The Anionic oxy-Cope Rearrangement: A Tool for Stereocontrolled Synthesis

A Thesis submitted in part fulfilment of the

requirements for the degree of Doctor of Philosophy

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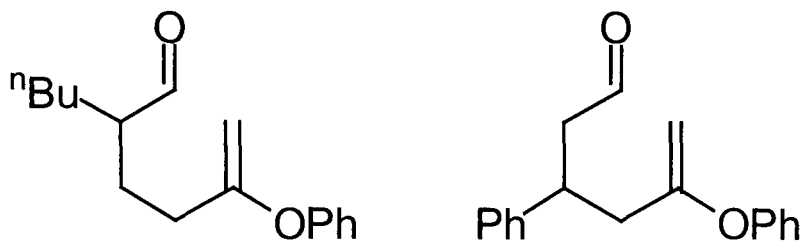
"Thats the whole problem with science. You've got a bunch of empiricists trying to describe things of unimaginable wonder."

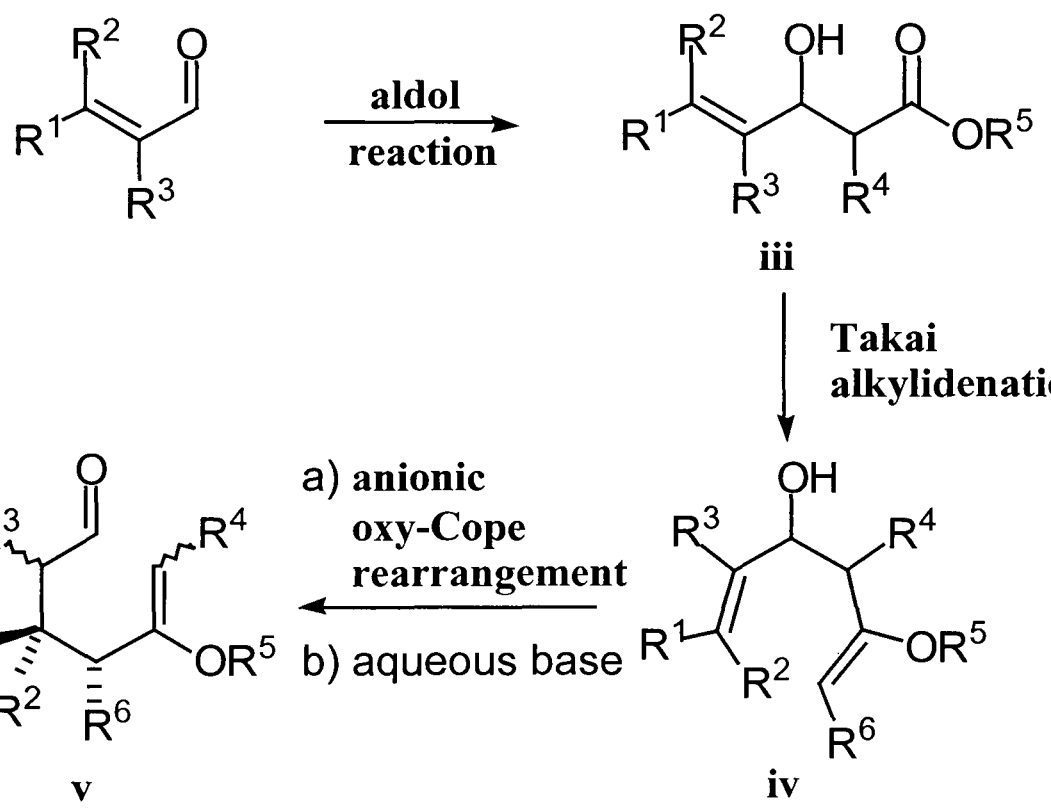
Bill Watterson.

ABSTRACT



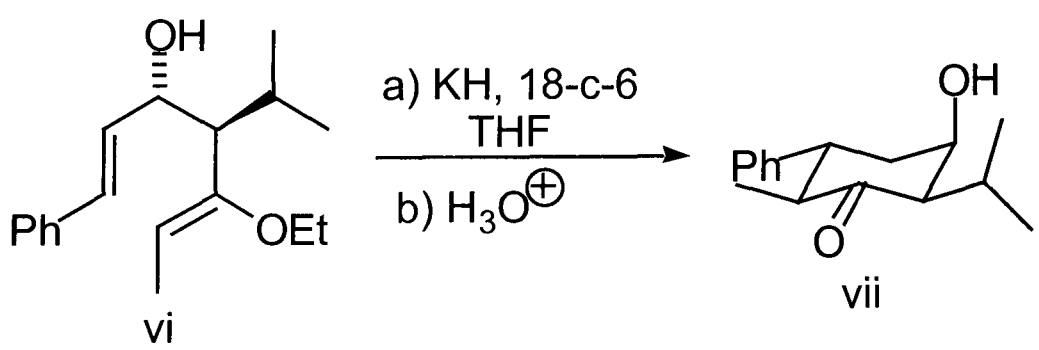
i **ii**

Novel enol ethers **i** and **ii** containing aldehyde groups have been synthesised by the route shown. An aldol reaction on an α,β-unsaturated aldehydes gives β-hydroxyesters **iii**. Takai's alkylidenation procedure generates hexadienols **iv** and anionic oxy-Cope (AOC) rearrangement of **iv** followed by aqueous base provides aldehydes **v**. Aldehydes **i** and **ii** are the first examples of aldehydes **v**, which bear an enol ether in a 1,5-relationship with an aldehyde group.



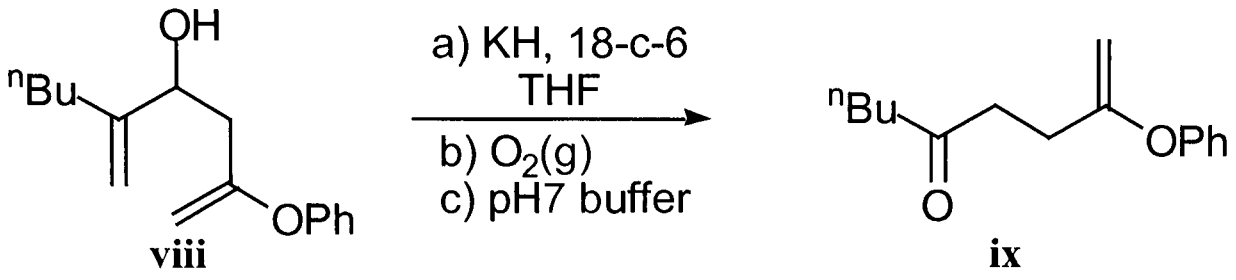
iii **iv** **v**

Alcohol **vi** was synthesised and used to prepare tetrasubstituted cyclohexanone **vii** by a one-pot AOC rearrangement/acid-induced aldol reaction. The stereochemical outcome of this and related rearrangements was investigated and the stereocontrol explained.



vi vii

The reaction between enolates, generated by AOC rearrangement, and molecular oxygen was investigated and was found to give the products of fragmentation, e.g. alcohol **viii** was converted into ketone **ix**.



viii **ix**

COMMON ABBREVIATIONS

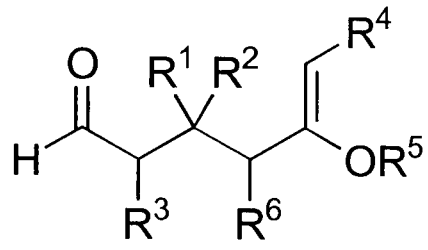
18-c-6	18-crown-6
AOC	anionic oxy-Cope
DCC	dicyclohexylcarbodiimide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMSO	dimethylsulfoxide
HMPA	hexamethylphosphoramide
HRMS	High resolution mass spectrum
KDA	potassium diisopropylamide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
pTSA	*para*-toluenesulfonic acid
Rf	retention factor
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethane sulfonate
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
THF	tetrahydrofuran
TEA	triethylamine
xs	excess

CONTENTS

1. INTRODUCTION

We wished to study the synthesis and chemistry of enol-ether-bearing aldehyde **1**, *Figure 1*. The synthesis of aldehyde **1** is based on three key reactions: an aldol reaction;[1] Takai's alkylidenation reaction[2] and the [3,3]sigmatropic anionic oxy-Cope (AOC) rearrangement.[3]

Figure 1



1

Our synthetic strategy and design are discussed at the end of this chapter. First I will briefly review the three key reactions.

1.1 The Aldol Reaction of Carboxylic Acid Derivatives

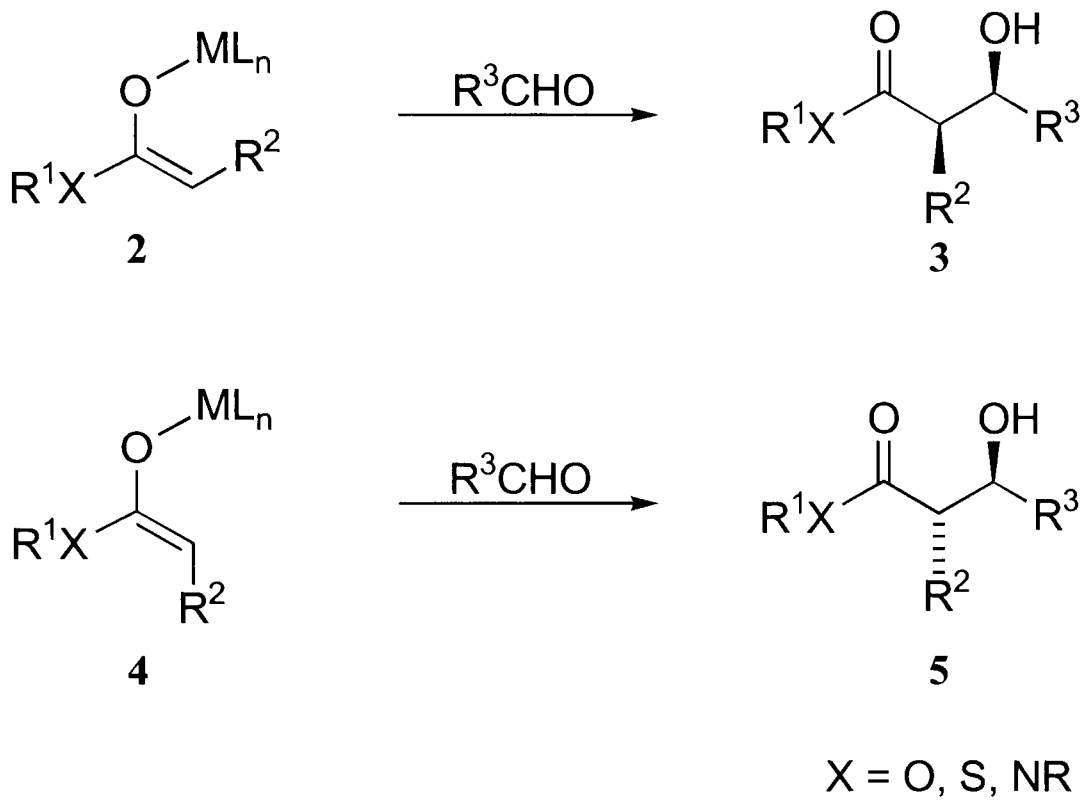
Control in carbon-carbon bond forming processes plays a fundamental role in modern organic synthesis. Over the years the aldol reaction has been developed into one of the most powerful and versatile weapons at the disposal of the organic chemist. A number of techniques can be employed to control both relative and absolute stereochemistry in the aldol reaction.

1.1.1 Control of Enolate Geometry and Relative Stereochemistry

The diastereoselection in aldols performed under kinetic conditions often depends on the geometry of the enolate employed. In general, *Z* enolates **2** give rise to *syn* aldols **3** and *E* enolates **4** produce *anti* aldols **5**, *scheme 1*. A number of

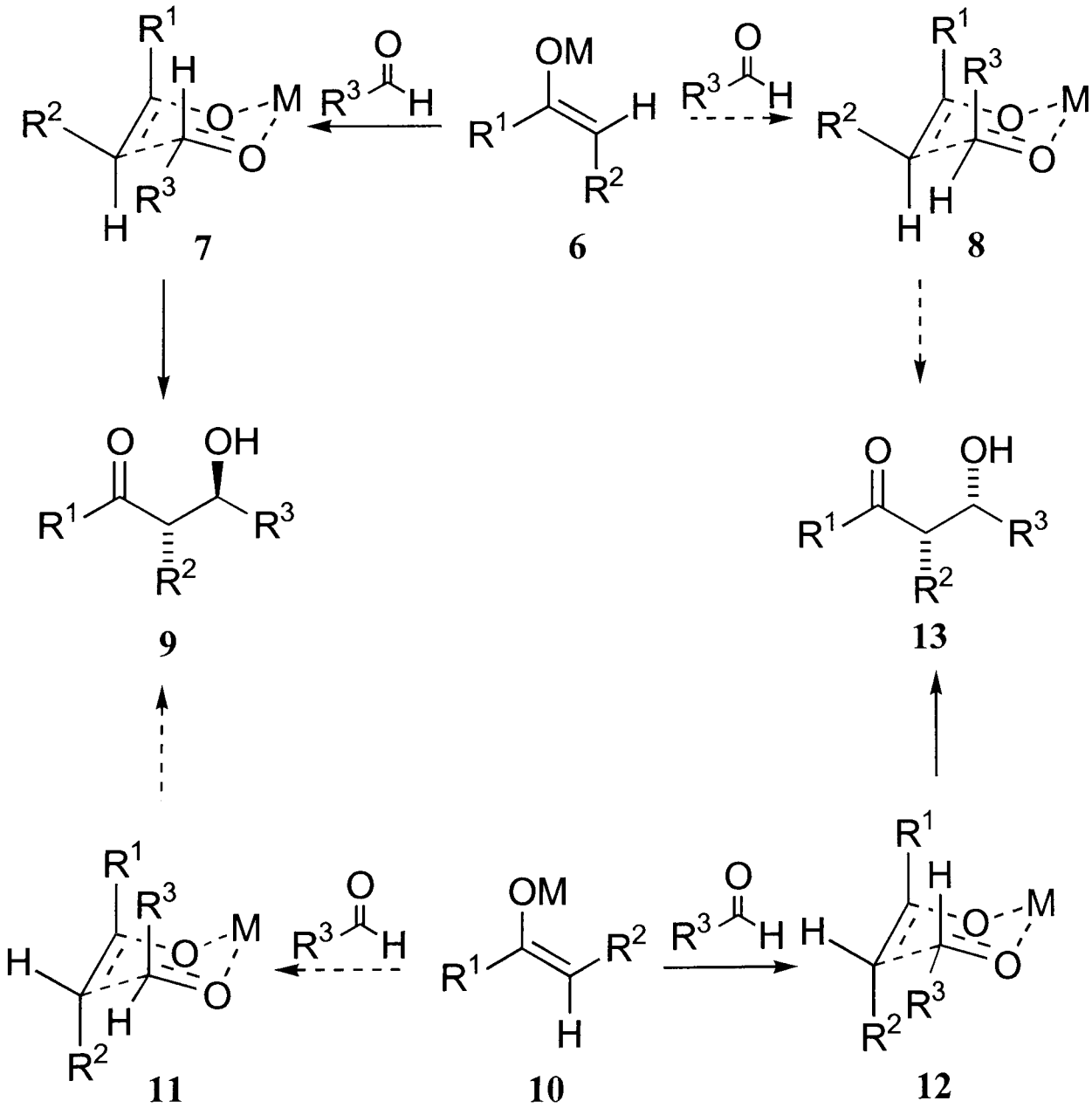
different transition state models have been proposed to explain the diastereoselectivity in aldol reactions.

Scheme 1



One such is that suggested by Zimmerman and Traxler[4] in 1957, *Scheme 2*.

Scheme 2

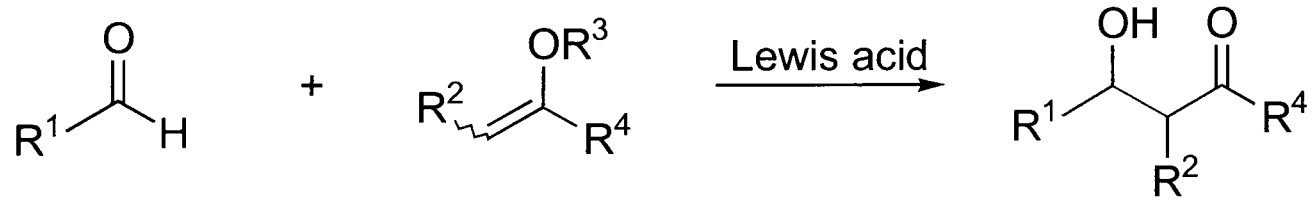


The Zimmerman-Traxler model involves chair-like transition states with the metal coordinated to both the enolate oxygen atom and the oxygen atom of the aldehyde. *E*-enolate **6** can combine with an aldehyde to give two possible transition states **7** and **8**. Transition state **8** is destabilised relative to **7** due to 1,3-*pseudo*diaxial interaction between R^1 and R^3, and so the *anti* aldol **9** is the major product. In like manner *Z*-enolate **10** gives rise to transition states **11** and **12**. Transition state **11** is destabilised by the same 1,3-*pseudo*diaxial interaction between R^1 and R^3, hence *syn* aldol **13** predominates in the product. A more detailed discussion with specific examples is outlined below.

A variety of different techniques for controlling enolate geometry are described in the literature. Metals such as lithium, titanium (directly or by transmetallation), magnesium, boron and tin have been utilised with varying degrees of success.[5]

Metal-free enolates, e.g. silyl enol ethers, generally undergo aldol reactions via open transition states. The Mukaiyama aldol reaction[6] is the Lewis acid mediated reaction of an aldehyde **14** with enol silanes **15**, *Scheme 3*. Regardless of whether we generate the *Z*- or the *E*-enol silane the reaction always selectively produces *syn* aldol products.

Scheme 3



14 **15** **16**

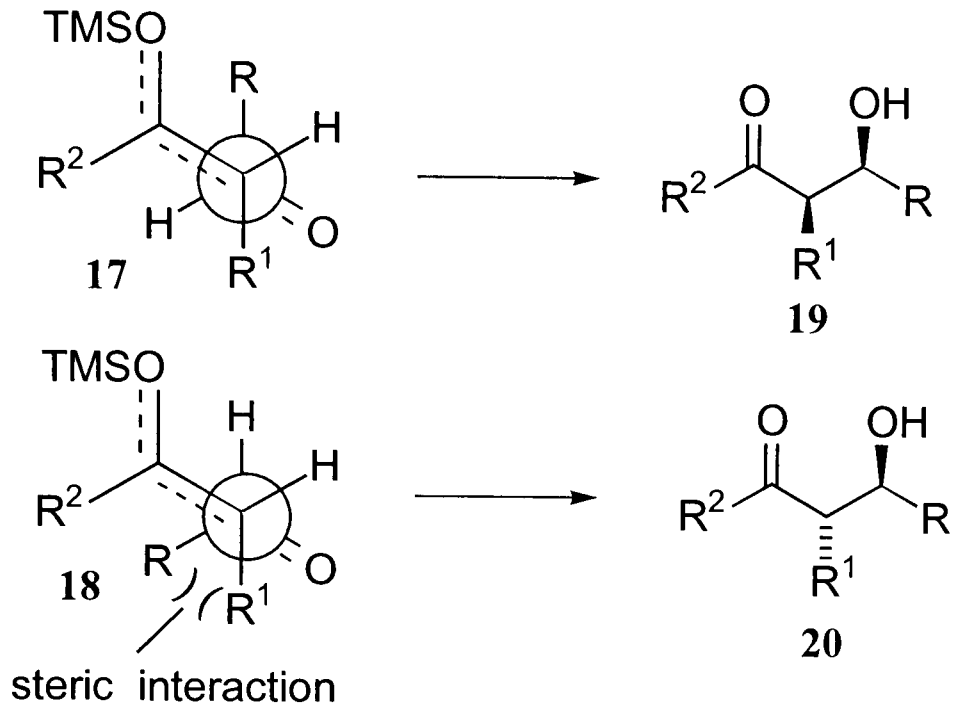
R^1 = alkyl, vinyl, aryl $R^3 = SiR_3$ X = O, S, NH

R^2 = H, alkyl, aryl R^4 = alky, aryl, X-alkyl, X-aryl

The selectivity in the reaction of *E*-silyl enol ethers can be explained in terms of the acyclic extended transition states **17** and **18**, *Scheme 4*. Overlap of the π-systems of the enol silane and the aldehyde is maximum in the fully extended

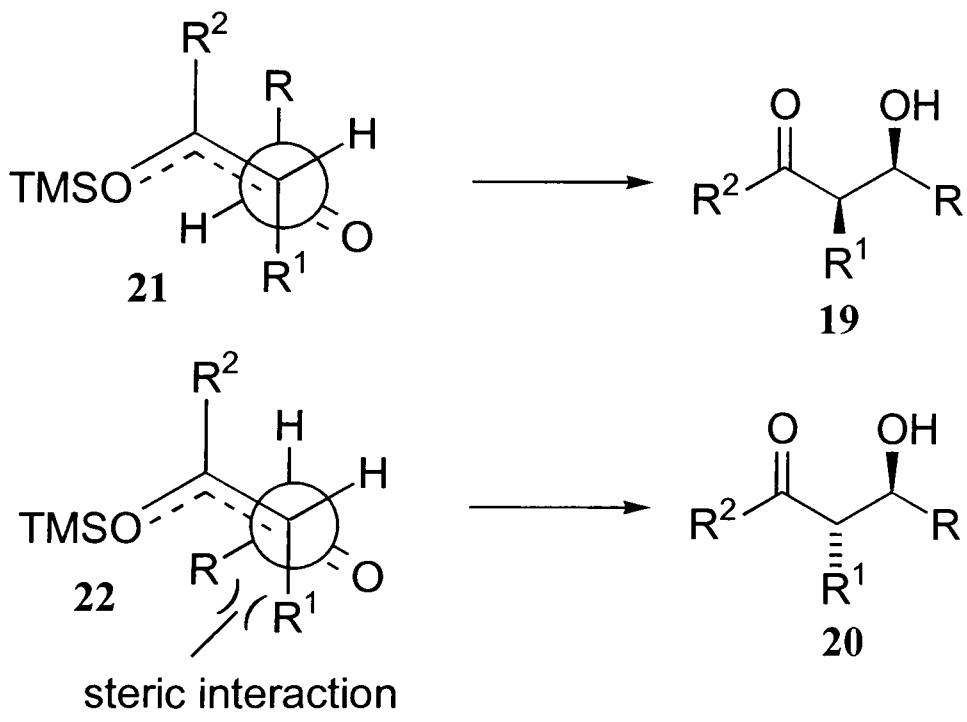
conformation.[7] Transition state **17**, for the *E*-silyl enol ethers gives rise to the *syn* aldol product **19**.

Scheme 4



Transition state **18** is destabilised by a gauche interaction between R and R^1 and hence the *anti* products **20** are disfavoured.

Scheme 5



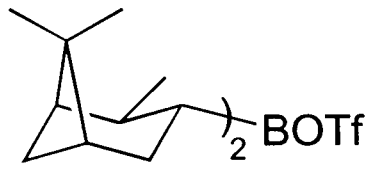
In the same manner *Z*-silyl enol ethers can react *via* transition states **21** and **22**, *Scheme 5*. Transition state **22** is also disfavoured by a gauche interaction between R and R^1. Hence we obtain the *syn* aldol products **19** whether we use the *E*- or the *Z*-enolates.

1.1.2 Asymmetric induction

1.1.2.1 Ligand mediated

If chiral ligands are attached to the metal of the enolate being employed in an aldol reaction then it is possible to differentiate between the two enantiotopic faces of the enolate. Paterson and co-workers have shown that di-isopinocamphenylboron trifluoromethane sulfonate **23**, *Figure 2*, derived from α-pinene, provides *syn* aldol products in high enantiomeric excess if used in the addition of ethyl ketones to sterically undemanding aldehydes.[8]

Figure 2



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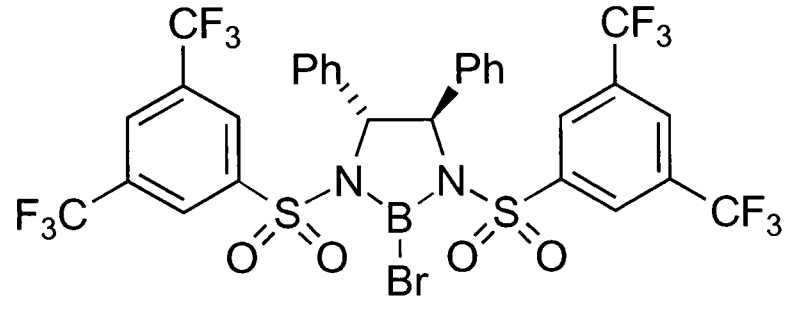

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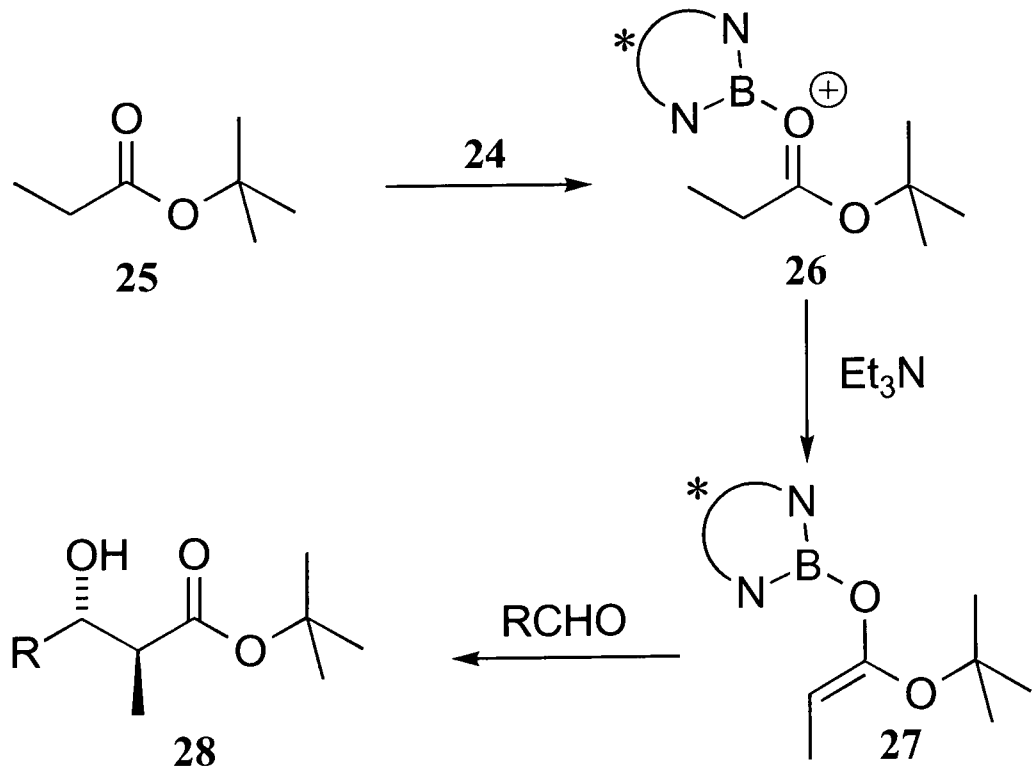
The C_2 symmetric bromoborane **24**, *Figure 2*, was developed by Corey and co-workers and has found use in enantioselective aldol reactions of propionates, α-bromoacetates and thioesters.[9]

Scheme 6

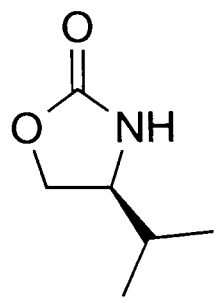


For example, treatment of ketone **25**, *Scheme 6*, with diazaborolidine **24** then triethylamine selectively generates *E*-enolate **27** bearing a chiral ligand. This can be used to differentiate between the enantiotopic faces of the enolate and hence selectively generate *syn* aldols **28** in high enantiomeric excess.

1.1.2.2 Auxiliary Mediated

Possibly the most commonly exploited means of controlling asymmetric induction in aldol reactions is through the use of a chiral auxiliary attached to the enolate component. Those which are the most relevant to this work have been developed by Evans,[10] Oppolzer[11] and Braun.[12]

Figure 3



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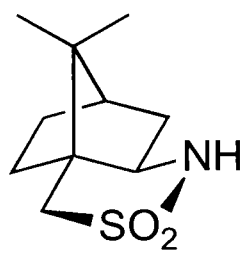

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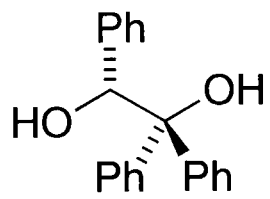

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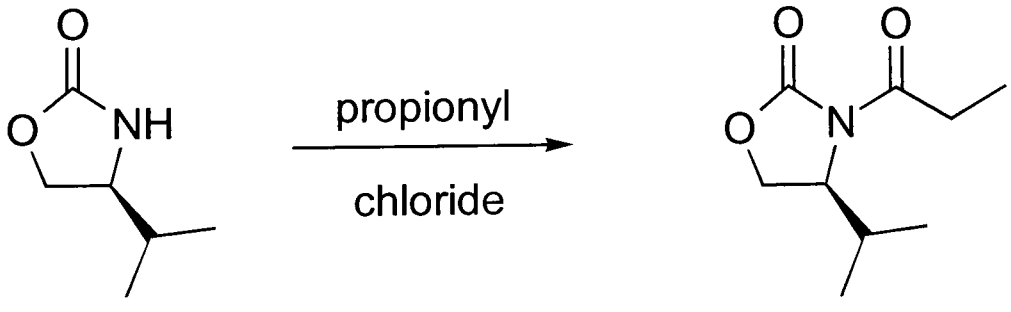
Evans oxazolidinone **29**, *figure 3*, is easily synthesised from the natural amino acid valine by reduction of the acid to the corresponding amino alcohol and subsequent treatment with diethyl carbonate. It allows highly enantiocontrolled synthesis of both *syn* and *anti* aldol products if used with the appropriate combination of reagents.[10] The oxazolidinone is converted to amide **32** by treatment with propionyl chloride, *Scheme 7*.

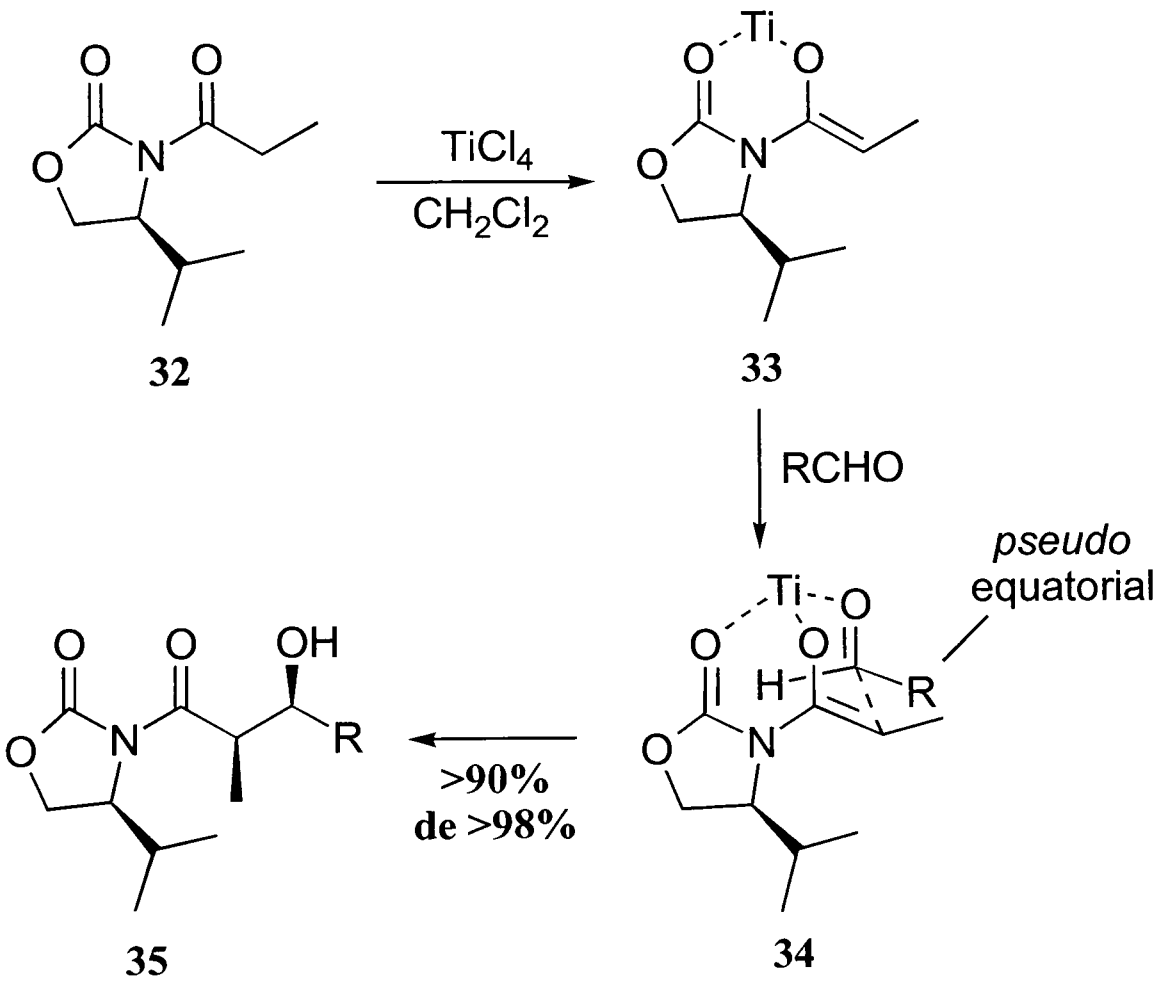
Scheme 7



29 **32**

If amide **32** is treated with $TiCl_4$ then *Z*-enolate **33** is formed, *Scheme 8*.[13] (Chloride ligands on the titanium have been omitted for clarity) The isopropyl group strongly disfavours formation of the corresponding *E*-enolate by allylic strain. The titanium metal is chelated to the oxygen atom of the enolate and the carbonyl oxygen atom **33**. Titanium can form octahedral complexes, so upon introduction of an aldehyde it releases one chloride ligand in order to complex the oxygen atom of the aldehyde. This is because titanium-oxygen bonds, which are virtually covalent, are far stronger than titanium-chlorine bonds. The approach of the aldehyde is from the bottom face of **33** because the top face is blocked by the isopropyl group.

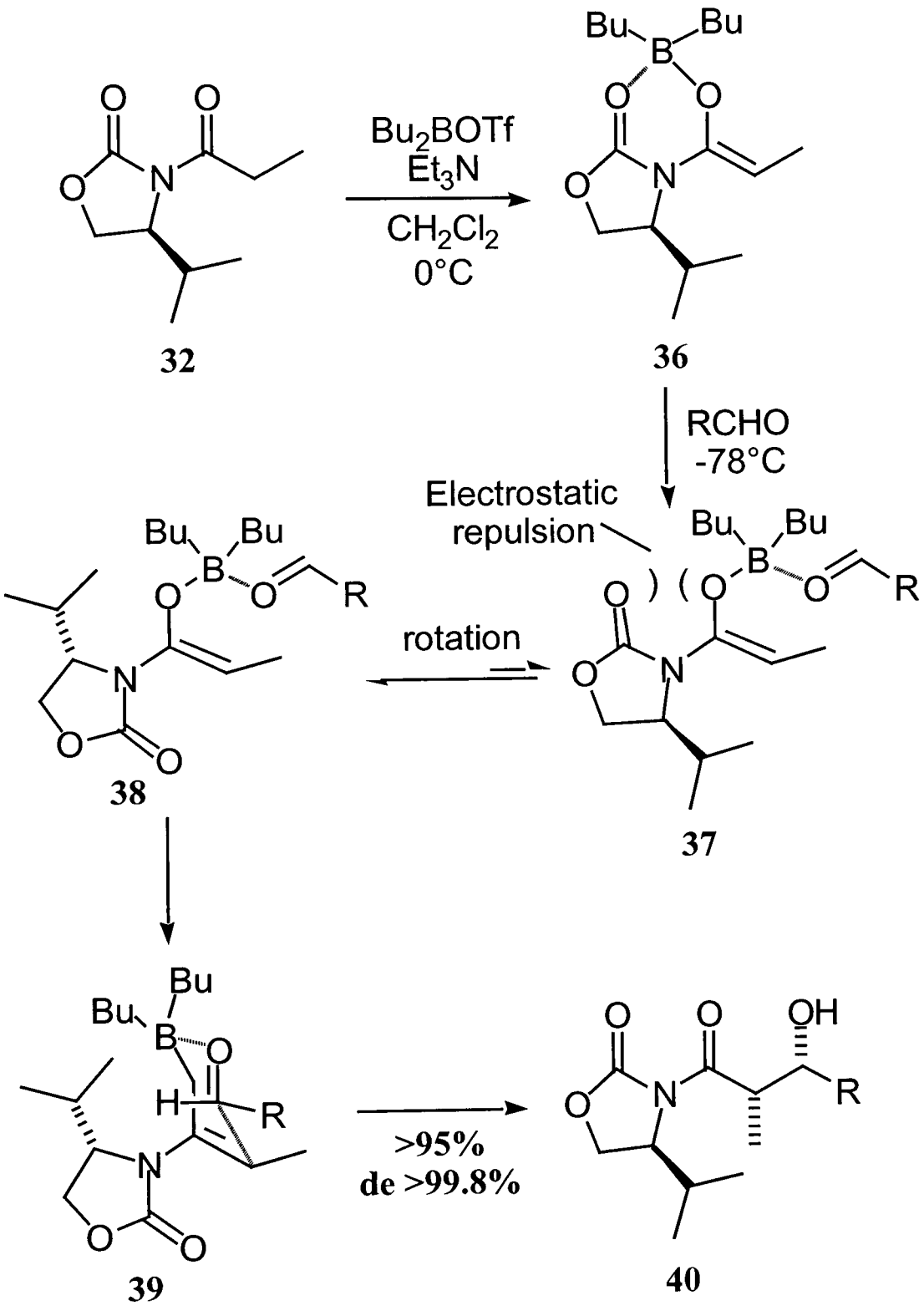
Scheme 8



The R group of the aldehyde is *pseudo*equatorial to avoid 1,3-*pseudo*diaxial interaction with the oxazolidinone portion in transition state **34**, hence, alcohols **35** are selectively generated. Treatment of amide **32** with dibutylboron trifluoromethane sulfonate generates chelated enolate **36**, *Scheme 9*.[14] Boron can only form up to tetravalent complexes so when the aldehyde is introduced the boron must release the carbonyl oxygen atom in order to coordinate to the aldehyde. The strong electrostatic

interaction between the oxygen atom of the enolate and the oxygen atom of the imide carbonyl in intermediate **37** is relieved by rotation of the auxiliary. This rotation blocks the bottom face of the intermediate and hence the aldehyde approaches the enolate from above. Again, the R group is *pseudo*equatorial in Zimmerman-Traxler transition state **39** and aldols **40** are selectively produced.

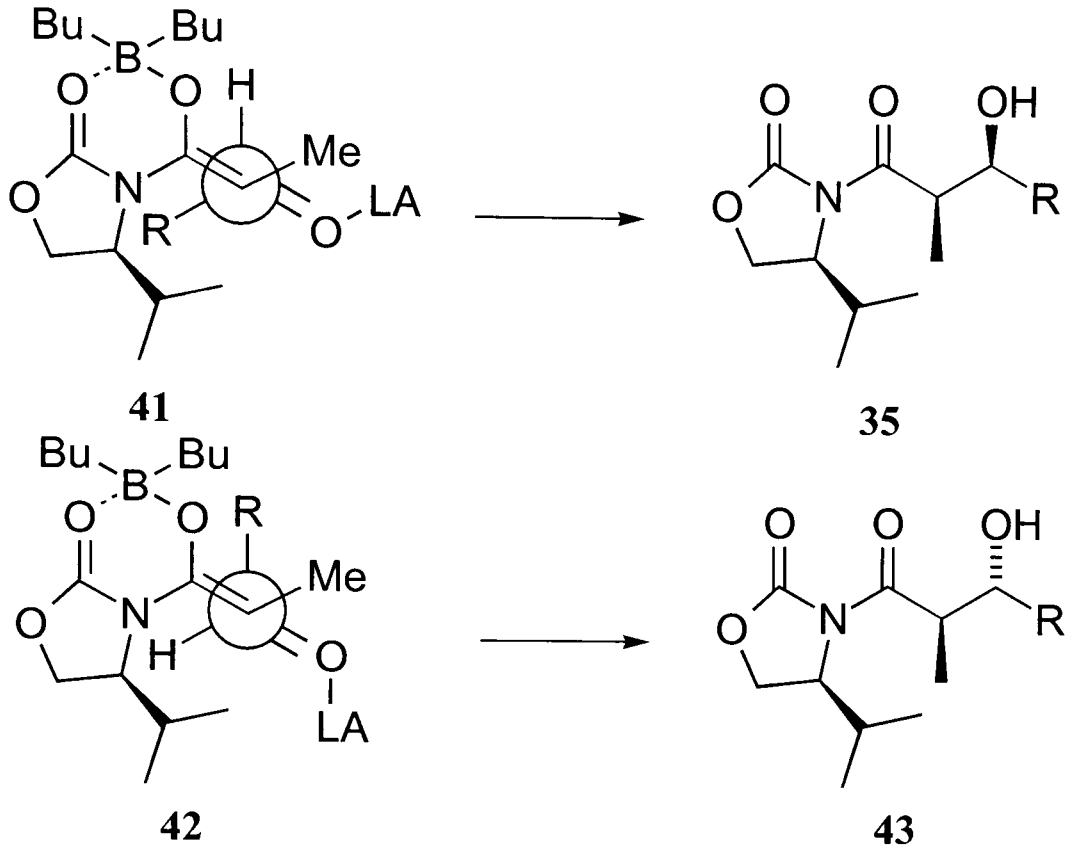
Scheme 9



Entry into *anti* aldols is possible if the aldehyde in use is precomplexed with a Lewis acid.[15] The aldol reaction between enolate **36** and a Lewis acid activated aldehyde proceeds *via* open chain transition states **41** and **42**, *Scheme 10*, analogous to transition states **17**, **18**, **21**, and **22** above. If the Lewis acid is sterically

undemanding, e.g. $SnCl_4$, transition state **41** is generated because gauche interactions around the forming bond are minimised and *syn alcohols* **35** are selectively produced.

Scheme 10



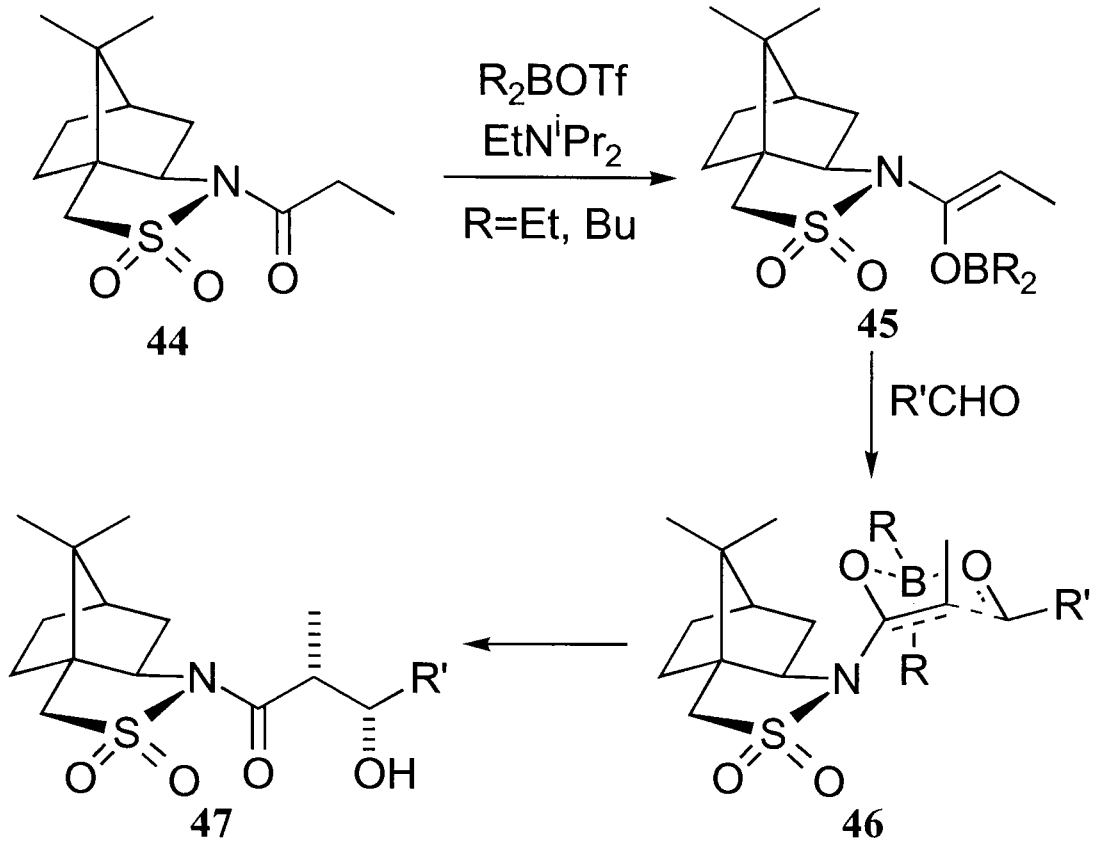
If the Lewis acid is sterically demanding, e.g. Et_2AlCl, transition state **41** is destabilised by the interaction of the Lewis acid and the methyl group of the enolate, hence, transition state **42** is favoured and *anti* aldols **43** are selectively generated.

Evans auxiliary cannot be used to prepare β-hydroxy carboxylic acid derivatives in high enantiomeric excess in the absence of an α substituent.

Oppoltzer's sultam **30** can be used in much the same manner as **29** but it has also been used in the synthesis of aldols where only the centre β to the carbonyl is stereogenic.[11] Sultam **30** is converted to amide **44** by treatment with propionyl chloride, *Scheme 11*. Dialkylboron trifluoromethane sulfonate and Hunig's base are used to form *Z*-enolate **45** which is reacted with an aldehyde, *via* Zimmerman-Traxler transition state **46** to selectively produce aldols **47**. The top face of the enolate is effectively blocked by the auxiliary, hence, the aldehyde approaches from below. Again, R' is *pseudo*equatorial to avoid 1,3-*pseudo*diaxial interactions with the auxiliary and the alkyl ligands on the boron atom. The enantiomeric aldols can be

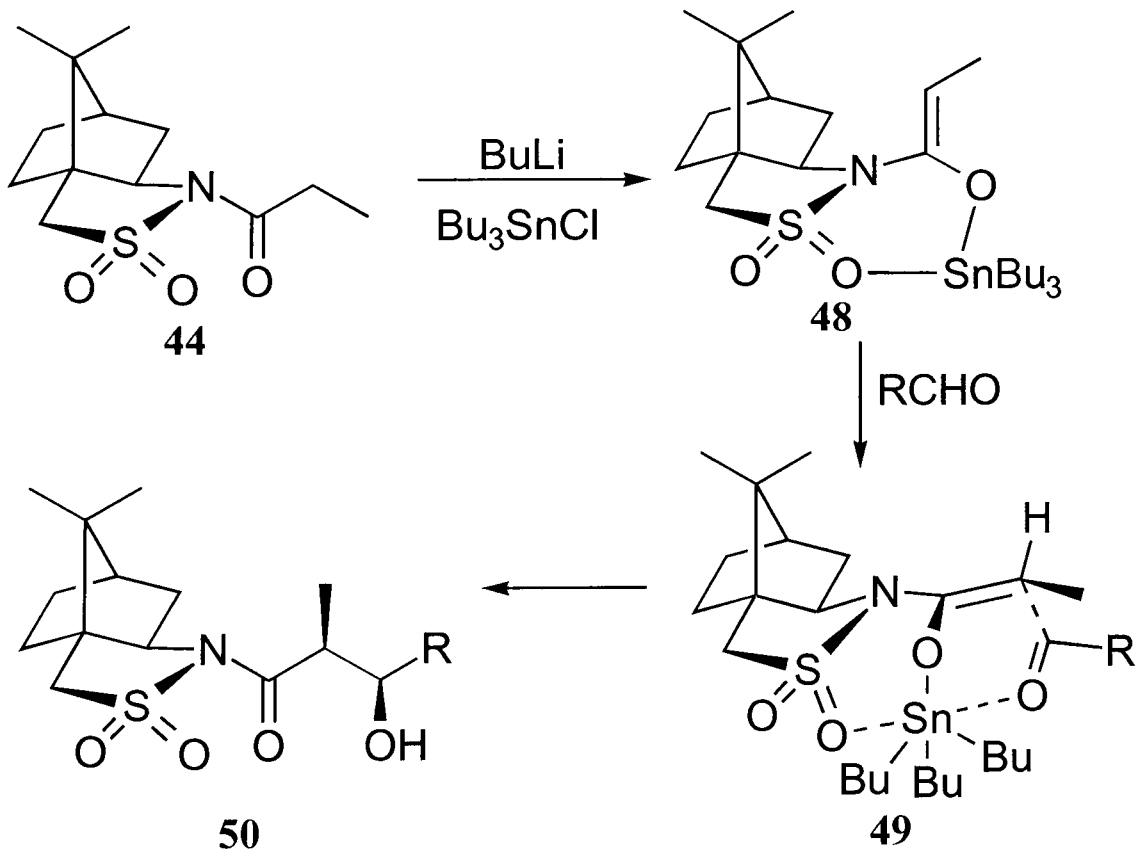
obtained by using the other enantiomer of sultam **30** or by exchanging tin for boron in the reaction using the same enantiomer of **30**.

Scheme 11



Treatment of amide **44** with ^{n}butyl lithium then subsequent transmetallation with tributyltin chloride generates chelated *Z*-enolate **48**, *Scheme 12*.

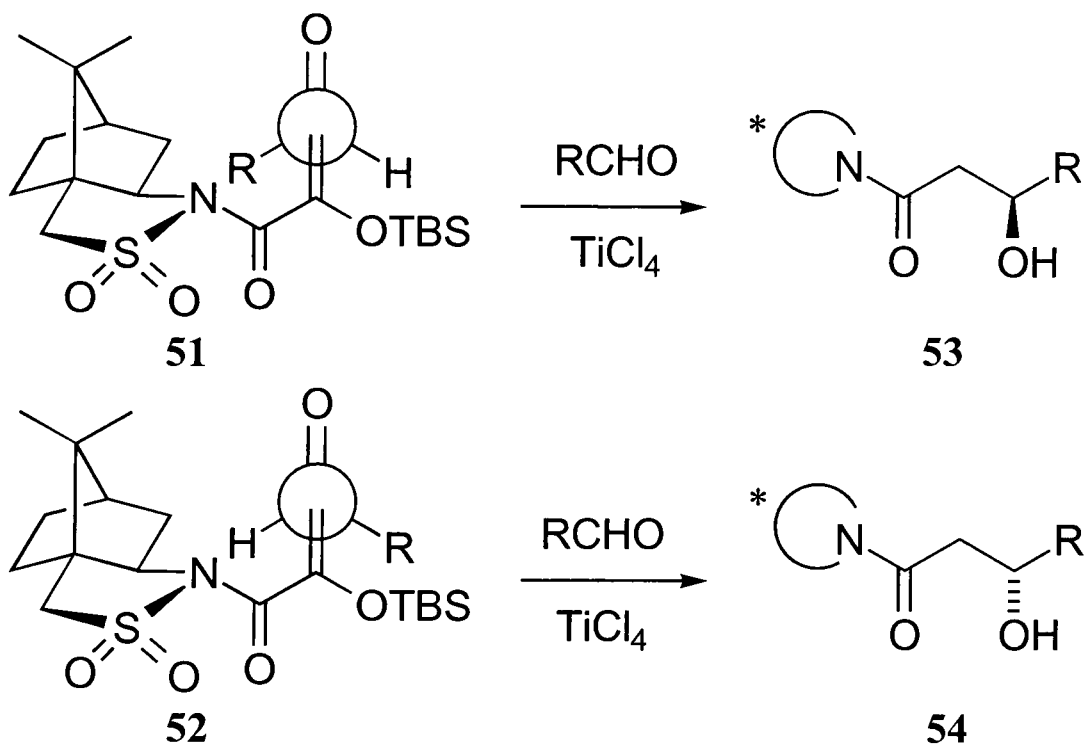
Scheme 12



Tin, like titanium, can also form octahedral complexes and can complex to one of the oxygen atoms of the sulfone and the oxygen atom of the aldehyde in Zimmerman-Traxler transition state **49**. R is *pseudo*equatorial, as for the previous example, and coordination of the aldehyde to tin atom ensures approach from the bottom face of the enolate generating alcohols **50**. However, the oxygen atom of the enolate is now oriented towards the sulfone rather than away as for transition state **47**, *Scheme 11*, hence the enantiomeric aldol products.

Mukaiyama type aldols using Oppolzer's sultam **30** proceed *via* open transition states **51** and **52**, *Scheme 13*. Transition state **51**, which gives rise to aldols **53**, is destabilised relative to transition state **52** because of the interaction between R and the auxiliary, hence alcohols **54** are formed selectively.

Scheme 13

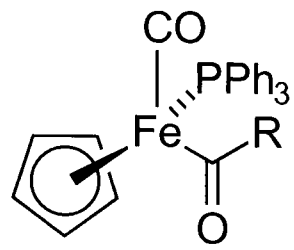


Braun introduced auxiliary **31**, *Figure 3*, in 1987. It is derived from naturally occurring mandelic acid and exhibits properties similar to that of sultam **30** with the added bonus that it is very easily removed after use.[12] It is the method of choice when introducing a single chiral centre. The mechanism of the selectivity using Braun's auxiliary is not described but one possible model is outlined in chapter 3.

Transition metal technology has yet to make a significant contribution to asymmetric aldol methodology; however, some examples have been reported in the

literature. The groups of Davies and Liebeskind independently developed iron complexes **55**,[16] *Figure 4*.

figure 4



55

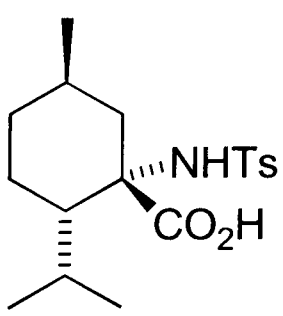
Diethylaluminium and copper (I) enolates produce *anti* and *syn* selectivity respectively in aldol reactions of propionate derivatives (**55**, R = Et). Asymmetric induction from iron auxiliary **55** is powerful enough to override any chirality present in the aldehyde component of the reaction.

Other auxiliary based approaches include chiral amides,[17] sulfoxides[18] and hydrazones.[19]

1.1.2.3 Chiral Catalysis

Masamune and co-workers developed boron Lewis acids **56** and **57**, *figure 5*, derived from menthol and dopamine respectively. This was the first reported system which allows use of the Lewis acid in less than stoichiometric quantities (20 mol %) without any loss in enantioselectivity.[20] Corey and co-workers have employed the tryptophan derived oxazaborolidine **58**, *figure 5*.

Figure 5



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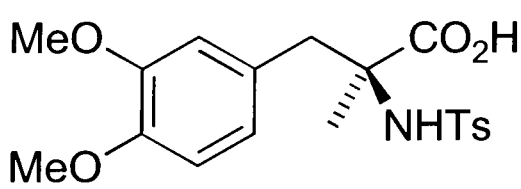

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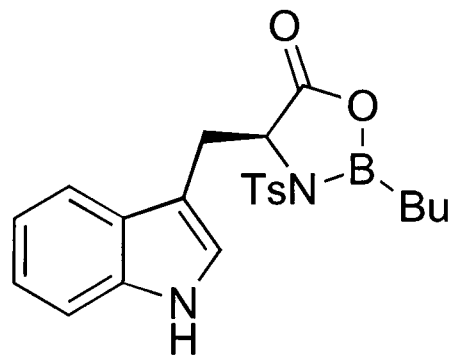


58

This is a true chiral Lewis acid and its performance is comparable to Masamune's system, however the catalyst is typically used in 40 mol % quantities.[21] It can be clearly observed, even from the very brief overview above, that aldol methodology has developed to a level of sophistication far in advance of most, if not all, other reaction types–a reflection of its wide applicability and general success as a synthetic tool.

1.2 Carbonyl Alkylidenation Reactions

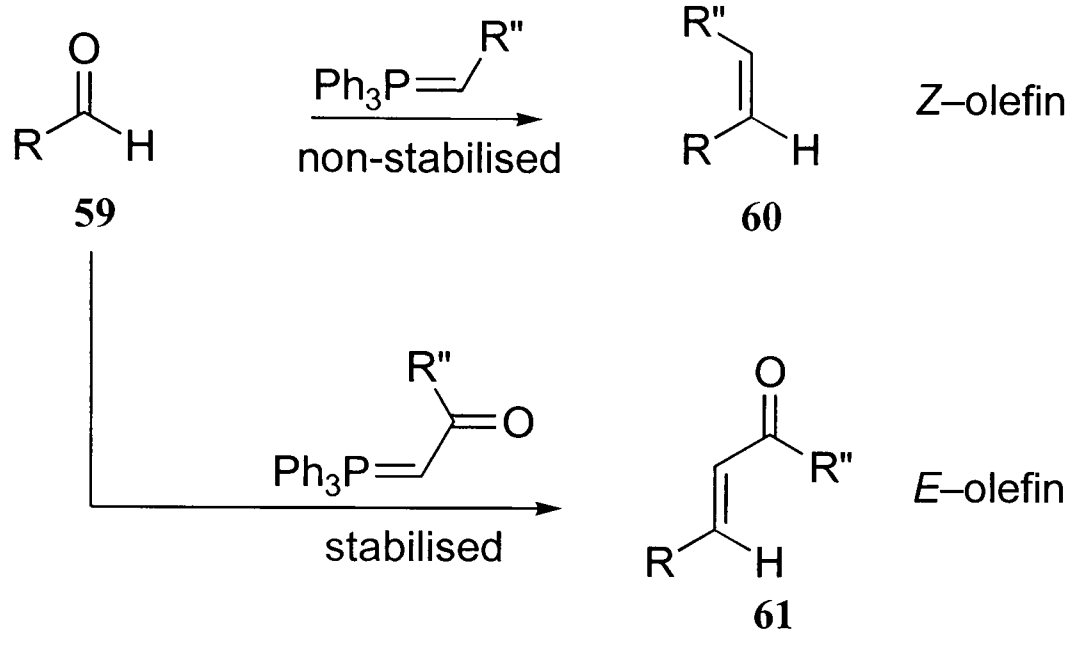
When designing a convergent synthetic strategy many organic chemists employ one of the many carbonyl alkylidenation reactions to combine their fragments. Given the large number of variants of this type of reaction and the fact that they are generally carried out under relatively mild conditions, such strategies are hardly surprising.

Some of the most difficult types of carbonyl group to alkylidenate are the carboxylic acid derivatives (e.g. esters and amides). These functional groups are reluctant to react in the same manner as aldehydes and ketones because they are resonance stabilised. The Wittig reaction,[22] which is commonly used to form double bonds in organic synthesis, is not powerful enough to alkylidenate carboxylic acid derivatives. In recent years the groups of Tebbe,[23] Grubbs,[24] Petasis[25] and Takeda[26] have introduced alkylidenating reagents based on titanocene. However, prior to Takeda's recent work,[26] Takai's alkylidenation of esters, which uses a combination of titanium, zinc, *N*,*N*,*N*',*N*'-tetramethylethylene diamine (TMEDA) and a 1,1–dibromoalkane, was by far the most reliable and synthetically useful variant described in the literature.[27]

1.2.1 The Wittig Reaction

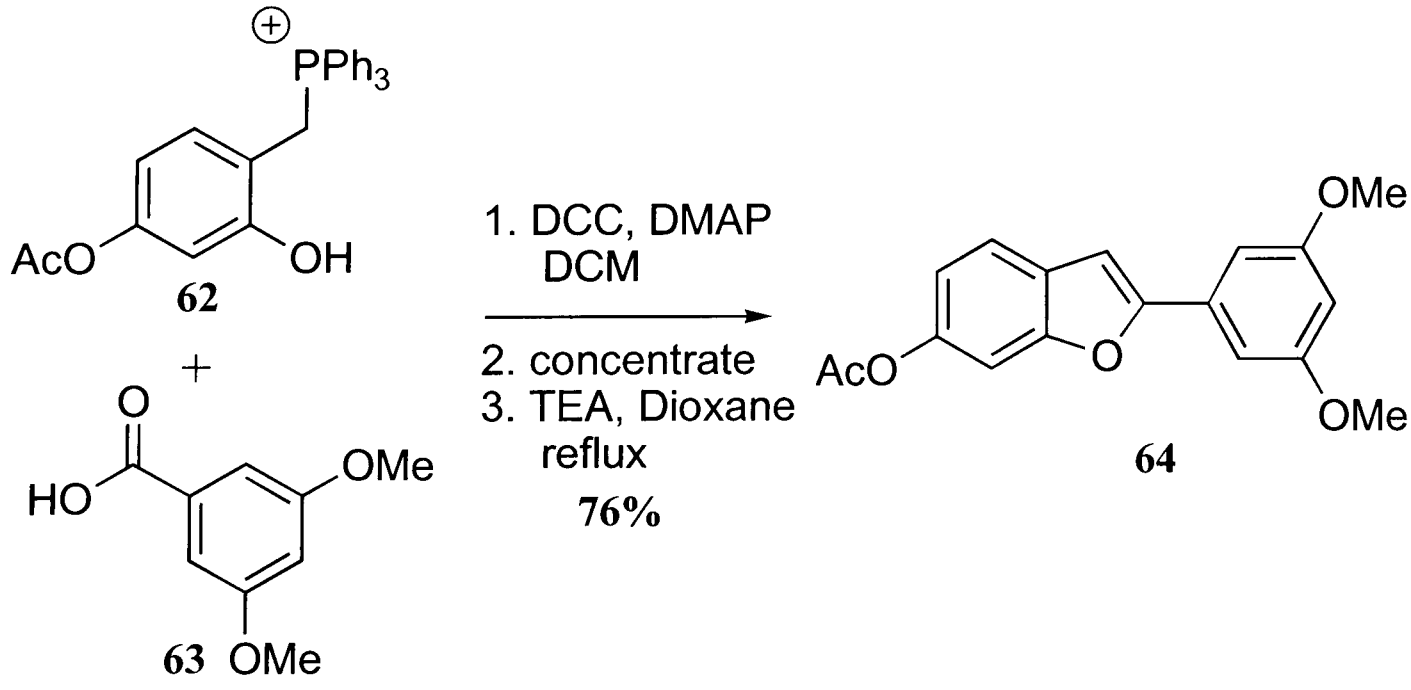
The classical Wittig reaction, *Scheme 14*, is the combination of a phosphonium ylid with either an aldehyde **59** or a ketone to form a carbon–carbon double bond.[22] Non–stabilised ylids selectively produce *E*–olefins **60** while *Z*–olefins **61** are formed using stabilised ylids.

Scheme 14



The major drawbacks of the Wittig reaction are very poor atom economy and the by–product, triphenylphosphine oxide, complicates the purification process. Furthermore, alkylidenation of esters using Wittig reagents is only successful when the reaction is intramolecular, e.g. synthesis of benzofuran **64, Scheme** *15*.[28]

Scheme 15

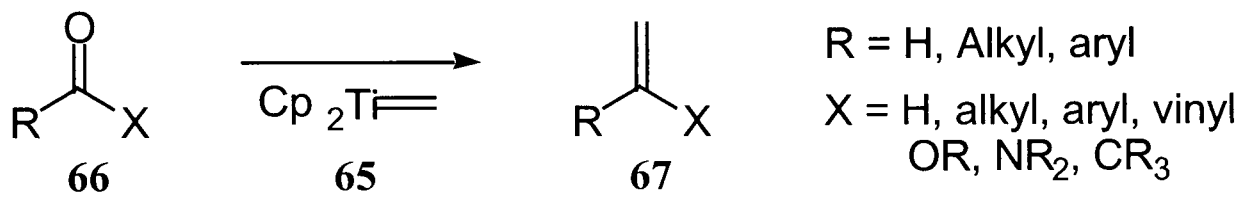


The Horner–Wittig modification[29] overcame the problem of the triphenylphosphine oxide. It employs a metallated phosphine which leads to a water soluble by–product. The Wadsworth–Emmons reaction[30] works in much the same fashion using a metallated phosphonate. Both of these Wittig–variants selectively yield *E*–olefins.

1.2.2 Tebbe, Grubbs and Petasis Reagents

Tebbe,[23] Grubbs[24] and Petasis[25] reagents utilise a titanium carbenoid species **65** as the alkylidenating agent. Broadly speaking, they are interchangeable in terms of choice of reagent since they all carry out the same transformation in similar yields on the same substrates, *Scheme 16*.

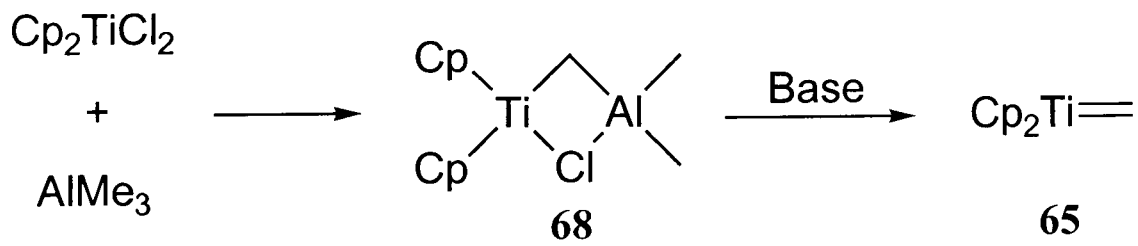
Scheme 16



66 **65** **67**

Tebbe's alkylidenating reagent **68**, introduced in 1978, is prepared from titanocene dichloride and trimethyl aluminium, *Scheme 17*.[23] The rate of alkylidenation of the carbonyl can be enhanced with the use of donating ligands on the metal, e.g. tetrahydrofuran or pyridine. The reagent is very sensitive to oxidation and is cumbersome to prepare.

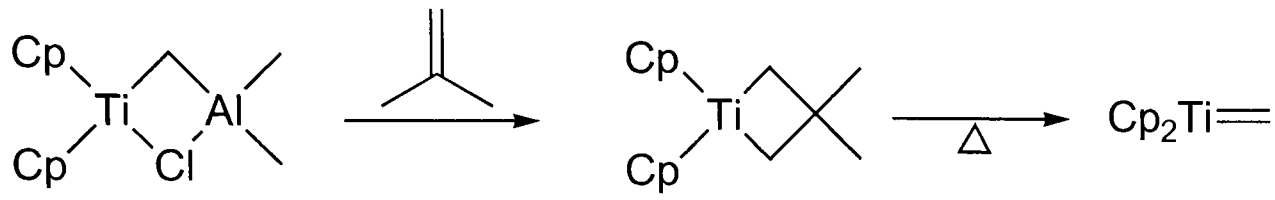
Scheme 17



68 **65**

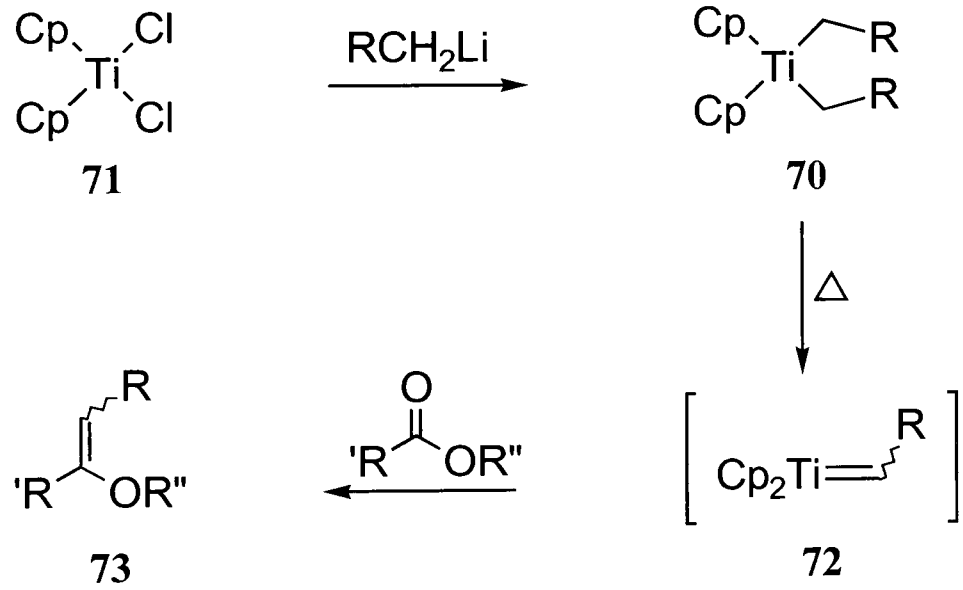
Grubbs reagent **69**, *Scheme 18*, works in much the same way but is prepared in a slightly different fashion. However, reagent **69** is air stable and can be crystallised allowing storage for some time in the freezer.[24]

Scheme 18



Tebbe and Grubbs reagents are limited to one carbon homologation. Petasis reagent **70**, reported in 1990, is simply prepared from titanocene dichloride **71** and an organolithium and is crystalline, *Scheme 19*.[25] Petasis' chemistry is not restricted to methylenation of carboxylic acid derivatives. A variety of alkylidenations can be carried out using reagent **70**, however, if an sp^3 carbon β to the titanium in the reagent bears any hydrogen atoms then β–hydride elimination occurs.

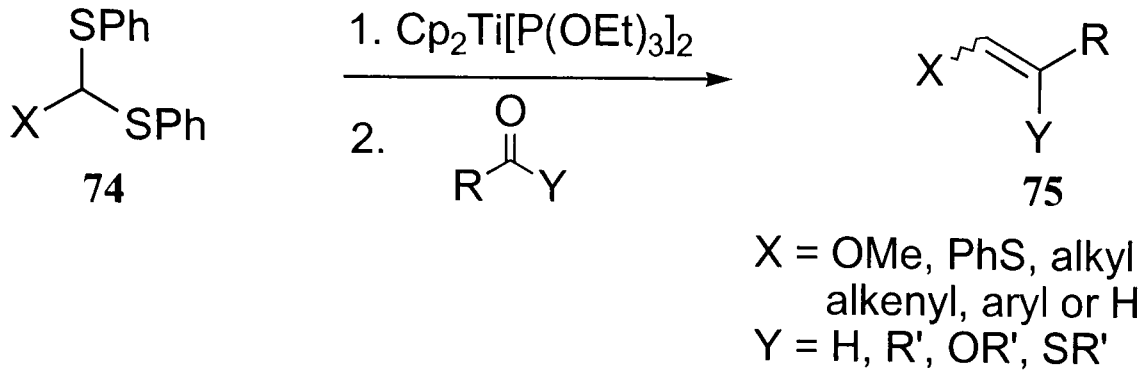
Scheme 19



1.2.3 Alkylidenation Using Dithioacetals

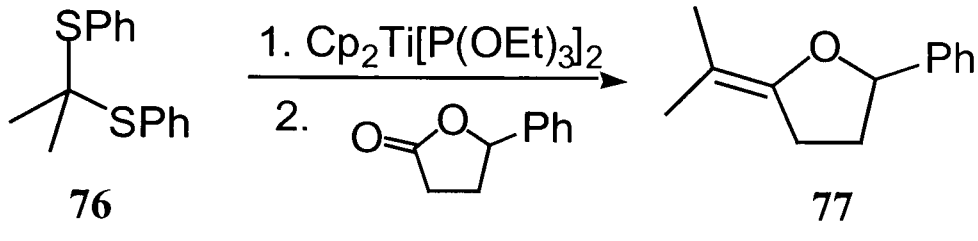
Takeda and co–workers recently published the use of dithioacetals **74** in combination with a low valent titanium species for the alkylidenation of aldehydes, ketones and carboxylic acid derivatives, *Scheme 20*.[26] Selectivity for a *Z*-enol ether product in the alkylidenation of esters is reasonable in most instances but particularly good in the case of lactone substrates.

Scheme 20



Takeda's procedure has several advantages over those of Tebbe, Grubbs and Petasis: it can be employed in the formation of tetra-substituted double bonds, *Scheme 21*; thioacetals are easily made from aldehydes and ketones and X can be almost any alkyl, alkenyl, alkynyl or aryl group.

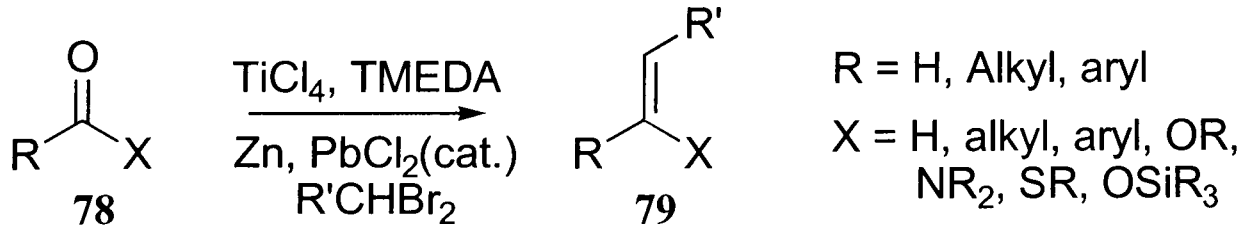
Scheme 21



1.2.4 Takai's Alkylidenation Reaction

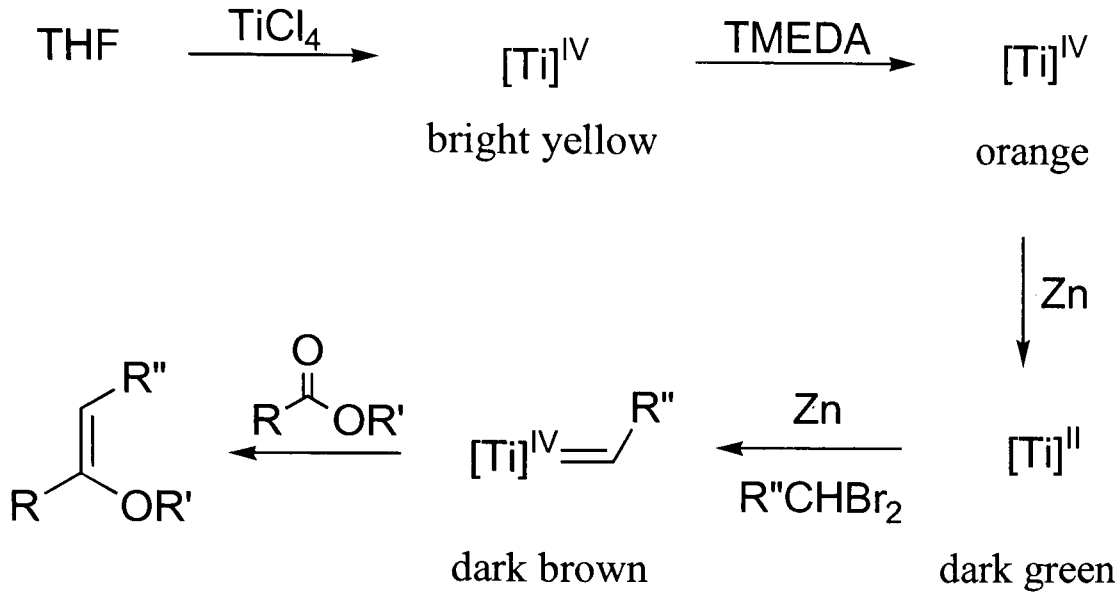
Takai's alkylidenation procedure[2] is probably the most useful and simplest reaction to carry out of all those mentioned in this chapter. It is used to selectively generate *Z*–enol ethers, vinyl sulfides, silyl enol ethers and *E*-enamines from ketones, esters, thioesters, silyl esters and amides respectively, *Scheme 22*. The reaction is carried out in one–pot, is complete in a matter of hours (depending on the electronic properties of the substrate in use), is very clean (in terms of conversion to products) and R' can be almost any alkyl group.

Scheme 22



The reagent is prepared from titanium tetrachloride, TMEDA, zinc, a 1,1–dibromoalkane and catalytic lead(II) chloride. *Scheme 23* outlines our suggested mechanism.

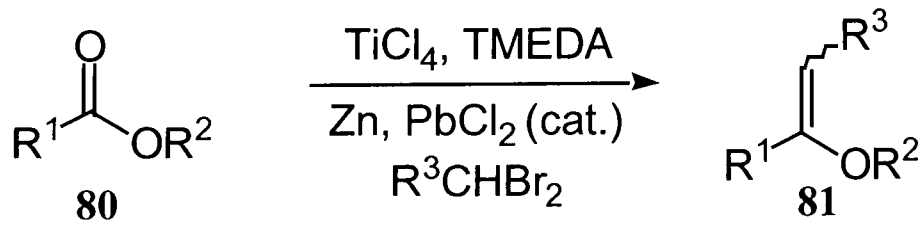
Scheme 23



Beginning with a titanium(IV) complex in THF, tetramethylethylene diamine is added. This complex is then reduced to titanium(II) with zinc, hence the colour change from orange to green. The 1,1–dibromoalkane and the ester are then added to the mixture together. It is thought that the Zn metal inserts into one carbon–bromine bond and the resultant organozinc combines with the titanium complex forming a carbenoid species similar to **65**, **68**, **69** and **70** previously described. The role of the lead(II) chloride is uncertain but it has been shown to accelerate a number of organometallic reactions.[31]

Below is a list of selected data for a number of alkylidenations using Takai's procedure. It should be noted that yields and ratios of products can be affected by prolonged reaction times and variations in temperature.

Scheme 24



Esters **80** react to give enol ethers **81**. The reactivity of the ester group is considered to be the standard throughout the following discussion.

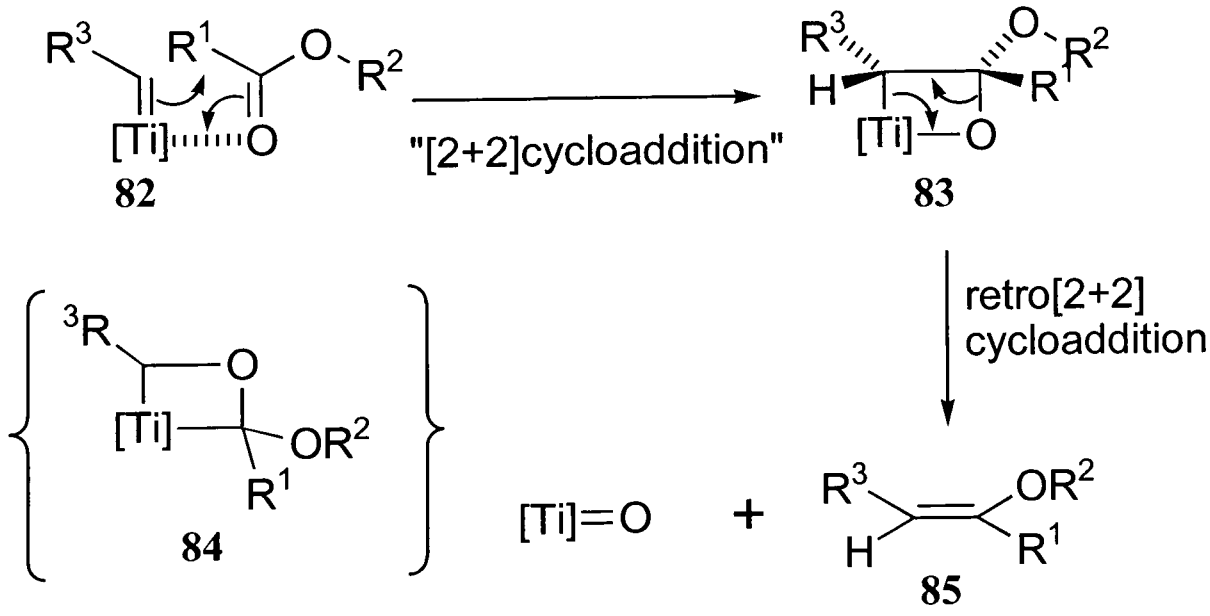
Table 1

R^1	R^2	R^3	time/h	*Z/E*	yield(%)
Ph	Me	Me	2	92/8	86
Ph	^{t}Bu	Me	2	71/29	81
^{i}Pr	Me	^{n}C$_5$H$_{11}$	2	100/0	89

It can clearly be seen that the ratio of isomers, *Table 1*, observed in the generation of **81**, *Scheme 24*, is determined by the steric interactions. For example, as R^2 gets larger a greater proportion of the *E*–enol ether is observed. Where R^3 increases in size (e.g. ^{n}pentyl) then the *Z*–isomer is formed specifically. In all cases yields are high.[2]

We propose the following mechanism to explain the stereoselection in the reaction. If we assume that the reactive species in the alkylidenation reaction can be reasonably represented as carbenoid **82**, then we can envisage a two step process involving titanium metallocycle **83**, *Scheme 25*.

Scheme 25



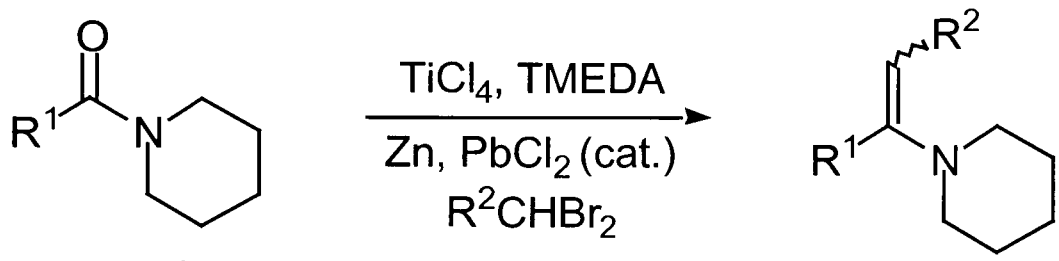
82 **83** **84** **85**

A form of [2+2] cycloaddition reaction occurs between the titanium carbenoid species and the carbonyl of the ester. It should be noted that the reaction may not be concerted and may involve an open chain intermediate. Titanium is strongly oxophilic hence formation of metallocycle **84** is unlikely. It is not possible to prove that the titanium is first complexed to the oxygen of the carbonyl, however, it seems

likely as such an interaction would activate the carbonyl group encouraging the reaction. Intermediate **83** collapses *via* a retro [2+2] cycloaddition generating enol ether **85** and an oxo-titanium species. Such a reaction is irreversible due to the high titanium-oxygen bond energy.

In general, as R^1 becomes more sterically demanding there is greater selectivity for *Z*-enol ethers. Our model suggests that when R^1 is sufficiently bulky it is oriented on the opposite face to R^3 in the 4-membered cyclic intermediate to reduce the steric interaction in the system as metallocycle **83** is forming. Since the retro [2+2] cyclisation is a concerted process both groups remain opposite each other in the product and hence we preferentially obtain *Z*-enol ethers, vinyl sulfides, etc. If R^2 is large then the steric interaction between R^2 and R^3 will reduce selectivity for the *Z*-isomer. A large R^3 group will accentuate the dominant steric interaction.

Scheme 26



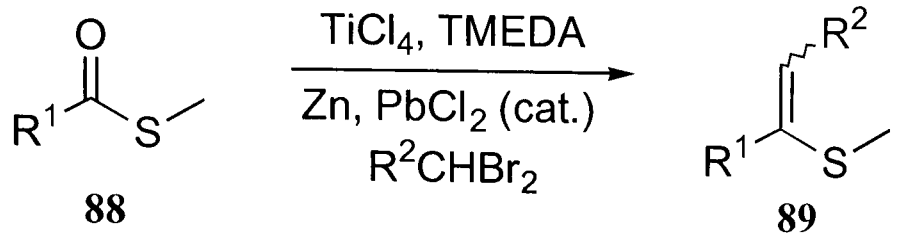
86 **87**

Table 2

R^1	R^2	time/h	*Z/E*	yield (%)
Ph	Me	3	2/98	70
Ph	$PhCH_2$	3	<1/>99	87
cyclohexyl	Me	18	47/53	82

In the case of amides, *Scheme 26*, the distribution of products, *Table 2*, is exactly opposite to that for esters. This can also be attributed to the steric interactions. Reaction times are longer than for esters–a reflection of the lower electrophilicity of the amide carbonyl.[32]

Scheme 27



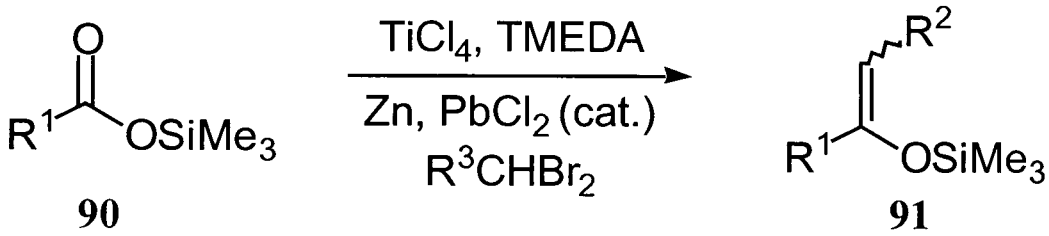
88 **89**

Table 3

R^1	R^2	time/min	*Z/E*	yield(%)
Ph	Me	30	80/20	77
cyclohexyl	Me	20	94/6	88
cyclohexyl	cyclohexyl	20	100/0	97

The apparent rate acceleration in the case of thioesters, *Scheme 27, Table 3*, is probably due to poor overlap of the 3p (S) and 2p (C) orbitals in the system; hence, the carbonyl is not resonance stabilised (cf. esters and amides) and the reaction proceeds more rapidly.[32]

Scheme 28



90 **91**

Table 4

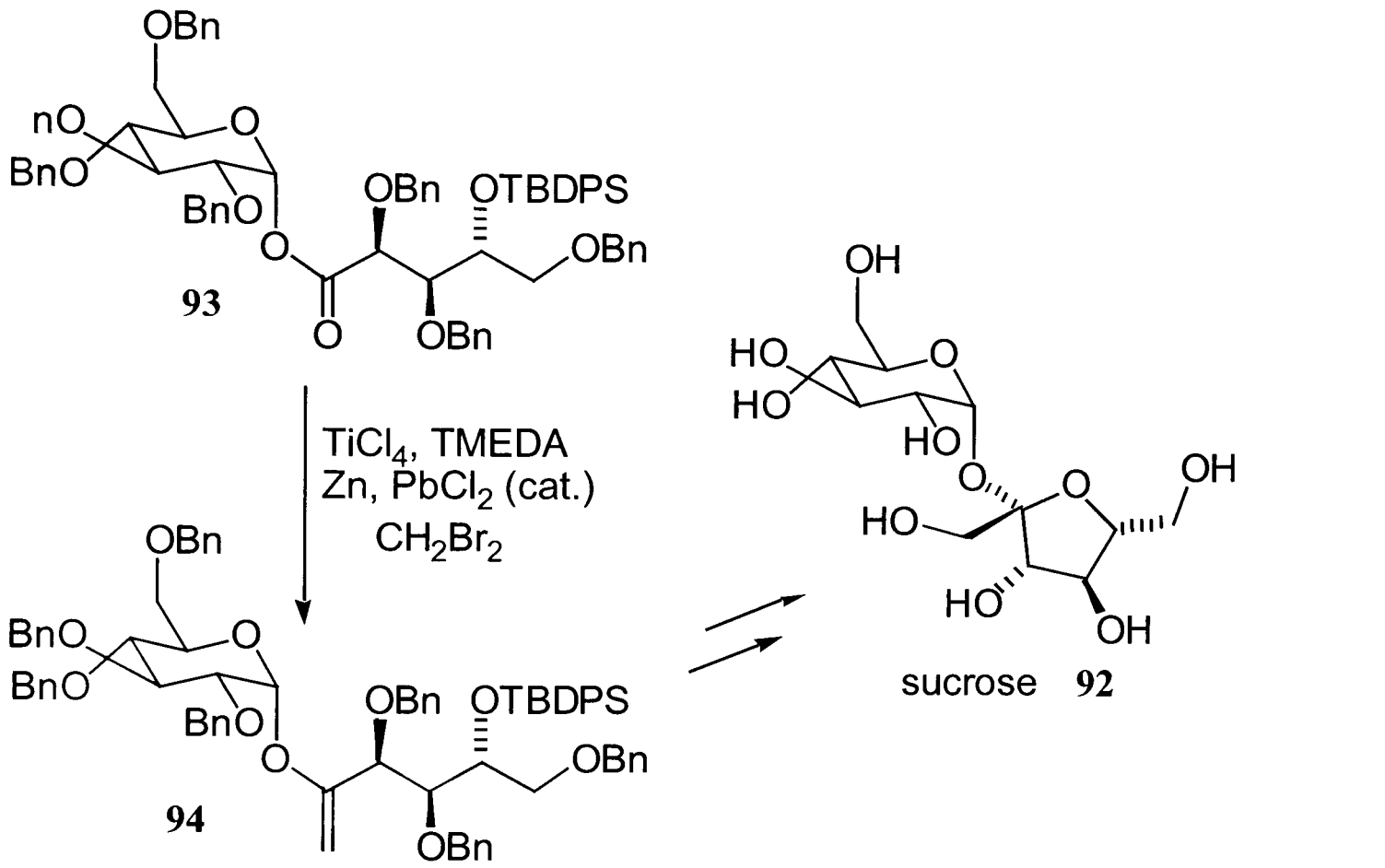
R^1	R^2	time/h	*Z/E*	yield(%)
Ph	Me	1.5	73/27	90
Ph	cyclohexyl	3	80/20	74
cyclohexyl	Me	2	100/0	80
$PhCH{=}CH_2$	$PhCH_2$	1.5	100/0	79

Little more information can be obtained from the alkylidenation of silyl esters,[33] *Scheme 28*, *Table 4*; however, silyl enol ethers are particularly useful intermediates in organic synthesis (e.g. Mukaiyama aldol reactions). Takai reagents generated from 1,1-dibromoalkanes with oxygen atoms in the α or β positions have not been reported.

1.2.5 Takai's Alkylidenation in Synthesis

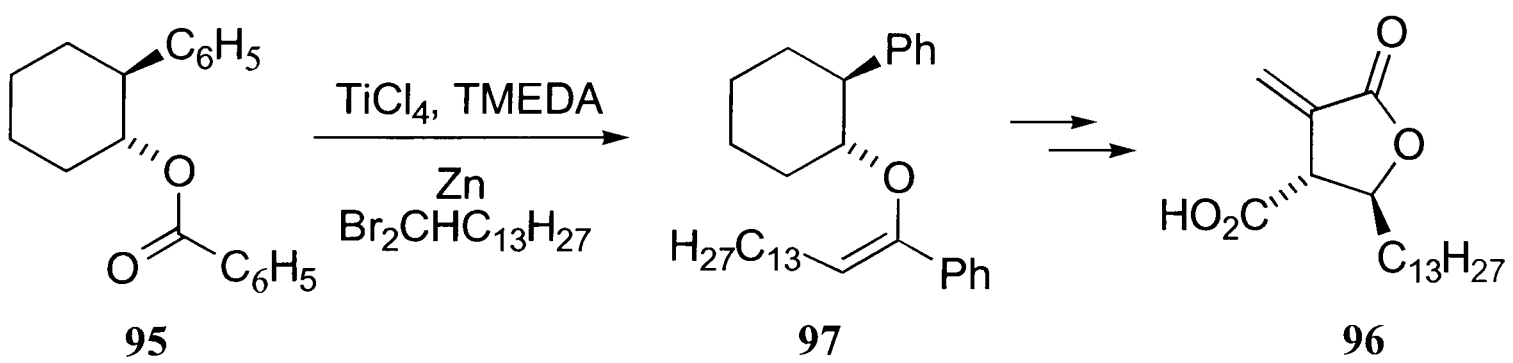
A number of syntheses reported in the literature make use of Takai's alkylidenation procedure. Barrett's synthesis of sucrose **92**,[34] *Scheme 29*, illustrates that Takai's alkylidenation has no effect on any chirality α to the ester. It was also noted that Tebbe's reagent was unsuccessful in carrying out the same transformation on this substrate.

Scheme 29



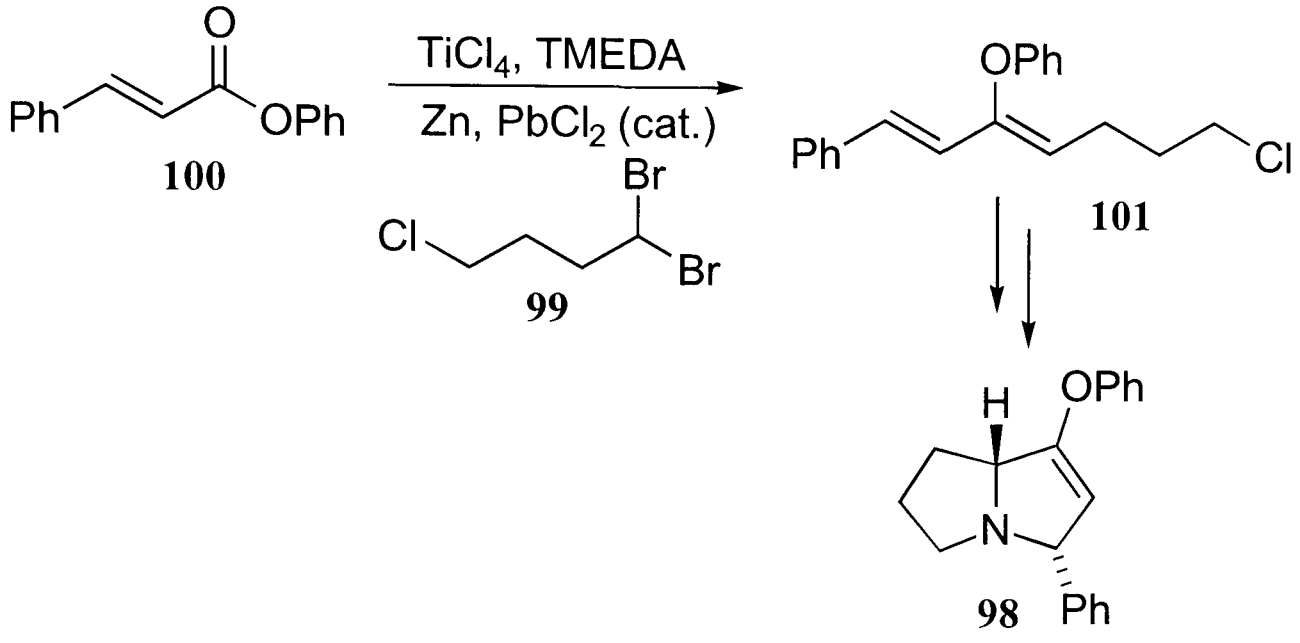
Greene and co–workers noted that a 94 : 6 ratio of *Z* to *E* isomers is produced in the alkylidenation of ester **95** using Takai's procedure. This reaction was part of their synthesis of protolichesterinic acid **96**,[35] *Scheme 30.*

Scheme 30



Pearson and co-workers employed Takai's alkylidenation in the synthesis of pyrrolizidines **98**,[36] *Scheme 31*. The authors make no comment on the kinetics or the chemoselectivity of the reaction. Interestingly the 1,1–dibromoalkane employed, **99**, also contains a chlorine atom. It is surprising to find that alkyl chlorides are stable to the reaction conditions. The synthetic utility of Takai's procedure is greatly enhanced by Pearson's work.

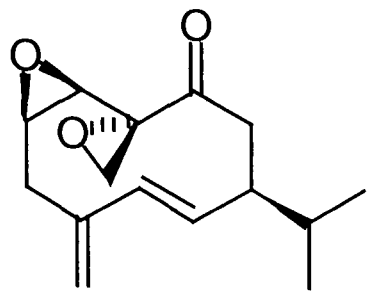
Scheme 31



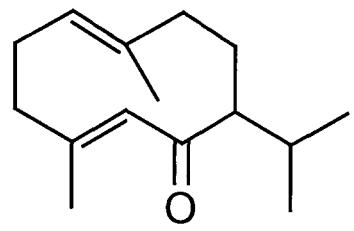
1.3 The Anionic oxy–Cope Rearrangement

The use of sigmatropic rearrangements in organic synthesis has seen a huge increase since the development of detailed stereochemical understanding of these reactions in terms of orbital symmetry.[37] Sigmatropic rearrangements, and anionic oxy-Cope (AOC) rearrangements in particular, allow transfer of chirality within complex molecules. The AOC rearrangement tolerates a wide variety of functionality and consequently has been used in many syntheses. Periplanone B **102**,[38] (+)–dihydromayurone **103**,[39] (±)–acoragermacrone **104**[40] and eucannabinolide **105**,[41] *Figure 6*, have all been synthesised by taking advantage of the AOC rearrangement. A comprehensive review of the AOC rearrangement has recently appeared.[3]

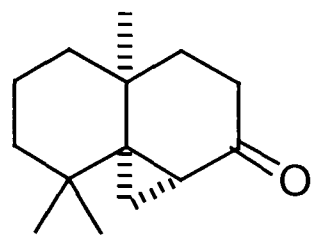
Figure 6



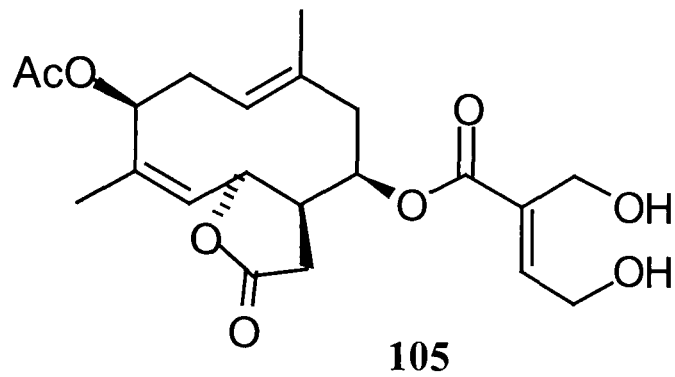
102



104



103

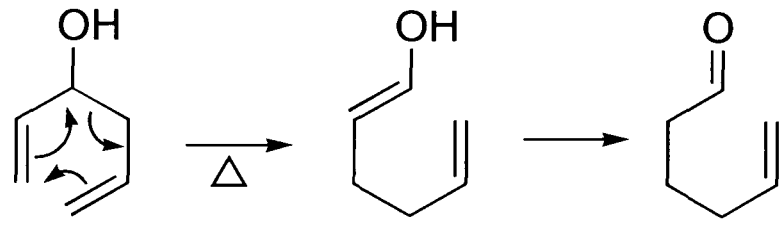


105

1.3.1 Thermal versus Anionic oxy–Cope rearrangements

The term "oxy–Cope" rearrangement was first applied, in 1964, to the electronic reorganisation of 1,5–hexadien–3–ol **106** to form 5–hexenal **107**, *Scheme 32*.[42]

Scheme 32



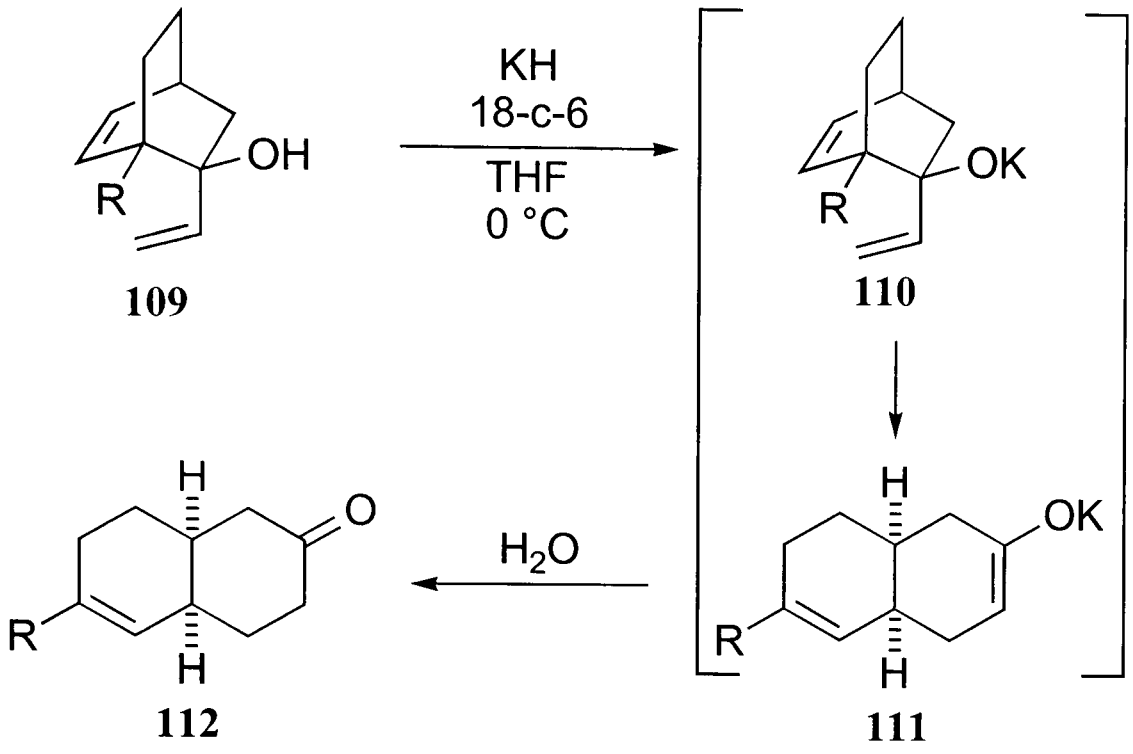
106 **108** **107**

In 1975 Evans reported that enormous rate accelerations (up to 10^{17}) were possible if the alcohol was converted into the corresponding potassium alkoxide, *Scheme 20*.[43]

The AOC rearrangement is a [3,3]–sigmatropic. Like the Cope and Claisen rearrangements, the reacting conformation is generally chair–like. However steric and electronic factors sometimes favour a boat–like transition state. The extent to which transition states will be populated can usually be reasonably accurately predicted. The stereochemical outcome of the rearrangement is directly derived from the transition

state geometry and high levels of chiral transfer can be achieved *via* highly ordered cyclic transition states.

Scheme 33



109 **110** **111** **112**

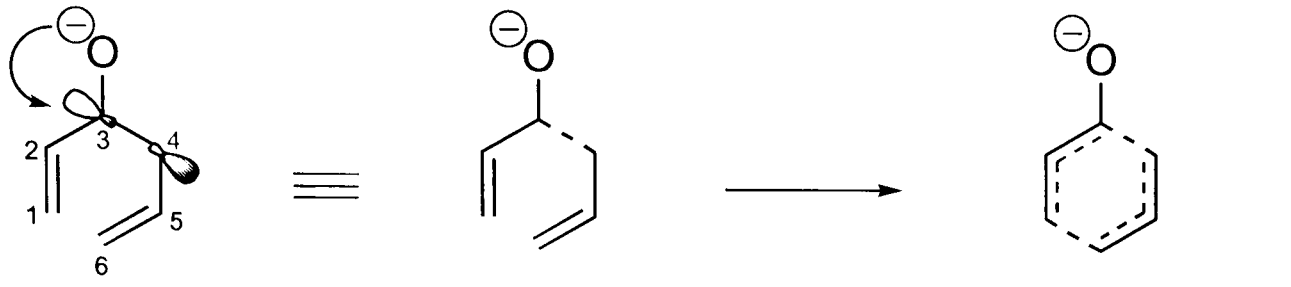
However, there is evidence, from experiments involving secondary isotope effects, that the transition state is in fact relatively diffuse, i.e. the transition state resembles two three carbon fragments loosely held together.[44] A loose transition state could reduce the efficiency of chiral transfer in the AOC rearrangement.

The AOC rearrangement is just one member of a family of anion accelerated reactions which also includes [5,5]–, [1,3]–, and [1,5]–sigmatropic rearrangements as well as retro–[2+2] and reverse Diels–Alder reactions.[45] The use of potassium alkoxides also means that the initial product of the rearrangement is an enolate anion. The considerable energy gain in going from an alkoxide to an enolate means that the AOC rearrangement is irreversible.

The rearrangement is believed to be accelerated by n donation from the electron rich oxyanion into the σ^* orbital of the sigma bond between carbons 3 and 4, *Scheme 34*.[3] This leads to a weakening of the bond and hence ground state destabilisation. Weight is leant to this argument since solvents which coordinate to the potassium ion (e.g. 18-c-6, DMSO and DMF) and thus increase the electron density at the oxyanion, further enhance the reaction rate.[46] Another argument says

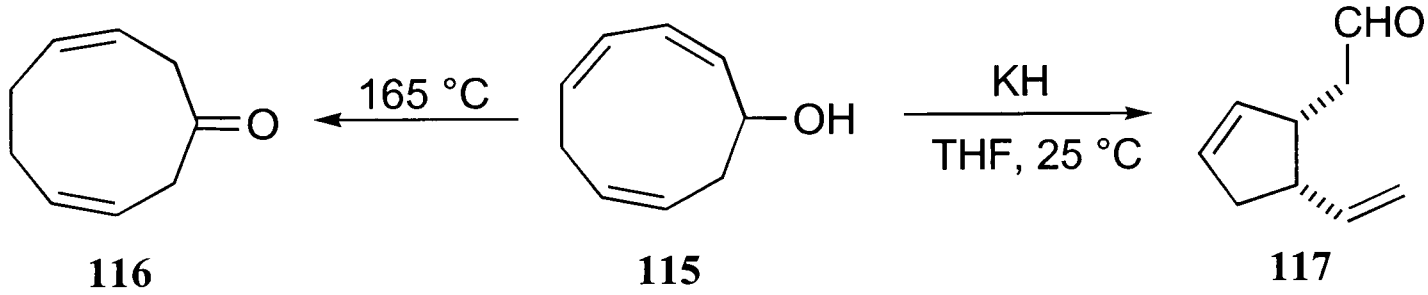
that the oxyanion is stabilised by conjugation in the transition state **113** relative to the ground state of the alkoxide **114**.

Scheme 34



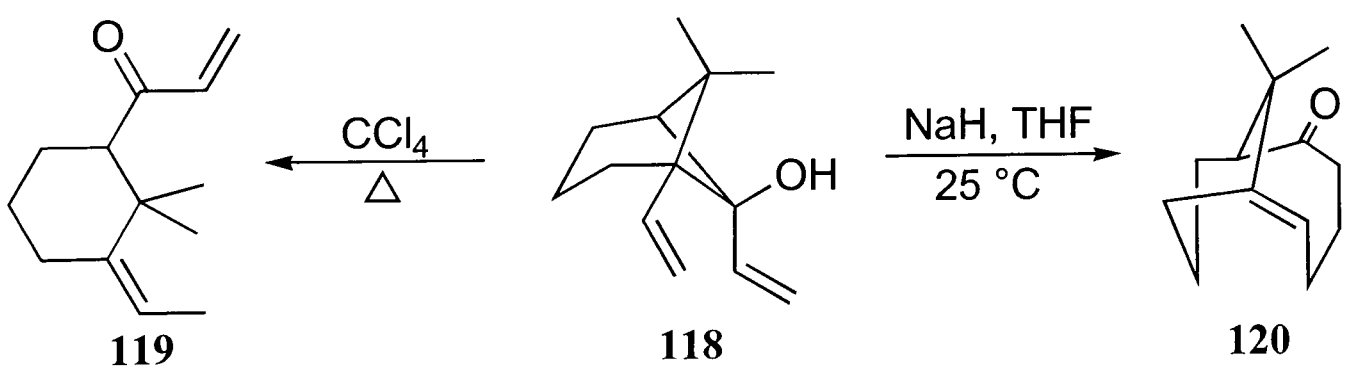
In some thermal oxy–Cope rearrangements a number of competing reactions have been observed. For example, if alcohol **115** is heated to 165 °C a [1,5]–sigmatropic shift takes place and results in the formation of **116**. If alcohol **115** is converted into its potassium alkoxide then only the product of the AOC rearrangement, aldehyde **117**, is observed. Aldehyde **117** has been used in the synthesis of all of the primary prostaglandins, *Scheme 35*.[47]

Scheme 35



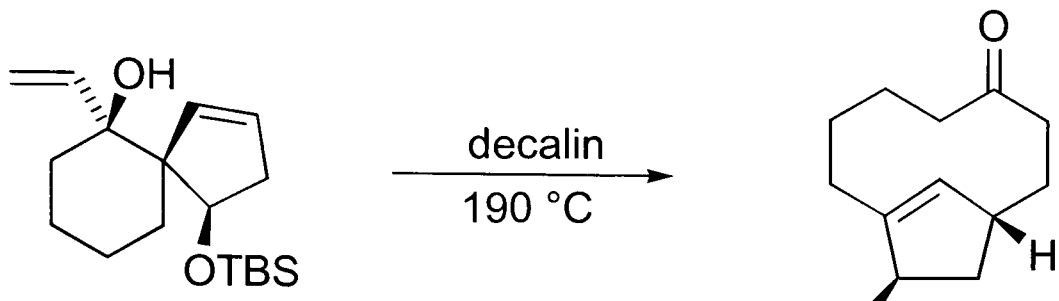
In another example, alcohol **118** undergoes a retro–ene reaction using thermal activation to give **119**, whereas treatment with NaH leads to formation of ketone **120** *via* the AOC rearrangement, *Scheme 36*.[48]

Scheme 36



However, in the case of the rearrangement of spirocyclic alcohol **121** to the ring expanded ketone **122**, it is thermal activation which gives the best result. The use of anionic conditions appears to carry out the intended reaction but the enolate produced is extremely sensitive and leads to rapid polymerisation, *Scheme 37*.[49]

Scheme 37

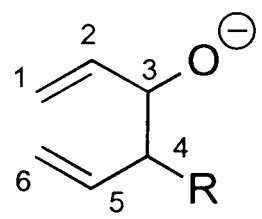


121 **122**

1.3.2 Conjugating Substituents and Allenes

In general, conjugating substituents (e.g. Ph, vinyl and carboxylic acid derivatives) directly attached to the 1,5-hexadien-3-ol do not impair the rearrangement. In fact, if the substituent is at position 4 on the carbon backbone, *figure 7*, the rearrangement is further accelerated.[45] Such substituents stabilise the developing negative charge as the bond becomes polarised by the n donation into the antibonding orbital (see above).

Figure 7

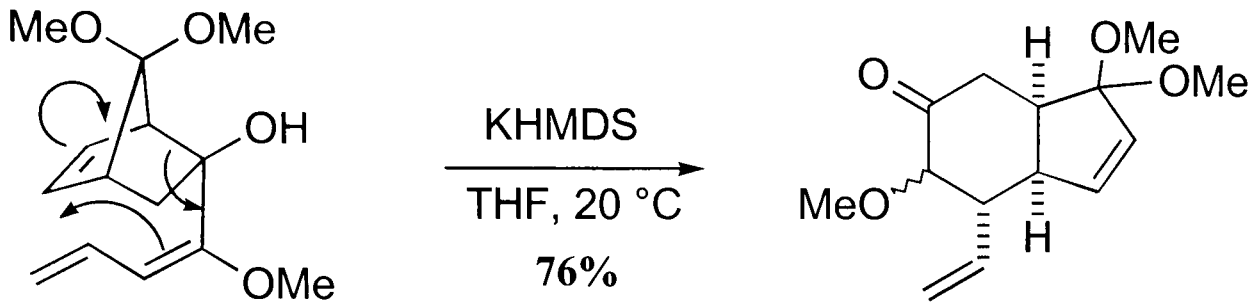


123

R = Ph, –CH=CH$_2$, –CO$_2$R', SAr

In the case of dienes, for example **124**, *Scheme 38*, which also contains an enol ether as part of the carbon skeleton, the possibility for alternative structural rearrangements exist (e.g. Diels Alder reactions). However, in general, if a substrate can rearrange *via* the oxy–Cope rearrangement pathway, it will do so.[50]

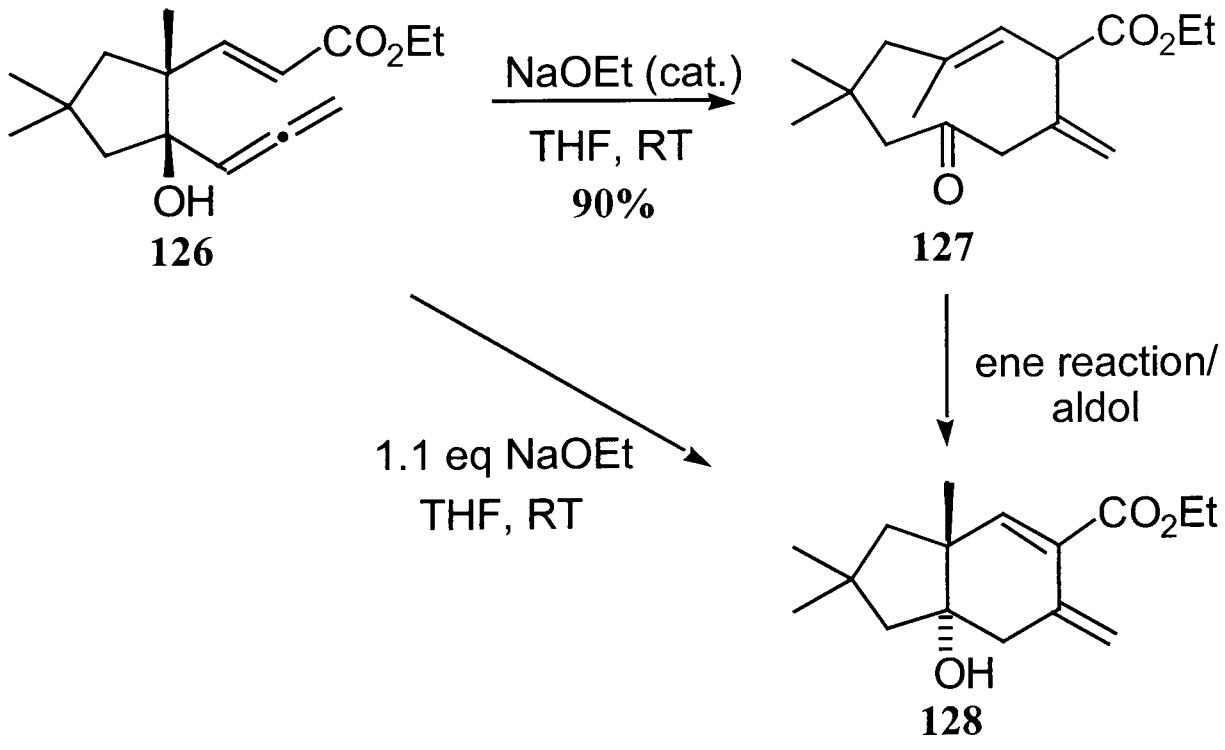
Scheme 38



124 **125**

Although there are very few examples in the literature, allenes have been used in AOC rearrangements, *Scheme 39*. If alcohol **126** is reacted with less than stoichiometric quantities of base then the intermediate ketone **127** can be isolated. However, if more than one equivalent of base is used, then α,β–unsaturated ester **128** is the sole product. Two possibilities exist for the transannular cyclisation, either an ene reaction or an aldol condensation.[51]

Scheme 39



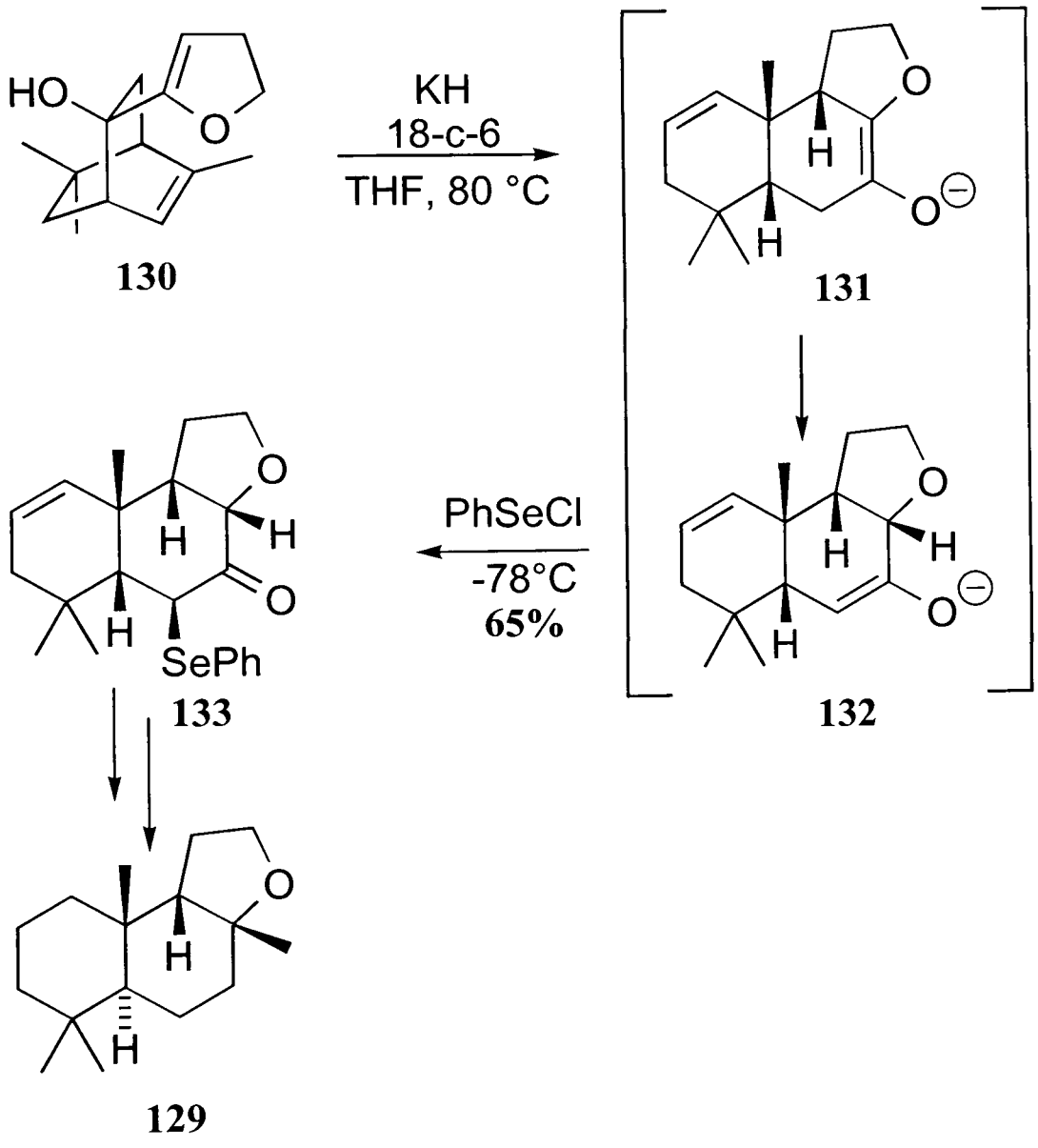
126 **127** **128**

Although alkynes have been employed in a number of thermally induced oxy–Cope rearrangements,[3] particularly for the synthesis of 8–membered carbocycles, no examples of their use in AOC rearrangements have been reported.

1.3.3 Enolate Equilibration

If the enolate initially formed in the AOC rearrangement is sterically or electronically destabilised then enolate equilibration is sometimes observed. This property has been exploited in the synthesis of (-)-9-epi-ambrox **129**. Enol ether **130**, *Scheme 40*, gives intermediate enolate **131** directly following the sigmatropic rearrangement. Enolate **131** reorganises to form **132** and is trapped at the soft carbon end of the enolate with phenylselenium chloride. Further manipulation provides natural product **129**.[52]

Scheme 40



1.3.4 AOC Rearrangement of Acyclic Substrates

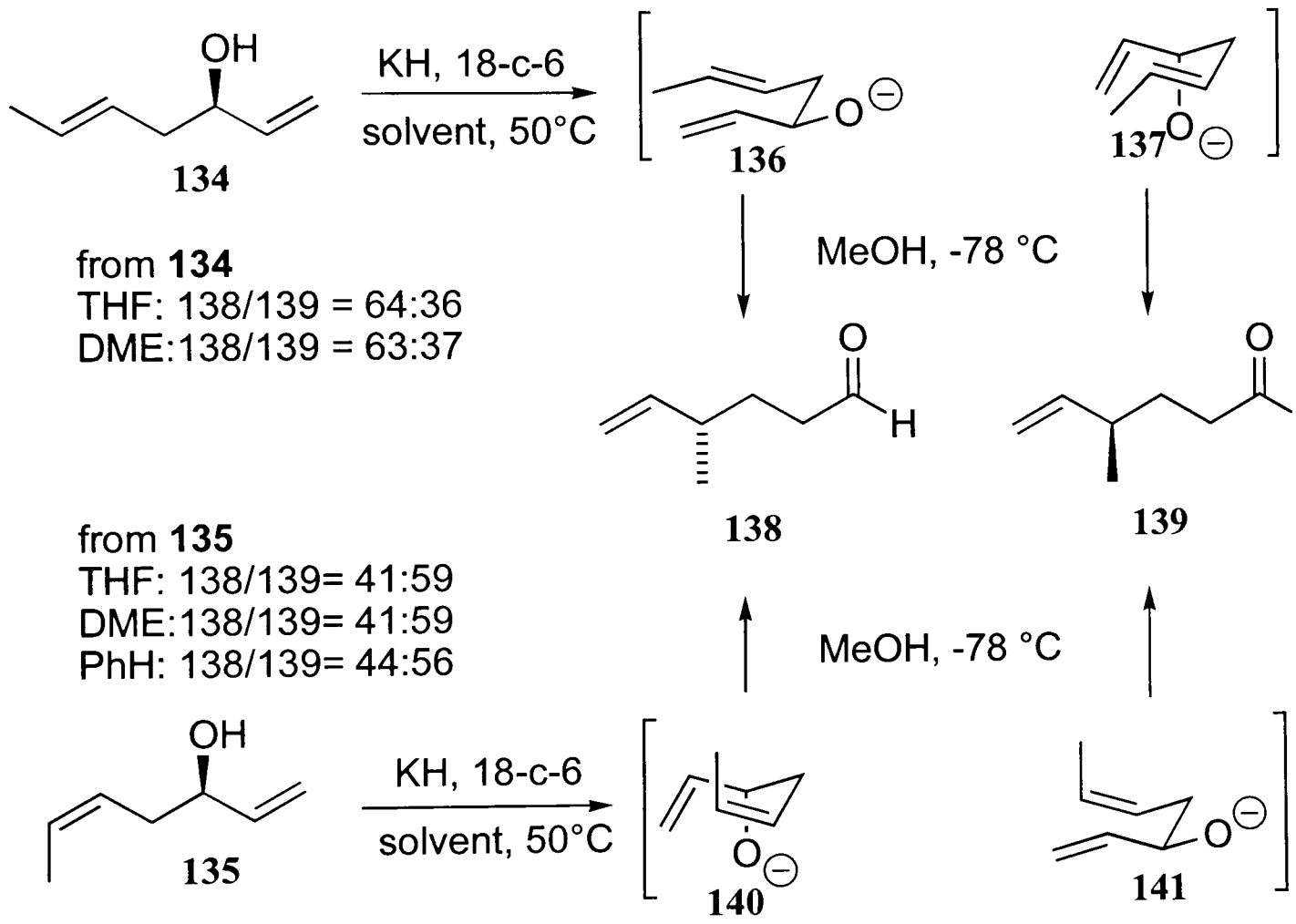
1.3.4.1 One Chiral Centre

The AOC rearrangement of cyclic substrates is now well understood.[3] However the AOC rearrangement of acyclic substrates has been less studied. In

virtually every study of the AOC rearrangement of acyclic substrates authors appear to have disregarded, unwisely, the boat–like reacting conformation. In the following discussion of their results I have made the same assumption. However, our research group and those of Greeves and Lythgoe have observed boat like transition states and this casts some doubt over the validity of this simple interpretation of their results.

In very simple examples, (e.g. **134** and **135**, *Scheme 41*), the level of chirality transfer depends solely on the favourability of each oxyanion orientation in the chair-like transition state.

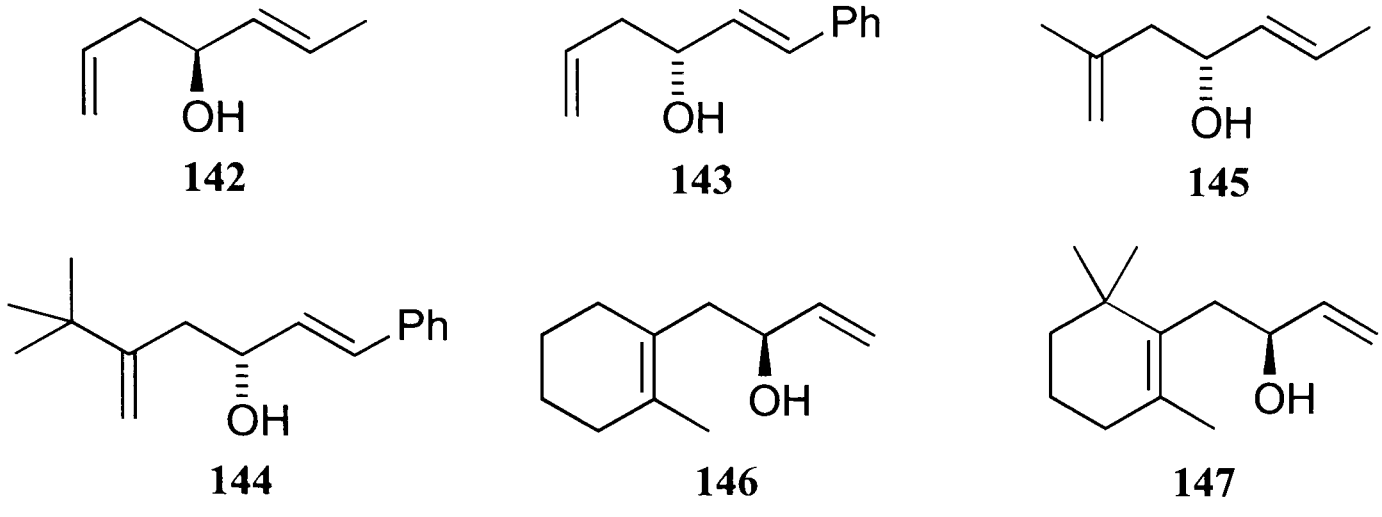
Scheme 41



These substrates rearrange with only a small preference for the oxyanion in a *pseudo*–equatorial orientation. For alcohol **135**, bearing the *Z*–alkene, the methyl group is *pseudo*–axial in both **140** and **141** and has no effect on the stereochemical outcome of the reaction. The solvent does not affect the stereochemistry of the product.[53]

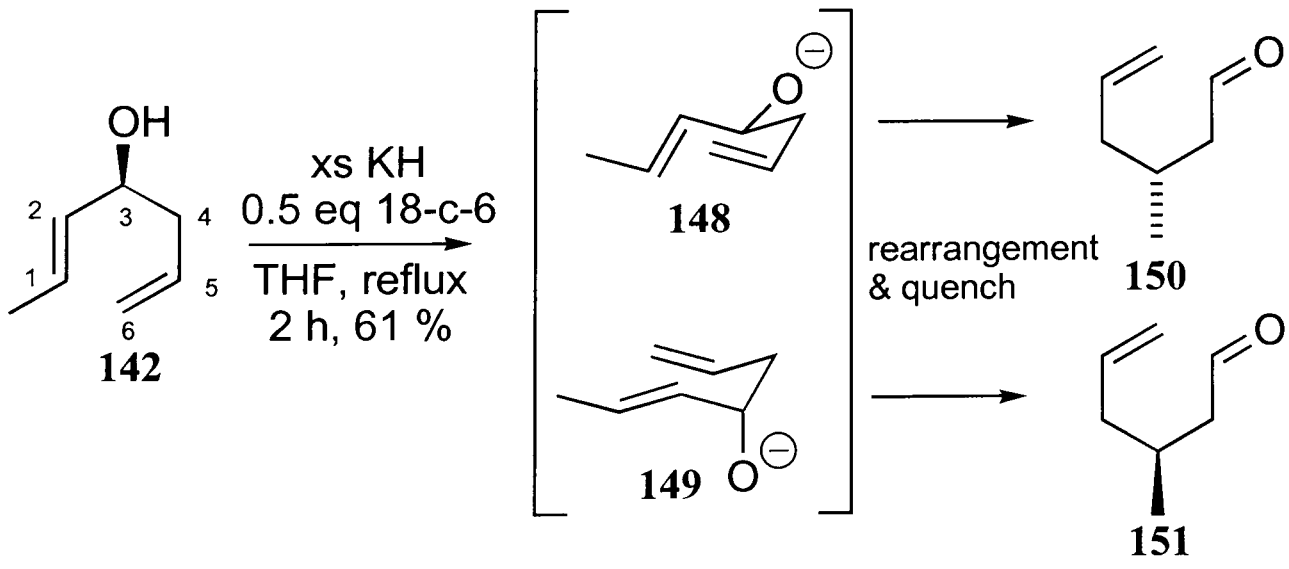
Lee and co–workers have carried out a substantial study of the AOC rearrangement of acyclic substrates bearing one chiral centre, *Figure 8*.[54] Focus in this study is on the effect of alkene substitution on the oxyanion orientation in the transition state.

Figure 8



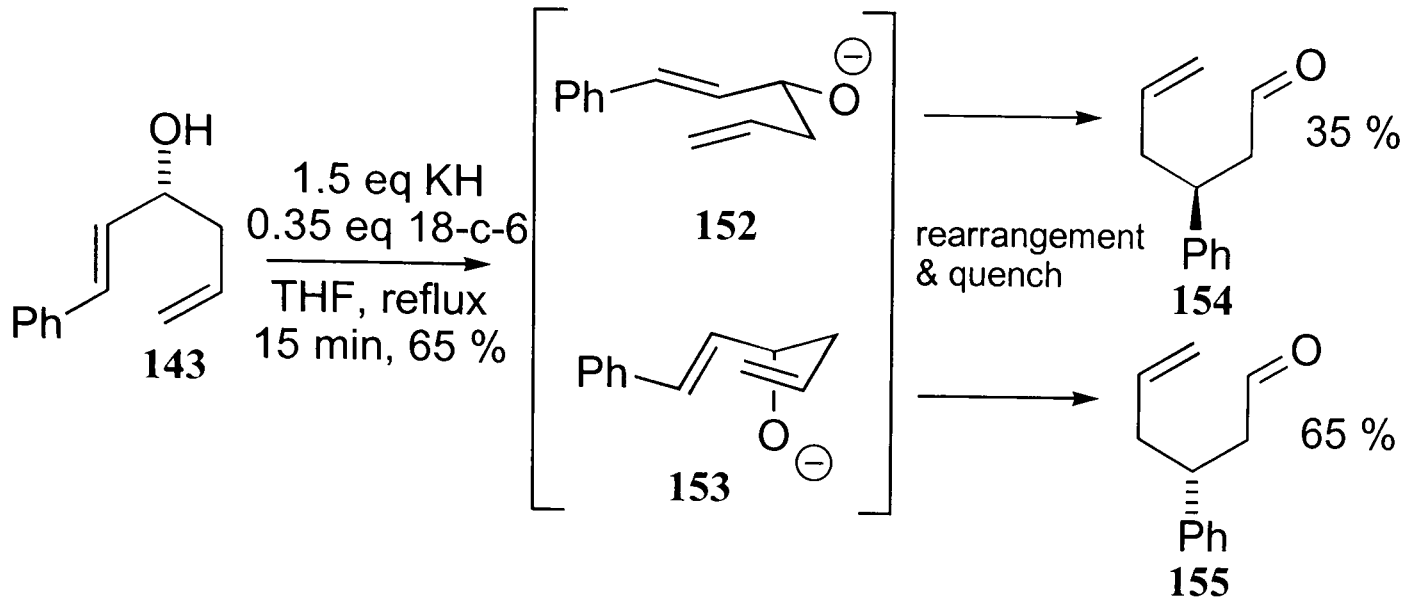
Substrate **142** has a methyl substituent at position 1 (transition state numbering as in *Scheme 34*). Enantiomers **150** and **151** were produced in ratio of 45 to 55 respectively indicating a 10 % bias for reacting conformation **149** with the oxyanion in a *pseudo*–axial orientation, *Scheme 42*.

Scheme 42



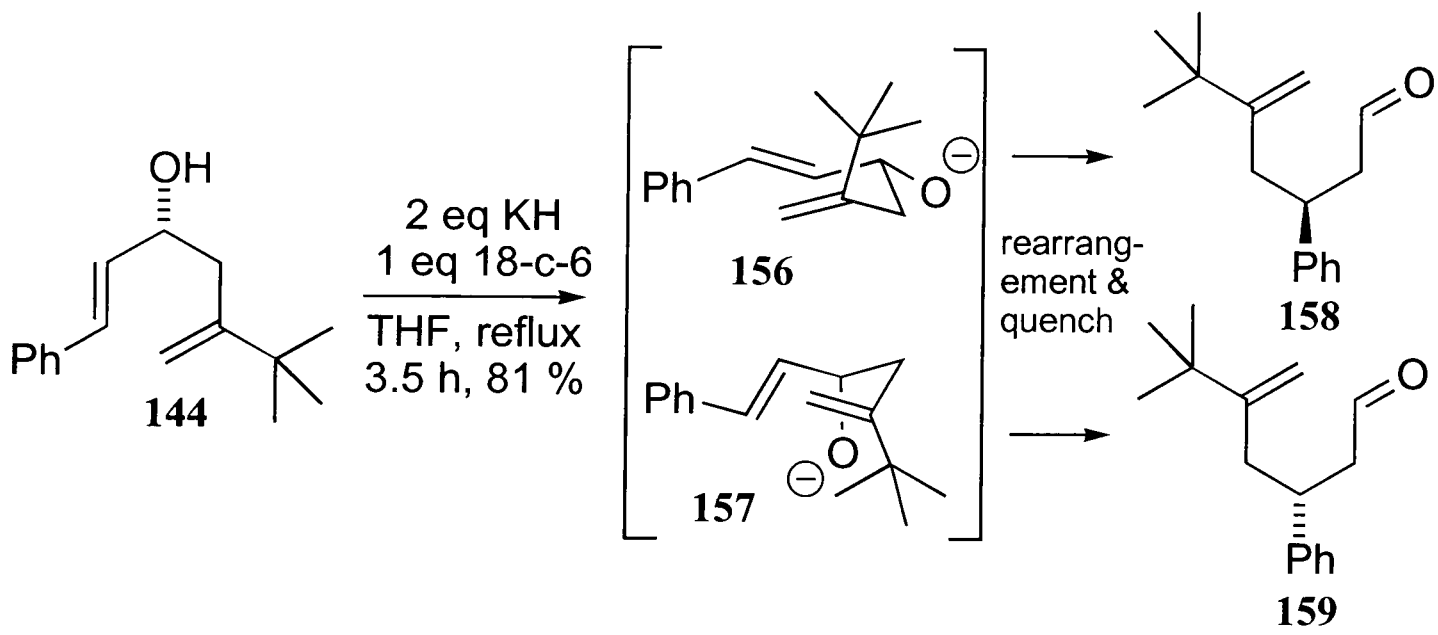
If the substituent at position 1 is larger (e.g. alcohol **143**, *Scheme 43*) a greater preference for a *pseudo*–axial oxyanion is observed.

Scheme 43



Sterically demanding groups at C–5 disfavour a *pseudo*–axial oxyanion through a 1.3–*pseudo*diaxial interaction in reacting conformation **157**. Thus alcohol **144** rearranges to give *S*–aldehyde **158** in 24 % ee, *Scheme 44*.

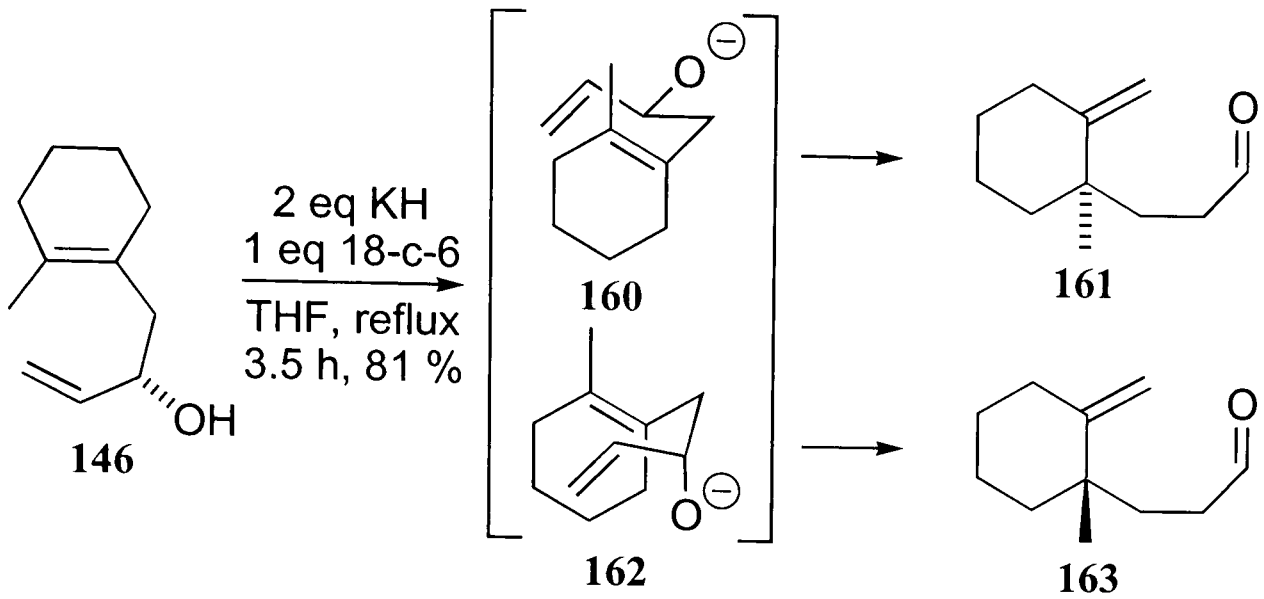
Scheme 44



When the substituents at positions 1 and 5 are both methyl (**145**, *Figure 8*) almost exactly the same ratio as that for **144** is observed. If only chair-like transition states are involved it would seem that the interaction of the methyl group with the oxyanion is comparable to that of the tertiary butyl group with the oxyanion!

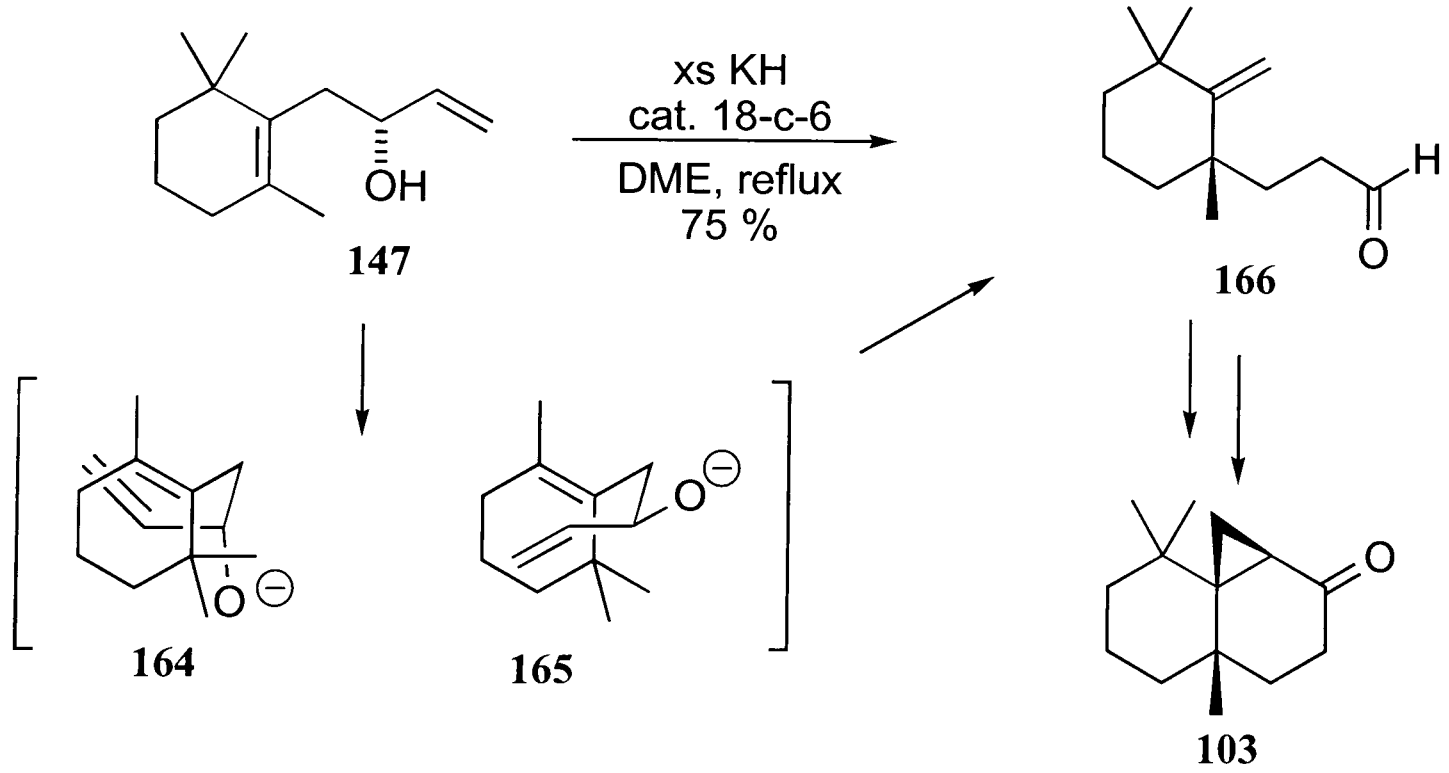
When the substrate is substituted at positions five and six a *pseudo*-equatorial oxyanion is favoured. Alcohol **146**, *Scheme 45*, rearranges to give aldehyde **161** in 38 % ee. Transition state **162** is destabilised by a *pseudo*–1,3–diaxial interaction as above.

Scheme 45



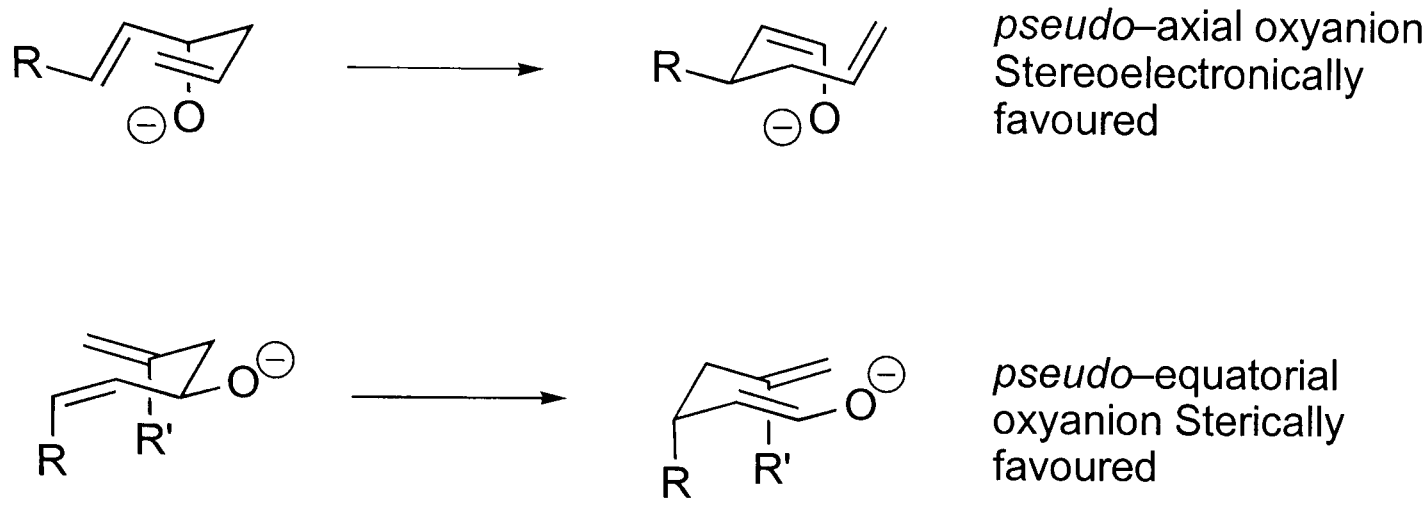
In Lee's synthesis of (+)-dihydromayurone **103**,[39] *Scheme 46*, a 98:2 ratio of enantiomers is obtained in the AOC rearrangement step. The presence of the geminal dimethyl groups on the cyclohexyl ring strongly disfavours a *pseudo*–axial oxyanion in the transition state of the rearrangement and hence the high degree of chiral transfer observed in the reaction.

Scheme 46



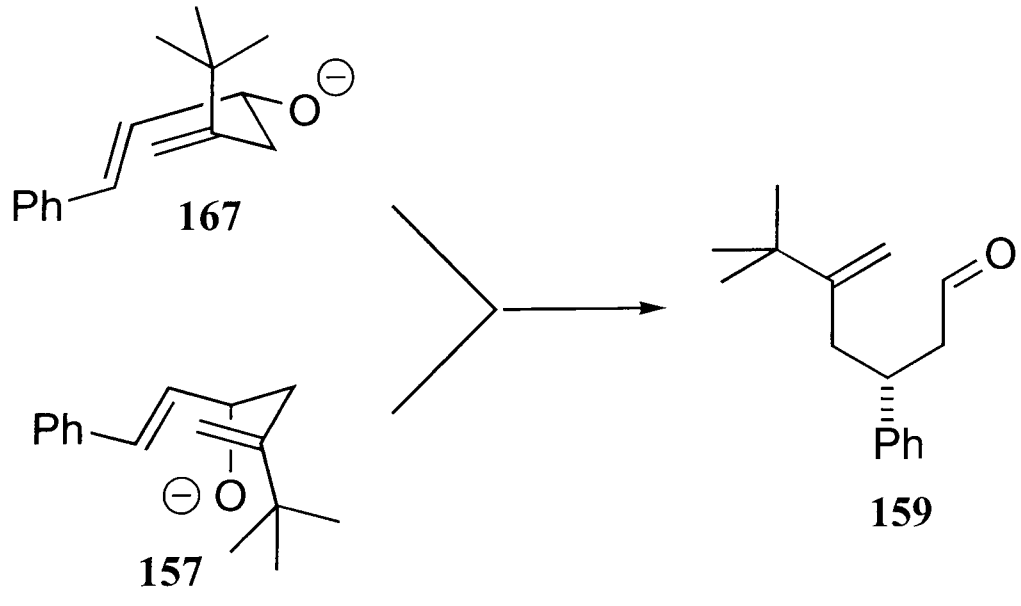
Lee concluded that a *pseudo*–axially oriented alkoxide is stereoelectronically favoured in substrates with *E*–aryl/alkyl substituents at position one. *Pseudo*–equatorial oxyanions become more favourable, for steric reasons, upon *Z*–alkyl substitution at position 1 and alkyl substitution at position 5, *Scheme 47*.

Scheme 47



Lee observes only a 24% enantiomeric excess in the rearrangement of substrate **144**, *Scheme 44.* Transition state **156** should be preferred to a greater extent than Lee's model suggests. The interaction between the oxyanion and the tertiary butyl group in conformation **157** would be considerable. Lee's model also implies that the interaction of a methyl group at position 5 with the oxyanion is comparable to that of the much more sterically demanding tertiary butyl group. These results could be more satisfactorily explained if the reaction proceeds with competition from a boat like transition state, *Scheme 48*. Reacting conformations **157** and **167** both give rise to aldehyde **159**. However, the 1,3-*pseudo*diaxial interaction between the tertiary butyl group and the oxyanion in conformation **157** is far greater than the 1,3-*pseudo*diaxial interaction between a tertiary butyl group and a hydrogen atom in conformation **167**. I believe that the involvement of boat-like reacting conformation **167** better explains the poor stereoselectivity in the AOC rearrangement of hexadienol **144**.

Scheme 48



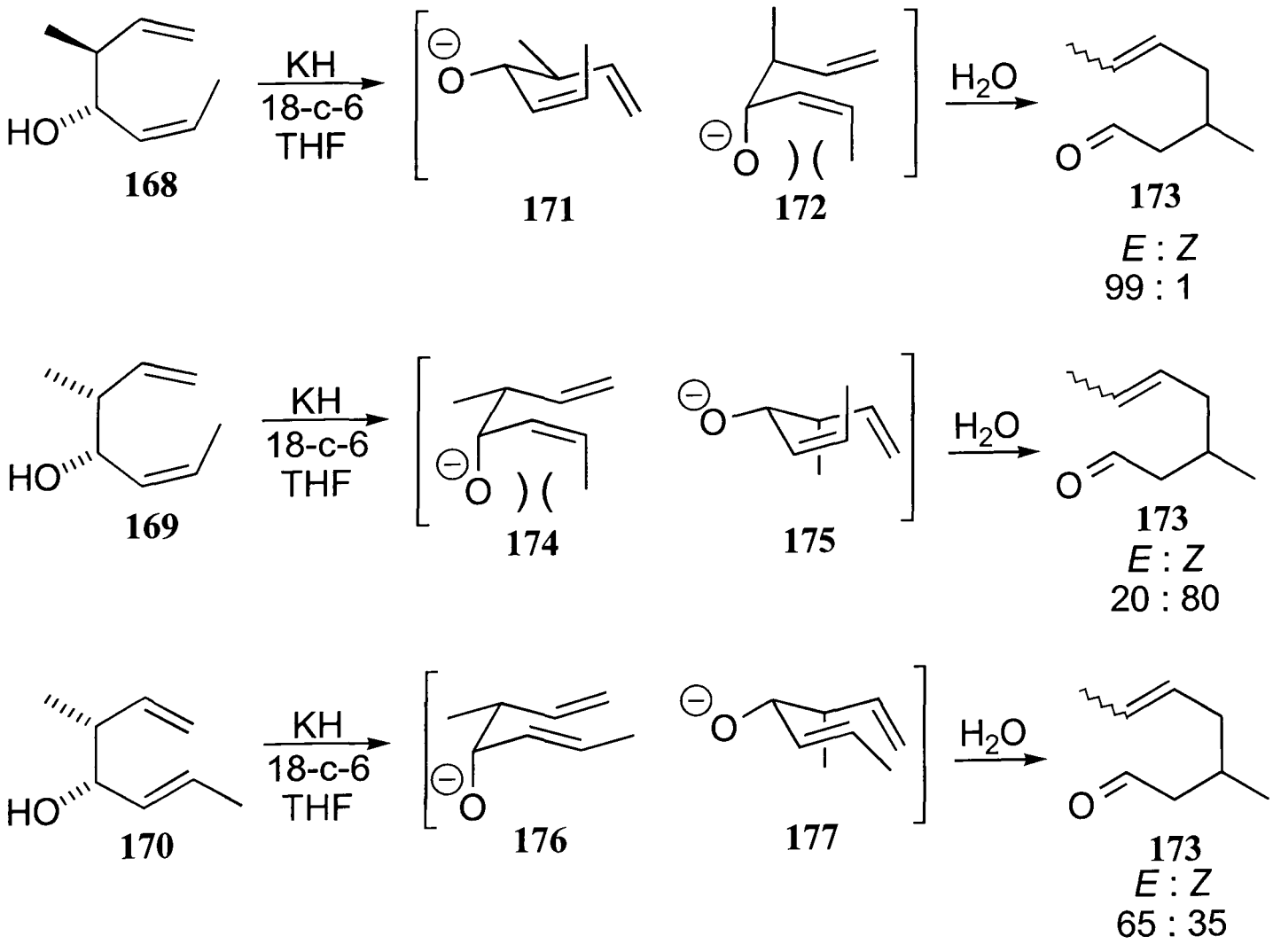
1.3.4.2 Two Chiral Centres

Selective double bond generation is the outcome of the AOC rearrangement of substrates bearing two chiral centres.[55] Let us consider the behaviour of alcohols **168-170**, *Scheme 49*. The *syn* substrate **168** gives greatest control of double bond geometry due to an unfavourable *pseudo* 1,3–diaxial interaction between the lone pairs on the oxyanion and the methyl group at position 1 in reacting conformation **172**.

Reacting conformation **175** for the rearrangement of alcohol **169** is destabilised, relative to conformation **171**, due to an increase in the number of *pseudo*–1,3–diaxial interactions hence control of the double bond geometry is poorer.

The two chair-like transition states possible for rearrangement of the alkoxide derived from alcohol **170** are more evenly populated. The oxyanion and the methyl groups are forced to compete for equatorial positioning. Since a higher proportion of the aldehyde derived from conformation **176** is observed, the methyl groups have a greater spatial requirement than the alkoxide.

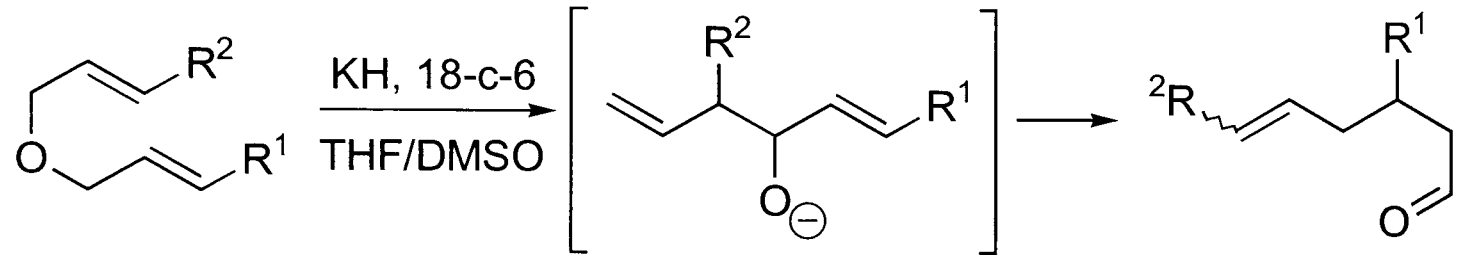
Scheme 49



The groups of Nakai[56] and Greeves[57] have reported the coupling of a [2,3]–Wittig rearrangement with the AOC rearrangement. The efficiency of the Wittig rearrangement is central to successful control in the AOC rearrangement, *Scheme 50.*

Nakai and co-workers carried out the two processes sequentially to ascertain the stereochemistry of the products of the [2,3]–Wittig rearrangement. The *E*–selectivity in the [2,3]–Wittig rearrangement has been established.[58] Later Greeves carried out both reactions in one-pot, taking advantage of the fact that the conditions for each reaction are very similar.[59]

Scheme 50



178 **179** **180**

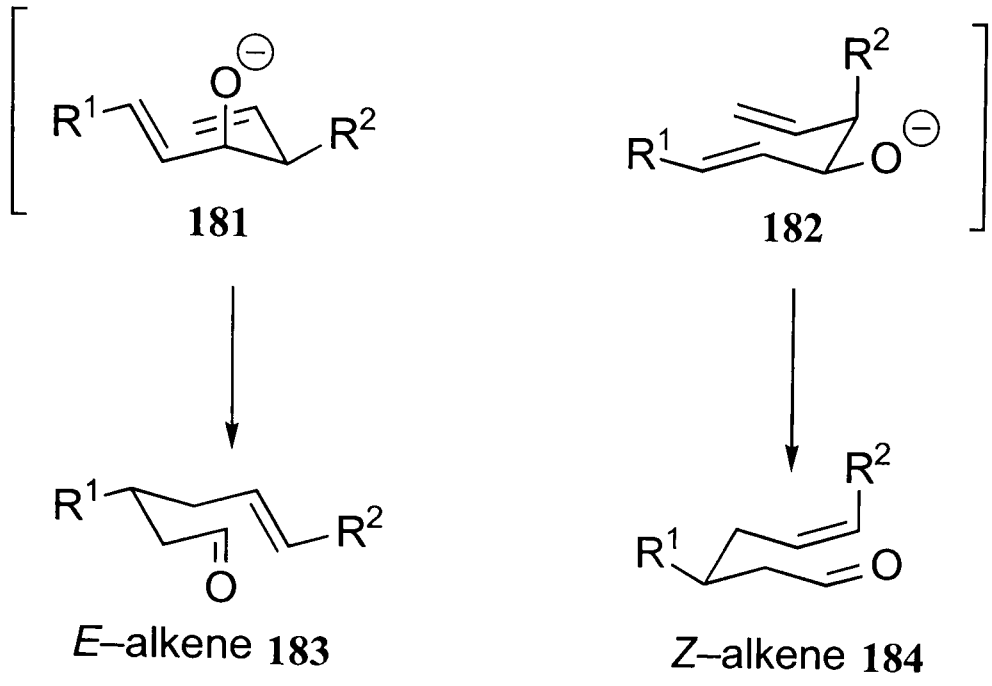
Table 5

R^1	R^2	solvent	*E*:*Z*	yield(%)
Ph	^{i}Pr	THF	100:0	67
Ph	^{n}Pr	THF	85:15	79
Ph	Me	THF	75:25	76
Ph	Me	DMSO	75:25	55

In order to understand the *E/Z* selectivities presented in *Table 5* it is necessary to examine the transition states of the AOC rearrangement, *Scheme 51.* The reaction can operate *via* two possible chair–like conformations, the preference for which is, in this case, determined by the steric bulk of the substituents on the carbon backbone. For example, when R^2 is very sterically demanding (e.g. isopropyl) the reaction is forced to proceed *via* reacting conformation **181** rather than reacting conformation **182**. The latter is destabilised by 1,3–*pseudo*–diaxial interactions and hence the *E* to *Z*

ratio of the alkene is determined by the steric bulk of R^2. As R^2 decreases in size there greater competition from reacting conformation **182**.

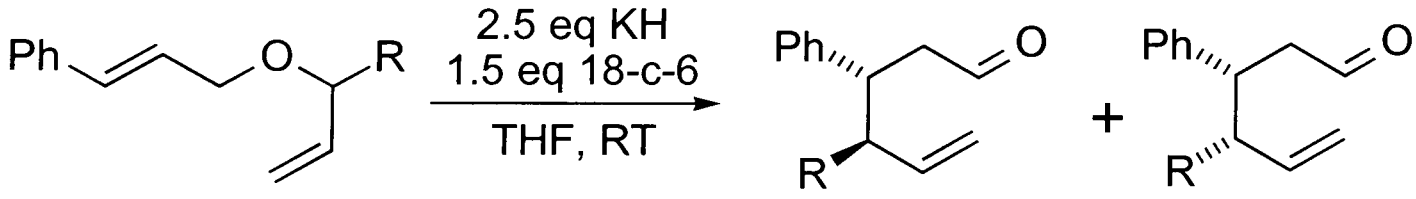
Scheme 51



In general the rate of the one–pot reaction is faster in dimethylsulfoxide but higher yields are obtained if tetrahydrofuran is used. In both cases the *E*:*Z*–selectivity is the same. All of the above explanations assume no competition from boat–like conformations.

If the system bears an alkyl substituent alpha to the oxygen prior to the Wittig rearrangement, *Scheme 52, Table 6*, then two chiral centres are selectively introduced into the product.[60]

Scheme 52



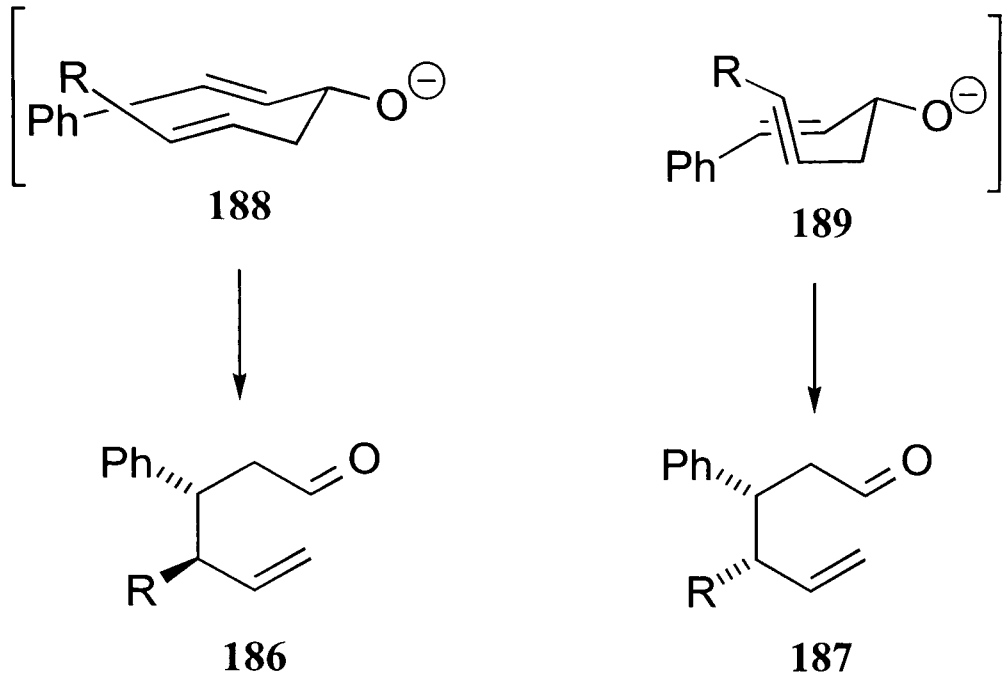
185 **186** **187**

Table 6

R	**186**	**187**	yield(%)
^{i}Pr	96	4	79
cyclohexyl	94	6	67
^{n}Pr	90	10	74

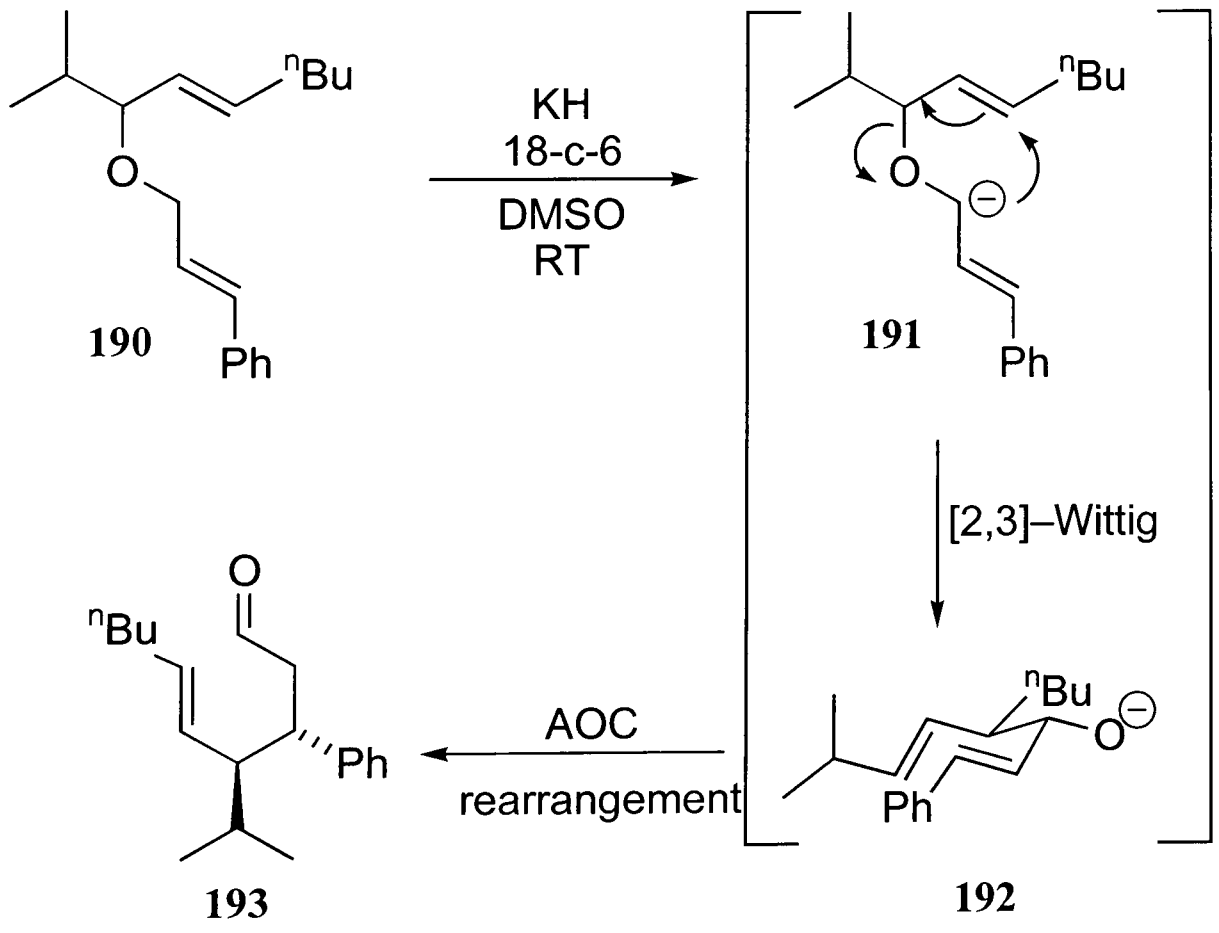
The 3,4–*syn* aldehyde **186** is the product of a chair–like reacting conformation **188** in the AOC rearrangement while *anti* aldehyde **187** is derived from a boat–like conformation **189**, *Scheme 53*.

Scheme 53



To complete the picture, the two previous processes have been combined. The products of the reaction contain two controlled stereogenic centres and one controlled double bond, *Scheme 54*.[57]

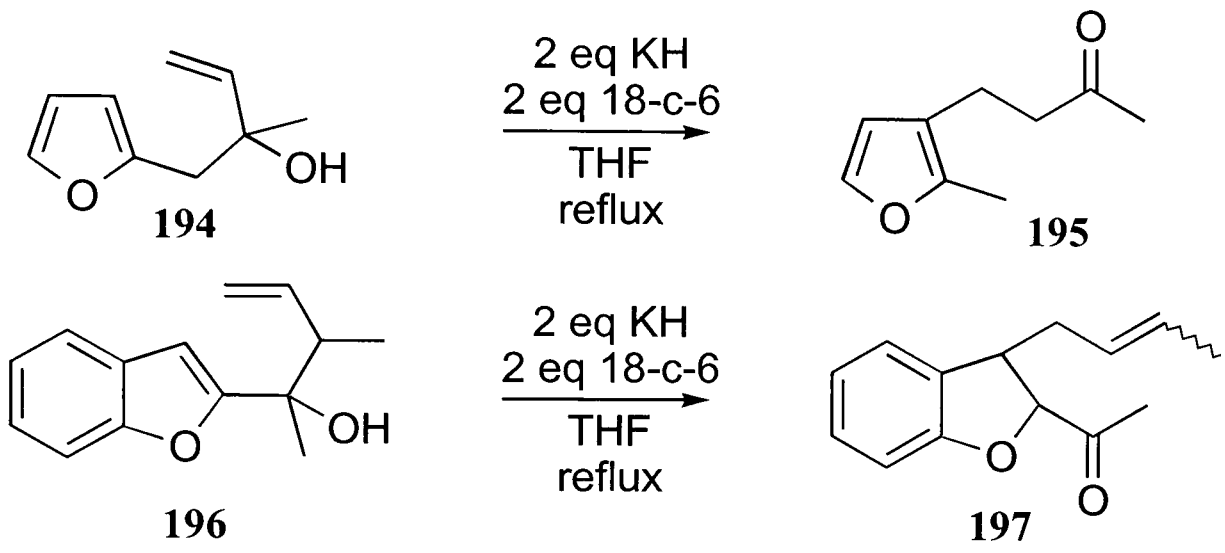
Scheme 54



1.3.5 Participation of Aromatic Rings

For the most part aromatic rings are reluctant to take part in AOC rearrangements because of the need to destroy the delocalisation of the system. However a few examples involving furans and benzofurans have been reported, *Scheme 55*, at elevated temperatures.[61]

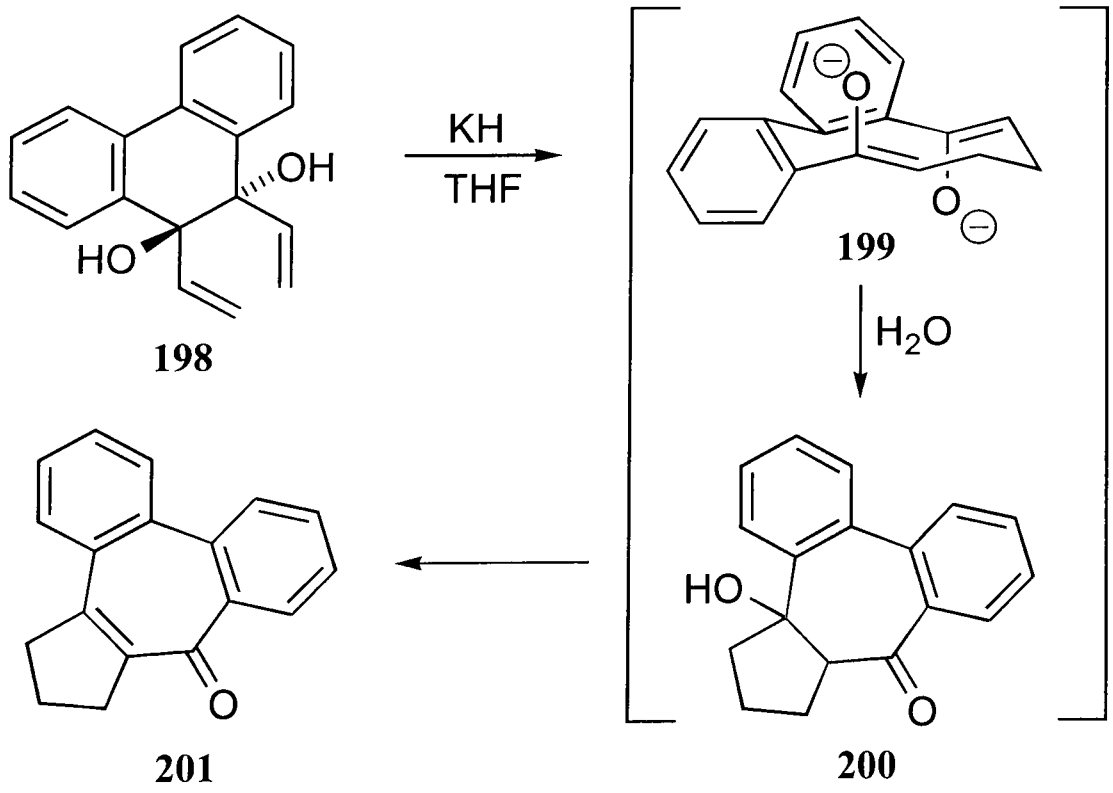
Scheme 55



1.3.6 Dianionic oxy–Cope Rearrangements

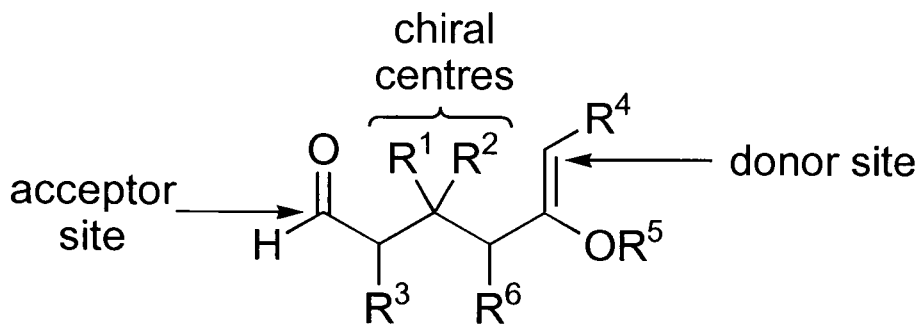
Doubly charged systems have recently been reported to undergo AOC rearrangements. The most significant difference in such systems is that the initial product contains two highly reactive enolates. Intramolecular aldol reactions, as outlined in *Scheme 56*, [62] commonly follow the dianionic oxy–Cope rearrangement.

Scheme 56



As illustrated above *Schemes 38* and *40*, the use of enol ethers in the AOC rearrangement of cyclic substrates has been reported but the oxygen atom of the enol ether has no controlling effect on the stereochemical outcome of the reaction. The use of enol ethers in the AOC rearrangement of acyclic substrates has nowhere been suggested. Enol ether containing aldehyde **1**, *Figure 9*, is central to the success of our proposed chemistry. It contains three contiguous stereocentres, one acceptor site and one donor site hence its synthetic utility is potentially enormous.

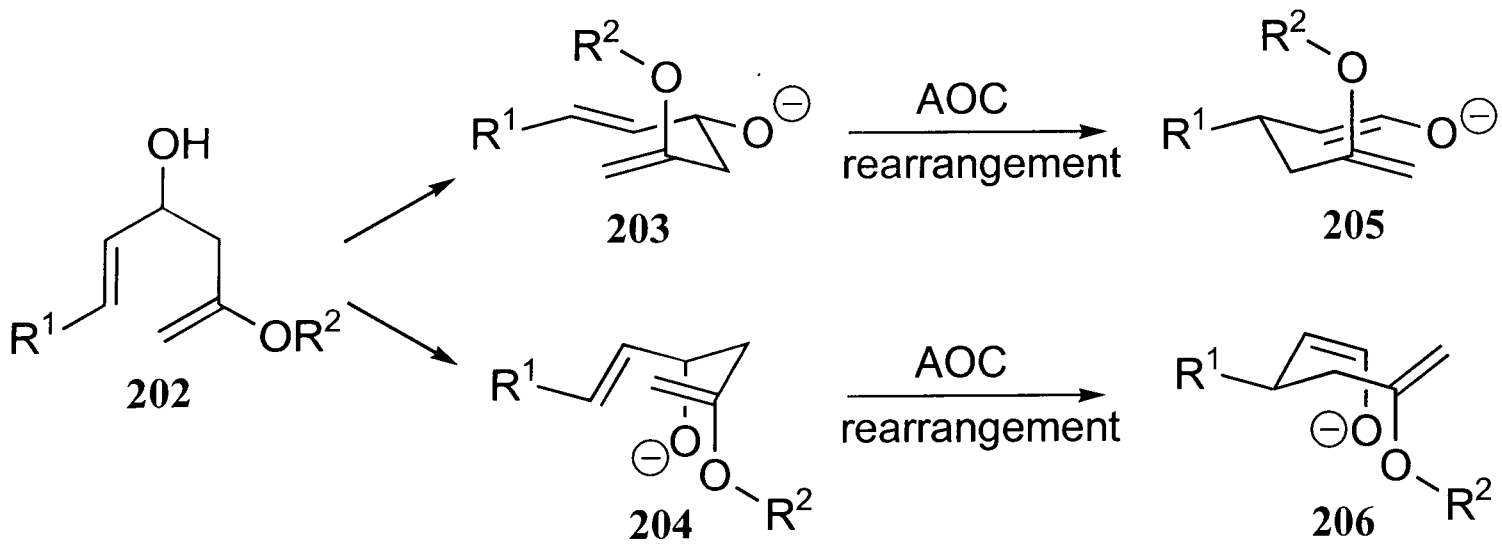
Figure 9



1

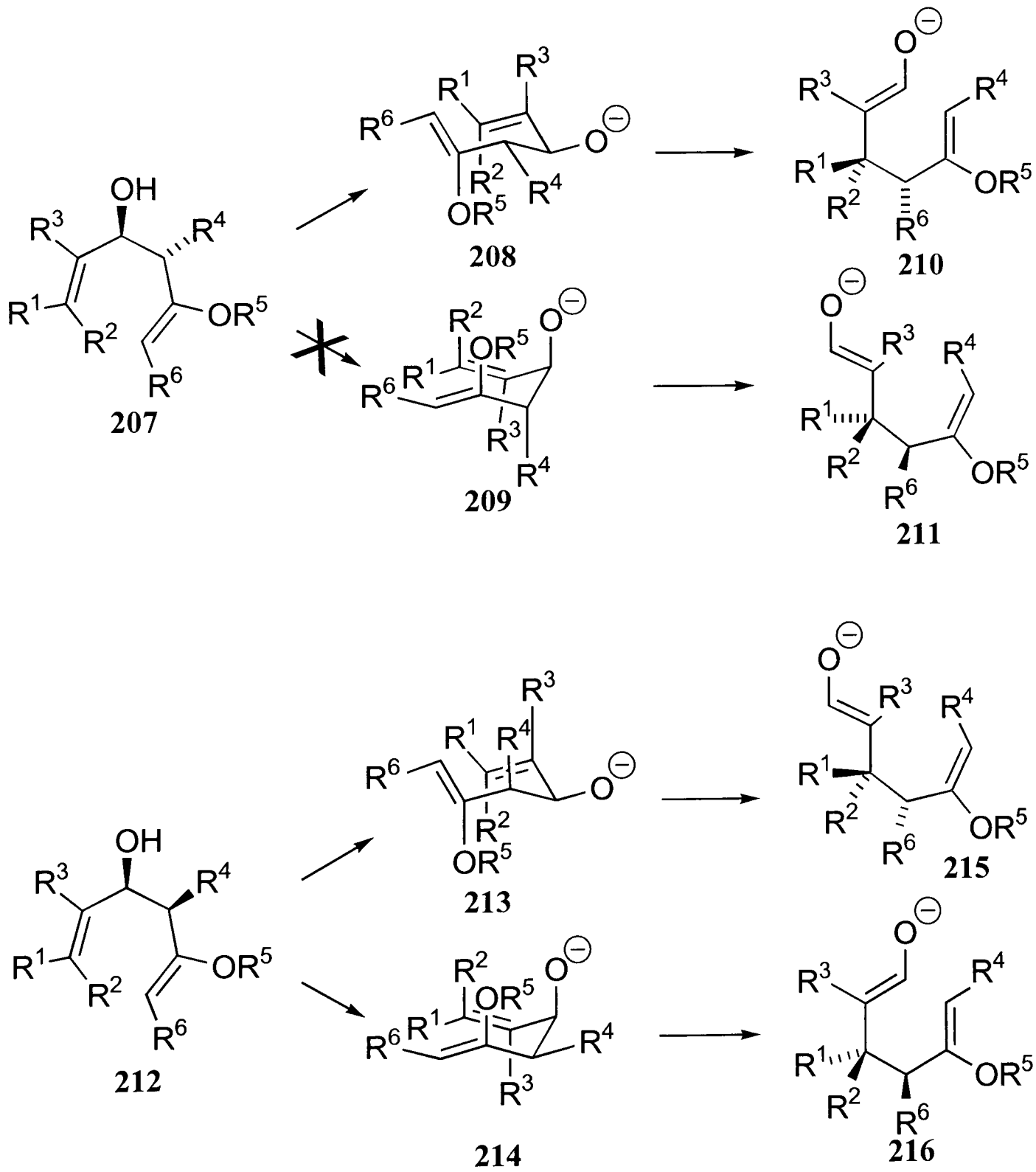
In simple substrates, e.g. alcohol **202**, *Scheme 57*, we expected the oxygen atom of the enol ether to have a major controlling effect on the stereochemical outcome of the rearrangement. The alkoxide derived from alcohol **202** can rearrange *via* reacting conformations **203** and **204**. We expected reacting conformation **204** to be destabilised relative to reacting conformation **203** by electrostatic repulsion between the oxyanion and the oxygen atom of the enol ether therefore intermediate **205** should predominate in the product.

Scheme 57



For more complex substrates we expect to obtain the best results with the use of *syn* alcohols **207** in the AOC rearrangement. The alkoxide derived from **207** can rearrange *via* reacting conformations **208** and **209**, *Scheme 58*, the latter is disfavoured by electrostatic interaction between the oxyanion and the oxygen atom of the enol ether, steric interactions between R^2 and the two oxygen atoms and 1,3 *pseudo*diaxial interaction of R^3 with R^4. The only significant destabilisation of reacting conformation **208** is between R^2 and the oxygen atom of the enol ether hence we expected enolate **210** to be generated selectively.

Scheme 58



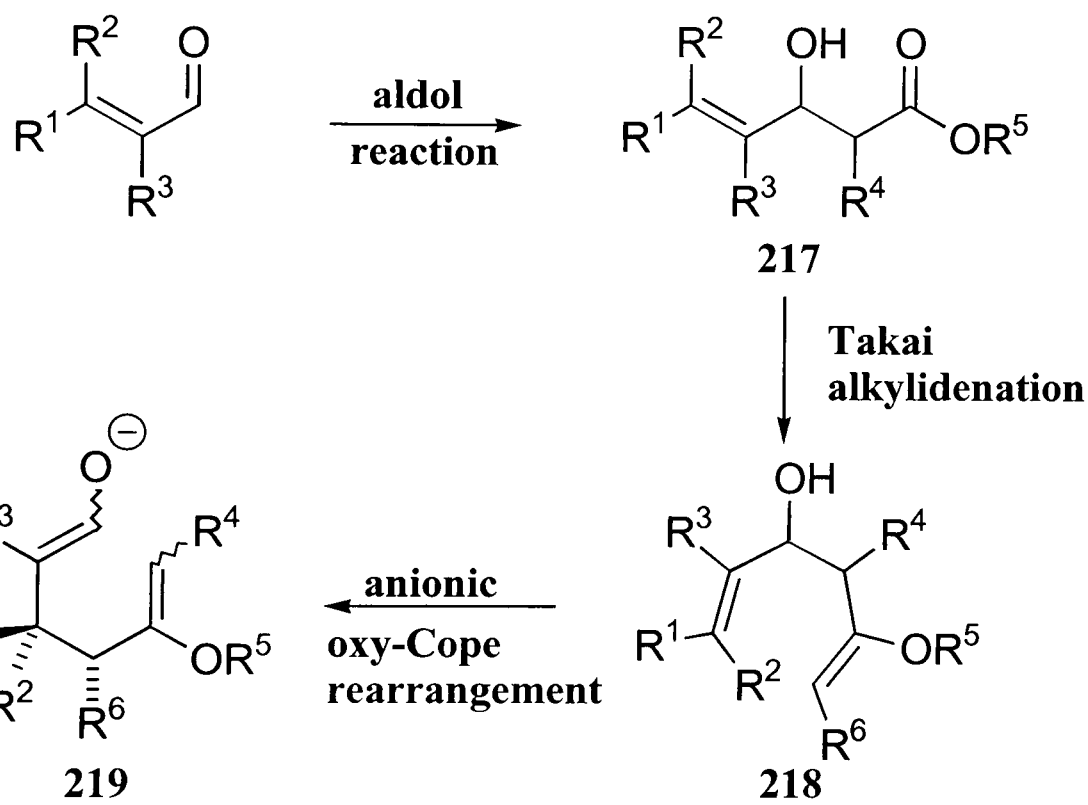
The alkoxide derived from *anti* alcohols **212** can rearrange *via* reacting conformations **213** and **214**. Reacting conformation **213** is disfavoured by electrostatic interaction between the oxyanion and the oxygen atom of the enol ether and steric interactions between R^2 and the two oxygen atoms and the 1,3-*pseudo*-diaxial interaction between R^2 and OR^5. Conformation **214** is destabilised by electrostatic interaction between the oxyanion and the oxygen atom of the enol ether and steric interactions between R^2 and the oxygen atoms of the enol ether and the oxyanion, so we expected **213** and **214** to be relatively evenly populated and that we would obtain a mixture of enolates **215** and **216**. Hence, we expect more faithful chiral transfer in the AOC rearrangement of *syn* substrates. R^6 was expected to exert little or no control over the stereochemical outcome of the AOC rearrangement except when it bore chelating constituents, e.g. oxygen atoms.

2. SYNTHESIS OF ALDEHYDES CONTAINING AN ENOL ETHER

Our aims for this research were as follows: (i) synthesis of aldehydes **1** containing an aldehyde and an enol ether using the AOC rearrangement; (ii) to investigate stereoselective synthesis of five- and six-membered carbocycles by generating and cyclising such enol ethers; (iii) to investigate the role of the oxygen atom of the enol ether in controlling the stereochemical outcome of the AOC rearrangement and (iv) to synthesise highly oxygenated cyclohexanes.

2.1 Synthetic Strategy

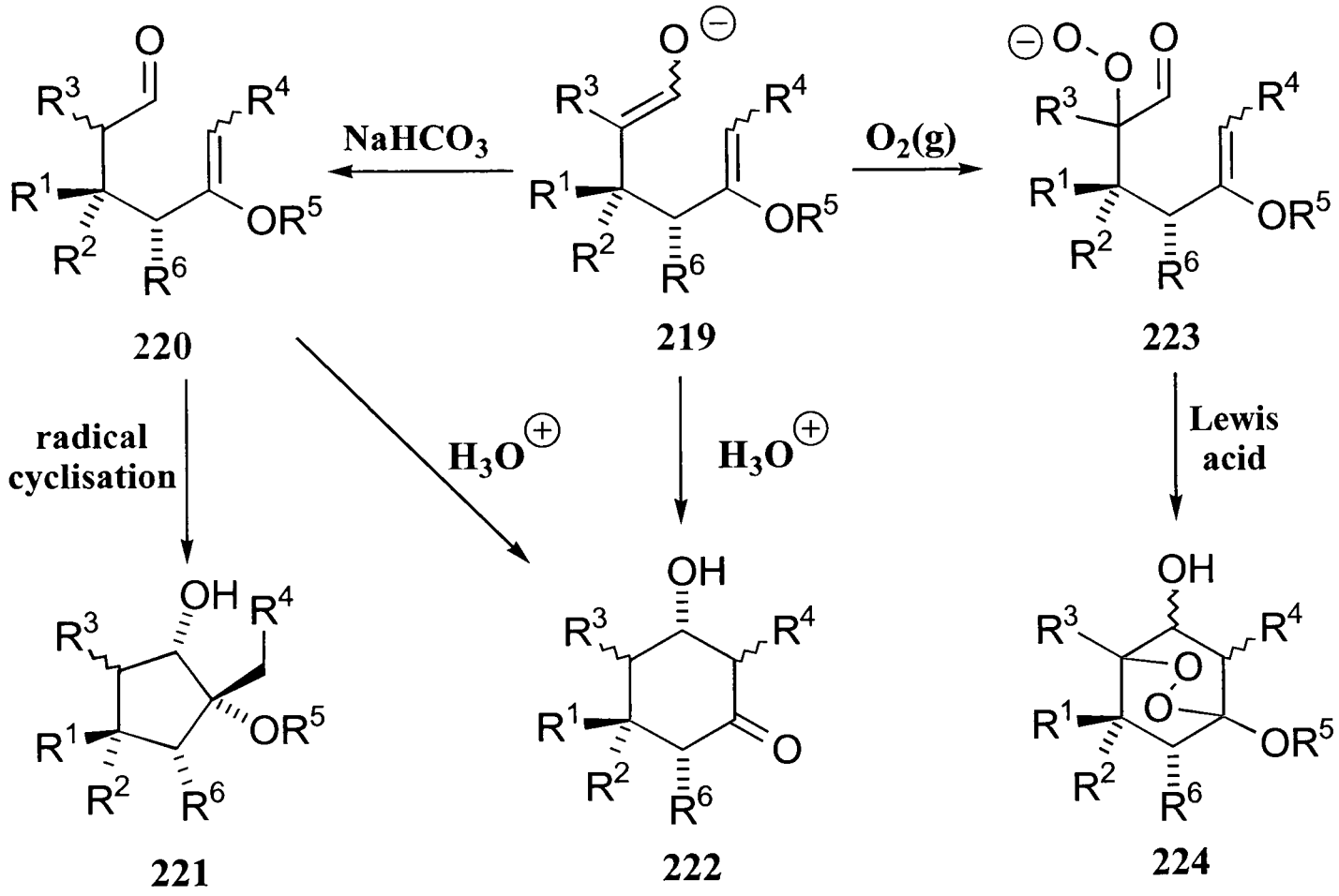
Scheme 59



Our synthetic strategy is based on three key reactions as outlined in *Scheme 59*. α,β-Unsaturated aldehydes bearing one piece of stereochemical information, the double bond geometry, are reacted with the enolate of an ester (or its equivalent) in an **aldol reaction**[1] to form β-hydroxyesters **217** allowing the introduction of up to two chiral centres. The aldol reaction is chosen for its versatility, i.e. it can be carried out unselectively, diastereoselectively or enantioselectively. **Takai's alkylidenation**

procedure[2] selectively converts ester **217** into the *Z* enol ether **218** adding one more element of stereochemistry. The chirality then present is transferred by means of the **AOC rearrangement**[3] to new sites in the product enolate **219**. The *anti* relationship between R^1 and R^6 in enolate **219** results from a chair-like transition state. The absolute stereochemistry at C-3 and C-4 and the geometry of the enol ether in enolate **219** depend on the absolute and relative stereochemistry at C-3 and C-4 in alcohol **218** and on the orientation of the oxyanion in the transition state. Only the 3,4-relative stereochemistry should be inferred from my drawing of enolate **219**.

Scheme 60



Once enolate **219** is formed several options are possible. Quenching with either aqueous base or pH 7 phosphate buffer should give compound **220** which contains an aldehyde and an enol ether in a 1,5–relationship. Unsurprisingly such a relationship has not been reported elsewhere since **220** contains both an electrophilic (aldehyde) and a nucleophilic (enol ether) component and is therefore inherently unstable. Radical cyclisation of aldehyde **220** should give cyclopentanones **221**. Acidic quench of enolate **219** or treatment of aldehyde **220** with aqueous acid should give β-hydroxycyclohexanone **222**. Quenching enolate **219** with molecular oxygen

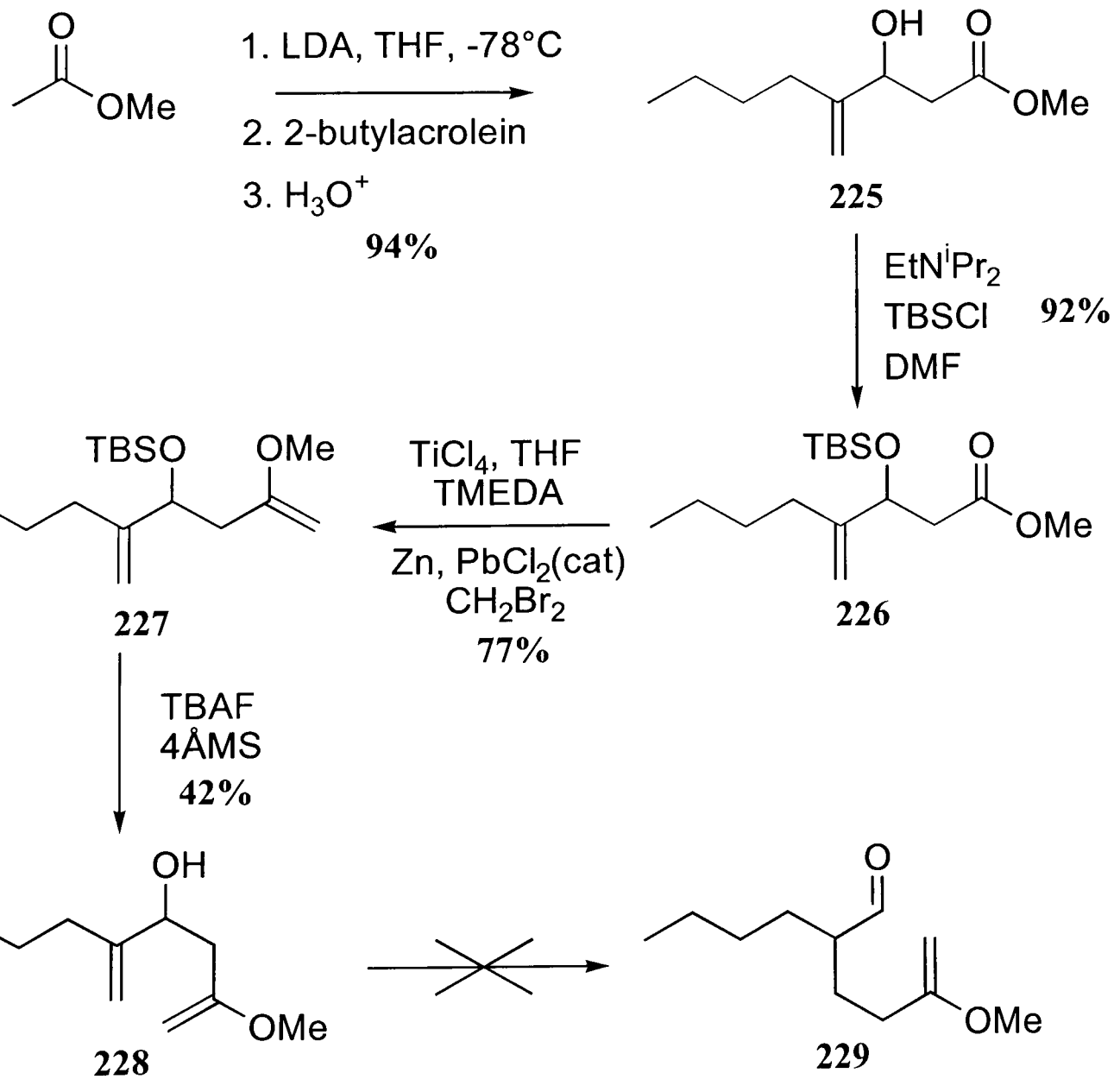
should lead to formation of hydroperoxide **223** which we wished to cyclise to give analogues **224** of the potent antimalarial drug artemisinin.

In this chapter I will discuss the synthesis of aldehyde **220** and the attempted synthesis of cyclopentane **221**. The synthesis of β-hydroxycyclohexanones is described in chapter 3 and oxygenation reactions are discussed in chapter 4.

2.2 Initial Studies

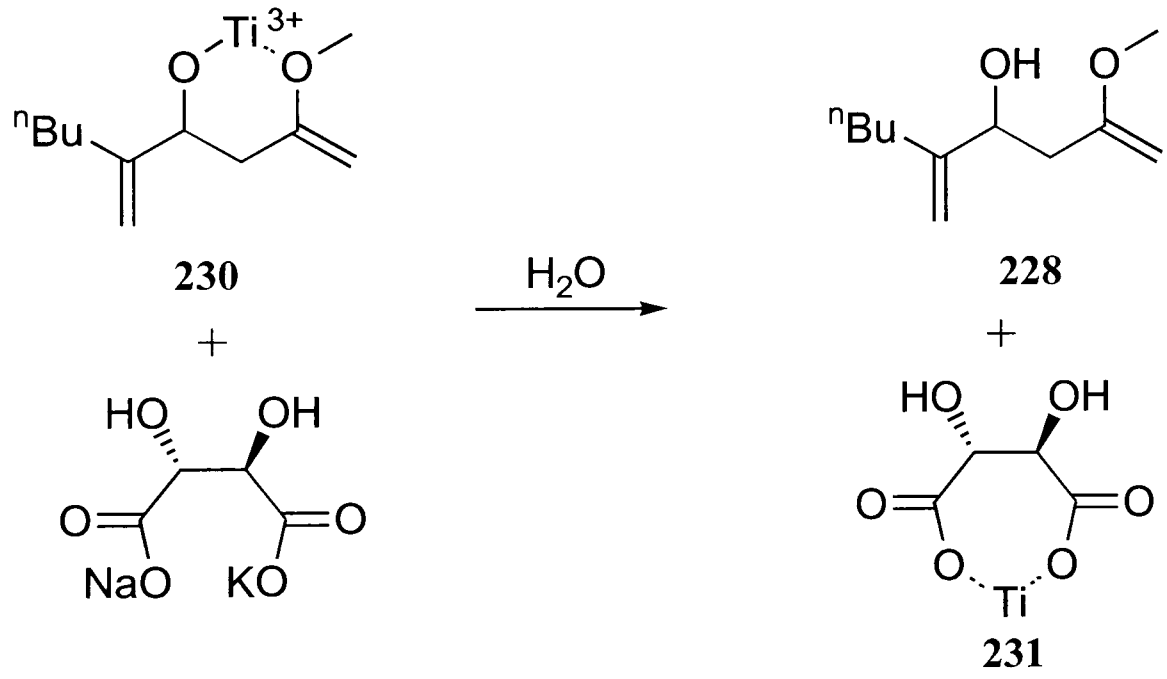
Firstly, we had to verify whether our proposed route to the substrates for AOC rearrangement was viable. Hexadienol **228**, *Scheme 61*, was chosen because we required a tertiary centre at position 2 during oxygenation reactions (described in chapter 4) to avoid forming hydroxyketones by rearrangement of α-hydroxyaldehydes.

Scheme 61



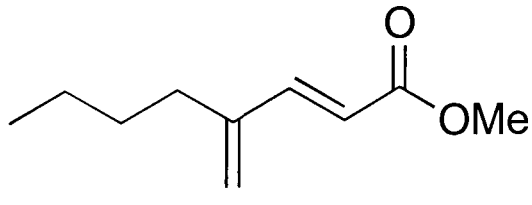
The lithium enolate of methyl acetate underwent aldol reaction with 2-butyl acrolein to form β-hydroxyester **225** in 94% yield. Attempted formation of hexadienol **228** by alkylidenation, using Takai's procedure, on hydroxyester **225** was unsuccessful. Although all the appropriate colour changes (described in chapter one) were observed, and the starting material was consumed (TLC analysis), the desired product could not be isolated from the reaction mixture. It is possible that the product was formed but had become strongly complexed to the titanium metal ion **230**. The reaction was repeated and quenched with potassium sodium tartrate rather than potassium carbonate. Potassium sodium tartrate is a bidentate ligand which should bind strongly to the titanium and so release the product, *Scheme 62*. This was unsuccessful.

Scheme 62



Protection of alcohol **225** as a TBS ether was effected in 92 % yield to make silyl ether **226**. In an attempt to combine the first two steps the aldol reaction was quenched with 1.1 mol equivalents of TBSCl at -78 °C instead of aqueous acid. However this produced a 62:38 mixture of silyl ether **226** and diene **232** respectively, *Figure 10*, in a combined yield of 95%.

Figure 10



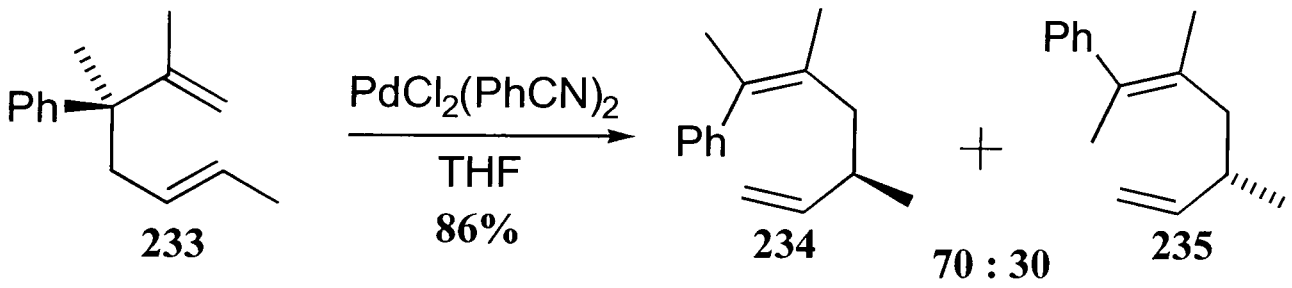
232

Takai's alkylidenation process was used to convert ester **226** into the corresponding enol ether **227** in 77 % yield. It should be noted that the reaction was only successful when neat, good quality $TiCl_4$ was employed. Using 1 mol dm^{-3} solutions of $TiCl_4$ in dichloromethane (ex Aldrich) the product could not be isolated in greater than 5% yield. Deprotection of enol ether **227** using TBAF gave the alcohol **228** in 42 % yield. 4 Å molecular sieves were used to remove water and so enhance the nucleophilicity of the fluoride ion.

The anionic oxy-Cope rearrangement was attempted on alcohol **228** using KH/18-crown-6 and also KDA/18-crown-6 without success. Other members of the Hartley research group have had similar poor results in the AOC rearrangement of methyl enol ethers, so an alternative rearrangements procedure was attempted.

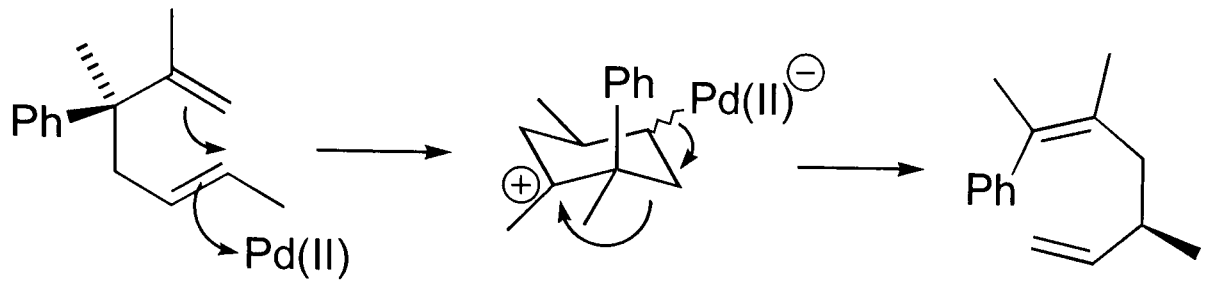
In 1982 Overman reported the use of palladium(II) for catalysing the Cope rearrangement of hexadiene **233**, *Scheme 63*.[63] They commented on the faithful nature of chiral transfer during the rearrangement and that the stereochemical results were consistent with chair-like transition states with an axially oriented phenyl group for the major isomer.

Scheme 63



The rearrangement can be represented as outlined in *Scheme 64*. The developing negative charge in the 6-membered carbocyclic intermediate **236** is distributed over three carbons and the palladium atom. Although an equatorial phenyl ring should be sterically favoured, the axial phenyl is consistent with the results. Boat like transition states would generate the enantiomers of the observed products.

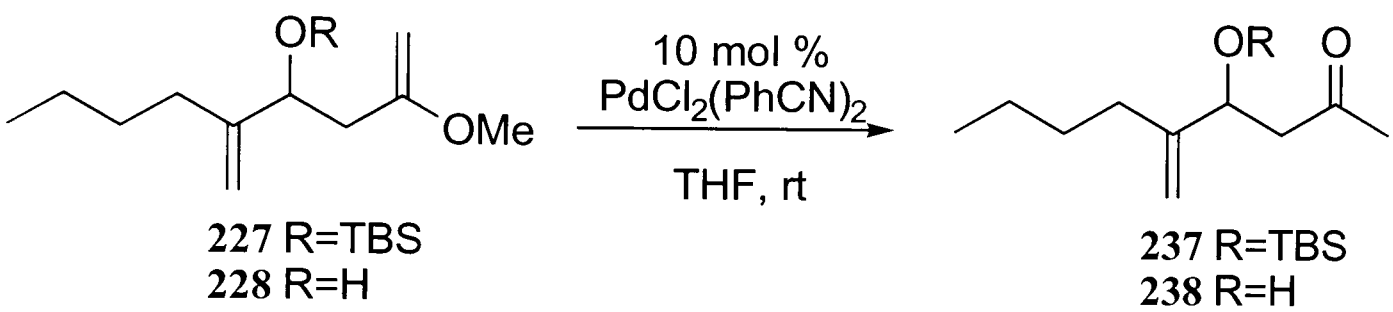
Scheme 64



233 **236** **234**

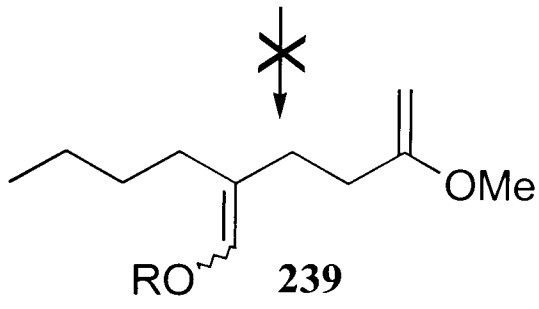
We intended to carry out analogous [3,3]-sigmatropic rearrangements on enol ethers **227** and **228**, *Scheme 65*. Treatment of both substrates with 10% $PdCl_2(PhCN)_2$ in THF resulted not in the desired oxy/silyloxy-Cope rearrangement but in clean conversion to ketones **237** and **238**.

Scheme 65



227 R=TBS
228 R=H

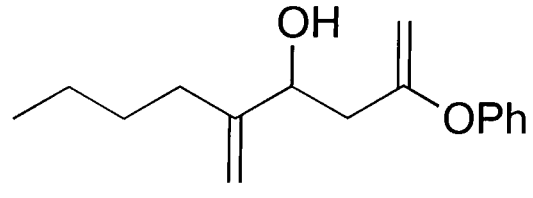
237 R=TBS
238 R=H



239

The above reaction requires water and is related to the Wacker process (the commercial preparation of acetaldehyde from ethylene employing $PdCl_2$ in an oxidative environment) and may form the basis of a mild method for enol ether cleavage. Overall we have converted a carboxylic ester to a ketone under non acidic conditions, a controlled alternative to Grignard/alkyl lithium addition to esters where double addition occurs.

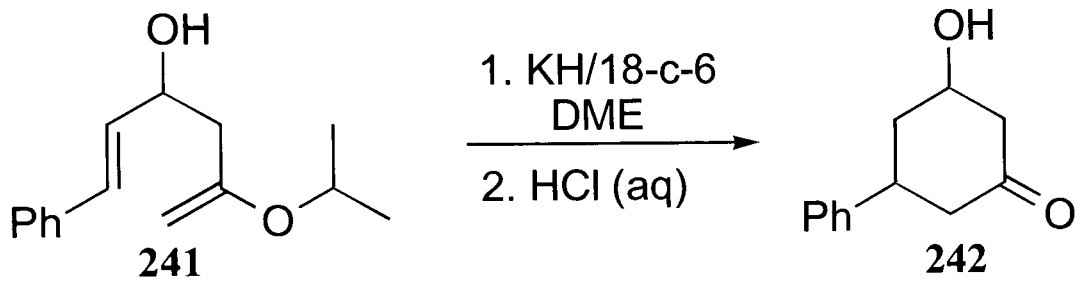
Figure 11



240

We decided that, rather than continue work on alcohol **228**, we would alter our strategy to prepare alcohol **240**, *Figure 11,* instead because: (i) volatility problems had been experienced when researching *Scheme 61*; (ii) the anionic oxy-Cope rearrangement had been successfully carried out on alcohol **241** and the product had cyclised to give β-hydroxycyclohexanone **242**, *Scheme 66*, whereas the corresponding methyl enol ether could not be rearranged satisfactorily; (iii) we believed that alcohol **240** would make it possible to prevent spontaneous cyclisation of the aldehyde product of anionic oxy-Cope rearrangement.

Scheme 66

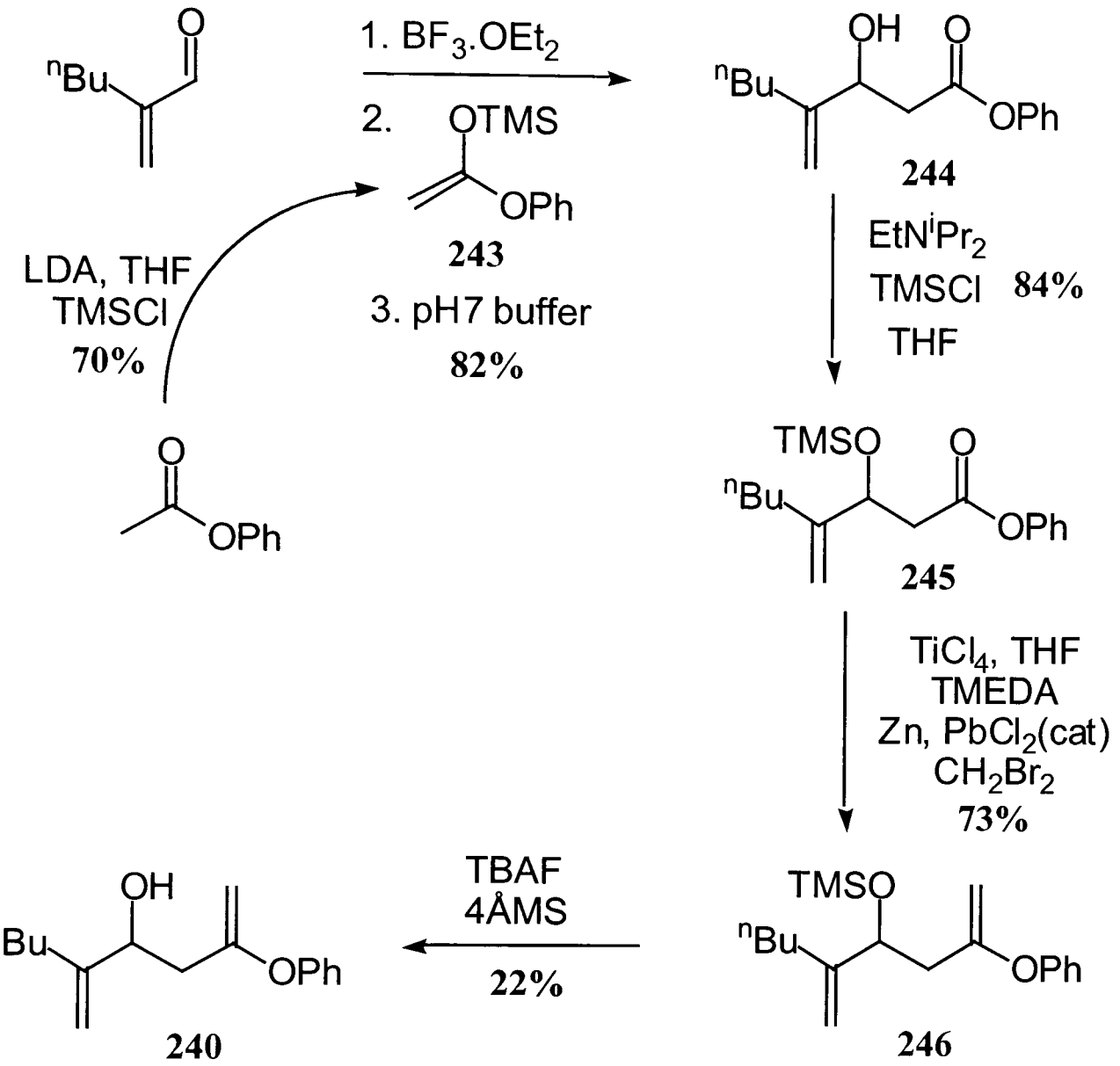


241 **242**

The failure of the methyl enol ethers is probably because they are far more readily hydrolysed compared to isopropyl and phenyl enol ethers. This would expain the instability of aldehyde **229**. Also, if hydrolysis of the methyl enol ether is faster than the intramolecular aldol reaction then it is impossible to form **242** from the methyl variant of alcohol **241**.

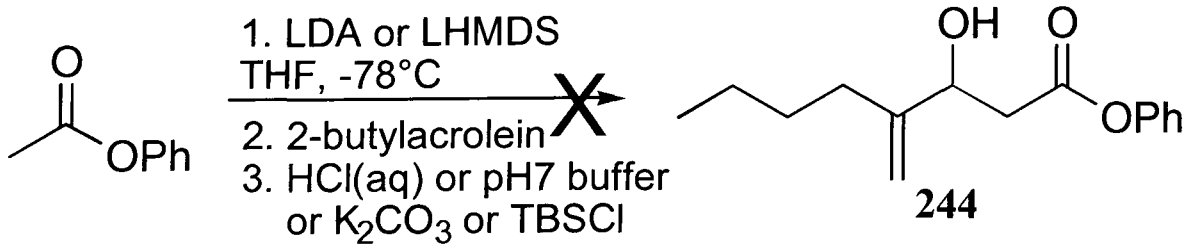
2.3 Synthesis of Aldehydes Containing an Enol Ether

Scheme 67



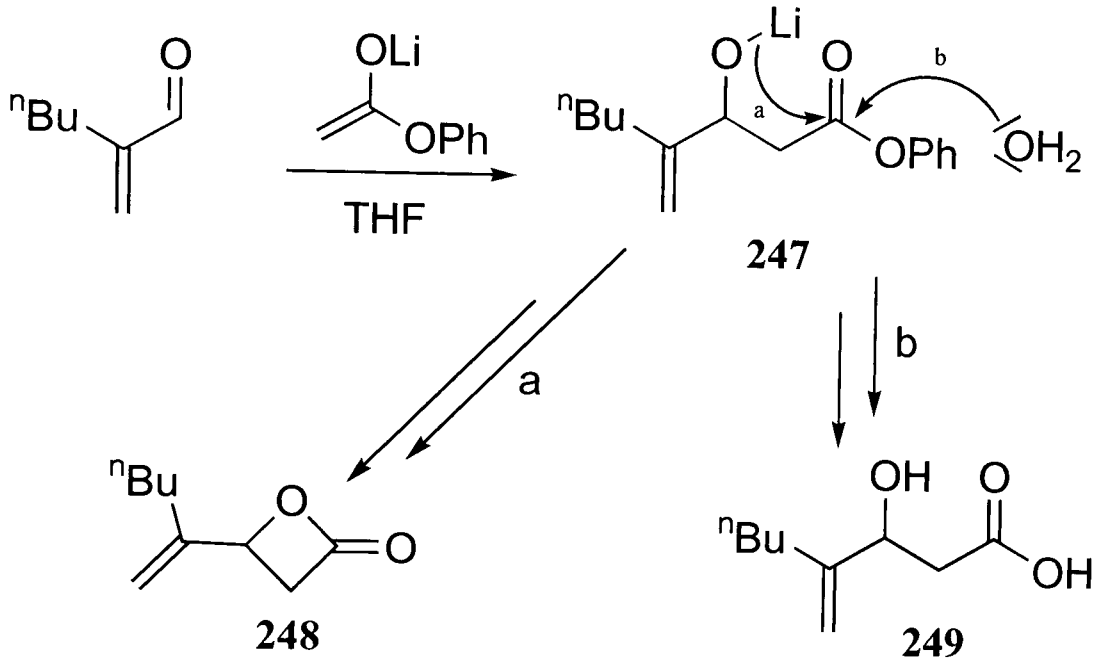
The reaction between silyl ketene acetal **243** and 2-butylacrolein, mediated by a Lewis acid, *Scheme 67*, is a Mukaiyama type aldol (see chapter one). We found it necessary to employ Mukaiyama conditions to prepare hydroxyester **244** because we were unable to form **244** using the lithium enolate of phenyl acetate, *Scheme 68*. A variety of reagents and conditions were attempted as shown. The Reformatsky reaction between phenyl bromoacetate and 2-butylacrolein mediated by activated zinc was also attempted.

Scheme 68



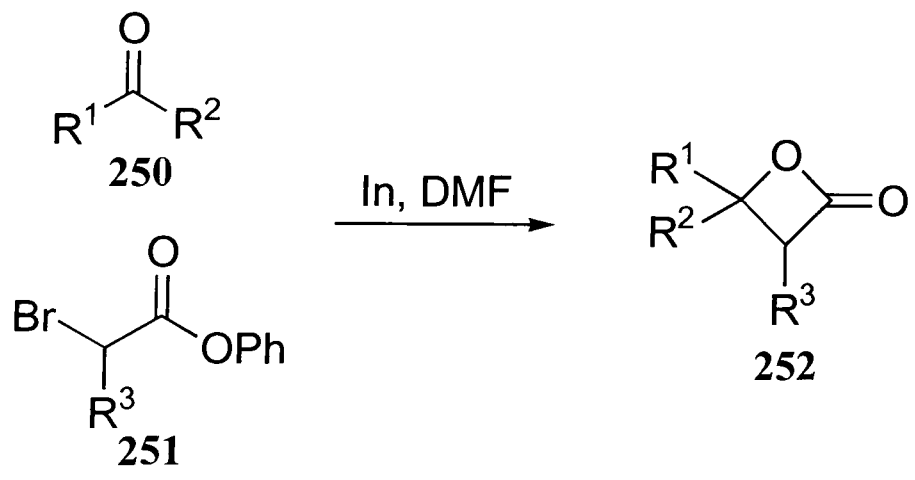
Phenoxide ion is an exceptionally good leaving group, having the negative charge distributed/stabilised over the aromatic ring, seemingly too good in this case. Intermediate alkoxide **247** is prone to intramolecular transesterification-forming β-lactone **248** (path a) and to hydrolysis - generating carboxylic acid **249** (path b), *scheme 69*.

Scheme 69



Schick and co-workers[64] reported β-lactone formation in yields of 51-81% in indium-mediated Reformatsky reactions, *Scheme 70*.

Scheme 70

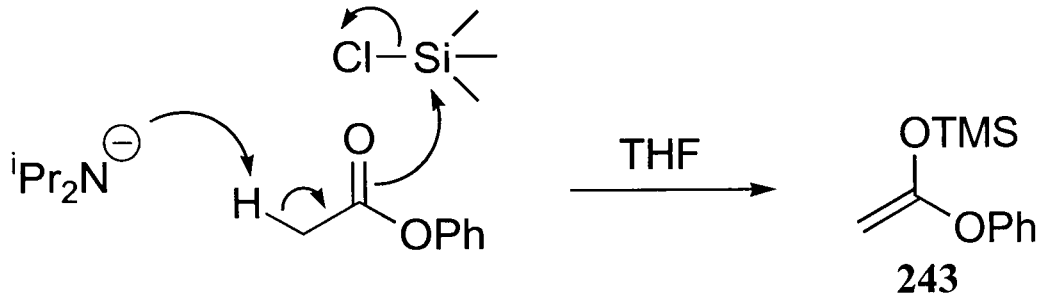


Also the groups of Danheiser and Darzens observed formation of β-lactones in aldol reactions using phenyl butanoate, isovalerate and 2-chlorobutanoate.[65] Phenyl acetate itself can form ketene (too volatile to be observed after concentration during work up) and phenoxide ion in the presence of a base, *Scheme 71*.

Scheme 71

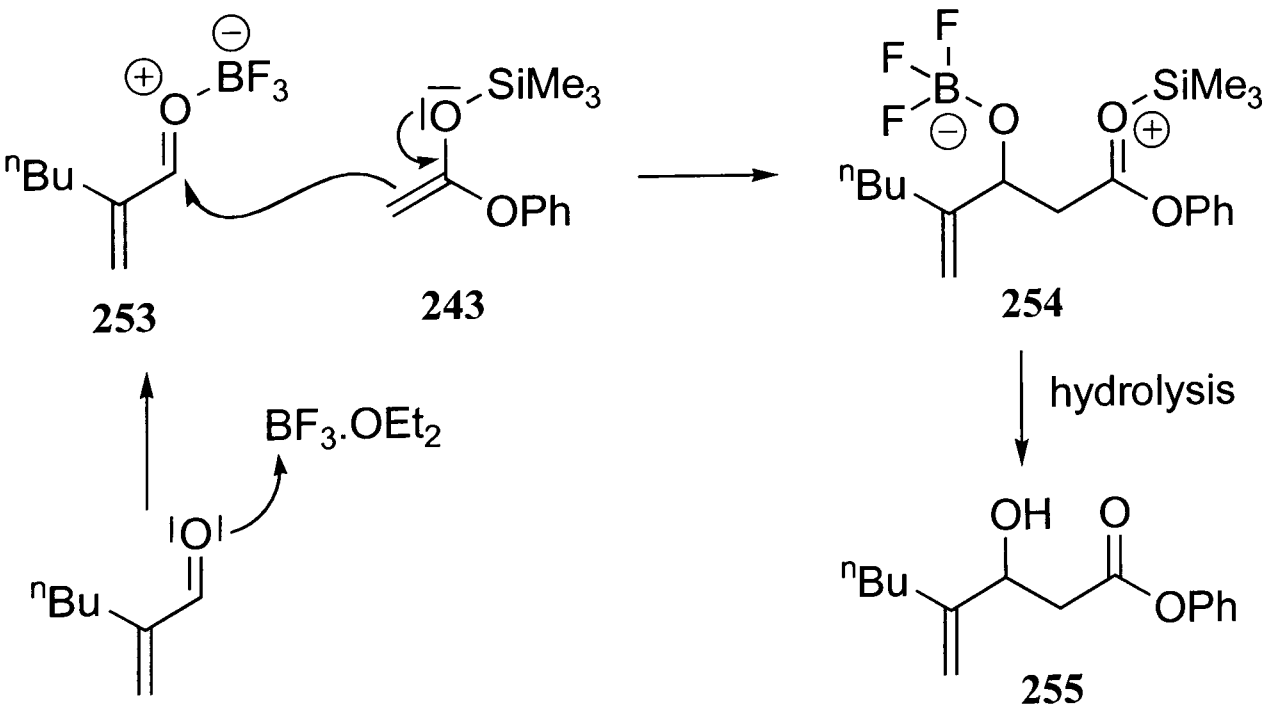
To generate 1-phenoxy-1-trimethylsilyloxyethene **243**, for use in the Mukaiyama aldol reaction, it is necessary to introduce a solution of phenyl acetate and TMSCl to a solution of LDA in THF/hexanes. This sets up an internal quenching mechanism whereby the enolate anion of the ester is trapped as it forms, *Scheme 72*. It is not possible to say whether the reaction is concerted or sequential.

Scheme 72



In this way we prevent both nucleophilic substitution and elimination of phenol from phenoxide. Silyl ketene acetal **243** was prepared in 70 % yield after distillation and was sufficiently pure (65-75%) to be used in the aldol reaction.

Scheme 73

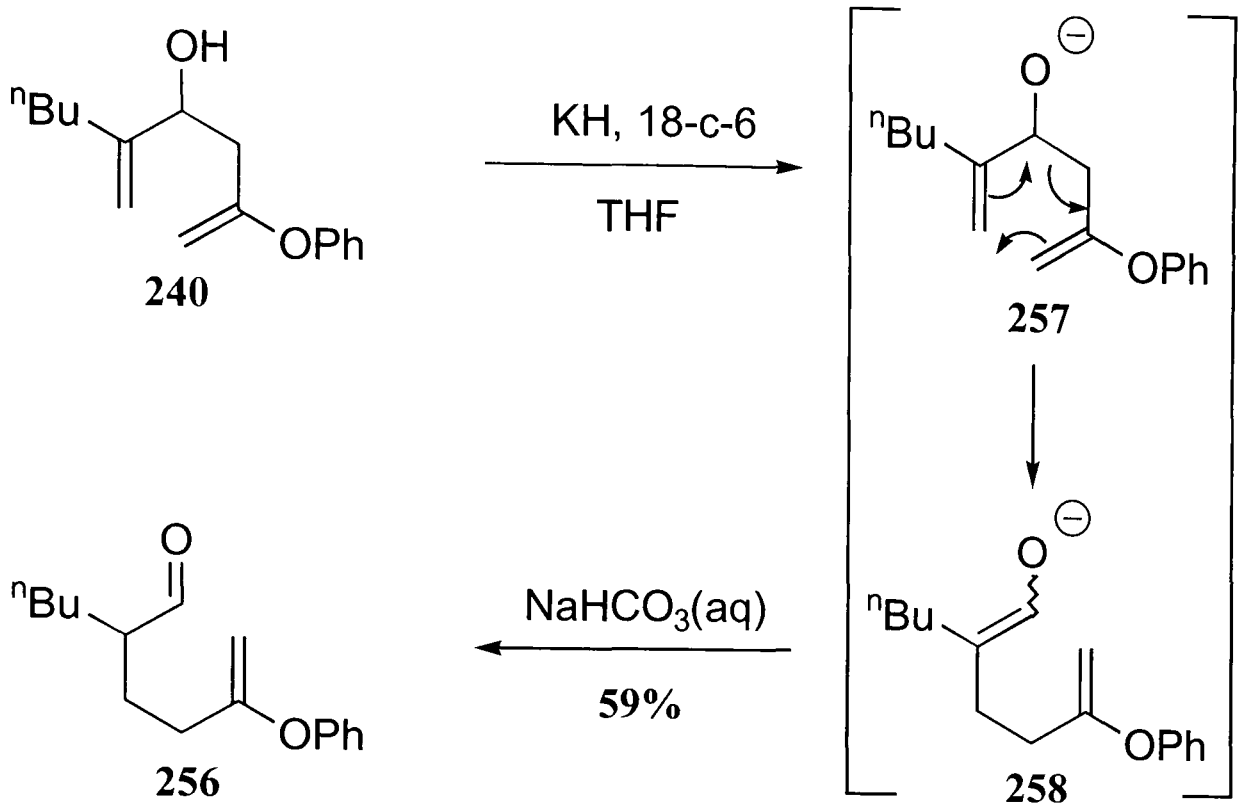


Scheme 73 illustrates the salient features of the Mukaiyama aldol reaction. The aldehyde is precomplexed to the Lewis acid, intermediate **253**, at -78 °C, *via* the empty p-orbital on boron, then the silyl ketene acetal is introduced. The 'electron push' from the silicon atom makes the silyl ketene acetal strongly nucleophilic at the terminal end of the double bond and it reacts with the activated aldehyde. Intermediate **254** illustrates why β-lactone formation is minimised. Whereas the alkoxide **247** generated in the LDA induced aldol is relatively labile, *Scheme 69*, the same is not true of intermediate **254**, *Scheme 73*. The negative charge is spread over the boron and fluoride atoms significantly reducing the nucleophilicity of the 'alkoxide' and hence depressing formation of β-lactone **248**.

β-Hydroxy ester **244**, *Scheme 67*, was prepared in 82% yield by Mukaiyama aldol reaction. While researching our route we found that we could obtain a higher overall yield for the preparation of the AOC rearrangement substrates by changing the protecting group from *tert*-butyldimethylsilyl to trimethylsilyl. This change made the route faster, simpler and less expensive, i.e. much more efficient. Alcohol **244** was protected as TMS ether **245** in THF in 84 % yield (crude). Takai's alkylidenation reaction afforded phenyl enol ether **246** in a crude yield of 73 %. Deprotection of enol ether **246** using 1 mol dm^{-3} TBAF in THF followed by exhaustive purification by chromatography on alumina gave hexadienol **240**, the substrate for the AOC rearrangement, in 22% yield. Treatment of **240** with 3 equivalents of potassium hydride and 2 equivalents of 18-crown-6 in 60 volumes of tetrahydrofuran, followed by quenching with aqueous saturated sodium hydrogen carbonate, furnished aldehyde **256**, *Scheme 74*, in 59 % yield, after chromatography on deactivated alumina.

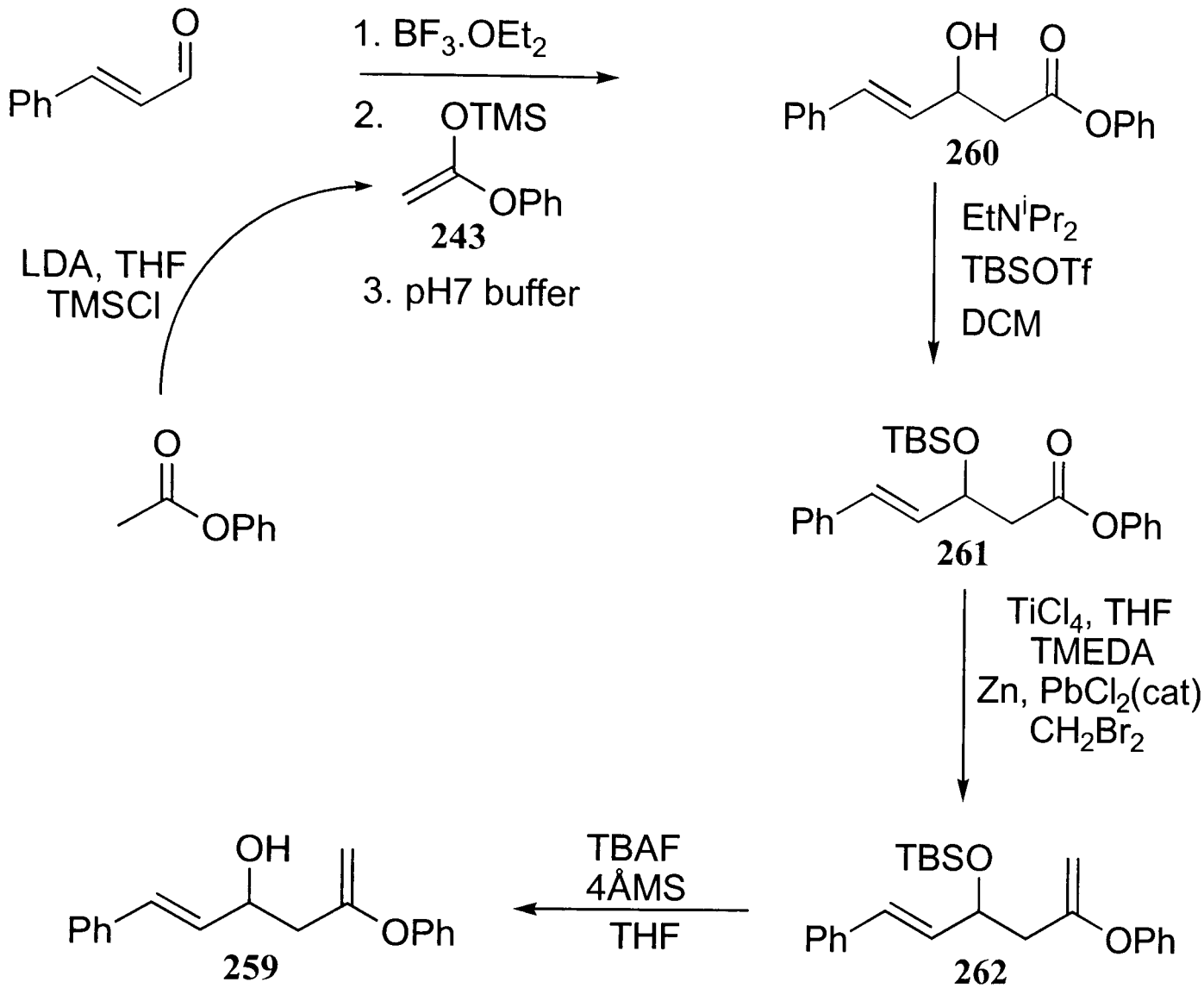
Compound **256** contains an electrophilic centre, the aldehyde portion, and a nucleophilic centre, the enol ether moiety, in a favourable relationship for cyclisation. The stability of this compound is probably due to the electron withdrawing nature of the phenyl ring as part of the enol ether moiety, since it reduces the nucleophilic character at carbon-6. Compound **256** is the first reported example of a compound bearing an aldehyde and an enol ether in a 1,5-relationship.

Scheme 74



Having established our route we went on to prepare alcohol **259**, *Scheme 75*. β-Hydroxy ester **260** was prepared in a modest yield of 52 % by Mukaiyama aldol reaction using **243** and *E*-cinnamaldehyde. We believe that the low yield was due to hydrolysis of the ester during work-up. In fact, we observed phenol as a by-product at every stage during preparation of alcohol **259**. The product was triturated from hexane, rather than chromatographed, and was partially contaminated with the aldehyde. Aldol **260** was protected as a TBS ether, **261**, by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate and Hunig's base in 80% yield after chromatography. Alkylidenation, using Takai's procedure, afforded enol ether **262** in 47 % yield (cf. methoxy enol ether **227**, *Scheme 61*). The lower yield in this case is probably a consequence of the greater steric demand of the phenyl ring over a methyl group. Deprotection of **262** using TBAF in THF provided hexadienol **259**, the substrate for the AOC rearrangement in 32 % yield, i.e. 6.2% overall from *trans*-cinnamaldehyde. and 12% from aldol **260**.

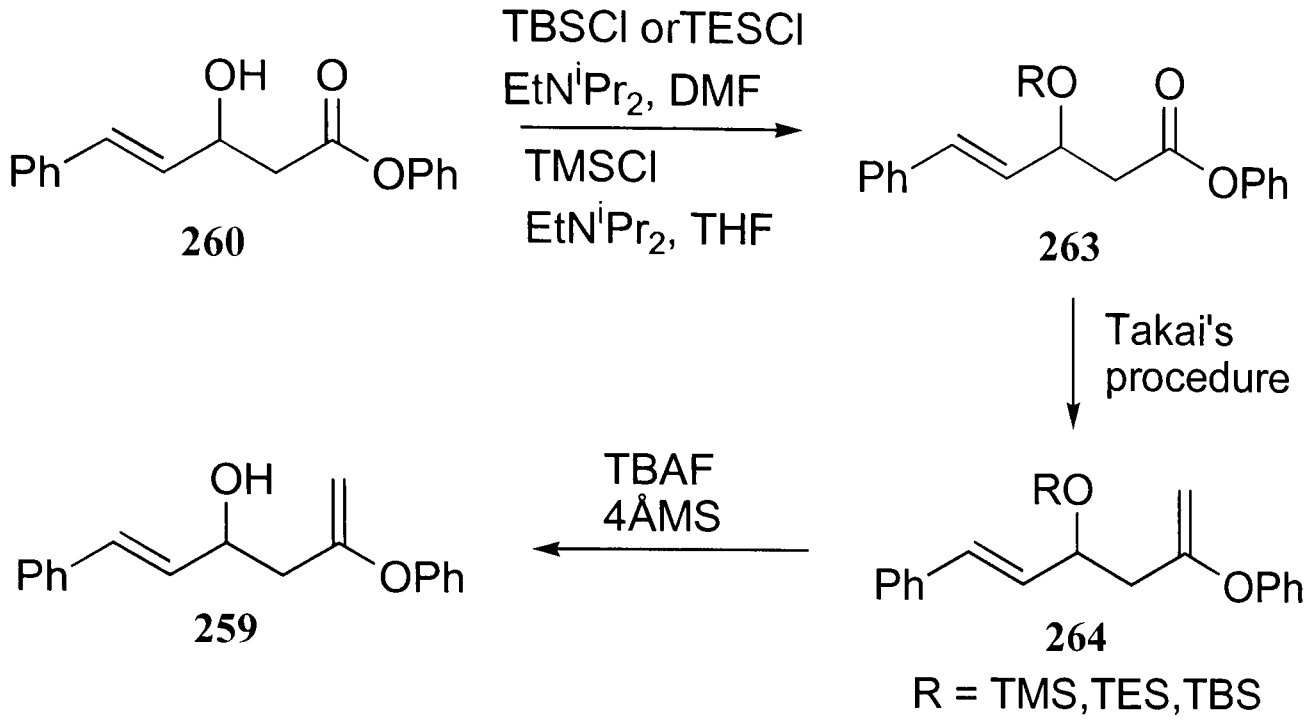
Scheme 75



It was not difficult to observe that the greatest problem with our route lay in the removal of the *tert*-butyldimethylsilyl protecting group, a yield of 32 % was not acceptable. We had limited options in the choice of protecting group; enol ethers are acid labile so we could not use an acetal and groups which require hydrogenolysis, e.g. benzyl groups, were also unacceptable because of the double bonds present in our substrates. Hence, we decided to study the route with other silicon based protecting groups that should be more easily removed.

We tried first the triethylsilyl group and observed an 8% increase in the overall yield of alcohol **259** over the three steps shown in *Scheme 76* in comparison with the TBS protecting group. The protection reaction was slightly less effective, 66% compared to 80%, but the deprotection was 100% more efficient than removal of the TBS group. The yield of the alkylidenation reaction was almost identical, 47% for R=TBS and 44% for R=TES.

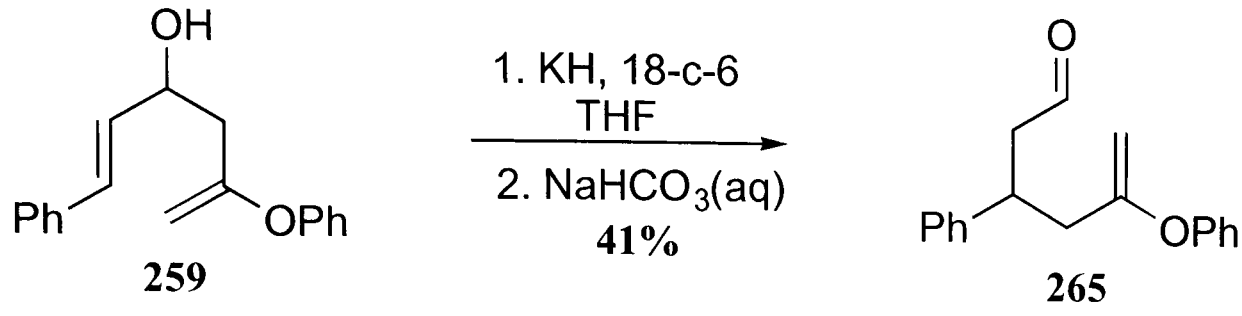
Scheme 76



When we evaluated the use of the trimethylsilyl protecting group we had to make a number of small alterations to the reaction conditions. The protection reaction used THF rather than DMF as solvent because the hydrochloride salt of Hunig's base was soluble in DMF but insoluble in THF. This simplified the work-up procedure to a filtration followed by concentration. The material produced was carried forward without further purification through to hexadiene **259**, which was purified by chromatography. This gave a substantial saving in time and expense relative to the TBS and TES protecting groups. Since we did not purify compounds **263** and **264** when R=TMS we considered the yields of the silylation and alkylidenation too inaccurate to report realistically, however, alcohol **259** was prepared in 25% yield over 3 steps from ester **260**, i.e. an average yield of 63% for each step. To summarise, using the TMS protecting group we generated hexadienol **259** 5% more efficiently than using TES and 13% more effectively than employing the TBS protecting group.

The AOC rearrangement of hexadienol **259** in THF followed by aqueous basic quench generated aldehyde **265**, *Scheme 77*, in 41% yield. Compound **265** is another member of the family of aldehydes bearing an enol ether group.

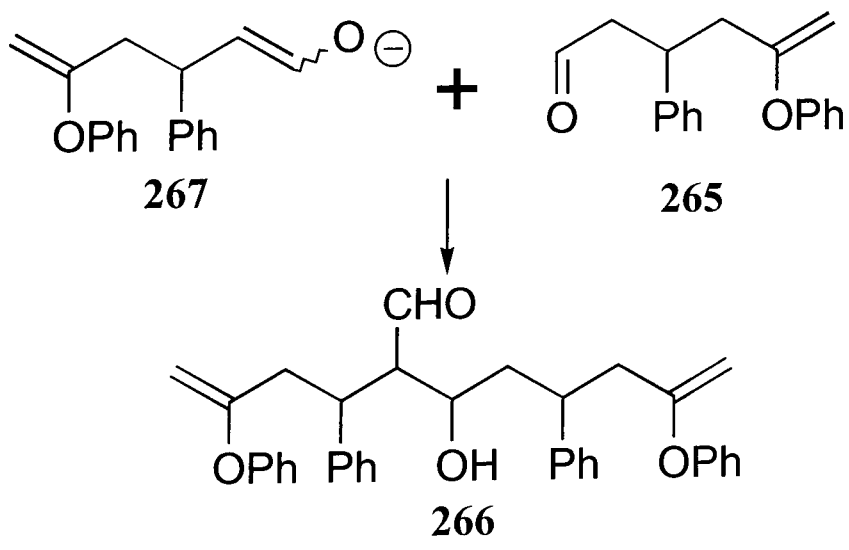
Scheme 77



A number of related AOC rearrangements had been carried out within our research group which had employed 1,2-dimethoxyethane as the reaction solvent. We decided to find out what effects, if any, DME might have on our reaction. We observed an increase in the yield of aldehyde **265** to 61 % with the crude product virtually pure by ^{1}H NMR spectroscopy. The contaminant, 18-crown-6, could be washed out with water with the yield falling to 56%.

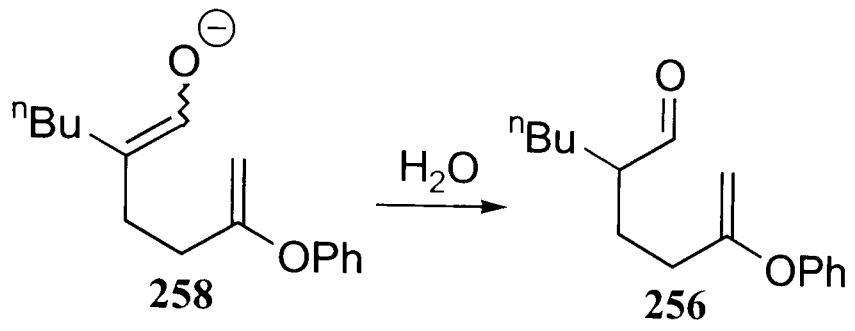
In early attempts to form aldehyde **265** we often observed the formation of aldehyde **266**, *Scheme 78*. **266** formed as the result of an aldol reaction between enolate **267** and aldehyde **265**, effectively a dimerisation during the quench. In fact, when the AOC rearrangement was carried out in only 12 volumes of THF bis enol ether **266** was the sole product (75 % yield). Although this was a potentially useful reaction, generating four stereocentres (three contiguously) and a number of manipulatable functional groups, it was difficult to envisage a strategy by which we could exert some measure of control over its stereochemical outcome. To overcome this problem we reversed the quench procedure, i.e. we poured the reaction mixture into aqueous sodium hydrogen carbonate, diluting the mixture, so that enolate **267** was quenched before it could react with aldehyde **265**.

Scheme 78



Enolate **258**, generated by the AOC rearrangement of alcohol **240**, is hindered and therefore less reactive than enolate **267**. Hence, when the reaction was partially quenched and enolate **258** and aldehyde **256** were present together for a short time, no dimerisation occurred, *Scheme 79*.

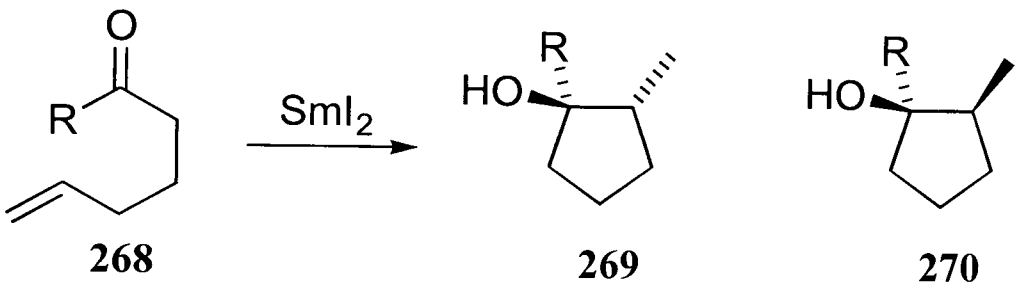
Scheme 79



258 **256**

2.4 Attempted Synthesis of Cyclopentanols

Scheme 80



268 **269** **270**

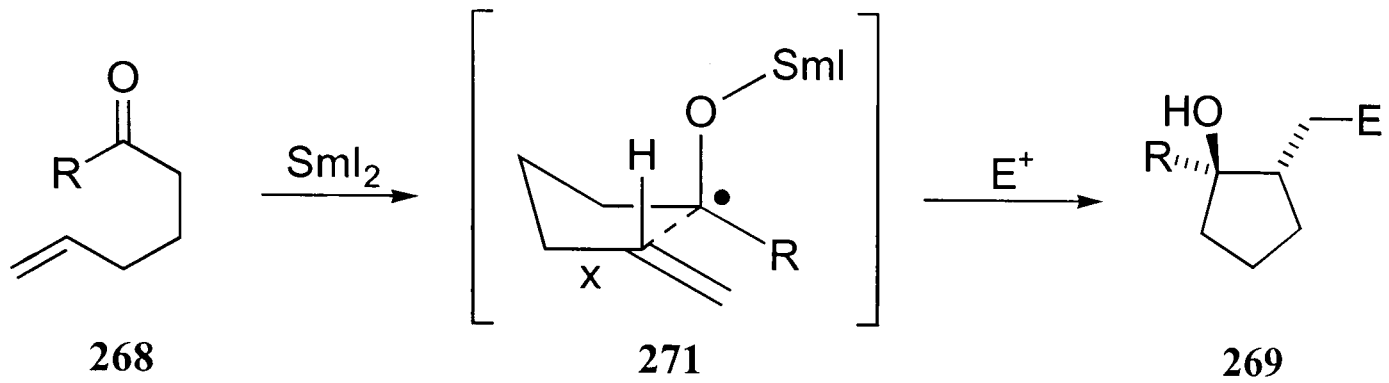
Having generated aldehydes **256** and **265** we wished to find a use for them. Molander and co-workers[66] have recently published the synthesis of 5-membered carbocycles **269** and **270** by reductive cyclisation of δ,ε–unsaturated ketones **268** using samarium diiodide, *Scheme 80*. Their results are shown in *Table 8*.

Table 8

R	Yield (**269**+**270**)	Ratio **269**:**270**	Reaction time/h
Me	86	>150:1	0.25
^{i}Pr	85	23:1	0.5
^{t}Bu	78	3:1	8
Ph	48	<1:150	2

The stereoselectivity in this reaction probably arises from electrostatic repulsion between the oxyanion and the filled π-orbital of the double bond, *Scheme 81*. Molander found that as the steric demand of R increased, the stereoselectivity in the reaction decreased, eventually reversing, and theorised that the steric strain in the folded envelope reacting conformation **271** was reduced by rotation around bond x orienting the π-system away from R.

Scheme 81

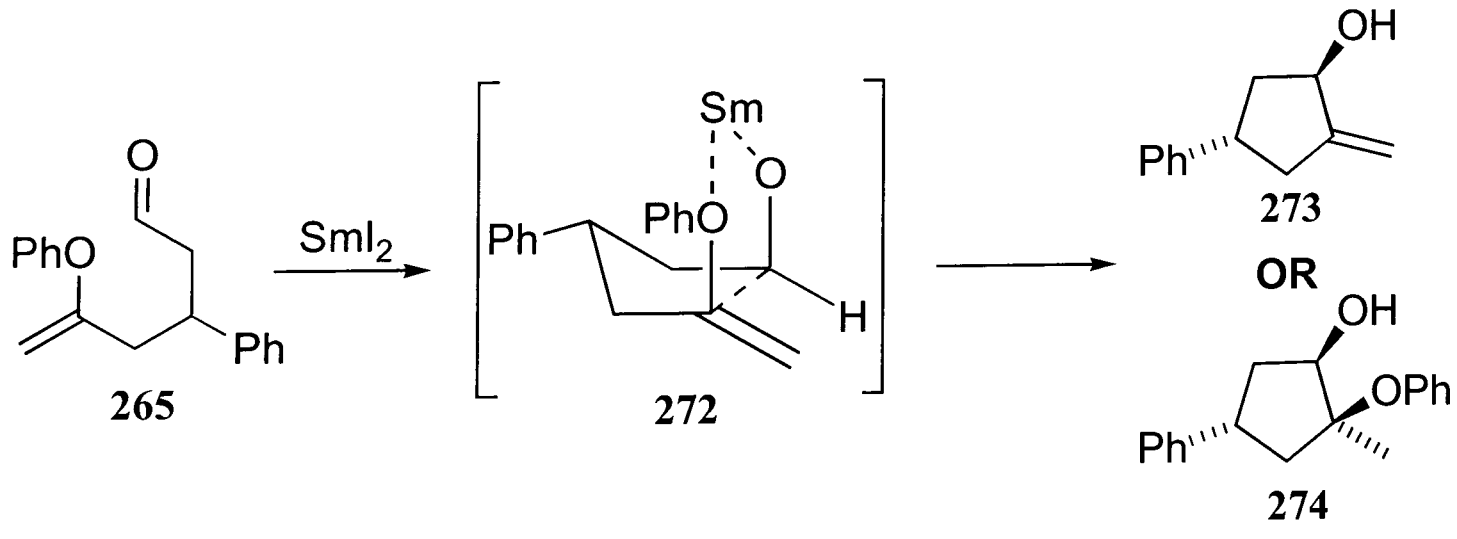


268 **271** **269**

We proposed to overcome such problems by introducing another chelation site in the substrate, *Scheme 82*, giving rise to enhanced selectivity even as R increases in volume. We also postulated that the phenyl substituent on the forming carbocycle would be oriented on the face opposite to the samarium metal.

We attempted the reductive cyclisation a number of times under a variety of different conditions. In all cases the samarium diiodide was freshly prepared by the reaction of samarium on 1,2-diiodoethane. Our results are outlined in *Table 9*.

Scheme 82



265 **272** **273** **274**

Table 9

SmI_2 equiv.	solvents	time (min)	result
2.8	THF/^{t}BuOH	60	aldehyde reduction
2.2	THF/DMPU	20	aldehyde reduction & pinacol formation
2.2	THF/DMPU/^{t}BuOH	120	aldehyde reduction & some cyclisation & pinacol formation
2.2	THF/DMPU ^{t}BuOH added after 3h	360	cyclisation & pinacol formation

Unfortunately we were unable to isolate either of the two postulated 5–membered carbocycles **273** and **274**. The most common result was simple reduction of the aldehyde in the substrate **265** to the corresponding alcohol.

Future work in this area might include slow addition of the aldehyde to lower its concentration and impede pinacol formation and use of HMPA as a co-solvent since it significantly enhances the reduction potential of the samarium diiodide.

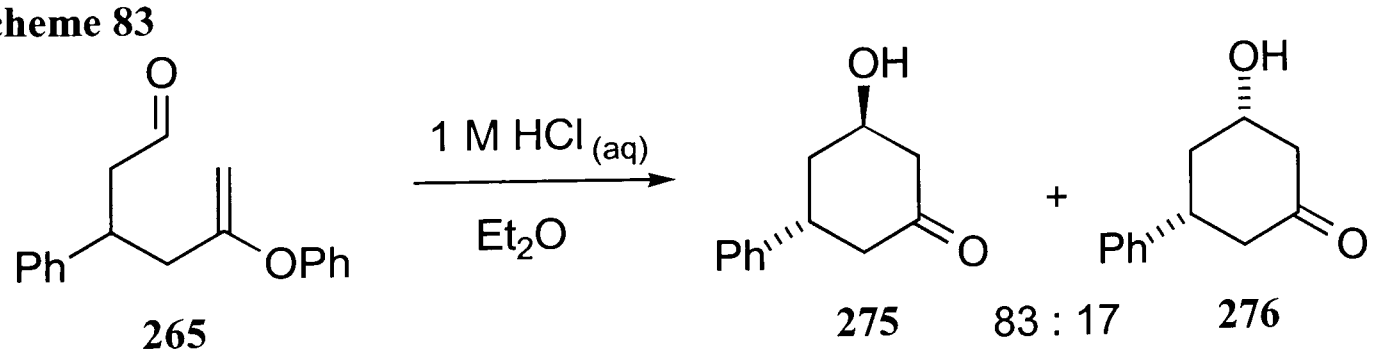
3. SYNTHESIS OF β–HYDROXYCYCLOHEXANONES

Aldehydes with an enol ether moiety in the 5-position, including **256**, *Scheme 74*, and **265**, *Scheme 77*, are the building blocks used for the preparation of β–hydroxycyclohexanones. As described below, our methodology can be used to generate such β–hydroxycyclohexanones bearing up to four controlled stereogenic centres. I will use our results to illustrate the factors which govern chiral transfer in the AOC rearrangement. Where the information is available I will discuss the reasons why we observe both boat and chair like transition states for the AOC rearrangement. Finally, I will describe our studies towards the synthesis of analogues of naturally occurring Penihydrone.

3.1 β–Hydroxycyclohexanones Bearing Two Chiral Centres (racemic)

Treatment of aldehyde/enol ether **265** with aqueous hydrochloric acid led to formation of β–hydroxycyclohexanones **275** and **276**, *Scheme 83*, as an 83:17 mixture of *anti* to *syn* isomers respectively, in a combined yield of 58%.

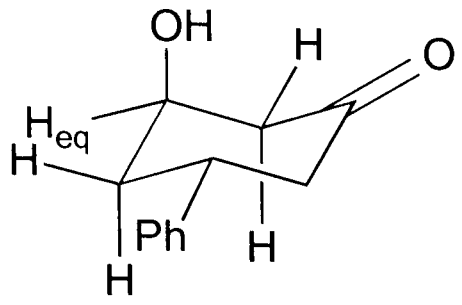
Scheme 83



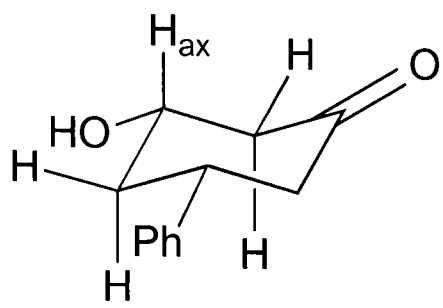
Thus, we observed a strong preference for an axially oriented hydroxyl group in the product. The signal in the ^{1}H NMR spectrum of the crude product at 4.57 ppm corresponds to C*H*OH for the major isomer. It is a poorly resolved, narrow quintet with a coupling constant of 3.0 Hz. This is typical of axial-equatorial and equatorial-

equatorial couplings in a cyclohexyl ring. The signal for C*H*OH of the minor isomer resonates at 4.05 ppm and is a triplet of triplets with couplings of 11.0 Hz and 4.6 Hz.

Figure 12



275

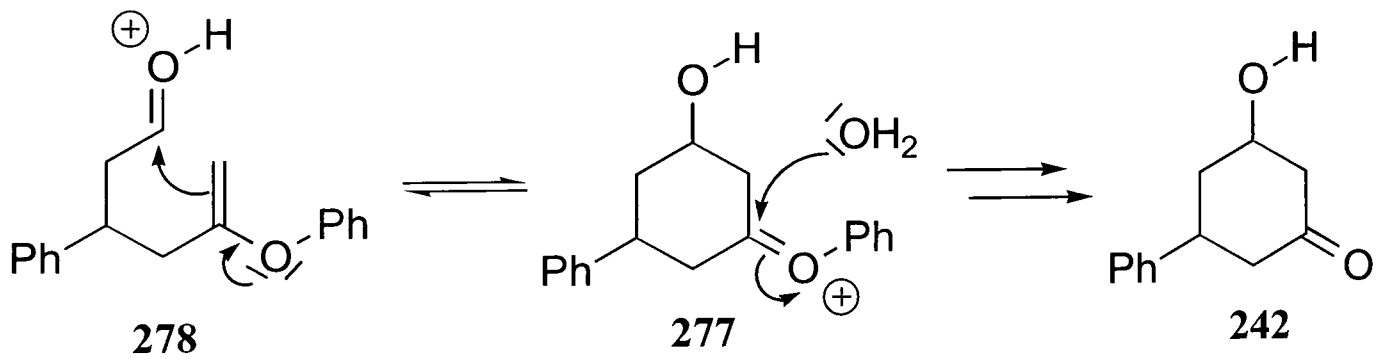


276

The larger *J* value is typical of axial-axial couplings which are impossible for H_{eq} **275** but possible for H_{ax} **276**, *Figure 12*, hence isomer **275**, with an axial hydroxyl, is the major product of the acid induced intramolecular aldol reaction.

The mechanism of the acid induced cyclisation and subsequent hydrolysis of intermediate oxonium ion **277** is briefly outlined in *Scheme 84*. Protonation, and therefore activation, of the aldehyde, followed by nucleophilic attack from the enol ether portion generates the 6–membered ring.

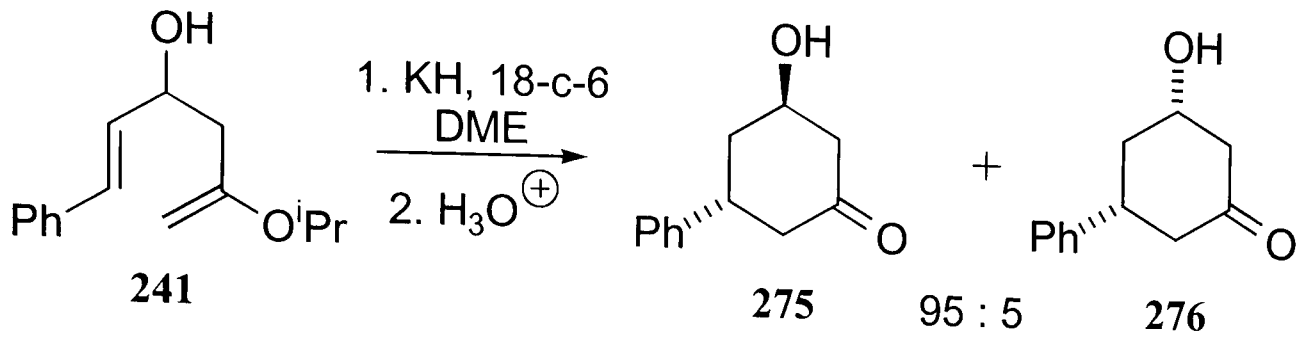
Scheme 84



278 **277** **242**

When the corresponding isopropyl ether **241**, *Scheme 85*, is used in the AOC rearrangement there is an even greater preference for the 3,5-*anti* relationship, i.e. an axial hydroxyl in the β-hydroxycyclohexanone. In this case compound **275** was isolated in 43% yield by trituration from diethyl ether at 0°C.

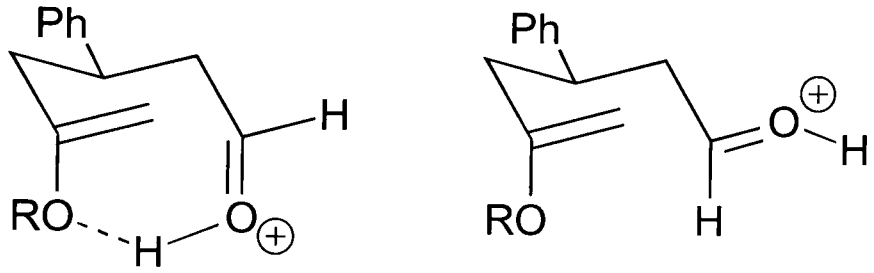
Scheme 85



241 **275** **276**

One explanation for the selectivity for the 3,5-*anti* diastereomer **275** is that intramolecular hydrogen bonding favours reaction *via* conformation **279**, *Figure 13*. When the aldehyde carbonyl is oriented *pseudo*equatorially **280** coordination is no longer possible. At first our results seem to lend weight to this theory. Phenyl rings are electron withdrawing and as such the electron density on the oxygen atom of a phenyl enol ether is lower than that on the oxygen atom of an isopropyl enol ether; consequently the former is less able to chelate to the proton and hence the lower selectivity for the 3,5-*anti*-β-hydroxycyclohexanone **275** in the cyclisation of **278**.

Figure 13



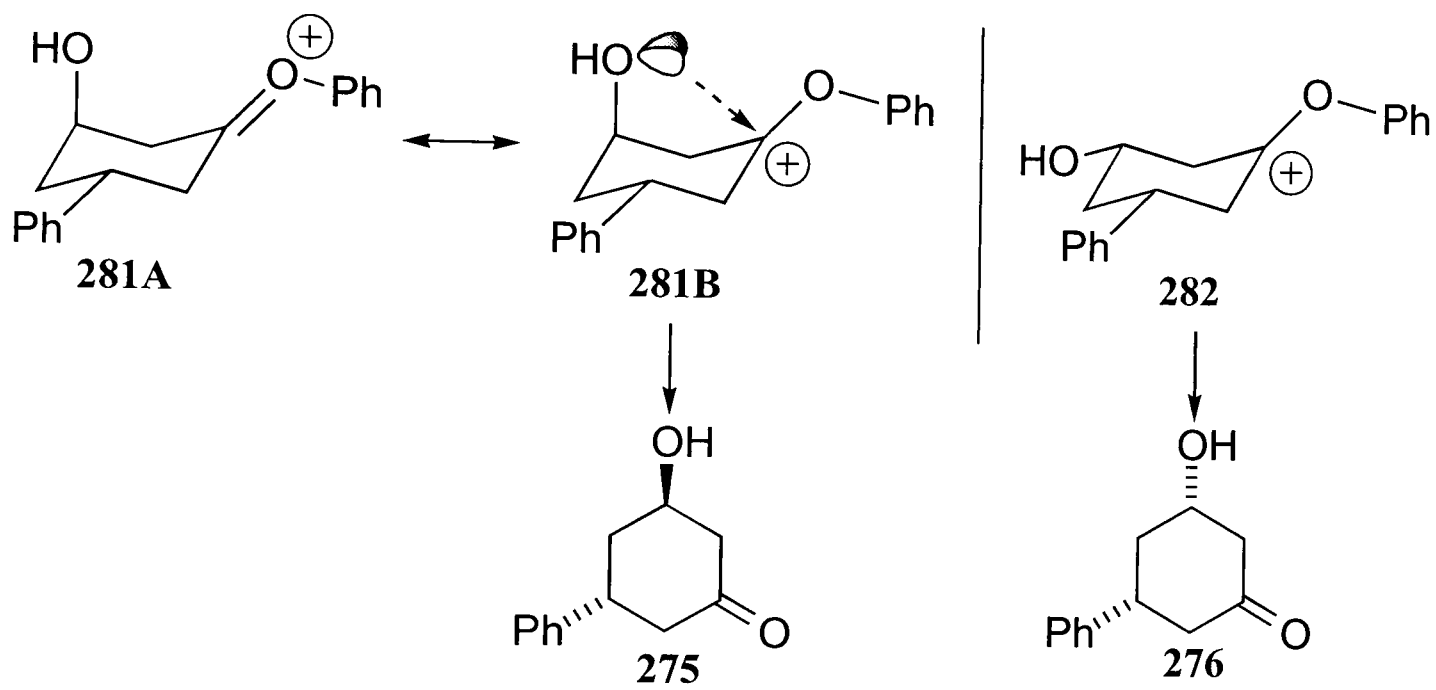
279 **280**

However, coordination of the oxygen atom of the enol ether with a proton would reduce the nucleophilicity of the enol ether and slow the cyclisation reaction. It was clear that the reaction was not under thermodynamic control as the ratio of **275** to **276** varied depending on the enol ether (isopropyl or phenyl). We decided to examine intermediate oxonium ion **281** and **282**, *Scheme 86*, in greater detail. **281A** and **281B** can be considered to be two extreme representations of an oxonium ion. In terms of bond length **281A** is more correct, however, the charge on the system resides mainly on the carbon end of the oxonium ion. The axial hydroxyl in intermediate **281** donates electron density into the empty p-orbital of the carbon atom of the oxonium

group. This interaction stabilises intermediate **281** relative to intermediate **282** that has an equatorial hydroxyl group. If the two intermediates can rapidly interconvert by retro-aldol/aldol reaction and rates of hydrolysis are similar. This accounts for selective formation of 3,5-*anti* cyclohexanone **175**.

Alternatively, the developing overlap between the axial hydroxyl and the oxonium group will stabilise the transition state leading to **281** and may favour it kinetically. Thus 3,5-*anti* cyclohexanone **275** will be favoured even if interconversion between **281** and **282** is slow.

Scheme 86

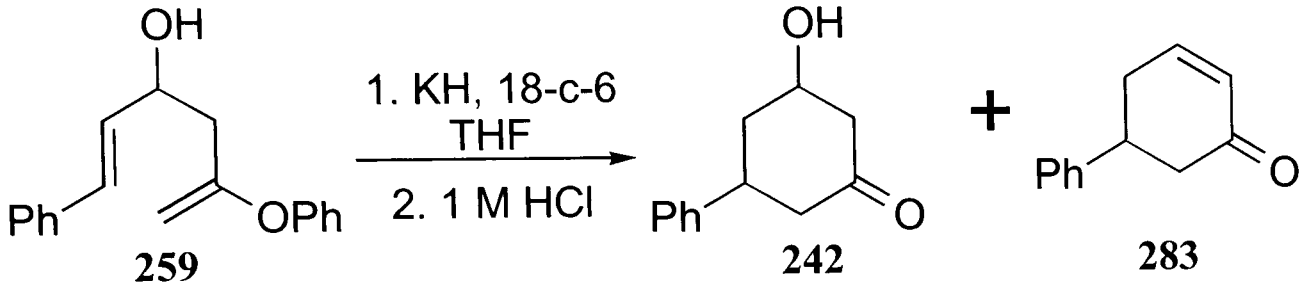


Dr. Jonathon Goodman of Cambridge University carried out a number of molecular modelling calculations on our behalf to test our revised theory. Using MM2* there is a bias of 1.2 $kJmol^{-1}$ for an axial hydroxyl which equates to a ratio of roughly 2:1 at room temperature. The reason is an electrostatic interaction between the lone pairs on the oxygen atom of the hydroxyl and the carbon atom of the carbonyl group. *ab initio* RHF/3-21G calculations also favoured an axial hydroxyl. The semi-empirical method AM1 favours an equatorial hydroxyl in a hydroxy cyclohexanone but for an oxonium ion, e.g. intermediate **281**, AM1 favours an axial hydroxyl group.

When the AOC rearrangement was carried out on alcohol **259** and the reaction was quenched with aqueous acid,[67] *Scheme 87*, rather than aqueous base,

hydroxycyclohexanone **242** is generated directly in 58% yield. The product distribution is little different (87:13 *anti–syn*) from the cyclisation of isolated aldehyde **265**. We also observed formation of enone **283**, as the result of elimination of water from **242**, as 9% of the product. [ratios determined by ^{1}H NMR spectroscopy]

Scheme 87

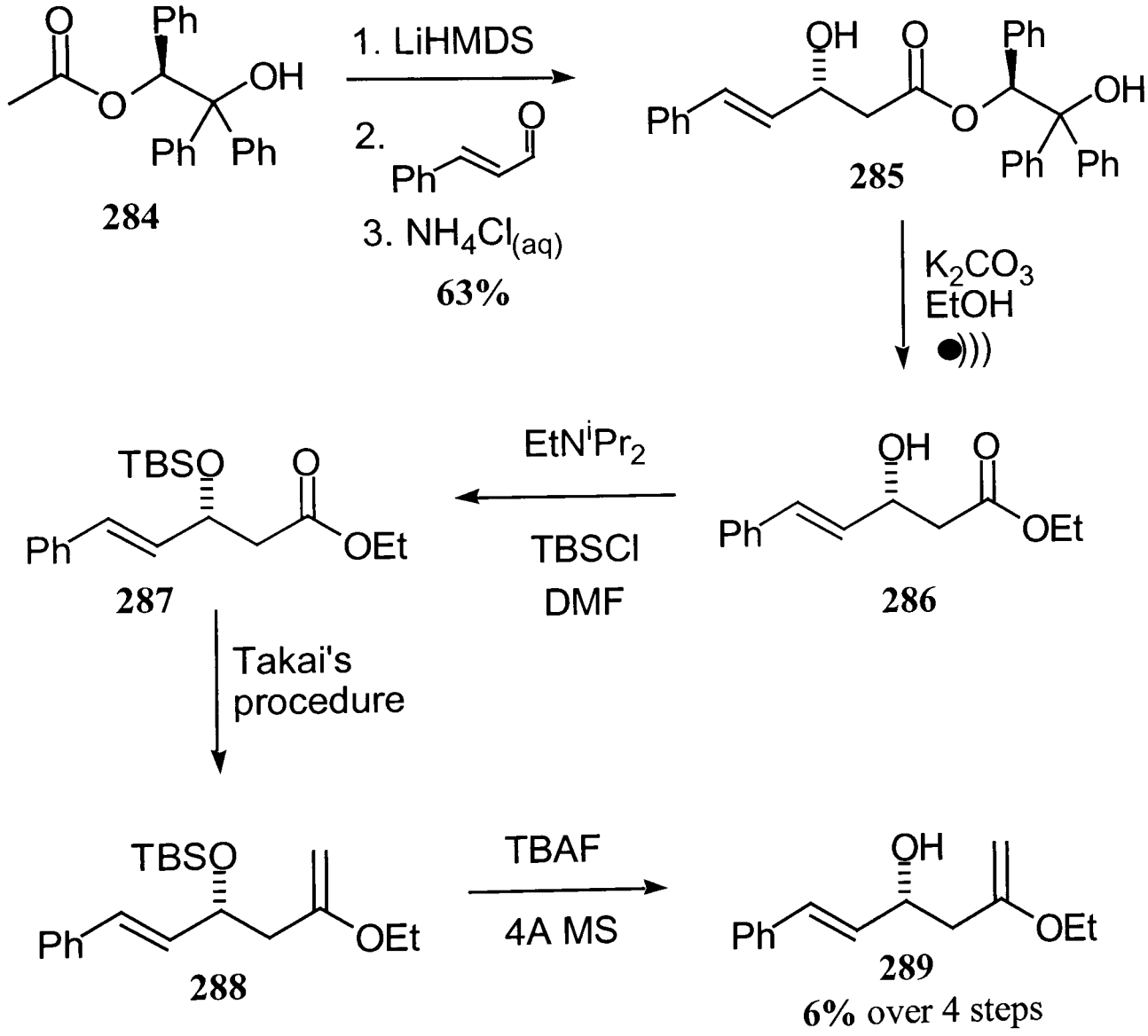


259 **242** **283**

3.2 β–Hydroxycyclohexanones Bearing Two Chiral Centres (enantiomerically enriched)

Having developed a route to racemic β-hydroxycyclohexanones bearing two chiral centres, we wished to develop a route to enantiomerically enriched compounds. The two most practical methods of introducing asymmetry into the synthesis were resolution and asymmetric induction in the aldol reaction using a chiral auxiliary. Resolution was not desirable since it is a lengthy and wasteful process. We chose to use the monoacetate of Braun's auxiliary **284** as a means of chiral induction.

Scheme 88

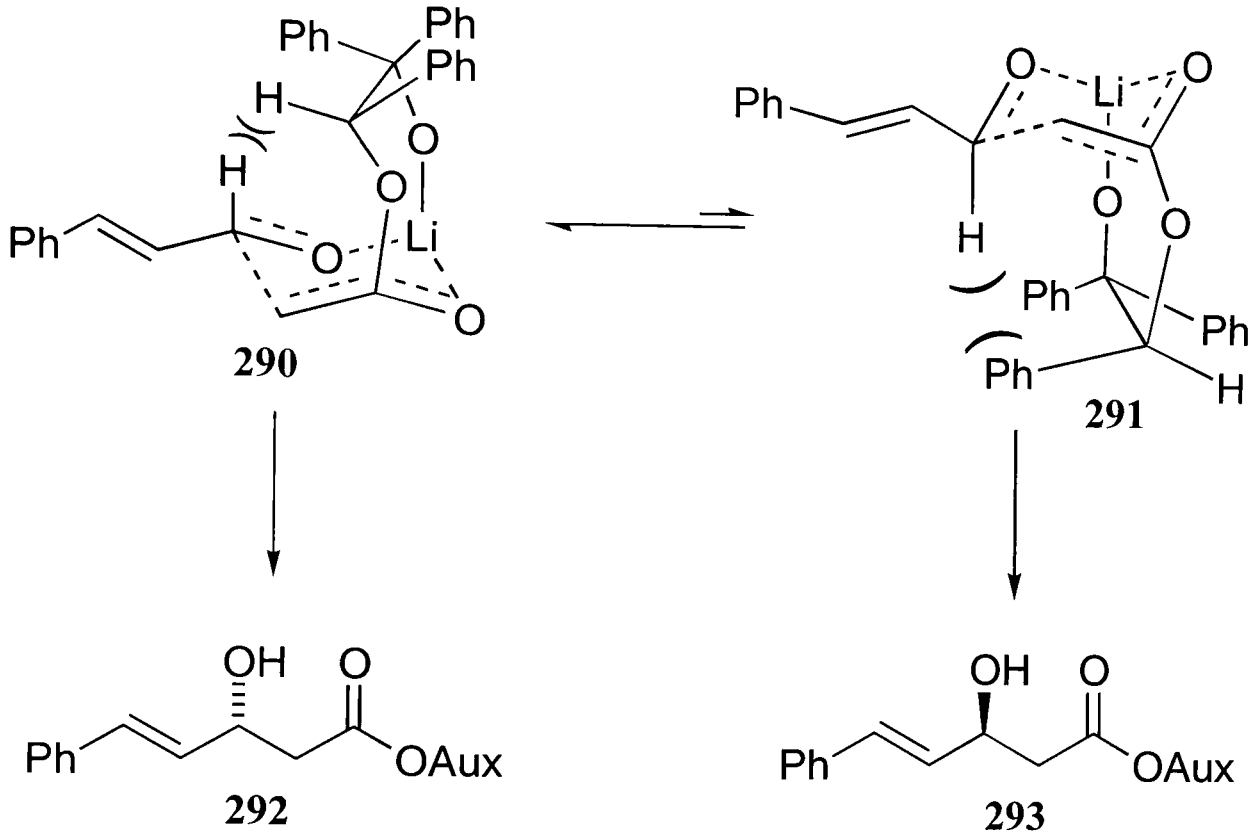


Braun's auxiliary is derived from naturally occurring mandelic acid by double addition of phenyl magnesium bromide followed by selective acetylation of the secondary alcohol. The mechanism for the stereoselectivity in the asymmetric aldol reaction has never been reported. The fact that Braun's auxiliary has not evolved over

the years and that Braun actually used resolution techniques to boost the enantiomeric excess points to a general lack of understanding concerning the transition state.

Braun's monoacetate was doubly deprotonated with lithium hexamethyldisilazide and reacted with *E*-cinnamaldehyde in THF/hexanes to generate aldol **285**, *Scheme 88*, in a crude yield of 97%, dr = 89:11. Recrystallisation from isopropanol lowers the yield to 63% but dr is now 96:4.

Scheme 89



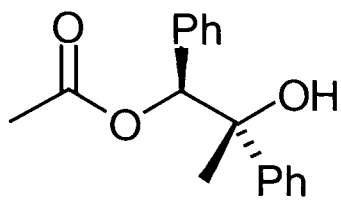
Scheme 89 illustrates one model which may explain the selectivity in the aldol reaction. It involves a bridged bicyclic system where the tertiary alkoxide is also coordinated to the lithium ion in a Zimmerman-Traxler transition state forming a seven membered trioxolo-metallocycle. In conformation **290** the aldehydic hydrogen atom interacts with one hydrogen atom and one phenyl ring. The same hydrogen atom in transition state **291** interacts with two phenyl rings and as such conformation **291** should be significantly more energetic than conformation **290**, hence, β-hydroxyester **292** is selectively generated.

Whether the lithium ion is large enough to accommodate three oxygen atoms is debatable but for there to be any selectivity in the aldol reaction at all, there must be some form of rigidity in the system. If the seven membered metallocycle is not

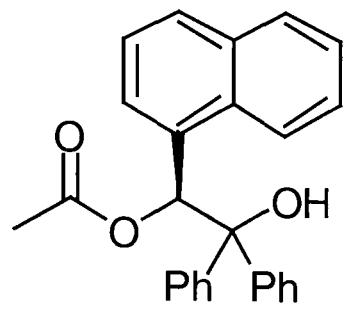
involved then the actual transition state probably consists of aggregates of two or more units.

If the above model is correct then two possibilities exist for development of the 'next generation' of Braun's auxiliary; reduction of the steric interactions in transition state **290** using acetate **294** or increasing the destabilisation of conformation **291** by means of alcohol **295**, *Figure 14*.

Figure 14



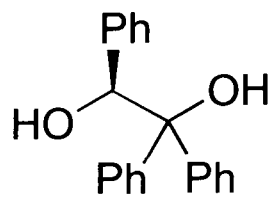
294



295

Transesterification, generating ester **286**, was induced by sonication of a mixture of ester **285** with potassium carbonate in dry ethanol. The product was contaminated with 1,1,2-triphenyl-ethylene glycol, **296** *Figure 13*, which could not easily be removed. We did not consider the presence of **296** to be particularly significant. Compound **296** should not interfere with our chemistry and we recalled that attempted alkylidenation of β-hydroxyester **225**, using Takai's procedure, effectively consumed the substrate bearing an unprotected alcohol. We also reasoned that the substrate for the AOC rearrangement **289** would be considerably less polar than alcohol **296** and therefore could be removed by chromatography. We were not to be disappointed.

Figure 15



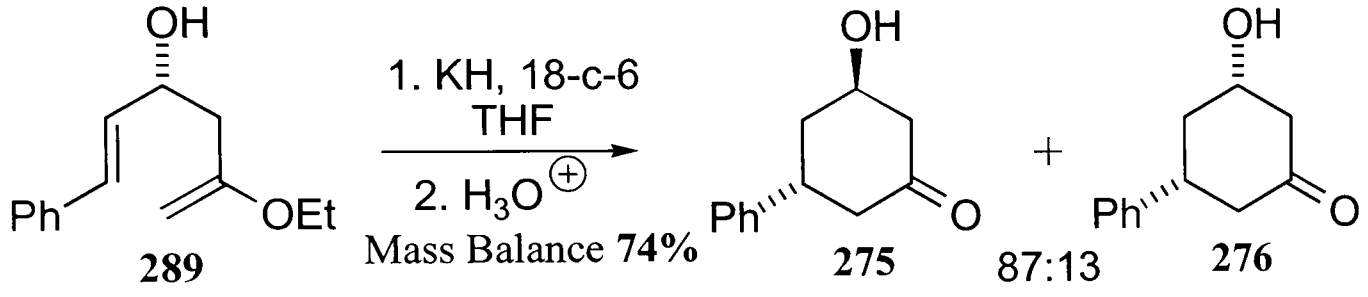
296

The mixture was treated with *tert*-butyldimethylsilyl chloride and Hunig's base producing a mixture of silyl ether **287** and 1,1,2-triphenyl-2-(*tert*-

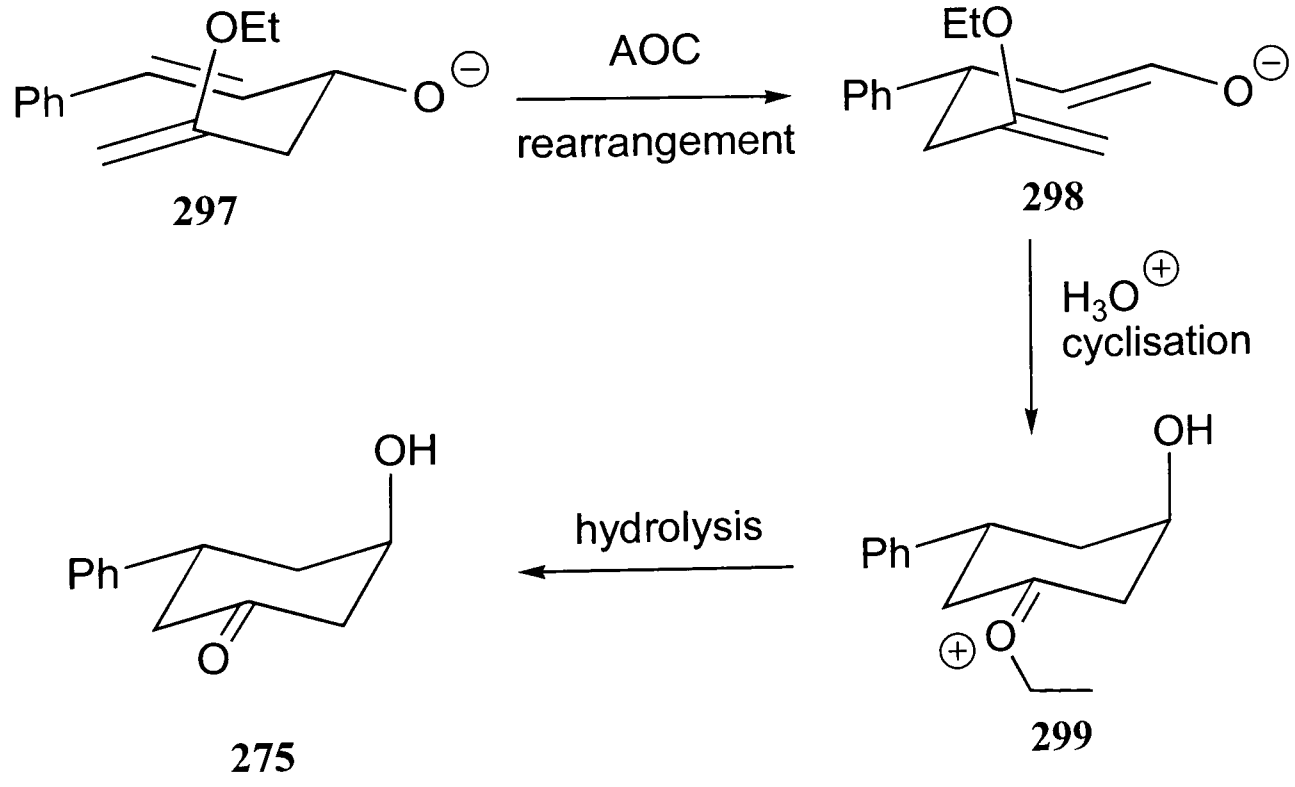
butyldimethylsilyl)ethanol that could not be separated. Methylenation using Takai's procedure, deprotection with TBAF and subsequent chromatography gave hexadienol **289** in yield of 6% over 4 steps from aldol **285**, i.e. an average of 49% for each step.

The removal of the chiral auxiliary resulted in the generation of compounds containing only one chiral centre. We must now address the question of enantiomeric excess rather than diastereomeric excess. Since no mechanism exists for epimerisation of the hydroxyl at any stage during our route under our reaction conditions, we assume that chiral integrity was maintained and alcohol **289** was prepared in 92% *ee*.

Scheme 90



Scheme 91

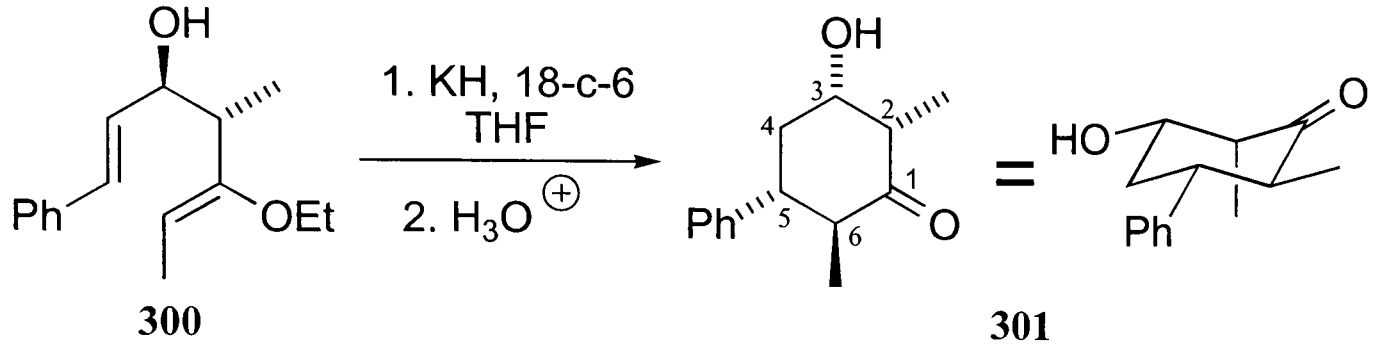


AOC rearrangement of alcohol **289** was carried out under the usual conditions and was quenched with 1 mol dm^{-3} aqueous hydrochloric acid to give an 87:13 mixture of β-hydroxycyclohexanones **275** and **276** respectively, mass balance 74%. Ratios were determined by ^1H NMR spectroscopy. *Scheme 91* illustrates the

anticipated result (see chapter one) of the AOC rearrangement followed by acidic quench of alcohol **289**.

Although we are certain of the relative stereochemistry of β-hydroxycyclohexanone **275** we have reason to doubt the absolute stereochemical relationship. In order to elaborate I will discuss some related work which was also carried out in the Hartley group. The AOC rearrangement of hexadienol **300** followed by acidic quench selectively produced β-hydroxy cyclohexanone **301**, *Scheme 92*.

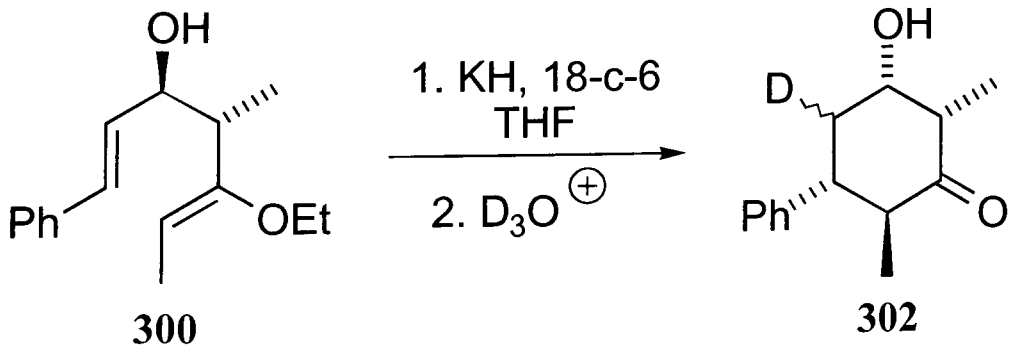
Scheme 92



300 **301**

Compound **301** contains an equatorial hydroxyl and an axial methyl group at position 2. The stereochemistry at C-2 can arise either from the geometry of the transition state or by acid-catalysed epimerisation following cyclisation. Quenching of the reaction with 1.1 mol dm^{-3} deuterium chloride led to incorporation of deuterium only at position 4, **302** *Scheme 93*. There was a reduction in the intensity of the signal for the C-4 methylene in the ^1H NMR spectrum and a simplification of the resonances for C*H*Ph and C*H*OH. The signals arising from the methine protons α to the carbonyl are unaffected. This result ruled out epimerisation following cyclisation.

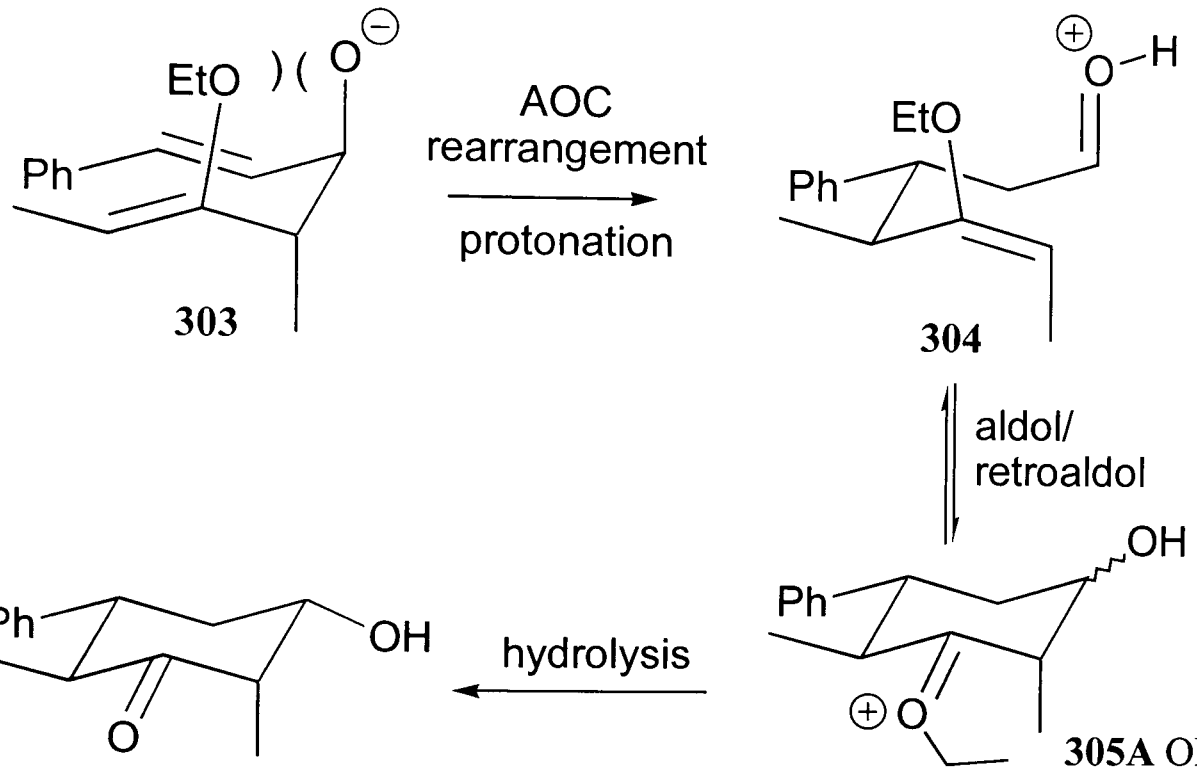
Scheme 93



300 **302**

The stereochemistry in the product must therefore arise from the geometry in the transition state. Conformation **303**, *Scheme 94*, should be strongly disfavoured due to the 1,3-*pseudo*diaxial electrostatic interaction between the lone pairs of the enol ether oxygen and alkoxide and by the steric interactions of the axially oriented methyl group.

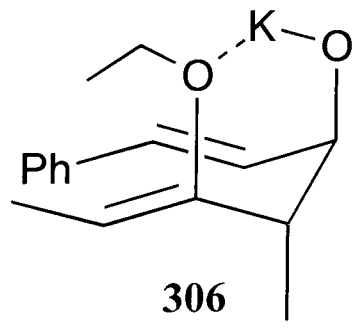
Scheme 94



303 **304** **305A** OH ax **305B** OH eq **301**

However, if the transition state is stabilised by chelation of a potassium ion the AOC rearrangement of alcohol **300** is forced to proceed with three *pseudo*axially oriented substituents **306**, *Figure 16*. It should be noted that only 2 equivalents of 18-crown-6 are used whereas we used 3 equivalents of potassium hydride hence potassium cations are available in the reaction mixture.

Figure 16

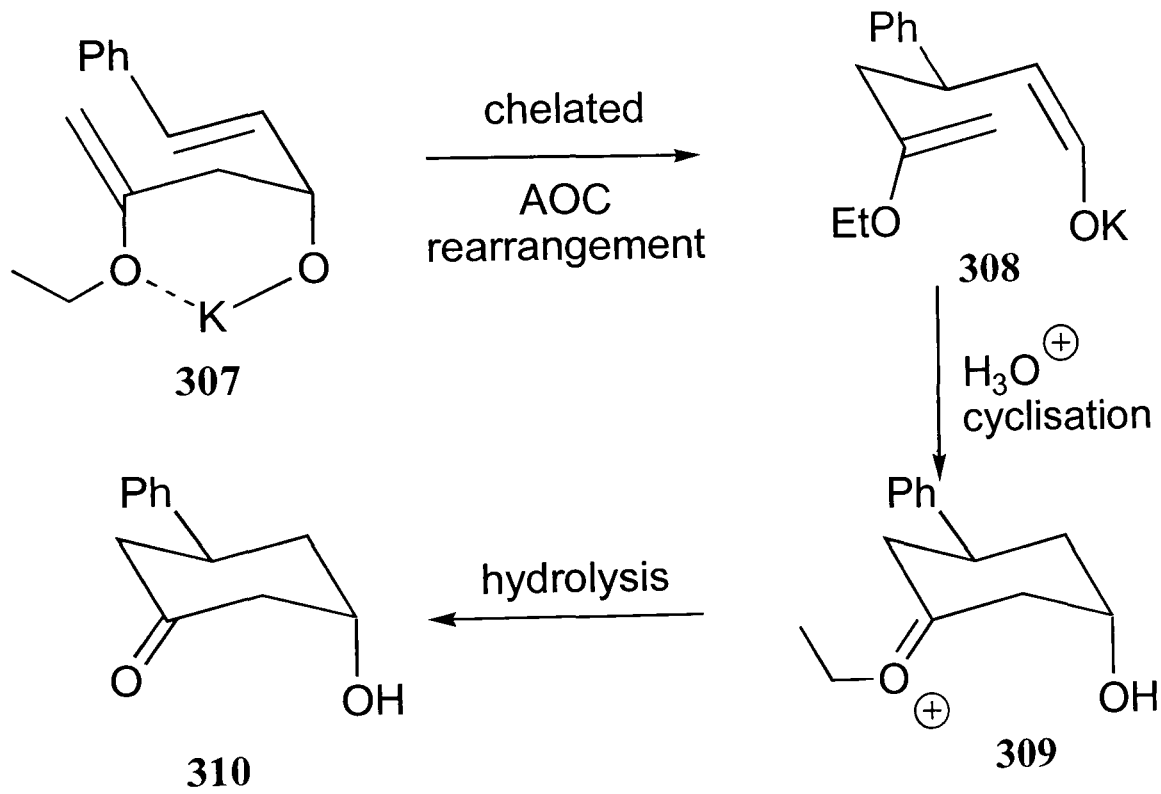


306

The orientation of the hydroxyl group is fixed following hydrolysis of oxonium ion **305**. The angle of approach for the water is from above and behind.[68] The axial methyl group at position 2 hinders approach from the lower face of the oxonium ion. With the hydroxyl axially oriented the upper face is also blocked so hydrolysis is slow. When the hydroxyl group is in the equatorial position approach of the water is no longer impaired on the upper face of intermediate **305** and hence hydrolysis is faster and compound **301** predominates in the product.

Given these results we believe that the AOC rearrangement and subsequent acidic quench of substrate **289** selectively generates (*3R, 5R*) 3-hydroxy-5-phenyl-1-cyclohexanone **310**, *Scheme 95*, rather than its enantiomer **275**, see *Scheme 90*.

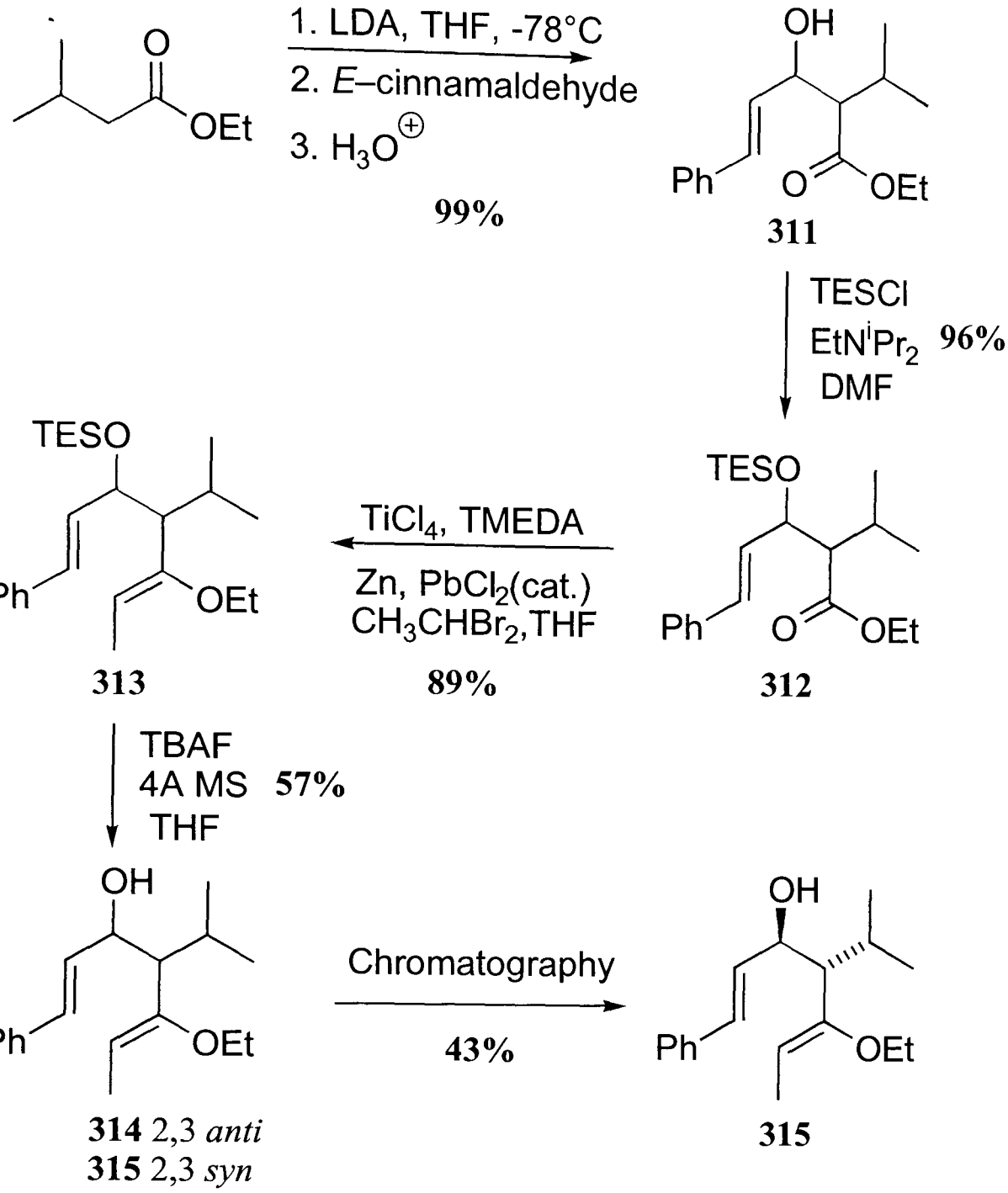
Scheme 95



Unfortunately we were unable to confirm our hypothesis. An authentic sample of (*3R, 5R*) 3-hydroxy-5-phenyl-1-cyclohexanone is not available for comparison and we were unable to crystallise the product for X-ray analysis. Also, attempts to use chiral shift reagents to determine the enantiomeric excess of **310** were unsuccessful. The sequence will be repeated on a larger scale by other members of the Hartley group and the theory tested.

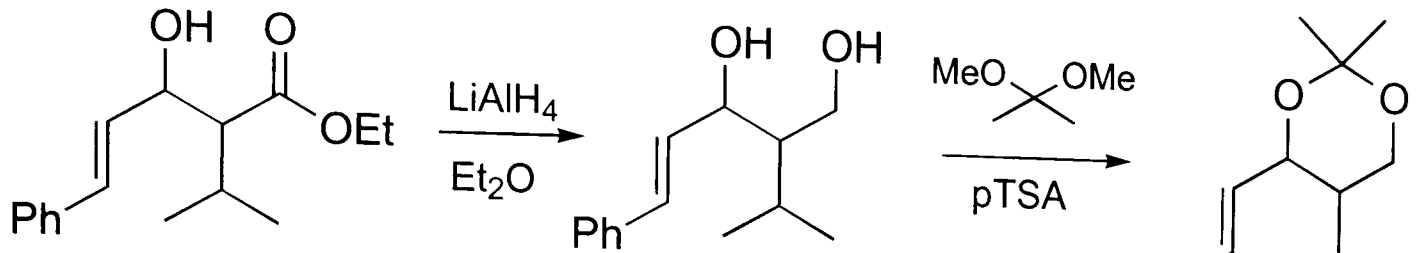
3.4 β–Hydroxycyclohexanones Bearing Four Chiral Centres

Scheme 96



The aldol reaction between the lithium enolate of ethyl isovalerate and *trans* cinnamaldehyde generates 92:8 mixture of *syn* and *anti* aldols **311** respectively, *Scheme 96*. Their relative stereochemistries were determined by lithium aluminium hydride reduction of **311** to the corresponding diols **316** then conversion to cyclic acetals **317** employing 2,2-dimethoxypropane and catalytic pTSA, *Scheme 97*. In cyclic acetals **317** the hydrogen atoms have fixed orientations.

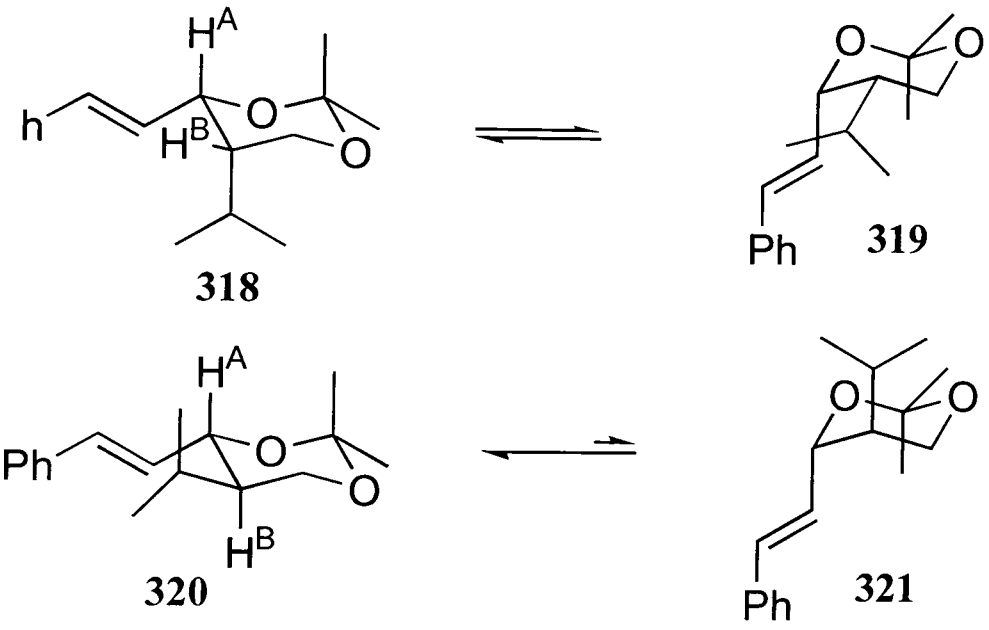
Scheme 97



311 **316** **317**

Two possible chairs can be drawn for both the 2,3-*syn* and 2,3-*anti* isomers **317**, *Scheme 98*. In the case of the 2,3-*syn* isomer both conformations, **318** and **319**, may be populated in solution but conformation **319** will predominate. The dihedral angle between H^A and H^B is approximately 60 ° in both forms and hence we expect J_{AB} to be 2-3 Hz.

Scheme 98



318 **319** **320** **321**

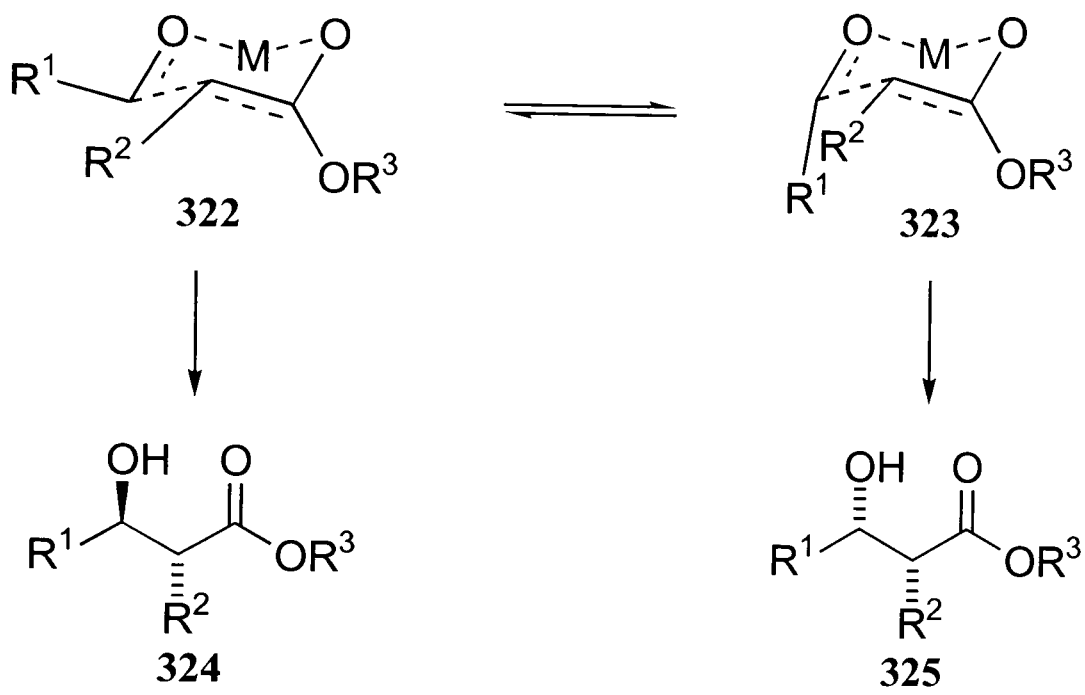
For the 2,3-*anti* isomer chair **320** will be substantially more heavily populated than chair **321**. As such H^A and H^B are in an antiperiplanar relationship and so we would expect J_{AB} to be in the range 9-13Hz. We observed J_{AB} = 2.1 Hz and hence the major component of the mixture is the 2,3-*syn* diastereomer.

In the absence of HMPA, esters give *E*-enolates when deprotonated by lithium diisopropylamide.[69] Reaction with aldehydes proceeds *via* chair-like six-membered chelated transition states **322** and **323**, *Scheme 99*, (Zimmerman-Traxler transition states).[70] Transition state **323** suffers from a 1,3-*pseudo*diaxial interaction

between R^1 and R^3. Consequently, when R^1 and R^3 are large transition state **322** is preferred and 2,3-*anti* aldol **324** is produced.

The Zimmerman-Traxler transition state is generally recognised to be skewed, so that the interaction between R^1 and R^2 is more severe in transition state **322** than in **323**. As a result, when R^2 is large and R^3 is small, transition state **323** will dominate and the *syn* product **325** is the major product. In our case R^2 is the relatively large isopropyl group while R^3 is the small ethyl group; hence the observed selectivity.

Scheme 99



Protection of alcohol **311** as TES ether **312**, *Scheme 96,* was effected in 96 % yield following chromatography. The 2,3-*syn* to 2,3-*anti* ratio was unchanged. Ethylidenation, using Takai's procedure, specifically generated *Z*-enol ether **238** in a crude yield of 89 %. ^{13}C NMR revealed a single peak for the methine portion of the enol ether at 108.7 ppm. In chapter 1 we proposed the following mechanism to explain the stereoselection in the Takai alkylidenation.

Scheme 25

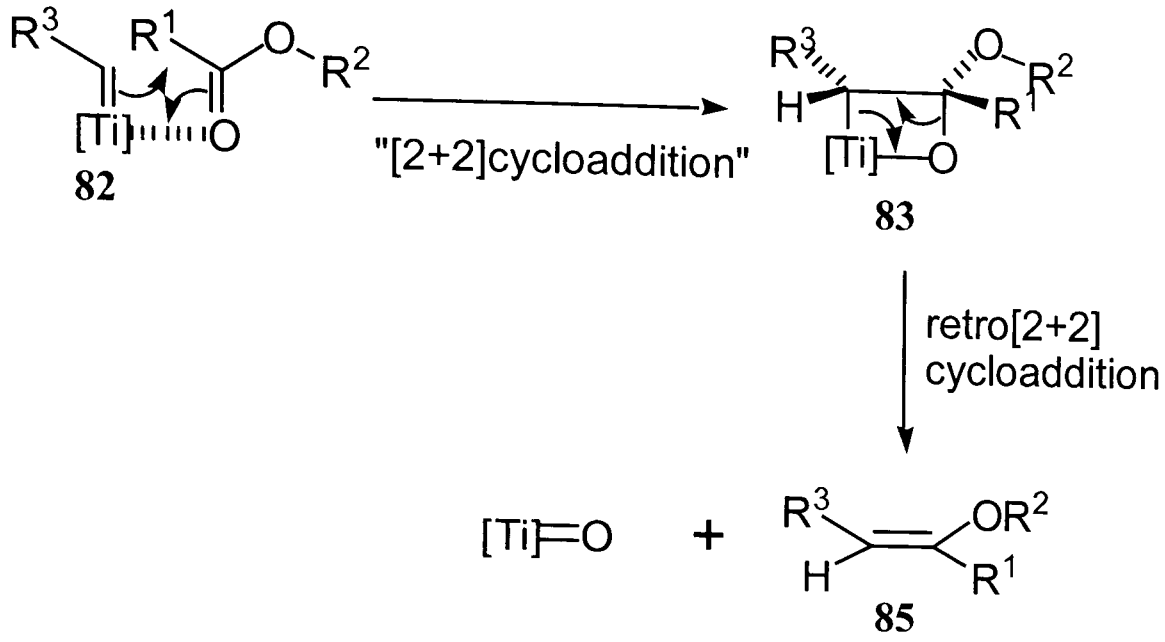
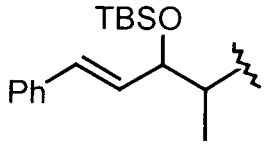
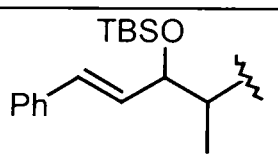
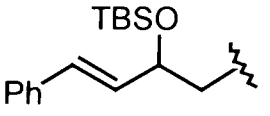
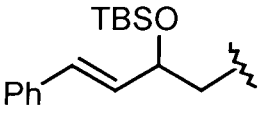


Table 9 illustrates the effect on the *Z*:*E* ratio in the product as we vary R^1 and R^2.

Table 9

R^1	R^2	*Z* : *E*	^{13}C NMR(ppm)
	ethyl	100 : 0	108.7(Z)
	isopropyl	>98 : 2	108.0 (*Z, syn*) 107.3 (*Z, anti*)
	methyl	98 : 2	–
	isopropyl	85 : 15	110.6 (*Z*) 94.8 (*E*)
	phenyl	65 : 35	–

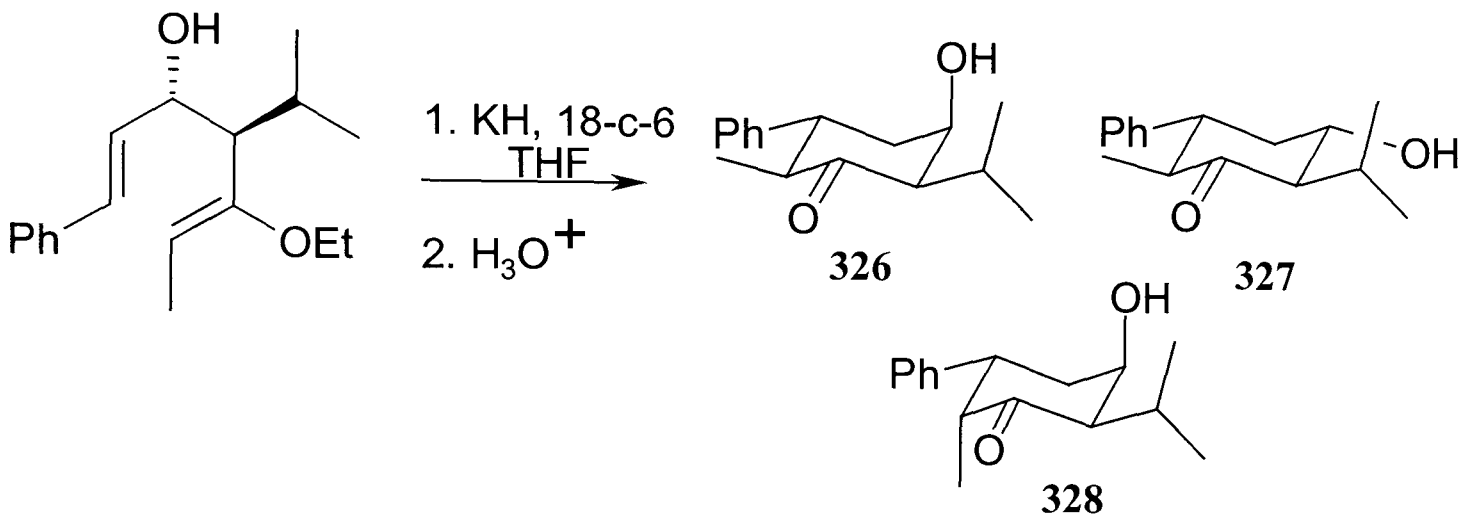
Where R^1 is very large i.e. entry 1 we observe complete *Z*-selectivity in the formation of the enol ether. As the steric demand of R^1 decreases and the steric demand of R^2 increases we observe a gradual increase in the quantity of the *E*-enol ether. However, even when R^1 is very small, e.g. CH_2 and R^2 is very large, e.g. phenyl, the Takai alkylidenation still selectively generates *Z*-enol ethers. The

geometry of the enol ether is assigned by carbon NMR. *Z*-enol ethers come in the range 97-101 ppm and *E*-enol ethers range from 92-95 ppm.

Deprotection of silyl ether **313** with TBAF in THF, followed by chromatography, afforded 2,3-*syn* alcohol **314** and a 2:1 mixture of *syn*:*anti* alcohol **239** respectively in an overall yield of 57%. Further chromatography allowed isolation of 2,3-*syn* alcohol in 43% yield, *Scheme 98.*

AOC rearrangement of alcohol **315** under the usual conditions followed by quenching with aqueous hydrochloric acid produced a 75:19:6 mixture of β-hydroxycyclohexanones **326**, **327** and **328** in a combined yield of 80 %, *Scheme 100.*

Scheme 100



Chromatography on alumina gave compound **326** in 65% yield and a mixture of ketones **327** and **328**. Trituration of the mixture with hexanes separated **327** and **328**. The stereochemistry and the relative ratios of **326**, **327** and **328** were determined by ^{1}H NMR spectroscopy. The signals for C*H*OH are clearly distinct in the spectrum of the crude product at δ_H 4.54, 4.38 and 4.16 ppm for **326**, **327** and **328** respectively and these were used to determine the ratios of the products. The phenyl and isopropyl substituents are fixed equatorially for chairs **326** and **327**.

First I will discuss the assignment of the major product **326**. δ_H for C*H*OH is 4.38 ppm and the signal is a narrow (20 Hz), poorly resolved doublet. There are no large couplings, i.e. axial-axial, hence, the hydrogen atom is equatorial and the hydroxyl substituent is axial. δ_H for C*H*Me is 2.65 ppm and the signal is a doublet of quartets with couplings of 6.2 Hz for the quartet and 12.5 Hz for the doublet. The

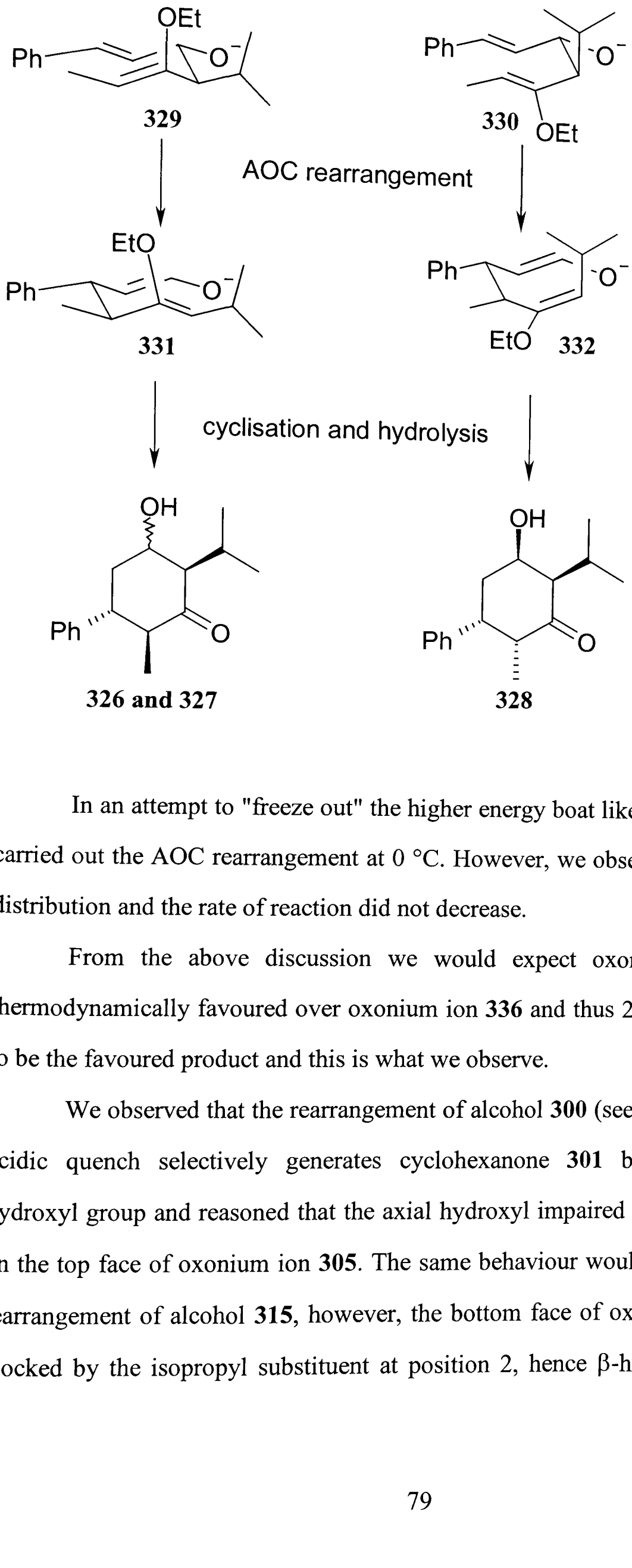
latter is an axial-axial coupling to C*H*Ph hence the methyl group at position 5 is equatorial.

In the spectrum of ketone **327**, δ_H for C*H*OH is 4.16 and the signal is a very broad (28 Hz), poorly resolved, overlapping double double doublet. The coupling constants cannot be properly measured but the multiplet is clearly very much broader than for C*H*OH in the spectrum of **326** and as such contains axial-axial couplings, hence, the hydroxyl group is equatorial. δ_H for C*H*Me is 2.59 with coupling constants of 6.2 Hz for the quartet and 12.4 Hz for the doublet, so again the methyl substituent is equatorial.

δ_H for C*H*OH in the spectrum of alcohol **328** is 4.63 and the signal is identical to that for **257** hence the hydroxyl group is axial. δ_H for C*H*Me is 2.77 but the resonance resembles a quintet, with a coupling constant of 6.4 Hz, rather than a double quartet. This indicates that the coupling to C*H*Ph is smaller, i.e. equatorial-axial rather than axial-axial, and that the methyl substituent is axial. This change is also reflected in the signal for C*H*Ph. Whereas for **326** and **327** it appears as a wide triplet of narrow doublets, indicating two axial-axial and one equatorial-axial coupling, the resonance in the spectrum of **328** is a triple doublet with couplings of 4.9 and 13.4 Hz respectively, i.e. one axial-axial and two equatorial-axial couplings.

β-Hydroxycyclohexanones **326** and **327** result from chair-like reacting conformation **329**, *Scheme 101*, and **328** from a boat-like reacting conformation which may be **330**. We can clearly see how the stereochemical relationship between the phenyl and methyl groups arises when we react 2,3-*syn* hexadienol **315**. In this case, the AOC rearrangement proceeds with a 94:6 bias for a chair-like conformation. Reacting conformation **330** is destabilised by an axially oriented oxyanion.

Scheme 101



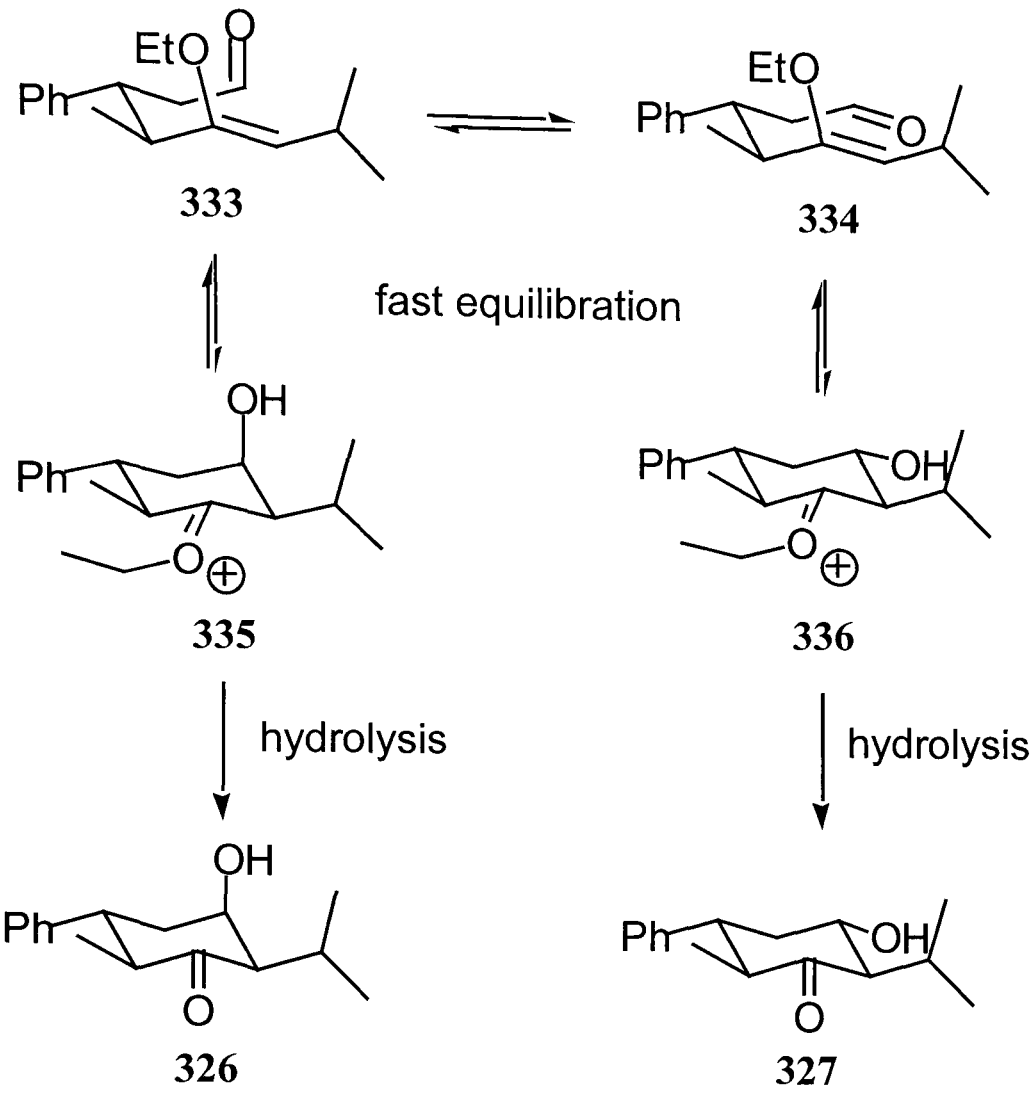
In an attempt to "freeze out" the higher energy boat like conformation **330** we carried out the AOC rearrangement at 0 °C. However, we observed identical product distribution and the rate of reaction did not decrease.

From the above discussion we would expect oxonium ion **335** to be thermodynamically favoured over oxonium ion **336** and thus 2,3-*anti* cyclohexanone to be the favoured product and this is what we observe.

We observed that the rearrangement of alcohol **300** (see page 70) followed by acidic quench selectively generates cyclohexanone **301** bearing an equatorial hydroxyl group and reasoned that the axial hydroxyl impaired the approach of water on the top face of oxonium ion **305**. The same behaviour would be mimicked in the rearrangement of alcohol **315**, however, the bottom face of oxonium ion **335** is not blocked by the isopropyl substituent at position 2, hence β-hydroxycyclohexanone

326 is the major diastereomer generated by the AOC rearrangement and subsequent aqueous acidic quench.

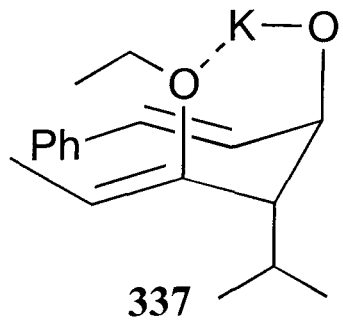
Scheme 102



326 **327**

The products of the chelated AOC rearrangement, see *Scheme 95*, are not observed because the destabilisation caused by an axially oriented isopropyl group in reacting conformation **337**, *Figure 16*, is too great to be overcome by coordination of a potassium ion.

Figure 16

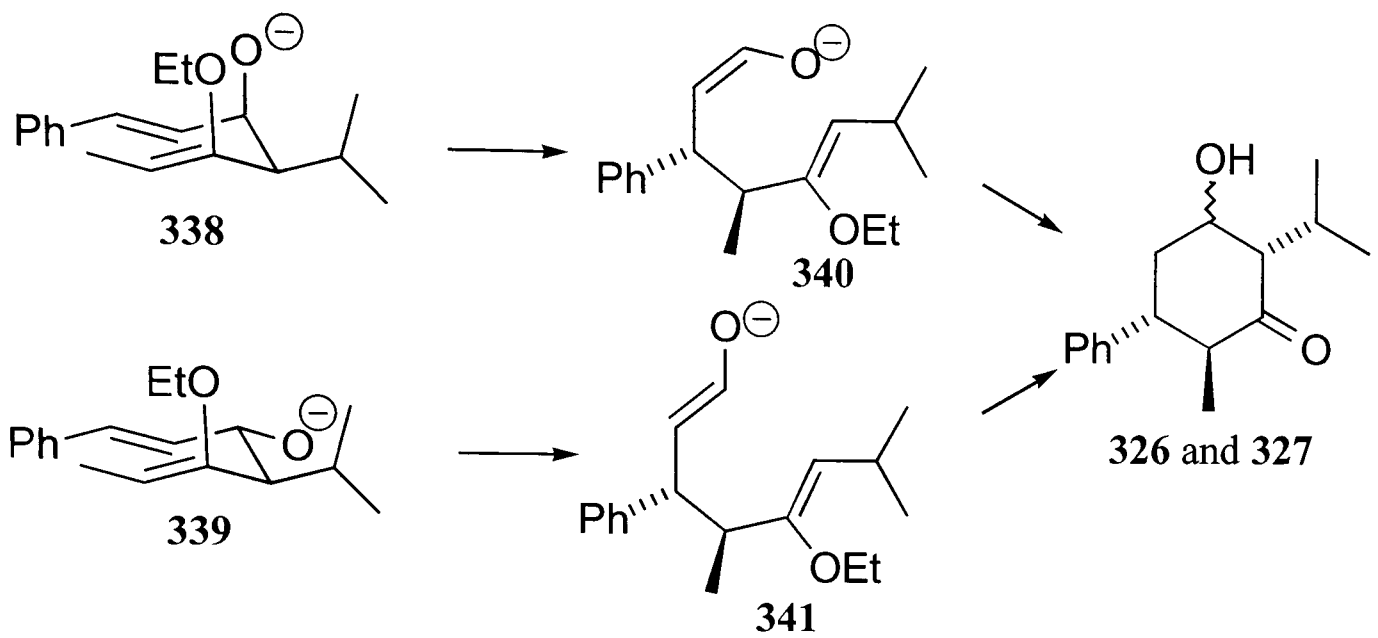


337

As discussed in chapter one, Greeves reported[58] that sterically demanding substituents at C-4 of the 1,5-hexadien-3-ol framework react with that substituent equatorial in the 6-membered chair-like transition state. If this were the case then

alkoxides **338** and **399**, derived from 2,3-*anti* alcohol **314** and 2,3-*syn* alcohol **315** should rearrange and cyclise to give the same β-hydroxycyclohexanones **326** and **327**.

Scheme 103

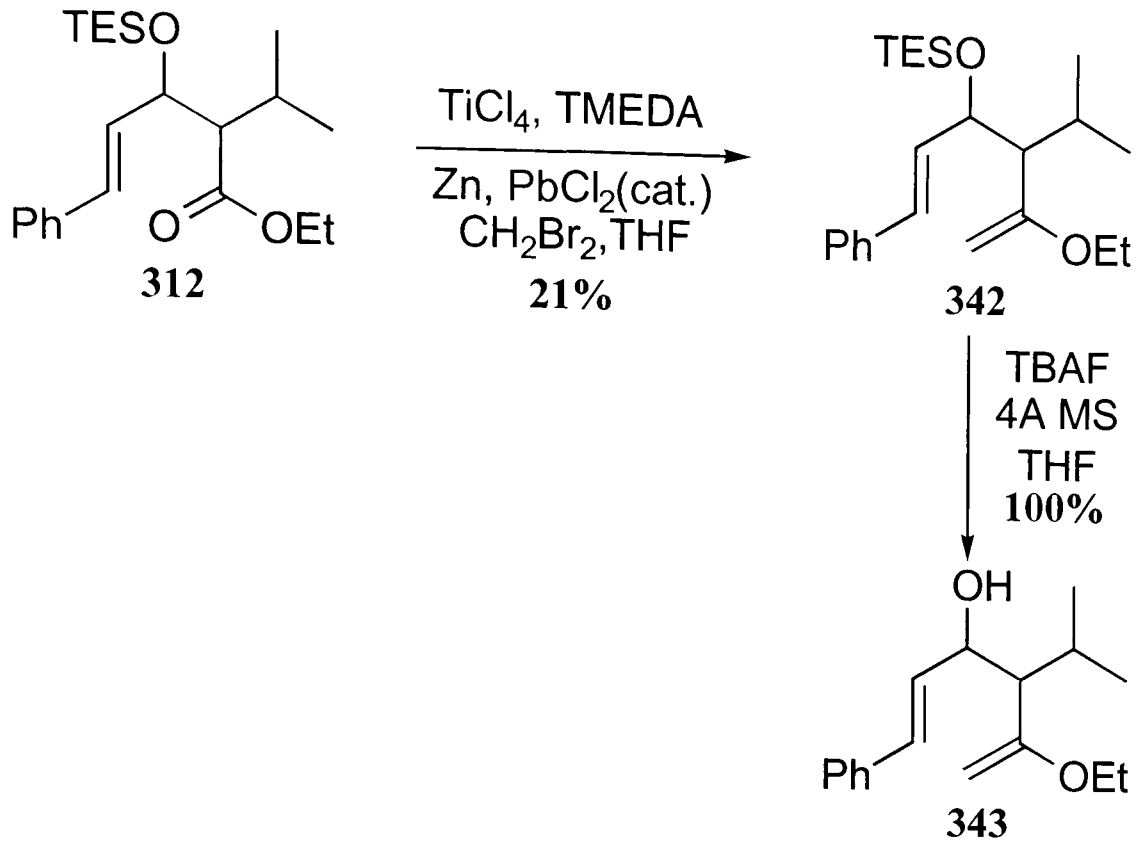


We found that a 65:35 mixture of alcohols **314** and **315** was rearranged and cyclised to give a 50:20:30 ratio of β-hydroxycyclohexanones **326**, **327** and **328** was isolated in 72% yield. This may mean that 2,3-*anti* alkoxide **338** rearranges *via* a boat-like transition state. However, since the ratio is not the same as before, epimerisation may have occurred in this experiment.

3.5 β–Hydroxycyclohexanones Bearing Three Chiral Centres

Having successfully demonstrated that we could prepare β-hydroxycyclohexanones bearing four controlled stereogenic centres, we decided to investigate whether we could do the same with three chiral centres. The substrate we chose to study could not give us information on whether the transition state was chair-like or boat-like in the AOC rearrangement but it would be simpler to interpret our results.

Scheme 104



Ester **312** (*syn-anti* 92:8) was converted into enol ether **342**, using Takai's alkylidenation reaction, in a yield of 21 % after chromatography on alumina. If we compare this to our result for the corresponding ethylenation, formation of **313** *Scheme 96*, we observe that the methylenation is the poor cousin of the family. Methylenation has consistently been reported to be a less successful transformation but to date no one has ascribed the reason why. It is possible that the methyl group in **344**, *Figure 17*, releases electron density, via the inductive effect, and enhances the nucleophilicity of titanium carbenoid **344** in comparison to **345**.

Figure 17

344 **345**

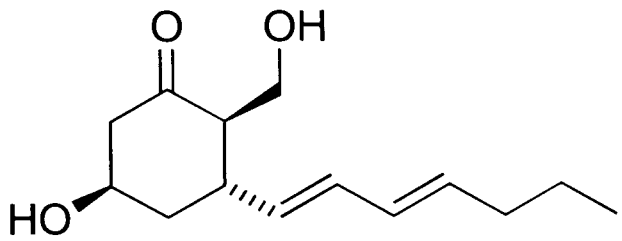
Deprotection of silyl enol ether **342** with TBAF in THF afforded 92:8 mixture of *syn* to *anti* hexadienols **343** in quantitative yield. It seems that the secret to this reaction, which proved problematic on every other occasion, is rigorous purification of the starting material. In this case we were unable to separate the 2,3-*syn* and 2,3-*anti* diastereomers by chromatography. AOC rearrangement of alcohol **343** followed

by aqueous acid quench gave a 79:21 mixture of diastereomers that decomposed on alumina. Consequently the isomers were not identified.

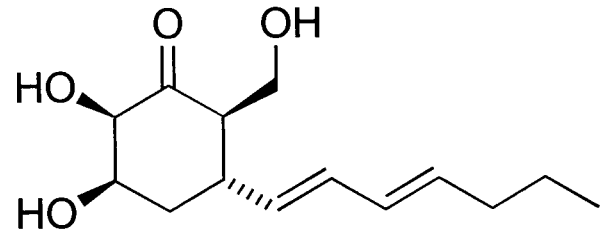
3.5 Studies Towards Selected Natural Product Analogues

Penihydrone,[71] palitantin[72] and frequentin,[73] *Figure 18*, have been isolated from *Penicillium* species. Penihydrone is a plant growth regulator and frequentin has shown both antibiotic and antifungal activity. All three compounds contain a β–hydroxycyclohexanone motif so perhaps, with a little modification, we could use our route to prepare either the natural products themselves or analogues thereof which may also be biologically interesting.

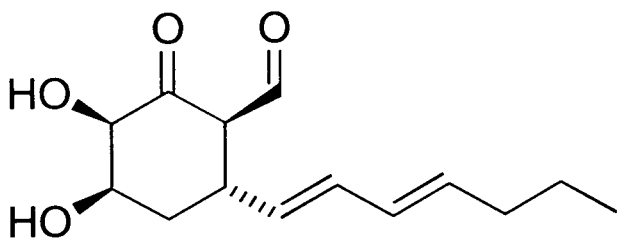
Figure 18



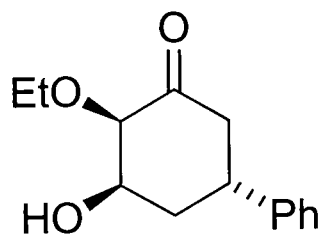
Penihydrone



Palitantin



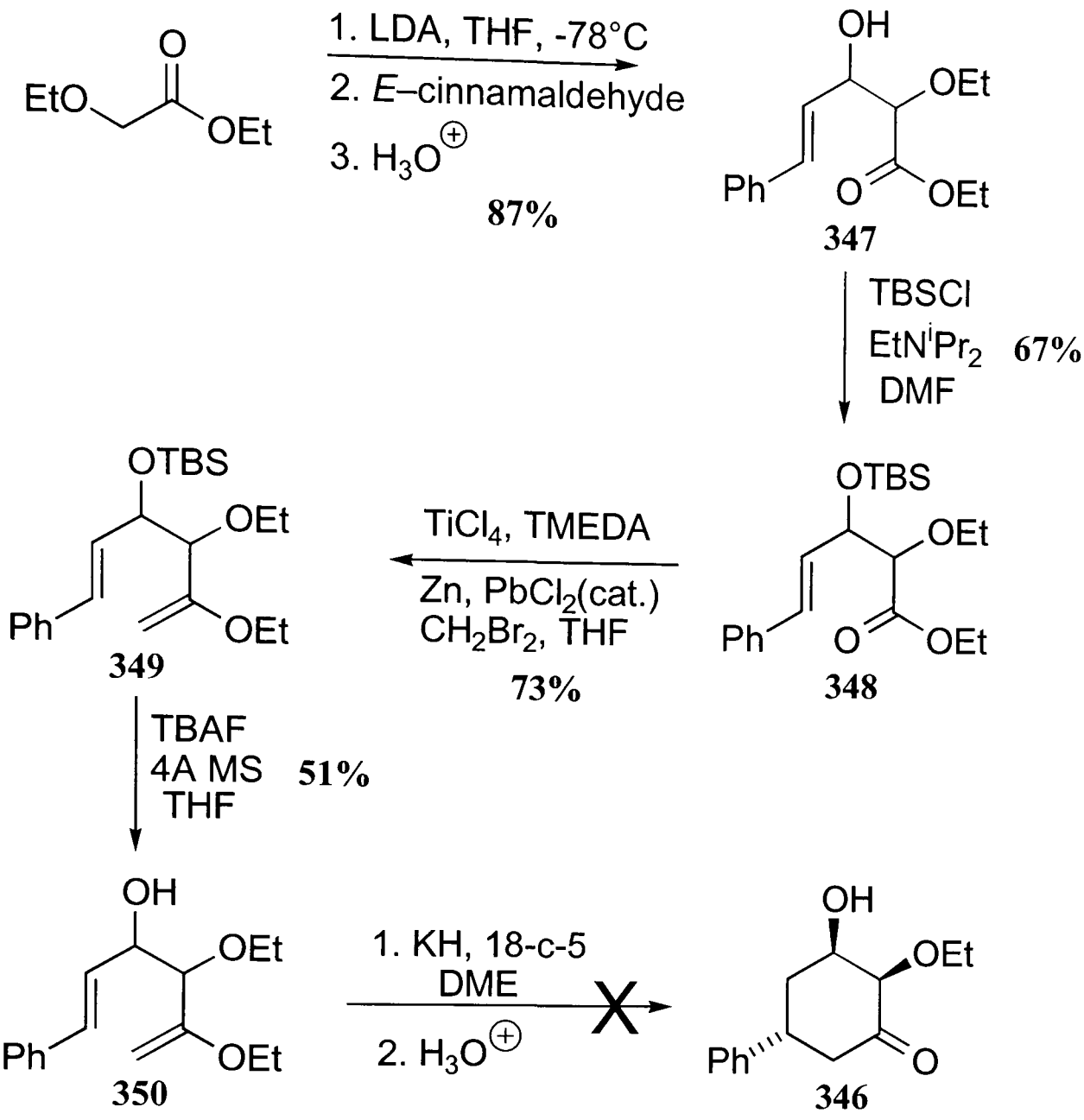
frequentin



346

With this idea in mind we embarked on the preparation of compound **346**, *Figure 18*. The synthetic route is outlined in *Scheme 105*. The lithium enolate of ethoxyethyl acetate was reacted with *trans*–cinnamaldehyde, in an aldol reaction, to form β-hydroxyester **347** in 87% yield. ^{1}H NMR spectroscopy indicated that we had prepared a 64:36 mixture of diastereomers.

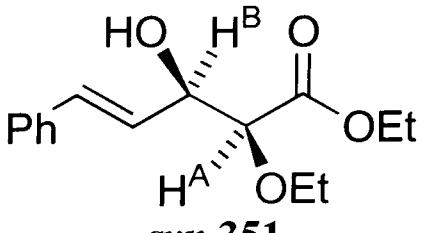
Scheme 105



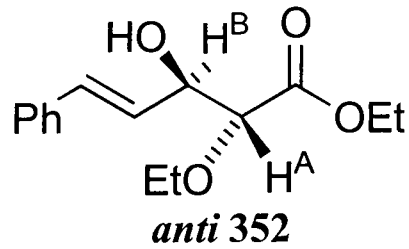
347 **348** **349** **350** **346**

We determined the relative stereochemistries of the aldols using ^{1}H NMR spectroscopy. The vicinal coupling constant, in this case J_{AB}, in intramolecularly hydrogen bonded aldols is normally 7–10 Hz for *anti* and 2–6 Hz for *syn* aldols.

Figure 19



***syn* 351**

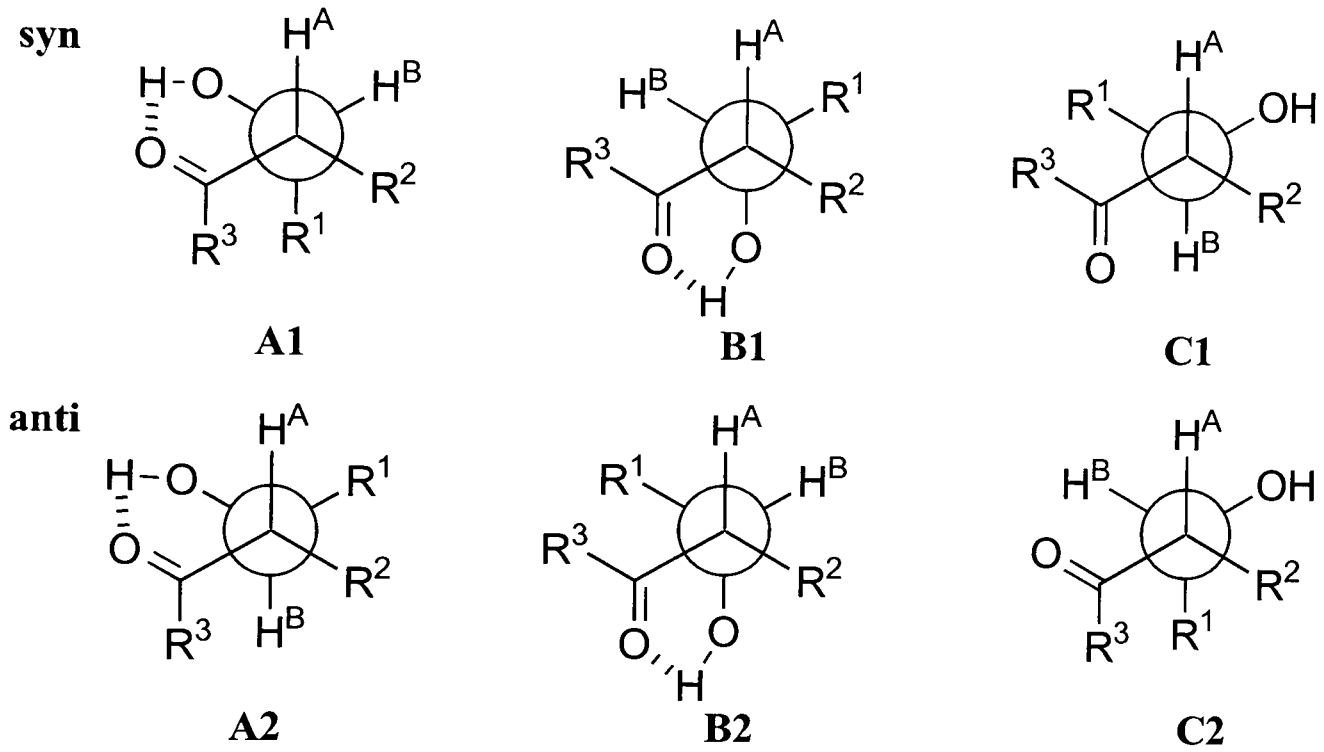


***anti* 352**

If we examine the three possible rotamers (**A**, **B**, and **C**) for *syn* and *anti* aldols, *Figure 20*, we can clearly see whence this trend arises. In conformations **A1** and **B1** the dihedral angle between H^A and H^B is 60° therefore the coupling constant is relatively small. In conformation **B2** H^A and H^B are again gauche to each other,

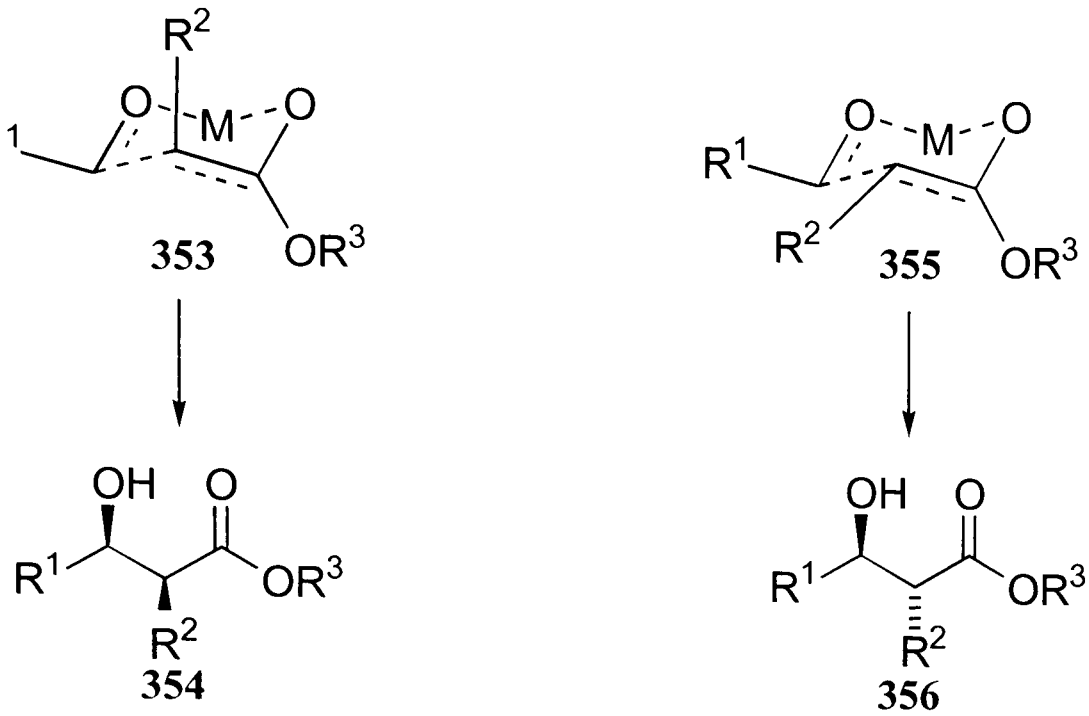
however, H^A and H^B are antiperiplanar in conformation **A2** and hence the coupling constant is of greater magnitude. Conformations **C1** and **C2** are relatively poorly populated since there is no stabilisation from intramolecular hydrogen bonding. Since we obtain a time averaged spectrum using NMR spectroscopy we can consider the coupling constant J_{AB} to be an average of the two occupied conformations **A** and **B**, therefore J_{AB} for *anti* aldols is greater than J_{AB} for *syn* aldols. In our case the major isomer has J_{AB} = 4.7 Hz and J_{AB} = 8.7 Hz for the minor; therefore, *syn* alcohol **351** is in excess.

Figure 20



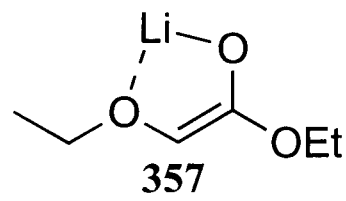
Having deduced that the *syn* aldol is the product we had then to ask why. The Zimmerman–Traxler transition state, *Scheme 106*, can be relatively accurately described as a pseudo chair. *Z*–Enolates in aldol reactions react *via* transition state **353** to form *syn* products **354** whereas *E*–enolates react *via* transition state **355** to give *anti* aldols **356** provided that OR_3 is relatively large and the R^2-R^1 interaction is small.

Scheme 106



Under normal circumstances we would expect to form *E*–enolates using a lithium base and since R^2 is relatively small we would expect to selectively generate *anti* aldols **356**. We have used lithium base and have obtained the *syn* alcohol preferentially. Lithium is strongly oxophilic so it is possible that the lithium ion becomes coordinated to the oxygen atom of the ether component of ethoxyethyl acetate and favours formation of the *Z*-enolate **357** illustrated in *Figure 21*. This would lead to *syn* aldol **351**.

Figure 21

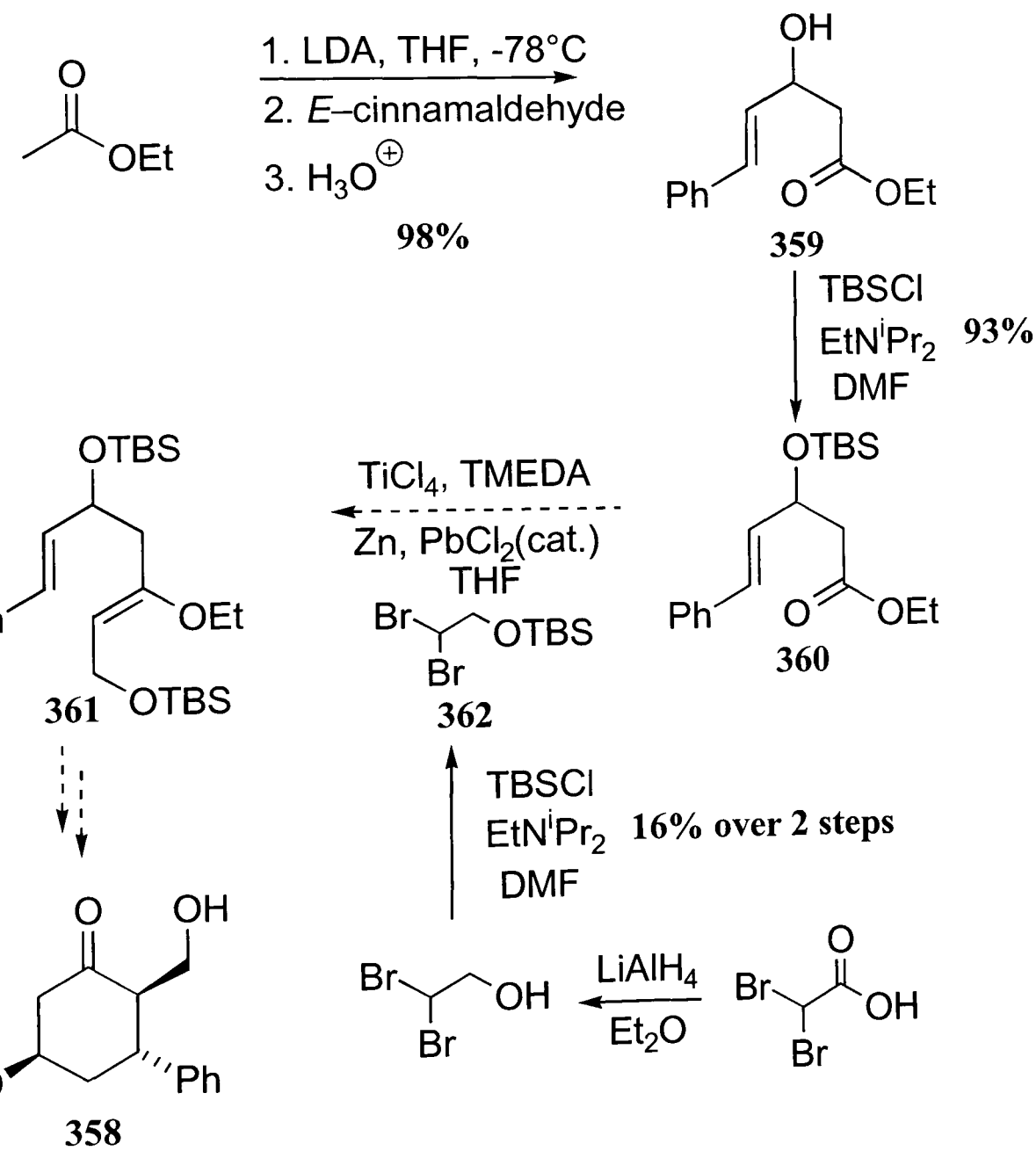


Protection of alcohols **347** as TBS ethers was effected in 67 % yield forming silyl ether **348**. Takai's alkylidenation reaction on **348** produced enol ethers **349** in a crude yield of 73%. Deprotection using TBAF afforded hexadienol **350** in 51% yield after chromatography. ^{1}H NMR spectroscopy confirmed that the ratio of isomers had not changed during the last two transformations, i.e. α-alkoxy substituents behave in the same manner as α-alkyl substituents in Takai's alkylidenation procedure.

Treatment of **350** with KH/18-crown-6 in DME at room temperature and at 50 °C did not produce the product. TLC analysis indicated that the starting material was being consumed at a painfully slow rate. If the reaction was left for several days, i.e. more than seven days, we finally observed the complete disappearance of the starting material, however we did not observe the desired product by ^{1}H NMR spectroscopy.

As discussed in chapter 1, conjugating substituents at position 4 on the hexadienol backbone accelerate the AOC rearrangement by stabilising the developing negative charge, at carbon 4, caused by n donation into the σ* orbital of the bond between carbons 3 and 4. If this is the case then electron releasing substituents, such as ethoxide groups, could destabilise the developing negative charge and hence impair the progress of the AOC rearrangement.

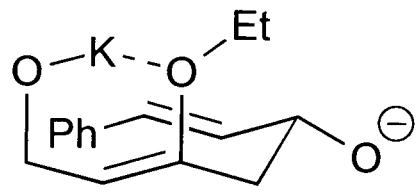
Scheme 107



Compound **358**, *Scheme 107*, (cf. penihydrone) was another of our targets. Hydroxyester **359** was prepared in 98 % yield and was pure enough for the next step without purification. Conversion of alcohol **359** to TBS ether **360** was effected in 93 % yield after dry flash chromatography.

In the next step we wished to introduce the ethanol substituent in compound **358** as its corresponding TBS protected ether. We chose the TBS ether so we could remove both protecting groups from enol ether **361** in a single step. We intended the primary hydroxyl group to have a controlling influence on the stereochemical outcome of the AOC rearrangement, *Figure 22*. If we could form intramolecularly chelated transition state **363** we should selectively generate the required *anti* relationship between the phenyl and methanol substituents in β-hydroxy cyclohexanone **358**.

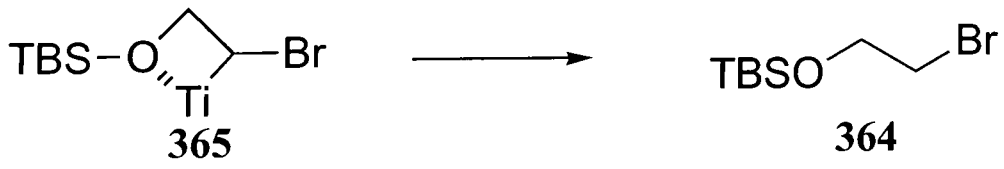
Figure 22



363

In order to introduce the TBS protected ethanol group in through Takai's alkylidenation reaction we had to prepare dibromoethyl silyl ether **362**. Lithium aluminium hydride reduction of 2,2–dibromoacetic acid followed by treatment of the resultant alcohol with TBSCl then arduous purification by chromatography produced compound **362** in 16 % yield over two steps. Use of **362** in the preparation of Takai's alkylidenation reagent did not afford the intended enol ether **361**. Instead we observed monodebromination of **362** to form **364**, *Scheme 108*.

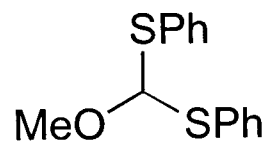
Scheme 108



Titanium, like lithium, is strongly oxophilic, i.e. titanium–oxygen bonds are relatively strong, so we can envisage formation of 4–membered cyclic chelate **365** during the attempted alkylidenation reaction. After the titanium metal inserts into one of the carbon bromine bonds, intermediate **365** is stabilised by coordination to the oxygen atom. After aqueous basic quench the titanium-carbon bond was hydrolysed and alkyl bromide **364** was generated.

Takeda and co-workers reported the use of titanium carbenoid reagents containing oxygen atoms from 1,1-phenylthio-1-methoxymethane **366**, *Figure 23*, and bis(triethylphosphite) titanocene.

Figure 23



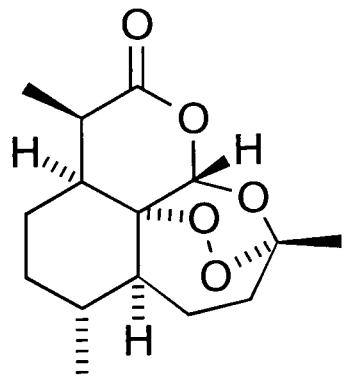
366

With a little modification we may be able to adapt Takeda's chemistry to introduce oxygen atom containing substituents and complete the synthesis of alcohol **339**. Time constraints did not allow us to investigate further.

4. OXYGENATION OF ENOLATES GENERATED BY AOC REARRANGEMENTS

Malaria has plagued the human race since time immemorial and in almost every corner of the globe. Even now there are several million cases every year.[74] Artemisinin, *Figure 24*, is the parent compound of the most potent class of antimalarial drugs available to date. It derives from ancient Chinese herbal medicines and the plant from which it is extracted *Qinghao* or sweet wormwood has been known to possess curative properties for malaria, fever and the common cold for at least two thousand years. Malaria is spread by the mosquito. Protozoal parasites of the *Plasmodium* family, found in the salivary glands of the mosquito, are actually responsible for the symptoms of the disease. Iron-oxo complex **367** is believed to be the active species generated from artemisinin *in vivo*. Such a strong oxidising agent would clearly be damaging to the nucleic acids of the *Plasmodium* parasite leading to cell death.

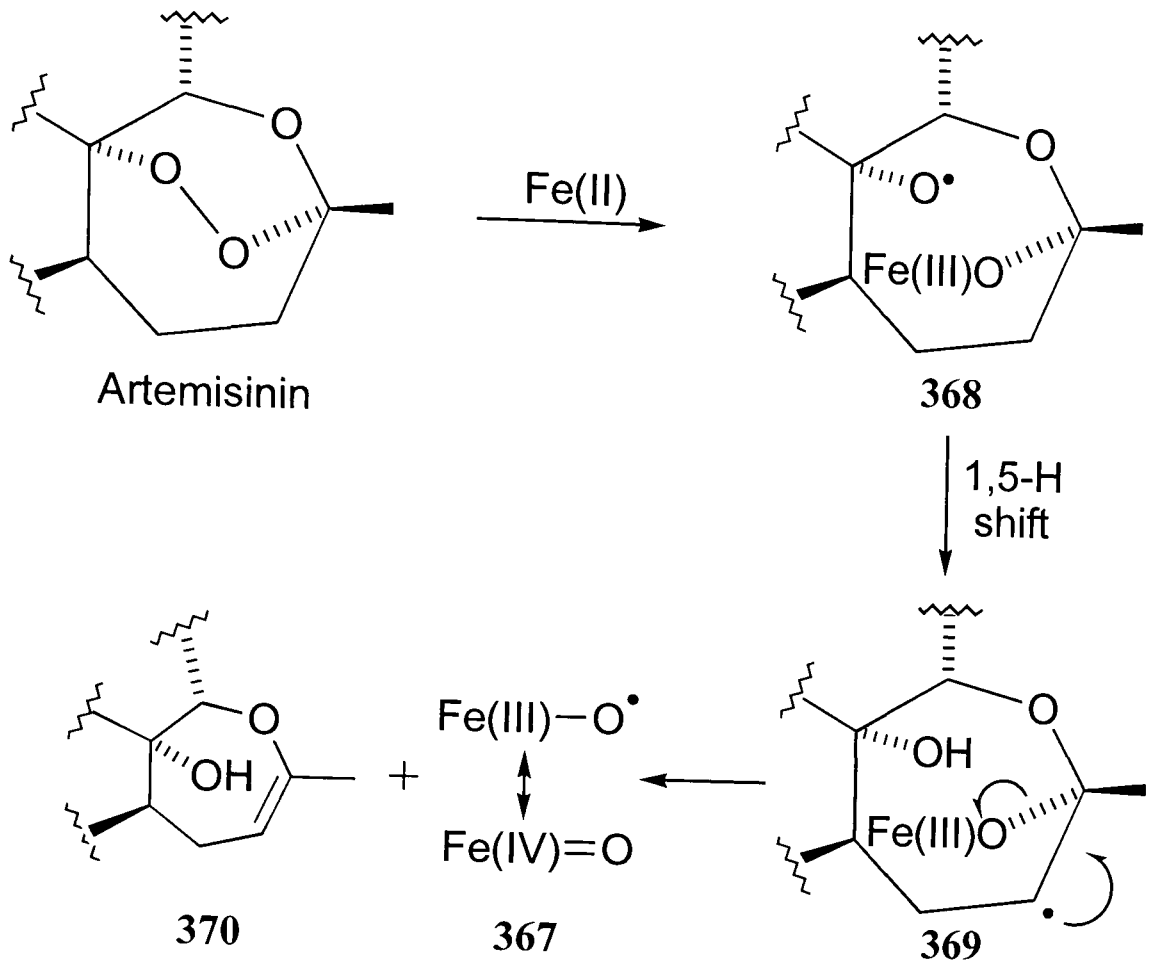
Figure 24



Artemisinin

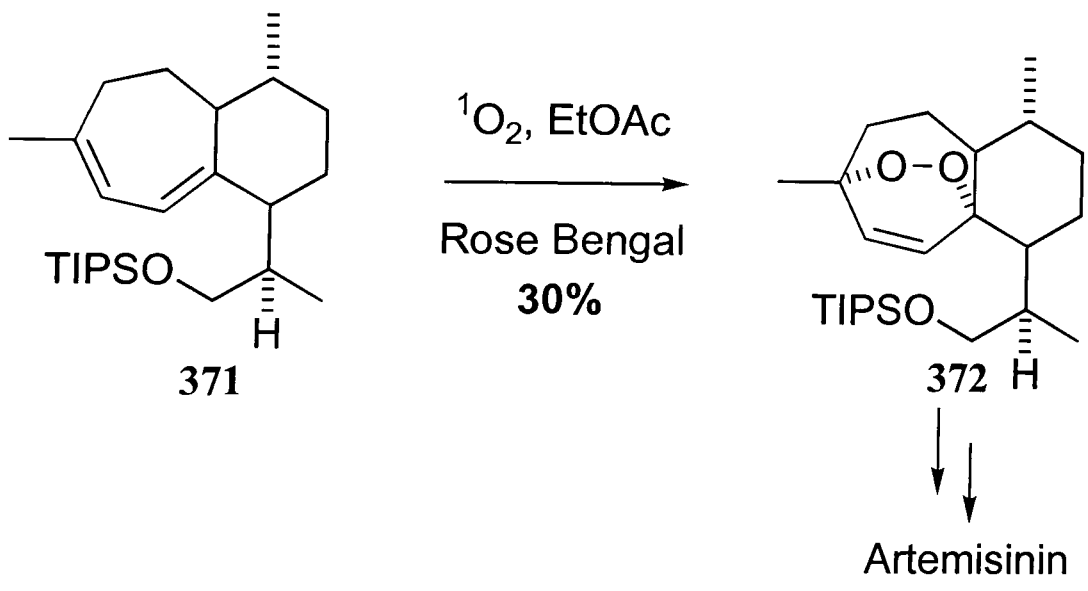
The mechanism of action of artemisinin and related analogues is believed to be as outlined in *Scheme 109*.[75] The peroxy bridge is broken down by iron(II) ions forming oxygen centred radical **368**. Hydrogen abstraction then occurs generating carbon centred radical **369**. Elimination generates high-valent iron-oxo species **367** and enol ether **370**.

Scheme 109



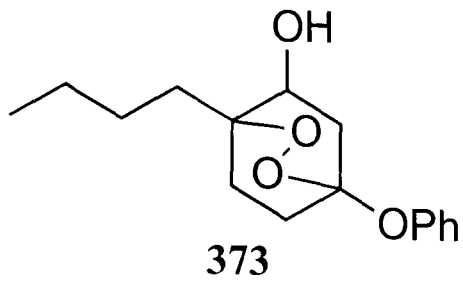
Total syntheses of artemisinin and analogues thereof have mainly relied on [2+2]cycloaddition reactions with singlet oxygen to introduce the peroxy bridge functionality and in one case a Diels Alder reaction, *Scheme 110*.[76]

Scheme 110



We wished to extend our methodoly for the synthesis of β-hydroxycyclohexanones to form artemisinin analogues **373**, *Figure 25*, by oxygenation of the enolates generated by AOC rearrangements.

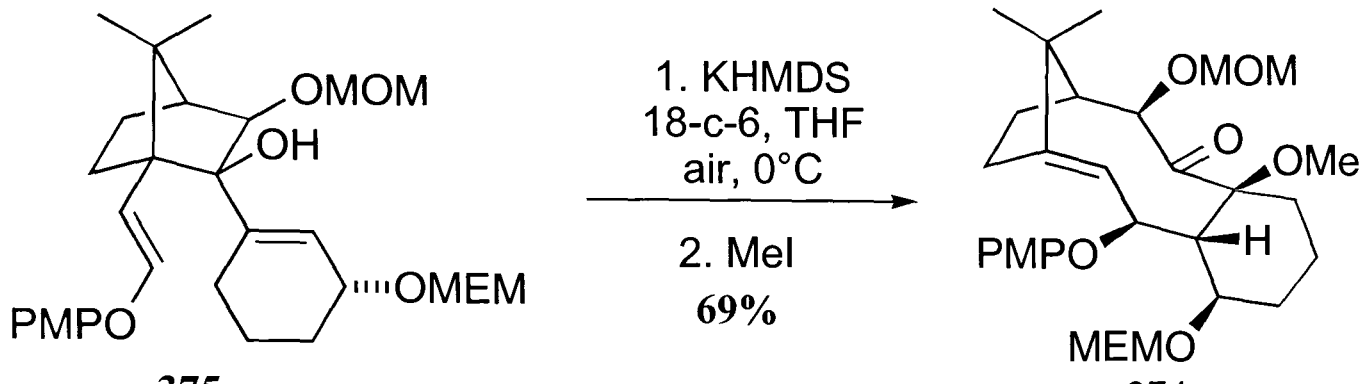
Figure 25



373

In 1995 Paquette and co-workers reported formation of ether **374**, *Scheme 111*, in their synthesis of Taxol precursors by carrying out the AOC rearrangement of alcohol **375** in air, and so trapping molecular oxygen. The methyl ether was formed by treatment with methyl iodide.[77]

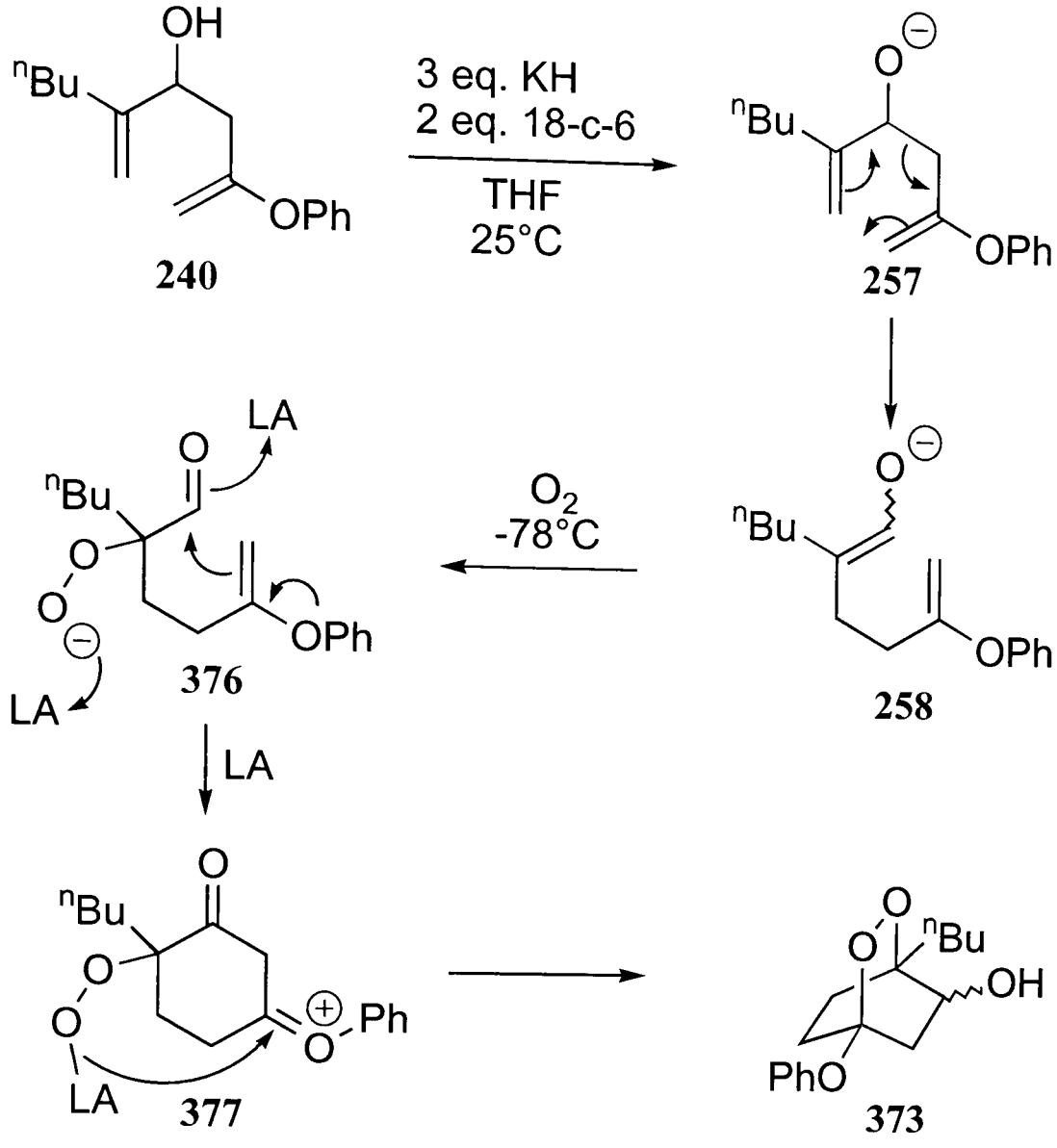
Scheme 111



375 **374**

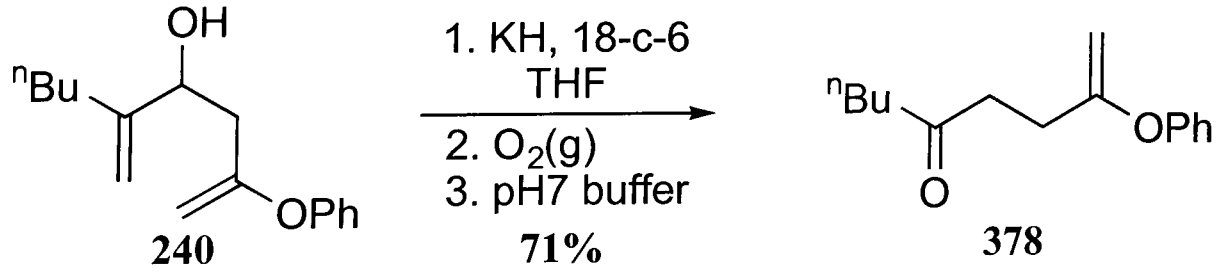
The AOC rearrangement of alcohol **240** generates enolate **258**. Reacting with molecular oxygen should generate hydroperoxide **376** which is the key intermediate for our proposed synthesis of endo peroxide **373**. If we introduce a Lewis acid after formation of the hydroperoxide we should induce the intramolecular cyclisation of the enol ether onto the aldehyde of intermediate **376** (similar cyclisations were observed in the construction of β-hydroxycyclohexanones, see chapter 3) generating oxonium ion **377**. In the absence of water another nucleophile may react with the oxonium ion **377**. If the hydroperoxide group is present it could cyclise onto the oxonium group forming *endo* peroxide **373**, *Scheme 112*.

Scheme 112



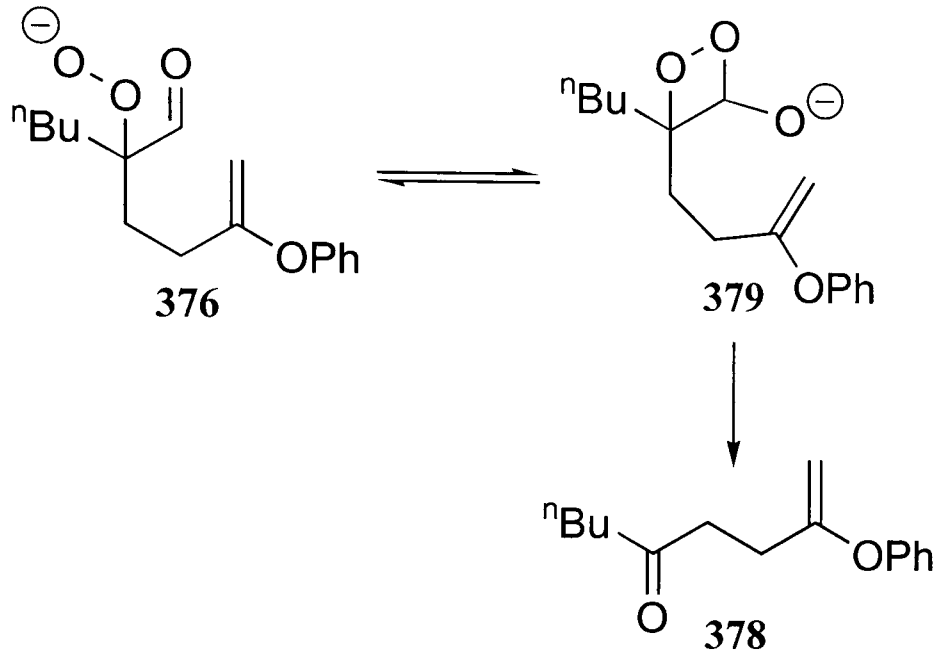
We carried out the AOC rearrangement of alcohol **240** and quenched with oxygen at -78°C. We employed a number of Lewis acids ($BF_3.OEt_2$, ethereal hydrochloric acid and TBSOTf) to induce cyclisation, but we consistently isolated only phenol from the reaction mixture, i.e. any other products were volatile or water soluble and lost during work-up. To test whether the oxygen had been incorporated the reaction was quenched at -78°C after the oxygenation with pH 7 phosphate buffer and we found that 1,4-keto enol ether **378** had formed in 71% yield, *Scheme 113*.

Scheme 113



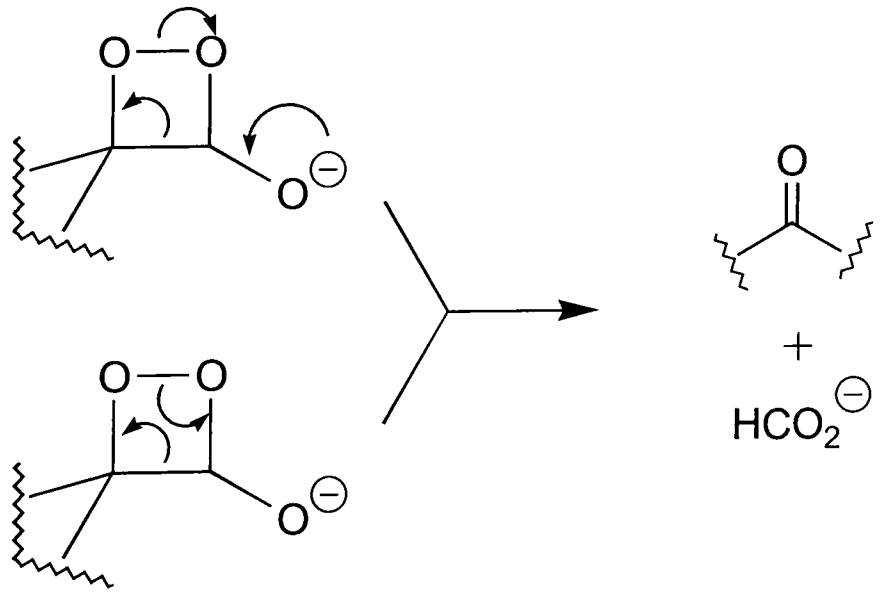
Hydroperoxide **376** exists in equilibrium with dioxetane **379**. Ketone **378** is the product of fragmentation of **379**, *Scheme 114*. Attempted trapping of dioxetane **379** with *tert*-butyldimethylsilyl trifluoromethanesulfonate at -78°C also resulted in formation of **378**. This observation implied that fragmentation of the dioxetane occurred as soon as it formed and that we would not be able to use our methodology to construct peroxy bridged compounds.

Scheme 114



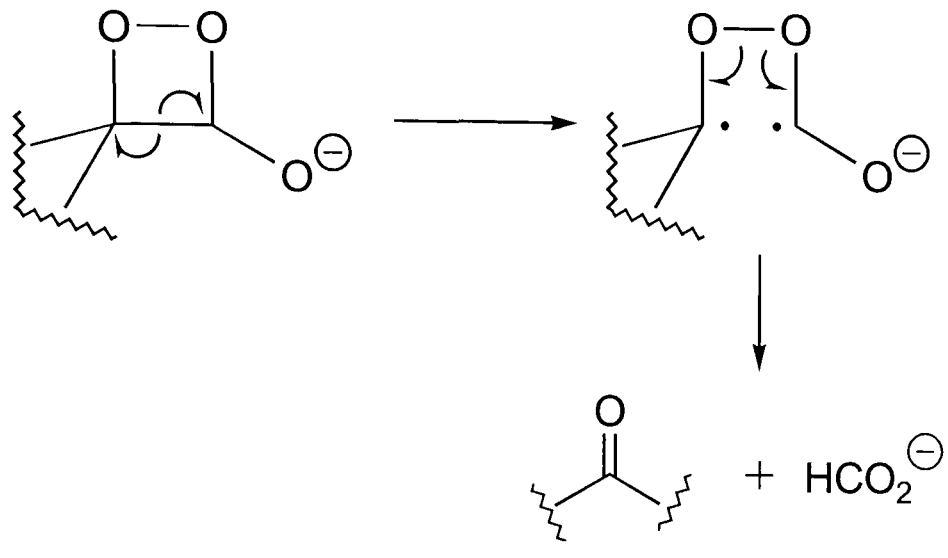
There are three possible mechanisms by which dioxetane **379** can fragment; an ionic process; a symmetry forbidden reverse [2+2]cycloaddition, *Scheme 115*, and homolytic fission, *Scheme 116*.

Scheme 115



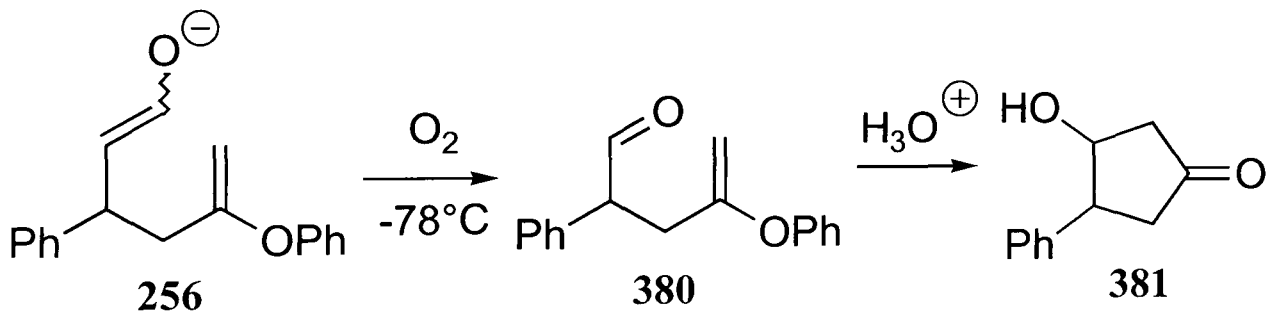
In the latter case two carbon centred radicals are generated which are stabilised by adjacent oxygen atoms.

Scheme 116



Having deduced that oxygenation of enolates generated by the AOC rearrangement led to fragmentation, we attempted to use this reaction to construct 5-membered rings in an analogous fashion to synthesis of cyclohexanones. Oxygenation of enolate **256** followed by fragmentation should generate aldehyde **380** and subsequent treatment with aqueous acid should furnish β-hydroxycyclopentanone **381**. All attempts proved to be unsuccessful.

Scheme 117

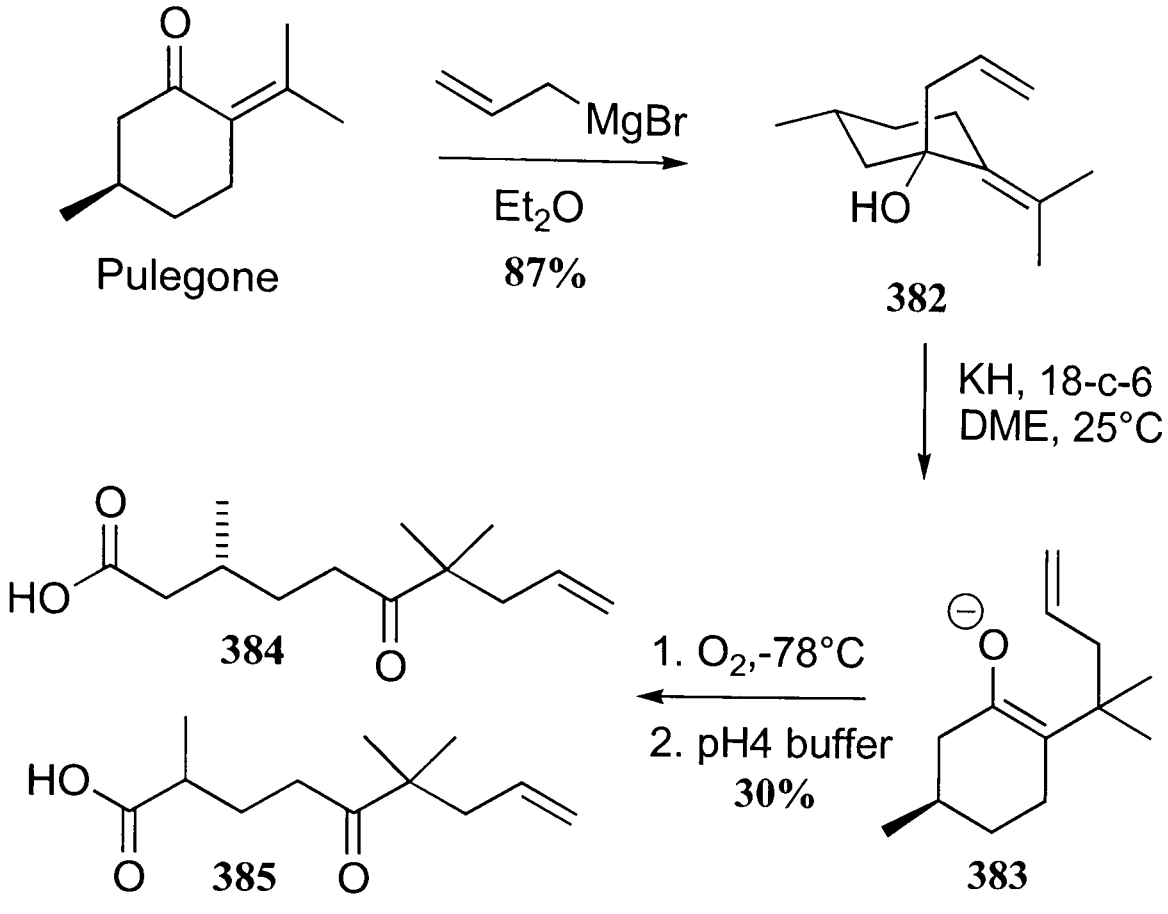


We decided to change our strategy slightly by trying to isolate aldehyde **380** by quenching after oxygenation with aqueous sodium hydrogen carbonate. **380** was isolated but only in 8% yield.

Autooxidation of enolisable carbonyl groups is well known. Regiocontrol can be problematic and multiple fragmentations can occur. Since our oxygenation-fragmentation occurs at low temperature and the position of the enolate is determined by the AOC rearrangement, we believed that our rearrangement-fragmentation would

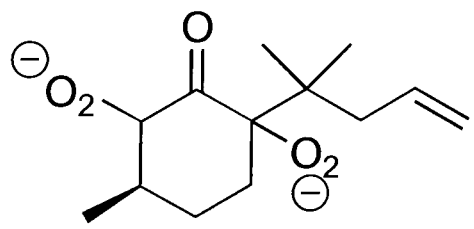
have great synthetic utility. Consequently, we investigated the cleavage of enolates generated from terpene derivatives.

Scheme 118



Treatment of pulegone with allyl magnesium bromide generated hexadienol **382**. The allyl substituent is axial in the product because an equatorial group is strongly disfavoured by 1,3-allylic strain. AOC rearrangement of **382** gave enolate **383** and subsequent oxygenation produced a mixture of **384** and **385**. Carboxylic acid **384** is the expected product but compound **385** is the product of double fragmentation of intermediate **386**, *Figure 26.*

Figure 26

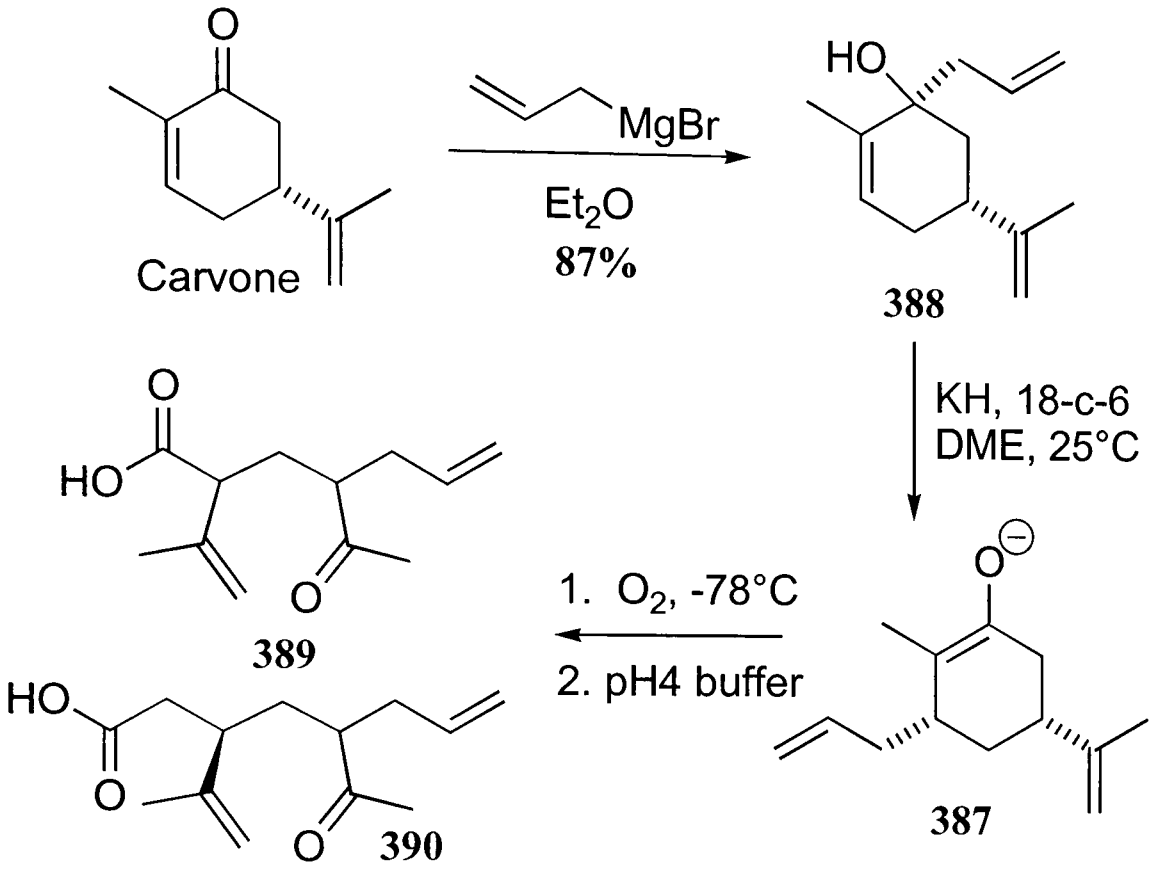


386

Three equivalents of potassium hydride are required to bring about the AOC rearrangement and hence after oxygenation the excess base deprotonates the ketone

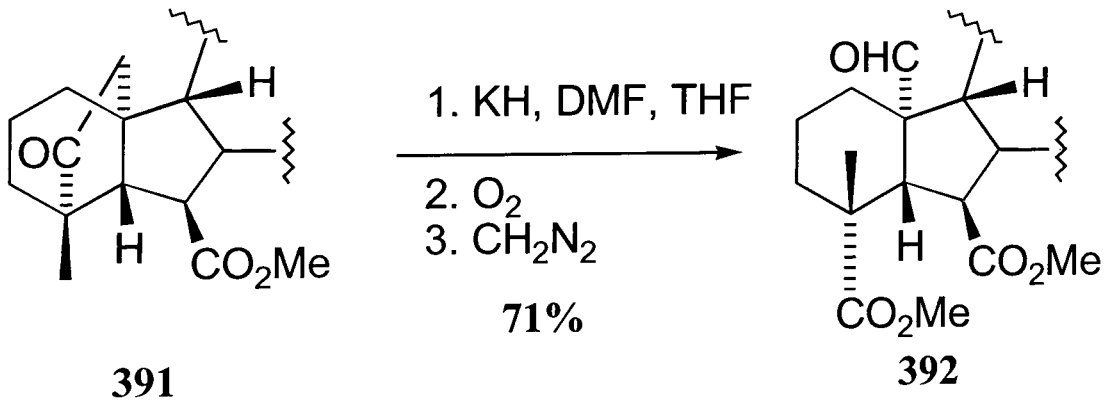
leading to further oxygenation and fragmentation and generation of carboxylic acid **385**. We observed the same behaviour for oxygenation of enolate **387**, *Scheme 119*.

Scheme 119



Alcohol **338** is formed by treatment of carvone with allyl magnesium bromide in 87% yield. AOC rearrangement and subsequent oxygenation generates carboxylic acids **389** and **390** in 58% combined yield. The stereochemical integrity could not be maintained α to the acetyl group.

Scheme 120



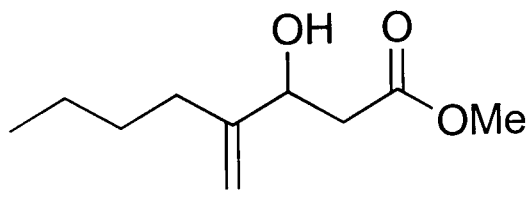
During the course of our work Mander and co-workers reported the oxygenation-fragmentation of a potassium enolate in high yield.[78] Ketone **391** can only enolise on one side, because the other side is blocked, so double fragmentation cannot occur.

One possible way around the problem of double oxygenation/fragmentation would be to trap enolates **383** and **387** as silyl enol ethers. [2+2]cycloaddition reactions of such enol silanes with singlet oxygen is many times faster than the corresponding reaction with unfunctionalised double bonds and it may be possible to selective generate carboxylic acids **384** and **390** since the problems with this route are all associated with the excess base required to induce the AOC rearrangement. Due to time constraints we were unable to test this theory.

5. EXPERIMENTAL

THF, ether and DME were freshly distilled from sodium/benzophenone. Dichloromethane, hexane and all amines were distilled from CaH_2 prior to use. DMF was distilled from BaO and stored over 4Å molecular sieves. 18-crown-6 was dried by azeotrope with toluene. Purification by column chromatography was carried out on Fisher Matrex™ silica gel, mesh size 35-70 μm, Fluka basic alumina Brockmann grade III or Aldrich neutral alumina Brockmann grade III mesh size ~150. Thin layer chromatography was carried out using Merck silica gel 60 F_{254} foil-backed plates, (0.25mm layer thickness), or Merck aluminium oxide 60 F_{254} neutral (type E) foil-backed plates (0.2mm layer thickness). The plates were visualised by illumination with UV light, iodine vapour, permanganate solution or vanillin solution. Melting points are uncorrected. IR spectra were recorded using a Nicolet Impact 410 FTIR spectrometer. NMR spectra were recorded using Bruker AM-200SY, WP-200SY, AM-360 and DPX-400 spectrometers. Chemical shifts are given using residual $CHCl_3$ as an internal standard (7.26 ppm). The multiplicities of ^{13}C nuclei were determined using the DEPT pulse sequence. Mass spectra were recorded on a Jeol JMS700 spectrometer. Combustion analysis was carried out using a Carlo-Erba 1106 elemental analyser.

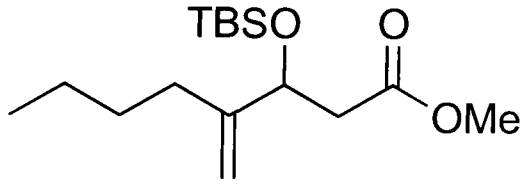
Methyl 3-hydroxy-4-methyleneoctanoate 225



Methyl acetate (3.97 cm^3, 0.05 mol) was added to a stirred solution of LDA [from 41.6 cm^3 of 1.2 mol dm^{-3} butyllithium in hexane and 6.5 cm^3 of diisopropylamine in dry THF (100 cm^3)] in THF/hexane at -78 °C, under nitrogen. Stirring was continued for 80 min after which time 2-butyl acrolein (6.65 cm^3, 0.05 mol) was added. Stirring

continued for a further 25 min, the mixture was then poured into aqueous hydrochloric acid (1 mol dm^{-3}, 250 cm^3), extracted with ether (2 × 200 cm^3), dried ($MgSO_4$) and concentration *in vacuo*. Chromatography on silica, eluting with hexane-ether (10:1) gave ester **225** as an oil (8.71 g, 94 %). R_f SiO_2 (hexane-ethyl acetate) 0.47; ν_{max} (Thin film) 3465, 2956, 1739 (C=O), 1649 (C=C), 1438 and 1038 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.02 (1H, br s, =C*H*H), 4.81 (1H, br s, =CH*H*), 4.42 (1H, dd, *J* 4.4 and 7.8, C*H*OH), 3.64 (3H, s, OMe), 2.88 (1H, br s, O*H*), 2.60-2.39 (2H, m, CH_2CO), 2.11-1.83 (2H, m, PrCH_2), 1.46-1.09 (4H, m, MeCH_2CH_2) and 0.84 (3H, t, *J* 7.02, CH_2Me); δ_C (50 MHz) 171.1 (C), 148.5 (C), 107.8 (CH_2), 69.1 (CH), 49.9 (CH_3), 38.8 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 20.8 (CH_2) and 12.2 (CH_3); *m/z* 186 (2.3, M^+), 143 (41), 129 (64), 112 (53), 97 (44) and 71 (100), [Found: M^+, 186.1250. $C_{10}H_{18}O_3$ requires *M*186.1256].

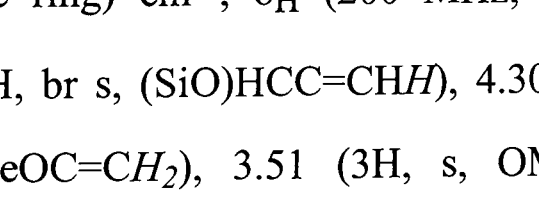
Methyl 3-(*tert*-butyldimethylsilyloxy)-5-methyleneoctanoate 226



N-Ethyldiisopropylamine (25 cm^3, 0.144 mol) then *tert*-butyldimethylsilyl chloride (14.6 g, 0.096 mol) were added to a stirred solution of ester **225** (9 g, 0.048 mol) in dry DMF (50 cm^3), under nitrogen at 0 °C. The ice bath was removed and stirring was continued for 17 h at room temperature. The solution was then poured into aqueous saturated sodium bicarbonate and extracted with ether (2 × 200 cm^3). The combined ethereal extracts were washed with aqueous hydrochloric acid (1 mol dm^{-3}, 2 × 150 cm^3) then brine (150 cm^3) and dried ($MgSO_4$). The solvent was removed and chromatography on silica, eluting with hexane-ether (10:1) gave silyl ether **226** as an oil (13.24 g, 92 %). R_f SiO_2 (CH_2Cl_2) 0.67; ν_{max} (Thin film) 2956, 2930, 1745 (C=O) and 1649 (C=C) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.03 (1H, br s, =C*H*H), 4.77 (1H, br s, =CH*H*), 4.52 (1H, dd, *J* 4.8 and 8.2, C*H*OSi), 3.63 (3H, s, OMe), 2.55-2.38

(2H, m, CH_2CO), 2.05-1.91 (2H, m, $PrCH_2$), 1.48-1.23 (4H, m, $MeCH_2CH_2$), 0.88 (3H, t, *J* 6.6, CH_2Me), 0.83 (9H, s, $SiCMe_3$), 0.00 (3H, s,Si*Me*) and -0.03 (3H, s,Si*Me*); δ_C (50 MHz) 170.3 (C), 149.3 (C), 108.3 (CH_2), 71.9 (CH), 49.8 (CH_3), 41.3 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 24.0 (CH_3), 21.0 (CH_2), 16.4 (C), 12.4 (CH_3), -6.3 (CH_3) and -7.1 (CH_3); *m/z* 243 (55, M^+ -^{t}Bu), 147 (100), 131 (20), 89 (71) and 75 (68), [Found: (M^+-^{t}Bu) 243.1422. $C_{12}H_{23}O_3Si$ requires *M-^{t}Bu·* 243.1416].

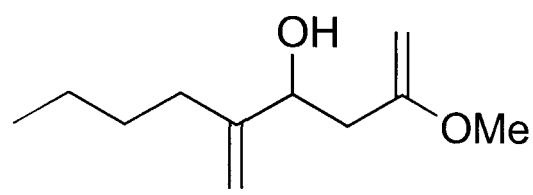
4-(*tert*-Butyldimethylsilyloxy)-2-methoxy-5-methylene-1-nonene 227



Tetramethylethylenediamine (12.1 cm^3, 80 mmol) was added to a stirred solution of titanium tetrachloride (4.4 cm^3, 40 mmol) in dry THF (40 cm^3) at 0 °C, under nitrogen and stirring was continued for 20 min. Zinc (5.9 g, 90 mmol) and a small portion of lead dichloride were then added and stirring was continued for a further 1 h. At this time a solution of dibromomethane (1.54 cm^3, 22 mmol) and ester **226** (3 g, 10 mmol) in dry THF was added over 5 min. The resulting mixture was stirred at room temperature for 2 h. Saturated potassium carbonate (25 cm^3) was added at 0 °C with stirring. After 15 min the mixture was poured into ether, filtered and the residue was washed through with ether until the residue turned pale green. The ethereal washings were combined and the solvent was removed under reduced pressure to give a white solid which was washed with hexane. The hexane washings were dried ($MgSO_4$), filtered through a short column of alumina and concentrated to give enol ether **227** as an oil (2.3 g, 77 %). R_f (hexane) 0.90; ν_{max} (Thin film) 2956, 2929, 1673 (C=C) and 1503 (aromatic ring) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 4.99 (1H, br s, (SiO)HCC=C*H*H), 4.76 (1H, br s, (SiO)HCC=CH*H*), 4.30 (1H, dd, *J* 5.4 and 7.2, C*H*OSi), 3.89 (2H, s, $MeOC=CH_2$), 3.51 (3H, s, OMe), 2.30-2.12 (2H, m, CH_2CHOSi), 2.08-1.87 (2H, m, $PrCH_2$), 1.53-1.26 (4H, m, $MeCH_2CH_2$), 0.92 (3H, t,

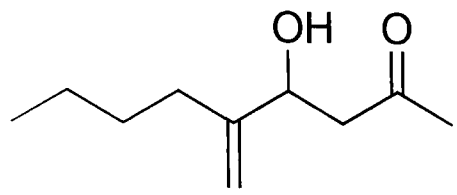
J 6.8, CH_2Me), 0.86 (9H, s, $SiCMe_3$), 0.00 (3H, s, $SiMe$) and -0.03 (3H, s, $SiMe$); δ_C (50 MHz) 159.1 (C), 150.4 (C), 107.2 (CH_2), 91.3 (CH_2), 72.4 (CH), 52.9 (CH_3), 41.9 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 24.2 CH_3), 21.1 (CH_2), 12.4 (CH_3), -6.4 (CH_3) and -6.9 (CH_3); *m/z* 298 (4, M^+), 241 (38, M^+ - ^tBu) and 227 (59, M^+ - $CH_3C(=CH_2)OCH_3$).

2-Methoxy-5-methylene-1-nonene-4-ol 228



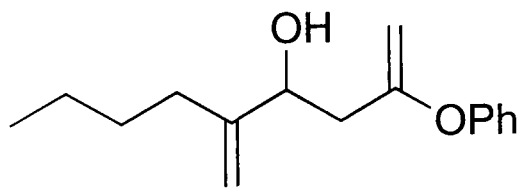
Tetrabutylammonium fluoride (3.04 cm^3 of a 1.1 mol dm^{-3} solution in dry THF) and 4Å molecular sieves (1.33 g, 4 weight eq.) were added to a solution of **227** (0.322 g, 1.11 mmol) in dry THF (15 cm^3). The resultant solution was stirred for 4 h then poured into pH 7 phosphate buffer solution (50 cm^3), extracted with ether (2 × 100 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure and purification by chromatography on alumina, eluting with hexane-ether (10:1) gave alcohol **228** as an oil (0.087 g, 42 %). ν_{max} 3491 (OH), 3074 (=CH), 1671, 1509 (aromatic ring), 1463 (aromatic ring), 1239, 1059 (C-O) and 793; δ_H (200 MHz; $CDCl_3$) 5.02 (1H, s, H(HO)CC=C*H*H), 4.79 (1H, s, (HO)HC=CH*H*), 4.17 (1H, dd, *J* 9.0 and 2.9, C*H*OH), 3.93 (1H, d, *J* 2.2, MeOC=CH*H*), 3.90 (1H, d, *J* 2.2, MeOC=C*H*H), 3.50 (3H, s, OMe), 2.41-2.11 (2H, m, CH_2CHOH), 2.04-1.91 (2H, m, PrCH_2), 1.46-1.18 (4H, m, MeCH_2CH_2) and 0.84 (3H, t, *J* 6.6, CH_2Me).

4-Hydroxy-5-methylene-2-nonnone 238



A solution of **228** (0.087 g, 0.047 mmol) in dry THF (5 cm^{-3}) was added to a flask containing palladium dichloride bisbenzonitrile (0.018 g, 0.047 mmol), under nitrogen, with stirring. The resulting solution was stirred for 1 h at room temperature. The solvent was evaporated and the residue was taken up into hexanes, filtered and the filtrate was concentrated *in vacuo* to give **238** as an oil. δ_H (200 MHz; $CDCl_3$) 5.03 (1H, s, H(HO)CC=C*H*H), 4.80 (1H, s, H(HO)C=CH*H*), 4.27 (1H, t, *J* 6.1, C*H*OH), 2.93 (1H, d, *J* 3.3, O*H*), 2.63-2.59 (2H, m, CH_2COMe), 2.13 (3H, s, CO*Me*), 2.04-1.90 (2H, m, PrCH_2), 1.47-1.18 (4H, m, MeCH_2CH_2) and 0.83 (3H,t, *J* 6.6, CH_2*Me*); δ_C (50 MHz) 207.8 (C), 148.5 (C), 107.9 (CH_2), 68.6 (CH), 47.3 (CH_2), 30.0 (CH_2), 29.1 (CH_3), 28.4 (CH_2),20.9 (CH_2) 12.3 (CH_3).

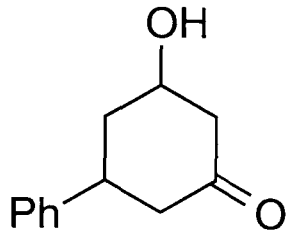
5-Methylene-2-phenoxy-1-nonen-4-ol 240



Silyl ether **246** (13.09 g, 41.2 mmol) was transformed into *Alcohol* **240** (2.2 g, 22 %) using the method described for **228** as a pale yellow oil. R_f (DCM) 0.71; ν_{max} (Thin film) 3450 (OH), 2954, 2929, 1645 (C=C), 1593 (aromatic ring) and 1493 (aromatic ring) cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.35-7.03 (5H, m, *Ph*), 5.15 (1H, s, (HO)HCC=CH*H*), 4.91 (1H, s, (HO)HCC=C*H*H), 4.45 (1H, dd, *J* 8.6 and 3.6, C*H*OH), 4.21 (1H, d, *J* 1.4, PhOC=C*H*H), 3.98 (1H, d, *J* 1.4, PhOC=CH*H*), 2.61 (1H, dd, *J* 14.3 and 3.6, CH^AH^BCHOH), 2.44 (1H, dd, *J* 14.3 and 8.6, CH^AH^B), 2.37 (1H,

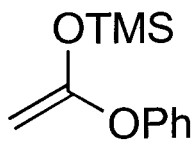
bs, OH), 2.18-1.98 (2H, m, =CCH_2), 1.52-1.26 (4H, m, MeCH_2CH_2) and 0.91 (3H, t, *J* 7.2, *Me*); δ_C (100 MHz) 160.5 (C), 154.8 (C), 150.9 (C), 129.6 (2 × CH), 124.4 (CH), 121.1 (2 × CH), 109.4 (CH_2), 90.5 (CH_2), 72.5 (CH), 41.1 (CH_2), 31.4 (CH_2), 30.1 (CH_2), 22.6 (CH_2) and 14.0 (CH_3); *m/z* 247 (43, $M+H^+$), 229 (100, $M+H^+-H_2O$), 169 (29), 153 (34) and 135 (65); HRMS Found $M+H^+$ 247.1700, $C_{16}H_{23}O_2$ requires 247.1702.

3-Hydroxy-5-phenylcyclohexanone 242



To a solution of **265** (0.1 g, 0.38 mmol) in ether (10 cm^3) was added aqueous hydrochloric acid (1 mol dm^{-3}, 10 cm^3) and the mixture was stirred for 15 min. The phases were separated and the aqueous was extracted with ether (10 cm^3). The organic phases were combined, dried (MgSO4) and concentrated to give alcohols **242** as an oil (0.49 g, mass balance 49 %). Products identified by comparison of ^1H NMR spectrum with definitive spectra supplied by A. P. Rutherford.[67]

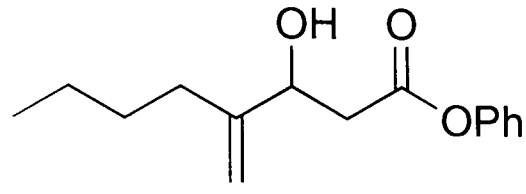
1-Phenoxy-1-trimethylsiloxyethylene 243



Silyl ketene acetal **243** was prepared on 10 mmol scale by the method of Slougui and Rousseau,[79] in 60 % yield, as a yellow oil of approximately 70% purity. ν_{max} (Thin film) 2960, 1662 (C=C), 1595 (aromatic ring), 1491 (aromatic ring), 1253 and 846 ($SiMe_3$) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.37-6.83 (5H, m, *Ph*), 3.52 (1H, d, *J* 2.4, =CH*H*), 3.29 (1H, d, *J* 2.4, =C*H*H) and 0.28 (9H, s, Si*Me*$_3$); δ_C (90 MHz) 167.1 (C),

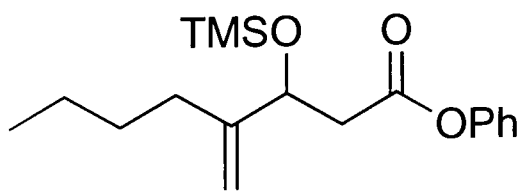
159.6 (C), 129.4 (2 × CH), 124.0 (CH), 119.8 (2 × CH), 68.4 (CH_2) and 1.3 (3 × CH_3); *m/z* 208 (2, M^+), 186 (3), 171 (39), 151 (80) and 135 (3, M^+ - TMS).

Phenyl 3-hydroxy-4-methyleneoctanoate 244



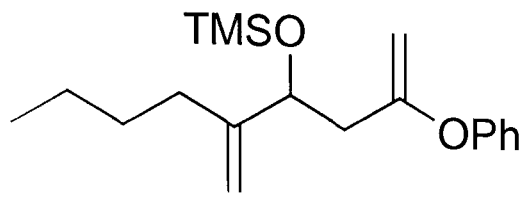
Aldol **244** (17.73 g, 82 %) was prepared from 2-butyl acrolein (11.5 g, 87 mmol) using the method described for **260** as an oil sufficiently pure for the next stage. R_f (DCM) 0.10; ν_{max} (Thin film) 3458 (OH), 2956, 2931, 1760 (C=O), 1650 (C=C), 1594 (aromatic ring) and 1493 (aromatic ring) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.42-7.04 (5H, m, *Ph*), 5.17 (1H, s, =CH*H*), 4.96 (1H, s, =C*H*H), 4.62 (1H, dd, *J* 7.6 and 5, C*H*OH), 2.93-2.74 (2H, m, CH_2C(O)), 2.30-1.97 (2H, m, =CCH_2), 1.93 (1H, d, *J* 1.6, O*H*), 1.67-1.15 (4H, m, MeCH_2CH_2) and 0.93 (3H, t, *J* 7.0, *Me*); *m/z* 249 (100, $M+H^+$), 231 (45, $M+H^+-H_20$) and 94 (61, PhOH); HRMS (CI mode) Found $M+H^+$ 249.1489, $C_{15}H_{21}O_3$ requires 249.1488.

Phenyl 4-Methylene-3-(trimethylsilyloxy)octanoate 245



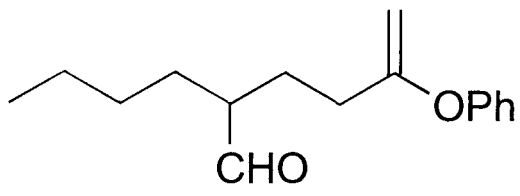
Using the method described for preparation of **264**, *alcohol* **244** (17 g, 68.5 mmol) was transformed into *silyl ether* **245** (18.5 g, 84 %, crude) as a red oil. This was used in the next step without further purification or characterisation.

4-(Trimethylsilyloxy)-2-phenoxy-5-methylene-1-nonene 246



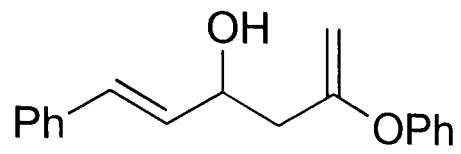
Using the method described for the preparation of **221**, enol ether **246** (13.09 g, 73 %, crude) was prepared from **245** (18 g, 0.225 mol) as a yellow oil. This was used in the next step without further purification or characterisation.

5-Formyl-2-phenoxy-1-nonene 256



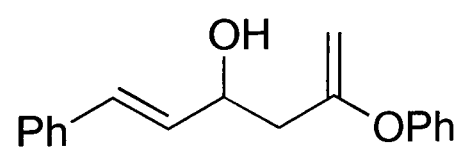
Aldehyde **256** was prepared (0.1 g, 59 %) as an oil from *hexadienol* **240** (0.17 g, 0.69 mmol) using the method described for synthesis of **265**. R_f (hexane-ether 5:1) 0.43; ν_{max} (Thin film) 2930, 1725 (C=O), 1593 (aromatic ring), 1491 (aromatic ring), 1220 and 693 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 9.63 (1H, d, *J* 2.5, C*H*O), 7.35-7.00 (5H, m, *Ph*), 4.15 (1H, s, =C*H*H), 3.94 (1H, s, =CH*H*), 2.40-2.36 (1H, m, C*H*CHO), 2.32-2.27 (2H, m, =CCH_2), 2.00-1.94 (2H, m, =CCH$_2$CH_2), 1.79-1.64 (2H, m, PrCH_2), 1.53-1.46 (2H, m, EtCH_2), 1.34-1.26 (2H, m, MeCH_2) and 0.90 (3H, t, *J* 7.2, *Me*); δ_C (50 MHz) 205.0 (CH), 162.3 (C), 155.1 (C), 129.5 (2 × CH), 124.0 (CH), 120.9 (2 × CH), 89.0 (CH_2), 51.0 (CH), 31.5 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 22.7 (CH_2) and 13.8 (CH_3); *m/z* 246 (5, $M^{+}\cdot$), 229 (14), 183 (23), 149 (32), 94 (45) and 43 (100) HRMS (EI mode) Found $M^{+}\cdot$ 246.2019, $C_{16}H_{22}O_2$ requires 246.2026.

2-Phenoxy-6-phenyl-1,5-hexadien-4-ol 259



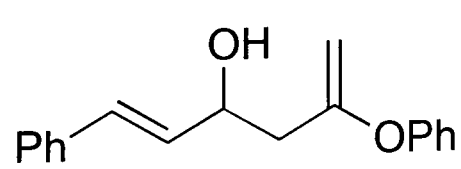
Using the method described for preparation of **228**, *enol ether* **262** (4.2 g, 11 mmol)was converted to *alcohol* **259** (0.93 g, 32 %). R_f (DCM) 0.63; ν_{max} (Thin film) 3384 (OH), 1640 (C=C), 1592 (aromatic ring), 1491 (aromatic ring) and 1218 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.43-7.02 (10H, m, 2 × *Ph*), 6.70 (1H, d, *J* 15.8, =C*H*Ph), 6.31 (1H, dd, *J* 15.8 and 6.1, =C*H*CHOH), 4.78-4.63 (1H, m, C*H*OH), 4.25 (1H, d, *J* 1.8, =C*H*H), 4.02 (1H, d, *J* 1.8, =CH*H*), 2.66 (1H, dd, *J* 12.9 and 4.6, C*H*^{A}H^B), 2.58 (1H, dd, *J* 12.9 and 7.9 CH^A*H*^{B}) and 2.31(1H, bs, O*H*); δ_C (50 MHz) 159.8 (C), 154.8 (C), 136.6(C), 131.1 (CH), 130.5 (CH), 129.6 (2 × CH), 128.5 (2 × CH), 127.6 (CH), 126.5 (2 × CH), 124.4 (CH), 121.1 (2 × CH), 91.0 (CH_2), 70.4 (CH) and 42.4 (CH_2); *m/z* 266 (3, M^+), 248 (6, $M^+ - H_2O$), 173 (10), 155 (8) and 133 (100); HRMS (EI mode) Found $M^{+\cdot}$ 266.1306, $C_{18}H_{18}O_2$ requires 266.1305.

5-Phenoxy-1-phenyl-1,5-hexadien-3-ol 259



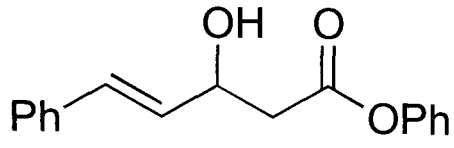
Using the method described for preparation of **228**, *silyl ether* **264**(TES) (1.5 g, 3 mmol) was converted to *alcohol* **259** (0.62g, 64 %) as a pale yellow oil. Data as above.

2-phenoxy-6-phenyl-1,5-hexadien-4-ol 259



The procedure described for preparation of **227** was used to convert silyl ether **264**(TMS) (30.7 mmol) to *enol ether* **258**. Crude **258** (30.7 mmol) carried forward without purification and used, according to the method described for synthesis of **228**, to generate *alcohol* **259** (1.801 g, 25 % from **260**) as a pale yellow oil. Data as above.

Phenyl 3-hydroxy-5-phenyl-4-pentenoate 260

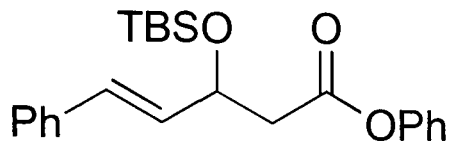


$BF_3.OEt_2$ (11.2 cm^3, 0.09 mol) was added to a stirred solution of *E* cinnamaldehyde (11.5 cm^3, 0.09 mol) in dry CH_2Cl_2 (200 cm^3) over 0.5 h at -78 °C under nitrogen. After stirring for 30 min at -78 °C, silyl ketene acetal **243** (19 g, 0.09 mol, approx. 70% pure) was added, over 30 min and stirring was continued at -78 °C for 30 min. The temperature was allowed to rise to -30 °C over 30 min and stirring was continued for a further 3 h. The mixture was then poured into pH 7 phosphate buffer (200 cm^3) and warmed to room temperature. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 cm^3), the organic washings were combined, dried ($MgSO_4$) and concentrated to give *ester* **260** as needles (8.25 g, 43 %*). R_f (DCM) 0.13; Mp 99-101 °C; ν_{max} (KBr) 3447 (OH), 1737 (C=O), 1489 (C=C), 1195, 1145, 743 and 690 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.35-6.99 (10H, m, 2 × *Ph*), 6.65 (1H, d, *J* 15.9, =C*H*Ph), 6.23 (1H, dd, *J* 15.9 and 6.2, =C*H*CHOH), 4.77 (1H, m, C*H*OH), 2.84 (2H, d, *J* 6.7, CH_2) and 2.76 (1H, bs, O*H*); δ_C (100 MHz) 170.6 (C), 150.3 (C), 136.2 (C), 131.1 (CH), 129.6 (CH), 129.5 (2 × CH), 128.6 (2 × CH), 127.9 (CH), 126.5 (2 × CH), 126.0 (CH), 121.4 (2 × CH), 68.9 (CH) and 41.7 (CH_2); *m/z* 268 (5, $M^{+}\cdot$), 175 (49, $M^{+}\cdot$ - PhO·), 157 (16.4, $M^{+}\cdot$ -PhO· and H_2O), 133

(96), 115 (29) and 94 (100, PhOH); Found C 75.91, H 5.91 %, $C_{17}H_{16}O_3$ requires C 76.12, H 5.97 %.

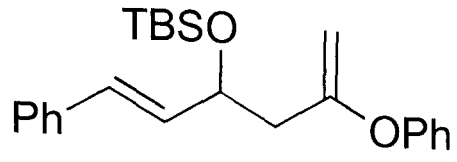
* based on the aldehyde

Phenyl 3-(*tert*-butyldimethylsilyloxy)-5-phenyl-4-pentenoate 261



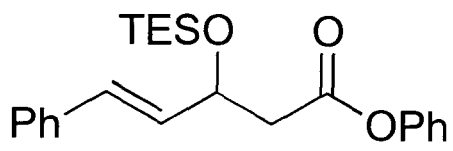
N-Ethyldiisopropylamine (10.5 cm^3, 0.06 mol) then *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.3 cm^3, 0.045 mol)were added to a stirred solution of ester **260** (8 g, 0.03 mol) in dry DCM (40 cm^3) at 0 °C under nitrogen. The ice bath was removed and stirring was continued for 30 min at room temperature. The mixture was then poured into aqueous saturated sodium bicarbonate (100 cm^3) and the product was extracted with ether (2 × 100 cm^3). The combined ethereal extracts were washed with aqueous hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3) then brine (50 cm^3) and dried ($MgSO_4$). The solvent was removed and chromatography on silica, eluting with hexane-ether (10:1), gave *silyl ether* **261** as an oil (9.16 g, 80 %). R_f (DCM) 0.70; ν_{max} (Thin film) 2955, 2929, 1760 (C=O), 1593 (C=C), 1492 (aromatic ring), 1192 and 837 (Si-C) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.38-7.02 (10H, m, 2 × *Ph*), 6.62 (1H, d, *J* 15.9, C*H*Ph), 6.25 (1H, dd, *J* 15.9 and 6.8, =C*H*COSi), 4.86 (1H, bq, C*H*OSi), 2.87 (1H, dd, *J* 14.8 and 7.6, C*H*^{A}H^B), 2.76 (1H, dd, *J* 14.8 and 5.7, CH^A*H*^{B}), 0.90 (9H, s, SiC*Me*$_3$), 0.08 (3H, s, Si*Me*) and 0.06 (3H, s, Si*Me*); δ_C (50 MHz) 169.4 (C), 150.5 (C), 136.4 (C), 131.3 (CH), 130.3 (CH), 129.3 (2 × CH), 128.6 (2 × CH), 127.7 (CH), 126.5 (2 × CH), 125.7 (CH), 121.5 (2 × CH), 70.6 (CH), 43.9 (CH_2), 25.8 (3 × CH_3), 18.1 (C), -4.1 (CH_3) and -4.8 (CH_3); *m/z* 325 (80, $M^{+\cdot}$ - ^{t}Bu), 247 (15), 193 (30), 151 (81) and 73 (100); HRMS (CI mode) Found M+NH_4^+ 400.2302, $C_{23}H_{34}O_3NSi$ requires 400.2296.

4-(*tert*-Butyldimethylsilyloxy)-2-phenoxy-6-phenyl-1,5-hexadiene 262



Ester **261** (9 g, 24 mmol) was converted to *Enol ether* **262** (4.32 g, 47 %) using the method desribed for synthesis of **221**, as an oil in a yield of 47 %. R_f (hexane) 0.92; ν_{max} (Thin film) 2955, 2930, 1717 (C=C), 1594 (aromatic ring), 1070 (C-O) and 811 (Si-C) cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.45-7.08 (10H, m, 2 × *Ph*), 6.65 (1H, br d, *J* 15.8, =C*H*Ph), 6.34 (1H, dd, *J* 15.8 and 6.4, =C*H*COSi), 4.73 (1H, br q, C*H*OSi), 4.27 (1H, d, *J* 1.4, =C*H*H), 4.07 (1H, d, *J* 1.4, =CH*H*), 2.68 (1H, dd, *J* 13.8 and 6.8, C*H*^{A}H^B), 2.54 (1H, dd, *J* 13.8 and 6.4, CH^A*H*^{B}), 1.00 (9H, s, SiC*Me*$_3$), 0.20 (3H, s, Si*Me*) and 0.14 (3H, s, Si*Me*); *m/z* 381 (6, $M+H^+$), 365 (4, M^+ - Me), 323 (12, M^+ - ^{t}Bu) 291 (12) and 249 (100); HRMS (CI mode) Found $M+H^+$ 381.2248, $C_{24}H_{33}O_2Si$ requires 381.2254.

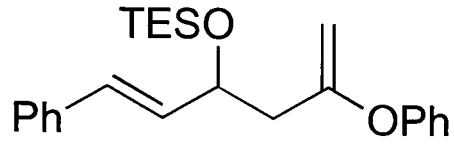
Phenyl 5-phenyl-3-(triethylsilyloxy)-4-pentenoate 263



N-Ethyldiisopropylamine (5.87 cm^3, 0.034 mol) then triethylsilyl chloride (5.63 g, 0.034 mol) to a stirred solution of ester **260** (4.5 g, 0.017 mol) in dry DMF (50 cm^3), under nitrogen at 0 °C. The ice bath was removed and stirring was continued for 17 h at room temperature. The solution was then poured into aqueous saturated sodium bicarbonate and extracted with ether (2 × 100 cm^3). The combined ethereal extracts were washed with aqueous hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3) then brine (50 cm^3) and dried ($MgSO_4$). The solvent was removed and chromatography on silica, eluting with hexane-ether (20:1) gave *silyl ether* **263** as an oil (4.23 g, 66 %). R_f (DCM) 0.70; ν_{max} (Thin film) 2955, 2876, 1718, 1359, and 745 cm^{-1}; δ_H (200 MHz;

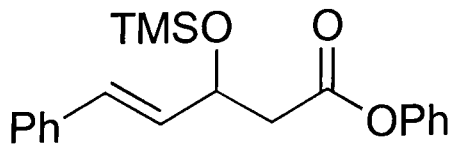
$CDCl_3$) 7.34-6.95 (10H, m, 2 × *Ph*), 6.52 (1H, d, *J* 15.8, =C*H*Ph), 6.20 (1H, dd, *J* 15.8 and 7.0, =C*H*COSi), 4.80 (1H, q, *J* 6.5 C*H*OSi), 2.84 (1H, dd, *J* 14.8 and 7.4 C*H*^{A}H^B), 2.70 (1H, dd, *J* 14.8 and 5.8, CH^A*H*^{B}), 0.89 (9H, t, *J* 8.1, 3 × CH_2CH_3) and 0.57 (6H, q, *J* 8.1, 3 × SiCH_2); *m/z* 325 (63, M^+-.-^{t}Bu), 304 (40, M^+ - PhH), 193 (32), 151 (83) and 94 (100, PhOH); HRMS (CI mode) Found M+NH_4^+ 400.2300, $C_{23}H_{34}O_3NSi$ requires 400.2296.

4-(triethylsilyloxy)-2-phenoxy-6-phenyl-1,5-hexadiene 264(TES)



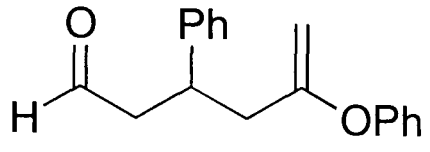
Enol ether **264**(TES) (1.68 g, 44 %) was prepared from *ester* **263** (4 g, 10 mmol) as a pale yellow oil using the method described for preparation of **221**. R_f (hexane) 0.88; ν_{max} (Thin film) 2954, 2876, 1593 (C=C), 1492 (aromatic ring) and 1219 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.42-7.04 (10H, m, 2 × *Ph*), 6.70 (1H, d, *J* 15.9, =C*H*Ph), 6.31 (1H, dd, *J* 15.9 and 6.0, =C*H*COSi), 4.68 (1H, bq, *J* 6.7 C*H*OSi), 4.22 (1H, d, *J* 1.6, =C*H*H), 4.00 (1H, d, *J* 1.6, =CH*H*), 2.76-2.47 (2H, m, CH_2), 0.95 (9H, q, *J* 8.1, 3 × SiCH_2*Me*) and 0.64 (6H, t, *J* 8.1, 2 × SiCH_2); δ_C (90 MHz) 159.5 (C), 155.1 (C), 137.0 (C), 132.4 (CH), 129.54 (CH), 129.50 (2 × CH), 128.5 (2 × CH), 127.3 (CH), 126.4 (2 × CH), 123.9 (CH), 120.8 (2 × CH), 91.1 (CH_2), 71.1 (CH), 43.6 (CH_2), 6.8 (3 × CH_3) and 4.9 (3 × CH_2); *m/z* 380 (1, M^+), 351 (2, M^+ - Et), 287 (M^+ - OPh) and 247 (100); HRMS (EI mode) Found M^+· 380.2169, $C_{24}H_{32}O_2Si$ requires 380.2166.

Phenyl 3-(trimethylsilyloxy)-5-phenyl-4-pentenoate 264



N-Ethyldiisopropylamine (8.04 cm^3, 0.046 mol) then chlorotrimethylsilane (5.84 cm^3, 0.046 mol) were added to a solution of ester **260** (8.25 g, 0.0307 mol) in dry CH_2Cl_2 (150 cm^3) with stirring at 0°C under nitrogen. Stirring was continued for 13 h at room temperature. Hexane was added to the mixture which was then filtered and concentrated to give the *silyl ether* **264**(TMS)**.** This material was used in the next stage without further purification or characterisation.

5-phenoxy-3-phenyl-5-hexenal 265

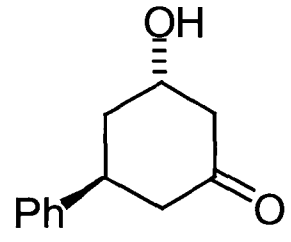


A solution of **259** (0.1 g, 0.38 mmol) and 18-crown-6 (0.2 g, 0.74 mmol) in dry THF (1 cm^3) was added to a flask containing potassium hydride (0.11 g of a 35 % dispersion in mineral oil prewashed with dry hexane 4 × 2 cm^3), in dry THF (5 cm^3) under nitrogen. The resulting mixture was stirred for 2 h at room temperature then poured into aqueous saturated sodium bicarbonate (50 cm^3). The product was extracted into ether (2 × 50 cm^3) and dried ($MgSO_4$). Purification by chromatography on alumina, eluting with hexane-ether (20:1), gave *aldehyde* **265** as an oil (0.041 g, 41 %). R_f (hexane-ether, 5:1) 0.40; ν_{max} (Thin film) 2924, 1724 (C=O), 1634 (C=C), 1592 (aromatic ring), 1491 (aromatic ring) and 1218 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 9.63 (1H, t, *J* 2.0, C*H*O), 7.29-6.82 (10H, m, 2 × *Ph*), 3.96 (1H, d, *J* 1.8, =CH*H*), 3.77 (1H, d, *J* 1.8, =C*H*H), 3.63 (1H, qn, *J* 7.6, C*H*Ph), 2.83 (1H, ddd, *J* 16.7, 6.2 and 1.9, C*H*^{A}H^{B}CHO), 2.71 (1H, ddd, *J* 16.7, 8.4 and 2.1, CH^A*H*^{B}CHO), 2.54 (1H, d, =CCH*H*) and 2.52 (1H, d, =CC*H*H); δ_C (50 MHz) 201.8 (CH), 160.4 (C), 154.8 (C), 142.9 (C), 129.5 (2 × CH), 128.6 (2 × CH), 127.5 (2 × CH), 126.6 (CH), 124.4 (CH), 121.0 (2 × CH), 90.3 (CH_2), 49.3 (CH_2), 41.3 (CH_2) and 37.7 (CH); *m/z* 267 (100, $M+H^+$), 249 (22) and 173 ($M+H^+$ - HOPh); HRMS (CI mode) Found $M+H^+$ 267.1386, $C_{18}H_{19}O_2$ requires 267.1385.

5-Phenoxy-3-phenyl-5-hexenal 265

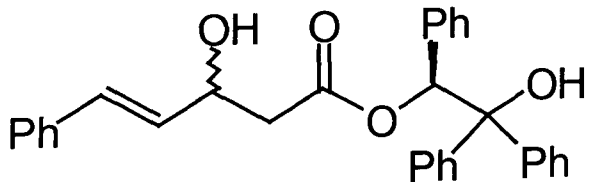
A solution of **259** (0.103 g, 0.38 mmol) and 18-crown-6 (0.2 g, 0.74 mmol) in dry DME (1 cm^3) was added to a flask containing potassium hydride (0.11 g of a 35 % dispersion in mineral oil prewashed with dry hexane 4 × 2 cm^3), in dry DME (5 cm^3) under nitrogen. The resulting mixture was stirred for 2 h at room temperature then poured into aqueous saturated sodium bicarbonate (50 cm^3). The product was extracted into ether (2 × 25 cm^3), dried ($MgSO_4$) and concentrated to give *aldehyde* **265** as an oil containing minor impurities (0.061 g, 61 %). Data as above.

3-Hydroxy-5-phenylcyclohexanone 275



Alcohol **289** (50 mg, 0.23 mmol) was transformed into *cyclohexanone* **275** (31 mg, 70 %), after trituration from diethyl ether at 0 °C, using the method described for the preparation of *alcohol* **326**. *Cyclohexanone* **275** identified by comparison with spectra supplied by A. P. Rutherford.[67]

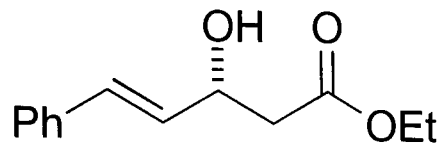
(1*R*, 3'*RS*, *E*) 2-Hydroxy-1,1,2-triphenyl-1-ethyl 3'-hydroxy-5'-phenyl-4'-pentenoate 285



2(*R*)-Acetoxy-1,1,2-triphenylethanol (3.0 g, 9 mmol) was added to a stirred solution of lithium bis(trimethylsilyl)amide [from 16.2 cm^3 of 2.5 mol dm^{-3} butyllithium in

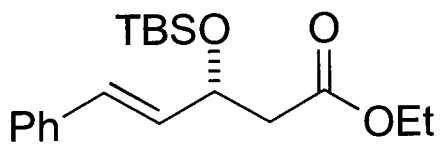
hexanes and hexamethyldisilazane (8.5 cm^3, 40.5 mmol) in dry THF] in THF/hexanes (c. 50 cm^3), at -35 °C under nitrogen, in portions. The mixture was warmed to -10 °C and stirred for 45 min to observe a yellow dianion solution. This solution was then chilled to -100 °C and a solution of *E*-cinnamaldehyde (1.25 cm^3, 9.9 mmol) in dry THF (5 cm^3) was added dropwise. The reaction mixture was stirred for 1.5 h and then quenched with aqueous saturated ammonium chloride (25 cm^3). Ethyl acetate (25 cm^3) was added and the organic phase was separated, washed with aqueous saturated ammonium chloride (2 × 20 cm^3) then brine (20 cm^3), dried ($MgSO_4$) and concentrated to a solid. This crude solid was washed with boiling propan-2-ol to give **285** as a 96:4 mixture of diastereomers (*R,R*) and (*S,R*) (2.62 g, 63 %). R_f (CH_2Cl_2-hexane, 5:1) 0.33; ν_{max} (KBr) 3434 (OH), 3059 (=CH), 2924, 1722 (C=O), 1494 (aromatic ring), 1448 (aromatic ring), 1156, 750 and 697cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.43-6.83 (20$H^{RR\&SR}$, m, 4 × *Ph*), 6.58 (1H^{RR}, s, OC*H*Ph), 6.52 (1H^{SR}, s, OC*H*Ph), 6.38 (1$H^{RR\&SR}$, dd, *J* 15.9 and 1.2, Ph C*H*=), 5.91 (1$H^{RR\&SR}$, dd, *J* 15.9 and 6.1, PhCH=C*H*), 4.40 (1$H^{RR\&SR}$, m, C*H*OH), 2.76 (1H^{SR}, s, O*H*), 2.72 (1H^{RR}, s, O*H*) and 2.41 (2$H^{RR\&SR}$, d, *J* 6.2, CH_2). δ_C (90 MHz) 170.6 (C), 144.4 (C), 142.4 (C), 136.2 (C), 135.3 (C), 130.8 (CH), 129.3 (CH), 128.4 (2 × CH), 128.36 (2 × CH), 128.30 (2 × CH), 128.0 (CH), 127.7 (3 × CH), 127.5 (2 × CH), 127.4 (CH), 127.0 (CH),126.4 (2 × CH), 126.1 (2 × CH), 126.0 (2 × CH), 80.1 (C), 79.0 (CH), 68.6 (CH) and 41.8 (CH_2); *m/z* 480 (2, $M+NH_4^+$), 462 (17, $M+NH_4^+ - H_2O$), 446 (33, M^+-H_2O), 378 (56), 209 (100), 154 (40), 78 (21) and 55 (11); HRMS (CI mode) Found $M+NH_4^+$ 482.2332, $C_{31}H_{32}NO_4$ requires 482.2331.

(*R*)-3-hydroxy-5-phenyl-4-pentenoate 286



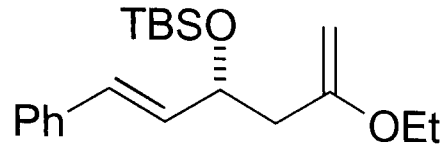
A mixture a **285** (2.56 g, 0.0055 mol) and potassium carbonate (0.38 g, 0.00275 mol), in dry ethanol (40 cm^3), was sonicated at 25 °C for 4h at which time a yellow solution formed. This solution was stirred for a further 20 h then poured into a mixture of aqueous saturated ammonium chloride (20 cm^3) and ethyl acetate (50 cm^3). The organic phase was separated, washed with water (20 cm^3) then brine (20 cm^3), dried ($MgSO_4$) and concentrated to give a mixture of *ester* **286** and 1,2-dihydroxy-1,1,2-triphenyl-ethane (treated as 100 % yield). These compounds could not be separated by chromatography and the mixture was carried forward without further purification or characterisation.

(*R*)-Ethyl 3-(tert-butyldimethylsilyloxy)-5-phenyl-4-pentenoate 287



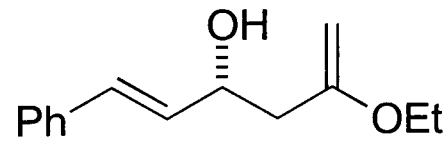
The procedure described for the preparation of **226** was used to generate a mixture of *silyl ether* **287** and 1,1,2-triphenyl-2-(tert-butyldimethylsilyloxy)ethanol (0.518 g) from the mixture of *ester* **286** and 1,2-dihydroxy-1,1,2-triphenyl-ethane as an oil. ^1H NMR confirms successful reaction only, data for **287**. δ_H (400 MHz; $CDCl_3$) 7.31-7.12 (5H, m, *Ph*), 6.50 (1H, d, *J* 15.8, PhC*H*), 6.13 (1H, dd, *J* 15.8 and 6.7, PhCH=C*H*), 4.70 (1H, bq, C*H*OSi), 4.12-4.03 (2H, m, OCH_2), 2.56 (1H, dd, *J* 14.4 and 8.1, $COCH^AH^B$), 2.45 (1H, dd, *J* 14.4 and 5.2, $COCH^AH^B$), 1.20 (3H, t, *J* 7.1, CH_2CH_3), 0.83 (9H, s, $SiC(CH_3)_3$) 0.03 (3H, s, $SiCH_3$) and 0.00 (3H, s, $SiCH_3$). Mixture was carried forward without purification.

(*R*)-2-Ethoxy-4-(*tert*-butyldimethylsilyloxy)-6-phenyl-1,6-hexadiene 288



The method decribed for preparation of **227** was used to convert the mixture of *silyl ether* **287** and 1,1,2-triphenyl-2-(tert-butyldimethylsilyloxy)ethanol (0.518 g) to *enol ether* **288** (0.205 g). δ_H (400 MHz; $CDCl_3$) 7.32-7.15 (5H, m, *Ph*), 6.48 (1H, d, *J* 15.8, PhC*H*), 6.17 (1H, dd, *J* 15.8 and 6.0, PhCH=C*H*), 4.50 (1H, bq, C*H*OSi), 3.84 (1H, m, =CH_2), 3.64 (2H, q, *J* 7.0, OCH_2), 2.31 (1H, dd, *J* 13.6 and 7.6, H_2C=CCH^AH^B), 2.31 (1H, dd, *J* 13.6 and 5.5, H_2C=CCH$^A H^B$), 1.25 (3H, t, *J* 7.0, CH_2CH_3), 0.86 (9H, s, $SiC(CH_3)_3$) and 0.00 (6H, d, *J* 5.3, 2 × $SiCH_3$). Data listed are from spectrum of crude product, carried forward without purification.

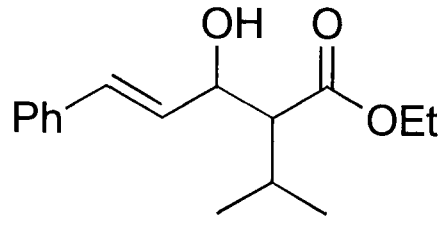
(R)-2-Ethoxy-6-phenyl-1,5-headien-4-ol 289



Enol ether **288** (0.205 g) was transformed into *alcohol* **289** by the method descibed for production of **227** (0.068 g) in an overall yield of 6 % [49% per step] over 4 steps from *alcohol* **285**. R_f (hexane-CH_2Cl_2) 0.13; ν_{max} (Thin film) 3319, 2976, 2926, 1654, 1292, 1070, 968, 747 and 693 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.40-7.12 (5H, m, *Ph*), 6.55 (1H, d, *J* 15.8, PhC*H*=), 6.15 (1H, dd, *J* 15.8 and 6.0, PhCH=C*H*), 4.43 (1H, m, C*H*OH), 3.90 (2H, d, *J* 1.5, =CH_2), 3.68 (2H, bq, OCH_2), 2.51 (1H, bs, O*H*), 2.38 (1H, dd, *J* 14.1 and 3.9, H_2C=CCH^AH^B), 2.31 (1H, dd, *J* 14.1 and 7.3, H_2C=CCH$^A H^B$) and 1.23 (3H, t *J* 7.0, CH_2CH_3); δ_C (100 MHz) 160.0 (C), 137.2 (C), 131.7 (CH), 130.2 (CH), 128.9 (2 × CH), 127.8 (CH), 126.8 (2 × CH), 84.3 (CH_2), 71.0 (CH), 63.4 (CH_2), 43.7 (CH_2) and 14.8 (CH_3); *m/z* 219 (17, $M+H^+$), 200 (20,

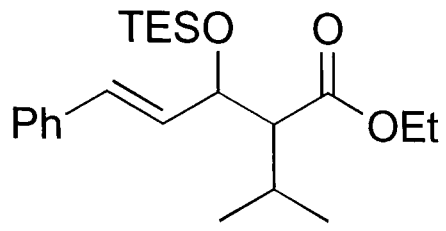
M^+-H_2O), 147 (57, $M+H^+$ - H_2C=CHOEt), 133 (100) 113 (48), 78 (25) and 55 (11); HRMS (CI mode) Found $M+H^+$ 219.1383, $C_{14}H_{18}O_2$ requires 219.1385.

(2*RS*, 3*SR*, *E*) & (2*RS*, 3*RS*, *E*) Ethyl 3-hydroxy-2-isopropyl-5-phenyl-4-pentenoate 311



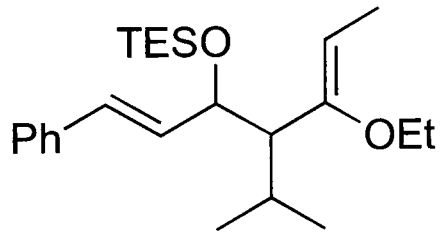
Ester **311** (19.98 g, 99 %) was generated as a 92:8 mixture of *syn* and *anti* diastereomers respectively from *trans* cinnamaldehyde (9.7 g, 76.8 mmol) using the method described for preparation of **225**. ν_{max} (Thin film) 3448 (OH), 2962, 2934, 2873, 1728 (C=O), 1181, 1027 (C-O), 968, 749 and 693 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.42-7.24 (5H$^{syn\&anti}$, m, *Ph*), 6.67 (1H^{anti}, d, *J* 15.9, PhC*H*=), 6.65 (1H^{syn}, d, *J* 15.9, PhC*H*=), 6.37 (1H^{syn}, dd, *J* 15.9 and 7.2, PhCH=C*H*), 6.20 (1H^{anti}, dd, *J* 15.9 and 5.5, PhCH=C*H*), 4.62-4.57 (1H$^{syn\&anti}$, m, C*H*OH), 4.24-4.11 (2H$^{syn\&anti}$, m, CH_2), 3.09 (1H^{anti}, d, *J* 8.8, O*H*), 2.55 (1H^{syn}, t, *J* 6.8, C*H*^{i}Pr), 2.34 (1H^{anti}, dd, *J* 8.4 and 4.7, C*H*^{i}Pr), 2.18 (1H^{syn}, d, *J* 4.0, O*H*), 2.15 (1H$^{syn\&anti}$, m, *J* 6.8, C*H*Me_2), 1.27 (3H$^{syn\&anti}$, t, *J* 7.1, CH_2*Me*), 1.04 (3H$^{syn\&anti}$, d, *J* 6.9, CH*Me*^{X}Me^{Y}) and 1.02 (3H$^{syn\&anti}$, d, *J* 6.9, CH*Me*^{X}Me^{Y}); δ_C (100 MHz) 173.7 (C), 136.9 (C), 132.5 (CH), 129.4 (CH), 128.9 (2 × CH), 128.1 (CH), 126.9 (2 × CH), 72.5 (CH), 60.6 (CH_2), 58.1 (CH), 27.4 (CH_3), 21.6 (CH_3), 20.1 (CH_3) and 14.7 (CH); *m/z* 262 (23, M^+·), 133 (100), 115 (46), 104 (22), 91 (13) and 55 (13); HRMS (EI mode) Found M^+ 262.1570, $C_{16}H_{22}O_3$ requires 262.1569.

(2*RS*, 3*SR*, *E*) & (2*RS*, 3*RS*, *E*) Ethyl 2-isopropyl-5-phenyl-3-(triethylsilyloxy)-4-pentenoate 312



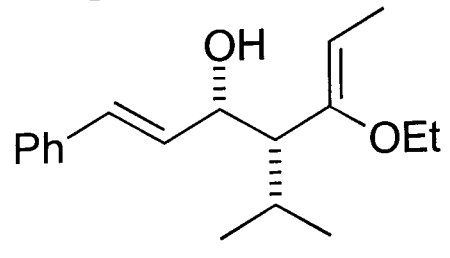
Alcohol **311** (10.0 g,38 mmol) was converted to *silyl ether* **312** (13.85 g, 96 %) assumed to be a 92:8 mixture of *syn* and *anti* diastereomers respectively using the method described for generation of **226**. The product was carried forward without further purification or characterisation.

(3*RS*, 4*SR*, 1*E*, 5*Z*) 5-Ethoxy-4-isopropyl-1-phenyl-3-(triethylsilyloxy)-1,5-heptadiene 313



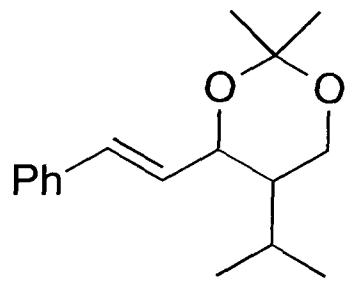
Enol ether **313** (9.16 g, 89 %)was prepared from *ester* **312** (10.03 g, 26.5 mmol) using the prodecure described for **227**. The product was carried forward without purification or characterisation.

(3*RS*,4*SR*, 1*E*,5*Z*) 5-Ethoxy-4-isopropyl-1-phenyl-1,5-heptadien-3-ol 315



Enol ether **313** was transformed into *alcohol* **315** (2.57 g, 40 %) using the method described for preparation of **228**. R_f (hexane-CH_2Cl_2) 0.32; ν_{max} (Thin film) 3432 (OH), 2958, 2928, 2870, 1663 (C=C), 1448 (aromatic ring), 1384, 966, 748 and 693 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.28-7.11 (5H, m, *Ph*), 6.50 (1H, d, *J* 15.9, PhC*H*=), 6.25 (1H, dd, *J* 15.9 and 6.7, PhCH=C*H*), 4.59 (1H, q, *J* 6.9, MeC*H*=), 4.38 (1H, bs, C*H*OH), 3.85-3.67 (2H, m, CH_2), 2.55 (1H, bs, O*H*), 2.05 (1H, dd, *J* 9.3 and 5.5, C*H*^{i}Pr), 1.81-1.72 (1H, m, C*H*Me_2), 1.57 (3H, d, *J* 6.9, =CH*Me*), 1.16 (3H, t, *J* 7.0, CH_2*Me*), 0.92 (3H, d, *J* 6.6, CH*Me*^{A}Me^B) and 0.88 (3H, d, *J* 6.6, CHMe^A*Me*^{B}); δ_C (100 MHz) 154.7 (C), 137.7 (C), 130.8 (2 × CH), 128.8 (2 × CH), 127.6 (CH), 126.8 (2 × CH), 108.7 (CH), 73.0 (CH), 66.3 (CH_2), 57.1 (CH), 27.2 (CH_3), 21.7 (CH_3), 21.3 (CH_3), 16.2 (CH) and 11.5 (CH_3); *m/z* 274 (5, M^+), 256 (1, M^+-H_2O), 142 (48), 133 (100), 127 (33), 100 (16) and 55 (15); HRMS Found M^+ 274.1934, $C_{18}H_{26}O_2$ requires 274.1933.

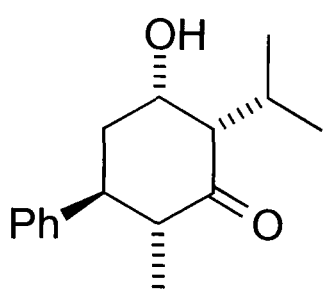
5-Isopropyl-2,2-dimethyl-4-(2-phenyl-1-ethenyl)-1.3-dioxane 317



Lithium aluminium hydride (0.076 g, 0.002 mol) was added to a stirred solution of ester **311** (0.281 g, 0.001 mol) in dry THF (20 cm^3) at 0 °C. Stirring was continued and the mixture was allowed to warm to room temperature over 1.5 h. The reaction was quenched with wet ether (20 cm^3) then aqueous hydrochloric acid (1 mol dm^{-3}, 10 cm^3). The product was extracted with ether (2 × 25 cm^3), washed with brine (30 cm^3) and dried (Mg_2SO_4). Concentration followed by chromatography on silica, eluting with ether-hexane (2:1) gave a mixture of diols as an oil (0.163 g, 74 %). To a solution of these diols (0.163 g, 0.74 mmol) in 2,2-dimethoxypropane (25 cm^3) were added a few crystals of 4-toluenesulfonic acid monohydrate and the solution was

stirred for 46 h. The solution was then diluted with CH_2Cl_2 (20 cm^3), washed with saturated aqueous sodium hydrogen carbonate (25 cm^3), dried ($MgSO_4$) and concentrated to give acetal **317** as an oil (0.148 g, 80 %). Product not isolable by chromatography. Selected data is described in chapter 3.

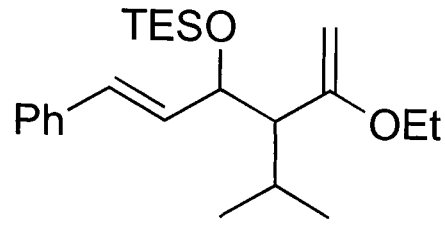
(2*RS*, 3*RS*, 5*RS*, 6*RS*) 3-Hydroxy-2-isopropyl-6-methyl-5-phenyl-cyclohexanone 326



A solution of alcohol **315** (0.106 g, 0.36 mmol) and 18-crown-6 (0.19 g, 0.72 mmol) in dry THF (1 cm^3) was added to a dry flask under nitrogen containing potassium hydride (0.043 g, 1.08 mmol of a 35 % dispersion in oil)-prewashed with dry hexane (4 × 2 cm^3), was added dry THF (3 cm^3). The resulting mixture was stirred for 1.75 h at room temperature then poured into aqueous hydrochloric acid (1 mol dm^{-3}, 15 cm^3). The product was extracted into ether (2 × 20 cm^3), dried ($MgSO_4$) and concentrated to give a 75:19:6 mixture of isomers A, B and C (0.076 g, 80 %). Chromatography on alumina, eluting with hexane-ether (20:1), separated **326** (0.058 g, 65 %). R_f (hexane-ether, 2:1) 0.27; ν_{max} (Thin film) 3423 (OH), 2963, 2930, 1702 (C=O), 1452 (aromatic ring), 1032 (C-O) and 699 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.28-7.15 (5H, m, *Ph*), 4.38 (1H, bd, C*H*OH), 2.98 (1H, td, *J* 12.5 and 4.1, C*H*Ph), 2.66 (1H, dq, *J* 12.5 and 6.2, COC*H*Me), 2.22-2.09 (2H, m, C*H*^{i}Pr and C*H*^{A}H^{B}), 2.08-1.98 (1H, m, C*H*Me_2), 1.98-1.91 (1H, m, CH^{A}*H*^{B}), 1.78 (1H, bs, O*H*), 1.01 (3H, d, *J* 6.2, COCH*Me*), 0.81 (3H, d, *J* 6.4, CH*Me*^{X}Me^{Y}) and 0.74 (3H, d, *J* 6.4, CHMe^{X}*Me*^{Y}); δ_C (100 MHz) 214.6 (C), 143.7 (CH), 129.0 (2 × CH), 127.8 (2 × CH), 127.1 (CH), 71.3 (CH), 66.8 (CH), 47.5 (CH), 47.1 (CH), 36.9 (CH_2), 29.4 (CH_3), 21.6 (CH_3), 21.4

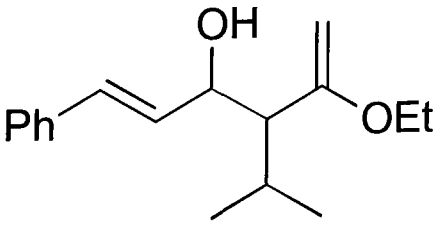
(CH_3) and 12.4 (CH); *m/z* 246 (80.1, M^+), 228 (24.8, M^+ - H_2O) and 118 (100); [Found: M^+, 246.1619. $C_{16}H_{22}O_2$ requires 246.1620].

2-Ethoxy-3-isopropyl-5-phenyl-4-(triethylsilyloxy)-1,5-hexadiene 342



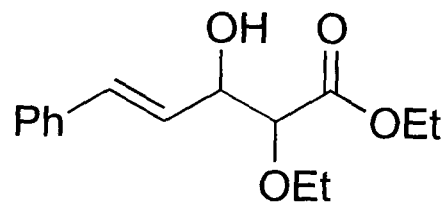
The method described for **227** was used to produce *enol ether* **342**(0.31 g, 21 %) as a 92:8 mixture of *syn* and *anti* diastereomers respectively from *ester* **312** (1.49 g, 3.98 mmol). Data for *syn* isomer only. R_f (hexane) 0.91; ν_{max} (Thin film) 2956, 2877, 1569, 1491, 1260, 1071, 1005, 910 and 743 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.38-7.20 (5H, m, *Ph*), 6.43 (1H, d, *J* 15.9, PhC*H*), 6.20 (1H, dd, *J* 15.9 and 7.6, PhCH=C*H*), 4.46 (1H, t, *J* 7.5, C*H*OSi), 3.86 (1H, s, C*H*H=), 3.78 (1H, s, CH*H*=), 3.68-3.53 (2H, m,OCH_2), 2.16-2.05 (2H, m, H_2C=CC*H* and CH_3CHCH_3), 1.26 (3H, t, *J* 7.0, OCH_2CH_3), 0.99-0.88 (15H, m, 3 × $SiCH_2CH_3$ and CH_3CHCH_3) and (6H, m, 3 × $SiCH_2$); δ_C (100 MHz) 161.3 (C), 137.9 (C), 132.9 (CH), 129.6 (CH), 128.8 (2 × CH), 127.4 (CH), 126.7 (2 × CH), 85.0 (CH_2), 73.5 (CH), 62.5 (CH_2), 59.4 (CH), 26.7 (CH_3), 22.1 (CH_3), 19.4 (CH_3), 15.0 (CH), 7.3 (3 × CH_3) and 5.5 (3 × CH_2); *m/z* 374 (<1, M^+), 331 (2.1, M^+ - ^iPr) and 247 (100) [Found: M^+, 374.2639. $C_{23}H_{38}O_2Si$ requires *M* 374.2641].

2-Ethoxy-3-isopropyl-6phenyl-1,5-dien-4-ol 343



Silyl ether **342** (0.3 g, 0.8 mmol) was converted to *alcohol* **343** (0.208 g, 100 %) using the method described for production of **228**. Data for *syn* isomer only. R_f (hexane-CH_2Cl_2) 0.27; ν_{max} (Thin film) 3423, 2958, 2928, 1663, 1494, 1448, 1384, 1103, 1048, 966, 748 and 693 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.37-7.12 (5H, m, *Ph*), 6.48 (1H, d, *J* 15.9, PhC*H*), 6.23 (1H, dd, *J* 15.9 and 7.6, PhCH=C*H*), 4.41 (1H, bq, C*H*OH), 3.94 (1H, s, C*H*H=), 3.85 (1H, s, CH*H*=), 3.62 (2H, q, *J* 7.0, CH_2), 2.15 (1H, d, *J* 7.4, O*H*), 2.03 (1H, dd, *J* 6.1 and 5.5, H_2C=CC*H*), 2.02-1.87 (1H, m, CH_3CHCH_3), 1.19 (3H, t, *J* 7.0, OCH_2CH_3), 0.89 (3H, d, *J* 6.5, CH_3CHCH_3) and 0.84 (3H, d, *J* 6.5, CH_3CHCH_3); δ_C (100 MHz) 161.2 (C), 137.7 (C), 131.0 (CH), 130.3 (CH), 128.8 (2 × CH), 127.6 (CH), 126.7 (2 × CH), 85.9 (CH_2), 72.2 (CH), 63.0 (CH_2), 59.1 (CH), 26.6 (CH_3), 21.4 (CH_3), 21.2 (CH_3) and 14.9 (CH); *m/z* 260 (4.2, M^+), 242 (2.1, M^+ - H_2O) and 133 (100) [Found: M^+, 260.1774. $C_{17}H_{24}O_2$ requires *M* 260.1776].

(2*RS*, 3*SR*, *E*) & (2*RS*, 3*RS*, *E*) Ethyl 2-ethoxy-3-hydroxy-5-phenyl-4-pentenoate 347



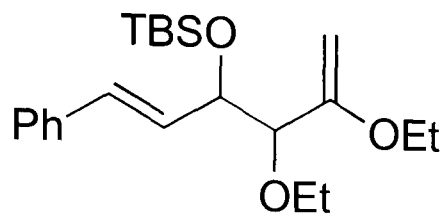
The method described for preparation of **225** was used to convert *E*-cinnamaldehyde (9.53 g, 75.6 mmol) into *alcohol* **347** (13.57 g, 68 %) as a 64:36 mixture of diastereomers A and B respectively following chromatography on silica, eluting with hexane-ether (2:1). R_f [silica, hexane-ether (2:1)] 0.12; ν_{max} (Thin Film) 3460 (OH), 1745 (C=O), 1482 (C=C), 1182, 1141, 1037 (C-O), 738 and 689 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.38-7.18 ($5H^{A\&B}$, m, *Ph*), 6.70 ($1H^B$, d, *J* 16, PhC*H*=), 6.66 ($1H^A$, d, *J* 15.9, PhC*H*=), 6.24 ($1H^A$, dd, *J* 15.9 and 6.7, PhCH=C*H*), 6.22 ($1H^B$, dd, *J* 16 and 6.7, PhCH=C*H*), 4.60-4.48 ($1H^{A\&B}$, m, C*H*OH), 4.25-4.14 ($2H^{A\&B}$, m, CO_2CH_2), 4.02

($1H^A$, d, *J* 4.7, C*H*OEt),), 3.86 ($1H^B$, d, *J* 8.7, C*H*OEt), 3.78-3.71 ($1H^{A\&B}$, m, CHOCH*H*), 3.55-3.46 ($1H^{A\&B}$, m, CHOC*H*H), 2.80 ($1H^B$, bd, O*H*), 2.80 ($1H^A$, bd, O*H*) and 1.31-1.16 ($6H^{A\&B}$, m, 2 × *Me*); m/z (EI mode) 264 (3, M^+), 246 (8, M^+-H_2O), 191 (35), 133 (100) and 73 (29); HRMS (EI mode) Found M^+ 264.1360, $C_{15}H_{20}O_4$ requires 264.1361.

(2*RS*, 3*SR*, *E*) & (2*RS*, 3*RS*, *E*) Ethyl 3-(*tert*-butyldimethylsilyloxy)-2-ethoxy-5-phenyl-4-pentenoate 348

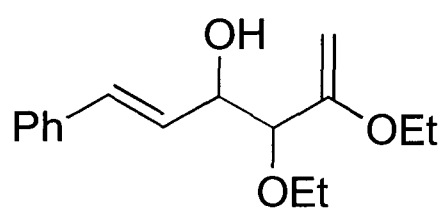
Silyl ether **348** (7.15 g, 67 %) was prepared as a 64:36 mixtue of diastereomers A and B respectively, from *aldol* **347** (7.5 g, 28.4 mmol) using the procedure described for synthesis of **226**. R_f (CH_2Cl_2) 0.64; ν_{max} (Thin film) 2955, 2857, 1789 (C=O), 1743 (C=O), 1472 (aromatic ring), 1255, 1113 (C-O), 837 (Si-C) and 779 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.39-7.22 ($5H^{A\&B}$, m, *Ph*), 6.60 ($1H^A$, d, *J* 15.9, PhC*H*=), 6.54 ($1H^B$, d, *J* 15.8, PhC*H*=), 6.28-6.13 ($1H^{A\&B}$, m, PhCH=C*H*), 4.53-4.46 ($1H^{A\&B}$, m, TBSOC*H*), 4.26-4.07 ($2H^{A\&B}$, m, CO_2CH_2), 3.84-3.77 ($1H^{A\&B}$, m, C*H*OEt), 3.70-3.43 ($2H^{A\&B}$, m, CHOCH_2), 1.32-1.14 ($6H^{A\&B}$, m, 2 × OCH_2Me), 0.88 ($9H^{A\&B}$, s, CMe_3) and 0.09-0.03 ($6H^{A\&B}$, m, SiMe_2). ^1H NMR spectrum confirms ratio of diastereomers and IR spectrum confirms presence of silyl group, but **348** was not isolated.

(3*RS*, 4*SR*, *E*) & (3*RS*, 4*RS*, *E*) 4-(*tert*-Butyldimethylsilyloxy)-2,3-diethoxy-6-phenyl-1,5-hexadiene 349



Ester **348** (7.15 g, 18.9 mmol) was converted to *enol ether* **349** (5.2 g, 73 %, crude) using the method described for preparation of **227.** The product was used in the next step without further purification or characterisation.

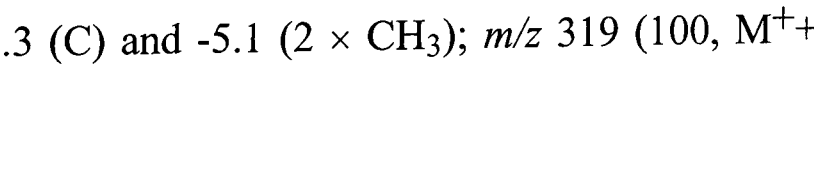
(3*RS*, 4*SR*, *E*) & (3*RS*, 4*RS*, *E*) 4,5-diethoxy-1-phenyl-1,5-hexadien-3-ol 350



Crude *enol ether* **349** (4.5 g, 11.9 mmol) was used to produce *alcohol* **350** (1.6 g, 51 %) as a 64:36 mixture of diastereomers A and B (1.60 g, 51 %) using the method described for **228**. The product was chromatographed on alumina eluting with hexane-ether (3:1). R_f alumina, hexane-ether (3:1) 0.16; ν_{max} (Thin film) 3455 (OH), 2977, 2880, 1659 (C=C), 1626 (C=C), 1447 (aromatic ring), 1295, 1234, 1102 (C-O), 1068 (C-O), 968 and 751 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.39-7.19 ($5H^{A\&B}$, m, *Ph*), 6.66 ($1H^B$, d, *J* 15.9, PhC*H*=), 6.64 ($1H^A$, d, *J* 15.9, PhC*H*=), 6.28 ($1H^A$, dd, *J* 15.9 and 6.0, PhCH=C*H*), 6.16 ($1H^B$, dd, *J* 15.9 and 6.2, PhCH=C*H*), 4.44 ($1H^A$, bq, C*H*OH),), 4.37 ($1H^B$, m, C*H*OH), 4.18 ($1H^A$, d, 2.1, H_2C=), 4.15 ($1H^B$, d, 2.1, H_2C=), 3.82-3.63 (complex multiplet $1H^A$, C*H*OEt and $2H^{A\&B}$, =COCH_2Me and $1H^{A\&B}$, CHOC*H*HMe), 3.55 ($1H^B$, d, *J* 7.3, C*H*OEt), 3.49-3.41 ($1H^{A\&B}$, CHOCH*H*Me), 2.89 ($1H^B$, d, *J* 2.4, O*H*), 2.46 ($1H^A$, d, *J* 6.5, O*H*) and 1.31-1.19

($6H^{A\&B}$, m, 2 × Me); δ_C (90 MHz) 158.6 (C), 158.4 (C), 137.0 (C), 136.9 (C), 131.3 (CH), 130.7 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.4 (CH), 127.3 (CH), 126.4 (2 × CH), 84.7 (CH_2), 84.2 (CH_2), 83.0 (CH), 73.4 (CH), 72.8 (CH), 65.1 (CH_2), 64.8 (CH_2), 62.9 (CH_2), 15.1 (CH_3), 14.3 (CH_3) and 14.2 (CH_3); *m/z* 262 (3, $M^{+}\cdot$), 130 (100), 101 (37), 73 (58, H_2C=CHOEt) and 55 (12); HRMS (EI mode) Found $M^{+}\cdot$ 262.1571, $C_{16}H_{22}O_3$ requires 262.1569.

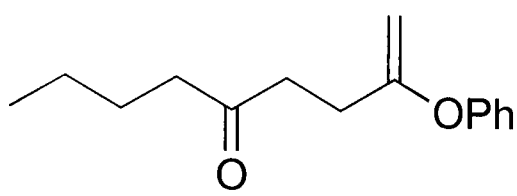
2,2-Dibromo-1-(*tert*-butyldimethylsilyloxy)-ethane 362



2,2-Dibromoethanol was prepared in 51 % yield (crude) on 45.8 mmol scale according to Sroog's procedure for the preparation of 2,2-dichloroethanol from 2,2-dichloroacetic acid. Diisopropylethylamine (12.2 cm^3, 69.9 mmol) then *tert*-butyldimethylsilyl chloride (7.02 g, 46.6 mmol) were added to a stirred solution of 2,2-dibromoethanol (4.74 g, 0.0233 mol) in dry DMF (50 cm^3), at 0 °C, under nitrogen. The ice bath was removed and stirring was continued for 95 h. The resultant solution was poured into aqueous saturated sodium bicarbonate (50 cm^3) and extracted with ether (2 × 75 cm^3). The combined ethereal extracts were washed with aqueous hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3) then brine (50 cm^3) and dried ($MgSO_4$). The solvent was removed and chromatography on silica, eluting with Pet (40-60°C)-CH_2Cl_2 (9:1) gave silyl ether **362** as an oil (1.39 g, 19 %). R_f (hexane-CH_2Cl_2) 0.93; ν_{max} (Thin film) 2955, 2929, 2855, 1471, 1463, 1255, 1122, 1053 and 838 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 5.51 (1H, t, *J* 6.2, C*H*), 4.04 (2H, d, *J* 6.2, CH_2), 0.90 (9H, s, SiCMe_3) and 0.12 (6H, s, SiMe_2); δ_C (90 MHz) 70.4 (CH), 45.9 (CH_2), 25.7 (3 × CH_3), 18.3 (C) and -5.1 (2 × CH_3); *m/z* 319 (100, M^{+}+H), 260 (22), 239

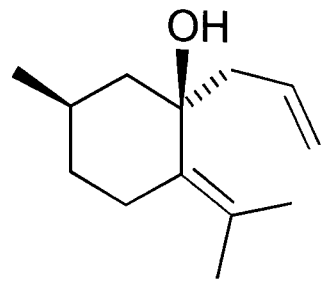
(18), 181 (8), 159 (6) and 115 (8); HRMS (CI mode) Found M^++H 318.9551, $C_8H_{19}Br_2OSi$ requires 318.9551.

2-phenoxy-1-nonen-5-one 378



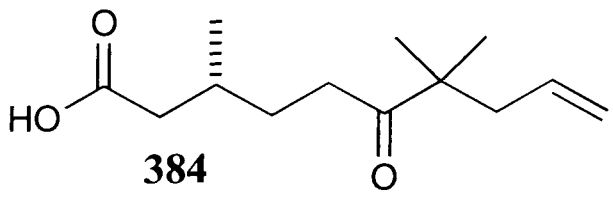
A solution of alcohol **240** (0.1 g, 0.41 mmol) and 18-crown-6 (0.21 g, 0.82 mmol) in dry THF (1 cm^3) was added to a flask containing potassium hydride (0.14 g of a 35 % dispersion in mineral oil prewashed with dry hexane 4 × 2 cm^3), in dry THF (5 cm^3). The resulting mixture was stirred for 1.5 h at room temperature then cooled to -78 °C and dry oxygen gas was bubbled through the solution over 30 min. pH 7 phosphate buffer (15 cm^3) was then added dropwise to the mixture and the solution was then allowed to warm to room temperature. The organic phase was separated and the aqueous was extracted with ether (2 × 25 cm^3). The ethereal extracts were combined, dried ($MgSO_4$) and concentrated. Chromatography on alumina, eluting with hexane-ether (10:1), gave *ketone* **378** as an oil (0.71 g, 71 %). R_f [alumina, hexane-ether (10:1)] 0.27; ν_{max} (Thin film) 2958, 2930, 2871, 1715 (C=O), 1657 (C=C), 1638, 1592 (aromatic ring), 1490 (aromatic ring) and 1220 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.35-7.00 (5H, m, *Ph*), 4.17 (1H, d, *J* 1.8, =C*H*H), 3.93 (1H, d, *J* 1.8, =CH*H*), 2.73 (2H, t, *J* 7.2, =CCH_2CH_2 or =CCH_2), 2.56 (2H, t, *J* 7.2, =CCH_2CH_2 or =CCH_2), 2.45 (2H, t, *J* 7.5, PrCH_2), 1.65-1.53 (2H, m, EtCH_2), 1.37-1.26 (2H, m, MeCH_2) and 0.90 (3H, t, *J* 7.7, *Me*); δ_C (50 MHz) 210.1 (C), 162.0 (C), 155.1 (C), 129.5 (2 × CH), 124.0 (CH), 120.7 (2 × CH), 89.0 (CH_2), 42.6 (CH_2), 40.1 (CH_2), 29.6 (CH_2), 28.2 (CH_2), 22.3 (CH_2) and 13.8 (CH_3); *m/z* (EI) 232 (M^+, 9%) and 147 (100); HRMS (CI mode) found $(M+H)^+$ 233.1544, $C_{15}H_{21}O_2$ requires $(M+H^+)$ 233.1541.

(1*R*, 5*R*)-1-(2-propen-1-yl)-2-(1-methylethylidene)-5-methylcyclohexanol 382[80]

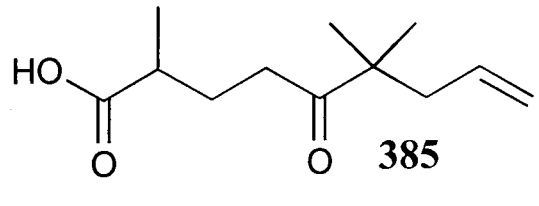


Compound **382** was prepared in 49% yield on a 7 mmol scale by a method slightly adapted from that of Santelli and co-workers.We employed allyl magnesium bromide where Santelli and co-workers used allyl magnesium chloride. ν_{max} (Thin film) 3463 (OH), 3074 (=CH), 2950, 2917, 2869, 1638 (C=C), 1455, 1149, 1025 (C-O) and 910 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 5.88-5.76 (1H, m, H_2C=C*H*), 5.11-5.06 (2H, m, =CH_2), 2.67 (1H, dt, *J* 15.1 and 3.8, $CH_2CH_{ax}H_{eq}C$=), 2.61 (1H, dd, *J* 14.0 and 6.4, H_2C=CHC*H*H), 2.20 (1H, dd, *J* 14.0 and 8.2, H_2C=CHCH*H*), 1.97 (3H, s, =C$Me^A$$Me^B$), 1.79-1.64 (3H, m, CH and CH_2), 1.68 (3H, s, =C$Me^A$$Me^B$), 1.25 (1H, bs, OH), 1.15 (1H, t, *J* 12.3, $CH_{eq}CH_{ax}$COH), 0.94-0.85 (2H, m, CH_2) and 0.87 (3H, d, J 6.2, $CHCH_3$); *m/z* (CI) 194 (23, M^+) and 177 (100).

6-Oxo-3,7,7-trimethyl-9-decenoic acid 384 and 5-Oxo-2,6,6-trimethyl-8-nonenoic acid 385



384

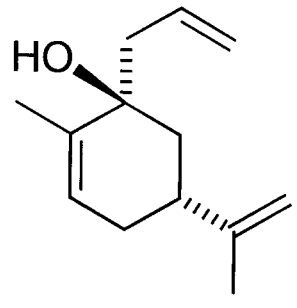


385

The method for preparation of **378** was used to prepare *acids* **384** and **385** (0.085 g, 30 %) after chromatography on silica, eluting with pet 40-60°C-ether (4:1). Data for **385**;ν_{max} (Thin film) 3077 (=CH), 2973, 2935, 2878, 2656, 1705 (C=O), 1640 (C=C) and 1467 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.70-5.49 (1H, m, H_2C=C*H*), 4.99-4.91 (2H,

m, =CH_2), 2.47 (2H, t, *J* 7.4, CH_2CO), 2.43-2.91 (1H, obscured m, C*H*CO_2H), 2.17 (2H, d, *J* 7.3, =CHCH_2), 1.86-1.62 (2H, m, C$H_2$$CH_2$CO), 1.13 (3H, d, *J* 7, CHCH_3) and 1.05 (6H, s, 2 × CH_3); *m/z* (EI mode) 212 (6, M^+·), 129 (91), 101 (88), 83 (67) and 55 (100); HRMS (EI mode) found M^+ 212.1414, $C_{12}H_{20}O_3$ requires 212.1412. Acid **384** was observable in the mass spectrum 226 (M^+, 1%). Ratio of **384** to **385** could not be determined with available spectroscopic methods.

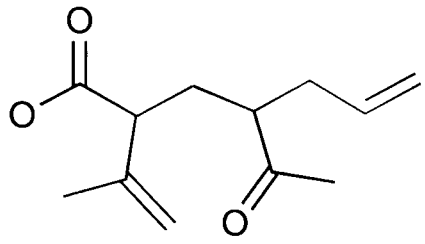
(1*S*, 5*R*)-1-allyl-5-isopropenyl-2-methylcyclohex-2-enol 388[81]



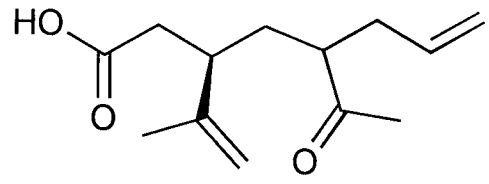
To a solution of allyl magnesium bromide [from magnesium (1.61 g, 0.0664 mol) and allyl bromide (5.65 cm^{-3}, 0.0664 mol)] in dry ether (150 cm^{-3}) was added a solution of (R)-carvone (5 g, 0.0332 mol) in dry ether (5 cm^{-3}) dropwise at 0 °C. The ice bath was removed and the resultant solution was stirred at room temperature for 40 h. The solution was then poured into ice/ammonium chloride and extracted with ether (2 × 100 cm^{-3}), dried ($MgSO_4$) and concentrated. Distillation (Kügelrohr) gave alcohol **388** (5.54 g, 87 %). R_f [silica, hexane-ether (5:1)] 0.20; ν_{max} (Thin film) 3392 (OH), 3075 (=CH), 2971, 2919, 2857, 1642 (C=C), 1439 and 1375 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.97 - 5.76 (1H, m, H_2C=C*H*CH_2), 5.46 (1H, bs, CH_3C=C*H*CH_2), 5.16 - 5.07 (2H, m, *H*$_2$C=CHCH_2), 4.71 (2H, s, *H*$_2$C=CCH_3CH), 2.52 - 2.27 [3H, m, CH_{ax}*H*$_{eq}$C(OH) and =CHC*H*$_2$COH], 2.13 - 1.92 [(4H, m, CHC*H*$_2$C=, CH_2C*H*CH_2 and O*H*)], 1.85 (6H, s, 2 × Me) and 1.32 [1H, t, *J* 12.4, C*H*$_{ax}$$H_{eq}$C(OH)]; δ_C (50 MHz; $CDCl_3$) 148.8 (C), 138.0 (C), 133.6 (CH), 123.7 (CH), 118.5 (CH_2), 109.0 (CH_2), 73.5 (C), 42.8 (CH_2), 40.3 (CH_2), 39.1 (CH), 30.7

(CH_2), 20.6 (CH_3) and 16.9 (CH_3); *m/z* (CI) 193 (4, $M+H^+$), 175 (100, $M+H^+-H_2O$) and 151 (15, $M+H^+$-$MeCH=CH_2$).

All isomers of 4-Acetyl-2-isopropenyl-6-heptenoate 390 and (3*R*, 5*R*) & (3*R*, 5*S*) 5-Acetyl-3-isopropenyl-7-octenoate 389



389



390

The method used for preparation of **378** was used to generate *acids* **390** as a (1:1 mixture of diastereomers A and B) and **389** (0.34 g, 58 %) after distillation (kügelrohr). ν_{max} (Thin film) 3077 (=CH), 2975, 2927, 1708 and 1642 (C=C) cm^{-1}; δ_H (360 MHz; $CDCl_3$) (**390** only) 5.73-5.62 ($1H^{A\&B}$, m, $H_2C=CH$), 5.08-4.80 ($4H,^{A\&B}$ m, 2 × $=CH_2$), 3.07 ($1H^A$, dd, *J* 9.2 and 6.3, $CHCO_2H$), 3.01 ($1H^B$, dd, *J* 8.5 and 6.6, $CHCO_2H$), 2.60-2.51 ($1H^{A\&B}$, m, CHCOMe), 2.37-2.14 ($2H^{A\&B}$, m, $=CHCH_2$), 2.14 ($3H^A$, s, CO*Me* or =C*Me*), 2.13 ($3H^B$, s, CO*Me* or =C*Me*), 1.94-1.87 ($1H^{A\&B}$, m, $CHCH^XH^YCH$), 1.76 ($3H^A$, s, CO*Me* or =C*Me*), 1.73 ($3H^B$, s, CO*Me* or =C*Me*) and 1.69-1.58 ($1H^{A\&B}$, m, $CHCH^XH^YCH$); δ_C (50 MHz; $CDCl_3$) 211.6 (C), 211.3 (C), 211.2 (C), 211.0 (C), 178.7 (C), 178.0 (C), 145.0 (C), 144.8 (C), 141.7 (C), 141.2 (C), 134.8 (CH), 134.5 (CH), 117.6 (CH_2), 117.4 (CH_2), 117.2 (CH_2), 115.5 (CH_2), 114.6 (CH_2), 113.7 (CH_2), 113.4 (CH_2), 50.5 (CH), 50.3 (CH), 50.1 (CH), 49.9 (CH), 49.7 (CH), 49.3 (CH), 41.6 (CH), 41.5 (CH), 39.2 (CH_2), 38.8 (CH_2), 36.8 (CH_2), 36.1 (CH_2), 36.0 (CH_2), 35.1 (CH_2), 33.4 (CH_2), 33.1 (CH_2), 30.6 (CH_2), 29.7 (CH_3), 29.6 (CH_2), 29.4 (CH_3), 29.3 (CH_3), 20.1 (CH_3), 19.5 (CH_3), 18.0 (CH_3) and 17.8 (CH_3); *m/z* (EI) 224 (**389** M^+, 1%), 210 (**390** M^+, 3), 78 (72), 63 (84) and 43 (100); HRMS (EI) found M^+ 224.1409, $C_{13}H_{20}O_3$ (**389**) requires 224.1412: found M^+ 210.1250, $C_{12}H_{18}O_3$ (**390**) requires 210.1256. Ratios of products could not be

obtained with available spectroscopic methods, several signals in NMR spectra coincident.

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