Chapter Four

Studies Towards Tridachiahydropyrone

4 Studies Towards Tridachiahydropyrone

This chapter extends the application of complex cis enones to syn cyclohexenone synthesis. Detailed is the preparation of a cis enone, which is converted via a syn cyclohexenone to a model system of syn tridachiahydropyrone. Attempts at the preparation of the natural product are also discussed.

4.1 A complex *cis* enone as a common precursor

The utility of *cis* enones in the formation of *syn* cyclohexenones was demonstrated in Chapter 3. The application of this methodology to the synthesis of *syn* tridachiahydropyrone (**42**) was thus investigated. To this end, a *cis* enone of type **286** (Figure 4.1) was required, which would allow the requisite γ-pyrone moiety to be assembled. Additionally, *cis* enone **286** could be utilised to synthesise both model system **282** of *syn* tridachiahydropyrone (**42**), and the proposed natural product **42**.

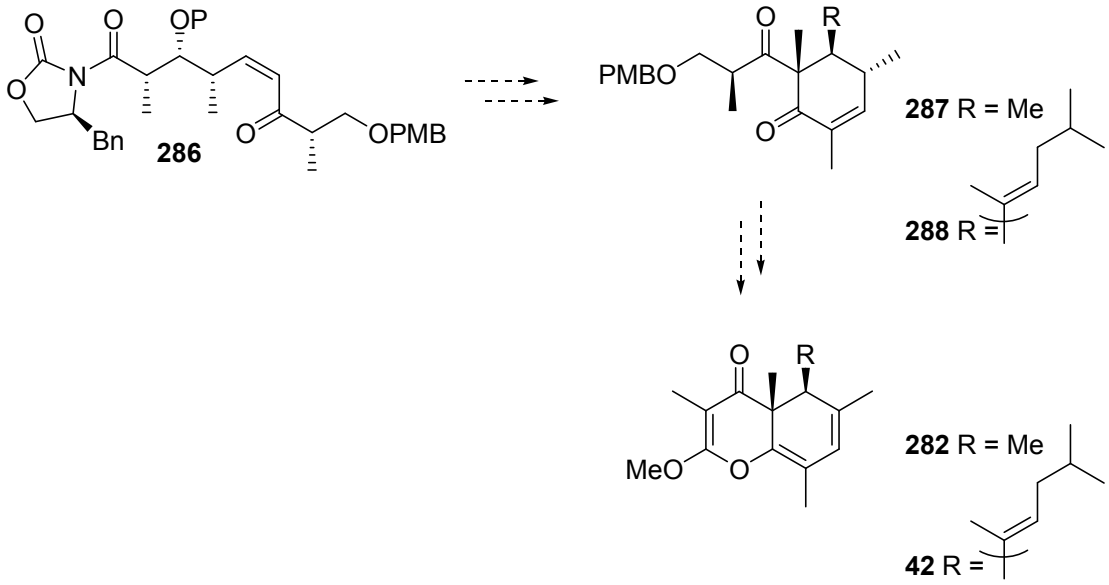


*Figure 4.1. Cis enone **286** as the common precursor.*

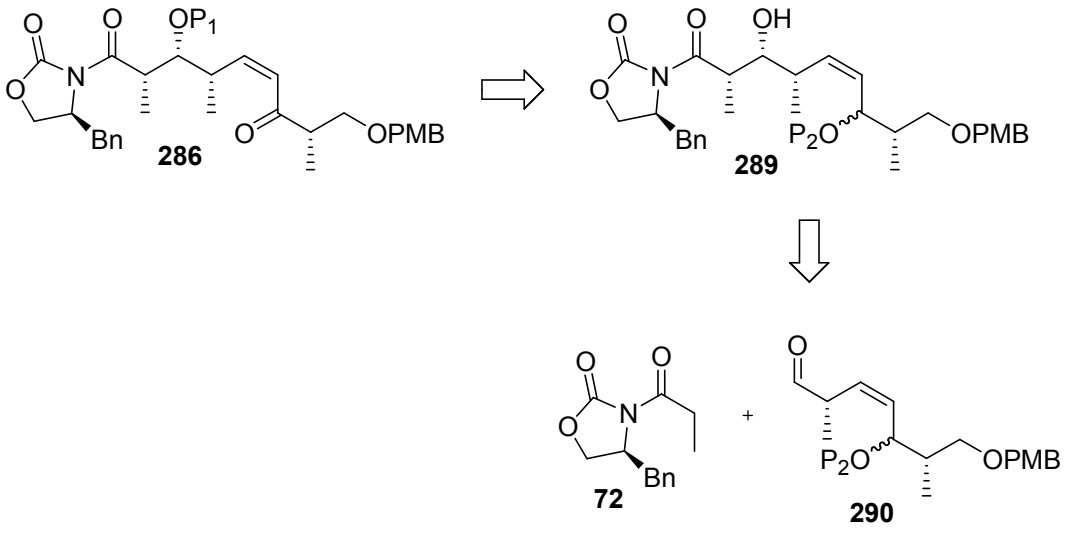
The issue of which protecting group (P) to use in *cis* enone **286** (Figure 4.1) needed to be addressed, due to the steric issues encountered with the use of the *tert*-butyldimethylsilyl (TBS) group (Chapter 3, Section 3.3.3.2) and the lability of the

triethylsilyl (TES) group (Chapter 3, Section 3.3.4) as identified in previous studies of *cis* enone systems. It was believed, however, that with an appropriate protecting group *cis* enone **286** would be a suitable precursor. Depending on which cuprate *cis* enone **286** was coupled to (Figure 4.1), either model system **282** (where R is a methyl group) or the proposed natural product **42** (where R is the alkene side-chain) could be synthesised *via* the corresponding *syn* cyclohexenone **287** or **288**, respectively.

The synthetic approach towards *cis* enone **286** was largely based on the methodology developed in Chapter 3 (Section 3.3.3) towards *cis* enones of this type, and is discussed in the following section.

4.1.1 Synthesis of a *cis* enone

Based on previous work with these systems, it was envisaged that *cis* enone **286** could be synthesised from alcohol **289** (Scheme 4.1), which itself could be obtained from the coupling of Evans auxiliary **72** and aldehyde **290**.

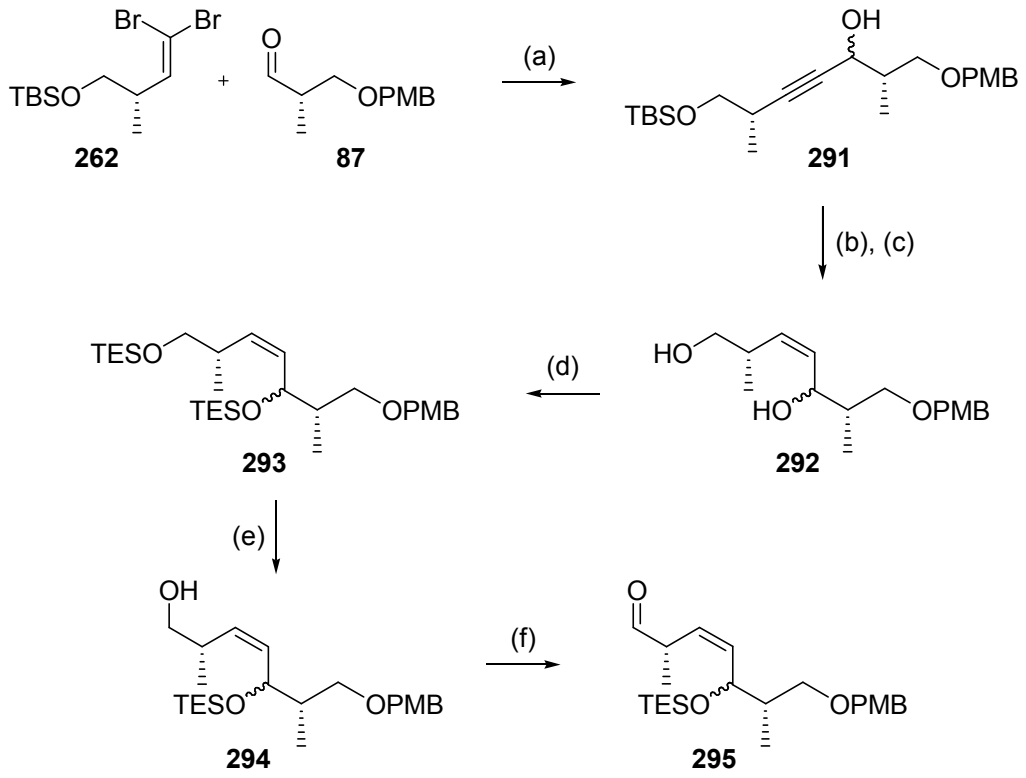


*Scheme 4.1. Proposed retrosynthesis of cis enone **286** to a complex aldehyde.*

Thus, based on the retrosynthetic analysis of *cis* enone **286** depicted in Scheme 4.1, the preparation of an aldehyde such as **290** was required.

4.1.1.1 Synthesis of a complex aldehyde

The preparation of an aldehyde of type **290** (Scheme 4.2) began with the coupling of alkyne **258** (generated *in situ* from di-bromoalkene **262**) with aldehyde **87**,[1] the preparation of which was described in Chapter 2 (Section 2.3.1).



Reagents and conditions. (a) i. **262**, *n*-BuLi, THF, – 40 °C → RT. ii. **87**, – 78 °C, 100%; (b) HF-pyr/pyr, – 20 °C, 80%; (c) Lindlar's catalyst, quinoline, H_2, MeOH, RT, 100%; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, – 78 °C, 92%; (e) HF-pyridine/pyridine, – 20 °C, 75% over three cycles from **292**; (f) DMP, CH_2Cl_2, RT, 78%.

*Scheme 4.2. Synthesis of aldehyde **295**.*

Propargylic alcohol **291** was formed in excellent yield (Scheme 4.2) and was converted to a diol by removal of the TBS group at – 20 °C using pyridinium hydrofluoride buffered with excess pyridine.[2] These mild reaction conditions were found to be necessary, as the use of tetrabutylammonium fluoride (TBAF) and/or higher temperatures resulted in decomposition of the product. The subsequent reduction to give **292** was carried out once again using Lindlar's catalyst poisoned

with quinoline. However, the use of MeOH as the solvent was required in this case,[3] as the diol was not solubilised to a satisfactory extent in hexane. It was also found that the reduction was significantly dependent on steric influences. In the presence of the TBS group, the reduction of **291** occurred in just under two weeks, while the absence of the TBS group allowed the reduction to give **292** to occur in as little as one hour. The purification of diol **292** was also simplified by the use of a washing procedure employing 10% HCl,[4] which removed the quinoline, leaving pure diol **292** and negating the need for purification by column chromatography.

In order to successfully synthesise aldehyde **295**, the secondary alcohol of diol **292** had to be protected with a suitable protecting group. The protecting group needed to possess two main qualities. The first was that it needed to be more labile than the group used to protect *syn* aldol product **289** (Scheme 4.1), as it needed to be removed in the presence of P_1 (Scheme 4.1). The second property was that it needed to be robust enough to allow the primary hydroxyl of diol **292** to be liberated, while allowing the secondary hydroxyl to remain protected.

At this stage, it was postulated that the protection of *syn* aldol product **289** would be attempted again using a TBS group, and therefore based on this fact, as well as the two requirements discussed previously, it was decided that the TES group would be the most appropriate choice for the protection of the secondary alcohol of **292**. Diol **292** was thus converted to *bis*-silyl ether **293**[5] in excellent yield, and the selective deprotection of the primary alcohol was attempted.

While a number of different variations on the method described by Askin *et al*[6] were explored (using a mixture of AcOH, THF and H_2O), in each case primary alcohol **294** was not recovered in suitable quantities, due to double-deprotection occurring at the same time to give diol **292** in large quantities. It was found that pyridinium hydrofluoride in excess pyridine[2] at – 20 ^{o}C was a more suitable method, as it allowed the deprotection to occur at a fairly slow rate. The reaction could therefore be quenched just as all the starting material was consumed, which, after purification, gave a 1:1 mixture of diol **292** to primary alcohol **294**. Diol **292** could then be protected again to give *bis*-silyl ether **293** followed by exposure to the deprotection conditions. It was found that when this cycle was repeated three times, the yield of

primary alcohol **294** from diol **292** was 75%. The oxidation of alcohol **294** using Dess-Martin Periodinane (DMP)[7] gave aldehyde **295** in good yield as a mixture of two isomers, as evidenced by ^{1}H NMR (Figure 4.2).

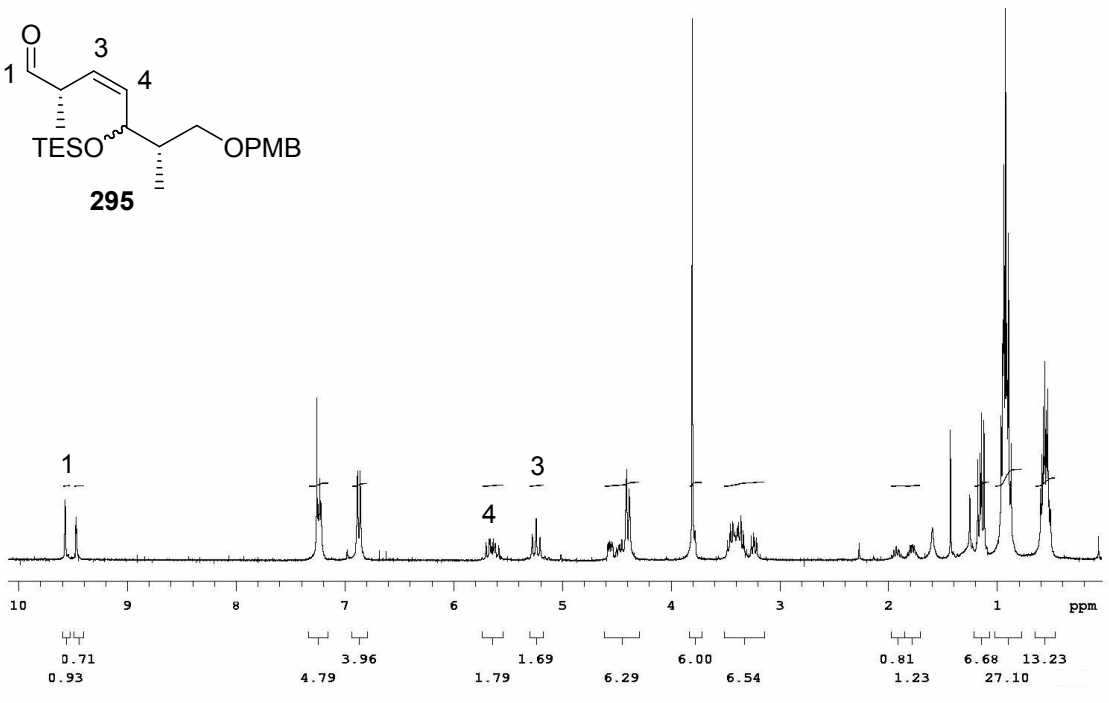


*Figure 4.2. ^{1}H NMR spectrum of aldehyde **295** in $CDCl_3$ at 300 MHz.*

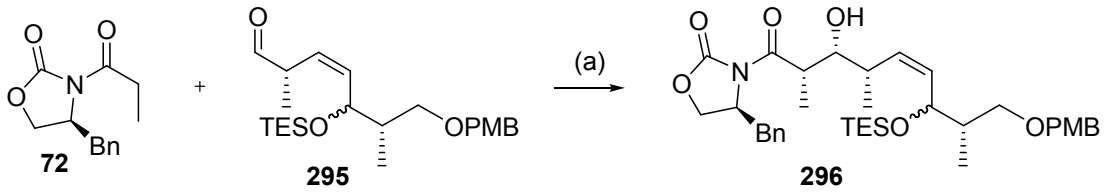
The diagnostic aldehyde proton appears as a doublet at δ 9.47 for one isomer and at δ 9.57 for the other isomer and couples to the adjacent methine proton, which appears as a multiplet at δ 3.31 – 3.48 for both isomers. This methine proton couples to the adjacent methyl protons, which appear as a doublet at δ 1.13 for one isomer and at δ 1.17 for the other isomer. The multiplet at δ 3.31 – 3.48 is also due to the methylene protons adjacent to the O-*p*-methoxybenzyl (PMB) group. Two protons of one isomer and one proton of the other isomer appear at this shift, while the other oxymethylene proton appears as a doublet of doublets at δ 3.24. The multiplicity of this proton can be attributed to it coupling also to the adjacent methine proton, which appears as a multiplet at δ 1.74 – 1.82 for one isomer and at δ 1.89 – 1.97 for the other isomer. This methine proton couples to the adjacent methyl protons, which appear as part of a multiplet at δ 0.87 – 0.96, along with the methylene protons of the TES group. The oxymethine proton appears as part of a multiplet at δ 4.38 – 4.58 for

both isomers, along with the methylene protons of the PMB group, and couples to the adjacent vinyl proton, which appears as a multiplet at δ 5.58 – 5.70. The other vinyl proton appears as an apparent triplet at δ 5.24 and the coupling constant between the two vinyl protons (J = 10.7 Hz) is indicative of a *cis* alkene. The remaining peaks can be attributed to the protons of the TES group, which appear as a multiplet at δ 0.51 – 0.60, and the PMB group, which appear at δ 3.80, δ 6.86 – 6.89 and δ 7.22 – 7.26, for both isomers. The ^{13}C NMR spectrum further corroborated the structural assignment with the carbon of the aldehyde group appearing at δ 201.0 for one isomer and at δ 201.3 for the other isomer. High resolution mass spectrometry confirmed the expected composition of $C_{23}H_{38}O_4Si$.

Thus, aldehyde **295** was synthesised in 43% yield over eight steps from bromoalkene **262** (Scheme 4.2). The route involved the use of a differential protection strategy, where the more labile primary TES group was cleaved in the presence of a secondary TES group. With aldehyde **295** in hand, the formation of a *cis* enone was pursued.

4.1.1.2 Synthesis of a cis enone

The first step towards the synthesis of a *cis* enone involved an aldol coupling of aldehyde **295** with Evans auxiliary **72** to form *syn* alcohol **296** (Scheme 4.3).



Reagents and conditions. (a) i. **72**, $TiCl_4$, (–)-sparteine, CH_2Cl_2, 0 °C. ii. *N*-methyl-2-pyrrolidinone, – 78 °C. iii. **295**, – 78 °C → – 50 °C, 73%.

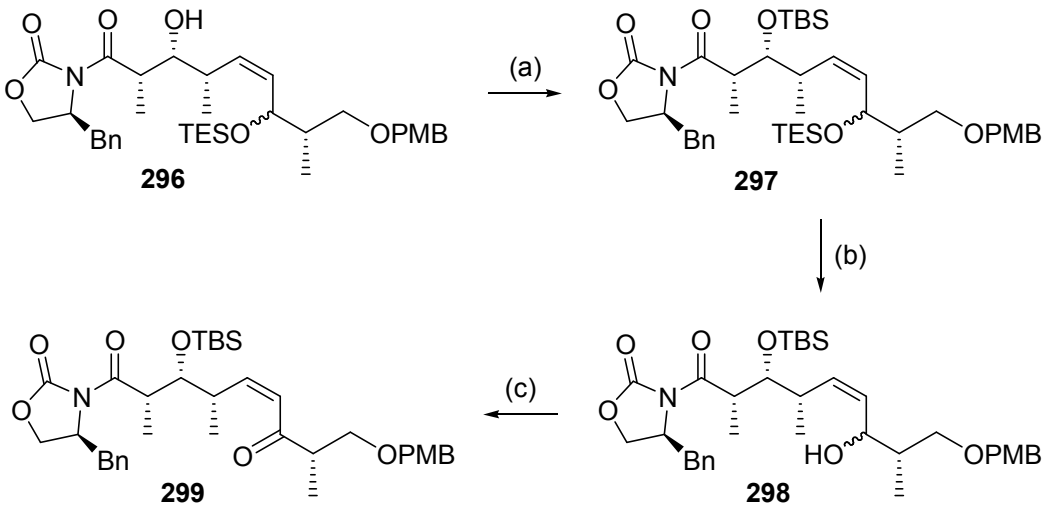
*Scheme 4.3. Formation of syn alcohol **296** by coupling of aldehyde **295** and Evans auxiliary **72**.*

The initial attempt at the formation of *syn* alcohol **296** (Scheme 4.3) involved generating the boron enolate of auxiliary **72** under the same conditions as had been

used previously for reactions of this type.[8] However, only aldehyde **295** and auxiliary **72** were recovered, and this was found to be the case even when the reaction was warmed to room temperature. It was postulated that this lack of reactivity may be due to steric hindrance between the enolate of **72** and aldehyde **295**. The bulky ligands of the boron in the enolate of **72** and the TES group of aldehyde **295** may have hindered the approach of aldehyde **295** to the enolate of **72**, resulting in no reaction occurring. It was deduced that a less-hindered and more reactive enolate of the auxiliary, which would also produce the desired *syn* stereochemistry in the aldol product, was required. To this end the use of a titanium enolate was explored, and it was found that the use of $TiCl_4$ with *N*,*N*-diisopropylethylamine (DIPEA) as the base[9] gave an improved, although still low, yield (39%) of *syn* aldol product **296**. Numerous attempts were made at improving the yield of alcohol **296**. It was found that warming of the reaction resulted in a diminished yield of alcohol **296** and an increase in the number of by-products, while using two equivalents of the titanium enolate gave only a slightly better yield of 41%.

In an effort to improve the yield of *syn* alcohol **296** an alternative protocol for the formation of titanium enolates was sought. A search of the literature uncovered an alternative protocol, as described in Crimmins *et al*,[10] which involved the use of (–)-sparteine as the base and *N*-methyl-2-pyrrolidinone. The advantages of this protocol were two-fold. The first was that the bulkier nature of the base meant that the reaction could be warmed up to 0 ^{o}C (leading to slightly improved conversion), without the danger of the base reacting detrimentally with the aldehyde as was the case when DIPEA was used. The second advantage was that only one equivalent of the aldehyde was required due to the use of *N*-methyl-2-pyrrolidinone. It was proposed by Crimmins *et al*[10] that the aldehyde had to be used in excess in standard aldol reactions involving $TiCl_4$, as the aldehyde acted as a ligand for the titanium and therefore was not available for reaction with the titanium enolate. Under the modified conditions, the tertiary amide was added as a ligand for the titanium, to prevent the complexation of the aldehyde to the metal from occurring. Applying this protocol to the reaction of aldehyde **295** with auxiliary **72**, using two equivalents of the titanium enolate and warming of the reaction to – 50 ^{o}C, gave *syn* aldol product **296** in a much improved yield of 73%.

Now that the problem of the aldol reaction had been solved, the next hurdle to overcome on the way to achieving the synthesis of a *cis* enone was the protection of the secondary hydroxyl group of **296** to give TBS ether **297** (Scheme 4.4).



Reagents and conditions. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, – 78 °C, 95%; (b) HF-pyr/pyr, 0 °C, 70%; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, – 78 °C → 0 °C, 78%.

*Scheme 4.4. Synthesis of cis enone **299**.*

Due to the problems encountered with the TBS protection of alcohols of type **296** before (as discussed in Chapter 3, Section 3.3.3.2), it was decided that one of the only options to improve the yield of TBS ether **297** that had not yet been investigated would be to use a large excess of both the base and the TBS trifluoromethanesulfonate (triflate). Thus, in a modified procedure to that reported by Paterson *et al*,[5] ten equivalents of TBS triflate and twelve equivalents of 2,6-lutidine were used. After seven hours at – 78 °C, an excellent yield of TBS ether **297** was obtained. The subsequent cleavage of the TES group to give alcohol **298** in good yield was achieved using pyridinium hydrofluoride buffered with excess pyridine[2] at 0 °C, and following oxidation of the liberated alcohol using Swern conditions,[11,12] *cis* enone **299** was obtained in good yield and high purity as one isomer. The ^{1}H NMR spectrum of *cis* enone **299** (Figure 4.3) indicates the presence of the requisite protons.

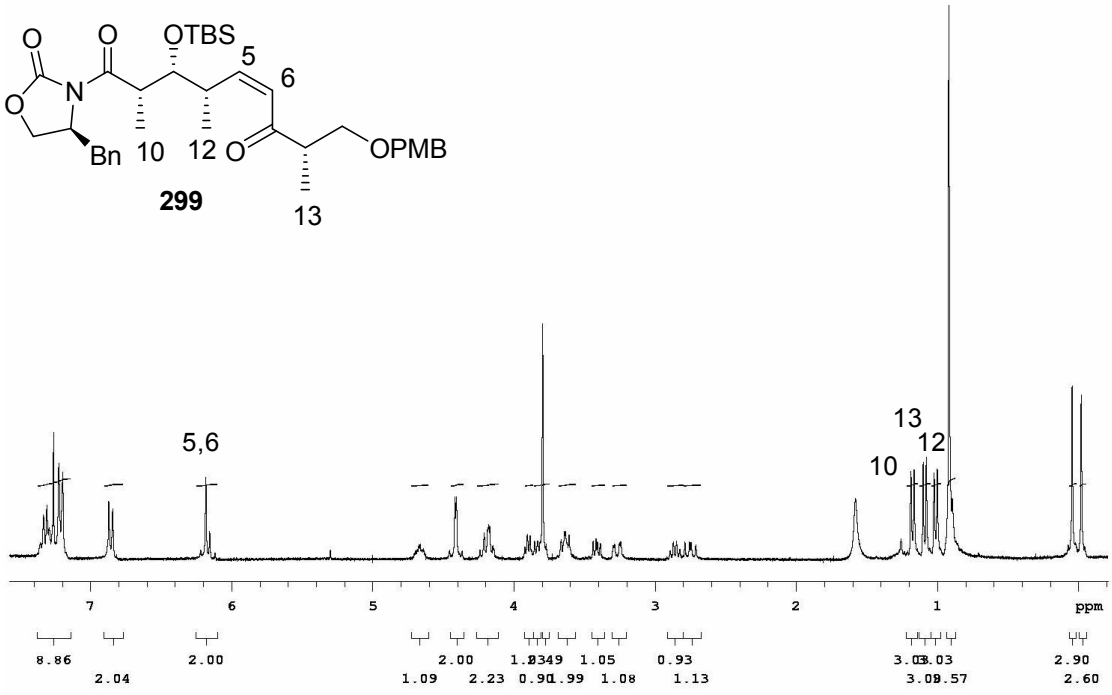
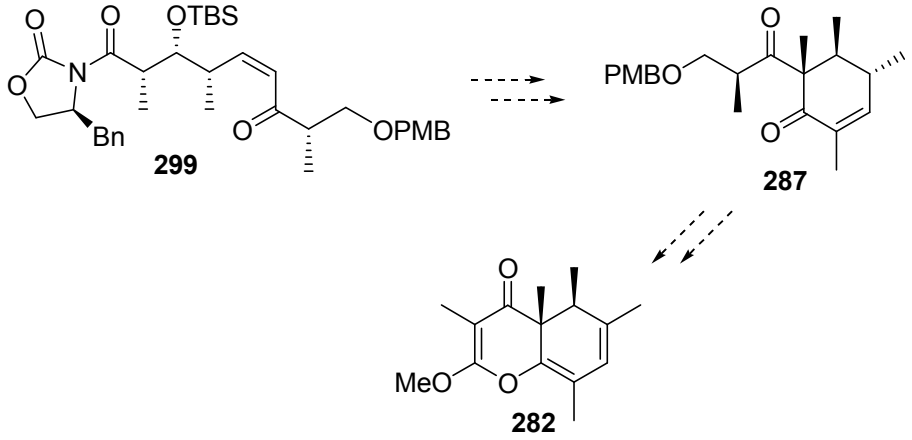


*Figure 4.3. ^{1}H NMR spectrum of cis enone **299** in $CDCl_3$ at 300 MHz.*

The two alkenyl protons appear as a multiplet at δ 6.12 – 6.22 (Figure 4.3) and the downfield position of these protons can be attributed to the electron-withdrawing nature of the adjacent carbonyl system. Additionally, these protons appear at approximately the same chemical shift as the vinyl protons of *cis* enone **278** (Chapter 3, Section 3.3.3.2), which indicates that the *cis* geometry was preserved from aldehyde **295**, through the synthetic sequence to *cis* enone **299**. The methine proton adjacent to the enone carbonyl appears as an apparent quartet at δ 2.86 and couples to both the adjacent methyl protons (which appear as a doublet at δ 1.09) and the adjacent oxymethylene protons, one of which appears as a doublet of doublets at δ 3.41 and the other as a multiplet δ 3.61 – 3.67. This multiplet is also due to the methine proton adjacent to the alkene, which couples to the adjacent methyl protons (which appear as a doublet at δ 1.01). The remaining doublet (at δ 1.18) can be attributed to the methyl adjacent to the exocyclic amide carbonyl and couples to the adjacent methine proton, which appears as a multiplet at δ 3.81 – 3.85. This methine proton couples to the adjacent oxymethine proton, which appears as a multiplet at δ 3.88 – 3.92. The protons of the PMB group appear at δ 3.80 and δ 4.41 with the aromatic protons appearing with the aromatic protons of the auxiliary, at δ 6.84 –

6.87 and δ 7.20 – 7.36. The remaining protons of the auxiliary appear at δ 2.75, δ 3.27, δ 4.15 – 4.24 and δ 4.64 – 4.70. The ^{13}C NMR spectrum further corroborated the success of the synthesis of *cis* enone **299** by the presence of three carbonyl carbons, which appeared at δ 153.1, δ 175.0 and δ 203.0. High resolution mass spectrometry confirmed the expected composition of $C_{36}H_{51}NO_7Si$.

Now that *cis* enone **299** was in hand, it was possible to attempt the synthesis of either model **282** of *syn* tridachiahydropyrone (**42**) or the proposed natural product, depending on which cuprate *cis* enone **299** was coupled with. It was decided that initially the synthesis of model system **282** would be pursued *via syn* methylated cyclohexenone **287** (Scheme 4.5).

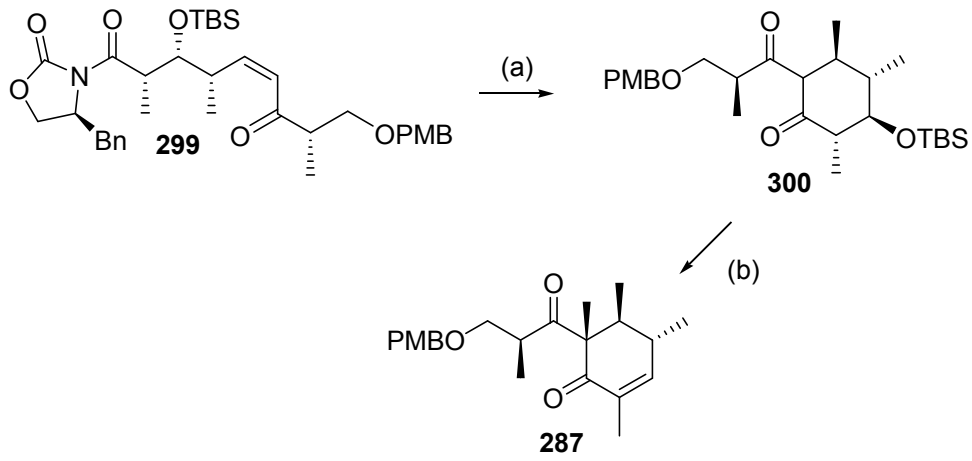


*Scheme 4.5. Proposed synthesis of model **282** via syn cyclohexenone **287**.*

4.2 Route to model system 282

4.2.1 Synthesis of *syn* methylated cyclohexenone 287

The first challenge in obtaining *syn* model **282** was being able to achieve the desired *syn* stereochemistry in cyclohexenone **287**. This had been accomplished previously with a simpler cyclohexanone system (as discussed in Chapter 3) and it was postulated that a similar synthetic methodology could be applied to prepare the more complex *syn* methylated cyclohexenone **287**. The first step involved reacting *cis* enone **299** with dimethyl cuprate (as discussed in Chapters 2 and 3), which gave cyclohexanone **300** (Scheme 4.6).



Reagents and conditions. (a) CuI, MeLi, Me_2S, Et_2O, RT, 89%; (b) i. NaH, MeI, THF, RT. ii. NaH, RT, 65%.

*Scheme 4.6. Synthesis of syn methylated cyclohexenone **287**.*

The dimethyl cuprate addition to *cis* enone **299** (Scheme 4.6) using MeLi and CuI[13] proceeded to give a high yield of cyclohexanone **300**. The stereochemistry of the addition was verified as that depicted in **300** by the large coupling constant (J = 12 Hz) between the proton situated between the two carbonyl groups and the adjacent proton (highlighted in blue), due to their antiperiplanar relationship in the favoured chair conformation of **300** (Figure 4.4).

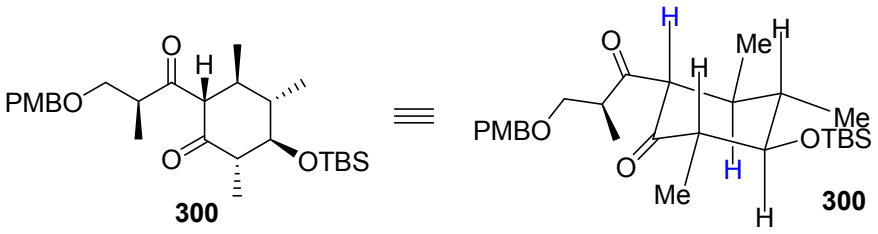


*Figure 4.4. Favoured chair conformation of cyclohexanone **300**.*

The subsequent methylation and elimination cascade of cyclohexanone **300** to give *syn* methylated cyclohexenone **287** (the stereochemistry of which was deduced as discussed later) was performed using only one equivalent of NaH and an excess of MeI to initially achieve the methylation, followed by the addition of the reaction mixture to another equivalent of NaH to promote the elimination (Scheme 4.6).[14]

This controlled methylation and elimination protocol was used to minimise the likelihood of the elimination occurring first, which may have resulted in a decrease in the stereoselectivity of the methylation, as discussed previously (Chapter 2, Section 2.1.6.3). The controlled methylation-elimination sequence was successful, with only one isomer of cyclohexenone **287** isolated in good yield. The ^{1}H NMR spectrum of *syn* methylated cyclohexenone **287** indicates the presence of the requisite protons (Figure 4.5).

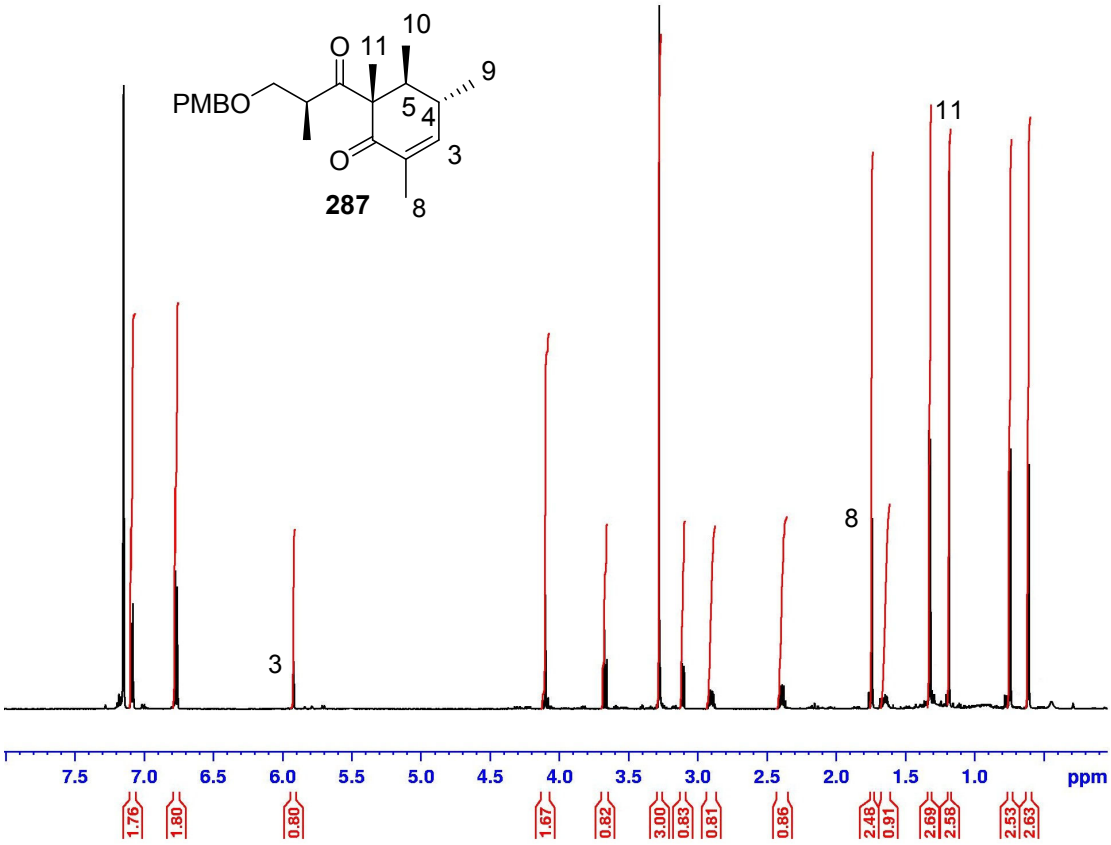


*Figure 4.5. ^{1}H NMR spectrum of syn cyclohexenone **287** in C_6D_6 at 600 MHz.*

The ^{1}H NMR spectrum of *syn* cyclohexenone **287** was obtained initially using $CDCl_3$ as the solvent, but it was found that better separation of the peaks occurred when the NMR was obtained in C_6D_6 (Figure 4.5). The presence of the diagnostic vinyl proton is immediately obvious at δ 5.94, while the vinyl methyl appears as an apparent doublet of doublets at δ 1.74. The vinyl proton couples to the adjacent methine proton, which appears as a multiplet at δ 1.62 – 1.68, and couples to both the

adjacent methyl protons (which appear as a doublet at δ 0.75) and the adjacent methine proton, which appears as a doublet of quartets at δ 2.39. This methine proton couples to the adjacent methyl protons, which appear as a doublet at δ 0.61, and the quaternary methyl protons appear as a singlet at δ 1.18. The remaining doublet at δ 1.32 can be attributed to the methyl protons of the PMB side-chain and these protons couple to the methine proton adjacent to the exocyclic carbonyl group, which appears as a quartet of triplets at δ 2.91. This methine proton also couples to the oxymethylene protons, one of which appears as a doublet of doublets at δ 3.13 and the other appears as an apparent triplet at δ 3.68. The remaining peaks at δ 3.29, δ 4.11, δ 6.75 – 6.79 and δ 7.08 – 7.10 can be attributed to the PMB group. The ^{13}C NMR spectrum further corroborated this structural assignment, with the two carbonyl peaks at δ 201.5 (due to the endocyclic carbonyl) and at δ 212.8 (due to the exocyclic carbonyl), the alkene carbons at δ 132.9 and δ 151.7, and the quaternary methyl at δ 19.0. High resolution mass spectrometry confirmed the expected composition of $C_{22}H_{30}O_4$.

While it was evident from the spectral data that the methylation-elimination cascade had been successful, the stereochemical outcome of the methylation needed to be elucidated. To this end, Nuclear Overhauser Effect Spectroscopy (NOESY) utilising selective irradiation was employed. This spectroscopic technique allows an individual proton or group of protons in a molecule to be selectively irradiated, and the protons *via* which the proton or group of protons relaxes appear as peaks in a 1-D spectrum. An example is given in Figure 4.7 (b) where the proton on C4 in **287** has been irradiated. The proton (H4) is phased negative, and the protons *via* which it relaxes appear as positive peaks.

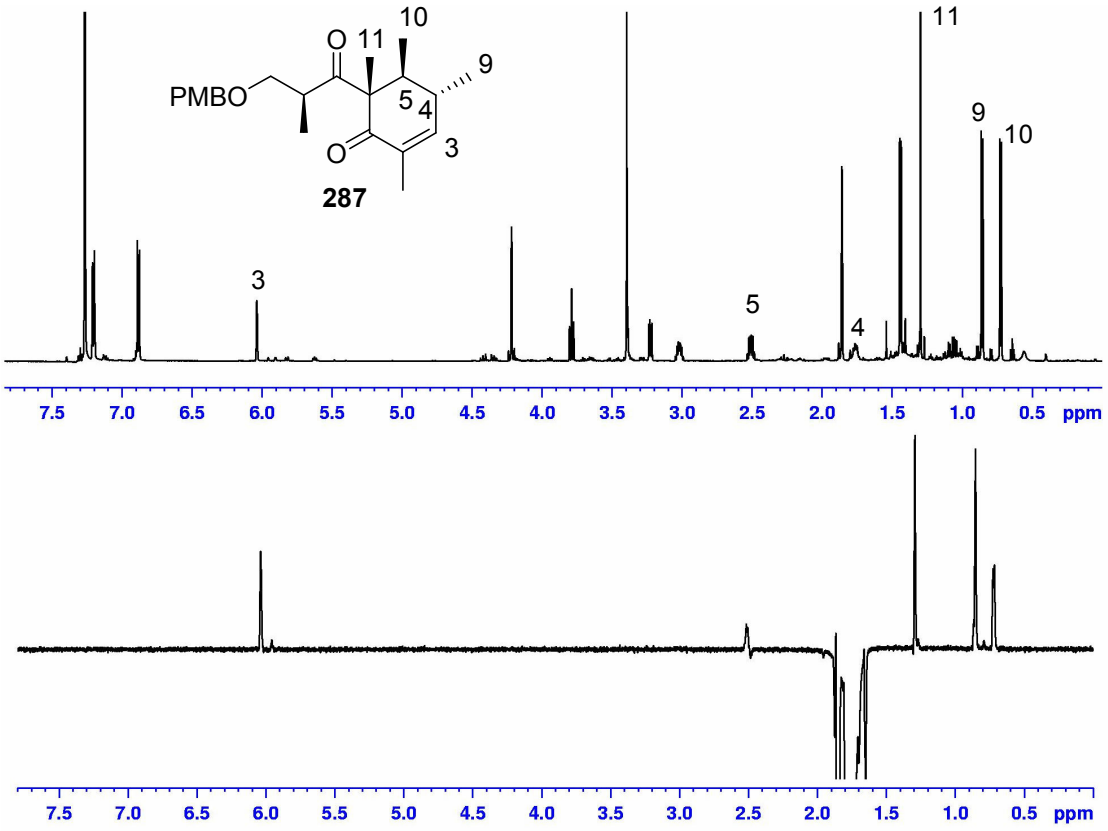


*Figure 4.6. (a) ^{1}H NMR spectrum of cyclohexenone **287** in C_6D_6 at 600 MHz. (b) Selective irradiation NOESY of H4 in C_6D_6 at 600 MHz.*

It is evident from the NOESY spectrum (Figure 4.6 (b)) that H4 relaxes *via* the protons on C10, C11 and C3, while the correlation to the protons on C5 and C9 is due to a COSY interaction. Based on this spectrum, it can be deduced that C11 must be on the same face as C10 and H4. Since the configuration of stereocentres C4 and C5 is known, it can be concluded that the methylation had indeed occurred from the axial direction to give the desired *syn* stereochemistry in cyclohexenone **287**. Other selective irradiation NOESY experiments were also conducted, which allowed the correlations depicted in Figure 4.7 to be observed.

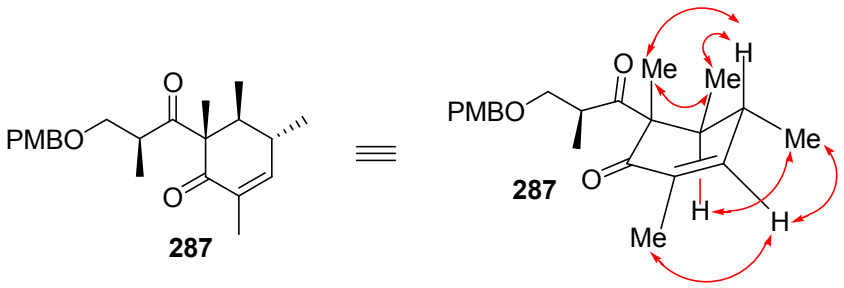
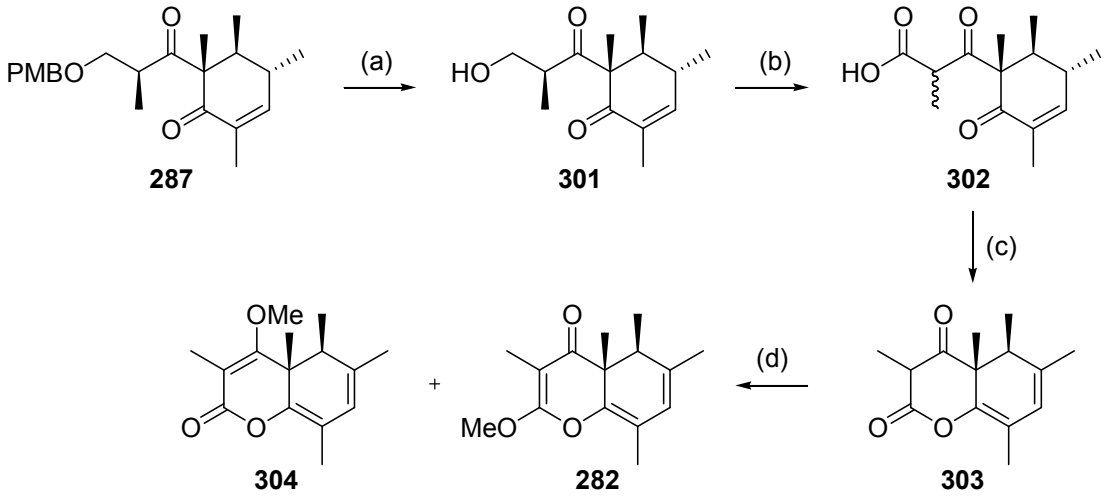


*Figure 4.7. NOESY correlations observed for syn methylated cyclohexenone **287** in C_6D_6 at 600 MHz.*

In summary, *syn* aldol product **296** was synthesised using a titanium-mediated aldol reaction between aldehyde **295** and Evans auxiliary **72**, and was successfully converted to *cis* enone **299** in 52% yield over three steps. The tandem conjugate addition-Dieckmann condensation of dimethyl cuprate with *cis* enone **299** proceeded as expected to give the desired stereochemistry in cyclohexanone **300**. The subsequent methylation of **300** and ensuing elimination produced *syn* methylated cyclohexenone **287**, the stereochemistry of which was confirmed by selective irradiation NOESY experiments. The successful synthesis of *syn* methylated cyclohexenone **287** allowed the synthesis of model system **282** to be pursued.

4.2.2 Synthesis of model system 282

The first step in the conversion of *syn* methylated cyclohexenone **287** to model system **282** involved cleaving the PMB protecting group of **287** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under buffered conditions,[15] to liberate primary alcohol **301** (Scheme 4.7).



Reagents and conditions. (a) DDQ, pH 7 buffer, CH_2Cl_2, 0 ^oC, 73%; (b) i. DMP, CH_2Cl_2, RT, 100%. ii. $NaClO_2$, $NaH_2PO_4.2H_2O$, *t*-BuOH, 2-methylbut-2-ene, RT, 66%; (c) P_2O_5-celite, CH_2Cl_2, RT, 50%; (d) CH_2N_2, Et_2O, 48% (1:1 **282**:**304**).

*Scheme 4.7. Synthesis of model system **282**.*

The subsequent oxidation of alcohol **301** to acid **302** was undertaken in two steps, as this had been deduced previously to be the best method of achieving the oxidation (Scheme 4.7).[14] The first step involved oxidation of alcohol **301** to the corresponding aldehyde using DMP,[7] which produced a mixture of two isomers of the aldehyde as a result of epimerisation of the methyl group situated between the ketone and aldehyde functionalities. The aldehyde was used crude in the subsequent oxidation, which employed $NaClO_2$ and NaH_2PO_4 in *t*-BuOH and H_2O, with the addition of 2-methylbut-2-ene, which acted as a chlorine scavenger.[16] It was found that the use of trifluoroacetic acid (TFA) in the product isolation procedure gave an improved yield of acid **302**, which was also present as a mixture of two epimers. Acid **302** could not be purified completely using conventional chromatographic methods, and even the addition of AcOH to the eluent, which had been previously found to improve the purification,[14] did not give a pure sample of acid **302**. However, exposure of **302** to dehydration conditions of P_2O_5 supported on celite[14,17,18] gave pyranone **303** in reasonable yield and good purity. Pyranone **303** existed in predominantly the *keto* form, as evidenced by ^1H NMR (Figure 4.8).

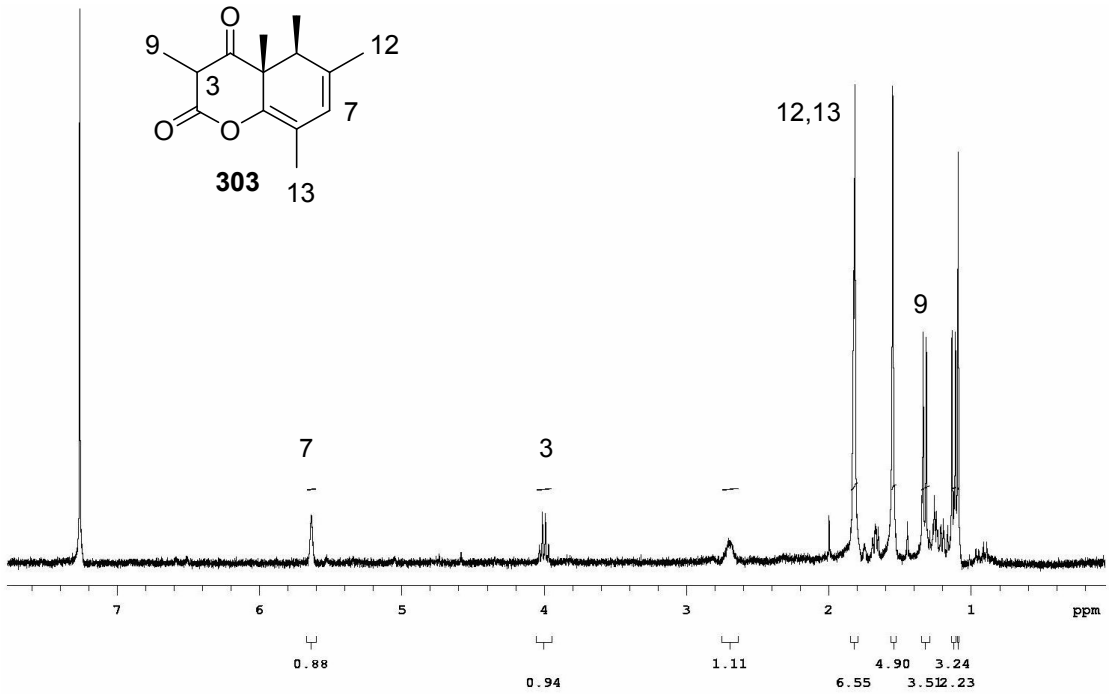
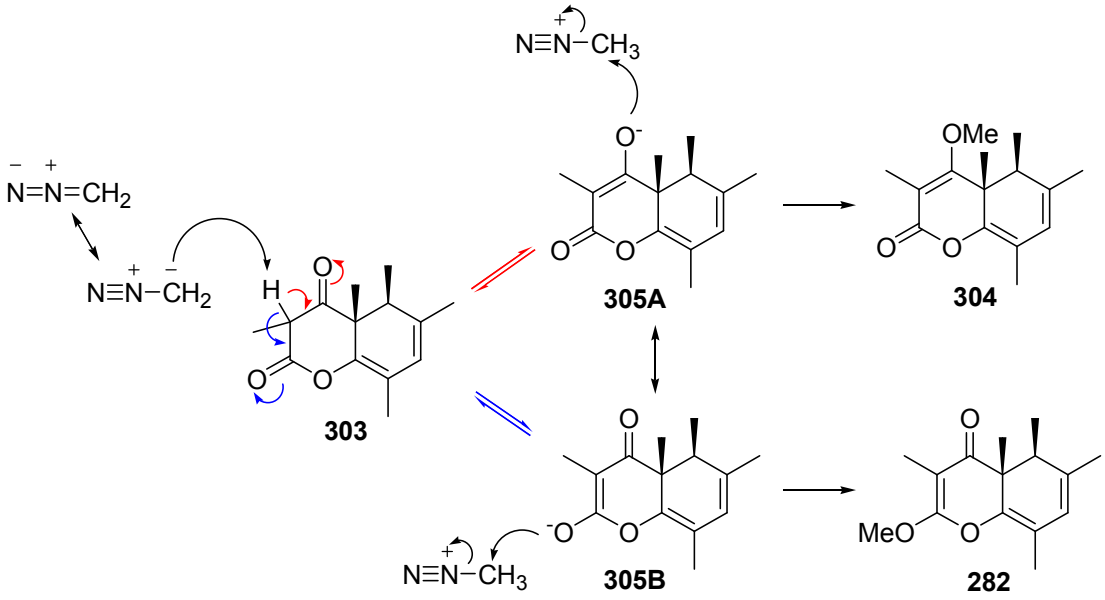


*Figure 4.8. ^{1}H NMR spectrum of pyranone **303** in $CDCl_3$ at 300 MHz.*

The vinyl proton of pyranone **303** appears as a singlet at δ 5.63, while the two sets of vinyl methyl protons appear as a single peak at δ 1.82 (Figure 4.8). The quaternary methyl appears as a singlet at δ 1.09 and the adjacent methyl methine proton appears as a multiplet at δ 2.70 – 2.78. This proton couples to the adjacent methyl protons, which appear as a doublet at δ 1.12. The remaining doublet at δ 1.33 is due to the methyl situated between the ketone and ester groups and couples to the proton on C3, which appears as a quartet at δ 4.00. The ^{13}C NMR spectrum further corroborated the structural assignment by the presence of an ester carbon at δ 167.4 and a ketone carbon at δ 203.9, and high resolution mass spectrometry confirmed the expected composition of $C_{14}H_{18}O_3$.

The subsequent methylation of pyranone **303** (Scheme 4.7) was performed by adding an excess of freshly prepared CH_2N_2 as a solution in Et_2O[19] to a solution of **303** in Et_2O at room temperature.[14,20] This resulted in the formation of γ- and α-pyrones **282** and **304** in a 1:1 ratio, which were separable by column chromatography. It was proposed that the two pyrones formed as a result of methylation of the two resonance contributors in nucleophile **305** (Scheme 4.8).



*Scheme 4.8. Proposed mechanism for the formation of α- and γ-pyrones **304** and **282** by treatment of **303** with CH_2N_2.*

Unfortunately, α-pyrone **304** decomposed quite quickly after purification and thus only a ^{1}H NMR spectrum of this compound was obtained. Fortuitously, γ-pyrone **282** (i.e. model system **282**) was stable and the ^{1}H NMR spectrum (Figure 4.9) indicates the presence of the requisite protons.

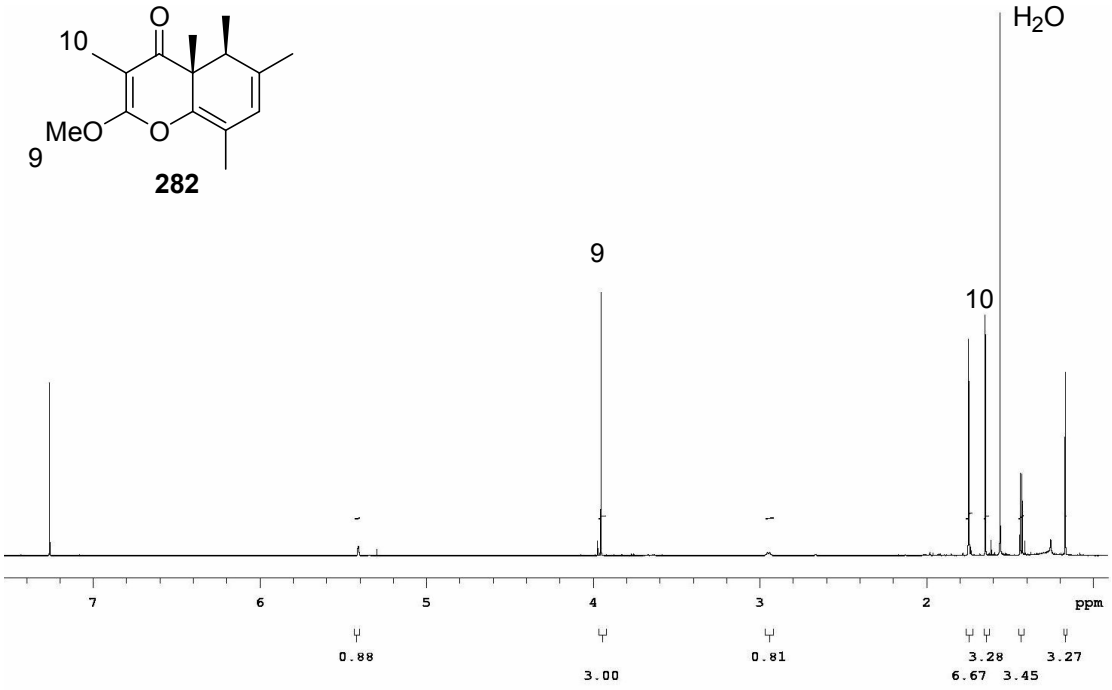
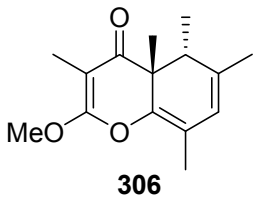


*Figure 4.9. ^{1}H NMR spectrum of γ-pyrone **282** in $CDCl_3$ at 600 MHz.*

The presence of a large singlet at δ 3.95 can be attributed to the protons of the methoxy group, and the vinyl methyl adjacent to the carbonyl has changed multiplicity and chemical shift from a doublet at δ 1.33 in pyranone **303** to a singlet at δ 1.65 in γ-pyrone **282**. The vinyl proton appears as a multiplet at δ 5.406 – 5.41 and the protons of the two vinyl methyl groups of the cyclohexadiene appear as one singlet at δ 1.75. The quaternary methyl protons appear as a singlet at δ 1.17 while the adjacent methine proton appears as a multiplet at δ 2.94 – 2.95 and couples to the adjacent methyl protons, which appear as a doublet at δ 1.43. The ^{13}C NMR spectrum provided further evidence for the presence of the γ-pyrone moiety, with a peak at δ 196.0 due to the carbonyl carbon, and the absence of the ester carbon, which appeared at δ 167.4 in the ^{13}C NMR spectrum of pyranone **303**. High resolution mass spectrometry confirmed the expected composition of $C_{15}H_{20}O_3$. The optical rotation (– 47.1) is also of the correct sign for the natural product (reported as – 476.1),[21] and it has been shown that the sign of the optical rotation is retained in the presence of the alkenyl side-chain.[22,14]

The successful synthesis of *syn* model **282** allowed some interesting comparisons to be drawn between **282** and both the natural product and *anti* model **306** (Figure 4.10) synthesised previously in the Perkins group.[14]



306

*Figure 4.10. Anti model **306**.*

4.3 Spectral analysis of model systems

A comparison of the spectral data of *syn* model **282** with *anti* model **306** yielded some significant differences between the two systems. The differences between the ^{1}H NMR of *syn* model **282** (Figure 4.11 (a)) and *anti* model **306** (Figure 4.11 (b)) are especially noticeable in the region between 1 – 3.2 ppm.

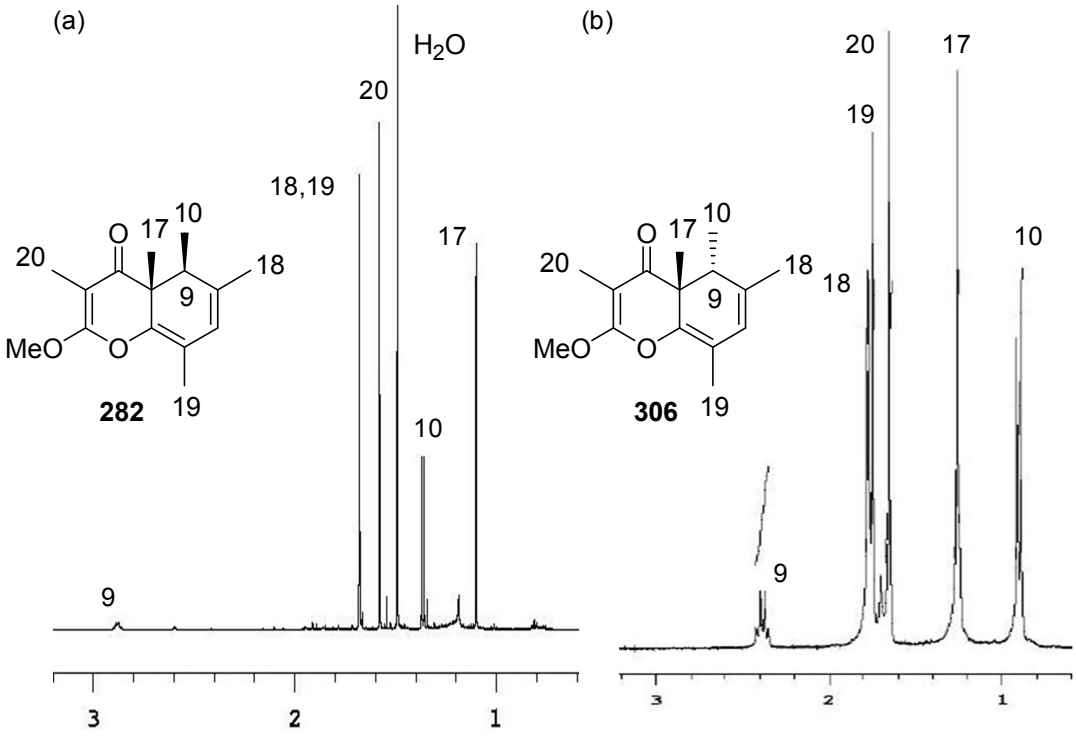


*Figure 4.11 (a) Expanded 0.6 – 3.2 ppm region of syn model **282** in $CDCl_3$ at 600 MHz; (b) Expanded 0.6 – 3.2 ppm region of anti model **306** in $CDCl_3$ at 300 MHz.*

Both models **282** and **306** have been re-numbered according to Figure 4.11 to correspond with the numbering reported for the natural product.[21] It is immediately evident that the proton on C9 appears at δ 2.95 in *syn* model **282**, which is significantly downfield of its position in *anti* model **306**, where it appears at δ 2.38. The protons on C18 and C19 are also in slightly different positions, with the protons appearing as one singlet at δ 1.75 in *syn* model **282** and as two singlets at δ 1.78 (H18) and δ 1.75 (H19) in *anti* model **306**. The biggest difference between the two spectra, however, occurs for the protons on C10 and C17, which have in effect swapped positions. In *anti* model **306** the protons on C10 appear at δ 0.9, while in *syn* model **282**, they appear at δ 1.43. The protons on C17 appear at δ 1.26 in *anti* model **306** and at δ 1.17 in *syn* model **282**. These differences are especially interesting, due to the fact that it was in this region of the molecule that most of the discrepancy occurred between the spectral data of the natural product and the synthesised *anti* tridachiahydropyrone (**14**),[22] as discussed in Chapter 1 (Section 1.3.2).

A comparison of the ^{1}H NMR data of each of models **282** and **306,** and *anti* tridachiahydropyrone (**14**) with the natural product also indicates that *syn* model **282** is a closer match to the natural product than both *anti* model **306** and *anti* tridachiahydropyrone (**14**), as depicted in Figure 4.12.

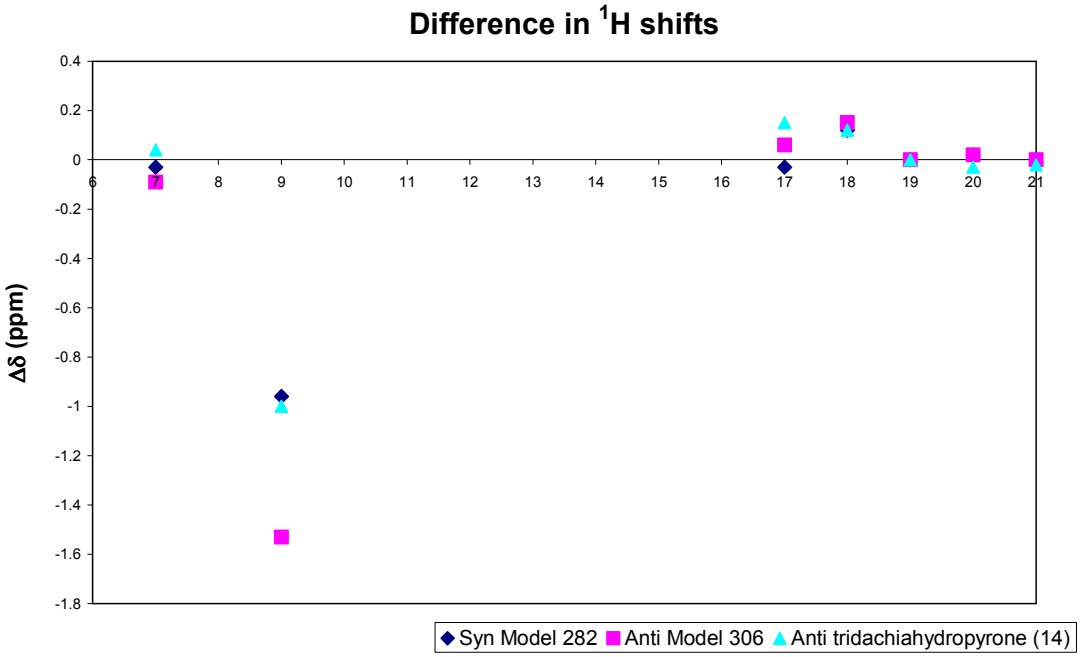


*Figure 4.12. Differences in ^{1}H NMR spectra between syn model **282**, anti model **306**, anti tridachiahydropyrone (**14**) and the natural product.*

It can be seen from Figure 4.12 that the chemical shifts of the protons of *syn* model **282** (blue data points) are closer in almost all instances to the natural product (represented by the zero point on the x-axis) than *anti* model **306** (pink data points) and *anti* tridachiahydropyrone (**14**) (turquoise data points). The same trend is evident for the ^{13}C chemical shifts (Figure 4.13).

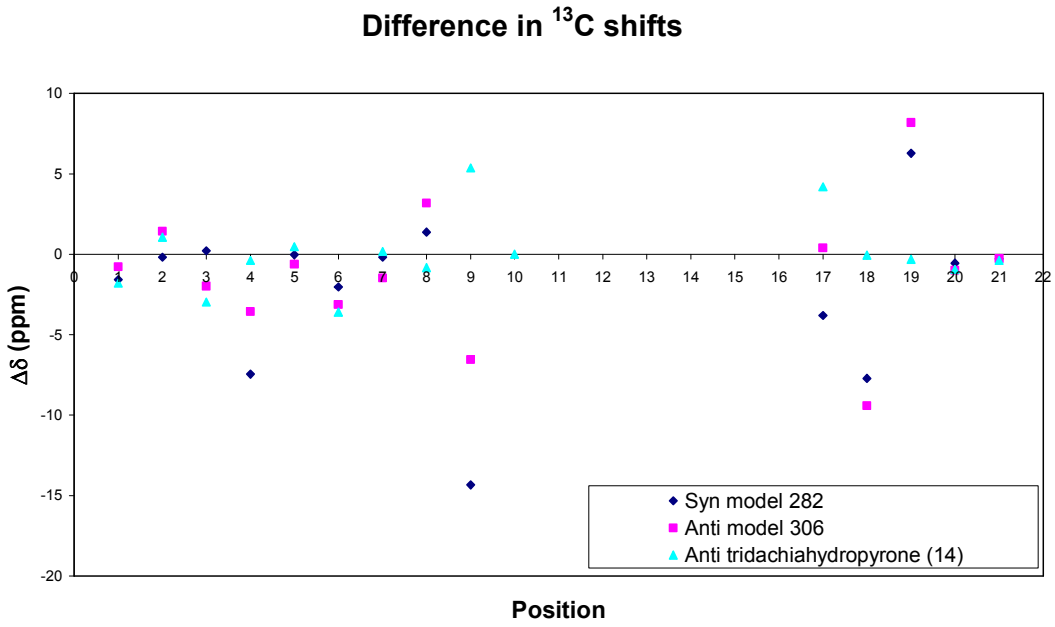


*Figure 4.13. Differences in ^{13}C NMR spectra between syn model **282**, anti model **306**, anti tridachiahydropyrone (**14**) and the natural product.*

The close relationship between *syn* model **282** and the natural tridachiahydropyrone is further exemplified in Table 4.1 on the following page.

*Table 4.1. Comparison of NMR data of syn model **282**, anti model **306**, anti tridachiahydropyrone (**14**) and the natural product.*

	***syn* Model 282**		**Natural**		**Anti (14)**		***anti* Model 306**	
Position	**δ ^{1}H**	**δ ^{13}C**	**δ ^{1}H**	**δ ^{13}C**	**δ ^{1}H**	**δ ^{13}C**	**δ ^{1}H**	**δ ^{13}C**
1		164.4		165.97		164.2		165.2
2		87.7		87.88		88.9		89.3
3		196.0		195.79		192.8		193.8
4		39.1		46.56		46.2		43.0
5		145.3		145.33		145.8		144.7
6		113.7		115.74		112.1		112.6
7	5.41	121.1	5.44	121.28	5.48	121.5	5.35	119.8
8		135.8		134.42		133.6		137.6
9	2.95	39.1	3.91	53.45	2.91	58.8	2.38	46.9
10	1.43	14.3					0.90	13.4
17	1.17	17.4	1.20	21.21	1.35	25.4	1.26	21.6
18	1.75	14.0	1.63	21.72	1.75	21.7	1.78	12.3
19	1.75	20.9	1.75	14.62	1.75	14.3	1.75	22.8
20	1.65	6.9	1.63	7.4	1.60	6.5	1.65	6.4
21	3.95	54.8	3.96	55.08	3.94	54.7	3.96	54.8

From Table 4.1, it can be seen that the proton on C9 (highlighted in yellow) experiences a significant shift downfield going from *anti* model **306** to *anti* tridachiahydropyrone (**14**), and if this trend continues moving from *syn* model **282** to the natural product, H9 will appear in the right region for tridachiahydropyrone. This trend is also evident for C9 itself (highlighted in green), where the difference between its position in *anti* model **306** and *anti* tridachiahydropyrone (**14**) is a downfield shift of approximately 12 ppm. If this trend continues for *syn* model **282**, an addition of 12 ppm to the shift of C9 will place it in the right chemical shift for the natural product. Similarly, for the protons on C17 (highlighted in yellow), the difference between their chemical shift going from *anti* model **306** to *anti* tridachiahydropyrone (**14**) is negligible, and if this trend continues, the protons will appear at the right chemical shift for the natural product. Additionally, a downfield shift of 4 ppm is observed for C17 going from *anti* model **306** to *anti* tridachiahydropyrone (**14**), and if this shift is added to the chemical shift observed for C17 in *syn* model **282**, the carbon will appear in the right region for the natural product.

Thus, based on the analyses described in Figure 4.12, Figure 4.13 and Table 4.1, it can be concluded that *syn* model **282** is a better approximation to the natural product than *anti* model **306** and therefore the stereochemistry between C9 and C17 is likely to be *syn* in the natural product. These promising conclusions regarding the true structure of the natural product led to attempts at the synthesis of *syn* tridachiahydropyrone (**42**), utilising the methodology employed in the synthesis of model system **282**.

4.4 Attempted synthesis of *syn* tridachiahydropyrone (42)

It was envisaged that the preparation of *syn* tridachiahydropyrone (**42**) would begin with the coupling of di-alkenyl cuprate **96** (generated from bromoalkene **93**) with *cis* enone **299** to give cyclohexanone **307** (Figure 4.14).

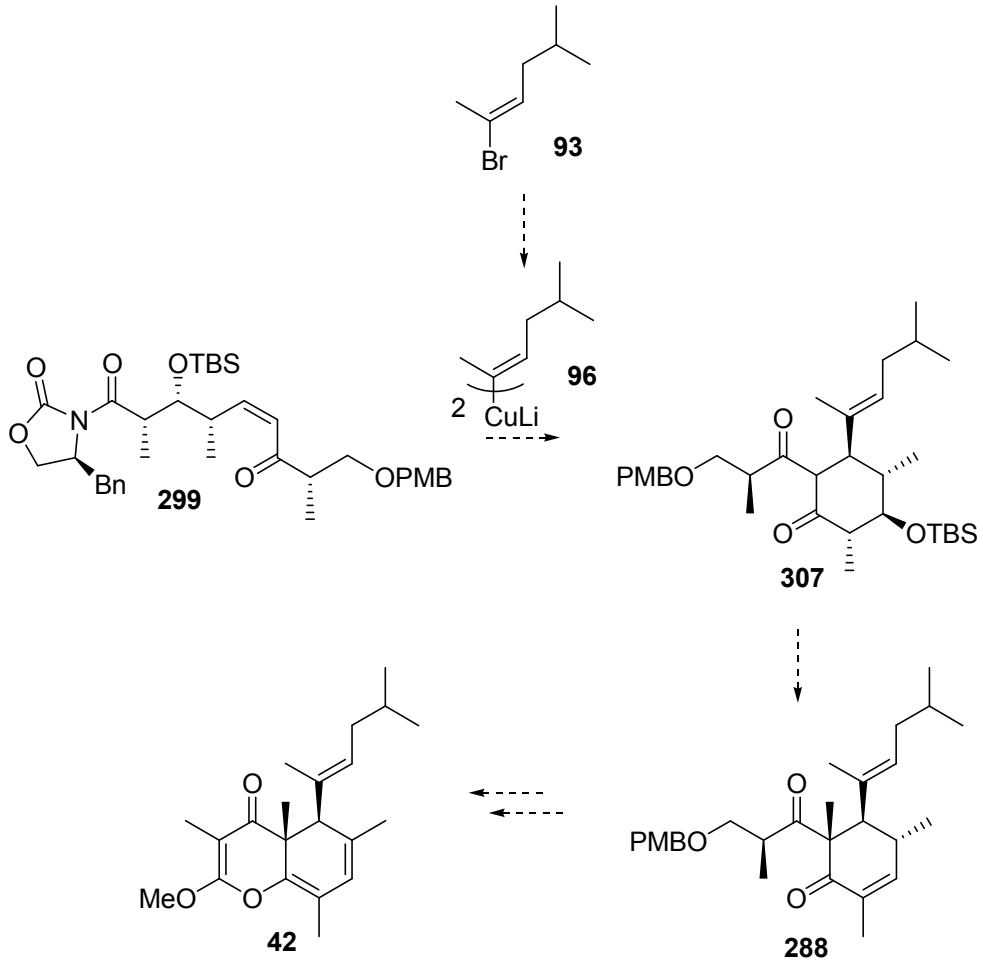


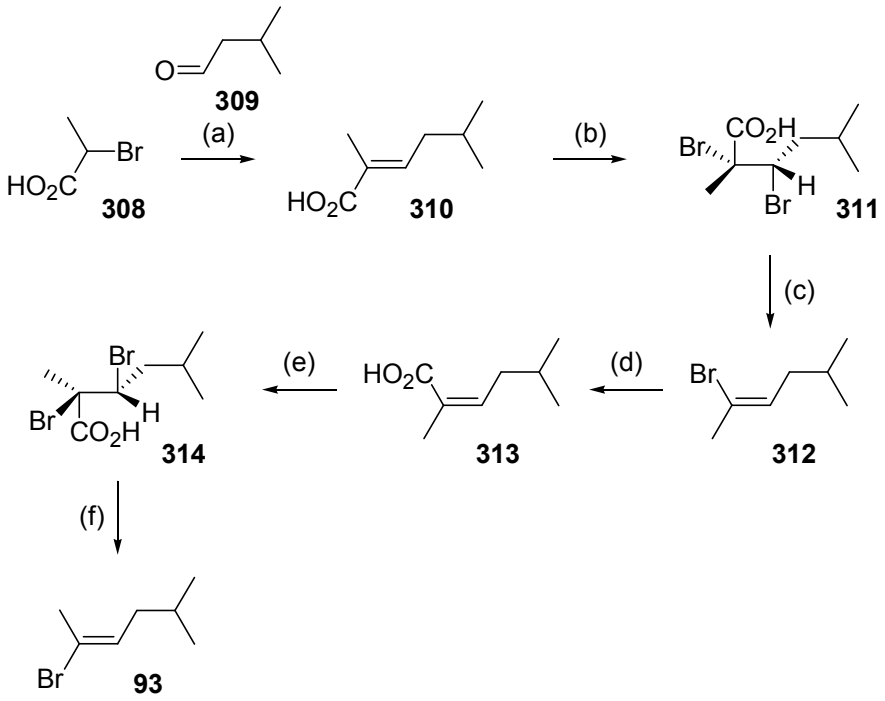
*Figure 4.14. Proposed synthesis of syn tridachiahydropyrone (**42**).*

Cyclohexanone **307** could then be methylated and following elimination, converted to *syn* methylated cyclohexenone **288** (Figure 4.14). By carrying out the required functional group manipulations (described previously in Section 4.2.2), *syn* methylated cyclohexenone **288** could be converted to proposed natural product **42**.

Thus, the first step towards the synthesis of *syn* tridachiahydropyrone (**42**) required cyclohexanone **307** to be prepared. Since *cis* enone **299** had been synthesised as described previously (Section 4.1.1.2), the synthesis of a suitable precursor to cuprate **96** was required. The synthesis of *anti* tridachiahydropyrone (**14**)[22] (discussed in Chapter 1, Section 1.5) had involved the use of bromoalkene **93** (Figure 4.14), and due to the fact that the preparation of this bromoalkene was experimentally straightforward and its use was well-developed within the Perkins group, it was decided that it would be employed as the precursor to cuprate **96**.

4.4.1 Synthesis of bromoalkene 93

The preparation of bromoalkene **93** began with commercially available 2-bromopropionic acid (**308**) (Scheme 4.9). Acid **308** was reacted with isovaleraldehyde (**309**) *via* a phosphonate to give alkene **310**,[22,23] which was then converted by the procedure described in Kim *et al*[24] to desired bromoalkene **93**.



Reagents and conditions. (a) i. NaH, DME, diethyl phosphite, 0 °C. ii. **308**, 0 °C → RT. iii. **309**, 0 °C → RT, 67%; (b) Br_2, CH_2Cl_2, – 78 °C, 89%; (c) $NaHCO_3$, DMF, 60 °C, 84%; (d) i. *t*-BuLi, THF, – 78 °C. ii. CO_2, – 78 °C → – 20 °C, 98%; (e) Br_2, CH_2Cl_2, – 78 °C, 88%; (f) $NaHCO_3$, DMF, 60 °C, 76%.

*Scheme 4.9. Synthesis of bromoalkene **93**.*

While the synthesis of bromoalkene **93** did involve a number of steps (Scheme 4.9), other attempts undertaken in the Perkins group at a condensed stereoselective synthesis of **93** were not fruitful, often producing a mixture of **93** and **312**.[25] Despite the length of the synthetic route to bromoalkene **93**, the intermediates either did not require any purification (as in the case of **311** and **314**) or could be purified by distillation, which made the synthesis of bromoalkene **93** relatively simple and amendable to a large scale. The ^{1}H NMR spectrum of **93** (Figure 4.15) contains the requisite protons, and is identical to that reported in the literature.[22]

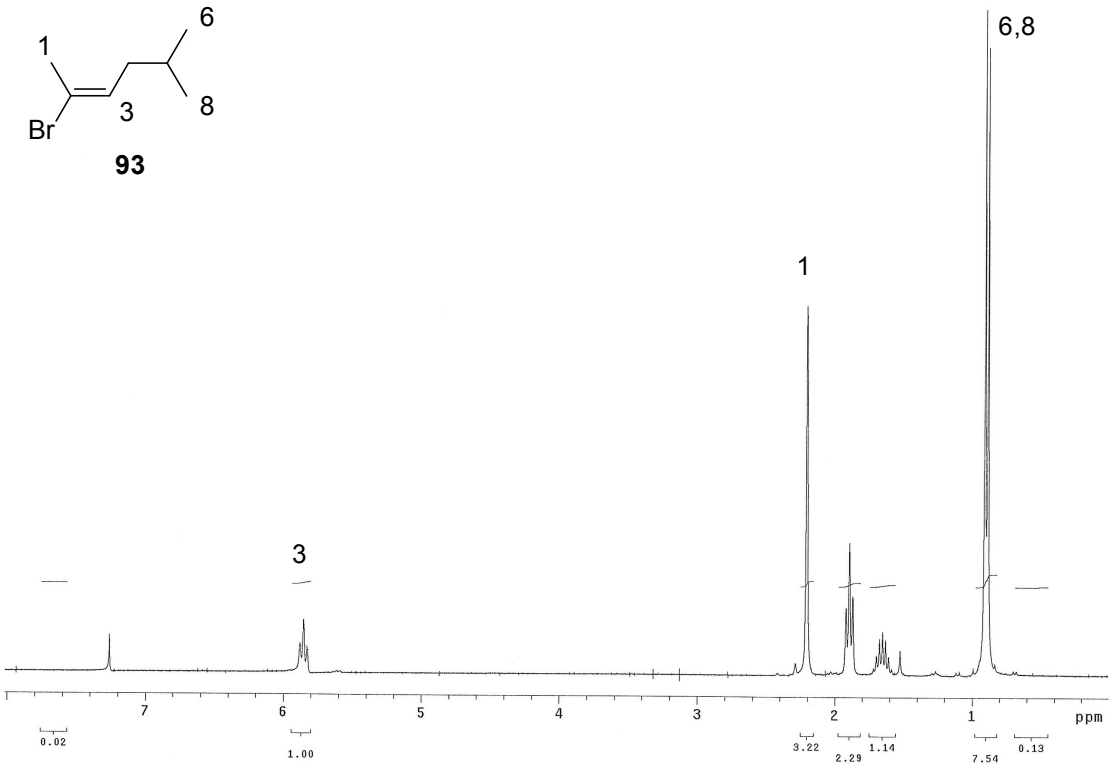
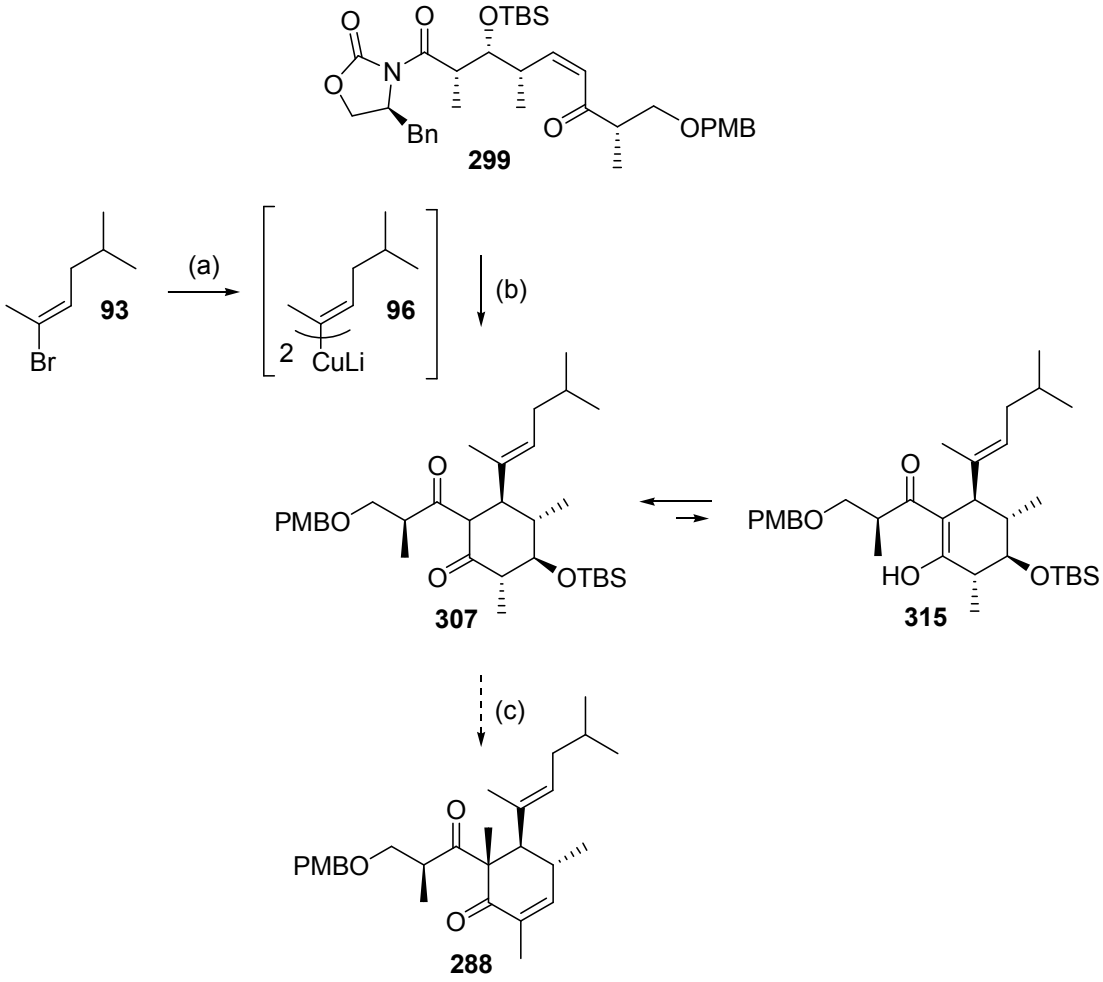


Figure 4.15. ^{1}H *NMR spectrum of bromoalkene* ***93*** *in* $CDCl_3$ *at 300 MHz.*

The synthesis of bromoalkene **93** was therefore achieved in 33% yield over six steps from commercially available 2-bromopropionic acid (**308**). With bromoalkene **93** now in hand, the preparation of *syn* methylated cyclohexenone **288** could be attempted *via* cyclohexanone **307**.

4.4.2 Attempted synthesis of *syn* methylated cyclohexenone 288

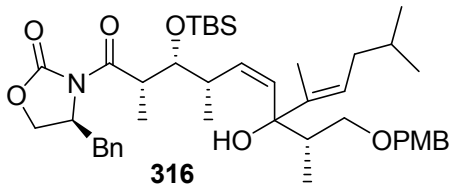
Utilising the standard conditions developed within the Perkins group for cuprate additions of this type,[22] cyclohexanone **307** was produced in only a low yield (Scheme 4.10).



Reagents and conditions. (a) i. **93**, *t*-BuLi, THF, – 100 °C. ii. CuCN, Et_2O, – 78 °C → – 50 °C; (b) **299**, – 50 °C → 0 °C, 31%; (c) i. NaH, MeI, THF, RT. ii. NaH, RT.

*Scheme 4.10. Attempted synthesis of syn methylated cyclohexenone **288** via cyclohexanone **307**.*

A number of different modifications of the addition of **96** to *cis* enone **299** (Scheme 4.10) were attempted, utilising different equivalents of reagents, temperatures and reaction times. However, none of the alterations gave an improved yield over that obtained using the standard conditions. Additionally, the standard conditions proved to be the cleanest, with the least amount of by-products formed, and allowed some *cis* enone **299** to be recovered. Occasionally, the 1,2-addition product **316** (Figure 4.16) was isolated, which led to the conclusion that the cuprate **96** may not have formed properly.



316

*Figure 4.16. 1,2-addition product **316** isolated from addition of cuprate **96** to cis enone **299**.*

In an effort to increase the amount of cuprate formed, all reagents were purified, titrated and dried. However, the yield of cyclohexanone **307** did not improve. The ^{1}H NMR spectrum of cyclohexanone **307** (Figure 4.17) on the following page contains the requisite protons and indicates that **307** exists predominantly in the *keto* form.

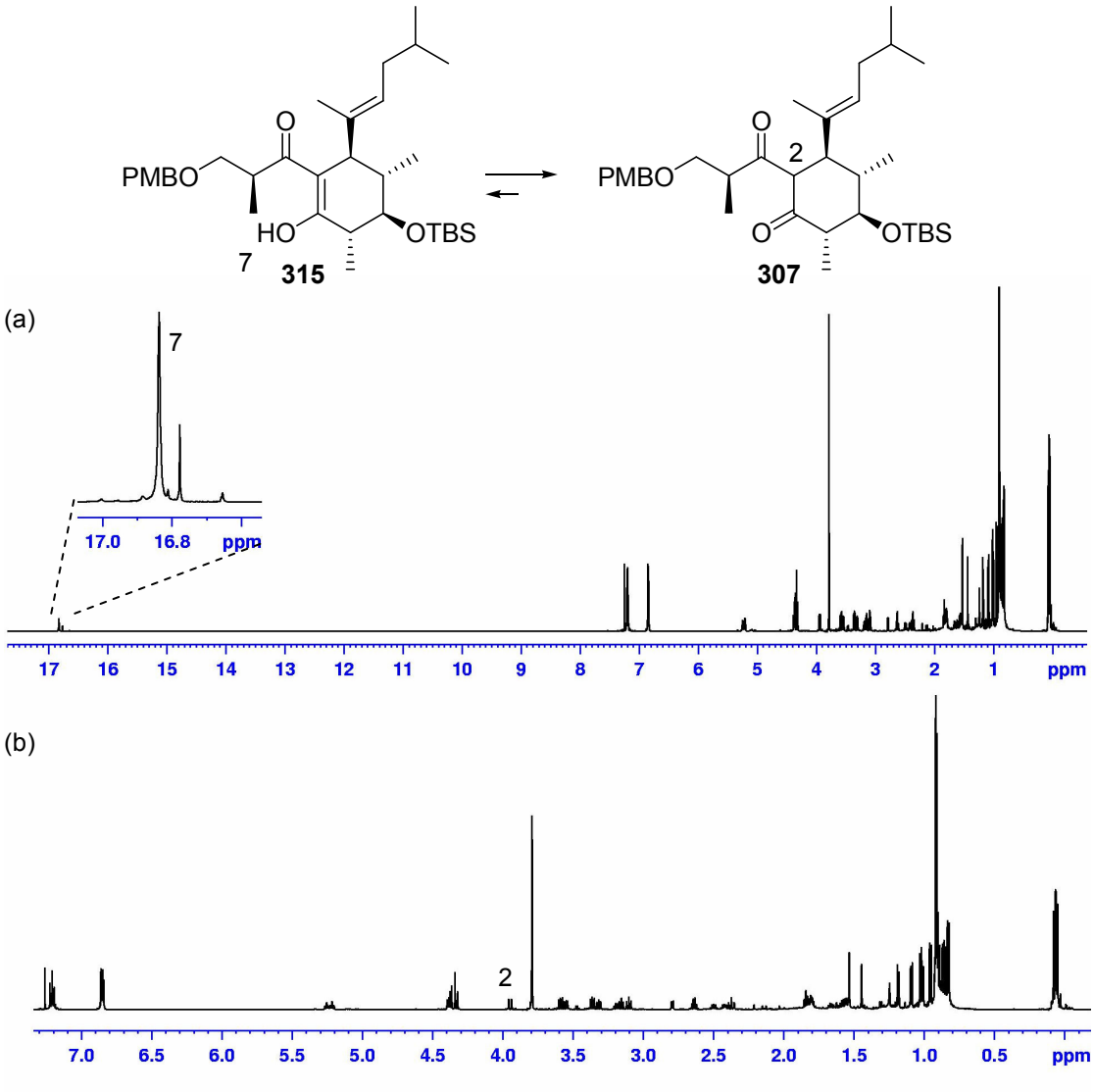


*Figure 4.17. (a) Full ^{1}H NMR spectrum of cyclohexanone **307** in $CDCl_3$ at 600 MHz; (b) Expanded ^{1}H NMR spectrum (0 – 7.3 ppm) of cyclohexanone **307** in $CDCl_3$ at 600 MHz.*

Due to the complexity of the spectrum of cyclohexanone **307** (Figure 4.17), the assignment will not be discussed in detail here. The success of the reaction is evident in the presence of the *enol* proton of **315**, which appears as a small singlet at δ 16.9. The dominance of the *keto* form in the spectrum is evidenced by the presence of a doublet at δ 3.97, which can be attributed to the proton between the two carbonyl groups. The large coupling constant exhibited by this proton (J = 12.2 Hz) indicates that it is in an antiperiplanar arrangement with the proton on the carbon bearing the alkenyl side-chain, which leads to the conclusion that the cuprate addition has

occurred from the expected face of *cis* enone **299**, to give the desired stereochemistry at this centre. The identity of cyclohexanone **307** was further corroborated by ^{13}C NMR, IR and high resolution mass spectrometry, which confirmed the expected composition of $C_{33}H_{54}O_5Si$.

Of significant interest is the presence of an additional isomer in the ^{1}H NMR spectrum of **307**, as evidenced by the existence of a second *enol* peak at δ 16.8 (Figure 4.17(a)). A comparison of the spectral data with that reported in the literature[22] identified the contaminant as the *eno*l form (**317**) of cyclohexanone **94**.

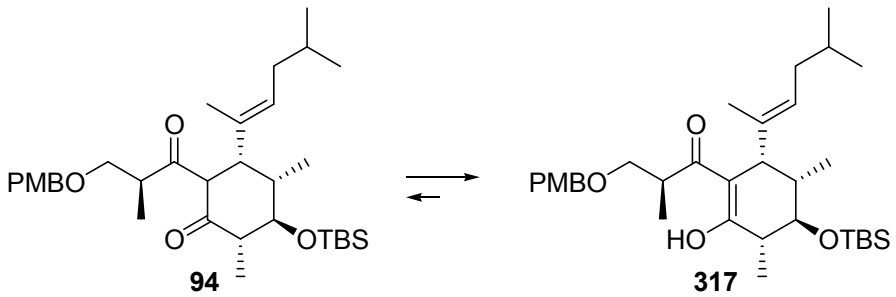


*Figure 4.18. Keto and enol forms of cyclohexanone **94**.*

Cyclohexanone **94** (Figure 4.18) may have formed as a result of either approach of cuprate **96** to the other face of *cis* enone **299** (Chapter 3, Section 3.3) or isomerisation of a small amount of *cis* enone **299** to a *trans* enone (Chapter 1, Section 1.5). However, experimentally, cyclohexanones **307** and **94** could not be separated by conventional chromatographic methods, and thus were utilised as a mixture in subsequent reactions.

With cyclohexanone **307** in hand, the synthesis of *syn* methylated cyclohexenone **288** was attempted, and initial efforts towards this goal focussed on the use of the standard methylation-elimination cascade, as described previously in Scheme 4.10. However, this reaction predominantly returned starting material **307**, with a small amount of a product identified as *anti* cyclohexenone **95**[22] and methylated cyclohexanone **318** (Figure 4.19).

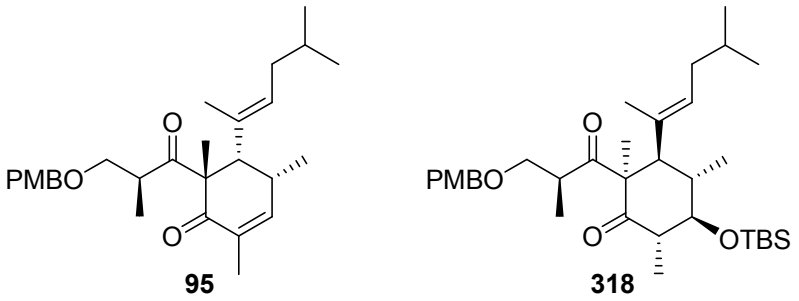


*Figure 4.19. Compounds **95** and **318** isolated in reaction of cyclohexanone **307** with NaH and MeI.*

The formation of *anti* cyclohexenone **95** indicated that the reaction to form the desired *syn* methylated cyclohexenone **288** had not been unsuccessful due to the reagents or conditions, but that the lack of success was due to the nature of cyclohexanone system **307**. The stereochemistry of methylated cyclohexanone **318** was later identified as that depicted in Figure 4.19 (discussed in Section 4.4.3). Initially, however, due to the small amount of **318** isolated, improved conditions to carry out this reaction were investigated. Additionally, at that stage it was believed that if the right conditions were found, the elimination of the OTBS group would occur to give the desired *syn* methylated cyclohexenone **288**.

*4.4.2.1 Investigations into an improved methylation of cyclohexanone **307***

A search of the literature for alternative methylation conditions indicated that the reaction could be performed using hexamethylphosphoramide (HMPA), tetrahydrofuran (THF) or *N*,*N*-dimethylformamide (DMF) as the solvent, and lithium (as lithium hexamethyldisilylazide (LiHMDS)), sodium (as NaH) or potassium (as *t*-BuOK) as the counter-ions.[26-29] These modifications were therefore trialled on cyclohexanone **307**, with all of the experiments conducted under N_2 at 25 ^{o}C. The first set of experiments focussed on the influence of the solvent on the success of the methylation of **307**.

Cyclohexanone **307** was treated with NaH and MeI in each of the different solvents and of the solvents used, DMF gave an improved yield (20%) of methylated cyclohexanone **318** (compared with 6% for THF and 10% for HMPA). This result

may be attributed to the fact that DMF is better able to solvate the anion of cyclohexanone **307**, compared with the other solvents trialled. However, no eliminated compounds were identified.

Due to this improvement in yield of methylated cyclohexanone **318** in the presence of DMF, the experiments into the effect of counter-ions on the methylation of cyclohexanone **307** were conducted. The alternative bases tested were LiHMDS and *t*-BuOK and these were reacted with cyclohexanone **307** in DMF under N_2 at 25 ^{o}C, with MeI used as the methylating agent. The lithium cation was not effective, with only starting material isolated from that reaction, while *t*-BuOK gave an improved yield of 50% of methylated cyclohexanone **318**. Once again, however, despite using a large excess of base (5 equivalents), no eliminated compounds were isolated. The ^{1}H NMR spectrum of methylated cyclohexanone **318** (Figure 4.20) indicates the presence of the requisite protons.

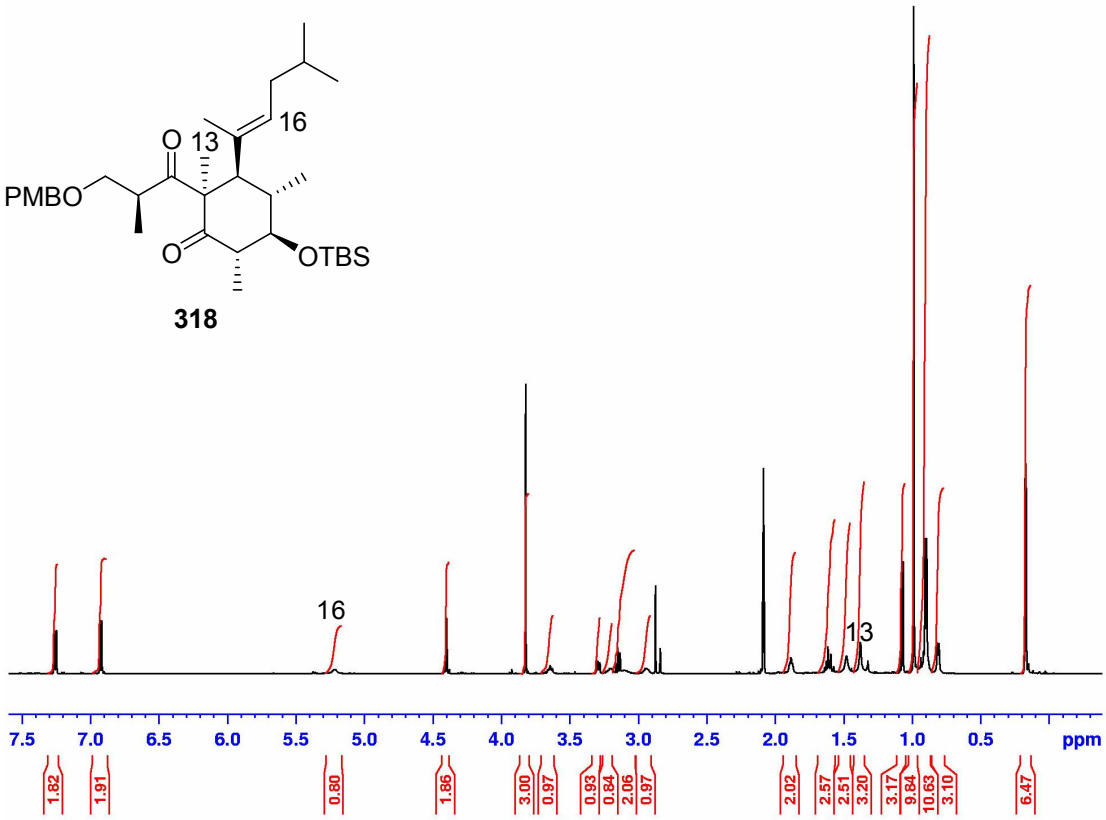


*Figure 4.20. ^{1}H NMR spectrum of methylated cyclohexanone **318** in d_6-acetone at 600 MHz.*

The ^{1}H NMR spectrum of methylated cyclohexanone **318** was obtained initially in $CDCl_3$, but it was found that better separation of the peaks occurred when the NMR spectrum was obtained in d_6-acetone (Figure 4.20). The absence of the doublet due to the proton between the two carbonyl groups (at δ 3.97 in $CDCl_3$) is immediately obvious in the spectrum, as is the absence of an *enol* tautomer, with no peak observed at the expected shift for *enol* protons (approximately δ 16). This supports the proposition that the methylation has occurred. It is also evident that **318** must be undergoing slow conformational changes at 20 ^oC, due to the broad nature of many of the peaks.

The vinyl proton of the alkenyl side-chain appears as a broad singlet at δ 5.22 and couples to both the vinyl methyl (*via* an allylic coupling), which appears as a broad singlet at δ 1.48, and the adjacent methylene protons, which appear as a multiplet at δ 1.88 – 1.90. The methylene protons also couple to the methine proton of the *iso*-propyl group, which appears as a multiplet at δ 1.60 – 1.64, along with the proton on the carbon of the cyclohexanone ring bearing the alkene side-chain, which appears as a doublet at δ 1.61. This proton has a coupling constant of 12.6 Hz, which means that it is in an antiperiplanar relationship with the adjacent methine proton. This lends more support to the proposition that the cuprate addition enone **299** occurred in the predicted manner. The methine proton of the *iso*-propyl group couples to the two sets of equivalent methyl protons, which appear as a multiplet at δ 0.9 – 0.91. The proton responsible for the doublet at δ 1.61 couples to the adjacent methine proton, which appears as a multiplet at δ 3.05 – 3.15. This methine proton couples to the adjacent methyl protons, which appear with the methyl protons of the *iso*-propyl group at δ 0.9 – 0.91, as well as the oxymethine proton, which appears as a multiplet at δ 3.14 – 3.17. The oxymethine proton couples to the methine proton adjacent to the endocyclic carbonyl, which appears as a multiplet at δ 2.91 – 2.98 and couples to the adjacent methyl protons, which appear as a doublet at δ 1.08. The methyl methine proton adjacent to the exocyclic carbonyl (of the PMB side-chain) is present as a multiplet at δ 3.19 – 3.24 and couples to both the adjacent methyl protons (which appear as a multiplet at δ 0.81 – 0.82) and the oxymethylene protons. One of the oxymethylene protons appears as a doublet of doublets at δ 3.30, while the other as a multiplet at δ 3.63 – 3.67. The quaternary methyl appears as a broad singlet at δ 1.38,

while the remaining peaks at δ 3.83, δ 4.38 – 4.42, δ 6.92 – 6.94 and δ 7.25 – 7.27 can be attributed to the PMB group. The protons of the TBS group appear at δ 0.17, δ 0.18 and δ 0.99. The ^{13}C NMR spectrum further corroborated this structural assignment with the presence of 28 non-equivalent carbons, including two carbonyl carbons at δ 206.1 and δ 212.6, and the quaternary methyl at δ 19.9. High resolution mass spectrometry confirmed the expected composition of $C_{34}H_{56}O_5$.

While the elimination of the OTBS group to form *syn* cyclohexenone **288** had not been successful, methylated cyclohexanone **318** could still potentially be used as an intermediate on the path towards the natural product, provided that the desired *syn* stereochemistry had been obtained. However, the stereochemistry of the methylation remained as yet undetermined. Due to the importance of the stereochemical outcome of this reaction in regards to the synthesis of *syn* tridachiahydropyrone (**42**), an investigation into the stereochemistry of this quaternary centre was instigated.

4.4.3 Investigations into the stereochemistry of methylated cyclohexanone 318

Initially, a 2D-NOESY spectrum of methylated cyclohexanone **318** in d_6-acetone at 600 MHz and 20 ^oC was obtained, to glean information about the stereochemistry of the methylation. The correlations observed in the NOESY spectrum are depicted in Figure 4.21 (which shows the proposed favoured chair conformation of **318**) on the following page, with the correlations observed between protons of the PMB side-chain omitted for clarity.

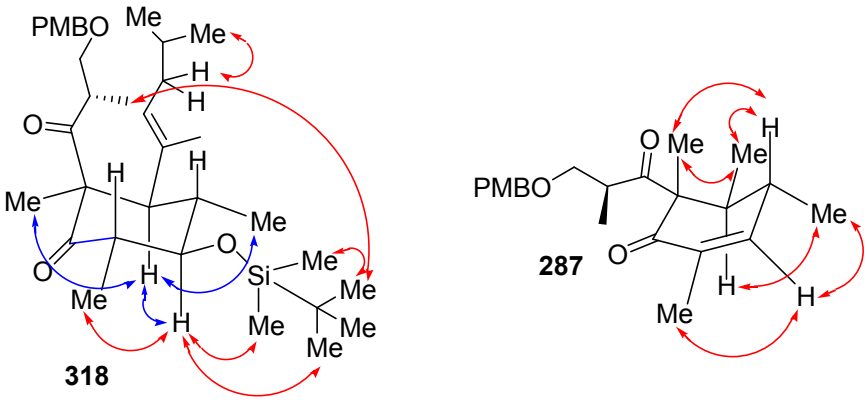


*Figure 4.21. NOESY correlations observed for methylated cyclohexanone **318** and syn methylated cyclohexenone **287**.*

The NOESY correlations observed between the methyl protons of the PMB side-chain and the methyl protons of the TBS group (Figure 4.21) indicate that the PMB side-chain may be in the axial position. Based on this proposition, it would be expected that the methyl of the PMB side-chain would also correlate with the protons on the top face of the ring. However, these correlations were not observed. Additionally, due to the fact that the proton on the carbon bearing the alkene side-chain had the same chemical shift as the proton of the *i*-propyl group, the NOESY correlations shown in blue could only be tentatively assigned as shown. Notably, the NOESY correlations observed between the protons on the top face of *syn* methylated cyclohexenone **287** (Section 4.2.1), were not observed in methylated cyclohexanone **318**. This may be due to the fact that these protons in **318** are relaxing *via* the adjacent oxygen atoms in preference to other protons of the ring, resulting in the absence of NOESY correlations.

The success of the selective irradiation NOESY experiments in determining the stereochemistry of *syn* methylated cyclohexenone **287** (Section 4.2.1), meant that this spectral analysis tool may provide more stereochemical information regarding methylated cyclohexanone **318**. However, in order for selective irradiation of one peak (and hence one proton or set of protons) to occur, the resolution between adjacent peaks has to be high enough, such that the irradiation at one point in the spectrum does not "spill-over" into adjacent peaks, thus reducing the selectivity of the irradiation.

From the ^{1}H NMR spectrum of **318** in d_6-acetone (Figure 4.20 and Figure 4.22(a)) it can be seen that many of the peaks are not well resolved, appearing as broad multiplets and singlets, and overlapping with each other in some instances. As discussed previously, it was postulated that this was a result of conformational changes of methylated cyclohexanone **318** occurring at a slow rate. Thus either heating or cooling of **318** would induce a change in the rate of conformational interchange, which may lead to better resolution of the peaks in the ^{1}H NMR spectrum. This would allow a higher level of selectivity to be achieved in the irradiation.

The initial set of experiments involved first heating a sample of **318** in d_6-acetone (with the aid of Variable Temperature (VT) NMR) in order to deduce the temperature at which the best resolution of peaks was obtained. Following this, selective irradiation NOESY was carried out on the sample to glean the desired stereochemical information.

4.4.3.1 High temperature VT NMR and selective irradiation NOESY

A sample of methylated cyclohexanone **318** in d_6-acetone was heated in 10 ^{o}C increments from 20 to 50 ^{o}C and the spectra were recorded at each temperature. The highest temperature (50 ^{o}C) was chosen based on the volatility of the solvent. Figure 4.22 on the following page shows the effect of this increase in temperature on the ^{1}H NMR spectrum of methylated cyclohexanone **318**.

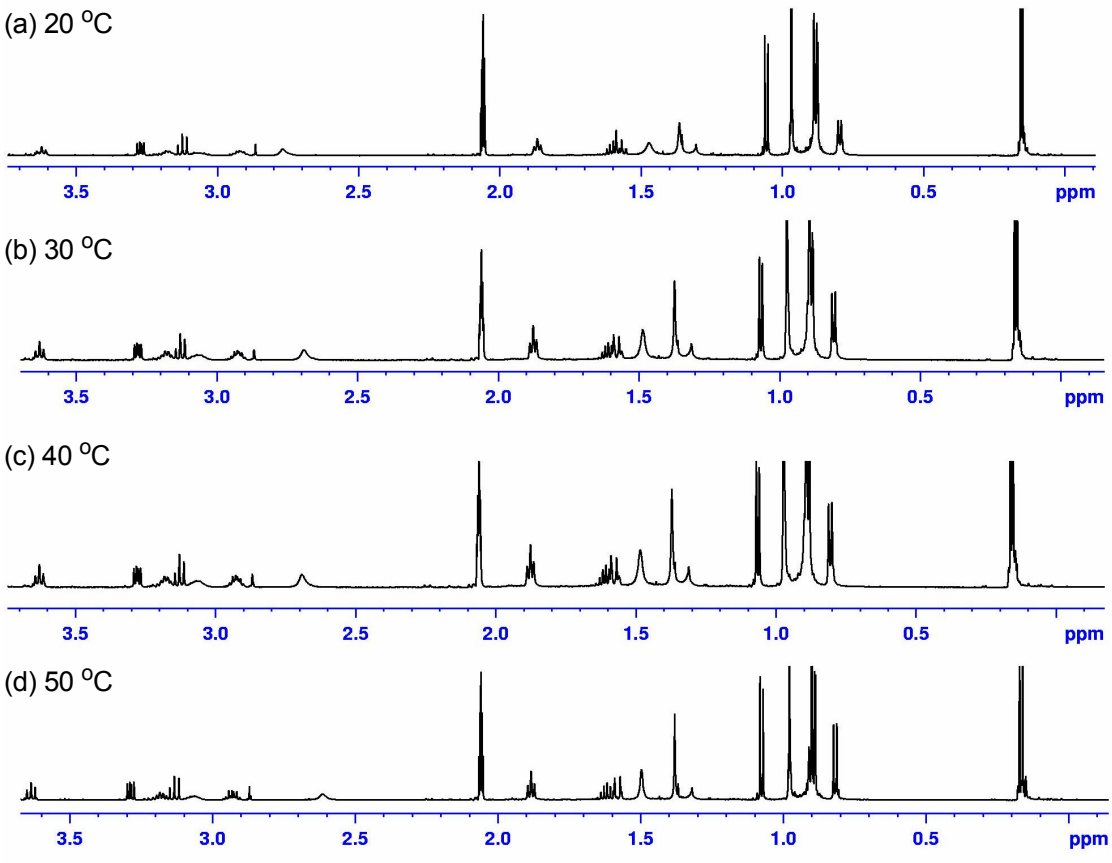


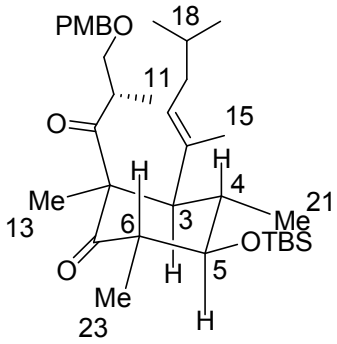
*Figure 4.22. High temperature VT ^{1}H NMR spectra of methylated cyclohexanone **318** in d_6-acetone at 600 MHz.*

While the whole ^{1}H NMR spectrum of cyclohexanone **318** was recorded at each temperature, the region 0 – 3.7 ppm has been displayed as this contains the majority of the peaks of interest for the purpose of stereochemical analysis. It can be seen in Figure 4.22 that an increase in the temperature of the sample has a marked effect on the resolution, with sharpening and increased resolution observed in a significant number of the peaks.

Additionally, as the temperature is increased, the nature of the conformer does not appear to change significantly, with the peaks merely becoming more refined and no extra peaks appearing or significant movement of the peaks occurring. The broadness of the peaks in the spectrum of cyclohexanone **318** at 20 °C (Figure 4.22 (a)) may therefore be attributed to slow movement of the TBS group, as well as the PMB and alkenyl side-chains, the rotation of which is not as restricted as the rest of the

molecule. Upon heating, the side-chains acquire more energy, allowing them to move faster. This increased rate of movement eventually becomes such that the effects of the side-chains on the ring are not observed on the NMR time-scale, leading to the greater resolution observed in the spectrum of cyclohexanone **318** at 50 ^{o}C (Figure 4.22 (d)). Based on the results obtained in these VT experiments, 50 ^{o}C was chosen as the optimum temperature for carrying out the selective irradiation NOESY experiments.

It was decided that the protons on C4, C6 and C13 would be chosen for these experiments (Figure 4.23).



318

*Figure 4.23. Numbering of substituents of methylated cyclohexanone **318**.*

It was believed, as discussed previously, that the lack of correlation observed between H4 and H6 (Figure 4.23) in the 2D-NOESY spectrum was due to relaxation *via* the adjacent oxygen atoms. It was therefore postulated that irradiating these protons individually with a strong pulse may allow the NOESY correlations of these protons to be revealed. Additionally, as the proton on C3 could now be more easily distinguished from the proton on C18, the NOESY correlation observed between H3 and H13 in the 2D experiment could be verified. The selective irradiation NOESY experiments were thus conducted at 50 ^{o}C on H4, H6 and H13, and the results are shown below in Figure 4.24.

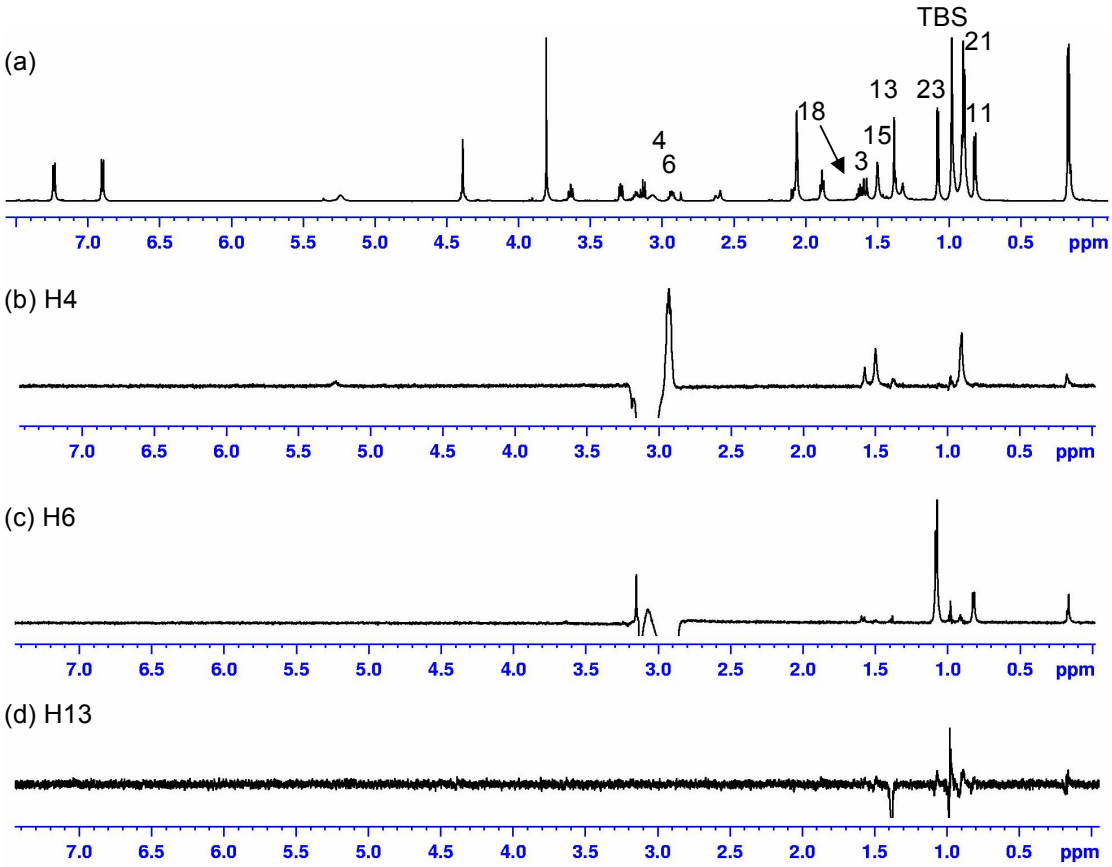


*Figure 4.24. (a) ^{1}H NMR spectrum of methylated cyclohexanone **318** at 50 ^{o}C in d_6-acetone at 600 MHz; (b) – (d) Selective irradiation NOESY of H4, H6 and H13 in d_6-acetone at 50 ^{o}C and 600 MHz.*

Spectrum (a) (Figure 4.24) is the ^{1}H NMR spectrum of methylated cyclohexanone **318** in d_6-acetone at 50 ^{o}C, while spectra (b), (c) and (d) show the results of irradiation of H4, H6 and H13, respectively.

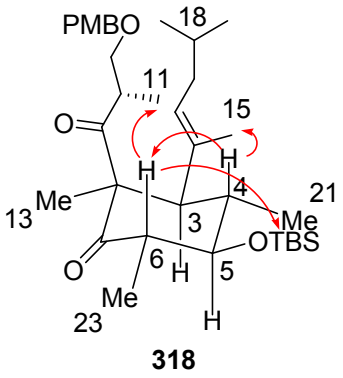
From spectrum (b) (Figure 4.24), it can be seen that irradiation of H4 has resulted in a significant response from a number of protons. However, due to the close proximity of H4 to H5, the irradiation was not completely selective, resulting in the appearance of extra correlations. Despite this limitation, a number of inferences may still be made regarding the interaction of this proton. The NOESY correlation with H6 is quite obvious, but this peak could also be due to a COSY interaction between H5 and H6. There also exists a COSY correlation between H4 and the methyl protons of C21. A NOESY correlation with the protons on C15 is also present, and would be unlikely to be the result of the irradiation of H5, as H5 is on the opposite

face of the ring. A small correlation to H3 is also present, and may be due to either a COSY interaction between H4 and H3, or a NOESY interaction between H4 and H5. If the latter is true, H3 is on the bottom face of the ring, which verifies the stereochemical outcome of the cuprate addition.

As depicted in spectrum (c) (Figure 4.24), H6 interacts *via* a COSY correlation with the protons on C23 and perhaps with H5, although this peak may be purely an artefact of the adjacent peak, which is out of phase. Two NOESY correlations are also present: to H11 and to the *tert*-butyl protons of the TBS group. The correlation to H11 is of particular interest, as this correlation, while not observed, was also expected in the 2D NOESY spectrum. This provides further evidence for the axial position of the PMB side-chain in methylated cyclohexanone **318**.

Spectrum (d) (Figure 4.24) shows the results of irradiation of the protons on C13. However, only tiny peaks are observed. As this methyl group is close in space to a number of groups, it would be expected that some peaks would be present in the NOESY spectrum. The absence of peaks may be due to the protons on C13 relaxing *via* the adjacent carbonyl oxygen. This would inhibit the relaxation of H13 *via* adjacent protons, and thus result in the lack of correlations observed in spectrum (d).

Based on the results obtained in the VT selective irradiation NOESY experiments described above (Figure 4.24 (b) – (d)), it may be concluded that the quaternary methyl is in the equatorial position in methylated cyclohexanone **318**, with the PMB side-chain occupying the axial position, due to the NOESY interactions observed between H6 and H11 (Figure 4.25). Additionally, it can be concluded that H4, H6 and H13 may indeed relax preferentially *via* the adjacent oxygen atoms (as discussed previously), with H4 and H6 relaxing *via* other adjacent protons only when irradiated with a strong pulse. The other NOESY correlations found in the selective irradiation experiments (Figure 4.24) are also summarised in Figure 4.25.



318

*Figure 4.25. NOESY correlations observed in selective irradiation experiments of methylated cyclohexanone **318** at 50 °C in d_6-acetone at 600 MHz.*

In summary, the results of the high temperature VT NMR-selective irradiation NOESY experiments on cyclohexanone **318** uncovered the correlations between the protons on C11 and H4 and H6 (Figure 4.25), which were not observed in the 2D-NOESY experiment conducted at room temperature (Section 4.4.3, Figure 4.21). This provided strong evidence for the axial orientation of the PMB side-chain. However, the absence of correlations between the protons of the quaternary methyl (C13) and the protons on the bottom face of the cyclohexanone ring when the protons on C13 were irradiated, was puzzling. This prompted a second investigation into the stereochemistry of methylated cyclohexanone **318** using selective irradiation NOESY, but this time at low temperatures.

4.4.3.2 Low temperature VT NMR and selective irradiation NOESY

As in the case of high temperature VT NMR, low temperature VT NMR was conducted in d_6-acetone in 10 °C increments from 20 °C to – 50 °C, and the ^{1}H NMR spectrum of methylated cyclohexanone **318** was recorded at each temperature. While the whole spectrum was recorded at each temperature, only the 0 – 3.7 ppm regions are shown in Figure 4.26 on the following page, as this region best exemplifies the observed changes.

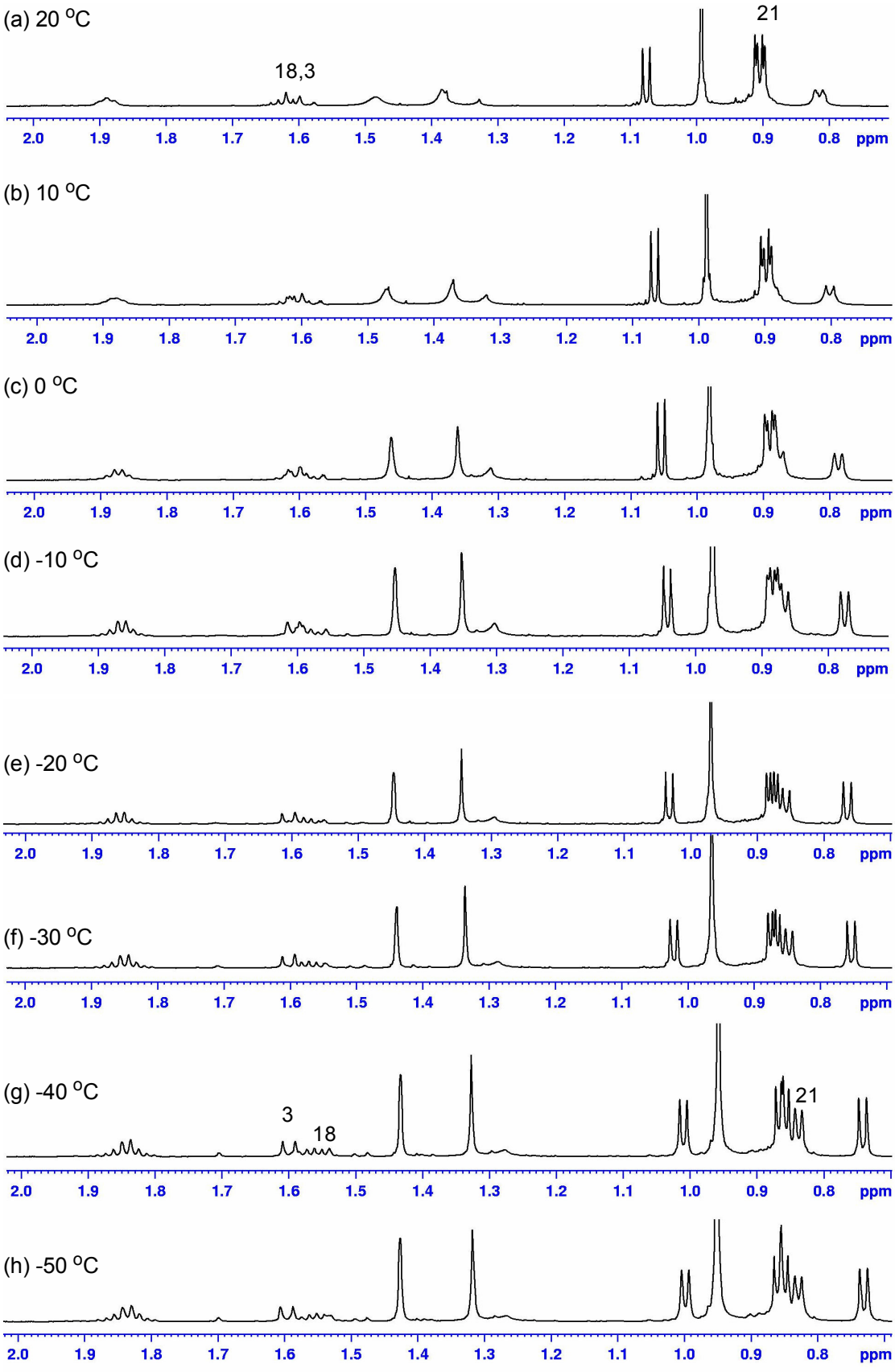


Figure 4.26. Low temperature VT NMR of methylated cyclohexanone ***318*** *in* d_6*-acetone at 600 MHz.*

It can be seen from Figure 4.26 that a decrease in the temperature of the sample has a marked effect on the resolution, with sharpening and increased resolution observed in a significant number of the peaks. This effect is observed until – 20 ^{o}C, after which time some of the peaks begin to broaden again as – 50 ^{o}C is approached. It therefore appears that the molecule undergoes numerous conformational changes as the temperature is decreased, due to movements of both the cyclohexanone ring and the side-chains. Notably, the ^{1}H NMR spectrum of cyclohexanone **318** at the low temperatures is different to the ^{1}H NMR spectrum at high temperatures, as depicted in Figure 4.27.

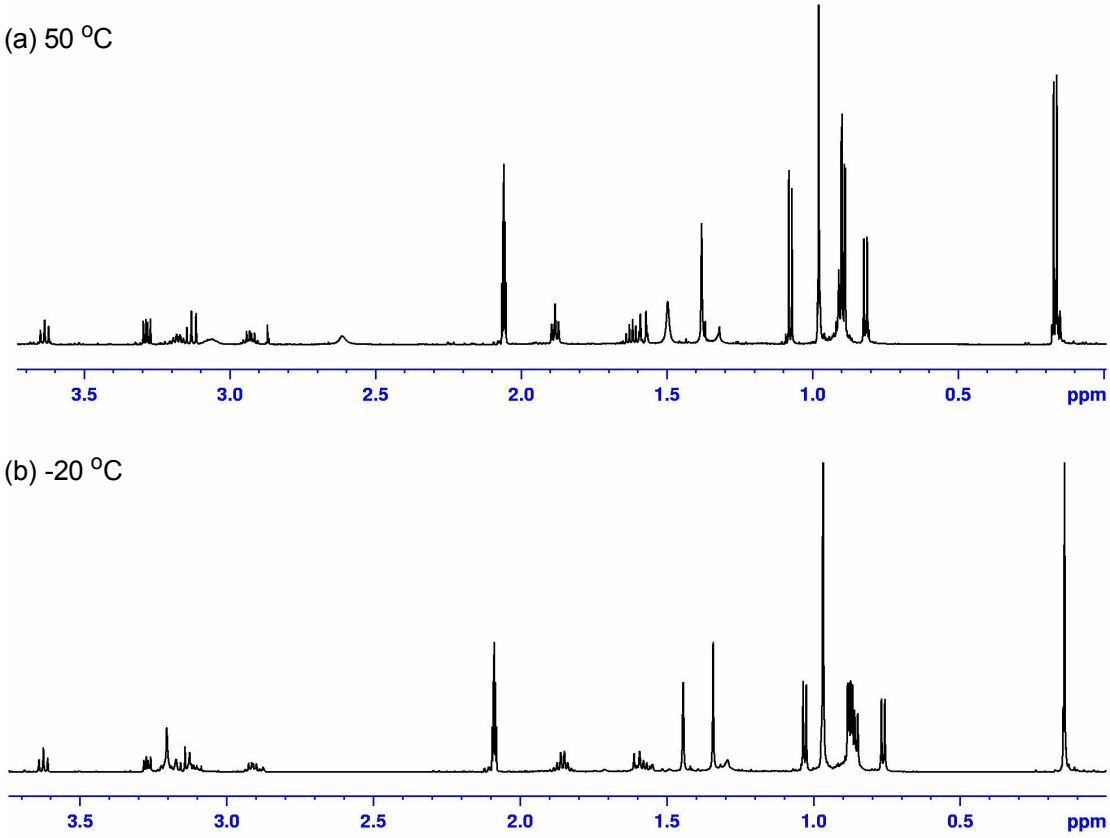
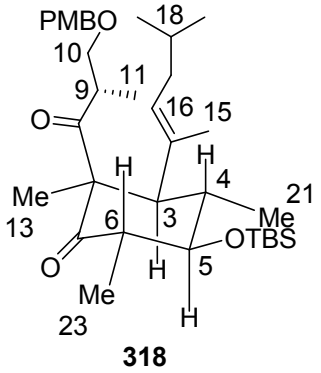


*Figure 4.27. (a) ^{1}H NMR spectrum (0 – 3.7 ppm) of methylated cyclohexanone **318** at 50 ^{o}C in d_6-acetone at 600 MHz; (b) ^{1}H NMR spectrum (0 – 3.7 ppm) of methylated cyclohexanone **318** at – 20 ^{o}C in d_6-acetone at 600 MHz.*

This may be due to slight differences in the movement and orientation of the TBS group, as well as the alkene and PMB side-chains of **318** at the different temperatures,

resulting in the differences observed between the ^{1}H NMR spectra at 50 ^{o}C (Figure 4.27 (a)) and – 20 ^{o}C (Figure 4.27 (b)).

Based on the results obtained in the low temperature VT NMR experiments (Figure 4.26), – 20 ^{o}C was chosen as the optimum temperature for carrying out the selective irradiation NOESY experiments. As for the high temperature selective irradiation NOESY experiments conducted previously, the protons on C4, C6 and C13 (Figure 4.28) were chosen for the low temperature selective irradiation NOESY experiments. Additionally, the protons on C11 were chosen, based on the results obtained in the high temperature experiments. The results from the selective irradiation NOESY experiments at – 20 ^{o}C on H4, H6, H13 and H11 and are shown below in Figure 4.29.



318

*Figure 4.28. Numbering of substituents of methylated cyclohexanone **318**.*

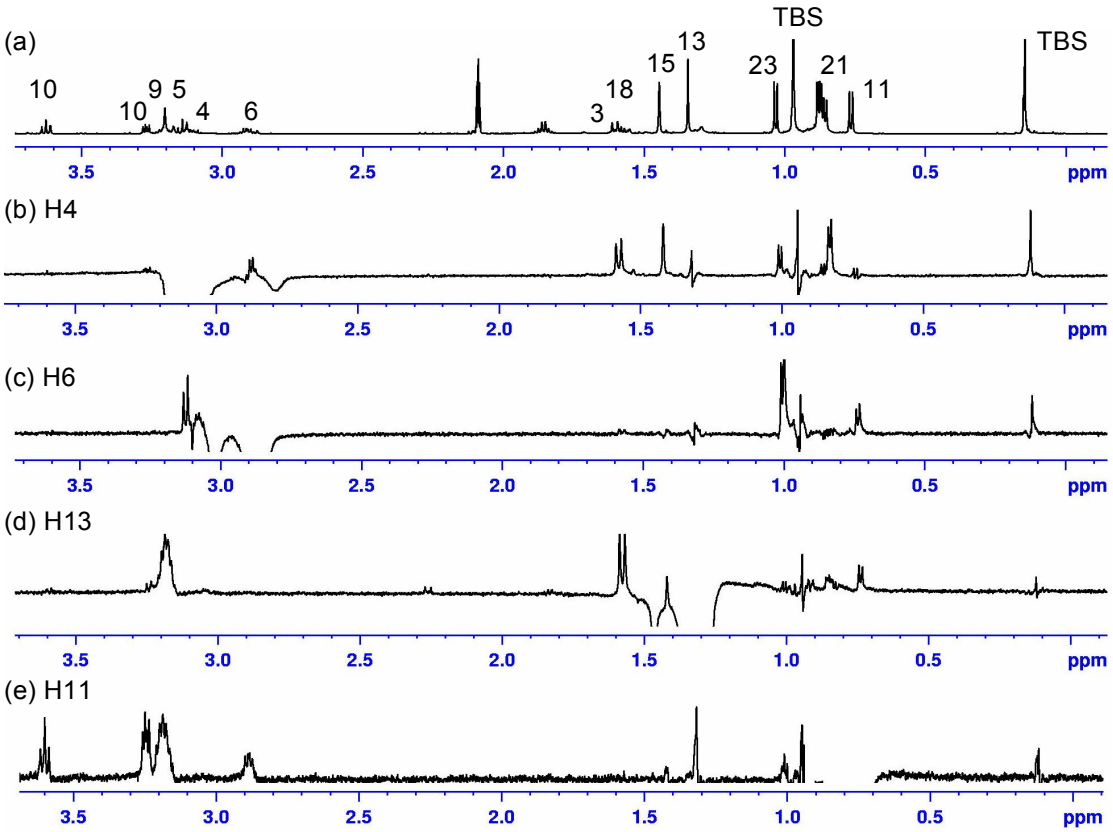


Figure 4.29. Selective irradiation NOESY (– 0.2 – 3.7 ppm) of H4, H6, H13 and H11 at – 20 °C in d_6-acetone at 600 MHz.

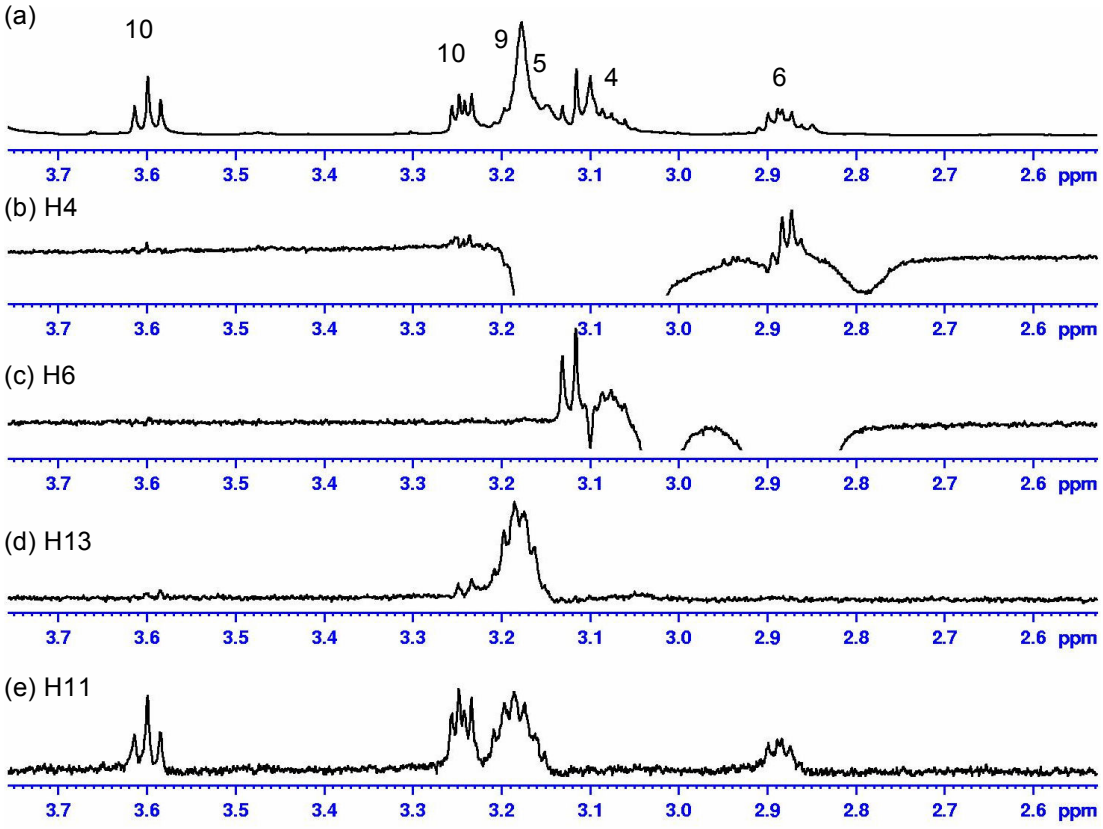


Figure 4.30. Expanded 2.5 – 3.8 ppm region of Figure 4.29.

Spectrum (a) (Figure 4.29 and Figure 4.30) is the ^{1}H NMR spectrum of methylated cyclohexanone **318** in d_6-acetone at – 20 ^{o}C, while spectra (b), (c), (d) and (e) show the results of irradiation of H4, H6, H13 and H11, respectively.

From Spectrum (b) (Figure 4.29 and Figure 4.30), it can be seen that irradiation of H4 has resulted in a significant response from a number of protons. However, due to the close proximity of H4 to other protons in the spectrum, the irradiation was not selective, with H5, H9 and H10 also being irradiated. This resulted in the appearance of extra correlations. Despite this limitation, a number of inferences may still be made regarding the interactions of this proton. There appears to be a correlation between H4 and/or H5 with H3. This could be a NOESY correlation between H5 and H3, or a COSY correlation between H4 and H3. There appears to be a correlation between H4 and H15, which was also observed in the high temperature selective irradiation NOESY experiments (Figure 4.24 (b)). A correlation to H23 is also evident, which is most likely due to a NOESY correlation with H5, and the correlation to the methyl protons of the TBS group is most likely due to H4. A COSY correlation between H4 and H21 can also be seen. A number of other correlations are also present in spectrum (b), however these are not considered real as they are out of phase.

Spectrum (c) (Figure 4.29 and Figure 4.30) shows the results of irradiation of H6, which appears to interact *via* a COSY correlation with H23 and H5. NOESY correlations are also evident, with H11, H4 and the methyl protons of the TBS group. The interaction of H6 with H11 was also present in the high temperature selective irradiation NOESY experiments (Section 4.4.3.1), and is important, as it provides strong evidence for the axial orientation of the PMB side-chain.

While the selective irradiation of the protons on C13 in the high temperature experiments did not result in the appearance of any correlations between H13 and the other protons of methylated cyclohexanone **318**, the irradiation of H13 at – 20 ^{o}C did result in the appearance of a number of correlations (Spectrum (d), Figure 4.29 and Figure 4.30). The protons on C13 exhibit NOESY correlations to H3, H9 and H11, with the correlation to H3 providing strong evidence for the equatorial position of the methyl group.

The irradiation of the protons on C11 (Spectrum (e), Figure 4.29 and Figure 4.30), which was not conducted in the high temperature VT-NMR selective irradiation NOESY experiments (Section 4.4.3.1), also resulted in a significant response from a number of protons. The NOESY correlations to H6 and H13 are evident and were also observed in the selective irradiation experiments of H6 and H13. Additionally, the correlation to H6 was also observed in the high temperature experiments (Section 4.4.3.1).The NOESY correlation to the protons on C10 is also evident, as is the COSY correlation to H9.

In summary, the results of the low temperature VT NMR experiments described above provide further evidence for the axial orientation of the PMB side-chain, with the correlations between H6 and H11 (which was also observed in the high temperature NOESY experiments, Section 4.4.3.1) and H13 and H3 strongly supporting this proposition. The equatorial position of the quaternary methyl is also supported by correlations with H9 and H11. The NOESY correlations observed in this set of experiments are summarised in Figure 4.31 and also indicate that the alkene side-chain is positioned as shown at – 20 ^{o}C, with the PMB side-chain rotating such that H11 can interact with both H6 and the protons on C13.

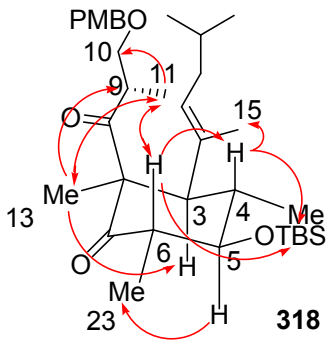
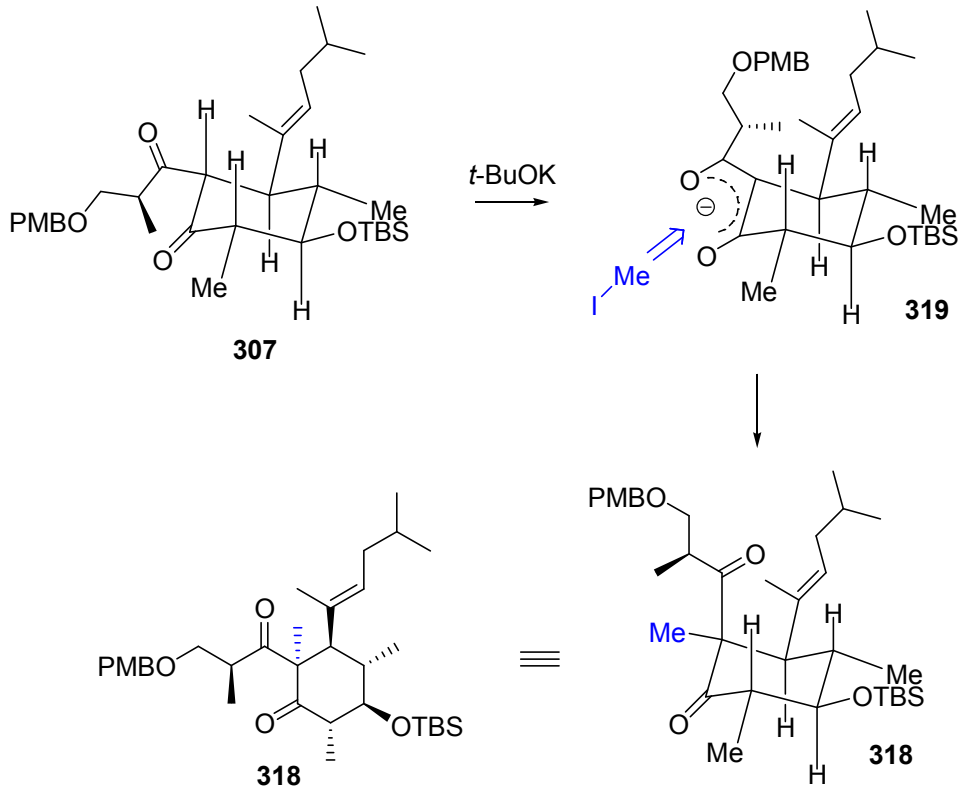


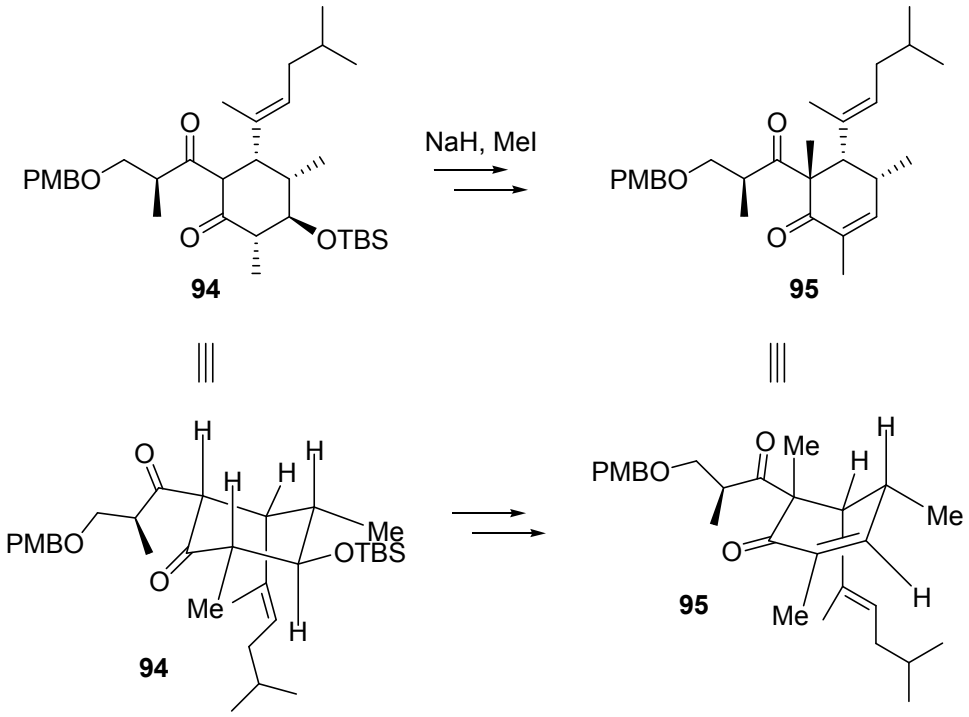
*Figure 4.31. NOESY correlations observed in selective irradiation experiments of methylated cyclohexanone **318** at – 20 ^{o}C in d_6-acetone at 600 MHz.*

The NOESY correlations observed in both the high and low temperature VT-NMR selective irradiation NOESY experiments indicate that the methylation of cyclohexanone **318** has proceeded from the equatorial position to give the *anti* stereochemistry in methylated cyclohexanone **318** (Scheme 4.11).



*Scheme 4.11. Equatorial methylation of cyclohexanone **307** to give anti methylated cyclohexanone **318**.*

Interestingly, in the synthesis of *anti* tridachiahydropyrone (**14**),[22] the methylation of cyclohexanone **94** occurred from the axial position to give (following elimination) *anti* methylated cyclohexenone **95** (Scheme 4.12).



*Scheme 4.12. Methylation of cyclohexanone **94** in the synthesis of anti tridachiahydropyrone (**14**).*

In the case of cyclohexanones of type **94**,[13,14,22] it was not clear whether the stereochemical outcome of the methylation to give *anti* methylated cyclohexenones of type **95** was influenced by the axial orientation of the adjacent alkyl/alkene group, and thus occurred *anti* to this group, or whether the methylation occurred from the axial position, due to steric hindrance from other substituents around the cyclohexanone ring. From the studies undertaken on cyclohexanones **226** and **279** in Chapter 3 and *syn* model system **282** in this chapter (Section 4.2), it can be concluded that the methylation does not have to occur *anti* to the adjacent alkyl group, but instead, the stereochemical outcome of the methylation is influenced by the substituents around the cyclohexanone ring.

Therefore, in the case of cyclohexanone **307** (Scheme 4.11), the methylating agent may have experienced more steric hindrance approaching from the top face of cyclohexanone **307**, compared to the model system (**300**, Section 4.2) where the side chain is smaller (a methyl group), making the equatorial methylation to give *anti* methylated cyclohexanone **318** more favourable. Further, the only difference

between cyclohexanone **94** used in the synthesis of *anti* tridachiahydropyrone (**14**) and cyclohexanone **307** used in this case, is the orientation of the alkene side-chain, which is in the axial position in **94** and in the equatorial position in **307**. Thus, based on the results of the methylation of **307**, it can be concluded that the approach of the methylating agent to the top face of cyclohexanone **307** may have been hindered by the equatorial alkenyl side-chain, resulting in equatorial methylation to give *anti* methylated cyclohexanone **318**.

Additionally, the lack of success with elimination of the OTBS group may be attributed to hindrance from the PMB side-chain. The NOESY data obtained for methylated cyclohexanone **318** indicated that the PMB side-chain is situated above the top face of the ring. The proton adjacent to the endocyclic carbonyl would thus be shielded by the PMB side-chain, preventing approach of the base and thus inhibiting the elimination of the OTBS group.

The inability to both generate the required *syn* stereochemistry in methylated cyclohexanone **318** and effect the required elimination to synthesise the corresponding *syn* cyclohexenone meant that the synthesis of *syn* tridachiahydropyrone (**42**) could not be achieved using the methodology developed for the synthesis of *syn* model **282**. Thus, in order for *syn* tridachiahydropyrone (**42**) to be successfully synthesised, a completely new approach would have to be devised.

4.5 Conclusion and future work

The methodology developed in Chapter 3 towards the conversion of *cis* enones into cyclohexanones of type **279** was successfully applied to the synthesis of more complex cyclohexanones **300** and **307** (Figure 4.32).

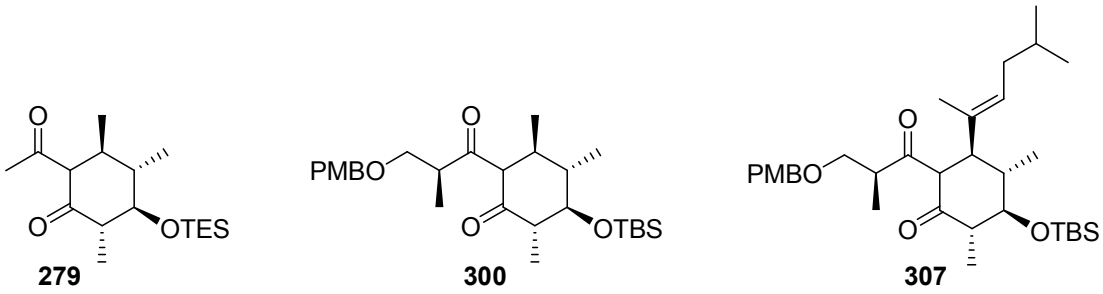
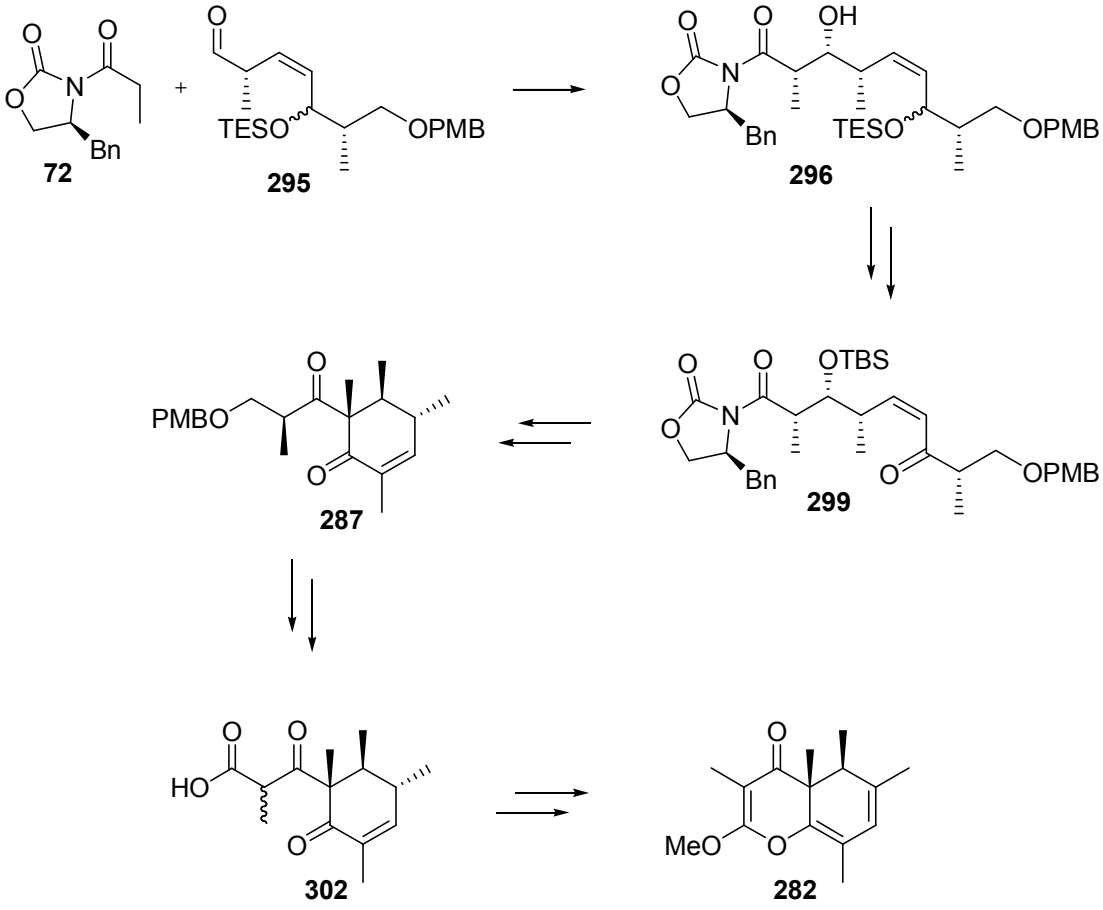


*Figure 4.32. Cyclohexanones **279**, **300** and **307** synthesised from cis enones.*

The precursor to cyclohexanones **300** and **307**, *cis* enone **299**, was synthesised utilising a selective deprotection strategy, with the stereochemical array on the molecule achieved *via* a titanium-mediated aldol reaction between complex aldehyde **295** and Evans auxiliary **72** (Scheme 4.13).



*Scheme 4.13. Synthesis of syn model **282** from cis enone **299**.*

The dimethyl cuprate addition to *cis* enone **299** proceeded in an *anti*-Felkin manner as predicted, to give cyclohexanone **300** (Figure 4.32), which, following methylation and elimination, gave *syn* methylated cyclohexenone **287** (Scheme 4.13). The stereochemical outcome of the methylation was elucidated using selective irradiation NOESY and *syn* methylated cyclohexenone **287** was subsequently converted to *syn* model **282** *via* functional group manipulations, which included a P_2O_5-mediated dehydration of acid **302**.

Comparative NMR analysis between the natural product and both *syn* model **282** and *anti* model **306** showed that the ^{1}H and ^{13}C NMR data of *syn* model **282** is a closer match to the natural product than both *anti* model **306** and *anti* tridachiahydropyrone (**14**), indicating that the stereochemistry in the natural tridachiahydropyrone may indeed be *syn*.

However, the application of similar synthetic methodology to the preparation of *syn* tridachiahydropyrone (**42**) was not successful. Synthesis of cyclohexanone **307** (Figure 4.32) was accomplished, with the addition of **96** to *cis* enone **299** proceeding *via anti*-Felkin addition, as predicted. Subsequent methylation of cyclohexanone **307** using modified conditions yielded the undesired *anti* methylated cyclohexanone **318** (Figure 4.33), the stereochemistry and conformation of which was deduced through extensive selective irradiation NOESY VT NMR experiments.

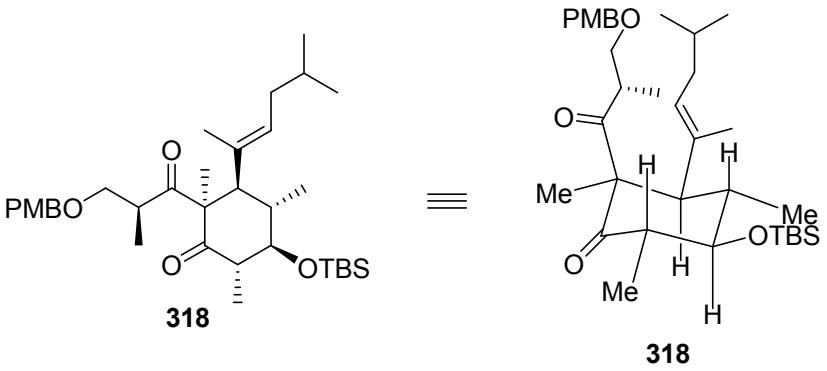
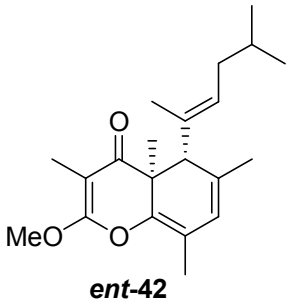


*Figure 4.33. Anti methylated cyclohexanone **318**.*

It was proposed that axial methylation was inhibited due to the presence of the equatorial alkenyl chain, and the desired elimination was inhibited by the resulting

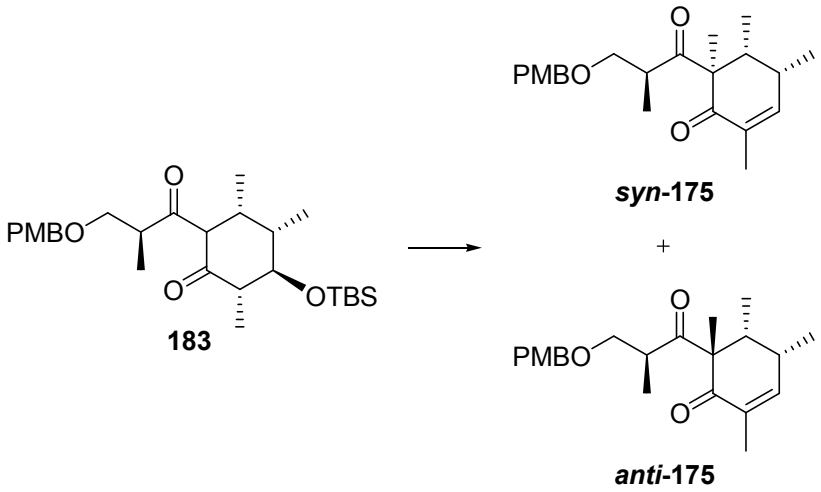
axial position of the PMB side-chain (Figure 4.33). Thus, the synthesis of *syn* methylated cyclohexenone **288** could not be achieved in this system and hence the synthesis of *syn* tridachiahydropyrone (**42**) could not be achieved *via* this route. It may be possible however, to synthesise the enantiomer (***ent*-42**) of *syn* tridachiahydropyrone (**42**).



***ent*-42**

*Figure 4.34. Enantiomer of syn tridachiahydropyrone (**42**).*

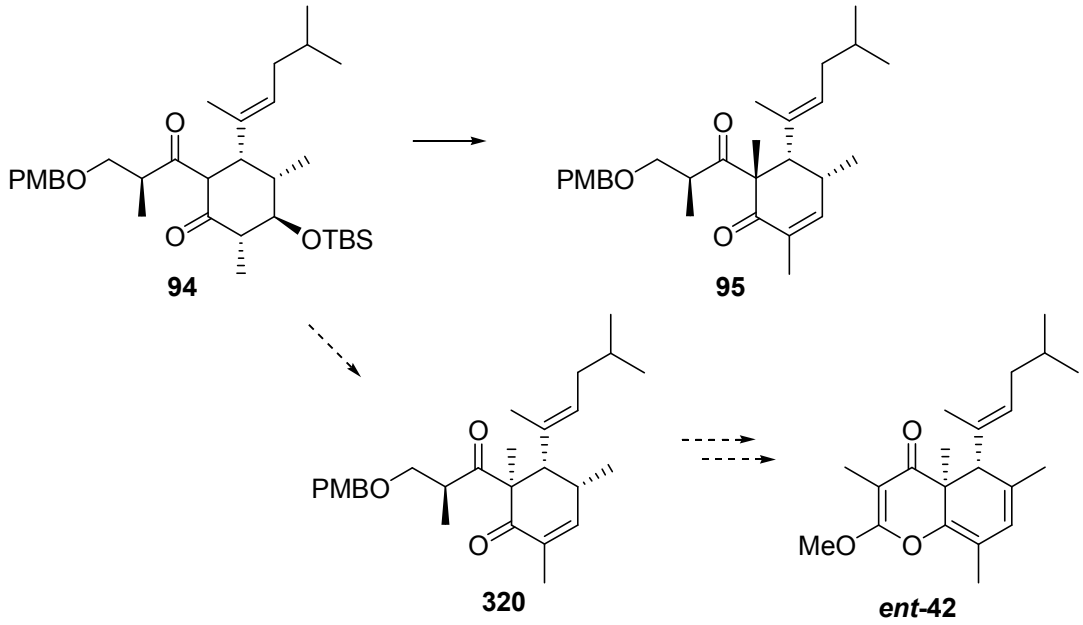
It has been shown that cyclohexanone **183** can produce *syn* methylated cyclohexenone ***syn*-175** (Scheme 4.14) following methylation, as discussed in Chapter 2, Section 2.6.1.3.



*Scheme 4.14. Formation of **syn-175** by methylation of cyclohexanone **183**.*

While it was found by David Jeffery[22] that the more complex cyclohexanone **94** (Scheme 4.15) gave only the *anti* methylated cyclohexenone **95** (as discussed in

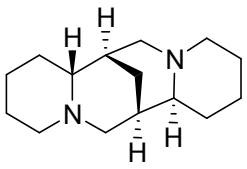
Chapter 1, Section 1.5), it may be possible to find alternative methylation conditions to form *syn* methylated cyclohexenone **320** (Scheme 4.15).



*Scheme 4.15. Proposed synthesis of **ent-42** from syn methylated cyclohexenone **320**.*

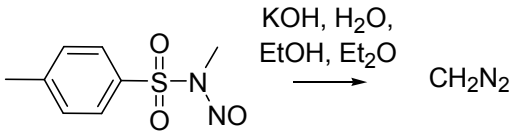
Cyclohexenone **320** could then be taken through the steps as herein before described to produce ***ent*-42**. The spectral data of ***ent*-42** could then be compared to that reported for the natural product, allowing the true structure of tridachiahydropyrone to be elucidated.

4.6 Experimental



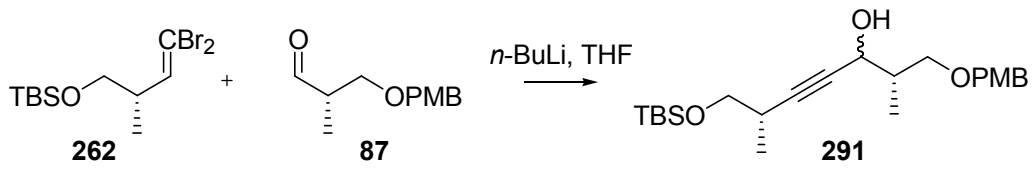
Sparteine

Pure (–)-sparteine was obtained from (–)-sparteine.HSO_4 by dissolving the salt (6.0 g) in NaOH (1 M, 100 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 50 mL) and Et_2O (3 x 50 mL). The organic extracts were combined and washed with brine (1 x 100 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 3.5 g of a yellow oil. The oil was purified by distillation under reduced pressure (Kugelrohr) to give 3.1 g of the title compound as a clear, colourless oil (BPt 120 ^oC at 0.1 mmHg, lit. BPt[26] 137 – 138 ^oC at 1 mmHg), with identical spectral data to that reported in the literature.[27]



Diazomethane

Diazomethane was prepared immediately prior to use by the following procedure.[19] To a solution of KOH (0.16 g, 2.90 mmol) in H_2O (0.3 mL) and EtOH (2 mL) was added slowly a solution of Diazald® (0.14 g, 0.65 mmol) in Et_2O (5 mL), with gentle heating of the KOH solution such that the yellow diazomethane was distilled over as it was formed. Extra Et_2O (1 mL) was added to the KOH solution to distill over the remaining diazomethane, which was stored under N_2.



(2*S*,3*R*,6*S*)-7-(*tert*-Butyldimethylsilanyloxy)-1-(4-methoxybenzyloxy)-dimethylhept-4-yn-3-ol and (2*S*,3*S*,6*S*)-7-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxybenzyloxy)-dimethylhept-4-yn-3-ol (291)

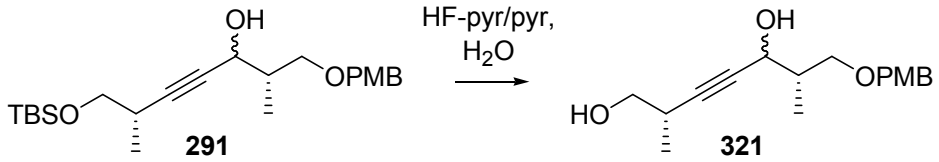
To a stirring solution of di-bromoalkene **262** (2.3 g, 6.5 mmol) in dry THF (32 mL) under N_2 at – 40 ^oC was added dropwise *n*-BuLi (1.37 M in hexanes, 10.4 mL, 14.2 mmol) and the resulting yellow solution was stirred at – 40 ^oC for 1 hr and at RT for 10 min. The solution was cooled to – 78 ^oC and was added dropwise a solution of aldehyde **87** (1.5 g, 7.1 mmol) in dry THF (10 mL) *via* cannula (3 mL rinse). The solution was stirred at – 78 ^oC for 1 hr after which time it was diluted with Et_2O (23 mL). The reaction was quenched by addition of NH_4Cl (sat., 42 mL) and warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic extracts were combined and washed with brine (1 x 80 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 3.4 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 2.6 g (100% yield) of the title compound as a clear, yellow oil (R_f = 0.28), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}) 3446.2, 2935.1, 1614.6, 1514.7, 1463.1, 1361.5, 1302.5, 1249.8, 1173.1, 1090.0, 1036.7; **HRESIMS** calculated for $C_{23}H_{38}O_4SiNa^+$ ($M+Na^+$): 429.2437; found 429.2439.

Isomer A: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 6H, TBS Si(CH_3)$_2$), 0.89 (s, 9H, TBS SiC(CH_3)$_3$), 1.02 (d, 3H, CH(OH)CH(CH_3), *J* = 7.2 Hz), 1.15 (d, 3H, CH(CH_3)C≡, *J* = 6.9 Hz), 1.98 – 2.06 (m, 1H, CH(OH)C*H*(CH_3)), 2.54 – 2.68 (m, 1H, C*H*(CH_3)C≡), 3.40 – 3.49 (m, 2H, TBSOCH_AH_B and CH_AH_BOPMB), 3.56 – 3.71 (m, 2H, TBSOCH$_A$$H_B$ and CH$_A$$H_B$OPMB), 3.80 (s, 3H, PMB OCH_3), 4.36 – 4.49 (m, 3H, PMB OCH_2 and C*H*(OH)), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.23 – 7.27 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 5.28 (2C), 13.2, 17.45,

18.3, 25.9, 29.12, 39.5, 55.2, 66.5, 67.1, 73.0, 73.4, 80.7, 87.8, 113.77, 129.1, 130.0, 159.20.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.06 (s, 6H, TBS Si(CH_3)$_2$), 0.89 – 0.90 (m, 12H, TBS SiC(CH_3)$_3$ and CH(OH)CH(CH_3)), 1.17 (d, 3H, CH(CH_3)C≡, J = 6.9 Hz), 2.14 – 2.27 (m, 1H, CH(OH)CH(CH$_3$)), 2.54 – 2.68 (m, 1H, CH(CH$_3$)C≡), 3.40 – 3.49 (m, 2H, TBSOCH_AH$_B$ and CH_AH$_B$OPMB), 3.56 – 3.71 (m, 2H, TBSOCH$_A$$H_B$ and CH$_A$$H_B$OPMB), 3.80 (s, 3H, PMB OCH_3), 4.36 – 4.49 (m, 3H, PMB OCH_2 and CH(OH)), 6.86 – 6.89 (m, 2H, PMB ArH), 7.23 – 7.27 (m, 2H, PMB ArH); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 5.33 (2C), 12.8, 17.53, 18.3, 25.9, 29.15, 38.7, 55.2, 66.5, 67.2, 73.0, 73.1, 80.0, 88.0, 113.75, 129.2, 129.9, 159.16.



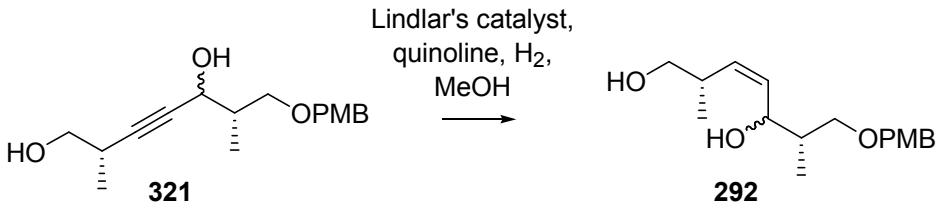
(2*S*,5*R*,6*S*)-7-(4-Methoxybenzyloxy)-dimethylhept-3-yne-1,5-diol and (2*S*,5*S*,6*S*)-7-(4-methoxybenzyloxy)-dimethylhept-3-yne-1,5-diol (321)

A solution of TBS ether **291** (0.40 g, 0.98 mmol) in H_2O (0.66 mL) and HF-pyr/pyr (6.5 mL, from a stock solution containing dry THF (10 mL), pyridine (5 mL) and pyridinium hydrofluoride (2.1 g)) in a Teflon screw-cap jar was stirred at 0 ^{o}C for 1 hr and then placed in the freezer for 25 hr. The solution was diluted with Et_2O (30 mL) and the organic phase was washed with $CuSO_4$ (sat., 1 x 15 mL), $NaHCO_3$ (sat., 1 x 15 mL) and brine (1 x 15 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.04 g of a clear, colourless oil. The oil was purifed by flash column chromatography on silica (40% EtOAc/hexanes → 60% EtOAc/hexanes) to give 0.28 g (80% yield) of the title compound as a clear, colourless oil (R_f = 0.2 in 60% EtOAc/hexanes), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}) 3401.0, 2933.4, 1514.0, 1248.4, 1035.6; **HRESIMS** calculated for $C_{17}H_{24}O_4Na^+$ ($M+Na^+$): 315.1573; found: 315.1572.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.01 (d, 3H, CH(OH)CH(C*H*$_3$), *J* = 6.9 Hz), 1.14 (d, 3H, CH(C*H*$_3$)C≡, *J* = 7.2 Hz), 2.00 – 2.08 (m, 1H, CH(OH)C*H*(CH$_3$)), 2.43 (bs, 2H, O*H*), 2.65 – 2.72 (m, 1H, C*H*(CH$_3$)C≡), 3.42 (d of d, 1H, C*H*$_A$H$_B$OPMB, *J* = 9.3, 7.2 Hz), 3.52 (d of d, 2H, HOC*H*$_2$, *J* = 8.1, 6 Hz), 3.61 – 3.68 (m, 1H, CH$_A$*H*$_B$OPMB), 3.80 (s, 3H, PMB OC*H*$_3$), 4.38 – 4.49 (m, 3H, PMB OC*H*$_2$ and ≡CC*H*(OH)), 6.86 – 6.90 (m, 2H, PMB Ar*H*), 7.23 – 7.27 (m, 2H, PMB Ar*H*); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 13.3, 17.0, 29.5, 39.5, 55.3, 66.6, 66.8, 73.06, 73.14, 81.1, 87.3, 113.81, 129.2, 129.9, 159.1.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.90 (d, 3H, CH(OH)CH(C*H*$_3$), *J* = 6.9 Hz), 1.16 (d, 3H, CH(C*H*$_3$)C≡, *J* = 7.2 Hz), 2.20 – 2.25 (m, 1H, CH(OH)C*H*(CH$_3$)), 2.43 (bs, 2H, O*H*), 2.65 – 2.72 (m, 1H, C*H*(CH$_3$)C≡), 3.46 – 3.58 (m, 3H, C*H*$_A$CH$_B$OPMB and HOC*H*$_2$), 3.61 – 3.68 (m, 1H, CH$_A$C*H*$_B$OPMB), 3.80 (s, 3H, PMB OC*H*$_3$), 4.38 – 4.49 (m, 3H, PMB OC*H*$_2$Ar and ≡CC*H*(OH)), 6.86 – 6.90 (m, 2H, PMB Ar*H*), 7.23 – 7.27 (m, 2H, PMB Ar*H*); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 12.9, 17.1, 29.5, 38.6, 55.3, 66.6, 66.85, 73.2, 73.3, 81.8, 87.5, 113.83, 129.4, 129.8, 159.1.



***cis*-(2*S*,5*R*,6*R*)-7-(4-Methoxybenzyloxy)-dimethyl-hept-3-ene-1,5-diol and *cis*-(2*S*,5*S*,6*R*)-7-(4-methoxybenzyloxy)-dimethyl-hept-3-ene-1,5-diol (292)**

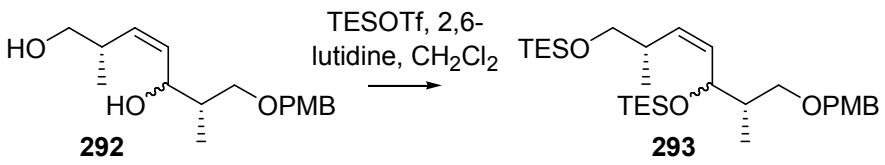
To a stirring solution of alkyne **321** (3.3 g, 11.4 mmol) in dry MeOH (380 mL) under N_2 at RT was added dropwise quinoline (1.9 mL, 16.0 mmol) followed by Lindlar's catalyst (1.1 g). The solution was placed under an atmosphere of H_2 and left to stir at RT for 2 hr. The reaction was quenched by flushing with N_2 and the solution was

filtered through celite (EtOAc used as eluent). The solvents were removed *in vacuo* and the residue was diluted with Et_2O (130 mL). The organic layer was washed with HCl (10%, 1 x 65 mL), H_2O (1 x 65 mL), $NaHCO_3$ (sat., 1 x 65 mL) and brine (1 x 65 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 3.4 g (100%) of the title compound as a clear, colourless oil, which was an inseparable mixture of two isomers.

IR (film, cm^{-1}) 3383.9, 2953.2, 1512.9, 1248.0, 1034.0; **HRESIMS** calculated for $C_{17}H_{26}O_4Na^+$ ($M+Na^+$): 317.1729; found: 317.1730.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.86 (d, 3H, CH(OH)CH(C*H*$_3$), *J* = 7.2 Hz), 0.97 (d, 3H, $CH_2CH(CH_3)CH=$, *J* = 6.9 Hz), 1.91-2.00 (m, 1H, =CHCH(OH)C*H*(CH_3)), 2.61 (bs, 2H, O*H*), 2.72 – 2.88 (m, 1H, $CH_2CH(CH_3)CH=$), 3.22 – 3.60 (m, 4H, HOC*H*$_2$ and C*H*$_2$OPMB), 3.80 (s, 3H, PMB OC*H*$_3$), 4.43 – 4.47 (m, 3H, PMB OC*H*$_2$ and =CHC*H*(OH)), 5.31 (app. t, 1H, C*H*=CH, *J* = 10.7 Hz), 5.52 (d of d, 1H, CH=C*H*, *J* = 11.1, 8.7 Hz), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.23 – 7.26 (m, 2H, PMB Ar*H*); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 13.5, 17.4, 35.3, 38.9, 55.3, 67.5, 72.4, 73.1, 74.5, 113.82, 129.3, 129.7, 132.0, 135.5, 159.1.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.92 (d, 3H, $CH_2CH(CH_3)CH=$, *J* = 6.9 Hz), 0.95 (d, 3H, =CHCH(OH)CH(C*H*$_3$), *J* = 6.9 Hz), 1.91 – 2.00 (m, 1H, =CHCH(OH)C*H*(CH_3)), 2.61 (bs, 2H, O*H*), 2.72 – 2.88 (m, 1H, $CH_2CH(CH_3)CH=$), 3.22 – 3.60 (m, 4H, HOC*H*$_2$ and C*H*$_2$OPMB), 3.80 (s, 3H, PMB OC*H*$_3$), 4.34 (app. t, 1H, =CHC*H*(OH), *J* = 8.1 Hz), 4.43 – 4.47 (m, 2H, PMB OC*H*$_2$), 5.31 (app. t, 1H, C*H*=CH, *J* = 10.7 Hz), 5.66 (d of d, 1H, CH=C*H*, *J* = 10.8, 8.4 Hz), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.23 – 7.26 (m, 2H, PMB Ar*H*); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 12.1, 17.0, 35.2, 38.5, 55.3, 66.9, 69.5, 73.1, 73.3, 113.77, 129.2, 130.1, 131.6, 136.4, 159.1.



292 **293**

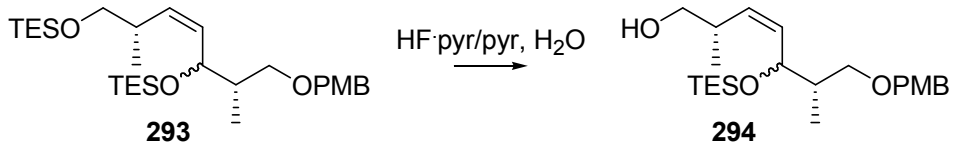
(2*S*,3*R*,6*R*)-*cis*-1-(4-Methoxybenzyloxy)-dimethyl-3,7-bis-triethylsilanyloxyhept-4-ene and (2*S*,3*S*,6*R*)-*cis*-1-(4-methoxybenzyloxy)-dimethyl-3,7-bis-triethyl-silanyloxyhept-4-ene (293)

To a stirring solution of diol **292** (0.04 g, 0.14 mmol) in dry CH_2Cl_2 (0.8 mL) under N_2 at – 78 ^oC was added dropwise 2,6-lutidine (0.07 mL, 0.57 mmol) followed immediately by dropwise addition of TESOTf (0.1 mL, 0.43 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., 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 0.14 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.07 g (92% yield) of the title compound as a clear, colourless oil (R_f = 0.6 in 20% EtOAc/hexanes), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}) 2957.1, 2875.3, 1514.4, 1247.7, 1090.0, 1008.0; **HRESIMS** calculated for $C_{29}H_{54}O_4SiNa^+$ ($M+Na^+$): 545.3459; found: 545.3449.

Isomer A: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.47-0.63 (m, 12H, TES Si(CH_2CH_3)$_3$), 0.90 – 1.00 (m, 24H, TES Si(CH_2CH_3)$_3$, TESOCH_2CH(CH_3) and =CHCH(OTES)CH(CH_3)), 1.75 – 1.87 (m, 1H, CH(OTES)C*H*(CH_3)), 2.54 – 2.67 (m, 1H, TESOCH_2C*H*(CH_3)), 3.17 – 3.55 (m, 4H, CH_2OPMB and TESOCH_2), 3.80 (s, 3H, PMB OCH_3), 4.34 – 4.41 (m, 3H, PMB OCH_2 and =CHC*H*(OTES)), 5.11 – 5.21 (m, 1H, C*H*=CH), 5.31 – 5.41 (m, 1H, CH=C*H*), 6.85 – 6.88 (m, 2H, PMB Ar*H*), 7.24 – 7.27 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 4.4, 5.1, 6.8, 6.9, 13.7, 17.3, 35.3, 40.7, 55.3, 67.5, 70.1, 72.0, 72.51, 113.59, 128.99, 131.0, 131.9, 132.7, 159.1.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.47 – 0.63 (m, 12H, TES Si(CH_2CH_3)$_3$), 0.90 – 1.00 (m, 24H, TES Si(CH_2CH_3)$_3$, TESO$CH_2CH(CH_3)$ and =CHCH(OTES)CH(CH_3)), 1.75 – 1.87 (m, 1H, CH(OTES)C*H*(CH_3)), 2.54 – 2.67 (m, 1H, TESO$CH_2CH(CH_3)$), 3.17 – 3.55 (m, 4H, CH_2OPMB and TESOCH_2), 3.80 (s, 3H, PMB OCH_3), 4.34 – 4.41 (m, 2H, PMB OCH_2), 4.50 – 4.54 (m, 1H, =CHC*H*(OTES)), 5.11 – 5.21 (m, 1H, C*H*=CH), 5.31 – 5.41 (m, 1H, CH=C*H*), 6.85 – 6.88 (m, 2H, PMB Ar*H*), 7.24 – 7.27 (m, 2H, PMB Ar*H*); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 4.4, 5.1, 6.8, 6.9, 11.7, 17.7, 35.2, 41.2, 55.3, 67.2, 69.1, 72.50, 72.6, 113.61, 128.96, 130.9, 131.9, 132.7, 159.1.



293 **294**

(2*S*,5*R*,6*R*)-*cis*-7-(4-Methoxybenzyloxy)-dimethyl-5-triethylsilanyloxyhept-3-en-1-ol and (2*S*,5*S*,6*R*)-*cis*-7-(4-methoxybenzyloxy)-dimethyl-5-triethylsilanyl-oxyhept-3-en-1-ol (294)

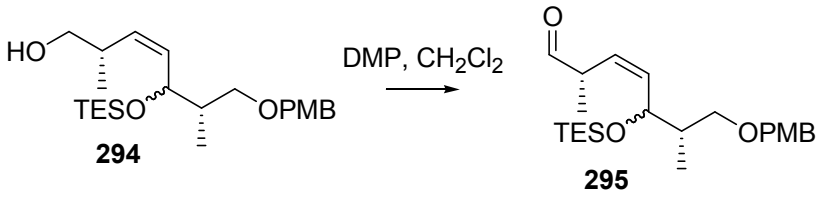
A solution of **293** (0.09 g, 0.18 mmol) in H_2O (0.12 mL) and HF-pyr/pyr (1.2 mL, from a stock solution containing dry THF (10 mL), pyridine (5 mL) and pyridinium hydrofluoride (2.1 g)) in a Teflon screw-cap jar was stirred at – 20 ^{o}C for 1.5 hr. The solution was diluted with Et_2O (30 mL) and the organic phase was washed with $CuSO_4$ (sat., 1 x 15 mL), $NaHCO_3$ (sat., 1 x 15 mL) and brine (1 x 15 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a clear, colourless oil. The oil was purified by flash column chromatography on silica (40% EtOAc/hexanes → 60% EtOAc/hexanes) to give 0.06 g (74% yield, over 3 cycles) of the title compound as a clear, colourless oil (R_f = 0.58 in 60% EtOAc/hexanes), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}) 3445.9, 2954.9, 2875.9, 1513.6, 1248.0, 1038.7; **HRESIMS** calculated for $C_{23}H_{40}O_4SiNa^+$ (M+Na$^+$): 431.2594; found: 431.2591.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.52 – 0.61 (m, 6H, TES Si(CH_2CH_3)$_3$), 0.87 – 1.00 (m, 15H, TES Si(CH_2CH_3)$_3$, HO$CH_2CH(CH_3)$ and

CH(TESO)CH(CH_3)), 1.63 (bs, 1H, O*H*), 1.76 – 1.85 (m, 1H, CH(TESO)C*H*(CH$_3$)), 2.60 – 2.70 (m, 1H, HOCH$_2$C*H*(CH$_3$)), 3.19 – 3.52 (m, 4H, CH_2OPMB and HOCH_2), 3.81 (s, 3H, PMB OCH_3), 4.41 – 4.30 (m, 2H, PMB OCH_2), 4.53 – 4.58 (m, 1H, C*H*(OTES)), 5.15 – 5.23 (m, 1H, C*H*=CH), 5.43 – 5.55 (m, 1H, CH=C*H*), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.23 – 7.27 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 5.09, 6.9, 11.7, 17.2, 35.3, 41.3, 67.6, 69.24, 72.3 (2C), 113.67, 129.1, 130.9, 131.9, 134.8, 159.1.

Isomer B: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.52 – 0.61 (m, 6H, TES Si(CH_2CH$_3$)$_3$), 0.87 – 1.00 (m, 15H, TES Si(CH$_2$CH_3)$_3$, HOCH$_2$CH(CH_3) and =CHCH(TESO)CH(CH_3)), 1.63 (bs, 1H, O*H*), 1.95 – 2.03 (m, 1H, CH(TESO)C*H*(CH$_3$)), 2.60 – 2.70 (m, 1H, HOCH$_2$C*H*(CH$_3$)), 3.19 – 3.52 (m, 4H, CH_2OPMB and HOCH_2), 3.81 (s, 3H, PMB OCH_3), 4.41 – 4.30 (m, 2H, PMB OCH_2), 4.45 – 4.52 (m, 1H, C*H*(OTES), 5.13 (app. t, 1H, C*H*=CH, *J* = 10.2 Hz), 5.43 – 5.55 (m, 1H, CH=C*H*), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.23 – 7.27 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 5.06, 6.9, 12.4, 16.9, 35.5, 40.1, 67.8, 69.20, 71.9, 72.7, 113.71, 129.0, 130.9, 131.4, 133.3, 159.1.



(2*S*,5*R*,6*R*)-*cis*-7-(4-Methoxybenzyloxy)-dimethyl-5-triethylsilanyloxyhept-3-enal and (2*S*,5*S*,6*R*)-*cis*-7-(4-methoxybenzyloxy)-dimethyl-5-triethylsilanyloxy-hept-3-enal (295)

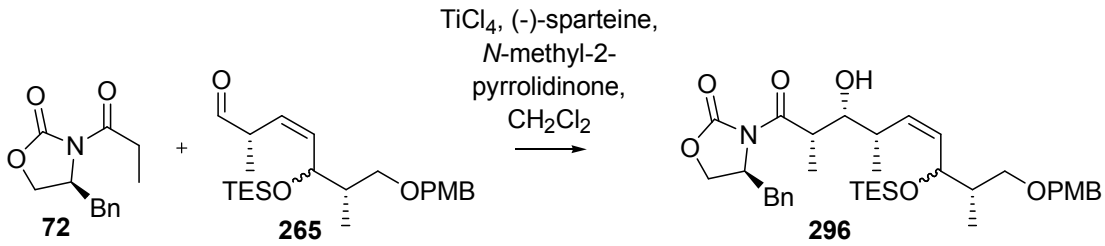
To a stirring solution of DMP (0.03 g, 0.07 mmol) in dry CH_2Cl_2 (0.2 mL) under N_2 at RT was added dropwise a solution of **294** (0.02 g, 0.04 mmol) in dry CH_2Cl_2 (0.2 mL) *via* cannula (0.1 mL rinse) and the solution was left to stir for 1 hr. The solution was diluted with Et_2O and the reaction was quenched by addition of a solution of $NaHCO_3$ (sat., 1.5 mL) containing $Na_2S_2O_3.5H_2O$ (0.18 g), and stirred for 5 min. The layers were separated and the organic layer was washed with $NaHCO_3$ (sat., 1 x 6 mL) and brine (1 x 6 mL), then dried ($MgSO_4$), filtered and solvent was removed *in*

vacuo to give 0.02 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.014 g (78% yield) of the title compound as a clear, colourless oil (R_f = 0.45), which was an inseparable mixture of two isomers.

IR (film, cm^{-1}) 2955.2, 1731.9, 1513.7, 1247.8, 1038.6, 743.1; **HRESIMS** calculated for $C_{23}H_{38}O_4SiNa^+$ ($M+Na^+$): 429.2437; found 429.2433.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.51 – 0.60 (m, 6H, TES Si(C*H*$_2$CH$_3$)$_3$), 0.87 – 0.96 (m, 12H, TES Si(CH$_2$C*H*$_3$)$_3$ and CH(OTES)CH(C*H*$_3$)), 1.13 (d, 3H, HC(O)CH(C*H*$_3$), *J* = 6.9 Hz), 1.74 – 1.82 (m, 1H, CH(OTES)C*H*(CH$_3$)), 3.24 (d of d, 1H, C*H*$_A$H$_B$OPMB, *J* = 9, 6 Hz), 3.33 – 3.48 (m, 2H, CH$_A$*H*$_B$OPMB and HC(O)C*H*(CH$_3$)), 3.80 (s, 3H, PMB OC*H*$_3$), 4.38 – 4.41 (m, 2H, PMB OC*H*$_2$), 4.56 (app. quart, 1H, C*H*(OTES), *J* = 4.5 Hz), 5.24 (app. t, 1H, C*H*=CH, *J* = 10.7 Hz), 5.58 – 5.70 (m, 1H, CH=C*H*), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.22 – 7.26 (m, 2H, PMB Ar*H*), 9.57 (d, 1H, *H*C(O), *J* = 1.8 Hz); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 5.0, 6.9, 11.7, 14.5, 41.1, 45.9, 55.3, 69.1, 72.1, 72.7, 113.7, 125.1, 129.02, 130.7, 136.9, 159.0, 201.0.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.51 – 0.60 (m, 6H, TES Si(C*H*$_2$CH$_3$)$_3$), 0.87 – 0.96 (m, 12H, TES Si(CH$_2$C*H*$_3$)$_3$ and CH(OTES)CH(C*H*$_3$)), 1.17 (d, 3H, HC(O)CH(C*H*$_3$), *J* = 6.9 Hz), 1.89 – 1.97 (m, 1H, CH(OTES)C*H*(CH$_3$)), 3.31 – 3.48 (m, 3H, C*H*$_2$OPMB and HC(O)C*H*(CH$_3$)), 3.80 (s, 3H, PMB OC*H*$_3$), 4.38 – 4.41 (m, 2H, PMB OC*H*$_2$), 4.48 (d of d, 1H, C*H*(OTES), *J* = 9.3, 6 Hz), 5.24 (app. t, 1H, C*H*=CH, *J* = 10.7 Hz), 5.58 – 5.70 (m, 1H, CH=C*H*), 6.86 – 6.89 (m, 2H, PMB Ar*H*), 7.22 – 7.26 (m, 2H, PMB Ar*H*), 9.47 (d, 1H, *H*C(O), *J* = 1.2 Hz); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 5.0, 6.9, 12.6, 14.0, 40.5, 46.4, 55.3, 69.5, 71.7, 72.5, 113.7, 126.3, 128.98, 130.7, 135.2, 159.0, 201.3.



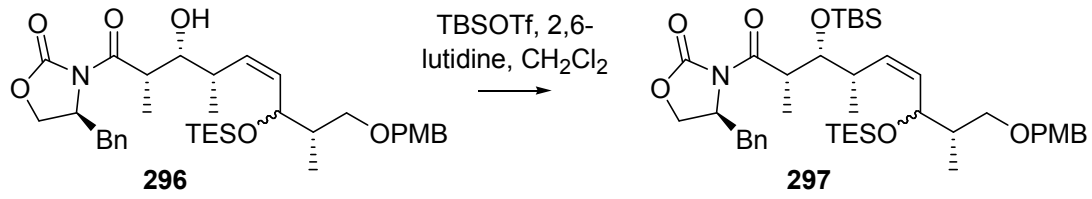
72 **265** **296**

(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*,7*R*,8*S*)-*cis*-3-hydroxy-9-(4-methoxybenzyloxy)-2,4,8-trimethyl-7-triethylsilanyloxynon-5-enoyl]-oxazolidin-2-one and (*S*)-4-benzyl-3-[(2*S*,3*R*,4*S*,7*S*,8*S*)-*cis*-3-hydroxy-9-(4-methoxybenzyloxy)-2,4,8-trimethyl-7-triethylsilanyloxynon-5-enoyl]-oxazolidin-2-one (296)

To a stirring solution of *N*-acyloxazolidinone **72** (3.0 g, 12.8 mmol) in dry CH_2Cl_2 (32 mL) under N_2 at 0 ^oC was added dropwise $TiCl_4$ (1 M solution in CH_2Cl_2, 12.9 mL, 12.8 mmol) and resulting yellow slurry was stirred for 5 min. After this time (–)-sparteine (3.0 mL, 12.8 mmol) was added dropwise, and the resulting dark red solution was stirred at 0 ^oC for 20 min, before being cooled to – 78 ^oC. To the solution was added dropwise *N*-methyl-2-pyrrolidinone (1.3 mL, 12.8 mmol) and stirring continued for 10 min, after which time a solution of aldehyde **265** (2.6 g, 6.4 mmol) in dry CH_2Cl_2 (8 mL) was added dropwise *via* cannula (3 mL rinse) solution. The solution was stirred at – 78 ^oC for 1 hr, after which time it was warmed to – 50 ^oC and stirring continued for 5 hr. The reaction was quenched by addition of NH_4Cl (sat., 20 mL) and warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined and washed with brine (1 x 100 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 6.0 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes → 40% EtOAc/hexanes) to give 3.0 g (73% yield) of the title compound as a pale yellow, clear oil (R_f = 0.12 in 40% EtOAc/hexanes), which was an inseparable mixture of two isomers. The two isomers were not distinguishable by NMR.

IR (film, cm^{-1}) 3530.3, 2957.7, 2875.3, 1784.9, 1696.7, 1382.7, 1245.9, 1209.8, 1111.7, 1037.5, 744.1; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.54 – 0.62 (m, 6H, $Si(CH_2CH_3)_3$), 0.86 – 0.97 (m, 12H, TES $Si(CH_2CH_3)_3$ and $CH(OTES)CH(CH_3)$), 1.07 (d, 3H, $CH(CH_3)CH$=, *J* = 6.6 Hz), 1.25 (d, 3H, $C(O)CH(CH_3)$, *J* = 6.9 Hz),

1.80 – 1.86 (m, 1H, CH(OTES)C*H*(CH_3)), 2.50 – 2.66 (m, 1H, C*H*(CH_3)CH=), 2.77 (d of d, 1H, aux. CH_AH_BAr, *J* = 13.5, 9.3 Hz), 3.20 – 3.28 (m, 3H, aux. CH_AH_BAr and CH_AH_BOPMB), 3.45 – 3.51 (m, 1H, CH_AH_BOPMB), 3.68 – 3.72 (m, 1H, C*H*(OH)), 3.80 (s, 3H, PMB OCH_3), 3.85 – 3.92 (m, 1H, C(O)C*H*), 4.16-4.18- 4.18 (m, 2H, aux. OCH_2), 4.37 – 4.47 (m, 2H, PMB OCH_2Ar), 4.63 – 4.69 (m, 2H, aux. NC*H* and C*H*(TESO)), 5.13 – 5.26 (m, 1H, C*H*=CH), 5.45 – 5.52 (m, 1H, CH=C*H*), 6.84 – 6.88 (m, 2H, aux. and PMB Ar*H*), 7.19 – 7.36 (m, 7H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 5.1, 6.9, 10.5, 10.6, 17.9, 35.5, 37.8, 40.4, 41.5, 55.1, 55.3, 66.1, 68.8, 72.6, 72.7, 75.4, 113.7, 127.4, 129.0, 120.1, 129.4, 130.1, 131.7, 134.5, 135.1, 152.6, 159.0, 177.7; **HRESIMS** calculated for $C_{36}H_{53}NO_7SiNa^+$ ($M+Na^+$) 662.3489; found 662.3487.



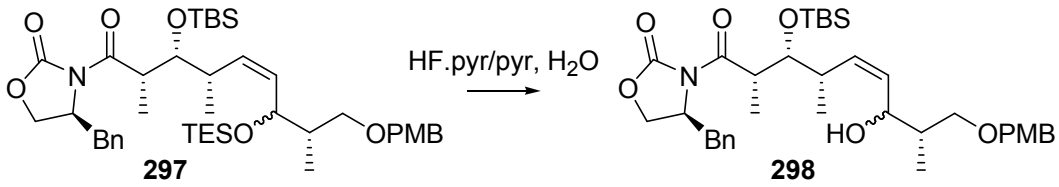
296 **297**

(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*,7*R*,8*S*)-*cis*-3-(*tert*-butyldimethylsilanyloxy)-9-(4-methoxybenzyloxy)-2,4,8-trimethyl-7-triethylsilanyloxynon-5-enoyl]-oxazolidin-2-one and (*S*)-4-benzyl-3-[(2*S*,3*R*,4*S*,7*S*,8*S*)-*cis*-3-(*tert*-butyldimethylsilanyloxy)-9-(4-methoxybenzyloxy)-2,4,8-trimethyl-7-triethylsilanyloxynon-5-enoyl]-oxazolidin-2-one (297)

To a stirring solution of alcohol **296** (3.0 g, 4.7 mmol) in dry CH_2Cl_2 (27 mL) under N_2 at – 78 ^oC was added dropwise 2,6-lutidine (6.5 mL, 55.9 mmol) followed immediately by dropwise addition of TBSOTf (9.6 mL, 41.9 mmol) and the resulting clear and colourless solution was left to stir at – 78 ^oC for 7 hr. The reaction was quenched by addition of $NaHCO_3$ (sat., 69 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 14.4 g of a yellow, clear oil. The oil was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give 3.3 g (95% yield) of the title compound as a clear, pale yellow oil (R_f = 0.21), which was

an inseparable mixture of two isomers. The two isomers were not distinguishable by NMR.

IR (film, cm^{-1}) 2956.2, 2933.8, 1785.0, 1694.0, 1380.7, 1248.7, 1116.1, 1044.6, 836.0; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) – 0.03 – 0.11 (m, 6H, TBS Si(C*H*$_3$)$_2$), 0.53 – 0.68 (m, 6H, TES Si(C*H*$_2$CH$_3$)$_3$), 0.86 – 1.06 (m, 24H, TBS SiC(C*H*$_3$)$_3$, TES Si(CH$_2$C*H*$_3$)$_3$, CH(C*H*$_3$)CH= and CH(OTES)CH(C*H*$_3$)), 1.24 – 1.26 (m, 3H, C(O)CH(C*H*$_3$)), 1.74 – 1.82 (m, 1H, CH(OTES)C*H*(CH$_3$)), 2.42 – 2.48 (m, 1H, C*H*(CH$_3$)CH=), 2.77 (d of d, 1H, aux. C*H*$_A$CH$_B$Ar, *J* = 13.2, 6 Hz), 3.19 – 3.24 (m, 2H, aux. CH$_A$C*H*$_B$Ar and C*H*$_A$H$_B$OPMB), 3.52 (d of d, 1H, CH$_A$*H*$_B$OPMB, *J* = 9, 6.9 Hz), 3.80 (s, 3H, PMB OC*H*$_3$), 3.89 – 4.13 (m, 4H, C(O)C*H*(CH$_3$), C*H*(OTBS) and aux. OC*H*$_2$), 4.37 (s, 2H, PMB OC*H*$_2$), 4.52 – 4.61 (m, 2H, C*H*(OTES) and aux. NC*H*), 5.38 – 5.41 (m, 2H, C*H*=C*H*), 6.82 – 6.87 (m, 2H, aux. and PMB Ar*H*), 7.19 – 7.37 (m, 7H, aux. and PMB Ar*H*), **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 3.9, – 3.4, 5.0, 7.0, 11.2, 13.7, 15.6, 26.2, 36.9, 41.4, 42.5, 55.2, 55.7, 65.9, 68.9, 72.6, 72.9, 76.8, 113.7, 127.3, 128.9, 129.4, 130.9, 132.4, 135.4, 152.5, 152.8, 159.0, 175.4; **HRESIMS** calculated for $C_{42}H_{67}NO_7SiNa^+$ (M+Na$^+$): 776.4354; found 776.4352.



(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*,7*R*,8*S*)-*cis*-3-(*tert*-butyldimethylsilanyloxy)-7-hydroxy-9-(4-methoxybenzyloxy)-2,4,8-trimethylnon-5-enoyl]-oxazolidin-2-one and (*S*)-4-benzyl-3-[(2*S*,3*R*,4*S*,7*S*,8*S*)-*cis*-3-(*tert*-butyldimethylsilanyloxy)-7-hydroxy-9-(4-methoxybenzyloxy)-2,4,8-trimethylnon-5-enoyl]-oxazolidin-2-one (298)

A solution of TES ether **297** (3.3 g, 4.4 mmol) in H_2O (3 mL) and HF-pyr/pyr (30 mL, from a stock solution containing dry THF (50 mL), pyridine (25 mL) and pyridinium hydrofluoride (10.5 g)) in a Teflon screw-cap jar was maintained at 0 ^oC for 44 hr. The solution was diluted with Et_2O (200 mL) and the organic phase was washed with $CuSO_4$ (sat., 1 x 100 mL), $NaHCO_3$ (sat., 1 x 100 mL) and brine (1 x

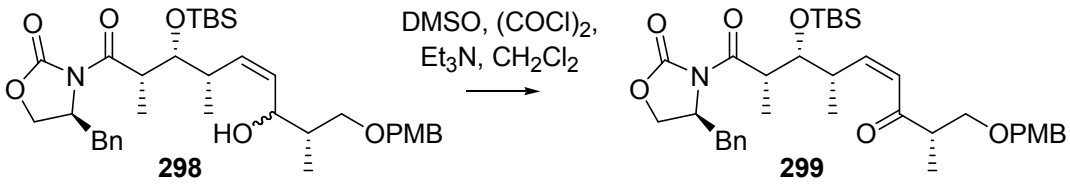
100 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 2.7 g of a yellow oil. The oil was purified by flash column chromatography on buffered silica (20% EtOAc → 40% EtOAc/hexanes) to give 2.0 g (70% yield) of the title compound as a clear, colourless oil (R_f = 0.45 (isomer 1) and 0.32 (isomer 2) in 40% EtOAc/hexanes).

IR (film, cm^{-1}) 3429.9, 2930.8, 2856.5, 1781.5, 1698.4, 1513.6, 1383.9, 1248.6, 1209.9, 1111.4, 836.5; **HRESIMS** calculated for $C_{36}H_{53}NO_7SiNa^+$ ($M+Na^+$): 662.3489; found: 662.3490.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.04 (s, 3H, TBS Si(CH_3)$_A$), 0.09 (s, 3H, TBS Si(CH_3)$_B$), 0.93 – 0.97 (m, 15H, TBS SiC(CH_3)$_3$, CH(OH)CH(CH_3) and CH(CH_3)CH), 1.23 (d, 3H, C(O)CH(CH_3), J = 6.9 Hz), 1.63 (bs, 1H, OH), 1.88 – 1.95 (m, 1H, CH(OH)CH(CH$_3$)), 2.54 – 2.79 (m, 2H, CH(CH$_3$)CH= and aux. CH_AH$_B$Ar), 3.22 – 3.26 (m, 1H, aux. CH$_A$$H_B$Ar), 3.40 (d of d, 1H, C$H_ACH_B$OPMB, J = 9, 5.1 Hz), 3.45 – 3.51 (m, 1H, CH$_A$CH_BOPMB), 3.80 (s, 3H, PMB OCH_3), 3.83 – 3.93 (m, 2H, CH(OTBS) and C(O)CHCH$_3$), 4.12 – 4.17 (m, 2H, aux. OCH_2), 4.37 – 4.47 (m, 3H, PMB OCH_2Ar and CH(OH)), 4.54 – 4.63 (m, 1H, aux. NCH), 5.36 – 5.46 (m, 2H, CH=CH), 6.84 – 6.89 (m, 2H, aux. and PMB ArH), 7.19 – 7.36 (m, 7H, aux. and PMB ArH); ^{13}**C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 3.7, – 3.3, 12.2, 13.2, 17.8, 18.5, 26.2, 37.8, 38.9, 39.3, 43.4, 55.3, 55.71, 66.0, 72.1, 73.2, 74.8, 76.2, 113.8, 127.2, 128.8, 129.0, 129.2, 129.4, 130.1, 135.0, 135.31, 153.1, 159.1, 175.6.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.00 (s, 3H, TBS Si(CH_3)$_A$), 0.06 (s, 3H, TBS Si(CH_3)$_B$), 0.927 – 0.931 (m, 12H, TBS SiC(CH_3)$_3$ and CH(OH)CH(CH_3)), 1.01 (d, 3H, CH(CH_3)CH=, J = 6.6 Hz), 1.20 (d, 3H, C(O)CH(CH_3), J = 6.3 Hz), 1.63 (bs, 1H, OH), 1.88 – 1.95 (m, 1H, CH(OH)CH(CH$_3$)), 2.54 – 2.79 (m, 2H, CH(CH$_3$)CH= and aux. CH_AH$_B$Ar), 3.22 – 3.26 (m, 1H, aux. CH$_A$$H_B$Ar), 3.52 – 3.58 (m, 1H, CH_ACH$_B$OPMB), 3.63 – 3.68 (m, 1H, CH$_A$CH_BOPMB), 3.80 (s, 3H, PMB OCH_3), 3.83 – 3.93 (m, 2H, CH(OTBS) and C(O)CHCH$_3$), 4.12 – 4.17 (m, 2H, aux. OCH_2), 4.24 – 4.29 (m, 1H, CH(OH)), 4.37 – 4.47 (m, 2H, PMB OCH_2Ar), 4.54 – 4.63 (m, 1H, aux. NCH), 5.36 – 5.46 (m, 1H, CH=CH), 5.59 (app. t, 1H, CH=CH), 6.84 – 6.89 (m, 2H, aux. and PMB ArH), 7.19 – 7.36 (m, 7H, aux. and PMB ArH);

^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) – 3.8, – 3.2, 13.2, 14.1, 16.7, 18.5, 26.2, 37.4, 37.7, 39.1, 42.6, 55.3, 55.66, 66.0, 69.5, 73.0, 74.8, 76.7, 113.8, 127.3, 128.8, 129.0, 129.2, 129.3, 130.3, 135.26, 136.4, 152.8, 159.1, 175.4.

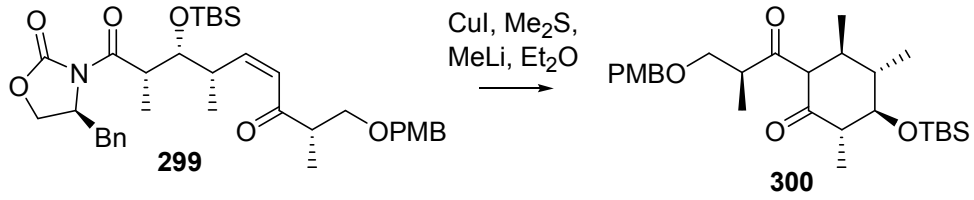


(2*S*,3*R*,4*S*,8*S*)-*cis*-1-[(*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyl-dimethylsilanyloxy)-9-(4-methoxybenzyloxy)-trimethylnon-5-ene-1,7-dione (299)

To a stirring solution of DMSO (0.66 mL, 9.3 mmol) in dry CH_2Cl_2 (20 mL) under N_2 at – 78 ^oC was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 2.4 mL, 4.7 mmol) and the solution was stirred at – 78 ^oC for 30 min. To this solution was added dropwise a solution of alcohol **298** (2.0 g, 3.1 mmol) in dry CH_2Cl_2 (7 mL) *via* cannula (4 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 (2.6 mL, 18.7 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, 47 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 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), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 2.0 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 1.6 g (78% yield) of the title compound as a colourless oil (R_f = 0.24).

$[\alpha]_D^{20}$ = + 84.8 (0.30, $CHCl_3$); **IR** (film, cm^{-1}) 2930.9, 2856.6, 1779.8, 1691.8, 1248.0, 1103.8, 1045.3; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) – 0.02 (s, 3H, TBS Si(CH_3)$_A$), 0.05 (s, 3H, TBS Si(CH_3)$_B$), 0.92 (s, 9H, TBS SiC(CH_3)$_3$), 1.01 (d, 3H, CH(CH_3)CH=, *J* = 6.6 Hz), 1.09 (d, 3H, CH(CH_3)CH_2, *J* = 7.2 Hz), 1.18 (d, 3H, C(O)CH(CH_3), *J* = 6.6 Hz), 2.75 (d of d, 1H, aux. CH_ACH_BAr, *J* = 13.2, 9.9 Hz),

2.86 (app. quart, 1H, C*H*(CH_3)CH_2, *J* = 6.9 Hz), 3.27 (d of d, 1H, CH_ACH_BAr, *J* = 13.8, 3.3 Hz), 3.41 (d of d, 1H, CH_AH_BOPMB, *J* = 8.7, 6 Hz), 3.61 – 3.67 (m, 2H, C*H*(CH_3)CH= and CH_AH_BOPMB), 3.80 (s, 3H, PMB OCH_3) 3.81 – 3.85 (m, 1H, C(O)C*H*(CH_3), 3.88 – 3.92 (m, 1H, C*H*(OTBS)), 4.15 – 4.24 (m, 2H, aux. OCH_2), 4.41 (d of d, 2H, PMB OCH_2Ar, *J* = 14.7, 12 Hz), 4.64 – 4.70 (m, 1H, aux. NC*H*), 6.12- 6.22 (m, 2H, C*H*=C*H*), 6.84 – 6.87 (m, 2H, aux. and PMB Ar*H*), 7.20 – 7.36 (m, 7H, aux. and PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 4.1, – 3.4, 11.8, 13.6, 16.3, 26.1, 37.6, 38.2, 42.9, 47.3, 55.3, 55.9, 66.1, 71.8, 72.9, 76.1, 76.7, 113.7, 125.2, 127.3, 128.9, 129.1, 129.4, 130.3, 135.4, 150.5, 153.1, 175.0, 203.0; **HRESIMS** calculated for $C_{36}H_{51}NO_7SiNa^+$ ($M+Na^+$): 660.3333; found 660.3329.

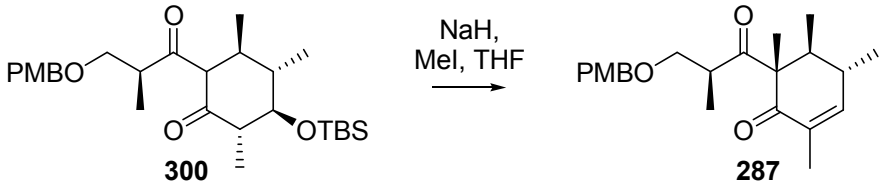


(2*S*,3*R*,4*S*,5*S*)-*cis*-3-(*tert*-Butyldimethylsilanyloxy)-6-[(2*S*)-3-(4-methoxybenzyl-oxy)-2-methylpropionyl]-2,4,5-trimethylcyclohexanone (300)

To a stirring suspension of CuI (0.01 g, 0.07 mmol) in dry Et_2O (0.5 mL) and dry Me_2S (1 mL) under N_2 at RT was added dropwise MeLi (approx. 1.6 M in Et_2O, 0.10 mL, 0.14 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 **299** (0.02 g, 0.03 mmol) in dry Et_2O (0.5 mL) *via* cannula (0.5 mL rinse), resulting in the formation of a yellow precipitate, and the suspension was stirred at RT for 1 hr (the solution changed in colour from yellow through orange to dark green). The mixture was diluted with Et_2O (2 mL) and the reaction was quenched by slow addition of a 10% NH_4OH/90% NH_4Cl solution (5 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 5 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 0.03 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.014 g (89% yield) of the

title compound as a colourless oil (R_f = 0.48 *keto* form, 0.35 *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) 0.06 (s, 3H, TBS Si(CH_3)$_A$), – 0.08 (s, 3H, Si(CH_3)$_B$), 0.91 – 0.93 (m, 9H, TBS SiC(CH_3)$_3$), 0.96 (d, 3H, C(O)CHCH(CH_3), *J* = 7.2 Hz), 1.03 – 1.06 (m, 3H, CH(CH_3)CH(OTBS)),1.09 – 1.14 (m, 3H, CH_2CH(CH_3)), 1.21 – 1.29 (m, 3H, C(O)CH(CH_3)), 1.58 – 1.60 (m, 1H, C*H*(CH_3)CH(OTBS)), 1.82 – 1.92 (m, 1H, C(O)CHC*H*(CH_3)), 2.40 – 2.57 (m, 1H, C(O)C*H*(CH_3)), 2.79 (app. quart, 1H, CH_2C*H*(CH_3), *J* = 6.9 Hz), 3.09 (app. t, 1H, C*H*(OTBS), *J* = 9.5 Hz), 3.39 – 3.49 (m, 1H, PMBOCH_AH$_B$), 3.57 (d, 1H, C(O)C*H*C(O), *J* = 12 Hz), 3.66 (d of d, 1H, PMBOCH$_A$*H*$_B$, *J* = 9.3, 6.3 Hz), 3.80 (s, 3H, PMB OCH_3), 4.35 – 4.50 (m, 2H, PMB OCH_2Ar), 6.85 – 7.25 (m, 4H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) – 3.1, – 2.9, 12.0, 13.2, 16.2, 19.0, 26.2, 36.0, 45.5, 48.3, 54.1, 55.3, 67.7, 71.2, 72.9, 80.2, 113.7, 129.0, 129.2, 130.2, 207.2, 209.9; **HRESIMS** calculated for $C_{27}H_{44}O_5SiNa^+$ (M+Na^+): 499.2856; found 499.2850.

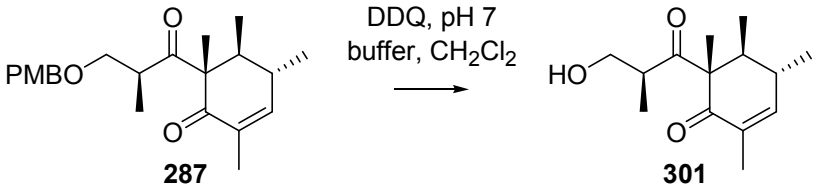


(4*S*,5*S*,6*S*)-6-[(2*S*)-3-(4-Methoxybenzyloxy)-2-methylpropionyl]-2,4,5,6-tetra-methylcyclohex-2-enone (287)

To a stirring suspension of NaH (60% dispersion in oil, 0.09 g, 2.20 mmol) in dry THF (19 mL) under N_2 at RT was added dropwise a solution of diketone **300** (1.1 g, 2.2 mmol) in dry THF (6 mL) *via* cannula (2.5 mL rinse) and the resulting yellow solution was stirred at RT for 10 min, after which time it became clear. To this solution was added dropwise MeI (1.4 mL, 22.0 mmol), and the resulting yellow solution was stirred under N_2 at RT for 22 hr. The solution was cannulated into NaH (0.09 g, 2.20 mmol) and stirred for 20 min. The reaction was quenched by addition of $NaHCO_3$ (sat., 63 mL) and the mixture was extracted with CH_2Cl_2 (3 x 40 mL). The organic layers were combined and washed with brine (1 x 100 mL), then dried

($MgSO_4$), filtered and solvent was removed *in vacuo* to give 1.1 g of a yellow oil. The oil was purified by flash column chromatography on silica (15% EtOAc/hexanes) to give 0.51 g (65% yield) of the title compound as a clear, colourless oil ($R_f = 0.34$).

$[\alpha]_D^{20} = -26.7$ (0.01, $CHCl_3$); **IR** (film, cm^{-1}) 2973.3, 2934.5, 1712.7, 1658.4, 1513.6, 1248.0, 1101.2, 1034.1; **^{1}H NMR** (C_6D_6, 600 MHz) δ (ppm) 0.61 (d, 3H, $C(CH_3)CH(CH_3)$, J = 6.6 Hz), 0.75 (d, 3H, $CH(CH_3)CH=$, J = 7.2 Hz), 1.18 (s, 3H, $C(CH_3)$), 1.32 (d, 3H, $CH_2CH(CH_3)$ J = 6.6 Hz), 1.74 (app. d of d, 3H, $CH=C(CH_3)$, J = 2.3, 1.4 Hz), 2.39 (d of quart, 1H, $C(CH_3)CH(CH_3)$, J = 10.2, 6.6 Hz), 2.91 (quart of t, 1H, $CH_2CH(CH_3)$, J = 6.6, 2.4, 1.8 Hz), 3.13 (d of d, 1H, $CH_AH_BCH(CH_3)$, J = 9, 4.8 Hz), 3.29 (s, 3H, PMB OCH_3), 3.68 (app. t, 1H, $CH_AH_BCH(CH_3)$, J = 9 Hz), 4.11 (s, 2H, PMB OCH_2Ar), 5.94 (s, 1H, $CH=$), 6.75 – 6.79 (m, 2H, PMB Ar*H*), 7.08 – 7.10 (m, 2H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm) 13.3, 14.0, 15.9, 16.2, 19.0, 34.6, 38.7, 44.8, 55.3, 64.2, 72.9, 73.5, 113.6, 129.2, 130.2, 132.9, 151.7, 201.5, 212.8; **HRESIMS** calculated for $C_{22}H_{30}O_4Na^+$ ($M+Na^+$): 381.2042; found 381.2040.



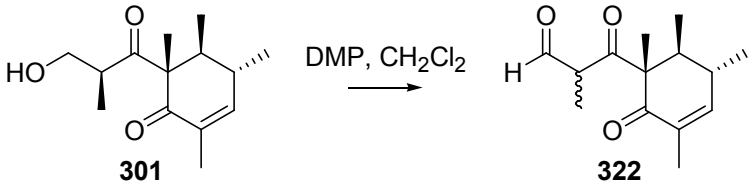
287 **301**

(4*S*,5*S*,6*S*)-6-[(2*S*)-3-Hydroxy-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (301)

To a stirring solution of cyclohexenone **287** (0.02 g, 0.06 mmol) in dry CH_2Cl_2 (1.5 mL) at RT was added pH 7 buffer (0.15 mL) and the two-phase mixture was cooled to 0 ^oC. To this solution was added DDQ (0.02 g, 0.07 mmol) and the resulting black mixture was stirred at 0 ^oC for 4 hr. The mixture was diluted with CH_2Cl_2 (1 mL), the reaction was quenched by the addition of $NaHCO_3$ (sat., 3 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The organic extracts were combined and washed with $NaHCO_3$ (sat., 1 x 15 mL), then dried ($MgSO_4$), filtered and solvent was removed *in*

vacuo to give 0.02 g of a yellow oil. The oil was purified by flash column chromatography on buffered silica (15% Et_2O/CH_2Cl_2) to give 0.01 g (73% yield) of the title compound as a colourless oil ($R_f = 0.34$).

$[\alpha]_D^{20} = -5.5$ (0.55, $CHCl_3$); **IR** (film, cm^{-1}) 3490.9, 2974.4, 1709.9, 1657.3, 1454.9, 1373.5, 1021.5, 984.2; **^{1}H NMR** (C_6D_6, 300 MHz) δ (ppm) 0.59 (d, 3H, $C(CH_3)CH(CH_3)$, J = 6.6 Hz), 0.73 (d, 3H, $CH(CH_3)CH=$, J = 6.9 Hz), 1.12 (s, 3H, $C(CH_3)$), 1.17 (d, 3H, $CH_2CH(CH_3)$, J = 6.9 Hz), 1.57 – 1.69 (m, 4H, $CH(CH_3)CH=$, $=C(CH_3)$), 1.92 (bs, 1H, OH), 2.24 (d of quart, 1H, $C(CH_3)CH(CH_3)$, J = 9.9, 6 Hz), 2.68 – 2.79 (m, 1H, $CH_2CH(CH_3)$), 3.36 – 3.39 (m, 1H, $CH_AH_BCH(CH_3)$), 3.68 – 3.71 (m, 1H, $CH_AH_BCH(CH_3)$), 5.89 (s, 1H, CH=), **^{13}C NMR** (C_6D_6, 75.5 MHz) δ (ppm) 14.0, 14.6, 16.3, 16.5, 19.4, 35.2, 40.4, 46.9, 64.5, 66.8, 133.6, 151.5, 202.1, 214.4; **HRESIMS** calculated for $C_{14}H_{22}O_3Na^+$ ($M+Na^+$): 261.1467; found 261.1472.



301 **322**

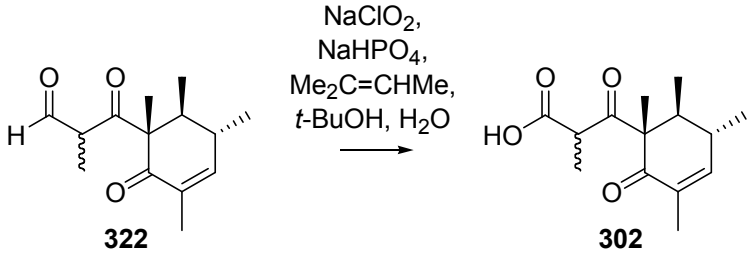
(2*R*)-2-Methyl-3-oxo-3-[(1*S*,5*S*,6*S*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]-propionaldehyde and (2*S*)-2-methyl-3-oxo-3-[(1*S*,5*S*,6*S*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]-propionaldehyde (322)

To a stirring solution of DMP (0.03 g, 0.07 mmol) in dry CH_2Cl_2 (0.5 mL) under N_2 at RT was added dropwise a solution of alcohol **301** (0.01 g, 0.05 mmol) in dry CH_2Cl_2 (0.5 mL) *via* cannula (0.5 mL rinse) and the solution was left to stir for 3 hr. The solution was diluted with Et_2O (5 mL) and the reaction was quenched by addition of a solution of $NaHCO_3$ (sat., 2.5 mL) containing $Na_2S_2O_3.5H_2O$ (0.11 g), and stirred for 5 min after which time the organic layer became clear The layers were separated and the organic layer was washed with $NaHCO_3$ (sat., 1 x 5 mL) and brine (1 x 5 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.01 g (100% yield) of the title compound as a yellow oil, which was used crude in the next step. Aldehyde **322** was present as an inseparable mixture of two isomers in a 1:1 ratio, as determined by ^{1}H NMR.

IR (film, cm^{-1}) 2975.6, 2927.9, 1703.3, 1454.3, 1376.3, 1025.2; **HRESIMS** calculated for $C_{14}H_{20}O_3Na^+$ ($M+Na^+$): 259.1310; found 259.1315.

Isomer A: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ (ppm) 0.74 (d, 3H, $C(CH_3)CH(CH_3)$, J = 6 Hz), 1.18 (s, 3H, $C(CH_3)$), 1.19 (d, 3H, $=CHCH(CH_3)$, J = 7.5 Hz), 1.43 (d, 3H, $CH(O)CH(CH_3)$, J = 6.8 Hz), 1.79 (s, 3H, $=C(CH_3)$), 2.18 – 2.34 (m, 2H, $C(CH_3)CH(CH_3)$ and $=CHCH(CH_3)$), 3.56 – 3.67 (m, 1H, $HC(O)CH(CH_3)$), 6.56 (s, 1H, =C*H*), 9.42 (d, 1H, *H*C(O), J = 0.9 Hz); ^{13}**C NMR** ($CDCl_3$, 100 MHz) δ (ppm) 12.9, 13.6, 14.4, 15.7, 18.9, 35.0, 39.1, 58.9, 64.6, 132.6, 151.7, 199.1, 201.4, 206.5.

Isomer B: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ (ppm) 0.74 (d, 3H, $C(CH_3)CH(CH_3)$, J = 6 Hz), 1.18 (s, 3H, $C(CH_3)$), 1.19 (d, 3H, $=CHCH(CH_3)$, J = 7.5 Hz), 1.43 (d, 3H, $CH(O)CH(CH_3)$, J = 6.8 Hz), 1.79 (s, 3H, $=C(CH_3)$), 2.18 – 2.34 (m, 2H, $C(CH_3)CH(CH_3)$ and $=CHCH(CH_3)$), 3.56 – 3.67 (m, 1H, $HC(O)CH(CH_3)$), 6.56 (s, 1H, =C*H*), 9.44 (d, 1H, *H*C(O), J = 1.2 Hz); ^{13}**C NMR** ($CDCl_3$, 100 MHz) δ (ppm) 12.9, 13.6, 14.4, 15.7, 18.9, 35.0, 39.1, 58.9, 64.6, 132.6, 151.7, 199.1, 201.4, 206.5.



322 **302**

(2*R*)-Methyl-3-oxo-3-[(1*S*,5*S*,6*S*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]-propionic acid and (2*S*)-methyl-3-oxo-3-[(1*S*,5*S*,6*S*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]-propionic acid (302)

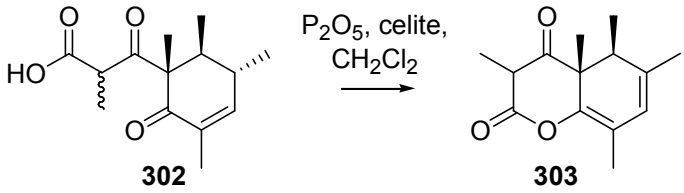
To a stirring solution of aldehyde **322** (0.02 g, 0.08 mmol) in *t*-BuOH (1.6 mL) and 2-methylbut-2-ene (1.6 mL) at RT was added dropwise a solution of $NaClO_2$ (0.04 g, 0.4 mmol) and $NaH_2PO_4.2H_2O$ (0.05 g, 0.3 mmol) in H_2O (0.4 mL) and the resulting pale yellow solution was stirred at RT for 1.5 hr. The reaction was quenched by addition of a CH_2Cl_2/H_2O mixture (2:1, 18 mL) and the solution was acidified to pH 3 by addition of TFA (5 drops). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, dried

($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.06 g of a solid/oil mixture. The mixture was purified by flash column chromatography on silica (40% Et_2O/CH_2Cl_2, 0.5% AcOH) to give 0.013 g (66% yield) of the title compound as a clear, colourless oil (R_f = 0.3). Acid **302** was present as an inseparable mixture of two isomers in a 1:1 ratio, as determined by ^{1}H NMR.

IR (film, cm^{-1}) 3489.2, 3182.8, 2979.5, 1709.6, 1659.2, 1454.2, 1377.8; **HRESIMS** calculated for $C_{14}H_{20}O_4Na^+$ ($M+Na^+$): 275.1260; found 275.1265.

Isomer A: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.87 (d, 3H, $C(CH_3)CH(CH_3)$, *J* = 6.6 Hz), 1.15 – 1.23 (m, 6H, $C(CH_3)$ and $=CHCH(CH_3)$), 1.41 (d, 3H, $HOC(O)CH(CH_3)$, *J* = 7.2 Hz), 1.76 – 1.79 (m, 3H, $=C(CH_3)$), 2.20 – 2.29 (m, 1H, $=CHCH(CH_3)$), 2.31 – 2.41 (m, 1H, $C(CH_3)CH(CH_3)$), 3.47 – 3.52 (m, 1H, $HOC(O)CH(CH_3)$), 6.57 (s, 1H, =C*H*), 9.72 (bs, 1H, *H*OC(O)), **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 13.4, 13.8, 15.6, 18.9, 20.7, 35.1, 41.8, 52.4, 63.9, 132.0, 152.3, 177.5, 199.3, 206.4.

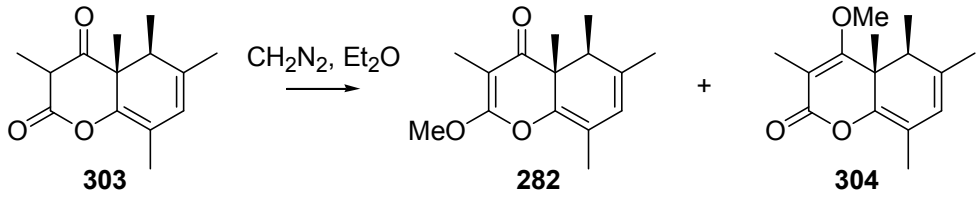
Isomer B; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.97 (d, 3H, $C(CH_3)CH(CH_3)$, *J* = 6.9 Hz), 1.15-1.23 (m, 3H, $=CHCH(CH_3)$), 1.30 (s, 3H, $C(CH_3)$), 1.47 (d, 3H, $HOC(O)CH(CH_3)$, *J* = 6.9 Hz), 1.76 – 1.79 (m, 3H, $=C(CH_3)$), 2.20 – 2.29 (m, 1H, $=CHCH(CH_3)$), 2.31 – 2.41 (m, 1H, $C(CH_3)CH(CH_3)$), 3.83 – 3.90 (m, 1H, $HOC(O)CH(CH_3)$), 6.49 (s, 1H, =C*H*), 9.72 (bs, 1H, *H*OC(O)), **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 13.2, 14.0, 15.9, 18.9, 20.7, 34.5, 40.3, 52.4, 63.9, 132.5, 150.8, 177.5, 199.3, 206.4.



(4a*R*,5*S*)-3,4a,5,6,8-Pentamethyl-3,4,4a,5-tetrahydro-2H-1-benzopyran-2,4-dione (303)

A mixture of celite (0.02 g) and P_2O_5 (0.01 g, 0.08 mmol) was stirred vigorously under N_2 at RT. To the mixture was added dropwise a solution of acid **302** (0.004 g, 0.02 mmol) in CH_2Cl_2 (0.3 mL) *via* cannula (0.3 mL rinse). The mixture was stirred at RT for 1 hr, after which time it was diluted with CH_2Cl_2 (2 mL) and filtered. The remaining solids were washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo* to give 0.004 g of a yellow oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.002 g (50% yield) of the title compound as a clear, colourless oil (R_f = 0.45).

IR (film, cm^{-1}) 2935.4, 1777.7, 1727.0, 1447.2, 1202.8; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.09 (s, 3H, C(C*H*$_3$)), 1.12 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.8 Hz), 1.33 (d, 3H, C(O)CH(C*H*$_3$)C(O), *J* = 6.3 Hz), 1.82 (s, 6H, C(O)OC=C(C*H*$_3$) and C(CH$_3$)CH(CH$_3$)C(C*H*$_3$)), 2.70 – 2.78 (m, 1H, C(CH$_3$)C*H*(CH$_3$), 4.00 (q, 1H, C(O)C*H*(CH$_3$)C(O)), 5.63 (s, 1H, C*H*=); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 7.5, 10.4, 12.6, 14.1, 20.8, 39.3, 50.7, 51.8, 117.2, 123.2, 135.2, 143.6, 167.4, 203.9; **HRESIMS** calculated for $C_{14}H_{18}O_3Na^+$ (M+Na^+): 257.1154; found 257.1154.



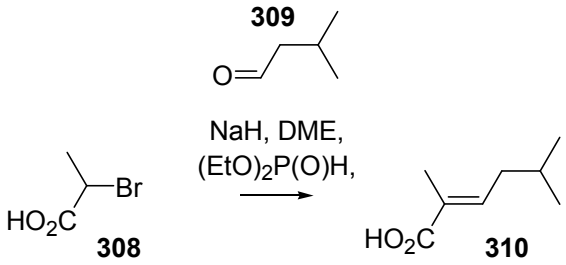
(4a*R*,5*S*)-2-Methoxy-3,4a,5,6,8-pentamethyl-4a,5-dihydro-4H-1-benzopyran-4-one (282) and (4a*S*,5*S*)-4-methoxy-3,4a,5,6,8-pentamethyl-4a,5-dihydro-2H-1-benzopyran-2-one (304)

To a stirring solution of pyranone **303** (0.01 g, 0.06 mmol) in dry Et_2O (1.1 mL) under N_2 at RT was added dropwise CH_2N_2/Et_2O until the yellow colour persisted. The solution was stirred at RT for 20 min and N_2 was bubbled through the solution until it became colourless. The solvent was removed *in vacuo* to give 0.02 g of a solid/oil mixture. The mixture was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give 0.002 g (29%) of γ-pyrone **282** (R_f = 0.4) and 0.002 g (29%) of the α-pyrone **304** (R_f = 0.3). α-Pyrone **304** decomposed upon standing.

γ-pyrone **282**: $[\alpha]_D^{20} = -47.1$ (0.1, $CHCl_3$); **IR** (film, cm^{-1}) 2924.8, 1609.4, 1461.1, 1351.3, 1160.9; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm) 1.17 (s, 3H, C(C*H*$_3$)), 1.43 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.8 Hz), 1.65 (s, 3H, (CH$_3$O)C=C(C*H*$_3$)), 1.75 (s, 6H, C(O)OC=C(C*H*$_3$) and CH=C(C*H*$_3$)), 2.94 – 2.95 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 3.95 (s, 3H, C*H*$_3$O), 5.406 – 5.41 (m, 1H, C*H*=), **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm) 6.9, 14.0, 14.3, 17.4, 20.9, 39.1, 45.9, 54.8, 87.8, 113.7, 121.1, 135.8, 145.3, 164.4, 196.0; **HRESIMS** calculated for $C_{15}H_{20}O_3K^+$ ($M+K^+$): 287.2395; found 287.1258.

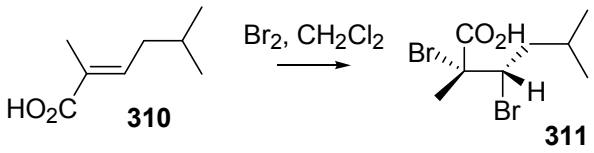
α-pyrone **304**: **^{1}H NMR** ($CDCl_3$, 200 MHz) δ (ppm) 1.15 (s, 3H, C(C*H*$_3$)), 1.32 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.8 Hz), 1.55 (s, 3H, (CH$_3$O)C=C(C*H*$_3$)), 1.78 (s, 6H, C(O)OC=C(C*H*$_3$) and CH=C(C*H*$_3$)), 2.71 – 2.84 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 3.90 (s, 3H, C*H*$_3$O), 5.49 (s, 1H, C*H*=).

No more spectral data could be obtained as the sample decomposed.



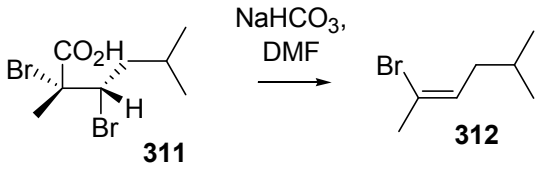
(*E*)-2,5-Dimethylhex-2-enoic acid (310)

To a stirring suspension of NaH (60% dispersion in oil, 9.2 g, 228.8 mmol) in dry DME (218 mL) under N_2 at 0 ^oC was added dropwise diethyl phosphite (8.4 mL, 65.4 mmol) and the mixture was stirred at 0 ^oC until H_2 evolution had ceased. To the mixture was added dropwise a solution of acid **308** (10.0 g, 65.4 mmol) in dry DME (65 mL) *via* cannula and the solution was warmed to RT and stirred until H_2 evolution had ceased. The mixture was then cooled to 0 ^oC and was added dropwise a solution of aldehyde **309** (7 mL, 65.4 mmol) in dry DME (8.4 mL) *via* cannula and the mixture was warmed to RT and stirred for 1 hr. The mixture was cooled to 0 ^oC and the reaction was quenched by very slow addition of EtOH (11 mL) and warmed to RT with stirring. The mixture was poured onto water (1050 mL) and the resulting mixture was washed, in 300 mL portions, with Et_2O (2 x 20 mL). The combined aqueous residue was acidified to pH 4 (using conc. HCl) and extracted, in 500 mL portions, with Et_2O (3 x 250 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 7.8 g of a clear, yellow oil. The oil was distilled under reduced pressure (Kugelrohr) to give 6.2 g (67% yield) of the title compound as a clear, colourless oil (BPt 150 ^oC at 30 mmHg, lit. BPt.[23] 135 – 140 ^oC at 30 mmHg), with identical spectral data to that reported in the literature.[22]



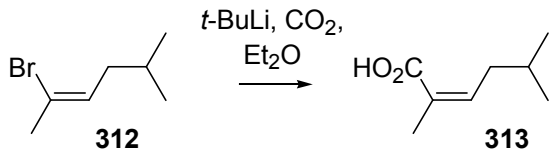
erythro-2,3-Dibromo-2,5-dimethylhexanoic acid (311)

To a stirring solution of alkene **310** (6.2 g, 43.9 mmol) in dry CH_2Cl_2 (55 mL) under N_2 at – 78 ^oC was added dropwise Br_2 (3.4 mL, 65.8 mmol) and the resulting orange solution was stirred at – 78 ^oC for 1 hr. The reaction was quenched by addition of a solution of $Na_2S_2O_3$ (1 M, 40 mL) and warmed to RT with stirring. The layers were separated and the residue was concentrated *in vacuo* to give 11.8 g (89% yield) of the title compound as a yellow solid, with identical spectral data to that given in the literature.[22]



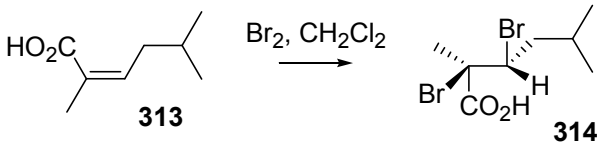
(*Z*)-2-Bromo-5-methylhex-2-ene (312)

To a stirring suspension of $NaHCO_3$ (3.3 g, 39.1 mmol) in dry DMF (15 mL) under N_2 at 60 ^oC was added dropwise a solution of bromoacid **311** (11.8 g, 39.1 mmol) in dry DMF (10 mL) *via* cannula (5 mL rinse) and the resulting mixture was stirred at 60 ^oC until evolution of CO_2 ceased. The light brown mixture was cooled to RT and the reaction was quenched by the addition of H_2O (10 mL). The mixture was extracted with *n*-pentane (8 x 25 mL) and the organic extracts were combined, washed with H_2O (10 x 10 mL), then dried ($MgSO_4$), filtered and solvent was removed by distillation. The resultant brown residue was distilled under reduced pressure to give 5.8 g (84% yield) of a clear, colourless oil (BPt 75 ^oC at 30 mmHg, lit. BPt.[22] 70 – 75 ^oC at 20 mmHg), with identical spectral data to that reported in the literature.[22]



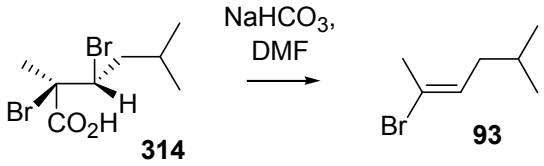
(*Z*)-2,5-Dimethylhex-2-enoic acid (313)

To a stirring solution of bromoalkene **312** (1.6 g, 9.0 mmol) in dry Et_2O (25 mL) under N_2 at – 78 ^oC was added dropwise *t*-BuLi (1.40 M solution in pentane) and the resulting pale yellow solution was stirred at – 78 ^oC for 1 hr. The solution was then transferred *via* cannula to solid CO_2 (excess) and warmed to – 20 ^oC with stirring. The reaction was quenched by addition of HCl (1 M, 12 mL) and warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 12 mL). The organic layers were combined and washed with brine (1 x 50 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 1.5 g of a clear, colourless oil. The oil was purified by distillation under reduced pressure to give 1.3 g (98% yield) of the title compound as a clear, colourless oil (BPt 60-70 ^oC at 0.1 mmHg, lit. BPt[22] 144 – 148 ^oC at 17 mmHg), with identical spectral data to that reported in the literature.[22]



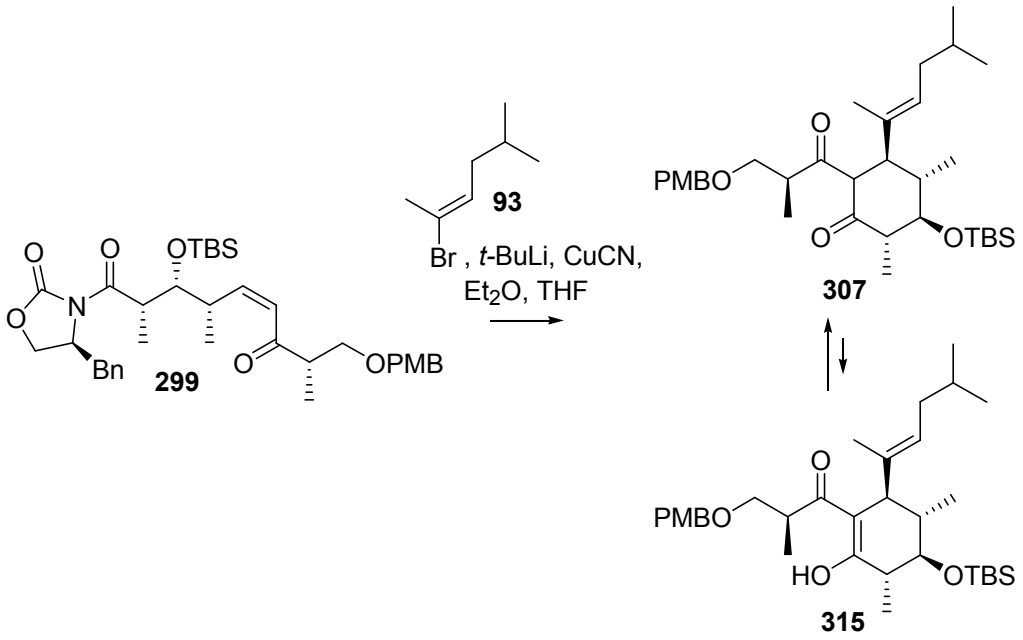
***threo*-2,3-Dibromo-2,5-dimethylhexanoic acid (314)**

To a stirring solution of alkene **313** (1.4 g, 10.0 mmol) in dry CH_2Cl_2 (12.5 mL) under N_2 at – 78 ^oC was added dropwise Br_2 (0.77 mL, 15.0 mmol) and the resulting orange solution was stirred at – 78 ^oC for 1 hr. The reaction was quenched by addition of $Na_2S_2O_3$ (1 M, 12.5 mL) and warmed to RT with stirring. The layers were separated and the residue was concentrated *in vacuo* to give 2.7 g (88% yield) of the title compound as a yellow solid, with identical spectral data to that given in the literature.[22]



(*E*)-2-Bromo-5-methylhex-2-ene (93)

To a stirring suspension of $NaHCO_3$ (0.74 g, 8.80 mmol) in dry DMF (3.4 mL) under N_2 at 60 ^oC was added dropwise a solution of bromoacid **314** (2.7 g, 8.8 mmol) in dry DMF (2.4 mL) *via* cannula (1 mL rinse) and the resulting mixture was stirred at 60 ^oC until evolution of CO_2 ceased. The light brown mixture was cooled to RT and the reaction was quenched by the addition of H_2O (2 mL). The mixture was extracted with *n*-pentane (8 x 9 mL) and the organic extracts were combined, washed with H_2O (10 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed by distillation. The resultant brown residue was distilled under reduced pressure to give 1.2 g (76% yield) of the title compound as a clear, colourless oil (BPt 75 ^oC at 13 mmHg, lit. BPt [22] 72 – 76 ^oC at 12 mmHg), with identical spectral data to that reported in the literature.[22]



(2*S*,3*R*,4*S*,5*S*)-3-(*tert*-Butyl-dimethylsilyloxy)-5-(1,4-dimethylpent-1-enyl)-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methyl-propionyl]-2,4-dimethylcyclohexanone (307) and (2*S*)-1-[(3*S*,4*R*,5*S*,6*R*)-4-(*tert*-butyl-dimethylsilyloxy)-6-(1,4-dimethylpent-1-enyl)-2-hydroxy-3,5-dimethylcyclohex-1-enyl]-3-(4-methoxybenzyloxy)-2-methyl-propan-1-one (315)

To a stirring solution of bromoalkene **93** (0.54 g, 3.07 mmol) in dry THF (7.8 mL) under N_2 at – 100 ^oC was added dropwise *t*-BuLi (1.55 M in pentane, 4.0 mL, 6.1 mmol) and the resulting bright yellow solution was stirred at – 100 ^oC for 15 min. The solution was then transferred *via* cannula (pre-cooled by adding – 78 ^oC Et_2O to the CuCN) to a stirring suspension of CuCN (0.14 g, 1.54 mmol) in dry Et_2O (7.8 mL) under N_2 at – 78 ^oC and the resulting colourless, cloudy mixture was warmed to – 50 ^oC over 15 min, after which time the solution became colourless and homogenous. To the solution was added dropwise a solution of enone **299** (0.49 g, 0.77 mmol) in dry Et_2O (1 mL) *via* cannula (1 mL rinse) and the resulting bright yellow mixture was stirred at – 50 ^oC for 2 hr and at 0 ^oC for 2 hr. The reaction was quenched by addition of 10% NH_4OH/90% NH_4Cl solution (15.5 mL) and warmed to RT with stirring, upon which time the aqeous layer became dark blue in colour. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 6 mL). The organic layers were combined and washed with brine (1 x 50 mL), then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give 0.7 g of a green

mixture. The mixture was purified by flash column chromatography on silica (10% EtOAc/hexanes → 20% EtOAc/hexanes) to give 0.13 g (31% yield) of the title compound as a pale orange oil (R_f = 0.57 *keto* form, 0.5 *enol* form), which existed predominantly in the *keto* form as evidenced by ^{1}H NMR.

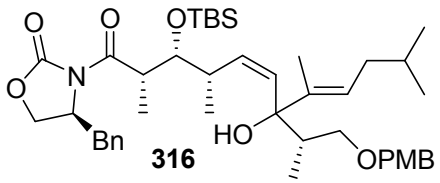
IR (film, cm^{-1}) 2955.3, 2930.0, 2857.5, 1725.9, 1701.0, 1513.8, 1463.2, 1249.5, 1084.2; **HRESIMS** calculated for $C_{33}H_{54}O_5SiNa^+$ ($M+Na^+$): 581.3639; found 581.3633.

***Keto* form 307: ^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm) 0.08 (s, 3H, TBS Si(CH_3)$_A$), 0.09 (s, 3H, TBS Si(CH_3)$_B$), 0.85 (d, 6H, CH(CH_3)$_2$, *J* = 6.7 Hz), 0.92 (d, 3H, CH(CH_3)CH(OTBS), *J* = 6.9 Hz), 0.94 (s, 9H, TBS SiC(CH_3)$_3$), 0.97 (d, 3H, CH_2CH(CH_3), *J* = 7.0 Hz), 1.21 (d, 3H, C(O)CH(CH_3), *J* = 6.9 Hz), 1.55 (s, 3H, C(CH_3)=), 1.56 – 1.59 (m, 1H, C*H*(CH_3)$_2$), 1.81 – 1.87 (m, 3H, =CHCH_2 and C*H*(CH_3)CH(OTBS)), 2.39 (app. t, 1H, C(O)CHC*H*(CH_3), *J* = 11.9 Hz), 2.52 (app. quint, 1H, C(O)C*H*(CH_3), *J* = 7.0 Hz), 2.66 (app. sex, 1H, CH_2C*H*(CH_3), *J* = 6.8 Hz), 3.12 (app. t, 1H, C*H*(OTBS), *J* = 9.7 Hz), 3.38 (d of d, 1H, CH_ACH_BCH(CH_3), *J* = 9.3, 6.8 Hz), 3.61 (d of d, 1H, CH_ACH_BCH(CH_3), *J* = 9.2, 6.7 Hz), 3.81 (s, 3H, PMB OCH_3), 3.97 (d, 1H, C(O)C*H*C(O), *J* = 12.2 Hz), 4.35 (d, 1H, PMB OCH_ACH_BAr, *J* = 11.5 Hz), 4.37 (d, 1H, PMB OCH_ACH_BAr, *J* = 14.2 Hz), 5.22 – 5.25 (m, 1H, C=C*H*), 6.87 – 6.88 (m, 2H, PMB Ar*H*), 7.23 – 7.24 (m, 2H, PMB Ar*H*), **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm) – 3.2, – 3.1, 11.8, 12.5, 15.5, 16.4, 18.3, 22.3, 22.5, 26.1, 28.7, 37.0, 41.6, 48.5, 51.3, 54.0, 55.2, 64.5, 71.2, 72.9, 79.9, 113.8, 129.3, 130.5, 132.6, 143.7, 159.2, 207.2, 208.7.

***Enol* form 315: ^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm) 0.07 (s, 3H, TBS Si(CH_3)$_A$), 0.10 (s, 3H, TBS Si(CH_3)$_B$), 0.87 (d, 3H, CH(CH_3)$_A$(CH_3)$_B$), 0.89 (d, 3H, CH(CH_3)$_A$(CH_3)$_B$), 0.93 (s, 9H, TBS SiC(CH_3)$_3$), 1.02 (d, 3H, CH(CH_3)CH(OTBS), *J* = 6.9 Hz), 1.03 (d, 3H, C(O)CH(CH_3), *J* = 6.9 Hz), 1.09 (d, 3H, CH_2CH(CH_3), *J* = 7.0 Hz), 1.47 (s, 3H, C(CH_3)=), 1.60 – 1.62 (m, 1H, C*H*(CH_3)$_2$), 1.68 (app. quart, 1H, C*H*(CH_3)CH(OTBS), *J* = 7.3 Hz), 1.85 – 1.87 (m, 2H, =CHCH_2), 2.44 (d of quart, 1H, C(O)C*H*(CH_3), *J* = 6.5, 1.0 Hz), 2.81 (d, 1H, C(O)C*H*, *J* = 7.2 Hz), 3.18 (app. trip, 1H, C*H*(OTBS), *J* = 8.5 Hz), 3.21 (app. quart, 1H, CH_2C*H*(CH_3), *J* = 6.9 Hz),

3.34 (d of d, 1H, CH_ACH$_B$CH(CH$_3$), J = 8.8, 7.3 Hz), 3.57 (d of d, 1H, CH$_A$CH_BCH(CH$_3$), J = 8.9, 6.5 Hz), 3.81 (s, 3H, PMB OCH_3), 4.40 (d, 1H, PMB OCH_ACH$_B$Ar, J = 6.9 Hz), 4.41 (d, 1H, PMB OCH$_A$CH_BAr, J = 4.6 Hz). 5.26 – 5.29 (m, 1H, =C*H*), 6.86 – 6.88 (m, 2H, PMB Ar*H*), 7.23 – 7.24 (m, 2H, PMB Ar*H*), 16.86 (s, 1H, O*H*); **^{13}C NMR** (CDCl$_3$, 150 MHz) δ (ppm) – 3.7, – 3.6, 11.7, 13.0, 13.9, 15.5, 22.4, 22.7, 26.1, 28.8, 37.3, 40.3, 48.5, 50.5, 53.9, 55.2, 64.5, 71.3, 72.7, 77.1, 106.9, 113.6, 126.8, 129.3, 130.2, 136.7, 159.0, 190.7, 198.0.

The 1,2-addition product **316** was also isolated on numerous occasions:

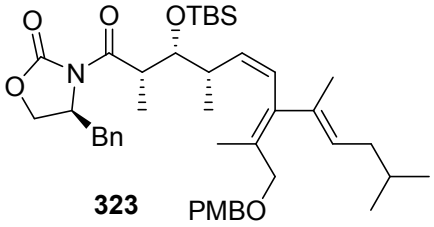


316

(*S*)-4-Benzyl-3-{*cis*-(2*S*,3*R*,4*S*,8*S*)-3-(*tert*-butyldimethylsilyloxy)-7-hydroxy-7-[(2*S*)-(4-methoxybenzyloxy)-1-methyl-ethyl]-2,4,8,11-tetramethyl-dodeca-5,8-dienoyl}-oxazolidin-2-one (316)

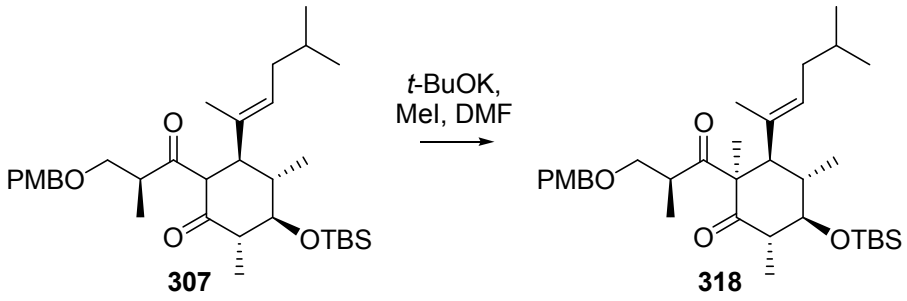
IR (film, cm^{-1}) 3477.0, 2955.4, 1783.3, 1698.6, 1382.5, 1249.1; **^{1}H NMR** (CDCl$_3$, 300 MHz) δ (ppm) 0.02 (s, 3H, TBS Si(CH_3)$_A$), 0.07 (s, 3H, TBS Si(CH_3)$_B$), 0.83 (d, 3H, CH(OTBS)CH(CH_3), J = 6.3 Hz), 0.87 (d, 6H, CH(CH_3)$_2$, J = 6.6 Hz), 0.92 (s, 9H, SiC(CH_3)$_3$), 1.00 (d, 3H, CH(CH_3)CH$_2$, J = 6.9 Hz), 1.24 (d, 3H, C(O)CH(CH_3), J = 6.9 Hz), 1.57 (s, 3H, C(CH_3) =), 1.57 – 1.66 (m, 1H, C*H*(CH$_3$)$_2$), 1.85 – 1.89 (m, 2H, =CHCH_2), 1.98 – 2.088 (m, 1H, C*H*(CH$_3$)CH$_2$), 2.74 (d of d, 1H, aux. CH_ACH$_B$Ar, J = 13.8, 9.6 Hz), 3.21 – 3.26 (m, 2H, aux. CH$_A$CH_BAr and CH(OTBS)C*H*(CH$_3$)), 3.42 – 3.46 (m, 2H, CH(CH$_3$)CH_2), 3.80 (s, 3H, PMB OCH_3), 3.88 – 3.92 (m, 2H, C*H*(OTBS) and C(O)C*H*(CH$_3$)), 4.08 – 4.10 (m, 2H, aux. OCH_2), 4.33 (d, 1H, PMB OCH_ACH$_B$Ar, J = 11.7 Hz), 4.42 (d, 1H, PMB OCH$_A$CH_BAr, J = 11.4 Hz), 4.58 – 4.64 (m, 1H, aux. NC*H*), 5.35 – 5.48 (m, 2H, C*H*=C*H*), 5.58-5.63 (m, 1H, C(CH$_3$)=C*H*), 6.94 – 6.96 (m, 2H, PMB Ar*H*), 7.18 – 7.32 (m, 7H, PMB and aux. Ar*H*), **^{13}C NMR** (CDCl$_3$, 75.5 MHz) δ (ppm) – 3.8, – 3.3, 12.5, 13.1, 13.3, 15.5, 18.5, 22.5, 22.6, 26.2, 28.9, 36.8, 37.1, 37.6, 39.7, 42.7, 55.3, 55.7, 65.9, 72.9, 73.1,

76.9, 81.2, 113.7, 123.4, 127.3, 128.9, 129.3, 129.5, 130.2, 131.0, 135.5, 136.3, 138.5, 152.9, 176.0; **HRESIMS** found only triene **323**:



323

Calculated for $C_{43}H_{63}NO_6SiNa^+$ (M+-18): 740.4322; found 740.4281.



307 **318**

(2*R*,3*R*,4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(1,4-dimethylpent-1-enyl)-2-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,6-trimethylcyclohexanone (318)

To a stirring suspension of *t*-BuOK (0.009 g, 0.08 mmol) in dry DMF (0.2 mL) under N_2 at RT was added dropwise a solution of diketone **318** (0.009 g, 0.02 mmol) in dry DMF (0.2 mL) *via* cannula (2 x 0.1 mL rinse) and the resulting yellow solution was stirred at RT for 10 min, after which time it became orange. To this solution was added dropwise MeI (0.01 mL, 0.20 mmol), and the resulting yellow solution was stirred under N_2 at RT for 22 hr. The solution was diluted with Et_2O (2 mL) and the reaction was quenched with $NaHCO_3$ (sat., 2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 2 mL). The organic layers were combined, washed with H_2O (3 x 4 mL) and brine (1 x 10 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.10 g of a bright yellow oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.004 g (50% yield) of the title compound as a clear, colourless oil (R_f = 0.41).

$[\alpha]_D^{20}$ = + 116.5 (0.50, $CHCl_3$); **IR** (film, cm^{-1}) 2955.1, 1694.7, 1513.8, 1462.1, 1249.7, 1088.1; **^{1}H NMR** (d_6-acetone, 600 MHz) δ (ppm) 0.17 (s, 3H, TBS Si(CH_3)$_A$), 0.18 (s, 3H, TBS Si(CH_3)$_B$), 0.81 – 0.82 (m, 3H,CH_2CH(CH_3)), 0.90 – 0.91 (m, 9H, CH(CH_3)$_2$ and CH(CH_3)CH(OTBS)), 0.99 (s, 9H, TBS SiC(CH_3)$_3$), 1.08 (d, 3H, C(O)CH(CH_3), *J* = 6.6 Hz), 1.38 (bs, 3H, C(CH_3)), 1.48 (bs, 3H, C(CH_3)=), 1.60 – 1.64 (m, 1H, C*H*(CH_3)$_2$), 1.61 (d, 1H, C(CH_3)C*H*(C(CH_3)=, *J* = 12.6 Hz), 1.88 – 1.90 (m, 2H, =CHCH_2), 2.91 – 2.98 (m, 1H, C(O)C*H*(CH_3)), 3.05 – 3.15 (m, 1H, C*H*(CH_3)CH(OTBS)), 3.14 – 3.17 (m, 2H, C*H*(OTBS)), 3.19 – 3.24 (m, 1H, CH_2C*H*(CH_3)), 3.30 (d of d, 1H, C$H_A$$CH_B$CH($CH_3$), *J* = 9, 5.4 Hz), 3.63 – 3.67 (m, 1H, CH_ACH_BCH(CH_3)), 3.83 (s, 3H, PMB OCH_3), 4.38 – 4.42 (m, 2H, PMB OCH_2Ar), 5.22 (bs, 1H, =C*H*), 6.92 – 6.94 (m, 2H, PMB Ar*H*), 7.25 – 7.27 (m, 2H, PMB Ar*H*); **^{13}C NMR** (C_6D_6, 150 MHz) δ (ppm) – 2.2, – 2.0, 13.6, 15.0, 15.7, 18.9, 19.2, 20.9, 23.2, 23.3, 27.0, 29.7, 30.8, 37.8, 38.5, 44.5, 50.7, 55.3, 73.0, 73.7, 83.5, 114.6, 129.4, 130.0, 131.3, 160.5, 206.1, 212.6; **HRESIMS** calculated for $C_{34}H_{56}O_5SiK^+$ ($M+K^+$): 611.3534; found 611.3527.

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