An Evans-Tishchenko/Ring Closing Metathesis Approach Towards the Medium Ring Lactone, Octalactin A

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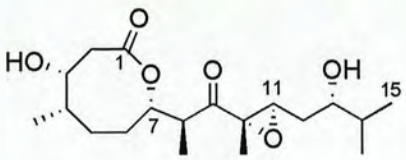
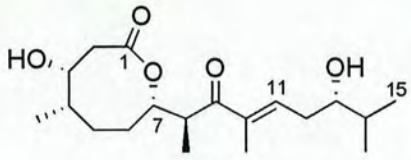
ABSTRACT

Medium-ring lactones have become important targets for synthesis as they have been isolated in an increasing number of biologically active natural products. The studies towards two 8-membered ring lactone natural products, octalactins A **1** and B **2**, will be described.

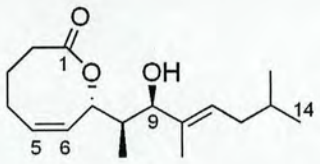


octalactin A **1**



octalactin B **2**

The first section of this thesis examines the application of key methodology (*anti* aldol reaction, Horner Wadsworth Emmons olefination, intermolecular Evans-Tishchenko coupling and Ring Closing Metathesis) towards the octalactins *via* the synthesis of a model lactone **3** (Chapter 2).



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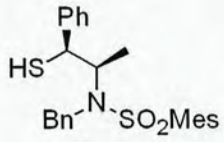

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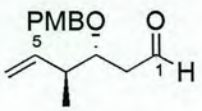
The second section (Chapter 3) discusses the extension of the aldol methodology from Chapter 2 towards the development of a novel chiral auxiliary **4** to mediate the *anti* aldol reaction. The generality of this new auxiliary in *anti* aldol reactions will also be discussed.

The final part of this thesis describes the synthesis of the octalactins based on the application of the methodology developed from the model studies using the key functionalised fragments: aldehyde **5**, β-ketophosphonate ester **6** and aldehyde **7**.



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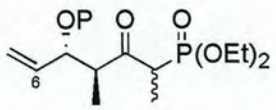

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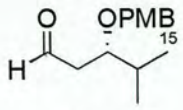

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CONTENTS

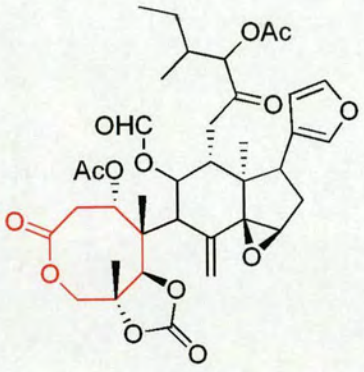
INTRODUCTION

CHAPTER 1

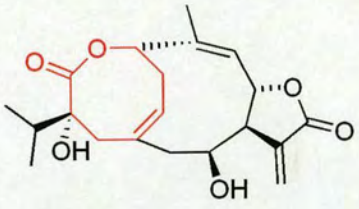
1.1 MEDIUM-RING NATURAL PRODUCTS

Medium-ring lactones (ring sizes 8 – 11) are important in organic synthesis, due to the increasing discovery of their presence in natural products that display biological activity.[1] A selection of natural products with the highlighted Medium-ring moiety is shown in **Figure 1**.

Eight-membered

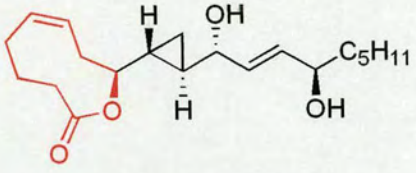


8 dregeanin



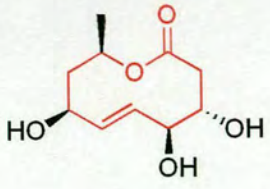
9 schkuhripinnatolide A

Nine-membered



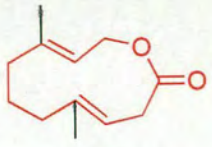
10 halicholactone

Ten-membered



11 decarestrictine D

Eleven-membered



12 suspensolide

Figure 1: *A selection of natural products containing a Medium-ring moiety*

The interesting novel lactone moiety and the overall complexity of these natural products, coupled with their biological properties, has resulted in many investigations into their synthesis.

A complex limonoid triterpene, dregeanin **8**, was isolated from the timber of the small West African tree, *Trichilia dreagoreora*[2] (and from *T. heudelotti*).[3] Schkuhripinnatolide A **9** belongs to a family of sesquiterpene lactones, which were found in the aerial part of *Schkuhria pinnata*,[4] a plant that grows principally in the tropical areas of Central and South America. Although natural products **8** and **9** have no reported biological activity, they have interesting structures that have provided a synthetic challenge for a number of groups.

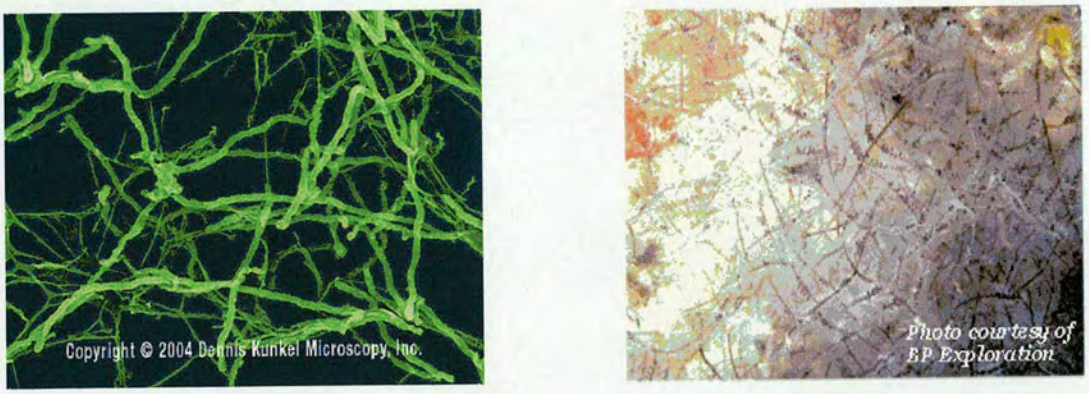
The 9-membered lactone halicholactone **10**, was isolated from a marine organism in 1989.[5,6] This fatty acid metabolite has been discovered in the sponge *Halichondri okadai*, found off the coast of Japan. It is an oxylipin has been shown to inhibit lipoxygenase.

Lactone **11** (**Figure 1**) belongs to a family of similar oxecan-2-ones called the decarestrictines. Decarestrictine D **11** (also known as tuckolide)[7] was identified during the fermentation of *Penicillum simplicissimum* and was first isolated in 1992.[8,9] This 10-membered lactone shows important inhibitory effects on cholesterol biosynthesis.[10,11]

There are a limited number of known natural products containing an 11-membered ring. The sex pheromone suspensolide **12** was isolated from the male Caribbean fruit fly, *Anastrepha suspensa Loew*, a major pest of fruit in Central and North America.[12]

1.2 THE OCTALACTINS

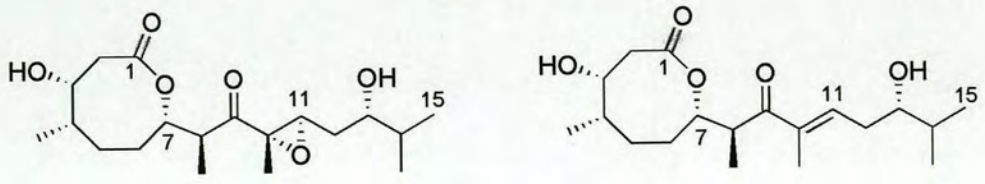
In 1991 Fenical and Clardy investigated the chemistry of micro-organisms of the marine-derived actinomycete *Streptomyces* sp. (**Figure 2a**).[13] This was collected from the gorgonian octacoral *Pacifigoria* sp. displayed in **Figure 2b**, found in the Sea of Cortez in the Gulf of Mexico.



(a) (b)

Figure 2: *(a) Electron microscopy image of Streptomyces sp.,(b) Gorgonian octacoral*

It was found that the ethyl acetate extraction of isolate PG-19 from the culture broth of *Streptomyces* sp. followed by chromatography, afforded the two metabolites octalactin A (**1**) and octalactin B (**2**) as shown in **Figure 3**.[13]



1 **2**

Figure 3: *Octalactin A 1 and octalactin B 2*

The two octalactins are interesting in that they both contain a highly oxygenated Medium-ring lactone moiety and are only differentiated from each other by a C(10) – C(11) epoxide moiety. Octalactin A has been shown to have significant *in vitro* cytotoxicity towards HCT-116 human colon cancer tumour cell lines and B-16-F10 murine melanoma.[13] Intriguingly octalactin B has no reported biological activity. This seems to suggest that the epoxide plays a key role in the biological activity of the octalactins.

The octalactins are polyketide derived natural products and it is hypothesised that they are made naturally by a series of enzymes in the Polyketide Synthase (PKS) pathway, as shown in **Figure 4**. It can be seen that the PKS pathway involves a series of aldol condensations and functional group manipulations (reductions and dehydrations) resulting in the linear polyketide. Then a thioesterase (TE) is used and the C(7) hydroxyl is activated to react with the terminal thioester to both release the polyketide from the PKS, and to allow cyclisation to occur to form octalactin B. A modification after release from the enzyme active site (selective epoxidation) would afford octalactin A. A synthetic strategy towards the octalactins could be designed on this pathway.

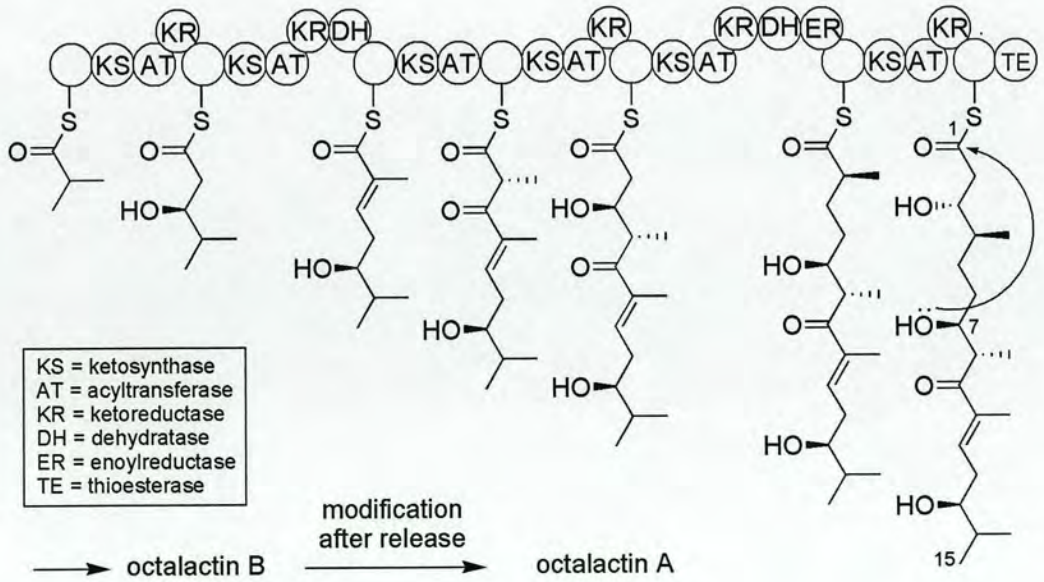


Figure 4: *Proposed PKS pathway for the synthesis of the octalactins*

1.3 PREVIOUS SYNTHESES

The presence of a novel 8-membered lactone makes octalactin A an interesting target for synthetic organic chemists. There have been a variety of synthetic approaches (**Figure 5**) towards the octalactins which involve the synthesis of lactone ring **13** *via* either: a ring closing metathesis (RCM);[14] an intramolecular Reformatsky reaction;[15] a Baeyer-Villiger oxidation;[16] a Claisen rearrangement;[17] and the most common route, a hydroxyacid macrolactonisation.[18-22] These routes towards the key fragment **13** will be discussed.

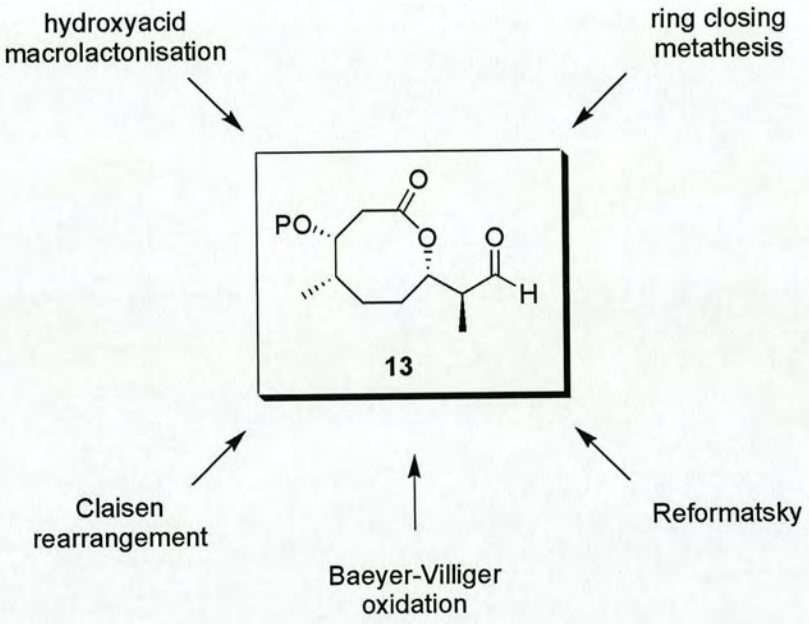
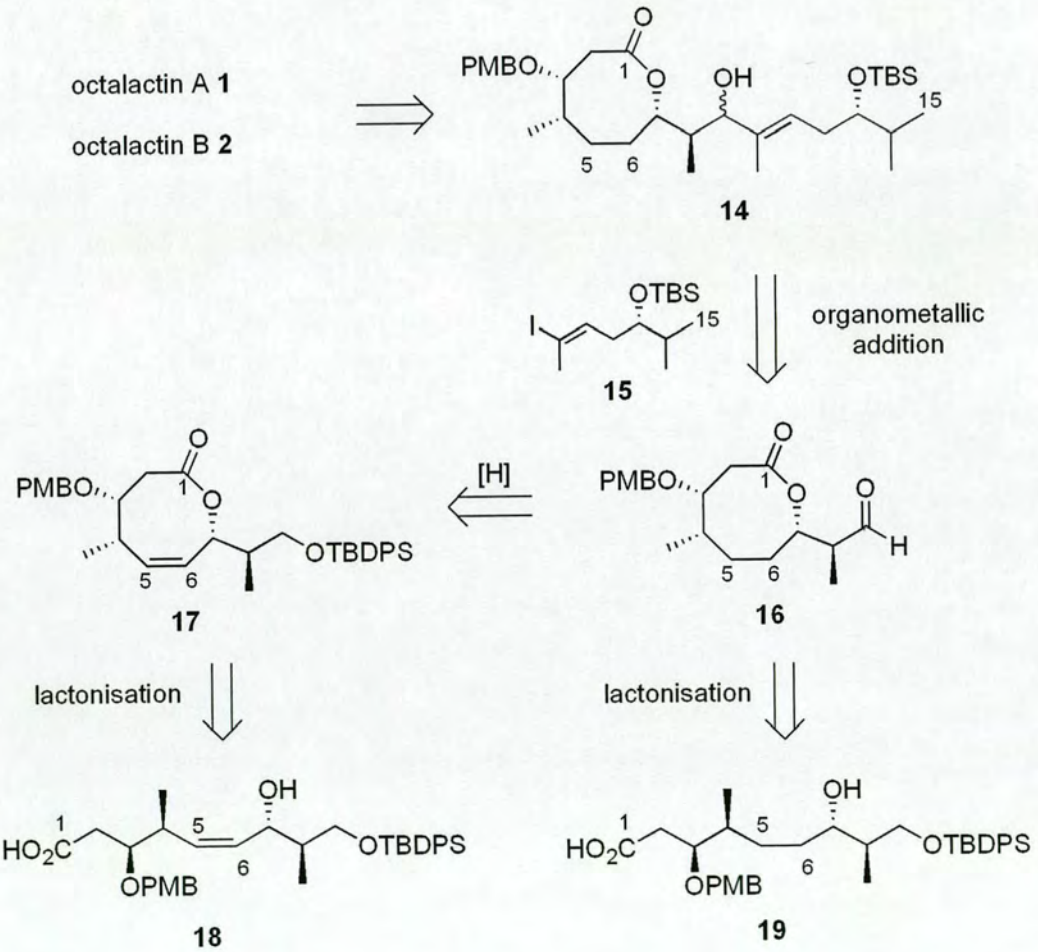


Figure 5: *Synthetic approaches to lactone 13*

1.3.1. Hydroxyacid Lactonisation

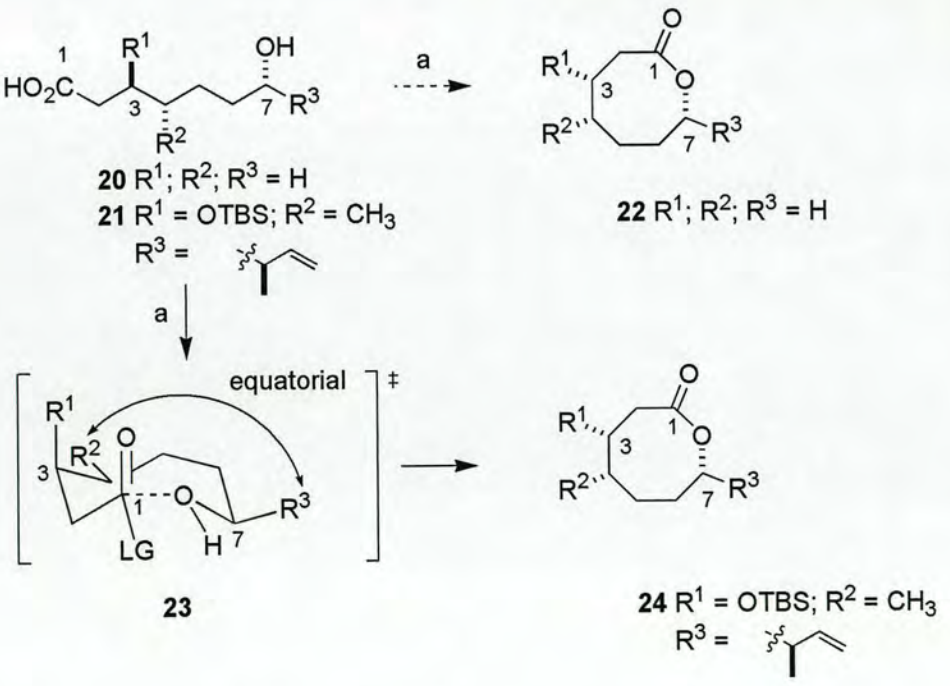
The first total synthesis of octalactin A (**Scheme 1**) was achieved by Buszek *et al.* in 1994.[18] This strategy relied upon the intramolecular lactonisation of an unsaturated carboxylic acid **18** to form oxocene **17**. Upon hydrogenation of unsaturated lactone **17** it was envisaged that aldehyde **16** could then undergo an organometallic addition with a derivative of vinyl iodide **15** at C(9) to introduce the C(10) – C(15) component of octalactin. The same reaction would result in the formation of a hydroxyl moiety and allow for a directed epoxidation onto the C(10) – C(11) alkene. Subsequent functional group manipulations would allow the formation of octalactin A.



Scheme 1: *Buszek's 1st synthesis of octalactin A*[18]

However, after the successful formation of oxocene **17** *via* lactonisation it was found that the C(5) – C(6) alkene could not be saturated even after attempts with numerous hydrogenation procedures.[18] Therefore they decided to synthesise lactone **16** from the saturated hydroxyacid **19**. Successful lactonisation of hydroxyacid **19** allowed for the efficient synthesis of lactone **16**. Organometallic addition of vinyl iodide **15** to the lactone **16** afforded advanced intermediate **14**. Subsequent functional group manipulations allowed for the first synthesis and full characterisation of the octalactins.

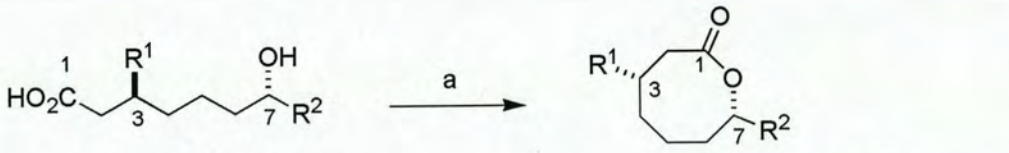
Interestingly, studies towards the lactonisation of simple hydroxyacid **20** have shown that it was impossible (**Scheme 2**) under a variety of lactonisation conditions.[23] The efficient lactonisation of hydroxyacid **21** suggests that the substituents on the hydroxyacid influence the conformation required for cyclisation. It has been proposed by Andrus *et al.*[24] that the cyclisation proceeds *via* a chair-boat conformation **23** which places the methyl and 3-butenyl groups in pseudo-equatorial positions upon cyclisation to form lactone **24**, as shown in **Scheme 2**.



Scheme 2: *Lactonisation of hydroxyacids*

Reagents and Conditions: (a) EDCI, DMAP, DMAP•HCl, $CHCl_3$, 65 °C (**22** = 0 %, **24** = 78 %).

Buszek *et al.*[23] have examined lactonisation of hydroxyacids with different substituents (**Scheme 3**) at C(3) – C(7), and have deduced that a single substituent at the C(3) is more beneficial to lactonisation than one at C(7).



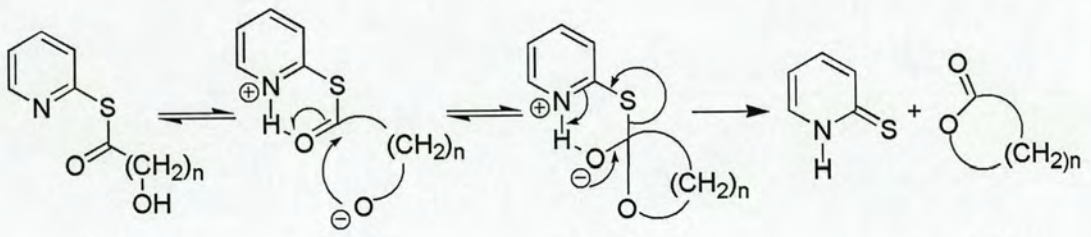
25 $R^1 = CH_3$; $R^2 = H$
26 $R^1 = H$; $R^2 = CH_2OPMB$

27 $R^1 = CH_3$; $R^2 = H$
28 $R^1 = H$; $R^2 = CH_2OPMB$

Scheme 3: *Lactonisation of hydroxyacids **25** and **26***

Reagents and Conditions: (a) (i) 2,2'-dipyridyl sulfide, PPh_3, CH_2Cl_2, RT; (ii) $AgBF_4$, PhMe, 110 °C, 48 h (**27** = 18 %, 28 = 34 %).

Since the initial synthesis of the octalactins there have been a variety of different routes to form hydroxyacid **19**.[18-21] The preceeding lactonisation of hydroxyacid **19** has been achieved using the Corey-Nicolaou double activation procedure,[25] as shown in **Scheme 4**. The method involves a proton transfer from the hydroxyl group onto the pyridine nitrogen atom to form intermediate **30**. With a nucleophilic alkoxide and an activated carbonyl group, intermediate **30** could participate in a facile, electrostatically driven, cyclisation *via* intermediate **31** to form lactone **34**.

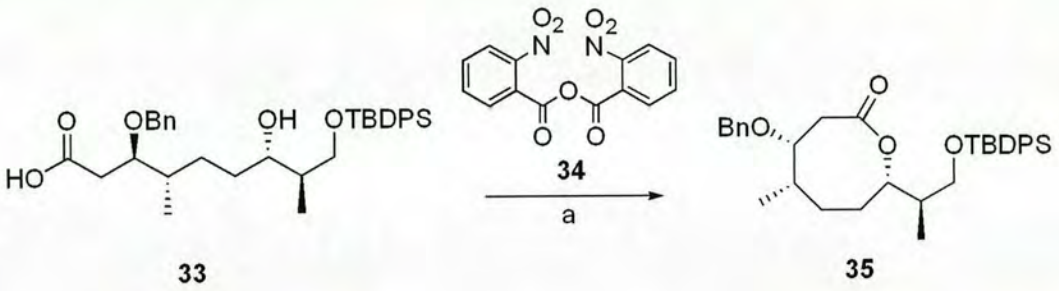


29 **30** **31** **34**

Scheme 4: *Corey-Nicolaou double activation lactonisation*

Although this technique is generally a very reliable method of lactonisation, Shiina *et al.* have reported problems with the formation of lactone **35** using the Corey-

Nicolaou protocol.[22] They have stated that high temperatures, silver additives and long reaction times (> 96 h) are required to obtain the optimum yield of only 63 %. Shiina *et al.* have reported (**Scheme 5**) an improved lactonisation procedure for the synthesis of octalactin A intermediate **35** using milder conditions. They found that treatment of hydroxyacid **33** with anhydride **34** at room temperature produced lactone **35** in good yield (90 %).[22,26]



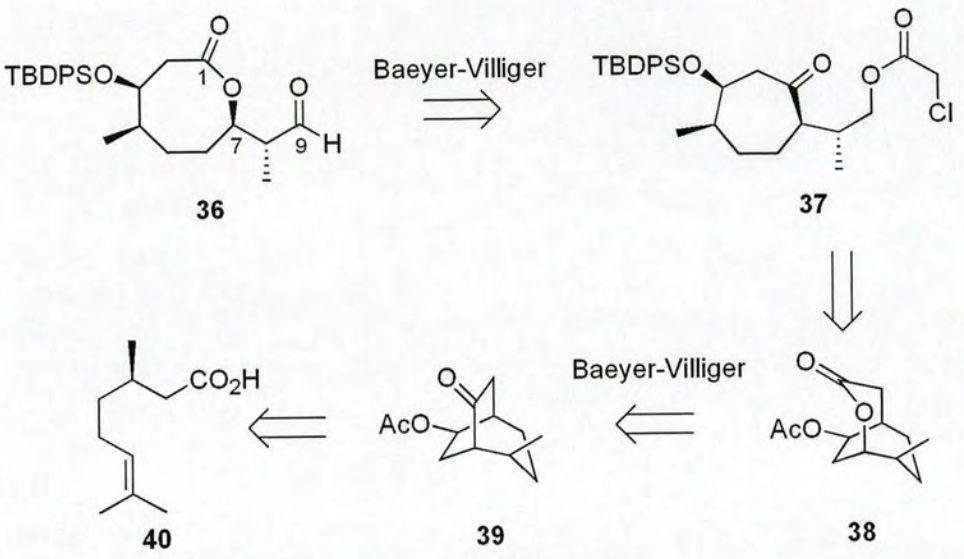
Scheme 5: *Shiina's lactonisation of hydroxyacid 33*

Reagents and Conditions: (a) **34**, DMAPO (10 mol%), Et_3N, CH_2Cl_2, RT (90 %).

Although hydroxyacid lactonisation has been a popular strategy towards intermediate **13**, there have been other interesting approaches to the formation of the 8-membered lactone.

1.3.2. Baeyer-Villiger Oxidation

In 1994 McWilliams and Clardy proposed a synthesis to determine the absolute configuration of octalactin A.[16] Their strategy involved the synthesis of lactone **36** *via* a Baeyer-Villiger oxidation of heptanone **37**. This fragment was synthesised *via* another Baeyer-Villiger oxidation of ketone **39**, derived from commercially available citronellic acid **40** (**Scheme 6**).

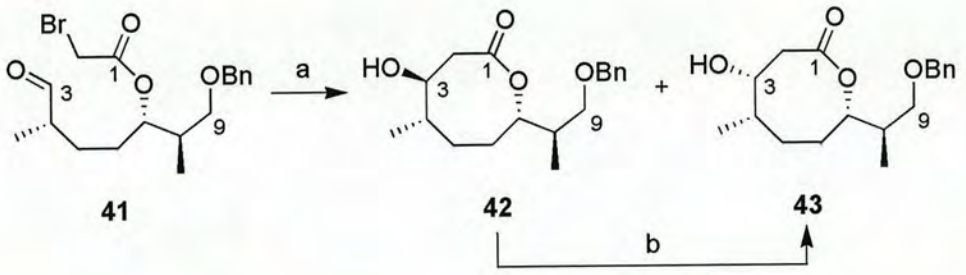


Scheme 6: *Clardy's synthesis of octalactins*

Due to the ambiguity of the absolute stereochemistry of the octalactins when Clardy *et al.* proposed their synthesis, it was found upon completion that they had synthesised the antipodes of the octalactins, *ent*-**1** and *ent*-**2**. Nevertheless, they had demonstrated an efficient method towards the key fragment **36**.

1.3.3. Reformatsky Cyclisation

Inoue *et al.* proposed a method of synthesising octalactin A in 1998 *via* an intramolecular SmI_2 promoted Reformatsky reaction of δ-(bromoacetoxy)aldehyde **41**, as shown in **Scheme 7**.[15]



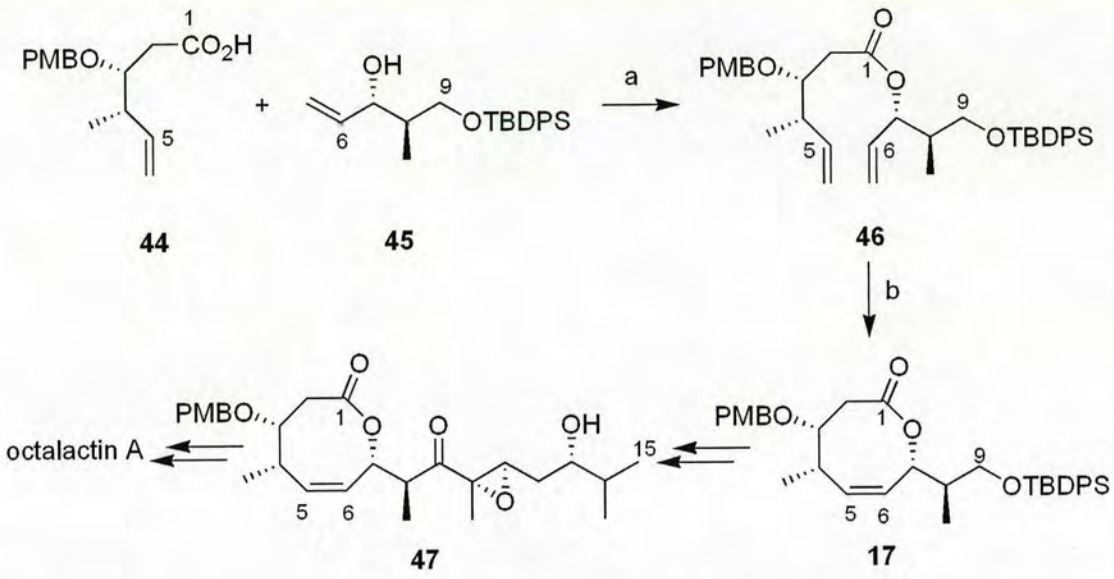
Scheme 7: *Reformatsky approach towards lactone* ***42***

Reagents and Conditions: (a) SmI_2, THF, 0 °C (63 %); (b) (i) Dess-Martin periodinane, CH_2Cl_2, (ii) $NaBH_4$, MeOH, -23 °C (92 %).

The SmI_2 promoted cyclisation of aldehyde **41**, carried out according to Inanga's protocol, resulted in the formation of the hydroxylactone as a 2:1 epimeric mixture of lactones **42** and **43**. The epimer was converted to the required alcohol *via* oxidation and subsequent reduction. Although this is a novel method of cyclisation to form the lactone **43**, the mixture of epimers at C(3) upon cyclisation makes this a less attractive route towards the octalactins.

1.3.4. Ring Closing Metathesis

Although Buszek *et al.* synthesised octalactin A *via* the novel lactonisation of saturated hydroxyacid **19**, they desired a more practical route to lactone **16**.[14] They decided to revise their original synthetic strategy and incorporate ring closing metathesis (RCM) into the construction of the 8-membered lactone ring. It was thought that stereochemical constraints favoured reactive diene formation which in turn allowed the formation of oxocene **17** *via* RCM (**Scheme 8**).

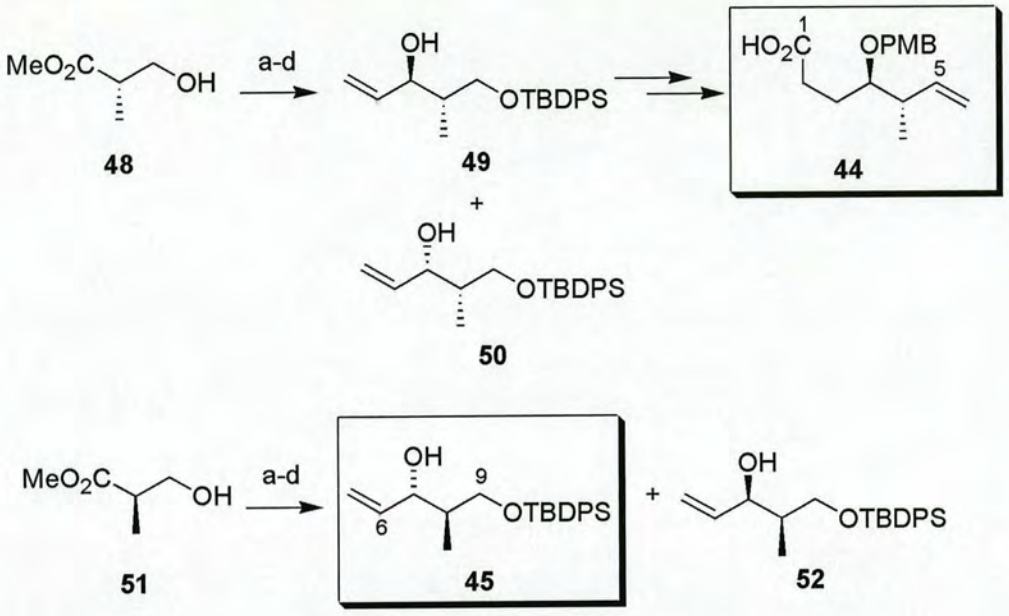


Scheme 8: *Synthesis of oxocene **19** via RCM*[14]

Reagents and Conditions: (a) DCC, DMAP, CH_2Cl_2, RT, 4 h (94 %); (b) Grubbs 1, CH_2Cl_2, 40 °C, 24 h (86 %).

The RCM precursor was synthesised by a DCC coupling of the respective C(1) – C(5) carboxylic acid **44** and the C(6) – C(9) alcohol **45**. Treatment of diene **46** with Grubbs 1st generation catalyst under reflux for 24 h afforded oxocene **17** in a good yield (86 %). Interestingly, when the alkyl chain was extended on lactone **17** to give the advanced intermediate **47**, the reduction of the C(5) – C(6) alkene was found to proceed smoothly using H_2 and Pearlman's catalyst, which was unsuccessful with oxocene **17**.[18]

Although the cyclisation of diene **46** gave the oxocene **17** in high yield, the fragments (**44** and **45**) required to synthesise the RCM precursor **46** are produced in a poor yield due to the formation of a 1:1 mixture of diastereomers in the initial synthetic steps, as shown in **Scheme 9**.



Scheme 9: *Synthesis of C(1)-C(5) and C(6)-C(9) segments*[14]

Reagents and Conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, RT; (b) DIBALH, Et_2O, -78 °C (87 % over 2 steps); (c) Dess-Martin periodinane, CH_2Cl_2, RT; (d) $(CH_2{=}CH)MgBr$, THF, -78 °C → RT (92 % over 2 steps).

The formation of the undesired diastereomers **50** and **52** allowed conformational analysis of the RCM in the formation of 8-membered lactones, as shown in **Table 1**.

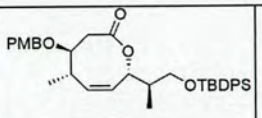
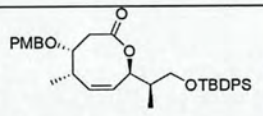
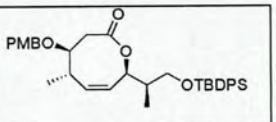
			
Epimer	**53**	**54**	**55**
Reaction Time /h	168	24	24
Yield /%	20	84	90

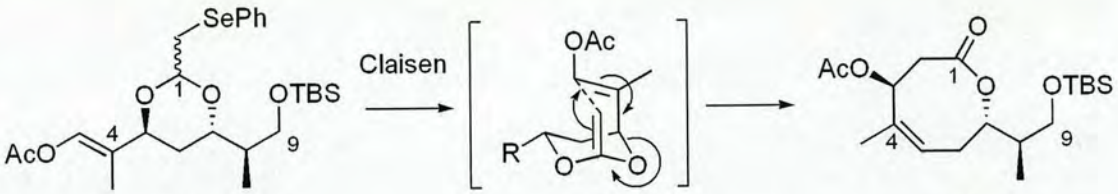
Table 1: *Synthesis of octalactin epimers via RCM*[14]

It was thought that the stereocentres in diene **46** restricted the bond angles in such a way that they lead to a conformation which favours RCM. The conformational effect

of the quaternary centres in controlling torsional angles for example, have been reported.[14] Consistent with this view is the observation that the other epimers of octalactin undergo RCM with difficulty. It was found that lactone **53** (derived from **45** and **50**) gave only a low yield under similar ring closing conditions, whereas lactones **54** (derived from **52** and **44**) and **55** (derived from **52** and **50**) formed readily *via* RCM (**Table 1**).[14]

1.3.5. Claisen Rearrangement

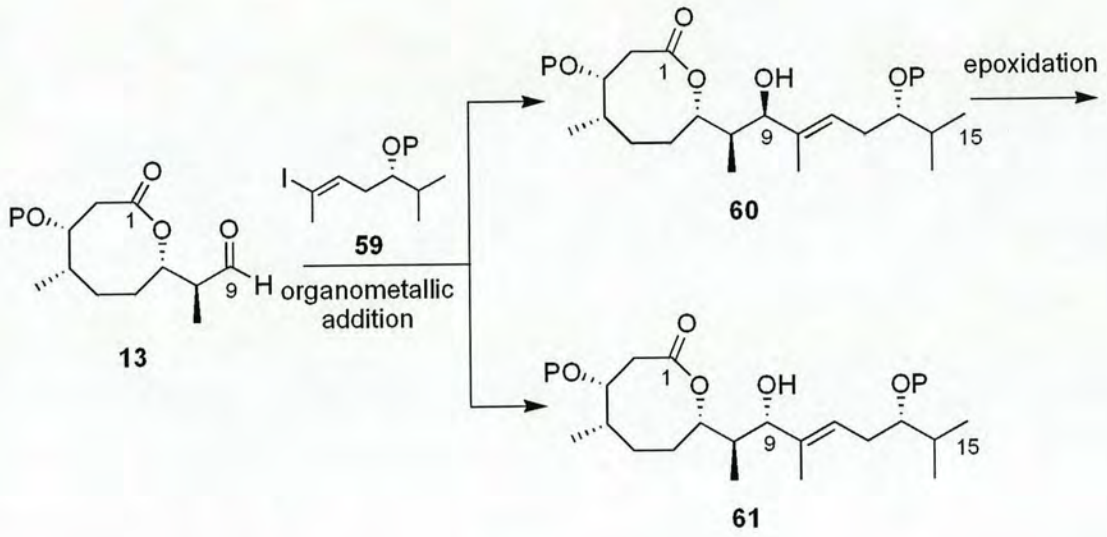
Since Buszek's synthesis of lactone **18**, there have been a variety of routes to the octalactins. Holmes *et al.* have utilized the Claisen rearrangement (**Scheme 10**) of ketene acetal **56** (9 steps from either tetraethoxymethylpropane or 3-ethoxymethacrolein) to give the key intermediate, oxocene **58** in moderate yield (40 %, 2 steps).[17] Selective hydrogenation of the C(4) – C(5) alkene allowed the formation of lactone, which could then undergo the organometallic addition, as reported by Buszek *et al.*[18]



56 **57** **58**

Scheme 10: *Holmes "Claisen" strategy to octalactin A*[17]

Most of the synthetic strategies throughout the past 12 years have relied upon the synthesis of lactone fragment **13**. However, all of these routes suffer from the significant problem of a non-selective addition to the aldehyde at C(8) leading to an epimeric mixture (**60** and **61**), as shown in **Scheme 11**.



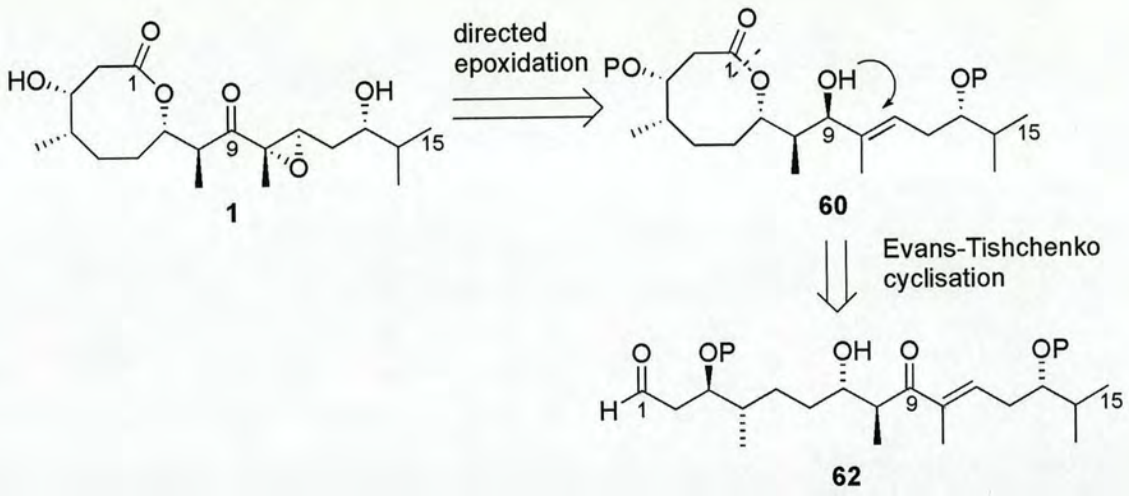
Scheme 11: *The problem of epimerisation after organometallic addition*

The original approach taken within the Hulme group was not focussed on the synthesis of oxocene **13**. This new strategy involved the analysis of the proposed enzymatic route with the aim of forming the fully functionalised backbone prior to cyclisation.

1.3.6. Intramolecular Evans-Tishchenko Cyclisation

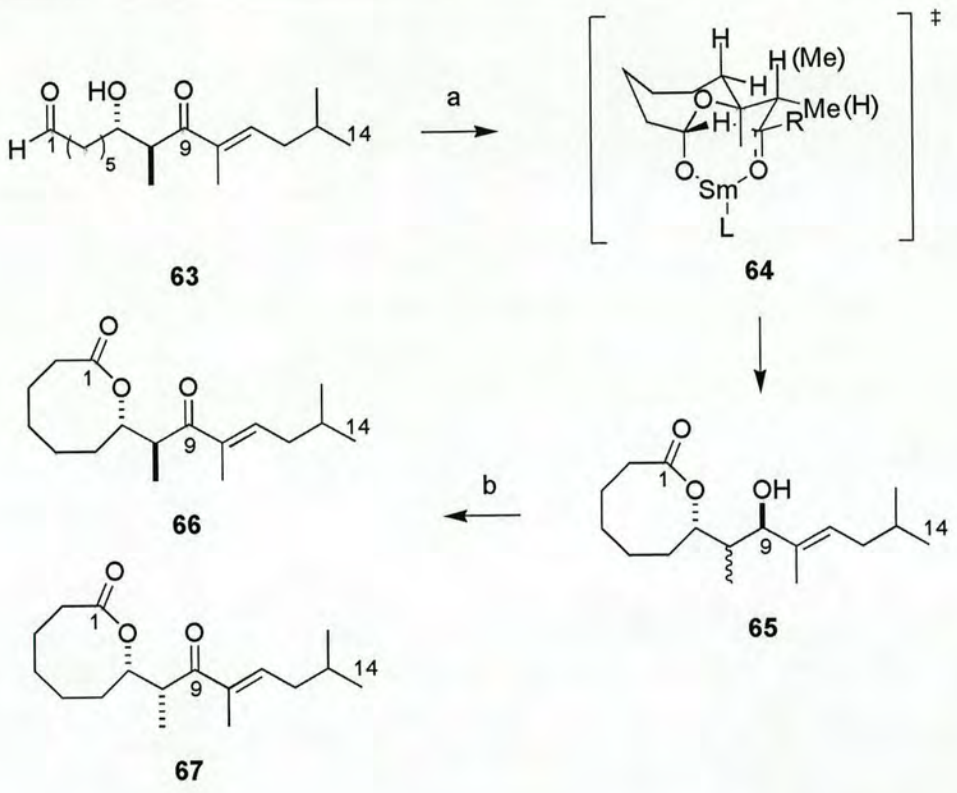
It is important to note that the simple hydroxyl selection and activation which facilitates release from the PKS, as discussed in section 1.2, is straightforward in an enzymatic environment, but to synthetically activate and target the same hydroxyl would require a careful protection strategy in order to proceed *via* a similar route. The first proposed synthetic route to octalactin A within the Hulme group involved the use of an intramolecular Evans-Tishchenko reaction[27] to cyclise seco-aldehyde **62**, as shown in **Scheme 12**. This methodology was based on the Evans-Tishchenko coupling of aldehydes and β-hydroxy ketones, which have been shown to form their respective *anti* diol monoesters in good yield with high *anti* selectivity.[28] Therefore it is proposed that when the C(1) aldehyde moiety of **62** undergoes an Evans-

Tishchenko cyclisation with the β-hydroxy enone, not only would lactonisation occur but the C(9) carbonyl would be selectively reduced to give the (*R*)-hydroxyl. With the desired hydroxyl stereochemistry, a stereoselective directed epoxidation of the C(10) – C(11) alkene could occur. The incorporation of a potentially high yielding lactonisation and the selective formation of the (*R*)-hydroxyl made this a more advantageous synthetic strategy to octalactin A than had been previously reported.



Scheme 12: *First "intramolecular Evans-Tishchenko" strategy towards octalactin A within the Hulme group*[29]

The initial model studies within the group (**Scheme 13**) had shown that treatment of simple seco-aldehyde **63** with preformed Sm(III) catalyst gave lactone **65** in a 30 % yield with an inseparable 3:1 mixture of diastereomers at C(8). Oxidation of the C(9) hydroxyl to the ketone allowed separation of the mixture and characterisation of lactone **66**.[27]



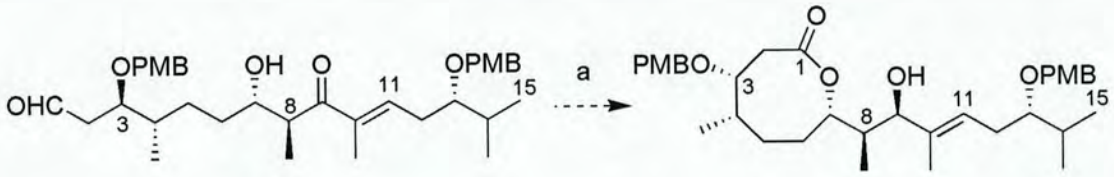
Scheme 13: *Model intramolecular Evans-Tishchenko cyclisation*

Reagents and Conditions: (a) PhCHO/SmI_2 (premixed, 0.1 M in THF, 30 mol%), THF, 0 °C, 3 h (30 %); (b) IBX, THF/DMSO, RT (82 %).

These model studies demonstrated that cyclisation to form the 8-membered lactone with formation of the (*R*)-hydroxyl could occur, albeit in low yield and as a mixture of epimers at C(8). It was believed that a more functionalised seco-aldehyde would experience the Thorpe Ingold effect[30] and improve the lactonisation yield and increase the rate of the ring forming step. The intramolecular Evans-Tishchenko cyclisation of seco-aldehyde **63** proceeds over a longer reaction time (3 h) than an intermolecular Evans-Tishchenko coupling (~30 min) which is believed to be responsible for epimerisation at C(8). If the rate of lactonisation was increased then the reaction time could be lowered and this could ultimately reduce epimerisation.

However treatment of the functionalised seco-aldehyde **68** with the Evans-Tishchenko conditions (**Scheme 14**) used for the synthesis of the model lactone gave

an inseparable mixture of unidentifiable products.[29] Further investigations towards the synthesis of octalactin A *via* an intramolecular Evans-Tishchenko cyclisation were not pursued due to a limited supply of material.



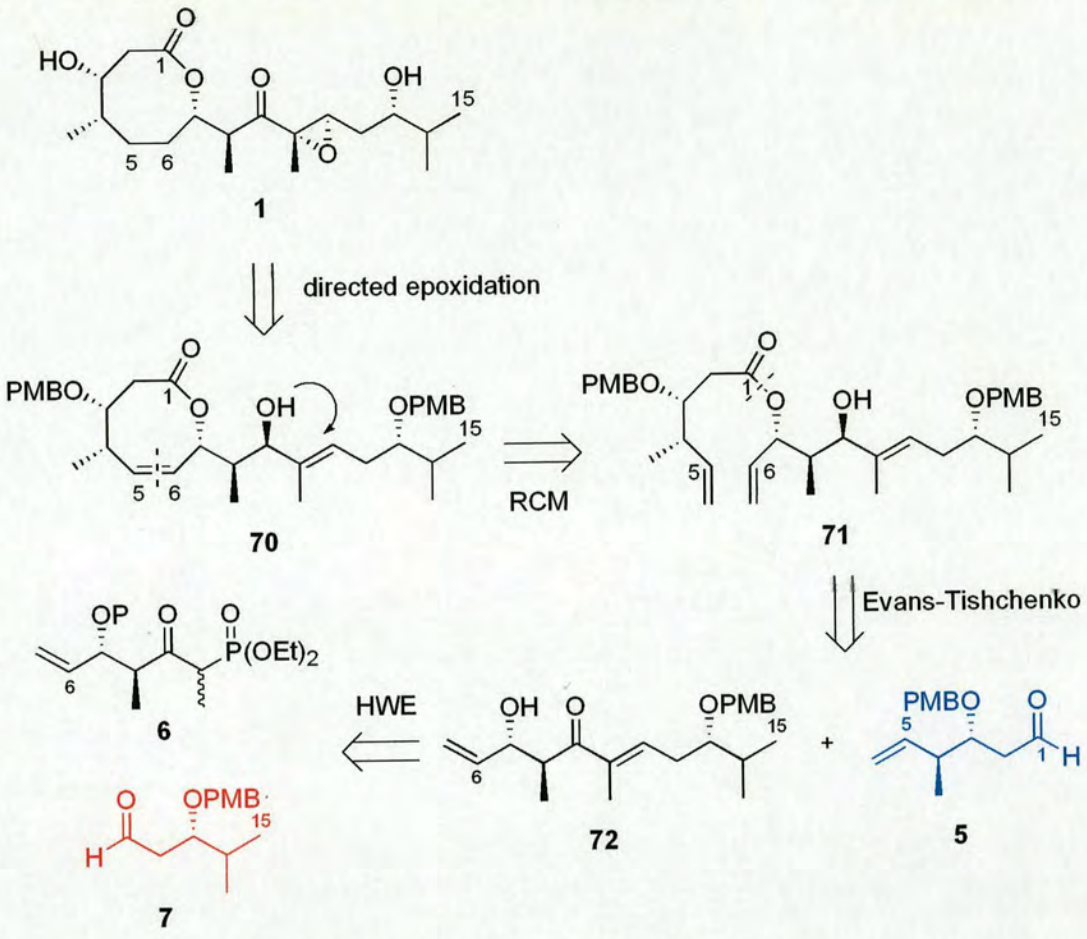
68 **69**

Scheme 14: *Model intramolecular Evans-Tishchenko cyclisation*

Reagents and Conditions: (a) PhCHO/SmI_2 (premixed, 0.1 M in THF, 30 mol%), THF, 0 °C, 3 h.

1.4. RETROSYNTHETIC ANALYSIS OF OCTALACTIN A

The octalactin A synthesis shown in **Scheme 12** was not as efficient as predicted, as shown by poor cyclisation yields and the new problem of epimerisation at C(8) causing a loss of stereochemical integrity. However, the incorporation of the Evans-Tishchenko reaction in the synthesis of octalactin A was still of interest within our group as the selective reduction of the enone moiety to allow a directed epoxidation was still considered a useful and key chemical transformation. An alternative strategy towards the synthesis of octalactin A was devised. The revised retrosynthetic approach taken in this project would involve an intermolecular Evans-Tishchenko reaction, also reported to give high yields and high *anti* selectivity,[27] and thus avoiding epimerisation issues at C(8) found in the first generation synthesis. The other key reaction in our synthesis of octalactin A is the closing of the Evans-Tishchenko ester, which will be carried out using ring closing metathesis. The new retrosynthetic analysis is shown in **Scheme 15**.



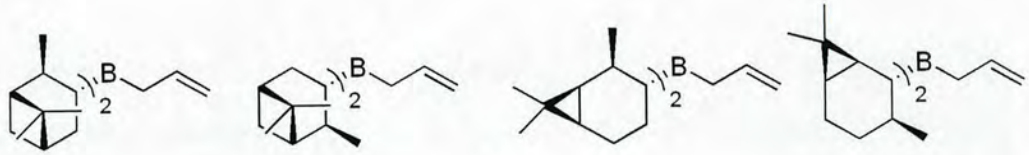
Scheme 15: *Second generation retrosynthetic analysis of octalactin A*

The intermolecular Evans-Tishchenko step in the strategy shown in **Scheme 15** shows the coupling of β-hydroxy enone **72** (generated from a Horner Wadsworth Emmons (HWE) coupling of β-ketophosphonate ester **6** and aldehyde **7**) and aldehyde **5** to give *anti* diol monoester **71**. The two terminal alkenes now participate in the ring closing metathesis step in order to form the unsaturated 8-membered lactone **70**. With the hydroxyl in the desired (*R*)-configuration, a Sharpless epoxidation followed by oxidation would install both the C(10) - C(11) epoxide and the C(9) ketone. Saturation of oxocene **70** *via* hydrogenation will afford the fully saturated 8-membered lactone that is distinctive in octalactin A.

The key intermediates of the revised octalactin A synthetic plan are aldehyde **5** and β-hydroxy enone **72**. The Evans-Tishchenko/ring closing metathesis reactions shown in **Scheme 15** will be discussed in this chapter and applied in the synthesis of an octalactin model (Chapter 2) and towards the total synthesis of octalactin A (Chapter 3). The key synthetic steps in the synthesis of β-ketophosphonate ester **6** and β-hydroxy enone **72** will be introduced in this chapter and the synthesis of β-keto phosphonate ester **6** will be discussed in detail in Chapter 2. The key synthetic steps towards aldehydes **5** and **7** incorporate both Brown's allyl and crotylborations which will be introduced in this Chapter and applied in Chapter 3.

1.4.1. Allylboration

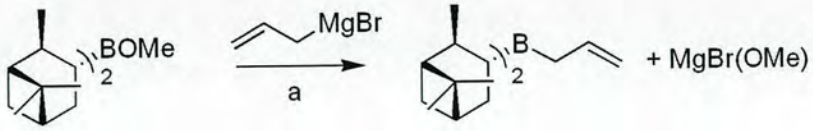
There are a variety of efficient methods for the formation of racemic allylic alcohols by nucleophilic addition of an allyl moiety to an aldehyde. However, the allylation of an aldehyde to give an allylic alcohol with high enantioselectivity is much less refined than the corresponding racemic reaction. The preparation of non-racemic homoallylic alcohols through the asymmetric allylboration of aldehydes represents an extremely important process that has undergone continuous evolution since its discovery by Hoffmann over 25 years ago.[31] Brown *et al.* have investigated the use of naturally occurring terpenes in the synthesis of allylboranes (**73** – **74**) , as shown in **Figure 6**.[32-35]



73 **74** **75** **76**

Figure 6: *Brown's allylation reagents*

The original synthesis of these allylation reagents consisted of the addition of allylmagnesium bromide to the methoxy diisopinocampheylborane **77**. This method produced the allylboration reagents and magnesium salts as a by-product (**Scheme 16**).[32]

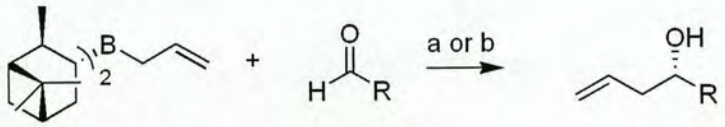


77 **73**

Scheme 16: *Formation of allyldiisopinocampheylborane 73*

Reagents and Conditions: (a) allylmagnesium bromide, Et_2O, 0 °C → RT, 1 h (99 %).

Brown has reported the addition of a range of aliphatic and aromatic aldehydes to β-(-)-allyldiisopinocampheylborane **73** at low temperatures (-78 °C) in the presence of magnesium salts. The respective allylic alcohols **78** (**Table 2**) were produced in good yield and enantioselectivity (87 – 96 % e.e.).[32,33]



73 **78**

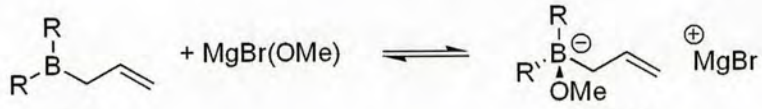
Entry	R	Yield (%)	e.e. (%)[a]	e.e. (%)[b]
1	CH_3	74	93	≥ 99
2	$^nC_3H_7$	71	86	--
3	$^nC_4H_9$	72	87	96
4	$^tC_4H_9$	88	83	≥ 99
6	C_6H_5	81	96	96

Table 2: *Allylboration using reagent 73*[32 33]

Reagents and Conditions: (a) (i) **73**, Et_2O, -78 °C, (ii) RCHO, overnight (**73** containing magnesium salts); (b) **73**, Et_2O, -100 °C, (ii) RCHO, 1 h (**73** containing no magnesium salts).

Further investigations by Brown *et al.* into the synthesis of allylic alcohols *via* allylboration, have shown that the presence of the magnesium salts can affect reactivity and enantioselectivity of the allylic alcohols. Addition of aldehydes (aliphatic and aromatic) to purified (-)-allyldiisopinocampheylborane **73** showed the instantaneous formation of the allylic alcohols (**Table 2**).[34,35] Brown *et al.* have postulated that the magnesium salt [MgBr(OMe)] generated in the synthesis of allylborane **73** (**Scheme 17**) coordinates to the electrophilic boron atom in borane **79**. Complex **80** must be stable at low temperatures (-78 °C or -100 °C) and the rate of allylboration is thus slowed down due to the low concentration of the uncomplexed allylborane **79**. They have also concluded that lowering the reaction temperature

from -78 °C to -100 °C improves the enantioselectivity of the allylboration and does not lengthen the reaction time.[34]

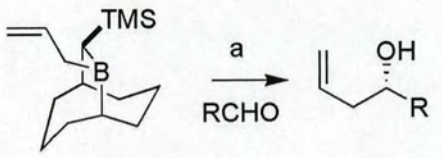


79 **80**

Scheme 17: *Complexation of allylborane with magnesium salts*

The work carried out by Brown *et al.* has clearly shown that allylboranes (**73**, **74**, **75** and **76**) can be used under salt free conditions at -100 °C in the allylation of aldehydes to give allylic alcohols with high yield and enantioselectivity.[34] The successful synthesis of allylic alcohols using Brown's reagents has allowed this allylboration procedure to become a valuable tool in natural product synthesis.

Recent studies by Soderquist *et al.* have shown that treatment of reagent **81** with aldehydes (**Scheme 18**) can give homoallylic alcohols **78** in good yield (70 – 92 %) and high enantioselectivity (96 - ≥99 % e.e.).[36] The formation of homoallylic alcohols using reagent **81** can be carried out at -78 °C without the enantioselectivity of the homoallylic alcohols being affected, unlike the lower temperatures needed (-100 °C) for Brown's reagents. The removal of the magnesium salts in the formation of reagent **81** is not required to improve reaction times, whereas it is essential to achieve the instantaneous reaction times when using Brown's reagents.



81 **78**

Scheme 18: *Soderquist reagent for the allylation of aldehydes*[36]

Reagents and Conditions: (a) (i) RCHO, Et_2O, -78 °C, 3 h; (ii) pseudoephedrine, 81 °C.

The use of reagent **81** in the synthesis of homoallylic alcohols is a suitable alternative to the allylboration of aldehydes using Brown's protocol. However, the application of Brown's allylboration in natural product synthesis is well established compared to reagent **81**.[35,37] The experience within our group in the application of the terpene based, chiral boranes made the synthesis of allylic alcohol required for the synthesis of aldehyde **7** *via* allylborane **73** the preferred route.

1.4.2. Crotylboration

There are a variety of methods to install the crotyl moiety, but until the 1980's achieving stereoselectivity was often a problem. Since then, the development of new organometallic reagents displaying high regio- and stereoselectivity has been an area of great interest to synthetic chemists.

In 1986, Brown *et al.* showed that the reaction of certain allylboranes with aldehydes produced homoallylic alcohols with high optical purities (86-96 % e.e.).[38] Interest in this work led to the extension of the asymmetric synthesis to achieve the enantioselective formation of both the *syn* and *anti* β-methyl homoallylic alcohols *via* crotylboration reactions using boranes (**82 -89**) (**Figure 7**).

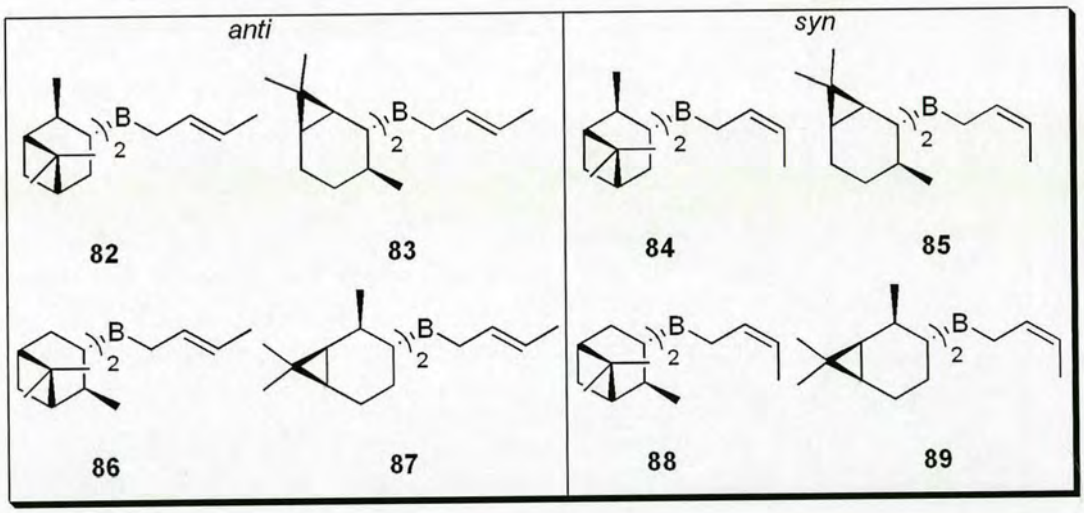
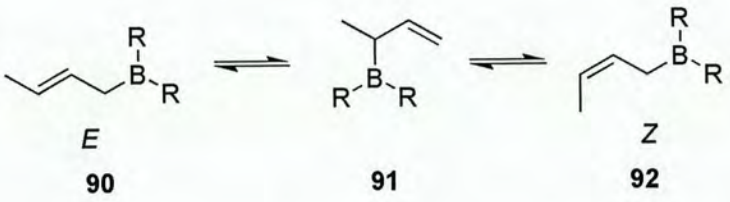


Figure 7: *Brown's crotylboration reagents*[38]

Unlike the allyl derivatives, little was known about the stability of the crotylboranes. It was known was that β-crotyl derivatives tend to exist as an interconvertible mixture of the *E*- and *Z*-isomers and that they can add to aldehydes to produce a mixture of regioisomers.[38]

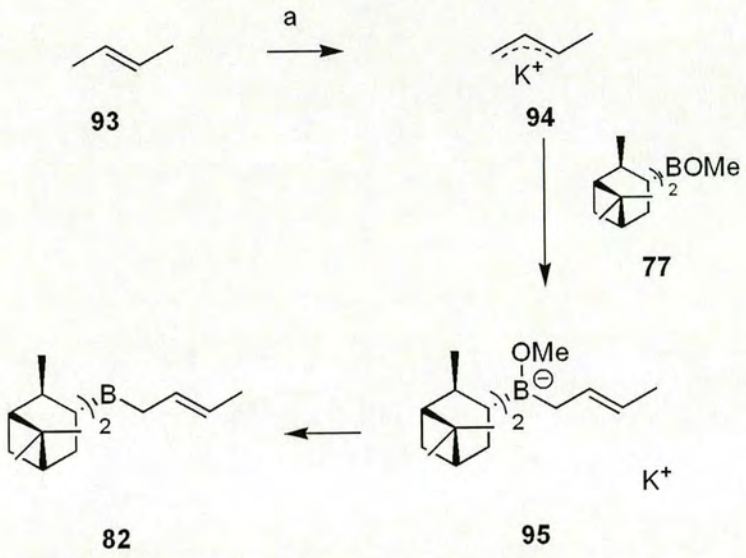
A rapid equilibrium exists between the pure *E*- and *Z*-crotylboranes (**90** and **92**) *via* a borotropic rearrangement involving a 1-methylallyl intermediate **91** (**Scheme 19**). The rate of isomerisation is dependent upon the R group attached to the boron: allyl-BR_2 > allyl-BR(OR') > allyl-$B(OR')_2$.[38]



Scheme 19: *Equilibrium between E- and Z-crotylboranes*

Additionally, the rate of reaction of crotylboranes with aldehydes follows the same order as the allylboration reaction, and greater optical purity can be seen when carrying out the reactions at lower temperatures. It was expected that these crotylboranes would react readily with aldehydes, and at a temperature low enough to achieve good optical purity, with limited isomerisation.

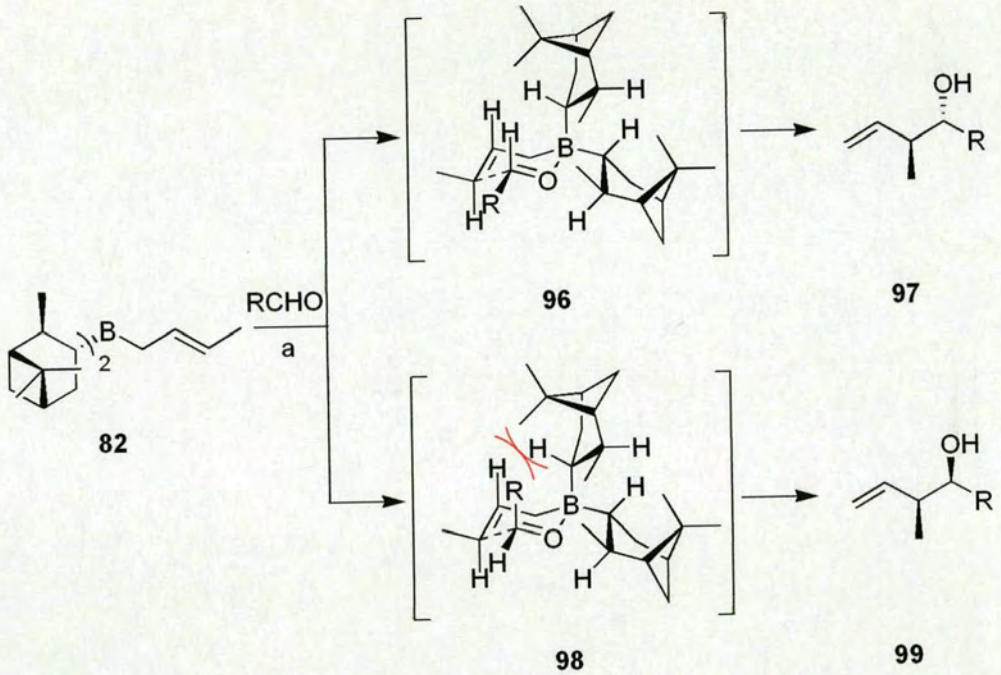
The reported synthesis of crotylborane **82** consisted of metallation of *trans*-but-2-ene **93** *via* a "superbase", using conditions discovered by Schlosser.[39] Treatment of the crotylpotassium salt **94** with (-)-methoxydiisopinocampheylborane **77** at -78 °C gave the boronate complex **95**. Treatment of complex **95** with boron trifluoride etherate generated the trialkylborane **82** which was used immediately in the crotyl boration reaction to avoid crotyl isomerisation (**Scheme 20**).



Scheme 20: *Preparation of E-crotylborane* ***82***[33]

Reagents and Conditions: (a) (i) ^{t}BuOK, ^{n}BuLi, THF, -45 °C, 10 min; (ii) **77**, Et_2O, -78 °C, 30 min; (iii) $BF_3 \bullet Et_2O$, -78 °C.

Immediate addition of a range of aldehydes to crotylborane **82** results in a crotylboration reaction which proceeds *via* transition state **96**, to give homoallylic alcohols in good yield (65 – 79 %) with excellent diastereoselectivity [95:5 *anti* (**97**):*syn* (**99**)] and good enantiomeric purity (88 – 90 % e.e.) as shown in **Table 3**.[40]

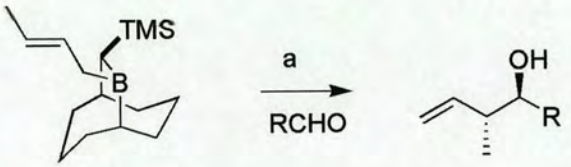


Entry	R	Yield (%)	97:99	e.e. (%)
1	CH_3	78	95:5	90
2	$^nC_2H_5$	70	95:5	90
3	$^nCH_2$=CH	65	95:5	90
4	C_6H_5	79	94:6	88

Table 3: *Crotylboration using crotyl borane* ***82***

Reagents and Conditions: (a) RCHO, THF, -78 °C, 3h.

Recent studies by Soderquist *et al.* have also shown that crotylation of aldehydes using reagent **100** under low temperatures (-78 °C) can give β-methyl homoallylic alcohols **101** in good yield (68 – 94 %) with high diastereoselectivity (≥ 98:2 *anti*:*syn*) and enantioselectivity (94 – 99 % e.e.).

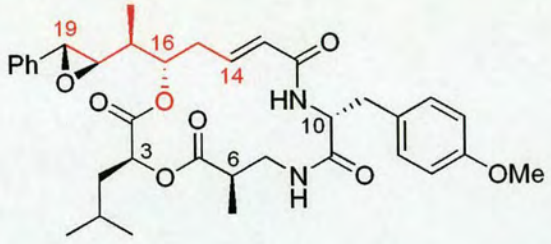


100 **101**

Scheme 21: *Soderquist reagent for crotylation of aldehydes*[36]

Reagents and Conditions: (a) (i) RCHO, Et_2O, -78 °C, 3 h; (ii) pseudoephedrine, 81 °C.

The use of reagent **100** in the synthesis (**Scheme 21**) of β-methylhomoallylic alcohols **101** is a suitable alternative to the crotylboration of aldehydes using Brown's protocol.[36] However, the application of Brown's method in natural product synthesis is more established.[41-43] Georg *et al.* have investigated the application of Brown's crotylboration towards the synthesis of cryptophycin-24 (**102**)(**Figure 8**).

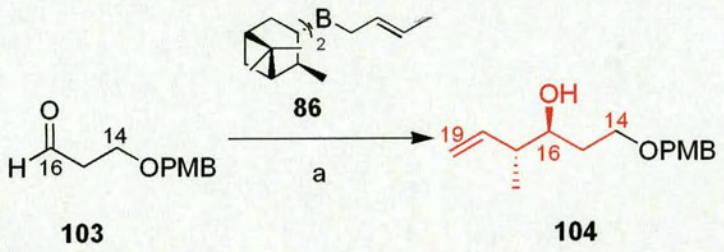


102

Figure 8: *Cryptophycin-24*

Treatment of aldehyde **103**, with *E*-crotylborane **86** afforded β-methyl homoallylic alcohol **104** in good yield (76 %) and with good enantioselectivity (91 % e.e.) as shown in **Scheme 22**. β-Methylhomoallylic alcohol **104** is the antipode of the alcohol desired for the synthesis of fragment **5** and it was thought that the opposite enantiomer could be synthesised with similarly high yield and enantioselectivity. This experience within our group in the application of the terpene based, chiral

boranes made the synthesis of β-methylhomoallylic alcohol required for the synthesis of fragment **5** *via* crotyl borane **82** the preferred route.



103 **104**

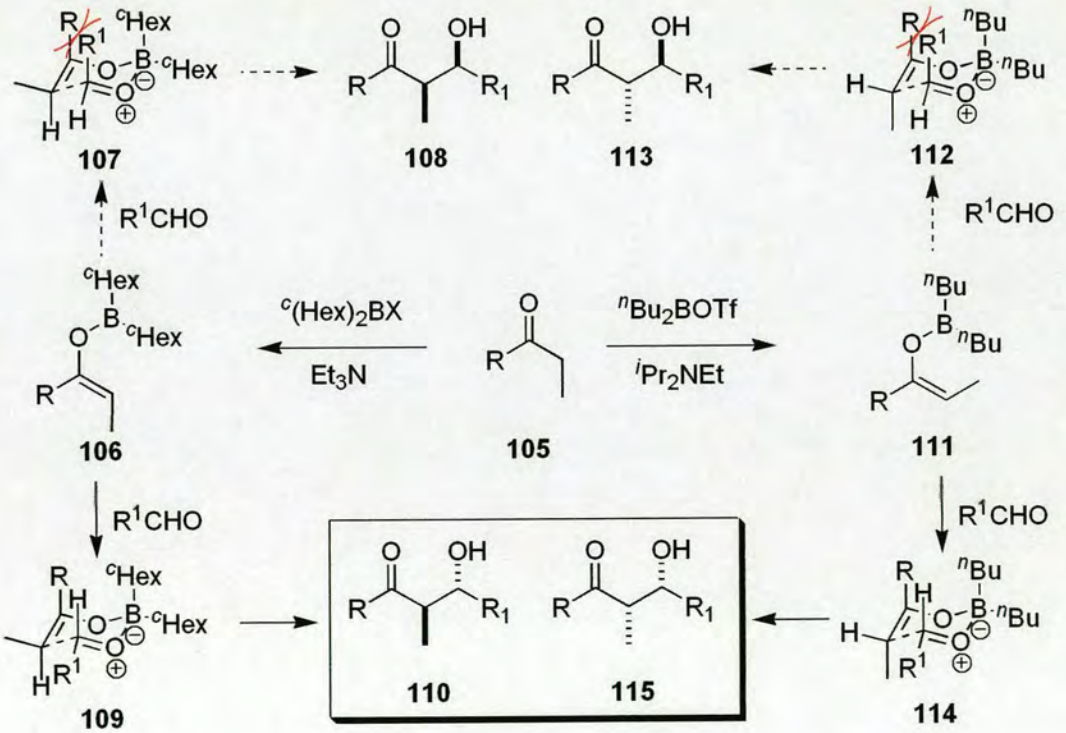
Scheme 22: *Synthesis of C(14) – C(19) fragment of Cryptophycin-24*

Reagents and Conditions: (a) (i) **86**, THF, -78 °C (ii) ethanolamine, RT (76 %, 91 % e.e.).

1.4.3. Boron Mediated Aldol Reaction

1.4.3.1. Relative Stereocontrol

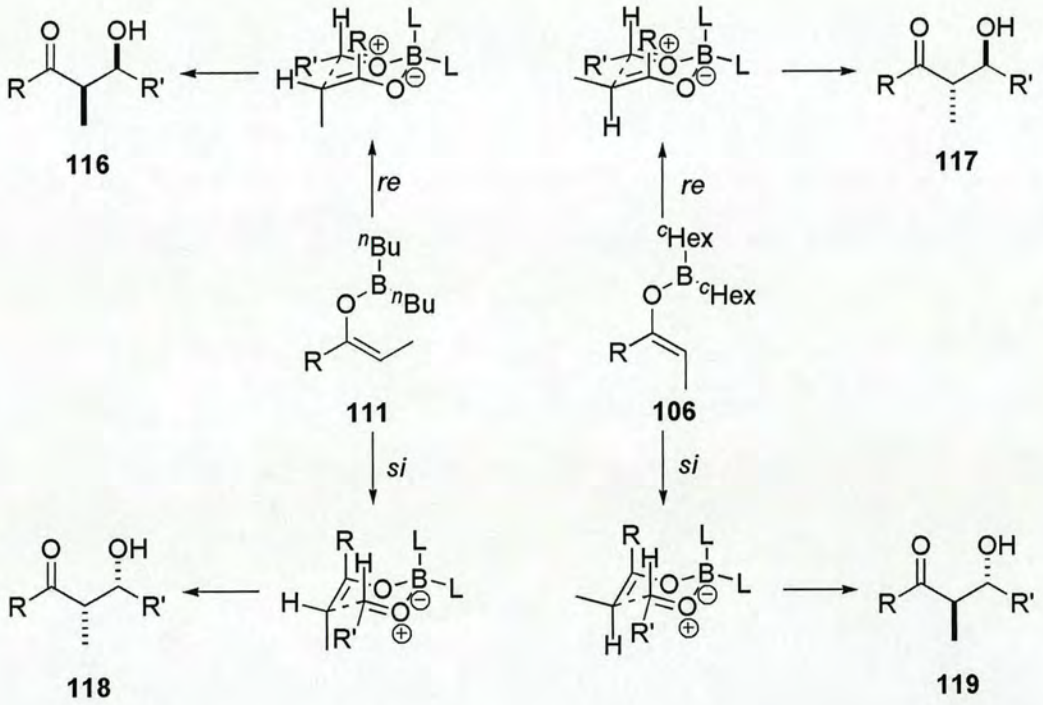
The relative stereochemistry of a kinetically controlled boron aldol reaction is directly proportional to the *E*:*Z* geometry of the boron enolates formed. The size of the ligands on the boron reagent can selectively form either the *E*- (where bulky cyclohexyl ligands are used) or *Z*-enolates (where small butyl ligands are used). The transfer of enolate geometry to the stereochemistry of the aldol adducts is controlled by a Zimmerman-Traxler[30] transition state (**107**, **109**, **112** and **114**) as shown in **Scheme 23**. The *E*-boron enolate **106** can potentially form two transitions states (**107** or **109**) to form either the *syn* (**108**) or *anti* aldol adducts (**110**). Due to diaxial interactions in transition state **107**, the aldol reaction proceeds *via* transition state **109** to form the *anti* aldol adduct **110**. Similarly *Z*-boron enolate **111** forms the *syn* aldol adduct **115** *via* transition state **114** due to less diaxial interactions.



Scheme 23: *Relative stereocontrol via enolate geometry*

1.4.3.2. Absolute Stereocontrol

It is of great importance in the synthesis of many natural products that the absolute stereochemistry of aldol reactions can be controlled and this is when the enolate shows a high level of π-facial selectivity (**Scheme 24**). Therefore one of the π-faces of the enolate must be selective for either the *si* or *re* face of the aldehyde.



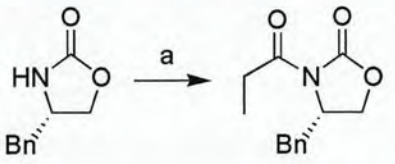
Scheme 24: *Enantiofacial selectivity*

A high level of π-selectivity for *anti* aldol reactions can be achieved by using:

- a chiral aldehyde;[44]
- a chiral auxiliary (e.g. Evans oxazolidinone **120**, **Scheme 25**);[45]
- chiral ligands on the boron enolate;[46-48]
- or a metal enolate derived from a chiral carbonyl compound.[49]

In our synthesis of C(6)-C(10) phosphonate fragment **6** we intend to use an achiral aldehyde and so cannot use the first method to control the aldol reaction. Potentially we could use any of the other three methods but some of them have problems with

the generality of reaction or relatively harsh conditions for conducting the reaction. Therefore for the synthesis of fragment **6**, it was proposed to use the most popular method for the formation and control of aldol adducts, the use of a chiral auxiliary.



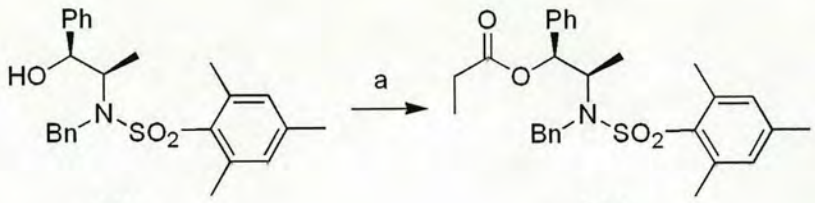
120 **121**

Scheme 25: *Propionate derivative of the Evans chiral auxiliary*
Reagents and Conditions: (a) (i) BuLi, THF; (ii) CH_3CH_2COCl, 0 °C, 1h, (90 %).

The most common chiral auxiliary used in the control of aldol reactions is the Evans oxazolidinone **120**, shown in **Scheme 25**. It is widely used for the synthesis of *syn* aldol adducts generally giving excellent relative and absolute control.[45] However the use of the propionate derivative of auxiliary **121** in the formation of *anti* aldol adducts was not reported to be as robust as the synthesis is reliant upon careful control of the boron reagent. Recently Evans and coworkers[50,51] have investigated the use of the propionate derivative **121** in the generation of *anti* aldol adducts and have discovered that by using chelating additives (e.g. $MgCl_2$), the desired *anti* aldol adduct can be obtained in good yields (86 – 94 %) and high diastereoselectivity (26:1 – 32:1 *anti*:*syn*).

Although the Evans oxazolidinone is compatible with the *anti* aldol reaction, this auxiliary is not an attractive candidate to use in our synthesis of octalactin A as it requires harsh conditions to remove it from the aldol substrate. Our synthesis of β-ketophosphonate ester **6**, relies upon the displacement of the chiral auxiliary with a mild phosphonate anion.

Abiko *et al.* have synthesised a carboxylic ester chiral auxiliary **122** for use in boron mediated aldol reactions, as shown in **Scheme 26**.[52-55] They have shown that both *anti* and *syn* aldol adducts can be formed selectively by using the appropriate boron triflate and tertiary amine.



122 **123**

Scheme 26: *Propionate derivative of the Abiko-Masamune chiral auxiliary*[53,54]

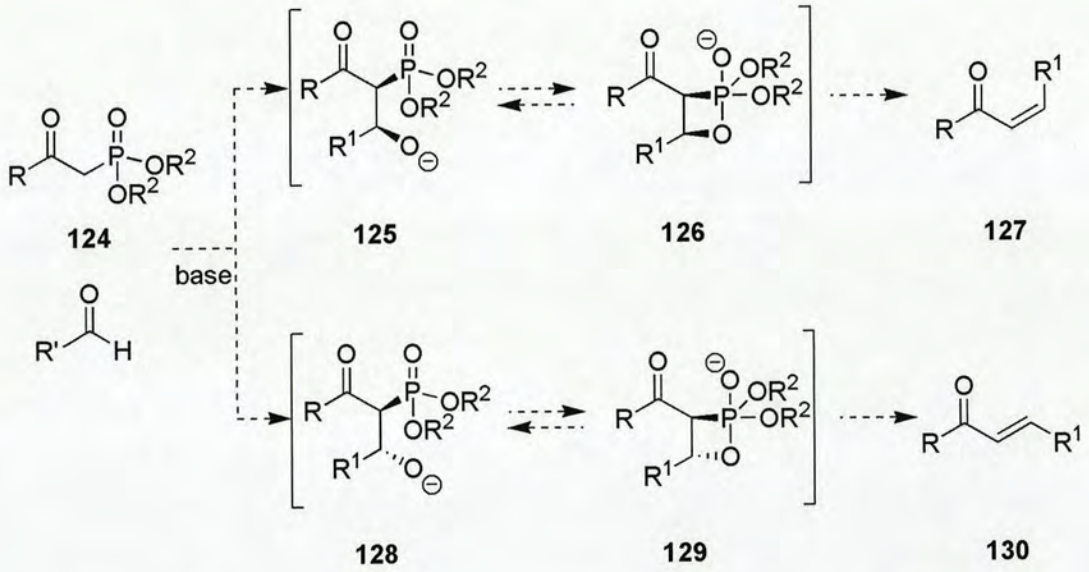
Reagents and Conditions: (a) CH_3CH_2COCl, pyridine, 0 °C → RT, 18 h (69 %).

Abiko *et al.* produced the propionate derivative of chiral auxiliary **123** from commercially available norephedrine in 3 simple steps.[53,54] The *syn* aldol reaction was carried out using a range of aldehydes (vinyl, aliphatic and aromatic) and produced the respective *syn* aldol adducts and the reported yields were high (93 – 98 %) with a high *syn:anti* ratio (95:5 – >97:3).[53,54] The *anti* aldol reaction was shown to be similarly versatile using a range of aldehydes and the *anti* aldol adducts were also produced in high yields (90 – 98 %) and diastereoselectivities(95:5 – >99:1).[53,54]

The development, by Masamune, of the norephedrine derived auxiliary for the reliable stereoselective construction of *anti* aldol adducts and its application in the synthesis of natural products has been demonstrated. The propionate derivative **123** is an appropriate candidate for use in our synthesis of octalactin A because of its availability, combined with the mildness of the boron-aldol reaction and the ease of use. As mentioned earlier, the acylated Evans oxazolidinone **121** requires strong conditions to remove it from the aldol substrate, however auxiliary **123** is attached to its aldol substrate *via* a carboxylic ester and so it is believed that it can be removed from the aldol substrate using milder conditions. Work within the Hulme group using propionate ester **123** has shown that it can be displaced with a phosphonate anion to form a β-ketophosphonate ester.[29] The mild displacement conditions warranted the use of propionated auxiliary **123** in the construction of the C(7)-C(8) bond of octalactin A.

1.4.4. Horner Wadsworth Emmons

The Horner Wadsworth Emmons (HWE) reaction is a versatile method for the formation of α,β-unsaturated carbonyl compounds using β-ketophosphonate **124** and an aldehyde to give either the *Z*- or *E*-enones (**127** or **130**). The mechanism is believed to proceed *via* an oxaphosphetane[56] (**125** or **128**) or the oxyanion intermediate[57] (**126** or **129**) (**Scheme 27**). The predominant formation of the *E*-enone **130** occurs when dialkylphosphonates **124** (R^2 = alkyl) are used due to the preferential formation of thermodynamically more stable *threo* adducts (**128** or **129**).[58]

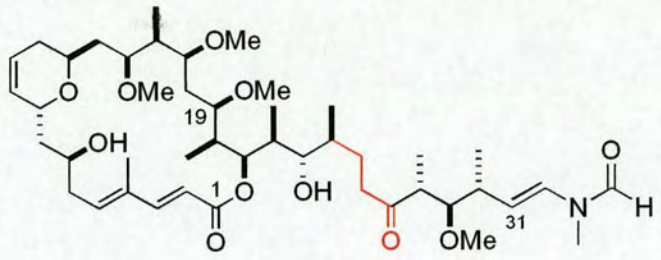


Scheme 27: *The HWE reaction and the possible mechanistic pathways*[58]

There have been numerous examples of the HWE coupling of aldehydes to β-keto phosphonates reported in the literature, including modifications to allow the use of milder conditions,[59] or conditions to promote higher *E:Z* selectivity.[60] The HWE reaction under mild conditions has seen extensive use in natural product synthesis. [61-64]

1.4.4.1. Barium Mediated HWE Reaction

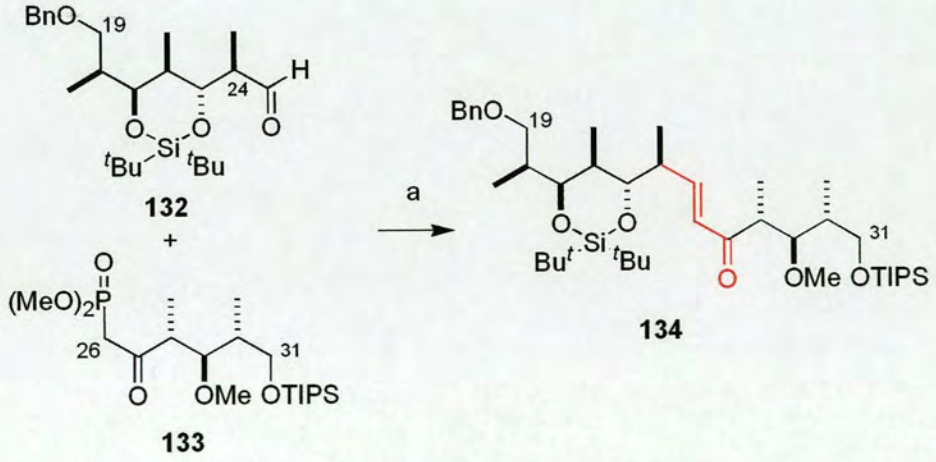
Paterson *et al.* have incorporated the use of a HWE into the synthesis of natural product scytophycin C **131** (**Figure 9**).[61,62]



131

Figure 9: *HWE coupling in the synthesis of scytophycin C **131***

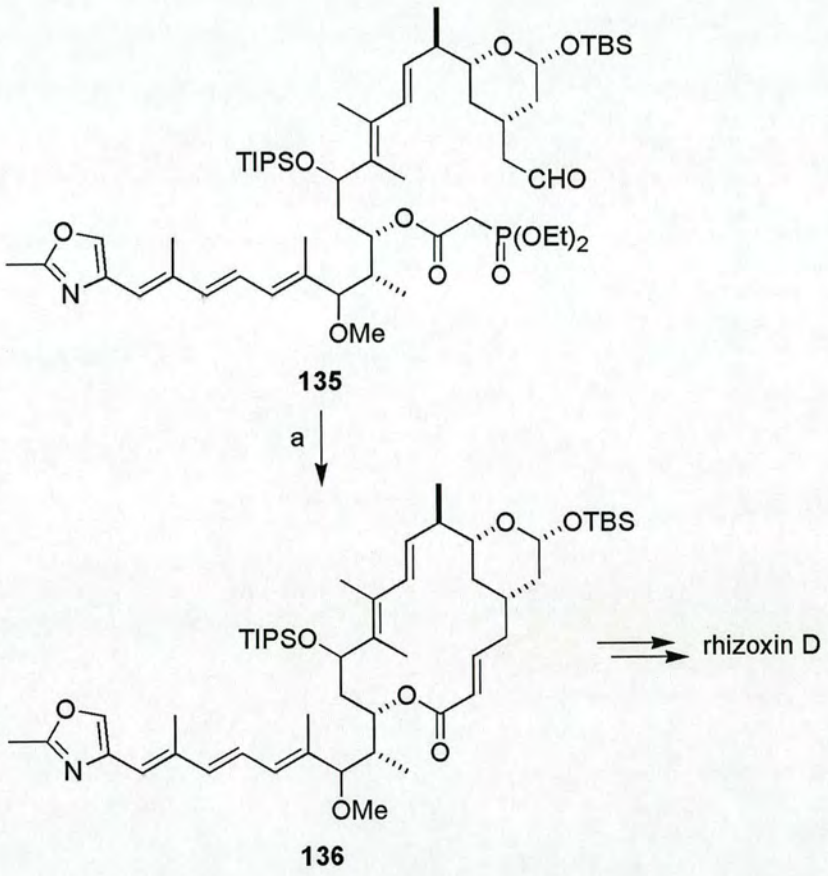
In the synthesis of the C(19)-C(31) segment **134**, attempts made to perform the coupling *via* conventional methods (e.g. NaH) gave poor *E*:*Z* selectivity. It was found that the mild base barium hydroxide induced HWE coupling of aldehyde **132** and β-ketophosphonate ester **133**, gave the *E*-enone **134** in a high yield (96 %) and high selectivity (**Scheme 28**).[61,62] It has been suggested that the microcrystalline structure of barium hydroxide is crucial to the catalytic activity in HWE reactions.[61]



Scheme 28: *HWE coupling in the synthesis of fragment **134***

Reagents and Conditions: (a) $Ba(OH)_2 \cdot 8H_2O$, 40:1 THF/ H_2O, RT, 6.5 h (96 %).

Leahy *et al.*, in their synthesis of natural product rhizoxin D, have also used the mild barium hydroxide mediated conditions with the HWE precursor **135** to allow the cyclisation of the 16-membered lactone **136**.[65,66] Although the cyclisation was slow and gave only a moderate yield (49 %), only the *E*-enone was isolated (**Scheme 29**).

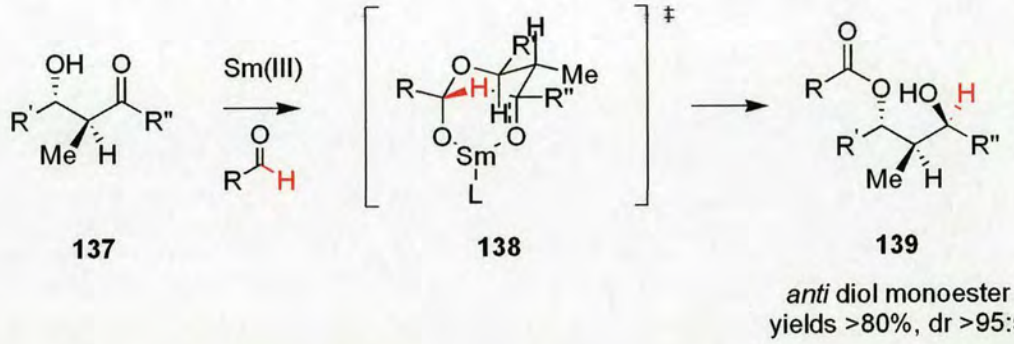


Scheme 29: *Incorporation of HWE coupling in the synthesis of rhizoxin D.*[65,66]

Reagents and Conditions: (a) $Ba(OH)_2$, THF/H_2O, RT, 4 days (49 %).

1.4.5. Evans-Tishchenko Coupling

The Evans-Tishchenko reaction was discovered 16 years ago by Evans and Hoveyda. It involves the coupling of β-hydroxy ketones **137** and aldehydes to give the respective *anti* diol monoesters **139** (**Scheme 30**).[28] The Evans-Tishchenko reaction typically requires catalysis by 15-30 mol% of a SmI_2 solution in THF, and results in the directed reduction of a β-hydroxy ketone to give an *anti* 1,3-diol with selective formation of a monoester (*anti:syn* >95:5).[28]

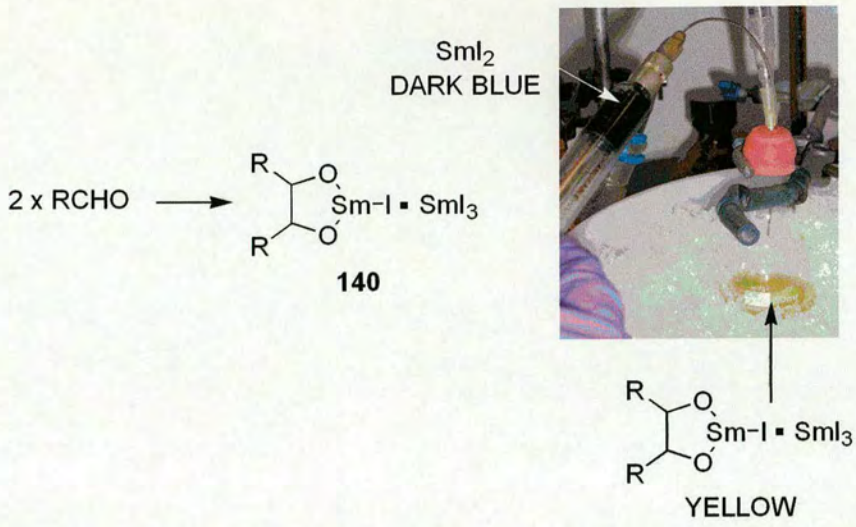


137 **138** **139**

anti diol monoester
yields >80%, dr >95:5

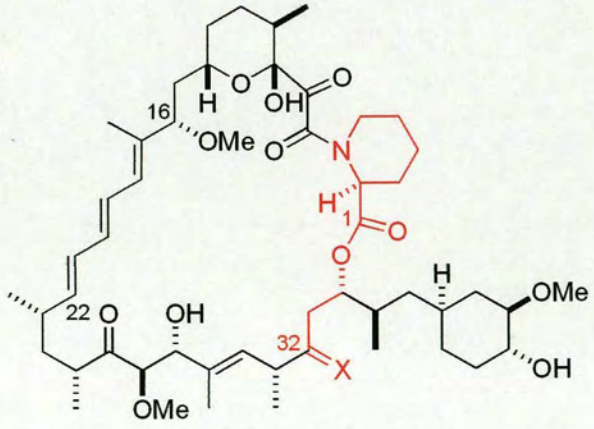
Scheme 30: *Intermolecular Evans-Tishchenko reaction*

The proposed mechanism involves intramolecular hydride transfer from an intermediate hemiacetal *via* a tricyclic transition state **138** similar to that shown in **Scheme 30**.[28] The active catalyst in the Evans-Tishchenko reaction is believed to be a SmI_3•$SmI(RCHO)_2$ pinacol adduct **140** which is preformed, or generated *in situ*. The formation of the pinacol adduct may be deduced by a colour change; upon addition of the SmI_2 solution (very dark blue solution) to an aldehyde (commonly acetaldehyde or benzaldehyde) a Sm(III) pinacol adduct is formed and can be recognised by the yellow colour as illustrated in **Scheme 31**.



Scheme 31: *Proposed active Sm(III) pinacol adduct catalyst*[28]

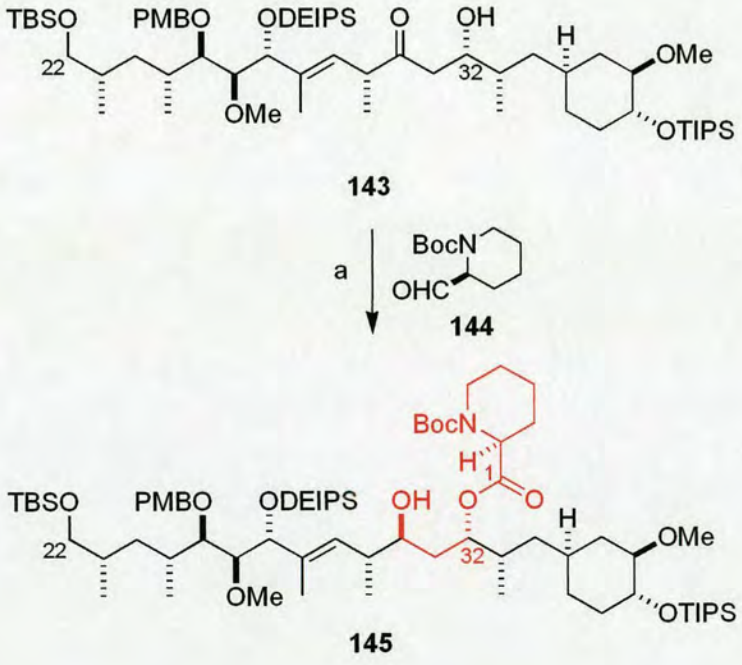
The Evans-Tishchenko reaction is an efficient method for the *anti* reduction of β-hydroxy ketone systems and it has been widely used in the synthesis of natural products. The first incorporation of the Evans-Tishchenko reaction into natural product synthesis was in 1993 by Schreiber *et al.* in their synthesis of rapamycin (**Figure 10**).[67]



Rapamycin **141** X = O
142 X = H, α -OH

Figure 10: *Rapamycin **141** and analogue **142***[67]

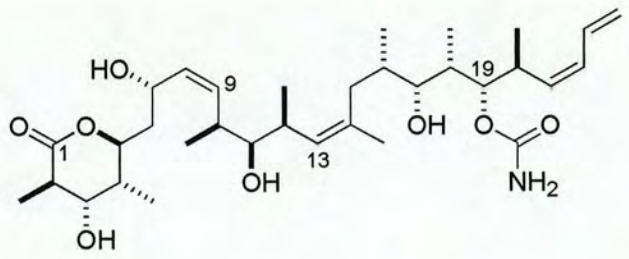
Rapamycin **141** was of interest because of the high affinity binding complex it forms with intracellular receptor FKBP12, which is believed to interfere with signalling components of the cell cycle. Crystallography studies of the FKBP-rapamycin complex suggested that reduction of the C(32) ketone to the (*S*)-hydroxyl would increase the binding affinity of analogue **142** to FKBP. Schreiber *et al.* then decided to install the highlighted fragment shown in **Figure 10** *via* an Evans-Tishchenko coupling with pipecolinal **144**.[67] Treatment of β-hydroxy ketone **143** with the pre-formed samarium pinacol catalyst (shown in **Scheme 31**), followed by pipecolinal **144** afforded *anti* diol monoester **145**, in excellent yield (95 %) as a >20:1 mixture of *anti* and *syn* diol monoesters as shown in **Scheme 32**.[67]



Scheme 32: *Rapamycin synthesis*[67]

Reagents and Conditions: (a) **144**, $(PhCHO)_2SmI$, THF, -10 °C (95 %).

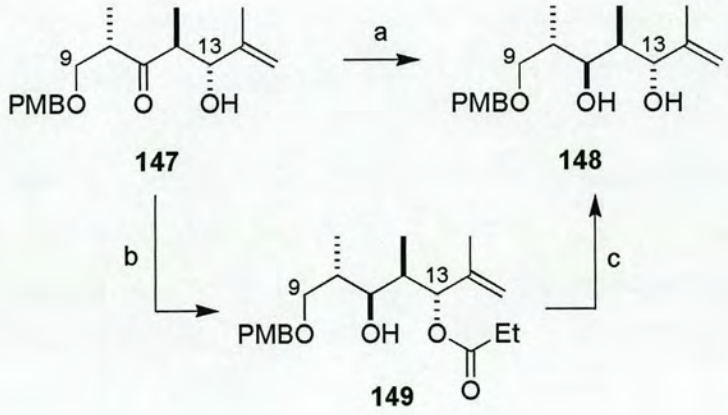
Paterson *et al.* have incorporated the Evans-Tishchenko reaction into the synthesis of the polyketide discodermolide **146**, shown in **Figure 11**.[44] The anti-cancer properties and its structural complexity made it an attractive synthetic target.



146

Figure 11: *Discodermolide*[44]

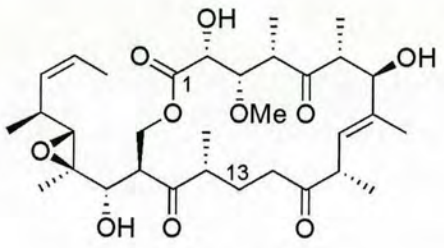
Paterson *et al.* have shown in the synthesis of C(9) – C(13) fragment **148** (**Scheme 33**) that the C(11) carbonyl of β-hydroxy ketone **147** can be reduced using either: $Me_4NBH(OAc)_3$ (which directly forms the diol **148**); or the Evans-Tishchenko reaction to give *anti* diol monoester **149**, followed by methanolysis. Although the reduction of β-hydroxy ketone **147** using $Me_4NBH(OAc)_3$ produced diol **148** in high yield (97 %) with high diastereoselectivity (>97 % ds), the two-step Evans-Tishchenko route was preferred due to the consistent high yields obtained upon the large scale synthesis of diol **148**.[44]



Scheme 33: *Reduction strategies towards fragment* ***148***[44]

Reagents and Conditions: (a) $Me_4NBH(OAc)_3$, MeCN/AcOH, -40 → -23 °C (94 %, >97% ds); (b) SmI_2, EtCHO, THF, -10 °C (96 %, >97 % ds); (c) K_2CO_3, MeOH, 20 °C (97 %).

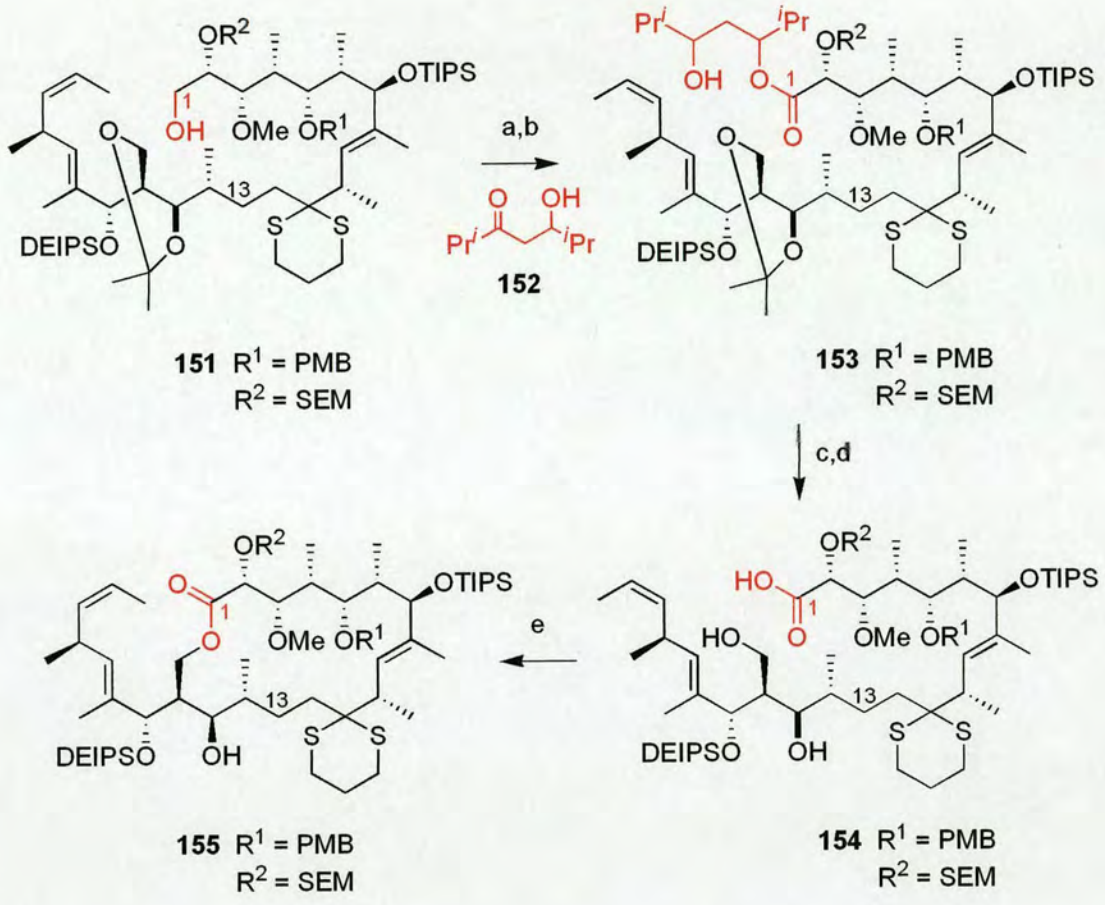
As shown in **Schemes 32** and **33**, the Evans-Tishchenko reaction has commonly been used to reduce a β-hydroxy ketone moiety giving an *anti* diol monoester in high yield and selectivity, but there have been other investigations into the versatility of this reaction. Smith III *et al.* have used the Evans-Tishchenko reaction in their synthesis of the 18-membered macrocycle 13-deoxytedanolide **150**, as shown in **Figure 12**.[68,69]



150

Figure 12: *13-deoxytedanolide **150**[68,69]*

Generally the oxidation of the C(1) hydroxyl to the carboxylic acid in the complex polyketide precursor **151** to allow cyclisation, would require harsh conditions that could result in the oxidation of other sensitive groups such as the dithiane at C(11), as shown in **Scheme 33**. A Parikh-Doering oxidation of alcohol **151** afforded the aldehyde (**Scheme 33**) which was then treated under Evans-Tishchenko conditions with a sacrificial β-hydroxy ketone **152** to form *anti* diol monoester **153** in excellent yield.[70] Hydrolysis of the ester **153** afforded the carboxylic acid **154** in excellent yield and a Yamaguchi macrolactonisation of carboxylic acid **154** g ave the 18-membered lactone **155**.[68,69] Thus Smith *et al.* have shrewdly shown that the Evans-Tishchenko coupling reaction can also be used as a mild oxidative procedure.



Scheme 33: *Mild alcohol oxidation in the synthesis of 13-deoxytedanolide.*[68,69]

Reagents and Conditions: (a) SO_3•pyr, DMSO, $^iPr_2NEt$; (b) SmI_2 (35 mol%), **152** (75 % over 2 steps); (c) PPTs, MeOH; (d) LiOH, THF/H_2O, Δ (63 % over 2 steps); (e) (i) 2,4,6-trichlorobenzoyl chloride, $^iPr_2NEt$, THF; (ii) DMAP, toluene (64 %).

There are a vast number of examples where the Evans-Tishchenko reaction is used in the reduction of β-hydroxy ketones, compared with very limited reports[27,71] of an Evans-Tishchenko reaction using a β-hydroxy enone, as would be required in this project for the synthesis of *anti* diol monoester **71**.

The first studies within the Hulme group on the synthesis of octalactin A investigated the intermolecular Evans-Tishchenko reaction with enones, as well as the

intramolecular cyclisation as shown in **Scheme 34**.[27] An Evans-Tishchenko reaction with benzaldehyde and protected enone **156** using standard conditions, afforded the *anti* aldol monoester **157** in 70 % yield as a single diastereomer.

156 **157**

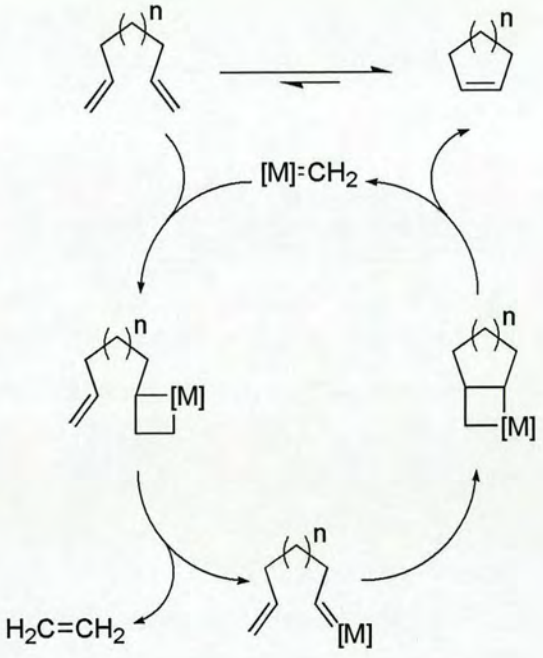
Scheme 34: *Evans-Tishchenko reaction with benzaldehyde*[27]

Reagents and Conditions: (a) PhCHO (4 eq.), SmI_2 (0.1 M in THF, 60 mol%), THF, 0 °C, 10 min (70 %).

The efficient and highly selective reductive nature of the Evans-Tishchenko reaction has merited its incorporation into the synthesis of many natural products. The application of the Evans-Tishchenko reaction of functionalised aldehydes containing alkene moieties with β-hydroxy enones will be demonstrated and discussed in Chapters 2 and 4.

1.4.6. Ring Closing Metathesis

Ring closing metathesis (RCM) was discovered in the 1960's but it was not until the early 1990's that this transformation became an important tool in synthetic organic chemistry.[72-74] It has been used in the construction of an impressive number of diverse cyclic structures *via* the general mechanism shown in **Scheme 35**.



Scheme 35: *General ring closing metathesis mechanism*

There are a variety of catalysts which can be used for RCM (**Figure 13**). The main two types are:

1. Ruthenium alkylidenes (Grubbs) (**158, 159, 160**)[75-77]
2. Molybdenum alkylidenes (Schrock) (**161, 162**)[72]

The molybdenum catalysts are very reactive and can undergo RCM with terminal alkenes and the less reactive trisubstituted alkenes.[78] Although the Schrock catalysts are highly reactive in RCM and can construct a variety of ring sizes, they are very

unstable and have to be handled under strictly anhydrous conditions to prevent decomposition of catalyst. The ruthenium based catalysts have a higher stability and have comparable efficiency in RCM reactions. We decided to use the ruthenium based catalysts in the synthesis of octalactin A on the basis that they have higher stability than the Schrock catalysts.

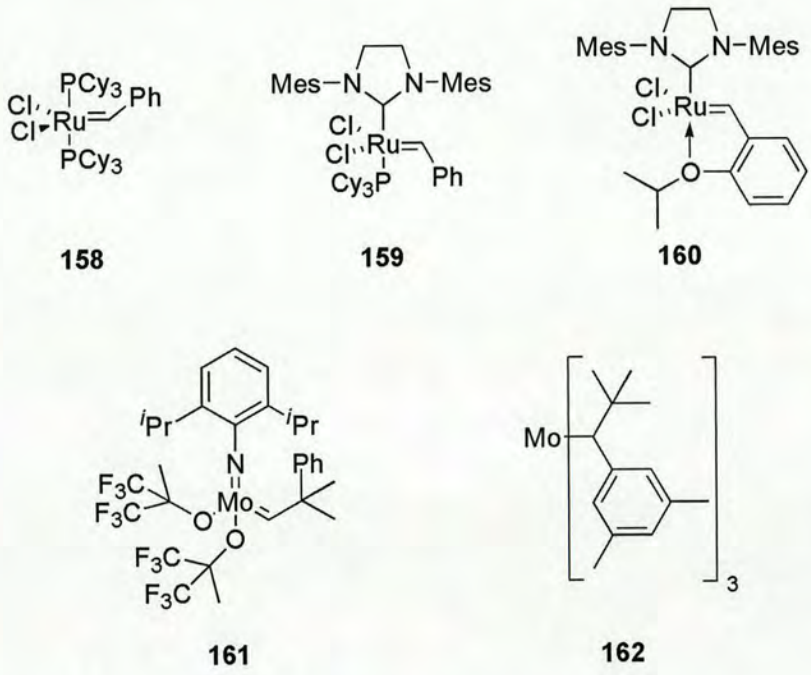


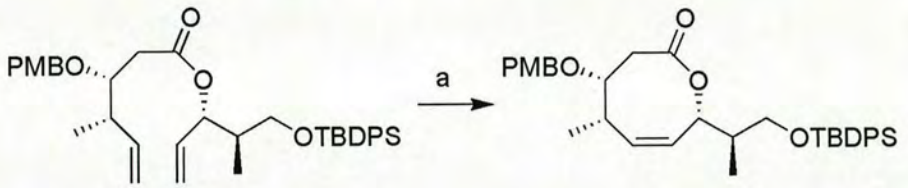
Figure 13: *Selection of Grubbs and Schrock catalysts*

Grubbs' 1st generation catalyst **158** has been shown to be effective when catalysing the reaction of terminal alkenes.[75,76] Although this catalyst is more stable than the molybdenum catalysts, anhydrous conditions are still required to give an efficient RCM. The addition of the *N*-heterocyclic carbene (NHC) ligand to catalyst **158** has been found to improve catalyst stability and has resulted in improved yields in RCM reactions.[77,79,80] Therefore, we have decided to use Grubbs 2nd generation catalyst **159** in the synthesis of octalactin A.

RCM has been responsible for the synthesis of many natural products containing a variety of ring sizes.[81,82] The synthesis of a selection of Medium-ring lactone natural products using this method will now be discussed.

1.4.6.1. Formation of 8- and 9-Membered Lactones *via* RCM

There are a variety of strategies towards the synthesis of 8-membered cyclic compounds which incorporate RCM. However the construction of 8-membered lactones using RCM is very limited. In fact the only reported synthesis of an 8-membered lactone (**Scheme 36**) was the synthesis of oxocene **19**, which was carried out by Buszek *et al.* in their synthesis of octalactin A, as discussed in section 1.3.4.[14]

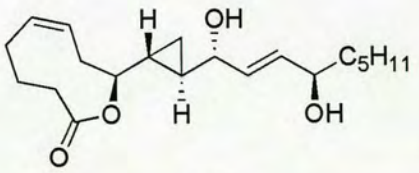


46 **19**

Scheme 36: *Buszek's synthesis of oxocene* ***19***[14]

Reagents and Conditions: (a) Grubbs 1 **158**, CH_2Cl_2, 40 °C, 24 h (86 %).

Similarly the use of RCM towards the synthesis of 9-membered lactones is also very limited. A rare example of preparing the 9-membered lactone moiety by RCM was reported by Takemoto *et al.* towards a synthesis of halicholactone **10**, as shown in **Figure 14**.[83,84]

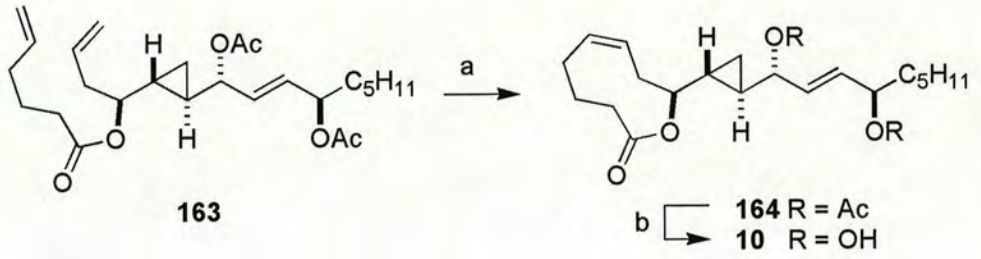


10

Figure 14: *Halicholactone* ***10***[83,84]

Treatment of triene **163** with Grubbs' 1st generation catalyst **158** under high dilution in the presence of $Ti(^iOPr)_4$ gave the *Z*-isomer **164** as the major product (72 %) along

with 11 % of the dimer, as shown in **Scheme 37**. Mild hydrolysis of the acetate groups afforded lactone **10** in a 61 % yield. Interestingly when the hydroxyl groups were protected as SEM or MOM ethers, the yield of RCM was lowered (19 %) with 45 % of recovered starting material and 9 % of the dimer.



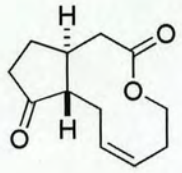
Scheme 37: *RCM in the synthesis of Halicholactone*[83,84]

Reagents and Conditions: (a) $Ti(^iOPr)_4$, Grubbs 1 **158**, CH_2Cl_2, 40 °C, 24 h (72 %); (b) K_2CO_3, MeOH, RT, 3 h (61 %).

1.4.6.2. Formation of 10-Membered Lactones *via* RCM

The synthesis of 10-membered lactones *via* RCM has been the subject of a number of investigations. A variety of natural products containing the 10-membered lactone moiety have been constructed and a brief selection is discussed below.

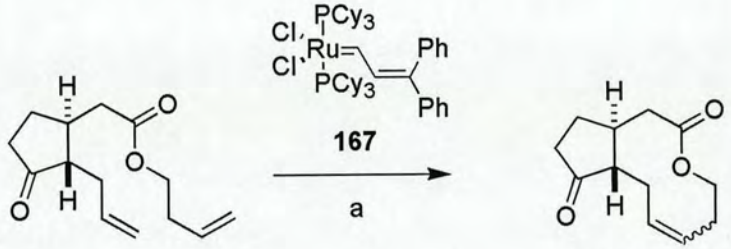
In 1997 Fürstner *et al.* carried out the first synthesis of a 10-membered lactone *via* RCM in the synthesis of jasmine ketolactone **165**, the oldest natural product known to possess an oxecan-2-one framework (**Figure 15**).[85] Lactone **165** is a component of the essential oil of *Jasmium grandiflorium* and was isolated in 1942.[86]



165

Figure 15: *Jasmine ketolactone **165***

Treatment of a highly dilute solution of diene **166** with Grubbs catalyst **167** under reflux afforded the lactone **165** in 88 % yield as a 1.4:1 (*E*:Z) mixture of isomers. Chromatography allowed the simple separation of the isomers to allow the isolation of the natural product, *Z*-**165**, as shown in **Scheme 38**.

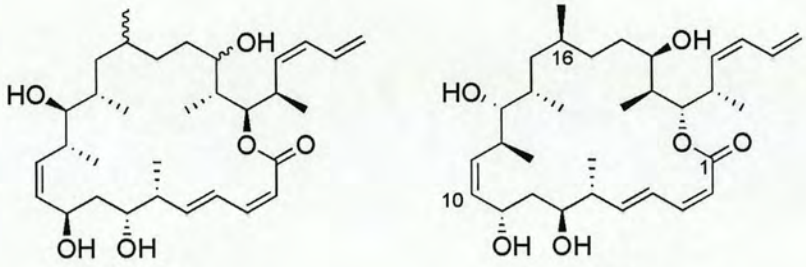


166 **165**

Scheme 38: *Synthesis of jasmine ketolactone **165***[85]

Reagents and Conditions: (a) Grubbs catalyst **167** (10 mol%), CH_2Cl_2, 40 °C, 24 h (88 %).

More recently, Curran *et al.* have used an esterification/RCM strategy[87]towards the potent anti-tumor agent dictyostatin **169** (**Figure 16**), which was first isolated in 1994 by Petit *et al.*,[88] when they proposed a partial structure **168**. However investigations into the structure of dictyostatin (**169**) by completion of the total synthesis have shown that the assignments of the stereocentres at C(7), C(9), C(12), C(20), C(21) and C(22) were incorrect.[89,90]

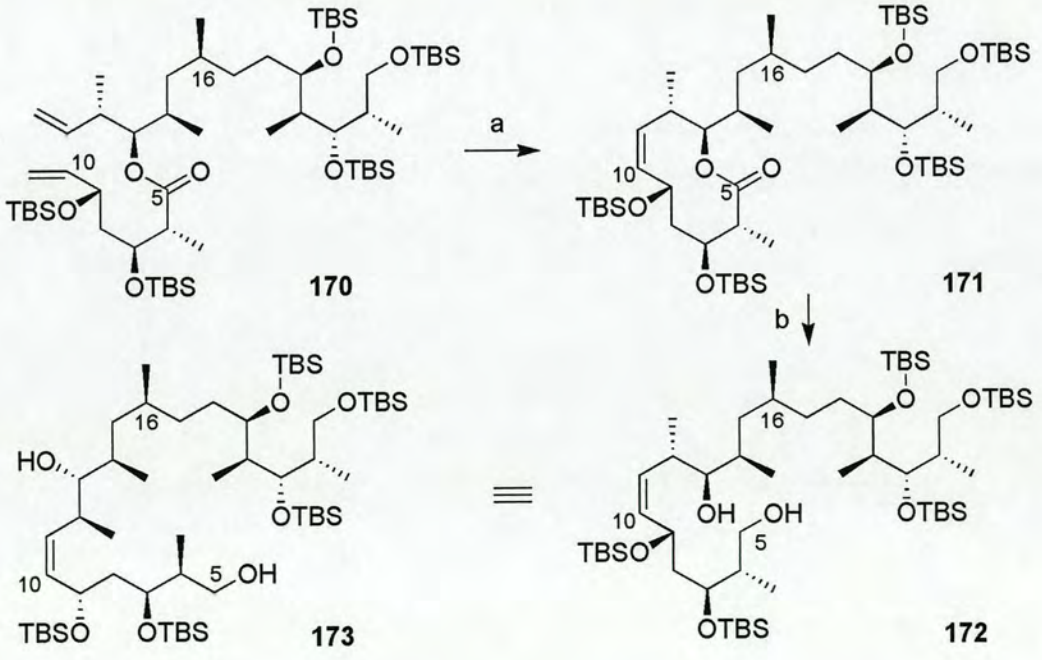


168
structure reported
Petit 1994

169
Paterson/Wright 2004
(structure confirmed)

Figure 16: *Original structure **168**[88] and actual structure **169** of dictyostatin*[89,90]

Curran *et al.* applied their esterification/RCM strategy (**Scheme 39**) based on the original structure **168**.[87] Treatment of a dilute solution of diene **170** with a high loading of Grubbs' 2nd generation catalyst **159** (50 mol%) under reflux for 24 h afforded lactone **171** in good yield (78 %) with the alkene formation giving only the *Z*-isomer. Reduction of the lactone moiety with $LiAlH_4$ afforded an advanced intermediate **172** towards dictyostatin A.



Scheme 39: *Esterification/RCM strategy towards dictyostatin **168***[87]

Reagents and Conditions: (a) Grubbs 2 **159** (50 mol%), CH_2Cl_2, 40 °C, 24 h (78 %); (b) $LiAlH_4$, THF, -20 °C to 0 °C (80 %).

1.5 CONCLUSIONS

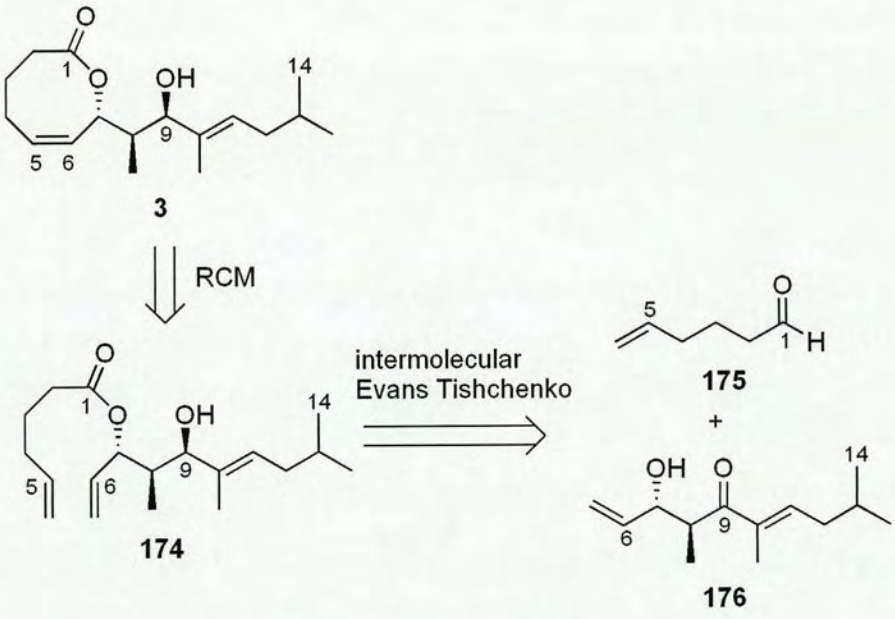
In summary, it has been shown that there are a variety of routes towards the octalactins, however they all suffer from the formation of C(9) epimers upon installation of the C(10)-C(15) alkyl chain to lactone **15**. The loss of stereochemical integrity affects the selective epoxidation of the C(10) – C(11) alkene, a moiety which has been reported to be important to the biological activity of octalactin A. Therefore, the route that we have proposed towards the octalactins incorporates the Evans-Tishchenko reaction followed by RCM. The reduction of β-hydroxy ketones as their *anti* diol monoester using the Evans-Tishchenko reaction has been shown to be very efficient and highly selective in a variety of natural products. Similarly, RCM has been shown to be very efficient in the construction of various medium lactones in natural product synthesis. The combination of both the Evans-Tishchenko reaction and RCM should allow for a highly selective and efficient synthesis of the octalactins.

RESULTS AND DISCUSSION PART 1

CHAPTER 2

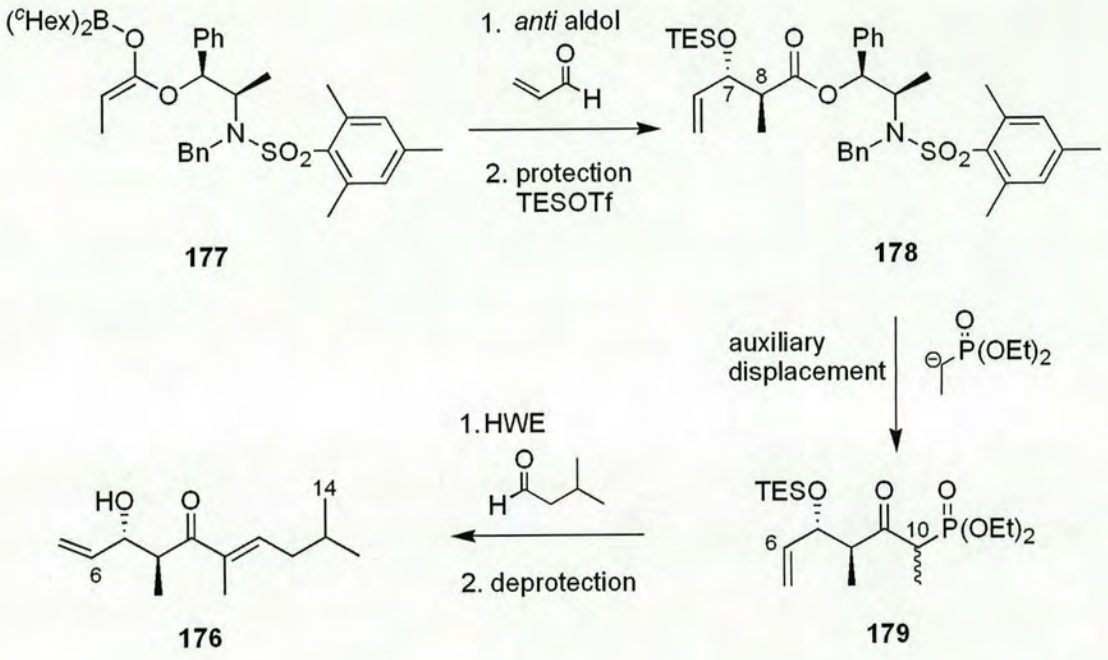
MODEL STUDIES

A model study was conducted so that the retrosynthetic analysis of octalactin A shown in Chapter 1 could be explored (**Scheme 40**). The model study involved the intermolecular Evans-Tishchenko coupling of β-hydroxy enone **176** and hex-6-en-1-al **175** to give *anti* diol monoester **174**. Ring closing metathesis of the terminal alkenes of triene **174** would give oxocene **3**, a simple model of octalactin A. Initial investigations centred around the preparation of model β-hydroxy enone **176**.



Scheme 40: *Retrosynthetic analysis of model lactone 3*

2.1. SYNTHESIS OF β-HYDROXY ENONE 176

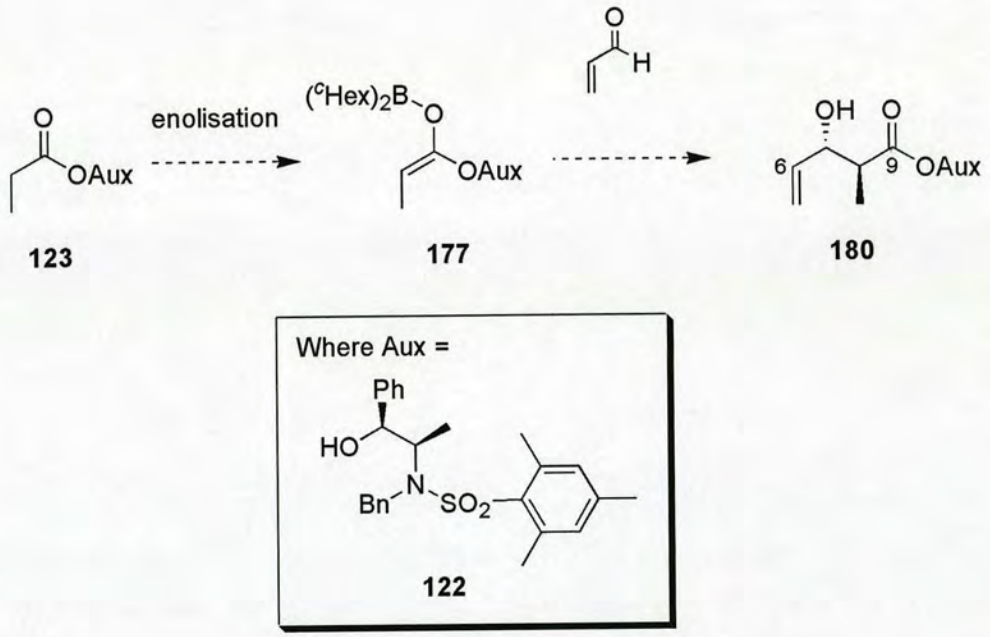


Scheme 41: *Proposed synthesis of β-hydroxy enone 176*

The strategy proposed for the synthesis of β-hydroxy enone **176** involved the use of a boron mediated *anti* aldol reaction of the acylated Abiko-Masamune auxiliary enolate **177** with acrolein (**Scheme 41**). This would give an *anti* aldol adduct which could be subsequently protected as the triethylsilyl ether **178**. Displacement of the Abiko-Masamune auxiliary with the anion of diethyl ethane phosphonate would give the β-ketophosphonate ester **179**. This β-ketophosphonate ester is similar to the key fragment presented in the retrosynthesis of octalactin A (**Scheme 15**). However in the synthesis of the model compound **3**, β-ketophosphonate ester **179** would then undergo a barium hydroxide induced Horner Wadsworth Emmons (HWE) olefination with isovaleraldehyde to give the protected *E*- enone. Desilylation of the *E*-enone would give the desired β-hydroxy enone **176**.

2.1.1. Construction of the C(6) – C(9) Fragment: Boron Mediated *Anti* Aldol reaction

The first step towards the synthesis of β-hydroxy enone **176** was the construction of the C(6) – C(9) moiety. This fragment contains a β-hydroxy ketone moiety with *anti* stereochemistry at C(7) – C(8). Therefore our strategy towards the synthesis of this fragment consisted of a boron mediated *anti* aldol reaction with a chiral auxiliary and acrolein as shown in **Scheme 42**. As discussed in Chapter 1 the Abiko-Masamune chiral auxiliary was chosen due to its formation of *anti* aldol adducts in high yields with high diastereocontrol.

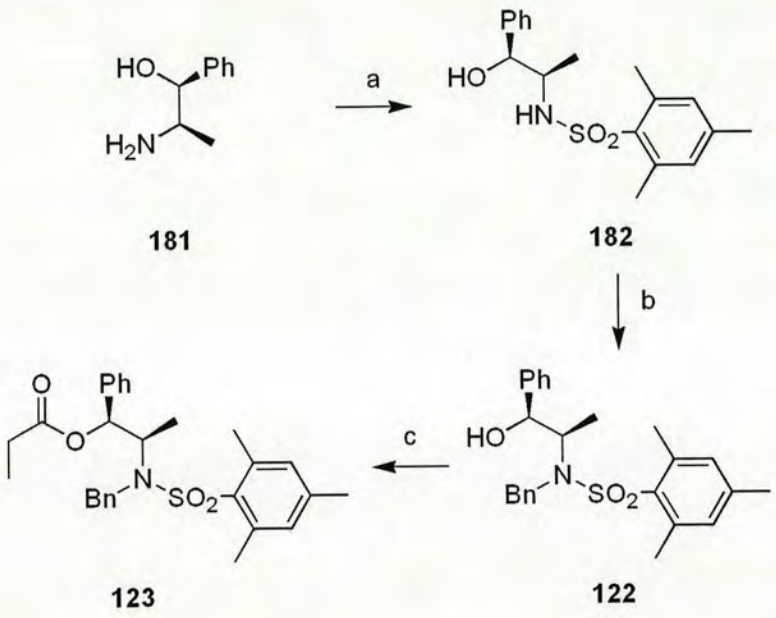


Scheme 42: *Strategy towards the construction of the C(6)-C(9) fragment*

2.1.1.1. Synthesis of the Abiko-Masamune Auxiliary

The propionate derivative of the Abiko-Masamune auxiliary **123** was synthesised (**Scheme 43**) using the conditions of Masamune in 3 steps (62 % overall yield).[53,54] Sulfonation of the amino group gave sulfonamide **182**, and this was followed by

selective *N*-benzylation to give auxiliary **122**. Finally, acylation gave the desired propionate derivative **123**.

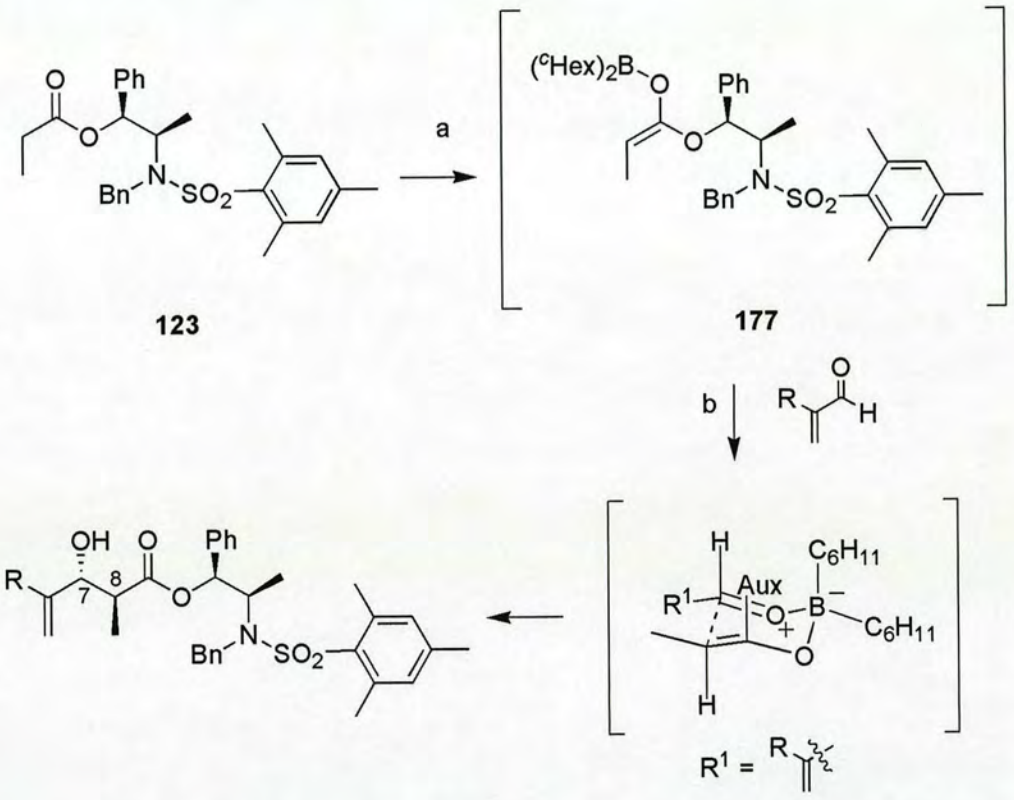


Scheme 43: *Synthesis of propionate derivative of the Abiko- Masamune auxiliary*[53,54]
Reagents and Conditions: (a) $MesSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 2 h (95 %); (b) ^tBuOK, DMF, 0 °C, 30 min; BnBr, RT, 4.5 h (71 %); (c) CH_3CH_2COCl, pyridine, 0 °C → RT (69 %).

2.1.1.2. *Anti* Aldol Reaction

Initial studies were carried out using methacrolein to compare the experimental results obtained with the synthesised Masamune auxiliary to those reported in the literature. The *anti* aldol reaction of propionate ester **123** with methacrolein using freshly prepared dicyclohexylboron triflate and triethylamine gave aldol adduct **183** in good yield (84 %) as shown in **Scheme 44**. Analysis of ^1H NMR showed the formation of aldol adduct **183** as a mixture of diastereomers (98:2 *anti*:*syn*) which was is good agreement with the literature. The stereochemistry of the major diastereomer of aldol adduct **183** was assigned on the basis of the large coupling (7.0 Hz) between the C(7)H and C(8)H protons, and the absolute stereochemistry was assumed by comparison of the experimental and literature optical rotations; ($[\alpha]_D$ = -

19.1 (c 1.32, $CHCl_3$), lit.[34] 19.7 (c 1.32, $CHCl_3$)). Encouraged by the high yield and diastereoselectivity, the reaction was attempted with commercially available acrolein.* The enolisation, using the conditions for the formation of aldol adduct **183** and an excess of enolate (2.5 equiv.), gave a high yield of the desired *anti* aldol adduct **180** as a colourless solid.



Entry	R	Yield (%)	ds (*anti*:*syn*)
183	Me	79	98:2
180	H	81	98:2

Scheme 44: *Anti aldol reaction with acrolein/methacrolein*

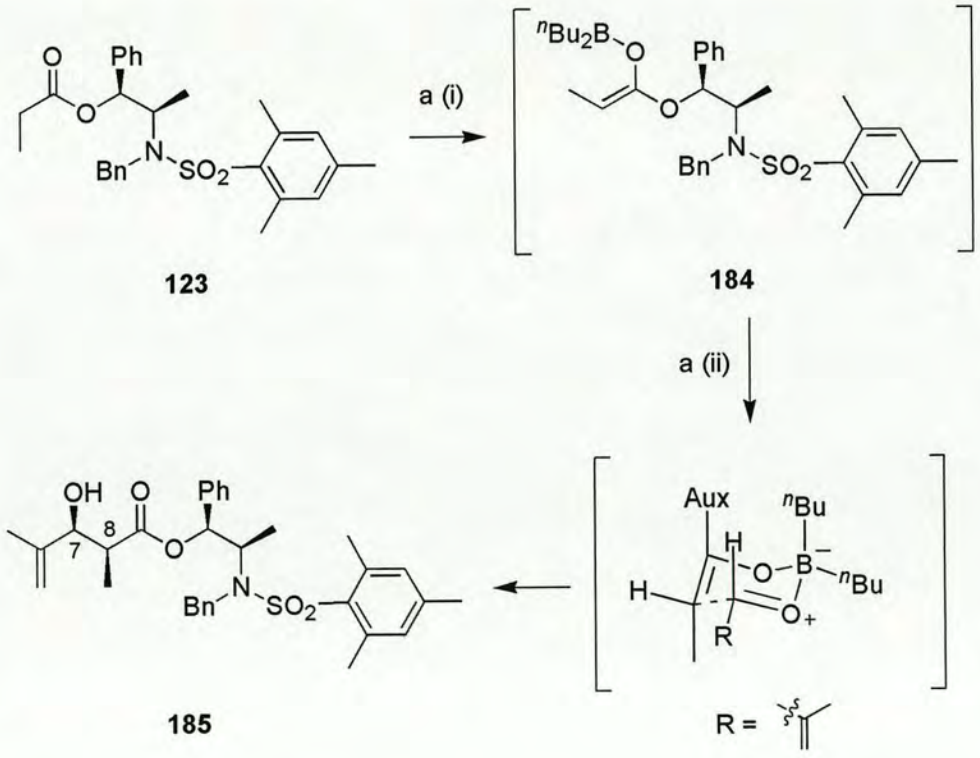
Reagents and Conditions: (a) Et_3N, $(C_6H_5)_2BOTf$, -78 °C, 2 h; (b) RCHO, -78 °C, 1 h then 0 °C for 1 h.

* There were concerns about the possibility of polymerisation when using acrolein, fortunately this was not observed.

The stereochemistry of the major diastereomer of aldol adduct **180** was determined by the large coupling (7.0 Hz) between the C(2)H and C(3)H protons and the absolute stereochemistry was assumed on the basis of literature precedent.[53,54]

2.1.1.3. *Syn* aldol Reaction

For comparative purposes, the *syn* aldol adduct **185** was also generated (**Scheme 45**) by treating propionate ester **123** with commercially available dibutyl boron triflate and Hünig's base to give *Z*-boron enolate **184**.[54] Treatment of enolate **184** with methacrolein gave the *syn* aldol adduct **185** in excellent yield (97 %) and high diastereoselectivity (>95:5 *syn*:*anti*). The stereochemistry of the major diastereomer **185** was assigned on the basis of the small coupling (3.7 Hz) between the C(2)H and C(3)H protons and the absolute stereochemistry was assumed based on literature precedent.[54]



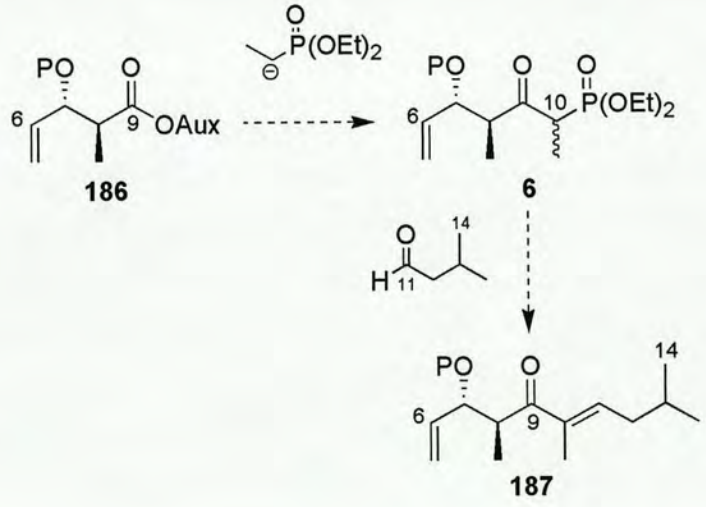
Scheme 45: *Syn aldol reaction with methacrolein*

Reagents and Conditions: (a) (i) $^{i}Pr_2NEt$, Bu_2BOTf, -78 °C, 2 h; (ii) methacrolein, -78 °C, 1 h then 0 °C for 1 h (97 %).

The application of auxiliary **122** in the high yielding and highly selective formation of *anti* aldol adducts has been demonstrated with the vinyl aldehyde methacrolein, and is comparable to the literature. The application of the propionate derivative of auxiliary **123** in the *anti* aldol reaction with acrolein has allowed the synthesis of adduct **181**, which contains the C(6) – C(9) fragment of octalactin A, in high yield and selectivity.

2.1.2. Carbon Backbone Extension: Anionic Displacement of Auxiliary 122

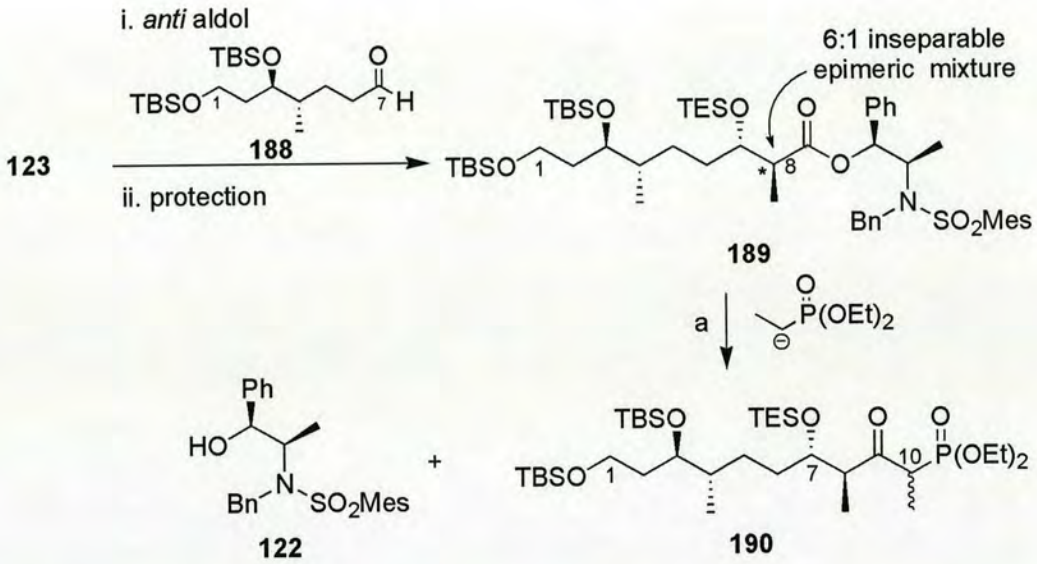
It was necessary to extend the carbon backbone of the aldol adduct to produce the required enone **187**, in order to obtain one of the key fragments in the synthesis of the octalactin model. This could be achieved by displacement of auxiliary **122** from the aldol adduct **186** with the lithiated anion of diethyl ethane phosphonate to form β-ketophosphonate ester **6**, followed by a Horner Wadsworth Emmons olefination with an appropriate aldehyde (**Scheme 46**).



Scheme 46: *Proposed displacement of Abiko-Masamune auxiliary*

Work has been carried out within the Hulme group using the Abiko-Masamune chiral auxiliary in the 1st generation synthesis of octalactin A (**Scheme 47**).[29] The

anti aldol reaction using the propionate derivative of the Abiko-Masamune chiral auxiliary **123** and aldehyde **188** gave the *anti* aldol adduct **189** as an inseparable (6:1) epimeric mixture at C(8). The C(1) – C(10) fragment was synthesised by displacement of auxiliary **122** using the anion of diethyl ethane phosphonate to produce the β-ketophosphonate ester **190** in 59 % yield as a 3:1 mixture of diastereomers at C(10). A further amount (11 %) of product material was also isolated and analysis of the 250 MHz ^{1}H NMR implied this was the minor diastereomer from the *anti* aldol reaction. Auxiliary **122** was recovered from the reaction in high yield (94 %).



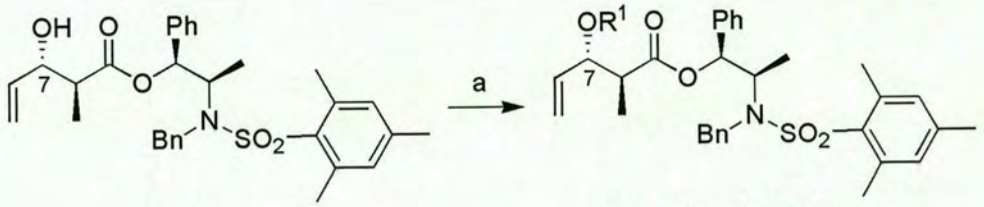
Scheme 47: *Phosphonate displacement of auxiliary 122*

Reagents and Conditions: (a) (i) $EtP(O)(OEt)_2$ (4.4 equiv.), ^{n}BuLi (4.4 equiv.), THF, -78 °C, 1 h; (ii) **190**, 20 min, THF, -78 °C followed by 10 min at 0 °C.

2.1.3. Hydroxyl Protection

The hydroxyl group at C(7) had to be protected prior to anionic displacement of the Masamune auxiliary to avoid anion quenching and epimerisation occurring. Treatment of aldol adduct **180** (**Scheme 48**) with both *tert*-butyldimethylsilyl triflate

and the triethylsilyl triflate gave the adduct protected as both the *tert*-butyldimethylsilyl ether **191** and the triethylsilyl ether **178** respectively in high yields (95 % and 94 %).



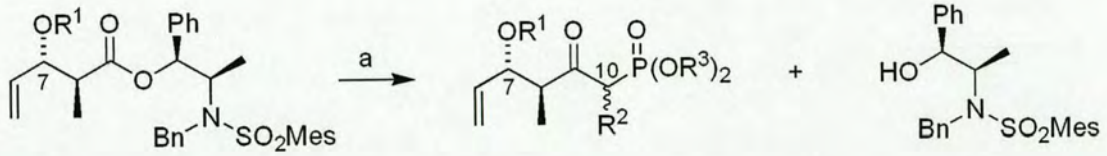
180

191 R^1 = TBS (95%)
178: R^1 = TES (94%)

Scheme 48: *Silyl protection of anti aldol adducts*

Reagents and Conditions: (a) 2,6-lutidine, 0 °C, 5 min; TBSOTf or TESOTf, 60 min, 0 °C.

The α-carbanionic alkylphosphonate displacement conditions developed from the displacement of thioesters[91] and Abiko-Masamune auxiliary **122**,[29] previously carried out by members of the Hulme group, were applied to aldol adducts **191** and **178** (**Scheme 49**).



191: R^1 = TBS
178: R^1 = TES

179: R^1 = TES, R^2 = Me, R^3 = Et
192: R^1 = TBS, R^2 = Me, R^3 = Et
193: R^1 = TES, R^2 = H, R^3 = Me

122

Scheme 49: *Anionic displacement of Masamune chiral auxiliary* ***122***

Reagents and Conditions: (a) (i) $R^2CH_2P(O)(OR^3)_2$ (4.4 equiv.), ^{n}BuLi (4.4 equiv.), THF, -78 °C, 1 h; (ii) **191/178**, 60 min, THF, -78 °C.

The reaction conditions were varied (**Table 4**) to optimise the yield of β-ketophosphonate esters **179** and **192**. The displacement was primarily studied with

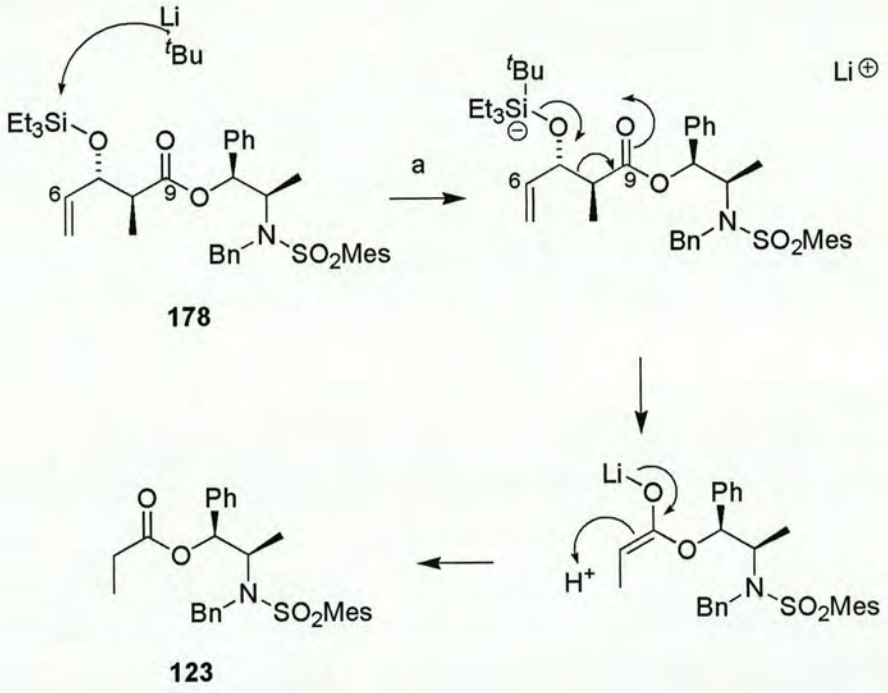
the TES protected compound **178** and it was found that treatment with the ethane phosphonate anion gave only recovered starting material (**Table 4, entry 1**). The reaction time was extended, followed by addition of a further 4.4 equivalents of the phosphonate anion, but again the reaction only gave recovered starting material (**Table 4, entry 2**).

Entry	R^1	R^2	R^3	Conditions	Yield **179/192/ 193** /%	Yield **122** /%	Recovery **191/178** /%
1	TES	Me	Et	^{n}BuLi, -78 °C, 50 min	--	--	98
2	TES	Me	Et	^{n}BuLi, -78 °C, 3 h, followed by 4.4 equivalents of anion	--	--	98
3	TES	Me	Et	DMPU, ^{t}BuLi, -78 °C → RT over 4 h	--	--	--
4	TBS	Me	Et	^{n}BuLi, -78 °C, 1 h	51	52	--
5	TBS	Me	Et	^{n}BuLi, -78 °C, 2 h	46	26	--
6	TBS	Me	Et	^{n}BuLi, -78 °C → RT over 4 h	41	19	--
7	TBS	Me	Et	^{n}BuLi, -78 °C → 0 °C over 4 h	16	50	--
8	TBS	Me	Et	^{n}BuLi, DMPU, 0 °C → RT over 4 h	13	35	--
9	TES	H	Me	^{n}BuLi, -78 °C, 3 h, 0 °C, 8 h	24	23	--
10	TBS	H	Me	^{n}BuLi, -78 °C, 3 h, 0 °C, 8 h	--	--	92

Table 4: *Phosphonate displacement of aldol adducts **194** and **179***

It was hoped that using stronger reaction conditions (DMPU, ^{t}BuLi, warmed from -78 °C to RT) would produce β-ketophosphonate ester **179** (**Table 4, entry 3**). However the reaction conditions were too forcing and the triethylsilyl protecting group was removed causing a retro-aldol reaction to occur, producing propionate

ester **123** in a high yield (97 %). A proposed mechanism for the retro-aldol reaction is shown in **Scheme 50**.

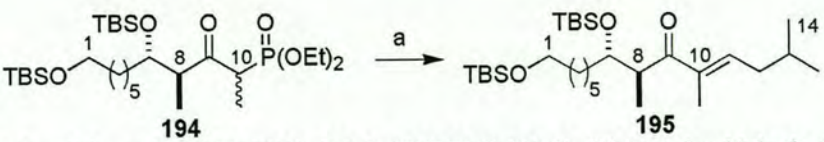


Scheme 50: *Retro-aldol reaction*

Reagents and Conditions: DMPU, ^{t}BuLi, -78 °C → RT over 4 h (97 %).

The protecting group on the aldol adduct was changed to a bulkier *tert*butyldimethylsilyl group to prevent desilylation and subsequent retro-aldol reactions. Treatment of aldol adduct **191** using standard phosphonate anion conditions (**Table 4, entry 4**) produced a 3:1 mixture of diastereomers (confirmed by ^{1}H NMR) of β-ketophosphonate ester **192** in a moderate yield (51 %) with moderate recovery of auxiliary **122** (52 %). These diastereomers were not separated since previous work within the group which has shown that similar β-ketophosphonate esters **194** afford only a single *E*-enone **195** upon HWE olefination.*[29] Extension of

*



Reagents and Conditions: (a) (i) $Ba(OH)_2 \cdot 8H_2O$, THF/H_2O (40:1); (ii) isovaleraldehyde, RT, 18 h (85 %).

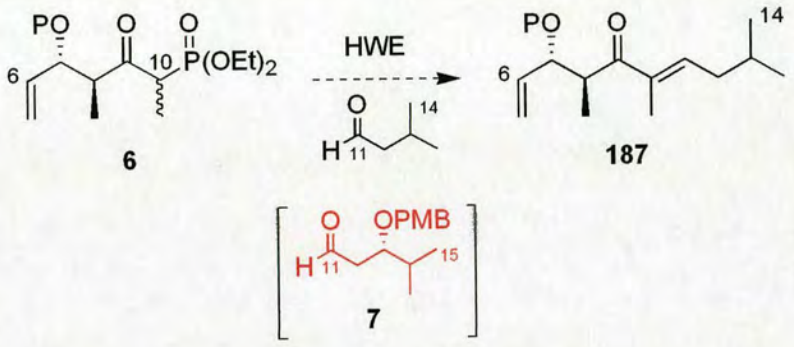
the reaction time (from 2 h to 4 h, **Table 4 entries 5 and 6**) did not improve the yield of β-ketophosphonate ester **192**. It has also been noted in previous studies of similar reactions,[29] that although the reaction may have appeared to have gone to completion when monitoring by TLC (indicated by the disappearance of starting material and the formation of two low R_f spots, one of which corresponds to that of the free auxiliary **122**), upon quenching the reaction at -78 °C only starting materials were recovered. This suggests that the reaction may have occurred during the sampling process (i.e. as the material warmed to > -78 °C). The reaction conditions were adapted to accommodate for this phenomenon by warming the reaction to 0 °C, unfortunately the yield of β-ketophosphonate ester **192** did not increase (**Table 4, entry 7**). Stronger reactions conditions were applied to aldol adduct **191** (^{n}BuLi, DMPU, 0 °C → RT over 4 h), and unfortunately β-ketophosphonate ester **192** was still obtained in a low yield (**Table 4, entry 8**).

The final approach taken was to alter the reaction conditions by changing the phosphonate anion from diethyl ethane phosphonate to dimethyl methane phosphonate. Addition of the anion of dimethyl methane phosphonate to TES adduct **178** produced β-ketophosphonate ester **193** in a low yield, and treatment of the TBS adduct **191** with dimethyl methane phosphonate gave no reaction.

Investigations towards the total synthesis of octalactin A into the displacement of auxiliary **122** with a phosphonate anion have shown that the C(6)-C(9) fragment, β-ketophosphonate ester **192** can be synthesised in a moderate yield. Therefore these studies have shown that the nucleophilic displacement of the ester moiety contained in chiral auxiliary **122** poses a problem for the synthesis of β-ketophosphonate ester **192**. Further investigations towards the optimisation of the β-ketophosphonate ester **192** will be discussed in Chapter 3.

2.1.4. Horner Wadsworth Emmons Coupling

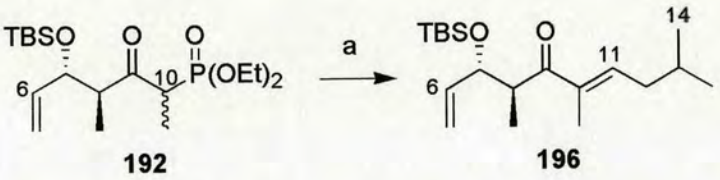
In the model synthesis of octalactin A, the introduction of the C(11) – C(14) fragment to β-ketophosphonate ester **6** was proposed *via* a Horner Wadsworth Emmons (HWE) reaction, as shown in **Scheme 51**. Based on previous work within the group,[29] the olefination of β-ketophosphonate ester **6** with a simple aldehyde, isovaleraldehyde (similar to aldehyde **7**), under mild conditions would afford enone **187** in high yield and high selectivity (*E*:*Z*).



Scheme 51: *HWE olefination*

Treatment of both diastereomers of β-ketophosphonate ester **192** with activated barium hydroxide* and isovaleraldehyde gave α,β-unsaturated enone **196** (**Scheme 52**) in 80 % yield with *E*/*Z* selectivity >95:5. Analysis of the crude products using 250 MHz ^{1}H NMR revealed a single geometrical isomer and a single diastereomer, thereby confirming that no epimerisation α to the carbonyl had occurred in the carbanionic displacement of auxiliary **122** or in the HWE reaction itself.

* Activation was achieved by heating $Ba(OH)_2 \cdot 8H_2O$ in a high temperature (110 °C) oven for >12 h.

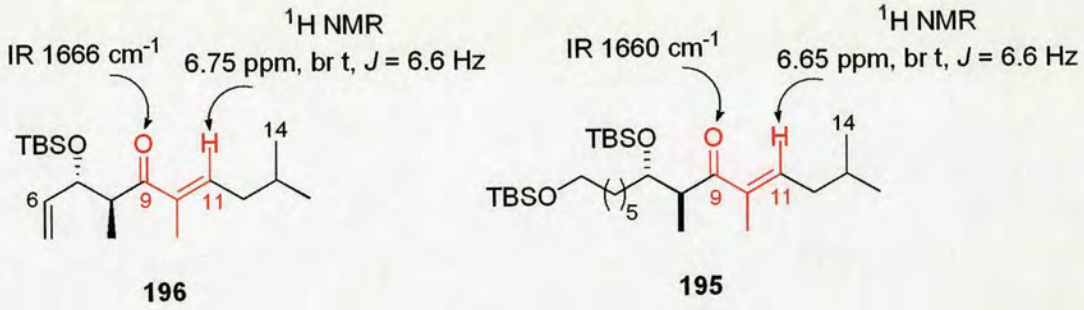


192 196

Scheme 52: *HWE coupling to form the E- enone* ***196***

Reagents and Conditions: (a) (i) $Ba(OH)_2 \cdot 8H_2O$, THF/H_2O (40:1); (ii) isovaleraldehyde, RT, 18 h (80 %).

Further analysis of ^1H NMR (**Figure 17**) of enone **196** showed a signal at $\delta = 6.75$, br t, $J = 6.6$ Hz, indicative of an enone proton, this was in good agreement with known compound **195** ($\delta = 6.65$, br t, $J = 6.6$ Hz).[29,91] Infrared spectroscopy of enone **196** showed a stretch at 1666 cm^{-1} indicative of an α,β-unsaturated carbonyl system, also in good agreement with that observed for known enone **195** (1660 cm^{-1}).



196 195

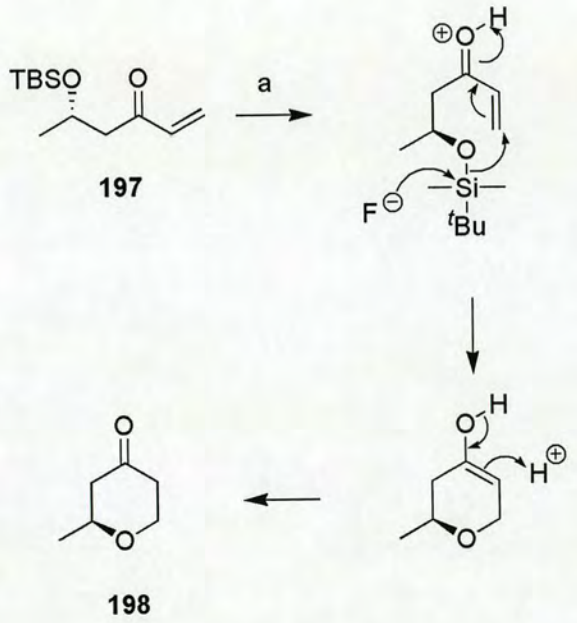
Figure 17: *Comparison of spectroscopic data with known compound* ***195***

The extension of the carbon backbone of enone **196** to introduce the C(11) – C(14) fragment and install the enone moiety was successfully achieved *via a* HWE olefination. Olefination of β-ketophosphonate ester **192** under mild conditions (barium hydroxide) afforded the *E*-enone **196** in high yield (80 %) with high *E*:*Z* selectivity. Deprotection of β-hydroxy enone **196** would allow further extension of the carbon skeleton of the octalactin A model *via* Evans-Tishchenko coupling.

2.1.5. Deprotection of Horner Wadsworth Emmons Adducts

The desilylation of primary and secondary hydroxyls with HF-based reagents has been shown to be milder than the conditions required for TBAF removal of TBS groups[92] and was used in the deprotection of HWE adduct **196**.

Care was taken in the monitoring of this reaction as previous studies have shown that extended reaction times (≥ 1 h), or improper quenching, can result in the disappearance of the desired products. Studies within the group on the synthesis of decarestrictine D (**Scheme 53**) have shown that extended exposure of β-hydroxy enone **197** to HF results in the formation of undesired product **198**. Analysis of 250 MHz ^{1}H NMR have shown that β-hydroxy enone **197** undergoes desilylation, followed by acid promoted cyclisation to form pyranone **198**.[93]

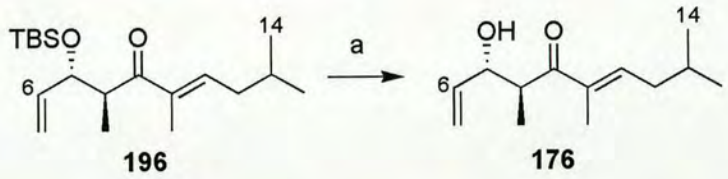


Scheme 53: *By-products from deprotection of β-hydroxy enone **197** using HF*

Reagents and Conditions: (a) HF (40 % aqueous), MeCN, 10 min.

In the deprotection of β-hydroxy enone **196**, the reaction time was strictly monitored followed by thorough quenching and immediate purification by chromatography to reduce the risk of by-product formation.

HWE adduct **196** was treated with 40 % aqueous HF in MeCN (**Scheme 54**) for 5 min and purification produced β-hydroxy enone **176** in excellent yield (95 %). Analysis of the ^{1}H NMR showed β-hydroxy enone **176** only and no other products. The single product indicated that deprotection of HWE adduct **196** had occurred with no epimerisation at C(7). Analysis of ^{1}H NMR showed the presence of the vinylic enone signal (δ = 6.62, br t, J = 7.4 Hz) and infra red spectroscopy showed a hydroxyl stretch (3422 cm^{-1}) and an α,β-unsaturated stretch (1662 cm^{-1}), confirming that by-products were not formed.



196 **176**

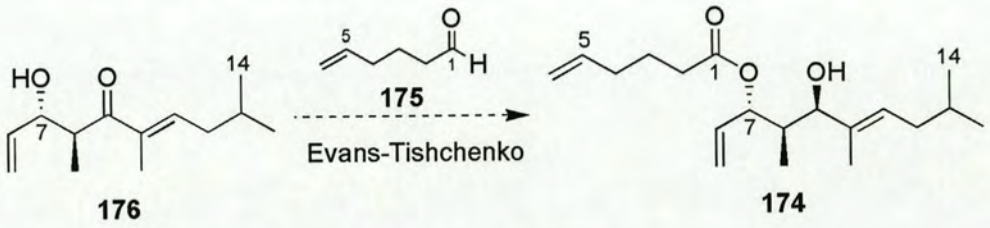
Scheme 54: *Deprotection of HWE adduct **196***

Reagents and Conditions: (a) HF (40 % aqueous), MeCN, 5 min (95 %).

Thus, HWE adduct **196** was efficiently deprotected to give β-hydroxy enone **176** in excellent yield (95 %) which has allowed the synthesis of a model C(6) – C(14) fragment.

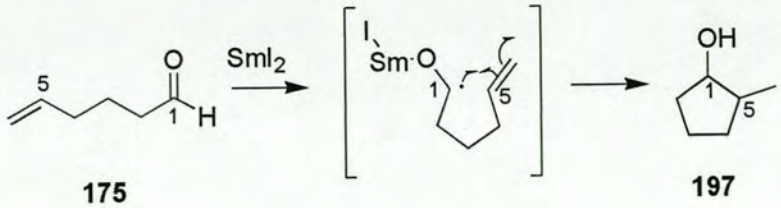
2.2 CARBON BACKBONE EXTENSION: EVANS-TISHCHENKO COUPLING

With the successful formation of β-hydroxy enone **176**, the installation of the C(1) – C(5) backbone *via* esterification of the C(8) hydroxyl and the selective reduction of the C(9) enone was now required for the synthesis of lactone **3**. As discussed in Chapter 1, we have proposed that the intermolecular Evans-Tishchenko reaction of β-hydroxy enone **176** and hexenal **175** can fulfil all of these criteria in one synthetic step, as shown in **Scheme 55**.



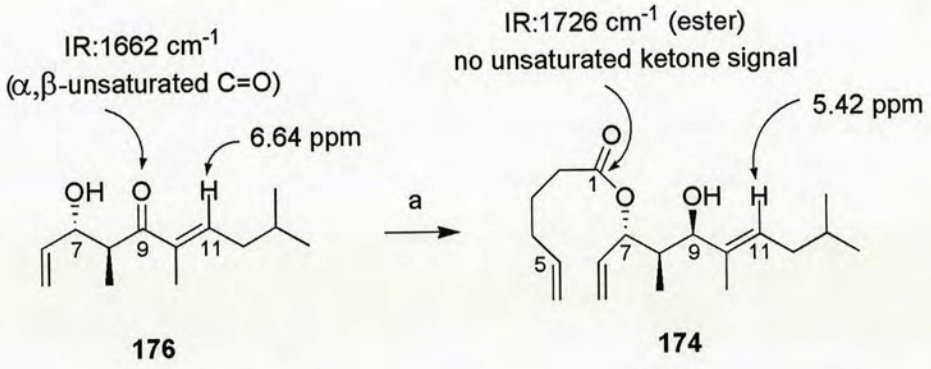
Scheme 55: *The Evans-Tishchenko coupling*

The intermolecular Evans-Tishchenko reaction in this synthesis of octalactin A required the coupling of β-hydroxy enone **176** with an aldehyde **175** containing an alkene moiety. Therefore, the Sm(III) pinacol catalyst was generated *in situ* before hexenal **175** was added to the reaction mixture to prevent unwanted cyclisation occurring *via* a ketyl radical anion, which could potentially form cyclopentenol **197** (**Scheme 56**).[94,95]



Scheme 56: *Proposed synthesis of by-product **197***

Treatment of Sm(III)•benzaldehyde pinacol adduct with hexenal **175** for 30 min, followed by the addition of β-hydroxy enone **176** with stirring for 30 min, afforded the *anti* diol monoester **174** in 93 % yield and as a 9:1 mixture of diastereomers (**Scheme 57**). ^{1}H NMR studies revealed a significant shift of the C(11) vinylic proton [δ = 6.64 ppm (**176**) → δ = 5.42 ppm (**174**)] indicating reduction of the enone functionality. Loss of an aldehyde peak (δ = 9.42 ppm), as well as a shift in the C(7) proton [δ = 4.19 ppm (**176**) → δ = 5.22 – 5.14 ppm (**174**)] also suggesting ester formation. Infrared spectroscopy showed a change in the carbonyl region from 1662 cm^{-1} (indicative of an α,β-unsaturated carbonyl) to 1726 cm^{-1} suggesting the formation of *anti* diol monoester **174**.

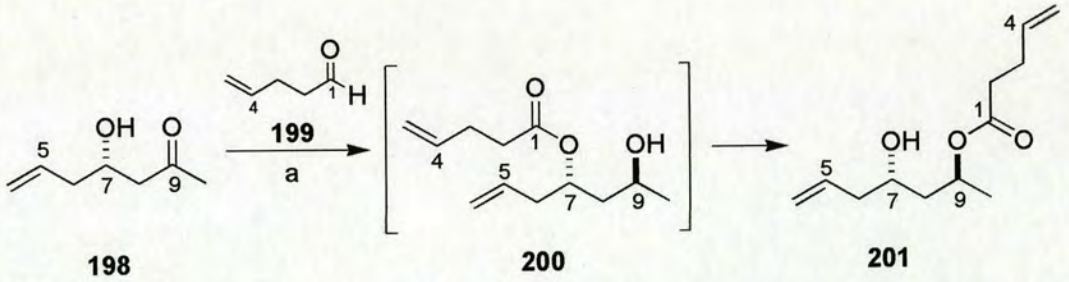


176 **174**

Scheme 57: *Evans-Tishchenko reaction*

Reagents and Conditions: (a) (i) PhCHO, SmI_2 (0.1 M in THF, 30 mol%), followed by hexenal, 30 min: (ii) **176**, THF, -10 °C, 30 min (93 %).

Other possible reactions that could have occurred include a Tishchenko, or a pinacol coupling onto the C(9) carbonyl itself. Studies within the group towards the synthesis of *anti* diol monoester **200** *via an* Evans-Tishchenko coupling of β-hydroxy ketone **198** and aldehyde **199**, have shown the migration of the ester moiety to give ester **201**, as shown in **Scheme 58**.[96]



Scheme 58: *Acyl migration*

Reagents and Conditions: (a) (i) PhCHO, SmI_2 (0.1 M in THF, 30 mol%), followed by **199**, 30 min: (ii) **198**, THF, -10 °C, 3 h (94 %).

These can be excluded on the basis of the ^{1}H NMR data for C(7)H (δ = 5.22 – 5.14, m) and C(9)H (δ = 3.88, d, J = 4.8 Hz for **174**). The data correlates well with the reported values for benzoate **202**: C(7)H (δ = 5.02, dt ≡ q, J = 6.8 Hz) and C(9)H (δ = 3.86, d, J = 3.8 Hz), as shown in **Figure 18**.

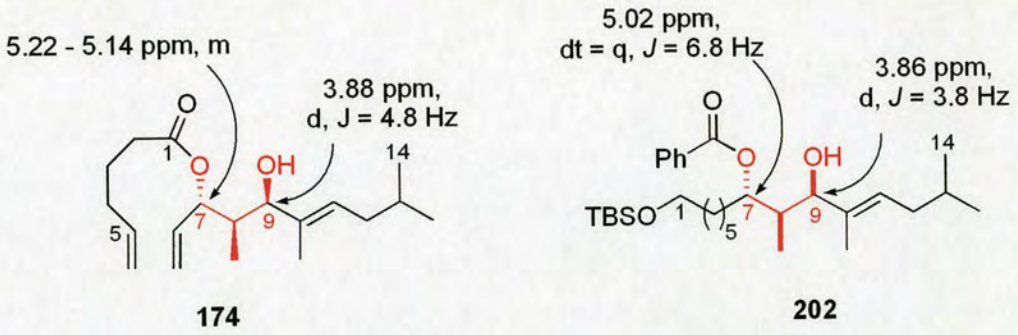
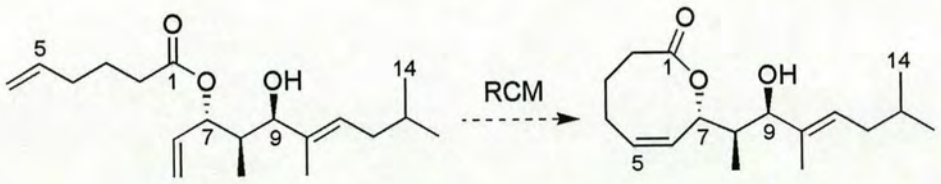


Figure 18: *NMR comparison of anti diol monoesters **174** and **202***

The successful intermolecular Evans-Tishchenko reaction with aldehyde **175** and β-hydroxy enone **176** formed the *anti* diol monoester **174** with high yield (93 %) as a 9:1 mixture of diastereomers. The inclusion of the two terminal alkenes in triene **174** could now allow cyclisation to occur, forming the desired 8-membered lactone.

2.3 FORMATION OF THE C(1) – C(7) LACTONE *VIA* RING CLOSING METATHESIS

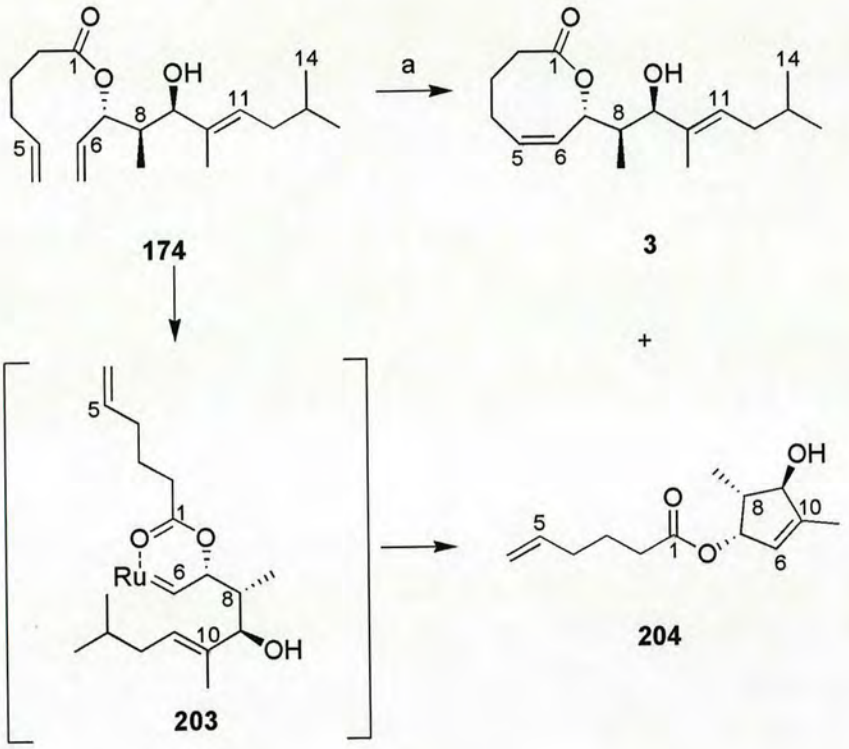
The elegant installation of the ester moiety and selective reduction of the C(9) enone of β-hydroxy enone **176** in the formation of *anti* diol monoester **174** has been achieved by the Evans-Tishchenko reaction. The resultant *anti* diol monoester **174** was synthesised to contain 2 terminal alkenes which could allow the formation of the C(1) – C(7) lactone **3** *via* Ring Closing Metathesis (RCM) as shown in **Scheme 59**.



174 **3**

Scheme 59: *Lactonisation via RCM*

A potential prerequisite for the RCM of triene **174** was the protection of the C(9) hydroxyl to allow the metathesis to proceed smoothly. However, previous studies within the group have shown that the protection of the C(9) hydroxyl is only required to prevent acyl migration in the Evans-Tishchenko coupling. Since no acyl migration was observed (**Scheme 58**) the RCM of triene **174** was attempted without protection of the C(9) hydroxyl. Treatment of *anti* diol monoester **174** (**Scheme 60**), with the Grubbs 2nd generation catalyst **159** (10 mol%) in degassed CH_2Cl_2 at room temperature for 24 h showed very slight formation (20 %) of lactone **3**. Increased catalyst loading (20 mol%) and heating under reflux for 24 h produced a 9:1 mixture of lactone **3** and substituted cyclopentene **204**.



Scheme 60: *RCM of triene* ***174***

Reagents and Conditions: (a) Grubbs' 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h (89 %).

^{1}H NMR of the major product revealed the loss of the two terminal alkene signals (δ = 4.98 – 4.90, m, C(5)H=CH_2; δ = 5.22 – 5.14, m, C(6)H=CH_2) and the formation of a new alkene signal (δ = 5.44 – 5.29, m, C(5)*H* & C(6)*H*) indicating the formation of the lactone. The presence of the C(11) – C(14) fragment was easily detected by the ^{1}H NMR (δ = 1.02, d, *J* = 6.9 Hz, C(13)H(CH_3)$_2$) showing that the RCM major product was lactone **3**. ^{1}H NMR analysis of the minor product has shown the presence of two distinctive terminal alkene signals (δ = 5.75, ddd, *J* = 17.0, 10.3 & 6.7 Hz, C(5)*H*=CH_2; and 5.07 – 4.92, m, C(5)H=CH_2) and the absence of signals corresponding to protons attached to C(11) – C(14), which suggested that substituted cyclopentene **204** is also formed in the RCM of triene **174**. The formation of by-product **204** is thought to be due to the formation of stable intermediate **203** which directs the C(5) alkene away from the C(6) alkene and then allows the metathesis with the C(10) tri-substituted alkene. It was thought that a more functionalised *anti*

diol monoester could potentially allow a conformation which would be preferable to the formation of an 8-membered lactone.[14]

A convergent approach to the carbon framework of octalactin A **1** has demonstrated the highly selective and efficient nature of the intermolecular Evans-Tishchenko reaction and the effectiveness of RCM. The synthetic strategy should allow for a more efficient synthesis of the octalactins than previously reported, and should also allow for the synthesis of novel analogues of octalactin A with potentially improved biological activity.

The key β-hydroxy enone **176** in this Evans-Tishchenko/RCM strategy was synthesised in high yield (95 %) using a highly efficient HWE reaction between isovaleraldehyde and β-ketophosphonate ester **192**.

β-Ketophosphonate ester **192** was synthesised with high stereo-control (due to the *anti* aldol reaction using auxiliary **122**) but only in moderate yield due to the poor displacement of auxiliary **122** with a phosphonate anion. Since this fragment is also required for the total synthesis of octalactin A, further investigation into the optimisation of the route leading to β-ketophosphonate ester **192** was required and will be discussed in Chapter 3.

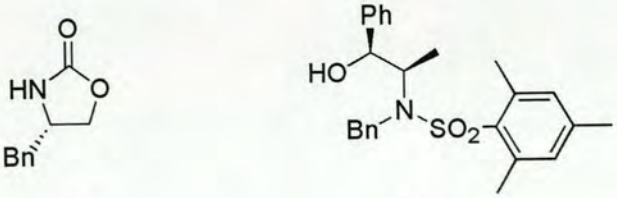
RESULTS AND DISCUSSION PART 2

CHAPTER 3

IMPROVING THE SYNTHESIS OF THE C(6) – C(10) FRAGMENT OF OCTALACTIN A: THE GENERATION OF A THIOL DERIVED ABIKO-MASAMUNE AUXILIARY

3.1 INTRODUCTION

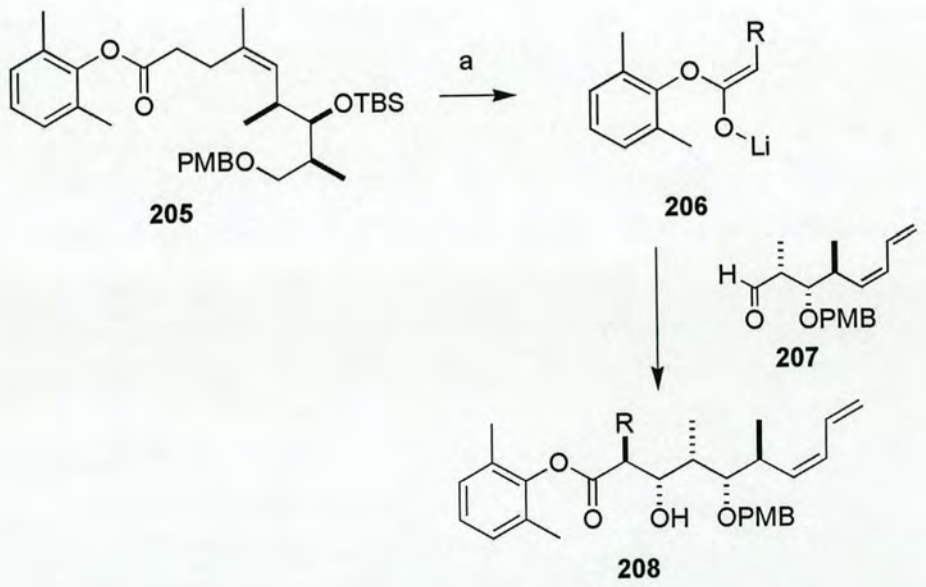
As explained in Chapter 2, the synthesis of the C(6) – C(10) fragment of octalactin A relies on the use of a chiral auxiliary (**Figure 19**) to direct a boron mediated *anti* aldol at the C(7) – C(8). The use of chiral auxiliaries in the synthesis of β-hydroxy ketones under these aldol conditions with relative and absolute stereocontrol is a very common and efficient tool. One of the most common auxiliaries used to form these adducts is an oxazolidinone synthesised by Evans *et al.*[45] Oxazolidinone **120** is widely used for the synthesis of *syn* aldol adducts giving generally excellent relative and absolute control. However using similar conditions and increasing the steric hindrance of the substituents on the boron ligand does not form the *E*-boron enolate required for *anti* aldol formation. Evans and co-workers have investigated the use of auxiliary **120** in the generation an *anti* aldol adducts and they have discovered that through careful control of the boron reagent, and by using chelating additives (e.g. $MgCl_2$), the desired *anti* aldol adducts can be obtained.[50,51] However, in general the investigation into the selective synthesis of *anti* aldol adducts using chiral auxiliary control has been very limited.



120 **122**

Figure 19: *Evans and Abiko-Masamune chiral auxiliaries*

The role of carboxylic esters in achiral *anti* aldol reactions is well known and although *E*-enolate formation is generally preferred, the selectivity in the formation of the *anti* aldol adducts can be poor. However, it has been found that treatment of the *E*-enolate of a hindered phenolic ester (2,6-dimethoxyphenyl propionate) with aldehydes can give *anti* aldol adducts with high diastereoselectivity. In their synthesis of discodermolide, Paterson *et al.* (**Scheme 61**) used low temperatures (-100 °C) to form the *E*-enolate of carboxylic ester **205**. Treatment of enolate **206** with the functionalised aldehyde **207** gave the *anti* aldol adduct **208** in high yield (81 %) and high dr (>97:3 *anti*:*syn*).[44]

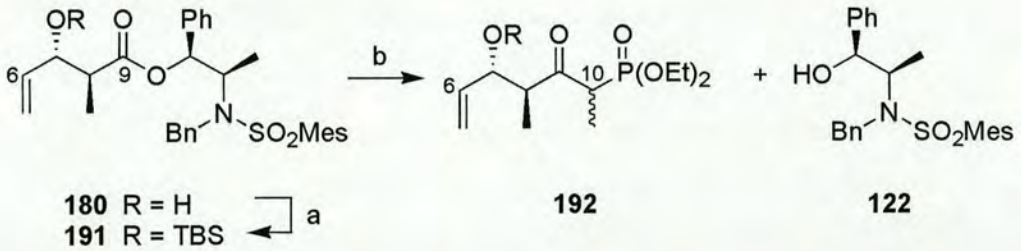


Scheme 61: *Paterson's synthesis of discodermolide*[44]

Reagents and Conditions: (a) (i) **205**, LiTMP, LiBr, THF; (ii) **207**, -100 °C (81%).

Recent studies[52-55,97] have shown that chiral carboxylic esters can undergo enolisation with alkyl boron triflates and tertiary amines, allowing them to be suitable candidates for boron mediated aldol reactions. Abiko *et al.* have investigated the synthesis of *anti* aldols and have synthesised a carboxylic ester chiral auxiliary which can generate aldol adducts in high yield and, in addition, the correct choice of reagents can control both *anti* and *syn* stereochemistry. The Abiko-Masamune

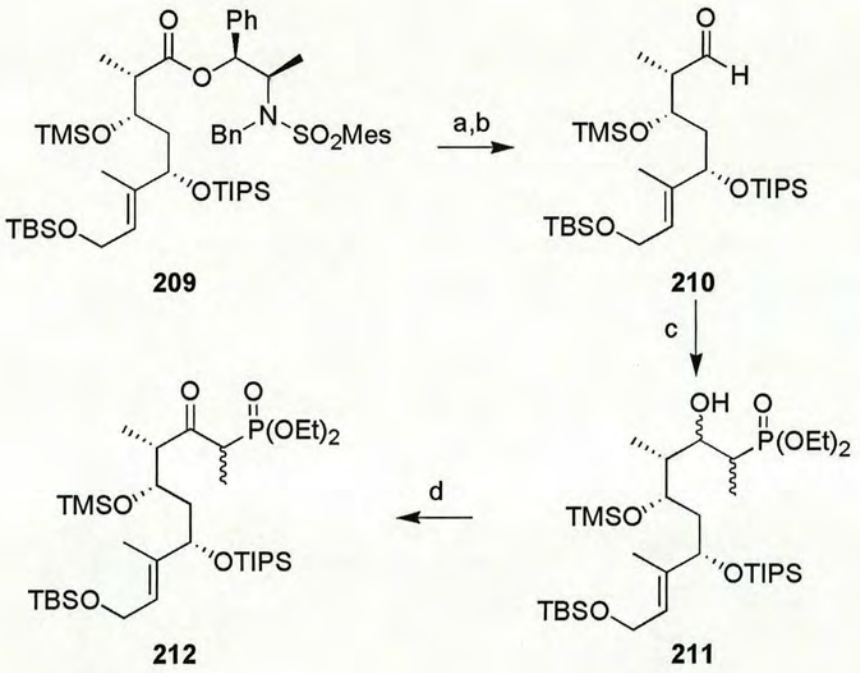
auxiliary **122** (derived in 2 steps from norephedrine) has been used to synthesise a variety of aldol adducts using bulky boron triflates and triethylamine with excellent selectivity for the *anti* diastereomer.[54] Therefore auxiliary **122** was used to construct the *anti* C(7) – C(8) fragment (**Scheme 62**) of octalactin A. As discussed in Chapter 2, the aldol reaction using propionate ester **123** and acrolein gave aldol adduct **180** in high yield and selectivity (81 %, 98:2 *anti*:*syn*). It was thought that displacement of the auxiliary with a phosphonate ester anion would efficiently afford β-ketophosphonate ester **192**, which could then undergo a HWE olefination with an aldehyde to synthesise a key fragment of octalactin A. Unfortunately displacement of the Abiko-Masamune auxiliary using this strategy proved problematic.



Scheme 62: *Synthesis of β-ketophosphonate ester **192***

Reagents and Conditions: (a) 2,6-lutidine, 0 °C, 5 min; TBSOTf, 60 min, 0 °C (51 %); (b) (i) ^{n}BuLi, $EtP(O)(OEt)_2$, THF, -78 °C; (ii)**191**, -78 °C (51 %).

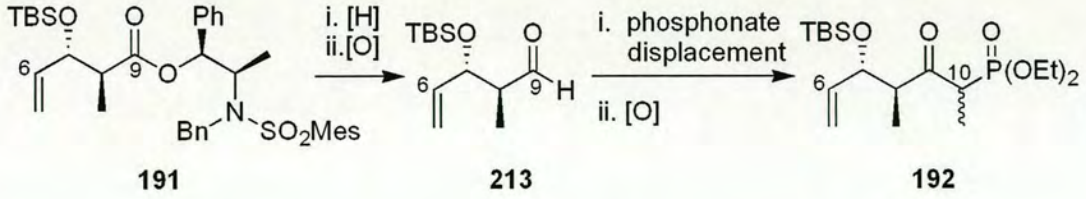
During their synthesis of rhizoxin D (**Scheme 63**) Leahy *et al.*[66] avoided the direct displacement of the Abiko-Masamune auxiliary with a phosphonate anion and instead used a 2-step conversion of aldol adduct **209** to intermediate aldehyde **210**, which reacted with the phosphonate ester anion to give phosphonate ester **211**. Oxidation of alcohol **211** gave the β-ketophosphonate ester **212** in good yield. However, avoiding the direct displacement of the Masamune-Abiko auxiliary added a further 4 steps to their synthesis.



Scheme 63: *Synthesis of fragment **212***

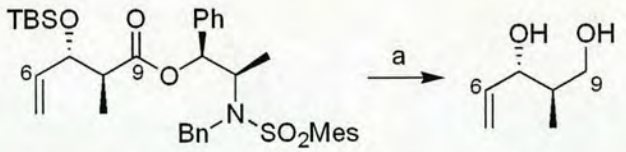
Reagents and Conditions: (a) DIBALH (100 %); (b) Dess-Martin periodinane (90 %); (c)(i) ^{t}BuLi, $EtP(O)(OEt)_2$, THF, -78 °C; (ii) **210**, -78 °C (100 %); (d) Dess-Martin periodinane (96 %).

Due to the poor yield of β-ketophosphonate ester **192** *via* direct displacement (**Scheme 62**) we initially decided to adapt our synthesis of the C(6) – C(10) fragment of octalactin A to investigate a longer route towards β-ketophosphonate ester **192** which could give a higher overall yield. Our new route (**Scheme 64**) was based upon reaction of the phosphonate anion with an intermediate aldehyde **213**, as reported by the Leahy group.



Scheme 64: *Revised synthesis of the C(6) – C(10) fragment of octalactin A*

Our substrate differed from that of Leahy *et al.* in that a more bulky protecting group on the C(3) hydroxyl was required to prevent the decomposition of the aldol adduct **191** when it was reacted with the phosphonate ester anion. As shown in Chapter 2, when a less bulky protecting group (TES) was used in the attempted formation of the β-ketophosphonate ester **192**, no product was found suggesting decomposition of the aldol adduct. The difficulty in displacing auxiliary **122** suggests that there is high steric hindrance around the carboxylic ester, preventing an efficient nucleophilic substitution. To overcome this, Abiko *et al.* reported the efficient cleavage of aldol adducts from auxiliary **122** *via* a reductive cleavage using $LiAlH_4$.[55] Treatment of aldol adduct **191** with $LiAlH_4$ (**Scheme 65**) for a longer reaction time than reported (2 h instead of 1 h), showed no starting material by TLC. However upon work up, diol **214** was isolated showing that the ester group was reduced but with concomitant removal of the TBS group. The requirement for protection of the C(3) hydroxyl prior to HWE olefination is crucial to prevent quenching the phosphonate anion and epimerisation. Furthermore, reprotection of the C(3) hydroxyl and would require a number of unnecessary protecting group manipulations. We therefore decided to revise our synthesis towards β-ketophosphonate ester **192**.

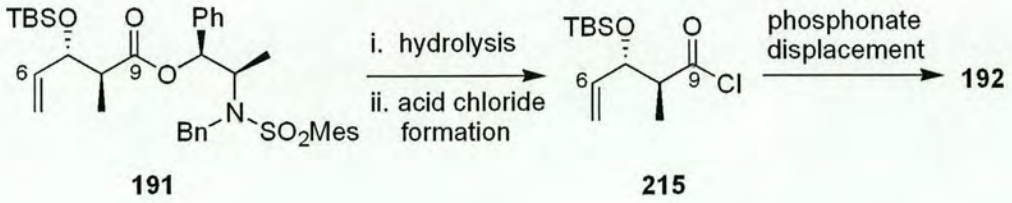


191 **214**

Scheme 65: *Reductive cleavage of auxiliary 122*

Reagents and Conditions: (a) $LiAlH_4$, THF, 0 °C, 2 h (90 %).

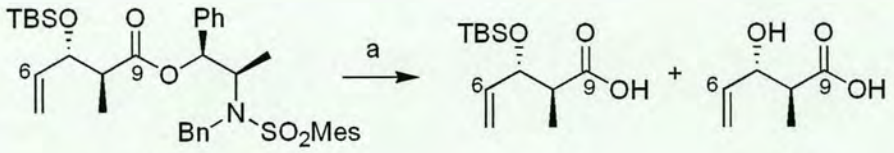
Due to these complications our new proposed synthesis (**Scheme 66**) of β-ketophosphonate ester **192** consisted of the hydrolysis of auxiliary[98] **122** to give a carboxylic acid, followed by conversion to the reactive acid chloride **215**. Treatment of acid chloride **215** with a phosphonate anion would give the desired fragment **192**.



191 215

Scheme 66: *Proposed hydrolytic synthesis of β-ketophosphonate ester **192***

However when aldol adduct **191** was treated with the lithium hydroperoxide no reaction took place, even when the reaction time was extended from 3 h to overnight. This surprising result suggested that the bulky ester group required stronger hydrolysis conditions (**Scheme 67**). Aldol adduct **191** was then treated with aqueous LiOH at room temperature for 3 days and still did not yield the carboxylic acid. The hydrolysis of aldol adduct **191** was repeated using aqueous LiOH under reflux with careful monitoring by TLC. When TLC showed that there was no starting material remaining, the reaction mixture was worked up under standard conditions to give an inseparable mixture of desired carboxylic acid **216** and deprotected acid **217**. The sluggish reaction times and resulting mixtures of protected and deprotected acids demonstrated a need for a new approach to solve the problem of the low yielding phosphonate displacement.



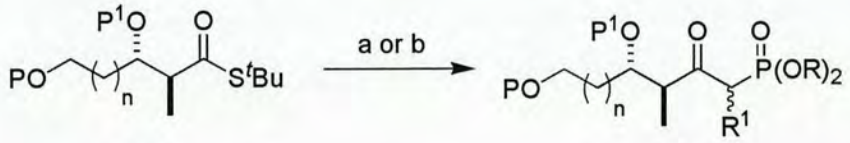
191 216 217

Scheme 67: *Hydrolysis of auxiliary **122***

Reagents and Conditions: LiOH, THF/H_2O (1:1), Δ, 3→18 h.

Previous studies within the Hulme group have shown that β-ketophosphonate esters can be easily synthesized *via* the direct displacement of thioesters using a

phosphonate anion.[91] An achiral propionate thioester was used in *anti* aldol reactions with simple aldehydes and gave excellent *anti*:*syn* selectivities. Treatment of the aldol adducts **218** with the anion of an alkyl phosphonate afforded β-ketophosphonate esters **219** in good yield (69 – 94 %) as illustrated in **Table 5**.[91]



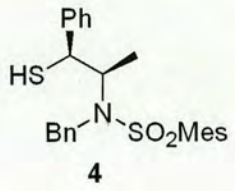
218 **219**

Entry	Method	n	R	R^1	P	P^1	T	Yield **219** (%)
1	a	3	Me	Me	TBS	TBS	-78 °C	69
2	b	3	Et	Me	TBS	TBS	-78 °C	85
3	b	3	Et	Me	PMB	TBS	-78 °C	86
4	b	5	Me	H	TBS	TBS	-78 °C	84
5	a	5	Me	Me	TBS	TBDPS	-42 °C	80
6	b	5	Et	Me	TBS	TBS	-78 °C	94
7	b	8	Et	Me	TBS	TBS	-78 °C	94

Table 5: *Phosphonate displacement*[91]

Reagents and conditions: (a) (i)^{t}BuLi, DMPU (1 eq.), $R^1CH_2P(O)(OR)_2$, THF, -78 °C; (ii) **218**, -78 °C or -42 °C, 4 h; (b)(i) ^{n}BuLi, $R^1CH_2P(O)(OR)_2$, THF, 1 h; (ii) **218**, -78 °C, 4 h.

Due to the successful formation of β-ketophosphonate esters *via* the displacement of *tert*-butyl thioesters, as shown in **Table 5**, we decided to apply a similar strategy to optimise the formation of fragment **192** in our synthesis of octalactin A. This methodology (**Table 5**) had only been applied to achiral aldol reactions, therefore the synthesis of a chiral auxiliary which would generate a thioester was necessary. We also wanted to synthesise an auxiliary which had similar functionality to the Abiko-Masamune auxiliary to maintain excellent relative and absolute stereocontrol in *anti* aldol reactions. Therefore the target for the new auxiliary was the thiol **4** shown in **Figure 20**.

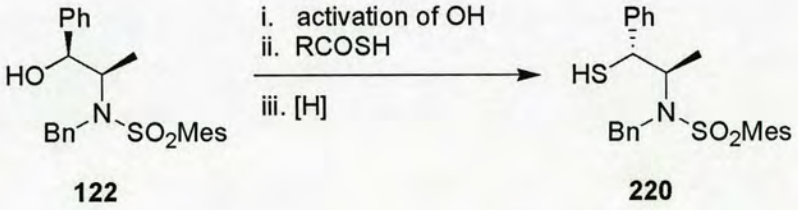


4

Figure 20: *Thiol auxiliary 4*

3.2. GENERAL STRATEGIES TOWARDS AUXLIARY 4

Our initial strategy was to perform a "direct displacement" (**Scheme 68**) reaction upon the Abiko-Masamune auxiliary **122** by activation of the alcohol and treatment with a thiolcarboxylic acid. A simple reduction of the respective thioester would give the shortest synthetic route towards auxiliary **220** (5 steps from norephedrine). Although this was the most efficient strategy towards auxiliary **220**, using this strategy would have synthesised the thiol auxiliary with inversion of stereochemistry at C(1). Inversion at this position could potentially lower the diastereoselectivity of the *anti* aldol reaction.



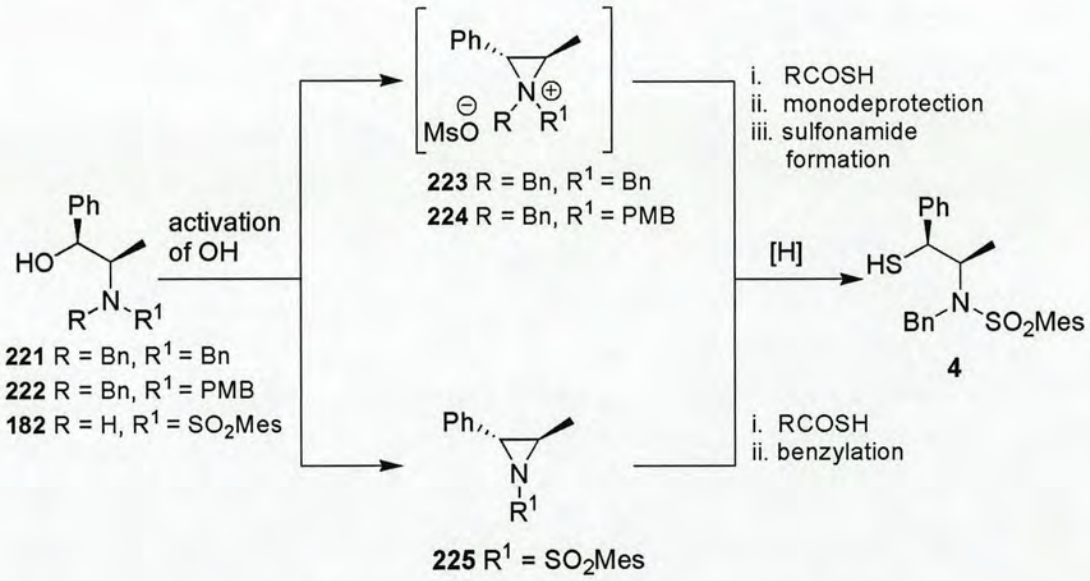
122 **220**

Scheme 68: *"Direct displacement" strategy*

We devised a further strategy towards thiol **4** which similarly involved activation of a norephedrine-derived compound. Here, activation of the *N,N*-diprotected norephedrine (**221** or **222**) (**Scheme 69, pathway 1**), should facilitate neighbouring group participation of the C(2) nitrogen to give an aziridinium ion, intermediate (**223** or **224**), with inversion of stereochemistry at C(1). Treatment with a thiolcarboxylic

acid should open the aziridinium ion and install the thiol moiety (masked as a thioester) with net retention of stereochemistry at C(1). Similarly if the sulfonamide of norephedrine **182** was activated (**Scheme 69**, pathway 2), the activated species could be converted into the stable aziridine **225**, with inversion of stereochemistry at C(1). Aziridine **225** could be opened with a thiolcarboxylic acid to install a thiol moiety with net retention of stereochemistry at C(1). Although the "double inversion" strategy was a slightly longer route to auxiliary **4** (6 steps for both pathway 1 and pathway 2) than the "direct displacement" (5 steps) the stereochemistry at C(1) is the same as the classical Abiko-Masamune auxiliary. Retention of stereochemistry at this position should maintain the high diastereoselectivity of the adducts formed when used in the *anti* aldol reaction.

Pathway 1 "Double inversion *via* an aziridinium ion"

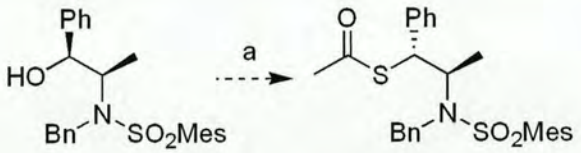


Pathway 2 "Double inversion *via* an aziridine sulfonamide"

Scheme 69: *The "double inversion" pathways towards auxiliary* ***4***

3.2.1. Direct Displacement of the Abiko-Masamune Auxiliary

Our initial strategy to form thioester **220** involved the direct conversion of alcohol **122** *via* a Mitsunobu coupling, followed by hydrolysis of thioacetate **226** (**Scheme 70**). This strategy was successfully used by Taylor *et al.* in the synthesis of *C*-linked disaccharides.[99] However initial investigations of the Mitsunobu pathway proved unsuccessful. Treatment of alcohol **122** with azo-coupling agents (DEAD and DIAD) resulted in the recovery of starting material.

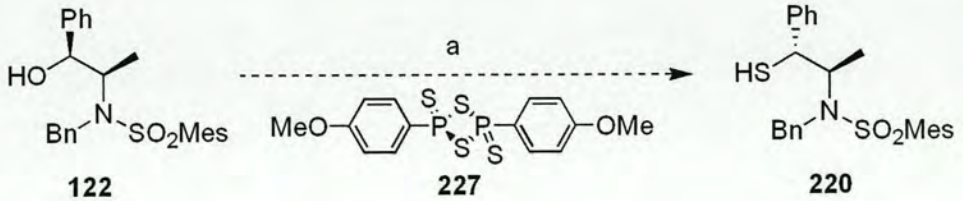


122 **226**

Scheme 70: *Attempted Mitsunobu inversion of alcohol 122*

Reagents and Conditions: (a) (i) PPh_3, DIAD or DEAD, 0 °C, 1 h; (ii) thiolacetic acid , **122**, THF, 0 °C, 1 h.

Another potential method to synthesise auxiliary **220** was to convert alcohol **122** into the corresponding thiol. Nishio *et al.* have extended the use of Lawesson's reagent **227** (**Scheme 71**), from its normal use in the conversion of carbonyls to thiocarbonyls, to the conversion of alcohols into thiols.[100-104] Unfortunately, treatment of alcohol **122** with a solution of Lawesson's reagent in DME, and heating under reflux afforded recovered starting material.

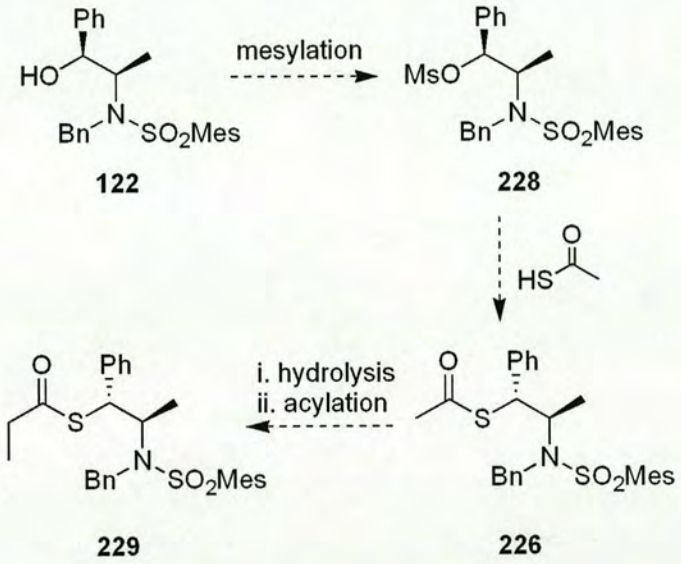


122 **227** **220**

Scheme 71: *Lawesson's Reagent strategy*

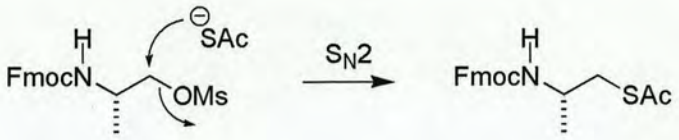
Reagents and Conditions: (a) **227**, DME, Δ, 3 h.

Another synthetic strategy (**Scheme 72**) was to convert the Abiko-Masamune auxiliary **122** into the propionate derivative of thiol **220** *via* the mesylate of the benzyl protected norephedrine sulfonamide **228**. The S_N2 nucleophilic displacement of mesylate **228** with thiolacetic acid would give the thioester **226**. Hydrolysis and acylation of this thioester would produce the required thiopropionate **229**.



Scheme 72: *Mesylate synthesis of thiopropionate 229*

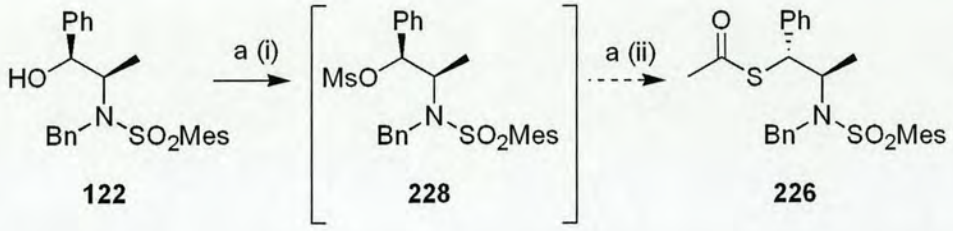
Studies[105,106] into the synthesis of thioesters from amino alcohols **231** (**Scheme 73**) have shown that mesylate **230**, generated from the respective hydroxycarbamate, does not undergo neighbouring group participation with the C(2) nitrogen. Instead a direct S_N2 displacement occurs, resulting in inversion of configuration at C(1). Since the sulfonamide moiety in mesylate **228** has similar electron-withdrawing properties to the carbamate (Fmoc) of mesylate **230**, a S_N2 displacement of mesylate **228** was expected.



230 **231**

Scheme 73: *"Direct" S_N2 nucleophilic displacement*

Alcohol **122** was treated (**Scheme 74**) with methanesulfonyl chloride and triethylamine at 0 °C and the reaction was stirred for 1 h, until mesylate formation was complete (no remaining starting material **122** by TLC). Thiolacetic acid was then added to mesylate **228** *in situ* and the reaction was stirred for a further 3 h. However, only starting material was recovered after aqueous work up conditions.



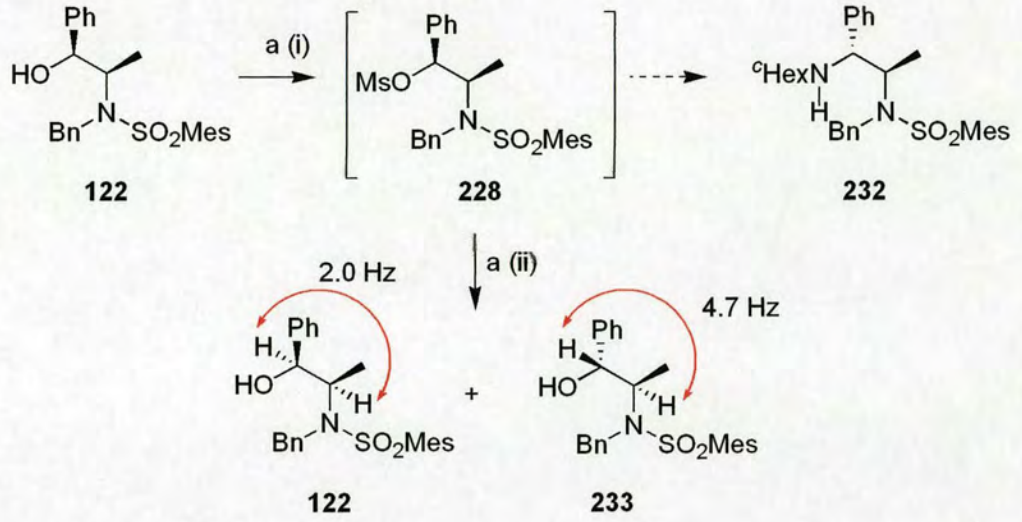
122 **228** **226**

Scheme 74: *Thioester formation of thioacetate **226** via mesylate*

Reagents and Conditions: (a) (i) MsCl, THF, 0 °C, 1 h; (ii) thiolacetic acid, MeCN, K_2CO_3, 3 h.

Further investigations (**Scheme 75**) into the displacement of mesylate moiety were attempted using amines as nucleophiles. Treatment of alcohol **122** with methanesulfonyl chloride and triethylamine generated the mesylate after 1 h at 0 °C, as indicated by TLC. However when cyclohexylamine was added to mesylate **228** the desired amine **232** was not formed, instead a mixture of alcohol **121** and its epimer **233** were obtained. The structure of epimer **233** was tentatively assigned using mass spectrometry and ^{1}H NMR. In the latter, the C(1)H displayed a coupling

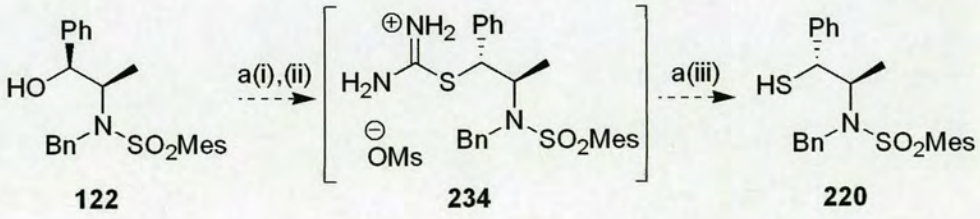
of J = 2.0 Hz for the norephedrine derivative **122** and had a J = 4.7 Hz for epimer **233**.



Scheme 75: *Direct displacement of mesylate **228** using cyclohexylamine*

Reagents and Conditions: (a) (i) MsCl, Et_3N, THF, 0 °C, 1 h; (ii) cyclohexylamine, Et_3N, toluene, Δ, 12 h (**122** = 24 %; **233** = 37 %).

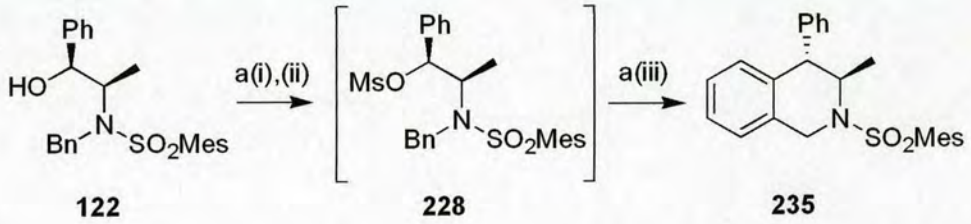
A common method to generate thiols is the hydrolysis of a thiouronium salt[107-109] as shown in **Scheme 76**. However, treatment of the mesylate **228** with thiourea followed by reduction with sodium metabisulfite did not produce thiol **220**.



Scheme 76: *Thiouronium salt strategy*

Reagents and Conditions: (a) (i) MsCl, Et_3N, THF, 0 °C, 1 h; (ii) Thiourea, Δ, 3 h; (iii) $Na_2S_2O_5$, acetone, RT, 8 h.

A serendipitous discovery was made when an unknown product **235**, formed when mesylate **228** was first treated with LiHMDS at -78 °C and then heated under reflux with HCl generated from MeOH/AcCl (**Scheme 77**) was isolated. X-Ray crystallography (**Appendix 1**) showed that this was in fact the isoquinoline **235**; presumably formed by a Friedel-Crafts type reaction of the intermediate mesylate.



Scheme 77: *Formation of isoquinoline 235*

Reagents and Conditions: (a) (i) MsCl, Et_3N, THF, 0 °C, 1 h; (ii) LiHMDS, THF, -78 °C, 4 h; (iii) MeOH, acetyl chloride, Δ, 3 h (53 %).

Isoquinolines are the core structures of a variety of biologically active natural products (e.g. napthyridinomycin[110,111] and saframycin A).[112-114] Further investigation into the elucidation of the mechanism of isoquinoline formation is currently underway within the Hulme group with application to the synthesis of pancratistatin **236** (**Figure 21**).[115-118]

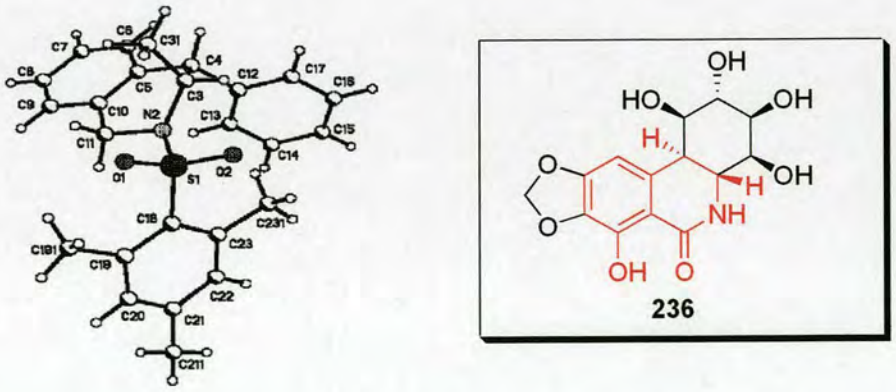
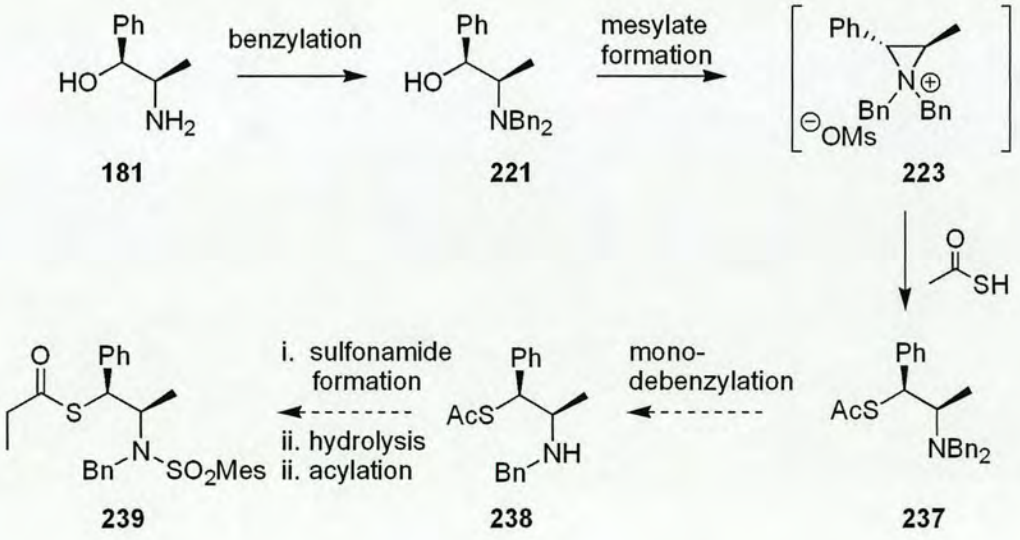


Figure 21: *The crystal structure of isoquinoline sulfonamide 235, and the highlighted isoquinoline core of pancratistatin 236*

In summary, the direct displacement pathway shown in **Scheme 68** has been attempted using a variety of techniques (mesylation followed by thiolcarboxylic acid displacement, thiouronium salt formation, Mitsunobu coupling of a thiolcarboxylic acid) as has proved unsuccessful. However, studies into the displacement of the mesylate **228** allowed for the serendipitous discovery of isoquinoline **246**. The unsuccessful formation of thiol **220** using the "direct displacement" strategy led us to investigate different routes towards thiol auxiliary **4**.

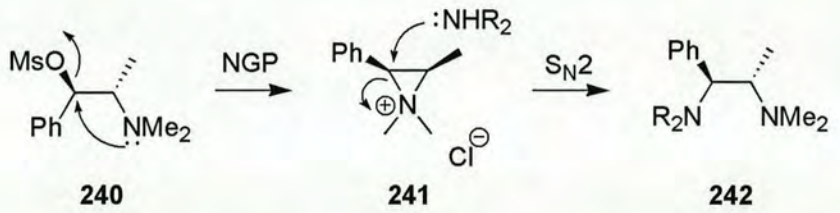
3.2.2. Double Inversion *via* Intermediate Aziridinium Ion

The new strategy (**Scheme 78**) was to convert dibenzylated alcohol **221** into an aziridinium ion **223** *via* the mesylate. Nucleophilic opening of aziridinium ion **223** with thiolacetic acid would afford thioester **237**. Mono-debenzylation of the C(2) amine **238** and treatment with mesitylenesulfonyl chloride should generate a thioacetate derivative of thiol **4**. Hydrolysis of this ester, and subsequent acylation of the resultant thiol would produce the desired thiopropionate **239**.



Scheme 78: *"Double inversion" strategy via the aziridinium salt 223*

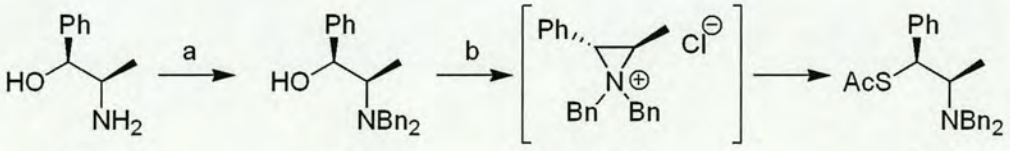
The mechanism of the mesylate displacement had to be carefully examined to confirm the stereochemistry at C(1). O'Brien *et al.*[119] have reported during their synthesis of chiral diamines **242**, that the stereochemistry of mesylate **240** can be temporarily inverted by nucleophilic attack from the neighbouring amine to form an aziridinium intermediate **241**, which is then opened with the nucleophile. The overall net retention is achieved *via* a "double S_N2" process shown in **Scheme 79**.



240 **241** **242**

Scheme 79: *Proposed "double inversion" mechanism*

Treatment of norephedrine (**Scheme 80**) with benzyl bromide and potassium carbonate efficiently produced dibenzylated alcohol **221**. Alcohol **221** was converted into the mesylate and treatment with thiol acetic acid and Et_3N produced thioacetate **237** with high yield (86 %).[120] The stereochemistry at C(1) was suggested by a C(1)H – C(2)H coupling constant of 10.7 Hz in the ^1H NMR and confirmed by X-ray crystallography (**Appendix 2**) which confirms that thioacetate **237** is formed *via* S_N2 displacement of the aziridinium salt **223**.



181 **221** **223** **237**

Scheme 80: *Synthesis of thioacetate 237*

Reagents and Conditions: (a) BnBr, K_2CO_3, MeCN, RT, 48 h (90 %); (b) (i) MsCl, Et_3N, Et_2O, 0 °C; (ii) CH_3COSH, Et_3N, RT, 48 h (86 %).

Reduction of thioacetate **237** could potentially result in a chiral auxiliary for use in aldol reactions. The first requirement for the new chiral auxiliary was that it had to contain a thioester moiety so that facile displacement with phosphonate ester anions could occur. Although thiol **243** did contain a thioester moiety, the second requirement for the new chiral auxiliary was that it had to have similar functionality to the Abiko-Masamune auxiliary to maintain excellent relative and absolute stereocontrol in *anti* aldol reactions. As can be seen in **Figure 22** the difference in the two new auxiliaries was the replacement of a smaller benzyl group with a bulkier sulfonamide substituent on thiol **243**.

Although thiols **243** and **4** had very similar structures, it was felt that the size and the electronic properties of the sulfonamide would provide a similar stereocontrol to the Abiko-Masamune auxiliary.

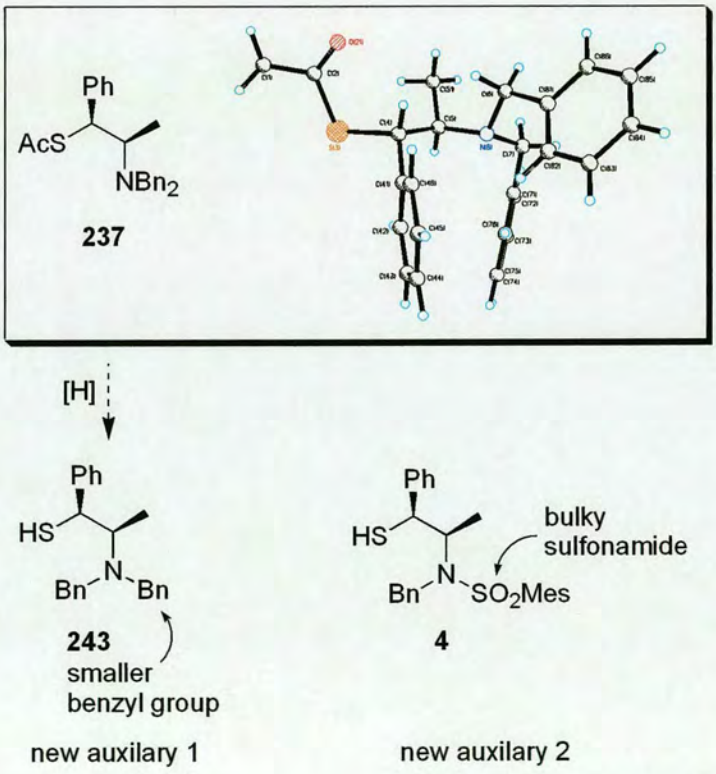
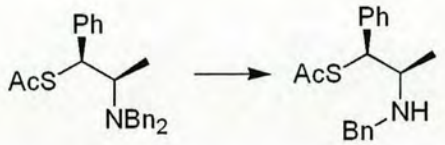


Figure 22: *Crystal structure of thioacetate **237** and comparison of potential chiral auxiliary **243** to target auxiliary **4***

Thioacetate **237** was treated with standard reductive conditions (H_2, Pd/C; H_2, $Pd(OH)_2$) to mono-debenzylate the C(2) amine (**Table 6, entries 1 and 2**), but only thioacetate **237** was recovered. It was believed that the presence of the thiol moiety poisoned the palladium catalyst. Mono-debenzylation of thioacetate **237** using stronger reducing conditions (LiDBB), as shown in **Table 6, entry 3**, only afforded recovered starting material. To overcome catalyst poisoning, cleavage of the benzyl group *via* oxidative formation (**Table 6, entry 4**) of the benzyl benzamide was attempted using ceric ammonium nitrate (CAN),[121] however, only starting material **237** was recovered.



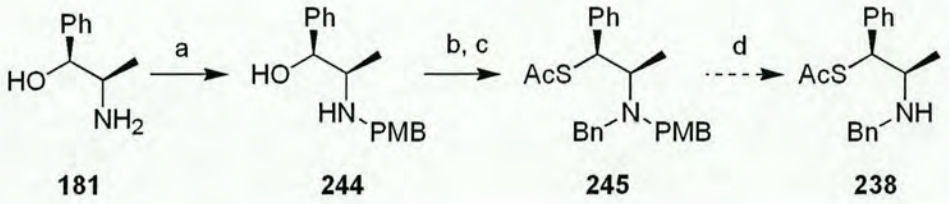
237 **238**

Entry	Reaction Conditions	Recovery of **237** (%)	Yield **238** (%)
1	Pd/C, H_2	83	0
2	$Pd(OH)_2$/C, H_2	90	0
3	LiDBB	46	0
4	CAN	90	0

Table 6: *Mono-debenzylation of thioacetate 237*

This aziridinium intermediate strategy was adapted to incorporate a protecting group that could be removed in the presence of a benzyl group without the requirement for reductive conditions as shown in **Scheme 81**. It was decided to protect the C(2) amine with both benzyl and 4-methoxybenzyl groups. Norephedrine was mono-PMB protected by treatment with anisaldehyde and $NaBH_4$ to give alcohol **244** in good yield. Benzyl protection and installation of the thioacetate moiety were achieved in a similar manner to the formation of thioacetate **237**. Singh[122] has reported the oxidative deprotection of PMB amines using DDQ, however this procedure was

found to give only a moderate yield of 30 % of the deprotected amine and can sometimes result in over-oxidation. Treatment of thioacetate **245** with DDQ unfortunately did not produce thioester **238** but an unidentifiable mixture of compounds.



181 **244** **245** **238**

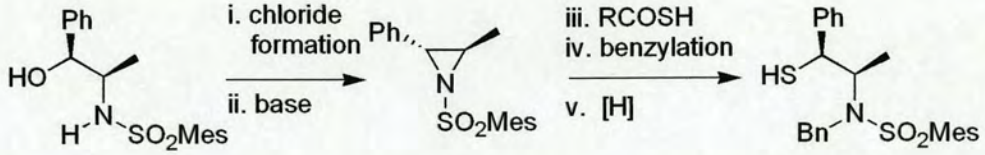
Scheme 82: *Formation of and attempted mono-deprotection thioester **245***

Reagents and Conditions: (a) (i) Anisaldehyde, EtOH, RT, 40 min; (ii) $NaBH_4$, RT, 30 min (70 %); (b) BnBr, K_2CO_3, RT, 16 h (96 %); (c) (i) Et_3N, MsCl, 0 °C, 45 min; (ii) Et_3N, CH_3COSH, RT, 16 h (60 %); (d) DDQ, CH_2Cl_2, RT, 24 h.

The "double displacement" pathway shown in **Scheme 69** has been used to successfully synthesise thioesters **237** and **245** in good yield (81 % over 2 steps for **237** and 60 % over 3 steps for **245**). X-ray crystallography confirmed that thioacetate **237** retained stereochemistry at C(1) and C(2), giving further evidence that "double inversion" and not direct displacement, occurred using these reaction conditions. The unsuccessful mono-deprotection of thioesters **237** or **245** led us to investigate alternative routes towards thiol auxiliary **4** which incorporate the "double inversion" mechanism.

3.2.3. Double Inversion *via* Aziridine Sulfonamide

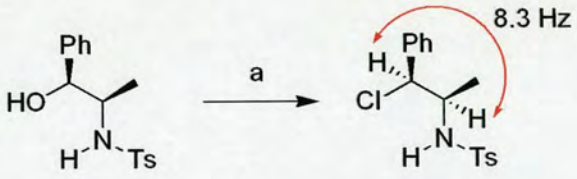
A new strategy towards thiol **4** was devised which incorporated the "double S_N2" reaction (**Scheme 82**). The alcohol of sulfonamide **182** (derived from norephedrine) was activated by conversion into the chloride, followed by treatment with base to form aziridine **225**. Selective opening with a thiocarboxylic acid, followed by benzylation and reduction would afford thiol **4**.



182 **225** **4**

Scheme 82: *Strategy towards the synthesis of thiol 4*

Cruz *et al.*[123] have reported (**Scheme 83**) the formation of chlorinated norephedrine derivatives **247**. They have found that the addition of thionyl chloride to an amino alcohol gives a mixture of chlorides with inversion and retention of stereochemistry at C(1). However, when *N*-tosyl norephedrine **246** was treated with thionyl chloride it was found that the chloride **247** was formed with retention of stereochemistry at C(1) only.

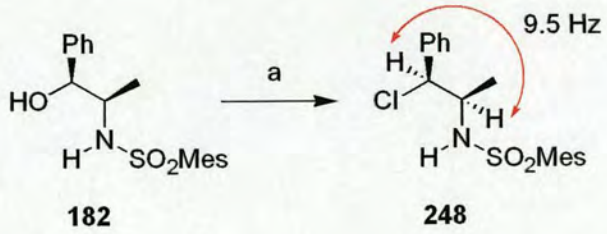


246 **247**

Scheme 83: *Chlorination with net retention*[123]

Reagents and Conditions: (a) $SOCl_2$, RT, 18 h (96 %).

The similarity between the tosyl and mesityl groups suggested that chlorination of **182** with $SOCl_2$ would proceed with retention of stereochemistry. Indeed treatment of sulfonamide **182** with thionyl chloride (**Scheme 84**) gave alkyl chloride **248** in excellent yield (97 %). ^{1}H NMR indicated a large coupling constant (9.5 Hz) between C(1)H and C(2)H which was similar to that of the tosyl derivative **247** (8.3 Hz) suggesting that the stereochemistry was retained.

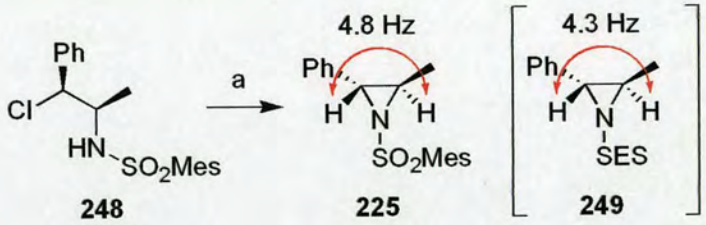


182 **248**

Scheme 84: *Chlorination of sulfonamide **182** and confirmation of stereochemistry*

Reagents and Conditions: (a) $SOCl_2$, RT, 18 h (97 %).

Due to the electron withdrawing nature of the sulfonamide group, **182** was treated with a strong base (^{t}BuOK) to effect deprotonation (**Scheme 85**), and intramolecular displacement of the chloride gave the aziridine **225** in good yield (92 %) with inversion of stereochemistry at C(1). ^{1}H NMR showed a reduced coupling constant (4.8 Hz) between C(1)H and C(2)H of aziridine **225** which was in good agreement with known compound **249** (4.3 Hz), implying inversion of stereochemistry at C(1).

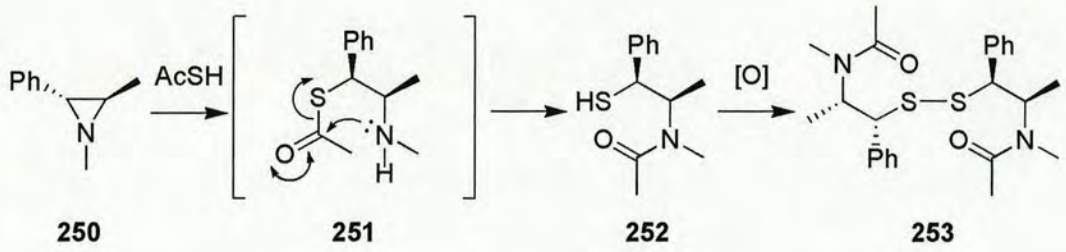


248 **225** **249**

Scheme 85: *Aziridine formation and confirmation of stereochemistry*

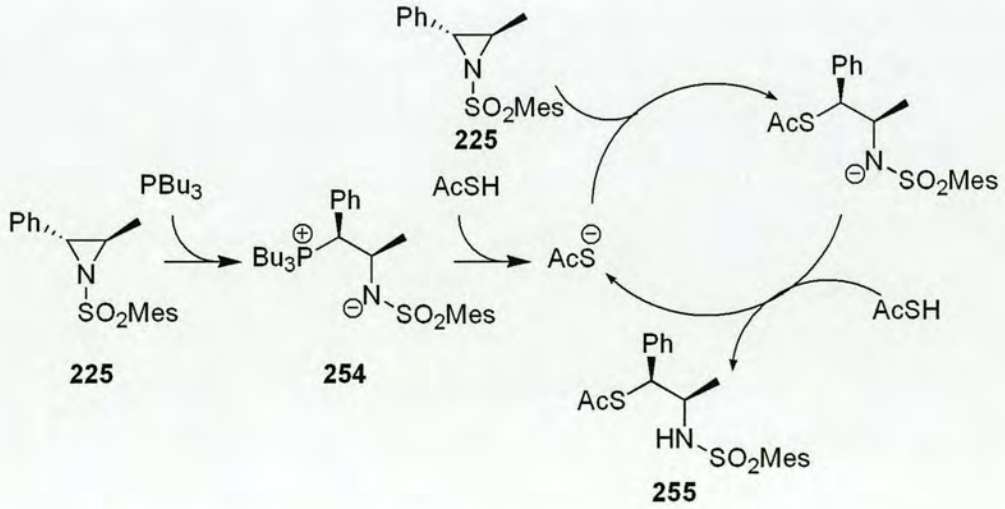
Reagents and conditions: (a) ^{t}BuOK, DMF, 0 °C, 30 min → RT, 4.5 h (92 %).

Reports by Kellogg *et al.*[124] have shown (**Scheme 86**) that the opening of ephedrine derived aziridines **250** can be achieved by treatment with thiols. It was also reported[124] that when thiol carboxylic acids are used the desired thioester **251** is not formed, but spontaneous acyl migration occurs to give an amide **252** followed by rapid aerobic oxidation to give disulfide **253**.



Scheme 86: *Disulfide formation after aziridine opening*

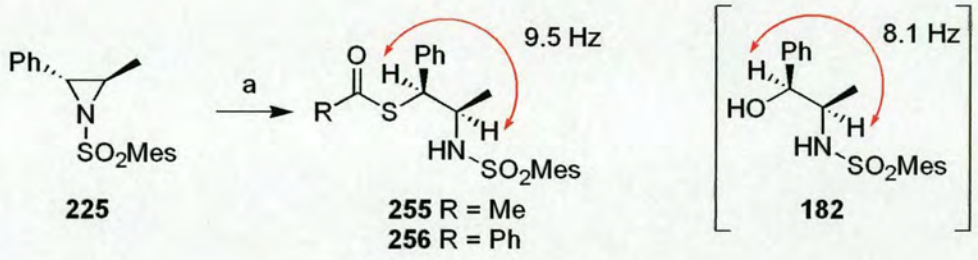
It was felt that the presence of the C(2) sulfonamide has reduced the nucleophilicity of the C(2) amine and this would stop acyl migration occurring. Initial attempts to open aziridine **225** with thiol acetic acid failed but Hou *et al.*[125,126] have reported the use of catalytic PBu_3 with amine and thiol nucleophiles to open tosylated amines under aqueous conditions. It is believed that the PBu_3 initially opens the aziridine **225** to give the zwitterion **254** which then proceeds to deprotonate the corresponding nucleophile. The aziridine opening and nucleophile deprotonation cycle then continues until reaction completion, as shown in **Scheme 87**.



Scheme 87: *Mechanism of aziridine opening*

Treatment of aziridine **225** with PBu_3 and thiolacetic acid gave thioacetate **255** in high yield (93 %) with exclusive regioselectivity. It was shown that acyl migration

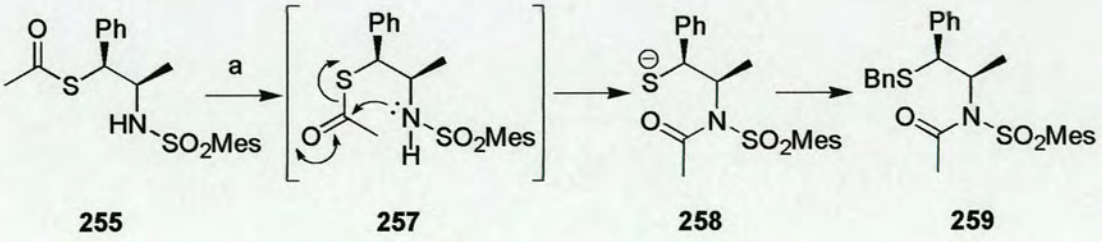
did not occur, thus implying that the presence of the electron withdrawing sulfonamide group hinders this phenomenon. The relative stereochemistry of acetate **255** was determined through increased coupling of the C(1)H and C(2)H signal (4.8 Hz) of the locked aziridine conformation to the large coupling (9.5 Hz) of the opened acetate. This is in good agreement with the C(1)H and C(2)H coupling of alcohol **182** (8.1 Hz) as shown in **Scheme 88**.



Scheme 88: *Opening of aziridine 225*

Reagents and Conditions: (a) RCOSH, PBu_3 (10 mol %), $MeCN/H_2O$ (1:4), RT, 24 h (93 %, R = Me), (93%, R = Ph).

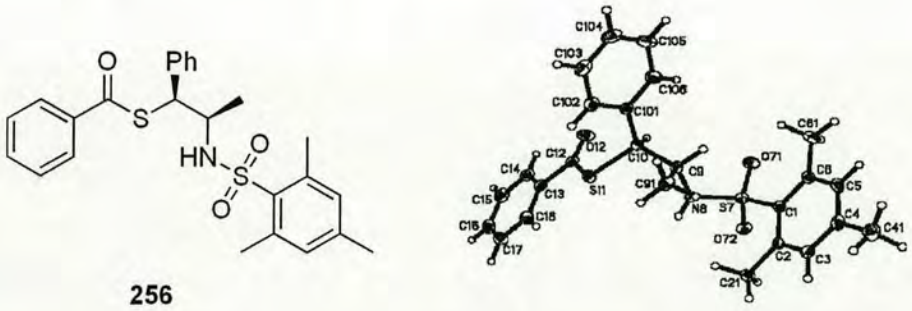
For the new auxiliary to mimic the classical Abiko-Masamune auxiliary, the C(2) sulfonamide required benzyl protection. However when sulfonamide **255** was treated (**Scheme 89**) with ^{t}BuOK and benzyl bromide, the sulfonamide was not protected, instead acetate migration *via* **257** and subsequent thiol protection occurred to give amide **259** in moderate yield (70 %).



Scheme 89: *Attempted benzylation of sulfonamide 255*

Reagents and Conditions: (a) ^{t}BuOK, BnBr, DMF, 0 °C, 30 min → RT, 4.5 h (70 %).

It has been reported that acetate protecting groups can be manipulated with specific conditions to promote migration, therefore in order to prevent acyl migration occurring the thiolcarboxylic acid was changed from the smaller, more versatile acetate to the less reactive benzoate group. Treatment of aziridine **225** with thiolbenzoic acid using similar conditions for the formation of thioacetate **255** gave thiobenzoate **256** as a colourless solid. The stereochemistry was determined by both ^{1}H NMR, and X-ray crystallography (**Appendix 3**). The crystal structure shows the required (2*R*,3*S*) stereochemistry in **Figure 23**.

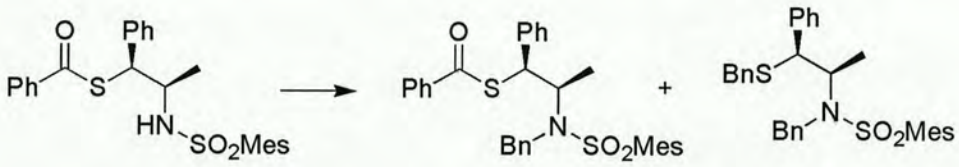


256

Figure 23: *Crystal structure of thiobenzoate* ***256***

When thiobenzoate was treated (**Table 7**) under reaction conditions used to synthesise migration product **259**, the desired benzoate **260** was produced in moderate yield (60 %) with a dibenzyl protected product **261** in low yield (30 %). ^{13}C NMR clearly showed a quaternary carbon at 190.24 ppm for **260**, which is indicative of thioester carbonyl and a signal at 48.53 ppm assigned to the benzylic carbon. ^{13}C NMR analysis of by-product **261** showed no signal in the thiocarbonyl region and two CH_2 signals (δ = 47.88 and 35.50) implying that dibenzyl protection has occurred. ^{1}H NMR of thiobenzoate **260** showed a pair of signals in an AB system (δ = 4.85, 1H, d, J = 16.2 Hz, CH_AH$_B$Ph; and 4.53, 1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), corresponding to the two benzylic protons. Whereas, by-product **261** showed two sets of distinct AB doublets (δ = 5.06, 1H, d, J = 16.4 Hz, CH_AH$_B$Ph; δ = 4.79, 1H, d, J = 16.4 Hz, CH$_A$$H_B$Ph; δ = 3.73, 1H, d, J = 13.0 Hz, CH_XH$_Y$Ph; and δ = 3.65, 1H, d, J = 13.0 Hz, CH$_X$$H_Y$Ph), confirming that by-product **261** contains four benzylic

protons. Subsequent studies within the group have shown that treatment with a milder base (K_2CO_3) to protect sulfonamide **256** with a benzyl group does not produce desired thioester **260**. Gratifyingly, treatment of sulfonamide **256** with sodium hydride and benzyl bromide gave thioester **260** exclusively.



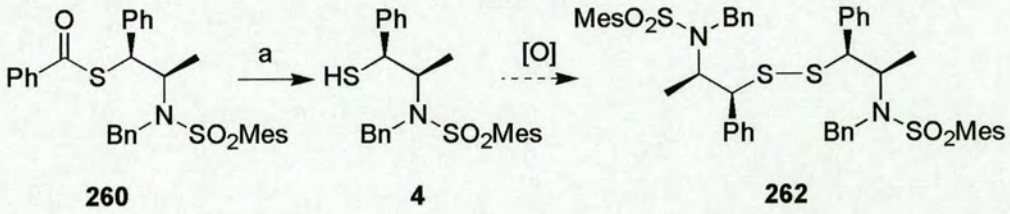
256 **260** **261**

Method	Conditions	Yield **260** (%)	Yield **261** (%)
a	^{t}BuOK, BnBr, DMF, 0 °C, 30 min → RT, 4.5 h	60	30
b	K_2CO_3, MeCN, RT, 24 h	0	0
c	NaH, BnBr, DMF, 0 °C, 30 min → RT, 18 h	100	0[127]

Table 7: *Protection of sulfonamide **256***

The next step towards the synthesis of thiol **4** required the removal of the benzoate group to give the thiol. A major concern regarding the synthesis of thiol auxiliary **4** was the stability of free thiol to aerial oxidation. As illustrated in the work of Kellogg *et al.* (**Scheme 86**), opening of aziridine **250** with a thiol carboxylic acid caused rapid rearrangement to a thiol **252**, which then spontaneously oxidized to give the disulfide **253**. Thiobenzoate **260** was reduced with $LiAlH_4$ to give thiol **4** as a stable colourless solid. A sample of thiol **4** was left at room temperature and was monitored by ^{1}H NMR as the thiol doublet will disappear if disulfide[124] is generated. The sample was monitored for a period of 6 months and thiol doublet was clearly present in the ^{1}H NMR (**Figure 24**), showing that no oxidation of thiol **4** had occurred. This implies that the steric hindrance of the substrate is high enough to disfavour the formation of

disulfide **262**. This is a welcome result as it shows that after the auxiliary has performed control of an aldol reaction it may be recovered and used in further reactions.



260 **4** **262**

Scheme 90: *Potential aerial oxidation of auxiliary **4***

Reagents and Conditions: (a) $LiAlH_4$, THF, 0 °C, 2.5 h (95 %).

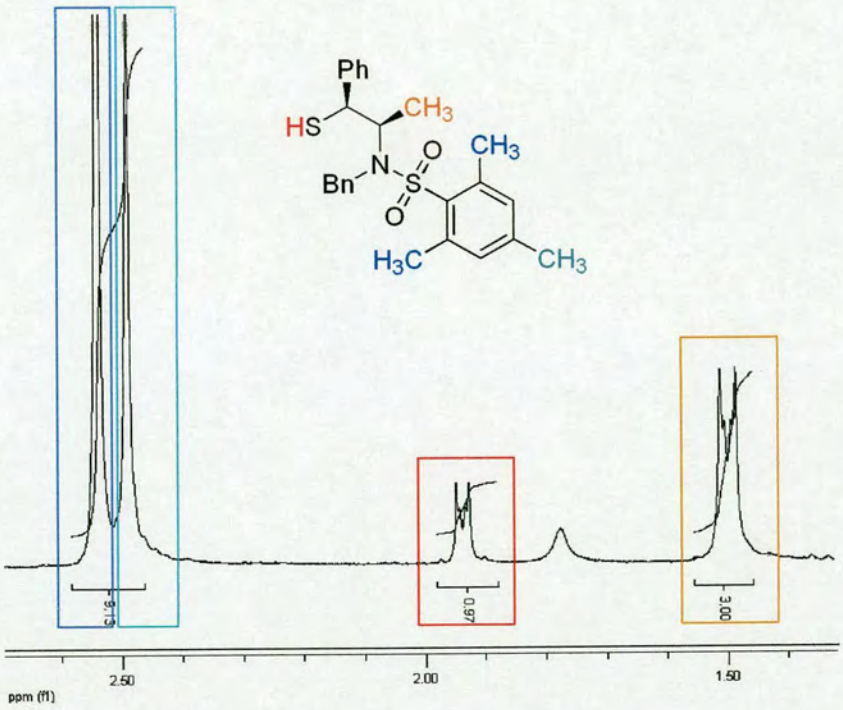
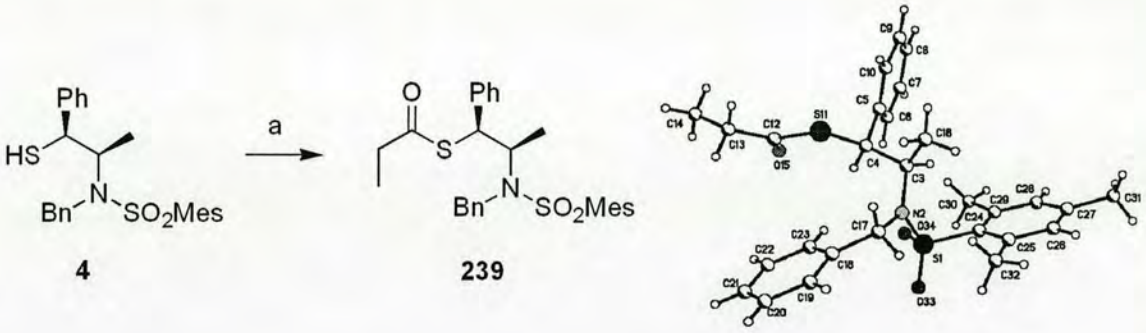


Figure 24: *^1H NMR oxidation study of thiol **4** showing relative integral sizes over 6 months*

Thiol **4** was treated (**Scheme 91**) with propionyl chloride and pyridine to give the thiopropionate **239** in good yield (93 %). X-ray crystallography of thiopropionate **239** (**Appendix 4**) was in good agreement with ^{1}H NMR analysis and confirmed the regioselectivity and stereoselectivity of the opened aziridine. X-ray crystallography of thiopropionate **239** was also in good agreement with the ^{13}C NMR confirming that no cleavage of the benzoate group occurred during the efficient benzylation of sulfonamide **256**, previously shown in **Table 7**.



Scheme 91: *Acylation of thiol **4** and crystal structure of thiopropionate **239***

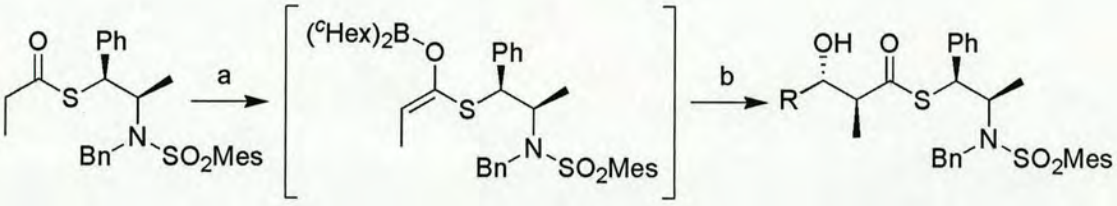
Reagents and Conditions: (a) CH_3CH_2COCl, pyridine, CH_2Cl_2, 0 °C, 18 h (93 %).

In summary, the "double inversion" pathway shown in **Scheme 69** has been used to successfully synthesise thioester **239** in good yield (75 % over 6 steps). X-ray crystallography and other spectroscopic techniques have confirmed the stereochemistry at C(1) and C(2) giving evidence that the formation and opening of aziridine **225** proceeds *via* a "double inversion" mechanism. The formation of thiol **4** can allow a direct comparison of yields and selectivities of aldol formation and auxiliary displacement with mild nucleophiles, with the classical Abiko-Masamune auxiliary.

3.3. BORON MEDIATED *ANTI* ALDOL USING AUXILIARY 4

As discussed in Chapter 2, Masamune *et al.* have reported that the enolisation conditions used for boron mediated aldols are governed by a selective choice of reagents. In the classical auxiliary the formation of the *anti* aldol is controlled by the

addition of a bulky boron compound (^{c}Hex)$_2$BOTf and triethylamine at low temperatures to form the kinetic *E*-enolate. We have used these optimised conditions with the propionate derivative **239**. Gratifyingly we have found that we can obtain *anti* aldol adducts in high yield and selectivity (**Table 8**). We have carried out the aldol reactions using a variety of aldehydes (vinyl, aliphatic and aromatic) to test the versatility of the auxiliary. It was found that using all of these substrates allowed the highly selective formation of *anti* aldol adducts in high yields. The relative stereochemistry of the major diastereomers were assigned on the basis of the large coupling (~7.0 Hz) between C(2)H and C(3)H protons of the aldol adducts. The stereochemistry of the minor diastereomers were assigned by analogy with literature precedent.



239 **263** **264**

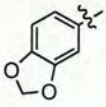
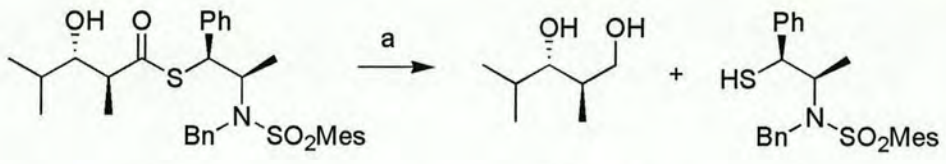
R	Product	Yield (%), ds (*anti*:*syn*)	*c.f.* Abiko-Masamune auxiliary
	**265**	92 (93:7)	79 (98:2)
	**266**	90 (92:8)	97 (96:4)[54]
	**267**	85 (93:7)	95 (98:2)[54]
	**268**	94 (94:6)	--
	**269**	85 (91:9)	93 (95:5)[54]
	**270**	91 (97:3)	--

Table 8: *Anti aldol reactions using thiopropionate **239***

Reagents and Conditions: (a) (^{c}Hex)$_2$BOTf, Et_3N, CH_2Cl_2, (b) RCHO.

In order to confirm the absolute stereochemistry of the major diastereomer at the C(1) – C(3) position, the aldol adduct **267** was subjected to a mild reduction ($NaBH_4$) to form the known diol[128] **271** (**Scheme 92**) in almost quantitative yield. The spectroscopic data for **271** was in good agreement with the literature values,[128] as was the optical rotation value [$[\alpha]_D$ = - 18.4 (c 1.0, $CHCl_3$), lit.[128] -18.6 (c 2.0, $CHCl_3$)].

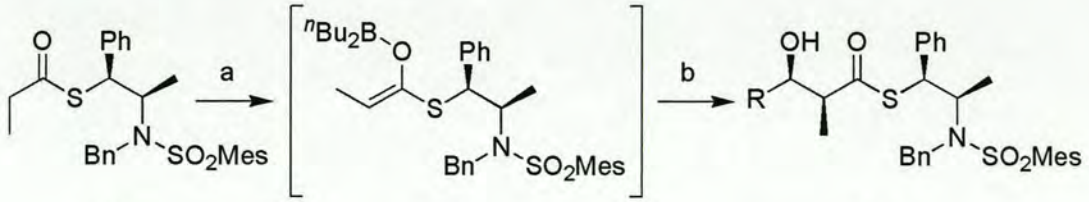


267 **271** **4**

Scheme 92: *Mild reduction of aldol adduct **267***

Reagents and Conditions: (a) $NaBH_4$, THF, 0 °C, 1 h (99 %).

Due to the successful formation of *anti* aldols with thiopropionate **239**, investigation into the auxiliary's versatility with the formation of *syn* adducts **273** (**Scheme 93**) is currently being carried out within the group. It has also been reported by Abiko *et al.* that the selective formation of *syn* adducts may be achieved by using the appropriate boron/base combination. In this case propionate **239** was treated with a less sterically hindered boron species ($^nBu_2BOTf$) and was used along with a bulky base ($^iPr_2NEt$) at low temperatures to form the *Z*-enolate **272**. Reactions of propionated auxiliary **239** with vinyl, aliphatic and aromatic aldehydes are proposed to give *syn* aldol adducts in high yield and high selectivity.

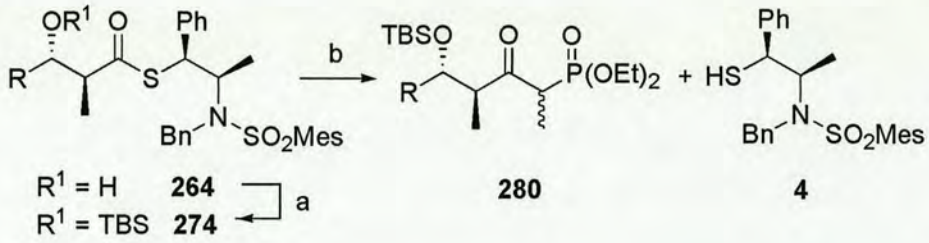


239 **272** **273**

Scheme 93: *Syn aldol reactions using thiopropionate **239***

Reagents and Conditions: (a) $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, -78 °C; (b) RCHO, CH_2Cl_2, -78 °C.

The main focus for the synthesis of the thioester auxiliary **4** was its potentially facile displacement with mild phosphonate nucleophiles, (**Table 9**) compared with the inefficient Masamune auxiliary. Treatment of protected aldol adducts (**Table 9**) with the anion of diethylethane phosphonate gave the desired □-ketophosphonate esters whilst simultaneously allowing the auxiliary to be recovered. It can be seen that the generation of the □-ketophosphonate esters of vinyl (**192** and **281**), alkyl (**282** and **283**) and aromatic (**284**) aldol adducts was achieved with high yield (78-91 %) and with high recovery of the thiol auxiliary **4** (79-81 %). □-Ketophosphonate esters **192**, **282** and **284** were produced as a mixture of diastereomers (diastereomeric ratios varied from 4:1 to 3:2 which were confirmed by ^{1}H NMR). These diastereomers were not separated since it has been reported that similar mixtures of □-ketophosphonate esters afford only *E*-enones upon HWE olefination.[29] □-Ketophosphonate esters **281** and **284** were produced as single diastereomers, but the lower yields (81 % and 78 %) suggested that the minor diastereomer might have been separated during purification.



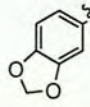
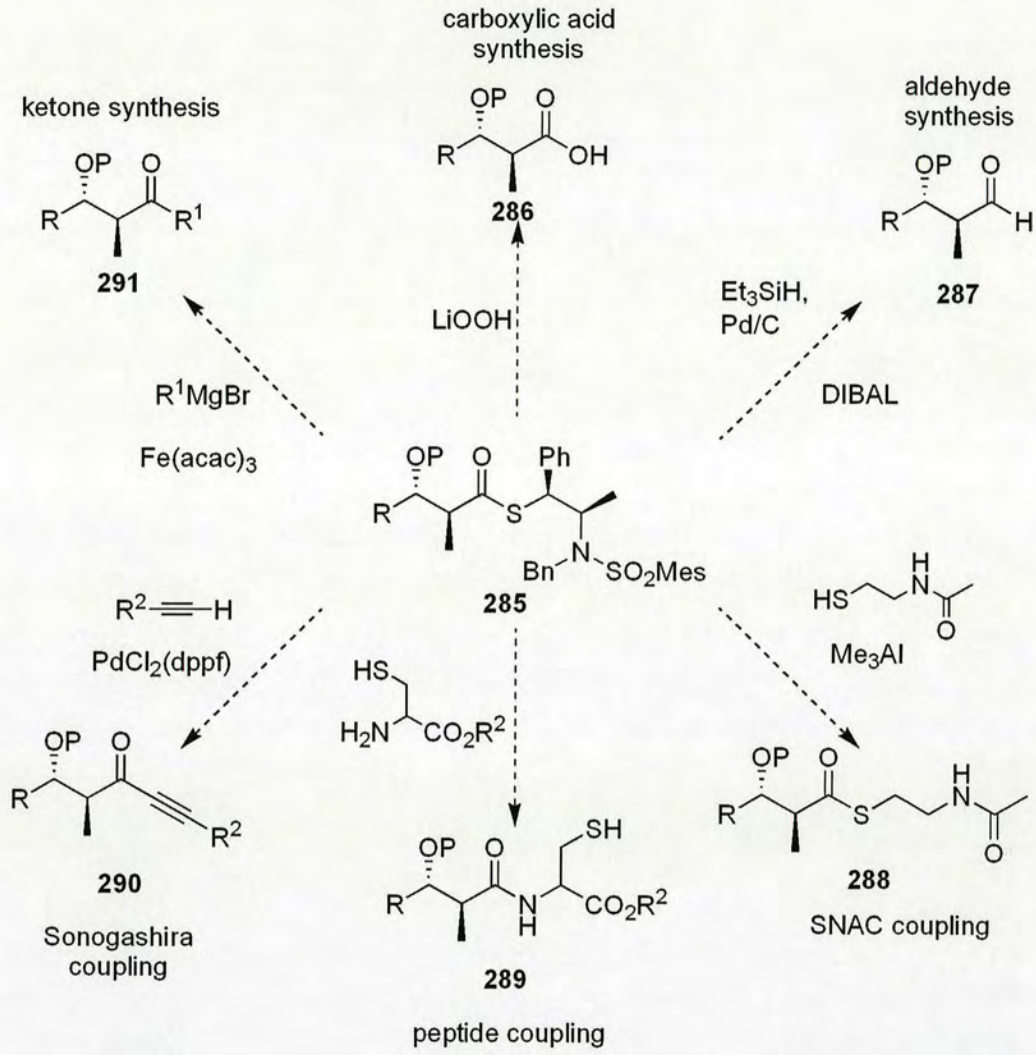
R	TBS	Yield (%)	Phosphonate	Yield (%)	Yield **4** (%)
	**275**	95	**192**	90 (4:1)	91
	**276**	94	**281**	81	85
	**277**	91	**282**	89 (4:1)	85
	**278**	94	**283**	91 (3:2)	79
	**279**	93	**284**	78	80

Table 9: *Displacement of auxiliary **4** with phoshonate anion*

Reagents and Conditions: (a) TBSOTf, CH_2Cl_2, 0 °C; (b) (i) ^{n}BuLi, $EtP(O)(OEt)_2$, THF, -78 °C; **275** - **279**, -78 °C.

The successful displacement of the auxiliary under mild conditions suggests that a number of other displacement reactions may be possible. These are summarised in **Scheme 94**. We have previously illustrated in **Scheme 92** the mild reductive conditions ($NaBH_4$) required to form diol **271** in high yield (99 %). These mild conditions prevent the application of harsh hydride sources ($LiAlH_4$, DIBALH) required with the classical auxiliary (which are generally incompatible with several protecting groups). The difficulty in hydrolysis of aldol substrates **191** from the classic auxiliary (as previously shown in **Scheme 67**) has led to the requirement for investigation of hydrolysis of aldol adducts **285** using mild conditions. The reduction of an ester moiety to an aldehyde can be achieved by the careful addition of DIBALH to an ester at low temperatures (-100 °C) over short reaction times (~30 min). However, the over-reduction of the ester moiety to the alcohol is a common problem. A more robust method for aldehyde formation is the reduction of Weinreb amides or thioesters. Fukuyama *et al.*[129,130] have reported the reduction of decanyl thioesters to synthesise aldehydes from thioesters under mild conditions (DIBALH or Pd/C and Et_3SiH). Therefore we are interested in the application of the reduction of aldol adducts **285** using the conditions described by Fukuyama *et al.*

Although the formation of alcohols, carboxylic acids **286** and aldehydes **287** from adduct **285** are useful chemical transformations, we are also interested in the displacement of aldol adduct **285** with more complex nucleophiles. The nucleophilic displacement of chiral auxiliaries with *N*-acetyl cysteamine (NAC), towards the formation of the NAC thiol esters are problematic under standard carbodiimide coupling conditions.[131] Hence the formation NAC thiol esters **288** *via* displacement of auxiliary **4** would be advantageous. An efficient method in the synthesis of peptides, is native chemical ligation. We are interested in utilising auxiliary **4** in a chemical ligation[132-134] for the synthesis of novel complex peptides **289**. Fukuyama *et al.* have also reported Grignard displacements and Sonogashira couplings using decanyl thioesters. The incorporation of these methods towards aldol adducts **285**, along with the others shown in **Scheme 94**, would display the versatility of chiral auxiliary **4** and its potential incorporation into organic synthesis.

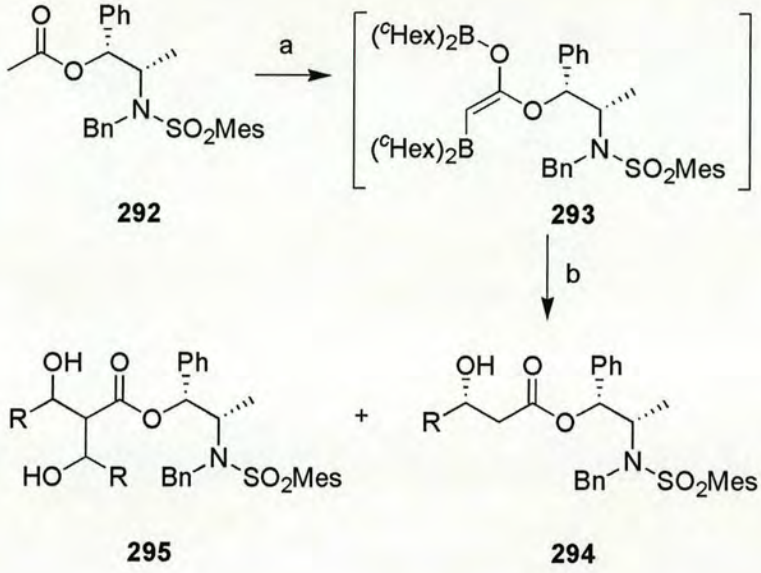


Scheme 94: *Proposed displacements of aldol adduct **285***

3.4 FURTHER WORK: BORON MEDIATED ACETATE ALDOL REACTION

Abiko *et al.* have investigated the use of carboxylic esters and their role in boron mediated acetate aldols (**Scheme 95**). They investigated this as an extension of the use of auxiliary **122** after having successful initial results using propionate esters. However, when the acetate **292** was treated with (^{c}Hex)$_2$BOTf and triethylamine the

desired aldol adduct was formed as the minor product of a mixture of **294** and diol **295** (5:95 **294**:**295**).

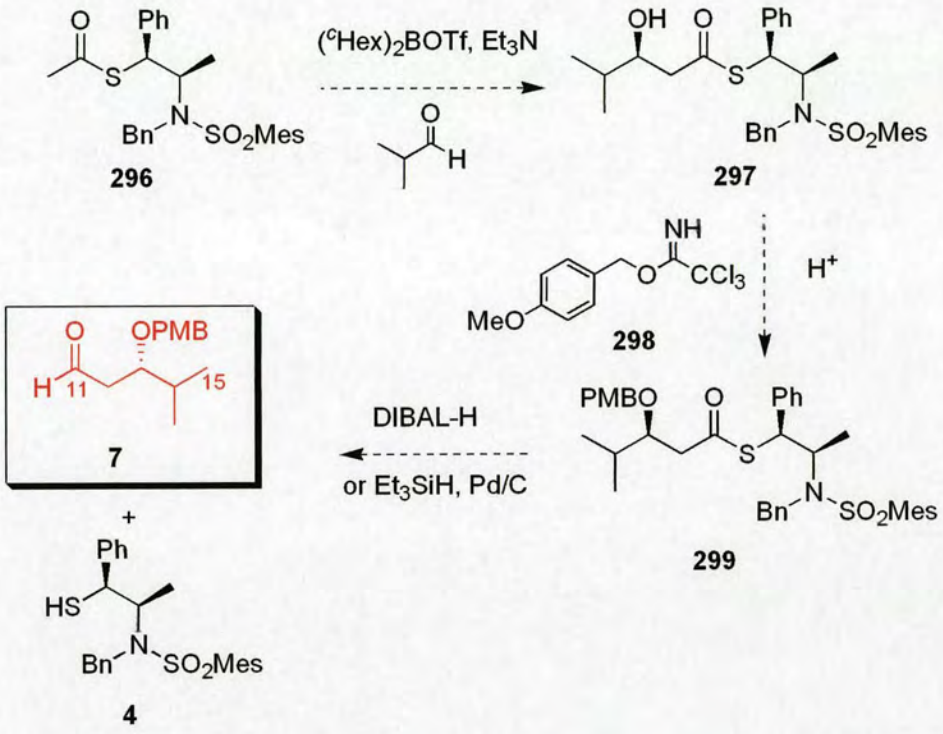


Scheme 95: *Double acetate aldol reaction*

Reagents and Conditions: (a) (^{c}Hex)$_2$BOTf, Et_3N, CH_2Cl_2, -78 °C, 10 min; (b) RCHO (95 %).

They have suggested from ^{1}H NMR analysis of an isolated boron enolate **293**, that the intermediate is doubly borylated[135,136] and this undergoes a double aldol reactions to give the diol. Although the formation of this diol *via* a double aldol process is a very interesting reaction, we are interested in the utilisation of thioacetate **296** towards the formation of mono-aldol adducts as shown in **Scheme 95**. We are encouraged to investigate auxiliary **4** in the acetate aldol reaction since Abiko *et al.* have stated that the double aldol phenomenon should only occur with an acetate ester source and not with other carbonyl containing compounds, such as methyl ketones, propionate esters and acetate thioesters. We would therefore like to investigate the boron mediated acetate aldol with thiol **4** with a variety of aldehydes (aliphatic, vinyl and aromatic). If the acetate aldol reaction is successful with these aldehydes, then auxiliary **4** can be applied to the synthesis of the C(11)-C(15) fragment of octalactin A. The proposed synthesis (**Scheme 95**) would consist of an aldol reaction with isobutyraldehyde to give the aldol adduct **297**. Protection of the adduct with

trichloroacetimidate **298** would give the protected aldol adduct **299**. Reductive cleavage of aldol adduct **299** using either DIBALH or Pd/C and Et_3SiH would give the aldehyde in 3-steps instead of the longer 4-, 5-step routes which will be discussed in Chapter 4.



Scheme 95: *Proposed synthesis of C(11)-C(15) aldehyde fragment 7*

3.5 CONCLUSIONS

The formation of auxiliary **4** has been attempted using three different pathways:

1. "Direct displacement"
2. "Double inversion" *via* an aziridinium ion
3. "Double inversion" *via* an aziridine sulfonamide

Investigations with "direct displacement" and "double inversion" *via* an aziridinium ion strategy were not successful in the synthesis of thiol auxiliary **237**. *Anti* aldol

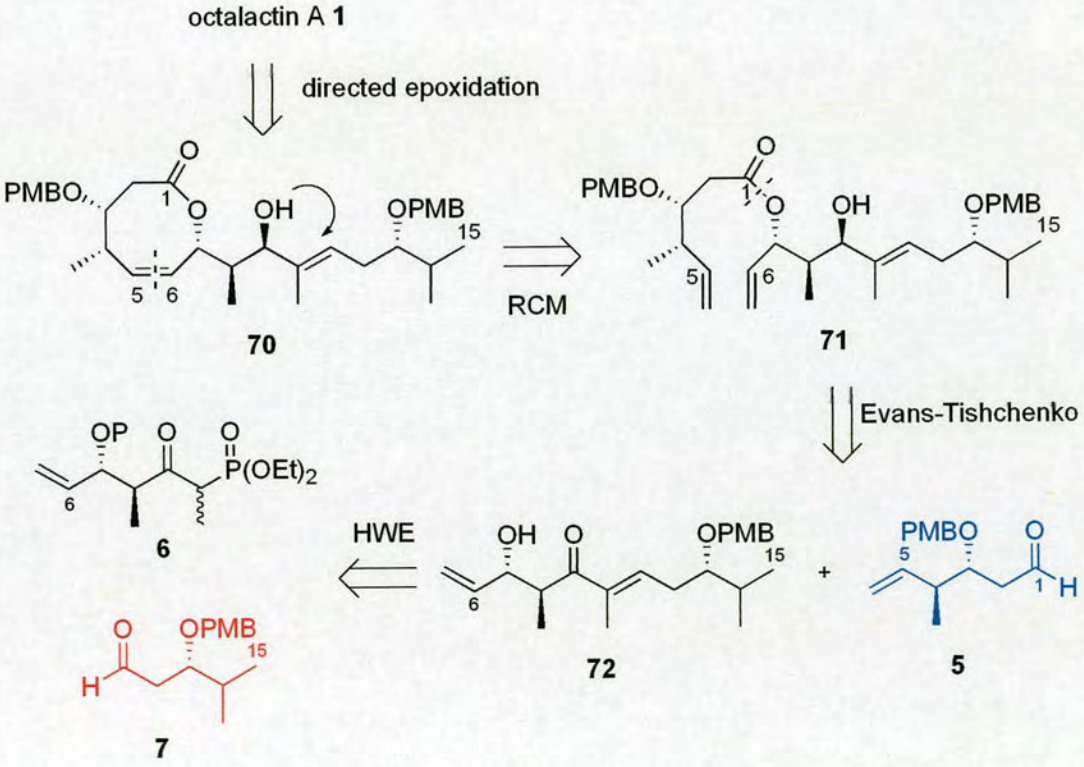
reactions were carried out using the propionate derivative **239** with various aldehydes and the resultant aldol adducts were formed in good yield with high selectivity, both of which were comparable to reported results with the classical Abiko-Masamune auxiliary. Displacement of the aldol adducts with phosphonate anions using mild conditions resulted in the formation of β-ketophosphonate esters with high yields. The high yielding synthesis of β-ketophosphonate esters using propionate derivative **239** has resulted in the optimisation of the synthesis of C(6) – C(10) fragment which can be used in the total synthesis of octalactin A, and will be discussed in Chapter 4. The ease of use in synthesis, its stability, its efficiency in aldol adduct formation and facile cleavage of auxiliary **4** with mild nucleophiles has led to further investigations into utilisation of this auxiliary in other aldol reactions.

RESULTS AND DISCUSSION PART 3

CHAPTER 4

TOTAL SYNTHESIS

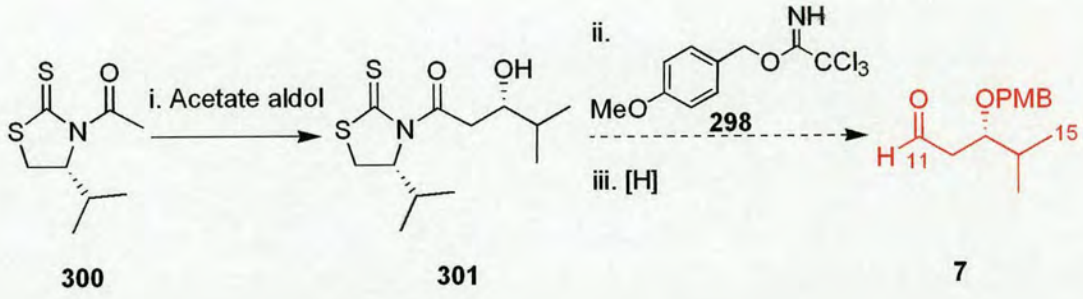
After conducting a series of model studies (discussed in Chapter 2), a total synthesis of octalactin A was attempted as shown in **Scheme 96**. The route to this natural product will be presented and discussed in the following chapter. The model studies had allowed the development of methodology for the major steps in the synthesis (including *anti* aldol coupling, phosphonate displacement, HWE coupling, intermolecular Evans-Tishchenko coupling and RCM). The next necessary step was to synthesise the two major aldehyde fragments **5** and **7** for the total synthesis.



Scheme 96: *Second generation retrosynthetic analysis of octalactin A*

4.1 SYNTHESIS OF THE C(11)-C(15) FRAGMENT

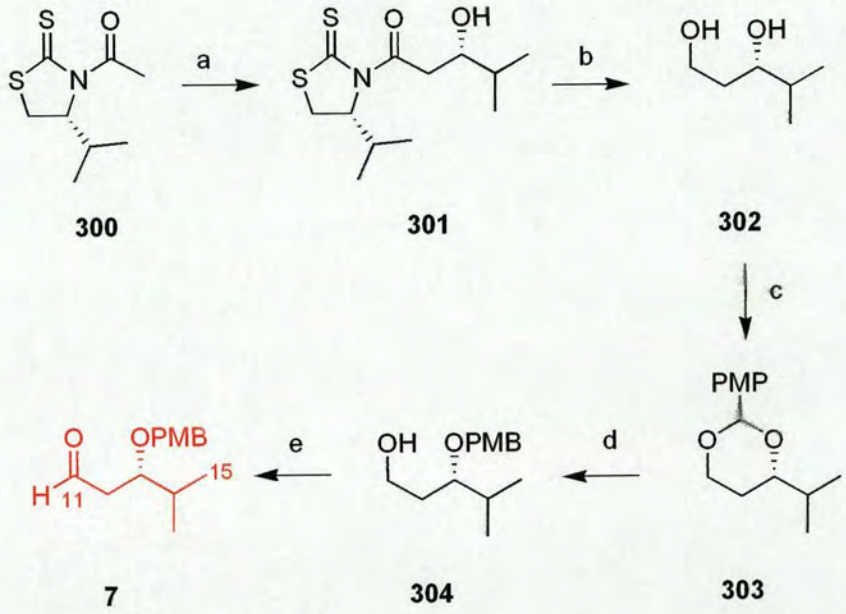
Fragment **7** was previously synthesised within the Hulme group (**Scheme 97**)[29] using a strategy based on an acetate aldol reaction using thiazolidine thione **300** (3 steps from valine) with isobutyraldehyde, to give the aldol adduct **301** in good yield (72 %) with high diastereocontrol (dr 97:3). It was initially thought that protection of the free hydroxyl of aldol adduct **301** using trichloroacetimidate **298** would allow for a facile and mild deprotection in the latter stages of the synthesis. Reduction of the protected aldol adduct would give the key aldehyde **7** in only 3 steps.



300 **301** **7**

Scheme 97: *Initial synthetic strategy towards aldehyde 7*

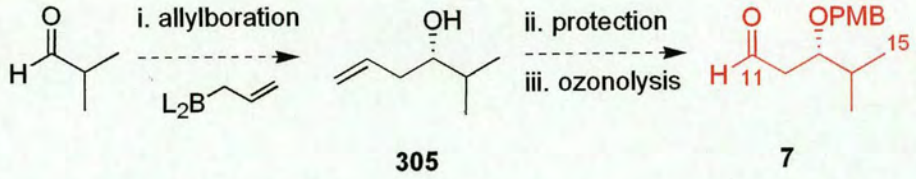
However, the direct installation of the PMB moiety *via* trichloroacetimidate **298** under acidic conditions gave no protected adduct,[29] therefore a new route was required to install the PMB group. Protection was achieved by cleavage of the aldol adduct from the chiral auxiliary to give diol **302**. This was followed by the formation of PMP acetal **303** and selective reduction to give protected alcohol **304**. Oxidation of the primary hydroxyl gave aldehyde **7**, as shown in **Scheme 98**. [29]



Scheme 98: *Initial synthesis of aldehyde 7*

Reagents and Conditions: (a) (i) $TiCl_4$, $^iPr_2NEt$, CH_2Cl_2, -78 °C, 40 min; (ii) isobutyraldehyde, CH_2Cl_2, -78 °C, 20 min (72 %, dr 97:3); (b) $NaBH_4$, THF, 0 °C, 1 h (88 %); (c) $TsOH{\bullet}H_2O$, *p*-methoxybenzyl dimethyl acetal, DMF, RT, 10 h (89 %); (d) DIBALH (1.0 M in toluene), CH_2Cl_2, RT, 15 min (72 %); (e) IBX, DMSO/THF, RT, 1 h (94 %).

This indirect protection of the C(13) hydroxyl resulted in two further steps being added to the acetate aldol approach towards the synthesis of aldehyde **7**. The auxiliary used in this approach (acetylated thiazolidine thione **300**) was synthesised from the less common amino acid (*R*)-valine. The increased cost of the less abundant valine enantiomer limited the scale of synthesis of acetylated auxiliary **300** and aldehyde **7**. Therefore a less expensive and more efficient route to aldehyde **7** had to be devised. The revised synthesis of aldehyde **7** (**Scheme 99**) consisted of an allylboration with isobutyraldehyde to give allylic alcohol **305**. Protection of the C(13) alcohol, followed by ozonolysis of the alkene, would afford the key aldehyde in 3 steps.

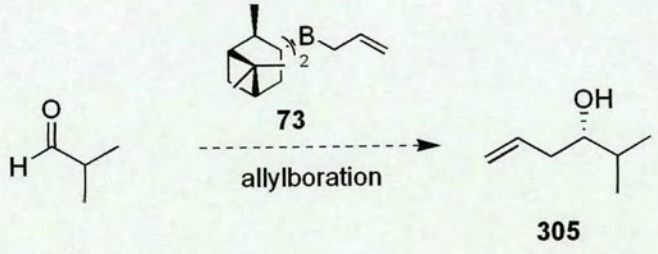


305 **7**

Scheme 99: *Revised synthetic strategy towards aldehyde 7*

4.1.1. Allylboration

There are a variety of different methods used for the synthesis of chiral homoallylic alcohols. As discussed in Chapter 1, Brown *et al.* have shown that the treatment of allylboranes (derived from naturally occurring terpenes) with aldehydes can allow for the efficient synthesis of homoallylic alcohols with high enantioselectivity.[32,34,35,38] The allylborane **73** (**Scheme 100**) was chosen as it was previously reported to give a high yield and high selectivity in the allylboration of isobutyraldehyde to give homoallylic alcohol **305**.

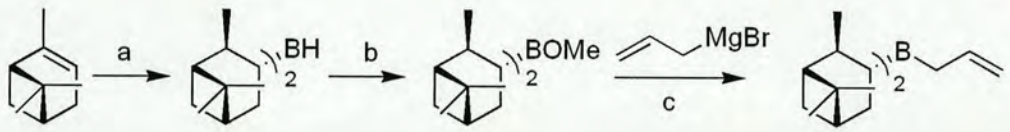


305

Scheme 100: *Allylboration of isobutyraldehyde using allylborane 73*

4.1.1.1. Synthesis of Allyldiisopinocampheylborane

Allylborane **73** was synthesised from the organometallic addition of allylmagnesium bromide to methoxydiisopinocampheylborane **77** as shown in **Scheme 101**. Synthesis of (-)-β-methoxydiisopinocampheylborane **77** from pinene **306** allowed the allylboration to be carried out on a large scale. Careful addition of BH_3•SMe_2 to α-pinene **306**, maintaining the reaction at room temperature, followed by a slow crystallisation, afforded borane **307**.[137,138] Slow methanolysis of borane **307** at low temperature prevents disproportionation occurring, which can lower the subsequent enantioselectivity of the allylboration. Dropwise addition of allylmagnesium bromide to methoxy borane **77** afforded the allylborane and magnesium salt by-product. Removal of the magnesium salts by filtration afforded allylborane **73**.

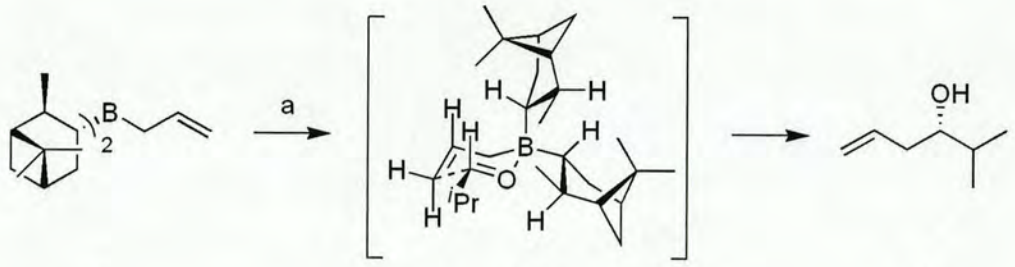


306 **307** **77** **73**

Scheme 101: *Synthesis of allyldiisopinocampheylborane 73*

Reagents and Conditions: (a) BH_3•SMe_2, THF, RT; (b) MeOH, Et_2O, 0 °C → RT, 2 h; (c) allylmagnesium bromide, Et_2O, 0 °C → RT, 1 h.

Slow addition of isobutyraldehyde (**Scheme 102**) to a cooled solution (-100 °C) of allyl borane **73** for 1 h, followed by an oxidative work up provided the homoallylic alcohol **305** in good yield (87 %). Although Brown has reported that allylboration takes place instantaneously using salt-free conditions, the reaction time was extended to 1 h to allow completion of the reaction.[34]

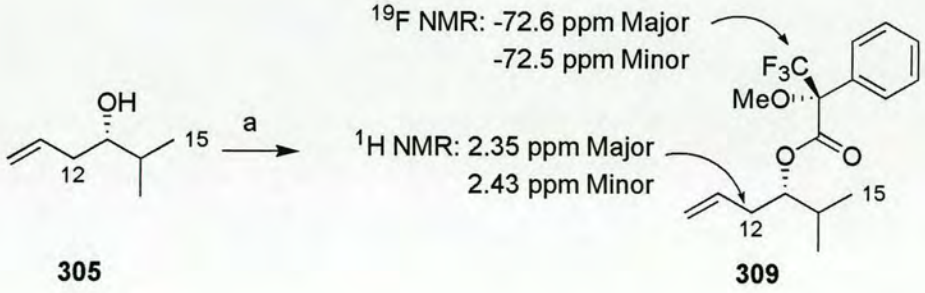


73 **308** **305**

Scheme 102: *Allylboration of isobutyraldehyde*

Reagents and Conditions: (a) isobutyraldehyde, Et_2O, -100 °C, 1 h, (87 %, 93 % e.e.).

The allylation of aldehydes proceeds through a chair-like transition state **308**, where the isopropyl group occupies an equatorial position and the facial selectivity of the aldehyde derives from the minimisation of steric interactions between the axial isopinocampheyl ligand and the allyl group, as shown in **Scheme 102**. The absolute stereochemistry of allylic alcohol **305** was assumed on the basis of precedent.[34] The enantiomeric purity (**Scheme 103**) of alcohol **305** was confirmed by ^1H NMR analysis (δ = 2.43 ppm, C(12)H_2 for the minor, and δ = 2.35 ppm for the major Mosher ester **309**) and ^{19}F NMR (δ = -72.5 ppm, CF_3 for the minor and δ = -72.6 ppm for the major Mosher ester **309**) showing that homoallylic alcohol was synthesised with a high selectivity (93 % e.e.).



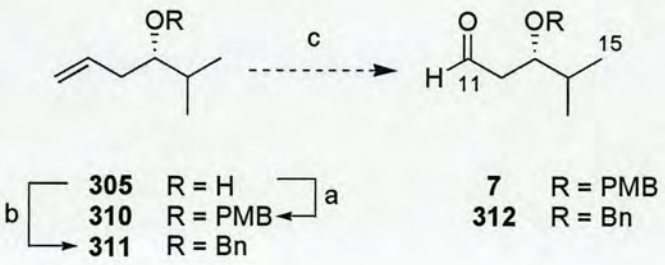
305 **309**

Scheme 103: *^1H and ^{19}F NMR analysis of Mosher ester **309***

Reagents and Conditions: (a) MTPA-Cl, DMAP, THF, 12 h, RT (80 %).

4.1.2 Oxidative Cleavage of the C(5)-C(6) Alkene

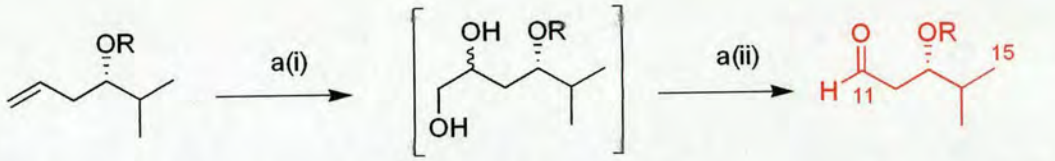
Protection of the C(13) hydroxyl (**Scheme 104**) as the PMB ether would allow a mild oxidative deprotection in the latter stages of the synthesis of octalactin A. It was also decided to protect the C(13) hydroxyl as the benzyl ether to allow selective deprotection in the latter stages of the synthesis of octalactin A. This selective deprotection strategy could allow the formation of analogues of octalactin A, and so facilitate further investigation into the biological activity of the octalactin series. Treatment of protected alcohol **305** with PMBCl (or BnBr) and ^{t}BuOK afforded the PMB ether **310** (or benzyl ether **311**). The conversion of protected alcohol **310** into the key aldehyde **7** was attempted using standard ozonolysis conditions, as reported by Evans *et al.*[139] Treatment of alcohol **310** with ozone followed by the addition of dimethyl sulfide, gave an inseparable mixture of aldehyde **7** and an unidentifiable by-product in poor yield (20 %). The conversion of alkenes to aldehydes using ozonolysis is generally a very reliable method. However, the addition of ozone to an alkene is a non-selective process and the substrate which undergoes ozonolysis must only contain alkenes which are required to be oxidatively cleaved. The low yield was believed to due to ozonolysis of the aromatic protecting group,[140] as well as the vinyl alkene, causing degradation of the aldehyde **7**. The low yield for the oxidative cleavage of the alkene moiety using ozonolysis demonstrated that a milder oxidative cleavage of the vinyl alkene was required.



Scheme 104: *Protection of alcohol **305** and attempted ozonolysis*

Reagents and Conditions: (a) PMBCl, ^{t}BuOK, THF, RT, 4 h (75 %); (b) BnBr, ^{t}BuOK, THF, RT, 4 h (69 %); (c) (i) O_3, CH_2Cl_2/MeOH, 10 min; (ii) SMe_2, 7 h, (20 %, R = PMB).

A new strategy (**Scheme 105**) towards the formation of PMB protected β-hydroxy aldehyde **7** from alcohol **310** required dihydroxylation of the vinyl alkene, followed by oxidative cleavage of the diol to give aldehyde **7**. Diol **313** was formed *in situ* by the addition of OsO_4 to protected alcohol **310**. Addition of $NaIO_4$ over 2 h as reported by Cossy *et al.*[141] gave aldehyde **7** in good yield (84 %). The same conditions were applied to Bn-protected alcohol **311** to afford aldehyde **312**, also in good yield.



310 R = PMB
311 R = Bn

313 R = PMB
314 R = Bn

7 R = PMB
312 R = Bn

Scheme 105: *The dihydroxylation and periodate cleavage of homoallylic alcohols 310 and 311*

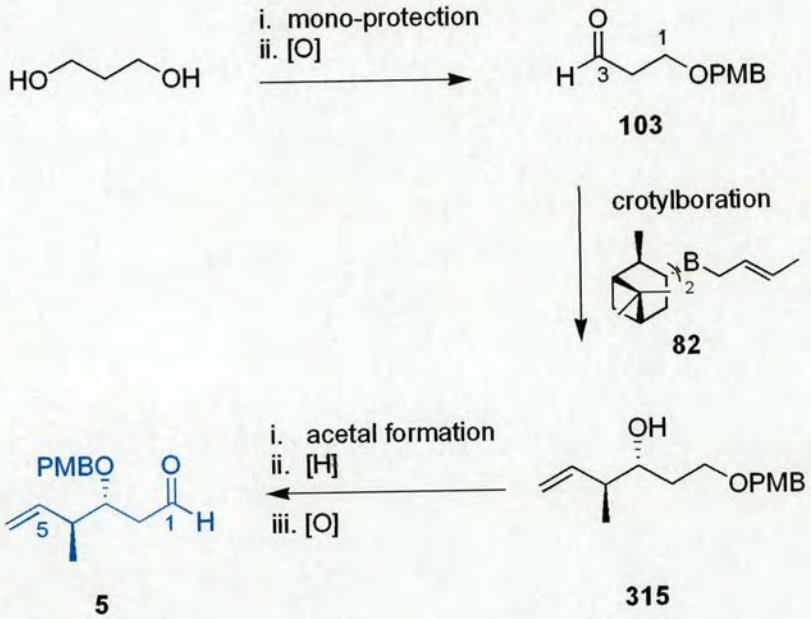
Reagents and Conditions: (a) (i) OsO_4, H_2O/THF, 10 min; (ii) $NaIO_4$, 2 h (**310** = 84 % and **311** = 79 %).

Using the modified method as shown in **Scheme 105**, aldehyde **7** could now be synthesised in 4 steps with an overall yield of 55 %. The relatively low cost of the pinene required to synthesise allylborane **73**, in comparison to the cost of (*R*)-valine required for acylated thiazolidine thione **300**, has allowed for the more economical large scale synthesis of aldehyde **7**. Fewer synthetic steps using this route have resulted in a more efficient route to aldehyde **7**.

4.2 SYNTHESIS OF C(1)-C(5) FRAGMENT

The synthesis of fragment **5** (**Scheme 106**) required mono-protection of propane diol, followed by oxidation of the remaining hydroxyl group to the aldehyde **103**. This aldehyde could then undergo an asymmetric crotylboration using reagent **82** to yield the chiral alcohol **315**. The manipulation of the PMB group *via* acetal formation and

selective reduction would protect the secondary alcohol, and subsequent oxidation of the primary alcohol would give aldehyde **5**.

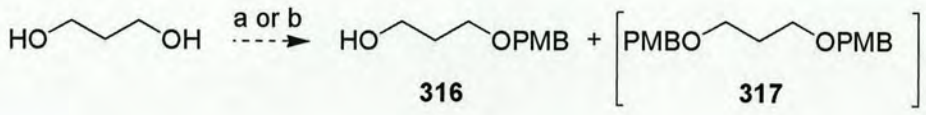


Scheme 106: *Synthetic strategy towards aldehyde* ***5***

4.2.1. Mono-Protection of the Diols

The first step taken was to mono-protect propane-1,3-diol using the *p*-methoxybenzyl (PMB) protecting group. One advantage of using this particular protecting group was that both aldehyde **5** and aldehyde **7** would be uniformly protected, thus facilitating a one-step global deprotection in the latter stages in the synthesis of octalactin A. An added advantage was that manipulation of the PMB group *via* acetal formation and selective reduction would allow an efficient protection of the C(3) hydroxyl.

Studies by Forsyth *et al.* have shown that the mono-protection of propane diol can be achieved in one-step (**Scheme 107**) to give mono-protected alcohol **316** in good yield (73 %).[142] However studies within our group using these conditions have only produced a mixture of compounds unidentifiable by ^{1}H NMR. To combat this problem, different conditions were used to synthesise alcohol **316**.



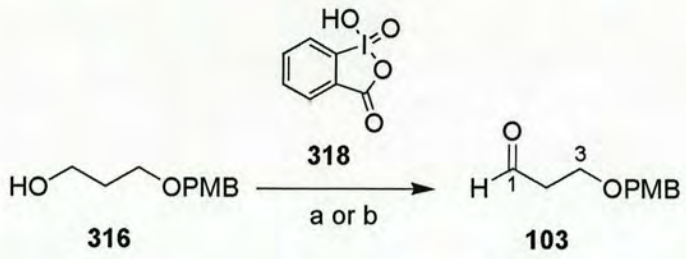
Scheme 107: *Mono-protection of 1,3-propane diol*

Reagents and Conditions: (a) NaH, PMBCl, $^{n}Bu_4NI$, THF, RT→25 °C, 21 h (73 %);[142] (b) NaH, PMBCl, DMF, 100 °C, 1 h, (**316** = 50 % and **317** = 40 %).

Propane-1,3-diol was treated with sodium hydride to generate the sodium salt, PMBCl was added and the reaction mixture was heated to 100 °C for 1 h. After this time all of the diol starting material had disappeared by TLC. ^{1}H NMR analysis of the crude reaction mixture showed both mono- and di-protected propane-(1,3)-diols, which were then separated by chromatography to give the mono-protected product **316** in moderate yield (50 %).

4.2.2 Oxidation of the Protected Diols

The mild oxidising agent (**Scheme 108**) *o*-iodoxybenzoic acid (IBX) **318** has been regularly used within our group for the oxidation of alcohols to aldehydes.[27,29] This compound is a precursor to the Dess-Martin periodinane, a well known oxidising agent for the transformation of alcohols to carbonyl compounds.[143,144] Both reagents are mild, have wide functional group tolerance and give good yields without evidence of over oxidation.[144] Due to it's limited solubility in common organic solvents, IBX has generally only been used as a precursor to the popular Dess-Martin periodinane. However, Frigerio *et al.* discovered in 1994 that IBX was soluble in DMSO, and for substrates insoluble in DMSO, THF could be used as a co-solvent.[145,146] Studies by Finney *et al.* have shown that IBX is partially soluble in EtOAc when heated under reflux and oxidations are successful under these conditions.[147]



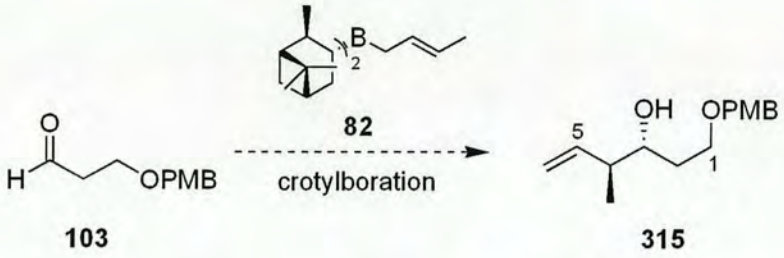
Scheme 108: *Oxidation of protected diol **316***

Reagents and Conditions: (a) **318**, EtOAc, Δ, 3 h (70 %); (b) DMSO, $(COCl)_2$, Et_3N, 1 h -78 °C to RT, (97 %).

Studies within the group[148] have shown that oxidation of alcohol **316** can be achieved in moderate yield (70 %) on small scale, using conditions discovered by Finney *et al.* However, these oxidation conditions require 3 equivalents of IBX and it was thought that a more efficient oxidation procedure may be applicable to a large scale synthesis of aldehyde **103**. Oxidation of alcohol **316** using Swern conditions afforded the aldehyde in an almost quantitative yield.

4.2.3. Crotylboration

The C(1) – C(5) aldehyde fragment **5** contained a β-methyl homoallylic alcohol moiety with two chiral centres at C(3) and C(4). There are a variety of methods to install the crotyl moiety, however loss of regio- and stereoselectivity is often a common problem. As discussed in Chapter 1, Brown *et al.* have extended their investigations from allylboration reactions to the crotylboration of aldehydes in order to synthesise β-methyl homoallylic alcohols in high yield and with high enantioselectivity.[38,40] Georg *et al.* synthesised the antipode **104** *via* a crotylboration of aldehyde **103**.[41-43] Therefore we envisage that aldehyde **103** can be efficiently synthesised using similar conditions and crotylborane **82**, as shown in **Scheme 109**.



103 **315**

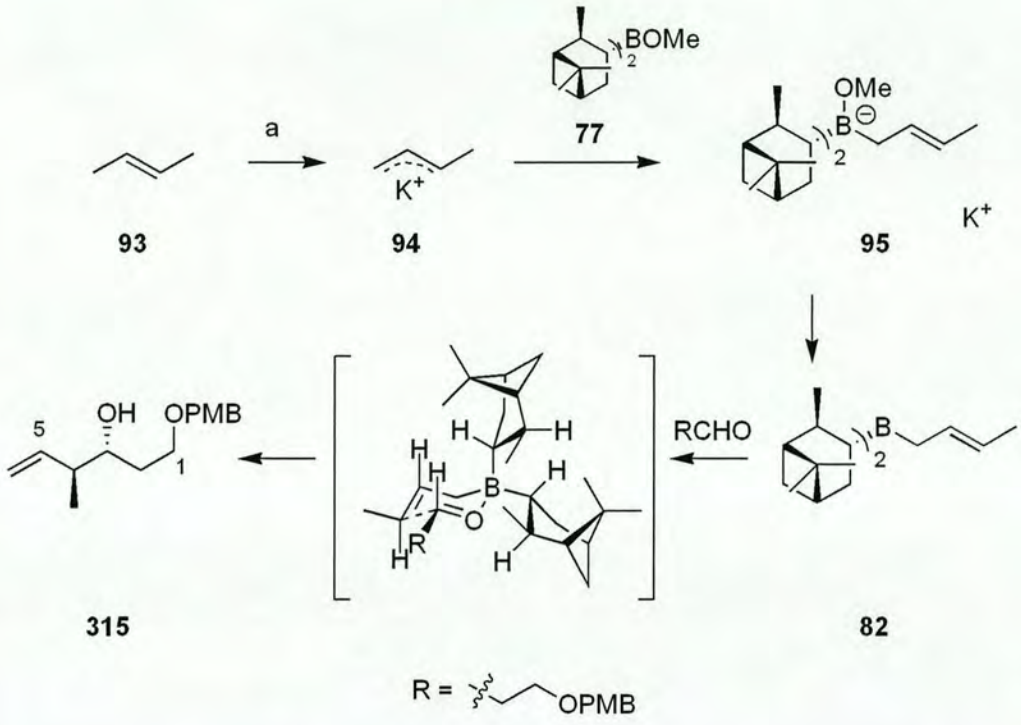
Scheme 109: *Proposed crotylboration of aldehyde **103***

4.2.3.1. Synthesis of the Homoallylic Alcohol **315**

For the synthesis of *E*-crotylborane **82**, *trans*-but-2-ene **93*** (**Scheme 110**) was metallated with a "superbase" using the Schlosser procedure[39] to generate an orange solution of *E*-crotylpotassium salt **94**. Treatment of salt **94** with (-)-β-methoxy diisopinocampheylborane **77** (synthesised from (+)-α-pinene) led to the formation of the boronate complex **95**. Addition of boron trifluoride etherate to complex **94** led to the generation of trialkylborane reagent **82**. The aldehyde **103** was then added quickly at low temperature and stirred at -78 °C. After 3 h the reaction was quenched with a basic hydrogen peroxide solution. Standard work-up procedures followed by careful chromatography provided homoallylic alcohol **315**. IpcOH and β-methylhomoallylic alcohol **315** have similar polarities and careful chromatography (8 % EtOAc in hexane) was required to separate the compounds.

Initial investigations into the crotylboration of aldehyde **103** were carried out using commercially available (-)-β-methoxydiisopinocampheylborane. Crotylboration of aldehyde **103** using the conditions described produced the allylic alcohol **315** in poor yield (35 %). The low yield of alcohol **315** was very surprising since Georg *et al.* have reported the synthesis of epimer **104** using similar crotylation conditions in a significantly higher yield (70 %) as previously shown in **Scheme 22**.

* *Trans*-but-2-ene is a gas, and was condensed at -78 °C to give a known value of liquid, before use.



Scheme 110: *Crotylboration of aldehyde **103***

Reagents and Conditions: (a) (i) ^{t}BuOK, ^{n}BuLi, THF, -45 °C, 10 min; (ii) **77**, Et_2O, -78 °C, 30 min; (iii) BF_3•Et_2O, -78 °C; (iv) **103**, -78 °C, 3.5 h; (v) H_2O_2, NaOH, RT, 18 h (71 %, 91 % e.e.).

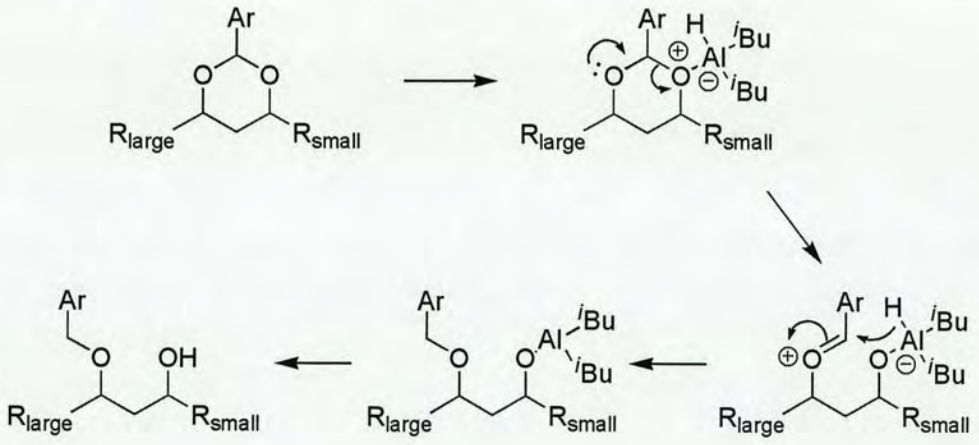
In order to optimise the yield of the crotylboration reaction it was decided that a large supply of methoxy borane **77** would be required. Due to the high cost of commercially available methoxy borane **77**, it was decided to prepare **77** (previously shown in **Scheme 101**). Interestingly, when freshly prepared methoxy borane **77** was used in the crotylboration of aldehyde **103** using the same conditions, homoallylic alcohol **315** was produced in a significantly higher yield (71 %). The lower yield of the alcohol when using the commercially available methoxy borane **77** could be due to the very hygroscopic nature of the borane **77** which led to its degradation.

Examination of the crude ^{1}H NMR showed alcohol **315** as a single diastereomer. The spectroscopic data and optical rotation values of alcohol **315** {$[\alpha]_D$ = -0.19 (c 2.0, $CHCl_3$)} were in good agreement with the literature value {$[\alpha]_D$ = -0.19 (c 2.0,

$CHCl_3$)}.[41-43] The enantiomeric purity was determined as 91 % by chiral HPLC analysis, (alcohol **315** was compared with alcohol **104** derived from (+)-borane, Daicel Chiracel OD-H, 254 nm, 99:1 hexane/propan-2-ol, 0.5 ml min^{-1}, retention time: **315** 38.1 min, **104** = 41.1 min).

4.2.4. PMB Manipulation

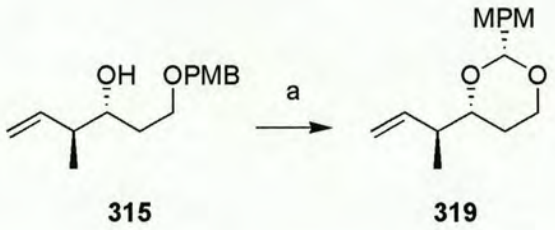
Crotylboration of aldehyde **103** has successfully installed the crotyl moiety with high yield, diastereoselectivity and enantioselectivity. However, before fragment **315** can be used in the synthesis, the PMB group must be manipulated so that the C(3) hydroxyl was protected and the primary hydroxyl was free to be oxidised to aldehyde **5**. Manipulation of the PMB protecting group could be achieved *via* the DIBALH reduction of a PMP acetal as illustrated in **Scheme 111**.[149]



Scheme 111: *Mechanism of the DIBALH reduction*[149]

The careful addition of DDQ (1 equivalent) to alcohol **315** at a low temperature (0 °C), in the presence of activated 4 Å molecular sieves for 2 h gave the crude PMB-acetal **319**, as shown in **Scheme 112**. Immediate purification by chromatography afforded acetal **319** in good yield (83 %). The immediate chromatography ensured that any residual DDQ was separated from the acetal in order to avoid deprotection. ^{1}H NMR analysis of acetal **319** clearly showed the loss of the signal at δ = 4.72 for

the benzylic protons of alcohol **315** and the formation of a peak at δ = 5.47 corresponding to the acetal. ^{13}C NMR analysis shows the loss of a benzylic CH_2 at 115.34 and the formation of an acetal CH at 100.85. Acetal **319** was used immediately in the reductive opening step in order to prevent decomposition.

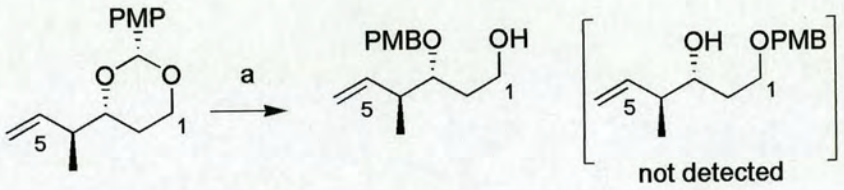


315 **319**

Scheme 112: *Acetal formation*

Reagents and Conditions: (a) DDQ, 4Å molecular sieves, CH_2Cl_2, -15 °C, 2 h (83 %).

The acetal **319** was treated with DIBALH (**Scheme 113**) at 0 °C for 2 h and after purification provided alcohol **320** in good yield as a single product. Analysis of the ^1H NMR of alcohol **320** showed the loss of acetal signal at δ = 5.47 indicating that no starting material remained, and the new AB signals at δ = 4.60 and 4.42 indicated the formation of a benzylic system. Comparison of ^1H NMR of primary alcohol **320** with secondary alcohol **315** showed a change in the signals for the benzylic system (δ = 4.72, singlet for primary alcohol **320** and δ = 4.60 & 4.42, AB for secondary alcohol **315**) and the movement of the C(5) vinyl proton signals from δ = 6.07 for primary alcohol **320** to δ = 5.79 for secondary alcohol **315**. ^{13}C NMR analysis shows the loss of an acetal CH at 100.85 and the formation of a benzylic CH_2 at 74.04. The differences in both ^1H and ^{13}C NMR of acetal **319**, alcohol **315** and alcohol **320** imply that acetal **319** was selectively reduced to give primary alcohol **320**.



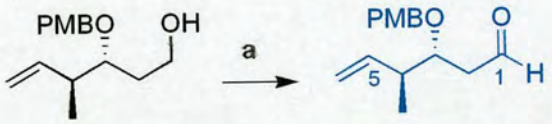
319 **320** **315**

Scheme 113: *Reductive opening of acetal **319***

Reagents and Conditions: (a) DIBALH, CH_2Cl_2, RT, 20 h (93 %).

4.2.5. Oxidation of Alcohol

A number of mild methods exist for the formation of aldehydes from primary alcohols. Since the oxidation of primary alcohol **316** using Swern conditions proceeded smoothly, it was decided to use similar conditions for the oxidation of alcohol **320**. Oxidation of alcohol **320** gave the desired aldehyde **5** in good yield (**Scheme 114**).



320 **5**

Scheme 114: *Oxidation of alcohol **320***

Reagents and Conditions: (a) DMSO, $(COCl)_2$, Et_3N, 1 h, -78 °C to RT, (99 %).

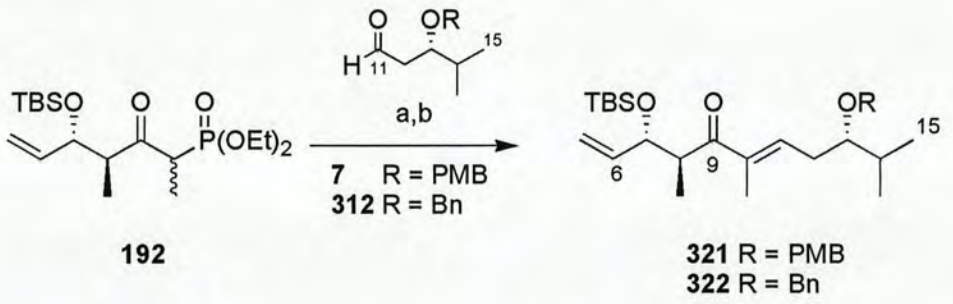
4.3 COMPLETION OF FRAGMENT SYNTHESIS

The highly selective introduction of the crotyl moiety was achieved using Brown's crotylboration conditions. Utilisation of high yielding protecting group manipulations and oxidations allowed the synthesis of aldehyde **5** in 5 steps (from propane-1,3 diol) with a 25 % overall yield. The two key aldehydes (**5** and **7**) were efficiently

synthesised and the third key fragment, β-ketophosphonate ester **192** has been synthesised (Chapter 1) and optimised in Chapter 2. The completion of the key fragments allowed the methodology developed in Chapter 1 to be applied towards the total synthesis of octalactin A.

4.4 HWE COUPLING: CONSTRUCTION OF THE C(10) – C(11) BOND

The barium hydroxide promoted HWE reaction was shown to be successful using isovaleraldehyde as a model for aldehyde **7**, as discussed in Chapter 2 giving good yields and selectivity in the formation of *E*-enones.



Scheme 115: *HWE of fragment **192** with aldehydes **7** and **312***

Reagents and Conditions: (a) (i) $Ba(OH)_2 \bullet 8H_2O$, THF/H_2O (40:1); (ii) **7** or **312**, RT, 18 h (**321** = 87 % and **322** = 85 %).

Treatment of the 4:1 mixture of diastereomers of β-ketophosphonate ester **192** with activated barium hydroxide and aldehyde **7** gave α,β-unsaturated enone **321** (**Scheme 115**) in 87 % yield with *E/Z* selectivity >95:5. HWE olefination using similar conditions and aldehyde **312** produced α,β-unsaturated enone **322** in good yield with high selectivity for the *E*-enone. Analysis of the crude ^{1}H NMR for both **321** and **322** showed no minor diastereomers, implying no *Z*-enone formation.

Analysis of the ^{1}H NMR of enones **321** and **322** showed signals for the vinyl protons (δ = 6.88, br t, *J* = 6.8 Hz, C(11)H for **321**; δ = 6.83, br t, *J* = 6.8 Hz, C(11)H for **322**) which are similar to vinyl proton signal (δ = 6.75, br t, *J* = 6.6 Hz, C(11)H) for model compound **195**, and gave further confirmation of the formation of the *E*-enone.

The enone system was believed to be quite rigid and it was thought that nuclear Overhauser measurements would confirm the expected stereochemistry.

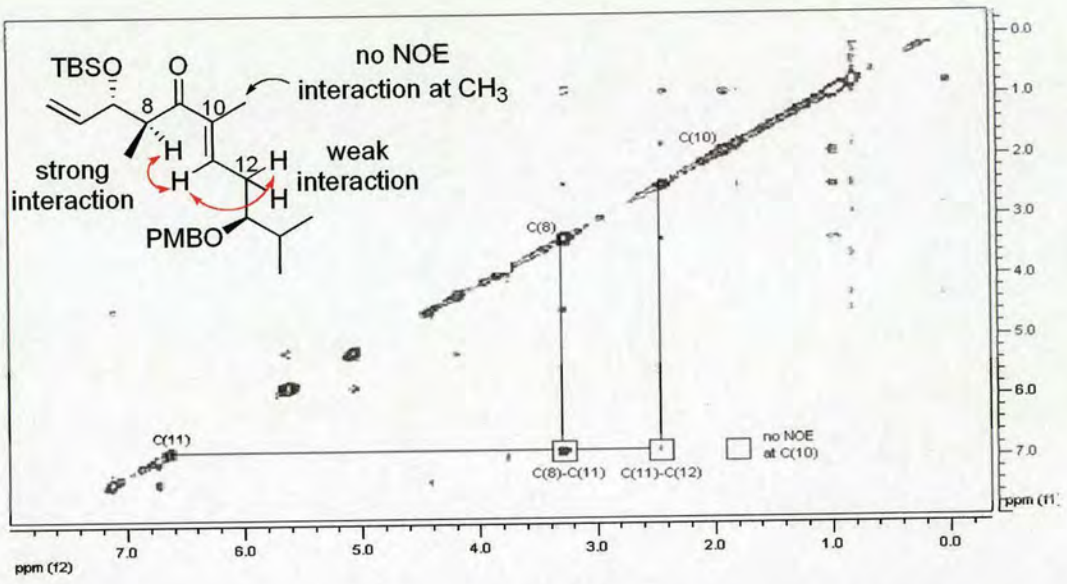


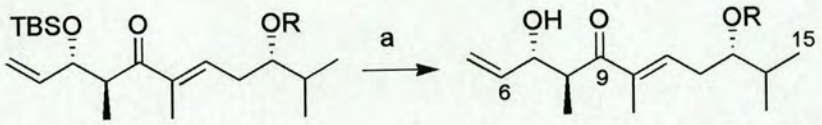
Figure 25: *NOESY measurements for the vinylic proton at δ = 6.78 ppm of* ***321***

Analysis of the NOESY results for enone **321** showed a strong interaction between the vinylic proton at δ = 6.78 and the C(8)H δ = 3.35 – 3.29, shown in **Figure 25**. There is also a weaker interaction of the vinylic proton at δ = 6.78 with $C(12)H_2$ at δ = 2.46 and there was no interaction between the vinylic proton at δ = 6.78 with the $C(10)CH_3$ at δ = 1.79, again confirming (*E*) selectivity of enone **321**.

4.5 DEPROTECTION OF HWE ADDUCTS

The removal of the TBS group to give a β-hydroxy enone was required to allow the Evans-Tishchenko coupling to proceed.

The successful conditions used for the deprotection of model enone **195** as discussed in Chapter 2, were applied to protected β-hydroxy enones **321** and **322**, as shown in **Scheme 116**. HWE adduct **321** was treated with 40 % aqueous HF in MeCN to give deprotected adduct **72** in excellent yield (94 %) with no epimerisation at the C(8). Similarly HWE adduct **322** was treated with 40 % aqueous HF in MeCN and gave the deprotected β-hydroxy enone **323** was achieved in excellent yield (95 %). The successful synthesis of the functionalised β-hydroxy enones (**72** and **323**) could permit the intermolecular Evans-Tishchenko coupling with aldehyde **5**.



321 R = PMB
322 R = Bn

72 R = PMB
323 R = Bn

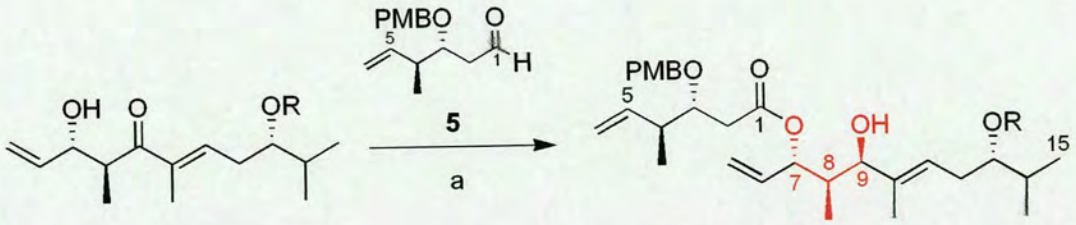
Scheme 116: *Deprotection of β-hydroxy enones 321 and 322*

Reagents and Conditions: (a) HF (40 % aqueous), MeCN, 15 min (**72** = PMB, 94 %; **323**= Bn, 95 %).

4.6 EVANS-TISHCHENKO COUPLING

Based on the successful synthesis of *anti* diol monoester **174** (discussed in Chapter 2), it was envisaged that the reaction of β-hydroxy enones **72** and **323** with a Sm(III)/benzaldehyde pinacol adduct and functionalised aldehyde **5** would result in the formation of the respective *anti* diol monoesters.

Treatment of β-hydroxy enone **72** with Sm(III)/benzaldehyde pinacol adduct for 30 min, followed by the addition of aldehyde **5** afforded the *anti* diol monoester **71** in 96 % yield as a single diastereomer (**Scheme 117**). Treatment of β-hydroxy enone **323** using these Evans-Tishchenko conditions successfully generated *anti* diol monoester **324** in good yield (91 %).



72 R = PMB
323 R = Bn

71 R = PMB
324 R = Bn

Scheme 117: *Evans-Tishchenko coupling of aldehyde 5 and β-hydroxy enones 72 and 323*

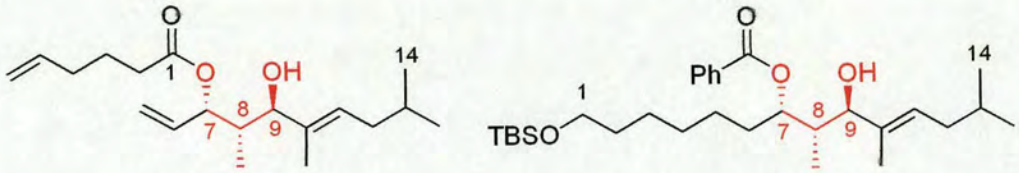
Reagents and Conditions: (a) (i) PhCHO, SmI_2 (0.1 M in THF, 30 mol%), followed by **5**, 30 min: (ii) **71** or **337**, THF, -10 °C, 30 min (**71** = PMB, 96 %; **324** = Bn, 91 %).

Analysis of the ^{1}H NMR for *anti* diol monoester **71** showed a significant shift of the C(11) vinylic proton (δ = 6.75 ppm (**72**) to δ = 5.52 ppm (**71**)) and indicated reduction of the enone. Loss of an aldehyde peak (δ = 9.88 ppm) also suggested ester formation. Infrared spectroscopy showed a change in the stretch from 1660 cm^{-1}, indicative of an α,β-unsaturated carbonyl, to 1720 cm^{-1} (ester C=O) suggested the formation of *anti* diol monoester **71**. Further analysis of ^{1}H NMR of **71** and **324** (**Table 10**) showed that esters were in good agreement with model **174** and the Evans-Tishchenko product **202** as shown in **Figure 26**.

Ester	δ /ppm	multiplicity	J /Hz	Assignment
71	5.23	t	6.9	C(7)*H*
324	5.29 – 5.20	m	--	C(7)*H*
174	5.22 – 2.14	m	--	C(7)*H*
202	5.02	dt ≡ q	6.8	C(7)*H*
71	1.91 – 1.78	m	--	C(8)*H*
324	1.91 – 1.78	m	--	C(8)*H*
174	1.91 – 1.84	m	--	C(8)*H*
202	1.69 – 1.18	m	--	C(8)*H*[*]
71	3.95	d	3.9	C(9)*H*
324	3.96 – 3.91	m	--	C(9)*H*
174	3.88	d	4.8	C(9)*H*
202	3.86	d	3.8	C(9)*H*

Table 10: ^{1}H NMR Assignments of the C(7)-C(9) sections of adducts **71**, **324**, **174** and **202**

[*] δ = 1.69 – 1.18, m, 11H, C(2)-C(6)H_2 & C(8)H.



174 **202**

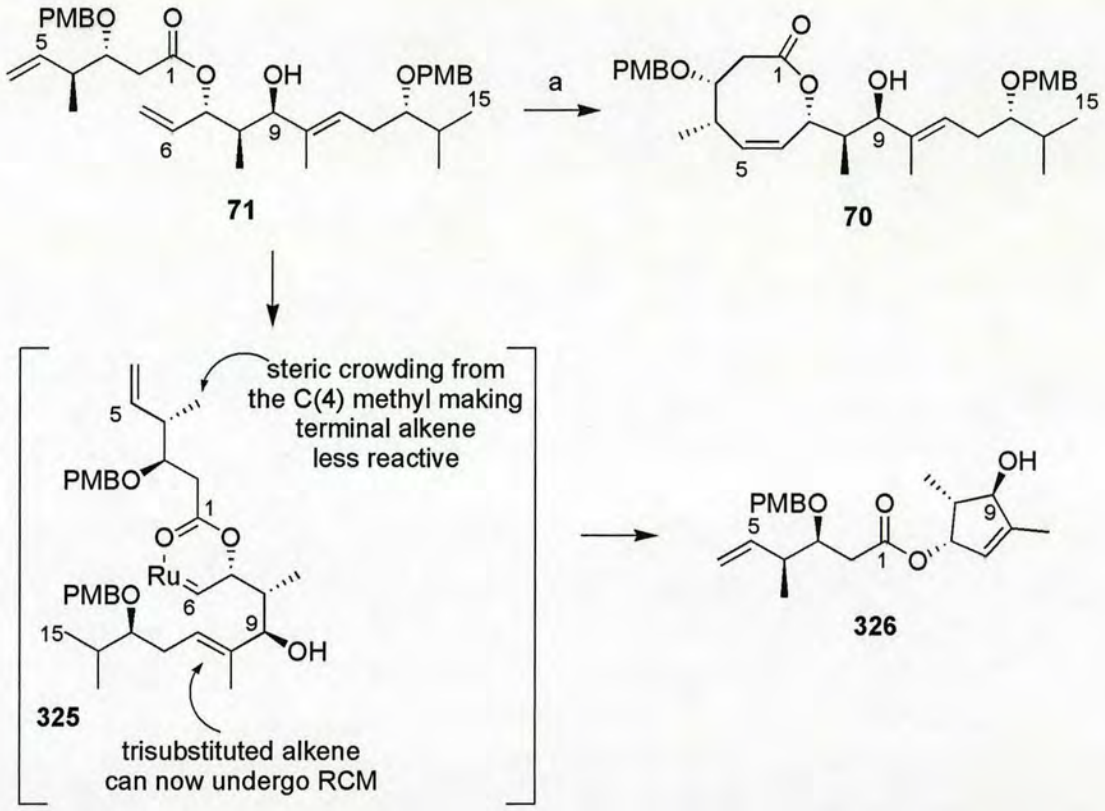
Figure 26: *Highlighted C(7)-C(9) sections of Evans-Tishchenko adducts **174** and **202***

The successful intermolecular Evans-Tishchenko coupling of functionalised β-hydroxy enones **72** and **323** with functionalised aldehyde **5** allowed the efficient synthesis of *anti* diol monoesters **71** and **324** with high yield and diastereoselectivity.

4.7 RING CLOSING METATHESIS

The use of ring closing metathesis (RCM) in the construction of various medium lactones have been reported and discussed in Chapter 1. In Chapter 2 RCM was applied to the successful formation of the octalactin A model **3**. The inclusion of the two terminal alkenes in trienes **71** and **324** could allow cyclisation to occur and formation of the 8-membered lactone.

Treatment of *anti* diol monoester **71** (**Scheme 118**) with Grubbs 2nd generation catalyst **159** (20 mol%) in degassed CH_2Cl_2 and heating under reflux for 24 h produced the desired lactone **70** and by-product **326** in an inseparable 1:1 mixture in moderate yield (70 %).

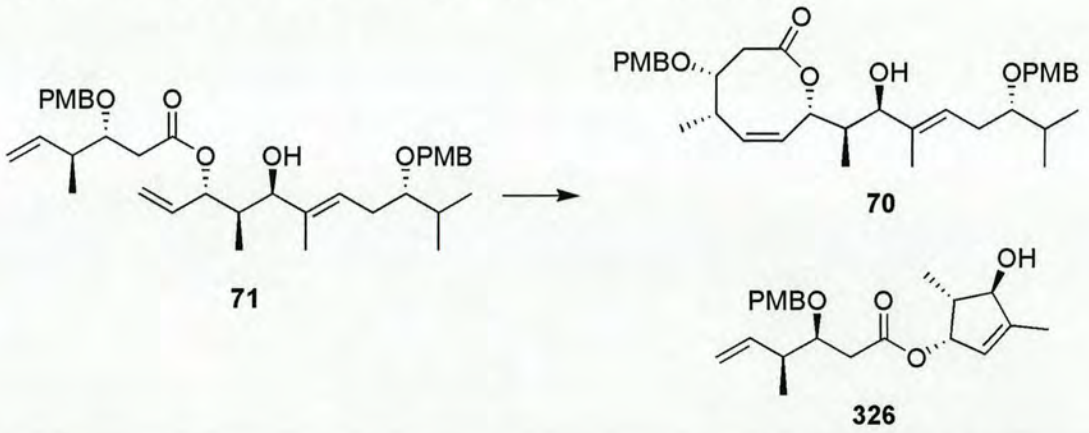


Scheme 118: *RCM of triene 71*

Reagents and Conditions: (a) Grubbs' 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h (70 %).

Lactone **70** was tentatively assigned by mass spectrometry and ^{1}H NMR analysis due to the loss of terminal alkene signals (δ = 5.07, d & 5.06, d, C(5)H=CH_2; δ = 5.26, d & 5.23, d, C(6)H=CH_2 for **71**) and the formation of new alkene signals (δ = 5.49-5.46, m, C(5)H; and δ = 5.39-5.36, m, C(6)H for **70**). These signals were in good agreement with model lactone **3**. Analysis of ^{1}H NMR also revealed the formation of signals indicative of a terminal alkene (δ = 5.72, ddd, C(5)H; δ = 4.98, d & 4.97, d; C(5)H=CH_2 for **326**). As discussed in the synthesis of model **3**, a small amount of cyclopentene by-product was detected by ^{1}H NMR. However RCM of fully functionalised precursor **71** has shown an increase in the formation of by-product **326**. The formation of cyclopentenol **326** was believed to be due to the addition of ruthenium to the C(6) alkene which then forms a stable 6-membered intermediate **325**. This reactive intermediate then directs the C(5) terminal alkene away from ruthenium, and the trisubstituted C(10) alkene can undergo metathesis to form by-

product **326** as shown in **Scheme 118**. The yield of the by-product **326** in the metathesis of fully functionalised precursor **71** has increased from a (9:1) mixture of product and by-product in the model studies (discussed in Chapter 2) to a (1:1) mixture. It is believed that the increased level of by-product in the metathesis is due to the presence of the C(4) methyl which makes the C(5) terminal alkene less reactive. The unsatisfactory level of by-product **326** led to investigations into the optimisation of the metathesis step, which are shown in **Table 11**.



Entry	Conditions	Yield **70** (%)	Yield **326** (%)	Recovery of **71** (%)
1	Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h	37	37	
2	Grubbs 1 **158** (5 mol%), CH_2Cl_2, RT, 24 h	0	0	69
3	Grubbs 1 **158** (10 mol%), CH_2Cl_2, RT, 24 h	0	0	62
4	Grubbs 1 **158** (20 mol%), CH_2Cl_2, RT, 24 h	0	0	73
5	Grubbs 1 **158** (20 mol%), CH_2Cl_2, Δ, 24 h	0	0	81
6	Grubbs 2 **159** (20 mol%), toluene, Δ, 10 min	--	--	--
7	$Ti(^iOPr)_4$ (10 mol %), Grubbs 2 **159** (20 mol%), CH_2Cl_2, RT, 24 h	30	0	35
8	$Ti(^iOPr)_4$ (10 mol %), Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h	70	0	0
9	$Ti(^iOPr)_4$ (20 mol %), Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h	69	0	0

Table 11: *RCM of triene 71*

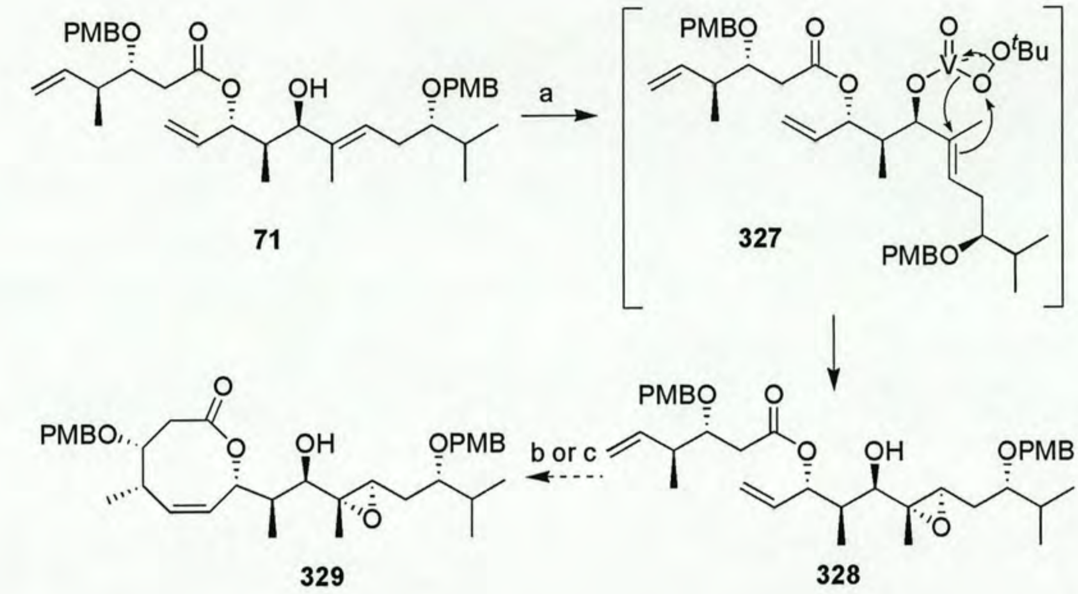
Previous investigations into the synthesis of lactone **3** focussed on the RCM of triene **174** using Grubbs 2nd generation catalyst **159**. In order to minimise the formation of by-product **326**, the less reactive Grubbs 1st generation catalyst **158** was used in order to RCM the terminal alkenes and leave the trisubstituted alkene intact.[150-152] Treatment of triene **71** with increasing amounts of Grubbs 1st generation catalyst **158** (from 5 to 20 mol % **Table 11, entries 2 – 4**) gave only recovered starting material even when the reaction temperature was increased to 40 °C (**Table 11, entry 5**). The recovery of purely starting material demonstrated that Grubbs 1st generation catalyst **158** was not reactive enough to RCM triene **71** and that Grubbs 2nd generation catalyst **159** would have to be used.

Danishefsky *et al.* have reported the use of RCM in the synthesis of epothilone 490.[153] They have shown that heating Grubbs 2nd generation catalyst **159** in toluene for 10 min afforded the kinetic product in moderate yield. However when the RCM was attempted on triene **71** using conditions described by Danishefsky *et al.*, (**Table 11, entry 6**) analysis of ^{1}H NMR showed an inseparable mixture of unidentifiable compounds.

Fürstner *et al.* have reported the use of titanium additives during their synthesis of (-)-gloeosporone.[154] They have postulated that the RCM step can be hindered due to the formation of a stable ruthenium reaction intermediate. They have shown that the addition of a catalytic amount of Ti(^{i}OPr)$_4$ can cause competitive chelation in the substrate, and therefore increase the yield of the RCM. The conditions described by Fürstner *et al.* were applied, (**Table 11, entry 7**) at room temperature and analysis of the ^{1}H NMR showed the formation of lactone **70** in low yield with a moderate recovery of starting material. It is important to note that there was no formation of by-product **326**. The reaction conditions were repeated with higher temperatures (**Table 11, entry 8**) and higher loading of the titanium additive (**Table 11, entry 9**) and the yields of lactone **70** were dramatically improved. The optimum conditions used for the RCM of triene **71** are shown in (**Table 11, entry 8**) and allowed for isolation of lactone **70** in good yield (70 %).

^{1}H NMR analysis of the purified lactone showed the loss of the terminal alkene (δ = 5.07, d and 5.06, d, C(5)H=CH_2, δ = 5.26, d and 5.23, d, C(6)H=CH_2 for **71**) and the formation of new alkene signals (δ = 5.49-5.46, m, C(5)H; and δ = 5.39-5.36, m, C(6)H for **70**) are in good agreement with model lactone **3**. The presence of a C(13)H signal (δ = 3.04, q, J = 5.8 Hz), and the C(14)H(CH_3)$_2$ signals (δ = 0.88, d, J = 6.9 Hz and δ = 0.87, d, J = 6.9 Hz) implied the presence of the intact C(11) – C(15) fragment of lactone **70**, which would be lost in the formation of by-product **326**. Analysis of the ^{1}H NMR showed that there were no signals indicative of a terminal alkene, as seen for the by-product **326** (δ = 5.72, ddd, C(5)H; δ = 4.98, d and 4.97, d, C(5)H=CH_2 for **326**). Although the methodology introduced by Fürstner *et al.* has shown a vast improvement in the yield of lactone **70** it was decided to investigate other strategies to optimise the RCM reaction.

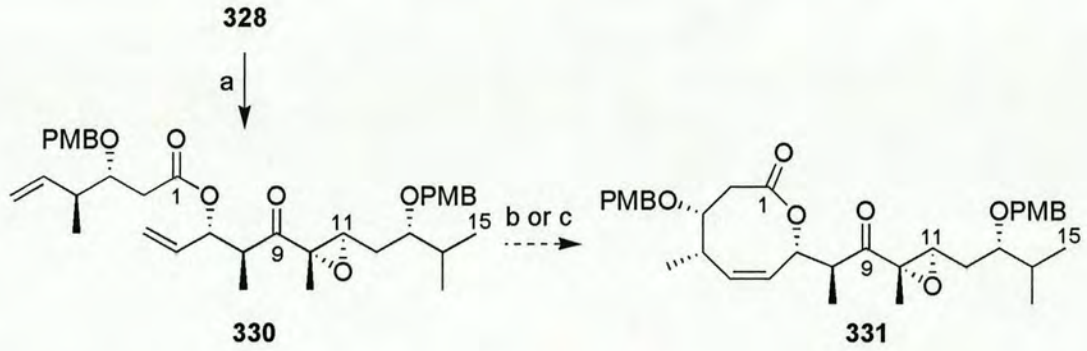
The formation of by-product **326** was due to the RCM of the C(6) alkene with the C(10) trisubstituted alkene. The latter stages of the synthesis of octalactin A *via* lactone **70** require the introduction of an epoxide moiety at C(10)-C(11).[18] The introduction of the epoxide, before attempting the RCM, would remove the possibility of reaction with the third alkene. The use of an epoxide to prevent competitive metathesis is a common tool in organic synthesis.[155] Treatment of triene **71** with VO(acac)$_2$ and ^{t}BuOOH (**Scheme 119**) allowed the epoxidation to occur *via* transition state **327**, to give epoxide **328** in good yield (87 %). Analysis of the ^{1}H NMR showed the epoxide as a 95:5 mixture of diastereomers. The absolute stereochemistry of epoxide **328** was based on literature precedent.[18] A shift in the signal of the C(11) proton (from δ = 5.52 to δ = 3.53 – 3.49) was seen suggesting the addition of epoxide over the C(10) – C(11) alkene. RCM was attempted using the Grubbs 2nd generation catalyst **159** (20 mol%) in CH_2Cl_2, with heating under reflux for 24 h, but unfortunately only starting material was recovered. RCM of epoxide **342** was repeated using the optimised conditions shown in **Table 11**, and again, only starting material was recovered.



Scheme 119: *RCM of epoxide 328*

Reagents and Conditions: (a) $VO(acac)_2$, ^tBuOOH, PhH, RT, 1 h (87 %); (b) Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h; (c) $Ti(^iOPr)_4$ (10 mol%), Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h.

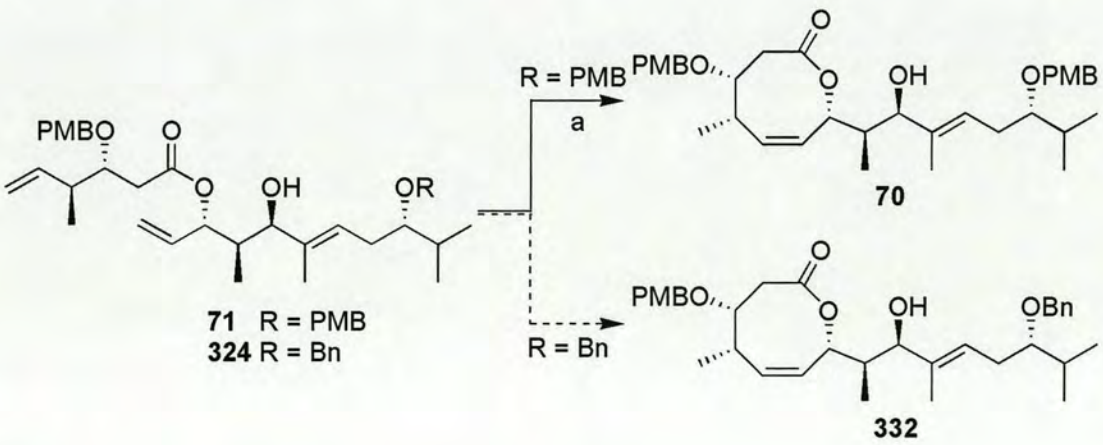
It was proposed that the free hydroxyl at C(9) might itself be causing deactivation of the catalyst. Since the free hydroxyl group was no longer required once the directed epoxidation has been achieved, the C(9) hydroxyl of epoxide **328** was oxidised using Dess-Martin periodinane, to give ketone **330** in good yield (98 %) as shown in **Scheme 120**. RCM was attempted using the Grubbs 2nd generation catalyst **159** (20 mol%) in CH_2Cl_2 with heating under reflux for 24 h, and also with the optimised conditions from **Table 11**, and only starting material was recovered. It was thought that stronger conditions were required to form the 8-membered ring. Recent reports have shown that RCM using microwave conditions can improve the yields and cyclise demanding substrates.[156-160] RCM of epoxide **330** using Grubbs 2nd generation catalyst **159** under microwave conditions resulted in the formation of an unidentifiable mixture of compounds.



Scheme 120: *RCM of epoxide **330***

Reagents and Conditions: (a) Dess-Martin periodinane, CH_2Cl_2, RT, 3 h (98 %); (b) Ti(^{i}OPr)$_4$ (10 mol%), Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h; (c) Grubbs 2 **159** (20 mol%), PhMe, 110 °C, 10 min, μwave.

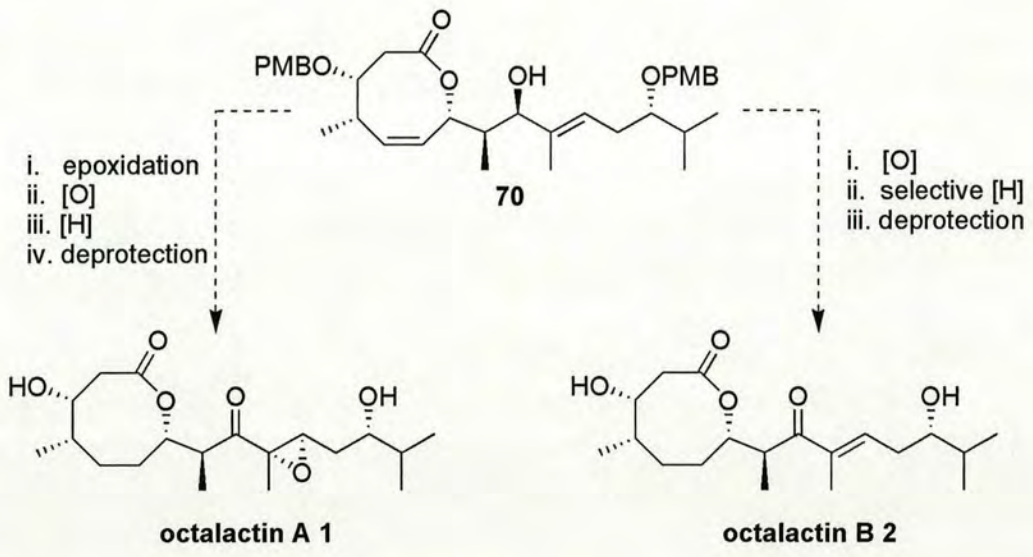
Investigation into the RCM of alternative substrates did not reveal a more efficient route towards the 8-membered lactone. In summary the best conditions were those shown in **Table 11**, treating triene **71** with Ti(^{i}OPr)$_4$ (10 mol%) followed by Grubbs 2nd generation catalyst **159** (20 mol%) with heating under reflux for 24 h. This route (**Scheme 121**) afforded lactone **70** in good yield with no formation of by-product **326**. The optimised conditions could be applied to the RCM of triene **324** to give the lactone **332**.



Scheme 121: *RCM of triene **71***

Reagents and Conditions: (a) Ti(^{i}OPr)$_4$ (10 mol%), Grubbs 2 **159** (20 mol%), CH_2Cl_2, Δ, 24 h (**70** = 70 %).

The final proposed stages of the synthesis of the octalactins are shown in **Scheme 122**. The reactions are very similar to those reported in the synthesis of octalactin A by Buszek *et al.*, where the only difference in the route to octalactin A is the choice of protecting group on the C(9) hydroxyl (lactone **70** has PMB, Buszek has TBS).[14] The current status is an efficient route to the precursor of both octalactin A **1** and octalactin B **2**.



Scheme 122: *Routes towards the octalactins from lactone **70***

4.8 CONFIRMATION OF THE OCTALACTIN SKELETON

Lactone **70** is the carbon skeleton of the octalactins (**Figure 26**) and contains all of the stereocentres required for octalactin B (5 stereocentres) and an extra stereocentre at C(9) to allow the selective installation (*via* epoxidation) of the other 2 stereocentres required for octalactin A.

The C(1) and C(5) fragment of lactone **70** was added to the carbon skeleton *via* the Evans-Tishchenko coupling of fragment **5**. The stereochemistry at C(3) and C(4) was generated *via* a crotyl boration using Brown's reagents. The relative and absolute stereochemistry of fragment **5** was assessed on the spectroscopic data of the epimer.

The C(11) and C(15) fragment was introduced to the carbon skeleton *via* a Horner Wadsworth Emmons olefination with fragment **7**. The stereochemistry at C(13) was installed *via* an allylboration using Brown's reagents. The absolute stereochemistry of fragment **7** was assumed on the basis of precedent[34] and the enantioselectivity of the allylboration reaction was determined by spectroscopic analysis of its Mosher's ester. The optical rotation of fragment **7** [$[\alpha]_D$ = - 65.3 (c 0.3, $CHCl_3$)] was in good agreement with literature value [$[\alpha]_D$ = - 65.7 (c 0.3, $CHCl_3$)],[29] further confirming the absolute stereochemistry. The C(5) – C(10) fragment of the octalactin carbon framework was also introduced by a Horner Wadsworth Emmons olefination with fragment **192**. The relative stereochemistry was based on the vicinal coupling between the C(7) and C(8) protons in the ^{1}H NMR (7.0 Hz).[54] The absolute stereochemistry for **192** was based on the good agreement of the spectroscopic data of diol **271** with the literature values,[128] as well as the optical rotation value [$[\alpha]_D$ = - 18.4 (c 1.0, $CHCl_3$), lit.[128] -18.6 (c 2.0, $CHCl_3$)].

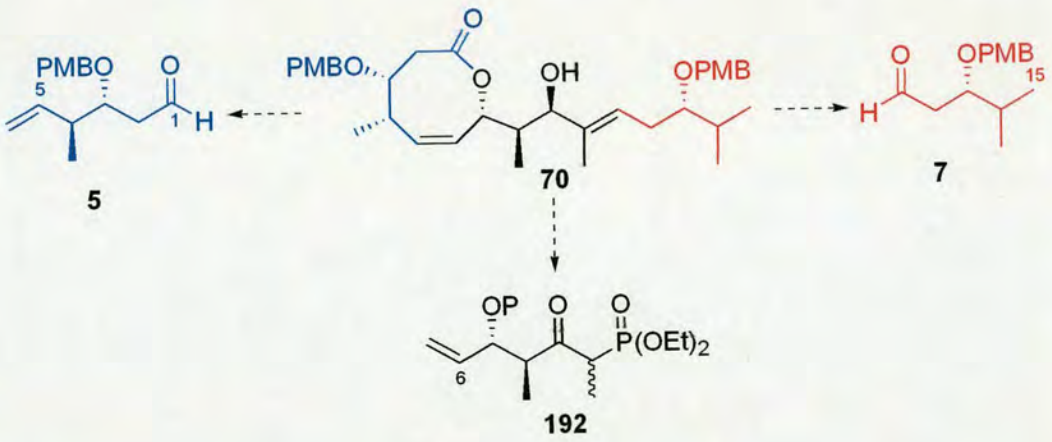


Figure 26: *Carbon skeleton of the octalactins*

NOE measurements with the vinylic C(11) proton have allowed the geometry of the C(10) - C(11) alkene to be assigned as (*E*), as discussed in section **4.3** of this chapter. The stereochemistry of the C(9) hydroxyl was introduced to lactone **70** as a selective reduction of C(9) ketone after the Evans-Tishchenko coupling of fragment **5**. Analysis of the ^{1}H NMR allowed the stereochemistry at C(7) and C(9) to be assumed

as *anti* based on the comparison of the coupling of the C(9) proton with known Evans-Tishchenko adducts.

Analysis of the COSY spectrum (**Figure 27**) of lactone **70** can clearly show the presence of the isopropyl group of the C(11) – C(15) fragment (pink) of the octalactins. The presence of this group implies that no competitive metathesis occurs in the RCM step since this fragment would be cleaved. The COSY spectrum also shows coupling of the C(1) – C(5) fragment (red) with the C(6)-C(9) fragment (blue) by a cross peak at 5.46 ppm. The long range coupling [C(9) – C(11)] at 1.70 ppm can allow for the complete assignment of the octalactin skeleton and shows that the lactone fragment [C(2) – C(9)] is linked to the C(11)-C(15) fragment.

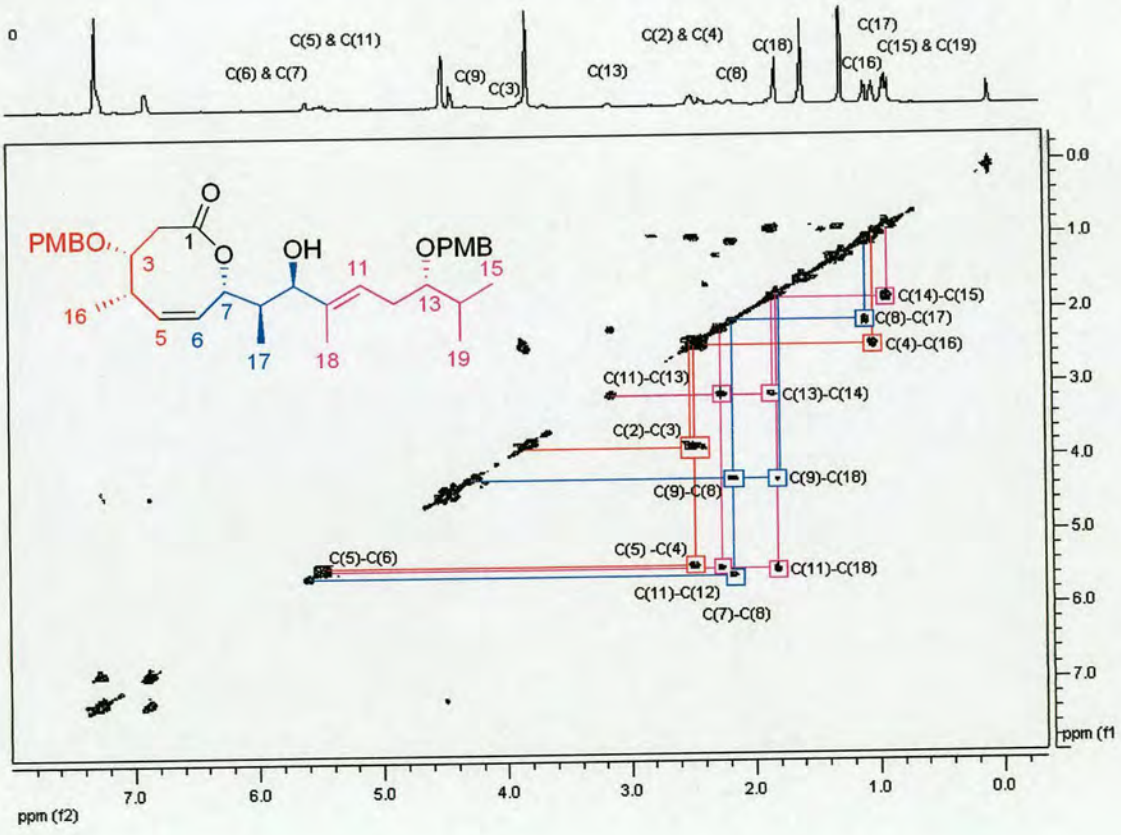


Figure 27: *COSY spectrum of lactone 70*

Analysis of the HSQC of lactone **70** (Figure **29**) implies that the signals (δ = 5.49 - 5.46 ppm, m and δ = 5.39 - 5.36 ppm) are not terminal alkenes or aliphatic CH, since

they are detected in the range of 140-125 ppm (commonly assigned to aromatic CH). Since the aromatic carbons for the PMB groups are distinctly shown (δ = 7.18, d, *J* = 8.7 Hz and δ = 6.78, d, *J* = 8.7 Hz) then it can be assumed the peaks at δ = 5.49 - 5.46 ppm, m and δ = 5.39 - 5.36 ppm belong to the C(5) – C(6) alkene of the lactone.

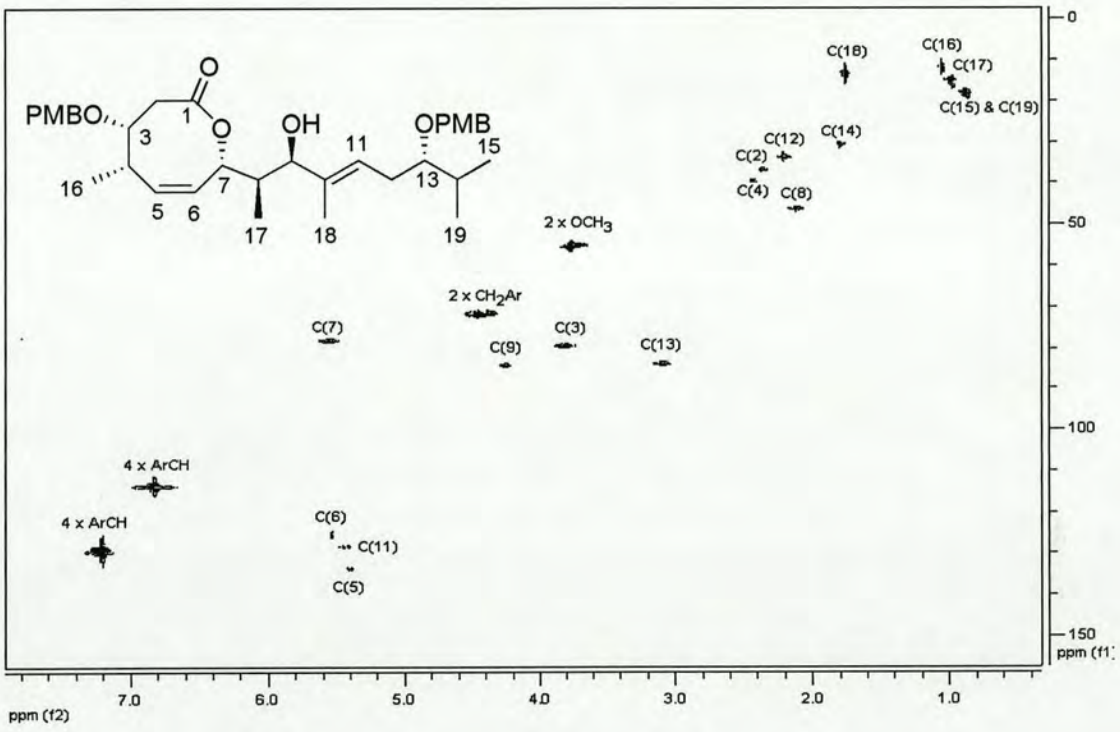


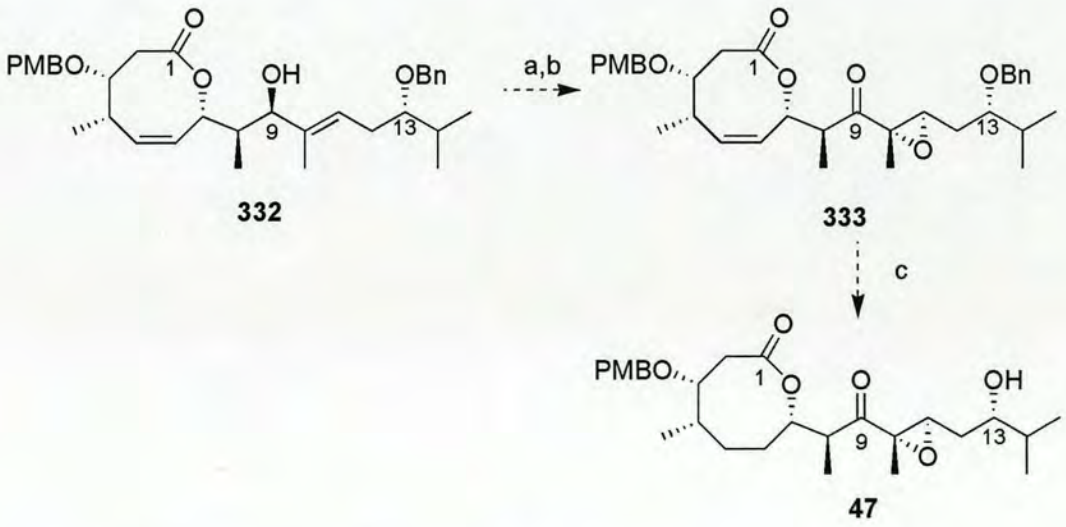
Figure 28: *HSQC spectrum of lactone* ***70***

4.9 STUDIES TOWARDS THE SYNTHESIS OF OCTALACTIN A ANALOGUES

As discussed in Chapter 1, the isolation of metabolites from the gorgonian octacoral afforded both octalactin A **1** and octalactin B **2**. The only difference in the two compounds is an epoxide moiety at C(10) – C(11) however biological screening has shown that octalactin A has activity against human colon cancer cell lines and murine melanoma, whereas octalactin B was shown to be inactive. Although the epoxide moiety seems to confer biological activity, there have been few investigations towards the synthesis of analogues of octalactin A to improve this activity. In fact there has been little investigation into the structural activity

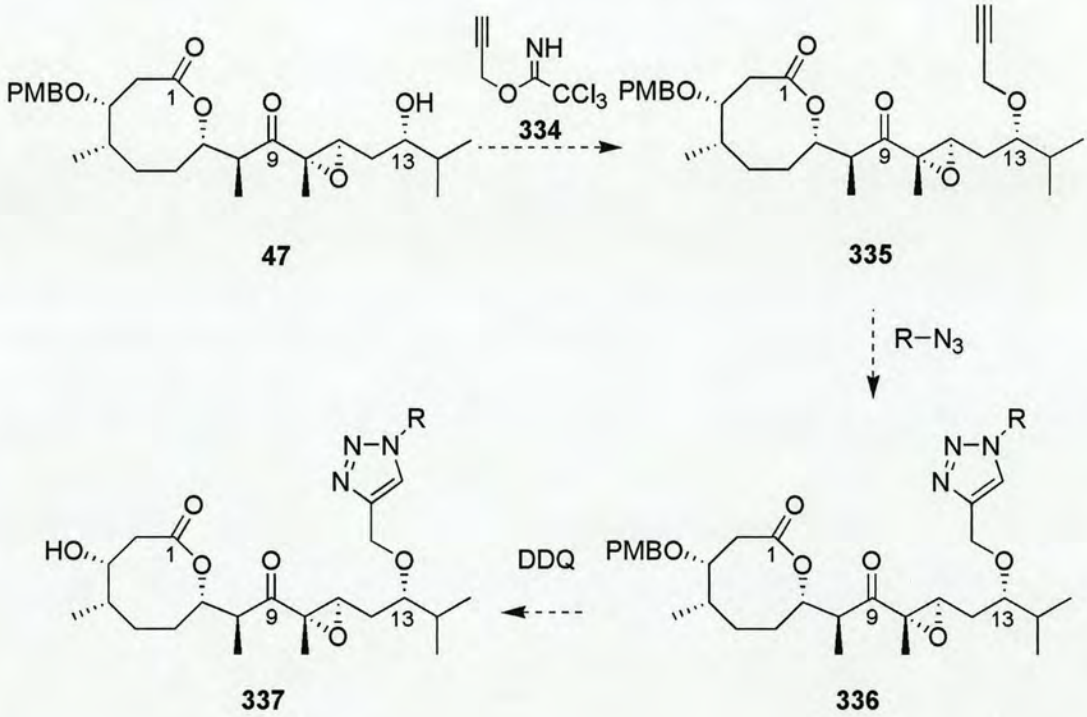
relationship of the octalactin series. Octalactin A and B also contain: a C(1) lactone carbonyl; C(9) ketone carbonyl; and C(3) and C(13) hydroxyl groups. These may have specific hydrogen bonding roles within cells. It would be interesting to synthesise analogues of octalactin A to protect some of these moieties. This would allow investigation into which other functional groups are required for the compound to display activity and highlight which areas could be targets for modification to improve the potency of octalactin A. Investigations towards the synthesis of octalactin A suggest that lactone **332** would be a suitable candidate for these studies.

Lactone **332** contains two different protecting groups and can ultimately result in the selective modification of either the C(3) or the C(13) hydroxyl groups. Although there have been a variety of strategies towards the synthesis of octalactin A containing two different protecting groups, these routes have more synthetic steps due to the additional deprotection adding to the overall yield lost. As shown in **Scheme 123**, epoxidation and oxidation using procedures reported by Buszek *et al.* would give lactone **333**. Removal of the C(5) – C(6) alkene *via* hydrogenation would also deprotect the C(13) benzyl ether to give the mono-protected octalactin A, without increasing the overall synthesis of the compound. It could then be envisaged the functionality of the hydroxyl groups could be modified independently.



Scheme 123: *Strategy towards mono-protected lactone **47***

Studies within the Hulme group on anisomycin[161] have shown that analogues can be synthesised *via* cycloaddition of an azide with a propargyl moiety to form a stable triazole. The synthesis of biologically active analogues *via* this efficient cycloaddition process, (commonly referred to as "click" chemistry), could be applied to the synthesis of octalactin A analogues. As shown in **Scheme 124**, the propargyl moiety could be installed on the C(13) hydroxyl using trichloroacetimidate **334** to give **334**. "Click" coupling of the lactone **335** with a series of azides (R = various substrates) to give triazole **336**. The functionality of the triazole **336** could be altered to contain fluorous tags and molecular probes to allow further investigation into why octalactin A is active. Such analysis using fluorescent microscopy would identify where in the cell the octalactin compound is found.



Scheme 124: *Synthesis of octalactin triazoles*

4.10 CONCLUSIONS

The two major aldehyde fragments **5** and **7** required for the synthesis of the octalactins were successfully synthesised. The synthetic strategy towards aldehyde **7** consisted of the Brown allylboration of isobutyraldehyde, protection and oxidative cleavage to give the C(11) – C(15) aldehyde **7** in 4 steps with an overall 40 % yield. The synthetic strategy towards aldehyde **5** consisted of the Brown crotylboration of aldehyde **103**, protecting group manipulation followed by oxidation to give the C(1) – C(5) aldehyde **5** in 5 steps with a 25 % overall yield.

The successful methodology developed for the major steps in the model synthesis of octalactin A and B (including HWE coupling and intermolecular Evans-Tishchenko coupling) was directly applied in the total synthesise of the octalactins. The incorporation of titanium additives into the RCM of the functionalised *anti* diol monoester **71** allowed for the efficient synthesis of the carbon skeleton of octalactin A and B, containing 5 of the 7 required stereocentres. The synthesis of octalactin A was halted after the ring closing metathesis of anti diol monoester **71**. Attempts to install the epoxide at C(10)-C(11) as shown in literature by Buszek were unsuccessful with starting material only recovered after reaction. The epoxide **328** was then installed prior to metathesis and unfortunately, previous conditions for cyclisation were unsuccessful.

It has been shown that installation of the desired stereochemistry at the C(9) can be achieved *via* Evans-Tishchenko coupling and the required 8-membered lactone can be efficiently formed using RCM. This strategy also introduces the potential for the synthesis of diverse analogues of octalactin A, for example *via* "click" coupling, to explore and determine the pharmacophore required for cancer toxicity.

EXPERIMENTAL

CHAPTER 5

EXPERIMENTAL PROCEDURES

5.1 GENERAL EXPERIMENTAL

^{1}H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Varian Gemini 200 (200 MHz) and Bruker AC250 (250 MHz), Bruker DPX360 (360 MHz) or Bruker AVA600 (600 MHz) Fourier transform instruments. The data is presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), coupling constant and the interpretation. ^{13}C NMR spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Bruker AC250 (62.9 MHz), Bruker DPX360 (90.5 MHz) or Bruker AVA600 (150 MHz) instruments and are reported in ppm on the δ scale. Where Distortionless Enhancement Polarisation Transfer (DEPT) spectra have been recorded, the carbon signals due to methyl (CH_3), methylene (CH_2), methine (CH) and quaternary carbon (C) are assigned.

Infra-red spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR instrument using 5 mm sodium chloride plates, or 0.1 mm sodium chloride solution cells. The wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}. Electron impact (EI) mass spectra were obtained using a finnigan 4500 mass spectrometer and fast atom bombardment (FAB) mass spectra were performed on a Kratos MS50TC by the service at the University of Edinburgh Chemistry department. The parent ion or relevant fragments are quoted, followed by significant fragments and their relative intensities. Optical rotations were measured on an AA-1000 polarimeter with a path length of 0.5 dm at the sodium D line (589 nm) and reported as follows: $[\alpha]_D$ concentration (*c* in g/100 ml)and solvent. Melting points were determined on a

Gallenkamp Electrothermal melting Point apparatus and are uncorrected. TLC was performed on Merck $60F_{254}$ (0.25 mm) glass silica plates and visualised by ultraviolet (UV) light and/or molybdate stain.* Flash column chromatography was carried out on Merck Kieselgel 60 (Merck 9385) under positive pressure by means of an air line or hand pump. Eluent compositions are quoted as v/v ratios. High performance liquid chromatography (HPLC) was carried out on a Gilson instrument using a Spherisorb column (internal diameter: 20 mm) and equipped with a Gilson refractive index detector. A standard flow of 10 ml/min was used. Chiral HPLC was performed using a Waters instrument with a Chiracel OD column (internal diameter: 4.6 mm) equipped with a UV detector. A standard flow rate of 0.5 ml/min was used. All solvents to be used for HPLC analysis were vacuum filtered and degassed prior to use. All HPLC samples were filtered through 0.45 μm nylon syringe filters prior to analysis.

Reagents were purified by standard means. Dichloromethane (CH_2Cl_2), diisopropylethylamine (DIPEA), hexane, pyridine, 2,6-lutidine and triethylamine (Et_3N) were distilled from calcium hydride and stored over calcium hydride under an argon atmosphere. The achiral aldehydes acrolein, isovaleraldehyde, isobutyraldehyde and methacrolein were freshly distilled from calcium chloride immediately prior to use. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl and stored an argon atmosphere. All other reagents were used as supplied. ^{n}Butyl lithium (^{n}BuLi) and ^{t}Butyl lithium (^{t}BuLi) solutions were titrated against *N*-pivalolyl-*o*-toluidine in solution in THF at ambient temperature immediately prior to use. All other reagents were used as supplied except where otherwise stated in the experimental text. Saturated aqueous solutions of inorganic salts are represented as (volume; sat.).

All experiments were performed in an inert atmosphere of argon or nitrogen under anhydrous conditions using oven dried apparatus cooled in a desiccator or flame

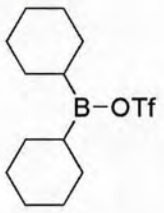
* Ammonium molybdate: dip prepared as follows: to water (950 cm^3) was added concentrated sulfuric acid (50 cm^3) and ceric sulfate (3 g). The mixture was stirred until all solid material had disappeared and a bright yellow solution remained.

dried under argon prior to use. Standard techniques for the handling of air-sensitive materials were employed.

Index of General Procedures

5.2 EXPERIMENTAL PROCEDURES FOR CHAPTER 2

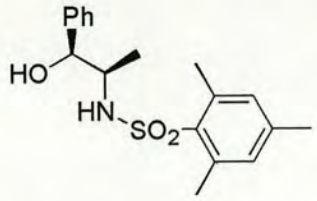
Synthesis of Dicyclohexylboron Triflate



An oven dried 250 ml round bottomed flask capped with septum was charged with cyclohexene (35.0 ml, 0.330 mol), and anhydrous Et_2O (100 ml), and was kept at 0 °C under nitrogen. Borane dimethyl sulfide complex (16.6 ml, 0.160 mol) was added dropwise during 30 min with stirring and the reaction mixture was stirred for 3 h at 0 °C, when the solid settled without stirring. The supernatant organic solution was removed by syringe and the residual solid was dried under vacuum to give dicyclohexylborane.

The solid was suspended in anhydrous hexane (100 ml) and triflic acid (25.0 g, 0.160 mol) was added dropwise *via* syringe during 30 min at 0 °C with constant stirring, during which time vigorous gas evolution occurred and the solid gradually disappeared. Stirring continued at room temperature for 1 h and the reaction was left for 2 h without stirring. Two layers appeared and the top layer of dicyclohexylboron triflate was transferred into a dry 250 ml storage flask. The solution was cooled to -20 °C overnight, the hexane layer was removed from the crystalline triflate and a stock solution of 1.0 M in hexane was prepared.

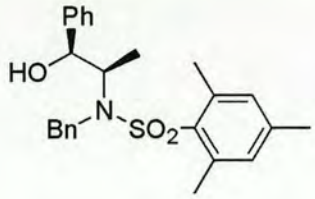
(1*S*,2*R*)-2-(*N*-mesitylenesulfonylamino)-1-phenylpropan-1-ol 182



To a stirred solution of (1*S*,2*R*) (+)-norephedrine (21.0 g, 0.140 mol) and Et_3N (20.0 ml, 0.140 mol) in CH_2Cl_2 (300 ml) was added mesitylenesulfonyl chloride (31.0 g, 0.140 mol) at 0 °C. The reaction was stirred at 0 °C for 2 h. The reaction mixture was diluted with Et_2O (400 ml) and was washed with H_2O (2 × 200 ml), HCl (2 × 200 ml, 1 N aq.), H_2O (2 × 200 ml), $NaHCO_3$ (2 × 200 ml, sat.) and NaCl (2 × 200 ml, sat.). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure to give sulfonamide **182** as a colourless solid which was recrystallised from CH_2Cl_2/hexane (44.0 g, 95 %); $\mathbf{R_f}$ (3:1-hexane/EtOAc) = 0.24; **mp** = 120-121 °C (CH_2Cl_2/hexane); lit.[54] 120.5 – 121.5 °C; $[\alpha]_D$ = 12.7 (c 1.10, $CHCl_3$); lit.[54] 12.8 (c 2.12, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3500 (OH), 3295 (NH), 1377 (SO_2N), 1155 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.41-7.25 (5H, m, Ar*H*), 7.01 (2H, s, Ar*H*), 4.85 (1H, d, *J* = 8.1 Hz, C(1)*H*Ph), 4.80 (1H, d, *J* = 3.2 Hz, C*H*OH), 3.57 (1H, dq, *J* = 6.8 and 3.2 Hz, C(2)*H*), 2.70 (6H, s, 2 x *o*-CH_3), 2.34 (3H, s, *p*-CH_3), 0.92 (3H, d, *J* = 6.8 Hz, C(2)HCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 142.1 (C), 140.2 (C), 138.7 (2 × C), 134.1 (C), 131.8 (2 × CH), 128.1 (2 × CH), 127.4 (CH), 125.8 (2 × CH), 75.5 (CH), 54.4 (CH), 22.8 (2 × CH_3), 20.7 (CH_3), 14.3 (CH_3); ***m/z*** (FAB, THIOG.) 334 ($[M+H]^+$, 56 %), 316 (87), 183 (64), 134 (75), 119 (100), 91 (80), 77 (67); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 334.1472, $C_{18}H_{24}NO_3S$ requires 334.1476.

^{1}H spectroscopic data in good agreement with the literature.[54]

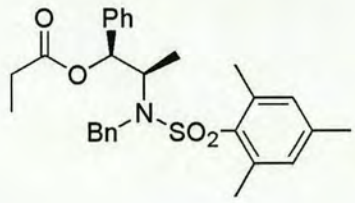
(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropan-1-ol 122



To a solution of sulfonamide **182** (10.2 g, 30.7 mmol) in DMF (140 ml) was added potassium *tert*-butoxide (3.46 g, 30.7 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide was added (3.66 ml, 30.7 mmol) and the reaction was stirred for a further 4.5 h at RT. NaCl (200 ml, sat.) was added and the mixture was extracted with CH_2Cl_2 (2 x 200 ml) and EtOAc (2 x 200 ml). The organics were combined, dried ($MgSO_4$), and the volatiles were removed under reduced pressure. Flash chromatography (CH_2Cl_2) gave benzyl protected sulfonamide **122** as a colourless solid (9.21 g, 71 %); $\mathbf{R_f}$ (17 % EtOAc in hexane) = 0.41; **mp** = 123 – 124 °C, lit.[54] 122 – 124; $[\alpha]_D$ = 6.2 (c 1.10, $CHCl_3$); lit.[54] 6.43 (c 2.05, $CHCl_3$); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.40 – 7.28 (8H, m, Ar*H*), 7.17 – 7.13 (2H, m, Ar*H*), 7.01 (2H, s, Ar*H*), 5.07 (1H, br s, C(1)*H*), 4.86 (1H, J = 16.0 Hz, CH_AH_BPh), 4.62 (1H, J = 16.0 Hz, CH_AH_BPh), 3.91 (1H, qd, J = 7.0 Hz & 2.0 Hz, C(2)*H*), 2.72 (6H, s, 2 x *o*-CH_3), 2.36 (3H, s, *p*-CH_3), 2.29 (1H, br d, J = 3.1 Hz, O*H*), 1.11 (3H, d, J = 7.0 Hz, C(2)HCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 142.51 (C), 142.64 (C), 140.31 (2 × C), 138.54 (C), 133.21 (C), 132.32 (2 × CH), 128.04 (2 × CH), 127.99 (2 × CH), 127.52 (2 × CH), 127.22 (CH), 127.13 (CH), 125.41 (2 × CH), 76.49 (CH), 59.66 (CH), 49.40 (CH_2), 22.83 (2 × CH_3) 20.72 (CH_3), 9.74 (CH_3); ***m/z*** (FAB, THIOG.) 424 ($[M+H]^+$, 33 %), 406 (48), 316 (73), 242 (59), 183 (38), 119 (82), 91 (100), 77 (47); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 424.1943, $C_{25}H_{30}NO_3S$ requires 424.1946.

^{1}H spectroscopic data in good agreement with the literature.[54]

(1'*S*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl propionate 123



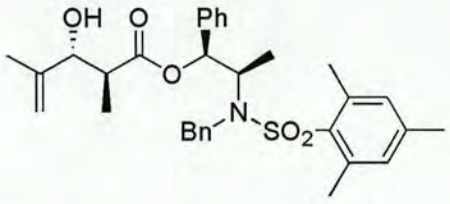
To a solution of alcohol **122** (9.00 g, 21.3 mmol) in CH_2Cl_2 (100 ml) was added pyridine (2.45 ml, 30.2 mmol) followed by propionyl chloride (2.45 ml, 28.1 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 (300 ml) and was washed with H_2O (200 ml), HCl (200 ml, 1N aq.), H_2O (200 ml), $NaHCO_3$ (200 ml, sat.) and NaCl (200 ml, sat.). The organics were dried ($MgSO_4$) and volatiles were removed under reduced pressure to give propionate **123** as a colourless solid, which was recrystallised from EtOAc / hexane (7.02 g, 69 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.56; **mp** = 146 – 148 °C, lit.[54] 146 – 148 °C; $\mathbf{[\alpha]_D}$ = -11.1 (c 2.00, $CHCl_3$); lit[54] -11.2 (c 2.18, $CHCl_3$); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.44 – 7.24 (8H, m, Ar*H*), 7.02 – 6.96 (4H, m, Ar*H*), 5.92 (1H, d, J = 4.1 Hz, C(1')*H*), 4.81 (1H, d, J = 16.6 Hz, CH_AH_BPh), 4.68 (1H, d, J = 16.6 Hz, CH_AH_BPh), 4.11 (1H, qd, J = 4.1 Hz & 7.0 Hz, C(2')*H*), 2.59 (6H, s, *o*-CH_3Ar), 2.35 (3H, s, *p*-CH_3Ar), 2.62 – 2.18 (2H, m, C(O)CH_2CH_3), 1.19 (3H, d, J = 7.0 Hz, C(2')HCH_3), 1.09 (3H, t, J = 7.4 Hz, C(O)CH_2CH_3).

^{1}H spectroscopic data in good agreement with the literature.[54]

General procedure A: *Anti* aldol reaction

To a solution of propionate **123** (148 mg, 0.309 mmol), in CH_2Cl_2 (4 ml) at –78 °C was added dicyclohexylboron triflate (697 µl, 1.0 M in hexane, 0.697 mmol), then Et_3N (129 µl, 0.927 mmol). The reaction mixture was stirred for 2 h, then aldehyde was added (3.71 mmol). The reaction mixture was stirred at –78 °C for 1 h and warmed to 0 °C for 1 h. The reaction was quenched by the addition of pH 7 buffer (4 ml), MeOH (10 ml) and the careful addition of H_2O_2 (1 ml). The reaction mixture was stirred vigorously for 14 h. H_2O (15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organics were washed with $NaHCO_3$ (30 ml, sat.) and NaCl (30 ml, sat.), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Kugelrohr distillation with mesitylene (3 ml) was used to remove residual cyclohexanol. Flash chromatography (10 % EtOAc in hexane) removed any impurities.

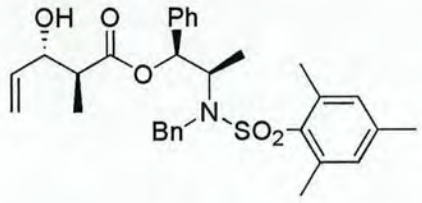
2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-2,4-dimethyl-3-hydroxypent-4-eneoate 183



General procedure A was followed with propionate **123** (148 mg, 0.309 mmol), in CH_2Cl_2 (4 ml) at –78 °C, to which was added dicyclohexylboron triflate (697 µl, 1.0 M in hexane, 0.697 mmol), then Et_3N (129 µl, 0.927 mmol). Methacrolein was added (320 µl, 3.71 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **183** as a colourless solid (132 mg, 79 %). Analysis of the crude 250 ^{1}H NMR showed this to be a >95:5 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.23; $[\alpha]_D$ = - 19.1 (c 1.32, $CHCl_3$), lit.(*ent*-**183**)[54] 19.7 (c 1.32, $CHCl_3$); **mp** = 97 – 98 °C, lit.[54] 97 – 98 °C; Major diastereomer: **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.41 – 7.11 (8H, m, Ar*H*), 6.82 – 6.75 (4H, m, Ar*H*), 5.75 (1H, d, J = 3.9 Hz, C(1')*H*), 4.86 (2H, br s, CCH_3=CH_2), 4.74 (1H, d, J = 16.6 Hz, CH_AH$_B$Ph), 4.52 (1H, d, J = 16.6 Hz, CH$_A$$H_B$Ph), 4.06 (1H, br d, J = 8.7 Hz, C*H*OH), 4.01 (1H, qd, J = 3.9 & 7.2 Hz, C(2')*H*), 2.51 (1H, qd, J = 8.7 Hz & 7.2 Hz, C*H*CH$_3$), 2.48 (6H, s, *o*-CH_3Ar), 2.22 (3H, s, *p*-CH_3Ar), 1.66 (3H, s, C(4)CH_3), 1.08 (3H, d, J = 7.0 Hz, C(2')HCH_3), 0.96 (3H, d, J = 7.2 Hz, CHCH_3); Minor diastereomer diagnostic peaks: 5.85 (1H, d, J = 3.9 Hz, C(1')*H*); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 174.99 (C), 144.33 (C), 142.96 (C), 140.67 (2 x C), 139.14 (C), 138.62 (C), 133.81 (C), 132.52 (2 x CH), 128.80 (2 x CH), 128.71 (2 x CH), 128.30 (CH), 127.99 (2 x CH), 127.52 (CH), 126.20 (2 x CH), 115.10 (CH_2), 78.70 (CH), 78.59 (CH), 57.18 (CH), 48.64 (CH_2), 43.51 (CH), 23.33 (2 x CH_3), 21.29 (CH_3), 16.99 (CH_3), 14.59 (CH_3), 13.73 (CH_3); ***m/z*** (FAB, NOBA) 572 ([M+Na]$^+$, 4 %), 550 ([M+H]$^+$, 4), 406 (96), 316 (95), 222 (52); **HRMS** (FAB, NOBA) [M+H]$^+$ found 550.2626, $C_{32}H_{40}NO_5S$ requires 550.2627.

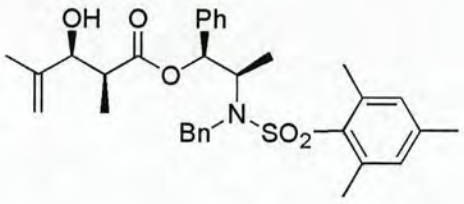
^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[54]

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-hydroxy-2-methyl pent-4-eneoate 180



General procedure A was followed with propionate **123** (148 mg, 0.309 mmol), in CH_2Cl_2 (4 ml) at –78 °C, to which was added dicyclohexylboron triflate (697 µl of a 1.0 M in hexane, 0.697 mmol), then Et_3N (129 µl, 0.927 mmol). Acrolein was added (247 µl, 3.71 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **180** as a colourless solid (137 mg, 84 %). Analysis of the crude 250 MHz ^1H NMR showed this to be a 98:2 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.23; ν_{max} (neat) / cm^{-1} 3684 (OH), 1736 (C=O); $[\alpha]_D$ = - 12.2 (c 2.0, $CHCl_3$); **mp** = 128 – 131 °C; Major diastereomer: **^1H NMR** δ (250 MHz, $CDCl_3$) 7.25– 7.09 (8H, m, Ar*H*), 6.81 – 6.76 (4H, m, Ar*H*), 5.76 (2H, d, *J* = 3.7 Hz, C(1')*H*), 5.72 (1H, ddd, *J* = 16.9, 10.4 & 6.7 Hz, C*H*=CH_2), 5.21 (1H, d, *J* = 16.9 Hz, CH=$CH_{CIS}H_{TRANS}$), 5.13 (1H, d, *J* = 10.4 Hz, CH=C$H_{CIS}H_{TRANS}$), 4.71 (1H, *J* = 16.6 Hz, CH_AH_BPh), 4.49 (1H, *J* = 16.6 Hz, CH_AH_BPh), 4.07 (1H, m, *CH*OH), 4.03 (1H, dq, *J* = 7.2 & 3.7 Hz, C(2')*H*), 2.54 - 2.49 (1H, m, *CH*CH_3), 2.42 (6H, s, *o*-CH_3Ar), 2.39 (3H, s, *p*-CH_3Ar), 1.12 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.03 (3H, d, *J* = 7.2 Hz, C(2')HCH_3); Minor diastereomer diagnostic peak: 5.70 - 5.63 (1H, m, C*H*=CH_2); **^{13}C NMR** *δ* (62.9 MHz, $CDCl_3$) 173.98 (C), 142.44 (C), 140.10 (2 x C), 138.01 (C), 138.43 (C), 137.73 (CH), 133.23 (C), 131.98 (2 x CH), 128.27 (2 x CH), 128.19 (2 x CH), 127.80 (CH), 127.45 (2 x CH), 126.99 (CH), 125.72 (2 x CH), 117.20 (CH_2), 78.18 (CH), 74.70 (CH), 56.62 (CH), 48.11 (CH_2), 45.22 (CH), 22.79 (2 x CH_3), 20.75 (CH_3), 13.78 (CH_3), 13.22 (CH_3); ***m/z*** (FAB, NOBA) 536 ($[M+H]^+$, 4 %), 406 (96), 316 (91), 222 (59); **HRMS** (FAB, NOBA) $[M+H]^+$ found 536.2467, $C_{31}H_{38}NO_5S$ requires 536.2471.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,4-dimethyl-3-hydroxypent-4-eneoate 185



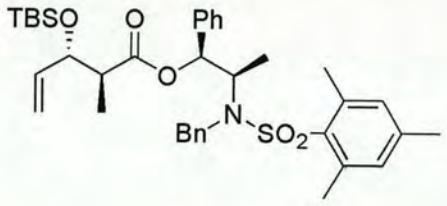
To a solution of propionate **123** (148 mg, 0.309 mmol), in CH_2Cl_2 (4 ml) at –78 °C was added $^nBu_2BOTf$ (309 µl, 1.0 M in CH_2Cl_2, 0.309 mmol), then DIPEA (161 µl, 0.927 mmol). The reaction mixture was stirred for 2 h, then methacrolein was added (306 µl, 3.71 mmol). The reaction mixture was stirred at –78 °C for 1 h, then warmed to 0 °C for 1 h. The reaction was quenched by the addition of pH 7 buffer (4 ml), MeOH (10 ml) and careful addition of H_2O_2 (1 ml). The reaction mixture was stirred vigorously for 14 h. H_2O (15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organics were washed with $NaHCO_3$ (30 ml, sat.) and NaCl (30 ml, sat.), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Flash chromatography (20 % EtOAc in hexane) gave aldol adduct **185** as a colourless oil (164 mg, 97 %). Analysis of the crude 250 MHz ^1H NMR showed this to be a >95:5 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.27, $[\alpha]_D$ = 6.9 (c 1.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3691 (OH), 1714 (C=O), 1364 (SO), 1154 (SO); Major diastereomer: **^1H NMR** δ (250 MHz, $CDCl_3$) 7.25 – 7.14 (8H, m, Ar*H*), 6.93 – 6.90 (2H, m, Ar*H*), 6.80 (2H, s, Ar*H*), 5.85 (1H, d, J = 3.7 Hz, C(1')*H*), 4.94 (1H, br s, CCH_3=C$H_{CIS}H_{TRANS}$), 4.82 (1H, br s, CCH_3=C$H_{CIS}H_{TRANS}$), 4.61 (1H, d, J = 16.6 Hz, CH_AH_BPh), 4.53 (1H, d, J = 16.6 Hz, CH_AH_BPh), 4.22 (1H, br s, C*H*OH), 4.00 (1H, dq J = 7.0 & 3.7 Hz, C(2')*H*), 2.48 (6H, s, *o*-CH_3Ar), 2.35 (1H, qd, J = 7.3 & 4.3 Hz, C*H*CH_3), 2.20 (3H, s, *p*-CH_3Ar) 1.61 (3H, s, C(4)CH_3), 1.24 (3H, d, J = 7.0 Hz, CHCH_3), 1.11 (3H, d, J = 7.0 Hz, CHCH_3); Minor diastereomer diagnostic peaks: 5.75 (1H, d, J = 3.9 Hz, (1')*H*); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$), 174.19 (C), 142.48 (C), 140.06 (2 x C), 138.36 (C), 138.11 (C), 133.10 (2 x C), 132.03 (2 x CH), 128.34 (4 x CH), 127.85 (CH), 126.98

(3 x CH), 125.76 (2 x CH), 111.69 (CH_2), 78.42 (CH), 73.39 (CH), 56.71 (CH), 48.06 (CH_2), 41.56 (CH), 22.90 (2 x CH_3), 20.70 (CH_3), 19.36 (CH_3), 12.47 (CH_3), 9.32 (CH_3); ***m/z*** (FAB, NOBA) 572 ($[M+Na]^+$, 3 %), 550 ($[M+H]^+$, 6), 406 (99), 316 (91), 222 (55); **HRMS** (FAB, NOBA) found 550.2625, $C_{32}H_{40}NO_5S$ requires 550.2627.

General procedure B: Silyl protection of aldol adducts

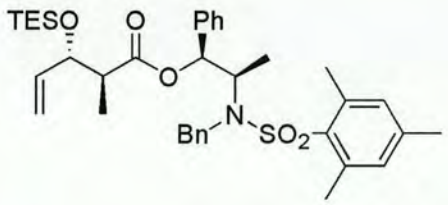
To a solution of aldol adduct (5.12 mmol) in CH_2Cl_2 (100 ml) at 0 °C was added dropwise 2,6-lutidine (893 µl, 7.68 mmol) followed after 5 min by silyl triflate (5.32 mmol) dropwise and the reaction mixture was stirred at 0 °C for 70 min. The reaction was diluted with CH_2Cl_2 (300 ml), washed with $NaHCO_3$ (500 ml, sat.), NaCl (500 ml, sat.), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude silyl-protected product. Flash chromatography (10 % EtOAc in hexane) removed trace impurities to give the silyl-protected compound.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-*tert*-butyldimethylsilyloxy-2-methylpent-4-eneoate 191



General procedure B was followed with aldol adduct **180** (4.01 g, 7.50 mmol) in CH_2Cl_2 (100 ml) at 0 °C, 2,6-lutidine (1.60 ml, 13.9 mmol) was added dropwise followed by TBSOTf (2.39 ml, 10.4 mmol). Flash chromatography (10 % EtOAc in hexane) gave protected aldol adduct **191** as a colourless oil (4.42 g, 95 %). $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.48; $[\alpha]_D$ = -2.3 (c 0.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1736 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.37 – 7.11 (8H, m, Ar*H*), 6.86 (2H, s, Ar*H*), 6.79 – 6.76 (2H, m, Ar*H*), 5.73 (1H, J = 5.2 Hz, C(1')*H*), 5.61 (1H, ddd, J = 13.7, 10.4 & 6.7 Hz, C*H*=CH_2), 5.12 (1H, d, J = 13.7 Hz, CH=$CH_{CIS}H_{TRANS}$), 5.11 (1H, d, J = 10.4 Hz, CH=C$H_{CIS}CH_{TRANS}$), 4.82 (1H, d, J = 16.4 Hz, CH_AH_BPh), 4.47 (1H, d, J = 16.4 Hz, CH_AH_BPh), 4.30 (1H, br t, J = 6.7 Hz, C*H*OTBS), 4.05 (1H, dq, J = 6.9 & 5.2 Hz, C(2')*H*), 2.49 (1H, dq ≡ qn, J = 6.7 Hz, C*H*CH_3), 2.46 (6H, s, *o*-CH_3Ar), 2.29 (3H, s, *p*-CH_3Ar), 1.16 (3H, d, J = 6.7 Hz, C*H*CH_3), 0.94 (3H, d, J = 6.9 Hz, C(2')HC*H*$_3$), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), - 0.12 (3H, s, SiC*H*$_3$), -0.05 (3H, s, SiC*H*$_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 172.52 (C), 142.31 (C), 140.21 (2 x C), 138.40 (C), 138.12 (C), 137.89 (CH), 133.00 (C), 131.99 (2 x CH), 128.24 (2 x CH), 128.08 (2 x CH), 127.85 (2 x CH), 127.69 (CH), 127.13 (CH), 126.19 (2 x CH), 116.51 (CH_2), 77.75 (CH), 74.90 (CH), 56.57 (CH), 48.04 (CH_2), 46.38 (CH), 25.73 (3 x CH_3), 22.79 (2 x CH_3), 20.75 (CH_3), 18.00 (C), 14.06 (CH_3), 12.07 (CH_3), - 4.58 (CH_3), - 4.98 (CH_3), ***m/z*** (FAB, NOBA) 648 ([M-H]$^+$, 4 %), 406 (92), 316 (80), 222 (60), 171 (62); **HRMS** (FAB, NOBA) [M-H]$^+$ found 648.3165, $C_{37}H_{50}NO_5SSi$ requires 648.3179.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-triethylsilyloxy-2-methylpent-4-eneoate 178

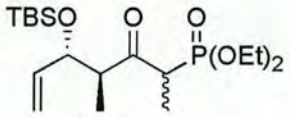


General procedure B was followed with aldol adduct **180** (2.74 g, 5.12 mmol) in CH_2Cl_2 (100 ml) at 0 °C, 2,6-lutidine (893 µl, 7.68 mmol) was added dropwise followed by TESOTf (1.22 ml, 5.32 mmol). Flash chromatography (EtOAc) gave protected aldol adduct **178** as a colourless oil (3.12 g, 94 %). $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.89; $[\alpha]_D$ = -1.42 (c 0.1, $CHCl_3$); ν_{max} (neat) /cm^{-1} 1735 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.42 - 7.06 (10H, m, Ar*H*), 6.87 (2H, s, Ar*H*), 5.97 (1H, d, *J* = 4.9 Hz, C(1')*H*), 5.88 (1H, ddd, *J* = 17.4, 10.1 & 7.0 Hz, C*H*=CH_2), 5.42 (1H, d, *J* = 17.4 Hz, CH=$CH_{CIS}H_{TRANS}$), 5.33 (1H, d, *J* = 10.1 Hz, CH=$CH_{CIS}H_{TRANS}$), 5.11 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.71 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.56 (1H, br t, *J* = 7.0 Hz, C*H*OTES), 4.26 (1H, dq, *J* = 7.0 & 4.9 Hz, C(2')*H*), 2.71 (1H, dq ≡ qn, *J* = 7.0 Hz, C*H*CH_3), 2.70 (6H, s, *o*-CH_3Ar), 2.56 (3H, s, *p*-CH_3Ar), 1.37 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.19 (3H, d, *J* = 7.0 Hz, C(2')HCH_3), 1.18 – 1.06 (9H, m, 3 x $SiCH_2CH_3$), 0.83 – 0.70 (6H, m, 3 x $SiCH_2CH_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 172.24 (C), 141.81 (C), 139.70 (2 x C), 138.07 (C), 137.68 (C), 137.54 (CH), 132.58 (C), 131.50 (2 x CH), 127.69 (2 x CH), 127.58 (2 x CH), 127.37 (2 x CH), 127.14 (2 x CH), 126.57 (CH), 125.55 (CH), 116.18 (CH_2), 77.20 (CH), 74.75 (CH), 56.11 (CH), 47.61 (CH_2), 46.10 (CH), 22.53 (2 x CH_3), 20.24 (CH_3), 13.42 (CH_3), 11.94 (CH_3), 6.17 (3 x CH_3), 5.76 (CH_2), 4.21 (2 x CH_2); ***m/z*** (FAB, NOBA) 650 ($[M+H]^+$, 3 %), 406 (76), 316 (66), 307 (52), 289 (40); **HRMS** (FAB, NOBA) found 650.3336, $C_{37}H_{52}NO_5SSi$ requires 650.3335.

General procedure C: Auxiliary displacement

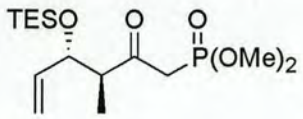
To a solution of phosphonate (1.32 mmol) in THF (15 ml) was added ^{n}BuLi (1.20 ml, 1.10 M solution in hexanes, 1.32 mmol) dropwise at –78 °C. After stirring for 60 min at –78 °C the light yellow solution was transferred *via* cannula into a solution of aldol adduct (0.300 mmol) in THF (15 ml) at –78 °C. The resulting solution was stirred for another 60 min before being carefully poured onto NH_4Cl (150 ml, sat.) The mixture was extracted with CH_2Cl_2 (3 x 100 ml), washed with NaCl (100 ml, sat.) and dried ($MgSO_4$). The organics were concentrated under reduced pressure to give a mixture of the crude β-ketophosphonate ester and auxiliary. Flash chromatography (gradient elution 20 – 30 % EtOAc in hexane) gave the recovered auxiliary as a colourless solid and the β-ketophosphonate ester as a colourless oil.

(2*SR*,4*S*,5*S*)-5-*tert*-Butyldimethylsilyloxy-2-diethoxyphosphoryl-4-methylhept-6-ene-3-one 192



General procedure C was followed with diethylethane phosphonate (212 μl, 1.32 mmol) and ^{n}BuLi (1.20 ml, 1.10 M solution in hexanes, 1.32 mmol) in THF (15 ml) which was added to a solution of aldol adduct **275** (200 mg, 0.300 mmol) in THF (15 ml). Flash chromatography (20 % EtOAc in hexane) gave the recovered auxiliary as a colourless solid (112 mg, 85 %) and flash chromatography (30 % EtOAc in hexane) afforded the β-ketophosphonate ester **192** as a 3:1 ratio of diastereomers and as a colourless oil (95 mg, 81 %). $\mathbf{R_f}$ (50 % EtOAc in hexane) = 0.25; ν_{max} (neat) / cm^{-1} 1715 (C=O), 1251 (P=O), 1027 (PO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 5.74 (1H, ddd, J = 17.5, 9.8 & 7.8 Hz, C*H*=CH_2), 5.22 (1H, d, J = 17.5 Hz, CH=C$H_{CIS}H_{TRANS}$), 5.16 (1H, d, J = 9.8 Hz, CH=$CH_{CIS}H_{TRANS}$), 4.15 (4H, m, 2 x OCH_2CH_3), 4.15 (1H, m, C*H*OTBS), 3.52 (0.8H, dq, J = 26.8 & 7.0 Hz, C*H*P(O)CH_2CH_3), 3.36 (0.2H, m, C*H*POCH_2CH_3), 3.22 (0.8H, dq, J = 9.0 Hz & 6.8 Hz, C*H*CH_3), 3.03 (0.2H, dq ≡ qn, J = 7.8 Hz, C*H*CH_3), 1.43 (6H, m, 2 x OCH_2CH_3), 1.43 (3H, m, POCHC*H*$_3$), 1.10 (0.6H, d, J = 6.8 Hz, CHC*H*$_3$), 1.00 (2.4H, J = 6.8 Hz, CHC*H*$_3$), 0.99 (1.8H, s, C(CH_3)$_3$), 0.89 (7.2H, s, C(CH_3)$_3$), 0.02 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 209.28 (C), 139.41 (CH), 116.88 (CH_2), 78.88 (CH), 62.36 (2 x CH_2), 51.97 (CH), 49.16 (CH, $^1J_{PC}$ = 124.1 Hz), 25.68 (3 x CH_3), 17.86 (C), 16.30 (2 x CH_3), 14.02 (2 x CH_3), -4.13 (CH_3), -4.87 (CH_3); m/z (FAB, NOBA) 393 ($[M+H]^+$, 17 %), 307 (57), 289 (46), 279 (22), 193 (40); **HRMS** (FAB, NOBA) $[M+H]^+$ found 393.2228, $C_{18}H_{38}O_5PSi$ requires 393.2226.

(3*S*,4*S*)-1-Dimethoxyphosphoryl-3-methyl--4-triethylsilyloxy-hex-5-ene-2-one 193

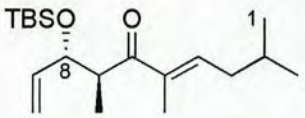


General procedure C was followed with dimethylmethane phosphonate (73.0 μl, 0.678 mmol) and ^{n}BuLi (424 μl, 1.6 M solution in hexanes, 0.678 mmol) in THF (15 ml) to which was added to a solution of aldol adduct **178** in THF (100 mg, 0.154 mmol). Flash chromatography (30 % EtOAc in hexane) afforded the β-ketophosphonate ester **193** as a colourless oil (12.0 mg, 23 %) and recovered auxiliary **122** (16.0 mg, 24 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.27; $[\alpha]_D$ = 16.7 (c 1.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} = 1711 (C=O), 1200 (P=O), 1017 (PO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 5.65 (1H, ddd, J = 16.8, 10.3 & 7.1 Hz, C*H*=CH_2), 5.13 (1H, d, J = 16.8 Hz, CH=$CH_{CIS}H_{TRANS}$), 5.10 (1H, d, J = 10.3 Hz, CH=$CH_{CIS}H_{TRANS}$), 4.01 (1H, br t, J = 8.7 Hz, C*H*OTES), 3.73 (3H, d, $^3J_{PH}$ = 9.1 Hz, POCH_3), 3.72 (3H, d, $^3J_{PH}$ = 9.1 Hz, POCH_3), 3.40 (1H, dd, J = 22.1 & 13.9 Hz, CH_AH_B), 3.06 (1H, dd, J = 21.7 & 13.9 Hz, CH_AH_B), 2.92 (1H, dq≡qn, J = 8.7 Hz, C*H*CH_3), 0.89 (3H, d, J = 7.1 Hz, CHCH_3), 0.92 – 0.88 (9H, m, $SiCH_2CH_3$), 0.51 – 0.45 (6H, m, $SiCH_2CH_3$); ***m/z*** (FAB, NOBA) 373 ($[M+Na]^+$, 13 %), 351 ($[M+H]^+$, 62) , 321 (65), 295 (70), 265 (80); **HRMS** (FAB, NOBA) $[M+H]^+$ found 351.1760, $C_{15}H_{32}O_5PSi$ requires 351.1757.

General Procedure D: Horner Wadsworth Emmons

To a solution of β-ketophosphonate ester (0.10 mmol) in THF (2 ml) was added $Ba(OH)_2 \cdot 8H_2O$ (40 mg, 0.12 mmol) and the mixture stirred for 30 min until it became cloudy. Aldehyde (0.15 mmol) in THF:H_2O (40:1, 5 ml) was added and the reaction stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with $NaHCO_3$ (30 ml, sat.), NaCl (30 ml, sat.) and dried ($MgSO_4$). Organics were removed under reduced pressure to give the crude enone product. Flash chromatography (10 % EtOAc in hexane) allowed separation from trace impurities.

(4*E*,7*S*,8*S*)-8-*tert*-Butyldimethylsilyloxy-2,5,7-trimethyldec-4,9-dien-6-one 196

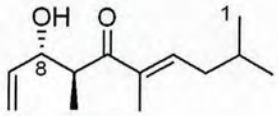


General procedure D was followed with β-ketophosphonate ester **192** (40 mg, 0.10 mmol), $Ba(OH)_2 \cdot 8H_2O$ (38 mg, 0.12 mmol) and isovaleraldehyde (16 μl, 0.15 mmol). Flash chromatography (10 % EtOAc in hexane) gave β-hydroxy enone **196** as a colourless oil (31 mg, 95 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.72; ν_{max} (neat) / cm^{-1} = 1666 (C=O); $[\alpha]_D$ = 9.3 (c 0.37, $CHCl_3$); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 6.75 (1H, t, J = 6.6 Hz, C(4)HCH$_2$), 5.79 (1H, ddd, J = 16.4, 10.2 & 7.8 Hz, CH=CH$_2$), 5.24 (1H, br d, J = 16.4 Hz, CH=CH$_{CIS}H_{TRANS}$), 5.18 (1H, br d, J = 10.2 Hz, CH=CH_{CIS}H$_{TRANS}$), 4.31 (1H, br t, J = 7.8 Hz, CHOTBS), 3.37 (1H, dq, J = 7.8 & 6.6 Hz, C(7)HCH$_3$), 2.19 (2H, br t, J = 6.6 Hz, C(3)H_2), 1.94 – 1.78 (1H, m, CH(CH$_3$)$_2$), 1.82 (3H, s, C(5)CH_3), 0.99 (3H, d, J = 6.6 Hz, CHCH_3), 0.95 (6H, d, J = 7.0 Hz, CH(CH_3)$_2$), 0.83 (9H, s, C(CH_3)$_3$), 0.02 (3H, s, SiCH_3), -0.01 (3H, s, SiCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 204.70 (C), 141.77 (CH), 139.50 (CH), 138.11 (C), 116.20 (CH_2), 77.22 (CH), 45.07 (CH), 38.16 (CH_2), 28.31 (CH), 25.55 (3 x CH_3), 22.45 (2 x CH_3), 17.83 (C), 14.41 (CH_3), 11.67 (CH_3), -4.35 (CH_3), -5.06 (CH_3); ***m/z*** (FAB, NOBA) 325 ($[M+H]^+$, 51 %), 307 (48), 267 (70), 171 (72), 155 (62); **HRMS** (FAB, NOBA) $[M+H]^+$ found 325.2562, $C_{19}H_{37}O_2Si$ requires 325.2563.

General Procedure E: Desilylation of β-hydroxy enones

To a solution of β-hydroxy enone (0.15 mmol) in MeCN (1 ml) at RT was added HF (100 μl, 40 % aq.) and the reaction mixture was stirred for 5 min. The reaction mixture was cautiously quenched with $NaHCO_3$ (solid) until effervescence had stopped. H_2O (20 ml) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 ml). The organics were dried (Na_2SO_4) and volatiles were removed under reduced pressure to give the crude β-hydroxy enone as a yellow oil. Purification by flash chromatography (20 % EtOAc in hexane) separated β-hydroxy enone from any trace impurities.

(4*E*,7*S*,8*S*)-8-Hydroxy-2,5,7-trimethyldec-4,9-dien-6-one 176



General Procedure E was followed with β-hydroxy enone **196** (50 mg, 0.15 mmol) in MeCN (1 ml) at RT and HF (100 μl, 40 % aqueous). Purification by flash chromatography (20 % EtOAc in hexane) afforded the β-hydroxy enone **176** as a colourless oil (31 mg, 95 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.32; ν_{max} (neat) / cm^{-1} = 3422 (OH), 1662 (C=O), 1607 (C=C); $[\alpha]_D$ = 1.08 (c 0.2, $CHCl_3$); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 6.62 (1H, br t, J = 7.4 Hz, C(4)*H*), 5.79 (1H, ddd, J = 17.1, 10.4 & 6.6 Hz, C*H*=CH_2), 5.22 (1H, dt, J = 17.1 & 1.6 Hz, $CH_{CIS}CH_{TRANS}$), 5.10 (1H, dt, J = 10.4 & 1.6 Hz, $CH_{CIS}CH_{TRANS}$), 4.19 (1H, br t, J = 6.6 Hz, C*H*OH), 3.28 (1H, dq ≡ qn, J = 6.6 Hz, C(7)*H*CH_3), 2.98 (1H, br s, O*H*), 2.09 (2H, t, J = 7.5 Hz, C(3)H_2), 1.76 – 1.68 (1H, m, C*H*$(CH_3)_2$), 1.69 (3H, s, C(5)CH_3), 1.07 (3H, d, J = 7.2 Hz, CHCH_3), 0.89 (6H, d, J = 6.5 Hz, CH$(CH_3)_2$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 206.41 (C), 143.03 (CH), 138.76 (CH), 137.41 (C), 116.08 (CH_2), 75.39 (CH), 43.87 (CH), 38.16 (CH_2), 28.31 (CH), 22.42 (2 x CH_3), 15.89 (CH_3), 11.37 (CH_3); ***m/z*** (FAB, THIOG.) 211 ($[M+H]^+$, 33 %), 210 (7), 209 (6), 195 (5), 193 (24); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 211.1702, $C_{13}H_{23}O_2$ requires 211.1698.

Samarium (II) Iodide

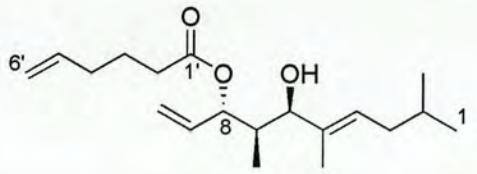
A suspension of iodine (259 mg, 1.00 mmol) and samarium (207 mg, 1.40 mmol, ~40 mesh) in THF (10 ml) was heated under reflux in the absence of light* for 1 h after which time a deep blue solution of SmI_2 (0.1 M in THF) had formed. The solution was then cooled to room temperature where it could be stored under Ar before oxidation to a yellow Sm (III) species occurred.

General procedure F: Evans-Tishchenko coupling

To a solution of benzaldehyde (100 μl) in THF (10 ml) at 0 °C was SmI_2 (5.00 ml, 0.1 M solution in THF) dropwise and the green solution was stirred for 30 min after which time the solution had become yellow (indicating formation of the Sm (III) pinacol adduct). To this solution was added aldehyde (2.0 mmol) and the solution was stirred at 0 °C for 30 min. A solution of β-hydroxy enone (1.0 mmol) in THF (10 ml) was added to the reaction mixture and was stirred for 30 min. The reaction mixture was added to a mixture potassium sodium tartrate tetrahydrate/K_2CO_3 (10:1 mixture (10:1 mixture, 10 % aq.; 50 ml) and CH_2Cl_2 (60 ml), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 60 ml). The combined organics were washed with NaCl (120 ml, sat.), dried ($MgSO_4$) and the volatiles removed under reduced pressure. Flash chromatography (10 % EtOAc in hexane) separated the ester from any trace impurities.

* This is not critical but SmI_2 is known to be light sensitive and should be treated accordingly.

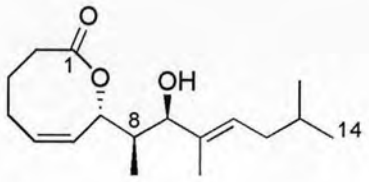
(4*E*,6*R*,7*R*,8*S*)-8-hex-5'enoyl-2,5,7-trimethyldec-4,9-en-6-ol 174



General procedure F was followed with benzaldehyde (100 μl) in THF (10 ml) and SmI_2 (3.00 ml, 0.1 M solution in THF), to which hexenal (186 mg, 1.90 mmol) followed by β-hydroxy enone **176** (200 mg, 0.952 mmol) in THF (10 ml) were added. Flash chromatography (10 % EtOAc in hexane) afforded ester **174** as a colourless oil (269 mg, 93 %). Analysis of the 360 MHz ^{1}H NMR showed this to be a 9:1 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.51; $[\alpha]_D$ = 0.67 (c 1.0, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3492 (OH), 1726 (C=O), 1643 (C=C); Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 5.81 - 5.61 (2H, m, 2 x C*H*=CH_2), 5.42 (1H, br t, *J* = 6.9 Hz, C(4)*H*), 5.22 – 5.14 (3H, m, C(10)H_2 & C(8)*H*), 4.98 – 4.90 (2H, m, C(6')H_2), 3.88 (1H, d, *J* = 4.8 Hz, C(6)*H*OH), 2.29 (2H, t, *J* = 7.0 Hz, C(2')H_2), 2.03 (2H, dt ≡ q, *J* = 7.0 Hz, C(4')H_2), 1.91 – 1.84 (3H, m, C(7)*H*CH_3 & C(3)H_2), 1.67 (2H, qn, *J* = 7.0 Hz, C(3')H_2), 1.65 – 1.52 (1H, m, C*H*$(CH_3)_2$), 1.52 (3H, s, C(5)CH_3), 0.83 (6H, d, *J* = 6.9 Hz, CH(CH_3)$_2$), 0.80 (3H, d, *J* = 6.9 Hz, C(7)HCH_3); Minor diastereomer diagnostic peak: 4.10 – 4.05; (1H, m, C(6)*H*OH) **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 178.39 (C), 137.97 (CH), 135.73 (C), 134.80 (CH), 125.75 (CH), 118.49 (CH_2), 115.82 (CH_2), 76.74 (CH), 76.11 (CH), 39.82 (CH), 37.16 (CH_2), 34.14 (CH_2), 33.40 (CH_2), 29.14 (CH), 24.44 (CH_2), 22.89 (2 x CH_3), 14.47 (CH_3), 9.72 (CH_3); ***m/z*** (FAB, THIOG.) 291 ([(M-H_2O)+H]$^+$, 26 %), 227 (12), 223 (8), 214 (23), 206 (8); **HRMS** (FAB, THIOG.) [(M-H_2O)+H]$^+$ found 291.2322 $C_{19}H_{31}O_2$ requires 291.2324.

(5*Z*,7*S*,8*R*,9*R*,10*E*,13*S*)-9-Hydroxy-(8,10,13-trimethyloct-10-enyl)-oxocene-1-one

3

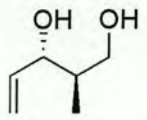


To a solution of ester **174** (100 mg, 0.325 mmol) in degassed CH_2Cl_2 (100 ml) was added Grubbs' 2 catalyst **159** (55 mg, 20 mol%) and the reaction mixture was heated under reflux for 24 h. After the reaction mixture was cooled to room temperature, DMSO (2.0 ml) was added and the reaction mixture was stirred for a further 24 h. Volatiles were removed under reduced pressure to give the crude lactone. Purification by flash chromatography (30 % EtOAc in hexane) afforded lactone (81 mg, 89 %). Analysis of the 360 MHz ^{1}H NMR showed this to be a 9:1 mixture of lactone **3** and cyclopentenol by product **204**; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.23; $[\alpha]_D$ = 0.30 (c 0.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3436 (OH), 1730 (C=O), 1655 (C=C); Major product: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 5.60 – 5.59 (1H, m, C(11)*H*CH_2), 5.58 (1H, s, C(7)*H*), 5.44 – 5.29 (2H, m, C(5)*H* & C(6)*H*), 4.30 (1H, br d, *J* = 6.6 Hz, C(9)*H*OH), 2.33 – 2.26 (2H, m, C(2)H_2), 2.19 – 2.11 (1H, m, C(8)*H*), 2.07 – 1.98 (2H, m, C(4)H_2), 1.79 (2H, qn, *J* = 7.2 Hz, CHC(12)H_2), 1.75 (3H, s, C(10)CH_3), 1.73 – 1.51 (3H, m, C(3)H_2 & C*H*$(CH_3)_2$), 1.04 (3H, d, *J* = 6.9 Hz, C(8)HCH_3), 1.02 (6H, d, *J* = 6.9 Hz, CH(CH_3)$_2$); Minor product diagnostic peaks: 5.85 (1H, m, C*H*=CH_2), 5.12 – 4.96 (2H, m, CH=CH_2); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 173.67 (C), 150.11 (C), 130.20 (CH), 129.93 (CH), 125.26 (CH), 84.03 (CH), 77.70 (CH), 46.36 (CH), 41.83 (CH_2), 33.63 (CH_2), 31.83 (CH_2), 28.49 (CH), 24.74 (CH_2), 22.24 (2 x CH_3), 13.57 (CH_3), 11.91 (CH_3); ***m/z*** (FAB, THIOG.) 281 ([M+H]$^+$, 3 %), (279 [M-H]$^+$, 10), 263 ([(M-H_2O)+H]$^+$, 37), 227 (13), 43 (100); **HRMS** (FAB, THIOG.) [M-H]$^+$ found 279.1961, $C_{17}H_{27}O_3$ requires 279.1960.

^{1}H NMR assignments were made on the basis of COSY and HSQC experiments.

5.3 EXPERIMENTAL PROCEDURES FOR CHAPTER 3

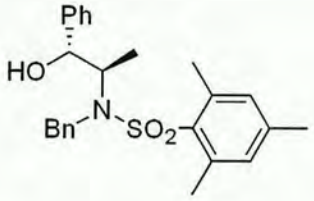
(2*R*,3*S*)-2-Methylpent-4-ene-1,3-diol 214



To a solution of aldol adduct **191** (200 mg, 0.308 mmol) in THF (100 ml) at 0 °C was added $LiAlH_4$ (13.0 mg, 0.332 mmol). The reaction mixture was warmed to RT and stirred for 2.5 h. The reaction mixture was cooled to 0 °C, $Na_2SO_4 \cdot 10H_2O$ was added slowly and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through celite and the volatiles removed under reduced pressure to give the crude diol. Flash chromatography (30 % EtOAc in hexane) afforded the 1,3-diol **214** as a colourless oil (32.0 mg, 90 %) and recovered auxiliary **4** (104 mg, 80 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.11; $[\alpha]_D$ = - 6.3 (c 0.4, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3432 (OH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 5.83 (1H, ddd, J = 17.0, 10.7 & 6.9 Hz, C*H*=CH_2), 5.22 (1H, d, J = 17.0 Hz, C*H*=C*H*$_{TRANS}$H$_{CIS}$), 5.14 (1H, d, J = 8.5 Hz, C*H*=CH$_{TRANS}$*H*$_{CIS}$), 3.96 (1H, br t, J = 6.9 Hz, C*H*OH), 3.71 (1H, dd, J = 8.5 & 3.5 Hz, C*H*$_A$H$_B$), 3.59 (1H, dd, J = 7.7 & 7.0 Hz, CH$_A$*H*$_B$), 3.28 (2H, br s, 2 x OH), 1.82 – 1.66 (1H, m, C*H*CH_3), 0.83 (3H, d, J = 7.1 Hz, CHC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 139.51 (CH), 116.07 (CH_2), 78.68 (CH), 67.14 (CH_2), 39.73 (CH), 13.34 (CH_3); ***m/z*** (FAB, NOBA) 117 ($[M+H]^+$, 43 %), 109 (63), 99 (63), 91 (95), 45 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 117.0919, $C_6H_{13}O_2$ requires 117.0916.

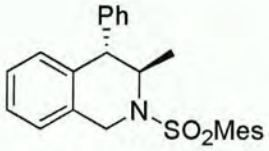
(1*R*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropan-1-ol 233

Attempted synthesis of (1'*R*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl thioacetate



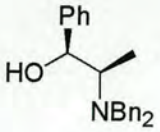
To a solution of alcohol **122** (200 mg, 0.470 mmol) in THF (10 ml) was added Et_3N (200 µl, 2.00 mmol) at 0 °C. Methanesulfonyl chloride (100 µl, 1.32 mmol) was added dropwise with vigorous stirring. A pale yellow precipitate resulted upon addition. The reaction mixture was stirred for 1 h and the solvent removed under reduced pressure. To a solution of residue in toluene (10 ml) was added Et_3N (180 µl, 1.32 mmol) in one portion. Cyclohexylamine (200 µl, 1.98 mmol) was added and the resulting suspension was heated under reflux for 12 h. NaOH (5 ml, 15 %) was added and the mixture was washed with NaCl (20 ml, sat.), dried (K_2CO_3) and concentrated under reduced pressure to give the crude amine product. Flash chromatography (CH_2Cl_2) gave alcohol **122** as a colourless solid (48 mg, 24 %) and alcohol **244** as a colourless oil (74 mg, 37 %); $\mathbf{R_f}$ (50 % EtOAc in hexane) = 0.25; ν_{max} (neat) / cm^{-1} 3514 (OH), 1235 (SO), 1146 (SO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.23 – 7.13 (8H, m, Ar*H*), 6.93 – 6.88 (2H, m, Ar*H*), 6.57 (2H, s, Ar*H*), 4.95 (1H, d, J = 4.7 Hz, C(1')*H*), 4.72 (1H, d, J = 16.6 Hz, CH_AH$_B$Ph), 4.65 (1H, d, J = 16.6 Hz, CH$_A$$H_B$Ph), 4.24 (1H, dq, J = 7.0 & 4.7 Hz, C(2')HCH$_3$), 2.42 (6H, s, *o*-CH_3Ar), 2.21 (3H, s, *p*-CH_3Ar), 1.80 (3H, d, J = 6.7 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 142.54 (C), 142.74 (C), 140.24 (2 × C), 138.34 (C), 133.18 (C), 132.75 (2 × CH), 127.99 (2 × CH), 127.96 (2 × CH), 127.43 (2 × CH), 127.18 (CH), 127.07 (CH), 125.26 (2 × CH), 76.21 (CH), 59.96 (CH), 49.38 (CH_2), 22.74 (2 × CH_3) 20.73 (CH_3), 9.71 (CH_3); ***m/z*** (FAB, NOBA) 424 ($[M+H]^+$, 33 %), 406 (48), 316 (73), 242 (59), 183 (38), 119 (82), 91 (100), 77 (47); **HRMS** (FAB, NOBA) $[M+H]^+$ found 424.1946, $C_{25}H_{30}NO_3S$ requires 424.1946.

(3*R*,4*S*)-2-(*N*-Mesitylenesulfonylamino)-3-methyl-4-phenyl-1,2,3,4-tetrahydro-isoquinoline 235



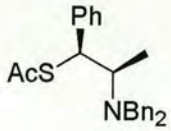
To a solution of alcohol **122** (200 mg, 0.470 mmol) in THF (10 ml) was added Et_3N (200 µl, 2.00 mmol) at 0 °C. Methanesulfonyl chloride (100 µl, 1.32 mmol) was added dropwise with vigorous stirring. A pale yellow precipitate resulted upon addition. The reaction mixture was stirred for 1 h and Et_3N (180 µl, 1.32 mmol) was added in one portion. LHMDS (177 µl, 0.94 mmol) was added and the resulting suspension was heated under reflux for 2 h and stirred at room temperature overnight. NaOH (15 ml, 15 %) was added and the mixture was washed with NaCl (20 ml, sat.), dried (K_2CO_3) and concentrated under reduced pressure to give the crude amine product. Flash chromatography (20 % EtOAc in hexane) gave isoquinoline **235** as a colourless solid (101 mg, 53 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.62; **mp** = 176-177 °C (hexane/CH_2Cl_2); $\mathbf{[\alpha]_D}$ = 1.75 (c 1.50, $CHCl_3$); $\mathbf{\nu_{max}}$ (neat)/cm^{-1} 1376 (SO_2), 1154 (SO_2); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.27 - 7.01 (8H, m, Ar*H*), 6.68 - 6.66 (3H, m, Ar*H*), 4.51 (2H, br s, CH_2N), 4.17 (1H, dq, J = 6.7 & 4.9 Hz, C*H*CH_3), 4.00 (1H, br s, C*H*Ph), 2.25 (6H, s, 2 x *o*-CH_3), 2.21 (3H, s, *p*-CH_3), 1.47 (3H, d, J = 6.7 Hz, CH_3CH); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 146.7 (C), 144.9 (C), 143.0 (2 × C), 136.0 (C), 135.0 (2 × C), 134.5 (2 × CH), 134.1 (CH), 130.9 (2 × CH), 130.7 (2 × CH), 130.0 (CH), 129.7 (CH), 129.2 (CH), 128.8 (CH), 57.5 (CH), 53.7 (CH), 44.5 (CH_2), 25.7 (2 × CH_3), 23.7 (CH_3), 20.5 (CH_3); ***m/z*** (FAB, THIOG.) 406 ($[M+H]^+$, 84 %), 222 (83), 119 (94), 91 (100); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 406.1840, $C_{25}H_{28}NO_2S$ requires 406.1840.

(1*S*,2*R*)-2-(*N*-dibenzyl)-1-phenylpropan-1-ol 221



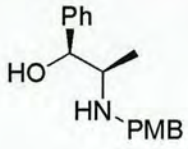
To a stirred solution of norephedrine (5.32 g, 35.2 mmol) in MeCN (70.0 ml) was added K_2CO_3 (13.8 g, 99.0 mmol) and benzyl bromide (8.37 ml, 70.0 mmol). The mixture was then stirred for 48 h at RT. EtOAc (50 ml) was added and the solution was washed with water (3 x 10 ml) and NaCl (2 x 20 ml, sat.). The organics were dried ($MgSO_4$) and removed under reduced pressure to give the crude alcohol as a yellow oil. Flash chromatography (10 % EtOAc in hexane) gave alcohol **221** as a colourless oil (10.3 g, 90 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.45; $[\alpha]_D$ = 5.03 (c 1.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3422 (OH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.48 - 7.33 (15H, m, Ar*H*), 4.88 (1H, d, J = 6.7 Hz, C*H*Ph), 3.94 (2H, d, J = 13.8 Hz, CH_AH$_B$Ph), 3.71 (2H, d, J = 13.8 Hz, CH_AH$_B$Ph), 3.24 (1H, dq ≡ qn, J = 6.7 Hz, C*H*CH$_3$), 2.88 (1H, brs, OH), 1.32 (3H, d, J = 6.7 Hz CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 142.53 (C), 139.27 (2 x C), 128.01 (4 x CH), 127.52 (4 x CH), 127.35 (2 x CH), 126.64 (CH), 126.18 (2 x CH), 126.09 (2 x CH), 75.32 (CH), 57.72 (CH), 53.87 (2 x CH_2), 8.43 (CH_3); ***m/z*** (FAB, NOBA) 332 ($[M+H]^+$, 25 %), 224 (96), 154 (38), 137 (21), 91 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 332.2015, $C_{23}H_{26}NO$ requires 332.2014.

(1*S*,2*R*)-2-(*N*-dibenzyl)-1-phenylpropyl thioacetate 237



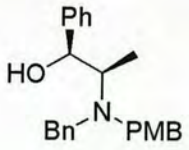
To a solution of alcohol **221** (3.13 g, 9.62 mmol) in Et_2O (40 ml) at 0 °C was added Et_3N (4.00 ml, 28.9 mmol), followed by methanesulfonyl chloride (900 µl, 11.5 mmol) and the reaction mixture was stirred for 1 h. Et_3N (2.70 ml, 19.3 mmol) was added and the reaction allowed to warm to RT before addition of thiolacetic acid (17.2 ml, 240 mmol). The reaction mixture, which had turned a bright yellow colour, was stirred for 48 h at RT. The reaction mixture was washed with H_2O (3 x 10 ml) and $NaHCO_3$ (5 x 10 ml, sat.). The resulting organic layer was dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thioacetate. Flash chromatography (2 % EtOAc in hexane) afforded the Thioacetate **237** as an orange/brown solid (2.40 g, 86 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.57; **mp** = 100 - 102 °C; ν_{max} (nujol) / cm^{-1} 1689 (C=O); $[\alpha]_D$ = 4.33 (c 1.29, $CHCl_3$); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.20 – 7.11 (8H, m, Ar*H*), 6.92 – 6.83 (7H, m, Ar*H*), 4.70 (1H, d, J = 10.7 Hz, C*H*Ph), 3.44 (2H, d, J = 13.6 Hz, CH_AH_BPh), 3.25 (2H, d, J = 13.6 Hz, CH_AH_BPh), 3.20 – 3.10 (1H, m, C*H*CH_3), 2.18 (3H, s, CH_3CO), 1.20 (3H, d, J = 6.5 Hz, $CHCH_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 194.21 (C), 141.43 (C), 139.24 (2 x C), 128.91 (4 x CH), 128.53 (2 x CH), 128.05 (2 x CH), 127.87 (4 x CH), 126.65 (CH), 126.58 (2 x CH), 55.72 (CH), 53.21 (2 x CH_2), 51.84 (CH), 30.34 (CH_2), 9.66 (CH_3); ***m/z*** (FAB, NOBA) 390 ($[M+H]^+$, 69 %), 307 (79), 224 (93), 154 (100), 91 (95); **HRMS** (FAB, NOBA) $[M+H]^+$ found 390.1894, $C_{25}H_{28}NOS$ requires 390.1892.

(1*S*,2*R*)-2-(*N*-4'-methoxybenzyl)-1-phenylpropan-1-ol 244



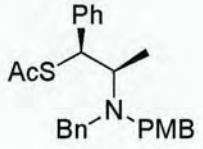
To a solution of norephedrine (453 mg, 3.00 mmol) in EtOH (3 ml) was added anisaldehyde (550 μl, 4.74 mmol) the reaction mixture was stirred at RT for 40 min. $NaBH_4$ (170 mg, 4.48 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was cooled to 0 °C and HCl (10 %) was cautiously added dropwise until the pH was 1 (litmus paper). Volatiles were removed under reduced pressure and a white solid (1.47 g) was retrieved. This was dissolved in H_2O (10.0 ml), filtered and basified with NaOH (1N aq.). The aqueous layer was extracted with CH_2Cl_2 and dried (Na_2SO_4). Flash chromatography (10 % EtOAc in hexane) afforded the alcohol **244** as a colourless oil (571 mg, 70 %); $\mathbf{R_f}$ (33 % EtOAc in hexane) = 0.13; ν_{max} (neat) / cm^{-1} 3335 (OH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.26 – 7.19 (5H, m, Ar*H*), 6.99 (2H, d, J = 11.6 Hz, Ar*H*), 6.81 (2H, d, J = 11.6 Hz, Ar*H*), 4.67 (1H, d, J = 3.9 Hz, C*H*Ph), 3.69 (5H, s, OCH_3 & CH_2Ph), 2.91 – 2.82 (1H, m, C*H*CH_3), 0.78 (3H, d, J = 6.5 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 158.63 (C), 141.22 (C), 131.91 (C), 129.24 (2 x CH), 127.90 (2 x CH), 126.80 (CH), 125.90 (2 x CH) 113.70 (2 x CH), 72.90 (CH), 57.40 (CH), 55.1(CH_3), 50.41(CH_2), 14.39 (CH_3); ***m/z*** (FAB NOBA) 272 ($[M+H]^+$, 87 %), 164 (60 %), 121 (100 %), 91 (76 %); **HRMS** (FAB, NOBA) $[M+H]^+$ found 272.1656, $C_{17}H_{22}NO_2$ requires 272.1651.

(1*S*,2*R*)-2-(*N*-benzyl-*N*-4'-methoxybenzyl)-1-phenylpropan-1-ol 222



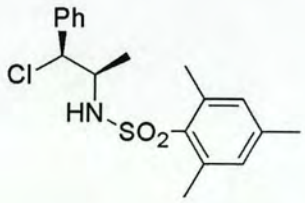
To a stirred solution of alcohol **244** (310 mg, 1.14 mmol) in MeCN (10 ml) was added K_2CO_3 (239 mg, 1.71 mmol), followed by benzyl bromide (200 µl, 1.71 mmol) and the resultant solution was stirred for at RT for 16 h. H_2O (10 ml) was added and the mixture was extracted with EtOAc (2 x 20 ml) was added and the organic layer extracted and dried ($NaSO_4$). Flash chromatography (10 % EtOAc in hexane) afforded the di-protected aminoalcohol **222** as a colourless gum. (265 mg, 96 %). $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.41; ν_{max} (neat) / cm^{-1} 3432 (OH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.39 – 7.32 (10H, m Ar*H*), 6.97 (2H, d, J = 11.6 Hz, Ar*H*), 6.79 (2H, d, J = 11.6 Hz, Ar*H*), 4.79 (1H, d, J = 6.4 Hz, C*H*Ph), 3.87 (3H, s, OCH_3), 3.60 (4H, m, CH_2Ph), 3.18 (1H, qn, J = 6.7 Hz C*H*CH_3), 2.75 (1H, br s, O*H*), 1.23 (3H, d, J = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 158.91 (C), 143.52 (C), 140.34 (C), 132.08 (C), 130.26 (2 x CH), 129.07 (2 x CH), 128.63 (2 x CH), 128.31 (2 x CH), 127.60 (2 x CH), 127.06 (2 x CH), 114.12 (2 x CH), 75.21 (CH), 58.63 (CH), 55.60 (CH_3), 54.68 (CH_2), 54.19 (CH_2), 9.52 (CH_3); ***m/z*** (FAB NOBA) 362 ($[M+H]^+$, 63 %), 360 (76), 254 (83), 121 (100), 91 (83); **HRMS** (FAB, NOBA) $[M+H]^+$ found 362.2120, $C_{24}H_{28}NO_2$ requires 362.2120.

(1*S*,2*R*)-2-(*N*-benzyl-*N*-4'-methoxy benzyl)-1-phenylpropyl thioacetate 245



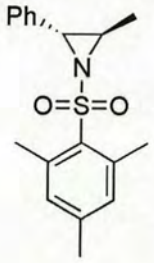
To a solution of the di-protected aminoalcohol **222** (235 mg, 0.650 mmol) in Et_2O (10 ml) was added Et_3N (270 µl, 1.95 mmol) at 0 °C, followed by methanesulfonyl chloride (80.0 µl, 0.980 mmol). The resultant solution was stirred for 30 min, during which time a white precipitate was observed. Et_3N (180 µl, 1.03 mmol.) was added to the reaction mixture followed by thiolacetic acid (1.16 ml, 16.3 mmol) and the reaction was stirred at RT for 16 h. To the reaction mixture was added H_2O (15 ml) and it was extracted with EtOAc (3 x 15 ml). The organics were combined, washed with $NaHCO_3$ (5 x 10 ml) and dried (Na_2SO_4). Flash chromatography (1.5 % EtOAc in hexane) afforded the thioacetate **245** as a brown gum (157 mg, 60 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.52; ν_{max} (neat) / cm^{-1} 1691 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.38 – 6.83 (14H, m, Ar*H*), 4.90 (1H, d, J = 10.8, C*H*Ph), 3.90 (3H, s, OCH_3), 3.89 - 3.38 (4H, m, 2 x CH_2Ph), 3.38 - 3.25 (1H, m, C*H*CH_3), 2.40 (3H, s, SCOCH_3), 1.38 (3H, d, J = 6.5 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 194.21 (C), 158.42 (C), 141.43 (C), 139.36 (C), 131.23 (C), 129.95 (2 x CH), 128.82 (2 x CH), 128.50 (2 x CH), 127.98 (2 x CH), 127 89 (2 x CH), 126.71 (CH), 126.62 (CH), 113.20 (2 x CH), 75.41 (CH), 55.46 (CH_3), 55.13 (CH), 52.98 (CH_2), 52.56 (CH_2), 30.30 (CH_3), 9.65 (CH_3); ***m/z*** (FAB, NOBA) 420 ($[M+H]^+$, 64 %), 419 (65), 418 (84), 254 (76), 121 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 420.2009, $C_{26}H_{30}NO_2S$ requires 420.1997.

(1*S*,2*R*)-2-(*N*-mesitylenesulfonylamino)-1-phenyl-1-chloropropane 248



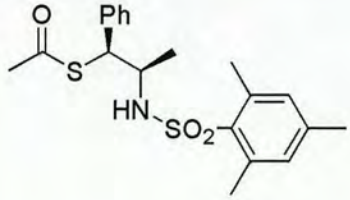
To sulfonamide **182** (42.0 g, 130 mmol) was added thionyl chloride (30.0 ml, 380 mmol) and the reaction was stirred at RT for 15 h. The excess thionyl chloride was removed under reduced pressure to give the crude chloride as a brown oil. Trituration using Et_2O/hexane gave chloride **248** as a colourless solid (43.1 g, 97 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.44; **mp** 137-138 °C; $[\alpha]_D$ = 27.2 (c 1.10, $CHCl_3$); ν_{max} (nujol)/cm^{-1} 3295 (NH), 1377 (SO), 1151 (SO), 723 (CCl); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.32 – 7.21 (5H, m, Ar*H*), 6.98 (2H, s, Ar*H*), 4.98 (1H, d, J = 3.5 Hz, N*H*), 4.94 (1H, d, J = 9.5 Hz, C(1)*H*), 3.77 – 3.64 (1H, m, C(2)*H*), 2.68 (6H, s, 2 x *o*-CH_3), 2.31 (3H, s, *p*-CH_3), 1.17 (3H, d, J = 4.4 Hz, C(2)HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 142.82 (C), 139.30 (2 x C), 137.89 (C), 134.85 (C), 132.49 (2 x CH), 128.91 (2 x CH), 128.72 (CH), 127.51 (2 x CH), 68.44 (CH), 55.46 (CH), 23.39 (2 x CH_3), 21.34 (CH_3), 15.50 (CH_3); ***m/z*** (FAB, THIOG.) 352 ($[M+H]^+$, 80 %), 316 (73), 183 (68), 119 (100), 91 (84), 77 (71); **HRMS** (FAB, THIOG.) found 352.1136, $C_{18}H_{23}ClNO_2S$ requires 352.1138.

(*2R,3R*)-2-Methyl-3-phenyl-1-(*N*-mesitylenesulfonylamino)-aziridine 225



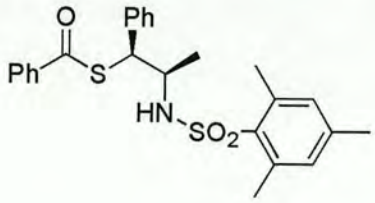
To a solution of chloride **248** (35.0 g, 100 mmol) in DMF (150 ml) was added potassium *tert*-butoxide (13.5 g, 120 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and the reaction was stirred for a further 18 h at RT. NaCl (300 ml, sat.) was added and the mixture was extracted with Et_2O (3 x 200 ml). The organics were combined and dried ($MgSO_4$) and volatiles were removed under reduced pressure to give a solid residue which was recrystallised from hexane to give aziridine **225** as a colourless solid (29.0 g, 92 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.65; **mp** 77-78 °C (hexane); ν_{max} (nujol) / cm^{-1} 1234 (SO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.18 (3H, m, Ar*H*), 7.05 – 7.01 (2H, m, Ar*H*), 6.82 (2H, s, Ar*H*), 3.89 (1H, d, J = 4.2 Hz, C(3)*H*), 2.77 (1H, dq, J = 6.2 & 4.2 Hz, C(2)*H*), 2.63 (6H, s, *o*-CH_3), 2.18 (3H, s, *p*-CH_3), 1.75 (3H, d, J = 6.2 Hz, C(2)HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 142.41 (C), 139.32 (2 x C), 136.04 (C), 134.93 (C), 131.59 (2 x CH), 128.37 (2 x CH), 127.81 (CH), 126.08 (2 x CH), 48.82 (CH), 48.64 (CH), 22.86 (2 x CH_3), 20.83 (CH_3), 14.10 (CH_3); ***m/z*** (FAB, THIOG.) 316 ($[M+H]^+$, 93 %), 314 (13), 183 (22), 167 (10), 165 (7); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 316.1372, $C_{18}H_{22}NO_2S$ requires 316.1371.

(1*S*,2*R*)-2-(*N*-Mesitylenesulfonylamino)-1-phenylpropyl thioacetate 255



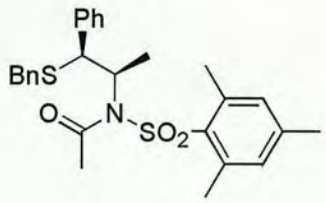
To a stirred solution of aziridine **225** (200 mg, 0.64 mmol) and thiolacetic acid (47 µl, 0.64 mmol) in MeCN (1.00 ml) was added tributylphosphine (17 µl, 60 µmol) followed by H_2O (1.00 ml), and the resulting mixture was stirred at RT for 18 h. The mixture was extracted with CH_2Cl_2 (3 x 25 ml), and dried (Na_2SO_4). The organics were removed under reduced pressure to give the crude thioacetate as a yellow oil. Purification by flash chromatography (10 % EtOAc in hexane) gave the thioacetate **255** as a colourless oil (207 mg, 93 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.38; $[\alpha]_D$ = 34 (c 0.5; $CHCl_3$); ν_{max} (neat) / cm^{-1} 1603 (C=O), 1266 (SO), 1158 (SO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.21 – 7.04 (5H, m, Ar*H*), 6.86 (2H, s, Ar*H*), 4.46 (1H, d, J = 9.5 Hz, C*H*Ph), 4.44 (1H, d, J = 5.5 Hz, N*H*), 3.67 – 3.56 (1H, m, C*H*CH_3), 2.54 (6H, s, 2 x *o*-C*H*$_3$), 2.28 (3H, s, COC*H*$_3$), 2.12 (3H, s, *p*-C*H*$_3$), 1.04 (3H, d, J = 6.7 Hz, CHC*H*$_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 193.83 (C), 142.05 (C), 139.09 (2 x C), 136.99 (C), 133.84 (C), 131.80 (2 x CH), 128.52 (2 x CH), 128.35 (2 x CH), 127.78 (CH), 53.40 (CH), 53.11 (CH), 30.25 (CH_3), 22.91 (2 x CH_3), 20.78 (CH_3), 19.64 (CH_3); ***m/z*** (FAB, NOBA) 392 ($[M+H]^+$, 57 %), 316 (32), 228 (29), 226 (62), 119 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 392.1353, $C_{20}H_{26}NO_3S_2$ requires 392.1354.

(1'*S*,2'*R*)-2'-(*N*-mesitylenesulfonylamino)-1'-phenylpropyl thiobenzoate 256



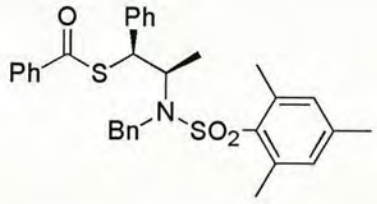
To a stirred solution of aziridine **225** (25.0 g, 80.0 mmol) and thiolbenzoic acid (12.3 g, 80.00 mmol) in MeCN (60 ml) was added tributylphosphine (2.10 ml, 8.00 mmol) followed by H_2O (50 ml) under argon, and the resulting mixture was stirred at RT for 18 h. The mixture was extracted with CH_2Cl_2 (3 x 50 ml), and dried (Na_2SO_4). The organics were removed under reduced pressure to give the crude thiobenzoate. Purification by flash chromatography (10 % EtOAc in hexane) gave the thiobenzoate **256** as a colourless solid (33.4 g, 93 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.42; **mp** 101-102 °C; $[\alpha]_D$ = 113 (c 1.10, $CHCl_3$); ν_{max} (nujol) / cm^{-1} 3288 (NH), 1659 (C=O), 1234 (SO), 1159 (SO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.81 – 7.45 (5H, m, Ar*H*), 7.29 - 7.23 (5H, m, Ar*H*), 6.83 (2H, s, Ar*H*), 4.71 (1H, d, J = 4.3 Hz, N*H*), 4.56 (1H, d. J = 9.6 Hz, C(1')*H*), 3.88 - 3.79 (1H, m, C*H*CH_3), 2.62 (6H, s, 2 x *o*-CH_3), 2.15 (3H, s, *p*-CH_3), 1.23 (3H, d, J = 6.7 Hz, C(2')HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 190.97 (C), 143.26 (2 x C), 138.02 (C), 137.41 (2 x C), 134.84 (C), 134.61 (CH), 132.97 (2 x CH), 129.74 (2 x CH), 129.56 (4 x CH), 129.06 (CH), 128.30 (CH), 54.51 (2 x CH), 24.18 (2 x CH_3), 21.92 (CH_3), 21.31 (CH_3); ***m/z*** (FAB, THIOG.) 455 ($[M+H]^+$, 47 %), 316 (29), 255 (38), 226 (31), 183 (29); **HRMS** (FAB, THIOG.) found 455.1511, $C_{25}H_{28}NO_3S_2$ requires 455.1511.

(1*S*,2*R*)-2-(*N*-Actetamido-*N*-mesitylenesulfonylamino)-1-phenyl-(*S*-benzyl)-1-propane thiol 259



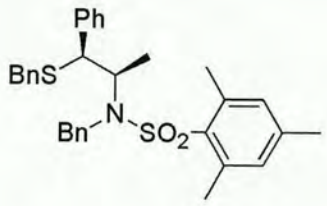
To a solution of thioacetate **255** (150 mg, 0.384 mmol) in DMF (10 ml) was added potassium *tert*-butoxide (43 mg, 0.384 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide was added (46.0 µl, 0.384 mmol) and the reaction was stirred for a further 4.5 h at RT. NaCl (20 ml, sat.) was added and the mixture was extracted with CH_2Cl_2 (2 x 20 ml) and EtOAc (2 x 20 ml). The organics were combined, dried ($MgSO_4$), and the volatiles were removed under reduced pressure. Flash chromatography (20 % EtOAc in hexane) gave amide **259** as a colourless oil (129 mg, 70 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.71; $\mathbf{[\alpha]_D}$ = 5.3 (c 1.3, $CHCl_3$); $\mathbf{\nu_{max}}$ (neat) / cm^{-1} 1732 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.30 – 7.13 (10 H, m, Ar*H*), 7.00 (2H, s, Ar*H*), 4.52 (1H, d, J = 10.2 Hz, C(1)*H*), 3.78 (1H, dq, J = 10.2 & 6.6 Hz, C(2)*H*), 3.47 (1H, d, J = 13.0 Hz, CH_AH_BPh), 3.42 (1H, d, J = 13.0 Hz, CH_AH_BPh), 2.48 (6H, s, 2 x *o*-CH_3), 2.41 (3H, s, CH_3), 2.22 (3H, s, *p*-CH_3), 1.33 (3H, d, J = 6.6 Hz, C(2)HCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 171.54 (C), 143.76 (C), 140.38 (2 x C), 138.82 (C), 137.33 (C), 132.61 (2 x CH), 131.83 (C), 129.05 (2 x CH), 128.65 (2 x CH), 128.15 (2 x CH), 127.79 (2 x CH), 127.10 (CH), 126.80 (CH), 59.25 (CH), 52.97 (CH), 36.05 (CH_2), 25.84 (CH_3), 22.51 (2 x CH_3), 26.52 (CH_3), 16.96 (CH_3); ***m/z*** (FAB, NOBA) 482 ($[M+H]^+$, 42 %), 406 (16), 360 (8), 358 (94), 91 (100) **HRMS** (FAB, NOBA) found 482.1823, $C_{27}H_{32}NO_3S_2$ requires 482.1824.

(1'*S*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl thiobenzoate 260



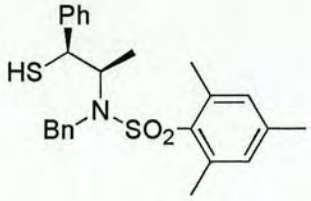
To a solution of thiobenzoate **256** (20.0 g, 43.3 mmol) in DMF (250 ml) was added potassium NaH (1.97 g, 46.6 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide was added (5.66 ml, 46.6 mmol) and the reaction was stirred for a further 18 h at RT. NaCl (200 ml, sat.) was added and the mixture was extracted with Et_2O (2 x 200 ml). The organics were combined and dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thiobenzoate. Flash chromatography (10 % EtOAc in hexane) gave benzyl protected sulfonamide **260** as a colourless solid (23.7 g, 100 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.47; **mp** = 60-61 °C; $[\alpha]_D$ = 71.3 (c 1.15, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1665 (C=O), 1234 (SO), 1155 (SO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.91 – 7.89 (2H, m, Ar*H*), 7.48 – 7.38 (5H, m, Ar*H*), 7.32 – 7.16 (4H, m, Ar*H*), 7.05 (2H, t, J = 6.3 Hz, Ar*H*), 6.86 (2H, s, Ar*H*), 6.79 (2H, d, J = 7.9 Hz, Ar*H*), 5.05 (1H, d, J = 9.0 Hz, C(1')*H*), 4.85 (1H, d, J = 16.2 Hz, CH_AH$_B$Ph), 4.53 (1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), 4.33 – 4.25 (1H, m, C(2')*H*), 2.24 (6H, s, 2 x *o*-CH_3), 2.32 (3H, s, *p*-CH_3), 1.36 (3H, d, J = 6.9 Hz, C(2')HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 190.24 (C), 143.41 (C), 141.66 (2 x C), 141.12 (C), 139.57 (C), 137.46 (C), 134.87 (C), 134.64 (CH), 133.86 (CH), 133.22 (2 x CH), 129.79 (2 x CH), 129.65 (2 x CH), 129.50 (2 x CH), 129.46 (2 x CH), 128.75 (2 x CH), 128.38 (2 x CH), 128.29 (CH), 57.77 (CH), 52.50 (CH), 48.53 (CH_2), 23.97 (2 x CH_3), 21.99 (CH_3), 18.61 (CH_3); ***m/z*** (FAB, NOBA) 544 ([M+H]$^+$, 11 %), 406 (16), 362 (10), 317 (20), 316 (51); **HRMS** (FAB, NOBA) found 544.1980, $C_{32}H_{34}NO_3S_2$ requires 544.1980.

(1*S*,2*R*)-1-(*S*-Benzyl)-2-(*N*-benzyl-*N*-mesitylenesulfonylamino)-1-phenyl-1-propane thiol 261



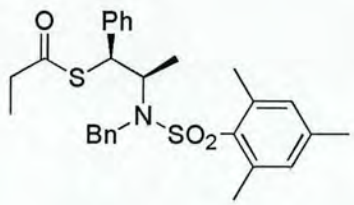
To a solution of thiobenzoate **256** (200 mg, 0.441 mmol) in DMF (10 ml) was added potassium *tert*-butoxide (50 mg, 0.441 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide was added (110 μl, 0.441 mmol) and the reaction was stirred for a further 4.5 h at RT. NaCl (20 ml, sat.) was added and the mixture was extracted with CH_2Cl_2 (2 x 20 ml) and EtOAc (2 x 20 ml). The organics were combined, dried ($MgSO_4$), and the volatiles were removed under reduced pressure to give a mixture of thiobenzoate **260** and amide **261**. Flash chromatography (20 % EtOAc in hexane) gave thiobenzoate **260** as a colourless solid (140 mg, 60 %) and dibenzylated thiol **261** as a colourless oil (69 mg, 30 %); (20 % EtOAc in hexane) = 0.58; $[\alpha]_D$ = 8.2 (c 2.0, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1206 (SO), 116 (SO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.56 – 7.34 (11H, m, Ar*H*), 7.08 (2H, s, Ar*H*), 6.97 (2H, d, J = 9.1 Hz, Ar*H*), 5.06 (1H, d, J = 16.4 Hz, CH_AH_BPh), 4.79 (1H, d, J = 16.4 Hz, CH_AH_BPh), 3.99 (1H, d, J = 4.5 Hz, C*H*Ph), 3.96 – 3.86 (1 H, m, C*H*CH_3), 3.73 (1H, d, J = 13.0 Hz, CH_XH_YPh), 3.65 (1H, d, J = 13.0 Hz, CH_XH_YPh), 2.86 (6H, s, 2 x *o*-CH_3), 2.46 (3H, s, *p*-CH_3), 1.33 (3H, d, J = 6.7 Hz, $CHCH_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 141.88 (C), 139.92 (C), 138.83 (2 x C), 138.38 (C), 137.15 (C), 134.25 (C), 131.79 (CH), 128.70 (CH), 128.43 (3 x CH), 128.30 (5 x CH), 127.42 (3 x CH), 126.99 (2 x CH), 56.09 (CH), 53.63 (CH), 47.88 (CH_2), 35.50 (CH_2), 22.81 (2 x CH_3), 20.77 (CH_3), 17.55 (CH_3); ***m/z*** (FAB, NOBA) 530 ($[M+H]^+$, 31 %), 528 (29), 406 (55), 346 (31), 178 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 530.2189, $C_{32}H_{36}NO_2S_2$ requires 530.2189.

(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropane-1-thiol 4



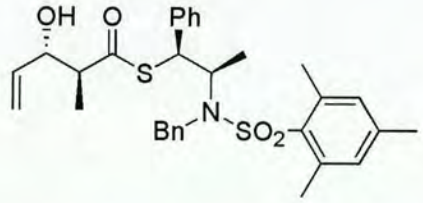
To a solution of thiobenzoate **260** (15.0 g, 28.0 mmol) in THF (100 ml) at 0 °C was added $LiAlH_4$ (1.20 g, 30.3 mmol). The reaction mixture was warmed to RT and stirred for 2.5 h. The reaction mixture was cooled to 0 °C, $Na_2SO_4 \bullet 10H_2O$ was added slowly and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through celite and the organics removed under reduced pressure to give the thiol **4** as a colourless solid (11.5 g, 95 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.60; **mp** = 57-58 °C; $[\alpha]_D$ = -10.9 (c 1.10, $CHCl_3$); ν_{max} (nujol) / cm^{-1} 2558 (SH), 1376 (SO), 1152 (SO); ^{1}**H NMR** δ (360 MHz, $CDCl_3$) 7.32 – 7.07 (8H, m, Ar*H*), 6.86 – 6.81 (4H, m, Ar*H*), 4.73 (1H, d, J = 16.4 Hz, CH_AH$_B$Ph), 4.48 (1H, d, J = 16.4 Hz, CH$_A$$H_B$Ph), 4.18 – 4.13 (2H, m, C(2)HCH$_3$ & C(1)*H*), 2.34 (6H, s, 2 x *o*-CH_3), 2.29 (3H, s, *p*-CH_3), 1.76 (1H, d, J = 5.4 Hz, S*H*), 1.31 (3H, d, J = 6.6 Hz, C(2)HCH_3); ^{13}**C NMR** δ (90.5 MHz, $CDCl_3$) 145.28 (C), 145.02 (C), 143.41 (2 x C), 141.39 (C), 135.81 (C), 135.03 (2 x CH), 131.41 (2 x CH), 131.33 (2 x CH), 131.24 (2 x CH), 130.32 (CH), 130.09 (CH), 129.94 (2 x CH), 61.02 (CH), 51.27 (CH), 50.73 (CH_2), 25.81 (2 x CH_3), 23.82 (CH_3), 20.00 (CH_3); ***m/z*** (FAB, NOBA) 440 ($[M+H]^+$, 15 %), 406 (13), 317 (30), 316 (81), 91 (100) **HRMS** (FAB, NOBA) $[M+H]^+$ found 440.1725, $C_{25}H_{30}NO_2S_2$ requires 440.1718.

(1'*S*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl thiopropionate 239



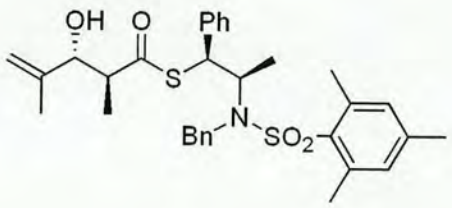
To a solution of thiol **4** (9.00 g, 20.5 mmol) in CH_2Cl_2 (100 ml) was added pyridine (2.18 ml, 24.9 mmol) followed by propionyl chloride (2.19 ml, 26.6 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 (300 ml) and was washed with H_2O (200 ml), HCl (200 ml, 1N aq.), H_2O (200 ml), $NaHCO_3$ (200 ml, sat.) and NaCl (200 ml, sat.). The organics were dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thioester as a colourless oil. Purification by flash chromatography (20 % EtOAc in hexane) gave the propionate thioester **239** as a colourless solid (9.39 g, 93 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.56; **mp** = 60-61 °C; $[\alpha]_D$ = 71.3 (c 1.15, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1697 (C=O), 1375 (SO), 1147 (SO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.45 (2H, d, J = 6.2 Hz, Ar*H*), 7.31 – 7.26 (3H, m, Ar*H*), 7.15 (1H, d, J = 7.1 Hz, Ar*H*), 7.03 (2H, t, J = 6.5 Hz, Ar*H*), 6.84 (2H, s, Ar*H*), 6.70 (2H, d, J = 7.1 Hz, Ar*H*), 4.81 (1H, d, J = 16.2 Hz, CH_AH_BPh), 4.80 (1H, d, J = 9.3 Hz, C(1')*H*), 4.47 (1H, d, J = 16.2 Hz, CH_AH_BPh), 4.16 (1H, dq, J = 9.3 & 6.8 Hz, C(2')*H*), 2.47 (2H, q, J = 7.4 Hz, CH_2CH_3), 2.45 (3H, s, *p*-CH_3), 2.44 (6H, s, 2 x *o*-CH_3), 1.28 (3H, d, J = 6.8 Hz, C(2')HCH_3), 1.11 (3H, t, J = 7.4 Hz, CH_2CH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 197.34 (C), 142.20 (C), 140.47 (2 x C), 140.00 (C), 138.39 (C), 132.62 (C), 128.62 (2 x CH), 128.33 (2 x CH), 128.27 (2 x CH), 127.40 (3 x CH), 127.28 (2 x CH), 127.25 (CH), 56.41 (CH), 50.94 (CH), 47.25 (CH_2), 37.09 (CH_2), 22.77 (2 x CH_3), 20.81 (CH_3), 17.34 (CH_3), 9.29 (CH_3); ***m/z*** (FAB, NOBA) 496 ($[M+H]^+$, 8 %), 406 (24), 316 (54), 207 (53), 91 (100); **HRMS** (FAB, NOBA) found 496.1985, $C_{28}H_{34}NO_3S_2$ requires 496.1980.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2-methyl-3-hydroxythiopent-4-eneoate 268



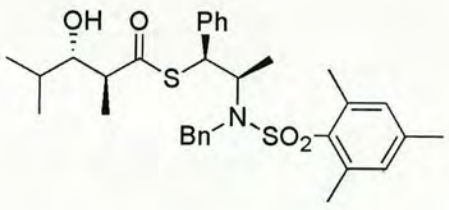
General procedure A was followed with thiopropionate **239** (200 mg, 0.404 mmol), in CH_2Cl_2 (5 ml) at –78 °C, to which was added dicyclohexylboron triflate (909 µl, 1.0 M in hexane, 0.909 mmol), then Et_3N (168 µl, 1.21 mmol). Acrolein was added (334 µl, 5.01 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **268** as a colourless oil (201 mg, 92 %). Analysis of the crude 360 MHz ^{1}H NMR showed this to be a 93:7 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.36; $[\alpha]_D$ = - 10.1 (c 0.8, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3476 (OH), 1642 (C=O), 1602 (C=C); Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.42, (2H, d, J = 8.3 Hz, *o*-Ar*H*), 7.29 - 7.26 (3H, m, Ar*H*), 7.16 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 7.04 (2H, t, J = 7.9 Hz, *m*-Ar*H*), 6.84 (2H, s, *m* - Ar*H*), 6.67 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 5.79 (1H, ddd, J = 17.0, 10.5 & 6.5 Hz, C*H*=CH_2), 5.28 (1H, d, J = 17.0 Hz, CH=CH_{TRANS}H$_{CIS}$), 5.19 (1H, d, J = 10.5 Hz, CH=CH$_{TRANS}H_{CIS}$), 4.82 (1H, d, J = 8.9 Hz, C(1')*H*), 4.78 (1H, d, J = 16.3 Hz, CH_AH$_B$Ph), 4.49 (1H, d, J = 16.3 Hz, CH_AH$_B$Ph), 4.22 - 4.17 (2H, m, C*H*OH & C(2')*H*), 1.96 (1H, dq ≡ qn, J = 7.1 Hz, C*H*CH$_3$), 2.31 (9H, s, 3 x CH_3), 1.29 (3H, d, J = 6.9 Hz, C(2')HCH_3), 1.06 (3H, d, J = 7.1 Hz, CHCH_3); Minor diastereomer diagnostic peaks: 5.69 (1H, ddd, J = 17.0, 10.5 & 6.6 Hz, C*H*=CH_2), 4.48 (1H, d, J = 16.2 Hz, CH$_A$*H*$_B$Ph), 4.31 (1H, t, J = 6.6 Hz, C*H*OH), 1.17 (3H, d, J = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.18 (C), 142.20 (C), 140.40 (2 x C), 140.39 (C), 138.31 (C), 137.61 (CH), 132.62 (C), 131.97 (2 x CH), 128.53 (2 x CH), 128.30 (2 x CH), 128.26 (2 x CH), 127.41 (2 x CH), 127.21 (CH), 117.07 (CH), 116.99 (CH_2), 75.04 (CH), 56.48 (CH), 53.42 (CH), 51.01 (CH), 47.29 (CH_2), 21.05 (2 x CH_3), 17.12 (CH_3), 14.37 (CH_3), 14.32 (CH_3); ***m/z*** (FAB, NOBA) 552 ([M+H]$^+$, 4 %), 406 (15), 317 (13), 316 (60) 91 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 552.2246, $C_{31}H_{38}NO_4S_2$ requires 552.2242.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-2,4-dimethyl-3-hydroxythiopent-4-eneoate 266



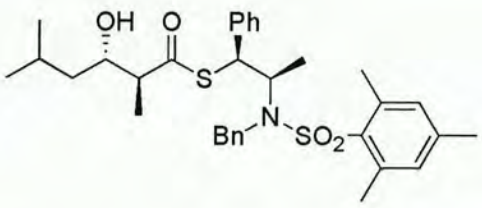
General procedure A was followed with thiopropionate **239** (200 mg, 0.404 mmol), in CH_2Cl_2 (5 ml) at –78 °C, to which was added dicyclohexylboron triflate (909 µl, 1.0 M in hexane, 0.909 mmol), then Et_3N (168 µl, 1.21 mmol). Methacrolein was added (412 µl, 5.01 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **266** as a colourless oil (209 mg, 90 %). Analysis of the crude 360 MHz ^1H NMR showed this to be a 92:8 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.32; $[\alpha]_D$ = -18.7 (c 1.3, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3466 (OH), 1679 (C=O); Major diastereomer: **^1H NMR** δ (360 MHz, $CDCl_3$) 7.43, (2H, d, J = 7.7 Hz, *o*-Ar*H*), 7.32 - 7.23 (3H, m, Ar*H*), 7.16 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 7.04 (2H, t, J = 7.4 Hz, *m*-Ar*H*), 6.82 (2H, s, Ar*H*), 6.67 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 4.94 (1H, br s, $CCH_3{=}CH_2$), 4.91 (1H, br s, $CCH_3{=}CH_2$), 4.82 (1H, d, J = 9.0 Hz, C*H*Ph), 4.79 (1H, d, J = 16.3 Hz, CH_AH_BPh), 4.49 (1H, d, J = 16.3 Hz, CH_AH_BPh), 4.22 - 4.12 (2H, m, C*H*OH & C(2')*H*CH_3), 2.78 (1H, dq ≡ qn, J = 7.1, C*H*CH_3), 2.31 (9H, s, 3 x CH_3), 1.71 (3H, s, C(4)CH_3), 1.30 (3H, d, J = 6.8 Hz, C(2')CH_3), 1.09 (3H, d, J = 7.1 Hz, CHCH_3); Minor diastereomer diagnostic peaks: 4.46 (1H, d, J = 16.3 Hz, CH_AH_BPh), 1.04 (3H, d, J = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.47 (C), 143.93 (C), 142.17 (C), 140.42 (2 x C), 139.58 (C), 138.36 (C), 132.67 (C), 131.97 (2 x CH), 128.58 (2 x CH), 128.30 (2 x CH), 128.19 (2 x CH), 127.36 (2 x CH), 127.21 (CH), 127.07 (CH), 114.23 (CH_2), 78.19 (CH), 56.72 (CH), 51.21 (CH), 51.01 (CH), 47.14 (CH_2), 22.74 (2 x CH_3), 20.76 (CH_3), 17.04 (CH_3), 16.66 (CH_3), 14.71 (CH_3); ***m/z*** (FAB, NOBA) 566 ($[M+H]^+$, 25 %), 407 (21), 406 (53), 318 (29) 91 (100); **HRMS** (FAB, NOBA) found 566.2397, $C_{32}H_{40}NO_4S_2$ requires 566.2399.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,5-dimethyl-3-hydroxy-thiopentanoate 267



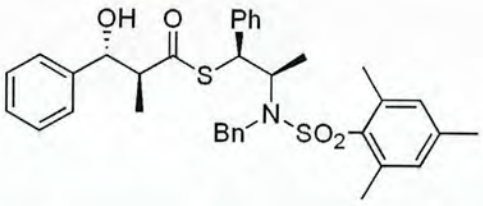
General procedure A was followed with thiopropionate **239** (148 mg, 0.309 mmol), in CH_2Cl_2 (4 ml) at –78 °C, to which was added dicyclohexylboron triflate (697 µl, 1.0 M in hexane, 0.309 mmol), then Et_3N (161 µl, 0.927 mmol). Isobutyraldehyde was added (320 µl, 3.71 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **267** as a colourless oil (132 mg, 85 %). Analysis of the crude 360 MHz ^{1}H NMR showed this to be a 97:3 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.34; $[\alpha]_D$ = - 16.2 (c 0.4, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3540 (OH), 1695 (C=O), Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.43, (2H, d, J = 7.7 Hz, *o*-Ar*H*), 7.32 - 7.23 (3H, m, Ar*H*), 7.16 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 7.04 (2H, t, J = 7.4 Hz, *m*-Ar*H*), 6.85 (2H, s, Ar*H*), 6.67 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 4.82 (1H, d, J = 9.1 Hz, C(1')*H*), 4.79 (1H, d, J = 16.2 Hz, CH_AH$_B$Ph), 4.48 (1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), 4.21 - 4.15 (1H, m, C(2')*H*CH$_3$), 3.40 (1H, dd, J = 6.8 & 5.4 Hz, C*H*OH), 2.75 (1H, dq ≡ qn, J = 6.8 Hz, C*H*CH$_3$), 2.31 (9H, s, 3 x CH_3), 1.67 (1H, dspt ≡ oct, J = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.30 (3H, d, J = 6.8 Hz, C(2')CH_3), 1.09 (3H, d, J = 7.1 Hz, CHCH_3), 0.98 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 0.90 (3H, d, J = 6.8 Hz, CH(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.94 (C), 142.73 (C), 140.11 (2 x C), 138.80 (2 x C), 133.20 (C), 132.51 (2 x CH), 129.09 (2 x CH), 128.84 (CH), 128.75 (2 x CH), 127.90 (2 x CH), 127.78 (2 x CH), 127.62 (CH), 78.98 (CH), 57.14 (CH), 51.68 (CH), 51.51 (CH), 47.74 (CH_2), 31.28 (CH), 23.28 (CH_3), 21.29 (CH_3), 20.16 (CH_3), 19.14 (CH_3), 17.65 (CH_3), 16.55 (CH_3), 15.63 (CH_3); ***m/z*** (FAB, NOBA) 568 ([M+H]$^+$, 16 %), 406 (24), 317 (45), 316 (83) 91 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 568.2550, $C_{32}H_{42}NO_4S_2$ requires 568.2555.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,5-dimethyl-3-hydroxy-thiohexanoate 268



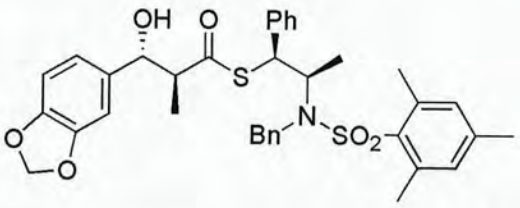
General procedure A was followed with thiopropionate **239** (200 mg, 0.404 mmol), in CH_2Cl_2 (5 ml) at –78 °C, to which was added dicyclohexylboron triflate (909 µl, 1.0 M in hexane, 0.909 mmol), then Et_3N (168 µl, 1.21 mmol). Isovaleraldehyde was added (536 µl, 5.01 mmol). Flash chromatography (10 % EtOAc in hexane) gave the aldol adduct **268** as a colourless foam (132 mg, 94 %). Analysis of the crude 360 MHz ^{1}H NMR showed this to be a 94:6 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.35; $[\alpha]_D$ = - 12.3 (c 0.2, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3532 (OH), 1688 (C=O); Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.42 (2H, d, J = 8.1 Hz, Ar*H*), 7.32 – 7.25 (3H, m, Ar*H*), 7.14 (1H, t, J = 7.8 Hz, Ar*H*), 7.03 (2H, t, J = 7.4 Hz, *m*-Ar*H*), 6.83 (2H, s, Ar*H*), 6.68 (2H, d, J = 7.1 Hz, Ar*H*), 4.78 (1H, d, J = 9.0 Hz, C(1')*H*), 4.76 (1H, d, J = 16.2 Hz, CH_AH$_B$Ph), 4.46 (1H, d, J = 16.2 Hz, CH_AH$_B$Ph), 4.19 (1H, dq, J = 9.0 & 6.8 Hz, C(2')*H*CH$_3$), 3.76 – 3.70 (1H, m, C*H*OH), 2.62 (1H, dq ≡ qn, J = 6.9 Hz, C*H*CH$_3$), 2.30 (9H, s, 3 x CH_3), 2.11 (1H, br d, J = 7.2 Hz, CHO*H*), 1.80 – 1.69 (1H, m, C*H*(CH$_3$)$_2$), 1.39 – 1.11 (2H, m, CH_2CH), 1.12 (3H, d, J = 6.8 Hz, C(2')HCH_3), 1.09 (3H, d, J = 6.8 Hz, CHCH_3), 0.89 (3H, d, J = 6.7 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 0.86 (3H, d, J = 6.5 Hz, CH(CH$_3$)$_A$(CH_3)$_B$); Minor diastereomer diagnostic peak: 0.78 (1H, d, J = 6.6 Hz, CH(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.39 (C), 142.56 (C), 140.76 (2 x C), 139.90 (C), 138.54 (C), 132.93 (2 x CH), 132.32 (C), 128.88 (2 x CH), 128.66 (CH), 128.56 (2 x CH), 127.72 (2 x CH), 127.61 (2 x CH), 127.45 (CH), 72.18 (CH), 56.88 (CH), 54.58 (CH), 51.36 (CH), 47.58 (CH_2), 44.14 (CH_2), 24.59 (CH), 23.79 (CH_3), 23.09 (2 x CH_3), 21.73 (CH_3), 21.11 (CH_3), 17.53 (CH_3), 14.92 (CH_3); ***m/z*** (FAB, NOBA) 582 ([M+H]$^+$, 20 %), 406 (32), 318 (29), 316 (84) 57 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 582.2713, $C_{33}H_{44}NO_4S_2$ requires 582.2712.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methyl-3-phenylthiopropionate 269



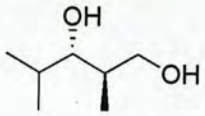
General procedure A was followed with thiopropionate **239** (200 mg, 0.404 mmol), in CH_2Cl_2 (5 ml) at –78 °C, to which was added dicyclohexylboron triflate (909 µl, 1.0 M in hexane, 0.909 mmol), then Et_3N (168 µl, 0.927 mmol). Benzaldehyde was added (508 µl, 5.01 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **269** as a colourless solid (206 mg, 85 %). Analysis of the crude 360 MHz ^{1}H NMR showed this to be a 91:9 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.41; **mp** = 56 – 59 °C; $[\alpha]_D$ = -15.3 (c 1.1, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3466 (OH), 1689 (C=O); Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.43 (2H, d, J = 7.7 Hz, *o*-Ar*H*), 7.33 - 7.24 (8H, m, Ar*H*), 7.16 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 7.05 (2H, t, J = 7.4 Hz, *m*-Ar*H*), 6.84 (2H, s, Ar*H*), 6.66 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 4.83 (1H, d, J = 8.8 Hz, C(1')*H*), 4.78 (1H, d, J = 16.4 Hz, CH_AH$_B$Ph), 4.77 (1H, d, J = 8.0 Hz, C*H*OH), 4.45 (1H, d, J = 16.4 Hz, CH$_A$*H*$_B$Ph), 4.20 - 4.12 (1H, m, C*H*CH$_3$), 2.92 (1H, dq ≡ qn, J = 7.1 Hz, C*H*CH$_3$), 2.31 (9H, s, 3 x C*H*$_3$), 1.21 (3H, d, J = 6.8 Hz, C(2')C*H*$_3$), 1.09 (3H, d, J = 7.1 Hz, CHC*H*$_3$); Minor diastereomer diagnostic peaks: 4.48 (1H, d, J = 16.4 Hz, CH$_A$*H*$_B$Ph), 0.96 (3H, d, J = 7.1 Hz, CHC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.71 (C), 142.24 (C), 141.35 (C), 140.48 (2 x C), 139.60 (C), 138.39 (C), 132.69 (C), 132.01 (2 x CH), 128.60 (2 x CH), 128.45 (2 x CH), 128.35 (2 x CH), 128.25 (CH), 128.06 (2 x CH), 127.40 (2 x CH), 127.26 (CH), 127.13 (CH), 126.29 (2 x CH), 76.52 (CH), 56.74 (CH), 55.35 (CH), 51.13 (CH), 47.19 (CH_2), 22.80 (2 x CH_3), 20.82 (CH_3), 17.00 (CH_3), 15.03 (CH_3); ***m/z*** (FAB, NOBA) 602 ([M+H]$^+$, 6 %), 406 (18), 317 (14), 316 (66) 91 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 602.2393, $C_{35}H_{40}NO_4S_2$ requires 602.2399.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methyl-3-piperonylthiopropionate 270



General procedure A was followed with thiopropionate **239** (200 mg, 0.404 mmol), in CH_2Cl_2 (5 ml) at –78 °C, to which was added dicyclohexylboron triflate (909 µl, 1.0 M in hexane, 0.909 mmol), then Et_3N (168 µl, 1.21 mmol). Piperonal was added (752 mg, 5.01 mmol). Flash chromatography (10 % EtOAc in hexane) gave aldol adduct **270** as a colourless foam (132 mg, 90 %). Analysis of the crude 360 MHz ^1H NMR showed this to be a 97:3 mixture of diastereomers; $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.36; $[\alpha]_D$ = - 21.1 (c 2.0, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3467 (OH), 1687 (C=O); Major diastereomer: **^1H NMR** δ (360 MHz, $CDCl_3$) 7.42 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 7.30 - 7.27 (3H, m, Ar*H*), 7.16 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 7.04 (2H, t, J = 7.9 Hz, *m*-Ar*H*), 6.85 (2H, s, *m* - Ar*H*), 6.82 (1H, s, Ar*H*), 6.73 (2H, s, Ar*H*), 6.67 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 5.96 – 5.93 (2H, m, OCH_2O), 4.82 (1H, d, J = 8.7 Hz, C(1')*H*), 4.79 (1H, d, J = 16.3 Hz, CH_AH$_B$Ph), 4.68 (1H, br d, J = 8.3 Hz, C*H*OH), 4.47 (1H, d, J = 16.3 Hz, CH$_A$$H_B$Ph), 4.21 - 4.15 (1H, m, C(2')*H*CH$_3$), 2.85 (1H, dq ≡ qn, J = 7.2 Hz, C(2)*H*CH$_3$), 2.32 (6H, s, *o*-CH$_3$), 2.31 (3H, s, *p*-CH$_3$), 1.25 (3H, d, J = 6.8 Hz, C(2')HCH_3), 0.89 (3H, d, J = 7.1 Hz, CHCH_3); Minor diastereomer diagnostic peak: 0.94 (3H, d, J = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.53 (C), 147.72 (C), 147.21 (C), 142.22 (C), 140.41 (2 x C), 139.59 (C), 138.39 (C), 132.66 (2 x C), 131.98 (2 x CH), 128.60 (2 x CH), 128.54 (2 x CH), 128.49 (CH), 128.20 (CH), 127.36 (2 x CH), 127.21 (CH), 127.08 (CH), 120.00 (CH), 107.91 (CH), 101.96 (CH), 100.95 (CH_2), 76.90 (CH), 56.74 (CH), 55.42 (CH), 51.11 (CH), 47.13 (CH_2), 22.75 (2 x CH_3), 20.78 (CH_3), 16.93 (CH_3), 14.91 (CH_3); ***m/z*** (FAB, NOBA) 646 ($[M+H]^+$, 11 %), 644 ($[M-H]^+$, 28 %), 406 (99), 316 (100), 307 (57); **HRMS** (FAB, NOBA) $[M-H]^+$ found 644.2134, $C_{36}H_{38}NO_6S_2$ requires 644.2140.

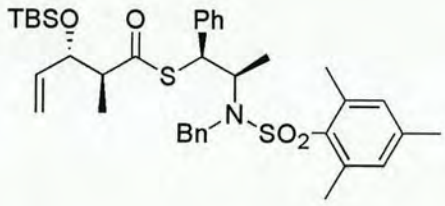
(2*R*,3*S*)-2,4-Dimethylpentane-1,3-diol 271



To a solution of aldol adduct **267** (200 mg, 0.352 mmol) in THF (10 ml) was added a solution of $NaBH_4$ (40.0 mg, 1.06 mmol) in THF (10 ml + 10 drops H_2O) and the reaction stirred at RT for 1 h. HCl (0.5 M aq.) was added carefully until no effervescence occurred and the solution extracted with CH_2Cl_2 (3 x 30 ml). The organics were dried and the volatiles removed under reduced pressure. Flash chromatography (30 % EtOAc in hexane) afforded the 1,3 diol **271** as a colourless oil (45.0 mg, 99 %) and recovered auxiliary **4** (130 mg, 84 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.14; $[\alpha]_D$ = - 18.4 (c 0.4, $CHCl_3$), lit.[128] -18.6 (c 2.0, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3450 (OH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 3.86 (1H, dd, J = 10.7 & 3.7 Hz, CH_AH_B), 3.74 (1H, dd, J = 10.7 & 7.6 Hz, CH_AH_B), 3.44 (1H, dd, J = 7.6 & 3.7 Hz, C*H*OH), 3.01 – 2.97 (2H, m, 2 x O*H*), 2.00 – 1.86 (1H, m, $CH(CH_3)_2$), 1.07 (3H, d, J = 6.9 Hz, $CHCH_3$), 1.00 (3H, d, J = 7.2 Hz, $CH(CH_3)_A(CH_3)_B$), 0.97 (3H, d, J = 7.2 Hz, $CH(CH_3)_A(CH_3)_B$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 82.40 (CH), 68.47 (CH_2), 37.50 (CH), 30.68 (CH), 20.19 (CH_3), 15.38 (CH_3), 14.23 (CH_3); ***m/z*** (FAB, NOBA) 133 ($[M+H]^+$, 9 %), 109 (58), 105 (17), 91 (100), 77 (17); **HRMS** (FAB, NOBA) $[M+H]^+$ found 133.1229, $C_7H_{17}O_2$ requires 133.1229.

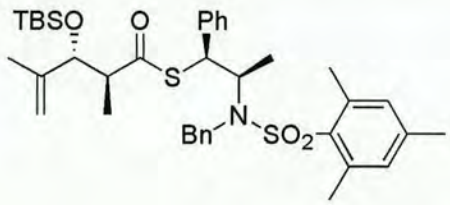
^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[128]

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-*tert*-butyldimethylsilyloxy-2-methylthiopent-4-eneoate 275



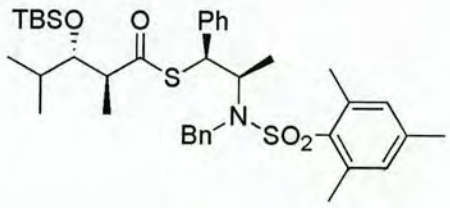
General procedure B was followed with aldol adduct **265** (200 mg, 0.360 mmol) in CH_2Cl_2 (10 ml) at 0 °C, 2,6-lutidine (62.0 µl, 0.540 mmol) was added dropwise followed by TBSOTf (92.0 µl, 0.400 mmol). Flash chromatography (10 % EtOAc in hexane) gave the protected aldol adduct **275** as a colourless oil (225 mg, 95 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.76; $[\alpha]_D$ = -5.7 (c 0.6, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1686 (C=O), 1601 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.42, (2H, d, J = 8.2 Hz, *o*-Ar*H*), 7.32 - 7.27 (3H, m, Ar*H*), 7.16 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 6.99 (2H, t, J = 7.9 Hz, *m*-Ar*H*), 6.84 (2H, s, Ar*H*), 6.66 (2H, d, J = 8.0 Hz, *o*-Ar*H*), 5.58 (1H, ddd, J = 17.3, 10.1 & 7.1 Hz, C*H*=CH_2), 5.14 (1H, d, J = 17.3 Hz, CH=C$H_{TRANS}H_{CIS}$), 5.10 (1H, d, J = 10.1 Hz, CH=C$H_{TRANS}H_{CIS}$), 4.84 (1H, d, J = 16.3 Hz, CH_AH_BPh), 4.79 (1H, d, J = 6.1 Hz, C(1')*H*Ph), 4.43 (1H, d, J = 16.3 Hz, CH_AH_BPh), 4.26 (1H, t, J = 7.4 Hz, C*H*OTBS), 4.17 (1H, dq, J = 6.8 & 6.1 Hz, C(2')*H*CH_3), 2.63 (1H, dq ≡ qn, J = 7.4 Hz, C*H*CH_3), 2.32 (3H, s, *p*-CH_3), 2.27 (6H, s, *o*-CH_3), 1.30 (3H, d, J = 6.8 Hz, C(2')HCH_3), 0.90 (3H, d, J = 7.1 Hz, CHCH_3), 0.83 (9H, s, C(CH_3)$_3$), -0.01 (6H, s, 2 x SiCH_3) ; **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 198.57 (C), 142.12 (C), 140.51 (2 x C), 140.10 (C), 138.36 (C), 137.96 (CH), 132.62 (C), 132.01 (2 x CH), 128.78 (2 x CH), 128.31 (2 x CH), 128.18 (3 x CH), 127.37 (2 x CH), 126.90 (CH), 116.78 (CH_2), 75.51 (CH), 56.09 (CH), 55.04 (CH), 50.91 (CH), 47.21 (CH_2), 25.66 (3 x CH_3), 22.74 (2 x CH_3), 20.80 (CH_3), 18.14 (CH_3), 17.93 (C), 13.22 (CH_3), -4.37 (2 x CH_3); ***m/z*** (FAB, NOBA) 666 ([M+H]$^+$, 3 %), 407 (15), 406 (49), 404 (25), 91 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 666.3107, $C_{37}H_{52}NO_4S_2Si$ requires 666.3105.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-*tert*-butyldimethylsilyloxy-2,4-dimethylthiopent-4-eneoate 276



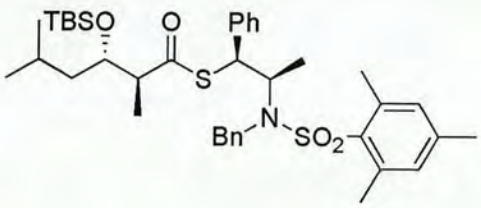
General procedure B was followed with aldol adduct **266** (200 mg, 0.350 mmol) in CH_2Cl_2 (10 ml) at 0 °C, 2,6-lutidine (62.0 µl, 0.540 mmol) was added dropwise followed by TBSOTf (92.0 µl, 0.400 mmol). Flash chromatography (10 % EtOAc in hexane) gave the protected aldol adduct **276** as a colourless oil (226 mg, 94 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.76; $[\alpha]_D$ = -9.1 (c 0.7, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1685 (C=O), 1602 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.54, (2H, d, J = 7.7 Hz, *o*-Ar*H*), 7.39 - 7.34 (3H, m, Ar*H*), 7.19 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 6.91 (2H, s, Ar*H*), 6.82 (2H, s, Ar*H*), 6.71 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 4.91 (1H, br s, CCH_3=CH_XH$_Y$), 4.91 (1H, br s, CCH_3=C$H_X$$H_Y$), 4.90 (1H, d, J = 15.9 Hz, CH_AH$_B$Ph), 4.82 (1H, d, J = 10.1 Hz, C(1')*H*Ph), 4.48 (1H, d, J = 15.9 Hz, CH$_A$$H_B$Ph), 4.30 (1H, d, J = 9.3 Hz, C*H*OTBS), 4.22 (1H, dq, J = 10.1 & 6.8 Hz, C(2')*H*CH_3), 2.72 (1H, dq, J = 9.3 & 6.8 Hz, C*H*CH_3), 2.39 (3H, s, *p*-CH_3), 2.33 (6H, s, *o*-CH_3), 1.67 (3H, s, CCH_3=CH_2), 1.38 (3H, d, J = 6.8 Hz, C(2')HCH_3), 0.86 (9H, s, C(CH_3)$_3$), 0.82 (3H, d, J = 7.1 Hz, CHCH_3), -0.05 (3H, s, SiCH_3), -0.13 (3H, s, SiCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.25 (C), 144.26 (C), 142.10 (C), 140.53 (2 x C), 140.20 (C), 138.35 (C), 132.58 (C), 132.01 (2 x CH), 128.85 (2 x CH), 128.33 (2 x CH), 128.12 (2 x CH), 127.37 (3 x CH), 126.84 (CH), 114.36 (CH_2), 78.76 (CH), 55.95 (CH), 53.09 (CH), 50.98 (CH), 47.20 (CH_2), 25.65 (3 x CH_3), 22.73 (2 x CH_3), 20.80 (CH_3), 18.43 (CH_3), 17.93 (C), 15.80 (CH_3), 14.74 (CH_3), -4.86 (CH_3), -4.61 (CH_3); ***m/z*** (FAB, NOBA) 680 ([M+H]$^+$, 6 %), 407 (24), 406 (62), 316 (79), 91 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 680.3246, $C_{38}H_{54}NO_4S_2Si$ requires 680.3246.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-*tert*-butyldimethylsilyloxy-5-dimethylthiopentanoate 277



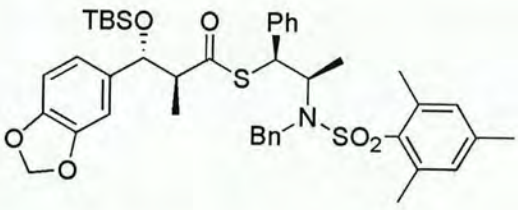
General procedure B was followed with aldol adduct **267** (100 mg, 0.168 mmol) in CH_2Cl_2 (10 ml) at 0 °C, 2,6-lutidine (30.0 µl, 0.255 mmol) was added dropwise followed by TBSOTf (44.0 µl, 0.190 mmol). Flash chromatography (10 % EtOAc in hexane) gave the protected aldol adduct **277** as a colourless oil (109 mg, 91 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.81; $[\alpha]_D$ = -14.3 (c 1.1, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1660 (C=O); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.41, (2H, d, J = 7.6 Hz, *o*-Ar*H*), 7.33 - 7.25 (3H, m, Ar*H*), 7.12 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 7.03 (2H, t, J = 7.4 Hz, *m*-Ar*H*), 6.84 (2H, s, *m*-Ar*H*), 6.69 (2H, d, J = 8.3 Hz, *o*-Ar*H*), 4.81 (1H, d, J = 9.1 Hz, C(1')*H*), 4.78 (1H, d, J = 16.2 Hz, CH_AH_BPh), 4.42 (1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), 4.23 - 4.17 (1H, m, C(2')*H*CH_3), 3.53 (1H, dd, J = 6.8 & 5.4 Hz, C*H*OTBS), 2.71 (1H, dq ≡ qn, J = 6.8 Hz, C*H*CH_3), 2.34 (9H, s, 3 x CH_3), 1.67 (1H, dspt ≡ oct, J = 6.8 Hz, C*H*$(CH_3)_2$), 1.24 (3H, d, J = 6.8 Hz, C(2')CH_3), 1.02 (3H, d, J = 7.1 Hz, CHCH_3), 0.97 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.91 (3H, d, J = 6.8 Hz, CH$(CH_3)_A$(CH_3)$_B$), 0.81 (3H, s, C(CH_3)), -0.02 (3H, s, SiCH_3), -0.04 (3H, s, SiCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.71 (C), 142.24 (C), 139.58 (2 x C), 138.62 (2 x C), 133.25 (C), 132.59 (2 x CH), 129.13 (2 x CH), 128.99 (CH), 128.82 (2 x CH), 127.87 (2 x CH), 127.71 (2 x CH), 127.67 (CH), 78.95 (CH), 57.01 (CH), 51.57 (CH), 51.49 (CH), 47.73 (CH_2), 31.20 (CH), 26.41 (2 x CH_3), 23.31 (CH_3), 21.24 (CH_3), 20.12 (CH_3), 19.17 (CH_3), 17.43 (CH_3), 16.29 (CH_3), 15.48 (CH_3), -4.62 (CH_3), -4.68 (CH_3); ***m/z*** (FAB, NOBA) 682 ($[M+H]^+$, 9 %), 406 (47), 316 (58), 290 (29) 91 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 682.3422, $C_{32}H_{42}NO_4S_2$ requires 682.3420.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-*tert*-butyldimethylsilyloxy--2,5-dimethylthiohexanoate 278



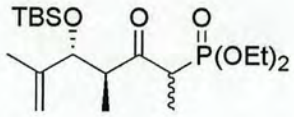
General procedure B was followed with aldol adduct **268** (200 mg, 0.340 mmol) in CH_2Cl_2 (10 ml) at 0 °C, 2,6-lutidine (60.0 µl, 0.510 mmol) was added dropwise followed by TBSOTf (87.0 µl, 0.380 mmol). Flash chromatography (10 % EtOAc in hexane) gave the protected aldol adduct **278** as a colourless oil (224 mg, 94 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.81; $[\alpha]_D$ = -14.3 (c 1.1, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1660 (C=O); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.45 (2H, d, J = 8.1 Hz, Ar*H*), 7.30 – 7.22 (3H, m, Ar*H*), 7.14 (1H, t, J = 7.1 Hz, Ar*H*), 7.00 (2H, t, J = 7.1 Hz, Ar*H*), 6.87 (2H, s, Ar*H*), 6.67 (2H, d, J = 7.1 Hz, Ar*H*), 4.82 (1H, d, J = 9.8 Hz, C(1')*H*Ph), 4.78 (1H, d, J = 16.2 Hz, CH_AH_BPh), 4.44 (1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), 4.17 (1H, dq, J = 9.8 & 6.8 Hz, C(2')*H*CH_3), 4.02 – 3.98 (1H, m, C*H*OTBS), 2.75 (1H, dq, J = 7.0 & 4.2 Hz, C*H*CH_3), 2.31 (3H, s, *p*-CH_3), 2.27 (6H, s, *o*-CH_3), 1.68 – 1.51 (1H, m, C*H*$(CH_3)_2$), 1.37 – 1.33 (1H, m, CH_AH_B), 1.28 (3H, d, J = 5.1 Hz, C(2')CH_3), 1.05 (3H, d, J = 7.0 Hz, CHCH_3), 0.86 (9H, s, C(CH_3)$_3$), 0.88 – 0.80 (1H, m, CH$_A$$H_B$), 0.84 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.72 (3H, d, J = 6.8 Hz, CH$(CH_3)_A$(CH_3)$_B$), 0.06 (3H, s, SiCH_3), 0.05 (3H, s, SiCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 198.22 (C), 142.47 (C), 140.79 (2 x C), 140.23 (C), 138.60 (C), 132.84 (C), 132.32 (2 x CH), 129.05 (2 x CH), 128.58 (3 x CH), 127.72 (2 x CH), 127.65 (2 x CH),127.30 (CH), 71.43 (CH), 56.51 (CH), 54.96 (CH), 50.96 (CH), 47.53 (CH_2), 41.41 (CH_2), 25.95 (3 x CH_3), 24.03 (CH_3), 23.06 (C), 21.69 (CH_3), 21.12 (2 x CH_3), 18.18 (2 x CH_3), 18.07 (C), 9.90 (CH_3), -4.34 (CH_3), -4.46 (CH_3); ***m/z*** (FAB, THIOG.) 696 ($[M+H]^+$, 10 %), 695 ($[M]^+$, 7 %) 514 (23), 460 (8), 406 (28), 29 (100); **HRMS** (FAB, THIOG.) $[M]^+$ found 695.3499, $C_{39}H_{57}NO_4S_2Si$ requires 695.3498.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-*tert*-butyldimethylsilyloxy-2-methyl-3-piperonylthiopropionate 279



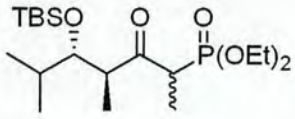
General procedure B was followed with aldol adduct **270** (200 mg, 0.310 mmol) in CH_2Cl_2 (10 ml) at 0 °C, 2,6-lutidine (54.0 µl, 0.470 mmol) was added dropwise followed by TBSOTf (78.0 µl, 0.340 mmol). Flash chromatography (10 % EtOAc in hexane) gave the protected aldol adduct **279** as a colourless oil (219 mg, 93 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.81; $[\alpha]_D$ = - 3.64 (c 0.4, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1685 (C=O); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.49, (2H, d, J = 8.3 Hz, *o*-Ar*H*), 7.33 - 7.30 (3H, m, Ar*H*), 7.13 (1H, t, J = 7.4 Hz, *p*-Ar*H*), 6.98 (2H, t, J = 7.9 Hz, *m*-Ar*H*), 6.96 (2H, s, *m*-Ar*H*), 6.84 (1H, s, Ar*H*), 6.73 – 6.61 (4H, m, Ar*H*), 5.94 – 5.93 (2H, m, OCH_2O), 4.85 (1H, d, J = 16.1 Hz, CH_AH_BPh), 4.79 (1H, d, J = 10.1 Hz, C(1')*H*Ph), 4.66 (1H, d, J = 8.9 Hz, C*H*OTBS), 4.42 (1H, d, J = 16.1 Hz, CH_AH_BPh), 4.16 (1H, dq, J = 10.1 & 6.9 Hz, C(2')*H*CH_3), 2.73 (1H, dq, J = 8.9 & 7.1 Hz, C*H*CH_3), 2.32 (3H, s, *p*-CH_3) 2.27 (6H, s, *o*-CH_3), 1.32 (3H, d, J = 6.9 Hz, C(2')HC*H*$_3$), 0.76 (9H, s, $C(CH_3)_3$), 0.64 (3H, d, J = 7.1 Hz, CHC*H*$_3$), -0.10 (3H, s, SiC*H*$_3$), -0.29 (3H, s, SiC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.19 (C), 147.46 (C), 146.92 (C), 142.12 (C), 140.54 (C), 140.16 (C), 138.36 (C), 136.01 (C), 132.58 (2 x C), 132.02 (2 x CH), 128.86 (2 x CH),128.35 (2 x CH), 128.17 (2 x CH), 127.37 (3 x CH), 126.88 (CH), 120.32 (CH), 107.55 (CH), 106.85 (CH), 100.84 (CH_2), 76.57 (CH), 57.44 (CH), 55.98 (CH), 50.98 (CH), 47.21 (CH_2), 25.64 (3 x CH_3), 22.74 (2 x CH_3), 20.81 (CH_3), 18.40 (CH_3), 17.86 (C), 14.64 (CH_3), -4.74 (CH_3), -6.41 (CH_3); ***m/z*** (FAB, NOBA) 759 ($[M]^+$, 9 %), 758 ($[M-H]^+$, 5), 406 (81), 316 (86), 73 (100); **HRMS** (FAB, NOBA) $[M]^+$ found 759.3090, $C_{42}H_{53}NO_6S_2Si$ requires 759.3084.

(2*SR*,4*S*,5*R*)-*tert*-Butyldimethylsilyloxy-2-diethoxyphosphoryl-4,6-dimethyl-hept-6-ene-3-one 281



General procedure C was followed with diethylethane phosphonate (209 μl, 1.29 mmol) and ^{n}BuLi (806 μl, 1.60 M solution in hexanes, 1.29 mmol) in THF (15 ml), to which was added to aldol adduct **276** (200 mg, 0.294 mmol). Flash chromatography (gradient elution 20 – 30 % EtOAc in hexane) gave the recovered auxiliary as a colourless solid (110 mg, 85 %) and β-ketophosphonate ester **281** as a colourless oil (109 mg, 81 %); $\mathbf{R_f}$ (50 % EtOAc in hexane) = 0.34; ν_{max} (neat) / cm^{-1} 1715 (C=O), 1252 (P=O), 1051 (PO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 4.95 (2H, s, C=CH_2), 4.25 – 4.04 (5H, m, 2 x OCH_2 & CHOTBS), 3.49 (1H, dq, J = 17.0 & 7.0 Hz, CHCH$_3$), 3.28 (1H, dq, J = 9.6 & 6.8 Hz, CHCH$_3$), 1.76 (3H, s, CH$_3$), 1.42 – 1.31 (9H, m, 2 x OCH$_2$CH_3 & CHCH_3), 0.94 (3H, d, J = 6.8 Hz, CHCH_3), 0.88 (9H, s, C(CH_3)$_3$), 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 210.00 (C), 144.91 (C), 114.86 (CH$_2$), 82.16 (CH), 62.62 (2 x CH$_2$), 49.77 (CH, $^{1}J_{PC}$ = 124.6 Hz), 49.69 (CH), 26.00 (3 x CH$_3$), 18.25 (C), 16.58 (CH$_3$), 16.12 (CH$_3$), 14.13 (2 x CH$_3$), 10.51 (CH$_3$), -4.40 (CH$_3$), -5.02 (CH$_3$); ***m/z*** (FAB, NOBA) 429 ([M+Na]$^+$, 7 %), 407 ([M+H]$^+$, 67), 49 (36), 275 (65), 73 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 407.2382, $C_{19}H_{40}O_5PSi$ requires 407.2383.

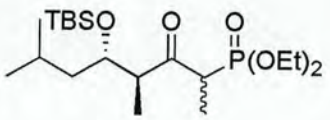
(2*SR*,4*S*,5*S*)-*tert*-Butyldimethylsilyloxy-2-diethoxyphosphoryl-4,6-dimethyl-heptan-3-one 282



General procedure C was followed with diethylethane phosphonate (105 μl, 0.645 mmol) and ^{n}BuLi (403 μl, 1.60 M solution in hexanes, 0.645 mmol) in THF (15 ml), to which was added to aldol adduct **277** (100 mg, 0.147 mmol). Flash chromatography (gradient elution 20 – 30 % EtOAc in hexane) gave the recovered auxiliary as a colourless solid (56 mg, 85 %) and β-ketophosphonate ester **282** as a colourless oil (53 mg, 89 %); $\mathbf{R_f}$ (50 % EtOAc in hexane) = 0.24; ν_{max} (neat) / cm^{-1} 1715 (C=O), 1257 (P=O), 1050 (PO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 4.15 – 4.06 (4H, m, 2 x OCH_2), 3.79 (0.2H, dd, J = 6.5 & 4.0 Hz, CHOTBS), 3.64 (0.8H, dd, J = 7.1 & 3.6 Hz, CHOTBS), 3.38 – 3.29 (1.8H, m, 2 x CHCH$_3$), 3.03 (0.2H, dq ≡ qn, J = 6.9 Hz, CHCH$_3$), 1.80 – 1.75 (1H, m, CH(CH$_3$)$_2$), 1.46 – 1.27 (9H, m , 2 x OCH$_2$CH_3 & CHCH_3), 1.11 (0.6H, d, J = 7.1 Hz, CHCH_3), 1.02 (2.4H, d, J = 6.8 Hz, CHCH_3), 0.92 – 0.84 (6H, m, CH(CH_3)$_2$), 0.84 (9H, s, C(CH_3)$_3$), 0.05 (0.6H, s, SiCH_3), 0.02 (2.4H, s, SiCH_3), -0.02 (0.6H, s, SiCH_3), -0.05 (2.4H, s, SiCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 209.33 (C),* 208.28 (C), 79.78 (CH), 78.35 (CH),* 62.55 (2 x CH_2, $^{2}J_{PC}$ = 3.5 Hz), 50.15 (CH), 48.58 (CH),* 46.71 (CH, $^{2}J_{PC}$ = 124.1 Hz), 45.21 (CH, $^{2}J_{PC}$ = 124.1 Hz),* 32.79 (CH), 31.45 (CH),* 26.34 (3 x CH_3),* 26.14 (3 x CH_3), 20.17 (CH_3),* 18.96 (CH_3), 18.57 (C),* 18.40 (C), 17.96 (2 x CH_3), 17.48 (CH_3),* 16.54 (CH_3), 13.86 (CH_3), 13.71 (CH_3),* 11.71 (CH_3),* 10.71 (CH_3), -3.69 (CH_3),* -3.81 (CH_3), -4.28 (CH_3), -4.56 (CH_3)*; ***m/z*** (FAB, NOBA) 431 ([M+Na]$^{+}$, 18%), 409 ([M+H]$^{+}$, 55), 393 (29), 365 (29), 73 (100); **HRMS** (FAB, NOBA) [M+H]$^{+}$ found 409.2538, $C_{19}H_{42}O_5PSi$ requires 409.2539.

* Indicates minor diastereomer.

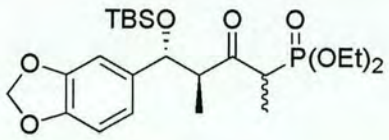
(*2SR*,*4S*,*5S*)-*tert*-Butyldimethylsilyloxy-2-diethoxyphosphoryl-4,7-dimethyl-octan-3-one 283



General procedure C was followed with diethylethane phosphonate (204 μl, 1.26 mmol) and ^{n}BuLi (788 μl, 1.60 M solution in hexanes, 1.26 mmol) in THF (15 ml), to which was added to aldol adduct **278** (200 mg, 0.287 mmol). Flash chromatography (gradient elution 20 – 30 % EtOAc in hexane) gave the recovered auxiliary as a colourless solid (91 mg, 74 %) β-ketophosphonate ester **283** as a colourless oil (110 mg, 91 %); $\mathbf{R_f}$ (50 % EtOAc in hexane) = 0.25; ν_{max} (neat) / cm^{-1} 1713 (C=O), 1251 (P=O), 1051 (PO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 4.17 – 4.07 (4H, m, 2 x OCH_2CH_3), 4.06 – 3.96 (1H, m, C*H*OTBS), 3.42 – 3.28 (1.6H, m, 2 x $CHCH_3$), 2.99 – 2.90 (0.4H, m, $CHCH_3$), 1.81 – 1.68 (1H, m, $CH(CH_3)_2$), 1.48 – 1.40 (1H, m, CH_AH_B), 1.39 – 1.21 (9H, m, 2 x OCH_2CH_3 & $CHCH_3$), 1.20 (1.2H, d, J = 6.9 Hz, $CHCH_3$), 1.04 (1.8H, d, J = 6.8 Hz, $CHCH_3$), 1.03 – 0.92 (1H, m, CH_AH_B), 0.91 – 0.85 (6H, m, $CH(CH_3)_2$), 0.87 (9H, s, $C(CH_3)_3$), 0.07 (1.8H, s, $SiCH_3$), 0.06 (1.2H, s, $SiCH_3$), 0.05 (1.2H, s, $SiCH_3$), 0.04 (1.8H, s, $SiCH_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 209.11 (C),* 207.88 (C), 71.84 (CH), 71.28 (CH),* 62.73 (2 x CH_2, $^{2}J_{PC}$ = 7.1 Hz), 53.20 (CH), 52.04 (CH),* 47.12 (CH, $^{1}J_{PC}$ = 125.8 Hz), 45.76 (CH, $^{1}J_{PC}$ = 125.6 Hz),* 42.69 (CH_2), 42.60 (CH_2),* 26.00 (3 x CH_3), 24.35 (CH_3),* 24.13 (CH), 24.05 (CH),* 22.38 (2 x CH_3), 22.24 (CH_3),* 18.18 (C), 16.60 (2 x CH_3), 16.54 (CH_3),* 11.97 (CH_3),* 11.89 (CH_3),* 11.79 (2 x CH_3), -4.33 (CH_3), -4.46 (CH_3); ***m/z*** (FAB, NOBA) 445 ([M+Na]$^+$, 38 %), 423 ([M+H]$^+$, 60), 407 (40), 397 (21), 45 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 423.2698, $C_{20}H_{44}O_5PSi$ requires 423.2696.

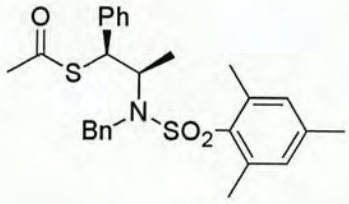
* Indicates minor diastereomer.

(3*SR*,4*S*,5*R*)-5-*tert*-Butyldimethylsilyloxy-2-diethoxyphosphoryl-4-methyl-5-piperonyl-pentan-3-one 284



General procedure C was followed with diethylethane phosphonate (186 μl, 1.16 mmol) and ^{n}BuLi (725 μl, 1.6 M solution in hexanes, 1.16 mmol) in THF (15 ml), to which was added to aldol adduct **279** (200 mg, 0.264 mmol). Flash chromatography (20 % EtOAc in hexane) gave the recovered auxiliary as a colourless solid (92 mg, 80 %) and flash chromatography (30 % EtOAc in hexane) afforded the β-ketophosphonate ester **284** as a colourless oil (100 mg, 78 %); $\mathbf{R_f}$ (50 % EtOAc in hexane) 0.32; ν_{max} (neat) / cm^{-1} 1714 (C=O), 1162 (P=O), 1139 (PO); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 6.83 (1H, s, Ar*H*), 6.73 (2H, s, Ar*H*), 6.08 – 6.07 (2H, m, OC*H*$_2$O), 4.57 (1H, d, J = 8.1 Hz, C*H*OTBS), 4.28 – 4.19 (4H, m, 2 x OC*H*$_2$CH$_3$), 3.50 (1H, dq, J = 30.0 & 7.0 Hz, C*H*CH$_3$), 3.30 (1H, dq, J = 8.1 & 6.6 Hz, C*H*CH$_3$), 1.40 - 1.21 (9H, m, 2 x OCH$_2$C*H*$_3$ & CHC*H*$_3$), 0.79 (9H, s, C(C*H*$_3$)$_3$), 0.78 (3H, d, J = 6.6 Hz, CHC*H*$_3$), -0.10 (3H, s, SiC*H*$_3$), -0.32 (3H, s, SiC*H*$_3$), **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 210.04 (C), 147.89 (C), 147.34 (C), 137.14 (C), 120.99 (CH), 107.94 (CH), 107.40 (CH), 101.27 (CH_2), 80.04 (CH), 62.76 (2 x CH_2), 54.96 (CH), 49.85 (CH, $^{1}J_{PC}$ = 124.9 Hz), 26.03 (3 x CH_3), 18.19 (C), 16.64 (CH_3), 14.31 (CH_3), 10.61 (2 x CH_3, $^{2}J_{PC}$ = 5.7 Hz), -4.30 (CH_3), -4.89 (CH_3); ***m/z*** (FAB, NOBA) 509 ([M+Na]$^+$, 23 %), 487 ([M+H]$^+$, 6), 429 (19), 355 (46), 73 (100); **HRMS** (FAB, NOBA) [M+H]$^+$ found 487.2280, $C_{23}H_{40}O_7PSi$ requires 487.2281.

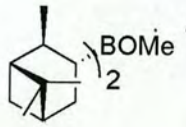
(1'*S*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl thioacetate 296



To a solution of thiol **4** (1.00 g, 2.27 mmol) in CH_2Cl_2 (10 ml) was added pyridine (242 µl, 2.77 mmol) followed by acetyl chloride (210 µl, 2.96 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and was washed with H_2O (20 ml), HCl (20 ml, 1N aq.), H_2O (20 ml), $NaHCO_3$ (20 ml, sat.) and NaCl (20 ml, sat.). The organics were dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thioester as a colourless oil. Purification by flash chromatography (20 % EtOAc in hexane) gave the thioacetate **296** as a colourless solid (9.39 g, 93 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.61; **mp** = 57 – 59 °C; $\mathbf{[\alpha]_D}$ = 60.3 (c 1.10, $CHCl_3$); $\mathbf{\nu_{max}}$ (neat) / cm^{-1} 1691 (C=O), 1387 (SO), 1154 (SO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.45 (2H, d, J = 6.2 Hz, Ar*H*), 7.31 – 7.26 (3H, m, Ar*H*), 7.15 (1H, d, 7.1 Hz, Ar*H*), 7.03 (2H, t, J = 6.5 Hz, Ar*H*), 6.84 (2H, s, Ar*H*), 6.70 (2H, d, J = 7.1 Hz, Ar*H*), 4.78 (1H, d, J = 16.0 Hz, CH_AH$_B$Ph), 4.77 (1H, d, J = 9.3 Hz, C*H*Ph), 4.45 (1H, d, J = 16.0 Hz, CH$_A$$H_B$Ph), 4.17 (1H, dq, J = 9.3 & 6.8 Hz, C*H*CH$_3$), 2.29 (9H, s, 2 x *o*-CH_3 & CH_3), 2.22 (3H, s, *p*-CH_3), 1.28 (3H, d, J = 6.8 Hz, CHCH_3), **^{13}C NMR** δ (60.9 MHz, $CDCl_3$) 192.20 (C), 142.21 (C), 140.47 (2 x C), 139.91 (C), 138.36 (C), 132.03 (C), 128.65 (2 x CH), 128.34 (2 x CH), 128.28 (2 x CH), 127.42 (3 x CH), 127.33 (2 x CH), 127.11 (CH), 56.31 (CH), 51.44 (CH), 47.27 (CH_2), 30.26 (CH_3), 22.76 (2 x CH_3), 20.81 (CH_3), 17.39 (CH_3); ***m/z*** (FAB, NOBA) 482 ($[M+H]^+$, 21 %), 404 (20), 336 (78), 143 (71), 89 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 482.1827, $C_{27}H_{32}NO_3S_2$ requires 482.1824.

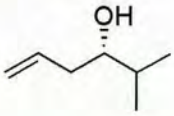
5.4 EXPERIMENTAL PROCEDURES FOR CHAPTER 4

Synthesis of (-)-β-Methoxydiisopinocampheylborane 77



To a solution of (+)-α-pinene (32.7 g, 240 mmol, 91% e.e.) in THF (30 ml) was added borane dimethyl sulfide (10.2 ml, 100 mmol) dropwise with stirring. During the addition the flask was immersed in a water bath and held at 20 – 25 °C. Immediately following the addition, stirring was discontinued and the reaction was left for 12 h to obtain a crystalline solid of diisopinocampheylborane **307**. The organic solvent was removed by cannula and the crystalline solid was washed with ice cold Et_2O (3 x 30 ml) and dried under vacuum to obtain a pure crystalline solid of diisopinocampheylborane **307** (24.3 g, 83 %). To a stirred suspension of borane **307** (14.3 g, 50.0 mmol) in Et_2O (50 ml) at 0 °C was added ice cold MeOH (1.92 g, 60.0 mmol) dropwise over 30 min. After evolution of hydrogen ceased (~ 2 h) a clear homogeneous solution was formed. The organics were removed under vacuum to give β-methoxydiisopinocampheylborane **77** as a white solid in quantitative yield.

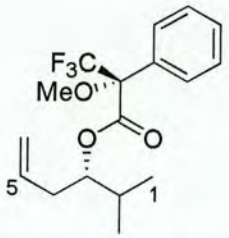
(3*S*)-2-Methyl-hex-5-ene-3-ol 305



Allylmagnesium bromide (48.0 ml, 1.0 M in Et_2O, 48.0 mmol) was added dropwise to a well stirred solution of (-)$(Ipc)_2$BOMe (15.8 g, 50 mmol) in Et_2O (100 ml) at 0 °C. The reaction was warmed to RT and stirred vigorously for 1 h. Stirring was discontinued and the organic layer was transferred *via* cannula to 500 ml flask and cooled to -100 °C. Isobutyraldehyde (4.60 ml, 50.0 mmol) was added slowly and the reaction was stirred for 1 h at -100 °C. The reaction mixture was then warmed to RT, NaOH (40 ml, 3N aq.) and H_2O_2 (15 ml) were added and the mixture was stirred overnight. The organic layer was separated and the aqueous layer was washed with Et_2O (3 x 50 ml). The organics were combined and dried (Na_2SO_4) and the volatiles were removed under reduced pressure. Kugelrohr distillation (100 °C, 6 torr) provided the pure allylic alcohol **305** (4.96 g, 87 %, 94 %e.e.); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.83, **bp** = 98 – 100 °C (6 torr); $\mathbf{[\alpha]_D}$ = - 3.00 (c 1.0, $CHCl_3$); $\mathbf{\nu_{max}}$ (neat)/cm^{-1} 3398 (OH), 1641 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 5.76 (1H, ddd, J = 16.6, 10.7 & 6.1 Hz, C*H*=CH_2), 5.08 (1H, d, J = 16.6 Hz, CH=C$H_{TRANS}H_{CIS}$), 5.06 (1H, d, J = 10.7 Hz, CH=$CH_{TRANS}H_{CIS}$), 3.34 (1H, ddd, J = 8.8, 6.8 & 2.1 Hz, C*H*OH), 2.30 - 2.22 (1H, m, CH_AH_B), 2.09 - 2.03 (1H, m, CH_AH_B), 1.71 – 1.58 (1H, m, C*H*$(CH_3)_2$), 1.10 (3H, d, J = 6.8 Hz, CH$(CH_3)_A(CH_3)_B$), 0.88 (3H, d, J = 6.8 Hz, CH$(CH_3)_A(CH_3)_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 135.31 (CH), 117.87 (CH_2), 75.21 (CH), 38.70 (CH_2), 32.96 (CH), 18.91 (CH_3), 17.44 (CH_3); ***m/z*** (FAB, THIOG.) 137 ($[M+Na]^+$, 6 %), 125 (11), 107 (22), 79 (10), 34 (100); **HRMS** (FAB, THIOG.) $[M+Na]^+$ found 137.0938, $C_7H_{14}ONa$ requires 137.0942.

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[34]

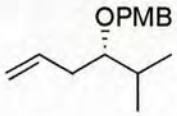
(3*S*)-2-Methyl-5-hexen-3-yl (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate 309



To a solution of alcohol **305** (10.0 mg, 0.400 mmol) and DMAP (54.0 mg, 0.440 mmol) in THF (3 ml) was added (*R*)-MTPA-Cl (111 mg, 0.440 mmol) and the reaction mixture was stirred for 12 h at RT. The reaction mixture was diluted with CH_2Cl_2 (5 ml), washed with H_2O (3 x 5 ml) and dried (K_2CO_3). Volatiles were removed under reduced pressure to give the crude Mosher's ester. Purification by flash chromatography (5 % EtOAc in hexane) afforded Mosher's ester **309** as a colourless oil (53.0 mg, 80 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.91; $[\alpha]_D$ = - 3.6 (c 0.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1726 (C=O), Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.56 - 7.54 (2H, m, Ar*H*), 7.42 - 7.40 (3H, m, ArH), 5.63 (1H, ddd, J = 17.2, 10.0 & 7.1 Hz, C(5)*H*=CH_2), 5.05 - 4.98 (3H, m, CH=CH_2 & C(3)*H*), 3.56 (3H, s, OCH_3), 2.35 (2H, t, J = 7.3 Hz, C(4)H_2), 1.95 (1H, dspt ≡ oct, J = 6.8 Hz, C*H*$(CH_3)_A(CH_3)_B$), 0.95 (3H, d, J = 6.8 Hz, CH(C$H_3)_A(CH_3)_B$), 0.93 (3H, d, J = 6.8 Hz, CH$(CH_3)_A$(C$H_3)_B$); Minor diastereomer diagnostic peak: 2.43 (1H, t, J = 7.3 Hz, C(4)H_2), 0.87 (3H, d, J = 6.8 Hz, CH(C$H_3)_A(CH_3)_B$), 0.85 (3H, d, J = 6.8 Hz, CH$(CH_3)_A$(C$H_3)_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 166.51 (C) 133.41 (CH), 132.40 (C), 129.70 (CH), 128.49 (2 x CH), 127.78 (CH), 125.16 (CH), 123.39 (CF_3, q, $^1J_{CF}$ = 288.1 Hz), 118.28 (CH_2), 84.37 (C, q, $^2J_{CF}$ = 27.8 Hz), 81.01 (CH), 55.61 (CH_3), 35.47 (CH_2), 30.89 (CH), 18.63 (CH_3), 17.55 (CH_3); ^{19}F NMR δ (50.3 MHz, $CDCl_3$) -72.5 (minor diastereomer), -72.6 (major diastereomer).

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[36]

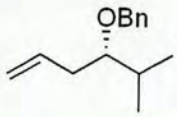
(3*S*)-2-Methyl-3-*p*-methoxybenzyloxyhex-5-ene 310



To a solution of alcohol **305** (4.20 g, 35.1 mmol) in THF (100 ml) was added potassium *tert*-butoxide (3.93 g, 35.1 mmol) followed by PMBCl (7.67 g, 50.0 mmol) at 0 °C. The reaction was warmed to RT and stirred fro 4 h. H_2O (100 ml) was added and the mixture was extracted with Et_2O (3 x 70 ml). The organics were combined, dried (Na_2SO_4) and the volatiles were removed under reduced pressure. Flash chromatography (5 % EtOAc in hexane) afforded the protected alcohol **310** as a colourless oil (6.47 g, 75 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.83, $[\alpha]_D$ = -1.12 (c 5.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1613 (C=C); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.14 (2H, d, J = 8.2 Hz, Ar*H*), 6.75 (2H, d, J = 8.2 Hz, Ar*H*), 5.76 (1H, ddd, J = 17.2, 9.7 & 6.9 Hz, C*H*=CH_2), 4.98 (1H, d, J = 17.2 Hz, CH=C$H_{TRANS}H_{CIS}$), 4.92 (1H, d, J = 9.7 Hz, CH=$CH_{TRANS}H_{CIS}$), 4.39 (1H, d, J = 16.6, 11.1 Hz, C$H_A$$H_B$Ph), 4.30 (1H, d, J = 16.6, 11.1 Hz, CH_AH_BPh), 3.68 (3H, s, OCH_3), 3.05 (1H, dt ≡ q, J = 6.3 Hz, C*H*OPMB), 2.17 (2H, br t, J = 6.9 Hz, C(4)H_2), 1.74 (1H, dsept ≡ oct, J = 6.3 Hz, C*H*$(CH_3)_2$, 0.82 (3H, d, J = 6.7 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.79 (3H, d, J = 6.7 Hz, CH$(CH_3)_A$(CH_3)$_B$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 158.90 (C), 135.63 (CH), 131.05 (C), 129.17 (2 x CH), 116.28 (CH_2), 113.54 (2 x CH), 83.40 (CH), 71.33 (CH_2), 55.15 (CH_3), 35.12 (CH_2), 30.78 (CH), 18.33 (CH_3), 18.09 (CH_3); ***m/z*** (EI) 234 ($[M]^+$, 29 %), 194 (14), 191 (59), 156 (14), 121 (100); **HRMS** (EI) $[M]^+$ found 234.1619, $C_{15}H_{22}O_2$ requires 234.1620.

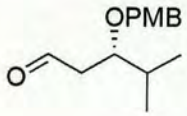
^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[37]

(3*S*)-3-Benzyloxy-2-Methyl-hex-5-ene 311



To a solution of alcohol **305** (4.20 g, 35.1 mmol) in THF (40 ml) was added ^{t}BuOK (3.93 g, 35.1 mmol) followed by BnBr (5.98 ml, 50.0 mmol) at 0 °C. The reaction was warmed to RT and stirred for 4 h. H_2O (100 ml) was added and the mixture was extracted with Et_2O (3 x 50 ml). The organics were combined, dried (Na_2SO_4) and the volatiles were removed under reduced pressure. Flash chromatography (5 % EtOAc in hexane) afforded the protected alcohol **311** as a colourless oil (4.94 g, 69 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.74, $[\alpha]_D$ = -4.3 (c 0.3 $CHCl_3$); ν_{max} (neat)/cm^{-1} 1612 (C=C); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.32 – 7.19 (5H, m, Ar*H*), 6.08 (1H, ddd, J = 17.1, 10.1 & 7.1 Hz, C*H*=CH_2), 5.34 (1H, d, J = 17.1 Hz, CH=C$H_{TRANS}H_{CIS}$), 5.31 (1H, d, J = 9.7 Hz, CH=C$H_{TRANS}H_{CIS}$), 4.65 (1H, d, J = 16.2 Hz, CH_AH$_B$Ph), 4.45 (1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), 3.45 (1H, dt ≡ q, J = 7.0 Hz, C*H*OBn), 2.57 (2H, br t, J = 7.1 Hz, CH_2O), 2.14 (1H, dsept ≡ oct, J = 6.8 Hz, C*H*(CH$_3$)$_2$, 1.22 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 1.19 (3H, d, J = 6.8 Hz, CH(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 156.42 (C), 133.32 (2 x CH), 131.24 (2 x CH), 130.53 (CH), 114.28 (CH_2), 110.49 (CH), 83.02 (CH), 70.42 (CH_2), 34.89 (CH_2), 31.23 (CH), 18.11 (CH_3), 17.98 (CH_3); ***m/z*** (EI) 204 ([M]$^+$, 15 %), 192 (24), 187 (34), 165 (11), 121 (100); **HRMS** (EI) [M]$^+$ found 204.1512, $C_{14}H_{20}O$ requires 204.1514.

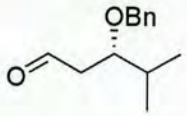
(3*S*)-3-4'-Methoxybenzyloxy-4-methylpentanal 7



To a solution of alkene **310** (5.00 g, 21.4 mmol) in a mixture of H_2O/THF (91 ml/364 ml) was added sequentially OsO_4 (4 % solution in H_2O, 6.64 ml, 1.05 mmol, 5 mol%) at 0 °C. The reaction mixture was stirred at RT for 10 min. To the reaction mixture was then added a solution of sodium periodate (1.07 g, 42.8 mmol) over a 2 h interval. To the mixture was added $Na_2S_2O_3$ (200 ml, sat.) and extracted with Et_2O (3 x 200 ml). The organic layer was washed with H_2O (60 ml), NaCl (60 ml, sat.) and dried (Na_2SO_4). The organics were removed under reduced pressure to give the crude aldehyde. Purification by flash chromatography (20 % EtOAc in hexane) gave aldehyde **7** as a colourless oil (4.23 g, 84 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.44; $[\alpha]_D$ = -65.3 (c 0.3, $CHCl_3$), lit.[29] -65.7 (c 0.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1710 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 9.78 (1H, t, J = 1.8 Hz, C*H*O), 7.18 (2H, d, J = 8.7 Hz, Ar*H*), 6.85 (2H, d, J = 8.7 Hz, Ar*H*), 4.53 (1H, d, J = 11.0 Hz, CH_AH$_B$Ph), 4.48 (1H, d, J = 11.0 Hz, CH_AH$_B$Ph), 3.79 (3H, s, OCH_3), 3.80-3.69 (1H, m, C*H*OPMB), 2.62 (1H, ddd, J = 16.0, 8.1 & 2.8 Hz, C(2)H_AH$_B$), 2.51 (1H, ddd, J = 16.0, 3.6 & 1.6 Hz, C(2)H$_A$$H_B$), 2.05 – 1.89 (1H, m, C*H*(CH$_3$)$_2$), 0.92 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 0.90 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 202.16 (CH), 159.59 (C), 130.78 (C), 129.76 (2 x CH), 114.63 (2 x CH), 79.07 (CH), 71.76 (CH_2), 55.63 (CH_3), 45.25 (CH_2), 31.20 (CH), 18.80 (CH_3), 17.64 (CH_3); ***m/z*** (EI) 236 ([M]$^+$, 43 %), 193 (8), 138 (50), 137 (87), 121 (100); **HRMS** (EI) [M]$^+$ found 236.1412, $C_{14}H_{20}O_3$ requires 236.1412.

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[29]

(3*S*)-3-benzyloxy-4-Methyl-3-pentanal 312



To a solution of alkene **311** (4.36 g, 21.4 mmol) in a mixture of H_2O/THF (91 ml/364 ml) was added sequentially OsO_4 (4 % solution in H_2O, 6.64 ml, 1.05 mmol, 5 mol%) at 0 °C. The reaction mixture was stirred at RT for 10 min. To the reaction mixture was then added a solution of sodium periodate (1.07 g, 42.8 mmol) over a 2 h interval. To the mixture was added $Na_2S_2O_3$ (200 ml, sat.) and extracted with Et_2O (3 x 200 ml). The organic layer was washed with H_2O (60 ml), NaCl (60 ml, sat.) and dried (Na_2SO_4). The volatiles were removed under reduced pressure to give the crude aldehyde. Purification by flash chromatography (20 % EtOAc in hexane) gave aldehyde **312** as a colourless oil (3.48 g, 79 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.58; $[\alpha]_D$ = -31.1 (c 0.4, $CHCl_3$), lit.[162] -34.5 (c 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1711 (C=O); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 10.0 (1H, t, J = 1.9 Hz, C*H*O), 7.41 – 7.22 (5H, m, Ar*H*), 4.82 (1H, d, J = 11.4 Hz, CH_AH$_B$Ph), 4.75 (1H, d, J = 11.4 Hz, CH$_A$$H_B$Ph), 4.06 – 4.00 (1H, m, J = C*H*OBn), 2.89 (1H, ddd, J = 16.3, 8.1 & 2.7 Hz, C(2)H_AH$_B$), 2.73 (1H, ddd, J = 16.3, 8.8 & 1.8 Hz, C(2)H_AH$_B$), 2.26 (1H, dspt, J = 8.6 & 6.8 Hz, C*H*(CH$_3$)$_2$), 1.18 (3H, d, J = 6.8 Hz, CHCH_3), 1.17 (3H, d, J = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 202.51 (CH), 138.67 (C), 128.76 (3 x CH), 128.11 (2 x CH), 79.43 (CH), 72.13 (CH_2), 45.25 (CH_2), 31.22 (CH), 18.77 (CH_3), 17.63 (CH_3); ***m/z*** (FAB, NOBA) 207 ($[M+H]^+$, 5 %), 205 ($[M-H]^+$, 27), 133 (19), 115 (37), 43 (100); **HRMS** (FAB, NOBA) $[M-H]^+$ found 205.1227, $C_{13}H_{17}O_2$ requires 205.1229.

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[162]

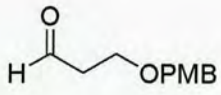
3-(4-Methoxy-benzyloxy)-propan-1-ol 316

Sodium hydride (1.58 g, 39.6 mmol) was washed with anhydrous ether several times and covered with DMF (100 ml). The suspension was treated dropwise at 0 °C with 1,3-propandiol (2.50 g, 33.0 mmol). The mixture was then stirred at RT with the exclusion of atmospheric moisture for 15 min until gas evolution had ceased. PMBCl (5.2 g, 33.0 mmol) was added and the mixture was stirred and heated at 100 °C for 1 h. the mixture was cooled to RT, H_2O (5.0 ml) was added and the mixture was stirred at RT for 15 min (to destroy unreacted sodium hydride). The mixture was concentrated under reduced pressure and was treated with H_2O (50 ml). The aqueous mixture was extracted with ether (3 x 100 ml). The combined organics were washed with NaCl (100 ml, sat), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude mono-protected diol product. Flash chromatography (20 % EtOAc in hexane) gave alcohol **316** as a colourless oil (3.41 g, 50 %); $\mathbf{R_f}$ (50 % EtOAc in hexane) = 0.28; $\mathbf{\nu_{max}}$ (Nujol mull)/cm^{-1} 3392 (OH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.32 (2H, d, J = 8.3 Hz, Ar*H*), 6.95 (2H, d, J = 8.3 Hz, Ar*H*), 4.51 (2H, s, OCH_2Ar), 3.87 (3H, s, OCH_3), 3.83 (2H, t, J = 5.9 Hz, CH_2OH), 3.69 (2H, t, J = 5.9 Hz, CH_2OPMB), 2.54 (1H, br s, O*H*), 1.91 (2H, qn, J = 5.9 Hz, CH_2CH_2OH); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 159.04 (C), 129.99 (C), 129.11 (2 x CH), 113.64 (2 x CH), 72.72 (CH_2), 68.83 (CH_2), 61.60 (CH_2), 55.08 (CH_3), 31.91 (CH_2); ***m/z*** (FAB, NOBA) 197 ($[M+H]^+$, 25 %), 196 (M^+, 58), 195 (59), 194 (14), 193 (21); **HRMS** (FAB, NOBA) $[M]^+$ found 196.1096, $C_{11}H_{16}O_3$ requires 196.1099.

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[142]

General Procedure G: Swern oxidation: Oxalyl chloride (2.49 ml, 28.1 mmol) in CH_2Cl_2 was cooled to 78 °C and DMSO (3.97 ml, 56.1 mmol) added dropwise and stirred for 5 min. The activated DMSO was transferred into a solution of alcohol (25.5 mmol) CH_2Cl_2 at -78 °C. After 15 min Et_3N (15.6 ml, 112 mmol) was added and the dry ice/acetone bath removed. The reaction mixture was allowed to proceed until it came to RT (~ 60 min) at which time H_2O (50 ml) was added. The layers were separated, and the organics washed with H_2O (25 ml), $NaHCO_3$ (25 ml, sat.), H_2O (2 x 25 ml). The organic layer was then dried and concentrated to give the crude aldehyde as a yellow oil. Purification by flash chromatography gave the aldehyde as a colourless oil.

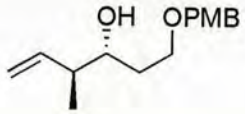
3-(4'-Methoxybenzyloxy)-propan-1-al 103



General procedure **G** was used for alcohol **316** (5.00 g, 25.5 mmol) Purification with flash chromatography (20 % EtOAc in hexane) gave the aldehyde **103** as a colourless oil (4.99 g, 97 %); $\mathbf{R_f}$ (30 % EtOAc in hexane) = 0.34; $\boldsymbol{\nu_{max}}$ (neat)/cm^{-1} 1731 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 9.88 (1H, t, J = 1.8 Hz, C*H*O), 7.34 (2H, d, J = 8.7 Hz, Ar*H*), 6.97 (2H, d, J = 8.7 Hz, Ar*H*), 4.56 (2H, s, CH_2Ar), 3.90 (3H, s, OCH_3), 3.88 (2H, t, J = 6.5 Hz, CH_2CH_2OPMB), 2.78 (2H, td, J = 6.5 & 1.8 Hz, CH_2CH_2OPMB); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 201.13 (C), 159.76 (C), 130.12 (C), 129.24 (2 x CH), 113.72 (2 x CH), 72.81 (CH_2), 63.40 (CH_2), 55.17 (CH_2), 43.77 (CH_3); ***m/z*** (FAB, NOBA) 195 ($[M+H]^+$, 4 %), 193 ($[M-H]^+$, 49), 137 (45), 135 (27), 121 (100); **HRMS** (FAB, NOBA) $[M-H]^+$ found 193.0865, $C_{11}H_{13}O_3$ requires 193.0865.

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature[42]

(3*R*,4*S*)-1-(4-Methoxybenzyloxy)-4-methyl-5-hexen-3-ol 315

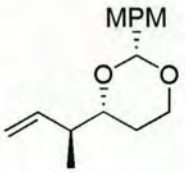


To a cloudy solution of potassium *tert*-butoxide (880 µl, 1.0 M in THF, 8.80 mmol) and *trans*-2-butene (excess) in THF (20 ml) at -78 °C was added dropwise ^{n}BuLi (5.50 ml, 1.6 M in hexane, 8.80 mmol). The resulting yellow solution was allowed to warm to -45 °C and stirred for 20 min. The reaction mixture was recooled to -78 °C and a solution of (-)-*β*-methoxydiisopinocampheylborane (3.61 g, 11.4 mmol) in THF (10 ml) was added. The resulting colourless reaction mixture was stirred at -78 °C for 35 min. BF_3•Et_2O (1.40 ml, 11.3 mmol) was added rapidly followed immediately by a solution of the crude aldehyde (1.00 g, 5.20 mmol) in THF (5.0 ml). The resulting cloudy reaction mixture was stirred at -78 °C for 4 h. The reaction was quenched by addition of NaOH (30 ml, 3N aq.) followed by H_2O_2 (30 ml). The reaction mixture was warmed to 25 °C and stirred overnight. The mixture was diluted with ethyl acetate (60 ml) and NaCl (50 ml, sat.). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 ml). The combined organics were dried (Na_2SO_4) and then concentrated under reduced pressure. Purification by flash chromatography (8 % EtOAc in hexane) gave the homoallylic alcohol (919 mg, 71 %); *91 % enantiomeric excess was determined by chiral HPLC comparing alcohol **315** with alcohol **104** derived from (+)-borane (Daicel Chiracel OD-H, 254nm, 99:1 hexanes/propan-2-ol, 0.5 ml/min)* **R_t 315** 38.1 min, **104** = 41.1 min; **R_f** (20 % EtOAc in hexane) = 0.29; **$[\alpha]_D$** = -0.19 (c 2.0, $CHCl_3$), lit[42] -0.19 (c 2.0, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3460 (OH), 1613 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.23 (2H, d, *J* = 8.3 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.3 Hz, Ar*H*), 5.77 (1H, ddd, *J* = 17.9, 11.9 & 7.9 Hz, C*H*=CH_2), 5.04 (1H, d, *J* = 11.9 Hz, CH=C$H_{CIS}H_{TRANS}$), 5.03 (1H, d, *J* = 17.9 Hz, CH=$CH_{CIS}H_{TRANS}$), 4.42 (2H, s, CH_2Ar), 3.77 (3H, s, OCH_3), 3.68 – 3.54 (3H, m, C(3)*H*OH & C(2)H_2), 2.76 (1H, br s, O*H*), 2.26 – 2.12 (1H, m, C(4)*H*CH_3), 1.68 (2H, q, *J* = 5.5 Hz, C(2)H_2), 1.00 (3H, d, *J* = 6.9 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 159.12 (C), 140.38 (CH), 129.97 (C), 129.22 (2 x CH),

115.34 (CH_2), 113.70 (2 x CH), 74.20 (CH), 72.86 (CH_2), 68.83 (CH_2), 55.16 (CH_3), 43.88 (CH), 33.40 (CH_2), 15.70 (CH_3); ***m/z*** (FAB, NOBA) 251 ($[M+H]^+$, 3 %), 249 ($[M-H]^+$, 43), 241 (4), 227 (40); **HRMS** (FAB, NOBA) $[M-H]^+$ found 249.1481, $C_{15}H_{21}O_3$ requires 249.1490.

^1H and ^{13}C NMR spectroscopic data in good agreement with the literature.[42]

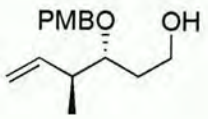
(1''*S*,2*R*,4*R*)-2-(4'-Methoxyphenyl)-4-(1''-methyl-prop-2''-enyl)-[1,3]-dioxane 319



To a solution of alcohol **315** (2.10 g, 8.36 mmol), in CH_2Cl_2 (50 ml) at 0 °C was added 4 Å molecular sieves (2.10 g), then DDQ (2.0 g, 8.78 mmol) was added in three portions over 5 min. The reaction mixture was then stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (2 x 20 ml). The organics were washed with H_2O (2 x 30 ml) and NaCl (2 x 30 ml) and dried (Na_2SO_4). The organics were removed under reduced pressure to give the crude acetal as a yellow oil. Purification using flash chromatography gave the pure acetal **319** as a colourless oil (1.74 g, 83 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.78; $[\alpha]_D$ = -15.3 (c 0.9, $CHCl_3$), lit.[163] -16.5 (c 0.35, CH_2Cl_2); ν_{max} (neat) / cm^{-1} 1616 (C=C); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.44 (2H, d, J = 8.7 Hz, Ar*H*), 6.90 (2H, d, J = 8.7 Hz, Ar*H*), 5.93 (1H, ddd, J = 18.0, 10.0 & 8.4 Hz, C*H*=CH_2), 5.47 (1H, s, C*H*Ar), 5.09 (1H, d, J = 18.0 Hz, CH=C$H_{TRANS}$$CH_{CIS}$), 5.07 (1H, d, J = 10.0 Hz, CH=CH_{TRANS}CH_{CIS}), 4.28 (1H, dd, J = 11.3 & 4.2 Hz, C(6)H_AH_B), 3.92 (1H, td, J = 12.2 & 2.5 Hz, C(6)H_AH_B), 3.81 (3H, s, OCH_3), 3.75 (1H, ddd, J = 11.3, 5.4 Hz & 2.2 Hz, C(4)H), 2.45 – 2.38 (1H, m, C(5)H_XH_Y), 1.88 (1H, qd, J = 12.4 & 5.0 Hz, C(5)H_XH_Y), 1.46 – 1.42 (1H, m, C*H*CH_3), 1.08 (3H, d, J = 6.9 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 159.65 (C), 140.09 (CH), 131.40 (C), 127.17 (2 x CH), 114.69 (CH_2), 113.38 (2 x CH), 100.85 (CH), 80.21 (CH), 66.86 (CH_2), 55.15 (CH_3), 42.30 (CH), 27.83 (CH_2), 14.99 (CH_3); ***m/z*** (FAB, THIOG.) 249 ($[M+H]^+$, 43 %), 248 (11), 247 (22), 222 (10), 221 (68); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 249.1483, $C_{15}H_{21}O_3$ requires 249.1491.

^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[163]

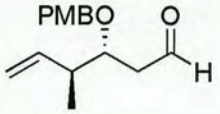
(3*R*,4*S*)-3-(4'-Methoxybenzyloxy)-4-methyl-5-hexen-1-ol 320



To a solution of acetal **319** (1.50 g, 6.02 mmol) in CH_2Cl_2 at 0 °C was added DIBAL (18.1 ml, 1.0 M in toluene, 18.1 mmol) and the reaction mixture was stirred for 2 h. Rochelle's salt (30 ml, sat.) was added and the reaction mixture was stirred for 30 min. HCl (50 ml, 1N aq.) was carefully added to the reaction mixture and was vigorously stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organics were washed with H_2O (2 x 50 ml), NaCl (2 x 50 ml) and dried (Na_2SO_4). The organics were removed under reduced pressure to give the crude alcohol as a yellow oil. Purification using flash chromatography gave alcohol **320** as a colourless oil (1.40 g, 93 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.14; $[\alpha]_D$ = 44.2 (c 0.7, $CHCl_3$), lit.[164] 93.8 (c 1.0, CH_2Cl_2); ν_{max} (neat) / cm^{-1} 3407 (OH), 1613 (C=C); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.28 (2H, d, J = 8.4 Hz, Ar*H*), 6.89 (2H, d, J = 8.4 Hz, Ar*H*), 5.79 (1H, ddd, J = 19.5, 10.5 & 6.9 Hz, C*H*=CH_2), 5.08 (1H, d, J = 19.5 Hz, CH=$CH_{CIS}H_{TRANS}$), 5.07 (1H, d, J = 10.5 Hz, CH=$CH_{CIS}H_{TRANS}$), 4.60 (1H, d, J = 11.0 Hz, CH_AH_BPh), 4.42 (1H, d, J = 11.0 Hz, CH_AH_BPh), 3.81 (3H, s, OCH_3), 3.73 (2H, t, J = 5.9 Hz, C(1)H_2OH), 3.61 – 3.56 (1H, m, C(3)*H*), 2.72 – 2.68 (1H, m, C(4)*H*CH_3), 2.09 (1H, br s, O*H*), 1.74 – 1.65 (2H, m, C(2)H_2), 1.03 (3H, d, J = 6.9 Hz, C(4)HCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 162.13 (C), 143.37 (CH), 133.18 (C), 132.42 (2 x CH), 117.82 (CH_2), 116.74 (2 x CH), 84.44 (CH), 74.04 (CH_2), 64.11 (CH_2), 58.14 (CH_3), 42.36 (CH), 34.99 (CH_2), 16.31 (CH_3); ***m/z*** (FAB, THIOG.) 251 ($[M+H]^+$, 57 %), 250 (41), 249 (68), 248 (12), 247 (16); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 251.1649, $C_{15}H_{23}O_3$ requires 251.1647.

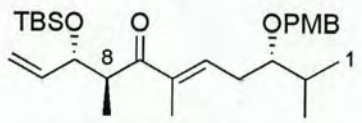
^{1}H and ^{13}C NMR spectroscopic data in good agreement with the literature.[164]

(3*R*,4*S*)-3-(4'-Methoxybenzyloxy)-4-methyl-5-hexenal 5



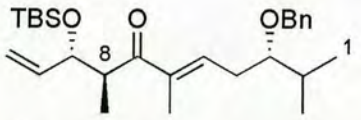
General procedure G was used with alcohol **320** (1.00 g, 4.03 mmol) to give aldehyde **5** (980 mg, 99 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.59; ν_{max} (neat) / cm^{-1} 1726 (C=O), 1613 (C=C); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 9.88 (1H, t, J = 1.5 Hz, C*H*O), 7.37 (2H, d, J = 8.8 Hz, Ar*H*), 7.01 (2H, d, J = 8.8 Hz, Ar*H*), 5.90 (1H, ddd, J = 17.9, 11.3 & 7.0 Hz, C*H*=CH_2), 5.22 (1H, d, J = 11.3 Hz, CH=C$H_{CIS}H_{TRANS}$), 5.21 (1H, d, J = 17.9 Hz, CH=$CH_{CIS}H_{TRANS}$), 4.67 (1H, d, J = 11.0 Hz, CH_AH_BPh), 4.58 (1H, d, J = 11.0 Hz, CH_AH_BPh), 4.08 (1H, q, J = 4.1 Hz, C(3)*H*), 3.98 (3H, s, OCH_3), 2.81 – 2.55 (3H, m, C(4)*H*CH_3 & C(2)H_2), 1.19 (3H, d, J = 7.0 Hz, C(4)HCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 201.71 (CH), 159.13 (C), 139.53 (CH), 130.10 (C), 129.28 (2 x CH), 115.60 (CH_2), 113.68 (2 x CH), 76.85 (CH), 71.35 (CH_2), 55.15 (CH_3), 45.05 (CH_2), 40.14 (CH), 13.84 (CH_3); ***m/z*** (FAB, THIOG.) 249 ($[M+H]^+$, 50 %), 241 (40), 235 (38), 227 (18), 43 (100); **HRMS** (FAB, THIOG.) $[M+H]^+$ found 249.1493, $C_{15}H_{21}O_3$ requires 249.1491.

(3*S*,5*E*,8*S*,9*S*)-9-*tert*-Butyldimethylsilyloxy-3-(4'-methoxybenzyloxy)-2,6,8-trimethylundec-5,10-dien-7-one 321



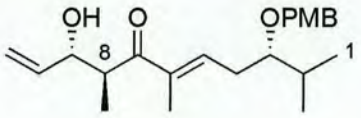
General procedure D was followed with β-ketophosphonate ester **193** (5.00 g, 12.7 mmol) in THF (50 ml) was added $Ba(OH)_2 \cdot 8H_2O$ (4.81 g, 15.00 mmol) to which aldehyde **7** (4.50 g, 19.1 mmol) was added. Flash chromatography (20 % EtOAc in hexane) gave HWE adduct **321** as a colourless oil (5.26 g, 87 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.81; ν_{max} (neat) / cm^{-1} = 1664 (C=O), 1613 (C=C); $[\alpha]_D$ = 0.16 (c 0.5, $CHCl_3$); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.88 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.78 (1H, br t, *J* = 6.8 Hz, C(5)*H*), 5.73 (1H, ddd, *J* = 17.2, 9.2 & 7.7 Hz, C*H*=CH_2), 5.19 (1H, d, *J* = 17.2 Hz, CH=C*H*$_{TRANS}$H$_{CIS}$), 5.16 (1H, d, *J* = 9.2 Hz, CH=CH$_{TRANS}$*H*$_{CIS}$), 4.48 (2H, s, C*H*$_2$Ar), 4.24 (1H, t, *J* = 9.2 Hz, C*H*OTBS), 3.81 (3H, s, OC*H*$_3$), 3.35 - 3.29 (2H, m, C(3)*H*OPMB & C(8)*H*CH_3), 2.46 (2H, br t, *J* = 6.8 Hz, C(4)*H*$_2$), 1.93 – 1.89 (1H, m, C*H*$(CH_3)_2$), 1.79 (3H, s, C(6)C*H*$_3$), 0.97 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_A$(CH_3)$_B$), 0.94 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_A$(C*H*$_3$)$_B$), 0.89 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 0.77 (9H, s, C(C*H*$_3$)$_3$), -0.03 (3H, s, SiC*H*$_3$), -0.05 (3H, s, SiC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 207.33 (C), 161.72 (C), 142.69 (CH), 142.23 (CH), 141.21 (C), 133.32 (C), 131.99 (2 x CH), 119.04 (CH_2), 116.34 (2 x CH), 85.43 (CH), 80.14 (CH), 74.08 (CH_2), 57.83 (CH_3), 47.51 (CH), 33.69 (CH), 33.05 (CH_2), 28.25 (3 x CH_3), 20.95 (CH_3), 20.63 (CH_3), 20.53 (C), 17.28 (CH_3), 14.42 (CH_3), -1.60 (CH_3), -2.69 (CH_3); ***m/z*** (FAB, NOBA) 475 ($[M+H]^+$, 6 %), 281 (24), 241 (11), 211 (24), 121 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 475.3243, $C_{28}H_{47}O_4Si$ requires 475.3243.

(3*S*,5*E*,8*S*,9S)-3-Benzyloxy-9-*tert*-butyldimethylsilyloxy-2,6,8-trimethylundec-5,10-dien-7-one 322



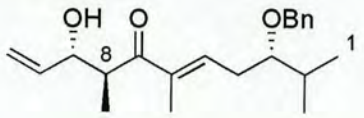
General procedure D was followed with β-ketophosphonate ester **193** (600 mg, 1.53 mmol) in THF (10 ml) was added $Ba(OH)_2 \cdot 8H_2O$ (600 mg, 1.80 mmol) to which aldehyde **312** (472 mg, 2.30 mmol) was added. Flash chromatography (20 % EtOAc in hexane) gave HWE adduct **322** as a colourless oil (577 mg, 85 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.89; ν_{max} (neat) / cm^{-1} = 1661 (C=O), 1601 (C=C); $[\alpha]_D$ 2.40 = (c 0.3, $CHCl_3$); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.40 – 7.30 (5H, m, Ar*H*), 6.83 (1H, br t, *J* = 6.8 Hz, C(5)*H*), 5.73 (1H, ddd, *J* = 17.3, 10.2 & 7.9 Hz, C*H*=CH_2), 5.21 (1H, d, *J* = 17.3 Hz, CH=$CH_{CIS}CH_{TRANS}$), 5.17 (1H, d, *J* = 10.2 Hz, CH=$CH_{CIS}CH_{TRANS}$), 4.59 (2H, s, CH_2OBn), 4.23 (1H, br t, *J* = 8.3 Hz, C*H*OTBS), 3.40 – 3.31 (2H, m, C*H*OBn & C(8)*H*CH_3), 2.51 (2H, br t, *J* = 6.8 Hz, C(4)H_2), 2.02 – 1.87 (1H, m, C*H*$(CH_3)_2$), 1.84 (3H, s, C(6)CH_3), 1.01 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.98 (3H, d, *J* = 7.0 Hz, CH$(CH_3)_A(CH_3)_B$), 0.92 (3H, d, *J* = 7.0 Hz, CH$(CH_3)_A(CH_3)_B$), 0.80 (9H, s, C$(CH_3)_3$), 0.00 (3H, s, SiCH_3), -0.04 (3H, s, SiCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 204.93 (C), 140.14 (CH), 139.81 (CH), 139.65 (C), 138.82 (C), 128.56 (2 x CH), 127.99 (2 x CH), 127.80 (CH), 116.63 (CH_2), 83.43 (CH), 75.55 (CH), 72.05 (CH_2), 45.28 (CH), 31.32 (CH), 30.66 (CH_2), 25.85 (3 x CH_3), 18.51 (CH_3), 18.24 (CH_3), 18.13 (C), 14.86 (CH_3), 12.03 (CH_3), -4.00 (CH_3), -5.08 (CH_3); ***m/z*** (FAB, NOBA) 445 ($[M+H]^+$, 6 %), 281 (27), 253 (12), 211 (29), 73 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 445.3130, $C_{27}H_{45}O_3Si$ requires 445.3138.

(3*S*,5*E*,8*S*,9*S*)-9-Hydroxy-3-(4'-methoxybenzyloxy)-2,6,8-trimethylundec-5,10-dien-7-one 72



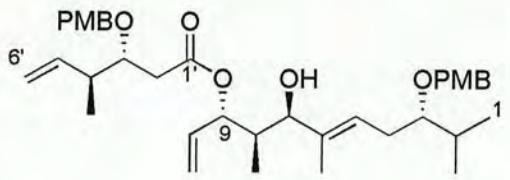
General Procedure E was followed with β-hydroxy enone **321** (4.50 g; 9.49 mmol) in MeCN (45 ml) at RT was added HF (2.0 ml, 40 % aq.) and stirred for 15 min. Purification by flash chromatography (20 % EtOAc in hexane) afforded the β-hydroxy enone **72** as a colourless oil (3.18 g, 94 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.31; ν_{max} (neat) / cm^{-1} = 3465 (OH), 1660 (C=O), 1612 (C=C); $[\alpha]_D$ 0.8 = (c 0.6, $CHCl_3$); **^{1}H NMR** δ (360 MHz, $CDCl_3$); 7.26 (2H, d, J = 8.7 Hz, Ar*H*), 6.88 (2H, d, J = 8.7 Hz, Ar*H*), 6.75 (1H, br t, J = 6.8 Hz, C(5)*H*), 5.83 (1H, ddd, J = 17.1, 10.4 & 6.4 Hz, C*H*=CH_2), 5.29 (1H, d, J = 17.1 Hz, CH=C$H_{TRANS}H_{CIS}$), 5.16 (1H, d, J = 10.4 Hz, CH=$CH_{TRANS}H_{CIS}$), 4.51 (1H, d, J = 11.3 Hz, CH_AH_BPh), 4.44 (1H, d, J = 11.3 Hz, CH_AH_BPh), 4.24 (1H, t, J = 6.4 Hz, C*H*OH), 3.81 (3H, s, OCH_3), 3.35 - 3.25 (2H, m, C(3)*H*OPMB & C(8)*H*CH_3), 2.46 (2H, br t, J = 6.8 Hz, C(4)H_2), 1.98 – 1.87 (1H, m, J = 6.8 Hz, C*H*$(CH_3)_2$), 1.78 (3H, s, C(6)CH_3), 1.12 (3H, d, J = 6.8 Hz, CHCH_3), 0.97 (3H, d, J = 6.8 Hz, CH$(CH_3)_A(CH_3)_B$), 0.94 (3H, d, J = 6.8 Hz, CH$(CH_3)_A(CH_3)_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 208.90 (C), 161.74 (C), 143.80 (CH), 141.42 (CH), 140.40 (C), 133.18 (C), 131.97 (2 x CH), 118.80 (CH_2), 116.35 (2 x CH), 85.10 (CH), 78.08 (CH), 73.96 (CH_2), 57.83 (CH_3), 46.41 (CH), 33.59 (CH), 32.89 (CH_2), 21.14 (CH_3), 20.36 (CH_3), 18.56 (CH_3), 14.11 (CH_3); ***m/z*** (FAB, NOBA) 361 ($[M+H]^+$, 14 %), 249 (11), 241 (14), 225 (12), 121 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 361.2378, $C_{22}H_{33}O_4$ requires 361.2379.

(3*S*,5*E*,8*S*,9*S*)-3-Benzyloxy-9-hydroxy-2,6,8-trimethylundec-5,10-dien-7-one 323



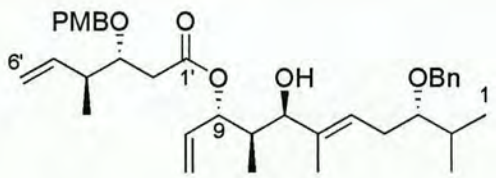
General Procedure E was followed with β-hydroxy enone **322** (550 mg, 1.24 mmol) in MeCN (10 ml) at RT was added HF (550 μl, 40 % aq.) and stirred for 15 min. Purification by flash chromatography (20 % EtOAc in hexane) afforded the β-hydroxy enone **323** as a colourless oil (388 mg, 95 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.31; ν_{max} (neat) / cm^{-1} = 3465 (OH), 1660 (C=O), 1642 (C=C); $[\alpha]_D$ 1.15 = (c 0.2, $CHCl_3$); **^{1}H NMR** δ (360 MHz, $CDCl_3$); 7.44 – 7.29 (5H, m, Ar*H*), 6.77 (1H, br t, *J* = 7.0 Hz, C(5)*H*), 5.84 (1H, ddd, *J* = 17.0, 10.4 & 6.3 Hz, C*H*=CH_2), 5.28 (1H, d, *J* = 17.0 Hz, CH=C$H_{TRANS}H_{CIS}$), 5.13 (1H, d, *J* = 10.4 Hz, CH=$CH_{TRANS}H_{CIS}$), 4.57 (1H, d, *J* = 11.7 Hz, CH_AH_BPh), 4.51 (1H, d, *J* = 11.7 Hz, CH_AH_BPh), 4.24 (1H, br t, *J* = 6.3 Hz, C*H*OH), 3.37 – 3.24 (2H, m, C(3)*H*OBn & C(8)*H*CH_3), 2.48 (2H, br t, *J* = 5.8 Hz, C(4)H_2), 2.00 – 1.91 (1H, m, C*H*$(CH_3)_2$), 1.79 (3H, s, C(6)CH_3), 1.16 (3H, d, *J* = 7.2 Hz, C(8)HCH_3), 0.97 (3H, d, *J* = 6.6 Hz, CH(C$H_3)_A(CH_3)_B$), 0.95 (3H, d, *J* = 6.6 Hz, CH$(CH_3)_A$(C$H_3)_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 206.57 (C), 141.32 (CH), 139.04 (CH), 138.76 (C), 138.12 (C), 128.63 (2 x CH), 128.00 (CH), 127.90 (2 x CH), 116.47 (CH_2) 83.20 (CH), 75.74 (CH), 71.99 (CH_2), 44.08 (CH), 31.27 (CH), 30.55 (CH_2), 18.74 (CH_3), 18.02 (CH_3), 16.18 (CH_3), 11.76 (CH_3); ***m/z*** (FAB, NOBA) 331 ($[M+H]^+$, 27 %), 220 (22), 163 (24), 145 (11), 43 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 331.2276, $C_{21}H_{31}O_3$ requires 331.2273.

(3*S*,3'*R*,4'*S*,5*E*,7*R*,8*R*,9*S*)-9-[3'-(4''-Methoxybenzyloxy)-4'-methyl-hex-5-enoyl]-3-(4'''-methoxybenzyloxy)-2,6,8-trimethylundec-5,10-dien-7-ol 71



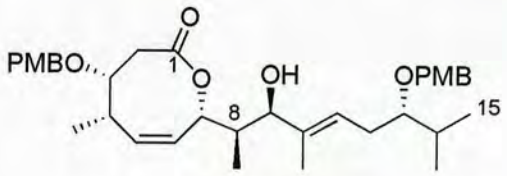
General procedure F was followed with a solution of benzaldehyde (100 μl) in THF (10 ml) and SmI_2 (5.00 ml, 0.1 M solution in THF), to which aldehyde **5** (973 mg, 3.88 mmol)) followed by β-hydroxy enone **72** (700 mg, 1.94 mmol) were added. Flash chromatography (10 % EtOAc in hexane) afforded ester **71** as a colourless oil (1.13 g, 96 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.56; $[\alpha]_D$ = 0.40 (c 0.4, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3459 (OH), 1720 (C=O), 1613 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.23 (4H, d, J = 8.9 Hz, Ar*H*), 6.83 (4H, d, J = 8.9 Hz, Ar*H*), 5.84 - 5.72 (2H, m, 2 x C*H*=CH_2), 5.52 (1H, br t, J = 7.0 Hz, C(5)*H*), 5.26 (1H, d, J = 17.1 Hz, C(10)HC$H_{TRANS}H_{CIS}$), 5.23 (1H, t, J = 6.9 Hz, C(9)*H*), 5.16 (1H, d, J = 10.0 Hz, C(10)HC$H_{TRANS}H_{CIS}$), 5.07 (1H, d, J = 17.1 Hz, C(5')HC$H_{TRANS}H_{CIS}$), 5.06 (1H, d, J = 10.0 Hz, C(5')HC$H_{TRANS}H_{CIS}$), 4.50 (1H, d, J = 11.2 Hz, CH_AH_BAr), 4.49 (2H, s, CH_2Ar), 4.42 (1H, d, J = 11.2 Hz, CH_AH_BAr), 3.95 (1H, br d, J = 3.9 Hz, C(7)*H*OH), 3.89 (1H, dt ≡ q, J = 4.2 Hz, C(3')*H*), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.20 (1H, dt ≡ q, J = 5.5 Hz, C(3)*H*), 2.58 - 2.42 (3H, m, C(4')*H*CH_3 & C(2')H_2), 2.31 - 2.24 (2H, m, C(4)H_2), 1.91 - 1.78 (2H, m, C(8)*H*CH_3 & C*H*$(CH_3)_2$), 1.56 (3H, s, C(6)CH_3), 1.05 (3H, d, J = 6.9 Hz, C(8)HCH_3), 0.93 (3H, d, J = 5.9 Hz, CH$(CH_3)_A(CH_3)_B$), 0.92 (3H, d, J = 5.9 Hz, CH$(CH_3)_A(CH_3)_B$), 0.80 (3H, d, J = 6.9 Hz, C(4')HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 171.70 (C), 159.01 (C), 158.89 (C), 139.68 (CH), 136.00 (C), 134.43 (CH), 131.16 (C), 130.48 (C), 129.16 (4 x CH), 122.36 (CH), 118.30 (CH_2), 115.39 (CH_2), 113.59 (4 x CH), 83.71 (CH), 79.00 (CH), 76.09 (CH), 74.84 (CH), 71.88 (CH_2), 71.37 (CH_2), 55.15 (2 x CH_3), 40.60 (CH), 39.32 (CH), 36.94 (CH_2), 30.92 (CH), 28.91 (CH_2), 18.62 (CH_3), 17.82 (CH_3), 14.30 (CH_3), 13.15 (CH_3), 9.11 (CH_3); ***m/z*** (FAB, NOBA) 607 ($[M-H]^+$, 4 %), 591 ($[(M-H_2O)+H]^+$, 5), 307 (56), 289 (50), 121 (100); **HRMS** (FAB, NOBA) $[M-H]^+$ found 607.3631, $C_{37}H_{51}O_7$ requires 607.3635.

(3*S*,3'*R*,4'*S*,5*E*,7*R*,8*R*,9*S*)-3-Benzyloxy-9-[3'-(4-methoxybenzyloxy)-4'-methyl-hex-5-enoyl]-2,6,8-trimethylundec-5,10-en-7-ol 324



General procedure F was followed with a solution of benzaldehyde (100 μl) in THF (10 ml) and SmI_2 (5.00 ml, 0.1 M solution in THF), to which aldehyde **5** (799 mg, 3.88 mmol) followed by β-hydroxy enone **323** (700 mg, 1.94 mmol) were added. Flash chromatography (10 % EtOAc in hexane) afforded ester **324** as a colourless oil (997 mg, 91 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.56; $[\alpha]_D$ = 0.60 (c 0.4, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3467 (OH), 1732 (C=O), 1613 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.36 – 7.28 (5H, m, Ar*H*), 7.24 (2H, d, J = 8.7 Hz, Ar*H*), 6.84 (2H, d, J = 8.7 Hz, Ar*H*), 5.83 – 5.70 (2H, m, 2 x C*H*=CH_2), 5.53 (1H, br t, J = 6.9 Hz, C(5)*H*), 5.29 – 5.20 (3H, m, C(11)H_2 & C(9)*H*), 5.09 (1H, d, J = 16.7 Hz, C(6')$H_{TRANS}H_{CIS}$), 5.07 (1H, d, J = 10.7 Hz, C(6')$H_{TRANS}H_{CIS}$), 4.57 (1H, d, J = 11.6 Hz, CH_AH_BPh), 4.49 (1H, d, J = 11.6 Hz, CH_AH_BPh), 4.48 (2H, s, CH_2Ph), 3.96 (1H, br d, J = 4.1 Hz, C(7)*H*OH), 3.91 (1H, dq, J = 8.3 & 4.3 Hz, C(3')*H*), 3.78 (3H, s, OCH_3), 3.21 (1H, dt ≡ q, J = 5.6 Hz, C(3)*H*), 2.56 – 2.46 (3H, m, C(2')H_2 & C(4')*H*CH_3), 2.34 – 2.27 (2H, m, C(4)H_2), 1.91 – 1.79 (2H, m, C(8)*H* & C*H*$(CH_3)_2$), 1.56 (3H, s, C(6)CH_3), 1.04 (3H, d, J = 6.9 Hz, C(8)HCH_3), 0.99 (3H, d, J = 5.9 Hz, CH$(CH_3)_A(CH_3)_B$), 0.98 (3H, d, J = 5.9 Hz, CH$(CH_3)_A(CH_3)_B$), 0.80 (3H, d, J = 6.9 Hz, C(4')HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 196.84 (C), 172.04 (C), 159.28 (C), 141.30 (C), 139.95 (C), 136.35 (CH), 134.70 (CH), 130.73 (CH), 129.33 (2 x CH), 128.53 (2 x CH), 127.90 (2 x CH), 127.53 (CH), 122.54 (CH), 118.64 (CH_2), 115.71 (CH_2), 113.86 (CH), 84.34 (CH), 78.43 (CH), 76.46 (CH), 75.06 (CH), 72.17 (CH_2), 71.99 (CH_2), 55.42 (CH_3), 40.68 (CH), 39.55 (CH), 37.19 (CH_2), 30.52 (CH), 29.12 (CH_2), 18.89 (CH_3), 18.09 (CH_3), 14.38 (CH_3), 13.45 (CH_3), 9.40 (CH_3); ***m/z*** (FAB, NOBA) 579 ($[M+H]^+$, 4 %), 460 (11), 307 (66), 154 (100), 137 (87); **HRMS** (FAB, NOBA) $[M+H]^+$ found 579.3686, $C_{36}H_{51}O_6$ requires 579.3686.

(3*R*,4*S*,5*Z*,7*S*,8*R*,9*R*,10*E*,13*S*)-9-Hydroxy-[13-(4'-methoxybenzyloxy)-8,10,14-trimethyloct-10-enyl]-3-(4''-methoxybenzyloxy)-4-methyl-oxocene-1-one 70

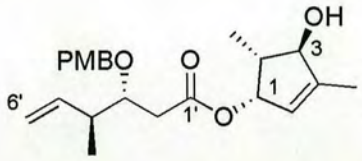


To a solution of ester **71** (80 mg, 0.13 mmol) in degassed CH_2Cl_2 (100 ml) was added Ti(^{i}OPr)$_4$ (5 μl, 10 mol%) and the solution was stirred for 30 min. Grubbs' 2 catalyst **159** (23 mg, 20 mol%) was then added and the reaction mixture was heated under reflux for 24 h. After the reaction mixture was cooled to RT, DMSO (2.0 ml) was added and the reaction mixture was stirred for a further 24 h. Volatiles were removed under reduced pressure to give the crude lactone. Purification by flash chromatography (20 % EtOAc in hexane) afforded a lactone **70** as a colourless oil (53 mg, 70 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.24; $[\alpha]_D$ = 1.22 (c 1.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3436 (OH), 1730 (C=O); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.22 (2H, d, J = 8.3 Hz, Ar*H*), 7.18 (2H, d, J = 8.3 Hz, Ar*H*), 6.78 (2H, J = 8.3 Hz, Ar*H*), 6.77 (2H, J = 8.3 Hz, Ar*H*), 5.49 – 5.46 (2H, m, C(5)*H* & C(7)*H*), 5.39 – 5.36 (2H, m, C(6)*H* & C(11)*H*), 4.42 (1H, d, J = 11.1 Hz, CH_AH$_B$Ar), 4.40 (2H, s, CH_2OPMB), 4.32 (1H, d, J = 11.1 Hz, CH$_A$$H_B$Ar), 4.19 (1H, br d, J = 6.1 Hz, C(9)*H*OH), 3.73 (1H, dq ≡ qn, J = 4.6 Hz, C(3)*H*), 3.72 (6H, s, 2 x OCH_3), 3.04 (1H, q, J = 5.8 Hz, C(13)*H*), 2.38 – 2.21 (3H, m, C(2)H_2 & C(4)*H*CH$_3$), 2.16 (2H, br t, J = 5.3 Hz, C(12)H_2), 2.15 – 2.13 (1H, m, C(8)CH_3), 1.81 – 1.69 (1H, m, C*H*(CH$_3$)$_2$), 1.70 (3H, s, C(10)CH_3), 1.00 (3H, d, J = 7.2 Hz, C(4)HCH_3), 0.95 (3H, d, J = 6.9 Hz, C(8)HCH_3), 0.88 (3H, d, J = 6.9 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 0.87 (3H, d, J = 6.9 Hz, CH(CH$_3$)$_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 171.27 (C), 158.03 (C), 150.09 (C), 149.76 (C), 132.22 (CH), 130.16 (C), 129.78 (C), 128.28 (4 x CH), 126.98 (CH), 124.24 (CH), 112.63 (4 x CH), 83.00 (CH), 82.75 (CH), 78.42 (CH), 77.15 (CH), 70.93 (CH_2), 70.35 (CH_2), 54.28 (2 x CH_3), 45.44 (CH), 38.78 (CH), 36.01 (CH_2), 32.93 (CH_2), 29.82 (CH), 17.45 (CH_3), 17.23 (CH_3), 14.15 (CH_3), 12.64 (CH_3), 11.05 (CH_3), ***m/z*** (FAB,

THIOG.) 581 ($[M+H]^+$, 1 %), 579(($[M-H]^+$, 2 %), 358 (7), 241 (39), 121 (100); **HRMS** (FAB, THIOG.) $[M-H]^+$ found 579.579.3320, $C_{35}H_{47}O_7$ requires 579.3322.

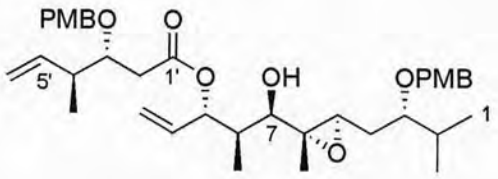
* Treatment of ester **71** with Grubbs' 2 catalyst **159** in the absence of $Ti(^iOPr)_4$ produces a 1:1 mixture of lactone **70** and by-product **326**.

(1*S*,2*R*,3*R*,4*Z*,3'R,4'*S*)-[3'-(4''-Methoxybenzyloxy)-4-methyl-hex-5'-enoic acid]-3-hydroxy-2,4,dimethyl-cyclopent-4-enyl ester 326



^{1}H NMR δ (360 MHz, $CDCl_3$) 7.22 (2H, d, J = 8.6 Hz, Ar*H*), 6.78 (2H, d, J = 8.6 Hz, Ar*H*), 5.72 (1H, ddd, J = 17.2, 10.8 & 7.2 Hz, C*H*=CH_2), 5.52-5.48 (2H, m, C(1)*H* & C(5)*H*), 4.98 (1H, d, J = 10.8 Hz, CH=C$H_{CIS}CH_{TRANS}$), 4.97 (1H, d, J = 17.2 Hz, CH=CH_{CIS}CH_{TRANS}), 4.42 (2H, s, CH_2Ar), 4.27 – 4.21 (1H, m, C(3)*H*OH), 3.82 (1H, dq, J = 8.3 & 4.3 Hz, C(3')*H*), 3.73 (3H, s, OCH_3), 2.47 – 2.28 (3H, m, C(2')H_2 & C(2)*H*), 2.08 (1H, dq, J = 6.6 Hz, C(4')*H*), 1.72 (3H, s, C(4)CH_3), 0.99 (3H, d, J = 7.2 Hz, C(2)HCH_3), 0.97 (3H, d, J = 6.6 Hz, C(4')HCH_3).

(3*S*,3'*R*,4'*S*,5*R*,6*R*,7*R*,8*R*,9*S*)-3-[3'-(4-Methoxybenzyloxy)-4'-methyl-hex-5-enoyl]-[3-(4-methoxybenzyloxy)-5,6-oxiranyl]-2,6,8-trimethylundec-5',10-dien-7-ol 328

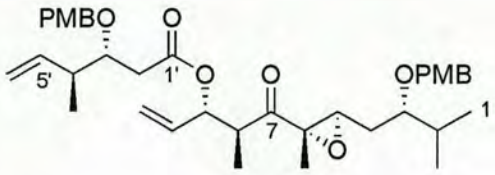


To solution of ester **71** (100 mg, 0.164 mmol) in benzene (10 ml) was added ^{t}BuOOH (100 µl, 576 µmol) and $VO(acac)_2$ (12 mg, 44.3 µmol) and the mixture was stirred at RT for 1 h. The volatiles were removed under reduced pressure to give the crude epoxide **328**. Flash chromatography (10 % EtOAc in hexane) afforded epoxide **328** as a 95:5 mixture of diastereomers (89 mg, 87 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.47; ν_{max} (neat) / cm^{-1} 3490 (OH), 1727 (C=O), 1612 (C=C); Major diastereomer: **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.61 – 7.40 (4H, m, Ar*H*), 7.04 (4H, d, J = 8.7 Hz, Ar*H*), 6.06 – 5.83 (2H, m, C(5')*H* & C(10)*H*), 5.56 – 5.37 (3H, m, C(11)H_2 & C(9)*H*), 5.23 (1H, d, J = 11.2 Hz, C(6')$H_{TRANS}H_{CIS}$), 5.22 (1H, d, J = 17.2 Hz, C(6')$H_{TRANS}H_{CIS}$), 4.69 – 4.61 (4H, m, 2 x CH_2Ar), 4.09 (1H, dq ≡ qn, J = 4.0 Hz, C(3')*H*), 3.96 (1H, d, J = 3.0 Hz, C(9)*H*), 3.93 (6H, s, 2 x OCH_3), 3.62 – 3.41 (2H, m, C(5)*H* & C(3)*H*), 2.72 – 2.64 (3H, m, C(4')*H* & C(2')H_2), 2.38 – 2.02 (2H, m, C(8)*H* & C(2)*H*), 1.95 (2H, br t, J = 5.8 Hz, C(4)H_2), 1.40 (3H, s, C(6)CH_3), 1.22 (3H, d, J = 6.9 Hz, C(4')HCH_3), 1.14 (3H, d, J = 6.8 Hz, C(2)H(CH_3)$_A$(CH_3)$_B$), 1.13 (3H, d, J = 6.8 Hz, C(2)H(CH_3)$_A$(CH_3)$_B$), 0.98 (3H, d, J = 6.7 Hz, C(8)HCH_3); Minor diastereomer diagnostic peak: 1.42 (3H, s, C(6)CH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 171.25 (C), 158.90 (C), 158.87 (C), 140.85 (CH), 136.20 (CH), 130.76 (C), 130.41 (C), 130.33 (4 x CH), 119.92 (CH_2), 116.53 (CH_2), 114.73 (4 x CH), 83.10 (CH), 82.57 (CH),* 80.27 (CH),* 78.49 (CH), 77.31 (CH), 77.01 (CH),* 72.43 (CH_2), 71.44 (CH_2), 70.94 (CH), 61.02 (C), 57.81 (CH), 56.26 (2 x CH_3), 41.79 (CH), 39.13 (CH), 38.79 (CH_2), 38.09 (CH_2),* 31.73 (CH), 30.44 (CH_2), 30.00 (CH_2),* 19.58 (CH_3), 18.63 (CH_3), 16.56 (CH_3), 16.21 (CH_3), 10.53 (CH_3); ***m/z*** (FAB, THIOG.) 623 ([M-H]$^+$, 9%), 361 (7), 263 (30), 241 (40), 121 (100); **HRMS** (FAB, THIOG.) [M-H]$^+$ found 623.3583, $C_{37}H_{51}O_8$ requires 623.3584.

* Indicates minor diastereomer.

(3*S*,3'*R*,4'*S*,5*R*,6*R*,8*R*,9*S*)-3-[3'-(4-Methoxybenzyloxy)-4'-methyl-hex-5-enoyl]-[3-(4-methoxybenzyloxy)-5,6-oxiranyl]-2,6,8-trimethylundec-5',10-dien-7-one

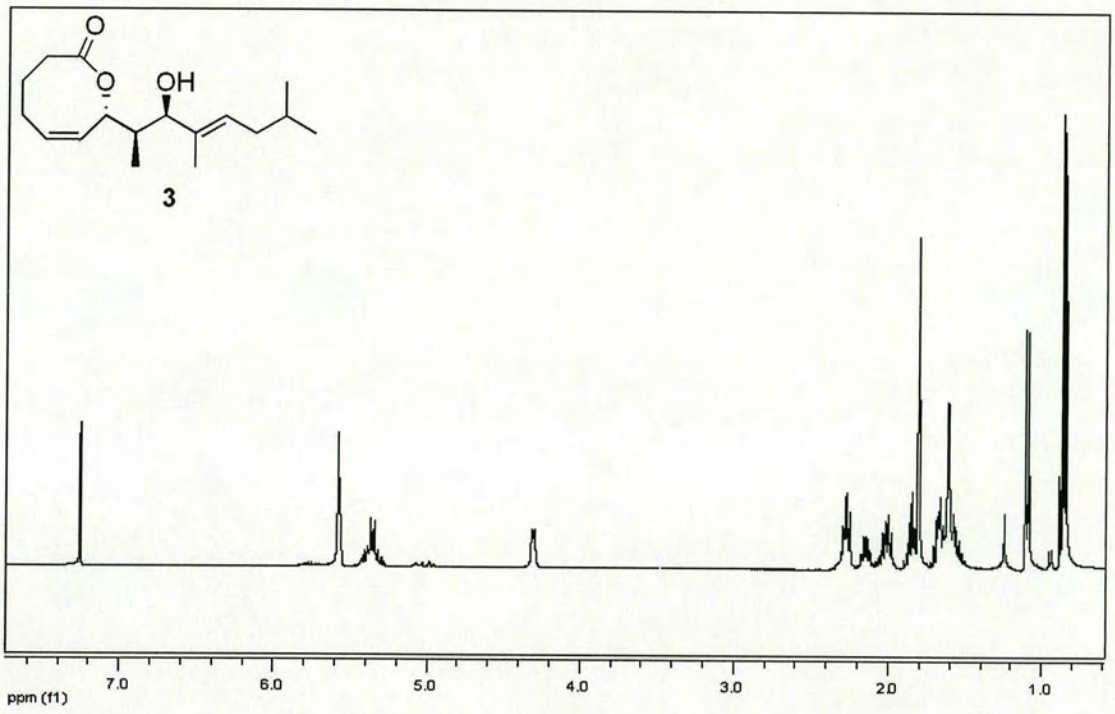
328



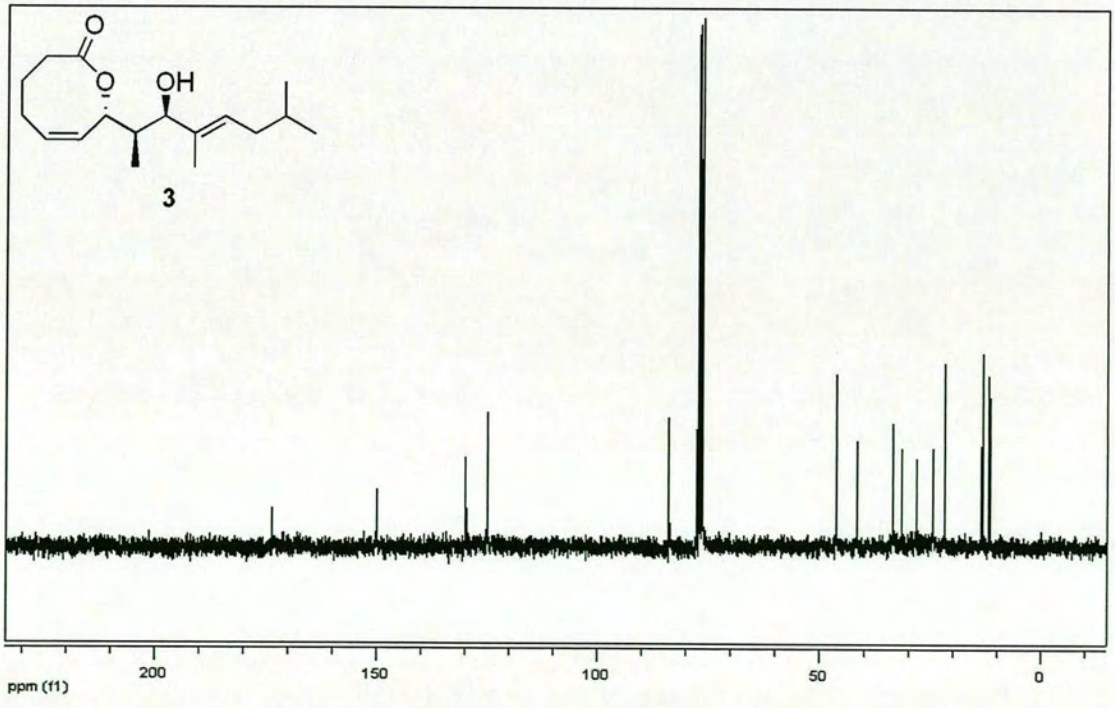
To a solution of epoxide **328** (60 mg, 0.097 mmol) in CH_2Cl_2 (5 ml) was added Dess Martin periodinane (255 mg, 0.60 mol) and the suspension was stirred at RT for 3 h. The solvent was exchanged on a rotary evaporator so that the solvent did not go dry. The resultant white suspension was filtered through a short plug of silica to provide ketone **330** as a colourless oil (58 mg, 98 %); $\mathbf{R_f}$ (20 % EtOAc in hexane) = 0.59; $[\alpha]_D$ = -0.35 (c 1.5, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1735 (C=O), 1711 (C=O), 1612 (C=C); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.29 – 7.23 (4H, m, Ar*H*), 6.86 (4H, d, J = 8.7 Hz, Ar*H*), 5.69 (1H, ddd, J = 17.1, 10.3 & 6.9 Hz, C(10)*H*), 5.67 (1H, ddd, J = 17.2, 10.5 & 6.7 Hz, C(5')*H*), 5.49 – 5.28 (3H, m, C(11)H_2 & C(9)*H*), 5.01 (1H, d, J = 17.2 Hz, C(6')$H_{TRANS}H_{CIS}$), 4.98 (1H, d, J = 10.5 Hz, C(6')$H_{TRANS}H_{CIS}$), 4.46 – 4.34 (4H, m, 2 x CH_2Ar), 4.06 (1H, dq ≡ qn, J = 4.0 Hz, C(3')*H*), 3.81 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.32– 3.28 (1H, m, C(3)*H*), 3.21 (1H, br t, J = 6.8 Hz, C(5)*H*), 2.91 (1H, dq, J = 7.1 & 6.9 Hz, C(8)*H*), 2.40 – 2.32 (1H, m, C(4')*H*), 2.29 (2H, br t, J = 5.9 Hz, C(2')H_2), 2.08 – 1.96 (1H, m, C(2)*H*), 1.86 – 1.64 (2H, m, C(4)H_2), 1.42 (3H, s, C(6)CH_3), 1.00 (3H, d, J = 6.7 Hz, C(8)HCH_3), 0.96 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$(CH_3)$_B$), 0.93 (3H, d, J = 6.8 Hz, C(2)H(CH_3)$_A$(CH_3)$_B$), 0.92 (3H, d, J = 6.7 Hz, C(4')HCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 211.02 (C), 170.89 (C), 159.34 (C), 159.22 (C), 139.98 (CH), 133.93 (CH), 130.92 (C), 130.76 (C), 129.64 (CH), 129.59 (CH), 129.49 (CH), 129.43 (CH), 120.30 (CH_2), 115.54 (CH_2),113.94 (CH), 113.92 (CH), 113.81 (CH), 113.78 (CH), 81.73 (CH), 79.01 (CH), 75.75 (CH), 72.13 (CH_2), 71.30 (CH_2), 62.73 (C), 57.74 (CH), 55.44 (CH_3), 55.42 (CH_3), 41.37 (CH), 41.35 (CH), 37.24 (CH_2), 31.11 (CH), 29.35 (CH_2), 18.79 (CH_3), 18.16 (CH_3), 15.23 (CH_3), 13.85 (CH_3), 13.33 (CH_3); ***m/z*** (FAB, NOBA) 621 ([M-H]$^+$, 7 %), 501 (25),

460 (26), 309 (14), 154 (100); **HRMS** (FAB, NOBA) $[M-H]^+$ found 621.3427, $C_{37}H_{49}O_8$ requires 621.3427.

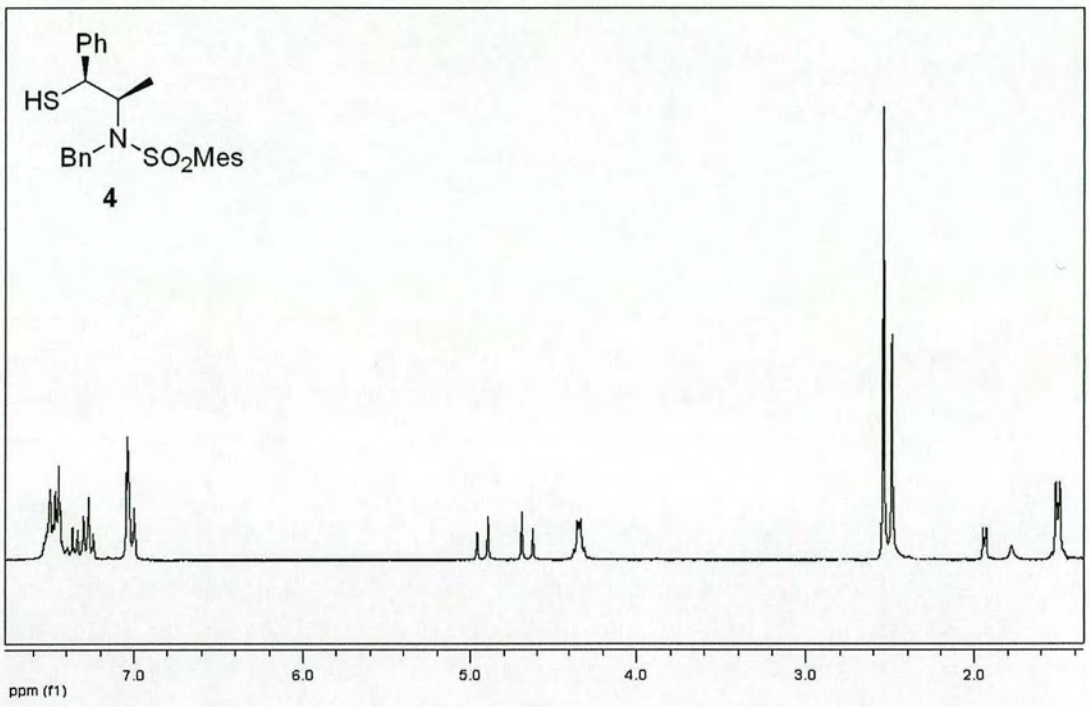
^{1}H NMR δ (360 MHz, $CDCl_3$) for lactone **3**



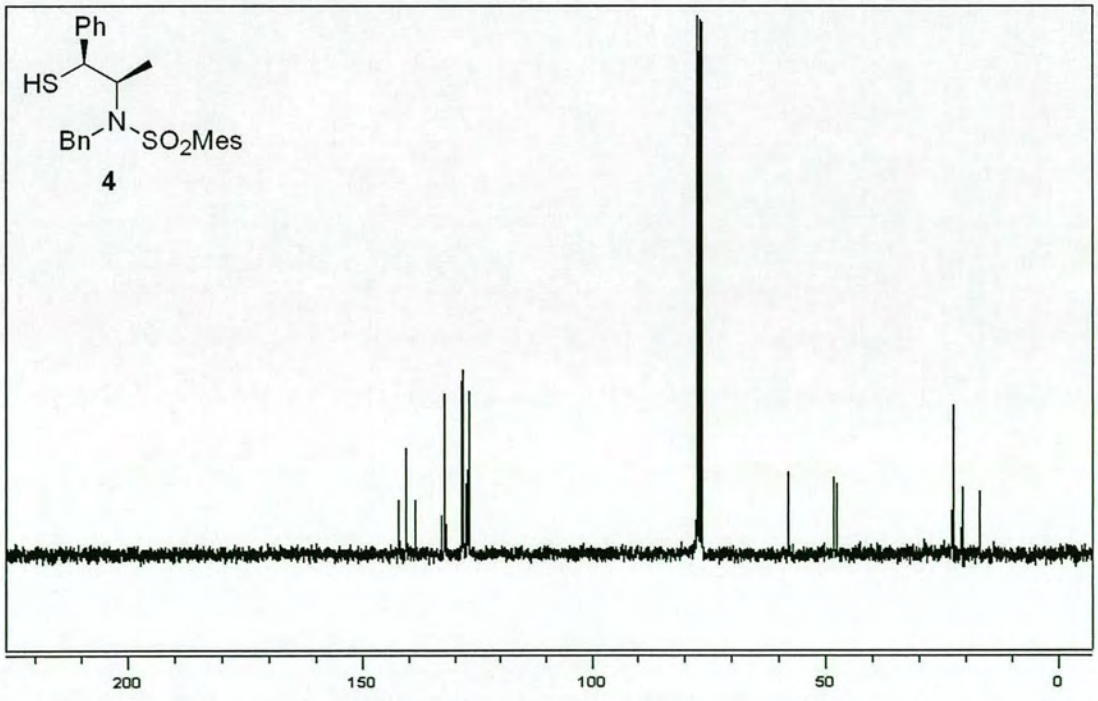
^{13}C NMR δ (90.5 MHz, $CDCl_3$) for lactone **3**



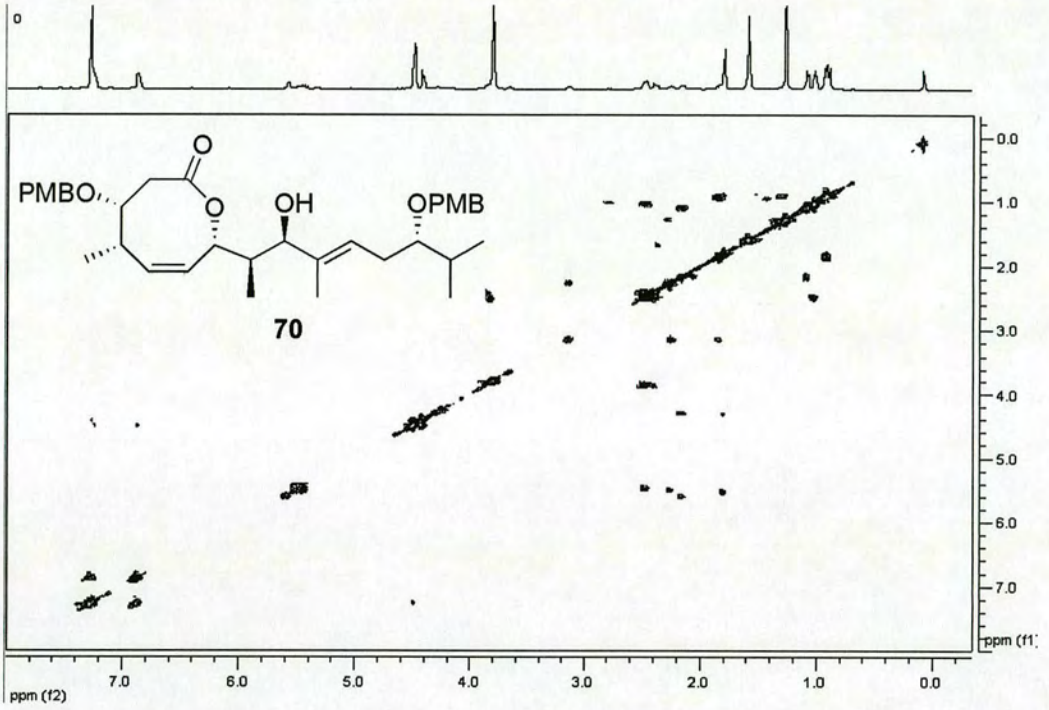
^{1}H NMR δ (360 MHz, $CDCl_3$) for thiol **4**

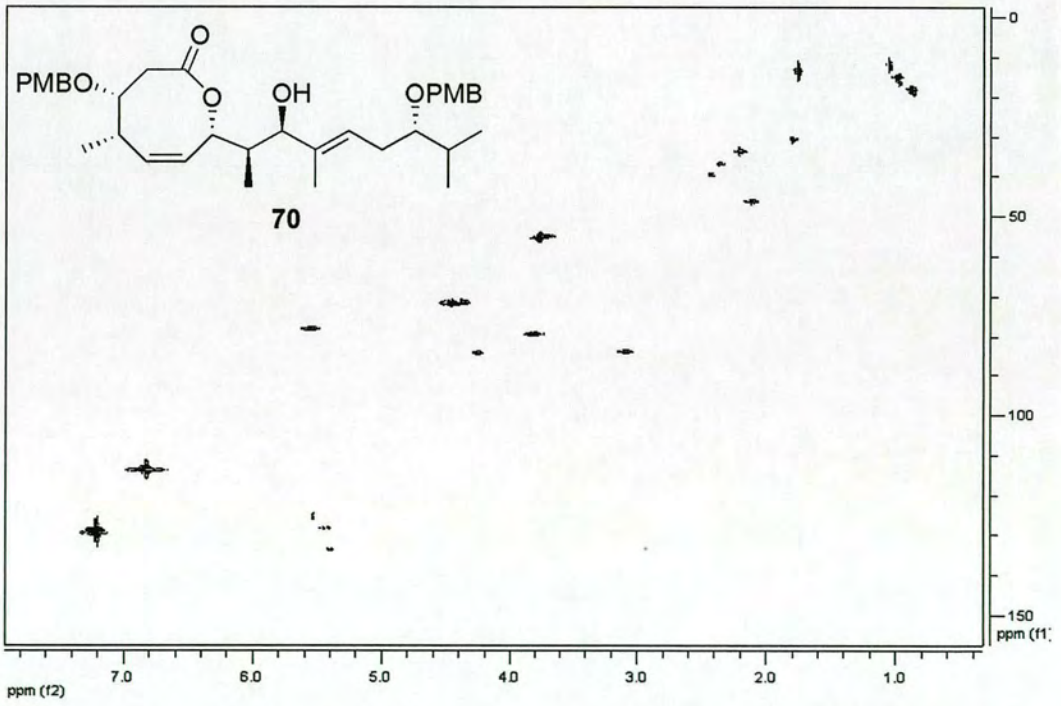


^{13}C NMR δ (90.5 MHz, $CDCl_3$) for thiol **4**



600 MHz COSY and HSQC spectra for lactone **70**





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ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Aq	aqueous
Ar	aryl
Bn	benzyl
^{c}Hex	cylcohexyl
DEAD	diethylazocarboxylate
DIAD	diisopropylazocarbxylate
DCC	dicyclohexylcarbodiimide
DDQ	dichlorodicyanoquinone
DMF	*N,N*-dimethylformamide
DMAPO	4-dimethylaminopyridine oxide
DMAP	4-dimethylaminopyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H) pyrimidone
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
d.s.	diastereoselectivity
e.e.	enantiomeric excess (i.e. % major diastereomer - % minor diastereomer)
EI	electron impact ionisation
Et	ethyl
FAB	fast atom bombardment
Fmoc	Fluorenylmethyloxycarbonyl
HMDS	hexamethyldisilazide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HWE	Horner-Wadsworth Emmons
IBX	iodobenzoic acid
IR	infra red
LDA	lithium diisopropylamine

Me	methyl
Mes	mesityl
mp	melting point
Ms, mesylate	methane sulfonate
MTPA	methoxytrifluoromethylphenylacetic acid
NAC	*N*-acetyl-cysteamine
P	unspecified protecting group
PMB	4-methoxybenzyl
ppm	parts per million
Pr	propyl
RCM	ring closing metathesis
R_f	retention factor
RT	room temperature
R_t	retention time
sat.	saturated
Tf, triflate	trifluoromethanesulfonate
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts, tosyl	toluenesulfonate

APPENDICES

CRYSTAL STRUCTURE DATA

APPENDIX 1: CRYSTAL STRUCTURE DATA OF ISOQUINOLONE 235

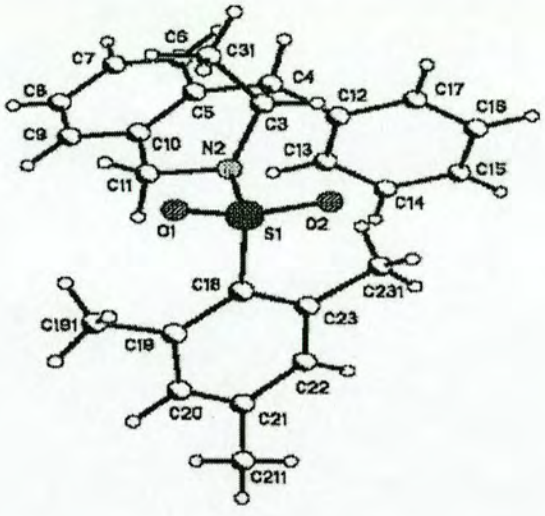

Figure 30: *Crystal structure of isoquinolone* ***235***

PART A *Crystal data*

Empirical formula	$C_{25}H_{27}NO_2S$
Formula weight	405.56
Wavelength	0.71073 Å
Temperature	150 K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.3591(14) Å alpha = 90 deg
	b = 10.6265(16) Å beta = 90 deg.
	c = 21.344(3) Å gamma = 90 deg.
Volume	2122.7(5) $Å^3$
Number of reflections for cell	6188 ($2 < \theta < 29$ deg.)
Z	4
Density (calculated)	1.269 Mg/m^3
Absorption coefficient	0.174 mm^{-1}
F(000)	864.000

PART B *Data collection*

Crystal description	colourless block
Crystal size	0.63 x 0.54 x 0.25 mm
Theta range for data collection	1.908 to 28.824 deg.
Index ranges	-12<=h<=12, -14<=k<=14, -27<=l<=28
Reflections collected	18994
Independent reflections	5181 [R(int) = 0.03]
Scan type	\w
Absorption correction	Semi-empirical from equivalents (T_{min}= 0.826, T_{max}=1.000)

PART C *Solution and refinement*

Solution	Patterson (DIRDIF)
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	Geom
Hydrogen atom treatment	Noref
Data	5180
Parameters	263
Goodness-of-fit on F^2	1.0267
R	0.0435
Rw	0.1120
Absolute structure parameter	-0.02(7)
Final maximum delta/sigma	0.000281
Weighting scheme	Sheldrick Weights
Largest diff. peak and hole	0.77 and -0.44 e.A^{-3}

Table 12: *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for* ***235****. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor*

	x	y	z	U(eq)
S(1)	718(1)	417(1)	1816(1)	22
O(1)	1141(2)	1227(1)	2322(1)	29
O(2)	-703(2)	-91(1)	1848(1)	31
N(2)	1825(2)	-788(1)	1753(1)	20
C(3)	1472(2)	-1929(2)	2125(1)	19
C(4)	2236(2)	-3043(2)	1809(1)	19
C(5)	3820(2)	-2768(2)	1747(1)	21
C(6)	4804(2)	-3753(2)	1717(1)	26
C(7)	6257(2)	-3522(2)	1670(1)	29
C(8)	6759(2)	-2293(2)	1664(1)	27
C(9)	5801(2)	-1306(2)	1695(1)	24
C(10)	4321(2)	-1533(2)	1730(1)	21
C(11)	3346(2)	-409(2)	1772(1)	23
C(12)	1520(2)	-3391(2)	1189(1)	20
C(13)	2101(2)	-3081(2)	609(1)	28
C(14)	1371(3)	-3362(2)	58(1)	34
C(15)	78(3)	-3979(2)	82(1)	36
C(16)	-510(2)	-4305(2)	654(1)	35
C(17)	212(2)	-4008(2)	1204(1)	27
C(18)	983(2)	1217(2)	1095(1)	22
C(19)	1699(2)	2384(2)	1069(1)	26
C(20)	1835(3)	2950(2)	482(1)	33
C(21)	1336(3)	2405(2)	-67(1)	37
C(22)	653(3)	1251(2)	-21(1)	34
C(23)	448(2)	636(2)	547(1)	27
C(31)	1865(2)	-1816(2)	2819(1)	26
C(191)	2330(3)	3086(2)	1618(1)	36
C(211)	1528(4)	3051(3)	-688(1)	59
C(231)	-369(3)	-581(2)	539(1)	36

Table 13: *Bond lengths (Å) for* ***235***

Bond	Length (Å)	Bond	Length (Å)
S(1)-O(1)	1.4365(15)	C(14)-H(141)	1.000
S(1)-O(2)	1.4371(15)	C(15)-C(16)	1.383(3)
S(1)-N(2)	1.6524(15)	C(15)-H(151)	1.000
S(1)-C(18)	1.7760(19)	C(16)-C(17)	1.392(3)
N(2)-C(3)	1.487(2)	C(16)-H(161)	1.000
N(2)-C(11)	1.480(2)	C(17)-H(171)	1.000
C(3)-C(4)	1.538(2)	C(18)-C(19)	1.412(3)
C(3)-C(31)	1.531(3)	C(18)-C(23)	1.413(3)
C(3)-H(31)	1.000	C(19)-C(20)	1.396(3)
C(4)-C(5)	1.517(2)	C(19)-C(191)	1.508(3)
C(4)-C(12)	1.528(2)	C(20)-C(21)	1.387(3)
C(4)-H(41)	1.000	C(20)-H(201)	1.000
C(5)-C(6)	1.396(3)	C(21)-C(22)	1.386(3)
C(5)-C(10)	1.395(2)	C(21)-C(211)	1.505(3)
C(6)-C(7)	1.386(3)	C(22)-C(23)	1.391(3)
C(6)-H(61)	1.000	C(22)-H(221)	1.000
C(7)-C(8)	1.388(3)	C(23)-C(231)	1.503(3)
C(7)-H(71)	1.000	C(31)-H(311)	1.000
C(8)-C(9)	1.382(3)	C(31)-H(312)	1.000
C(8)-H(81)	1.000	C(31)-H(313)	1.000
C(9)-C(10)	1.408(3)	C(191)-H(1911)	1.000
C(9)-H(91)	1.000	C(191)-H(1912)	1.000
C(10)-C(11)	1.505(3)	C(191)-H(1913)	1.000
C(11)-H(111)	1.000	C(211)-H(2111)	1.000
C(11)-H(112)	1.000	C(211)-H(2112)	1.000
C(12)-C(13)	1.392(3)	C(211)-H(2113)	1.000
C(12)-C(17)	1.389(3)	C(231)-H(2311)	1.000
C(13)-C(14)	1.393(3)	C(231)-H(2312)	1.000
C(13)-H(131)	1.000	C(231)-H(2313)	1.000
C(14)-C(15)	1.378(4)		

Table 14: *Bond angles (degrees) for* ***235***

Bond	Angle (degrees)	Bond	Angle (degrees)
O(1)-S(1)-O(2)	116.41(9)	C(10)-C(9)-H(91)	119.659
O(1)-S(1)-N(2)	110.70(8)	C(5)-C(10)-C(9)	119.59(16)
O(2)-S(1)-N(2)	107.04(8)	C(5)-C(10)-C(11)	122.75(16)
O(1)-S(1)-C(18)	109.07(9)	C(9)-C(10)-C(11)	117.62(16)
O(2)-S(1)-C(18)	110.44(9)	N(2)-C(11)-C(10)	111.47(15)
N(2)-S(1)-C(18)	102.23(8)	N(2)-C(11)-H(111)	108.967
S(1)-N(2)-C(3)	116.68(12)	C(10)-C(11)-H(111)	108.963
S(1)-N(2)-C(11)	112.96(12)	N(2)-C(11)-H(112)	108.975
C(3)-N(2)-C(11)	114.86(14)	C(10)-C(11)-H(112)	108.966
N(2)-C(3)-C(4)	106.89(14)	H(111)-C(11)-H(112)	109.476
N(2)-C(3)-C(31)	113.57(15)	C(4)-C(12)-C(13)	122.73(17)
C(4)-C(3)-C(31)	111.89(16)	C(4)-C(12)-C(17)	118.77(17)
N(2)-C(3)-H(31)	109.348	C(13)-C(12)-C(17)	118.47(18)
C(4)-C(3)-H(31)	111.136	C(12)-C(13)-C(14)	120.6(2)
C(31)-C(3)-H(31)	104.057	C(12)-C(13)-H(131)	119.714
C(3)-C(4)-C(5)	110.13(14)	C(14)-C(13)-H(131)	119.719
C(3)-C(4)-C(12)	111.21(14)	C(13)-C(14)-C(15)	120.1(2)
C(5)-C(4)-C(12)	113.55(16)	C(13)-C(14)-H(141)	119.929
C(3)-C(4)-H(41)	109.334	C(15)-C(14)-H(141)	119.933
C(5)-C(4)-H(41)	106.769	C(14)-C(15)-C(16)	120.1(2)
C(12)-C(4)-H(41)	105.591	C(14)-C(15)-H(151)	119.971
C(4)-C(5)-C(6)	120.31(17)	C(16)-C(15)-H(151)	119.941
C(4)-C(5)-C(10)	120.83(16)	C(15)-C(16)-C(17)	119.6(2)
C(6)-C(5)-C(10)	118.85(17)	C(15)-C(16)-H(161)	120.189
C(5)-C(6)-C(7)	121.24(19)	C(17)-C(16)-H(161)	120.172
C(5)-C(6)-H(61)	119.392	C(12)-C(17)-C(16)	121.1(2)
C(7)-C(6)-H(61)	119.369	C(12)-C(17)-H(171)	119.473
C(6)-C(7)-C(8)	119.95(18)	C(16)-C(17)-H(171)	119.447
C(6)-C(7)-H(71)	120.006	S(1)-C(18)-C(19)	121.37(15)
C(8)-C(7)-H(71)	120.049	S(1)-C(18)-C(23)	117.31(15)
C(7)-C(8)-C(9)	119.66(18)	C(19)-C(18)-C(23)	121.32(18)
C(7)-C(8)-H(81)	120.16	C(18)-C(19)-C(20)	117.17(19)
C(9)-C(8)-H(81)	120.185	C(18)-C(19)-C(191)	126.18(19)
C(8)-C(9)-C(10)	120.70(18)	C(20)-C(19)-C(191)	116.65(19)
C(8)-C(9)-H(91)	119.641	C(19)-C(20)-C(21)	123.2(2)

Bond	Angle (degrees)	Bond	Angle (degrees)
C(19)-C(20)-H(201)	118.408	H(1912)-C(191)-H(1913)	109.489
C(21)-C(20)-H(201)	118.406	C(21)-C(211)-H(2111)	109.464
C(20)-C(21)-C(22)	117.8(2)	C(19)-C(191)-H(1912)	109.474
C(20)-C(21)-C(211)	120.9(2)	C(21)-C(211)-H(2112)	109.461
C(3)-C(31)-H(312)	109.464	H(2111)-C(211)-H(2112)	109.478
H(311)-C(31)-H(312)	109.481	C(21)-C(211)-H(2113)	109.46
C(3)-C(31)-H(313)	109.468	H(2111)-C(211)-H(2113)	109.491
H(311)-C(31)-H(313)	109.474	H(2112)-C(211)-H(2113)	109.472
H(312)-C(31)-H(313)	109.477	C(23)-C(231)-H(2311)	109.467
C(19)-C(191)-H(1911)	109.457	C(23)-C(231)-H(2312)	109.466
C(19)-C(191)-H(1912)	109.474	H(2311)-C(231)-H(2312)	109.472
H(1911)-C(191)-H(1912)	109.481	C(23)-C(231)-H(2313)	109.47
C(19)-C(191)-H(1913)	109.465	H(2311)-C(231)-H(2313)	109.477
H(1911)-C(191)-H(1913)	109.46	H(2312)-C(231)-H(2313)	109.475

Symmetry transformations used to generate equivalent atoms:

	U11	U22	U33	U23	U13	U12
S(1)	19(1)	20(1)	26(1)	-1(1)	4(1)	2(1)
O(1)	33(1)	25(1)	28(1)	-4(1)	4(1)	5(1)
O(2)	19(1)	28(1)	45(1)	1(1)	6(1)	1(1)
N(2)	16(1)	18(1)	25(1)	2(1)	2(1)	0(1)
C(3)	19(1)	18(1)	21(1)	2(1)	4(1)	-3(1)
C(4)	17(1)	18(1)	21(1)	0(1)	-2(1)	-1(1)
C(5)	17(1)	23(1)	22(1)	1(1)	1(1)	0(1)
C(6)	23(1)	21(1)	35(1)	1(1)	-3(1)	1(1)
C(7)	22(1)	30(1)	34(1)	0(1)	-3(1)	7(1)
C(8)	16(1)	37(1)	29(1)	5(1)	-1(1)	1(1)
C(9)	19(1)	26(1)	26(1)	4(1)	0(1)	-3(1)
C(10)	18(1)	23(1)	21(1)	2(1)	1(1)	0(1)
C(11)	18(1)	21(1)	31(1)	3(1)	4(1)	-2(1)
C(12)	18(1)	21(1)	22(1)	-3(1)	0(1)	3(1)
C(13)	23(1)	33(1)	28(1)	1(1)	3(1)	4(1)
C(14)	36(1)	44(1)	22(1)	0(1)	4(1)	14(1)
C(15)	35(1)	45(1)	28(1)	-12(1)	-8(1)	13(1)
C(16)	24(1)	43(1)	37(1)	-11(1)	-6(1)	-4(1)
C(17)	24(1)	32(1)	27(1)	-4(1)	-1(1)	-5(1)
C(18)	21(1)	20(1)	24(1)	3(1)	0(1)	2(1)
C(19)	26(1)	23(1)	31(1)	-2(1)	1(1)	0(1)
C(20)	36(1)	27(1)	37(1)	4(1)	3(1)	-6(1)
C(21)	46(1)	36(1)	30(1)	3(1)	4(1)	4(1)
C(22)	41(1)	34(1)	27(1)	-5(1)	-6(1)	4(1)
C(23)	25(1)	23(1)	32(1)	-3(1)	-6(1)	2(1)
C(31)	30(1)	26(1)	22(1)	2(1)	2(1)	-5(1)
C(191)	44(1)	26(1)	37(1)	-3(1)	-5(1)	-13(1)
C(211)	93(3)	53(2)	31(1)	8(1)	10(1)	-3(2)
C(231)	37(1)	26(1)	44(1)	-5(1)	-14(1)	-4(1)

Table 15: *Anisotropic displacement parameters (A^2 x 10^3) for* ***235****. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12]*

	x	y	Z	U(eq)
H(31)	413	-2054	2127	23
H(41)	2147	-3806	2080	23
H(61)	4454	-4641	1729	32
H(71)	6944	-4241	1640	35
H(81)	7808	-2124	1637	33
H(91)	6163	-420	1693	28
H(111)	3536	44	2174	28
H(112)	3547	165	1411	28
H(131)	3052	-2653	588	34
H(141)	1787	-3114	-356	41
H(151)	-436	-4192	-315	43
H(161)	-1450	-4752	671	42
H(171)	-216	-4244	1617	33
H(201)	2316	3788	455	40
H(221)	294	844	-413	41
H(311)	1601	-2612	3041	32
H(312)	2916	-1670	2860	32
H(313)	1334	-1094	3009	32
H(1911)	2774	3887	1467	43
H(1912)	1558	3284	1926	43
H(1913)	3075	2553	1823	43
H(2111)	1103	2521	-1027	71
H(2112)	1039	3888	-679	71
H(2113)	2570	3175	-771	71
H(2311)	-631	-796	97	43
H(2312)	-1257	-491	795	43
H(2313)	239	-1267	718	43

APPENDIX 2: CRYSTAL STRUCTURE DATA OF THIOACETATE 237

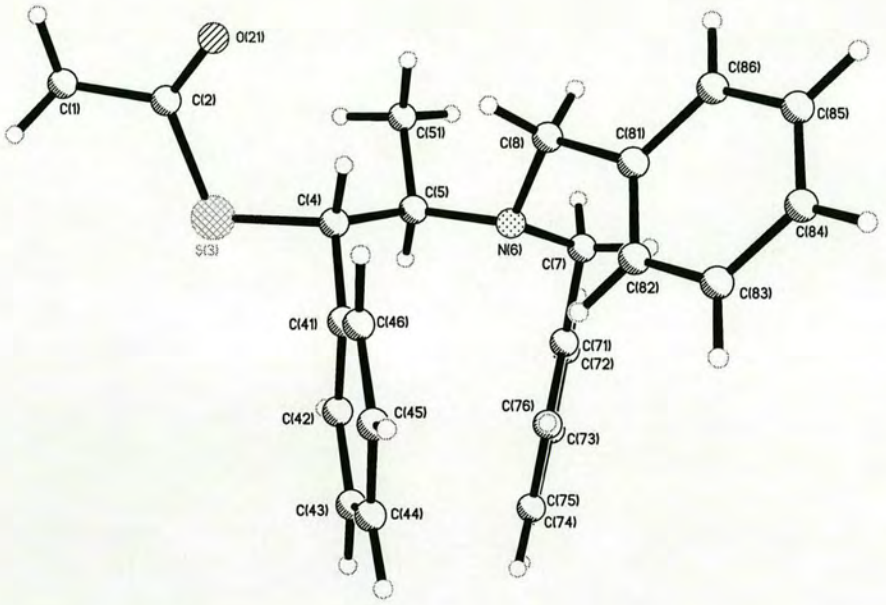

Figure 31: *Crystal structure of thioacetate* ***237***

PART A *Crystal data*

Empirical formula	$C_{25}H_{27}NOS$
Formula weight	389.56
Wavelength	0.71073 Å
Temperature	150 K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 7.8897(5) Å alpha = 90 deg.
	b = 14.1144(9) Å beta = 90 deg.
	c = 19.2079(13) Å gamma = 90 deg.
Volume	
Number of reflections for cell	5507 ($3 < \theta < 29$ deg)
Z	4
Density (calculated)	1.210 Mg/m^3
Absorption coefficient	0.166 mm^{-1}
F(000)	832

PART B *Data collection*

Crystal description	colourless tablet
Crystal size	0.67 x 0.65 x 0.24 mm
Theta range for data collection	1.790 to 28.844 deg.
Index ranges	-10<=h<=10, -18<=k<=18, 24<=l<=25
Reflections collected	19372
Independent reflections	5244 [R(int) = 0.03]
Scan type	\f & ω scans
Absorption correction	Semi-empirical from equivalents (T_{min}= 0.890, T_{max}=1.000)

PART C *Solution and refinement*

Solution	direct (SIR-92)
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	Geom.
Hydrogen atom treatment	Noref
Data	5227
Parameters	254
Goodness-of-fit on F2	0.9825
R	0.0433
Rw	0.1054
Absolute structure parameter	0.04(6)
Final maximum delta/sigma	0.000313
Weighting scheme	Calc

Table 16: *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **237**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor*

	x	y	z	U(eq)
C(1)	9161(3)	7469(2)	590(1)	41
C(2)	8008(2)	6630(1)	668(1)	30
S(3)	7813(1)	6265(1)	1552(1)	33
C(4)	6486(2)	5206(1)	1476(1)	24
C(5)	4675(2)	5392(1)	1745(1)	24
N(6)	3725(2)	4491(1)	1728(1)	21
C(7)	2260(2)	4487(1)	2201(1)	28
C(8)	3176(2)	4217(1)	1029(1)	26
O(21)	7291(2)	6233(1)	179(1)	41
C(41)	7370(2)	4397(1)	1846(1)	25
C(42)	7669(2)	4429(1)	2558(1)	32
C(43)	8399(3)	3666(2)	2895(1)	43
C(44)	8855(3)	2862(2)	2528(1)	44
C(45)	8617(3)	2836(1)	1819(1)	43
C(46)	7878(2)	3600(1)	1476(1)	34
C(51)	3808(3)	6207(1)	1357(1)	35
C(71)	2757(2)	4515(1)	2961(1)	25
C(72)	1944(2)	5128(1)	3419(1)	31
C(73)	2390(3)	5151(1)	4117(1)	39
C(74)	3662(3)	4567(2)	4365(1)	37
C(75)	4464(3)	3947(1)	3917(1)	33
C(76)	4004(2)	3913(1)	3218(1)	28
C(81)	2870(2)	3161(1)	954(1)	25
C(82)	3842(2)	2504(1)	1315(1)	30
C(83)	3621(3)	1537(1)	1200(1)	36
C(84)	2411(3)	1225(1)	733(1)	41
C(85)	1434(3)	1870(2)	380(1)	41
C(86)	1656(2)	2838(1)	484(1)	32

Table 17: *Bond lengths (Å) for* ***237***

Bond	Length (Å)	Bond	Length (Å)
C(1)-H(13)	1.000	C(45)-H(451)	1.000
C(1)-H(12)	1.000	C(45)-C(46)	1.392(3)
C(1)-H(11)	1.000	C(46)-H(461)	1.000
C(1)-C(2)	1.501(3)	C(51)-H(513)	1.000
C(2)-O(21)	1.232(2)	C(51)-H(512)	1.000
C(2)-S(3)	1.7805(18)	C(51)-H(511)	1.000
S(3)-C(4)	1.8306(16)	C(71)-C(76)	1.390(2)
C(4)-H(41)	1.000	C(71)-C(72)	1.391(2)
C(4)-C(41)	1.515(2)	C(72)-H(721)	1.000
C(4)-C(5)	1.543(2)	C(72)-C(73)	1.387(3)
C(5)-H(51)	1.000	C(73)-H(731)	1.000
C(5)-C(51)	1.532(2)	C(73)-C(74)	1.383(3)
C(5)-N(6)	1.477(2)	C(74)-H(741)	1.000
N(6)-C(8)	1.462(2)	C(74)-C(75)	1.381(3)
N(6)-C(7)	1.470(2)	C(75)-H(751)	1.000
C(7)-H(72)	1.000	C(75)-C(76)	1.392(2)
C(7)-H(71)	1.000	C(76)-H(761)	1.000
C(7)-C(71)	1.512(2)	C(81)-C(86)	1.394(2)
C(8)-H(82)	1.000	C(81)-C(82)	1.388(2)
C(8)-H(81)	1.000	C(82)-H(821)	1.000
C(8)-C(81)	1.517(2)	C(82)-C(83)	1.394(3)
C(41)-C(46)	1.390(2)	C(83)-H(831)	1.000
C(41)-C(42)	1.390(2)	C(83)-C(84)	1.383(3)
C(42)-H(421)	1.000	C(84)-H(841)	1.000
C(42)-C(43)	1.381(3)	C(84)-C(85)	1.372(3)
C(43)-H(431)	1.000	C(85)-H(851)	1.000
C(43)-C(44)	1.384(3)	C(85)-C(86)	1.393(3)
C(44)-H(441)	1.000	C(86)-H(861)	1.000
C(44)-C(45)	1.376(3)		

Table 18: *Bond angles (degrees) for* ***237***

Bond	Angle (degrees)	Bond	Angle (degrees)
H(13)-C(1)-H(12)	109.475	H(81)-C(8)-N(6)	108.528
H(13)-C(1)-H(11)	109.475	C(81)-C(8)-N(6)	113.21(13)
H(12)-C(1)-H(11)	109.478	C(46)-C(41)-C(42)	118.74(16)
H(13)-C(1)-C(2)	109.465	C(46)-C(41)-C(4)	120.17(16)
H(12)-C(1)-C(2)	109.467	C(42)-C(41)-C(4)	121.08(15)
H(11)-C(1)-C(2)	109.466	H(421)-C(42)-C(43)	119.783
O(21)-C(2)-S(3)	123.80(14)	H(421)-C(42)-C(41)	119.781
O(21)-C(2)-C(1)	124.07(17)	C(43)-C(42)-C(41)	120.44(18)
S(3)-C(2)-C(1)	112.13(14)	H(431)-C(43)-C(44)	119.699
C(4)-S(3)-C(2)	102.11(8)	H(431)-C(43)-C(42)	119.695
H(41)-C(4)-C(41)	108.232	C(44)-C(43)-C(42)	120.61(19)
H(41)-C(4)-C(5)	105.011	H(441)-C(44)-C(45)	120.283
C(41)-C(4)-C(5)	113.43(13)	H(441)-C(44)-C(43)	120.285
H(41)-C(4)-S(3)	110.456	C(45)-C(44)-C(43)	119.43(19)
C(41)-C(4)-S(3)	108.31(11)	H(451)-C(45)-C(46)	119.837
C(5)-C(4)-S(3)	111.33(11)	H(451)-C(45)-C(44)	119.839
H(51)-C(5)-C(51)	103.828	C(46)-C(45)-C(44)	120.3(2)
H(51)-C(5)-N(6)	107.977	H(461)-C(46)-C(41)	119.803
C(51)-C(5)-N(6)	114.16(14)	H(461)-C(46)-C(45)	119.804
H(51)-C(5)-C(4)	110.117	C(41)-C(46)-C(45)	120.39(19)
C(51)-C(5)-C(4)	112.19(14)	H(513)-C(51)-H(512)	109.474
N(6)-C(5)-C(4)	108.40(12)	H(513)-C(51)-H(511)	109.477
C(8)-N(6)-C(7)	109.43(13)	H(512)-C(51)-H(511)	109.476
C(8)-N(6)-C(5)	113.49(12)	H(513)-C(51)-C(5)	109.467
C(7)-N(6)-C(5)	112.88(13)	H(512)-C(51)-C(5)	109.466
H(72)-C(7)-H(71)	109.465	H(511)-C(51)-C(5)	109.467
H(72)-C(7)-C(71)	108.561	C(76)-C(71)-C(72)	118.80(15)
H(71)-C(7)-C(71)	108.562	C(76)-C(71)-C(7)	120.68(14)
H(72)-C(7)-N(6)	108.562	C(72)-C(71)-C(7)	120.50(16)
H(71)-C(7)-N(6)	108.564	H(721)-C(72)-C(73)	119.702
C(71)-C(7)-N(6)	113.08(14)	H(721)-C(72)-C(71)	119.701
H(82)-C(8)-H(81)	109.464	C(73)-C(72)-C(71)	120.60(17)
H(82)-C(8)-C(81)	108.53	H(731)-C(73)-C(74)	119.887
H(81)-C(8)-C(81)	108.531	H(731)-C(73)-C(72)	119.886
H(82)-C(8)-N(6)	108.529	C(74)-C(73)-C(72)	120.23(17)

Bond	Angle (degrees)	Bond	Angle (degrees)
H(741)-C(74)-C(75)	120.149	C(83)-C(82)-C(81)	120.43(17)
H(741)-C(74)-C(73)	120.152	H(831)-C(83)-C(84)	119.965
C(75)-C(74)-C(73)	119.70(17)	H(831)-C(83)-C(82)	119.964
H(751)-C(75)-C(76)	119.89	C(84)-C(83)-C(82)	120.07(19)
H(751)-C(75)-C(74)	119.889	H(841)-C(84)-C(85)	120.101
C(76)-C(75)-C(74)	120.22(18)	H(841)-C(84)-C(83)	120.101
H(761)-C(76)-C(71)	119.788	C(85)-C(84)-C(83)	119.80(18)
H(761)-C(76)-C(75)	119.789	H(851)-C(85)-C(86)	119.652
C(71)-C(76)-C(75)	120.42(16)	H(851)-C(85)-C(84)	119.654
C(86)-C(81)-C(82)	119.00(16)	C(86)-C(85)-C(84)	120.69(18)
C(86)-C(81)-C(8)	119.50(16)	H(861)-C(86)-C(85)	119.999
C(82)-C(81)-C(8)	121.40(15)	H(861)-C(86)-C(81)	119.999
H(821)-C(82)-C(83)	119.788	C(85)-C(86)-C(81)	120.00(18)
H(821)-C(82)-C(81)	119.782	H(841)-C(84)-C(83)	120.101

Symmetry transformations used to generate equivalent atoms:

	U11	U22	U33	U23	U13	U12
C(1)	43(1)	34(1)	44(1)	12(1)	10(1)	-6(1)
C(2)	29(1)	31(1)	32(1)	8(1)	6(1)	2(1)
S(3)	41(1)	32(1)	28(1)	5(1)	-3(1)	-16(1)
C(4)	25(1)	23(1)	23(1)	1(1)	0(1)	-7(1)
C(5)	27(1)	21(1)	23(1)	-1(1)	1(1)	-1(1)
N(6)	21(1)	25(1)	18(1)	-1(1)	1(1)	-2(1)
C(7)	22(1)	36(1)	25(1)	-1(1)	2(1)	-1(1)
C(8)	27(1)	30(1)	20(1)	2(1)	-3(1)	0(1)
O(21)	47(1)	46(1)	30(1)	6(1)	5(1)	-7(1)
C(41)	17(1)	26(1)	31(1)	5(1)	3(1)	-5(1)
C(42)	27(1)	38(1)	32(1)	4(1)	1(1)	3(1)
C(43)	29(1)	59(1)	42(1)	21(1)	5(1)	7(1)
C(44)	28(1)	40(1)	65(1)	22(1)	6(1)	3(1)
C(45)	33(1)	27(1)	69(1)	-1(1)	7(1)	-1(1)
C(46)	28(1)	31(1)	44(1)	-4(1)	2(1)	-5(1)
C(51)	37(1)	26(1)	41(1)	5(1)	0(1)	6(1)
C(71)	23(1)	28(1)	23(1)	-2(1)	5(1)	-6(1)
C(72)	31(1)	31(1)	32(1)	-5(1)	3(1)	3(1)
C(73)	45(1)	41(1)	31(1)	-12(1)	8(1)	3(1)
C(74)	47(1)	40(1)	23(1)	-2(1)	2(1)	-5(1)
C(75)	40(1)	34(1)	25(1)	3(1)	2(1)	3(1)
C(76)	34(1)	26(1)	24(1)	-1(1)	5(1)	0(1)
C(81)	23(1)	30(1)	20(1)	-3(1)	4(1)	-4(1)
C(82)	30(1)	30(1)	29(1)	-1(1)	-2(1)	-7(1)
C(83)	42(1)	31(1)	36(1)	2(1)	4(1)	-4(1)
C(84)	52(1)	34(1)	38(1)	-7(1)	7(1)	-15(1)
C(85)	42(1)	50(1)	30(1)	-9(1)	-2(1)	-19(1)
C(86)	29(1)	44(1)	25(1)	-2(1)	-1(1)	-6(1)

Table 19: *Anisotropic displacement parameters (A^2 x 10^3) for **237**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12]*

	x	y	z	U(eq)
H(11)	9234	7650	87	49
H(12)	8701	8013	864	49
H(13)	10316	7303	766	49
H(41)	6340	5026	976	29
H(51)	4714	5616	2239	29
H(71)	1543	5053	2097	33
H(72)	1588	3897	2115	33
H(81)	4072	4410	690	31
H(82)	2098	4558	920	31
H(421)	7354	5007	2829	39
H(431)	8599	3695	3409	52
H(441)	9354	2305	2776	53
H(451)	8976	2264	1548	52
H(461)	7712	3575	960	41
H(511)	2642	6303	1548	42
H(512)	4484	6801	1419	42
H(513)	3734	6049	850	42
H(721)	1029	5557	3243	38
H(731)	1789	5590	4443	47
H(741)	4001	4595	4866	44
H(751)	5378	3520	4095	39
H(761)	4574	3453	2898	34
H(821)	4706	2726	1659	35
H(831)	4339	1068	1456	43
H(841)	2248	530	652	50
H(851)	553	1642	45	49
H(861)	943	3302	221	39

APPENDIX 3: CRYSTAL STRUCTURE DATA OF THIOBENZOATE 256

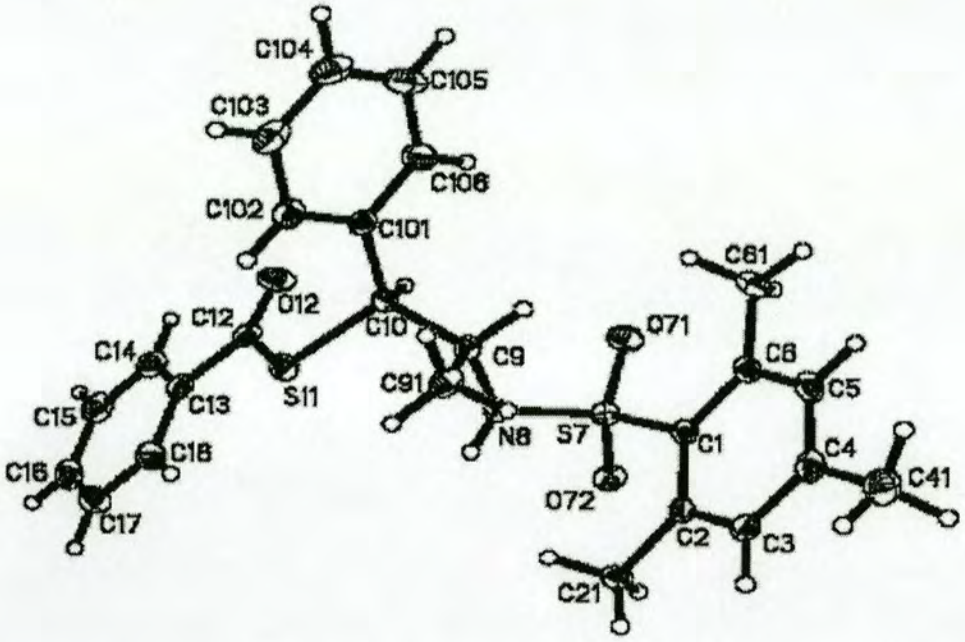

Figure 31: *Crystal structure of thiobenzoate* ***256***

PART A *Crystal data*

Empirical formula	$C_{25}H_{27}NO_3S_2$
Formula weight	453.62
Wavelength	0.71073 Å
Temperature	150 (2) K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	A = 6.3431(2) Å alpha = 90 deg.
	B = 15.4067(5) Å beta = 90 deg.
	C = 28.3836(7) Å gamma = 90 deg.
Volume	2285.19 (12)
Number of reflections for cell	8956 ($2.6 < \theta < 23.4$ deg)
Z	4
Density (calculated)	1.318 Mg/m^3
Absorption coefficient	0.260 mm^{-1}
F(000)	960

PART B *Data collection*

Crystal description	colourless block
Crystal size	0.40 x 0.40 x 0.25 mm
Theta range for data collection	1.58 to 30.50 deg.
Index ranges	-8<=h<=8, -21<=k<=21, -30<=l<=33
Reflections collected	66415
Independent reflections	6883 [R(int) = 0.0565]
Scan type	Omega/phi scans
Absorption correction	Multiscans(T_{min}= 0.8429, T_{max}=0.9400

PART C *Solution and refinement*

Solution	Direct (SHELXS-97 (Sheldrick, 1990))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	Geom.
Hydrogen atom treatment	Mixed
Data	6883
Parameters	289
Goodness-of-fit on F2	1.031
R	0.0419
Rw	0.1029
Absolute structure parameter	0.00(5)
Final maximum delta/sigma	0.001
Weighting scheme	Sheldrick Weights

Table 20: *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for* ***256****. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor*

	x	y	z	U(eq)
C(1)	11362(3)	7787(1)	8582(1)	24(1)
C(2)	13237(3)	7291(1)	8578(1)	25(1)
C(21)	14195(3)	6877(1)	9102(1)	32(1)
C(3)	14308(3)	7195(1)	8063(1)	29(1)
C(4)	13602(4)	7574(1)	7561(1)	34(1)
C(41)	14876(4)	7481(2)	7015(1)	46(1)
C(5)	11750(3)	8045(1)	7578(1)	32(1)
C(6)	10596(3)	8171(1)	8076(1)	27(1)
C(61)	8636(3)	8731(1)	8024(1)	37(1)
S(7)	10097(1)	7956(1)	9256(1)	26(1)
O(71)	8167(2)	8410(1)	9155(1)	37(1)
O(72)	10013(2)	7149(1)	9561(1)	32(1)
N(8)	11595(3)	8595(1)	9624(1)	26(1)
C(9)	12025(3)	9477(1)	9413(1)	26(1)
C(91)	14295(3)	9563(1)	9206(1)	33(1)
C(10)	11386(3)	10153(1)	9864(1)	25(1)
C(101)	11398(3)	11065(1)	9619(1)	27(1)
C(102)	13095(4)	11624(1)	9663(1)	35(1)
C(103)	13050(4)	12443(1)	9408(1)	43(1)
C(104)	11310(4)	12703(1)	9111(1)	45(1)
C(105)	9604(4)	12155(2)	9064(1)	51(1)
C(106)	9640(4)	11339(1)	9317(1)	39(1)
S(11)	13082(1)	10012(1)	10489(1)	31(1)
O(12)	9464(3)	10473(1)	10951(1)	45(1)
C(12)	11215(3)	10191(1)	11043(1)	30(1)
C(13)	11953(3)	9946(1)	11628(1)	32(1)
C(14)	10585(4)	10090(1)	12079(1)	38(1)
C(15)	11141(4)	9840(1)	12627(1)	43(1)
C(16)	13056(4)	9440(2)	12725(1)	45(1)
C(17)	14417(4)	9289(2)	12281(1)	43(1)
C(18)	13885(4)	9547(1)	11728(1)	38(1)

Table 21: *Bond lengths (Å) for* ***256***

Bond	length (A)
C(1)-C(6)	1.409(3)
C(1)-C(2)	1.414(3)
C(1)-S(7)	1.7874(18)
C(2)-C(3)	1.392(3)
C(2)-C(21)	1.509(3)
C(3)-C(4)	1.383(3)
C(4)-C(5)	1.382(3)
C(4)-C(41)	1.518(3)
C(5)-C(6)	1.388(3)
C(6)-C(61)	1.517(3)
S(7)-O(71)	1.4298(15)
S(7)-O(72)	1.4349(13)
S(7)-N(8)	1.6171(17)
N(8)-C(9)	1.471(2)
C(9)-C(91)	1.525(3)
C(9)-C(10)	1.537(2)
C(10)-C(101)	1.518(2)
C(10)-S(11)	1.8262(18)
C(101)-C(102)	1.383(3)
C(101)-C(106)	1.385(3)
C(102)-C(103)	1.396(3)
C(103)-C(104)	1.364(4)
C(104)-C(105)	1.377(4)
C(105)-C(106)	1.390(3)
S(11)-C(12)	1.777(2)
O(12)-C(12)	1.211(3)
C(12)-C(13)	1.496(3)
C(13)-C(14)	1.383(3)
C(13)-C(18)	1.390(3)
C(14)-C(15)	1.385(3)
C(15)-C(16)	1.381(4)
C(16)-C(17)	1.369(4)
C(17)-C(18)	1.393(3)

Table 22: *Bond angles (degrees) for* ***256***

Bond	Angle (degrees)	Bond	Angle (degrees)
C(6)-C(1)-C(2)	120.82(16)	C(9)-C(10)-S(11)	108.24(12)
C(6)-C(1)-S(7)	121.62(14)	C(102)-C(101)-C(106)	118.40(18)
C(2)-C(1)-S(7)	117.46(13)	C(102)-C(101)-C(10)	123.47(18)
C(3)-C(2)-C(1)	118.22(17)	C(106)-C(101)-C(10)	118.08(18)
C(3)-C(2)-C(21)	117.52(17)	C(101)-C(102)-C(103)	121.0(2)
C(1)-C(2)-C(21)	124.24(17)	C(104)-C(103)-C(102)	119.9(2)
C(4)-C(3)-C(2)	122.09(19)	C(103)-C(104)-C(105)	119.8(2)
C(5)-C(4)-C(3)	118.20(18)	C(104)-C(105)-C(106)	120.5(2)
C(5)-C(4)-C(41)	121.71(19)	C(101)-C(106)-C(105)	120.4(2)
C(3)-C(4)-C(41)	120.1(2)	C(12)-S(11)-C(10)	99.91(9)
C(4)-C(5)-C(6)	123.09(18)	O(12)-C(12)-C(13)	122.63(18)
C(5)-C(6)-C(1)	117.57(17)	O(12)-C(12)-S(11)	122.54(16)
C(5)-C(6)-C(61)	116.44(17)	C(13)-C(12)-S(11)	114.82(15)
C(1)-C(6)-C(61)	125.98(18)	C(14)-C(13)-C(12)	117.40(19)
O(71)-S(7)-O(72)	118.32(9)	C(18)-C(13)-C(12)	122.76(18)
O(71)-S(7)-N(8)	106.99(9)	C(13)-C(14)-C(15)	120.1(2)
O(72)-S(7)-N(8)	106.53(8)	C(16)-C(15)-C(14)	120.1(2)
O(71)-S(7)-C(1)	108.09(9)	C(17)-C(16)-C(15)	120.3(2)
O(72)-S(7)-C(1)	109.30(8)	C(16)-C(17)-C(18)	120.1(2)
N(8)-S(7)-C(1)	107.08(9)	C(13)-C(18)-C(17)	119.7(2)
C(9)-N(8)-S(7)	119.62(13)	C(14)-C(13)-C(12)	117.40(19)
N(8)-C(9)-C(91)	111.18(16)	C(18)-C(13)-C(12)	122.76(18)
N(8)-C(9)-C(10)	110.34(14)	C(13)-C(14)-C(15)	120.1(2)
C(91)-C(9)-C(10)	114.07(16)	C(16)-C(15)-C(14)	120.1(2)
C(101)-C(10)-C(9)	111.48(14)	C(17)-C(16)-C(15)	120.3(2)
C(101)-C(10)-S(11)	114.21(13)		

Symmetry transformations used to generate equivalent atoms

	U11	U22	U33	U23	U13	U12
C(1)	26(1)	23(1)	22(1)	0(1)	0(1)	-4(1)
C(2)	29(1)	24(1)	23(1)	-2(1)	-3(1)	-2(1)
C(21)	35(1)	34(1)	27(1)	2(1)	-2(1)	8(1)
C(3)	33(1)	27(1)	27(1)	-5(1)	1(1)	2(1)
C(4)	47(1)	31(1)	23(1)	-2(1)	1(1)	-7(1)
C(41)	59(2)	51(1)	28(1)	-2(1)	6(1)	4(1)
C(5)	40(1)	32(1)	23(1)	4(1)	-6(1)	-7(1)
C(6)	27(1)	26(1)	28(1)	1(1)	-5(1)	-6(1)
C(61)	34(1)	41(1)	36(1)	10(1)	-9(1)	2(1)
S(7)	25(1)	26(1)	27(1)	2(1)	3(1)	-1(1)
O(71)	25(1)	45(1)	42(1)	4(1)	4(1)	6(1)
O(72)	38(1)	28(1)	31(1)	5(1)	7(1)	-4(1)
N(8)	33(1)	23(1)	23(1)	1(1)	-2(1)	3(1)
C(9)	32(1)	26(1)	20(1)	0(1)	0(1)	0(1)
C(91)	35(1)	31(1)	32(1)	-3(1)	9(1)	1(1)
C(10)	26(1)	27(1)	23(1)	-1(1)	1(1)	2(1)
C(101)	35(1)	24(1)	22(1)	-4(1)	3(1)	3(1)
C(102)	42(1)	32(1)	32(1)	-4(1)	1(1)	-3(1)
C(103)	60(2)	31(1)	38(1)	-4(1)	12(1)	-8(1)
C(104)	67(2)	29(1)	40(1)	5(1)	15(1)	6(1)
C(105)	56(2)	47(1)	49(1)	13(1)	-2(1)	18(1)
C(106)	37(1)	38(1)	41(1)	2(1)	-2(1)	3(1)
S(11)	32(1)	38(1)	23(1)	0(1)	-1(1)	1(1)
O(12)	52(1)	54(1)	31(1)	1(1)	3(1)	25(1)
C(12)	42(1)	23(1)	26(1)	-4(1)	4(1)	4(1)
C(13)	46(1)	24(1)	25(1)	-4(1)	1(1)	0(1)
C(14)	54(1)	32(1)	28(1)	-3(1)	3(1)	5(1)
C(15)	63(2)	39(1)	25(1)	-4(1)	6(1)	-2(1)
C(16)	67(2)	42(1)	25(1)	1(1)	-9(1)	-10(1)
C(17)	47(1)	45(1)	37(1)	4(1)	-10(1)	1(1)
C(18)	42(1)	42(1)	28(1)	-2(1)	-2(1)	0(1)

Table 23: *Anisotropic displacement parameters (A^2 x 10^3) for* ***256****. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12]*

	x	y	Z	U(eq)
H(21A)	15574	6631	9004	48
H(21B)	13265	6414	9240	48
H(21C)	14368	7316	9402	48
H(3)	15563	6859	8054	35
H(41A)	14557	6922	6836	69
H(41B)	16383	7510	7106	69
H(41C)	14509	7953	6752	69
H(5)	11242	8294	7233	38
H(61A)	8472	8922	7627	55
H(61B)	8774	9239	8274	55
H(61C)	7398	8393	8139	55
H(8)	12520(40)	8375(15)	9801(10)	38(7)
H(9)	11096	9572	9073	31
H(91A)	14556	9141	8901	49
H(91B)	15260	9452	9525	49
H(91C)	14527	10151	9059	49
H(10)	9909	10020	9985	30
H(102)	14311	11448	9870	43
H(103)	14230	12820	9442	51
H(104)	11276	13260	8937	54
H(105)	8393	12336	8857	61
H(106)	8453	10967	9283	47
H(14)	9262	10361	12012	46
H(15)	10204	9943	12937	51
H(16)	13432	9268	13101	54
H(17)	15726	9008	12350	52
H(18)	14837	9450	11421	45

APPENDIX 4: CRYSTAL STRUCTURE DATA OF THIOPROPIONATE 239

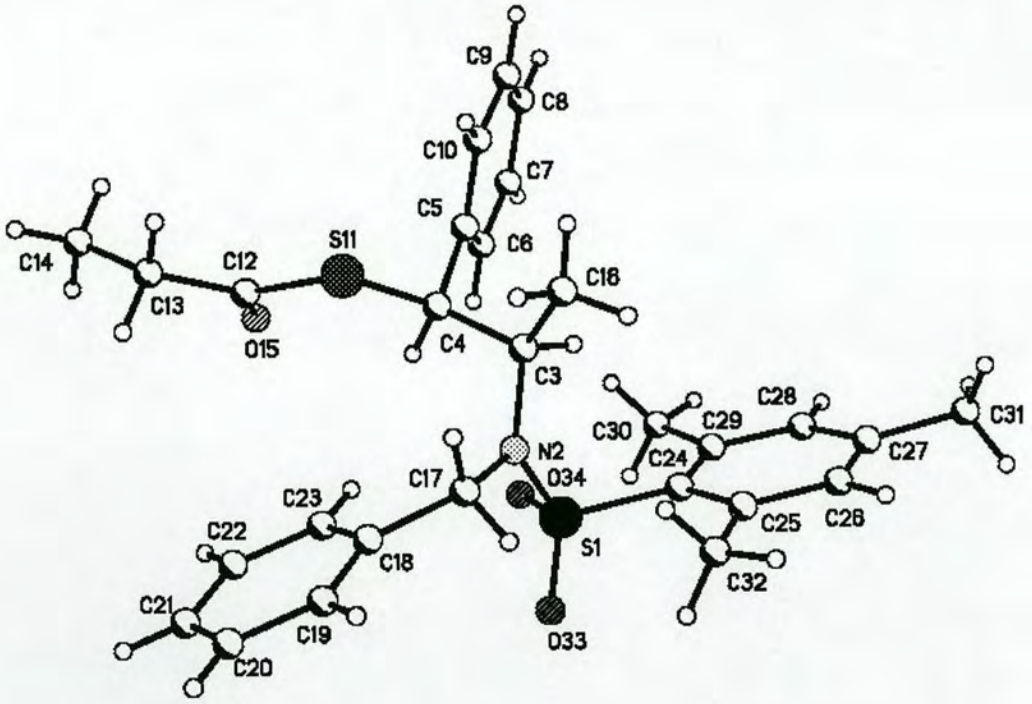

Figure 32: *Crystal structure of thiopropionate* ***239***

PART A *Crystal data*

Empirical formula	$C_{28}H_{33}NO_3S_2$
Formula weight	495.71
Wavelength	0.71073 Å
Temperature	150 (2) K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	A = 6.5383(2) Å alpha = 90 deg.
	B = 17.7883(5) Å beta = 90 deg.
	C = 21.7315(5) Å gamma = 90 deg.
Volume	2527.49 $Å^3$
Number of reflections for cell	5096 ($2.0 < \theta < 28.0$ deg)
Z	4
Density (calculated)	1.303 Mg/m^3
Absorption coefficient	0.241 mm^{-1}
F(000)	1056

PART B *Data collection*

Crystal description	colourless block
Crystal size	0.46 x 0.25 x 0.15 mm
Theta range for data collection	1.874 to 29.907 deg.
Index ranges	-8<=h<=7, -15<=k<=24, -29<=l<=29
Reflections collected	24671
Independent reflections	6532 [R(int) = 0.032]
Scan type	Omega scans
Absorption correction	Semi-empirical from equivalents (T_{min}= 0.75, T_{max}=0.96)

PART C *Solution and refinement*

Solution	Direct (SIR92 (Altomare et al., 1994))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	Geom.
Hydrogen atom treatment	Noref
Data	6532
Parameters	308
Goodness-of-fit on F2	0.7824
R	0.0431
Rw	0.0979
Absolute structure parameter	-0.01(6)
Final maximum delta/sigma	0.001
Weighting scheme	Sheldrick Weights

Table 24: *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for* ***239****. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor*

	X	y	Z	U(eq)
S(1)	4134(1)	-823(1)	4359(1)	24
N(2)	5574(3)	-106(1)	4170(1)	23
C(3)	6164(3)	-49(1)	3516(1)	23
C(4)	4821(3)	495(1)	3138(1)	23
C(5)	4787(3)	266(1)	2462(1)	24
C(6)	3200(4)	-185(1)	2262(1)	31
C(7)	3108(4)	-446(2)	1662(1)	40
C(8)	4652(5)	-255(2)	1254(1)	45
C(9)	6243(5)	192(1)	1446(1)	41
C(10)	6313(4)	456(1)	2046(1)	31
S(11)	5607(1)	1473(1)	3245(1)	26
C(12)	3213(4)	1937(1)	3139(1)	28
C(13)	3381(4)	2783(1)	3205(1)	38
C(14)	1800(5)	3209(2)	2836(1)	44
O(15)	1632(3)	1609(1)	3036(1)	37
C(16)	8447(4)	68(2)	3439(1)	40
C(17)	6196(3)	431(1)	4638(1)	31
C(18)	4565(3)	954(1)	4885(1)	25
C(19)	4992(4)	1364(1)	5415(1)	34
C(20)	3604(5)	1885(1)	5641(1)	40
C(21)	1763(5)	1993(1)	5346(1)	39
C(22)	1310(4)	1580(1)	4826(1)	33
C(23)	2698(4)	1057(1)	4602(1)	28
C(24)	5532(3)	-1641(1)	4140(1)	22
C(25)	7361(3)	-1808(1)	4453(1)	24
C(26)	8457(3)	-2444(1)	4282(1)	27
C(27)	7823(4)	-2913(1)	3809(1)	29
C(28)	5995(4)	-2743(1)	3519(1)	28
C(29)	4818(3)	-2121(1)	3661(1)	26
C(30)	2915(4)	-2007(1)	3277(1)	34
C(31)	9071(4)	-3579(1)	3615(1)	38
C(32)	8271(4)	-1332(1)	4957(1)	30
O(33)	3910(3)	-792(1)	5011(1)	36

Table 25: *Bond lengths (Å) for* ***239***

Bond	Length (Å)	Bond	Length (Å)
S(1)-N(2)	1.6362(18)	C(20)-C(21)	1.377(4)
S(1)-C(24)	1.783(2)	C(16)-H(163)	0.98
S(1)-O(33)	1.4273(16)	C(17)-C(18)	1.513(3)
S(1)-O(34)	1.4338(16)	C(17)-H(171)	0.99
N(2)-C(3)	1.475(3)	C(17)-H(172)	0.99
N(2)-C(17)	1.456(3)	C(18)-C(19)	1.390(3)
C(3)-C(4)	1.545(3)	C(18)-C(23)	1.380(3)
C(3)-C(16)	1.516(3)	C(19)-C(20)	1.388(4)
C(3)-H(3)	1.000	C(20)-H(20)	0.95
C(4)-C(5)	1.523(3)	C(21)-C(22)	1.380(4)
C(4)-S(11)	1.828(2)	C(21)-H(21)	0.95
C(4)-H(4)	1.000	C(22)-C(23)	1.388(3)
C(5)-C(6)	1.383(3)	C(22)-H(22)	0.95
C(5)-C(10)	1.388(3)	C(23)-H(23)	0.95
C(6)-C(7)	1.385(3)	C(24)-C(25)	1.408(3)
C(6)-H(6)	0.95	C(24)-C(29)	1.425(3)
C(7)-C(8)	1.386(4)	C(25)-C(26)	1.390(3)
C(7)-H(7)	0.95	C(25)-C(32)	1.507(3)
C(8)-C(9)	1.374(4)	C(26)-C(27)	1.386(3)
C(8)-H(8)	0.95	C(26)-H(26)	0.95
C(9)-C(10)	1.387(3)	C(27)-C(28)	1.385(3)
C(9)-H(9)	0.95	C(27)-C(31)	1.501(3)
C(10)-H(10)	0.95	C(28)-C(29)	1.383(3)
S(11)-C(12)	1.784(2)	C(28)-H(28)	0.95
C(12)-C(13)	1.517(3)	C(29)-C(30)	1.512(3)
C(12)-O(15)	1.207(3)	C(30)-H(301)	0.98
C(13)-C(14)	1.512(4)	C(30)-H(302)	0.98
C(13)-H(131)	0.99	C(30)-H(303)	0.98
C(13)-H(132)	0.99	C(31)-H(311)	0.98
C(14)-H(141)	0.98	C(31)-H(312)	0.98
C(14)-H(142)	0.98	C(31)-H(313)	0.98
C(14)-H(143)	0.98	C(32)-H(321)	0.98
C(16)-H(161)	0.98	C(32)-H(322)	0.98
C(16)-H(162)	0.98	C(32)-H(323)	0.98

Table 26: *Bond angles (degrees) for* ***239***

Bond	Angle (degrees)	Bond	Angle (degrees)
N(2)-S(1)-C(24)	105.91(9)	C(10)-C(9)-H(9)	119.8
N(2)-S(1)-O(33)	106.21(10)	C(5)-C(10)-C(9)	120.4(2)
C(24)-S(1)-O(33)	110.36(10)	C(5)-C(10)-H(10)	119.8
N(2)-S(1)-O(34)	108.19(10)	C(9)-C(10)-H(10)	119.8
C(24)-S(1)-O(34)	107.56(10)	C(4)-S(11)-C(12)	100.17(11)
O(33)-S(1)-O(34)	117.97(10)	S(11)-C(12)-O(15)	123.47(19)
S(1)-N(2)-C(3)	116.46(14)	C(13)-C(12)-O(15)	124.0(2)
S(1)-N(2)-C(17)	119.80(14)	C(12)-C(13)-C(14)	113.4(2)
C(3)-N(2)-C(17)	123.74(18)	C(12)-C(13)-H(131)	108.5
N(2)-C(3)-C(4)	114.01(17)	C(14)-C(13)-H(131)	108.5
N(2)-C(3)-C(16)	111.91(19)	C(12)-C(13)-H(132)	108.5
C(4)-C(3)-C(16)	114.48(18)	C(14)-C(13)-H(132)	108.5
N(2)-C(3)-H(3)	105.1	H(131)-C(13)-H(132)	109.5
C(4)-C(3)-H(3)	105.1	C(13)-C(14)-H(141)	109.5
C(16)-C(3)-H(3)	105.1	C(13)-C(14)-H(142)	109.5
C(3)-C(4)-C(5)	110.68(17)	H(141)-C(14)-H(142)	109.5
C(3)-C(4)-S(11)	111.65(14)	C(13)-C(14)-H(143)	109.5
C(5)-C(4)-S(11)	112.41(14)	H(141)-C(14)-H(143)	109.5
C(3)-C(4)-H(4)	107.3	H(142)-C(14)-H(143)	109.5
C(5)-C(4)-H(4)	107.3	C(3)-C(16)-H(161)	109.5
S(11)-C(4)-H(4)	107.3	C(3)-C(16)-H(162)	109.5
C(4)-C(5)-C(6)	118.01(19)	H(161)-C(16)-H(162)	109.5
C(4)-C(5)-C(10)	123.5(2)	C(3)-C(16)-H(163)	109.5
C(6)-C(5)-C(10)	118.4(2)	H(161)-C(16)-H(163)	109.5
C(5)-C(6)-C(7)	121.6(2)	H(162)-C(16)-H(163)	109.5
C(5)-C(6)-H(6)	119.2	N(2)-C(17)-C(18)	117.08(18)
C(7)-C(6)-H(6)	119.2	N(2)-C(17)-H(171)	107.5
C(6)-C(7)-C(8)	119.3(2)	C(18)-C(17)-H(171)	107.5
C(6)-C(7)-H(7)	120.4	N(2)-C(17)-H(172)	107.5
C(8)-C(7)-H(7)	120.4	C(18)-C(17)-H(172)	107.5
C(7)-C(8)-C(9)	119.9(2)	H(171)-C(17)-H(172)	109.5
C(7)-C(8)-H(8)	120	C(17)-C(18)-C(19)	118.3(2)
C(9)-C(8)-H(8)	120	C(17)-C(18)-C(23)	123.13(19)
C(8)-C(9)-C(10)	120.5(2)	C(19)-C(18)-C(23)	118.5(2)
C(8)-C(9)-H(9)	119.8	C(18)-C(19)-C(20)	120.8(2)

Bond	Angle (degrees)	Bond	Angle (degrees)
C(18)-C(19)-H(19)	119.6	C(27)-C(28)-C(29)	123.6(2)
C(20)-C(19)-H(19)	119.6	C(27)-C(28)-H(28)	118.2
C(19)-C(20)-C(21)	120.0(2)	C(29)-C(28)-H(28)	118.2
C(19)-C(20)-H(20)	120	C(24)-C(29)-C(28)	117.4(2)
C(21)-C(20)-H(20)	120	C(24)-C(29)-C(30)	126.4(2)
C(20)-C(21)-C(22)	119.7(2)	C(28)-C(29)-C(30)	116.2(2)
C(20)-C(21)-H(21)	120.2	C(29)-C(30)-H(301)	109.5
C(22)-C(21)-H(21)	120.2	C(29)-C(30)-H(302)	109.5
C(21)-C(22)-C(23)	120.2(2)	H(301)-C(30)-H(302)	109.5
C(21)-C(22)-H(22)	119.9	C(29)-C(30)-H(303)	109.5
C(22)-C(23)-C(18)	120.7(2)	H(301)-C(30)-H(303)	109.5
C(22)-C(23)-H(23)	119.6	H(302)-C(30)-H(303)	109.5
C(18)-C(23)-H(23)	119.6	C(27)-C(31)-H(311)	109.5
S(1)-C(24)-C(25)	118.61(16)	C(27)-C(31)-H(312)	109.5
S(1)-C(24)-C(29)	121.03(16)	H(311)-C(31)-H(312)	109.5
C(25)-C(24)-C(29)	120.36(19)	C(27)-C(31)-H(313)	109.5
C(24)-C(25)-C(26)	118.7(2)	H(311)-C(31)-H(313)	109.5
C(24)-C(25)-C(32)	124.6(2)	H(312)-C(31)-H(313)	109.5
C(26)-C(25)-C(32)	116.6(2)	C(25)-C(32)-H(321)	109.5
C(25)-C(26)-C(27)	122.3(2)	C(25)-C(32)-H(322)	109.5
C(25)-C(26)-H(26)	118.9	H(321)-C(32)-H(322)	109.5
C(27)-C(26)-H(26)	118.9	C(25)-C(32)-H(323)	109.5
C(26)-C(27)-C(28)	117.7(2)	H(321)-C(32)-H(323)	109.5
C(26)-C(27)-C(31)	121.4(2)	H(322)-C(32)-H(323)	109.5
C(28)-C(27)-C(31)	120.9(2)		

Symmetry transformations used to generate equivalent atoms

	U11	U22	U33	U23	U13	U12
S(1)	21(1)	24(1)	25(1)	2(1)	3(1)	2(1)
N(2)	25(1)	22(1)	22(1)	0(1)	2(1)	0(1)
C(3)	21(1)	24(1)	25(1)	3(1)	4(1)	5(1)
C(4)	24(1)	19(1)	26(1)	2(1)	2(1)	-1(1)
C(5)	30(1)	17(1)	24(1)	3(1)	-1(1)	4(1)
C(6)	33(1)	28(1)	31(1)	1(1)	2(1)	0(1)
C(7)	51(2)	31(1)	37(1)	-7(1)	-10(1)	-4(1)
C(8)	75(2)	34(1)	26(1)	-5(1)	1(1)	-1(2)
C(9)	65(2)	27(1)	31(1)	2(1)	15(1)	-3(1)
C(10)	40(1)	23(1)	29(1)	2(1)	7(1)	-4(1)
S(11)	25(1)	22(1)	29(1)	0(1)	-2(1)	-1(1)
C(12)	31(1)	29(1)	25(1)	-1(1)	0(1)	7(1)
C(13)	45(1)	25(1)	45(2)	-5(1)	0(1)	5(1)
C(14)	65(2)	30(1)	38(1)	1(1)	3(1)	14(1)
O(15)	31(1)	31(1)	49(1)	4(1)	-7(1)	2(1)
C(16)	22(1)	53(2)	43(2)	17(1)	4(1)	10(1)
C(17)	31(1)	32(1)	30(1)	-3(1)	-11(1)	-1(1)
C(18)	34(1)	19(1)	22(1)	0(1)	0(1)	-2(1)
C(19)	51(2)	26(1)	24(1)	1(1)	-6(1)	-7(1)
C(20)	69(2)	27(1)	24(1)	-4(1)	8(1)	-7(1)
C(21)	58(2)	24(1)	35(1)	-1(1)	21(1)	0(1)
C(22)	37(1)	25(1)	37(1)	3(1)	8(1)	4(1)
C(23)	35(1)	24(1)	26(1)	-4(1)	3(1)	0(1)
C(24)	23(1)	22(1)	21(1)	3(1)	4(1)	0(1)
C(25)	27(1)	25(1)	20(1)	3(1)	4(1)	1(1)
C(26)	28(1)	30(1)	22(1)	3(1)	-1(1)	4(1)
C(27)	39(1)	24(1)	24(1)	4(1)	6(1)	3(1)
C(28)	36(1)	26(1)	21(1)	1(1)	4(1)	-2(1)
C(29)	26(1)	29(1)	22(1)	4(1)	4(1)	-7(1)
C(30)	30(1)	36(1)	38(1)	-1(1)	-6(1)	-4(1)
C(31)	55(2)	29(1)	29(1)	-2(1)	-1(1)	14(1)
C(32)	30(1)	33(1)	27(1)	-2(1)	-5(1)	6(1)
O(33)	44(1)	34(1)	29(1)	5(1)	13(1)	9(1)
O(34)	23(1)	35(1)	47(1)	-1(1)	-4(1)	2(1)

Table 27: *Anisotropic displacement parameters (A^2 x 10^3) for* ***239****. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a^{*2} U11 + ... + 2 h k a* b* U12]*

	x	y	z	U(eq)
H(3)	5888	-558	3339	28
H(4)	3390	449	3296	27
H(6)	2147	-320	2543	37
H(7)	1999	-752	1532	48
H(8)	4610	-432	842	54
H(9)	7302	321	1166	49
H(10)	7412	769	2174	37
H(131)	3210	2914	3645	46
H(132)	4757	2940	3065	46
H(141)	1988	3750	2898	66
H(142)	427	3063	2972	66
H(143)	1959	3089	2398	66
H(161)	8778	103	3000	59
H(162)	9184	-357	3621	59
H(163)	8854	534	3646	59
H(171)	6747	142	4991	37
H(172)	7293	747	4460	37
H(19)	6249	1285	5624	41
H(20)	3925	2168	5998	48
H(21)	810	2349	5500	47
H(22)	43	1655	4620	40
H(23)	2359	767	4249	34
H(26)	9683	-2562	4496	32
H(28)	5523	-3072	3205	33
H(301)	2787	-2420	2981	52
H(302)	1712	-1999	3546	52
H(303)	3014	-1529	3055	52
H(311)	8378	-3840	3276	56
H(312)	9229	-3924	3963	56
H(313)	10422	-3410	3477	56
H(321)	9542	-1563	5103	45
H(322)	7300	-1295	5299	45
H(323)	8563	-828	4797	45