Stereoselective Synthesis of \( \beta \)-Hydroxycyclohexanones Using the Anionic Oxy-Cope Rearrangement

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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Dedicated to my Mum
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Summary

We have developed a method for the rapid and stereoselective synthesis of β-hydroxycyclohexanones v, using a route that relies on four key reactions as shown below.

Substrates for the anionic oxy-Cope (AOC) rearrangement iii were obtained by Takai alkylidenation of aldol products ii derived from α,β-unsaturated aldehydes i. The AOC rearrangement of alcohols iii containing an enol ether was investigated. Conditions were developed that resulted in the formation of cyclohexanones v from alcohols iii in a one-pot process. The stereochemistry of this rearrangement/cyclisation process was investigated. Substrate alcohols iii were found to rearrange predominantly through a chair-like transition state vi, with the potassium counterion chelated to the oxyanion and the enol ether oxygen atom.
The acid-catalysed intramolecular aldol reaction of intermediate aldehydes \textit{iv} was found to result in the preferential formation of an axial hydroxyl group in cyclohexanones \textit{v}. This result was explained in terms of a stabilising interaction present in intermediate oxonium ion \textit{viii}, between an axial hydroxyl group and the oxonium ion. The corresponding intermediate with an equatorial hydroxyl group \textit{vii}, does not contain such an interaction and so is disfavoured. Modelling studies were used to show that this interaction was significant.
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## Abbreviations

<table>
<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>AOC</td>
<td>anionic oxy-Cope</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>°C</td>
<td>degrees centigrade</td>
</tr>
<tr>
<td>CDI</td>
<td>carbonyldiimidazole</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR spectroscopy)</td>
</tr>
<tr>
<td>d</td>
<td>day(s)</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement through polarisation transfer</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EEO</td>
<td>ethoxyethyl</td>
</tr>
<tr>
<td>er</td>
<td>enantiomeric ratio</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylyphosphoramid</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>IR</td>
<td>infra red</td>
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</table>
KIE  kinetic isotope effect
LDA  lithium diisopropylamide
LG   leaving group
LUMO lowest unoccupied molecular orbital
LRMS low resolution mass spectrum
m    multiplet (NMR spectroscopy)
m    medium (IR spectroscopy)
mCPBA meta chloroperbenzoic acid
min  minute(s)
mL   millilitre(s)
mol  mole(s)
MOM  methoxymethyl
NMR  nuclear magnetic resonance
TBAF tetrabutylammonium fluoride
TBS  tert-butylidimethylsilyl
TES  triethyllsilyl
THF  tetrahydrofuran
TLC  thin layer chromatography
TMEDA N,N',N'-tetramethyleneediamine
TMS  trimethylsilyl
TS   transition state
Xc   chiral auxiliary
Introduction

1.1 Background

Our research has focused on the development of methodology for the rapid and stereoselective synthesis of polyfunctionalised ring systems, in particular the formation of β-hydroxycyclohexanones. The route we have developed is shown below, Scheme 1.

Scheme 1

[Diagram of Scheme 1 showing the synthesis process from 1 to 5 with specific reactions and structures labeled.]
Assembly of the target cyclic product 5 relies on four key reactions:

- an intermolecular aldol reaction
- a Takai alkylidenation reaction
- the anionic oxy-Cope (AOC) rearrangement
- an intramolecular aldol reaction

Stereochemical complexity is built up rapidly in the sequence. Starting with an α,β-unsaturated aldehyde 1, an intermolecular aldol reaction adds two new chiral centres to give hydroxy ester 2. Takai alkylidenation of 2 results in the selective formation of a Z enol ether to give AOC substrate 3. Alcohol 3 undergoes AOC rearrangement to give, after quenching with an electrophile, the final acyclic precursor 4, which contains an aldehyde and an enol ether ideally placed for cyclisation. Finally, compound 4 undergoes an acid-induced intramolecular aldol reaction to give the target β-hydroxycyclohexanone 5.

The intermolecular aldol reaction\(^1\) is well-known and will be discussed in brief in a later section. The remaining three key reactions however, are less well established. The rest of this chapter will therefore be divided into the following sections:

- a short overview of alkylidenation reactions
- a more comprehensive review of work carried out to date on the AOC rearrangement of acyclic substrates
- an overview of the intramolecular aldol reaction.

### 1.2 Alkyldenation Reactions

#### 1.2.1 The Wittig Reaction

The most commonly used alkyldenation reaction is the Wittig olefination.\(^2\) A phosphorous ylid 7, and a carbonyl compound 8 react together to give an alkene 9 and a trialkylphosphine oxide 10. Variations on this reaction have been developed by Wadsworth, Horner and Emmons,\(^3\) which employ a trialkylphosphinite in place of
a phosphine. In these cases 11 reacts with 8 to give alkene 9 as before, but the water soluble by-product 12 is formed instead of the trialkylphosphine oxide 10, Scheme 2.

**Scheme 2**

**Wittig Reaction**

[Diagram of Wittig Reaction]

**Horner-Wadsworth-Emmons Reaction**

[Diagram of Horner-Wadsworth-Emmons Reaction]

As well as being routinely employed for simple olefinations, the Wittig reaction can be used as a key coupling step late in the synthesis of complex natural products. An impressive recent example is provided by Evans and co-workers in their synthesis of Spongistatin 2,4 Scheme 3. The ylid formed from phosphonium salt 13 is reacted with aldehyde 14 to give predominantly the Z alkene 15.

The Wittig reaction however, is effective only for ketone and aldehyde carbonyl compounds. Carboxylic acid derivatives such as esters and amides are resistant to olefination, and so considerable research has gone into finding a suitable equivalent to the Wittig reaction that is effective on these substrate types.
1.2.2 Titanocene Based Reagents

Early progress in this area was made by Tebbe, who found that titanocene derived compound 16 was effective for the methylation of esters and amides,$^5$ Figure 1.

**Figure 1**

![Diagrams of titanocene reagents](image)

Similar reagents were also developed by Grubbs $^{17,6}$ and later Petasis $^{18,7}$ All three reagents are believed to give titanium-alkylidene species 19 as the reactive intermediate, Scheme 4.$^8$
Scheme 4

![Scheme 4](image)

Petasis and co-workers have also used dibenzyltitanocenes and a tris(trimethylsilylmethyl)titanium complex to alkylidenate carbonyl compounds. However, titanium alkylidenes cannot be generated from alkyl groups that are capable of β-elimination. A more general method for the preparation of substituted enol ethers was reported by Takai and co-workers in 1987.

1.2.3 The Takai Reaction

Takai found that the titanium-alkylidene (or 1,1-dimetalloalkane), formed in situ from titanium tetrachloride, zinc and a 1,1-dibromoalkane in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA), was capable of cleanly transforming esters 20 into the corresponding enol ethers 21 with high levels of Z-selectivity, Scheme 5.

Scheme 5

![Scheme 5](image)

The reaction has proven to be effective in the alkylidenation of amides 22 to give enamines 23, thioesters 24 to give alkenyl sulfides 25, and silyl esters 26.
to give silyl enol ethers $27.^{12}$ Thioesters and silyl esters react with high levels of $Z$ selectivity. Amides react to give $E$-enamines, Scheme 6.

**Scheme 6**

The mechanism of the reaction is poorly understood. We propose the following process occurs, Scheme 7.
Titanium tetrachloride is added to THF to give bright yellow complex 28. TMEDA is then added and the orange/brown adduct 29 is formed. (A crystal structure of a titanium(II) complex analogous to titanium(IV) complex 29 has been published.\textsuperscript{133}) Geminal dizinc compound 31, formed by double zinc-insertion into the C-Br bonds of 1,1-dibromoalkane 30, reacts with 29 by transmetallation to give
the active alkylidenating species 32. Takai has investigated the catalytic effect of lead on the zinc-insertion process,\textsuperscript{13b} Scheme 8.

Transmetallation of zinc-carbenoid 34 with lead (II) gives the lead-carbenoid 35. This is then readily reduced by zinc to give the lead-zinc species 36. Finally, transmetallation from lead to zinc gives geminal dizinc compound 37.

Once the active species 32 has formed, the carbonyl compound must also bind to Ti to allow transfer of the alkylidene moiety, Scheme 9.

\textbf{Scheme 9}

Stereocontrol in the reaction must also arise at this stage. Scheme 10 shows how selectivity for the \textit{Z} geometrical isomer of an enol ether could arise in the reaction between a titanium alkylidene 43 and an ester 44. The transition state leading to oxatitanacyclobutane 46 is higher in energy than that leading to oxatitanocyclobutane 45 due to the developing steric crowding between the alkyl group \( R_1 \) of the titanium alkylidene 43 and alkyl group \( R_2 \) of the ester 44. The fact that branching \( \alpha \) to the carbonyl (\textit{ie} increasing the size of \( R_2 \)) greatly improves the stereoselectivity of the reaction agrees with this model. The model also explains the reversed selectivity observed during the alkylidena\textit{tion of amides.}
Scheme 10

The Takai reaction has not been widely used in synthesis to date. This is surprising as it is superior to alternative methods, both in terms of versatility and ease of use. The reaction has also been shown to be effective where other more popular methods fail. For example, the Tebbe reagent failed to methylenate ester 49, but methylenation occurred smoothly under Takai conditions to give enol ether 50 in good yield, Scheme 11.  

Scheme 11

Until recently, the main drawback of the Takai method was the relative inaccessibility of 1,1-dibromoalkane compounds 51, which were usually prepared by alkylation of dibromomethane at low temperature, Scheme 12.  

9
A method has now been reported for the formation of these compounds from hydrazones 53, which are readily prepared from carbonyl compounds 52, Scheme 13.\textsuperscript{15b}

**Scheme 13**

\[
\begin{align*}
\text{O} & \quad \text{H}_2\text{NNH}_2/\text{MeOH} \\
\text{R}_1\text{R}_2 & \quad \text{molecular sieves} \\
\text{52} & \quad \text{53} \\
\end{align*}
\]

**1.2.4 Takeda Alkylidenation**

Recently Takeda and co-workers showed that when dithioacetals 55 were reacted with titanocene 56, the titanium-alkylidene complex 57 was formed. This could then be reacted with carbonyl compounds to yield the corresponding olefins 58, Scheme 14.\textsuperscript{16}

**Scheme 14**

\[
\begin{align*}
\text{RS} & \quad \text{SR} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{55} & \quad \text{56} \\
\text{Cp}_2\text{Ti[P(OEt)}_3\text{]}_2 & \quad \text{57} \\
\end{align*}
\]

The attractiveness of this method lies in the easy access to dithioacetals 55 which are formed in a single step from aldehydes or ketones. At present the $E:Z$ ratios obtained in the reaction are not good for aldehydes and ketones, but are better for esters, Scheme 15. For example, ketone 60 is alkylidenated to give the
alkenes 61 with an E:Z ratio of 54:46, while the ester 63 is alkylidenated to give the enol ethers 64 with a better E:Z ratio of 14:86.

**Scheme 15**

\[
\begin{align*}
\text{PhS} & \quad \text{SPh} \\
\text{Ph} & \quad \text{H} \\
59 & \\
\text{Ph} & \quad \text{SPh} \\
\text{PhS} & \quad \text{SPh} \\
\text{62} & \\
\text{Cp}_2\text{Ti[P(OEt)}_3\text{]}_2 & \\
\text{O} & \\
\text{60} & \text{80\%} \\
\text{Ph} & \quad \text{OEt} \\
63 & \\
\text{Cp}_2\text{Ti[P(OEt)}_3\text{]}_2 & \\
\text{O} & \\
\text{Ph} & \quad \text{OEt} \\
64 & \text{75\%} \\
\end{align*}
\]
1.3 The Anionic Oxy-Cope (AOC) Rearrangement

1.3.1 Sigmatropic rearrangements

In 1965, Woodward and Hoffmann introduced the term sigmatropic rearrangement, defining “a sigmatropic change of order \([i,j]\) is the migration of a \(\sigma\) bond, flanked by one or more \(\pi\) electron systems, to a new position whose termini are \(i-1\) and \(j-1\) atoms removed from the original bonded loci, in an uncatalysed intramolecular process”.\(^{17}\) This definition grouped together processes as diverse as hydrogen atom-shifts and Claisen rearrangements, Scheme 16. Hence the H-atom shift of diene 65 is order \([1,5]\) as the original 1’-1 \(\sigma\)-bond moves to 1’-5, i.e. one of the loci remains the same (\(i = 1\)) and the other is 4 atoms removed from the original position (\(j = 5\)). Similarly, the Claisen rearrangement of ether 67 is order \([3,3]\) as the original loci (1-1’) and the new loci (3-3’) are two atoms removed.

Scheme 16

Such processes can be used to bring about useful structural changes in the carbon skeletons of organic compounds by, for example, creating new functionality. The most important aspect of these reactions is however their ability to establish new chiral centres in a molecule, often at positions which are inaccessible to direct chemical synthesis. In other words, they can be used to transfer chirality from one centre which can be set up by direct methods (nucleophile/electrophile reactions, etc.) to another, remote site without loss of stereochemical information.
1.3.2 Development of the anionic oxy-Cope rearrangement

The thermal rearrangement of a 1,5-diene through a [3,3]-sigmatropic process is known as the Cope rearrangement. Discovered in 1940 by Cope, it is the all-carbon variant of the Claisen rearrangement and is the parent reaction for a range of related rearrangements, Scheme 17. Although this rearrangement has been used widely in synthesis, its scope is limited by the high reaction temperatures required, and, as the process is reversible, by unfavourable equilibria in some cases.

Scheme 17

![Scheme 17](image)

An important advance was made in 1964 when Berson and Jones realised that the placement of a hydroxyl group at C-3 of the 1,5-diene would lead, after rearrangement, to the formation of an enol. Subsequent tautomerisation would yield an aldehyde and so render the rearrangement irreversible, Scheme 18.

Scheme 18

![Scheme 18](image)

The oxy-Cope rearrangement is much more synthetically useful than the Cope rearrangement. In addition to the valuable carbonyl functionality generated, the reaction takes place at much lower temperatures. The utility of the oxy-Cope reaction was further enhanced when, in 1975, Evans and Golob discovered that the formation of an alkoxide anion resulted in remarkable accelerations in the rate of reaction (up to $10^{17}$). Under these conditions the rearrangement takes place
at, or near to ambient temperature. The anionic variant of the oxy-Cope rearrangement has seen wide application in synthesis, as the following sections will show.

1.3.3 Rate acceleration

The enormous rate accelerations achieved on formation of the oxyanion in the [3,3]-sigmatropic rearrangement have been investigated in several theoretical studies. In all cases the origin of the effect was found to be a charge-induced weakening of the C-3/C-4 bond, rather than stabilisation of the transition state, Figure 2.

Figure 2

The ability of the oxyanion to weaken the bond increases with the 'nakedness' of the anion. The use of a potassium base and 18-crown-6 is therefore commonly used to enhance this effect. The potassium counterion is chelated by the crown ether and so ion pair formation with the alkoxide is generally believed to be prevented (see Section 3.3 for an exception). Deuterium labelling experiments have provided experimental evidence for the existence of a highly dissociated transition state, Figure 3. A secondary kinetic isotope effect (KIE) is observed for rearrangement of compound 75. No KIE is found for compound 76. Secondary KIEs are observed when a change takes place in the hybridisation of the carbon atom to which the label is attached before the transition state of a reaction is reached. Hence, a KIE for 75 means that the hybridisation of C-4 changes from sp$^3$ to sp$^2$, i.e. the C-3/C-4 σ bond is substantially broken before the transition state of the AOC rearrangement. The fact that no KIE is observed for 76 shows that the degree of C-1/C-6 bond formation before the transition state is minimal.
The rest of this section will give an overview of the most interesting and impressive uses of the rearrangement to date. (It should be noted that most of the examples shown were selected from the recent comprehensive review by Paquette.\textsuperscript{25}) This will be followed by a more detailed examination of the work that has been carried out on acyclic systems.

1.3.4 Ring expansions

Perhaps the most common early use of the anionic oxy-Cope rearrangement was in the formation of cyclodecanones. An elegant example is illustrated below, Scheme 19.\textsuperscript{26} In an efficient one-pot process the enolate resulting from AOC rearrangement of 77 is trapped as its TMS enol ether 82 (see Scheme 20), and then oxidised by the action of mCPBA to give the hydroxy ketone 78.

Scheme 19

The above example illustrates the use of a \textit{trans} 1,2-divinylcyclohexanol. In such systems, the anionic oxy-Cope reaction proceeds through a chair-like transition state with an axial oxyanion, 80. This arrangement generates an \textit{E}-double bond in the resulting silyl enol ether 82, Scheme 20.
When the vinyl substituents are cis to each other, two chair-like reacting conformations are possible, Scheme 21.

The geometry of the product is dependent upon the conformation of the transition state. In reacting conformation 84, the oxyanion adopts an equatorial orientation with respect to the cyclohexane, but is axial with respect to the rearranging system. A Z-double bond is formed. In conformation 85, the situation is reversed to give an E-double bond. Experimentally, it is found that 86 and 87 are produced in a ratio of 10:86.27 Clearly there is a preference for an equatorial oxyanion during the [3,3]-sigmatropic event.
1.3.5 Construction of bicyclic ketones

Bicyclic ketones can be constructed if one or more of the rearranging double bonds is contained within a ring. In Still's synthesis of eucannabinolide 90, the formation of the bicyclic ketone 89 from alcohol 88 is accompanied by ring expansion, Scheme 22.28

Scheme 22

This type of reaction has been used in the construction of decalins. For example, AOC rearrangement of alcohol 92, obtained from the microbially-derived dehydrocatechol 91, gives the enantiopure cis-decalin 93, Scheme 23.29

Scheme 23
1.3.6 Polycyclic ketones

If the complexity of the starting alcohols is increased to include several fused rings, impressive polycyclic arrays can be generated in a single step, e.g. the highly complex tetracycle 95 is formed by AOC rearrangement of the relatively simple alcohol 94 Scheme 24.30

Scheme 24

1.3.7 Formation of bridgehead double bonds

The use of spirocyclic alcohols as substrates for the rearrangement leads to the formation of compounds containing bridgehead double bonds, Scheme 25.31a-c

For example ketone 97 is obtained by the rearrangement of spirocyclic alcohol 96. The formation of such compounds by other methods is difficult.

Scheme 25

The use of the rearrangement for the formation of the taxane skeleton has been extensively investigated,32a-e eg the AOC rearrangement of alcohol 98 gives, after alkylation of the resulting enolate, the taxane 99 Scheme 26.32c
A spectacular example of the use of the rearrangement for the formation of a bridgehead double bond is provided in Paquette’s synthesis of cerorubenic acid-III 102, Scheme 27.\cite{33a,b}

1.3.8 Participation of other double bond types

The rearrangement is not limited to the use of simple olefins. Allenes,\textsuperscript{34} enol ethers,\textsuperscript{35} dienes\textsuperscript{35} and aromatic compounds\textsuperscript{36} have also been used as substrates, as the following examples illustrate, Scheme 28.
Unsurprisingly, loss of aromaticity during the rearrangement means that aromatic compounds such as alcohol 109 are poor substrates for the reaction.
However, if strain is present in the starting material, the thermodynamics of the reaction can become more favourable, as shown in the formation of steroidal hormone analogues eg 112, Scheme 29.$^{37}$

**Scheme 29**

111 \[\text{NaH} \rightarrow \text{THF, } \Delta \text{ \ 75\%} \rightarrow 112\]

1.3.9 Doubly-charged systems

In recent years, the behaviour of doubly-charged systems has been investigated.$^{38a-e}$ Rapid access to very complex structures, eg 117, is possible Scheme 30.$^{38a}$ Diisopropyl squarate 113 is treated sequentially with lithiated dihydrofuran 114 and lithiated cyclopentene 115 to give the dianionic species 116. 114 then undergoes AOC rearrangement to give the bis-enolate 117 which reacts further as shown to give tetracyclic hydroxyenone 119 as the major product.
1.3.10 Tandem Processes

The initial product of the rearrangement is an enolate anion. Most tandem processes take advantage of this situation by using the inherent reactivity of the enolate to carry out further chemical transformations. Several examples of this type of tandem process have already been illustrated. The enolate can of course react at oxygen\(^{39a,b}\) (120 → 121) *Scheme 31a* or at carbon\(^{40}\) (122 → 123) *Scheme 31b*.  

26 %, major isomer
The initially formed enolate is subject to equilibration in some cases, *eg* enolate 126, formed initially on AOC rearrangement of alcohol 125, undergoes equilibration to enolate 127, which is quenched by the addition of PhSeCl to give the observed product, selenide 128 *Scheme 32*.41
Scheme 32

The enolate can be trapped by oxygen to form α-hydroxy ketones, *Scheme 33.*\(^\text{42}\) Note in the example below that enolate equilibration takes place prior to oxygenation to give hydroxy ketone 130.

**Scheme 33**

In certain cases, a second enolate can be generated after rearrangement via a proton transfer mechanism. The new enolate can then react with the carbonyl group formed from the original enolate. For example, enolate 133, formed on AOC rearrangement of alcohol 132, undergoes proton transfer to generate enolate 134. A transannular ring closure onto the ketone formed during proton transfer gives the observed product, alcohol 135, *Scheme 34.*\(^\text{43}\)
In cases where proper orbital alignment can be achieved, the enolate anion can displace remote alkoxide substituents in an intramolecular $s_N^1$ reaction as shown in the conversion of alcohol 136 into polycyclic ketone 138 via enolate 137, Scheme 34. Again structural complexity is greatly increased.

Scheme 35

In the previous examples, the oxy-Cope rearrangement has been followed by another chemical process. Cases where the oxy-Cope takes place after a preliminary transformation are less well known. Two examples where the AOC rearrangement is preceded by a [2,3]-Wittig rearrangement are illustrated below,
**1.4 Rearrangement of Acyclic Substrates**

The previous sections have dealt with the rearrangement of cyclic substrates, that is, substrates in which at least one of the \( \sigma \)-bonds connecting the two reacting \( \pi \)-bonds are contained within a ring. This imposes steric constraints upon the system and is often the source of the excellent chiral transfer observed in these cases. The rearrangement of acyclic systems, in which the \( \pi \)-bonds are free to adopt essentially any conformation has been less well explored.

**General considerations**

The rearrangement can proceed through two 6-membered reacting conformations a chair-like conformation 145 and a boat-like conformation 146, *Figure 4*. 
The relative stereochemistry of substituents positioned at C-1 and C-6 is determined by which of these two transition states the rearrangement adopts. A chair-like transition state results in an anti relationship \(147\), while a boat-like transition state gives syn stereochemistry \(148\). The absolute stereochemistry of substituents at C-1 and C-6 is determined by the orientation of the oxyanion. Rearrangement through a transition state with an axial oxyanion \(149\) gives opposite absolute stereochemistry to that produced by rearrangement through the corresponding transition state with an equatorial oxyanion \(145\), Figure 5.
Most of the work carried out to date on the AOC rearrangement of acyclic substrates has centred on whether the oxyanion prefers to adopt a pseudoequatorial or a pseudoaxial position.

The first example of the rearrangement of an acyclic substrate (as defined above) was reported in 1990 by Lee and co-workers, *Scheme 37.*

**Scheme 37**

They found that there was a > 95:5 preference for an equatorial oxyanion, *Scheme 38.*

**Scheme 38**

The observed stereoselectivity can be explained as illustrated in *Scheme 38.* When the oxyanion adopts a pseudoaxial orientation, it experiences a severe 1,3-pseudodiaxial interaction with one of the methyl substituents on the cyclohexene ring (153). However, this interaction is avoided when the oxyanion adopts an equatorial orientation (155).
The first example of a substrate containing no rings was reported by Paquette and Maynard in 1991. They studied the rearrangement of compounds 157 and 158, Figure 6.

**Figure 6**

They found that a preference for an equatorial anion existed, but that the preference was modest, Scheme 39. Hence, the major product of AOC rearrangement of alcohol 157 was aldehyde (S)-167, produced via reacting conformation 159 which contains an equatorial oxyanion. Similarly, alcohol 158 rearranges predominantly through conformation 164 to give (R)-167. However, in both cases a significant amount of the other enantiomer is formed via rearrangement through the corresponding reacting conformations containing an axial oxyanion.
They also investigated post-rearrangement enolate geometry. Quenching the rearrangement of 157 with TBSCI gave a 64:36 mixture of cis and trans silyl enol ethers. Hydrogenation of each pure isomer lead to samples of 168 each enriched (60 %) in the R enantiomer, Figure 7.

Figure 7
This shows that enolate geometry is not fixed under the reaction conditions, as examination of reacting conformations 159 and 160 reveals that the E-enolate should have given enantiomerically pure R-isomer (161) and the Z-enolate (162) the S-enantiomer, provided the reaction proceeds only through a chair-like transition state. This result shows that the ratio of enolate geometry after rearrangement is not a proper guide to the ratio of reaction through the two chair-like transition states.

In a later study, Paquette and coworkers went on to explore the effect of a cyclohexene ring on the rearrangement. They were prompted by Ireland’s study of the Claisen rearrangement, which showed that there was a preference for the formation of an axial bond on the cyclohexene ring.

**Figure 8**

![](image)

Paquette and co-workers observed a similar effect during the AOC rearrangement of alcohols 171 and 172, Scheme 40.
Alcohol 171 gave (after borohydride reduction) a 61:1 ratio of alcohols 177 and 178, while 172 gave an essentially 1:1 mixture of the two. The results show that there are two conflicting stereoelectronic factors operating in this system. There is a bias in favour of the formation of an axial bond, and there is also a bias in favour of an equatorial oxyanion. When the two factors co-operate, as in 173, there are high levels of stereoselectivity. However, when the two factors compete as in 175 and 176, no stereoselectivity is observed. The two processes are therefore energetically equivalent.

Nakai and co-workers in 1991 and later in 1993 reported investigations into the effect of substituents at C-4 of the 1,5-hexadien-3-ol system. They proposed that if the hydroxyl group and the substituent at C-4 were syn to each
other, as in 179 and 183, good stereocontrol could be achieved via a large bias in favour of reacting conformations 181 and 185 respectively, *Scheme 41*.

Scheme 41

They prepared suitable substrates via a [2,3]-Wittig rearrangement. Anionic oxy-Cope rearrangement afforded aldehydes 191 and 192 with 94% de, 99% E and 88% de, 97% E respectively, showing that the rearrangement proceeds almost exclusively through transition state 181 for E,E-substrates and transition state 185 for E,Z-substrates, *Scheme 42*.

Scheme 42

They also investigated the rearrangement of alcohols of type 193 and 197. These substrates contain no substituent at C-4, and have a Z C-1 – C-2 double bond. This leaves the 1,3-diaxial interaction between the oxyanion and R³ as the sole controlling influence in the reaction *Scheme 43*. The results show a decreased level of stereoselectivity, indicating that the 1,3-diaxial interaction is
large enough for effective stereocontrol, but does not provide complete transfer of chirality.

**Scheme 43**

\[
\begin{align*}
&\text{HO} \quad R_2 \quad R_3 \\
&\text{193} \quad R, Z, E \\
\end{align*}
\]

\[
\begin{align*}
&\text{HO} \quad R_2 \quad R_3 \\
&\text{197} \quad R, Z, Z \\
\end{align*}
\]

Example: OTr KH, 18-C-6

\[
\begin{align*}
&\text{201} \quad \text{OTr} \quad \text{OH} \\
&\text{202} \quad \text{OTr} \quad \text{OTr} \\
&80\% \text{ de, 84\% ee} \\
\end{align*}
\]

Nakai proposed a boat-like transition state to account for the decreased diastereoselectivity, *Figure 10.*

**Figure 10**

\[
\begin{align*}
&\text{OTr} \quad \text{OH} \\
&\text{203} \quad \text{OTr} \\
\end{align*}
\]

This is the first reported example of a boat-like transition state operating in the AOC rearrangement of an acyclic substrate. Previous work had disregarded this as a possibility. As a note, Nakai reports that the rearrangement of 204 also proceeds to some extent through a boat-like TS, *Scheme 44.* Aldehydes 208 and
209 both result from a chair-like TS, but \textit{E; anti} aldehyde 210 results from a boat-like TS.

\textbf{Scheme 44}

\begin{align*}
\text{HO} & \quad \text{KH} \quad \text{DMSO} \\
\text{204} & \quad \rightarrow \\
\text{205, 206, 207} & \\
\text{208} & \quad \text{Z; syn} \quad 57\% \\
\text{209} & \quad \text{E; syn} \quad 31\% \\
\text{210} & \quad \text{E; anti} \quad 12\%
\end{align*}

In an extension to their earlier work, Lee and co-workers prepared a series of compounds to further investigate substituent effects, \textit{Figure 11}.$^{53}$

\textbf{Figure 11}

\text{ratio of equatorial : axial in AOC rearrangement oxyanion : oxyanion}

\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{Ph} \\
\text{211} & \quad 45:55 & \quad 63:37 & \quad 35:65 \\
\text{212} & \\
\text{213} & \\
\text{OH} & \quad \text{OH} & \quad \text{OH} \\
\text{214} & \quad 62:38 & \quad 69:31 & \quad 81:19 \\
\text{215} & \\
\text{216} & 
\end{align*}

Lee drew the following conclusions from these results, and the previous work of Paquette and Nakai:
1. There is a modest bias for a pseudoaxial oxyanion for substrates with $E$-alkyl and aryl substituents at C-1.
2. Equatorial oxyanion orientation becomes favoured with $Z$-substituents at C-1 and substituents at C-5; very efficient chiral transfer is possible with sterically demanding groups at these positions.
3. Substituents at C-4 tend to be oriented equatorially in the absence of other effects.

His conclusions are summarised in Figure 12.

**Figure 12**

Conclusion 2 should be viewed with some caution with respect to substituents at C-5 as the ratios for a methyl substituent (212) and a tert-butyl group (214) are almost identical. The tert-butyl group can obviously move to avoid a severe steric interaction. Good stereocontrol is only achieved via this 1,3-interaction when bulky groups are rigidly held in place, and point towards the oxyanion when it adopts an axial orientation. The gem-dimethyl groups on the cyclohexene ring in Lee's first example illustrate this point nicely, see Scheme 38.

In work closely related to that of Nakai, Greeves and co-workers have reported a one-pot [2,3]-Wittig/AOC rearrangement tandem process, Scheme 45. For example, when bis allylic alcohol 221 is treated with potassium hydride and 18-crown-6 in DMSO, [2,3]-Wittig rearrangement to give alkoxide 222 is followed by AOC rearrangement to give aldehydes 223-225.
The major syn-isomers 223 and 224 are formed through chair-like transition states, while the anti-isomer 225 is derived from a boat-like transition state. This is an interesting result in view of the fact that Nakai only observed the operation of a boat-like transition state for the rearrangement of anti substrates. Syn substrates rearranged exclusively through a chair-like transition state. Greeves later reported the results of extensive investigations into substituent effects on this one-pot process.\textsuperscript{46c} For example, [2,3]-Wittig/AOC rearrangement of substrate 226 resulted, via 227, in the formation of aldehyde 228 as the sole product, Scheme 46.

The significance of this result is shown in Scheme 47. The rearrangement of 225 proceeds solely through reacting conformation 229, containing an axial oxyanion. In reacting conformation 230 with an equatorial oxyanion, the isopropyl
group experiences 1,3-diaxial interactions large enough to force the oxyanion into an axial orientation.

**Scheme 47**

![Scheme 47](image)

Finally, several reports have been made recently on the use of chiral auxiliaries in acyclic oxy-Cope and silyloxy-Cope rearrangements. A representative example is given below, **Scheme 46**.

**Scheme 46**

![Scheme 46](image)

The transition state geometry is controlled by the bulky chiral auxiliary adopting an equatorial orientation. Indeed, the steric bulk of the silyl group makes little difference, as the TMS ether rearranges more slowly and with poorer selectivity. A drawback of this approach is the requirement for high temperatures...
and sealed tube techniques. (The anionic rearrangement of these systems was attempted, but resulted in retro-aldol reaction.)

**Conclusion**

The exciting work detailed in this review clearly demonstrates that with careful placement of suitable substituents, good stereocontrol is possible in the anionic oxy-Cope rearrangement of acyclic substrates. The review also serves to place our work on the rearrangement of substrates containing an enol ether in context.

**1.5 Choice of enol ethers as substrates**

Prior to our work, only five examples of the rearrangement of substrates containing enol ethers had been reported. In addition, only two of these examples bear the same 1,3-relationship between the enol ether and the oxyanion as in 237, *Figure 13*.

*Figure 13*

![Scheme 47](image)

However, all of the examples are cyclic, and the orientation of the oxyanion during rearrangement is controlled by the ring(s) present in the substrate. We were therefore interested in investigating whether the transition state geometry of the AOC rearrangement of an acyclic substrate could be controlled by the oxygen atom of the enol ether. The type of controlling interaction we envisaged is illustrated in *Scheme 47*. 
In transition state (TS) 238, the oxyanion would experience both a 1,3-steric and a strong repulsive electrostatic interaction with the enol ether oxygen. In TS 239 these interactions are not present, so TS 239 should be favoured over TS 238.

**Substituent effects**

We considered the effect that substituents on the 1,5-hexadiene-3-ol framework would have on the proposed controlling interaction. In particular, we hoped that by defining the relative stereochemistry between the oxyanion and a substituent at C-4, good stereocontrol could be achieved in the rearrangement of acyclic enol ether substrates, *Schemes 48a and 48b.*

**Scheme 48a**
**Scheme 48b**

Syn alkoxide 240 can rearrange through either transition state (TS) 241, with a pseudoequatorial oxyanion, or through TS 242, with a pseudoaxial oxyanion. Similarly, anti alkoxide 245, can rearrange through TS 246 or TS 247. Examination of the transition states for syn alkoxide 240 shows that TS 241 should be favoured over TS 242, since TS 241 contains only one large 1,3-pseudodiaxial interaction, (between R\(^1\) and OR\(^5\)), while TS 242 contains a total of four (between the oxyanion and R\(^1\) and OR\(^5\), between R\(^3\) and R\(^4\), and between OR\(^5\) and R\(^1\)). The repulsive electrostatic interaction between the enol ether and the alkoxide is also present in TS 242. This means that the difference in energy between these two competing transition states would be large, and so the population of TS 241 would be far greater than that of TS 242; hence only one diastereomer (243) should be produced in the reaction. The situation for anti alkoxide 245 is not so clear-cut. TS 246 contains two large 1,3-interactions (between R\(^1\) and OR\(^5\) and between R\(^3\) and R\(^4\)), while TS 247 contains three (between the oxyanion, R\(^1\) and OR\(^5\)). TS 247 also contains the electrostatic interaction. This means that the difference in energy between these two competing transition states should be relatively small, and so
the bias in favour of the production of 248 over 249 would be relatively small. We therefore decided to investigate primarily the rearrangement of syn alkoxides.

1.6 The Intramolecular Aldol Reaction

The presence of an alkoxide substituent at C-5 performs two functions in the AOC rearrangement of substrate alcohols 237. In addition to the electrostatic interaction discussed above, the alkoxide also generates new functionality, as illustrated in Scheme 49.

Scheme 49

The initial product of the rearrangement is enolate 250. Quenching with an electrophile gives 251 which contains a new enol ether and an aldehyde. The newly formed enol ether is ideally placed to take part in an intramolecular aldol reaction with the aldehyde to give hydroxycyclohexanone 252.

This type of cyclisation is termed a 6-(enolendo)-exo-trig process. Similar intramolecular aldol reactions are some of the most important synthetic (e.g. Robinson annulation) and biological transformations (e.g. aromatic ring formation in polyketide synthesis.) However, prior to our work, the 6-(enolendo)-exo-trig cyclisation of an enol ether onto an aldehyde was unknown. Furthermore, no systematic study of the orientation of the hydroxyl group produced in the reaction had been reported.

The selectivity may be determined by face selectivity on a ring. For example, the enolate generated from the methyl ketone in 253 can react only with
the lower face of the cyclooctanone carbonyl group to give bicyclic alcohol 254, 
Scheme 50.5

Scheme 50

If the selectivity is not determined by a ring, the hydroxyl can be axial or equatorial. Reported selectivities have varied from only axial69 to mostly equatorial,60 Scheme 51.

Scheme 51
For example, alcohol 256 with an axial hydroxyl, is the sole product of the intramolecular aldol reaction of ketone 255, while the tandem Michael addition/intramolecular aldol reaction of ketone 257 with vinyl formaldehyde gives a mixture of axial and equatorial isomers.

Finally, Ley\textsuperscript{61} has reported a 6-(enolexo)-exo-trig intramolecular aldol reaction between an enol ether and an acetal under acidic conditions, \textit{Scheme 52}. Again, a mixture of isomers 261 – 263 is produced.

\textbf{Scheme 52}
Synthesis of substrates for rearrangement

2.1 Initial Studies

To test the efficacy of our route, our initial studies of the AOC rearrangement focused on the construction of some simple substrates 276-278, Scheme 53.

Scheme 53

\[
\begin{align*}
264 \quad R &= \text{CH}_3 \\
265 \quad R &= \text{iPr}
\end{align*}
\]

\[
\begin{align*}
266 \quad R &= \text{CH}_3 \\
267 \quad R &= \text{iPr}
\end{align*}
\]

\[
\begin{align*}
268 \quad R &= \text{CH}_3, P = \text{TBS} \\
269 \quad R &= \text{iPr}, P = \text{TBS} \\
270 \quad R &= \text{iPr}, P = \text{TES}
\end{align*}
\]

Reagents and conditions: i) LDA, THF, -78 °C, 40 mins, b) E-cinnamaldehyde, THF, -78 °C, 30 mins; ii) TBSCI or TESCI, iPrEtN, DMF, rt, 17 h; iii) TiCl4, TMEDA, Zn, PbCl2, R'CBr2, THF, 0 °C-rt; 4-17 h; iv) TBAF, 4 Å MS, THF, rt, 2-4 h.

Cinnamaldehyde was reacted with the lithium enolate of the appropriate acetate ester to give the aldol products 266 and 267 in quantitative yield. Protection of the aldols with tert-butyldimethylsilyl chloride (TBSCI) or triethylsilyl chloride (TESCI) gave silyl ethers 268-270 in excellent yield (80-97% yield).
Takai alkylidenation of the protected aldols afforded enol ethers 271-275 in 50-80 % yield and finally, deprotection using tetrabutylammonium fluoride (TBAF) gave the substrate alcohols 276-278 in 50-80 % yield.

The Takai reaction initially proved problematic. Alkylidenation of esters 268 and 269 using commercially available 1 mol dm$^{-3}$ titanium tetrachloride solution in dichloromethane (DCM) as described by Takai was unreliable in our hands, giving poor yields or no reaction. We overcame this problem by instead using neat titanium tetrachloride. This modification resulted in the smooth and reliable formation of enol ethers in moderate to good yield. We also found that protection of the hydroxyl group was vital to the success of the reaction. Hoping to avoid the need for protection/deprotection steps, we subjected the unprotected aldols to alkylidenation conditions. However, even when using double the normal ratio of reactants to ester, we were unable to isolate the product enol ethers, or even unreacted starting material. We believe that due to the high strength of Ti-O bonds the alcohol becomes irreversibly bound to titanium and so, even if alkylidenation does take place, the product is not released from the metal during work-up. The type of silicon protecting group used made little difference to the overall yield of the process. As mentioned previously, the Takai reaction is $Z$ selective. We found that the reaction proceeded with good selectivity; enol ethers 274 and 275 were both formed with an $E:Z$ ratio of 15:85. The isomers were separated after deprotection by column chromatography. A fuller discussion of the determination of the $E:Z$ ratios produced in the Takai reaction is given in Section 2.3.

Deprotection surprisingly proved to be the poorest yielding step in our sequence. The reasons for this are unclear, but may be due in part to the loss of material during the repeated chromatography required to purify the product alcohols.

We also employed a route using trimethylsilyl (TMS) as the alcohol protecting group. This avoided the need for purification until the final step, but did not allow the isolation and characterisation of the intermediate compounds, *Scheme 54.*
Scheme 54

\[ \text{OEt} \xrightarrow{\text{i}} \text{Ph} \xrightarrow{\text{ii}} \text{R} \]

Scheme 54

\[ \text{OEt} \xrightarrow{\text{i}} \text{Ph} \xrightarrow{\text{ii}} \text{R} \]

Reagents and conditions: i) LDA, THF, -78°C, 40 min; ii) E-cinnamaldehyde, THF, -78°C, 30 min; iii) TMSCI, Et,PrgN, THF, rt, 17 h; iv) TiCl₄, TMEDA, Zn, PbCl₂, RCHBr₂, THF, 0°C-rt, 4-17 h; v) TBAF, THF, rt, 1 h.

The overall yield of alcohols 284 and 285 (34-34 %) was comparable to that obtained for TBS/TES protection.

2.2 Other substrates synthesised

Having developed our route to AOC substrates 286, we were able to readily alter the substituents on the 1,5-hexadien-3-ol framework, Figure 14.

Figure 14

2.2.1 Aliphatic substitution at C-1

By employing E-hexenal as the starting aldehyde, we synthesised substrate alcohol 290, bearing a propyl chain at C-1, Scheme 55.
Reagents and conditions i a) LDA, THF, -78 °C, 40 mins, b) E-hexenal, THF, -78 °C, 30 mins; ii TESCl, 1Pr2EtN, DMF, rt, 17 h; iii TiCl4, TMEDA, Zn, PbCl2, CH2Br2, THF, 0 °C-rt; 4-17 h; iv TBAF, 4 Å MS, THF, rt, 2-4 h.

The aldol 287 (89 %) was protected to give TES ether 288 in 88 % yield. Takai methylenation (85 %) followed by deprotection gave alcohol 290 in 38 % yield.

2.2.2 Endocyclic C-1 – C-2 double bond

In order to investigate the effect of including one of the double bonds in a ring and to gain access to synthetically interesting decalin compounds, we constructed the substrates 295 and 296, Scheme 57. 1-Cyclohexene-carboxaldehyde 253 was synthesised via Shapiro reaction of the tosyl hydrazone of cyclohexanone, Scheme 56.
Scheme 57

\[
\begin{align*}
&\text{AcO}^\text{Pr} \quad \text{i} \quad \text{OH} \quad \text{TESO} \\
&294 \quad \text{i} \quad 295 \\
&\text{OH} \quad \text{TESO} \\
&298 \quad \text{R= H} \\
&299 \quad \text{R= CH}_3 \\
&\text{296} \quad \text{R= H} \\
&\text{297} \quad \text{R= CH}_3
\end{align*}
\]

Reagents and conditions i a) LDA, THF, -78°C, 40 min, b) 1-cyclohexenecarboxaldehyde 293, THF, -78°C, 30 min; ii TMSCl, Et\text{Pr}_2N, THF, rt, 17 h; iii TiCl_4, TMEDA, Zn, PbCl_2, RCHBr_2, THF, 0°C-rt, 4-17 h; iv TBAF, THF, rt, 1 h.

Aldol 294 (92 %) was protected as its TES ether (85 %). Takai alkylidenation gave enol ethers 296 (51 %) and 297. (297 was formed with a Z:E ratio of 88:12, see Section 2.3.) Finally, deprotection gave enol ethers 298 (60 %) and 299 (as a similar mixture of isomers, 58 % over two steps). Further chromatography was required to obtain enol ether 299 as a single Z-isomer.

2.2.3 Substitution at C-4

The introduction of an additional stereocentre at C-4 (ie R^3 ≠ H in AOC substrate 286) raises the question of stereoselectivity during the aldol reaction. The formation of up to four stereoisomers is possible, eg the aldol reaction between cinnamaldehyde 300 and isopropylpropionate 301 would give rise to stereoisomers 302-305, Scheme 58.
Two types of stereoselectivity are possible. *Diastereoselectivity* in which the relative 2,3-stereochemistry is controlled to be either *syn* or *anti* and *enantioselectivity* in which the absolute stereochemistry at either C-2 or C-3 is controlled. Many methods have been developed for controlling both types of selectivity. We were interested in the AOC rearrangement of both *syn* and *anti* alcohols. For reasons discussed in the Chapter 1, we were particularly interested in *syn* aldol products. We therefore used an enantioselective reaction to obtain one enantiomer of a *syn* aldol and used an unselective aldol to obtain a mixture of racemic *syn* and *anti* alcohols in the hope that these could be separated, and used for comparison with the enantiopure products.

**Unselective aldol reaction**

Aldol reaction of *E*-cinnamaldehyde and isopropyl propionate gave a 1:1 mixture of *syn* and *anti* diastereomers 307. TES protection, followed by Takai alkylidenation using 1,1-dibromoethane gave enol ethers 309. (It is interesting to note that only the *Z* enol ether was formed, see *Section 2.3.*) Deprotection gave substrate alcohols 310a and 310b in 33 % overall yield from cinnamaldehyde, *Scheme 59.*
The boron-mediated aldol reaction of chiral oxazolidinones 311, with aldehydes developed by Evans and coworkers gives excellent levels of diastereo- and enantioselectivity, and is widely used in synthesis. *Scheme 60.* We therefore chose to use this reaction as a route to enantiopure syn aldols.

The origin of the stereocontrol observed in the Evans aldol reaction is illustrated in *Scheme 61.* When acyl oxazolidinone 311 is treated with dibutylboron triflate in the presence of triethylamine, Z-enolate 313 is formed. (The formation of the corresponding *E* enolate is strongly disfavoured by allylic strain.) When the aldehyde is added it coordinates to the boron atom. This causes the release of the imide carbonyl, which in turn leads to rotation of the chiral auxiliary to minimise electrostatic repulsion between the oxygens.
The bulky benzyl substituent on the oxazolidinone now blocks the bottom face of the enolate and fixes the facial selectivity. The aldol reaction then proceeds through a chelated chair-like transition state, with the hydrogen of the aldehyde adopting a pseudoaxial position (316) to give the enantiomerically pure syn aldol product 312.

Scheme 61

Our synthesis of enantiopure anionic oxy-Cope substrate 324, began with acylation of the commercially available oxazolidinone auxiliary 317 using propionyl chloride, to give 318 in 97 % yield, Scheme 62.
Reagents and conditions i) BuLi, THF, −78 °C, b) propionyl chloride; ii) Bu₂BOTf, Et₃N, DCM b) E-cinnamaldehyde, −78 – 0 °C; iii) TBSCI, EtPr₂N, DMF, rt, 17 h; iv) a) H₂O₂, LiOH, THF-H₂O, b) Na₂SO₃; v) PPh₃, DEAD, EtOH, THF, −40 °C – rt, 17 h; vi, vii as Scheme 47.

The boron-mediated reaction of 318 with E-cinnamaldehyde gave the known aldol product 319 as one diastereomer by ¹H NMR spectroscopy, but in only 55 % yield. Attempts to improve the yield by using freshly prepared dibutylboron triflate met with no success. Protection of the hydroxyl group with TBSCI gave silyl ether 320 as a solid in 93 % yield. TES Protection was also used, but gave an oil which was less easy to isolate and purify than the corresponding TBS compound. Removal of the chiral auxiliary with hydroperoxide anion under standard conditions⁶⁵ (5:1 THF-water, 0 °C) was unsuccessful, returning only unreacted starting material. After some experimentation, it was found that changing the ratio of THF-water to 10:1, and
carrying out the reaction at rt gave the desired acid 321 in 83 % yield. The chiral auxiliary was not recovered - under these conditions, endocyclic attack of hydroperoxide anion on the oxazoline carbonyl group occurred.

The esterification of acid 321 without epimerisation at C-2 proved difficult. We initially attempted to form the isopropyl ester using carbonyldiimidazole (CDI) 325 and isopropanol in dimethylformamide (DMF).66 This resulted in the formation of the imidazoamide 326 which was identified by its \(^1\)H NMR spectrum, Scheme 63. When 326 was treated with additional isopropanol and N,N-dimethylaminopyridine (DMAP) (without further characterisation), esterification with epimerisation occurred. Treatment of acid 321 with dicyclohexylcarbodiimide (DCC) and DMAP in isopropanol also resulted in epimerisation.

Scheme 63

We abandoned attempts to form the isopropyl ester, and instead tried to form the ethyl ester. Esterification with CDI and ethanol in THF was successful, but proceeded in only 50 % yield. Finally, we found that Mitsunobu conditions\(^67\) gave the desired ethyl ester 322 in 79 % yield.

Takai alkylidenation of ester 322 using 1,1-dibromoethane (81 %), followed by deprotection (63 %) gave the enantio-and diastereomerically pure AOC substrate 324.
2.3 Selectivity in the Takai Reaction

2.3.1 Identification of isomers

The $E$ and $Z$ enol ethers formed in the Takai reaction could be identified by their $^{13}$C NMR spectra. $E$-enol ethers $E-278$, $E-285$ and $E-299$ gave signals for the carbon atom $\beta$ to the alkoxy substituent in the enol ether functional group at $\sim 95$ ppm, while $Z$-enol ethers $Z-278$, $Z-285$, $Z-299$, $310a/b$ and $324$ gave corresponding signals at $\sim 110$ ppm. Table 1 gives a full list of the diagnostic signals used. The enol ethers were separated after removal of the silyl protecting group. The $^1$H NMR spectrum of each pure isomer could then be used to assign the corresponding signals in the spectrum of the crude reaction product. Integration of the signals due to the enol ether vinylic protons of each isomer provided an easy and reliable way of determining the $E:Z$ ratio, as the signals corresponding to these protons in all the enol ethers we synthesised did not overlap with each other, or other signals in the spectrum.

2.3.2 Comments

Table 1 shows the $E:Z$ ratios in which the enol ethers were formed. The $E:Z$ ratio is unaffected both by the type of silyl protecting group and by the type of ester used. A large increase in selectivity is only observed when there is a tertiary carbon atom $\alpha$ to the ester functionality, in which case the $E$-isomer is not observed in the $^1$H NMR spectrum.
<table>
<thead>
<tr>
<th>Enol ethers</th>
<th>$\delta_c$ ppm</th>
<th>Ratio Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 278" /></td>
<td>110.6 94.8</td>
<td>85:15 from TBS ether 85:15 from TES ether</td>
</tr>
<tr>
<td><img src="image" alt="Structure 285" /></td>
<td>109.5 93.7</td>
<td>85:15 from TMS ether</td>
</tr>
<tr>
<td><img src="image" alt="Structure 299" /></td>
<td>110.3 94.2</td>
<td>88:12 from TES ether</td>
</tr>
<tr>
<td><img src="image" alt="Structure 310a/b" /></td>
<td>108.0 –</td>
<td>&gt;98:2 from TES ether</td>
</tr>
<tr>
<td><img src="image" alt="Structure 324" /></td>
<td>107.3 –</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 324" /></td>
<td>110.3 –</td>
<td>&gt;98:2 from TBS ether</td>
</tr>
</tbody>
</table>

### 2.4 Alternative routes to $\beta$-hydroxy enol ethers

Several alternative routes to $\beta$-hydroxy enol ethers have been reported. Preliminary results in this area were reported by Kuwajima and co-workers in 1993.\(^6\) They described the dimethylaluminium chloride mediated ene reaction of enol ether 328 with cyclohexanecarboxaldehyde 327 to give hydroxy enol ether 329, *Scheme 64.*
Also in 1993, Ciufolini reported the Ytterbium-catalysed ene reaction of aldehydes with vinyl ethers. Aldehydes 330 were reacted with excess methoxypropene 331 in the presence of 0.5 mol % Yb(fod)$_3$ to give protected adducts 333, via the ene products 332. When a small amount of potassium carbonate was added to the reaction mixture, the intermediate alcohols could be isolated, Scheme 65.

Scheme 65

When an $\alpha,\beta$-unsaturated aldehyde is used, the alcohol products 332 correspond exactly to the type of compounds that we use as the substrates for AOC rearrangement. Indeed, Ciufolini has made compound 276 by this method. We made a brief attempt to utilise this methodology for our own work, but were unable to reproduce the reported results.

Finally, Carreira has reported the use of chiral titanium complex 335, which catalyses the ene reaction of aldehydes with methoxypropene. For example, aldehyde 334 could be converted into ketone 337 in 99 % yield and 91 % ee via the enol ether 336, Scheme 66.
Enol ethers 336 can be isolated if the acidic work-up is avoided. Carreira reports that the reaction of α,β-enals, which would give AOC substrates directly, do not proceed in good yield, although good enantioselectivity is achieved. In fact, the reason proposed for the low yields in these cases is oxy-Cope rearrangement of the hydroxy enol ethers and subsequent decomposition.

Although these routes offer an attractive method for the formation of substrates for AOC rearrangement, they lack the flexibility for the stereocontrolled introduction of substituents which our methodology possesses.

2.5 Summary

We have developed an efficient and versatile route to hydroxy enol ethers. The compounds that we have constructed using this route are summarised in Figure 15.
How we used these alcohols to develop our understanding of the AOC rearrangement of acyclic substrates is described in the next chapter.
The anionic oxy-Cope rearrangement

3.1 Preliminary investigations

Preliminary experiments on the anionic oxy-Cope rearrangement were carried out using alcohol 276, Scheme 67. Attempted rearrangement of 276 using previously published conditions, Table 2, resulted in the formation of a complex mixture of products.

Scheme 67

We thought at first that this was due to the basic quench, which we hoped would allow the isolation of aldehyde 338. However, switching to an acid quench in an attempt to induce the intramolecular aldol reaction to give alcohol 339 also failed to produce a clean reaction.

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Quench</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH, 18-C-6</td>
<td>THF</td>
<td>NaHCO₃</td>
<td>complex mixture</td>
<td>49</td>
</tr>
<tr>
<td>KH, 18-C-6</td>
<td>THF</td>
<td>NH₄Cl</td>
<td>complex mixture</td>
<td>49</td>
</tr>
</tbody>
</table>

Attempted rearrangement of the isopropyl enol ether Z-278 using the published methods shown in Table 3, also failed to produce a clean reaction, Scheme 68.
Scheme 68

Table 3

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Quench</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH, 18-C-6</td>
<td>THF</td>
<td>NaHCO₃</td>
<td>complex mixture</td>
<td>49</td>
</tr>
<tr>
<td>KH, 18-C-6</td>
<td>THF</td>
<td>NH₄Cl</td>
<td>complex mixture</td>
<td>49</td>
</tr>
<tr>
<td>KH, 18-C-6</td>
<td>DMSO</td>
<td>NH₄Cl</td>
<td>complex mixture</td>
<td>46b</td>
</tr>
<tr>
<td>KHMDS, 18-C-6</td>
<td>THF</td>
<td>TMSCl</td>
<td>TMS ether of SM</td>
<td>42</td>
</tr>
<tr>
<td>KDA</td>
<td>THF</td>
<td>NH₄Cl</td>
<td>no reaction</td>
<td>72</td>
</tr>
</tbody>
</table>

After some experimentation, the key to the reaction was found to be a switch of solvent to dimethoxyethane (DME) and the use of a more strongly acidic quench, Scheme 69.

Scheme 69

Enol ethers 277 and Z-278 were treated with 2.5 equivalents of potassium hydride and 2 equivalents of 18-crown-6. After 3 h at rt, the reaction was quenched by the addition of 1 mol dm⁻³ aqueous hydrochloric acid.
Gratifyingly, we observed the formation of the desired β-hydroxycyclohexanones 339 and 341 in 80 – 91 % w/w as essentially the only products after extraction into ether. Complete conversion from the 1,5-dienes 277 and Z-278 was shown by the absence of signals in the region δ 5 – 6 ppm in the $^1$H NMR spectrum of the crude mixture.

The stereochemistry and isolation of the individual products resulting from this one-pot rearrangement/cyclisation reaction will be discussed in the next section.

3.1.2 Stereochemistry of the rearrangement/cyclisation reaction

The origins of the different stereochemical relationships generated during the reaction sequence are illustrated below, Scheme 70.

Scheme 70

The orientation of the hydroxyl group is determined solely by the stereochemistry of the intramolecular aldol reaction. The 5,6 relative stereochemistry is established during the AOC rearrangement and reflects whether the reacting conformation is chair-like 345, or boat-like 348 Scheme 71.
If the rearrangement proceeds through a chair-like transition state resulting from reacting conformation 345, the substituents at C-5 and C-6 in the product cyclohexanone 347 adopt an anti relationship. However, if the rearrangement proceeds through a boat-like transition state resulting from reacting conformation 348, the C-5 and C-6 substituents are formed with a syn relationship. The ratio of syn and anti isomers formed in the rearrangement therefore reflects the populations of the two transition states.

A more detailed picture of the stereochemical outcome of the reactions described in Scheme 69 is given in Scheme 72.

The ratios shown were obtained from the AOC rearrangement of geometrically pure enol ether substrates 278 and 351 and were determined by integration of the signals corresponding to the CHO protons in the $^1$H NMR spectra of the crude reaction mixtures. The crude mixture of isomers was obtained as a solid in 80 – 100 % mass balance after extraction into ether and work-up. Pure samples of the major products of the rearrangement of 277 and 278, ketones 352 and 354 were isolated in 43 % and 31 % yield by trituration with ether. Separation of the other isomers proved to be more difficult, as they were unstable to column chromatography on silica or basic alumina. Chapter 4 describes in full how all these compounds were separated and characterised.
Scheme 72

Reagents and conditions i KH (2.5 equiv.), 18-crown-6 (2 equiv.), DME, rt, 3h; ii 1 mol dm$^{-3}$ aqueous HCl, 0 °C to rt, 30 min.

3.1.3 Results

3.1.3.1 Chair/boat ratio

Rearrangement of Z-278 gave a ratio of 5,6-anti hydroxycyclohexanones 353 and 355 to 5,6-syn hydroxycyclohexanone 354 of 88:11. Therefore there is an 88:11 bias in favour of a chair-like transition state. Similarly, compound E-278, rearranges predominantly through a chair-like transition state, as 354 is the major product, Scheme 73.
Since C-6 is an epimerisable centre, it was essential to prove that the 5,6-syn/5,6-anti ratio of the products was a true reflection of the populations of the chair and boat-like transition states, and not simply the result of post-rearrangement epimerisation. To rule out the latter possibility, we performed a deuterium labelling experiment, Scheme 74.

**Scheme 74**

When we quenched the AOC rearrangement reaction with a 1 mol dm\(^{-3}\) solution of DCI, we found that deuterium was incorporated only at position 4 in the major isomer. This was evident from the loss of couplings to CHOH and CHPh, and a reduction in the size of the signal for the C-4 methylene in the \(^1\)H NMR spectrum of the product. The doublet due to the methyl group showed no trace of collapse to a singlet, and the C-2 protons were also unaffected, Scheme 75. The high resolution mass spectrum of 356 showed the incorporation of only one deuterium atom.
This result also highlights a contradiction in our results for the rearrangement of Z-278 and E-278. Since there is no epimerisation, the ratio of products 353:355 should be the same in both cases. However, in the rearrangement of Z-278 the ratio is ~8:1, while for E-278 the ratio is 3:1. There are two possible explanations for this discrepancy.

1) The quench conditions for the two reactions were different

2) There is another signal under the CHOH of 355 in the $^1$H NMR spectrum of the crude reaction mixture, corresponding to 355a (Figure 16) and the true ratio of 353:354:355:355a is 24:67:3:5

The first possibility can be ruled out. The second is more likely, as the signal for CHOH of 355 is complicated and could be the result of two overlapping signals. There would be less than 1 % of 355a produced in the rearrangement of alcohols Z-278 and Z-285.
To investigate the effect of the size of the group attached to the enol ether oxygen, compounds $Z$-$285$ and $E$-$285$ were rearranged under the same conditions as above, *Scheme 76*.

**Scheme 76**

$Z$-$285$

\[
\begin{align*}
&\text{OH} \\
&\text{Ph} \\
&\text{OEt} \xrightarrow{\text{HO}^-} \\
&\text{353} \\
&\text{354} \\
&\text{355} \\
\end{align*}
\]


$E$-$278$

\[
\begin{align*}
&\text{OH} \\
&\text{Ph} \\
&\text{OEt} \xrightarrow{\text{HO}^-} \\
&\text{353} \\
&\text{354} \\
&\text{355, 355a} \\
&\text{+cyclohexenones} \\
\end{align*}
\]


*Reagents and conditions* i KH (2.5 equiv.), 18-crown-6 (2 equiv.), DME, rt, 3h; ii 1 mol dm$^{-3}$ aqueous HCl, 0 °C to rt, 30 min.

Alcohol $Z$-$285$ rearranged to give a slightly poorer ratio of products to that given by alcohol $Z$-$278$, while alcohol $E$-$285$ rearranged to give an essentially identical ratio of compounds to that given by alcohol $E$-$278$. We conclude that the bulk of the alkoxy group does not significantly affect the populations of chair and boat transition states.

Elimination of the hydroxyl group to give $\alpha,\beta$-unsaturated cyclohexanones was investigated. We initially thought that this would be a convenient way to measure the chair/boat ratios, as complication from the stereochemistry of the hydroxyl group would be eliminated. Unfortunately, we were unable to eliminate without also epimerising the C-6 centre, *Scheme 77*. Diastereomerically pure alcohol 353 gave an 87:13 mixture of cyclohexenones in 57 % yield.
Scheme 77

When the crude reaction mixture of the rearrangement of 278 was subjected to the above conditions, 360 and 361 were isolated in 51% yield over two steps, Scheme 78. This result shows that the rather poor yields obtained for the hydroxycyclohexanones are due to problems of isolation and are not a reflection on the efficiency of the transformation itself. Rearrangement, cyclisation and elimination of alcohol 277 gave cyclohexenone 362 in 61% yield over two steps, again a higher yield than the corresponding alcohol 352.

Scheme 78

3.1.3.2 The intramolecular aldol reaction

The results show a remarkable preference for the formation of an axial hydroxyl group. This was contrary to the expected formation of an equatorial hydroxyl, which we assumed would be more stable and therefore thermodynamically favoured. There are several possible explanations for this.
result. Firstly, orbital interactions in the transition state of the aldol reaction could favour an axial over an equatorial hydroxyl group, Figure 17.

**Figure 17**

An inspection of HOMO ($\pi$) – LUMO ($\pi^*$) orbital interactions for the formation of an equatorial 363 and an axial 364 hydroxyl group does not reveal any obvious bias in favour of one over the other. Modelling studies would be required to determine if HOMO-LUMO interactions of this type are significant.

Alternatively, the aldol reaction may proceed through a kinetically favoured, chelated transition state 365 Figure 18.

**Figure 18**

However, other sources of hydrogen bonding were plentiful in the reaction mixture. Furthermore coordination of the proton with the lone pairs of the oxygen atom of the enol ether is unlikely to favour a reaction where a positive charge develops on that oxygen. We focused instead on the stabilisation that could be provided by an axial hydroxyl group to the oxonium ion formed as the first step in the aldol reaction, Figure 19. A 1,4-interaction between the electron-rich oxygen and the electron-deficient carbon of the oxonium ion is possible when the hydroxyl is axial 366. Such an interaction is impossible when the hydroxyl lies equatorial 367. Intermediate structure 366 should therefore be favoured over 367.
To determine the validity of this explanation, modelling studies were carried out by Dr Jonathan Goodman of Cambridge University. The results of his calculations are shown below, *Figure 20*.

The first row of results were obtained using MM2*. These show that there is a modest bias in favour of an axial hydroxyl group. (1.2 kJmol\(^{-1}\) corresponds to ratio of approximately 2:1 at room temperature.) The reason for this, according to the force field, is an electrostatic interaction between the lone pairs of the hydroxyl group and the carbon of the carbonyl group, as illustrated in *Figure 19*. Interestingly, the results in the second row, obtained from the semi-empirical AM1 method favour an equatorial hydroxyl group. Dr Goodman believes this is the wrong answer, as this method is unreliable for interactions at approximately van der Waals separation. The highest level of theory used was the *ab initio* RHF/3-21G. This method again favours an axial hydroxyl group.
The most interesting results are given in the third row. These refer to structures bearing an oxonium ion with an isopropyl group (e.g., 366 and 367). AM1 now favours an axial hydroxyl group, which strongly suggests that these are the preferred conformations, as the errors in the AM1 method work against this result.

The mechanism can be summarised as follows, *Scheme 79.*

Scheme 79

Aldehyde 340 is protonated to give 368. Intramolecular aldol reaction then gives 366 or 367. These two intermediates can then rapidly interconvert via a retro aldol/aldol process in favour of 366. If interconversion is slow, then the preference for 366 is kinetic, and results from stabilisation of the transition state leading to 366 by the developing electrostatic interaction shown. Hydrolysis of the oxonium ions then leads to the product hydroxycyclohexanones 353 and 355. In order to investigate whether the final ratio of products obtained in the reaction was thermodynamic or kinetic, alcohol 353 was treated with 1 equivalent of LDA at −78 °C and allowed to warm to
room temperature. The ratio of isomers obtained was different to that produced in the reaction, Scheme 80. This result suggests that the ratio is kinetic, although the ratio obtained in this experiment is due to equilibration of oxyanions, not alcohols.

Scheme 80

3.1.4 Summary

Our initial studies have shown that although the AOC rearrangement of acyclic substrates containing an enol ether proceeds predominantly through a chair-like transition state, a boat-like transition state also operates to some extent. We have also demonstrated that the intramolecular aldol reaction exhibits a strong preference for the formation of an axial hydroxyl group. This preference is explained in terms of an electrostatic interaction in the transition state leading to oxonium ion 366.
3.2 Formation of decalins

3.2.1 Introduction

One of the initial aims of this research was to produce analogues of the powerful antimalarial drug Artemesinin\textsuperscript{73} 369, and other highly functionalised rings, such as Forskolin\textsuperscript{74} 370, which affects cardiovascular functions and intracellular transport, \textit{Figure 21}.

\textbf{Figure 21}

\begin{center}
\includegraphics[width=\textwidth]{figure21}
\end{center}

We aimed to produce simple analogues of these highly complex natural products using our methodology, \textit{Scheme 81}.

\textbf{Scheme 81}

\begin{center}
\includegraphics[width=\textwidth]{scheme81}
\end{center}

Substrates of type 371 could lead to analogues of both natural products. Straightforward AOC rearrangement/aldol cyclisation would give analogues of Forskolin, while the more ambitious AOC rearrangement with oxygen quench could install the unusual peroxy bridge found in Artemesinin.
3.2.2 Results

Armed with the conditions developed in our initial studies, we were confident that the rearrangement of substrates 298 and 299, which were synthesised as described in Chapter 2, would present no problems. However, when subjected to the conditions that we found were successful for the rearrangement of the previous set of substrates, no reaction took place, *Scheme 82*.

**Scheme 82**

![Scheme 82](image)

We were at first puzzled by this result. However, the stereoelectronic properties of 298 and 299 are very different to those of substrates with only a phenyl group at C-1. We tried several different sets of conditions, all of which resulted in failure, *Table 4*.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>KH, 18-C-6, DME, 50 °C, 1 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>298</td>
<td>KH, 18-C-6, DME, rt, 2 h, 50 °C, 3 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>299</td>
<td>KH, 18-C-6, THF, rt, 17 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>299</td>
<td>KH, 18-C-6, DMSO, rt, 50 °C, 5 h</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

We therefore turned our attention to the rearrangement of 290, which was more readily available than 298 and 299, and which we thought would possess similar electronic properties to these compounds. Again rearrangement of was attempted under several different conditions, *Table 5*. 

74
<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>KH, 18-C-6, DME, rt, 17 h, then reflux 8 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>KH, 18-C-6, THF, rt, 17 h, then reflux 8 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>KH, 18-C-6, THF, reflux, 4 h</td>
<td>some rearranged product, some decomposition</td>
</tr>
</tbody>
</table>

Finally, the best conditions were found to be long reaction times at ambient temperature. (An extra 0.5 equivalents of KH and 18-C-6 were also used.) These conditions avoided decomposition, but allowed rearrangement to take place, Scheme 83.

**Scheme 83**

![Scheme 83](image)

The β-hydroxycyclohexanone 375 was formed in good yield and with an axial:equatorial hydroxyl ratio of 90:10. With these conditions in hand, we returned to the rearrangement of 298 and 299, Scheme 84.

**Scheme 84**

![Scheme 84](image)

Enol ether 299 rearranged after 2 days at room temperature to give 376 in a crude yield of 74 % as a mixture of several isomers. The stereochemistry of the different isomers was not determined rigorously, although characteristic narrow signals in the $^1$H NMR spectrum at δ 4.4-4.5 ppm for axial hydroxyl groups were observed. The reaction was repeated using both 298 and 299 as substrates. However, the reliable formation of the target β-hydroxycyclohexanones was not achieved. Rearrangement appeared to have
taken place by TLC analysis, but when the reaction was worked-up as above, no product was isolated. In an attempt to separate the rearrangement and cyclisation reactions, we decided to quench the reaction with TBSCI, and so trap the enolate as its silyl enol ether, *Scheme 85*.

**Scheme 85**

When 298 was treated with KH and 18-C-6 as before, TLC showed that rearrangement had taken place after 48 h at rt. The reaction was then quenched at -78 °C by the addition of TBSCI. After work-up, the ¹H NMR spectrum of the crude material showed no evidence for the formation of the desired silyl enol ether 377. However, evaporation of the NMR solvent and addition of hexane to the residue resulted in the formation of a white solid, which was identified as the cyclohexanone 378. The isolated yield of this compound was < 10 %. Another attempt to isolate a silyl enol ether was made using compound 299 and TBSOTf as the silylating agent, *Scheme 86*.

**Scheme 86**
The rearrangement of 299 took place over 3 days at room temperature, and was quenched by the addition of TBSOTf at −78 °C. Gratifyingly, the $^1$H NMR spectrum of the crude reaction product showed evidence for the formation of the desired silyl enol ether 379. [Singlet at $\delta$ 5.97 ppm corresponding to CH(OTBS).] Subsequent chromatography on neutral alumina gave a mixture of 379 and the hydrolysed product 380, in 43 % combined yield. It is interesting to note that in compounds 379 and 380, the substituent on the cyclohexane ring adopts an axial orientation, Figure 22.

Figure 22

![Figure 22](image)

This effect is due to 1,3-allylic strain$^{75}$ as illustrated in Figure 23. When the substituent lies in an axial orientation, this interaction is minimised. However, when the substituent lies in an equatorial position 381, the interaction shown becomes very large, and so this conformation is disfavoured.

Figure 23

![Figure 23](image)

The enol ether in compound 379 is more susceptible to hydrolysis than the silyl enol ether. This is probably because the quaternary carbon of the silyl enol ether double bond, which has to be protonated during hydrolysis, is extremely hindered and therefore resistant to attack by electrophiles. This is useful, as it allows the two enol ether systems to be differentiated chemically.
This reaction was repeated, again with 299, and also with 298 as the substrate. However, as with the simple acidic quench, the results obtained were not reliable. The reasons for this are unclear, but further work in this area should solve these problems.

3.2.3 Discussion

These results show that aliphatic substitution at C-1 significantly retards the rate of rearrangement when compared with phenyl substitution at the same position. This effect can perhaps be attributed to stabilisation of the transition state by the phenyl group through $\pi$-p interactions. An aliphatic group could only participate through weaker inductive effects. When the C-1 – C-2 double bond is contained within a cyclohexene ring, the rate of rearrangement is again significantly reduced. This is probably the result of electronic effects, although the ring also places additional steric demands on the system. Our substrates are similar to those used by Paquette (see Scheme 40), who showed that there was a preference for the formation of an axial bond during rearrangement. This may inhibit the reaction if the substituent is large, as in our examples.

3.2.4 Summary

Rearrangement of substrate 290 containing aliphatic substutution at C-1 was found to be significantly slower than the corresponding phenyl substituted compounds. The rearrangement of substrates 298 and 299 was attempted in an effort to gain access to interesting decalin compounds, but the results achieved are not yet satisfactory, in terms of yield and reproducibility.
3.3 Rearrangement of enantiomerically enriched substrates – substitution at C-4

3.3.1 Introduction

Finally, we turned our attention to the rearrangement of substrates with substituents at C-4. As mentioned previously, we hoped that syn aldol products would provide excellent levels of chiral transfer, see Chapter 1.

3.3.2 Results

We initially studied the rearrangement of a readily accessible 1:1 mixture of racemic syn and anti substrates 310a and 310b, to find conditions for rearrangement, and to provide samples of racemic products for comparison with the enantiomerically enriched compounds we hoped to produce. When a mixture of 310a and 310b, obtained as described previously, was treated with 3 equivalents of KH and 2 equivalents of 18-C-6 in THF, we were delighted to find that rearrangement took place after only 3 h at rt. The reaction was quenched by the addition of 1.1 mol dm\(^{-3}\) aqueous hydrochloric acid solution. After work-up several cyclohexanones were obtained in the ratio shown and in ~ 100 % crude yield, Scheme 87. These compounds, unlike those prepared previously, were found to be relatively stable to column chromatography on neutral alumina, and were obtained free from other contaminants in a combined yield of 56 %.

Scheme 87

\[
\begin{align*}
310a & \quad \text{Ph} & \quad \text{OH} & \quad \text{HC} & \quad \text{O}^\text{Pr} \\
310b & \quad \text{Ph} & \quad \text{OH} & \quad \text{HC} & \quad \text{O}^\text{Pr} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
382 & \quad \text{Ph} & \quad \text{OH} & \quad \text{HC} & \quad \text{O}^\text{Pr} \\
383 & \quad \text{Ph} & \quad \text{OH} & \quad \text{HC} & \quad \text{O}^\text{Pr} \\
384 & \quad \text{Ph} & \quad \text{OH} & \quad \text{HC} & \quad \text{O}^\text{Pr} \\
382:383:384: \text{minor isomer} & = 8:3:7:1
\end{align*}
\]
Although the compounds could be chromatographed, some isomerisation took place and it was not possible to obtain a sample of each isomer free from the others even using preparative TLC. However, it was possible to assign the stereochemistry of each of the isomers shown using the \(^1\)H NMR spectra of the mixtures obtained from chromatography, see Chapter 4.

We were unconcerned that the reaction gave a mixture of isomers, the anti and syn substrates 310a and 310b were expected to give rise to different 2,6 relative stereochemistry. We then turned our attention to the rearrangement of the enantiomerically enriched, diastereomerically pure substrate 324, obtained as described in Chapter 2. When 324 was treated with KH and 18-C-6 then quenched with hydrochloric acid as before, we found to our dismay that a mixture of isomers was produced in the reaction, Scheme 88.

**Scheme 88**

![Scheme 88](image)

There were several extremely puzzling questions raised by this result. Although the chair:boat ratio was 11:1, poor 2,3-diastereoselectivity was achieved. In addition, the major isomer produced contained an equatorial hydroxyl group at C-3 and an axial methyl group at C-2. This result was entirely inconsistent with the one we had predicted using the model shown, Scheme 89. A radical alteration to our model for the rearrangement/cyclisation process which was consistent with both these results, and those obtained previously was required.
We first addressed the preferential formation of an axial methyl group. We ruled out the possibility of epimerisation by quenching the rearrangement with 1.1 mol dm$^{-3}$ solution of DCI as described previously. Again, the deuterium was incorporated only at C-4. The only way we could explain the formation of an axial methyl at C-2 was to assume that the rearrangement proceeded through a chair-like transition state with the oxyanion axial, and not equatorial as had been previously assumed, Scheme 90.
At first, this explanation seems unlikely, as there should be a strong repulsive electrostatic and steric interaction between the oxyanion and the enol ether oxygen. However, we propose that the potassium cation is chelated between the two oxygen atoms during rearrangement, which proceeds through TS 397 as shown, Figure 24.

The fact that the methyl group is axial does not raise the energy of the TS by a large amount, as it is highly dissociated.\textsuperscript{24} In addition, the methyl group lies in an equatorial position in the six-membered ring formed by the chelated potassium cation.
Examination of the ratios of the cyclohexanones obtained by the rearrangement of the 1:1 mixture of syn and anti substrates shows that one of the major products 384 must have arisen from the anti substrate. The preference for the 2,3 syn cyclohexanone when the anti alcohol 310b is rearranged and cyclised is also consistent with the chelated model, Scheme 91.

**Scheme 91**

Examination of the products obtained from the rearrangement of the syn aldol substrate 324 (Scheme 88) shows that 385 and 386 are both produced via a chair-like TS, with an axially oriented oxyanion. The minor isomer, whose stereochemistry could not be determined, showed a characteristic signal at δ 4.36 ppm (quartet with J 2.4 Hz), for an axial hydroxyl group. Since the 1H NMR spectrum does not resemble that of racemic alcohol 384, we can assign a 5,6-syn relative configuration to the minor isomer. Hence, the chair:boat ratio for the rearrangement of the syn aldol product is 11:1. The enantiomeric ratio of the rearrangement was determined to be ~96:4 by 1H NMR spectroscopy. This determination is discussed in Chapter 4. The chelated TS model raises some interesting questions, and some experiments that could be carried out to answer them. The model predicts that the rearrangement should in theory proceed without the presence of 18-C-6, and indeed should occur with better selectivity. However, the rate of reaction without 18-C-6 may be retarded to such an extent that no reaction takes place. Also, the model predicts that the rearrangement of anti substrates should proceed with greater selectivity than observed in other systems. The rearrangement of the 1:1 mixture goes some way to proving this, but the reaction of diastereomerically pure substrates needs to be investigated. Work in this area is ongoing in our group.

Since the chair/boat ratio is 11:1, the relatively poor diastereoselectivity obtained in the rearrangement/cyclisation process is due to the intramolecular aldol reaction. We searched for an explanation as to why the stabilisation
provided by an axial hydroxyl group, Figure 25, which we used to explain the selectivity in the previous examples was not as effective in this case.

Figure 25

![Diagram](image)

The full mechanism of the intramolecular aldol reaction is given in Scheme 92. The aldehyde 398 is protonated, to give oxonium ion 399, which undergoes intramolecular aldol reaction to give oxonium ions 397 or 400. These intermediates then undergo hydrolysis to give the product β-hydroxycyclohexanones 386 and 385 respectively. Intermediates 397 and 400 can equilibrate via 399 by an aldol/retroaldol process. Our previous reasoning would suggest that formation of an axial hydroxyl group should be favoured by stabilisation in oxonium ion 397 or in the transition state leading to 397. In this case, this equilibrium is obviously not biased in favour of 397. We propose that oxonium ion 400 is hydrolysed faster than oxonium ion 397, as the carbonyl of 397 is considerably more hindered than that of 400. A nucleophile (e.g. water) approaching the carbonyl of 397 along the Bürgi-Dunitz angle of approach would encounter steric hindrance on both faces of the cyclohexane ring. The top face is blocked by the methyl group and the bottom face is blocked by the hydroxyl group. The top face of oxonium ion 400 is also blocked by the methyl group. However, the bottom face is accessible to nucleophilic attack. A fast equilibrium between 397 and 400 would then explain the preference for an equatorial hydroxyl group.
It is interesting at this point to mention some other work carried out in our group. The rearrangement of compound 401 is shown in Scheme 93. The major product of this reaction is the cyclohexanone 404, as predicted by our original model. This result is consistent with our revised mechanism. A chelated TS requires a pseudoaxially oriented isopropyl group 405. The barrier to such a conformation is simply too large, and the isopropyl group forces the rearrangement to proceed through conformation 402 as shown.
An axial hydroxyl group is formed preferentially. This means that the aldol reaction proceeds predominantly through oxonium ion intermediate 403. This ion is not sterically hindered on the upper face.

3.3.3 Summary

An unexpected result for the rearrangement of substrates with substituents at C-4 of the 1,5-headiene-3-ol framework lead us to revise our model for the rearrangement. We proposed that the rearrangement proceeds through a chelated transition state, with the potassium counterion bonded to the oxyanion and the enol ether oxygen. This model gives the enol ether oxygen atom a much more interesting role in the rearrangement than we first postulated, and more work is being carried out in our group to further investigate our proposed mechanism.

3.4 Alternative routes to $\beta$-hydroxycyclohexanaones

The conjugate addition of an organocuprate to an $\alpha,\beta$-unsaturated cyclohexenone followed by quench with an electrophile is a commonly used method for the construction of substituted cyclohexanones of type 408, Scheme 94.
The introduction of a β-hydroxyl group is commonly achieved by the reductive opening of an α,β-epoxycyclohexanone 409, Scheme 95.

Several methods have been developed for this transformation, including the use of samarium diiodide,80 lithium/ammonia,81 and sodium phenylselenide.82 The selectivity of these processes is variable, and epimerisation at the α-position usually occurs.

Alternatively, a masked form of the hydroxyl group can be introduced by a conjugate addition mechanism. Extensive work in this area has been carried out by Fleming and coworkers,83 Scheme 96. For example, conjugate addition of the phenyldimethylsilylcuprate 412 to enone 411 yields ketone 413. Treatment of 413 with tetrafluoroboric acid followed by oxidation with meta-chloroperbenzoic acid (mCPBA) gives the hydroxycyclohexanone 351.

These methods offer straightforward access to the type of compound that we synthesise using our methodology, but ultimately lack the brevity and flexibility that our route provides for the introduction of different substituents in a stereoselective manner.
3.5 Applications for our methodology

In 1997, Kimura and co-workers reported that metabolites, e.g. Penihydrone 414, isolated from Penicillium sp. No 13 possessed interesting activity as plant growth regulators, Figure 26. The stereochemistry of these compounds corresponds exactly to that produced in our methodology. In addition, our route should prove flexible enough to produce analogues of the natural product.

Figure 26
Stereochemical assignments for β-hydroxycyclohexanones

4.1 Introduction

The correct assignment of the stereochemistry of the cyclohexanone compounds produced in the rearrangement/cyclisation reaction is essential, as this forms the basis for the determination of the chair/boat ratios in the rearrangement. As described previously, these assignments were made on the basis of the $^1$H NMR spectra of these compounds. This chapter gives details of these spectra, and the other NMR experiments used to identify them.

4.2 Compounds in section 3.1.2

The compounds produced in the rearrangement of Z-278 and Z-285 are shown in Scheme 97.

Scheme 97

The major product of the rearrangement was 353, obtained as an amorphous solid. Full NMR data for this compound is given in the experimental section, however, it is useful to tabulate the assignments and key coupling constants, Table 4.
Key features are:

- **CHOH 4.59 ppm, quintet $J = 2.9$ Hz; this establishes that the hydroxyl group is axial, as no large axial-axial couplings for this proton are observed**

- Protons H$^6$ and H$^7$ show a large axial-axial coupling to each other, proving that the stereochemistry of the substituents at C-5 and C-6 is *anti* as shown

The other diastereomers in this reaction were not amenable to chromatography, as mentioned previously. We overcame this problem after some experimentation, by converting the alcohols into their TBS ethers, *Scheme 98*. A mixture of the alcohols **353, 354 and 355** was treated with TBSCI and Et$^1$Pr$_2$N in DMF. After 3 days at rt the TBS ethers **415, 416** and **417** were formed. Only a small amount of **417** was formed, as alcohol **353** proved...
resistant to silylation. The other isomers were subjected to extensive chromatography, and were eventually separated by preparative TLC.

**Scheme 98**

415 gave the following data

**Table 8**

<table>
<thead>
<tr>
<th>δ assignment</th>
<th>H^1</th>
<th>H^2</th>
<th>H^3</th>
<th>H^4</th>
<th>H^5</th>
<th>H^6</th>
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<tr>
<td>2.76</td>
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<td>12.0</td>
<td>3.8</td>
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</tr>
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<td>3.95</td>
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<td></td>
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<td>10.7</td>
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</tr>
<tr>
<td>2.52</td>
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<td></td>
</tr>
</tbody>
</table>

* = coupling constant could not be determined

- = no coupling

Key points:

- H^3 shows large axial-axial couplings to H^1 and H^4, and smaller axial-equatorial couplings to H^2 and H^5
• H\textsuperscript{7} shows a large axial-axial coupling to H\textsuperscript{6}.

The rather poor matches in this table are due to the averaging of two or more similar couplings. We performed an additional NMR experiment on this compound. When the methyl group was irradiated, the signal corresponding to H\textsuperscript{7} collapsed to a doublet, from which we were able to obtain an accurate value for the H\textsuperscript{6}-H\textsuperscript{7} coupling constant.

416 gave the following data, Table 5.

Table 7

<table>
<thead>
<tr>
<th>δ assignment</th>
<th>H\textsuperscript{1}</th>
<th>H\textsuperscript{2}</th>
<th>H\textsuperscript{3}</th>
<th>H\textsuperscript{4}</th>
<th>H\textsuperscript{5}</th>
<th>H\textsuperscript{6}</th>
<th>H\textsuperscript{7}</th>
<th>Me</th>
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</thead>
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<td>2.38</td>
<td>H\textsuperscript{2}</td>
<td>14.5</td>
<td>4.6</td>
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<td>1.6</td>
<td>-</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
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<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>H\textsuperscript{5}</td>
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<td>13.4</td>
<td>5.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3.71</td>
<td>H\textsuperscript{6}</td>
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<td>0.88</td>
<td>Me</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>7.2</td>
</tr>
</tbody>
</table>

* = coupling constant could not be determined
- = no coupling

Key features:

• H\textsuperscript{3} is a narrow multiplet (range 16 Hz), so the silyloxy group is axial
• H\textsuperscript{7} shows no large axial-axial couplings - the methyl group is therefore axial

To obtain the H\textsuperscript{6}-H\textsuperscript{7} coupling constant, we again irradiated the methyl group.
We attempted to remove the silyl groups to obtain the hydroxycyclohexanones themselves. However, when 415 and 416 were treated with TBAF, a mixture of isomers was obtained, presumably via a fluoride-induced retro-aldol process.

We were confident, however, that from the assignments made of the silyl ethers we could identify the corresponding alcohols in the spectra of the crude material obtained after rearrangement. This confidence was based on the fact that the signals corresponding to the CHOH and CHOTBS protons had the same shape and almost the same chemical shift.

4.3 Compounds in Section 3.2.1

Rearrangement/cyclisation of 290 lead to the formation of 375, see Scheme 83.

Because of the large number of multiplets in the $^1$H NMR spectrum of 375, the data cannot be displayed in a table as above. The key stereochemical feature of the spectrum is:

- the CHOH signal is a narrow multiplet, range 14 Hz, showing the hydroxyl is axial

The signal for the CHPr signal is very broad, and individual couplings are not resolved. However, it is highly unlikely that the Pr group is also axial.

Decalone 378

The only hydroxydecalone characterised, 378, gave the following data, Table 9
The key features of the spectrum are

- $H^3$ is a broad singlet-no large couplings are observed
- $H^4$ shows an axial-axial coupling to $H^5$

Our assignment is supported by the work of Fleming and coworkers, who have synthesised the C-5 epimer (equatorial hydroxyl group). \(^{83b}\)

### 4.4 Compounds in Section 3.3

The rearrangement of a 1:1 mixture of syn and anti substrates gave rise to four compounds as previously described, see Scheme 87.

The three major isomers could not be separated completely, but assignment of their stereochemistry was possible from the mixtures obtained after preparative TLC.

382 gave the following data, Table 10.
Table 10

<table>
<thead>
<tr>
<th>δ assignment</th>
<th>H¹</th>
<th>H²</th>
<th>H³</th>
<th>H⁴</th>
<th>H⁵</th>
<th>H⁶</th>
<th>Me¹</th>
<th>Me²</th>
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<td>2.90</td>
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</tr>
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</tr>
<tr>
<td>0.79</td>
<td>Me²</td>
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<td></td>
<td></td>
<td>6.8</td>
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</tr>
</tbody>
</table>

* = coupling constant could not be determined
- = no coupling

Key features:

- H² shows a large axial-axial coupling, and two smaller axial-equatorial couplings. The hydroxyl group is therefore equatorial, and Me¹ must lie in an axial position (if it were equatorial H² would have two large couplings and one smaller one).
- H⁵ and H⁶ show a large axial-axial coupling to each other.
383 gives the following data, Table 11.

**Table 11**

![Structure](image-url)  

<table>
<thead>
<tr>
<th>δ assignment</th>
<th>H¹</th>
<th>H²</th>
<th>H³</th>
<th>H⁴</th>
<th>H⁵</th>
<th>H⁶</th>
<th>Me¹</th>
<th>Me²</th>
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<tr>
<td>2.25-2.13</td>
<td>H³</td>
<td>-</td>
<td>*</td>
<td>-</td>
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<tr>
<td>2.25-2.13</td>
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<td>6.4</td>
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</tr>
</tbody>
</table>

* = coupling constant could not be determined  
- = no coupling

Key features:

- H² shows no large couplings - the hydroxyl group must therefore be axial  
- H¹ shows a small equatorial - equatorial coupling to H², characteristically 1 Hz smaller than the corresponding axial-equatorial coupling (see Table 12)  
- H⁵ and H⁶ show a large diaxial coupling
384 gives the following data, Table 12:

![Chemical structure of 384](image)

<table>
<thead>
<tr>
<th>δ assignment</th>
<th>H₁</th>
<th>H²</th>
<th>H³</th>
<th>H⁴</th>
<th>H⁵</th>
<th>H⁶</th>
<th>Me¹</th>
<th>Me²</th>
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<td>6.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* = coupling constant could not be determined
- = no coupling

Key features:
- H² is a narrow multiplet, therefore the hydroxyl group is axial
- H¹ shows a coupling to H² 1 Hz larger than that found in 384 (Table 11)
- H⁵ and H⁶ again show a diaxial coupling

Although the stereochemical assignment of H-1 as equatorial in 383 and axial in 384 is not absolutely definitive based on coupling constants alone, we are certain from the mechanistic reasons discussed in Chapter 3 that these assignments are correct.

Finally, the enantiomeric ratio of the rearrangement of the enantiopure syn substrate 324, was determined by the addition of the chiral shift reagent 418. Figure 27.
The addition of ~10 mg of this compound to an NMR sample containing ~10 mg of a mixture of racemic hydroxycyclohexanones resulted in a splitting of the signal for H-2 of compound 382. The splitting of the signal was not complete. However, when the experiment was repeated with a mixture of non-racemic alcohols, an estimation of the enantiomeric ratio could be obtained from the splitting of H-2 in alcohol 385. This was found to be approximately 96:4.
Experimental

General

All reactions were carried out under an atmosphere of nitrogen, using oven-dried glassware. All solutions were added *via* syringe unless otherwise stated. THF, ether and DME were freshly distilled from sodium/benzophenone. DCM, hexane and all amines were distilled from CaH$_2$ prior to use. DMF was distilled from BaO and stored over 4Å MS. Cinnamaldehyde was distilled. Ethanol was distilled from magnesium. 18-crown-6 was dried by azeotrope with toluene. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Purification by column chromatography was carried out using Fisher Matrex™ silica gel, mesh size 35-70 μm, Fluka basic alumina Brockmann grade III or Aldrich neutral alumina Brockmann grade III mesh size ~150 as the stationary phase. Thin layer chromatography was carried out using Merck silica gel 60 F$_{254}$ foil-backed plates, (0.25mm layer thickness), or Merck aluminium oxide 60 F$_{254}$ neutral (type E) foil-backed plates (0.2mm layer thickness). The plates were visualised by illumination with UV light, iodine vapour or vanillin solution.

Melting points are uncorrected. IR spectra were recorded using a Nicolet Impact 410 FTIR spectrometer. NMR spectra were recorded using Bruker AM-200SY, AM-360 and DPX-400 spectrometers. Chemical shifts are given relative to tetramethylsilane using residual CHCl$_3$ as an internal standard (7.26 ppm). The multiplicities of $^{13}$C nuclei were determined using the DEPT pulse sequence. Mass spectra were recorded on a Jeol JMS700 spectrometer. Combustion analysis was carried out using a Carlo-Erba 1106 elemental analyser and optical rotations were obtained using an Optical Activity PolAAr 2000 polarimeter.
General Procedures

The following general procedures were used.

A. Intermolecular aldol reaction

\[ \text{R}^1\text{C} = \text{O} \text{OR}^2 + \text{R}^3\text{C} = \text{O} \rightarrow \text{R}^1\text{R}^3\text{C} = \text{O} \text{OR}^2 \]

A solution of the ester (1 equivalent) in THF is added to a stirred solution of lithium diisopropylamide [made from butyllithium (1 equivalent) and diisopropylamine (1 equivalent)] in THF under nitrogen at \(-78^\circ\text{C}\). The resulting mixture is stirred for 40 min, whereupon the aldehyde (1 equivalent) is added. Stirring is continued for a further 20 min, then the mixture is poured into aqueous hydrochloric acid solution (1.1 mol dm\(^{-3}\)). The layers are separated and the aqueous phase extracted with ether. The combined organic extracts are washed with aqueous hydrochloric acid solution and saturated aqueous sodium bicarbonate solution, then dried and concentrated under reduced pressure to give the aldol product.

B. Silyl protection reaction

\[ \text{R}^2\text{C} = \text{O} \text{OR}^2 + \text{R}_3\text{SiCl} \rightarrow \text{R}^2\text{R}_3\text{SiO} \text{C} = \text{O} \text{OR}^2 \]

The alcohol (1 equivalent) is dissolved in dry DMF under nitrogen with stirring. The solution is cooled on an ice bath. The silyl chloride (2 equivalents) then diisopropylethylamine (3 equivalents) are added and the mixture allowed to warm to room temperature. Stirring is continued for 17 h, then the reaction mixture is poured into saturated aqueous sodium bicarbonate solution. Ether is added and the layers separated. The aqueous phase is extracted with ether, and the combined organic extracts washed with hydrochloric acid (1.1 mol dm\(^{-3}\)) and brine, then dried and concentrated under reduced pressure to give the silyl ether.
C. Modified Takai alkylidene reaction

Titanium tetrachloride (4 equivalents) is added slowly to THF under nitrogen at 0 °C. To the resulting bright yellow suspension is added TMEDA (8 equivalents) to give an orange/brown suspension. The mixture is stirred at 0 °C for 20 min, then zinc powder (9 equivalents) (activated by sequential washing with 5 % aqueous hydrochloric acid, water, acetone and ether) mixed with a small amount of lead (II) chloride (~10-20 mg) is added. An exotherm occurs and the mixture turns a grey/blue colour. The ice bath is removed and the suspension stirred for 40 min, over which time a dark green colour develops. The mixture is then re-cooled in an ice bath and a solution of the ester (1 equivalent) and the 1,1-dibromoalkane (2.2 equivalents) in THF is added dropwise. After addition is complete the ice bath is removed and the reaction mixture stirred for 4-17 h. (The suspension turns dark brown/black after ~20 min at rt.) The reaction mixture is then re-cooled with an ice bath, and saturated potassium carbonate solution added via syringe. The resulting thick black slurry is stirred for a further 15 min, then poured into ether. The reaction vessel is washed repeatedly with ether and the combined washings are then passed through a short column of basic alumina to filter off the solid formed during the quench. After washing the filtrate with additional ether, the combined washings are dried and concentrated under reduced pressure. The residue is treated with hexane, and the insoluble white precipitate formed on concentration is filtered off by passing the hexane solution through a short column of basic alumina. The precipitate is washed with additional hexane and the combined washings concentrated under reduced pressure to give the enol ether.
D. The silyl deprotection reaction

To the silyl ether (1 equivalent) is added TBAF (2-3 equivalents of a 1.0 mol dm$^{-3}$ solution in THF) at rt under nitrogen. The mixture is stirred for 5 min to dissolve the silyl ether, then 4 Å MS (1.3 wt equivalents) are added. The resulting dark orange suspension is stirred for 1-4 h, then poured through filter paper into saturated aqueous sodium bicarbonate solution. Ether is added and the layers separated. The aqueous phase is extracted with ether and the combined organic extracts dried. Concentration under reduced pressure gives the crude alcohol.
Methyl (E)-3-Hydroxy-5-phenyl-4-pentenoate.\(^{86}\)

Following general procedure A, methyl acetate (2.15 cm\(^3\), 27.0 mmol) in dry THF (50 cm\(^3\)) was added to a stirred solution of LDA [made from butyllithium (1.2 mol dm\(^{-3}\) solution in THF, 22.7 cm\(^3\), 27.0 mmol) and diisopropylamine (3.5 cm\(^3\), 27.0 mmol)]. After 40 min, E-cinnamaldehyde (3.4 cm\(^3\), 27.0 mmol) was added and stirring continued for 20 min, whereupon the mixture was poured into aqueous hydrochloric acid solution (100 cm\(^3\), 1 mol dm\(^{-3}\)). The layers were separated and the aqueous phase extracted with ether (2 x 100 cm\(^3\)). The combined organic extracts were washed with aqueous hydrochloric acid (100 cm\(^3\)) and saturated aqueous sodium bicarbonate solution (100 cm\(^3\)). The organic phase was dried (MgSO\(_4\)) and the solvent removed under reduced pressure to give a yellow oil (6.02 g, 108 %). The crude product was purified by column chromatography (silica, eluent 10:1 pet ether 40/60-ether) to yield the aldol 266 as a pale yellow oil (4.33 g, 78 %); \(\delta\)\(_{\text{H}}\) (200 MHz, CDCl\(_3\)) 7.44-7.19 (5H, m, Ph), 6.65 (1H, dd, \(J\) 16.0 and 0.8, PhCH=), 6.21 (1H, dd, \(J\) 16.0 and 6.0, PhCH=CH\(_2\)), 4.73 (1H, m, CHOH), 3.71 (3H, s, OMe), 3.03 (1H, br s, OH) and 2.66-2.62 (2H, m, CH\(^4\)H\(^5\)CO\(_2\)Me), in agreement with data given in reference 86.

Isopropyl (E)-3-Hydroxy-5-phenyl-4-pentenoate.\(^{87}\)

Following general procedure A, isopropyl acetate (11.5 cm\(^3\), 97.9 mmol) was added to LDA [ex butyllithium (1.6 mol dm\(^{-3}\) solution in THF, 61.2 cm\(^3\), 97.9 mmol) and diisopropylamine (9.9 g, 12.8 cm\(^3\), 97.9 mmol)]. E-cinnamaldehyde (12.3 cm\(^3\), 97.9 mmol) was then added, and the procedure followed as above to yield the aldol (23.63 g, 103 %) as a pale yellow oil, sufficiently pure for the silyl
protection reaction; $R_f$ (alumina, 1:1 ether-hexane) 0.21; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3449 br s (OH), 2981 m, 2935 w, 1726 s (C=O), 1495 m, 1374 w, 1107 m, 966 m, 818 m and 751 s; $\delta_H$ (400 MHz, CDCl$_3$) 7.37-7.21 (5H, m, Ph), 6.64 (1H, d, $J$ 16.0, PhCH$_2$), 6.21 (1H, dd, $J$ 16.0 and 6.0, PhCH=CH), 5.06 (1H, sep, $J$ 6.4, OCH$\text{Me}_2$), 4.74-4.68 (1H, br m, CHO$_{\text{OH}}$), 3.26 (1H, d, $J$ 4.2, OH), 2.63 [1H, dd, $J$ 16.0 and 4.8, CH(OH)CH$_4$H$_3$], 2.58 [1H, dd, $J$ 16.0 and 7.4, CH(OH)CH$_4$H$_3$] and 1.24 (6H, d, $J$ 6.4, OCH$\text{Me}_2$); $\delta_C$ (100 MHz, CDCl$_3$) 171.7 (C), 136.5 (C), 130.6 (CH), 130.1 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 68.9 (CH), 67.9 (CH), 41.9 (CH$_2$) and 21.8 (CH$_3$); $m/z$ (EI$^+$) 234.1 (M$^+$, 25%), 174.1 (40), 133.1 (100); HRMS (EI$^+$) found 234.1256, C$_{14}$H$_{18}$O$_3$ requires 234.1256.

268

Methyl (E)-3-( tert-Butyldimethylsilyloxy)-5-phenyl-4-pentenoate.

Following general procedure B, alcohol 266 (1.0 g, 4.9 mmol) was dissolved in dry DMF (20 cm$^3$). Diisopropylethylamine (2.5 cm$^3$, 14.9 mmol) then tert-butyldimethylsilylchloride (1.5 g, 9.7 mmol) were added. After 17 h, the mixture was poured into saturated aqueous sodium bicarbonate solution (200 cm$^3$). The aqueous phase was separated and extracted with ether (2 x 100 cm$^3$). The combined organic extracts were washed with aqueous hydrochloric acid (2 x 100 cm$^3$, 1 mol dm$^{-3}$ solution) then brine (50 cm$^3$) and dried (MgSO$_4$). Concentration under reduced pressure and purification by column chromatography (silica, eluent 20:1 pet ether 40/60-ether), gave the silyl ether 268 as a pale yellow oil (1.5 g, 97%); $R_f$ (alumina, 1:1 ether-hexane) 0.62; $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2954 m, 2929 m, 2855 m, 1742 s (C=O), 1437m, 1362 m, 1166 m, 838 m and 778 m; $\delta_H$ (400 MHz, CDCl$_3$) 7.32-7.17 (5H, m, Ph), 6.57 (1H, d, $J$ 16.0, PhCH$_2$), 6.19 (1H, dd, $J$ 16.0 and 6.8, PhCH=CH), 4.79-4.74 (1H, m, CHOSi), 3.57 (3H, s, OMe), 2.63 [1H, dd, $J$ 14.4 and 8.4, CH(Os)$\text{CH}_4$H$_3$], 2.53 [1H, dd, $J$ 14.4 and 4.8, CH(Os)$\text{CH}_4$H$_3$], 0.78 (9H, s, SiC$\text{Me}_3$), -0.03 (3H, s, SiMe$_4$A$^2$Me$_2$) and -0.06 (3H, s, SiMe$_4$A$^2$Me$_2$); $\delta_C$ (100 MHz, CDCl$_3$) 171.5 (C), 136.6 (C), 131.5 (CH), 129.9 (CH), 128.6 (CH), 127.6 (CH), 104
126.5 (CH), 70.7 (CH), 51.6 (CH₃), 43.8 (CH₂), 25.7 (CH₃), 18.1 (C), -4.2 (CH₃) and -5.1 (CH₃); m/z (Cl+) 338.2 [(M+NH₄)+, 10 %], 263.1 (15), 206.1 (100); HRMS (Cl+) found 338.2167, C₁₈H₃₂NO₃Si [(M+NH₄)+] requires 338.2151.

Isopropyl (E)-3-(tert-Butyldimethylsilyloxy)-5-phenyl-4-pentenoate

Following general procedure B, the ester 267 (8.90 g, 38.31 mmol) was dissolved in dry DMF (80 cm³) and diisopropylethylamine (20.0 cm³, 114.9 mmol), then TBSCI (11.55 g, 76.6 mmol) were added. After 17 h the mixture was poured into saturated aqueous sodium bicarbonate solution (100 cm³) and extracted with ether (2 x 100 cm³). The combined ethereal extracts were washed with aqueous hydrochloric acid solution (2 x 100 cm³, 1.1 moldm⁻³) then brine (100 cm³) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give, after chromatography on silica gel using 10:1 hexane-ether as eluent, the silyl ether 269 as a pale yellow oil (12.95 g, 97 %); Rᵣ (alumina, 1:1 ether-hexane) 0.76; νmax (thin film)/cm⁻¹ 2930 s, 2886 s, 1736 s (C=O), 1495 m, 1472 m, 1374 m, 1257 w, 965 m, 840 m, 777 m, 746 m and 693 m; δᵣ (400 MHz, CDCl₃) 7.38-7.24 (5H, m, Ph), 6.58 (1H, d, J 16.0, PhCH=), 6.21 (1H, dd, J 16.8 and 6.8, PhCH=CH), 5.02 (1H, sep, J 6.4, CHMe₂), 4.78 (1H, dd, J 12.8 and 6.8, CHOSi), 2.61 (1H, dd, J 14.4 and 7.6, CH(OSi)CH=H), 2.50 (1H, dd, J 14.4 and 5.2, CH(OSi)CH=H), 1.26 (3H, d, J 6.4, CHMe₄Me), 1.23 (3H, d, J 6.4, CHMe₄Me), 0.75 (9H, s, SiMe₃), -0.08 (3H, s, SiMe₄Me) and -0.10 (3H, s, SiMe₄Me); δc (100 MHz, CDCl₃) 170.5 (C), 136.6 (C), 131.7 (CH), 129.8 (CH), 128.5 (CH), 127.6 (CH), 126.4 (CH), 70.7 (CH), 67.8 (CH), 44.2 (CH₂), 25.8 (CH₃), 21.87 (CH₃), 21.82 (CH₃), 18.1 (C), -4.2 (CH₃) and -5.0 (CH₃); m/z (Cl, NH₃) 366 [(M+NH₄)+], 234 (100); HRMS found 366.2459, C₂₀H₃₆NO₃Si [(M+NH₄)+] requires 366.2464.
270

Isopropyl (E)-3-(Triethylsilyloxy)-5-phenyl-4-pentenoate.

In the same way as above for 269, the ester 267 (5.0 g, 21.4 mmol), diisopropylamine (11.2 cm$^3$, 64.1 mmol) and triethylsilylchloride (7.2 cm$^3$, 42.7 mmol) gave the silyl ether 270 as a pale yellow oil after work-up and purification by column chromatography (on silica using 10:1 hexane-ether as eluent), (6.0 g, 81 %); $R_f$ (alumina, 1:1 ether-hexane) 0.86; $\nu_{\text{max}}$(thin film)/cm$^{-1}$ 2955 s, 2877 s, 1732 s (C=O), 1496 m, 1467 m, 961 w, 742 m, 693 m; $\delta$ (360 MHz, CDCl$_3$) 7.38-7.22 (5H, m, Ph), 6.57 (1H, d, $J$ 15.8, PhCH=), 6.21 (1H, dd, $J$ 15.8 and 6.9, PhCH=CH), 5.02 (1H, sep, $J$ 6.3, CHMe$_2$), 4.77 (1H, br q, $J$ 6.8, CHOSi), 2.62 [1H, dd, $J$ 14.6 and 7.7, CH(OSi)CH$_2$H$_3^+$], 2.50 [1H, dd, $J$ 14.6 and 5.7, CH(OSi)CH$_2$H$_3^+$], 1.24 (3H, d, $J$ 6.3, CHMe$^+$Me$^+$), 1.22 (3H, d, $J$ 6.4, CHMe$^+$Me$^+$), 0.96 (9H, q, $J$ 8.0, SiCH$_2$CH$_3$) and 0.63 (6H, q, $J$ 8.0, SiCH$_2$CH$_3$); $\delta$(90 MHz, CDCl$_3$) 170.5 (C), 136.6 (C), 131.6 (CH), 129.9 (CH), 128.5 (CH), 127.6 (CH), 126.4 (CH), 70.6 (CH), 67.8 (CH), 44.2 (CH$_2$), 21.83 (CH$_3$), 21.80 (CH$_3$), 6.8 (CH$_3$) and 4.8 (CH$_2$); $m/z$ (EI$^+$) 348.3 (M$^+$, 12 %), 319.2 (35), 277.2 (100); HRMS (EI$^+$) found 348.2122, C$_{20}$H$_{32}$O$_3$Si requires 348.2121.

271

(1E)-4-(tert-Butyldimethylsilyloxy)-2-methoxy-6-phenyl-1,5-hexadiene.

Following general procedure C, a solution of ester 268 (3.0 g, 9.4 mmol) and dibromomethane (1.5 cm$^3$, 20.7 mmol) in THF (10 cm$^3$) was added to the mixture formed from titanium tetrachloride (1 mol dm$^{-3}$ solution in DCM, 37.6 cm$^3$, 37.6 mmol), TMEDA (11.3 cm$^3$, 75.1 mmol), zinc (5.52 g, 84.5 mmol) and lead (II) chloride (~10 mg) in THF (20 cm$^3$). The resulting mixture was stirred for 4 h, then saturated aqueous potassium carbonate solution (20 cm$^3$) was added.
at 0 °C. After work-up the enol ether 271 was isolated as a colourless oil (1.75 g, 59 %); Rf (alumina, hexane) 0.61; δH (200 MHz, CDCl3) 7.39-7.16 (5H, m, Ph), 6.40 (1H, d, J 15.8, PhCH=), 6.23 (1H, dd, J 15.8 and 6.0, PhCH=CH), 4.47 (1H, br dd, J 12.6 and 6.0, CHOSi), 3.94 (1H, br s, =CHa/Hb), 3.88 (1H, br s, =CHa/Hb), 3.44 (3H, s, OCH3), 2.50-2.46 (2H, m, CHa/HbCO2Me), 0.84 (9H, s, SiMe3), 0.00 (3H, s, SiMeaMeb) and -0.02 (3H, s, Smeameb). This material was then subjected to deprotection conditions following general procedure D without further characterisation.

![Structure](image)

272

(1E)-3-(tert-Butyldimethylsilyloxy)-5-isopropoxy-1-phenyl-1,5-hexadiene.

Following general procedure C, a solution of the ester 269 (13.0 g, 37.3 mmol) and dibromomethane (5.8 cm³, 82.1 mmol) in THF (5 cm³) was added to the mixture formed from titanium tetrachloride (16.4 cm³, 149.2 mmol), TMEDA (45.0 cm³, 298.4 mmol), zinc powder (21.9 g, 335.7 mmol) and lead (II) chloride (~20 mg) in THF (150 cm³). Stirring was continued for 17 h, whereupon the reaction mixture was cooled in an ice bath. Saturated potassium carbonate solution (40 cm³) was added and the resulting thick black slurry stirred for 15 mins. The contents of the reaction flask were poured into ether (200 cm³) and worked up as described to give a pale yellow oil (9.35 g) which was subjected immediately to deprotection conditions without purification or characterisation.

![Structure](image)

273

(1E)-3-(Triethylsilyloxy)-5-isopropoxy-1-phenyl-1,5-hexadiene.

In the same way as above for 272, a solution of the ester 270 (20 g, 57.7 mmol) and dibromomethane (6.6 cm³, 94.6 mmol) in THF (5 cm³), was added to the mixture formed from titanium tetrachloride (18.9 cm³, 172.1 mmol), TMEDA
(51.9 cm³, 344.0 mmol), activated zinc (25.3 g, 387.0 mmol) and catalytic lead (II) chloride (~10 mg) in THF (200 cm³). The reaction mixture was stirred for 17 h, and worked-up as above to give the enol ether 273 as a pale yellow oil (14.66 g, 74 %), which was used in the deprotection reaction without further purification. A small sample was purified by chromatography on alumina using hexane as eluent (60 % yield); Rᵣ (alumina, hexane) 0.45; ν_max(thin film)/cm⁻¹ 2955 vs, 2876 vs, 1727 w, 1645 m, 1370 m, 1118 m, 965 m, 799 m and 745 m; δ_H (400 MHz, CDCl₃) 7.46-7.25 (5H, m, Ph), 6.55 (1H, d, J 16.0, PhCH=), 6.26 (1H, dd, J 16.0 and 6.4, PhCH=CH), 4.57 (1H, br q, J 6.4, CHOSi), 4.25 (1H, sep, J 6.0, CHMe₂), 3.99 (1H, d, J 1.6, =CH₄H₃), 3.91 (1H, d, J 1.6, =CH₄H₃), 2.46 [1H, dd, J 13.6 and 6.8, CH(OSi)CH₄H₃], 2.30 [1H, dd, J 13.6 and 6.8, CH(OSi)CH₄H₃], 1.27 (3H, d, J 6.4, CHMe₄Me₃), 1.26 (3H, d, J 6.4, CHMe₄Me₃), 1.02 (9H, t, J 8.0, SiCH₂CH₃) and 0.68 (6H, q, J 8.0, SiCH₂CH₃); δ_C (100 MHz, CDCl₃) 157.6 (C), 137.2 (C), 132.8 (CH), 128.8 (CH), 128.5 (CH), 127.2 (CH), 126.3 (CH), 83.6 (CH₂), 71.3 (CH), 68.2 (CH), 45.3 (CH₃), 21.8 (CH₃), 21.4 (CH₃), 6.8 (CH₃) and 4.9 (CH₂); m/z (EI+) 346.3 (M⁺, 5 %), 247.2 (100); HRMS (EI+) found 346.2328, C₂₁H₃₄O₂Si requires 346.2328.

274
(1E,5Z)-3-(tert-Butyldimethylsilyloxy)-5-isopropoxy-1-phenyl-1,5-heptadiene.

In the same way as above for 273, a solution of the ester 269 (4.0 g, 11.5 mmol) and 1,1-dibromoethane (2.3 cm³, 25.2 mmol) in THF (3 cm³) was added to the suspension formed from titanium tetrachloride (5.0 cm³, 8.7 mmol), TMEDA (13.9 cm³, 91.8 mmol), activated zinc powder (6.75 g, 103.3 mmol) and lead (II) chloride (~10 mg) in THF (15 cm³). The reaction was stirred for 4h, then worked-up as above to give the enol ether as a pale yellow oil (3.37 g, 81 %). A pure sample (2.449 g, 60 %) was obtained after chromatography on basic alumina using hexane as eluent. It should be noted that in the reaction a 15:85 mixture of E:Z enol ethers is formed. The NMR data given is for the major Z
isomer; Rᵣ (alumina, hexane) 0.71; νₓₓₓₙₓₙ (thin film)/cm⁻¹ 2956, 2929, 2857, 1679, 1494, 1369, 1254, 1196, 838 m; δₓₓₓₙ (360 MHz, CDCl₃) 7.38-7.22 (5H, m, Ph), 6.53 (1H, d, J 15.9, PhCH=), 6.26 (1H, dd, J 15.9 and 5.8, PhCH=CH₂), 4.73 (1H, q, J 6.7, =CHMe), 4.42 (1H, br q, J 6.6, CH(OSi), 4.10 (1H, sep, J 6.1, CHMe₂), 2.36 [1H, br dd, J 14.2 and 6.7, CH(Osi)CH₄H], 2.28 [1H, dd, J 14.6 and 6.6, CH(Osi)CH₄H], 1.57 (3H, d, J 6.7, =CHMe), 1.21 (3H, d, J 6.1, CHMe₁Me₂), 1.20 (3H, d, J 6.1, CHMe₁Me₂), 0.92 (9H, s, SiCMe₃) 0.08 (3H, s, SiMe₄Me₃) and 0.07 (3H, s, SiMe₄Me₃); δₓₓₓₙ (90 MHz, CDCl₃) 149.3 (C), 137.2 (C), 132.9 (CH), 128.43 (CH), 127.1 (CH), 126.31 (CH), 126.26 (CH), 109.5 (CH), 71.1 (CH), 68.8 (CH), 41.8 (CH₂), 25.8 (CH₃), 22.5 (CH₃), 22.3 (CH₃), 18.2 (C), 10.6 (CH₃), −4.6 (CH₃) and −5.0 (CH₃); m/z (EI+) 360.2 (M⁺, 2%), 247.2 (100); HRMS (EI+) found 360.2487, C₂₂H₃₆O₂Si requires 360.2485.

![TESO](https://via.placeholder.com/150)

**275**

(1E,5Z)-3-(triethylsilyloxy)-5-isopropoxy-1-phenyl-1,5-heptadiene.

In the same way as above for 274, a solution of the ester 270 (6.0 g, 17.2 mmol) and 1,1-dibromoethane (3.4 cm³, 37.8 mmol) in THF (5 cm³) was added to the suspension formed from titanium tetrachloride (7.5 cm³, 68.8 mmol), TMEDA (20.8 cm³, 137.6 mmol), activated zinc powder (10.12 g, 154.8 mmol) and lead (II) chloride (~10 mg) in THF (60 cm³). The reaction was stirred for 4 h, then worked-up as above to give the enol ether as a pale yellow oil (4.76 g, 77%). A pure sample was obtained after chromatography on basic alumina using hexane as eluent. As above a 15:85 mixture of E:Z isomers is formed. The data given is for the major isomer; Rᵣ (alumina, hexane) 0.70; νₓₓₓₙₓₙ (thin film)/cm⁻¹ 2955 vs, 2913 vs, 2876 vs, 1670 m, 1494 m, 1369 m, 1117 m and 744 m; δₓₓₓₙ (400 MHz, CDCl₃) 7.40-7.23 (5H, m, Ph), 6.54 (1H, d, J 16.0, PhCH=), 6.27 (1H, dd, J 16.0 and 6.0, PhCH=CH₂), 4.74 (1H, q, J 6.4, =CHMe), 4.45 (1H, br q, J 6.8, CH(OSi), 4.13 (1H, sep, J 6.0, CHMe₂), 2.41 [1H, br dd, J 14.4 and 7.2, CH(OSi)CH₄H], 2.30 [1H, dd, J 14.4 and 7.2, CH(OSi)CH₄H], 1.58 (3H, d, J
Following general procedure D, TBAF (1.1 mol dm\(^{-3}\) solution in THF, 1.22 cm\(^3\), 1.34 mmol) and 4 Å MS (185 mg) were added to silyl ether 271 (142 mg, 0.48 mmol). The mixture was stirred for 2 h then poured through filter paper into saturated aqueous sodium bicarbonate solution (3 cm\(^3\)). The layers were separated and the aqueous phase extracted with ether (3 x 5 cm\(^3\)). The organic extracts were combined, and dried (Na\(_2\)SO\(_4\)). Solvent removal under reduced pressure gave a brown oil. \(^1\)H NMR spectroscopy revealed this contained large amounts of tert-butyldimethylsilanol, which is produced in the reaction. Repeated column chromatography [alumina (8 % water), eluent 20:1 pet ether 40/60-ether] failed to rid the product of silanol. The silanol was finally removed by distillation (Kügelrohr) to give the alcohol 276 as an oil (yield < 10 %), \(R_f\) (alumina, 1:1 ether-hexane) 0.65; \(n_{\text{max}}\) (thin film)/cm\(^{-1}\) 3340 br m (OH), 2955 w, 1656 m, 1495 m, 1449 m, 1294 m, 966 m, 806 m, 749 m and 694 m; \(\delta_h\) (360 MHz, CDCl\(_3\)) 7.40-7.21 (5H, m, Ph), 6.64 (1H, d, \(J\) 15.9, PhCH=), 6.23 (1H, dd, \(J\) 15.9 and 6.2, PhCH=CH), 4.54-4.48 (1H, m, CHOH), 4.04 (1H, d, \(J\) 2.2, =CH\(^2\)H\(^2\)), 4.02 (1H, d, \(J\) 2.2, =CH\(^3\)H\(^3\)), 3.58 (3H, s, OMe), 2.48 [2H, br s obscured by dd, \(J\) 14.1 and 4.0, CH(OH)CH\(^4\)H\(^4\)] and 2.37 [1H, dd, \(J\) 14.1 and 8.4, CH(OH)CH\(^4\)H\(^4\)]; \(\delta_c\) (90 MHz, CDCl\(_3\)) 160.5 (C), 136.8 (C), 131.3 (CH), 130.0 (CH), 128.5 (CH), 127.5 (CH), 126.4 (CH), 83.6 (CH\(_2\)), 70.6 (CH), 55.0 (CH\(_3\)) and 43.2 (CH\(_2\)); \(m/z\) (El+) 204.1 (M\(^{+}\), 9 %), 133.06 (100); HRMS (El+) found 204.1153, C\(_{13}\)H\(_{16}\)O\(_2\) requires 204.1150.
Following general procedure D, tetrabutylammonium fluoride (67.5 cm$^3$ of a 1.0 mol dm$^{-3}$ solution in THF) and 4Å MS (12.2 g) were added to the enol ether 272 (9.35 g, 27.0 mmol). After stirring for 2.5 h, the reaction mixture was poured through filter paper into saturated sodium bicarbonate solution (50 cm$^3$). The layers were separated and the aqueous phase extracted with ether (2 x 50 cm$^3$). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark brown oil. The alcohol was obtained as a pale yellow oil (3.52 g, 56 %) after column chromatography on alumina, using 1:1 ether-hexane as eluent; $R_f$ (alumina 1:1 ether-hexane) 0.46; $v_{\text{max}}$(thin film)/cm$^{-1}$ 3415 br s (OH), 2976 s, 2926 sm, 1653 s (enol ether C=C), 1619 m, 1495 m, 1291 m, 1001 m, 965 m, 801 m, 749 s and 693 m; $\delta_t$(400 MHz, CDCl$_3$) 7.39 (2H, d, 7.2, o-Ph), 7.32 (2H, t, 7.2, m-Ph), 7.24 (1H, t, 7.2, p-Ph), 6.65 (1H, d, J 16.0, PhCH=), 6.26 (1H, dd, J 16.0 and 6.4, PhCH=CH), 4.54-4.51 (1H, m, CHO), 4.29 (1H, sep, J 6.0, CHMe$_2$), 4.05 (1H, d, J 2.0, =CH$_2$H$^B$), 3.99 (1H, d, J 2.0, =CH$_2$H$^A$), 2.87 (1H, d, J 3.6, OH), 2.45 [1H, dd, J 14.0 and 4.4, CH(OH)CH$_2$H$^B$], 2.36 [1H, dd, J 14.0 and 8.0, CH(OH)CH$_2$H$^A$], 1.28 (3H, d, J 6.0, CHMe$_2$H$^B$) and 1.27 (3H, d, J 6.0, CHMe$_2$H$^A$); $\delta_c$(100 MHz, CDCl$_3$) 157.7 (C), 136.8 (C), 131.3 (CH), 129.6 (CH), 128.6 (CH), 127.3 (CH), 126.3 (CH), 84.1 (CH$_2$), 70.6 (CH), 68.7 (CH), 43.5 (CH$_2$), 21.44 (CH$_3$) and 21.37 (CH$_3$); $m/z$ (Cl+) 233.2 [(M+H)$^+$, 15 %], 215.2 (40), 173.1 (100); HRMS (Cl+) found 233.1541, C$_{15}$H$_{21}$O$_2$ [(M+H)$^+$] requires 233.1542.

In the same way as above, 273 (14.5 g, 41.8 mmol) was treated with TBAF (62.7 cm$^3$ of a 1 mol dm$^{-3}$ solution in THF). The mixture was stirred for 1 h 50 min, then worked-up and purified as above to give enol ether 277 (5.16 g, 53 %).
In the same way as above for 277, silyl ether 274 (2.4 g, 6.65 mmol) was dissolved in a solution of TBAF in THF (18.1 cm$^3$, 1.1 mol dm$^{-3}$). 4 Å MS were added and the mixture stirred for 2 h. Work-up as above gave a yellow oil which was chromatographed on basic alumina using 1:1 hexane-ether as eluent to give the alcohols as a pale yellow oil (1.446 g, 88%). Repeated chromatography was required to obtain a sample of each isomer free from the other.

In the same way as above, silyl ether 275 (4.76 g, 13.2 mmol) was treated with TBAF (40 cm$^3$ of a 1 mol dm$^{-3}$ solution in THF) and 4 Å MS (6.2 g) to give after work-up and extensive chromatography the alcohol Z-278 (550 mg, 17%).

(1E,5Z)-5-Isopropoxy-1-phenyl-1,5-heptadiene-3-ol, Z-278.

R$_f$ (alumina, 2:1 pet ether 40/60-ether) 0.61, $v_{\text{max}}$(thin film)/cm$^{-1}$ 3425 br m, (OH), 2974 m, 1678 m, 1494 m, 1449 m, 1196 m, 1113 m, 965 m, 747 m and 693 m; $\delta_{\text{H}}$(360 MHz, CDCl$_3$) 7.39 (2H, d, $J$ 7.2 o-Ph), 7.31 (2H, t, $J$ 7.2, m-Ph), 7.24 (1H, t, $J$ 7.2, p-Ph), 6.63 (1H, d, $J$ 15.9, PhCH=), 6.26 (1H, dd, $J$ 15.9 and 6.1, PhCH=CH), 4.87 (1H, q, $J$ 6.7, =CHMe), 4.49-4.41 (1H, m, CHOH), 4.17 (1H, sep, $J$ 6.1, CHMe$_2$), 2.57 (1H, br d, $J$ 2.5, OH), 2.45 [1H, dd, $J$ 14.4 and 4.1, CH(OH)CH$_2$H$_2$], 2.29 [1H, dd, $J$ 14.4 and 8.5, CH(OH)CH$_2$H$_2$], 1.63 (3H, d, $J$ 6.7, =CHMe), 1.25 (3H, d, $J$ 6.1, CHMe$_2$), and 1.22 (3H, d, $J$ 6.1, CHMe$_2$); $\delta_{\text{C}}$(90 MHz, CDCl$_3$) 149.7 (C), 136.8 (C), 131.4 (CH), 129.7 (CH), 128.4 (CH), 127.4 (CH), 126.4 (CH), 110.6 (CH), 70.5 (CH), 69.8 (CH), 40.6 (CH$_2$), 22.4 (CH$_3$), 22.2 (CH$_3$) and 10.7 (CH$_3$); $m/z$ (Cl+) 247.2 [(M+H)$^+$, 9 %], 229.2 (90), 187.2 (100); HRMS (Cl+) found 247.1697, C$_{16}$H$_{23}$O$_2$ [(M+H)$^+$] requires 247.1698.
(1E,5E)-5-Isopropoxy-1-phenyl-1,5-heptadiene-3-ol, E-278.

R_f (alumina, 2:1 pet ether 40/60-ether) 0.69; \( \delta_v (400 \text{ MHz, CDCl}_3) \) 7.38 (2H, d, \( J 7.2 \) o-Ph), 7.26 (2H, t, \( J 7.2, m-\text{Ph} \)), 7.23 (1H, t, \( J 7.2, p-\text{Ph} \)), 6.63 (1H, d, \( J 15.9, \text{PhCH}= \)), 6.24 (1H, dd, \( J 15.9 \) and 6.1, \( \text{PhCH}=\text{CH} \)), 4.58 (1H, q, \( J 6.8, =\text{CHMe} \)), 4.53-4.48 (1H, m, \( \text{CHOH} \)), 4.25 (1H, sep, \( J 6.0, \text{CHMe}_2 \)), 2.88 (1H, d, \( J 3.7, \text{OH} \)), 2.48 [1H, dd, \( J 14.3 \) and 4.6, \( \text{CH(OH)CH}=\text{CH}^B \)], 2.43 [1H, dd, \( J 14.4 \) and 7.4, \( \text{CH(OH)CH}=\text{CH}^A \)], 1.62 (3H, d, \( J 6.8, =\text{CHMe} \)), 1.23 (3H, d, \( J 6.0, \text{CHMe}^A \text{Me}^B \)) and 1.22 (3H, d, \( J 6.0, \text{CHMe}^A \text{Me}^B \)); \( \delta_C (90 \text{ MHz, CDCl}_3) \) 151.1 (C), 137.0 (C), 131.7 (CH), 129.6 (CH), 128.4 (CH), 127.4 (CH), 126.4 (CH), 94.8 (CH), 71.3 (CH), 67.7 (CH), 37.5 (CH3), 21.9 (CH3), 21.8 (CH3) and 11.9 (CH3).

**280**

**Ethyl (E)-3-Hydroxy-5-phenyl-4-pentenoate.**

Following general procedure A, ethyl acetate (11.1 cm\(^3\), 113.5 mmol) in dry THF (230 cm\(^3\)) was added to a stirred solution of LDA [made from butyllithium (1.0 mol dm\(^{-3}\) solution in THF, 113.5 cm\(^3\), 113.5 mmol) and diisopropylamine (14.9 cm\(^3\), 113.5 mmol)]. After 40 min \( E \)-cinnamaldehyde (14.3 cm\(^3\), 113.5 mmol) was added. Stirring continued for 20 min, then the mixture was poured into aqueous hydrochloric acid (200 cm\(^3\), 1 mol dm\(^{-3}\)). The layers were separated and the aqueous phase extracted with ether (2 x 200 cm\(^3\)). The combined organic extracts were washed with aqueous hydrochloric acid (100 cm\(^3\)) and saturated aqueous sodium bicarbonate solution (100 cm\(^3\)). The organic phase was dried (MgSO\(_4\)) and the solvent removed under reduced pressure to give a yellow oil (23.43 g, 101%), sufficiently pure for the silyl protection reaction; \( \delta_v (200 \text{ MHz, CDCl}_3) \) 7.40-7.19 (5H, m, Ph), 6.65 (1H, dd, \( J 16.0 \) and 1.2, \( \text{PhCH}= \)), 6.21 (1H,
dd, $J$ 16.0 and 6.0, PhCH=CH), 4.89-4.64 (1H, br m, CHO), 4.18 (2H, q, $J$ 6.0, OCH$_2$CH$_3$), 2.62-2.59 [2H, m, CH(OH)CH$_3$H$_3$] and 1.26 (3H, d, $J$ 6.0, OCH$_2$CH$_3$), in agreement with data given in reference 88.

![Diagram](attachment:image.png)

281

Ethyl (E)-3-(trimethylsilyloxy)-5-phenyl-4-pentenoate.

The aldol 280 (23.43 g, 114.7 mmol) was dissolved in THF (100 cm$^3$). TMSCl (16.0 cm$^3$, 125.4 mmol) and diisopropylethylamine (19.8 cm$^3$, 125.4 mmol) were added and the reaction stirred at rt for 17 h. The bulk of the amine hydrochloride salt formed during the reaction was filtered off and the precipitate washed with hexane. The combined washings were concentrated under reduced pressure, and the process repeated to remove the remaining salt. The silyl ether was obtained as a yellow oil which was subjected, without purification or characterisation, to Takai conditions.

![Diagram](attachment:image.png)

282

(1E)-3-(Trimethylsilyloxy)-5-ethoxy-1-phenyl-1,5-hexadiene.

Following general procedure C, a solution of the ester 281 (5.0 g, 17.2 mmol) and dibromomethane (2.6 cm$^3$, 37.7 mmol) in THF (2 cm$^3$) was added to the mixture formed from titanium tetrachloride (7.5 cm$^3$, 68.6 mmol), TMEDA (20.7 cm$^3$, 137.2 mmol), zinc powder (10.09 g, 154.4 mmol) and lead (II) chloride (-20 mg) in THF (50 cm$^3$). Stirring was continued for 4 h, whereupon the reaction mixture was cooled in an ice bath. Saturated potassium carbonate solution (20 cm$^3$) was added and the resulting thick black slurry stirred for 15 min. After work-up as described, a pale yellow oil (2.57 g) was isolated which was subjected immediately to deprotection conditions without purification or characterisation.
(1E,5Z)-3-(Trimethylsilyloxy)-5-ethoxy-1-phenyl-1,5-heptadiene.

In the same way as above, a solution of the ester 282 (7.54 g, 25.8 mmol) and 1,1-dibromoethane (5.7 cm³, 62.7 mmol) in THF (5 cm³) was added to the suspension formed from titanium tetrachloride (12.5 cm³, 114.0 mmol), TMEDA (34.4 cm³, 228.0 mmol), activated zinc powder (16.8 g, 256.5 mmol) and lead (II) chloride (~10 mg) in THF (50 cm³). The reaction was stirred for 4h, then worked-up as above to give the enol ether as a yellow oil (5.25 g) which was deprotected without purification or characterisation.

(7E)-5-Ethoxy-1-phenyl-1,5-hexadiene-3-ol.

Following general procedure D, tetrabutylammonium fluoride (9.0 cm³ of a 1.0 moldm⁻³ solution in THF) was added to the enol ether 282 (2.57 g, 8.8 mmol) under nitrogen at rt. The mixture was stirred for 1 h, then poured into saturated sodium bicarbonate solution (25 cm³). The layers were separated and the aqueous phase extracted with ether (2 x 25 cm³). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark brown oil. The alcohol was obtained as a yellow oil (350 mg, 18 %) after column chromatography on basic alumina using 1:1 ether-hexane as eluent; Rf (alumina, 1:1 ether-hexane) 0.44; νmax(thin film)/cm⁻¹ 3421 br s (OH), 2979 m, 2903 m, 2878 m, 1655 s (enol ether C=C), 1618 m, 1495 m, 1293 m, 1173 m, 966 m, 804 m, 748 m and 694 m; δH(400 MHz, CDCl₃) 7.39 (2H, d, J 7.2 o-Ph), 7.33 (2H, t, J 7.2, m-Ph), 7.23 (1H, t, J 7.2, p-Ph), 6.64 (1H, dd, J 15.9 and 0.8, PhCH=), 6.24 (1H, dd, J 15.9 and 6.1,
PhCH=CH\textsubscript{2}, 4.55-4.50 (1H, m, CHO\textsubscript{2}), 4.01 (1H, d, J 1.9, =CH\textsubscript{2}H\textsubscript{3}), 3.99 (1H, d, J 1.9, =CH\textsubscript{2}H\textsubscript{3}), 3.88-3.76 (2H, m, OCH\textsubscript{2}CH\textsubscript{3}), 2.64 (1H, d, J 3.4, OH), 2.47 [1H, dd, J 14.0 and 3.9, CH(OH)CH\textsubscript{2}H\textsubscript{3}], 2.37 [1H, dd, J 14.0 and 8.4, CH(OH)CH\textsubscript{2}H\textsubscript{3}] and 1.23 (3H, t, J 7.0, OCH\textsubscript{2}CH\textsubscript{3}); \text{\delta}\text{C}(100 MHz, CDCl\textsubscript{3}) 159.6 (C), 136.8 (C), 131.3 (CH), 129.8 (CH), 128.5 (CH), 127.4 (CH), 126.4 (CH), 83.9 (CH\textsubscript{2}), 70.6 (CH), 63.0 (CH\textsubscript{2}), 43.3 (CH\textsubscript{2}) and 14.4 (CH\textsubscript{3}); m/z (EI+) 218.2 (M\textsuperscript{+}, 7 %), 133.1 (100); HRMS (EI) found 218.1305, C\textsubscript{14}H\textsubscript{18}O\textsubscript{2} requires 218.1307.

\begin{tikzpicture}
\draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- (0,0);
\draw (0.5,0.5) circle (0.1);
\draw (0.5,0.5) -- (0.7,0.7);
\draw (0.5,0.5) -- (0.3,0.3);
\draw (0.5,0.5) -- (0.5,0.5+0.1);
\draw (0.5,0.5) -- (0.5,0.5-0.1);
\end{tikzpicture}

In the same way as above, silyl ether 283 (5.25 g) was dissolved in a solution of TBAF in THF (18.0 cm\textsuperscript{3}, 1.0 mol dm\textsuperscript{-3}) and the mixture stirred for 1 h. Work-up as above gave a yellow oil which was chromatographed on basic alumina using 1:1 hexane-ether as eluent to give the alcohols as a pale yellow oil (2.06 g, 31 % over 4 steps). Repeated chromatography was required to obtain a sample of each isomer free from the other.

\begin{tikzpicture}
\draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- (0,0);
\draw (0.5,0.5) circle (0.1);
\draw (0.5,0.5) -- (0.7,0.7);
\draw (0.5,0.5) -- (0.3,0.3);
\draw (0.5,0.5) -- (0.5,0.5+0.1);
\draw (0.5,0.5) -- (0.5,0.5-0.1);
\end{tikzpicture}

(1\textsubscript{E},5\textsubscript{Z})-5-Ethoxy-1-phenyl-1,5-heptadiene-3-ol, E-285.

R\textsubscript{f} (alumina, 1:1 hexane-ether) 0.57; \nu\text{max}(thin film)/cm\textsuperscript{-1} 3409 br m (OH), 2977 m, 2915 m, 2863 m, 1670 m (enol ether C=C), 1494 m, 1448 m, 1193 m, 966 m, 743 m and 694 m; \text{\delta}\text{H}(400 MHz, CDCl\textsubscript{3}) 7.38 (2H, d, J 7.2 o-Ph), 7.31 (2H, t, J 7.2, m-Ph), 7.23 (1H, t, J 7.2, p-Ph), 6.65 (1H, d, J 16.0, PhCH=), 6.26 (1H, dd, J 16.0 and 4.4, PhCH=CH\textsubscript{2}), 4.81 (1H, q, J 6.4, =CHMe), 4.48-4.43 (1H, m, CHO\textsubscript{2}), 3.87-3.75 (2H, m, OCH\textsubscript{2}CH\textsubscript{3}), 2.56 (1H, d, J 2.8, OH), 2.46 [1H, dd, J 14.4 and 4.0, CH(OH)CH\textsubscript{2}H\textsubscript{3}], 2.30 [1H, dd, J 14.4 and 8.4, CH(OH)CH\textsubscript{2}H\textsubscript{3}], 1.64 (3H, d, J 6.8, =CHMe) and 1.29 (3H, t, J 7.0, OCH\textsubscript{2}CH\textsubscript{3}); \text{\delta}\text{C}(100 MHz, 116
$\text{CDCl}_3 \) 151.4 (C), 136.8 (C), 131.4 (CH), 129.8 (CH), 128.5 (CH), 127.5 (CH), 126.4 (CH), 109.5 (CH), 70.5 (CH), 68.5 (CH$_2$), 40.5 (CH$_2$), 15.4 (CH$_3$) and 10.5 (CH$_3$); m/z (El+) 232.2 (M$, 5 \%$), 133.1 (100); HRMS (El+) found 232.1463, $C_{15}H_{20}O_2$ requires 232.1463.

$$\text{HO} \quad \text{OEt}$$

$(1E,5E)$-5-Ethoxy-1-phenyl-1,5-heptadiene-3-ol, E-285.

$R_t$ (alumina, 1:1 hexane-ether) 0.60; $v_{\text{max}}$(thin film) 3458 br s (OH), 2861 w, 1668 m (enol ether C=C), 1495 w, 1226 w, 1103 w, 963 w and 748 w; $\delta_H$ (360 MHz, CDCl$_3$) 7.37 (2H, d, $J$ 7.2 o-Ph), 7.31 (2H, t, $J$ 7.2, m-Ph), 7.23 (1H, t, $J$ 7.2, p-Ph), 6.63 (1H, d, $J$ 15.9, PhCH=), 6.26 (1H, dd, $J$ 15.9 and 6.1, PhCH=CH$_2$), 4.58 (1H, q, $J$ 6.8, =CHMe), 4.55-4.48 (1H, partly obscured m, CHO$_2$), 3.74-3.66 (2H, m, OCH$_2$CH$_3$), 2.75 (1H, br d, $J$ 3.0, OH), 2.48 [2H, m, CH(OH)CH$_2$H$_2$], 1.62 (3H, d, $J$ 6.8, =CHMe) and 1.29 (3H, t, $J$ 7.0, OCH$_2$CH$_3$); $\delta_C$ (90 MHz, CDCl$_3$) 153.0 (C), 137.0 (C), 131.7 (CH), 129.6 (CH), 128.5 (CH), 127.4 (CH), 126.4 (CH), 93.7 (CH), 71.2 (CH), 62.0 (CH), 37.5 (CH$_2$), 14.7 (CH$_3$) and 11.8 (CH$_3$); m/z (El+) 232 (M$, 7 \%$), 133 (100); HRMS (El+) found 232.1464, $C_{15}H_{20}O_2$ requires 232.1463.

$$\text{OH} \quad \text{O}^\text{Pr}$$

(E)-Isopropyl-3-hydroxy-4-octenoate.

Following general procedure A, isopropyl acetate (7.2 cm$^3$, 61.1 mmol) was added to a stirred solution of lithium diisopropylamide [ex. 38.2 cm$^3$ of a 1.6 moldm$^{-3}$ solution of butyllithium in hexane and 8.0 cm$^3$, 61.1 mmol of diisopropylamine] in THF (150 cm$^3$). After 50 mins E-Hexenal (7.1 cm$^3$, 61.1 mmol) was added and the mixture stirred for a further 25 mins. The reaction mixture was then poured into aqueous hydrochloric acid (220 cm$^3$, 1.1 mol dm$^{-3}$)
and extracted with ether (2 x 100 cm³). The combined organic extracts were washed with aqueous hydrochloric acid (100 cm³, 1.1 moldm⁻³) then saturated aqueous sodium bicarbonate solution (100 cm³) and dried over magnesium sulfate. The solvent was removed in vacuo to give the aldol as a pale yellow oil (12.68 g, 103 %) sufficiently pure for the silyl protection reaction. A pure sample was obtained by column chromatography on silica using 1:1 ether-hexane as eluent to give a colourless oil (89 %), Rf (silica, 1:1 ether-hexane) 0.42; \( \nu_{\text{max}} \) (thin film) 3448 s br (OH), 2961 s, 2932 s, 1732 s (C=O), 1468 m, 1108 m and 966 m; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 5.68 (1H, dt, \( J_{15.2} \) and 6.8, \( CH₂CH=CH \)), 5.02 (1H, sep, \( J_{6.4} \), \( CHMe₂ \)), 4.45 (1H, m, \( CHOH \)), 2.51-2.45[2H, m, \( CH(OH)CH₄H² \)], 1.97 (2H, dt, \( J_{7.4} \) and 6.8, \( CH₂CH=CH \)), 1.36 (2H, sex, \( J_{7.2} \), \( CH₂CH₂ \)), 1.22 (6H, d, \( J_{6.4} \), \( CHMe₂ \)) and 0.86 (3H, t, \( J_{7.2} \), \( CH₃CH₂ \)); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 172.3 (C), 132.8 (CH), 131.1 (CH), 69.4 (CH), 68.5 (CH), 42.3 (CH₂), 34.6 (CH₂), 22.6 (CH₂), 22.2 (CH₃) and 14.0 (CH₃); m/z (Cl⁺) 218.2 [(M+NH₄)⁺, 45 %], 200.0 (52), 183.1 (100); HRMS (EI⁺) found 200.1413, \( C_{11}H_{26}O₃ \) requires 200.1412.

\[
\begin{align*}
\text{TESO} & \quad \text{(E)-Isopropyl-3-triethylsilyloxy-4-octenoate.}
\end{align*}
\]

Following general procedure B, the ester 287 (11.0 g, 55.0 mmol) was dissolved in dry DMF (110 cm³) and diisopropylethylamine (28.7 cm³, 165.0 mmol), then TESCl (18.4 cm³, 110.0 mmol) were added. The mixture was stirred at rt for 17 h, then poured into saturated aqueous sodium bicarbonate solution (200 cm³) and extracted with ether (2 x 150 cm³). The combined ethereal extracts were washed with aqueous hydrochloric acid solution (2 x 100 cm³, 1.1 moldm⁻³) then brine (100 cm³) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give the silyl ether as a pale yellow oil (23.27 g) which was used in the Takai reaction without further purification. A pure sample (88 % yield) was obtained by column chromatography on silica gel using 10:1 hexane-ether as eluent to give a colourless oil; \( \nu_{\text{max}} \) (thin film) 2956 s, 2877 s,
1735 s (C=O), 1466 w, 1374 m, 968 m and 744 m; δ\text{H}(400 MHz, CDCl\textsubscript{3}) 5.57 (1H, dt, J 15.3 and 6.8, CH\textsubscript{2}CH=), 5.39 (1H, ddt, J 15.3, 7.2 and 1.2, CH\textsubscript{2}CH=CH\textsubscript{2}), 4.94 (1H, sep, J 6.4, CHMe\textsubscript{2}), 4.49 (1H, br dt, J 7.2 and 6.4, CHOSi), 2.46 [1H, dd, J 14.4 and 7.6, CH(OSi)CH\textsuperscript{2}H\textsuperscript{3}], 2.33 [1H, dd, J 14.4 and 6.0, CH(OSi)CH\textsuperscript{2}H\textsuperscript{3}], 1.93 (2H, brq, J 7.2, CH\textsubscript{2}CH=), 1.34 (2H, sex, J 7.2, CH\textsubscript{3}CH\textsubscript{2}), 1.18 (3H, d, J 6.4, CH\textsuperscript{3}CH\textsubscript{2}), 1.17 (3H, dd, J 6.4, CH\textsuperscript{3}Me\textsuperscript{2}), 0.89 (9H, t, J 8.0, SiCH\textsubscript{2}CH\textsubscript{3}), 0.84 (3H, t, J 7.2, CH\textsubscript{3}CH\textsubscript{2}) and 0.54 (6H, q, J 8.0, SiCH\textsubscript{2}CH\textsubscript{3}); δ\text{C}(100 MHz, CDCl\textsubscript{3}) 171.0 (C), 132.6 (CH), 131.7 (CH), 71.1 (CH), 67.9 (CH), 44.7 (CH\textsubscript{2}), 34.5 (CH\textsubscript{2}), 22.6 (CH\textsubscript{2}), 22.2 (CH\textsubscript{3}), 22.1 (CH\textsubscript{3}), 14.0 (CH\textsubscript{3}), 7.1 (CH\textsubscript{3}) and 5.2 (CH\textsubscript{2}); m/z (Cl+) 315.3 [(M+H)+, 7 %], 285.2 (20), 183.2 (100); HRMS (Cl+) found 315.2352, C\textsubscript{17}H\textsubscript{34}O\textsubscript{3}Si requires 315.2355.

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(5E)-2-Isopropoxy-4-triethylsilyloxy-1,5-nonadiene.

Following general procedure C, a solution of the ester 288 (9.98 g, 31.8 mmol) and dibromomethane (4.9 cm\textsuperscript{3}, 70.0 mmol) in THF (5 cm\textsuperscript{3}) was added to the mixture formed from titanium tetrachloride (13.9 cm\textsuperscript{3}, 127.2 mmol), TMEDA (38.4 cm\textsuperscript{3}, 254.4 mmol), zinc powder (18.7 g, 286.2 mmol) and lead (II) chloride (~20 mg) in THF (100 cm\textsuperscript{3}). Stirring was continued for 17 h, whereupon the reaction mixture was cooled in an ice bath. Saturated potassium carbonate solution (40 cm\textsuperscript{3}) was added and the resulting thick black slurry stirred for 15 mins. The contents of the reaction flask were poured into ether (200 cm\textsuperscript{3}) and worked-up as before to give a pale yellow oil (8.46 g, 85 %) containing the enol ether and a small amount of TMEDA. This was used without further purification in the deprotection reaction. A pure sample was obtained as a colourless oil by chromatography on basic alumina using hexane as eluent, R\textsub{f} (alumina, hexane) 0.63; v\textsubscript{max}(thin film) 2956 s, 2876 s, 1655 m, 1459 m, 1370 m, 1005 m and 741 m; δ\text{H}(400 MHz, CDCl\textsubscript{3}) 5.53 (1H, dt, J 15.2 and 6.4, CH\textsubscript{2}CH=), 5.40 (1H, ddt, J 15.2, 6.8 and 1.2, CH\textsubscript{2}CH=CH\textsubscript{2}), 4.28 (1H, q, J 6.8, CHOSi), 4.17 (1H, sep, J 6.0, CHMe\textsubscript{2}), 3.88 (1H, d, J 1.6, =CH\textsuperscript{2}H\textsuperscript{3}), 3.81(1H, d, J 1.6, =CH\textsuperscript{2}H\textsuperscript{3}), 2.29 [1H,
dd, \( J \) 13.6 and 6.8, \( \text{CH(OSi)CH}_2^\text{H}^\text{B} \), 2.12 \( [1H, dd, \( J \) 13.6 and 6.4, \( \text{CH(OSi)CH}_2^\text{H}^\text{B} \) ], 2.03-1.89 \( [2H, m, \text{CH}_2\text{CH}=-] \), 1.37 \( [2H, \text{sex}, \( J \) 7.2, \text{CH}_3\text{CH}_2 \) ], 1.22 \( [3H, d, \( J \) 6.0, \text{CHMe}^\text{A}^\text{Me}^\text{B} \), 1.19 \( [3H, d, \( J \) 6.0, \text{CHMe}^\text{A}^\text{Me}^\text{B} \), 0.94 \( [9H, t, \( J \) 8.0, \text{SiCH}_2\text{CH}_3 \), 0.88 \( [3H, t, \( J \) 7.2, \text{CH}_3\text{CH}_2 \) ] and 0.58 \( [6H, q, \( J \) 8.0, \text{SiCH}_2\text{CH}_3 \) ]);
\( \delta_c \) \( \text{(100 MHz, CDCl}_3 \) 158.5 \( (\text{C}) \), 133.4 \( (\text{CH}) \), 130.6 \( (\text{CH}) \), 83.6 \( (\text{CH}_2 \) ), 71.8 \( (\text{CH}) \), 68.5 \( (\text{CH}) \), 45.7 \( (\text{CH}_2 \) ), 34.6 \( (\text{CH}_2 \) ), 22.8 \( (\text{CH}_2 \) ), 22.2 \( (\text{CH}_3 \) ), 21.7 \( (\text{CH}_3 \) ), 14.1 \( (\text{CH}_3 \) ), 7.2 \( (\text{CH}_3 \) ) and 5.3 \( (\text{CH}_2 \) ); \( m/z \) \( (\text{EI}+) \) 312.2 \( (\text{M}^+, 11 \%) \), 213 \( (100) \); HRMS (\( \text{EI} \) ) found 312.2487, \( C_{18}H_{36}O_2Si \) requires 312.2485.

\[\text{OH}\]
\[\text{O^\text{Pr}}\]

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\((5\text{E})\)-\text{Isopropoxy-1,5-nonadiene-4-ol}.

Following general procedure D, tetrabutylammonium fluoride \( (52 \text{ cm}^3 \) of a 1.0 \text{ moldm}^-3 \) solution in THF) and 4 \( \text{Å MS (10 g) were added to the enol ether 289} \) \( (8.02 \text{ g}, 25.7 \text{ mmol). The orange solution was stirred for 2.5 h, then poured through filter paper into saturated sodium bicarbonate solution \( (50 \text{ cm}^3 \) ), washing the sieves with ether. The layers were separated and the aqueous phase extracted with ether \( (2 \times 50 \text{ cm}^3 \) ). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark brown oil. The \textit{alcohol} was obtained as a pale yellow oil \( (1.91 \text{ g}, 38 \%) \) after column chromatography on alumina, using 1:1 ether:hexane as eluent, \( R_f \) \( (\text{alumina, 1:1 ether-hexane}) 0.61; \( \nu_{\text{max}} \text{(thin film)} 3399 \text{ br s (OH), 2560 s, 2929 s, 1654 m, 1294 m, 1121 m and 799 m; } \delta_c(400 \text{ MHz, CDCl}_3) 5.67 \text{ (1H, dtd, } J 15.2, 6.8 \text{ and 0.8, } \text{CH}_2\text{CH}=-) \), 5.44 \( \text{ (1H, dtd, } J 15.2 6.8 \text{ and 1.2, } \text{CH}_2\text{CH}=\text{CH}_2) \), 4.25 \( \text{ (1H, sep, } J 6.0, \text{CHMe}_2) \), 4.25-4.20 \( \text{ (1H, m, CHOH) , 3.96 (1H, t, } J 1.6, =\text{CH}^\text{A}^\text{H}^\text{B} \) ), 3.92 \( \text{ (1H, d, } J 1.6, =\text{CH}^\text{A}^\text{H}^\text{B} \), 2.49 \( \text{ (1H, d, } J 3.2, \text{OH)} \), 2.29 \( [1H, dd, J 14.0 \text{ and 3.8, } \text{CH(OH)}\text{CH}^\text{A}^\text{H}^\text{B} \), 2.20 \( [1H, dd, J 14.0 \text{ and 8.4, } \text{CH(OH)}\text{CH}^\text{A}^\text{H}^\text{B} \), 1.99 \( (2H, br q, J 7.2, \text{CH}_2\text{CH}=-) \), 1.38 \( (2H, \text{sex, } J 7.2, \text{CH}_3\text{CH}_2) \), 1.23 \( (3H, d, J 6.0, \text{CHMe}^\text{A}^\text{Me}^\text{B} \), 1.22 \( (3H, d, J 6.0, \text{CHMe}^\text{A}^\text{Me}^\text{B} \) and 0.88 \( (3H, t, J 7.2, \text{CH}_3\text{CH}_2) ; \delta_c(100 \text{ MHz, CDCl}_3) 158.6 \text{ (C) , 132.2 (CH), 131.9 (CH), 84.3 (CH}_2 \), 71.3 (CH), 69.2 (CH), 44.2 (CH}_2 \), 37.4 (CH}_2 \), 22.7 (CH}_2 \), 22.0 (CH}_3 \), 14.1 (CH}_3 \), 7.2 (CH}_3 \) and 5.3 (CH}_2 \); \( m/z \) \( (\text{EI}) \) 312.2 (M^+, 11 \%) , 213 (100); HRMS (\( \text{EI} \) ) found 312.2487, \( C_{18}H_{36}O_2Si \) requires 312.2485.\]
21.9 (CH₃) and 14.1 (CH₃); m/z (Cl⁺) 199.2 [(M+H)⁺, 95 %], 101.1 (100); HRMS (EI⁺) found 198.1617, C₁₂H₂₂O₂ requires 198.1620.

292
(p-Toluenesulfonyl)-cyclohexylhydrazone.⁸⁹

Tosyl hydrazine (50.12 g, 0.27 mol), was placed in a 1 L three-neck flask equipped with a stirrer and condenser. Absolute ethanol (440 cm³) was added and the flask flushed with nitrogen. Cyclohexanone (27.0 cm³, 0.27 mol) was added dropwise via syringe. Catalytic TsOH (0.50 g) was then added to the reaction mixture, which was stirred for 17 h at rt. The resulting solid was filtered, washed with cold ethanol and dried under high vacuum to give the tosyl hydrazone as a white crystalline solid (18.9 g, 76 %); \( \delta_H (400 \text{ MHz, CDCl}_3) \) 7.84 (2H, d, \( J = 8.3 \), protons ortho to Me), 7.46 (1H, brs, NH), 7.30 (2H, \( J = 8.3 \), protons meta to Me), 2.44 (3H, s, Me), 2.21 (4H, m, \( \text{CH}_2\text{C(=N)CH}_2 \)) and 1.66-1.54 (6H, m, 3 x CH₂), in agreement with data given in reference 89.

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1-Cyclohexene-carboxaldehyde.⁹⁰

Tosyl hydrazone 292 (31.58 g, 119 mmol) was suspended in TMEDA (400 cm³) under nitrogen and cooled to -78 °C. Butyllithium (340 cm³ of 1.4 mol dm⁻³, 476 mmol), was then added via syringe over 15 min. The resulting red suspension was allowed to warm to rt over 1 h. Nitrogen gas evolution occurred over 1 h. DMF (37.0 cm³, 476 mmol) was added dropwise to the reaction mixture at 0 °C.
After stirring for a further hour at 0 °C, the reaction mixture was poured into brine (400 cm³) and the layers separated. The aqueous phase was extracted with ether (3 x 200 cm³) and the combined extracts dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue distilled. The aldehyde was obtained as a pale yellow liquid (bp 70-75 °C at ~18 mmHg), (5.482 g, 48 %), δ(400 MHz, CDCl₃) 9.38 (1H, s, CHO), 6.81-6.78 (1H, m, =CH), 2.34-2.29 (2H, m, CH₂CH=CCHO), 2.19-2.17 [2H, m, CH₂C(CHO)=C], 1.70-1.61 (4H, m, cy-CH₂CH₂), in agreement with data given in reference 90.

Isopropyl 3-Hydroxy-3-(1-cyclohexenyl)-propanoate.

Following general procedure A, isopropyl acetate (4.5 cm³, 38.0 mmol) was added to a stirred solution of lithium diisopropylamide [ex. 27.1 cm³ of a 1.4 moldm⁻³ solution of butyllithium in hexane and 5.0 cm³, 38.0 mmol of diisopropylamine] in THF (80 cm³). After 50 min 293 (74.19 g, 38.0 mmol) was added and the mixture stirred for a further 45 min. The reaction mixture was then poured into aqueous hydrochloric acid solution (200 cm³, 1.1 moldm⁻³) and extracted with ether (2 x 100 cm³). The combined organic extracts were washed with aqueous hydrochloric acid solution (100 cm³, 1.1 moldm⁻³) then saturated aqueous sodium bicarbonate solution (100 cm³) and dried over magnesium sulfate. The solvent was removed in vacuo to give the aldol as a pale yellow oil (7.44 g, 92 %) sufficiently pure for the silyl protection reaction. A pure sample (81 %) was obtained as a colourless oil by chromatography on silica, using 1:1 hexane-ether as eluent, Rf (silica, 1:1 ether-hexane) 0.31; v_max(thin film) 3604 br s (OH), 2928 s, 1751 vs (C=O), 1374 s, 964 m, and 820 m; δH (400 MHz, CDCl₃) 5.69 (1H, brs, =CH), 5.03 (1H, sep, J 6.4, CHMe₂), 4.34 ( 1H, m, CHOH), 2.92 (1H, d, J 3.2, OH), 2.52 [1H, dd, J 15.6 and 8.0, CH(OH)CH³H⁸], 2.46 [1H, dd, J 15.6 and 4.8, CH(OH)CH³H⁸], 2.08-1.83 (4H, m, cy-CH₂C=CCH₂), 1.68-1.48 (4H, m, cy-CH₂CH₂) and 1.23 (6H, d, J 6.4, CHMe₂);
Isopropyl 3-Triethylsilyloxy-3-(1-cyclohexenyl)-propanoate.

Following general procedure B, the ester 294 (7.28 g, 34.3 mmol) was dissolved in dry DMF (70 cm³) and diisopropylethylamine (17.9 cm³, 102.9 mmol), then TESCl (11.5 cm³, 68.6 mmol) were added. The mixture was stirred at rt for 17 h, then poured into saturated aqueous sodium bicarbonate solution (100 cm³) and extracted with ether (2 x 100 cm³). The combined ethereal extracts were washed with aqueous hydrochloric acid solution (100 cm³, 1.1 moldm⁻³) then brine (100 cm³) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give the silyl ether as a pale yellow oil (11.96 g) which was used in the Takai reaction without further purification. A pure sample (85 %) was obtained as a colourless oil by chromatography on silica gel, using 2:1 hexane-ether as eluent, Rf (silica, 1:1 ether-hexane) 0.80; νmax (thin film) 2953 s, 2876 s, 1756 s (C=O), 4.97 (1H, brs, =CH), 4.45 (1H, dd, J 8.1 and 5.5, CHOSi), 2.52 (1H, dd, J 14.1 and 8.3, CH(OSi)CH²H²B), 2.15-1.83 (4H, m, cy-CH₂C=CCH₂), 1.72-1.35 (4H, m, cy-CH₂CH₂), 1.21 (3H, d, J 6.3, CHMe²Me²B) 1.00 (3H, d, J 6.3, CHMe²Me²B), 0.92 (9H, t, J 8.0, SiCH₂CH₃) and 0.57 (6H, q, J 8.0, SiCH₂CH₃); δc(90 MHz, CDCl₃) 171.1 (C), 139.1 (C), 123.3 (CH), 74.4 (CH), 67.5 (CH), 42.6 (CH₂), 24.9 (CH₂), 22.7 (CH₂), 22.6 (CH₂), 22.5 (CH₂), 21.9 (CH₃), 21.8 (CH₃), 6.8 (CH₃) and 4.7 (CH₂); m/z (EI+) 326.2 (M⁺, 7 %), 297.2 (32), 255.2 (100); HRMS (EI+) found 326.2276, C₁₈H₃₄O₃Si requires 326.2277.
2-Isopropoxy-4-triethylsilyloxy-4-(1-cyclohexenyl)-1-butene.

Following general procedure C, a solution of the ester 295 (8.0 g, 24.5 mmol) and dibromomethane (3.8 cm$^3$, 53.9 mmol) in THF (3 cm$^3$) was added to the mixture formed from titanium tetrachloride (10.7 cm$^3$, 98.0 mmol), TMEDA (29.6 cm$^3$, 196.0 mmol), zinc powder (14.4 g, 220.5 mmol) and lead (II) chloride (~10 mg) in THF (40 cm$^3$). Stirring was continued for 6h, whereupon the reaction mixture was cooled in an ice bath. Saturated potassium carbonate solution (40 cm$^3$) was added and the resulting thick black slurry stirred for 15 mins. The contents of the reaction flask were poured into ether (100 cm$^3$) and worked up as described to give a pale yellow oil which was chromatographed on basic alumina using hexane as eluent, giving the enol ether as a colourless oil (4.07 g, 51 %), $R_f$ (alumina, hexane) 0.68; $v_{\text{max}}$ (thin film) 2934 s, 1635 m (C=C), 1067 s, 1007 s, 946 m, 797 m and 742 s; $\delta$ (400 MHz, CDCl$_3$) 5.53 (1H, brs, cy=CH), 4.19-4.13 (2H, m, CHMe$_2$ and CHOSi), 3.86 (1H, d, $J$ 1.6, $=CH^A$H$^B$), 3.80 (1H, d, $J$ 1.6, $=CH^A$H$^B$), 2.28 [1H, dd, $J$ 13.6 and 7.2, CH(OSi)CH$^A$H$^B$], 2.21 [1H, dd, $J$ 13.6 and 6.4, CH(OSi)CH$^A$H$^B$], 2.15-2.06 (1H, brd, $J$ ~14, one of cy-CH$^A$CH$^B$, 2.00-1.86 (3H, m, cy-CH$_2$CH$^A$H$_{eq}$C=C), 1.69-1.47 (4H, m, cy-CH$^A$CH$^B$, 1.22 (3H, d, $J$ 6.0, CHMe$^A$Me$^B$) 1.19 (3H, d, $J$ 6.0, CHMe$^A$Me$^B$), 0.92 (9H, t, $J$ 8.0, SiCH$_2$CH$_3$) and 0.52 (6H, q, $J$ 8.0, SiCH$_2$CH$_3$); $\delta$ (100 MHz, CDCl$_3$) 159.0 (C), 140.1 (C), 123.0 (CH), 83.2 (CH$_2$), 76.0 (CH), 68.5 (CH$_2$), 43.5 (CH$_2$), 25.3 (CH$_2$), 23.2 (CH$_2$), 23.0 (2 x CH$_2$), 22.2 (CH$_3$), 21.8 (CH$_3$), 7.3 (CH$_3$) and 5.2 (CH$_2$); $m/z$ (El$^+$) 324.2 (M$^+$, 2 %), 225.1 (100), 193.1 (7), 132.1 (42); HRMS (El$^+$) found 324.2483, C$_{19}$H$_{36}$O$_2$Si requires 324.2485.
In the same way as above, a solution of the ester 295 (3.0 g, 9.2 mmol) and 1,1-dibromoethane (1.8 cm\(^3\), 20.2 mmol) in THF (3 cm\(^3\)) was added to the reaction mixture formed from titanium tetrachloride (4.0 cm\(^3\), 36.8 mmol), TMEDA (11.1 cm\(^3\), 73.6 mmol), Zn powder (5.4 g, 82.2 mmol) and lead (II) chloride (~10 mg) in THF (15 cm\(^3\)). The mixture was stirred for 5.5 h, and then quenched by the addition of saturated potassium carbonate solution (20 cm\(^3\)). The product was isolated as above, and obtained as a yellow oil (2.53 g) which was used in the deprotection reaction without further purification.

\(^1\)H NMR showed the formation of a 7:1 mixture of Z and E enol ethers. A pure sample of the 7:1 mixture was obtained by chromatography on basic alumina, using hexane as eluent. Data given is for the major Z isomer, \(R_f\) (alumina, hexane) 0.71; \(\nu_{\text{max}}\) (thin film) 2953 s, 2877 s, 1680 w, 1459 w, 1005 w and 741 w; \(\delta\) (400 MHz CDCl\(_3\)) 5.55 (1H, brs, cy-\(=\text{CH}\)), 4.64 (1H, q, \(J_{6.4} = \text{CHMe}\)), 4.09 (1H, brt, \(J_{6.0}\), CHOSi), 4.05 (1H, sep, \(J_{6.0}\), CHMe\(_2\)), 2.25-2.18 \([2H, m, \text{CH(OSi)}CH^{4}H^{6}]\), 2.15-2.05 (1H, m, one of cy-\(=\text{CH}_2=\text{CCH}_2\)), 2.02-1.94 (2H, m, 2 of cy-\(=\text{CH}_2=\text{CCH}_2\)), 1.93-1.82 (1H, m, one of cy-\(=\text{CH}_2=\text{CCH}_2\)), 1.70-1.45 (4H, m, cy-\(=\text{CH}_2\)), 1.53 (3H, d, \(J_{6.4} = \text{CHMe}\)), 1.19 (3H, d, \(J_{6.0}\), CHMe\(_4\)Me\(_3\)), 1.17 (3H, d, \(J_{6.0}\), CHMe\(_4\)Me\(_3\)), 0.92 (9H, t, \(J_{8.0}\), SiCH\(_2\)CH\(_3\)) and 0.55 (6H, q, \(J_{8.0}\), SiCH\(_2\)CH\(_3\)); \(\delta\) (100 MHz, CDCl\(_3\)) 150.5 (C), 140.3 (C), 122.9 (CH), 108.8 (CH), 75.4 (CH), 68.9 (CH), 40.0 (CH\(_2\)), 25.4 (CH\(_2\)), 23.24 (CH\(_2\)), 23.16 (CH\(_2\)), 23.1 (CH\(_2\)), 22.9 (CH\(_3\)), 22.7 (CH\(_3\)), 10.9 (CH\(_3\)), 7.2 (CH\(_3\)) and 5.1 (CH\(_2\)); \(m/z\) (EI\(^+\)) 338.5 (M\(^+\), 5 %), 267.2 (7), 225.2 (100); HRMS (EI\(^+\)) found 338.2641, \(C_{20}H_{36}O_2Si\) requires 338.2641.
Following general procedure D, tetrabutylammonium fluoride (37.6 cm$^3$ of a 1.0 moldm$^{-3}$ solution in THF) and 4 Å MS (5.3 g) were added to the enol ether (8.02 g, 25.7 mmol). The orange solution was stirred for 1.5 h, then poured through filter paper into saturated sodium bicarbonate solution (50 cm$^3$), washing the sieves with ether. The layers were separated and the aqueous phase extracted with ether (2 x 50 cm$^3$). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark brown oil. The alcohol was obtained as a pale yellow oil (1.58 g, 60 %) after column chromatography on basic alumina, using 3:2 hexane-ether as eluent, R$_f$ (alumina, 2:1 ether-hexane) 0.62; $\nu$$_{max}$(thin film)/cm$^{-1}$ 3536 br (OH), 2927 s, 1654 m (C=C), 1620 m and 995 s; $\delta$$_n$(400 MHz, CDCl$_3$) 5.69 (1H, brs, cy-=CH), 4.24 (1H, sep, J 6.0, CHMe$_2$) 4.12 (1H, m, CHOH), 3.96 (1H, d, J 1.7, $=$CH$^A$H$^B$), 3.91 (1H, d, J 1.6, $=$CH$^A$H$^B$), 2.41 (1H, brs, OH), 2.30 [1H, dd, J 13.9 and 4.0, CH(OH)CH$^A$H$^B$], 2.24 [1H, dd, J 13.6 and 8.3, CH(OH)CH$^A$H$^B$], 1.99-1.88 (4H, m, cy-CH$^2$C=CCH$_2$), 1.68-1.48 (4H, m, cy-CH$_2$CH$_2$), 1.23 (3H, d, J 6.0, CHMe$^A$Me$^B$) and 1.22 (3H, d, J 6.0, CHMe$^A$Me$^B$); $\delta$$_c$(100 MHz, CDCl$_3$) 159.2 (C), 139.3 (C), 122.9 (CH), 84.0 (CH$_2$), 74.7 (CH), 69.2 (CH), 42.3 (CH$_2$), 25.3 (CH$_2$), 24.4 (CH$_2$), 23.02 (CH$_2$), 23.01 (CH$_2$), 22.0 (CH$_3$) and 21.9 (CH$_3$); m/z (Cl+) 211.1 [(M+H)$^+$, 45 %], 193.1 (100); HRMS (Cl+) found 211.1697, C$_{13}$H$_{23}$O$_2$ [(M+H)$^+$] requires 211.1698.
(Z)-3-Isopropoxy-1-(1-cyclohexenyl)-3-penten-1-ol.

In the same way as above, TBAF (22.4 cm$^3$ of a 1.0 moldm$^{-3}$ solution in THF) was added to enol ether 297 (2.53 g, 7.46 mmol). 4 Å MS (3.3 g) were also added and the mixture stirred for 2 h. The reaction mixture was poured through filter paper and worked up as above to give the product as a dark brown oil. A mixture of $E$ and $Z$ alcohols was isolated as a pale yellow oil (840 mg, 58 %) after column chromatography on basic alumina, using 3:2 hexane-ether as eluent. A geometrically pure sample of the $Z$ alcohol (269 mg) was obtained after further chromatography, $R_f$ (alumina, 2:1 ether-hexane) 0.73 ($E$), 0.68 ($Z$); $v_{\text{max}}$(thin film) 3423 br (OH), 2973 s, 2928 s, 1678 m (C=C), 1449 w, 1114 m and 919 w; $\delta_{\text{H}}$(400 MHz CDCl$_3$) 5.71 (1H, brs, cy-\(=\text{CH}\)), 4.79 (1H, q, $J$ 6.7, \(=\text{CHMe}\)), 4.10 (1H, sep, $J$ 6.1, CHMe$_2$), 4.10-4.08 (1H, m, CHO$_2$), 2.34 [1H, ddd, $J$ 14.5, 2.2 and 1.1, CH(OH)CH$_2$], 2.25 (1H, d, $J$ 2.4, OH), 2.17 [1H, dd, $J$ 14.5 and 9.4, CH(OH)CH$_2$], 2.13-1.88 (4H, m, cy-CH$_\text{Ph}$C=CH$_2$), 1.68-1.48 (4H, m, cy-CH$_\text{Ph}$C=CH$_2$), 1.58 (3H, d, $J$ 6.7, \(=\text{CHMe}\)), 1.22 (3H, d, $J$ 6.1, CHMe$_2$) and 1.18 (3H, dd, $J$ 6.1, CHMe$_2$); $\delta_C$(100 MHz, CDCl$_3$) 150.8 (C), 139.5 (C), 123.0 (CH), 110.3 (CH), 74.2 (CH), 70.0 (CH), 39.3 (CH$_2$), 25.3 (CH$_2$), 24.3 (CH$_2$), 23.0 (CH$_2$), 22.99 (CH$_2$), 22.94 (CH$_3$), 22.6 (CH$_3$) and 11.1 (CH$_3$); $m/z$ (Cl$^+$) 225.2 [(M+H)$^+$, 5 %), 207.2 (99), 115.2 (100); HRMS (Cl$^+$) found 225.1854, C$_{14}$H$_{25}$O$_2$ [(M+H)$^+$] requires 225.1855.

\begin{center}
\includegraphics[width=0.4\textwidth]{image.png}
\end{center}

307

Isopropyl (E)-2-Methyl-3-hydroxy-5-phenyl-4-pentenoate.

Following general procedure A, isopropyl propionate (11.5 cm$^3$, 86.1 mmol) was added to a stirred solution of lithium diisopropylamide [ex. 34.4 cm$^3$ of a 2.5
moldm$^{-3}$ solution of butyllithium in hexane and 12.1 cm$^3$, 86.1 mmol of diisopropylamine] in THF (170 cm$^3$). After 45 min, E-Cinnamaldehyde (10.9 cm$^3$, 86.1 mmol) was added and the mixture stirred for a further 50 min. The reaction mixture was then poured into aqueous hydrochloric acid solution (220 cm$^3$, 1.1 moldm$^{-3}$) and extracted with ether (2 x 100 cm$^3$). The combined organic extracts were washed with aqueous hydrochloric acid solution (100 cm$^3$, 1.1 moldm$^{-3}$), then saturated aqueous sodium bicarbonate solution (100 cm$^3$) and dried over magnesium sulfate. The solvent was removed in vacuo to give a 1:1 mixture of diastereomeric aldols as a pale yellow oil (18.54 g, 87 %) sufficiently pure for the silyl protection reaction. A pure sample was obtained by chromatography on silica using 1:1 ether-hexane as eluent, to give the aldols as a colourless oil (~80 %), $R_f$ (alumina, 1:1 ether-hexane) 0.39; $\nu_{max}$ (thin film)/cm$^{-1}$ 3449 br s (OH), 2980 s, 2937 m, 1726 vs (C=O), 1451 m, 1375 m, 1182 s, 1108 s, 750 s and 694 s; $\delta$ (360 MHz, CDCl$_3$) 7.39-7.22 (10H, m, Ph$^A$ and Ph$^B$), 6.65 (1H, d, $J$ 15.9, Ph$^B$OH), 6.64 (1H, d, $J$ 15.9, Ph$^A$OH), 6.19 (2H, dd, $J$ 15.9 and 6.5, Ph$^A$=CH$^A$ and Ph$^B$=CH$^B$), 5.11-5.00 (2H, m, CH$_2$Me$_2$ and CH$_2$Me), 4.56 (1H, q with poorly resolved smaller couplings, $J$ 4.6, CH$_3$OH), 4.37 (1H br dd, $J$ 12.6 and 5.8, CH$_3$OH), 2.92 (1H, brs, OH$^A$), 2.90 (1H, brs, OH$^B$), 2.71-2.58 [2H, m, CH(OH)CH$_2$(Me) and CH(OH)CH$_2$(Me)] and 1.26-1.21 (18H, doublets, Me groups); $\delta$ (90 MHz, CDCl$_3$) 175.0 (C), 174.9 (C), 136.5 (C), 136.4 (C), 132.0 (CH), 131.4 (CH), 129.3 (CH), 128.6 (CH), 128.54 (CH), 128.53 (CH), 127.8 (CH), 127.7 (CH), 126.51 (CH), 126.46 (CH), 74.6 (CH), 73.0 (CH), 68.2 (CH), 68.1 (CH), 45.6 (CH), 45.1 (CH), 21.79 (CH$_3$), 21.78 (CH$_3$), 21.70 (CH$_3$), 14.14 (CH$_3$) and 11.55 (CH$_3$); $m/z$ (EI$^+$) 248.1 (M$^+$, 20%), 206.1 (10), 133.1 (100); HRMS (EI$^+$) found 248.1411, C$_{15}$H$_{20}$O$_3$ requires 248.1412.

Isopropyl (E)-2-Methyl-3-triethylsilyloxy-5-phenyl-4-pentenoate.

Following general procedure B, the ester 307 (17.6 g, 71.0 mmol) was dissolved in dry DMF (140 cm$^3$), and diisopropylethylamine (37.0 cm$^3$, 213.0 mmol), then
TESCI (24.0 cm³, 142.0 mmol) were added. The mixture was stirred at rt for 23 h, then poured into saturated aqueous sodium bicarbonate solution (200 cm³) and extracted with ether (3 x 200 cm³). The combined ethereal extracts were washed with aqueous hydrochloric acid solution (2 x 100 cm³, 1.1 mol dm⁻³) then brine (100 cm³) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil. The silyl ethers (1:1 mixture of diastereomers) were obtained as a pale yellow oil sufficiently pure for the Takai reaction (27.46 g) after passing the crude material through a short column of alumina, using gradient elution (10:1 hexane-ether to ether). A pure sample (~70 %) was obtained by column chromatography on alumina using 10:1 hexane:ether as eluent to give a very pale yellow oil, $v_{\text{max}}$ (thin film)/cm⁻¹ 2956 s, 2877 s, 1731 vs (C=O), 1458 m, 1374 s, 1236 s, 1110 vs, 1064 s and 746 vs; $\delta$ (400 MHz, CDCl₃) 7.45-7.21 (10H, m, PhA and PhB), 6.53 (1H, d, J 15.6, PhCH=), 6.50 (1H, d, J 14.0, PhCH=), 6.19 (1H, dd, J 16.0 and 7.2, PhCH=CH⁺), 6.09 (1H, dd, J 15.6 and 7.6, PhCH=CH⁻), 5.03 (1H, sep, J 6.0, CH₃Me), 4.95 (1H, sep, J 6.0, CH₂Me), 4.44 (2H, dd, J 16.7 and 7.9, CH³OSi and CH⁴OSi), 2.59 [1H, qn, J 7.6, CH(OSi)CH⁺(Me)], 2.56 [1H, qn, J 6.8, CH(OSi)CH⁻(Me)], 1.26 (3H, d, J 6.0, CHMe⁺Me⁻), 1.24 (3H, d, J 6.0, CHMe⁺Me⁻), 1.21 (3H, d, J 6.0, CHMe⁺Me⁻), 1.20 (3H, d, J 6.0, CHMe⁺Me⁻), 1.13 [3H, d, J 6.4, CH(OSi)CH(Me⁺)], 1.06 [3H, d, J 6.4, CH(OSi)CH(Me⁻)], 0.99-0.92 (18H, m, OSiCH₂Me⁺ and OSiCH₂Me⁻) and 0.64-0.55 (12H, m, OSiCH₂A and OSiCH₂B); $\delta$ (100 MHz, CDCl₃) 174.4 (C), 173.9 (C), 136.7 (C), 136.6 (C), 131.7 (CH), 130.9 (CH), 130.7 (CH), 130.1 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.5 (CH), 126.4 (CH), 75.8 (CH), 75.3 (CH), 67.51 (CH), 67.48 (CH), 47.5 (CH), 47.4 (CH), 21.9 (CH₃), 21.8 (CH₃), 13.1 (CH₃), 12.9 (CH₃), 6.8 (CH₃), 4.94 (CH₂) and 4.91 (CH₂); m/z (El⁺) 362.2 (M⁺, 3 %), 333.2 (12), 291.1 (30), 247.2 (100); HRMS (El⁺) found 362.2278, C₂₁H₃₄O₃Si requires 362.2277.
Following general procedure C, a solution of the ester 308 (10.0 g, 27.6 mmol) and 1,1-dibromoethane (5.5 cm³, 60.7 mmol) in THF (5 cm³) was added to the mixture formed from titanium tetrachloride (12.1 cm³, 110.4 mmol), TMEDA (33.3 cm³, 220.8 mmol), zinc powder (16.24 g, 248.4 mmol) and lead (II) chloride (~20 mg) in THF (90 cm³). Stirring was continued for 17 h, whereupon the reaction mixture was cooled in an ice bath. Saturated potassium carbonate solution (40 cm³) was added and the resulting thick black slurry stirred for 15 min. The contents of the reaction flask were poured into ether (200 cm³) and worked-up as previously described to give a pale yellow oil (7.59 g, 75 %) containing the enol ethers and a small amount of TMEDA. ¹H NMR Spectroscopy showed the formation of only the Z isomer of each diastereomer.

This material was used without further purification in the deprotection reaction;

δH (400 MHz, CDCI₃) 7.39-7.19 (10H, m, PhA and PhB), 6.53 (1H, d, J 15.9, PhCHₐ =), 6.52 (1H, dd, J 15.9 and 1.0, PhCHₜ =), 6.27 (1H, dd, J 15.9 and 6.0, PhCH=CHₜ), 6.09 (1H, dd, J 15.9 and 5.5, PhCH=CHₐ), 4.79 (1H, q, J 6.8, =CHₚMe), 4.78 (1H, q, J 6.8, =CHₚMe), 4.59-4.56 (1H, m, CHₐOSi), 4.44-4.41 (1H, m, CHₚOSi), 4.19 (1H, sep, J 6.1, CHₚMe₂), 4.10 (1H, sep, J 6.1, CHₚMe₂), 2.60-2.54 [1H, m, CH(OSi)CHₚ(Me)], 2.37-2.33 [1H, m, CH(OSi)CHₚ(Me)], 1.62 (3H, d, J 6.8, =CHMeₚ), 1.60 (3H, d, J 6.8, =CHMeₚ), 1.32 (3H, d, J 6.1, CHₚMeₚMeₚ), 1.25 (3H, d, J 6.1, CHₚMeₚMeₚ), 1.18 (3H, d, J 6.1, CHₚMeₚMeₚ), 1.15 (3H, d, J 6.1, CHₚMeₚMeₚ), 1.07 [3H, d, J 6.9, CH(OSi)CH(Meₚ)], 1.00-0.93 [21H, m, CH(OSi)CH(Meₚ), SiCH₂Meₚ and SiCH₂Meₚ] and 0.64-0.58 (12H, m, OSiCH₂ and OSiCH₂); δC (100 MHz, CDCI₃) 155.0 (C), 154.7 (C), 137.5 (C), 137.4 (C), 133.2 (CH), 130.0 (CH), 129.8 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.1 (CH), 127.0 (CH), 126.34 (CH), 126.31 (CH), 107.3 (CH), 106.8 (CH), 74.4 (CH), 73.5 (CH), 69.7 (CH), 69.3 (CH), 42.1 (CH), 42.4 (CH), 23.08
(CH₃), 23.06 (CH₃), 22.1 (CH₃), 22.0 (CH₃), 13.0 (CH₃), 12.1 (CH₃), 10.9 (CH₃),
6.9 (CH₃), 6.8 (CH₃) 6.4 (CH₃), 5.1 (CH₂) and 4.9 (CH₂).

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\begin{align*}
&\text{OH} \\
&\text{Ph} \\
&\text{O}^\text{Pr}
\end{align*}
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310a/b

(\textit{1E,5Z})-5-isopropoxy-4-methyl-1-phenyl-1,5-heptadiene-3-ol.

Following general procedure D, tetrabutylammonium fluoride (40 cm³ of a 1.0
moldm⁻³ solution in THF) and 4 Å MS (10 g) were added to the enol ether 309
(7.59 g, 20.3 mmol). The orange solution was stirred for 1.5 h, then poured
through filter paper into saturated sodium bicarbonate solution (100 cm³),
washing the sieves with ether. The layers were separated and the aqueous
phase extracted with ether (3 x 100 cm³). The combined organic extracts were
dried over magnesium sulfate and the solvent removed under reduced pressure
to give a dark brown oil. The alcohols (1:1 mixture of diastereomers) were
obtained as a pale yellow oil (2.172 g, 41 %) after column chromatography on
alumina using gradient elution (pet ether 40/60 to ether); Rₗ (alumina, 1:1
hexane-ether) 0.62; νmax(thin film)/cm⁻¹ 3448 br s (OH), 2973 s, 2916 s, 1672 s,
1450, s, 1370 s, 1187 s, 1112 s, 1043 s, 967 s, 748 m and 694 m; δm(400 MHz,
CDCl₃) 7.39 (4H, d, J 7.9, o-PhA and o-PhB), 7.31 (4H, d, J 7.8, m-PhA and m-
PhB), 7.23 (2H, t, J 7.8, p-PhA and p-PhB), 6.61 (1H, d, J 15.9, PhCH₄=), 6.60
(1H, d, J 15.9, PhCH₂=), 6.22 (1H, dd, J 15.9 and 6.0, PhCH=CH₄), 6.21 (1H,
dd, J 15.9 and 7.0, PhCH=CH₂), 4.90 (1H, q, J 6.8, =CH²Me), 4.87 (1H, q, J
6.8, =CH²Me), 4.44-4.40 (1H, m, CH²OH), 4.28-4.16 (3H, m, CH²OH, CH²Me
and CH²Me₂), 2.86 (1H, d, J 3.4, OH²), 2.62-2.59 [1H, m, CH(OH)CH²(Me)],
2.54 (1H, d, J 4.8, OH²), 2.45 [1H, br qn, J 7.0, CH(OH)CH²(Me)], 1.66 (6H, d, J
6.8, =CHMe² and =CHMe²), 1.31 (3H, d, J 6.1, CHMe²Me²), 1.29 (3H, d, J
6.1, CHMe²Me²), 1.20 (3H, d, J 6.1, CHMe²Me²), 1.19 (3H, d, J 6.1,
CHMe²Me²), 1.05 [3H, d, J 7.1, CH(OH)CH(Me²)], and 1.03 [3H, d, J 6.4,
CH(OH)CH(Me²)], δm(100 MHz, CDCl₃) 155.2 (C), 154.7 (C), 137.1 (C), 136.9
(C), 131.2 (CH), 130.5 (CH), 130.3 (CH), 130.2 (CH), 128.4 (CH), 127.4 (CH),
127.3 (CH), 126.44 (CH), 126.36 (CH), 108.0 (CH), 107.3 (CH), 76.7 (CH),
73.8 (CH), 70.6 (CH), 42.5 (CH), 41.4 (CH), 23.0 (CH₃), 22.9 (CH₃), 22.1 (CH₃),
22.0 (CH₃), 15.0 (CH₃), 12.3 (CH₃), 11.04 (CH₃) and 10.97 (CH₃); m/z (EI+)
260.2 (M⁺, 5 %), 205 2 (12), 133.1 (100); HRMS (EI+) found 260.1779 C₁₇H₂₄O₂
requires 260.1776.

318
(S)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone.⁶⁴

(S)-4-Benzyl-2-oxazolininone (5.426 g, 29.60 mmol) was reacted with propionyl
chloride (2.7 cm³, 31.02 mmol) according to the method of Evans⁶⁴ to give the
acylated oxazolidinone as a white crystalline solid (6.727 g, 97 %), [α]₀ +79.9 (c
0.118 in CHCl₃) literature value⁹¹ +77.5

Dibutylboron triflate

Tributylborane (9.75 cm³, 40.0 mmol) was reacted with triflic acid (3.5 cm³, 40.0
mmol) according to the method of Evans,⁹² to give dibutylboron triflate (8.976 g,
82 %) after distillation.
The oxazolidinone 318 (4.008 g, 17.15 mmol) was dissolved in dry DCM (43 cm$^3$) under nitrogen and cooled to -78 °C. Triethylamine (2.90 cm$^3$, 20.52 mmol) was added, followed by freshly distilled dibutylboron triflate (4.70 cm$^3$, 18.87 mmol). The solution was stirred at -78 °C for 1 h and at 0 °C for 15 min. The reaction mixture was recooled to -78 °C and cinnamaldehyde (2.27 cm$^3$, 18.01 mmol) added in one portion. The pale yellow solution was stirred at -78 °C for 30 min, 15 min at -78 to 0 °C and a further 30 min at 0 °C. The reaction was quenched by the addition of sodium acetate (40 cm$^3$, 1 moldm$^{-3}$ solution in 90 % methanol/water). After 10 min 30 % w/w aqueous hydrogen peroxide (9 cm$^3$) was added dropwise and the mixture stirred for an additional 15 min at 10-15 °C. The mixture was then partitioned between water (400 cm$^3$) and hexane (250 cm$^3$) and the layers separated. The organic phase was washed with saturated sodium bicarbonate solution (100 cm$^3$), then brine (100 cm$^3$). [Note: on pouring the reaction mixture into the hexane/water mixture, a solid precipitated in the hexane phase. This was redissolved by the addition of DCM]. The organic phase was dried over sodium sulfate, and concentrated under reduced pressure to give the crude aldol as a sticky yellow solid (6.36 g). $^1$H NMR spectroscopy showed this to be a 2:1 mixture of the aldol and unreacted cinnamaldehyde. Trituration with hexane gave the aldol as a white solid pure enough for the protection reaction (one diastereomer), (3.446 g, 55 %); $\delta_H$(400 MHz, CDCl$_3$) 7.46-7.22 (10H, m, ArH), 6.71 (1H, dd, $J$ 16.0 and 1.0, PhCH=CH), 6.24 (1H dd, $J$ 16.0 and 5.9, PhCH=), 4.76-4.70 (2H, m, CHO and NCH), 4.25-4.19 (2H, m, OCH$_2$), 4.02 (1H, dq, $J$ 7.0 and 3.9, CHMe), 3.28 (1H dd, $J$ 13.4 and 3.8, PhCH$_3$H$_2$), 2.96 (1H, d, $J$ 2.6, OH), 2.83 (1H, dd, $J$ 13.4 and 9.4, PhCH$_3$H$_2$) and 1.33 (3H, d, $J$ 7.0, Me).
320

[3(2S,3R,4E),4S]-3-[3-(tert-Butyldimethylsilyloxy)-2-methyl-1-oxo-5-phenyl-4-pentenyl]-4-(phenylmethyl)-2-oxazolidinone.

The aldol 319 (3.446 g, 9.40 mmol) was dissolved in dry DMF (23.5 cm³) under nitrogen and diisopropylethylamine (4.9 cm³, 28.40 mmol), then TBSCI (12.83 g, 18.80 mmol) were added with cooling on an ice bath. The ice bath was removed and the mixture stirred at rt for 17 h, then poured into saturated aqueous sodium bicarbonate solution (50 cm³) and extracted with ether (2 x 50 cm³). The combined ethereal extracts were washed with aqueous hydrochloric acid solution (50 cm³, 1.1 moldm⁻³) then brine (50 cm³) and dried over sodium sulfate. The solvent was removed under reduced pressure to give the diastereomerically pure silyl ether as a sticky white solid (5.29 g). A sample pure enough for the next reaction (4.19 g, 93 %) was obtained as a white solid by column chromatography on neutral alumina, using 1:1 ether-pet ether 40/60 as eluent. An analytically pure sample gave the following data, Rₜ (alumina, 1:1 ether:hexane) 0.64; (Found C 70.0; H 7.6; N 2.8, C₂₈H₃₇N₀₄Si requires C 70.1; H 7.8; N 2.9); mp 81-82°c; [α]D +74.59° (c=0.089 in CHCl₃); νmax(KBr) 2931 w, 2856 w, 1764 vs [0(C=0)N], 1693 s, (NC=O), 1389 m, 1200 m, 1074 s, 835 m and 773 m; δH(360 MHz, CDCl₃) 7.38-7.19 (10H, m, Ar), 6.50 (1H, d, J 16.0, PhCH=), 6.22 (1H, dd, J 16.0 and 7.2, PhCH=CH₂), 4.54 (1H, ddt, J 7.6, 3.2 and 2.2, NCH), 4.46 (1H, btt, J 6.79, CHOSi), 4.10 (1H, qn, J 6.8, CHMe), 4.08 (1H, dd, J 9.1 and 2.1, OCH₄H₅B), 3.92 (1H, t, 8.0, OCH₄H₅B), 3.26 (1H, dd, J 13.4 and 3.2, CH₄H₅BPh), 2.76 (1H, dd, J 13.4 and 9.7, CH₄H₅BPh), 1.27 (3H, d, J 6.8, Me), 0.90 (9H, s, SiCMe₃), 0.06 (3H, s, SiMe₅Me₅B) and 0.02 (3H, s, SiMe₅Me₅B); δC(90 MHz, CDCl₃) 174.7 (C), 153.2 (C), 136.6 (C), 135.3 (C), 130.7 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.4 (CH), 75.5 (CH), 65.9 (CH₂), 55.6 (CH), 44.5 (CH), 37.8 (CH₂), 25.7 (CH₃), 18.1 (C), 12.9 (CH₃), -4.1 (CH₃) and -5.0 (CH₃); m/z (El⁺) 479 (M⁺, 0.1 %), 422 [M-
(2S,3R,4E)-2-Methyl-3-(tert-butyldimethylsilyloxy)-5-phenyl-4-pentenoic acid.

The oxazolidinone 320 (4.19 g, 8.73 mmol) was dissolved in aqueous THF (30 cm³, 10:1 THF-H₂O) and cooled on an ice bath. Hydrogen peroxide (3.97 cm³ of a 30 % w/w aqueous solution, 34.92 mmol) was added dropwise over 5 min, followed by a solution of lithium hydroxide (586 mg LiOH.H₂O, 13.97 mmol) in water (17 cm³) in one portion. The resulting white emulsion was stirred at 0 °C for 2 h, then allowed to warm to rt. After a further 2 h, TLC analysis of the reaction mixture showed the absence of starting material. The mixture was diluted with DCM (25 cm³) and the layers separated. The aqueous phase was extracted with DCM (3 x 25 cm³), and the combined extracts dried over magnesium sulfate. Concentration under reduced pressure gave a pale yellow oil which was chromatographed on silica using 1:1 EtOAc-hexane containing 2 % AcOH as eluent, to give the acid as a very pale yellow viscous oil containing one diastereomer (2.33 g, 83 %). An analytically pure sample gave the following data; [α]₀ -15.9° (c=0.07 in CHCl₃); Rₖ (silica, EtOAc) 0.93; νmax (thin film) 2958 vbr vs (OH), 1713 vs (C=O), 1472 s, 1254 m, 1023 m and 776 s; δH (400 MHz, CDCl₃) 7.38-7.16 (5H, m, Ph), 6.56 (1H, d, J 15.8, PhCH=), 6.13 (1H, dd, J 15.8 and 7.2, PhCH=CH₂), 4.57 (1H, dd, J 6.8 and 5.2, CHOSi), 2.71 (1H, dq, J 7.2 and 4.8, CHMe), 1.18 (3H, d, J 7.2, Me), 0.91 (9H, s, SiCMe₃), 0.10 (3H, s, SiMe₃Me₀) and 0.06 (3H, s, SiMe₃Me₀); δC (90 MHz, CDCl₃) 177.2 (C), 136.3 (C), 132.1 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 126.6 (CH), 75.2 (CH), 46.2 (CH), 25.7 (CH₃), 18.1 (C), 11.8 (CH₃), -4.2 (CH₃) and -5.1 (CH₃); m/z (Cl, NH₃) 338.3 [(M+NH₄)⁺, 60 %], 206.2 (100); HRMS (Cl, NH₃) found 338.2158, C₁₈H₃₈NO₃Si [(M+NH₄)⁺] requires 338.2151.
Ethyl (2S,3R,4E)-2-Methyl-3-(tert-butyldimethylsilyloxy)-5-phenyl-4-pentenoate.

The acid 321 (2.33 g, 7.27 mmol) and triphenylphosphine (2.10 g, 8.00 mmol) were dissolved in dry THF (25 cm³) under nitrogen. Anyhydrous ethanol (0.47 cm³, 8.00 mmol) was added and the clear, colorless solution immersed in a dry ice bath at -40 °C. Diethylazodicarboxylate (1.26 cm³, 8.00 mmol) was then added dropwise to the reaction mixture. The resulting pale orange solution was allowed to warm slowly to ambient temperature and stirred for 17 h. The reaction mixture was then concentrated under reduced pressure, and 100 cm³ 1:1 ether-hexane added to the residue. The precipitate (triphenylphosphine oxide) was pulverised and filtered off through a short plug of neutral alumina. The filtrate was washed with an additional 100 cm³ 1:1 ether-hexane and the combined washings dried over sodium sulfate. Concentration in vacuo gave the ester as a yellow oil (2.18 g, 86 %) containing one diastereomer. A pure sample was obtained by washing the oil through a short column of neutral alumina with hexane to give a colourless oil (1.872 g, 74 %); [α]D -26.39° (c=0.036 in CHCl₃); vₘₚₜₜ(thin film) 2956 m, 2930 m, 1735 s (C=O), 1252 m, 1062 m and 836 m; δH(400 MHz, CDCl₃) 7.38-7.22 (5H, m, Ph), 6.52 (1H, d, J 16.0, PhCH=), 6.19 (1H, dd, J 16.0 and 7.2, PhCH=CH), 4.55 (1H, t, J 6.8, CHO), 4.14-4.06 (2H, m, OCH₂), 2.60 (1H, qn, J 6.8, CH₂Me), 1.22 (3H, t, J 7.2, CH₂Me), 1.21 (3H, d, J 7.2, CHMe), 0.91 (9H, s, SiMe₃), 0.07 (3H, s, SiMe³A-MeB) and 0.03 (3H, s, SiMe³A-MeB); δC(100 MHz, CDCl₃) 174.8 (C), 137.2 (C), 131.3 (CH), 131.0 (CH), 129.0 (CH), 127.0 (CH), 126.9 (CH), 75.4 (CH), 60.7 (CH₂), 47.6 (CH), 26.2 (CH₃), 18.5 (C), 14.6 (CH₃), 12.4 (CH₃), -3.6 (CH₃) and -4.6 (CH₃); m/z (Cl, NH₃) 366.2 [(M+NH₄)⁺, 6 %], 234.1 (100); HRMS (Cl, NH₃) found 366.2459, C₂₀H₃₆NO₃Si [(M+NH₄)⁺] requires 366.2464.
323

\[(1E,3R,4S,5Z)\text{-}4\text{-Methyl-3-}\left(\text{tert-butyl}+\text{dimethylsilyloxy}\right)\text{-}5\text{-ethoxy-1-phenyl-1,5-heptadiene.}\]

Following general procedure C, a solution of the ester 322 (1.817 g, 5.21 mmol) and 1,1-dibromoethane (1.04 cm\(^3\), 11.46 mmol) in THF (5 cm\(^3\)) was added to the mixture formed from titanium tetrachloride (2.29 cm\(^3\), 20.84 mmol), TMEDA (6.29 cm\(^3\), 41.68 mmol), zinc powder (3.07 g, 46.89 mmol) and lead (II) chloride (~10 mg) in THF (7 cm\(^3\)). Stirring was continued for 14 h, whereupon the reaction mixture was cooled in an ice bath. Saturated potassium carbonate solution (10 cm\(^3\)) was added and the resulting thick black slurry stirred for 15 min. The contents of the reaction flask were poured into ether (50 cm\(^3\)) and worked-up as previously to give a pale yellow oil, which was chromatographed on neutral alumina using hexane as eluent to give the diastereomerically pure enol ether (Z isomer only by \(^1\)H NMR spectroscopy) as a colourless oil (1.521 g, 81 %); [\(\alpha\)]\(_D\)\(-10.85\) (c=0.0357 in CHCl\(_3\)); \(v\)\(_{\text{max}}\)(thin film) 2956 s, 2857 s, 1677 m, 1252 m, 110 m and 692 m; \(\delta\)(400 MHz, CDCl\(_3\)) 7.37 (2H, d, J 7.6, o-Ph), 7.32 (2H, t, J 7.2, m-Ph), 7.23 (1H, d, J 7.2, p-Ph), 6.53 (1H, d, J 15.6, PhCH\(=\)H), 6.24 (1H, dd, J 15.6 and 6.0, PhCH=CH), 4.72 (1H, q, J 6.7, =CHMe), 4.41 (1H, brt, J 5.2, CHOSi), 3.84 (1H, dq, J 9.6 and 6.8, CH\(^2\)H\(^2\)), 3.71 (1H, dq, J 9.6 and 6.8, CH\(^2\)H\(^2\)), 2.35 (1H, br qn, J 6.0, CHMe), 1.60 (3H, d, J 6.4, =CHMe), 1.27 (3H, t, J 7.0, CH\(_2\)Me), 1.06 (3H, d, J 6.8, CHMe), 0.93 (9H, s, SiMe\(_3\)) , 0.04 (3H, s, SiMe\(_3\)) and 0.02 (3H, s, SiMe\(_3\)) ; \(\delta\)(100 MHz, CDCl\(_3\)) 157.2 (C), 137.8 (C), 133.6 (CH), 129.4 (CH), 128.9 (CH), 127.5 (CH), 126.7 (CH), 106.8 (CH), 74.3 (CH), 65.7 (CH\(_2\)), 43.8 (CH), 26.3 (CH\(_3\)), 18.7 (C), 16.1 (CH\(_3\)); 13.3 (CH\(_3\)), 11.2 (CH\(_3\)), -3.9 (CH\(_3\)) and -4.6 (CH\(_3\)); \(m/z\) (El\(^+\)) 360.3 (M\(^+\), 0.1 %), 247.2 (100); HRMS (El\(^+\)) found 360.2481, C\(_{22}\)H\(_{36}\)O\(_2\)Si requires 360.2485.
324

\((1E,3R,4S,5Z)\) 4-Methyl-5-ethoxy-1-phenyl-1,5-heptadiene-3-ol.

Following general procedure D, tetrabutylammonium fluoride (12.7 cm\(^3\) of a 1.0 moldm\(^{-3}\) solution in THF) and 4 Å MS (2 g) were added to the enol ether 323 (1.521 g, 4.22 mmol). The orange solution was stirred for 1 h, then poured through filter paper into saturated sodium bicarbonate solution (50 cm\(^3\)). The layers were separated and the aqueous phase extracted with ether (2 x 50 cm\(^3\)). The combined organic extracts were dried over sodium sulfate and the solvent removed under reduced pressure to give a brown oil. Column chromatography on neutral alumina using 2:1 hexane-ether as eluent gave the alcohol (799 mg, 77 %) as a pale yellow viscous oil. Surprisingly, some equilibration of the enol ether geometry took place during chromatography, and several columns were required to give the pure \(Z\) isomer (659 mg, 63 %), \(R_t\) (alumina, 1:1 ether-hexane) 0.54; \([\alpha]_D\) +44.6\(^\circ\) (c=0.034 in CHCl\(_3\)); \(\nu_{\max}\) (thin film) 3448 br s (OH), 2976 s, 1672 s (C=CHMe), 1495 m, 1180 m, 965 s, 748 s and 694 s; \(\delta_t\) (400 MHz, CDCl\(_3\)) 7.38 (2H, d, \(J 7.6, \alpha\)-Ph), 7.31 (2H, t, \(J 7.2, m\)-Ph), 7.23 (1H, d, \(J 7.2, p\)-Ph), 6.61 (1H, d, \(J 16.0, PhCH=\)), 6.22 (1H, dd, \(J 16.0\) and 6.0, PhCH=CH\(_2\)), 4.82 (1H, q, \(J 6.7, \text{=CHMe}\)), 4.45-4.40 (1H, m, CHOSi), 3.94 (1H, dq, \(J 9,6\) and 7.2, \(CH^A\)), 3.74 (1H, dq, \(J 9.6\) and 7.2, \(CH^A\)), 2.65 (1H, d, \(J 4.8, OH\)), 2.59-2.57 (1H, m, \(CHMe\)), 1.65 (3H, d, \(J 6.8, \text{=CHMe}\)), 1.31 (3H, t, \(J 7.2, CH_2Me\)) and 1.04 (3H, d, \(J 7.2, CHMe\)); \(\delta_\text{c}(100 \text{ MHz, CDCl}_3) 157.6 \text{ (C)}, 137.5 \text{ (C)}, 130.8 \text{ (CH)}, 130.7 \text{ (CH)}, 128.9 \text{ (CH)}, 127.8 \text{ (CH)}, 126.8 \text{ (CH)}, 107.9 \text{ (CH)}, 74.6 \text{ (CH)}, 69.9 \text{ (CH)}_2, 42.7 \text{ (CH)}, 16.1 \text{ (CH)}_3, 12.8 \text{ (CH)}_3\) and 11.2 (CH\(_3\)); \(m/z\) (EI+) 246.2 (M\(^+\), 3 %), 133.1 (100); HRMS (EI+) found 246.1621, \(C_{16}H_{22}O_2\) requires 246.1620.
(3SR,5SR)-3-Hydroxy-5-phenylcyclohexanone.

In the same way as for the synthesis of cyclohexanone 353, alcohol 277 (500 mg, 2.15 mmol) and 18-C-6 (1.14 g, 4.30 mmol) in DME (4 cm³) were added with stirring to a suspension of potassium hydride (617 mg of 35 % suspension in mineral oil, 5.38 mmol) in DME (6 cm³). After stirring for 4 h, the mixture was poured into cold aqueous hydrochloric acid (25 cm³, 1 mol dm⁻³) and worked up as before to yield a yellow solid (402 mg, 80 % w/w). Purification by trituration with ether gave the cyclohexanone 351 as a white solid (215 mg, 43 %); δ(360 MHz, CDCl₃) 7.35-7.19 (5H, m, Ph), 4.60 [1H, qn, J 3.0, CH(OH)], 3.57 [1H, tt, J 12.2 and 4.1, CH(Ph)], 2.69-2.51 [4H, m, CH₂C(O)CH₂], 2.35-2.19 (1H, br s, OH), 2.21 (1H, m with large doublet splitting, J 14.0, CH(Ph)CH(eq)H(ax)) and 2.06 [1H, distorted ddd, J 14.1, 12.2 and 2.4, CH(Ph)CH(eq)H(ax)].

New data: δc(100 MHz, CDCl₃) 209.7 (C), 143.7 (C), 128.7 (CH), 126.7 (2 x CH), 68.3 (CH), 48.7 (2 x CH₂), 39.2 (CH₂) and 38.2 (CH).

(3SR,5SR,6RS)-3-Hydroxy-6-methyl-5-phenylcyclohexanone.

Potassium hydride (1.16 g of 35 % suspension in mineral oil, 10.15 mmol), was washed with hexane (3 x 2 cm³) to remove oil and then suspended in dry dimethoxyethane (DME) (15 cm³) under nitrogen. To the suspension was added a solution of alcohol 278 (1 g, 4.06 mmol) and 18-crown-6 (2.15 g, 8.12 mmol), in DME (5 cm³) with stirring at rt. The resulting dark brown mixture was stirred for 3 h, whereupon it was poured into cold (ice bath) aqueous hydrochloric acid
(50 cm$^3$, 1 mol dm$^{-3}$) with vigorous stirring. The mixture was stirred for 15 min at 0 °C, then allowed to warm to room temperature over 15 min. After an additional 15 min at rt, ether (50 cm$^3$) was added and the layers separated. The aqueous phase was extracted with ether (10 cm$^3$) and the combined organic extracts were washed with hydrochloric acid (10 cm$^3$), water (10 cm$^3$) and brine (10 cm$^3$). Solvent removal under reduced pressure yielded a brown solid (757 mg, 91 % w/w). Purification was achieved by trituration with cold ether to give **cyclohexanone 353** as a white solid (150 mg, 31 %); mp 156-157°C; \( \nu_{\text{max}}(KBr)/\text{cm}^{-1} \) 3369 br (OH), 1713 vs (C=O), 1492 m, 1452 m, 1230 m, 1015 m, 753 m and 700 s; \( \delta_{H}(360 \text{ MHz, CDCl}_3) \) 7.36-7.22 (5H, m, Ph), 4.59 [1H, qn, \( J = 2.9 \), CH(OH)], 3.13 [1H, ddd, \( J = 11.8, 9.1 \) and 7.5, CH(Ph)], 2.77 [1H, dd, \( J = 14.1 \) and 3.0, C(O)CH(eq H(ax))], 2.64 [1H, partly obscured dq, \( J = 11.9 \) (by irradiation of Me) and 6.6, CHMe], 2.62 (1H, d with poorly resolved smaller couplings, \( J = 14.1 \), C(O)CH(eq H(ax))], 2.19-2.13 (2H, m, CH(Ph)CH$_2$), 1.94 (1H, br s, OH), 0.84 (3H, d, \( J = 6.5 \), Me); \( \delta_{C}(90 \text{ MHz, CDCl}_3) \) 210.92 (C), 143.15 (C), 128.70 (CH), 127.43 (CH), 126.75 (CH), 68.92 (CH), 50.63 (CH), 49.05 (CH$_2$), 46.50 (CH), 40.58 (CH$_2$) and 11.99 (CH$_3$); \( m/z \) 204 (M$^+$, 62 %), 186 (M$^+$- H$_2$O, 29), 91 (100), 77 (Ph, 49); HRMS (EI$^+$) found 204.1151, C$_{13}$H$_{16}$O$_2$ requires 204.1150.

![Cyclohexanone 353](image)

**356**

(3SR,4SR,5SR,6RS) and (3SR,4RS,5SR,6RS)-4-Deutero-3-hydroxy-6-methyl-5-phenylcyclohexanone.

In the same way as above, alcohol 285 (100 mg, 0.43 mmol) and 18-C-6 (227 mg, 0.86 mmol) were added to a stirring suspension of KH (123 mg of a 35 % suspension in mineral oil, 1.08 mmol) in DME (2 cm$^3$). After 3 h, the reaction was quenched by the addition of 1 mol dm$^{-3}$ DCl (2 cm$^3$). Work-up and trituration with ether gave a mixture of 353 and 356 as a white solid. Because a mixture of undeuterated and deuterated alcohols was formed, the $^1$H NMR spectrum of the product was difficult to interpret. However, some key data were
obtained: δH (360 MHz, CDCl3) 4.58 (1H, q, J 3.0, CHOH), 0.83 (3H, d, J 6.5, Me). No collapse of this signal to a singlet was observed. HRMS (EI+) found 205.1213, C13H15DO2 requires 205.1213.

(5SR,6SR)-6-Methyl-5-phenyl-2-cyclohexenone.

The crude alcohols 353-355 (241 mg, 1.18 mmol) were dissolved in DCM (10 cm³) under nitrogen and cooled in an ice bath. Methanesulfonylchloride (0.1 cm³, 1.18 mmol) was added in one portion, then triethylamine (0.7 cm³, 4.72 mmol) was added dropwise. The resulting solution was stirred for 15 mins then poured into water (10 cm³) and the layers separated. The organic phase was washed with hydrochloric acid (10 cm³, 1.1 moldm⁻³) then brine (10 cm³) and dried over magnesium sulfate. Concentration under reduced pressure followed by column chromatography on silica using DCM as eluent gave the cyclohexenone as a pale yellow oil (125 mg, 57 %), containing a 13:87 mixture of syn and anti isomers; data for anti isomer: Rf (silica, DCM) 0.79; νmax(thin film)/cm⁻¹ 3029 w, 2970 w, 2929 w, 2877 w, 1676 vs (C=O), 1494 m, 1454 m, 1388 m, 1232 m, 769 m, 748 m and 702 s; δH(400 MHz, CDCl3) 7.30-7.10 (5H, m, Ph), 6.97 [1H, ddd, J 10.0, 4.8 and 2.8, CH=CHC(0)], 6.12 [1H, brd, J 10.0, CH=CHC(O)], 2.97 (1H, ddd, J 12.8, 9.6 and 6.0, CHPh), 2.69 (1H, dq, J 12.8 and 6.8, CHMe), 2.65-2.55 (2H, m, CH₂) and 0.94 (3H d, J 6.8, Me); δC(100 MHz, CDCl3) 201.3 (C), 148.2 (CH), 142.8 (C), 129.3 (CH), 128.7 (CH), 127.4 (CH), 126.9 (CH), 48.6 (CH), 46.8 (CH), 34.9 (CH₂) and 12.5 (CH₃); m/z (EI+) 186.1 (M⁺, 40 %), 118.1 (100); HRMS (EI+) found 186.1044, C₁₃H₁₄O requires 186.1045.
362
5-phenyl-2-cyclohexenone.\textsuperscript{94}

In the same way, crude alcohol 351 (211 mg, 1.11 mmol) was dissolved in DCM (10 cm\textsuperscript{3}) and treated with methanesulfonyl chloride (0.1 cm\textsuperscript{3}, 1.2 mmol) and triethylamine (0.62 cm\textsuperscript{3}, 4.44 mmol). Work-up as before gave the cyclohexenone as a yellow oil (117 mg, 61\%). A pure sample was obtained as a solid in 34\% yield after further chromatography using DCM as eluent; $\delta_H$(400 MHz, CDCl\textsubscript{3}) 7.40-7.24 (5H, m, Ph), 7.06 [1H, ddd, $J$ 10.0, 6.0 and 2.8, CH=CHC(O)], 6.13 [1H, d br d, $J$ 10.0 and 2.8, CH=CHC(O)], 3.36 (1H, ddt, $J$ 12.4, 10.4 and 5.2, CHPh), 2.72-2.61 [3H, m, C(O)CH\textsubscript{2} and =CHCH\textsubscript{eq}H\textsubscript{ax}] and 2.54 (1H, ddt, $J$ 18.8, 10.8 and 2.4, =CHCH\textsubscript{eq}H\textsubscript{ax}), in agreement with data given in reference 94.

375
(3SR,5RS)-3-Hydroxy-5-(n-propyl)-cyclohexanone.

Potassium hydride (173 mg of a 35\% suspension in mineral oil, 1.50 mmol), was washed with hexane (3 x 4 cm\textsuperscript{3}) to remove oil and then suspended in dry THF (1.5 cm\textsuperscript{3}) under nitrogen. To the suspension was added a solution of alcohol 290 (100 mg, 0.50 mmol) and 18-crown-6 (269 mg, 1.00 mmol), in THF (1 cm\textsuperscript{3}) with stirring at rt. The resulting dark brown mixture was stirred for 5 days, whereupon it was poured into cold (ice bath) aqueous hydrochloric acid (5 cm\textsuperscript{3}, 1 mol dm\textsuperscript{-3}) with vigorous stirring. The mixture was stirred at 0\textdegree C for 10 mins, then the ice bath was removed and stirring continued for an additional 15 min. Ether (10 cm\textsuperscript{3}) was then added and the layers separated. The aqueous
phase was extracted with ether (2 x 10 cm$^3$) and the combined organic extracts were dried over magnesium sulfate. Solvent removal under reduced pressure yielded the alcohol 376 (54 mg, 69 %) as a brown oil. This was washed quickly through a short column of neutral alumina with ether to give a pure sample of a 90:10 anti:syn mixture of isomers as a yellow oil (40 mg, 51 %); data for the major isomer: $\nu_{\text{max}}$(thin film)/cm$^{-1}$ 3423 brs (OH), 2958 s, 2928 s, 1708 s (C=O), 1413 m, 1292 m, 1236 m, 1095 m, 1062 m, 1037 m and 970 m; $\delta_{\text{H}}$(360 MHz, CDCl$_3$) 4.50-4.44 (1H, m, CHOH), 2.54 [1H, dd, $J$ 14.2 and 3.7, CH(OH)CH$_{ax}$HeqC(O)], 2.50-2.40 [2H, m, CH(OH)CH$_{ax}$HeqC(O)CH$_{ax}$Heq], 2.30-2.21 (1H, m, CHPr), 2.03-1.96 [2H, m, CH(Pr)CH$_{ax}$HeqC(O) and CH(OH)CH$_{ax}$HeqCH(Pr)], 1.89 (1H, brs, OH), 1.56 [1H, ddd, $J$ 13.9, 11.4 and 2.5, CH(OH)CH$_{eq}$CH$_{ax}$CH(Pr)], 1.40-1.25 (4H, m, MeCH$_2$CH$_2$) and 0.91-0.88 (3H, m, Me); $\delta_{C}$(90 MHz, CDCl$_3$) 210.4 (C), 68.4 (CH), 49.1 (CH$_2$), 47.7 (CH$_2$), 38.5 (CH$_2$), 38.0 (CH$_2$), 32.4 (CH), 19.7 (CH$_2$) and 14.0 (CH$_3$); $m/z$ (EI+) 156 (M$^+$, 45 %), 113 (52), 96 (90), 69 (100); HRMS (EI+) found 156.1150, C$_9$H$_{16}$O$_2$ requires 156.1150.

376

5-Hydroxy-2-methylbicyclo[4.4.0]decan-3-one.

In the same way as for the synthesis of 378, alcohol 299 (150 mg, 0.67 mmol) and 18-C-6 (354 mg, 1.34 mmol) in degassed THF (2 cm$^3$) were added with stirring to a suspension of potassium hydride (267 mg of a 35 % suspension in mineral oil, 2.00 mmol) in degassed THF (2 cm$^3$). After stirring for 48 hours, the mixture was poured into of aqueous hydrochloric acid (5 cm$^3$, 1.1 mol dm$^{-3}$) at 0 °C. After work-up as above, the cyclohexanone was obtained as a pale yellow oil containing several isomers. The major isomer gave a characteristic CHOH signal at $\delta$ 4.60 ppm (q, $J$ 4.0 Hz)

In a separate experiment, a solution of alcohol 299 (100 mg, 0.45 mmol) and 18-crown-6 (238 mg, 0.89 mmol) in degassed THF (1 cm$^3$) was added to a
stirring suspension of potassium hydride (155 mg of a 35 % suspension in oil, 1.34 mmol) in degassed THF (1.25 cm³). After 48 h, the mixture was cooled to −78 °C, and tert-butyldimethylsilyltriflate (0.1 cm³, 0.45 mmol) added in one portion. The mixture was stirred for 30 min at −78 °C, then after 30 min at rt was poured into brine (10 cm³). The aqueous phase was extracted with ether (2 x 10 cm³) and dried over sodium sulfate to give a brown oil (184 mg) after concentration under reduced pressure. The oil was dissolved in ether and passed quickly through a short column of neutral alumina to give a sticky white solid containing a mixture of isomers different from that obtained above. (Two overlapping CHOH signals at δ 4.30 ppm and a broad septet (J 4.4 Hz) at δ 3.80 ppm.)

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\begin{align*}
\text{(1RS,5RS,6SR)-5-Hydroxybicyclo[4.4.0]decan-3-one.}
\end{align*}
\]

Potassium hydride (101 mg of a 35 % suspension in mineral oil, 0.88 mmol), was washed with hexane (3 x 4 cm³) to remove oil and then suspended in dry, degassed THF (1.4 cm³) under nitrogen. To the suspension was added a solution of alcohol 298 (100 mg, 0.48 mmol) and 18-crown-6 (256 mg, 0.96 mmol), in degassed THF (1 cm³) with stirring at rt. The resulting green mixture gradually turned black and was stirred for 48 h. TLC showed the absence of starting material. The mixture was cooled to −78 °C and a solution of TBSCI (87 mg, 0.58 mmol) in THF (1 cm³) was added in one portion. The dry ice bath was removed and the mixture stirrred for 2.5 h, whereupon it was poured into saturated aqueous sodium bicarbonate solution (5 cm³). The aqueous phase was extracted with ether (3 x 5 cm³). The combined organic extracts were washed with brine then dried over magnesium sulfate. Solvent removal under reduced pressure yielded a brown oil. ¹H NMR of this material showed no evidence for the formation of the TBS enol. However, evaporation of the CDCl₃
under reduced pressure lead to the formation of the alcohol \textbf{378} as a white solid (<10 mg) mp 139-140 °C; \( \nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} 3399 \) br s (OH), 2932 s, 2852 m, 1692 vs (C=O), 1453 m, 1412 m, 1314 m, 1244 m, 1126 m, 1041 m, 981 w, 931 w, 875 w and 808 w; \( \delta_{\text{H}}(400 \text{ MHz, CDCl}_3) 4.17 \) (1H, brs, CHO), 2.57 [1H, dd, \( J \) 14.8 and 3.2, CH(OH)CH\(_{ax}\)H\(_{eq}\)C(O)], 2.52 [1H, ddd, \( J \) 14.8, 2.8 and 2.0, CH(OH)CH\(_{ax}\)H\(_{eq}\)C(O)], 2.35 [1H, ddd, \( J \) 14.0, 4.0 and 2.0, CH(OH)CH\(_2\)C(O)CH\(_{eq}\)H\(_{ax}\)], 2.05 [1H, dd, \( J \) 13.6 and 12.8, CH(OH)CH\(_2\)C(O)CH\(_{eq}\)H\(_{ax}\)], 1.93 [1H, tt, \( J \) 11.2 and 4.0, CH\(_{ax}\)CH(OH)CH\(_2\)C(O)], 1.91-1.81 [1H, m, CH\(_{ax}\)CH\(_2\)C(O)], 1.80-1.64 (4H, m, -CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)) and 1.52-1.05 (4H, m, -CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)); \( \delta_{\text{C}}(100 \text{ MHz, CDCl}_3) 210.1 \) (C), 73.2 (CH), 49.9 (CH\(_2\)), 48.6 (CH\(_2\)), 45.8 (CH), 35.7 (CH), 34.2 (CH\(_2\)), 28.6 (CH\(_2\)), 26.1 (CH\(_2\)) and 25.3 (CH\(_2\)); \( m/z \) (El+) 168.1 (M\(^+\), 25 %), 107.8 (100); HRMS (El+) found 168.1151, \( \text{C}_{10}\text{H}_{16}\text{O}_2 \) requires 168.1150.

\[ \begin{align*}
\text{OTBS} & \quad \text{OTBS} \\
\text{H} & \quad \text{H} \\
\text{OPr} & \quad \text{O} \\
\text{379} & \quad \text{380}
\end{align*} \]

In the same way as above, a solution of alcohol \textbf{299} (100 mg, 0.45 mmol) and 18-crown-6 (238 mg, 0.89 mmol) in degassed THF (1 cm\(^3\)) was added to a stirring suspension of potassium hydride (155 mg of a 35 % suspension in oil, 1.34 mmol) in degassed THF (1.25 cm\(^3\)). After 48 h, the mixture was cooled to –78 °C, and tert-butyldimethylsilyl triflate (0.1 cm\(^3\), 0.45 mmol) added in one portion. The mixture was stirred for 30 min at –78 °C, 15 min at –78 °C to rt then for a further 10 min at rt, whereupon it was poured into brine (10 cm\(^3\)) and worked-up as above to give the \textit{silyl enol ether} \textbf{379} as a brown oil. The crude product was dissolved in ether and passed through a short column of neutral alumina to give the \textit{silyl enol ether} \textbf{379} (43 mg) and the \textit{enol ether} \textbf{380} (20 mg) as pale yellow oils (43 % combined yield).
379

\([2RS,2(2RS)]-1-(1\text{-}\text{tert-Butyldimethylsilyloxy-methylene})-2-(3\text{-}\text{isopropoxy-3-buten-2-yl})\text{-cyclohexane.}\)

δ\(\text{H}(400 \text{ MHz, CDCI}_3)\) 5.98 [1H, brd, J 1.2, =CH(OTBS)], 4.13 (1H, sep, J 6.0, CHMe\(_2\)), 3.76 (1H, d, J 1.6, =CH\(_A^H\))\(_B^B\)), 3.66 (1H, d, J 1.6, =CH\(_A^H\))\(_B^B\)), 2.51 [1H, dt, J 13.6 and 4.0, CH\(_{ax}\)H\(_{eq}\)C(=C)], 2.45 [1H, dq, J 10.8 and 6.8, CHMe(C=CH\(_2\))], 2.07 [1H, dbrt, J 10.8 and 4.0, CH\(_{eq}\)CH(Me)], 1.82-1.35 (7H, m, remaining ring protons), 1.20 (3H, d, J 6.0, OCHMe\(_A^A\))\(_B^B\)), 1.18 (3H, d, J 6.0, OCHMe\(_A^A\))\(_B^B\)), 1.03 (3H, d, J 6.8, CHMe), 0.90 (9H, s, SiMe\(_3\)), 0.08 (3H, s, SiMe\(_A^A\))\(_B^B\) and 0.07 (3H, s, SiMe\(_A^A\))\(_B^B\)); δ\(\text{C}(100 \text{ MHz, CDCI}_3)\) 164.7 (C), 132.1 (CH), 122.6 (C), 80.0 (CH\(_2\)), 67.6 (CH), 41.7 (CH), 39.3 (CH), 29.3 (CH\(_2\)), 27.1 (CH\(_2\)), 25.8 (CH\(_3\)), 22.0 (CH\(_2\)), 21.93 (CH\(_2\)), 21.91 (CH\(_2\)), 21.2 (CH\(_3\)), 18.3 (C), 17.1 (CH\(_3\)), −5.3 (CH\(_3\)) and −5.4 (CH\(_3\)).

380

\([2RS,2(2RS)]-1-(1\text{-}\text{tert-Butyldimethylsilyloxy-methylene})-2-(3\text{-}\text{oxobut-2-yl})\text{-cyclohexane.}\)

R\(_f\) (alumina, ether) 0.90; ν\(_{\text{max}}\)(thin film)/cm\(^{-1}\) 2929 s, 2857 s, 1713 s (C=O), 1666 (C=C), 1471 m, 1448 m, 1256 m, 1169 m, 873 m, 846 m, 778 m and 675 m; δ\(\text{H}(400 \text{ MHz, CDCI}_3)\) 5.97 (1H br s, =CH), 2.92 [1H, dq, J 10.8 and 6.8, AcCH(Me)], 2.51 (1H, dt, J 13.6 and 4.4, CH\(_{ax}\)H\(_{eq}\)C=), 2.17 [1H, ddd, J 10.8, 4.4 and 3.6, CH\(_{eq}\)CH(Me)Ac], 2.04 (3H, s, COMe), 1.92 (1H, dddd, J 13.6, 12.0,
4.8 and 1.6, CH\textsubscript{ax}, H\textsubscript{eq}=), 1.75-1.24 (6H, m, 3 x CH\textsubscript{2}), 1.03 (3H, d, J 7.2, CHMe), 0.88 (9H, s, SiCMe\textsubscript{3}), 0.07 (3H, s, SiMe\textsuperscript{A}Me\textsuperscript{B}) and 0.06 (3H, s, SiMe\textsuperscript{A}Me\textsuperscript{B}); \(\delta_{c}(100 \text{ MHz}, \text{CDCl}_3) 213.3 \text{ (C), 133.0 (CH), 121.4 (C), 46.6 (CH), 41.6 (CH), 29.6 (CH}_3); 29.5 (CH\textsubscript{2}), 27.3 (CH\textsubscript{2}), 26.1 (CH\textsubscript{3}), 22.6 (CH\textsubscript{2}), 22.5 (CH\textsubscript{2}), 18.7 (C), 15.1 (CH\textsubscript{3}), –4.9 (CH\textsubscript{3}) and –5.0 (CH\textsubscript{3}); m/z (Cl\textsuperscript{+}) 297.3 [(M+H\textsuperscript{+}), 100 %]; HRMS (Cl\textsuperscript{+}) found 297.2251, C\textsubscript{17}H\textsubscript{33}O\textsubscript{2}Si [(M+H\textsuperscript{+})] requires 297.2250.

\[
\begin{align*}
\text{382-384}
\end{align*}
\]

2,6-Dimethyl-3-hydroxy-5-phenylcyclohexanone.

Potassium hydride (1.32 g of a 35 % suspension in mineral oil, 11.52 mmol), was washed with hexane (3 x 10 cm\textsuperscript{3}) to remove oil and then suspended in dry THF (10.2 cm\textsuperscript{3}) under nitrogen. To the suspension was added a solution of alcohol 310a/b (1.00 g, 3.84 mmol) and 18-crown-6 (2.03 g, 7.68 mmol), in THF (9 cm\textsuperscript{3}) with stirring at rt. The resulting dark brown mixture was stirred for 3 h, whereupon it was poured into cold (ice bath) aqueous hydrochloric acid (100 cm\textsuperscript{3}, 1.1 mol dm\textsuperscript{-3}) with vigorous stirring. The mixture was stirred at 0 °C for 15 mins, then for an additional 20 min at rt. Ether (100 cm\textsuperscript{3}) was then added and the layers separated. The aqueous phase was extracted with ether (2 x 100 cm\textsuperscript{3}) and the combined organic extracts were dried over sodium sulfate. Solvent removal under reduced pressure yielded the alcohols 382-384 (867 mg, 100 % w/w) as a 8:3:7:1 mixture of 4 diastereoisomers. Column chromatography on neutral alumina using 1:1 ether-hexane as eluent gave the isomers as a colourless oil (470 mg, 56 %). Preparatory TLC on alumina (ether-hexane mixtures) failed to separate the isomers completely, but allowed the unambiguous determination of the relative stereochemistry in the three major compounds.
(2RS,3RS,5SR,6RS)-2,6-Dimethyl-3-hydroxy-5-phenylcyclohexanone.

v_{max}(\text{thin film})/\text{cm}^{-1} \ [\text{crude mixture of isomers}] 3449 \text{ br s (OH)}, 2974 \text{ s}, 2935 \text{ s}, 2876 \text{ s}, 1708 \text{ vs (C=O)}, 1496 \text{ m}, 1454 \text{ s}, 1377 \text{ m}, 1062 \text{ m}, 1038 \text{ m}, 910 \text{ s}, 735 \text{ s} \text{ and } 701 \text{ s}; \delta_{\nu}(400 \text{ MHz, CDCl}_3) 7.36-7.19 (5\text{H, m, Ph}), 4.12 (1\text{H, dq, } J 10.0 \text{ and } 5.0, \text{ CH(OH)}), 2.90 [1\text{H, brqn, } J 6.8, \text{ CH(OH)CH_{eq}(Me)CO}], 2.76 [1\text{H, dq, } J 12.4 \text{ and } 6.4, \text{ CH(Ph)CH_{ax}(Me)}], 2.44 (1\text{H, td, } J 12.0 \text{ and } 4.8, \text{ CHPh}), 2.17 (1\text{H, distorted ddd, } J 13.2, 11.6 \text{ and } 10.4, \text{ CH_{ax}H_{eq}}), 2.10 (1\text{H, dbrt, } J 13.2 \text{ and } 4.8, \text{ CH_{ax}H_{eq}}), 1.86 (1\text{H, d, } J 4.4, \text{ OH}), 1.30 [3\text{H, d, } J 7.2, \text{ CH(OH)CHMe}] \text{ and } 0.79 [3\text{H, d, } J 6.8, \text{ CH(Ph)CHMe}]; \delta_{\nu}(100, \text{ MHz, CDCl}_3) 214.0 (C), 143.0 (C), 128.7 (CH), 127.3 (CH), 126.8 (CH), 70.3 (CH), 51.0 (CH), 46.1 (CH), 44.9 (CH), 37.5 (CH$_2$), 12.2 (CH$_3$) \text{ and } 10.8 (CH$_3$); m/z [\text{crude mixture of isomers}] (EI+) 218.2 (M$^+$, 75 %), 144.0 (100); HRMS (EI$^+$) found 218.1306, C$_{14}$H$_{18}$O$_2$ requires 218.1307.

(2RS,3SR,5SR,6RS)-2,6-Dimethyl-3-hydroxy-5-phenylcyclohexanone.

$\delta_{\nu}(400 \text{ MHz, CDCl}_3) 7.36-7.19 (5\text{H, m, Ph}), 4.33 (1\text{H, qn, } J 2.8, \text{ CH(OH)}), 3.06 (1\text{H, td, } J 11.6 \text{ and } 5.2, \text{ CHPh}), 2.80 [1\text{H, qbrd, } J 6.8 \text{ and } 2.0, \text{ CH(OH)CH_{eq}Me}], 2.64 [1\text{H, } dq, J 12.0 \text{ and } 6.4, \text{ CH(Ph)CH_{ax}Me}], 2.25-2.13 (2\text{H, m, CH$_2$}), 1.17 [3\text{H, d, } J 6.8, \text{ CH(OH)CHMe}] \text{ and } 0.82 [3\text{H, d, } J 6.4 \text{ CH(Ph)CHMe}]; \delta_{\nu}(100, \text{ MHz, CDCl}_3) 211.6 (C), 143.2 (C), 128.7 (CH), 127.4 (CH), 126.7 (CH), 74.1 (CH), 51.4 (CH), 49.4 (CH), 47.1 (CH), 41.4 (CH$_2$), 12.1 (CH$_3$) \text{ and } 11.1 (CH$_3$).
(2S,3S,5S,6R)-2,6-Dimethyl-3-hydroxy-5-phenylcyclohexanone.

\( \delta_h \) (400 MHz, CDCl\(_3\)) 7.36-7.19 (5H, m, Ph), 4.17-4.13 (1H, m, CHO\( \text{OH} \)), 3.09 (1H, td, \( J \) 11.8 and 4.0, CH(Ph)), 2.83 [1H, dq, \( J \) 11.6 and 6.4, CH(Ph)CH\( \text{Me} \)], 2.68 [1H, qdd, \( J \) 7.6, 3.2 and 1.6, CH(OH)CH\( \text{Me} \)], 2.30 (1H, ddd, \( J \) 13.5, 12.4 and 2.0, CH\( \text{ax} \)H\( \text{eq} \)), 2.01 (1H, dt, \( J \) 14.4, 4.0 and 1.6, CH\( \text{eq} \)H\( \text{ax} \)), 1.94 (1H, m, OH), 1.32 [3H, d, \( J \) 7.6, CH(OH)CH\( \text{Me} \)], 0.85 [3H, d, \( J \) 6.4, CH(Ph)CH\( \text{Me} \)]; \( \delta_c \) (100 MHz, CDCl\(_3\)) 215.1 (C), 143.3 (C), 128.7 (CH), 127.4 (CH), 126.7 (CH), 73.7 (CH), 52.3 (CH), 46.1 (CH), 45.8 (CH), 36.1 (CH\(_2\)), 15.6 (CH\(_3\)) and 12.5 (CH\(_3\)).

(2S,3S,5R,6S)-2,6-Dimethyl-3-hydroxy-5-phenylcyclohexanone, 385

(2S,3R,5R,6S)-2,6-Dimethyl-3-hydroxy-5-phenylcyclohexanone, 386.

In the same way as above, alcohol 324 (201 mg, 0.81 mmol) and 18-C-6 (428 mg, 1.62 mmol) were added to a suspension of potassium hydride (285 mg of a 35% suspension in oil, 2.44 mmol) in THF (4 cm\(^3\)). After 3 h, the reaction was quenched at 0°C by the addition of aqueous hydrochloric acid (8 cm\(^3\), 1.1 mol dm\(^{-3}\)). Work-up as above gave alcohols 385 and 386 as a brown oil (114 mg, 65% w/w).
(3RS,5SR,6SR)- and (3RS,5SR,6RS)-3-tert-Butyldimethylsilyloxy-6-methyl-5-phenylcyclohexanone, 415 and 416.

A mixture of alcohols 353, 354 and 355 (776 mg, 3.7 mmol) was dissolved in dry DMF (10 cm³) under nitrogen. Diisopropylethylamine (1.2 cm³, 6.7 mmol) then tert-butyldimethylsilyl chloride (468 mg, 3.1 mmol) were added at 0 °C. The reaction mixture was allowed to warm to room temperature and then left to stir over three days (~60 h). The mixture was then poured into saturated aqueous sodium bicarbonate solution (20 cm³). The aqueous phase was separated and extracted with ether (2 x 10 cm³). The combined organic extracts were washed with aqueous hydrochloric acid (2 x 10 cm³, 1 mol dm⁻³ solution) then brine (10 cm³) and dried (MgSO₄). Concentration under reduced pressure gave a mixture of the unprotected alcohol 353, its TBS ether, and silyl ethers 415 and 416. Separation of the two diastereoisomers was achieved by column chromatography followed by preparative TLC.

415

(3RS,5SR,6RS)-3-tert-Butyldimethylsilyloxy-6-methyl-5-phenylcyclohexanone.

Spectral data for 415: \( \nu_{\text{max}} \text{(thin film)} \) 2956 m, 2856 m, 1715 vs (C=O), 1376 m, 1254 m, 1095 s, 777 m and 700 m; \( \delta_H \) (360 MHz, CDCl₃) 7.40-7.15 (5H, m, Ph), 3.95 [1H, tt, \( J = 10.9 \) and 4.7, CH(OTBS)], 2.76 [1H, ddd, \( J = 12.8, 3.8 \) and 2.4, C(O)CH₃H₆ax], 2.58 [1H, t, \( J = 12.0 \), C(O)CH₆axH₆eq], 2.52 [1H, dq, \( J = 11.0 \) (by irradiation of Me) and 6.4, CHMe], 2.38 [1H, td, \( J = 12.2 \) and 3.2, CH(Ph)], 2.20 [1H, doublet with poorly-resolved smaller couplings, \( J = 13.0 \), CH(Ph)CH₆axH₆eq],
2.04 [1H, td, J 13.0 and 10.7, CH(Ph)CH_{ax,Heq}], 0.87 (9H, s, Si''Bu), 0.78 (3H, d, J 6.4, CHMe), 0.06 (3H, s, SiMe^4Me^8), 0.05 (3H, s, SiMe^4Me^8); m/z (EI+) 261 (M^-Bu^+, 7 %) 157 (38), 31 (100); HRMS (Cl+) found 319.2090, C_{19}H_{31}O_2Si [(M+H)^+] requires 319.2093.

416

(3RS,5SR,6SR)-3-tert-Butyldimethylsilyloxy-6-methyl-5-phenylcyclohexanone.

Spectral data for 416: v_{max}(thin film) δ H (360 MHz, CDCl_3) 7.37-7.13 (5H, m, Ph), 4.40 [1H, m, ΣJ ~16, CH(OTBS)], 3.71 [1H, dt, J 10.4 and 4.7, CH(Ph)], 2.74 [1H, dd, J 14.5 and 3.7, C(O)CH_{ax,Heq}], 2.70 [1H, qd, J 7.2 and 6.0 (by irradiation of Me), CHMe], 2.38 [1H, ddt, J 14.5, 4.6 and 1.6, C(O)CH_{eq,Ha}], 2.29 [1H, ddd, J 13.4, 11.0 and 2.5, CH(Ph)CH_{eq,Ha}], 1.96 [1H, d br t, J 13.4 and 5.3, CH(Ph)CH_{ax,Heq}], 0.88 (3H, d, J 7.2, CHMe), 0.84 (9H, s, Si''Bu), 0.03 (3H, s, SiMe^4Me^8), -0.01 (3H, s, SiMe^4Me^8); m/z (EI+) 261 (M^-Bu^+, 20 %) 157 (100); HRMS (Cl+) found 336.2345, C_{19}H_{34}NO_2Si [(M+NH_3)^+] requires 336.2359.
References


70. Personal communication with R.C. Hartley.


