CH₂), 38.83 (6-CH₂), 43.63 (5-CH), 45.03
(4-CH), 76.55 (1-CH) and 84.21 (3-CH); and for isomer 251, δ_H (250)
0.83 (6H, t, J = 6.8, 2 x CH₃), 1.11-1.13 (1H, m, 6-Hᴬ), 1.21-1.34 (10H,
m, 4 x CH₂), 1.40-1.42 (1H, m, 7-Hᴬ), 1.70 (1H, br s, 7-Hᴮ), 1.78-1.82
(2H, m, 5-H and 6-Hᴮ), 2.17 (1H, br s, 4-H), 3.77 (1H, t, J = 6.5, 3-H)
and 4.23 (1H, br s, 1-H); δ_C (270) 13.40 (CH₃), 14.28 (CH₃), 24.17 (CH₂),
29.76 (CH₂), 31.51 (CH₂), 35.76 (CH₂), 36.41 (7-CH₂), 37.81 (6-CH₂),
40.95 (5-CH), 44.08 (4-CH), 75.85 (1-CH) and 77.40 (3-CH); and b) the
alkane 252 (46 mg, 13%), which showed, ν_max 1468, 1327 and 1063
cm⁻¹; δ_H (250) 0.85 (3H, t, J = 6.9, CH₃), 0.87 (3H, t, J = 7.0, CH₃), 1.05
(1H, dd, J = 12.1 and 2.0, 6-Hᴬ), 1.15-1.40 (10H, m, 7'-CH₂ and 4 x
CH₂), 1.78-1.80 (1H, m, 5-H), 1.87 (1H, dd, J = 12.1 and 1.0, 6-Hᴮ),
2.13 (1H, br s, 4-H), 3.78 (1H, td, J = 6.9 and 2.1, 3-H) and 4.24 (1H, br
s, 1-H); δ_C (270) 12.08 (CH₃), 14.05 (CH₃), 22.31 (CH₂), 28.64 (CH₂),
31.76 (CH₂), 34.12 (CH₂), 34.62 (5-CH), 35.77 (7-CH₂), 39.23 (6-CH₂),
43.85 (4-CH), 77.22 (1-CH) and 81.66 (3-CH); m/z 182 (1%, M⁺), 125
(42%, M⁺-Bu), 96 (22), 67 (100) and 55 (30) [Found: M⁺-Bu, 125.0965.
C₈H₁₃O requires M, 125.0966].
(3-exo,5-exo)-3-Butyl-5-(2-oxapropyl)-2-oxabicyclo-[2.2.1]-heptane (253), (3-exo,5-endo)-3-butyl-5-(2-oxapropyl)-2-oxabicyclo-[2.2.1]-heptane (254) and (3-endo,5-exo)-3-butyl-5-(2-oxa-propyl)-2-oxabicyclo-[2.2.1]-heptane (255)

Triphenyltin hydride (12 ml of a 0.02M solution in dry benzene, 0.24 mmol, 1.5 eq) and azobis isobutyronitrile (8 ml of a 0.006M solution in dry benzene, 0.047 mmol, 0.3 eq) were added to a solution of the iodo-alkene 247 (53 mg, 0.16 mmol, 1 eq) in dry benzene (18 ml) at 80°C, under an atmosphere of argon, over a period of 2h. The resulting solution was heated for a further 2h and then cooled to RT. Carbon tetrachloride (20 ml) was added and the resulting solution was treated with iodine (~15 mg) until the colour just persisted. Evaporation gave a clear oil (100 mg) which was dissolved in ethyl acetate (20 ml) and washed with saturated aqueous potassium fluoride until there was no further precipitation. The combined organic phases were dried and evaporated to give a colourless oil (90 mg) which was chromatographed on silica (eluting with 4% ethyl acetate in petrol) to give a) the ketones 253 and 254 as a colourless oil (26 mg, 77%, as a 3:1 ratio), which showed ν<sub>MAX</sub> 1713 (C=O), 1462, 1357, 1155 and 1041...
c m⁻¹; m/z 210 (8%, M⁺), 153 (35), 135 (34), 95 (41), 66 (46) and 43 (100)

[Found: M⁺, 210.1602. C₁₃H₂₂O₂ requires M, 210.1620]; for isomer

δ_H (250) 0.87 (3H, t, J = 6.7, CH₃), 1.00-1.40 (7H, m, 6-Hₐ and 3 x CH₂), 1.53-1.65 (2H, m, 7-CH₂), 1.83-1.89 (2H, m, 5-H and 6-H₉), 2.04 (1H, br s, 4-H), 2.13 (3H, s, 1'-CH₃), 2.41-2.47 (1H, m, 3'-CH₃), 2.64 (1H, dd, J = 6.5 and 1.6, 3'-CH₉), 3.49 (1H, t, J = 7.0, 3-H) and 4.23 (1H, br s, 1-H); δ_C (270) 14.29 (CH₃), 22.97 (CH₂), 25.39 (CH₂), 28.23 (CH₂), 31.84 (1'-CH₃), 35.49 (CH₂), 36.46 (5-CH), 38.87 (6-CH₂), 45.24 (4-CH), 49.95 (3-CH₂), 76.46 (1-CH) and 83.95 (3-CH); and for isomer

δ_H (250) 0.89 (3H, t, J = 6.7, CH₃), 1.00-1.40 (7H, m, 6-Hₐ and 3 x CH₂), 1.53-1.65 (2H, m, 7-CH₂), 1.83-1.89 (2H, m, 5-H and 6-H₉), 2.01 (1H, br s, 4-H), 2.15 (3H, s, 1'-Me), 2.32-2.52 (2H, m, 3'-CH₂), 3.70 (1H, t, J = 7.0, 3-H) and 4.26 (1H, br s, 1-H); δ_C (270) 14.28 (CH₃), 24.00 (CH₂), 28.29 (CH₂), 30.24 (CH), 31.94 (CH₃), 35.60 (CH₂), 36.40 (CH₂), 38.41 (CH₂), 45.03 (CH), 76.42 (1-CH) and 77.46 (3-CH); and b) the

ketone 255 (6 mg, 20%), which showed υ_max 1713 (C=O), 1462, 1357, 1155 and 1041 cm⁻¹; δ_H (250) 0.92 (3H, t, J = 6.8, CH₃), 1.06 (1H, m, 6-Hₐ), 1.25-1.40 (4H, m, 2 x CH₂), 1.52-1.68 (5H, m, 5'-H, 7-CH₂ and 1 x CH₂), 1.91 (1H, m, 6-H₉), 2.11 (1H, br s, 4-H), 2.14 (3H, s, 1'-CH₃), 2.39 (1H, dd, J = 12.4 and 4.3, 3'-CH₃), 2.47 (1H, dd, J = 12.4 and 4.8, 3'-CH₉), 3.81 (1H, td, J = 7.0 and 2.5, 3-H) and 4.25 (1H, br s, 1'-H); δ_C (270) 14.05 (Me), 22.84 (CH₂), 27.87 (CH₂), 28.55 (CH₂), 30.19 (Me), 31.31 (CH₂), 35.97 (CH₂), 39.30 (5-CH), 44.13 (4-CH), 49.81 (3-CH₂), 77.20 (1-CH) and 81.38 (3-CH); m/z 210 (3%, M⁺), 124 (41%, M⁺-Bu), 95
(38), 66 (75) and 43 (100); [Found: M⁺, 210.1602. C₁₃H₂₂O₂ requires M, 210.1619].

(2'SR,4'RS,5'SR)-Methyl (5'-butyl-4'-triisopropylsilyloxytetrahydrofuran-2'-yl) acetate (256)

![Chemical Structure](image)

The hydroxytetrahydrofuran 72 (3.50 g, 16.5 mmol, 1 eq) was silylated exactly as in the preparation of compound 150, to give an oil (5 g) which was chromatographed on silica (eluting with 3% ethyl acetate in petrol) to give the silyloxy-tetrahydrofuran 256 as a colourless oil (2.33 g, 40%), νmax 1739 (C=O), 1464, 1437, 1382, 1329, 1246, 1107 and 1048 cm⁻¹; δH (250) 0.87 (3H, t, J = 6.4, CH₃), 1.00-1.10 (21H, m, TIPS), 1.21-1.47 (6H, m, 3 x CH₂), 1.67 (1H, ddd, J = 12.7, 9.8 and 5.7, 3'-H), 1.94 (1H, ddd, J = 12.7, 6.2 and 2.8, 3'-H), 2.45 (1H, dd, J = 15.2 and 6.3, 2-CH₃CH₂), 2.59 (1H, dd, J = 15.2 and 6.6, 2-CH₃CH₂), 3.63 (3H, s, OMe), 3.70 (1H, td, J = 6.4 and 3.1, 5'-H), 4.07 (1H, ddd, J = 9.8, 3.1 and 2.8, 4'-H) and 4.42 (1H, dddd, J = 6.6, 6.3, 6.2 and 5.7, 2'-H); δC (270) 12.20 (3 x CH, TIPS), 13.80 (CH₃), 17.56 (6 x CH₃, TIPS), 22.54 (CH₂), 27.89 (CH₂), 34.09 (CH₂), 40.41 (3'-CH₂), 41.24 (2-CH₂), 51.39 (OMe), 73.93 (CH), 77.46 (CH), 87.35 (5'-CH) and 171.46 (C=O); m/z 329 (20%, M⁺-iPr), 229 (31), 131 (92), 103 (83) and 75 (100) [Found: M⁺-iPr, 329.2158. C₁₇H₃₃O₄Si requires M, 329.2148].
(2'SR,4'RS,5'SR)-(5'-Butyl-4'-triisopropylsilyloxytetrahydro-furan-2'-yl)acetaldehyde (257)

The silyloxytetrahydrofuran 256 (2.33 g, 6.3 mmol, 1 eq) was reduced exactly as in the preparation of compound 244, to give the aldehyde 257 as a colourless oil (1.83 g, 85%), v_max 1731 (C=O) cm⁻¹; δ_H (250) 0.87 (3H, t, J = 6.4, CH₃), 1.00-1.10 (21H, m, TIPS), 1.21-1.47 (6H, m, 3 x CH₂), 1.52 (1H, ddd, J = 12.7, 8.7 and 6.3, 3'-H), 2.02 (1H, ddd, J = 12.7, 6.0 and 2.4, 3'-H), 2.61 (1H, dd, J = 10.2 and 5.6, 2-CHₐCHₖ), 2.61 (1H, dd, J = 10.2 and 3.4, 2-CHₐCHₖ), 3.68 (1H, t, J = 6.3 and 3.2, 5'-H), 4.09 (1H, ddd, J = 6.3, 3.2 and 2.4, 4'-H), 4.51 (1H, dddd, J = 8.7, 6.0, 5.6 and 3.4, 2'-H) and 9.55 (1H, br.s, CHO); δ_C (270) 12.58 (3 x CH, TIPS), 14.23(CH₃), 17.97 (6 x CH₃, TIPS), 22.93 (CH₂), 28.36 (CH₂), 34.49 (CH₂), 41.92 (3'-CH₂), 49.58 (2-CH₂), 73.17 (CH), 77.05 (CH), 87.82 (5'-CH) and 201.65 (C=O); m/z 299 (44%, M⁺+Pr), 229 (100), 131 (93), 99 (74) and 75 (81) [Found: M 329.2158. C₁₇H₃₃O₄Si requires M, 329.2148].

(5SR,7RS,8SR,2E)-Methyl 7-triisopropylsilyloxy-5,8-oxadodec-2-enoate (258)
The aldehyde $257$ (800 mg, 2.34 mmol, 1 eq) was treated exactly as in the preparation of compound $245$, to give the alkenoate $258$ as a colourless oil (475 mg, 51%), $\nu_{\text{MAX}}$ 1729 (C=O), 1659, 1463, 1270, 1161 and 1056 cm$^{-1}$; $\delta_H$ (250) 0.85 (3H, t, $J = 7.0$, CH$_3$), 1.01-1.10 (21H, m, TIPS), 1.25-1.47 (6H, m, 3 x CH$_2$), 1.63 (1H, ddd, $J = 12.6$, 5.8 and 3.0, 6-H), 1.87 (1H, ddd, $J = 12.6$, 5.5 and 2.1, 6-H), 2.44 (1H, m, 4-CH$_2$), 3.72 (3H, s, Me ester), 3.73-3.82 (1H, m, 8-H), 4.08-4.12 (1H, m, 7-H), 4.13-4.28 (1H, m, 5-H), 5.84 (1H, dd, $J = 15.7$ and 1.3, 2-H) and 6.88 (1H, dt, $J = 15.7$ and 7.2, 3-H); $\delta_C$ (270) 12.11 (3 x CH, TIPS), 13.96 (CH$_3$), 17.97 (6 x CH$_3$, TIPS), 22.54 (CH$_2$), 27.89 (CH$_2$), 34.09 (CH$_2$), 40.41 (6-CH$_2$), 41.24 (4-CH$_2$), 51.39 (OMe), 73.93 (CH), 77.46 (CH), 87.35 (8-CH), 122.97 (3-CH), 145.43 (2-CH) and 171.46 (C=O); m/z 355 (25%, M$^+$.iPr), 229 (100), 131 (34), 103 (38) and 75 (53)[Found: M$^+$.iPr, 355.2358. C$_{19}$H$_{35}$O$_4$Si requires M, 355.2304].

(5SR,7RS,8SR,Z)-7-Triisopropylsilyloxy-5,8-oxadodec-2-ene ($259$)

The aldehyde $257$ (800 mg, 2.34 mmol, 1 eq) was subjected to Wittig olefination exactly as in the preparation of compound $246$, to give the alkene $259$ as a colourless oil (140 mg, 17%), $\nu_{\text{MAX}}$ 1464, 1245, 1118 and 1091 cm$^{-1}$; $\delta_H$ (250) 0.87 (3H, t, $J = 7.0$, 12-CH$_3$), 0.97-1.12 (21H, m, TIPS), 1.20-1.47 (6H, m, 9-, 10- and 11-CH$_2$), 1.61 (3H, d, $J =$
6.5, 1-CH₃), 1.75 (1H, ddd, J = 10.7, 5.7 and 1.7, 6-Hₐ), 1.80-2.03 (1H, m, 6-Hₐ), 2.12-2.49 (2H, m, 4-CH₂), 3.65-3.73 (1H, m, 8-H), 4.01-4.19 (2H, m, 5- and 7-H) and 5.27-5.69 (2H, 2- and 3-H); δ_C (270) 12.11 (3 x CH, TIPS), 12.96 (1-CH₃), 13.96 (CH₃), 17.95 (6 x CH₃, TIPS), 22.67 (CH₂), 28.14 (CH₂), 34.22 (CH₂), 40.99 (6-CH₂), 41.23 (4-CH₂), 76.52 (CH), 77.14 (CH), 87.10 (8-CH), 125.84 (2-H) and 126.07 (3-H); m/z 311 (20%, M⁺-Pr), 229 (100), 131 (73), 81 (25) and 59 (21) [Found: M⁺-Pr, 311.2424. C₁₈H₃₅O₂Si requires M, 311.2406].

(5SR,7RS,8SR,2E)-Methyl 7-hydroxy-5,8-oxadodec-2-enoate (260)

The silyl-alkenoate 258 (374 mg, 0.94 mmol, 1 eq) was treated exactly as in the preparation of compound 163, to give the hydroxy-alkenoate 260 as a colourless oil (171 mg, 75%), ν_MAX 3414 (OH), 1726 (C=O), 1659, 1437, 1271, 1163 and 1091 cm⁻¹; δ_H (250) 0.90 (3H, t, J = 6.4, 12-CH₃), 1.20-1.47 (6H, m, 9-, 10- and 11-CH₂), 1.80 (1H, ddd, J = 13.2, 6.8 and 3.8, 6-H), 1.92 (1H, ddd, J =13.2, 5.7 and 2.2, 6-H), 2.41 (1H, ddd, J = 7.4, 6.1 and 1.0, 4-CH₂), 3.60 (3H, s, Me ester), 3.90-4.22 (3H, m, 5-, 7- and 8-H), 5.86 (1H, dt, J = 15.4 and 1.0, 2-H) and 6.91 (1H, dt, J = 15.4 and 7.4, 3-H); δ_C (270) 14.45 (CH₃), 23.15 (CH₂), 28.47 (CH₂), 34.45 (CH₂), 38.58 (6-CH₂), 41.24 (4-CH₂), 51.36 (OMe), 76.95 (CH), 77.42 (CH), 88.43 (8-CH), 123.59 (2-H), 143.21 (3-H) and 171.46
(C=O); m/z 144 (100%, M+–CH₂CH=CHCO₂Me), 100 (43), 99 (47), 81 (40) and 55 (34) [Found: M+–CH₂CH=CHCO₂Me, 142.0997. C₈H₁₄O₂ requires M, 142.0993].

(5RS,7RS,8SR,2Z)-7-Hydroxy-5,8-oxadodec-2-ene (261)

The silyl-alkene 259 (136 mg, 0.38 mmol, 1 eq) was treated exactly as in the preparation of compound 163, to give the hydroxy-alkene 261 as a colourless oil (30 mg, 40%), v_max 3445 (OH), 1659, 1462, 1260, 1158 and 1050 cm⁻¹; δ_H (250) 0.93 (3H, t, J = 6.5, 12-CH₃), 1.21-1.52 (6H, m, 9-, 10- and 11-CH₂), 1.62 (3H, dd, J = 6.2 and 0.8, 1-CH₃), 1.72 (1H, ddd, J = 13.2, 9.7 and 6.4, 6-H_A), 1.88 (1H, ddd, J = 13.2, 5.7 and 2.3, 6-H_B), 2.13-2.30 (1H, m, 4-H_A), 2.37-2.53 (1H, m, 4-H_B), 3.69 (1H, td, J = 6.1 and 3.1, 8-H), 4.01-4.19 (2H, m, 7- and 5-CH) and 5.33-5.63 (2H, m, 2- and 3-H); δ_C (270) 12.96 (1-CH₃), 13.98 (CH₃), 22.72 (CH₂), 28.02 (CH₂), 32.94 (CH₂), 34.07 (6-CH₂), 40.49 (4-CH₂), 76.53 (CH), 77.47 (CH), 86.81 (8-CH), 125.75 (2-H) and 126.11 (3-CH); m/z 143 (100%, M+–Bu), 99 (69), 81 (76), 57 (71) and 55 (65) [Found: M+–Bu, 142.1035. C₈H₁₄O₂ requires M, 142.0993].
Thiocarbonyldiimidazole (378 mg, 2.1 mmol, 3 eq) was added to a solution of the hydroxy-alkenoate \( \text{260} \) (171 mg, 0.71 mmol, 1 eq) in dry tetrahydrofuran (5 ml) and the resulting solution was heated at reflux for 16h. The resulting solution was cooled and evaporated and the residue filtered through silica (eluting with dichloromethane), to give the thioimidazole ester \( \text{262} \) (220 mg). This derivative was dissolved in toluene (70 ml) and the solution heated at reflux while a solution of tributyltin hydride (280 \( \mu \text{l} \), 1.05 mmol, 1.5 eq) in toluene (15 ml) was added dropwise over 8h. The solution was then cooled and evaporated to give an oil (500 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the ester \( \text{264} \) as a colourless oil (121 mg, 77%), \( \nu_{\max} \) 1738 (C=O), 1434 and 1153 cm\(^{-1}\); \( \delta_H \) (250) 0.89 (3H, t, \( J = 6.8 \), CH\(_3\)), 1.05-1.12 (1H, m, 6'-H\(_A\)), 1.21-1.53 (8H, m, 7'-CH\(_2\) and 3 x CH\(_2\)), 1.82-1.95 (1H, m, 6'-H\(_B\)), 2.04 (1H, br s, 4'-H), 2.17 (1H, br s, 5'-H), 2.29 (2H, dd, \( J = 7.8 \) and 4.5, 2-CH\(_2\)), 3.68 (3H, s, Me ester), 3.81 (1H, td, \( J = 7.0 \) and 2.6, 3'-H) and 4.26 (1H, br s, 1'-H); \( \delta_C \) (270) 13.85 (CH\(_3\)), 17.85 (CH\(_2\)).
23.31 (CH₂), 27.85 (CH₂), 28.14 (CH₂), 29.85 (CH₂), 36.15 (CH), 39.90 (2-CH₂), 40.03 (4'-CH), 51.54 (OMe), 77.10 (1'-CH), 81.31 (3'-CH) and 173.41 (C=O); m/z 226 (6%, M⁺), 169 (66), 140 (62), 108 (92) and 67 (100) [Found: M⁺, 226.1632. C₁₃H₂₂O₃ requires M, 226.1569].

(5SR,8SR,Z)-5,8-Oxadodec-2-ene (265)

The hydroxy-alkene 261 (30 mg, 0.15 mmol, 1 eq), was treated exactly as in the preparation of compound 264, to give a clear oil (90 mg) which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the tetrahydrofuran 265 as a clear oil (23 mg, 80%), ν_max 1462, 1378 and 1090 cm⁻¹; δ_H (250) 0.93 (3H, t, J = 6.8, 12-CH₃), 1.25-1.54 (6H, m, 9-, 10- and 11-CH₂), 1.65 (3H, d, J = 6.2, 1-CH₃), 1.83-1.96 (4H, m, 6- and 7-CH₂), 2.12-2.49 (2H, m, 4-CH₂), 3.72-3.92 (2H, m, 5- and 8-CH) and 5.35-5.63 (2H, m, 2- and 3-H); δ_C (270) 12.98 (CH₃), 14.03 (CH₃), 22.81 (CH₂), 28.36 (CH₂), 29.99 (CH₂), 30.48 (CH₂), 33.44 (CH₂), 35.80 (CH₂), 76.52 (8-CH), 77.18 (5-CH), 125.71 (2-H) and 126.36 (3-CH); m/z 127 (100%, M⁺-Pr), 109 (100), 83 (29), 67 (58) and 57 (33) [Found: M⁺-Pr, 127.1112. C₈H₁₅O requires M, 127.1123].

(5SR,7RS,8SR,2E)-Methyl 7-ido-5,8-oxadodec-2-enoate (245) and (5SR,7SR,8SR,2E)-methyl 7-ido-5,8-oxadodec-2-enoate (265)
A stirred solution of the iodo-alkene 245 (180 mg, 0.51 mmol, 1 eq) and hexabutylditin (30 mg, 0.026 ml, 0.1 eq) in dry, degassed benzene (20 ml), at reflux, was irradiated from a distance of 14 cm with a 275 W sun lamp for 65 mins, under an atmosphere of argon. 1,8-Diazabicyclo-[5,4,0]-undec-7-ene (0.15 ml) was added and, after 5 mins, iodine was added until the colour just persisted. The resulting solution was filtered through silica (washing with ether) and evaporated to give the iodo-alkenes 245 and 235, free of tin residues, as a colourless oil (180 mg, 76%), \( \nu_{\text{max}} \) 1723 (C=O), 1659, 1436, 1326, 1274 and 1175 cm\(^{-1}\); \( \delta_H \) (250) 0.82 (3H, t, \( J = 7.0 \), 12-CH\(_3\)), 1.23-1.48 (6H, m, 9-, 10- and 11-CH\(_2\)), 1.99 (1H, ddd, \( J = 14.5, 3.0 \) and 1.0, 6-H\(_A\)), 2.30-2.52 (2H, m, 4-H\(_A\) and 6-H\(_B\)), 2.63 (1H, ddd, \( J = 14.0, 6.6, 1.3, 4\)-H\(_B\)), 3.69 (3H, s, Me ester), 3.68-3.71 (1H, m, 7-H), 3.90-4.10 (2H, m, 5- and 8-H), 5.84 (1H, dt, \( J = 15.7 \) and 1.3, 2-H) and 6.88 (1H, dd, \( J = 15.7 \) and 6.6 3-H); \( \delta_C \) (270) 14.22 (12-Me), 22.19 (7-CH), 22.95 (CH\(_2\)), 28.32 (CH\(_2\)), 32.24 (CH\(_2\)), 38.82 (6-CH\(_2\)), 44.67 (4-CH\(_2\)), 51.72 (OMe), 76.78 (5-CH), 86.96 (8-CH), 123.68 (2-CH), 144.65 (3-CH) and 166.85 (C=O) and for iodo-alkene 235, \( \delta_C \) (270) 13.89 (12-Me), 22.63 (CH\(_2\)), 23.47 (7-CH), 27.93 (CH\(_2\)), 31.92 (CH\(_2\)), 37.67 (6-CH\(_2\)), 43.13 (4-CH\(_2\)), 51.43 (OMe), 76.35 (5-CH), 88.98 (8-CH), 123.38 (2-CH), 144.33 (3-CH) and 166.58 (C=O).
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