Chapter Three

Formation of Syn Cyclohexenones
3 Formation of Syn Cyclohexenones

This chapter details investigations into the stereoselectivity of the conjugate addition of cuprates to stereo- and regio-chemically different enones, with the aim of producing cyclohexenones with syn stereochemistry.

3.1 Stereochemically-diverse cyclohexenones

The puzzle of the true structure of tridachiahydropyrone (Figure 3.1), as discussed in Chapter 1 (Section 1.3.2), paved the way for investigations into the generation of stereochemically-different cyclohexanones.

Figure 3.1. Reported structure (14) and proposed structure (42) of tridachiahydropyrone.

The main aim was to probe how the effect of changing the stereochemistry in complex enone precursors of type 209 would affect the stereochemical outcome of the cuprate additions to give 210, and how this, in turn, would affect the stereochemistry in cyclohexenones such as 211 (Scheme 3.1).
The potential existed of using the addition-cyclisation strategy illustrated in Scheme 3.1 to synthesise a wide variety of chiral cyclohexenones. However, it was decided to focus on attempting to prepare cyclohexenones with syn stereochemistry between the quaternary methyl and the adjacent carbon centre, due to their potential utility in the synthesis of syn tridachiahydropyrone (42) (Figure 3.1). Based on the knowledge acquired through past studies of these types of cuprate additions to complex enones, two alternative pathways were proposed for achieving the syn stereochemistry in cyclohexenone 212: the use of epimeric trans enone 203 or the use of cis enone 213 (Scheme 3.2).

Enones 203 and 213 depicted in Scheme 3.2 were chosen based on their relative simplicity and proposed ability to direct the cuprate addition (the stereochemical rationale for this will be discussed in the following section). This would produce cyclohexanones (such as 214) with the opposite stereochemistry to that obtained previously at the generated stereocentre (designated as *) and, hopefully, give the
desired syn stereochemistry following methylation, as shown in 212. Initially, trans enone 203 was chosen as the starting point for the synthesis of syn cyclohexenones, as the methodology for the synthesis of similar enones had already been developed and utilised (Chapter 2).

### 3.2 Attempted formation of a simple syn cyclohexenone from a trans enone

#### 3.2.1 Stereochemical rationale for the outcome of the cuprate addition to trans enone 203

The reason for using trans enone 203 to achieve the desired equatorial orientation of the alkyl substituent in cyclohexanone 215 (Scheme 3.3) was based on the analysis of the approach of the nucleophile (i.e. the cuprate) to the favoured rotamer of trans enone 203 (rot-203), using the modified Felkin-Ahn model.

*Scheme 3.3. Modified Felkin-Ahn model of cuprate addition to trans enone 203.*
Based on the outcomes of past cuprate additions to complex enones of this nature, it can be postulated that the cuprate will add to rot-203 from the least hindered position (Scheme 3.3) to give intermediate 216. Ring closure and elimination of auxiliary 98 produces the Felkin product, cyclohexanone 215. If the favoured chair conformation of 215 is as depicted in Scheme 3.4, it can be seen that the alkyl group affixed as a result of the cuprate addition (R) is now in the equatorial position, while the adjacent methyl group is now in the axial position (both highlighted in blue).

\[ \text{Scheme 3.4. Methylation of the favoured chair conformation of 215.} \]

The subsequent methylation can potentially occur from two different approaches (Scheme 3.4, 217). Methylation from the axial position would give the desired syn methylated product, which would produce cyclohexenone 219 after elimination of the O-tert-butylidimethylsilyl (OTBS) group, while methylation from the equatorial position would ultimately result in the formation of the undesired anti cyclohexenone 218, following elimination. While the theory behind the formation of syn cyclohexenone 219 from trans enone 203 was compelling, the proposed synthesis would allow it to be tested.
3.2.2 Synthesis of trans enone 203

It was envisaged that the simplest synthetic route to trans enone 203 would be through aldehyde 220 (Scheme 3.8), as this methodology was well-established in the Perkins group (Chapter 2, Section 2.3.1). In keeping with this synthetic sequence, the synthesis of trans enone 203 began with aldehyde ent-87 (Scheme 3.5), derived from commercially-available Roche ester ent-88.

![Scheme 3.5. Synthesis of aldehyde ent-87 from commercially available ester ent-88.]

Reagents and conditions. (a) i. NaH, Et₂O, 0 °C. ii. Cl₃CC≡N, 0 °C → RT, 100%; (b) 114, CF₃SO₂H (0.3 mol %), Et₂O, RT, 75%; (c) LiAlH₄, THF, 0 °C, 100%; (d) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, -78 °C → 0 °C, 92%.

The first step involved protecting the primary alcohol functionality of Roche ester ent-88 (Scheme 3.5) using p-methoxybenzyl (PMB) imidate 114 to give ester ent-115, which was reduced using LiAlH₄. Subsequent oxidation of the corresponding alcohol using Swern conditions afforded aldehyde ent-87 in excellent yield (69% over three steps) without the need for further purification.

Aldehyde ent-87 was then reacted with Evans auxiliary 72 to give the Felkin syn aldol product (221) (as discussed in Chapter 1, Section 1.4.2.2) in modest yield (Scheme 3.6).
Reagents and conditions. (a) i. 72, Bu$_3$BOTf, Et$_3$N, CH$_2$Cl$_2$, 0 °C. ii. ent-87, –78 °C → 0 °C, 57% as inseparable mixture of 221 and 222.

Scheme 3.6. Synthesis of aldol adduct 221.

A small amount of alkene 222 was also identified in the $^1$H Nuclear Magnetic Resonance (NMR) spectrum of syn aldol product 221 (Scheme 3.6), and possessed identical $^1$H NMR spectral data to that reported in the literature. However, alcohols 221 and 222 could not be separated by conventional chromatography methods. The formation of alkene 222 was most likely due to the presence of Et$_3$N in the aldol reaction, which may have caused the elimination of the OPMB group of aldol product 221.

The subsequent protection of the mixture containing syn aldol product 221 and alkene 222 to give TBS ether 223 proceeded in good yield, with alkene 222 also undergoing protection to give 224 (Scheme 3.7).
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Reagents and conditions. (a) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, –78 °C, 68% 223 and 16% of 224.

Scheme 3.7. TBS-protection of the mixture containing aldol adduct 221 and alkene 222.

Fortuitously, TBS ethers 223 and 224 (Scheme 3.7) were separable by column chromatography. The subsequent cleavage of PMB ether 223 using 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) under buffered conditions$^{11}$ gave primary alcohol 225 in good yield (Scheme 3.8).

Reagents and conditions. (a) DDQ, CH$_2$Cl$_2$, pH 7 buffer, 0 °C, 64%; (b) DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$, –78 °C → 0 °C, 100%.

Scheme 3.8. Synthesis of aldehyde 220.
Swern oxidation\textsuperscript{6,7} of the liberated alcohol gave aldehyde 220 in high (100\%) yield, without the need for further purification. The success of the synthesis is evident in the $^1$H NMR spectrum of 220 (Figure 3.2).

The diagnostic aldehyde proton is present as a doublet at $\delta$ 9.70 and couples with the methine proton adjacent to the carbonyl, which appears as a multiplet at $\delta$ 2.60 – 2.64. This proton is split into a multiplet by virtue of coupling to both the oxymethine proton (which appears as a doublet of doublets at $\delta$ 4.38) and the methyl protons (which appear as a doublet at $\delta$ 1.09). The methine proton on C4 appears as a multiplet at $\delta$ 3.87 – 3.99 and couples to the methyl protons, which appear as a doublet at $\delta$ 1.28. The auxiliary protons appear at $\delta$ 2.76, $\delta$ 3.21, $\delta$ 4.15 – 4.16, $\delta$ 4.52 – 4.60 and $\delta$ 7.18 – 7.35. While the differences between the spectra of aldehyde 220 and the diastereomeric aldehyde 90\textsuperscript{1} synthesised in Chapter 2 (Section 2.3.1) are not dramatic, some variation is evident. The aldehyde proton has moved slightly upfield from $\delta$ 9.80 in aldehyde 90\textsuperscript{1} to $\delta$ 9.70 in aldehyde 220, and the methine proton on C2 has moved downfield from $\delta$ 2.44 – 2.52 to $\delta$ 2.60 – 2.64. A change of shift is
expected for this proton, as it is the stereochemistry at this centre that is different between aldehydes 90 and 220.

With aldehyde 220 now in hand, the synthesis of trans enone 203 was undertaken. To this end, aldehyde 220 was reacted with ylide 117 to give trans enone 203 in good yield (Scheme 3.9).

\[
\begin{align*}
\text{Ph}_3\text{P} & \quad \text{COMe} \\
\text{OTBS} & \\
\text{Bn} & \quad \text{220} \\
\text{N} & \\
\text{OTBS} & \quad \text{O} \\
\text{Bn} & \quad \text{203} \\
\end{align*}
\]

**Reagents and conditions.** (a) 117, toluene, 60 °C, 5 days, 77%.

*Scheme 3.9. Synthesis of trans enone 203.*

In contrast to the previous reaction of aldehyde 90 with ylide 117 (Chapter 2, Section 2.3.1), the reaction of aldehyde 220 with 117 (Scheme 3.9) did not produce any epimeric product. This is shown in the \(^1\text{H} \text{NMR} \) spectrum of trans enone 203 (Figure 3.3), where only one set of resonances is present for each proton.
The $^1$H NMR spectrum of trans enone 203 (Figure 3.3) is identical to that reported in the literature (where it formed as a minor by-product), displaying the requisite vinyl protons at $\delta$ 5.95 and $\delta$ 6.81. The vinyl proton adjacent to the carbonyl appears as a doublet by virtue of coupling to the vinyl proton on C5, which appears as a doublet of doublets due to coupling to both H6, as well as the adjacent methine proton. The downfield position of the alkene protons can be attributed to the delocalised nature of the alkene electrons, due to resonance contributors in the $\alpha,\beta$-unsaturated carbonyl system. The $^{13}$C NMR spectrum confirmed the success of the synthesis by the presence of a peak at $\delta$ 198.6, which can be attributed to the carbonyl of the enone group, as well as two peaks at $\delta$ 130.7 and $\delta$ 148.8, due to the two vinyl carbons.

In summary, trans enone 203 was prepared from commercially-available (R)-Roche ester ent-88 in six steps and 13% overall yield. With trans enone 203 in hand, the formation of a syn cyclohexenone was attempted.
3.2.3 Attempted synthesis of a syn cyclohexenone

It was initially postulated that a simple syn cyclohexenone would be prepared and to this end, trans enone 203 had to be converted into a cyclohexanone via a cuprate addition-cyclisation protocol. It had been found through previous studies of this reaction (Chapter 2)\(^1,12\) that the use of dimethyl cuprates was synthetically simpler than other alkyl/alkenyl analogues. Dimethyl cuprates were both easier to generate and more reliable, producing the desired cyclohexanones in good yield. Therefore, trans enone 203 was reacted with a methyl cuprate to give cyclohexanone 226 (Scheme 3.10).

![Scheme 3.10. Synthesis of cyclohexanone 226.](image)

**Reagents and conditions.** (a) CuI, MeLi, Me\(_2\)S, Et\(_2\)O, RT, 63%.

The addition of dimethyl cuprate to trans enone 203 (as described in Chapter 2, Section 2.3.1) gave cyclohexanone 226 in good yield (Scheme 3.10). Cyclohexanone 226 was found to exist in predominantly the keto form, as exhibited by \(^1\)H NMR (Figure 3.4).
In previous cyclohexanones formed (Chapter 2), the enol form was dominant in the NMR spectra. However, the presence of a doublet at δ 3.28 in the spectrum of cyclohexanone 226 (Figure 3.4) was clear evidence of the prevalence of the keto form of 226. This peak can be attributed to the proton between the two carbonyl groups and the multiplicity of this resonance is due to coupling to the adjacent methine proton on C3. The large coupling constant \( J = 12.6 \text{ Hz} \) indicates that the two protons were in an antiperiplanar arrangement. If the favoured chair conformation of 226 is that shown in Figure 3.5, the antiperiplanar arrangement of the protons on C2 and C3 (highlighted in blue) implies that the cuprate addition to enone 203 occurred in the predicted manner (Section 3.2.1), to give the equatorial position of the methyl group (highlighted in pink) in Felkin product 226.
The success of the formation of cyclohexanone 226 is further evidenced in the $^1$H NMR spectrum (Figure 3.4) by the absence of the resonances associated with the auxiliary and alkenyl protons. The $^{13}$C NMR spectrum further corroborated the success of the cyclisation, with the presence of two ketone carbons at $\delta$ 206.4 and $\delta$ 207.6.

As the NMR data confirmed that the required stereochemical outcome had been achieved in the dimethyl cuprate addition to give cyclohexanone 226, the methylation-elimination cascade was carried out in an attempt to form desired syn cyclohexenone 227 (Scheme 3.11).

**Scheme 3.11. Methylation and elimination of cyclohexanone 226.**
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However, treatment of cyclohexanone 226 with the methylation-elimination protocol used previously to effect these transformations (Chapter 2)\(^1\) resulted in formation of anti cyclohexenone \textit{ent-110} (Scheme 3.11). Immediately, the stereochemical outcome of the methylation was obvious, by comparison of the NMR data of cyclohexenone \textit{ent-110} with the NMR data of the cyclohexenones synthesised in Chapter 2. This resulted in the observation that \textit{ent-110} possessed the same \(^1\)H and \(^{13}\)C NMR data as cyclohexenone 110 (Chapter 2, Section 2.3.1) depicted in Figure 3.6. On this basis, it was deduced that \textit{ent-110} must be the enantiomer of 110.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ent110_110.png}
\caption{The enantiomeric relationship between \textit{ent-110} and 110.}
\end{figure}

While an optical rotation of cyclohexenone \textit{ent-110} was not obtained due to inadequate purity of the sample, the correlations depicted in \textit{ent-110B} (Figure 3.7) were identified by Nuclear Overhauser Effect Spectroscopy (NOESY).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ent110B.png}
\caption{NOESY correlations observed for cyclohexenone \textit{ent-110} in CDCl\textsubscript{3} at 600 MHz.}
\end{figure}

Based on the NOESY correlations depicted in Figure 3.7, it can be concluded that the stereochemistry between the quaternary methyl and the adjacent methyl is \textit{anti}. The NOESY correlation between the protons of the quaternary methyl and the methine
proton (highlighted in blue) is diagnostic in this case for anti methylation, and indicates that \textit{ent-110} exists in the conformation depicted in \textit{ent-110B} (Figure 3.7). It can be postulated that conformation B is more favourable than conformation A, due to the presence of the unfavourable 1,3-diaxial interaction in conformation A.

As discussed previously in Section 3.2.1, the desired syn stereochemistry between the two methyl centres could only arise as a result of axial methylation of cyclohexanone 226. It therefore follows that the methylation must have occurred from the equatorial position to give anti methylated cyclohexenone \textit{ent-110}. Previously, the methylation of the cyclohexanones synthesised in Chapter 2 occurred predominantly from the axial position. This leads to the conclusion that the cyclohexanone system 226 used in this case must possess some characteristic, which prevents axial methylation from occurring. It is postulated that the axial approach of the methylating agent was hindered (as depicted in 228, Scheme 3.12) by the presence of the axial methyl group (highlighted in blue), resulting in methylation occurring from the equatorial position to give anti methylated cyclohexenone \textit{ent-110}.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{\textit{ent-110}}};
\node at (2,0) {\textbf{\textit{226}}};
\node at (4,0) {\textbf{\textit{226}}};
\node at (6,0) {\textbf{\textit{229}}};
\node at (8,0) {\textbf{\textit{228}}};
\node at (10,0) {equatorial methylation};
\node at (12,0) {\textbf{\textit{226}}};
\node at (14,0) {\textbf{\textit{NaH}}};
\end{tikzpicture}
\end{center}

\textit{Scheme 3.12. Steric hindrance in 226 leading to equatorial methylation and production of anti methylated cyclohexenone \textit{ent-110}.}
The “blue” methyl group depicted in Scheme 3.12 was in the equatorial position in the cyclohexanones discussed in Chapter 2. This equatorial orientation negated the possibility of steric hindrance from this group, leading to axial methylation. In contrast, the postulate of methylation occurring from the equatorial position as illustrated in the case of cyclohexanone 226 is due to the axial methyl (Scheme 3.12).

It can be concluded based on the results of this study that while *trans* enone 203 did produce the desired outcome in the cuprate addition, the axial position of the methyl group in the favoured chair conformation of cyclohexanone 226 (Scheme 3.12) did not lead to the desired *syn* stereochemistry in methylated cyclohexenone *ent*−110. Thus, an alternative strategy was required for the formation of *syn* cyclohexenones.

### 3.3 Formation of a simple *syn* cyclohexenone from a *cis* enone

The deduction that *cis* enone 213 would be a useful candidate for achieving the desired outcome in the cuprate addition was based once again on the analysis of the approach of the nucleophile (Scheme 3.13).
Scheme 3.13. Modified Felkin-Ahn model of cuprate addition to cis enone 213, leading to anti-Felkin product 231.

In the case of *trans* enone 203 (Section 3.2.1, Scheme 3.3), the favoured rotamer gave Felkin addition product 226. In contrast, the favoured rotamer of *cis* enone 213 is rot-213A (Scheme 3.13), which will produce *anti*-Felkin product 231. This can be attributed to the fact that rot-213B, which would lead to the Felkin product, is unfavourable due to the allylic strain between the methyl on C4 and the carbonyl group (as discussed in Chapter 1, Section 1.4.1). Therefore, *cis* enone 213 adopts the energetically-favourable conformation depicted in rot-213A, where the C4 methyl group eclipses the proton on C5. This is in contrast to the position of these groups in *trans* enone 203, where the methyl group on C4 is situated on the same face as the carbonyl. According to the Felkin-Ahn model, the nucleophile approaches from the less hindered face. In the case of the favoured *cis* enone rotamer (rot-213A), the cuprate would thus approach from the opposite face to that occupied by R1, leading to the formation of intermediate 230. Following cyclisation and concurrent elimination of auxiliary 98, the *anti*-Felkin product (cyclohexanone 231) would form.
If the favoured chair conformation of 231 is as that illustrated in Scheme 3.14, it can now be seen that the alkyl group (R) affixed as a result of the cuprate addition is in the equatorial position (highlighted in blue), as in the case of trans enone 203, and more importantly, the adjacent methyl group (also highlighted in blue) is now in the equatorial position.


The axial methyl in the previous cyclohexanone system 226 (Section 3.2.3) resulted in the formation of the undesired anti methylated cyclohexenone ent-110, due to steric interactions. The change in orientation of this methyl group to the equatorial position (as depicted in Scheme 3.14) would potentially eliminate the steric issues to produce the desired syn cyclohexenone 234.

Acquisition of syn cyclohexenone 234 required the development of a synthetic methodology towards cis enone 213. Initially it was envisaged that the simplest method to synthesise 213 would be through the manipulation of existing synthetic intermediates, and the studies towards this are detailed in the following section.
3.3.1 Attempted synthesis of cis enone 219 from aldehyde 90

Aldehyde 90 was identified as the most suitable candidate for the synthesis of cis enone 213, via the retrosynthesis described in Scheme 3.15.

\[
\text{O} \quad \text{OTBS} \quad \text{O} \quad \text{Bn} \quad 213 \quad \rightarrow \quad \text{O} \quad \text{OTBS} \quad \text{O} \quad \text{Bn} \quad 235
\]

\[
\text{O} \quad \text{OTBS} \quad \text{Bn} \quad 90 \quad \leftarrow \quad \text{O} \quad \text{OTBS} \quad \text{Bn} \quad 236 + \text{237}
\]

Scheme 3.15. Retrosynthetic analysis of cis enone 213 to precursor aldehyde 90.

It was postulated that the cis alkene functionality in enone 213 could be obtained from a reduction of alkyne 235 (Scheme 3.15), which in turn could be formed from coupling of the terminal alkyne 236 and acetaldehyde (237), followed by oxidation of the generated propargylic alcohol. The terminal alkyne 236 could be synthesised by direct manipulation of the aldehyde functionality in 90 and initial synthetic efforts focussed on achieving this transformation.

3.3.1.1 Attempted conversion of aldehyde 90 to terminal alkyne 236

Initial attempts at the synthesis of alkyne 236 from aldehyde 90 focussed on the use of di-bromoalkene 238 as an intermediate (Scheme 3.16).
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Reagents and conditions. (a) PPh$_3$, CBr$_4$, CH$_2$Cl$_2$, 0 °C, 87%; (b) n-BuLi, THF, – 50 °C → – 40 °C → 0 °C or – 78 °C → 0 °C, 9%.

Scheme 3.16. Formation of alkyne 236 via di-bromoalkene 238.

Aldehyde 90 was synthesised as described in Chapter 2 (Section 2.3.1)$^1$ and a number of options existed for conversion to di-bromoalkene 238. The most successful conditions involved adding aldehyde 90 to an orange mixture of PPh$_3$ and CBr$_4$ in CH$_2$Cl$_2$ at 0 °C. Subsequent warming to room temperature produced di-bromoalkene 238 in high yield (Scheme 3.16).$^{13}$ The synthesis of alkyne 236 from 238 using n-BuLi was not as successful. The first attempt involved treating di-bromoalkene 238 with two equivalents of n-BuLi at – 50 °C, using a modified procedure to that described by Mulzer $et$ $al.$.$^{14}$ The solution was warmed to – 40 °C and then room temperature, and following quenching and purification, a number of compounds were isolated. While alkyne 236 was isolated (9% yield), along with addition product 239 (Figure 3.8), these compounds only made up a small portion of the isolated mass, with the majority consisting of the starting material, di-bromoalkene 238.

Figure 3.8. Addition product 239 isolated from reaction of di-bromoalkene 238 with n-BuLi.
The $^1$H NMR spectra of alkyne 236 and addition product 239 are shown below (Figure 3.9 and Figure 3.10, respectively).

![Figure 3.9. $^1$H NMR spectrum of alkyne 236 in CDCl₃ at 300 MHz.](image)

The requisite alkyne proton appears as a multiplet at δ 2.09, with the protons of the two methyl groups appearing as doublets at δ 1.18 and δ 1.29 (Figure 3.9). The methyl doublet at δ 1.18 couples to the methine proton multiplet at δ 2.62, while the other methyl doublet couples to the methine proton adjacent to the exocyclic carbonyl. This methine proton appears as a multiplet at δ 4.10, as does the oxymethine proton. The protons of the TBS group appear at δ 0.06, δ 0.13 and δ 0.92, while the auxiliary protons appear at δ 2.75, δ 3.27, δ 4.17, and δ 7.20 – 7.33. The alkyne carbons appeared in the $^{13}$C NMR spectrum at δ 70.5 and δ 86.6, and high resolution mass spectrometry confirmed the expected composition of C₂₄H₃₅NO₄Si.

The $^1$H NMR spectrum of addition product 239 (Figure 3.10) also indicates the presence of the alkyne proton, which appears as a multiplet at δ 2.06.
However, a number of additional peaks (Figure 3.10) to those in the $^1$H NMR spectrum of alkyne 236 (Figure 3.9) are present, which can be attributed to the presence of the $n$-Bu group. The methyl protons of the $n$-Bu group appear as a triplet at $\delta$ 0.92 and couple to the adjacent methylene protons, which appear as a multiplet at $\delta$ 1.30 – 1.42. The remaining four $n$-Bu protons appear as a multiplet at $\delta$ 1.59 – 1.68 (along with the hydroxyl proton) and as a triplet at $\delta$ 2.34. It is proposed that the addition occurred to the carbonyl of the oxazolidinone, rather than to the external carbonyl, based on the $^{13}$C NMR spectrum, which indicated the presence of only one carbonyl carbon, at $\delta$ 173.7. The oxazolidinone carbonyl usually appears at approximately $\delta$ 150, and hence the absence of this peak indicated that the addition occurred to this carbon. Additionally, an absorption due to the hydroxyl group was present at 3432.0 cm$^{-1}$ in the infrared (IR) spectrum, and high resolution mass spectrometry confirmed the expected composition of C$_{28}$H$_{45}$NO$_4$Si.

Due to the problems encountered with addition of $n$-BuLi to the auxiliary, it was theorised that a lower temperature may inhibit the addition. To test this hypothesis, the second attempt at the formation of alkyne 236 involved treating di-bromoalkene
with $n$-BuLi at $-78^\circ$C, followed by warming to room temperature.\textsuperscript{13} By Thin Layer Chromatography (TLC) analysis, the reaction mixture did not appear to change when the temperature was increased from $-78^\circ$C to room temperature and thus it appeared that the lower temperature was not the problem. Once again, predominantly starting material 238 was isolated, as well as alkynes 236 and 239. While addition product 239 was still potentially a useful compound, only very small amounts of alkynes 236 and 239 were ever isolated, and hence another method had to be found for the conversion of aldehyde 90 to alkyne 236.

The next attempt at the synthesis of 236 involved the use of $\alpha$-diazo-$\beta$-ketophosphonate 240 (Scheme 3.17), which would allow the synthesis of alkyne 236 to be achieved directly from aldehyde 90.\textsuperscript{15} This reaction proceeds via an Horner-Wadsworth-Emmons (HWE)-type mechanism, where initially the reactive species (dimethyldiazomethylphosphonate 241) is generated \textit{in situ} from methanolysis of $\alpha$-diazo-$\beta$-ketophosphonate 240 (Scheme 3.17).\textsuperscript{16}

![Scheme 3.17. Proposed mechanism for the formation of dimethyldiazomethylphosphonate 241.](image)

Intermediate 241 then reacts with an aldehyde (81) to give alkyne 245 (Scheme 3.18).\textsuperscript{16}
The synthesis of α-diazo-β-ketophosphonate 240 began with the synthesis of 2-oxopropanephosphonate (252), which was formed from treatment of dimethyl methyl phosphonate (182) with n-BuLi to generate the lithiated anion, followed by addition of methyl acetate (244) (Scheme 3.19). $^{17}$
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![Chemical structures](image)

**Reagents and conditions.** (a) i. *n*-BuLi, THF, – 78 °C. ii. 243, – 78 °C → 0 °C, 48%; (b) i. NaH, THF, C₆H₆, 0 °C. ii. p-TsN₃, 0 °C → RT, 65%.

**Scheme 3.19. Synthesis of α-diazo-β-ketophosphonate 240.**

Phosphonate 252 was then converted to azide 240 in good yield by reaction with NaH and p-TsN₃ at 0 °C.¹⁷,¹⁸ α-Diazo-β-ketophosphonate 240 was not stored, but was synthesised prior to use each time from phosphonate 252. A number of attempts were made at the synthesis of alkyne 236 from aldehyde 90 using α-diazo-β-ketophosphonate 240 (Scheme 3.20).

![Chemical structures](image)

**Reagents and conditions.** (a) 240, K₂CO₃, MeOH, – 50 °C → – 20 °C → 0 °C → RT, 10%.

**Scheme 3.20. Attempted synthesis of alkyne 236 from aldehyde 90 using α-diazo-β-ketophosphonate 240.**
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The first attempt involved adding phosphonate 240 to a solution of aldehyde 90 and K$_2$CO$_3$ in MeOH.$^{16,17}$ This, however, only returned a complex mixture of compounds. The second attempt involved adding phosphonate 240 to a solution of aldehyde 90 in MeOH, followed by immediate addition of K$_2$CO$_3$.\textsuperscript{15} Following purification a number of components were isolated including oxazolidinone 98 (Section 3.3, Scheme 3.13) aldehyde 90, α-diazo-β-ketophosphonate 240 and methyl ester 253. The $^1$H NMR (Figure 3.11) confirms the structure of ester 253.

![Figure 3.11. $^1$H NMR spectrum of ester 253 in CDCl$_3$ at 300 MHz.](image)

The absence of peaks due to the protons of the auxiliary is immediately evident (Figure 3.11), as is the presence of a large singlet at δ 3.69, which can be attributed to the protons of the methoxy group. The presence of a multiplet at δ 2.10 – 2.11 can be attributed to the proton of the alkyne. The $^{13}$C NMR further corroborated the structural assignment, with the absence of the peak due to the oxazolidinone carbonyl, which appears at around δ 150, and the presence of the alkyne carbons at δ 70.7 and δ 86.4, the methoxy carbon at δ 51.7 and the ester carbonyl at δ 175.3. High resolution mass spectrometry confirmed the expected composition of C$_{15}$H$_{28}$O$_3$Si.

The formation of methyl ester 253 led to the theory that perhaps the active species (dimethyldiazomethylphosphonate (241)) was not forming in adequate amounts prior
to addition of aldehyde 90. To this end, the final attempt at this reaction involved adding K$_2$CO$_3$ to a solution of phosphonate 240 in MeOH, so as to allow the reactive species 241 to form, followed by addition of aldehyde 90. However, this procedure also did not produce any desired compounds. While ester 253 could have been a suitable candidate for the synthesis of cis enone 213, it never formed in sufficient quantities to render this a synthetically viable route.

It can be deduced from the above attempts at the synthesis of alkyne 236 that the auxiliary interacted in a detrimental fashion with the reagents used in these reactions. Thus, a new approach to cis enone 213 was devised. It was postulated that cis enone 213 could be disconnected in a different location on the molecule (as depicted in Scheme 3.21), which would allow auxiliary 72 to be added at a later stage in the synthesis, but would still allow the desired stereochemistry to be inserted into cis enone 213.

![Scheme 3.21. Alternative synthetic approach to cis enone 213.](image)

This approach required the preparation of keto-aldehyde 254, which upon reaction with Evans auxiliary 72 would produce syn aldol product 255 (Scheme 3.22). The generated secondary alcohol could then be protected and following reduction using hydrogenation conditions, cis enone 213 would be obtained.
3.3.2 Attempted synthesis of cis enone 213 from keto-aldehyde 254

Two options existed for the synthesis of keto-aldehyde 254 (Scheme 3.23): the use of alcohol 256 (Scheme 3.23 A), which could be oxidised to aldehyde 254, or the use of diol 257 (Scheme 3.23 B), which could be subjected to a double-oxidation to give aldehyde 254.

Both of these options (Scheme 3.23) required the synthesis of alkyne 258, which was prepared as shown in Scheme 3.24 from (R)-Roche ester ent-88.
Chapter Three  Formation of Syn Cyclohexenones

Reagents and conditions. (a) TBSCI, imidazole, CH₂Cl₂ 0 °C → RT, 98%; (b) DIBAL, CH₂Cl₂, – 78 °C → RT, 82%; (c) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, – 78 °C → 0 °C, 89%; (d) PPh₃, CBr₄, 0 °C → RT, 81%; (e) n-BuLi, THF, – 50 °C → – 40 °C → RT, 78%.


The protection of Roche ester ent-88 (Scheme 3.24) using TBSCI and imidazole proceeded in excellent yield to give 259, which was then readily reduced to alcohol 260 with the aid of diisobutylaluminium hydride (DIBAL). The subsequent oxidation of 266 under Swern conditions gave aldehyde 261 in good yield and purity. Compounds 259 – 261 were all purified by distillation under reduced pressure, which made the synthesis of aldehyde 261 amenable to a large scale. Treatment of aldehyde 261 with PPh₃ and CBr₄ gave di-bromoalkene 262, which after isolation and purification was treated with n-BuLi to give alkyne 258 in reasonable yield.

The synthesis of alkyne 258 allowed the two options discussed above for the synthesis of keto-aldehyde 254 to be pursued. Initially the synthesis of diol 257 was attempted as this appeared to be the simpler of the two options.

3.3.2.1 Attempted synthesis of keto-aldehyde 254 from diol 257

The synthesis of diol 257 began with treatment of alkyne 258 with n-BuLi to generate the alkyl lithium species, followed by addition of acetaldehyde (237) (Scheme 3.25).
Reagents and conditions. (a) i. n-BuLi, THF, –78 °C. ii. 237, –78 °C, 75% (b) TBAF, THF, RT, 85%.

Scheme 3.25. Attempted synthesis of keto-aldehyde 254 via diol 257.

The reaction of alkyne 258 with acetaldehyde (237) (Scheme 3.25) was carried out at –78 °C and a significant excess (5 equivalents) of aldehyde 237 was added neat to lithiated 258. Propargylic alcohol 263 was thus formed as a mixture of two isomers in good yield and the \(^1\)H NMR spectrum indicates the presence of the requisite protons (Figure 3.12).
Chapter Three  Formation of Syn Cyclohexenones

Figure 3.12. $^1H$ NMR spectrum of propargylic alcohol 263 in CDCl$_3$ at 300 MHz.

The oxymethine proton is present furthest downfield at approximately $\delta$ 4.51 (Figure 3.12) and appears as two overlapping quartets (at $\delta$ 4.51 and $\delta$ 4.52). The presence of two quartets indicates that propargylic alcohol 263 is present as two isomers, and the multiplicity of this splitting is due to coupling to the adjacent methyl protons, which appear as a doublet at $\delta$ 1.42. Interestingly, the presence of two isomers is not evident from the other protons in the spectrum, with only one resonance observed for each set of protons. The methine proton on C5 appears as a multiplet at $\delta$ 2.51 – 2.68 for both isomers and couples to both the methyl protons, which appear as a doublet at $\delta$ 1.15, and the adjacent methylene protons, both of which appear as a doublet of doublets at $\delta$ 3.43 and $\delta$ 3.66. The protons of the TBS group appear furthest upfield, at $\delta$ 0.06 and $\delta$ 0.90, while the hydroxyl proton appears as a broad singlet at $\delta$ 1.66. The $^{13}$C NMR spectrum further corroborated the structural assignment with the presence of two alkyne carbons at $\delta$ 73.1 and $\delta$ 86.6, and the presence of the carbon
bearing the hydroxyl group, which appeared at $\delta$ 58.6. The IR spectrum indicated the presence of a hydroxyl absorption at 3717.0 cm$^{-1}$ and high resolution mass spectrometry confirmed the expected composition of C$_{13}$H$_{26}$O$_2$Si.

The subsequent deprotection of 263 using tetrabutylammonium fluoride (TBAF)$^{21}$ (Scheme 3.25) proceeded efficiently to give diol 257, which was to be utilised as the precursor to keto-aldehyde 254. However, subsequent oxidation attempts did not prove fruitful. Swern conditions$^{6,7}$ gave a complex mixture of compounds and use of Dess-Martin Periodinane (DMP)$^{22}$ with a catalytic amount of water$^{23}$ (to accelerate the oxidation of the secondary alcohol), resulted in the formation of allene 264 (Figure 3.13), which was characterised by a coupling constant of 3 Hz$^{24}$ between the methyl protons and the proton of the allene (highlighted in blue).

![Figure 3.13. Allene 264 formed in the reaction of diol 257 with DMP-H$_2$O.](image)

Due to the lack of success in generating keto-aldehyde 254 from diol 257, the alternative route to 254, via alcohol 256, was explored.

### 3.3.2.2 Attempted synthesis of keto-aldehyde 254 from alcohol 256

The preparation of alcohol 256 required alkyne 258 to be coupled to an appropriate carbonyl-containing compound. Weinreb amide 265 was identified as the best candidate for the reaction, as it would prevent the addition of more than one alkyl lithium (generated from the treatment of alkyne 258 with $n$-BuLi) to the amide. Weinreb amide 265 was synthesised according to Scheme 3.26.
Reagents and conditions. (a) MeON(H)Me·HCl, i-PrMgCl, THF/Et₂O, – 20 °C → 0 °C, 40%; (b) i. n-BuLi, THF, – 40 °C. ii. 265, – 78 °C → – 20 °C → RT.


The preparation of amide 265 from methyl acetate (243)¹⁰ (Scheme 3.26) proceeded in modest yield, with purification of amide 265 carried out by distillation under reduced pressure. The low yield can be attributed to the following two factors. Amide 265 has quite a low boiling point (100 °C at one atmosphere) and a portion may therefore have been lost during the isolation and purification stages. Alternatively, the reaction may not have proceeded to completion, as due to the volatility of both starting material 243 and product 265, it was not possible to easily monitor the reaction by TLC. The subsequent reaction of amide 265 with alkyne 258 involved first generating the alkyl lithium by treatment of alkyne 258 with n-BuLi, followed by addition of amide 265.¹⁴ This reaction was not successful, with only alkyne 258 being isolated following purification.

Based on the results of the synthetic attempts described above to form keto-aldehyde 254, it was concluded that it was difficult to maintain the integrity of the alkyne functionality in the synthesis due to its sensitive nature. It was postulated that the reduction of the alkyne to the cis alkene may need to be effected at an earlier stage in the synthesis and thus a new approach to the synthesis of cis enone 213 was required.
3.3.3 A new intermediate in the synthesis of cis enone 213

Reduction of the alkyne at an earlier stage in the synthetic sequence would require the preparation of an aldehyde of type 267 depicted in Scheme 3.27.

Due to the absence of the alkyne moiety in aldehyde 267 (Scheme 3.27), the enone carbonyl functionality of cis enone 213 would have to be masked as the protected alcohol (OP$_1$), until the secondary alcohol in aldol product 268 was protected as the TBS silyl ether. This measure was deemed necessary in order to prevent cyclisation and production of hemiacetal 269, due to attack of the hydroxyl of 270 onto the enone carbonyl (Scheme 3.28).

Thus, a synthetic approach involving the differential protection of the two hydroxyl groups was required.
3.3.3.1 Synthesis of a cis-aldehyde

To this end, the synthesis of a cis aldehyde (271) was carried out as depicted in Scheme 3.29 and began with propargylic alcohol 263.

**Reagents and conditions.** (a) Lindlar’s catalyst, quinoline, H₂, hexanes, RT, 100%; (b) 114, CF₃SO₃H (0.3 mol %), Et₂O, RT, 71%; (c) TBAF, THF, RT, 88%; (d) DMP, CH₂Cl₂, RT, 70%.

**Scheme 3.29. Synthesis of aldehyde 271.**

Propargylic alcohol 263 was reduced to cis alkene 272 by a hydrogenation reaction using Lindlar’s catalyst (Scheme 3.29). It was found that although the palladium is poisoned with lead in this catalyst, over-reduction to the alkane did occur. Thus, the catalyst had to be poisoned further with quinoline. This inhibited the over-reduction, producing alkene 272 in excellent yield. Secondary alcohol 272 was protected with PMB imidate 114 to give PMB ether 273, and the TBS group was cleaved using TBAF to give 274. Alcohol 274 was oxidised using DMP to give aldehyde 271 as two inseparable isomers in good yield and high purity, following purification by flash column chromatography. DMP was the oxidising agent of choice in this conversion, as Swern conditions were found to give a low yield of 271 and produced conjugated aldehyde 275 (Figure 3.14).
The $^1$H NMR spectrum of desired aldehyde 271 (Figure 3.15) indicates the presence of the requisite protons.

The diagnostic aldehyde proton for the two isomers appears as a doublet at $\delta$ 9.56 and $\delta$ 9.46 (Figure 3.15). The alkenyl proton on C3 appears as an apparent triplet at $\delta$ 5.45 for one isomer and at $\delta$ 5.35 for the other isomer, while the other alkenyl proton appears as an apparent quartet at $\delta$ 5.66 for both isomers. The coupling constant for the vinyl protons (approximately $J = 10$ Hz) indicates that the integrity of the cis stereochemistry has been preserved through the synthetic sequence from alkene 272 to aldehyde 271. The protons of the methyl group adjacent to the aldehyde...
functionality appear at δ 1.16 for one isomer and at δ 1.22 for the other isomer, and couple to the corresponding methine proton on C2, which appears as a multiplet at δ 3.22 – 3.34 for both isomers. The oxymethine proton appears as a multiplet at δ 4.22 – 4.33 for both isomers and couples to the methyl protons, which appear as a doublet at δ 1.28 for one isomer and at δ 1.29 for the other isomer. The remaining peaks at δ 3.801, δ 3.804, δ 4.22 – 4.33, δ 4.49, δ 6.87, and δ 7.24 can be attributed to the PMB group. The $^{13}$C NMR spectrum corroborated the success of the synthesis of aldehyde 271 with the presence of aldehyde carbons at δ 200.4 for one isomer and at δ 201.0 for the other isomer, along with the absorbance for the aldehyde appearing at 1727.7 cm$^{-1}$ in the IR spectrum. High resolution mass spectrometry confirmed the expected composition of C$_{15}$H$_{20}$O$_{3}$.

In summary, the synthesis of aldehyde 271 was achieved from propargylic alcohol 263 in four steps and 44% overall yield, employing a strategy based on the differential protection of hydroxyl groups. The successful preparation of aldehyde 271 allowed the synthesis of cis enone 213 to be pursued.

3.3.3.2 Synthesis of a cis enone

The preparation of a cis enone began with the coupling of aldehyde 271 with Evans auxiliary 72 under the conditions utilised previously$^8$ to give syn aldol product 276 (Scheme 3.30) in good yield (68%) and high diastereoselectivity, with no additional isomers identified in the $^1$H NMR spectrum.
Reagents and conditions. (a) i. 72, Bu₂BOTf, Et₃N, CH₂Cl₂, 0 °C. ii. 271, –78 °C → 0 °C, 68%; (b) TESOTf, 2,6-lutidine, CH₂Cl₂, –78 °C, 100%; (c) DDQ, CH₂Cl₂, pH 7 buffer, 0 °C, 100%; (d) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, –78 °C → 0 °C, 71%.

Scheme 3.30. Synthesis of cis enone 278.

In previous protections of secondary alcohols of type 276 (Scheme 3.30), TBS was the protecting group of choice, as it had proven to be sufficiently robust under the conditions used in subsequent reactions. In this case, however, it was found that alcohol 276 could not be protected easily as the TBS ether, despite a number of attempts utilising different reagents and conditions. The main problem with the protection was perceived to be steric hindrance, due to the large bulk of the TBS group. The triethylsilyl (TES) group was identified as a possible alternative, as it was not as sterically demanding as the TBS group, and the protection of alcohol 276 using TES trifluoromethanesulfonate (triflate)¹⁰ proceeded in excellent yield to give the TES ether. Subsequent cleavage of the PMB group, under buffered conditions using DDQ¹¹ resulted in the liberation of the other secondary hydroxyl group to give alcohol 277 in high yield. Fortuitously, Swern oxidation⁶,⁷ gave the desired cis enone (278) as one isomer, due to the loss of the tertiary stereocentre as a result of the oxidation. The ¹H NMR spectrum of cis enone 278 (Figure 3.16) displays the requisite protons.
The alkenyl protons appear as a multiplet at $\delta$ 6.04 – 6.16, and the shift downfield of these protons (from around $\delta$ 5.5 in aldehyde 271) can be attributed to the presence of the ketone, which results in the formation of a conjugated system. Notably, the vinyl protons of cis enone 278 differ in both multiplicity and chemical shift from the vinyl protons of trans enone 118 (Figure 3.17), synthesised in Chapter 2 (Section 2.3.1).

Figure 3.16. $^1$H NMR spectrum of cis enone 278 in CDCl$_3$ at 300 MHz.

Figure 3.17. Trans enone 118 displaying the $^1$H NMR shifts and multiplicities of H5 and H6 in CDCl$_3$. 

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From Figure 3.16 and Figure 3.17, it can be seen that the vinyl protons of cis enone 278 appear upfield of the vinyl protons of trans enone 118. As discussed in Chapter 2 (Section 2.3.1), the downfield position of the vinyl protons of trans enone 118 may be attributed to magnetic anisotropy, induced by the adjacent carbonyl system. It therefore follows that the conformation of the α,β-unsaturated system in cis enone 278 must be such that the carbonyl shields the adjacent vinyl protons from the magnetic field in the NMR spectrometer, resulting in the upfield shift of the vinyl protons of cis enone 278 relative to that exhibited by the vinyl protons of trans enone 118. This provides further evidence for the successful synthesis of the cis stereochemistry in enone 278, and indicates that the cis geometry was preserved from aldehyde 271, through the synthetic sequence to cis enone 278. The success of the oxidation is further evidenced by the presence of a singlet at δ 2.21 (Figure 3.16), which is due to the protons of the methyl ketone. The methine proton adjacent to the alkene appears as a multiplet at δ 3.58 – 3.70, and couples to the methyl protons (which appear as a doublet at δ 1.02) and the adjacent oxymethine proton, which appears as an apparent triplet at δ 3.95. This oxymethine proton couples to the methine proton on C2, which appears as a multiplet at δ 3.81 – 3.90, and this proton couples to the adjacent methyl protons, which appear as a doublet at δ 1.20. The remaining peaks can be attributed to the TES group (δ 0.61 and δ 0.98) and the protons of the auxiliary, which appear at δ 2.78, δ 3.28, δ 4.18 – 4.26, δ 4.67 – 4.73 and δ 7.22 – 7.37. The $^{13}$C NMR spectrum also indicated that cis enone 278 was successfully prepared by the presence of three carbonyl peaks at δ 153.2, δ 175.1 and δ 199.0, and the presence of the two alkene carbons at δ 125.9 and δ 150.0. High resolution mass spectrometry confirmed the expected composition of C$_{26}$H$_{39}$NO$_5$Si.

The successful preparation of cis enone 278 allowed the stereospecificity of the cuprate addition to be tested, as well as the subsequent methylation to form the desired syn stereochemistry in the cyclohexenone.

### 3.3.4 Synthesis of a syn cyclohexenone

In Section 3.3 it was postulated that the addition of a cuprate to cis enone 213 would form the anti-Felkin product cyclohexanone 231 (Scheme 3.13). Upon reaction of cis
enone 278 with a methyl cuprate, it was found that the predicted *anti*-Felkin product, cyclohexanone 279, did indeed form (Scheme 3.31).

Reagents and conditions. (a) CuI, MeLi, Me₂S, Et₂O, RT, 64%.

Scheme 3.31. Synthesis of cyclohexanone 279.

The large coupling constant ($J = 12.3$ Hz) between the two protons highlighted in blue in Scheme 3.31 (which appear at $\delta 3.23$ and $\delta 1.74 – 1.88$ in the $^1$H NMR spectrum of cyclohexanone 279, Figure 3.18) indicates that the two protons were in an antiperiplanar arrangement. Therefore, the methyl cuprate added from the predicted face of cis enone 278 to give the methyl (highlighted in pink) in the equatorial position. It can also be seen in the favoured chair conformation of 279 (Scheme 3.31) that the methyl group highlighted in red is in the equatorial position, which will negate the possibility of steric hindrance from this methyl group to the axial approach of the methylating agent. The remaining features of the $^1$H NMR spectrum of 279 (Figure 3.18) provide further proof for the success of the cuprate addition.
The absence of the protons of the auxiliary and alkenyl groups is immediately evident, as is the presence of the doublet at $\delta$ 3.23, which can be attributed to the proton between the two carbonyl groups. This indicates that 279 exists in predominantly the keto form and as discussed above, this proton couples to the adjacent methine proton on C3, which appears as a multiplet at $\delta$ 1.74 – 1.88. This proton couples to the corresponding methyl protons, which appear as a doublet at $\delta$ 0.99. The methine proton adjacent to the endocyclic carbonyl appears as a multiplet at $\delta$ 2.57 and couples to both the corresponding methyl protons (which appear as a doublet at $\delta$ 1.09) and the adjacent oxymethine proton, which appears as an apparent triplet at $\delta$ 3.15. The large coupling constant of the oxymethine proton ($J = 9.6$ Hz) indicates that it is in an antiperiplanar arrangement with the two adjacent protons (as proposed for the favoured chair conformation of 279 depicted in Scheme 3.31). The protons of the methyl ketone appear as a singlet at $\delta$ 2.18, while the methine proton on C4 appears as a multiplet at $\delta$ 1.50 – 1.63 and couples to the adjacent methyl protons, which appear as part of the doublet at $\delta$ 1.09. The presence of the TES group is evidenced by the quartet at $\delta$ 0.66 and the triplet at $\delta$ 0.98. The $^{13}$C NMR spectrum
confirmed the success of the cuprate addition by the presence of two ketone carbons (at $\delta$ 206.4 and $\delta$ 207.3), and the presence of a significant number of small peaks indicated that cyclohexanone 279 did exist to a very small extent in the enol form (also evidenced by extra resonances in the $^1$H NMR spectrum, Figure 3.18). High resolution mass spectrometry confirmed the expected composition of C$_{17}$H$_{32}$O$_3$Si.

The methylation and subsequent elimination of cyclohexanone 279 proceeded as expected to give syn cyclohexenone 280 (Scheme 3.32).

\[
\begin{array}{c}
\text{279} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{TES} \\
\end{array}
\xrightarrow{(a)}
\begin{array}{c}
\text{280} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

**Reagents and conditions.** (a) i. NaH, MeI, THF, 0 °C → RT. ii. NaH, 0 °C → RT, 32%.

*Scheme 3.32. Synthesis of syn methylated cyclohexenone 280.*

The yield in the methylation-elimination cascade to give cyclohexenone 280 (Scheme 3.32) utilising the standard conditions for this transformation (Chapter 2) was very low (13%). This was attributed to the lability of the TES group in the presence of NaH, as the free alcohol 281 (Figure 3.19) was isolated on a number of occasions.

**Figure 3.19. Alcohol 281 isolated in attempted methylation and elimination reactions of cyclohexanone 279.**
Alcohol 281 (Figure 3.19) was not a suitable candidate for elimination under these conditions, and thus the procedure was modified26,27 in an effort to prevent the formation of alcohol 281. Cyclohexanone 279 was cannulated into a solution of one equivalent of NaH in THF at 0 °C and following the addition of MeI the solution was stirred at room temperature for almost three days. The solution was then added to another equivalent of NaH in THF at 0 °C and left to stir at room temperature to promote elimination. The use of lower temperatures to effect the methylation-elimination to give syn methylated cyclohexenone 280 did result in a slightly improved yield of 280 (32%). However, the need for an alternative protecting group to TES was highlighted.

The presence of a significant amount of TESOH is obvious in the 1H NMR spectrum of 280 in CDCl3 (Figure 3.20).

![Figure 3.20. 1H NMR spectrum of syn cyclohexenone 280 in CDCl3 at 200 MHz.](image)

Additionally, two of the resonances overlap, with the two methine protons appearing together at δ 2.25. Thus, in an effort to obtain a better spectrum of methylated
cyclohexenone 280, the sample was purified once again and the spectra were recorded in C\textsubscript{6}D\textsubscript{6}. While the change in solvent did improve the separation of the peaks in the \textsuperscript{1}H NMR spectrum of syn methylated cyclohexenone 280 (Figure 3.21), some impurities were still present, which could not be removed using conventional chromatographic procedures.

![Figure 3.21. \textsuperscript{1}H NMR spectrum of cyclohexenone 280 in C\textsubscript{6}D\textsubscript{6} at 300 MHz.](image)

The presence of the diagnostic alkenyl proton (as a singlet at \(\delta\) 5.84) and absence of the peaks of the TES group is a good indication of the success of the reaction, as is the presence of only two methyl doublets (at \(\delta\) 0.49 and \(\delta\) 0.67). The vinyl methyl appears as a multiplet at \(\delta\) 1.69 – 1.70 and the appearance of the singlet at \(\delta\) 1.09 can be attributed to the quaternary methyl. The \textsuperscript{13}C NMR spectrum further corroborated the assignment, with the presence of two alkenyl carbons at \(\delta\) 133.3 and \(\delta\) 150.5, one enone carbon at \(\delta\) 201.5 and the ketone carbon at \(\delta\) 206.6. High resolution mass spectrometry confirmed the expected composition of C\textsubscript{12}H\textsubscript{18}O\textsubscript{2}.
A comparison of the $^1$H NMR spectra (in CDCl$_3$) of $syn$ methylated cyclohexenone 280 with $anti$ methylated cyclohexenone 110 (synthesised in Chapter 2, Section 2.3.1) and the data reported for the natural product, allows some interesting inferences to be made (Table 3.1).

**Table 3.1. Comparison of $^1$H NMR data (in CDCl$_3$) of syn cyclohexenone 280 with anti cyclohexenone 110 and the natural product.**

<table>
<thead>
<tr>
<th>Position</th>
<th>Syn 280</th>
<th>Anti 110</th>
<th>Natural</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.10</td>
<td>2.24</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6.52</td>
<td>6.36</td>
<td>5.44</td>
</tr>
<tr>
<td>8</td>
<td>2.25</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2.25</td>
<td>2.17</td>
<td>3.91</td>
</tr>
<tr>
<td>10</td>
<td>0.85</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1.15</td>
<td>1.35</td>
<td>1.2</td>
</tr>
<tr>
<td>18</td>
<td>1.19</td>
<td>1.08</td>
<td>1.63</td>
</tr>
<tr>
<td>19</td>
<td>1.79</td>
<td>1.81</td>
<td>1.75</td>
</tr>
</tbody>
</table>

It can be seen in Table 3.1 that differences do exist in a number of the resonances between $syn$ methylated cyclohexenone 280 and $anti$ methylated cyclohexenone 110. This indicates that the synthetic pathway towards 280 indeed produced a compound bearing different stereochemistry to $anti$ methylated cyclohexenone 110. Additionally, if the data for the natural product is compared with both cyclohexenones 280 and 110, it can be seen that $syn$ methylated cyclohexenone 280 is a closer match than $anti$ methylated cyclohexenone 110. This is especially evident for the protons on C9 and C17 (entries highlighted in yellow). The proton on C9 is at a position further downfield in $syn$ methylated cyclohexenone 280 than in $anti$ methylated cyclohexenone 110, bringing it closer to the right chemical shift for the natural product. The protons on C17 of 280 are also closer to the chemical shift for the natural product than the C17 protons of 110. Notably, it was in this region of the molecule that most of the discrepancy occurred between the spectral data of $anti$
tridachiahydropyrene (14) and the natural product (as discussed in Chapter 1, Section 1.3.2). Therefore, based on the $^1$H NMR data exhibited in Table 3.1 it may be tentatively concluded that the stereochemistry between C4 and C9 is syn in the natural product. However, due to the simplicity of the cyclohexenone system 280 described here, a more accurate model would have to be prepared before any tangible assumptions regarding the stereochemistry in the natural product could be made.

### 3.4 Conclusion

The studies undertaken in this chapter allowed some interesting inferences to be made regarding the addition of cuprates to complex enones. It was found that the modified Felkin-Ahn model\(^2\) was indeed a suitable tool for deducing the stereochemical outcome of cuprate additions, producing the expected results for enones 203 and 278 (Scheme 3.33).

![Scheme 3.33. Methylated cyclohexenones ent-110 and 280 produced from enones 203 and 278.](image)

The methylation of the resulting cyclohexanones 226 and 279 to give methylated cyclohexenones ent-110 and 280 (Scheme 3.33), respectively, was influenced by steric issues, and directed by the orientation of groups around the cyclohexanone ring.

As a result of the ability of cis enone 278 to generate the syn stereochemistry in methylated cyclohexenone 280, the attention of the project now turned towards more
complex cis enones. The aim was to synthesise a cis enone, which, via conversion to the appropriate syn cyclohexenone, would be amenable to the synthesis of both model system 282 and syn tridachiahydropyrone (42) (Figure 3.22).

Figure 3.22. Model system 282 and syn tridachiahydropyrone (42).
3.5 Experimental

\[
\begin{align*}
\text{CH}_3 & \quad \text{NaN}_3, \\
\text{O=S=O} & \quad (\text{CH}_3)_2\text{CO}, \\
\text{Cl} & \quad \text{H}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{NaN}_3, \\
\text{O=S=O} & \quad (\text{CH}_3)_2\text{CO}, \\
\text{Cl} & \quad \text{H}_2\text{O}
\end{align*}
\]

\[\text{O=S=O N}_3\]

\[\text{N}_3, \quad (\text{CH}_3)_2\text{CO}, \quad \text{H}_2\text{O}\]

\[\text{p-Toluenesulfonyl azide}\]

To a stirring solution of NaN\(_3\) (2.0 g, 32.2 mmol) in acetone (14.5 mL), and H\(_2\)O (8.8 mL) at RT was added rapidly a solution p-TsCl (5.6 g, 29.4 mmol) in acetone (14.5 mL). Upon addition of the chloride, the solution effervesced slightly, became darker and two phases formed. After 2 hr, solvents were removed \textit{in vacuo} and CH\(_2\)Cl\(_2\) (30 mL) was added. The phases were separated and the organic phase was washed with water (2 x 30 mL), then dried (MgSO\(_4\)), filtered and the solvent was removed \textit{in vacuo} to give 5.6 g (99% yield) of the title compound as a colourless oil with identical spectral data to that given in the literature.\(^{28}\) The oil crystallised upon cooling.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{KBrO}_3, \\
\text{I} & \quad \text{H}_2\text{SO}_4
\end{align*}
\]

\[\text{HO}^{-}\]

\[
\begin{align*}
\text{HO}^{-} & \quad \text{O}^-
\end{align*}
\]

\[\text{1-Hydroxy-1,2-benziodoxol-3(1H)-one-1-oxide}\]

To a vigorously stirred mixture of 2-iodobenzoic acid (85.2 g, 0.3 mol) in H\(_2\)SO\(_4\) (0.73 M, 730 mL, 1.0 mol) at 55 °C was added potassium bromate (76 g, 0.5 mol). The mixture was stirred at 68 °C for 3.6 hr after which time it was cooled to 0 °C. The solid was filtered and washed with H\(_2\)O (1000 mL) and EtOH (2 x 50 mL) to give 84.4 g (89% yield) of the title compound as a white solid.
1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one

A mixture of 1-hydroxy-1,2-benziodoxol-3(1H)-one-1-oxide (84.4 g, 0.3 mol), p-TsOH (0.4 g, 1.5 mmol) and Ac₂O (336 mL) was stirred at 80 °C for 2 hr, after which time it was cooled to 0 °C. The mixture was filtered and the solid was washed with dry Et₂O (5 x 42 mL), producing 104.7 g (83% yield) of the title compound as a white crystalline solid, with identical spectral data to that reported in the literature.²²

(R)-Methyl-3-(4-methoxybenzylxyloxy)-2-methylpropionate (ent-115)

To a stirring solution of alcohol ent-88 (2.9 mL, 24.6 mmol) and PMB imidate (10.8 g, 38.2 mmol) in dry Et₂O (30 mL) under N₂ at RT was added CF₃SO₂H (10 x 7 µL, 10 x 0.08 mmol aliquots) over a period of 3 hr. The mixture was diluted with Et₂O (30 mL) and the organic mixture was washed with NaHCO₃ (sat. 1 x 30 mL) and brine (1 x 30 mL). The organic extracts were dried (MgSO₄), filtered and solvent was removed in vacuo to give a white crystalline solid. The solid was triturated with a 1:1 mixture of hexanes/CH₂Cl₂, filtered and the filtrate was evaporated in vacuo to give 9.9 g of a yellow oil. The oil was purified by distillation under reduced pressure to give 4.6 g (75% yield) of the title compound as a clear and colourless oil (BPT 140 °C at 1.25 mmHg), with identical spectral data to that reported in the literature.²⁹
(S)-Methyl-3-(4-methoxybenzyloxy)-2-methylpropan-1-ol (ent-201)

To a stirring suspension of LiAlH₄ (0.93 g, 24.6 mmol) in dry THF (40 mL) under N₂ at 0 °C was added dropwise ester ent-115 (4.5 g, 18.9 mmol) in dry THF (15 mL) via cannula (13 mL rinse). The solution was warmed to RT and stirred for 30 min. The solution was cooled to 0 °C and the reaction was quenched by the addition of H₂O (2 mL), NaOH (5 M, 2 mL) and once again H₂O (3 mL). The mixture was diluted by the addition of Et₂O (40 mL), then dried (MgSO₄) and filtered. The filter cake was washed with Et₂O and the filtrate was evaporated in vacuo to give 4.0 g (100% yield) of the title compound as a pale yellow oil, with identical spectral data to that reported in the literature.²⁹

(R)-Methyl-3-(4-methoxybenzyloxy)-2-methylpropanal (ent-87)

To a stirring solution of DMSO (2.1 mL, 28.9 mmol) in dry CH₂Cl₂ (30 mL) under N₂ at –78 °C was added dropwise (COCl)₂ (2 M in CH₂Cl₂, 7.2 mL, 15.2 mmol) and the solution was stirred at –78 °C for 30 min. To this solution was added dropwise a solution of alcohol ent-201 (2.0 g, 9.5 mmol) in dry CH₂Cl₂ (10 mL) via cannula (7 mL rinse) and the resulting cloudy pale yellow solution was stirred at –78 °C for 45 min. To this solution was added dropwise Et₃N (8.0 mL, 57.4 mmol) and the resulting slurry was stirred at –78 °C for 30 min, after which time the solution was slowly warmed to 0 °C. The reaction was quenched by addition to a vigorously stirring solution of NaHSO₄ (1 M, 62 mL) and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 50 mL) and the organic extracts were combined and solvent was removed in vacuo. The residue was diluted with Et₂O
(100 mL) and washed with NaHSO₄ (1 M, 3 x 40 mL), H₂O (1 x 40 mL), NaHCO₃ (1 x 40 mL) and brine (1 x 40 mL). The organic extract was dried (MgSO₄), filtered and solvent was removed in vacuo to give 1.8 g (92% yield) of the title compound as a pale yellow oil, with identical spectral data to that reported in the literature.

\[
\text{Bn} \quad \text{OPMB} \quad \text{O} \quad \text{H} \quad \text{Bn} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{OPMB} \quad \text{Bn} \quad \text{O} \quad \text{OPMB} \quad \text{Bu}_2\text{BOTf}, \quad \text{Et}_3\text{N}, \quad \text{CH}_2\text{Cl}_2
\]

\[
\begin{align*}
\text{221} & \quad \text{ent-87} \\
\text{222}
\end{align*}
\]

\[(S)-4\text{-Benzyl-3-}[(2S,3R,4R)-3\text{-hydroxy-5-}-(4\text{-methoxybenzyl}xyloxy)-2,4\text{-dimethylpentanoyl}]-\text{oxazolidin-2-one} \quad (221) \quad \text{and} \quad (S)-4\text{-benzyl-3-}[(2S,3R)-3\text{-hydroxy-2,4\text{-dimethylpent-4-enoyl}}]-\text{oxazolidin-2-one} \quad (222)
\]

To a stirring solution of N-acyloxazolidinone 72 (4.1 g, 17.4 mmol) in dry CH₂Cl₂ (25 mL) under N₂ at 0 °C was added dropwise Bu₂BOTf (1 M in CH₂Cl₂, 21.0 mL, 21.0 mmol), and the resulting dark red solution was stirred at 0 °C for 30 mins. To this stirring solution was added dropwise Et₃N (3.2 mL, 23.0 mmol), and the resulting orange/yellow solution was stirred at 0 °C for a further 30 min, after which time it was cooled to −78 °C. To this was added dropwise a solution of aldehyde ent-87 (1.8 g, 8.6 mmol) in dry CH₂Cl₂ (10 mL) via cannula (5 mL rinse) and the resulting clear, yellow solution was stirred at −78 °C for 1 hr and at 0 °C for 3 hr. The reaction was quenched by addition of pH 7 buffer (15.5 mL), MeOH (48 mL) and a 2:1 solution of MeOH/30% H₂O₂ (60 mL), and the resulting two-phase mixture was stirred at 0 °C for 1 hr. The organic solvents were removed in vacuo and the resulting slurry was extracted with CH₂Cl₂ (3 x 50 mL). The organic extracts were combined, washed with NaHCO₃ (sat., 1 x 90 mL) and brine (1 x 100 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 6.3 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH₂Cl₂) to give 2.2 g (57% yield) of the title compounds as a colourless oil (Rₚ = 0.11) with identical spectral data to that reported in the literature.
(S)-4-Benzyl-3-[(2S,3R,4R)-3-(tert-butyldimethylsilyloxy)-5-(4-methoxybenzyl-oxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (223) and (S)-4-benzyl-3-[2S,3R]-3-(tert-butyldimethylsilanyloxy)-2,4-dimethylpent-4-enoyl]-oxazolidin-2-one (224)

To a stirring solution of the mixture containing alcohol 221 and alkene 222 (2.2 g, 5.0 mmol) in dry CH\(_2\)Cl\(_2\) (29.5 mL) under N\(_2\) at –78 °C was added dropwise 2,6-*lutidine* (1.2 mL, 10.3 mmol) followed immediately by dropwise addition of TBSOTf (1.8 mL, 7.8 mmol) and the resulting clear and colourless solution was left to stir at –78 °C for 3 hr. The reaction was quenched by addition of NaHCO\(_3\) (sat., 30 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL). The organic extracts were combined, dried (MgSO\(_4\)), filtered and solvent was removed *in vacuo* to give 3.9 g of an amber coloured liquid. The liquid was purified by flash column chromatography on silica (2.5% Et\(_2\)O/CH\(_2\)Cl\(_2\)) to give two products: alkene 224 (0.45g, 16% yield, R\(_f\) = 0.66) as a white solid and PMB ether 223 (1.88g, 68% yield, R\(_f\) = 0.34) as a colourless oil.

**Alkene 224:** \([\alpha]_D^{20} = +41.3 (1.12, \text{CHCl}_3)\); **IR** (film, cm\(^{-1}\)) 2927.2, 1782.5, 1700.0, 1472.4, 1380.1, 1208.4, 1086.2; **\(^1\)H NMR** (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) – 0.014 (s, 3H, \(\text{Si(C}_3\text{H}_3)\)), – 0.011 (s, 3H, \(\text{Si(C}_3\text{H}_3)\)), 0.90 (s, 9H, \(\text{SiC}_3\text{H}_3\)), 1.21 (d, 3H, \(\text{C(O)CH(C}_3\text{H}_3)\)), \(J = 6.6\) Hz), 1.55 (s, 3H, \(\text{C(CH}_3\text{C} =\)), 2.76 (d of d, 1H, aux. \(\text{CH}_3\text{Ar}, J = 13.2, 9.6\) Hz), 3.27 (d of d, 1H, aux. \(\text{CH}_3\text{Ar}, J = 12.9, 4.8\) Hz), 4.00 – 4.05 (m, 1H, \(\text{C(O)CH(CH}_3\text{)}\)), 4.13 – 4.16 (m, 2H, aux. \(\text{OCH}_2\)), 4.34 (d, 1H, \(\text{CH(OTBS)}\)), \(J = 6.3\) Hz), 4.54 – 4.59 (m, 1H, aux. NCH), 4.84 (s, 1H, \(\text{=CH}_2\text{H}_9\)), 4.93
(s, 1H, =CH$_{A}H_{B}$), 7.20 – 7.36 (m, 5H, aux. Ar$H$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) – 5.2, – 4.6, 12.5, 17.9, 18.3, 25.9, 37.8, 42.5, 55.8, 66.0, 77.2, 112.5, 127.3, 128.9, 129.4, 135.3, 145.6, 152.8, 174.7; HRESIMS calculated for C$_{23}$H$_{35}$NO$_4$SiNa$^+$ (M+Na$^+$): 440.2233; found: 440.2228.

PMB ether 223: [α]$^D_{20}$ = + 62.7 (0.59, CHCl$_3$); IR (film, cm$^{-1}$) 2930.6, 1781.1, 1512.6, 1248.4; $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 0.05 (s, 6H, Si(C$_H$$_3$)$_2$), 0.89 (s, 9H, SiC(C$_H$$_3$)$_3$), 1.01 (d, 3H, CH(CH$_3$)CH$_2$O, $J = 6.9$ Hz), 1.23 (d, 3H, C(O)CH(CH$_3$), $J = 6.6$ Hz), 1.90 – 2.00 (m, 1H, CH$_A$H$_B$Ar, $J = 13.2$, 9.6 Hz), 3.15 (d of d, 1H, CH$_A$H$_B$OPMB, $J = 9.3$, 6.3 Hz), 3.21 (d of d, 1H, aux. CH$_A$H$_B$Ar, $J = 13.5$, 3.3 Hz), 3.53 (d of d, 1H, CH$_A$H$_B$OPMB, $J = 9.3$, 5.7 Hz), 3.75 – 3.82 (m, 1H, aux. OCH$_A$H$_B$), 3.77 (s, 3H, PMB OC$_H$$_3$), 3.96 – 4.05 (m, 3H, aux. OCH$_A$H$_B$, CH(OTBS) and C(O)CH(CH$_3$)), 4.35 (d, 2H, PMB CH$_2$, $J = 11.4$ Hz), 4.43 – 4.51 (m, 1H, aux. NCH$_2$H$_2$, 6.82 – 6.85 (m, 2H, aux. and PMB Ar$H$), 7.17 – 7.35 (m, 7H, aux. and PMB Ar$H$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) – 3.9, – 3.8, 14.9, 15.0, 18.4, 26.1, 37.7, 38.9, 41.6, 55.3, 55.4, 65.7, 71.7, 72.6, 75.3, 113.7, 127.2, 128.9, 129.0, 129.4, 130.7, 135.4, 152.7, 159.0, 176.0.

(5)-4-Benzy1-3-[2S,3R,4R]-3-(tert-butyldimethylsilyloxy)-5-hydroxy-2,4-dimethylpentanoyl]-oxazolidin-2-one (225)

To a stirring solution of PMB ether 223 (0.47 g, 0.85 mmol) in dry CH$_2$Cl$_2$ (22.5 mL) at RT was added pH 7 buffer (2.5 mL) and the two-phase mixture was cooled to 0 °C. To this solution was added DDQ (0.26 g, 1.15 mmol) and the resulting black mixture was stirred at 0 °C for 1.5 hr. The mixture was diluted with CH$_2$Cl$_2$ (10 mL) and the reaction was quenched by the addition of NaHCO$_3$ (sat., 35 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 40 mL). The organic extracts were combined and washed with NaHCO$_3$ (sat., 1 x 50 mL), then dried (MgSO$_4$), filtered and solvent was
removed \textit{in vacuo} to give 0.50 g of a yellow oil. The oil was purified by flash column chromatography on buffered silica (30% EtOAc/hexanes) to give 0.25 g (64% yield) of the title compound as a colourless oil ($R_f = 0.17$).

$$\left[\alpha\right]_D^{20} = + 48.0$$ (0.50, CHCl$_3$); \textbf{IR} (film, cm$^{-1}$) 2925.6, 1781.3, 1210.7; $^1$H \textbf{NMR} (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.07 (s, 3H, Si(CH$_3$)$_A$), 0.12 (s, 3H, Si(CH$_3$)$_B$), 0.92 (s, 9H, SiC(CH$_3$)$_3$), 0.98 (d, 3H, CH(CH$_3$)$_2$CH$_2$OH, $J = 7.2$ Hz), 1.27 (d, 3H, C(O)CH(CH$_3$), $J = 6.6$ Hz), 1.60 (bs, 1H, OH), 1.84 – 1.95 (m, 1H, CH(CH$_3$)$_2$OH), 2.77 (d of d, 1H, aux. CH$_A$H$_B$Ar, $J = 13.2$, 9.3 Hz), 3.26 (d of d, 1H, aux. CH$_A$H$_B$Ar, $J = 13.2$, 3.3 Hz), 3.47 – 3.60 (m, 2H, CH$_2$OH), 3.99 (app. quint, 1H, C(O)CH(CH$_3$), $J = 6.6$ Hz), 4.11 – 4.20 (m, 2H, aux. OCH$_2$), 4.60 – 4.68 (m, 1H, aux. NCH), 7.20 – 7.37 (m, 5H, aux. ArH); $^{13}$C \textbf{NMR} (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) – 4.3, – 3.8, 14.0, 14.4, 18.3, 26.1, 37.7, 40.8, 41.7, 55.6, 65.0, 66.1, 75.1, 127.3, 128.9, 129.4, 135.1, 152.8, 175.9.

(2$S$,3$R$,4$S$)-5-[(S)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(\textit{tert}-butyldimethylsilyloxy)-2,4-dimethyl-5-oxopentanal (220)

To a stirring solution of DMSO (0.12 mL, 1.65 mmol) in dry CH$_2$Cl$_2$ (2 mL) under N$_2$ at -78 °C was added dropwise (COCl)$_2$ (2 M in CH$_2$Cl$_2$, 0.45 mL, 0.90 mmol) and the solution was stirred at -78 °C for 30 min. To this solution was added dropwise a solution of alcohol 225 (0.24 g, 0.55 mmol) in dry CH$_2$Cl$_2$ (2 mL) \textit{via} cannula (1.5 mL rinse), and the resulting cloudy pale yellow solution was stirred at -78 °C for 45 min. To this solution was added dropwise Et$_3$N (0.46 mL, 3.30 mmol) and the resulting slurry was stirred at -78 °C for 30 min, after which time it was warmed to 0 °C. The reaction was quenched by addition to a vigorously stirring solution of NaHSO$_4$ (1 M, 9 mL) and the layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 10 mL), the organic extracts were combined and solvent was removed \textit{in vacuo}. The concentrate was diluted with Et$_2$O (30 mL) and washed
with NaHSO$_4$ (1 M, 3 x 10 mL), H$_2$O (1 x 10 mL), NaHCO$_3$ (sat., 1 x 10 mL) and brine (1 x 10 mL). The organic extract was dried (MgSO$_4$), filtered and solvent was removed \textit{in vacuo} to give 0.24 g (100\% yield) of the title compound as a pale yellow oil, which was used crude in subsequent reactions.

$[\alpha]_D^{20} = +87.0$ (0.7, CHCl$_3$); \textbf{IR} (film, cm$^{-1}$) 2934.4, 1781.8, 1685.5, 1384.5, 1210.6, 1110.0; \textbf{H NMR} (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.10 (s, 3H, Si(CH$_3$)$_3$A), 0.11 (s, 3H, Si(CH$_3$)$_3$B), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 1.09 (d, 3H, CH(CH$_3$)C(O)H, $J = 6.9$ Hz), 1.28 (d, 3H, C(O)CH(CH$_3$)$_3$, $J = 6.9$ Hz), 2.60 - 2.64 (m, 1H, CH(CH$_3$)C(O)H), 2.76 (d of d, 1H, aux. CH$_3$H$_2$Ar, $J = 13.5$, 9.6 Hz), 3.21 (d of d, 1H, aux. CH$_3$H$_2$Ar, $J = 13.2$, 3.3 Hz), 3.87-3.99 (m, 1H, C(O)CH(CH$_3$)$_3$), 4.15 - 4.26 (m, 2H, aux. OCH$_2$), 4.38 (d of d, 1H, CH(OTBS), $J = 7.5$, 3.6 Hz), 4.52 - 4.60 (m, 1H, aux. NCH$_2$), 7.18 - 7.35 (m, 5H, ArH), 9.70 (d, 1H, C(O)H, $J = 1.8$ Hz); \textbf{C NMR} (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) – 4.4, – 4.1, 9.6, 14.6, 18.1, 25.8, 37.6, 41.4, 52.7, 55.4, 66.2, 73.5, 127.4, 128.9, 129.4, 135.0, 152.9, 175.1, 202.7.

A stirring solution of aldehyde 220 (0.23 g, 0.53 mmol) and ylide 117 (0.27 g, 0.85 mmol) in dry toluene (5.5 mL) was heated at 60 °C under N$_2$ for 4.5 days. The solution was cooled to RT and the volatile components were removed \textit{in vacuo}. The resulting dark brown oil was triturated with hexanes and the tritate was passed through a short silica plug. The solvents were removed \textit{in vacuo} to give a pale yellow oil, which was purified by flash column chromatography on silica (5\% hexanes/CH$_2$Cl$_2$) to give 0.20 g (77\% yield) of the title compound as a colourless oil ($R_f = 0.24$), with identical spectral data to that reported in the literature.$^{31}$
(3S,4R,5R,6S)-2-Acetyl-5-(tert-butyldimethylsilyloxy)-3,4,6-trimethylcyclohexanone (226)

To a stirring suspension of CuI (0.17 g, 0.89 mmol) in dry Et₂O (1.2 mL) and dry Me₂S (2.4 mL) under N₂ at RT was added dropwise MeLi (1.6 M in Et₂O, 1.05 mL, 1.68 mmol) until the initially formed yellow precipitate just dissolved to give a pale yellow solution. To this solution was added dropwise a solution of enone 203 (0.20 g, 0.42 mmol) in dry Et₂O (1 mL) via cannula (1 mL rinse), resulting in the formation of a yellow precipitate, and the suspension was stirred at RT for 1 hr (the solution changed in colour from yellow to orange green to black). The mixture was diluted with Et₂O (3 mL) and the reaction was quenched by slow addition of a 10% NH₄OH/90% NH₄Cl solution (10 mL). The two-phase system was stirred at RT for 10 mins, after which time the aqueous layer became dark blue in colour. The mixture was filtered through celite, the layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 40 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.19 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH₂Cl₂) to give 0.08 g (63% yield) of the title compound as a colourless oil (Rₚ = 0.56 keto form, 0.28 enol form). The compound existed predominantly in the keto form, as evidenced by ¹H NMR.

¹H NMR (CDCl₃, 300 MHz) δ (ppm) 0.06 (s, 3H, Si(CH₃)₃), 0.07 (s, 3H, Si(CH₃)₂), 0.92 (s, 9H, Si(C(CH₃)₃)), 0.97 (d, 3H, C(O)CHCH(CH₃), J = 6.6 Hz), 1.04 (d, 3H, C(O)CH(CH₃), J = 5.1 Hz), 1.06 (d, 3H, CH(CH₃)CH(OTBS), J = 5.7 Hz), 2.00 – 2.11 (m, 1H, CH(CH₃)CH(OTBS)), 2.19 (s, 3H, CH₃C(O)), 2.23 – 2.40 (m, 1H, C(O)CHCH(CH₃)), 2.44 – 2.59 (m, 1H, C(O)CH(CH₃)), 3.28 (d, 1H, C(O)CHC(O), J = 12.6 Hz), 3.44 – 3.56 (m, 1H, CH(OTBS)) ; ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) – 4.8, – 4.3, 6.4, 10.8, 17.5, 18.3, 25.8, 30.9, 33.4, 40.4, 48.1, 64.7, 77.3, 206.4, 207.6.
(4S,5S,6R)-6-Acetyl-2,4,5,6-tetramethylcyclohex-2-enone (ent-110)

To a stirring suspension of NaH (60% dispersion in oil, 0.03 g, 0.73 mmol) in dry THF (2.2 mL) under N₂ at RT was added dropwise a solution of diketone 226 (0.08 g, 0.26 mmol) in dry THF (2 mL) via cannula (1 mL rinse), and the resulting colourless solution was stirred at RT for 10 min. To this solution was added dropwise MeI (0.08 mL, 1.32 mmol) and the solution was left to stir at RT for 2 days. The reaction mixture was diluted with Et₂O (3 mL) and the reaction was quenched by addition of NaHCO₃ (sat., 8 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The organic extracts were combined and washed with brine (1 x 25 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give a brown oil. The oil was purified by flash column chromatography on silica (10% Et₂O/hexanes) to give 0.03g (60% yield) of the title compound as a colourless oil (R_f = 0.23), with identical ¹H and ¹³C NMR spectral data to that reported in the literature for its enantiomer, 110.

(5)-4-Benzyl-3-[(2S,3R,4S)-6,6-dibromo-3-(tert-butyldimethylsilyloxy)-2,4-dimethylhex-5-enoyl]-oxazolidin-2-one (238)

To a clear, bright yellow stirring solution of PPh₃ (0.27 g, 1.01 mmol) and CBr₄ (0.17 g, 0.50 mmol) in dry CH₂Cl₂ (1.5 mL) under N₂ at 0 °C was added dropwise a solution of aldehyde 90 (0.11 g, 0.25 mmol) in dry CH₂Cl₂ (0.7 mL) via cannula (0.3 mL rinse) and the solution was stirred at 0 °C for 10 min and at RT for 10 min. The solvent was removed in vacuo and the solid was triturated with hexanes. The organic phase was passed through a silica plug (Et₂O was used as the eluent), giving 0.19 g...
of a colourless oil. The oil was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give 0.13 g (87% yield) of the title compound as a colourless oil (Rf = 0.33).

\[ \alpha \] = +41.9 (0.43, CHCl₃); IR (film, cm⁻¹) 2933.1, 1782.9, 1698.9, 1109.5; \[^1\]H NMR (CDCl₃, 300 MHz) δ (ppm) 0.04 (s, 3H, Si(CH₃)₃), 0.10 (s, 3H, Si(CH₃)B), 0.95 (s, 9H, SiC(CH₃)₃), 1.04 (d, 3H, CH(CH₃)CH≡, J = 6.6 Hz), 1.26 (d, 3H, C(O)CH(CH₃), J = 6.9 Hz), 2.55 – 2.63 (m, 1H, CH(CH₃)CH≡), 2.76 (d of d, 1H, aux. CHₐHₐAr, J = 13.2, 2.4 Hz), 3.28 (d of d, 1H aux. CHₐHₐAr, J = 13.5, 3.3 Hz), 3.84 (app. quint, 1H, C(O)CH(CH₃), J = 6.6 Hz), 4.01 (app. t, 1H, CH(OTBS), J = 6.3 Hz), 4.18 – 4.28 (m, 2H, aux. OCH₂), 4.63 – 4.71 (m, 1H, aux. NCH), 6.40 (d, 1H, CH≡, J = 9.9 Hz), 7.22 – 7.38 (m, 5H, ArH); \[^{13}\]C NMR (CDCl₃, 75.5 MHz) δ (ppm) – 3.9, – 3.6, 13.2, 15.5, 18.3, 26.0, 37.6, 43.0, 44.3, 55.7, 66.1, 74.8, 88.4, 127.4, 128.9, 129.4, 135.2, 141.6, 153.0, 174.9; HRESIMS calculated for C₂₄H₃₅Br₂NO₄SiNa⁺ (M+Na⁺): 610.0600; found: 610.0605.

\( \text{(S)-4-Benzyl-3-[(2S,3R,4S)-3-(\text{tert-butyl}dimethyldimethylsilyloxy)-2,4-dimethylhex-5-ynoyl]-oxazolidin-2-one (236) and 1-(4-benzyl-2-butyl-2-hydroxyoxazolidin-3-yl)-3-[(2S,3R,4S)-3-(\text{tert-butyl}dimethyldimethylsilyloxy)-2,4-dimethylhex-5-yn-1-one] (239) } \)

To a stirring solution of bromoalkene 238 (0.05 g, 0.09 mmol) in dry THF (0.3 mL) under N₂ at – 50 °C was added dropwise n-BuLi (1.16 M in hexanes, 0.15 mL, 0.17 mmol) and the cloudy white solution was stirred at – 40 °C for 1 hr and at RT for 30
min. The reaction was quenched by dropwise addition of NH₄Cl (sat., 0.08 mL) and solvents were removed in vacuo. The aqueous residue was extracted with Et₂O (3 x 2 mL) and the organic extracts were combined, washed with brine (1 x 10 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.04 g of a colourless oil. The oil was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give a number of compounds: starting material 238 (0.014 g, R_f = 0.28), alkyne 236 (0.003 g, R_f = 0.16) and addition product 239 (0.003 g, R_f = 0.09).

**Alkyne 236:** \[
\alpha_{D}^{20} = +26.8 \ (0.49, \text{CHCl}_3); \ IR \ (\text{film}, \text{cm}^{-1}) 2927.6, 1783.6, 1694.9, 1385.7, 1209.7, 1108.5; \ ^1H \ NMR \ (\text{CDCl}_3, 300 \text{ MHz}) \delta \ (\text{ppm}) 0.06 \ (s, 3H, Si(CH₃)₃), 0.13 \ (s, 3H, Si(CH₃)₃), 0.92 \ (s, 9H, SiC(CH₃)₃), 1.18 \ (d, 3H, CH(CH₃)C≡, J = 7.2 Hz), 1.29 \ (d, 3H, C(O)CH(CH₃), J = 5.1 Hz), 2.08 – 2.09 \ (m, 1H, ≡CH); 2.58 – 2.69 \ (m, 1H, CH(CH₃)); 2.75 \ (d \text{ of } d, 1H, \text{aux. CH}_A\text{H}_B\text{Ar}, J = 13.8, 3.0 Hz), 3.25 – 3.30 \ (m, 1H, aux. CH_AH_BAr), 4.09 – 4.10 \ (m, 2H, C(O)CH(CH₃) and CH(OTBS)), 4.16 – 4.18 \ (m, 2H, aux. OCH₂), 4.58 – 4.69 \ (m, 1H, aux. NCH), 7.20 – 7.33 \ (m, 5H, ArH); ^{13}C \ NMR \ (\text{CDCl}_3, 75.5 \text{ MHz}) \delta \ (\text{ppm}) – 4.2, – 3.7, 13.6, 17.0, 18.4, 26.1, 32.3, 37.8, 42.6, 55.6, 66.0, 70.5, 75.0, 86.6, 127.3, 128.9, 129.4, 135.2, 152.8, 175.3; HRESIMS calculated for C₂₄H₃₅NO₄Si⁺Na⁺ (M+Na⁺): 452.2223; found: 452.2221.

**Addition product 239:** \(^1H \ NMR \ (\text{CDCl}_3, 300 \text{ MHz}) \delta \ (\text{ppm}) 0.06 \ (s, 3H, Si(CH₃)₃), 0.12 \ (s, 3H, Si(CH₃)₃), 0.90 \ (s, 9H, SiC(CH₃)₃), 0.92 \ (t, 3H, n-Bu CH₃, J = 3.6 Hz), 1.13 \ (d, 3H, CH(CH₃)C≡ or C(O)CH(CH₃), J = 6.9 Hz), 1.14 \ (d, 3H, CH(CH₃)C≡ or C(O)CH(CH₃), J = 6.9 Hz), 1.30 – 1.42 \ (m, 2H, n-Bu CH₃CH₂), 1.59 – 1.68 \ (m, 2H, n-Bu CH₃CH₂), 2.06 \ (d, 1H, ≡CH, J = 2.4 Hz), 2.34 \ (t, 2H, n-Bu CH₃CH₂), 2.76 – 2.92 \ (m, 1H, aux. CH₃H₂Ar), 3.92 \ (app. t, 1H, CH(OTBS), J = 5.3 Hz), 3.99 – 4.10 \ (m, 2H, aux. OCH₂), 4.37 – 4.48 \ (m, 1H, aux. NCH), 7.17 – 7.32 \ (m, 5H, ArH); ^{13}C \ NMR \ (\text{CDCl}_3, 75.5 \text{ MHz}) \delta \ (\text{ppm}) – 4.2 \ (2C), 13.7, 13.8, 17.1, 18.3, 22.4, 26.1, 27.1, 31.3, 34.0, 37.7, 45.4, 49.4, 64.5, 70.5, 74.4, 76.2, 86.8, 126.8, 128.6, 129.2, 137.0, 173.7; HRESIMS calculated for C₂₈H₄₅NO₄SiNa⁺ (M+Na⁺): 510.3016; found: 510.3004.
**Dimethyl-2-oxopropanephosphonate (252)**

To a stirring solution of phosphonate 182 (0.17 g, 1.4 mmol) in dry THF (1 mL) under N₂ at -78 °C was added dropwise n-BuLi (1.30 M in hexanes, 1.1 mL, 1.4 mmol) and the resulting creamy solution was stirred at – 78 °C for 1 hr. To this solution was added dropwise a solution of ester 244 (0.24 g, 3.18 mmol) in dry THF (0.7 mL) via cannula (0.3 mL rinse) and the resulting solution was stirred at – 78 °C for 30 min. The solution was warmed to 0 °C and reaction was quenched by addition of AcOH (10%, 0.7mL). The solution was warmed to RT with stirring and concentrated in vacuo to give a white solid. The solid was triturated with EtOAc, filtered and the filtrate was concentrated in vacuo to give 0.17 g of a colourless oil. The oil was purified by flash column chromatography on silica (5% MeOH/CH₂Cl₂) to give 0.11 g (48% yield) of the title compound as a colourless oil ($R_f$ = 0.29), with identical spectral data to that reported in the literature.¹⁷

**Dimethyl-1-diazo-2-oxopropylphosphonate (240)**

To a stirring solution of NaH (0.02 g, 0.92 mmol) in dry THF (0.5 mL) and dry benzene (1 mL) under N₂ at 0 °C was added dropwise a solution of phosphonate 252 (0.11 g, 0.66 mmol) in dry THF (0.36 mL) via cannula (0.2 mL rinse) and the resulting suspension was stirred at 0 °C for 1.5 hr. To the suspension was added dropwise a solution of $p$-TsN₃ (0.18 g, 0.91 mmol) in dry C₆H₆ (0.6 mL) via cannula (0.4 mL rinse) and the creamy solution was left to stir at RT for 2 hr. The reaction mixture was filtered through celite (EtOAc used as eluent) and solvents were
removed *in vacuo* to give 0.22 g of a clear, yellow oil. The oil was purified by flash column chromatography on silica (1:1 EtOAc/hexanes) to give 0.09 g (65% yield) of the title compound as a yellow oil \((R_f = 0.09)\), with identical spectral data to that reported in the literature.\(^{17,18}\)

\[
\text{90} \xrightarrow{\text{K}_2\text{CO}_3, \text{MeOH}} \text{240} \xrightarrow{\text{N}_2} \text{253}
\]

**\((2S,3R,4S)-3-(\text{tert-Butyldimethylsilyloxy})-2,4-dimethyl\text{-}5\text{-ynoic acid methyl ester} (253)\)**

(a) To a stirring solution of aldehyde \textbf{90} (0.05 g, 0.11 mmol) in dry MeOH (1 mL) under \(\text{N}_2\) at \(-50^\circ\text{C}\) was added dropwise a solution of \(\alpha\)-diazo-\(\beta\)-ketophosphonate \textbf{240} (0.03 g, 0.17 mmol) in dry MeOH (0.3 mL) \textit{via} cannula (0.3 mL rinse), followed immediately by the addition of \(\text{K}_2\text{CO}_3\) (0.032 g, 0.23 mmol). The solution was stirred at \(-50^\circ\text{C}\) for 30 min, at \(-20^\circ\text{C}\) for 1.5 hr and at \(0^\circ\text{C}\) for 1.5 hr, after which time TLC (5% MeOH/CH\(_2\)Cl\(_2\)) did not indicate any further changes. The solution was diluted with Et\(_2\)O (2.5 mL) and the reaction was quenched by addition of H\(_2\)O (3 mL). Solvents were removed *in vacuo* and the aqueous residue was extracted with EtOAc (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried (MgSO\(_4\)), filtered and solvent was removed *in vacuo* to give 0.05 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH\(_2\)Cl\(_2\), then 2% MeOH/CH\(_2\)Cl\(_2\)) to give methyl ester \textbf{253} (0.003 g) as a colourless oil \((R_f = 0.53\) in CH\(_2\)Cl\(_2\)) and oxazolidinone \textbf{98} (0.03 g) as a white solid \((R_f = 0.09\) in CH\(_2\)Cl\(_2\)).

**\(^1\text{H}\) NMR** (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) – 0.03 (s, 3H, Si(CH\(_3\))\(_3\)), 0.09 (s, 3H, Si(CH\(_3\))\(_2\)), 0.88 (s, 9H, SiC(CH\(_3\))\(_3\)), 1.17 (d, 3H, C(O)CH(CH\(_3\))), \(J = 7.2\) Hz), 1.22 (d, 3H, CH(CH\(_3\))C\(\equiv\)), \(J = 7.2\) Hz), 2.10 – 2.11 (m, 1H, \(=\text{CH}\)), 2.52 – 2.57 (m, 1H, CH(CH\(_3\))C\(\equiv\)), 3.02 (d of quart, 1H, C(O)CH(CH\(_3\))), \(J = 6.9, 3\) Hz), 3.69 (s, 3H, CH\(_3\)O), 4.11 (d of d, 1H, CH(OTBS), \(J = 7.8, 3.3\) Hz); **\(^{13}\text{C}\) NMR** (CDCl\(_3\), 75.5 MHz)
(b) To a stirring mixture of aldehyde 90 (0.05 g, 0.11 mmol) and K₂CO₃ (0.03 g, 0.23 mmol) in dry MeOH (0.8 mL) under N₂ at 0 °C was added dropwise a solution of α-diazo-β-ketophosphonate 240 (0.04 g, 0.20 mmol) in dry MeOH (0.5 mL) via cannula (0.3 mL rinse) and the yellow, cloudy solution was left to stir at 0 °C for 30 min and at RT overnight. The solution was diluted with Et₂O (1 mL) and the reaction was quenched by addition of H₂O (2 mL). The volatiles were removed in vacuo and the aqueous residue was extracted with EtOAc (3 x 3 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.05 g of a clear, yellow oil. The oil was purified by flash column chromatography on silica (5% MeOH/CH₂Cl₂) to give 0.03 g of oxazolidinone 98 as a colourless oil.

(c) To a stirring solution of α-diazo-β-ketophosphonate 240 (0.04 g, 0.19 mmol) in dry MeOH (1.5 mL) under N₂ at 0 °C was added dry K₂CO₃ (0.05 g, 0.33 mmol) followed immediately by the dropwise addition of a solution of aldehyde 90 (0.07 g, 0.15 mmol) in dry MeOH (0.5 mL) via cannula (0.3 mL rinse) and the solution stirred at 0 °C for 30 min and at RT for 1 hr. The reaction was quenched by addition of NH₄Cl (sat., 2.3 mL) and pentane (5.8 mL). The layers were separated and the organic extract was dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.008 g of a pale yellow oil. ¹H NMR indicated presence of a complex mixture of compounds, none of which indicated that the desired compound had formed. The aqueous layer was re-extracted with EtOAc (3 x 5 mL) and the organic extracts were combined, dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.04 g of oxazolidinone 98 as a yellow oil.
(R)-Methyl-3-(tert-butyldimethylsilyloxy)-2-methylpropionate (259)

To a stirring solution of alcohol ent-88 (6.0 g, 50.8 mmol) in dry CH$_2$Cl$_2$ (50.5 mL) under N$_2$ at 0 °C were added sequentially imidazole (7.6 g, 112.1 mmol) and TBSCl (10.8 g, 71.3 mmol) and the resulting pale yellow slurry was warmed to RT with stirring. After 1 hr the mixture was filtered through celite (Et$_2$O used as eluent) and the organic layer was washed with HCl (10%, 1 x 70 mL), water (1 x 70 mL), NaHCO$_3$ (sat., 1 x 70 mL) and brine (1 x 70 mL). The organic extract was dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 13.7 g of a clear, colourless oil. The oil was purified by distillation under reduced pressure (BPT 50 °C at 0.05 mmHg, lit. BPT 19 59 °C at 0.2 mmHg) to give 11.9 g (98% yield) of the title compound as a colourless oil with identical spectral data to that reported in the literature.$^{19}$

(S)-Methyl-3-(tert-butyldimethylsilyloxy)-2-methylpropan-1-ol (260)

To a stirring solution of ester 259 (8.3 g, 35.0 mmol) in dry CH$_2$Cl$_2$ (166 mL) under N$_2$ at –78 °C was added dropwise DIBAL (1 M in toluene, 70.0 mL, 70.0 mmol) and the resulting colourless solution was stirred at –78 °C for 15 min and then at RT for 1 hr. The solution was cooled to –78 °C and the reaction was quenched by addition of pH 7 buffer (84 mL). The mixture was warmed to RT, stirred for 1.5 hr and filtered through celite. The celite was rinsed with EtOAc and the combined filtrate was washed with H$_2$O (1 x 200 mL) and brine (1 x 200 mL). The aqueous layer was re-extracted with EtOAc (2 x 100 mL) and the organic extracts were combined, dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 6.37 g of a clear, colourless oil. The oil was purified by distillation under reduced pressure (BPT 60 °C
at 0.6 mmHg, lit. BPt$^{19}$ 60 °C at 0.8 mmHg) to give 5.9 g (82% yield) of the title compound as a clear, colourless oil, with identical spectral data to that reported in the literature.$^{19}$

\[
\begin{align*}
\text{DMSO, (COCl)}_2, & \quad \text{Et}_3\text{N, CH}_2\text{Cl}_2 \\
\text{TBSO} & \quad \text{OH} & \quad \text{TBSO} \\
\rightarrow & \quad \rightarrow \\
\end{align*}
\]

\((R)-\text{Methyl-3-} (\text{tert-} \text{butyldimethylsilyloxy})-\text{2-methylpropanal (261)}\)

To a stirring solution of DMSO (7.0 mL, 98.4 mmol) in dry CH$_2$Cl$_2$ (300 mL) under N$_2$ at −78 °C was added dropwise (COCl)$_2$ (2 M in CH$_2$Cl$_2$, 24.6 mL, 49.2 mmol) and the solution was stirred at −78 °C for 30 min. To this solution was added dropwise a solution of alcohol 260 (6.7 g, 32.8 mmol) in dry CH$_2$Cl$_2$ (8 mL) via cannula (3 mL rinse), and the resulting cloudy pale yellow solution was stirred at −78 °C for 45 min. To this solution was added dropwise Et$_3$N (27.6 mL, 196.7 mmol) and the resulting slurry was stirred at −78 °C for 30 min, after which time it was warmed to 0 °C. The reaction was quenched by addition to a vigorously stirring solution of NaHSO$_4$ (1 M, 500 mL) and the layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 200 mL), the organic extracts were combined and solvent was removed in vacuo. The concentrate was diluted with Et$_2$O (100 mL) and washed with NaHSO$_4$ (1 M, 3 x 50 mL), H$_2$O (1 x 50 mL), NaHCO$_3$ (sat., 1 x 50 mL) and brine (1 x 50 mL). The organic extract was dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 6.6 g of a yellow oil. The oil was purified by distillation under reduced pressure (BPT 70 °C at 0.5 mmHg, lit. BPT$^{19}$ 60 °C at 0.9 mmHg) to give 5.9 g (89% yield) of the title compound as a clear, pale yellow oil with identical spectral data to that reported in the literature.$^{19}$
**tert-Butyl-[(2S)-4,4-dibromo-2-methylbut-3-enyloxy]-dimethylsilane (262)**

To a stirring solution of PPh₃ (27.9 g, 106.1 mmol) and CBr₄ (17.7 g, 53.1 mmol) in dry CH₂Cl₂ (246 mL) under N₂ at 0 °C was added dropwise a solution of 261 (5.4 g, 26.5 mmol) in dry CH₂Cl₂ (15 mL) via cannula (5 mL rinse) and the resulting orange solution was stirred at 0 °C for 10 min and at RT for 10 min. The volatile components were removed *in vacuo* and the brown solid was triturated with hexanes. The extract was passed through a silica plug (Et₂O used as eluent) to give 9.4 g of a colourless oil, which was purified by flash column chromatography on silica (1:1 hexanes/CH₂Cl₂) to give 7.7 g (81% yield) of the title compound as a colourless oil (Rᵣ = 0.72), with identical spectral data to that reported in the literature.³²,³³

**tert-Butyl-[(2S)-2-methylbut-3-ynyloxy]-dimethylsilane (258)**

To a stirring solution of di-bromoalkene 262 (0.21 g, 0.59 mmol) in dry THF (2 mL) under N₂ at – 50 °C was added dropwise n-BuLi (1.36 M in hexanes, 0.86 mL, 1.17 mmol). The solution was warmed to – 40 °C and stirred at this temperature for 1 hr and at RT for 30 min. The solution was diluted with Et₂O (1 mL) and the reaction was quenched by addition of NH₄Cl (sat., 1 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried (MgSO₄), filtered and solvent was removed *in vacuo* to give 0.10 g of a colourless, cloudy oil. The oil was purified by flash column chromatography on silica (CH₂Cl₂) to give 0.09 g (78% yield) of the title compound as a colourless oil (Rᵣ = 0.69), with identical spectral data to that given in the literature.³²,³³
Chapter Three  Formation of Syn Cyclohexenones

(2S,5S)-6-(tert-Butyldimethylsilyloxy)-5-methylhex-3-yn-2-ol and (2R,5S)-6-(tert-butyldimethylsilyloxy)-5-methylhex-3-yn-2-ol (263)

To a stirring solution of alkyne 258 (0.05 g, 0.25 mmol) in dry THF (2 mL) under N₂ at –78 °C was added dropwise n-BuLi (1.36 M in hexanes, 0.37 mL, 0.50 mmol) and the resulting orange solution was stirred at –78 °C for 45 min. To the solution was added dropwise aldehyde 237 (0.07 mL, 1.26 mmol) upon which time the solution became colourless. After 10 min at –78 °C, the solution was diluted with Et₂O (2 mL) and the reaction was quenched by addition of NH₄Cl (sat., 2 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 3 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.08 g of a pale yellow, clear oil. The oil was purified by flash column chromatography on silica (5% Et₂O/CH₂Cl₂) to give 0.05 g (75% yield) of the title compound as a colourless oil (Rᵢ = 0.41), which was an inseparable mixture of two isomers.

IR (film, cm⁻¹): 3717.0, 2931.1, 2859.0, 1257.5, 1132.0, 1087.2; HRESIMS calculated for C₁₃H₂₆O₂SiNa⁺ (M+Na⁺): 265.1600; found: 265.1612.

Isomer A: ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 0.06 (s, 6H, Si(CH₃)₂), 0.90 (s, 9H, SiC(CH₃)₃), 1.15 (d, 3H, CH(CH₃)C=, J = 6.8 Hz), 1.42 (d, 3H, CH(OH)CH₃, J = 6.6 Hz), 1.66 (bs, 1H, OH), 2.51 – 2.68 (m, 1H, CH(CH₃)C=), 3.43 (d of d, 1H, TBSOCH₂H₂, J = 9.4, 7.8 Hz), 3.66 (d of d, 1H, TBSOCH₂H₂), 4.51 (quart, 1H, CH(OH), J = 9.9 Hz); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) –5.34, –5.29, 17.3, 18.3, 24.7, 25.9, 29.0, 58.6, 67.1, 83.1, 86.6.
Isomer B: $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 0.06 (s, 6H, Si(CH$_3$)$_2$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 1.15 (d, 3H, CH(CH$_3$)C≡, $J = 6.8$ Hz), 1.42 (d, 3H, CH(OH)CH$_3$, $J = 6.6$ Hz), 1.66 (bs, 1H, OH), 2.51 – 2.68 (m, 1H, CH(CH$_3$)C≡), 3.43 (d of d, 1H, TBSOCH$_2$A, $J = 9.4$, 7.8 Hz), 3.66 (d of d, 1H, TBSOCH$_2$B), 4.52 (quart., 1H, CH(OH), $J = 9.9$ Hz); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) – 5.34, – 5.29, 17.3, 18.3, 24.7, 25.9, 29.0, 58.6, 67.1, 83.1, 86.6.

(5S,2S)-2-Methylhex-3-yne-1,5-diol and (5R,2S)-2-methylhex-3-yne-1,5-diol (257)

To a stirring solution of TBS ether 263 (0.10 g, 0.41 mmol) in dry THF (1.8 mL) under N$_2$ at RT was added dropwise TBAF (1 M in THF, 0.62 mL, 0.62 mmol) and the solution was left to stir at RT for 1 hr. The solution was diluted with Et$_2$O (2 mL) and the reaction was quenched by addition of brine (3 mL). The layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 3 mL) and EtOAc (3 x 3 mL). The organic extracts were combined, dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.21 g of a clear, yellow oil. The oil was purified by flash column chromatography on silica (20% hexanes/EtOAc) to give 0.05 g (85% yield) of the title compound as a colourless oil ($R_f = 0.30$), which was an inseparable mixture of two isomers.

IR (film, cm$^{-1}$): 3322.2, 2977.0, 1076.1, 1030.9; HRESIMS calculated for C$_7$H$_{12}$O$_2$Na$^+$ (M+Na$^+$): 151.0735; found: 151.0741.

Isomer A: $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 1.15 (d, 3H, CH(CH$_3$)C≡, $J = 7.2$ Hz), 1.43 (d, 3H, CH(OH)CH$_3$, $J = 6.6$ Hz), 2.39 (bs, 1H, OH), 2.62 – 2.74 (m, 1H, CH(CH$_3$)C≡), 3.47 – 3.61 (m, 2H, HOCH$_2$), 4.49 – 4.56 (m, 1H, CH(OH)); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) 16.9, 24.6, 29.3, 58.3, 66.7, 83.9, 86.0;
Isomer B: $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 1.15 (d, 3H, CH(CH$_3$)C≡, $J = 7.2$ Hz), 1.43 (d, 3H, CH(OH)CH$_3$, $J = 6.6$ Hz), 2.39 (bs, 1H, OH), 2.62 – 2.74 (m, 1H, CH(CH$_3$)C≡), 3.47 – 3.61 (m, 2H, HOC)$_2$, 4.49 – 4.56 (m, 1H, CH(OH)); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) 16.9, 24.6, 29.3, 58.3, 66.7, 83.9, 86.0.

(2S)-2-Methyl-5-oxohex-3-ynal (254)

(a) To a stirring solution of DMSO (0.14 mL, 2.01 mmol) in dry CH$_2$Cl$_2$ (0.8 mL) under N$_2$ at – 78 °C was added dropwise (COCl)$_2$ (2 M in CH$_2$Cl$_2$, 0.50 mL, 1.01 mmol) and the solution was stirred at -78 °C for 30 min. To this solution was added dropwise a solution of diol 257 (0.04 g, 0.34 mmol) in dry CH$_2$Cl$_2$ (5 mL) via cannula (0.4 mL rinse), and the resulting cloudy pale yellow solution was stirred at – 78 °C for 45 min. To this solution was added dropwise Et$_3$N (0.60 mL, 4.30 mmol) and the resulting slurry was stirred at – 78 °C for 30 min, after which time it was warmed to 0 °C. The reaction was quenched by addition of NH$_4$Cl (sat., 5 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL) and the organic extracts were combined, dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.20 g of an orange oil/solid mixture. The material was purified by flash column chromatography on silica (5% MeOH/CH$_2$Cl$_2$) to give no useful compounds.

(b) To a stirring solution of diol 257 (0.05 g, 0.35 mmol) in dry CH$_2$Cl$_2$ (3.5 mL) at RT was added DMP (0.46 g, 1.08 mmol) followed immediately by the addition of a H$_2$O/CH$_2$Cl$_2$ mixture (0.58 mL, 0.01 mL of H$_2$O in 7.0 mL of CH$_2$Cl$_2$) and addition of the moist CH$_2$Cl$_2$ continued every 5 min (total added was 12 x 0.58 mL aliquots) for 1 hr. The solution was diluted with Et$_2$O (20 mL) and the reaction was quenched by addition of a solution of NaHCO$_3$ (sat., 12 mL) containing Na$_2$S$_2$O$_3.5$H$_2$O (1.6 g), and stirred for 5 min. The layers were separated and the organic layer was washed with NaHCO$_3$ (sat., 1 x 25 mL) and brine (1 x 25 mL), then dried (MgSO$_4$), filtered
and solvent was removed *in vacuo* to give 0.04 g of a yellow oil/solid material. The mixture was purified by flash column chromatography on silica (CH₂Cl₂) to give allene 264 (0.016 g) as a colourless oil (R<sub>f</sub> = 0.31).

![Image of allene 264](image)

**2-Methyl-5-oxohexa-2,3-dienal (264)**

**<sup>1</sup>H NMR** (CDCl₃, 300 MHz) δ (ppm) 1.95 (d, 3H, =C(CH₃), J = 3 Hz), 2.28 (s, 3H, C(O)CH₃), 6.24 (quart, 1H, CH=, J = 3 Hz), 9.65 (s, 1H, C(O)H).

![Image of 2-Methyl-5-oxohexa-2,3-dienal (264)](image)

**N-Methoxy-N-methylacetamide (265)**

To a stirring suspension of ester 243 (0.05 g, 6.75 mmol) and MeON(H)Me.HCl (1.40 g, 14.4 mmol) in dry THF and Et₂O (1:1, 16.4 mL) under N₂ at −20 °C was added dropwise i-PrMgCl (2 M in THF, 16.9 mL, 33.8 mmol) and the resulting cloudy, light brown solution was stirred at −20 °C for 30 min and at RT for 30 min. The solution was cooled to 0 °C and the reaction was quenched by addition of NH₄Cl (sat., 115 mL). The aqueous layer was extracted with Et₂O (3 x 50 mL) and CH₂Cl₂ (3 x 50 mL). The organic extracts were combined, washed with brine (1 x 100 mL), then dried (MgSO₄), filtered and solvent was removed *in vacuo* to give 0.65 g of a yellow oil. The oil was purified by distillation under N₂ to give 0.28 g (40% yield) of the title compound as a colourless oil (BPt 100 °C at 760 mmHg, lit. BPt<sup>34</sup> 40 – 44 °C at 20 mmHg), with identical spectral data to that given in the literature.<sup>34</sup>
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Formation of Syn Cyclohexenones

(5S)-6-(tert-Butyldimethylsilyloxy)-5-methylhex-3-yn-2-one (256)

To a stirring solution of alkyne 258 (0.09 g, 0.45 mmol) in dry THF (1.5 mL) under N₂ at – 40 °C was added dropwise n-BuLi (1.36 M in hexanes, 0.36 mL, 0.50 mmol) and the solution was stirred at – 40 °C for 1 hr and at RT for 10 min. The solution was cooled to – 78 °C and was added dropwise a solution of the amide 265 (0.056 g, 0.54 mmol) in dry THF (1 mL) via cannula (0.5 mL rinse). The resulting light brown/yellow solution was warmed to – 20 °C and after 1 hr, TLC (20% hexanes/CH₂Cl₂) did not indicate consumption of starting material. The solution was warmed to 0 °C and after 30 min, TLC did not indicate any further consumption of starting material. The solution was cooled to −20 °C and the reaction was quenched by addition of NH₄Cl (sat., 2 mL), and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 3 mL). The organic extracts were combined and washed with brine (1 x 25 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.11 g of predominantly starting material as a brown oil.

(2R,5S)-cis-6-(tert-Butyldimethylsilyloxy)-5-methylhex-3-en-2-ol and (2S,5S)-cis-6-(tert-butyldimethylsilyloxy)-5-methylhex-3-en-2-ol (272)

To a stirring solution of alkyne 263 (0.05 g, 0.20 mmol) in dry hexanes (7 mL) under N₂ at RT was added dropwise quinoline (0.04 mL, 0.29 mmol) followed by Lindlar’s catalyst (5% Pd on CaCO₃, poisoned with Pb, 0.05 g). The solution was placed under
an atmosphere of H\(_2\) and left to stir at RT for 1.5 hr, after which time the reaction was quenched by flushing with N\(_2\). The solution was filtered through celite (EtOAc used as eluent) and the solvents were removed \textit{in vacuo} to give 0.09 g of a pale yellow, clear oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.05 g (100% yield) of the title compound as a colourless oil, which was a separable mixture of two isomers: isomer 1 (0.024 g, R\(_f\) = 0.55) and isomer 2 (0.024 g, R\(_f\) = 0.38). The isomers were recombined for subsequent reactions.

**Isomer A:** \(\left[\alpha\right]_{D}^{20} = +1.90\) (1.05, CHCl\(_3\)); IR (film, cm\(^{-1}\)): 3624.1, 2958.0, 2929.2, 2857.7, 1256.8, 1100.2, \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 0.06 (s, 6H, Si(CH\(_3\))\(_2\)), 0.89 (s, 9H SiC(CH\(_3\))\(_3\)), 0.90 (d, 3H, CH(CH\(_3\))C=, \(J = 6.3\) Hz), 1.24 (d, 3H, CH(OH)CH\(_3\), \(J = 6.3\) Hz), 2.62 (bs, 1H, OH), 2.71 – 2.84 (m, 1H, CH(CH\(_3\))C=), 3.27 (app. t, 1H, TBSOCH\(_3\)CH\(_3\), \(J = 9.6\) Hz), 3.56 (d of d, 1H, TBSOCH\(_3\)CH\(_3\), \(J = 9.3, 4.5\) Hz), 4.47 – 4.57 (m, 1H, CH(OH)), 5.18 (app. t, 1H, HC=, \(J = 10.8\) Hz), 5.58 (d of d, 1H, =CH, \(J = 10.5, 7.8\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 75.5 MHz) \(\delta\) (ppm) – 5.4, 17.0, 18.7, 22.7, 26.1, 35.2, 62.5, 67.9, 135.4, 135.5; HRESIMS calculated for C\(_{13}\)H\(_{28}\)O\(_2\)SiNa\(^+\) (M+Na\(^+\)): 267.1757; found: 267.1755.

**Isomer B:** \(\left[\alpha\right]_{D}^{20} = +7.6\) (1.63, CHCl\(_3\)); IR (film, cm\(^{-1}\)): 3624.1, 2958.0, 2929.2, 2857.7, 1256.8, 1100.2, \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) (ppm) 0.03 (s, 6H, Si(CH\(_3\))\(_2\)), 0.88 (s, 9H SiC(CH\(_3\))\(_3\)), 0.95 (d, 3H, CH(CH\(_3\))C=, \(J = 6.3\) Hz), 1.25 (d, 3H, CH(OH)CH\(_3\), \(J = 6.3\) Hz), 1.94 (bs, 1H, OH), 2.76 – 2.86 (m, 1H, CH(CH\(_3\))C=), 3.32 (d of d, 1H, TBSOCH\(_3\)CH\(_3\), \(J = 9.9, 7.5\) Hz), 3.44 (d of d, 1H, TBSOCH\(_3\)CH\(_3\), \(J = 9.6, 6\) Hz), 4.56 – 4.65 (m, 1H, CH(OH)), 5.16 (app. t, 1H, HC=, \(J = 10.8\) Hz), 5.47 (d of d, 1H, =CH, \(J = 10.8, 7.8\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 75.5 MHz) \(\delta\) (ppm) – 5.30, – 5.26, 17.5, 18.5, 23.9, 26.0, 35.1, 64.9, 68.0, 133.6, 134.1; HRESIMS calculated for C\(_{13}\)H\(_{28}\)O\(_2\)SiNa\(^+\) (M+Na\(^+\)): 267.1757; found: 267.1755.
cis-tert-Butyl-[(2S,5R)-5-(4-methoxybenzyloxy)-2-methylhex-3-enyloxy]-dimethylsilane and cis-tert-butyl-[(2S,5S)-5-(4-methoxybenzyloxy)-2-methylhex-3-enyloxy]-dimethylsilane (273)

To a stirring solution of alcohol 272 (0.88 g, 3.61 mmol) and PMB imidate 114 (1.5 g, 5.4 mmol) in dry Et₂O (10.5 mL) under N₂ was added CF₃SO₃H (3 x 1 µL, 0.01 mmol, aliquots) over a period of 2 hr. The mixture was diluted with Et₂O (3 mL) and the organic mixture was washed with NaHCO₃ (sat. 1 x 20 mL) and brine (1 x 20 mL). The organic extract was dried (MgSO₄), filtered and solvent was removed in vacuo to give a white crystalline solid. The solid was triturated with a 1:1 mixture of hexanes and CH₂Cl₂, filtered and the filtrate was evaporated in vacuo to give 2.5 g of a yellow oil. The oil was purified by flash column chromatography on silica (1:1 hexanes/CH₂Cl₂) to give 0.94 g (71% yield) of the title compound as a colourless oil (Rₛ = 0.28), which was an inseparable mixture of two isomers.

IR (film, cm⁻¹): 2956.5, 2928.2, 2856.9, 1514.3, 1248.5, 1090.9; HRESIMS calculated for C₂₁H₃₆O₃SiNa⁺ (M+Na⁺): 387.2332; found: 387.2360.

Isomer A: ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 0.04 (s, 6H, Si(CH₃)₂), 0.89 (s, 9H SiC(CH₃)₃), 0.92 (d, 3H, CH(CH₃)CH=, J = 6.6 Hz), 1.24 (d, 3H, =CHCH(CH₃), J = 6.3 Hz), 2.51-2.70 (m, 1H, CH(CH₃)CH=), 3.36 – 3.52 (m, 2H, TBSOCH₂), 3.80 (s, 3H, PMB OCH₃), 4.25 – 4.30 (m, 2H, =CHCH(CH₃) and PMB CH₃CH₂), 4.47 – 4.52 (m, 1H, PMB CH₃CH₂), 5.30 – 5.42 (m, 2H, CH=CH), 6.85 – 6.89 (m, 2H, PMB ArH), 7.24 – 7.28 (m, 2H, PMB ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) – 5.3 (2C), 17.8, 18.4, 22.05, 26.0, 35.2, 55.3, 68.0, 69.53, 70.3, 113.70, 129.3, 131.1, 132.34, 135.07, 159.1.
**Isomer B:** $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 0.04 (s, 6H, Si(CH$_3$)$_2$), 0.89 (s, 9H SiC(CH$_3$)$_3$), 0.97 (d, 3H, CH(CH$_3$)C=, $J = 7.2$ Hz), 1.21 – 1.23 (m, 3H, =CHCH(CH$_3$)), 2.51 – 2.70 (m, 1H, CH(CH$_3$)CH=), 3.36 – 3.52 (m, 2H, TBSOCH$_2$), 3.80 (s, 3H, PMB OCH$_3$), 4.25 – 4.30 (m, 1H, PMB CH$_2$HB), 4.47 – 4.52 (m, 2H, =CHCH(CH$_3$) and PMB CH$_2$HB), 5.30 – 5.42 (m, 2H, CH=CH), 6.85 – 6.89 (m, 2H, PMB ArH), 7.24 – 7.28 (m, 2H, PMB ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) – 5.3 (2C), 17.4, 18.4, 22.0, 26.0, 35.4, 55.3, 68.0, 69.46, 70.2, 113.72, 129.2, 131.1, 132.30, 135.1, 159.1.

(2S,5R)-cis-5-(4-Methoxybenzyloxy)-2-methylhex-3-en-1-ol and (2S,5S)-cis-5-(4-methoxybenzyloxy)-2-methylhex-3-en-1-ol (274)

To a stirring solution of silyl ether 273 (0.23 g, 0.63 mmol) in dry THF (2.7 mL) under N$_2$ at RT was added dropwise TBAF (1 M in THF, 0.95 mL, 0.95 mmol) and the solution was left to stir at RT for 30 min. The solution was diluted with Et$_2$O (3 mL) and the reaction was quenched by addition of brine (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The organic extracts were combined, dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.69 g of a clear, yellow oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give 0.14 g (88% yield) of the title compound as a colourless oil ($R_f = 0.19$), which was an inseparable mixture of two isomers.

IR (film, cm$^{-1}$): 3438.0, 2967.8, 1614.7, 1514.8, 1247.3, 1085.9, 1035.9; HRESIMS calculated for C$_{15}$H$_{22}$O$_3$Na$^+$ (M+Na$^+$): 273.1467; found: 273.1476.

**Isomer A:** $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 0.93 (d, 3H, =CHCH(CH$_3$), $J = 6.9$ Hz), 1.27 (d, 3H, CH(CH$_3$)OPMB, $J = 6.3$ Hz), 1.64 (bs, 1H, OH), 2.57 – 2.69 (m, 1H, =CHCH(CH$_3$)), 3.36 (d of d, 1H, CH$_2$HB$_2$OH $J = 14.4$, 8.1 Hz), 3.47 (d of d, 1H,
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CH$_3$H$_2$OH), 3.80 (s, 3H, PMB OCH$_3$), 4.23 – 4.33 (m, 1H, =CHCH(CH$_3$)), 4.28 (d, 1H, PMB CH$_3$CH$_3$, $J$ = 11.4 Hz), 4.48 (d of d, 1H, PMB CH$_3$CH$_3$, $J$ = 11.7, 4.2 Hz), 5.28 – 5.35 (m, 1H, CH=), 5.47 – 5.56 (m, 1H, =CH), 6.85 – 6.88 (m, 2H, PMB ArH), 7.24 – 7.29 (m, 2H, PMB ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) 17.2, 21.4, 35.35, 55.3, 67.5, 69.6, 70.0, 113.8, 129.4, 130.6, 134.13, 134.4, 159.1.

Isomer B: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.99 (d, 3H, –CHCH(CH$_3$)), $J$ = 6.9 Hz), 1.26 (d, 3H, CH(CH$_3$)OPMB, $J$ = 6.3 Hz), 1.64 (bs, 1H, OH), 2.57 – 2.69 (m, 1H, =CHCH(CH$_3$)), 3.32 (d of d, 1H, CH$_3$H$_2$OH, $J$ = 14.7, 8.4 Hz), 3.51 (d of d, 1H, CH$_3$H$_2$OH, $J$ = 11.7, 5.4 Hz), 3.79 (s, 3H, PMB OCH$_3$), 4.23 – 4.33 (m, 1H, =CHCH(CH$_3$)), 4.37 (d, 1H, PMB CH$_3$CH$_3$, $J$ = 11.1 Hz), 4.48 (d of d, 1H, PMB CH$_3$CH$_3$, $J$ = 11.7, 4.2 Hz), 5.28 – 5.35 (m, 1H, CH=), 5.47 – 5.56 (m, 1H, =CH), 6.85 – 6.88 (m, 2H, PMB ArH), 7.24 – 7.29 (m, 2H, PMB ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) 17.0, 21.9, 35.40, 55.3, 67.4, 69.5, 70.2, 113.8, 129.2, 130.7, 134.15, 134.8, 159.1.

![Diagram](image-url)

(2S,5R)-cis-5-(4-Methoxybenzyloxy)-2-methylhex-3-enal and (2S,5S)-cis-5-(4-methoxybenzyloxy)-2-methylhex-3-enal (271)

To a stirring solution of DMP (0.13 g, 0.30 mmol) in dry CH$_2$Cl$_2$ (1 mL) under N$_2$ at RT was added dropwise a solution of alcohol 274 (0.05 g, 0.20 mmol) in dry CH$_2$Cl$_2$ (0.5 mL) via cannula (0.5 mL rinse) and the solution was left to stir at RT for 1 hr. The solution was diluted with Et$_2$O (4 mL) and the reaction was quenched by dropwise addition of a solution of NaHCO$_3$ (sat., 4 mL) containing Na$_2$S$_2$O$_3$.5H$_2$O (0.5 g), and was left to stir for 5 min. The layers were separated and the organic layer was washed with NaHCO$_3$ (sat., 1 x 12 mL) and brine (1 x 12 mL), then dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.05 g of a clear and colourless oil. The oil was purified by flash column chromatography on silica (20%
EtOAc/hexanes) to give 0.04 g (70% yield) of the title compound as a colourless oil (R_f = 0.30), which was an inseparable mixture of two isomers.

**IR** (film, cm⁻¹): 2971.4, 1727.7, 1514.2, 1247.8, 1087.1, 1034.7; **HRESIMS** calculated for C_{15}H_{20}O_3Na⁺ (M+Na⁺): 271.1310; found: 271.1310.

**Isomer A:**

**¹H NMR** (CDCl₃, 300 MHz) δ (ppm) 1.16 (d, 3H, HC(O)CH(CH₃), J = 6.9 Hz), 1.28 (d, 3H, CH(CH₃)OPMB, J = 6.3 Hz), 3.22 – 3.34 (m, 1H, HC(O)CH(CH₃)), 3.80 (s, 3H, PMB OCH₃), 4.22 – 4.27 (m, 1H, CHCH(CH₃)), 4.31 (d of d, 1H, PMB CHₐCHₐ, J = 11.4, 2.4 Hz), 4.49 (d, 1H, PMB CHₐCH₂B, J = 11.7 Hz), 5.45 (app. t, 1H, CH=, J = 10.4 Hz), 5.66 (app. quart, 1H, =CH, J = 9.7 Hz), 6.85 – 6.88 (m, 2H, PMB ArH), 7.24 – 7.29 (m, 2H, PMB ArH), 9.46 (d, 1H, HC(O), J = 1.5 Hz); **¹³C NMR** (CDCl₃, 75.5 MHz) δ (ppm) 14.7, 21.7, 46.4, 55.3, 69.7, 70.1, 113.7, 127.6, 129.2, 130.4, 136.1, 159.1, 200.4.

**Isomer B:**

**¹H NMR** (CDCl₃, 300 MHz) δ (ppm) 1.22 (d, 3H, HC(O)CH(CH₃), J = 6.9 Hz), 1.29 (d, 3H, CH(CH₃)OPMB, J = 6.3 Hz), 3.22 – 3.34 (m, 1H, HC(O)CH(CH₃)), 3.804 (s, 3H, PMB OCH₃), 4.22 – 4.37 (m, 1H, =CHCH(CH₃)), 4.31 (d of d, 1H, PMB CHₐCH₂B, J = 11.4, 2.4 Hz), 4.49 (d, 1H, PMB CHₐCHB, J = 11.7 Hz), 5.35 (app. t, 1H, CH=, J = 10.4 Hz), 5.66 (app. quart., 1H, =CH, J = 9.7 Hz), 6.85 – 6.88 (m, 2H, PMB ArH), 7.24 – 7.29 (m, 2H, PMB ArH), 9.56 (d, 1H, HC(O), J = 1.5 Hz); **¹³C NMR** (CDCl₃, 75.5 MHz) δ (ppm) 14.7, 21.65, 45.8, 55.3, 69.7, 69.9, 113.7, 127.5, 129.1, 130.4, 136.6, 159.1, 201.0.
(S)-4-Benzyl-3-[cis-(2S,3R,4S,7R)-3-hydroxy-7-(4-methoxybenzyl)oxy]-2,4-dimethyl-oct-5-enoyl]-oxazolidin-2-one and (S)-4-benzyl-3-[cis-(2S,3R,4S,7S)-3-hydroxy-7-(4-methoxybenzyl)oxy]-2,4-dimethyl-oct-5-enoyl]-oxazolidin-2-one (276)

To a stirring solution of N-acyloxazolidinone 72 (0.40 g, 1.70 mmol) in dry CH$_2$Cl$_2$ (1.9 mL) under N$_2$ at 0 °C was added dropwise Bu$_2$BOTf (1 M in CH$_2$Cl$_2$, 2.05 mL, 2.05 mmol), and the resulting pale red solution was stirred at 0 °C for 30 min. To this stirring solution was added dropwise Et$_3$N (0.31 mL, 2.21 mmol), and the resulting yellow solution was stirred at 0 °C for a further 30 min, after which time it was cooled to –78 °C. A solution of aldehyde 271 (0.21 g, 0.85 mmol) in dry CH$_2$Cl$_2$ (1 mL) was then added dropwise via cannula (1 mL rinse) and the resulting clear, yellow solution was stirred at –78 °C for 30 min and at 0 °C for 30 min. The reaction was quenched by addition of pH 7 buffer (2.6 mL), MeOH (3.7 mL) and a 2:1 solution of MeOH/30% H$_2$O$_2$ (9 mL), and the resulting two-phase mixture was stirred at RT for 1 hr. The organic solvents were removed in vacuo and the resulting slurry was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic extracts were combined, washed with NaHCO$_3$ (sat., 1 x 25 mL) and brine (1 x 25 mL), then dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.68 g of a yellow oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give 0.19 g (68% yield) of the title compound as a colourless oil (R$_f$ = 0.10), which was an inseparable mixture of two isomers.

IR (film, cm$^{-1}$): 3514.1, 2971.3, 1782.9, 1694.4, 1514.4, 1455.2, 1385.8, 1246.1, 1210.1, 1108.6, 1034.2; HRESIMS calculated for C$_{28}$H$_{35}$NO$_6$Na$^+$ (M+Na$^+$): 504.2362; found: 504.2356.

Isomer A: $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 1.15 (d, 3H, CH(CH$_3$)CH=, J = 6.6 Hz), 1.22 (d, 3H, C(O)CH(CH$_3$), J = 7.5 Hz), 1.28 (d, 3H, =CHCH(CH$_3$), J = 6.3 Hz),
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2.28 (bs, 1H, OH), 2.55 – 2.63 (m, 1H, CH(CH₃)CH=), 2.78 (d of d, 1H, aux. CH₃Ar, J = 12.9, 9.6 Hz), 3.19 – 3.22 (m, 1H, aux. CH₃Ar), 3.71 (d of d, 1H, CH(OH), J = 9.3, 2.1 Hz), 3.79 (s, 3H, PMB OCH₃), 3.79 – 3.81 (m, 1H, C(O)CH(CH₃)), 3.92 (quart of d, 1H, C(O)CH(CH₃)), 4.17 – 4.38 (m, 4H, =CHCH₃ and aux. PMB Ar), 4.54 (d, 1H, PMB CH₃), 4.65 – 4.71 (m, 1H, aux. NC₃H), 5.29 – 5.39 (m, 1H, CH=), 5.43 – 5.52 (m, 1H, =C=), 6.85 – 6.88 (m, 3H, aux. and PMB Ar), 7.18 – 7.36 (m, 6H, aux. and PMB Ar); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 10.4, 18.3, 22.1, 35.7, 37.8, 40.4, 55.04, 55.3, 66.1, 70.0, 71.2, 75.0, 113.73, 127.4, 128.9, 129.3, 130.8, 132.9, 133.74, 134.91, 152.6, 158.95, 177.9.

**Isomer B:** ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 1.09 (d, 3H, CH(CH₃)O, J = 6.6 Hz), 1.18 (d, 3H, C(O)CH(CH₃), J = 7.2 Hz), 1.31 (d, 3H, =CHCH(CH₃), J = 6.3 Hz), 2.28 (bs, 1H, OH), 2.55 – 2.63 (m, 1H, CH(CH₃)CH=), 2.78 (d of d, 1H, aux. CH₃Ar, J = 12.9, 9.6 Hz), 3.24 – 3.27 (m, 1H, aux. CH₃Ar), 3.67 (d of d, 1H, CH(OH), J = 9.6, 1.8 Hz), 3.79 – 3.81 (m, 4H, PMB OCH₃ and C(O)CH(CH₃)), 4.48 (d, 1H, PMB CH₃), 5.29 – 5.39 (m, 3H, CH=CH), 6.85 – 6.88 (m, 3H, aux. and PMB Ar), 7.18 – 7.36 (m, 6H, aux. and PMB Ar); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 10.0, 18.1, 21.5, 35.7, 40.1, 54.97, 66.2, 69.6, 70.2, 74.7, 113.68, 129.0, 130.9, 132.6, 133.70, 134.85, 158.87, 177.8.

(5)-4-Benzyl-3-[cis-(2S,3R,4S,7R)-3-(tert-butyldimethylsilyloxy)-7-(4-methoxy-benzyloxy)-2,4-dimethyloct-5-enoyl]-oxazolidin-2-one and (S)-4-benzyl-3-[cis-(2S,3R,4S,7S)-3-(tert-butyldimethylsilyloxy)-7-(4-methoxy-benzyloxy)-2,4-dimethyloct-5-enoyl]-oxazolidin-2-one (284)

(a) To a stirring solution of alcohol 276 (0.05 g, 0.10 mmol) in dry CH₂Cl₂ (0.7 mL) under N₂ at – 78 °C was added dropwise 2,6-lutidine (0.05 mL, 0.42 mmol) followed
immediately by dropwise addition of TBSOTf (0.07 mL, 0.31 mmol) and the resulting clear and colourless solution was left to stir at –78 °C for 5 hr. The reaction was quenched by addition of NaHCO₃ (sat., 2 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 2 mL). The organic extracts were combined, dried (MgSO₄), filtered and solvent was removed \textit{in vacuo} to give 0.10 g of a yellow oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give 0.02 g (33% yield) of the title compound as a colourless oil (Rₜ =0.44), which was an inseparable mixture of two isomers.

\textbf{IR} (film, cm\(^{-1}\)): 2933.0, 2856.1, 1783.1, 1703.1, 1694.6, 1514.6, 1385.8, 1248.2, 1210.0, 1110.1; \textbf{HRESIMS} calculated for C₃₄H₄₉NO₆SiNa\(^+\) (M+Na\(^+\)): 618.3227; found: 618.3234.

\textbf{Isomer A}: \textbf{\(^1\)H NMR} (CDCl₃, 300 MHz) \(\delta\) (ppm) 0.00 (s, 6H, Si(CH₃)₂), 0.91 (s, 9H, SiC(CH₃)₃), 1.01 (d, 3H, CH(CH₃)CH=, \(J = 6.9\) Hz), 1.17 – 1.31 (m, 6H, C(O)CH(CH₃) and =CHCH(CH₃)), 2.53 – 2.62 (m, 1H, CH(CH₃)CH=), 2.67 – 2.78 (m, 1H, aux. CH₃H₃Ar), 3.18 – 3.32 (m, 1H, aux. CH₃H₃Ar), 3.78 (s, 3H, PMB OC₃H₃), 3.83 – 4.02 (m, 2H, C(O)CH(CH₃) and CH(OTBS)), 4.08 – 4.16 (m, 2H, aux. OCH₂), 4.24 – 4.28 (m, 2H, =CHCH(CH₃) and PMB CH₃CH₃), 4.44 – 4.57 (m, 2H, aux. OCH₂), 5.33 (app. t, 1H, =C₃H₃, \(J = 11.4\) Hz), 5.54 – 5.61 (m, 2H, CH=), 6.79 – 6.88 (m, 3H, aux. and PMB ArH), 7.19 – 7.35 (m, 6H, aux. and PMB ArH); \textbf{\(^{13}\)C NMR} (CDCl₃, 75.5 MHz) \(\delta\) (ppm) – 4.0 (2C), 12.4, 15.3, 16.7, 17.7, 18.4, 21.9, 26.1, 37.58, 37.8, 43.0, 55.3, 55.7, 66.0, 69.7, 70.0, 76.2, 113.73, 128.9, 129.1, 131.1, 131.4, 134.4, 135.3, 152.9, 158.9, 175.4.

\textbf{Isomer B}: \textbf{\(^1\)H NMR} (CDCl₃, 300 MHz) \(\delta\) (ppm) 0.10 (s, 3H, Si(CH₃)₃), 0.11 (s, 3H, Si(CH₃)₃), 0.91 – 0.93 (m, 9H, SiC(CH₃)₃), 0.97 (d, 3H, CH(CH₃)CH=, \(J = 6.9\) Hz), 1.17 – 1.31 (m, 6H, C(O)CH(CH₃) and =CHCH(CH₃)), 2.42 – 2.52 (m, 1H, CH(CH₃)CH=), 2.67 – 2.78 (m, 1H, aux. CH₃H₃Ar), 3.18 – 3.32 (m, 1H, aux. CH₃H₃Ar), 3.73 (s, 3H, PMB OCH₃), 3.83 – 4.02 (m, 2H, C(O)CH(CH₃) and CH(OTBS)), 4.08 – 4.16 (m, 2H, aux. OCH₂), 4.33 – 4.37 (m, 1H, =CHCH(CH₃) and PMB CH₃H₃), 4.44 – 4.57 (m, 2H, aux. NCH and PMB CH₃H₃), 5.41 (app. t,
1H, =CH, J = 8.7 Hz), 5.54 – 5.61 (m, 1H, CH=), 6.79 – 6.88 (m, 3H, aux. and PMB ArH), 7.19 – 7.35 (m, 6H, aux. and PMB ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) – 3.4, – 3.3, 12.8, 15.3, 17.7, 18.4, 21.6, 26.1, 37.58, 37.63, 42.6, 55.2, 55.6, 66.0, 69.3, 71.2, 76.2, 113.66, 127.3, 129.2, 129.4, 131.1, 132.2, 135.3, 135.9, 152.9, 158.9, 175.2.

(b) To a stirring solution of alcohol 276 (0.04 g, 0.083 mmol) in dry CH$_2$Cl$_2$ (0.5 mL) under N$_2$ at -78 °C was added dropwise 2,6-lutidine (0.036 mL, 0.31 mmol) followed immediately by dropwise addition of TBSOTf (0.053 mL, 0.23 mmol) and the resulting clear and colourless solution was left to stir at – 78 °C for 24 hr. The reaction was quenched by addition of NaHCO$_3$ (sat., 1.5 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 2 mL). The organic extracts were combined, dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.06 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH$_2$Cl$_2$ → 30% EtOAc/hexanes) to give 0.01 g (24% yield) of the title compound as a colourless oil (R$_f$ = 0.32 in CH$_2$Cl$_2$), with identical spectral data to that given above.

(c) To a stirring solution of alcohol 276 (0.03 g, 0.05 mmol) in dry CH$_2$Cl$_2$ (0.05 mL) under N$_2$ at 0 °C was added imidazole (0.008 g, 0.11 mmol) and TBSCl (0.01 g, 0.07 mmol) and the resulting white slurry was left to stir at RT. After 22 hr, TLC (30% EtOAc/hexanes) did not indicate any consumption of starting material and the solution was cooled to 0 °C. Another aliquot of imidazole (0.007 g, 0.10 mmol) and TBSCl (0.02 g, 0.11 mmol) were added and the white slurry was warmed to RT and left to stir. After a further 46 hr, TLC did not indicate the consumption of starting material and the slurry was filtered through celite (Et$_2$O used as eluent). The organic phase was washed with HCl (10%, 1 x 20 mL), H$_2$O (1 x 20 mL), NaHCO$_3$ (sat., 1 x 20 mL) and brine (1 x 20 mL), then dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.05 g of a yellow oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give 0.02 g of the starting material.

(d) To a stirring solution of alcohol 276 (0.06 g, 0.13 mmol) in dry DMF (1.3 mL) under N$_2$ at 0 °C was added imidazole (0.04 g, 0.53 mmol) and TBSCl (0.06 g, 0.38
mmol) and the resulting clear and colourless solution was warmed to RT and left to stir. After 22 hr, TLC (30% EtOAc/hexanes) did not indicate the consumption of starting material. The solution was diluted with Et₂O (4 mL) and the mixture was filtered through celite (Et₂O used as eluent). The organic phase was washed with H₂O (3 x 15 mL), HCl (10%, 1 x 25 mL), H₂O (1 x 25 mL), NaHCO₃ (sat., 1 x 25 mL) and brine (1 x 25 mL), then dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.07 g of a white oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give 0.05 g of starting material.

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\text{(S)-4-Benzyl-3-[cis-(2S,3S,4S,7R)-7-(4-methoxybenzyl)oxazolidin-2-one and (S)-4-benzyl-3-[cis-(2S,3R,4S,7S)-7-(4-methoxybenzyl)oxazolidin-2-one (285) }
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To a stirring solution of alcohol 276 (0.15 g, 0.31 mmol) in dry CH₂Cl₂ (1.8 mL) under N₂ at – 78 °C was added dropwise 2,6*lutidine (0.15 mL, 1.25 mmol) followed immediately by dropwise addition of TESOTf (0.21 mL, 0.93 mmol) and the resulting clear and colourless solution was left to stir at – 78 °C for 30 min. The reaction was quenched by addition of NaHCO₃ (sat., 5.5 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 6 mL). The organic extracts were combined, dried (MgSO₄), filtered and solvent was removed in vacuo to give 0.38 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH₂Cl₂) to give 0.18 g (100% yield) of the title compound as a colourless oil (Rₖ = 0.36), which was an inseparable mixture of two isomers.

\text{IR (film, cm}⁻¹\text{): 2960.0, 1783.3, 1698.9, 1514.4, 1245.9; HRESIMS calculated for C₃₄H₄₉NO₆SiNa}⁺\text{ (M+Na}⁺\text{): 618.3227; found: 618.3213.}
Isomer A: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.58 – 0.68 (m, 6H, Si(CH$_2$CH$_3$)$_3$), 0.95 – 1.02 (m, 12H, Si(CH$_2$CH$_3$)$_3$ and CH(CH$_3$)CH=), 1.18 (d, 3H, C(O)CH(CH$_3$), J = 6.9 Hz), 1.25 (d, 3H, =CHCH(CH$_3$), J = 6Hz), 2.51 – 2.59 (m, 1H, CH(CH$_3$)CH=), 2.69 – 2.79 (m, 1H, aux. CH$_A$H$_B$Ar), 3.21 – 3.29 (m, 1H, aux. CH$_A$H$_B$Ar), 1.18 (d, 3H, C(O)CH(CH$_3$)), J = 6.9 Hz), 1.25 (d, 3H, =CHCH(CH$_3$), J = 6Hz), 2.51 – 2.59 (m, 1H, CH(CH$_3$)CH=), 2.69 – 2.79 (m, 1H, aux. CH$_A$H$_B$Ar), 3.21 – 3.29 (m, 1H, aux. CH$_A$H$_B$Ar), 3.79 (s, 3H, PMB OCH$_3$), 3.95 – 3.99 (m, 1H, CH(OTES)), 4.13 – 4.15 (m, 2H, aux. OCH$_2$), 4.24 – 4.28 (m, 1H, PMB CH$_A$H$_B$), 4.33 – 4.37 (m, 1H, =CHCH(CH$_3$)), 4.46 – 4.52 (m, 1H, PMB CH$_A$H$_B$ and aux. NCH), 5.43 (d, 1H, =CH, J = 8.4 Hz), 5.53 (app. t, 1H, CH=, J = 10.5 Hz), 6.82 – 6.88 (m, 3H, aux. and PMB ArH), 7.20 – 7.35 (m, 6H, aux. and PMB ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) 5.5, 7.1, 12.5, 17.4, 21.6, 37.5, 37.7, 42.4, 55.2, 55.3, 66.0, 69.8, 70.0, 76.7, 113.71, 127.3, 128.9, 129.2, 131.11, 132.4, 134.2, 135.3, 152.9, 159.0, 175.5.

Isomer B: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.58 – 0.68 (m, 6H, Si(CH$_2$CH$_3$)$_3$), 0.95 – 1.02 (m, 9H, Si(CH$_2$CH$_3$)$_3$ and CH(CH$_3$)CH=), 1.22 (d, 3H, C(O)CH(CH$_3$), J = 6.9 Hz), 1.30 (d, 3H, =CHCH(CH$_3$), J = 6.3 Hz), 2.41 – 2.48 (m, 1H, CH(CH$_3$)CH=), 2.69 – 2.79 (m, 1H, aux. CH$_A$H$_B$Ar), 3.21 – 3.29 (m, 1H, aux. CH$_A$H$_B$Ar), 3.79 (s, 3H, PMB OCH$_3$), 3.86 – 3.92 (m, 2H, C(O)CH(CH$_3$) and CH(OTES)), 4.13 – 4.15 (m, 2H, aux. OCH$_2$), 4.24 – 4.28 (m, 1H, =CHCH(CH$_3$)), 4.33 – 4.37 (m, 1H, PMB CH$_A$CH$_B$), 4.46 – 4.52 (m, 1H, PMB CH$_A$CH$_B$), 4.56 – 4.60 (m, 1H, aux. NCH), 5.36 (app. quart, 1H, =CH, J = 9.6 Hz), 5.53 (app. t, 1H, CH=, J = 10.5 Hz), 6.82 – 6.88 (m, 3H, aux. and PMB ArH), 7.20 – 7.35 (m, 6H, aux. and PMB ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) 5.5, 7.1, 12.8, 16.5, 21.9, 37.5, 37.7, 42.8, 55.5, 55.7, 66.0, 69.3, 71.3, 77.2, 113.65, 127.3, 129.0, 129.4, 131.06, 131.6, 135.3, 135.7, 152.9, 159.0, 175.4.
(S)-4-Benzyl-3-(cis-(2S,3R,4S,7R)-7-hydroxy-2,4-dimethyl-3-triethylsilanyloxy-oct-5-enoyl)-oxazolidin-2-one and (S)-4-benzyl-3-(cis-(2S,3R,4S,7S)-7-hydroxy-2,4-dimethyl-3-triethylsilanyloxy-oct-5-enoyl)-oxazolidin-2-one (277)

To a stirring solution of PMB ether 285 (0.18 g, 0.30 mmol) in dry CH$_2$Cl$_2$ (7.5 mL) at RT was added pH 7 buffer (0.75 mL) and the two-phase mixture was cooled to 0 °C. To this solution was added DDQ (0.08 g, 0.36 mmol) and the resulting black mixture was stirred at 0 °C for 2 hr. The mixture was diluted with CH$_2$Cl$_2$ (3 mL) and the reaction was quenched by the addition of NaHCO$_3$ (sat., 19 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 25 mL). The organic extracts were combined and washed with NaHCO$_3$ (sat., 1 x 50 mL), then dried (MgSO$_4$), filtered and solvent was removed *in vacuo* to give 0.19 g of a yellow oil. The oil was purified by flash column chromatography on buffered silica (CH$_2$Cl$_2$ → 5% Et$_2$O/CH$_2$Cl$_2$) to give 0.14 g (100% yield) of the title compound as a colourless oil ($R_f$ = 0.24 and 0.17 in 5% Et$_2$O/CH$_2$Cl$_2$), which was an inseparable mixture of two isomers.

IR (film, cm$^{-1}$): 2959.1, 1385.8, 1210.1, 1113.3, 1010.8; HRESIMS calculated for C$_{26}$H$_{41}$NO$_5$SiNa$^+$ (M+Na$^+$): 498.2652; found: 498.2645.

**Isomer A:** $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 0.58 – 0.70 (m, 6H, Si(CH$_2$CH$_3$)$_3$), 0.95 – 1.02 (m, 12H, Si(CH$_2$CH$_3$)$_3$ and CH(CH$_3$)CH=), 1.18 – 1.30 (m, 6H, C(O)CH(CH$_3$) and =CHCH(CH$_3$)), 1.87 (bs, 1H, OH), 2.54 – 2.64 (m, 1H, CH(CH$_3$)CH=), 2.72 – 2.79 (m, 1H, aux. CH$_A$H$_B$Ar), 3.20 – 3.28 (m, 1H, aux. CH$_A$H$_B$Ar), 3.85 (app. quart, 1H, C(O)CH(CH$_3$), $J$ = 6.9 Hz), 3.91 – 3.94 (m, 1H, CH(OTES)), 4.13 – 4.23 (m, 2H, aux. OCH$_2$), 4.58 – 4.67 (m, 2H, aux. NCH and =CHCH(CH$_3$)), 5.22 – 5.46 (m, 2H, CH=CH), 7.20 – 7.36 (m, 5H, aux. ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) 5.5, 7.1, 13.6, 17.7, 23.5, 37.8, 38.8, 42.8, 55.4, 63.5, 66.04, 76.7, 127.3, 128.9, 129.4, 133.22, 134.2, 135.2, 152.8, 175.5.
Isomer B: $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm) 0.58 – 0.70 (m, 6H, Si(CH$_2$CH$_3$)$_3$), 0.95 – 1.02 (m, 12H, Si(CH$_2$CH$_3$)$_3$ and CH(CH$_3$)CH=), 1.18 – 1.30 (m, 6H, C(O)CH(CH$_3$) and =CHCH(CH$_3$)), 1.87 (bs, 1H, OH), 2.54 – 2.64 (m, 1H, CH(CH$_3$)CH=), 2.72 – 2.79 (m, 1H, aux. CH$_3$H$_6$Ar), 3.20 – 3.28 (m, 1H, aux. CH$_3$H$_6$Ar), 3.85 (app. quart, 1H, C(O)C(CH$_3$)), $J$ = 6.9 Hz), 3.91 – 3.94 (m, 1H, CH(OTES)), 4.13 – 4.23 (m, 2H, aux. OC$_2$H$_5$), 4.58 – 4.67 (m, 2H, aux. NCH and =CHCH(CH$_3$)), 5.22 – 5.46 (m, 2H, CH=CH), 7.20 – 7.36 (m, 5H, aux. ArH), $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ (ppm) 5.4, 7.1, 13.6, 16.9, 23.7, 37.5, 37.7, 42.5, 55.5, 64.0, 65.97, 77.1, 127.3, 128.9, 129.4, 133.18, 134.4, 135.1, 153.2, 175.9.

cis-(2S,3R,4S)-1-(4-Benzyl-2-oxo-oxazolidin-3-yl)-2,4-dimethyl-3-
triethylsilyloxy-oct-5-ene-1,7-dione (278)

To a stirring solution of DMSO (0.06 mL, 0.88 mmol) in dry CH$_2$Cl$_2$ (1.5 mL) under N$_2$ at – 78 °C was added dropwise (COCl)$_2$ (2 M in CH$_2$Cl$_2$, 0.22 mL, 0.44 mmol) and the solution was stirred at – 78 °C for 30 min. To this solution was added dropwise a solution of alcohol 277 (0.14 g, 0.29 mmol) in dry CH$_2$Cl$_2$ (1 mL) via cannula (0.5 mL rinse), and the resulting cloudy pale yellow solution was stirred at – 78 °C for 45 min. To this solution was added dropwise Et$_3$N (0.24 mL, 1.74 mmol) and the resulting slurry was stirred at – 78 °C for 30 min, after which time it was warmed to 0 °C. The reaction was quenched by addition to a vigorously stirring solution of NaHSO$_4$ (1 M, 4.5 mL) and the layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 5 mL), the organic extracts were combined and solvent was removed in vacuo. The concentrate was diluted with Et$_2$O (20 mL) and washed with NaHSO$_4$ (1 M, 3 x 20 mL), H$_2$O (1 x 20 mL), NaHCO$_3$ (sat., 1 x 20 mL) and brine (1 x 20 mL), then dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.14 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% hexanes/CH$_2$Cl$_2$) to give 0.10 g (71% yield) of the title compound as a colourless oil ($R_f$ = 0.14).
Chapter Three  Formation of Syn Cyclohexenones

$[\alpha]_D^{20} = +60.5$ (0.98, CHCl$_3$); IR (film, cm$^{-1}$): 2958.0, 1779.1, 1694.5, 1385.0, 1209.8, 1107.2; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.57 – 0.65 (m, 6H, Si(CH$_2$CH$_3$)$_3$), 0.96 – 1.03 (m, 9H, Si(CH$_2$CH$_3$)$_3$), 1.02 (d, 3H, CH(CH$_3$)CH=, $J$ = 6.6 Hz), 1.20 (d, 3H, C(O)CH(CH$_3$), $J$ = 6.6 Hz), 2.21 (s, 3H, C(O)CH$_3$), 2.78 (d of d, 1H, aux. CH$_A$H$_B$Ar, $J$ = 12.9, 9.6 Hz), 3.28 (d of d, 1H, aux. CH$_A$H$_B$Ar, $J$ = 12.9, 3 Hz), 3.58 – 3.70 (m, 1H, CH(CH$_3$)CH=), 3.81 – 3.90 (m, 1H, C(O)CH(CH$_3$)), 3.95 (app. t, 1H, CH(OTES), $J$ = 5.6 Hz), 4.18 – 4.26 (m, 2H, aux. OCH$_2$), 4.67 – 4.73 (m, 1H, aux. NCH$_3$), 6.04 – 6.16 (m, 2H, CH=CH), 7.22-7.37 (m, 5H, aux. ArH); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) 5.5, 7.0, 12.0, 15.8, 31.7, 37.65, 37.67, 42.6, 55.8, 66.1, 76.7, 125.9, 127.3, 128.9, 129.5, 135.4, 150.0, 153.2, 175.1, 199.0; HRESIMS calculated for C$_{26}$H$_{39}$NO$_5$SiNa$^+$ (M+Na$^+$): 496.2496; found: 496.2495.

(3S,4S,5R,6S)-2-Acetyl-5-triethylsilyloxy-3,4,6-trimethylcyclohexanone (279)

To a stirring suspension of CuI (0.08 g, 0.42 mmol) in dry Et$_2$O (1 mL) and dry Me$_2$S (2 mL) under N$_2$ at RT was added dropwise MeLi (1.6 M in Et$_2$O, 0.53 mL, 0.84 mmol) until the initially formed yellow precipitate just dissolved to give a pale yellow solution. To this solution was added dropwise a solution of enone 278 (0.10 g, 0.21 mmol) in dry Et$_2$O (1 mL) via cannula (1 mL rinse), resulting in the formation of a yellow precipitate, and the suspension was stirred at RT for 30 min (the solution changed in colour from yellow to orange green to black). The mixture was diluted with Et$_2$O (5 mL) and the reaction was quenched by slow addition of a 10% NH$_4$OH/90% NH$_4$Cl solution (10 mL). The two-phase system was stirred at RT for 10 min, after which time the aqueous layer became dark blue in colour. The mixture was filtered through celite, the layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 50 mL), then dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.10 g of a yellow oil. The oil was purified by flash column chromatography on silica (10% hexanes/CH$_2$Cl$_2$) to give 0.04 g (64% yield) of the
title compound as a colourless oil (R_f = 0.29 keto form, 0.19 enol form). The product existed in predominantly the keto form, as evidenced by ^1H NMR.

^1H NMR (CDCl_3, 300 MHz) δ (ppm) 0.62 – 0.70 (m, 6H, Si(CH_2CH_3)_3), 0.95 – 1.00 (m, 9H, Si(CH_2CH_3)_3), 0.99 (d, 3H, C(O)CHCH(CH_3), J = 6.9 Hz), 1.09 (d, 6H, C(O)CH(CH_3) and CH(CH_3)CH(OTES), J = 6.6 Hz), 1.50 – 1.63 (m, 1H, CH(CH_3)CH(OTES)), 1.74 – 1.88 (m, 1H, C(O)CHCH(CH_3)), 2.18 (s, 3H, CH_3C(O)), 2.45 – 2.57 (m, 1H, C(O)CH(CH_3)), 3.15 (app. t, 1H, CH(OTES), J = 9.6 Hz), 3.23 (d, 1H, C(O)CHC(O), J = 12.3 Hz); ^13C NMR (CDCl_3, 75.5 MHz) δ (ppm) 5.6, 7.0, 11.4, 15.8, 18.7, 30.9, 36.1, 45.4, 54.0, 69.8, 80.9, 206.4, 207.3; HRESIMS calculated for C_{17}H_{32}O_3SiNa^+ (M+Na^+): 335.2019; found: 335.2010.

\( (4R,5S,6S)-6\text{-Acetyl-2,4,5,6-tetramethylcyclohex-2-enone (280)} \)

(a) To a stirring suspension of NaH (60% dispersion in oil, 0.006 g, 0.16 mmol) in dry THF (2 mL) under N_2 at 0 °C was added dropwise a solution of diketone 279 (0.05 g, 0.16 mmol) in dry THF (1 mL) via cannula (0.2 mL rinse), and the resulting yellow solution was stirred at 0 °C for 30 min, during which time it became clear and colourless. To this solution was added dropwise MeI (0.10 mL, 1.57 mmol) and the solution was warmed to RT and left to stir for 67 hr. After this time TLC (10% EtOAc/hexanes) did not indicate any further change. The solution was cannulated into another equivalent of NaH (0.006 g, 0.16 mmol) in dry THF (1 mL) at 0 °C, warmed to RT and left to stir. After 3 days, TLC did not indicate any further changes. The reaction mixture was diluted with Et_2O (2 mL) and the reaction was quenched by addition of NaHCO_3 (sat., 6 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (1 x 25 mL), then dried (MgSO_4), filtered and solvent was removed in vacuo to give 0.04 g of a yellow oil. The oil was purified by flash column
chromatography on silica (10% EtOAc/hexanes, 100x silica) to give 0.01 g (32% yield) of the title compound as a clear, colourless oil ($R_f = 0.21$).

$^1\text{H NMR}$ (CDCl$_3$, 300 MHz) $\delta$ (ppm) 0.85 (d, 3H, C(CH$_3$)CH(CH$_3$), $J = 6.0$ Hz), 1.15 (s, 3H, C(CH$_3$)), 1.19 (d, 3H, =CHCH(CH$_3$), $J = 6.6$ Hz), 1.78 – 1.79 (m, 3H, (CH$_3$)C=), 2.10 (s, 3H, CH$_3$(CO)), 2.22 – 2.28 (m, 2H, =CHCH(CH$_3$) and C(CH$_3$)CH(CH$_3$)), 5.84 (s, 1H, =CH$_2$); $^1\text{H NMR}$ (C$_6$D$_6$, 300 MHz) $\delta$ (ppm) 0.49 (d, 3H, C(CH$_3$)CH(CH$_3$), $J = 6.9$ Hz), 0.97 (d, 3H, =CHCH(CH$_3$), $J = 7.2$ Hz), 1.09 (s, 3H, C(CH$_3$)), 1.52 – 1.65 (m, 1H, =CHCH(CH$_3$)), 1.69 – 1.70 (m, 3H, (CH$_3$)C=), 1.85 – 1.92 (m, 1H, C(CH$_3$)CH(CH$_3$)), 1.92 (s, 3H, CH$_3$(CO)), 5.84 (s, 1H, =CH$_2$); $^{13}\text{C NMR}$ (CDCl$_3$, 75.5 MHz) $\delta$ (ppm) 13.6, 13.9, 16.6, 19.3, 27.2, 35.3, 41.8, 63.9, 77.1, 150.5, 201.5, 206.6; HRESIMS calculated for C$_{12}$H$_{18}$O$_2$H$^+$ (M$+$H$^+$): 195.1386; found: 195.1385.

(b) To a stirring suspension of NaH (60% dispersion in oil, 0.008 g, 0.19 mmol) in dry THF (1 mL) under N$_2$ at RT was added dropwise a solution of diketone 279 (0.03 g, 0.10 mmol) in dry THF (0.5 mL) via cannula (0.3 mL rinse), and the resulting colourless solution was stirred at RT for 10 min. To this solution was added dropwise MeI (0.03 mL, 0.45 mmol) and the solution was left to stir at RT for 22 hr. The reaction mixture was diluted with Et$_2$O (1 mL) and the reaction was quenched by addition of NaHCO$_3$ (sat., 3 mL). The layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 3 mL). The organic extracts were combined and washed with brine (1 x 20 mL), then dried (MgSO$_4$), filtered and solvent was removed in vacuo to give 0.03 g of a yellow oil. The oil was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give 0.002 g (13% yield) of the title compound as a clear, colourless oil ($R_f = 0.18$).
3.6 References