Chapter Two

Studies Towards 9,10-Deoxytridachione

2 Studies Towards 9,10-Deoxytridachione

This chapter details the synthetic efforts made towards the natural product 9,10-deoxytridachione, focussing on the formation of the cyclohexadiene component via a selective 1,2-reduction and dehydration sequence of complex cyclohexenones.

2.1 9,10-Deoxytridachione

As discussed in Chapter One, the development of synthetic methodology that provided access to complex cyclohexenones unlocked the possibility of applying the tandem conjugate addition-Dieckmann condensation (Chapter 1, Section 1.5) to other polypropionate natural products, which possess a cyclohexadiene moiety. A probable target presented itself in 9,10-deoxytridachione (**8**) (Figure 2.1). Of particular interest in this case was the presence of a cyclohexadiene moiety tethered to an α-methoxy-γ-pyrone, which presented a new synthetic challenge for the application of the cyclohexenone synthesis to other natural products.

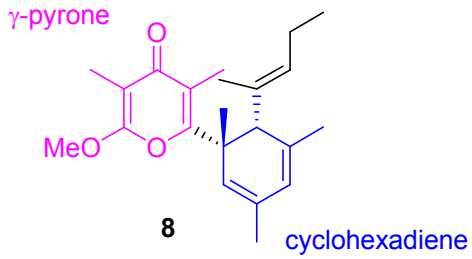


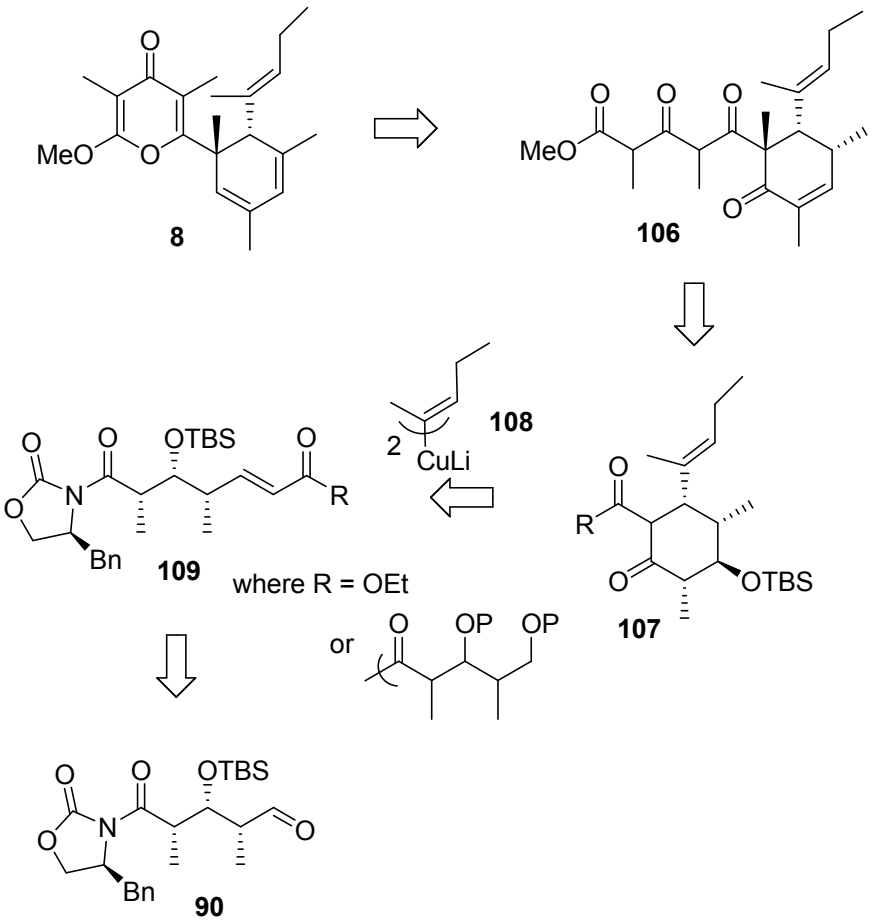
*Figure 2.1. Reported structure of 9,10-Deoxytridachione(**8**).*

9,10-Deoxytridachione (**8**) (Figure 2.1) was isolated from the sacoglossan mollusc *Elysia chlorotica* by Dawe and Wright and the structure was reported as shown above.[1] Specimens of the mollusc were collected from the Bay of Fundy, which is located on the Atlantic Coast of North America. Following homogenization and extraction of the mollusc, **8** was isolated as one of the major metabolites. The compound was found to have the same ^{1}H Nuclear Magnetic Resonance (NMR) and

^{13}C NMR data but the opposite optical rotation to that found by Ireland and Faulkner, when they isolated 9,10-deoxytridachione from *Tridachiella diomedea*.[2] However, since the natural product has only been synthesised as a racemic mixture (discussed in Chapter 1, Section 1.3.1), the absolute stereochemistry and optical rotation have not been unambiguously assigned.

2.2 Retrosynthetic analysis

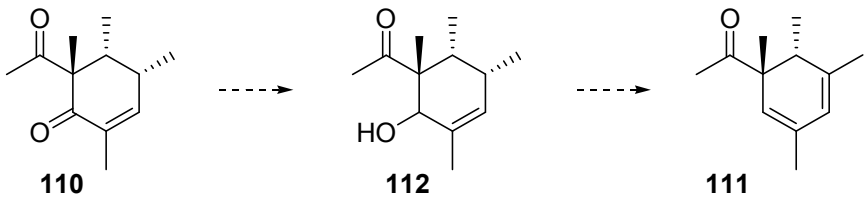
With the aim of developing a 'universal' synthesis of the tridachione family of marine natural products, the retrosynthesis devised for **8** (Scheme 2.1) was based on that utilised for the synthesis of *anti* tridachiahydropyrone (**14**) (detailed in Chapter 1, Section 1.5).



*Scheme 2.1. Retrosynthetic analysis of 9,10-deoxytridachione (**8**).*

The cyclohexadiene moiety in natural product **8** (Scheme 2.1) could be obtained by a selective 1,2-reduction-dehydration sequence of cyclohexenone **106**, while the γ-pyrone unit could be accessed through a cyclisation of the triketide functionality in **106**. The cyclohexenone **106** could in turn be formed from the *anti* methylation and subsequent elimination of **107**, which can be synthesised from the addition of cuprate **108** to *trans* enone **109**, with ensuing cyclisation. *Trans* enone **109** can in turn be obtained from addition of the desired ylide to known aldehyde **90** (Chapter 1, Section 1.5).[3]

It can be seen from the retrosynthetic analysis of **8** (Scheme 2.1) that a number of variables existed, which added flexibility to the synthetic approach. There was the possibility of forming the γ-pyrone ring prior to the cyclohexadiene or *vice versa*. This, in turn, would influence the type of ylide used to form *trans* enone **109**. Initially, it was decided that synthetic attempts would focus on the synthesis of the cyclohexadiene moiety, and to this end a cyclohexenone was required which was stereochemically similar to that present in 9,10-deoxytridachione (**8**) and simple to synthesise. Cyclohexenone **110**, which had been previously synthesised in the Perkins group,[3] was chosen for this purpose and it was envisaged that the formation of cyclohexadiene **111** from cyclohexenone **110** would occur *via* allylic alcohol **112** (Scheme 2.2).

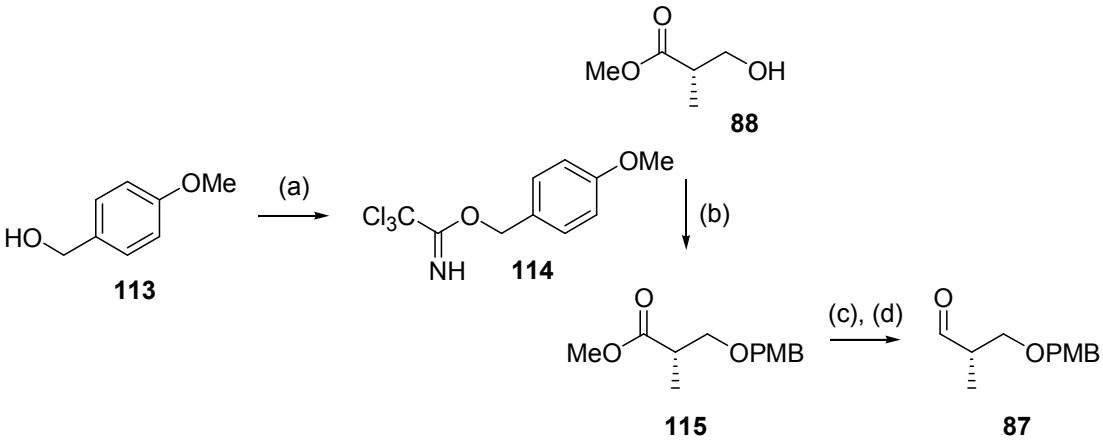


*Scheme 2.2. Proposed formation of cyclohexadiene **111**.*

2.3 Cyclohexadiene formation attempts

2.3.1 Formation of cyclohexenone 110

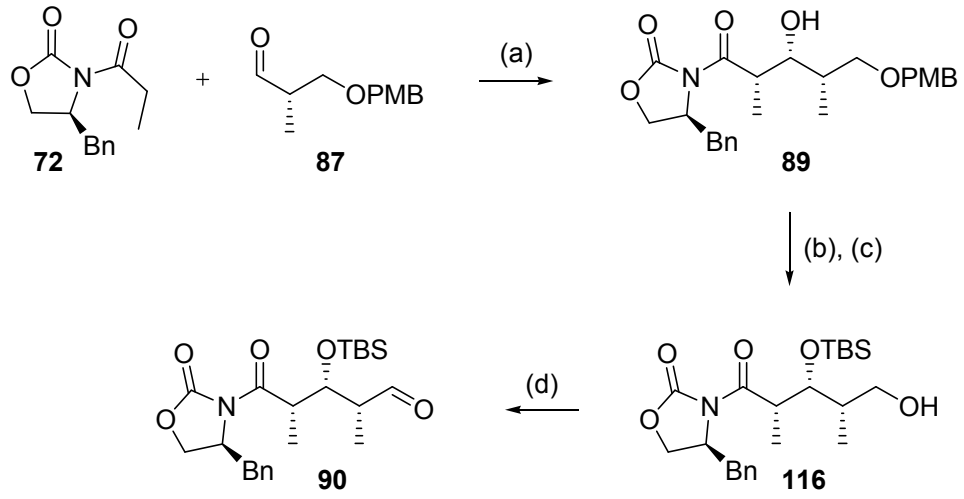
The synthesis of cyclohexenone **110** began with simple aldehyde **87** (Scheme 2.3), which was prepared according to a literature procedure.[3]



Reagents and conditions. (a) i. NaH, Et_2O, 0 °C. ii. $Cl_3CC{\equiv}CN$, RT, 100%; (b) **114**, CF_3SO_3H (0.3 mol %), Et_2O, RT, 93%; (c) $LiAlH_4$, THF, 0 °C, 97%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, – 78 °C → 0 °C, 100%.

*Scheme 2.3. Synthesis of aldehyde **87**.*

The synthesis of aldehyde **87** was achieved *via* a literature procedure[3] (Scheme 2.3), which began with commercially available (*S*)-Roche ester **88**. The primary alcohol functionality of **88** was protected as the *p*-methoxybenzyl (PMB) ether **115**,[4] using synthesised PMB imidate **114**[5] and a catalytic amount of trifluoromethane sulfonic (triflic) acid. The amount of acid had to be carefully monitored, as an excess caused the imidate to decompose. Despite the delicate nature of this protection, the product was able to be purified by distillation under reduced pressure to give ester **115** in high yield and purity. Both the $LiAlH_4$-mediated reduction[6] of ester **115** to the corrersponding primary alcohol and the subsequent oxidation to give aldehyde **87** using Swern conditions[7] (with a modified washing procedure using $NaHSO_4$ and $NaHCO_3$)[8] both proceeded in high yield, producing very clean products, which could be used without further purification. While a pyridinium chlorochromate (PCC) oxidation[9] was also utilised on numerous occasions to give aldehyde **87**, the yield obtained using the Swern protocol was often higher and the isolation was also simpler. This sequence allowed the synthesis of **87** to be carried out with ease and on a relatively large scale. Aldehyde **87** was then transformed into the key aldehyde intermediate **90** as outlined in Scheme 2.4.[3]



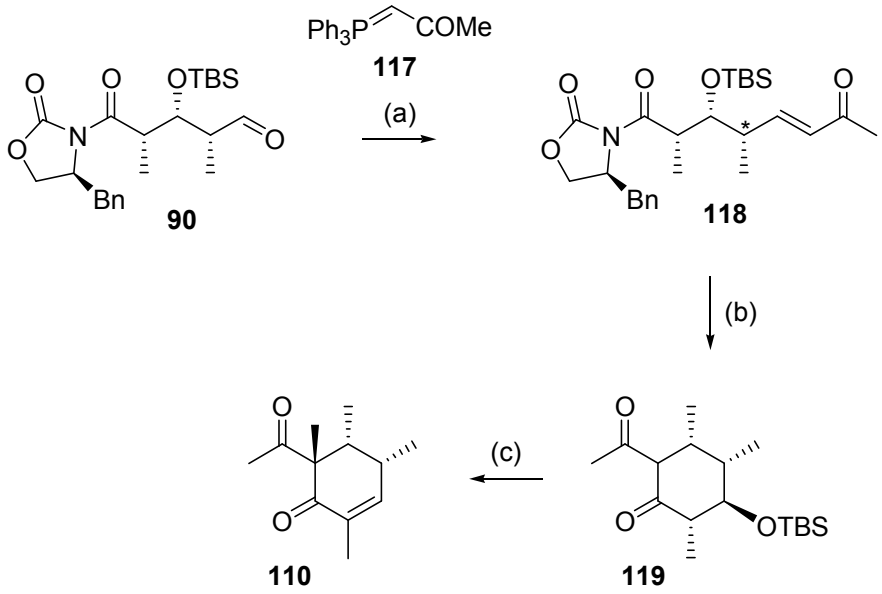
Reagents and conditions. (a) **72**, Bu_2BOTf, Et_3N, CH_2Cl_2. ii. **87**, – 78 °C → 0 °C, 60%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, – 78 °C, 94%; (c) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 78%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, – 78 °C → 0 °C, 97 %

*Scheme 2.4. Synthesis of aldehyde **90**.*

The stereo-triad in **89** was achieved by coupling *N*-acyloxazolidinone **72**[10] with aldehyde **87** using Evans aldol chemistry[11] (Scheme 2.4), which furnished the desired *anti*-Felkin *syn* aldol product **89** (as discussed in Chapter 1, Section 1.4.2.2) in reasonable yield and very high diastereoselectivity (no other product was observed in the NMR spectra). In order to furnish aldehyde **90**, which required the PMB protecting group to be cleaved, the secondary alcohol **89** had to be differentially protected. Thus it was protected as the *tert*-butyldimethylsilyl (TBS) ether, and due to the sensitive nature of alcohol **89** (which was prone to base-induced elimination of the PMB ether to give the terminal alkene), the protection was carried out at low temperature using 2,6-lutidine as the base and TBS triflate as the silylating agent.[12] This furnished the secondary silyl ether in high yield, following purification by flash column chromatography. The PMB group was then selectively removed using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under conditions buffered to pH 7.[13] The buffered conditions were essential to prevent the liberated alcohol from cyclising under the influence of acid. The neutral conditions extended to the purification stage where primary alcohol **116** was purified on silica buffered to pH 7, also to prevent cyclisation.[3] The oxidation of primary alcohol **116** to aldehyde **90** was carried out using the modified Swern protocol.[7,8] This produced aldehyde **90** in high yield and

purity, with identical spectral data to that reported in the literature.[3] Acquisition of pure aldehyde **90** provided an avenue for the synthesis of cyclohexadiene **111**.

To this end, 1-triphenylphosphoranylidene-2-propanone (**117**) was reacted with aldehyde **90** and the product (**118**) was taken through to cyclohexenone **110** (Scheme 2.5).[3]



Reagents and conditions. (a) **117**, toluene, 60 ^{o}C, 5 days, 46%; (b) CuI, MeLi, Me_2S, Et_2O, RT, 67%; (c) NaH, MeI, THF, RT, 87%

*Scheme 2.5. Synthesis of cyclohexenone **110**.*

The reaction of aldehyde **90** with stabilised ylide **117**[3] yielded enone **118** with very high *E*-selectivity (Scheme 2.5). It was found that upon heating of the reaction to 80 ^{o}C to form **118**, a significant amount of epimer at C* was also produced. However, when the reaction temperature was maintained at 60 ^{o}C, the epimerisation was minimal, with only a tiny amount of the epimer observed in the ^{1}H NMR spectrum (Figure 2.2).

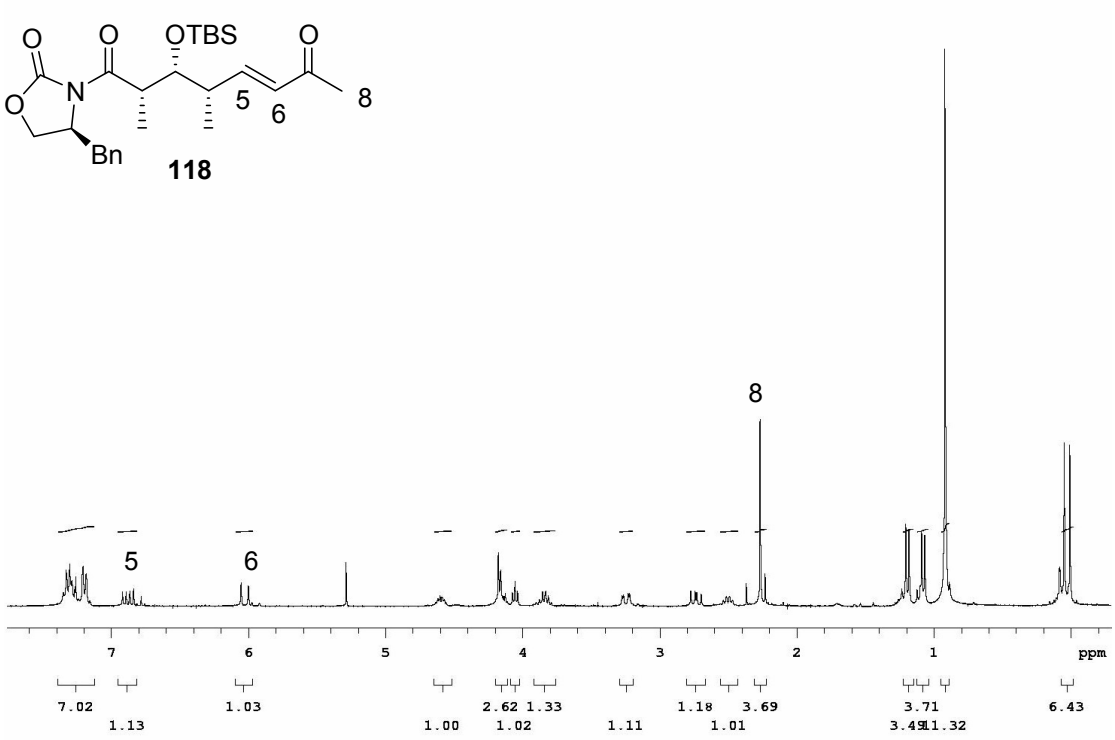


*Figure 2.2. ^{1}H NMR spectrum of trans enone **118** in $CDCl_3$ at 300 MHz.*

The ^{1}H NMR spectrum of **118** was identical to that reported in the literature,[14] with the presence of two alkenyl protons at δ 6.88 and δ 6.02 (Figure 2.2). The downfield shift of these protons may be attributed to the influence of the adjacent carbonyl system through magnetic anisotropy. The conformation of the α,β-unsaturated system may be such that the vinyl protons are not shielded from the magnetic field in the NMR spectrometer by the adjacent carbonyl, and this, coupled with the electron-withdrawing nature of the carbonyl group, shifts the vinyl protons down-field of the normal shift for protons of this type. The proton adjacent to the carbonyl functionality appears as a doublet and the other alkenyl proton appears as a doublet of doublets, by virtue of coupling to the adjacent methine proton. The large coupling constant (J = 16 Hz) between the two alkenyl protons is indicative of a *trans* alkene. Additionally, the appearance of a singlet resonance at δ 2.27 can be attributed to the protons of the methyl ketone. The presence of the other epimer of **118** can also be discerned in the spectrum, with small resonances appearing next to a number of the major peaks.

Cyclohexanone **119** was synthesised from *trans* enone **118** by reaction with dimethyl cuprate, generated from MeLi and CuI, in the presence of Me_2S (Scheme 2.5).[3,15] It was observed that upon initial addition of the MeLi to the CuI-Me_2S complex in Et_2O at room temperature, a bright yellow precipitate formed, which dissolved to give a clear and colourless solution upon formation of the dimethyllithium cuprate. Addition of enone **118** to the dimethyl cuprate resulted in re-appearance of the bright yellow precipitate, which changed colour to green and then black during the course of the reaction. The reaction was complete within one hour and was quenched by addition of a 90% NH_4Cl/10% NH_4OH solution, which developed a dark blue colour after stirring for ten minutes. The reaction proceeded in high stereoselectivity at room temperature (no other isomers were detected by ^1H NMR), producing the expected Felkin product **119** (for reasons discussed in Chapter 1, Section 1.5). The cuprate addition could also be carried out using MeLi as the LiBr complex with a loss in yield (decreased to 47% yield). The ^1H NMR spectrum of cyclohexanone **119** (Figure 2.3) does not exhibit the resonances associated with the auxiliary (which are present at δ 2.77, δ 3.25, δ 4.16, δ 4.56 – 4.61, and δ 7.15 – 7.36 in the spectrum of *trans* enone **118**, Figure 2.2) and indicates that **119** exists in the *enol* form (**120**) by the presence of a peak at δ 16.40. The other resonances are in accord with the spectral data reported in the literature for **119**.[3]

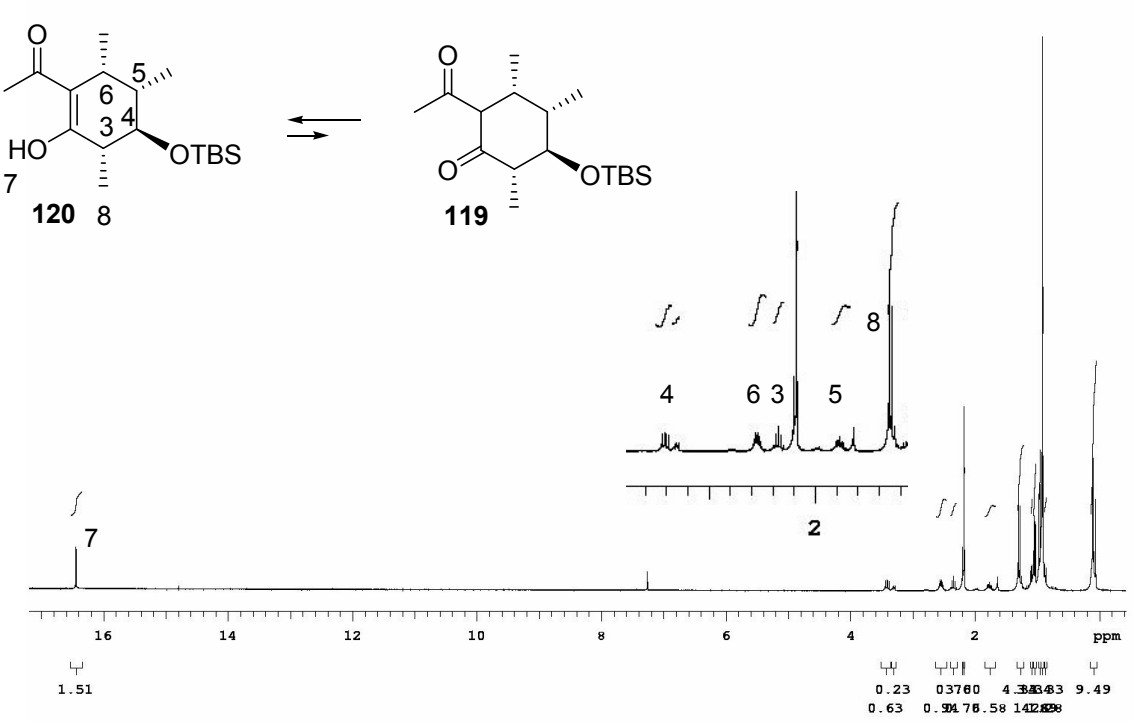


*Figure 2.3. ^{1}H NMR spectrum of cyclohexanone **119** and enol **120** in $CDCl_3$ at 300 MHz.*

The *anti* stereochemistry[3,15-18] in methylated cyclohexenone **110** (Scheme 2.5) was subsequently achieved by treating cyclohexanone **119** with two equivalents of NaH in THF, followed by a large excess of MeI and stirring at room temperature overnight. The extra equivalent of hydride resulted in the elimination of the OTBS group, to give the desired *anti* methylated cyclohexenone **110** (as discussed in Chapter 1, Section 1.5) in high yield and stereoselectivity. The success of the methylation-elimination cascade is evident in the ^{1}H NMR spectrum of **110** (Figure 2.4), which is identical to that reported in the literature for this compound.[3]

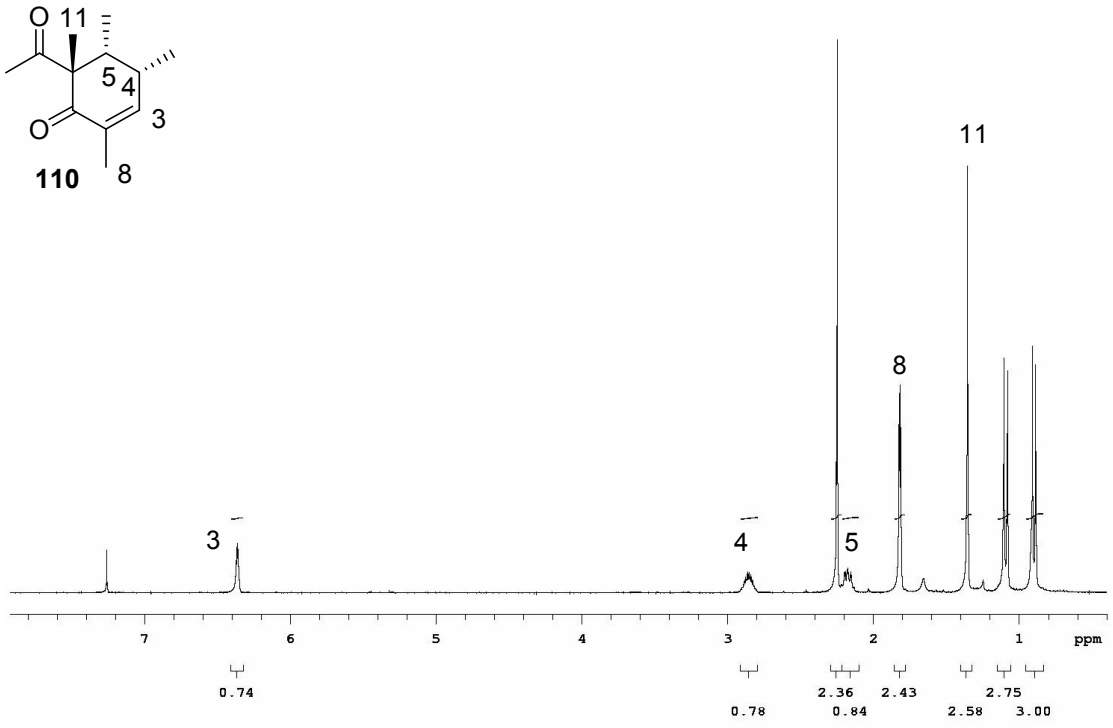
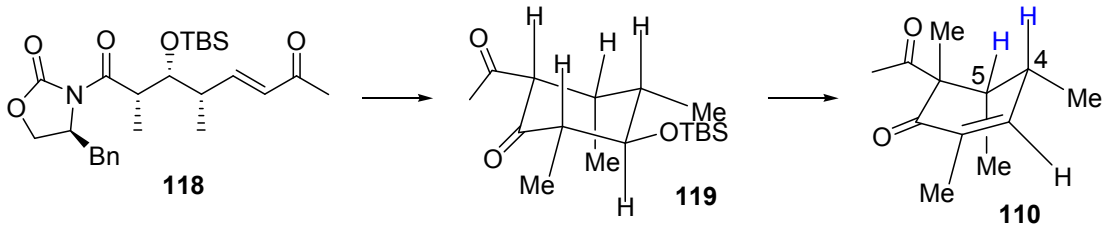


*Figure 2.4. ^{1}H NMR spectrum of anti methylated cyclohexenone **110** in $CDCl_3$ at 300 MHz.*

The multiplet at δ 6.35 – 6.37 is indicative of the presence of an alkene conjugated with a carbonyl, and the peak at δ 1.81 can be attributed to the vinyl methyl, which was present as a doublet at δ 1.28 in the ^{1}H NMR spectrum of the precursor, cyclohexanone **119** (Figure 2.3). The singlet at δ 1.35 can be attributed to the protons of the quaternary methyl group. The evidence for the correct stereochemistry of the cuprate addition is obvious in this compound, where the methine proton on C5 (which appears as a doublet of doublets at δ 2.17) couples to the adjacent methine proton on C4, with a coupling constant of 1.2 Hz. This small coupling constant indicates that the protons on C5 and C4 are not in an antiperiplanar arrangement (highlighted in blue in Scheme 2.6). Furthermore, since the stereochemistry at C4 originates from *trans* enone **118** and is conserved during cyclisation, this leads to the conclusion that the addition of the methyl cuprate must have occurred to give the axial orientation of the methyl group at C5 in cyclohexanone **119** (as discussed in Chapter 1, Section 1.5).



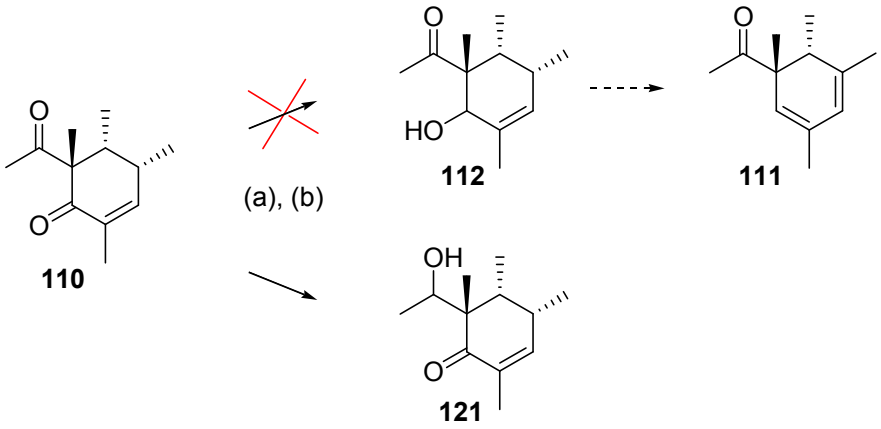
*Scheme 2.6. Stereochemistry generated in methylated cyclohexenone **110** as a result of the dimethyl cuprate addition to trans enone **118**.*

The stereochemistry of the quaternary centre bearing the methyl group in cyclohexenone **110** was confirmed previously by Nucelar Overhauser Effect Spectroscopy (NOESY).[3] *Anti* methylated cyclohexenone **110** could now be utilised as the starting point for testing the reaction sequence to form the cyclohexadiene moiety.

2.3.2 Initial attempts at the formation of the cyclohexadiene system

As discussed previously in Section 2.2, it was envisaged that selective 1,2-reduction of *anti* methylated cyclohexenone **110** and subsequent dehydration of the generated allylic alcohol **112** would afford cyclohexadiene **111** (Scheme 2.7 on the following page).

It has been shown in the literature that one of the most effective ways of achieving the selective 1,2-reduction of enones is through the Luche protocol.[16-18] The reaction involves the use of lanthanoid chlorides (in most cases $CeCl_3$) as catalysts for the $NaBH_4$-mediated 1,2-reduction of α,β-unsaturated carbonyl compounds. In the first instance, *anti* methylated cyclohexenone **110** was reacted with $CeCl_3$ (0.5 molar equivalents) in MeOH at – 78 ^oC, followed by warming to 0 ^oC and addition of $NaBH_4$ (1.1 molar equivalents, Scheme 2.7 (a)), according to a procedure specified in Gemal *et al*.[17]



Reagents and conditions. (a) $NaBH_4$, $CeCl_3$, MeOH, – 78 °C → 0 °C → RT, 52% of **121**; (b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C → RT, 12% of **121**.

*Scheme 2.7. Attempted 1,2-reduction of anti methylated cyclohexenone **110**.*

This procedure resulted in the undesired reduction of the exocyclic carbonyl of **110** to give **121** (Scheme 2.7) instead of allylic alcohol **112**. Initially this was attributed to the fact that only 0.5 equivalents of the $CeCl_3$ had been used, which may have meant not enough catalyst was present in solution to favour the 1,2-reduction over the 1,4-reduction. The next attempt at the selective 1,2-reduction of **110** involved the use of three molar equivalents of $CeCl_3.7H_2O$ and 1.5 molar equivalents of $NaBH_4$ (Scheme 2.7 (b)).[18] However, this too produced only secondary alcohol **121**, which is evident in the ^1H NMR spectrum of **121** (Figure 2.5).

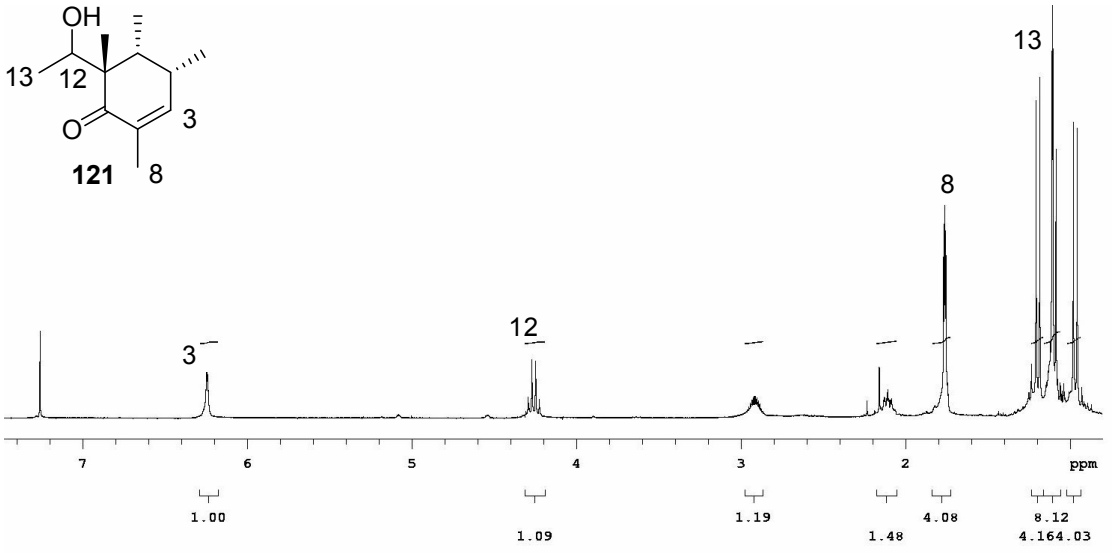


*Figure 2.5. ^{1}H NMR spectrum of alcohol **121** in $CDCl_3$ at 300 MHz.*

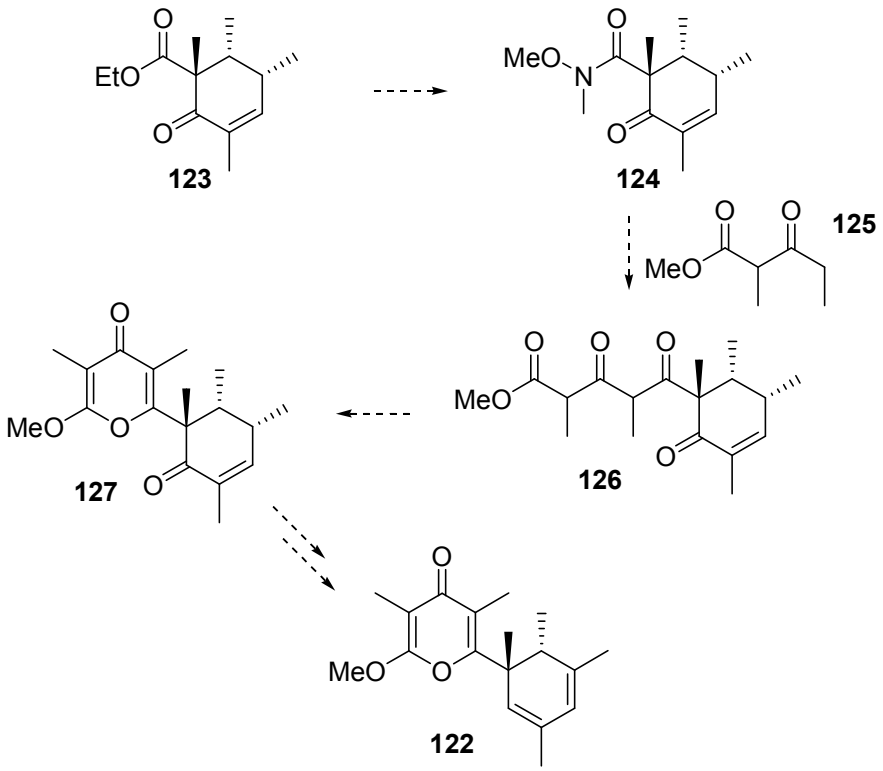
From the ^{1}H NMR spectrum of **121** (Figure 2.5) it can be deduced that the reduction was selective, as only one isomer of secondary alcohol **121** appears to have formed. The vinyl proton appears unchanged at δ 6.25, which indicates that the α,β-unsaturated carbonyl system is intact. The presence of a quartet at δ 4.26 can be attributed to the oxymethine proton on C12, which couples with the exocyclic methyl, (present as a doublet at δ 1.19).

As the exocyclic ketone functionality proved to be very susceptible to functionally-specific reduction conditions it was decided that it may be worthwhile to attempt the formation of the γ-pyrone ring before any attempts were made at the reduction of the cyclohexenone. It is well known that γ-pyrone rings, due to their aromatic nature, exhibit resistance to reduction, and hence this would prove a more useful synthetic strategy in light of the results obtained in the afore-mentioned experiments.

2.4 γ-Pyrone formation attempts

In order to test the feasibility of forming the γ-pyrone ring prior to the cyclohexadiene moiety, model **122** was chosen as the synthetic target. It was envisaged that the γ-pyrone moiety in model **122** could be formed from cyclohexenone **123** *via* Weinreb amide **124** (Scheme 2.8). Amide **124** could be

coupled with the enolate of **125** to form diketo-ester **126**, which, when subjected to the correct conditions, should cyclise to yield γ-pyrone ring-containing cyclohexenone **127**.

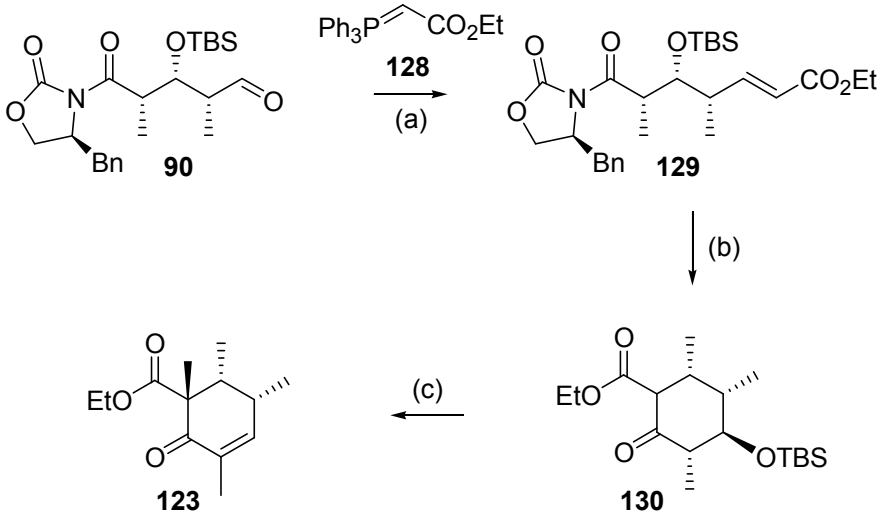


Scheme 2.8. Synthetic sequence depicting the formation of the γ-pyrone ring prior to the cyclohexadiene.

Conversion of ester **123** to Weinreb amide **124** (as depicted in Scheme 2.8) was believed to be the most effective means of forming diketo-ester **126**, as the use of the Weinreb amide functionality would prevent multiple addition of the enolate of **125** onto the exocyclic carbonyl of **124**. Cyclohexenone **123** bearing the ester functionality was thus required, and fortuitously the synthesis of this compound had been developed in the Perkins group.[3]

2.4.1 Attempted synthesis of Weinreb amide 124

The synthesis of ester-containing *anti* methylated cyclohexenone **123** began with aldehyde **90**, which was coupled with ylide **128** to give *trans* enone **129** (Scheme 2.9).[3]



Reagents and conditions. (a) **128**, CH_2Cl_2, RT, 5 days, 83%; (b) CuI, MeLi.LiBr, Me_2S, Et_2O, RT, 41%; (c) NaH, MeI, THF, 79%.

*Scheme 2.9. Synthesis of cyclohexenone **123**.*

The Wittig reaction between ylide **128** and aldehyde **90**[3] (Scheme 2.9) was carried out at room temperature in this case, which resulted in stereochemically-pure *trans* enone **129**, with no epimers observed in the NMR spectra. The cuprate addition to form cyclohexanone **130** was carried out using MeLi-LiBr complex (as described in Section 2.3.1), which gave a modest yield of **130**. The subsequent methylation-elimination sequence proceeded in high yield to give exclusively *anti* methylated cyclohexenone **123** in 79% yield. The ^{1}H NMR spectrum of **123** (Figure 2.6) shows the diagnostic protons and is identical to that reported in the literature.[3]

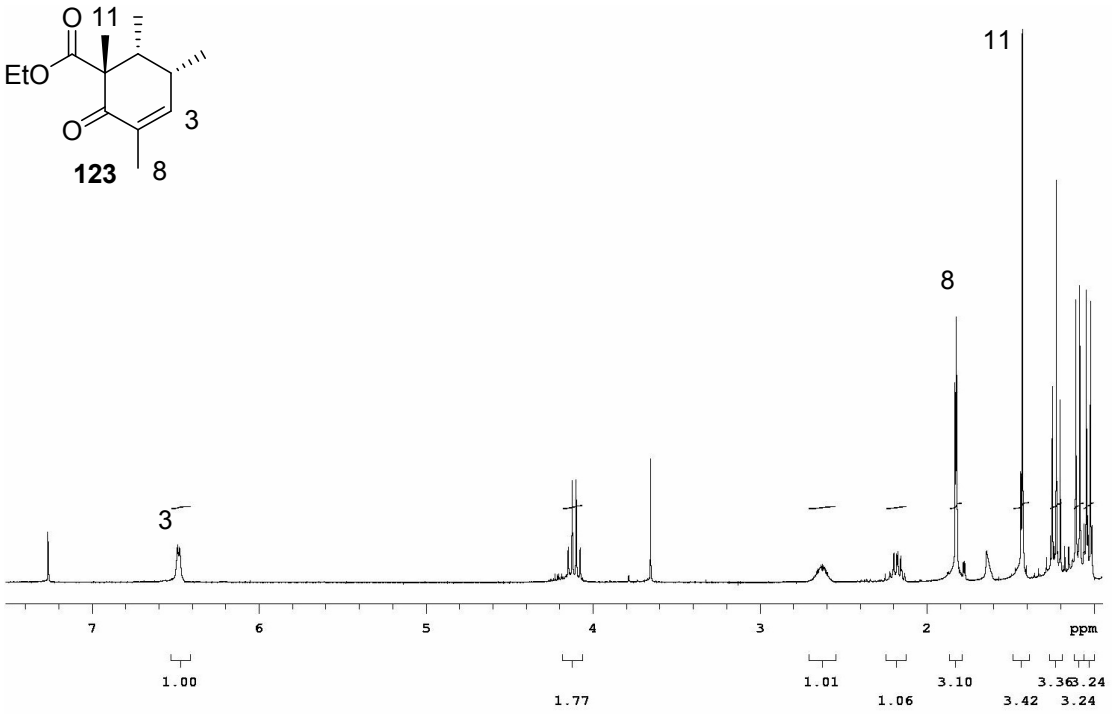
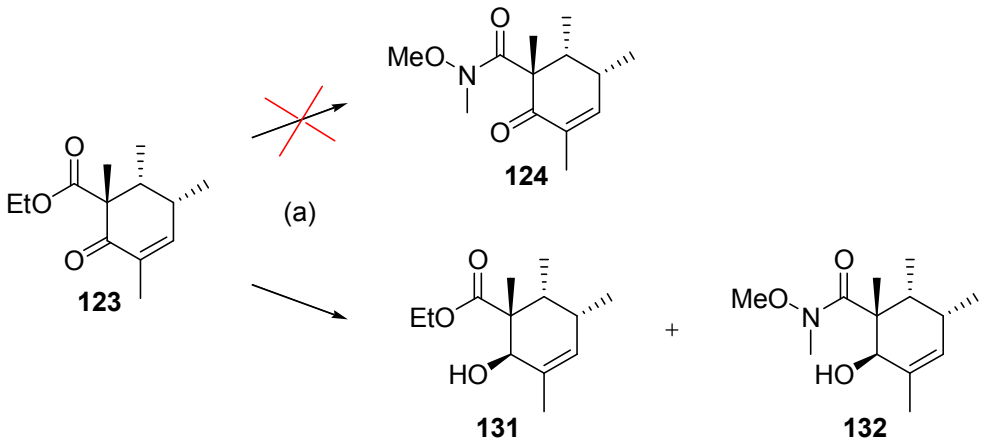


*Figure 2.6. ^{1}H NMR spectrum of anti methylated cyclohexenone **123** in $CDCl_3$ at 300 MHz.*

The vinyl proton appears as a multiplet at δ 6.47 – 6.49 (Figure 2.6), while the quartet (δ 4.11) and triplet (δ 1.23) are due to the ethyl ester. The multiplet at δ 1.82 – 1.83 can be attributed to the vinyl methyl and the quaternary methyl appears as a large singlet at δ 1.43.

With **123** in hand, the conversion of ester **123** to amide **124** was attempted. The reaction was carried out under anhydrous conditions using two different methods. The first attempt involved addition of *i*-PrMgCl to a stirring suspension of *N,O*-dimethylhydroxylamine hydrochloride (MeON(H)Me.HCl) and cyclohexenone **123** in a 1:1 solution of tetrahydrofuran (THF):Et_2O at – 20 ^{o}C (Scheme 2.10).[12] Stirring continued for 30 minutes, after which time the mixture was warmed to room temperature and stirred for a further 30 minutes. At this time, it was found that all of the starting material had been consumed and the reaction was worked up by quenching with saturated aqueous NH_4Cl, followed by extraction with CH_2Cl_2. The standard isolation procedure and purification by flash column chromatography

yielded an unexpected result, with compounds **131** and **132** being isolated as the major components (in a 2:1 ratio by mass of ester **131**:amide **132**).



Reagents and conditions. (a) i. MeON(H)Me.HCl, **123**, 1:1 THF/Et_2O, – 20 °C. ii. *i*-PrMgCl, – 20 °C → RT; or i. MeON(H)Me.HCl, *i*-PrMgCl, 1:1 THF/Et_2O, – 20 °C. ii. **123**, 1:1 THF/Et_2O, – 20 °C → RT

*Scheme 2.10. Attempted formation of Weinreb amide **124**.*

In order to improve the yield of amide and decrease the extent of the reduction, an alternative method was attempted, which involved addition of cyclohexenone **123** to a mixture of MeON(H)Me.HCl and *i*-PrMgCl. However, this method also produced ester **131** and amide **132**, albeit in a different ratio of 3:1 (ester:amide).

The ^{1}H NMR spectra of ester **131** (Figure 2.7) and amide **132** (Figure 2.8) are given on the following page.

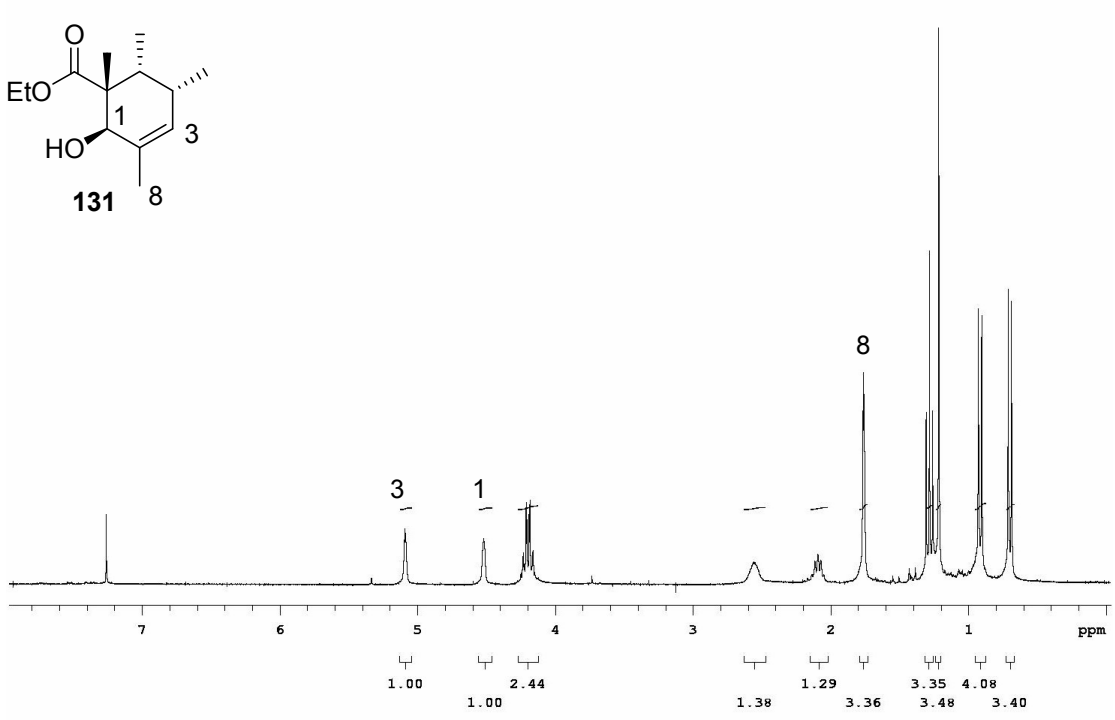


*Figure 2.7. ^{1}H NMR spectrum of ester **131** in $CDCl_3$ at 300 MHz.*

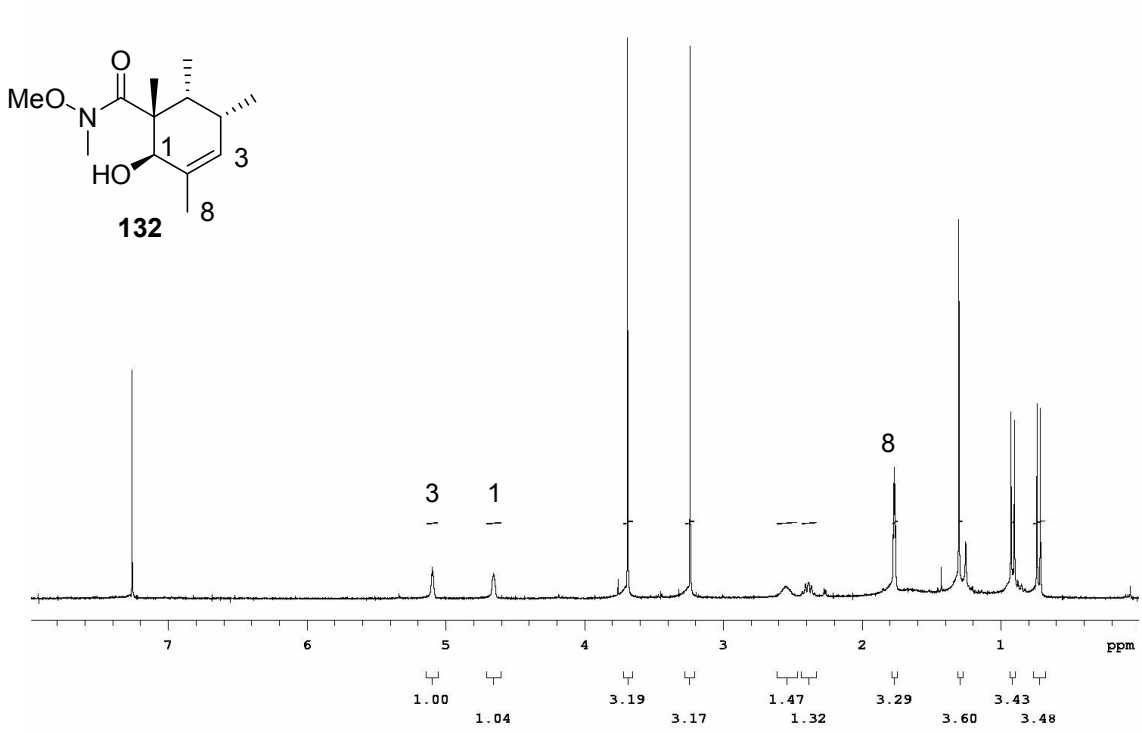


*Figure 2.8. ^{1}H NMR spectrum of amide **132** in $CDCl_3$ at 300 MHz.*

The stereochemistry at C1 of ester **131** and amide **132** was deduced using NOESY and will be discussed shortly. It can be seen from the spectra that the allylic proton is present in the starting material at approx δ 6.47 – 6.49 (Figure 2.6), and in the products it has moved significantly upfield to δ 5.10 in both ester **131** and amide **132** (Figure 2.7 and Figure 2.8, respectively). This is consistent with the loss of resonance due to reduction of the carbonyl, and hence a decrease in the electron-withdrawing character of the allylic environment. Additionally, the appearance of a peak at δ 4.52 in the spectrum of ester **131** (Figure 2.7) and at δ 4.65 in the spectrum of amide **132** (Figure 2.8) is indicative of the presence of a proton on a carbon bearing a hydroxyl functionality. In both the spectra the vinyl methyl, which appeared at δ 1.82 – 1.83 in the ^{1}H NMR spectrum of cyclohexenone **123** (Figure 2.6), maintains its position in the spectrum of ester **131** (at δ 1.75 – 1.77, Figure 2.7) and amide **132** (at δ 1.76 – 1.78, Figure 2.8). This indicates that the alkene functionality is intact in the products and the slight shift upfield is most likely due to the loss of resonance as a result of the reduction of the carbonyl. The spectrum of amide **132** also indicates the presence of the *N*-methyl and *N*-methoxy protons of the amide at δ 3.24 and δ 3.69, respectively. The ^{13}C NMR spectra further corroborated the proposed structures of **131** and **132**, indicating that only one carbonyl peak is present: at δ 178.7 in the case of ester **131** and at δ 178.8 in the case of amide **132.**[*]

Additionally, it is of interest to note that both the ^{1}H (Figure 2.7 and Figure 2.8) and ^{13}C NMR spectra indicated that only one isomer of the allylic alcohol is formed in each case. In order to elucidate the stereochemistry of the generated stereocentre NOESY experiments were conducted on ester **131** and amide **132**. It was found that the alcohol was present in the equatorial position, due to the correlations observed between the proton on C1 and the protons on the bottom face of the ring (Figure 2.9).

[*] The ^{13}C NMR spectra discussed in this thesis can be found in the Appendices.

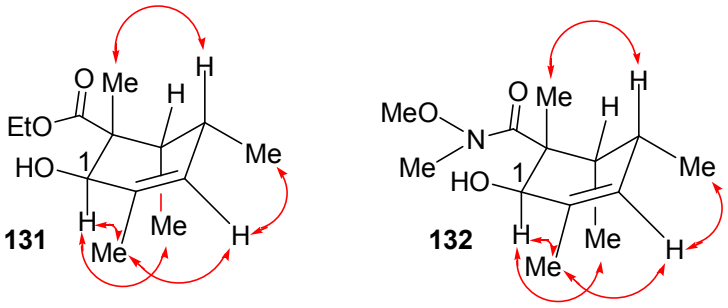


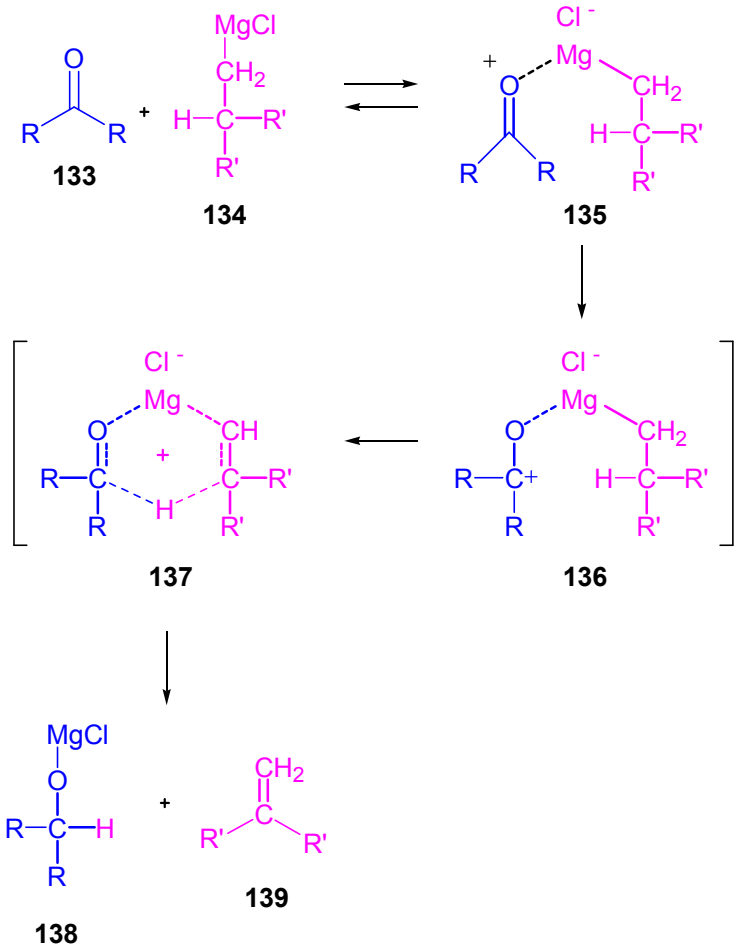
*Figure 2.9. NOESY correlations observed at 300 MHz in $CDCl_3$ for ester **131** and amide **132**.*

The IR spectra further confirmed the structure of the compounds with an absorption characteristic of a hydroxyl stretch appearing at 3547.9 cm^{-1} in the case of ester **131** and 3518.7 cm^{-1} in the case of amide **132**. High resolution mass spectrometry confirmed the expected composition of $C_{13}H_{22}O_3$ (ester **131**) and $C_{13}H_{23}NO_3$ (amide **132**).

The fact that the selective 1,2-reduction was taking place was fortuitous, due to the problems encountered using conventional methods (Section 2.3.2). However, the mechanism of this reduction was not immediately obvious. A search through the literature indicated that Grignard-mediated reductions of this type have been previously reported and the mechanism has been studied. This will be discussed in the following section.

2.5 Asymmetric Grignard-mediated reductions

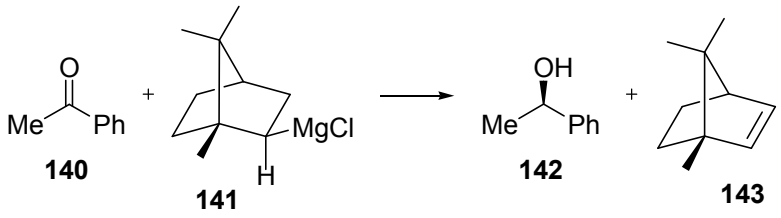
The reduction reaction of Grignard reagents was recognised by Grignard in his original work.[19] Later, Conant and Blatt[20] found that reduction was favoured (over addition) with sterically-demanding ketones. The correlation between the availability of β-hydrogens on the Grignard reagent and reduction was observed by Whitmore and George,[21] who, based on these findings, proposed the Whitmore mechanism (Scheme 2.11).



Scheme 2.11. Whitmore mechanism for the reduction of carbonyls by Grignard reagents.[21]

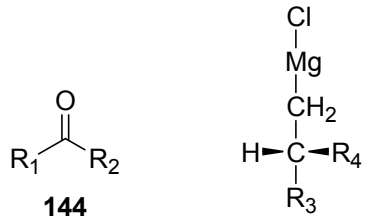
The mechanism depicted in Scheme 2.11 is essentially the same as the Meerwein-Pondorf-Verley (MPV) mechanism for reductions using aluminium species, but the Grignard reaction is irreversible.[22] Additionally, the β-hydrogen transfer has been verified by deuterium tracer experiments.[23]

The asymmetric Grignard reduction was first observed in the reaction of acetophenone (**140**) with the Grignard reagent (**141**) derived from pinene hydrochloride. The active isobornyl species **141** gave (*R*)-(+)-methylphenylcarbinol (**142**) and olefin **143** (Scheme 2.12).[24]



*Scheme 2.12. Asymmetric reduction of ketone **140** by Grignard reagent **141**.*

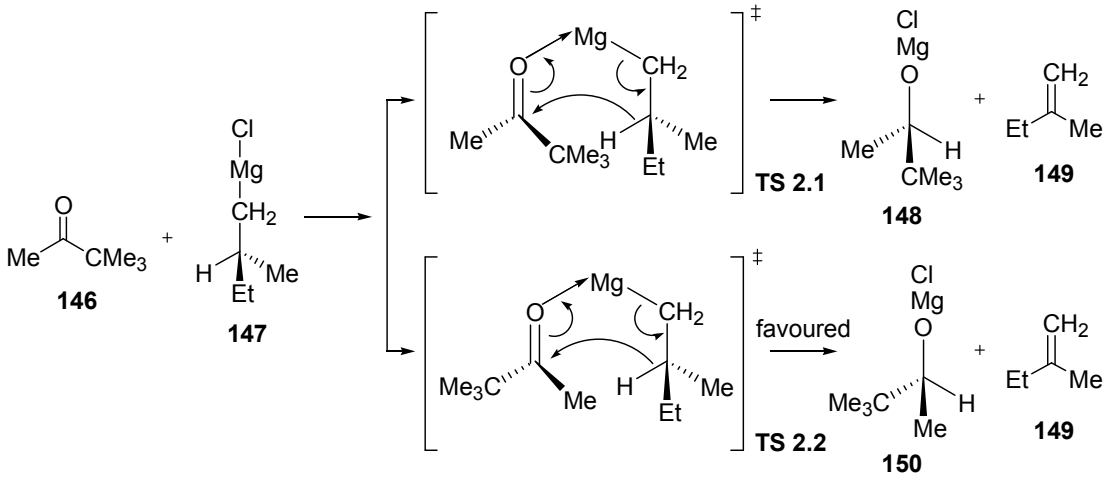
However, no attempts were made to interpret the reaction or stereochemical outcome in terms of a Whitmore-MPV mechanism. Since that time numerous studies into the nature of the Grignard-mediated reduction have been undertaken. Most experiments have utilised achiral ketones of type **144** and chiral Grignard reagents of type **145** (Figure 2.10).[22]



where R_1 and R_2 = Me, Et, *n*-Pr, *n*-Bu, *i*-Bu, *i*-Pr, *t*-Bu, Ph and CF_3
R_3 and R_4 = Me, Et, *i*-Pr, *t*-Bu and Ph

Figure 2.10. Ketones and Grignard reagents employed in studies of the Grignard reduction reaction.

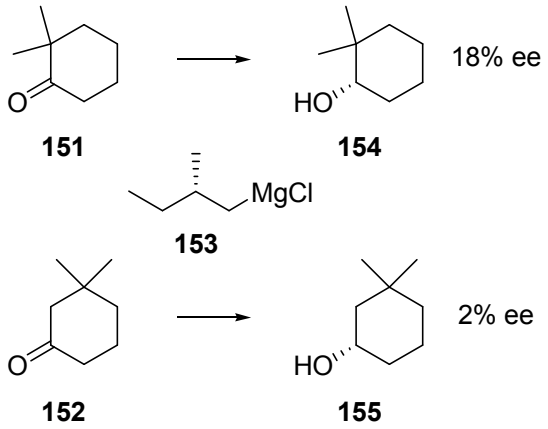
In these studies the stereochemical outcome has been correctly predicted by the model depicted in Scheme 2.13, which in this case shows a reaction between *t*-Bu ketone **146** and the Grignard reagent **147** from (*S*)-(+)-1-chloro-2-methylbutane.



*Scheme 2.13. Grignard-mediated reduction of t-Bu ketone **146** by reagent **147**.*

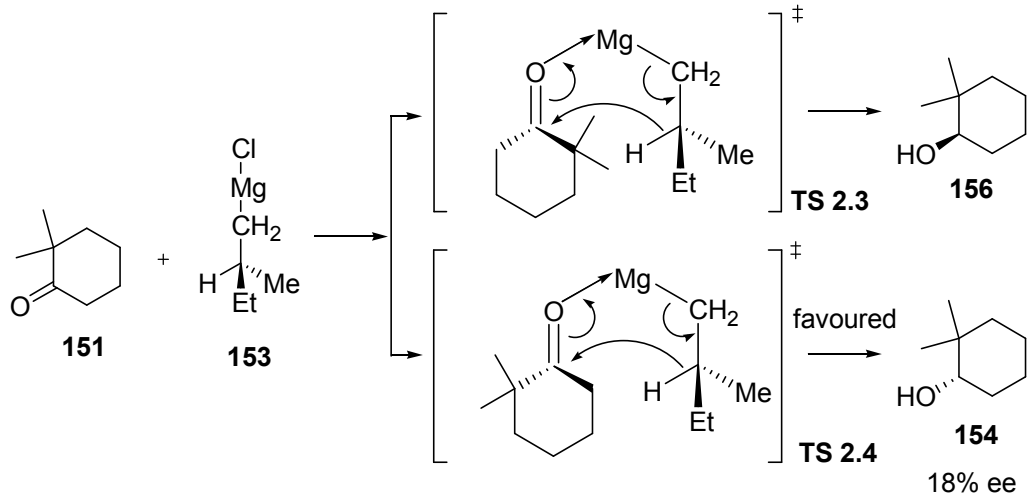
Grignard reagent **147** can attack either enantiotopic face of ketone **146** *via* transition states **TS 2.1** and **TS 2.2** (Scheme 2.13). In **TS 2.1** the two largest groups of the ketone and reagent (*t*-Bu and Et, respectively) are on the same face of the transition state, while in **TS 2.2** the two large groups oppose each other. Thus, **TS 2.2** is a better "fit" for both ketone **146** and Grignard reagent **147**, rendering it lower in energy. Therefore, the predicted product of this reaction would be **150**, which is true in practice, with **150** formed in 12% ee.

Of interest to the work described in this thesis is the reduction of 2,2-dimethylcyclohexanone (**151**) and 3,3-dimethylcyclohexanone (**152**) with Grignard reagent **153**, reported by La Combe and Edelstein (Scheme 2.14).[25,26]



*Scheme 2.14. Asymmetric reduction of cyclohexanones **151** and **152**.*

The dominant product of the reaction of **151** with **153** was (*S*)-isomer **154** (18% ee), which can be rationalised by applying the MPV-Whitmore transition states **TS 2.3** and **TS 2.4** (Scheme 2.15).



*Scheme 2.15. Asymmetric reduction of cyclohexanone **151** by Grignard reagent **153**.*

The favoured transition state in Scheme 2.15 is **TS 2.4**, where the sterically-demanding methyl substituents of ketone **151** are opposed to the ethyl group on Grignard reagent **153**, leading to the formation of alcohol **154** in favour of **156**. In the case of 3,3-dimethylcyclohexanone (**152**) (Scheme 2.14) the asymmetric reduction

gives an ee of less than 2%. Thus, it can be concluded that the important interactions in these systems are those close to the developing stereocentre.

Additional studies have also been undertaken in the literature using Grignard reagents with multiple chiral centres, such as **157**,[27] as well as chiral reagents of type **158**[28] and reagents derived from cyclohexenes (**159**).[29]

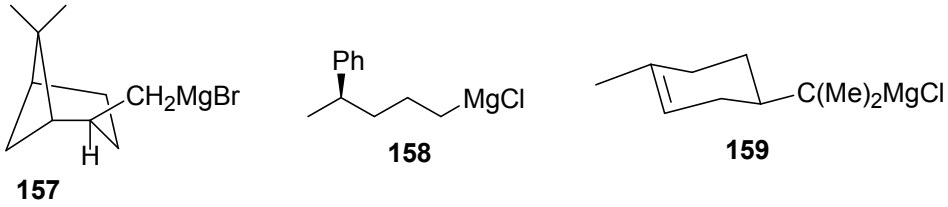
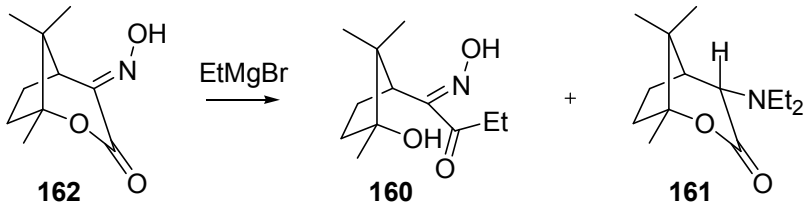


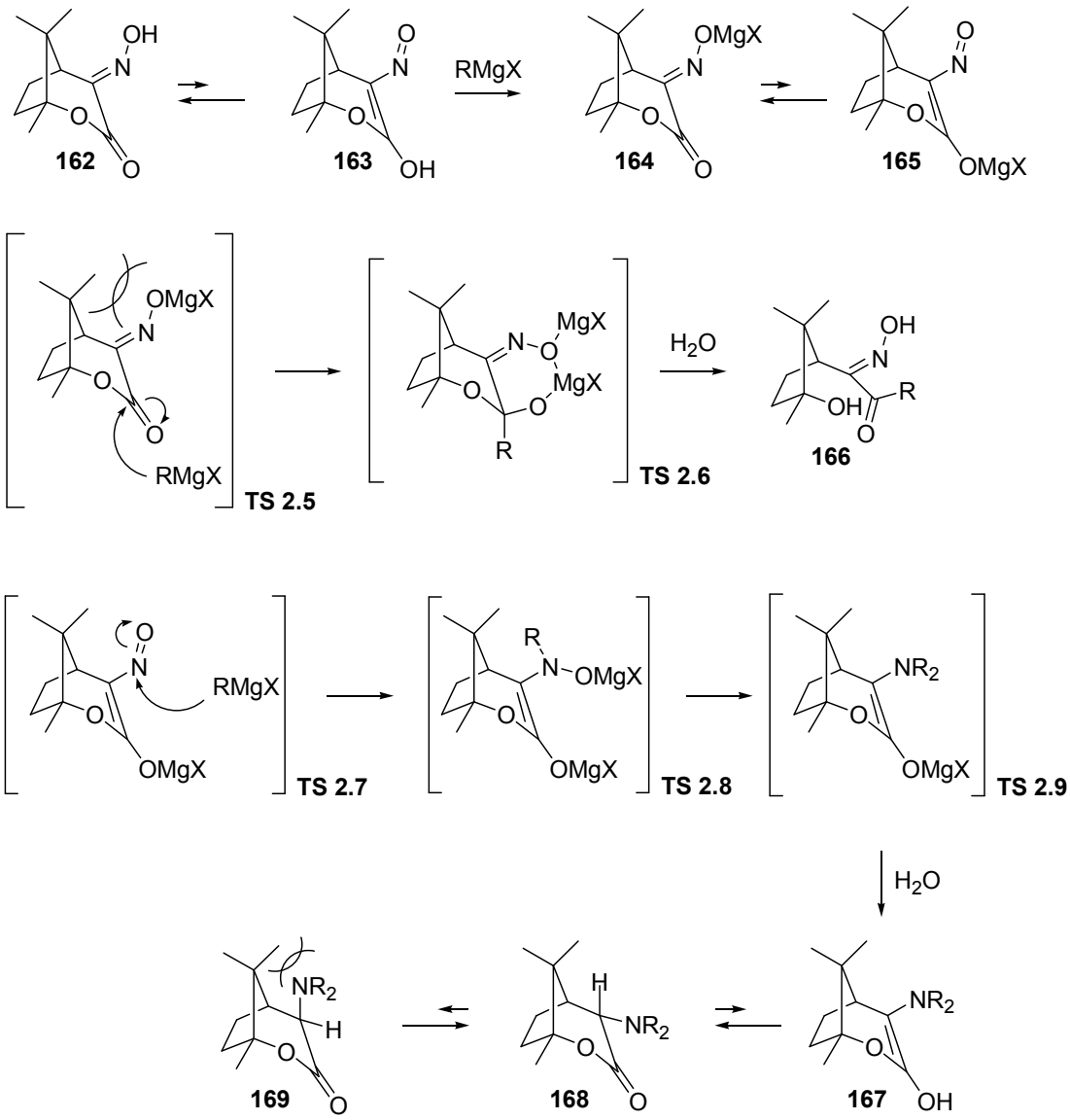
Figure 2.11. Grignard reagents used in reductions of ketones.

A recent study by Grošelj *et al*[30] reported the reduction of camphor-derived enaminones, where the two products **160** and **161** were isolated from a reaction of **162** with EtMgBr (Scheme 2.16).



*Scheme 2.16. Products of the reaction of **162** with EtMgBr.*

Following further studies into this reaction using different Grignard reagents, it was found that alcohol **160** formed preferentially when the groups on the Grignard reagent were sterically less demanding (eg Me, Ph) while *N*-alkylation (to give **161**) occurred when the R groups on the Grignard reagent were bigger (eg. *n*-Bu or Et). The mechanism depicted in Scheme 2.17 was proposed to explain these results.[30]



*Scheme 2.17. Proposed mechanism for the formation of alcohols of type **166** and N-alkylated products of type **168** and/or **169** from reaction of **162** with Grignard reagents.*

Thus, based on the studies reported in the literature and the outcome of the *i*-PrMgCl-mediated reduction of ester **123**, it can be concluded that steric effects influence the outcome of the Grignard-mediated reduction to a large extent. Despite the utility of these reductions as demonstrated in the literature, Grignard reagents have not experienced wide-spread use as reducing agents in synthesis. This may be due to a number of reasons, including generally low ee, slow reduction rates due to steric hindrance between the reagent and substrate, competing addition and

enolisation reactions, as well as the fact that electronic factors associated with Grignard reagents inhibit the reduction reaction.[31]

It is of interest to note that not many studies have been performed on chiral ketones or enones. The unusually facile reduction of ester **123** and amide **124** (Section 2.4.1) thus prompted an investigation into the outcome of the Grignard-mediated reduction on cyclohexenones, with the aim of providing additional insight into the reaction and mechanism. Additionally, the synthesis of allylic alcohols was of significant interest in terms of being able to generate the cyclohexadiene moiety in the natural product. The following section describes the work undertaken in this thesis towards the *i*–PrMgCl-mediated reduction of nine complex cyclohexenones.

2.6 Grignard-facilitated formation of allylic alcohols

A variety of cyclohexenone derivatives (all consisting of the same basic cyclohexenone skeleton) were chosen for this study based on their structural and functional features (Figure 2.12).

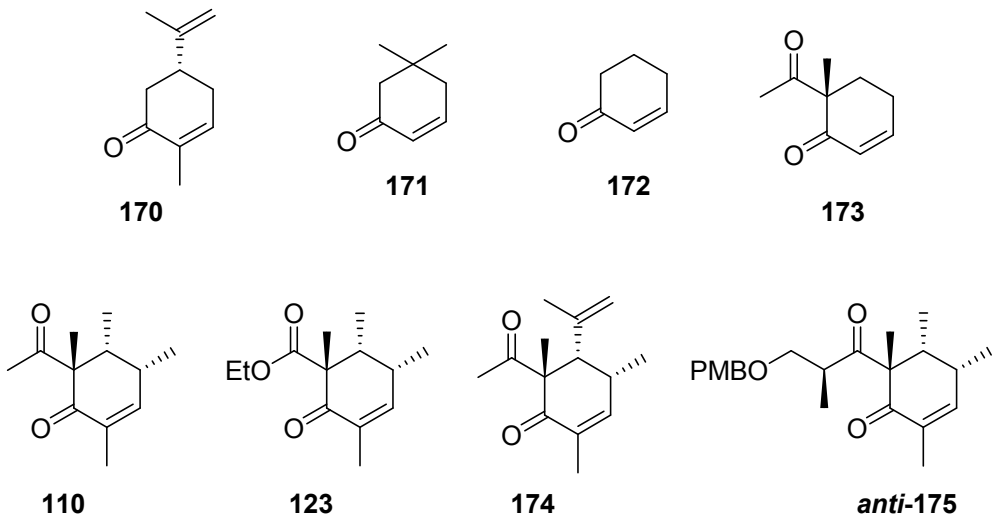


Figure 2.12. Cyclohexenones used to test the scope of the i-PrMgCl-mediated reduction.

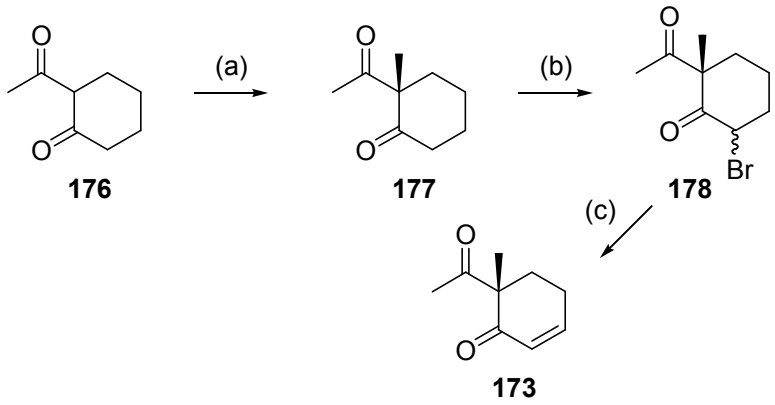
These compounds (Figure 2.12) allowed two facets of the *i*-PrMgCl-mediated reduction to be investigated: the effect of the absence or presence of the exocyclic carbonyl and the effect of changing the complexity and position of the substituents

around the ring. Carvone (**170**), isophorone (**171**) and cyclohexen-2-one (**172**) were obtained commercially, while cyclohexenones **173** to **175** were synthesised (in addition to **110** and **123**, which were synthesised previously).

2.6.1 Formation of cyclohexenones 173 – 175

*2.6.1.1 Synthesis of cyclohexenone **173***

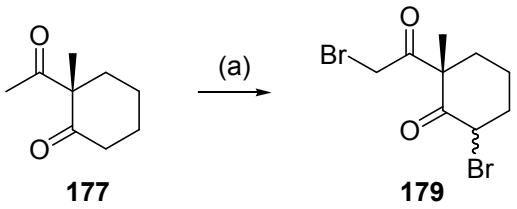
Cyclohexenone **173** was prepared from 2-acetylcyclohexanone (**176**) *via* the scheme shown below (Scheme 2.18).



Reagents and conditions. (a) NaH, MeI, THF, RT, 69%; (b) Glacial AcOH, $CHCl_3$, Br_2, 0 $^oC \rightarrow$ RT, 90%; (c) LiBr, Li_2CO_3, DMF, 150 ^oC, 40%.

*Scheme 2.18. Synthesis of cyclohexenone **173***

The mono-methylation of 2-acetylcyclohexanone (**176**) to give **177** (Scheme 2.18) was conducted utilising only one equivalent of NaH and a large excess of MeI (7 equivalents), to ensure the dimethylated product did not form. A number of different methods were attempted in the formation of bromoketone **178**. One procedure, which involved generating the enolate of **177** using lithium hexamethyldisilylazide (LiHMDS), trapping of the enolate using trimethylchlorosilane (TMSCl) and brominating using Br_2,[32] gave a complex mixture, of which one component was identified as *bis*-brominated adduct **179** (Scheme 2.19). This occurred despite using only stoichiometric quantities of the base and hence a new method was required.



Reagents and conditions. (a) LiHMDS, TMSCl, Br_2, THF, – 78 ^oC.

*Scheme 2.19. Bromination of **177** via a silyl enol ether.*

The solution to this problem was found in a reaction involving the use of glacial AcOH and Br_2 in $CHCl_3$.[33] This produced the desired bromoketone **178** as a mixture of two isomers ***syn*-178** and ***anti*-178** (Figure 2.13), which were separable by flash column chromatography.

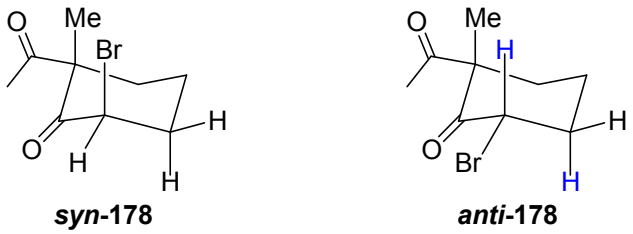


*Figure 2.13. Isomers **syn-** and **anti-178** formed from the bromination of **177**.*

Isomers ***syn*-** and ***anti*-178** (Figure 2.13) were formed in approximately a 1:1 ratio and high yield, and the stereochemistry in isomer ***anti*-178**, which was isolated in a slightly smaller yield (39%) than ***syn*-178** (51%), was confirmed by the large coupling constant (J = 12.9 Hz) between the two diaxial protons (highlighted in blue). The original literature procedure[33] to convert isomers **178** to cyclohexenone **173** involved reacting crude **178** as a solution in $CHCl_3$ with pyridine at reflux. However, when this was attempted (using either crude **178** or purified mixture) only starting material was isolated. The elimination was, however, successfully effected under the conditions described in Wender *et al*,[34] by heating purified **178** in *N*,*N*-dimethylformamide (DMF) in the presence of LiBr and Li_2CO_3, to give cyclohexenone **173** in modest yield. Due to the fact that cyclohexenone **173** was not required in large quantities, other options for improving this yield were not

investigated. The ^{1}H NMR spectrum of **173** (Figure 2.14) shows the requisite resonances.

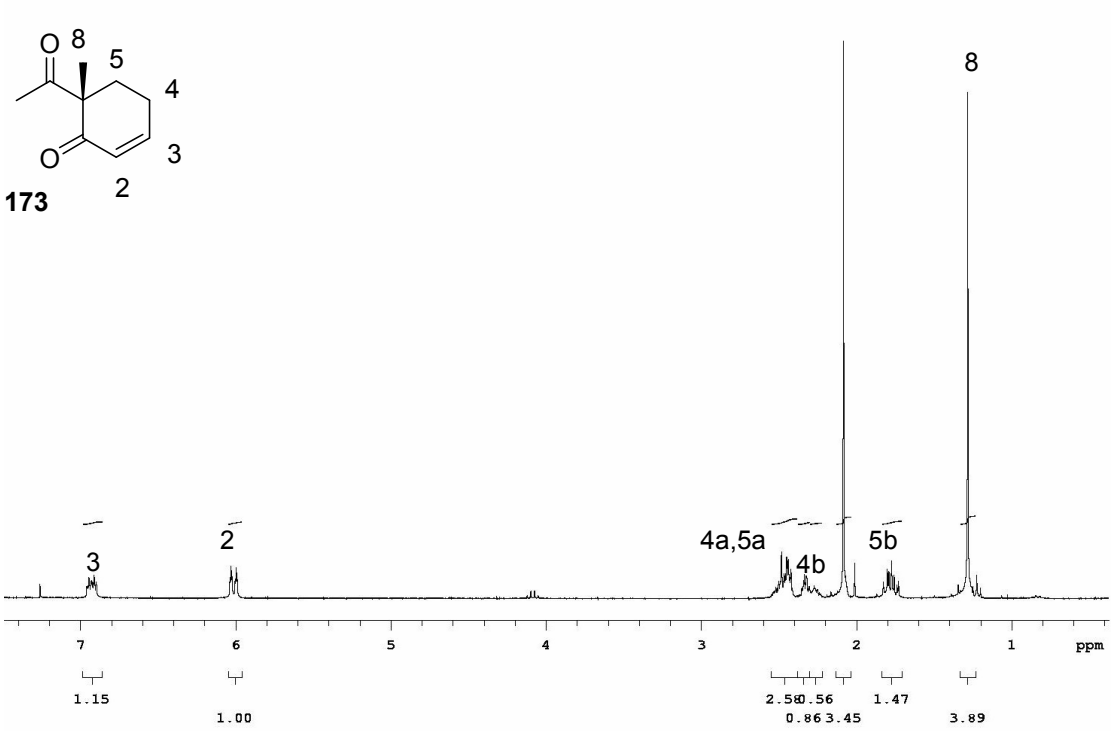
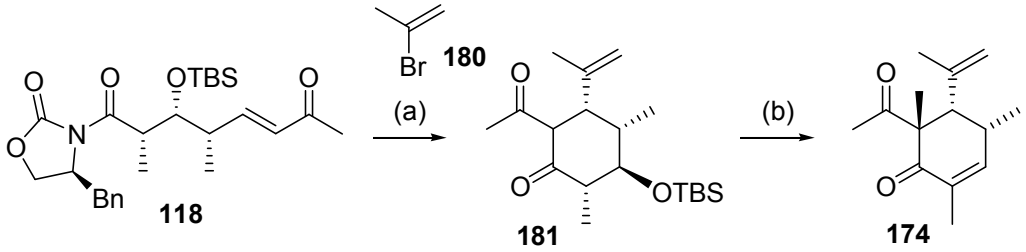


*Figure 2.14. ^{1}H NMR spectrum of cyclohexenone **173** in $CDCl_3$ at 300 MHz.*

The two singlets at δ 1.31 and δ 2.11 can be attributed to the quaternary and ketone methyl protons, respectively (Figure 2.14). The methylene protons adjacent to the alkene functionality appear as multiplets at δ 2.32 – 2.37 and δ 2.44 – 2.57, in conjunction with one of the methylene protons on C5. The other C5 methylene proton appears as a multiplet at δ 1.75 – 1.85, and the two vinyl protons appear as a doublet of triplets at δ 6.04 and a multiplet at δ 6.92 – 6.98. The proton adjacent to the endocyclic carbonyl appears further upfield of the two resonances. The ^{13}C NMR spectrum indicated the presence of the requisite carbons: two vinyl carbons at δ 128.8 and δ 150.6, one enone carbon at δ 198.9 and one ketone carbon at δ 206.4. The IR spectrum contained a diagnostic peak due to the α,β-unsaturated carbonyl at 1672.8 cm^{-1} and a peak due to the exocyclic carbonyl at 1700 cm^{-1}, and high resolution mass spectrometry confirmed the expected composition of $C_9H_{12}O_2$.

*2.6.1.2 Synthesis of cyclohexenone **174***

Cyclohexenone **174** was prepared to determine how an alkene substituent (similar to that present in the natural product) would influence the *i*-PrMgCl reduction. The synthesis of cyclohexenone **174** required the use of the more complex dipropene cuprate (derived from bromopropene (**180**)) for reaction with *trans* enone **118**. The cuprate addition was undertaken using conditions developed within the Perkins group[14] and the resulting cyclohexanone **181** was converted to *anti* methylated cyclohexenone **174** (Scheme 2.20) using a similar protocol to that utilised for the synthesis of cyclohexenones **110** (Section 2.3.1) and **123** (Section 2.4.1).



Reagents and conditions. (a) i. **180**, *t*-BuLi, THF, – 100 °C. ii. CuCN, Et_2O – 78 °C. iii. **118**, – 60 °C → 0 °C, 30%; (b) NaH, MeI, THF, RT, 67%.

*Scheme 2.20. Synthesis of cyclohexenone **174**.*

The generation of more complex cuprates, such as that required for the synthesis of cyclohexanone **181** (Scheme 2.20), involved formation of the alkyl lithium species at – 100 °C by reaction of two equivalents (relative to the cyclohexanone) of bromoalkene **180** with 4 equivalents of *t*-BuLi, which resulted in the formation of a bright yellow solution. After 15 minutes the solution was transferred *via* a pre-cooled cannula to a stirring suspension of CuCN in Et_2O at – 78 °C. In this case CuCN was used as a substitute for CuI (as utilised in previous cuprate additions), due to its increased reactivity at the low temperatures required to maintain the integrity of the alkyl lithium reagent. The cannula was pre-cooled by first transferring the Et_2O (cooled to – 78 °C) into the CuCN, which was followed by immediate transfer of the alkyl lithium to the CuCN suspension. The cooling of the cannula was found to be necessary in order to prevent the decomposition of the alkyl lithium and it was found

that a loss of colour of the alkyl lithium solution during transfer was an indicator of decomposition of the alkyl lithium species. The successful formation of the cuprate was signified by a change in colour of the CuCN suspension from yellow to clear and homogenous upon addition of the alkyl lithium and stirring at – 78 ^{o}C for 30 minutes. The addition of *trans* enone **118** resulted in the formation of an orange precipitate, which changed colour to brown as the reaction progressed, with the colour change being especially pronounced as the solution was warmed to 0 ^{o}C. It was found that all the colour and state changes described above were necessary for the success of the cuprate addition, as on a number of occasions the reaction failed when the observed changes were not consistent with those described. The reaction was quenched using the now standard method for reactions of this type, which involved quenching with a 90% NH_4Cl/10% NH_4OH solution and following product isolation and purification, the desired compound **181** was obtained in low yield (29%). This may be due to a number of factors including not using enough *t*-BuLi to generate the alkyl lithium species (due to erroneous concentration determination of the base) or slight decomposition of the alkyl lithium species during transfer *via* cannula to the CuCN suspension. Finally, conversion of cyclohexanone **181** to cyclohexenone **174** (carried out using the now standard conditions of NaH and MeI in THF) gave *anti* methylated cyclohexenone **174** in good yield (73%), with identical spectral data to that reported in the literature.[3]

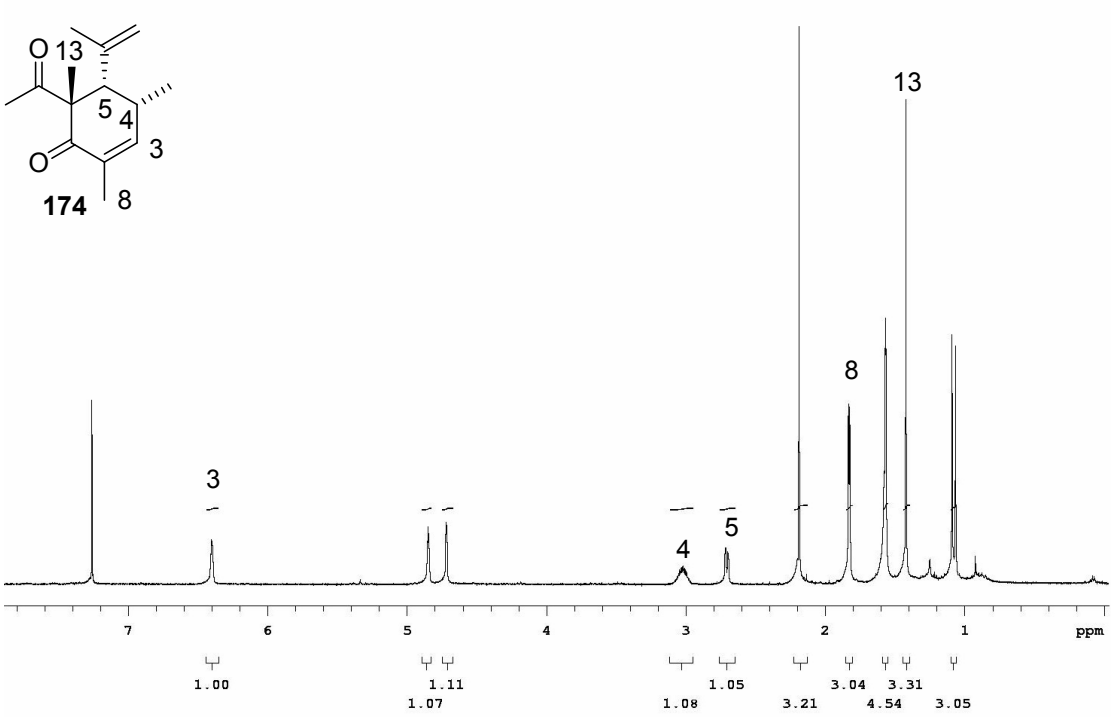
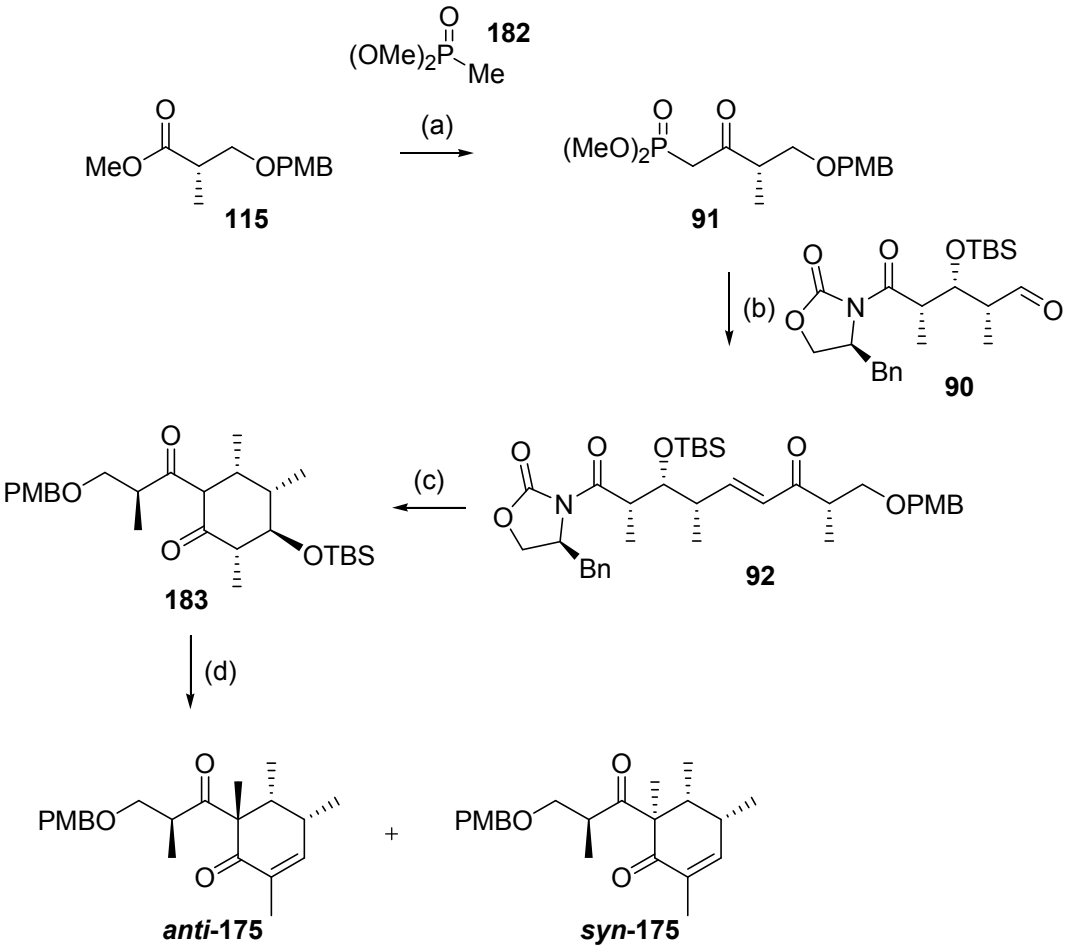


*Figure 2.15. ^{1}H NMR spectrum of cyclohexenone **174** in $CDCl_3$ at 300 MHz.*

The vinyl proton of the enone appears as a multiplet at δ 6.39 – 6.41, while the endocyclic vinyl methyl appears as a multiplet at δ 1.82 – 1.84. The singlet at δ 1.42 can be attributed to the protons of the quaternary methyl. The coupling constant of J = 4.2 Hz between the two methine protons on C4 and C5 indicates that the vinyl side-chain is in the axial position, as discussed in Section 2.3.1.

*2.6.1.3 Synthesis of cyclohexenone **anti-175***

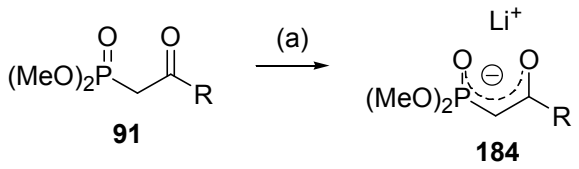
The last of the complex cyclohexenones (***anti*-175**) was synthesised according to a procedure developed within the Perkins group,[35] employing a modified Horner/Wadsworth/Emmons (H/W/E) reaction (Scheme 2.21).



Reagents and conditions. (a) **182**, *n*-BuLi, THF, – 78 °C, 65%; (b) **90**, LiCl, DIPEA, CH_3CN, RT, 53%; (c) CuI, MeLi, Me_2S, Et_2O, RT, 55%; (d) NaH, THF, MeI, RT, 32%.

*Scheme 2.21. Synthesis of cyclohexenones **anti-** and **syn-175**.*

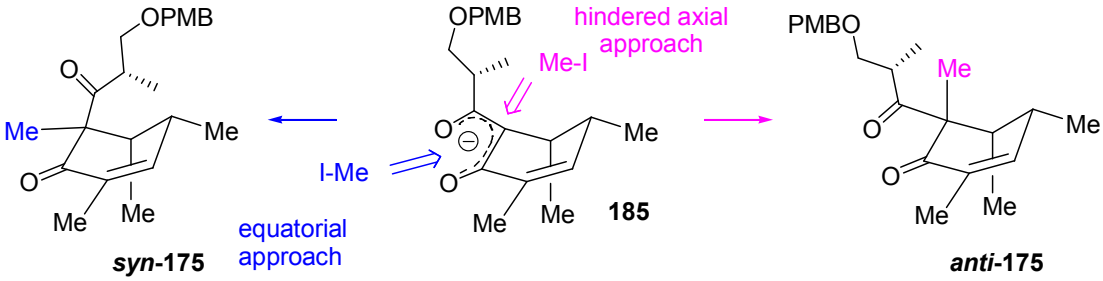
The previously-synthesised PMB-protected (*S*)-Roche ester **115** (Section 2.3.1) was converted into β-ketophosphonate **91** by treatment with an excess of dimethyl(α-lithiomethyl)phosphonate (**182**) in THF at – 78 °C (Scheme 2.21).[36] Phosphonate **91** was then reacted with aldehyde **90** to generate the desired *trans*-alkene **92** using a modified H/W/E protocol.[37] The reaction involved the use of a hindered base (in this case diisopropylethylamine (DIPEA)) and a chelating agent (LiCl), which increased the acidity and hence reactivity of the phosphonate (Scheme 2.22).



Reagents and conditions. (a) LiCl, DIPEA, MeCN, RT.

*Scheme 2.22. Chelation of phosphonate **91** by LiCl.*

The chelation effect (Scheme 2.22) allowed the reaction to occur in mild conditions, which was of significant importance in the olefination of **90**, as it was found that alkene **92** was sensitive to other bases that had been employed in previous attempts at its synthesis.[14] The subsequent reaction to generate cyclohexanone **183** was performed using dimethyl cuprate as described previously (Section 2.3.1) to produce **183** as one isomer in modest yield. The methylation-elimination cascade, which had been used previously to great effect to produce *anti* methylated cyclohexenones **110, 123** and **174** as one isomer, gave a different result in this case. It was found that subjecting the compound to the same reaction conditions yielded an inseparable mixture of both *anti* and *syn* methylated cyclohexenones **175** in approximately a 1:1 ratio. It has been postulated that this decrease in the selectivity of the methylation can be attributed to the presence of two equivalents of NaH. This resulted in the elimination occuring prior to methylation, to give non-methylated cyclohexenone **185** (Scheme 2.23).[35] The result was a flattening-out of the chair conformation, which, coupled with the extra length of the side-chain (compared with that of cyclohexanones **119** (Section 2.3.1) and **130** (Section 2.4.1)), resulted in increased hindrance to the axial approach of the methylating agent.



*Scheme 2.23. Rationale for observed decrease in the stereoselectivity of the methylation of **183**.*

It had been found in previous studies within the Perkins group that the stereoselectivity of the reaction could be improved in favour of the axially-methylated product ***anti*-175** (Scheme 2.23), by treating cyclohexanone **183** with only one equivalent of NaH in the first instance, followed by treatment with an excess of MeI so as to produce only the methylated diketone.[35] Subsequent treatment with another equivalent of NaH to promote elimination gave methylated cyclohexenones ***anti*-** and ***syn*-175** in a 9:1 ratio (*anti*:*syn*).[35] This sequential addition of NaH was not attempted in this experiment.

The ^{1}H NMR spectrum (Figure 2.16) is identical to that reported in the literature for ***anti*-** and ***syn*-175**[35] and clearly indicates that the two isomers are present in a 1:1.3 ratio.

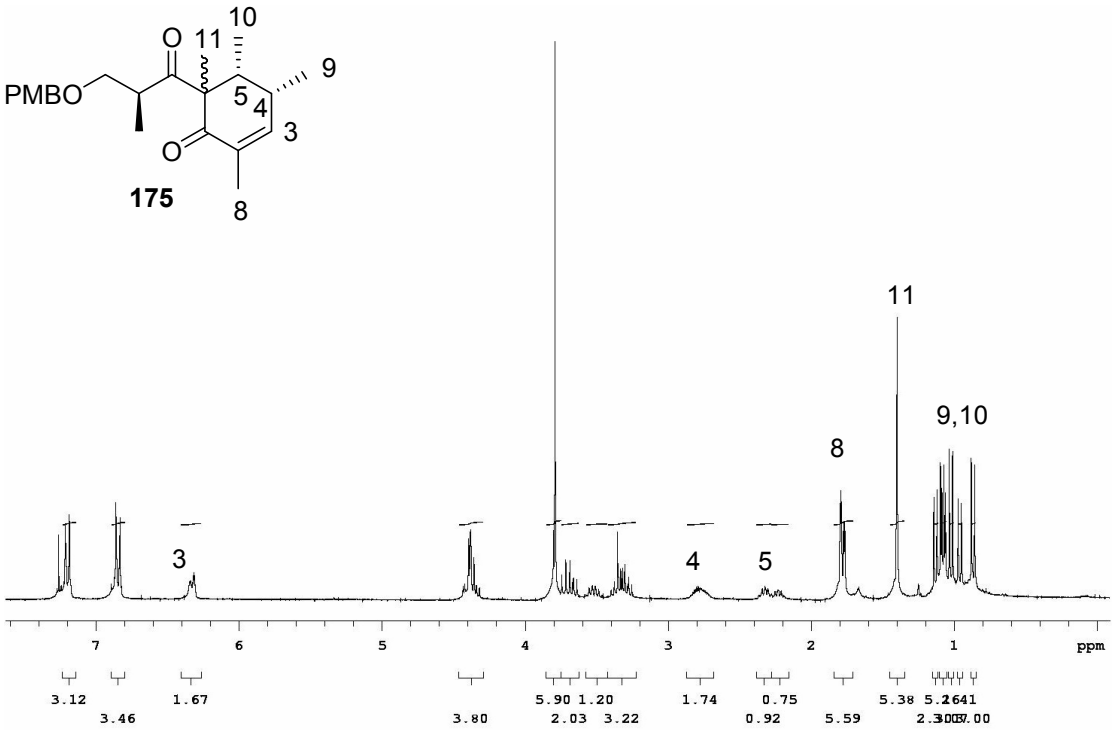


*Figure 2.16. ^{1}H NMR spectrum of methylated cyclohexenones **anti-** and **syn-175** in $CDCl_3$ at 300 MHz.*

A comparison of the NMR spectra of **175** with that reported in the literature for ***syn***- and ***anti*-175**[35] indicated that the major product in this case was the *syn* isomer. The requisite proton resonances include a multiplet at δ 6.30 – 6.36 (Figure 2.16), which can be attributed to the vinyl protons of both isomers, two singlets at δ 1.39, which can be attributed to the quaternary methyl protons, and two doublet of doublets at δ 1.79 (*syn* isomer) and δ 1.77 (*anti* isomer), which can be attributed to the vinyl methyl protons.

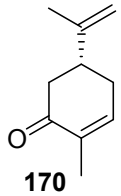
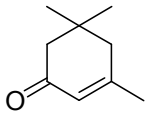
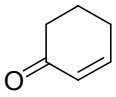
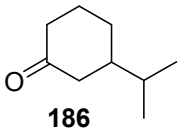
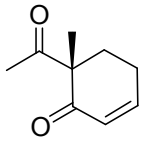
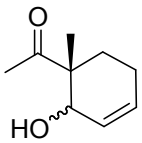
Although the two methylated cyclohexenones ***anti-*** and ***syn*-175** could not be separated from each other using conventional methods, it was decided that the mixture would be subjected to the Grignard-mediated reduction conditions. While the original aim of synthesising ***anti*-175** was to test the effect the presence of a complex side-chain would have on the outcome of the *i*-PrMgCl-mediated reduction, the unexpected synthesis of the two isomers ***anti-*** and ***syn*-175** allowed the effect of a change in the stereochemistry of the quaternary stereocentre to also be tested.

Thus, the synthesis of cyclohexenones **173**, **174** and ***anti-*** and ***syn*-175** afforded a total of nine cyclohexenones, which could be utilised to test the scope and implications of the *i*-PrMgCl-facilitated reduction on the synthesis of 9,10-deoxytridachione (**8**). Cyclohexenones **110**, **123** and **170** – **175** were all subjected to identical reaction conditions, which involved dissolving the substrate in THF and cooling the solution to – 50 ^{o}C. One equivalent of *i*-PrMgCl was added and stirring continued at – 50 ^{o}C for 30 minutes. If starting material was still found to be present (as determined by TLC), another equivalent of *i*-PrMgCl was added, followed by stirring for an additional 30 minutes. If starting material was still found to be present, the solution was warmed to 0 ^{o}C, followed by warming to room temperature if complete consumption of starting material had still failed to occur. The outcomes of the reactions undertaken with substrates **110**, **123** and **170 – 175** are outlined in the following sections, with all stereochemistry, where applicable, was deduced using NOESY.

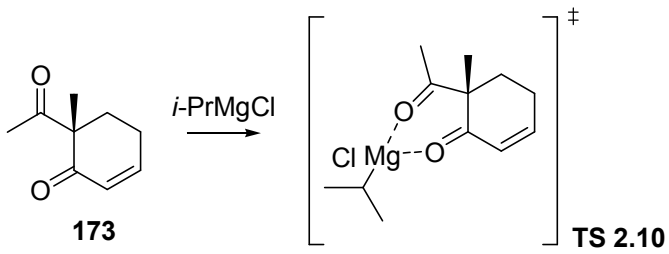
2.6.2 Reaction of cyclohexenones 170 – 173 with *i*-PrMgCl

The first series of cyclohexenones to be subjected to the *i*-PrMgCl reduction protocol were **170** – **173** and the results are shown in Table 2.1 on the following page.

*Table 2.1. Outcome of i-PrMgCl-mediated reduction on substrates **170** – **173**.*

Entry	Substrate	Conditions	Outcome	Yield
1	 **170**	2 equiv *i*-PrMgCl - 50 °C → 0 °C → RT	Starting material	
2	 **171**	4.5 equiv *i*-PrMgCl - 50 °C → 0 °C → RT	Starting material	
3	 **172**	2 equiv *i*-PrMgCl - 50 °C → 0 °C	 **186**	66%
4	 **173**	2 equiv *i*-PrMgCl - 50 °C → 0 °C	 **187**	26%

It is evident in from the results obtained in this series of reactions (Table 2.1) that the exocyclic carbonyl is essential to the success of the reduction. The absence of this functionality (as in the case of **170** (Entry 1), **171** (Entry 2) and **172** (Entry 3)) leads to no reaction occurring and, as in the case of **172**, the 1,4-addition occurring instead to give **186** (Entry 3). The presence of subsituents around the alkene is also found to inhibit the 1,4-addition, as in the case of **170** (Entry 1) and **171** (Entry 2). The reason for the success of the reduction in the presence of the exocyclic carbonyl (Entry 4) is not clear. However, it can be theorised that the exocyclic carbonyl may aid in chelation of the Grignard reagent, thus inducing the reduction of the enone carbonyl (Scheme 2.24).



*Scheme 2.24. Chelation of Mg by the endo and exocyclic carbonyl groups in cyclohexenone **173**.*

Additionally, the steric bulk of the Mg complex (due to the presence of the acetyl and quaternary methyl group) may inhibit the addition reaction (as discussed in Section 2.5), resulting in reduction occurring in preference to addition.

The reduction of **173** (Table 2.1, Entry 4) by *i*-PrMgCl led to the formation of two diastereomers in a 1:3 ratio, based on the ^{1}H NMR spectrum (Figure 2.17).

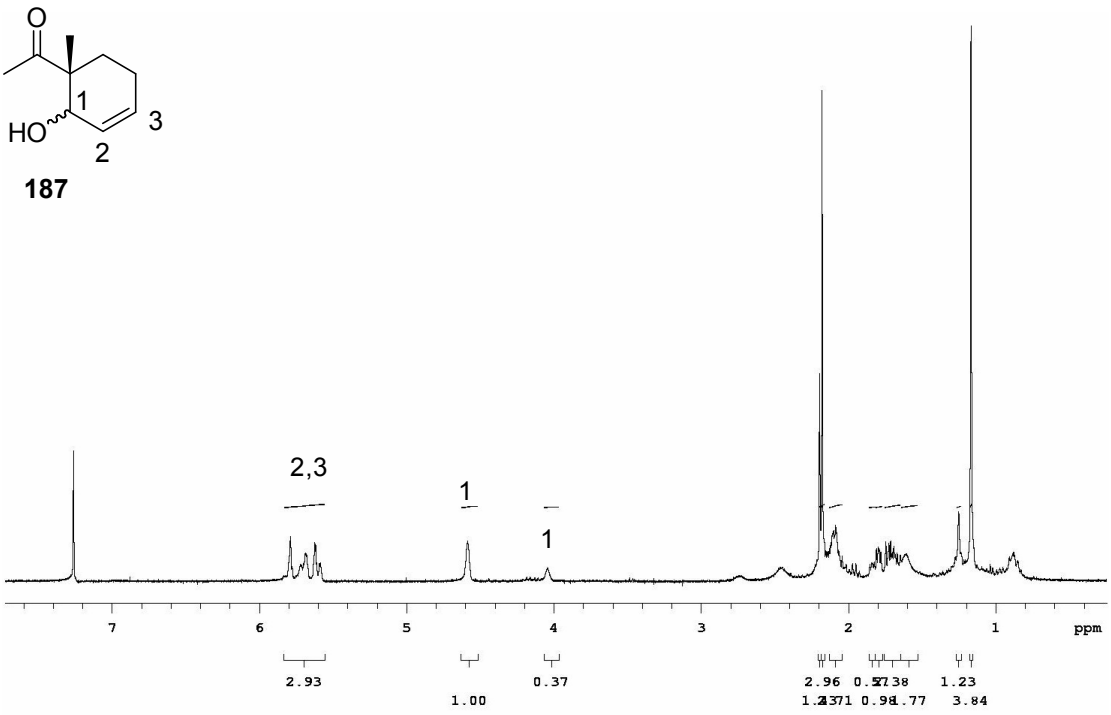
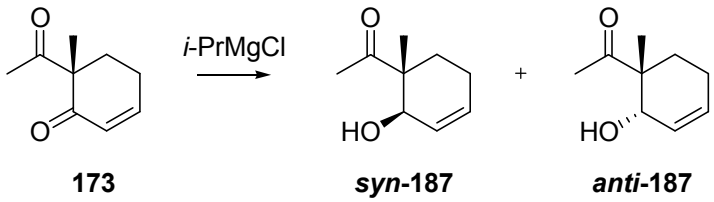


*Figure 2.17. ^{1}H NMR spectrum of allylic alcohol **187** in $CDCl_3$ at 300 MHz.*

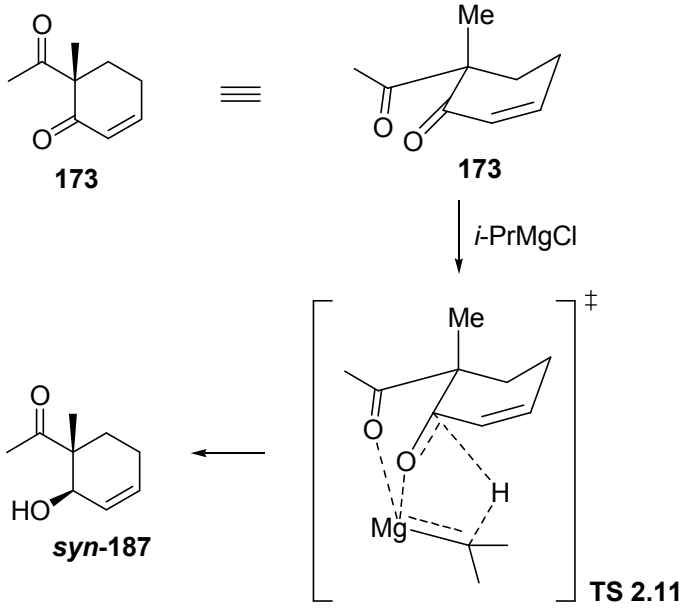
The low yield of allylic alcohol **187** (26%) was due to the presence of additional compounds in the product mixture, which could not be identified. The presence of two isomers in the ^{1}H NMR spectrum of **187** and the complex multiplicity of the resonances does not allow for simple assignment of the spectrum (Figure 2.17). However, there are a number of resonances that can be considered diagnostic for this compound based on previous experiences with these systems. The presence of peaks at δ 5.58 – 5.79 indicates that the alkene functionality is still intact. These peaks have, however, shifted upfield (from δ 6.04 and δ 6.92 – 6.98 in the starting material **173**), which is indicative of a loss of conjugation (as witnessed in ester **131** and amide **132** described above) due to the reduction of the carbonyl. The vinyl proton on C3 couples to the adjacent methylene protons, which appear as a multiplet at δ 2.05 – 2.16 (for both the minor and major isomer). These protons couple to the methylene protons adjacent to the quaternary methyl, which have moved upfield from two multiplets at δ 2.44 – 2.47 and δ 1.75 – 1.85 to what appear to be three resonances: a multiplet at δ 1.67 – 1.75 and two doublets of doublets at δ 1.80 and δ 1.84. The doublet of doublets at δ 1.80 is due to the equatorial methylene proton of the major isomer (evidenced by the small coupling constant of J = 5.4 Hz), while the other doublet of doublets can be attributed to the same proton of the minor isomer (where J = 5.4 Hz also). The axial methylene proton appears as the multiplet at δ 1.67 – 1.75 for both isomers. The appearance of two new peaks (at δ 4.58 and δ 4.05) can be attributed to the oxymethine proton. This proton appears as two peaks (the peak at δ 4.05 being much smaller) due to the presence of two isomers. The quaternary methyl protons appear as a singlet at δ 1.25 and the protons of the methyl ketone appear as two singlets: at δ 2.18 (due to the major isomer) and δ 2.20 (due to the minor isomer). The presence of two broad singlets at δ 2.45 and δ 2.74 can be attributed to the hydroxyl protons of the major and minor isomers, respectively. Further evidence for the presence of two isomers was presented in the ^{13}C NMR spectrum. Each isomer contains 9 non-equivalent carbons and 17 peaks were present, with the ketone carbon appearing at the same resonance for both isomers (δ 215.1). The IR spectrum displayed the requisite hydroxyl absorption at 3446.1 cm^{-1} and a carbonyl absorption at 1698.7 cm^{-1}. High resolution mass spectrometry confirmed the expected composition of $C_9H_{14}O_2$.

The fact that only two diastereomers are present in the ^{1}H NMR spectrum (Figure 2.17) leads to the conclusion that the reduction occurred from both faces of **173** to give the two allylic alcohols ***syn*-** and ***anti*-187** (Scheme 2.25).



*Scheme 2.25. Proposed stereochemical outcome of i-PrMgCl-mediated reduction of cyclohexenone **173**.*

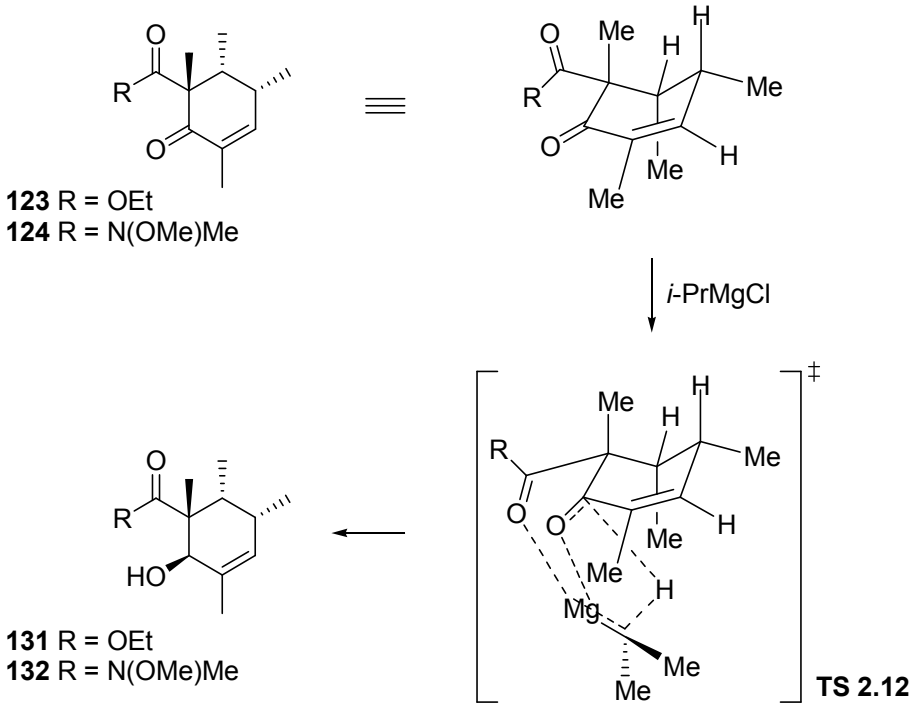
While it was not verified by NOESY which allylic alcohol was the major reduction product, it can be postulated, based on the chelation model described previously (Scheme 2.24), that the major isomer is ***syn*-187** (Scheme 2.26).



*Scheme 2.26. Chelation model of i-PrMgCl-mediated reduction of cyclohexenone **173**.*

In **TS 2.11** (depicted in Scheme 2.26) magnesium is chelated to both the exo-and endocyclic carbonyl groups. This results in reduction occurring from the bottom face of cyclohexenone **173** to give ***syn*-187**. The enantiomer of **TS 2.11** can be utilised to rationalise the stereochemical outcome in the reduction of the enantiomer of **173**.

The same chelation model can be used to explain the stereochemical outcome of the reduction of ester **123** and Weinreb amide **124** (discussed in Section 2.4.1) to give allylic alcohols **131** and **132**, respectively.



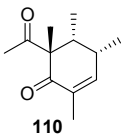
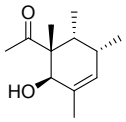
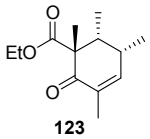
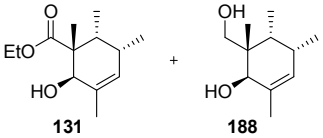
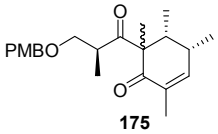
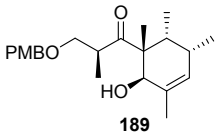
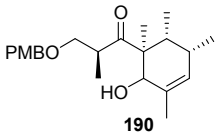
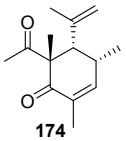
*Scheme 2.27. Chelation model of i-PrMgCl-mediated reduction of ester **123** and amide **124**.*

In summary, a number of conclusions can be drawn about the *i*-PrMgCl-mediated reduction of the cyclohexenone systems depicted in Table 2.1. The presence of the exocyclic carbonyl is essential for the reduction to occur and extra substituents around the ring lead to an increase in the facial-selectivity of the reduction, as well as a decrease in the potential for 1,4-addition to occur. Based on these observations, the outcome of the reduction for cyclohexenones **110**, **123**, **174** and ***anti*-** and ***syn*-175** was predicted to occur with high stereo- and regio-selectivity.

2.6.3 Reaction of cyclohexenones 110, 123, 174 and *anti*- and *syn*-175 with *i*-PrMgCl

Table 2.2 on the following page shows the outcomes of the *i*-PrMgCl-mediated reductions of cyclohexenones **110**, **123**, **174** and ***anti*-** and ***syn*-175**, and allows more information about the reduction to be gleaned.

*Table 2.2. Outcome of i-PrMgCl-mediated reduction on substrates **110**, **123**, **174** and **anti**- and **syn-175**.*

Entry	Substrate	Conditions	Outcome	Yield
1	 **110**	1 equiv *i*-PrMgCl - 50 °C → 0 °C	 **(*R*)-112**	62%
2	 **123**	2 equiv *i*-PrMgCl - 50 °C → 0 °C	 **131** **188**	59% **130**, 4% **190**
3	 **175**	2 equiv *i*-PrMgCl - 50 °C → 0 °C	 **189** +  **190**	31% 25%
4	 **174**	2 equiv *i*-PrMgCl - 50 °C → 0 °C → RT	Starting material	

The reduction of *anti* methylated cyclohexenone **110** to give allylic alcohol **(*R*)-112** (Table 2.2, Entry 1) proceeded in moderate yield and high stereoselectivity, with no other isomers observed in the ^{1}H NMR spectrum (Figure 2.18).

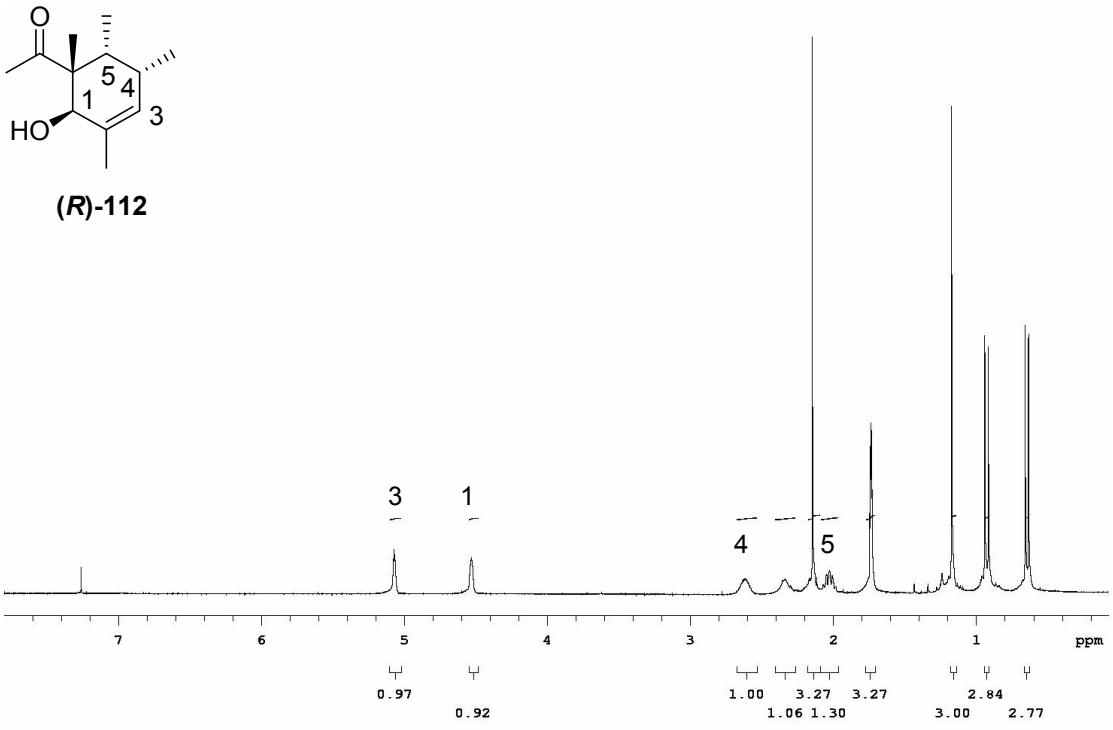


Figure 2.18. ^{1}H NMR spectrum of allylic alcohol ***(R)-112*** *in $CDCl_3$ at 300 MHz.*

The upfield shift of the vinyl proton (from a multiplet at δ 6.35 - 6.37 to a multiplet at δ 5.07 - 5.08) is consistent with a loss in conjugation and the presence of a new singlet at δ 4.53 can be attributed to the proton on C1 (Figure 2.18). Most of the other resonances present in the spectrum have also moved significantly upfield of their positions in the spectrum of the starting material (**110**) (Figure 2.4). The methine proton on C4 (which couples to the methyl protons at δ 0.93) has moved upfield from δ 2.84 – 2.87 to δ 2.61 – 2.63, as has the proton adjacent to the quaternary stereocentre (which couples to the methyl protons at δ 0.65): from δ 2.14 – 2.20 to δ 1.98 – 2.07. The protons of the methyl ketone have moved from δ 2.25 to δ 2.15 and the protons of the vinyl methyl have moved from δ 1.81 – 1.82 to δ 1.73 – 1.75. While the protons of the quaternary methyl do not exhibit a difference in shift, the protons of the two remaining methyl groups (which appear as doublets) have moved quite significantly upfield: from δ 1.09 and δ 0.90 to δ 0.93 and δ 0.65, respectively. The appearance of a broad singlet at δ 2.29 can be attributed to the presence of the hydroxyl proton and the IR spectrum corroborated this finding with the presence of a peak due to a hydroxyl stretch at 3500.0 cm^{-1}. The ^{13}C NMR

spectrum clearly showed the presence of only one carbonyl peak at δ 216, and high resolution mass spectrometry confirmed the expected composition of $C_{12}H_{20}O_2$. The stereochemistry of allylic alcohol **(*R*)-112** indicates that reduction of methylated cyclohexenone **110** proceeded *via* the MPV-Whitmore transition state model, possibly with chelation of the Grignard reagent, as predicted for cyclohexenones **173** (Section 2.6.2, Scheme 2.26), as well as **123** and **124** (Section 2.6.2, Scheme 2.27).

The reduction of cyclohexenone **123** in the presence of *i*-PrMgCl yielded ester **131** and a small amount of diol **188** (Table 2.2, Entry 2). The reaction required 5 equivalents of the Grignard reagent and was warmed to 0 ^oC before all the starting material was consumed (as indicated by TLC). The excess equivalents may have contributed to the over-reduction to give diol **188**, the ^1H NMR spectrum of which shows the requisite proton resonances (Figure 2.19).

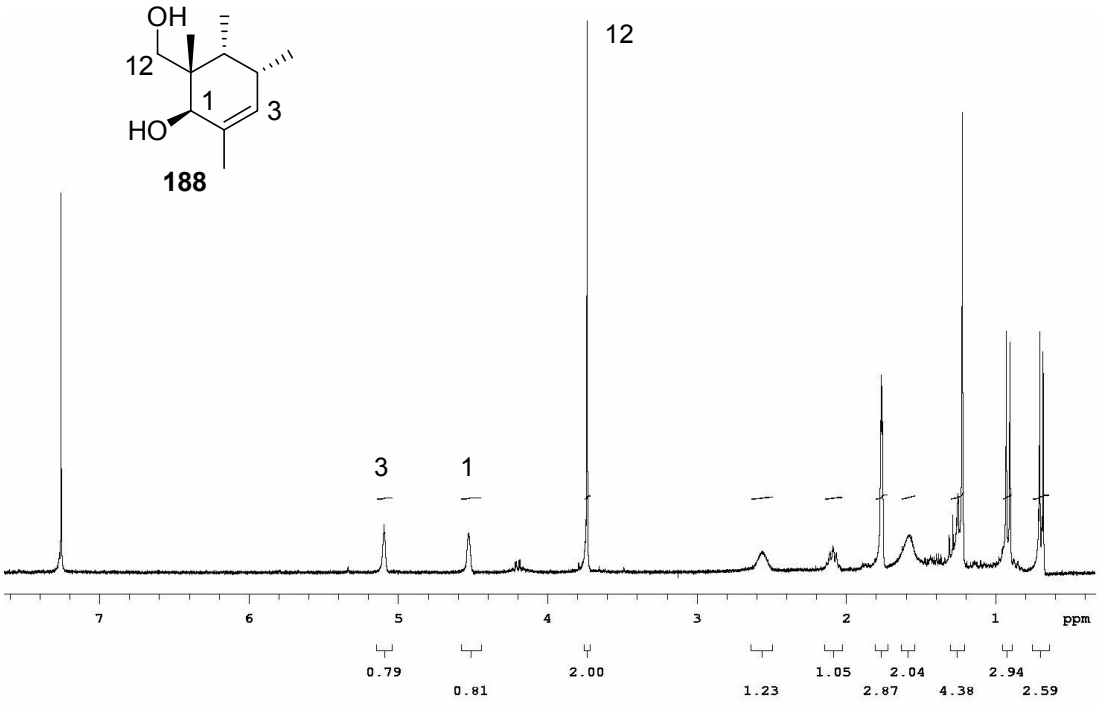
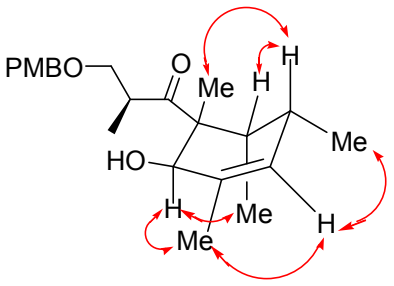


*Figure 2.19. ^1H NMR spectrum of diol **188** in $CDCl_3$ at 300 MHz.*

The ester functionality is obviously absent in the spectrum (Figure 2.19) and the presence of a singlet at δ 3.74 is found to integrate for two protons, which can be attributed to the two methylene protons. As in the case of the allylic alcohols

described above, the vinyl proton is shifted upfield to δ 5.10 and the oxymethine proton appears at δ 4.53. The protons of the vinyl methyl appear as a singlet at δ 1.76, while the protons of the quaternary methyl group appear as a singlet at δ 1.22. The methine proton adjacent to the quaternary methyl appears as a multiplet at δ 2.06 – 2.11 and couples to the adjacent methyl protons, which appear as a doublet at δ 0.92. The methine proton adjacent to the alkene appears at δ 2.54 – 2.56 and couples to the methyl protons, which appear as a doublet at δ 0.69. The remaining resonance, which appears as a broad singlet at δ 1.58, can be attributed to the hydroxyl proton. While the stereochemistry of diol **188** was not deduced by NOESY, it can be postulated that the stereochemistry is that depicted in **188**. The ^{13}C NMR spectrum showed the absence of carbonyl peaks, which is further evidence that the double-reduction has occurred.

The reduction of the mixture containing methylated cyclohexenones ***anti-*** and ***syn-*** **175** by *i*-PrMgCl yielded allylic alcohols **189** and **190** (Table 2.2, Entry 3), which were separable by column chromatography. The stereochemistry at the stereocentre bearing the quaternary methyl was assigned with the aid of NOESY for **189** (Figure 2.20), which was the major isomer isolated. The stereochemistry of the minor isomer could not be assigned, due to the small amount of material, which did not allow a NOESY to be obtained.



189

*Figure 2.20. NOESY correlations observed for anti methylated allylic alcohol **189** in $CDCl_3$ at 600 MHz.*

The ^{1}H NMR spectra of the two isomers **189** and **190** (Figure 2.21 and Figure 2.22, repsectively) indicate that the allylic alcohol was produced in each case, by the

presence of two diagnostic features: the upfield shift of the vinyl proton (to δ 5.08 for both the isomers) and the appearance of the oxymethine proton, which is present at δ 4.60 in *anti* isomer **189** (Figure 2.21) and at δ 4.56 in *syn* isomer **190** (Figure 2.22). A significant change in the positions of other resonances is also evident. The trend of an upfield shift of the protons, as observed in the cases of **131**, **132**, **(*R*)-112** and **188** described above, is also present in the spectra of **189** and **190**. In the case of *anti* isomer **189**, the noticeable differences include the movement of the oxymethylene protons, which have changed multiplicity and position, from a doublet of doublets at δ 3.35 and δ 3.70 to a multiplet at δ 3.29 – 3.37.

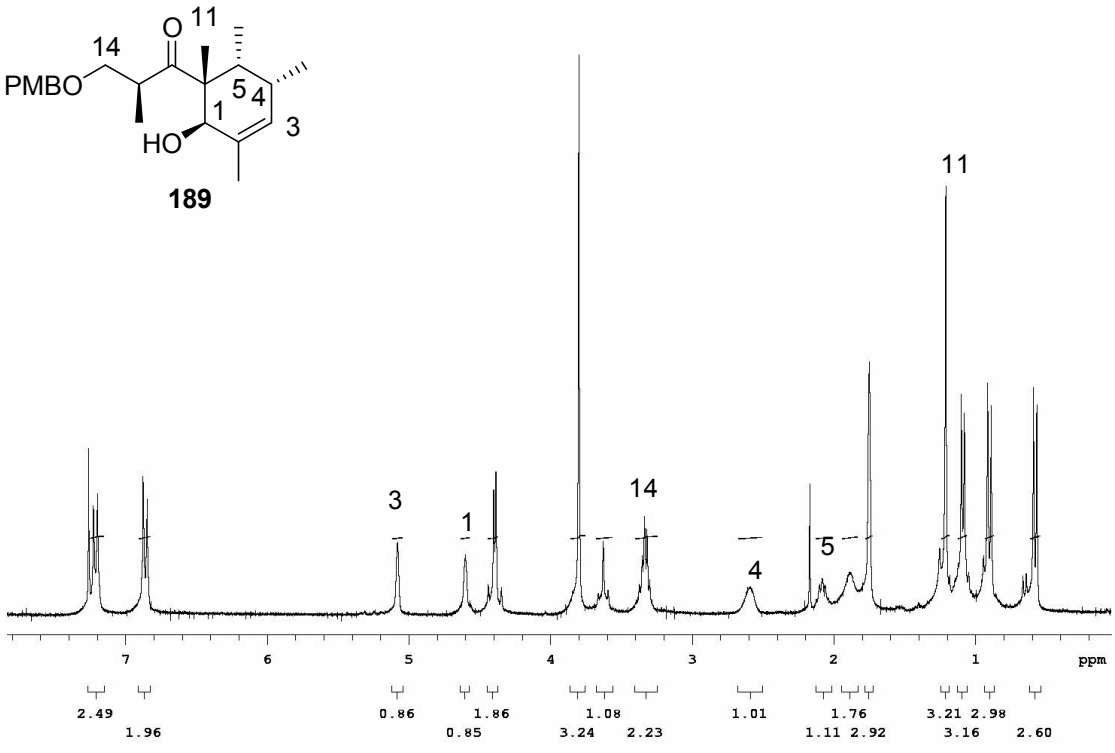


*Figure 2.21. ^{1}H NMR spectrum of anti methylated allylic alcohol **189** in $CDCl_3$ at 300 MHz.*

The methine proton on C4 has experienced a small shift upfield, from δ 2.72 – 2.83 to δ 2.55 – 2.67 (Figure 2.21), while the methyl protons it couples to, which appear as a doublet, have not experienced any significant shift. The methine proton on C5 has shifted from δ 2.28 – 2.36 to δ 2.06 – 2.10 and the methyl protons it couples to, which appear as a doublet, have moved significantly downfield to δ 0.90. The only other significant difference between the spectra of cyclohexenone ***anti*-175** and

allylic alcohol **189** is the upfield shift of the quaternary methyl protons, which have moved from δ 1.40 to δ 1.21, and the presence of a broad singlet at δ 1.90, which can be attributed to the hydroxyl proton.

Similar trends are evident in the ^{1}H NMR spectrum of minor isomer **190** (Figure 2.22).

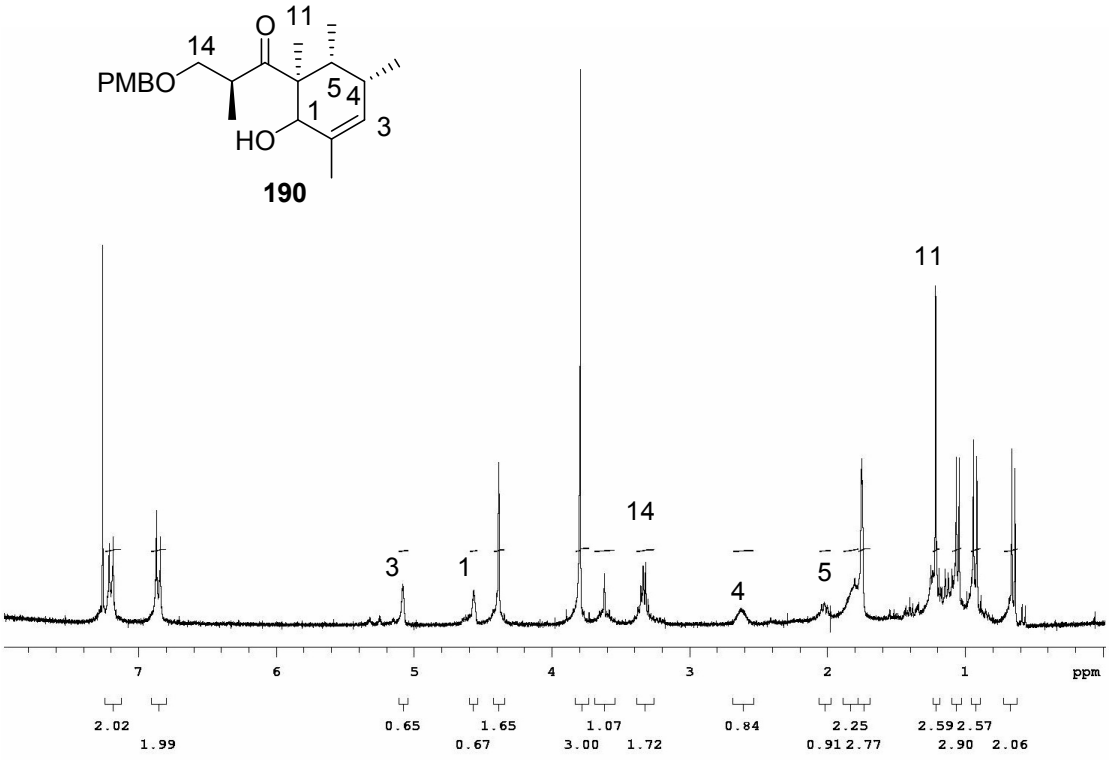
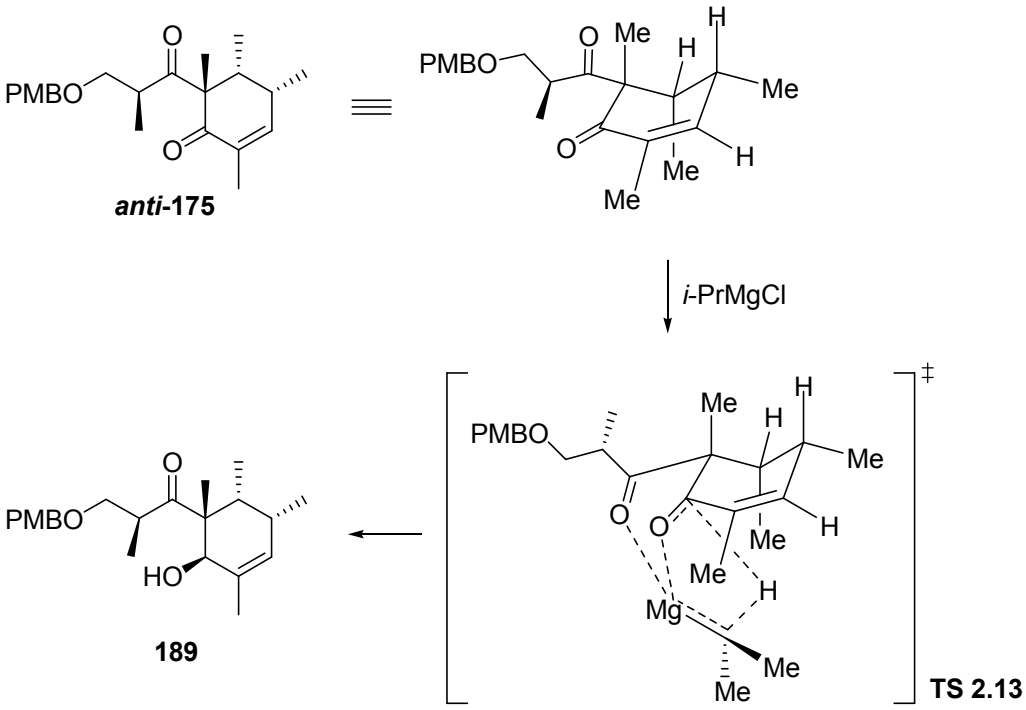


*Figure 2.22. ^{1}H NMR spectrum of syn methylated allylic alcohol **190** in $CDCl_3$ at 300 MHz.*

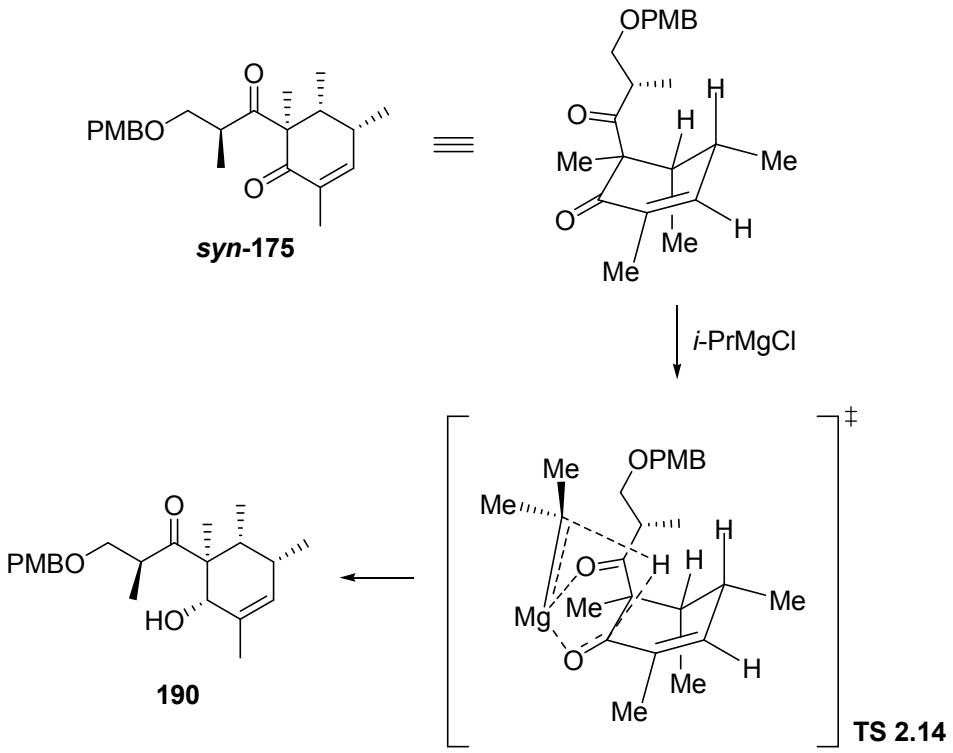
The ^{13}C NMR spectra indicated the presence of one exocyclic carbonyl group in each isomer (present at δ 220.3 for *anti* isomer **189** and at δ 219.8 for *syn* isomer **190**) and the IR spectra confirmed the presence of the alcohol functionality, displaying a broad absorbance at 3481.0 cm^{-1} in **189** and at 3570.9 cm^{-1} in **190**. High resolution mass spectrometry confirmed the expected composition of $C_{22}H_{32}O_4$ for both **189** and **190**.

By applying the chelation model shown in Scheme 2.27 (Section 2.6.2, above) to *anti*-**175**, the stereochemical outcome of the reduction can be rationalised (Scheme 2.28).



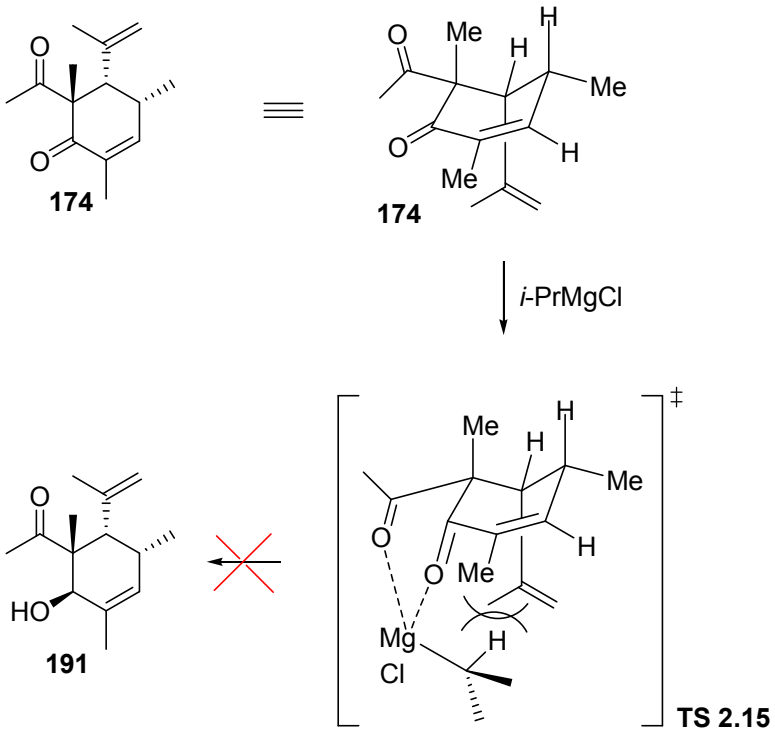
Scheme 2.28. i-PrMgCl-mediated reduction of ***anti-175****.*

Although the stereochemistry of **190** could not be determined (as discussed above), it can be postulated that the reduction is most likely to have occurred from the top face of ***syn*-175** (Scheme 2.29), based on the *i*-PrMgCl chelation model.



Scheme 2.29. i-PrMgCl-mediated reduction of ***syn-175****.*

The last cyclohexenone in Table 2.2 to be subjected to the *i*-PrMgCl-mediated reduction was **174** (Entry 4). This result is of significant interest, particularly to the synthesis of the natural product, as it appears that the presence of the alkene side-chain inhibits the reduction. It is postulated that this is most likely due to the alkene causing an unfavourable steric interaction in the potential transition state **TS 2.15**, thus preventing the reduction from occurring (Scheme 2.30).



*Scheme 2.30. Proposed mechanism for reduction of cyclohexenone **174** with i-PrMgCl.*

This result (Table 2.2, Entry 4) has significant implications for the synthesis of the natural product, which possesses a larger alkene side-chain in the axial position. There is a significant possibility that the synthesis of an allylic alcohol utilising *i*-PrMgCl would be impeded in the presence of the larger side-chain, rendering this mode of achieving the 1,2-reduction ineffective.

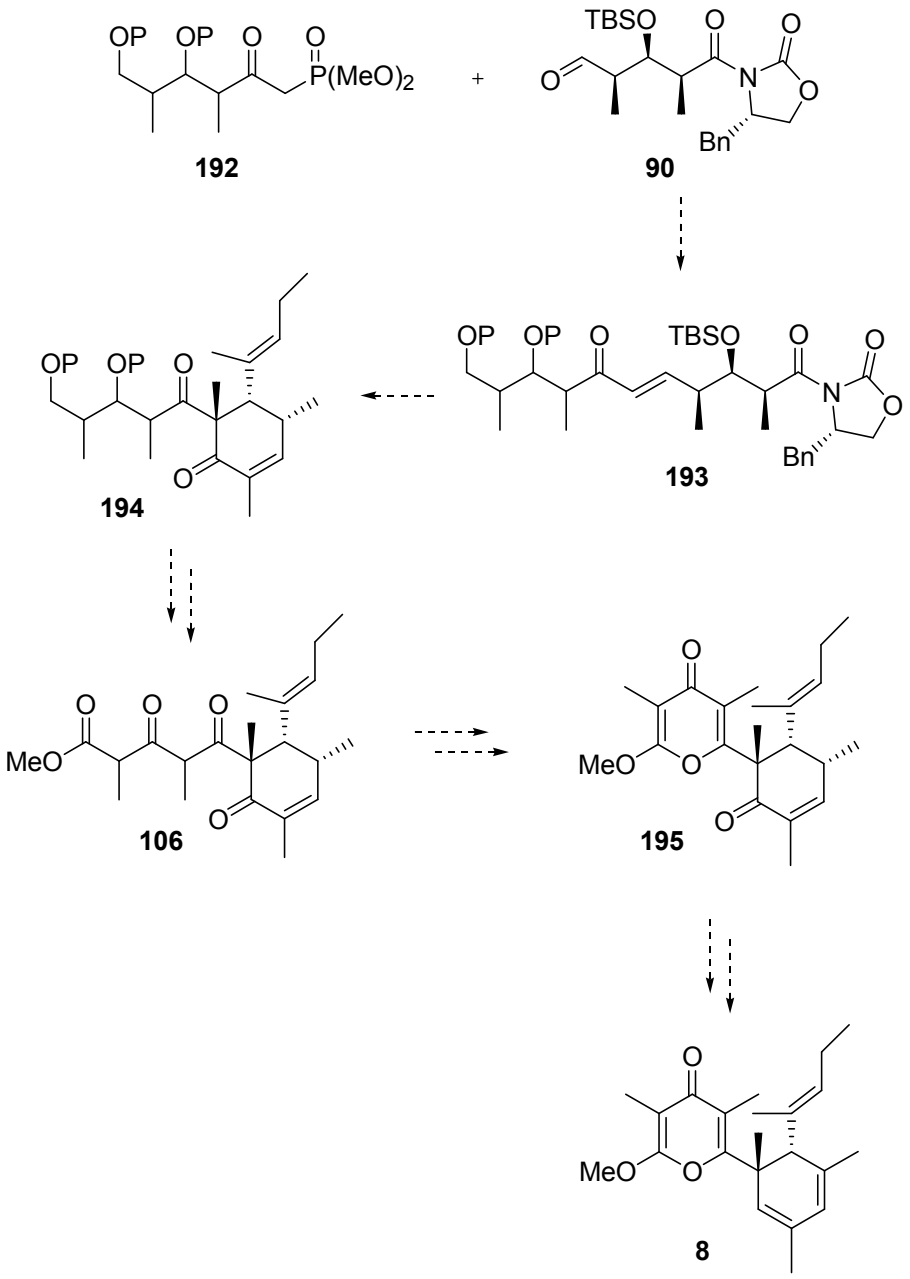
In summary, the reaction of methylated cyclohexenones **110**, **123**, **174** and ***anti*-** and ***syn*-175** with *i*-PrMgCl (Table 2.2) also occurred *via* the chelation model to give the predicted stereochemistry in allylic alcohols **(*R*)-112**, **131** and **189**. It was proposed that the reduction of these methylated cyclohexenones proceeded *via* a chelated transition state and the reduction of methylated cyclohexenone **174** was inhibited by the presence of the alkene side-chain.

The results of the above reduction experiments (Table 2.1 and Table 2.2) allow some interesting inferences to be made about the mechanism and scope of the *i*-PrMgCl-mediated reduction of cyclohexenones. In summary, the exocyclic carbonyl was

identified as an integral component of the reduction mechanism with reduction potentially occurring *via* a chelated transition state. Methyl substitution around the enone functionality prevented the 1,4-addition of the Grignard reagent from occurring and the presence of substituents around the ring led to the observed increase in the stereoselectivity of the reaction. Additionally, bulky substituents adjacent to the exocyclic carbonyl were found to inhibit the reduction, by blocking the bottom face of the cyclohexenone ring and preventing the formation of the requisite transition state.

2.6.4 Implications for the synthesis of the natural product

The results obtained in the series of experiments described in Sections 2.6.2 and 2.6.3 have significant implications for the use of the *i*-PrMgCl reduction in the synthesis of 9,10-deoxytridachione (**8**). The fact that the exocyclic carbonyl was essential for the reduction means that the reduction would need to be carried out prior to formation of the γ-pyrone ring. However, the fact that the reduction cannot be carried out in the presence of a bulky alkene side-chain (as demonstrated in the case of **174**), leads to the conclusion that this may not be a feasible route for formation of the allylic alcohol and hence the cyclohexadiene system. Based on these deductions, the most logical sequence to synthesise 9,10-deoxytridachione (**8**) would involve forming the γ-pyrone ring prior to the cyclohexadiene (as depicted in Scheme 2.31 on the following page). Other reduction protocols would then have to be attempted for the selective 1,2-reduction of the cyclohexenone system, in order to allow subsequent formation of the cyclohexadiene to occur. Additionally, based on the lack of success in synthesising a Weinreb amide (Section 2.4.1), a more complex ylide such as **192** would have to be coupled with aldehyde **90** to give *trans* enone **193**, negating the need to add the diketo-ester functionality at a later stage.



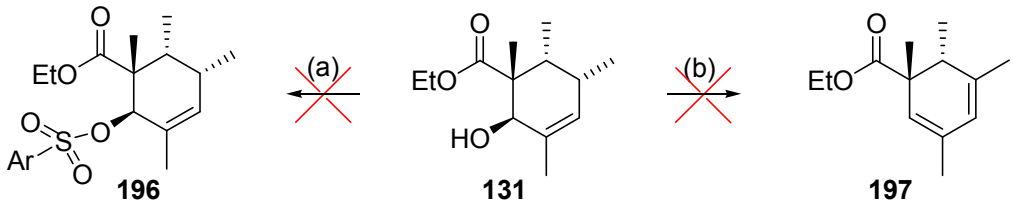
*Scheme 2.31. Proposed synthesis of 9,10-deoxytridachione (**8**).*

While the investigations into the *i*-PrMgCl-facilitated reduction were being carried out, a number of attempts were also made at the synthesis of the cyclohexadiene moiety.

2.7 Final attempts at the formation of the cyclohexadiene system

2.7.1 Dehydration attempts of allylic alcohol 131

Allylic alcohols **(*R*)-112** and **131** synthesised as described in Section 2.6.3 were utilised as model systems for cyclohexadiene formation, with allylic alcohol **131** (containing the exocyclic ester functionality) used in the initial trials. However, numerous attempts at dehydrating or even derivatising ester-funtionalised allylic alcohol **131** proved unsuccessful (Scheme 2.32). A derivatisation of alcohol **131** was attempted utilising *p*-toluenesulfonyl chloride (*p*-TsCl) and Et_3N but this, as well as treatment of **131** with *p*-toluenesulfonic acid (*p*-TsOH) in C_6D_6 (which allowed the reaction to be monitored by NMR) returned only starting material. The use of a stronger acid, such as trifluoroacetic acid (TFA), resulted in the decomposition of **131** to a complex mixture of compounds.



Reagents and conditions. (a) *p*-TsCl, Et_3N, Et_2O, RT; (b) (i) *p*-TsOH, CD_6D_6, RT (ii) TFA, RT

*Scheme 2.32. Attempts at the derivatisation and dehydration of **131**.*

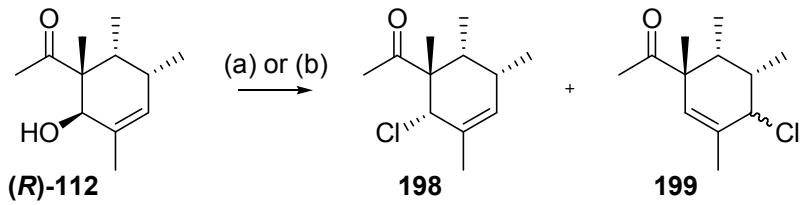
The ^{1}H NMR spectrum indicated that the ester functionality of **131** was affected by the presence of TFA. Thus, it was decided that allylic alcohol **(*R*)-112** would be utilised. This would allow the dehydration to be attempted on a simpler system with less interference from sensitive functional groups.

2.7.2 Dehydration attempts of allylic alcohol (*R*)-112

A number of different reagents and conditions were trialled on allylic alcohol **(*R*)-112** in an attempt to form cyclohexadiene **111**, but were met with limited success.

Treatment of **(*R*)-112** with P_2O_5 on celite (which had been utilised previously in the Perkins group to effect dehydrations)[35] gave a complex mixture of compounds, while reactions involving methyltriphenoxyphosphonium iodide (MTPI) in hexamethylphosphoramide (HMPA),[38] 2,4-dinitrobenzenesulfonyl chloride in the presence of Et_3N[39] and $MeSO_2Cl$ in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) returned only starting material. The lack of success in the formation of cyclohexadiene **111** using these bulky reagents may be due to the steric demands of the allylic alcohol **(*R*)-112**.

Interestingly, reaction of allylic alcohol **(*R*)-112** with $MeSO_2Cl$ in the presence of Et_3N[40] and $SOCl_2$ in the presence of pyridine[41] yielded the two chlorinated species **198** and **199** (Scheme 2.33).



(*R*)-112 **198** **199**

Reagents and conditions. (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, – 78 °C → 0 °C → 35 °C, 10% **198** (single isomer) and 32% **199** (mixture); (b) $SOCl_2$, pyridine, 0 °C → RT, 7% **198** (single isomer) and 14% **199** (mixture).

*Scheme 2.33. Synthesis of chlorinated isomers **198** and **199**.*

While the ^{1}H NMR spectra do not allow the presence of halogens to be unambiguously determined, the changes observed in the ^{1}H NMR spectra of the halogenated compounds **198** and **199** (Figure 2.23 and Figure 2.26) compared to that of the allylic alcohol **(*R*)-112** can be attributed to the influence of the chlorine substituent. The ^{1}H NMR spectrum of **198** (Figure 2.23) illustrates these changes.

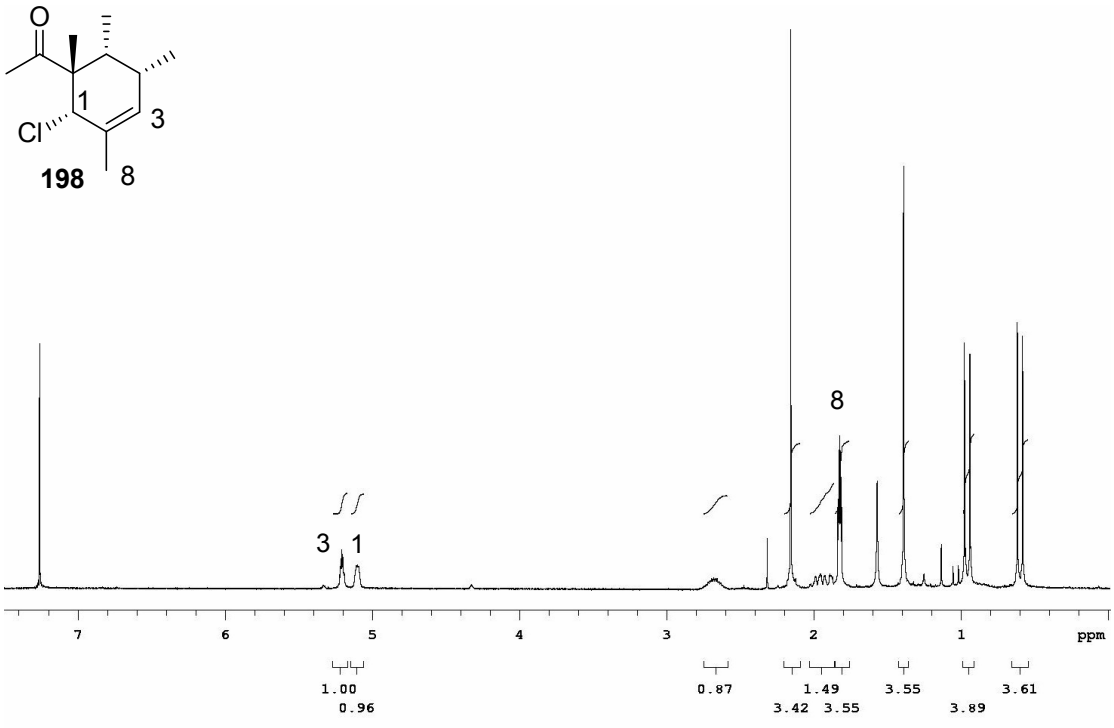
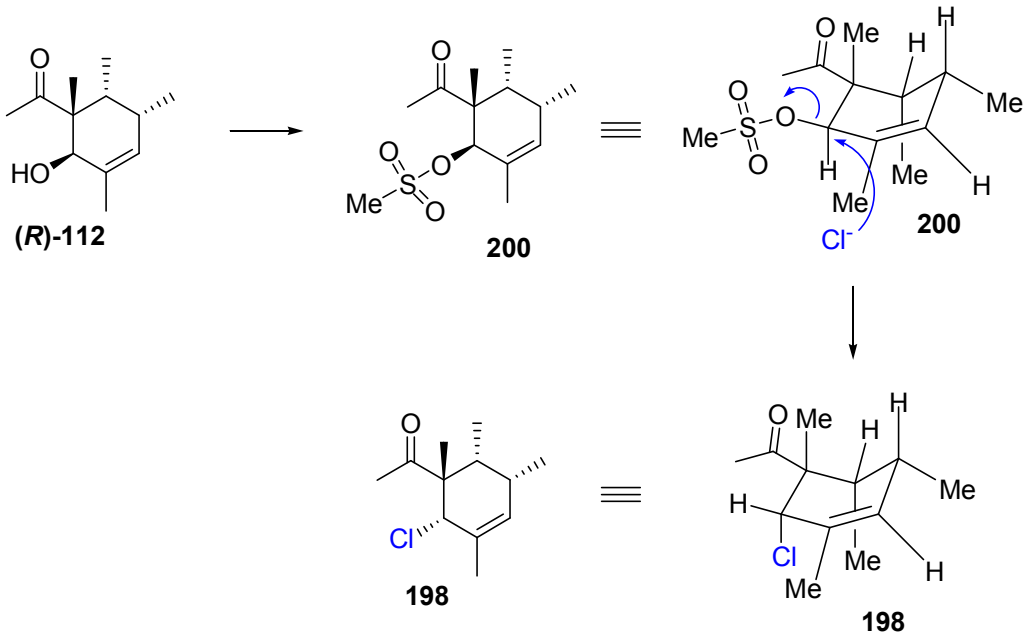


*Figure 2.23. ^{1}H NMR spectrum of chlorinated alkene **198** in $CDCl_3$ at 200 MHz.*

The vinyl proton appears as a multiplet at δ 5.19 – 5.21 (shifted downfield from δ 5.07 – 5.08), while the proton on C1 appears as a broad singlet at δ 5.11 (Figure 2.23). This proton has shifted significantly downfield compared to that observed for alcohol **(*R*)-112**, where the proton on the same carbon appeared at δ 4.53. This shift can be attributed to the more electron-withdrawing character of the halogen compared with that of the hydroxyl group. The protons of the vinyl methyl group have also shifted downfield from δ 1.73 – 1.75 to δ 1.81 – 1.84. It is evident from the spectrum that **198** exists as only one isomer and although no NOESY data was obtained, it may be postulated that the chlorine is in the axial position, based on the proposed S_N2 mechanism shown on the following page (Scheme 2.34).



*Scheme 2.34. Proposed mechanism for the formation of **198** as one isomer.*

Additionally, the chemical ionisation mass spectrum (CI-MS) indicated the presence of an ion of mass 179, which may be cyclohexadiene **111** (Figure 2.24).

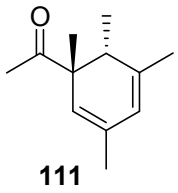


Figure 2.24. Proposed structure of compound of mass 179.

The other chlorinated products isolated from the reaction of allylic alcohol **(*R*)-112** with either of $SOCl_2$ or $MeSO_2Cl$ were the two isomers of **199**, which may have formed *via* the mechanism proposed in Figure 2.25.

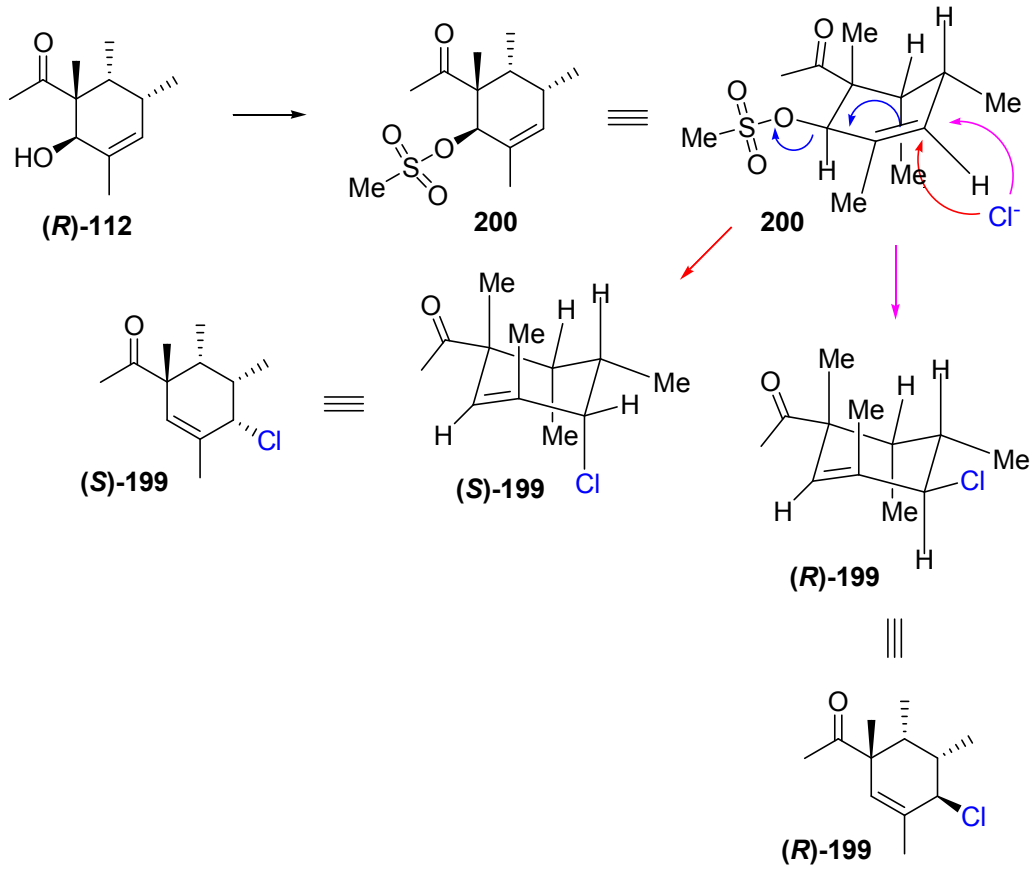


*Figure 2.25. Proposed mechanism for the formation of two isomers of **199**.*

Isomers **(*R*)-** and **(*S*)-199** were present as an inseparable mixture in a 1:3 ratio, as evidenced by ^{1}H NMR (Figure 2.26).

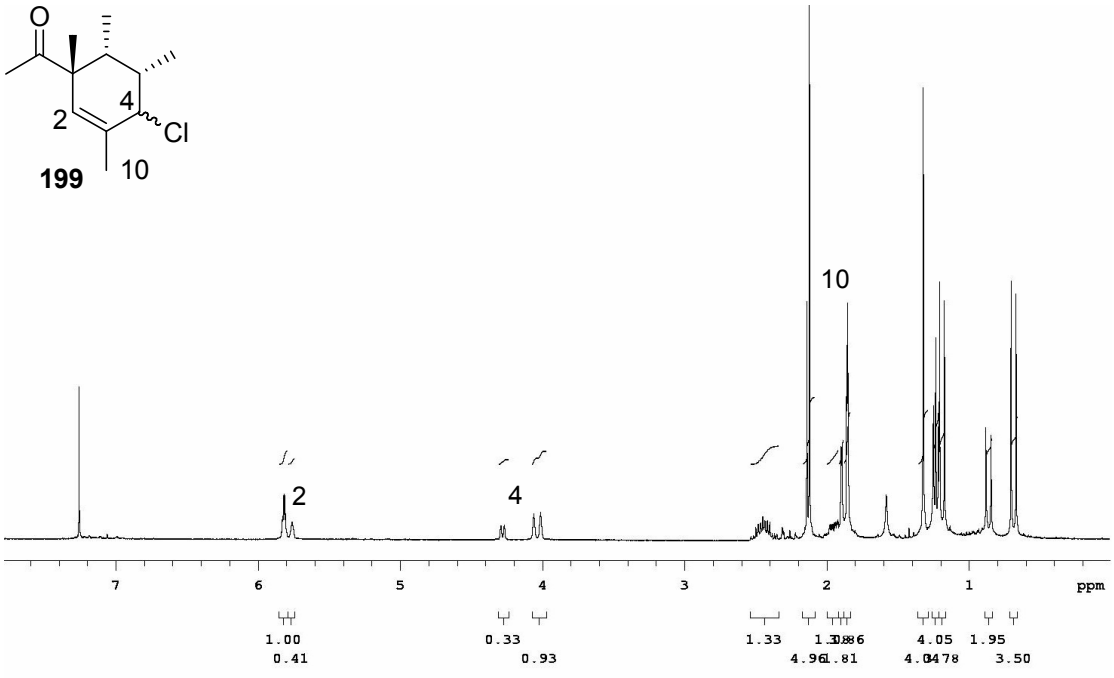


*Figure 2.26. ^{1}H NMR spectrum of chlorinated alkenes **(R)-** and **(S)-199** in $CDCl_3$ at 200 MHz.*

The differences between the two isomers of **199** and the starting material (allylic alcohol **(*R*)-112**) are once again noticeable (Figure 2.26). The vinyl proton has shifted from δ 5.07 – 5.08 in allylic alcohol **(*R*)-112** to δ 5.81 – 5.83 for the major isomer and δ 5.76 for the minor isomer. The change in the chemical shift of this proton can be attributed to the fact that it is now in a different environment than in allylic alcohol **(*R*)-112**, and the downfield shift may also be due to the electron-withdrawing nature of the adjacent halogen. The vinyl methyl protons have also moved from δ 1.73 – 1.75 to δ 1.85 – 1.86 (major isomer) and δ 1.89 – 1.90 (minor isomer). The two doublets at δ 4.28 (minor isomer) and δ 4.04 (major isomer) can be attributed to the proton on C4. This proton couples to the adjacent methine proton (which appears at δ 2.40 – 2.50 for both isomers), with a coupling constant J = 9.6 Hz (major isomer) and J = 5.2 Hz (minor isomer). The coupling constant between these two protons of the major isomer indicates that the protons were in an antiperiplanar orientation. Therefore, the stereochemistry of the major isomer can be assigned as **(*R*)-199**, with the chlorine of the minor isomer **(*S*)-199** in the axial position (Figure 2.27).

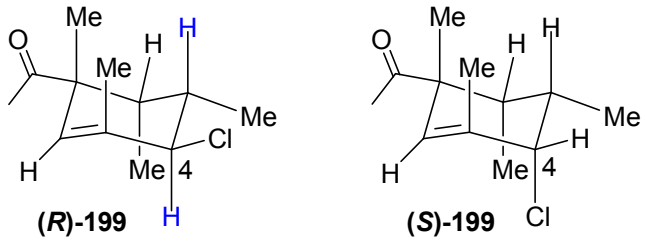


*Figure 2.27. Stereochemistry of major isomer **(R)-199** (antiperiplanar arrangement of protons highlighted) and minor isomer **(S)-199**.*

The methine proton adjacent to C4 also couples to the protons of the methyl group, which appear as a doublet at δ 1.19 for both the major and minor isomers (Figure 2.26). The methine proton adjacent to the quaternary methyl has shifted upfield, from a multiplet at δ 1.98 – 2.08 in allylic alcohol **(*R*)-112** to a quartet of doublets at δ 1.95, by virtue of coupling to both the methyl protons, which appear as doublets at δ 0.69 (major isomer) and δ 0.86 (minor isomer), and the adjacent methine proton. The protons of the quaternary methyl group appear at the same chemical shift for both isomers (δ 1.32) and the protons of the methyl ketone appear as a singlet at δ 2.12 (major isomer) and δ 2.14 (minor isomer). The IR spectra no longer showed the presence of the hydroxyl absorption (present at approximately 3500.0 cm^{-1} in allylic alcohol **(*R*)-112**) and CIMS confirmed the expected composition of $C_{12}H_{19}ClO$ for both isomers.

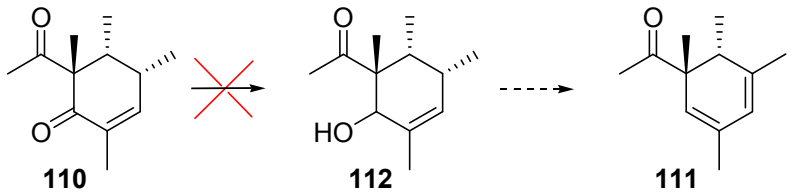
The presence of the cyclohexadiene moiety **111** in the mass spectrum of single isomer **198** indicated that elimination of the chlorine to give the desired cyclohexadiene is indeed possible. However, despite synthetic attempts at the formation of cyclohexadiene **111**, the halogenated alkenes **198** and **199** proved resistant to elimination, with only starting material isolated when the compounds were subjected to either DBU or the strong base *t*-BuOK. It was therefore apparent that high temperatures (in the order of those present in the injector port of the Gas Chromatogram-Mass Sspectrometer, GC-MS) may be required for the elimination to occur. An increase in temperature was not trialled as it was believed that while it may lead to the formation of the cyclohexadiene in the simple model system, high

temperatures may prove detrimental to more complex exocyclic functionalities and therefore this strategy was not applied to the synthesis of the natural product.

2.8 Conclusion

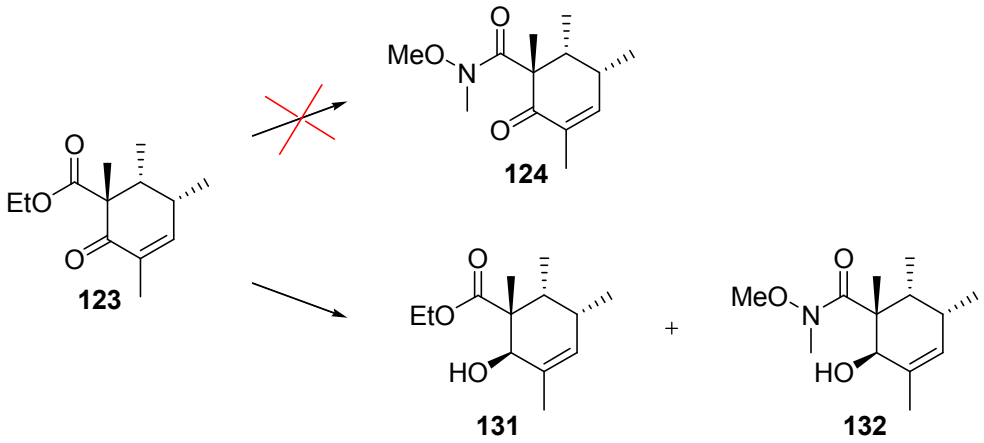
The various attempts at the synthesis of 9,10-deoxytridachione (**8**) described in this chapter led to the discovery of some interesting properties of the cyclohexenone systems studied.

Initial attempts at the formation of a cyclohexadiene system from methylated cyclohexenone **110** were not successful, due to the inability to generate allylic alcohol **112** using Luche reduction conditions (Scheme 2.35).[16-18]



*Scheme 2.35.Attempted conversion of methylated cyclohexenone **110** to cyclohexadiene **111**.*

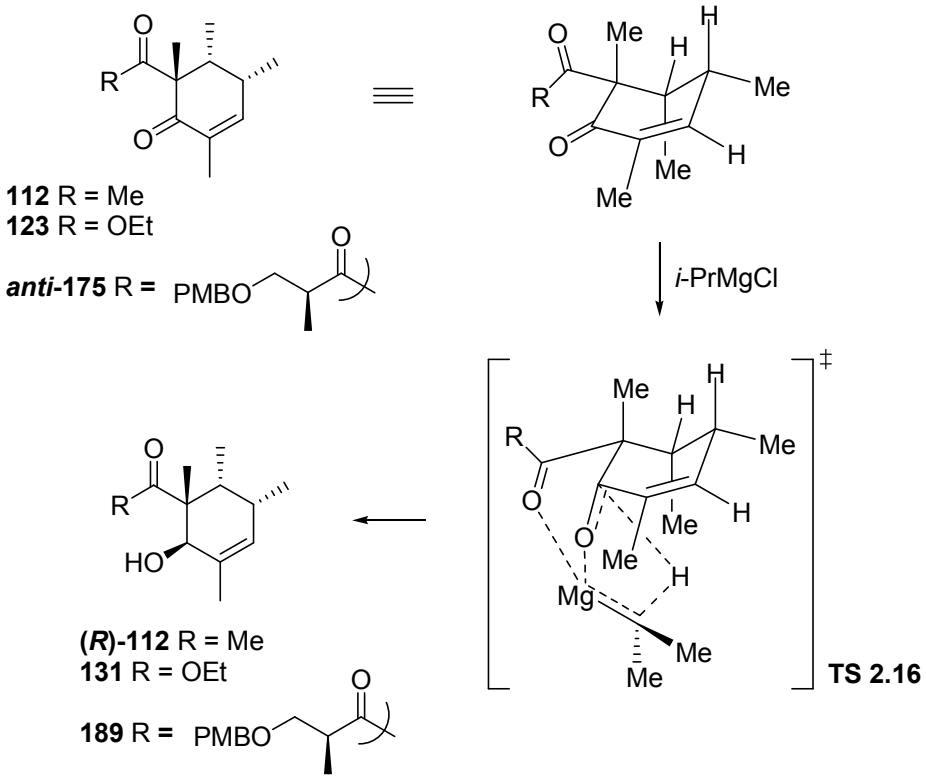
Subsequent attempts at the formation of a γ-pyrone moiety *via* Weinreb amide **124**[12] were also unsuccessful (Scheme 2.36).



*Scheme 2.36. Attempted formation of Weinreb amide **124**.*

Fortuitously, it was found that reaction of ester **123** under Weinreb amidation condtions[12] formed allylic alcohols **131** and **132** (Scheme 2.36). The Grignard reagent (*i*-PrMgCl) used in the reaction was implicated in the selective 1,2-reduction and the scope and utility of this reaction was investigated on nine different cyclohexenone systems.

It was found that an exocyclic carbonyl was essential for the reduction to occur, and it was proposed that the reduction was facilitated through chelation of the Grignard reagent by the endo- and exocyclic carbonyl groups (Scheme 2.37, showing only three of the nine cyclohexenones studied).

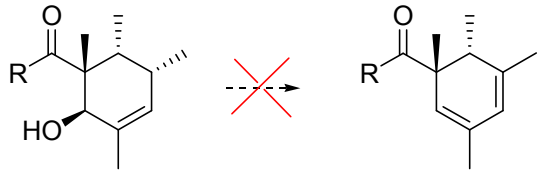


Scheme 2.37. General scheme for the reduction of cyclohexenones by i-PrMgCl.

Additionally, the reduction was inhibited by the presence of large axial groups on the cyclohexenone ring system.

The ability to generate allylic alcohols in the cyclohexenone systems allowed the formation of the cyclohexadiene moiety to be investigated. Allylic alcohols **(*R*)-112**

and **131** were employed in a number of different attempts at the formation of cyclohexadiene **111** and **197** (Scheme 2.38).

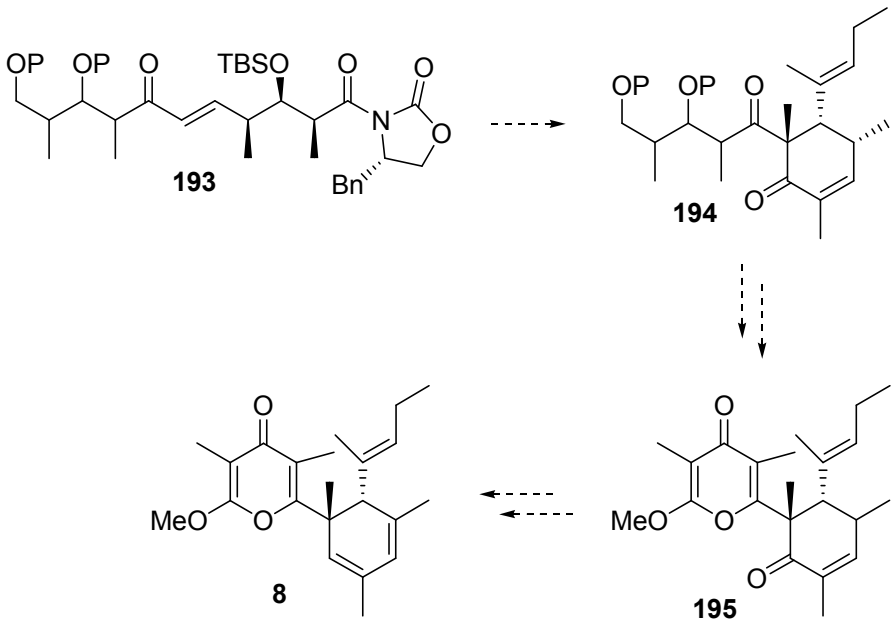


(*R*)-112 R = Me
131 R = OEt

111 R = Me
197 R = OEt

*Scheme 2.38. Attempted formation of cyclohexadienes **111** and **197** from allylic alcohols **(R)-112** and **131**.*

However, no synthetically-viable procedure for generating the cyclohexadiene moiety was found. It was postulated that the inability to dehydrate allylic alcohols **(*R*)-112** and **131** (Scheme 2.38) may be linked to the steric bulk around these allylic alcohol systems. An alternative route to 9,10-deoxytridachione (**8**) was proposed, which involved generating the γ-pyrone prior to the cyclohexadiene, *via* the complex cyclohexenone **194** (Scheme 2.39).



*Scheme 2.39. Alternative synthetic route towards 9,10-deoxytridachione (**8**).*

While the synthesis outlined in Scheme 2.39 was a potential strategy for the synthesis of 9,10-deoxytridachione (**8**), the ability to generate stereochemically diverse cyclohexenones was also of significant interest to the Perkins group. The focus of the project turned towards how changes in stereo- and regiochemistry in complex enones affect the stereochemistry of the cyclohexanones produced (*via* cuprate addition of different alkyl cuprates), as well as how the stereochemistry of the cyclohexanones thus produced affects the subsequent methylation and elimination. The development of a synthesis of stereochemically-different cyclohexenones could produce compounds that may be potential candidates for 9,10-deoxytridachione (**8**), as well as for the synthesis of the true proposed structure of tridachiahydropyrone (**42**) (as discussed in Chapter 1, Section 1.3.2). These studies will be discussed in the following chapters.

2.9 Experimental

2.9.1 General Experimental Procedures

2.9.1.1 Instrumentation

Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra were obtained on either a Varian Gemini 300 (operating at 300 MHz for proton (^{1}H) and 75.5 MHz for carbon (^{13}C)), a Bruker Ultrashield 400 (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C), a Varian Unity Inova 600 operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C) or a Bruker Ultrashield Plus 600 (operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C) spectrometer.

Chemical shift values were recorded as δ values in parts per million (ppm).

Where ^{1}H NMR spectra were recorded in deuterated chloroform ($CDCl_3$) the peak due to residual chloroform ($C\mathit{H}Cl_3$) was referenced to δ 7.26 ppm, where spectra were recorded in deuterated benzene (C_6D_6) the peak due to residual benzene ($C_6\mathit{H}_6$) was referenced to δ 7.15 ppm and where spectra were recorded in deuterated acetone (d_6-acetone), the peak due to residual acetone was referenced to δ 2.09 ppm.

Where proton-decoupled ^{13}C NMR spectra were recorded in $CDCl_3$ the central peak was referenced to δ 77.0 ppm, where spectra were recorded in C_6D_6 the central peak was referenced to δ 128.6 ppm and where the spectra were recorded in d_6-acetone, the central peak of the carbonyl carbon was referenced to δ 205.9 ppm.

^{1}H NMR data are reported as follows: chemical shift, multiplicity, relative integral, assignment and coupling constant *J* (Hz). Multiplicity assignments have been abbreviated as follows: s = singlet; d = doublet, t = triplet, quart = quartet, quint = quintet, sex = sextet, m = multiplet, bs = broad singlet, app. = apparent.

^{1}H and ^{13}C NMR assignments were confirmed with the aid of ^{1}H-^{1}H Correlation Spectroscopy (COSY), Nuclear Overhauser Effect Spectroscopy (NOESY), ^{1}H-^{13}C Heteronuclear Correlation (HETCOR) spectroscopy and Heteronuclear Multiple Quantum Coherence (HMQC) spectroscopy, and Attached Proton Test (APT). Selective Irradiation NOESY experiments were performed with standard Bruker pulse programs using shaped pulses for selectivity, inversion of the signal and resolution set at approximately 0.2 ppm. The experiments were conducted over 384 scans for high temperature NMR, and 64 scans for low temperature NMR, with a mixing time (d8) of 0.75 sec and delay (d1) of 5 sec. For selective irradiation NOESY performed at ambient temperature (20 ^{o}C), experiments were conducted over 512 scans, with d8 of 0.6 sec and d1 of 2.0 sec.

Infrared (IR) Spectroscopy

IR spectra were recorded on either a Perkin Elmer 1600 Series FTIR or a Nicolet Avatar 370 DTGS Fourier Transform spectrophotometer and absorptions are reported in wavenumbers (ν_{max}, cm^{-1}). Samples were analysed as a film on a NaCl window and prepared as a solution in either dichloromethane (CH_2Cl_2) or $CHCl_3$, which was then applied to the disc and the solvent was allowed to evaporate off.

Optical rotation

Optical rotation data was recorded on a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 20 ^{o}C. Spectroscopic grade $CHCl_3$ was used for all dilutions and the optical rotation is reported as: optical rotation, concentration (in g/100 mL). Measurements were carried out in a cell with a path length of 1 dm.

Mass Spectrometry

Chemical Ionisation Mass Spectra (CI-MS) were recorded on a Saturn GC-MS-MS 4D MS utilising a Varian Star 3400CX GC. High resolution mass spectra were recorded on either a Bruker BioApex II 47e FT-MS fitted with an Analytica ESI source or an Agilent G1969A LC-TOF utilizing an Agilent 1100 Series LC. Mass

spectral data are reported as follows: molecular formula, molecular ion [($M+H^+$), ($M+Na^+$) or ($M-H^+$)], calculated mass, accurate mass.

2.9.1.2 Chemical

Most reagents and starting materials were purchased from Sigma-Aldrich Company and were used as supplied and stored as specified. Where handling under an inert atmosphere was required, the reagents were handled under N_2 using standard techniques. Commercially available aldehydes were distilled from $CaCl_2$ prior to use. Triethylamine (Et_3N) and pyridine were distilled from CaH_2 under N_2 prior to use. Purchased *n*-BuLi and *t*-BuLi were standardised by titration against *N*-pivaloyl-*o*-toluidine prior to use.[42] Inorganic compounds were used as received or purified using standard purification procedures prior to use.[43]

Ethyl acetate (EtOAc), hexanes, CH_2Cl_2, ethanol (EtOH) and methanol (MeOH) were distilled prior to use and stored over 4Å molecular sieves. Diethyl ether (Et_2O) was used as received and stored over 4Å molecular sieves. For reactions under anhydrous conditions, anhydrous solvents were either used as purchased (in anhydrous form) and handled under N_2 using standard procedures, or distilled. Et_2O and tetrahydrofuran (THF) were dried using Na wire and stored under N_2, and distilled from Na-benzophenone ketyl under N_2 prior to use. CH_2Cl_2 was dried using CaH_2 and stored under N_2, and distilled from CaH_2 under N_2 prior to use.

All glassware was washed with acetone and dried overnight in an oven (80 ^oC) or with a heat gun (350 ^oC/540 ^oC) prior to use. Anhydrous reactions were carried out under either a N_2 or Ar atmosphere (as specified) using standard techniques.

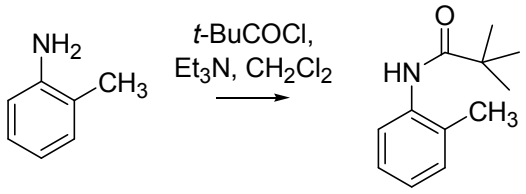
Room temperature (RT) varied between 19 – 25 ^oC. To achieve temperatures of 0 ^oC an ice slurry was used, to achieve temperatures of – 20 ^oC, – 50 ^oC and – 78 ^oC solid CO_2/acetone cold baths were used and to achieve temperature of – 100 ^oC, EtOH/liquid N_2 cold baths were used.

Column chromatography was carried out using Merck Keiselgel 60 (0.040 – 0.063 mm) mesh silica as the stationary phase and distilled solvents (as described above)

were used as the mobile phase. Buffered silica was prepared by adding pH 7 phosphate buffer (10 mL) to silica (100 g) and spinning overnight on a rotary evaporator at atmospheric pressure.

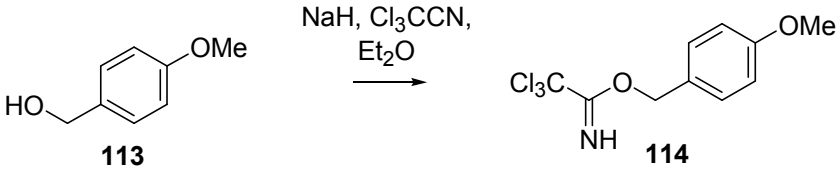
Thin Layer Chromatography (TLC) analyses were carried out using Merck Keiselgel 60 F_{254} silica gel aluminium sheets and visualised under a 254 nm UV lamp and/or anisaldehyde or potassium permanganate dip, followed by heating with a heat gun. Anisaldehyde dip was prepared by the following method: to a stirred solution of anisaldehyde (25 mL) in EtOH (450 mL) was added dropwise H_2SO_4 (98%, 25 mL), followed by glacial AcOH (3 – 4 mL). Potassium permanganate ($KMnO_4$) dip was prepared by the following method: to stirring H_2O (300 mL) was added $KMnO_4$ (3 g), K_2CO_3 (20 g) and NaOH (5%, 5 mL).

2.9.2 Experimental for Chapter 2



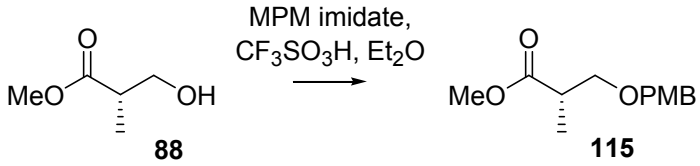
_N_-Pivaloyl-_o_-toluidine

To a stirring mixture of *o*-toluidine (20.0 g, 186 mmol) and Et_3N (26.1 mL, 187 mmol) in dry CH_2Cl_2 (100 mL) under N_2 at 0 ^oC was added dropwise a solution of pivaloyl chloride (16.0 mL, 187 mmol) in dry CH_2Cl_2 (20 mL) over a 40 min period. The resulting mixture was stirred at RT for 1 hr, after which time it was poured into H_2O (400 mL). The layers were separated and the organic layer was washed with H_2O (3 x 200 mL) then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a white solid. The solid was recrystallised from CH_2Cl_2 (hexanes were added to aid precipitation) to give 19.2 g (54 % yield) of the title compound as a white, crystalline solid, with identical spectral data to that given in the literature.[42]



4-Methoxybenzyl-2,2,2-trichloroacetimidate (114)

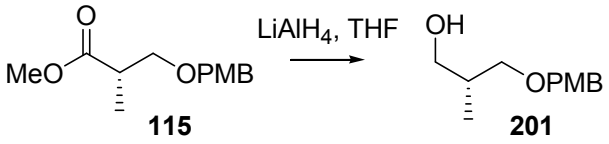
To a stirring suspension of NaH (60% dispersion in oil, 0.60 g, 0.015 mmol) in dry Et_2O (110 mL) under N_2 at RT was added alcohol **113** (18.0 mL, 0.145 mmol). The resulting mixture was cooled to 0 ^oC and Cl_3CCN (14.5 mL, 0.145 mmol) was added dropwise. The mixture was stirred under N_2 at RT for 1.5 hr, after which time the solvent was removed *in vacuo*. To the residue obtained was added a mixture of *n*-pentane (190 mL) and MeOH (10 mL), and the resulting solution was shaken vigorously for 2 min. The brown solid was removed by filtration (cotton wool) and the filtrate was concentrated *in vacuo* to give 36.8 g of a light brown oil. The oil was purified by distillation under reduced pressure to give 36.8 g (90% yield) of the title compound as a clear, colourless oil (BPt 100 ^oC at 0.05 mmHg, lit. BPt[5] 135 – 137 ^oC at 0.7 mmHg) with identical spectral data to that reported in the literature.[5]



***(S)*-Methyl-3-(4-methoxybenzyloxy)-2-methylpropionate (115)**

To a stirring solution of alcohol **88** (9.4 mL, 84.8 mmol) and imidate **114** (36.0 g, 127.6 mmol) in dry Et_2O (244 mL) under N_2 was added CF_3SO_3H (6 x 22 μL, 6 x 0.25 mmol aliquots) over a period of 3 hr. The mixture was diluted by addition of Et_2O (100 mL). The organic mixture was washed with $NaHCO_3$ (sat., 1 x 100 mL) and brine (1 x 100 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a white crystalline solid. The solid was triturated with a 1:1 mixture of hexanes and CH_2Cl_2, filtered and filtrate was evaporated *in vacuo* to give 23.1 g of a yellow oil. The oil was purified by distillation under reduced pressure to give 18.8 g (93% yield) of the title compound as a clear and colourless oil (BPt 99 – 110 ^oC at

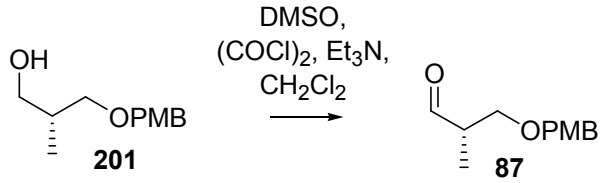
0.05 mmHg, lit. BPt[4] 98 – 110 °C at 0.07 mmHg), with identical spectral data to that reported in the literature.[3]



115 **201**

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

To a stirring suspension of $LiAlH_4$ (0.53 g, 14.0 mmol) in dry THF (20 mL) under N_2 at 0 °C was added dropwise ester **115** (2.7 g, 11.5 mmol) in dry THF (13 mL) *via* cannula (8 mL rinse) over 10 min. The solution was slowly warmed to RT and stirred for 30 min. The solution was cooled to 0 °C and the reaction was quenched by addition of H_2O (0.5 mL), NaOH (5 M, 0.5 mL) and once again H_2O (1.5 mL). The solution was diluted by the addition of Et_2O (25 mL) then dried ($MgSO_4$) and filtered. The filter cake was washed with Et_2O (25 mL) and the filtrate was evaporated *in vacuo* to give 2.35 g (97% yield) of the title compound as a pale yellow oil, with identical spectral data to that reported in the literature.[3] The oil was used crude in subsequent reactions.

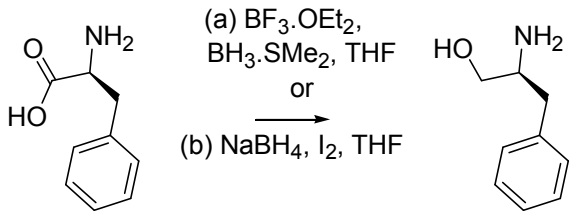


201 **87**

(*R*)-3-(4-methoxybenzyloxy)-2-methylpropional (87)

To a stirring solution of DMSO (8.0 mL, 7.3 mmol) in dry CH_2Cl_2 (8 mL) under N_2 at – 78 °C was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 1.8 mL, 3.6 mmol) and the solution was stirred at – 78 °C for 30 min. To this solution was added dropwise a solution of alcohol **201** (0.51 g, 2.4 mmol) in dry CH_2Cl_2 (3 mL) *via* cannula (1 mL rinse). The resulting murky pale yellow solution was stirred at -78 °C for 45 min, after which time Et_3N (2.0 mL, 14.3 mmol) was added dropwise and the resulting slurry was stirred at -78 °C for 30 min. The solution was slowly warmed to 0 °C with

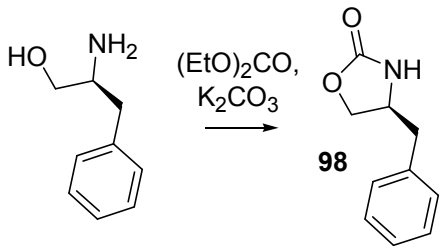
stirring and the reaction was quenched by addition to a vigorously stirring solution of $NaHSO_4$ (1 M, 15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The organic extracts were combined and the solvent was removed *in vacuo*. The residue was diluted with Et_2O (15 mL) and washed with $NaHSO_4$ (1 M, 3 x 5mL), H_2O (1 x 5mL), $NaHCO_3$ (sat., 1 x 5mL) and brine (1 x 5mL). The organic extract was dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.47 g (94% yield) of the title compound as a pale yellow oil with identical spectral data to that reported in the literature.[3] The oil was used crude in subsequent reactions.



(*S*)-Phenylalaninol

(a) To a stirring suspension of (*S*)-phenylalanine (10.0 g, 60.7 mmol) in dry THF (31 mL) under N_2 at RT was added dropwise re-distilled $BF_3.EtO_2$ (8.5 mL, 66.7 mmol) over 10 mins, and the resulting mixture was heated at reflux under N_2 for 2 hr. To the colourless refluxing solution was added dropwise $BH_3.SMe_2$ (10 M, 7.0 mL, 70.0 mmol) and the resulting solution was heated at reflux under N_2 for a further 6 hr. The solution was cooled to RT and the reaction was quenched by addition of a 1:1 solution of THF/H_2O (10 mL) followed by NaOH (5 M, 45 mL). The resulting two-phase mixture was heated at reflux for 12 hr, after which time it was cooled to RT and filtered under vacuum. The solid residue was washed with THF (2 x 25 mL) and the filtrate was concentrated *in vacuo*. The resulting slurry was extracted with CH_2Cl_2 (3 x 60 mL) and the organic extracts were combined, then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 9.47 g (104% yield) of a cream crystalline solid. The solid was recrystallised from EtOAc to give 7.15 g (78% yield) of the title compound as white crystals, with identical spectral data to that reported in the literature.[10]

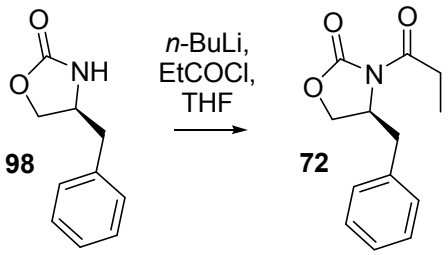
(b) To a stirring suspension of $NaBH_4$ (2.8 g, 74.0 mmol) in dry THF (76 mL) under N_2 at RT was added in one portion (*S*)-phenylalanine (5.0 g, 30.3 mmol) and the suspension was cooled to 0 ^oC. To the mixture was added dropwise a solution of iodine (resublimed, 7.7 g, 30.3 mmol) in dry THF (21 mL, followed by rinsing with extra THF, 2 x 4 mL) and the solution was stirred at 0 ^oC until evolution of H_2 ceased. The mixture was heated at reflux for 18 hr after which time it was cooled to RT and MeOH (100 mL) was slowly added. The mixture was stirred for 30 min and the solvent was removed *in vacuo* to give a white paste. The paste was dissolved by addition of KOH (20%, 75 mL) and stirred at RT for 4 hr. The white mixture was extracted with CH_2Cl_2 (3 x 75 mL) then dried (Na_2SO_4), filtered and solvent was removed *in vacuo* to give 4.8 g of a white solid. The solid was recrystallised from toluene to give 3.4 g (75% yield) of the title compound as a white crystalline solid with identical spectral data to that reported in the literature.[10]



98

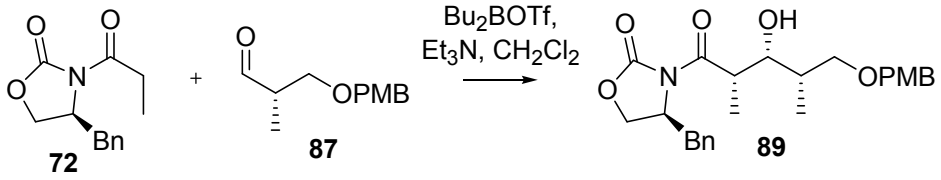
(*S*)-4-(Phenylmethyl)-2-oxazolidinone (98)

A mixture of (*S*)-phenylalaninol (4.0 g, 26.5 mmol), dry K_2CO_3 (0.41 g, 2.97 mmol) and $(EtO)_2CO$ (7.4 mL, 61.0 mmol) was heated at 135 ^oC with stirring under N_2 (Vigreux column used) and the EtOH produced was collected in a distillation receiver cooled to 0 ^oC. Once the distillation of EtOH ceased, the solution was cooled to RT and diluted with CH_2Cl_2 (24 mL). The organic layer was washed with water (1 x 25 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 4.9 g of a pale orange solid. The solid was taken up in a hot 2:1 solution of EtOAc/hexanes and left overnight in the freezer to crystallise, giving 4.2 g (81% yield) of the title compound as light yellow crystals with identical spectral data to that reported in the literature.[10]



(*S*)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (72)

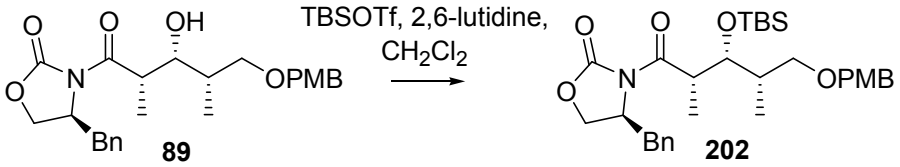
To a stirring solution of oxazolidinone **98** (6.5 g, 42.7 mmol) in dry THF (142 mL) under N_2 at – 78 ^oC was added dropwise *n*-BuLi (1.6 M in hexanes, 27.0 mL, 43.1 mmol) followed by freshly distilled EtCOCl (4.1 mL, 47.2 mmol) in one aliquot, and the resulting colourless solution was left to stir at – 78 ^oC for 30 min. The solution was warmed to RT and reaction was quenched by addition of NH_4Cl (sat., 55 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, washed with NaOH (1 M, 1 x 30 mL) and brine (1 x 30 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a pale yellow oil, which was placed in the freezer overnight to crystallise. The solid was pulverized, triturated with hexanes and filtered to give 7.9 g (79% yield) of the title compound as white crystals with identical spectral data to that reported in the literature.[10]



(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*R*)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethyl-pentanoyl]-oxazolidin-2-one (89)

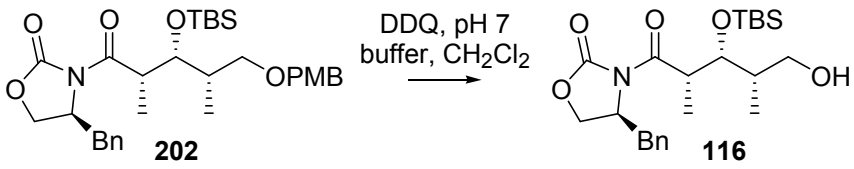
To a stirring solution of *N*-acyloxazolidinone **72** (5.0 g, 21.6 mmol) in dry CH_2Cl_2 (30 mL) under N_2 at 0 ^oC was added dropwise Bu_2BOTf (1 M in CH_2Cl_2, 26.0 mL, 26.0 mmol), and the resulting dark red solution was stirred at 0 ^oC for 30 min. To this stirring solution was added dropwise Et_3N (4.0 mL, 28.7 mmol), and the resulting orange/yellow solution was stirred at 0 ^oC for a further 30 min, after which time it

was cooled to – 78 °C. A solution of aldehyde **87** (3.0 g, 14.5 mmol) in dry CH_2Cl_2 (30 mL) was then added dropwise *via* cannula (5.6 mL rinse) and the resulting clear, yellow solution was stirred at – 78 °C for 1 hr and at 0 °C for 4 hr. The reaction was quenched by addition of pH 7 buffer (30 mL), MeOH (90 mL) and a 2:1 solution of MeOH/30% H_2O_2 (120 mL), and the resulting two-phase mixture was stirred at 0 °C for 1 hr. The organic solvents were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with $NaHCO_3$ (sat., 1 x 75 mL) and brine (1 x 100 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 9.7 g of a yellow oil. The oil was purified by flash column chromatography on silica (5% Et_2O/CH_2Cl_2) to give 3.8 g (59% yield) of the title compound as a colourless oil (R_f = 0.18), with identical spectral data to that reported in the literature.[14]



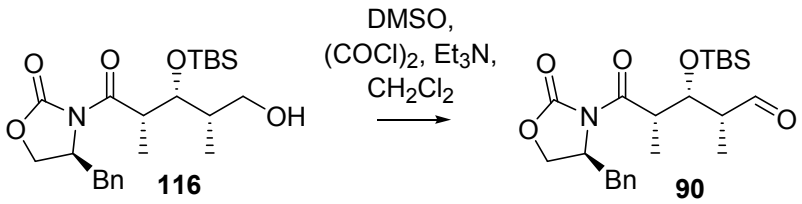
(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyl-oxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (202)

To a stirring solution of alcohol **89** (3.8 g, 8.5 mmol) in dry CH_2Cl_2 (50 mL) under N_2 at – 78 °C was added dropwise 2,6-lutidine (2.0 mL, 17.2 mmol) followed immediately by dropwise addition of TBSOTf (3.0 mL, 13.1 mmol) and the resulting clear and colourless solution was left to stir at – 78 °C for 2.5 hr. The reaction was quenched by addition of $NaHCO_3$ (sat., 50 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 6.8 g of an amber-coloured oil. The oil was purified by flash column chromatography on silica (10% hexanes/CH_2Cl_2) to give 4.4 g (94% yield) of the title compound as a colourless oil (R_f = 0.31), with identical spectral data to that reported in the literature.[14]



(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4-dimethylpentanoyl]-oxazolidin-2-one (116)

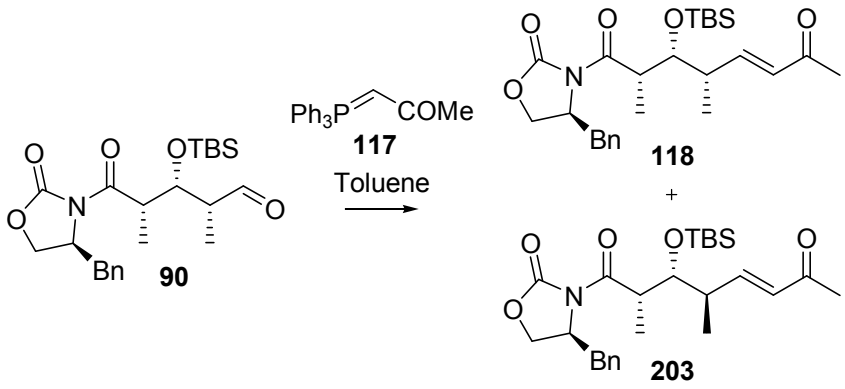
To a stirring solution of PMB ether **202** (1.7 g, 3.1 mmol) in dry CH_2Cl_2 (78 mL) at RT was added pH 7 buffer (7.8 mL) and the two-phase mixture was cooled to 0 ^oC. To this solution was added DDQ (0.85 g, 3.73 mmol) and the resulting black mixture was stirred at 0 ^oC for 1.5 hr. The mixture was diluted with CH_2Cl_2 (35 mL) and reaction was quenched by the addition of $NaHCO_3$ (sat., 85 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 85mL). The organic extracts were combined, dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 1.4 g of a yellow oil, which was purified by flash column chromatography on buffered silica (pH 7, 30% EtOAc/hexanes) to give 1.1 g (78% yield) of the title compound as a colourless oil (R_f = 0.21), with identical spectral data to that reported in the literature.[14]



(2*S*,3*S*,4*S*)-5-[(*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-oxopentanal (90)

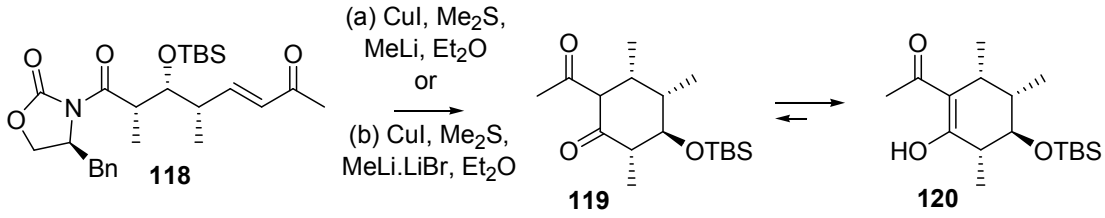
To a stirring solution of DMSO (0.6 mL, 8.46 mmol) in dry CH_2Cl_2 (5 mL) under N_2 at – 78 ^oC was added dropwise $(COCl)_2$ (2 M in CH_2Cl_2, 2.1 mL, 4.2 mmol) and the resulting cloudy white solution was stirred at – 78 ^oC for 30 mins. To this solution was added dropwise a solution of alcohol **116** (1.2 g, 2.7 mmol) in dry CH_2Cl_2 (5 mL) *via* cannula (4 mL rinse), and the resulting mixture was stirred at – 78 ^oC for 45 min, after which time Et_3N (2.3 mL, 16.5 mmol) was added dropwise and the resulting slurry was stirred at – 78 ^oC for 30 min. The solution was slowly warmed to

0 ^{o}C with stirring and the reaction was quenched by addition to a vigorously stirring solution of $NaHSO_4$ (1 M, 35 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The organic extracts were combined and solvent was removed *in vacuo*. The residue was diluted with Et_2O (25 mL) and washed with $NaHSO_4$ (1 M, 3 x 10 mL), H_2O (1 x 10 mL), $NaHCO_3$ (sat., 1 x 10 mL) and brine (1 x 10 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 1.1 g (93% yield) of the title compound as a pale yellow oil with identical spectral data to that reported in the literature.[14] The oil was used crude in subsequent reactions.



(2*S*,3*R*,4*S*,5*E*)-1-[(*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethyl-silyloxy)-2,4-dimethyloct-5-ene-1,7-dione (118) and (2*S*),3*R*,4*R*,5*E*)-1-[(*S*)-4-benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyloct-5-ene-1,7-dione (203)

A stirring solution of aldehyde **90** (0.49 g, 1.13 mmol) and ylide **117** (0.55 g, 1.73 mmol) in dry toluene (11.3 mL) was heated under N_2 at 60 ^{o}C for 5 days. The solution was cooled to RT and volatile components were removed *in vacuo*. The resulting dark brown oil was triturated with hexanes and triturate was passed through a silica plug. The solvents were removed *in vacuo* yielding a pale yellow oil, which was purified by flash column chromatography on silica (2.5% Et_2O in CH_2Cl_2) to give 0.33 g (61% yield) of an inseperable mixture of **118** and **203** as a colourless oil (R_f = 0.17) with identical spectral data to that reported in the literature.[14]

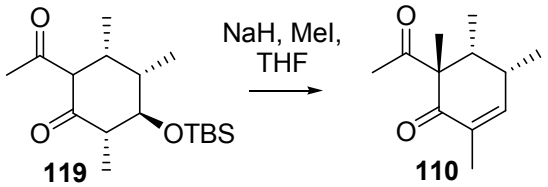


(3*R*,4*S*,5*R*,6*S*)-2-Acetyl-5-(*tert*-butyldimethylsilyloxy)-3,4,6-trimethylcyclohexanone (119) and 1-[(3*S*,4*R*,5*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-3,5,6-trimethylcyclohex-1-enyl]-ethanone (120)

(a) To a stirring suspension of CuI (0.44 g, 2.29 mmol) in dry Et_2O (4 mL) and dry Me_2S (8 mL) under N_2 at RT was added dropwise MeLi (1.6 M in Et_2O, 2.9 mL, 4.6 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 **118** (0.49 g, 1.03 mmol) in dry Et_2O (3 mL) *via* cannula (2 mL rinse) resulting in the formation of a yellow precipitate, and the suspension was stirred at RT for 1 hr (the solution changed colour from yellow to orange to black). The mixture was diluted with Et_2O (10 mL) and reaction was quenched by addition of a 10% NH_4OH/90% NH_4Cl solution (27 mL). The two-phase system was stirred at RT for 10 min, after which time the aqueous layer became dark blue in colour. The mixture was filtered through celite, the layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The organic extracts were combined and washed with brine (1 x 50 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.57 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% hexanes/CH_2Cl_2) to give 0.24 g (67% yield) of the title compound as a colourless oil (R_f = 0.46). The compound existed predominantly in the *enol* form, with identical spectral data to that reported in the literature.[3]

(b) To a stirring suspension of CuI (0.06 g, 0.31 mmol) in dry Et_2O (1 mL) and dry Me_2S (2 mL) under N_2 at RT was added dropwise MeLi (as the LiBr complex, 1.5 M in Et_2O, 0.58 mL, 0.87 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 **118** (0.07 g, 0.14 mmol) in dry Et_2O (1 mL) *via* cannula (1 mL rinse), resulting in the formation of a yellow precipitate, and the suspension was stirred at RT for 1 hr (the solution changed colour from yellow to orange to black).

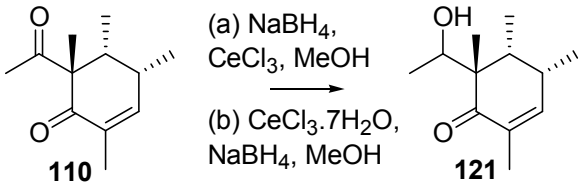
The mixture was diluted with Et_2O (5 mL) and reaction was quenched by addition of a 10% NH_4OH/90% NH_4Cl solution (10 mL). The two-phase system was stirred at RT for 10 mins, after which time the aqueous layer became dark blue in colour. The mixture was filtered through celite, the layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 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 0.06 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% hexanes/CH_2Cl_2) to give 0.02 g (47% yield) of the title compound as a colourless oil (R_f = 0.46). The compound existed predominantly in the *enol* form, with identical spectral data to that reported in the literature.[3]



119 **110**

(4*R*,5*R*,6*S*)-6-Acetyl-2,4,5,6-tetramethylcyclohex-2-enone (110)

To a stirring suspension of NaH (60% dispersion in oil, 0.06 g, 1.54 mmol) in dry THF (9 mL) under N_2 at RT was added dropwise a solution of diketone **119** (0.24 g, 0.77 mmol) in dry THF (4 mL) *via* cannula (3 mL rinse) and the resulting yellow solution was stirred at RT for 10 min. To this solution was added dropwise MeI (0.35 mL, 5.62 mmol), and the resulting yellow solution was stirred under N_2 at RT for 3 days. The reaction was quenched with $NaHCO_3$ (sat., 47 mL) and the mixture was extracted with Et_2O (3 x 40 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 0.16 g of a brown oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.13 g (87% yield) of the title compound as a light yellow oil (R_f = 0.24), with identical spectral data to that reported in the literature.[3]



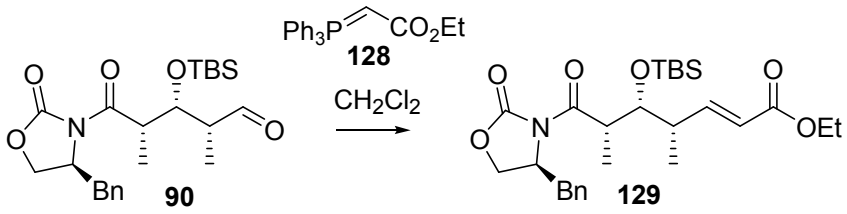
6-(1-Hydroxy-ethyl)-2,4,5,6-tetramethylcyclohex-2-enone (121)

(a) To a stirring solution of cyclohexenone **110** (0.021 g, 0.11 mmol) in dry MeOH (0.5 mL) under N_2 at – 78 ^oC was added anhydrous $CeCl_3$ (0.04 g, 0.16 mmol, 0.5 mL rinse with dry MeOH) and the white suspension was warmed to 0 ^oC with stirring. After 15 min was added $NaBH_4$ (0.01 g, 0.27 mmol) and the mixture was left to stir at 0 ^oC. After 1 hr, the mixture was warmed to RT and once again $NaBH_4$ (0.02 g, 0.44 mmol) was added. After 30 min the reaction was quenched by addition of H_2O (6 mL). The volatile components were removed *in vacuo* and the slurry was extracted with Et_2O (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.02 g of a colourless oil. The oil was purified by flash column chromatography on silica (2.5% Et_2O/CH_2Cl_2) to give 0.01 g (52% yield) of the title compound as a colourless oil (R_f = 0.22).

IR (film, cm^{-1}) 3469.3, 2925.3, 2854.1, 1660.5, 1454.2, 1378.7; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.97 (d, 3H, =CHCH(C*H*$_3$), *J* = 6.9 Hz), 1.10 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.2 Hz), 1.11 (s, 3H, C(C*H*$_3$)), 1.20 (d, 3H, C*H*$_3$CH(OH), *J* = 6.6 Hz), 1.76 – 1.77 (m, 3H, C(C*H*$_3$)=CH), 2.06 – 2.15 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 2.87 - 2.96 (m, 1H, =CHC*H*(CH$_3$), 4.26 (quart, 1H, CH$_3$C*H*(OH), *J* = 6.6 Hz), 6.24 – 6.25 (m, 1H, =C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 9.9, 15.8, 16.0, 18.1, 21.1, 32.5, 41.1, 53.3, 72.3, 132.9, 147.1, 198.1; **HRESIMS** calculated for $C_{12}H_{20}O_2Na^+$ (M+Na^+): 219.1361; found 219.1357.

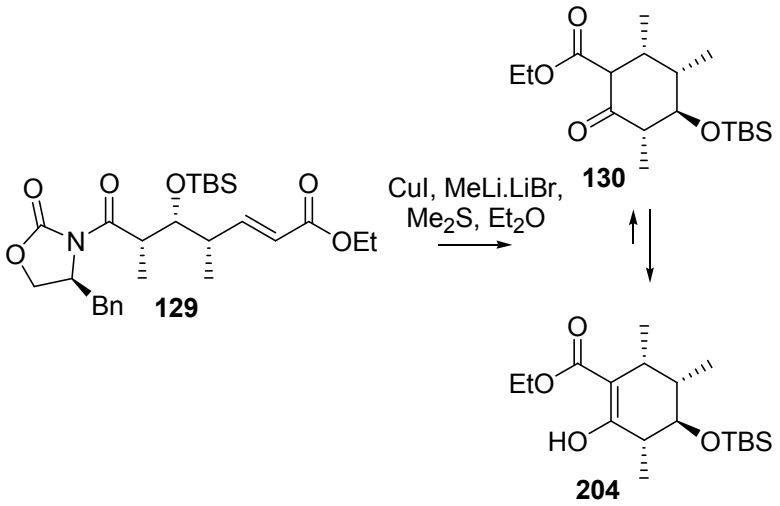
(b) To a stirring solution of cyclohexenone **110** (0.02 g, 0.11 mmol) in MeOH (1 mL) at 0 ^oC was added $CeCl_3$ (hydrated, 0.14 g, 0.38 mmol), followed by $NaBH_4$ (0.006 g, 0.17 mmol) and the reaction was warmed to RT and stirred for 15 min. The reaction was quenched by addition of H_2O (3 mL) and the volatile components were removed *in vacuo*. The slurry was extracted with Et_2O (3 x 10 mL) and the organic

extracts were combined, washed with brine (1 x 30 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.02 g of a clear, colourless oil. The oil was purified by flash column chromatography on silica (2.5% Et_2O/CH_2Cl_2) to give 0.003 g (12% yield) of the title compound as a colourless oil (R_f = 0.23), with identical spectral data to that given above.



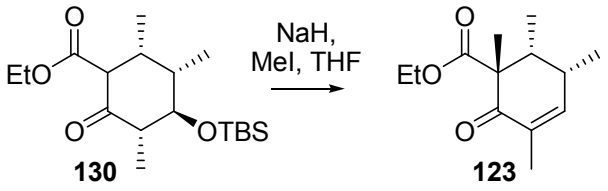
(2*E*,4*S*,5*R*,6*S*)-Ethyl-7-[(*S*)-4-benzyl-2-oxo-oxazolidin-3-yl]-5-(*tert*-butyldimethylsilyloxy)-4,6-dimethyl-7-oxohept-2-enoate (129)

A solution of aldehyde **90** (0.56 g, 1.28 mmol) and ylide **128** (0.67 g, 1.93 mmol) in dry CH_2Cl_2 (13 mL) was stirred under N_2 at RT for 5 days. The volatile components were removed *in vacuo* and the resulting brown oil was triturated with hexanes. The triturate was passed through a plug of silica and solvent was removed *in vacuo* to give a pale yellow oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.53 g (83% yield) of the title compound as a colourless oil (R_f = 0.40), with identical spectral data to that reported in the literature.[14]



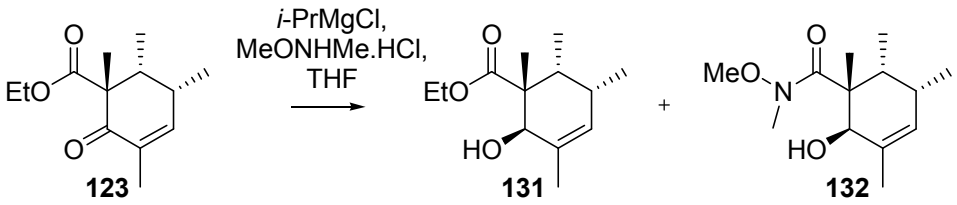
(2*R*,3*S*,4*R*,5*S*)-Ethyl-4-(*tert*-butyldimethylsilyloxy)-2,3,5-trimethyl-6-oxocyclohexanecarboxylate (130) and (3*S*,4*R*,5*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-3,5,6-trimethylcyclohex-1-enecarboxylic acid ethyl ester (204)

To a stirring solution of CuI (0.27 g, 0.54 mmol) in dry Et_2O (2 mL) and Me_2S (4 mL) under N_2 at RT was added dropwise MeLi (as the LiBr complex, 1.5 M in Et_2O, 2.0 mL, 3.0 mmol) until the bright yellow precipitate just dissolved. To the clear solution was added dropwise a solution of enone **129** (0.34 g, 0.68 mmol) in dry Et_2O (2 mL) *via* cannula (1.2 mL rinse) and the suspension was stirred at RT for 1 hr (the solution changed colour from yellow to orange to black). The solution was diluted with Et_2O (8 mL) and the reaction was quenched by slow addition of a 10% NH_4OH/90% NH_4Cl solution (16 mL). The two-phase system was stirred at RT for 10 min, after which time the aqueous layer became dark blue in colour. The mixture was filtered through celite, the layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 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 0.37 g of a yellow oil. The oil was purified by flash column chromatography on silica (20%EtOAC/hexanes) to give 0.09g (41% yield) of the title compound as a colourless oil (R_f = 0.63 *keto* form, 0.27 *enol* form). The product existed in predominantly the *enol* form, with identical spectral data to that reported in the literature.[3]



(1*S*,5*R*,6*R*)-Ethyl-1,3,5,6-tetramethyl-2-oxocyclohex-3-enecarboxylate (123)

To a stirring suspension of NaH (60% dispersion in oil, 0.03 g, 0.63 mmol) in dry THF (2 mL) under N_2 at RT was added dropwise a solution of keto-ester **130** (0.09 g, 0.29 mmol) in dry THF (2 mL) *via* cannula (2 mL rinse), and the resulting colourless solution was stirred at RT for 10 min. To this solution was added dropwise MeI (0.15 mL, 2.41 mmol) and the solution was left to stir under N_2 at RT for 2 days. The solution was diluted with CH_2Cl_2 (10 mL) and reaction was quenched by addition of $NaHCO_3$ (sat., 20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined and washed with brine (1 x 30 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a brown oil. The oil was purified by flash column chromatography on silica (20% Et_2O/ hexanes) to give 0.05 g (78% yield) of the title compound as a yellow oil (R_f = 0.33), with identical spectral data to that reported in the literature.[3]



(1*R*,2*R*,5*R*,6*R*)-2-Hydroxy-1,3,5,6-tetramethylcyclohex-3-ene-ethylester (131) and (1*R*,2*R*,5*R*,6*R*)-2-hydroxy-1,3,5,6-tetramethylcyclohex-3-enemethoxy-methylamide (132)

(a) To a stirring suspension of cyclohexenone **123** (0.05 g, 0.23 mmol) and MeON(H)Me.HCl (0.05 g, 0.51 mmol) in dry THF and Et_2O (1:1, 0.6 mL) under N_2 at – 20 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.60 mL, 1.20 mmol), and the solution was stirred at – 20 ^oC for 30 min and then at 0 ^oC for 30 min. The reaction was quenched by addition of NH_4Cl (sat., 4 mL) and slowly warmed to RT

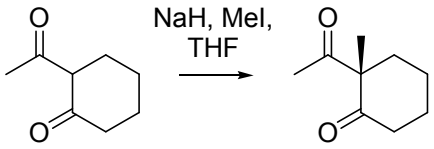
with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL). The organic layers were combined and washed with brine (1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.05 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% Et_2O/hexanes) to give two major products: ester **131** (0.02 g, 35% yield) and amide **132** (0.01 g, 20% yield) as colourless oils (R_f = 0.26 and R_f = 0.07, respectively).

Ester 131: $[\alpha]_D^{20}$ = – 51.4 (0.88, $CHCl_3$); **IR** (film, cm^{-1}) 3547.9, 2973.0, 1713.0, 1450.4, 1376.2, 1245.8, 1168.9, 1133.3, 1106.5, 1082.3, 1041.4, 1002.7; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.70 (d, 3H, =CHCH(C*H*$_3$), *J* = 7.2 Hz), 0.92 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.5 Hz), 1.21 (s, 3H, C(C*H*$_3$)), 1.29 (t, 3H, C*H*$_3$CH$_2$, *J* = 7.2 Hz), 1.75 – 1.77 (m, 3H, C(C*H*$_3$)=CH), 2.05 – 2.14 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 2.55 – 2.56 (m, 1H, =CHC*H*(CH$_3$), 4.20 (quart, 2H, CH$_3$C*H*$_2$, *J* = 6.9 Hz), 4.52 (bs, 1H, =C*H*), 5.08 – 5.09 (m, 1H, C*H*(OH)); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 11.4, 14.3, 17.9, 18.0, 19.4, 29.8, 40.2, 51.4, 60.8, 69.8, 126.7, 132.7, 178.7; **HRESIMS** calculated for $C_{13}H_{22}O_3$-H^+ (M-H^+): 225.1490; found 225.1478.

Amide 132: $[\alpha]_D^{20}$ = – 102.1 (0.24, $CHCl_3$); **IR** (film, cm^{-1}) 3518.7, 2965.1, 1622.1, 1456.1, 1375.5, 1082.7, 1044.4; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.73 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.2 Hz), 0.91 (d, 3H, C(CH$_3$)=CHCH(C*H*$_3$), *J* = 7.2 Hz), 1.30 (s, 3H, C(C*H*$_3$)), 1.76 – 1.77 (m, 3H, C(C*H*$_3$)=CH), 2.36 – 2.40 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 2.48 – 2.60 (m, 1H, =CHC*H*(CH$_3$)), 3.24 (s, 3H, N(C*H*$_3$)), 3.69 (s, 3H, N(OC*H*$_3$)), 4.65 (bs, 1H, =C*H*), 5.09 (s, 1H, C*H*(OH)); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 11.6, 16.3, 18.1, 19.7, 29.9, 33.8, 37.8, 52.7, 60.7, 71.0, 126.1, 133.1, 178.8; **HRESIMS** calculated for $C_{13}H_{23}NO_3$-H^+ (M-H^+): 240.1599; found 240.1595.

(b) To a stirring suspension of MeON(H)Me.HCl (0.06 g, 0.6 mmol) in dry THF and dry Et_2O (1:1, 0.4 mL) under N_2 at – 20 ^oC was added dropwise *i*-PrMgCl (2M in THF, 0.58 mL, 1.16 mmol), followed by dropwise addition of a solution of cyclohexenone **123** (0.05 g, 0.23 mmol) in dry THF and dry Et_2O (1:1, 0.2 mL) *via* cannula (0.2 mL rinse) and the resulting yellow solution was left to stir at – 20 ^oC for 30 mins. The solution was warmed to RT and stirred for a further 30 mins, after

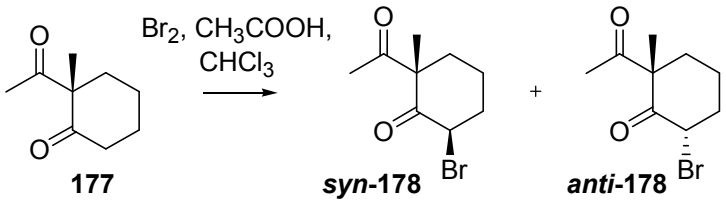
which time the reaction was quenched by addition of NH_4Cl (sat., 4 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL) and CH_2Cl_2 (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 25 mL), then dried, filtered and solvent was removed *in vacuo* to give 0.05 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% Et_2O/hexanes) to give two major products: ester **131** (0.03 g, 60% yield) and amide **132** (0.01 g, 20% yield) as colourless oils (R_f = 0.26 and R_f = 0.07, respectively), with identical spectral data to that given above.



176 **177**

2-Acetyl-2-methylcyclohexanone (177)

To a stirring solution of NaH (0.16 g, 4.0 mmol) in dry THF (26 mL) under N_2 at RT was added dropwise a solution of cyclohexanone **176** (0.49 g, 3.50 mmol) in dry THF (6 mL) *via* cannula (4 mL rinse) and the solution was stirred at RT for 10 min. To this solution was added dropwise MeI (1.2 mL, 19.3 mmol) and the solution was left to stir at RT overnight. The solution was diluted with Et_2O (30 mL) and the reaction was quenched by addition of $NaHCO_3$ (sat., 54 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50mL). 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 0.46 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.38 g (69% yield) of the title compound as a colourless oil (R_f = 0.27), with identical spectral data to that reported in the literature.[44]



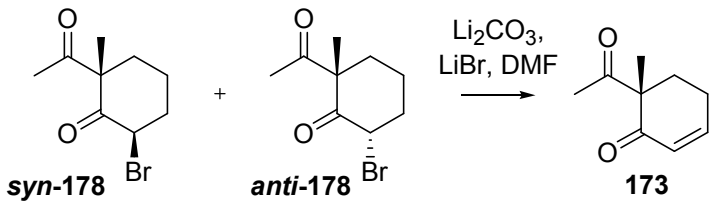
(*R*)-2-Acetyl-6-bromo-2-methylcyclohexanone (*syn*-178) and *(S)*-2-acetyl-6-bromo-2-methylcyclohexanone (*anti*-178)

To a stirring solution of cyclohexanone **177** (0.10 g, 0.65 mmol) in dry $CHCl_3$ (0.8 mL) and AcOH (glacial, 0.004 mL) under N_2 at 0 ^oC was added dropwise a bromine solution (30% Br_2 in $CHCl_3$, 0.12 mL, 0.71 mmol), with the yellow colour dissipating after addition of approx. 0.03 mL of the bromine solution, followed by a change in colour of the solution to orange. The solution was stirred at RT for 30 min and the reaction was quenched by addition of H_2O (1.5 mL). The two-phase mixture was stirred until the solution became cream in colour and the layers were separated. The organic layer was washed with $Na_2S_2O_3$ (1 M, 1 x 10 mL), $NaHCO_3$ (sat., 1 x 10 mL) and brine (1 x 10 mL), then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give 0.17 g of a colourless oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give the title compounds as colourless oils: ***syn*-178** (0.06 g, 39% yield, R_f = 0.38) and ***anti*-178** (0.08 g, 51% yield, R_f =0.25).

***syn*-178**: **IR** (film, cm^{-1}) 2944.1, 1696.1; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.30 (s, 3H, C(CH_3)), 1.35 – 1.41 (m, 1H, C(CH_3)CH_AH$_B$), 1.62 – 1.76 (m, 1H, C(CH_3)CH_2CH_ACH$_B$), 2.20 (s, 3H, C(O)CH_3), 2.23 – 2.27 (m, 3H, CH(Br)CH_2 and C(CH_3)CH_2CH$_A$CH_B), 2.56 – 2.62 (m, 1H, C(CH_3)CH$_A$$H_B$), 4.55 – 4.58 (m, 1H, C*H*(Br)); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 18.0, 22.6, 25.2, 34.7, 35.8, 52.9, 62.4, 201.7, 203.0; **HRESIMS** calculated for $C_9H_{13}BrO_2Na^+$ ($M+Na^+$): 254.9997; found: 254.9997.

***anti*-178**: **IR** (film, cm^{-1}) 2937.1, 1731.7, 1704.6; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.35 (s, 3H, C(CH_3), 1.50 – 1.62 (m, 1H, C(CH_3)CH_AH$_B$), 1.74 – 1.84 (m, 2H, C(CH_3)CH_2CH_2), 2.03 – 2.11 (m, 1H, CH(Br)CH_ACH$_B$), 2.14 (s, 3H, C(O)CH_3), 2.49 (d of quart, 1H, C(CH_3)CH$_A$$H_B$, J = 13.8, 3 Hz), 2.54 – 2.64 (m, 1H,

CH(Br)$CH_AC\mathit{H}_B$), 4.74 (d of d, 1H, C*H*(Br), *J* = 12.9, 6 Hz); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 21.6, 23.5, 25.4, 37.0, 39.5, 55.6, 64.8, 200.1, 207.2; **HRESIMS** calculated for $C_9H_{13}BrO_2Na^+$ ($M+Na^+$): 254.9997; found: 254.9997.

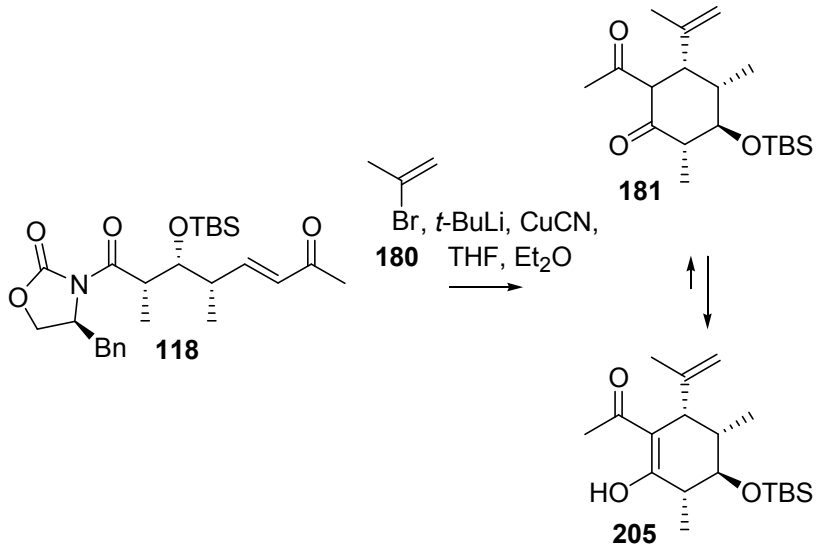


***syn*-178** ***anti*-178** **173**

6-Acetyl-6-methyl-cyclohex-2-enone (173)

To a stirring solution of bromoketones ***syn-*** and ***anti*-178** (0.10 g, 0.42 mmol) in dry DMF (14.5 mL) under N_2 at RT was added Li_2CO_3 (anhyd., 0.63 g, 8.58 mmol) and LiBr (anhyd., 0.68 g, 7.83 mmol) and the solution was heated to 150 ^oC and stirred for 15 min. After cooling to RT, the solution was filtered through a silica plug (1:1 EtOAc/hexanes) and the eluent was concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL) and the solution was washed with H_2O (1 x 50 mL, 5 x 20 mL) and brine (1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.03 g of a brown oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.03 g (40% yield) of the title compound as a colourless oil (R_f = 0.17).

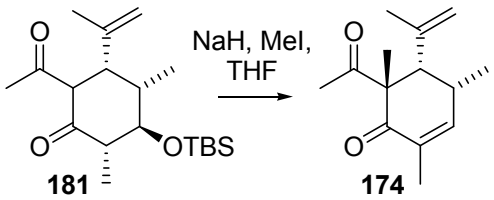
IR (film, cm^{-1}); 2931.9, 1700.0, 1672.8, 1425.2, 1357.2, 1295.2, 1221.2, 1100.6; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 1.31 (s, 3H, C($C\mathit{H}_3$), 1.75 – 1.85 (m, 1H, $C(CH_3)C\mathit{H}_ACH_B$), 2.11 (s, 3H, C(O)$C\mathit{H}_3$), 2.32 – 2.37 (m, 1H, =$CHC\mathit{H}_ACH_B$), 2.44 – 2.57 (m, 2H, $C(CH_3)CH_AC\mathit{H}_B$ and =$CHCH_AC\mathit{H}_B$), 6.04 (t of d, 1H, C(O)C*H*=, *J* = 9.9, 2.0 Hz), 6.92 – 6.98 (m, 1H, C(O)CH=C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 20.4, 23.7, 26.1, 31.7, 59.5, 128.8, 150.6, 198.9, 206.4; **HRESIMS** calculated for $C_9H_{12}O_2Na^+$ ($M+Na^+$): 175.0735; found: 175.0732.



(3*R*,4*S*,5*R*,6*S*)-2-Acetyl-5-(*tert*-butyldimethylsilyloxy)-3-isopropenyl-4,6-dimethylcyclohexanone (181) and 1-[(3*S*,4*R*,5*S*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-6-isopropenyl-3,5-dimethylcyclohex-1-enyl]-ethanone (205)

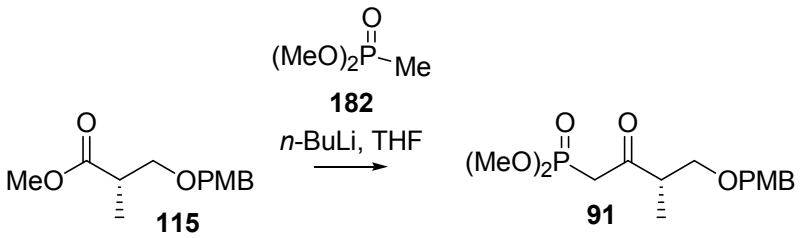
To a stirring solution of bromoalkene **180** (0.03 mL, 0.32 mmol) in dry THF (1 mL) under N_2 at – 100 ^oC was added dropwise *t*-BuLi (1.61 M in pentane, 0.45 mL, 0.72 mmol) and the resulting bright yellow solution was stirred at – 100 ^oC for 30 min. The alkyl lithium solution was added dropwise *via* pre-cooled cannula (pre-cooled by adding – 78 ^oC Et_2O to the CuCN) to a suspension of CuCN (0.016 g, 0.18 mmol) in dry Et_2O (1 mL) under N_2 at – 78 ^oC, and the resulting bright yellow solution was stirred at – 78 ^oC for 30 min, after which time the solution became colourless and homogenous. To the cuprate was added dropwise a pre-cooled solution of enone **118** (0.05 g, 0.11 mmol) in dry Et_2O (1 mL) *via* cannula and the resulting orange solution was stirred at – 60 ^oC for 40 min (colour changed from orange to brown) and the solution was warmed to 0 ^oC and stirred for a further 2 hr. The reaction was quenched at 0 ^oC by the addition of a 10% NH_4OH/90% NH_4Cl solution (10 mL) followed by stirring at RT for 10 min, after which time the aqueous layer became dark blue in colour. The two-phase system was filtered through celite and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20mL) and the organic extracts were combined, washed with brine (1 x 20mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.04 g of a clear, yellow oil. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.01 g

(29% yield) of the title compound as a colourless oil (R_f = 0.55). The compound existed predominantly in the *enol* form as indicated by ^{1}H NMR with identical spectral data to that reported in the literature.[3]



(4*R*,5*S*,6*S*)-6-Acetyl-5-isopropenyl-2,4,6-trimethylcyclohex-2-enone (174)

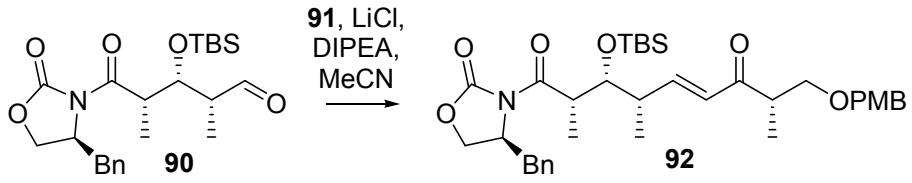
To a stirring suspension of NaH (60% dispersion in oil, 0.04 g, 0.89 mmol) in dry THF (4 mL) under N_2 at RT was added dropwise a solution of diketone **181** (0.14 g, 0.40 mmol) in dry THF (2 mL) *via* cannula (2 mL rinse) and the resulting yellow solution was stirred at RT for 10 min. To this solution was added dropwise MeI (0.20 mL, 0.32 mmol), and the resulting yellow solution was stirred at RT for 3 days. The reaction was quenched with $NaHCO_3$ (sat., 20 mL) and the mixture was extracted with Et_2O (3 x 25mL). 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 0.12 g of a brown oil. The oil was purified by flash column chromatography on silica (20% Et_2O/hexanes) to give 0.06 g (67% yield) of the title compound as a light yellow oil (R_f = 0.23), with identical spectral data to that reported in the literature.[3]



(3*S*)-Dimethyl-[4-(4-methoxybenzyloxy)-3-methyl-2-oxobutyl]-phosphonate (91)

To a stirring solution of phosphonate **182** (4.2 g, 33.7 mmol) in dry THF (40 mL) under N_2 at – 78 ^{o}C was added dropwise *n*-BuLi (1.6 M in hexanes, 21.0 mL, 33.6 mmol) and the resulting creamy suspension was stirred at – 78 ^{o}C for 1 hr. To this

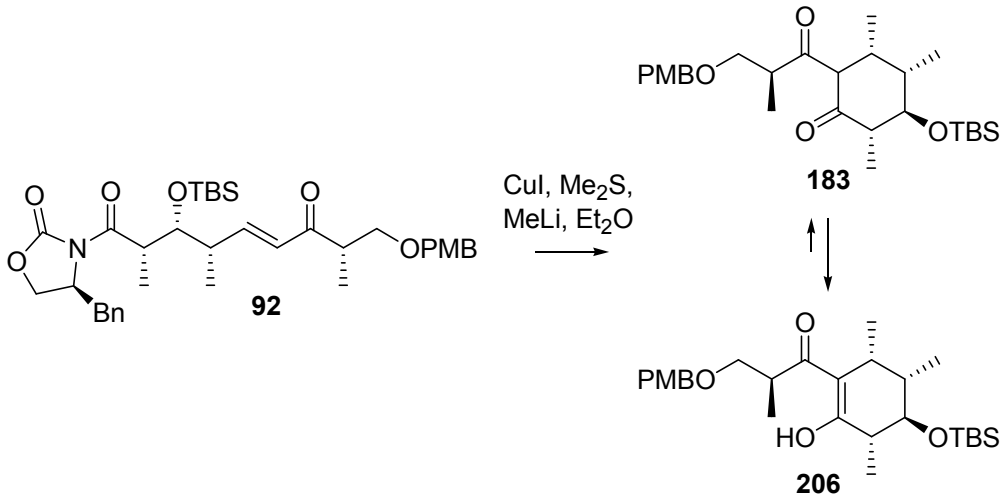
suspension was added dropwise a solution of ester **115** (2.0 g, 8.5 mmol) in dry THF (15 mL) *via* cannula (5 mL rinse) and the resulting yellow solution was stirred at – 78 ^{o}C for 30 min. The reaction was quenched by addition of AcOH (10%, 20 mL) and slowly warmed to RT with stirring. The mixture was extracted with Et_2O (3 x 20 mL) and the organic layers were combined and washed with $NaHCO_3$ (sat., 1 x 40 mL), H_2O (1 x 40 mL) and brine (1 x 40 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 1.5 g of a cloudy oil. The oil was purified by flash column chromatography on silica (2.5% MeOH/CH_2Cl_2) to give 0.96 g (65% yield) of the title compound as a colourless oil (R_f = 0.18) with identical spectral data to that reported in the literature.[35]



90 **92**

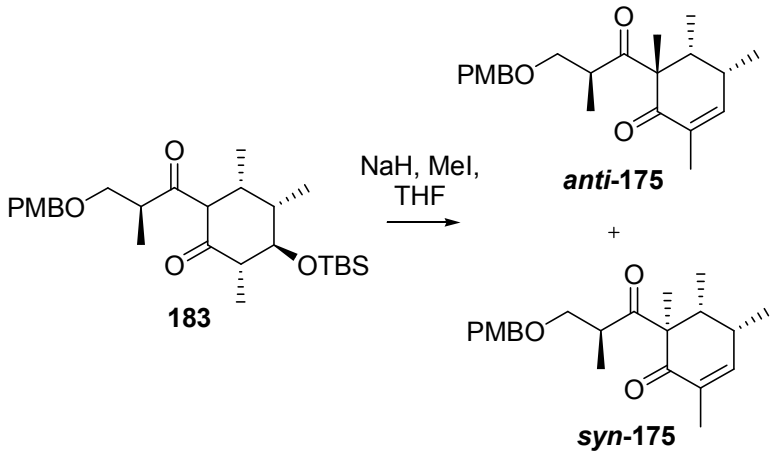
(2*S*,3*R*,4*S*,5*E*,8*S*)-1-(4-Benzyl-2-oxo-oxazolidin-3-yl)-3-(*tert*-butyldimethyl-silyloxy)-9-(4-methoxybenzyloxy)-2,4,8-trimethylnon-5-ene-1,7-dione (92)

To a stirring solution of phosphonate **91** (0.74 g, 2.24 mmol) and LiCl (anhyd., 0.10 g, 2.36 mmol) in dry MeCN (7 mL) under N_2 at RT was added dropwise DIPEA (0.35 mL, 2.01 mmol) followed by a solution of aldehyde **90** (0.81 g, 1.87 mmol) in dry MeCN (4 mL) *via* cannula (2 mL rinse), and the resulting yellow solution was left to stir at RT for 4 days. The reaction was diluted with Et_2O (7 mL) and quenched with $NaHCO_3$ (sat., 12 mL). 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 50 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 1.6 g of a light brown oil. The oil was purified by flash column chromatography on silica (2.5% Et_2O/CH_2Cl_2) to give 0.63 g (53% yield) of the title compound as a cloudy, pale yellow oil (R_f = 0.26) with identical spectral data to that reported in the literature.[35]



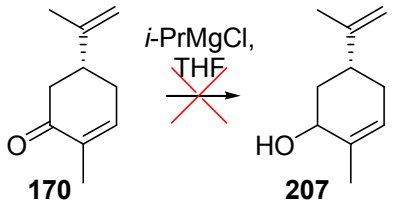
(2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,5-trimethylcyclohexanone (183) and (2*S*)-1-[(3*S*,4*R*,5*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-3,5,6-trimethylcyclo-hex-1-enyl]-3-(4-methoxy-benzyloxy)-2-methylpropan-1-one (206)

To a stirring suspension of CuI (0.12 g, 0.62 mmol) in dry Et_2O (1 mL) and dry Me_2S (2 mL) under N_2 at RT was added dropwise MeLi (1.6 M in Et_2O, 0.78 mL, 1.24 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 **92** (0.19 g, 0.31 mmol) in dry Et_2O (1 mL) *via* cannula (0.4 mL rinse), resulting in the formation of a yellow precipitate and the suspension was stirred at RT for 1 hr (the solution changed in colour from yellow to orange/green to black). The mixture was diluted with Et_2O (3 mL) and the reaction was quenched by slow addition of a 10% NH_4OH/90% NH_4Cl solution (7.2 mL). The two-phase system was stirred for 10 min at RT, 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 20 mL). The organic extracts were combined and washed with brine (1 x 40 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.17 g of a yellow oil. The oil was purified by flash column chromatography on silica (20% Et_2O/hexanes) to give 0.08 g (55% yield) of the title compound as a colourless oil (R_f = 0.65 *keto* form, 0.15 *enol* form). The compound existed in predominantly the *enol* form, with identical spectral data to that reported in the literature.[35]



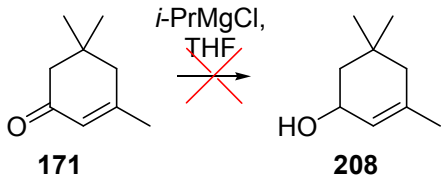
(4*R*,5*R*,6*S*)-6-[(2*S*)-3-(4-Methoxybenzyloxy)-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (*anti*-175) and (4*R*,5*R*,6*R*)-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (*syn*-175)

To a stirring suspension of NaH (60% dispersion in oil, 0.015 g, 0.38 mmol) in dry THF (2 mL) under N_2 at RT was added dropwise a solution of the diketone **183** (0.08 g, 0.17 mmol) in dry THF (1 mL) *via* cannula (0.4 mL rinse), and the resulting colourless solution was stirred at RT for 10 min. To this solution was added dropwise MeI (0.074 mL, 1.19 mmol) and the solution was left to stir at RT for 5 days (during this time, an additional 3 aliquots (3 x 0.004 g) of NaH were added to aid in elimination). The reaction mixture was diluted with Et_2O (2 mL) and reaction was quenched by addition of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined and washed with brine (1 x 30 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a brown oil. The oil was purified by flash column chromatography on silica (30% Et_2O/hexanes) to give 0.02 g (32% yield) of the title compounds as a colourless oil and an inseparable mixture in a 1:1.3 (*anti*:*syn*) ratio (R_f = 0.21), with identical spectral data to that reported in the literature.[35]



(*R*)-5-Isopropenyl-2-methylcyclohex-2-enol (207)

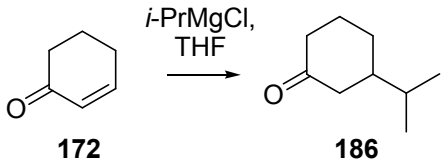
To a stirring solution of cyclohexenone **170** (0.05 g, 0.33 mmol) in dry THF (0.9 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.17 mL, 0.33 mmol) and the solution was stirred at – 50 ^oC for 30 min. After this time, was added another aliquot of *i*-PrMgCl (0.17 mL, 0.33 mmol) and the solution was stirred at – 50 ^oC for 30 min. The solution was warmed to 0 ^oC and stirring continued at 0 ^oC for 1 hr and at RT for 1 hr. The solution was cooled to 0 ^oC and was diluted with Et_2O (1 mL). The reaction was quenched by addition of NH_4Cl (sat., 2 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL) and CH_2Cl_2 (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 0.02 g of starting material.



3,5,5-Trimethylcyclohex-2-enol (208)

To a stirring solution of cyclohexenone **171** (0.10 g, 0.72 mmol) in dry THF (1.9 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 3 x 0.36 mL, 3 x 0.72 mmol) every 30 min for 1.5 hr. The solution was warmed to 0 ^oC and stirring continued at 0 ^oC for 30 min and at RT for 30 min. The solution was cooled to 0 ^oC and diluted with Et_2O (1 mL). The reaction was quenched by addition of NH_4Cl (sat., 15 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL) and CH_2Cl_2 (3 x 25 mL). The organic extracts were combined and washed with brine (1 x 50 mL), then dried

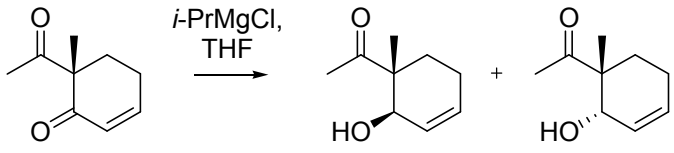
($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.09 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.06 g of starting material (R_f = 0.11).



172 **186**

3-Isopropylcyclohexanone (186)

To a stirring solution of cyclohexenone **172** (0.05 g, 0.52 mmol) in dry THF (1.4 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.52 mL, 1.04 mmol) and the resulting solution was stirred at – 50 ^oC for 30 min and at 0 ^oC for 30 min. The solution was diluted with Et_2O (3 mL) and the reaction was quenched by addition of NH_4Cl (sat., 6 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and CH_2Cl_2 (3 x 10 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 0.078 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.05 g (67% yield) of the title compound as a colourless oil (R_f = 0.28), with identical spectral data to that reported in the literature.[45]



173 ***syn*-187** ***anti*-187**

1-(2-Hydroxy-1-methylcyclohex-3-enyl)-ethanone (187)

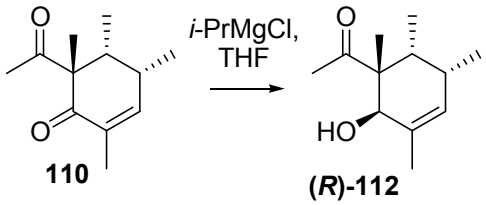
To a stirring solution of cyclohexenone **173** (0.02 g, 0.13 mmol) in dry THF (0.4 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.07 mL, 0.13 mmol) and the resulting solution was stirred at – 50 ^oC for 30 min after which time was added another aliquot of *i*-PrMgCl (0.07 mL, 0.13 mmol) and stirring continued

at – 50 ^{o}C for a further 30 min. The solution was then warmed to 0 ^{o}C and stirred at this temperature for a further 30 min. The reaction was quenched by addition of NH_4Cl (sat., 3 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 3 mL) and CH_2Cl_2 (3 x 3 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.024 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give a complex mixture, of which 0.005 g of the title compound was obtained as a colourless oil (R_f = 0.09). This was a mixture of two isomers in a 3:1 ratio, as determined by ^{1}H NMR.

IR (film, cm^{-1}) 3446.1, 1698.7, 1462.4, 1356.4, 1062.7; **HRESIMS** calculated for $C_9H_{14}O_2Na^+$ (M+Na$^+$): 177.0891; found 177.0892.

Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.17 (s, 3H, C(C*H*$_3$)), 1.67 – 1.75 (m, 1H, C(CH$_3$)C*H*$_A$H$_B$), 1.80 (d of d, 1H, C(CH$_3$)CH$_A$C*H*$_B$, *J* = 5.4 Hz), 2.05 – 2.16 (m, 2H, CH=CHC*H*$_2$), 2.18 (s, 3H, C(O)C*H*$_3$), 2.45 (s, 1H, O*H*), 4.04 (s, 1H, C*H*(OH)), 5.58 – 5.79 (m, 2H, C*H*=C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 14.9, 22.3, 25.2, 28.6, 50.8, 69.1, 127.3, 129.3, 215.1.

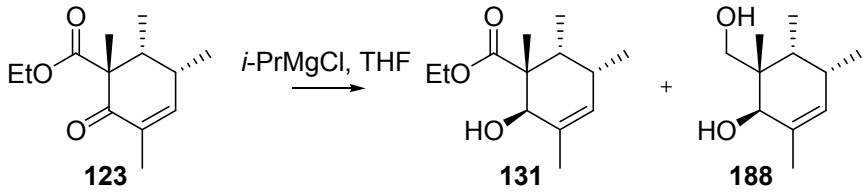
Minor isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.17 (s, 3H, C(C*H*$_3$)), 1.67 – 1.75 (m, 1H, C(CH$_3$)C*H*$_A$H$_B$), 1.84 (d of d, 1H, C(CH$_3$)CH$_A$C*H*$_B$, *J* = 5.4 Hz), 2.05 – 2.16 (m, 2H, CH=CHC*H*$_2$), 2.20 (s, 3H, C(O)C*H*$_3$), 2.74 (s, 1H, O*H*), 4.58 (s, 0.5H, C*H*(OH)), 5.58 – 5.79 (m, 2H, C*H*=C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 20.0, 22.8, 25.2, 26.6, 51.0, 71.1, 128.3, 129.0, 215.1.



(1*R*,2*R*,5*R*,6*R*)-1-(2-Hydroxy-1,3,5,6-tetramethylcyclohex-3-enyl)-ethanone ((*R*)-112)

To a stirring solution of cyclohexenone **110** (0.05 g, 0.25 mmol) in dry THF (0.7 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.15 mL, 0.30 mmol) and the resulting solution was stirred at – 50 ^oC for 30 min and at 0 ^oC for 30 min. The solution was diluted with Et_2O (2 mL) and the reaction was quenched by addition of NH_4Cl (sat., 5 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and CH_2Cl_2 (3 x 10 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 0.05 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.03 g (48% yield) of the title compound as a colourless oil (R_f = 0.10).

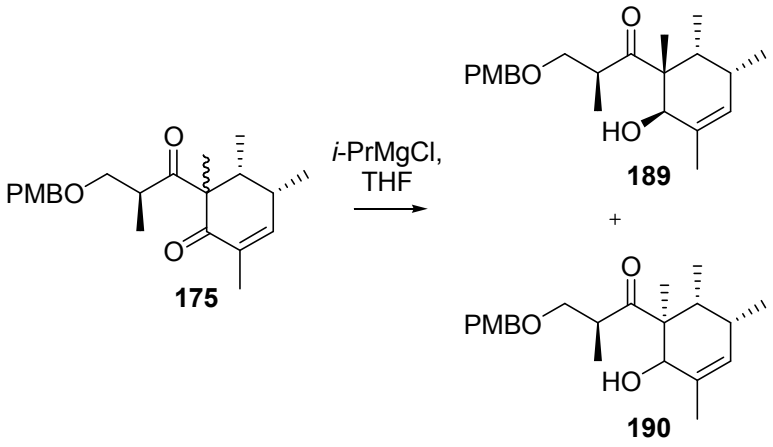
$[\alpha]_D^{20}$ = – 105.9 (1.35, $CHCl_3$); **IR** (film, cm^{-1}) 3500.0, 2971.2, 1694.9; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.65 (d, 3H, C(CH_3)CH(C*H*$_3$), *J* = 7.2 Hz), 0.93 (d, 3H, =CHCH(C*H*$_3$), *J* = 7.5 Hz), 1.17 (s, 3H, C(C*H*$_3$)), 1.73 – 1.75 (m, 3H, C(C*H*$_3$)=), 1.98 – 2.08 (m, 1H, C(CH_3)C*H*(CH_3)), 2.15 (s, 3H, C*H*$_3$C(O)), 2.34 (bs, 1H, O*H*), 2.56 – 2.70 (m, 1H, =CHC*H*(CH_3)), 4.53 (s, 1H, C*H*(OH)), 5.07 – 5.08 (m, 1H, =C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 11.3, 17.5, 18.1, 19.4, 24.5, 30.0, 40.2, 56.6, 69.2, 126.0, 133.5, 216.0; **HRESIMS** calculated for $C_{12}H_{20}O_2Na^+$ ($M+Na^+$): 219.1361; found 219.1362.



(1*R*,2*R*,5*R*,6*R*)-2-Hydroxy-1,3,5,6-tetramethylcyclohex-3-ene-ethylester (131) and (1*R*,4*R*,5*R*,6*S*)-6-hydroxy-methyl-2,4,5,6-tetramethylcyclohex-2-enol (188)

To a stirring solution of cyclohexenone **123** (0.069 g, 0.031 mmol) in dry THF (1 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.30 mL, 0.062 mmol), and the resulting clear and colourless solution was left to stir at – 50 ^oC for 30 min. The solution was warmed to 0 ^oC and stirred at this temperature for 30 min. The reaction was quenched by addition of NH_4Cl (sat., 2 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL). The organic layers were combined and washed with brine (1 x 40 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give a colourless oil. The oil was purified by flash column chromatography on silica (20% Et_2O/hexanes) to give two products: ester **131** (0.04 g, 59% yield, $R_f = 0.26$) and diol **188** (0.003g, 4% yield, $R_f = 0.18$) as colourless oils. Ester **131** had identical spectral data to that reported previously.

Diol 188: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.69 (d, 3H, =CHCH(C*H*$_3$), *J* = 6.9 Hz), 0.92 (d, 3H, C(CH$_3$)CH(C*H*$_3$), *J* = 7.5 Hz), 1.22 (s, 3H, C(C*H*$_3$)), 1.58 (bs, 2H, O*H*), 1.76 (s, 3H, C(C*H*$_3$)=CH), 2.06 – 2.11 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 2.54 – 2.56 (m, 1H, =CHC*H*(CH$_3$)), 3.74 (s, 2H, C*H*$_2$), 4.53 (s, 1H, C*H*(OH)), 5.10 (s, 1H, =C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 11.6, 17.9, 18.0, 19.4, 29.8, 40.3, 51.6, 52.1, 69.8, 126.7, 132.7.



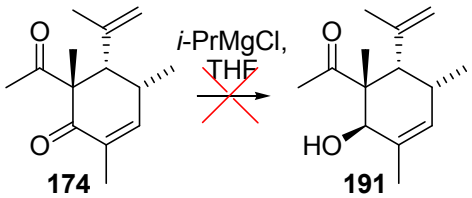
1-[(1*R*,2*R*,5*R*,6*R*)-(2-Hydroxy-1,3,5,6-tetramethyl-cyclohex-3-enyl)]-3-(4-methoxy-benzyloxy)-2*S*-methylpropan-1-one (189) and 1-[(1*S*,5*R*,6*R*)-(2-hydroxy-1,3,5,6-tetramethyl-cyclohex-3-enyl)]-3-(4-methoxy-benzyloxy)-2*S*-methylpropan-1-one (190)

To a stirring solution of ***anti*-** and ***syn*-175** (0.02 g, 0.05 mmol) in dry THF (0.2 mL) under N_2 at – 50 ^oC was added dropwise *i*-PrMgCl (2 M in THF, 0.06 mL, 0.12 mmol) and the resulting solution was stirred at – 50 ^oC for 1 hr and at 0 ^oC for 30 min. The solution was diluted with Et_2O (1 mL) and the reaction was quenched by addition of NH_4Cl (sat., 2 mL), and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL) and CH_2Cl_2 (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 0.02 g of a colourless oil. The oil was purified by flash column chromatography on silica (30% EtOAc/hexanes) to give the title compounds as colourless oils: **189** (0.006 g, 31% yield, $R_f = 0.16$) and **190** (0.005 g, 25% yield, $R_f = 0.28$).

Alcohol 189: $[\alpha]_D^{20}$ = – 42.9 (0.07, $CHCl_3$); **IR** (film, cm^{-1}) 3481.0, 2966.2, 2876.3, 1695.3, 1519.6, 1458.3, 1254.0, 1098.8, 1037.5; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.58 (d, 3H, C(CH_3)CH(CH_3), J = 6.9 Hz), 0.90 (d, 3H, =CHCH(CH_3), J = 7.5 Hz), 1.09 (d, 3H, CH_2CH(CH_3), J = 6.3 Hz), 1.21 (s, 3H, C(CH_3)), 1.75 (s, 3H, C(CH_3)=), 1.89 (bs, 1H, O*H*), 2.06 – 2.10 (m, 1H, C(CH_3)C*H*(CH_3)), 2.55 – 2.67 (m, 1H, =CHC*H*(CH_3)), 3.30 – 3.37 (m, 2H, OCH_2), 3.60 – 3.68 (m, 1H, CH_2C*H*(CH_3)), 3.80 (s, 3H, OCH_3), 4.35 – 4.44 (m, 2H, CH_2Ar), 4.60 (s, 1H, C*H*(OH)), 5.08 (s, 1H,

=C*H*), 6.85 – 7.23 (m, 4H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 11.2, 13.4, 16.7, 17.9, 19.4, 30.1, 39.1, 40.7, 55.4, 57.5, 66.0, 69.1, 72.9, 73.1, 113.9, 126.5, 129.4, 132.2, 133.6, 220.3; **HRESIMS** calculated for $C_{22}H_{32}O_4Na^+$ ($M+Na^+$): 383.2199; found 383.2188.

Alcohol 190: $[\alpha]_D^{20}$ = – 30.0 (0.10, $CHCl_3$); **IR** (film, cm^{-1}) 3570.9, 2974.3, 2876.3, 1699.4, 1617.7, 1519.6, 1462.4, 1249.9, 1102.8, 1037.5; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ (ppm) 0.65 (d, 3H, C(CH_3)CH(CH_3), *J* = 7.2 Hz), 0.93 (d, 3H, =CHCH(CH_3), *J* = 7.2 Hz), 1.06 (d, 3H, CH_2CH(CH_3), *J* = 6.3 Hz), 1.22 (s, 3H, C(CH_3)), 1.75 – 1.76 (m, 3H, C(CH_3)=), 1.78 (bs, 1H, O*H*), 1.98 – 2.06 (m, 1H, C(CH_3)C*H*(CH_3)), 2.56 – 2.66 (m, 1H, =CHC*H*(CH_3)), 3.33 (d of d, 2H, OCH_2, *J* = 10.5, 4.8 Hz), 3.59 – 3.65 (m, 1H, CH_2C*H*(CH_3)), 3.80 (s, 3H, OCH_3), 4.39 (s, 2H, CH_2Ar), 4.56 (s, 1H, C*H*(OH)), 5.08 (s, 1H, =C*H*), 6.84 – 7.22 (m, 4H, PMB Ar*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 11.8, 15.8, 16.3, 17.9, 19.4, 30.0, 39.1, 40.4, 55.4, 57.4, 66.1, 69.1, 73.0, 73.5, 113.9, 126.3, 129.3, 130.3, 133.7, 219.8; **HRESIMS** calculated for $C_{22}H_{32}O_4Na^+$ ($M+Na^+$): 383.2199; found 383.2188.

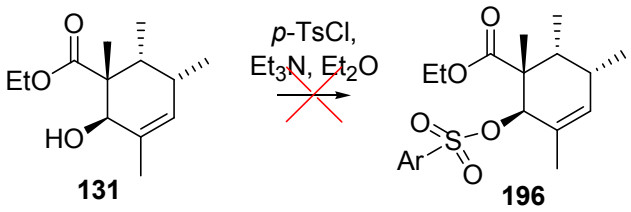


174 **191**

(1*R*,2*R*,5*R*,6*S*)-1-(2-Hydroxy-6-isopropenyl-1,3,5-trimethylcyclohex-3-enyl)-ethanone (191)

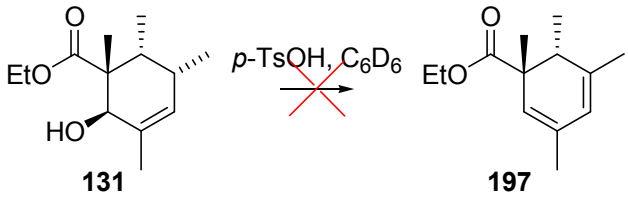
To a stirring solution of cyclohexenone **174** (0.06 g, 0.27 mmol) in dry THF (1 mL) under N_2 at – 50 °C was added dropwise *i*-PrMgCl (2 M in THF, 0.13 mL, 0.26 mmol) and the resulting solution was stirred at – 50 °C for 30 min, after which time was added dropwise another aliquot (0.13 mL, 0.26 mmol) of *i*-PrMgCl. Stirring continued at – 50 °C for 30 min, then at 0 °C for 30 min and at RT for 1 hr. The solution was cooled to 0 °C and diluted with Et_2O (1 mL). The reaction was quenched by addition of NH_4Cl (sat., 8 mL) and slowly warmed to RT with stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15

mL) and CH_2Cl_2 (3 x 15 mL). The organic extracts were combined and washed with brine (1 x 50 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.05 g of a colourless oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.03 g of starting material.



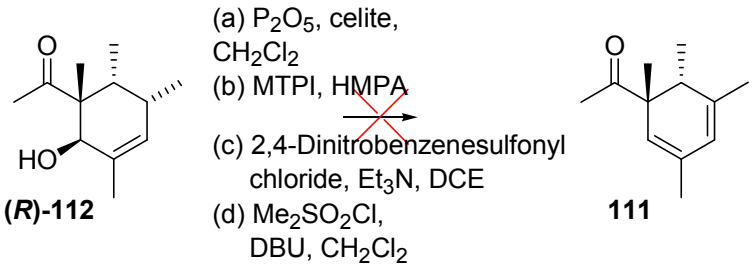
2-Benzenesulfonyloxy-1,3,5,6-tetramethylcyclohex-3-ene-ethylester (196)

To a stirring solution of allylic alcohol **131** (0.02 g, 0.08 mmol) in dry Et_2O (1 mL) under N_2 at RT was added dropwise Et_3N (0.02 mL, 0.15 mmol) and the solution was left to stir for 10 min. To the mixture was added dropwise a solution *p*-TsCl (0.02 g, 0.09 mmol) in dry Et_2O (1 mL) *via* cannula (0.2 mL rinse). After 2 days at RT, TLC (20% Et_2O/hexanes) indicated the consumption of *p*-TsCl, and therefore another aliquot of Et_3N (0.01 mL, 0.09 mmol) and *p*-TsCl (0.02 g, 0.09 mmol) was added. After 5 days, TLC did not indicate consumption of starting material or presence of *p*-TsCl. The reaction was quenched by addition of $NaHCO_3$ (sat., 2 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the organic extracts were combined, washed with brine (1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.029 g of a yellow oil and salt. The oil was purified by flash column chromatography on silica (CH_2Cl_2) to give 0.01 g of starting material.



(1*S*,6*R*)-1,3,5,6-Tetramethylcyclohexa-2,4-diene-ethylester (197)

To an NMR tube containing allylic alcohol **131** (0.009 g, 0.04 mmol) in dry C_6D_6 were added a few crystals of *p*-TsOH and the reaction was monitored by ^{1}H NMR. After 2 hr no change was observed. Two drops of TFA were added and the reaction continued to be monitored by ^{1}H NMR. After 2 hr NMR indicated significant changes and hence reaction was quenched by addition to stirring $NaHCO_3$ (sat., 3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.013 g of a light brown oil. ^{1}H NMR indicated that a complex mixture of compounds had formed.



(1*S*,6*R*)-1-(1,3,5,6-Tetramethylcyclohexa-2,4-dienyl)-ethanone (111)

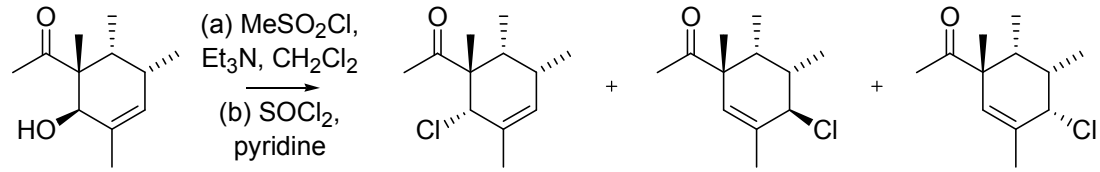
(a) To a stirring solution of MTPI (0.06 g, 0.14 mmol) in dry HMPA (0.1 mL) under N_2 at RT was added dropwise a solution of allylic alcohol **(*R*)-112** (0.025 g, 0.13 mmol) in dry HMPA (0.1 mL) *via* cannula (0.1 mL rinse), and the solution was warmed to 50 ^{o}C. After 72 hr, TLC (20% EtOAc/hexanes) indicated the presence of only starting material. To the solution was added another aliquot of MTPI (0.056 g, 0.12 mmol) and after stirring at 50 ^{o}C for 85 hr, TLC did not indicate the consumption of starting material. The solution was cooled to RT and diluted with Et_2O. The reaction was quenched by addition of H_2O (2 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 2 mL) and the organic

extracts were combined, washed with H_2O (3 x 10 mL) and brine (1 x 10 mL), and solvents were removed *in vacuo*. The brown residue was diluted with CH_2Cl_2 (10 mL) and the solution was passed through a silica plug to give 0.03 g of a red oil, which was identified as MTPI by ^1H NMR. The silica plug was flushed with Et_2O to give 0.008 g of starting material as a colourless oil.

(b) To a stirring solution of allylic alcohol **(*R*)-112** (0.02 g, 0.10 mmol) and DBU (0.02 mL, 0.13 mmol) in dry CH_2Cl_2 (0.2 mL) under N_2 at – 78 ^oC was added dropwise $MeSO_2Cl$ (0.01 mL, 0.12 mmol). After 1 hr, TLC (20% EtOAc/hexanes) did not indicate the consumption of starting material and the solution was warmed to 0 ^oC and then RT. After 19 hr at RT, TLC did not indicate further consumption of starting material and to the solution was added dropwise another aliquot of DBU (0.02 mL, 0.13 mmol). The solution was cooled to 0 ^oC and was added dropwise an additional aliquot of $MeSO_2Cl$ (0.009 mL, 0.12 mmol) and the solution was warmed to RT. After 18 hr, TLC did not indicate further consumption of starting material, and reaction was warmed to 30 ^oC and left to stir at this temperature overnight. TLC did not indicate further consumption of starting material and the solution was cooled to 0 ^oC. The reaction was quenched by 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 5 mL). The organic extracts were combined, washed with $NaHCO_3$ (sat., 1 x 20 mL) and brine (1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.02 g of the starting material as a yellow oil.

(c) To a stirring solution of allylic alcohol **(*R*)-112** (0.04 g, 0.18 mmol) in dry DCE (1.7 mL) and Et_3N (0.15 mL, 0.11 mmol) under N_2 at RT was added 2,4-dinitrobenzenesulfonyl chloride (0.14 g, 0.60 mmol), and the resulting brown mixture was heated rapidly to relfux. After 20 hr at reflux, TLC (20% EtOAc/hexanes) did not indicate consumption of starting material. The solution was cooled to RT and poured onto pentane (10 mL). The yellow solution was filtered and the filtrate was concentrated *in vacuo* to give 0.06 g of a dark red oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give 0.02 g of starting material.

(d) A mixture of celite (0.07 g) and P_2O_5 (0.05 g, 0.34 mmol) was stirred vigorously under N_2 at RT for 5 min. To the mixture was added dropwise a solution of allylic alcohol **(*R*)-112** (0.009 g, 0.05 mmol) in dry CH_2Cl_2 *via* cannula (2 mL rinse) and the solution was stirred at RT for 2 hr. The solid and liquid phases were separated and the solid was washed three times with CH_2Cl_2. The organic extracts were combined and solvent was removed *in vacuo* to give 0.02 g of compound. ^{1}H NMR did not indicate the presence of any useful products. The solid was triturated with Et_2O and the organic extract was concentrated *in vacuo* to give 0.01 g of compound. ^{1}H NMR did not indicate the presence of any useful products.



(*R*)-112 **198** **(*R*)-199** **(*S*)-199**

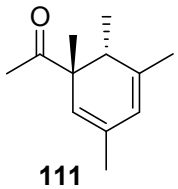
(1*S*,2*S*,5*R*,6*R*)-1-(2-Chloro-1,3,5,6-tetramethylcyclohex-3-enyl)-ethanone (198), (1*R*,4*R*,5*S*,6*R*)-1-(4-chloro-1,3,5,6-tetramethylcyclohex-2-enyl)-ethanone ((*R*)-199) and (1*R*,4*S*,5*S*,6*R*)-1-(4-chloro-1,3,5,6-tetramethylcyclohex-2-enyl)-ethanone ((*S*)-199)

(a) To a stirring solution of allylic alcohol **(*R*)-112** (0.02 g, 0.12 mmol) in dry CH_2Cl_2 (0.45 mL) and Et_3N (0.03 mL, 0.18 mmol) under N_2 at – 78 ^{o}C was added dropwise $MeSO_2Cl$ (0.02 mL, 0.19 mmol) and the solution was warmed to 0 ^{o}C. After 30 min, TLC (20% EtOAc/hexanes) indicated the presence of predominantly starting material, and reaction was warmed to RT. After 30 min, TLC indicated no further consumption of starting material and hence the reaction was warmed to 35 ^{o}C and monitored by TLC over a 3 day period. After 3 days, TLC indicated some consumption of starting material and the appearance of a two more compounds. The solution was cooled to 0 ^{o}C and were added dropwise additional aliquots of Et_3N (0.03 mL) and $MeSO_2Cl$ (0.02 mL). The solution was heated to 35 ^{o}C and stirring continued at this temperature for 2 days, after which time starting material was still found to be present by TLC analysis. Therefore, the solution was cooled to 0 ^{o}C and were added dropwise additional aliquots of Et_3N (0.03 mL) and $MeSO_2Cl$ (0.02 mL). The solution was then warmed to 35 ^{o}C and stirring continued for 24 hr, after which

time TLC indicated complete consumption of starting material. The solution was cooled to 0 ^{o}C and the reaction was quenched by addition of $NaHCO_3$ (sat., 1 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, washed with $NaHCO_3$ (sat., 1 x 20 mL) and brine (1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.03 g of a yellow oil. The oil was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give two compounds: **198** as a white crystalline solid (0.003 g, 10% yield, R_f = 0.31), and an inseparable mixture of **(*R*)-** and **(*S*)-199** as a colourless oil (0.009 g, 32% yield, R_f = 0.25), in a 3:1 ratio ((*R*):(*S*)) as determined by ^{1}H NMR.

Chloride 198: ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.60 (d, 3H, C(CH_3)CH(CH_3), *J* = 7.0 Hz), 0.96 (d, 3H, =CHCH(CH_3), *J* = 7.4 Hz), 1.39 (s, 3H, C(CH_3)), 1.81 – 1.84 (m, 3H, C(CH_3)=), 1.83 – 2.03 (m, 1H, C(CH_3)C*H*(CH_3)), 2.16 (s, 3H, CH_3C(O)), 2.60 – 2.77 (m, 1H, =CHC*H*(CH_3)), 5.11 (bs, 1H, C*H*Cl), 5.19 – 5.21 (m, 1H, =C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 9.8, 18.1, 20.0, 21.6, 24.8, 29.6, 41.6, 56.6, 62.5, 128.7, 131.5, 209.7;.

The following compound was found in the CI-MS of **198**:



111

CIMS calculated for $C_{12}H_{18}OH^+$ ($M+H^+$): 179.1; found 179.0.

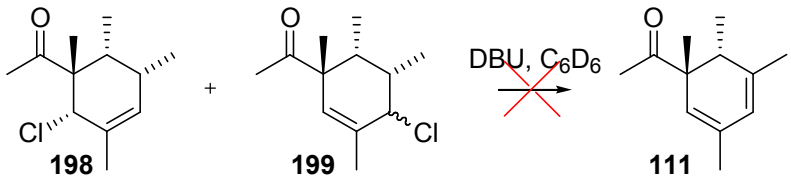
Isomers 199: IR (film, cm^{-1}): 2925.8, 1707.4, 1454.2, 1354.6, 1150.0; **CI-MS** calculated for $C_{12}H_{19}ClOH^+$ (M^+-Cl): 214.1124; found: 215.0000.

Major isomer (*R*)-199:; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ (ppm) 0.69 (d, 3H, C(CH_3)CH(CH_3), *J* = 6.8 Hz), 1.19 (d, 3H, CH(Cl)CH(CH_3), *J* = 6.8 Hz), 1.32 (s, 3H, C(CH_3)), 1.85 – 1.86 (m, 3H, =C(CH_3)), 1.95 (quart of d, 1H, C(CH_3)C*H*(CH_3), *J* = 4.8, 2.1 Hz), 2.12 (s, 3H, CH_3C(O)), 2.40 – 2.50 (m, 1H, CH(Cl)C*H*(CH_3)), 4.04 (d,

1H, C*H*(Cl), *J* = 9.6 Hz), 5.81 – 5.83 (m, 1H, C*H*=); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ (ppm) 10.1, 17.4, 21.6, 24.8, 25.6, 38.3, 41.9, 53.6, 66.3, 128.4, 132.3, 211.1.

Minor isomer (*S*)-199: ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.86 (d, 3H, C(CH_3)CH(CH_3), *J* = 7.2 Hz), 1.19 (d, 3H, CH(Cl)CH(CH_3), *J* = 6.8 Hz), 1.32 (s, 3H, C(CH_3)), 1.89 – 1.90 (m, 3H, =C(CH_3)), 1.95 (quart of d, 1H, C(CH_3)C*H*(CH_3), *J* = 4.8 ,2.1 Hz), 2.14 (s, 3H, CH_3C(O)), 2.40 – 2.50 (m, 1H, CH(Cl)C*H*(CH_3)), 4.28 (d, 1H, C*H*(Cl), *J* = 5.2 Hz), 5.76 (s, 1H, C*H*=); **^{13}C NMR** ($CDCl_3$, 300 MHz) δ (ppm) 11.7, 24.5, 24.8, 26.4, 32.1, 39.6, 41.9, 55.0, 63.5, 128.5, 132.4, 211.1.

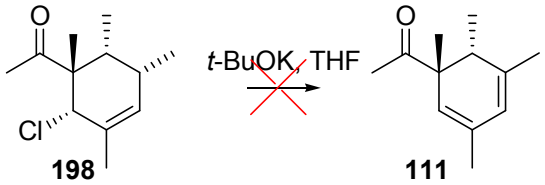
(b) To a stirring solution of allylic alcohol **(*R*)-112** (0.03 g, 0.14 mmol) in dry pyridine (0.10 mL) under N_2 at 0 °C was added dropwise $SOCl_2$ (0.01 mL, 0.15 mmol) and the resulting yellow/brown solution was warmed to RT with stirring. After 4 hr, the dark brown mixture was diluted with Et_2O (3 mL) and the reaction was quenched by addition of H_2O (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (7 x 10 mL). The organic extracts were combined, washed with H_2O (3 x 30 mL) and brine (1 x 50 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.01 g of a brown oil. The oil was purified by flash column chromatography on silica (20% EtOAc/hexanes) to give **198** and **199** (0.006 g, 20% yield) as a mixture (R_f = 0.17 – 0.31 in 10% EtOAc/hexanes), with identical spectral data to that reported previously.



(1*S*,6*R*)-1-(1,3,5,6-Tetramethyl-cyclohexa-2,4-dienyl)-ethanone (111)

To an NMR tube containing the mixture of halides **198** and **199** (0.006 g) in dry C_6D_6 was added a drop of DBU and the solution was monitored by ^{1}H NMR. After 5 hr, NMR did not indicate any change, and hence reaction was quenched by addition to stirring NH_4Cl (sat., 1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined and washed

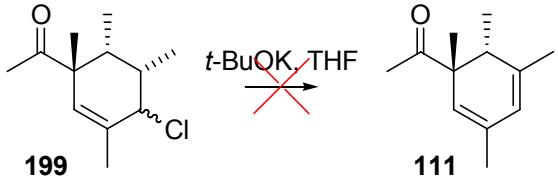
with $NaHCO_3$ (sat., 1 x 20 mL), then dried ($MgSO_4$), filtered and solvent was removed *in vacuo* to give 0.003 g of the starting materials as a brown oil.



198 **111**

(1*S*,6*R*)-1-(1,3,5,6-Tetramethyl-cyclohexa-2,4-dienyl)-ethanone (111)

To a stirring solution of halide **(*R*)-198** (0.003 g, 0.01 mmol) in dry THF (0.15 mL) under N_2 at 0 ^oC was added *t*-BuOK (0.01 g, 0.05 mmol), producing a yellow solution. After 40 min TLC (10% EtOAc/hexanes) indicated the presence of only starting material. The solution was warmed to RT and stirring continued. After 18 hr, TLC indicated presence of starting material and was added another aliquot of *t*-BuOK (0.01g, 0.05 mmol). After 24 hr, TLC did not indicate further consumption of starting material. The solution was diluted with Et_2O (1 mL) and the reaction was quenched by addition of NH_4Cl (sat., 1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 4 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried ($MgSO_4$), filtered and solvents were removed *in vacuo* to give 0.007 g of a colourless oil. The oil was purified by flash column chromatography on silica (10% EtOAc/hexanes) to give 0.002 g of starting material.



199 **111**

(1*S*,6*R*)-1-(1,3,5,6-Tetramethyl-cyclohexa-2,4-dienyl)-ethanone (111)

To a stirring solution of chlorides **(*S*)-** and **(*R*)-199** (0.01 g, 0.04 mmol) in dry THF (0.4 mL) under N_2 at 0 ^oC was added *t*-BuOK (0.02 g, 0.13 mmol), producing a yellow solution. After 40 min at 0 ^oC, TLC (10% EtOAc/hexanes) indicated presence

of only starting material. The solution was warmed to RT and stirring continued. After 18 hr, TLC indicated the presence of starting material and was added another aliquot of *t*-BuOK (0.01 g, 0.05 mmol). After 24 hr, TLC did not indicate further consumption of starting material. The solution was diluted with Et_2O (2 mL) and the reaction was quenched by addition of NH_4Cl (sat., 2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 2 mL). The organic extracts were combined and washed with brine (1 x 10 mL), then dried ($MgSO_4$), filtered and solvents were removed *in vacuo* to give 0.006 g of the starting material as a colourless oil.

2.10 References

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