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THE OXIDATION OF α-FARNESENE

A thesis presented in partial
fulfilment of the requirements for the degree of
DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Julie Ann Spicer
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ABSTRACT

Autoxidation products of the sesquiterpene α-farnesene **1** increase rapidly in apples during cold storage and are believed to play an important role in the production of the cold storage disorder, superficial scald. The site selectivity of the oxidation of α-farnesene was investigated with a variety of useful reagents for photochemical allylic oxidation, hydroxylation and epoxidation. Oxidation products **33-47** were isolated and characterised.

The synthesis of conjugated trienes and related oxidation products of α-farnesene **1**, principally from the epoxides of α-farnesene, is described. Base-promoted ring opening of 6,7-epoxide **44** by the mixed base potassium *tert*-butoxide / lithium disopropylamide afforded the conjugated triene **3** whilst the 3,4-epoxide **45** afforded triene **50**. In contrast, 10,11-epoxide **43** failed to undergo epoxide ring opening; rearranging instead to the conjugated triene epoxide **51**. Base-promoted ring opening of *bis*-epoxide **46** afforded trienol epoxide **56** at -30°C, whilst cyclisation to tetrahydrofurans **55a** and **55b** occurred at room temperature. Photosensitised oxidation of 10,11-epoxide **43** followed by *in situ* treatment with acid gave the cyclic peroxide **4** and upon reduction, tetrahydrofurans **55a** and **55b**. Bisallylic alcohol **61** was prepared by alkylation of 3-methylsulpholene **29** with geranial **59** followed by thermolysis. Trienes **3** and **4** have been isolated previously as autoxidation products of α-farnesene **1** and are implicated as the causal agents of the superficial scald of stored apples.

The asymmetric dihydroxylation of α-farnesene **1** using the Sharpless ligands $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL was investigated. The isolation and characterisation of the 3,4-, 6,7- and 10,11-diols **41**, **42** and **114** as well as the tetraol **115** is described. High enantioselectivity and preferential addition to the 6,7-olefin was observed. The isomeric β-farnesene **2** showed a preference for reaction at the 10,11-position.

The enantioselective synthesis of an apple aroma constituent, bicyclic acetal **17**, is described. Asymmetric dihydroxylation of 6-methylhept-5-en-2-one **15** was carried out using the ligands $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL according to the method of Sharpless. Acid-catalysed cyclisation then afforded the required acetal **17** in high enantiomeric excess. Enantiomeric excesses were measured using chiral solvating agent **113** and/or synthesis of the corresponding Mosher ester derivatives, followed by ^1H or ^{19}F nmr.

TABLE OF CONTENTS

PART 2: THE ASYMMETRIC DIHYDROXYLATION OF α- AND β-FARNESENE

PART 3: ENANTIOSELECTIVE SYNTHESIS OF AN APPLE AROMA CONSTITUENT

ABBREVIATIONS

AD	=	asymmetric dihydroxylation
AD-mix-α	=	asymmetric dihydroxylation mixture containing 1,4-*bis*-(9-*O*-dihydroquininyl)phthalazine
AD-mix-β	=	asymmetric dihydroxylation mixture containing 1,4-*bis*-(9-*O*-dihydroquinidinyl)phthalazine
BHT	=	butylated hydroxytoluene
t-BuOK	=	potassium *tert*-butoxide
cat.	=	catalytic
COSY	=	correlated spectroscopy
DATMP	=	diethylaluminium 2,2,6,6-tetramethylpiperidide
DEPT	=	distortionless enhancement by polarisation transfer
DHQ	=	dihydroquinine
DHQD	=	dihydroquinidine
DHQD-IND	=	(9-*O*-indolinylcarbamoyl)dihydroquinindine
$(DHQ)_2$-PHAL	=	1,4-*bis*-(9-*O*-dihydroquininyl)phthalazine
$(DHQD)_2$-PHAL	=	1,4-*bis*-(9-*O*-dihydroquinidinyl)phthalazine
$(DHQ)_2$-PYR	=	*bis*-dihydroquinine pyrimidine
$(DHQD)_2$-PYR	=	*bis*-dihydroquinidine pyrimidine
DMAP	=	4-dimethylaminopyridine
DMPU	=	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DPA	=	diphenylamine
ee	=	enantiomeric excess
equiv.	=	equivalent
ethoxyquin	=	6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline
GC	=	gas chromatography
GC/MS	=	gas chromatography - mass spectroscopy
HETCOR	=	heteronuclear correlation spectroscopy
HPLC	=	high pressure liquid chromatography
IR	=	infra red
LDA	=	lithium diisopropylamide
m-CPBA	=	*meta*-chloroperbenzoic acid
MEQ	=	9-*O*-(4'-methyl-2'-quinidyl)
NBS	=	*N*-bromosuccinimide
n.O.e.	=	nuclear Overhauser enhancement
NMO	=	*N*-methylmorpholine-*N*-oxide
nmr	=	nuclear magnetic resonance
NOESY	=	nuclear Overhauser enhancement spectroscopy

p-TSA	=	*para*-toluenesulphonic acid
PCB	=	*para*-chlorobenzoate
PHN	=	9-*O*-(9'-phenanthryl)
RT	=	room temperature
R-(-)-TFAE	=	*R*-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol
THF	=	tetrahydrofuran
tlc	=	thin layer chromatography
TMEDA	=	tetramethylethylenediamine
TMS	=	tetramethylsilane
UV	=	ultraviolet
$VO(acac)_2$	=	vanadium oxide acetylacetonate

PART 1: THE OXIDATION OF α–FARNESENE

1. INTRODUCTION

1.1 Origin and Sources of α-Farnesene

The acyclic sesquiterpene α-farnesene (3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraene) **1** is an important aroma constituent of apples[1a,b], pears[2], quinces[3a,b] and berries of the genus Vismia (*Vismia japurensis*, *V. cayennensis* and *V. mexicana*)[4]. It also occurs in the scent of many flower species[5]. α-Farnesene has been isolated from the Dufour's (accessory venom) gland of the Myrmicine ant, *Aphaenoghaster longiceps*[6] and postulated as an attractant and oviposition stimulant of the Codling moth, *Laspeyresia pomonella*.[7a,b]

The isomeric β-farnesene (7,11-dimethyl-3-methylenedodeca-1,6*E*,10-triene) **2** has also been isolated from numerous natural sources. β-Farnesene has been identified as a constituent of a wide variety of plant essential oils, including marijuana[8], lavandin[9], chrysanthemum[10] and orange[11] oils as well as being a mouse[12] and insect (aphid, bee, ant)[13-15] pheromone where it is usually accompanied by α-farnesene.

1.2 α-Farnesene and Superficial Scald

1.2.1 Chemical Basis to the Occurrence of Scald

α-Farnesene has long been implicated in the occurrence of superficial scald (storage, common scald), a physiological disorder in pome fruit (apple, pear, quince) resulting in a blackening of the skin after cold storage[16a-c]. Superficial scald is a postharvest disorder, characterised by a browning of hypodermal cell contents. In mild cases only the outer hypodermal cells are affected, but in more severe cases the entire hypodermis of five or six layers is darkened. In very severe cases of scald the cells collapse in a radial direction, causing the affected area to sink[17a,b]. The discoloured appearance of the fruit does not extend into the flesh and the eating quality is unaffected, however, the unsightly appearance of such fruit makes them difficult to market.

Although the level of superficial scald was initially related to α-farnesene levels in the skin, it was later found to be more closely correlated with the conjugated triene autoxidation products of α-farnesene[16c]. Anet[18] first identified and characterised oxidation products from the autoxidation of α-farnesene, isolating the two conjugated trienes **3** and **4** after reduction of the intermediate hydroperoxides. The UV absorbance

spectra of these species are similar to those reported for the hexane extracts of the natural coating of apples after prolonged cold storage (figure 1).

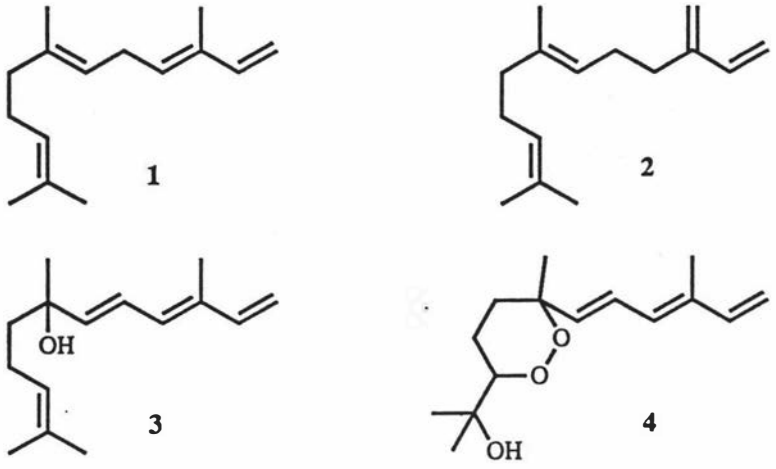
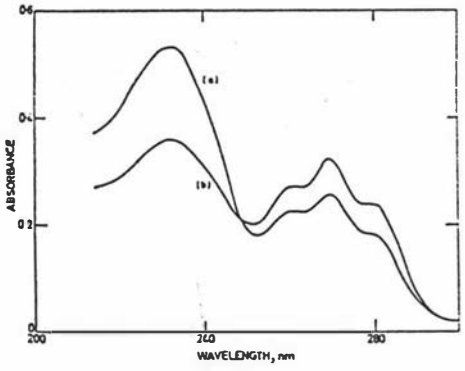
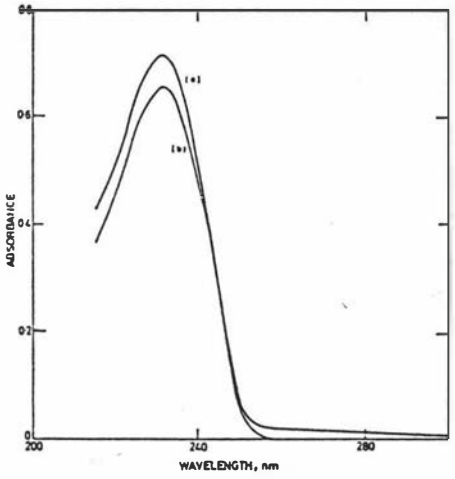


Figure 1



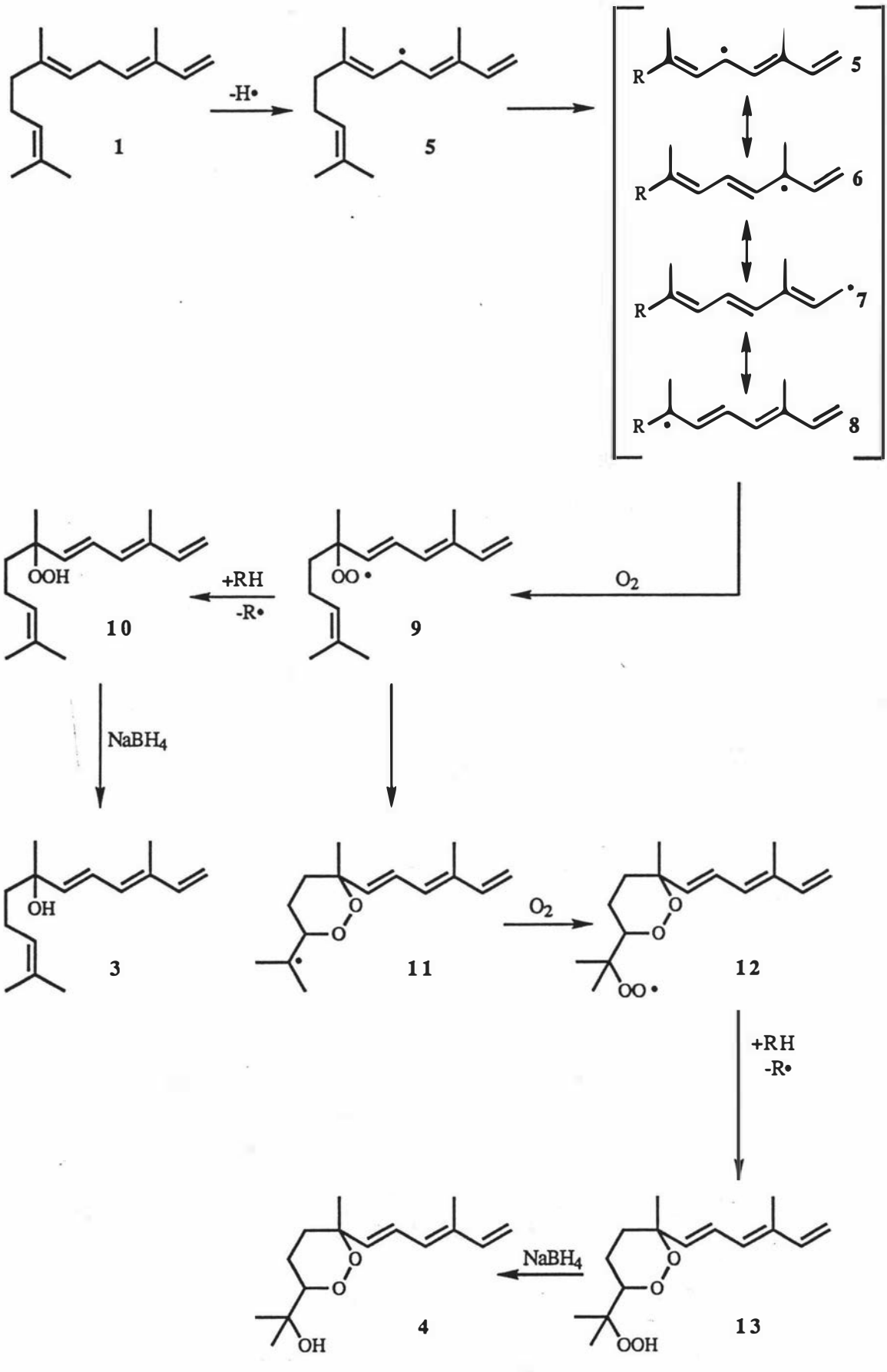
(a) and (b): Absorbance curves for two "Granny Smith" coating extracts, 22 weeks, 1°C, untreated.



(a) and (b): Absorbance curves for two "Granny Smith" coating extracts, 22 weeks, 1°C, DPA treated.

Anet[18] proposed a free radical mechanism for the autoxidation of α-farnesene (scheme 1), initiated by abstraction of a hydrogen atom from the bis-allylic C-5 position. Since the bis-allylic C-H bond is the most susceptible to free radical cleavage, this could be expected to be the predominant reaction, with the other allylic hydrogen atoms making only a small contribution to the overall autoxidation process. The resulting α-farnesene free radical **5** can be drawn in the resonance forms shown (**5-8**, scheme 1) and rapidly reacts with molecular oxygen to afford the intermediate peroxy radical **9** which is common to both the pathway leading to trienol **3** and that leading to cyclic peroxide **4**. Trienol **3** results from abstraction of a hydrogen atom from either α-farnesene or another autoxidation product to give **10**, followed by reduction using $NaBH_4$ to form the alcohol

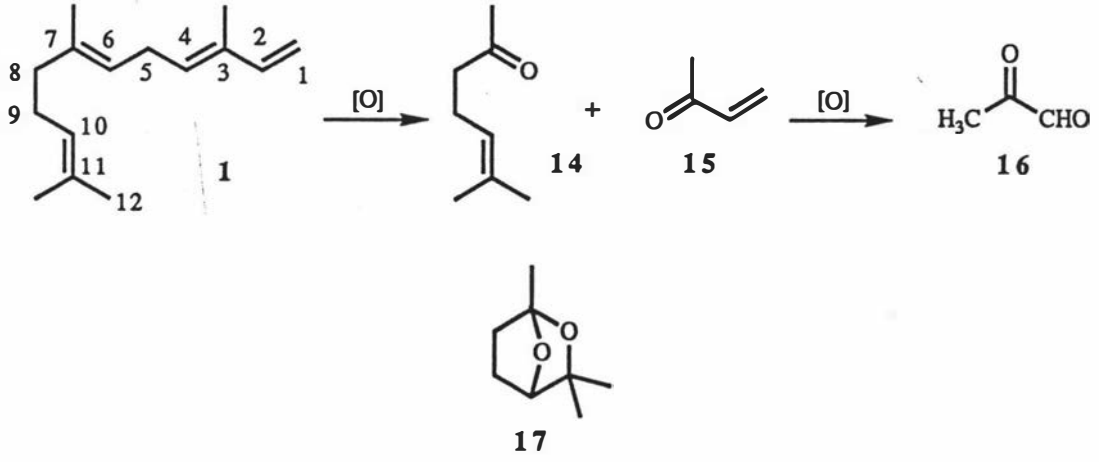
Scheme 1



3. Cyclic peroxide **4** results from initial cyclisation of the peroxy radical **9** to give **11**, followed by addition of a further oxygen molecule, then abstraction of a hydrogen atom to form the hydroperoxide **13**. This was also reduced using $NaBH_4$ to form the corresponding alcohol **4**.

Several subsequent studies have been carried out in order to isolate oxygenated derivatives of α-farnesene. These involved the photosensitised oxygenation of α-farnesene[19] and autoxidation of pure α-farnesene on glass wool[20], as a film[21], or in solution[22]. In the autoxidation studies, several unsaturated volatile carbonyl compounds were identified, including 6-methylhept-5-en-2-one **14**, methyl vinyl ketone **15** and pyruvaldehyde **16**. These are thought to derive from fragmentation of an α-farnesene derivative at C-3 and C-6 (scheme 2). 6-Methylhept-5-en-2-one **14** was found to be the main oxidation product during the early stages of autoxidation. 1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane **17** has been identified in the headspace of "Granny Smith" apples and has also been postulated as an autoxidation product of α-farnesene by Stanley *et al*[20]. The intermediacy of 6-methylhept-5-en-2-one **14** in this process was investigated and it was concluded that this was unlikely.

Scheme 2



In relation to scald, Anet[22] has suggested that since these ketones are only formed in trace amounts, they would need to have a high specific toxicity to cause damage to the cells of the apple epidermis during scald development. It was further postulated that free radicals generated from the autoxidation of α-farnesene were more likely to be the toxic agents responsible for scald induction.

The level of α-farnesene on the apple surface varies with the cultivar[23]; susceptible varieties such as "Granny Smith" and "Cortland" exhibit higher levels than a scald

resistant variety such as "Crofton". In a study investigating superficial scald in "d'Anjou" pears[2], the level of α-farnesene was found to peak at three months storage at -1°C, declining thereafter. Conjugated trienes (as measured by UV) became apparent at three months and increased to reach a maximum after five months. Superficial scald was first detected at three months with incidence and severity rapidly increasing after four and five months storage. This same pattern was observed in studies on "Granny Smith" apples[16a,c]. Pre-oxidised α-farnesene was also applied to stored apples, inducing an injury that upon microscopic examination was indistinguishable from typical superficial scald. These studies provide further evidence for the role of conjugated trienes derived from α-farnesene in the occurrence of superficial scald.

1.2.2 Natural Scald Resistance

A major factor determining the extent of the oxidation of α-farnesene on apples is probably the presence of antioxidants such as α–, γ– and δ– tocopherol and carotenoids in the apple cuticle. It seems likely that these compounds provide the apple with a form of natural protection[24a,b]. The concentration of these antioxidants has been found to be highest at picking, declining during subsequent storage[16c].

Maturity and harvest date are also known to greatly influence the development of scald after storage. Early harvest apples are more liable to scald, an observation which has been attributed to higher levels of α-farnesene as well as a less efficient antioxidant system than in mature fruit[25]. The degree of scald in a harvest , however, is not easily predicted. Susceptiblity varies greatly amongst cultivars, seasons, growing areas and environmental conditions[26].

1.2.3 Treatment of Superficial Scald

Many of the measures employed to prevent scald also provide circumstantial evidence for the involvement of α-farnesene and its oxidation products. The application of oiled wraps as a scald preventative, for instance, reduces scald and since high concentrations of α-farnesene can be found in the wraps after storage (over twice as much as on the fruit)[16a], it may be concluded that the reduced level of α-farnesene on the actual fruit results in less scald. This same argument may be applied to the prevention of scald *via* additional ventilation as the α-farnesene concentration on the apples may be reduced through evaporative losses.

The major commercial treatment for scald is the application of antioxidants such as diphenylamine (DPA) or 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin) as a spray or dip. These compounds are believed to inhibit α-farnesene autoxidation in the same manner as the apple's natural antioxidant system. A study of extracts from the skins of untreated and DPA treated cold-stored apples[16b] revealed the presence of conjugated trienes (by UV spectrum) in the untreated sample, and their complete absence in the DPA treated sample (figure1). Scald was negligible in this latter sample, providing further evidence for the involvement of these conjugated trienes in the disorder.

Many other treatments have also been investigated and show varying degrees of success. The waxing of apples and hot water dips prior to cold storage provides a significant but incomplete reduction in scald, however, the effectiveness of these treatments is highly dependent on the cultivar. Maintainance of high levels of calcium in apple fruit tissue is known to result in improved fruit firmness and can delay the onset of scald. When this method is used in conjunction with various heat treatments it can provide partial scald control[27].

Butylated hydroxytoluene (BHT), an antioxidant food additive which is "generally recognised as safe" by the American Food and Drug Administration[28] has also proved effective in the reduction of scald, however much higher concentrations of BHT are required to produce an equivalent reduction in scald compared with DPA or ethoxyquin[25,29].

Oxygen and carbon dioxide concentrations in storage also affect the incidence of scald. Low oxygen storage (1-1.7% O_2, 0°C) has been shown to be reasonably effective, and additional benefits in scald control can be gained by subjecting the fruit to initial oxygen stress (0-0.5% O_2, 0°C) followed by storage at 1% oxygen and 1% carbon dioxide[25]. Controlled atmosphere storage is a useful, non-chemical method for controlling superficial scald but is still somewhat dependent on variety, fruit maturity and location of harvest.

A review by Ingle and D'Souza[25] provides a more detailed discussion of the physiology and treatment of scald.

1.3 Rationale and Objectives for the Present Work

While at present, DPA and ethoxyquin provide the most effective form of control for superficial scald, concern as to the safety of the consumer from chemical residues and the

possibility of changes in antioxidant regulations means that alternative non-chemical control measures are increasingly being sought[25,29,30].

Controlled atmosphere storage provides one answer to this problem, and is widely used commercially. Aside from the exact atmosphere for storage being somewhat dependent on variety, fruit maturity and location, an additional drawback for low oxygen storage is the possibility of low oxygen stress. This disorder is characterised by ribbon-like, depressed skin browning, flesh and/or core browning and the development of an alcoholic flavour due to alcohol accumulation in fruit tissue during anaerobiosis[31].

Since the work of Anet[18,22], Cavill and Coggiola[19] and Filmer and Meigh[21] from 1969 to 1972 and of Stanley *et al*[20] in 1986, no further work on the chemical oxidation of α-farnesene has been carried out and the exact mechanism of scald induction and the role of α-farnesene oxidation products still remains unclear. With the withdrawal of DPA from commercial use regarded as inevitable, there has been a worldwide resurgence of interest in alternative control measures for superficial scald, hence research has been undertaken to re-examine the oxidative chemistry of α-farnesene.

To this end, α-farnesene has been synthesised and then oxidised with various reagents in order to examine the site specificity of the α-farnesene oxidation process and to isolate and characterise functionalised α-farnesene derivatives. These oxidation products could then be used as standards to investigate the presence or absence of α-farnesene oxidation products on the apples themselves. In addition, Anet's conjugated trienes **3** and **4**, which are prime suspects in the initiation of scald, have only been isolated twice[18,32] and have never been synthesised. In the current work, the first syntheses of trienol **3** and endoperoxide **4** were carried out, facilitating identification and quantification of these products on fresh and stored apples. Further possible oxidation products were also synthesised, providing pure and fully characterised material with which to carry out biological testing.

Once extensive biological testing has been carried out with these α-farnesene oxidation products, it may well be possible to gain some insight into the cause of this disorder, thereby enabling a suitable non-chemical treatment for the prevention of superficial scald to be devised.

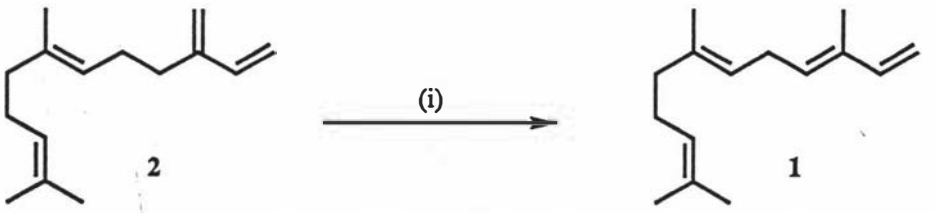
1.4 The Synthesis of α-Farnesene

1.41 Previous Syntheses of α-Farnesene

The initial objective for the present work necessitated a supply of reasonable quantities of α-farnesene in order to study its oxidation. A review of methods to synthesise α-farnesene is summarised below.

Several stereoselective syntheses of (3*E*,6*E*)-α-farnesene **1** (hereafter referred to as α-farnesene) have been reported since its initial isolation (1964)[33] and identification (1966)[1a] in the natural coating of apples. The preparation of α-farnesene was first carried out by Brieger *et al*[34] *via* the rhodium chloride-catalysed isomerisation of (6*E*)-β-farnesene **2** (scheme 3). The β-farnesene starting material was obtained in 65% yield *via* catalytic dehydration of farnesol using activated alumina at 260-270°C[35], followed by isomerisation, whereupon α-farnesene was isolated as the major component (57% by GC), along with several other isomeric products.

Scheme 3



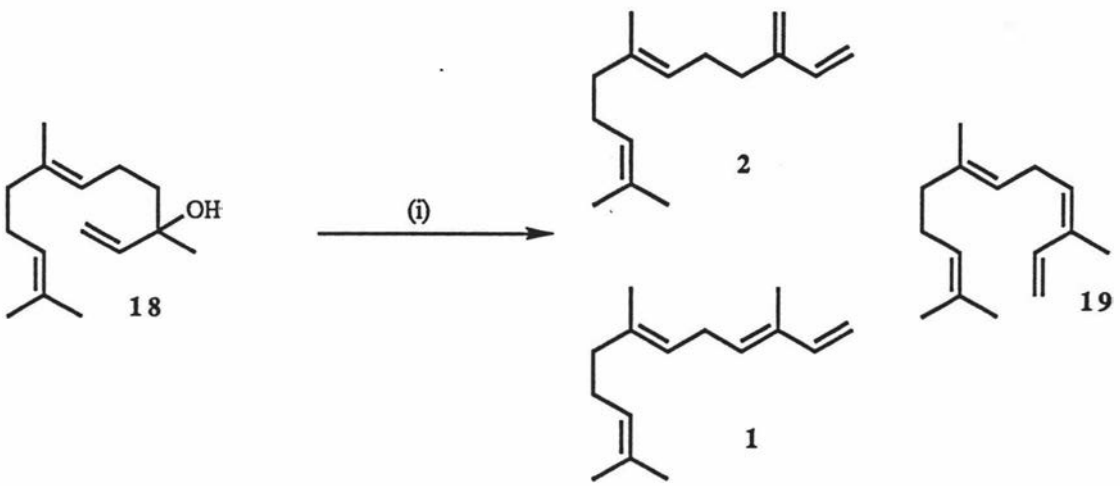
Reagents and conditions: (i) $RhCl_3.3H_2O$, ethanol, -70°C, 0.5hr (57%).

In 1970, Anet[36] prepared three farnesenes by the careful dehydration of (6*E*)-nerolidol **18**. The (6*E*)-nerolidol **18** was obtained by preparative GC of a commercially available sample of the mixed (*Z*)- and (*E*)-isomers and was dehydrated with phosphoryl chloride in pyridine. (6*E*)-β-Farnesene **2**, (3*E*,6*E*)-α-farnesene **1** and (3*Z*,6*E*)-α-farnesene **19** were identified by GC from the "crude product" obtained from the reaction mixture (scheme 4). The three farnesenes **1**, **2** and **19** were then further purified and isolated by preparative GC.

Tanaka *et al* [37] carried out a stereospecific synthesis of α-farnesene in 1975, utilising the conversion of an allylic alcohol to a 1,3-diene (scheme 5). Reaction of commercial (2*E*,6*E*)-farnesol **20** with vanadium oxide acetylacetonate and *t*-butyl hydroperoxide in benzene and subsequent treatment with trimethylsilylchloride-hexamethyldisilazane-pyridine afforded epoxy silyl ether **22**. Stereospecific ring-opening of the crude epoxide was carried out using diethylaluminium 2,2,6,6-tetramethylpiperidide (DATMP),

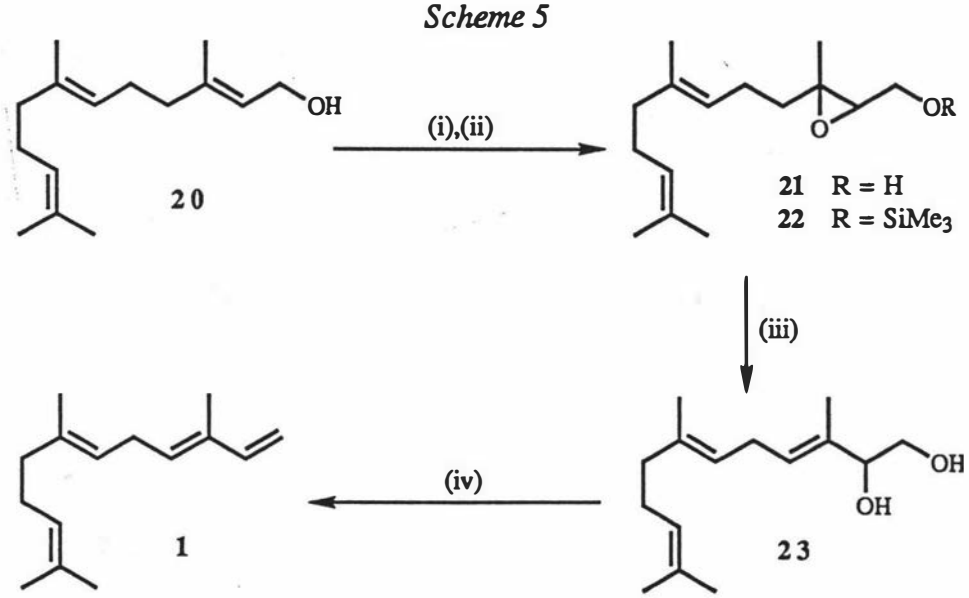
followed by desilylation with excess potassium fluoride in aqueous methanol to afford farnesyl diol **23** in 71% overall yield. Treatment of this diol **23** with phosphorous tribromide in ether in the presence of cuprous bromide followed by the addition of excess zinc powder gave α-farnesene **1** in 49% yield.

Scheme 4



Reagents and conditions: (i) a: phosphoryl chloride, pyridine, 24hr; b: 100°C, 1hr.

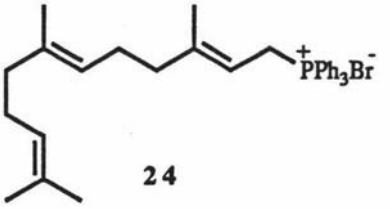
Scheme 5



Reagents and conditions: (i) $VO(acac)_2$, *t*-BuOOH, benzene, 25°C, 2hr; (ii) Me_3SiCl, hexamethyldisilazane, pyridine, 25°C, 0.5hr; (iii) a: DATMP, benzene, 0°C, 2hr; b: KF (excess), aqueous MeOH, 25°C, 0.5hr (71%); (iv) a: PBr_3, CuBr, ether, -78°C, 5min.; b: Zn powder, 0°C, 2hr (49%).

Formation of α-farnesene was also observed in the attempted coupling of (3*E*,6*E*)-farnesyltriphenylphosphonium bromide **24** by cathodic reduction[38]. The expected

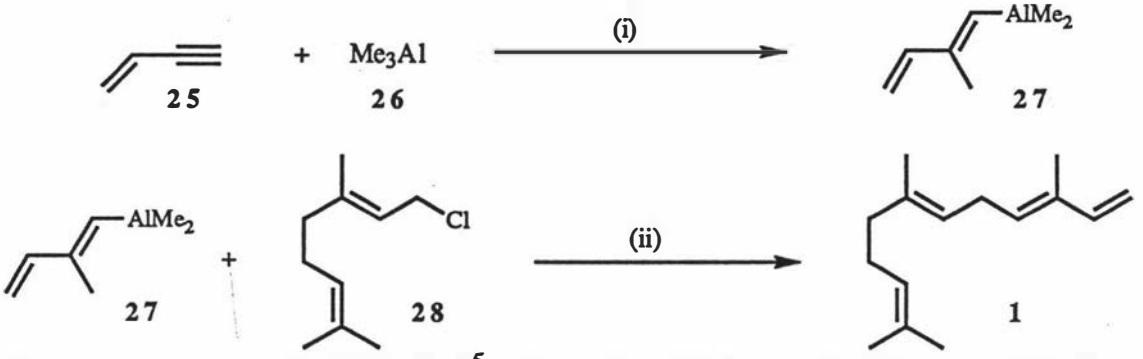
product (squalene) was not obtained and α-farnesene was the major product (32%), obtained *via* cleavage of the triphenylphosphonium salt **24**.



24

In 1984, Negishi and Matsushita[39] synthesised α-farnesene *via* the palladium-catalysed allylation of vinylalane **27** (scheme 6). (*E*)-(2-Methyl-1,3-butadienyl)dimethylalane **27** was prepared from solutions of but-1-en-3-yne **25** and trimethylaluminium **26** using zirconocene dichloride. Direct palladium-catalysed allylation of dimethylalane **27** using (*E*)-geranyl chloride **28** then afforded α-farnesene **1** (83% yield based on geranyl chloride **28**).

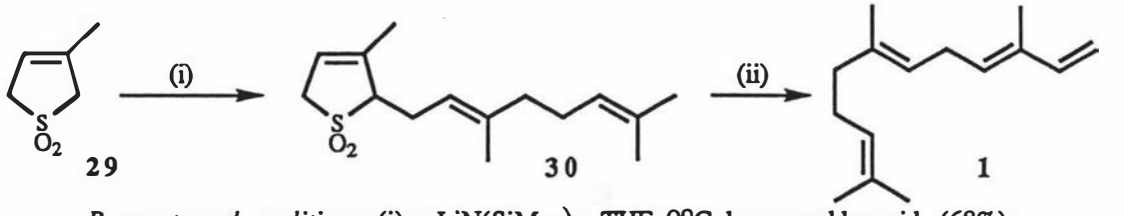
Scheme 6



Reagents and conditions: (i) dichlorobis(η^5-cyclopentadienyl)zirconium, 1,2-dichloroethane, RT, 12hr; (ii) tetrakis(triphenylphosphine)palladium, THF, RT, then HCl, 0°C (83%).

Chou *et al*[40] also reported in 1984 an effective procedure to prepare an α-farnesene precusor **30**, which possessed a masked diene moiety, *via* alkylation of 3-methylsulpholene **29** with (*E*)-geranyl bromide (scheme 7).

Scheme 7



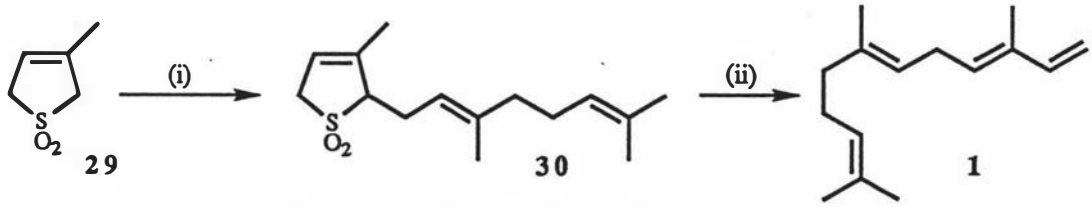
Reagents and conditions: (i) a: $LiN(SiMe_3)_2$, THF, 0°C; b: geranyl bromide (68%); (ii) thermolysis, GC, 240°C.

Deprotonation of 3-methylsulpholene **29** was carried out using lithium hexamethyldisilazide followed by alkylation with geranyl bromide to give **30** in 68%

yield. It was found that reaction took place exclusively at the 2-position, presumably *via* the C-2 intermediate anion. The diene was then able to be deprotected using preparative GC to give α-farnesene **1**.

The method of Chou *et al* [40] has recently been adapted by Fielder, Rowan and Reay[41] in order to synthesise preparative quantities of deuterated α-farnesene. This method was readily applicable to the synthesis of non-deuterated α-farnesene and was used in the course of the current research to synthesise α-farnesene for oxidation studies (scheme 8).

Scheme 8



Reagents and conditions: (i) a: *n*-BuLi, THF, DMPU, -105°C; b: geranyl bromide (60%); (ii) xylene, reflux (85-95%).

3-Methylsulpholene **29** was deprotonated using *n*-butyl lithium in tetrahydrofuran. Ring opening may be a competitive pathway to anion formation but can be minimised by using hexamethylphosphoramide (HMPA) as co-solvent, however, in view of its carcinogenicity[42] the less toxic 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[42] (2.2 equivalents) was used instead. Addition of geranyl bromide gave the expected α-farnesene precursor **30** (60% yield) from which the diene functionality was unmasked upon thermolysis by heating under reflux in degassed xylene to afford α-farnesene in 85-95% yield[41].

2. DISCUSSION

2.1 Improvements to the Synthesis of α-Farnesene

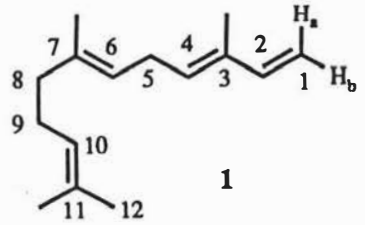
To routinely prepare the larger quantities of α-farnesene required for synthetic work, two modifications were made to the procedure of Fielder *et al*[41]. As discussed in the previous section, this procedure involved generation of the anion of 3-methylsulpholene **29** at -105°C using *n*-butyl lithium, followed by alkylation with geranyl bromide. The resultant sulpholene **30** then underwent thermolysis to α-farnesene **1** upon heating in xylene. In the current case, after formation of the anion was indicated by development of an orange colour, a 15 minute delay was introduced before addition of the geranyl bromide, thereby allowing more time for anion formation and improving the yield of **30** from 60% to 89%. During this period, careful maintainance of the temperature at -105°C was found to be essential as the yield was much reduced if the temperature was allowed to go above this level. Use of too little solvent (THF) also resulted in a reduced yield of **30** as the reaction mixture solidified at -105°C if the solution was too concentrated.

The second modification was made due to the difficulty of removing the xylene solvent completely after the thermolysis of **30** (scheme 8). Xylene was consequently replaced by the lower boiling point solvent toluene, which aided the eventual purification of the required product and thereby increased the yield to 98% for this step and 87% for the synthesis overall.

The ^{1}H nmr spectrum of α-farnesene **1** (figure 2) exhibited four methyl singlets at δ1.60, δ1.64, δ1.68 and δ1.77 which were assigned as 12-H, 11-Me, 7-Me and 3-Me respectively. The 8-H and 9-H methylenes were observed between δ2.02 and δ2.09, whereas the bis-allylic methylene group, 5-H, was seen as a triplet resonating at δ2.84. In the olefinic region a doublet at δ4.92 was assigned to 1b-H and a triplet at δ5.46 assigned to 4-H. A double doublet resonating at δ6.37 was found to be characteristic of 2-H and the remaining olefinic protons were located as a multiplet, integrating for three protons, at δ5.05-δ5.13. All mass spectral, IR, ^{1}H nmr and ^{13}C nmr data obtained for this compound were in agreement with the literature.[4,36]

When the alkylation of sulpholene **29** was carried out with less solvent, small amounts of the 2,2- and 2,5-disubstituted sulpholenes **31** (1.7%) and **32** (0.8%) were isolated from the reaction mixture. Although the predominant anionic species is the sulpholene resulting from proton abstraction at the 2-position, which forms the desired product, the isolation of **31** and **32** suggests the possibility an anion exchange process taking place[41] during

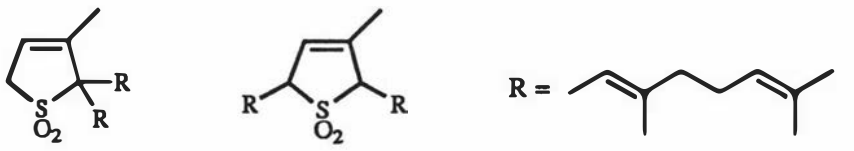
Figure 2



1

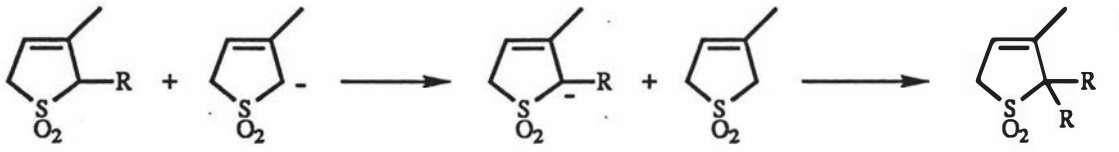
(2*E*,6*E*)-3,7,11-Trimethyldodeca-1,3,6,10-tetraene (1)

the alkylation process (an example of this process is illustrated in scheme 9).



31 32

Scheme 9



31

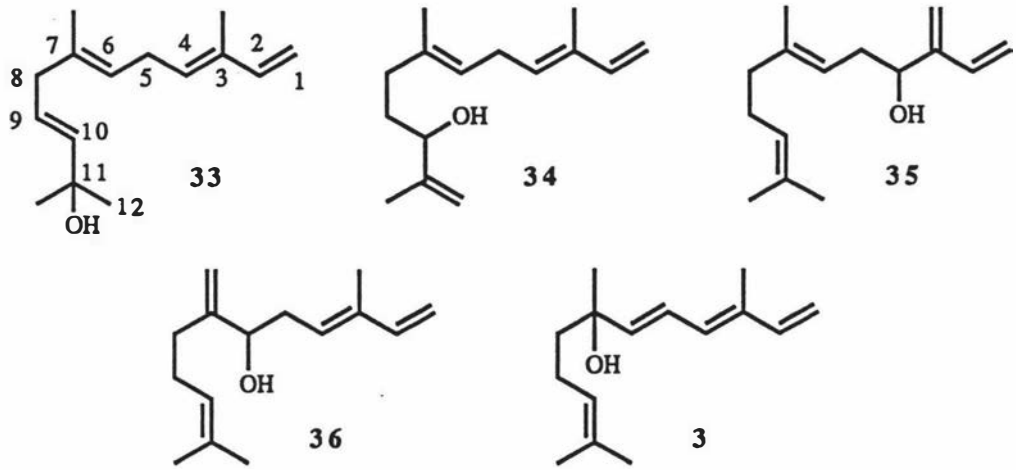
2.2 Synthesis of α-Farnesene Oxidation Products

2.2.1 The Oxidation of α-Farnesene

Whilst superficial scald may be effectively controlled by postharvest treatment with DPA or ethoxyquin, alternative non-chemical control measures are still being sought[25,29,30]. The development of such alternatives requires a better understanding of the mechanism of scald induction and of the role of α-farnesene oxidation products in this disorder. Given the postulated involvement of α-farnesene oxidation products, particularly conjugated trienes **3** and **4**, in the induction of scald, research was undertaken to investigate the site specificity of α-farnesene oxidation using several traditional oxidation reagents. This work would thereby provide a source of functionalised α-farnesene derivatives for further synthesis and for biological testing†.

Initial investigations focussed on the photo-oxidative chemistry of α-farnesene. In 1971, Cavill and Coggiola[19] carried out the photosensitised oxygenation of α-farnesene in ethanol, in the presence of the dye eosin, using a high pressure Hg lamp. A mixture of hydroperoxides was obtained which were reduced to the corresponding alcohols **33, 34, 35** and **36** using sodium borohydride. In the current work, this oxygenation of α-farnesene was repeated in acetonitrile using Rose-Bengal as photosensitizer. Reduction of the reaction mixture using triphenylphosphine afforded allylic alcohols **33, 34** and **35** (in 12, 9 and 15% yields respectively) for which the ^{1}H nmr data was in agreement with that reported by Cavill and Coggiola[19].

† For consistency, all acyclic derivatives of α-farnesene are numbered as for the parent compound (3,7,11-trimethyldodeca-1,3,6,10-tetraene **1**).

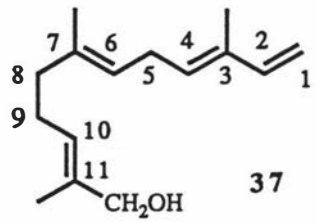


Anet's[18] conjugated triene alcohol **3** was also identified spectroscopically in a fraction which was an inseparable mixture (5:3) of alcohol **35** and conjugated triene **3**. The presence of **3** was indicated in the ^{1}H nmr spectrum of the mixture by a double doublet at δ6.58 assigned to 5-H and two doublets at δ6.07 and δ5.81 assigned to 4-H and 6-H respectively. A UV spectrum of the mixture showed characteristic absorbances at 251, 259, 269 and 281 nm, in agreement with data for triene **3** reported by Anet[18].

Use of selenium dioxide, the classical reagent for allylic oxidation, in a stoichiometric amount in 95% aqueous ethanol resulted in a mixture of products from which the primary allylic alcohol **37** was isolated albeit in 3% yield. When selenium dioxide (catalytic) was used in conjunction with *N*-methylmorpholine-*N*-oxide (NMO) as a re-oxidant, alcohol **38** was isolated in 1% yield, in addition to **37** (1%).

Both products were clearly alcohols from the infra-red spectrum which exhibited an OH stretch at 3360 cm^{-1} and a molecular ion at m/z 220 was consistent with the molecular formula $C_{15}H_{24}O$. The ^{1}H nmr spectra of alcohols **37** and **38** were very similar. Deuterium oxide exchange established that the hydroxyl proton resonated at δ1.59 in both isomers. Retention of the conjugated diene system was evidenced by the double doublet at δ6.37 assigned to 2-H for which the chemical shift was the same as in α-farnesene.The vinylic proton 10-H resonated as a triplet at δ5.37 in **37** and δ5.39 in **38** and was deshielded relative to this same proton in α-farnesene which resonated at δ5.09. In alcohol **37** the presence of a primary allylic alcohol was established by the observation of a resonance at δ3.99 integrating for two protons assigned to the CH_2OH group. In the ^{13}C spectrum, this $\underline{C}H_2OH$ carbon (C-12) resonated at 69.0ppm which by comparison with ^{13}C data obtained by Bhalerao and Rapoport[43] (who investigated the stereospecific oxidation of *gem*-dimethyl olefins using selenium dioxide) was established to be the *trans* alcohol. For alcohol **38**, the presence of a secondary allylic alcohol was established by

the presence of a broad triplet (-C<u>H</u>(OH)CH_2-) δ3.99 integrating for one proton only, assigned to 8-H. Consistent with these assignments were the presence of three methyl groups at δ1.64, 1.66 and 1.76 in alcohol **37** and four methyl groups at δ1.64, 1.67, 1.72 and 1.77 in alcohol **38**.



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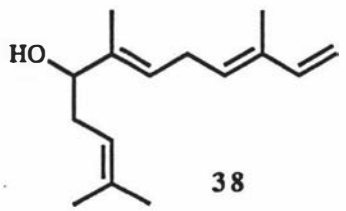
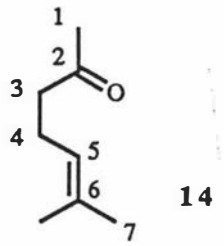
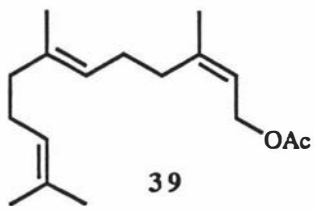


38

The use of chromium trioxide / 3,5-dimethylpyrazole complex[44], a reagent also used for allylic oxidation, was then investigated. Surprisingly, the major product observed was 6-methyl-5-hepten-2-one **14**, resulting from cleavage of the C-6, C-7 carbon-carbon bond of α-farnesene **1**. This distinctive smelling ketone **14** is a major volatile product of α-farnesene auto-oxidation[20,25] and an apple aroma constituent. One further reagent for allylic oxidation, manganese triacetate[45], was also investigated. No reaction was observed in either toluene or ethanol whereas use of acetic acid and acetic anhydride as solvent lead to the isolation of (*E*,*Z*)-farnesyl acetate **39** identified by comparison with commercially available (*E*,*E*)-farnesyl acetate **40**.



14



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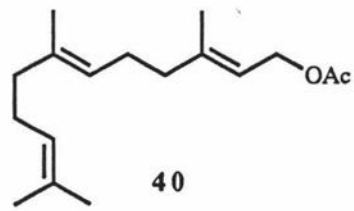

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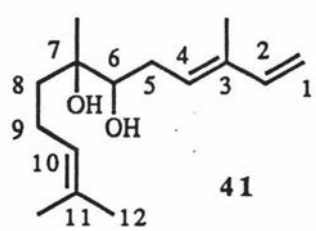
Hydroxylation of the double bonds was then accomplished by the use of OsO_4 (catalytic) with NMO as re-oxidant. An unstable, inseparable 5:1 mixture of the two diols **41** and **42** was obtained, with complex ^1H and ^{13}C nmr spectra. GC/MS however, allowed separation of the two regioisomers and facilitated interpretation of the mass spectra. Both the monoacetate and acetonide derivatives of the diol mixture were prepared, however, although characterised by nmr and GC/MS, neither of the derivatives could be separated by flash chromatography.



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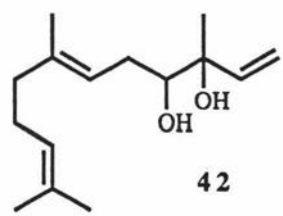
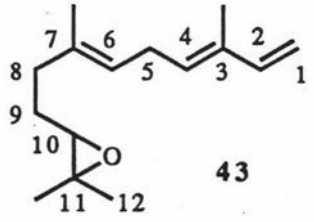


42

In view of the disappointing results in the hydroxylation reaction attention was turned to the epoxidation of α-farnesene **1**. The use of dimethyldioxirane[46] resulted in formation of three monoepoxides **43**, **44** and **45** in a 1:1:1 ratio, indicating no selectivity for any of the more electron rich trisubstituted double bonds. The three epoxides were separated by flash chromatography and all exhibited molecular ions at *m/z* 220, supporting the molecular formula $C_{15}H_{24}O$.

The structure of epoxide **43** was assigned from the ^1H nmr spectrum (table 1) by the upfield shift of the two terminal methyl groups from δ1.60 and 1.64 in α-farnesene to δ1.26 and δ1.30 in **43** and the disappearance of the vinylic proton 10-H at δ5.09 in α-farnesene together with the appearance of a methine proton attached to an epoxide at δ2.70. The infra-red spectrum exhibited a C-O stretch at 1220 cm^{-1} whilst resonances at δ58.3 and 64.1 in the ^{13}C nmr spectrum assigned to C-10 and C-11 were consistent with these carbons being attached to an oxygen atom as required in epoxide **43** (table 2).



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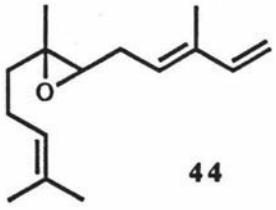
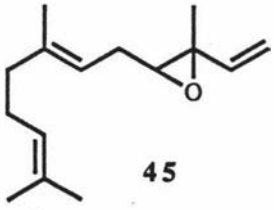


44



45

In the ^1H nmr spectrum of epoxide **44** (table 1) only the 7-methyl group was shifted upfield from δ1.68 in α-farnesene to δ1.30. The other three methyl groups resonated at the same position as in α-farnesene. The methylene protons, 5-H, appeared as a multiplet at δ2.22-2.56 while the resonance at δ2.77 was assigned to 6-H being characteristic of a proton attached to an epoxide. Again, the infra-red spectrum showed a C-O absorption at 1206 cm^{-1} and the ^{13}C nmr exhibited six vinylic carbons and resonances at δ 60.8 and 62.6 assigned to the carbons adjacent to an oxygen atom, namely C-6 and C-7 (table 2).

The structure of epoxide **45** was established from the ^1H nmr (table 1) by the large shift in the resonance of the vinylic proton 2-H from δ6.37 in α-farnesene where it was part of a conjugated diene system, to δ5.66 in epoxide **45** where 2-H is part of a monosubstituted alkene. The two allylic methylene groups 8-H and 9-H retained their position relative to α-farnesene at δ2.05, in contrast to epoxides **44** and **43** where 8-H and 9-H respectively were shifted further upfield to δ1.65 ppm.

Epoxidation of α-farnesene was also carried out using *meta*-chloroperbenzoic acid (*m*-CPBA) at 0°C to give epoxides **43**, **44** and **45** in a different product ratio, namely,

Table 1: ^{1}H nmr Shifts (ppm) for α-Farnesene **1**, Epoxides **43**, **44**, **45** and *Bis*-epoxides **46**, **47**.

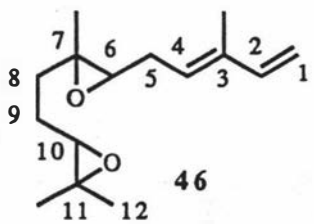
	1a-H	1b-H	2-H	4-H	5-H	6-H	8-H	9-H	10-H	12-H	3-Me	7-Me	11-Me
1	5.05	4.92	6.37	5.46	2.84	5.05	2.02	2.02	5.09	1.60	1.77	1.68	1.64
43	5.09	4.93	6.35	5.45	2.84	5.17	2.11	1.65	2.70	1.26	1.76	1.66	1.30
44	5.14	4.98	6.39	5.51	2.39	2.77	1.65	2.07	5.07	1.60	1.74	1.30	1.68
45	5.32	5.17	5.66	2.82	2.31	5.18	2.05	2.05	5.08	1.60	1.42	1.67	1.64
46	5.14	4.99	6.38	5.51	2.53	2.82	1.65	1.62	2.79	1.27	1.77	1.30	1.32
47	5.31	5.17	5.65	2.81	2.29	5.24	2.17	1.66	2.71	1.26	1.30	1.67	1.24

Table 2: ^{13}C nmr Shifts (ppm) for α-Farnesene **1**, Epoxides **43**, **44**, **45** and *Bis*-epoxides **46**, **47**.

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	3-Me	7-Me	11-Me
1	110.5	141.7	133.7	131.8	27.2	122.1	135.8	39.6	26.7	124.3	131.3	25.7	11.7	16.1	17.6
43	110.7	141.4	133.8	131.4	27.2	122.7	134.6	36.2	27.2	64.1	58.3	24.8	11.7	16.1	18.7
44	111.6	141.0	136.0	126.9	23.8	62.6	60.8	38.6	28.2	123.5	132.0	25.7	11.9	16.5	17.7
45	115.8	140.9	59.5	64.8	27.8	118.4	138.0	39.7	26.5	124.0	131.5	25.7	14.9	16.3	17.7
46	111.6	140.9	136.2	126.7	24.5	62.4	60.3	35.2	28.0	63.8	58.3	24.8	11.9	16.5	18.6
47	115.8	140.8	59.5	64.7	27.8	119.1	137.2	36.3	27.3	64.0	58.3	24.8	14.9	16.3	18.7

10:5:1. Epoxide **43**, which resulted from the epoxidation of the C-10,11 double bond was therefore isolated in greater yield than epoxide **44** (epoxidation of the C-6,7 double bond) which in turn was isolated in greater yield than epoxide **45**. This product ratio reflects the greater nucleophilicity of the two isolated trisubstituted alkenes over that of the trisubstituted double bond of the diene system. The larger amount of **43** relative to **44** reflects the decreased steric hindrance towards attack at the terminal double bonds relative to the internal double bond. The epoxide which would result from attack at the least reactive C-1,2 double bond was not observed. The greater selectivity of *m*-CPBA over dimethyldioxirane [*m*-CPBA **43:44:45**, 10:5:1 and dimethyldioxirane **43:44:45**, 1:1:1] reflects the higher reactivity (i.e. lower selectivity) of the latter reagent.

When epoxidation of α-farnesene with *m*-CPBA was conducted at room temperature or with an excess of reagent, two additional products, bisepoxides **46** and **47**, were isolated in a 2:1 ratio. A molecular ion at *m/z* 236 for bisepoxides **46** and **47** confirmed the molecular formula as $C_{15}H_{24}O_2$. The ^1H nmr spectrum of bis-epoxide **46** (table 1) was a hybrid of those obtained for epoxides **43** and **44**. Three methyl groups were shifted upfield, with only the 3-methyl group maintaining its position at δ1.77. The two methylene groups , 8-H and 9-H, located between the epoxides, were also both shifted upfield and were found as a multiplet centred at δ1.63. The epoxide protons, 6-H and 10-H, resonated as multiplets at δ2.77-2.84, with the remaining olefinic protons resonating at δ4.97-6.44 (integrating for four protons). The ^{13}C nmr spectrum confirmed the presence of the two epoxides with four carbons, C-6, C-7, C-10 and C-11 resonating in the range δ58.3-63.8 ppm (table 2). The infra-red spectrum again showed a C-O stretch at 1247 cm^{-1}, and C=C absorptions at 1609 and 1640 cm^{-1} confirmed retention of the diene system.



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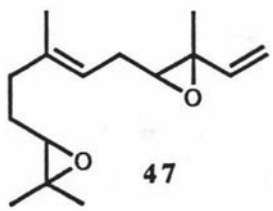
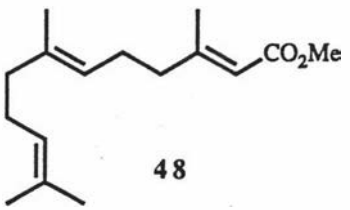


47

Bisepoxide **47** possessed a ^1H nmr spectrum (table 1) which was essentially a hybrid of those for epoxides **43** and **45**. Three methyls were again shifted upfield, this time the 7-methyl remained in its original position of δ1.67. Of 8-H and 9-H, however, only 9-H showed a shift (to δ1.66) due to a neighbouring epoxide. Partially superimposed upon the 8-H multiplet was a multiplet at δ2.19-2.47 assigned to 5-H. The epoxide protons, 4-H and 10-H, resonated characteristically at δ2.81 and 2.71 respectively. The remaining olefinic protons were observed at δ5.15-5.71, with 1-H and 2-H showing significant

changes in position due to the proximity of the epoxide and loss of the conjugated diene system. Loss of the diene system was confirmed in the infra-red spectrum with the disappearance of the C=C stretch at 1609 and 1639cm^{-1} found in α-farnesene. The ^{13}C nmr spectrum for bisepoxide **47** also showed four peaks between δ58.3 and 64.7 ppm assigned to C-3, C-4, C-10 and C-11 (table 2).

The epoxidation of methyl farnesoate **48** has been studied extensively[47-50] since the identification of methyl (2*E*)-6,7,10,11-*bis*-epoxyfarnesoate **49** as a juvenile hormone in *Drosophila melanogaster* ("fruit" fly), *Musca domestica* (house fly) and *Calliphora vicina* and *C. vomitoria* (blowflies)[49]. The results reported for methyl farnesoate[47] are in general agreement with those reported herein on the epoxidation of α-farnesene in that the 10,11-position was preferred over the 6,7-position for epoxidation, and when the reaction temperature was raised[47] or an excess of reagent added[48] a *bis*-epoxide was obtained.



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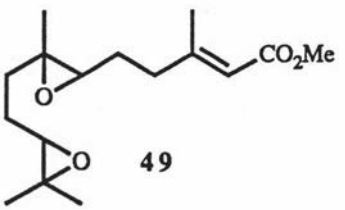


49

The successful synthesis and characterisation of allylic alcohols **33-38**, diols **41** and **42**, epoxides **43**, **44**, **45** and *bis*-epoxides **46**, **47** has provided a library of oxidation products of α-farnesene to use as standards to aid the identification of α-farnesene oxidation products formed in stored fruit. This study, however, failed to produce pure samples of trienes **3** or **4**. Attention was therefore turned to direct chemical syntheses of the required trienes.

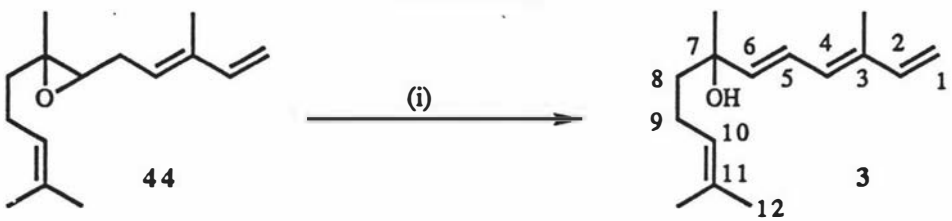
2.2.2 Synthesis of Other Oxidation Products

The photosensitised oxidation of α-farnesene **1** using Rose-Bengal as photosensitiser, discussed in the previous section, only provided the required triene **3** as an inseparable minor component of allylic alcohol **35**[51] whereas autoxidation studies similar to those reported by Anet[18] proved unreliable as a source of trienes **3** or **4** (personal communication; D.D. Rowan, HortResearch). Direct chemical syntheses of trienes **3** and **4** were therefore carried out utilising the monoepoxides **43**, **44** and **45** described in the previous section[51].

Epoxidation of α-farnesene **1** using dimethyldioxirane or *meta*-chloroperbenzoic acid provided the three mono-epoxides **43**, **44** and **45** of α-farnesene which were readily separable by flash chromatography. Directing our attention firstly to the synthesis of triene **3**,

the base promoted rearrangement of 6,7-epoxide **44** to triene **3** was investigated (scheme 10). Treatment of epoxide **44** with lithium diisopropylamide (LDA) using a variety of conditions failed to effect the desired rearrangement. Use of the mixed base potassium *tert*-butoxide (^{t}BuOK) / lithium diisopropylamide[52] in THF at -78°C to -50°C, however, resulted in clean rearrangement to triene **3** in 90% yield after purification by flash chromatography. The UV and ^{1}H nmr of triene **3** were in excellent agreement with those reported by Anet[18]. In addition the ^{1}H nmr data recorded at higher field (270 MHz) in the present case afforded a spectrum with enhanced resolution allowing complete assignment of the methyl and olefinic regions (figure 3).

Scheme 10



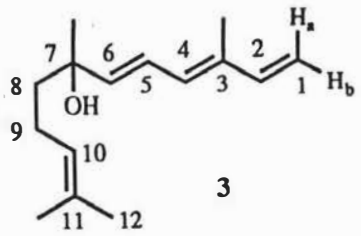
44 **3**

Reagents and conditions: (i) a: ^{t}BuOK, LDA, THF, -78°C to -50°C, 0.25h; b: warm to RT (90%).

The two terminal methyl groups (11-Me and C-12) maintained their positions as for epoxide **44**, at δ1.60 and δ1.67 respectively, as did the 10-H proton, indicating conservation of this end of the molecule. The 7-methyl group also remained in approximately the same position in both **44** and **3** (δ1.30 in 44 and δ1.32 in **3**). The 3-methyl group, however, exhibited a downfield shift from δ1.74 to δ1.88 reflecting its new position in a conjugated triene system as opposed to a conjugated diene system. The disappearance of the triplet at δ2.39 in **44**, representing the bisallylic 5-H protons, along with the appearance of a new double doublet at δ6.58 indicated the presence of a new double bond at C-5. Conversion of the 4-H and 6-H triplets at δ5.51 and δ2.77 respectively, to doublets at δ6.07 and δ5.81 confirmed the presence of double bonds at positions 3 and 5. The doublets at δ5.04 and δ5.21 and the double doublet at δ6.41, assigned to 1b-H, 1a-H and 2-H indicated the retention of the conjugated diene system as in epoxide **44**. A COSY experiment established the connectivity of the triene system whereas a NOESY experiment (figures 4 and 5) indicated interactions between the 3-methyl group and 5-H, and between 4-H and 6-H. These interactions, as well as the magnitude of the coupling constant $J_{5,6}$ 15.0 Hz, confirmed the 3*E*,5*E* stereochemistry of the newly conjugated double bonds.

Alcohol **50** is also a potential autoxidation product of α-farnesene **1**, and subsequent acid treatment might provide an alternative synthesis of triene **3**[53]. Hence the synthesis of alcohol **50** *via* rearrangement of 3,4-epoxide **45** was undertaken (scheme 11). Epoxide **45** was less reactive than epoxide **44** towards base induced rearrangement requiring use of a co-solvent

Figure 3



3

(3*E*,5*E*)-3,7,11-Trimethyldodeca-1,3,5,10-tetraen-7-ol (3)

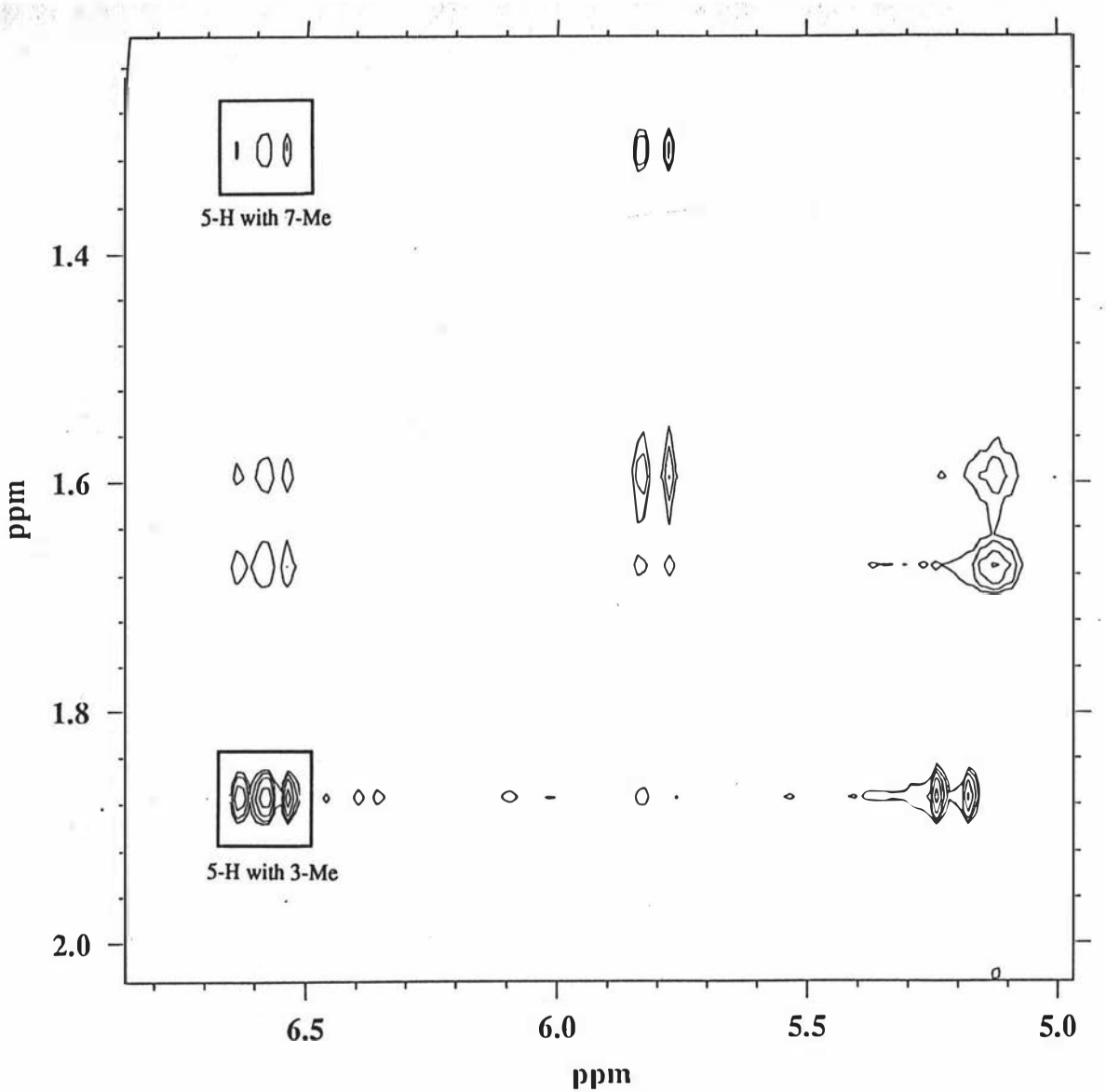
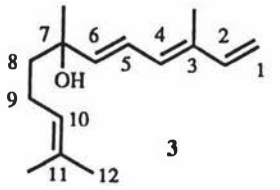

5-H with 7-Me
5-H with 3-Me
1.4
1.6
1.8
2.0
ppm
6.5
6.0
5.5
5.0
ppm

Figure 4


7
6
4
2
8
OH
5
3
1
9
10
11
12

3

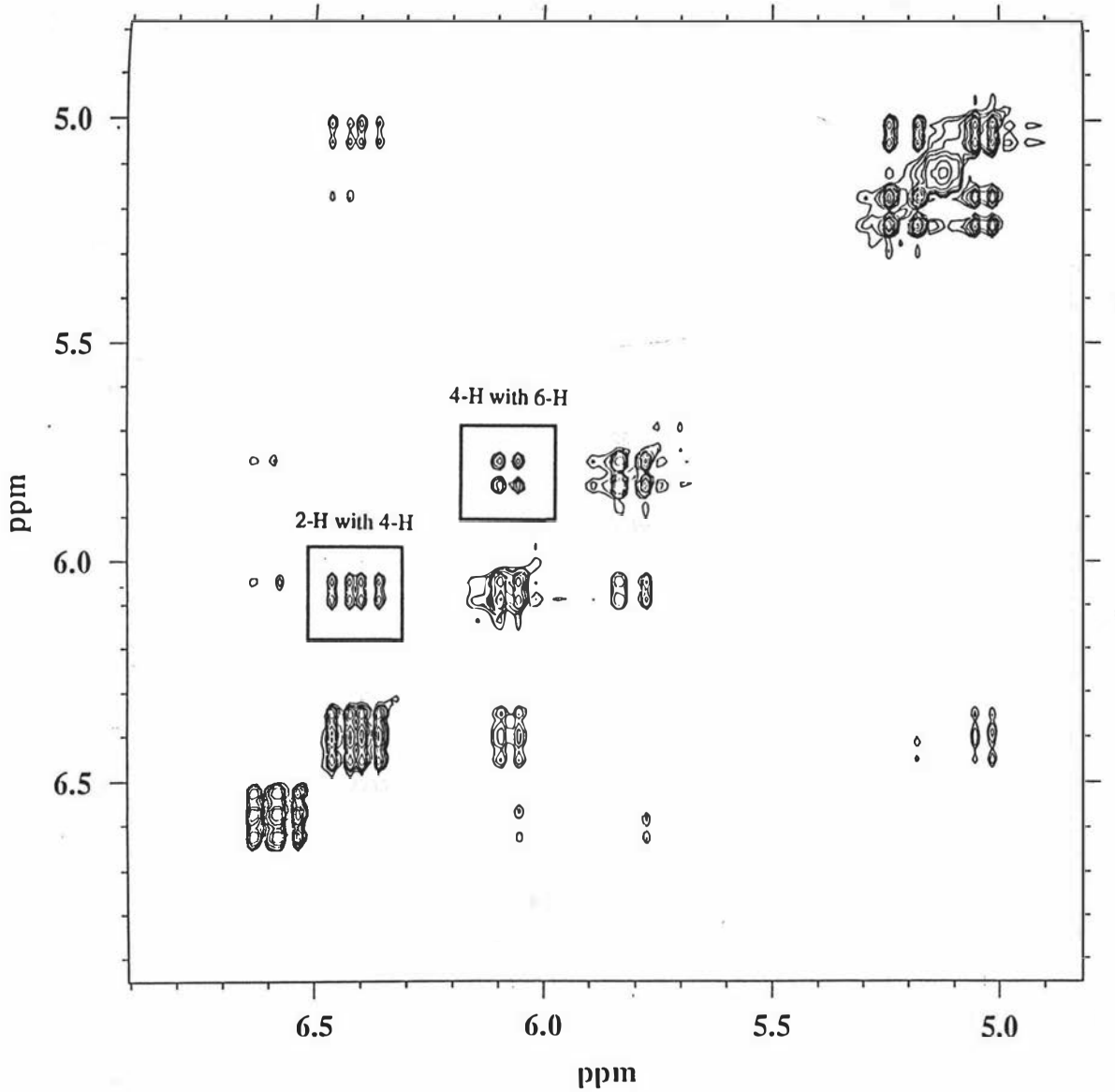
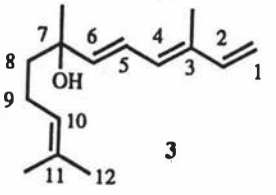

5.0
5.5
6.0
6.5
ppm
4-H with 6-H
2-H with 4-H
6.5
6.0
5.5
5.0
ppm

Figure 5


7
6
4
2
8
OH
5
3
1
9
10
3
11
12

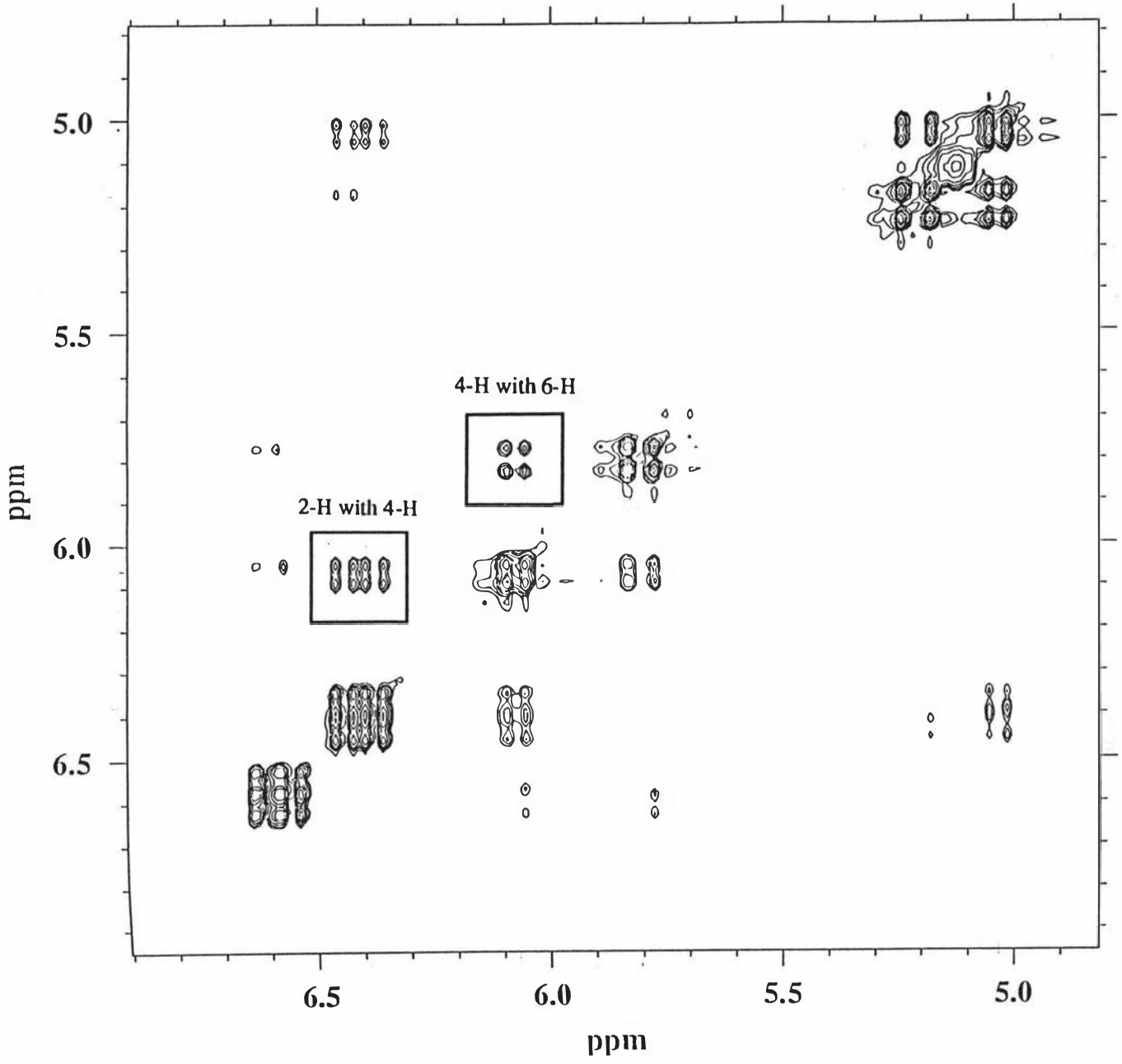
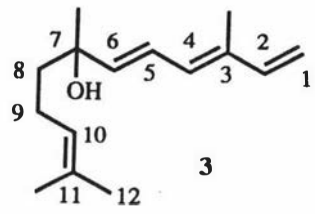

5.0
5.5
6.0
6.5
ppm
4-H with 6-H
2-H with 4-H
6.5
6.0
5.5
5.0
ppm

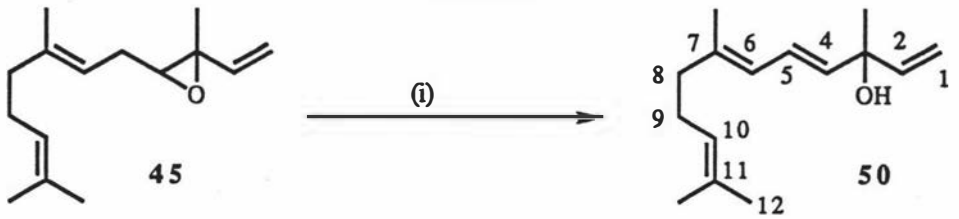
Figure 5


7
6
4
2
8
5
3
1
OH
9
10
11
12

3

(tetramethylethylenediamine) with the ^{t}BuOK / LDA base providing trienol **50** in 62% yield after purification by flash chromatography. The UV spectrum obtained for trienol **50** confirmed the lack of conjugation of the triene system with λ_{max} 242 nm observed at shorter wavelength than λ_{max} 251, 259, 269, 281 nm observed for conjugated triene **3**. A significant feature of the ^{1}H nmr spectrum for triene **50** were the resonances at δ5.98 and δ5.68 assigned to the vinylic protons 2-H and 4-H respectively, which had shifted considerably upfield relative to these same protons in triene **3** where they resonated at δ6.40 (2-H) and δ6.07 (4-H). The coupling constant $J_{4,5}$ 15.4 Hz clearly established the *E* stereochemistry of the 4,5-double bond. Treatment of triene **50**[53] with acid (*p*-TSA, CH_2Cl_2, RT) gave dehydration rather than conversion to triene **3**.

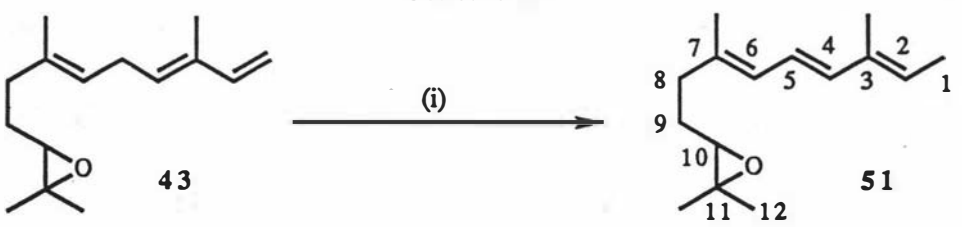
Scheme 11



Reagents and conditions: (i) a: ^{t}BuOK,TMEDA, LDA, THF, -78°C to -50°C, 0.25h; b: RT (62%).

In contrast to epoxides **44** and **45**, the 10,11-epoxide **43** failed to undergo rearrangement to an allylic alcohol. Treatment of 10,11-epoxide **43** with the same reagents as those used successfully for the conversion of epoxide **45** to trienol **50** resulted in formation of a conjugated triene **51** with the 10,11-epoxide remaining intact (scheme 12). Clearly anion formation at the bisallylic position had occurred followed by rearrangement to the more stable conjugated triene **51**. The ^{1}H nmr spectrum confirmed the structure of the triene **51** with a doublet at δ1.74, a singlet at δ1.77 and a singlet at δ1.80 (each integrating for three protons) establishing the presence of three methyl groups attached to double bonds. Two singlets further upfield at δ1.26 and δ1.30 characteristic of methyl groups attached to an epoxide together with a triplet at δ2.72 assigned to 10-H also clearly indicated that the 10,11-epoxide had not undergone ring opening. The *E*-stereochemistry of the 2,3- and 4,5-double bonds was once again established by the magnitude of the coupling constant $J_{4,5}$ 15.4 Hz and n.O.e. experiments in which irradiation at 2-H resulted in enhancement at 4-H.

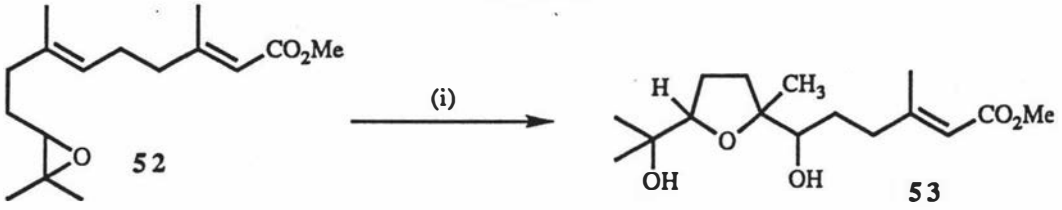
Scheme 12



Reagents and conditions: (i) a: ^{t}BuOK, TMEDA, LDA, THF, -78°C to -40°C, 0.25h; b: RT (65%).

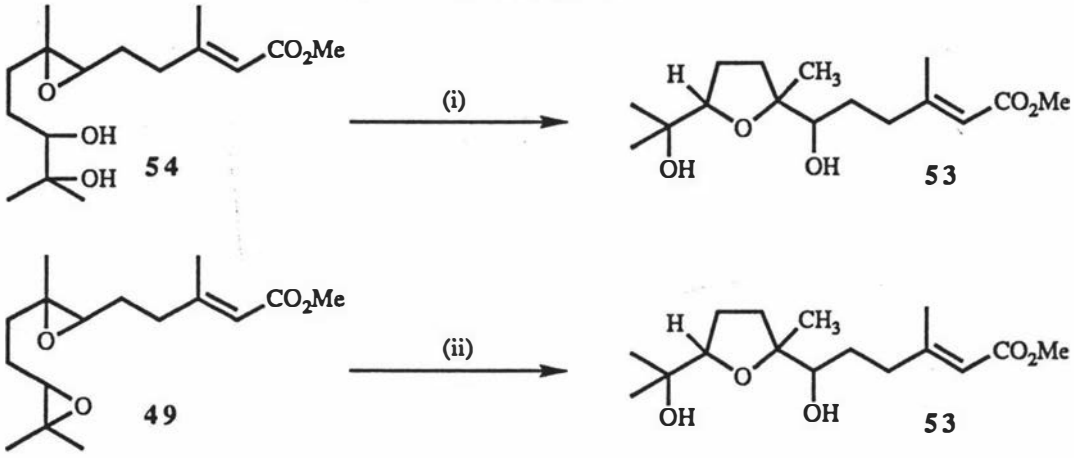
It then remained to synthesize the second triene autoxidation product **4**. Therefore, *bis*-epoxide **46**, prepared by epoxidation of α-farnesene **1**[51], was used as a model to prepare the tetrahydrofuran analogue of **4**, namely **55**. Similar products have been reported (as a mixture of diastereomers) both by Imai and Maruma[54] and Messeguer *et al*[48]; the former *via* fungal transformation of juvenile hormone **52** (scheme 13) and the latter as a byproduct from acid-catalysed cyclisation of the desired epoxy-diol **54** (scheme 14). A reference sample of tetrahydrofuran derivative **53** was also prepared by Messeguer *et al*[48] *via* acid-catalysed cyclisation of bis-epoxide **49** (scheme 14).

Scheme 13



Reagents and condtions: (i) *Colletotrichum nicotianae*, shaken 9h.

Scheme 14



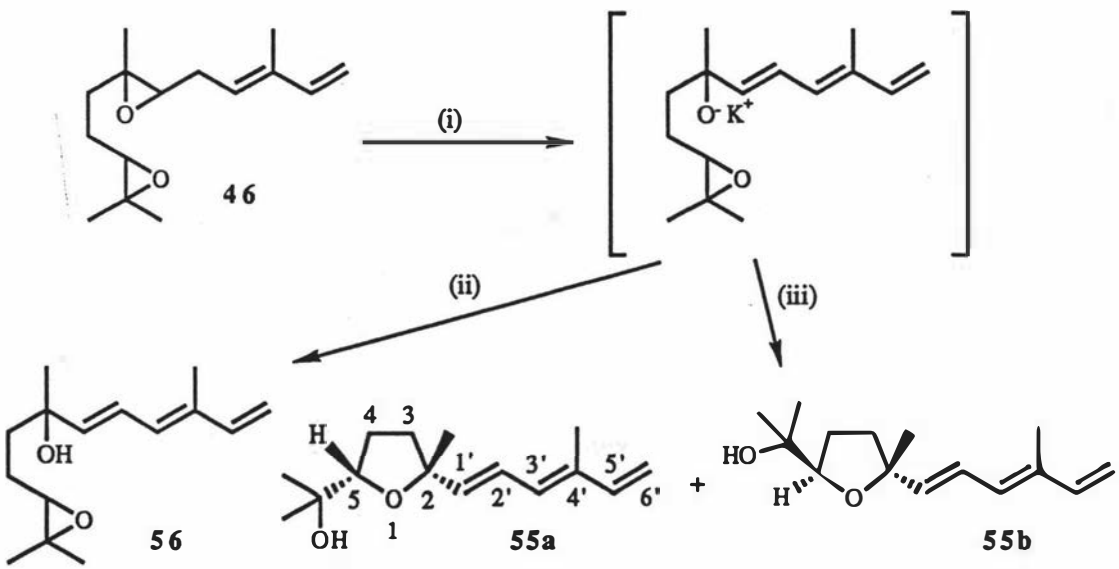
Reagents and conditions: (i) trace H^+; (ii) 2.5% $HClO_4$, RT, 1h.

Treatment of bis-epoxide **46** with ^{t}BuOK / LDA at -78°C in THF followed by warming to room temperature resulted in formation of a triene-alkoxide intermediate which cyclized *in situ* onto the epoxide forming the tetrahydrofurans **55a** and **55b** in 65% yield (Scheme 15). The two tetrahydrofurans **55a** and **55b** were separable by flash chromatography and their relative stereochemistries were assigned on the basis of their NOESY spectra. Thus, in isomer **55a** (higher R_f) the NOESY spectrum showed a correlation between the resonance assigned to the methyl group at C-2 and the methine proton 5-H which was absent in the other isomer **55b** (figure 8). This established a 1,3-*syn* relationship between 5-H and 2-Me for isomer **55a** as depicted (scheme 15). Therefore **55b** (lower R_f) which showed no n.O.e.

between the C-2 methyl group and 5-H was assigned as having the *trans* configuration. These results are in excellent agreement with those of Messeguer *et al*[48], who determined the configurations of the diastereomeric mixture of isomers **53** using molecular modelling and nmr studies. One difference, in contrast to the above results, was that in the current case, the *cis* isomer was slightly favoured (55:45) over the *trans* isomer, whereas Messeguer *et al*[48] reported a slight excess of the *trans* isomer. The chemical shifts and coupling constants assigned to the protons of the triene portion of tetrahydrofurans **55a** and **55b** were similar to that observed for triene **3** (figures 6 and 7). Previous workers[55,56] have prepared a similar *bis*-epoxide from farnesol, however, in their case, use of lithium diethylamide or diethylaluminium 2,2,6,6-tetramethyl-piperidide effected formation of only the *bis*-allylic alcohols with no cyclization occurring.

Repeating the cyclisation reaction at a lower temperature (-30°C) enabled isolation of the intermediate trienol **56** in 48% yield (scheme 15). The triene portion of the ^{1}H nmr spectrum of epoxy-alcohol **56** closely resembled that of triene **3** and the presence of the 10,11-epoxide was clearly established by the resonances at δ1.26 and δ1.30 assigned to the methyl groups attached to the epoxide and the resonance at δ2.72-2.76 assigned to the epoxide proton, 10-H, as for epoxide **43**.

Scheme 15



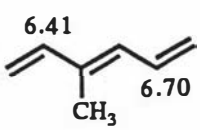
46 **56** **55a** **55b**

Reagents and conditions: (i) a: ^{t}BuOK, LDA, THF, -78°C to -60°C; (ii) warm to -30°C (48%); (iii) warm to RT (65%).

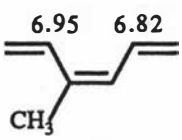
Whilst the successful preparation of tetrahydrofurans **55a** and **55b** represents a synthesis of analogues of Anet's triene **4**, a synthetic sample of **4** required for biological investigation remained elusive. Attempts to prepare **4** *via* cyclization of the peroxy radical generated from α-farnesene **1** (using NBS / CCl_4), onto the 10,11-double bond were fruitless, resulting in

an inseparable mixture of many products. Success, however, was realised utilizing the photoxidative chemistry of 10,11-epoxide **43** (scheme 16). Thus, photosensitized oxidation of epoxide **43** using Rose-Bengal as photosensitiser in acetonitrile, followed by immediate treatment with a catalytic quantity of *p*-toluenesulphonic acid and then finally treatment with triphenylphosphine afforded triene peroxide **4** albeit in 3% yield after flash chromatography.

The UV and ^{1}H nmr spectra confirmed the presence of the conjugated triene moiety. In addition, the ^{1}H nmr spectrum (figure 9) showed three higher field methyl singlets at δ1.23, δ1.29 and δ1.40, assigned to the isopropyl group and 3-Me respectively, and signals for the diastereomeric protons attached to C-6 at δ3.66 and δ4.11 (4:1 respectively) were in reasonable agreement with the values reported by Anet[18] (δ3.9 and 4.2; 3:2 respectively, 60MHz). By interpretation of the ^{1}H nmr spectrum, it was calculated that the product consisted of 85-90% of the 3*E*,5*E* isomer and 10-15% of the 3*Z*,5*E* isomer. Additional quartets representing 2'-H and 5'-H from the 3*Z*,5*E* isomer were observed at δ6.68 and δ6.95 respectively, compared to δ6.54 and δ6.40 for the all 3*E*,5*E*- form (figure 9). These results are in agreement with those reported by Brouwer *et al*[57], who reported shifts from δ6.70 and δ6.41 downfield to δ6.82 and δ6.95 for (*E*)-3-methyl-1,3,5-hexatriene **57** and (*Z*)-3-methyl-1,3,5-hexatriene **58** respectively.



57

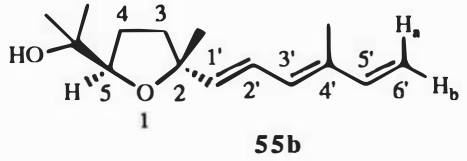


58

The mass spectrum indicated a molecular ion *m/z* 252 with fragment ions *m/z* 235 $(M\text{-}OH)^-$ and 217 $(M\text{-}OH\text{-}H_2O)^-$ showing loss of two oxygen atoms being observed in the negative ion spectrum. Further evidence for the structure of cyclic triene **4** was obtained upon reduction of **4** with lithium aluminium hydride affording a mixture of the tetrahydrofurans **55a** and **55b** in 28% yield, presumably *via* cyclisation of a triol intermediate arising from cleavage of the peroxide ring.

An alternative approach to form triene peroxide **4** was investigated *via* base catalysed cyclisation of the intermediate hydroperoxide onto the epoxide using NaOH. This approach, however, was unsuccessful in effecting the cyclisation.

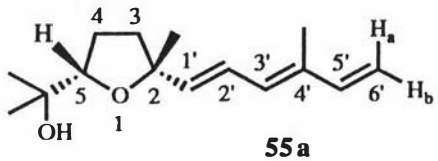
Figure 6



55b

(2*R,5*R**,1'*E*,3'*E*)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-(4-methylhexa-1,3,5-trienyl)tetrahydrofuran (55b)**

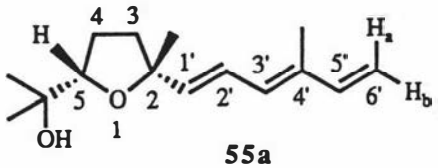
Figure 7



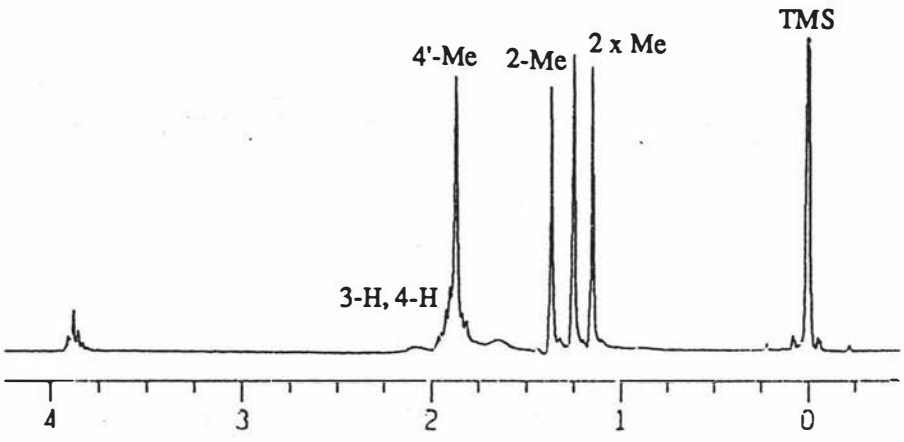
55a

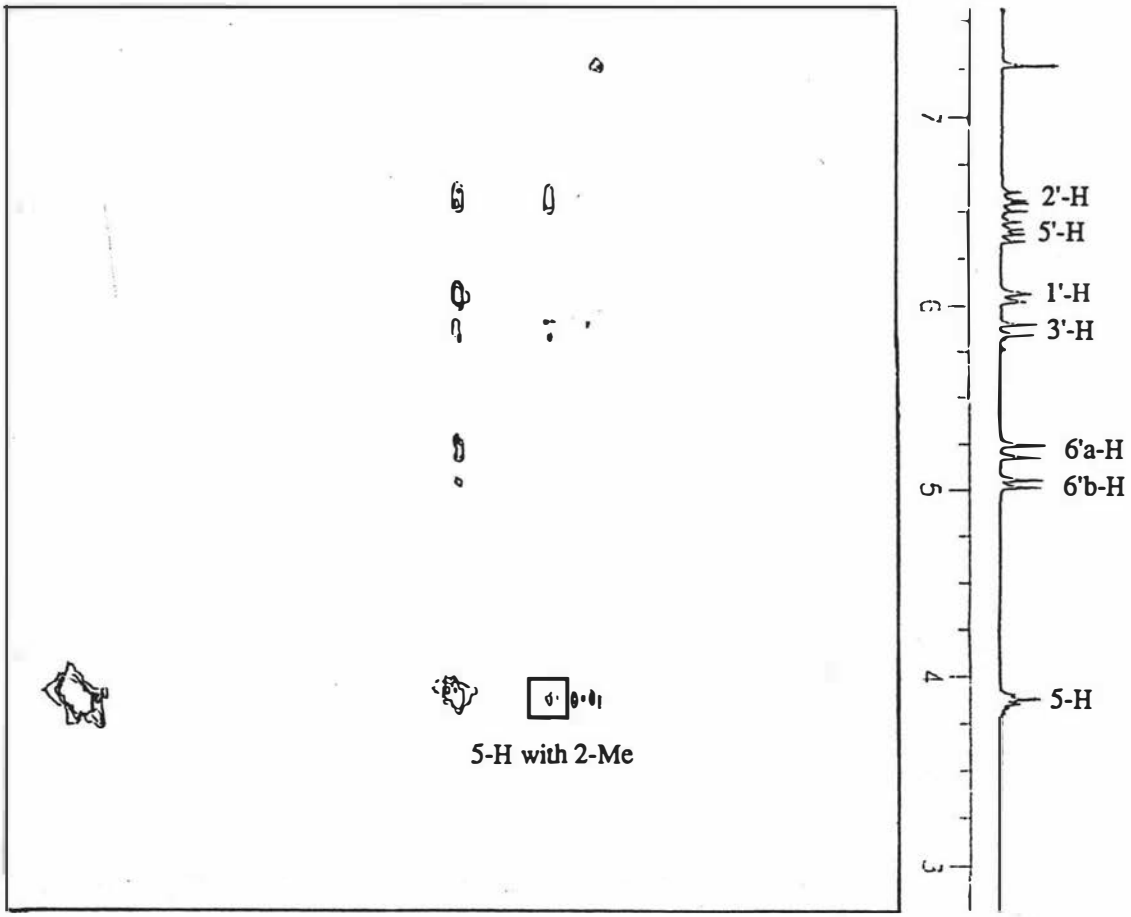
(2*R,5*S**,1'*E*,3'*E*)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-(4-methylhexa-1,3,5-trienyl)tetrahydrofuran (55a)**

Figure 8



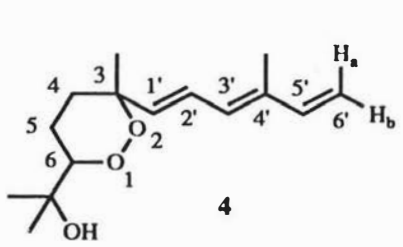
55a





5-H with 2-Me

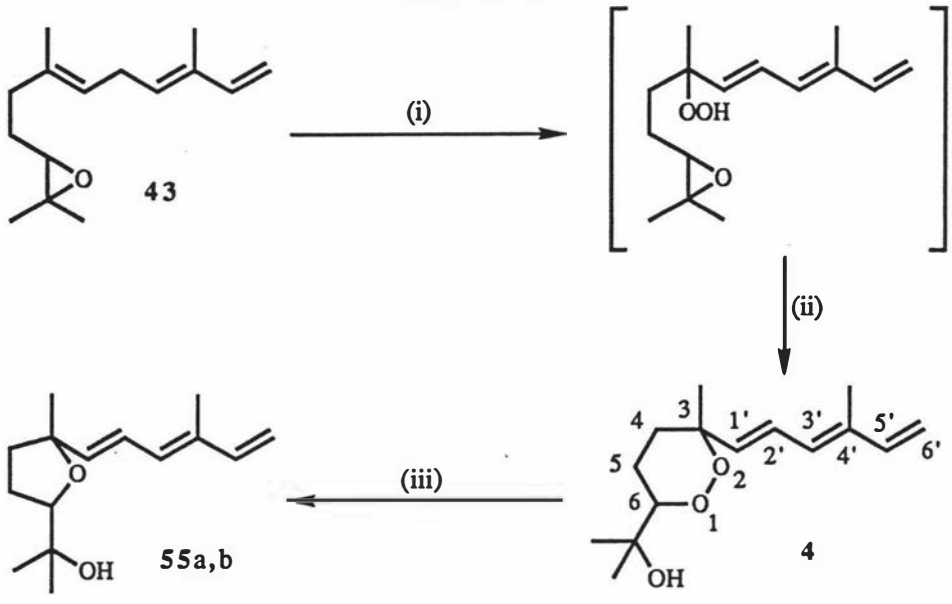
Figure 9



4

(3*R,6*S,1'E,3'E)- and (3*R,6*R,1'E,6'E)-6-(1-Hydroxyl-1-methylethyl)-3-methyl-3-(4-methylhexa-1,3,5-trienyl)-2-dioxacyclohexane (4)

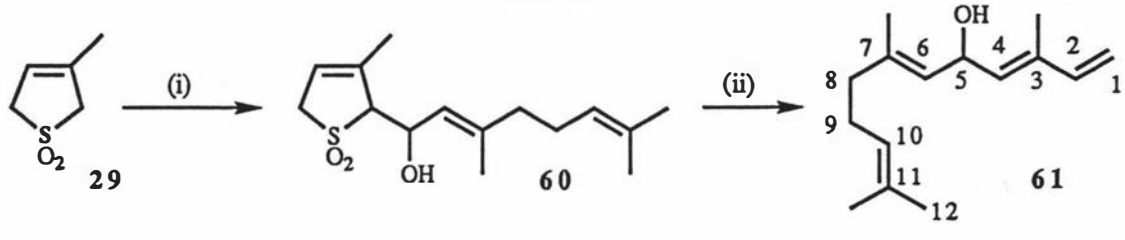
Scheme 16



Reagents and conditions: (i) O_2, Rose-Bengal, hν, MeCN, 0.75h; (ii) a: p-TSA (cat), 5 min; b: EtOAc, PPh_3, 5 min (3%); (iii) $LiAlH_4$, Et_2O, RT, 5 min (28%).

Bis-allylic alcohol **61** is another potential autoxidation product of α-farnesene **1** which had not been reported previously. Attempts to prepare alcohol **61** involving generation of the *bis*-allylic anion or radical were unsuccessful as were allylic oxidation methods. Alkylation of the C-2 anion of 3-methylsulpholene **29** with geranyl bromide followed by thermal extrusion of sulphur dioxide according to the method of Fielder *et al*[41] provides an efficient preparation of α-farnesene **1**. Modification of this procedure by using geranial **59** instead of geranyl bromide allowed preparation of the required *bis*-allylic alcohol **61** (Scheme 17).

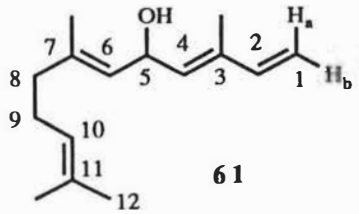
Scheme 17



Reagents and conditions: (i) a: n-BuLi, THF, TMEDA, -105°C, 0.25h (64%); b: geranial, -105°C, 10 min; (ii) xylene, reflux, 5min (13%).

Generation of the anion of sulpholene **29** using *n*-butyllithium at -105°C for 0.25h followed by the addition of geranial **59**, carefully maintaining the temperature at -105°C, afforded the 2-substituted sulpholene **60** in 64% yield. Heating sulpholene **59** for 5 min in xylene resulted in elimination of sulphur dioxide to give the alcohol **61** in 13% yield. The low yield for this cheleotropic elimination compared to the high yield obtained for this step in the

Figure 10



61

3,7,11-Trimethyldodeca-1,3,6,10-tetraen-5-ol (61)

synthesis of α-farnesene[41,51] is attributed to the tendency of alcohol **61** to also undergo elimination of water. Dehydration of **60** affords an stable α,β-unsaturated sulphone whilst the product **61** readily dehydrates upon storage at room temperature.

Product **61** was clearly an alcohol from the infra-red spectrum which exibited an OH stretch at 3330 cm^{-1}. The absence of a conjugated triene system was confirmed by the UV spectrum with λ_{max} 238 nm observed at a shorter wavelength than λ_{max} 251, 259, 269, 281 nm observed for triene **3**, and a molecular ion at *m/z* 220 was consistent with the molecular formula $C_{15}H_{24}O$. The ^1H nmr spectrum (figure 10) resembles that observed for α-farnesene (figure 2), with the distinguishing features being greater resolution of the four methyl peaks which resonate at δ1.59, δ1.67, δ1.74 and δ1.82 (for 12-H, 11-Me, 7-Me, 3-Me respectively) compared to δ1.60, δ1.64, δ1.68, and δ1.77 for α-farnesene, as well as the absence of the two proton triplet at δ2.84 due to 5-H. The ^{13}C nmr spectrum exhibited a peak at δ65.5 assigned to C-5, consistent with that carbon being attached to an oxygen as required in alcohol **61**.

2.2.3 Isolation of Farnesyl Autoxidation Products

Examination, by thin layer chromatography, of a sample of α-farnesene which had been stored as the neat oil at -20°C for several months revealed the presence of two polar UV-active autoxidation products. The first of these products had a ^1H nmr spectrum virtually identical to that of trienol **3** except that the 7-methyl group, formerly at δ1.32, was shifted to δ1.40. The UV-spectrum showed maxima at λ 247 (infl.), 261, 269 and 280 nm, confirming the presence of a triene system as in trienol **3**. The mass spectrum showed a molecular ion at *m/z* 236 which was consistent with the molecular formula $C_{15}H_{24}O_2$, as well as major fragment ions at *m/z* 219 (M-OH) and *m/z* 203 (M-OOH) which indicated the presence of a hydroperoxide. The absence of a significant fragment ion at *m/z* 218 ($M-H_2O$) provided further evidence that the unknown autoxidation product was in fact a hydroperoxide rather than an alcohol. The presence of a singlet assigned to the 7-methyl group at δ1.40 in the ^1H nmr spectrum showed that the hydroperoxide was located at C-7. Thus the autoxidation product was (3*E*,5*E*)-7-hydroperoxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene **10**, the hydroperoxide precursor of trienol **3**, as postulated by Anet[18].

As in the case of triene peroxide **4**, hydroperoxide **10** was composed of a small amount (<5%) of the 3*Z*,5*E* isomer. This was indicated in the ^1H nmr spectrum by the presence of two additional quartets at δ6.72 and δ6.96, representing 2-H and 5-H from the 3*Z*,5*E* isomer, compared to δ6.58 and δ6.41 for the 3*E*,5*E* form. Finally, reduction of

hydroperoxide **10** with 0.1 M triphenylphosphine in ethyl acetate afforded trienol **3**, identical by both GC/MS and HPLC with an authentic sample.

It was presumed that the second autoxidation product isolated from the mixture by flash chromatography would be the second hydroperoxide isolated by Anet[18], namely cyclic peroxide **13**. This second autoxidation product was too unstable to characterise directly, however, reduction with triphenylphosphine provided a more stable derivative for nmr analysis. The ^{1}H nmr spectrum did not match that of the synthetic peroxide **4** nor the spectra of any of the other compounds with oxygen substituents at C-7 which were synthesised during the course of this research. For the moment, the identity of this compound remains unknown.

2.3 Identification of α-Farnesene Oxidation Products on Apples

As part of on-going research being carried out by the staff of the Horticultural and Food Research Institute of New Zealand (Palmerston North) (HortResearch) into the effects of long term cold storage on the occurence of superficial scald, the presence or absence of Anet's conjugated trienes **3** and **4** has been investigated in several varieties of apple[58]. "Red Delicious", "Fuji", "Golden Delicious" and "Granny Smith" were obtained from local retailers and sampled to determine the concentration of trienes using HPLC methods developed at Hort+Research.

Extraction of conjugated trienes from apple wax for analysis by HPLC was carried out as follows: Individual apples were placed in glass beakers of slightly larger diameter, heptane (25 ml) was added, and the apple gently washed with solvent for two minutes. An aliquot (10 ml) of solvent was removed and stored at -20°C prior to analysis. The heptane extract (2 ml) was applied under gravity to a 100 mg silica extraction column conditioned with pentane (0.5 ml). The column was washed with pentane (0.5 ml) then with ether/pentane (1:1, 1 ml) to elute the conjugated trienes. The solvent was then removed under reduced pressure and the residue dissolved in heptane (200 µl) and filtered through a 2 µl syringe filter prior to analysis by HPLC.

Using this procedure, trienol **3** was identified in the skin of all four apple varieties which were examined. The material isolated from the apples coinjected with the synthetic trienol **3** on both HPLC and GC/MS. The synthetic trienol was composed of greater than 95% of the 3*E*,5*E*-form by HPLC and ^{1}H nmr, however, the apple trienol was found to be a mixture of the 3*E*,5*E* (88-95%) and 3*Z*,5*E* (5-11%) isomers. The corresponding hydroperoxide

precursor **10** of trienol **3** was only identified (by HPLC) on apples which were extracted immediately after removal from cold storage. Anet's[18] cyclic peroxide **4** was not identified in any of the samples tested.

Having identified trienol **3** on the apple skin surface, bioassays were carried out by HortResearch staff to investigate whether the application of additional trienol would affect the occurrence of superficial scald. Two methods were employed, using "Granny Smith" apples:

(i) Coated apples: Trienol **3** was dissolved in squalene and painted onto the apple skin surface such that each apple was evenly coated with 100μg of trienol. Control apples received a squalene coating only.

(ii) Exposure to vapour: 100μg of trienol **3** in pentane was placed onto a plastic disc in the bottom of a plastic cup and the pentane was allowed to evaporate. A "Granny Smith" apple was placed on top of the cup and air gaps between the cup and apple sealed. The surface inside the cup was considered to have been treated, whilst the exposed side of the apple served as a control. Untreated apples were also used as experimental controls.

The apples were stored at 2°C for 4-5 months and scald symptoms were assessed on removal from storage after 7 days in the dark at room temperature. Scald symptoms were observed using both methods. In the case of the vapour phase method, the symptoms were indistinguishable from those of superficial scald.

Thus preliminary results confirm the presence of the trienol **3** on the surface of apples which have undergone cold storage, and indicate that this same compound is indeed capable of inducing scald-like symptoms.

In summary, the synthesis of several known and potential autoxidation products of α-farnesene **1** including Anet's conjugated trienes **3** and **4** has been accomplished. Preliminary bioassays with trienol **3** indicate that this compound is capable of producing scald-like symptoms on stored fruit (section 2.3). Samples of the compounds reported herein are being employed in ongoing research to probe the autoxidation of α-farnesene **1** on apples and to relate this to the occurrence of superficial scald.

PART 2: THE ASYMMETRIC DIHYDROXYLATION OF α- AND β-FARNESENE

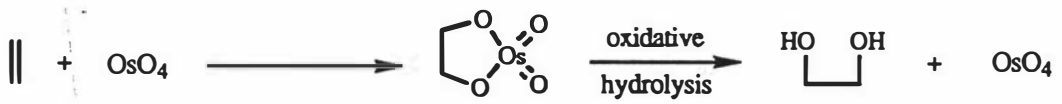
1. INTRODUCTION

1.1 The Osmium Tetroxide Asymmetric Dihydroxylation Reaction

1.1.1 History of the Osmium Tetroxide *cis*-Dihydroxylation Reaction

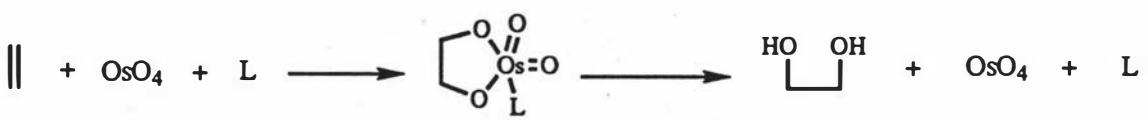
In 1912, Hofmann[59a,b] demonstrated that OsO_4 could be used to effect catalytic dihydroxylation of alkenes, using sodium or potassium chlorate as a secondary oxidant. Subsequently, many other secondary oxidising agents incuding metal chlorates, H_2O_2, *t*-butylhydroperoxide, oxygen, sodium periodate, sodium hypochlorite and *N*-methylmorpholine *N*-oxide (NMO)[60] have been used in conjunction with OsO_4 for the catalytic dihydroxylation of alkenes.

Criegee[61a,b] (1945) reported that this reaction could also be conducted in a stoichiometric fashion, in the absence of secondary oxidants. Criegee surmised that the reaction proceeded *via* an intermediate osmium (VI) ester, similar to the analagous potassium permanganate reaction. This ester then undergoes reductive or oxidative hydrolysis to yield the required diol and an insoluble osmium salt or regenerated OsO_4 (scheme 18).



Scheme 18

Criegee observed that the formation of these osmate ester complexes was accelerated by the addition of an excess of tertiary amine, in particular pyridine, to the reaction mixture[61b]. Pyridine is thought to exert its effect upon the reaction by coordination to the metal centre, forming a more reactive osmium-amine complex and thereby increasing the rate of reaction of OsO_4 with the olefin. Although the osmate ester-amine complex was more difficult to hydrolyse, this system remained the method of choice for small scale preparations until 1980, mainly due to its mildness and generality (scheme 19).



Scheme 19

At this stage, all components were available to enable the *enantioselective* preparation of *cis*-diols using a catalytic quantity of OsO_4 in conjunction with a secondary oxidant, in

the presence of a chiral amine ligand with the potential to induce chirality in the product. It then remained for the specific ligand and reaction conditions to be developed by subsequent workers.

1.1.2 Development of Reaction Conditions

In 1980, Hentges and Sharpless[62], reported the use of the cinchona alkaloid derivatives dihydroquinine acetate and dihydroquinidine acetate **62a** and **63a** (page 45) as chiral ligands for asymmetric induction under stoichiometric conditions. These amines, which contain a chiral centre adjacent to the site of coordination, effected asymmetric induction in the hydroxylation of a variety of olefins in fair to high enantiomeric excess (ee) (25-80%). Subsequently, throughout the 1980's, numerous groups reported asymmetric osmylations under both stoichiometric and catalytic conditions. The conditions employed included the aforementioned Sharpless method[63], as well as the use of internal sulphoxides[64,65], chiral diamines[66-71] and catalytic osmylation using bovine serum albumin[72].

The expense and high toxicity of OsO_4, however, provided the motivation for the development of a reliable catalytic method[73,74] which would also proceed with high enantioselectivity. In 1988 Sharpless *et al* reported a new catalytic procedure[75] using cinchona alkaloids as chiral ligands, a catalytic quantity of OsO_4 and NMO as reoxidant. This method was essentially a hybrid of the group's previous stoichiometric procedure[62], and the well-known Upjohn[73], *N*-oxide based, catalytic method. This procedure went a significant way toward addressing the aforementioned problems in that: (1) OsO_4 was only present in catalytic quantities (0.002 mol%), (2) the cinchona alkaloid diastereomers (quinine and quinidine) which were employed as ligands, were readily available and easily recoverable and, importantly, (3) the reaction was unaffected by exposure to either air or water.

A seemingly small modification was then made to the procedure, that of adding the olefin slowly to the reaction mixture[76], which resulted in improved enantiomeric excesses and increased rate of reaction. Sharpless theorised that there might be a second diol producing, non-enantioselective cycle, which proceeded at a slower rate and which could be minimised by simply adding the olefin slowly (figure 11). In the first cycle the alkaloid-osmium complex **64** reacts with a single equivalent of olefin to afford monoglycolate ester **65**. This ester is then oxidised to key intermediate species **66**, which may then either add an additional equivalent of olefin to give bisglycolate ester **67** or undergo hydrolysis to form the required diol and regenerated catalyst. Slow addition of the olefin substrate allows intermediate **66** sufficient time to hydrolyse so that the osmium

catalyst does not get trapped into the second cycle, reducing enantioselectivity and reaction rate. Thus the root of the problem lies in the fact that oxidation precedes hydrolysis and the osmium catalyst is consequently available to bind another olefin molecule before the first equivalent is released as the diol.

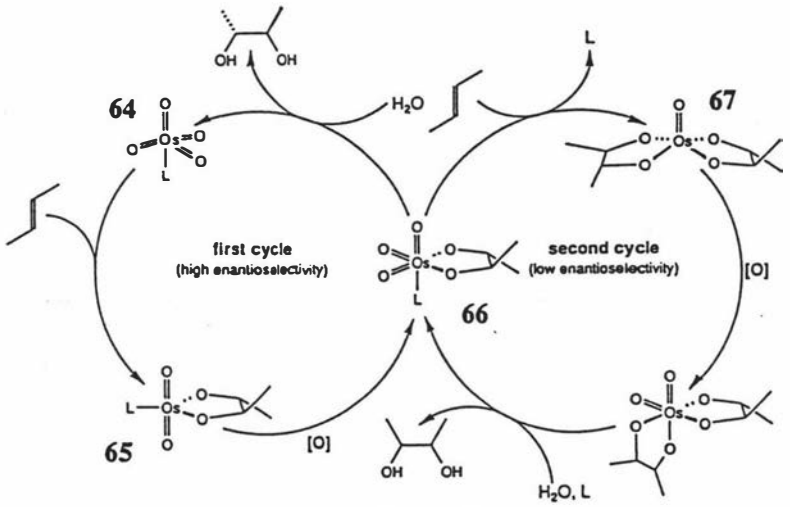


Figure 11

Additional circumstantial evidence for the existence of this "second cycle" was obtained using the "one electron oxidant" potassium ferricyanide instead of NMO with *t*-butanol/water (1:1) as solvent. The procedure was initially reported by Minato, Yamamoto and Tsuji[77], then later applied by Sharpless *et al* [78], and avoided the necessity of adding the olefin slowly whilst affording increased enantioslectivities. The success of potassium ferricyanide is believed to lie in the apparent complete supression of the "second cycle", which seems to afflict the NMO system. A second effect which is believed to contribute to increased enantioselectivity is the use of a biphasic *t*-butanol-water solvent system. *t*-Butanol was found to be the best solvent to date for optimum enantioselectivity[78]. Addition of potassium ferricyanide and/or potassium carbonate was observed to "salt out" the aqueous layer in the biphasic system, enabling optimum enantioselectivities to be achieved by reaction in the *t*-butanol phase. This solvent system is not, however, effective when using NMO as the oxidant due to the absence of this "salting out" effect.

Upon further study, the Sharpless group proposed that the general sequence of events depicted in figure 12 was taking place in the biphasic solvent system[79]. Initially, OsO_4 reacts with the ligand and the olefin to afford osmate ester **65**. The ester subsequently undergoes hydrolysis, releasing the diol and ligand into the organic phase and the resulting $OsO_2(OH)_4^{-2}$ passes into the aqueous phase. The potassium ferricyanide present in the aqueous phase then oxidises the $OsO_2(OH)_4^{-2}$ [*via* $OsO_4(OH)_2^{-2}$] back to OsO_4, which is then able to migrate back into the organic phase - a true catalytic cycle. Thus, the

absence of the non-enantioselective "second cycle" results from ester hydrolysis preceding oxidation.

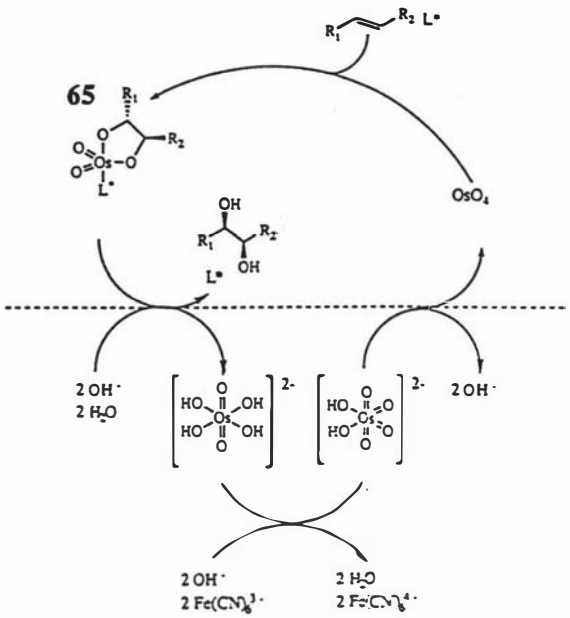


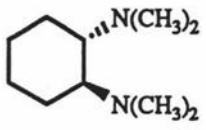
Figure 12

The use of acetates to facilitate the hydrolysis of osmate esters and to consequently increase the rate of reaction has been known since 1978[80] and in 1992, it was reported by Amberg *et al* that osmate ester hydrolysis was also accelerated in the presence of organic sulphonamides[81]. Thus in cases where osmate ester hydrolysis was turnover limiting, the presence of methanesulphonamide for instance, led to shorter reaction times. This procedure was effective for all non-terminal olefins, but did inhibit the reaction rates of terminal olefins.

1.1.3 Evolution of the Optimum Asymmetric Ligand

Prior to the publication of the Sharpless procedure employing the cinchona alkaloids quinine and quinidine as chiral ligands in the asymmetric dihydroxylation (AD)[75], several other groups developed chiral diamines as auxiliary ligands for the procedure. Notably, the ligands of Tokles and Snyder[66] **68**, Hirama *et al* [69] **69**, Tomioka *et al* [67,68] **70**, Yamada and Narasaka[70] **71** and Corey *et al* [71] **72** were used to achieve a high level of asymmetric induction with a variety of trisubstituted and particularly *trans*-disubstituted olefins.

Unlike the quinine/quinidine class of ligands developed by Sharpless *et al*, the chiral diamines function as bidentate ligands. OsO_4 was used in a stoichiometric amount, and the diol was isolated by reductive hydrolysis of the osmate ester using $LiAlH_4$. This procedure was non-catalytic but the ligand was easily recovered (80-90%)[67,71] in its optically pure form.



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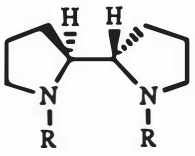
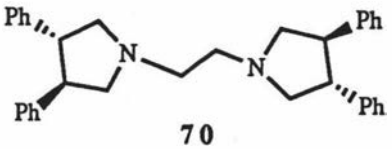


69 R = H
R = Alkyl



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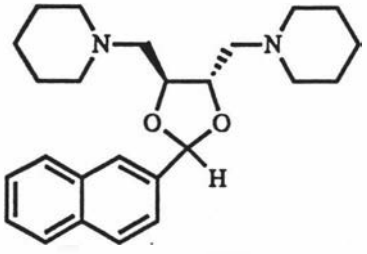

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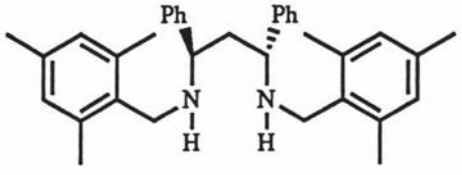


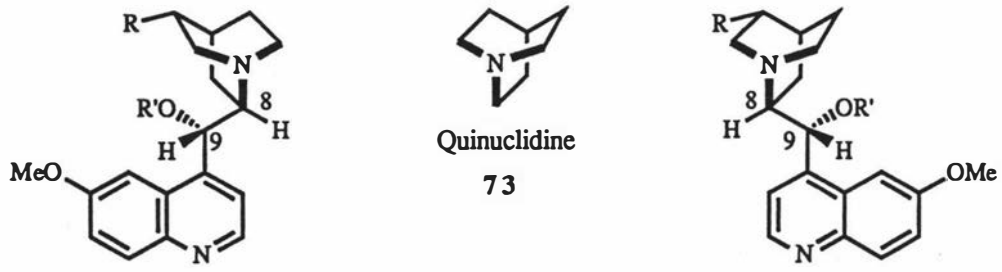
72

These ligands, however, have been largely superceded by the Sharpless quinine/quinidine-based ligands (figure 13) due to the increased utility of a system catalytic in both ligand and osmium. With the improved experimental conditions detailed in the preceding section (section 1.1.2) the asymmetric dihydroxylation can now be applied to a wide variety of olefins using a relatively simple procedure.

With the methodology of the AD using the cinchona alkaloid-catalytic OsO_4 system established, attention turned to modification of the ligands, in order to improve asymmetric induction. In the initial stoichiometric system[62], Sharpless *et al* employed the cinchona alkaloid derivatives dihydroquinidine acetate and dihydroquinine acetate (figure 13, **62a** and **63a**).

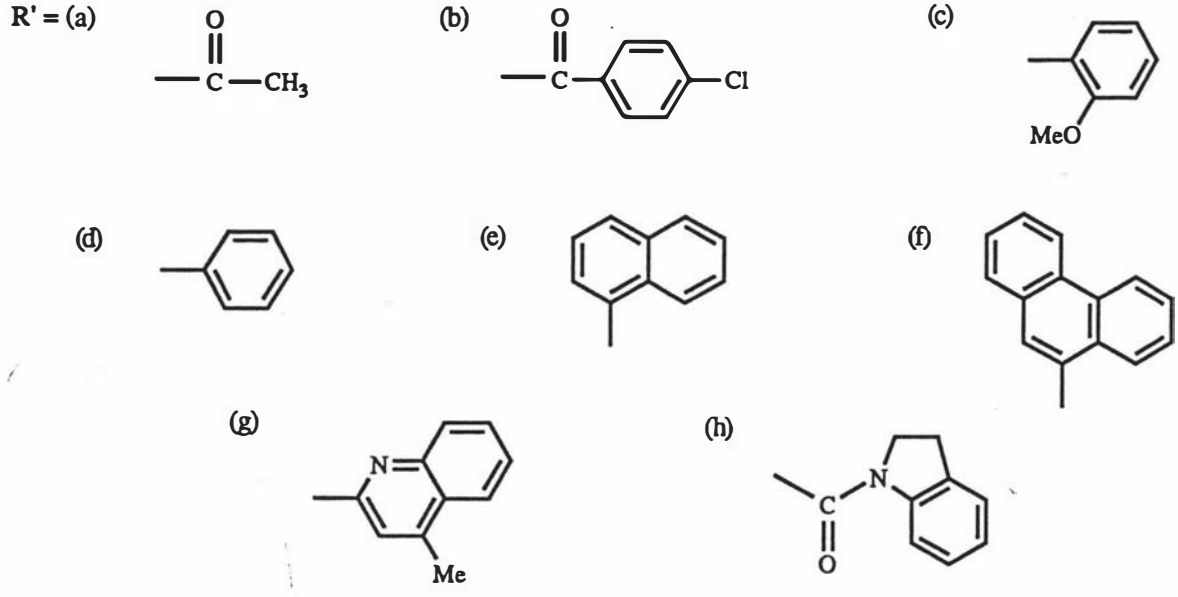
When Sharpless *et al* subsequently combined this stoichiometric method with the Upjohn NMO procedure[75], it was found that the most readily available cinchona alkaloids, quinine and quinidine, acted like enantiomers. Although quinine and quinidine are a diastereomeric pair (figure 13, **74** and **75**), their opposite stereochemistries at the crucial carbons 8 and 9, give behaviour more characteristic of enantiomers.[82] In addition, this new procedure was proclaimed to be "a dramatic example of ligand accelerated catalysis".[75] When the process was conducted in the presence of dihydroquinidine *p*-chlorobenzoate derivative **62b**, the alkaloid strongly accelerated the rate of reaction at all concentrations examined (0.02-0.8M). Following a mechanistic study[83], it was suggested that the observed rate acceleration might be attibuted to the formation of an OsO_4-alkaloid complex which was more reactive than the free OsO_4. This topic is addressed further in the following section (1.1.4) on reaction mechanism.

Figure 13: Ligands for the Asymmetric Dihydroxylation



74 R = $CH{=}CH_2$, R'= H Quinidine
62 R = Et Dihydroquinidine (DHQD)

75 R = $CH{=}CH_2$, R'= H Quinine
63 R = Et Dihydroquinine (DHQ)



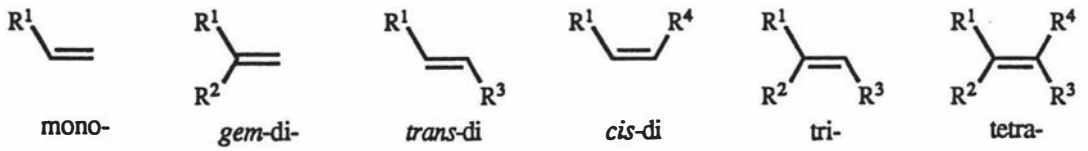
Key: (a) acetate; (b) *p*-chlorobenzoyl (PCB); (c) *o*-methoxyphenyl; (d) phenyl; (e) 9-*O*-(1'-naphthyl); (f) 9-*O*-(9'-phenanthryl) (PHN); (g) 9-*O*-(4'-methyl-2'-quinidyl) (MEQ); (h) 9-*O*-indolinylcarbamoyl (IND).

By 1990, the cinchona alkaloid-OsO_4 system for the asymmetric dihydroxylation of *trans*-disubstituted olefins[75], was well established. The ee's for aryl substituted olefins were satisfactory (>90%), however, those for alkyl substituted olefins remained for the most part much lower. It was at this stage that Sharpless *et al* introduced the aryl ethers of dihydroquinidine[84] **62d, 62e** and **62f** as ligands for the AD of dialkyl substituted olefins. Enantiomeric excesses were dramatically improved compared to those achieved with the *p*-chlorobenzoate ligand **62b,** although this latter ligand still remained the most effective for aryl substituted olefins. Enantiomeric excesses which were previously only attainable under stoichiometric conditions at low temperature[84] were now accessible using catalytic OsO_4 at room temperature.

Satisfactory ee's for terminal olefins, however, remained elusive, and the search for new ligands with which to treat this problem continued. The 9-*O*-(9'-phenanthryl) (PHN)

ethers and the 9-*O*-(4'-methyl-2'-quinolyl) ethers of dihydroquinidine **62f** and **62g** and dihydroquinine **63f** and **63g** were reported in 1991 to be effective for monosubstituted and *gem*-disubstituted olefins[85], thereby rendering four of the possible six substitution patterns for olefins (figure 14) accessible to efficient asymmetric dihydroxylation.

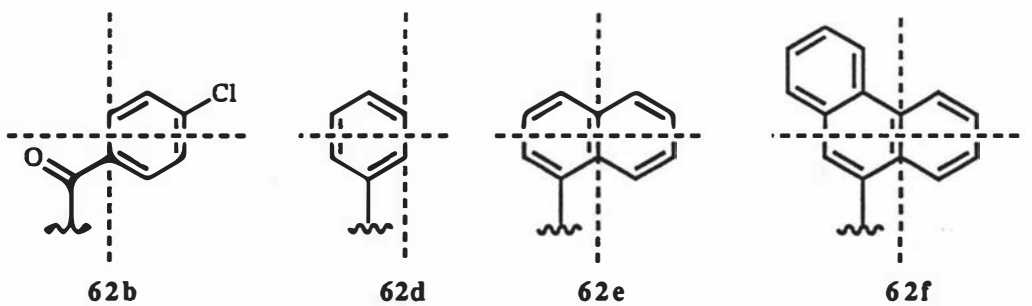
Figure 14: Olefin Substitution Patterns



Between these two ligands, improvements in enantioselectivity over the previous "best" ligand, *p*-chlorobenzoate derivative **62b**, were apparent for all of the four accessible classes of olefin. When a comparison was made between the dihydroquinidine ligands and their dihydroquinine counterparts, the quinine ethers gave slightly lower ee's, similar to the two *p*-chlorobenzoate ligands **62b** and **63b**, reflecting that they are not in fact true enantiomers. This difference, however, is small and the two ligands provide a means of obtaining enantiomeric diols.

A comparative study was then made of the 9-*O*-phenyl **62d**, 9-*O*-(1'-naphthyl) **62e** and 9-*O*-(9'-phenanthryl) **62f** dihydroquinidine ethers in an attempt to deduce the relationship between enantioselectivity and ligand structure[86]. Generally, the 9-*O*-(9'-phenanthryl) **62f** gave the best ee's for both aromatic and aliphatic substrates, followed by the 9-*O*-(1'-naphthyl) **62e** derivative, the 9-*O*-phenyl **62d** derivative, and lastly, the original *p*-chlorobenzoate derivative **62b**. The dihydroquinine counterparts gave similar results.

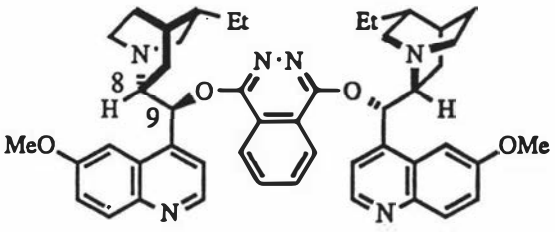
Figure 15: Enantioselectivity and Ligand Structure



The X-ray crystal structure of an osmate ester reaction intermediate[86] (obtained from the stoichiometric AD of *trans*-2,5-dimethylhex-3-ene) was analysed in a purely qualitative manner, with the following observations made: (1) increased bulk in the upper left hand quadrant (figure 15) may be responsible for larger ee's, as the only apparent difference

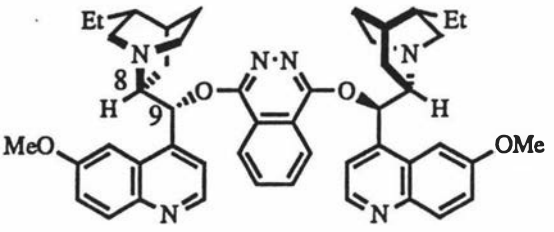
between the substituents was the increased size in this area, (2) the presence of an aromatic ring in the right two quadrants seemed to help to produce high ee's for both aromatic and aliphatic substrates, and (3) the "best" ligands seem to have in common two "plate-like" aromatic substituents attached at C-9 (the methoxyquinoline ring and the 9-*O*-substituent), which are positioned approximately perpendicularly to one another.

In 1992, the discovery of a new class of ligands, dihydroquinidine and dihydroquinine phthalazine derivatives **76** and **77** was reported[81]. These ligands are composed of two dihydroquinidine/dihydroquinine moieties, connected by a 1,4-phthalazine linker at the 9-*O* positions.



76

$(DHQD)_2$-PHAL
ligand used in AD-mix-β



77

$(DHQ)_2$-PHAL
ligand used in AD-mix-α

When the phthalazine ligands were employed in the AD reaction, the enantiomeric excesses of each of the four accessible olefin classes: namely mono-, *gem*-di-, *trans*-di- and trisubstituted classes either equalled or surpassed those obtained previously[85]. For the *trans*-di- and trisubstituted classes, all substrates tested yielded ee's in excess of 90%. When the temperature was reduced, even smaller quantities of the chiral ligands were required to achieve comparable ee's. The phthalazine ligands were found to be so superior in fact, that they have now been incorporated into two commercially available AD formulations (AD-mix-α and AD-mix-β). These formulations are comprised of the chiral amine ligands 1,4-*bis*-(9-*O*-dihydroquinidine)phthalazine [$(DHQD)_2$-PHAL] **76** or 1,4-*bis*-(9-*O*-dihydroquinine)phthalazine [$(DHQ)_2$-PHAL] **77**, potassium ferricyanide, potassium carbonate and the solid and non-volatile osmium salt $K_2OsO_2(OH)_4$ in place of OsO_4. Use of this osmylation source minimises the risk of exposure to volatile osmium species.

This new system was superior to its predecessors in virtually every way, not only resulting in greatly improved ee's, but requiring only trace amounts of chiral ligand and osmium salt. The closer mirror image reciprocity between the two phthalazine ligands **76** and **77** (closer than any of the previous quinine/quinidine based classes) ensured that the

ee's for the dihydroquinine phthalazine ligand **77** were virtually the same as those obtained for its dihydroquinidine analogue[81] **76**.

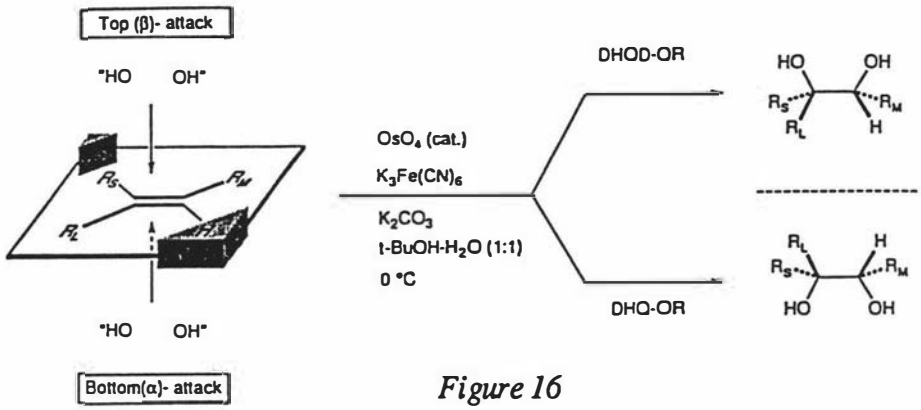


Figure 16

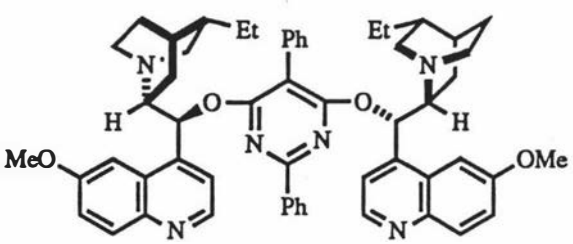
Sharpless *et al* also developed a mnemonic device (figure 16) in order to predict the absolute sterochemical outcome of the asymmetric dihydroxylation[81]. Only one exception has been documented to date[87]. Dihydroquinidine derivatives bring about dihydroxylation from the "top (β) face" when the largest substituent, R_L, is directed toward the observer as depicted, whereas dihydroquinine derivatives dihydroxylate from the "bottom (α) face".

At this point, attention turned to one of the two remaining classes of olefins which hitherto remained inaccessible; namely the *cis*-disubstituted class. Up to 80% ee in the AD of *cis*-disubstituted olefins was finally attained using the (9-*O*-indolinylcarbamoyl) dihydroquinidine (DHQD-IND) ligand **62h**[88], which represented an increase of 40-50% on previous levels. Generally higher ee's were obtained with aromatic rather than aliphatic substrates. Once again, the dihydroquinine analogue **63h** delivered lower ee's. In this case the difference between the two ligands was the largest yet observed.

The relationship between olefin substitution pattern and the rate of dihydroxylation has also been investigated[89]. Comparative studies of the dihydroxylation rate in the absence of a ligand and in the presence of $(DHQD)_2$-PHAL were carried out using one representative from each olefin class[89] (each reaction was conducted in the presence or absence of the phthalazine ligand). The reaction proceded faster with ligand than the analogous reaction without ligand present. In the absence of the phthalazine ligand, the tetrasubstituted olefin was the most reactive, with reactivity increasing with substitution: tetra- > tri- > *trans*-di- > *gem*-di- > *cis*-di- > monosubstituted. Addition of the phthalazine ligand to the reaction mixture not only caused the rate of reaction to increase greatly, but the relative order of reaction of the variously substituted olefins changed as well. The trisubstituted olefin was now the most reactive, followed the by *trans*-di-, *gem*-di-, tetra-, mono- and *cis*-disubstituted cases.

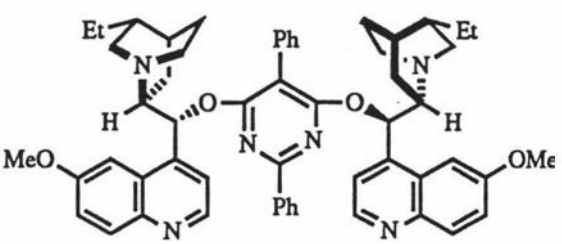
Ligand accelerated rate increases were most pronounced for the tri- and *trans*-disubstituted olefin classes. Initially this seemed somewhat surprising since these more substituted olefins may have been expected to react more slowly in a sterically congested ligand-osmium tetroxide environment. The tetrasubstituted case was the only olefin substrate to support this assumption, experiencing a significant rate decrease under these conditions. Sharpless, however, demonstrated that the *trans*-di- and trisubstituted olefins represented an especially good fit for the $(DHDQ)_2$-PHAL system[89], accounting for the results obtained in the study. The rate accelerations were also found to be related to increases in enantioselectivity; the *trans*-di- and trisubstituted olefins generally gave higher ee's than the mono, *gem*-di-, tetra- or *cis*-disubstituted classes. A particular problem with the *cis*-disubstituted class is that as R_1 approaches R_4 in size (figure 14), the diminishing prochiral asymmetry results in difficulty in ligand differentiation between the two enantiofaces.

Improved enantioselectivity in the AD of terminal olefins was achieved in 1993[90], by replacing the 1,4-phthalazine "linker", employed in the *bis*-dihydroquinidine and *bis*-dihydroquinine phthalazine ligands **76** and **77** by a 2,5-diphenylpyrimidine, linked at positions 4 and 6. This gave the two ligands *bis*-dihydroquinindine pyrimidine **78** and *bis*-dihydroquinine pyrimidine **79** [$(DHQD)_2$-PYR and $(DHQ)_2$-PYR]. The pyrimidine ligands complemented the phthalazine ligands, being superior with respect to monosubstituted terminal olefins, but inferior with *gem*-di-, 1,2-disubstituted and trisubstituted olefins.



78

$(DHQD)_2$-PYR



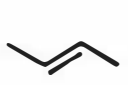
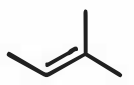
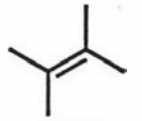
79

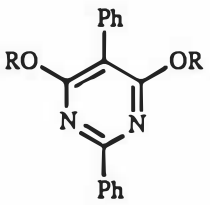
$(DHQ)_2$-PYR

By employing either the phthalazine or pyrimidine ligands, the AD of tetrasubstituted olefins was carried out by Sharpless *et al*[91]. This made the sixth and final class of olefin finally accessible to catalytic dihydroxylation. This result was achieved by employing methanesulphonamide (3 molar equivalents) to speed ester hydrolysis, increasing the quantity of osmium catalyst added (to 1 mol%) and, in the slowest cases, operating at room temperature.

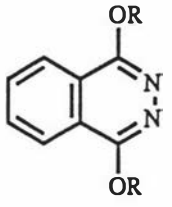
The current situation with respect to ligand-based improvement of enantioselectivity is illustrated in figure 17, with only the cis-disubstituted olefins requiring a unique ligand (IND) and yielding ee's of less than 80%. Research in this area continues, and the current set of "best" ligands are sure to be replaced by improved versions in the near future.

Figure 17: Ligand Preference as a Function of Olefin Pattern

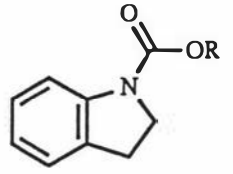
Type of olefin	 mono-	 *gem*-di-	 *cis*-di-	 *trans*-di-	 tri-	 tetra-
Preferred ligand	PYR PHAL	PHAL	IND	PHAL	PHAL	PYR PHAL
ee range	80-97%ee	70-97%ee	20-80%ee	90-99.8%ee	90-99%ee	20-97%ee



PYR-class



PHAL-class



IND-class

Key: R = dihydroquinidine or dihydroquinine

1.1.4 The Mechanism for the Asymmetric Dihydroxylation

Currently, two different mechanisms for the asymmetric dihydroxylation of olefins are being considered[92] (figure 18). Corey *et al* support a concerted [3+2] cycloaddition of the olefin to OsO_4 (path A). Alternatively, Sharpless *et al* have proposed a stepwise mechanism involving formation of an osmaoxetane intermediate **80** *via* a [2+2] cycloaddition of the olefin to an Os=O bond, which subsequently rearranges in a rate determining step to afford five-membered intermediate **65**, which is common to both mechanisms.

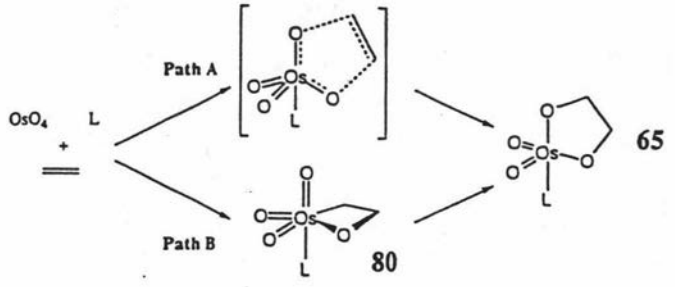
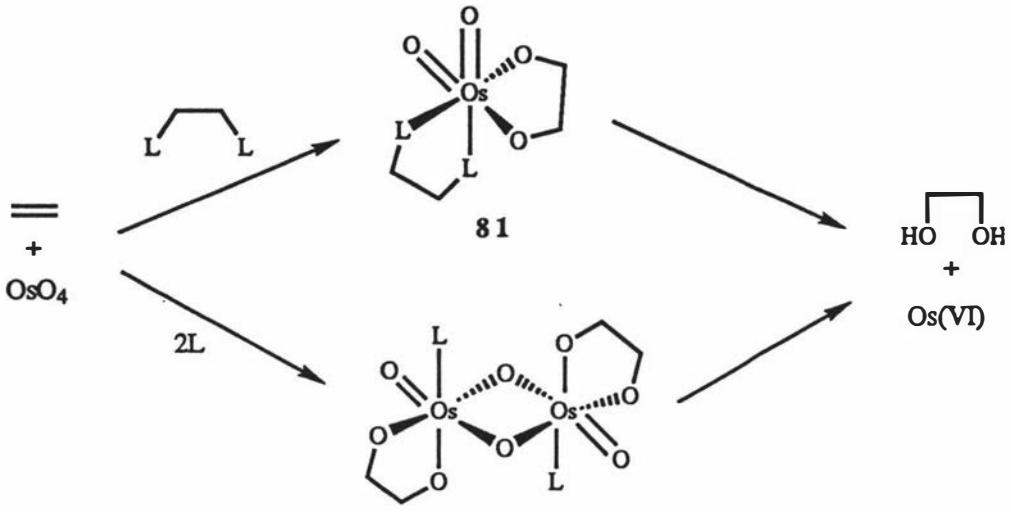


Figure 18

Corey[93] has further suggested, that in the presence of a bidentate ligand such as the 1,2-diamine class, an asymmetric octahedral intermediate **81** (scheme 20) is formed in the [3+2] cycloaddition, and in the case of monodentate ligands such as the cinchona alkaloids, the intermediate formed is a dimeric osmium species **82.**



Scheme 20

Many investigations into the mechanism of this reaction have been carried out, including nmr[82,94a,b], X-ray[82,94a,c,95], molecular modelling[82,93] and kinetic studies[83,96a,b], as well as the effect of ligand structure[86,97], olefin structure[89] and temperature[98]. Although the full mechanism is yet to be elucidated, much evidence about the various steps involved has been uncovered. As has been mentioned previously (section 1.1.2), apart from imparting a high level of asymmetric induction to the diol products, the cinchona alkaloid ligands accelerate the rate of addition of olefin to OsO_4. It has been established that the rate limiting step is the formation of the osmate ester, and that a single ligand molecule is involved in this step[83,96b]. It has also been suggested[60,98], that the Sharpless model involving an osmaoxetane intermediate **80** might provide an explanation for this increase in rate, due to a greater propensity for it to undergo bond migration to the five-membered intermediate **65.**

Electron donation from the tertiary amine to the osmium would induce osmium-carbon bond cleavage with a corresponding increase in this rate determining step. At elevated ligand concentrations in the OsO_4/ chiral ligand/ NMO system, however, the resulting osmate ester binds a second ligand molecule, which retards catalysis as the reoxidation/hydrolysis steps of the catalytic cycle are inhibited and become rate limiting. Thus it seems that a vacant coordination site on the Os(VI) ester is required to achieve reoxidation/ hydrolysis. The timing of the hydrolysis and reoxidation steps in the OsO_4/

chiral ligand/ potassium ferricyanide system has already been discussed in this introduction[79] (section 1.1.2) and the theory is now well established.

The cinchona alkaloid ligands have been extensively studied to discover the reasons for such high enantioselectivity. Enantioselectivity was mainly influenced by the nature of the substituent at *O*-9 (figure 13), with Sharpless *et al* [92] suggesting that the presence of a large, aromatic system at this position leads to a stabilisation of the transition state. This theory is supported by the fact that increasing the size of the aromatic groups in both ligand and substrate results in larger rate constants, which could be explained by transition state-stabilising, attractive interactions between the aromatic groups. This also explains the fact that the rate of reaction in olefins with aliphatic substituents is less sensitive to changes in the ligand.

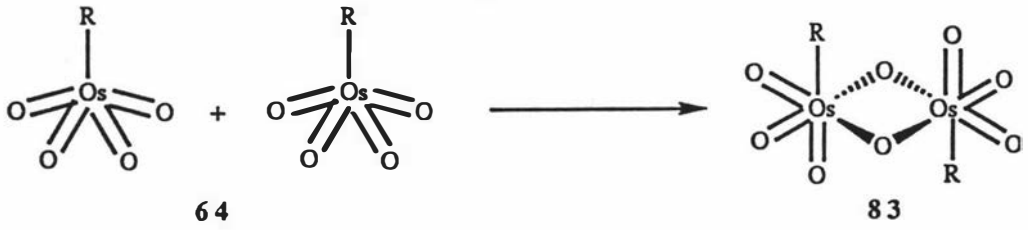
The phthalazine class of ligands **76** and **77**, particularly, have proved most effective in inducing high ee's. Consequently, one might conclude that the structural features in this class are ideally set up for the catalytic AD[92]. Sharpless *et al* [95] provided evidence that the two quinuclidine **73** moieties which bond to the osmium centre acted independently. Synthesis of a quaternary salt at one of the quinuclidine groups rendered that moiety incapable of binding to the osmium centre however the ee was just as high as for the parent ligand, indicating that only one group was required. Although the second alkaloid unit is not a requirement for high ee's, it seems that it may further stabilise the transition state by positioning its flat methoxyquinoline ring system in the correct relative orientation to the phthalazine unit[96b]. With the quinoline and phthalazine moieties positioned approximately perpendicularly to one another, a "binding pocket" is set up, leading to attractive interactions and perhaps further stabilisation of the transition state, therefore higher reaction rates. Corey[94c] has also reported x-ray crystallographic evidence to support the existence of this "binding pocket" using ligand **95**.

Surprisingly, the methoxy group on the quinoline unit has a beneficial effect on binding, although the reason for this is not clear. The ethyl group on the quinuclidine also contributes to the effectiveness of the phthalazine class of ligands, as it also enhances the binding affinity to OsO_4, as well as increasing solubility[92].

The effect of the substitution pattern of the olefin on this reaction has already been discussed (section 1.1.3), however, the role of the OsO_4 and its mode of reaction with both olefin and ligand, remains the subject for great debate[96a,b]. In 1990, Corey and Lotto[99] suggested that an enantioselective reaction with an alkaloid/ OsO_4 complex containing a pentacoordinate osmium **64** seemed unlikely, as the structure lacks the steric bias required which would lead to such high ee's. It was further postulated that this steric

bias could be introduced by a formal [2+2] cycloaddition of metal-oxo linkages to form an octahedral binuclear structure **83** (scheme 21) (in a *trans* configuration as the *cis* structure is very unfavourable sterically).

Scheme 21

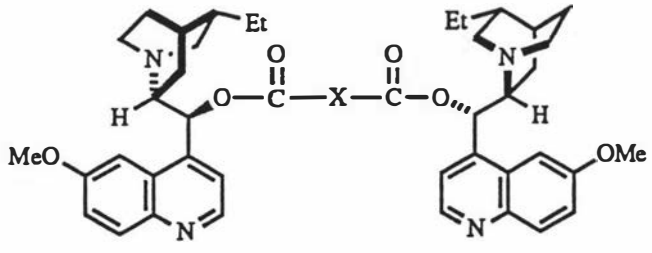


64 **83**

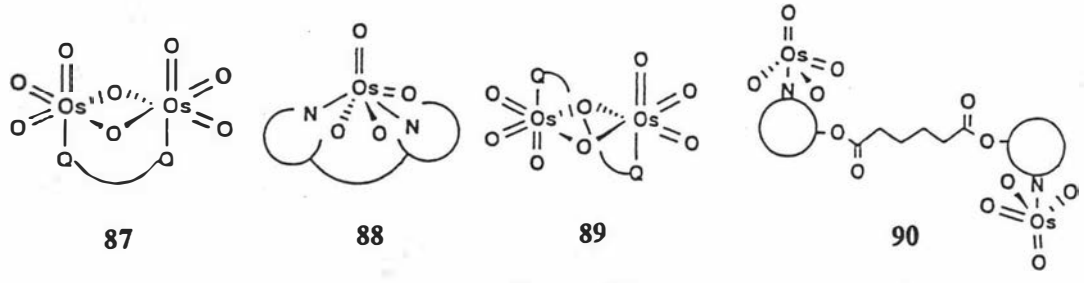
Key: R = dihydroquinidine or dihydroquinine

A significant rate acceleration could be expected from such a dimer, as it contains two hexacoordinate osmium centres, analogous to the centre in 1,2-diamine ligands, which cause large rate increases. The dimer was also suggested to have a geometry more favourable for a [3+2] cycloaddition to an olefin. Furthermore, octahedral complexes of this type have been observed for other metals, and the above dimeric structure **83** has been characterised in the solid phase[99].

Lohray and Bhushan[97] examined the validity of this model in 1992, by employing different ligands with *E*-stilbene as substrate, and comparing the resultant ee's. Ligand **84** represents the reaction control as it may only form a very crowded *cis*-dimer **87** (figure 19) (suggested by Corey[99] to be improbable), or bind as a bidentate ligand **88** which would inhibit catalytic turnover (similar to diamines). Ligand **85** is able to form a *trans*-dimer **89**, and as such is a good model for the Corey[99] system, or alternatively, each quinuclidine moiety may coordinate an OsO_4 molecule separately as in structure **90**.



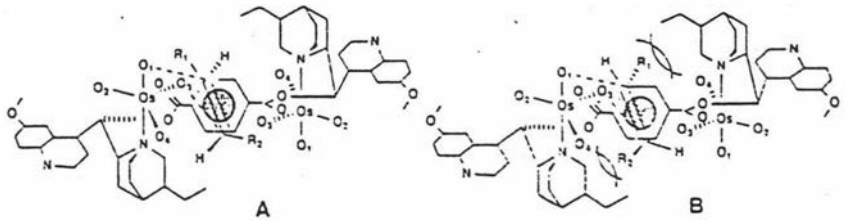
84 X = $-CH_2-$
85 X = $-(CH_2)_4-$
86 X = $-C_6H_4-$



87 **88** **89** **90**

Figure 19

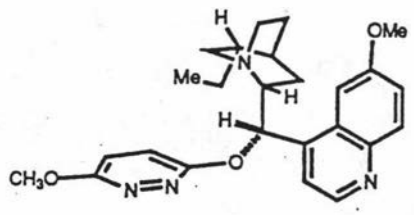
Using **85** as the chiral ligand, the ee was found to be >90%. This high selectivity could be explained through the intermediacy of either **89** or **90**. To test this hypothesis, **86** was used, as this ligand is unable to form a dimeric species (so two OsO_4 molecules are coordinated separately as in structure **90**) and therefore would give a low ee if Corey's theory[99] is indeed the case. The enantiomeric excess from this reaction was >98%, indicating that each quinuclidine moiety must be functioning independently in the enantiofacial process. Lohray and Bhushan then suggested a model **91** in which the olefin is held over the π-cloud of the ligand "linker", and the OsO_4 is able to catalyse the dihydroxylation from one face of the alkene only .



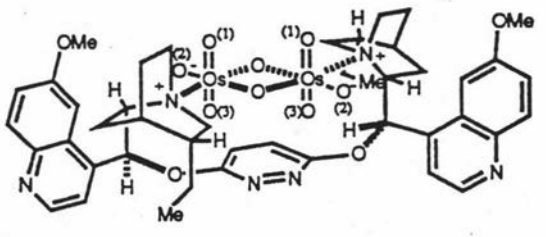
91

Corey *et al* [96a] then applied the aforementioned dimer theory to the pyrazine , and by analogy the phthalazine classes of ligands, proposing a structure in which the *bis* -Os(VIII) species bridges the two quinuclidine units of the pyrazine or phthalazine ligand **93**. Once again, it was suggested that a pentacoordinate structure provided no basis for explaining such high enantioselectivities for either a [3+2] cycloaddition at O=Os=O, or a [2+2] cycloaddition at Os=O, whilst bridged species **93** allowed for such facial preferences.

To examine whether the bridged intermediate **93** was indeed responsible for the high ee obtained, or whether it was a result of the two quinuclidine units each binding an OsO_4 molecule separately, ligand **92** was synthesised as a model for this latter possibility. Poor enantioselectivity was observed, providing supporting evidence for the proposed bridged intermediate **93**. Kinetic evidence was also forwarded to support Corey *et al* 's theory that the mechanism procedes *via* a [3+2] cycloaddition of a bridged *bis*-osmium(VIII) species to the olefin.



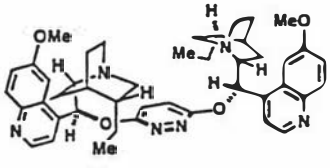
92



93

Sharpless *et al* , however, argued that the operation of the two quinuclidine units in concert simply was not possible, for several reasons. Firstly, the reaction has been shown to proceed under first order kinetics in OsO_4, but for the reaction to involve a *bis*-OsO_4 species, the rate law would require a second order component in OsO_4. Secondly, temperature studies carried out by Göbel and Sharpless[98] afforded results which were consistent with a stepwise [2+2] process rather than a concerted [3+2] mechanism. Finally, as was mentioned earlier, the monoquaternary salt of the dihydroquinidine phthalazine ligand was prepared, thereby preventing the two quinuclidine moieties from acting in concert. The ee's observed were virtually identical to those observed with the parent phthalazine ligand, therefore ruling out the possibility of a bridged intermediate. A series of unsymmetrically substituted phthalazine ligands were also prepared[96b], and it was found that the second alkaloid unit was not necessary for high ee's and as discussed earlier, most probably contributes to a more stabilised transition state.

In 1993, Corey and Noe[100] reported new data which allowed the pathway involving the bridged *bis*-osmium (VIII) species **93** to be excluded from consideration. A "bridged" pyrazine ligand **95** was synthesised in which the two quinuclidine nitrogens were held so far apart that any mechanism which involved both nitrogens participating in a bridged *bis*-osmium (VIII) species was impossible. High enantioselectivities were nevertheless still obtained and were found to be essentially the same as those obtained when using the unbridged pyrazine ligand **94**.[100] The catalytic rates for **94** and **95** were also found to be the same under standardised conditions, leading Corey and Noe to conclude that ligand **95** is a structurally rigid model for the active conformation of ligand **94**. It was also suggested that the mode of addition of the olefin to the bound OsO_4 is to one axial and one equatorial oxygen rather than to two equatorial oxygens since "the former leads most directly to the experimentally observed geometry for ligand-OsO_4-olefin adducts".[100]



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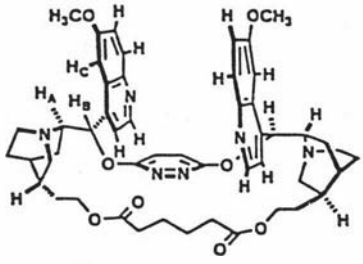


95

X-ray crystallography and ^1H nmr analysis of the bis-methiodide derivatives of **94** and **95** confirmed the presence of U-shaped binding pockets in both solid state and solution, created by the pyrazine ring and the two methoxyquinoline rings which extend in parallel planes to form the sides of the pocket. From the above evidence, Corey Noe and Grogan[101] have proposed a model for the cinchona ligands which possesses the following properties: (1) a preference for a U-shaped conformation when the OsO_4 is

bound (although not for the free ligand), (2) the ability, when in this U-shaped conformation, to hold olefinic substrates in the binding pocket created by the two methoxyquinoline rings and the pyrazine ring, (3) the proximity of one axial and one equatorial oxygen of the bound OsO_4 to the olefinic substrate and (4) the possibility of a [3+2] cycloaddition which directly produces the pentacoordinate osmate ester in the energetically most favourable geometry.

Thus, the Corey and Sharpless proposals seem to essentially agree on the mode of action of the cinchona alkaloid class of ligands in the ligand accelerated asymmetric dihydroxylation. The matter of whether the mechanism proceeds *via* a concerted [3+2] addition rather than a stepwise [2+2] addition, however, remains a point of contention. There is evidence both for and against each mechanism, and a more detailed discussion has been published by JØrgensen and SchiØtt[102], outlining the formation of osmaoxetane intermediates and comparing the two mechanisms.

The likelihood of each mechanism was also studied by Veldcamp and Frenking[93] using quantum mechanical *ab initio* calculations with ethylene and NH_3 as model compounds. The following questions were addressed: (1) What is the mode of attack of OsO_4 on the olefin, and is it a nucleophilic or electrophilic process, and (2) how is chirality transmitted from the chiral ligand to the product? It was suggested that the initial reaction is a [2+2] cycloaddition with two phases. Firstly, one oxygen atom from the OsO_4 attacks an olefinic carbon in a nucleophilic phase, and secondly the other olefinic carbon attacks the osmium atom in an electrophilic phase, yielding the four-membered osmaoxetane intermediate **80**. With the chiral ligand in such close proximity to the olefin, the formation of the osmaoxetane intermediate provides a possible explanation for the high enantioselectivity observed. This mechanism also provides evidence for the results of Haltermann and McEvoy,[103] who in 1992 demonstrated that the asymmetric induction in this reaction is not wholly dependent on steric interactions and that stereoelectronic control also plays a part. From the theoretical results obtained, Veldcamp and Frenking[93] concluded that although the mechanism suggested by Corey (a [3+2] cycloaddition) was possible, the mechanism suggested by Sharpless (a stepwise process involving a [2+2] cycloaddition) was more plausible.

Despite intensive study in recent years, the mechanism of the AD reaction remains elusive. Further study is underway[94b,98,104] in an attempt to finally solve this problem†. Until such a time, when there is a more generally accepted theory, the mechanism remains subject to intense debate.

†This section covers literature published up until November 1994.

1.1.5 The Asymmetric Dihydroxylation of Polyenes

The selectivity of the asymmetric dihydroxylation for particular olefin substitution patterns discussed earlier (section 1.1.3), has been utilised by several groups to preferentially dihydroxylate specific double bonds in polyenes. Such reactions have potential to convert readily available terpenes into valuable chiral synthetic intermediates. Using the modified Sharpless procedure employing the phthalazine class of ligands[81], this is now possible in high enantiomeric excess.

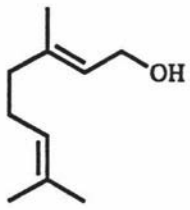
Initially, the selective mono-dihydroxylation of dienes was investigated[105] by Sharpless, Crispino and Xu in order to synthesise specific ene-diols. Using symmetrical, conjugated dienes, it was found that dihydroxylation only occurred at one of the double bonds; once the ene-diol product was formed, the second double bond was sufficiently deactivated by the electron-withdrawing hydroxyl groups to prevent the second dihydroxylation from occurring. For unsymmetrical dienes, the dihydroxylation occurred preferentially at the more substituted and electron-rich double bond. In the case of non-conjugated dienes, the product distribution was governed by the preferences discussed earlier, i.e. tri- > *trans*-di- > *gem*-di- > tetra- > mono- > *cis*-disubstituted double bonds[89]. The selectivity for a particular double bond in the non-conjugated diene system is dependent upon how far apart the two double bonds are in this order of preference. For instance, a trisubstituted double bond placed in competition with a monosubstituted double bond is highly favoured for asymmetric dihydroxylation, whereas if both double bonds have a lower degree of substitution, the selectivity observed is less. Although the regioselectivity differed between the diene systems studied, in all cases the ee [using $(DHQD)_2$-PHAL as the AD ligand] was high (74-98%).

Vidari *et al* [106,107] investigated the mono-dihydroxylation of some simple terpenes (table 3) using AD mixes α and β. In each case, dihydroxylation occurred preferentially at the more electron-rich 6,7 double bond. Reaction at the 2,3 double bond in **96**, **97** and **98** is inhibited due to a more crowded steric environment and reduced electron density due to the electronegative substituent at C-1. Linalool **99** affords only the 6,7 diol product where dihydroxylation at the trisubstituted double bond is favoured over reaction at the monosubstituted double bond.

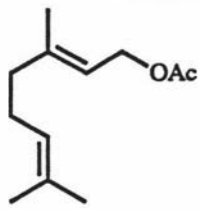
The dihydroxylation of sesquiterpenes **40**, **48** and **18** has also been carried out[106-108] (table 4). Although the results were similar in that preferential attack occurred at the terminal, less congested olefinic site, the presence of an additional internal trisubstituted double bond (at C-6, C-7) was a complicating factor. This resulted in a lower degree of

selectivity and the formation of tetraols where dihydroxylation had occurred at both positions. In all cases, a significant amount of starting material was also recovered.

Table 3



96



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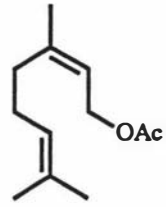

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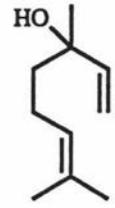
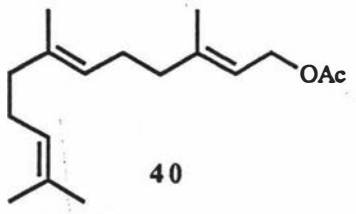


99

	Geraniol		Geranyl acetate		Neryl acetate		Linalool	
	α	β	α	β	α	β	α	β
6,7 diol	46%	-	78%	82%	92%	94%	80%	77%
2,3 diol	6%	-	6%	3%	trace	trace	-	-

Table: Reactions carried out at 0°C for 24h using AD-mix-α (α) or AD-mix-β (β).

Table 4



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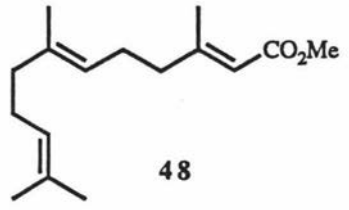

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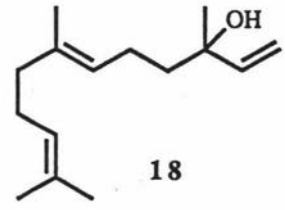


18

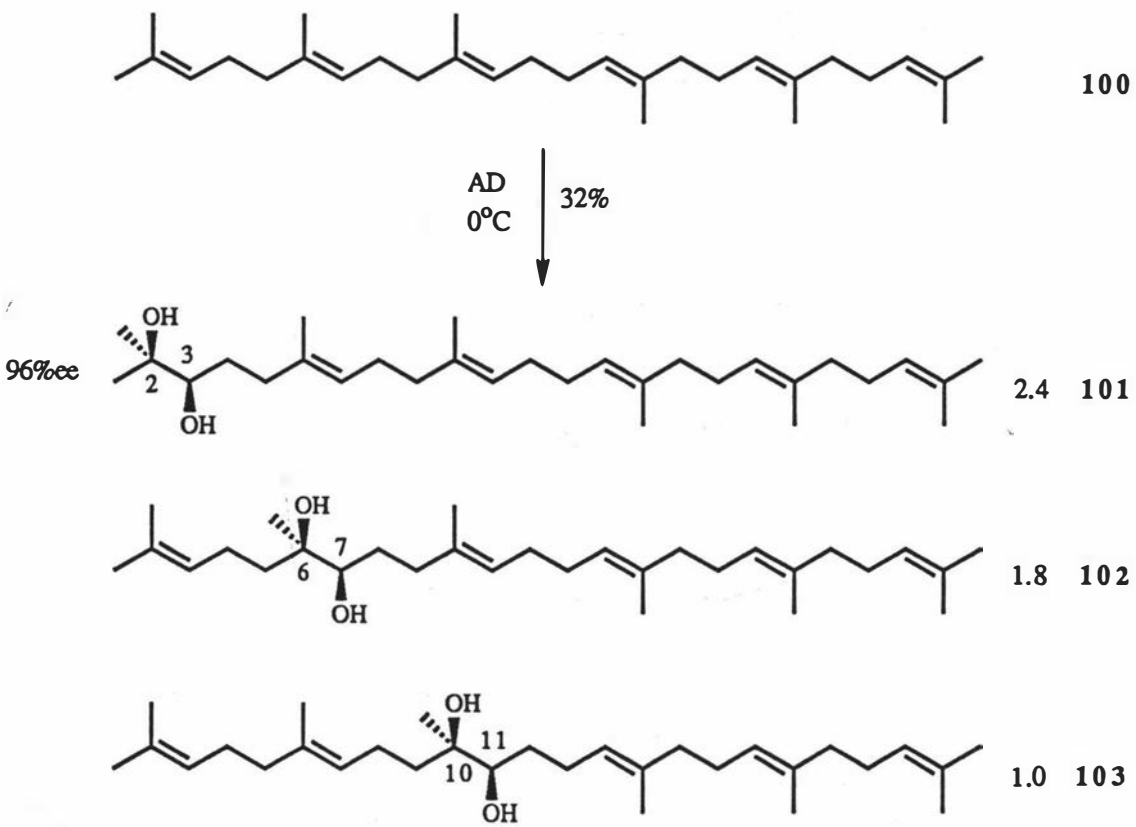
	(*E*,*E*)-Farnesyl acetate	(*E*,*E*)-Methyl farnesoate		(*E*)-Nerolidol
	AD-mix-β[a]	$(DHQD)_2$-PHAL[b]	$(DHQ)_2$-PHAL[b]	AD-mix-α[c]
10,11 diol	34%	37%	31%	33%
6,7 diol	16%	2%	3%	27%
tetraol	27%	37%	29%	3%
recovered SM[d]	20%	15%	14%	30%

Table: a: Reaction carried out at 0°C for 24h using AD-mix-β, similar data was obtained using AD-mix-α but yields were not reported; b: Reaction carried out at 0°C for 24h using $(DHQD)_2$PHAL or $(DHQ)_2$PHAL; c: Reaction carried out at 0°C for 50h using AD-mix-α, similar data was obtained using AD-mix-β but yields were not reported; d: starting material.

Sharpless and Crispino[108] also investigated the difference in regioselectivity between the two AD ligands $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL, using methyl farnesoate **48** as substrate. $(DHQD)_2$-PHAL gave a 20:1 ratio of 10,11 diol to 6,7 diol with 98% ee whilst $(DHQ)_2$-PHAL gave a 9:1 ratio with 92% ee. Both the drop in regioselectivity and enantioselectivity is attributed to the non-enantiomeric relationship between the two ligands.

In 1992, Sharpless and Crispino[109] carried out the asymmetric dihydroxylation of the triterpene squalene **100** (scheme 22) using $(DHQD)_2$-PHAL as ligand.

Scheme 22

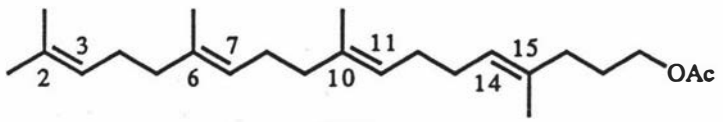


Reagents and conditions: $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, OsO_4, t-BuOH / H_2O, 24h, 0°C.

Regioselective dihydroxylation of squalene presents a considerable synthetic challenge in that it contains three pairs of trisubstituted double bonds in only slightly different steric environments. Some preference was observed, however, with the 2,3 diol **101** favoured over the 6,7 diol **102** which was in turn preferred over the 10,11 diol **103**. Since there are no substituent effects and all double bonds are trisubstituted, the only possible explanation for the observed selectivity must be the degree of steric hindrance presented to the OsO_4-ligand complex by each double bond. The "exhaustive" AD of squalene has

also been carried out, with the isolation of squalene dodecanol **104** where each of the six double bonds has been dihydroxylated[110].

Madden and Prestwich[111] (1994) subsequently used the asymmetric dihydroxylation with (4*E*,8*E*,12*E*)-4,9,13,17-tetramethyl-4,8,12,16-octadecatetraenyl acetate **105** as substrate in order to synthesise an enantiomerically-enriched inhibitor for the enzyme oxidosqualene cyclase. The conditions of the reaction (using AD-mix-β) were optimised to obtain a maximum yield of the required 2,3-diol **106**, however, the steric influences observed in the AD of squalene **100** above were still evident. The least congested 2,3-diol **106** was obtained in the greatest yield (26%), followed by the 14,15-diol **109** (13%, as a mixture with **106**), the 6,7- and 10,11-diols **107** and **108** (as a mixture, 4.2% and 4.3% respectively), and the 6,7,10,11- and 10,11,14,15-tetraols **110** and **111** (as a mixture, 29% combined yield). The desired chiral 2,3-diol **106** was then employed in the synthesis of a tritium-labelled substrate for oxidosqualene cyclase.



105

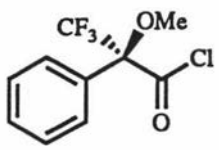
2,3-diol	**106**	14,15-diol	**109**
6,7-diol	**107**	6,7,10,11-tetraol	**110**
10,11-diol	**108**	10,11,14,15-tetraol	**111**

Thus, it seems that the regioselectivity of the AD of polyenes is dependent upon three factors: (1) the presence or absence of substituents which may deactivate a double bond, (2) the degree of substitution of the double bond, and (3) the steric hindrance presented by the double bond to access by the OsO_4-ligand complex.

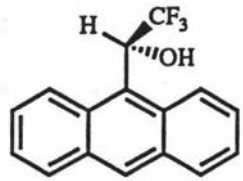
1.1.6 Methods Used to Determine Enantiomeric Excess

The enantiomeric excess of a compound may be determined in several ways. The most direct method is the use of chiral chromatographic media, and several types of chiral columns suitable for HPLC or GC are currently available. Alternatively, derivatisation of an optically active compound with a chiral non-racemic reagent such as α-methoxy-α-trifluoromethyl phenylacetic acid (MTPA, Mosher's acid)[112] or acid chloride **112**, menthyl chloroformate[113], mandelates[114], camphanic chloride[115], trivalent phosphorus derivatives[116] and organoboron[117] or organosilicon[118] compounds, affords a mixture of diastereomers which are distinguishable by GC[113,119], HPLC[120] or nmr[121a,b] methods, allowing calculation of a diastereomeric ratio to determine optical purity.

A closely related method which is not based on covalent bond formation and therefore does not necessitate conversion to the corresponding diastereomer, is the use of a chiral solvating agent[122a,b]. This method is based on the fact that enantiomers exhibit different spectra when in a chiral solvent, through formation of short-lived diastereomeric solvates which are non-equivalent by nmr. Another nmr method which is based on a similar principle is the use of an achiral solvent but with the addition of a chiral lanthanide shift reagent[123a,b] which can form coordination compounds with, for example, alcohols, carbonyl compounds and amines[124]. Lanthanide shift reagents may also be used to gain additional resolution when added to a mixture of diastereomers which have been derivatised by one of the above methods[125].



112



113

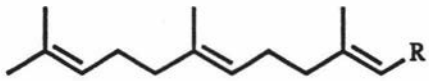
In the current research, two methods were employed. Firstly, the use of the chiral solvating agent *R*-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol **113** and secondly, conversion of the enantiomeric mixtures to the diastereomeric Mosher esters for analysis by ^{1}H and ^{19}F nmr.

2. DISCUSSION

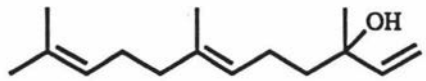
2.1 The Asymmetric Dihydroxylation of α- and β-Farnesene

2.1.1 The Regioselective Functionalisation of Polyenes

The ability to selectively place oxygen funtionality onto an unsaturated hydrocarbon skeleton is of great importance in organic synthesis. The osmium-catalysed asymmetric dihydroxylation using the phthalazine ligands **76** and **77**, developed by Sharpless, provides a means of achieving this. The high enantioselectivity of this reaction has already been established, however, the investigation of regioselectivity in polyenes still allows considerable scope for further developments. As was discussed in section 1.1.5, the regioselectivity of this method with respect to dienes[105], geraniol **96**, geranyl and neryl acetates **97** and **98**[106], linalool **99**, farnesyl acetate **40**[107], methyl farnesoate **48**[108], nerolidol **18**[107] and squalene **100**[109,110] has already been investigated. The regioselectivity of the AD using members of the farnesyl family of sesquiterpenes has only been examined using those which are functionalised at C-1 or C-3 (**18**, **40** and **48**).



40 R=CH_2OAc
48 R=CO_2Me



18

The regioselectivity of the AD is strongly influenced by the nature of the functionality at C-1. Nerolidol **18** exhibits only a slight preference (1.2:1) for dihydroxylation under Sharpless conditions at the 10,11-double bond over the 6,7-double bond. This selectivity, however, increases to 2.2:1 for farnesyl acetate **40**, whilst a dramatic increase (20:1) is observed for methyl farnesoate **48**. In the absence of substituent effects, as in squalene, it was demonstrated that attack occurred preferentially at the terminal, less congested, site[109].

In the current work, the AD of α- and β-farnesene **1** and **2** has been undertaken. α-Farnesene **1** possesses four double bonds, of which two are trisubstituted and two are incorporated into a conjugated diene unit. β-Farnesene provides an interesting comparison, as it also has four double bonds, but differs from the α-form by virtue of a 3-methylene rather than a 3,4-double bond. Given the synthetic potential of chiral hydroxylated farnesene derivatives as precursors to juvenile hormone analogues[47,108] and the implication that the oxidation products of α-farnesene play an important role in

the production of superficial scald, as well as the potential utility of these derivatives as chiral intermediates generally, the asymmetric dihydroxylation of α- and β-farnesene warrants detailed examination.

2.1.2 The Isolation and Identification of the α - and β-Farnesene Diols

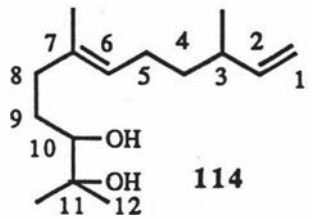
The dihydroxylation of α-farnesene detailed earlier, using an OsO_4/NMO system provided the 3,4-diol **42** and the 6,7 diol **41** (5:1) as an inseparable mixture in 9% yield. Use of the Sharpless system [10 mol% of $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, 2 mol% of OsO_4, 3 equiv. $K_3Fe(CN)_6$, 3 equiv. K_2CO_3 and 1 equiv. methanesulphonamide] resulted in a much cleaner reaction with higher yields and improved mass recovery. In addition, the unstable 10,11-diol **114** and the 6,7:10,11-tetraol **115** were isolated.

Table 5: The Asymmetric Dihydroxylation of α-Farnesene

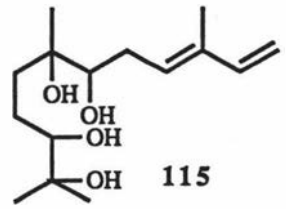
	$(DHQ)_2$-PHAL		$(DHQD)_2$-PHAL	
	Yield	$[\alpha]_D$	Yield	$[\alpha]_D$
41, 42 (20:1)	28%	-24.5	18%	+22.8
114	11%	-20.8	15%	+21.2
115	7%	-39.8	14%	+42.0
Recovered **1**	25%	-	29%	-

Reagents and conditions: $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, OsO_4, t-BuOH / H_2O, 6h, 0°C.

Upon purification by flash chromatography, the 6,7- and 3,4-diols **41** and **42** were once again obtained as an inseparable mixture, but in increased yield (table 5). The ratio of **41** to **42** (5:1 in the OsO_4/NMO system) was also improved considerably to 20:1, using these ligands. The later-eluting 10,11-diol **114** was also isolated and the structure assigned from the ^1H nmr spectrum (table 6) by the upfield shift of the two terminal methyl groups from δ1.60 and δ1.64 in α-farnesene to δ1.16 and δ1.20 in **115** as well as the disappearance of the vinylic proton 10-H at δ5.09 in α-farnesene together with the appearance of a methine proton at δ3.35. These shifts are analogous to those observed for the 10,11-epoxide **43** (page 18). The infra-red spectrum exhibited a strong OH peak at 3405 cm^{-1} as well as peaks at 1602 and 1636 cm^{-1} which indicated retention of the diene moiety. Due to the instability of diol **114**, the more stable acetonide derivative was prepared and as expected, the mass spectrum exhibited a molecular ion at *m/z* 278.

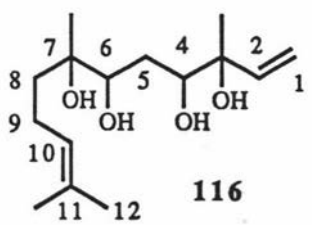


114

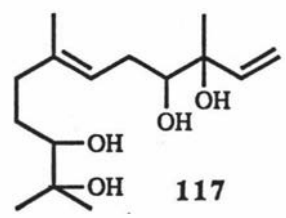


115

The highly polar 2,3:6,7-tetraol **115** eluted last and the spectroscopic data was analogous to that of *bis*-epoxide **46**. The ^{1}H nmr spectrum (table 6) showed the shift of three methyl groups upfield, with only the 3-methyl group maintaining its position at δ1.77, whilst 6-H and 10-H disappeared from δ5.05 and δ5.09 in α-farnesene and two methine protons appeared at δ3.35 and δ3.48. The two methylene groups, located between the two diols, were also both shifted upfield and resonated as a multiplet centred at δ1.59. The infra-red spectrum showed a strong OH peak at 3410 cm^{-1} and oxygenation at four carbon centres was confirmed in the ^{13}C nmr spectrum (table 7), with four carbons, C-6, C-7, C-10 and C-11, resonating in the range δ73.1-79.0. An additional quartet in the ^{1}H nmr, resonating at δ5.94 and integrating for 0.07 H of the 6,7:10,11-tetraol **115**, indicated the presence of an isomeric tetraol, in which dihydroxylation had occurred at the 3,4-double bond. This isomeric tetraol was either the 3,4:6,7-tetraol **116** or the 3,4:10,11-tetraol **117** but no assignment between the two could be made as both 10-H in the former and 6-H in the latter, were obscured by 6-H and 10-H of the major 6,7:10,11-tetraol **115**. This minor tetraol isomer was not observed in the ^{13}C nmr spectrum.



116

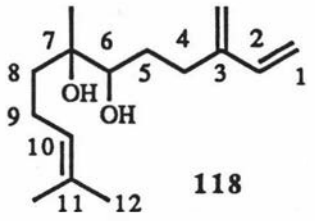


117

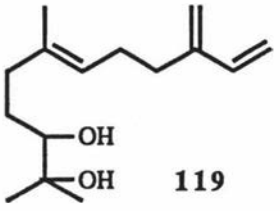
When the asymmetric dihydroxylation of β-farnesene **2** was carried out under the same conditions, using the $(DHQ)_2$-PHAL ligand, two diols were isolated. These were the 6,7-diol **118** and the 10,11-diol **119**. The ^{1}H nmr spectrum of diol **118** indicated dihydroxylation of the 6,7-double bond in that the 7-methyl group was shifted from δ1.68 in β-farnesene (figure 20), to δ1.12 in the diol. In addition, the disappearance of the 6-H triplet from the olefinic region together with the appearance of a broad multiplet (1 H) at δ3.47 also supported this assignment.

The ^{1}H nmr spectrum of the 10,11-diol **119** was very similar to diol **114**. The two terminal methyl groups were shifted upfield to δ1.16 and δ1.21 from δ1.60 in β-farnesene (δ1.16 and δ1.20 from δ1.60 and δ1.68 in α-farnesene) and the absence of the 10-H proton from the olefinic region, as well as the presence of a multiplet centred at

δ3.36 which integrated for one proton in β-farnesene, was comparable to the shift from δ5.09 to δ3.35 which was observed with α-farnesene. Due to the instability of the 10,11-diol, the acetonide derivative was made, and the location of the diol confirmed in the ^{13}C nmr spectrum, with resonances at δ80.1 and δ82.8 assigned to C-10 and C-11 consistent with these carbons being attached to an oxygen as required in diol **119**.



118



119

2.1.3 The Regioselectivity of the Asymmetric Dihydroxylation

Based on the results reported by Sharpless and Crispino[109] on the AD of the polyene squalene **100**, it would be expected that in the absence of substituent effects, the dihydroxylation of α-farnesene would occur preferentially at the less congested terminal site (the 10,11-double bond). The experimental observation, however, was that preferential reaction occurred at the internal trisubstituted double bond. Using $(DHQ)_2$-PHAL, a mixture (20:1) of the (*S*,*S*)-6,7- and 3,4-diols **41** and **42** was obtained in 28% yield, with the more electron-rich 6,7-double bond being favoured over the relatively electron deficient 3,4-double bond which is part of the conjugated diene. The 6,7-double bond was also favoured, by almost 3:1, over the 10,11-double bond (11% yield) as shown by the product ratios in table 5. A small amount of (*S*,*S*,*S*)-6,7:10,11-tetraol **115** was also isolated (7% yield), along with 25% recovered starting material.

By comparison, when using the $(DHQD)_2$-PHAL ligand, selection for the 6,7-olefin dropped, in that the 20:1 ratio of the (*R*,*R*)-6,7-diol **41** to 3,4-diol **42** was formed in 18% yield with more of both the (*R*)-10,11-diol **114** (15%) and (*R*,*R*,*R*)-6,7:10,11-tetraol **115** (14%) produced, as well as 29% recovered starting material. (table 5).

Asymmetric dihydroxylation of β-farnesene **2**, under the same conditions as that described above for α-farnesene **1**, was carried out using the ligand $(DHQ)_2$-PHAL. The expected selectivity for the 10,11-double bond over the 6,7-double bond was observed in this case, in a 2:1 ratio, with diol **119** isolated in 18% yield and diol **118** in 9% yield as well as recovered starting material (19%).

Table 6: ^{1}H nmr Shifts (ppm) for α-Farnesene **1**, Diols **41**, **42**, **111** and Tetraol **112**.

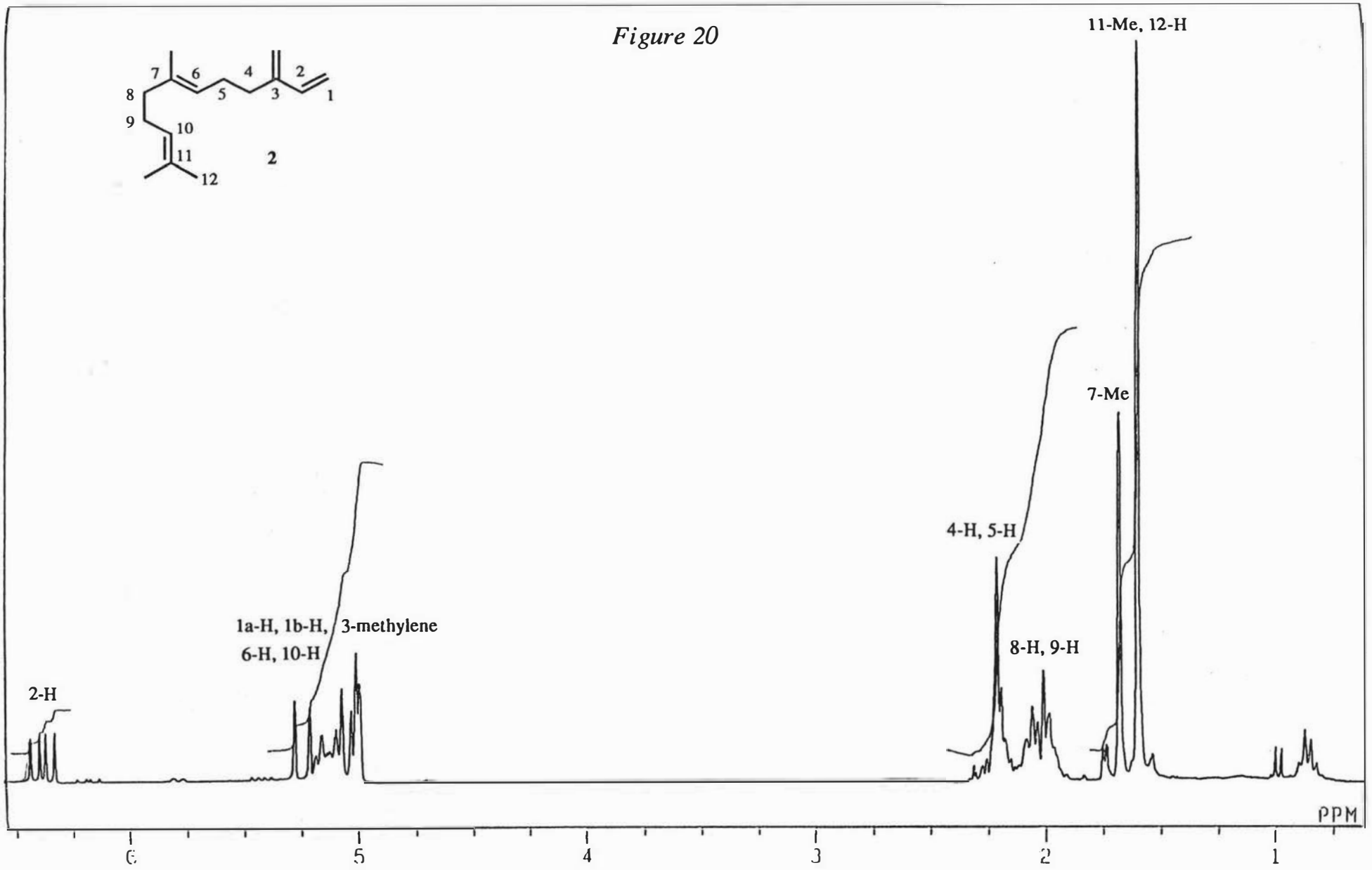
	1a-H	1b-H	2-H	4-H	5-H	6-H	8-H	9-H	10-H	12-H	3-Me	7-Me	11-Me
1	5.05	4.92	6.37	5.46	2.84	5.05	2.02	2.02	5.09	1.60	1.77	1.68	1.64
114	5.09	4.93	6.36	5.45	2.85	5.21	2.12	1.61	3.35	1.16	1.76	1.66	1.20
41	5.13	4.98	6.41	5.59	2.31	3.47	1.55	2.16	5.12	1.63	1.78	1.16	1.69
42	5.34	5.15	5.95	3.47	2.31	5.19	2.16	2.16	5.12	1.63	1.26	1.69	1.69
115	5.13	4.98	6.41	5.60	2.31	3.48	1.59	1.59	3.35	1.16	1.77	1.17	1.22

Table 7: ^{13}C nmr Shifts (ppm) for α-Farnesene **1**, Diols **41**, **42** and Tetraol **112**.

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	3-Me	7-Me	11-Me
1	110.5	141.7	133.7	131.8	27.2	122.1	135.8	39.6	26.7	124.3	131.3	25.7	11.7	16.1	17.6
41	111.4	141.1	131.9	129.0	30.5	74.6	*	38.9	22.1	124.3	136.6	25.7	11.9	21.1	17.6
42	113.8	142.7	*	75.0	29.8	120.3	139.0	39.8	26.4	124.3	136.6	25.7	15.2	16.2	17.6
115	111.5	141.1	136.7	128.9	30.7	73.1	*	35.9	23.3	79.0	74.3	26.5	12.0	21.0	25.2

Notes: (*) ^{13}C nmr data for these peaks obscured by chloroform peaks.

Figure 20



7,11-Dimethyl-3-methylene-1,6,10-dodecatriene (2)

These results indicate that regioselectivity in the AD reaction of polyenes is extremely sensitive to the presence of additional functionality. Thus, the presence of a diene such as that in α-farnesene as opposed to a CO_2Me group at C-1, was sufficient to overcome the inherent preferential reactivity of the terminal 10,11-double bond that was observed for squalene. The observed differences in reaction rates between α- and β-farnesene could be due to different steric interactions with the osmium-ligand complexes, however, a more detailed understanding of the topology of the osmium-ligand complex is required to fully appreciate the exact extent of these influences.

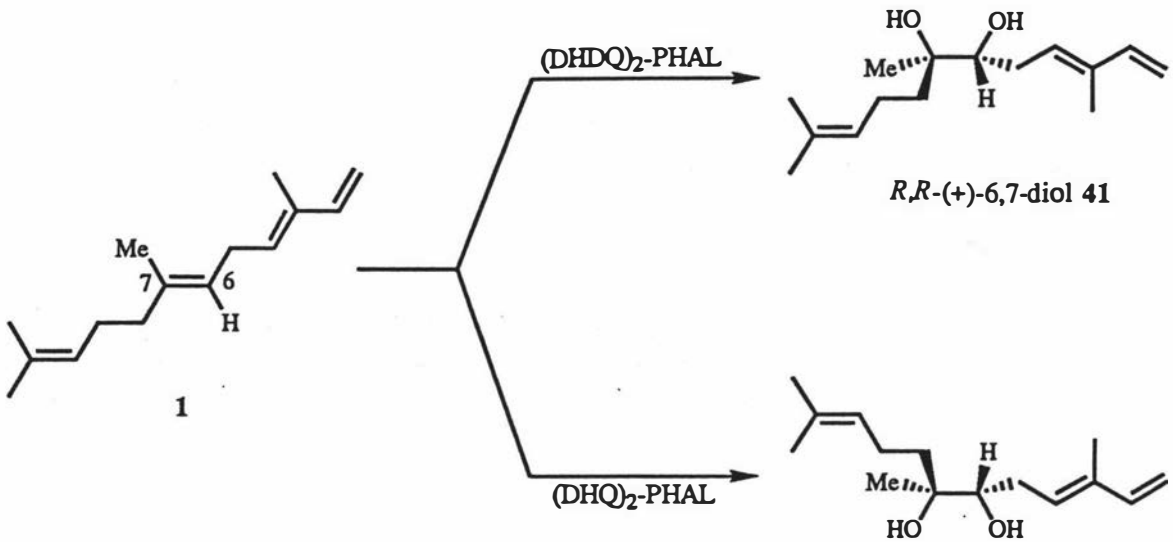
2.1.4 The Enantioselectivity of the Asymmetric Dihydroxylation

The absolute configuration of the stereogenic carbon atoms C-6 and C-7 of the enantiomeric diols was assigned using the mnemonic device described by Sharpless *et al*[81] (schemes 23-26). Enantiomeric excesses were determined by ^1H (270 MHz) and ^{19}F (282 MHz) nmr spectroscopy upon conversion to the Mosher ester derivatives[112] using *R*-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(-)-MTPA-Cl] **112** as described earlier.

The Mosher esters were prepared by addition of the Mosher acid chloride **112** to a solution of the substrate in a mixture of pyridine (2 ml) and triethylamine (0.1 ml), followed by a catalytic amount of DMAP. After the reaction was allowed to stir for 7 hours, the Mosher ester derivative was isolated and purified by flash chromatography. For the Mosher ester derivatives of diols **41, 42** and **114** (**120a** and **b**, **121a** and **b**, **122a** and **b** respectively), the presence of a single ester group was indicated in the ^1H nmr spectrum with the peak at δ3.55 assigned to OMe integrating for 3 protons only. Mass spectral analysis confirmed this fact, exhibiting a molecular ion at *m/z* 454 which was consistent with a molecular formula of $C_{25}H_{33}O_4F_3$ as required for esterification at one position. With only one ester present, esterification would be expected to take place at the less congested secondary hydroxyl group and this was indeed the case, evidenced by the disappearance of the C<u>H</u>OH proton for diols **41, 42** and **114** (δ3.35-3.48), along with the presence of an additional proton at δ4.95-5.32. From the ^{13}C nmr spectrum for diols **41** and **42**, the resonance assigned to C-6 was shifted from δ74.6 to δ81.2.

Tetraol **115** was converted to the corresponding diastereomeric bis-esters **123a** and **b**. Two peaks, which were assigned to the OMe groups, were observed in the ^1H nmr spectrum at δ3.48 and δ3.59, and the C<u>H</u>OH protons, 6-H and 10-H, were absent from the region between δ3.30 and δ3.60. The mass spectrum of esters **123a** and **b** gave a molecular ion at *m/z* 704, consistent with the formula $C_{35}H_{42}O_8F_6$, confirming the presence of two ester groups, and the resonances representing C-6 and C-10

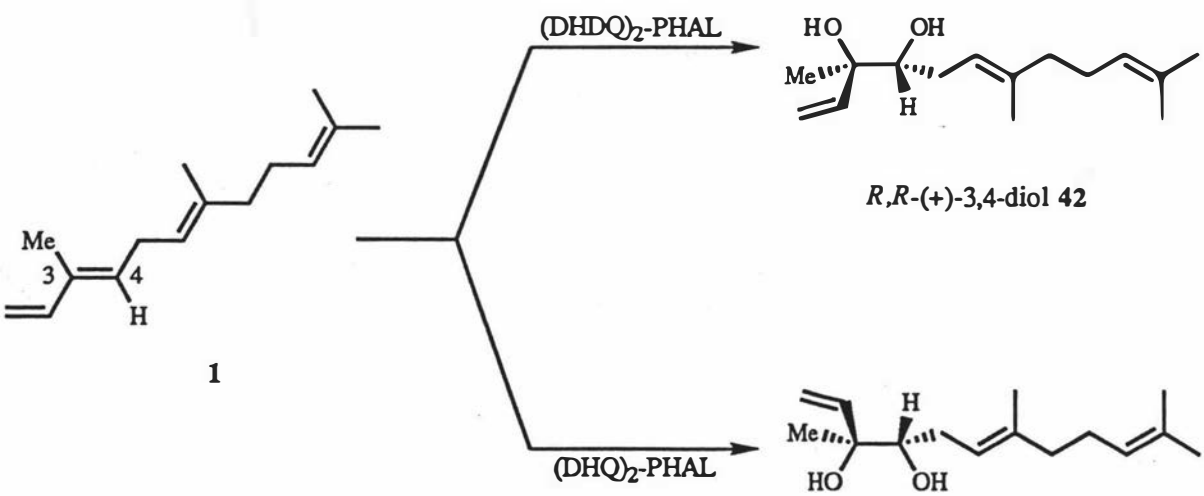
Scheme 23



R,R-(+)-6,7-diol **41**

S,S-(-)-6,7-diol **41**

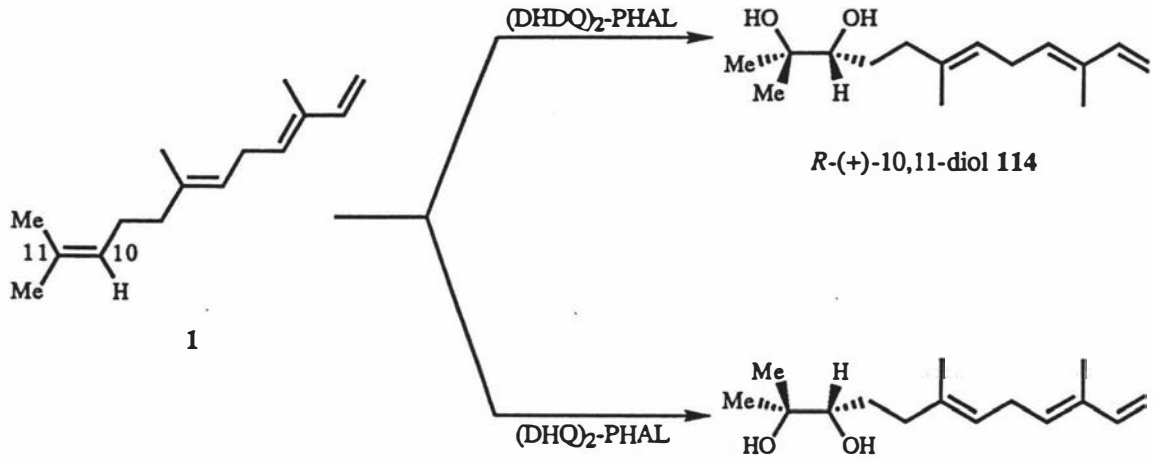
Scheme 24



R,R-(+)-3,4-diol **42**

S,S-(-)-3,4-diol **42**

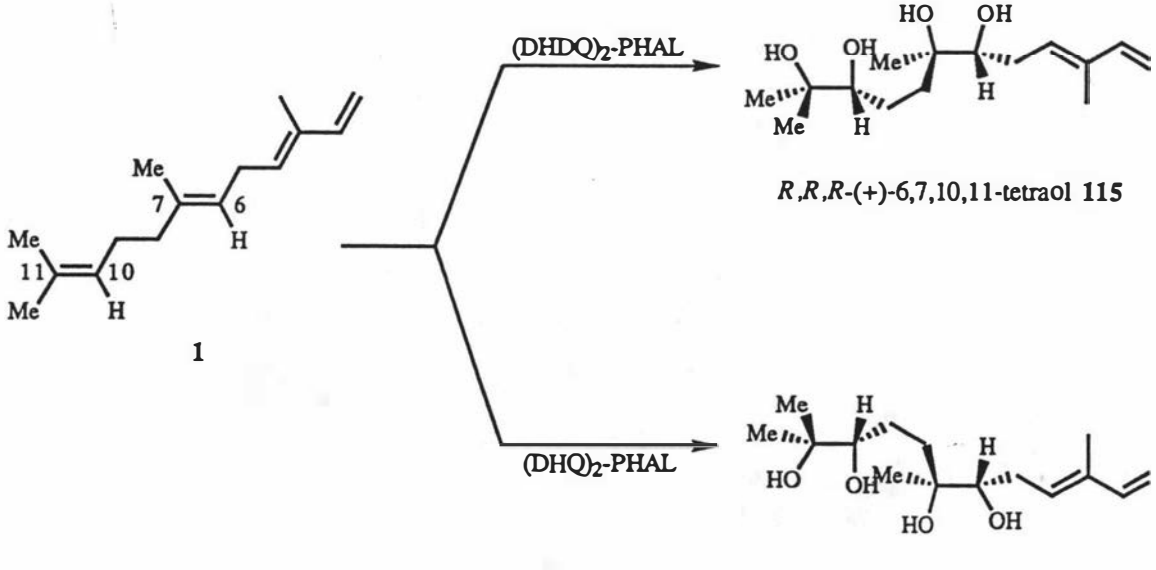
Scheme 25



R-(+)-10,11-diol **114**

S-(-)-10,11-diol **114**

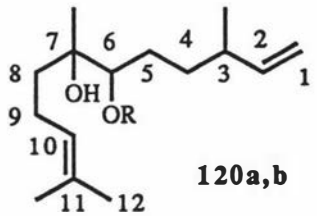
Scheme 26



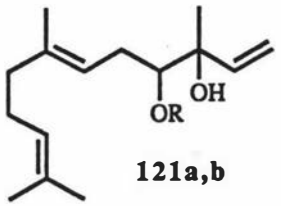
R,*R*,*R*-(+)-6,7,10,11-tetraol **115**

S,*S*,*S*-(-)-6,7,10,11-tetraol **115**

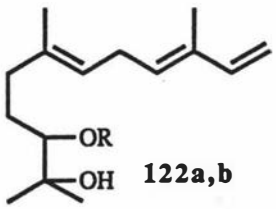
in the ^{13}C nmr spectrum were shifted from δ73.1 and δ79.0 to δ88.1 and δ82.9 respectively.



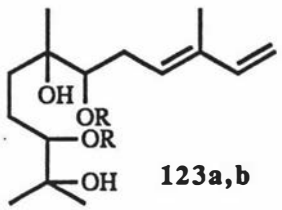
120a,b



121a,b



122a,b



123a,b

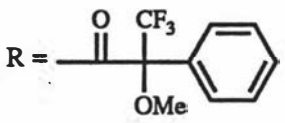


Table 8: ^{19}F nmr Shifts (ppm) For Mosher Esters[a]

	(DHQD)$_2$-PHAL (a)	(DHQ)$_2$-PHAL (b)
120, 121	-71.60	-71.65
122	-71.25	-71.25
123	-71.21, -71.49	-71.04, -71.63

a: Data obtained at 282 MHz, shifts quoted in ppm relative to $CFCl_3$.

In the cases of diols **41**, **42** and tetraol **115**, the ^1H nmr spectrum of the derived Mosher esters established that the ee was greater than 95% using either ligand. For the 10,11-diol **114**, no differences were observed between the spectra of the diastereomeric Mosher esters **122a** and **122b** derived from the respective enantiomers, so no ee could obtained. The ^{19}F nmr data (table 8) was in agreement with the ^1H nmr data, with the diols **41**, **42** and the tetraol **115** (both enantiomers) all showing enantiomeric excesses of at least 95%. Unfortunately, the ^{19}F nmr peaks for the unstable diastereomeric Mosher ester derivatives of the enantiomeric 10,11-diols were also coincident, however, given the high ee obtained for the diols **41**, **42** and tetraol **115**, it seems unlikely that **114** would possess an ee of less than 95%.

PART 3: ENANTIOSELECTIVE SYNTHESIS OF AN APPLE AROMA CONSTITUENT

1. INTRODUCTION

1.1 Sources and Isolation of Bicyclic Acetal (17)

Bicyclic acetal **17** (1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane) has been identified as a constituent of the anal gland of the "meat" ant *Iridomyrmex purpureus*[126]. It has also been reported in the aroma of "Granny Smith" apples, where a likely source was thought to be α-farnesene **1**[20].

17

Klein and Rojahn[127] in 1967, and subsequent workers in 1968[128] and 1973[129] showed that 6-methylhept-5-en-2-one **14** is easily oxidised by peracids to bicyclic acetal **17** (scheme 27). Since 6-methylhept-5-en-2-one **14** is a known major volatile oxidation product of α-farnesene[20,21], it was postulated that this might be the route by which 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane **17** was produced on the apples. Stanley *et al*[20] applied α-farnesene **1** (10 mg) to glass wool (3 g) and allowed the α-farnesene to oxidise in an enclosed vessel for 24 hours, with periodic sampling of the vessel atmosphere, followed by analysis by GC/MS. Both the 6-methylhept-5-en-2-one **14** and bicyclic acetal **17** were identified as major oxidation products, supporting the possibility that the oxidation of α-farnesene to the bicyclic acetal may proceed *via* 6-methylhept-5-en-2-one **14**. The experiment, however, was then repeated under the same conditions using 6-methylhept-5-en-2-one **14** as substrate and no change in the peak representing **14** was observed over 36 hours. This result suggested that 6-methylhept-5-en-2-one **14** was in fact an unlikely intermediate in the autoxidation.

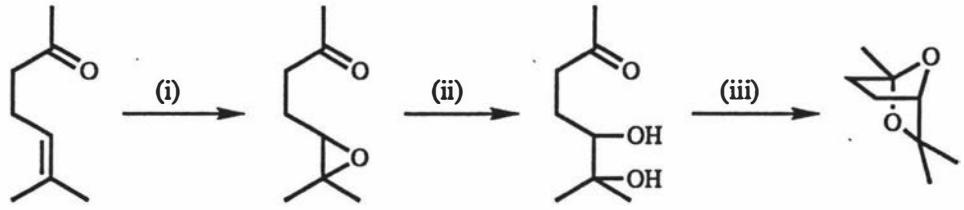
In the current research, the asymmetric synthesis of 1,3,3-trimethyl-2,7-dioxabicyclo-[2.2.1]heptane **17** has been carried out, using the Sharpless asymmetric dihydroxylation to introduce chirality and thereby generate both enantiomers. With the pure and fully characterised bicyclic acetal **17** in hand, its presence both on the apple and in the autoxidation mixture of α-farnesene can be verified and quantified. Biological testing to investigate whether **17**, as an oxidation product of α-farnesene, is involved in the induction of superficial scald can also be carried out. Lastly, since this asymmetric synthesis provides samples of both enantiomers of **17**, the stereochemistry of the oxidation process occurring on apples can be investigated *via* chiral GC or HPLC

analysis. Chiral synthesis of **17** by apples would be indicative of a biosynthetic rather than an autoxidative origin for this compound.

1.2 Achiral Synthesis of Bicyclic Acetal (17)

Klein and Rojahn[127] (1967) carried out the synthesis of **17** in good yield, employing 6-methylhept-5-en-2-one **14** as starting material (scheme 27).

Scheme 27



14 **124** **125** **17**

Reagents and conditions: (i) 40% AcOOH, NaOAc, 0°C, 2h (97%); (ii) H_2O, 50°C, 3h (75%); (iii) distillation at atmospheric pressure (77%).

Epoxidation of **14** with peracetic acid afforded epoxide **124** in 97% yield. Hydrolysis of the epoxide gave the unstable ketone-diol **125** (75% yield) and distillation of this compound produced the required 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane **17** in 77% yield (56% overall). Gaoni[128] subsequently showed that isolation of epoxide **124** or diol **125** was unnecessary, with Gaoni[128], Wasserman *et al*[130] and Ishihara *et al*[131], reporting that the conversion could be made complete by epoxidation with *m*-CPBA followed by warming the reaction mixture (100-110°C) under anhydrous conditions.

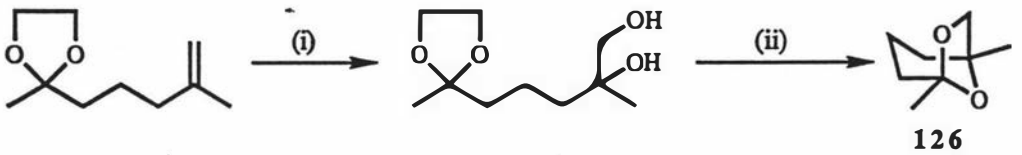
1.3 Synthesis of Related Compounds Using the Asymmetric Dihydroxylation

Several syntheses of bicyclic acetals related to **17** have been reported recently which employ the Sharpless asymmetric dihydroxylation methodology as the key chiral induction step[132-135]. These syntheses were examined to investigate the feasibility of using this method to synthesise bicyclic acetal **17**.

Frontalin **126** and exo-brevicomin **127**, aggregation pheromones of pine beetles *Dendroctonus frontalis* and *Dendroctonus brevicomis*, are popular synthetic targets and have been prepared previously using a variety of synthetic strategies. The 6,8-dioxabicyclo[3.2.1]octane skeleton present in these compounds was synthesised in 1992

by Turpin and Weigel[135] using the asymmetric dihydroxylation. Soderquist *et al*[132,133] have prepared both compounds *via* assembly of the carbon framework using copper and palladium-based couplings, followed by Sharpless asymmetric dihydroxylation and cyclisation to afford the (-)-enantiomer of frontalin **126** and both enantiomers of exobrevicomin (+)-**127** and (-)-**127** (schemes 28 and 29).

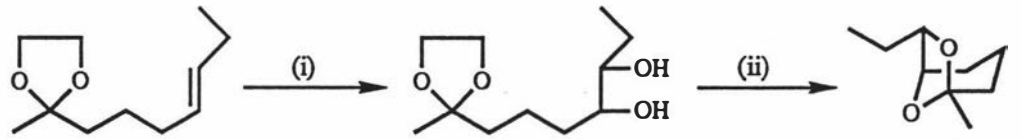
Scheme 28



126

Reagents and conditions: (i) AD-mix-α or AD-mix-β (72%); (ii) *p*-TSA, RT, 2h (80%).

Scheme 29



127

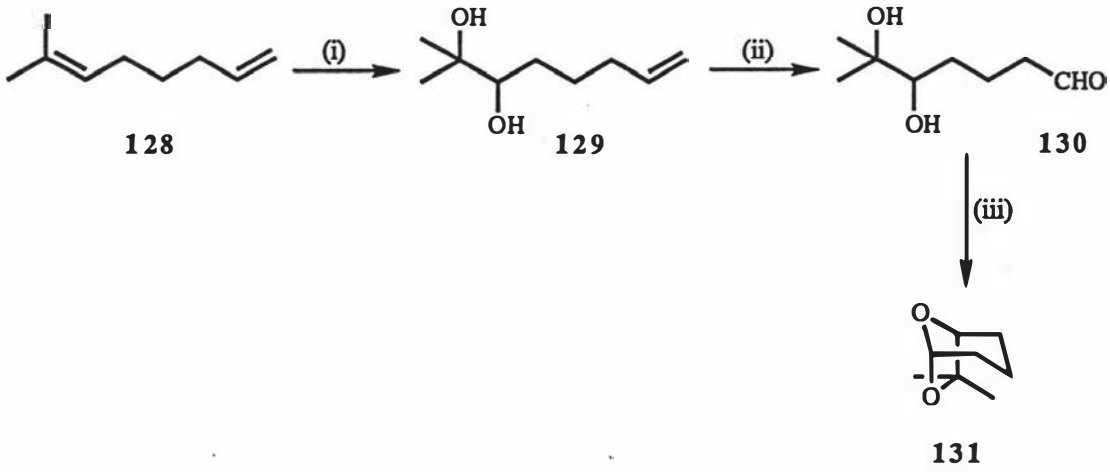
Reagents and conditions: (i) AD-mix-α or AD-mix-β (96%); (ii) 0.75 equiv. *p*-TSA, 25°C, 2h (90%).

Although the enantiomeric excess of (-)-frontalin **126** was modest, (35%), the optical yield for both the (+)- and (-)-enantiomer of exo-brevicomin **127** was excellent, at 95%. 7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane **131** also shares the same 6,8-dioxabicyclooctane nucleus as both frontalin and brevicomin. This bicyclic acetal **131** is a volatile contributor to the aroma of beer and has also been synthesised previously by different methods. In 1993, Sharpless and Crispino[134] applied the AD in the synthesis of **131**, obtaining both enantiomers in high yield and enantiomeric excess (scheme 30).

The asymmetric dihydroxylation of commercially available 7-methyl-1,6-octadiene **128** using either $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL gave the diols (-)-**129** and (+)-**129** respectively. No reaction occurred at the monosubstituted double bond. Ozonolysis followed by treatment with acid gave (-)-**131** (86% yield, 94% ee) and (+)-**131** (82% yield, 98% ee).

Given the excellent precedent set by the above syntheses, the synthesis of bicyclic acetal **17** was undertaken, using the asymmetric dihydroxylation for the key chiral induction step.

Scheme 30



128 **129** **130** **131**

Reagents and Conditions: (i) $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$ OsO_4, t-BuOH/ H_2O, 0^oC, 15h (69%); (ii) a: O_3, -78^oC; b: PPh_3, RT, 3h; (iii) *p*-TSA, RT, overnight (86%).

2. DISCUSSION

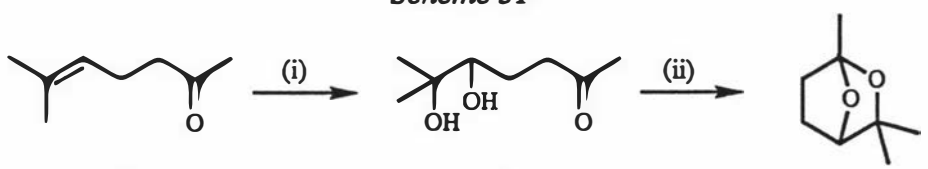
2.1 Synthesis of 1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane (17)

2.1.1 Synthesis of Racemic Bicyclic Acetal 17

Initially, the epoxidation of **14** using *m*-CPBA, followed by cyclisation to the bicyclic acetal **17** according to the method of Gaoni[128] (scheme 27), was attempted in order to obtain a sample of the required product. Epoxidation proceded smoothly at room temperature (76% yield when purified by flash chromatography using 2:1 hexane / ethyl acetate as eluent), however, upon heating the reaction mixture only a small amount of the required acetal **17** was formed, along with a large number of byproducts.

Dihydroxylation of **14** using OsO_4 and NMO (scheme 31) afforded the more reactive diol **125** in 94% yield, which was subsequently cyclised to **17** using *p*-TSA (5-10 mg) as catalyst. Cyclisation and purification of the acetal proved to be problematic, with both the sensitivity of the cyclisation reaction to the presence of water and the volatility of the product **17** presenting difficulties which had to be overcome before a satisfactory yield could be achieved. The cyclisation was therefore carried out in the presence of activated, powdered molecular sieves using recrystallised *p*-TSA and dry dichloromethane. The reaction was quenched *via* the addition of solid $NaHCO_3$ and the entire mixture filtered through a plug of flash silica using 1:1 diethyl ether / pentane as eluent. Isolation of **17**, in 58% yield, was achieved by removal of this more volatile eluent under reduced pressure at 0°C.

Scheme 31



14 **125** **17**

Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O, 0°C, 6h (94%); (ii) *p*-TSA, CH_2Cl_2, powdered molecular sieves, RT, 1h (58%).

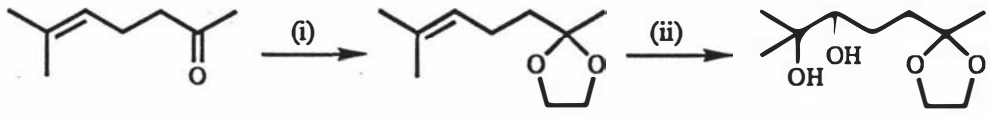
2.1.2 Use of the Asymmetric Dihydroxylation in the Synthesis of 17

With the racemic acetal **17** in hand, attention was turned to the asymmetric dihydroxylation of **14** in order to obtain each enantiomer. The attempted dihydroxylation of **14** using AD-mix-α or AD-mix-β was unsuccessful as no reaction occurred. Addition

of methanesulphonamide, reported by Sharpless *et al*[81] to speed hydrolysis of the osmate ester when dihydroxylating tri- or 1,2-disubstituted double bonds, did lead to formation of the required diol **125**, but the reaction was sluggish and did not proceed to completion. Since the AD-mixes contain only 0.6% by weight ligand and osmium salt, it was thought that by increasing the concentrations of these components in the reaction mixture, an increase in yield might be achieved. The method of Sharpless and Crispino[134] was therefore employed, using 1 mol% OsO_4, 5 mol% phthalazine ligand [$(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL] and 1 equivalent of methane-sulphonamide. This resulted in much improved yields.

Using the above method an aqueous workup is required to remove the methane-sulphonamide (2 x 1 M KOH washes). The highly polar keto-diol **125** was difficult to isolate from this medium, thus the ketone was protected as acetal **132** (in 73% yield) which then underwent dihydroxylation, resulting in an improved 94% yield for diol **133** (scheme 32).

Scheme 32

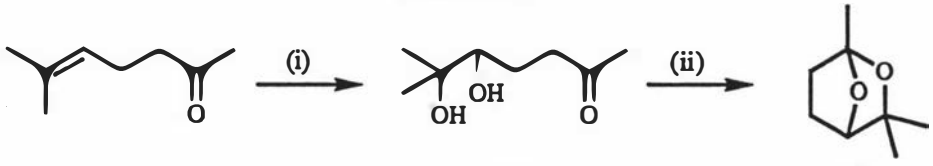


14 **132** **133**

Reagents and conditions: (i) ethylene glycol, *p*-TSA, benzene, reflux, 4h (73%); (ii) $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, OsO_4, 1:1 t-BuOH/H_2O, 0°C, 6h (94%).

Unfortunately, although there was precedent for the cyclisation of diol-acetal **133** to acetal **17** to proceed in high yield[133], it did not occur. Several different methods were attempted; CF_3COOH / dichloromethane, SiO_2 / dichloromethane and 0.75 equivalents of *p*-TSA at room temperature for a number of hours or heating under reflux for 0.5 h. In each case, either no reaction occurred, or no isolable products were detected.

Scheme 33



14 **125** **17**

Reagents and conditions: (i) $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, OsO_4, 1:1 t-BuOH/H_2O, 0°C, 6h (72% or 77%); (ii) *p*-TSA, CH_2Cl_2, powdered molecular sieves, RT, 1h (58% or 64%).

Thus, the dihydroxylation of the unprotected ketone **14** proved the most profitable route

(Scheme 33). The aqueous workup was modified, using a minimal amount of 1 M KOH (2 x 5 ml) to remove the methanesulphonamide and a more polar solvent (ethyl acetate) with which to extract the product **17**. These optimised conditions afforded keto-diol **125** in 72% (using $(DHQ)_2$-PHAL) or 77% (using $(DHQD)_2$-PHAL) and are detailed, along with yields and optical rotations in table 9.

Table 9: The Asymmetric Dihydroxylation of Ketone **14**

	Yield 125	$[\alpha]_D$	Yield 17	$[\alpha]_D$
$(DHQ)_2$-PHAL	77%	-10.6	58%	-29.0
$(DHQD)_2$-PHAL	72%	+10.2	64%	+27.7

2.2 Characterisation of Bicyclic Acetal (17)

The ^1H nmr spectrum of the product isolated from the cyclisation of keto-diol **125** exhibited three singlets, each integrating for 3 protons, at δ1.20, δ1.26 and δ1.58. The peaks at δ1.20 and δ1.26 represent the two 3-methyl groups, whereas the peak at δ1.58 is the 1-methyl which is relatively deshielded, being β to two oxygen atoms. 5-H and 6-H resonated as a multiplet located at δ1.60–δ2.09 and 4-H resonates as a doublet (J=4.2 Hz) at δ4.22. Literature values for these ^1H nmr shifts[128,131] differ slightly from the current work (table 10), however, all values are similar, the required multiplicities are present, and the value of the coupling constant for 4-H is in agreement with that previously reported. Thus, it seems likely that the difference is probably due to the different conditions under which each spectrum was recorded.

Table 10: ^1H nmr Shifts (ppm) for Bicyclic Acetal **17**

Proton	Gaoni[3,a]	Ishihara et al[6,b]	270MHz[c]	200MHz[d]
1-Me	1.47	1.45	1.58	1.53
3-Me	1.11	1.01	1.20	1.15
3-Me	1.18	1.17	1.26	1.21
4-H	4.09	4.04 (J=4.2)	4.22(J=4.2)	4.16(J=4.2)
5-H, 6-H	1.35-2.26	1.30-2.28	1.60-2.09	1.54-2.06

Table: a: 60 MHz, CCl_4, 30°C; b: 60 MHz, CCl_4, RT; c: 270 MHz, $CDCl_3$, RT; d: 200 MHz, $CDCl_3$, RT; all values in ppm relative to TMS.

The major peaks in both the IR[131] and mass spectra[20] were in agreement with the literature and a molecular ion, at *m/z* 142, was obtained confirming the molecular formula $C_8H_{14}O_2$. In the ^{13}C nmr, three peaks representing the 3-methyl and 1-methyl groups were observed. In addition, C-5 and C-6 resonated at δ24.7 and δ35.3 and were assigned using DEPT spectra. The quaternary carbon at δ80.3 and the methine carbon at δ83.5 were assigned to C-3 and C-4 respectively and a resonance at δ109.2 was indicative of the acetal carbon C-1 in structure **17**. No carbonyl peak was observed in either the ^{13}C nmr or the IR spectrum, confirming that cyclisation had indeed occurred. A HETCOR nmr spectrum was also obtained and this showed the expected correlations between the respective carbons and hydrogens.

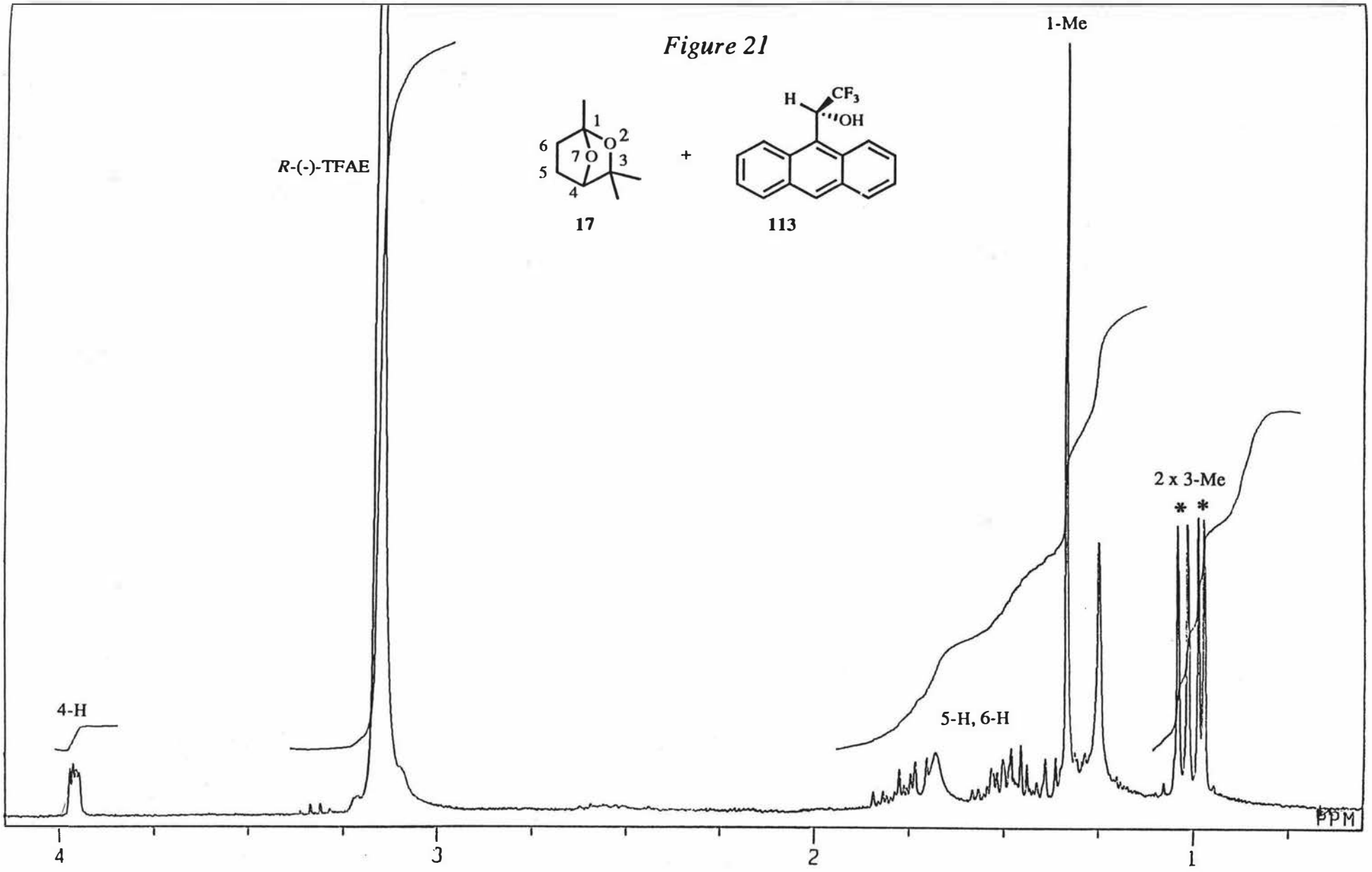
2.3 Measurement of the Enantiomeric Excess of (17)

2.3.1 Use of *R*-(-)-2,2,2-Trifluoro-1-(9-anthryl)ethanol **110**

The first method employed to determine the enantiomeric excess of acetal **17**, was the use of a chiral solvating agent; *R*-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol **113** [*R*-(-)-TFAE]. Chiral aryltrifluoromethylcarbinols are known to render the nmr spectra of enantiomers "non-equivalent" for a number of solute types, including enantiomeric benzylic, allylic or propargylic alcohols and their ethers[122a] as well as lactones[122b].

Initially, the work was carried out using the racemic acetal (±)-**17**, in order to investigate how much chiral solvent would be required to achieve resolution of the enantiomers. Satisfactory resolution of the two enantiomers was obtained upon the addition of seven equivalents of *R*-(-)-TFAE (figure 21) wherein the resonances for both of the 3-methyl groups, at δ1.20 and δ1.26, separated into two peaks due to the different solute/solvent interactions for the individual enantiomers. The other peaks in the spectrum were shifted slightly but remained unresolved. When this same amount of *R*-(-)-TFAE was added to the separate enantiomers, the enantiomeric excesses were calculated to be 87% for (-)-**17** and between 91% and 95% for (+)-**17**. The ee for (+)-**17** was obtained as a range because baseline and peak width variations meant that the higher the ee, the less accurate the calculation. The difference in ee for (-)-**17** is directly attributable to the non-enantiomeric relationship between the two phthalazine ligands used in the asymmetric dihydroxylation reaction. Crispino and Sharpless[108] also observed a lower ee using the $(DHQ)_2$-PHAL ligand (as opposed to the $(DHQD)_2$-PHAL ligand) when they carried out the AD of methyl farnesoate **48**.

Figure 21



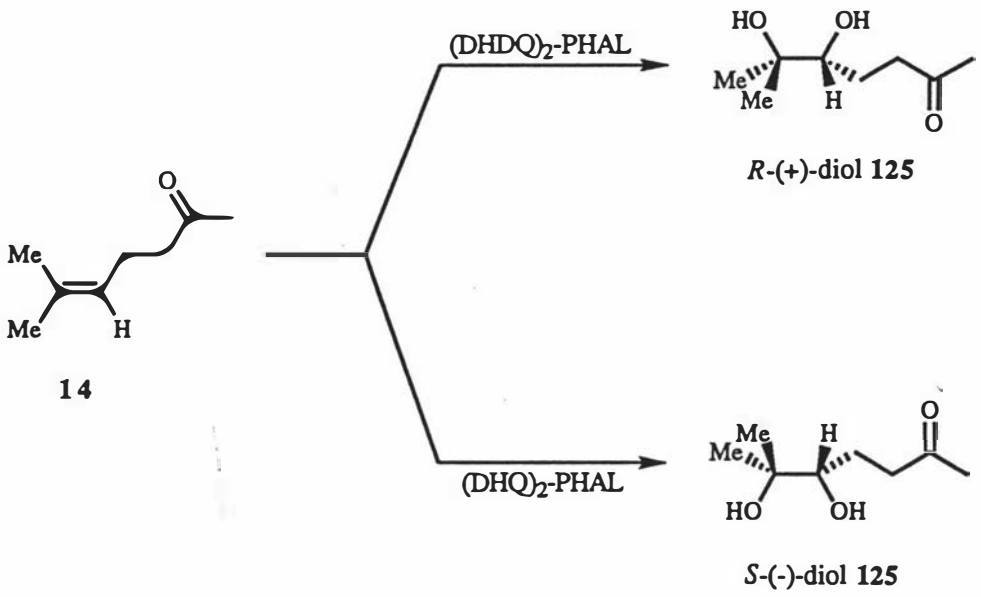
17 + **113**

(±)-1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane (17)

2.3.2 Use of Mosher Ester Derivatives to Determine Enantiomeric Excess

The second method used to determine the enantiomeric excess of **17** was to make the Mosher ester[112] derivatives of the chiral diols (+)-**125** and (-)-**125**. The two derivatives were synthesised by dissolving the diol in pyridine, adding triethylamine, DMAP and Mosher's acid chloride **112** and stirring at room temperature for 1.5 hours. The ^{1}H nmr spectra of the Mosher esters **134a** and **134b** (figures 22 and 23) allowed more accurate calculation of the enantiomeric excesses, due to better peak resolution and a cleaner spectrum. Differences between the peaks of up to 0.05 ppm (table 11) were observed, and ee calculations based on 1-H (* on figures 22 and 23) confirmed 95% ee for *R*-(+)-**125** and 86% for *S*-(-)-**125** (scheme 34), in agreement with those values obtained using the chiral solvent **113**.

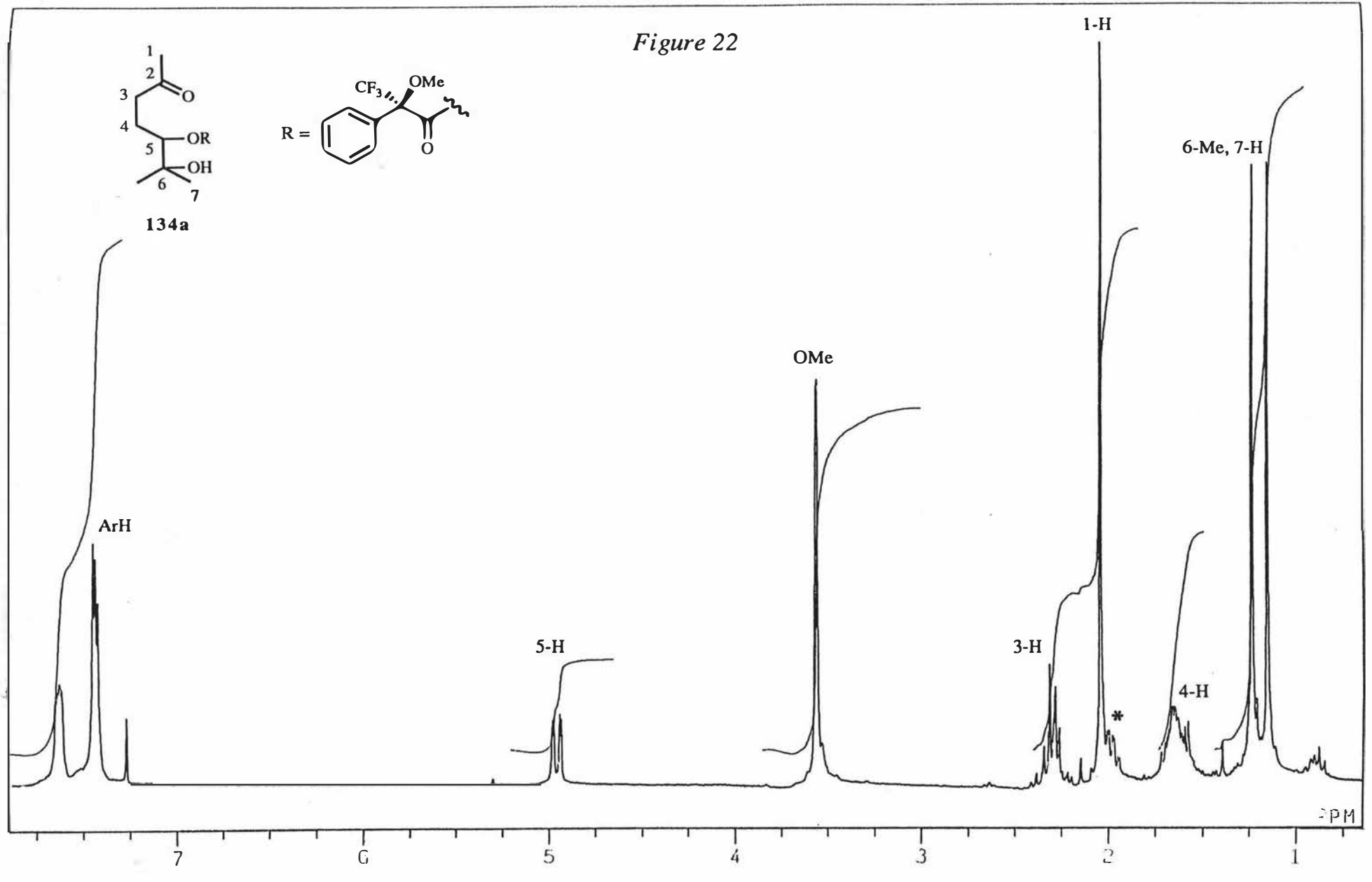
Scheme 34



The ^{19}F nmr spectra of the two Mosher esters **134a** and **134b** were also obtained. The values for the ee calculated from these spectra are considered to be more accurate, due to the absence of any other peaks in the spectrum. Two peaks at -71.25 and -71.08 ppm relative to $CFCl_3$ were observed for the diastereomeric mixture of Mosher esters **134a** and **134b** obtained from racemate (±)-**125**. Calculation using the peak integrations for the enantiomers revealed an ee of 98% for *R*-(+)-**125** and 89% for *S*-(-)-**125**, in excellent agreement with the above two methods (table 12).

One possible disadvantage of using the unprotected ketone **14** for the AD substrate (as opposed to the protected ketone **132**), however, was that a remote carbonyl functionality may lower the observed enantiomeric excess[133,135].

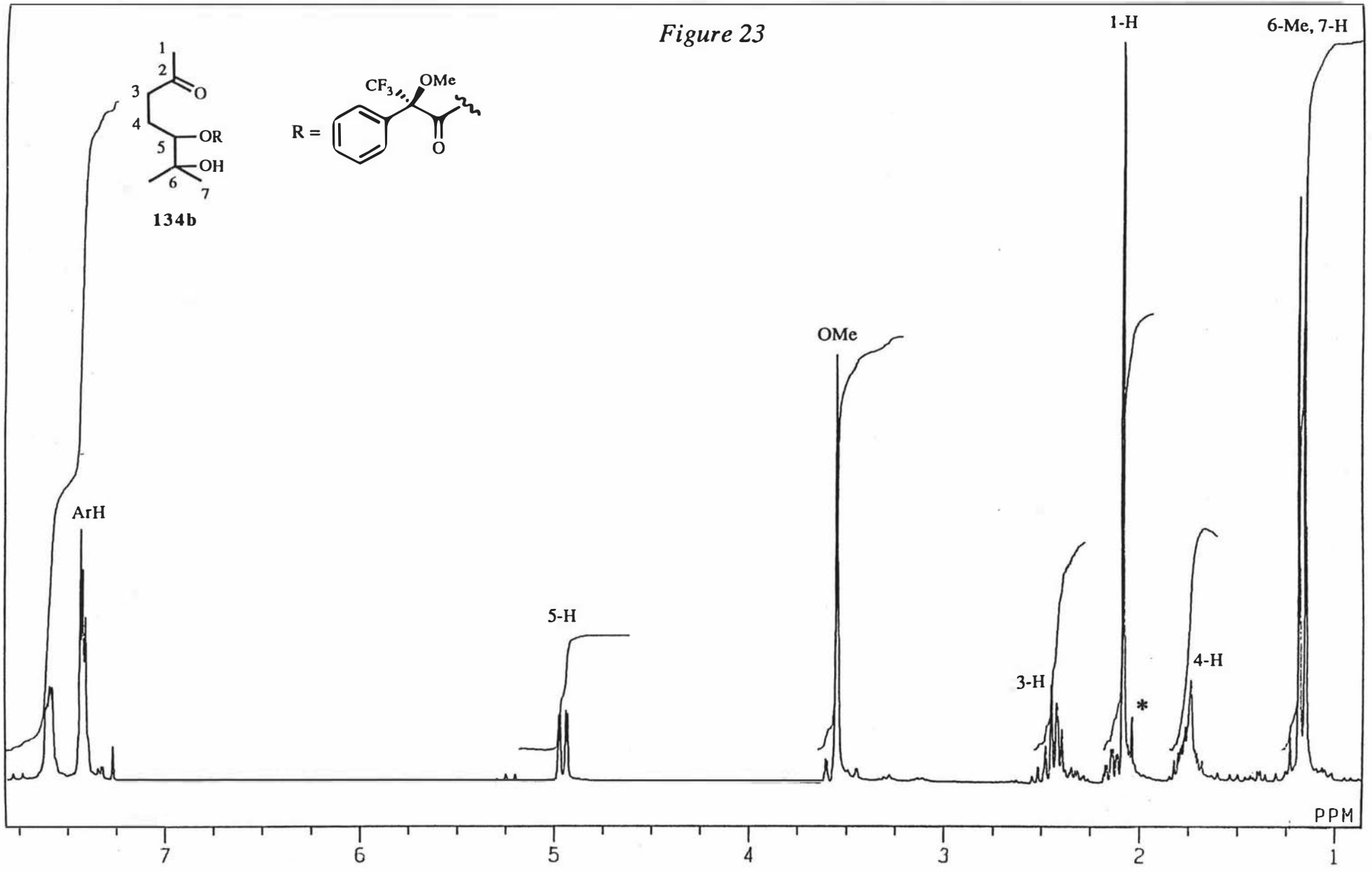
Figure 22



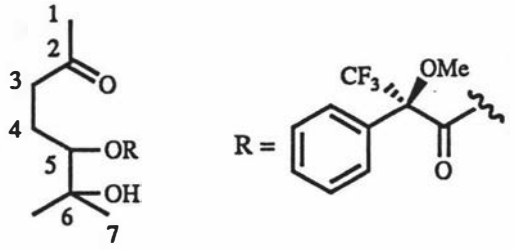
134a

6-Hydroxy-6-methyl-2-oxo-hept-5-yl α-methoxy-α-(trifluoromethyl)phenylacetate (134a)

Figure 23



6-Hydroxy-6-methyl-2-oxo-hept-5-yl α-methoxy-α-(trifluoromethyl)phenylacetate (134b)



134a,b

Table 11: Chemical Shifts of Mosher Esters **134a** and **134b**

	Chemical Shift (ppm)	
Proton	**$(DHQ)_2$-PHAL**	**$(DHQD)_2$-PHAL**
1-H	2.09, s	2.05, s
3-H	2.40-2.45, m	2.27-2.32, m
4-H	1.74-1.77, m	1.63-1.66, m
5-H	4.95, d	4.95, d
6-Me, 7-H	1.16, 1.19, s	1.16, 1.24, s
OMe	3.55, s	3.57, s
Ar	7.41-7.61, m	7.42-7.63, s

Table: s=singlet, d=doublet, m=multiplet; spectra recorded in $CDCl_3$ at 270 MHz; data in ppm relative to TMS.

Table 12: Calculated Enantiomeric Excesses

	Enantiomeric Excess	
Method	**$(DHQ)_2$-PHAL**	**$(DHQD)_2$-PHAL**
R-(-)-TFAE	91-95%	87%
Mosher ^1H	95%	86%
Mosher ^{19}F	98%	89%

Soderquist and Rane[133] overcame this problem *via* protection of the ketone as an acetal, whereas Sharpless and Crispino[134] carried out the AD on a diene followed by conversion of the less reactive monosubstituted alkene to an aldehyde *via* ozonolysis. The enantiomeric excesses in the current work, discussed above, were higher than those obtained by Soderquist and Rane[133] when they carried out the reaction using the

unprotected ketone, and indeed were more consistent with those observed when they carried out the reaction using the protected ketone[133].

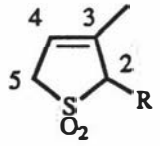
Thus the synthesis of 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane **17** has been carried out efficiently and enantioselectively, using the Sharpless asymmetric dihydroxylation to induce chirality in the product. With the desired acetal **17** in hand, biological testing to investigate the origin (biosynthetic or autoxidative) and the quantity of this compound on apples can be carried out, as well as investigating its possible implication in the occurrence of superficial scald.

PART 4: EXPERIMENTAL AND REFERENCES

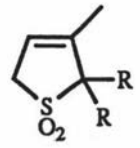
1. EXPERIMENTAL

$[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1} and concentrations are expressed in mol L^{-1}. IR spectra were recorded on a Bio-Rad FTS 40V spectrophotometer as Nujol mulls or thin films between sodium chloride discs. ^1H nmr spectra were recorded at 270 MHz in $CDCl_3$ using tetramethylsilane as internal standard on a JEOL GX270 spectrometer. ^{13}C nmr spectra were recorded at 67.8 MHz on a JEOL GX270 spectrometer. ^{19}F nmr spectra were recorded at 282 MHz in $CDCl_3$ using $CFCl_3$ as internal standard on a Bruker AC300 spectrometer. All chemical shift values are given in parts per million (ppm) and *J* values are given in Hz. Mass spectra and accurate mass measurements were recorded on a VG70-250S double focussing magnetic sector mass spectrometer with an ionisation potential of 70 eV. GC/MS used a 30 m by 0.25 mm i.d. DB1 column (0.25 μm film thickness) with a temperature program from 40°C (5 min), then 5°C/min to 280°C (10 min); injector temperature 180°C, mass spectral interface 180°C with 1 s scans and a 0.2 s delay. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography. Thin-layer chromatography (tlc) was carried out on precoated silica gel plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence or vanillin in methanolic sulphuric acid. All compounds were obtained as unstable oils for which purity and elemental composition were determined by high resolution GC/MS and/or high resolution electron impact directly or, in the case of unstable diols,*via* conversion to the corresponding acetonide.

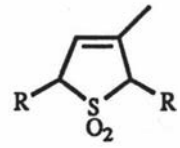
(2'*E*)-2,5-Bis(3',7'-dimethylocta-2',6'-dienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide (32), (2'*E*)-2,2-Bis(3',7'-dimethylocta-2',6'-dienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide (31) and (2'*E*)-2-(3',7'-dimethylocta-2',6'-dienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide (30)



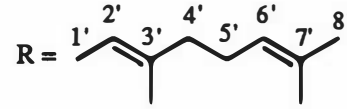
30



31



32



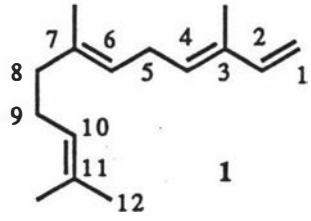
The *title* compounds were prepared from 2,5-dihydro-3-methylthiophen-1,1-dioxide (1 g, 7.57 mmol) **29** by alkylation with geranyl bromide according to the procedure described by Fielder *et al* [41] affording a pale yellow oil which was purified by flash chromatography using hexane-ethyl acetate (10:1) as eluent to give (i) *(2'E)-2,5-bis-(3',7'-dimethyloctadienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide* **32** (16.3 mg,

0.8%) (Found: M^+, 404.2756. $C_{25}H_{40}O_2S$ requires *M*, 404.2749); δ_H (270 MHz, $CDCl_3$) 1.60-1.69 (18 H, m, br, 2 x 3'-Me, 2 x 7'-Me and 8'-H), 1.82 (3 H, s, br, 3-Me), 1.97-2.13 (8 H, m, br, 2 x 4'-H and 2 x 5'-H), 2.26-2.67 (4 H, m, 2 x 1 '-H), 3.45-3.64 (2 H, m, br, 2-H and 5-H), 5.02-5.28 (4 H, m, 2 x 2'-H and 2 x 6'-H) and 5.55-5.60 (1 H, s, br, 4-H); *m/z* 404 (M^+, 3%), 339 (12), 203 (18), 147 (33), 123 (37), 109 (41), 93 (45), 81 (90), 69 (100), 55 (39) and 41 (99).

(ii) *(2'E)-2,2-Bis(3',7'-dimethylocta-2',6'-dienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide* **31** (35.2 mg, 1.7%) (Found: M^+, 404.2706. $C_{25}H_{40}O_2S$ requires *M*, 404.2749); δ_H (270MHz, $CDCl_3$) 1.60-1.67 (18 H, m, 2 x 3 '-Me, 2 x 7'-Me and 8'-H), 1.80 (3 H, s, 3-Me), 1.98-2.12 (8 H, m, br, 2 x 4'-H and 2 x 5'-H), 2.43-2.69 (4 H, m, 2 x 1'-H), 3.50-3.56 (2 H, s, br, H-5), 5.02-5.10 (2 H, m, br, 2 x 6'-H), 5.24 (2 H, t, *J* 7.1, 2 x 2'-H) and 5.71 (1 H, s, br, 4-H); *m/z* 404 (M^+, 1%), 339 (11), 270 (5), 159 (8), 109 (17), 69 (100) and 41 (99).

(iii) (2'*E*)-2-(3',7'-dimethylocta-2',6'-dienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide **30** (1.80 g, 89%) (Found: M^+, 268.1496. $C_{15}H_{24}O_2S$ requires *M*, 268.1497); υ_{max} (film) /cm^{-1} 3048 ($CH=CH_2$), 1442 [$C=C(CH_3)_2$], 1311 and 1116 (SO_2). δ_H (270MHz, $CDCl_3$) 1.57 (3 H, s, 3'-Me), 1.63 (6 H, s, 7'-Me, 8'-H), 1.82 (3 H, s, 3-Me), 1.97-2.06 (4 H, m, 4'-H and 5'-H), 2.45-2.63 (2 H, m, br, 1'-H), 3.43-3.51 (1 H, m, br, 2-H), 3.55-3.73 (2 H, m, br, 5-H), 4.98-5.06 and 5.15-5.22 (2 H, m, br, 2'-H and 6'-H), 5.62-5.68 (1 H, m, br, 4-H); δ_C (67.8 MHz, $CDCl_3$) 16.1 (CH_3, 3'-Me), 17.5 (CH_3, 3-Me), 18.1 (CH_3, 7'-Me), 25.5 (CH_3, C-8'), 26.2 (CH_2, C-1' and C-5'), 39.5 (CH_2, C-4'), 55.5 (CH_2, C-5), 67.1 (CH, C-2), 117.0 (CH, C-4), 118.1 (CH, C-2'), 123.8 (CH, C-6'), 131.1 (quat., C-7'), 138.6 and 138.7 (both quat., C-3 and C-3'); *m/z* 268 (M^+, 5%), 253 (1, M-CH_3), 225 (12), 204 (7, M-SO_2), 203 (28), 160 (15), 132 (33), 134 (39), 119 (40), 107 (28), 93 (58), 81 (27), 69 (100), 55 (32) and 41 (63).

(3*E*,6*E*)-3,7,11-Trimethyldodeca-1,3,6,10-tetraene (1) [α-Farnesene]

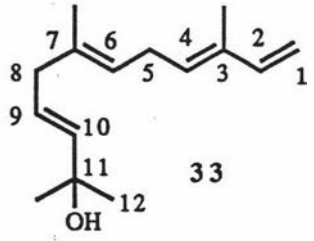


1

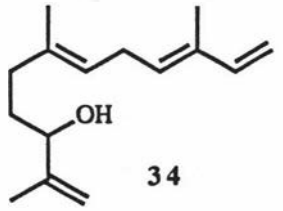
α-Farnesene **1** was prepared by heating sulpholene **30** (607mg, 2.27mmol) under reflux in toluene. Purification by flash chromatography using pentane as eluent afforded α-farnesene **1** (448mg, 97%) as a colourless, mobile oil. υ_{max} (film) /cm^{-1} 3087 ($CH=CH_2$), 2922 (-CH_3 and -CH_2) and 1639, 1609 (C=C-C=C); δ_H (270MHz, $CDCl_3$)

1.60 (3 H, s, 12-H), 1.64 (3 H, s, 11-Me), 1.68 (3 H, s, 7-Me), 1.77 (3 H, s, 3-Me), 2.02-2.09 (4 H, m, 8-H and 9-H), 2.84 (2 H, t, *J* 7.1, 5-H), 4.92 (1 H, d, *J* 10.8, 1b-H), 5.05-5.13 (3 H, m, 1a-H, 6-H, 10-H), 5.46 (1 H, m, 4-H) and 6.37 (1 H, dd, $J_{2,1b}$ 10.8, $J_{2,1a}$ 17.2, 2-H); δ_C (67.8MHz, $CDCl_3$) 11.7 (CH_3, 3-Me), 16.1 (CH_3, 7-Me), 17.6 (CH_3, 11-Me), 25.7 (CH_3, C-12), 26.7 (CH_2, C-9), 27.2 (CH_2, C-5), 39.6 (CH_2, C-8), 110.5 (CH_2, C-1), 122.1 (CH, C-6), 124.3 (CH, C-10), 131.3 (quat., C-11), 131.8 (CH, C-4), 133.7 (quat., C-3), 135.8 (quat., C-7) and 141.5 (CH, C-2); *m/z* 204 (M^+, 3%), (3, M -CH_3), 123 (20), 119 (28), 107 (38), 105 (17), 93 (100), 91 (25), 79 (35), 69 (59), 55 (52) and 41 (78). All mass spectra, IR, ^1H nmr and ^{13}C nmr data were in agreement with the literature[4,35].

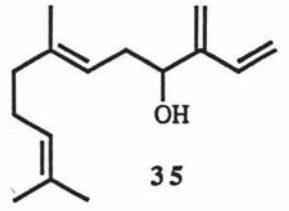
7,11-Dimethyl-3-methylenedodeca-1,6,10-trien-4-ol (35), 3,7,11-trimethyldodeca-1,3,5,10-tetraen-7-ol (3), 3,7-dimethyl-11-methylenedodeca-1,3,6-trien-10-ol (34) and 3,7,11-trimethyldodeca-1,3,6,9-tetraen-11-ol (33)†



33



34

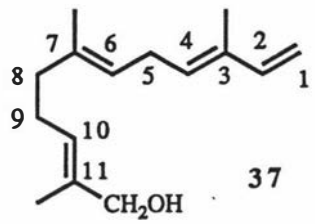


35

A solution of α-farnesene **1** (183 mg, 0.90 mmol) in acetonitrile (5ml) was irradiated for three fifteen minute periods with a 250W tungsten lamp in the presence of the dye, Rose-Bengal (5 mg). A small amount of 2,6-di-*t*-butyl-*p*-cresol (1-2 mg) was added to stabilise the solution, then the acetonitrile removed under reduced pressure. Ethyl acetate (5 ml) was added to the residue, followed by a 0.1M solution of triphenylphosphine in ethyl acetate (0.1 ml) and the mixture stirred for five minutes. Following removal of the solvent under reduced pressure, the residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to yield 7,11-dimethyl-3-methylenedodeca-1,6,10-trien-4-ol **35** and 3,7,11-trimethyldodeca-1,3,5,10-tetraen-7-ol **3** as an inseparable mixture (5:3) (29.2 mg, 15%), 3,7-dimethyl-11-methylenedodeca-1,3,6-trien-10-ol **34** (17.4 mg, 9%) and 3,7,11-trimethyldodeca-1,3,6,9-tetraen-11-ol **33** (24.2 mg, 12%), as colourless oils for which the mass spectra, uv data and ^1H nmr data were in agreement with the literature[18,19].

† The nomenclature of the acyclic derivatives of α-farnesene has been adapted to preserve a common numbering system with the systematic name of α-farnesene; 3,7,11-trimethyldodeca-1,3,6,10-tetraene.

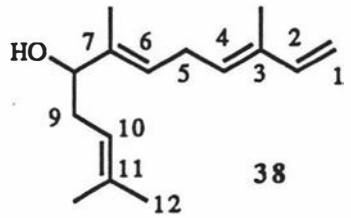
3,7,11-Trimethyldodeca-1,3,6,10-tetraen-12-ol (37)



37

The title compound was prepared by the portionwise addition of SeO_2 (90mg, 0.81 mmol) to a solution of α-farnesene **1** (227mg, 1.11 mmol) in 95% aqueous ethanol (10ml). The solution was maintained at 80°C for 20 minutes, then the solvent removed under reduced pressure. The residue was extracted with diethyl ether (2 x 10ml) and the resultant extract filtered. Removal of the solvent at reduced pressure followed by flash chromatography using hexane-ethyl acetate (9:1) as eluent yielded 3,7,11-trimethyldodeca-1,3,6,10-tetraen-12-ol **37** as pale yellow oil (7.3 mg, 3%) (Found: M^+, 220.1824. $C_{15}H_{24}O$ requires *M*, 220.1827); υ_{max} (film) /cm^{-1} 3366 (OH), 3084 ($CH=CH_2$), 1635 and 1587 (C=C-C=C), 1439 and 1375 [$CH=C(CH_3)_2$], 833 and 994 ($CH=CH_2$). δ_H (270MHz, $CDCl_3$) 1.61 (1 H, s, OH), 1.64 (3 H, s, 11-Me), 1.66 (3 H, s, 7-Me), 1.76 (3 H, s, 3-Me), 2.03-2.16 (4 H, m, 8-H and 9-H), 2.84 (2 H, t, *J* 7.3, 5-H), 3.99 (2 H, s, 12-H), 4.93 (1 H, d, *J* 10.8, 1b-H), 5.06-5.14 (2 H, m, 6-H and 1a-H), 5.38-5.45 (2 H, m, 10-H and 4-H) and 6.37 (1 H, dd, $J_{2,1b}$ 10.8, $J_{2,1a}$ 17.5, 2-H); δ_C (67.8 MHz, $CDCl_3$) 11.7 (CH_3, 3-Me), 13.7 (CH_3, 11-Me), 16.1 (CH_3, 7-Me), 26.1, 27.2 (both CH_2, C-5 and C-9), 39.2 (CH_2, C-8), 69.0 (CH_2, C-12), 110.7 (CH_2, C-1), 122.3 (CH, C-6), 125.9 (CH, C-10), 131.7 (quat., C-11), 133.8 (quat., C-3), 134.8 (CH, C-4), 135.3 (quat., C-7) and 141.5 (CH, C-2); *m/z* 220 (M^+, 11%), 202 (12, M- H_2O), 187 (18, M-H_2O,CH_3), 134 (46), 107 (45), 93 (100), 55 (55) and 43 (45).

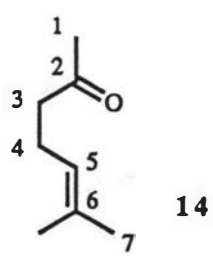
3,7,11-Trimethylodeca-1,3,6,10-tetraen-8-ol (38)



38

To a stirred solution of α-farnesene **1** (184 mg, 0.90 mmol) in dichloromethane/methanol (1:1, 10 ml) was added portionwise, *N*-methylmorpholine-*N*-oxide (399 mg, 3.41 mmol) followed by SeO_2 (94 mg, 0.85 mmol). The solution was heated under reflux for 6 h, then cooled and filtered through Celite. The solvent was removed under reduced pressure, and the residue extracted with diethyl ether (50 ml). The ethereal extract was washed with H_2O (1 x 20 ml), brine (20 ml) and dried over anhydrous $MgSO_4$. After removal of the diethyl ether under reduced pressure the resulting orange oil was further purified by flash chromatography using hexane-ethyl acetate (9:1) as eluent to yield *3,7,11-trimethyldodeca-1,3,6,10-tetraen-8-ol* **38** (2.3 mg, 1%) as a colourless oil (Found M^+, 220.1830. $C_{15}H_{24}O$ requires *M*, 220.1827); δ_H (270MHz, $CDCl_3$) 1.59 (1 H, s, OH), 1.64 (3 H, s, 12-H), 1.67 (3 H, s, 11-Me), 1.72 (3 H, s, 7-Me), 1.77 (3 H, s, 3-Me), 2.10-2.15 (2 H, m, 9-H), 2.84 (2 H, t, *J* 7.1, 5-H), 3.98-4.00 (1 H, t, br, 8-H), 4.93 (1 H, d, *J* 10.6, 1b-H), 5.06-5.12 (2 H, m, 1a-H, 6-H), 5.38-5.46 (2 H, m, 4-H, 10-H) and 6.36 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); *m/z* 220 (M^+, 1%), 202 (2, $M-H_2O$), 151 (12), 133 (12), 105 (13), 93 (19), 81 (100), 71 (87), 55 (22), 41 (42) and 3,7,11-trimethyl-1,3,6,10-dodecatetraen-12-ol **37** (2.5 mg, 1%) for which the ^1H nmr data was in agreement with that listed previously (page 91).

6-Methylhept-5-en-2-one (14)

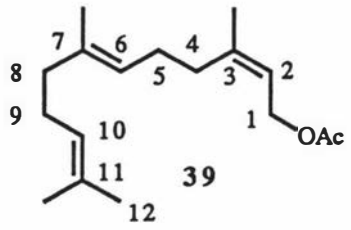


14

3,5-Dimethylpyrazole (117 mg, 1.21 mmol) was added to a suspension of CrO_3 (121 mg, 1.21 mmol) in dichloromethane (10 ml) under argon and the mixture stirred for 15 minutes. A solution of α-farnesene **1** (124 mg, 0.61 mmol) in dichloromethane (2 ml) was then added in a single portion and after a further two hours the reaction mixture was

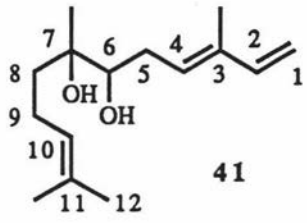
diluted with diethyl ether and filtered through Celite. The solvent was removed under reduced pressure and the crude oil purified by flash chromatography using hexane-ethyl acetate (10:1) as eluent to give 6-methylhept-5-en-2-one **14** as a colourless oil (4.8 mg, 6%). υ_{max} (film) /cm^{-1} 1710 (C=0) and 1350 [C=C(CH_3)$_2$]; δ_H (270MHz, $CDCl_3$) 1.62 (3 H, s, 6-Me), 1.67 (3 H, s, 7-H), 2.14 (3 H, s, 1-H), 2.27 (2 H, q, *J* 8.2, 4-H), 2.45 (2 H, t, *J* 7.3, 3-H) and 5.06 (1 H, m, 5-H); *m/z* 126 (M^+, 5%), 111 (12, M-CH_3), 108 (28, M-H_2O), 69 (27), 55 (29), 43 (100) and 41 (55). The infra-red, nmr and mass spectral data were identical to that of a commerical sample (Aldrich Chemical Company).

(2*Z*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate (39)



A solution of α-farnesene **1** (233 mg, 1.14 mmol) in acetic acid (5 ml) was heated under reflux in the presence of acetic anhydride (1.2 ml) and manganese triacetate (611 mg, 2.28 mmol) for 1.5 h. The reaction mixture was then diluted with water (150 ml) and extracted with diethyl ether (3 x 50 ml). The ethereal solution was washed with $NaHCO_3$ (3 x 50 ml), H_2O (1 x 50 ml), and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded a yellow-brown oil that was purified by flash chromatography using hexane-ethyl acetate (20:1) as eluent) to yield (2*Z*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate **39** as a colourless oil (13.5 mg, 4%) (Found: $(M-2)^+$, 262.1910. $C_{17}H_{28}O_2$ requires *(M-2)*, 262.1932); δ_H (270MHz, $CDCl_3$) 1.60 (6 H, s, 11-Me and 12-H), 1.67 and 1.70 (total 6 H, both s, 3-Me and 7-Me), 1.96-2.36 (11 H, m, $COCH_3$, 4-H, 5-H, 8-H and 9-H), 4.61 (2 H, d, *J* 6.6, 1-H), 5.02-5.14 (2 H, m, 6-H and 10-H) and 5.53-5.61 (1 H, m, 2-H); δ_C (67.8 MHz, $CDCl_3$) 12.8 (CH_3, 7-Me), 16.2 (CH_3, 3-Me), 17.7 (CH_3, 11-Me), 21.2 (CO<u>C</u>H_3), 25.7 (CH_3, C-12), 26.5 (CH_2, C-9), 29.7 (CH_2, C-5), 31.4 (CH_2, C-4), 39.7 (CH_2, C-8), 60.7 (<u>C</u>H_2OAc), 118.6 (CH, C-2), 121.3 (CH, C-6), 124.0 (CH, C-10), 131.5 (quat., C-11) 138.2 and 138.6 (both quat., C-3 and C-7) and 170.5 (C=0); *m/z* 262 (M^+-2, 2%), 202 (3), 159 (5), 133 (20), 83 (100), 69 (37), 55 (12) and 43 (95).

3,7,11-Trimethyldodeca-1,3,10-trien-6,7-diol (41), 3,7,11-Trimethyldodeca-1,6,10-trien-3,4-diol (42) and Acetonides (135) and (136)



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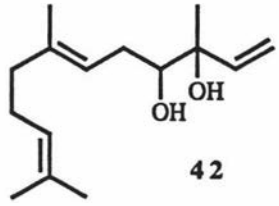

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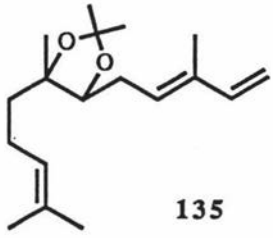

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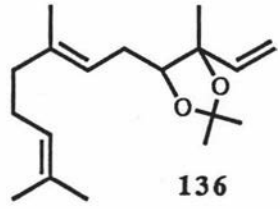


136

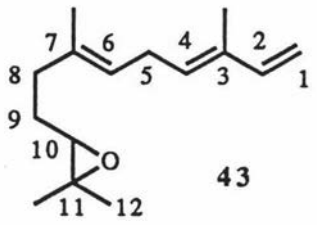
The *title* compounds were prepared by the addition of *N*-methylmorpholine-*N*-oxide (161 mg, 1.37 mmol) to an ice-cooled solution of α-farnesene **1** (234 mg, 1.15 mmol) in acetone/water (enough water to solubilise the *N*-methylmorpholine-*N*-oxide) followed by OsO_4 (0.76ml of a 2.5% w/w solution in t-butanol, 5.75 x 10^{-5} mol). Immediately after the addition of the OsO_4, the solution turned black and after 1 hour the reaction was quenched with a $Na_2S_2O_4$ solution, (0.1 M in water, 2.88 ml, 0.29 mmol) then diluted with further acetone (5 ml) and water (0.5 ml). This mixture was stirred for 0.5 h, then sufficient anhydrous $MgSO_4$ added to remove all water. The suspension was filtered through a plug of celite and the solvent removed under reduced pressure to yield a brown oil which was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford an inseparable mixture (5:1) of 3,7,11-trimethyldodeca-1,3,10-trien-6,7-diol **41** and 3,7,11-trimethyldodeca-1,6,10-trien-3,4-diol **42** (*) as a colourless oil δ_H (270MHz, $CDCl_3$) 1.16 (2.5 H, s, 7-Me), 1.26 (0.5 H, s, 3*-Me), 1.50-1.76 (7.5 H, m, OH, 7*-Me, 11-Me, 11*-Me, 12-H and 12*-H), 1.78 (2.5 H, s, 3-Me), 1.98-2.23 (4 H, m, 8-H, 8*-H, 9-H and 9*-H), 2.27-2.37 (2 H, m, 5-H and 5*-H), 3.42-3.53 (1 H, m, 4*-H and 6-H), 4.98 (0.8 H, d, *J* 10.6, 1b-H), 5.06-5.24 (2.2 H, m, 1a-H, 1b*-H, 6*-H, 10-H, 10*-H), 5.34 (0.2 H, d, *J* 17.2, 1a*-H), 5.59 (0.8 H, t, *J* 7.3, 4-H), 5.95 (0.2 H, dd, $J_{2^*,1b^*}$ 10.6, $J_{2^*,1a^*}$ 17.2, 2*-H) and 6.41 (0.8 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); δ_C (67.8 MHz, $CDCl_3$) 11.9 (CH_3, 3-Me), 15.2 (CH_3, 3-Me*), 16.2 (CH_3, 7-Me*), 17.6 (CH_3, 11-Me and 11-Me*), 21.1 (CH_3, 7-Me), 22.1 (CH_2, C-9), 25.7 (CH_2, C-12 and C-12*), 26.4 (CH_2, C-9*), 29.8 (CH_2, C-5*), 30.5 (CH_2, C-5), 38.9 (CH_2, C-8), 39.8 (CH_2, C-8*), 74.6 (CH, C-6), 75.0 (CH, C-4*), 111.4 (CH_2, C-1), 113.8 (CH_2, C-1*), 120.3 (CH, C-6*), 124.3 (CH, C-10 and C-10*), 129.0 (CH, C-4), 131.9 (quat., C-3), 136.6 (quat., C-11 and C-11*), 139.0 (quat., C-7*), 141.1 (CH,

C-2) and 142.7 (CH, C-2*)†; *m/z* 238 (M^+, 1%), 220 (2, M-H_2O), 202 (1, M-2H_2O), 127 (6), 109 (47), 95 (8), 81 (23), 69 (100), 55 (15) and 43 (40).

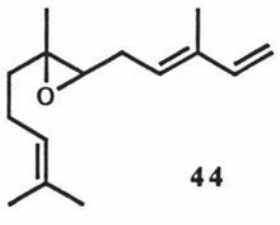
Conversion of diols **41** and **42** to the corresponding acetonides **135** and **136** was carried out as follows: To a solution of **41** and **42** (an inseparable 5:1 mixture) (32.3 mg, 1.36 x 10^{-4} mol) in acetone (3 ml) was added a catalytic amount of camphorsulphonic acid (5 mg). This mixture was allowed to stir overnight, then the solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent, to yield an inseparable mixture of acetonides **135** and **136** (5:1) as a colourless oil (33.0 mg, 88%) (Found: M^+, 278.2243. $C_{18}H_{30}O_2$ requires *M*, 278.2245); δ_H (270MHz, $CDCl_3$) 1.12 (2.5 H, s, 7-Me), 1.20 (0.5 H, s, 3*-Me), 1.34, 1.44 (both 3 H, both s, acetonide Me), 1.60-1.67 (6.5 H, m, 7*-Me, 11-Me, 11*-Me, 12-H and 12*-H), 1.77 (2.5 H, s, 3-Me), 2.04-2.28 (4 H, m, 8-H, 8*-H, 9-H and 9*-H), 2.32-2.46 (2 H, m, 5-H and 5*-H), 3.79-3.86 (1 H, m, 4*-H and 6-H), 4.97 (0.8 H, d, *J* 10.6, 1b-H), 5.06-5.15 (2.2 H, m, 1a-H, 1b*-H, 6*-H, 10-H, 10*-H), 5.33 (0.2 H, d, *J* 17.2, 1a*-H), 5.54 (0.8 H, t, *J* 7.0, 4-H), 5.83 (0.2 H, dd, $J_{2^*,1b^*}$ 10.6, $J_{2^*,1a^*}$ 17.2, 2*-H) and 6.39 (0.8 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); *m/z* 278 (M^+, 3%), 263 (5, M-CH_3), 220 (10), 139 (3), 121 (10), 112 (14), 95 (11), 79 (31), 81 (33), 69 (100), 59 (31), 55 (12) and 43 (29).

† C-3* and C-7 were obscured by the $CDCl_3$ triplet at δ76.5-77.5.

10,11-Epoxy-3,7,11-trimethyldodeca-1,3,6-triene (43), 6,7-Epoxy-3,7,11-trimethyldodeca-1,3,10-triene (44) and 3,4-Epoxy-3,7,11-trimethyldodeca-1,6,10-triene (45)



43



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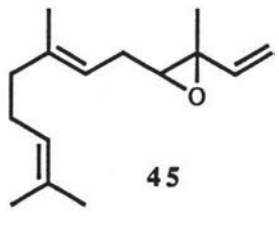


45

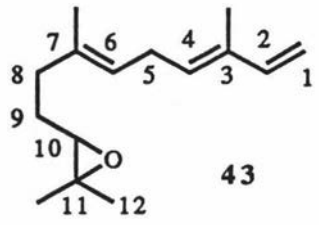
To an ice-cooled solution of α-farnesene **1** (367 mg, 1.80 mmol) in dichloromethane (20 ml), was added sodium acetate (74 mg,) and *meta*-chloroperbenzoic acid (442 mg, 1.80 mmol). The ice-bath was removed after fifteen minutes and the reaction was allowed to stir for 1 h. Activated KF (100°C, 0.1mm Hg, 1h) was then added in excess, and the resulting insoluble salt removed by gravity filtration. Removal of the solvent under reduced pressure gave an oil which was purified by flash chromatography using hexane-ethyl acetate (20:1) as eluent to yield (i) *10,11-epoxy-3,7,11-trimethyldodeca-1,3,6-*

triene **43** (118.8 mg, 30%) as a colourless oil (Found: M^+ 220.1838. $C_{15}H_{24}O$ requires *M*, 220.1827); υ_{max} (film) /cm^{-1} 3016 (C=CH), 1582 and 1544 (C=C-C=C), 1220 and 1082 (C-O) and 854 ($CH=CH_2$); δ_H (270MHz, $CDCl_3$) 1.26, 1.30 (total 6 H, each s, 12-H, 11-Me), 1.61-1.69 (5 H, m, 7-Me, 9-H), 1.76 (3 H, s, 3-Me), 2.09-2.14 (2 H, m, 8-H), 2.70 (1 H, t, *J* 6.2, 10-H), 2.84 (2 H, t, *J* 7.2, 5-H), 4.93 (1 H, d, *J* 10.6, 1b-H), 5.12 (2 H, m, 6-H, 1a-H), 5.45 (1 H, m, 4-H) and 6.35 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.6, 2-H); δ_C (67.8 MHz, $CDCl_3$) 11.7 (CH_3, 3-Me), 16.1 (CH_3, 7-Me), 18.7 (CH_3, 11-Me), 24.8 (CH_3, C-12), 27.2 (CH_2, C-5 and C-9), 36.2 (CH_2, C-8), 58.3 (quat., C-11), 64.1 (CH, C-10), 110.7 (CH_2, C-1), 122.7 (CH, C-6), 131.4 (CH, C-4), 133.8 (quat., C-3), 134.6 (quat., C-7) and 141.4 (CH, C-2); *m/z* 220 (M^+, 9%), 205 (10, M-CH_3), 187 (23, M-2xCH_3), 159 (48), 134 (52), 119 (100), 93 (87), 80 (76), 59 (51), 55 (47) and 41 (64).

(ii) *6,7-Epoxy-3,7,11-trimethyldodeca-1,3,10-triene* **44** (55.9 mg, 14%) was also isolated as a colourless oil (Found: M^+, 220.1822. $C_{15}H_{24}O$ requires *M*, 220.1827); υ_{max} (film) /cm^{-1} 3016 ($CH=CH_2$), 1577 and 1611 (C=C-C=C), 1354 and 1436 ($C=C(CH_3)_2$) and 1049 (epoxide C-O); δ_H (270MHz, $CDCl_3$) 1.30 (3 H, s, 7-Me), 1.57-1.73 (8 H, m, 8-H, 11-Me, 12-H), 1.74 (3 H, s, 3-Me), 2.06-2.13 (2 H, m, 9-H), 2.22-2.56 (2 H, m, 5-H), 2.77 (1 H, t, *J* 6.2, 6-H), 4.98 (1 H, d, *J* 10.6, 1b-H), 5.07-5.17 (2 H, m, 1a-H, 10-H), 5.51 (1 H, t, 4-H) and 6.39 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.6, 2-H); δ_C (67.8 MHz, $CDCl_3$) 11.9 (CH_3, 3-Me), 16.5 (CH_3, 7-Me), 17.7 (CH_3, 11-Me), 23.8 and 28.2 (both CH_2, C-5 and C-9), 25.7 (CH_3, C-12), 38.6 (CH_2, C-8), 60.8 (quat., C-7), 62.6 (CH, C-6), 111.6 (CH_2, C-1), 123.5 (CH, C-10), 126.9 (CH, C-4), 132.0, 136.0 (both quat., C-3 and C-11) and 141.0 (CH, C-2); *m/z* 220 (M^+, 2%), 139 (7), 119 (18), 93 (35), 81 (70), 79 (100), 69 (73), 55 (29) and 41 (69).

(iii) *3,4-Epoxy-3,7,11-trimethyldodeca-1,6,10-triene* **45** (12.7 mg, 3%) was isolated as a colourless oil (Found: M^+, 220.1833. $C_{15}H_{24}O$ requires *M*, 220.1827); υ_{max} (film) /cm^{-1} 3048 ($CH=CH_2$), 1357 and 1421 [$C=C(CH_3)_2$] and 1175 (epoxide C-O). δ_H (270MHz, $CDCl_3$) 1.42 (3 H, s, 3-Me), 1.60 (3 H, s, 12-H), 1.64 (3 H, s, 11-Me), 1.67 (3 H, s, 7-Me), 2.02-2.10 (4 H, m, 8-H, 9-H), 2.25-2.38 (2 H, m, 5-H), 2.82 (1 H, t, *J* 6.2, 4-H), 5.15-5.20 (3 H, m, 1b-H, 6-H, 10-H), 5.32 (1 H, d, *J* 17.4, 1a-H) and 5.66 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.6, 2-H); δ_C (67.8 MHz, $CDCl_3$) 14.9 (CH_3, 3-Me), 16.3 (CH_3, 7-Me), 17.7 (CH_3, 11-Me), 25.7 (CH_3, C-12), 26.5 and 27.8 (both CH_2, C-5 and C-9), 39.7 (CH_2, C-8), 59.5 (quat., C-3), 64.8 (CH, C-4), 115.8 (CH_2, C-1), 118.4 (CH, C-6), 124.0 (CH, C-10), 131.5 (quat., C-11), 138.0 (quat., C-7) and 140.9 (CH, C-2); *m/z* 236 (M^+, 3%), 220 (4, M-H_2O), 205 (7, M-H_2O, CH_3), 177 (13), 151 (17), 147 (19), 83 (17), 69 (100), 55 (13) and 41 (32). Traces of 3,4:10,11-bisepoxy-3,7,11-trimethyldodeca-1,6-diene **47** and 6,7:10,11-bisepoxy-3,7,11-trimethyldodeca-1,3-diene **46** were present but were not isolated.

10,11-Epoxy-3,7,11-trimethyldodeca-1,3,6-triene (43), 6,7-Epoxy-3,7,11-trimethyldodeca-1,3,10-triene (44) and 3,4-Epoxy-3,7,11-trimethyldodeca-1,6,10-triene (45)



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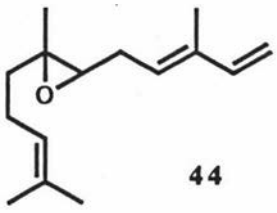

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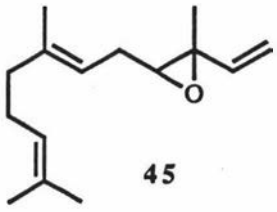

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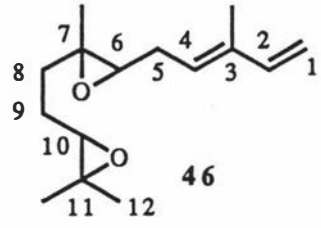
To a solution of α-farnesene **1** (539 mg, 2.64 mmol) in dichloromethane (8 ml) under argon was added a solution of dimethyldioxirane (approximately 0.1M, Adam *et al*[46]) in two 13.2 ml (0.5 equivalent) portions. The mixture was allowed to stir for 1 h, whereupon the solvent was removed under reduced pressure to yield a yellow oil which was purified by flash chromatography (1% diethyl ether in hexane) to afford 10,11-epoxy-3,7,11-trimethyldodeca-1,3,6-triene **43** (42.5 mg, 7%), 6,7-epoxy-3,7,11-trimethyldodeca-1,3,10-triene **44** (28.6 mg, 5%) and 3,4-epoxy-3,7,11-trimethyldodeca-1,6,10-triene **45** (53.5 mg, 9%) as colourless oils for which infra-red, ^{1}H nmr and mass spectra were identical to that listed previously.

3,4:10,11-Bisepoxy-3,7,11-trimethyldodeca-1,6-diene (47) and 6,7:10,11-Bisepoxy-3,7,11-trimethyldodeca-1,3-diene (46)



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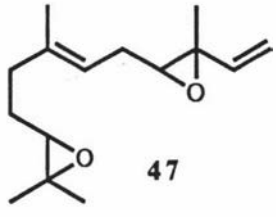


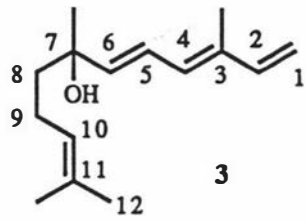
47

The procedure used was the same as that detailed for epoxides **43**, **44** and **45** except that 1.5 equivalents (225mg, 1.31 mmol) of *meta*- chloroperbenzoic acid was added to a solution of α-farnesene **1** (179 mg, 0.87 mmol) in dichloromethane (10 ml). After standard workup, the resulting oil was purified by flash chromatography using hexane-ethyl acetate (20:1) as eluent to afford *3,4:10,11-bisepoxy-3,7,11-trimethyldodeca-1,6-diene* **47** (18 mg, 9%) as a colourless oil (Found: M$^+$, 236.1776. $C_{15}H_{24}O_2$ requires *M*, 236.1776); υ_{max} (film) /cm^{-1} 3048 (epoxide C-H) and 1248 (epoxide C-O); δ_H (270MHz, $CDCl_3$) 1.24 (3 H, s, 11-Me), 1.26 (3 H, s, 12-H), 1.30 (3 H, s, 3-Me), 1.61-1.69 (5 H, m, 7-Me, 9-H), 2.12-2.37 (4 H, m, 5-H, 8-H), 2.71 (1 H, t, *J* 6.2, 10-H), 2.81 (1 H, t, *J* 6.2, 4-H), 5.17 (1 H, d, *J* 10.8, 1b-H), 5.24 (1 H, t, *J* 7.4, 6-H),

5.31 (1 H, d, *J* 17.2, 1a-H) and 5.65 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); δ_C (67.8 MHz, $CDCl_3$) 14.9 (CH_3, 3-Me), 16.3 (CH_3, 7-Me), 18.7 (CH_3, 11-Me), 24.8 (CH_3, C-12), 27.3 and 27.8 (both CH_2, C-5, C-9), 36.3 (CH_2, C-8), 58.3 and 59.5 (both quat., C-3 and C-11), 64.0 and 64.7 (both CH, C-4 and C-10), 115.8 (CH_2, C-1), 119.1 (CH, C-6), 137.2 (quat., C-7) and 140.8 (CH, C-2); *m/z* 236 (M^+, 2%), 203 (3, M-CH_3, H_2O), 121 (12), 107 (18), 93 (37), 85 (74), 83 (100), 71 (63), 59 (47), 55 (40).

(ii) *6,7:10,11-bisepoxy-3,7,11-trimethyldodeca-1,3-diene* **46** (38.5 mg, 19%) was isolated as a colourless oil (Found: M^+, 236.1784. $C_{15}H_{24}O_2$ requires *M*, 236.1776); υ_{max} (film) /cm^{-1} 3082 ($CH=CH_2$), 1609 and 1640 (C=C-C=C) and 1247 (epoxide C-O); δ_H (270MHz, $CDCl_3$) 1.27-1.32 (9 H, m, 7-Me, 11-Me, 12-H), 1.57-1.67 (4 H, m, 8-H, 9-H), 2.34-2.48 (2 H, m, H-5), 2.79 and 2.82 (2 H, both m, 6-H and 10-H), 4.99 (1 H, d, *J* 10.6, 1b-H), 5.14 (1 H, d, *J* 17.2, 1a-H), 5.51 (1 H, m, 4-H) and 6.36 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); δ_C (67.8 MHz, $CDCl_3$) 11.9 (CH_3, 3-Me), 16.5 (CH_3, 7-Me), 18.6 (CH_3, 11-Me), 24.5 and 28.0 (both CH_2, C-5 and C-9), 24.8 (CH_3, C-12), 35.2 (CH_2, C-8), 58.3 (quat., C-11), 60.3 (quat., C-7), 62.4 (CH, C-6), 63.8 (CH, C-10), 111.6 (CH_2, C-1), 126.7 (CH, C-4), 136.2 (quat., C-3) and 140.9 (CH, C-2); *m/z* 236 (M^+, 2%), 221 (2, M-CH_3), 155 (15), 119 (28), 111 (22), 93 (67), 81 (100), 71 (54), 43 (92) and 41 (81).

(3*E*,5*E*)-3,7,11-Trimethydodeca-1,3,5,10-tetraen-7-ol (3)

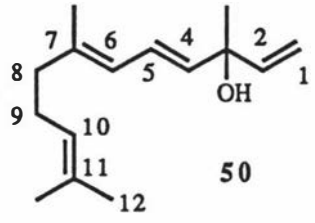


3

To a mixture of potassium *tert* -butoxide (*t*-BuOK) (88 mg, 0.78 mmol) and diisopropylamine (0.03 ml, 0.2 mmol) in dry tetrahydrofuran (1 ml) at -78°C under nitrogen was added butyllithium (0.12 ml of a 1.6 mol L^{-1} solution in hexane, 0.2 mmol) and the solution allowed to warm to -50°C for 0.25 h. A solution of epoxide **44** (43 mg, 0.2 mmol) in dry tetrahydrofuran (2 ml) was then added and the mixture allowed to warm to room temperature slowly, whereupon all of epoxide **44** had reacted (as observable by t.l.c). The solvent was removed at reduced pressure and the residue extracted with diethyl ether (2 x 10 ml). Removal of solvent at reduced pressure followed by purification by flash chromatography using hexane-ethyl acetate (4:1) as eluent afforded the title compound **3** (38.5 mg, 90%) as a colourless oil (Found: M^+, 220.1829. $C_{15}H_{24}O$

requires *M*, 220.1827); λ_{max} (hexane) /nm 251 (infl), 259, 269 and 281; υ_{max} (neat) /cm^{-1} 3363 (OH), 2922, 1608 (C=C), 967 (CH=CH) and 889 ($CH=CH_2$); δ_H (270 MHz, $CDCl_3$) 1.32 (3 H, s, 7-Me), 1.56-1.63 (6 H, m, 8-H, 11-Me, OH), 1.67 (3 H, s, 12-H), 1.88 (3 H, s, 3-Me), 2.00-2.06 (2 H, m, 9-H), 5.04 (1 H, d, *J* 10.6, 1b-H), 5.12 (1 H, m, 10-H), 5.21 (1 H, d, *J* 17.2, 1a-H), 5.81 (1 H, d, *J* 15.0, 6-H), 6.07 (1 H, d, *J* 11.4, 4-H), 6.40 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 6.58 (1 H, dd, $J_{5,4}$ 11.4, $J_{5,6}$ 15.0, 5-H); δ_C (67.8 MHz, $CDCl_3$) 12.1 (CH_3, 3-Me), 17.7 (CH_3, 11-Me), 22.9 (CH_2, C-9), 25.7 (CH_3, C-12), 28.4 (CH_3, 7-Me), 42.4 (CH_2, C-8), 73.5 (quat., C-7), 112.5 (CH_2, C-1), 123.7 (CH, C-5), 124.3 (CH, C-10), 130.8 (CH, C-4), 132.1, 135.0 (both quat., C-3, C-11), 141.2 (CH, C-2) and 141.3 (CH, C-6); *m/z* 220 (M^+, 3%), 202 (4, M-H_2O), 187 (3, M-H_2O, CH_3), 162 (15), 137 (23), 109 (16), 93 (34), 69 (35), 55 (31) and 43 (100).

(4*E*,6*E*)-3,7,11-Trimethyldodeca-1,4,6,10-tetraen-3-ol (50)

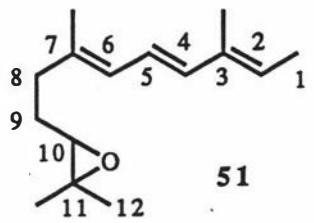


50

To a mixture of *t*-BuOK (41 mg, 0.37 mmol), tetramethylethylenediamine (0.06 ml, 0.37 mmol) and diisopropylamine (0.05 ml, 0.37 mmol) in dry tetrahydrofuran (5 ml) cooled to -78°C under nitrogen was added butyllithium (0.23 ml of a 1.6 mol L^{-1} solution in hexane, 0.37 mmol) and the solution allowed to warm to -50°C for 0.25h. A solution of epoxide **45** (53.5 mg, 0.24 mmol) in dry tetrahydrofuran (5 ml) was then added and the reaction mixture allowed to warm to room temperature slowly, whereupon all of epoxide **45** had reacted (as observable by t.l.c). The solvent was removed at reduced pressure and the residue extracted with diethyl ether (2 x 10 ml). Removal of solvent at reduced pressure followed by purification by flash chromatography using hexane-ethyl acetate (9:1) as eluent afforded the *title* compound **50** (33.4 mg, 62%) as a colourless oil (Found: M^+, 220.1821. $C_{15}H_{24}O$ requires *M*, 220.1827); λ_{max} (hexane) /nm 242; υ_{max} (neat) /cm^{-1} 3377 (OH), 2920 and 1650 (C=C-C=C); δ_H (270 MHz, $CDCl_3$) 1.40 (3 H, s, 3-Me), 1.60 (3 H, s, 11-Me), 1.68 (3 H, s, 12-H), 1.70 (1 H, s, OH), 1.76 (3 H, s, 7-Me), 1.95-2.17 (4 H, m, 8-H, 9-H), 5.07 (1 H, d, *J* 10.8, 1b-H), 5.05-5.09 (1 H, m, 10-H), 5.26 (1 H, d, *J* 17.2, 1a-H), 5.68 (1 H, d, *J* 15.4, 4-H), 5.83 (1 H, d, *J* 10.6, 6-H), 5.98 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 6.46 (1 H, dd, $J_{5,6}$ 10.6, $J_{5,4}$ 15.4, 5-H); δ_C (67.8 MHz, $CDCl_3$) 15.2 (CH_3, 7-Me), 16.6 (CH_3, 11-Me), 25.7 (CH_3,

C-12), 26.5 (CH_2, C-9), 28.0 (CH_3, 3-Me), 39.9 (CH_2, C-8), 65.8 (quat., C-3), 112.0 (CH_2, C-1), 123.8 (CH, C-6 and C-10), 124.5 (CH, C-5), 131.7 (quat., C-11), 136.1 (CH, C-4), 139.6 (quat., C-7) and 143.9 (CH, C-2); *m/z* 220 (M^+, 8%), 202 (2, M-H_2O), 109 (11), 93 (21), 69 (57), 55 (21), 43 (100) and 41 (48).

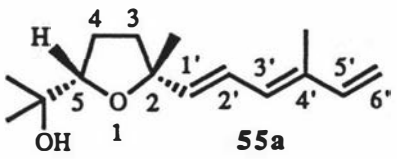
(2*E*,4*E*,6*E*)-10,11-Epoxy-3,7,11-trimethyldodeca-2,4,6-triene (51)



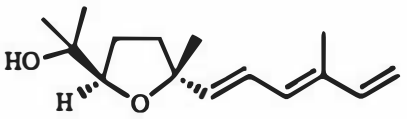
51

To a mixture of potassium *tert*-butoxide (33 mg, 0.29 mmol), tetramethylethylenediamine (0.02 ml, 0.29 mmol) and diisopropylamine (0.04 ml, 0.29 mmol) in dry tetrahydrofuran (5 ml) cooled to -78°C under nitrogen was added butyllithium (0.18 ml of a 1.6 mol L^{-1} solution in hexane, 0.29 mmol) and the solution warmed to -40°C for 0.25 h. A solution of epoxide **43** (42.5 mg, 0.19 mmol) in dry tetrahydrofuran (3 ml) was added and the mixture allowed to warm slowly to room temperature whereupon all of epoxide **43** had reacted (as observable by t.l.c). The solvent was removed at reduced pressure and the residue extracted with diethyl ether (2 x 10 ml). Removal of solvent at reduced pressure followed by purification by flash chromatography using hexane-ethyl acetate (9:1) as eluent afforded the *title* compound **51** (27.2 mg, 64%) as a colourless oil (Found: M^+, 220.1827. $C_{15}H_{24}O$ requires *M*, 220.1827); λ_{max} (hexane) /nm 236, 246, 253 and 259; υ_{max} (neat) /cm^{-1} 2976, 1623 (C=C-C=C) and 1249 (C-O); δ_H (270 MHz, $CDCl_3$) 1.26 (3 H, s, 11-Me), 1.30 (3 H, s, 12-H), 1.63-1.88 (2 H, m, 9-H), 1.74 (3 H, d, *J* 7.3, 1-H), 1.78 (3 H, s, 3-Me), 1.80 (3 H, s, 7-Me), 2.17-2.26 (2 H, m, 8-H), 2.72 (1 H, t, *J* 6.2, 10-H), 5.53-5.56 (1 H, m, 2-H), 5.91 (1 H, d, *J* 10.6, 6-H), 6.17 (1 H, d, *J* 15.4, 4-H) and 6.31 (1 H, dd, $J_{5,6}$ 10.6, $J_{5,4}$ 15.4, 5-H); δ_C (67.8 MHz, $CDCl_3$) 12.0 (CH_3, 3-Me), 14.1 (CH_3, C-1), 16.7 (CH_3, 7-Me), 18.7 (CH_3, 11-Me), 24.8 (CH_3, C-12), 27.4 (CH_2, C-9), 36.6 (CH_2, C-8), 58.4 (quat., C-11), 64.0 (CH, C-10), 122.1 (CH, C-5), 125.9 (CH, C-6), 126.5 (CH, C-2), 134.9 (quat., C-3), 136.0 (CH, C-4) and 136.4 (quat., C-7); *m/z* 220 (M^+, 38%), 148 (21), 134 (100), 121 (85), 119 (70), 107 (53), 91 (43), 79 (27), 59 (32) and 43 (45).

(2*R,5*S**,1'*E*,3'*E*)- and (2*R**,5*R**,1'*E*,3'*E*)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-(4-methylhexa-1,3,5-trienyl)tetrahydrofuran (55a) and (55b)**



55a

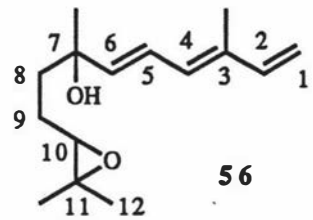


55b

To a mixture of *t*-BuOK (130 mg, 1.15 mmol) and diisopropylamine (0.04 ml, 0.26 mmol) in dry tetrahydrofuran (5 ml) under argon, cooled to -78°C was added butyllithium (10.16 ml of a 1.6 mol L^{-1} solution in hexane, 0.26 mmol) and the solution allowed to warm to -50°C for 0.25 h., then recooled to -78°C. A solution of *bis* -epoxide **46** (60 mg, 0.26 mmol) in dry tetrahydrofuran (5 ml) was then added as a single portion. The reaction mixture was left to warm slowly to room temperature. After removal of solvent at reduced pressure the residue was extracted with diethyl ether (2 x 10 ml). Removal of solvent at reduced pressure followed by purification by flash chromatography using hexane-ethyl acetate (20:1) as eluent afforded the *title* compound **55a** (21.5 mg, 36%) as a colourless oil (Found: M^+, 236.1786. $C_{15}H_{24}O_2$ requires *M*, 236.1776); λ_{max} (hexane) /nm 259, 267 and 279; υ_{max} (neat) /cm^{-1} 3448 (OH), 2970, 1613 (triene) and 1079 (C-0); δ_H (270 MHz, $CDCl_3$) 1.15 (3 H, s, 2"-H), 1.25 (3 H, s, 1"-Me), 1.36 (3 H, s, 2-Me), 1.81-1.96 (5 H, m, 3-H, 4-H, OH), 1.87 (3 H, s, 4'-Me), 3.88 (1 H, t, *J* 7.0, 5-H), 5.10 (1H, d, *J* 10.6, 6'b-H), 5.20 (1 H, d, *J* 17.2, 6'a-H), 5.85 (1 H, d, *J* 15.2, 1'-H), 6.04 (1 H, d, *J* 11.4, 3'-H), 6.41 (1 H, dd, $J_{5',6'b}$ 10.6, $J_{5',6'a}$ 17.2, 5'-H) and 6.55 (1 H, dd, $J_{2',3'}$ 11.4, $J_{2',1'}$ 15.2, 2'-H); δ_C (67.8 MHz, $CDCl_3$) 12.0 (CH_3, 4'-Me), 24.4 (CH_3, 2-Me), 26.4, 27.2 (CH_3, C-2", 1"-Me), 26.6 (CH_2, C-3), 38.6 (CH_2, C-4), 71.3 (quat., C-1"), 82.7 (quat., C-2), 85.5 (CH, C-5), 112.6 (CH_2, C-6'), 123.5 (CH, C-1'), 130.8 (CH, C-3'), 135.4 (quat., C-4') and 140.4, 141.2 (CH, C-5', C-2'); *m/z* 236 (M^+, 88%), 221 (32, M-CH_3), 177 (22), 134 (73), 127 (39), 119 (100), 105 (38), 93 (63), 81 (42), 59 (81) and 43 (59) and the *title* compound **55b** (17.6 mg, 29%) as a colourless oil (Found: M^+, 236.1774. $C_{15}H_{24}O_2$ requires *M*, 236.1776); λ_{max} (hexane) /nm 259, 266 and 279; υ_{max} (neat) /cm^{-1} 3455 (OH), 2971, 1613 (triene) and 1039 (C-0); δ_H (270 MHz, $CDCl_3$) 1.15 (3 H, s, 2"-H), 1.25 (3 H, s, 1"-Me), 1.36 (3 H, s, 2-Me), 1.74-1.95 (5 H, m, 3-H, 4-H, OH), 1.87 (3 H, s, 4'-Me), 3.88 (1 H, t, *J* 7.0, 5-H), 5.10 (1 H, d, *J* 10.6, 6'b-H), 5.20 (1 H, d, *J* 17.2, 6'a-H), 5.79 (1 H, d, *J* 15.2, 1'-H), 6.05 (1 H, d, *J* 11.2, 3'-H), 6.40 (1 H, dd, $J_{5',6'b}$ 10.6, $J_{5',6'a}$ 17.2, 5"-H) and 6.53 (1 H, dd, $J_{2',3'}$ 11.2, $J_{2',1'}$ 15.2, 2'-H); δ_C (67.8 MHz, $CDCl_3$) 12.0 (CH_3, 4'-Me), 24.2 (CH_3, 2-Me), 26.4 (CH_2, C-3), 27.2 (CH_3, C-2" and 1"-Me), 38.1 (CH_2, C-4), 71.2 (quat., C-1"), 82.9 (quat., C-2), 85.6 (CH, C-5), 112.4 (CH_2, C-6'), 123.1 (CH, C-1'), 130.7 (CH, C-3'), 135.1 (quat., C-

4') and 140.3, 141.2 (CH, C-5', C-2'); *m/z* 236 (M^+, 96%), 221 (27, M-CH_3), 177 (22), 134 (62), 119 (100), 93 (72), 81 (55), 59 (88) and 43 (79).

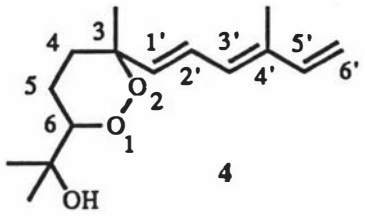
(7*R,10*R**,3*E*,5*E*)- and (7*R**,10*S**,3*E*,5*E*)-10,11-Epoxy-3,7,11-trimethydodeca-1,3,5-trien-7-ol (56)**



56

To a mixture of potassium *tert* -butoxide (8.6 mg, 0.076 mmol) and diisopropylamine (0.01 ml, 0.071 mmol) in dry tetrahydrofuran (2 ml) cooled to -78°C under argon, was added butyllithium (0.05 ml of a 1.6 mol L^{-1} solution in hexane, 0.076 mmol) and the solution warmed to -60°C for 0.25 h. then recooled to -78°C. A solution of *bis* -epoxide **46** (12.0 mg, 0.051 mmol) in dry tetrahydrofuran (2 ml) was then added in one portion and the reaction mixture warmed slowly to -30°C. After removal of solvent at reduced pressure the residue was extracted with diethyl ether (2 x 10 ml). Removal of solvent at reduced pressure followed by purification by flash chromatography using hexane-ethyl acetate (9:1) as eluent afforded the *title* compound **56** (5.8 mg, 48%) as a colourless oil and as a mixture of stereoisomers (by ^1H nmr) (Found: M^+, 236.1775. $C_{15}H_{24}O_2$ requires *M*, 236.1776); λ_{max} (hexane) /nm 250 (infl), 259, 268 and 279; υ_{max} (neat) /cm^{-1} 3440 (OH), 2966, 1615 (triene) and 1119 (C-0); δ_H (270 MHz, $CDCl_3$) 1.26 (3 H, s, 12-H), 1.30 (3 H, s, 11-Me), 1.34 (3 H, s, 7-Me), 1.57-1.88 (5 H, m, 8-H, 9-H, OH), 1.87 (3 H, s, 3-Me), 2.72-2.76 (1 H, m, 10-H), 5.04 (1 H, d, *J* 10.6, 1b-H), 5.21 (1 H, d, *J* 17.4, 1a-H), 5.76 (1 H, d, *J* 15.0, 6-H), 6.06 (1 H, d, *J* 11.4, 4-H), 6.40 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.4, 2-H) and 6.59 (1 H, dd, $J_{5,4}$ 11.4, $J_{5,6}$ 15.0, H-5); δ_C (67.8 MHz, $CDCl_3$) 12.0 (CH_3, 3-Me), 18.7 (CH_3, 11-Me), 23.7 (CH_2, C-9), 24.8 (CH_3, C-12), 28.4 (CH_3, 7-Me), 39.1 (CH_2, C-8), 59.2 (quat., C-11), 64.6 (CH, C-10), 72.8 (quat., C-7), 112.6 (CH_2, C-1), 124.1 (CH, C-6), 130.6 (CH, C-4), 135.3 (quat., C-3) and 140.9, 141.1 (CH, C-2, C-5); *m/z* 236 (M^+, 72%), 221 (29, M-CH_3), 203 (7, M-H_2O,CH_3), 177 (17), 134 (51), 119 (100), 105 (40), 93 (70), 81 (48), 59 (86) and 43 (79).

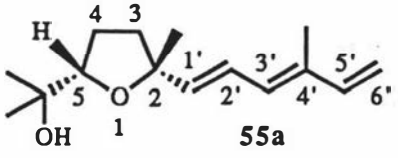
(3R*,6S*,1'E,3'E)- and (3R*,6R*,1'E,3'E)-6-(1-Hydroxy-1-methylethyl)-3-methyl-3-(4-methylhexa-1,3,5-trienyl)-2-dioxacyclohexane (4)



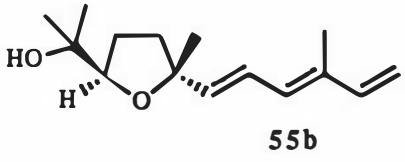
4

Oxygen was bubbled through a solution of epoxide **43** (169 mg, 0.77 mmol) in acetonitrile (5 ml) whilst irradiating for three fifteen minute periods with a 250 W tungsten lamp in the presence of Rose Bengal (5 mg). *p* -Toluenesulphonic acid (5 mg) was then added and the solution stirred for 5 min. before removing the acetonitrile at reduced pressure. Ethyl acetate (5 ml) was added to the residue followed by triphenylphosphine (0.1 ml of a 0.1 mol L^{-1} solution in ethyl acetate) and the mixture stirred for 5 min. After removal of solvent at reduced pressure the residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent affording the title compound **4** (5.8 mg, 3%) as a colourless oil and as a 4:1 mixture of stereoisomers (Found: M^+, 252.1722. $C_{15}H_{24}O_3$ requires *M*, 252.1725); λ_{max} (hexane) /nm 259, 269 and 280; δ_H (270 MHz, $CDCl_3$) 1.23, 1.29 (each 3 H, s, 2"-H, 1"-Me), 1.40 (3 H, s, 3-Me), 1.87 (3 H, s, 4'-Me) 1.70-2.05 (5 H, m, 4-H, 5-H, OH), 3.66 (0.2 H, m, 6-H*), 4.11 (0.8 H, t, *J* 6.5, 6-H), 5.04 (1 H, d, *J* 10.6, 6'b-H), 5.22 (1 H, d, *J* 17.2, 6'a-H), 5.76 (1 H, d, *J* 15.2, 1'-H), 6.05 (1 H, d, *J* 11.4, 3'-H), 6.40 (1 H, dd, $J_{5',6'b}$ 10.6, $J_{5',6'a}$ 17.2, 5'-H) and 6.54 (1 H, dd, $J_{2',3'}$ 11.2, $J_{2',1'}$ 15.2, 2'-H); *m/z* 252 (M^+, 20%), 237 (9, $M-CH_3$), 177 (23), 159 (18), 133 (59), 119 (57), 105 (39), 93 (58), 81 (77), 77 (26), 55 (42) and 43 (100).

(2*R,5*S**,1'*E*,3'*E*)- and (2*R**,5*R**,1'*E*,3'*E*)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-(4-methylhexa-1,3,5-trienyl)tetrahydrofuran (55a) and (55b)**



55a

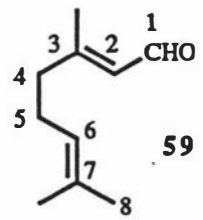


55b

To a stirred solution of 1,2-dioxacyclohexane **4** (5.8 mg, 2.30 x 10^{-5} mol) in diethyl ether (2 ml) was added lithium aluminium hydride (10 mg). After 5 min., the excess lithium aluminium hydride was removed by filtration, water (0.2 ml) added, and the

solvent removed at reduced pressure to yield a clear residue which was purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to give the title compounds **55a** and **55b** as a clear oil and as a mixture of stereoisomers (1.6 mg, 28%) for which the mass spectral, UV and ^{1}H nmr data was in aggreement with that listed earlier (page 101).

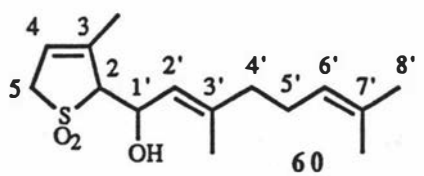
(2*E*)-3,7-Dimethylocta-2,6-dienal (59) [geranial]



59

Geranial **59** was prepared from (2*E*)-3,7-dimethylocta-2,6-dienol [geraniol] (200 mg, 1.30 mmol) *via* oxidation with MnO_2 (2.30 g, 26.0 mmol) according to the procedure described by Corey *et al*[136], affording a clear oil which was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the title compound **59** (164 mg, 83%). υ_{max} (neat) /cm^{-1} 1672 (C=O); δ_H (270 MHz, $CDCl_3$) 1.57, 1.64 (each 3H, s, 7-Me and 8-H), 2.08-2.22 (4H, m, 4-H, 5-H), 2.13 (3H, s, 3-Me), 5.00-5.05 (1H, m, 6-H), 5.83 (1H, d, *J* 8.1, 2-H) and 9.95 (1H, d, *J* 8.1, 1-H).

(2*R,1'*S**,2'*E*)- and (2*R**,1'*R**,2'*E*)-2-(1-Hydroxy-3,7-dimethylocta-2,6-dienyl)-3-methyl-2,5-dihydrothiophen-1,1-dioxide (60)**

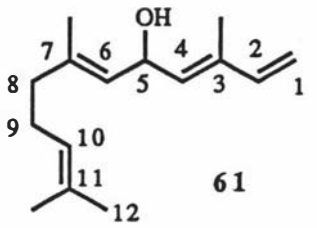


60

To a solution of 2,5-dihydro-3-methylthiophene **29** (150 mg, 1.1 mmol) in tetrahydrofuran-tetramethylethylenediamine (10:1) (10 ml) cooled to -105°C (95% ethanol / liquid air bath) under argon was added butyllithium (0.68 ml of a 1.6 mol L^{-1} solution in hexane, 1.1 mmol) dropwise. The resultant orange solution was stirred at this temperature for 0.25 h., then geranial **59** (165 mg, 1.1 mmol) was added. The reaction was stirred at -105°C for 10 min., then quenched with saturated ammonium chloride solution (1 ml) and extracted with diethyl ether (2 x 50 ml). After drying ($MgSO_4$) the solvent was removed at reduced pressure yielding a yellow oil which was purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent affording the *title*

compound **60** (199 mg, 64%) as a pale yellow viscous oil and as a mixture of diastereoisomers (Found: $(M+NH_4)^+$, 302.1813. $C_{15}H_{24}O_3S$ requires *(M+NH4)* , 302.1790); υ_{max} (neat) /cm^{-1} 3500 (OH), 2919, 1663 (C=C) and 1311, 1114 (SO_2); δ_H (270 MHz, $CDCl_3$) 1.61 (3 H, s, 3'-Me), 1.68, 1.71 (each 3 H, s, 7'-Me, 8'-H), 1.92 (3 H, s, 3-Me), 2.05-2.16 (4 H, m, 4'-H, 5'-H), 3.19 (1 H, m, br, OH), 3.56-3.81 (3 H, m, 2-H, 5-H), 4.73-4.77 (1 H, m, br, 1'-H), 5.06-5.11 (1 H, m, br, 6'-H), 5.52 (1 H, d, *J* 8.8, 2'-H) and 5.80-5.82 (1 H, s, br, 4-H); *m/z* (CI, NH_3) 302 [$(M+NH_4)^+$, 37%], 284 (22), 267 (26), 203 (100), 201 (59), 159 (21), 153 (53), 135 (47), 95 (40) and 69 (66).

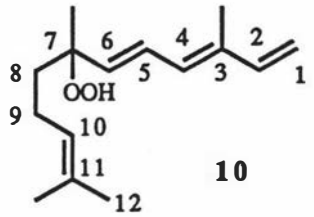
3,7,11-Trimethyldodeca-1,3,6,10-tetraen-5-ol (61)



61

A solution of sulpholene **60** (115 mg, 0.83 mmol) in xylene (5 ml) was heated under reflux for 5 min. The xylene was removed at reduced pressure, yielding a yellow oil which was purified by flash chromatography using hexane-ethyl acetate (9:1) as eluent affording the *title* compound **61** (23.7 mg, 13%) as a colourless oil (Found: M^+, 220.1823. $C_{15}H_{24}O$ requires *M*, 220.1827); λ_{max} (hexane) /nm 238; υ_{max} (neat) /cm^{-1} 3330 (OH), 2915, 1654 and 1598; δ_H (270 MHz, $CDCl_3$) 1.59 (3 H, s, 12-H), 1.67 (3 H, s, 11-Me), 1.74 (3 H, s, 7-Me), 1.82 (3 H, s, 3-Me), 2.01-2.10 (4 H, m, 8-H and 9-H), 5.05 (1 H, d, *J* 10.6, 1b-H), 5.03-5.09 (1 H, m, 10-H), 5.20 (1 H, d, *J* 17.6, 1a-H), 5.17-5.26 (1 H, m, 6-H), 5.51-5.53 (1 H, m, br, 4-H) and 6.37 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.6, 2-H); δ_C (67.8 MHz, $CDCl_3$) 12.2 (CH_3, 3-Me), 16.7 (CH_3, 7-Me), 17.7 (CH_3, 11-Me), 25.6 (CH_3, C-12), 26.3 (CH_2, C-9), 39.5 (CH_2, C-8), 65.5 (CH_2, C-5), 113.0 (CH_2, C-1), 123.8 (CH, C-6), 126.0 (CH, C-10), 131.8, 134.8, 138.7 (quat., C-3, C-7, C-11), 133.7 (CH, C-4) and 141.0 (CH, C-2); *m/z* 220 (M^+, 21%), 202 (16, M-H_2O), 159 (17), 133 (27), 105 (31), 93 (52), 81 (48), 69 (92), 55 (30) and 43 (100).

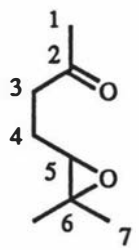
(3*E*,5*E*)-7-Hydroperoxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene (10)



10

Tlc examination (using 4:1 hexane-ethyl acetate) of a sample of α-farnesene which had been stored as the neat oil at -20°C for several months showed two UV active autoxidation products at R_f 0.70 and R_f 0.45. Purification by flash chromatography using hexane-ethyl acetate (9:1) as eluent afforded the title compound **10** (R_f 0.70) as a colourless oil (Found: M^+, 236.1769. $C_{15}H_{24}O$ requires *M*, 236.1776); λ_{max} (hexane) /nm 247 (infl), 261, 269 and 280; δ_H (270 MHz, $CDCl_3$) 1.40 (3 H, s, 7-Me), 1.58-1.70 (2 H, m, 8-H), 1.61 (3 H, s, 11-Me), 1.69 (3 H, s, 12-H), 1.89 (3 H, s, 3-Me), 1.98-2.05 (2 H, m, 9-H), 5.05-5.13 (2 H, m, 1b-H, 10-H), 5.24 (1 H, d, *J* 17.2, 1a-H), 5.76 (1 H, d, *J* 15.8, 6-H), 6.09 (1 H, d, *J* 11.4, 4-H), 6.41 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 6.58 (1 H, dd, $J_{5,4}$ 11.4, $J_{5,6}$ 15.8, 5-H); *m/z* 236 (M^+, 1%), 219 (10, M-OH), 203 (15, M-OOH, CH_3), 161 (24), 147 (16), 136 (16), 119 (27), 105 (28), 93 (47), 81 (36), 77 (26), 69 (100), 55 (42) and 43 (67). The second autoxidation product (R_f 0.45) was too unstable to characterise.

5,6-Epoxy-6-methylheptan-2-one (124)

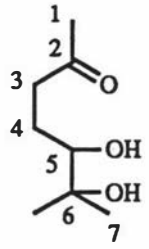


124

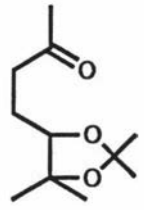
To an ice-cooled solution of 6-methylhept-5-en-2-one **14** (1.48 ml. 10 mmol) and sodium acetate (410 mg, 5 mmol) in CH_2Cl_2 (30 ml) was added, portionwise, *meta* -chloroperbenzoic acid (70%, 2.46 g, 10 mmol). The reaction mixture was allowed to stir for two hours, then activated (100°C, 1mm Hg, 1 hour) potassium fluoride (870 mg, 15 mmol) was added. After an additional ten minutes of stirring, all solids were removed by gravity filtration and the solvent removed under reduced pressure. The resultant crude oil was purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to give 5,6-epoxy-6-methylheptan-2-one **124** as a colourless oil (1.08 g, 76%) (Found: M^+,

142.0991. $C_8H_{14}O_2$ requires *M*, 142.0993); δ_C (67.8 MHz, $CDCl_3$) 18.5 (CH_3, 6-Me), 22.7 (CH_2, C-4), 24.6 (CH_3, C-7), 29.7 (CH_3, C-1), 40.0 (CH_2, C-3), 58.5 (quat., C-6), 63.1 (CH, C-5) and 207.6 (C=O, C-2); m/z 142 (M^+, 2%), 127 (7), 84 (40), 82 (26), 72 (61) and 43 (100). The IR and ^1H nmr data obtained was in agreement with the literature[128].

(±)-5,6-Dihydroxy-6-methylheptan-2-one (125) and Acetonide derivative (137)



(±)-125



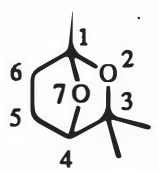
137

The *title* compound was prepared by the addition of *N*-methylmorpholine-*N*-oxide (321 mg, 2.74 mmol) to an ice-cooled solution of 6-methylhept-5-en-2-one **14** (288 mg, 2.28 mmol) in acetone/water (5 ml) (enough water to solublise the *N*-methylmorpholine-*N*-oxide) followed by OsO_4 (0.5 ml of a 2.5% w/w solution in *t*-butanol). Immediately after the addition of the OsO_4, the solution turned black, and after four hours the reaction was quenched with a $Na_2S_2O_4$ solution (0.1M in water, 1.89 ml, 0.19 mmol) then diluted with further acetone (5 ml) and water (0.5 ml). This mixture was stirred for 0.5h, then sufficient anhydrous $MgSO_4$ was added to remove all water. The suspension was filtered through a plug of Celite and the solvent was removed under reduced pressure, to yield a colourless oil which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to afford 5,6-dihydroxy-6-methylheptan-2-one **125** as a colourless oil (337mg, 94%) (Found: M^+-H_2O, 142.0993. $C_8H_{16}O_3$ requires *M* -H_2O, 142.0993); υ_{max} (neat) /cm^{-1} 1708 (C=O) and 1110 (C-O); *m/z* (CI, NH_3) 161 [$(M+H)^+$, 37%], 159 (48), 143 [100, (M+H)-H_2O], 118 (5), 100 (10), 60 (18) and 43 (9).

By ^1H and ^{13}C nmr, diol **125** was found to be an unstable mixture of hemiacetals in addition to the required product. Conversion of diol **125** to the corresponding acetonide **137** was carried out as follows: To a solution of **125** (25.8 mg, 1.61 x 10^{-4} mol) in acetone (3 ml) was added a catalytic amount of camphorsulphonic acid (5 mg). This mixture was allowed to stir overnight, then the solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent, to yield acetonide **137** as a colourless oil (9.8 mg, 30%) (Found: M^+, 200.1412. $C_{11}H_{20}O_3$ requires *M*, 200.1412); υ_{max} (neat) /cm^{-1} 2960 (-CH_2, -CH_3), 1708 (C=O) and 1110 (C-O); δ_H (270 MHz, $CDCl_3$) (acetonide derivative) 1.11, 1.26

(total 6 H, each s, 6-Me and 7-H), 1.32,1.41 (total 6 H, each s, acetonide Me), 1.63-1.76 (2 H, m, 4-H), 2.18 (3 H, s, 1-H), 2.49-2.79 (2 H, m, 3-H), and 3.62-3.67 (1 H, m, 5-H); δ_C (67.8 MHz, $CDCl_3$) (acetonide derivative) 22.9, 25.9, 26.9, 28.5 (all CH_3, 6-Me, C-7, acetonide Me), 23.2 (CH_2,C-4), 30.0 (CH_3, C-1), 40.9 (CH_2, C-3), 80.2 (quat., C-6), 82.5 (CH, C-5), 106.7 (quat., acetonide) and 208.1 (C=O, C-2); *m/z* 200 (M^+, 0.5%), 185 (40, M-CH_3), 143 (32), 125 (27), 107 (7), 84 (79), 71 (13), 59 (20) and 43 (100).

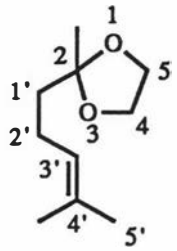
(±)-1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane (17)



(±)-17

To a suspension of powdered molecular seives (4A, 10 mg) in dichloromethane (15 ml) was added a solution of (±)-5,6-dihydroxy-6-methylheptan-2-one **125** (160 mg, 1.0 mmol) in dichloromethane (2 ml) and a catalytic quantity of *para*-toluenesulphonic acid (15 mg). When all of the diol **125** had reacted (as observable by tlc), solid sodium bicarbonate (20 mg) was added to the reaction mixture which was then allowed to stir for an additional five minutes. The entire mixture was then filtered through a plug of flash silica using pentane-diethyl ether (1:1) as eluent and the solvent removed under reduced pressure to yield the title compound **17** as a colourless oil (93 mg, 64%) (Found: M^+, 142.0988. $C_8H_{14}O_2$ requires *M*, 142.0993); υ_{max} (neat) /cm^{-1} 2981 (-CH_3, -CH_2) and 1172 (C-O); δ_H (270 MHz, $CDCl_3$) 1.20, 1.26 (total 6 H, each s, 3-Me), 1.58 (3 H, s, 1-H), 1.60-2.09 (4 H, m, 5-H and 6-H) and 4.22 (1 H, d, *J* 4.4, 4-H); δ_C (67.8 MHz, $CDCl_3$) 19.3 (CH_3, 1-Me), 23.5, 27.9 (both CH_3, 3-Me), 24.7 (CH_2, C-5), 35.3 (CH_2, C-6), 80.3 (quat., C-3), 83.5 (CH, C-4) and 109.2 (quat., C-1); *m/z* 142 (M^+, 2%), 127 (7), 84 (41), 82 (30), 72 (61) and 43 (100). The mass spectral, IR and ^1H nmr data obtained was in agreement with the literature[20,128,131].

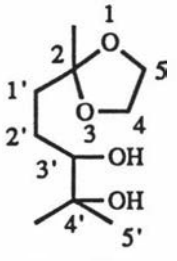
2-Methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane (132)



132

To a solution of 6-methylhept-5-en-2-one **14** (4.00 g, 32.0 mmol) in benzene (200 ml) was added ethylene glycol (3.94 g, 64.0 mmol) and a catalytic amount of *para* -toluenesulphonic acid (300 mg, 1.58mmol). The mixture was then treated under reflux for 5h using a Dean and Stark apparatus. The solvent was removed under reduced pressure followed by purification of the crude oil by flash chromatography using hexane-ethyl acetate (9:1) as eluent to yield 2-methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane **132** (3.95 g, 73%) (Found: M^+, 170.1312. $C_{10}H_{18}O_2$ requires *M*, 170.1307); υ_{max} (neat) /cm^{-1} 1667 (C=C) and 1135 (C-O); δ_C (67.8 MHz, $CDCl_3$) 17.5 (CH_3, 2-Me), 22.7 (CH_2, C-2'), 23.7, 25.5 (CH_3, 4'-Me, C-5'), 39.0 (CH_2, C-1'), 64.5 (CH_2, C-4 and C-5), 109.8 (quat., C-2), 124.0 (CH, C-3') and 131.4 (quat., C-4'). ^1H nmr and mass spectral data was in agreement with the literature[43,137].

(-)-2-(3,4-dihydroxy-4-methylpent-1-yl)-2-methyl-1,3-dioxolane (133)

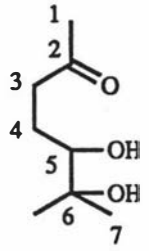


(-)-133

A suspension of $K_3Fe(CN)_6$ (1.51 g, 4.59 mmol), K_2CO_3 (633 mg, 4.59 mmol), methanesulphonamide (145 mg, 1.53 mmol) and 1,4-*bis*-(9-*O*-dihydroquininyl)-phthalazine [$(DHQ)_2PHAL$] (59.5 mg, 7.65×10^{-5} mol) was prepared in water/*t* -butanol (12 ml, 1:1) and cooled to 0°C. To this mixture was added OsO_4 (0.19 ml of a 2.5% w/w solution in *t* -butanol, 1.53×10^{-5} mol), followed by 2-methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane **132** (260 mg, 1.53 mmol) as a single portion. The reaction was maintained at 0°C and stirred for a further six hours, then quenched by the addition of solid $Na_2S_2O_4$ (500 mg, 2.87 mmol).The reaction was stirred for a further 0.5hr, then

solid $Na_2S_2O_4$ (500 mg, 2.87 mmol).The reaction was stirred for a further 0.5hr, then extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extract was washed with KOH (2 x 5 ml, 1M solution in water) and dried over anhydrous $MgSO_4$ followed by removal of the solvent under reduced pressure. A clear oil was obtained which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to give *(-)-2-(3,4-dihydroxy-4-methylpent-1-yl)-2-methyl-1,3-dioxolane* **133** (280 mg, 94%) [Found (acetonide derivative): $(M\text{-}CH_3)^+$, 229.1443. $C_{13}H_{24}O_4$ requires $(M\text{-}CH_3)^+$, 229.1440]; υ_{max} (neat) /cm^{-1} 3410 (OH) and 1065 (C-O); δ_H (270 MHz, $CDCl_3$) 1.15, 1.20 (total 6 H, both s, 4'-Me and 5'-H), 1.34 (3 H, s, 2-Me), 1.38-1.98 (4 H, m, 1'-H and 2'-H), 2.71-2.80 (1 H, s, br, OH), 3.29-3.36 (2 H, m, 3'-H and OH) and 3.96-3.99 (4 H, m, 4-H and 5-H); δ_C (67.8 MHz, $CDCl_3$) 23.3, 23.6 (both CH_3, 4'-Me and C-5'), 25.7 (CH_2, C-2'), 26.3 (CH_3, 2-Me), 36.1 (CH_2, C-1'), 64.4, 64.5 (both CH_2, C-4 and C-5), 72.8 (quat., C-4'), 78.3 (CH, C-3') and 110.0 (quat., C-2); *m/z* (acetonide derivative) 229 [$(M\text{-}CH_3)^+$, 12%], 185 (65), 143 (97), 125 (76), 108 (18), 82 (30), 84 (34) and 43 (100).

(-)-5,6-Dihydroxy-6-methylheptan-2-one (125)

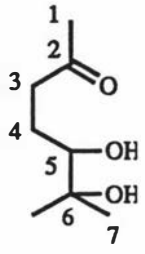


(+)-125

A suspension of $K_3Fe(CN)_6$ (1.69 g, 5.13 mmol), K_2CO_3 (708 mg, 5.13 mmol), methanesulphonamide (162 mg, 1.71 mmol) and $(DHQ)_2PHAL$ (66.5 mg, 8.55×10^{-5} mol) was prepared in water/*t*-butanol (12 ml, 1:1) and cooled to 0°C. To this mixture was added OsO_4 (0.25 ml of a 2.5% w/w solution in *t*-butanol, 1.97×10^{-5} mol), followed by 6-methylhept-5-en-2-one **14** (215 mg, 1.71 mmol) as a single portion. The reaction was maintained at 0°C and stirred for a further six hours, then quenched by the addition of solid $Na_2S_2O_4$ (500 mg, 2.87 mmol).The reaction was stirred for a further 0.5hr, then extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extract was washed with KOH (2 x 5 ml, 1M solution in water) and dried over anhydrous $MgSO_4$ followed by removal of the solvent under reduced pressure. A clear oil was obtained which was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give (-)-5,6-dihydroxy-6-methylheptan-2-one **125** (198 mg, 72%) for which the IR, ^1H, ^{13}C and MS data was in agreement with that listed previously (page107); $[\alpha]_D$ -10.6 (*c* 0.62

in $CHCl_3$). Conversion to the Mosher ester derivative **134b** *(vide infra)* established the enantiomeric excess to be 89 %.

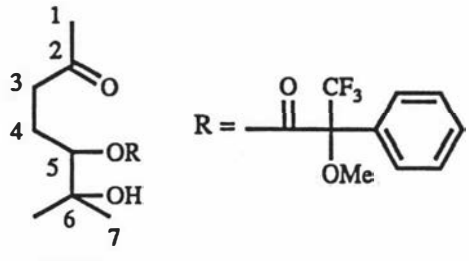
(+)-5,6-Dihydroxy-6-methylheptan-2-one (125)



(-)-125

Using the procedure described for the preparation of (-)-5,6-dihydroxy-6-methylheptan-2-one **125** from 6-methylhept-5-en-2-one **14** (page 110), the (+)-enantiomer of **125** was prepared from 6-methylhept-5-en-2-one **14** (203 mg, 1.61 mmol) using $K_3Fe(CN)_6$ (1.59 g, 4.83 mmol), K_2CO_3 (667 mg, 4.83 mmol), methanesulphonamide (153 mg, 1.61 mmol), 1,4-*bis*-(9-*O*-dihydroquinidinyl)phthalazine [$(DHQD)_2PHAL$] (62.6 mg, 8.05×10^{-5} mol) and OsO_4 (0.25 ml of a 2.5% w/w solution in *t* -butanol, 1.97×10^{-5} mol). After workup, a clear oil was obtained which was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give (+)-5,6-dihydroxy-6-methylheptan-2-one **125** (197mg, 77%) for which the IR, ^1H, ^{13}C and MS data was in agreement with that listed previously (page 107); $[\alpha]_D$ +10.2 (*c* 0.62 in $CHCl_3$). Conversion to the Mosher ester derivative **134a** *(vide infra)* established the enantiomeric excess to be 98 %.

6-Hydroxy-6-methyl-2-oxo-hept-5-yl α-methoxy-α-(trifluoromethyl) phenylacetate (134b)



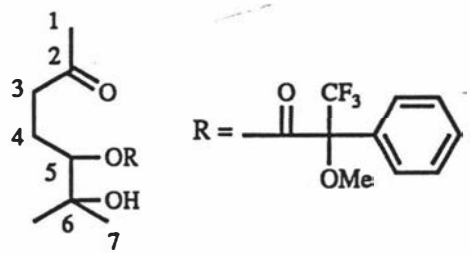
134b

To a solution of (-)-5,6-dihydroxy-6-methylheptan-2-one **125** (26.6 mg, 1.66×10^{-4} mol) in pyridine (2 ml), was added triethylamine (0.1 ml, 6.65×10^{-4} mol) and *R*-(-)-α-

methoxy-α-(trifluoromethyl)phenylacetyl chloride [(-)-MTPA-Cl] **112** (0.03 ml, 1.66 x 10^{-4} mol) followed by a catalytic amount of dimethylaminopyridine (DMAP) (1-2 mg). This mixture was allowed to stir for 7 hours, the pyridine removed under reduced pressure, and the resultant residue purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to give the *Mosher ester derivative* **134b** as a colourless oil (50.6 mg, 81%) [Found: $(M+H)^+$, 377.1573. $C_{18}H_{24}O_5F_3$ requires *(M+H)*, 377.1576]; υ_{max} (neat) /cm^{-1} 3448 (OH), 1740 [C=O (ester)], 1712 [C=O (ketone)] and 2847 (C-O-Me); δ_F (282 MHz, $CDCl_3$) -71.25 (s, CF_3); δ_H (270 MHz, $CDCl_3$) 1.16, 1.19 (total 6 H, both s, 6-Me and 7-H), 1.74-1.78 (2 H, m, 4-H), 2.09 (3 H, s, 1-H), 2.40-2.45 (2 H, m, 3-H), 3.55 (3 H, s, OMe), 4.95 (1 H, d, *J* 7.3, 5 H) and 7.41-7.61 (5 H, m, ArH); δ_C (67.8 MHz, $CDCl_3$) 23.7 (CH_2, C-4), 24.7, 26.0 (both CH_3, 6-Me and C-7), 30.0 (CH_3, C-1), 39.5 (CH_2, C-3), 55.4 (CH_3, OMe), 72.2 (quat., C-6), 82.1 (CH, C-5), 127.4, 128.5, 129.8 (CH, ArC), 131.8 (quat., ArC), 166.6 (quat., C=O) and 207.4 (quat., C-2); *m/z* 377 [$(M+H)^+$, 1%], 359 (20), 189 (100), 143 (50), 125 (52), 105 (32), 85 (24), 77 (18), 71 (36), 59 (36) and 43 (66).†

† Optical rotations for Mosher esters were not obtained due to their instablility when using a small amount of compound in a relatively large amount of solvent, resulting in variable readings.

6-Hydroxy-6-methyl-2-oxo-hept-5-yl α-methoxy-α-(trifluoromethyl) phenylacetate (134a)

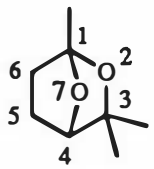


134a

Using the procedure described for the preparation of Mosher ester **134b** (above), the *title* compound **134a** was prepared from (+)-5,6-dihydroxy-6-methylheptan-2-one **125** (52.2 mg, 3.26 x 10^{-4} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-)-MTPA-Cl **112** (0.06 ml, 3.50 x 10^{-4} mol) and a catalytic amount of DMAP (5 mg). Purification was carried out by flash chromatography using hexane-ethyl acetate (2:1) as eluent, to afford the *Mosher ester derivative* **134a** as a colourless oil (47.4 mg, 39%); δ_F (282 MHz, $CDCl_3$) -71.08 (s, CF_3); δ_H (270 MHz, $CDCl_3$) 1.16, 1.24 (total 6 H, both s, 6-Me and 7-H), 1.58-1.68 (2 H, m, 4-H), 2.05 (3 H, s, 1-H), 2.27-2.32 (2 H, m, 3-H),

3.57 (3 H, s, OMe), 4.95 (1 H, d, *J* 8.1, 5-H) and 7.42-7.63 (5 H, m, ArH); δ_C (67.8 MHz, $CDCl_3$) 23.6 (CH_2, C-4), 24.8, 25.9 (both CH_3, 6-Me and C-7), 29.9 (CH_3, C-1), 39.4 (CH_2, C-3), 55.4 (CH_3, OMe), 72.1 (quat., C-6), 82.0 (CH, C-5), 127.4, 128.5, 129.7 (CH, ArC), 131.8 (quat., ArC), 166.5 (quat., C=O) and 207.4 (quat., C-2); All IR and MS data was in agreement with that listed previously (page 112).

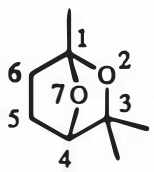
(-)-1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane (17)



(-)-17

Using the procedure described for the preparation of the racemic 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane (±)-**17** (page 108), the title compound (-)-**17** was prepared from (-)-5,6-dihydroxy-6-methylheptan-2-one **125** (47.6 mg, 2.98 x 10^{-4} mol) using powdered molecular sieves (4A, 10 mg) and a catalytic quantity of *para*-toluenesulphonic acid (15 mg). After workup, the entire mixture was then filtered through a plug of flash silica using pentane-diethyl ether (1:1) as eluent and the solvent removed under reduced pressure to yield (-)-1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane **17** as a colourless oil (24.5 mg, 58%) for which the IR, ^1H, ^{13}C and MS data was in agreement with that listed previously (page 108); $[\alpha]_D$ -29.0 (*c* 0.18 in $CHCl_3$). Addition of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol **113** (7 equiv.), followed by ^1H nmr, established the enantiomeric excess to be 87%.

(+)-1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane (17)

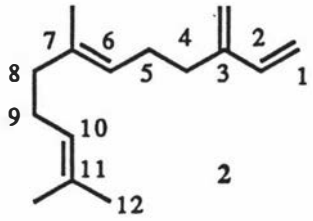


(+)-17

Using the procedure described for the preparation of the racemic 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane (±)-**17** (page 108), the title compound (+)-**17** was prepared from (+)-5,6-dihydroxy-6-methylheptan-2-one **125** (159 mg, 9.94 x 10^{-4} mol) using powdered molecular sieves (4A, 10 mg) and a catalytic quantity of *para*-toluenesulphonic

acid (15 mg). After workup, the entire mixture was then filtered through a plug of flash silica using pentane-diethyl ether (1:1) as eluent and the solvent removed under reduced pressure to yield (+)-1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane **17** as a colourless oil (90.4 mg, 64%) for which the IR, ^1H, ^{13}C and MS data was in agreement with that listed previously (page 108); $[\alpha]_D$ +27.7 (*c* 0.13 in $CHCl_3$). Addition of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol **113** (7 equiv.), followed by ^1H nmr, established the enantiomeric excess to be 95%.

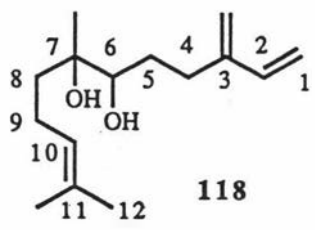
(6*E*)-7,11-Dimethyl-3-methylenedodeca-1,6,10-triene (2) [β-Farnesene]



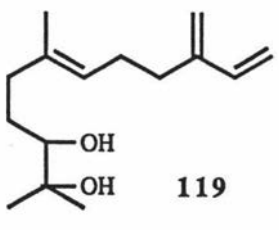
2

A commercial sample of unknown origin (37.9 mg) was purified to by flash chromatography using pentane as eluent to give (6*E*)-7,11-dimethyl-3-methylenedodeca-1,6,10-triene **2** as a clear oil (31.6 mg, 83%) (Found: M^+, 204.1876. $C_{15}H_{24}$ requires *M* , 204.1878); υ_{max} (neat) /cm^{-1} 1446 [$C=C(CH_3)_2$] and 1590 (conjugated methylenes); δ_H (270 MHz, $CDCl_3$) 1.60 (total 6 H, s, 11-Me and 12-H), 1.68 (3 H, s, 7-Me), 1.95-2.09 (4 H, m, 8-H and 9-H), 2.18-2.24 (4 H, m, 4-H and 5-H), 4.99-5.19 (5 H, m, 1b-H, 6-H, 10-H, 3-methylene), 5.24 (1 H, d, *J* 18.0, 1a-H) and 6.38 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 18.0, 2-H); δ_C (67.8 MHz, $CDCl_3$) 16.0 (CH_3, 7-Me), 17.7 (CH_3, 11-Me), 25.7 (CH_3, C-12), 26.6 (CH_2, C-9), 31.4 (CH_2, C-5), 39.7 (CH_2, C-4 and C-8), 113.0 (CH_2, C-1), 115.7 (CH_2, 3-methylene), 124.1 (CH, C-6), 124.4 (CH, C-10), 131.3, 135.4 (both quat., C-7 and C-11), 139.0 (CH, C-2) and 146.1 (quat., C-3); *m/z* 204 (M^+, 6%), 161 (9), 133 (17), 120 (11), 93 (44), 81 (13), 69 (100), 55 (12) and 41 (56).

(6*E*)-7,11-Dimethyl-3-methylenedodeca-1,10-diene-6,7-diol (118) and (6*E*)-7,11-Dimethyl-3-methylenedodeca-1,6-diene-10,11-diol (119)



118

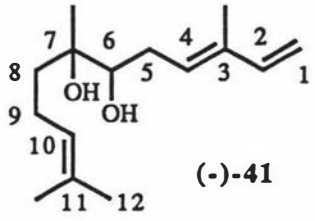


119

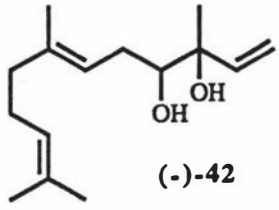
A suspension of $K_3Fe(CN)_6$ (153 mg, 4.65 x 10^{-4} mol), K_2CO_3 (66mg, 4.65 x 10^{-4} mol), methanesulphonamide (15 mg, 1.55 x 10^{-4} mol) and $(DHQ)_2PHAL$ (12 mg, 1.55 x 10^{-5} mol) was prepared in water/*t*-butanol (12 ml, 1:1) and cooled to 0°C. To this mixture was added OsO_4 (0.05 ml of a 2.5% w/w solution in *t* -butanol, 3.10 x 10^{-6} mol), followed by β-farnesene **2** (31.6 mg, 1.55 x 10^{-4} mol) as a single portion. The reaction was maintained at 0°C and stirred for a further six hours, then quenched by the addition of solid $Na_2S_2O_4$ (500 mg, 2.87 mmol).The reaction was stirred for a further 0.5 h, then extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extract was washed with KOH (2 x 5 ml, 1M solution in water) and dried over anhydrous $MgSO_4$ followed by removal of the solvent under reduced pressure. An unstable clear oil was obtained which was purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to give (i) *(6E)-7,11-dimethyl-3-methylenedodeca-1,10-diene-6,7-diol* **118** (3.2mg, 9%); δ_H (270 MHz, $CDCl_3$) 1.12 (3 H, s, 7-Me), 1.62, 1.69 (total 6 H, both s, 11-Me and 12-H), 2.03-2.55 (8 H, m, 4-H, 5-H, 8-H, 9-H), 3.45-3.48 (1 H, m, 6-H), 5.04-5.10 (4 H, m, 1b-H, 10-H, 3-methylene), 5.27 (1 H, d, *J* 17.6, 1a-H) and 6.38 (1 H, dd, $J_{2,1b}$ 11.0, $J_{2,1a}$ 17.6, 2-H).

(ii) *(6E)-7,11-dimethyl-3-methylenedodeca-1,6-diene-10,11-diol* **119** (6.7 mg, 18%); υ_{max} (neat) /cm^{-1} 3385 (OH),1455 [$C=C(CH_3)_2$] and 1590 (conjugated methylenes); δ_H (270 MHz, $CDCl_3$) 1.16, 1.21 (total 6 H, both s, 11-Me, 12-H), 1.62 (3 H, s, 7-Me), 2.02-2.25 (8 H, m, 4-H, 5-H, 8-H, 9-H), 3.36 (1 H, d, br, *J* 10.2, 10-H), 5.01 (2 H, d, *J* 7.0, 3-methylene), 5.06 (1 H, d, *J* 11.0, 1b-H), 5.21-5.28 (2 H, m, 1a-H and 6-H) and 6.38 (1 H, dd, $J_{2,1b}$ 11.0, $J_{2,1a}$ 17.6, 2-H); δ_C (acetonide derivative) (67.8 MHz, $CDCl_3$) 16.0 (CH_3, 7-Me), 22.9 (CH_3, 11-Me), 26.1, 26.9 (CH_3, acetonide Me), 26.6 (CH_2, C-9), 27.7, 31.4, 36.6 (CH_2, C-4, C-5, C-8), 28.6 (CH_3, C-12), 80.1 (quat., C-11), 82.8 (CH, C-10), 106.4 (quat., acetonide), 113.1 (CH_2, C-1), 115.7 (CH_2, 3-methylene), 124.5 (CH, C-6), 134.7 (quat., C-7), 139.0 (CH, C-2) and 146.0 (quat., C-3) and (iii) unreacted β-farnesene **2** (6.0 mg, 19%).

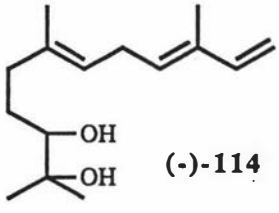
(-)-3,7,11-Trimethyldodeca-1,3,10-triene-6,7-diol (41),
(-)-3,7,11-Trimethyldodeca-1,6,10-triene-3,4-diol (42),
(-)-3,7,11-Trimethyldodeca-1,3,6-triene-10,11-diol (114),
(-)-3,7,11-Trimethyldodeca-1,3-diene-6,7,10,11-tetraol (115) and Acetonide (138)



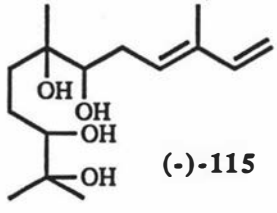
(-)-41



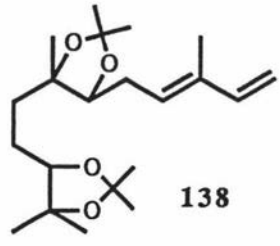
(-)-42



(-)-114



(-)-115



138

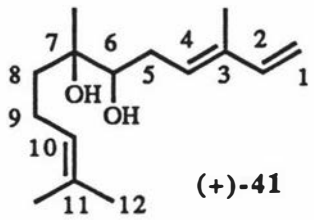
Using the procedure described for the preparation of the β-farnesene diols **118** and **119** (page 115), the *title* compounds (-)-**41**, **42**, **114** and **115** were prepared from α-farnesene **1** (118 mg, 5.78 x 10^{-4} mol) using $K_3Fe(CN)_6$ (570 mg, 1.73 mmol), K_2CO_3 (244 mg, 1.73 mmol), methane-sulphonamide (54 mg, 5.78 x 10^{-4} mol), $(DHQ)_2PHAL$ (45 mg, 5.78 x 10^{-5} mol) and OsO_4 (0.14 ml of a 2.5% w/w solution in *t* -butanol, 1.10 x 10^{-5} mol). After workup, a clear, unstable oil was obtained which was purified by flash chromatography using hexane-ethyl acetate (4:1) followed by ethyl acetate (100%) as eluent to afford (i) an inseparable mixture (20:1) of (-)-3,7,11-trimethyldodeca-1,3,10-triene-6,7-diol **41** and (-)-3,7,11-trimethyldodeca-1,6,10-triene-3,4-diol **42** (37.9 mg, 28%) for which the IR, ^1H, ^{13}C and MS data was in agreement with that listed previously (page 94). $[\alpha]_D$ -24.5 (*c* 0.08 in $CHCl_3$). Conversion to the Mosher ester derivatives **120b** and **121b** *(vide infra)* established the enantiomeric excess to be >89%.
(ii) *(-)-3,7,11-trimethyldodeca-1,3,6-triene-10,11-diol* **114** (115.3 mg, 11%) [Found (acetonide derivative: M^+, 278.2261. $C_{18}H_{30}O_2$ requires *M*, 278.2246]; $[\alpha]_D$ -20.8 (*c* 0.03 in $CHCl_3$); υ_{max} (neat) /cm^{-1} 3405 (OH) and 1602, 1636 (C=C-C=C); δ_H (270 MHz, $CDCl_3$) 1.16, 1.20 (total 6 H, both s, 11-Me and 12H), 1.53-1.67 (2 H, m, 9-H), 1.66 (3 H, s, 7-Me), 1.76 (3 H, s, 3-Me), 2.02-2.26 (2 H, m, 8-H), 2.85 (2 H, t, *J* 7.1, 5-H), 3.35 (1 H, d, br, *J* 10.3, 10-H), 4.93 (1 H, d, *J* 10.6, 1b-H), 5.09 (1 H, d, *J* 17.2, 1a-H), 5.21 (1 H, t, *J* 7.0, 6-H), 5.45 (1 H, t, *J* 7.3, 4-H) and 6.36 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); *m/z* (acetonide derivative) 278 (M^+, 12%), 263 (51, M-CH_3), 236 (15), 220 (22), 162 (39), 134 (70), 119 (100), 93 (89), 81 (38), 59 (41) and 43 (72).

(iii) *(-)-3,7,11-trimethyldodeca-1,3-diene-6,7,10,11-tetraol* **115** [as an inseparable mixture (14:1) with either isomer **116** or **117**] (7.4mg, 7%) $[\alpha]_D$ -39.8 (*c* 0.03 in $CHCl_3$); υ_{max} (neat) /cm^{-1} 3410 (OH); δ_H (major isomer **115**) (270 MHz, $CDCl_3$) 1.16, 1.17, 1.22 (total 9 H, all s, 7-Me, 11-Me, 12-H), 1.51-1.67 (4 H, m, 8-H, 9-H), 1.77 (3 H, s, 3-Me), 2.27-2.34 (2 H, m, 5-H), 3.35 (1 H, d, *J* 9.2, 10-H), 3.46-3.50 (1 H, m, 6-H), 4.98 (1 H, d, *J* 10.6, 1b-H), 5.13 (1 H, d, *J* 17.2, 1a-H), 5.60 (1 H, t, *J* 7.3, 4-H) and 6.41 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); δ_C (major isomer **112**) (67.8 MHz, $CDCl_3$) 12.0 (CH_3, 3-Me), 21.0 (CH_3, 7-Me), 23.3 (CH_2, C-9), 25.2, 26.5 (both CH_3, 11-Me, C-12), 30.7 (CH_2, C-5), 35.9 (CH_2, C-8), 73.1, 79.0 (both CH, C-6, C-10), 74.3 (quat., C-11), 111.5 (CH_2, C-1), 128.9 (CH, C-4), 136.7 (quat., C-3) and 141.1 (CH, C-2)†. Conversion to the Mosher ester derivative **123b** *(vide infra)* established the enantiomeric excess to be >98%.

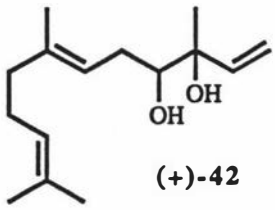
Conversion of tetraol **115** to the corresponding acetonide **138** was carried out as follows: To a solution of **115** (7.4 mg, 2.72 x 10^{-5} mol) in acetone (2 ml) was added a catalytic amount of camphorsulphonic acid (5 mg). This mixture was allowed to stir overnight, then the solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent, to yield acetonide **138** as a colourless oil (7.2 mg, 75%) [Found: $(M\text{-}CH_3)^+$, 337.2377. $C_{20}H_{33}O_4$ requires (*M*-CH_3), 337.2379]; δ_H (270 MHz, $CDCl_3$) 1.10, 1.14 (both 3 H, both s, 11-Me and 12-H), 1.25 (3 H, s, 7-Me), 1.33, 1.34, 1.41, 1.44 (each 3 H, all s, acetonide Me), 1.47-1.69 (4 H, m, 8-H, 9-H), 1.77 (3 H, s, 3-Me), 2.32-2.44 (2 H, m, 5-H), 3.60-3.65 (1 H, m, 10-H), 3.84-3.89 (1 H, m, 6-H), 4.97 (1 H, d, *J* 10.6, 1b-H), 5.12 (1 H, d, *J* 17.2, 1a-H), 5.55 (1 H, t, *J* 7.0, 4-H) and 6.39 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H); δ_C (67.8 MHz, $CDCl_3$) 12.0 (CH_3, 3-Me), 21.8 (CH_3, 7-Me), 23.0, 26.3 (both CH_3, 11-Me, C-12), 23.8 (CH_2, C-9), 26.3, 26.9, 28.6, 28.7, (all CH_3, acetonide Me), 35.9 (CH_2, C-5 and C-8), 80.2, 81.9 (quat., C-7, C-11) 80.6, 83.8 (both CH, C-6, C-10), 96.1, 106.6 (quat., acetonide C), 111.3 (CH_2, C-1), 128.0 (CH, C-4), 135.8 (quat., C-3) and 141.1 (CH, C-2); *m/z* 337 (M^+, 45%), 219 (10), 213 (21), 155 (100), 137 (13), 109 (10), 81 (17), 71 (14), 59 (15) and 43 (26).

† C-7 was obscured by the $CDCl_3$ triplet at δ76.5-77.5.

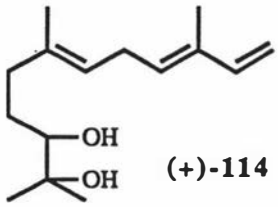
(+)-3,7,11-Trimethyldodeca-1,3,10-triene-6,7-diol (41),
(+)-3,7,11-Trimethyldodeca-1,6,10-triene-3,4-diol (42),
(+)-3,7,11-Trimethyldodeca-1,3,6-triene-10,11-diol (114) and
(+)-3,7,11-Trimethyldodeca-1,3-diene-6,7,10,11-tetraol (115)



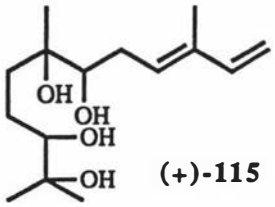
(+)-41



(+)-42



(+)-114



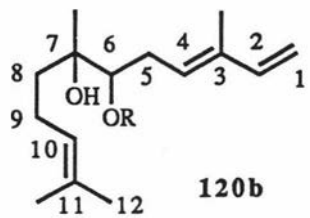
(+)-115

Using the procedure described for the preparation of the β-farnesene diols **118** and **119** (page 115), the *title* compounds (+)-**41**, **42**, **114** and **115** were prepared from α-farnesene **1** (127 mg, 6.21 x 10^{-4} mol) using $K_3Fe(CN)_6$ (613 mg, 1.86 mmol), K_2CO_3 (263 mg, 1.86 mmol), methanesulphonamide (58 mg, 6.21 x 10^{-4} mol), $(DHQD)_2PHAL$ (48 mg, 6.21 x 10^{-5} mol) and OsO_4 (0.15 ml of a 2.5% w/w solution in *t*-butanol, 1.18 x 10^{-5} mol). After workup, a clear, unstable oil was obtained which was purified by flash chromatography using hexane-ethyl acetate (4:1) followed by ethyl acetate (100%) as eluent to afford (i) an inseparable mixture (20:1) of (+)-3,7,11-trimethyldodeca-1,3,10-triene-6,7-diol **41** and (+)-3,7,11-trimethyldodeca-1,6,10-triene-3,4-diol **42** (26.7 mg, 18%); $[\alpha]_D$ +22.8 (*c* 0.06 in $CHCl_3$). Conversion to the Mosher ester derivatives **120a** and **121a** *(vide infra)* established the enantiomeric excess to be >90%.

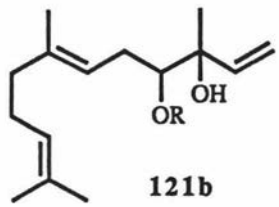
(ii) *(+)-3,7,11-trimethyldodeca-1,3,6-triene-10,11-diol* **111** (22.4 mg, 15%); $[\alpha]_D$ +21.2 (*c* 0.05 in $CHCl_3$).

(iii) *(+)-3,7,11-trimethyldodeca-1,3-diene-6,7,10,11-tetraol* **115** [as an inseparable mixture (15:1) with either isomer **116** or **117**] (23.5 mg, 14%); $[\alpha]_D$ +42.0 (*c* 0.04 in $CHCl_3$). Conversion to the Mosher ester derivative **123a** *(vide infra)* established the enantiomeric excess to be >98%. All IR, ^1H, ^{13}C and MS data were in agreement with that listed previously (pages 94, 116 and 117).

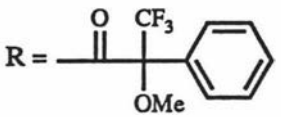
7-Hydroxy-3,7,11-trimethyldodeca-1,3,10-trien-6-yl α-methoxy-α-(trifluoromethyl)phenylacetate (120b) and 3-Hydroxy-3,7,11-trimethyldodeca-1,6,10-trien-4-yl α-methoxy-α-(trifluoromethyl)-phenylacetate (121b)



120b

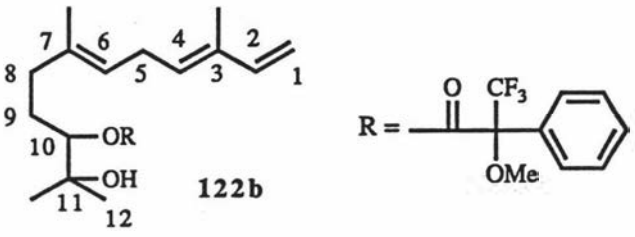


121b



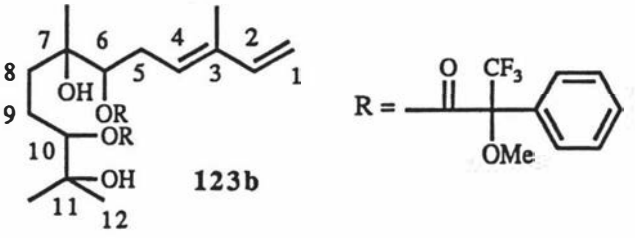
Using the procedure described for the preparation of Mosher ester **134b** (page 111), the *title* compounds **120b** and **121b** were prepared from an inseparable mixture of (-)-3,7,11-trimethyldodeca-1,3,10-triene-6,7-diol **41** and (-)-3,7,11-trimethyldodeca-1,6,10-triene-3,4-diol **42** (20.0 mg, 8.40 x 10^{-5} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-) -MTPA-Cl **112** (0.02 ml, 1.26 x 10^{-4} mol) and a catalytic amount of DMAP (5 mg) and stirring for 2 hours. Purification was carried out using hexane-ethyl acetate (9:1) as eluent, to afford an inseparable (5:1) mixture of the *Mosher ester derivatives* **120b** and **121b** (*) as a colourless oil (35.8mg, 94%) (Found, M^+ 454.2331. $C_{25}H_{33}F_3O_4$ requires 454.2331); υ_{max} (neat) /cm^{-1} 3531 (OH), 2852 (OMe), 1743 (C=O) and 764, 717 (ArH); δ_F (282 MHz, $CDCl_3$) -71.65 (s, CF_3); δ_H (270 MHz, $CDCl_3$) 1.20 (3 H, s, 7-Me and 7-Me*), 1.28 (0.6 H, s, 3-Me*), 1.51-1.74 (10.4 H, m, 3-Me, 8-H and 8-H*, 11-Me and 11-Me*, 12-H and 12-H*), 2.07-2.13 (2 H, m, 9-H and 9-H*), 2.46 (2 H, t, *J* 7.2, 5-H and 5-H*), 3.51-3.55 (4 H, m, OH and OMe), 4.97 (1-H, d, *J* 10.6, 1b-H and 1b-H*), 4.99-5.12 (1 H, m, 6-H and 6-H* or 10-H and 10-H*), 5.08 (1 H, d, *J* 17.2, 1a-H and 1a-H*), 5.20 (1 H, t, *J* 7.2, 6-H and 6-H* or 10-H and 10-H*), 5.35 (1 H, t, *J* 7.2, 4-H and 4-H*), 5.94 (0.2 H, dd, $J_{2^*,1b^*}$ 10.6, $J_{2^*,1a^*}$ 17.2, 2-H*), 6.27 (0.8 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 7.37-7.56 (5 H, m , ArH); δ_C (67.8 MHz, $CDCl_3$) 11.7 (CH_3, 3-Me), 17.7 (CH_3, 11-Me), 21.7 (CH_3, 7-Me), 21.9, 28.9 (both CH_2, C-5, C-9), 25.7 (CH_3, C-12), 39.2 (CH_2, C-8), 55.4 (CH_3, OMe), 74.4 (quat., C-7), 81.1 (CH, C-6), 111.8 (CH_2, C-1), 123.6 (CH, C-10), 127.1, 127.7, 128.4 and 129.5 (all CH, C-4 and Ar-C), 132.5 (quat., C-11), 136.6 (quat., C-3), 140.9 (CH, C-2) and 166.7 (quat., C=O); *m/z* 454 (M^+, 1%), 220 (8), 189 (100), 162 (26), 137 (27), 95 (19), 81 (41), 69 (54) and 43 (39).

11-Hydroxy-3,7,11-trimethyldodeca-1,3,6-trien-10-yl α-methoxy-α–(trifluoromethyl)phenylacetate (122b)



Using the procedure described for the preparation of Mosher ester **134b** (page 111), the *title* compound **122b** was prepared from (-)-3,7,11-trimethyldodeca-1,3,6-triene-10,11-diol **114** (15.2 mg, 6.39 x 10^{-5} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-)-MTPA-Cl **112** (0.02 ml, 9.59 x 10^{-5} mol) and a catalytic amount of DMAP (5 mg) after stirring for 2 hours. Purification by flash chromatography was carried out using hexane-ethyl acetate (4:1) as eluent, to afford the *Mosher ester derivative* **122b** as an unstable colourless oil (26.0 mg, 90%); υ_{max} (neat) /cm^{-1} 3548 (OH), 2844 (OMe), 1743 (C=O) and 764, 717 (ArH); δ_F (282 MHz, $CDCl_3$) -71.25 (s, CF_3); δ_H (270 MHz, $CDCl_3$) 1.16, 1.22 (total 6 H, both s, 11-Me and 12-H), 1.52-1.91 (7 H, m, 3-Me, 8-H, 9-H), 1.56 (3 H, s, 7-Me), 2.81 (2 H, t, *J* 7.1, 5-H), 3.52-3.62 (4 H, m, OH and OMe), 4.92-5.13 (4 H, m, 1a-H, 1b-H, 6-H, 10-H), 5.43 (1 H, t, *J* 7.3, 4-H), 6.36 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 7.40-7.65 (5 H, m, ArH); *m/z* 454 (M^+, 0.5%), 189 [100, -$C(CF_3)$(OMe)Ar], 125 (15), 105 (22), 102 (21) and 43 (59).

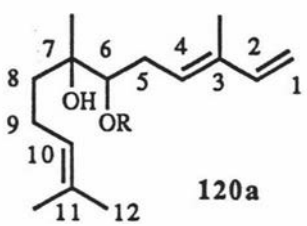
7,11-Dihydroxy-3,7,11-trimethyldodeca-1,3-dien-6,10-di-yl *bis*-[α-methoxy-α–(trifluoromethyl)phenylacetate] (123b)



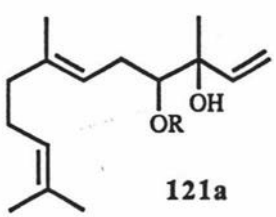
Using the procedure described for the preparation of Mosher ester **134b** (page 111), the *title* compound **123b** was prepared from (-)-3,7,11-trimethyldodeca-1,3-diene-6,7,10,11-tetraol **115** (20.0 mg, 7.35 x 10^{-5} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-)-MTPA-Cl **112** (0.03 ml, 1.50 x 10^{-4} mol) and a catalytic amount of DMAP (5 mg) after stirring for 2 hours. Purification was carried out using hexane-ethyl acetate (1:1) as eluent, to afford the *Mosher ester derivative* **123b** as a colourless oil [an

inseparable mixture (6:1) with the corresponding Mosher ester of **116** or **117**] (37.5 mg, 73%) (Found, M^+ 704.2806. $C_{35}H_{42}F_6O_8$ requires 704.2784); υ_{max} (neat) /cm^{-1} 3571 (OH), 2847 (OMe), 1741 (C=O) and 764,716 (ArH); δ_F (282 MHz, $CDCl_3$) -71.04 and -71.63 (both s, CF_3, major isomer), -71.23 and -71.50 (both s, CF_3, minor isomer); δ_H (major isomer) (270 MHz, $CDCl_3$) 1.08 (3 H, s, 7-Me), 1.17, 1.23 (total 6 H, both s, 11-Me and 12-H), 1.46-1.78 (7 H, m, 3-Me, 8-H, 9-H), 2.16-2.30 (2 H, m, 5-H), 3.45-3.60 (8 H, m, 2 x OH and 2 x OMe), 4.91-5.13 (4 H, m, 1a-H, 1b-H, 6-H, 10-H), 5.24 (1 H, t, *J* 7.3, 4-H), 6.25 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 7.36-7.59 (5 H, m , ArH); δ_C (major isomer) (67.8 MHz, $CDCl_3$) 11.6 (CH_3, 3-Me), 21.9 (CH_3, 7-Me), 23.7, 27.0 (both CH_3, 11-Me, C-12), 23.9 (CH_2, C-9), 28.6 (CH_2, C-5), 35.8 (CH_2, C-8), 55.4, 55.7 (both CH_3, OMe), 72.7, 73.9, (both quat., C-7, C-11), 80.5, 82.7 (both CH, C-6, C-10), 112.0 (CH_2, C-1), 126.5, 127.4, 127.6, 128.5, 129.6, 129.8 (all CH, ArC), 132.0, 132.2 (both quat., ArC), 136.8 (quat., C-3), 140.8 (CH, C-2) and 166.8, 167.1 (both quat., C=O); *m/z* 704 (M^+, 0.5%), 452 (2), 236 (3), 218 (4), 189 (100), 137 (7), 119 (7), 105 (23), 77 (14), 59 (6) and 43 (7).

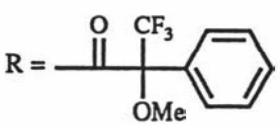
7-Hydroxy-3,7,11-trimethyldodeca-1,3,10-trien-6-yl α-methoxy-α–(trifluoromethyl)phenylacetate (120a) and 3-Hydroxy-3,7,11-trimethyldodeca-1,6,10-trien-4-yl α-methoxy-α–(trifluoromethyl)-phenylacetate (121a)



120a



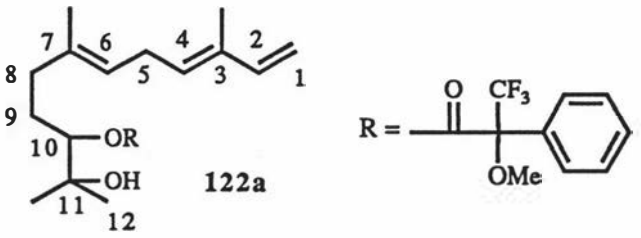
121a



Using the procedure described for the preparation of Mosher ester **134b** (page 111), the *title* compounds **120a** and **121a** were prepared from an inseparable mixture of (+)-3,7,11-trimethyldodeca-1,3,10-triene-6,7-diol **41** and (+)-3,7,11-trimethyldodeca-1,6,10-triene-3,4-diol **42** (14.5 mg, 6.09 x 10^{-5} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-)-MTPA-Cl **112** (0.02 ml, 9.14x 10^{-5} mol) and a catalytic amount of DMAP (5 mg) after stirring for 2 hours. Purification was carried out by flash chromatography using hexane-ethyl acetate (9:1) as eluent, to afford an inseparable (3:1) mixture of the *Mosher ester derivatives* **120a** and **121a** (*) as a colourless oil (27.4 mg, 99%); δ_F (282 MHz, $CDCl_3$) -71.60 (s, CF_3); δ_H (270 MHz, $CDCl_3$) 1.14 (3 H, s, 7-Me and 7-Me*), 1.21 (0.75 H, s, 3-Me*), 1.43-1.52 (2 H, m, 8-H and 8-H*), 1.60-1.73 (8.25 H, m, 3-Me, 11-Me and 11-Me*, 12-H and 12-H*), 1.82-2.05 (2 H, m, 9-H

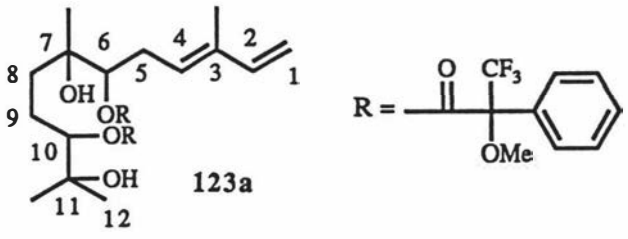
and 9-H*), 2.39-2.67 (2 H, m, 5-H and 5-H*), 3.52-3.69 (4 H, m, OH and OMe), 4.99-5.32 (4 H, m, 1a-H and 1a-H*, 1b-H and 1b-H*, 6-H and 6-H*, 10-H and 10-H*), 5.49 (1 H, t, J 7.0, 4-H and 4-H*), 5.87 (0.25 H, dd, $J_{2^*,1b^*}$ 10.6, $J_{2^*,1a^*}$ 17.4, 2-H*), 6.35 (0.75 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.4, 2-H) and 7.36-7.52 (5 H, m , ArH); δ_C (67.8 MHz, $CDCl_3$) 11.8 (CH_3, 3-Me), 17.6 (CH_3, 11-Me), 21.8 (CH_3, 7-Me), 21.9 (CH_2, C-9), 25.7 (CH_3, C-12), 28.9 (CH_2, C-5), 38.8 (CH_2, C-8), 55.4 (CH_3, OMe), 74.3 (quat., C-7), 81.2 (CH, C-6), 112.0 (CH_2, C-1), 123.7 (CH, C-10), 127.5, 128.4, 129.5 (CH, ArC), 128.2 (quat., ArC), 132.3 (quat., C-3), 136.8 (quat., C-11), 140.8 (CH, C-2) and 166.4 (quat., C=O). All IR and MS data was in agreement with that listed previously (page 119).

11-Hydroxy-3,7,11-trimethyldodeca-1,3,6-trien-10-yl α-methoxy-α-(trifluoromethyl)phenylacetate (122a)



Using the procedure described for the preparation of Mosher ester **134b** (page 111), the *title* compound **122a** was prepared from (+)-3,7,11-trimethyldodeca-1,3,6-triene-10,11-diol **114** (15.8 mg, 6.64 x 10^{-5} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-)-MTPA-Cl **112** (0.02 ml, 9.96 x 10^{-5} mol) and a catalytic amount of DMAP (5 mg) and stirring for 2 hours. Purification was carried out by flash chromatography using hexane-ethyl acetate (4:1) as eluent, to afford the *Mosher ester derivative* **122a** as an unstable colourless oil (26.1 mg, 88%); δ_F (282 MHz, $CDCl_3$) -71.25 (s, CF_3); δ_H (270 MHz, $CDCl_3$) 1.13, 1.17 (total 6 H, both s, 11-Me and 12-H), 1.55-1.82 (8 H, m, 3-Me, 7-Me, 9-H), 1.99 (2 H, t, J 7.9, 8-H), 2.83 (2 H, t, J 7.1, 5-H), 3.56-3.58 (4 H, s, br, OH and OMe), 4.92-5.13 (4 H, m, 1a-H, 1b-H, 6-H, 10-H), 5.44 (1 H, t, J 7.3, 4-H), 6.37 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.6, 2-H) and 7.36-7.60 (5 H, m , ArH). IR data was in agreement with that listed previously (page 120).

7,11-Dihydroxy-3,7,11-trimethyldodeca-1,3-dien-6,10-di-yl *bis*-[α-methoxy-α–(trifluoromethyl)phenylacetate] (123a)



123a

Using the procedure described for the preparation of Mosher ester **134a** (page 111), the *title* compound **123a** was prepared from (+)-3,7,11-trimethyldodeca-1,3-diene-6,7,10,11-tetraol **115** (16.7 mg, 6.13 x 10^{-5} mol) using pyridine (1 ml), triethylamine (0.3 ml), (-)-MTPA-Cl **112** (0.06 ml, 2.21 x 10^{-4} mol) and a catalytic amount of DMAP (5 mg) and stirring for 2 hours. Purification was carried out by flash chromatography using hexane-ethyl acetate (1:1) as eluent, to afford the *Mosher ester derivative* **123a** as a colourless oil [an inseparable mixture (6:1) with the corresponding Mosher ester of either **116** or **117**] (29.3 mg, 68%); δ_F (282 MHz, $CDCl_3$) -70.86 and -71.49 (both s, CF_3, major isomer), -71.21 and -71.66 (both s, CF_3, minor isomer); δ_H (major isomer) (270 MHz, $CDCl_3$) 1.07 (3 H, s, 7-Me), 1.16, 1.19 (total 6 H, both s, 11-Me and 12-H), 1.26-1.86 (7 H, m, 3-Me, 8-H, 9-H), 2.34-2.42 (2 H, m, 5-H), 3.46-3.53 (8 H, m, 2 x OH and 2 x OMe), 4.91-5.18 (4 H, m, 1a-H, 1b-H, 6-H, 10-H), 5.36-5.46 (1 H, m, 4-H), 6.34 (1 H, dd, $J_{2,1b}$ 10.6, $J_{2,1a}$ 17.2, 2-H) and 7.37-7.59 (5 H, m, ArH); δ_C (major isomer) (67.8 MHz, $CDCl_3$) 11.8 (CH_3, 3-Me), 21.7 (CH_3, 7-Me), 23.6 (CH_2, C-9), 24.9, 26.1 (both CH_3, 11-Me, C-12), 28.8 (CH_2, C-5), 35.2 (CH_2, C-8), 55.4 (CH_3, both OMe), 72.4, 73.8 (both quat., C-7, C-11), 81.1, 82.9 (both CH, C-6, C-10), 112.2 (CH_2, C-1), 127.0, 127.4, 128.5, 128.6, 129.6, 129.8 (all CH, ArC), 131.8, 132.2 (quat., ArC), 137.0 (quat., C-3), 140.7 (CH, C-2) and 166.5 (quat., both C=O). All IR and MS data was in agreement with that listed previously (page 121).

2. REFERENCES

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