New Routes to the Synthesis of Small and Medium Ring Lactones: Applications to Natural Product Synthesis

By

Jennifer I. Aird

Thesis presented for the degree of
DOCTOR OF PHILOSOPHY

Department of Chemistry
The University of Edinburgh
April 2003

Declaration

This thesis is submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at The University of Edinburgh. Unless otherwise stated the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualification at this, or any other university. In accordance with the regulations this thesis does not exceed 70,000 words in length.

Jennifer Irene Aird

Acknowledgements

I would like to thank my supervisor, Dr Alison Hulme, for her help and advice throughout and for her thorough proof-reading of this thesis.

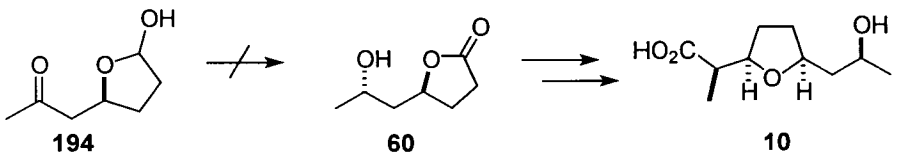
I would also like to thank Dr David Reed, John Millar and Wesley Kerr for running nmr spectra. Thanks also to Alan Taylor and Harry McKenzie for mass spectrometry.

Thanks also go to past and present members of the Hulme group. Garnet Howells who showed me the ropes in lab 55; Charlie Montgomery for his memorable christmas music; Sarah Barron, Karen Curley and Ed Rosser for help, advice and nights at the union.

Thanks also to my parents for support over the years and babysitting during the write up! And finally thanks to Alan for love, support and patience throughout the writing of this thesis.

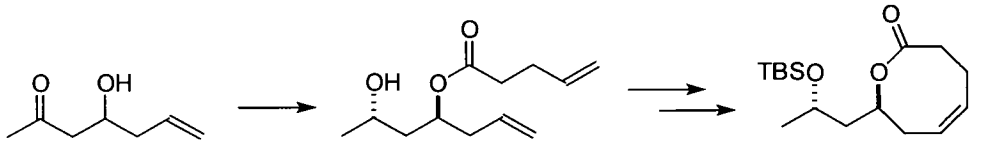
Abstract

Chapter Two of this thesis describes a route to nonactic acid **10**, a key intermediate in the biosynthesis of the polyether ionophore nonactin. Based on the Hulme group precedent for the formation of medium rings, an intramolecular Evans-Tishchenko reaction was attempted on lactol **194** to give the known lactone intermediate **60**. A mechanistic rationale for the failure of this reaction in the synthesis of small rings is presented.



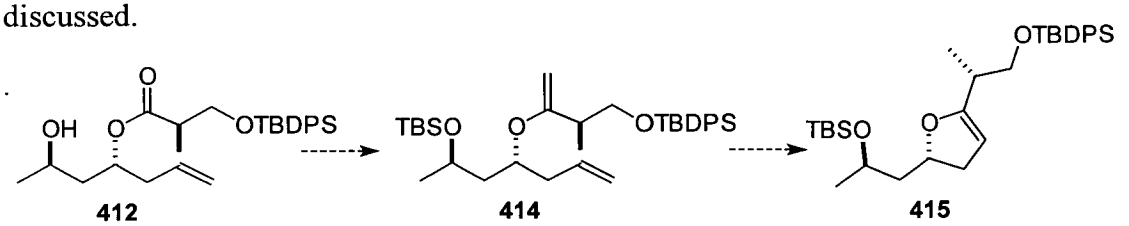
194 **60** **10**

Two alternative strategies for the synthesis of small and medium ring lactones were subsequently investigated. In chapter Three, an Evans-Tishchenko reaction of β-hydroxy ketone **263** and 4-pentenal gave β-hydroxy ester **289** with high diastereocontrol. Ring closing metathesis was then used to generate the unsaturated 8-membered lactone **291**; a model for the cytotoxic marine metabolite octalactin A.



263 **289** **291**

In Chapter Four the extension of this combined Evans-Tishchenko / RCM strategy to the synthesis of an advanced nonactic acid intermediate **415** *via* enol ether **414** is discussed.



412 **414** **415**

Contents

Chapter 1 : Introduction

Polynactin Antibiotics: Biosynthesis, Mode of Action and Chemical Synthesis

1.1 Polynactin Antibiotics

The polynactin antibiotics **1-5** are a series of 32 membered macrolides isolated from several strains of *Streptomyces* sp..[1-3] The macrocyclic ring is unusual in that it is formed from four subunits of the nactic acids **10-12** arranged in alternating (+)(–)(+)(–) order; the enantiomeric subunits joined by ester linkages to form the large tetralactone ring. The polynactins are neutral lipophilic compounds which are soluble in organic solvents, but not in water.[3] They form colourless crystals with low melting points and either display S_4 symmetry with a *meso* configuration (nonactin **1**, tetranactin **5**), or have very low optical activities. The antibiotic activity of these macrotetrolides is due to their ability to act as ionophores, transporting ions through lipid membranes.[4]

		R_1	R_2	R_3	R_4
1	nonactin	Me	Me	Me	Me
2	monactin	Me	Me	Me	Et
3	dinactin	Me	Et	Me	Et
4	trinactin	Me	Et	Et	Et
5	tetranactin	Et	Et	Et	Et
6	macrotetrolide G	Et	Me	^{i}Pr	Me
7	macrotetrolide D	Et	Me	Et	^{i}Pr
8	macrotetrolide C	Et	Me	^{i}Pr	^{i}Pr
9	macrotetrolide B	Et	^{i}Pr	Et	^{i}Pr

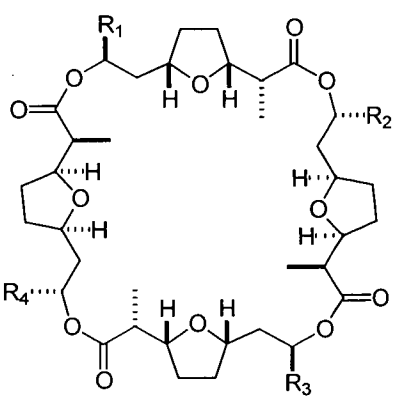


Figure 1.1: Polynactin Antibiotics

The nactic acids **10-12** possess a carbon backbone centred on a 2,4-*cis*-fused tetrahydrofuran core. They differ in the side-chain at C(8) (R = Me, Et, ^{i}Pr) giving rise to changes in conformation and hence ion-selectivity upon incorporation into the macrotetrolides.

10	(+)-nonactic acid	R=Me
11	(+)-homononactic acid	R=Et
12	(+)-bishomononactic acid	R=^{i}Pr

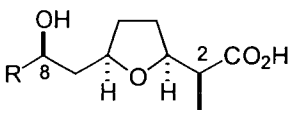


Figure 1.2: Nactic Acids

The polynactins are constituted from nonactic acid **10** and homononactic acid **11**. *Streptomyces* sp. produce predominantly nonactin **1**, monactin **2**, dinactin **3**, trinactin **4** and tetranactin **5**. The commercial preparation 'polynactin', which is isolated from *S. aureus* S-3466, consists of a 1:4:5 mixture of dinactin, trinactin and tetranactin.[5] By comparison *S. griseus* 34/249 produces the macrotetrolides nonactin, monactin, dinactin and trinactin in the ratio of 8:27:57:8.[5] Due to the relative ease of isolation of compounds **1-5**, studies of these antibiotic macrotetrolides has mainly focused on the polynactins with very little being known about the related macrotetrolides **6-9**. However, a wealth of synthetic routes to the nactic acids **10** and **11** and the recent development of routes to bishomononactic acid **12**, is allowing new biological activities and applications of these unusual molecules to be explored.

1.2 Biosynthesis of Nonactin

The nactic acids are assembled by *Streptomyces* sp. from acetate, propionate and succinate units *via* a pathway based on polyketide biosynthesis. Feeding studies

carried out by Robinson *et al.* indicated the origins of the carbon atoms in nonactic acid **10** to be as shown in figure 1.3.[1,6]

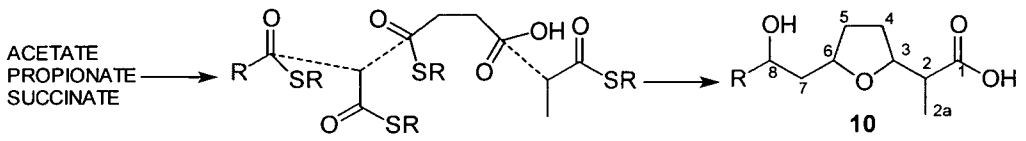
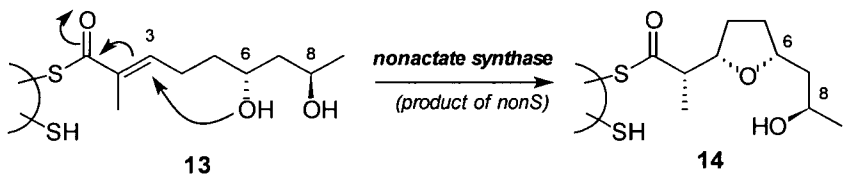


Figure 1.3: Biosynthetic origin of the Nonactic Acid Backbone

It is thought that the coupling of the acetate, propionate and succinate subunits is controlled by a multienzyme template referred to as the nonactin polyketide synthase (PKS) complex.[7] However, whole-cell analysis of the nonactin biosynthetic pathway has not allowed the exact sequence of reactions of the nonactin PKS complex to be determined. More recent studies have focussed on cloning and synthesising the potential nonactin biosynthesis gene cluster.[8]



Scheme 1.1: Tetrahydrofuran Ring Formation in Nonactic Acid

Both double labelling studies [9-10] and the isolation of a gene *nonS* which codes for an enzyme named nonactate synthase [2,11] support the theory that the tetrahydrofuran ring of nonactic acid is made from intermediate **13** by formation of the C(3)-O bond, most probably by a Michael-type process (scheme 1.1).

Thus the biosynthetic origin of the nonactic acid backbone appears to have been identified and a wealth of evidence supports the existence of a functionalised nonenoic acid precursor **13** which undergoes tetrahydrofuran ring closure catalysed by the enzyme nonactate synthase. However, there are many factors that remain unknown in the synthesis of the polynactins. In particular, there is little understanding of the stereochemical divergence which gives rise to the synthesis of both enantiomers of nonactic acid (**10** and (*ent*)-**10**), but which, under normal feeding conditions, leads to a preference for the synthesis of (+)-homononactic acid (**11**). Furthermore, the biosynthetic pathway from a PKS bound nactic acid equivalent to the fully formed polynactin, with its alternating (+)/(–) nactic acid subunits remains largely uninvestigated. The formation of dimeric or tetrameric subunits prior to cyclisation is a question that has been the subject of investigation in several recent synthetic routes to the polynactins, as discussed in Section 1.4. Some investigators have even proposed that the alternating pattern of (+)/(–) subunits observed in polynactin biosynthesis is the result of an ion-templated thermodynamic well.[12] Clearly, a deeper understanding of the biosynthetic route to macrocycle formation, and identification of the associated genetic material might allow the ability to bioengineer the synthesis of tetranactin and other more-substituted macrotetrolide homologues.

1.3 Mode of Action

1.3.1 Biological Activity

The antibiotic properties of the polynactins were originally identified in the 1950's and 60's.[13] They are effective against Gram positive bacteria [nonactin **1**: *Staphylococcus aureus* (M.I.C. = 0.95 μg/ml), *Mycobacterium bovis* (M.I.C. = 0.96

μg/ml)], whereas Gram negative species are less sensitive to these compounds.[14] The polynactins were the first naturally occurring crown ethers to be identified, and the earliest for which antibiotic activity could be traced to their ability to act as ionophores. The potency of the polynactins has been shown to vary with the difference in the stability of their Na^+ and K^+ complexes. Hence dinactin **3** is over an order of magnitude more potent against *Staphylococcus aureus* (M.I.C. = 0.05 μg/ml) than nonactin **1**,[15] and of the macrotetrolides tested (**1-5**), tetranactin **5** has proved to be the most potent antibiotic.[5] Due to the relative ease of isolation of compounds **1-5** (Figure 1.1), studies of these antibiotic macrotetrolides has mainly focused on the polynactins with very little being known about the related macrotetrolides **6-9**.[3]

The polynactins **1-5** have also been reported to have coccidiostatic, anthelminthic, insecticidal and miticidal properties which are well documented in a review in 1998 by Zizka.[3] Nonactin **1** has also been shown to possess antitumour activity against mammalian cell lines *in vitro* and against Crocker sarcoma 180 in studies with mice,[15] and to be an effective inhibitor of the P170-glycoprotein responsible for drug resistance in multiple drug-resistant cancer cell lines.[16]

1.3.2 Ion Binding and Selectivity

The antibiotic activity of the polynactins is due to their ability to act as lipid soluble ion carriers, transporting potassium ions through bacteria cell membranes thus disrupting the ionic balance of the cell.[4] For a compound to be a good ionophore it must be able to bind the ion selectively and tightly to give a complex with a hydrophobic exterior and a hydrophilic interior and it must also be able to release the

ion once it has passed through the membrane. The relative selectivity of ion-binding of nonactin **1** has been shown to be $NH_4^+ > K^+ = Rb^+ > Cs^+ > Na^+ > Ba^{2+}$. [4]

When nonactin forms a complex with K^+, the potassium ion is not hydrated but adopts a nearly cubic co-ordination with the four carbonyl oxygens and the four THF ring oxygens. This gives the nonactin molecule a 'tennis-ball seam' shape with the K^+ in the hydrophilic interior of the ball and the hydrophobic groups on the outside. The free nonactin molecule has a similar shape to that of the K^+ complex but it is much flatter with a central hole large enough to allow the approach of a hydrated K^+ ion. The nonactin ring system is fairly flexible and can also bind the smaller Na^+ ion and the larger Cs^+ ion with similar affinity in dry acetone. However nonactin is highly selective in ion transport through lipid bilayers where K^+ transport is highly favoured over that of Na^+ or Cs^+. [4]

Uncomplexed tetranactin has a more elongated and twisted shape. The conformation about the (+)-homononactic acid units is very similar to the conformation of (+)-nonactic acid in nonactin but the conformation about the (–)-homononactic acid units is quite different. [13, 17] X-ray diffraction studies of dinactin suggest its shape can be approximately described as a hybrid of the nonactin and tetranactin conformations.[18] In an effort to design new more-potent antibiotic ionophores, several groups have attempted to mimic these structures. The unnatural 'trishomononactate' with a ^{t}Bu side-chain has been synthesised by Walkup and Park in an attempt to increase ion-binding (section 1.4.4).[19] Hara *et al.* have used homononactic acid to synthesise a series of 16-membered macrodiolides resembling pamamycin-607 **15**. The macrodiolide **16** (figure 1.4) was found to show a moderate selectivity for binding

Li^+ over Na^+ or K^+.[20] Burke *et al.* have synthesised macrodiolide **17** and macrotriolide **18**, ionophores based on a hydropyran unit (figure 1.4).[21] Macrodiolide **17** was found to exhibit selectivity for $Li^+ > Na^+ > K^+$ as was expected based on its cavity size. The macrotriolide **18** was found to be less rigid and exhibited little selectivity.

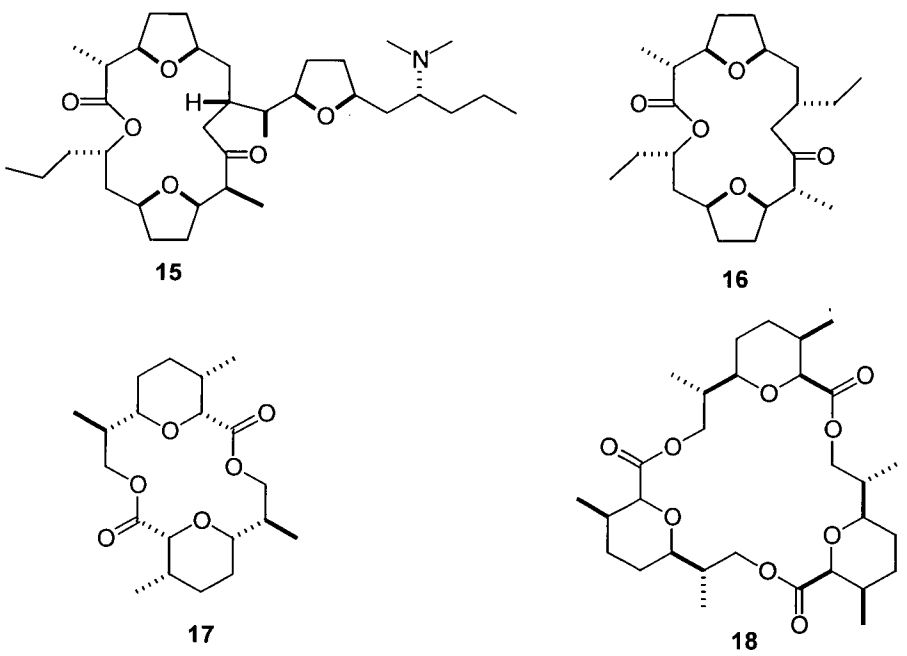
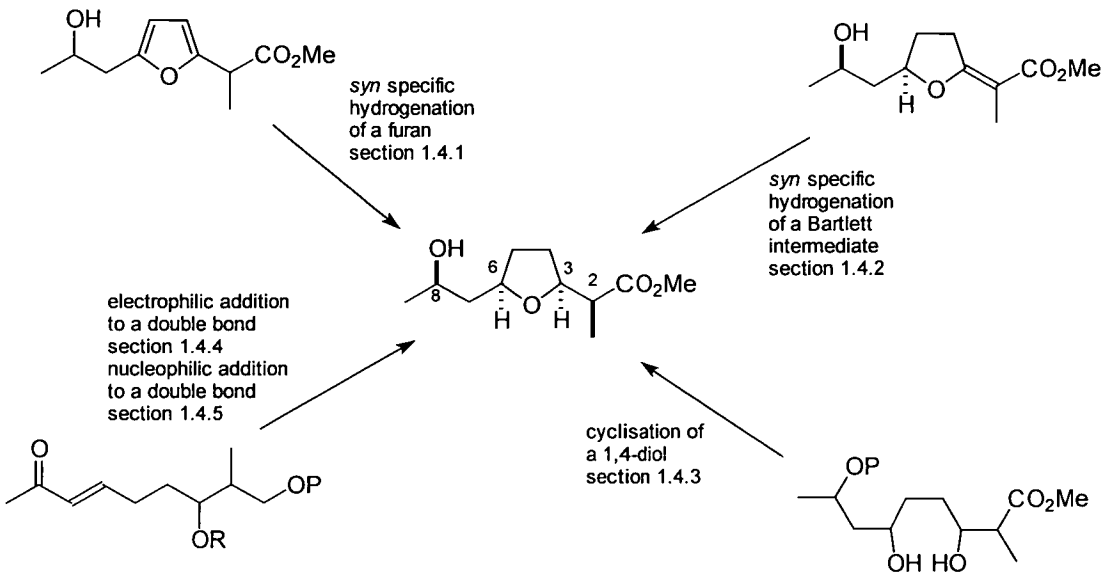


Figure 1.4: Synthetic Polynactin Ionophore Models

1.4 Chemical Synthesis of the Nactic Acids

The many interesting biological and structural properties of the polynactins have made them the focus of a large number of synthetic studies, which have concentrated mostly on the synthesis of nonactic acid itself. Although nonactic acid is a small molecule it contains 4 chiral centres and the problem of controlling the stereochemistry at these centres has resulted in a wealth of different strategies for the synthesis of nonactic acid (scheme 1.2).



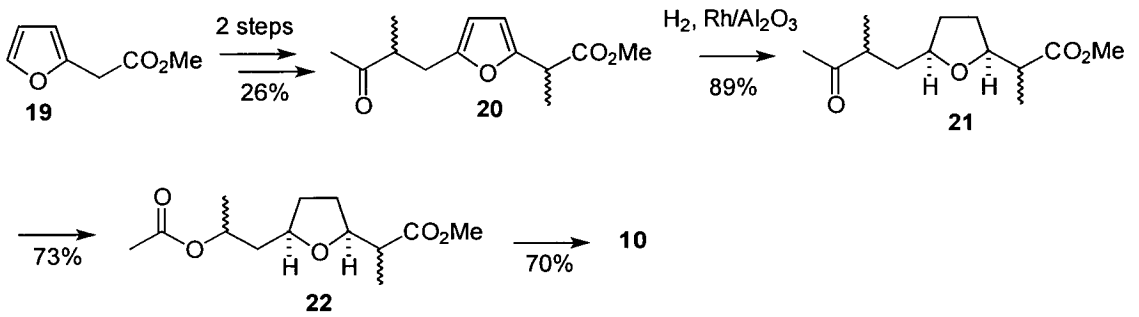
Scheme 1.2: Strategies used in the Synthesis of the Nactic Acids

The first 2 approaches discussed are based on *syn*-specific catalytic hydrogenation of unsaturated intermediates as a method of controlling the stereochemistry about the tetrahydrofuran ring. Early approaches focussed on the catalytic hydrogenation of a furan derivative (section 1.4.1). This route provides good control of the relative C(3), C(6) stereochemistry allowing formation of the *cis*-tetrahydrofuran. However, this approach does not give good control of the acylic stereocentres at C(2) and C(8). The second route, hydrogenation of a Bartlett type intermediate, has proved to be the most popular route to the nactic acids since its introduction by Bartlett *et al.* in 1980. This approach is based on the hydrogenation of an exocyclic double bond, simultaneously establishing the desired stereochemistry between C(2) and C(3) due to the *syn* stereospecificity of the reaction, and between C(3) and C(6) as hydrogenation takes place on the less hindered face *anti* to the C(6) side-chain. Cyclisation of a 1,4-diol has proved to be a less popular route due to the difficulty of controlling all 4 stereocentres in an acyclic precursor (section 1.4.3). Strategies that

form the tetrahydrofuran ring *via* additions to a double bond can be broken down further into electrophilic additions (section 1.4.4) and nucleophilic Michael-type additions (section 1.4.5).

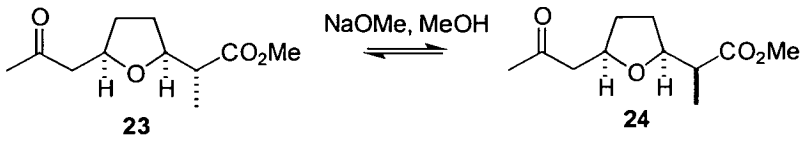
1.4.1 *Syn* Specific Hydrogenation of substituted Furan Intermediates

The first synthesis of nonactic acid was carried out by Beck and Henseleit in 1971.[22] Methylation and Friedel-Crafts alkylation were used to form the carbon skeleton **20** of nonactic acid **10** in 2 steps from 2-methoxycarbonylmethylfuran **19** with no control of the C(2) or C(8) stereochemistry. Hydrogenation over rhodium on alumina gave a mixture of the diastereoisomeric *cis*-2,5-disubstituted tetrahydrofurans **21**. Baeyer-Villager oxidation of the ketone **21** and hydrolysis of the resultant ester **22** then completed the synthesis of nonactic acid **10** (scheme 1.3).



Scheme 1.3: Beck and Hensleit Synthesis of Nonactic Acid

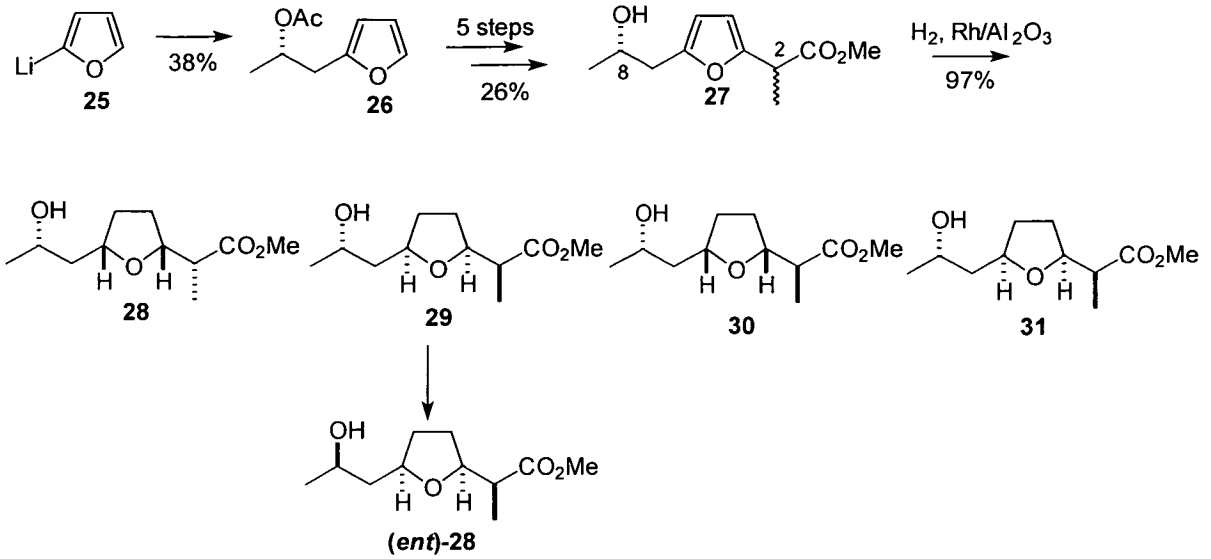
Gerlach and Wetter used a similar strategy to synthesise nonactic acid **10**, but achieved a degree of stereochemical control at C(2) by carrying out a base catalysed epimerisation of intermediate **23**. This favoured the natural *threo* relationship between C(2) and C(3) and resulted in a 1:4 mixture of diastereomers **23**:**24** being formed (figure 1.5).[23]



23 **24**

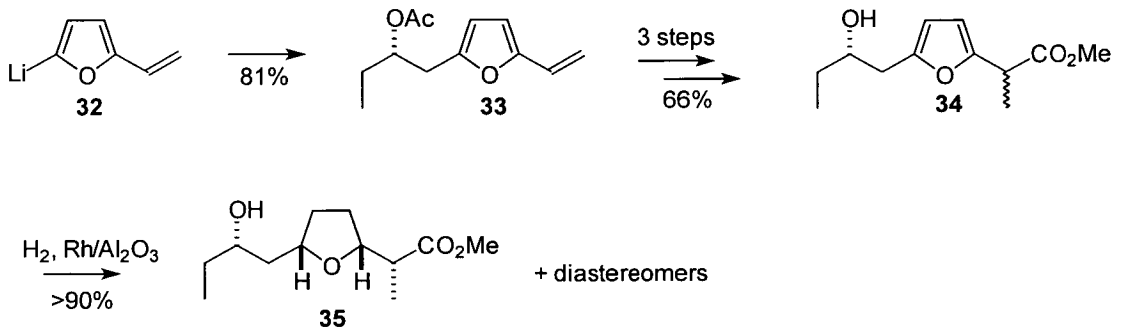
Figure 1.5: Epimerisation at C(2)

The first homochiral synthesis of (-)-nonactic acid methyl ester and its enantiomer was reported by Schmidt *et al.* in 1975.[24] Reaction of 2-lithiofuran **25** with (*S*)-propylene oxide gave the chiral alcohol that was converted to acetate **26** in 38% yield over the 2 steps. A further 5 steps were required to add the C(1)-C(2a) side chain with no control over the C(2) stereochemistry. Hydrogenation of **27** over rhodium on alumina produced a mixture of the 4 *cis*-tetrahydrofuran derivatives with (*S*) configuration at C(8) (**28-31**). (-)-Nonactic acid methyl ester **28** was separated by chromatography. Conversion of the C(8) alcohol to the corresponding tosylate and subsequent displacement of the tosylate with potassium acetate allowed inversion of the configuration at C(8) of the other 3 diastereomers. Hydrolysis of the acetate then allowed (+)-nonactic acid methyl ester (*ent*)-**28** to be separated from the reaction mixture.



Scheme 1.4: Schmidt Synthesis of Nonactic Acid Methyl Ester

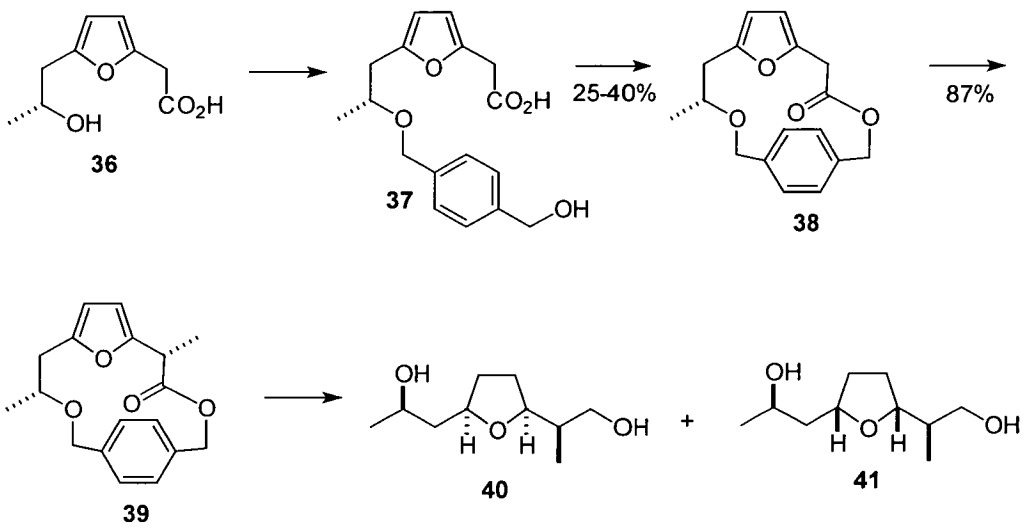
Schmidt *et al.* used similar chemistry to carry out the first synthesis of homononactic acid methyl ester in 1986.[25]



Scheme 1.5: Schmidt Synthesis of Homononactic Acid Methyl Ester

2-Vinyl furan **32** was α-lithiated and reacted with (*S*)-1,2-epoxybutane to give a chiral alcohol which was acylated to give **33**. A further 3 steps were required to complete the synthesis of the homononactic acid skeleton **34**. As in the synthesis of nonactic acid hydrogenation was carried out over rhodium on alumina to give a mixture of 4 diastereomers from which (-)-homononactic acid methyl ester **35** was isolated.

The synthesis of nonactic acid by Still *et al.* differs from the other approaches discussed in that it displays excellent control over the remote C(2), C(8) stereorelationship. As in the other examples the C(3), C(6) stereochemistry is controlled by *syn* specific hydrogenation of a furan (scheme 1.6).[26]



Scheme 1.6: Still Synthesis of Reduced Nonactic Acid

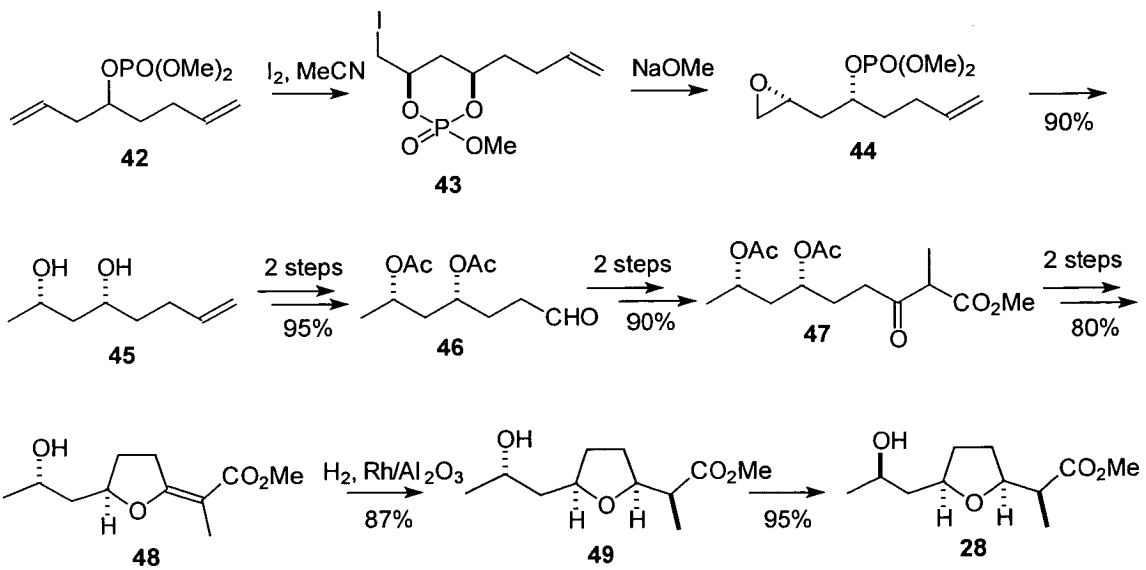
The 2,5-disubstituted furan **36** was attached to a benzyl spacer group to give the intermediate **37**. Cyclisation of this intermediate was carried out under Corey-Nicolaou conditions to give a 25-40% yield of the macrocycle **38**. Treatment with strong base and methyl iodide gave only the *cis* dimethyl lactone **39** with the stereochemistry of the methylation being controlled by the conformation of the macrocycle. Reduction with $LiAlH_4$ followed by catalytic hydrogenation gave a 1:1 mixture of the reduced nonactic acid derivative **40** and its diastereomer **41**.

1.4.2 *Syn*-Specific Hydrogenation of a Bartlett intermediate

By far the most popular approach to nonactic acid synthesis has involved the *syn* specific hydrogenation of a double bond exocyclic to a tetrahydrofuran ring. The *syn*

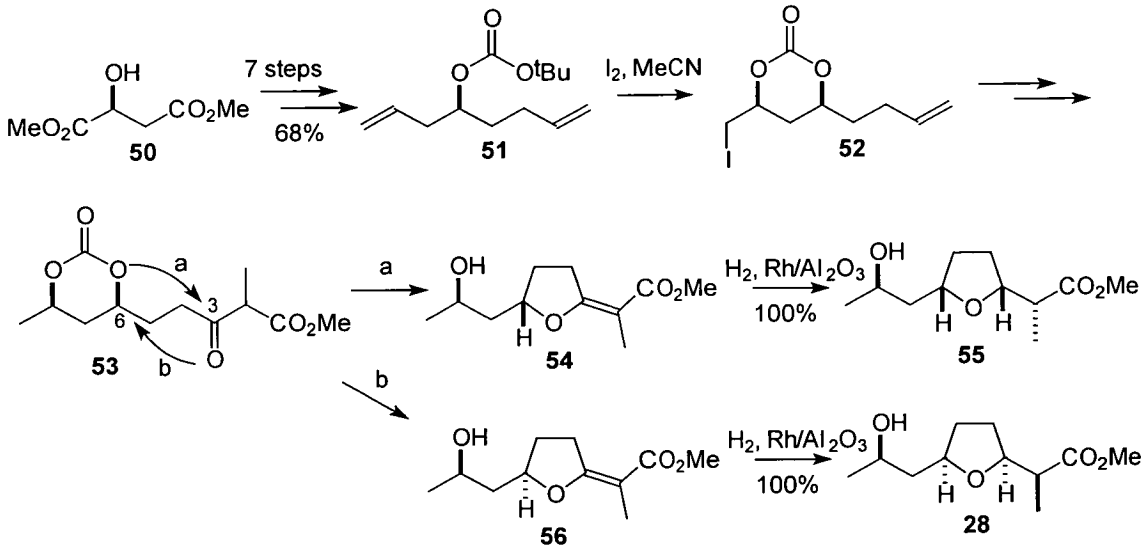
specificity of the hydrogenation controls the relative C(2),C(3) stereochemistry and the bulk of the side chain on C(6) controls the face onto which hydrogen adds and thus controls the absolute stereochemistry of C(2) and C(3) with the *cis* tetrahydrofuran ring predominating.

Bartlett and Jernstedt introduced this approach in 1980 for the synthesis of racemic nonactic acid methyl ester. The phosphate **42** was epoxidized stereo- and regio-specifically in 63% yield in a 2-step process. An iodine catalysed phosphate cyclisation was used to form cyclic phosphate ester **43** which was converted to the epoxide **44** with sodium methoxide. Reaction of the epoxide with $LiAlH_4$ gave *syn* diol **45**. Acylation of the diol and ozonolysis of the alkene gave aldehyde **46** which underwent an aldol coupling followed by Jones oxidation to give the β-keto ester **47**. Acetate cleavage and dehydration gave the tetrahydrofuran ring **48** with *E* geometry about the exocyclic double bond. Hydrogenation of the double bond over rhodium on alumina gave an 85:15 ratio of *cis*: *trans* tetrahydrofuran rings. Mitsunobu inversion of C(8) was then used to form nonactic acid methyl ester (scheme 1.7). [27]



Scheme 1.7: Bartlett Synthesis of Racemic Nonactic Acid Methyl Ester

Further work by Bartlett *et al.* led to the discovery that *t*-butyl carbonate group gave better stereochemical control than the phosphate group in the iodocyclisation.[28] This reaction was then applied to an enantiodivergent synthesis of (+)-nonactic acid methyl ester and (-)-8-*epi*-nonactic acid methyl ester (scheme 1.8).

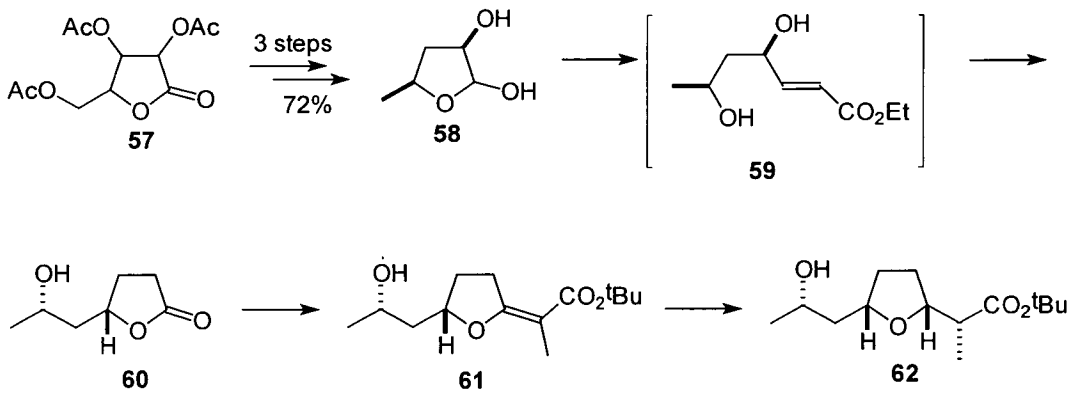


Scheme 1.8: Bartlett Synthesis of Nonactic Acid Methyl Ester

The chiral starting material dimethyl-(*S*)-(-)-malate **50** was converted to the *tert*-butyl carbonate **51** in 7 steps. Iodocyclisation proceeded in 55% yield to give the *cis* cyclic carbonate **52**. The iodine was removed with tributyltin hydride and β-keto ester **53** was synthesised as in the racemic case. Deprotection of the carbonate and dehydration gave the Bartlett intermediate **54** (path a) which was hydrogenated to give (-)-8-*epi*-nonactic acid methyl ester **55**. The β-keto ester **53** was also used to form (+)-nonactic acid methyl ester. Treatment of **53** with potassium hydride and HMPA led to enolisation of the β-keto ester and cyclisation occurred *via* path b with the carbonate functioning as a leaving group. This leads to inversion of configuration at C(6) and the resultant Bartlett intermediate **56** was then converted to (+)-nonactic

acid methyl ester **28**.[29] Bartlett *et al.* then used **28** and **55** in the synthesis of nonactin (section 1.5).

An interesting route to the formation of a Bartlett type intermediate and hence nonactic acid was introduced by Barrett *et al.* in 1983.[30]

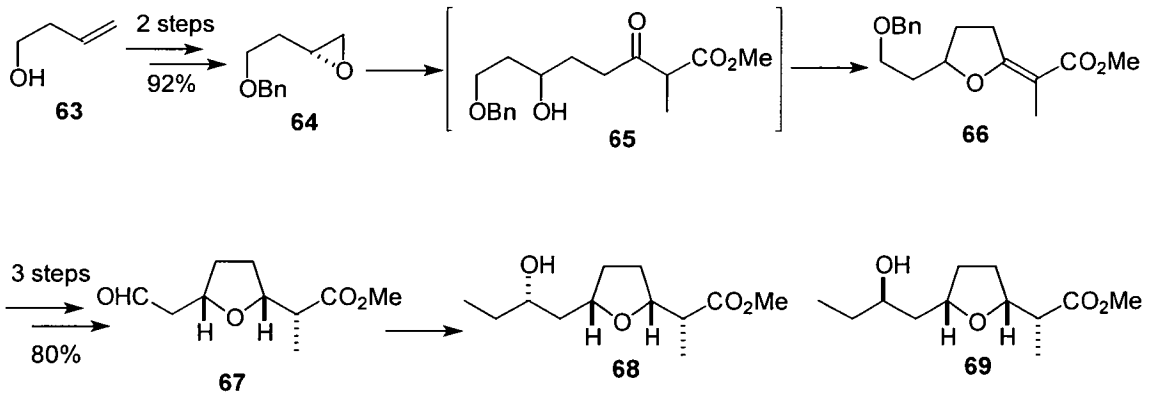


Scheme 1.9: Barrett Synthesis of Nonactic Acid *tert*-Butyl Ester

2,3,5-*O*-Triacetyl-D-ribonolactone **57** was converted to lactol **58** in 3 steps. A Wittig reaction gave intermediate **59** which was not isolated but hydrogenated over rhodium on alumina and acidified to give lactone **60**. A cross-Claisen condensation was carried out between lactone **60** and the lithium enolate of *tert*-butyl propanoate to give the Bartlett intermediate **61**. Hydrogenation of the Bartlett intermediate gave an 85:15 ratio of *cis:trans* tetrahydrofuran rings of the nonactic acid derivative **62**.

Many other groups have used these routes to nonactic acid. Johnson *et al.*[31,32] and Kim and Lee[33] have synthesised nonactic acid *via* Bartlett's *syn* 1,3-diol **45** (scheme 1.7). Barrett's lactone **60** (scheme 1.9) has been synthesised by Sutherland *et al.*,[34] Batmangherlich and Davidson,[35] and Honda *et al.*.[36] Different routes for the synthesis of the Bartlett intermediate **48** have also been investigated by Deschenaux and Jacot-

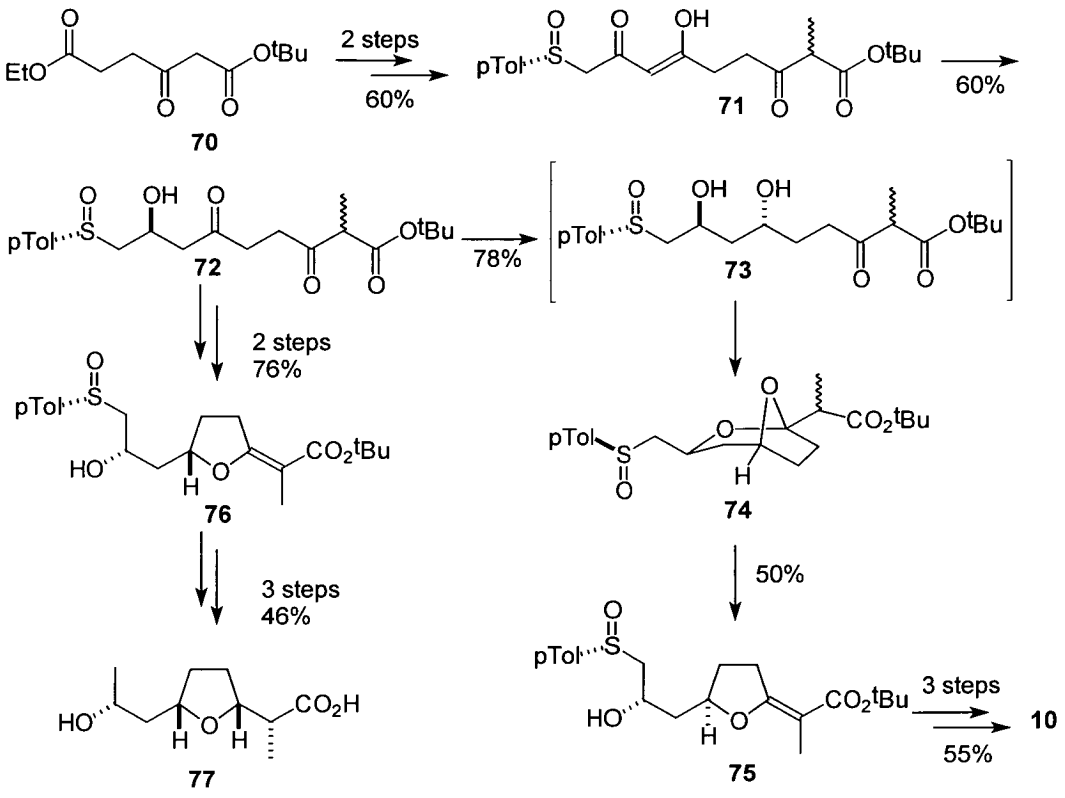
Guillarmod, [37] and Kim and Lee.[38] These approaches to the synthesis of nonactic acid are all discussed in a review of nonactic acid synthesis by Fleming and Ghosh.[39] One example of the hydrogenation of a Bartlett intermediate which is not discussed in Fleming's review is Lygo's synthesis of homononactic acid (scheme 1.10).[40,41]



Scheme 1.10: Lygo Synthesis of Homononactic Acid Methyl Ester

Epoxide **64** was synthesised from 3-buten-1-ol **63** in 2 steps, then reacted with the dianion of methyl (2-methyl-3-oxo)butanoate to give hydroxy β-keto ester **65**. This material was cyclised to give the Bartlett intermediate **66**. Debenzylation followed by *syn* hydrogenation at high pressure over rhodium on alumina to remove the double bond and oxidation of the hydroxy group gave aldehyde **67**. Addition of diethyl zinc in the presence of titanium tetrachloride gave a 4:1 ratio of diastereomers **68:69** in favour of homononactic acid methyl ester. The use of diethyl zinc and boron trifluoride etherate was found to give a 10:1 ratio of diastereomers **69:68** in favour of 8-*epi*-homononactic acid methyl ester.

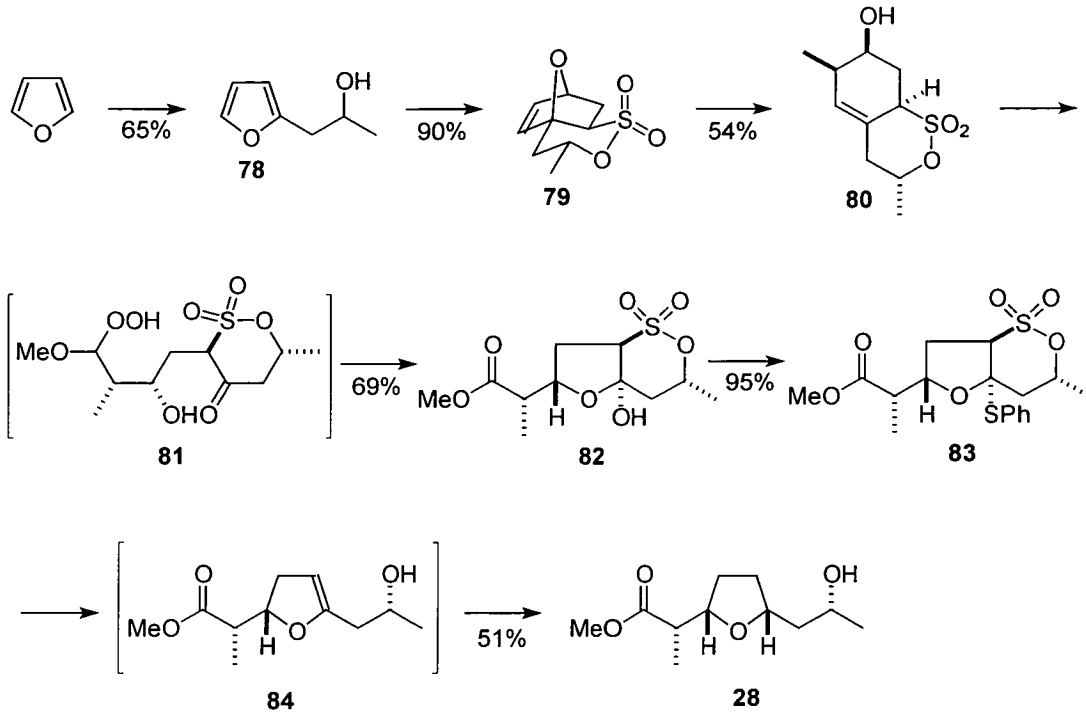
A more recent application of the Bartlett intermediate in the synthesis of nonactic acid is seen in the work of Solladie and Dominguez.[42]



Scheme 1.11: Solladie and Dominguez Nonactic Acid Synthesis

The diester of 3-oxoadipic acid **70** was methylated and the ethyl ester displaced with the dianion of a chiral sulfoxide to give **71**. Reduction of **71** with DIBAL gave the [S(*R*),8(*S*)] hydroxy sulfoxide **72**. *Anti* reduction with tetramethylammonium triacetoxyborohydride gave the *anti* diol **73** which spontaneously cyclised to give the bicyclic acetal **74**. Acid treatment of acetal **74** resulted in the opening of the 7-membered ring to form the Bartlett intermediate **75**. Desulfurization with Raney nickel, hydrogenation over rhodium on alumina and hydrolysis of the ester gave (+)-nonactic acid **10**. Hydroxy sulfoxide **72** was also used as an intermediate in the synthesis of (-)-8-*epi* nonactic acid. *Syn* reduction of **72** with diethylmethoxyborane and sodium borohydride followed by dehydration led to the formation of the Bartlett intermediate **76**. Conversion to (-)-8-*epi* nonactic acid was as described above.

The approach taken by Metz *et al.* also controls the stereochemistry about the tetrahydrofuran ring by hydrogenation.[43]



Scheme 1.12: Metz Synthesis of Nonactic Acid Methyl Ester

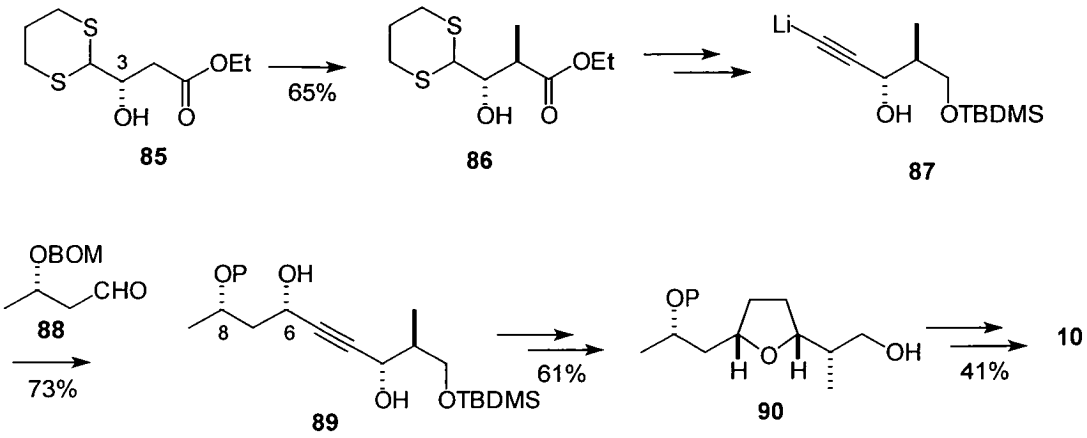
Lithiation of furan followed by allylation with epoxypropane gave compound **78**. A tandem esterification/ cycloaddition reaction with ethenesulfonyl chloride then gave **79**. Only the *exo* adduct with an equatorial alkyl group on the chair δ sultone was formed thus controlling the eventual stereochemistry at C(8). Treatment of this compound with methyl lithium induced a tandem elimination/ alkoxide directed 1,6-addition to give sultone **80** which now also has the correct stereochemistry for C(2) and C(3) of nonactic acid. On ozonolysis the primary ozonide undergoes a regioselective cycloreversion and trapping of the carbonyl oxide, which is distal to the electron withdrawing sulfonate, with methanol gives intermediate **81**. Treatment with pyridine and acetic anhydride led to formation of the tetrahydrofuran ring of **82**. Lewis acid catalysed exchange of the hydroxy group for a phenylthio group gave **83**.

Cleavage of both C-S bonds on treatment with Raney nickel led to nonactic acid methyl ester **28** *via* intermediate **84** which is hydrogenated by the hydrogen absorbed on the Raney nickel. The bulk of the C(3) side-chain controls the stereochemistry of hydrogenation with hydrogenation occurring from the least hindered side to give a ratio of *cis: trans* tetrahydrofuran rings of 96:4.

Thus since its introduction by Bartlett in 1980 the hydrogenation of a double bond exocyclic to a tetrahydrofuran ring has proved to be a very popular route to the synthesis of nonactic acid. The bulk of the C(6) side-chain has consistently given an 85:15 ratio of *cis:trans* tetrahydrofurans with the *syn* specificity of the hydrogenation also controlling the stereochemistry at C(2). The alternative strategy used by Metz *et al.* also uses the bulk of one side-chain to control the specificity of hydrogenation. In this case the bulk of the C(3) side-chain resulted in a 96:4 ratio of *cis:trans* tetrahydrofurans. Although this is better stereoselectivity than is observed for the Bartlett intermediate this route does not have the associated benefit of simultaneous control over the C(2) chiral centre.

1.4.3 Cyclisation of a 1,4-Diol Derivative

This strategy has proved to be less popular than the hydrogenation of the Bartlett intermediate due to the fact that all 4 chiral centres must be controlled in an acylic precursor. Cyclisation to form the tetrahydrofuran ring then involves inversion of configuration at either the C(3) or C(6) centre.



Scheme 1.13: Kajiwara Synthesis of Nonactic Acid

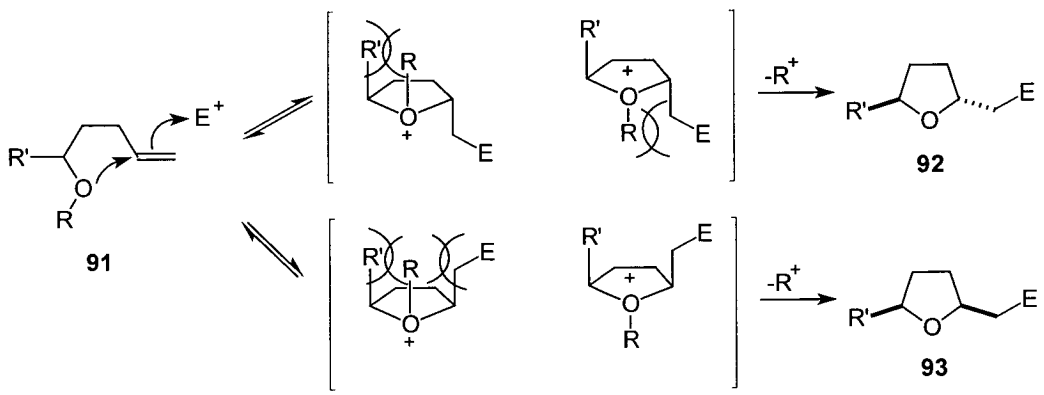
The strategy used by Kajiwara and co-workers is shown in scheme 1.13.[44] The C(3) chiral centre was controlled by the use of the chiral ester **85** which was derived by a yeast reduction. The C(2) chiral centre was introduced stereoselectively by methylenation of **85** by the method of Frater.[45] This product was then converted to the lithium acetylide **87** in a further 4 steps. Homochiral aldehyde **88** provided the chiral centre at C(8) and although the addition resulted in an epimeric mixture at C(6) the 2 diastereomers were separated and a Mitsonobu inversion employed to convert the undesired material into the correct diastereomer **89**. The C(6) hydroxy group was tosylated and C(1) and C(3) were deprotected leading to the formation of the tetrahydrofuran ring **90**. A further 4 steps were required to form (-)-nonactic acid.

Two other strategies involving the ring closure of 1,4-diol derivatives have been developed by the group of Fleming.[46,47] The stereochemical control needed for the synthesis of the appropriately substituted 1,4-diol derivatives is based on their work on acyclic stereocontrol using organosilicon compounds. These syntheses are discussed in detail in the review of nonactic acid synthesis by Fleming and Ghosh.[39]

The difficulty of controlling all the stereocentres in an acyclic precursor has limited this approach to the work of these 2 groups.

1.4.4 Electrophilic Addition to a Double Bond

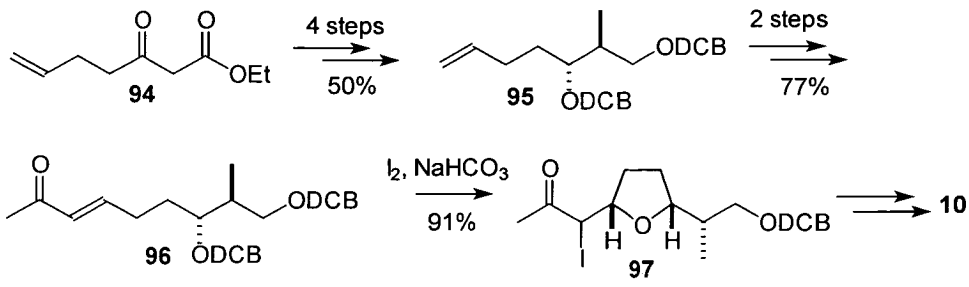
Although electrophilic cyclisation of γ,δ-unsaturated alcohols (**91**, R = H) often favours the formation of a *trans*-tetrahydrofuran ring **92**, the use of olefinic ethers can favour formation of the *cis*-fused rings **93**. The bulk of the ether group induces steric hindrance in the transition states required for formation of the *trans*-fused ring and thus the *cis*-ring **93** is favoured (Scheme 1.14).[48]



Scheme 1.14: Electrophilic Cyclisation

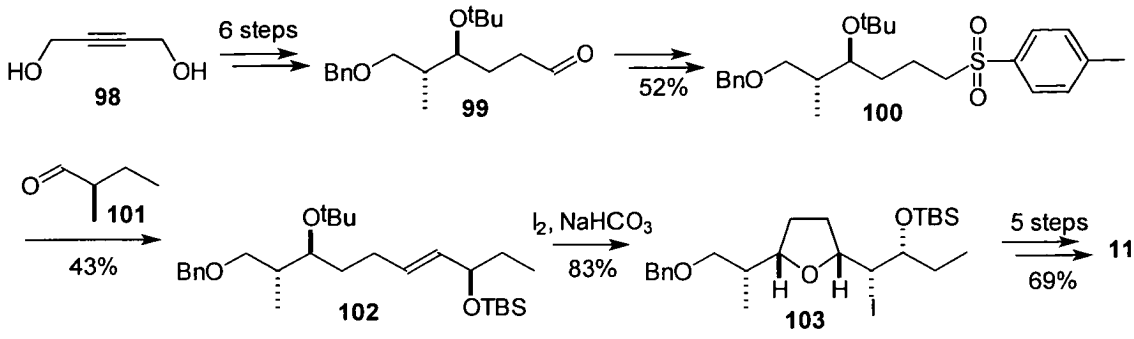
When carrying out these reactions R must be bulky enough to exert a significant steric effect without being so large it hinders cyclisation. It must also allow formation of an oxonium ion intermediate which is stable enough to favour this *cis*-product thermodynamically as well as kinetically, but not so stable as to encourage side reactions such as cleavage of the other carbon-oxygen bond. A study of the iodocyclisation of such compounds by Bartlett and Rychnovsky found the 2,6-dichlorobenzyl (DCB) group to be the optimal group for this purpose with ratios of

up to 50:1 *cis:trans* being obtained for the iodocyclisation of DCB ethers. This reaction was utilised by Kajiwara in the synthesis of nonactic acid.[49]



Scheme 1.15: Kajiwara synthesis of Nonactic Acid

β-Keto ester **94** was prepared from the dianion of ethyl acetoacetate and allyl bromide. Reduction with sodium borohydride gave the racemic alcohol which underwent an *anti* selective methylation reaction at the α-position of the ester (*anti:syn* 98:2). Reduction of the ester to the alcohol and DCB protection of both hydroxy groups gave **95**. Ozonolysis with reductive workup gave the aldehyde which underwent a Horner Wadsworth Emmons reaction to give the (*E*)-α,β-unsaturated ketone **96** in 77% yield. The iodoetherification reaction was then used to form the *cis* tetrahydrofuran ring selectively (*cis:trans* 96:4). Radical cleavage of the C-I bond was carried out with tributyltin hydride and AIBN. Microbial reduction of the racemic ketone **97** with Baker's yeast proceeded with high enantioselectivity to give a mixture of (+)-nonactic acid and (-)-8-*epi*-nonactic acid both with optical purity >97% ee. Iodoetherification has also been used by Kiyota in the synthesis of homononactic acid (Scheme 1.16).[50]

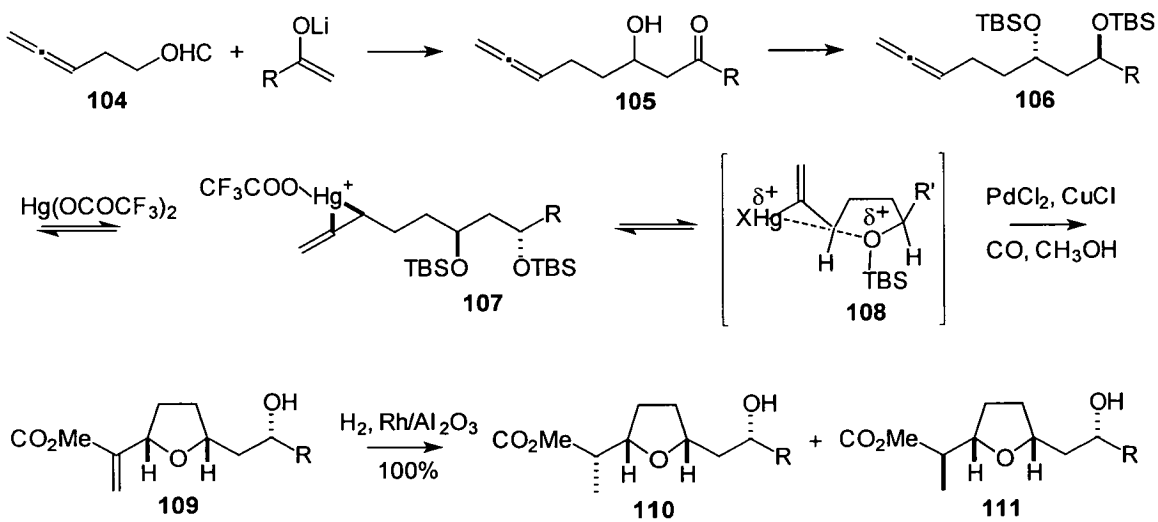


Scheme 1.16: Kiyota Nonactic Acid Synthesis

Aldehyde **99** which incorporates the C(2) and C(3) chiral centres was synthesised in 6 steps from 2-butyne-1,4-diol **98**. The aldehyde **99** was transformed to sulfone **100** *via* the corresponding iodide. α-Silyloxyolefin **102** was then formed by a Julia coupling reaction of the sulfone **100** with chiral aldehyde **101**. Iodocyclisation of the olefinic ether proceeded in 83% yield giving a >20:1 ratio of *cis:trans* tetrahydrofurans **103**. Removal of the iodide was carried out in 83% yield with tributyltin hydride and AIBN. Removal of the benzyl group, oxidation of the resultant alcohol to the corresponding acid and deprotection of the secondary alcohol then completed the synthesis of homononactic acid **11**.

The electrophilic cyclisation of alkenes is a strategy which has also been used by Walkup and Park in the synthesis of nonactic acid methyl ester, homononactic acid methyl ester, bishomononactic acid methyl ester and the unnatural analogue trishomononactic acid methyl ester (scheme 1.17).[19] In this case the cyclisation precursors were a range of 6,7-octadiene-1,3-diol derivatives **106**. These were synthesised by the addition of the lithium enolates of acetone, 2-butanone, 3-methyl-2-butanone and 3,3-dimethyl-2-butanone to 4,5-hexadienal **104** to give a series of β-

hydroxy ketones **105**. The β-hydroxy ketones were reduced with tetramethylammonium triacetoxyborohydride to give *anti* 1,3-diols (*anti:syn* >90:10) and these diols were converted to the bis(*tert*-butyl-dimethylsilyl)oxy allenes **106**. The electrophilic cyclisation was carried out using mercuric trifluoroacetate to form cyclised vinylmercuric intermediate **107**. Reaction of the C(6) oxygen at C(3) gives intermediate **108**. As in the iodocyclisation it is the bulk of the ether which controls the stereochemistry of the mercury-mediated cyclisation and results in formation of the *cis* tetrahydrofuran (*cis:trans* >98:2). A transmetalation-methoxycarbonylation of the mercuric intermediate with $PdCl_2$ in methanol under carbon monoxide then gives the dehydrononactates **109** in good yields. The 2-step oxymercuration, transmetallation-methoxycarbonylation procedure is necessary as the conditions required for a direct oxypalladation methoxycarbonylation have been shown to cleave the silyl ether which is imparting the stereoselectivity. Hydrogenation of **109** was carried out over rhodium on alumina to give nonactate ester diastereomers **110:111** (50:50).

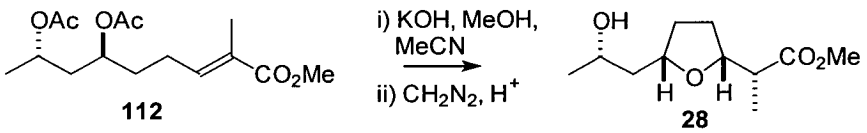


Scheme 1.17: Walkup and Park Nactic Acid Synthesis

An iodocyclisation strategy similar to those discussed has also been used by Baldwin and McIver.[51] Iqbal *et al.* have used an electrophilic addition strategy based on cyclising a γ,δ-unsaturated alcohol with MCPBA.[52] In this case the stereochemistry is controlled by a remote methoxycarbonyl group. These syntheses are discussed in the review of nonactic acid synthesis by Fleming and Ghosh.[39]

1.4.5 Conjugate Addition of Alkoxides

The base catalysed addition of an alkoxide ion onto an unsaturated ester was a strategy which was introduced by Gerlach and Wetter in 1974.[23] They produced the racemic *anti*-1,3-acetate **112** in 5 steps from acetylacetone.

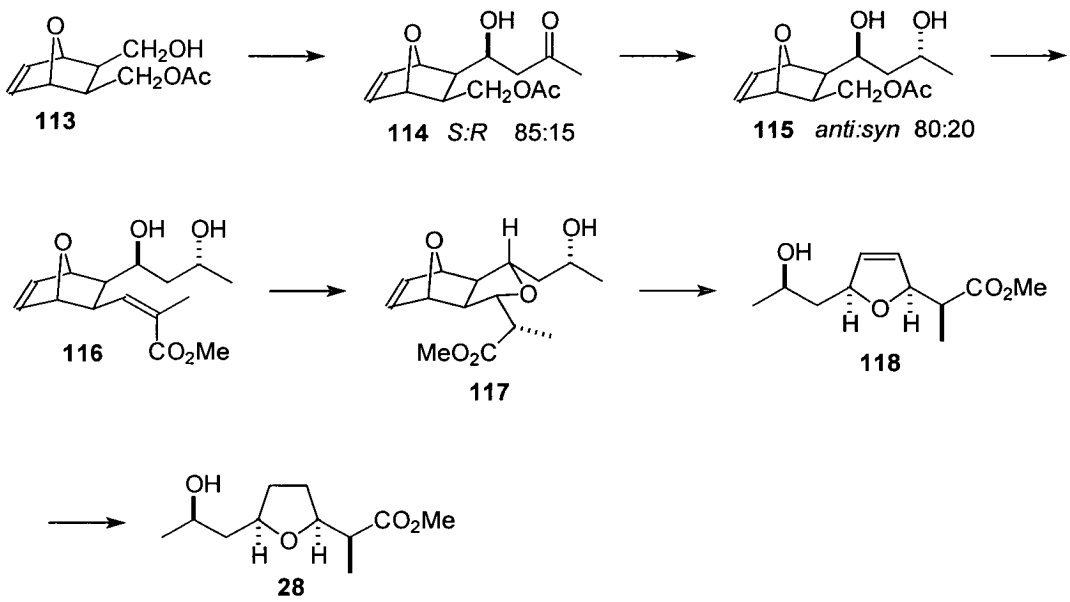


Scheme 1.18: Gerlach and Wetter Synthesis of Nonactic Acid Methyl Ester

Base catalysed cyclisation of **112** (*E:Z* 70:30) gave a mixture of 4 diastereomers in the ratio 34:23:19:24. Nonactic acid methyl ester **28** was isolated as the major product from the mixture.

More recently Bloch *et al.* have used a stereoselective Michael addition to form the tetrahydrofuran ring.[53] The enantiomerically pure hydroxy acetate **113** was prepared by esterification of the corresponding diol in the presence of lipase PS. Oxidation to the aldehyde and condensation with the lithium enolate of acetone gave the hydroxy ketone **114** selectively (*S:R* 85:15). Reduction of the ketone with tetramethylammonium triacetoxy borohydride gave the *anti* diol **115** (*anti:syn*

80:20). Protection of the diol and conversion of the acetate to an aldehyde followed by Horner Emmons reaction of the aldehyde with methyl diphenoxyphosphonopropionate and deprotection of the diol gave unsaturated ester **116**. Treatment with benzyltrimethylammonium methoxide effected the cyclisation with only the *cis* tetrahydrofuran ring being produced. A 1:1 mixture of isomers at C(2) was obtained but these were separated and the undesired isomer equilibrated to a mixture of the two isomers to improve the yield of the desired product **117**. Heating of the tricyclic compound **117** gave dihydrofuran **118** which was hydrogenated to give (+)-nonactic acid methyl ester **28**.



Scheme 1.19: Bloch Synthesis of Nonactic Acid Methyl Ester

Although the alkoxide addition introduced by Gerlach and Wetter[23] had little stereochemical control (scheme 1.18) the bicyclic system introduced by Bloch *et al.*[53] (scheme 1.19) allowed the *cis* tetrahydrofuran to be formed selectively. The use of bicyclic intermediates in the synthesis of nonactic acid is a strategy which was first used by White *et al.* in 1976 to control the stereochemistry about the tetrahydrofuran

ring.[54] Warm and Vogel have used a bicyclic intermediate to control the relative stereochemistry of C(2) and C(3).[55] The use of these bicyclic intermediates has been reviewed by Fleming and Ghosh.[39]

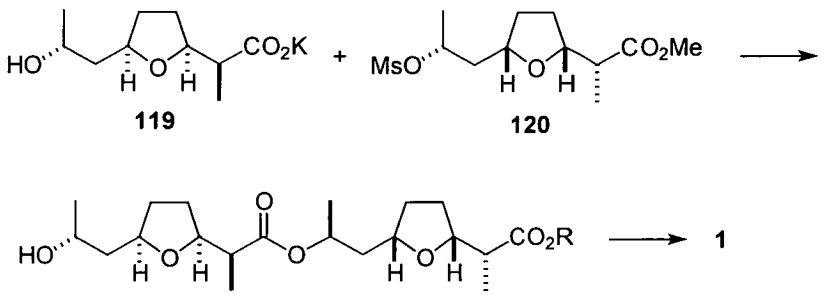
1.5 Macrocycle Construction

There have been two basic strategies used in the construction of the polynactins. The cyclodimerization strategy involves forming dimers of the nactic acid then coupling two of these dimers and carrying out the macrotetrolisation in one step (section 1.5.1). The alternative strategy involves first forming a linear tetramer from the nactic acids and cyclising this to form the macrotetrolide in a separate step (section 1.5.2). There are also two different coupling strategies which can be used to link the nactic acid subunits. The nonactic acid enantiomers can be linked by standard esterification techniques which preserve the C(8) stereochemistry on formation of the ester linkage. Alternatively one enantiomer of nonactic acid can be used as a carboxylate nucleophile to displace, with inversion of configuration, the 8-mesylate or tosylate of the 8-*epi* diastereomer of the other enantiomer.

1.5.1 Cyclodimerization

Bartlett *et al.* employed a cyclodimerization strategy for the synthesis of nonactin in which the dimeric nonactic acid units were obtained by coupling the potassium salt of (+)-nonactic acid **119** with the mesylate of (-)-8-*epi*-nonactic acid methyl ester **120** (scheme 1.20). Treatment of **120** with 1.5 equivalents of **119** in DMF at 75 °C gave an 86% yield of the dimeric ester **121** where inversion of configuration at C(8) to that of the naturally occurring material had occurred. The methyl ester was cleaved with lithium propyl mercaptide to give an 80% yield of **122**, however 25%

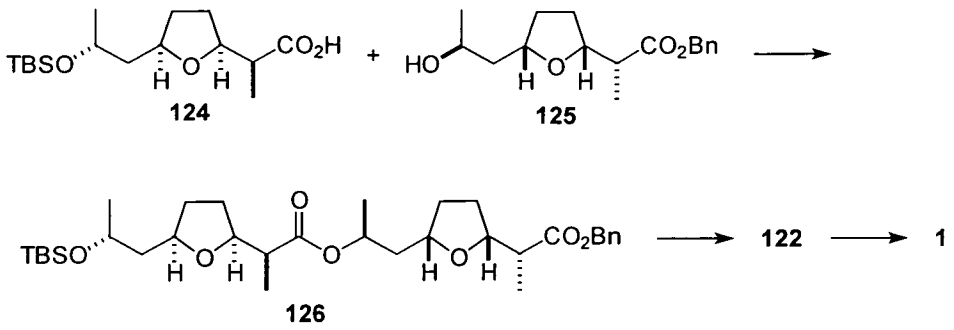
epimerisation at C(2) was found to have occurred. Cyclodimerization was caried out according to Masamune's macrolactonisation procedure. The dimeric acid **122** was converted to the mixed anhydride **123** with diphenyl phosphorochloridate and then was dimerized/cyclised in refluxing benzene in the presence of DMAP. A 15-29% yield of nonactin **1** was isolated with cyclic dimer, oligomers and polymeric material also being formed.[29]



121 R = Me
122 R = H
123 R = $PO(OPh)_2$

Scheme 1.20: Bartlett Nonactin Synthesis

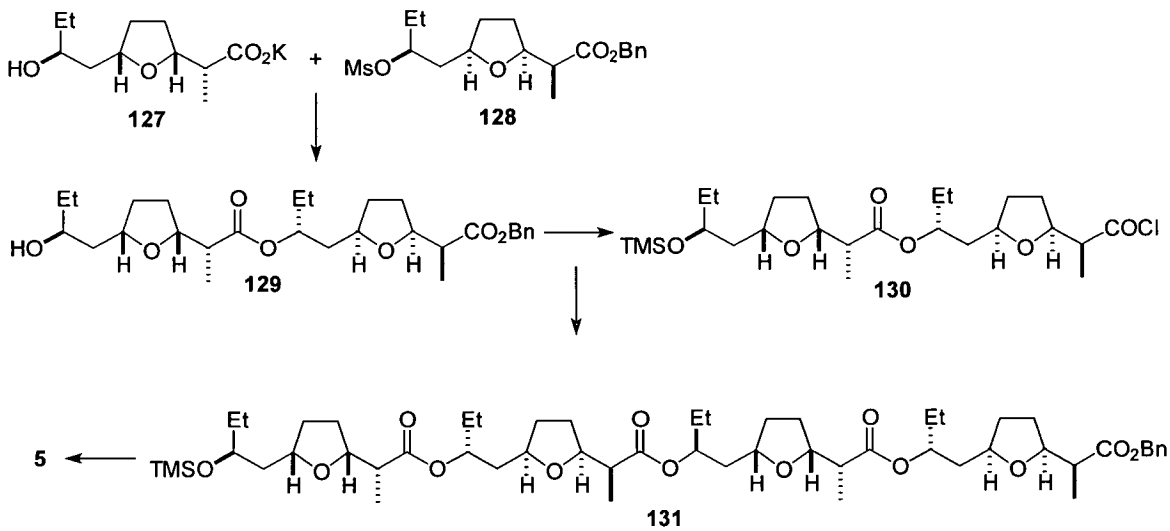
The alternative coupling strategy where the enantiomers of nonactic acid are linked with retention of configuration at C(8) has been used by Fleming and Ghosh (scheme 1.21).[56] *Tert*-butyldimethylsilyl protected (+)-nonactic acid **124** was coupled to (-)-nonactic acid benzyl ester **125** using DCC and DMAP to give a 93% yield of the dimeric material **126**. Removal of the silyl protecting group and hydrogenation of the benzyl ester gave the fully deprotected dimeric material **122** in 97% yield with no epimerisation occuring at C(2). The cyclodimerization step was carried out under Yamaguchi conditions with 2,4,6-trichlorobenzoyl chloride, DMAP and 4Å sieves gave a 52% yield of nonactin **1**, again with formation of the cyclic dimer, oligomers and polymeric material.



Scheme 1.21: Fleming Nonactin Synthesis

1.5.2 Cyclisation of Linear Tetramer

The cyclisation of a linear tetramer of homononactic acid was the strategy used by Schmidt *et al.* in the synthesis of tetranactin (scheme 1.22).[25]



Scheme 1.22: Schmidt Tetranactin Synthesis

The potassium salt of (-)-homononactic acid **127** and the mesylate of (+)-8-*epi*-homononactic acid benzyl ester **128** were coupled with inversion of configuration at C(8) to give an 80% yield of the dimer **129**. The cyclodimerization of this material was attempted; however only a very low yield of tetranactin was obtained. Instead

some of **129** was TMS protected, debenzylated and converted to acid chloride **130**. The two dimeric molecules **129** and **130** were then reacted in the presence of 4-pyrrolidinopyridine to give an 83% yield of the linear tetramer **131**. Lactonisation was then carried out with the thiolester of 3-cyano-4,6-dimethyl-2-thiopyridone under high dilution conditions to give a 51% yield of the macrocycle tetranactin **5**. Schmidt has also applied this strategy to the synthesis of nonactin.[57]

Kim and Lee have also reported the total synthesis of nonactin.[58,59] They synthesised the dimeric species **122** according to Bartlett's methods (scheme 1.20). They found the cyclodimerization route described by Bartlett gave only a 14% yield. Attempts to improve the yield of the cyclodimerization by adding potassium perchlorate to provide a potassium ion to act as an external template to aid cyclisation were unsuccessful. Having failed to improve on Bartlett's yields for cyclodimerization Kim and Lee turned to the alternative strategy of cyclising a linear tetramer. The linear tetramer was formed by similar methods to those described for Schmidt's synthesis of tetranactin (scheme 1.22). Yamaguchi high dilution conditions were used for the final macrolactonisation giving a 54% yield of nonactin. The presence of potassium perchlorate was found not to improve the macrolactonisation reaction.

Cyclisation of a linear tetramer is a strategy which has also been used by Fleming and Ghosh.[56,60] They carried out the synthesis of the dimeric nonactic acid unit **126** as described in scheme 1.21. The silyl protecting group was removed from half of this ester and the benzyl protecting group was removed from the other half. The two dimeric units were then coupled under Yamaguchi conditions. The resultant linear tetramer was deprotected and subjected again to Yamaguchi conditions to give a

73% yield of nonactin. Again potassium co-ordination was found not to improve the cyclisation.

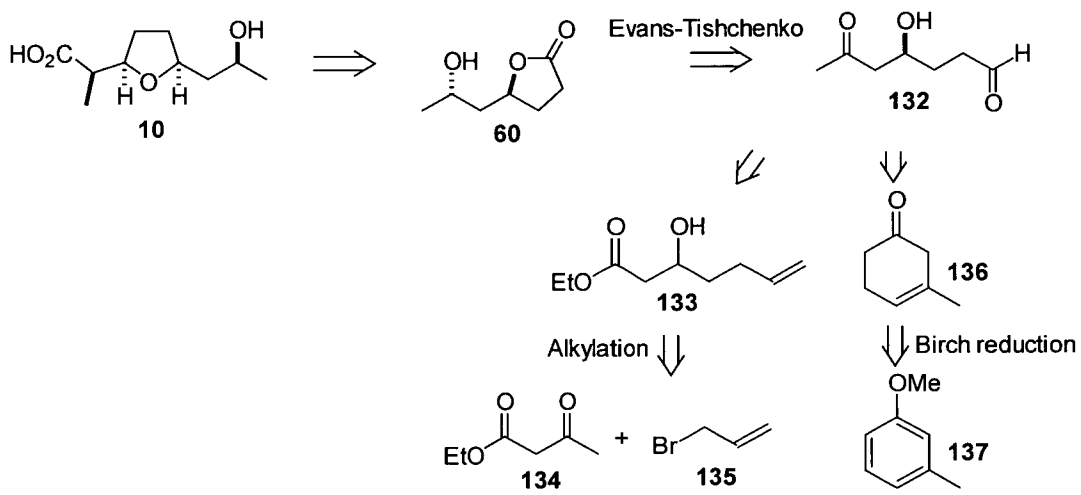
Thus, although the cyclisation of a linear tetramer is a longer approach to the synthesis of the polynactins it gives better control over the cyclisation than cyclodimerization does. This can be useful for obtaining improved yields of the symmetrical polynactins nonactin and tetranactin. If synthesis of the less symmetrical macrotetrolides was undertaken the linear tetramer route would have to be employed.

Chapter 2 : Results and Discussion Part 1

An Intramolecular Evans-Tishchenko Approach to Nonactic Acid

2.1 Retrosynthetic Analysis of Nonactic Acid

A retrosynthetic analysis of nonactic acid **10** is shown in scheme 2.1. The Barrett lactone **60** is a known intermediate in the synthesis of nonactic acid (scheme 1.9).



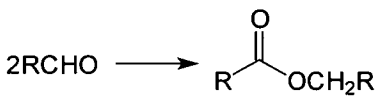
Scheme 2.1: Retrosynthetic Analysis of Nonactic Acid

It was proposed that an intramolecular Evans-Tishchenko reaction of **132** could be used to form the Barrett lactone **60**. Two routes were investigated for the synthesis of this Evans-Tishchenko precursor **132**. The first route (section 2.7) is based on the alkylation of ethyl acetoacetate **134** with allyl bromide **135** to give intermediate **133**. The second route (section 2.8) involves a Birch reduction of *m*-methylanisole **137** to give intermediate **136**. The final step in both of these routes involves an ozonolysis reaction and this is discussed in section 2.9. The synthesis of a suitable precursor for

an intramolecular Evans-Tishchenko reaction to form a 6-membered ring was also undertaken (section 2.10).

2.2 The Tishchenko Reaction

In 1887 Claisen discovered a modification of the Cannizzaro reaction where benzaldehyde was converted into benzyl benzoate in the presence of sodium alkoxide. Tishchenko and co-workers extended these findings, showing that in the presence of aluminium alkoxides both aliphatic and aromatic aldehydes condensed in this way. The coupling of two moles of an aldehyde to form an ester as shown in scheme 2.2 is now known as the Tishchenko reaction.[61]

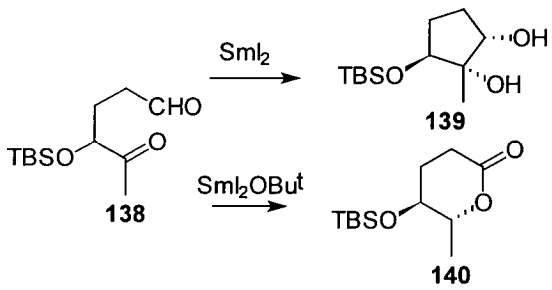


Scheme 2.2: Tishchenko reaction

This reaction is often catalysed by aluminium alkoxides or boron alkoxides[62] although a wide range of catalytic systems such as $LiNO_2$, $Fe_2(CO)_4$, Cp_2MH_2 (M=Zr, Hf), EtLnI (Ln=Pr, Nd, Sm), have also been reported.[63] $RuH_2(PPh_3)_4$ catalyses not only the dimerization of aldehydes to esters but also the oxidative transformation of alcohols and diols to esters and lactones respectively.[64]

Kagan *et al.* have carried out Tishchenko-type couplings on a range of aliphatic and aromatic aldehydes in the presence of an active Sm(III) catalyst formed from SmI_2.[65] An intramolecular Tishchenko-type reaction has also been shown to be promoted by the use of a Sm(III) species by the group of Uenishi (scheme 2.3). When the keto

aldehyde **138** was treated with SmI_2 the Sm(II) catalyst promoted a pinacol coupling to give **139**, however when a Sm(III) catalyst SmI_2OBu^t was used an intramolecular Tishchenko reaction occurred instead with the formation of **140** as shown in scheme 2.3.[66]



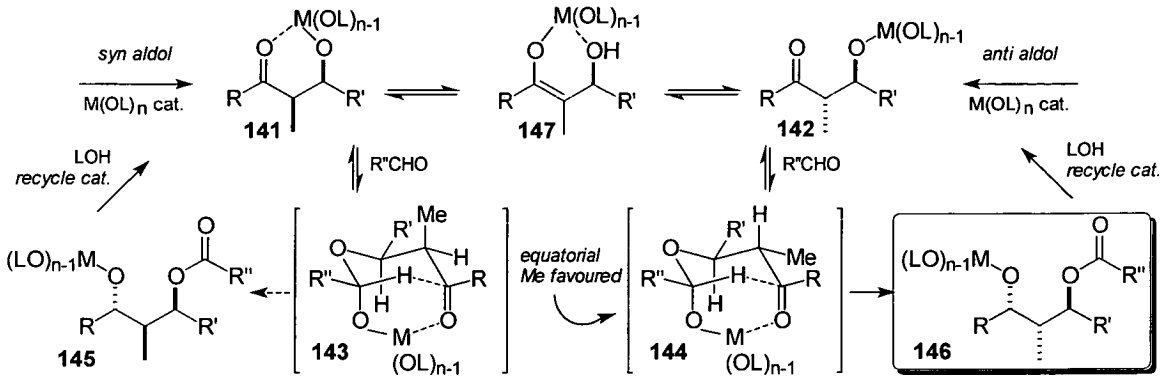
Scheme 2.3: Intramolecular Tishchenko reaction

2.3 Aldol-Tishchenko Reaction

The aldol-Tishchenko reaction involves reaction of the enolate of an aldehyde or ketone with two moles of an aldehyde to form an *anti* 1,3-diol monoester (scheme 2.4). The first step of this reaction involves an aldol condensation between the enolate and one mole of the aldehyde to form β-hydroxy carbonyl compounds **141** and **142**. The second mole of the aldehyde then reacts to form a hemiacetal which undergoes intramolecular hydride transfer to form the *anti* 1,3-diol monoester.

In all cases the stereochemical outcome of the 1,3-hydride transfer is high (>10:1) with the resultant hydroxyl groups *anti* related, indicating a highly ordered hemiacetal transition state (**143** and **144**, Scheme 2.4). However, differing levels of aldol-derived selectivity are observed (dependent on the exact nature of the metal catalyst used), favouring the *anti* aldol product **146**. This has been rationalised in terms of a rapid equilibration between *syn* and *anti* aldolates (**141** and **142**) either

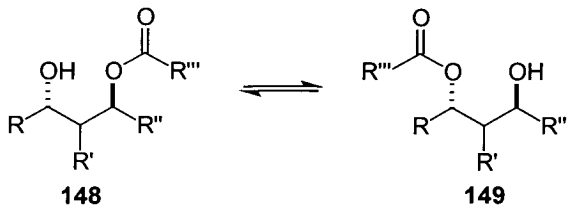
through α-deprotonation (**147**) or a retroaldol/aldol reaction, followed by a stereochemistry-determining irreversible Tishchenko hydride transfer which exhibits a preference for the transition state **144** in which the intermediate methyl group occupies a pseudo-equatorial position.[68]



Scheme 2.4: Aldol-Tishchenko Reaction

A range of catalysts including metal alkoxides,[61,69] $BuTi(OPr^i)_4Li$,[70] LDA,[71] Et_2Zn and Me_3Ga[72] have been used in the aldol-Tishchenko reaction. Samarium has also been used as a catalyst by Ishii in the form of $Cp_2Sm(thf)_2$ [73] and by Fang in the form of SmI_2 and SmI_3.[68]

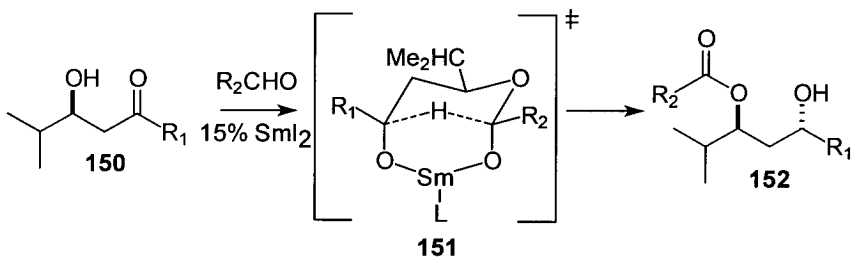
Intramolecular acyl migration has been observed to occur in the 1,3-diol monoester products of the aldol-Tishchenko reaction (scheme 2.5). This acyl migration is promoted by alkoxide formation which results in an equilibrium between the 2 diol monoesters **148** and **149**.[67,73] Increasing the reaction time and temperature has been reported to increase the amount of acyl migration which occurs.[68,70] Other factors which affect the equilibrium between the 2 products are the structure of the substrate, the solvent and the catalyst used for the reaction.[70]



Scheme 2.5: Acyl Migration in the Aldol-Tishchenko Reaction

2.4 Evans-Tishchenko Reaction

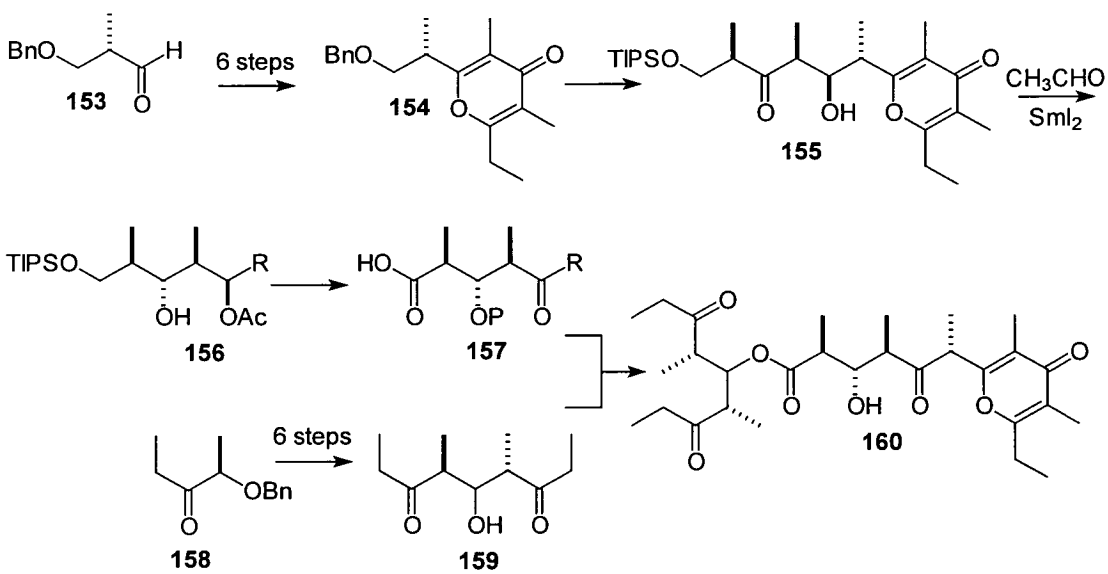
In 1990 Evans *et al.* used SmI_2 to catalyse the reaction between a β-hydroxyketone and an aldehyde as shown in scheme 2.6.[74]



Scheme 2.6: Evans-Tishchenko reaction

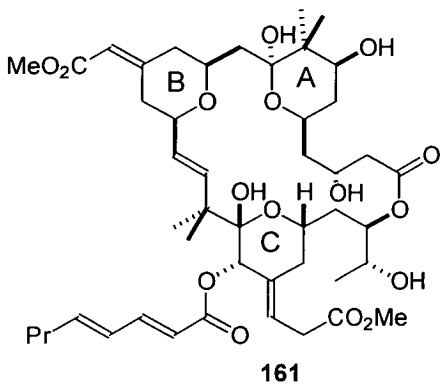
The mechanism proposed by Evans *et al.* is similar to that proposed for the aldol-Tishchenko reaction, however in the Evans-Tishchenko reaction a pre-formed hydroxy-ketone is used. The aldehyde and the β-hydroxyketone are thought to coordinate to the samarium and the reaction proceeds *via* hemiacetal formation and intramolecular hydride transfer. Evans *et al.* carry out these reactions using a catalyst made from an aldehyde and SmI_2 (scheme 2.10). The reactions are carried out at –10 °C for 30-45 minutes and under these conditions the *anti* diol monoester is obtained in high yields with the stereoselectivity for *anti*:*syn* generally being > 95:5. In addition little acyl migration (<5%) is reported under these conditions. This variation on the aldol-Tishchenko reaction where a pre-formed β-hydroxyketone is used has

allowed for the formation of more complex products. In many cases a more functionalised β-hydroxyketone has been used in conjunction with a simple aldehyde to afford the monoprotected *anti* 1,3-diol. Paterson's synthesis of baconipyrone C **160** (scheme 2.7)[75] involved the formation of γ-pyrone **154** in 6 steps from aldehyde **153**. Removal of the protecting group, Dess-Martin oxidation and a tin catalysed aldol reaction gave the Evans-Tishchenko precursor **155**. The Evans-Tishchenko reaction, carried out with acetaldehyde, proceeded in quantitative yield to give the *anti* diol monoester **156**. The resulting free hydroxyl group was PMB protected then the other hydroxy groups were deprotected and oxidised to give compound **157**. Esterification of this fragment **157** with fragment **159** which was synthesised from the lactate derived ketone **158** in 6 steps, using a modified Yamaguchi protocol, followed by removal of the PMB group gave baconipyrone C **160**. Paterson has also reported the use of the Evans-Tishchenko reaction on solid support.[76]



Scheme 2.7: Baconipyrone C synthesis

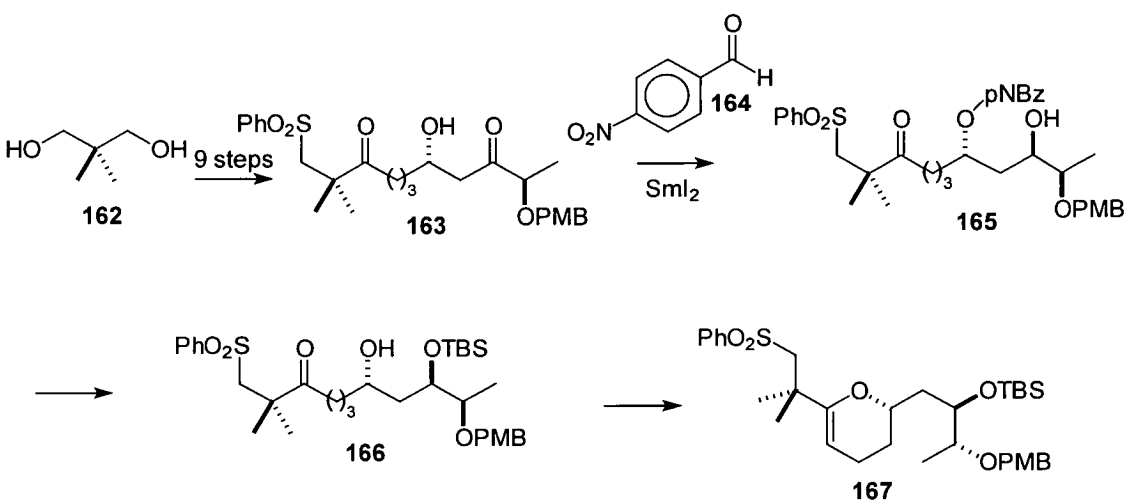
Another example of the use of the Evans-Tishchenko reaction in natural product synthesis is seen in Evans' synthesis of bryostatin 2 **161** (figure 2.1).[77]



161

Figure 2.1: Bryostatin 2

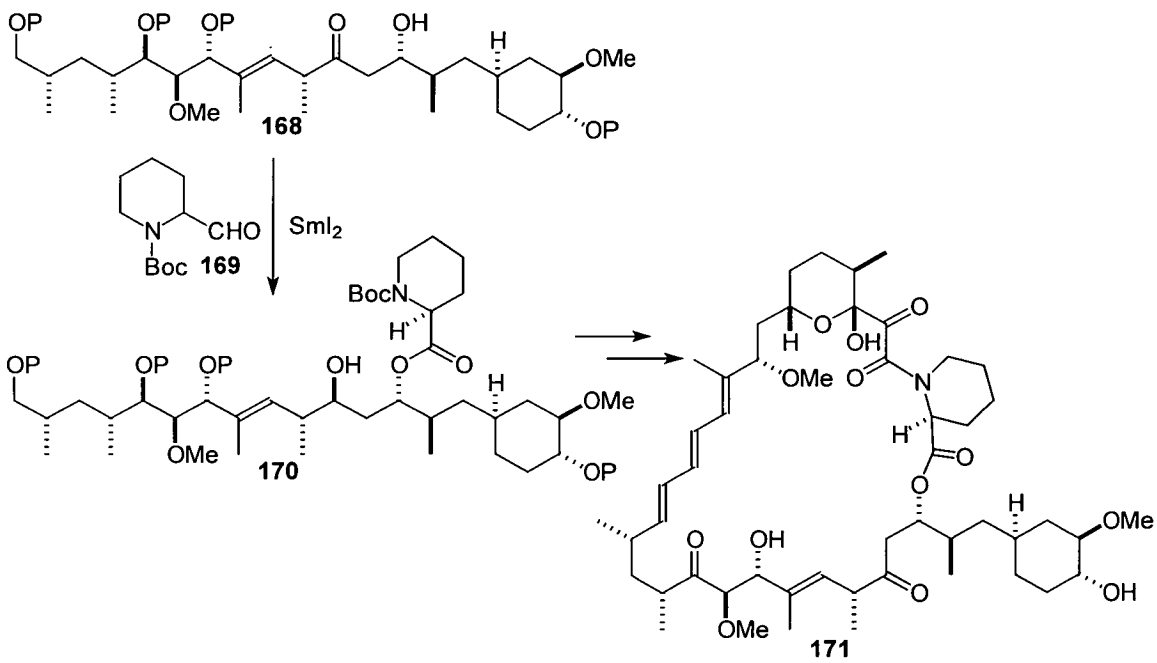
Synthesis of the C ring fragment of bryostatin 2 (scheme 2.8) involved an Evans-Tishchenko reaction on aldol adduct **163** which was prepared in 9 steps from diol **162**. The Evans-Tishchenko reaction with *p*-nitrobenzaldehyde **164** proceeded in 76% yield with a diastereoselectivity >95:5 to give **165**. The free hydroxyl group was TBS protected and the *p*-nitrobenzoyl ester was cleaved to give **166** which was cyclised with Camphor sulfonic acid to form the C ring of bryostatin 2 **167**.



162 **163** **164** **165** **166** **167**

Scheme 2.8: Bryostatin 2 synthesis

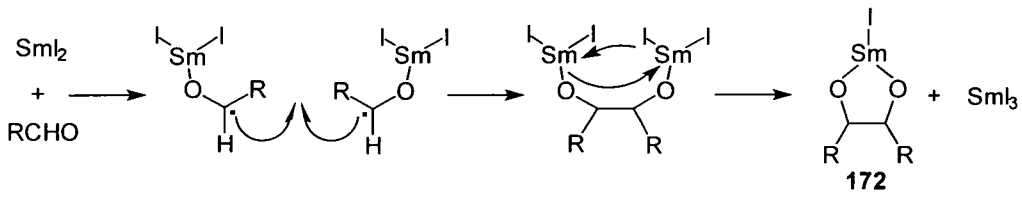
Schreiber's strategy for the use of the Evans-Tishchenko reaction in the synthesis of rapamycin **171**[78] differs from the examples discussed previously in that the aldehyde used was the more complex Boc-pipcolinal **169**, which rather than being removed to reveal the diol functionality, was actually incorporated into the structure of rapamycin. The Evans-Tishchenko reaction was carried out on the functionalised β-hydroxyketone **168** using a SmI_2•PhCHO catalyst giving a 95% yield of **170** with a selectivity of >20:1 *anti*:*syn*. Further elaboration of the chain and cyclisation were used to form rapamycin **171**.



Scheme 2.9: Rapamycin synthesis

2.5 Evans-Tishchenko Catalysts

In the majority of cases where the Evans-Tishchenko reaction has been carried out a samarium(III) species formed from SmI_2 and an aldehyde (scheme 2.10) has been used as the catalyst.



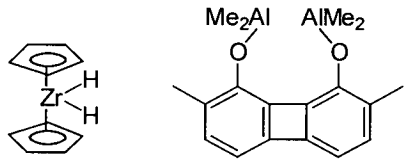
Scheme 2.10: Catalyst formation

It is the Sm(III) pinocol adduct **172** rather than SmI_2 or SmI_3 which is thought to catalyse the Evans-Tishchenko reaction. When a simple aldehyde is being used in the Evans-Tishchenko reaction then this aldehyde is often used to form the catalyst. This is seen in Paterson's synthesis of baconipyrone C **160** where acetaldehyde was used (scheme 2.7)[75] and in Evan's synthesis of bryostatin 2 **167** where *p*-nitrobenzaldehyde was used (scheme 2.8).[77] However, if a more complex aldehyde is required for the synthesis a catalyst can be made using SmI_2 and a simple aldehyde. This strategy was seen in Schreiber's synthesis of rapamycin **171** where the aldehyde used in the Evans-Tishchenko reaction was Boc-pipcolinal **169** but the catalyst used was a pinacol adduct of SmI_2•PhCHO.[78]

Only a few examples of catalysts other than those based on the formation of a Sm(III) species have been reported. Ishii has found that the zirconocene complex Cp_2ZrH_2 **173** (figure 2.2)[79] can be used to catalyse Evans-Tishchenko reactions with aliphatic aldehydes to give *anti* diol monoesters with moderate to good yields and selectivities. In addition no acyl migration is seen in thease reactions which are carried out in THF at 25 °C even when the reaction time is extended to 24 hours. However, benzaldehyde and crotonaldehyde failed to react when this catalyst is used. These aldehydes have also been found to be inert in Cp_2ZrH_2 catalysed Tishchenko

reactions and it is thought that the electron withdrawing properties of the group attached to the aldehyde hydrogen may be preventing the required hydride shift from occurring.

Maruoka has reported the bis aluminium alkoxide **174**[80] as a catalyst for both Tishchenko and Evans-Tishchenko reactions. Evans-Tishchenko reactions with benzaldehyde and hexanal were found to proceed in excellent yield giving >95:5 ratio of *anti:syn* diol monoesters.



173 **174**

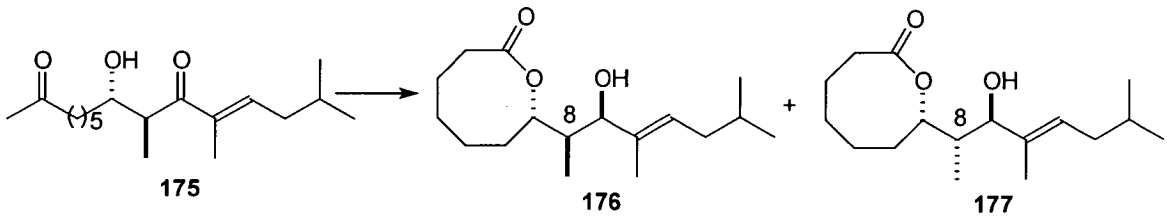
Figure 2.2: Evans-Tishchenko Catalysts

One of the disadvantages of the SmI_2•RCHO catalyst system is the sensitivity of SmI_2 to air and light. Recently the water- and air-tolerant compound scandium triflate $Sc(OTf)_3$ [81] has been used as an Evans-Tishchenko catalyst. Reactions with a range of aromatic hydroxyketones and isobutyraldehyde gave the *anti* diol monoester in yields of 17-93% with selectivities of 76-95%. Scott *et al.* report that there is no sign of acyl migration occuring with this catalyst.

2.6 Intramolecular Evans-Tishchenko Reactions

Recently, the first example of an intramolecular Evans-Tishchenko cyclisation has been carried out within the Hulme group.[82] The reaction of **175** shown in scheme 2.11 was found to proceed best with a preformed SmI_2•PhCHO catalyst which gave a

30% yield of a 1:1 mixture of diastereomers **176:177**. It is thought that the epimerisation at C(8) occurred prior to cyclisation. This strategy has also been used to form an eleven membered lactone ring.[83]

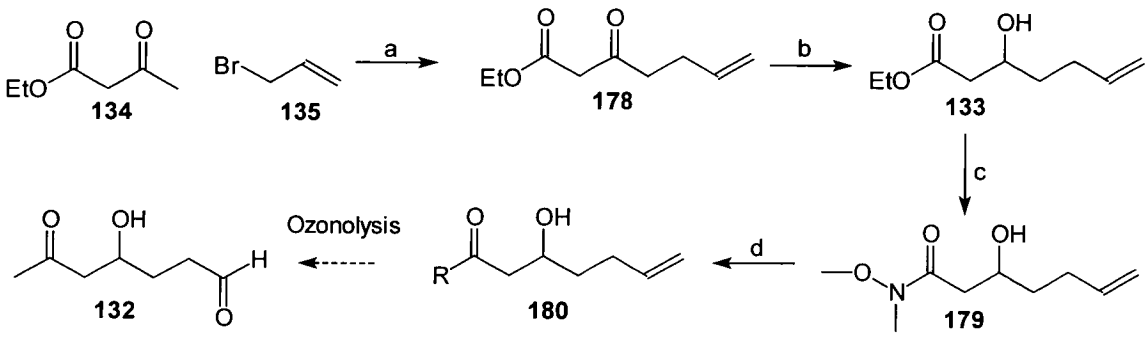


Scheme 2.11: Intramolecular Evans-Tishchenko reaction

The initial aim of this project was to investigate the use of the intramolecular Evans-Tishchenko reaction in the formation of smaller lactone rings and to see if this strategy could be applied to the synthesis of nonactic acid as discussed in section 2.1.

2.7 The Alkylation Approach

To investigate the use of an intramolecular Evans-Tishchenko reaction in the synthesis of a 5-membered lactone ring the synthesis of the acyclic precursor **132** was undertaken. In this approach to the synthesis of compound **132** the dianion of ethyl acetoacetate is reacted with allyl bromide **135** to form keto ester **178** as shown in scheme 2.12.

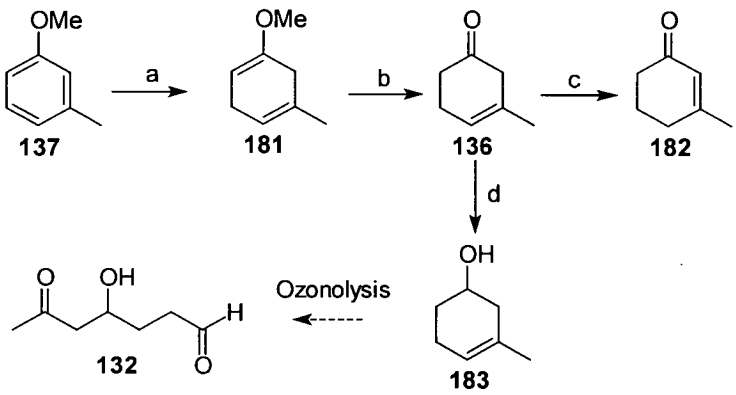


Scheme 2.12: The Alkylation Approach: *Reagents and conditions*: (a) NaH, THF, 0 °C, 10 min; BuLi, 0 °C, 10 min; allyl bromide, RT, 8 h, (89%); (b) $NaBH_4$, THF, MeOH, 0 °C, 30 min, (91%); (c) (MeO)MeNH•HCl, Me_3Al, THF, RT, 8 h, (83%); (d) MeMgBr, THF, 0 °C, 30 min (100%).

The dianion of ethyl acetoacetate was prepared by reacting ethyl acetoacetate **134** with one equivalent of sodium hydride then one equivalent of butyllithium according to Weiler's procedure.[84] The dianion was then reacted with allyl bromide **135** to form keto ester **178** in 89% yield. Selective reduction of the ketone in the presence of the ester was carried out using sodium borohydride and the resulting racemic alcohol **133** was obtained in 91% yield. Conversion of the hydroxy ester to the Weinreb amide **179** was carried out in 83% yield using (MeO)MeNH.HCl and trimethylaluminium.[85] The Weinreb amide was easily converted to the ketone **180** using MeMgBr. This strategy allows for the synthesis of nonactic acid analogues (e.g. homononactic acid R = Et) by the reaction of different Grignard reagents with Weinreb amide **179**. Ozonolysis is then required to convert the terminal alkene into the aldehyde thus setting up the required functionality for the Evans-Tishchenko reaction. This is discussed in section 2.9.

2.8 The Birch Reduction Approach

A Birch reduction of *m*-methylanisole **137** can also be used as a key step in the synthesis of the Evans Tishchenko precursor **132** (scheme 2.13). This stategy uses a starting material which contains the entire carbon skeleton of **132** and is the shorter of the two routes.



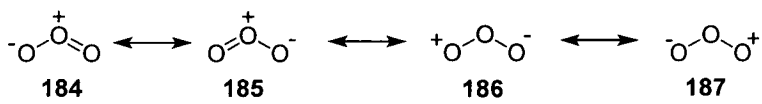
Scheme 2.13: Birch Reduction Approach: *Reagents and conditions*: (a) Li, NH_3, Bu^tOH, Et_2O, -33 °C, 3.5 h; (b) oxalic acid, MeOH, H_2O, RT, 1.5 h; (c) heat/silica; (d) $NaBH_4$, THF, MeOH, 0 °C, 40 min (36% over 3 steps).

A Birch reduction was carried out on *m*-methylanisole **137**, refluxing in liquid ammonia with Li metal and Bu^tOH as a proton source. The crude enol ether **181** which was formed in the reaction was reacted with oxalic acid in $MeOH/H_2O$ to form ketone **136**.[86] Attempted purification of this compound by distillation led to isomerisation and formation of enone **182**. Compound **136** was also found to rearrange on silica gel and purification by column chromatography led to reduced yields. To overcome these problems, the crude material was reduced using sodium borohydride in THF/MeOH to form unsaturated racemic alcohol **183** in 36% yield over 3 stages. Ozonolysis of the double bond should then open the ring and form the Evans Tishchenko precursor. This is discussed in section 2.9. The principal

disadvantage of this route is that it is not as flexible as the route which employs Weinreb amide chemistry.

2.9 Ozonolysis

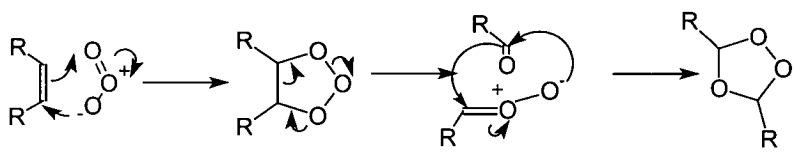
Ozone is a powerful oxidising agent which is produced in the laboratory by electric discharge in oxygen. Ozone can be viewed as a hybrid (figure 2.3).



184 **185** **186** **187**

Figure 2.3: Resonance structures of Ozone

The reaction of ozone with alkene **188** gives a 1,2,3-trioxolane product **189** (scheme 2.14). This trioxolane is thermally unstable and rapidly rearranges to a 1,2,4-trioxolane **190**, better known as an ozonide.[87]

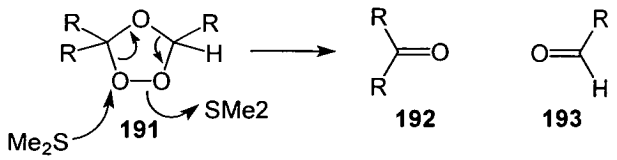


188 **189** **190**

Scheme 2.14: Mechanism of Ozonolysis

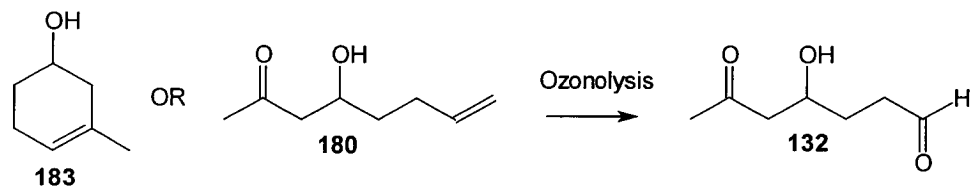
Ozonides can be decomposed by four methods: reduction, oxidation, hydrolysis or thermolysis. As the target compound is an aldehyde a reductive decomposition is appropriate. It is thought that reduction of the peroxide linkage in the ozonide **191** (Scheme 2.15) results in fragmentation to form the carbonyl compounds **192** and **193**. Mildly reducing conditions such as dimethyl sulfide or zinc and acetic acid need

to be used, as stronger reducing agents such as lithium aluminium hydride or sodium borohydride further reduce the carbonyl compounds to alcohols.



Scheme 2.15: Decomposition of Ozonide

Ozonolysis of both compounds **180** and **183** (scheme 2.16), using dimethyl sulfide to decompose the ozonide, was expected to lead to the required compound **132**.



Scheme 2.16: Expected Ozonolysis Products

The results of the first attempted ozonolysis reactions, where the ozonolysis was carried out in CH_2Cl_2/MeOH (8:1) and worked up using dimethyl sulfide showed that rather than the expected product a mixture of compounds **194** and **195** was in fact formed.

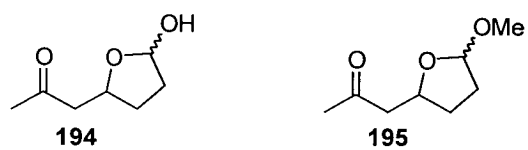


Figure 2.4: Products from Ozonolysis Reactions carried out in CH_2Cl_2/MeOH

Lactol **194**, the minor product from the reaction, is derived from cyclisation of the anticipated product **132**. At this point it was not clear whether the dimethyl sulfide or

the methanol was responsible for the formation of methyl acetal **195** so ozonolysis reactions were carried out under a variety of conditions as summarised in Table 1.

	Starting material	Solvent	Work-up	% yield	Product **194:195**	Comments
1	**183**	CH_2Cl_2/ MeOH 8:1	DMS	20-30	10:90	Trace impurities
2	**180**	CH_2Cl_2/ MeOH 8:1	DMS	20-30	10:90	Trace impurities
3	**183**	CH_2Cl_2/ MeOH 8:1	PPh_3	40-50	85:15	PPh_3O difficult to remove
4	**183**	CH_2Cl_2	DMS	62	100:0	-
5	**183**	CH_2Cl_2	Zn/AcOH	35-45	-	Mixture of products

Table 1: Ozonolysis conditions

Entry **3** shows that when PPh3 replaced dimethyl sulfide in the work-up, then the majority of the product formed was the lactol **194** rather than the acetal despite the fact that the reaction solvent still contained methanol. However, when the MeOH was removed from the solvent and dimethyl sulfide used in the work-up (entry **4**), none of acetal **195** was formed and the yield was improved. In an attempt to optimise the yield still further, a reaction was also performed in CH_2Cl_2 using a zinc/ acetic acid work-up (entry **5**), but only a trace of the desired compound **194** was formed.

The main products from the reaction in entry **5** were thought to be the acylated compound **196** and some of the reduced compound **197** (figure 2.5).

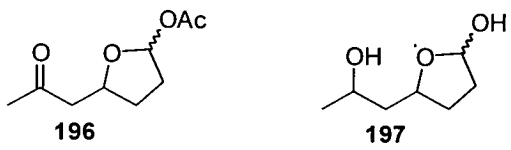
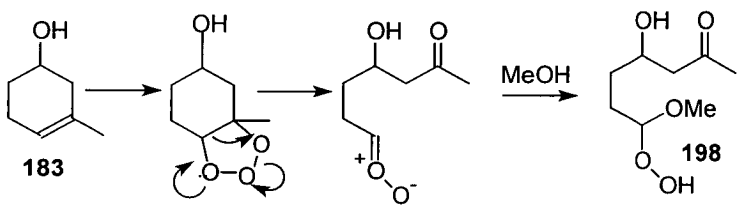


Figure 2.5: Ozonolysis Products from Zn/AcOH Reductive Work-up

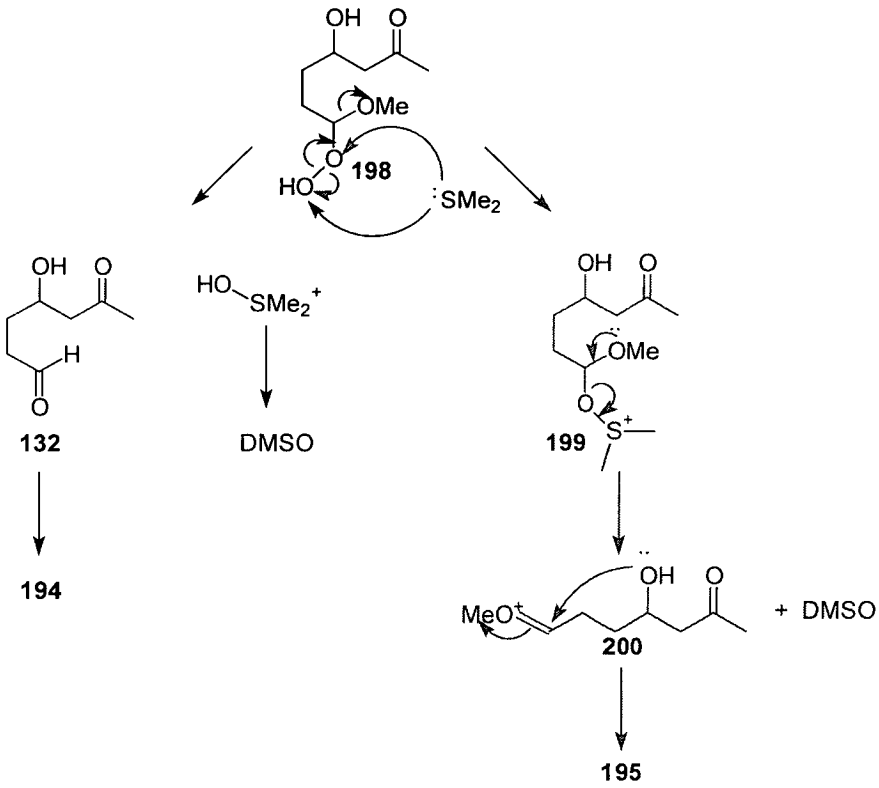
It is apparent from the results of the ozonolysis reactions that methanol is essential for the formation of the methyl acetal, however the presence of dimethyl sulfide is also important. As discussed previously, during ozonolysis the thermally unstable 1,2,3-trioxolane rearranges to a 1,2,4-trioxolane, however in the presence of methanol a peroxo-acetal **198** can be formed instead (scheme 2.17).[87]



Scheme 2.17: Peroxoacetal Formation

Considering reduction of the peroxo-acetal with dimethyl sulfide, it is possible that the dimethyl sulfide could attack either peroxide oxygen. Scheme 2.18 shows in blue how attack at the terminal oxygen of peroxo-acetal **198** followed by loss of the methoxy group leads to the formation of aldehyde **132** which will cyclise to give lactol **194**. The pathway shown in red involves the attack of dimethyl sulfide at the internal oxygen atom of the peroxo-acetal to form intermediate **199**. The loss of

dimethyl sulfoxide (DMSO) results in the formation of compound **200** which cyclises to form the acetal **195**.

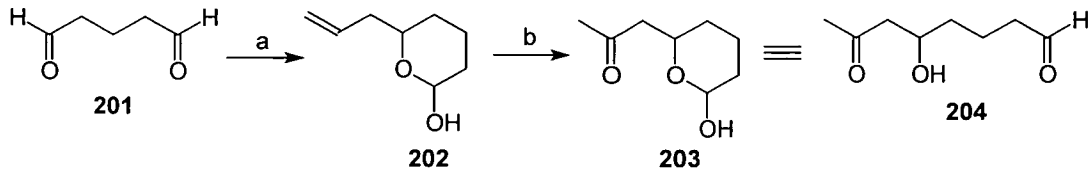


Scheme 2.18: Peroxoacetal Reduction

The ratio of lactol **194**:acetal **195** observed in entries **1**, **2** and **3** suggests that the second pathway is the favoured route for decomposition of the peroxo-acetal **198** by DMS. However when triphenyl phosphine was used the major product was found to be the lactol **194**. A similar mechanism with PPh_3 inducing collapse of the peroxo-acetal, forming triphenyl phosphine oxide as the by-product can explain the presence of both products. In this case, decomposition of the peroxo-acetal seems to favour the first route leading to the lactol. This observed switch in selectivity could be due to electronic or steric factors.

2.10 Six-Membered Ring Precursor

The substrate for the intramolecular Evans-Tishchenko reaction to form a 6-membered ring was also synthesised as the cyclised version **203** of the required compound **204** (scheme 2.19).



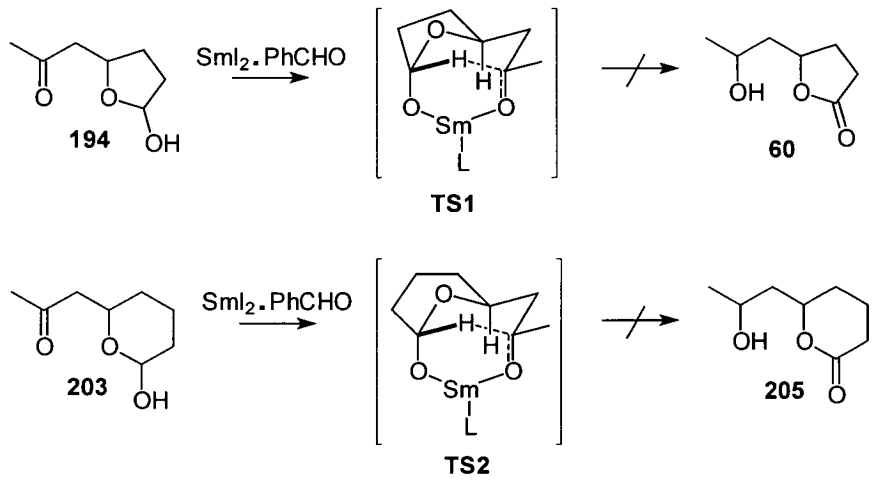
Scheme 2.19: 6-membered ring: *Reagents and conditions*: (a) Tetraallyltin, THF, 2N HCl, RT, 3 h, (51%); (b) $PdCl_2$, CuCl, DMF, H_2O, O_2, RT, 48 h, (75%).

The reaction of tetraallyltin with glutaraldehyde **201** gave a 51% yield of lactol **202**.[88] Wacker oxidation of the alkene to the methyl ketone using 10mol% $PdCl_2$, 20mol% CuCl and air was initially carried out in DMF:H_2O (7:1).[89] Purification by column chromatography gave an approximate yield of 50% of the hemiacetal **203**. However, this volatile compound was found to be contaminated with DMF. In an attempt to optimise the yield an alternative solvent system MeOH:H_2O (7:1) was used but the reaction was found to be sluggish in this solvent system. A yield of 75% was achieved by using the original solvent system of DMF:H_2O (7:1), but carrying the reaction out under an atmosphere of oxygen and purifying the product by Kugelrohr distillation.

2.11 Attempted Evans-Tishchenko reactions

The 5- and 6- membered Evans-Tishchenko precursors were found to exist exclusively as the cyclic hemiacetals **194** and **203** rather than the corresponding open- chain aldehydes **132** and **204**. Given that the first step in the Evans-Tishchenko

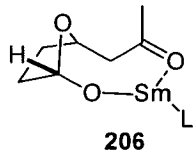
reaction has been proposed as samarium promoted hemiacetal formation it was anticipated that these hemiacetals themselves would provide suitable Evans-Tishchenko substrates. However, treatment with SmI_2•PhCHO, generated *in situ* from freshly prepared SmI_2 and benzaldehyde, failed to promote the transfer of the acetal hydride to give the *anti* diol monoester and hence the expected lactones **60** and **205** were not formed (scheme 2.20). Possible reasons for the failure of these reactions are discussed in section 2.12.



Scheme 2.20: Attempted Evans-Tishchenko Cyclisations

2.12 Conformation of Hemiacetal Intermediates

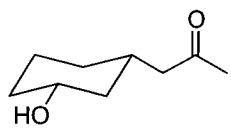
Inspection of the transition states **TS1** and **TS2** (scheme 2.20) required for the hydride transfer to occur reveals that the geometry about the ring must be *trans* to bring the acetal hydrogen towards the carbonyl group into a position which would allow hydride transfer. A *cis* lactol such as **206** (figure 2.6) would not be able to undergo hydride transfer as the acetal hydrogen is orientated away from the carbonyl group.



206

Figure 2.6: *Cis* Lactol

The incorporation of oxygen into cyclic molecules affects the conformational characteristics of the molecule. In a 1,3-disubstituted cyclohexane ring such as **207** (figure 2.7) we would expect the substituents to preferentially occupy equatorial positions, thus favouring the *cis* 1,3-disubstituted compound.



207

Figure 2.7: 1,3-disubstituted cyclohexane

However, in the equivalent disubstituted tetrahydropyran the polar hydroxyl substituent adjacent to the ring oxygen means that a phenomenon known as the anomeric effect comes into play. The anomeric effect was first discovered in 1955 and refers to the tendency of an electronegative substituent at C(1) of a pyranoid ring to assume the axial rather than the equatorial orientation, in contrast to predictions based solely on steric grounds.[90]

This effect was seen when the conformation of 2-hydroxypyran was examined by Booth *et al.*. Low temperature nmr of 2-hydroxytetrahydopyran in $CFCl_3/CDCl_3$ gave an equilibrium constant (e/a) of 1.96-2.01 (figure 2.8).[91]

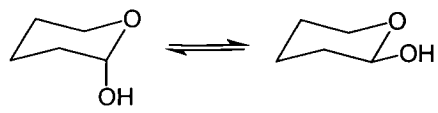


Figure 2.8: Equilibrium of 2-hydroxytetrahydropyran

Comparable equilibrium constants of 1.56-3.0 have been determined for 2-hydroxytetrahydropyran at higher temperatures in CS_2. The acid catalysed equilibrium of 2-hydroxy-4-methyltetrahydropyran has also been studied by Booth *et al.*. This compound was found to exist as a 1:1 mixture of the *cis* and *trans* isomers where the methyl group was always in an equatorial position (figure 2.9).[91]

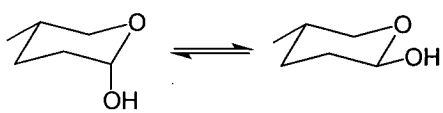


Figure 2.9: Conformation of 2-hydroxy-4-methyltetrahydropyran

One possible explanation of the anomeric effect is that an unfavourable dipole-dipole interaction between C-O bonds and the substituent is greater when the substituent is equatorial than when it is axial (figure 2.10).[92]

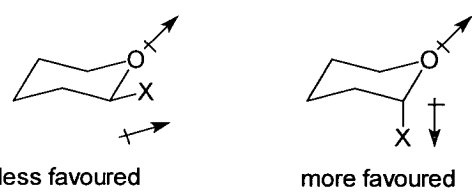


Figure 2.10: Dipole-Dipole Interactions

The rationalisation of the anomeric effect solely in terms of dipole-dipole interactions fails to account quantitatively for observed axial preferences and does not predict the bond-length and bond-angle changes which are a characteristic feature of the anomeric effect. In compounds where the anomeric effect plays a role in the conformation, the preference for axial orientation of the electronegative substituent X is accompanied by a significant lengthening of the C-X bond, and a concomitant shortening of the adjacent C-O bond. This effect can be rationalised by considering an explanation for the anomeric effect based on resonance stabilisation (figure 2.11).[92]

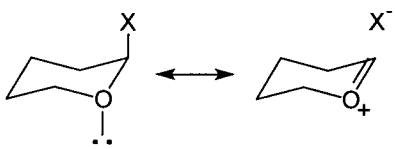
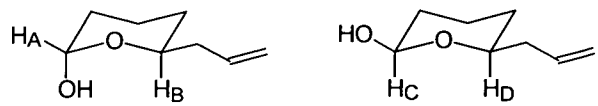


Figure 2.11: Resonance Stabilisation of Axial Substituents

We can consider an axial substituent to be stabilised relative to the equatorial by donation of a lone pair from the ring oxygen into the antibonding orbital of the C-X bond. When the substituent is axial the overlap of the orbitals involved is better than if the substituent was equatorial. Hence the axial substituent will have more effective electron delocalisation and be more stabilised than an equatorial substituent would be. The donation of electrons into the antibonding orbital of the C-X bond is consistent with the observed lengthening of the C-X bond, whereas the shortening of the C-O bond can be explained by its increasing double bond character.[92]

Examination of the nmr data for compounds **202** and **203** reveal that both of these compounds exist as a mixture of *cis* and *trans* isomers.

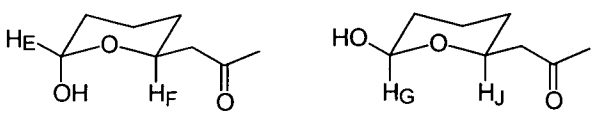


trans **202** *cis* **202**

Figure 2.12: Configuration of Compound **202**

The ^1H nmr of compound **202** shows a broad singlet at 5.29 ppm corresponding to the equatorial acetal hydrogen H_A which has small coupling constants to its neighbouring hydrogen atoms. The axial acetal hydrogen H_C from *cis* **202** is seen as a doublet of doublets at 4.70 ppm with J_{aa} = 9.1 Hz and J_{ae} = 3.3 Hz. The ratio of integrals from the signals for H_A and H_C suggest that **202** exists as a 4:5 mixture of *trans: cis* isomers. Separate signals for H_B and H_D can also be seen on the ^1H nmr. H_B appears as a dtd at 4.01 ppm with a large value of J_{aa} = 11.5 Hz and a smaller J_{ae} = 2.1 Hz confirming that this proton is in an axial position. A coupling constant $J_{triplet}$ = 5.7 Hz to the CH_2 adjacent to the alkene is also seen. A similar dtd is seen for H_D at 3.47 ppm with J_{aa} = 12.5 Hz, J_{ae} = 2.1 Hz and $J_{triplet}$ = 5.7 Hz. The ^{13}C nmr also confirms that **202** exists as a mixture of 2 isomers.

Wacker oxidation of compound **202** results in the retention of the 4:5 mixture of *trans: cis* **203** (figure 2.13).

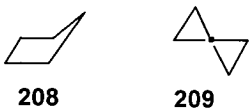


trans **203** *cis* **203**

Figure 2.13: Conformation of Compound **203**

Similarly to the case for H_A and H_C, H_E appears as a broad singlet at 5.22 ppm with the signal for H_G at 4.73 ppm being split into a dd with J_{aa} = 9.7 Hz and J_{ae} = 3.3 Hz. The signals for H_F and H_J have now become more complex as the 2 hydrogen atoms of the CH_2 group adjacent to the carbonyl group are no longer equivalent. This suggests that there is now restricted rotation about this carbon, possibly due to dipole-dipole interactions between the ring oxygen and the carbonyl group. Alternatively the increased bulk of the carbonyl substituent could be hindering rotation. H_F appears as a dddd at 4.42 ppm with the large J_{aa} = 11.4 Hz and the small J_{ae} = 2.2 Hz showing that the proton is still in an axial position. Coupling constants of 8.4 Hz and 4.4 Hz to the protons adjacent to the carbonyl group are also seen. The signal for H_J appears at 3.98-3.84 ppm but is overlapped by the OH of *cis* **203**. Again the ^{13}C nmr confirms the presence of 2 isomers of **203**.

If we consider the structure of a 5-membered ring, although a planar cyclopentane molecule would be relatively free of angle strain, considerable strain would arise from 5 perfectly eclipsed C-C bonds. There are 2 ways that cyclopentane can deform to relieve this strain. Displacement of one carbon atom above the plane of the other four gives the envelope form **208**, alternatively, displacement of two adjacent carbon atoms on either side of the plane of the remaining three gives the half chair form **209** (figure 2.14).[93]



208 **209**

Figure 2.14: Conformations of Cyclopentane

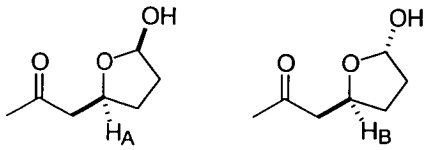
Calculations indicate that there is a very small energy barrier between these forms of cyclopentane. Movement between the two forms is called a pseudorotation and these pseudorotation equilibria are found to dominate the conformational analysis not only of cyclopentane but also of 5-membered heterocycles. Substituents on 5-membered rings can occupy pseudoaxial or pseudoequatorial positions and the anomeric effect can be generalised beyond 6-membered heterocycles to explain why the pseudoaxial substituent would be more stable than expected. The generalised anomeric effect is defined as the preference of the synclinal (*gauche*) position over the antiperiplanar (*anti*) position in segments R-X-A-Y, where A is an element of intermediate electronegativity (e.g C, S,P), Y is a more electronegative element, X is an element with lone pairs and R stands for H or C (figure 2.15).[90]

anti *gauche*

Figure 2.15: Generalised Anomeric Effect

As with pyranose rings, having a lone pair *anti* to the electronegative substituent Y stabilises this form so the *gauche* conformation is stabilised. This argument can be applied to non-cyclic molecules and rings of different sizes, including 5-membered rings. In fact, there is evidence to suggest that the anomeric effect is more pronounced in 5-membered rings than 6-membered rings due to the increased flexibility of the 5-membered ring reducing the steric effects which favour the pseudoequatorial substituent.[94]

Analysis of the ^{1}H nmr of **194** shows that the compound exists as a mixture of *cis* and *trans* isomers (figure 2.16).



cis **194** *trans* **194**

Figure 2.16: Conformation of Compound **194**

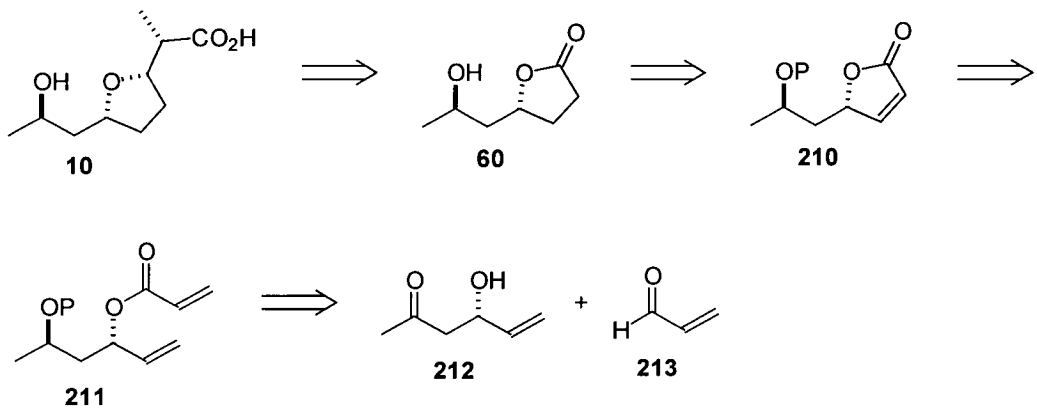
Separate signals are seen for the protons H_A and H_B. One signal appears at 4.52 ppm, the other at 4.38 ppm, and both are seen as quintets with J = 6 Hz, due to coupling to the 2 ring hydrogens and the 2 hydrogen atoms adjacent to the carbonyl group. The integrals of these signals indicate that the lactol exists as a 1:1 mixture of *cis: trans* isomers.

In both the 5- and 6-membered ring cases the required *trans* isomer has been shown to be present by nmr techniques but the Evans-Tishchenko reactions on these substrates still failed with only starting material, with the same composition of isomers, being recovered. It is thought that the transition state required for the hydride transfer to occur is just too strained to allow the formation of smaller lactone rings although earlier work has shown this to be a feasible route for the synthesis of medium sized lactone rings.

Chapter 3 : Results and Discussion Part 2

Evans-Tishchenko/Ring Closing Metathesis Approach to Nonactic Acid – Route 1

3.1 Combined Evans-Tishchenko/RCM Approach to Nonactic Acid

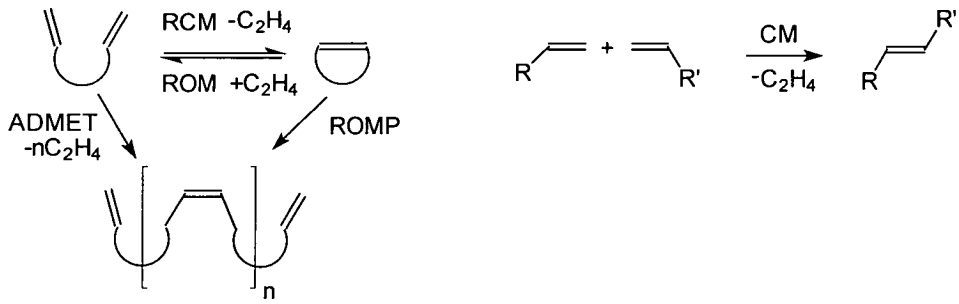


Scheme 3.1: Use of RCM in Nonactic Acid Synthesis

An alternative retrosynthetic analysis for nonactic acid which avoids the use of an intramolecular Evans-Tishchenko reaction is shown in scheme 3.1. It was proposed that carrying out an Evans-Tishchenko reaction between β-hydroxy ketone **212** and acrolein **213** would set up the required C(6), C(8) stereochemistry for nonactic acid whilst providing a substrate **211** that would be suitable for ring closure by ring closing metathesis (RCM). Hydrogenation of the ring closed product **210** would then give the Barrett lactone **60**, a known intermediate in previous nonactic acid syntheses (scheme 1.9).

3.2 Alkene Metathesis

Ziegler's discovery of catalysts that promote the polymerisation of olefins under exceptionally mild conditions led to the observation that these catalysts can also effect the mutual alkylidene exchange reaction of alkenes now known as alkene metathesis. There are different types of metathesis reaction and these are shown in scheme 3.2.[95]



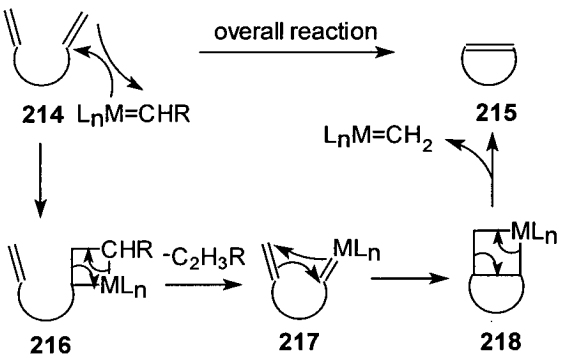
Scheme 3.2: Types of metathesis reactions: RCM = ring closing metathesis; ROM = ring opening metathesis; ADMET = acyclic diene metathesis polymerisation; ROMP = ring opening metathesis polymerisation; CM = cross metathesis.

Early examples of metathesis focused mainly on ring opening metathesis (ROM) or ring opening metathesis polymerisation (ROMP) where the release of ring strain provides the driving force for the reaction. These early reactions were carried out with catalysts which were formed *in situ* from certain transition metal salts and main group alkylating agents. These catalysts have a strongly Lewis-acidic and alkylating character which essentially restricted the scope of olefin metathesis to the production of unfunctionalised polymers.[95] Examples of ring closing metathesis (RCM) using these catalyst systems generally proceeded in poor yield with the formation of 15- and 16-membered rings in 60-65% yield as a notable exception.[96] The discovery of metal alkylidene complexes has led to a new generation of single component

metathesis catalysts that are tolerant to many functional groups and reactive towards a diverse range of substrates. These catalysts (section 3.4) have fuelled developments in the other types of metathesis reaction, particularly RCM.[95,97,98]

3.3 Mechanism of RCM

In Ziegler's catalytic systems where an *in situ* catalyst is formed from 2 organometallic species, the nature of the active catalyst is not known making it difficult to confirm any postulated mechanism. However, there is evidence to support the proposed 'Chauvin mechanism' (scheme 3.3) for alkene metathesis catalysed by metal alkylidene complexes.[97]



Scheme 3.3: Catalytic cycle of RCM

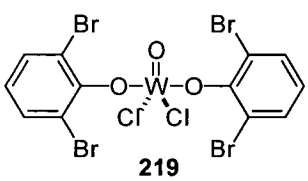
The initial step of the RCM reaction is thought to be a formal [2 + 2] cycloaddition between one of the alkene moieties of diene **214** and the metal alkylidene catalyst L_nM=CHR. This leads to the formation of a metallocyclobutane intermediate **216**, which subsequently undergoes a formal [2 + 2] cycloreversion to form metal alkylidene **217**. An intramolecular formal [2 + 2] cycloaddition forms another metallocyclobutane **218** which again undergoes a formal [2 + 2] cycloreversion, this time forming the required cycloalkene **215**.[95,97] For terminal alkenes, in the first

catalytic cycle the by-product is $CHR=CH_2$ but for successive cycles the by-product is ethene and the propagating carbene catalyst is $L_nM=CH_2$. For internal alkenes the by-product is a disubstituted alkene in the first cycle and a monosubstituted alkene in subsequent cycles.

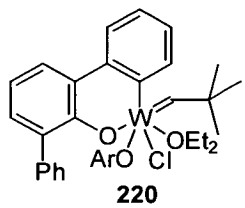
All of the steps involved and thus the overall reaction are reversible. However, the forward process is entropically driven as RCM cuts the substrate molecule into 2 products. If one of the products is volatile, e.g. ethene, then evaporation of this product will drive the equilibrium in favour of the cycloalkene and this product will accumulate in solution. Intrinsic competition between RCM and acyclic diene metathesis polymerisation (ADMET) can be controlled via the dilution of the reaction mixture.[95]

3.4 Metathesis Catalysts

Amongst the catalysts known to promote RCM are the rhenium based catalyst $MeReO_3$ and tungsten based catalysts **219**[95] and **220**.[99] However, undoubtedly the most important advances in the use of metal alkylidene catalysts for RCM have resulted from the development of molybdenum based catalysts by Schrock (section 3.4.1) and ruthenium based catalysts by Grubbs (section 3.4.2).



219

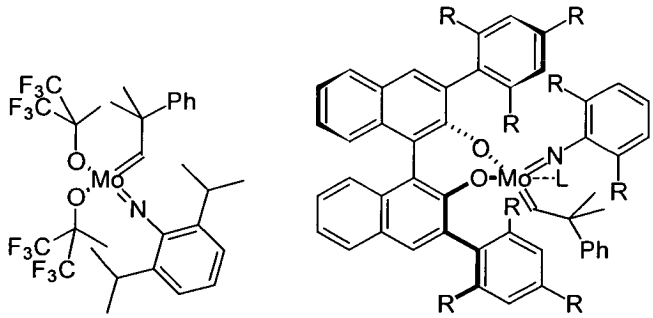


220

Figure 3.1 Tungsten based Metathesis Catalysts

3.4.1 Schrock Molybdenum Catalyst

Schrock introduced metathesis catalysts which were tetracoordinate species of the general formula $[M(=CHCMe_2Ph)(=NAr)(OR)_2]$ (M = Mo, W) with bulky substituents Ar and R.[100] Compound **221** from this series proved to be particularly active and is now commercially available.[101]

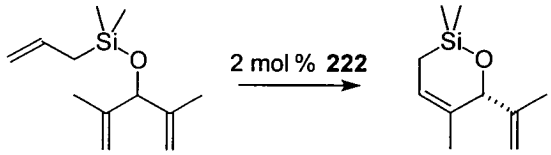


221 **222**

Figure 3.2: Molybdenum based RCM catalysts

Catalyst **221** can be used to form more hindered tri- and tetra-substituted alkene products. This catalyst is hardly affected by the electronic properties of the olefinic substrates and can react with both electron rich enol ethers [102] and electron poor acrylates.[103] It has also been found to tolerate sulfides as substrates unlike the ruthenium based catalysts (section 3.4.2).[104] However, the ruthenium based catalysts are generally accepted to have better functional group tolerance. The Schrock catalyst does not generally tolerate alcohol, aldehyde, ketone and carboxylic acid groups although there are exceptions to this. Another drawback of the Shrock catalyst is its high sensitivity to oxygen and water. The catalyst needs to be handled using Schlenck techniques and rigorously dried solvents.[95,97]

The replacement of the $OCMe(CF_3)_2$ units of **221** with substituted BINOL- or BIPHEN- ligands has allowed the scope of these molybdenum catalysts to be expanded to asymmetric RCM reactions (scheme 3.4).

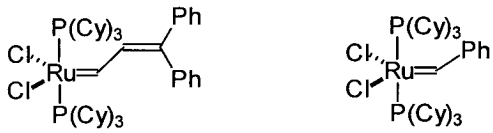


223 **224**

Scheme 3.4: Asymmetric RCM

When BINOL-based catalyst **222** (R = ^{i}Pr) was used on diene **223** a 98% yield of the product **224** was obtained with an ee > 99%. [105]

3.4.2 Ruthenium Based Catalysts



225 **226**

Figure 3.3: Grubbs Ruthenium based RCM catalysts

The first catalyst introduced by Grubbs *et al.* for alkene metathesis was the diphenylvinylcarbene complex **225**.[106] Although this catalyst was found to be less active than Schrock's molybdenum based catalyst **221** its functional group tolerance is greater and its reasonable water and oxygen stability makes it easier to handle. One disadvantage of this catalyst is the fact it is difficult to synthesise, the catalyst being formed by a Ru(II) induced rearrangement of diphenylcyclopropene.[106] As mechanistic studies have shown the diphenylvinyl substituent at the carbene unit to be lost during the first catalytic cycle [95,97] (see section 3.3) catalysts with other

groups at this position were investigated by Grubbs *et al.*. Compound **226** was found to be a suitable catalyst which can be prepared by a variety of routes.[107-110] This compound is now commercially available which has resulted in its widespread use in RCM.

During metathesis reactions with catalysts **225** and **226** it has been found that one of the $P(Cy)_3$ ligands dissociates from the complex and the bulk and electron donating character of the remaining $P(Cy)_3$ ligand helps to stabilise the intermediates in the catalytic cycle. Replacement of one of the $P(Cy)_3$ ligands by a more basic and more sterically demanding ligand has been found to increase the lifetime and reactivity of the catalyst.[95]

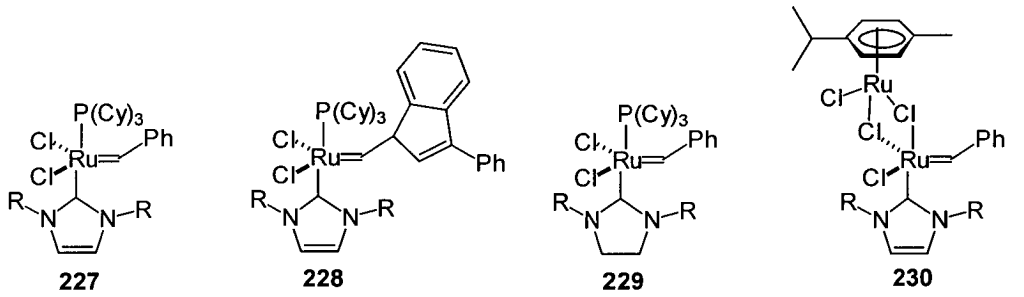
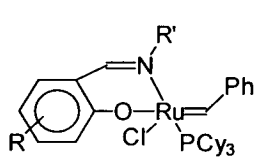


Figure 3.4: Second generation Ruthenium based RCM catalysts

Three different groups have recently reported the use of *N*-heterocyclic carbenes as metathesis catalysts (figure 3.4).[111-113] These catalysts all have an *N*-heterocyclic ligand which can be saturated or unsaturated and can have different R groups. There is also scope to vary the alkylidene fragment (compound **228**) and the dissociative ligand (compound **230**). Initial results suggest that these compounds have activity similar to that of the Schrock molybdenum catalyst **221** combined with the

compatibility with different functional groups and the stability of the Grubbs catalysts.



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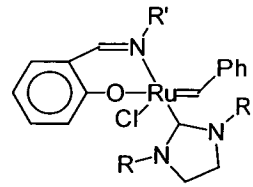


232

Figure 3.5: Schiff base catalysts

A series of air and moisture stable Schiff-base substituted ruthenium carbene complexes **231** have also been tested for metathesis activity. Although these compounds were found to be less active than the Grubbs catalyst **226** at room temperature their activity was found to increase dramatically at higher temperatures.[114] Combining the stability of the Schiff base compounds **231** with the activity of the NHC-ligands has led to a new series of compounds **232**.[115] Initial results show these compounds to be highly active metathesis catalysts which retain the stability of the initial Schiff-base series **231**.

3.5 Formation of Lactones by RCM

Many of the first preparations of lactone rings by RCM focused on synthesising larger ring sizes where the ester group of the substrate acts as a 'relay' functionality, co-ordinating to the carbene catalyst and thus helping to bring the ends of the ring together (figure 3.6).[116]

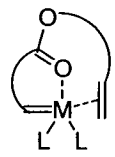
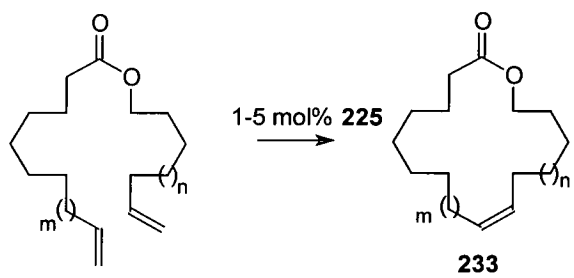


Figure 3.6: Relay Functionality

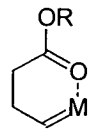
A series of 19-, 20- and 21-membered lactone rings **233** were prepared by Litinas *et al.* by RCM of a series of dienes using 1-5 mol% of Grubbs catalyst **225** in benzene at 60 °C to give 63-83% yields of the lactones (scheme 3.5). The products were all obtained as mixtures of the *E*- and *Z*-isomers.[117]



Scheme 3.5: Formation of Large Lactone Rings

Studies by Furstner's group showed that ethers, ketones and amides could also be used as the relay functionality in RCM and a series of 12- to 21-membered macrocyclic lactones, lactams, ethers and ketones were prepared.[118]

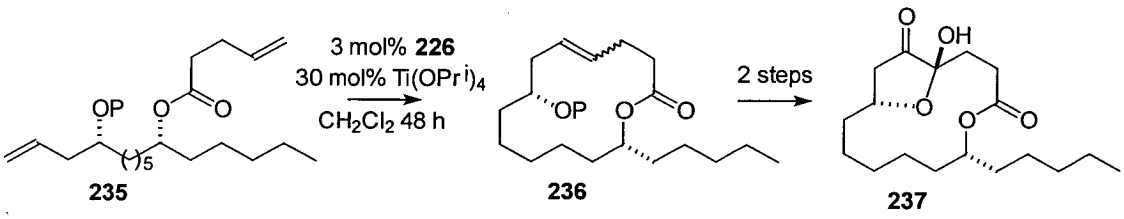
However, if pentenoates such as **234** are used as substrates, co-ordination of the substrate to the catalyst can lead to a stable 6-membered chelate (figure 3.7).



234

Figure 3.7: Stable 6-membered Chelate

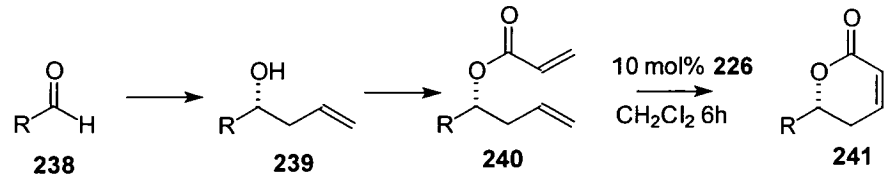
This problem can be overcome by the addition of $Ti(OPr^i)_4$, a Lewis acid additive, which competes with the ruthenium carbene for co-ordination onto the ester and prevents the formation of a stable chelate. In the synthesis of gloeosporone **237** by Furstner *et al.* the pentenoate **235** failed to react with the Grubbs catalyst **226** alone but underwent RCM using **226** in 80% yield when 30 mol% of $Ti(OPr^i)_4$ was added to the reaction mixture (scheme 3.6).[119]



Scheme 3.6: Gloeosporone Synthesis

Oxidation of the resulting double bond of **236** gave the 1,2-diketone and when the alcohol was deprotected this compound cyclised to give gloeosporone **237**.[119]

Smaller lactone rings have also been formed by RCM with the use of acrylate esters. Ramachandran *et al.* have synthesised a series of naturally occurring 5,6-dihydro-2*H*-pyran-2-ones **241** by RCM as shown in scheme 3.7.[120]



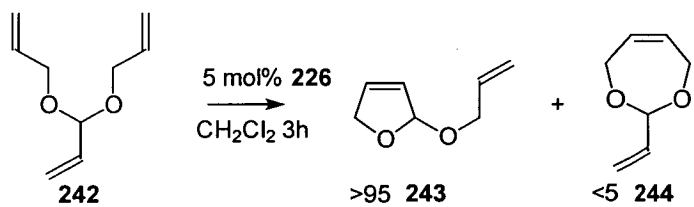
238 **239** **240** **241**

R = CH_3 , C_5H_{11} , PhCH=CH , $C_{11}H_{23}$

Scheme 3.7: Synthesis of 5,6-dihydro-2*H*-pyran-2-ones

Allylboration of the required aldehyde **238** with (+)-B-allyldiisopinocamphenylborane gave the chiral alcohols **239** which were esterified with acryloyl chloride. RCM was carried out with 10 mol% of the Grubbs catalyst **226** in refluxing CH_2Cl_2. The metathesis reactions proceeded in 76-86% yield even in the case where the side chain PhCH=CH- containing an internal double bond was used. The presence of a catalytic amount of the additive $Ti(OPr^i)_4$ was found to have no effect on the metathesis reaction.[120]

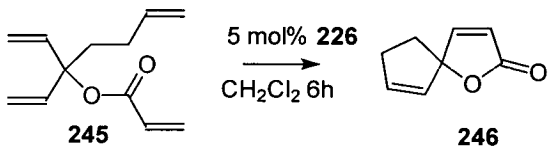
Not every ring size is accessible by RCM with the same ease. Due to enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain ends meeting) medium rings are generally more difficult to prepare. This is illustrated by the metathesis of alkene **242** (scheme 3.8).[121]



242 >95 **243** <5 **244**

Scheme 3.8: 5- versus 7-membered Ring Formation

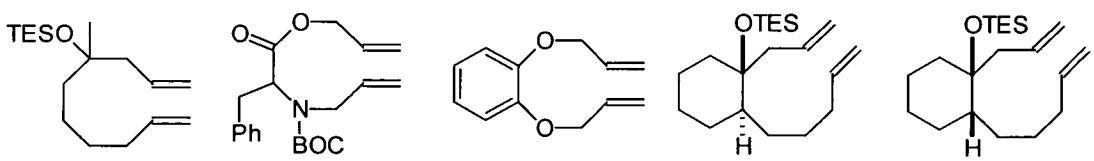
Metathesis of **242** with 5 mol% of Grubbs catalyst **226** proceeded in 3 hours at room temperature to give the 5-membered ring **243** selectively with no trace of the 7-membered ring **244** being seen. Having established this Harrity's group have gone on to synthesise a series of spirocycles, including the 5-membered lactone **246**, by RCM of the acrylate ester **245** using Grubbs catalyst **226** (scheme 3.9).[121]



245 **246**

Scheme 3.9: Spirocycle Formation

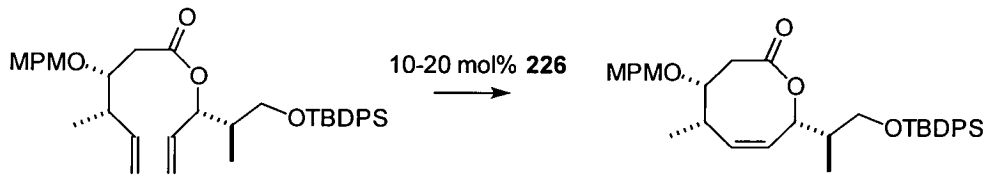
Studies by Grubbs *et al.* have shown that the introduction of conformational constraints into the acyclic precursors can make formation of 8-membered rings by RCM much more favourable. In contrast to smaller ring analogs, compounds **247** and **248** with no conformational constraints did not undergo RCM at all with catalyst **225**. (Figure 3.8) However, the catechol derivative **249** and *trans*-substituted cyclohexane **250** both underwent RCM in 75% yield. The conformational constraints in these compounds put the double bonds in close proximity with each other thus making the reaction more favourable entropically. In contrast the *cis*-substituted cyclohexane **251** proved to be a poor substrate for RCM with only a 35% yield of the 8-membered ring produced.[122]



247 **248** **249** **250** **251**

Figure 3.8: Formation of 8-membered Rings by RCM

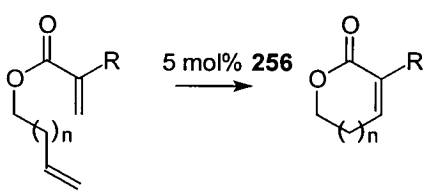
Buszek *et al.* have carried out RCM on a simple acyclic diene ester **252** to form an 8-membered lactone ring **253** which was elaborated to form octalactin A. (Section 2.6).[123] In this case there is no fused ring to impart conformational constraints as there was in the work of Grubbs *et al.* However, the stereocentres in the precursor **252** are thought to restrict bond angles and thus result in a conformation that favours RCM. This theory was supported by the observation that related compounds with varying stereochemistry undergo RCM with varying degrees of success.



252 **253**

Scheme 3.10: RCM in the synthesis of Octalactin A

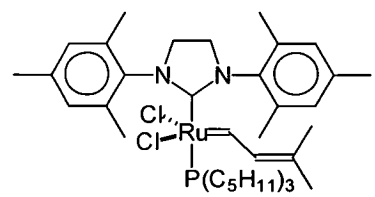
Recently Grubbs *et al.* have used a second generation ruthenium based catalyst for the formation of lactone rings as shown in scheme 3.11.[124] The formation of the 7- and 8- membered rings **255a** and **255b** proceeded in excellent yield from simple acyclic precursors with no conformational constraints. The catalyst was also used to form the 6-membered ring **255c** with a tri-substituted double bond also in excellent yield.



254 **255**

a R=H, n=2
b R=H, n=3
c R=Me, n=1

a R=H, n=2 97%
b R=H, n=3 92%
c R=Me, n=1 86%



256

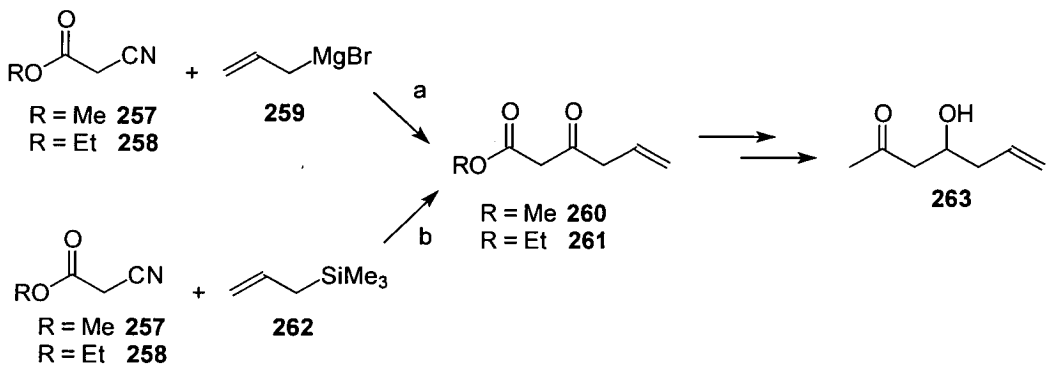
Scheme 3.11: Formation of lactones with a second generation catalyst **256**

3.6 Formation of an 8-Membered Lactone Ring

The synthesis of 8-membered lactone rings is of interest within the Hulme group in regard to the synthesis of the natural product octalactin A (section 2.6). It was thought that combining the Evans-Tishchenko reaction with RCM would provide a good route to this type of compound. In order to investigate this route it was necessary to form an appropriate β-hydroxy ketone **263**.

3.6.1 Formation of β-Hydroxy ketone 263

Initially the synthesis of ethyl 3-oxohex-5-enoate **261** was attempted (scheme 3.12) following modifications of two existing literature procedures.[125,126]

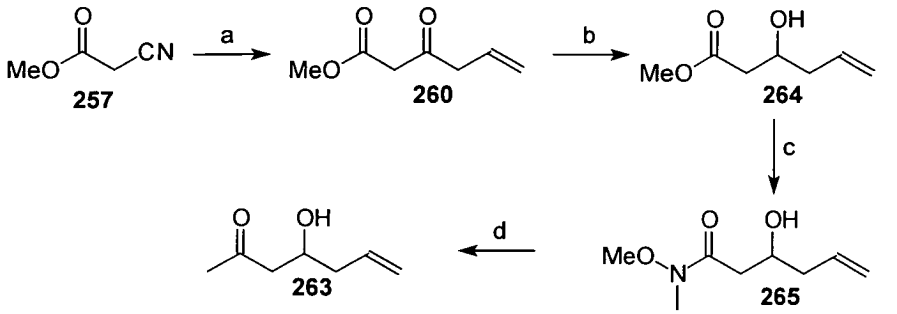


Scheme 3.12: Formation of ethyl 3-oxohex-5-enoate **261**: *Reagents and Conditions*: (a) RT, 48 h; 1N HCl, 3 h; (b) BCl_3, CH_2Cl_2, 0°C, 16 h.

The reaction between ethyl cyanoacetate **258** and allylmagnesium bromide **259**[125] was carried out in both ether and THF but no reaction was seen. The freshly prepared Grignard reagent was found to be reactive in a reaction with benzaldehyde, but even when iodine or copper (I) bromide was added during the formation of the Grignard reagent no product was obtained from the reaction with ethyl cyanoacetate. It was

also attempted to form **261** by the reaction of ethyl cyanoacetate **258** with allyltrimethyl silane **262** in the presence of boron trichloride.[126] Only very poor yields (<10%) were obtained from this reaction. It has been suggested that to obtain moderate yields for this reaction syringe pump addition of the allyltrimethyl silane over a long period of time is necessary.[127] The failure of these reactions led us to investigate the use of methyl cyanoacetate **257** rather than ethyl cyanoacetate **258**. The reaction of methyl cyanoacetate **257** with allyltrimethyl silane in the presence of boron trichloride also proceeded in poor yield (<10%) due to the unavailability of a syringe pump for allyltrimethyl silane addition.

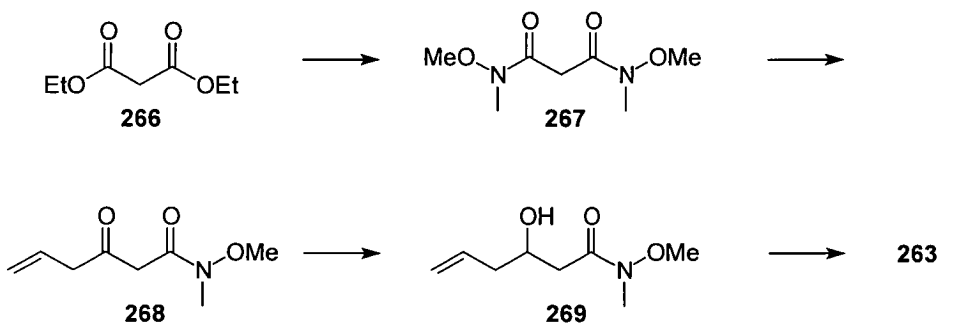
Thus the route that was eventually used was the reaction of methyl cyanoacetate **257** with allyl magnesium bromide **259**. The yields were found to be better when the reaction was carried out in ether rather than in THF possibly due to some of the volatile product being lost when the reaction solvent was removed. It was attempted to use the product **260** of this reaction without purification but reduction to the less volatile alcohol **264** gives a product that could not easily be separated from the remaining methyl cyanoacetate **257**. Thus purification by flash chromatography gave 28% of the ketoester **260**. The ketoester **260** was converted to β-hydroxy ketone **263** as shown in scheme 3.13. Reduction of the ketoester **260** using sodium borohydride gave racemic alcohol **264** in 82% yield. Conversion of the hydroxy ester **264** to the Weinreb amide **265** was carried out in quantitative yield using (MeO)MeNH•HCl and trimethylaluminium. Reaction of **265** with methylmagnesium chloride gave the methyl ketone **263** in 97% yield. [It is worthwhile noting that the use of different Grignard reagents at this point in the synthesis would provide an easy method of varying the side chain of the eventual lactone product.]



Scheme 3.13: Formation of β-hydroxy ketone **263**: *Reagents and Conditions*: (a) Allyl magnesium bromide, RT, 48 h; 1N HCl, 3 h (28%); (b) $NaBH_4$, THF, MeOH, 0°C, 30 min (82%); (c) (MeO)MeNH•HCl, Me_3Al, THF, RT, 8 h (100%); (d) MeMgCl, THF, 0°C, 1 h (97%).

3.6.2 Alternative Routes to β-hydroxy ketone 263

Given the problems in forming methyl 3-oxohex-5-enoate **260** some alternative routes to the β-hydroxy ketone **263** which did not require intermediate **260** were also considered. Scheme 3.14 shows a proposed route from diethyl malonate **266** to the β-hydroxy ketone **263**.

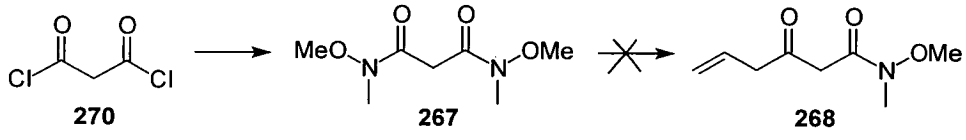


Scheme 3.14: Alternative route to β-hydroxy ketone **263** from diethyl malonate

It was proposed that diethyl malonate **266** could be used to form the *bis* Weinreb amide **267** which could undergo reaction with 1 molar equivalent of allylmagnesium

bromide to give keto amide **268**. Conversion to the hydroxy ketone **263** would be completed by reduction of the ketone to give alcohol **269** followed by displacement of the remaining Weinreb amide.

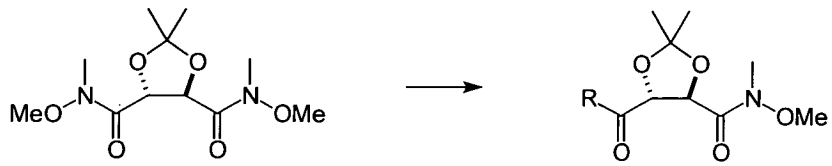
Diethyl malonate was treated with 5 equivalents of (MeO)MeNH•HCl and 5 equivalents of trimethylaluminium but no reaction was found to occur. Similarly when the reaction was attempted using *i*PrMgCl in place of the trimethylaluminium no reaction occurred. However, when the more reactive malonyl dichloride **270** was used in place of diethyl malonate **266** the initial reaction with 2.5 equivalents of (MeO)MeNH•HCl and 5 equivalents of triethylamine resulted in a 23% yield of the *bis* Weinreb amide **267** as shown in scheme 3.15.



Scheme 3.15: Attempted Route to **263** from malonyl dichloride

Attempted reaction of the *bis* Weinreb amide **267** with both allylmagnesium bromide and methylmagnesium bromide failed with only the *bis* Weinreb amide being recovered. It is interesting to note that while the literature contains examples of the mono addition of a Grignard reagent to both 1,2-*bis*-amides and 1,4-*bis*-amides there are no examples of addition to 1,3-*bis*-amides.

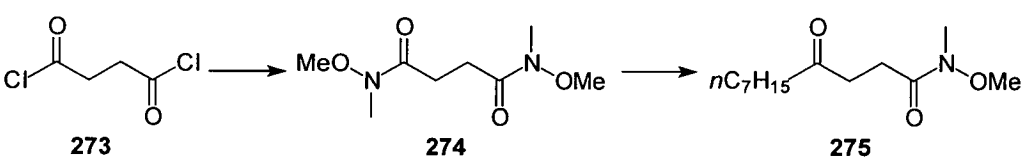
M^{c}Nulty *et al.* have investigated addition of Grignard reagents to the 1,4-*bis*-Weinreb amide **271** derived from L-Tartaric acid (scheme 3.16).[128]



Scheme 3.16 : Addition of Grignard Reagents to a 1,4-*bis*-Weinreb amide

Various Grignard reagents were added to **271** and it was reported that where R is a simple alkyl group (R = Me, Et; 1.1 equivalents of RMgX added) monoaddition to **271** occurs with good selectivity. As R increases from primary to secondary (R = *i*Pr) the reaction became more sluggish. Allyl magnesium chloride was found to be extremely reactive and the temperature had to be lowered (-78 °C) and the reaction diluted to obtain a 52% yield of the monoacylated product.

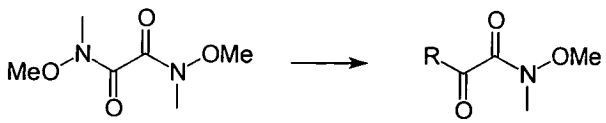
Narasaka and co-workers have synthesised the 1,4-*bis*-amide **274** by reaction of **273** and *N,O*-dimethylhydroxylamine hydrochloride.[129] Reaction of **274** with an equimolar amount of heptylmagnesium bromide gave a 77% yield of the β-keto amide **275**.



Scheme 3.17: Reaction of a 1,4-*bis*-amide **274**: *Reagents and Conditions*: (a) MeONHMe•HCl, Et_3N, CH_2Cl_2, 0 °C, (65%); (b) $C_7H_{15}MgBr$, THF, 0 °C, (77%).

Within the Hulme group the synthesis of the 1,4-*bis*-amide **274** has been repeated but, despite the reactivity of M^{c}Nulty's 1,4-*bis*-amide **271** to allyl Grignards, this

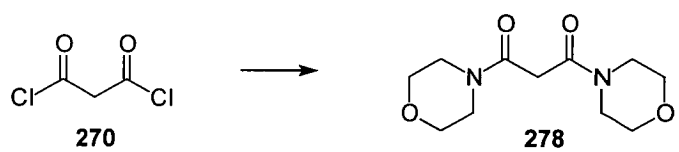
compound failed to react with allylmagnesium bromide. Studies by Sibi *et al.* on 1,2-*bis*-amides have shown allyl Grignard reagents to be less reactive than other Grignard reagents with 1,2-*bis*-amides (scheme 3.18).[130] Preparation of the ketoamides **277** proceeded in good to excellent yield with a variety of nucleophiles (aryl, alkyl, secondary alkyl, benzyl). However it was noted that reactions with allyl magnesium chloride were very sluggish and resulted in the formation of several products.



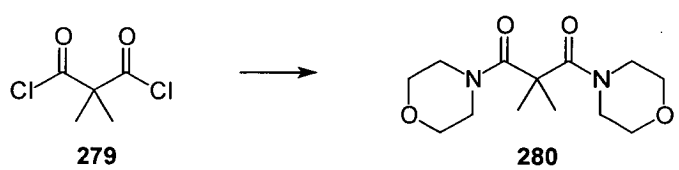
276 **277**

Scheme 3.18: Studies By Sibi *et al.*

Within the Hulme group the 1,3-*bis*-morpholine amides **278** and **280** have also been synthesised from the corresponding chlorides **270** and **279** (scheme 3.19). These compounds have also proved to be unreactive to allyl Grignards.



270 **278**



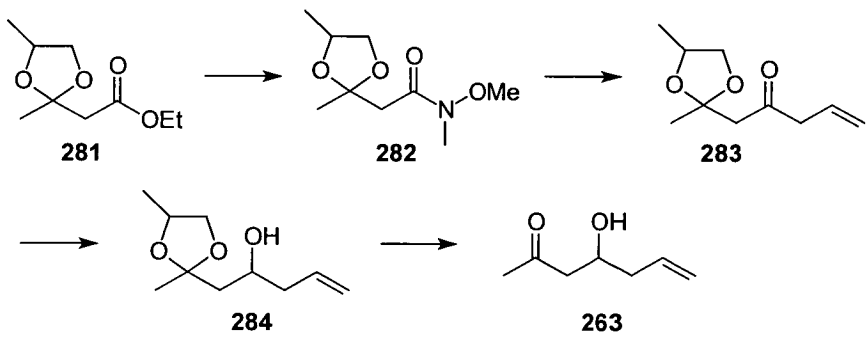
279 **280**

Scheme 3.19: Formation of 1,3-*bis*-morpholine amides

One possible reason for the failure of the reactions between 1,3-*bis*-amides and the Grignard reagents is that the Grignard reagent may simply act as a base and

deprotonate the methylene hydrogens in these compounds. Although Grignard reagents normally act as nucleophiles they can deprotonate hydrogens with a pKa ~ 35. If deprotonation is occurring then quenching the reaction will regenerate the starting material. It could be confirmed whether this is happening or not by quenching the reaction with an alternative nucleophile such as D_2O or MeI to give the deuterated or methylated products.

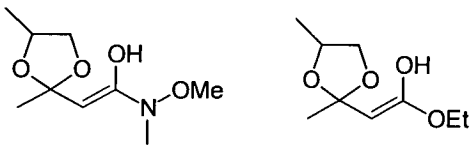
Another proposed route to compound **263** involved the use of the commercially available ethyl acetoacetate propylene glycol ketal **281** (scheme 3.20). It was hoped that the ester could be used to form a Weinreb amide **282** which could then undergo Grignard addition and reduction before deprotection of the acetal to form **263**.



281 **282** **283** **284** **263**

Scheme 3.20: Route to **263** From Ethyl Acetoacetate Propylene Glycol Ketal

Although reaction of **281** with (MeO)MeNH•HCl (2 equivalents) and *i*PrMgCl (4 equivalents) resulted in 2 products being isolated these were identified as **285** and **286** shown in figure 3.9.

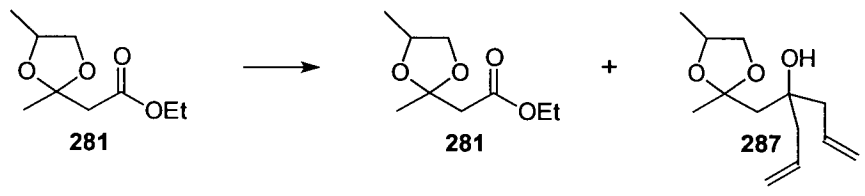


285 **286**

Figure 3.9: Products from Reaction of **281**

Rather than the desired Weinreb amide **282** the major product isolated (29%) was the enol form **285** of this compound with the enol form of the starting material **286** also being isolated (24%). Reaction of the enol form of the Weinreb amide **285** with allyl magnesium chloride to form **283** was attempted but only the enol starting material **285** was recovered from the reaction.

It was also attempted to form **283** directly from the ketal **281** using 1 equivalent of allyl magnesium chloride. The rational behind this was that if the product enolised it may inhibit the addition of a second unit of the Grignard reagent. However, this reaction resulted in a 1:1 mixture of starting material and the *tertiary* alcohol **287** with no evidence of enolisation in the remaining starting material.



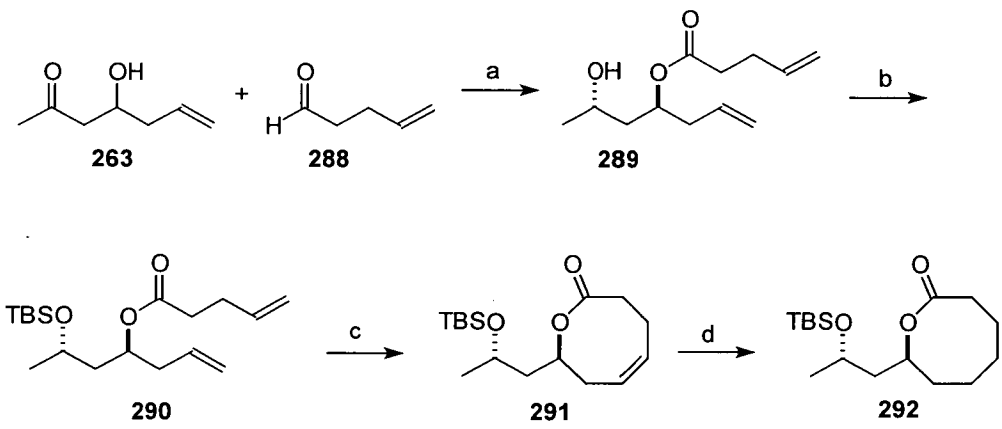
281 **281** **287**

Scheme 3.21: Reaction of Compound **281**

Due to the problems with these alternative routes to β-hydroxy ketone **263** the initial route *via* methyl 3-oxohex-5-enoate **260** (scheme 3.13) was employed despite the poor yield of the initial step.

3.6.3 Formation of the Lactone Ring

The Evans-Tishchenko reaction between β-hydroxy ketone **263** and 4-pentenal **288** was carried out using a freshly prepared SmI_2•PhCHO pinacol adduct as the catalyst (scheme 3.22). The reaction took 3 hours to reach completion, significantly longer than the 10 minute reaction time quoted by Evans for Evans-Tishchenko reactions with saturated β-hydroxy ketones and benzaldehyde, acetaldehyde or isobutyraldehyde. It is thought the longer reaction time may be due to stronger co-ordination of the samarium to the unsaturated hydroxy ketone substrate resulting in reduced turnover rates. This will be discussed in greater detail in chapter 4.



Scheme 3.22: 8-Membered Ring Formation: *Reagents and Conditions*: (a) SmI_2•PhCHO (30 mol%), THF, 0°C, 3 h (85%); (b) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0°C, 1 h (89%); (c) 5 mol% **226**, CH_2Cl_2, RT, 16 h (100%); (d) 5% Pd/C, H_2, MeOH, 24 h.

The Evans-Tishchenko reaction proceeded cleanly in 85% yield and the resulting product **289** was immediately protected in 89% yield using TBSOTf and 2,6-lutidine, in order to prevent any acyl migration. The protected product **290** underwent RCM using Grubbs ruthenium based catalyst **226** (figure 3.2). The reaction proceeded in quantitative yield to give the 8-membered lactone **291**, although after flash chromatography the product was still found to contain traces of ruthenium. Compound **291** decomposed before it could be fully analysed, however, the ^{1}H nmr spectrum did suggest that the reaction was successful.^{1}H nmr of diene **290** gives a multiplet at 5.90-5.63 ppm corresponding to the two C*H*=CH_2 protons and a multiplet at 5.09-4.94 ppm which corresponds to the four CH=CH_2 protons + C*H*Oester. In the product **291**, as we would expect, there are less signals in the alkene region of the spectrum. The signal at 5.90-5.63 ppm disappears completely and a new signal is seen at 5.50-5.41 ppm, corresponding to the two new alkene protons. A signal at 5.09-4.94 ppm still remainsbut it now integrates for only one protons, C*H*Olactone.

It was thought that the decomposition of compound **291** was due to the traces of ruthenium remaining in the product so the metathesis was repeated using the polymer supported Grubbs catalyst **293** (figure 3.10)

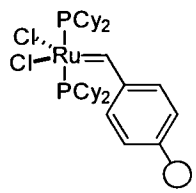


Figure 3.10: Polymer Supported Catalyst

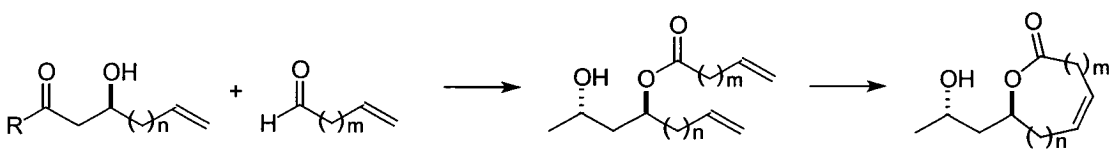
By attaching the catalyst to a polystyrene resin it has been suggested that purification of the products is likely to be more succesful. However reaction of diene **290** with 15 mol% of **293** in CH_2Cl_2 did not proceed to completion, with the majority of the starting material remaining unchanged. The polymer supported catalyst **293** was successfully removed by flash chromatography, but it proved impossible to separate the product from the remaining starting material. Hence, the mixture was treated with 10 mol% of the Grubbs catalyst **226**. This reaction still did not proceed to completion and a 1:1 mixture of **290**:**291** was obtained. A COSY spectrum of the mixture shows the new alkene protons at 5.41-5.50 ppm are adjacent to protons in a chemical shift range of 2.80-2.00 ppm, which correlates with the expected signals for axial and equatorial protons of the allylic positions of the ring. Some of these allylic protons are also shown to be adjacent to C*H*Olactone. An HSQC spectrum shows the new alkene signal at 5.50-5.41 ppm appears to correlate to four carbons in the alkene region. These four new carbon signals may result from the new alkene existing as a mixture of *cis* and *trans* isomers.

The mixture of **290**:**291** was hydrogenated with 5% Pd/C to remove the double bond, in the hope that this would make a more stable product less susceptible to degredation by residual ruthenium, which could then undergo complete characterisation. However, after hydrogenation a complex mixture of products was obtained. Although ^1H nmr indicated that the double bonds had been reduced there also appeared to be deprotection of the TBS protecting group.

Due to problems of highly coloured ruthenium by-products in metathesis reactions causing complications with olefin isomerisation and product decomposition a

number of improved work up procedures have recently been reported. Grubbs *et al.* have developed a procedure where excess tris(hydroxymethyl)phosphine is added to the crude reaction mixture.[131] This polar ligand complexes to the ruthenium and the resulting complex can either be extracted in a standard aqueous work-up or can be deposited onto silica and removed by filtration. This work-up procedure is reported to reduce ruthenium impurities in the RCM products by factors of 10-100 and is particularly useful for large scale reactions. Paquette *et al.* have added 1.5 equivalents (relative to Grubbs catalyst) of $Pb(OAc)_4$ to the reaction mixture.[132] The $Pb(OAc)_4$ oxidises the Grubbs catalyst to give insoluble metal by-products which can be removed by filtration through a pad of silica. Georg *et al.* have achieved a similar result by adding 50 equivalents (relative to Grubbs catalyst) of triphenylphosphine or DMSO to the crude reaction mixture.[133] After stirring for a minimum of 12 hours the ruthenium could again be removed by filtration through a pad of silica. It is hoped that these techniques could be used to improve the isolated yield of alkene **291**.

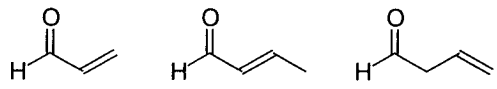
3.7 Extension to Other Ring Sizes



Scheme 3.23: Combined Evans-Tishchenko/RCM

The Evans-Tishchenko and RCM reactions with β-hydroxy ketone **263** and 4-pentenal **288** provide an excellent route to the formation of 8-membered rings. It is envisaged that other ring sizes could be formed by varying the chain lengths of the

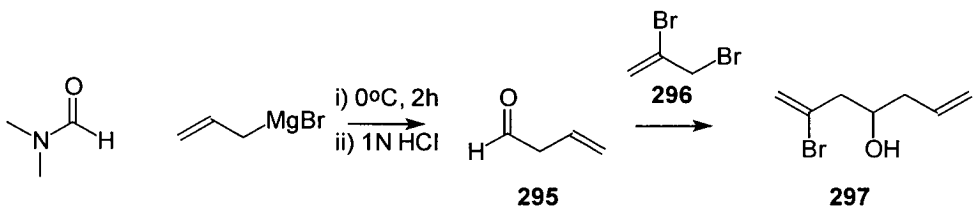
hydroxy ketone and the aldehyde (scheme 3.23). When acrolein **213** (figure 3.10) was used as the aldehyde in an Evans-Tishchenko reaction with β-hydroxy ketone **263** no reaction was observed to take place. Crotonaldehyde **294** has previously been shown to be inactive in Evans-Tishchenko reactions catalysed by zirconocene complex **173** (section 2.5) possibly due to the electron withdrawing properties of the double bond preventing the hydride shift from occuring. It is possible that a similar effect occurs with acrolein and when this is combined with the apparent lower reactivity of the unsaturated β-hydroxy ketone this may account for the observed lack of reactivity.



213 **294** **295**

Figure 3.11: Smaller Chain Aldehydes

The synthesis of 3-butenal **295** (figure 3.11) by oxidation of 3-butenol was attempted. Although Swern oxidation and IBX oxidation did lead to formation of the aldehyde the reactions were not clean and the product could not be purified without decomposition occuring.



295 **297**

Scheme 3.24: Synthesis of 3-butenal

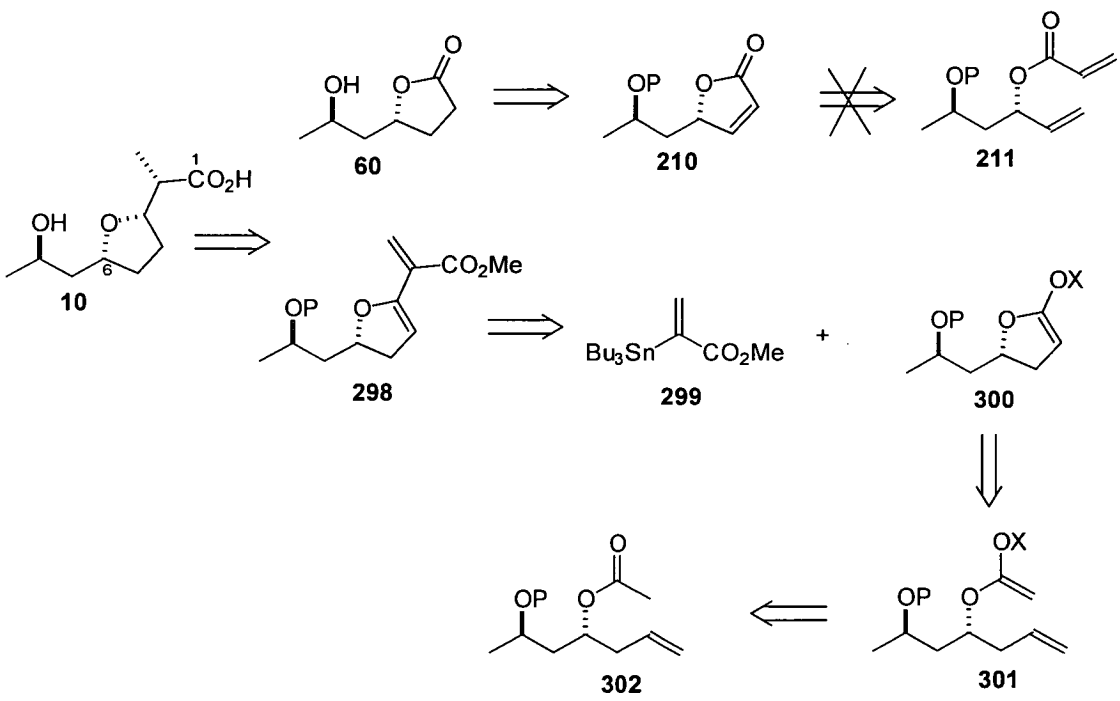
Scheme 3.24 shows the formation of 3-butenal **295** by the reaction of allyl magnesium bromide with DMF. Crude 3-butenal formed by this route was reported to give a 75% yield of **297** when reacted with 2,3-dibromopropene **296** in the presence of tin and HBr.[134] When this route was used to form 3-butenal the product was still found not to be clean. The crude samples of 3-butenal formed by both this route and the oxidation of 3-butenol were used in the Evans-Tishchenko reaction. A pre-formed SmI_2•PhCHO catalyst and β-hydroxy ketone **263** were used along with the crude aldehyde but no reaction occurred. This may be due to impurities in the 3-butenal poisoning the Evans-Tishchenko catalyst. Thus it is apparent that although this methodology may be extended to larger ring sizes an alternative strategy is needed for the formation of smaller 5- and 6-membered rings.

Chapter 4 : Results and Discussion Part 3

Evans-Tishchenko/RCM Approach to Nonactic Acid – Route 2

4.1 Ketene Acetal/ RCM Approach to Nonactic Acid

As discussed in chapter 3 the Evans-Tishchenko reaction of unsaturated aldehydes with unsaturated β-hydroxy ketones failed when acrolein and 3-butenal were used (figure 3.12). Hence a different route was needed to allow the formation of 5- and 6-membered rings including the 5-membered ring of nonactic acid **10** (scheme 4.1).

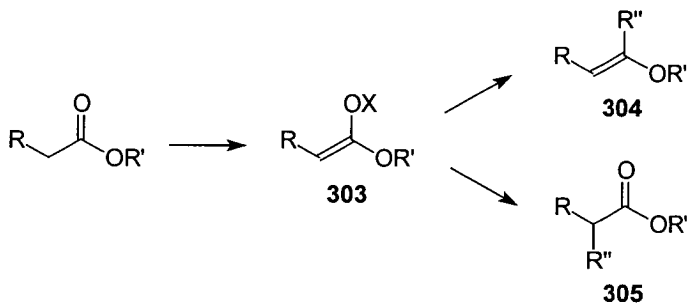


Scheme 4.1: Use of Ketene Acetal Derivatives in Nonactic Acid Synthesis

An alternative strategy is shown by the second retrosynthesis in scheme 4.1. An Evans-Tishchenko reaction of β-hydroxy ketone **180** with acetaldehyde could be used to form the *anti*-diol monoester **302**. Then a second double bond could be created by forming the ketene acetal derivative of the acetate. RCM of the ketene

acetal **301** could then lead to formation of the 5-membered ring **300**. Coupling to vinyl stannane **299** would give diene **298**. Hydrogenation of the two double bonds could then be used to form nonactic acid. Literature precedent suggests that the C(6) side chain may control the stereoselectivity of hydrogenation at C(3) (section 1.4.2) but a stereoselective reduction of the double bond at C(2) may be required.

4.2 Coupling Reactions of Ketene Acetal Derivatives

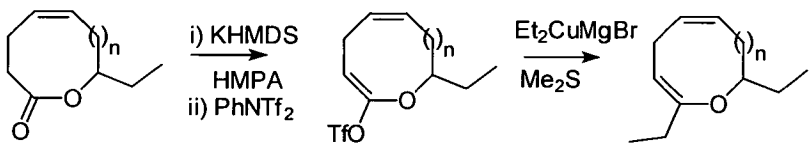


Scheme 4.2: Coupling Reactions of Ketene Acetal Derivatives

Ketene acetals can be derived from esters and lactones containing at least one α-hydrogen. Ketene acetal derivatives **303** may allow coupling reactions to take place to form substituted enol ethers **304**. Stille and Suzuki couplings of ketene acetal triflates (section 4.2.1) and phosphates (section 4.2.2) are examples of the type of reaction that could then be used to put the C(1)-C(2a) side chain of nonactic acid **10** in place. A second reaction pathway is often exhibited by silyl ketene acetals (section 4.2.3) which may undergo electrophilic attack at the double bond to form functionalised esters and lactones **305**.

4.2.1 Ketene Acetal Triflates

Murai *et al.* have investigated the reaction of ketene acetal triflates with $Et_2CuMgBr$ as part of a strategy aimed at synthesising a range of naturally occurring 8- and 9-membered cyclic bromoethers (scheme 4.3).[135, 136]



n =1 **306**
n =2 **307**

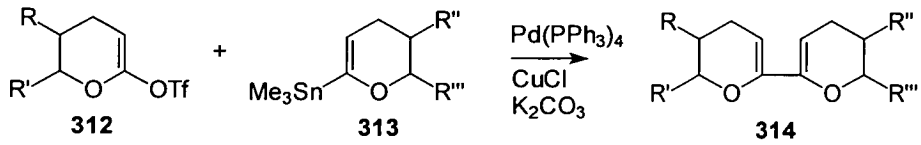
n =1 **308**
n =2 **309**

n =1 **310**
n =2 **311**

Scheme 4.3: Reaction of Ketene Acetal Triflates with $Et_2CuMgBr$

Lactones **306** and **307** were treated with KHMDS in the presence of HMPA to form the respective unsaturated enolates which were converted to the ketene acetal triflates **308** and **309** by reaction with $PhNTf_2$. The ketene acetal triflates were found to be stable only at low temperatures and could not be isolated, however immediate treatment of the solutions of the triflates with $Et_2CuMgBr$ in the presence of Me_2S gave 82% and 80% yields of the dienol ethers **310** and **311** respectively. Although the 9-membered dienol ether **311** was found to be relatively stable the 8-membered compound **310** was reported to be extremely unstable to water.

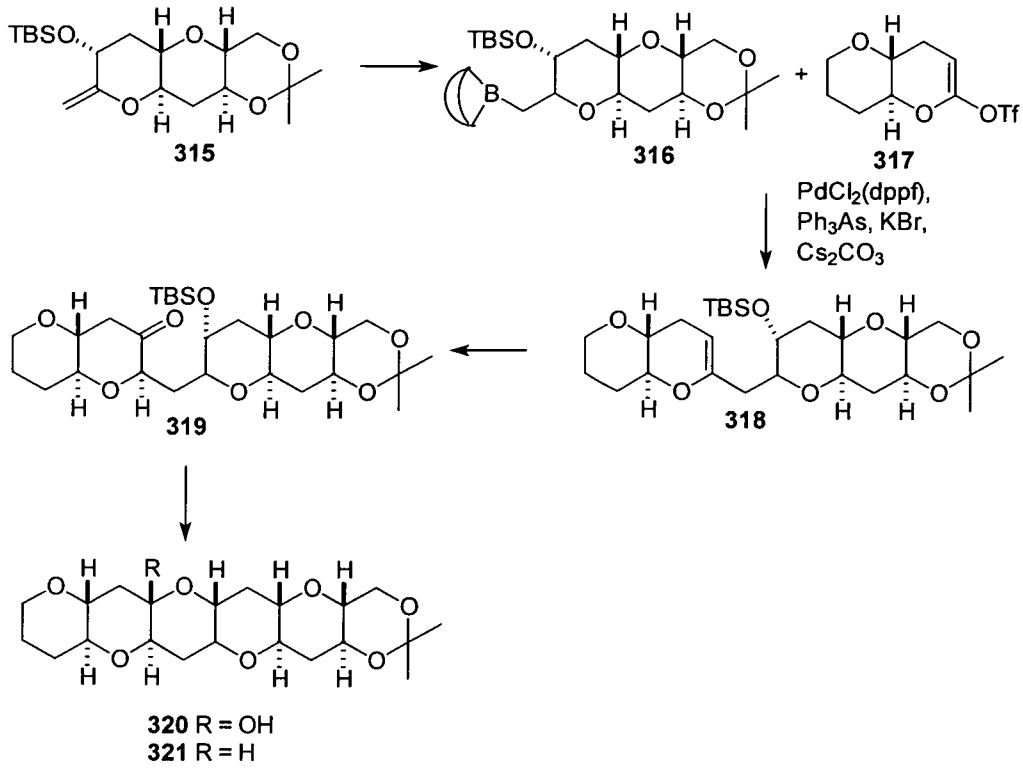
The group of Nicolaou has used ketene acetal triflates in Stille cross-coupling reactions, to develop a route to *bis*-tetrahydropyran systems (scheme 4.4) which are found in polyether marine natural products such as maitotoxin.[137]



Scheme 4.4: Stille Reaction of Ketene Acetal Triflates

The cross-coupling of ketene acetal triflate **312** with trimethylstannyl enol ether **313** was found to proceed best with 10 mol% of the [$Pd(PPh_3)_4$] catalyst and 2 equivalents of copper(I) chloride and potassium carbonate, giving yields of around 80% for a range of these substrates. The copper(I) chloride was found to be particularly important in this reaction with yields dropping below 50% when only 0.1 equivalent was used. It is proposed that the CuCl may act as a scavenger of free PPh_3 ligands or may form a discrete, reactive organocuprate as a result of an Sn/Cu transmetallation.

Sasaki *et al.* has recently expanded the Pd(0) cross-coupling of ketene acetal triflates to include Suzuki couplings with alkyl boranes (scheme 4.5) as a route to the synthesis of *trans*-fused polyether frameworks.[138]



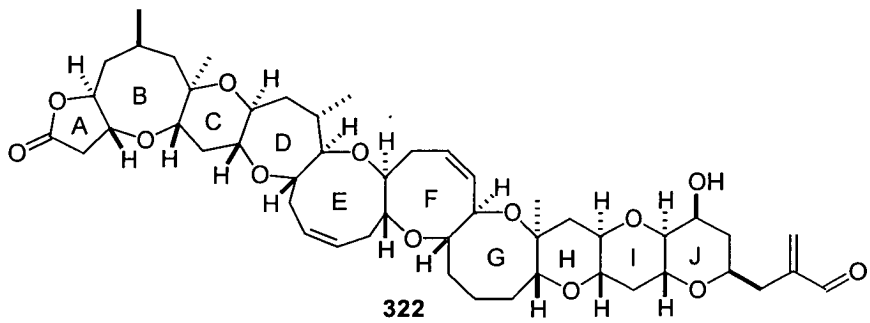
Scheme 4.5: Suzuki Coupling of Ketene Acetal Triflates

The Suzuki coupling of ketene acetal triflate **317** with alkyl borane **316**, which was generated *in situ* from the *exo*-alkene **315** and 9-BBN, was carried out using 10 mol% $PdCl_2$(dppf) as a catalyst. Aqueous caesium carbonate was used as the base, triphenylarsine as a co-ligand and potassium bromide was used to prevent catalyst decomposition. This gave a 66% yield of the coupled product **318**. Hydroboration of the enol ether and oxidation of the resultant alcohol gave ketone **319** in 82% yield over the 2 steps. Acidic removal of the silyl protecting group led to formation of the *trans*-fused hemiketal **320** which was converted to the *trans*-fused polyether **321** by treatment with triethylsilane and boron trifluoride etherate. Although this methodology has proved effective for 6-membered ketene acetal triflates, 7-membered ketene acetal triflates have been found to be unstable to the basic aqueous conditions required for the Suzuki coupling.

4.2.2 Ketene Acetal Phosphates

One problem with the cross-coupling reactions discussed in section 4.2 is the lack of stability of the ketene acetal triflates. This has led to the use of ketene acetal phosphates as substrates in Pd(0) catalysed cross-coupling reactions.

The group of Nicolaou have used cross-coupling reactions of ketene acetal phosphates with stannanes both in model studies for,[139] and the total synthesis of, brevetoxin A **322**.[140]

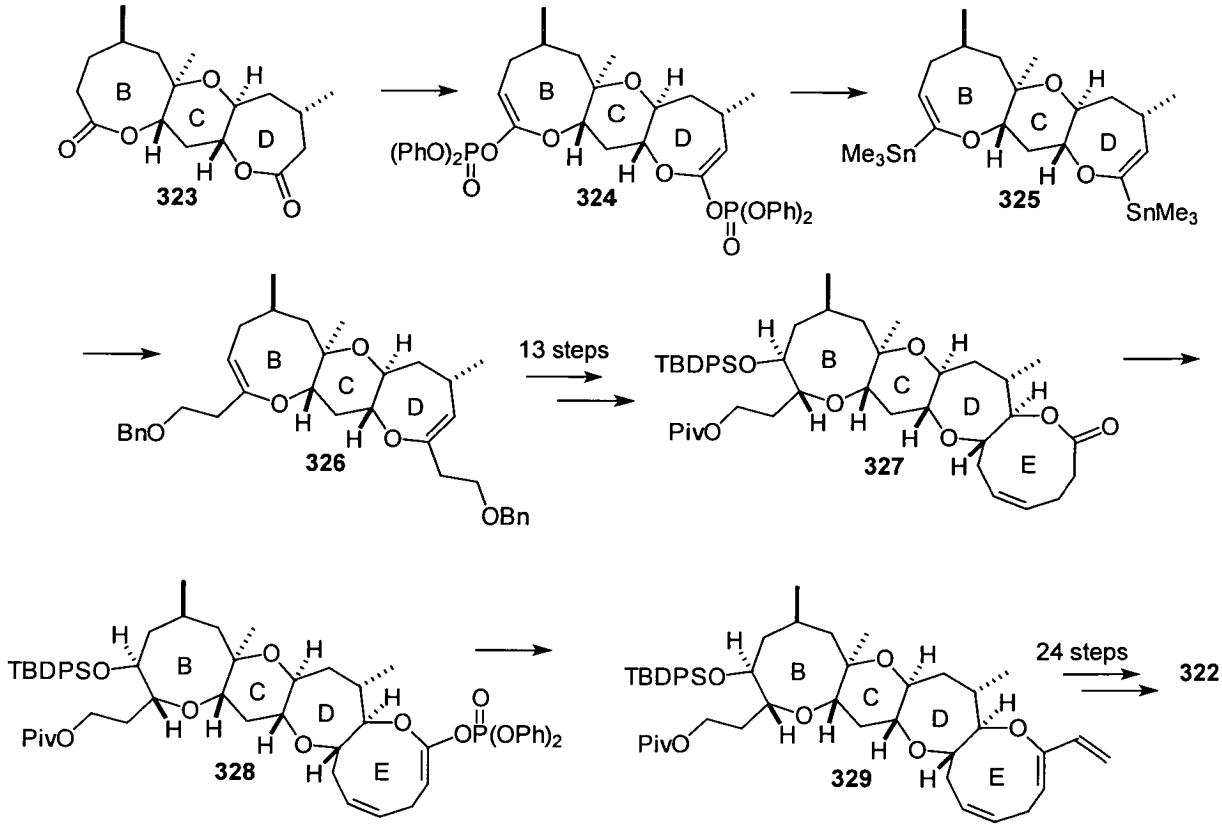


322

Figure 4.1: Brevetoxin A

The use of ketene acetal phosphates in the synthesis of brevetoxin A is shown in scheme 4.6. The bis lactone **323** was converted to bis ketene acetal phosphate **324** in 85% yield by reaction with KHMDS and $(PhO)_2P(O)Cl$ in the presence of HMPA. Nicolaou has reported that other phosphoryl chlorides such as $(EtO)_2P(O)Cl$ may be used to form the corresponding phosphates but these generally have lower stabilities, yields of formation and coupling reactivity than the diphenyl phosphates.[139] Reaction of the *bis*-diphenyl phosphate **324** with $Me_3SnSnMe_3$, LiCl and a catalytic amount of $Pd(PPh_3)_4$ gave the *bis*-trimethylstannyl enol ether **325** in 81% yield. **325** was then converted to *bis*-enol ether **326** by reaction with $TfOCH_2CH_2OBn$ in the presence of BuLi, CuC≡CPr and HMPT. A further 13 steps were required to convert **326** into

327 where the E ring of brevetoxin A has also been formed. At this point in the synthesis the lactone was again converted to a ketene acetal phosphate **328** and subsequently coupled with $Bu_3SnCH{=}CH_2$ in the presence of $Pd(PPh_3)_4$ and LiCl to give triene **329** in 81% yield over the 2 steps. Another 24 steps including the coupling of the BCDE fragment to a pre-formed GHIJ fragment were required to complete the synthesis of brevetoxin A **322**.



Scheme 4.6: Synthesis of Brevetoxin A

Sasaki *et al.* have recently introduced Suzuki coupling of ketene acetal phosphates with alkyl boranes in order to overcome the problems they had encountered with the instability of ketene acetal triflates (section 4.2). They have used Suzuki cross-

coupling of ketene acetal phosphates in the synthesis of both the ABCD[141] and HIJK[142] ring systems of ciguatoxin **330**.

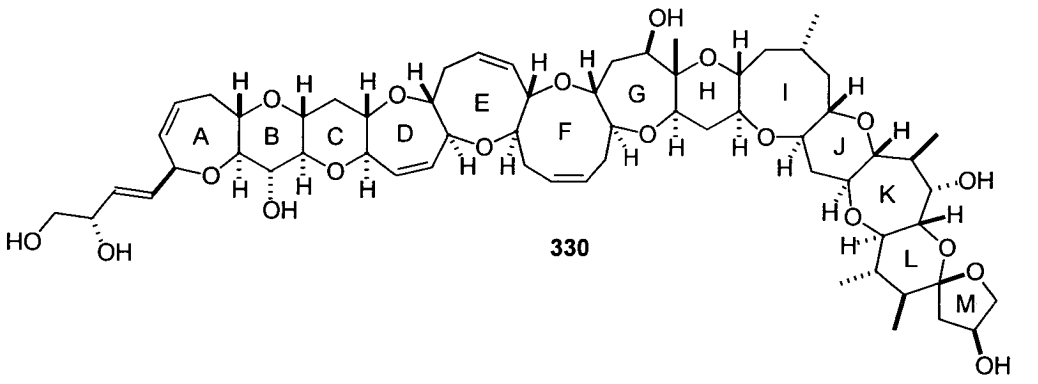
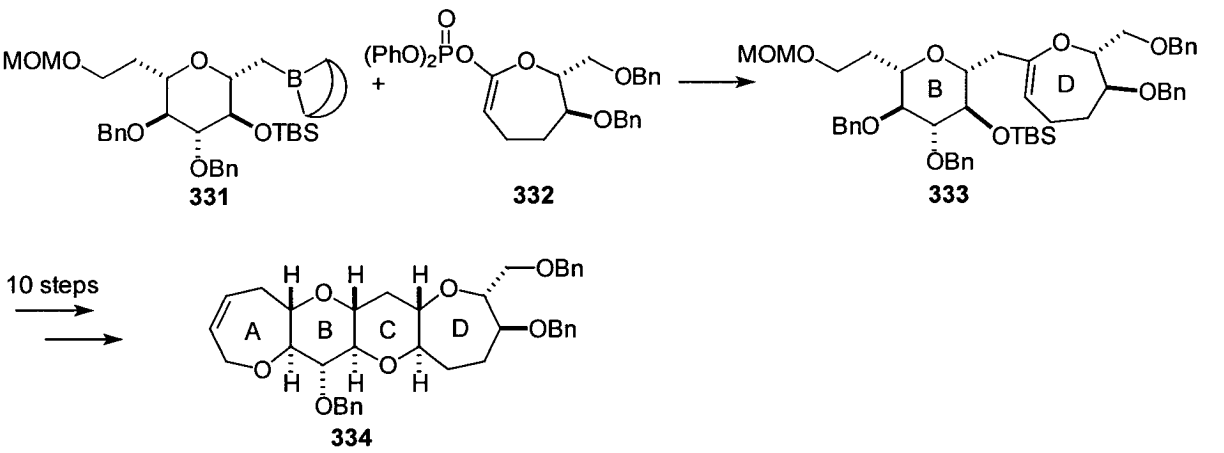


Figure 4.2: Ciguatoxin

When carrying out Suzuki couplings with ketene acetal triflates Sasaki *et al.* had found 7-membered ketene acetal triflates to be unstable to the Suzuki coupling conditions so the synthesis of the ABCD ring fragment of ciguatoxin was carried out using a 7-membered ketene acetal phosphate **332** (scheme 4.7).

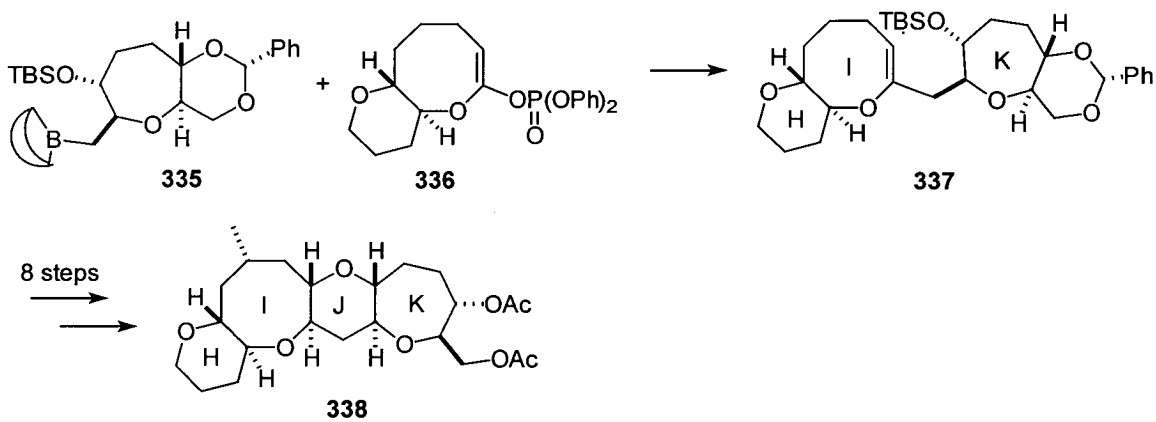


Scheme 4.7: Synthesis of the ABCD ring of Ciguatoxin

As in the work carried out on ketene acetal triflates, the borane **331** was generated *in situ* by reaction of the *exo*-alkene with 9-BBN. The ketene acetal phosphate **332** was

synthesised from the lactone with KHMDS, HMPA and $(PhO)_2P(O)Cl$ according to the procedure of Nicolaou. The Suzuki coupling was carried out using $Pd(PPh_3)_4$ as a catalyst and aqueous $NaHCO_3$ as a mild base to prevent hydrolysis of the phosphate. The ketene acetal phosphate is less reactive than ketene acetal triflates and so 2 equivalents of **332** were required to obtain a 97% yield of **333**. Phosphine-free palladium catalysts were found to be ineffective for this coupling. As with the earlier work carried out on the Suzuki coupling of ketene acetal triflates this product was converted to a *trans*-fused polyether and so the ABCD ring system of ciguatoxin was synthesised in a further 10 steps.

Expansion of this methodology to include the use of medium ring ethers with pendant alkyl borane functionality has allowed the HIJK ring system of ciguatoxin to be synthesised by a similar route (scheme 4.8).[142]



Scheme 4.8: Synthesis of the HIJK Ring System of Ciguatoxin

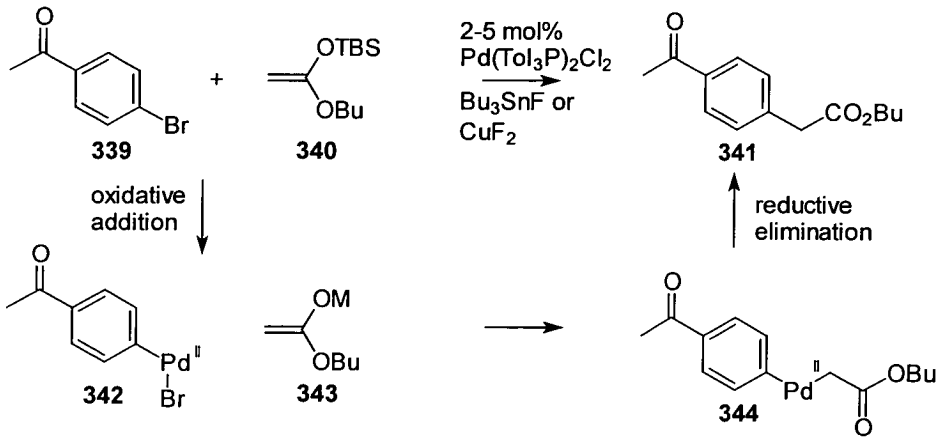
As in the synthesis of the ABCD ring system the ketene acetal phosphate **336** was prepared according to Nicolaou's procedures and reacted with alkyl borane **335** which was prepared *in situ*. The same coupling conditions as described for the

ABCD ring system were used and the coupled product **337** was obtained in 86% yield. **337** was converted to the *trans*-fused polyether framework **338** which comprises the HIJK ring system of ciguatoxin in a further 8 steps. The coupling methodology for ketene acetal phosphates has been shown to be more generally applicable than in the case of ketene acetal triflates. Examples of the coupling of 6- to 16-membered ketene acetal phosphates can be found in the literature due to the improved stability of these compounds.[139]

4.2.3 Silyl Ketene Acetals

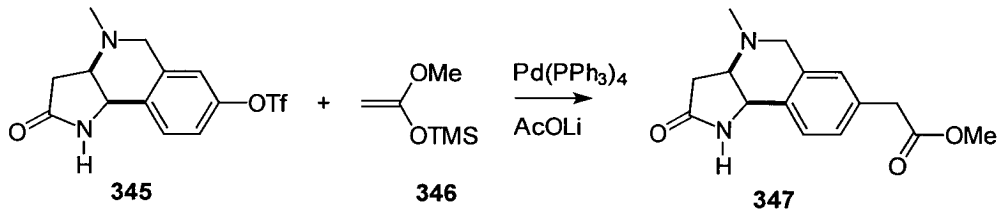
Palladium catalysed couplings of silyl ketene acetals are limited to the couplings of silyl ketene acetals with aryl triflates or halides to produce aryl acetates. In this case the role of the ketene acetal is to form a metal enolate which reacts with a Pd(II) intermediate (scheme 4.9).

Sulikowski *et al.* have reacted aryl bromides such as **339** with silyl ketene acetal **342** using either tributyltin fluoride or copper (II) fluoride as an activating agent and 2-5 mol% of $Pd(Tol_3P)_2Cl_2$ as a catalyst. The reaction is thought to proceed *via* an oxidative addition of the aryl bromide **339** to Pd(0) to produce a Pd(II) species **342** that will react with a copper or tin enolate **343** generated from the silyl ketene acetal and Bu_3SnF or CuF_2. The CuF_2 promoted reaction has the advantage of not involving tin by-products and generally has equally good or better yields with 73-95% yield being obtained by this method for a variety of aryl bromides.[143]



Scheme 4.9: Reaction of Aryl Bromides with Silyl Ketene Acetals

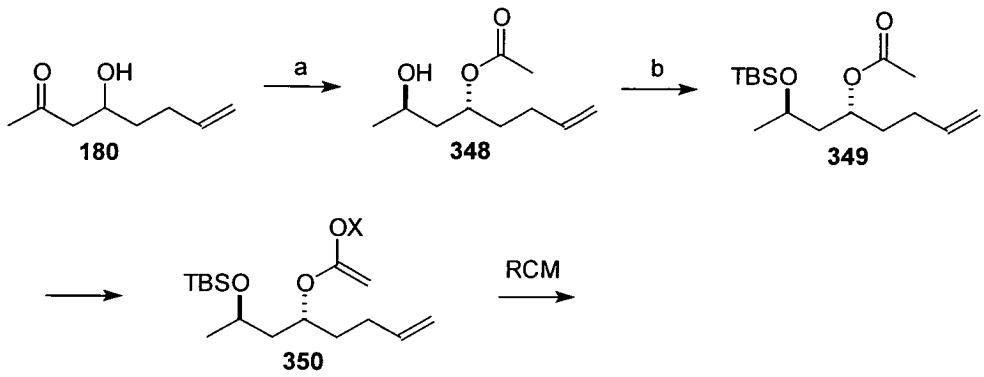
Dupas *et al.* have used aryl triflate **345** to carry out a Pd(0) catalysed coupling with the trimethylsilyl ketene acetal of methyl acetate **346** (scheme 4.10). Lithium acetate was used to generate the lithium enolate from the silyl ketene acetal and the reaction was catalysed by $Pd(PPh_3)_4$ to give 50-65% yields of the product **347**.[144]



Scheme 4.10: Reaction of Aryl Triflates with Silyl Ketene Acetals

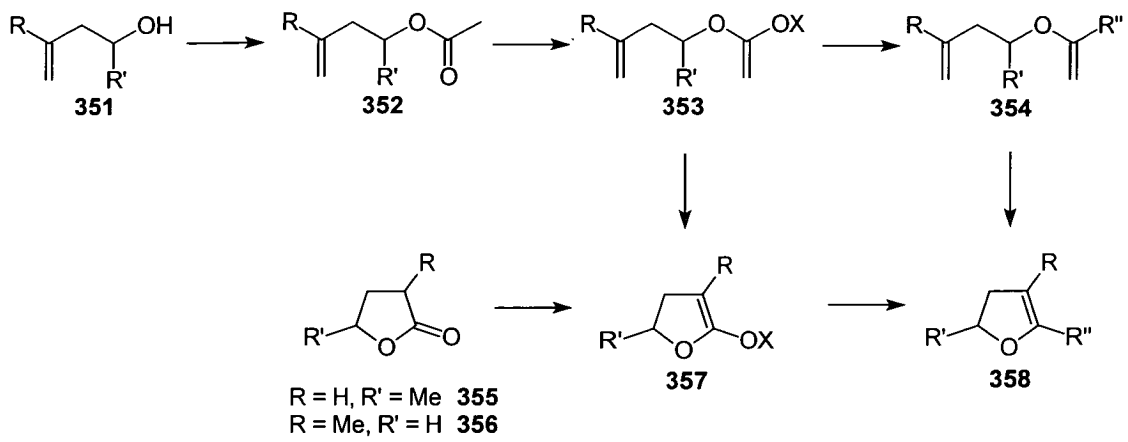
4.3 RCM of Ketene Acetal Derivatives

To investigate the strategy outlined in section 4.1 an Evans-Tishchenko reaction was carried out using β-hydroxy ketone **180** with acetaldehyde and a $SmI_2 \cdot CH_3CHO$ catalyst (scheme 4.11).



Scheme 4.11: RCM of Ketene Acetal Derivatives: *Reagents and conditions:* (a) SmI_2, CH_3CHO, THF, 2 h, 0 °C, (85%); (b) TBSOTf, 2,6-lutidine, 20 min, 0 °C, (90%).

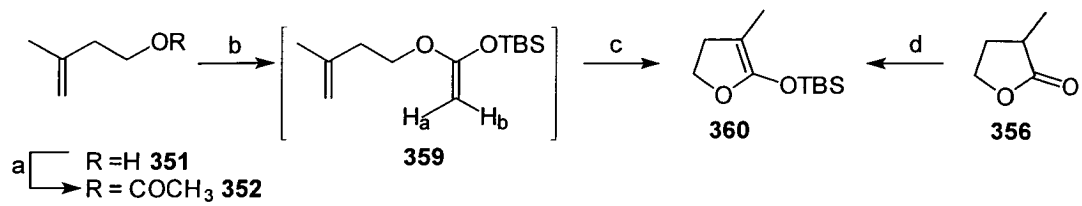
The Evans-Tishchenko reaction took 2 hours, significantly longer than the 10 minute reaction time quoted by Evans for such reactions with saturated β-hydroxy ketones and acetaldehyde. This suggested that the longer reaction times for this reaction and the Evans-Tishchenko reactions discussed in section 3.6 were due to the unsaturated β-hydroxy ketone rather than the aldehyde component. The longer reaction time may be due to stronger coordination of the samarium to the unsaturated β-hydroxy ketone resulting in reduced turnover rates for the catalyst. The Evans-Tishchenko adduct **348** was obtained in 85% yield and the free hydroxyl group was immediately protected using TBSOTf and 2,6-lutidene to give a 90% yield of the protected product **349** without significant levels of acyl migration. It was then envisaged that converting the acetate into a ketene acetal **350** would provide a route to both cyclise the molecule by RCM, and functionalise the molecule further using the coupling reactions of ketene acetals previously discussed. This strategy was tested on a model system shown in scheme 4.12.



Scheme 4.12: Model System for the Synthesis of 5-Membered Rings from Ketene Acetals.

Although there are examples of RCM of enol ethers in the literature (section 4.5) there are no examples of RCM of ketene acetals. This model system should allow ketene acetals **353** to be tested to see if they will undergo RCM to give 5-membered cyclic ketene acetals **357**. But it would also allow coupling reactions of the ketene acetals to give enol ethers either prior to RCM, or after the 5-membered ring has been formed. Thus if RCM of the ketene acetal **353** fails, a coupling reaction could be carried out first to form the enol ether **354**, which could then undergo RCM to form the 5-membered ring **358**.

Since there are many known routes to the preparation of silyl ketene acetals, and they are generally stable to work-up and purification, it was initially attempted to synthesise **359**. The further aim was to investigate whether RCM would work on substrates of this type (scheme 4.13).



Scheme 4.13: Attempted RCM of Silyl Ketene Acetal **359**: *Reagents and conditions:* (a) Ac_2O, pyridine, (63%); (b) LiHMDS, TBSCl, 1 h, 0 °C; (c) 5 mol% **226**, CH_2Cl_2, 16 h, RT; (d) LiHMDS, TBSCl, 1 h, 0 °C.

Acetate **352** was synthesised from alcohol **351** in 63% yield by reaction with acetic anhydride and pyridine. The acetate **352** was then treated with LiHMDS and TBSCl and kept at 0 °C for 1 hour. The reaction proved difficult to monitor as the silyl ketene acetal was found to decompose when tlc was carried out. The presence of the silyl ketene acetal was confirmed by nmr when a crude sample of the reaction mixture still containing some solvent showed the presence of 2 doublets at 3.03 and 3.18 ppm with a coupling constant J = 1.9 Hz. This signal corresponds to the protons H_a and H_b of the silyl ketene acetal (scheme 4.13). The sample also contained some of the ester starting material **352** and all of the other peaks of the silyl ketene acetal were found to be obscured by starting material and solvent peaks. The product could not be purified as even removal of all of the solvent under reduced pressure was found to cause total decomposition of the silyl ketene acetal back to the ester **352**. RCM of the crude silyl ketene acetal with 5 mol% of Grubbs catalyst **226** (figure 3.3) in CH_2Cl_2 was found to be unsuccessful. A mixture of silyl ketene acetal **359** and ester **352** was recovered from the RCM reaction mixture. ^1H nmr showed that further decomposition of the silyl ketene acetal had occurred

Direct synthesis of the cyclic silyl ketene acetal from valerolactone **356** gave similar results with the product decomposing on concentrating the sample.

Formation of the ketene acetal triflate of ester **352** was also attempted. The reaction was carried out in THF at –78 °C using LiHMDS and $PhNTf_2$, KHMDS and $PhNTf_2$ and LiHMDS, HMPA and $PhNTf_2$ but in all cases the instability of the product was found to cause problems. Once again tlc was of limited use for following the reactions due to decomposition of the product on the tlc plate. The crude reaction mixture from these reactions proved to be more complex than in the reactions to form the silyl ketene acetal, possibly due to the ketene acetal triflate being even less stable than the silyl ketene acetal and more decomposition occurring as the reaction mixture warmed from –78 °C to room temperature. As with the silyl ketene acetal, removal of the solvent was found to cause complete decomposition of the product. RCM of the crude reaction mixture with 5 mol% of Grubbs catalyst **226** in a THF/CH_2Cl_2 mixture at –78 °C → 25 °C was also found to give none of the cyclised product.

Within the group, the synthesis of ketene acetal diphenyl phosphates **361**, **362** and **363** and of ketene acetal tosylate **364** were also attempted but again the products proved to be unstable (figure 4.3).[145] Suzuki coupling of the crude ketene acetal phosphate **361** was also unsuccessful.

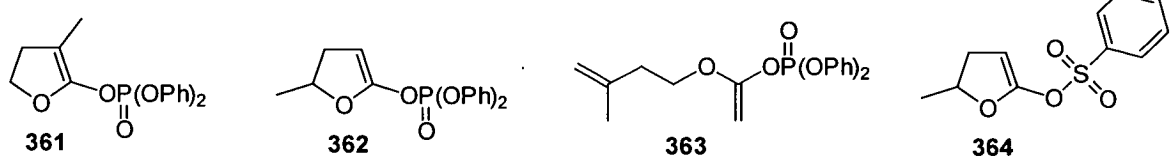
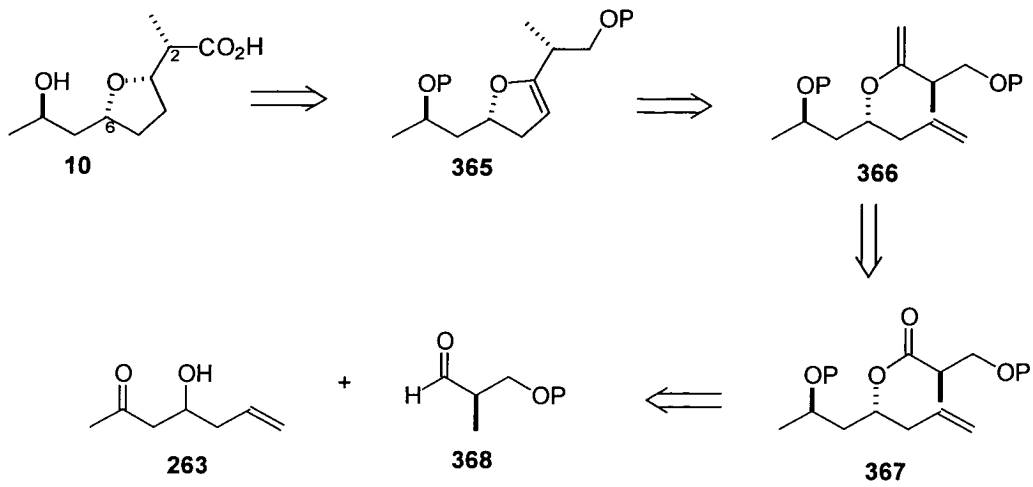


Figure 4.3: Ketene Acetal Phosphates

It is perhaps unsurprising that the attempted RCM was unsuccessful. The Grubbs catalyst **226** has often failed for RCM of enol ethers (section 4.5) and hence is probably not the best choice of catalyst for RCM of ketene acetals. In addition we were attempting to form a tetrasubstituted double bond, and this would probably also require a more active catalyst. As the ketene acetal must be used without purification the sensitive Schrock catalyst **221** may also be unsuitable. However the new generation of ruthenium catalysts which have been found to be capable of forming tetrasubstituted double bonds and have also recently been used in the RCM of enol ethers may prove to be suitable for this type of reaction.[152, 153]

4.4 Enol Ether/ RCM Approach to Nonactic Acid

Due to the problems encountered with the stability of the ketene acetal derivatives it was decided that olefination of an ester produced by the Evans-Tishchenko reaction to give an enol ether which could then undergo RCM may prove to be a more viable route to the synthesis of medium rings. An additional benefit of this route is that the use of more complex aldehydes in the Evans-Tishchenko reaction could lead directly to the formation of more functionalised products thus removing the need for the coupling reactions discussed in the ketene acetal case (scheme 4.14)



Scheme 4.14: Use of RCM of Enol Ethers in Nonactic Acid Synthesis

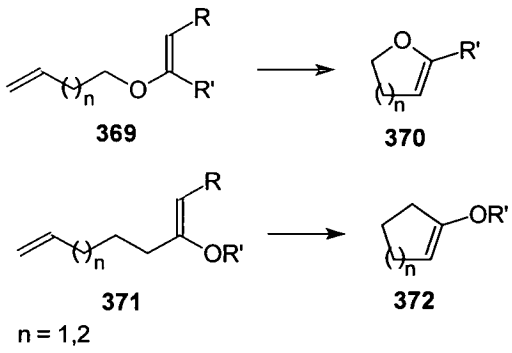
Scheme 4.14 shows a retrosynthetic analysis of nonactic acid where the Evans-Tishchenko reaction of the chiral aldehyde **368** with β-hydroxy ketone **263**, olefination of the resultant ester **367** and RCM of the enol ether **366** are key synthetic steps leading to formation of the 5-membered ring **365**. As well as avoiding the coupling reactions with ketene acetals, this route also allows the stereochemistry at C(2) to be controlled *via* the chiral aldehyde. As mentioned in section 4.1 it is envisaged that the stereochemistry at C(6) should help to control the stereochemistry at C(3) with the required *cis*-tetrahydrofuran being favoured.

4.5 RCM of Enol Ethers

Due to the sensitivity of enol ethers to acid, RCM of these compounds was impossible until the development of the well defined transition metal alkylidene catalysts discussed in chapter 3.

4.5.1 Schrock Molybdenum Catalyst in Enol Ether RCM

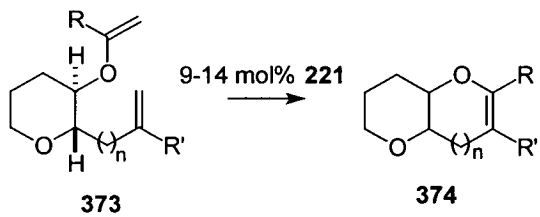
The use of the Schrock molybdenum catalyst **221** enabled Grubbs *et al.* to carry out RCM of acyclic olefinic enol ethers **369** and **371** to give a range of 5- and 6-membered cyclic enol ethers as either heterocycles **370** or carbocycles **372** (scheme 4.15).[146]



Scheme 4.15: Formation of 5- and 6-membered enol ethers by RCM

The less active Grubbs ruthenium catalyst **226** did not catalyse these reactions, instead a slow dimerisation was seen due to cross metathesis between the more active alkene bonds of two molecules of the starting material.

Clark and co-workers have also investigated the RCM of enol ethers with the aim of developing a route for the preparation of fused polyethers which could be used in natural product synthesis.[147]



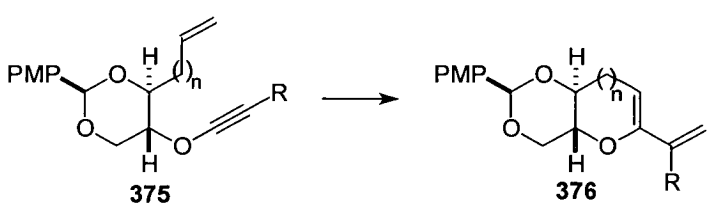
Scheme 4.16: RCM of enol ethers

RCM of substrates **373** where the alkene was unhindered (R' = H, n = 1,2) gave moderate 40-72% yields of the cyclic enol ethers **374** when 9-14 mol% of the Schrock molybdenum catalyst **221** was used, When a more hindered alkene was used with an unhindered enol ether (R = H, R' = Me), yields of 93 and 94% were obtained for n = 1, and n = 2 respectively. It is proposed that this increase in yield is due to the less hindered enol ether reacting first and ring closure occurring onto the more reactive alkene double bond. In cases where a less hindered alkene is used, this is the bond that will initially react with the catalyst and ring closure will have to take place onto the less reactive enol ether. This is thought to result in a longer lived intermediate which is more likely to undergo other reactions due to its increased lifetime.

Although this reaction worked well for the formation of 6- and 7-membered rings (n = 1,2) it was unsuccessful for the formation of the corresponding 8-membered ring (n = 3). As with the reactions carried out by Grubbs to form 5- and 6-membered enol ethers, the Schrock molybdenum catalyst was required and attempts at this reaction with the Grubbs catalyst **226** failed.

4.5.2 Grubbs Ruthenium Catalyst in Enol Ether RCM

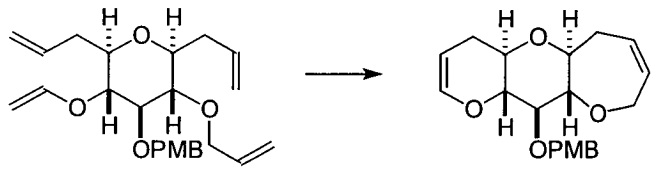
In addition to their experiments with the Schrock catalyst Clark *et al.* have also carried out RCM on alkynyl ethers using ruthenium catalysts (scheme 4.17).[148]



Scheme 4.17: RCM of Alkynyl Ethers

The reactions were carried out using 10 mol% of Grubbs catalyst **226** which was 'pre-activated' by the passage of ethene through the catalyst prior to the addition of the substrate. The reaction was found to proceed well for the formation of 6-membered enol ethers (65-77% yield), but much poorer yields (27-33%) were obtained when the formation of the corresponding 7-membered enol ethers was attempted. When the second generation ruthenium catalyst **229** was used the yields for the 6-membered enol ethers improved to 88-98%. The only substrate which proved to be a problem for the catalyst **229** was the alcohol **375** (R = CH_2OH) which produced only a trace of the product. In this case the alcohol appeared to complex to the ruthenium catalyst rendering it inactive.

Clark *et al.* have recently expanded their methodology to include double RCM reactions of allylic ethers, enol ethers or alkynyl ethers (scheme 4.18).[149]



377 **378**

Scheme 4.18: Double RCM reactions

The simultaneous RCM reactions of an enol ether and an allylic ether were carried out on substrate **377** to form **378** the ABC ring of ciguatoxin **330** (figure 4.2). The reaction was found to proceed in 63% yield when 20 mol% of the Schrock catalyst **221** was used. But interestingly, a 71% yield was obtained using 30 mol% of the Grubbs catalyst **226**, despite previous studies suggesting that this catalyst was ineffective for the RCM of enol ethers.[149]

There are other examples of RCM of enol ethers using the Grubbs catalyst **226**. Postema *et al.* have used RCM of enol ethers in the preparation of C-disaccharide glycals such as **379** (figure 4.4).[150] They found 50 mol% of **226** was required for a 50% yield of disaccharide. The Schrock catalyst **221** was found to give higher yields at lower catalyst loadings. Sturino *et al.* have also investigated the RCM of enol ethers with the Grubbs catalyst.[151] Although they have achieved moderate yields of a series of dihydropyrans including **380** and **381** (figure 4.4) using this methodology, the catalyst appeared to be very sensitive to the particular substitution pattern in the enol ether.

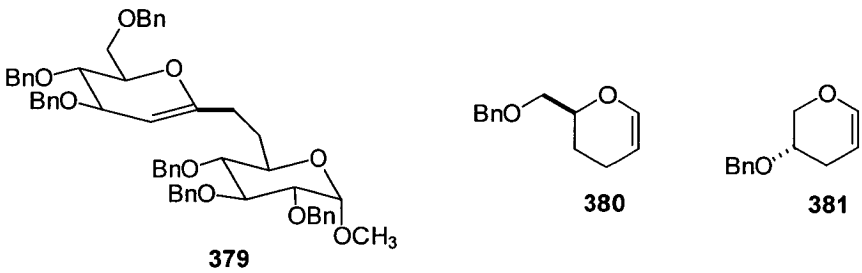
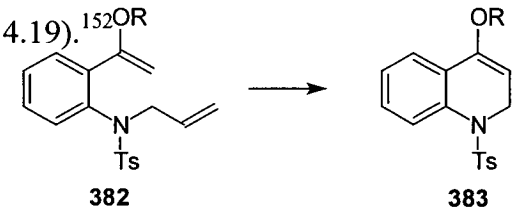


Figure 4.4: Enol Ethers Synthesised by RCM with the Grubbs Catalyst

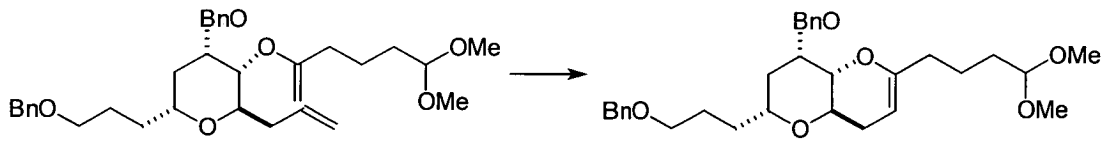
Nakagawa and co-workers have investigated enol ether – olefin metathesis with the second generation catalyst **229** in the synthesis of 1,2-dihydroquinolines (scheme 4.19).[152]



Scheme 4.19: Synthesis of 1,2-dihydroquinolines

While reactions of the enol ether **382** R = Me and silyl enol ether **382** R = TBS with Grubbs catalyst **226** gave no product, use of the catalyst **229** gave a 95% yield of the cyclised product **383** in both cases.

Rainier *et al.* have used catalyst **229** in enol ether – olefin metathesis reactions to produce intermediates in the syntheses of natural products including hemibrevetoxin B (scheme 4.20).[153]



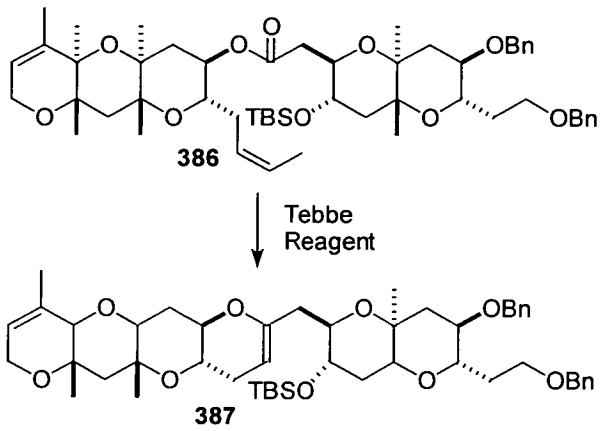
Scheme 4.20: Enol ether – olefin metathesis in hemibrevetoxin B synthesis

Despite the fact that the cyclisation puts the 2 substituents of the pyran ring in a 1,3-diaxial relationship the reaction proceeded in 84% yield to give the bicyclic compound **385**. This was even higher than the 79% yield obtained with the Schrock molybdenum catalyst. Thus recent advances suggest that the second generation ruthenium catalysts may make RCM of enol ethers a very useful and practical reaction.

4.5.3 *In Situ* Formation of the Enol Ether

Unsaturated esters have also been converted to cyclic enol ethers. Grubbs *et al.* reported the stoichiometric ring closure of olefinic esters to give cyclic enol ethers using the tungsten alkylidene complex $W(CHCMe_3)(Nar)(OCMe(CF_3)_2)_2$. The reaction proceeds *via* an acyclic enol ether which is not isolated but undergoes RCM catalysed by the tungsten complex to give the cyclic enol ether.[154]

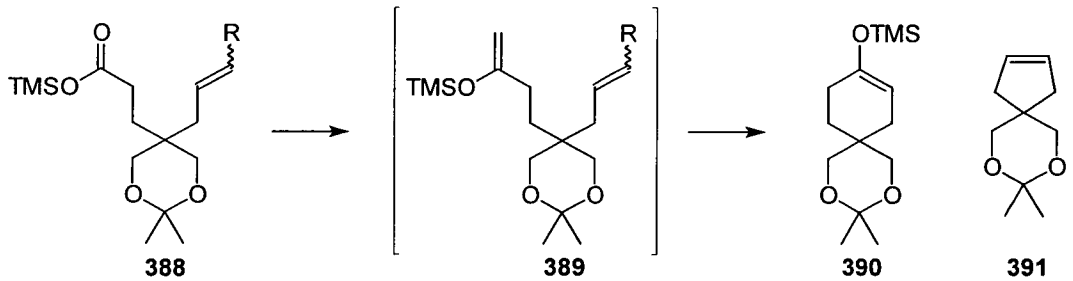
A similar strategy was used by Nicolaou *et al.*in the synthesis of the polyether **387** (scheme 4.21). [155]



Scheme 4.21: RCM of Olefinic Ester **386**

The RCM of olefinic ester **386** proceeded *via* methylenation of the ester to give an acyclic enol ether intermediate which then underwent RCM. Four equivalents of Tebbe reagent were required to give a 61% yield of the cyclic enol ether **387**.

Work by Shibasaki and co-workers on the silyl ester **388** found that treatment with Tebbe reagent formed the acyclic enol ether **389** but RCM could not be brought about with this reagent (scheme 4.22).[156]



Scheme 4.22: Studies by Shibasaki and co-workers

Treatment of the silyl enol ether with Grubbs catalyst **226** promoted migration of the double bond moiety of the silyl enol ether to give a product which underwent RCM

to give the 5-membered ring **391**. Changing the reaction solvent from CH_2Cl_2 to benzene allowed a 10% yield of the cyclic enol ether **390** to be isolated. When the second generation catalyst **229** was used instead >99% yield of the cyclic enol ether **390** was obtained when reactions were carried out in benzene or CH_2Cl_2. The use of this catalyst allowed 5-, 6- or 7-membered cyclic enol ethers to be formed in 88-98% yields.

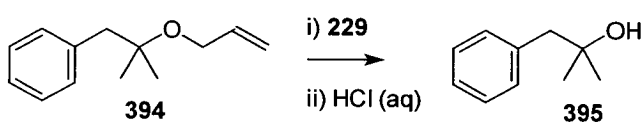
The ability of the ruthenium catalysts to promote migration of a double bond has itself been used in the synthesis of cyclic enol ethers (scheme 4.23).

392 **393**

Scheme 4.23: Tandem RCM-olefin isomerisation

Snapper *et al.* have produced a range of enol ethers such as **393** in moderate yield by a tandem RCM-olefin isomerisation sequence. They used the second generation ruthenium catalyst **229** which had been treated with a 95:5 N_2:H_2 gas mixture to generate a catalyst which promoted this isomerisation.[157]

This isomerisation has also been utilised by Cossy *et al.* as a method for the deprotection of allyl ethers such as **394** (scheme 4.24). Treatment of the allyl ether with the ruthenium catalyst **229** resulted in formation of an enol ether which was hydrolysed to give the alcohol **395** in 90% yield.[158]

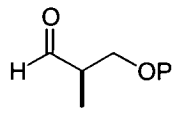


394 **395**

Figure 4.24: Deprotection of Allyl Ethers

4.6 Synthesis of Nonactic Acid C(1)-C(2a) Component

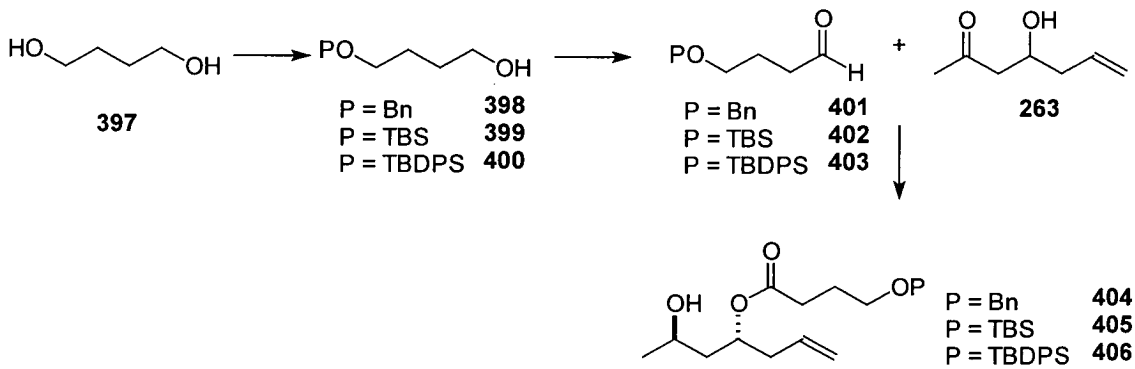
The use of the enol ether/ RCM strategy discussed in section 4.4 for the synthesis of nonactic acid **10** requires the use of the chiral aldehyde **396** which will eventually form C(1)-C(2a) of nonactic acid (figure 4.4).



396

Figure 4.5: Chiral Aldehyde

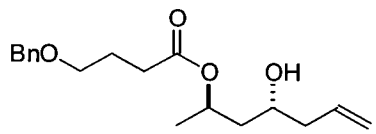
To decide which protecting group would be best suited for use with this aldehyde a range of protecting groups were tested in the Evans-Tishchenko reaction of model aldehydes **401**, **402** and **403** (scheme 4.25).



Scheme 4.25: Protecting Groups in the Evans-Tishchenko Reaction: *Reagents and Conditions:* (a) NaH, BnBr (or TBSCl or TBDPSCl), 1.5 h, RT; (b) IBX, DMSO, THF, 2 h, RT; (c) SmI_2, THF, 0 °C.

Monoprotection of butane-1,4-diol **397** was carried out by reacting **397** with sodium hydride causing the monosodium salt to precipitate. This salt was then reacted with benzyl bromide, TBSCl or TBDPSCl to form the monoprotected diols **398**, **399** and **400**, in 86%, 80% and 79% yields respectively.[159] Oxidation to the aldehyde was

carried out with iodoxybenzoic acid (IBX) in each case. This proceeded in excellent yields for the benzyl protected (95%) and TBDPS protected (88%) materials but only in 50% yield in the case of the TBS protected material. Evans-Tishchenko reactions were carried out between the resultant aldehydes and the β-hydroxy ketone **263**. The catalyst for the Evans-Tishchenko reactions was formed *in situ* from SmI_2 and the aldehyde being used in the reaction. The Evans-Tishchenko reaction with the benzyl protected aldehyde **401** took 8 hours and proceeded in 77% yield but the product was found to be a mixture of 2 compounds, the required product **404** and **407** where acyl migration had occurred (figure 4.6). Further acyl migration was observed after chromatography. The cause of this migration is uncertain, but appears to be due in part to the extended reaction times required for the Evans-Tishchenko reaction of this unsaturated β-hydroxy ketone **263**. However, it is clear that the protecting group used in **401** also plays a significant role.



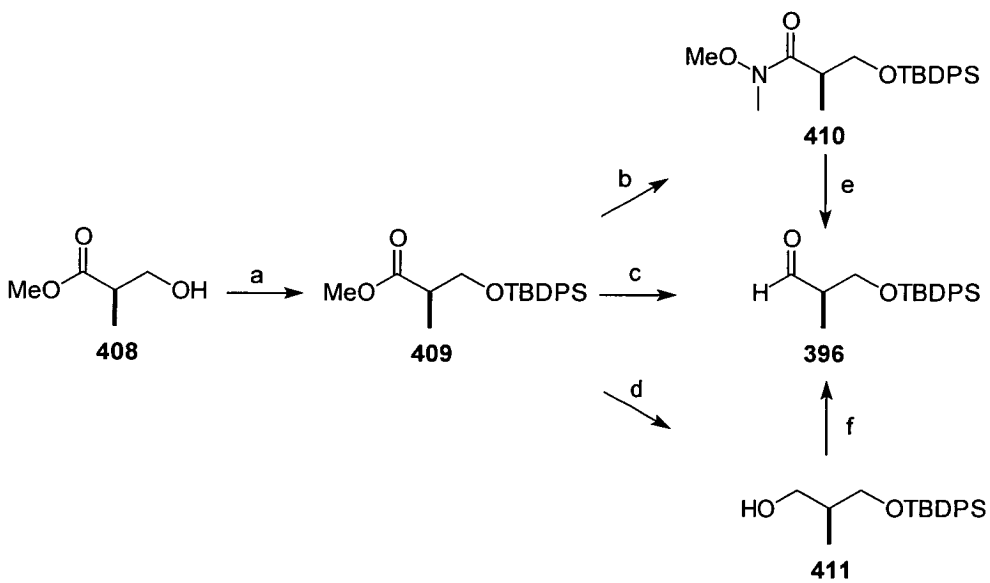
407

Figure 4.6: Acyl Migrated Product

When the TBS protected aldehyde **402** was used the reaction did not go to completion but was quenched after 3 days at 0 °C. The product **405** was isolated in 61% yield and no trace of acyl migration was seen. The ^1H nmr spectrum of **405** was found to correlate very closely with that of the benzyl protected adduct **404**. Of particular note was the lack of internal H-bonding.

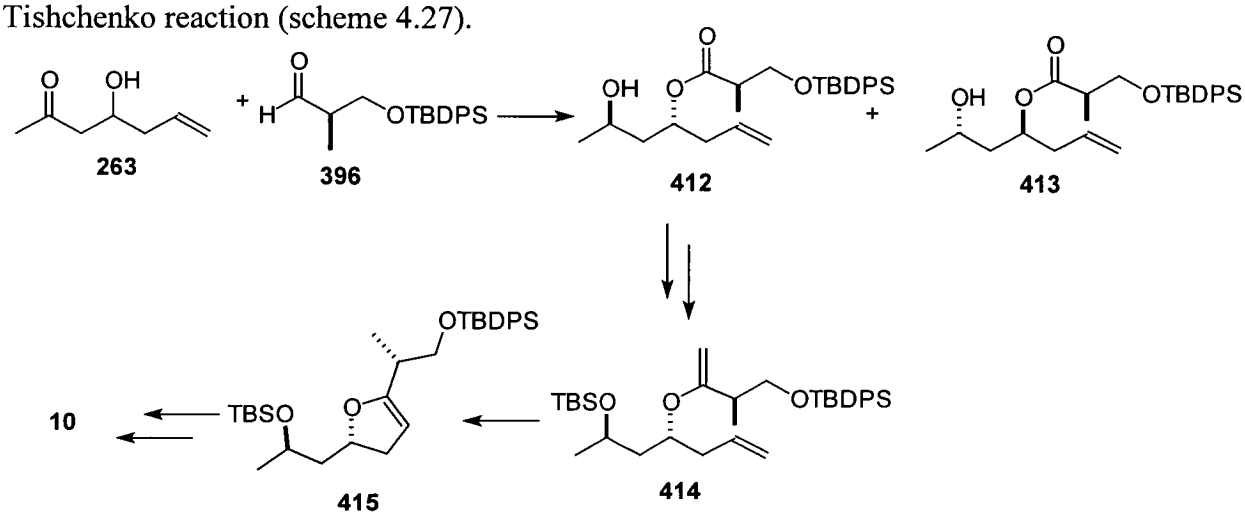
The TBDPS protected aldehyde **403** was found to give the best results with the Evans-Tishchenko reaction taking 3 hours and an 87% yield of the Evans-Tishchenko adduct **406** being isolated. Again no trace of acyl migration was seen. These results suggested that a bulky protecting group that prevented additional co-ordination to the Sm catalyst was likely to give the highest yields in the desired Evans-Tishchenko reaction. Thus the TBDPS protecting group was chosen for the chiral aldehyde **396**.

The chiral aldehyde **396** was synthesised from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate **408** as shown in scheme 4.26.



Scheme 4.26: Synthesis of Chiral Aldehyde **396**: *Reagents and conditions:* (a) TBDPSCl, imidazole, CH_2Cl_2, 40 min, RT, (100%); (b) Me(MeO)NH•HCl, Me_3Al, THF, 8 h, RT, (97%); (c) DIBAL-H, CH_2Cl_2, 1 h, -78 °C; (d) DIBAL-H, CH_2Cl_2, 2 h, -78 °C; (e) DIBAL-H, CH_2Cl_2, 1.5 h, -78 °C; (f) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, 1 h, -78 °C, (92%).

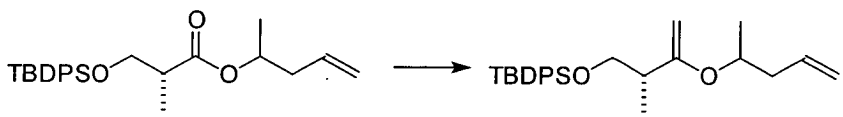
Protection of the alcohol **408** with TBDPSCl and imidazole proceeded in quantitative yield to give **409**.[160] Reduction of the methyl ester **409** directly to the aldehyde **396** was attempted using 1 equivalent of DIBAL-H at –78 °C. The reaction proved difficult to monitor as the product was found to have the same R_f value as the starting material, however a mixture of the desired aldehyde **396**, the methyl ester **409** and material which had been over reduced to the alcohol **411** was obtained. The aldehyde **396** is difficult to purify and hence it was hoped to find a method of synthesising the aldehyde that was clean enough to allow the crude material to be used in the Evans-Tishchenko reaction. The methyl ester **409** was converted to Weinreb amide **410** in 97% yield using *N,O*-dimethylhydroxylamine hydrochloride and trimethyl aluminium.[161] Reduction of the Weinreb amide **410** to the aldehyde **396** proceeded fairly cleanly but the product contained some unidentified baseline material. The cleanest sample of aldehyde **396** was obtained by reducing the methyl ester **409** to the alcohol **411** with DIBAL-H and then re-oxidising the alcohol to give the aldehyde **396**. Oxidation was attempted using the hypervalent iodine species IBX and under Swern conditions. The Swern oxidation was found to give a very clean sample of the aldehyde **396** in 92% yield and this was used directly in the Evans-Tishchenko reaction (scheme 4.27).



Scheme 4.27: Enol Ether Approach to Nonactic Acid

The Evans-Tishchenko reaction was carried out with the chiral aldehyde **396** and racemic β-hydroxy ketone **263**. When aldehyde **396** was used along with SmI_2 to form the active catalyst, only a 5% yield of the product was obtained after 2 days with the rest of the material remaining unreacted. When the catalyst was pre-formed from SmI_2 and benzaldehyde the reaction went to completion within 2 hours and an 80% yield of the products was obtained. The 2 diastereomeric products **412** and **413** were separated by flash chromatography.

Although olefination of the ester **412** has not yet been carried out there is precedent within the group to suggest this reaction should work (scheme 4.28).[145]



416 **417**

Scheme 4.28: Takai Olefination

Ester **416** underwent Takai olefination with $TiCl_4$, TMEDA, CH_2Br_2 and activated zinc to give a 20% yield of enol ether **417**. The low yield was thought to be due to decomposition of the enol ether on purification.

4.7 Conclusion

Although nonactic acid **10** has not yet been synthesised by this route it has been shown that the Evans-Tishchenko reaction can be carried out with more complex aldehydes including the chiral aldehyde **396** required for the synthesis of nonactic acid. There is precedent for the olefination of the resultant diol monoester to form an enol ether and for the RCM of enol ethers. This would suggest that the Evans-

Tishchenko reaction in combination with RCM could prove to be a viable route to 5- and 6-membered rings, thus complementing the methodology discussed in chapter 3 for the formation of medium sized rings.

Chapter 5 : Experimental

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), Bruker AC250 (250 MHz), Bruker AM360 (360 MHz) or Varian Inova 600 (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 Varian Gemini 200 (50.3 MHz), Bruker AC250 (62.9 MHz) or Bruker AM360 (90.6 MHz) instruments and are reported in ppm on the δ scale.

Infra-red spectra were recorded on a Biorad FTS-7 or 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}.

Fast atom bombardment (FAB) mass spectra were performed on a Kratos MS50TC mass spectrometer. Electron impact (EI) mass spectra were performed on a Finnigan 4500 mass spectrometer. Electrospray (ESI) mass spectra were performed on a Finnigan IQ mass spectrometer. The parent ion or relevant fragment are quoted, followed by significant fragments and their relative intensities.

Optical rotations were measured on an AA-1000 polarimeter with a path length of 1.0 dm at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D$, concentration (*c* in g/100 cm^3), and solvent. All optical rotations were measured at a temperature of 23 °C.

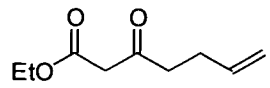
T.l.c. was performed on Merck $60F_{254}$ (0.25 mm) glass backed silica plates and visualised by ultraviolet (UV) light and/or ammonium molybdate stain.[φ] Flash column chromatography was carried out on Merck Kieselgel 60 (Merck 9385) under positive pressure by means of a hand pump. Eluent compositions are quoted as v/v ratios.

Reagents were purified by standard means.[162] Dichloromethane (DCM), dimethylformamide (DMF), triethylamine, diisoproylethylamine and 2,6-lutidine were distilled from calcium hydride and stored over calcium hydride under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl and stored under an argon atmosphere. Acetaldehyde and benzaldehyde were distilled immediately prior to use. All other reagents were used as supplied.

All experiments were performed in an inert atmosphere of argon under anhydrous conditions using oven dried apparatus cooled in a desiccator or flame dried under argon prior to use. Standard techniques for the handling of air-sensitive materials were employed.[163] All products were obtained as colourless oils unless stated otherwise.

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

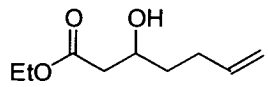
Ethyl 3-oxohept-6-enoic acid 178



Ethyl acetoacetate (1.95 ml, 15.4 mmol) was added dropwise to a suspension of sodium hydride (620 mg, 15.4 mmol) in THF (30 ml) at 0 °C. The solution was stirred at 0 °C for 10 min, butyllithium (19.3 ml, 15.4 mmol) was added and the solution stirred at 0 °C for a further 10 min. Allyl bromide (932 mg, 7.70 mmol) was added and the reaction mixture stirred at room temperature for 8 hours. Aqueous HCl (15 ml, 2N) was added and the reaction mixture was extracted with diethyl ether (3 x 20 ml). The combined extracts were washed with brine (50 ml, sat.), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexane:ether (90:10) to give a colourless oil (1.17 g, 89%). $\mathbf{R_f}$ 0.48 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3076 (alkene C-H), 1741 (ester C=O), 1715 (ketone C=O), 1641 (C=C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 5.87-5.70 (1H, ddt, *J* 17.2, 10.2, 6.2, C*H*=CH_2), 5.08-4.97 (2H, m, CH=CH_2), 4.19 (2H, q, *J* 7.1, CH_3CH_2O), 3.43 (2H, s, C(O)CH_2C(O)), 2.65 (2H, t, *J* 7.1, C(O)CH_2CH_2) 2.34 (2H, br q, *J* 6.6, C(O)CH_2CH_2), 1.28 (3H, t, *J* 7.1, CH_3); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 201.4 (C=O), 166.6 (C=O ester), 136.0 (CH), 114.9 (CH_2), 60.7 (CH_2), 48.7 (CH_2), 41.3 (CH_2), 26.7 (CH_2), 13.2 (CH_3); **m/z** (ESI) 249 (6), 225 (10), 209 ($[M + K]^+$, 100), 189 (3%).

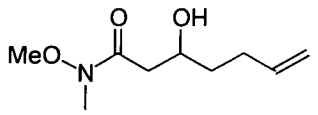
^{1}H NMR spectroscopic data in good agreement with those of the literature.[164]

Ethyl 3-hydroxy-hept-6-enoate 133



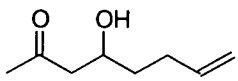
Keto ester **178** (1.17 g, 6.85 mmol) was dissolved in THF (10 ml) and cooled to 0 °C. Sodium borohydride (291 mg, 7.70 mmol) and methanol (1 ml) were added and the reaction was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The organic extracts were combined, washed with brine (40 ml, sat.), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane:EtOAc (80:20) to give the hydroxy ester **133** (1.07 g, 91%) as a colourless oil. $\mathbf{R_f}$ 0.11 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3448 (OH), 3074 (alkene C-H), 1732 (C=O), 1640 (C=C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 5.76 (1H, ddt, *J* 17.0, 10.0, 6.6, C*H*=CH_2), 4.98 (1H, dd, *J* 17.0, 1.8, CH=CH_aH_b), 4.91 (1H, dd, *J* 10.0, 1.8, CH=CH_aH_b), 4.14 (2H, q, *J* 7.1, CH_3CH_2O), 3.99 (1H, dddd, *J* 8.5, 8.0, 4.8, 3.7, C*H*OH), 2.83 (1H, br s, O*H*), 2.48 (1H, dd, *J* 16.4, 3.7, C(O)CH_AH_B), 2.38 (1H, dd, *J* 16.4, 8.5, C(O)CH_AH_B) 2.30-2.05 (2H, m, CH_2CH=CH_2), 1.70-1.45 (2H, m, CHOHCH_2), 1.24 (3H, t, *J* 7.1, CH_3); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 172.7 (C=O), 137.9 (alkene CH), 114.7 (alkene CH_2), 67.1 (CH), 60.3 (CH_2), 41.1 (CH_2), 35.3 (CH_2), 29.4 (CH_2), 13.8 (CH_3); **m/z** (ESI) 367 ($[2M + Na]^+$, 80), 227 (8), 195 ($[M + Na]^+$, 100), 173 ($[M + H]^+$,7%).

_N_-Methoxy-_N_-methyl 3-hydroxy-hept-6-enoyl amide 179



Trimethylaluminium (4.36 ml, 8.71 mmol, 2M in toluene) was added to a slurry of (MeO)MeNH.HCl (850 mg, 8.71 mmol) in THF (5 ml) at 0 °C. This mixture was stirred at 0 °C for 15 min until a colourless solution was formed. To this solution was added a solution of ester **133** (300 mg, 1.74 mmol) in THF (2 ml). The reaction mixture was stirred at room temperature for 8 hours then warmed to 35 °C for 1.5 hours. Aqueous HCl (5 ml, 1N) was added dropwise and the solution was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic extracts were washed with brine (40 ml, sat.), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexane:EtOAc (75:25) to give Weinreb amide **179** (272 mg, 83%). $\mathbf{R_f}$ 0.29 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3428 (OH), 3073 (alkene C-H), 1640 (C=O); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.81 (1H, ddt, *J* 17.2, 10.6, 6.9, C*H*=CH_2), 5.02 (1H, dd, *J* 17.2, 2.2, CH=CH_aH$_b$), 4.94 (1H, dd, *J* 10.6, 2.2, CH=CH$_a$*H$_b$*), 4.10-3.95 (1H, m, C*H*OH), 3.80 (1H, s, O*H*), 3.68 (3H, s, OC*H$_3$*), 3.18 (3H, s, NC*H$_3$*), 2.65 (1H, d, *J* 14.7, CH_aH$_b$C=O), 2.45 (1H, dd, *J* 14.7, 9.2, CH$_a$*H$_b$*C=O), 2.30-2.09 (2H, m, C*H$_2$*CH=CH_2), 1.80-1.42 (2H, m, C*H$_2$*); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 173.6 (C=O), 138.1 (alkene CH), 114.5 (alkene CH_2), 67.1, 61.0, 37.9, 35.4, 31.5, 29.5; **m/z** (ESI) 397 ([2M + Na]$^+$, 28), 251 (36), 210 ([M + Na]$^+$, 100), 188 ([M + H]$^+$, 14%).

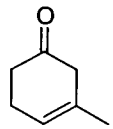
4-Hydroxy-2-oxo-oct-7-ene 180



Methyl magnesium bromide (1.28 ml, 3.85 mmol, 3M in ether) was added to a solution of Weinreb amide **179** (160 mg, 0.855 mmol) in THF (20 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Aqueous citric acid solution (20 ml; 10% w/v) was added and the resulting mixture extracted with diethyl ether (3 x 25 ml). The combined extracts were washed with aqueous $NaHCO_3$ solution (40 ml, sat.) and brine (40 ml, sat.), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:EtOAc (80:20) to give the methyl ketone **180** (122 mg, 100%). $\mathbf{R_f}$ 0.48 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3423 (OH), 3075 (alkene C-H), 1707 (C=O); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.79 (1H, ddt, *J* 16.8, 10.3, 6.6, C*H*=CH_2), 5.01 (1H, dd, *J* 16.8, 1.3, CH=C$H_a$$H_b$), 4.94 (1H, dd, *J* 10.3, 1.3, CH=C$H_a$$H_b$), 4.15-3.96 (1H, m, C*H*OH), 3.05 (1H, s, O*H*), 2.62 (1H, dd, *J* 17.8, 4.0, C(O)C$H_a$$H_b$), 2.51(1H, dd, *J* 17.8, 7.7, C(O)C$H_a$$H_b$), 2.23-2.08 (2H, m, C$H_2$CH=$CH_2$), 2.15 (3H, s, C$H_3$), 1.68-1.41 (2H, m, C$H_2$); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 209.9 (C=O), 138.0 (alkene CH), 114.8 (alkene CH_2), 66.8, 49.7, 35.2, 30.5, 29.5; **m/z** (ESI) 307 (17), 250 (35), 206 (9), 197 (11), 165 ($[M + Na]^+$, 100%).

^{1}H NMR and ^{13}C NMR spectroscopic data in good agreement with those of the literature.[165]

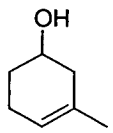
3-Methyl-cyclohex-3-ene-1-one 136



To cold (-78 °C), stirred liquid NH_3 (~20 ml) was added a solution of *m*-methylanisole (830 μl, 6.60 mmol) in dry Et_2O (5 ml) followed by *t*-butanol (6.2 ml, 66 mmol). Lithium metal (230 mg, 33.1 mmol) was added and the resulting blue solution was refluxed at –33 °C for 3 h. Solid NH_4Cl (5.20 g, 97.2 mmol) was added and the resulting cloudy white solution was allowed to warm to room temperature. Pentane (15 ml) was added and the flask warmed to remove any residual ammonia. Water (15 ml) was added, the solution was extracted with pentane (2 x 10 ml) and the combined organic extracts were washed with water (2 x 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude enol ether was dissolved in MeOH:H_2O (12 ml, 3:1), oxalic acid (30.0 mg, 0.333 mmol) was added and the mixture stirred at room temperature for 1.5 hours. Water (20 ml) was added and the suspension extracted with CH_2Cl_2 (5 x 10 ml). The organic extracts were combined, washed with NaOH (20 ml, 1N), H_2O (20 ml) and brine (20 ml, sat.), dried over $MgSO_4$ and concentrated *in vacuo* to yield ketone **136** (393 mg, 54%) which was used crude in the subsequent step. $\mathbf{R_f}$ 0.54 (hexane:EtOAc, 50:50);); ν_{max} (neat)/cm^{-1} 3039, 2967, 2927, 2853, 1718 (C=O), 1447, 1195; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.62-5.55 (1H, m, =CH), 2.76 (2H, s, CH_2), 2.44-2.38 (4H, m, 2 x CH_2), 1.71 (3H, br s, CH_3); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 209.4 (C=O), 131.2 (alkene CH), 120.0 (alkene CH_2), 43.5, 37.3, 24.0, 21.7; **m/z** (ESI) 243 (25), 133 ($[M + Na]^+$, 100), 111($[M + H]^+$ 80%).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[166]

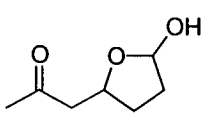
3-Methylcyclohex-3-ene-1-ol 183



Ketone **136** (393 mg, 3.57 mmol) was dissolved in THF (10 ml) and cooled to 0 °C. Sodium borohydride (250 mg, 6.61 mmol) and methanol (1 ml) were added and the reaction stirred at 0 °C for 40 min. The reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The combined organics were washed with brine (25 ml, sat.), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography, eluting with hexane:EtOAc (80:20) to give alcohol **183** (270 mg, 36% from **137**). $\mathbf{R_f}$ 0.24 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3364 (OH), 2927, 2085, 1644 (C=C), 1441, 1072, 1042; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.40-5.31 (1H, m, =CH), 4.03-3.87 (1H, m, C*H*OH), 2.38-1.52 (6H, m, 3 x C*H*$_2$), 1.64 (3H, s, C*H*$_3$); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 130.2 (alkene CH), 119.5 (alkene CH_2), 66.4, 38.3, 29.6, 22.5, 22.2; **m/z** (EI) 108 (2), 90 (61), 77 (62), 61 (95), 44 (100), 32 (95%).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[167]

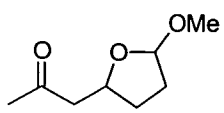
1-(2-hydroxytetrahydrofuran-5-yl)propan-2-one 194



Alkene **183** (50.0 mg, 0.446 mmol) was dissolved in CH_2Cl_2 (10 ml) under Ar at –78 °C. Ozone was bubbled through the solution for 30 min until a persistent blue colour

indicated that ozonolysis was complete. Ar was bubbled through the solution to remove the excess ozone, dimethyl sulfide (0.2 ml) was added, and the solution was allowed to warm to room temperature. The solution was stirred at room temperature for 8 hours then the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexane:EtOAc (75:25) to give lactol **194** as a mixture of *cis* and *trans* isomers (40.0 mg, 62%). $\mathbf{R_f}$ 0.17 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3411 (OH), 2950, 2360, 1710 (C=O), 1420, 1359, 1063; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.56-5.42 (1H, m, C*H*OH), 4.52 (0.5H, qn, *J* 6, C*H*O), 4.38 (0.5H, qn, *J* 6, C*H*O), 2.94-2.41 (2H, m, CH_2C=O), 2.18 (3H, s, CH_3), 2.38-1.40 (4H, m, 2xCH_2);); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 206.2, 205.7, 97.7, 97.6, 75.1, 73.1, 50.0, 48.5, 32.9, 31.9, 29.7, 29.6, 28.5, 28.1; **m/z** (FAB) 127 ([M – OH]$^+$, 67), 73 (62), 57 (60), 43(100%).

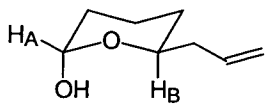
1-(2-methoxytetrahydrofuran-5-yl)propan-2-one 195



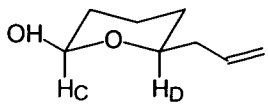
Ozonolysis was carried out with alkene **183** (50.0 mg, 0.446 mmol) in CH_2Cl_2:MeOH (8:1, 10 ml) as described for the synthesis of compound **194**. Compound **195** was obtained as a colourless oil (14 mg). $\mathbf{R_f}$ 0.55 (hexane:EtOAc 50:50); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.07-4.91 (1H, m, C*H*OMe), 4.58-4.38 (1H, m, C*H*O-), 3.30 (3H, s, OCH_3), 2.94-2.30 (2H, m, CH_2C=O), 2.19 (3H, s, CH_3C=O), 2.20-1.25 (4H, m, 2 x CH_2).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[168]

6-Allyltetrahydropyran-2-ol 202



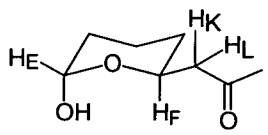
trans **202**



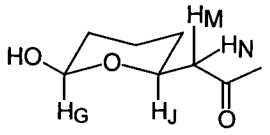
cis **202**

Glutaraldehyde (800 mg, 4.00 mmol, 50% w/w in H_2O) and tetraallyltin (283 mg, 1.00 mmol) were dissolved in THF (32 ml) and aqueous HCl (2 ml, 2N) was added dropwise. After stirring for 3 hours the reaction was quenched by the addition of aqueous sodium bicarbonate (30 ml, sat.). The organic layer was separated and the aqueous layer was extracted with ether (20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with hexane:EtOAc (90:10) gave the product **202** (286 mg, 51%) as a 4:5 mixture of *trans*:*cis* isomers. $\mathbf{R_f}$ 0.59 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3402, 3077, 2941, 1642, 1440, 1196, 1029, 980 914 and 733 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.92-5.68 (1H, m, C*H*=CH_2), 5.29 (0.5H, br s, H_A), 5.12-5.01 (2H, m, CH=CH_2), 4.70 (0.5H, dd, *J* 9.1, 3.3, H_C), 4.01 (0.5H, dtd, *J* 11.5, 5.7, 2.1, H_B), 3.85 (0.5H, br s , O*H*), 3.47 (0.5H, dtd, *J* 12.5, 6.3, 2.1, H_D), 3.22 (0.5H, br s, O*H*), 2.42-2.08 (2H, m, CH_2), 1.91-1.15 (6H, m, 3 x ring CH_2); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 134.8, 134.5, 117.0, 116.8, 96.4, 91.8, 75.8, 68.2, 40.5, 40.3, 32.5, 30.6, 29.8, 29.6, 21.8, 17.2; **m/z** (ESI) 307 ($[2M + Na]^+$, 7), 197 (29), 165 ($[M + Na]^+$, 100), 125 (13%).

1-(2-hydroxytetrahydropyran-6-yl)-propane-2-one 203



trans **203**



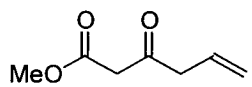
cis **203**

Palladium (II) chloride (60.3 mg, 0.340 mmol) and copper (I) chloride (67.3 mg, 0.680 mmol) were stirred in DMF:H_2O (25 ml, 7:1) for 30 min. The alkene **202** (477 mg, 3.35 mmol) was added and the reaction stirred under O_2 for 48 hours. The reaction mixture was extracted with dichloromethane (3 x 30 ml) and the extracts were combined, washed with brine (50 ml, sat.) and concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with hexane:EtOAc (90:10) gave the product **203** (400 mg, 75%) as a 4:5 mixture of *trans*:*cis* isomers. $\mathbf{R_f}$ 0.22 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3408, 2942, 1706, 1360, 1196, 1063, 1031 and 972 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.22 (0.5H, br s, H_E), 4.73 (0.5H, dd, *J* 9.7, 3.3, H_G), 4.42 (0.5H, dddd, *J* 11.4, 8.4, 4.4, 2.2, H_F), 3.98-3.84 (1H, m, H_J + O*H*), 3.51 (0.5H, br s, O*H*), 2.76 (0.5H, dd, *J* 16.4, 7.7, H_M), 2.60 (0.5H, dd, *J* 16.1, 8.4, H_K), 2.46 (0.5H, dd, *J* 16.4, 4.7, H_N), 2.40 (0.5H, dd, *J* 16.1, 4.4, H_L), 2.15 (1.5H, s, CH_3), 2.14 (1.5H, s, CH_3), 1.96-1.04 (6H, m, 3 x CH_2); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 207.9 (C=O), 207.3 (C=O), 96.1 (CH), 91.4 (CH), 71.8 (CH), 64.7 (CH), 49.7 (CH_2), 49.3 (CH_2), 31.9 (CH_2), 30.8 (CH_2), 30.8 (CH_3), 30.6 (CH_3), 30.0 (CH_2), 29.3 (CH_2), 21.7 (CH_2), 17.0 (CH_2); **m/z** (EI) 339 ([2M + Na]$^+$, 1), 321 ([2M + Na - H_2O]$^+$, 100), 181 ([M + Na]$^+$, 5%).

Samarium Diiodide

A suspension of iodine (127mg, 0.5mmol) and samarium (104mg, 0.7mmol) in THF (5ml) was heated under reflux in the absence of light (not critical but SmI_2 is known to be light sensitive) for 1 h whereupon a deep blue solution of SmI_2 (0.1M in THF) has formed. The solution was then cooled to RT and used immediately.

Methyl 3-oxohex-5-enoate 260

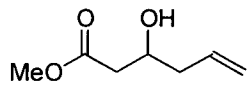


Allyl bromide (14.7 ml, 170 mmol) was added dropwise to a suspension of magnesium turnings (4.3 g, 175 mmol) in ether (100 ml) at 0 °C. When the reaction mixture stopped refluxing the resulting green solution was allowed to cool to room temperature. The reaction mixture was stirred vigorously and methyl cyanoacetate (5.62 g, 56.7 mmol) was added dropwise. The reaction mixture was left to stand for 48 h, aqueous ammonium chloride (70 ml, sat.) was added cautiously and the reaction mixture was stirred for 1.5 h. Aqueous HCl (50 ml, 1N) was added to clarify the solution. The mixture was extracted with ether (3 x 40 ml), the aqueous layer was acidified with HCl (5 ml, conc.) and extracted again with ether (2 x 40 ml). The combined organic extracts were stirred with aqueous HCl (150 ml, 1N) for 3 h. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:ether (80:20) to give a colourless oil (2.26g 28%). $\mathbf{R_f}$ 0.74 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3072 (alkene C-H), 1748 (ester C=O), 1719 (ketone C=O), 1640 (C=C), 1439, 1326, 1233, 911, 733; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.86 (1H, ddt, *J* 17.0,

10.3, 6.9, C*H*=CH_2), 5.19 (1H, dq, *J* 10.3, 1.4, CH=C$H_a$$H_b$), 5.13 (1H, dq, *J* 17.0, 1.4, CH=$CH_a$$H_b$), 3.69 (3H, s, OC$H_3$), 3.45 (2H, s, C$H_2$$CO_2$Me), 3.27 (2H, dt, *J* 6.9, 1.4, C(O)CH_2); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 200.4 (C=O), 167.3 (*C*O_2Me), 129.4 (*C*H=CH_2), 119.5 (CH=*C*H_2), 52.1, 48.1, 47.4; **m/z** (ESI) 336 (5), 300 (2), 217 (5), 197 (5), 165 ($[M + Na]^+$, 100), 143 ($[M + H]^+$, 15), 101 (3), 69 (6%).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[169]

Methyl 3-hydroxyhex-5-enoate 264

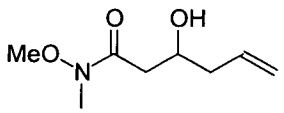


Keto ester **260** (1.40 g, 9.8 mmol) was dissolved in THF (10 ml) and cooled to 0 °C. Sodium borohydride (373 mg, 9.80 mmol) and methanol (1 ml) were added and the reaction was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic extracts were combined, washed with brine (40 ml, sat.), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane:ether (80:20) to give the hydroxy ester **264** (1.20 g, 82%) as a colourless oil. $\mathbf{R_f}$ 0.50 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3437 (OH), 3079 (alkene C-H), 1731 (C=O), 1642 (C=C), 1440, 1170, 1055, 997, 920, 734; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.81 (1H, ddt, *J* 17.6, 9.9, 7.2, C*H*=CH_2), 5.12 (1H, dq, *J* 17.6, 1.3, CH=C$H_a$$H_b$), 5.10 (1H, dq, *J* 9.9, 1.3, CH=$CH_a$$H_b$), 4.07 (1H, dtd, *J* 8.2, 6.4, 4.0, C*H*OH), 3.70 (3H, s, OCH_3), 2.79 (1H, s, O*H*), 2.53 (1H, dd, *J* 16.5, 4.0, C(O)C$H_c$$H_d$), 2.41 (1H, dd, *J* 16.5, 8.2, C(O)$CH_c$$H_d$), 2.27 (2H, tq, *J* 6.6, 1.3, CH_2CH=CH_2); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_H 173.0 (C=O), 133.8 (*C*H=CH_2), 118.0 (CH=*C*H_2), 67.1 (CH), 51.6

(CH_3), 40.8 (CH_2), 40.3 (CH_2); **m/z** (ESI) 195 (10), 167 ($[M + Na]^+$, 100), 145 ($[M + H]^+$, 7), 127 (14), 85 (6%).

^1H NMR and ν_{max} spectroscopic data in good agreement with those of the literature.[170]

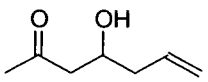
_N_-Methoxy-_N_-methyl 3-hydroxyhex-5-enoyl amide 265



Trimethylaluminium (12.8 ml, 25.7 mmol, 2M in toluene) was added to a slurry of (MeO)MeNH.HCl (2.50 g, 25.7 mmol) in THF (20 ml) at 0 °C. This mixture was stirred at 0 °C for 15 min until a colourless solution was formed. To this solution was added a solution of ester **264** (740 mg, 5.13 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 30 min. Aqueous HCl (15 ml, 1N) was added dropwise and the solution was extracted with CH_2Cl_2 (3 x 35 ml). The combined organic extracts were washed with brine (60 ml, sat.), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexane:ether (50:50) to give Weinreb amide **265** (900 mg, 100%). $\mathbf{R_f}$ 0.20 (hexane:EtOAc 50:50); ν_{max} (neat)/cm^{-1} 3428 (OH), 3076 (alkene C-H), 1641 (C=O), 1439, 1389, 1179, 1117, 1050, 999, 918; **^1H NMR** (250 MHz, $CDCl_3$) δ_H 5.84 (1H, ddt, *J* 17.2, 10.2, 7.0, C*H*=CH_2), 5.11 (1H, dq, *J* 17.2, 1.3, CH=C$H_a$$H_b$), 5.09 (1H, dq, *J* 10.2, 1.3, CH=C$H_a$$H_b$), 4.08 (1H, dtd, *J* 9.2, 6.4, 2.9, C*H*OH), 3.79 (1H, br s, O*H*), 3.66 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 2.62 (1H, dd, *J* 16.8, 2.9, C(O)C$H_c$$H_d$), 2.42 (1H, dd, *J* 16.8, 9.2, C(O)C$H_c$$H_d$), 2.30 (1H, dtt, *J* 14.0, 6.8, 1.3, C$H_e$$H_f$CH=$CH_2$), 2.21 (1H, dtt, *J* 14.0, 6.8, 1.3,

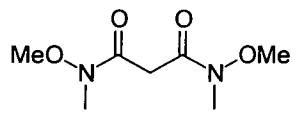
$CH_eH_fCH=CH_2$); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 173.4 (C=O), 134.2 ($CH=CH_2$), 117.4 ($CH=CH_2$), 67.2 (CH), 61.0 (CH_3), 40.7 (CH_2), 37.3 (CH_2), 31.6 (CH_3); **m/z** (ESI) 228 (4), 196 ([M = Na]$^+$, 100), 174 ([M = H]$^+$, 38), 156 (3), 134 (5%).

4-Hydroxy-2-oxohept-6-ene 263



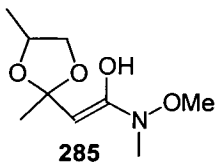
Methylmagnesium chloride (3.80 ml, 11.5 mmol, 3M in ether) was added to a solution of Weinreb amide **265** (665 mg, 3.80 mmol) in THF (20 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Aqueous citric acid solution (20 ml; 10% w/v) was added and the resulting mixture extracted with diethyl ether (3 x 25 ml). The combined extracts were washed with aqueous $NaHCO_3$ solution (40 ml, sat.) and brine (40 ml, sat.), dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:ether (60:40) to give the methyl ketone **263** (477 mg, 97%). $\mathbf{R_f}$ 0.40 (hexane:EtOAc 50:50); ν_{max} (neat)/cm^{-1} 3430 (OH), 3078 (alkene C-H), 1711 (C=O), 1642 (C=C), 1420, 1361, 1166, 1079, 998; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.76 (1H, ddt, *J* 17.1, 9.6, 7.1, $CH=CH_2$), 5.06 (1H, br d, *J* 17.1, $CH=CH_aH_b$), 5.05 (1H, br d, *J* 9.6, $CH=CH_aH_b$), 4.06 (1H, dtd, *J* 7.8, 6.9, 4.4, $CHOH$), 3.01 (1H, br s, OH), 2.58 (1H, dd, *J* 17.6, 4.4, $C(O)CH_cH_d$), 2.48(1H, dd, *J* 17.6, 7.8, $C(O)CH_cH_d$), 2.19 (2H, br t, *J* 6.9, $CH_2CH=CH_2$), 2.12 (3H, s, CH_3); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 209.5 (C=O), 133.9 ($CH=CH_2$), 114.8 ($CH=CH_2$), 66.6 (CH), 49.0 (CH_2), 40.7 (CH_2), 30.5 (CH_3); **m/z** (FAB) 129 ([M + H]$^+$, 52), 177 (52), 91 (55), 71 (57), 57 (56), 43 (100%); **HRMS** (FAB) $C_7H_{12}O_2$ [M + H]$^+$ requires 129.09146 found 129.09127.

***N,N'*-dimethoxy-*N,N'*-dimethyl-propan-1,3-diamide 267**

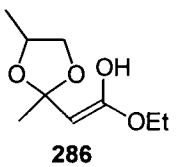


Triethylamine (7.0 ml, 50 mmol) was added to a slurry of (MeO)MeNH•HCl (2.44 g, 25.0 mmol) in CH_2Cl_2 (20 ml) and the solution was cooled to 0 °C. A solution of malonyl dichloride (1.0 ml, 10 mmol) in CH_2Cl_2 (10 ml) was added and the resulting solution was stirred at 0 °C for 40 min. Aqueous sodium hydrogen carbonate (30 ml, sat.) was added and the mixture extracted with CH_2Cl_2 (2 x 20 ml). The combined extracts were washed with aqueous NaOH (50 ml, 1N) and brine (50 ml, sat.), dried over $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash chromatography on siloica gel eluting with CH_2Cl_2:MeOH (95:5) to give **267** as a yellow oil (450 mg, 23%). $\mathbf{R_f}$ 0.51 (CH_2Cl_2:MeOH, 90:10); ν_{max} (neat)/cm^{-1} 3498, 2974, 2940, 2247, 1656(C=O), 1387; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 3.75 (6H, s, 2 x OC*H*$_3$), 3.66 (2H, s, C*H*$_2$), 3.25 (6H, s, 2 x NC*H*$_3$); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 167.3 (2C), 60.4 (2C), 37.5 (2C), 31.3; **m/z** (FAB) 381 ([2M + H]$^+$, 12), 213 ([M + Na]$^+$, 36), 191 ([M + H]$^+$, 100%); **HRMS** (FAB) $C_7H_{14}N_2O_4$ [M + H]$^+$ requires 191.10310 found 191.10298.

Reaction of Ethyl Acetoacetate Propylene Glycol Ketal 281



285



286

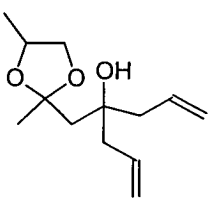
A slurry of ethyl acetoacetate propylene glycol ketal (200 mg, 1.06 mmol) and (MeO)MeNH•HCl (207 mg, 2.12 mmol) in THF (5 ml) was cooled to -30°C. To this slurry, ^{i}PrMgCl (20 ml, 4.0 mmol, 2M in THF) was added dropwise. The reaction

mixture was stirred at –30 → -10 °C for 1 hour. Aqueous NH_4Cl (10 ml, sat.) was added and the solution was extracted with CH_2Cl_2 (3 x 10 ml). The combined extracts were washed with brine (20 ml, sat.), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (80:20 → 60:40) to give **285** (63 mg, 27%) and **286** (48 mg, 24%) as colourless oils.

285 $\mathbf{R_f}$ 0.15 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3408 (OH), 2936, 1645(C=C), 1600, 1437, 1374, 1232; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.68 (1H, s, C*H*=), 4.44 (1H, sextet, *J* 5.5, CH_3CHCH_2), 3.80-3.65 (2H, m, CH_2O), 3.73 (3H, s, OCH_3), 3.25(3H, s, NCH_3), 2.36 (3H, s, CH_3), 1.31 (3H, d, *J* 6.2, CH_3CH); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 168.5, 168.1, 89.3, 73.0, 64.8, 60.3, 31.5, 18.3, 14.3.

286 $\mathbf{R_f}$ 0.23 (hexane:EtOAc, 80:20); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.24 (0.3H, s, C*H*=), 4.98 (0.7H, s, C*H*=), 4.26-3.91 (5H, m, OCH_2CH_3 + 2 x OC*H* +O*H*), 3.63-3.53 (1H, m, OC*H*), 1.98(0.9H, s, CH_3), 1.92 (2.1H, s, CH_3), 1.44-1.11 (6H, m, 2 x CH_3); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 166.3, 165.0, 98.5, 73.4, 64.6, 59.4, 58.5, 18.1, 17.0, 13.3.

4-(2,4-Dimethyl-[1,3]dioxolan-2-ylmethyl)-hepta-1,6-dien-4-ol 287

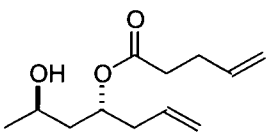


Allyl magnesium chloride (0.60 ml, 1.20 mmol, 2M in THF) was added dropwise to a solution of ethyl acetoacetate propylene glycol ketal (200 mg, 1.06 mmol) in THF

(10 ml) at 0°C. After 30 min. an aqueous solution of NH_4Cl (10 ml, 20% w/w) was added. The solution was extracted with CH_2Cl_2 (3 x 15 ml). The combined extracts were washed with brine (25 ml, sat.), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (80:20). Compound **287** (100 mg) was obtained as a colourless oil. Ethyl acetoacetate propylene glycol ketal (100 mg, 50%) was also recovered as a colourless oil.

287 $\mathbf{R_f}$ 0.59 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3505 (OH), 3075, 2979, 2932, 1639 (C=C), 1439, 1376; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 5.96-5.73 (2H, m, 2 x C*H*=CH_2), 5.07-4.97 (4H, m, 2 x CH=CH_2), 4.34-4.00 (2.5H, m, 2 x OC*H* + 0.5 x O*H*), 3.88 (0.5H, s, 0.5 x O*H*), 3.49-3.37 (1H, m, OC*H*), 2.29-2.23 (4H, m, 2 x CH_2CH=CH_2), 1.89 (1H, s, 0.5 x CH_2), 1.84 (1H, s, 0.5 x CH_2), 1.38-1.22 (6H, m, 2 x CH_3).

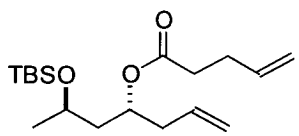
2-Hydroxy-4-(pent-4'-enoyloxy)hept-6-ene 289



A freshly prepared solution of SmI_2 (4.68 ml, 0.1M in THF) was added dropwise to a solution of benzaldehyde (49 mg, 0.47 mmol) in THF (10 ml) at 0°C. A solution of 4-pentenal (197 mg, 2.34 mmol) in THF (5 ml) was added followed by a solution of **263** (100 mg, 0.78 mmol) in THF (5 ml). The reaction mixture was stirred at 0°C for 3 hours. An aqueous solution of potassium sodium tartrate/potassium carbonate (35 ml, 10:1 mixture, 10% w/v) was added to the reaction mixture. The organic layer was

separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to yield the product as a colourless oil (141 mg, 85%). $\mathbf{R_f}$ 0.71 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3448 (OH), 3079, 1732 (C=O), 1642 (C=C); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.91-5.63 (2H, m, 2 x C*H*=CH_2), 5.19-4.98 (5H, m, 2 x CH=C*H*$_2$ + C*H*OC(O)), 3.67 (1H, sextet, *J* 6.2, C*H*OH), 2.89 (1H, br s, O*H*), 2.48-2.10 (6H, m, 3 x C*H*$_2$), 1.62-1.55 (2H, m, C(O)CH_2C*H*$_2$), 1.16 (3H, d, *J* 6.2, C*H*$_3$); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 174.0 (C=O), 136.4 (alkene CH), 133.4 (alkene CH), 117.8 (alkene CH_2), 115.5 (alkene CH_2), 70.7, 63.2, 43.7, 39.0, 33.5, 28.7, 22.7; **m/z** (FAB) 451 (25), 411 (35), 221 (73), 203 (53), 145 (42), 91 (82), 45 (100%).

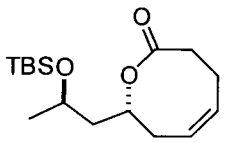
2-*tert*-butyldimethylsilyloxy-4-(pent-4'-enoyloxy)hept-6-ene 290



2,6-Lutidine (76 mg, 0.71 mmol) was added to a solution of diol monoester **289** (100 mg, 0.47 mmol) in CH_2Cl_2 (10 ml) at 0°C. *Tert*-butyldimethylsilyl triflate (132 µl, 0.75 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 1 hour. Aqueous sodium bicarbonate (30 ml, sat.) was added, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:ether (90:10) to give a colourless oil (137 mg, 89%). $\mathbf{R_f}$ 0.85 (hexane:EtOAc, 50:50); ν_{max}

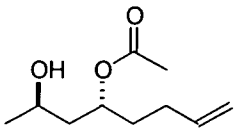
(neat)/cm^{-1} 3080, 1737 (C=O), 1642 (C=C), 1254 (Si-Me); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.91-5.64 (2H, m, 2 x C*H*=CH_2), 5.10-4.95 (5H, m, 2 x CH=CH_2 + C*H*OC(O)), 3.85 (1H, sextet, *J* 6.2, C*H*OTBS), 2.40-2.29 (6H, m, 3 x CH_2), 1.65-1.59 (2H, m, C(O)CH_2CH_2), 1.13 (3H, d, *J* 6.2, CH_3CHOTBS), 0.87 (9H, s, $SiBu^t$), 0.03 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3);); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 171.8 (C=O), 136.2 (alkene CH), 132.9 (alkene CH), 117.1 (alkene CH_2), 114.8 (alkene CH_2), 70.4, 64.5, 43.0, 38.5, 33.2, 28.3, 25.2 (3C), 23.8, 17.3, -4.8 (2C); **m/z** (FAB) 411 (10), 335 (30), 203 (51), 159 (65), 73 (100), 43 (82%).

8-(2-*tert* butyl dimethylsilyoxy-propyl)-3,4,7,8-tetrahydro-oxocin-2-one 291



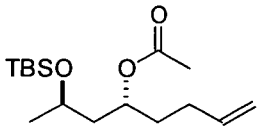
A solution of diene **290** (100 mg, 0.31 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of Grubbs ruthenium based catalyst **226** (5 mol%) in CH_2Cl_2 (100ml). The reaction mixture was stirred at room temperature for 16 hours before the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel eluting with hexane:ether (90:10). The product was obtained as a reddish brown oil indicating that some ruthenium is still present. **R_f** 0.68 (hexane:EtOAc, 50:50); **^{1}H NMR** (200 MHz, $CDCl_3$)δ_H 5.56-5.39 (2H, m, C*H*=C*H*), 4.93-5.02 (1H, m, C*H*OC(O)), 3.80-3.91 (1H, m, C*H*OTBS), 2.42-2.29 (6H, m, 3 x CH_2), 1.71-1.56 (2H, m, CH_2), 1.13 (3H, d, *J* 6.2, CH_3), 0.87 (9H, s, $SiBu^t$), 0.03 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3).

(2*RS*, 4*RS*)-4-Acetoxy-oct-7-en-2-ol 348



Freshly prepared SmI_2 (4.20 ml, 0.1 M, 0.420 mmol) was added dropwise to a solution of β-hydroxy ketone **180** (100 mg, 0.703 mmol) and acetaldehyde (159 μl, 2.81 mmol) in THF (20 ml) at 0 °C. The resulting yellow solution was stirred at 0 °C for 2 h. Aqueous potassium sodium tartrate/ potassium carbonate (10:1 w/w mixture, 10% w/v, 30 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product as a colourless oil (111 mg, 85%). $\mathbf{R_f}$ 0.61 (hexane:EtOAc, 50:50); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.74 (1H, ddt, *J* 17.2, 10.3, 6.6, C*H*=CH_2), 5.10-4.90 (3H, m, C*H*OCOCH_3 + CH=CH_2), 3.64 (1H, sextet, *J* 6.2, C*H*OH), 3.08 (1H, br s, O*H*), 2.14-1.95 (2H, m, CH_2), 2.06 (3H, s, COCH_3), 1.79-1.51 (4H, m, 2 x CH_2), 1.14 (3H, d, *J* 6.2, CH_3CHOH); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 172.1 (C=O), 137.3 (*C*H=CH_2), 115.0 (CH=*C*H_2), 71.1, 63.1, 44.3, 33.8, 29.5, 22.6, 20.8.

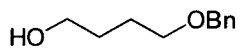
(2*RS*, 4*RS*)-2-*tert*-butyldimethylsilyloxy-4-acetoxy-oct-7-ene 349



2,6-Lutidine (246 mg, 2.30 mmol) was added to a solution of alcohol **348** (256 mg, 1.50 mmol) in CH_2Cl_2 (10 ml) at 0 °C. TBSOTf (0.55 ml, 2.39 mmol) was added

dropwise and the reaction mixture was stirred at 0 °C for 20 min. Aqueous $NaHCO_3$ (15 ml, sat.) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (95:5) to give the product as a colourless oil (407 mg, 90%). $\mathbf{R_f}$ 0.84 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3078 (alkene C-H), 1741 (C=O), 1642 (C=C), 1240; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.77 (1H, ddt, *J* 17.0, 10.4, 6.6, C*H*=CH_2), 5.05-4.87 (3H, m, C*H*OCOCH_3 + CH=CH_2), 3.84 (1H, sextet, *J* 6.0, C*H*OTBS), 2.14-1.99 (2H, m, CH_2), 2.00 (3H, s, COCH_3), 1.73-1.57 (4H, m, 2 x CH_2), 1.12 (3H, d, *J* 6.0, CH_3CHOTBS), 0.85 (9H, s, SiBu^t), 0.01 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 170.5 (C=O), 137.8 (*C*H=CH_2), 114.7 (CH=*C*H_2), 71.6, 65.2, 44.0, 33.8, 29.2, 25.7 (3C), 24.3, 21.1, 17.8, -4.4, -5.2; **m/z** (ESI) 323 ([M + Na]$^+$, 24), 320 (18), 279 (100), 263 (47), 235 (16), 197 (17%).

4-Benzyloxybutan-1-ol 398

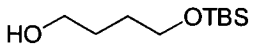


Butane-1,4-diol (2.00 g, 22.0 mmol) was added to a suspension of freshly washed sodium hydride (888 mg, 60% suspension in mineral oil, 22.0 mmol) in THF (30 ml) and the mixture was stirred for 40 min until the monosodium salt precipitated. Benzyl bromide (2.64 ml, 22.0 mmol) was added dropwise followed by tetrabutylammonium iodide (8.23 g, 22.0 mmol). The reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ether (250 ml) and washed with aqueous K_2CO_3 (500 ml, 10% w/v.) and aqueous NaCl (250 ml, sat.).

The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **398** (3.46 g, 86%) as a colourless oil. $\mathbf{R_f}$ 0.19 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3385 (OH), 2939, 2864, 1496, 1453; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.35-7.26 (5H, m, Ar*H*), 4.53 (2H, s, OCH_2Ph), 3.62 (2H, t, *J* 5.9, OCH_2), 3.53 (2H, t, *J* 5.9, OCH_2), 2.05 (1H, s, O*H*), 1.75-1.65 (4H, m, 2 x CH_2).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[171]

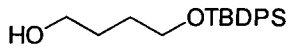
4-*tert*-Butyldimethylsilyloxybutan-1-ol 399



Butane-1,4-diol (1.35 g, 15.0 mmol) was added to a suspension of freshly washed sodium hydride (0.60 g, 60% suspension in mineral oil, 15.0 mmol) in THF (30 ml) and the mixture was stirred for 40 min until the monosodium salt precipitated. TBDMSCl (2.26 g, 15.0 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ether (75 ml) and washed with aqueous $NaHCO_3$ (50 ml, sat.) and aqueous NaCl (50 ml, sat.). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **399** (2.42 g, 80%) as a colourless oil. $\mathbf{R_f}$ 0.30 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3330 (OH), 2929, 2884, 2857, 1256; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 3.67-3.56 (4H, m, 2 x OCH_2), 2.66 (1H, br s, O*H*), 1.66-1.57 (4H, m, 2 x CH_2), 0.85 (9H, s, SiBu^t), 0.04 (6H, s, 2 x SiCH_3).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[159]

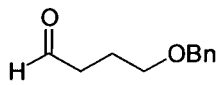
4-*tert*-Butyldiphenylsilyloxybutan-1-ol 400



Butane-1,4-diol (1.00 g, 11.1 mmol) was added to a suspension of freshly washed sodium hydride (0.44 g, 60% suspension in mineral oil, 11.1 mmol) in THF (30 ml) and the mixture was stirred for 40 min until the monosodium salt precipitated. TBDPSCl (3.02 g, 11.1 mmol) was added and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ether (75 ml) and washed with aqueous $NaHCO_3$ (50 ml, sat.) and aqueous NaCl (50 ml, sat.). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **400** (2.60 g, 79%) as a colourless oil. $\mathbf{R_f}$ 0.25 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3355 (OH), 3070, 2931, 2857, 1472, 1427; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.74-7.69 (4H, m, Ar*H*), 7.46-7.38 (6H, m, Ar*H*), 3.73 (2H, t, *J* 5.5, OCH_2), 3.67 (2H, t, *J* 6.1, OCH_2), 2.33 (1H, s, O*H*), 1.74-1.64 (4H, m, 2 x CH_2), 1.09 (9H, s, SiBu^t); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 135.5 (4C), 133.5 (2C), 129.5 (2C), 127.6 (4C), 63.8, 62.5, 29.6, 29.0, 26.6 (3C), 18.9; **m/z** (ESI) 351 ([M + Na]$^+$, 100), 329 ([M + H]$^+$, 40), 253 (6), 251 (9%).

^{1}H NMR and ^{13}C NMR spectroscopic data in good agreement with those of the literature.[172]

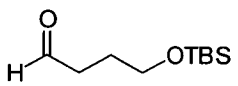
4-Benzyloxybutanal 401



A solution of alcohol **398** (500 mg, 2.77 mmol) in THF (5 ml) was added to a colourless solution of IBX (1.40 g, 4.99 mmol) in DMSO (5 ml). The reaction mixture was stirred at room temperature for 1.5 h. Water (50 ml) was added, the solution was filtered and extracted with EtOAc (4 x 20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **401** (470 mg, 95%) as a pale oil. $\mathbf{R_f}$ 0.40 (hexane:EtOAc, 80:20); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.78 (1H, t, *J* 1.5, C*H*O), 7.34-7.29 (5H, m, Ar*H*), 4.49 (2H, s, OCH_2Ph), 3.51 (2H, t, *J* 6.0, CH_2OBn), 2.55 (2H, td, *J* 7.1, 1.5, CH_2CHO), 1.95 (2H, qn, *J* 6.6, CH_2).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[173]

4-*tert*-Butyldimethylsilyloxybutanal 402

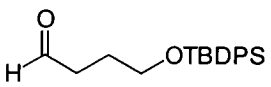


A solution of alcohol **399** (570 mg, 2.79 mmol) in THF (5 ml) was added to a colourless solution of IBX (1.40 g, 4.99 mmol) in DMSO (5 ml). The reaction mixture was stirred at room temperature for 3 h. Water (50 ml) was added, the solution was filtered and extracted with EtOAc (4 x 20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **402** (282 mg, 50%) as a pale oil. $\mathbf{R_f}$ 0.63 (hexane:EtOAc, 80:20); **^{1}H NMR**

(200 MHz, $CDCl_3$) δ_H 9.77 (1H, t, *J* 1.7, C*H*O), 3.63 (2H, t, *J* 5.9, CH_2OTBS), 2.48 (2H, td, *J* 7.1, 1.7, CH_2CHO), 1.90-1.77 (2H, m, CH_2), 0.86 (9H, s, SiBu^t), 0.02 (6H, s, 2 x CH_3).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[174]

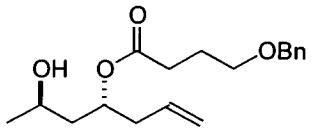
4-*tert*-Butyldiphenylsilyloxybutanal 403



A solution of alcohol **400** (920 mg, 2.80 mmol) in THF (5 ml) was added to a colourless solution of IBX (1.40 g, 4.99 mmol) in DMSO (5 ml). The reaction mixture was stirred at room temperature for 2 h. Water (50 ml) was added, the solution was filtered and extracted with EtOAc (4 x 20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **403** (800 mg, 88%) as a colourless oil. $\mathbf{R_f}$ 0.64 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3071, 2930, 2857, 1725 (C=O), 1428; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.79 (1H, t, *J* 1.5, C*H*O), 7.67-7.64 (4H, m, Ar*H*), 7.47-7.36 (6H, m, Ar*H*), 3.70 (2H, t, *J* 5.9, CH_2OTBDPS), 2.55 (2H, td, *J* 7.1, 1.5, CH_2CHO), 1.90 (2H, qn, *J* 6.6, CH_2), 1.06 (9H, s, SiBu^t); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_H 202.5, 135.5 (4C), 133.5 (2C), 129.6 (2C), 127.6 (4C), 62.8, 40.6, 26.7 (3C), 25.1, 19.0; **m/z** (ESI) 381 (100), 365 ([M + K]$^+$, 29), 350 ([M + Na]$^+$, 20), 327 ([M + H]$^+$, 18).

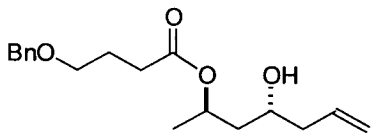
^{1}H NMR spectroscopic data in good agreement with those of the literature.[172]

(2*RS*, 4*RS*)-4-(4'-benzyloxy)butanoyloxy-hept-6-en-2-ol 404



Freshly prepared SmI_2 (4.20 ml, 0.1 M, 0.420 mmol) was added dropwise to a solution of aldehyde **401** (470 mg, 2.64 mmol) in THF (10 ml) at 0 °C. A cooled solution of β-hydroxy ketone **263** (90.0 mg, 0.702 mmol) in THF (5 ml) was added slowly and the reaction mixture was stirred at 0 °C for 6 h. Aqueous potassium sodium tartrate/ potassium carbonate (10:1 w/w mixture, 10% w/v, 30 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (80:20) to give the products **404** (133 mg, 62%) and **407** (33 mg, 15%). $\mathbf{R_f}$ 0.62 (hexane:EtOAc, 50:50); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.39-7.26 (5H, m, Ar*H*), 5.72 (1H, ddt, *J* 17.6, 10.6, 7.0, C*H*=CH_2), 5.18-5.03 (3H, m, CH=CH_2 + C*H*OCO), 4.49 (2H, s, OCH_2Ph), 3.66 (1H, sextet, *J* 6.2, C*H*OH), 3.50 (2H, t, *J* 6.0, CH_2OBn), 2.46 (2H, t, *J* 7.3, C(O)CH_2), 2.32 (2H, t, *J* 6.6, CH(OH)CH_2), 2.00-1.88 (2H, m, CH_2), 1.61-1.55 (2H, m, CH_2CH=CH_2), 1.15 (3H, d, *J* 6.2, CH_3).

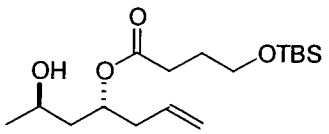
(2*RS*, 4*RS*)-2-(4'-benzyloxy)butanoyloxy-hept-6-en-4-ol 407



$\mathbf{R_f}$ 0.69 (hexane:EtOAc, 50:50); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.39-7.25 (5H, m, Ar*H*), 5.90-5.75 (1H, m, C*H*=CH_2), 5.21-5.04 (3H, m, CH=CH_2 + C*H*OC(O)), 4.49

(2H, s, OCH_2Ph), 3.64-3.49 (3H, m, C*H*OH + CH_2OBn), 2.76 (1H, br s, O*H*), 2.46 (2H, t, *J* 7.3, C(O)CH_2), 2.20 (2H, t, *J* 6.6 CH_2CH(OH)), 2.00-1.86 (2H, m, CH_2), 1.62-1.54 (2H, m, CH_2CH=CH_2), 1.24 (3H, d, *J* 6.6, CH_3).

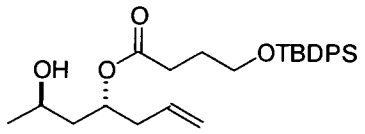
(2*RS*, 4*RS*)-4-(4'-*tert*-Butyldimethylsilyloxy)butanoyloxy-hept-6-en-2-ol 405



Freshly prepared SmI_2 (2.10 ml, 0.1 M, 0.210 mmol) was added dropwise to a solution of aldehyde **402** (177 mg, 0.875 mmol) in THF (5 ml) at 0 °C. A cooled solution of β-hydroxy ketone **263** (45.0 mg, 0.351 mmol) in THF (5 ml) was added slowly and the reaction mixture was stirred at 0 °C for 72 h. Aqueous potassium sodium tartrate/ potassium carbonate (10:1 w/w mixture, 10% w/v, 15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give the product **405** (70 mg, 61%) as a colourless oil. $\mathbf{R_f}$ 0.77 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3451 (OH), 3078 (alkene C-H), 2956, 2921, 2857, 1732 (C=O), 1643 (C=C), 1256; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.73 (1H, ddt, *J* 16.5, 9.5, 7.0, C*H*=CH_2), 5.15-5.03 (3H, m, CH=CH_2 + C*H*OCO), 3.69-3.59 (1H, m, C*H*OH), 3.62 (2H, t, *J* 6.0, CH_2OTBS), 2.95 (1H, br s, O*H*), 2.45-2.29 (4H, m, C(O)CH_2 + CH(OH)CH_2), 1.88-1.75 (2H, m, CH_2), 1.62-1.55 (2H, m, CH_2CH=CH_2), 1.16 (3H, d, *J* 6.6, CH_3), 0.88 (9H, s, SiBu^t), 0.03 (6H, s, 2 x SiCH_3); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 174.8 (C=O), 133.4, 117.8, 70.6, 63.2, 61.7, 43.8, 39.0, 30.6, 27.8, 25.7

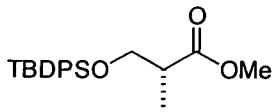
(3C), 22.7, 18.1, -4.5, -5.3; **m/z** (ESI) 376 (23), 353 ($[M + Na]^+$, 91), 348 ($[M + NH_4]^+$, 100), 331 ($[M + H]^+$, 33%).

(2*RS*, 4*RS*)-4-(4'-*tert*-Butyldiphenylsilyloxy)butanoyloxy-hept-6-en-2-ol 406



Freshly prepared SmI_2 (4.20 ml, 0.1 M, 0.42o mmol) was added dropwise to a solution of aldehyde **403** (750 mg, 2.30 mmol) in THF (10 ml) at 0 °C. A cooled solution of β-hydroxy ketone **263** (90.0 mg, 0.702 mmol) in THF (5 ml) was added slowly and the reaction mixture was stirred at 0 °C for 3 h. Aqueous potassium sodium tartrate/ potassium carbonate (10:1 w/w mixture, 10% w/v, 30 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (95:5) to give the product **406** (278 mg, 87%). $\mathbf{R_f}$ 0.76 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3448 (OH), 3072 (alkene C-H), 2962, 2931, 2858, 1734 (C=O), 1428, 1259; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.67-7.63 (4H, m, Ar*H*), 7.43-7.36 (6H, m, Ar*H*), 5.73 (1H, ddt, *J* 16.8, 10.3, 7.1, C*H*=CH_2), 5.15-5.03 (3H, m, CH=CH_2 + C*H*OCO), 3.71-3.60 (1H, m, C*H*OH), 3.69 (2H, t, *J* 6.2, CH_2OTBDPS), 2.49 (2H, t, *J* 7.5, C(O)CH_2), 2.32 (2H, t, *J* 6.4, CH(OH)CH_2), 1.94-1.81 (2H, m, CH_2), 1.62-1.55 (2H, m, CH_2CH=CH_2), 1.16 (3H, d, *J* 6.2, CH_3), 1.05 (9H, s, SiBu^t); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 174.7, 135.5 (4C), 133.6 (2C), 133.4, 129.6 (2C), 127.6 (4C), 117.9, 70.6, 63.2, 62.6, 43.8, 39.1, 30.7, 27.7, 26.9 (3C), 22.8, 19.0.

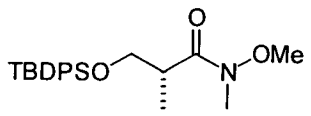
Methyl (2*R*)-3-*tert*-butyldiphenylsilyloxy-2-methylpropionate 408



Tert-butyldiphenylsilyl chloride (2.42 ml, 9.31 mmol) was added to a solution of methyl-(*R*)-3-hydroxy-2-methylpropionate **407** (1.00 g, 8.46 mmol) and imidazole (1.26 g, 18.6 mmol) in CH_2Cl_2 (8 ml). The reaction mixture was stirred for 40 min. Water (30 ml) was added to the reaction mixture, the organic phase was separated and the aqueous phase extracted with diethyl ether (3 x 20 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel eluting with hexane:ether (95:5) to give the product **408** (3.02 g, 100%) as a colourless oil. $\mathbf{R_f}$ 0.64 (hexane:EtOAc, 80:20); $[\alpha]_D$ −16.7° (c 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3071, 3050, 2932, 2858, 1741 (C=O), 1473, 1428, 1199, 1112, 701, 613; **^{1}H NMR** (200MHz, $CDCl_3$) δ_H 7.68-7.63 (4H, m, Ar*H*), 7.42-7.35 (6H, m, Ar*H*), 3.86 (1H, dd, *J* 9.7, 7.0, CH_aH$_b$OTBDPS), 3.75 (1H, dd, *J* 9.7, 5.8, CH$_a$$H_b$OTBDPS), 3.68 (3H, s, OC$H_3$), 2.74 (1H, qn d, *J* 7.0, 5.8, C*H*CO$_2$Me), 1.15 (3H, d, *J* 7.0, CH_3), 1.03 (9H, s, SiBu^t); **^{13}CNMR** (62.9 MHz, $CDCl_3$) δ_C 175.8 (C=O), 136.0 (4CH), 134.0 (C), 133.9 (C), 130.1 (2CH), 128.1 (4CH), 66.4 (CH_2), 52.0 (CH_3), 42.8 (CH), 27.2 (3CH_3), 19.7 (C), 13.9 (CH_3); **m/z** (FAB) 325([M-OMe]$^+$, 8), 299([M-^{t}Bu]$^+$, 100), 213 (84), 183 (48), 181 (30).

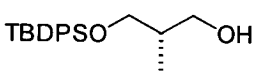
^{1}H NMR spectroscopic data in good agreement with those of the literature.[160]

(*R*)-3-*tert*-Butyldiphenylsilyloxy-*N*-methoxy-2,*N*-dimethylpropionate 409



A slurry of ester **408** (210 mg, 0.590 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (89.0 mg, 0.912 mmol) in THF (5 ml) was cooled to –20 °C. *iso*-Propylmagnesium chloride (0.65 ml, 2M solution in THF, 1.30 mmol) was added dropwise and the reaction stirred at –5 °C for 1.5 h. Aqueous NH_4Cl (30 ml, sat.) was added and the mixture was extracted with ether (3 x 20 ml). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:EtOAc (90:10) to give **409** (221 mg, 97%) as a colourless oil. $\mathbf{R_f}$ 0.28 (hexane:EtOAc, 80:20); ν_{max} (neat)/cm^{-1} 3070, 2932, 2857, 1660 (C=O), 1472, 1428, 1388; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.71-7.65 (4H, m, Ar*H*), 7.43-7.33 (6H, m, Ar*H*), 3.94 (1H, dd, *J* 9.5, 8.1, CH_aH$_b$OTBDPS), 3.66 (3H, s, OCH_3), 3.60 (1H, dd, *J* 9.5, 6.2, CH$_a$$H_b$OTBDPS), 3.20 (3H, s, NC$H_3$), 3.21-3.16 (1H, m, C*H*CH$_3$), 1.08 (3H, d, *J* 7.0, CH_3), 1.04 (9H, s, SiBu^t); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 135.6 (2C), 135.4 (2C), 133.7, 133.4, 129.5 (2C), 127.5 (4C), 66.1, 61.3, 37.8, 31.9, 26.5 (3C), 19.0, 13.6, C=O missing; **m/z** (ESI) 431 (11), 408 ([M + Na]$^+$, 100), 386 ([M + H]$^+$, 26), 308 (14%).

(*S*)-3-*tert*-Butyldiphenylsilyloxy-2-methylpropan-1-ol 410

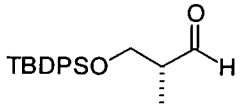


DIBAL-H (3.20 ml, 1.0M in hexane, 3.20 mmol) was added dropwise to a solution of methyl (2*R*)-3-*tert*-butyldiphenylsilyloxy-2-methylpropionate **408** (500 mg, 1.40

mmol) in CH_2Cl_2 (20 ml) at -78°C. After 2 h aqueous potassium sodium tartrate (50 ml; sat.) was added and the mixture stirred for 3 h at 25 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel eluting hexane:EtOAc (90:10) to give alcohol **410** (370 mg, 80%) as a colourless oil. $\mathbf{R_f}$ 0.41 (hexane:EtOAc, 80:20); $[\alpha]_D$ –6.3° (c 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3387 (OH), 3072, 2959, 2858, 1472, 1428; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.70-7.65 (4H, m, Ar*H*), 7.49-7.35 (6H, m, Ar*H*), 3.73 (1H, dd, *J* 10.1, 4.8, C*H*$_a$H$_b$OTBDPS), 3.67 (2H, d, *J* 5.9, C*H*$_2$OH), 3.59 (1H, dd, *J* 10.1, 7.7, CH$_a$*H*$_b$OTBDPS), 2.04-1.95 (1H, m, C*H*CH$_3$), 1.06 (9H, s, SiBu^t), 0.83 (3H, d, *J* 7.0, C*H*$_3$); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ_C 135.4 (4CH), 133.0 (2C), 129.7 (2CH), 127.6 (4CH), 68.6 (CH_2), 67.5 (CH_2), 37.1 (CH), 26.7 ($3CH_3$), 19.0 (C), 13.0 (CH_3).

^{1}H NMR spectroscopic data in good agreement with those of the literature.[160]

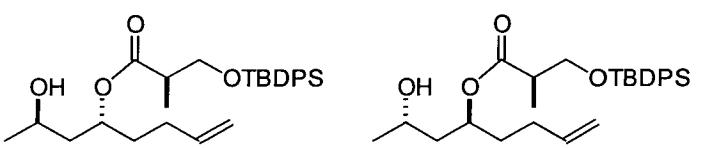
(*R*)-3-*tert*-Butyldiphenylsilyloxy-2-methylpropanal 396



DMSO (265 mg, 3.39 mmol) was added to a solution of oxalyl chloride (351 mg, 2.70 mmol) in CH_2Cl_2 (15 ml) at –78 °C. The solution was stirred for 30 min then a solution of (*S*)-3-*tert*-butyldiphenylsilyloxy-2-methylpropanol **410** (370 mg, 1.13 mmol) in CH_2Cl_2 (3 ml) was added. The reaction was stirred at –78 °C for 1 h, triethylamine (2.00 ml, 14.4 mmol) was added and the solution warmed to 25 °C. Water (20 ml) was added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15ml). The organic layers were

combined, washed with aqueous HCl (50 ml, 1% w/v), water (50 ml), aqueous $NaHCO_3$ (50 ml, sat.) and brine (50 ml, sat.), dried over $MgSO_4$ and concentrated under reduced pressure to give the aldehyde **396** (340 mg, 92%) as a yellow oil which was used without purification. $\mathbf{R_f}$ 0.65 (hexane:EtOAc 80:20); $[\alpha]_D$ –23.8° (c 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2930, 1711 (C=O), 1472, 1427; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.81 (1H, d, *J* 1.8, C*H*O), 7.73-7.64 (4H, m, Ar*H*), 7.52-7.38 (6H, m, Ar*H*), 3.95 (1H, dd, *J* 10.3, 5.1, CH_aH$_b$OTBDPS), 3.88 (1H, dd, *J* 10.3, 6.2, CH$_a$$H_b$OTBDPS), 2.65-2.53 (1H, m, C*H*CHO), 1.14 (3H, d, *J* 7.0, CH_3), 1.09 (9H, s, SiBu^t); **^{13}CNMR** (50.3 MHz, $CDCl_3$) δ_C 204.6, 135.5 (4C), 133.1 (2C), 129.7(2C), 127.8 (4C), 64.0, 48.7, 26.8 (3C), 19.1, 10.1; **m/z** (ESI) 327 ([M+H]$^+$, 7), 377 (5), 201 (18), 165 (50), 162 (98), 160 (100).

Evans-Tishchenko Adducts 411 and 412



Freshly prepared SmI_2 (3.30 ml, 0.1 M, 0.330 mmol) was added dropwise to a solution of benzaldehyde (35.0 mg, 0.330 mmol) in THF (5 ml) at 0 °C. The resultant yellow solution was added dropwise to a solution of the aldehyde **396** (340 mg, 1.04 mmol) and β-hydroxy ketone **263** (70.0 mg, 0.492 mmol) in THF (5 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Aqueous potassium sodium tartrate/ potassium carbonate (10:1 w/w mixture, 10% w/v, 20 ml) was added and the solution was extracted with CH_2Cl_2 (3 x 20 ml). The organic layers were combined, washed with brine (60 ml) and dried over $MgSO_4$. The solvent was removed under

reduced pressure and the residue was purified by flash chromatography on silica gel eluting with hexane:EtOAC (95:5) to give **411** (93 mg, 40%) and **412** (93 mg, 40%).

R_f 0.75 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3514, 3072, 3050, 2965, 2934, 2858, 1719 (C=O), 1428; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.61-7.57 (4H, m, Ar*H*), 7.41-7.27 (6H, m, Ar*H*), 5.68 (1H, ddt, *J* 17.0, 10.4, 6.6), 5.11-4.86 (3H, m, C*H*OC(O) + CH=CH_2), 3.79 (1H, dd, *J* 9.9, 7.2, CH_aH$_b$OTBDPS), 3.66-3.56 (1H, m, *CH*OH), 3.63 (1H, dd, *J* 9.9, 5.1, CH$_a$$H_b$OTBDPS), 3.12 (1H, d, *J* 3.7, O*H*), 2.65 (1H, qn d, *J* 7.2, 5.1, C(O)C*H*), 2.07-1.94 (2H, m, CH_2CHOH), 1.77-1.41 (4H, m, 2 x CH_2), 1.07 (3H, d, *J* 7.2, CH_3CHC(O)), 1.05 (3H, d, *J* 6.2, CH_3CHOH), 0.97 (9H, s, SiBu^t); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 176.3, 137.4, 135.5 (4C), 133.2 (2C), 129.7 (2C), 127.7 (4C), 115.1, 71.1, 65.8, 63.0, 44.6, 42.9, 34.0, 29.6, 26.6 (3C), 22.6, 19.1, 13.7.

R_f 0.80 (hexane:EtOAc, 50:50); ν_{max} (neat)/cm^{-1} 3462, 3071, 3050, 2964, 2933, 2858, 1720 (C=O), 1428, 1195, 1112, 1081, 701; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.62-7.57 (4H, m, Ar*H*), 7.41-7.29 (6H, m, Ar*H*), 5.71 (1H, ddt, *J* 16.8, 10.3, 6.6), 5.11-4.88 (3H, m, C*H*OC(O) + CH=CH_2), 3.79 (1H, dd, *J* 9.5, 7.7, CH_aH$_b$OTBDPS), 3.70-3.53 (1H, m, C*H*OH), 3.63 (1H, dd, *J* 9.5, 4.8, CH$_a$$H_b$OTBDPS), 3.22 (1H, d, *J* 7.3, O*H*), 2.65 (1H, sextet, *J* 7.0, C(O)C*H*), 2.10-1.97 (2H, m, CH_2CHOH), 1.71-1.47 (4H, m, 2 x CH_2), 1.06 (3H, d, *J* 7.0, CH_3CHC(O)), 1.03 (3H, d, *J* 6.2, CH_3CHOH), 0.97 (9H, s, SiBu^t); **^{13}C NMR** (50.3 MHz, $CDCl_3$) δ_C 176.5, 137.4, 135.5(4C), 133.2 (2C), 129.7 (2C), 127.6 (4C), 115.1, 71.2, 65.8, 62.9, 44.7, 42.6, 34.0, 29.6, 26.6 (3C), 22.5, 19.0, 13.6.

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Abbreviations

aq.	aqueous
Bn	benzyl
Bu	butyl
DCB	2,6-dichlorobenzyl
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EI	electron impact ionisation
ESI	electrospray ionisation
Et	ethyl
Ether	diethyl ether
FAB	fast atom bombardment
HRMS	high resolution mass spectrum
Hz	hertz
IBX	iodoxybenzoic acid
IR	infra red
Me	methyl
nmr	nuclear magnetic resonance
P	unspecified protecting group
PKS	polyketide synthase
PMB	para methoxy benzyl

ppm	parts per million
Pr	propyl
RCM	ring closing metathesis
TBDPS	*tert*-butyl diphenylsilyl
TBS	*tert*-butyl dimethylsilyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TS	transition state