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.

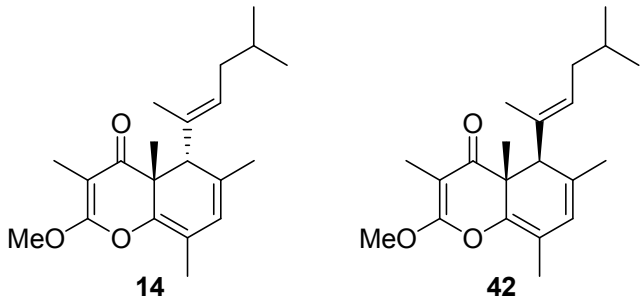
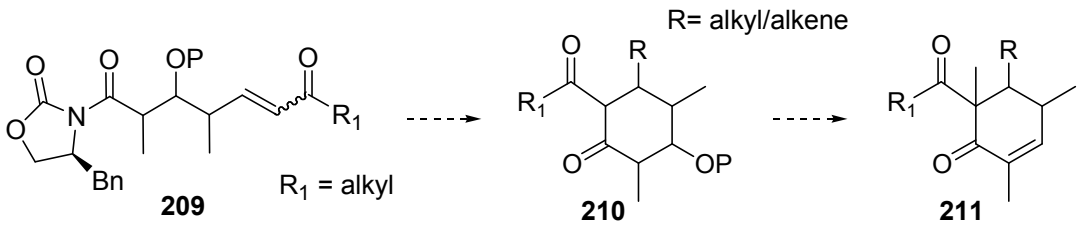


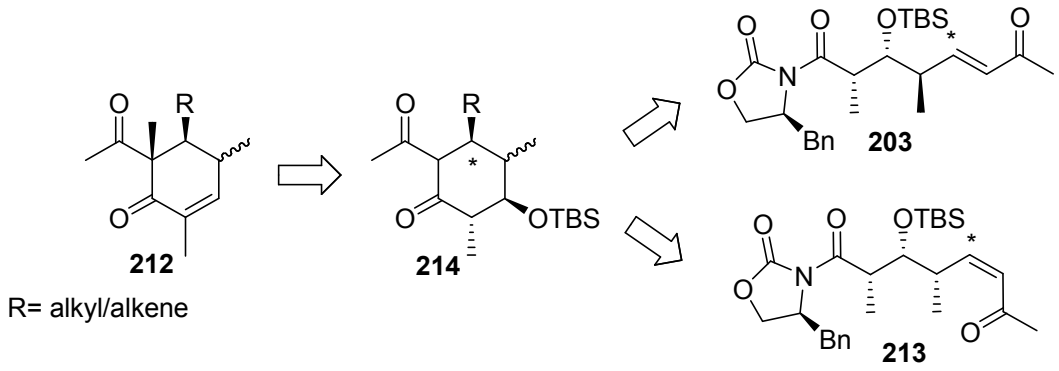
*Figure 3.1. Reported structure (**14**) and proposed structure (**42**) of tridachiahydropyrone.*

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).



Scheme 3.1. Synthesis of stereochemically different cyclohexenones.

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).



*Scheme 3.2. Potential enone candidates **203** and **213** for the synthesis of syn cyclohexenones of the type **212**.*

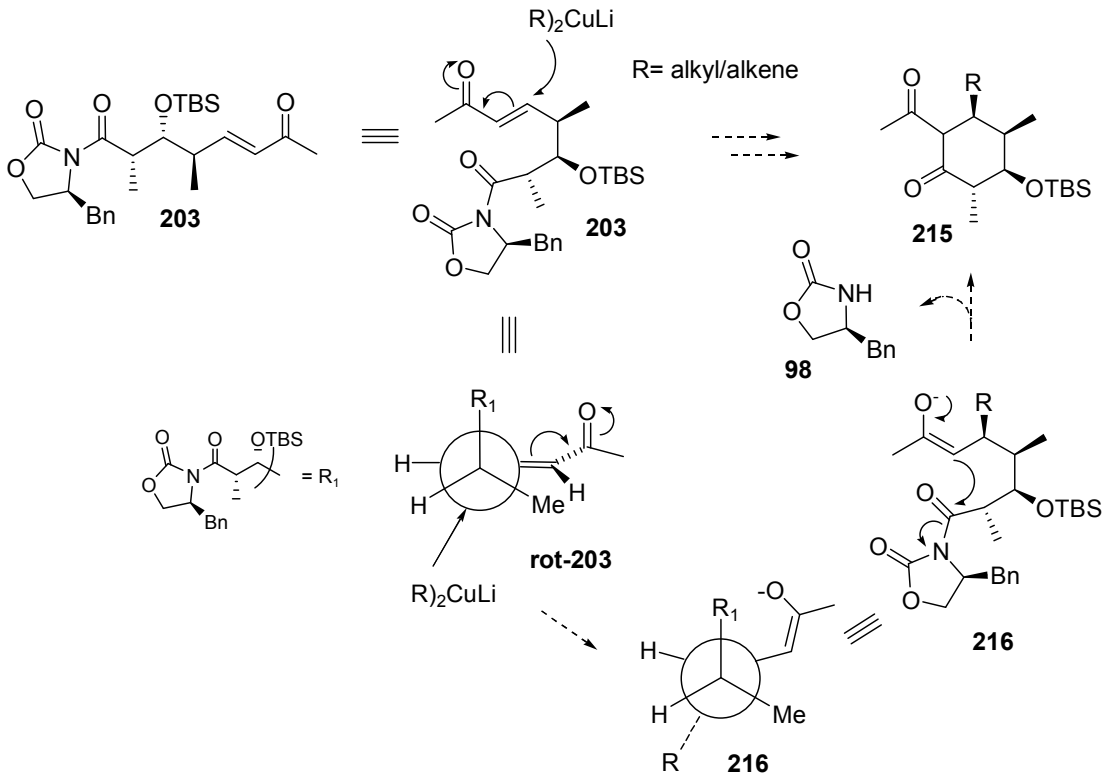
Enones **203** and **213** depicted in Scheme 3.2 were chosen based on their relative simplicity and proposed ability to direct the cuprate addition (the stereochemical rationale for this will be discussed in the following section). This would produce cyclohexanones (such as **214**) with the opposite 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).[1]

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

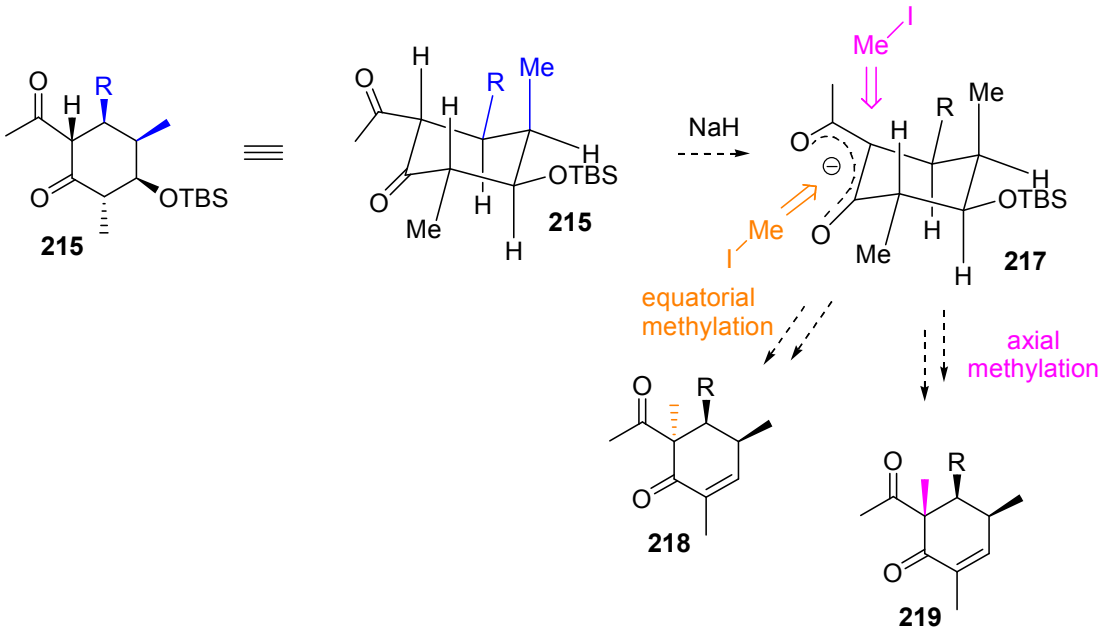
3.2.1 Stereochemical rationale for the outcome of the cuprate addition to *trans* enone 203

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.[2]



*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).

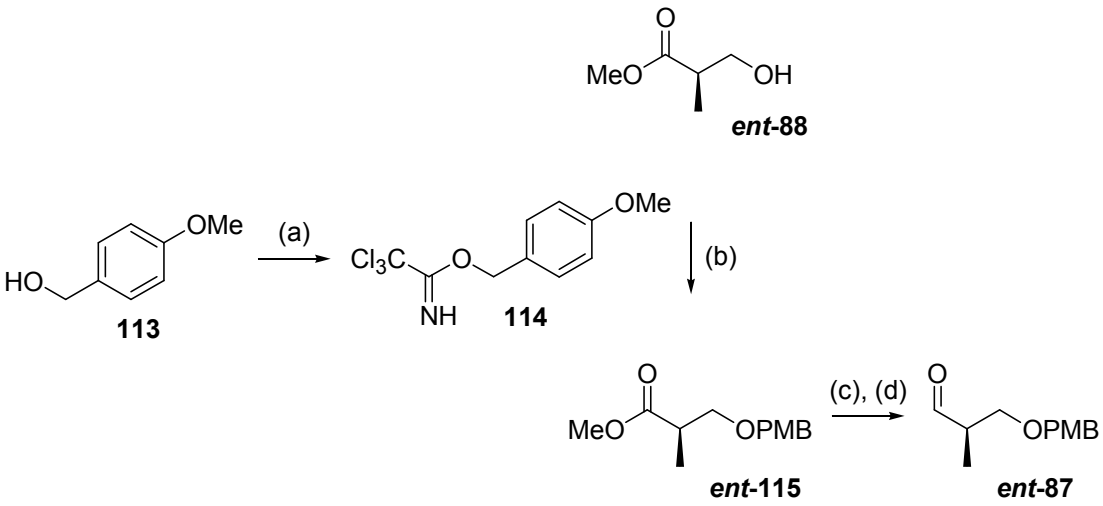


*Scheme 3.4. Methylation of the favoured chair conformation of **215**.*

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*-butyldimethylsilyl (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).[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**.

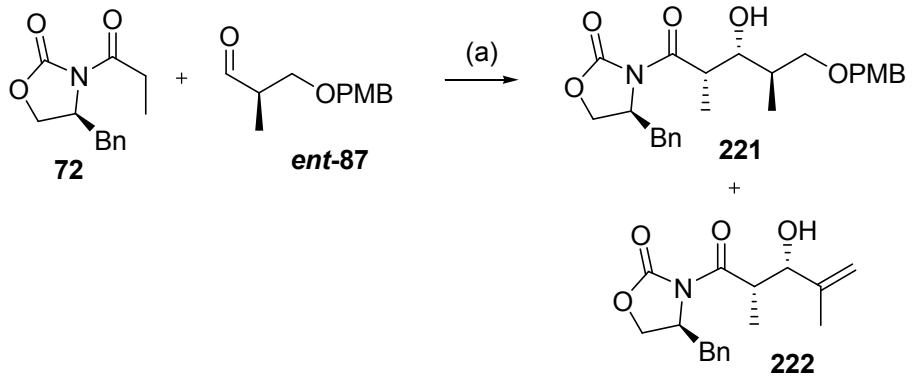


Reagents and conditions. (a) i. NaH, Et_2O, 0 °C. ii. $Cl_3CC{\equiv}N$, 0 °C → RT, 100%; (b) **114**, CF_3SO_3H (0.3 mol %), Et_2O, RT, 75%; (c) $LiAlH_4$, THF, 0 °C, 100%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C → 0 °C, 92%.

*Scheme 3.5. Synthesis of aldehyde **ent-87** from commercially available ester **ent-88**.*

The first step involved protecting the primary alcohol functionality of Roche ester ***ent*-88** (Scheme 3.5) using *p*-methoxybenzyl (PMB) imidate **114**[3,4] to give ester ***ent*-115**, which was reduced using $LiAlH_4$.[5] Subsequent oxidation of the corresponding alcohol using Swern conditions[6,7] 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).[8]

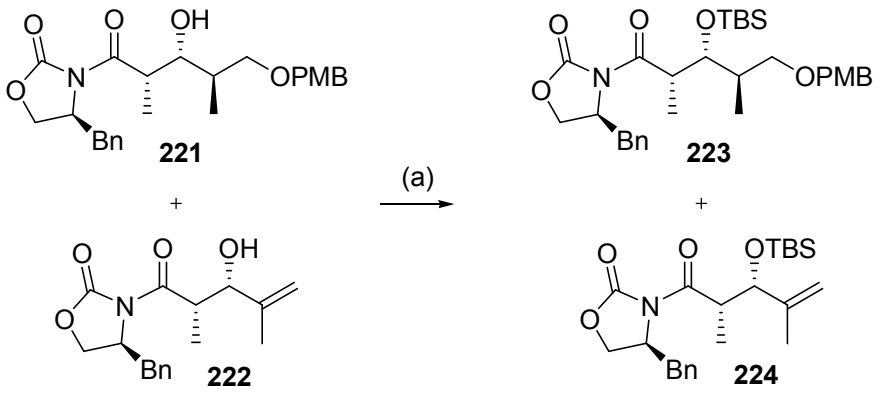


Reagents and conditions. (a) i. **72**, Bu_2BOTf, Et_3N, CH_2Cl_2, 0 ^oC. ii. ***ent*-87**, – 78 $^oC \rightarrow$ 0 ^oC, 57% as inseparable mixture of **221** and **222**.

*Scheme 3.6. Synthesis of aldol adduct **221**.*

A small amount of alkene **222** was also identified in the ^1H Nuclear Magnetic Resonance (NMR) spectrum of *syn* aldol product **221** (Scheme 3.6), and possessed identical ^1H NMR spectral data to that reported in the literature.[9] 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_3N in the aldol reaction, which may have caused the elimination of the OPMB group of aldol product **221**.

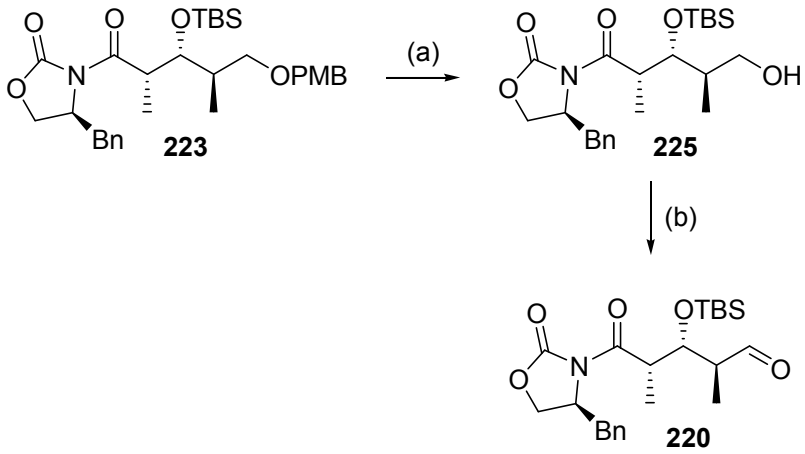
The subsequent protection[10] of the mixture containing *syn* aldol product **221** and alkene **222** to give TBS ether **223** proceeded in good yield, with alkene **222** also undergoing protection to give **224** (Scheme 3.7).



Reagents and conditions. (a) TBSOTf, 2,6-lutidine, CH_2Cl_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_2Cl_2, pH 7 buffer, 0 °C, 64%; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, – 78 °C → 0 °C, 100%.

*Scheme 3.8. Synthesis of aldehyde **220**.*

Swern oxidation[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).

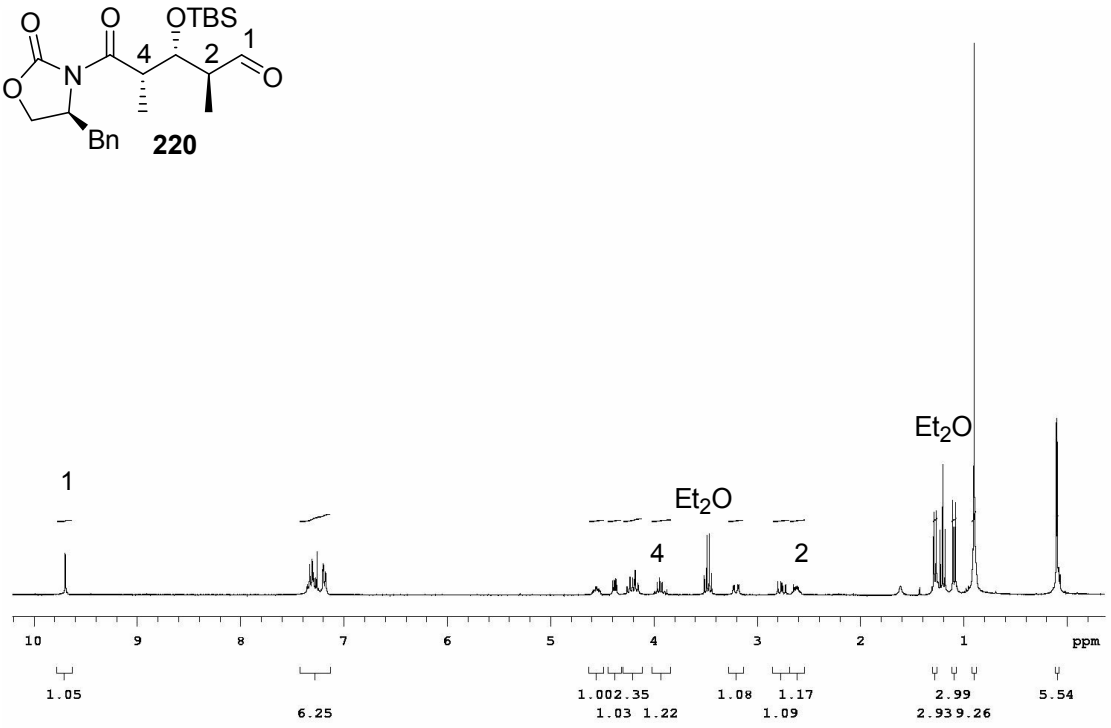
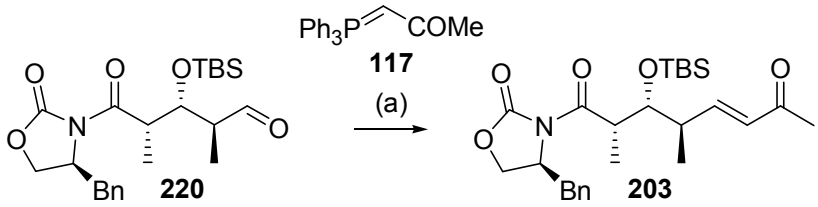


*Figure 3.2. ^{1}H NMR spectrum of aldehyde **220** in $CDCl_3$ at 300 MHz.*

The diagnostic aldehyde proton is present as a doublet at δ 9.70 and couples with the methine proton adjacent to the carbonyl, which appears as a multiplet at δ 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 δ 4.38) and the methyl protons (which appear as a doublet at δ 1.09). The methine proton on C4 appears as a multiplet at δ 3.87 – 3.99 and couples to the methyl protons, which appear as a doublet at δ 1.28. The auxiliary protons appear at δ 2.76, δ 3.21, δ 4.15 – 4.16, δ 4.52 – 4.60 and δ 7.18 – 7.35. While the differences between the spectra of aldehyde **220** and the diastereomeric aldehyde **90**[1] synthesised in Chapter 2 (Section 2.3.1) are not dramatic, some variation is evident. The aldehyde proton has moved slightly upfield from δ 9.80 in aldehyde **90**[1] to δ 9.70 in aldehyde **220**, and the methine proton on C2 has moved downfield from δ 2.44 – 2.52 to δ 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).



Reagents and conditions. (a) **117**, toluene, 60 ^{o}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}H NMR spectrum of *trans* enone **203** (Figure 3.3), where only one set of resonances is present for each proton.

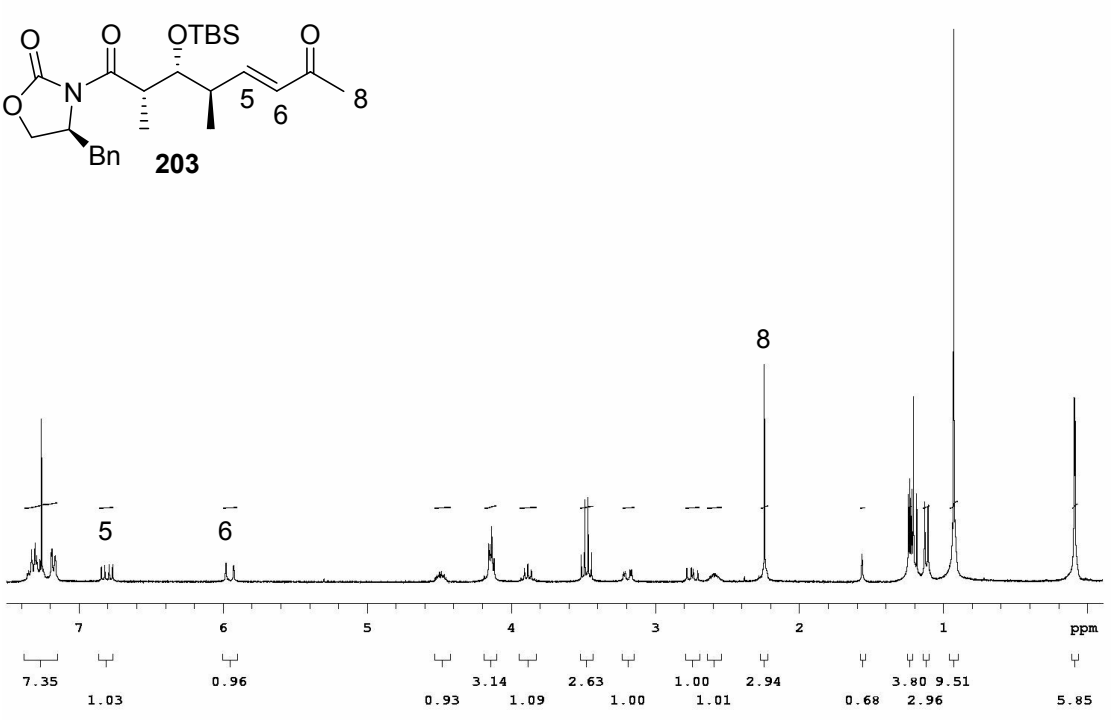


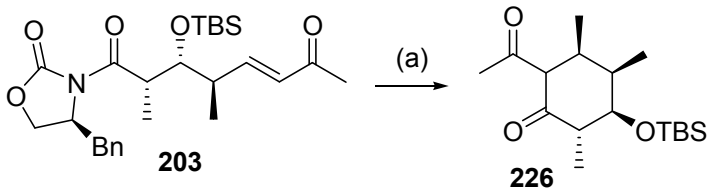
*Figure 3.3. ^{1}H NMR spectrum of trans enone **203** in $CDCl_3$ at 300 MHz.*

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),[1] displaying the requisite vinyl protons at δ 5.95 and δ 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 α,β-unsaturated carbonyl system. The ^{13}C NMR spectrum confirmed the success of the synthesis by the presence of a peak at δ 198.6, which can be attributed to the carbonyl of the enone group, as well as two peaks at δ 130.7 and δ 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).



Reagents and conditions. (a) CuI, MeLi, Me_2S, Et_2O, RT, 63%.

*Scheme 3.10. Synthesis of cyclohexanone **226**.*

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).

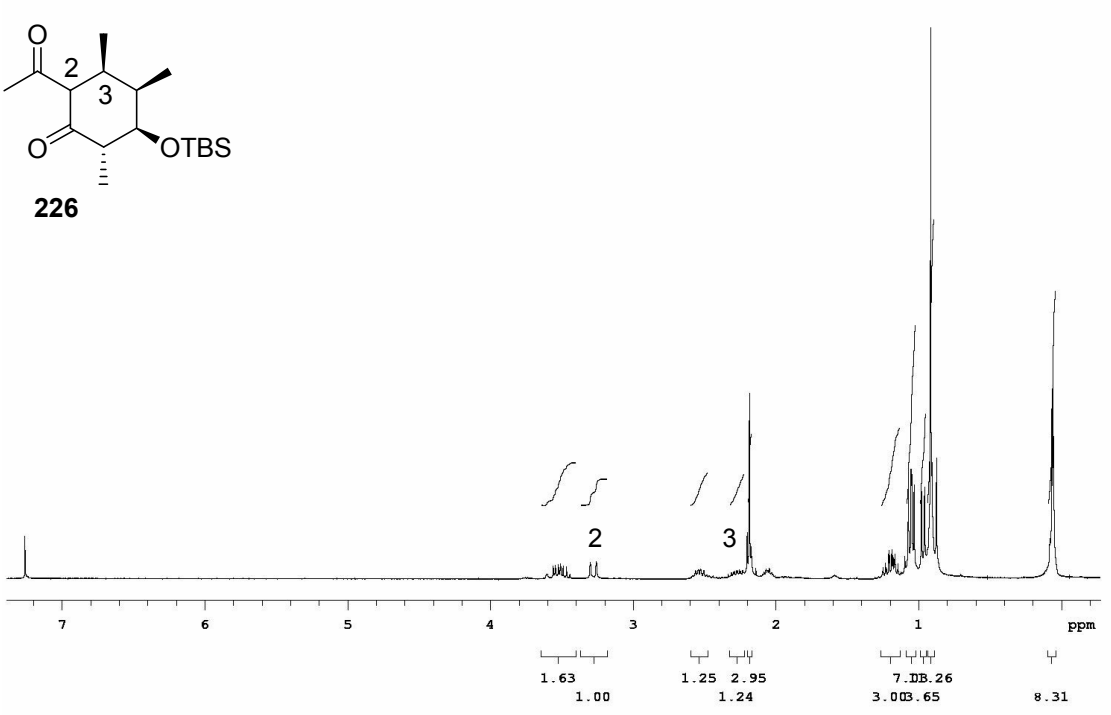


*Figure 3.4. ^{1}H NMR spectrum of cyclohexanone **226** in $CDCl_3$ at 300 MHz.*

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 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**.

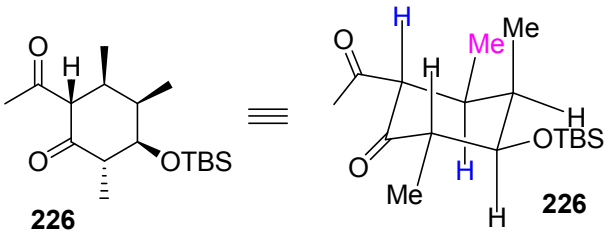
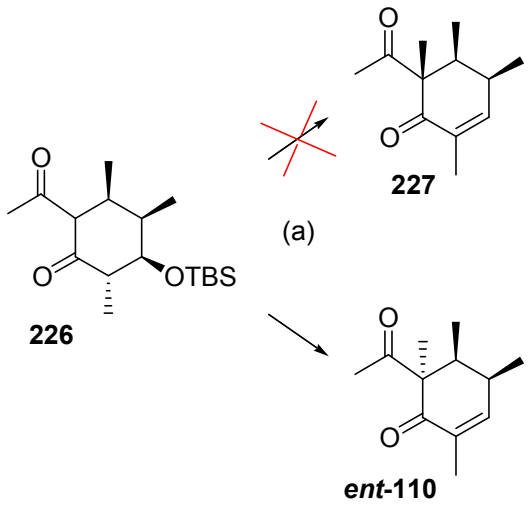


*Figure 3.5. The favoured chair conformation of **226**.*

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 δ 206.4 and δ 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).



Reagents and conditions. (a) NaH, MeI, THF, RT, 60%.

*Scheme 3.11. Methylation and elimination of cyclohexanone **226**.*

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 ***ent*-110** (Scheme 3.11). Immediately, the stereochemical outcome of the methylation was obvious, by comparison of the NMR data of cyclohexenone ***ent*-110** with the NMR data of the cyclohexenones synthesised in Chapter 2. This resulted in the observation that ***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 ***ent*-110** must be the enantiomer of **110**.

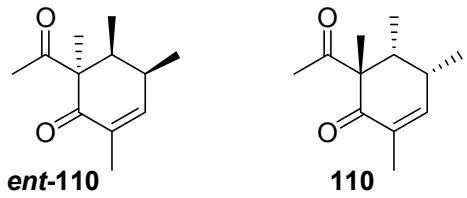


*Figure 3.6. The enantiomeric relationship between **ent-110** and **110**.*

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

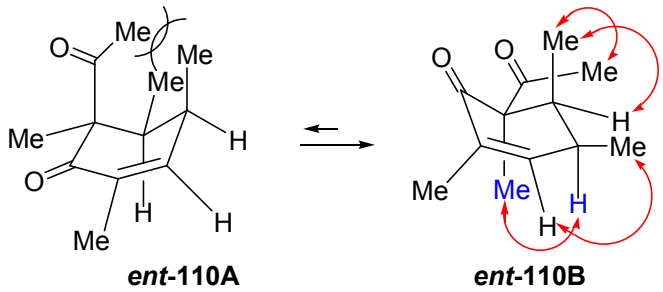
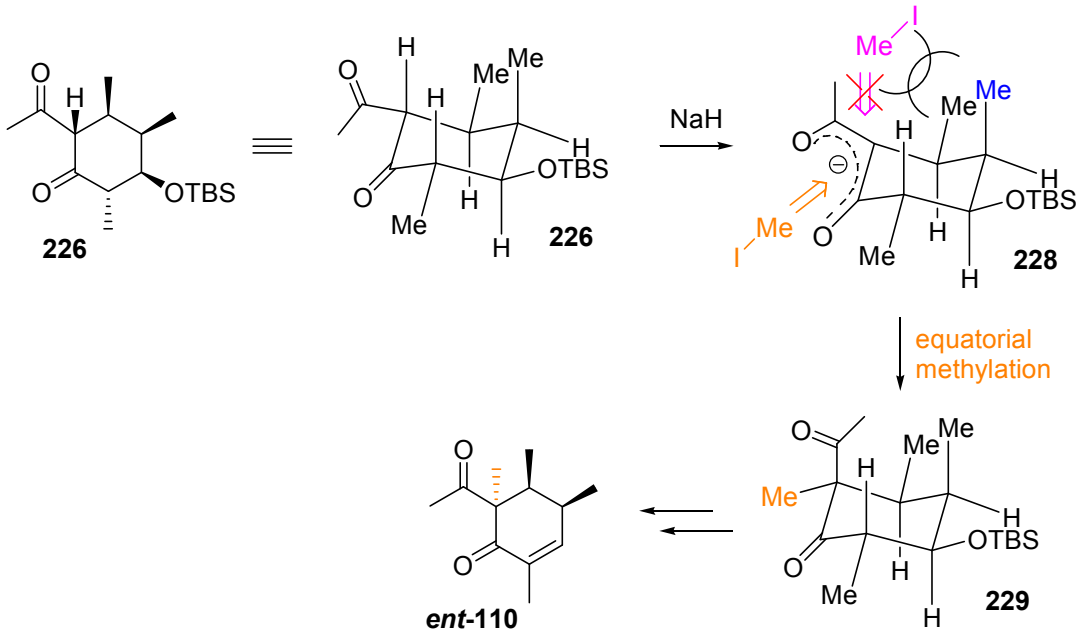


*Figure 3.7. NOESY correlations observed for cyclohexenone **ent-110** in $CDCl_3$ at 600 MHz.*

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 *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 ***ent*-110** exists in the conformation depicted in ***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 ***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 ***ent*-110**.



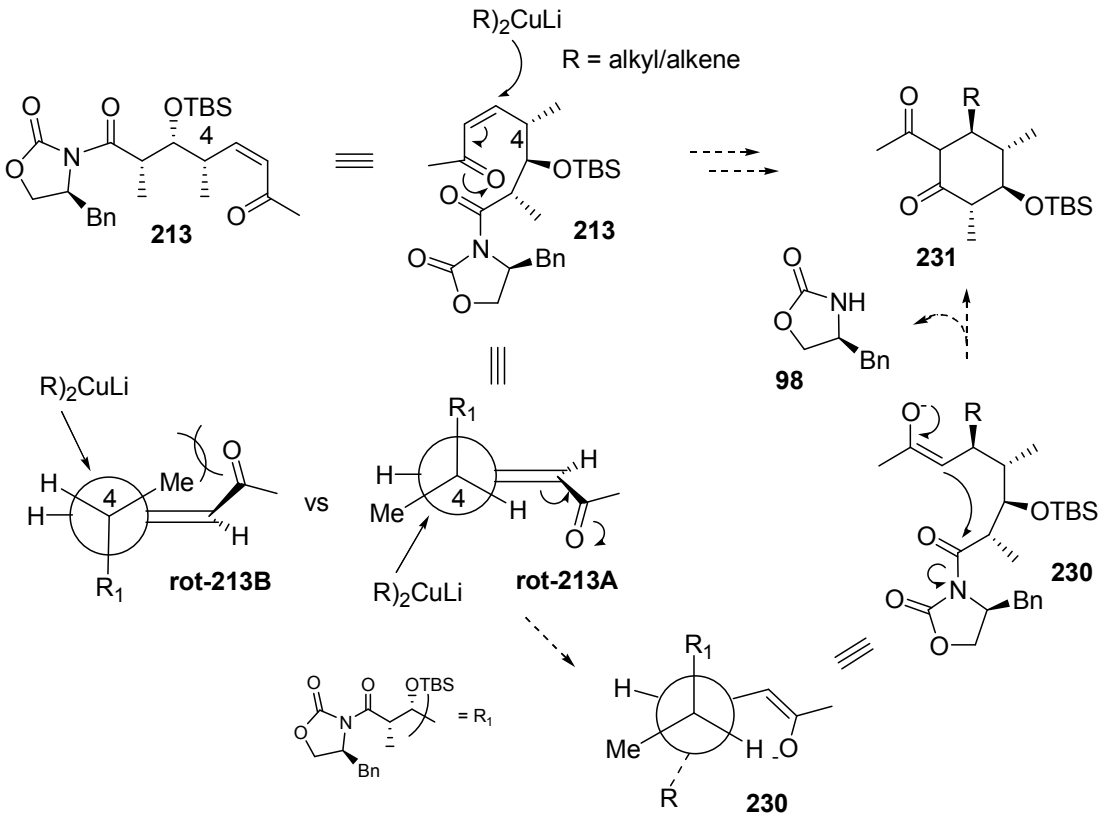
*Scheme 3.12. Steric hindrance in **226** leading to equatorial methylation and production of anti methylated cyclohexenone **ent-110**.*

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

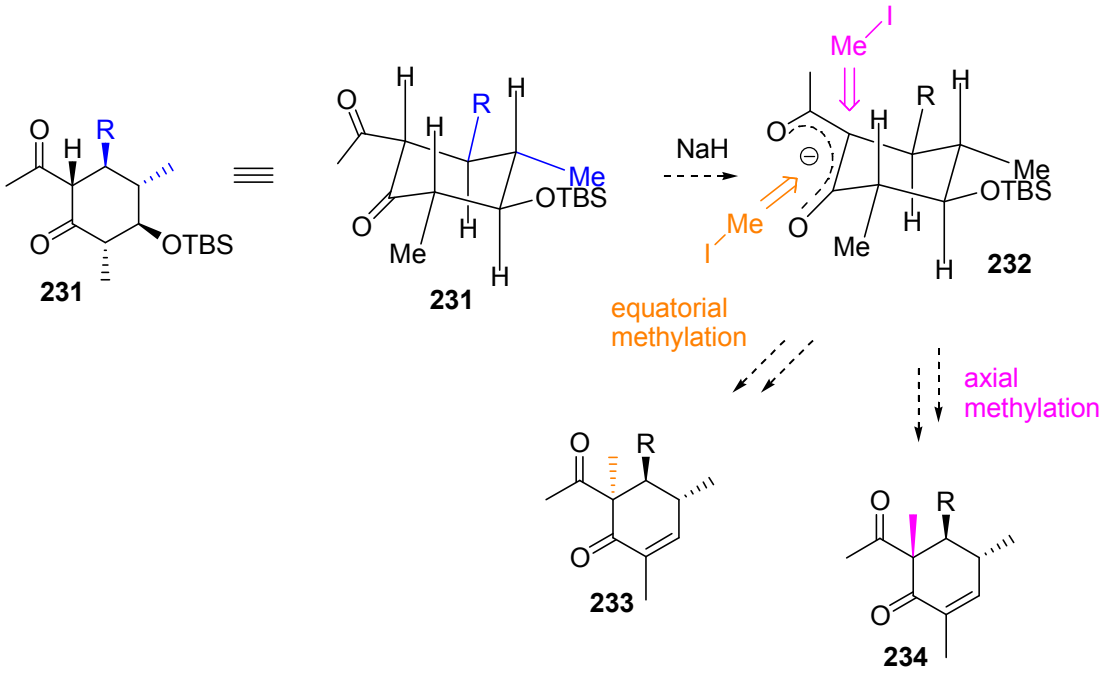
The deduction that *cis* enone **213** would be a useful candidate for achieving the desired outcome in the cuprate addition was based once again on the analysis of the approach of the nucleophile (Scheme 3.13).



*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 R_1, 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.



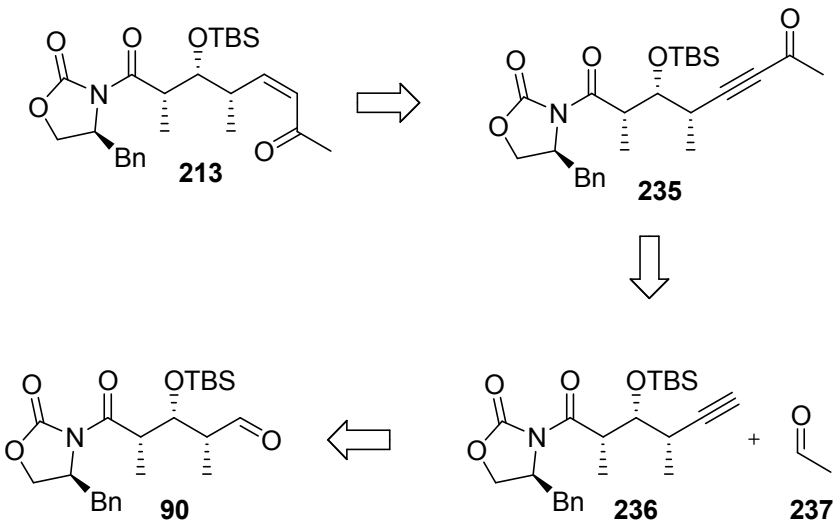
*Scheme 3.14. Methylation of the favoured chair conformation of **231**.*

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.

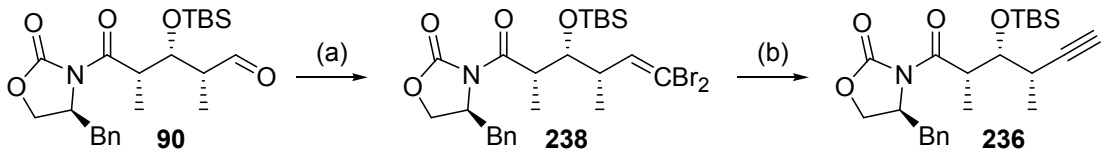


*Scheme 3.15. Retrosynthetic analysis of cis enone **213** to precursor aldehyde **90**.*

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).



Reagents and conditions. (a) PPh_3, CBr_4, CH_2Cl_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_2Cl_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**.

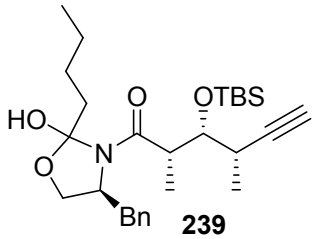


*Figure 3.8. Addition product **239** isolated from reaction of di-bromoalkene **238** with n-BuLi.*

The ^{1}H NMR spectra of alkyne **236** and addition product **239** are shown below (Figure 3.9 and Figure 3.10, respectively).

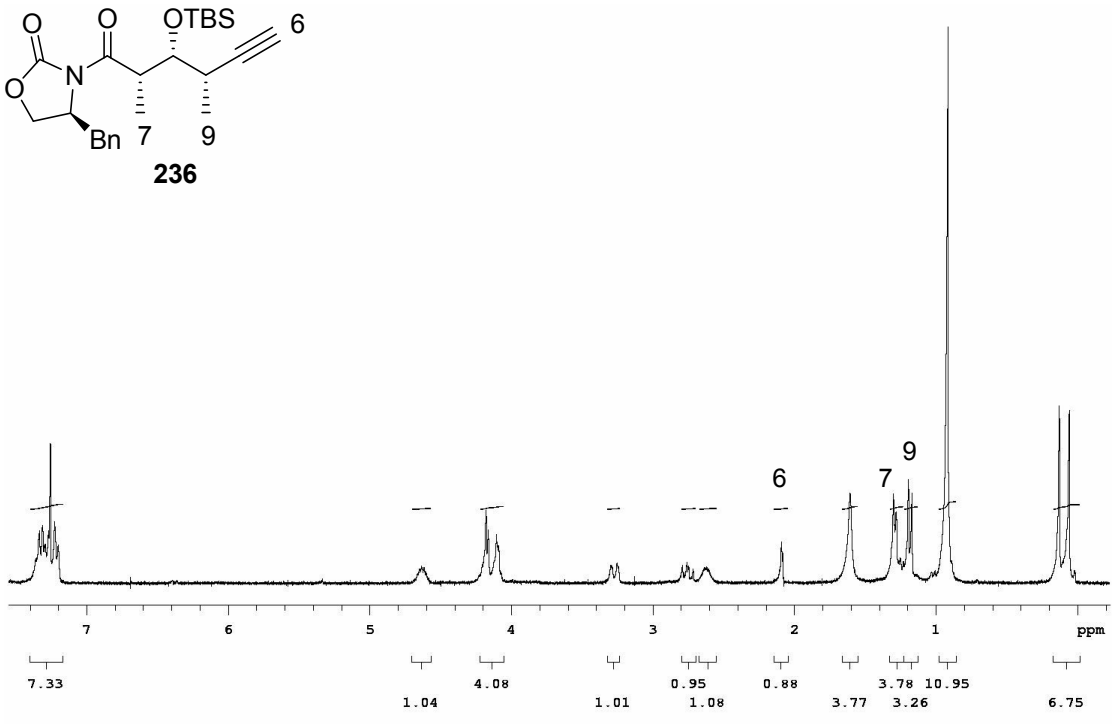


*Figure 3.9. ^{1}H NMR spectrum of alkyne **236** in $CDCl_3$ at 300 MHz.*

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 $C_{24}H_{35}NO_4Si$.

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.

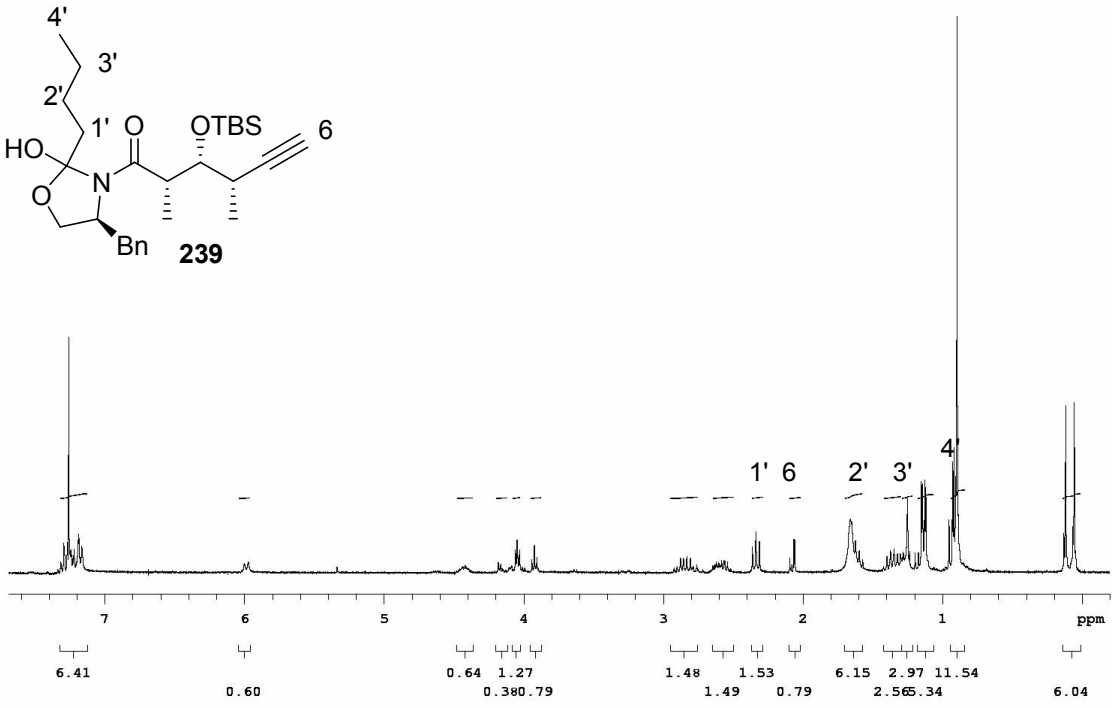


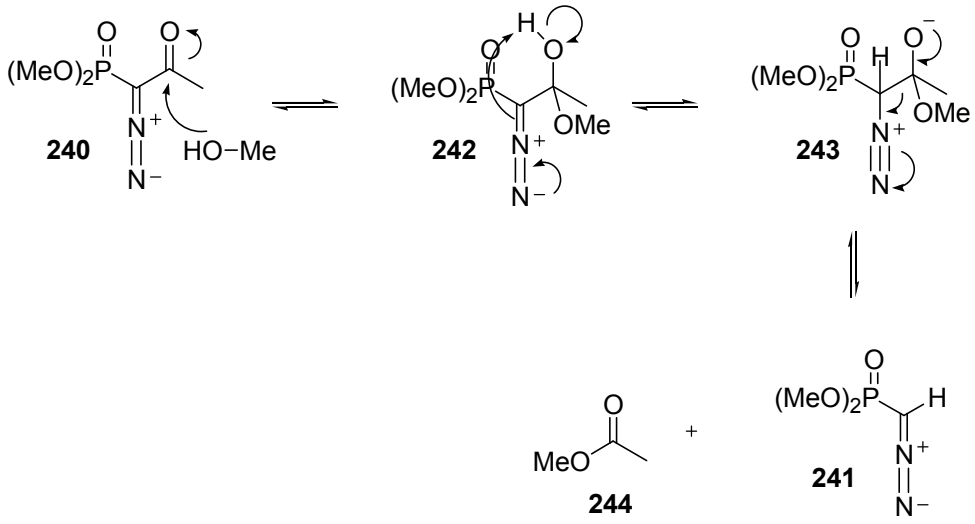
*Figure 3.10. ^{1}H NMR spectrum of addition product **239** in $CDCl_3$ at 300 MHz.*

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 δ 0.92 and couple to the adjacent methylene protons, which appear as a multiplet at δ 1.30 – 1.42. The remaining four *n*-Bu protons appear as a multiplet at δ 1.59 – 1.68 (along with the hydroxyl proton) and as a triplet at δ 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 δ 173.7. The oxazolidinone carbonyl usually appears at approximately δ 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 $C_{28}H_{45}NO_4Si$.

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

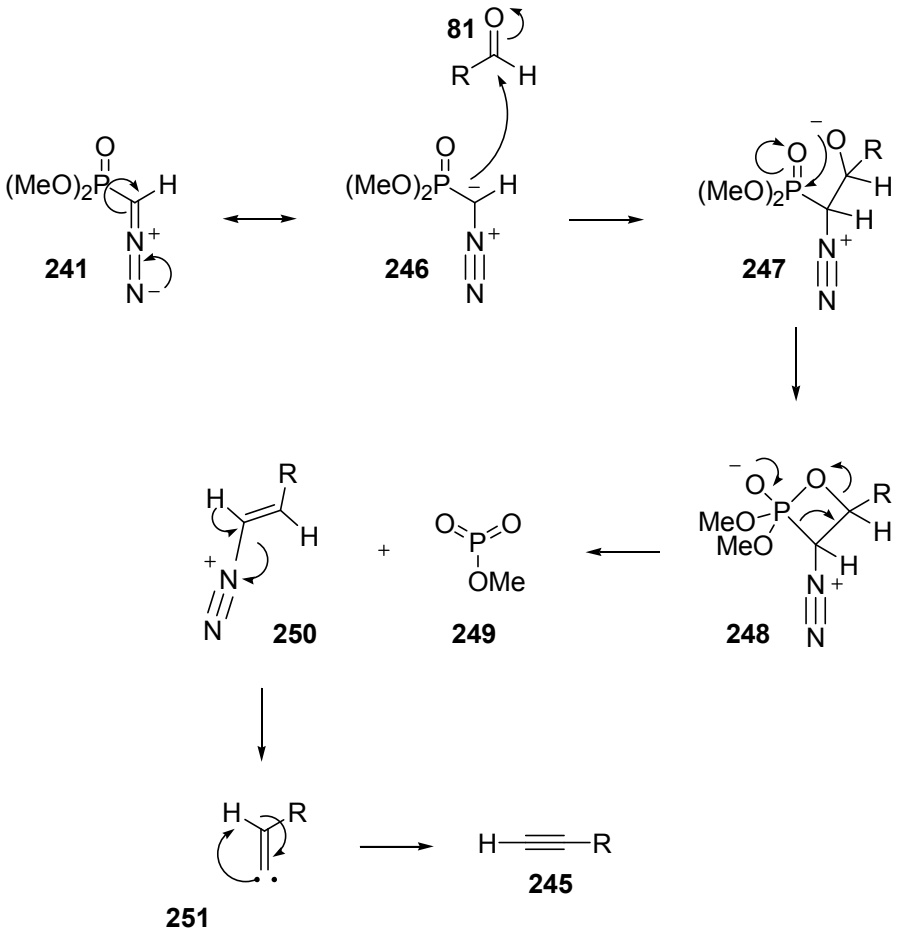
238 with *n*-BuLi at – 78 °C, followed by warming to room temperature.[13] By Thin Layer Chromatography (TLC) analysis, the reaction mixture did not appear to change when the temperature was increased from – 78 °C to room temperature and thus it appeared that the lower temperature was not the problem. 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 α-diazo-β-ketophosphonate **240** (Scheme 3.17), which would allow the synthesis of alkyne **236** to be achieved directly from aldehyde **90**.[15] This reaction proceeds *via* an Horner-Wadworth-Emmons (HWE)-type mechanism, where initially the reactive species (dimethyldiazomethylphosphonate **241**) is generated *in situ* from methanolysis of α-diazo-β-ketophosphonate **240** (Scheme 3.17).[16]



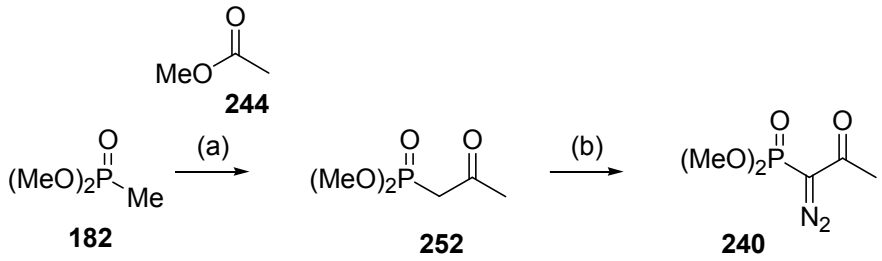
*Scheme 3.17. Proposed mechanism for the formation of dimethyldiazomethylphosphonate **241**.*

Intermediate **241** then reacts with an aldehyde (**81**) to give alkyne **245** (Scheme 3.18).[16]



*Scheme 3.18. Proposed mechanism of alkyne **245** formation.*

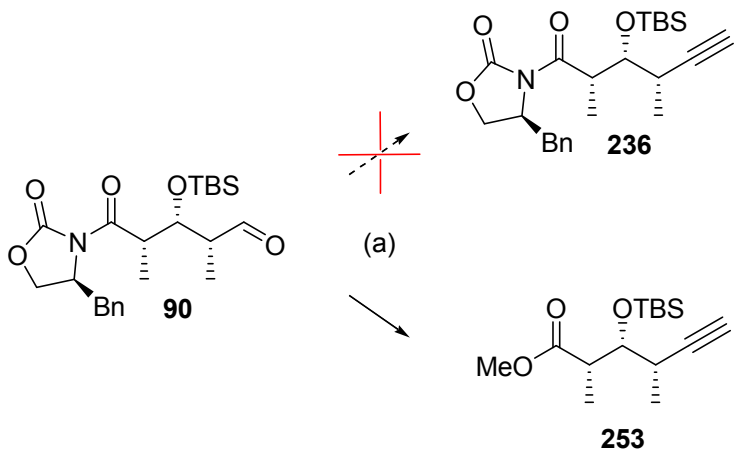
The synthesis of α-diazo-β-ketophosphonate **240** began with the synthesis of 2-oxopropanephosphonate (**252**), which was formed from treatment of dimethyl methyl phosphonate (**182**) with *n*-BuLi to generate the lithiated anion, followed by addition of methyl acetate (**244**) (Scheme 3.19).[17]



Reagents and conditions. (a) i. *n*-BuLi, THF, – 78 °C. ii. **243**, – 78 °C → 0 °C, 48%; (b) i. NaH, THF, C_6H_6, 0 °C. ii. *p*-TsN_3, 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*-TsN_3 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).



Reagents and conditions. (a) **240**, K_2CO_3, 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**.*

The first attempt involved adding phosphonate **240** to a solution of aldehyde **90** and K_2CO_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_2CO_3.[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**.

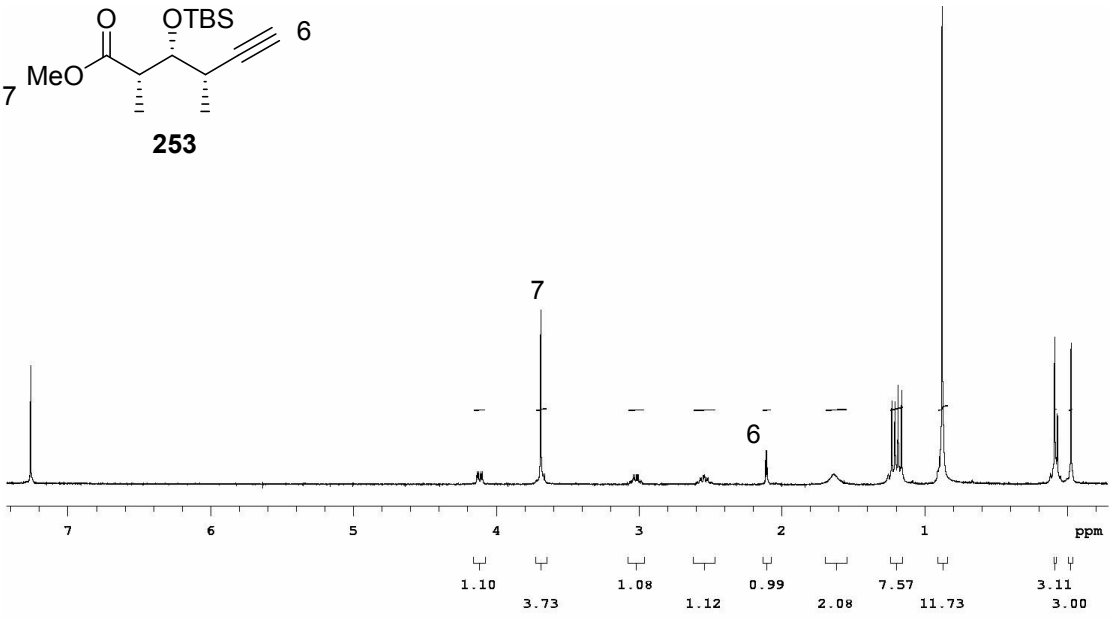


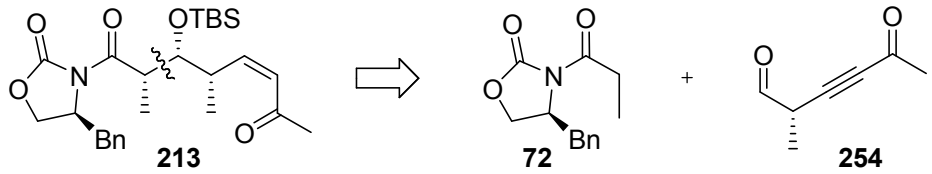
*Figure 3.11. ^{1}H NMR spectrum of ester **253** in $CDCl_3$ at 300 MHz.*

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 $C_{15}H_{28}O_3Si$.

The formation of methyl ester **253** led to the theory that perhaps the active species (dimethyldiazomethylphosphonate (**241**)) was not forming in adequate amounts prior

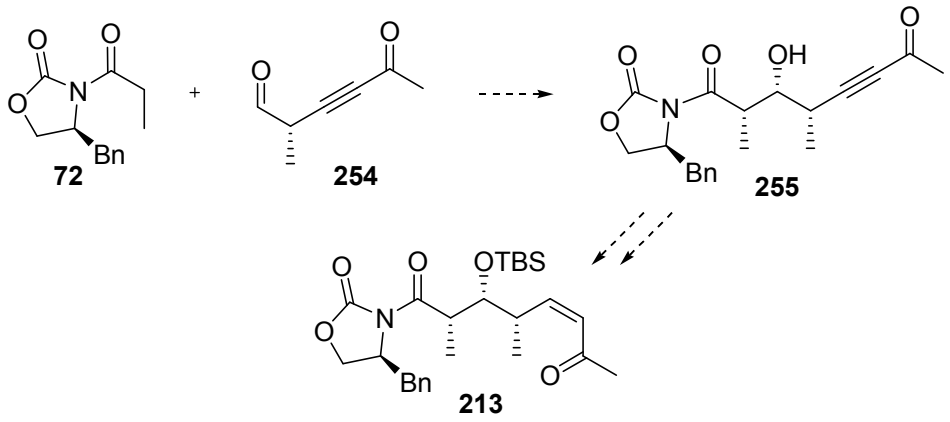
to addition of aldehyde **90**. To this end, the final attempt at this reaction involved adding K_2CO_3 to a solution of phosphonate **240** in MeOH, so as to allow the reactive species **241** to form, followed by addition of aldehyde **90**. However, this procedure also did not produce any desired 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**.*

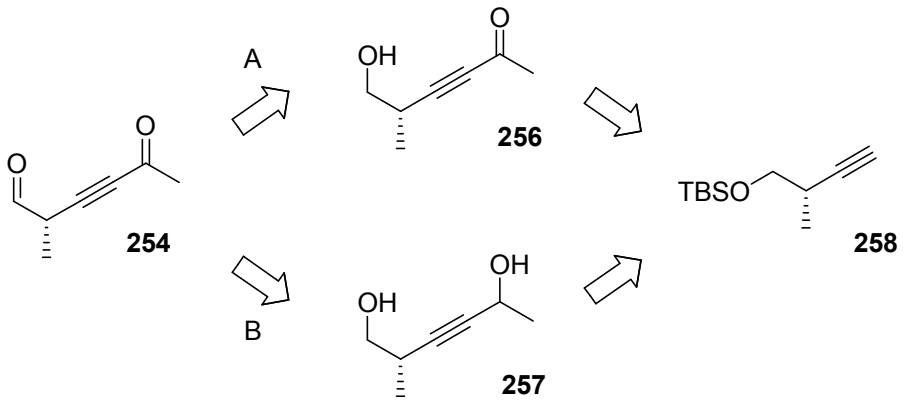
This approach required the preparation of keto-aldehyde **254**, which upon reaction with Evans auxiliary **72** would produce *syn* aldol product **255** (Scheme 3.22). The generated secondary alcohol could then be protected and following reduction using hydrogenation conditions, *cis* enone **213**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



*Scheme 3.22. Proposed synthesis of cis enone **213** from alkyne **254**.*

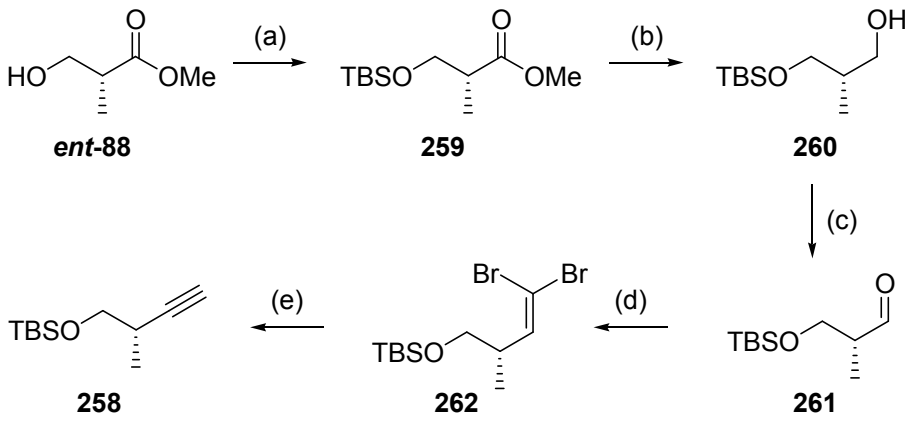
3.3.2 Attempted synthesis of *cis* enone 213 from keto-aldehyde 254

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**



*Scheme 3.23. Two potential avenues for the synthesis of **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**.



Reagents and conditions. (a) TBSCl, imidazole, CH_2Cl_2 0 °C → RT, 98%; (b) DIBAL, CH_2Cl_2, – 78 °C → RT, 82%; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, – 78 °C → 0 °C, 89%; (d) PPh_3, CBr_4, 0 °C → RT, 81%; (e) *n*-BuLi, THF, – 50 °C → – 40 °C → RT, 78%.

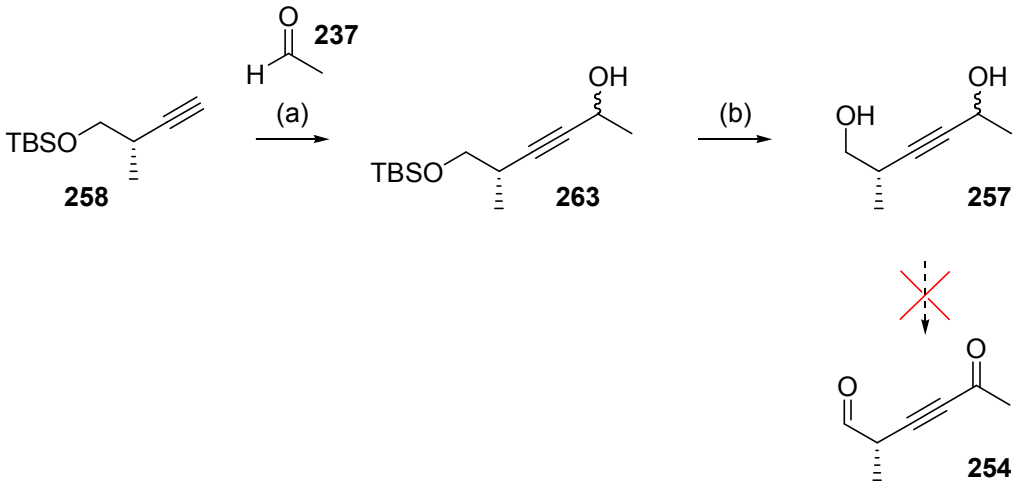
*Scheme 3.24. Synthesis of alkyne **258**.*

The protection of Roche ester ***ent*-88** (Scheme 3.24) using TBSCl and imidazole[19] proceeded in excellent yield to give **259**, which was then readily reduced to alcohol **260** with the aid of diisobutylaluminium hydride (DIBAL).[19] The subsequent oxidation of **266** under Swern conditions[20,7] 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 PPh_3 and CBr_4[13] gave di-bromoalkene **262**, which after isolation and purification was treated with *n*-BuLi[14] 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**.[20] 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).

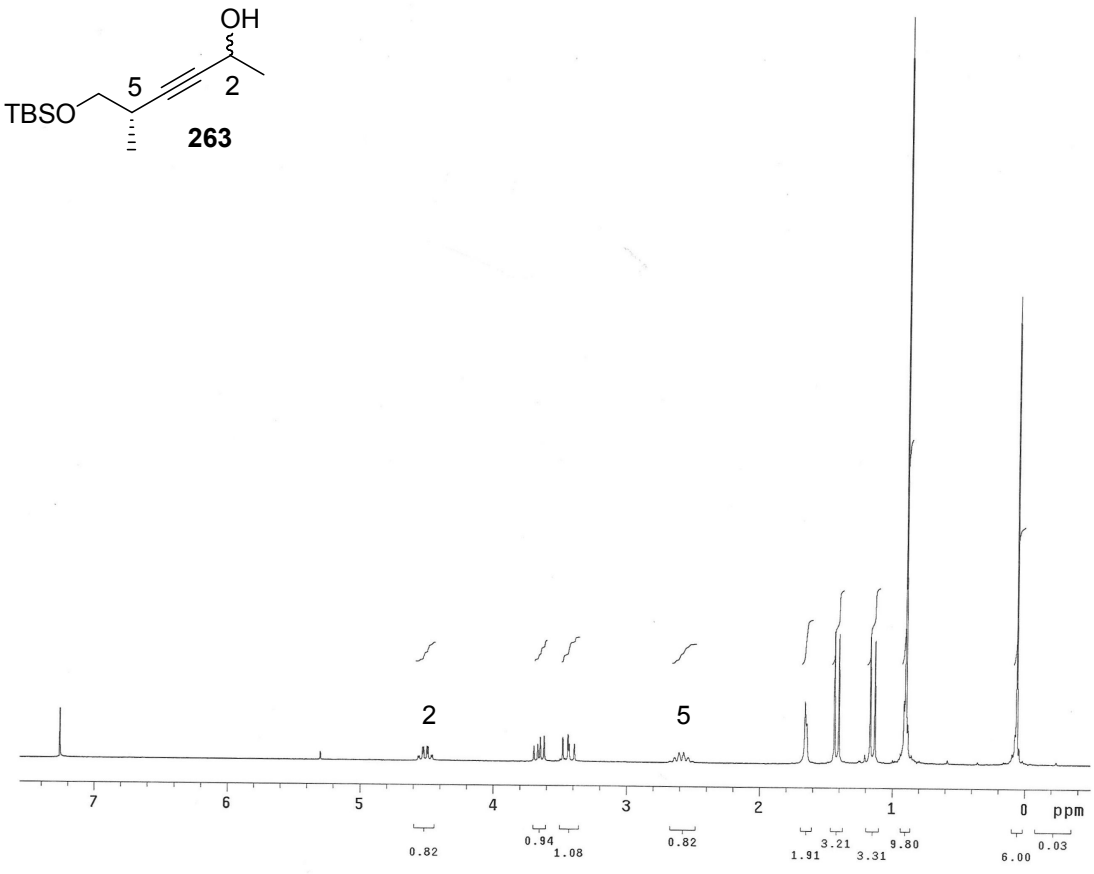
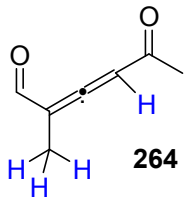


*Figure 3.12. ^{1}H NMR spectrum of propargylic alcohol **263** in $CDCl_3$ at 300 MHz.*

The oxymethine proton is present furthest downfield at approximately δ 4.51 (Figure 3.12) and appears as two overlapping quartets (at δ 4.51 and δ 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 δ 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 δ 2.51 – 2.68 for both isomers and couples to both the methyl protons, which appear as a doublet at δ 1.15, and the adjacent methylene protons, both of which appear as a doublet of doublets at δ 3.43 and δ 3.66. The protons of the TBS group appear furthest upfield, at δ 0.06 and δ 0.90, while the hydroxyl proton appears as a broad singlet at δ 1.66. The ^{13}C NMR spectrum further corroborated the structural assignment with the presence of two alkyne carbons at δ 73.1 and δ 86.6, and the presence of the carbon

bearing the hydroxyl group, which appeared at δ 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 $C_{13}H_{26}O_2Si$.

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).



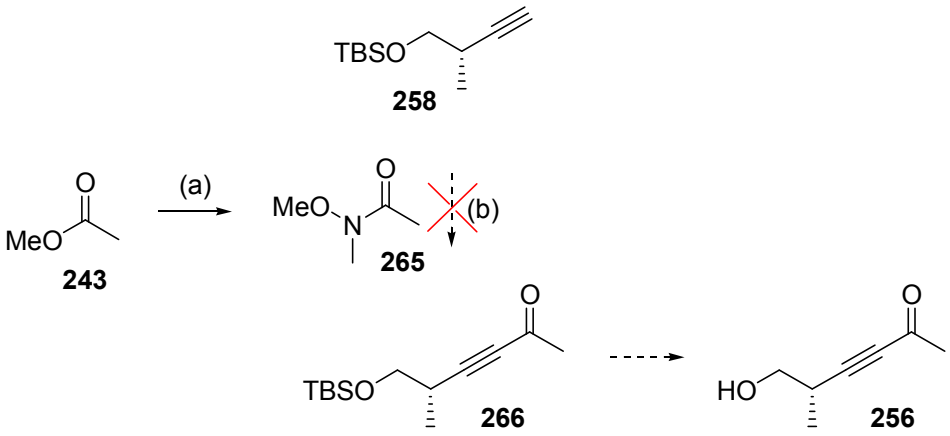
264

*Figure 3.13. Allene **264** formed in the reaction of diol **257** with DMP-H_2O.*

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/Et_2O, – 20 °C → 0 °C, 40%; (b) i. *n*-BuLi, THF, – 40 °C. ii. **265**, – 78 °C → – 20 °C → RT.

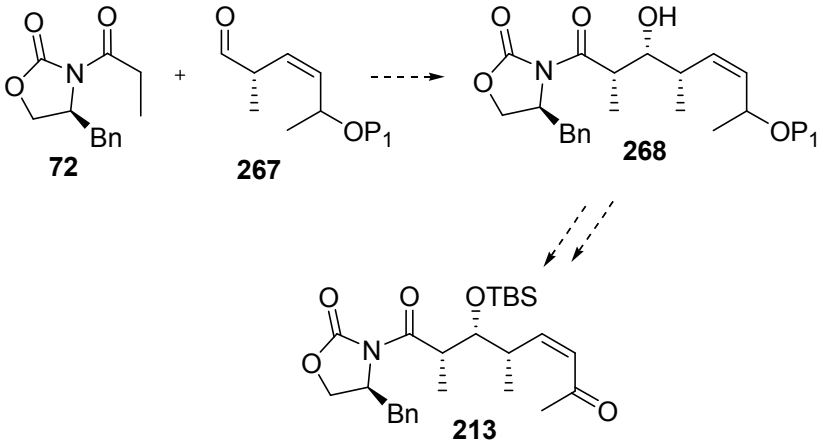
*Scheme 3.26. Attempted formation of alcohol **256**.*

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.

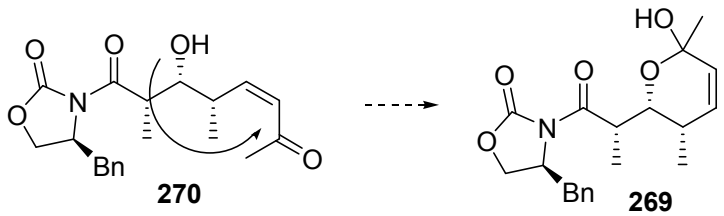
3.3.3 A new intermediate in the synthesis of *cis* enone 213

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.



*Scheme 3.27. Proposed synthesis of cis enone **213** from aldehyde **267**.*

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).

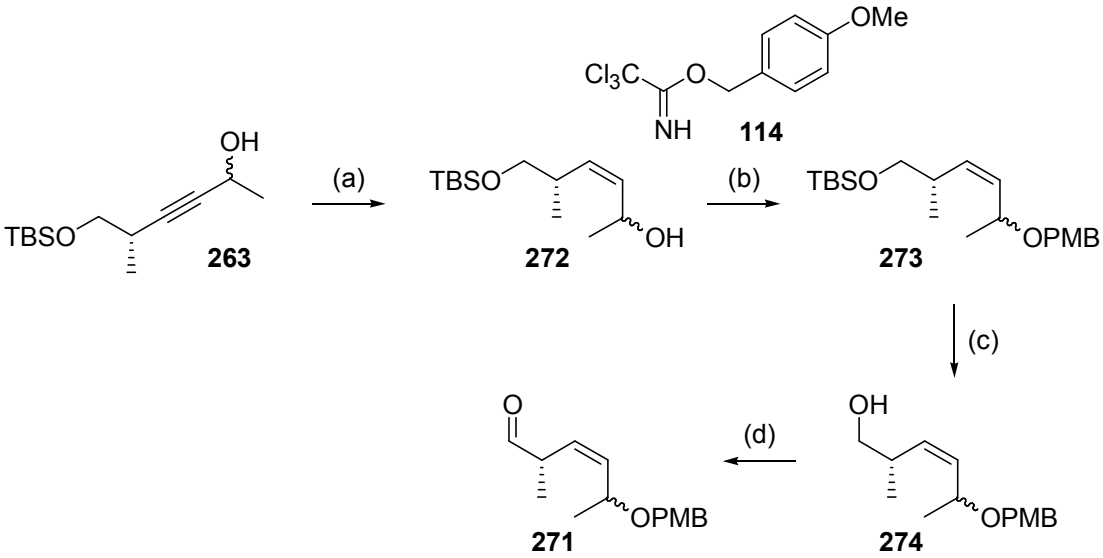


*Scheme 3.28. Hemiacetal **269** formation as a result of cyclisation of **270**.*

Thus, a synthetic approach involving the differential protection of the two hydroxyl groups was required.

3.3.3.1 Synthesis of a cis-aldehyde

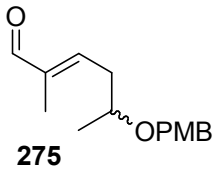
To this end, the synthesis of a *cis* aldehyde (**271**) was carried out as depicted in Scheme 3.29 and began with propargylic alcohol **263**.



Reagents and conditions. (a) Lindlar's catalyst, quinoline, H_2, hexanes, RT, 100%; (b) **114**, CF_3SO_3H (0.3 mol %), Et_2O, RT, 71%; (c) TBAF, THF, RT, 88%; (d) DMP, CH_2Cl_2, 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.[25] This inhibited the over-reduction, producing alkene **272** in excellent yield. Secondary alcohol **272** was protected with PMB imidate **114**[3] to give PMB ether **273**, and the TBS group was cleaved using TBAF[21] to give **274**. Alcohol **274** was oxidised using DMP[22] to give aldehyde **271** as two inseparable isomers in good yield and high purity, following purification by flash column chromatography. DMP[22] was the oxidising agent of choice in this conversion, as Swern[6,7] conditions were found to give a low yield of **271** and produced conjugated aldehyde **275** (Figure 3.14).



275

*Figure 3.14. Aldehyde **275** formed in Swern oxidation of alcohol **274**.*

The ^{1}H NMR spectrum of desired aldehyde **271** (Figure 3.15) indicates the presence of the requisite protons.

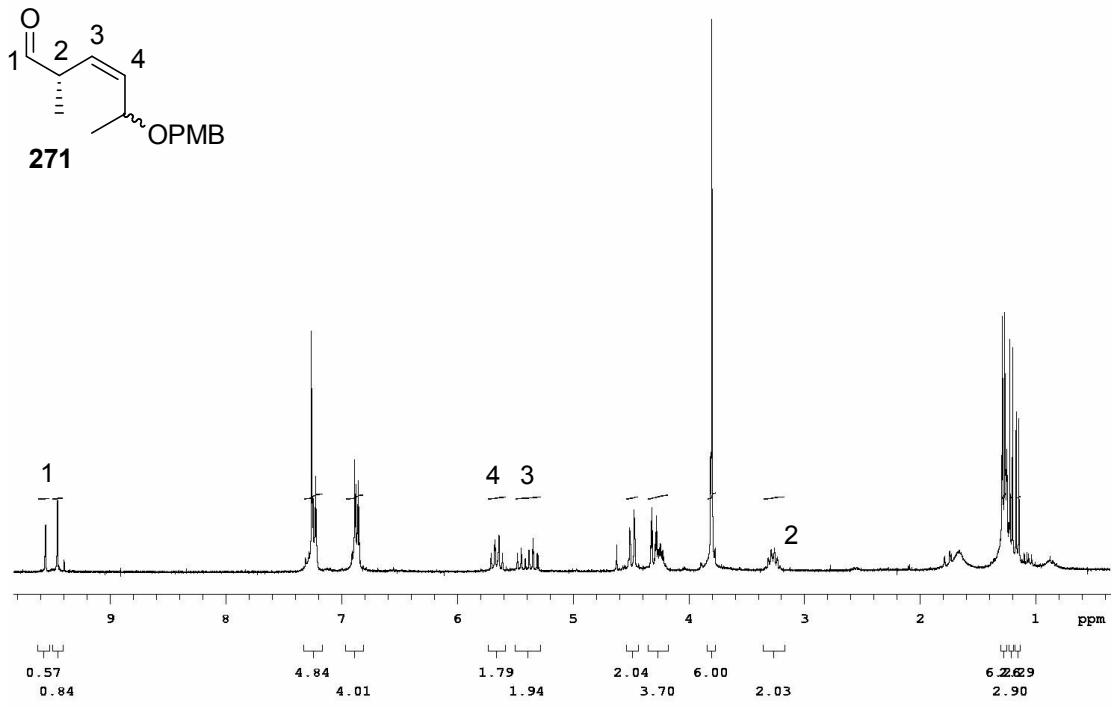


*Figure 3.15. ^{1}H NMR spectrum of aldehyde **271** in $CDCl_3$ at 300 MHz.*

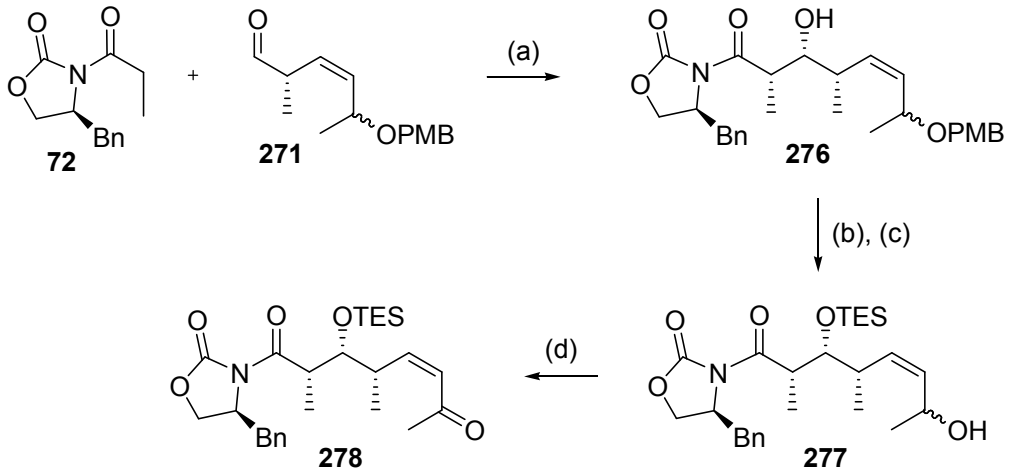
The diagnostic aldehyde proton for the two isomers appears as a doublet at δ 9.56 and δ 9.46 (Figure 3.15). The alkenyl proton on C3 appears as an apparent triplet at δ 5.45 for one isomer and at δ 5.35 for the other isomer, while the other alkenyl proton appears as an apparent quartet at δ 5.66 for 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 ^1H NMR spectrum.



Reagents and conditions. (a) i. **72**, Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C. ii. **271**, – 78 °C → 0 °C, 68%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, – 78 °C, 100%; (c) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 100%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, – 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 DDQ[11] resulted in the liberation of the other secondary hydroxyl group to give alcohol **277** in high yield. Fortuitously, Swern oxidation[6,7] 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.

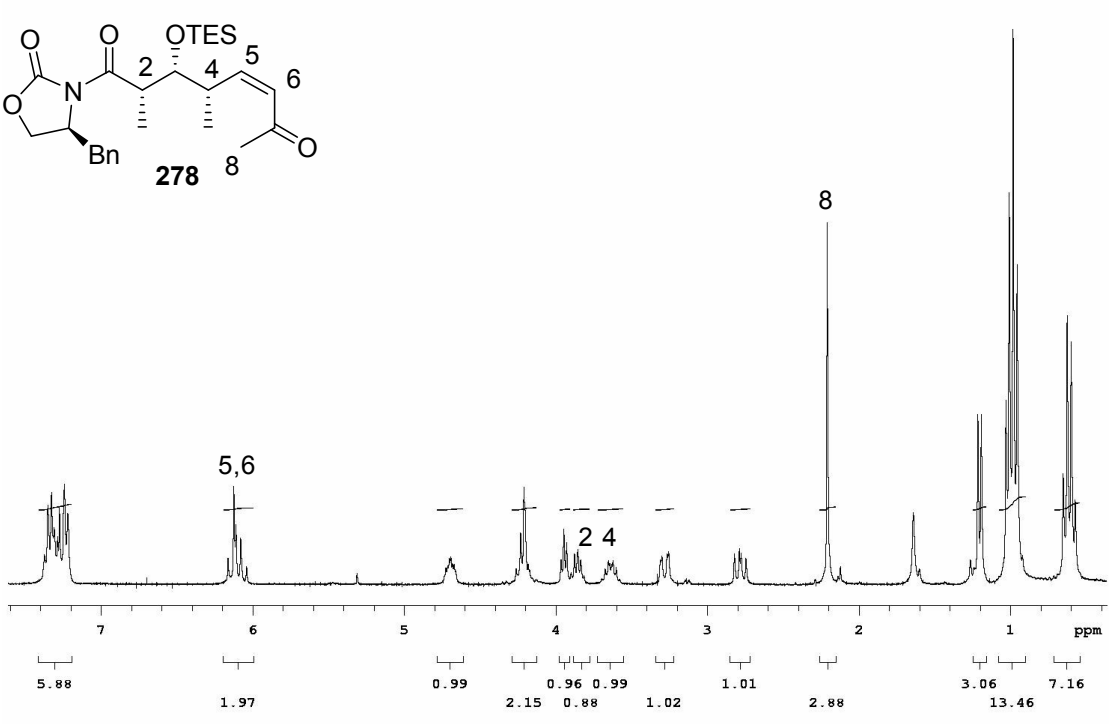


*Figure 3.16. ^{1}H NMR spectrum of cis enone **278** in $CDCl_3$ at 300 MHz.*

The alkenyl protons appear as a multiplet at δ 6.04 – 6.16, and the shift downfield of these protons (from around δ 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).[1]

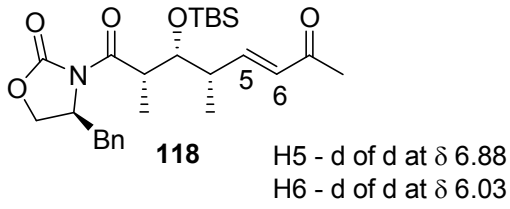


*Figure 3.17. Trans enone **118** displaying the ^{1}H NMR shifts and multiplicities of H5 and H6 in $CDCl_3$.*

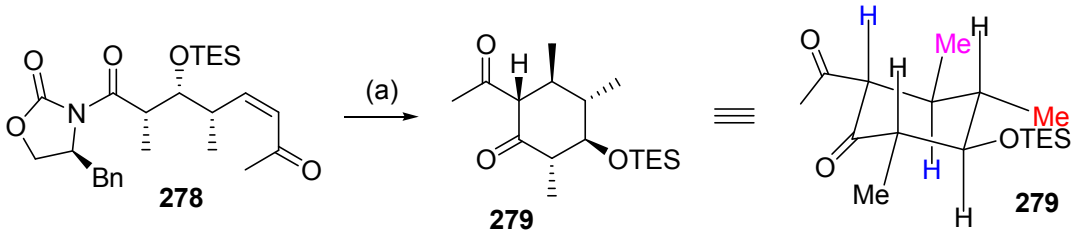
From Figure 3.16 and Figure 3.17, it can be seen that the vinyl protons of *cis* enone **278** appear upfield of the vinyl protons of *trans* enone **118**. As discussed in Chapter 2 (Section 2.3.1), the downfield position of the vinyl protons of *trans* enone **118** may be attributed to magnetic anisotropy, 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 $C_{26}H_{39}NO_5Si$.

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, Me_2S, Et_2O, 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 δ 3.23 and δ 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.

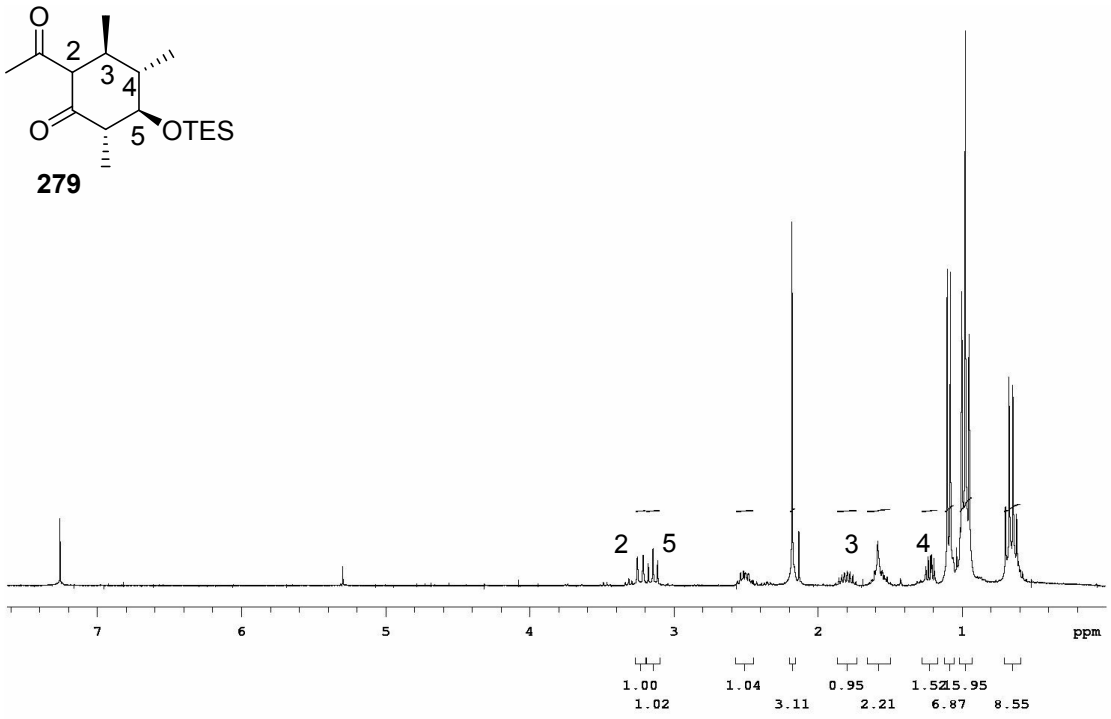
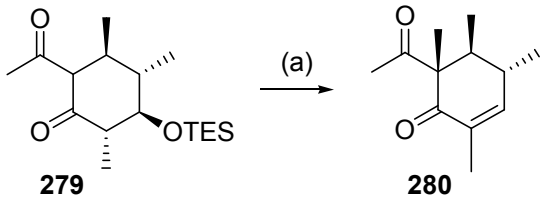


*Figure 3.18. ^{1}H NMR spectrum of cyclohexanone **279** in $CDCl_3$ at 300 MHz.*

The absence of the protons of the auxiliary and alkenyl groups is immediately evident, as is the presence of the doublet at δ 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 δ 1.74 – 1.88. This proton couples to the corresponding methyl protons, which appear as a doublet at δ 0.99. The methine proton adjacent to the endocyclic carbonyl appears as a multiplet at δ 2.57 and couples to both the corresponding methyl protons (which appear as a doublet at δ 1.09) and the adjacent oxymethine proton, which appears as an apparent triplet at δ 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 δ 2.18, while the methine proton on C4 appears as a multiplet at δ 1.50 – 1.63 and couples to the adjacent methyl protons, which appear as part of the doublet at δ 1.09. The presence of the TES group is evidenced by the quartet at δ 0.66 and the triplet at δ 0.98. The ^{13}C NMR spectrum

confirmed the success of the cuprate addition by the presence of two ketone carbons (at δ 206.4 and δ 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 $C_{17}H_{32}O_3Si$.

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

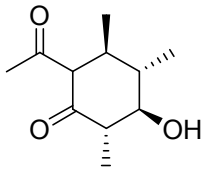


279 **280**

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.



281

*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 modified[26,27] 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 ^{o}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 ^{o}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 ^{1}H NMR spectrum of **280** in $CDCl_3$ (Figure 3.20).

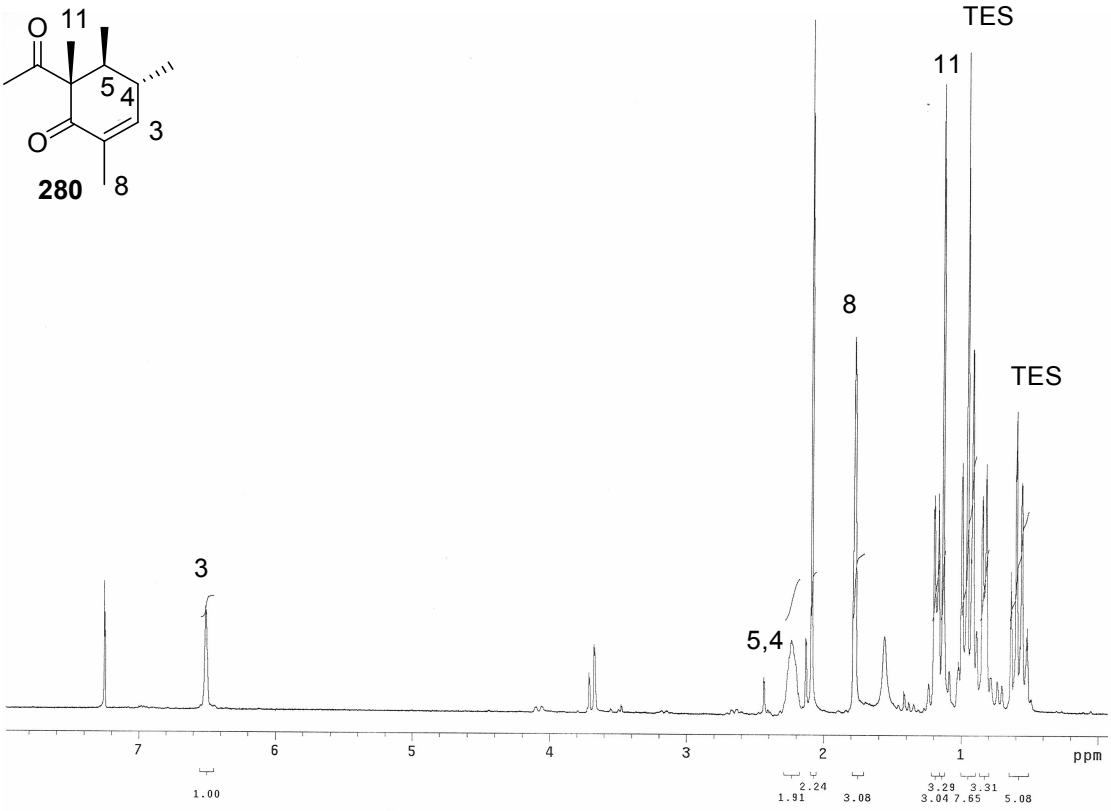


*Figure 3.20. ^{1}H NMR spectrum of syn cyclohexenone **280** in $CDCl_3$ at 200 MHz.*

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_6D_6. While the change in solvent did improve the separation of the peaks in the ^{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.

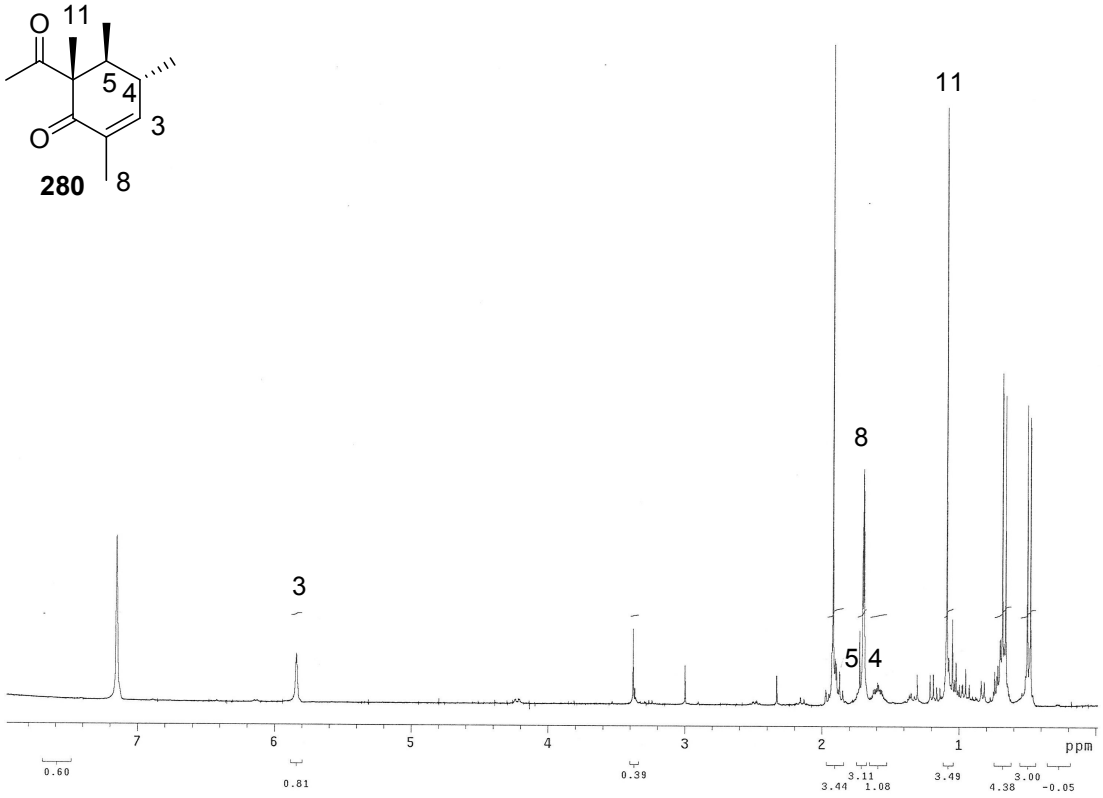
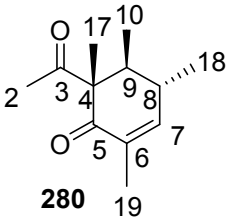


*Figure 3.21. ^{1}H NMR spectrum of cyclohexenone **280** in C_6D_6 at 300 MHz.*

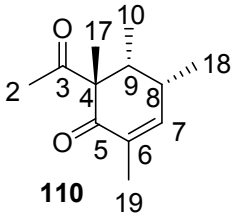
The presence of the diagnostic alkenyl proton (as a singlet at δ 5.84) and absence of the peaks of the TES group is a good indication of the success of the reaction, as is the presence of only two methyl doublets (at δ 0.49 and δ 0.67). The vinyl methyl appears as a multiplet at δ 1.69 – 1.70 and the appearance of the singlet at δ 1.09 can be attributed to the quaternary methyl. The ^{13}C NMR spectrum further corroborated the assignment, with the presence of two alkenyl carbons at δ 133.3 and δ 150.5, one enone carbon at δ 201.5 and the ketone carbon at δ 206.6. High resolution mass spectrometry confirmed the expected composition of $C_{12}H_{18}O_2$.

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.*



Position	*Syn* 280 δ ^{1}H	*Anti* 110 δ ^{1}H	Natural δ ^{1}H
2	2.10	2.24	
3	-	-	
4	-	-	
5	-	-	
6	-	-	
7	6.52	6.36	5.44
8	2.25	2.85	
9	2.25	2.17	3.91
10	0.85	0.89	
17	1.15	1.35	1.2
18	1.19	1.08	1.63
19	1.79	1.81	1.75

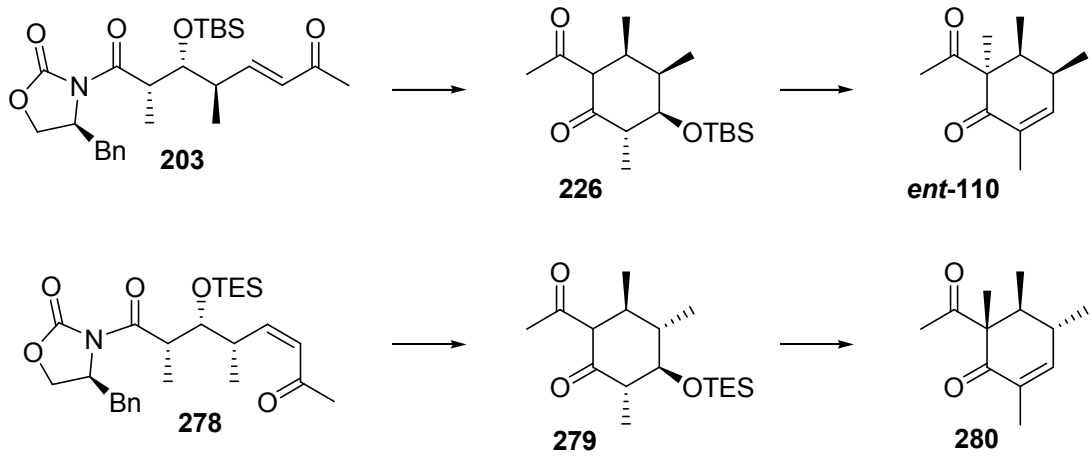


It can be seen in Table 3.1 that differences do exist in a number of the resonances between *syn* methylated cyclohexenone **280** and *anti* methylated cyclohexenone **110**. This indicates that the synthetic pathway towards **280** indeed produced a compound bearing different stereochemistry to *anti* 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*

tridachiahydropyrone (**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).

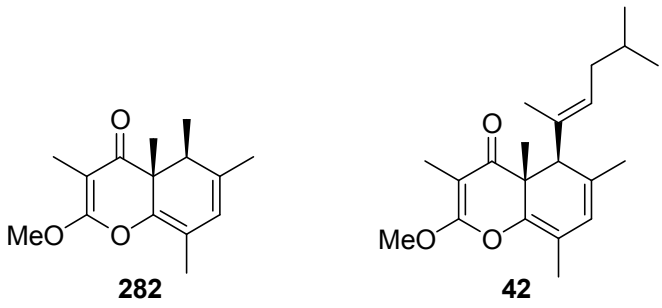


*Scheme 3.33. Methylated cyclohexenones **ent-110** and **280** produced from enones **203** and **278**.*

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

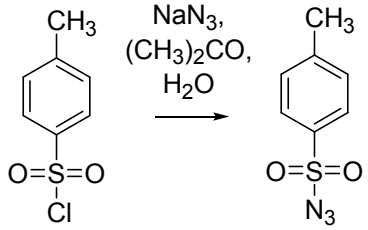
complex *cis* enones. The aim was to synthesise a *cis* enone, which, *via* conversion to the appropriate *syn* cyclohexenone, would be amenable to the synthesis of both model system **282** and *syn* tridachiahydropyrone (**42**) (Figure 3.22).



282 **42**

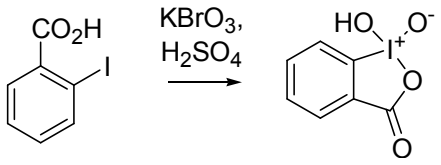
*Figure 3.22. Model system **282** and syn tridachiahydropyrone (**42**).*

3.5 Experimental



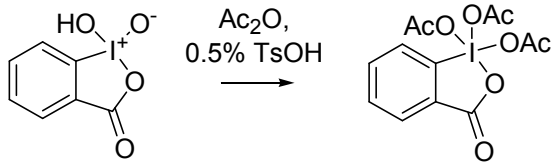
***p*-Toluenesulfonyl azide**

To a stirring solution of NaN_3 (2.0 g, 32.2 mmol) in acetone (14.5 mL), and H_2O (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 *in vacuo* and CH_2Cl_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 *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.



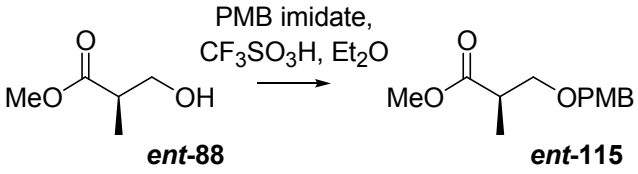
1-Hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide

To a vigorously stirred mixture of 2-iodobenzoic acid (85.2 g, 0.3 mol) in H_2SO_4 (0.73 M, 730 mL, 1.0 mol) at 55 ^oC was added potassium bromate (76 g, 0.5 mol). The mixture was stirred at 68 ^oC for 3.6 hr after which time it was cooled to 0 ^oC. The solid was filtered and washed with H_2O (1000 mL) and EtOH (2 x 50 mL) to give 84.4 g (89% yield) of the title compound as a white solid.



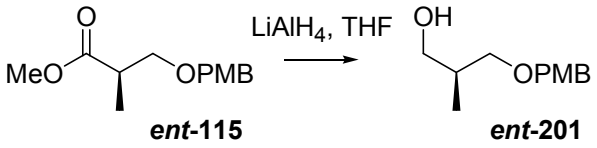
1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one

A mixture of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (84.4 g, 0.3 mol), *p*-TsOH (0.4 g, 1.5 mmol) and Ac_2O (336 mL) was stirred at 80 ^oC for 2 hr, after which time it was cooled to 0 ^oC. The mixture was filtered and the solid was washed with dry Et_2O (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-methoxybenzyloxy)-2-methylpropionate (*ent*-115)**

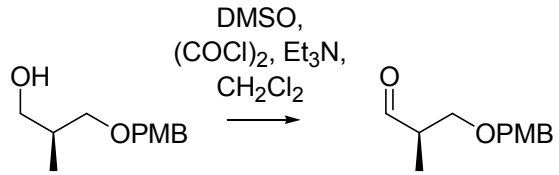
To a stirring solution of alcohol ***ent*-88** (2.9 mL, 24.6 mmol) and PMB imidate (10.8 g, 38.2 mmol) in dry Et_2O (30 mL) under N_2 at RT was added CF_3SO_3H (10 x 7 μL, 10 x 0.08 mmol aliquots) over a period of 3 hr. The mixture was diluted with Et_2O (30 mL) and the organic mixture was washed with $NaHCO_3$ (sat. 1 x 30 mL) and brine (1 x 30 mL). The organic extracts were dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a white crystalline solid. The solid was triturated with a 1:1 mixture of hexanes/CH_2Cl_2, 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 ^oC at 1.25 mmHg), with identical spectral data to that reported in the literature.[29]



***ent*-115** ***ent*-201**

(*S*)-Methyl-3-(4-methoxybenzyloxy)-2-methylpropan-1-ol (*ent*-201)

To a stirring suspension of $LiAlH_4$ (0.93g, 24.6 mmol) in dry THF (40 mL) under N_2 at 0 ^oC 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 ^oC and the reaction was quenched by the addition of H_2O (2 mL), NaOH (5 M, 2 mL) and once again H_2O (3 mL). The mixture was diluted by the addition of Et_2O (40 mL), then dried ($MgSO_4$) and filtered. The filter cake was washed with Et_2O 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]

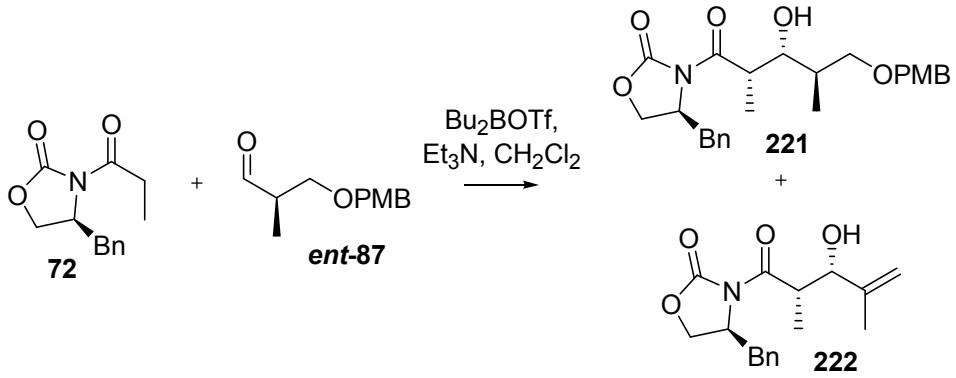


***ent*-201** ***ent*-87**

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

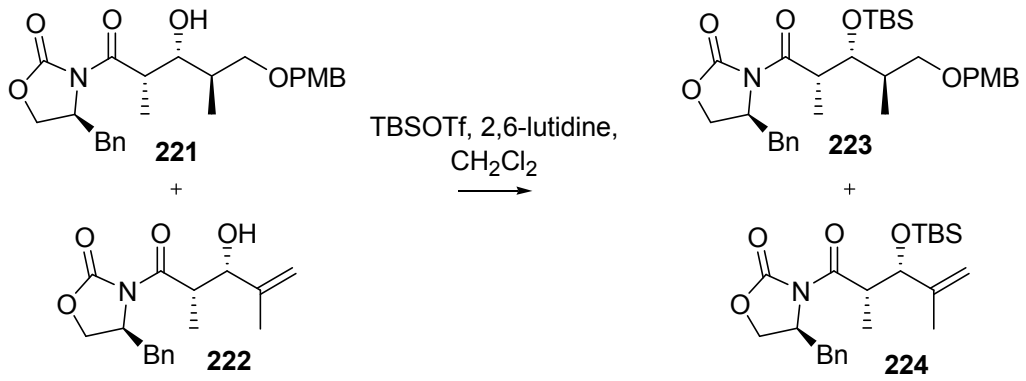
To a stirring solution of DMSO (2.1 mL, 28.9 mmol) in dry CH_2Cl_2 (30 mL) under N_2 at – 78 ^oC was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 7.2 mL, 15.2 mmol) and the solution was stirred at – 78 ^oC for 30 min. To this solution was added dropwise a solution of alcohol ***ent*-201** (2.0 g, 9.5 mmol) in dry CH_2Cl_2 (10 mL) *via* cannula (7 mL rinse) and the resulting cloudy pale yellow solution was stirred at – 78 ^oC for 45 min. To this solution was added dropwise Et_3N (8.0 mL, 57.4 mmol) and the resulting slurry was stirred at – 78 ^oC for 30 min, after which time the solution was slowly warmed to 0 ^oC. The reaction was quenched by addition to a vigorously stirring solution of $NaHSO_4$ (1 M, 62 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the organic extracts were combined and solvent was removed *in vacuo*. The residue was diluted with Et_2O

(100 mL) and washed with $NaHSO_4$ (1 M, 3 x 40 mL), H_2O (1 x 40 mL), $NaHCO_3$ (1 x 40 mL) and brine (1 x 40 mL). The organic extract was dried ($MgSO_4$), 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.[29]



(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*R*)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethyl-pentanoyl]-oxazolidin-2-one (221) and (*S*)-4-benzyl-3-[(2*S*,3*R*)-(3-hydroxy-2,4-dimethylpent-4-enoyl)]-oxazolidin-2-one (222)

To a stirring solution of *N*-acyloxazolidinone **72** (4.1 g, 17.4 mmol) in dry CH_2Cl_2 (25 mL) under N_2 at 0 ^oC was added dropwise Bu_2BOTf (1 M in CH_2Cl_2, 21.0 mL, 21.0 mmol), and the resulting dark red solution was stirred at 0 ^oC for 30 mins. To this stirring solution was added dropwise Et_3N (3.2 mL, 23.0 mmol), and the resulting orange/yellow solution was stirred at 0 ^oC for a further 30 min, after which time it was cooled to – 78 ^oC. To this was added dropwise a solution of aldehyde ***ent*-87** (1.8 g, 8.6 mmol) in dry CH_2Cl_2 (10 mL) *via* cannula (5 mL rinse) and the resulting clear, yellow solution was stirred at – 78 ^oC for 1 hr and at 0 ^oC 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% H_2O_2 (60 mL), and the resulting two-phase mixture was stirred at 0 ^oC for 1 hr. The organic solvents were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with $NaHCO_3$ (sat., 1 x 90 mL) and brine (1 x 100 mL), then dried ($MgSO_4$), 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 (CH_2Cl_2) to give 2.2 g (57% yield) of the title compounds as a colourless oil ($R_f = 0.11$) with identical spectral data to that reported in the literature.[9,30]



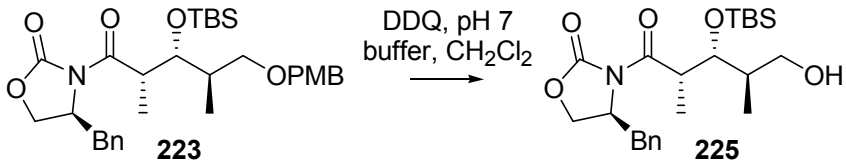
(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyl-oxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (223) and (*S*)-4-benzyl-3-[2*S*,3*R*]-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylpent-4-enoyl]-oxazolidin-2-one (224)

To a stirring solution of the mixture containing alcohol **221** and alkene **222** (2.2 g, 5.0 mmol) in dry CH_2Cl_2 (29.5 mL) under N_2 at – 78 ^oC 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 ^oC 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_2Cl_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_2O/CH_2Cl_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, $CHCl_3$); **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) δ (ppm) – 0.014 (s, 3H, Si(CH_3)$_A$), – 0.011 (s, 3H, Si(CH_3)$_B$), 0.90 (s, 9H, SiC(CH_3)$_3$), 1.21 (d, 3H, C(O)CH(CH_3), *J* = 6.6 Hz), 1.55 (s, 3H, C(CH_3)C=), 2.76 (d of d, 1H, aux. CH_AH$_B$Ar, *J* = 13.2, 9.6 Hz), 3.27 (d of d, 1H, aux. CH$_A$$H_B$Ar, *J* = 12.9, 4.8 Hz), 4.00 – 4.05 (m, 1H, C(O)C*H*(CH$_3$)), 4.13 – 4.16 (m, 2H, aux. OCH_2), 4.34 (d, 1H, C*H*(OTBS), *J* = 6.3 Hz), 4.54 – 4.59 (m, 1H, aux. NC*H*), 4.84 (s, 1H, =CH_AH$_B$), 4.93

(s, 1H, =CH_AH_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 $C_{23}H_{35}NO_4SiNa^+$ ($M+Na^+$): 440.2233; found: 440.2228.

PMB ether 223: $[\alpha]_D^{20}$ = + 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(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 1.01 (d, 3H, CH(CH_3)CH_2O, *J* = 6.9 Hz), 1.23 (d, 3H, C(O)CH(CH_3), *J* = 6.6 Hz), 1.90 – 2.00 (m, 1H, C*H*(CH_3)CH_2O), 2.71 (d of d, 1H, aux. CH_AH_BAr, *J* = 13.2, 9.6 Hz), 3.15 (d of d, 1H, CH_AH_BOPMB, *J* = 9.3, 6.3 Hz), 3.21 (d of d, 1H, aux. CH_AH_BAr, *J* = 13.5, 3.3 Hz), 3.53 (d of d, 1H, CH_AH_BOPMB, *J* = 9.3, 5.7 Hz), 3.75 – 3.82 (m, 1H, aux. OCH_AH_B), 3.77 (s, 3H, PMB OCH_3), 3.96 – 4.05 (m, 3H, aux. OCH_AH_B, C*H*(OTBS) and C(O)C*H*(CH_3)), 4.35 (d, 2H, PMB CH_2, *J* = 11.4 Hz), 4.43 – 4.51 (m, 1H, aux. NC*H*), 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.

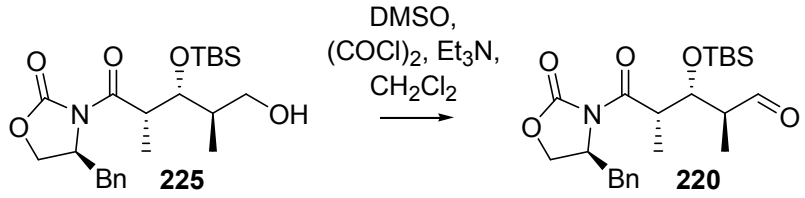


(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4-dimethylpentanoyl]-oxazolidin-2-one (225)

To a stirring solution of PMB ether **223** (0.47 g, 0.85 mmol) in dry CH_2Cl_2 (22.5 mL) at RT was added pH 7 buffer (2.5 mL) and the two-phase mixture was cooled to 0 ^oC. To this solution was added DDQ (0.26 g, 1.15 mmol) and the resulting black mixture was stirred at 0 ^oC for 1.5 hr. The mixture was diluted with CH_2Cl_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_2Cl_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 *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 ($R_f = 0.17$).

$[\alpha]_D^{20}$ = +48.0 (0.50, $CHCl_3$); **IR** (film, cm^{-1}) 2925.6, 1781.3, 1210.7; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (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)CH_2OH, *J* = 7.2 Hz), 1.27 (d, 3H, C(O)CH(CH_3), *J* = 6.6 Hz), 1.60 (bs, 1H, O*H*), 1.84 – 1.95 (m, 1H, C*H*(CH_3)CH_2OH), 2.77 (d of d, 1H, aux. CH_AH$_B$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_2OH), 3.99 (app. quint, 1H, C(O)C*H*(CH_3), *J* = 6.6 Hz), 4.11 – 4.20 (m, 2H, aux. OCH_2), 4.60 – 4.68 (m, 1H, aux. NC*H*), 7.20 – 7.37 (m, 5H, aux. Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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.

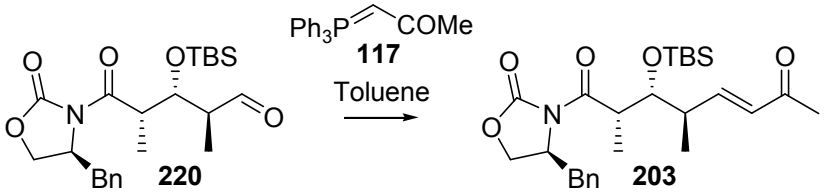


(2*S*,3*R*,4*S*)-5-[(*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-oxopentanal (220)

To a stirring solution of DMSO (0.12 mL, 1.65 mmol) in dry CH_2Cl_2 (2 mL) under N_2 at -78 ^oC was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 0.45 mL, 0.90 mmol) and the solution was stirred at -78 ^oC for 30 min. To this solution was added dropwise a solution of alcohol **225** (0.24 g, 0.55 mmol) in dry CH_2Cl_2 (2 mL) *via* cannula (1.5 mL rinse), and the resulting cloudy pale yellow solution was stirred at – 78 ^oC for 45 min. To this solution was added dropwise Et_3N (0.46 mL, 3.30 mmol) and the resulting slurry was stirred at – 78 ^oC for 30 min, after which time it was warmed to 0 ^oC. 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_2O (3 x 10 mL), the organic extracts were combined and solvent was removed *in vacuo*. The concentrate was diluted with Et_2O (30 mL) and washed

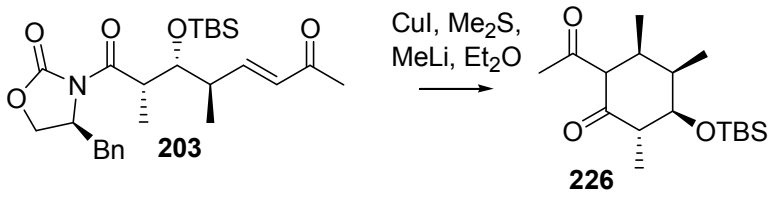
with $NaHSO_4$ (1 M, 3 x 10 mL), H_2O (1 x 10 mL), $NaHCO_3$ (sat., 1 x 10 mL) and brine (1 x 10 mL). The organic extract was dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.24 g (100% yield) of the title compound as a pale yellow oil, which was used crude in subsequent reactions.

$[\alpha]_D^{20}$ = + 87.0 (0.7, $CHCl_3$); **IR** (film, cm^{-1}) 2934.4, 1781.8, 1685.5, 1384.5, 1210.6, 1110.0; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.10 (s, 3H, Si(CH_3)$_A$), 0.11 (s, 3H, Si(CH_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), *J* = 6.9 Hz), 2.60 – 2.64 (m, 1H, C*H*(CH$_3$)C(O)H), 2.76 (d of d, 1H, aux. CH_AH$_B$Ar, *J* = 13.5, 9.6 Hz), 3.21 (d of d, 1H, aux. CH$_A$$H_B$Ar, *J* = 13.2, 3.3 Hz), 3.87-3.99 (m, 1H, C(O)C*H*(CH$_3$)), 4.15 – 4.26 (m, 2H, aux. OCH_2), 4.38 (d of d, 1H, C*H*(OTBS), *J* = 7.5, 3.6 Hz), 4.52 – 4.60 (m, 1H, aux. NC*H*), 7.18 – 7.35 (m, 5H, Ar*H*), 9.70 (d, 1H, C(O)*H*, *J* = 1.8 Hz); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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.



(2*S*,3*R*,4*R*,5*E*)-1-[(*S*)-4-benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethyl-silyloxy)-2,4-dimethyloct-5-ene-1,7-dione (203)

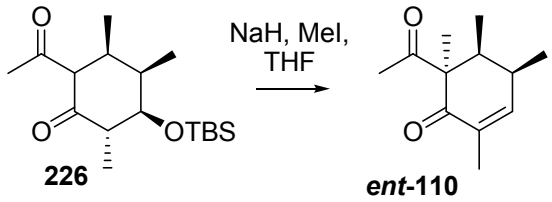
A stirring solution of aldehyde **220** (0.23 g, 0.53 mmol) and ylide **117** (0.27 g, 0.85 mmol) in dry toluene (5.5 mL) was heated at 60 ^oC under N_2 for 4.5 days. The solution was cooled to RT and the volatile components were removed *in vacuo*. The resulting dark brown oil was triturated with hexanes and the triturate was passed through a short silica plug. The solvents were removed *in vacuo* to give a pale yellow oil, which was purified by flash column chromatography on silica (5% hexanes/CH_2Cl_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]



(3*S*,4*R*,5*R*,6*S*)-2-Acetyl-5-(*tert*-butyldimethylsilyloxy)-3,4,6-trimethylcyclo-hexanone (226)

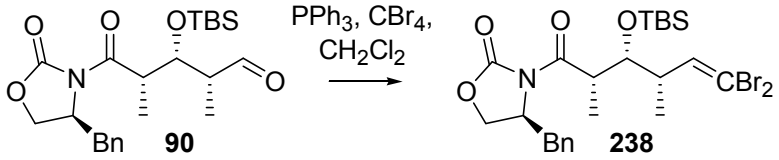
To a stirring suspension of CuI (0.17 g, 0.89 mmol) in dry Et_2O (1.2 mL) and dry Me_2S (2.4 mL) under N_2 at RT was added dropwise MeLi (1.6 M in Et_2O, 1.05 mL, 1.68 mmol) until the initially formed yellow precipitate just dissolved to give a pale yellow solution. To this solution was added dropwise a solution of enone **203** (0.20 g, 0.42 mmol) in dry Et_2O (1 mL) *via* cannula (1mL 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 Et_2O (3 mL) and the reaction was quenched by slow addition of a 10% NH_4OH/90% NH_4Cl 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 Et_2O (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 40 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 silica (CH_2Cl_2) to give 0.08 g (63% yield) of the title compound as a colourless oil (R_f = 0.56 *keto* form, 0.28 *enol* form). The compound existed predominantly in the *keto* form, as evidenced by ^{1}H NMR.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 3H, Si(CH_3)$_A$), 0.07 (s, 3H, Si(CH_3)$_B$), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.97 (d, 3H, C(O)CHCH(CH_3), J = 6.6 Hz), 1.04 (d, 3H, C(O)CH(CH_3), J = 5.1 Hz), 1.06 (d, 3H, CH(CH_3)CH(OTBS), J = 5.7 Hz), 2.00 – 2.11 (m, 1H, CH(CH$_3$)CH(OTBS)), 2.19 (s, 3H, CH_3C(O)), 2.23 – 2.40 (m, 1H, C(O)CHCH(CH$_3$)), 2.44 – 2.59 (m, 1H, C(O)CH(CH$_3$)), 3.28 (d, 1H, C(O)CHC(O), J = 12.6 Hz), 3.44 – 3.56 (m, 1H, CH(OTBS)) ; **^{13}C NMR** ($CDCl_3$, 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.



(4*S*,5*S*,6*R*)-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 N_2 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 Et_2O (3 mL) and the reaction was quenched by addition of $NaHCO_3$ (sat., 8 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The organic extracts were combined and washed with brine (1 x 25 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a brown oil. The oil was purified by flash column chromatography on silica (10% Et_2O/ hexanes) to give 0.03g (60% yield) of the title compound as a colourless oil (R_f = 0.23), with identical ^1H and ^{13}C NMR spectral data to that reported in the literature for its enantiomer, **110**.[1]

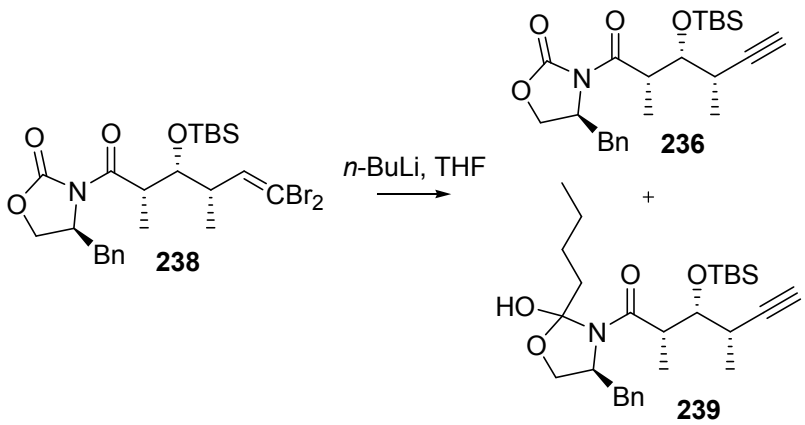


(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*)-6,6-dibromo-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhex-5-enoyl]-oxazolidin-2-one (238)

To a clear, bright yellow stirring solution of PPh_3 (0.27 g, 1.01 mmol) and CBr_4 (0.17 g, 0.50 mmol) in dry CH_2Cl_2 (1.5 mL) under N_2 at 0 ^oC was added dropwise a solution of aldehyde **90** (0.11 g, 0.25 mmol) in dry CH_2Cl_2 (0.7 mL) *via* cannula (0.3 mL rinse) and the solution was stirred at 0 ^oC 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 (Et_2O 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 (R_f = 0.33).

$[\alpha]_D^{20}$ = + 41.9 (0.43, $CHCl_3$); **IR** (film, cm^{-1}) 2933.1, 1782.9, 1698.9, 1109.5; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.04 (s, 3H, Si(CH_3)$_A$), 0.10 (s, 3H, Si(CH_3)$_B$), 0.95 (s, 9H, SiC(CH_3)$_3$), 1.04 (d, 3H, CH(CH_3)CH=, *J* = 6.6 Hz), 1.26 (d, 3H, C(O)CH(CH_3), *J* = 6.9 Hz), 2.55 – 2.63 (m, 1H, C*H*(CH$_3$)CH=), 2.76 (d of d, 1H, aux. CH_AH$_B$Ar, *J* = 13.2, 2.4 Hz), 3.28 (d of d, 1H aux. CH$_A$$H_B$Ar, *J* = 13.5, 3.3 Hz), 3.84 (app. quint, 1H, C(O)C*H*(CH$_3$), *J* = 6.6 Hz), 4.01 (app. t, 1H, C*H*(OTBS), *J* = 6.3 Hz), 4.18 – 4.28 (m, 2H, aux. OCH_2), 4.63 – 4.71 (m, 1H, aux. NC*H*), 6.40 (d, 1H, C*H*=, *J* = 9.9 Hz), 7.22 – 7.38 (m, 5H, Ar*H*); **^{13}C NMR** ($CDCl_3$, 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 $C_{24}H_{35}Br_2NO_4SiNa^+$ (M+Na$^+$): 610.0600; found: 610.0605.



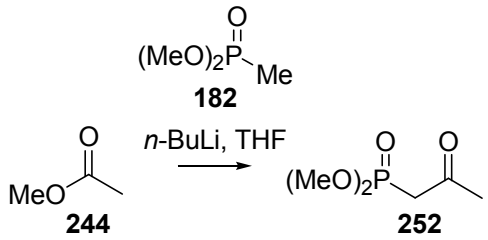
(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhex-5-ynoyl]-oxazolidin-2-one (236) and 1-(4-benzyl-2-butyl-2-hydroxyoxazolidin-3-yl)-3-[(2*S*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhex-5-yn-1-one] (239)

To a stirring solution of bromoalkene **238** (0.05 g, 0.09 mmol) in dry THF (0.3 mL) under N_2 at – 50 ^{o}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 ^{o}C for 1 hr and at RT for 30

min. The reaction was quenched by dropwise addition of NH_4Cl (sat., 0.08 mL) and solvents were removed *in vacuo*. The aqueous residue was extracted with Et_2O (3 x 2 mL) and the organic extracts were combined, washed with brine (1 x 10 mL), then dried ($MgSO_4$), 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).

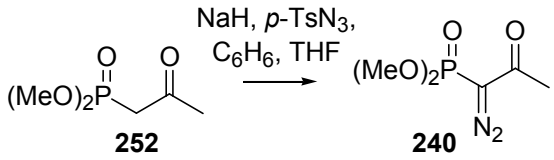
Alkyne 236: $[\alpha]_D^{20}$ = + 26.8 (0.49, $CHCl_3$); **IR** (film, cm^{-1}) 2927.6, 1783.6, 1694.9, 1385.7, 1209.7, 1108.5; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 3H, Si(CH_3)$_A$), 0.13 (s, 3H, Si(CH_3)$_B$), 0.92 (s, 9H, SiC(CH_3)$_3$), 1.18 (d, 3H, CH(CH_3)C≡, *J* = 7.2 Hz), 1.29 (d, 3H, C(O)CH(CH_3), *J* = 5.1 Hz), 2.08 – 2.09 (m, 1H, ≡C*H*), 2.58 – 2.69 (m, 1H, C*H*(CH$_3$)C≡), 2.75 (d of d, 1H, aux. CH_AH$_B$Ar, *J* = 13.8, 3.0 Hz), 3.25 – 3.30 (m, 1H aux. CH$_A$*H*$_B$Ar), 4.09 – 4.10 (m, 2H, C(O)C*H*(CH$_3$) and C*H*(OTBS)), 4.16 – 4.18 (m, 2H, aux. OCH_2), 4.58 – 4.69 (m, 1H, aux. NC*H*), 7.20 – 7.33 (m, 5H, Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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 $C_{24}H_{35}NO_4SiNa^+$ (M+Na^+): 452.2223; found: 452.2221.

Addition product 239: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 3H, Si(CH_3)$_A$), 0.12 (s, 3H, Si(CH_3)$_B$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.92 (t, 3H, *n*-Bu CH_3, *J* = 3.6 Hz), 1.13 (d, 3H, CH(CH_3)C≡ or C(O)CH(CH_3), *J* = 6.9 Hz), 1.14 (d, 3H, CH(CH_3)C≡ or C(O)CH(CH_3), *J* = 6.9 Hz), 1.30 – 1.42 (m, 2H, *n*-Bu CH$_3$CH_2), 1.59 – 1.68 (m, 2H, *n*-Bu CH$_3$CH$_2$CH_2), 2.06 (d, 1H, ≡C*H*, *J* = 2.4 Hz), 2.34 (t, 2H, *n*-Bu CH$_3$(CH$_2$)$_2$CH_2, *J* = 7.7 Hz), 2.54 – 2.65 (m, 2H, C*H*(CH$_3$)C≡ and C(O)C*H*(CH$_3$)), 2.76 – 2.92 (m, 1H, aux. CH_AH$_B$Ar), 3.92 (app. t, 1H, C*H*(OTBS), *J* = 5.3 Hz), 3.99 – 4.10 (m, 2H, aux. OCH_2), 4.37 – 4.48 (m, 1H, aux. NC*H*), 7.17 – 7.32 (m, 5H, Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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 $C_{28}H_{45}NO_4SiNa^+$ (M+Na^+): 510.3016; found: 510.3004.



Dimethyl-2-oxopropanephosphonate (252)

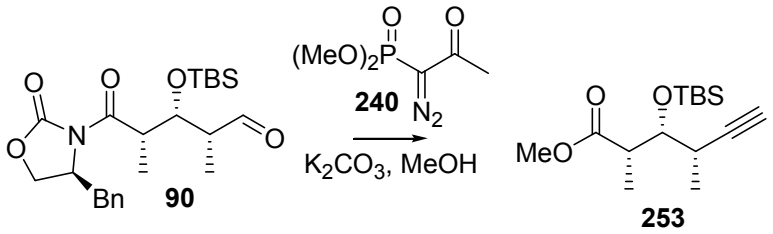
To a stirring solution of phosphonate **182** (0.17 g, 1.4 mmol) in dry THF (1 mL) under N_2 at -78 ^oC was added dropwise *n*-BuLi (1.30 M in hexanes, 1.1 mL, 1.4 mmol) and the resulting creamy solution was stirred at – 78 ^oC for 1 hr. To this solution was added dropwise a solution of ester **244** (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 ^oC for 30 min. The solution was warmed to 0 ^oC 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/CH_2Cl_2) 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 N_2 at 0 ^oC 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 ^oC for 1.5 hr. To the suspension was added dropwise a solution of *p*-TsN_3 (0.18 g, 0.91 mmol) in dry C_6H_6 (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]



(2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhex-5-ynoic acid methyl ester (253)

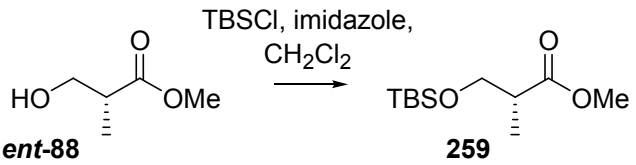
(a) To a stirring solution of aldehyde **90** (0.05g, 0.11mmol) in dry MeOH (1 mL) under N_2 at – 50 ^oC was added dropwise a solution of α-diazo-β-ketophosphonate **240** (0.03 g, 0.17 mmol) in dry MeOH (0.3 mL) *via* cannula (0.3 mL rinse), followed immediately by the addition of K_2CO_3 (0.032 g, 0.23 mmol). The solution was stirred at – 50 ^oC for 30 min, at – 20 ^oC for 1.5 hr and at 0^oC for 1.5 hr, after which time TLC (5% MeOH/CH_2Cl_2) did not indicate any further changes. The solution was diluted with Et_2O (2.5 mL) and the reaction was quenched by addition of H_2O (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 purifed by flash column chromatography on silica (CH_2Cl_2, then 2% MeOH/CH_2Cl_2) to give methyl ester **253** (0.003g) as a colourless oil (R_f = 0.53 in CH_2Cl_2) and oxazolidinone **98** (0.03 g) as a white solid (R_f = 0.09 in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) – 0.03 (s, 3H, Si(CH_3)$_A$), 0.09 (s, 3H, Si(CH_3)$_B$), 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≡, *J* = 7.2 Hz), 2.10 – 2.11 (m, 1H, ≡C*H*), 2.52 – 2.57 (m, 1H, C*H*(CH$_3$)C≡), 3.02 (d of quart, 1H, C(O)C*H*(CH$_3$), *J* = 6.9, 3 Hz), 3.69 (s, 3H, CH_3O), 4.11 (d of d, 1H, C*H*(OTBS), *J* = 7.8, 3.3 Hz); **^{13}C NMR** ($CDCl_3$, 75.5 MHz)

δ (ppm) – 4.4, – 4.2, 9.9, 17.7, 18.3, 26.0, 31.5, 43.5, 51.7, 70.7, 76.0, 86.4, 175.3; **HRESIMS** calculated for $C_{15}H_{28}O_3SiH^+$ ($M+H^+$): 285.1887; found: 285.1889.

(b) To a stirring mixture of aldehyde **90** (0.05 g, 0.11 mmol) and K_2CO_3 (0.03 g, 0.23 mmol) in dry MeOH (0.8 mL) under N_2 at 0 ^oC 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 ^oC for 30 min and at RT overnight. The solution was diluted with Et_2O (1 mL) and the reaction was quenched by addition of H_2O (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 ($MgSO_4$), 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/CH_2Cl_2) to give 0.03 g of oxazolidinone **98** as a colourless oil.

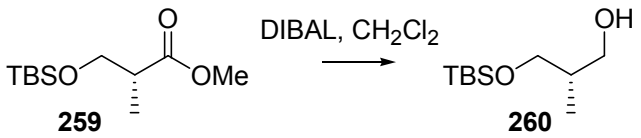
(c) To a stirring solution of α-diazo-β-ketophosphonate **240** (0.04 g, 0.19 mmol) in dry MeOH (1.5 mL) under N_2 at 0 ^oC was added dry K_2CO_3 (0.05 g, 0.33 mmol) followed immediately by the dropwise addition of a solution of aldehyde **90** (0.07 g, 0.15 mmol) in dry MeOH (0.5 mL) *via* cannula (0.3 mL rinse) and the solution stirred at 0 ^oC for 30 min and at RT for 1 hr. The reaction was quenched by addition of NH_4Cl (sat., 2.3 mL) and pentane (5.8 mL). The layers were separated and the organic extract was dried ($MgSO_4$), 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 ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.04 g of oxazolidinone **98** as a yellow oil.



***ent*-88** **259**

(*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_2Cl_2 (50.5 mL) under N_2 at 0 ^oC 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_2O 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 ^oC at 0.05 mmHg, lit. BPt[19] 59 ^oC 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]

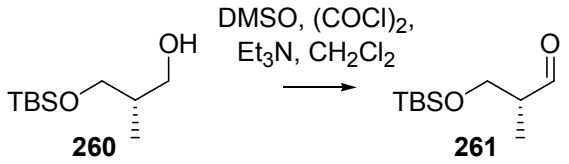


259 **260**

(*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_2Cl_2 (166 mL) under N_2 at – 78 ^oC was added dropwise DIBAL (1 M in toluene, 70.0 mL, 70.0 mmol) and the resulting colourless solution was stirred at – 78 ^oC for 15 min and then at RT for 1 hr. The solution was cooled to – 78 ^oC 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_2O (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 ^oC

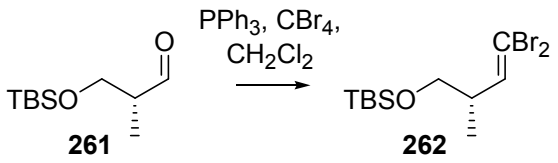
at 0.6 mmHg, lit. BPt[19] 60 °C at 0.8 mmHg) to give 5.9 g (82% yield) of the title compound as a clear, colourless oil, with identical spectral data to that reported in the literature.[19]



260 **261**

(*R*)-Methyl-3-(*tert*-butyldimethylsilyloxy)-2-methylpropanal (261)

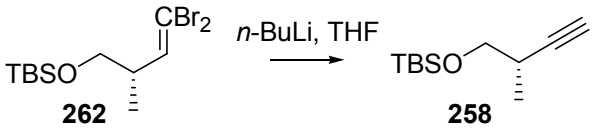
To a stirring solution of DMSO (7.0 mL, 98.4 mmol) in dry CH_2Cl_2 (300 mL) under N_2 at – 78 °C was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 24.6 mL, 49.2 mmol) and the solution was stirred at – 78 °C for 30 min. To this solution was added dropwise a solution of alcohol **260** (6.7 g, 32.8 mmol) in dry CH_2Cl_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_3N (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_2O (3 x 200 mL), the organic extracts were combined and solvent was removed *in vacuo*. The concentrate was diluted with Et_2O (100 mL) and washed with $NaHSO_4$ (1 M, 3 x 50 mL), H_2O (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]



261 **262**

***tert*-Butyl-[(2*S*)-4,4-dibromo-2-methylbut-3-enyloxy)-dimethylsilane (262)**

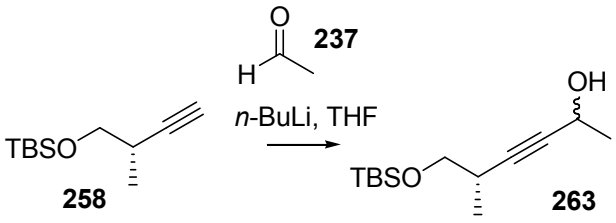
To a stirring solution of PPh_3 (27.9 g, 106.1 mmol) and CBr_4 (17.7 g, 53.1 mmol) in dry CH_2Cl_2 (246 mL) under N_2 at 0 ^oC was added dropwise a solution of **261** (5.4 g, 26.5 mmol) in dry CH_2Cl_2 (15 mL) *via* cannula (5 mL rinse) and the resulting orange solution was stirred at 0 ^oC for 10 min 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 (Et_2O used as eluent) to give 9.4 g of a colourless oil, which was purified by flash column chromatography on silica (1:1 hexanes/CH_2Cl_2) to give 7.7 g (81% yield) of the title compound as a colourless oil (R_f = 0.72), with identical spectral data to that reported in the literature.[32,33]



262 **258**

***tert*-Butyl-((2*S*)-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 N_2 at – 50 ^oC was added dropwise *n*-BuLi (1.36 M in hexanes, 0.86 mL, 1.17 mmol). The solution was warmed to – 40 ^oC and stirred at this temperature for 1 hr and at RT for 30 min. The solution was diluted with Et_2O (1 mL) and the reaction was quenched by addition of NH_4Cl (sat., 1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 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 0.10 g of a colourless, cloudy oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.09 g (78% yield) of the title compound as a colourless oil (R_f = 0.69), with identical spectral data to that given in the literature.[32,33]



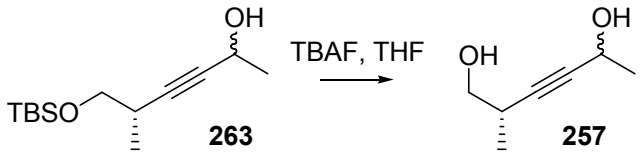
(2*S*,5*S*)-6-(*tert*-Butyldimethylsilyloxy)-5-methylhex-3-yn-2-ol and (2*R*,5*S*)-6-(*tert*-butyldimethylsilyloxy)-5-methylhex-3-yn-2-ol (263)

To a stirring solution of alkyne **258** (0.05 g, 0.25 mmol) in dry THF (2 mL) under N_2 at – 78 ^oC 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 ^oC 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 ^oC, the solution was diluted with Et_2O (2 mL) and the reaction was quenched by addition of NH_4Cl (sat., 2 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 3 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 0.08 g of a pale yellow, clear oil. The oil was purified by flash column chromatography on silica (5% Et_2O/CH_2Cl_2) to give 0.05 g (75% yield) of the title compound as a colourless oil (R_f = 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 $C_{13}H_{26}O_2SiNa^+$ ($M+Na^+$): 265.1600; found: 265.1612.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 6H, Si(C*H*$_3$)$_2$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 1.15 (d, 3H, CH(C*H*$_3$)C≡, *J* = 6.8 Hz), 1.42 (d, 3H, CH(OH)C*H*$_3$, *J* = 6.6 Hz), 1.66 (bs, 1H, O*H*), 2.51 – 2.68 (m, 1H, C*H*(CH$_3$)C≡), 3.43 (d of d, 1H, TBSOC*H*$_A$H$_B$, *J* = 9.4, 7.8 Hz), 3.66 (d of d, 1H, TBSOCH$_A$*H*$_B$), 4.51 (quart, 1H, C*H*(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.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 6H, Si(C*H*$_3$)$_2$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 1.15 (d, 3H, CH(C*H*$_3$)C≡, *J* = 6.8 Hz), 1.42 (d, 3H, CH(OH)C*H*$_3$, *J* = 6.6 Hz), 1.66 (bs, 1H, O*H*), 2.51 – 2.68 (m, 1H, C*H*(CH$_3$)C≡), 3.43 (d of d, 1H, TBSOC*H*$_A$H$_B$, *J* = 9.4, 7.8 Hz), 3.66 (d of d, 1H, TBSOCH$_A$*H*$_B$), 4.52 (quart., 1H, C*H*(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.



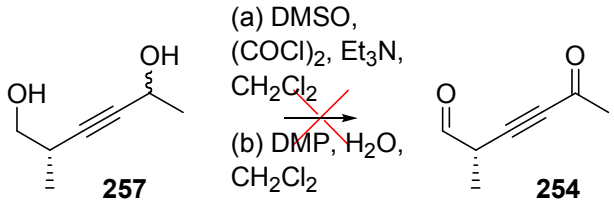
(5*S*,2*S*)-2-Methylhex-3-yne-1,5-diol and (5*R*,2*S*)-2-methylhex-3-yne-1,5-diol (257)

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_2O (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_2O (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 $C_7H_{12}O_2Na^+$ (M+Na$^+$): 151.0735; found: 151.0741.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.15 (d, 3H, CH(C*H*$_3$)C≡, *J* = 7.2 Hz), 1.43 (d, 3H, CH(OH)C*H*$_3$, *J* = 6.6 Hz), 2.39 (bs, 1H, O*H*), 2.62 – 2.74 (m, 1H, C*H*(CH$_3$)C≡), 3.47 – 3.61 (m, 2H, HOC*H*$_2$), 4.49 – 4.56 (m, 1H, C*H*(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(C*H*$_3$)C≡, *J* = 7.2 Hz), 1.43 (d, 3H, CH(OH)C*H*$_3$, *J* = 6.6 Hz), 2.39 (bs, 1H, O*H*), 2.62 – 2.74 (m, 1H, C*H*(CH$_3$)C≡), 3.47 – 3.61 (m, 2H, HOC*H*$_2$), 4.49 – 4.56 (m, 1H, C*H*(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.

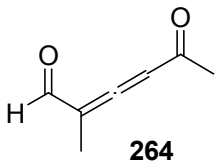


(2*S*)-2-Methyl-5-oxohex-3-ynal (254)

(a) To a stirring solution of DMSO (0.14 mL, 2.01 mmol) in dry CH_2Cl_2 (0.8 mL) under N_2 at – 78 ^{o}C was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 0.50 mL, 1.01 mmol) and the solution was stirred at -78 ^{o}C for 30 min. To this solution was added dropwise a solution of diol **257** (0.04 g, 0.34 mmol) in dry CH_2Cl_2 (5 mL) *via* cannula (0.4 mL rinse), and the resulting cloudy pale yellow solution was stirred at – 78 ^{o}C for 45 min. To this solution was added dropwise Et_3N (0.60 mL, 4.30 mmol) and the resulting slurry was stirred at – 78 ^{o}C for 30 min, after which time it was warmed to 0 ^{o}C. The reaction was quenched by addition of NH_4Cl (sat., 5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_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_2Cl_2) to give no useful compounds.

(b) To a stirring solution of diol **257** (0.05 g, 0.35 mmol) in dry CH_2Cl_2 (3.5 mL) at RT was added DMP (0.46 g, 1.08 mmol) followed immediately by the addition of a H_2O/CH_2Cl_2 mixture (0.58 mL, 0.01 mL of H_2O in 7.0 mL of CH_2Cl_2) and addition of the moist CH_2Cl_2 continued every 5 min (total added was 12 x 0.58 mL aliquots) for 1 hr. The solution was diluted with Et_2O (20 mL) and the reaction was quenched by addition of a solution of $NaHCO_3$ (sat., 12 mL) containing $Na_2S_2O_3.5H_2O$ (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

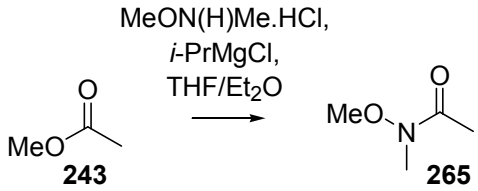
and solvent was removed *in vacuo* to give 0.04 g of a yellow oil/solid material. The mixture was purified by flash column chromatography on silica (CH_2Cl_2) to give allene **264** (0.016 g) as a colourless oil (R_f = 0.31).



264

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

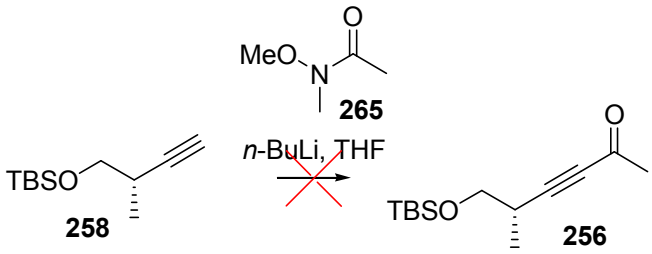
^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.95 (d, 3H, =C(C*H*$_3$), *J* = 3 Hz), 2.28 (s, 3H, C(O)C*H*$_3$), 6.24 (quart, 1H, C*H*=, *J* = 3 Hz), 9.65 (s, 1H, C(O)*H*).



243 **265**

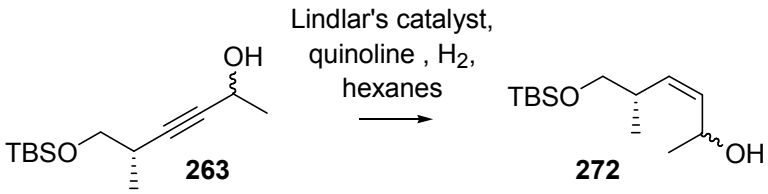
***N*-Methoxy-*N*-methylacetamide (265)**

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 Et_2O (1:1, 16.4 mL) under N_2 at – 20 ^oC 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 ^oC for 30 min and at RT for 30 min. The solution was cooled to 0 ^oC and the reaction was quenched by addition of NH_4Cl (sat., 115 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (1 x 100 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.65 g of a yellow oil. The oil was purified by distillation under N_2 to give 0.28 g (40% yield) of the title compound as a colourless oil (BPt 100 ^oC at 760 mmHg, lit. BPt[34] 40 – 44 ^oC at 20 mmHg), with identical spectral data to that given in the literature.[34]



(5*S*)-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 N_2 at – 40 ^oC was added dropwise *n*-BuLi (1.36 M in hexanes, 0.36 mL, 0.50 mmol) and the solution was stirred at – 40 ^oC for 1 hr and at RT for 10 min. The solution was cooled to – 78 ^oC 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 ^oC and after 1 hr, TLC (20% hexanes/CH_2Cl_2) did not indicate consumption of starting material. The solution was warmed to 0 ^oC and after 30 min, TLC did not indicate any further consumption of starting material. The solution was cooled to – 20 ^oC and the reaction was quenched by addition of NH_4Cl (sat., 2 mL), and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 3 mL). The organic extracts were combined and washed with brine (1 x 25 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.11 g of predominantly starting material as a brown oil.



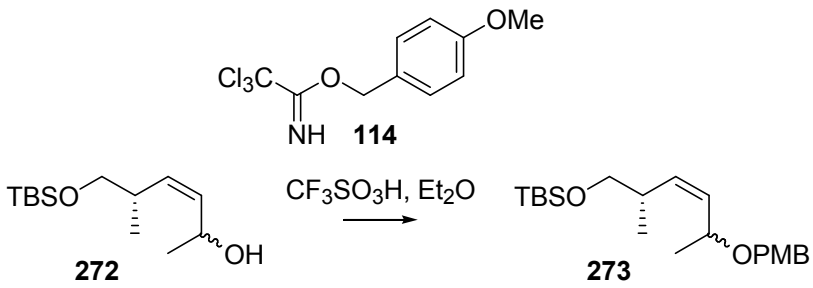
(2*R*,5*S*)-*cis*-6-(*tert*-Butyldimethylsilyloxy)-5-methylhex-3-en-2-ol and (2*S*,5*S*)-*cis*-6-(*tert*-butyldimethylsilyloxy)-5-methylhex-3-en-2-ol (272)

To a stirring solution of alkyne **263** (0.05 g, 0.20 mmol) in dry hexanes (7 mL) under N_2 at RT was added dropwise quinoline (0.04 mL, 0.29 mmol) followed by Lindlar's catalyst (5% Pd on $CaCO_3$, 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 *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: $[\alpha]_D^{20}$ = + 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) δ (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, O*H*), 2.71 – 2.84 (m, 1H, C*H*(CH$_3$)C=), 3.27 (app. t, 1H, TBSOCH_ACH$_B$, *J* = 9.6 Hz), 3.56 (d of d, 1H, TBSOCH$_A$CH_B, *J* = 9.3, 4.5 Hz), 4.47 – 4.57 (m, 1H, C*H*(OH)), 5.18 (app. t, 1H, *H*C=, *J* = 10.8 Hz), 5.58 (d of d, 1H, =C*H*, *J* = 10.5, 7.8 Hz); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 5.4, 17.0, 18.7, 22.7, 26.1, 35.2, 62.5, 67.9, 135.4, 135.5; **HRESIMS** calculated for $C_{13}H_{28}O_2SiNa^+$ (M+Na^+): 267.1757; found: 267.1755.

Isomer B: $[\alpha]_D^{20}$ = + 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) δ (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, O*H*), 2.76 – 2.86 (m, 1H, C*H*(CH$_3$)C=), 3.32 (d of d, 1H, TBSOCH_ACH$_B$, *J* = 9.9, 7.5 Hz), 3.44 (d of d, 1H, TBSOCH$_A$CH_B, *J* = 9.6, 6 Hz), 4.56 – 4.65 (m, 1H, C*H*(OH)), 5.16 (app. t, 1H, *H*C=, *J* = 10.8 Hz), 5.47 (d of d, 1H, =C*H*, *J* = 10.8, 7.8 Hz); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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 $C_{13}H_{28}O_2SiNa^+$ (M+Na^+): 267.1757; found: 267.1755.



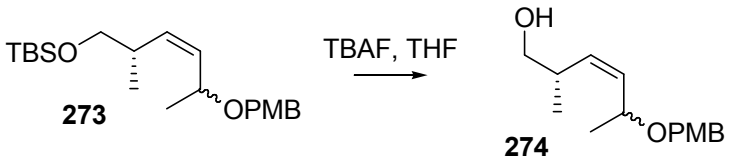
***cis-tert*-Butyl-[(2*S*,5*R*)-5-(4-methoxybenzyloxy)-2-methylhex-3-enyloxy]-dimethylsilane and *cis-tert*-butyl-[(2*S*,5*S*)-5-(4-methoxybenzyloxy)-2-methylhex-3-enyloxy]-dimethylsilane (273)**

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 Et_2O (10.5 mL) under N_2 was added CF_3SO_3H (3 x 1 μL, 0.01 mmol, aliquots) over a period of 2 hr. The mixture was diluted with Et_2O (3 mL) and the organic mixture was washed with $NaHCO_3$ (sat. 1 x 20 mL) and brine (1 x 20 mL). The organic extract was dried ($MgSO_4$), 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 CH_2Cl_2, 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/CH_2Cl_2) to give 0.94 g (71% yield) of the title compound as a colourless oil (R_f = 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 $C_{21}H_{36}O_3SiNa^+$ ($M+Na^+$): 387.2332; found: 387.2360.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.04 (s, 6H, Si(C*H*$_3$)$_2$), 0.89 (s, 9H SiC(C*H*$_3$)$_3$), 0.92 (d, 3H, CH(C*H*$_3$)CH=, *J* = 6.6 Hz), 1.24 (d, 3H, =CHCH(C*H*$_3$), *J* = 6.3 Hz), 2.51-2.70 (m, 1H, C*H*(CH$_3$)CH=), 3.36 – 3.52 (m, 2H, TBSOC*H*$_2$), 3.80 (s, 3H, PMB OC*H*$_3$), 4.25 – 4.30 (m, 2H, =CHC*H*(CH$_3$) and PMB C*H*$_A$H$_B$), 4.47 – 4.52 (m, 1H, PMB CH$_A$*H*$_B$), 5.30 – 5.42 (m, 2H, C*H*=C*H*), 6.85 – 6.89 (m, 2H, PMB Ar*H*), 7.24 – 7.28 (m, 2H, PMB Ar*H*); ^{13}**C NMR** ($CDCl_3$, 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, C*H*(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_AH$_B$), 4.47 – 4.52 (m, 2H, =CHC*H*(CH_3) and PMB CH$_A$$H_B$), 5.30 – 5.42 (m, 2H, C*H*=C*H*), 6.85 – 6.89 (m, 2H, PMB Ar*H*), 7.24 – 7.28 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($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.



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

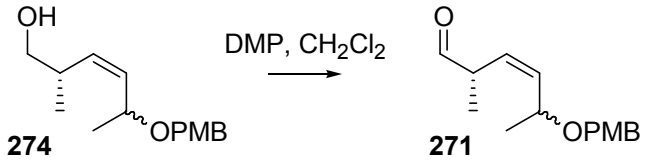
To a stirring solution of silyl ether **273** (0.23 g, 0.63 mmol) in dry THF (2.7 mL) under N_2 at RT was added dropwise TBAF (1 M in THF, 0.95 mL, 0.95 mmol) and the solution was left to stir at RT for 30 min. The solution was diluted with Et_2O (3 mL) and the reaction was quenched by addition of brine (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 $C_{15}H_{22}O_3Na^+$ (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, O*H*), 2.57 – 2.69 (m, 1H, =CHC*H*(CH_3)), 3.36 (d of d, 1H, CH_AH$_B$OH *J* = 14.4, 8.1 Hz), 3.47 (d of d, 1H,

CH_AH_BOH), 3.80 (s, 3H, PMB OCH_3), 4.23 – 4.33 (m, 1H, =CHC*H*(CH_3)), 4.28 (d, 1H, PMB CH_ACH_B, J = 11.4 Hz), 4.48 (d of d, 1H, PMB CH_ACH_B, J = 11.7, 4.2 Hz), 5.28 – 5.35 (m, 1H, C*H*=), 5.47 – 5.56 (m, 1H, =C*H*), 6.85 – 6.88 (m, 2H, PMB Ar*H*), 7.24 – 7.29 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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) δ (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, O*H*), 2.57 – 2.69 (m, 1H, =CHC*H*(CH_3)), 3.32 (d of d, 1H, CH_AH_BOH, J = 14.7, 8.4 Hz), 3.51 (d of d, 1H, CH_AH_BOH, J = 11.7, 5.4 Hz), 3.79 (s, 3H, PMB OCH_3), 4.23 – 4.33 (m, 1H, =CHC*H*(CH_3)), 4.37 (d, 1H, PMB CH_ACH_B, J = 11.1 Hz), 4.48 (d of d, 1H, PMB CH_ACH_B, J = 11.7, 4.2 Hz), 5.28 – 5.35 (m, 1H, C*H*=), 5.47 – 5.56 (m, 1H, =C*H*), 6.85 – 6.88 (m, 2H, PMB Ar*H*), 7.24 – 7.29 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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.



274 **271**

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

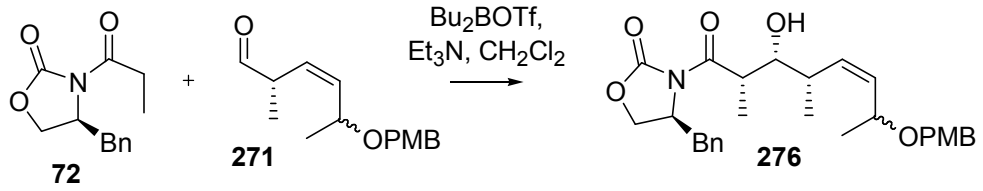
To a stirring solution of DMP (0.13 g, 0.30 mmol) in dry CH_2Cl_2 (1 mL) under N_2 at RT was added dropwise a solution of alcohol **274** (0.05 g, 0.20 mmol) in dry CH_2Cl_2 (0.5 mL) *via* cannula (0.5 mL rinse) and the solution was left to stir at RT for 1 hr. The solution was diluted with Et_2O (4 mL) and the reaction was quenched by dropwise addition of a solution of $NaHCO_3$ (sat., 4 mL) containing $Na_2S_2O_3.5H_2O$ (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: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.16 (d, 3H, HC(O)CH(C*H*$_3$), *J* = 6.9 Hz), 1.28 (d, 3H, CH(C*H*$_3$)OPMB, *J* = 6.3 Hz), 3.22 – 3.34 (m, 1H, HC(O)C*H*(CH$_3$)), 3.80 (s, 3H, PMB OC*H*$_3$), 4.22 – 4.27 (m, 1H, CHC*H*(CH$_3$)), 4.31 (d of d, 1H, PMB C*H*$_A$CH$_B$, *J* = 11.4, 2.4 Hz), 4.49 (d, 1H, PMB CH$_A$C*H*$_B$, *J* = 11.7 Hz), 5.45 (app. t, 1H, C*H*=, *J* = 10.4 Hz), 5.66 (app. quart, 1H, =C*H*, *J* = 9.7 Hz), 6.85 – 6.88 (m, 2H, PMB Ar*H*), 7.24 – 7.29 (m, 2H, PMB Ar*H*), 9.46 (d, 1H, *H*C(O), *J* = 1.5 Hz); ^{13}**C NMR** ($CDCl_3$, 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: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.22 (d, 3H, HC(O)CH(C*H*$_3$), *J* = 6.9 Hz), 1.29 (d, 3H, CH(C*H*$_3$)OPMB, *J* = 6.3 Hz), 3.22 – 3.34 (m, 1H, HC(O)C*H*(CH$_3$)), 3.804 (s, 3H, PMB OC*H*$_3$), 4.22 – 4.37 (m, 1H, =CHC*H*(CH$_3$)), 4.31 (d of d, 1H, PMB C*H*$_A$CH$_B$, *J* = 11.4, 2.4 Hz), 4.49 (d, 1H, PMB CH$_A$C*H*$_B$, *J* = 11.7 Hz), 5.35 (app. t, 1H, C*H*=, *J* = 10.4 Hz), 5.66 (app. quart., 1H, =C*H*, *J* = 9.7 Hz), 6.85 – 6.88 (m, 2H, PMB Ar*H*), 7.24 – 7.29 (m, 2H, PMB Ar*H*), 9.56 (d, 1H, *H*C(O), *J* = 1.5 Hz); ^{13}**C NMR** ($CDCl_3$, 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.



72 271 276

(*S*)-4-Benzyl-3-[*cis*-(2*S*,3*R*,4*S*,7*R*)-3-hydroxy-7-(4-methoxybenzyloxy)-2,4-dimethyl-oct-5-enoyl]-oxazolidin-2-one and (*S*)-4-benzyl-3-[*cis*-(2*S*,3*R*,4*S*,7*S*)-3-hydroxy-7-(4-methoxybenzyloxy)-2,4-dimethyl-oct-5-enoyl]-oxazolidin-2-one (276)

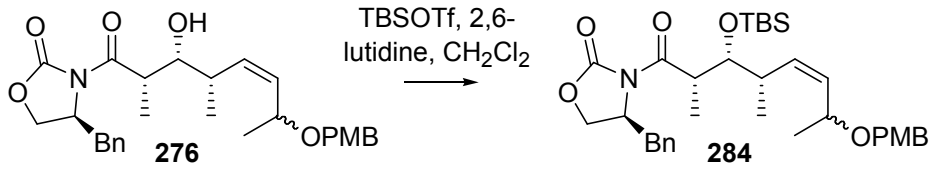
To a stirring solution of *N*-acyloxazolidinone **72** (0.40 g, 1.70 mmol) in dry CH_2Cl_2 (1.9 mL) under N_2 at 0 ^oC was added dropwise Bu_2BOTf (1 M in CH_2Cl_2, 2.05 mL, 2.05 mmol), and the resulting pale red solution was stirred at 0 ^oC for 30 min. To this stirring solution was added dropwise Et_3N (0.31 mL, 2.21 mmol), and the resulting yellow solution was stirred at 0 ^oC for a further 30 min, after which time it was cooled to – 78 ^oC. A solution of aldehyde **271** (0.21 g, 0.85 mmol) in dry CH_2Cl_2 (1 mL) was then added dropwise *via* cannula (1 mL rinse) and the resulting clear, yellow solution was stirred at – 78 ^oC for 30 min and at 0 ^oC 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_2O_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_2Cl_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 $C_{28}H_{35}NO_6Na^+$ ($M+Na^+$): 504.2362; found: 504.2356.

Isomer A: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.15 (d, 3H, CH(C*H*$_3$)CH=, *J* = 6.6 Hz), 1.22 (d, 3H, C(O)CH(C*H*$_3$), *J* = 7.5 Hz), 1.28 (d, 3H, =CHCH(C*H*$_3$), *J* = 6.3 Hz),

2.28 (bs, 1H, O*H*), 2.55 – 2.63 (m, 1H, C*H*(CH_3)CH=), 2.78 (d of d, 1H, aux. CH_AH$_B$Ar, *J* =12.9, 9.6 Hz), 3.19 – 3.22 (m, 1H, aux. CH$_A$$H_B$Ar), 3.71 (d of d, 1H, C*H*(OH), *J* = 9.3, 2.1 Hz), 3.79 (s, 3H, PMB OCH_3), 3.79 – 3.81 (m, 1H, C(O)C*H*(CH_3)), 3.92 (quart of d, 1H, C(O)C*H*(CH_3), *J* = 6.9, 1.8 Hz), 4.17 – 4.38 (m, 4H, =CHC*H*(CH_3), PMB CH_ACH$_B$ and aux. OCH_2), 4.54 (d, 1H, PMB CH$_A$CH_B, *J* = 11.1 Hz), 4.65 – 4.71 (m, 1H, aux. NC*H*), 5.29 – 5.39 (m, 1H, C*H*=), 5.43 – 5.52 (m, 1H, =C*H*), 6.85 – 6.88 (m, 3H, aux. and PMB Ar*H*), 7.18 – 7.36 (m, 6H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 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: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.09 (d, 3H, CH(CH_3)CH=, *J* = 6.6 Hz), 1.18 (d, 3H, C(O)CH(CH_3), *J* = 7.2 Hz), 1.31 (d, 3H, =CHCH(CH_3), *J* = 6.3 Hz), 2.28 (bs, 1H, O*H*), 2.55 – 2.63 (m, 1H, C*H*(CH_3)CH=), 2.78 (d of d, 1H, aux. CH_AH$_B$Ar, *J* =12.9, 9.6 Hz), 3.24 – 3.27 (m, 1H, aux. CH$_A$$H_B$Ar), 3.67 (d of d, 1H, C*H*(OH), *J* = 9.6, 1.8 Hz), 3.79 – 3.81 (m, 4H, PMB OCH_3 and C(O)C*H*(CH_3)), 4.48 (d, 1H, PMB CH$_A$CH_B, *J* = 11.4 Hz), 4.65 – 4.71 (m, 1H, aux. NC*H*), 5.29 – 5.39 (m, 3H, C*H*=C*H*), 6.85 – 6.88 (m, 3H, aux. and PMB Ar*H*), 7.18 – 7.36 (m, 6H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 10.0, 18.1, 21.5, 35.6, 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.



(*S*)-4-Benzyl-3-[*cis*-(2*S*,3*R*,4*S*,7*R*)-3-(*tert*-butyldimethylsilyloxy)-7-(4-methoxy-benzyloxy)-2,4-dimethyloct-5-enoyl]-oxazolidin-2-one and (*S*)-4-benzyl-3-[*cis*-(2*S*,3*R*,4*S*,7*S*)-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 CH_2Cl_2 (0.7 mL) under N_2 at – 78 ^{o}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 ^{o}C for 5 hr. The reaction was quenched by addition of $NaHCO_3$ (sat., 2 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The organic extracts were combined, 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 (30% EtOAc/hexanes) to give 0.02 g (33% yield) of the title compound as a colourless oil (R_f =0.44), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}): 2933.0, 2856.1, 1783.1, 1703.1, 1698.9, 1694.6, 1514.6, 1385.8, 1248.2, 1210.0, 1110.1; **HRESIMS** calculated for $C_{34}H_{49}NO_6SiNa^+$ (M+Na$^+$): 618.3227; found: 618.3234.

Isomer A: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.00 (s, 6H, Si(C*H*$_3$)$_2$), 0.91 (s, 9H, SiC(C*H*$_3$)$_3$), 1.01 (d, 3H, CH(C*H*$_3$)CH=, *J* = 6.9 Hz), 1.17 – 1.31 (m, 6H, C(O)CH(C*H*$_3$) and =CHCH(C*H*$_3$)), 2.53 – 2.62 (m, 1H, C*H*(CH$_3$)CH=), 2.67 – 2.78 (m, 1H, aux. C*H*$_A$H$_B$Ar), 3.18 – 3.32 (m, 1H, aux. CH$_A$*H*$_B$Ar), 3.78 (s, 3H, PMB OC*H*$_3$), 3.83 – 4.02 (m, 2H, C(O)C*H*(CH$_3$) and C*H*(OTBS)), 4.08 – 4.16 (m, 2H, aux. OC*H*$_2$), 4.24 – 4.28 (m, 2H, =CHC*H*(CH$_3$) and PMB C*H*$_A$CH$_B$), 4.44 – 4.57 (m, 2H, aux. NC*H* and PMB CH$_A$C*H*$_B$), 5.33 (app. t, 1H, =C*H*, *J* = 11.4 Hz), 5.54 – 5.61 (m, 2H, C*H*=), 6.79 – 6.88 (m, 3H, aux. and PMB Ar*H*), 7.19 – 7.35 (m, 6H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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.

Isomer B: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.10 (s, 3H, Si(C*H*$_3$)$_A$), 0.11 (s, 3H, Si(C*H*$_3$)$_B$), 0.91 – 0.93 (m, 9H, Si(C(C*H*$_3$)$_3$), 0.97 (d, 3H, CH(C*H*$_3$)CH=, *J* = 6.9 Hz), 1.17 – 1.31 (m, 6H, C(O)CH(C*H*$_3$) and =CHCH(C*H*$_3$)), 2.42 – 2.52 (m, 1H, C*H*(CH$_3$)CH=), 2.67 – 2.78 (m, 1H, aux. C*H*$_A$H$_B$Ar), 3.18 – 3.32 (m, 1H, aux. CH$_A$*H*$_B$Ar), 3.73 (s, 3H, PMB OC*H*$_3$), 3.83 – 4.02 (m, 2H, C(O)C*H*(CH$_3$) and C*H*(OTBS)), 4.08 – 4.16 (m, 2H, aux. OC*H*$_2$), 4.33 – 4.37 (m, 1H, =CHC*H*(CH$_3$) and PMB C*H*$_A$H$_B$), 4.44 – 4.57 (m, 2H, aux. NC*H* and PMB CH$_A$*H*$_B$), 5.41 (app. t,

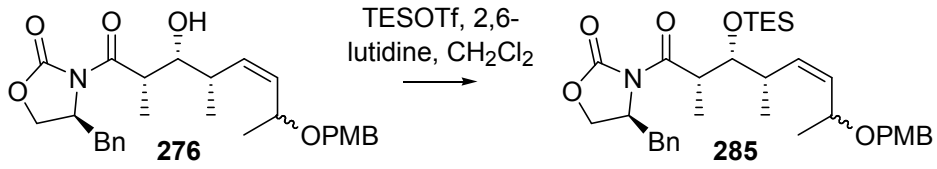
1H, =C*H*, *J* = 8.7 Hz), 5.54 – 5.61 (m, 1H, C*H*=), 6.79 – 6.88 (m, 3H, aux. and PMB Ar*H*), 7.19 – 7.35 (m, 6H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 3.4, – 3.3, 12.8, 15.3, 17.7, 18.4, 21.6, 26.1, 37.58, 37.63, 42.6, 55.2, 55.6, 66.0, 69.3, 71.2, 76.2, 113.66, 127.3, 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_2Cl_2 (0.5 mL) under N_2 at -78 ^oC 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 ^oC 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_2Cl_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_2Cl_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_2Cl_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_2Cl_2 (0.05 mL) under N_2 at 0 ^oC 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 ^oC. 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_2O used as eluent). The organic phase was washed with HCl (10%, 1 x 20 mL), H_2O (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 purifed 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 ^oC 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 Et_2O (4 mL) and the mixture was filtered through celite (Et_2O used as eluent). The organic phase was washed with H_2O (3 x 15 mL), HCl (10%, 1 x 25 mL), H_2O (1 x 25 mL), $NaHCO_3$ (sat., 1 x 25 mL) and brine (1 x 25 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.07 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.



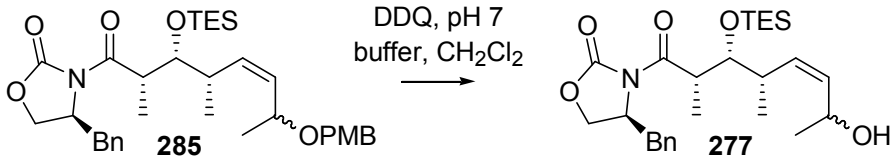
(*S*)-4-Benzyl-3-[*cis*-(2*S*,3*R*,4*S*,7*R*)-7-(4-methoxybenzyloxy)-2,4-dimethyl-3-triethyl-silyloxyoct-5-enoyl]-oxazolidin-2-one and (*S*)-4-benzyl-3-[*cis*-(2*S*,3*R*,4*S*,7*S*)-7-(4-methoxybenzyloxy)-2,4-dimethyl-3-triethyl-silyloxyoct-5-enoyl]-oxazolidin-2-one (285)

To a stirring solution of alcohol **276** (0.15 g, 0.31 mmol) in dry CH_2Cl_2 (1.8 mL) under N_2 at – 78 ^oC 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 ^oC for 30 min. The reaction was quenched by addition of $NaHCO_3$ (sat., 5.5 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL). The organic extracts were combined, dried ($MgSO_4$), 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 (CH_2Cl_2) to give 0.18 g (100% yield) of the title compound as a colourless oil (R_f = 0.36), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}): 2960.0, 1783.3, 1698.9, 1514.4, 1245.9; **HRESIMS** calculated for $C_{34}H_{49}NO_6SiNa^+$ ($M+Na^+$): 618.3227; found: 618.3213.

Isomer A: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.58 – 0.68 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.95 – 1.02 (m, 12H, Si(CH$_2$C*H*$_3$)$_3$ and CH(C*H*$_3$)CH=), 1.18 (d, 3H, C(O)CH(C*H*$_3$), *J* = 6.9 Hz), 1.25 (d, 3H, =CHCH(C*H*$_3$), *J* = 6Hz), 2.51 – 2.59 (m, 1H, C*H*(CH$_3$)CH=), 2.69 – 2.79 (m, 1H, aux. C*H*$_A$H$_B$Ar), 3.21 – 3.29 (m, 1H, aux. CH$_A$*H*$_B$Ar), 3.79 (s, 3H, PMB OC*H*$_3$), 3.95 – 3.99 (m, 1H, C*H*(OTES)), 4.13 – 4.15 (m, 2H, aux. OC*H*$_2$), 4.24 – 4.28 (m, 1H, PMB C*H*$_A$H$_B$), 4.33 – 4.37 (m, 1H, =CHC*H*(CH$_3$)), 4.46 – 4.52 (m, 1H, PMB CH$_A$*H*$_B$ and aux. NC*H*), 5.43 (d, 1H, =C*H*, *J* = 8.4 Hz), 5.53 (app. t, 1H, C*H*=, *J* = 10.5 Hz), 6.82 – 6.88 (m, 3H, aux. and PMB Ar*H*), 7.20 – 7.35 (m, 6H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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) δ (ppm) 0.58 – 0.68 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.95 – 1.02 (m, 9H, Si(CH$_2$C*H*$_3$)$_3$ and CH(C*H*$_3$)CH=), 1.22 (d, 3H, C(O)CH(C*H*$_3$), *J* = 6.9 Hz), 1.30 (d, 3H, =CHCH(C*H*$_3$), *J* = 6.3 Hz), 2.41 – 2.48 (m, 1H, C*H*(CH$_3$)CH=), 2.69 – 2.79 (m, 1H, aux. C*H*$_A$H$_B$Ar), 3.21 – 3.29 (m, 1H, aux. CH$_A$*H*$_B$Ar), 3.79 (s, 3H, PMB OC*H*$_3$), 3.86 – 3.92 (m, 2H, C(O)C*H*(CH$_3$) and C*H*(OTES)), 4.13 – 4.15 (m, 2H, aux. OC*H*$_2$), 4.24 – 4.28 (m, 1H, =CHC*H*(CH$_3$)), 4.33 – 4.37 (m, 1H, PMB C*H*$_A$CH$_B$), 4.46 – 4.52 (m, 1H, PMB CH$_A$C*H*$_B$), 4.56 – 4.60 (m, 1H, aux. NC*H*), 5.36 (app. quart, 1H, =C*H*, *J* = 9.6 Hz), 5.53 (app. t, 1H, C*H*=, *J* = 10.5 Hz), 6.82 – 6.88 (m, 3H, aux. and PMB Ar*H*), 7.20 – 7.35 (m, 6H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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.



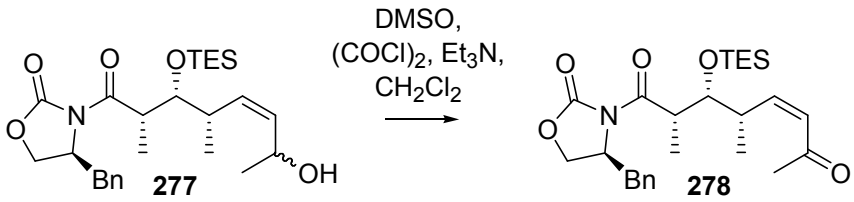
(*S*)-4-Benzyl-3-(*cis*-(2*S*,3*R*,4*S*,7*R*)-7-hydroxy-2,4-dimethyl-3-triethylsilanyloxy-oct-5-enoyl)-oxazolidin-2-one and (*S*)-4-benzyl-3-(*cis*-(2*S*,3*R*,4*S*,7*S*)-7-hydroxy-2,4-dimethyl-3-triethylsilanyloxy-oct-5-enoyl)-oxazolidin-2-one (277)

To a stirring solution of PMB ether **285** (0.18 g, 0.30 mmol) in dry CH_2Cl_2 (7.5 mL) at RT was added pH 7 buffer (0.75 mL) and the two-phase mixture was cooled to 0 ^oC. To this solution was added DDQ (0.08 g, 0.36 mmol) and the resulting black mixture was stirred at 0 ^oC for 2 hr. The mixture was diluted with CH_2Cl_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_2Cl_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_2Cl_2 → 5% Et_2O/CH_2Cl_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_2O/CH_2Cl_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 $C_{26}H_{41}NO_5SiNa^+$ ($M+Na^+$): 498.2652; found: 498.2645.

Isomer A: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.58 – 0.70 (m, 6H, $Si(CH_2CH_3)_3$), 0.95 – 1.02 (m, 12H, $Si(CH_2CH_3)_3$ and $CH(CH_3)CH$=), 1.18 – 1.30 (m, 6H, $C(O)CH(CH_3)$ and $=CHCH(CH_3)$), 1.87 (bs, 1H, O*H*), 2.54 – 2.64 (m, 1H, $CH(CH_3)CH$=), 2.72 – 2.79 (m, 1H, aux. CH_AH_BAr), 3.20 – 3.28 (m, 1H, aux. CH_AH_BAr), 3.85 (app. quart, 1H, $C(O)CH(CH_3)$, *J* = 6.9 Hz), 3.91 – 3.94 (m, 1H, C*H*(OTES)), 4.13 – 4.23 (m, 2H, aux. OCH_2), 4.58 – 4.67 (m, 2H, aux. NC*H* and $=CHCH(CH_3)$), 5.22 – 5.46 (m, 2H, C*H*=C*H*), 7.20 – 7.36 (m, 5H, aux. Ar*H*); **^{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.

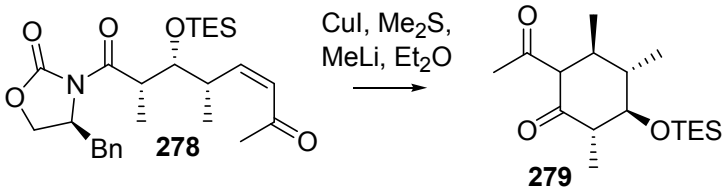
Isomer B: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.58 – 0.70 (m, 6H, Si(CH_2CH_3)$_3$), 0.95 – 1.02 (m, 12H, Si(CH_2CH_3)$_3$ and CH(CH_3)CH=), 1.18 – 1.30 (m, 6H, C(O)CH(CH_3) and =CHCH(CH_3)), 1.87 (bs, 1H, O*H*), 2.54 – 2.64 (m, 1H, C*H*(CH_3)CH=), 2.72 – 2.79 (m, 1H, aux. CH_AH_BAr), 3.20 – 3.28 (m, 1H, aux. CH_AH_BAr), 3.85 (app. quart, 1H, C(O)C*H*(CH_3), J = 6.9 Hz), 3.91 – 3.94 (m, 1H, C*H*(OTES)), 4.13 – 4.23 (m, 2H, aux. OCH_2), 4.58 – 4.67 (m, 2H, aux. NC*H* and =CHC*H*(CH_3)), 5.22 – 5.46 (m, 2H, C*H*=C*H*), 7.20 – 7.36 (m, 5H, aux. Ar*H*); **^{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*-(2*S*,3*R*,4*S*)-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_2Cl_2 (1.5 mL) under N_2 at – 78 ^oC was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 0.22 mL, 0.44 mmol) and the solution was stirred at – 78 ^oC for 30 min. To this solution was added dropwise a solution of alcohol **277** (0.14 g, 0.29 mmol) in dry CH_2Cl_2 (1 mL) *via* cannula (0.5 mL rinse), and the resulting cloudy pale yellow solution was stirred at – 78 ^oC for 45 min. To this solution was added dropwise Et_3N (0.24 mL, 1.74 mmol) and the resulting slurry was stirred at – 78 ^oC for 30 min, after which time it was warmed to 0 ^oC. 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_2O (3 x 5 mL), the organic extracts were combined and solvent was removed *in vacuo*. The concentrate was diluted with Et_2O (20 mL) and washed with $NaHSO_4$ (1 M, 3 x 20 mL), H_2O (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_2Cl_2) to give 0.10 g (71% yield) of the title compound as a colourless oil (R_f = 0.14).

$[\alpha]_D^{20}$ = + 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) δ (ppm) 0.57 – 0.65 (m, 6H, Si(CH_2CH$_3$)$_3$), 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_AH$_B$Ar, *J* = 12.9, 9.6 Hz), 3.28 (d of d, 1H, aux. CH$_A$$H_B$Ar, *J* = 12.9, 3 Hz), 3.58 – 3.70 (m, 1H, C*H*(CH$_3$)CH=), 3.81 – 3.90 (m, 1H, C(O)C*H*(CH$_3$)), 3.95 (app. t, 1H, C*H*(OTES), *J* = 5.6 Hz), 4.18 – 4.26 (m, 2H, aux. OCH_2), 4.67 – 4.73 (m, 1H, aux. NC*H*), 6.04 – 6.16 (m, 2H, C*H*=C*H*), 7.22-7.37 (m, 5H, aux. Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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 $C_{26}H_{39}NO_5SiNa^+$ (M+Na$^+$): 496.2496; found: 496.2495.

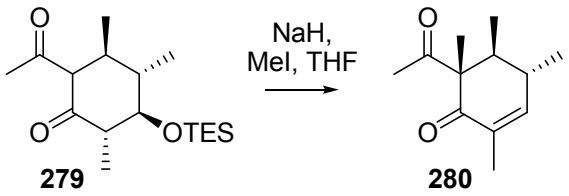


(3*S*,4*S*,5*R*,6*S*)-2-Acetyl-5-triethylsilyloxy-3,4,6-trimethylcyclohexanone (279)

To a stirring suspension of CuI (0.08 g, 0.42 mmol) in dry Et_2O (1 mL) and dry Me_2S (2 mL) under N_2 at RT was added dropwise MeLi (1.6 M in Et_2O, 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_2O (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_2O (5 mL) and the reaction was quenched by slow addition of a 10% NH_4OH/90% NH_4Cl 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_2O (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_2Cl_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 ^{1}H NMR.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.62 – 0.70 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.95 – 1.00 (m, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.99 (d, 3H, C(O)CHCH(C*H*$_3$), *J* = 6.9 Hz), 1.09 (d, 6H, C(O)CH(C*H*$_3$) and CH(C*H*$_3$)CH(OTES), *J* = 6.6 Hz), 1.50 – 1.63 (m, 1H, C*H*(CH$_3$)CH(OTES)), 1.74 – 1.88 (m, 1H, C(O)CHC*H*(CH$_3$)), 2.18 (s, 3H, C*H*$_3$C(O)), 2.45 – 2.57 (m, 1H, C(O)C*H*(CH$_3$)), 3.15 (app. t, 1H, C*H*(OTES), *J* = 9.6 Hz), 3.23 (d, 1H, C(O)C*H*C(O), *J* = 12.3 Hz); **^{13}C 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.



279 **280**

(4*R*,5*S*,6*S*)-6-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 ^{o}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 ^{o}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 ^{o}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}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.85 (d, 3H, C(CH_3)CH(C*H*$_3$), *J* = 6.0 Hz), 1.15 (s, 3H, C(C*H*$_3$)), 1.19 (d, 3H, =CHCH(C*H*$_3$), *J* = 6.6 Hz), 1.78 – 1.79 (m, 3H, (C*H*$_3$)C=), 2.10 (s, 3H, C*H*$_3$(CO)), 2.22 – 2.28 (m, 2H, =CHC*H*(CH_3) and C(CH_3)C*H*(CH_3)), 5.84 (s, 1H, =C*H*); **^{1}H NMR** (C_6D_6, 300 MHz) δ (ppm) 0.49 (d, 3H, C(CH_3)CH(C*H*$_3$), *J* = 6.9 Hz), 0.97 (d, 3H, =CHCH(C*H*$_3$), *J* = 7.2 Hz), 1.09 (s, 3H, C(C*H*$_3$)), 1.52 – 1.65 (m, 1H, =CHC*H*(CH_3)), 1.69 – 1.70 (m, 3H, (C*H*$_3$)C=), 1.85 – 1.92 (m, 1H, C(CH_3)C*H*(CH_3)), 1.92 (s, 3H, C*H*$_3$(CO)), 5.84 (s, 1H, =C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (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 $C_{12}H_{18}O_2H^+$ ($M+H^+$): 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_2O (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_2O (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).

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