SOME STUDIES ON ACYL RADICAL CYCLISATIONS

by

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ABSTRACT

This thesis is concerned with the development of acyl radical cyclisations and their applications to organic synthesis. It is divided into five theoretical chapters and an experimental chapter.

The first chapter consists of a survey of the literature on acyl radicals and their reactions.

The second chapter describes a convenient method for the preparation of phenyl selenoesters, the precursors of choice for acyl radicals, by the reaction of the corresponding carboxylic acid, as its triethylammonium salt, with phenylselenenyl chloride and tributylphosphine. Several examples are presented and the results contrasted with those obtained by alternative methods.

The third chapter describes the preparation of two synthons for the 'A' ring of 1α,25-dihydroxyvitamin D3. The first involves a highly efficient 6-*exo* mode cyclisation of a 6-heptenoyl radical, to give a highly functionalised cyclohexanone in which the exomethylene group is masked as a phenylthiomethyl group. Oxidation and *syn* elimination of this substance gives the exomethylene cyclohexanone. Attempts at elaboration of the side chain to give a second, known synthon of 1α,25-dihydroxyvitamin D3, the so-called 'Lythgoe Synthon', are described. The methodology developed for the 6-heptenoyl radical cyclisation is extended to a vinyl radical cyclisation. The successful synthesis of the 'Lythgoe Synthon'by this vinyl radical cyclisation is described.

The fourth chapter deals with extensive model studies aimed at the determination of substituent patterns necessary for the 7-*endo* cyclisation of 6-heptenoyl radicals, leading to the formation of cycloheptanones and bicyclo-[5,3,0]-decanones. It is demonstrated that the inefficient 7-*endo* mode cyclisation of 5-alkoxy-6-heptenoyl radicals occurs by a direct 7-*endo* mode cyclisation, rather than by a ring expansion or reversible ring closure mechanism and that the influence of the 5-alkoxy residue on the mode of cyclisation is not simply steric. An efficient entry into 4,5-di-*O*-isopropylidene 6-heptenoyl radicals is described. When the relative configuration is *erythro*, efficient cyclisation is observed, with preferential 7-*endo* mode cyclisation, whilst for the *threo*-isopropylidene the cyclisation is inefficient, with preferential 6-*exo* mode cyclisation. The introduction of an alkyl substituent into the 7-position of the 4,5-di-*O*-isopropylidene 6-heptenoyl radical reverses the mode of cyclisation, to give predominantly the 6-*exo* mode product. The yield of the 7-*endo* mode product can be increased by using more dilute reaction conditions. The knowledge gained in these studies is applied to a 7,5 double ring closure with the successful formation of a bicyclo-[5,3,0]-decane system. Various spectroscopic, chemical and computational techniques are employed to determine the stereochemistry of the bicyclo-[5,3,0]-decanone systems formed.

The fifth chapter concerns the development of an acyl radical initiated multiple radical cyclisation/fragmentation sequence aimed at the formation of medium sized rings. It is demonstrated that *E*-butenyl cyclohexanones can be efficiently prepared by preferential 6-exo mode cyclisation of 6-heptenoyl radicals bearing a cyclopropane ring in the 7-position. Selective ring opening of a cyclopropylmethyl radical bearing a phenyl substituent at the radical centre, to preferentially give the *Z*-homoallylic radical is described. The attempted cyclisation of 5-methyl-5-hexenoyl, 6-methyl-6-heptenoyl radicals and an attempted allylic radical cyclisation is also described.

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TABLE OF CONTENTS

	Title	i
	Abstract	ii
	Acknowledgements	iv
	Table of Contents	v
	Abbreviations	ix
	CHAPTER 1	
	A REVIEW OF ACYL RADICALS AND THEIR REACTIONS	1
1.1	INTRODUCTION	2
1.2	STRUCTURE AND PHYSICAL PROPERTIES OF ACYL RADICALS	2
1.3	METHODS FOR THE GENERATION OF ACYL RADICALS	4
1.3.1	From Aldehydes	4
1.3.2	Carbonylation of Alkyl Radicals	9
1.3.3	From Acyl Halides	10
1.3.4	From Acyl Selenides	11
1.3.5	From Other Acyl-Heteroatom Derivatives	14
1.3.6	From Acyl Xanthates	15
1.3.7	From Acylcobalt (III) Complexes	15
1.3.8	Acyl Radical Equivalents	16
1.3.9	Other Methods	17
1.3.10	Other Reactions of Acyl Radicals	18
1.4	OBJECTIVES	18
	REFERENCES TO CHAPTER 1	19

CHAPTER 2

AN IMPROVED PROCEDURE FOR THE PREPARATION OF ACYL SELENIDES 25

2.1 INTRODUCTION 26

2.2 SELENOESTER PREPARATION 27

2.3 CONCLUSIONS 30

2.4 TABLE OF ACIDS CONVERTED TO SELENOESTERS BY THE PHENYLSELENENYL CHLORIDE/TRIBUTYLPHOSPHINE METHOD 31

REFERENCES FOR CHAPTER 2 34

CHAPTER 3

SYNTHESIS OF 'A' RING MODELS FOR 1α,25-DIHYDROXYVITAMIN D_3 35

3.1 INTRODUCTION 36

3.2 INITIAL STUDIES OF 6-HEPTENOYL RADICAL CYCLISATIONS 38

3.3 A CONCISE SYNTHESIS FOR α-METHYLENE-CYCLOHEXANONE 41

3.4 ATTEMPTS AT THE INTRODUCTION OF THE SIDE CHAIN 45

3.4.1 Via a Horner-Emmons Reaction 45

3.4.2 Via an Acetylenic Grignard Addition 46

3.5 A NOVEL SYNTHESIS FOR A KNOWN 'A' RING SYNTHON VIA A VINYL RADICAL CYCLISATION 50

3.6 ATTEMPTS TO PREPARE VINYL PHENYLSELENIDES 53

3.7 FURTHER WORK AND CONCLUSIONS 60

REFERENCES FOR CHAPTER 3 62

CHAPTER 4

STUDIES INTO THE PREPARATION OF BICYCLO-[5,3,0]-DECANONES VIA A TANDEM RADICAL CYCLISATION 66

4.1	INTRODUCTION	67
4.1.1	Mechanistic Studies on the Cyclisation of 5-Alkoxy-6-heptenoyl Radicals	67
4.1.2	Ring Expansion via Cyclopropyloxy Radicals	68
4.1.3	β-Oxygen Effects	70
4.1.4	Reversibility of Acyl Radical Addition to Double Bonds	71
4.1.5	Steric Effects	72
4.1.6	Allylic Ethers and Conformational Effects	73
4.1.7	Experimental Probe 1	73
4.1.8	Experimental Probe 2	76
4.2	OPTIMISATION OF 7-ENDO MODE CYCLISATIONS	78
4.3	STUDIES TOWARDS A SYNTHESIS OF A 4,5-DI-*O*-ISOPROPYLIDENE-6-HEPTENOYL SYSTEM	78
4.4	SYNTHESIS FROM CARBOHYDRATES	81
4.5	CYCLISATION REACTIONS	92
4.6	STUDY OF THE EFFECTS OF A SUBSTITUENT IN THE TERMINAL OLEFIN POSITION ON THE MODE AND EFFICIENCY OF CYCLISATION	98
4.7	A DIRECT ENTRY INTO BICYCLO-[5,3,0]-DECANES VIA A TANDEM RADICAL CYCLISATION	104
4.8	DETERMINATION OF STEREOCHEMISTRY FOR THE BICYCLO-[5,3,0]-DECANE SYSTEMS	107
4.9	CONCLUSIONS	110

REFERENCES FOR CHAPTER 4 111

CHAPTER 5

MULTIPLE CYCLISATION/FRAGMENTATION SEQUENCES 114

5.1 INTRODUCTION 115

5.2 CYCLISATION/FRAGMENTATION SEQUENCE 118

5.3 PROPOSED ENTRY INTO CYCLONONENONES 135

5.4 CONCLUSIONS 142

REFERENCES FOR CHAPTER 5 143

EXPERIMENTAL SECTION 146

GENERAL EXPERIMENTAL 147

EXPERIMENTAL SECTION FOR CHAPTER 2 149

EXPERIMENTAL SECTION FOR CHAPTER 3 153

EXPERIMENTAL SECTION FOR CHAPTER 4 180

EXPERIMENTAL SECTION FOR CHAPTER 5 218

REFERENCES FOR EXPERIMENTAL SECTION 247

APPENDIX 249

RESULTS OF FORCE FIELD CALCULATIONS 250

ABBREVIATIONS

Å	Ångström unit,
Ac	Acetyl,
AIBN	2,2'-Azoisobutyronitrile,
Ar	Aryl,
Bn	Benzyl,
bp	Boiling Point,
Bu	Butyl,
DCC	Dicyclohexylcarbodiimide,
DMAP	4-Dimethylaminopyridine,
DMF	*N,N*-Dimethylformamide,
DMSO	Dimethyl sulphoxide,
Et	Ethyl,
HMPA	Hexamethylphosphoramide,
HPLC	High Performance Liquid Chromatography,
h	Hours,
IR	Infrared,
LDA	Lithium Diisopropylamide,
Me	Methyl,
Mesyl	Methanesulphonyl,
min	Minutes,
MMPP	Magnesium Monoperoxyphthalate
mp.	Melting Point,
NBS	N-Bromosuccinimide,
NCS	N-Chlorosuccinimide,
NPSP	N-Phenylselenophthalimide,
nmr	Nuclear Magnetic Resonance,
nOe	Nuclear Overhauser Effect,
PCC	Pyridinium Chlorochromate,

Ph	Phenyl,
py	Pyridine,
rt	Room Temperature,
TBDMS	t-Butyldimethylsilyl,
THF	Tetrahydrofuran,
tlc	Thin Layer Chromatography,
TMS	Trimethylsilyl,
Tosyl or Ts	4-Methylphenylsulphonyl,
X	t-Butyldimethylsilyl,
Δ	Reflux.

CHAPTER 1

A REVIEW OF ACYL RADICALS AND THEIR REACTIONS

1.1 INTRODUCTION

The subject of this thesis is the use of acyl radicals in organic synthesis. Although the recent literature contains several books[1] and review articles[2] on free radicals in general, there has been no specific review on acyl radicals in their own right. As such, a brief overview of the chemistry of acyl radicals is presented below.

1.2 STRUCTURE AND PHYSICAL PROPERTIES OF ACYL RADICALS

There are two possible electronic configurations for an acyl radical. The single electron can either occupy an sp^2 orbital, to give a so-called σ-radical (Figure 1.1 Structure A), or it can occupy a p-orbital on the carbon centre, to give a π-radical (Figure 1.1 Structure B). Both structures are feasible, and it could be argued that in A, the electron will possibly be more strongly bound whilst in B, the possibility of conjugation with p-orbitals on the oxygen atom exists.

A B

Figure 1.1 Possible Structures for Acyl Radicals

A wealth of physical methods have been used to determine the structures of acyl radicals[3] . A variety of electron spin resonance spectroscopy techniques have been employed: Table 1.1 shows the g-factors and hyperfine splittings for some simple acyl radicals. Typically, π-radical systems such as alkyl radicals exhibit hyperfine splittings (a_H) of the order of -30 Gauss. On the other hand, σ-radicals have a_H large and/or $a_{\alpha\text{-}H}$ small and positive. Consequently, acyl radicals can be identified as σ-radicals (Figure 1.1 Structure A). Similarly, the value for the hyperfine splitting due to carbon-13,

a_{C-13} stands as confirmation for the σ-character of acyl radicals.[3a,3c]

ACYL RADICAL	g-FACTOR	$a_{\alpha-H}$ (Gauss)	a_{C-13} (Gauss)
FORMYL	2.0009	+ 136.5 (a_α)	+ 134.5
ACETYL	2.0007	+ 5.3	
BENZOYL	2.0008	H_{ortho} + 0.10 H_{meta} + 1.16 H_{para} + 0.10	+ 128.2

Table 1.1 ESR Data for some acyl radicals

Further confirmation of the structure has been obtained by infrared spectroscopy in either solid matrices[4] or solution.[5] The force constant for the carbonyl stretching frequency in the formyl radical indicates a bent structure with a bond angle of 123.8°, and a bond order of 2.3. Similar results have been observed for acetyl[6] and benzoyl radicals[7] ; calculations from esr data also support the magnitude of this bond angle.[3d]

As there is no significant difference in the electronic configuration of the radical when a substituent is introduced, it would appear that there is no extra stabilisation of the radical through conjugation or hyperconjugation with the substituent. The inherent stability must be derived from conjugation of the unpaired electron with the lone-pairs of electrons on oxygen. Resonance structures can be drawn for the acyl radical: one extreme being that with the electron on the carbon centre only, and the other with a formal negative charge on the carbon atom (Figure.1.2). This suggests that acyl radicals may be nucleophilic in nature and will preferentially attack electron deficient double bonds.

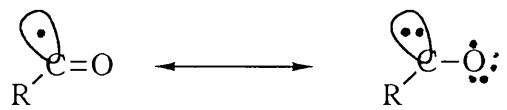
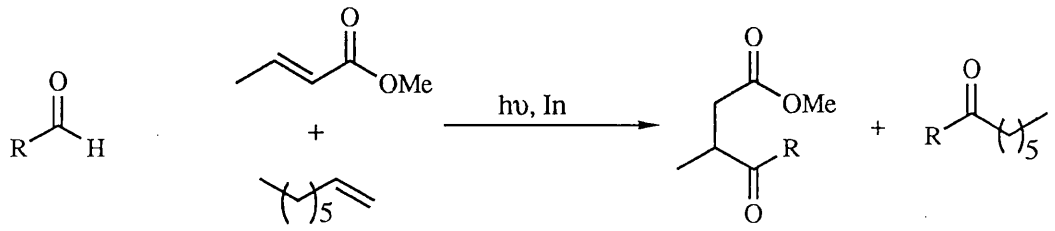


Figure 1.2 Resonance Structures for Acyl Radicals

This postulate is confirmed experimentally: competition reactions for the addition of acyl radicals to a mixture of methyl crotonate and 1-hexene at various temperatures show there is a significant bias towards the product formed from methyl crotonate (Scheme 1.1).[8]



R	T (°C)		
CH_3	4	10	1
CH_3	78	2	1
$(CH_3)_2CH$	4	23	1
$(CH_3)_2CH$	25	15	1

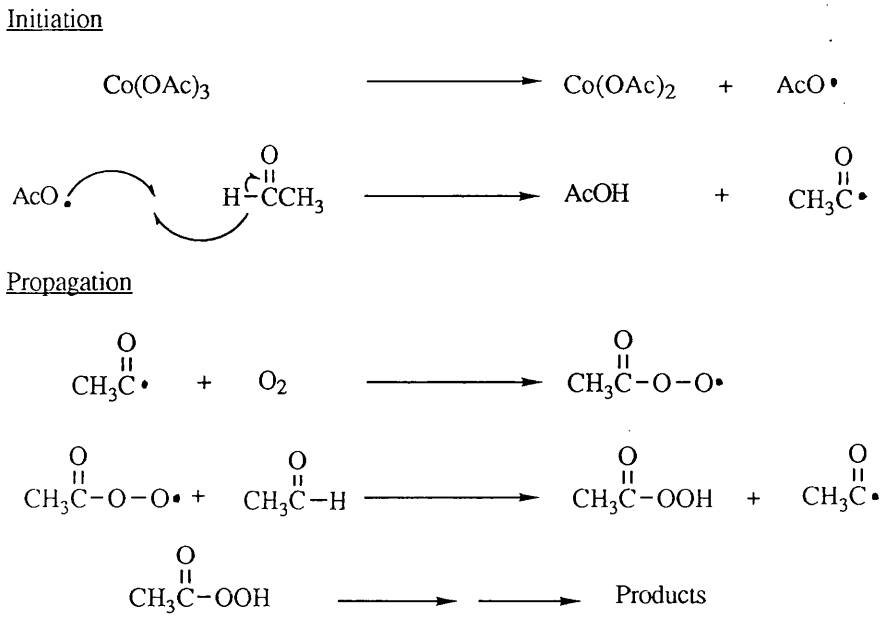
Scheme 1.1 Competitive Addition of Acyl Radicals to Olefins

1.3 METHODS FOR THE GENERATION OF ACYL RADICALS

1.3.1 FROM ALDEHYDES

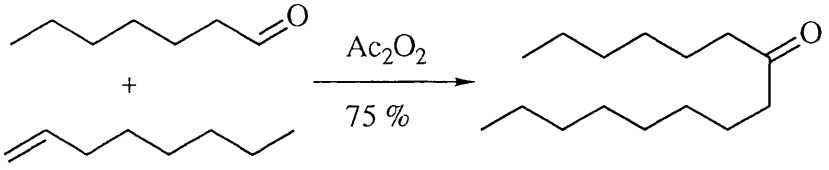
The earliest examples of acyl radicals involve their generation from aldehydes. The carbon-hydrogen bond in aldehydes is sufficiently activated to allow homolytic cleavage. The industrial processes of oxidation of acetaldehyde to acetic acid, peracetic acid and acetic anhydride are all acyl radical reactions.[9] All are catalysed by transition metal salts, with the eventual product being determined by the temperature and the amount of oxygen present (Scheme 1.2).[10,11]

Although these processes are operated on a large tonnage, continuous flow basis, the general method has not been widely used in synthetic work, with only a few isolated examples being reported for the addition of acetaldehyde to olefins.

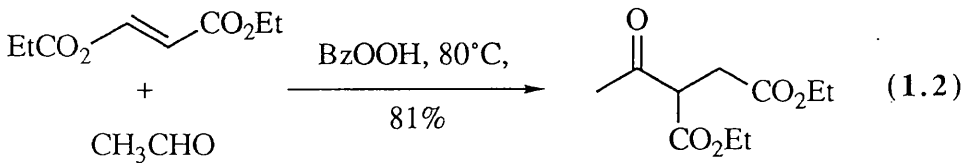


Scheme 1.2 Mechanism for Preparation of Peracetic Acid

The classical laboratory method for generating acyl radicals from aldehydes is by hydrogen abstraction. Kharasch *et al*[12] first descibed the addition of aldehydes to olefins by both thermal and photochemical means (Equation 1.1). They found that the acetoxyl radical from the thermal decomposition of diacetyl peroxide, was able to abstract hydrogen from aliphatic aldehydes to generate the acyl radical. However, they also found that telomer formation and decarbonylation were competing reactions. Photochemical initiation reduced the amount of side products, but reaction proceeded so slowly that yields were not recorded. Thermolysis with di-t-butyl peroxide[13] and dibenzoyl peroxide[14] gave similar results. To overcome these side reactions an excess of aldehyde, often as solvent, was used. The best results[15] from this particular method were obtained when an electron deficient olefin was used, reflecting the nucleophilic nature of acyl radicals (Equation 1.2).

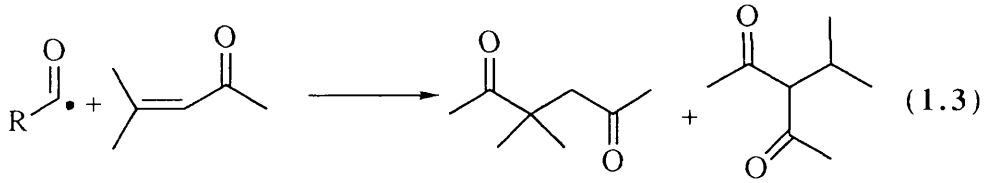


(1.1)



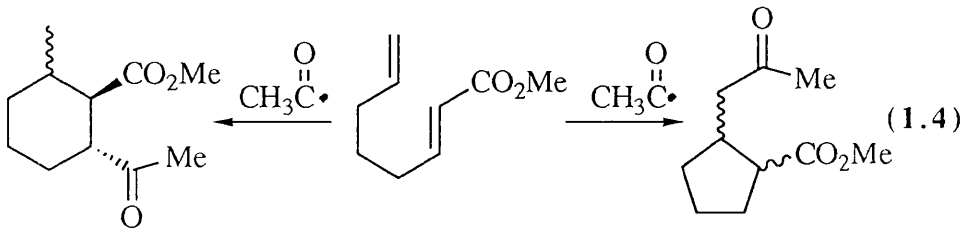
(1.2)

The nucleophilic nature of acyl radicals has been put to good use in regioselective acyl radical addition reactions. For example, Hey[16] showed that intermoleculer addition onto an enone, gave the 1,4-adduct as the major product, with only a minor amount of the 1,2 adduct being formed (Equation 1.3). Evidently, the steric factors which would normally be a major consideration under ionic conditions were negligible. Similarly, this regioselectivity has been used to prepare cyclohexane (1) (Equation 1.4) via an addition-cyclisation reaction. As none of the cyclopentane (2) was detected in this reaction sequence and only the diastereoisomers of (1) were recovered, the addition must have occured at the 3-position.



(1.3)

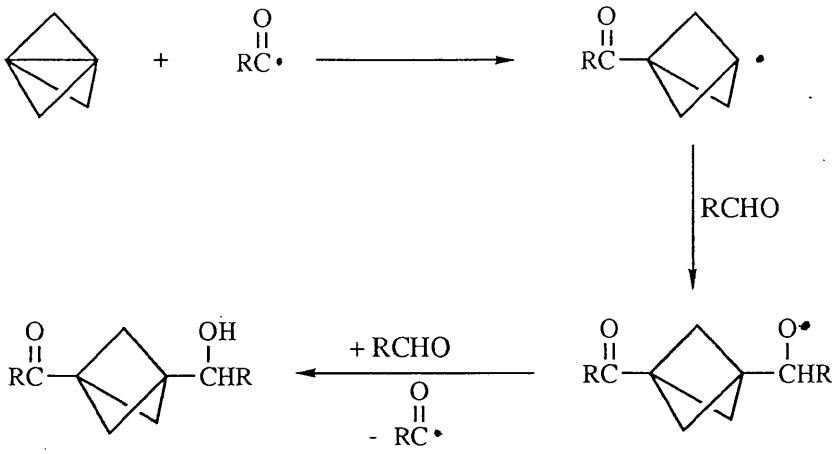
Major Minor



(1.4)

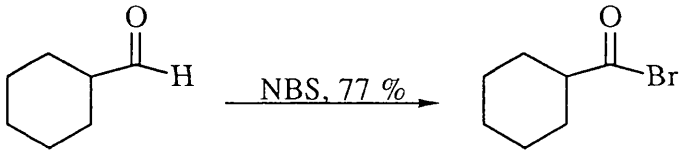
(1) (2)

A recent, novel use of acyl radicals generated from aldehydes is their addition to [1,1,1]-propellane,[17] giving a 2:1 adduct (Scheme 1.3).



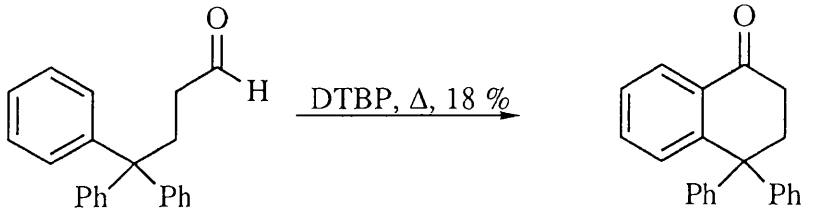
Scheme 1.3 Acyl Radical Addition to [1,1,1]-Propellane

Aldehydes have also been oxidatively transformed into acyl bromides, with NBS and a trace of AIBN (Equation 1.5).[18] When the reaction is conducted in alcoholic solvents esters are formed.[19]

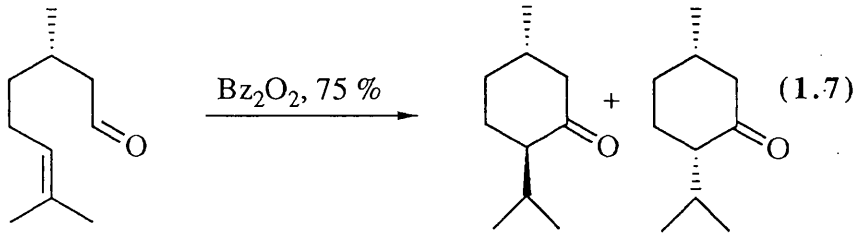


(1.5)

Relatively few examples of cyclisations have been reported for acyl radicals generated from aldehydes. Cyclisations of acyl radicals onto aromatic rings[20,21] have been reported, but the yields, when given, are very poor (Equation 1.6). The cyclisation of citronellal to yield a 2:1 mixture of menthone and isomenthone has also been reported (Equation 1.7).[22]



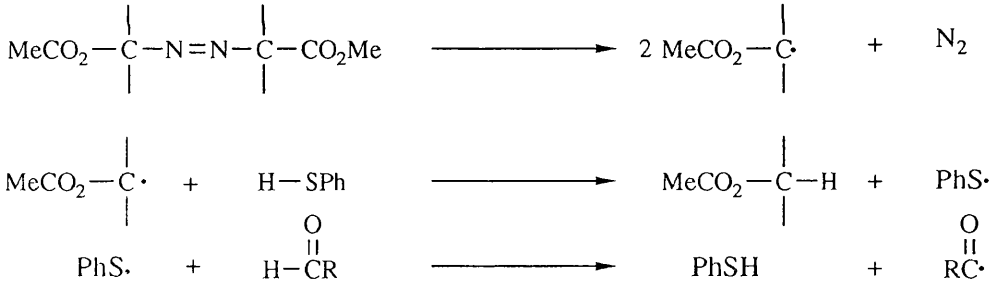
(1.6)



(1.7)

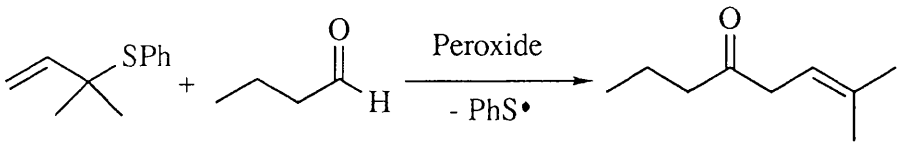
These early studies highlighted the major problems encountered with acyl radical chemistry: telomer formation and decarbonylation at elevated temperatures, with poor reactivity at lower temperatures. Several attempts to circumvent these problems have been described.

The thermal decomposition of azo compounds occurs at lower temperatures than peroxide decomposition. However, the radicals produced are not sufficiently reactive to abstract hydrogen atoms from aldehydes. Nevertheless, they will abstract from thiols to generate thiyl radicals, which in turn can abstract hydrogen from aldehydes (Scheme 1.4). However, reported examples lead mainly to the decarbonylated products.[23]



Scheme 1.4 Generation of Acyl Radicals with Thiyl Radical Mediation.

S_H2' reactions have also been described for allylic thioethers (Equation 1.8).[24]

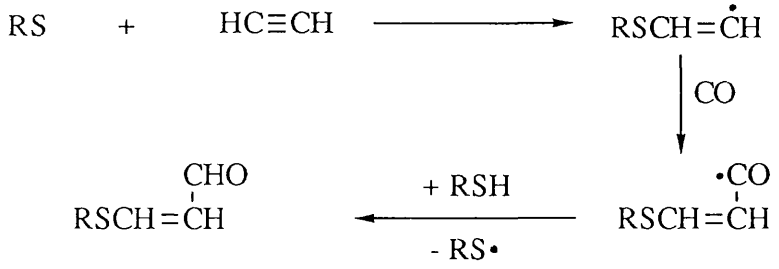


(1.8)

Other investigations include initiation by high energy photolysis with γ-rays,[25] laser flash photolysis[5,26] and transition metal catalysed decomposition of peroxides.[27]

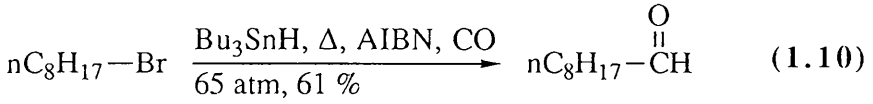
1.3.2 CARBONYLATION OF ALKYL RADICALS.

One of the major problems with acyl radicals is that at elevated temperatures they tend to decarbonylate, to give the corresponding alkyl radical. This reaction should be reversible at high concentrations of carbon monoxide. Early studies,[28,29] concerned with the radical polymerisation of ethylene, showed that polyketones were formed under high pressures of CO. Varying the pressure altered the amount of CO incorporated into the polymer. The first attempt to produce a 1:1 adduct from CO insertion gave mainly telomers.[30] Modest yields of thiopropenals were reported[31] for the reaction of thiyl radicals with acetylene under a high pressure of CO (Equation 1.9).



(1.9)

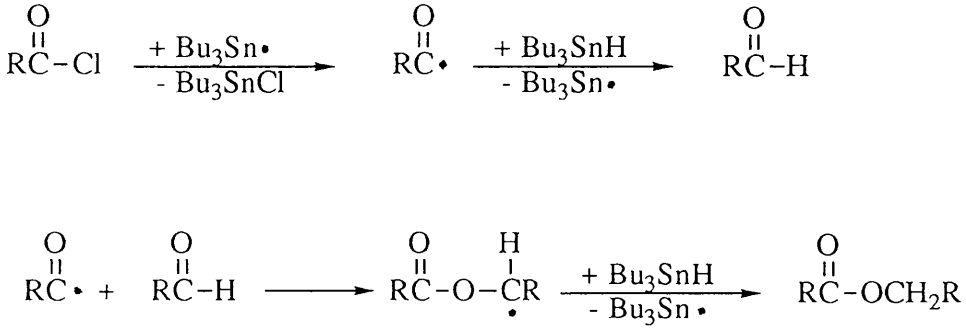
It is only recently that insertions of this type have been shown to give acceptable yields. Alkyl[32] and aryl[33] aldehydes have been synthesised by the reaction of alkyl and aryl halides with tri-n-butyltin hydride under 65-90 atm of CO (Equation 1.10). Similarly, preparation of methylcyclopentanones by carbonylation of 4-pentenyl radicals have also been reported.[34] However, low concentrations of the tin hydride have to be used in order to stop reduction of the product aldehyde, and alkane formation from the alkyl radical.



(1.10)

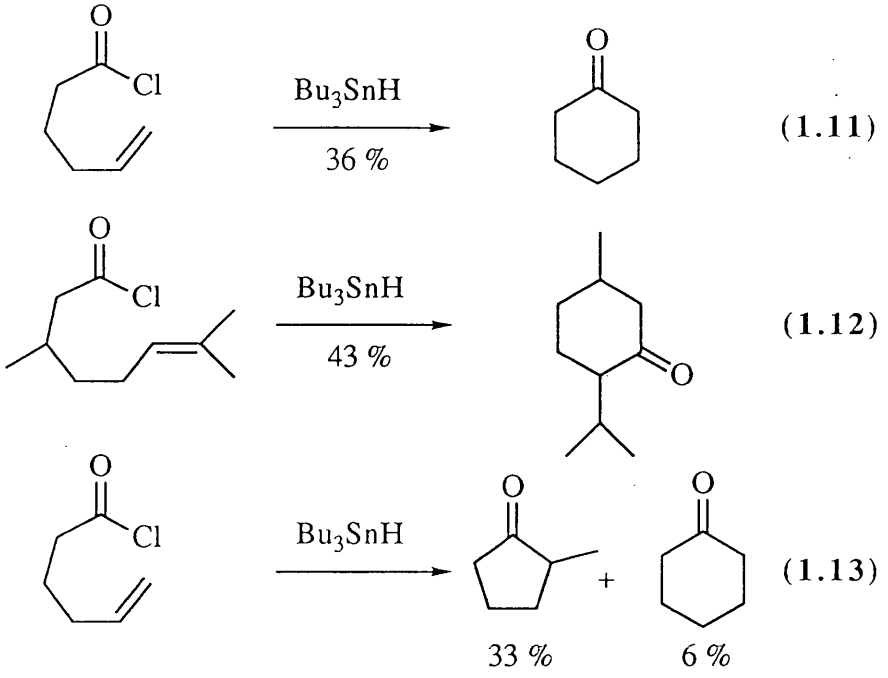
1.3.3 FROM ACYL HALIDES.

Acyl halides have been shown to be reduced by trialkyltin[35] and triaryltin[36,37,38] hydrides at room temperature, to give the corresponding aldehyde. In the absence of a solvent there is competition between aldehyde formation and ester formation (Scheme 1.5).[34] Formation of esters is presumed to occur through condensation of the acyl radicals with the aldehyde generated. This was substantiated by carring out the reaction in the presence of another aldehyde, when the mixed ester was obtained.[39] Acyl bromides react more rapidly than acyl chlorides and consequently a higher yield of aldehyde is obtained.[34]

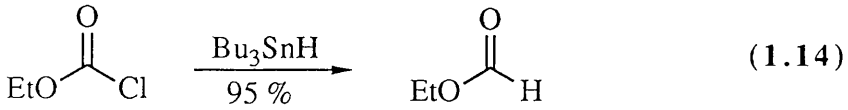


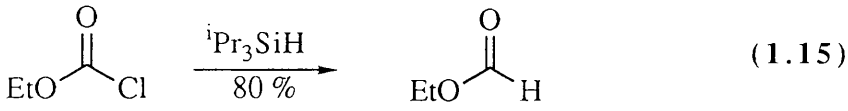
Scheme 1.5 The Action of Tributyltin Hydride on Acyl Chlorides

Cyclisations have been reported from acyl chlorides in which cyclisation of 5-hexenoyl and 6-heptenoyl radicals give the 6-*endo*[40] and 6-*exo* products respectively as the only cyclised products (Equations 1.11 and 1.12).[41] However, later reports[42] suggest that the major cyclisation product for the 5-hexenoyl radical is that from 5-*exo*-trig cyclisation, namely 2-methyl cyclopentanone and that the 6-*endo* product, cyclohexanone is only the minor product (Equation 1.13). Furthermore, Ingold[43,44] reports that the reaction of acyl halides with tri-n-butyltin hydride is not a simple radical reaction and that the radical pathway is only a minor one.



The reduction of ethyl chloroformate by tri-n-butyltin hydride[38] however, is slow, even at 80°C. But the reaction is facile, at 80°C, when a trace of AIBN is added, cleanly giving ethyl formate (Equation 1.14). Jackson has reduced chloroformates with trialkylsilanes in good yields (Equation 1.15).[45]

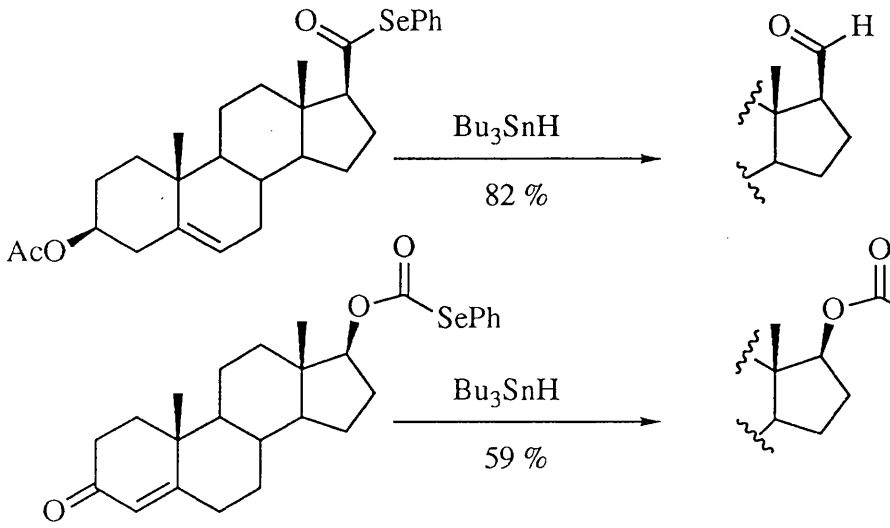




1.3.4 FROM ACYL SELENIDES.

The tri-n-butyltin hydride reduction of acyl phenylselenides, initiated by a trace of AIBN, to the corresponding aldehyde has been shown to proceed cleanly at 80°C (Equation 1.16).[46] Decarbonylation only becomes a problem at higher temperatures (120-140°C). Similarly, alkoxycarbonyl radicals can be generated by this method from

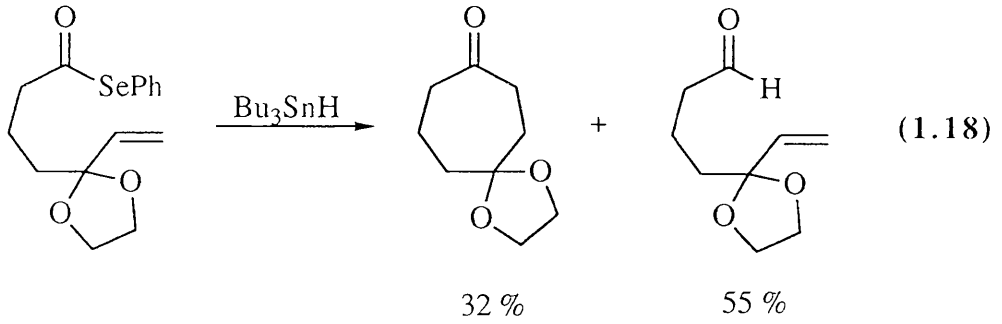
selenocarbonates , to yield the corresponding formates (Equation 1.17).[45] Acyl phenylsulphides, on the other hand, have been shown to be very poor precursors to acyl radicals.[47,48]



(1.16)

(1.17)

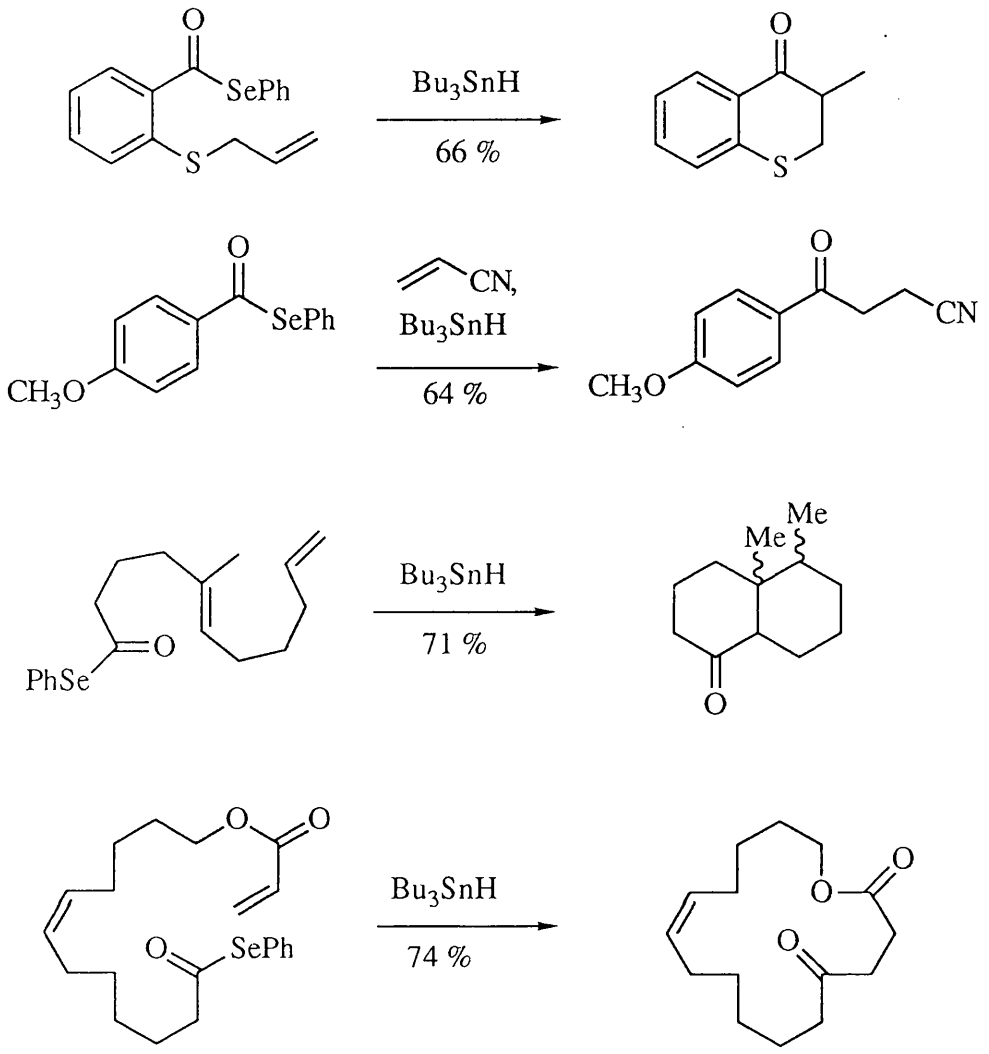
The first reported use of an acyl radical generated from an acyl selenide in C-C bond formation, was the cyclisation of a 6-heptenoyl radical to give a cycloheptanone[49] in modest yield (Equation 1.18).



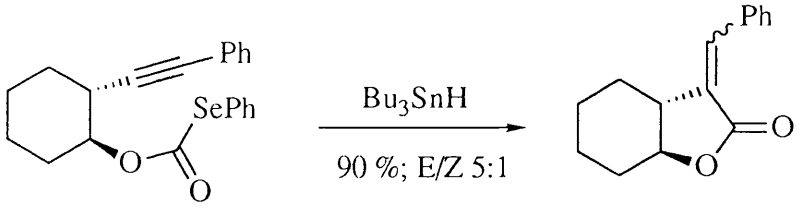
(1.18)

Further intramolecular reactions[50,47] have since been reported as well as intermolecular,[51] tandem[52] and macrocyclisation[53] reactions (Scheme 1.6).

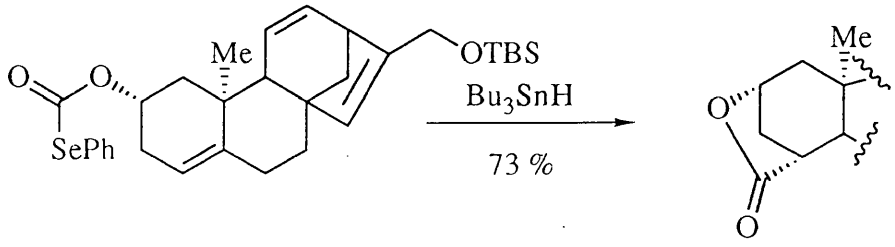
Similarly, Bachi[54] has shown that the closely related alkoxycarbonyl radicals undergo cyclisations, to give lactones in high yields (Equation 1.19). Corey[55] has used this process in his synthesis of (±)-Atractyligen (Equation 1.20).



Scheme 1.6 Typical Acyl Radical Reactions From Acyl Selenides



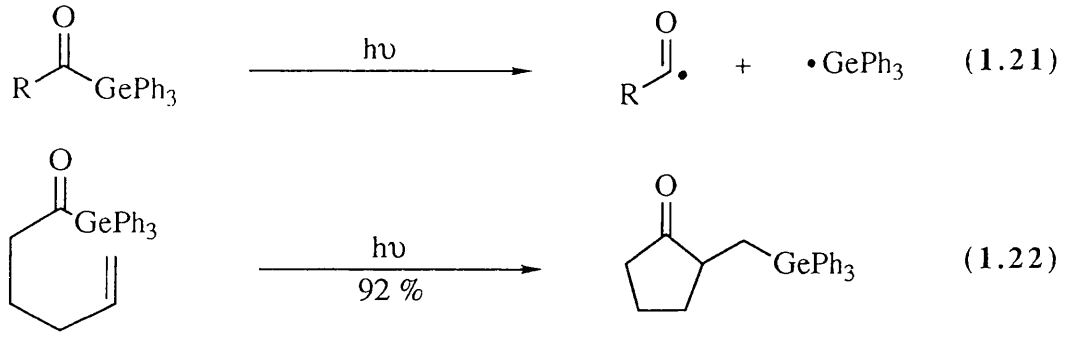
(1.19)



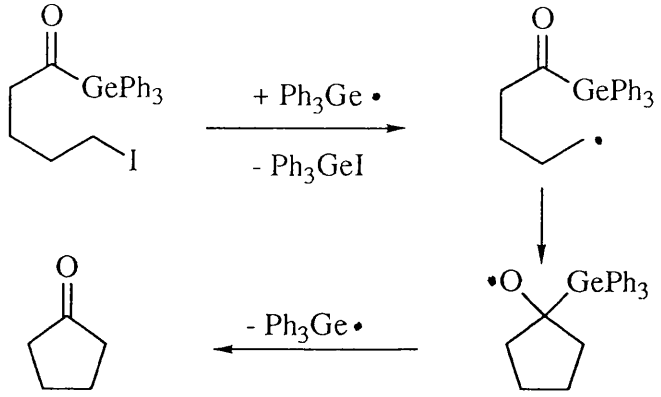
(1.20)

1.3.5 FROM OTHER ACYL-HETEROATOM DERIVATIVES.

Photochemical reactions on acyl silanes are well known to give silyloxycarbenes.[56] In marked contrast, acyl germanes are thought to undergo a Norrish Type 1 reaction, to generate a germyl radical and acyl radical pair (Equation 1.21).[57] This cleavage has been used synthetically to give novel ketones with α-(triphenyl-germyl)methyl functions, after cyclisation (Equation 1.22).[58]

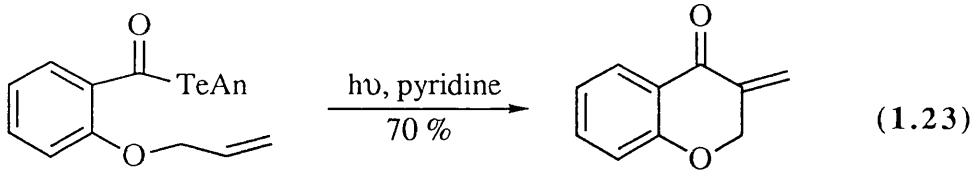


However, Curran[59] suggests that the mechanism for cyclisation does not involve the acyl radical, but that the chain transfer agent is the triphenylgermyl radical itself. In this mechanism the acyl germane acts as a radical acceptor. This is demonstrated by the cyclisation of the iodo-germylester to cyclopentanone (Scheme 1.7).

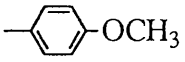


Scheme 1.7 Proposed Mechanism for Iodo-Acyl Germanes

In this laboratory, the photolysis of certain acyl tellurides has been demonstrated to be an efficacious entry into α-methyleneketones (Equation 1.23).[60]

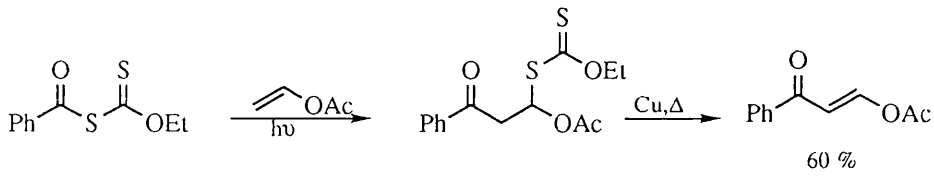


(1.23)

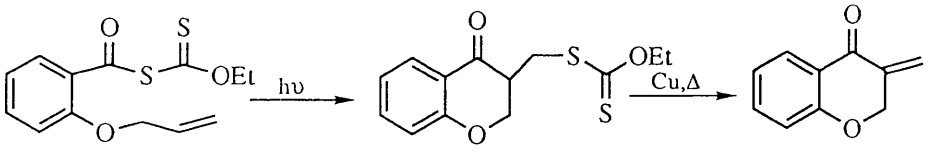
An = 

1.3.6 FROM ACYL XANTHATES.

The use of O-acyl thiohydroxamates as precursors to alkyl radicals is well established.[2f,61,62] Zard[63,64] has shown that O-acyl xanthates will cleave photolytically to generate acyl radicals, and that they will undergo intermolecular (Equation 1.24) and intramolecular (Equation 1.25) addition reactions onto alkenes. The advantage in this method is that the radical process is oxidative, rather than reductive. Consequently, there is no loss of functionality upon reaction.



(1.24)

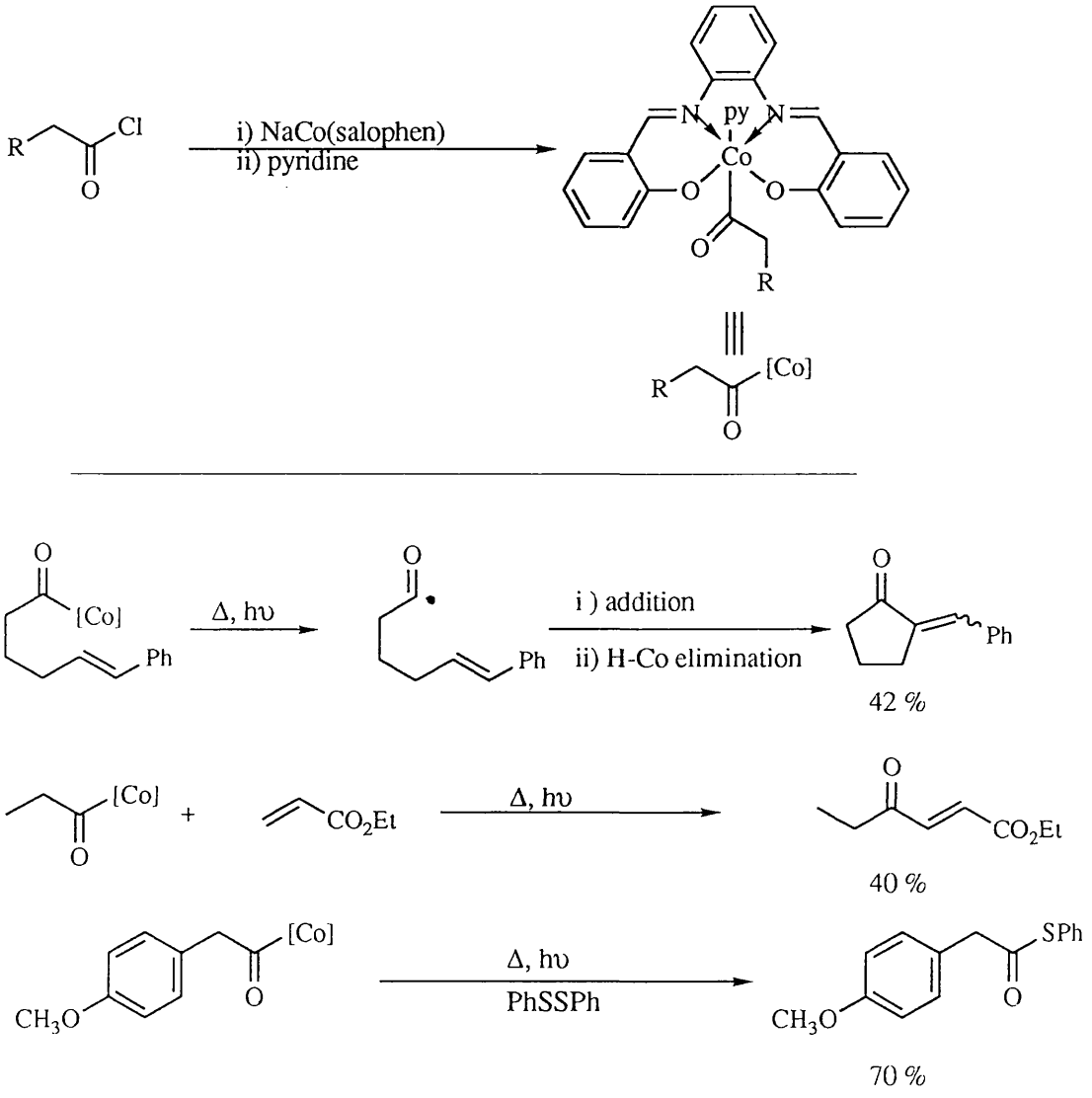


(1.25)

1.3.7 FROM ACYLCOBALT(III) COMPLEXES.

Pattenden has shown that acylcobalt(III) complexes can be efficient precursors to acyl radicals. They are capable of undergoing all the normal intermolecular[65] intramolecular[66,67] and decarbonylation reactions (Scheme 1.8).[68]

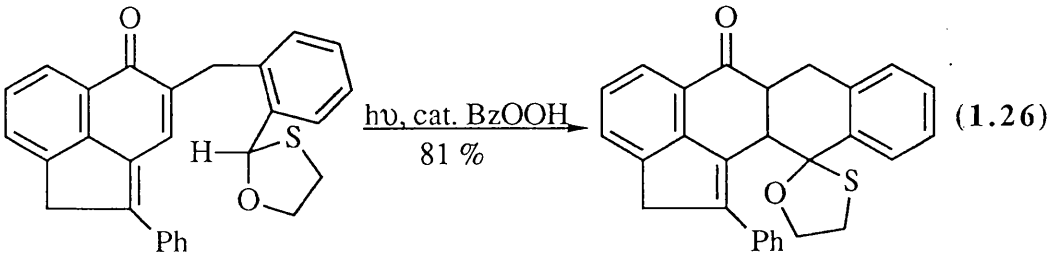
Like the acyl xanthates this is also an oxidative process with no consequent loss of functionality.



Scheme 1.8 Acyl Radical Reactions from Acylcobalt (III) Complexes

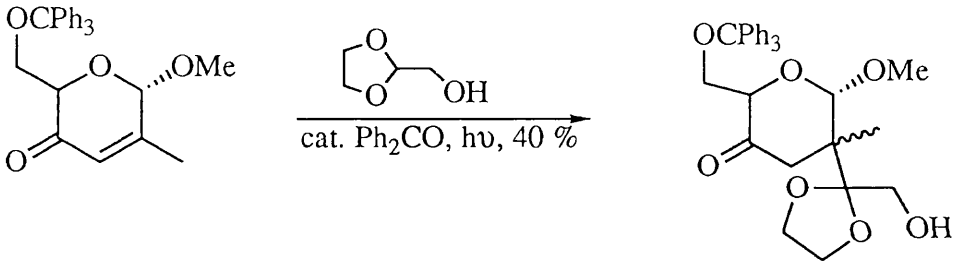
1.3.8 ACYL RADICAL EQUIVALENTS.

Aldehydes, protected as their acetals, hemithioacetals and thioacetals have been used as acyl radical equivalents. For example, Barton[69] obtained good to excellent yields in forming the B ring of tetracycline by a radical cyclisation (Equation 1.26).

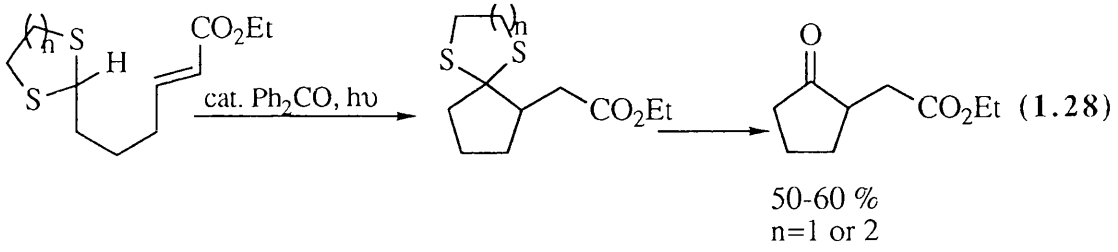


(1.26)

More recently, Fraser-Reid[70] has used the addition of oxycarbinyl radicals to enones to good effect (Equation 1.27). Others[71] have found that 5-*exo*-trig cyclisations can be performed to give 5-membered rings in good yield when the aldehyde is protected as a dithiolane or dithiane (Equation 1.28).



(1.27)



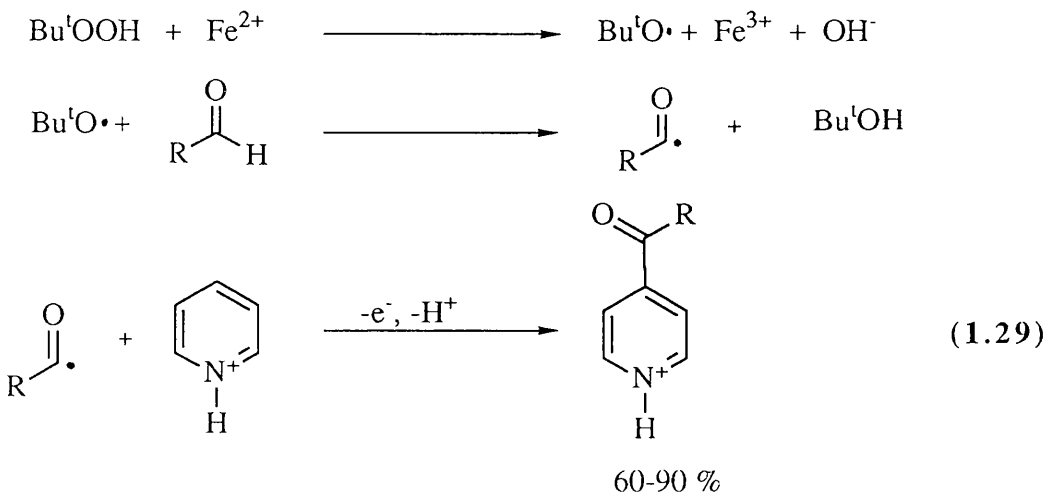
(1.28)

1.3.9 OTHER METHODS.

There are several other methods that have been used to generate acyl radicals. They include the fragmentations of α-hydroxyketones,[72] α–diketones,[73] α-keto-acids,[74] and α-ketoepoxides.[75]

1.3.10 OTHER REACTIONS OF ACYL RADICALS.

The nucleophilic nature of acyl radicals has been put to good use in additions to heteroaromatic bases. It is well known that protonated heterocyclic bases have a good reactivity towards nucleophiles, but that normal ionic reactions are hampered by preferential deprotonation. Minisci[76] has shown that homolytic acylation of these compounds can be readily accomplished by acyl radicals in high yield. Heterocycles with a single reactive site give the monoacylated product (Equation 1.29),[73,77,78] whilst those with more than one site are fully acylated.[79] Some absolute rate data for this system has also been provided.[80]



(1.29)

1.4 OBJECTIVES.

The object of the research described in this thesis was to study the application of acyl radicals, in particular, 6-heptenoyl radicals, in the formation of 6-, 7- and medium sized rings, and to develop an improved method for the formation of the preferred acyl radical precursor, the acyl selenides.

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1c. *Reactive Free Radicals* J.M. Hay, Academic Press, 1974.

For more recent work see

1d. *Best Synthetic Methods: Free Radical Chain Reactions in Organic Synthesis* D. Crich and W.B. Motherwell, Academic Press, 1991

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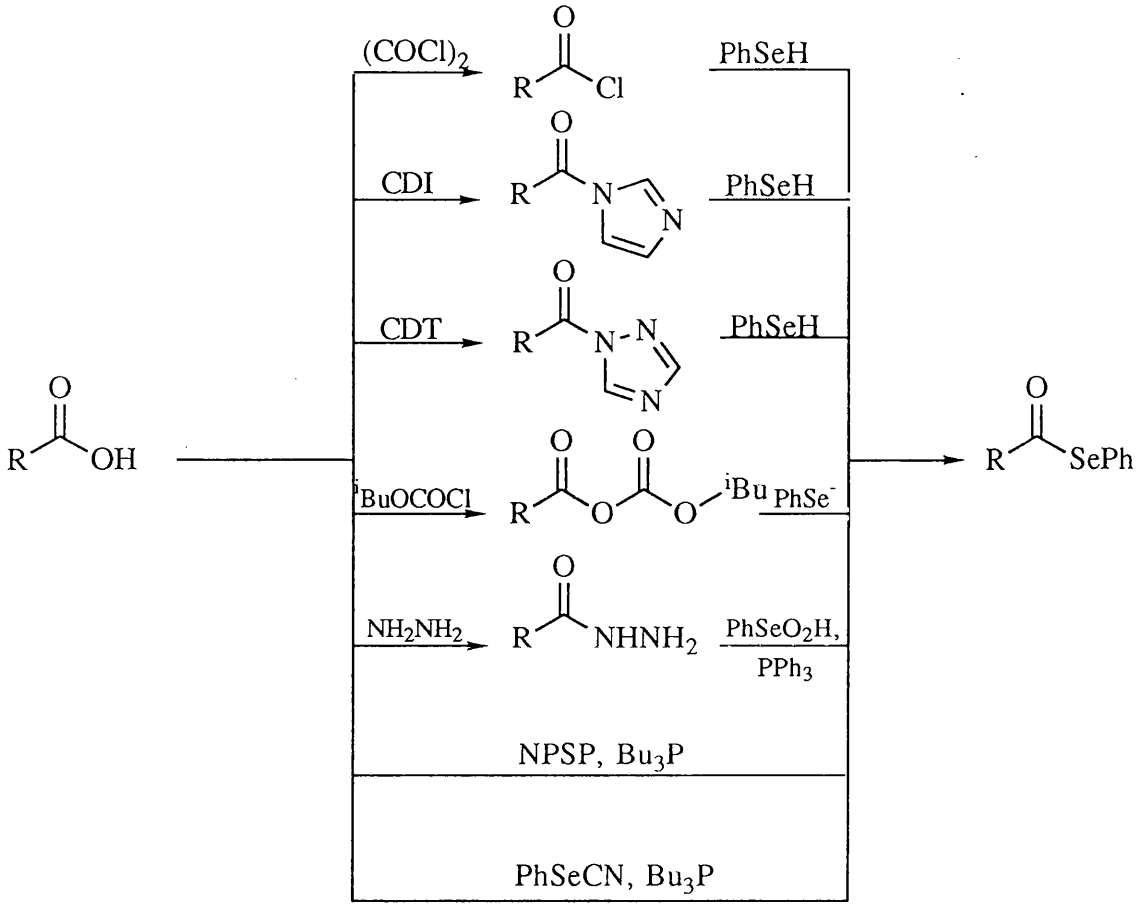
CHAPTER 2

AN IMPROVED PROCEDURE FOR THE PREPARATION OF ACYL SELENIDES

2.1 INTRODUCTION

Phenyl selenoesters are the precursors of choice for the generation of acyl radicals. Of the existing methods for preparation of phenyl selenoesters[1] the strategy of reacting a carboxylic acid, or its derivative, with a species capable of donating phenylselenide has proved the most successful. Acid chlorides,[2,3] imidazolides,[4,5] triazolides[4] and mixed anhydrides,[3] have all been demonstrated to react with selenophenol or its sodium salt, to give the corresponding phenyl selenoester in high yields (Scheme 2.1). Similarly, acyl hydrazides[6] have been converted to selenoesters by reaction with a mixture of benzeneseleninic acid and triphenylphosphine (Scheme 2.1). However, some of these acid derivatives are tedious to prepare and are not compatable with all functional groups. Furthermore, selenophenol is itself difficult to handle, readily oxidising on standing in air and is noxious, whilst its sodium salt has to be generated *in situ.* under reducing conditions. Therefore, these methods cannot be considered to be general procedures and more stable intermediates and selenium reagents are required. Interestingly, in this context, reduction of diphenyl diselenide on an anionic exchange resin, pretreated with sodium borohydride, has resulted in a resin stabilised phenylselenide that is stable and easy to handle.[7] Reaction of this resin with acyl chlorides gave selenoesters in good yields, but the method has not found wide use.

Grieco has shown that tributylphosphine, in conjunction with either phenylselenocyanate[8] or *N*-phenylselenophthalimide (NPSP)[9] readily converts carboxylic acids to selenoesters (Scheme 2.1). The advantage of this method is that prior derivatisation of the acid is not necessary. However, phenylselenocyanate is a malodorous liquid and is not commercially available, whilst NPSP is an somewhat air-sensitive and expensive solid.



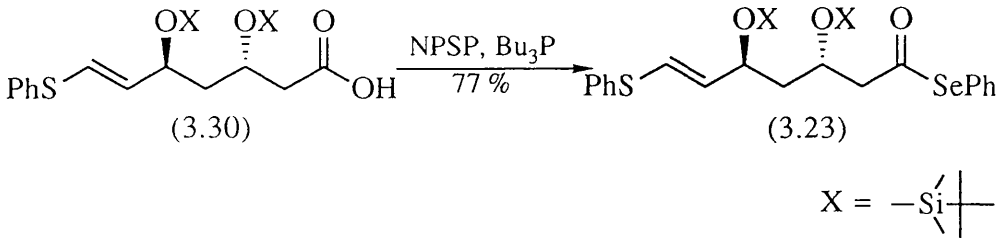
Scheme 2.1 Literature Procedures for Preparation of Selenoesters

For the work described in this thesis, it was initially thought that the NPSP method would be sufficient. However it soon became clear that an improvement on this procedure was necessary.

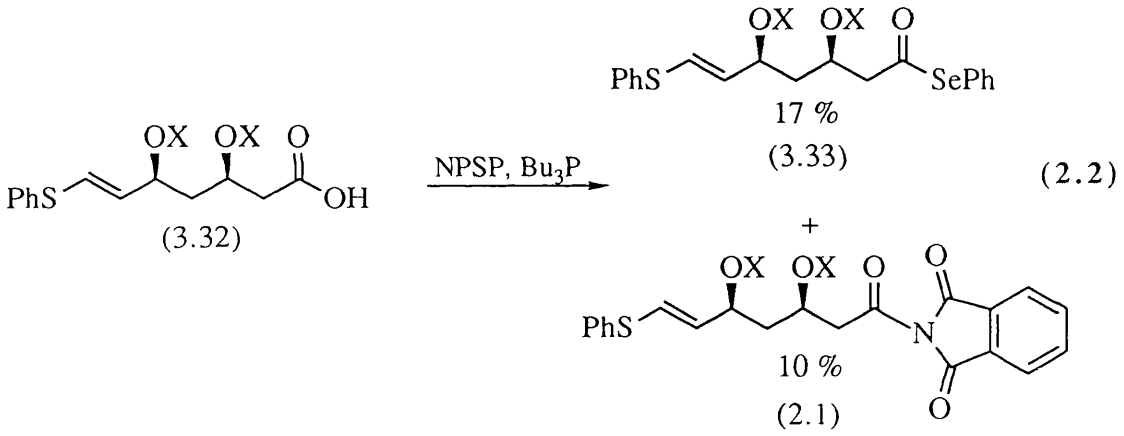
2.2 SELENOESTER PREPARATION

Initial experiments[10] from this laboratory have shown that reaction of the *anti*-bis silyloxy acid(3.30) with NPSP and tributylphosphine yielded the expected selenoester (3.23) in 77 % (Equation 2.1). In subsequent experiments with the *syn*-bis-silyloxy acid (3.32), only 17 % of the expected selenoester (3.33) was obtained, along with 10

% of the acyl phthalimide (2.1) (Equation 2.2). The low yield of selenoester and formation of acyl phthalimide was attributed to the low purity of the NPSP. It would appear that in order to obtain high yields from this method, highly purified NPSP is required. High purity NPSP is however, difficult to obtain on a reasonable scale and this is perhaps reflected in the commercial price. Hence, an investigation into other more stable and accessible phenylselenenyl containing compounds that could perform the same reaction was initiated.

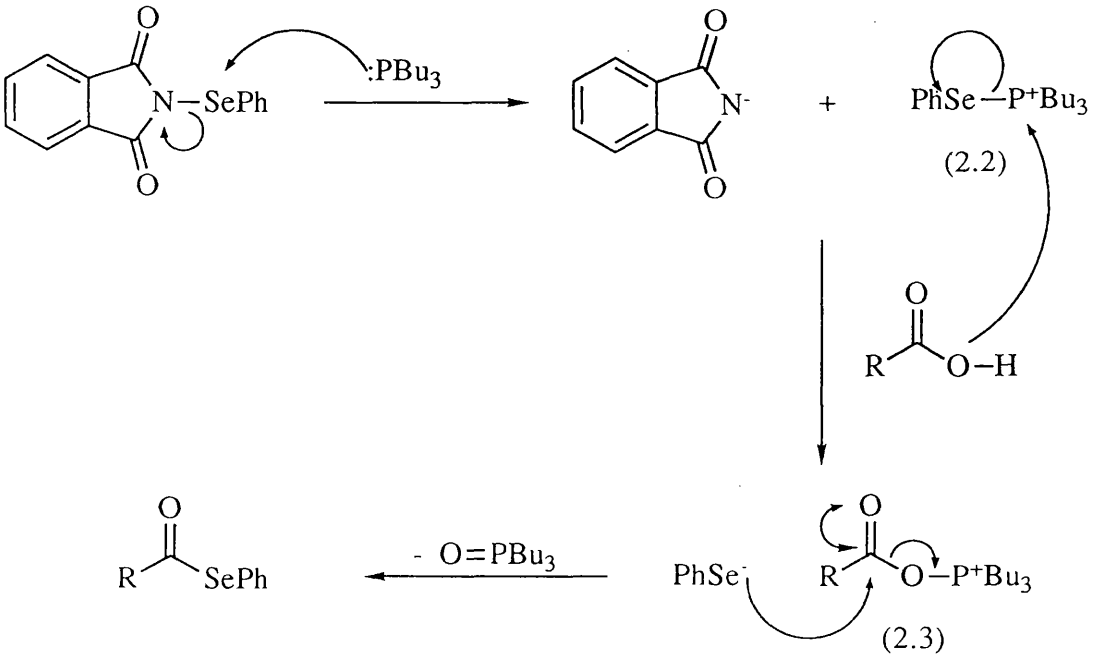


(3.30) (3.23) (2.1)



(3.32) (3.33) (2.1) (2.2)

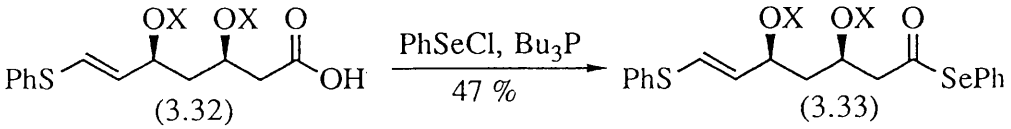
In the reaction procedures that involve either NPSP or phenylselenocyanate, the proposed active species are the phenylselenotributylphosphonium (2.2) and the acyloxytributylphosphonium ions (2.3). As both reagents gave the same reactive intermediate and perform the same reaction, it would appear that the identity of the counter ion does not affect the reaction. Therefore, replacing NPSP with any species capable of donating the phenylselenenium ion ($PhSe^+$) should effect the same transformation.



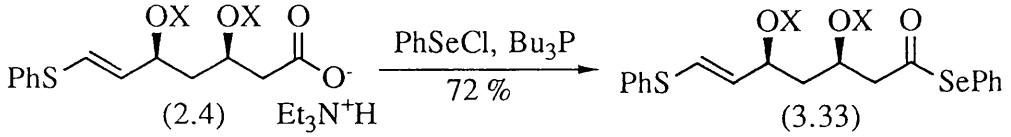
Scheme 2.2 Mechanism for NPSP Selenoester Generation

Of the readily available selenium containing species, diphenyl diselenide, phenylselenenyl chloride and phenylselenenyl bromide seemed the most suitable, as all are highly crystalline stable solids. For the purpose of this investigation, only phenylselenenyl chloride was examined.[11]

When the preparation of selenoester (3.33) was repeated replacing NPSP with phenylselenenyl chloride, a yield of 47 % was recorded (Equation 2.3). This result confirmed that the role of the counter ion is minor. However, the overall yield was not comparable to results from other procedures. It seeemed likely that the inclusion of a stoichiometric quantity of base would improve matters by initially forming the more nucleophilic carboxylate ion and subsequently by scavenging the hydrogen chloride formed. In the event, reaction of the triethylammonium salt (2.4) with a mixture of phenylselenenyl chloride and tributylphosphine yielded the required selenoester (3.33) in a pleasing 72 % yield (Equation 2.4).



(2.3)



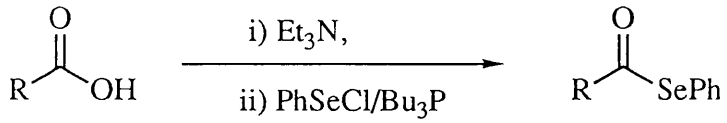
(2.4)

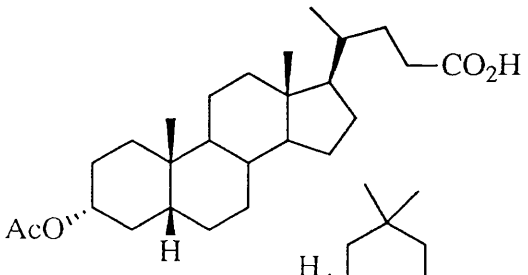
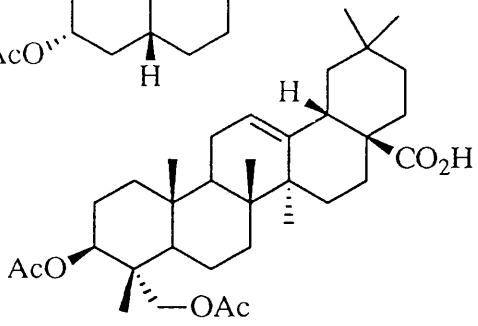
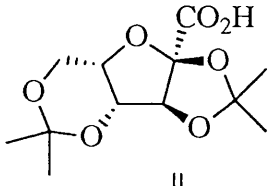
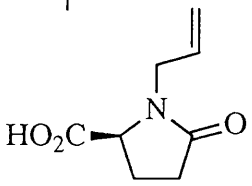
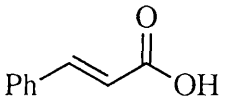
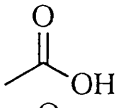
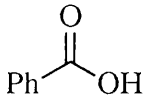
2.3 CONCLUSIONS

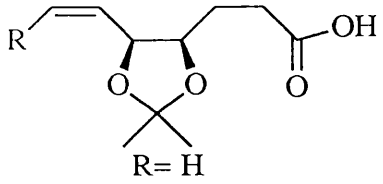
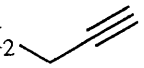
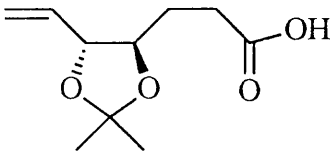
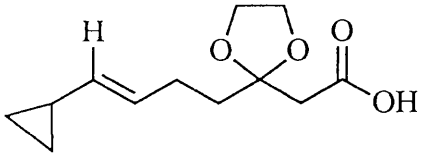
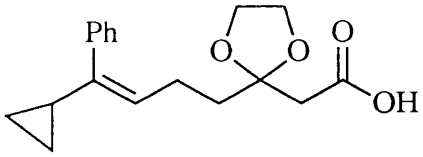
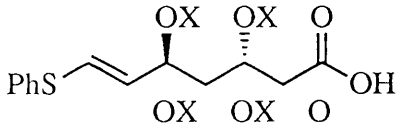
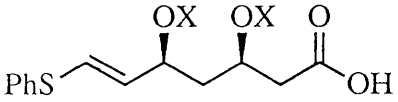
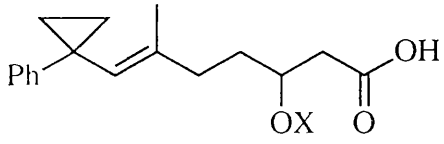
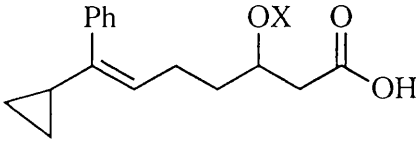
This method has been shown to be applicable to a wide range of highly functionalised carboxylic acids, summarised in Section 2.4. Overall, the yields are comparable to those obtained by existing method. Therefore, due to the lower cost and /or shorter laboratory preparation of phenylselenenyl chloride over NPSP, this method was used throughout this work as a general procedure.[12] Individual cases will be discussed at the appropriate places in the following chapters.

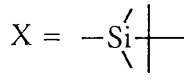
After this study was completed , other workers[13] showed that phenyl selenoesters can indeed be prepared from a diphenyl diselenide-tributylphosphine mixture.

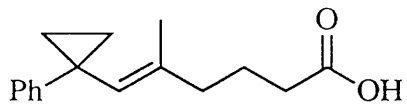
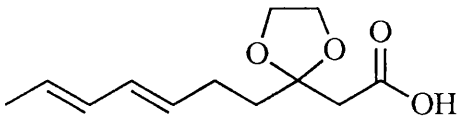
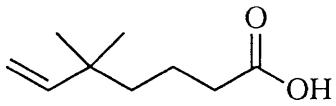
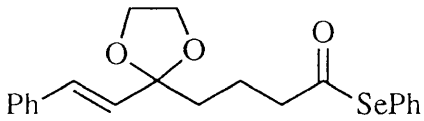
2.4 TABLE OF ACIDS CONVERTED TO SELENOESTERS BY THE PHENYLSELENENYL CHLORIDE-TRIBUTYLPHOSHINE METHOD.



		YIELD (%)
(2.5)		85
(2.6)		62
(2.7)		81
(2.8)		65 [69][3a]
(2.9)		65 [16][1e]
(2.10)		74 [94][6], [79][8]
(2.11)		83 [84][8]

		YIELD (%)
	 R= H	72
	R=CH_3	80
	R= CH_2 	76
		60
		67
		61
(3.30)		73 [77][10,a]
(3.32)		72
		29
		26



	YIELD (%)
	75
	71
	76
	86 [54][14]

1. For general reviews on organoselenium chemistry see;

1a. *Organoselenium Compounds : Their Chemistry and Biochemistry*, D.L. Klayman, W.H.H. Gunther; Wiley, New York, (1973).

1b. *Selenium Reagents and Intermediates in Organic Synthesis*, C. Paulmier; Pergamon Press, (1986).

1c. *Organoselenium Chemistry*, Ed. D. Liotta; Wiley, New York, (1987).

1d. D.L.J. Clive, *Tetrahedron*, **34**, 1049, (1978).

1e. S. Kato, T. Murai and M. Ishida, *Org. Prep. Proc. Int.*, **18**, 369, (1986).

2. J. Pfenninger, C. Heuberger and W. Graf, *Helv. Chim. Acta,* **63**, 2328, (1980).

3a. D. Crich, K.A. Eustace and T.J. Ritchie, *Heterocycles*, **28**, 67, (1989).

3b. D.L. Boger and R.J. Mathvink, *J. Am. Chem. Soc.*, **112**, 4008, (1990).

4. H-J. Gais, *Angew. Chem. Int. Ed. Engl.*, **16**, 244, (1977).

5. G.S. Bates, J. Diakur and S. Masemune, *Tetrahedron Lett.*, 4423, (1976).

6. T.G. Back, S. Collins and R.G. Kerr, *J. Org. Chem.*, **46**, 1564, (1981).

7. J.V. Weber, P. Faller, G. Kirsch and M. Schneider, *Synthesis,* 1044, (1984).

8. P.A. Grieco, Y. Yokoyama and E. Williams, *J. Org. Chem.*, **43**, 1283, (1978).

9. P.A. Grieco, J.Y. Jaw, D.A. Claremon and K.C. Nicolaou, *J. Org. Chem.*, **46**, 1215, (1981).

10. S.M. Fortt Ph.D. Thesis, University of London, 1989.

11. There is one isolated report in the literature of the formation of a simple acyl selenide by reaction of a carboxylic acid with phenylselenenyl chloride and trioctylphosphine, but no yield or reaction conditions were given:
S. Masemune, W. Schilling, W.K. Chan and G.S. Bates, *J. Am. Chem. Soc.*, **99**, 6756, (1977).

12. D.Batty and D.Crich, *Synthesis,* 273, (1990).

13. V. Singh, S.K. Ghosh, M.S. Chadha and V. R Mamdapur, *Tetrahedron Lett.*, **32**,255, (1991).

14. D. Crich and S.M. Fortt, *Tetrahedron*, **45**, 6581, (1989).

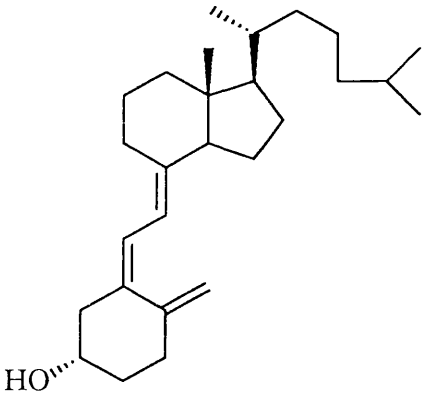
CHAPTER 3

SYNTHESIS OF 'A' RING MODELS FOR

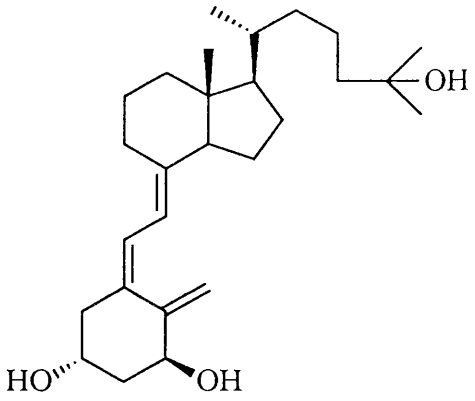
1α,25-DIHYDROXYVITAMIN D_3

3.1 INTRODUCTION

The vital role of vitamin D_3 (3.1) or more importantly, its hormonally active metabolite 1α, 25-dihydroxyvitamin D_3 (3.2), in calcium homeostasis is well understood.[1] More recently, the discovery of the involvement of this metabolite in regulating cell differentiation and proliferation in human myeloid leukemia cells[2] has generated new interest in its synthesis .

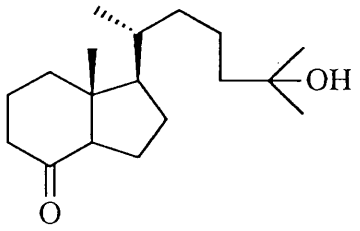


(3.1)
vitamin D_3

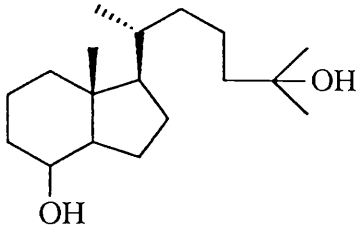


(3.2)
1α,25-dihydroxyvitamin D_3

There have been two major strategies developed towards the synthesis of hydroxylated vitamin D_3 metabolites. The more direct route involves the regio- and stereospecific hydroxylation of the parent Vitamin, as a mimic for the biosynthesis.[3] The second and more flexible strategy involves the preparation of the 'A' and 'C/D' ring fragments separately, with subsequent coupling of the two portions to provide the triene system. It is this latter method, pioneered by Lythgoe,[4] that has been the strategy of choice in many groups. The C/D ring fragment is readily available as either the Grundmann-Windaus ketone (3.3),[5] or the Inhoffen diol (3.4).[6] Consequently, most reports in this field have been directed towards the synthesis of an 'A' ring synthon and methods for coupling the two portions.[7]



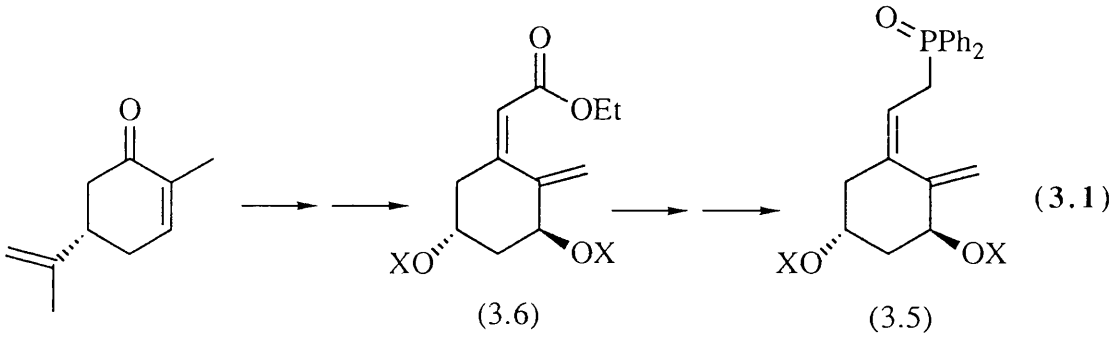
(3.3)



(3.4)

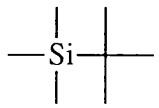
It is worthwhile at this point to examine briefly two approaches for the synthesis of Vitamin D_3 metabolites which are directly concerned with the work presented in this chapter.

Firstly, Baggiolini has synthesised the key phosphine oxide (3.5), via the α,β-unsaturated ester (3.6), as a synthon for the 'A' ring of 1α, 25-dihydroxyvitamin D_3, in 14 steps from (S)-(-)-carvone, in an overall yield of 21 % (Equation 3.1).[8] Wittig reaction between the phosphine oxide (3.5) and the Grundmann ketone (3.3) leads directly, after deprotection, to the product (3.2). The validity of this particular scheme has been vindicated by recent reports on alternative syntheses of phosphine oxide (3.5),[9] which also constitute formal syntheses of (3.2).

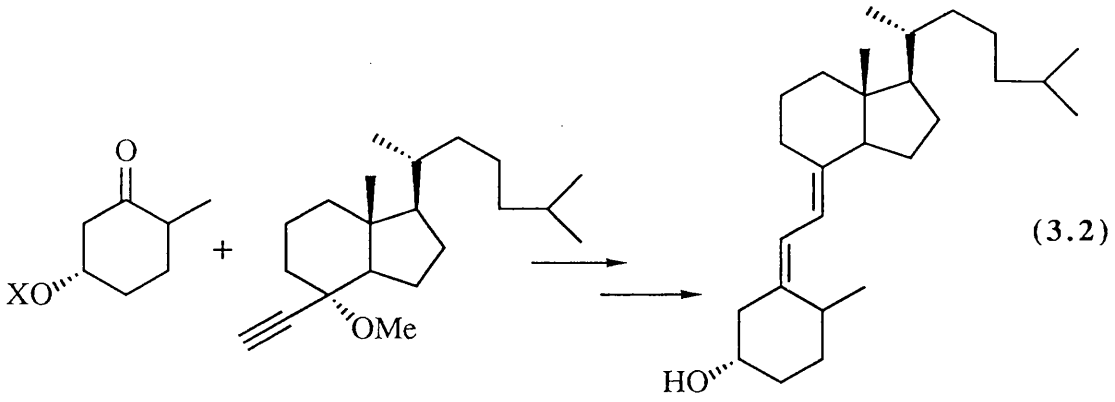


(3.6) (3.5) **(3.1)**

X =



Alternatively, Solladie has coupled the cyclohexanone derivative (3.7) to the propargylic ether (3.8) as the key step in a synthesis of the related dihydrovitamin D_3 (3.9) (Equation 3.2).[10]



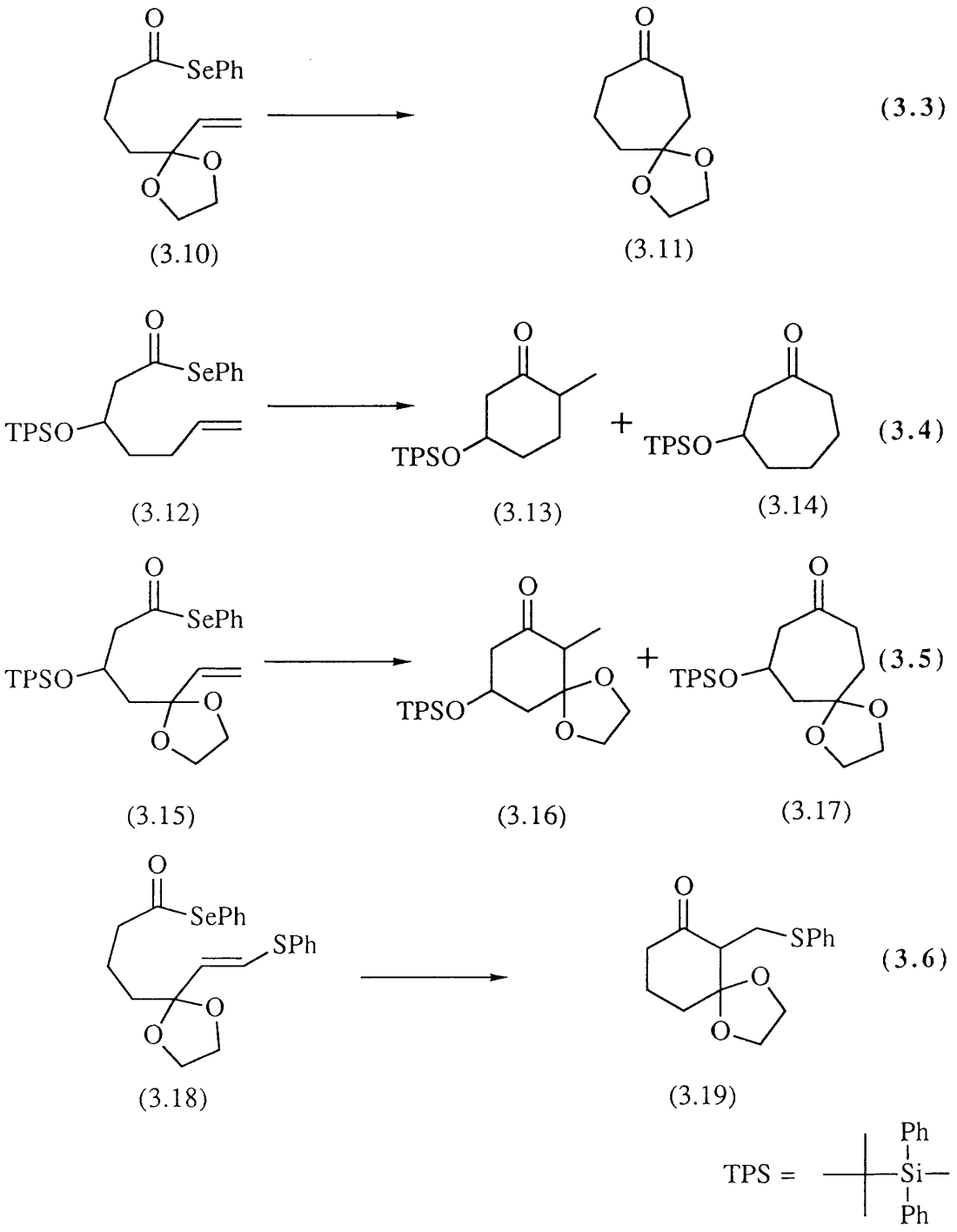
(3.2)

(3.7) (3.8) (3.9)

However, the syntheses of the 'A' ring synthon in all of these cases are lengthy, and drawn out. Therefore, in this laboratory a concise synthetic approach to an 'A' ring synthon, via an acyl radical cyclisation, was proposed; its realisation will be discussed in this chapter.

3.2 INITIAL STUDIES OF 6-HEPTENOYL RADICAL CYCLISATIONS

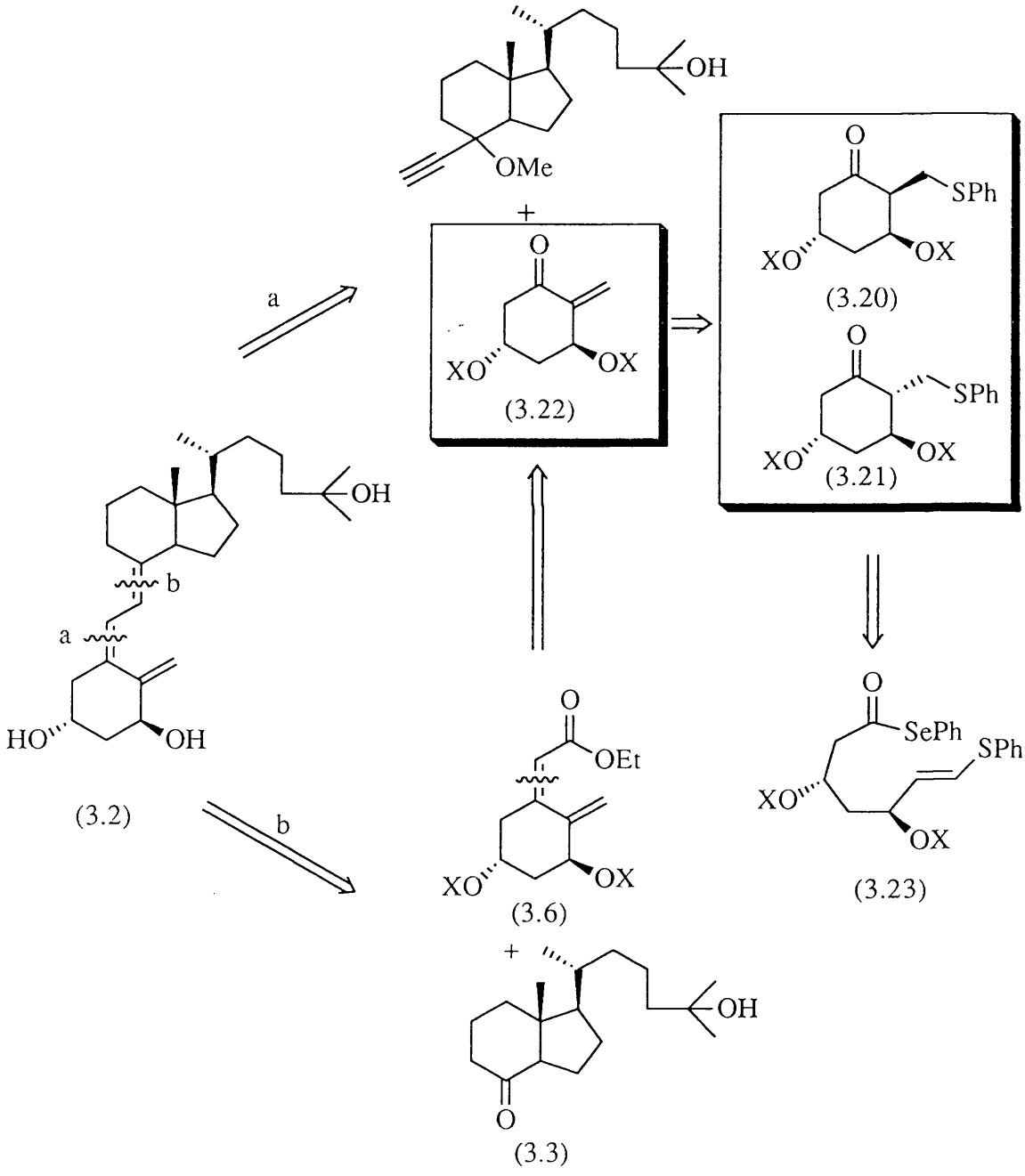
Initial studies performed in this laboratory have shown that 6-heptenoyl radicals bearing an oxygen substituent in the 5-position (3.10) give poor cyclisation yields, with the 7-*endo* product (3.11) as the only cyclised product (Equation 3.3, Scheme 3.1).[11] However, when the oxygen functionality was transposed to the 3-position (3.12), or when both the 3- and 5- positions carry oxygen substituents (3.15), not only was the efficiency of cyclisation improved, but the mode of cyclisation was reversed, with the 6-*exo* product (3.13 and 3.16 respectively) being formed predominantly (Equation 3.4 and 3.5, Scheme 3.1).[11,12] Furthermore, when a phenylthio moiety was introduced in the terminal olefinic position (3.18), the effect of the allylic oxygen substituent was overridden, with the 6-*exo* product (3.19) being the only cyclised product (Equation 3.6, Scheme 3.1).[12]



Scheme 3.1 Early Studies in 6-Heptenoyl Cyclisations

The results of these early studies indicate that with careful choice of substituents a direct entry into highly functionalised cyclohexanones can be accomplished. Moreover, it was envisaged that either of the 2-(phenylthiomethyl)cyclohexanones

(3.20) and (3.21) could give, after *syn* elimination, the 2-methylenecyclohexanone (3.22), a possible synthon for the 'A' ring using the Solladie methodology (Scheme 3.2, Path a). A further Horner-Emmons or Wittig reaction onto the cyclohexanone could introduce the α,β-unsaturated ester side-chain to give (3.6) a known precursor from the Baggiolini route (Scheme 3.2, Path b).

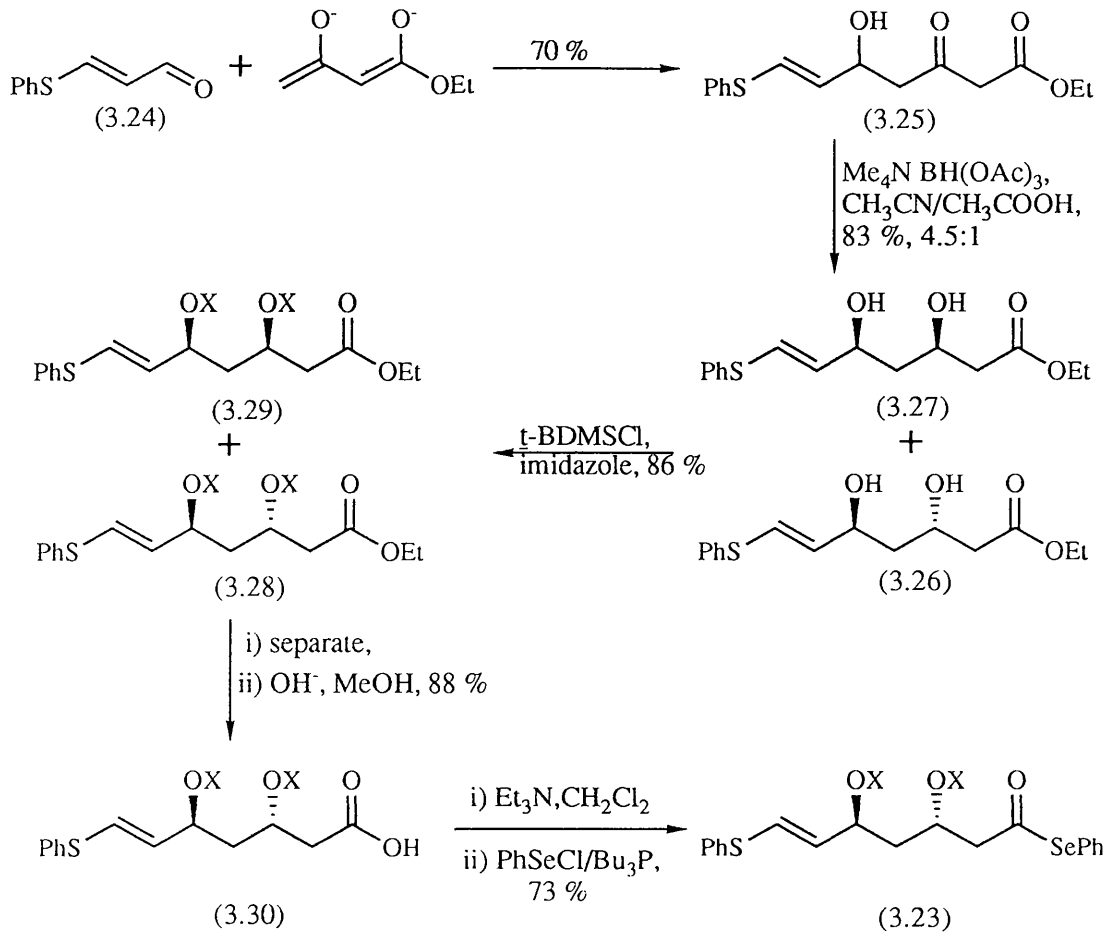


Scheme 3.2 Retrosynthetic Scheme for 1α,25-Dihydroxyvitamin D_3

3.3 A CONCISE SYNTHESIS FOR α-METHYLENECYCLOHEXANONE

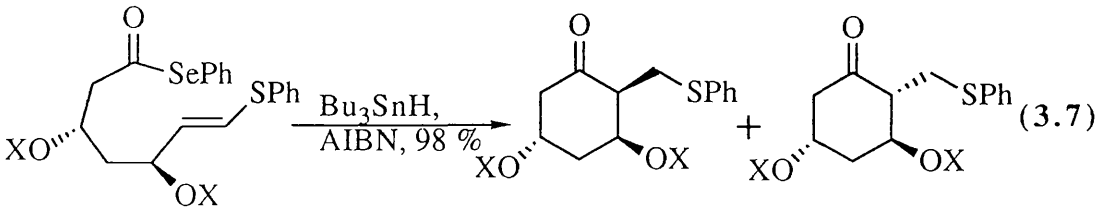
A direct entry into the carbon skeleton for the required acyl radical precursor was accomplished by the aldol condensation of the Wieler dianion[13] of ethyl acetoacetate with 3-(phenylthio)prop-2-enal (3.24) in a 70 % isolated yield. The propenal (3.24) was prepared by modification of the analogous preparation of 3-phenylthioacrylonitrile described by Bakuzis.[14] Conjugate addition of thiophenol to acrolein and subsequent chlorination with *N*-chlorosuccinimide (NCS) and dehydrochlorination gave the propenal (3.24) as a colourless oil in an overall yield of 38 %. Although this 3-stage, 2-pot reaction is not particularly efficient, it is operable on a multigram scale from readily available starting materials. It was noted that when NCS was replaced with *N*-bromosuccinimide (NBS) the overall yield was drastically reduced.

Stereoselective reduction of the β-hydroxyketone (3.25) with tetramethyl-ammonium triacetoxyborohydride[15] generated *in situ* from tetramethylammonium borohydride[16] and acetic acid, gave the racemic *anti*- (3.26) and *syn*-diols (3.27) in an 83 % yield, as a 4.5:1 mixture. The stereochemistry of the major product was assigned as *anti*, in accordance with the mechanistic rationale of Evans.[15] Silylation of this mixture with t-butyldimethylsilyl chloride gave the *anti*- and *syn*-bis(t-butyl-dimethylsilyl) ethers (3.28) and (3.29). Careful silica gel column chromatography at this stage separated (3.28) and (3.29) in 70 % and 16 % yields respectively. Saponification of the *anti*-bissilyl ether (3.28) with aqueous potassium hydroxide in a methanol-THF mixture afforded the acid (3.30) in an 88 % yield. Reaction of the triethylammonium salt of acid (3.30) with a mixture of phenylselenenyl chloride and tributylphosphine, yielded the selenoester (3.23) as a colourless oil in a 73 % yield (Scheme 3.3).

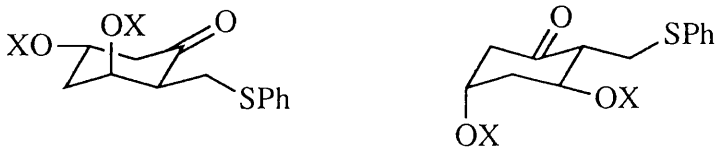


Scheme 3.3 Synthesis of 6-Heptenoyl Radical Precursor

The crucial acyl radical cyclisation was carried out in refluxing benzene with dropwise addition of a solution of tri-n-butyltin hydride in benzene, containing a trace of azoisobutyronitrile (AIBN), to give the cyclohexanones (3.20) and (3.21) as a 1 : 1.2 mixture in 98 % yield (Equation 3.7).



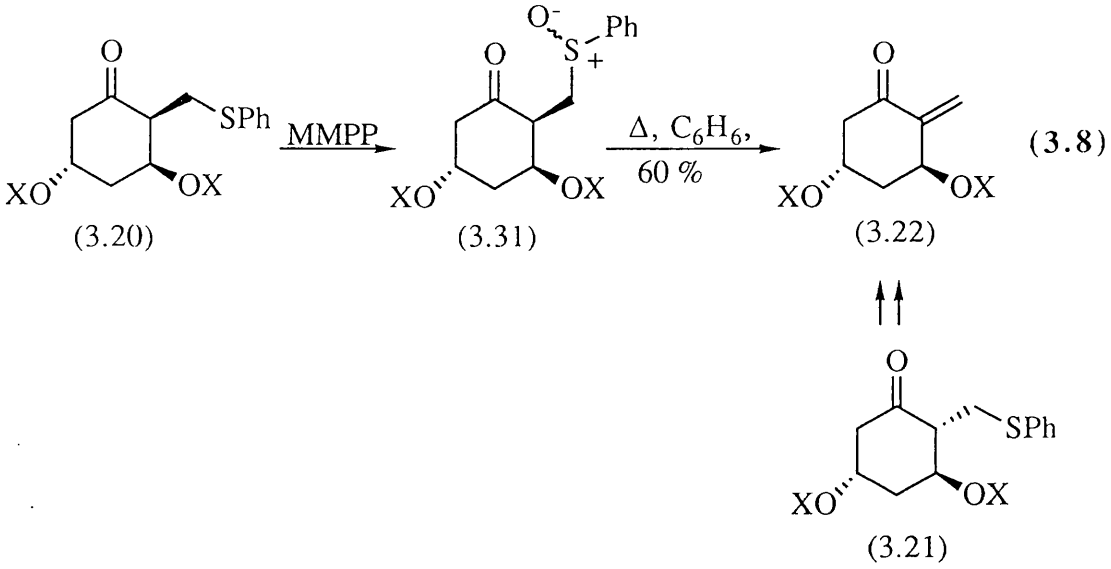
Careful examination of the high field nmr spectra for each *cyclohexanone*, especially the coupling constants and half-line widths for the 2-, 3- and 5-H signals, indicated that in both (3.20) and (3.21) the phenylthiomethyl residue occupies an equatorial position (Figure 3.1).



(3.20) (3.21)

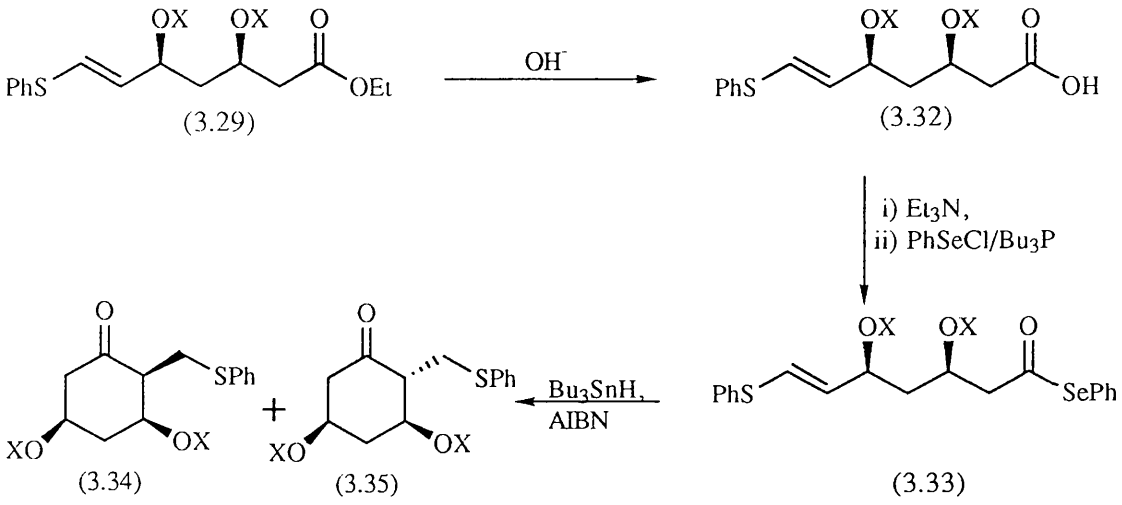
Figure 3.1 Structures of Phenylthiomethyl Cyclohexanone Derivatives

Careful oxidation of (3.20) with 1 molar equivalent of magnesium monoperoxyphthalate (MMPP)[17] in ethanol gave the sulphoxides (3.31). After extractive work-up, pyrolysis of (3.31)[18] in refluxing benzene in the presence of 2,3-dihydropyran as a scavenger for benzenesulphenic acid, gave the crystalline (±)-α-methylene cyclohexanone (3.22) in a 60 % isolated yield. An identical oxidation and *syn*-elimination was carried out on the isomeric cyclohexanone (3.21), giving the α-methylene compound (3.22) in a 34 % yield (Equation 3.8).



(3.20) (3.31) (3.22) (3.21) **(3.8)**

To emphasise the efficiency of the radical cyclisation of suitably substituted 6-heptenoyl radicals, the *syn*-bissilyl ether (3.29) was saponified to the acid (3.32) and converted to the selenoester (3.33) in a 53 % overall yield. Radical cyclisation of (3.33) under the same conditions used on the *anti*-selenoester (3.23) afforded the cyclohexanones (3.34) and (3.35) in an 81 % yield, as a 1.1 :1 mixture of stereoisomers, in which the 2,3-*cis* isomer predominated (Scheme 3.4).



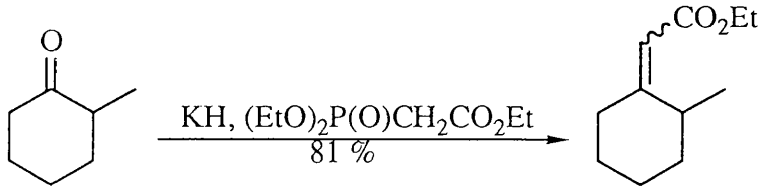
Scheme 3.4 Further Elaboration of 6-Heptenoyl Radical Cyclisation.

The phenylthiomethyl-cyclohexanones (3.20) and (3.21) and the α–methylene cyclohexanone (3.22) are all possible 'A' ring precursors for the Solladie route. Coupling of (3.20) and (3.21) with an appropriate propargyl-ether and subsequent oxidation *syn*-elimination or direct coupling of (3.23) with an appropriate propargyl-ether would ultimately give (3.2). However, this method has not gained in popularity, and it is the Baggiolini scheme that has gained widespread acceptance. Therefore, in order to show the compatability of this novel cyclisation with this more accepted route, further functional group manipulation was required to give the unsaturated ester (3.6).

3.4 ATTEMPTS AT INTRODUCTION OF THE SIDE CHAIN.

3.4.1 VIA A HORNER-EMMONS REACTION.

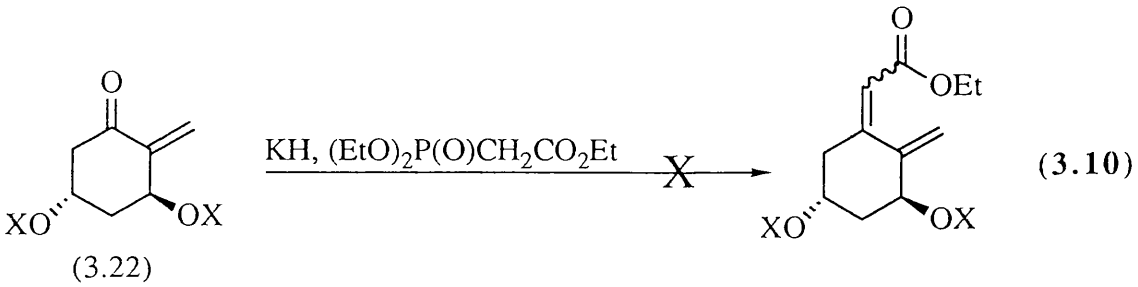
It was envisaged that a simple Horner-Emmons reaction on (3.22) would be an efficacious entry into the unsaturated ester (3.6). The action of triethyl phosphono-acetate and potassium hydride on 2-methyl cylcohexanone is well documented, giving ethyl 2-methylcyclohexylideneacetate (3.36) in high yield (Equation 3.9).[19]



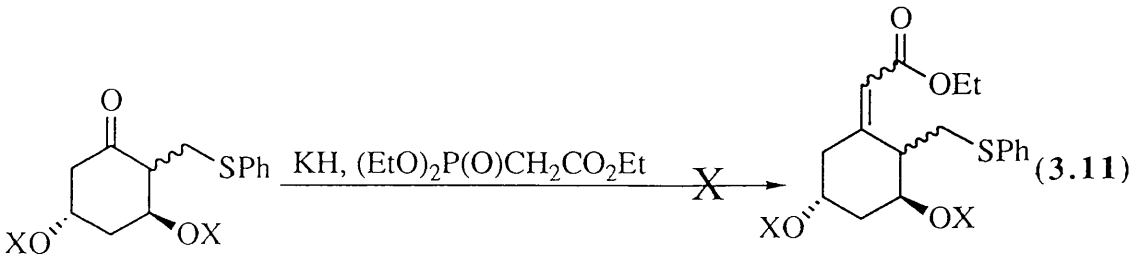
(3.9)

(3.36)

However, when the α-methylene compound (3.22) was subjected to these conditions a complex mixture was recovered (Equation 3.10). Similar results were obtained for reaction with (3.20) and (3.21) (Equation 3.11).



(3.22) (3.10)



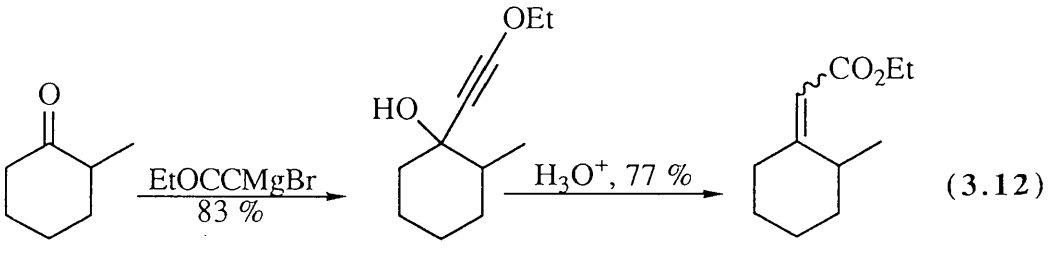
(3.20) or (3.21) (3.11)

These disappointing results were attributed to the ease of elimination of the 5-(t-butyldimethylsilyloxy) residue with subsequent aromatisation.

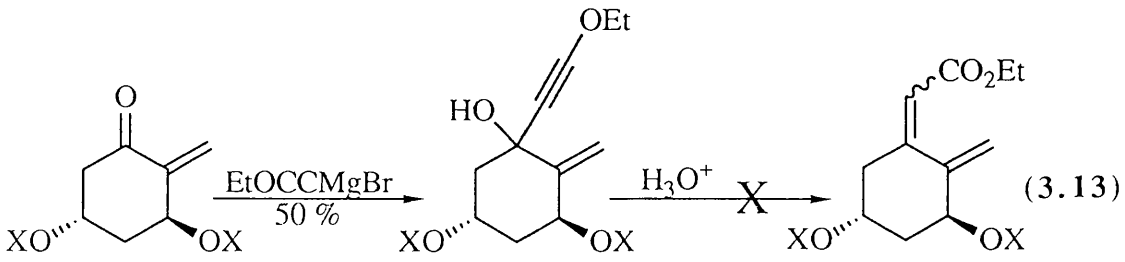
Therefore, in order to provide a method for the introduction the side chain, the addition of acetylenic Grignard reagents to the cyclohexanones (3.20) and (3.21) was investigated.

3.4.2 VIA AN ACETYLENIC GRIGNARD ADDITION.

In a trial reaction of 2-methylcyclohexanone with ethoxyethynyl magnesium bromide, prepared from a solution of ethyl magnesium bromide and freshly distilled ethoxyethyne,[20] the expected carbinol (3.37) was produced in an 83 % yield. Aqueous acidic rearrangement gave the ethyl 2-methylcyclohexylideneacetate (3.36) in a 64 % overall yield (Equation 3.12). Repeating these reaction conditions on (3.22) gave the requisite carbinol (3.38) in a 50 % crude yield, but acidic rearrangement gave a mixture of compounds, with a lqrge amount of aromatic signals apparent in the proton nmr spectrum (Equation 3.13).

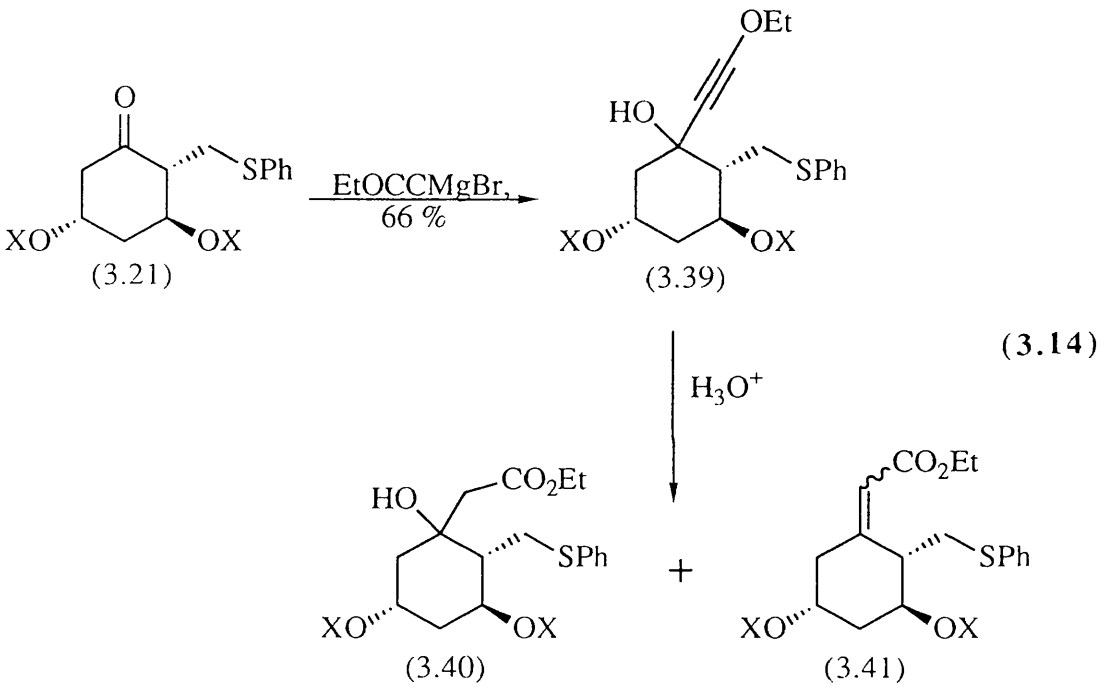


(3.37) (3.36) **(3.12)**



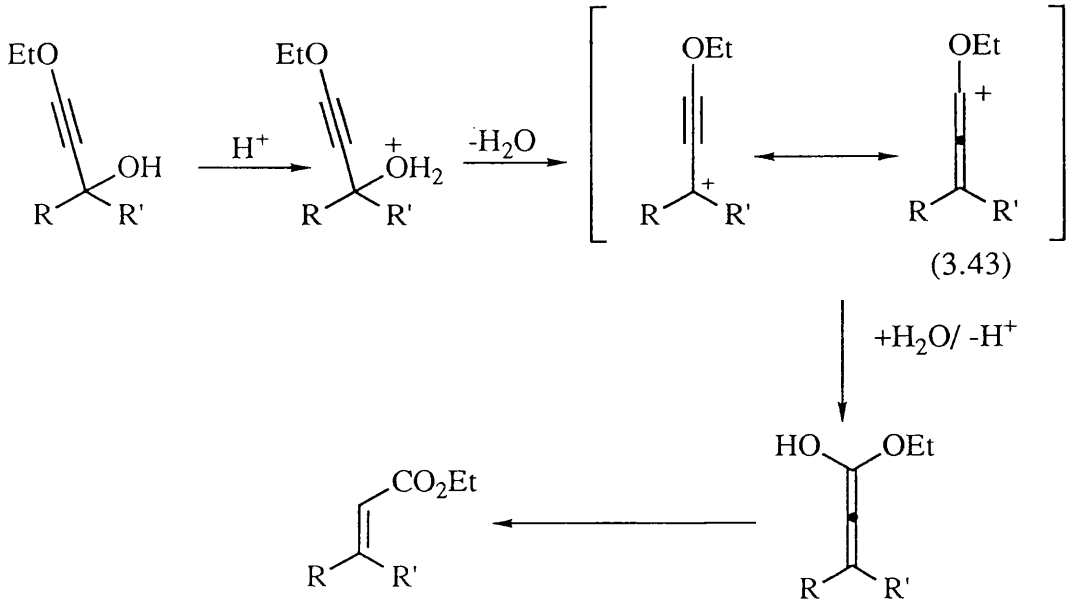
(3.22) (3.38) **(3.13)**

The action of ethoxyethynyl magnesium bromide on (3.21) gave the corresponding carbinol (3.39) in 66 % yield. However, aqueous acidic rearrangement on carbinol (3.39) gave the unexpected β-hydroxyester (3.40) in a 41 % yield. Although formation of hydroxyesters are known for this reaction, they are usually only a minor product under the conditions used.[20,21] In the course of several further attempts, the required unsaturated ester (3.41) was never recovered in greater than 3-4 % yield, after preparative HPLC (Equation 3.14).



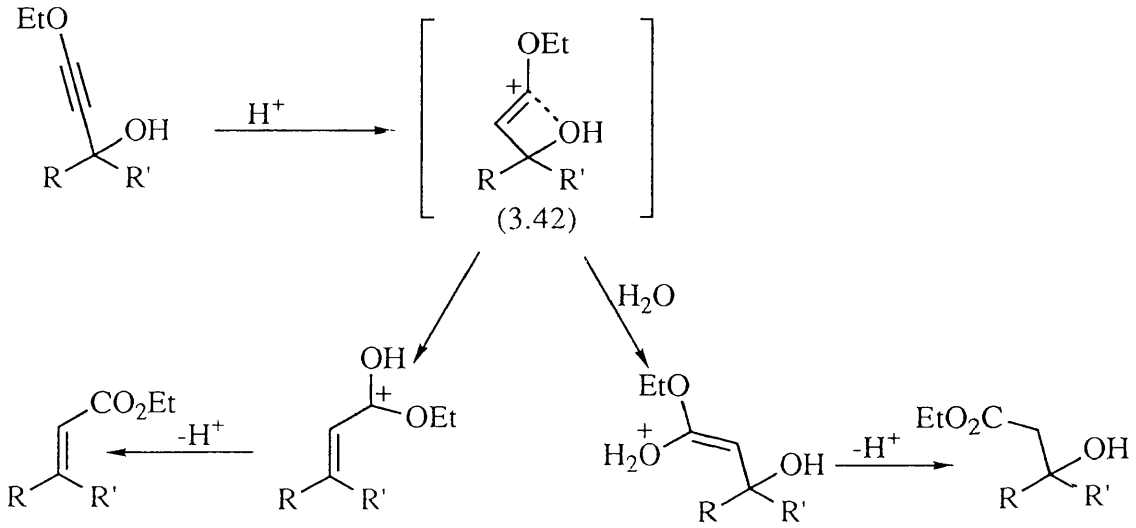
(3.14)

A possible explanation for this observation can be formed by inspection of the proposed mechanism for the reaction. Early studies suggested that the reaction might proceed via the allene carbonium ion (3.42) formed by protonation of the hydroxyl group with subsequent loss of water. Reaction with water would ultimately lead to the unsaturated ester. β-Hydroxy-ester formation was assumed to be by hydration of the triple bond (Scheme 3.5).



Scheme 3.5 Allenyl Carbonium Ion Mechanism

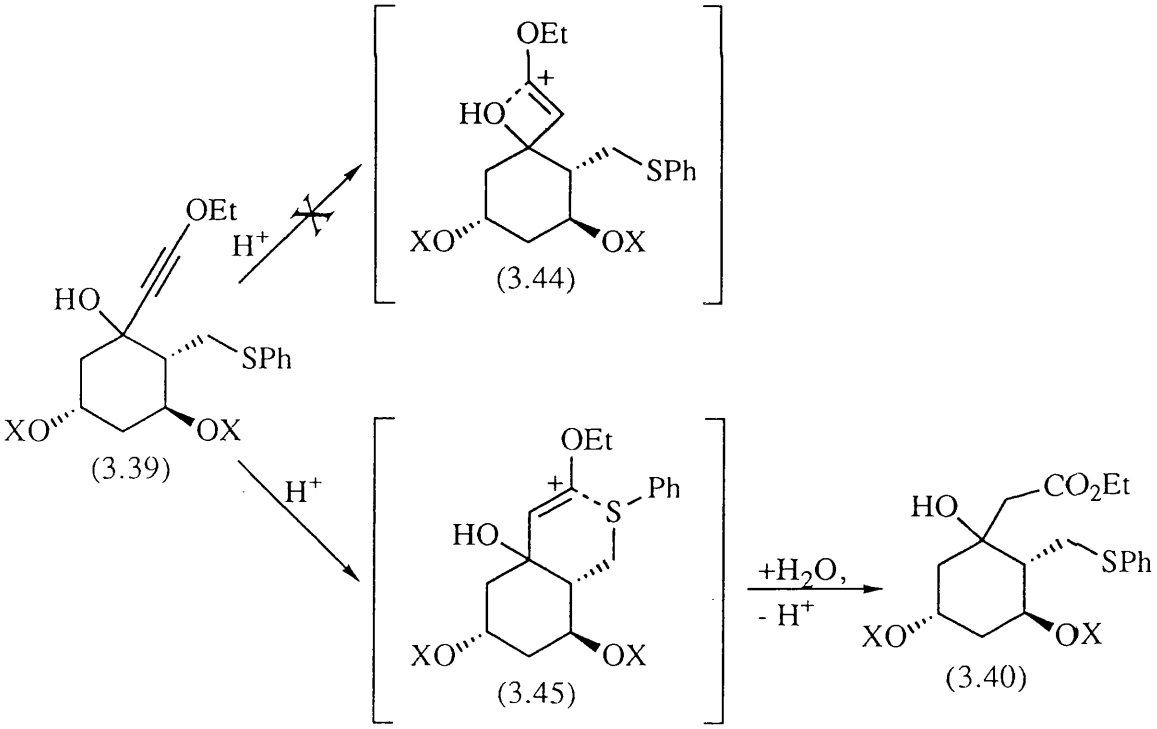
However, when the rate of reaction was measured and comparison between the rates of formation of the unsaturated ester and the hydroxyester made, it was postulated that formation of both the hydroxyester and unsaturated ester went through the same intermediate. Moreover, the driving force for unsaturated ester formation was a neighbouring group participation effect from the hydroxyl group (Scheme 3.6).



Scheme 3.6 Vinyl Carbonium Ion Mechanism

Therefore, protonation of the triple bond leading to the cyclic intermediate (3.43) was assumed to be the rate determining step. Intramolecular rearrangement then leads to the unsaturated ester, whilst attack of water gives the β-hydroxy-ester. In most cases, the intramolecular rearrangement is fast and hence, the unsaturated ester is the predominant product.

Applying this rationale to the case in question, protonation of the triple bond in carbinol (3.39) should give the 4-membered cyclic intermediate (3.44) (Scheme 3.7). However, it would also appear possible that the more thermodynamically favourable 6-membered intermediate (3.45) would be formed. If this were the case, then intramolecular rearrangement would have to be ruled out as a possible reaction pathway. Thus, the slower intermolecular reaction of addition of water would be the most likely reaction and hence the β-hydroxy-ester (3.40) is the major product (Scheme 3.7).



Scheme 3.7 Proposed Mechanism for Formation of Saturated Hydroxyester (3.40)

There are several possible solutions to this problem. The action of a Lewis acid in non-aqueous media would prevent addition of water and hence formation of β-hydroxy-ester.[22] Whether this would help the slow rearrangement remains to be seen. Alternatively, if formation of (3.45) was prevented by oxidation to the sulphoxide, then the required rearrangement might be promoted.

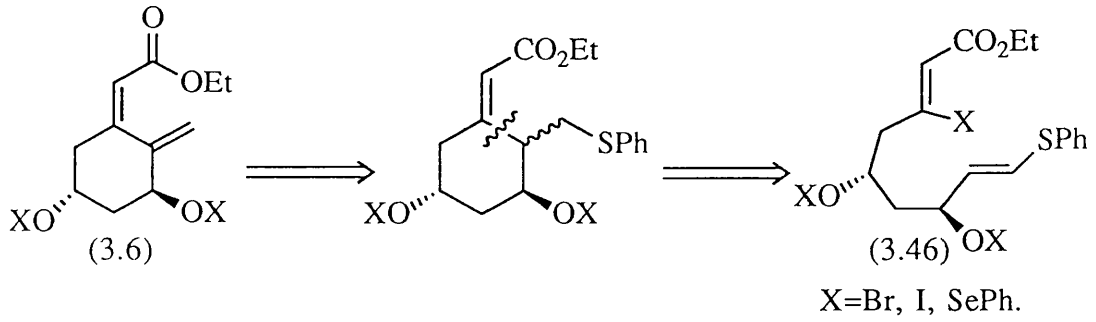
Attempts to dehydrate the hydroxy-ester (3.40) by either elimination as the mesylate or by Martin sulphurane agent [23] did not yield the required unsaturated ester owing respectively to decomposition and lack of reaction.

Due to these unexpected problems incurred with the introduction of the 2 carbon side-chain, attention was then given to the incorporation of this chain into the molecule before cyclisation.

3.5 A NOVEL SYNTHESIS OF A KNOWN 'A' RING SYNTHON VIA A VINYL RADICAL CYCLISATION.

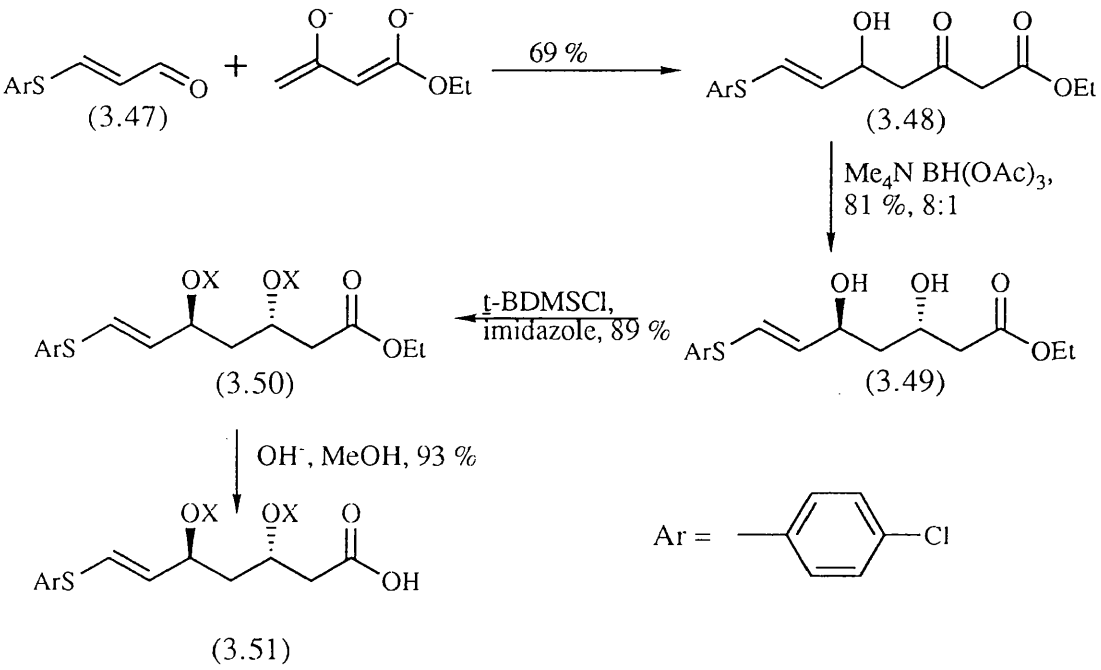
The use of vinyl radicals in free radical chemistry is well documented.[24] Vinyl radicals can either be designated as σ-radicals or as π-radicals, depending on the electronic nature of substituents.[25] In contrast to acyl radicals, vinyl radicals, even in cases where σ-radical formation is enhanced, are electrophilic in nature. Consequently, cyclisation reactions with vinyl radicals onto alkene and alkynes are common.[26] It was presumed that for the system in question, vinyl and acyl radicals would react in a similar fashion, owing to the intramolecular nature of the reaction. With this in mind, re-examination of the retrosynthetic analysis for the target molecule (3.6) (Scheme 3.8) indicated that the vinyl radical precursor (3.46) would be an ideal choice for this

cyclisation. Moreover, the existing methodology, developed for the preparation of (3.22), could be readily modified to give a direct entry into this vinyl radical precursor.



Scheme 3.8 Retrosynthetic Analysis of 'A' Ring Precursor

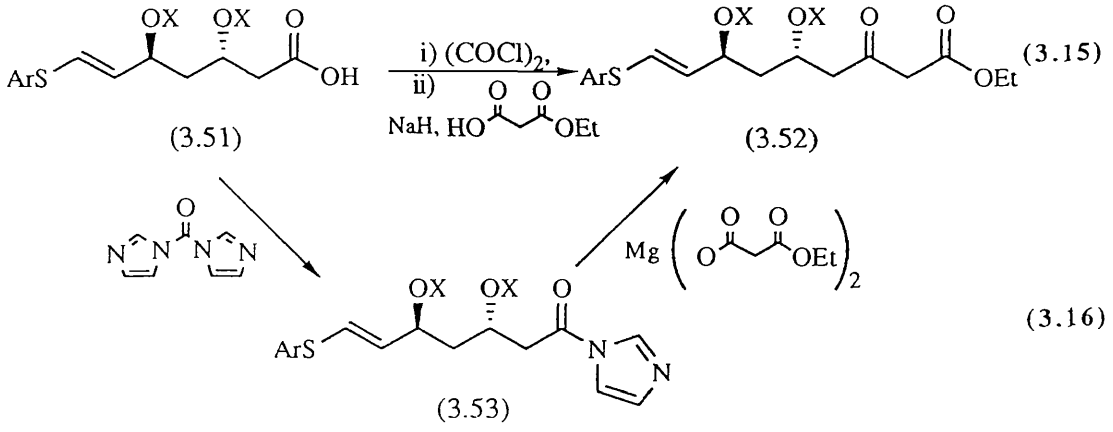
To this end, the acid (3.51) was prepared in an analogous fashion to the *anti*-acid (3.30) (Scheme 3.9). The phenylthio- residue was replaced by a 4-chlorophenylthio- residue with the view to enhancing the cystallinity and hence ease of purification of various intermediates: a strategy that was moderately successful.



Scheme 3.9 Improved Synthetic Route With 4-(Chlorophenylthio) Residue.

The stereoselective reduction of the β-hydroxyketone (3.48) was performed with commercial tetramethylammonium triacetoxyborohydride to give the diol (3.49) in an 81 % yield as an 8:1 mixture of *anti-* and *syn-* isomers. The overall yield of the *anti-* acid (3.51) was 41 % in 4 steps from ethyl acetoacetate.

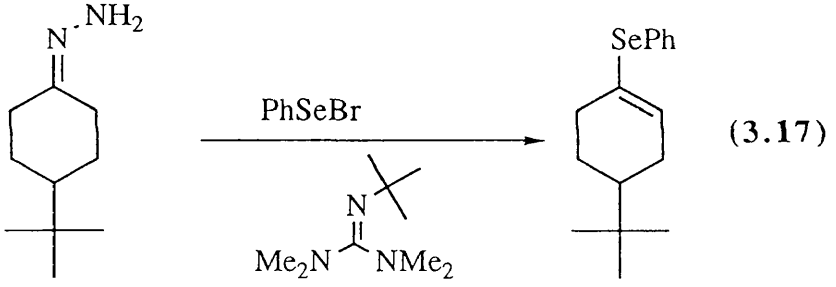
Initial attempts at the homologation of (3.51) to the β-ketoester (3.52) by reaction of the derivatised acid chloride with the dianion of monoethyl malonate resulted in a disappointing 17 % yield (Equation 3.15).[27] Once again, ease of elimination of a silyloxy function was thought to be the cause of this low yield. However, when the acid was derivatised as the imidazolide (3.53) and stirred with magnesium monoethyl malonate, as descibed by Masamune,[28] the β-ketoester (3.52) was isolated in a yield of 81 % (Equation 3.16).



The final hurdle before cyclisation was the conversion of the β-ketoester into a vinyl selenide or halide. Although all the existing methods for vinyl radical cyclisation involve the use of vinyl halides, it was decided a vinyl phenylselenide, was preferable, due to the ease of removal of the tin-selenium residues from the reaction mixture.

3.6 ATTEMPTS TO PREPARE VINYL PHENYLSELENIDES

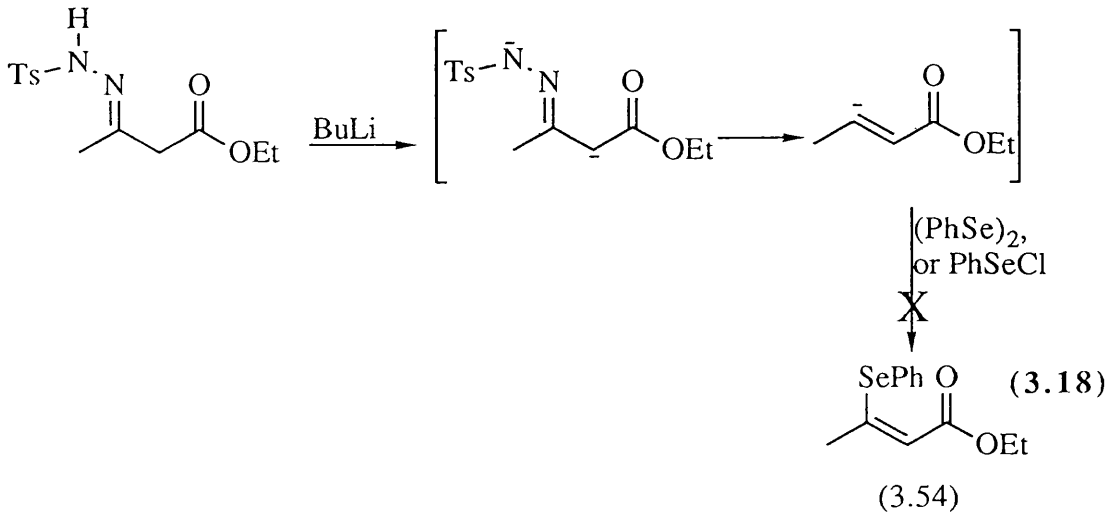
Most of the existing methods for the generation of vinyl selenides involve the formation of a 1-arylseleno-1-alkene.[29] The usual methods for formation of a vinyl selenide involving the addition of selenophenol across a triple bond,[30] addition-elimination of phenylselenenyl bromide on an olefin[31] or displacement of bromine from a vinyl bromide,[32] appeared to be incompatable with the system in hand. An isolated report by Barton[33] describes the preparation of vinyl selenides from hydrazones by reaction with phenylselenenyl bromide in the presence of a hindered guanidine base (Equation 3.17). However, in all the examples quoted, only stable hydrazones of cyclic ketones were used, which brings into doubt the viability of this method with less stable aliphatic hydrazones.



(3.17)

Therefore, a new method for the preparation of vinyl selenides, from β-ketoesters was required.

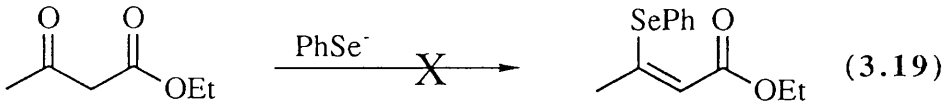
It is well known that in the Shapiro reaction, double deprotonation of tosyl hydrazones generates the corresponding vinyl anions, which can be quenched with electrophilic species.[34] However, when the tosylhydrazone of ethyl acetoacetate[35] was treated in a similar fashion and the reaction quenched with either diphenyl diselenide or phenylselenenyl bromide, none of the required unsaturated phenylselenide (3.54) was formed (Equation 3.18).



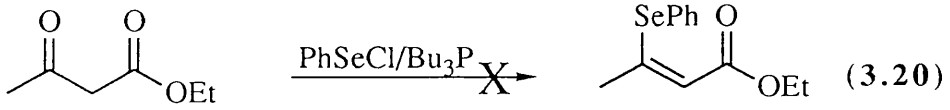
(3.18)

(3.54)

Attempts to prepare (3.54) in a one pot procedure by reaction of ethyl acetoacetate with either sodium phenylselenide (Equation 3.19) or a mixture of phenylselenenyl chloride and tributylphosphine (Equation 3.20) were unsuccessful.



(3.19)

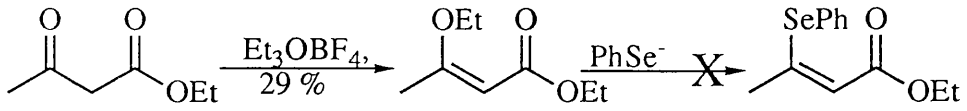


(3.20)

(3.54)

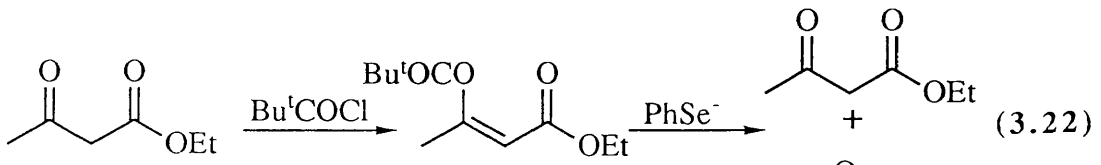
As none of these approaches gave the required product, investigations into preparing enol derivatives of ethyl acetoacetate with subsequent substitution by sodium phenylselenide were carried out. Reaction of triethyloxonium tetrafluoroborate and pyridine with ethyl acetoacetate gave the requisite enol ether (3.55) in 29 % yield, but subsequent reaction of (3.55) with sodium phenylselenide did not yield (3.54) (Equation 3.21). Reaction of ethyl acetoacetate with pivaloyl chloride gave the acyl enol ether (3.56) in a 60 % yield, but further reaction with sodium phenylselenide gave the pivaloyl selenoester (3.57) and recovered ethyl acetoacetate (Equation 3.22). It would appear that alkyl enol ethers are too stable for nucleophilic attack by

phenylselenide, whilst acyl enol ethers are preferentially attacked at the carbonyl centre, even under sterically unfavourable conditions.



(3.21)

(3.55)

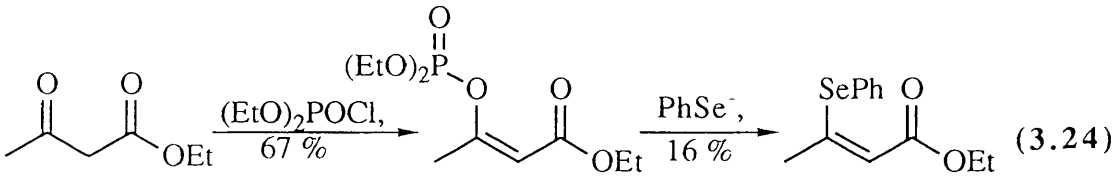


(3.22)

(3.56)

(3.57)

Enol sulphonates and phosphonates were therefore investigated. However, preparation of enol sulphonates proved difficult, despite the work of Rosling,[36] and so eventually, in the light of the work of Jones[37] who showed that reaction of diethyl chlorophosphate with ethyl acetoacetate under phase transfer conditions gave the unsaturated phosphate (3.58) in high yield, enol phosphonates were turned to. Reaction of (3.58) with sodium phenylselenide gave the requisite unsaturated phenylselenide (3.54) in a 16 % yield, together with significant quantities of ethyl phenylselenide (Equation 3.24).

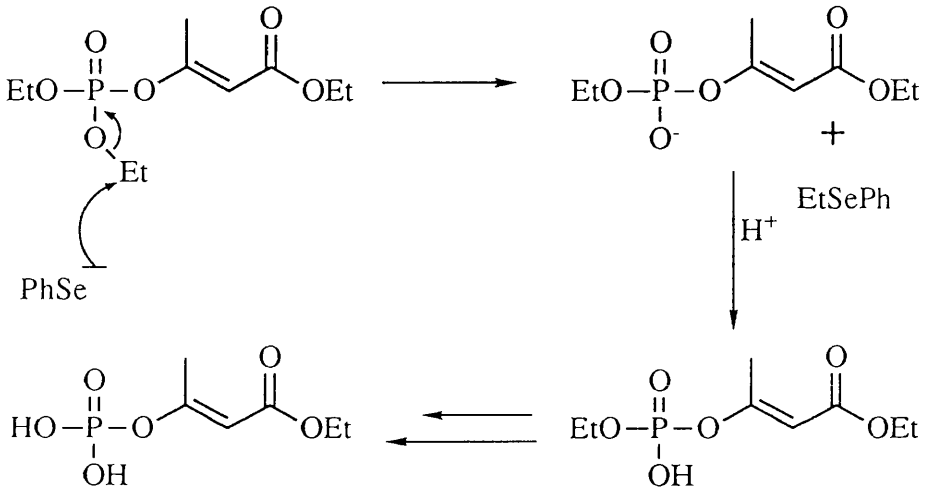


(3.24)

(3.58)

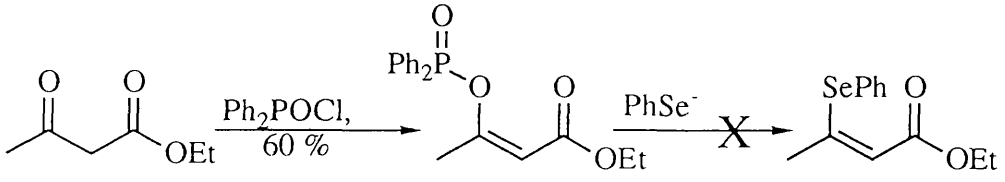
(3.54)
+
EtSePh

The unexpected ethyl phenylselenide was presumed to be generated by competing Arbuzov reaction between the unsaturated phosphate and phenylselenide (Scheme 3.10).

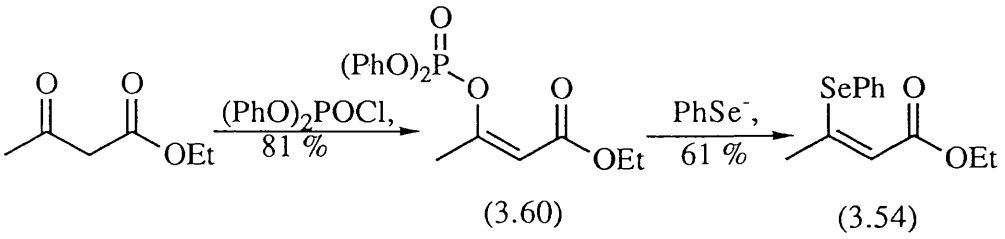


Scheme 3.10 Arbuzov Reaction Mechanism

In order to prevent this side reaction, unsaturated phosphonates, not susceptable to the Arbuzov reaction were prepared. Therefore, using the same phase transfer conditions, (3.59) and (3.60) were prepared from diphenyl chlorophosphinate and diphenyl chlorophosphate in 60 % and 81 % yields in a ratio of 4:1 for *E*- and *Z*-isomers. Reaction of (3.59) with sodium phenylselenide gave a complex mixture of products (Equation 3.25), whilst reaction of (3.60) with sodium phenylselenide gave the required unsaturated phenylselenide (3.54) in 66 % yield also in a 4:1 mixture of *E*- and *Z*- isomers (Equation 3.26).



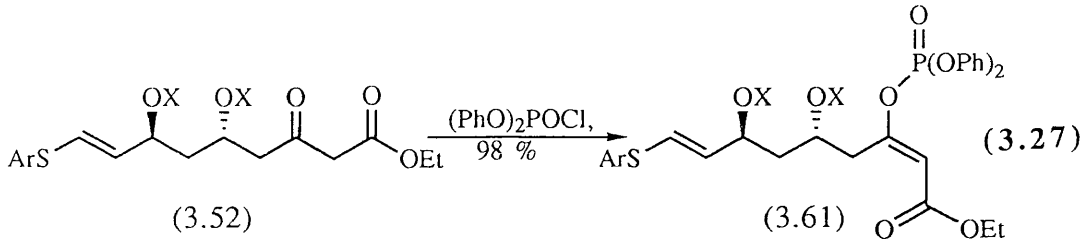
(3.59) (3.54) (3.25)



(3.26)

(3.60) (3.54)

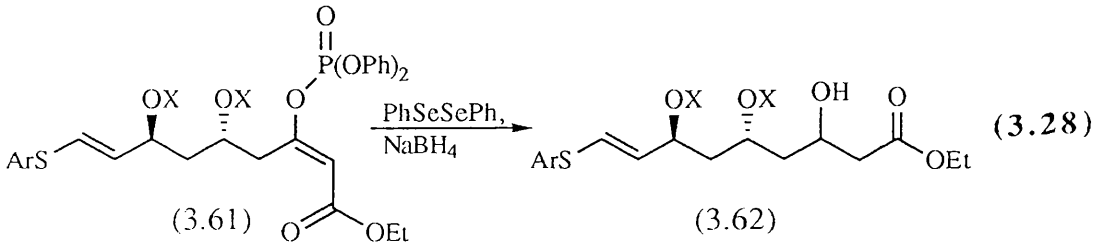
Therefore, in view of the results from these trial reactions, the β-ketoester (3.52) was treated with diphenyl chlorophosphonate under the same phase transfer conditions to give the expected unsaturated phosphonate (3.61) in a 98 % yield as a 10:1 mixture of *E*- and *Z*- isomers (Equation 3.27).



(3.27)

(3.52) (3.61)

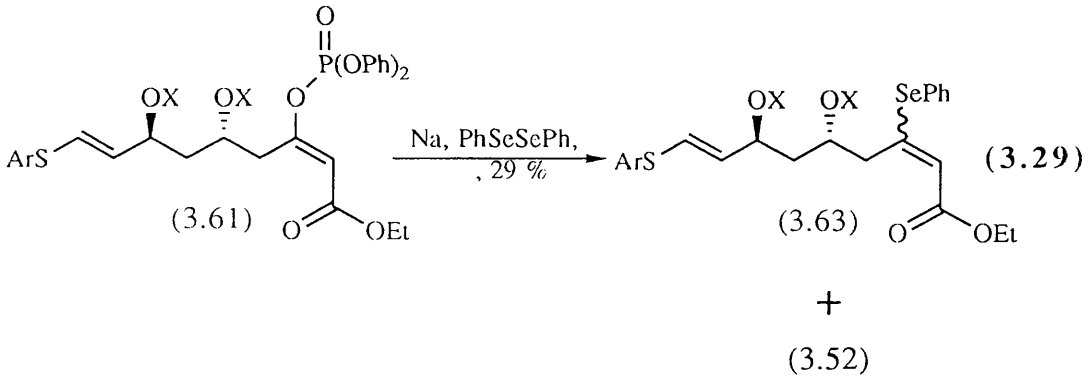
Reaction of the unsaturated phosphonate (3.61) with sodium phenylselenide gave the unexpected β-hydroxy-ester (3.62) and recovered starting material (3.61) in 30 % and 25 % yields respectively (Equation 3.28). It appeared that there was competitive elimination at the phosphorus centre rather than attack at the carbon centre due to the severe steric hindrance around the C-3 centre. The liberated β-ketoester (3.52) from this elimination was then reduced by excess borohydride, used in the preparation of the sodium phenylselenide, to give the hydroxy-ester (3.62).



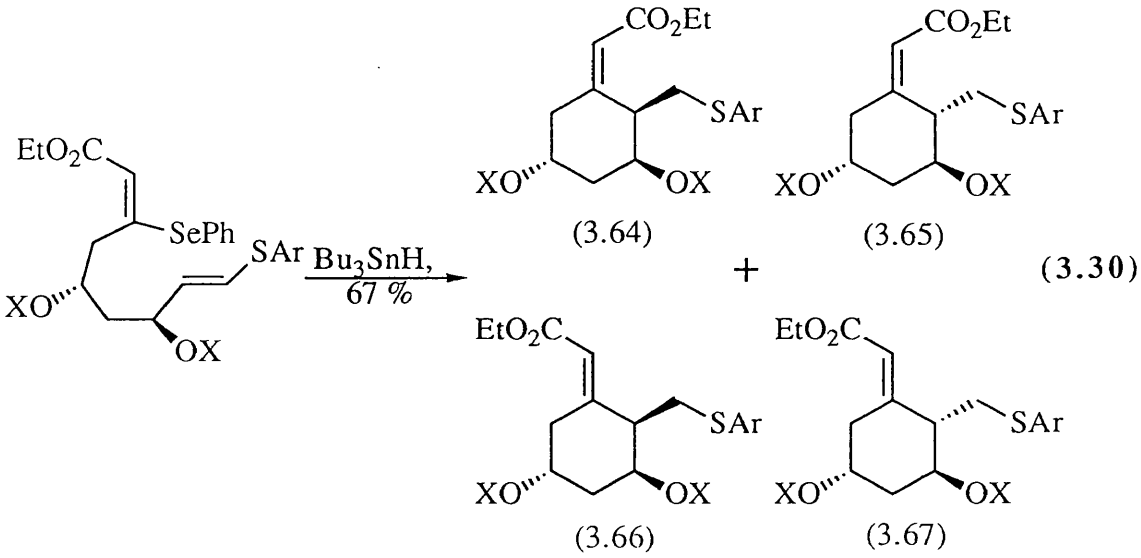
(3.28)

(3.61) (3.62)

All the "sodium phenylselenide" in these examples had been generated by the action of sodium borohydride on diphenyl diselenide in ethanol, to give the somewhat bulky phenylseleno(triethoxy)borate complex. The preparation of sodium phenylselenide was therefore changed and the anion was generated ultrasonically from sodium dispersion and diphenyl diselenide.[38] This pale cream suspension was reacted with the model unsaturated phosphate (3.60) to give a 70 % yield of (3.54). When this ultrasonically generated sodium phenylselenide was reacted with the unsaturated phosphonate (3.61) it gave the desired unsaturated phenylselenide (3.63) in a 29 % yield, as a 1:1 mixture of *E*- and *Z*- isomers (Equation 3.29), with 64 % recovery of the β-ketoester (3.52). Once again, the recovery of β-ketoester was presumed to be due to the steric constraints around the C-3 centre. Although the yield is low and further efforts to optimise the procedure were unsuccessful, the clean recovery of β-ketoester enabled it to be recycled to give respectable amounts of unsaturated phenylselenide.



The slow addition of tin hydride and AIBN to a refluxing solution of the unsaturated phenylselenide (3.63) in benzene gave the expected cyclised products in a 1:1:2:1 ratio of the *Z*-2,3-*cis* (3.64), *Z*-2,3-*trans* (3.65), *E*-2,3-*cis* (3.66) and *E*-2,3-*trans* (3.67) isomers respectively (Equation 3.30). The reaction time was considerably longer than in the analogous acyl radical cyclisation emphasing the lower reactivity of the vinyl selenide over that of the acyl selenide.



(3.30)

The high field nmr spectra for compounds (3.64) to (3.67) indicated that both the *E*-isomers have the arylthio residue in an equatorial position (Figure 3.2), as was seen in the cyclohexanones (3.20) and (3.21) (Figure 3.1). Conversely, both the *Z*-isomers for the cyclised products have the arylthio residue in an axial position (Figure 3.2). This change in orientation is attributed to the steric congestion around the C-2 centre for the *Z*-isomers (allylic strain).

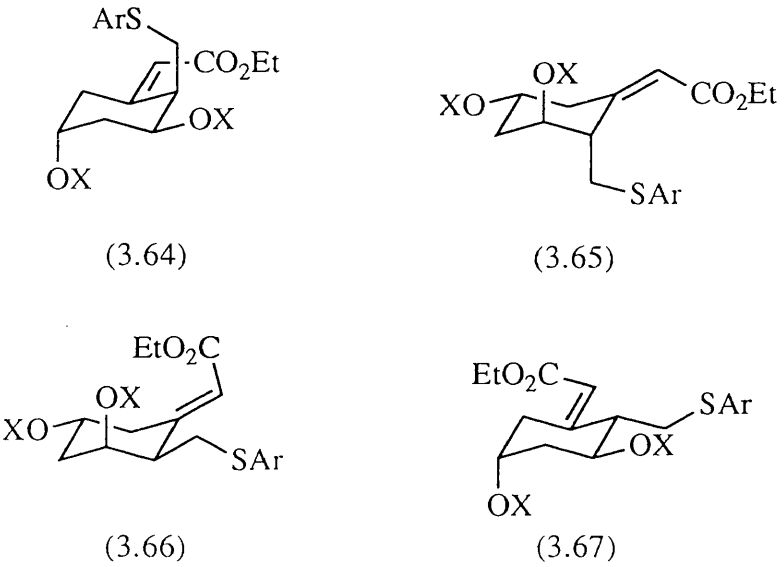
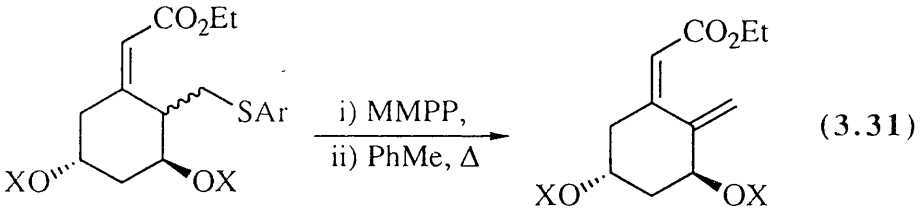


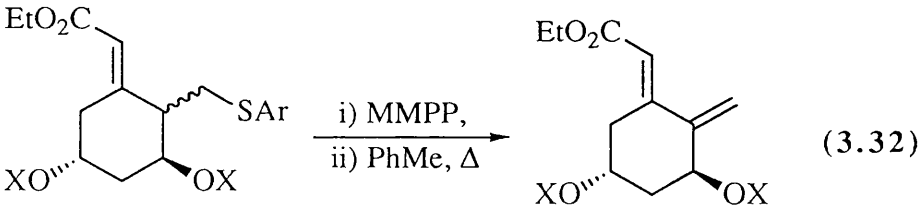
Figure 3.2 Proposed Stereochemistry of Products

Oxidation of (3.64) and (3.65) with MMPP and pyrolytic *syn*-elimination in refluxing toluene gave the known precursor of the 'A' ring of 1α, 25-dihydroxyvitamin D_3 (3.6) in 60 % and 79 % yields respectively (Equation 3.31). Likewise, oxidation and *syn*-elimination of the two *E*-isomers (3.66) and (3.67) gave the *E*-product (3.68) in similar yields (Equation 3.32). It was noted, that under an extended period in refluxing toluene, the *E*-isomer (3.68) equilibriates somewhat to the *Z*-isomer (3.6). As the photostimulated equilibrium of (3.68) in favour of (3.6) is an established process (Equation 3.33)[8] then this synthesis constitutes a formal synthesis of (±)-1α, 25-dihydroxyvitamin D_3.



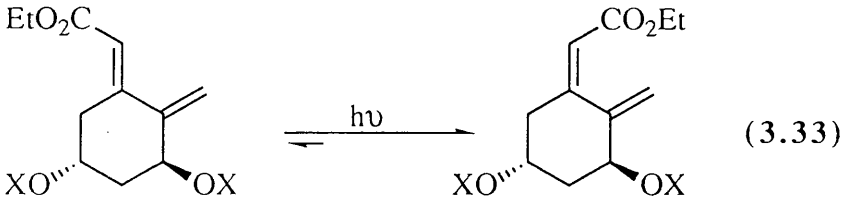
(3.31)

(3.6)



(3.32)

(3.68)

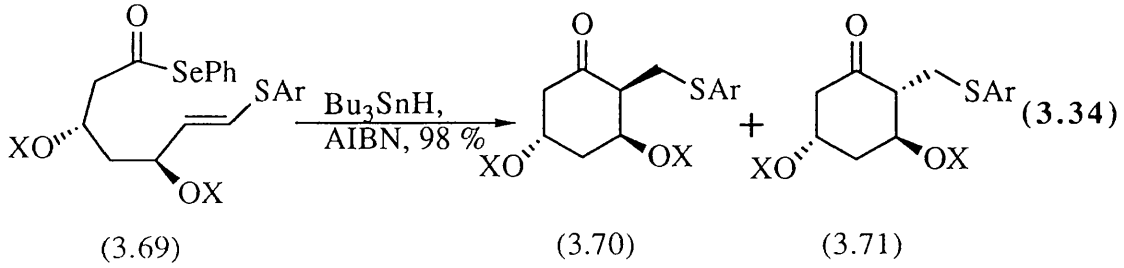


(3.33)

3.7 FURTHER WORK AND CONCLUSIONS

In conclusion, it has been shown that both acyl and vinyl radical cyclisations of 6-heptenyl systems can give,with the correct choice of substituents, good to excellent yields of cyclohexanones and alkylidenecyclohexanes . When the acyl radical

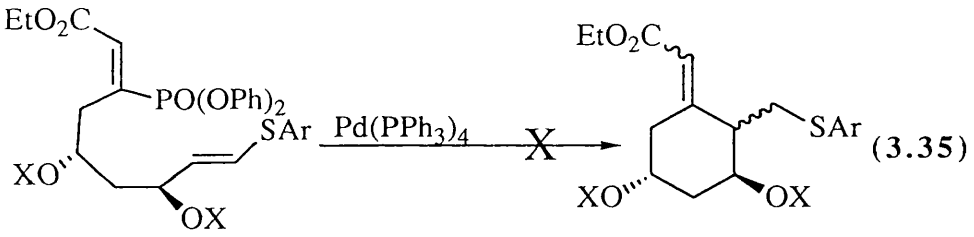
cyclisation was repeated on the arylthio selenoester (3.69), the cyclised products (3.70) and (3.71) were obtained in a 96 % yield, both as crystalline solids (Equation 3.34).



(3.34)

(3.69) (3.70) (3.71)

An attempt to circumvent the preparation of the unsaturated phenylselenide (3.63) by cyclisation of the unsaturated phosphate (3.61) via a palladium (0) catalysed Heck reaction proved unsuccessful (Equation 3.35).



(3.35)

Work is continuing in this laboratory into the development of an asymmetric variant of this approach toward 1α,25-dihydroxyvitamin D_3.

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CHAPTER 4

STUDIES INTO THE PREPARATION OF BICYCLO-[5,3,0]-DECANONES VIA A TANDEM RADICAL CYCLISATION

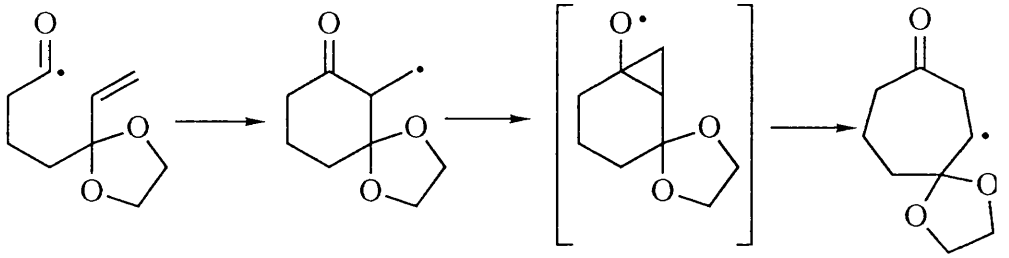
4.1 INTRODUCTION

The propensity of 6-heptenoyl radicals substituted with alkoxy residues in the 5-position (allylic position) to undergo cyclisation in the 7-*endo* mode was noted in Chapter 3 (Scheme 3.1). In this chapter, studies aimed at probing the underlying reasons for this regioselectivity and the application of the phenomenum to the synthesis of the bicyclo-[5,3,0]-decane skeleton, as evidenced in perhydroazulene-sesquiterpenoids, are described.

4.1.1 MECHANISTIC STUDIES ON THE CYCLISATION OF 5-ALKOXY-6-HEPTENOYL RADICALS

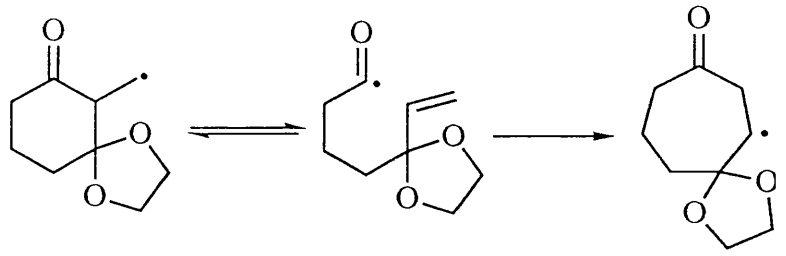
At the outset, three separate mechanisms for the observed regiochemistry in the cyclisation of 5-alkoxy-6-heptenoyl radicals (Scheme 3.1) were considered.

In the first mechanism, the ring closure occurs via kinetic cyclisation in the *exo*-mode, followed by rapid ring expansion via a cyclopropyloxy radical (either as an intermediate or as a transition state) to the thermodynamically more stable ring-expanded radical, with additional stabilisation by the β-oxygen substituent (Scheme 4.1).



Scheme 4.1 Ring Expansion Mechanism

The second possibility considered also invokes kinetic 6-*exo* cyclisation, but considered this cyclisation to be reversible, leading ultimately to the thermodynamically more stable *endo* mode product, again with β-oxygen stabilisation (Scheme 4.2).

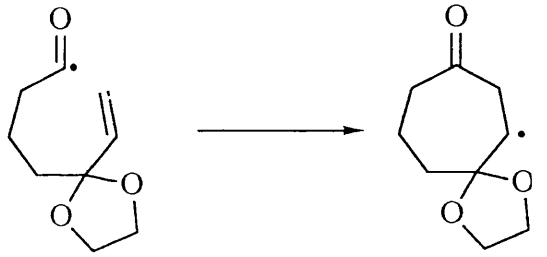


Scheme 4.2 Reversible 6-*exo* mode Cyclisation

The third possibility considered was that the cyclisation takes place directly in the 7-*endo* mode and that the regioselectivity was the result of either:

i) Steric hindrance around the internal position of the double bond or

ii) A preferred conformation of the allylic ether function, predisposed to endo mode cyclisation (Scheme 4.3).

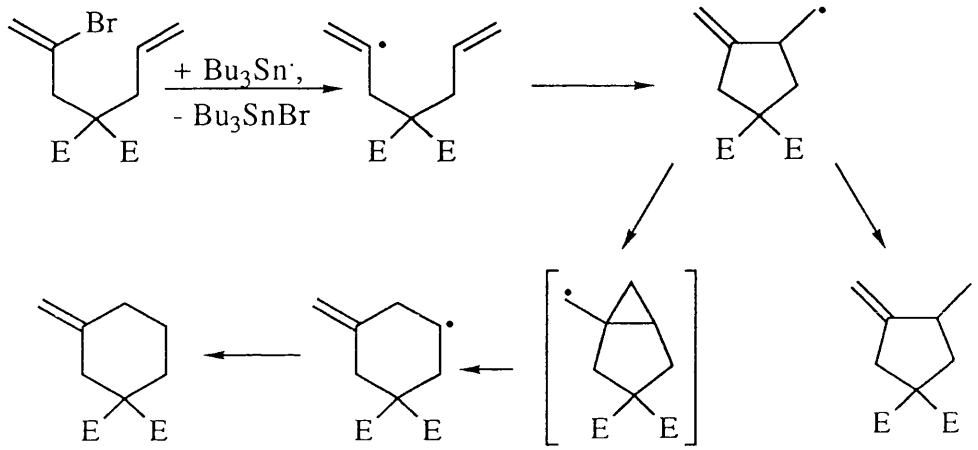


Scheme 4.3 Direct 7-*endo* mode Cyclisation

4.1.2 RING EXPANSION VIA CYCLOPROPYLOXY RADICALS

Vinyl radical cyclisations are known to proceed with the formation of both *endo* and *exo* mode products, depending upon the conditions employed. The seminal

contributions of Beckwith[1] and Stork[2] clearly showed that such cyclisations proceed with the initial formation of a kinetic *exo* mode radical and that, under appropriate conditions, this radical undergoes ring expansion via a cyclopropylmethyl radical (Scheme 4.4).



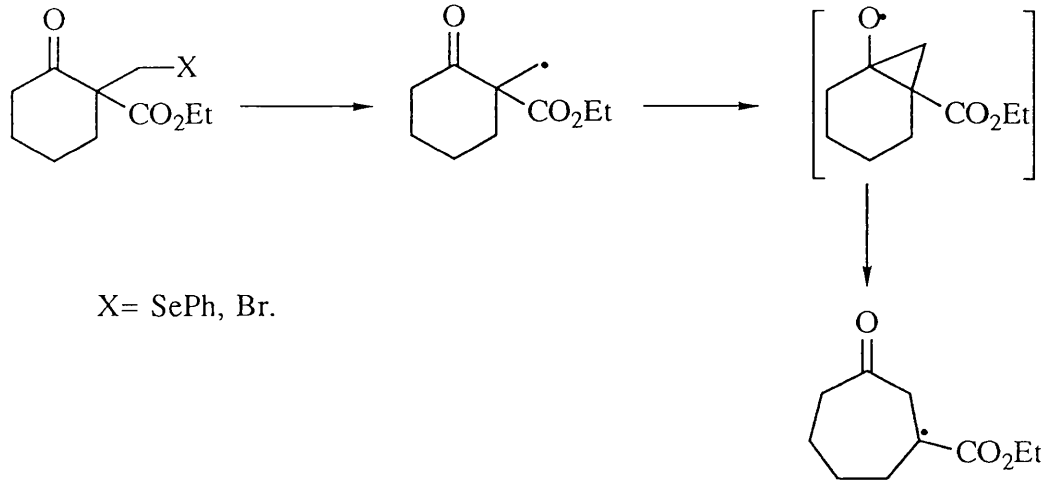
E= COOEt

Scheme 4.4 Vinyl Radical Cyclisation via Initial 5-*exo* mode Cyclisation.

Extending the analogy between acyl and vinyl radicals clearly leads to the first mechanistic hypothesis outlined above.

Evidence in support of this hypothesis is provided by the elegant studies of Beckwith[3] and Dowd[4], in which it was clearly demonstrated that cyclic ketones may be ring expanded under radical conditions via the probable intermediacy of cyclopropyloxy radicals (Scheme 4.5).

Nevertheless, all the examples provided carry an electron withdrawing (stabilising) group α- to the final product radical and so the extent to which such ring expansions proceed in the absence of such a group is unclear.



Scheme 4.5 Ring Expansion of a Cyclohexanone via Cyclopropyloxy Radical

4.1.3 β-OXYGEN EFFECTS

The stabilisation of carbon centred radicals by β-carbon-oxygen single bonds is a controversial area.

E.S.R. studies on β-alkoxyethyl radicals indicate that there is no bridging and no spin density on oxygen[5]. Which is to say, that there is no thermodynamic stabilising effect of carbon radicals by β-alkoxy substituents (Figure 4.1).

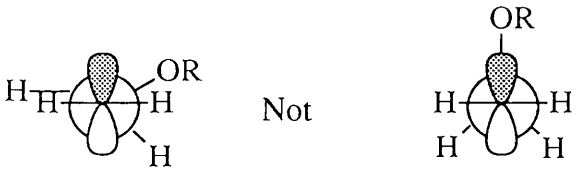


Figure 4.1 Preferred Conformation of β-Alkoxyethyl Radical.

However, studies in the early 1980's by the Barton group[6] revealed that the radical reductive deamination of primary amines by AIBN initiated reaction of tri-n-

butyltin hydride with the derived isonitrile was accelerated by the presence of β–oxygen bonds. Similar results were also observed for primary thioformate esters. This phenomenom was rationalised in terms of radical stabilisation by the β-oxygen substituent. Furthermore, the Giese-Sustmann collaboration[7] has demonstrated, by e.s.r. spectroscopy, that tetraacetyl glucopyranos-1-yl radicals adopt a boat-like conformation, which it was suggested was a result of a stabilisation conferred by a co-planar β-CO bond (Figure 4.2).

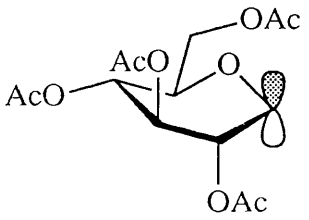


Figure 4.2 Boat Conformation of the Tetraacetyl Glucopyranos-1-yl Radical.

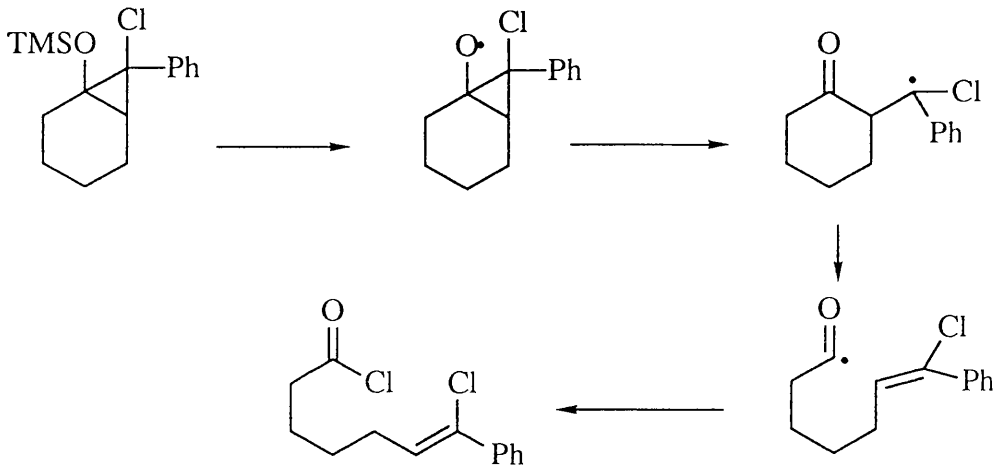
Nevertheless, unpublished results from this[8] and other laboratories[9] suggest that an alternative rationalisation for the Barton results may be more valid.

In the light of such conflicting results, caution must be exercised in the formulation of mechanistic hypotheses based on a β-oxygen effect.

4.1.4 REVERSIBILITY OF ACYL RADICAL ADDITION TO DOUBLE BONDS

The classical work of Julia[10] demonstrated that under appropriate conditions and with appropriate stabilisation of the ring opened radical, reversible radical cyclisations leading ultimately to the thermodynamically more stable product, may be observed.

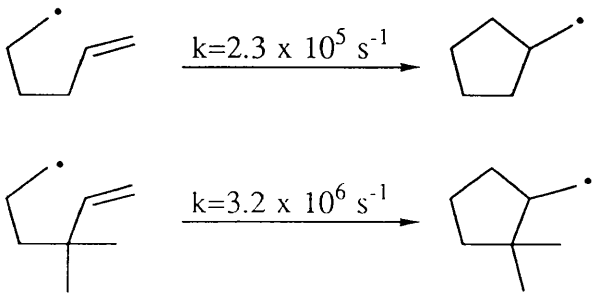
The recent experiments of Blanco and Mansouri[11] appear to lend weight to the suggestion that acyl radical cyclisations may be reversible, under appropriate conditions (Scheme 4.6).



Scheme 4.6 Acyl Radical Formation via Ring Opening.

4.1.5 STERIC EFFECTS

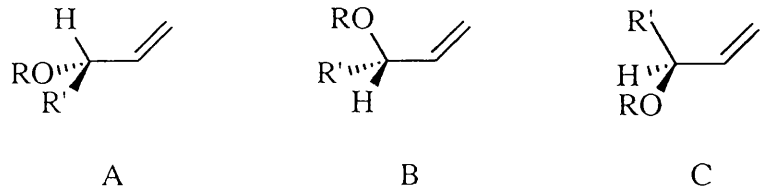
In the 5-hexenyl series, the inclusion of a gem 4,4-dimethyl group has the effect of increasing the rate of the *exo* mode cyclisation (Scheme 4.7),[12] doubtless due to a Thorpe-Ingold effect, rather than retarding cyclisation by any steric effect. By direct analogy, 5,5-disubstituted 6-heptenoyl radicals would be expected to cyclise in the *exo* mode more rapidly than the parent radical.



Scheme 4.7 Cyclisation Rates for Some 5-Hexenyl Systems.

4.1.6 ALLYLIC ETHERS AND CONFORMATIONAL EFFECTS

The preferred conformation of allylic ethers is generally considered to be that in which the smallest substituent eclipses the double bond (Figure 4.3, Structure A).[13] Perhaps the most widely known application of this premise is the empirical rule formulated by Kishi[14] for the osmoylation of allylic ethers and alcohols, although even these rules have been subject to much theoretical scrutiny recently.[15]



A B C

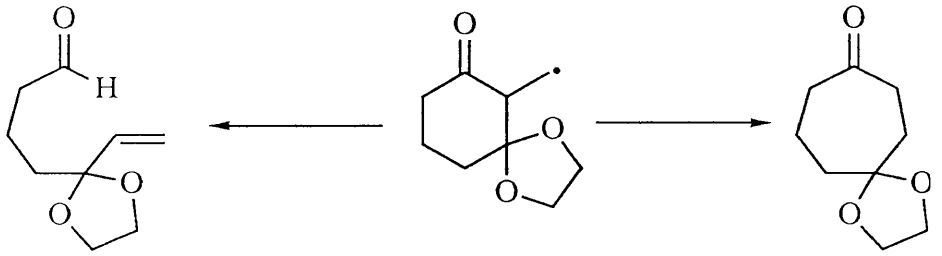
Figure 4.3 Eclipsed Conformations for Allyl Ethers

Within the context of free radical chemistry, RajanBabu[16] has extensively studied 5-hexenyl cyclisations with heavily substituted systems, each of which carried an allylic ether function. In these cyclisations the conformation of the allylic ether moiety was determined to be a factor in the stereochemical outcome, although it was clear that 1,3 diaxial strain in the transition state was of greater significance.

4.1.7 EXPERIMENTAL PROBE 1

In order to probe the possibilities of ring expansion and/or reversible cyclisation in a system as close as possible to that involved in the earlier work from this laboratory, it was decided to prepare unambiguously radical (4.1) and to study its behaviour in the presence of tin hydride under the standard conditions. If the formation of aldehyde (4.2) (Scheme 4.8) was observed, this would indicate the reversible nature of the acyl radical cyclisation, whilst if the formation of cycloheptanone (4.3), in the absence of

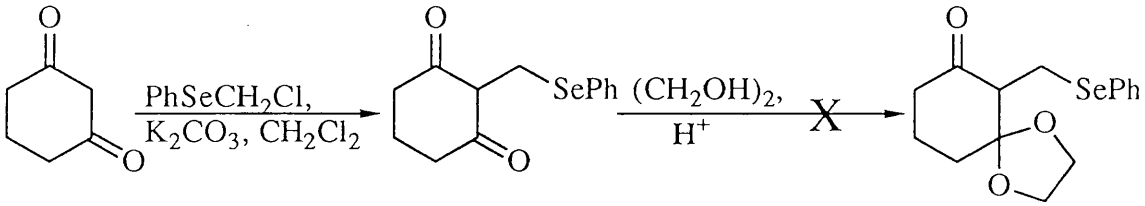
aldehyde (4.2) was observed, this would indicate ring expansion via the cyclopropyloxy radical (Scheme 4.8). On the other hand, observation of the aldehyde (4.2) and the cycloheptanone (4.3) would not enable differentiation between the two mechanisms.



(4.2) (4.1) (4.3)

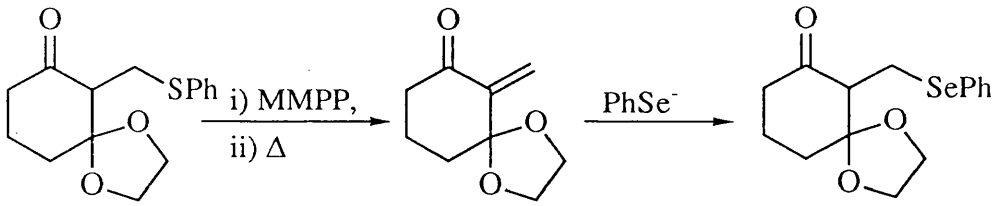
Scheme 4.8 Possible Radical Rearrangements.

The phenylselenide (4.4) was thought to be the most appropriate precursor to this radical. The obvious entry into this phenylselenide (4.4) was precluded when the selenide (4.5), itself prepared by alkylation of 1,3-cyclohexanedione with phenylselenenylchloromethane, was found to undergo extensive decomposition on attempted ketalisation, under various conditions (Scheme 4.9). Ultimately, compound (4.4) was prepared by *syn* elimination from the phenylthiomethylcyclohexanone (4.6)[17] to give the α-methylene cyclohexanone (4.7), followed by Michael addition of phenylselenide (Scheme 4.10), in a 23 % yield.



(4.5) (4.4)

Scheme 4.9 Attempted Preparation of Phenylselenide (4.4)

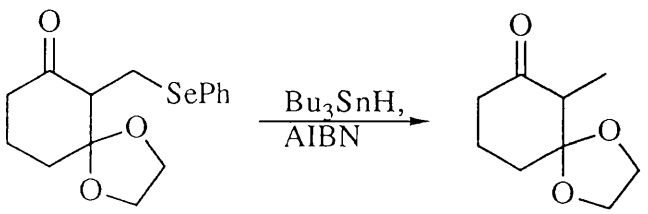


(4.6) (4.7) (4.4)

Scheme 4.10 Preparation of Phenylselenide (4.4)

The low yield of this crystalline substance is largely due to decomposition on silica gel, demonstrating its acid lability as alluded to above. The phenylselenide anion used in the Michael addition was prepared, abnormally, in tetrahydrofuran by borohydride reduction in the presence of the stoichiometric amount of ethanol, as under the more usual conditions, with ethanol as the solvent, the major product was the ethanol adduct, suggesting that the phenylselenide (4.4) was also unstable under basic conditions.

Treatment of selenide (4.4) with tri-n-butyltin hydride under the conditions employed originally for the cyclisation of (3.3) (Scheme 3.1), under high dilution conditions and also by inverse addition to tin hydride, gave the methylcyclohexanone (4.8) as the only identified product (Equation 4.1). None of the aldehyde (4.2) or the cycloheptanone (4.3) were identified in any of the reaction mixtures, by comparison with spectra of authentic samples. The cyclohexanone (4.8) was identified by comparison with an authentic sample prepared by bis-ketalisation of 2-methyl-1,3-cyclohexanedione and mono deketalisation.



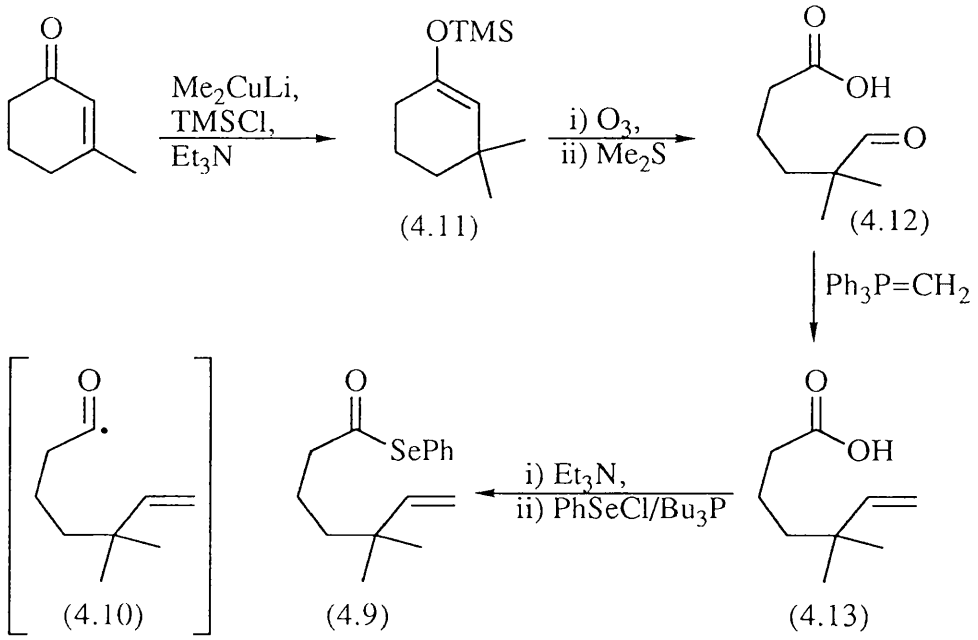
(4.4) (4.8) **(4.1)**

From these experiments, it can be concluded that the formation of cycloheptanones in the tin hydride mediated, acyl phenylselenide derived, cyclisation of 5-alkoxy-6-heptenoyl radicals is not the result of ring expansion or reversible cyclisation.

4.1.8 EXPERIMENTAL PROBE 2

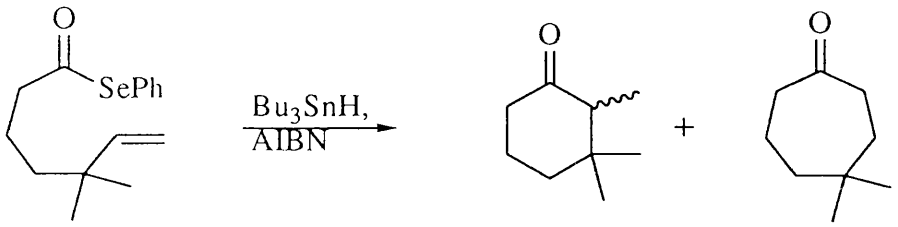
In order to differentiate between the steric effects and conformational effects of the allylic ether moiety, it was determined to study the cyclisation of the 5,5-dimethyl-6-heptenoyl radical (4.10), derived from its selenoester (4.9).

Addition of lithium dimethylcuprate to 3-methylcyclohex-2-enone, in the presence of HMPA, trimethylsilyl chloride and triethylamine gave the silyl enol-ether (4.11), as alluded to by Plamondon and Cannonne,[18] in a virtually quantitative yield. Ozonolysis in dichloromethane and methanol followed by work up with dimethyl sulphide, gave the aldehydo-acid (4.12), which was immediately subjected to a Wittig reaction, giving the acid (4.13) in 19 % unoptimised yield. This acid was converted to the selenoester (4.9) in the usual manner in 76 % yield (Scheme 4.11).



Scheme 4.11 Preparation of Selenoester (4.9).

Reaction of the selenoester (4.9) with tri-n-butyltin hydride, under as near identical conditions as possible with those used in the cyclisation of selenoester (3.3) (Scheme 3.1), gave the 6-*exo* (4.14) and 7-*endo* (4.15) products in 20 and 30 % yields respectively. The products were identified unambiguously by comparison of spectral data with literature values (Scheme 4.12).[19,20]



20 %

30 %

(4.9)

(4.14)

(4.15)

Scheme 4.12 Cyclisation of the 5,5-dimethyl-6-heptenoyl Radical.

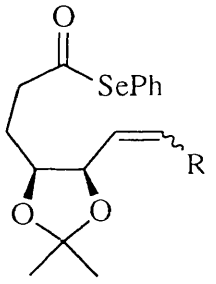
Comparison of these results with those observed in cyclisation of selenoester (3.10) (Scheme 3.1), clearly points to the fact the the effect exerted by the ethylene-dioxy group is not purely steric.

The overall conclusion from these studies (by a process of elimination), is that the preferential formation of cycloheptanones in the cyclisation of 5,5-ethylenedioxy-6-heptenoyl and related radicals must be the result of the allylic ether moiety adopting a conformation that is predisposed to direct 7-*endo* mode cyclisation.

4.2 OPTIMISATION OF 7-ENDO MODE CYCLISATIONS.

It was envisaged that the above findings could be utilised to design a 6-heptenoyl radical system that would cyclise efficiently in the 7-*endo* mode and, with an appropriate substituent on the terminal end of the vinyl residue, undergo tandem cyclisation, ultimately giving a bicyclo-[5,3,0]-decane framework.

'Dreiding' molecular models were examined as an aid to formulating an efficient precursor for 7-*endo* cyclisation from a 5-alkoxy-6-heptenoyl system. From these models it was apparent that another substituent, in the C-4 position in the chain, could increase the yield of cyclisation. Furthermore, if the C-4 and C-5 substituents were incorporated into a *cis*-fused 5- membered ring, which essentially 'locks' the C-3 to C-6 portion of the molecule, then advantageous cyclisation in the 7-*endo* mode could be achieved. Hence, it was decided to conduct a study of selenoesters of the type 'X'.

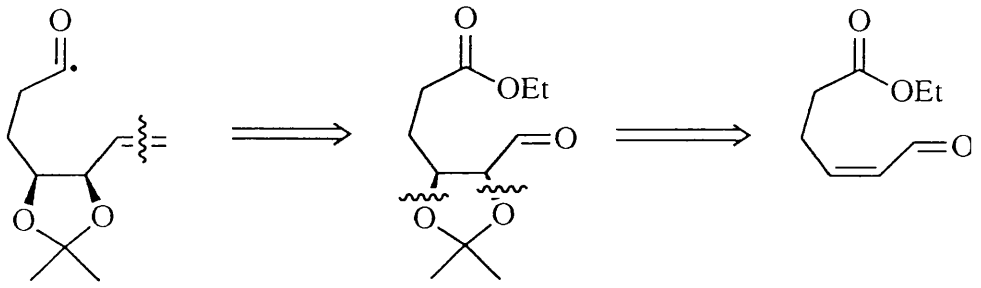


'X'

4.3 STUDIES TOWARDS THE SYNTHESIS OF A 4,5-*O*-ISOPROPYLIDENE-6-HEPTENOYL SYSTEM

From a synthetic viewpoint, it was considered that the C-4 substituent could be a second alkoxy residue and hence that the 5-membered ring would be a cyclic isopropylidene ketal. Retrosynthetic analysis of the 6-heptenoyl radical containing a

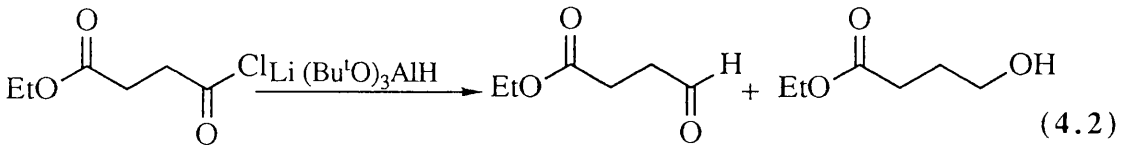
4,5-isopropylidene group (4.16), with the intention of introducing the isopropylidene function into the molecule at a late stage in the synthesis, indicated that the two key intermediates were the vinyl isopropylidene ester (4.17) and the α,β-unsaturated ester (4.18) (Scheme 4.13).



(4.16) (4.17) (4.18)

Scheme 4.13 Retrosynthesis of 4,5-Di-*O*-isopropylidene-6-heptenoyl Radical.

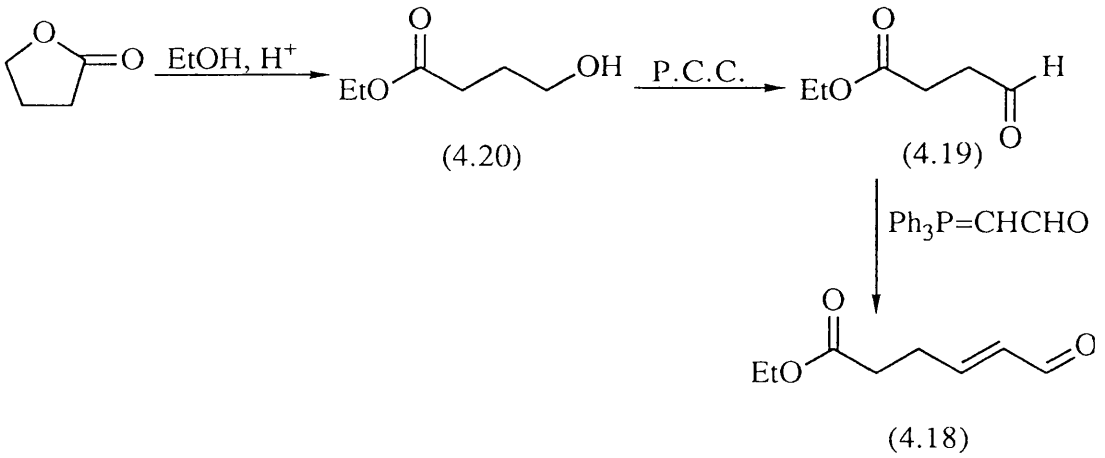
The unsaturated oxo-ester (4.18) had been previously prepared by either the ring opening of a suitably substituted cyclopropane[21] or the by the ring opening of a suitably substituted tetrahydrofuran,[22] but neither of these methods appeared to be suitable for large scale synthesis. A more viable approach appeared to be from ethyl 4-oxobutyrate (4.19). A direct entry into the aldehydo-ester (4.19) by the selective reduction of ethyl succinyl chloride with lithium tri-t-butoxyaluminium hydride has been reported by Brown,[23] but in this laboratory a significant quantity of the alcohol (4.20), the product of further reduction, was also recovered (Equation 4.2).



(4.19) (4.20) **(4.2)**

The procedure of choice for the preparation of the unsaturated-aldehyde (4.18) was by a 3 step process, starting with the acidic ring opening of γ-butyrolactone in ethanol, to give the alcohol (4.20) in a 70 % yield.[24] Oxidation of this alcohol with

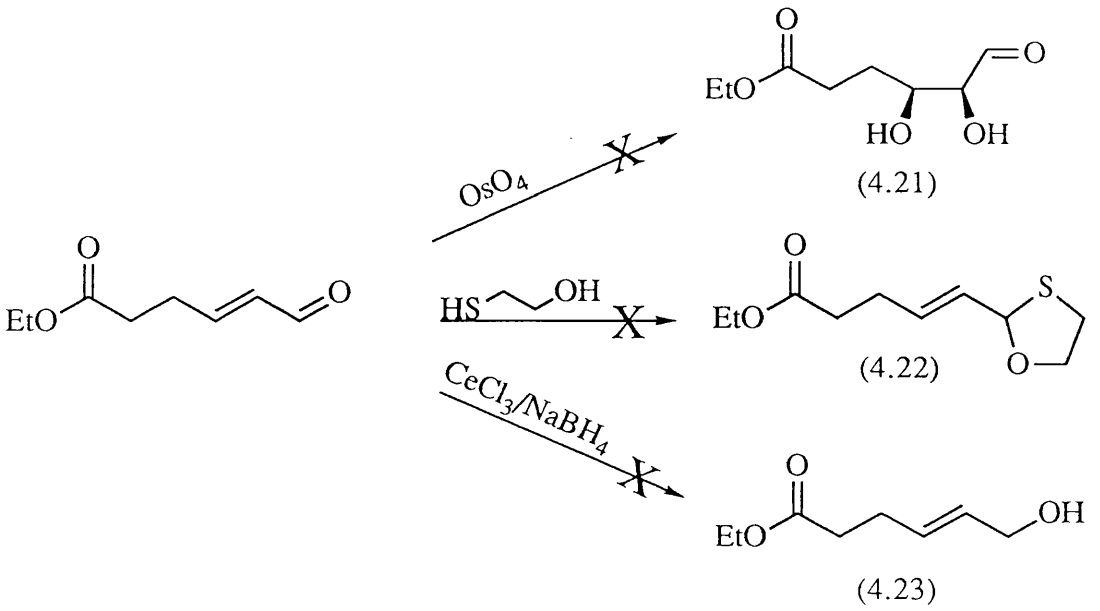
pyridinium chlorochromate (PCC) then gave the aldehyde (4.19) in 68 % yield, as reported by Vanderhaege.[25] Wittig reaction between (4.19) and (triphenylphosphoranylidene)acetaldehyde[26] gave the α,β-unsaturated aldehyde (4.18) in 61 % yield (Scheme 4.14).



Scheme 4.14 Preparation of Ethyl 6-Oxohex-4-enoate

Osmoylation of (4.18) with a catalytic amount of osmium tetroxide and excess N-methyl-morpholine N-oxide under either aqueous or non-aqueous conditions failed to give the required *cis*-diol (4.21) (Scheme 4.15). It was tentatively assumed that either a self condensation /polymerisation of the aldehyde function, or lactonisation[27] of the product diol was the major reaction pathway. Attempted protection of the aldehyde function in (4.18) as either a hemithioacetal (4.22)[28] or by selective reduction to the alcohol (4.23)[29] with ceric chloride and sodium borohydride, failed to give the expected products (Scheme 4.15).

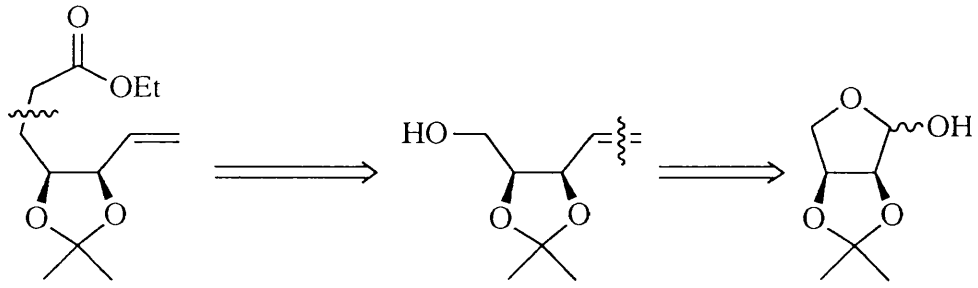
As these attempts to introduce the isopropylidene moiety into the hexenal carbon skeleton proved unsuccessful, the retrosynthetic scheme for the vinyl isopropylidene ester (4.17) was re-examined, with a view to the introduction of the isopropylidene group in an alternative manner.



Scheme 4.15 Attempted Manipulation of the Unsaturated Aldehyde.

4.4 SYNTHESIS FROM CARBOHYDRATES

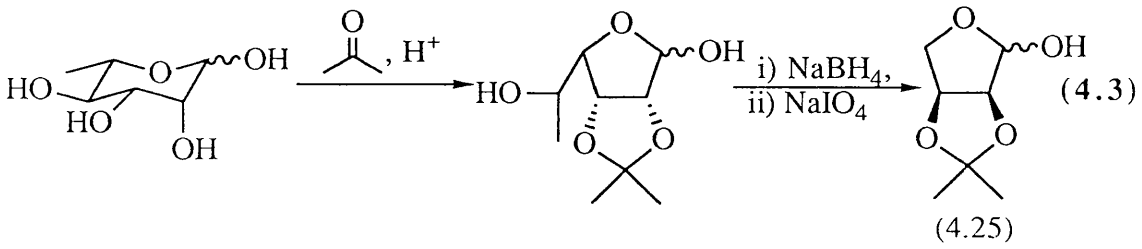
The new retrosynthetic analysis for the vinyl isopropylidene ester (4.17), involved disconnection of the ester function to the hydroxyolefin (4.24) and a further disconnection of the olefin back to the L-isopropylidene erythrose (4.25) (Scheme 4.16).



(4.17) (4.24) (4.25)

Scheme 4.16 Alternative Retrosynthetic Analysis for (4.17)

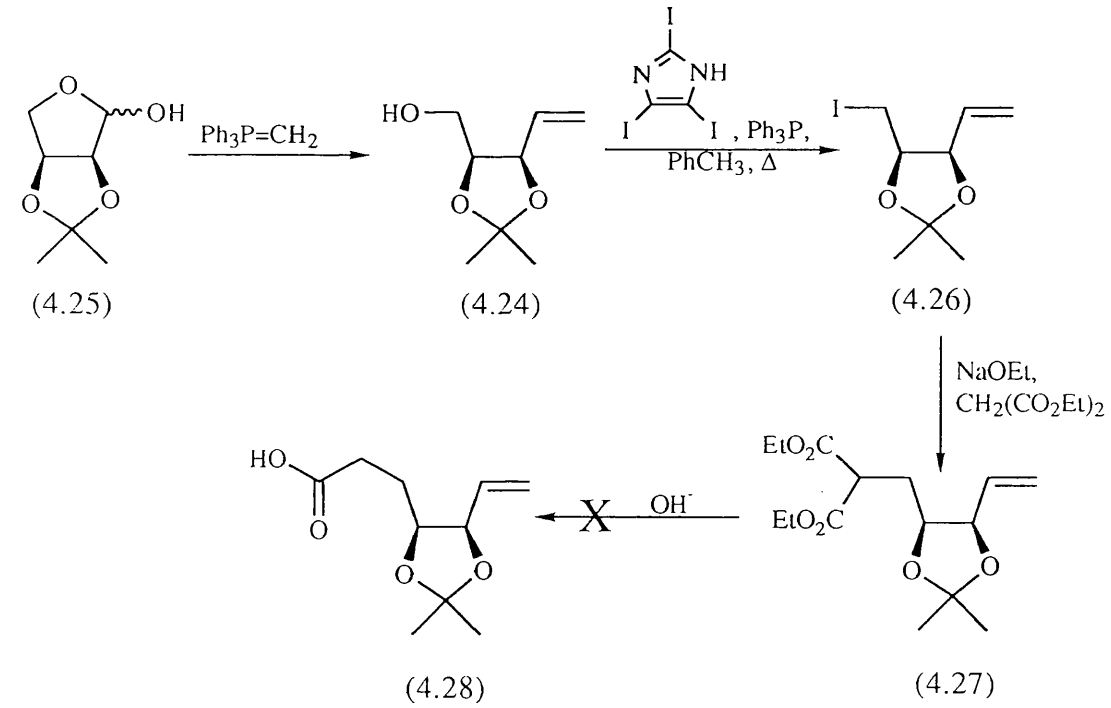
Both L- and D-2,3-O-isopropylidene erythrose have been prepared from a variety of carbohydrates.[30] The method described by Baxter[31] which provides L-isopropylidene erythrose (4.25) in a three steps from readily available L-rhamnose was selected. In our hands an overall yield of 71 % was obtained (Equation 4.3).



(4.3)

(4.25)

Wittig reaction on L-erythrose (4.25) with methylenetriphenylphosphorane gave the anticipated hydroxyolefin (4.24) in a 49 % yield (Scheme 4.17). Further reaction of this hydroxyolefin (4.24) with triiodoimidazole in refluxing toluene gave the iodoalkene (4.26) in 39 % yield.[32]



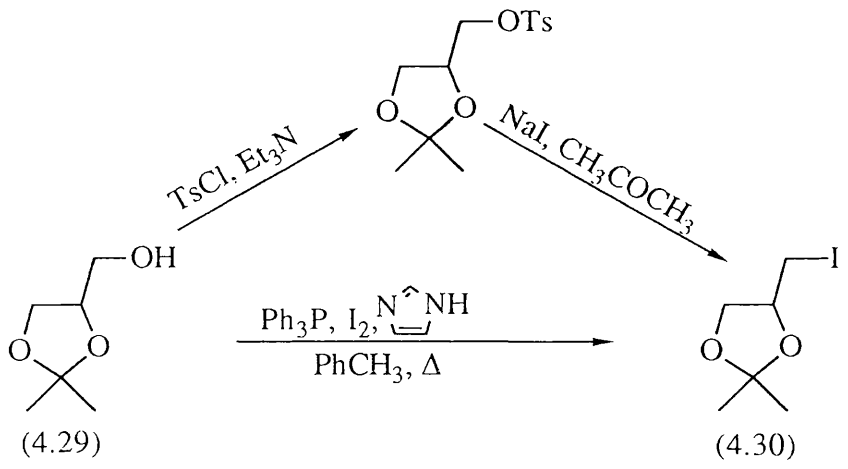
(4.25) (4.24) (4.26)

(4.28) (4.27)

Scheme 4.17 Attempted Synthesis via Malonate Alkylation

Alkylation of iodoalkene (4.26) with diethyl malonate and sodium ethoxide in ethanol gave the diester (4.27), but gentle heating of this diester (4.27) in dilute aqueous sodium hydroxide did not yield the expected olefinic acid (4.28) (Scheme 4.17). The recovered material from the saponification reaction indicated that the isopropylidene group had been cleaved, presumably on work-up.

In the light of this unsuccessful decarboxylation, model reactions were carried out with the commercial 1,2-*O*-isopropylidene glycerol (Solketal) (4.29). The iodo derivative of Solketal (4.30) was prepared by reaction of (4.29) with either triphenylphosphine, imidazole and iodine in refluxing toluene[32] or by the reaction of the derived tosylate with sodium iodide, as described by Jung and Shaw[33], in 34 % and 39 % yields respectively (Scheme 4.18).

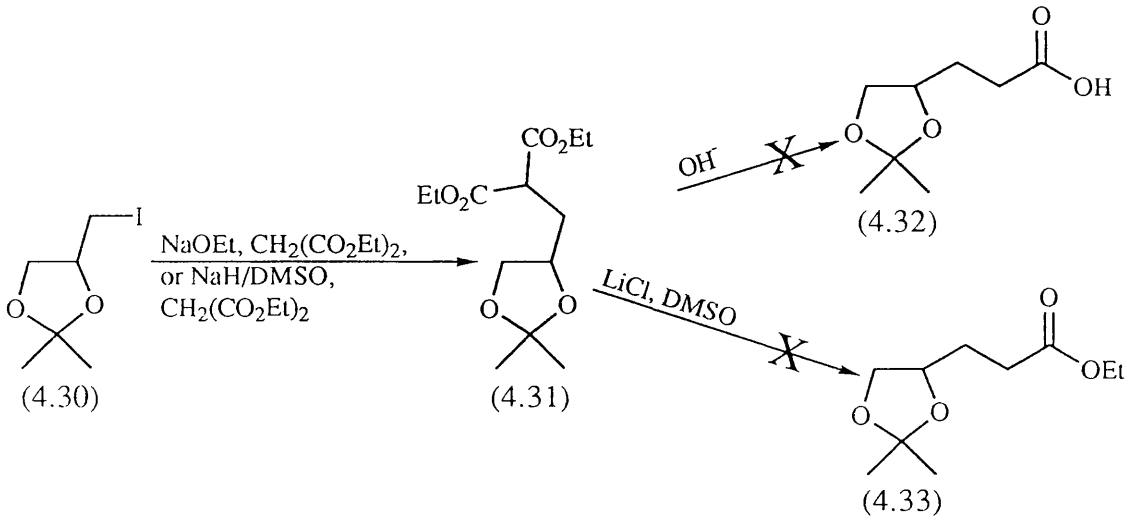


(4.29) (4.30)

Scheme 4.18 Preparation of the Iodo-derivative of Solketal

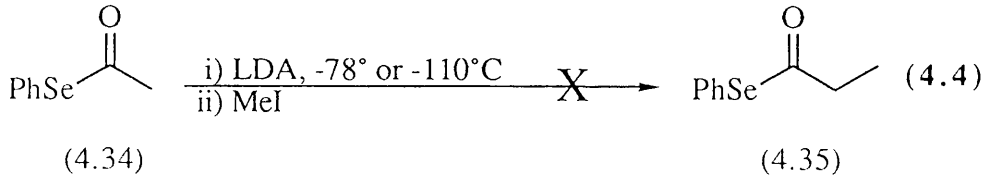
Alkylation of this iodo species (4.30) with the anion of diethyl malonate, generated either by sodium ethoxide or dimsyl sodium, gave the diester (4.31) in modest yields (30-50 %). Unfortunately, decarboxylation of the diester (4.31) to give either the acid (4.32), by gently heating in aqueous base, or the ester (4.33), by gently heating in non-aqueous base, gave a complex mixture of products (Scheme 4.19).

Further trial alkylations of the iodo derivative (4.30) with the dianion of monoethyl malonate did not work, with only starting materials recovered.

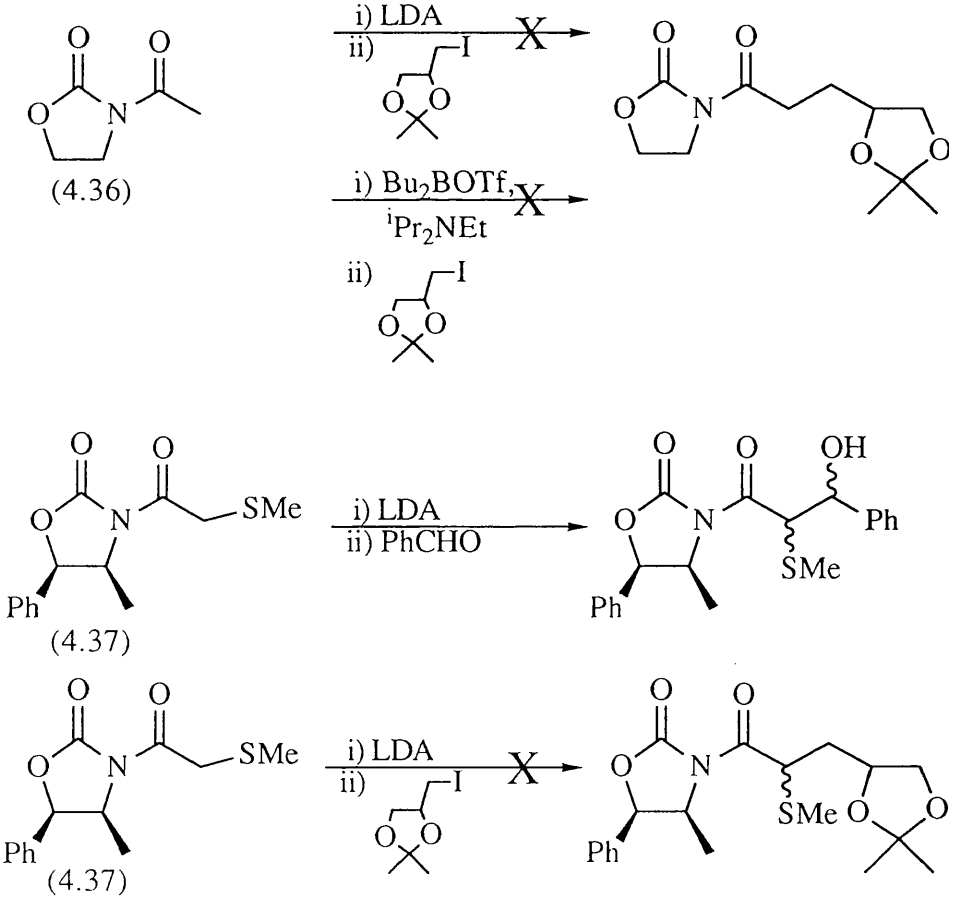


Scheme 4.19 Attempted Decarboxylations

Attention was then turned to simple enolate anions. It is well known that ethyl acetate forms a stable enolate when treated with lithium diisopropylamine (LDA) at low temperatures. Similarly, it has been reported that t-butylthio acetate reacts with LDA at low temperatures also to give a stable enolate and that this enolate reacts efficiently with carbon electrophiles.[34] By analogy and bearing in mind the ultimate requirement of a selenoester, phenylselenenyl acetate (4.34) was prepared by the standard method. Unfortunately, deprotonation with LDA at -78°C and -110°C, and attempted quenching with methyl iodide led only to decomposition, with the ultimate formation of diphenyl diselenide (Equation 4.4).



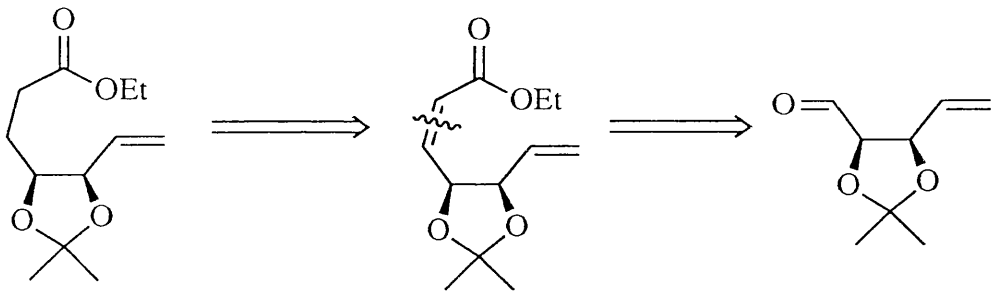
The use of oxazolidone derivatives in asymmetric alkylation and aldol condensations has been well documented.[35] Moreover, the alkylation of *N*-propyl-oxazolidones with various hindered iodides or bromides has been reported to be an efficient process.[36] Therefore, in the present synthesis, the use of *N*-acetyl-oxazolidone (4.36) as an acetate enolate equivalent was investigated. Unfortunately, deprotonation by either LDA or Hunigs base in the presence of di-butylboron triflate at -78°C and quenching with the iodide (4.30) gave only recovered oxazolidone (4.36), ketene polymer and recovered iodide (4.30) (Scheme 4.20). Similarly, oxazolidone (4.37) is known to undergo aldol condensation with benzaldehyde,[37] but when the stabilised enolate of (4.37) was quenched with iodide (4.30) only starting materials were recovered (Scheme 4.20).



Scheme 4.20 Attempted Alkylations of Oxazolidinones

The main reason for the difficulty in alkylation was attributed to the known difficulties of S_N2 attack on β-alkoxyalkyl halides.

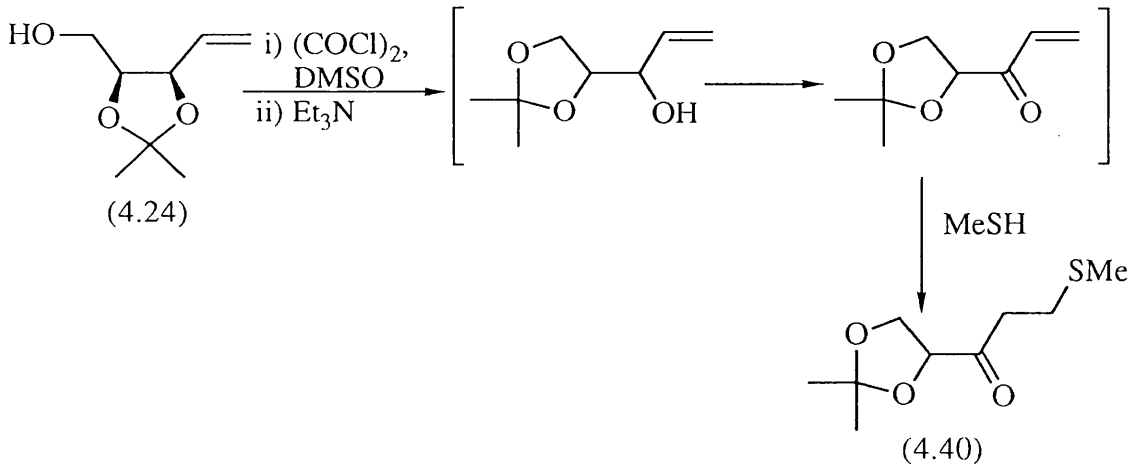
Given the failure of this enolate alkylation approach, it was decided to employ a two step procedure involving Wittig olefination and subsequent reduction as outlined in Scheme 4.21



(4.17) (4.38) (4.39)

Scheme 4.21 Retrosynthesis via a Vinylaldehyde

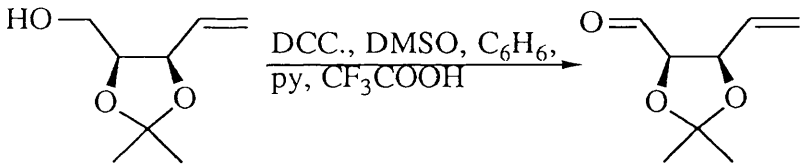
The oxidation of the hydroxyolefin (4.24) proved to be more difficult than anticipated. Swern oxidation[38], using oxalyl chloride and DMSO, repeatedly gave the unexpected sulphide (4.40) in 33 % yield. It appeared that the isopropylidene group had migrated to the primary alcohol and that the secondary alcohol thus formed was oxidised to the ketone. The so formed enone presumably then underwent Michael addition of methanethiol, a by-product of the oxidation reaction, giving the isolated product (4.40) (Scheme 4.22).



(4.24) (4.40)

Scheme 4.22 Migration of Isopropylidene Group under Swern Oxidation Conditions.

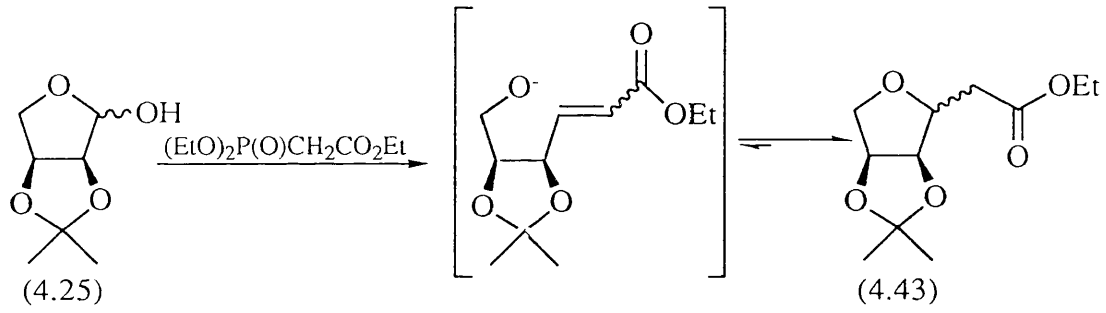
Oxidation of hydroxyolefin (4.24) under Pfitzner-Moffat conditions[39] however, did give the required aldehyde (4.39) in a 62 % yield (Equation 4.5). This aldehyde (4.39) proved to be unstable and decomposed overnight, even when stored at -20°C.



(4.24) (4.39) **(4.5)**

To overcome the problem of stability of the aldehyde (4.39), it was envisaged that the existing reaction sequence could be modified, so that the ester function would be incorporated into the molecule before the vinyl group, to give the enantiomeric vinyl-ester (4.41). The distinct advantages of this modified sequence over the original 'double Wittig' sequence were that there was no need to selectively hydrogenate the α,β-unsaturated ester in the presence of the vinyl group and that the aldehyde (4.42) would serve as a common intermediate for any subsequent studies, enabling incorporation of a variety of side chains.

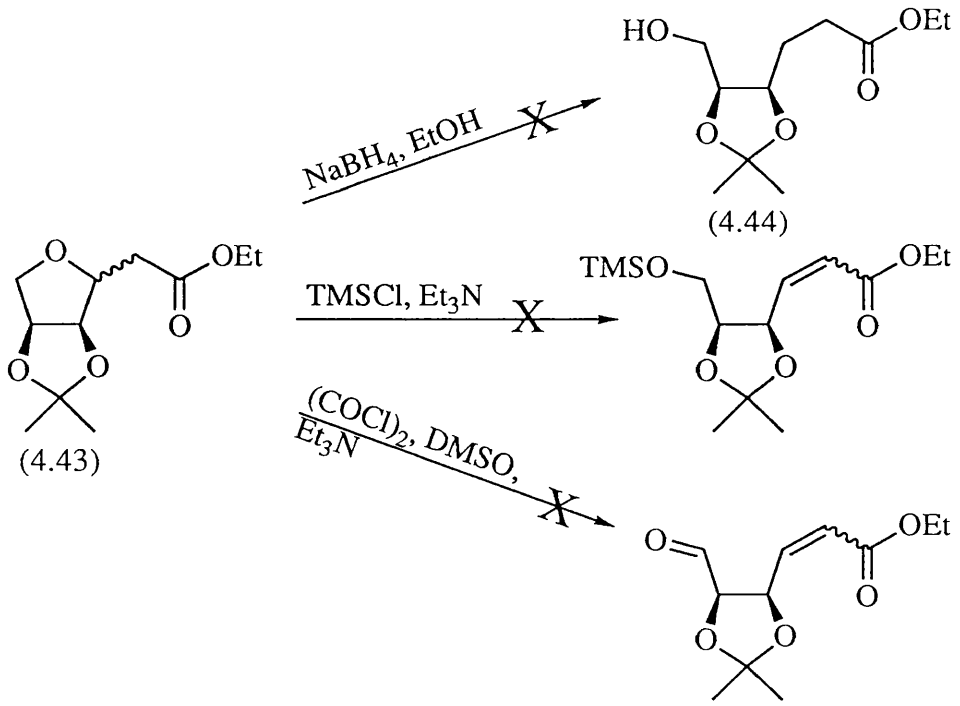
Reaction of the erythrose derivative (4.25) with triethyl phosphonoacetate under standard Horner-Emmons reaction conditions gave none of the expected hydroxyester (4.24), but only the ring closed product (4.43), recovered in an 86 % yield as a 1.4:1 mixture of anomers. The reaction conditions were obviously basic enough to open the tetrahydrofuran ring and the so-formed aldehyde was able to react with the phosphonoacetate. However, under these reaction conditions, the initial product underwent intramolecular 1,4-addition, to give the ring closed products (4.43) (Scheme 4.23).



(4.25) (4.43)

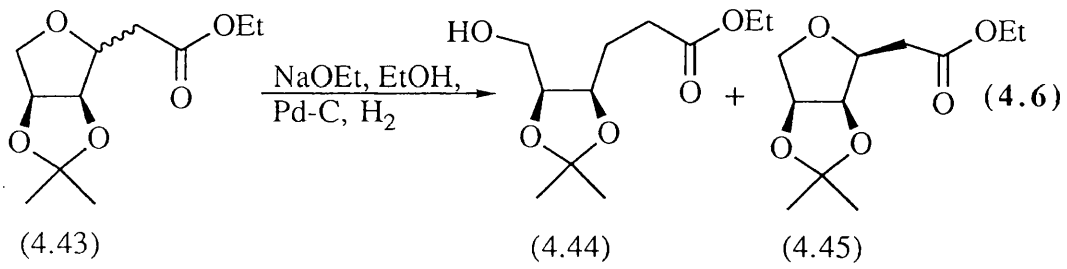
Scheme 4.23 Horner-Emmons Reaction on L-Isopropylidene Erythrose (4.25).

Various attempts at opening the tetrahydrofuran ring and trapping the ring opened product were made. Reduction of α,β-unsaturated esters by sodium borohydride have been reported by Kodin[40] however, when the cyclised esters (4.43) was treated with an ethanolic solution of sodium borohydride none of the required hydroxyester (4.44) was isolated. Similarly, reaction of (4.43) with either trimethylsilyl chloride in triethylamine or oxidation under Swern conditions gave only recovered starting material (Scheme 4.24).



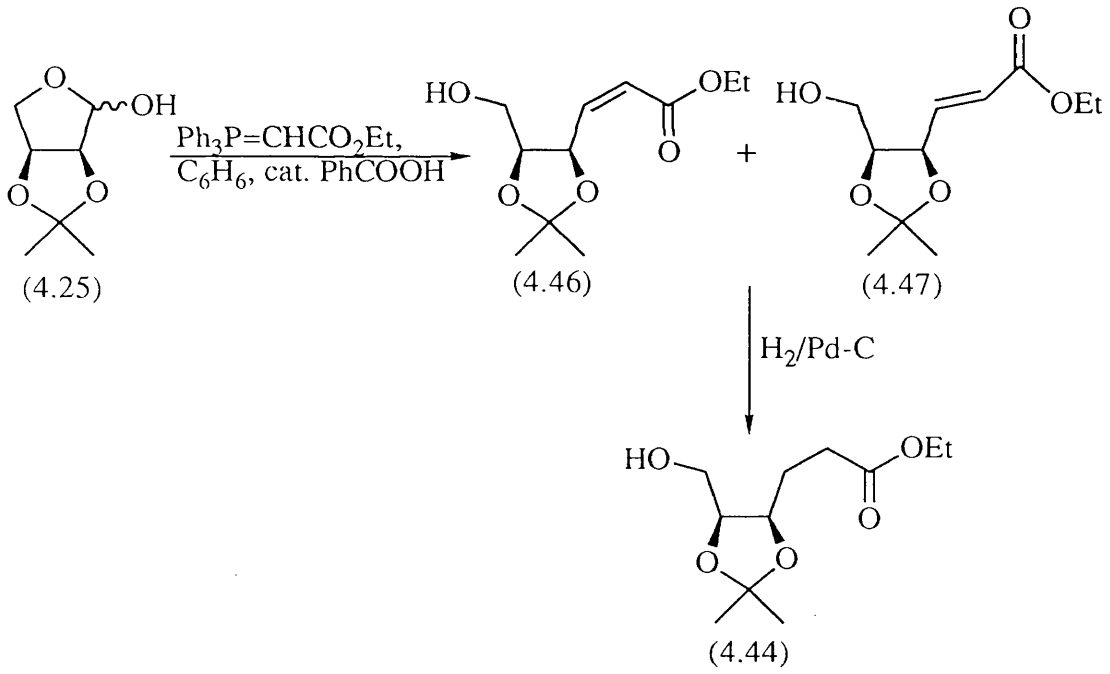
Scheme 4.24 Attempts to Open the Tetrahydrofuran Ring

Furanose derivatives, on reaction with sodium ethoxide, have been observed to undergo an equilibration reaction, giving the more thermodynamically stable anomer via the ring opened form.[41] Therefore, the ring opened product could possibly be isolated by establishing the equlibrium of the cyclised esters (4.43) under reducing conditions. When the cyclised ester (4.43) was stirred in an ethanolic solution of sodium ethoxide in the presence of palladium on activated charcoal under a balloon of hydrogen for 7 days, the saturated hydroxyester (4.44) was indeed isolated in 36 % yield (Equation 4.6). A single pure anomer of the cyclised ester (4.45) was also isolated, in 15 % yield and was assigned to be the 2S-isomer, with the 2-H, 3-H and 4-H protons all *cis*, by comparison with the results described by Moffatt.[41]



This reaction sequence of Horner-Emmons reaction with *in situ* equilibration has been used by Jones in the synthesis of the hexahydrofuro[3,2-b]furan unit of erythroskyrine.[42] Although this Horner-Emmons reduction sequence gave the desired product, it was inefficient and a more appropriate procedure was sought.

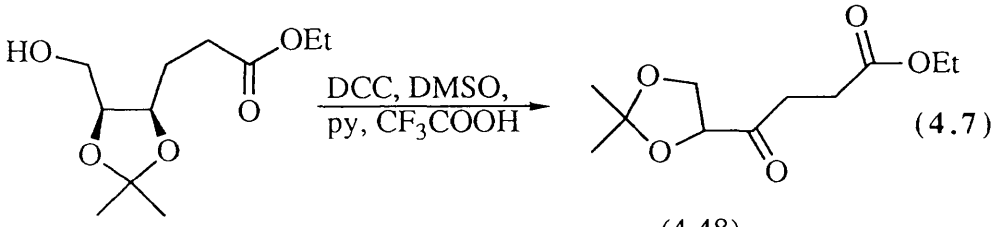
It had been reported that Wittig reactions on pyranoses in the presence of a catalytic amount of benzoic acid, gave the ring opened product in high yields.[43] Pleasingly, in our hands, reaction of the erythrose derivative (4.25) with carbethoxy-methylenetriphenylphosphorane with a trace of benzoic acid in refluxing benzene gave the unsaturated esters (4.46) and (4.47) in 38 % and 51 % yields respectively (Scheme 4.25). Hydrogenolysis of a mixture of (4.46) and (4.47) with palladium on activated charcoal in ethanol under a balloon of hydrogen, gave the saturated hydroxyester (4.44) in a 91 % yield (Scheme 4.25).



Scheme 4.25 Preparation of Hydroxyester (4.44).

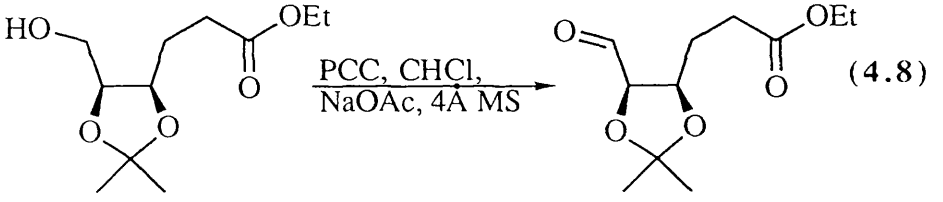
When the Pfitzner-Moffatt oxidation conditions used for preparing the vinyl-aldehyde (4.39) (Equation 4.5) were repeated on the saturated hydroxyester (4.44),

only the γ-ketoester (4.48) was isolated in a 41 % yield (Equation 4.7). Once again the isopropylidene group had migrated onto the primary alcohol, with subsequent oxidation of the secondary alcohol to the ketone.



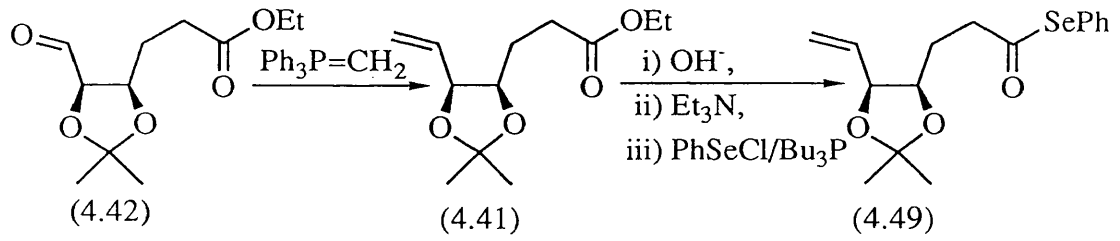
(4.44) (4.48) **(4.7)**

This migration problem was overcome by oxidation of the hydroxyester (4.44) with pyridinium chlorochromate, buffered with anhydrous sodium acetate, in the presence of powdered 4Å molecular sieves, giving the crude aldehyde (4.42) in a 93 % yield (Equation 4.8).



(4.44) (4.42) **(4.8)**

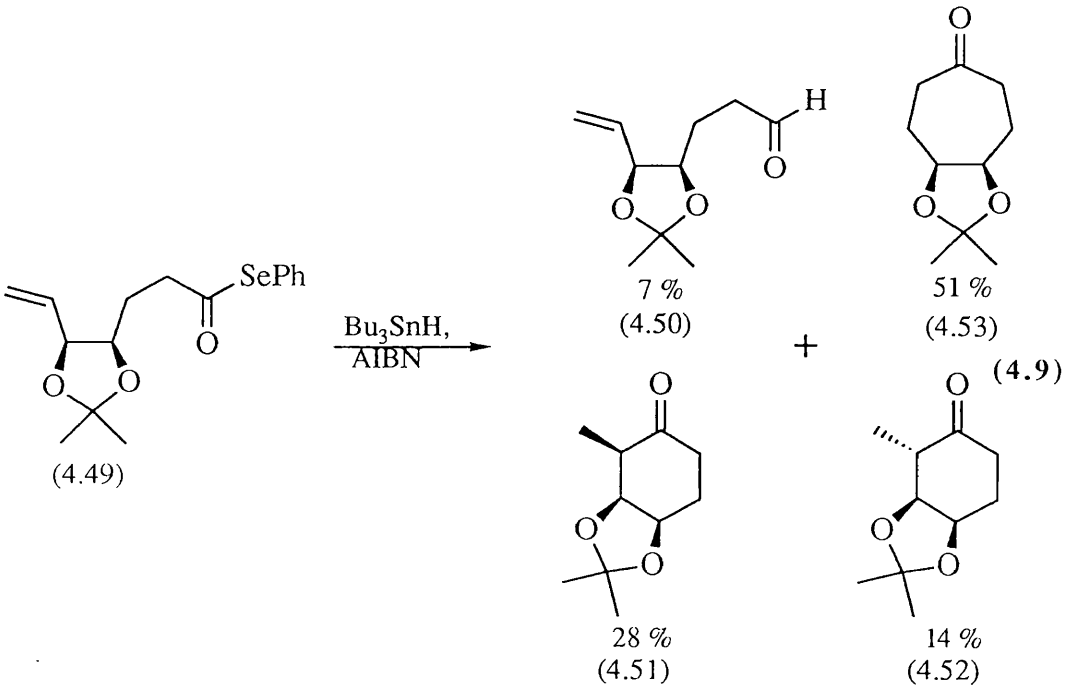
A further Wittig reaction, performed on aldehyde (4.42) with methylenetriphenylphosphorane, gave the vinyl ester (4.41) in a 71 % yield (Scheme 4.26), the enantiomer of the initially proposed isopropylidene vinyl ester (4.17). Saponification of this vinyl ester (4.41) with aqueous potassium hydroxide in methanol and standard selenoester preparation gave the selenoester (4.49) in a 62 % yield, from vinyl ester (4.41) (Scheme 4.26).



Scheme 4.26 Preparation of Selenoester (4.49)

4.5 CYCLISATION REACTIONS

The reaction conditions used for the cyclisation of the selenoester (4.49) were, as near as possible, identical to those used for cyclisation of the 5,5-ethylenedioxy selenoester (3.3) (Scheme 3.1). In the event, dropwise addition of a solution of tri-n-butyltin hydride in benzene, containing a catalytic amount of AIBN, to a refluxing solution of the selenoester (4.49) in benzene gave 7 % of the reduction product (4.50), a 2:1 mixture of the cyclohexanones (4.51) and (4.52) in a 41 % yield, and the required cycloheptanone derivative (4.53) in a 51 % yield (Equation 4.9).



The high efficiency in the cyclisation of the 4,5-di-*O*-isopropylidene-6-heptenoyl radical, with over 90 % cyclised products recovered, was indicative that the 4,5-di-*O*-isopropylidene functionality did indeed have a positive influence on the cyclisation. Moreover, the 7-endo mode product was formed in greater than 50 % yield. It appeared however, that the factors that inhibited the 6-exo mode cyclisation in the 5,5-ethylenedioxy case (Scheme 3.1), had been somewhat overridden, with 41 % of the cyclohexanone derivatives being formed. The relative proportions of the two cyclohexanone derivatives (4.51) and (4.52), indicated that one face of the olefin was attacked preferentially by the acyl radical. Dreiding models indicate that for either a chair-like transition state (Figure 4.4, Structure A), or a boat-like transition state (Figure 4.4, Structure B), with the alkene pseudoequatorial, the same all *cis*-product will be formed whilst, when the alkene is pseudoaxial (Figure 4.4, Structures C and D), the methyl group will end up *trans* to the isopropylidene group. The former case is probably the preferred pathway.

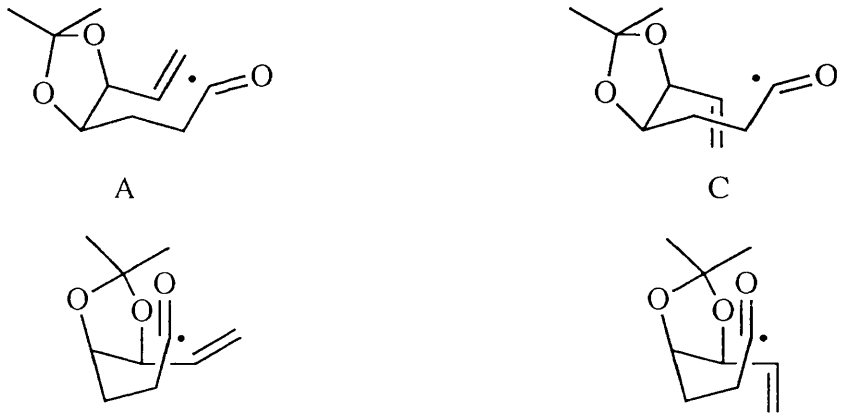
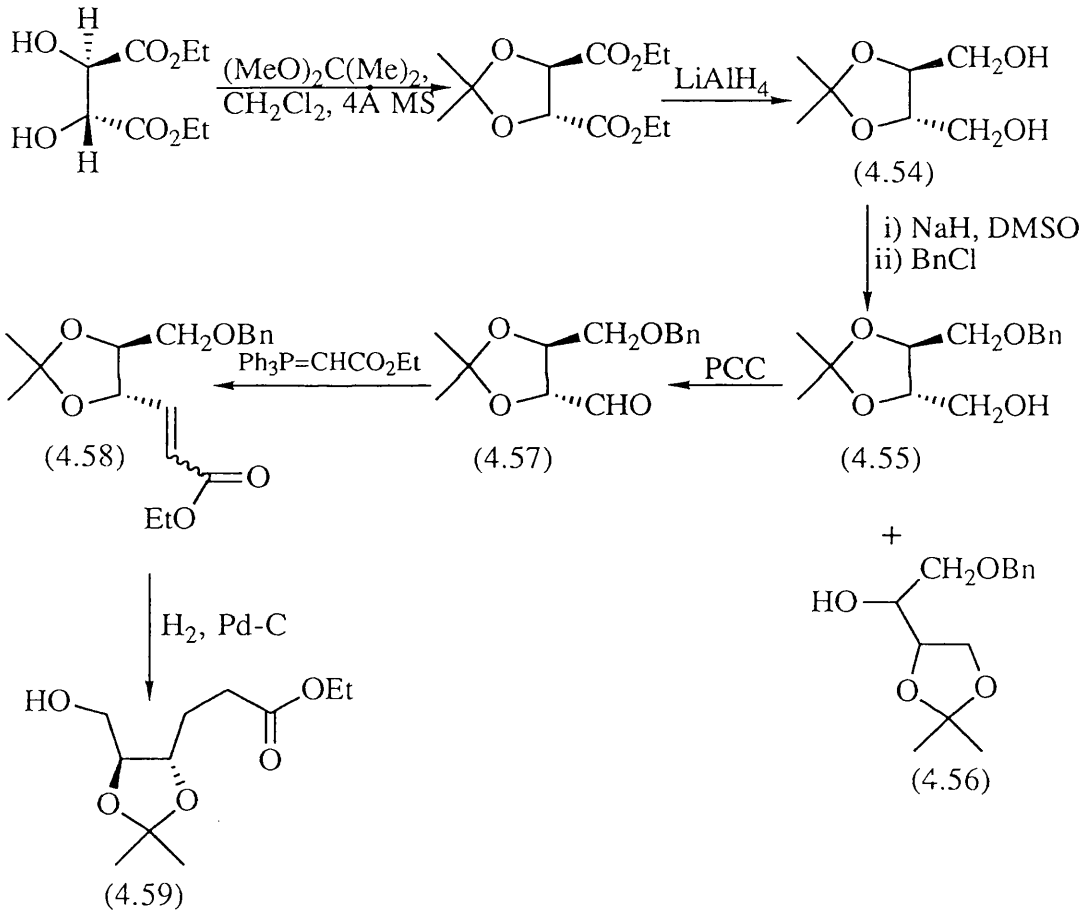


Figure 4.4 Rationalisation of Products From 6-*exo* mode Cyclisation.

At this stage, an efficient entry into the 4,5-isopropylidene-6-heptenoyl radical precursor has been developed and the cyclisation demonstrated to proceed in high yield.

At this stage, an efficient entry into the 4,5-isopropylidene-6-heptenoyl radical precursor has been developed and the cyclisation demonstrated to proceed in high yield. Furthermore, the yield of the 7-*endo* product was shown to be greater than that in the simple 5-alkoxy system. In order to fully investigate this system, a study of the efficiency and mode of cyclisation for the *trans* fused 4,5-di-*O*-isopropylidene isomer was then undertaken.

The synthetic route developed for the *cis*-fused isopropylidene system was modified for the *trans* fused isopropylidene system, which is outlined in Scheme 4.27.

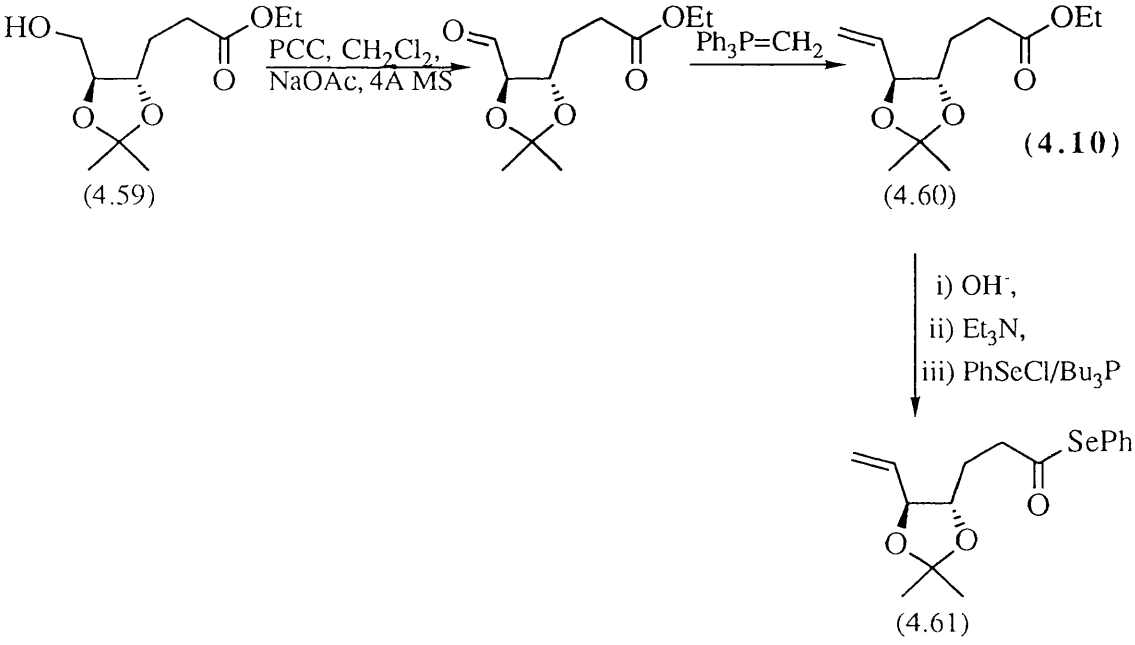


Scheme 4.27 Preparation of *trans*-Isopropylidene Hydroxyester (4.59)

L-Threitol (4.54) was prepared in 2 steps from L-(+)-diethyl tartrate in a 47 % yield.[44] Selective protection of one of the hydroxy groups as a benzyl ether, gave the

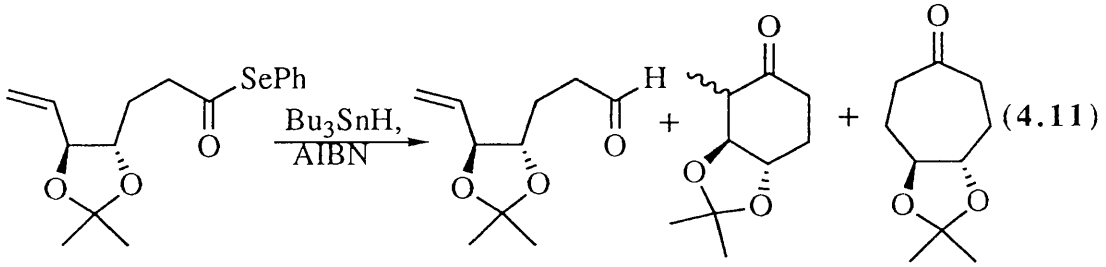
mono-benzylated alcohol (4.55) in 54 % yield. Migration of the isopropylidene group to give the mono-benzylated secondary alcohol (4.56) only occurring to a minor extent on a larger scale synthesis. Oxidation of the mono-benzylated alcohol (4.55) under the standard buffered P.C.C. conditions then gave the unstable aldehyde (4.57) which was immediately reacted with carbethoxymethylenetriphenylphosphorane to give a 1:1 mixture of the mono-benzylated unsaturated esters (4.58) in 71 % yield. The choice of the benzyl protecting group was vindicated when hydrogenation of the mixture of the unsaturated esters (4.58) with hydrogen and palladium on activated charcoal not only saturated the double bond, but released the protected alcohol for further manipulation, giving the *trans*-isopropylidene hydroxyester (4.59) in a 91 % yield.

Further oxidation with buffered PCC and immediate Wittig reaction with methylenetriphenylphosphorane gave the vinyl ester (4.60) in 39 % yield from the hydroxyester (4.59). The standard conditions for saponification and selenoester formation were repeated on the vinyl ester (4.60) to give the selenoester (4.61) in 49 % overall yield (Equation 4.10).



The reaction conditions used for the cyclisation of the *cis*-isopropylidene selenoester (4.49) were also used for the cyclisation of the *trans*-fused isopropylidene

selenoester (4.61). In this manner, the aldehyde (4.62) was obtained in 44 %, together with 19 % of the cyclohexanone derivatives (4.63), as a 1:1 mixture and the cycloheptanone derivative (4.64) in 10 % yield (Equation 4.11).



44 % 19 % 10 %

(4.61) (4.62) (4.63) (4.64)

The high yield of the reduction product, aldehyde (4.64), indicated that the rate of cyclisation was slow when compared with the rate of hydrogen abstraction from the stannane. Therefore, the cyclisation procedure was repeated with addition of tin hydride over 11 h (syringe pump). The yield of the cyclohexanone derivatives (4.63)was increased to 29 %, still as a 1:1 mixture (nmr) and the yield of the cycloheptanone derivative (4.64) was also increased to 23 %.

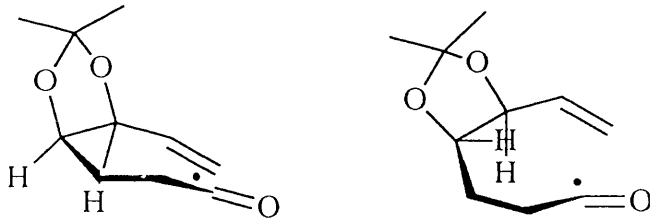
The ratio of the two 6-*exo* products in both reactions was the same (1:1), indicating that there is no preferential attack of the acyl radical on either face of the alkene.

It is interesting to compare the overall cyclisation yields and the ratios of the 6-*exo* and 7-*endo* mode products for the *cis*- and *trans*- isopropylidene series with the ketalisation of both *cis*- and *trans*-cyclohexane and cycloheptane-1,2-diols.

It is well known amongst carbohydrate chemists that *cis*-vicinal diols on the pyranose skeleton are much more readily ketalised under the traditional acidic conditions than their *trans*-isomers and that special conditions have to be adopted for the formation of acetonides of the latter. In the cyclohexane-1,2-diol series this phenomenom was recorded by Cromartie and Hamied[45], *inter alia*, who noted that

higher yields were obtained and less forcing conditions required for the ketalisation of *cis*-cyclohexane-1,2-diols than the *trans*-isomer. Conversely, Cope, Liss and Wood demonstrated[46] that both *cis*- and *trans*-cycloheptane-1,2-diol could be ketalised under typical conditions with equal ease.

It would appear that *trans*-1,2-*O*-isopropylidene cycloheptane is more stable and more readily formed than its lower homologue. Indeed this knowledge had been the main factor in the decision to extend our cyclisation study from the *erythro*- to the *threo*- series, where it was hoped that higher yields of the cycloheptanone would be obtained. The experimental results clearly demonstrate that this reasoning was only partly true (Equation 4.9 and 4.11). Less cyclohexanone was obtained in the *threo*- series than the *erythro*- series in apparent accordance with the postulate that the *trans*-isopropylidene cyclohexane would be less readily available than the *cis*-isomer. However, less of the cycloheptanone was also obtained. This result probably reflects a more extended conformation of the radical in the *threo*- series than in the *erythro*- series with a consequently greater loss of entropy required in order for the transition state for cyclisation to be attained, as schematised in Figure 4.5.



CIS TRANS

Figure 4.5 Preferred Conformation for 7-*endo* Cyclisations.

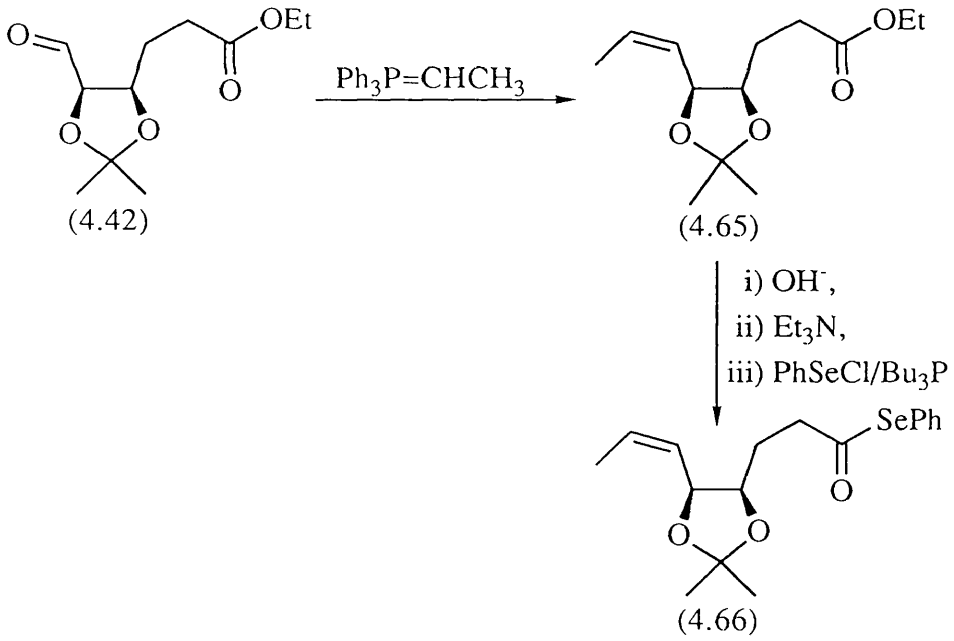
In conclusion, in order to get preferential 7-*endo* mode cyclisation of the 4,5-di-*O*-isopropylidene-6-heptenoyl radical, the 4,5-isopropylidene functionality needs to be *cis*-fused.

The next step towards the perceived eventual tandem cyclisation was to study what effect a substituent at the terminal position of the olefin within the 4,5-

isopropylidene-6-heptenoyl radical system would have on the mode and efficiency of cyclisation.

4.6 STUDY OF THE EFFECTS OF A SUBSTITUENT IN THE TERMINAL OLEFIN POSITION ON THE MODE AND EFFICIENCY OF CYCLISATION.

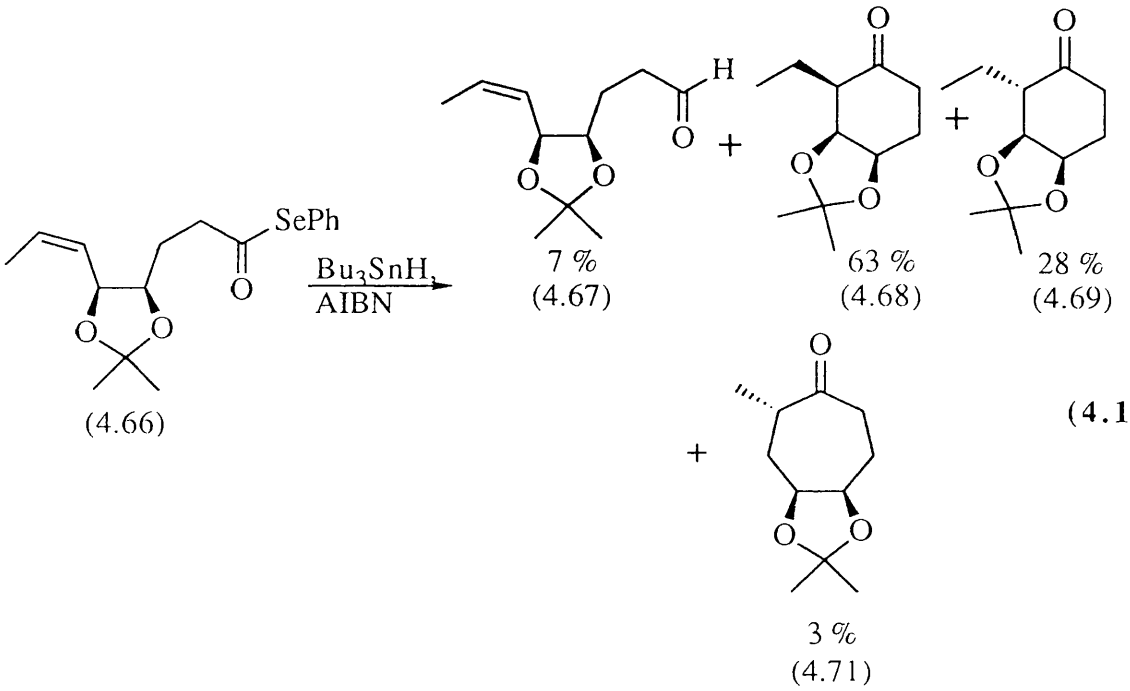
The *cis*-octenoate ester (4.65) was prepared in a 73 % yield by a Wittig reaction between the aldehyde (4.42) and ethylenetriphenylphosphorane. The stereochemistry of the olefin was determined by a positive n.O e effect between the allylic methyl group and the 5-H proton. Saponification of the ester (4.65) and standard selenoester preparation yielded the corresponding selenoester (4.66) in 66 % yield (Scheme 4.28).



Scheme 4.28 Preparation of Selenoester (4.66).

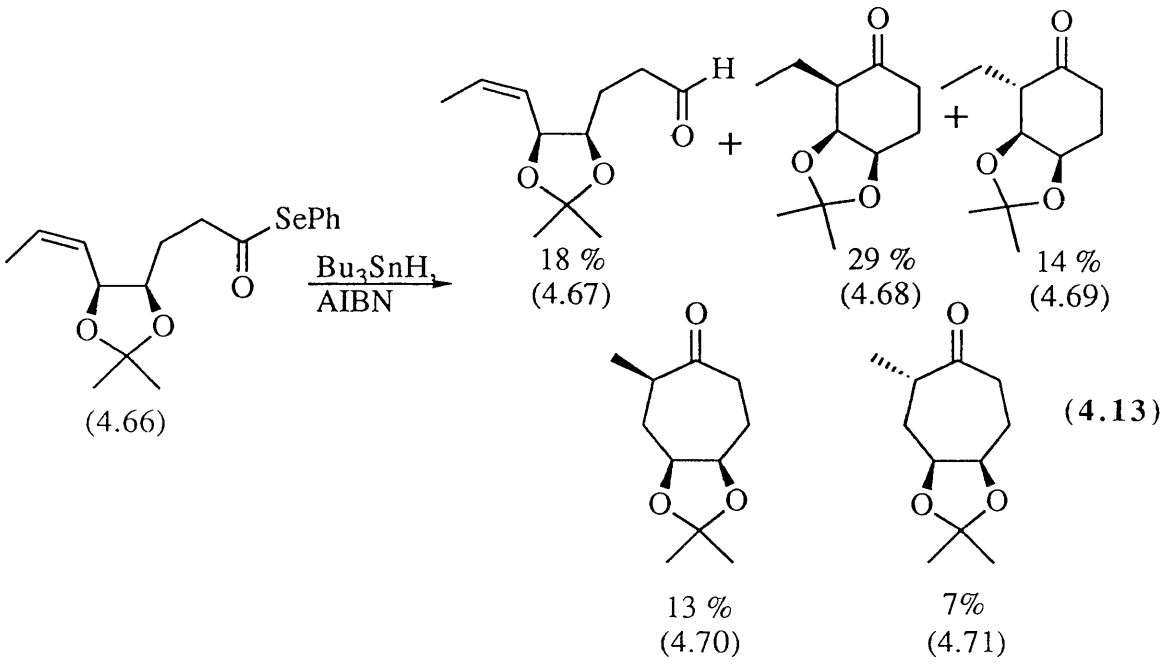
Cyclisation of this selenoester (4.66) was accomplished under the same reaction conditions employed for cyclisation of the selenoester (4.49) (Equation 4.9). From this

reaction the aldehyde (4.67) was obtained in 7 % yield together with approximately 63 % and 28 % of the two cyclohexanones (4.68) and (4.69), and 3 % of the cycloheptanone (4.71) (Equation 4.12). The yields are approximate in view of the difficulties encountered in separation of the cyclised products.



(4.12)

Nevertheless, from this result it is apparent that the introduction of the methyl residue onto the olefin hinders the cyclisation in the 7-*endo* mode to the extent that the cyclisation in the 6-*exo* mode becomes the major pathway. In order to overcome this preferred cyclisation in the 6-*exo* mode, the reaction was repeated with the addition of the tin hydride solution over 8 h (syringe pump). From this slow addition reaction, 18 % of the reduction product, aldehyde (4.67) was recovered. The major ethyl cyclohexanone derivative (4.68) was obtained in 29 % yield, the minor cyclohexanone (4.69) in 13 % and the two cycloheptanones (4.70) and (4.71) in 14 % and 7 % yields respectively (Equation 4.13).



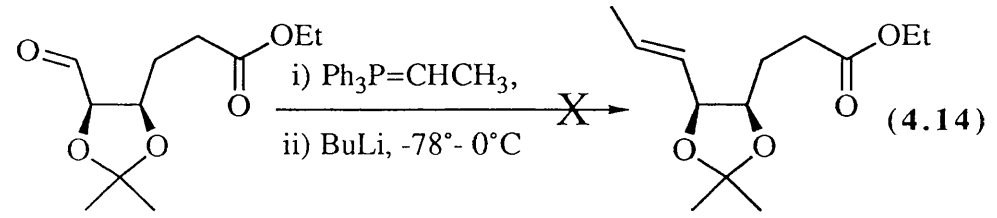
(4.13)

By analogy with the cyclisation of the selenoester (4.49), the major 6-exo product (4.68) was assigned to be the 2R- isomer. By extrapolation, the same argument was used to assign the stereochemistry of the major methyl cycloheptanone derivative (4.70), also to be the 2R- isomer.

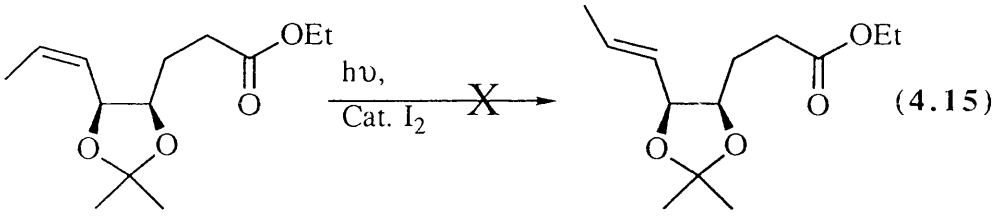
In conclusion, for *cis*-4,5-di-*O*-isopropylidene-6-octenoyl radicals, cyclisation in the 7-*endo* mode is slow. Decreasing the rate of addition of the tin hydride solution increased the yield of the 7-*endo* mode products, but the yield was at best modest.

In the *cis*-system above, even thought the overall cyclisation yield was high, the yield for 7-*endo* mode cyclisation was at best modest. The conformation of the allylic ether residue was known to have a large influence on the mode of cyclisation, but any effect due to the *cis*-nature of the alkene was unclear. Unfortunately, all attempts to prepare the corresponding *trans*-alkene (4.72) via either a Schlosser-Wittig[47] reaction on the aldehyde (4.42) (Equation 4.14), or photoisomerisation of the *cis*-allylic ester (4.65) (Equation 4.15) were unsuccessful. However, subsequent experiments on

related 7-substituted 6-heptenoyl systems, discussed in Chapter 5, indicated that the stereochemistry of the olefin did not influence the cyclisation yield.



(4.42) (4.72)



(4.65) (4.72)

A further option that was considered for increasing the ratio of 7-*endo*/6-*exo* mode cyclisation was the inclusion of a *cis*-2,3-olefinic bond into the heptenoyl radical chain. The reasoning behind this idea being that the increase of two backbone bond angles from 109.5° to 120° would open up the conformation to the extent that the 6-exo mode attack would be disfavoured relative to the 7-endo mode (Figure 4.6).

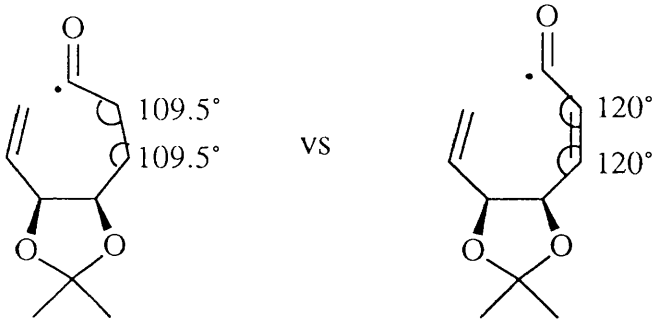
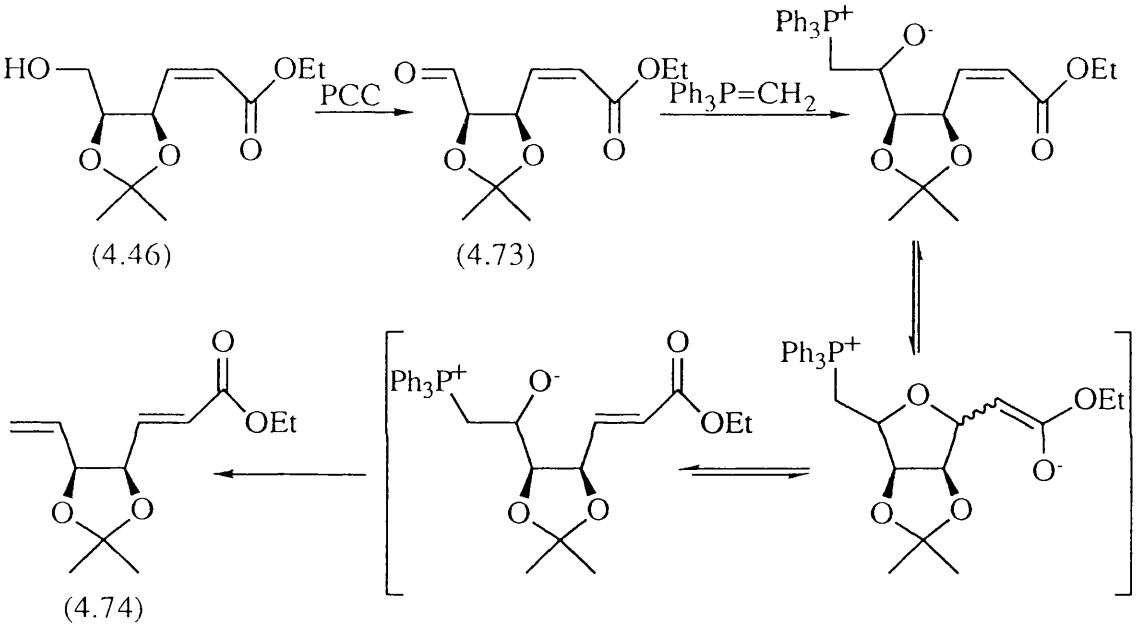


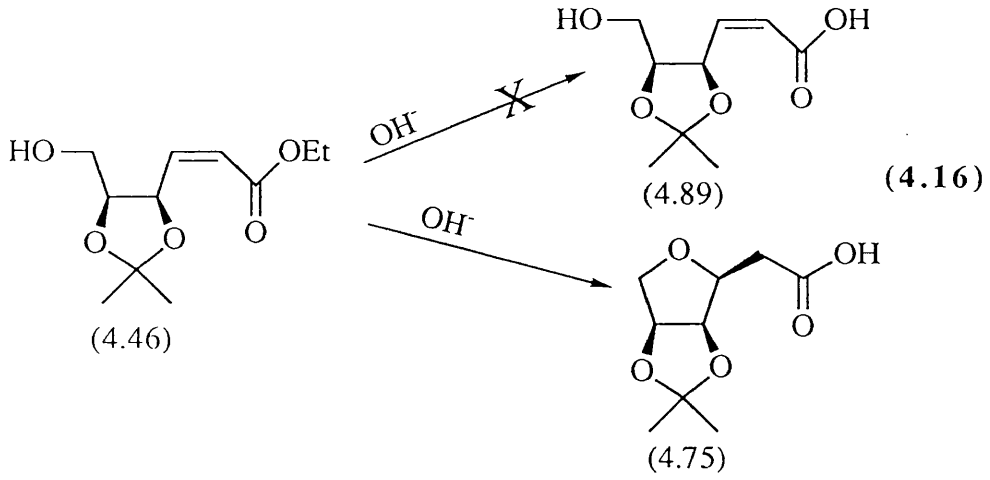
Figure 4.6 More Open Conformation for *cis*-2,3-Olefin.

To this end, oxidation of the *cis*-α,β-unsaturated ester (4.46) by the standard buffered PCC protocol gave the crude aldehyde (4.73) in 93 % yield. Immediate Wittig reaction with methylenetriphenylphosphorane gave the unexpected *trans* -α,β-unsaturated ester (4.74) in 19 % yield (Scheme 4.29). It was presumed that a reversible intramolecular Michael addition onto the α,β-unsaturated ester by the intermediate betaine was occuring, which ultimately gave the thermodynamically more stable *trans*-olefin.



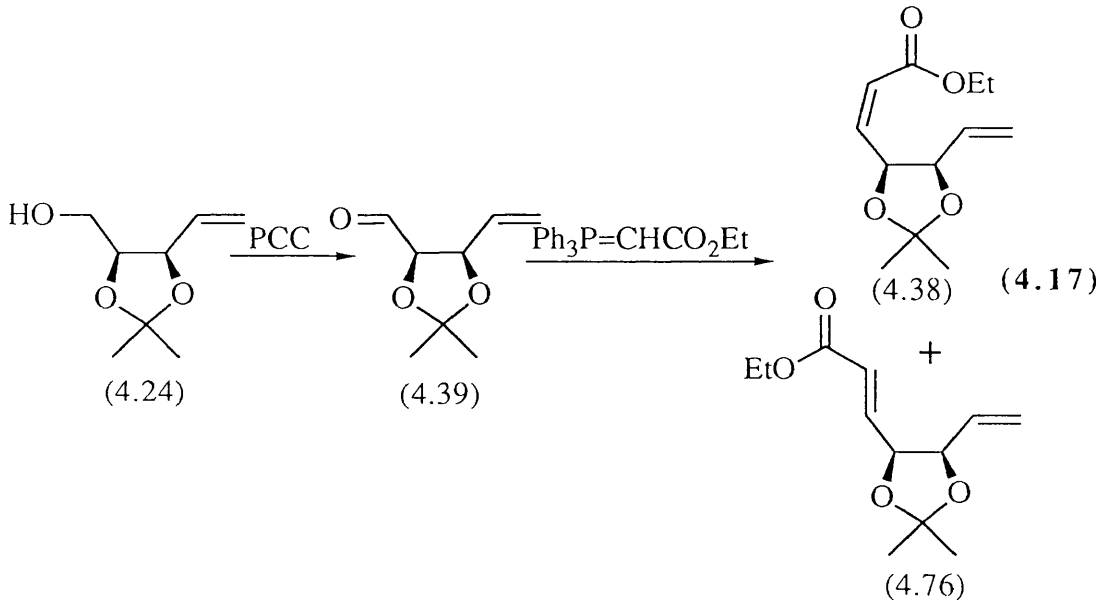
Scheme 4.29 Preparation of *trans*-Ester (4.74) via Intramolecular 1,4-Addition.

In order to avoid this isomerisation, it was proposed that the oxidation/Wittig reaction sequence could be repeated on the α,β-unsaturated acid (4.89), whereby intramolecular 1,4-addition to the unsaturated carboxylate would be avoided. However, saponification of the unsaturated hydroxyester (4.46) under the standard conditions gave only the cyclised acid (4.75) (Equation 4.16). Once again, the conditions were basic enough to promote cyclisation to give a tetrahydrofuran derivative.



(4.16)

To avoid any cyclisation, preparation of the enantiomeric α,β-unsaturated vinylester (4.38), via the hydroxyolefin (4.24) was re-investigated. Buffered P.C.C. oxidation of the hydroxyolefin (4.24) and immediate Wittig reaction of the resulting unstable aldehyde (4.39) with carbethoxymethylenetriphenylphosphorane gave 21 % of the required *cis*-α,β-unsaturated vinylester (4.38), with 17 % of the *trans*-isomer (4.76) (Equation 4.17).

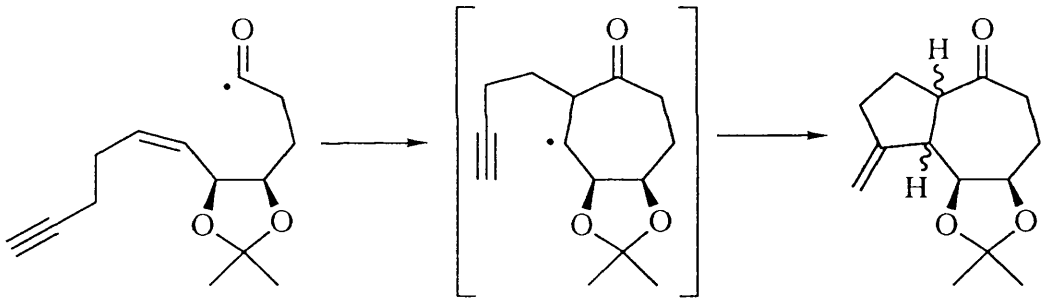


(4.17)

Use of the Pfitzner-Moffatt oxidation on the hydroxyolefin (4.24) and subsequent Wittig reaction gave predominantly the *trans*-isomer, in a 50 % yield. In view of the low yield and other constraints this idea was not pursued further.

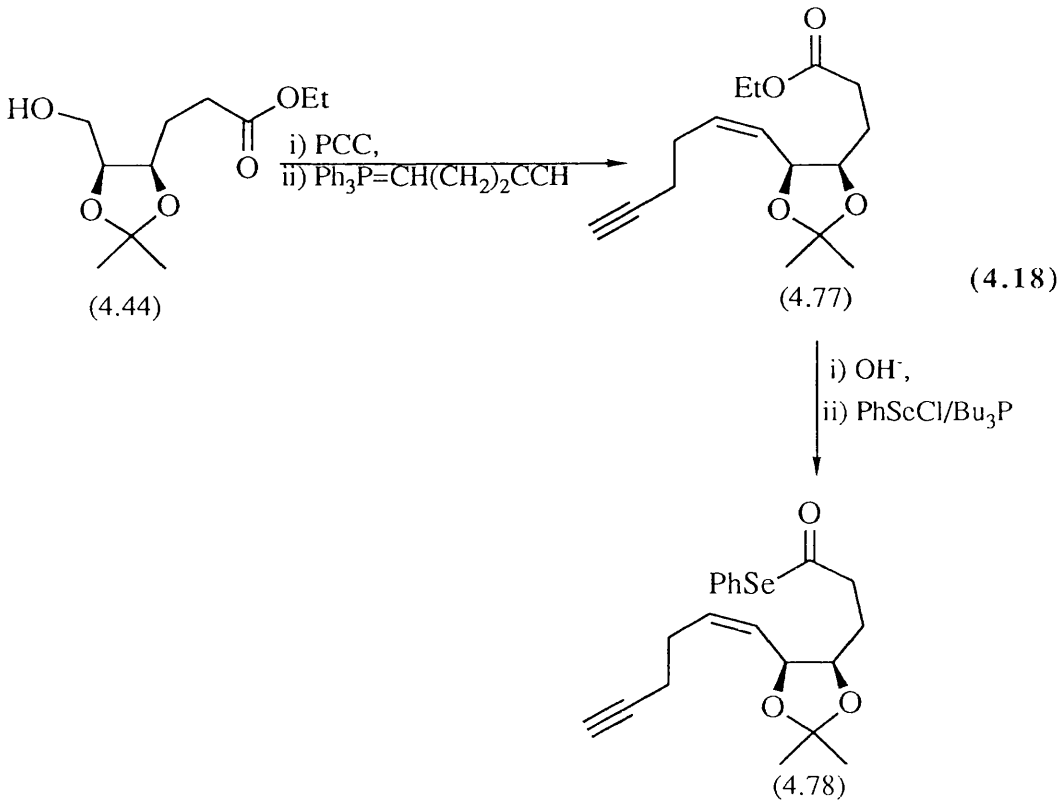
4.7 A DIRECT ENTRY INTO BICYCLO-[5,3,0]-DECANES VIA A TANDEM RADICAL CYCLISATION

To prepare the bicyclo-[5,3,0]-decane skeleton, common to the perhydroazulene class of sesquiterpenoids[48] by a tandem radical cyclisation, the radical formed on 7-*endo* mode cyclisation has to undergo a further cyclisation, this in the 5-*exo* mode, onto a suitably placed multiple bond. In order to reduce the number of possible stereoisomeric products, this latter cyclisation terminus was chosen to be a terminal triple bond (Scheme 4.30). The advantages of this approach to sesquiterpenoids lie in the carbohydrate origins of the backbone, resulting in formation of enantiomerically pure products, and the ideal disposition of the substituents for further elaboration into actual terpenoids.



Scheme 4.30 Proposed Tandem Cyclisation.

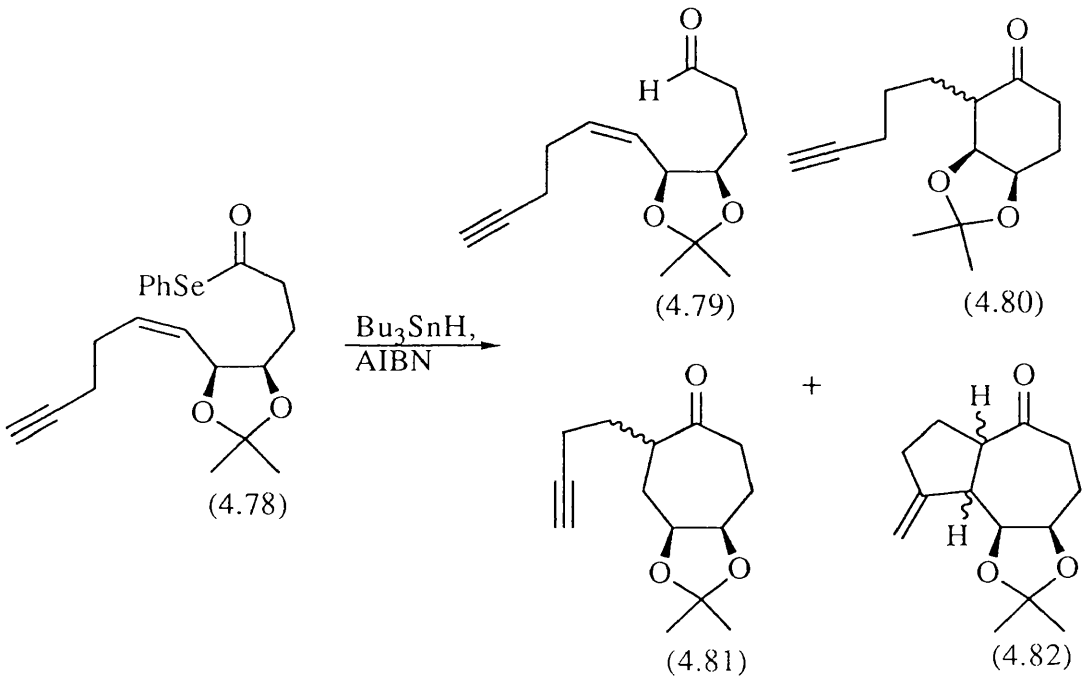
In the event, oxidation and immediate Wittig reaction performed on the hydroxyester (4.44) with pentynylidenetriphenylphosporane, gave the acetylenic vinyl ester (4.77) in 64 % yield (Equation 4.18). The corresponding selenoester (4.78) was prepared in the usual manner from the ester (4.77) in a 76 % overall yield (Equation 4.18).



(4.44) (4.77) (4.78) **(4.18)**

In order to determine optimum conditions for the tandem cyclisation, a series of reactions were performed on the selenoester (4.78), in which the rate of addition of the tri-n-butyltin hydride solution and the concentration of the reaction mixture were varied. In the first trial reaction, the reaction conditions used previously for the cyclisation of the selenoester (4.49), with the addition of the tin hydride solution over 30 min, were repeated. This gave a complex mixture in which significant quantities of the reduction product , aldehyde (4.79), and the products from 6-*exo* mode (4.80) and single 7-*endo* mode (4.81) cyclisation were detected. Only minor amounts of the products from the tandem cyclisation (4.82) were detected, as characterised by the presence of an exocyclic methylene group in the nmr spectra (Scheme 4.31). The second trial reaction involved the addition of the tin hydride solution over 8 h (syringe pump). In the crude mixture of products, very little aldehyde (4.79) was detected, whilst the relative proportion of all the cyclised products was seen to have increased, in particular the amount of exocyclic methylene signals detected was significantly greater. In the third and final cyclisation reaction the tin hydride solution was added over a period of 24 h,

to an extremely dilute solution (ca. 0.003M) of the selenoester. The chain transfer in this reaction was poor, such that further AIBN had to be added over another 24 h, for all of the starting selenoester to be consumed. However, spectra of the recovered mixture indicated that no aldehyde was present and that the amount of products due to 6-*exo* cyclisation was minimal. A small amount of the singly cyclised 7-*endo* products was detected, but the major component, 40-50 % (nmr) was a mixture of the tandem cyclisation products.



Scheme 4.31 Tandem Cyclisation Reaction.

It was possible to identify all four stereoisomeric products resulting from the tandem cyclisation, by high field nmr spectroscopy, in the reaction mixture. The four products were formed in the approximate ratio 5:3:2:1. Purification and complete identification of each of the products however, proved difficult. Ultimately, only one diastereoisomer was obtained completely pure. A variety of chemical, spectroscopic and modelling techniques were the used to assign the relative stereochemistries of all four isomers.

4.8 DETERMINATION OF STEREOCHEMISTRY FOR THE BICYCLO-[5,3,0]-DECANE SYSTEMS

From the high field nmr spectra of the various mixtures obtained by chromatography, salient features for all four diastereoisomers were identified and the coupling constants in the 4-H, 5-H and 6-H system are summarised in Table 4.1.

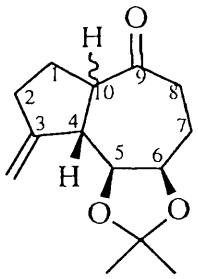
ISOMER	δ C=CH_2 (ppm)	$J_{4,5}$ (Hz)	$J_{5,6}$ (Hz)
A	5.00 & 5.23	9.6	5.8
B	4.96 & 5.08	7.7	2.0
C	4.61 & 6.09	11.1	4.0
D	4.98 & 5.06	7.1	0

Table 4.1 Salient Features.from nmr Spectra of Tandem Products.

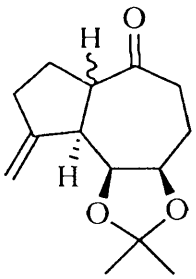
The 4-H and 5-H coupling constant ($J_{4,5}$) in both isomers 'A' and 'C' was large (9.6 and 11.1 Hz respectively), indicating that the dihedral angle between 4-H and 5-H was either small, such that the two protons were nearly eclipsed, or was appproaching 180°. Inspection of simple molecular models for all four diastereoisomers indicated that it was not possible for the 4-H and 5-H protons to be eclipsed and hence, the two diastereoisomers , 'A' and 'C', with the large $J_{4,5}$, had a dihedral angle of approximately 180° for 4-H-C-C-5-H. Therefore, isomers 'A' and 'C' differ only in configuration at 10-C. A similar treatment of the coupling constants for isomers 'B' and 'D' indicated that the 4-H and 5-H protons were *cis* and therefore, isomers 'B' and 'D' also differ only in the configuration at 10-C.

In each of the four stereoisomers, 'A', 'B', 'C' and 'D', the signals due to the 4-H and 10-H were insufficiently resolved to enable the measurement of $J_{4,10}$. The coupling constants $J_{4,5}$ were measured from the cleanly resolved signal for 5-H

Further evidence in support of the above assignments was obtained from a series of equilibriation reactions on the various mixtures. When a mixture containing isomers 'A' and 'C', was treated with lithium hydroxide in methanol for 48 h, all of isomer 'C' was converted to isomer 'A', reinforcing the conclusions drawn from the high field nmr spectra that 'A' and 'C' are epimers at 10-C (Figure 4.7). Furthermore, this experiment shows that isomer 'A' is thermodynamically more stable than isomer 'C' . When isomers 'B' and 'D' were treated in a similar fashion, the equilibrium mixture was found to be enriched in isomer 'B', confirming the conclusions drawn from the nmr data that isomers 'B' and 'D' are epimers at 10-C (Figure 4.7).



(4.83)
'A' and 'C'



(4.84)
'B' and 'D'

Figure 4.7 Differentiation of Pairs of Epimers

It can therefore be conclusively stated that the four products consist of two pairs of epimers, 'A' and 'C' and 'B' and 'D', represented by the formulae (4.83) and (4.84) respectively.

The remaining problem was therefore the assignment of configuration at 10-C for each pair of epimers. Given the inaccessibility of $J_{4,10}$ attempts were therefore

made to determine the lower energy epimer in each pair by means of Dreiding models and molecular mechanics calculations, as these would correspond to the major products from the equilibration reactions.

The study of Dreiding molecular models for all four diastereoisomers was helpful but inconclusive for the determination of low energy conformations and dihedral angles. Therefore, in collaboration with Dr. J.W. Davies of the Chemistry Support Group at Smith Kline and Beechams, molecular mechanics studies (Cosmic 90)[49] were performed on all four diastereoisomers as well as for both the simple *cis*-fused (4.53) and *trans*-fused cycloheptanones (4.64) and the results are summarised in Figure 4.8.

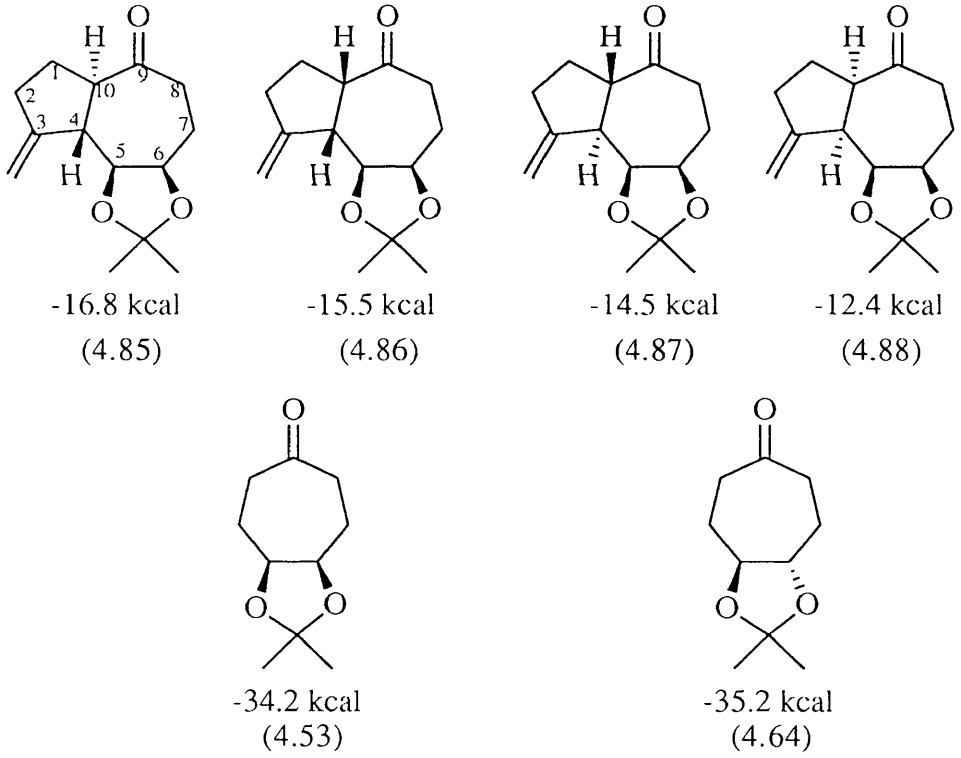
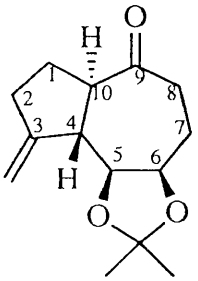


Figure 4.8 Lowest Energy Configurations for Some of the Cyclised Products.

The molecular mechanics calculations indicate that of the two structures possible for 'A' and 'C', (4.85) and (4.86), (4.85) has the lower energy and is therefore

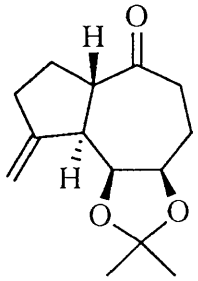
compound 'A'. Similarly, the molecular mechanics calculations indicate that of the two structures possible for 'B' and 'D', (4.87) and (4.88), (4.87) has the lower energy and is therefore compound 'B'. Furthermore, the stereoisomer that was isolated pure was (4.88), isomer 'D'. The structures are represented below with their approximate yields.



20 %

(4.85)

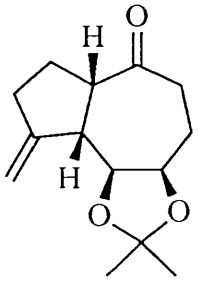
'A'



13 %

(4.87)

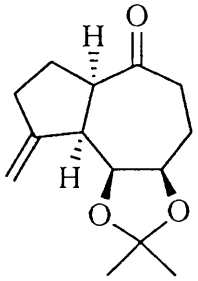
'B'



8 %

(4.86)

'C'



4 %

(4.88)

'D'

4.8 CONCLUSIONS

A protocol for entry into *cis*-4,5-di-*O*-isopropylidene 6-heptenoyl systems has been developed and it has been demonstrated that *cis*-4,5-di-*O*-isopropylidene 6-heptenoyl radicals can be cyclised in high yield, giving both 6-*exo* and 7-*endo* mode cyclisation products. This methodology has been extended to give an entry into the bicyclo-[5,3,0]-decane skeleton via a tandem cyclisation process.

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CHAPTER 5

MULTIPLE CYCLISATION/FRAGMENTATION SEQUENCES

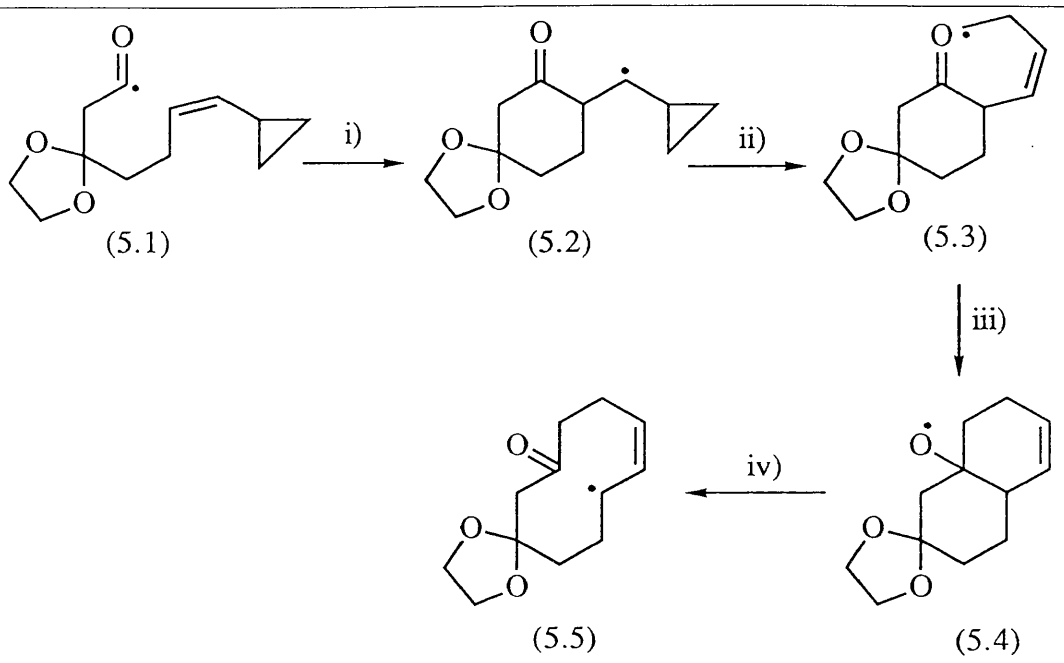
5.1 INTRODUCTION

The propensity of 6-heptenoyl radicals carrying alkoxy substituents in the 3-position to undergo 6-*exo* mode cyclisations forms the basis of the synthesis outlined in Chapter 3 (Scheme 3.1). The central theme of this chapter is the attempted coupling of this highly efficient radical cyclisation in tandem with other, well precedented radical rearrangements in such a manner as to provide an entry into medium sized rings.

It was envisaged that the cyclodecenone skeleton could be advantageously accessed by a series of radical cyclisations and fragmentation reactions as outlined in Scheme 5.1. The key radical reactions involved in such a scheme are:

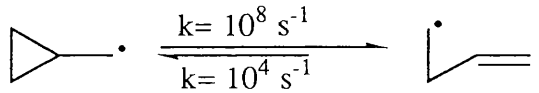
i) Preferential 6-*exo* mode cyclisation of a suitably substituted 6-heptenoyl radical (5.1),
ii) Ring opening of the so formed α–cyclopropylmethyl radical (5.2) to give the homoallyl radical (5.3),
iii) Cyclisation of the homoallyl radical (5.3) onto the preformed cyclohexanone,
iv) β-fission of the alkoxybicyclodecene radical (5.4) to give ultimately the cyclodecenone (5.5).

Each of the individual radical reactions in this scheme has ample literature precedent. The acyl radical cyclisation step forms the basis of Chapter 3 and is not discussed further here.



Scheme 5.1 Proposed Radical Cyclisation/Fragmentation Sequence

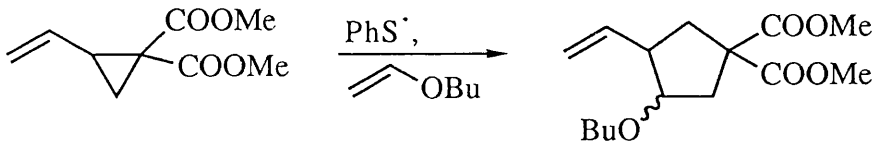
There have been extensive kinetics studies reported for both the ring opening and the ring closure of substituted and non-substituted α-cyclopropylmethyl radicals over a wide range of temperatures.[1] In the parent system (5.6), the rate constant for ring opening is *ca.* 10^8 s^{-1} at 25°C (Equation 5.1), whilst for the reverse reaction, the ring closure of the 3-butenyl radical (5.7), a rate constant of *ca.* 10^4 s^{-1} was observed, at the same temperature.



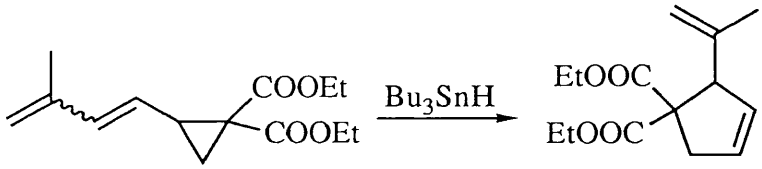
(5.6) (5.7) **(5.1)**

This rapid radical rearrangement has found various synthetic applications in recent years.[2] Two interesting tandem addition/fragmentations with vinyl cyclopropanes have been recently reported and are summarised in Equations 5.2 and 5.3.[3] A further notable example is found in the mechanism, described in Chapter 4,

Scheme 4.4 for the formation of *exo*-methylenecyclohexanes from 5-bromohexa-1,5-diene.

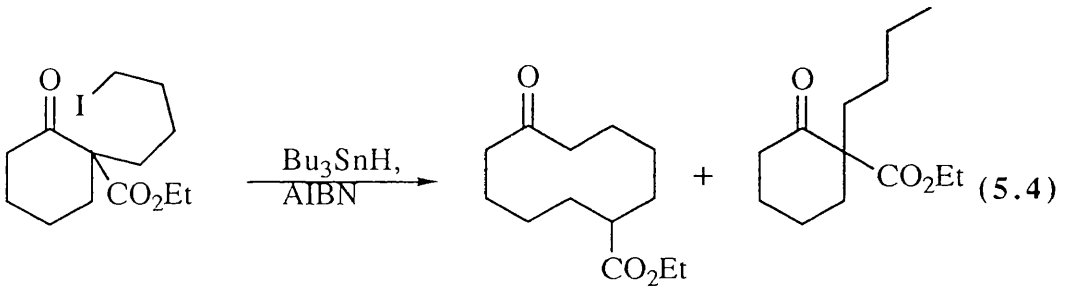


(5.2)



(5.3)

The addition of alkyl radicals to cyclic ketones has already been alluded to in Chapter 4, in connection with the ring expansion mechanism of cyclohexanones via cyclopropyloxy radicals (Scheme 4.5). Furthermore, Dowd[4] has also reported the intramolecular addition of propyl and butyl radicals onto the carbonyl group of cyclopentanones, cyclohexanones and cycloheptanones, to give, after β–fission, ring expanded products. Of direct relevence to the subject in hand,is the example outlined in Equation 5.4 in which a cyclodecanone (5.8) is formed via a decalinoxyl radical (5.9).

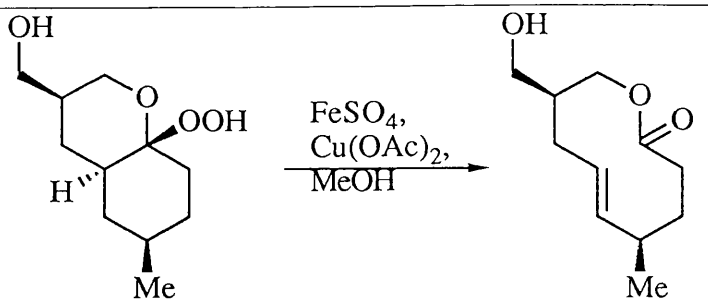


71 %
(5.8)

25 %

(5.4)

Further evidence for the β-fission of the 9-C/10-C bond in bicyclo-[4,4,0] systems has been provided by Schreiber[5] in the transition metal catalysed ring expansion of a hydroperoxide to give a 10 membered lactone (Equation 5.5).



(5.5)

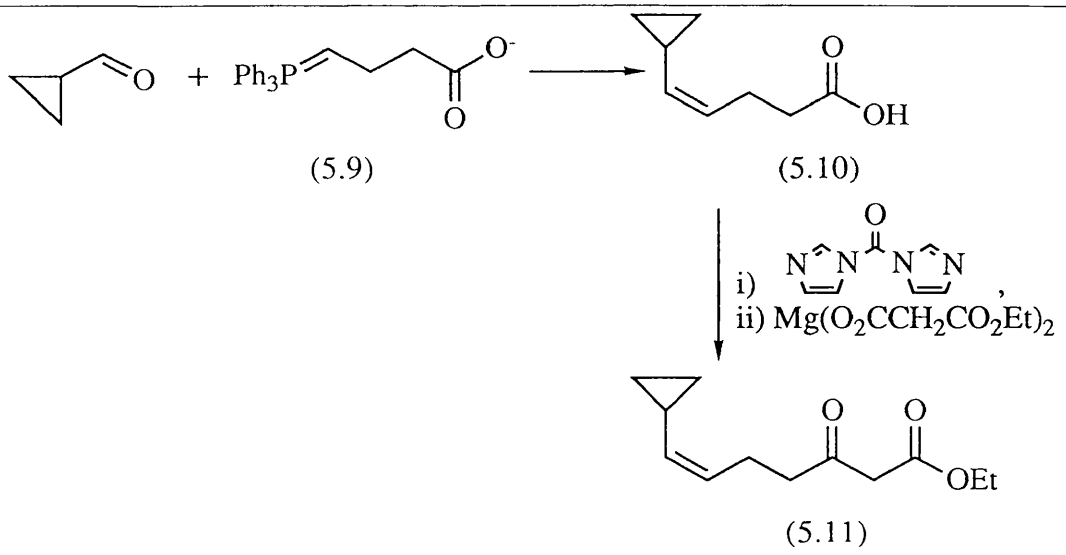
76%

Beckwith[6] has reported, however, that although β-fission of the 9-C/10-C bond in 9-decalinoxyl radicals is fast, it is reversible under appropriate conditions. Nevertheless, in the proposed reaction scheme the 10-membered ring radical was expected to be the thermodynamically more stable radical owing to its allylic nature.

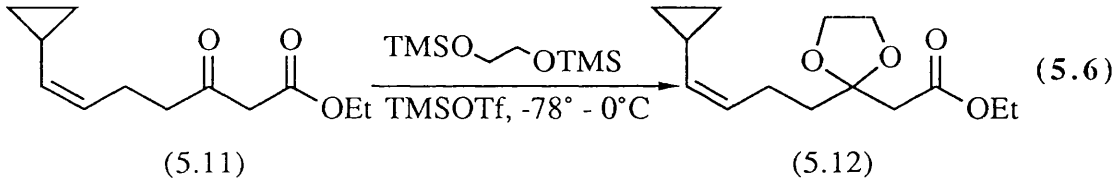
5.2 CYCLISATION/FRAGMENTATION SEQUENCE

The carbon framework for the cyclisation/fragmentation sequence to be attempted was prepared in two steps from cyclopropane carboxaldehyde. An initial Wittig reaction of the aldehyde with 4-(triphenylphosphoranylidene)butanoic acid (5.9),[7] gave the unsaturated cyclopropyl acid (5.10) in a virtually quantitative yield as a 3:1 mixture of the *Z*- and *E*-isomers (Scheme 5.2). Homologation of the derived imidazolide of (5.10) with magnesium monoethyl malonate, as described by Masamune,[8] gave the β-ketoester (5.11) in 91 % yield (Scheme 5.2).

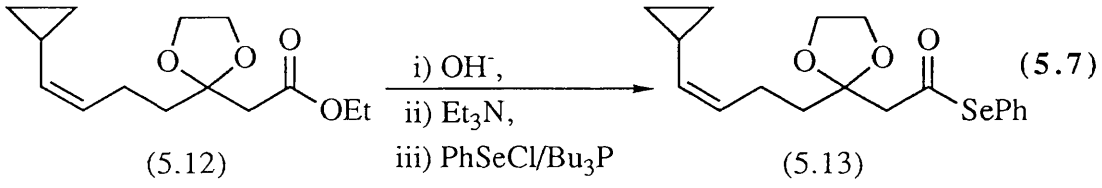
Acid catalysed ketalisation of the β-ketoester (5.11) with camphor 10-sulphonic acid and azeotropic removal of water gave only an 18 % yield of the ketal (5.12), with 34 % recovered starting material and considerable degradation. The ketal (5.12) was preferentially prepared by reaction of (5.11) with bis(trimethylsilyl)ethylene glycol and a catalytic amount of trimethylsilyl triflate, as described by Noyori,[9] in a pleasing 79 % yield (Equation 5.6).



Scheme 5.2 Preparation of the Carbon Framework for the Cyclisation/Fragmentation Sequence.

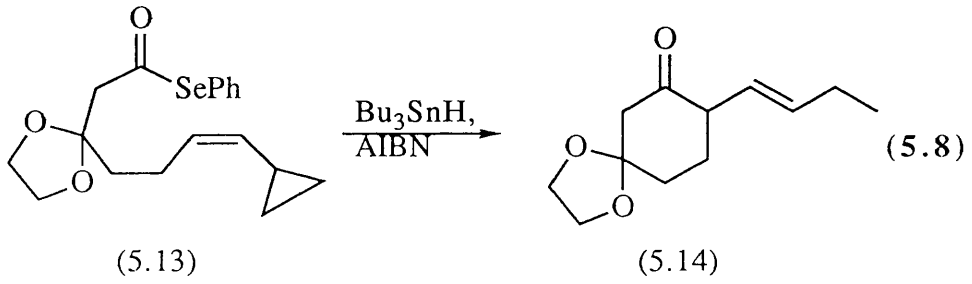


Saponification of the ester (5.12), and reaction with tributylphosphine and phenylselenenyl chloride gave the required selenoester (5.13) in a 43 % yield (Equation 5.7), so setting the stage for the study of the multiple cyclisation/fragmentation sequence.



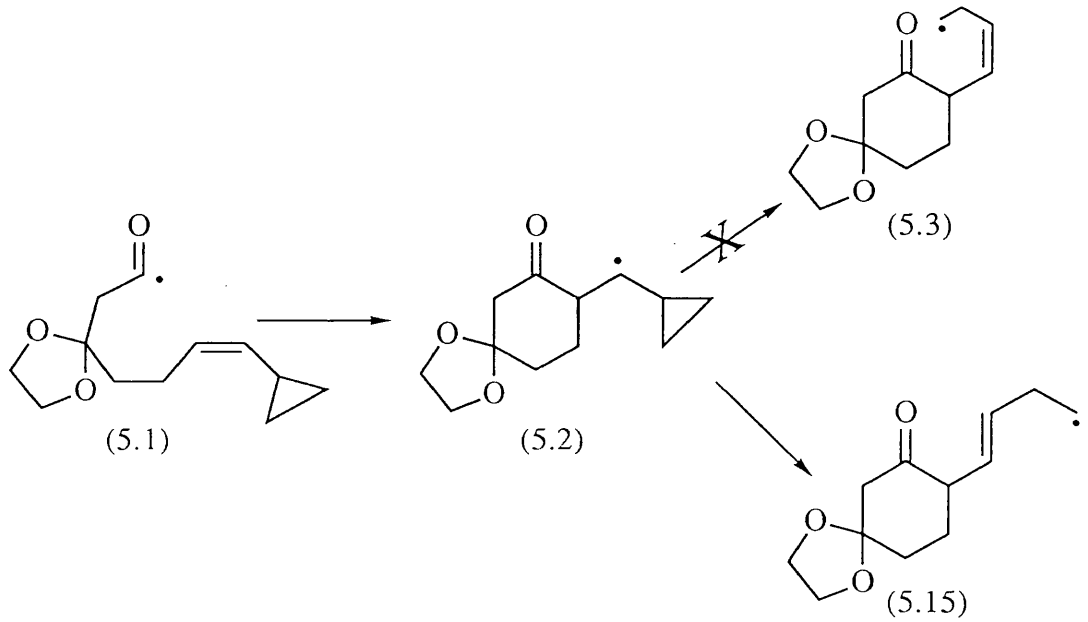
The critical radical cyclisation reaction was performed by the dropwise addition, over 30 min, of a dilute solution of tri-n-butyltin hydride and a catalytic quantity of AIBN to a refluxing solution of selenoester (5.13) in benzene. This reaction was very

clean, unfortunately the only product recovered was the *E*-butenylcyclohexanone (5.14) in a 95 % yield (Equation 5.8).



(5.13) (5.14) **(5.8)**

Comparison of this result with the proposed reaction sequence (Scheme 5.1) indicated that the acyl cyclisation and cyclopropylmethyl ring opening steps had taken place as anticipated. However, the ring opening of the cyclopropylmethyl radical (5.2) had selectively given the *E*-homoallyl radical (5.15), which was unable to cyclise further, rather than the required *Z*-isomer (5.3) (Scheme 5.3). This problem had been anticipated, but it had been thought that under high dilution conditions the reversible nature of this ring opening would provide the *Z*-isomer and enable the sequence to proceed. Evidently, this logic was flawed.

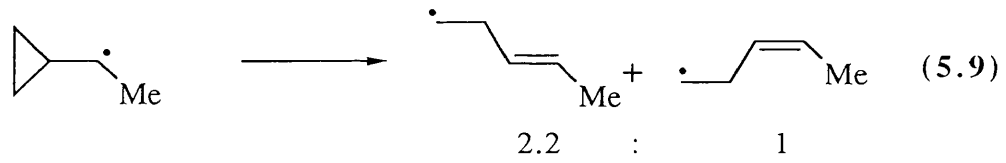


(5.1) (5.2) (5.3) (5.15)

Scheme 5.3 Actual Route of Cyclisation

An attempt to force the equilibrium for the ring opening of the cyclopropylmethyl radical towards the *cis*-ring opened product by repeating the reaction in refluxing toluene still only gave the *trans*-alkene (5.14) in 74 % yield. Moreover, as all the selenoester was consumed before a stoichiometric amount of tin hydride had been added, it appeared that decomposition was occuring.

The proposed reaction sequence therefore, had to be somewhat modified so that stereoselective ring opening of the cyclopropylmethyl radical to give the *Z*- olefin (5.3) would occur. It was thought that this could be achieved by the introduction of appropriate substituents. Indeed, Beckwith[10] has observed that for cyclopropylmethyl radicals with a single substituent at the radical centre, ring opening gave a ratio of 2.2:1 of the *E*-pent-2-ene over the *Z*-isomer (Equation 5.9).



(5.9)

This predominance of the *E*-isomer was rationalised in terms of the possible conformations of the radicals required for ring opening. For ring opening to occur, the single, unpaired, electron needs to eclipse the bond to be cleaved (Figure 5.1). Therefore, Structure A , with the α-proton eclipsing the cyclopropane ring, was considered to be of a lower energy than Structure B, in which the α-methyl group eclipses the cyclopropane ring.

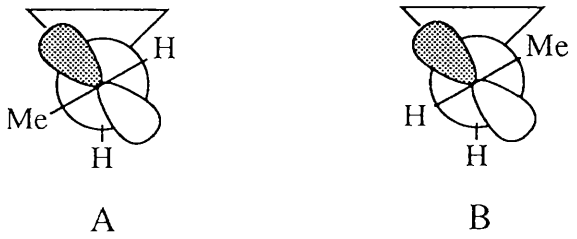
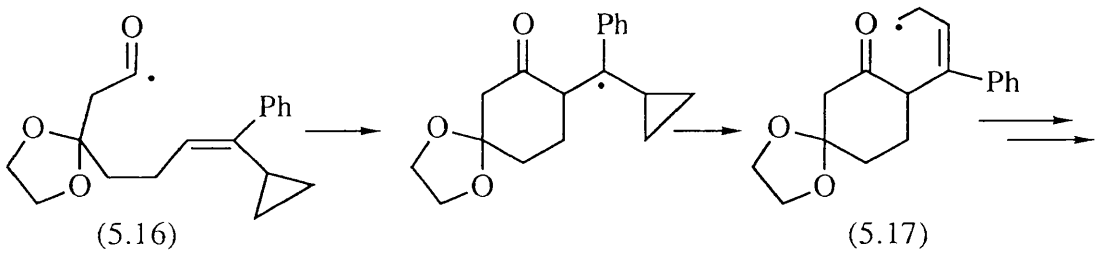


Figure 5.1 Preferred Conformations for Ring Opening

Hence, it was thought that the introduction of a phenyl group into the 7-position of the acyl radical (5.16), would lead to predominant formation of the *E*-isomer (5.17) on ring opening and so enable the homoallyl radical to cyclise onto the preformed cyclohexanone (Scheme 5.4).



Scheme 5.4 Proposed Cyclisation with Selective Cyclopropane Ring Opening

The carbon framework for this modification was prepared by repeating the initial synthetic scheme with cyclopropyl phenyl ketone rather than cyclopropane carboxaldehyde. To this end, Wittig reaction with the butanoic acid 4-phosphorane derivative (5.9) gave the *E*-phenylcyclopropyl acid (5.18) in 97 % yield and subsequent homologation gave the β-ketoester (5.19) in 78 % yield as a 20:1 mixture (nmr) of the *E*- and *Z*- isomers (Scheme 5.5). The regiochemistry about the double bond was determined by nOe difference spectroscopy, whereby a positive effect between the vinylic proton and the *ortho*-subtituted protons on the phenyl substituent was observed for the acid (5.18) (Figure 5.2).

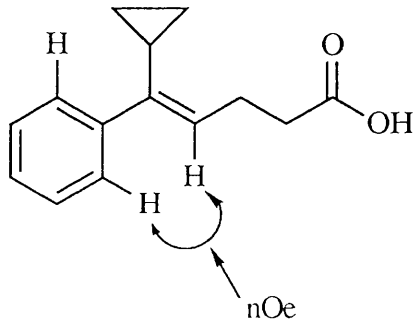
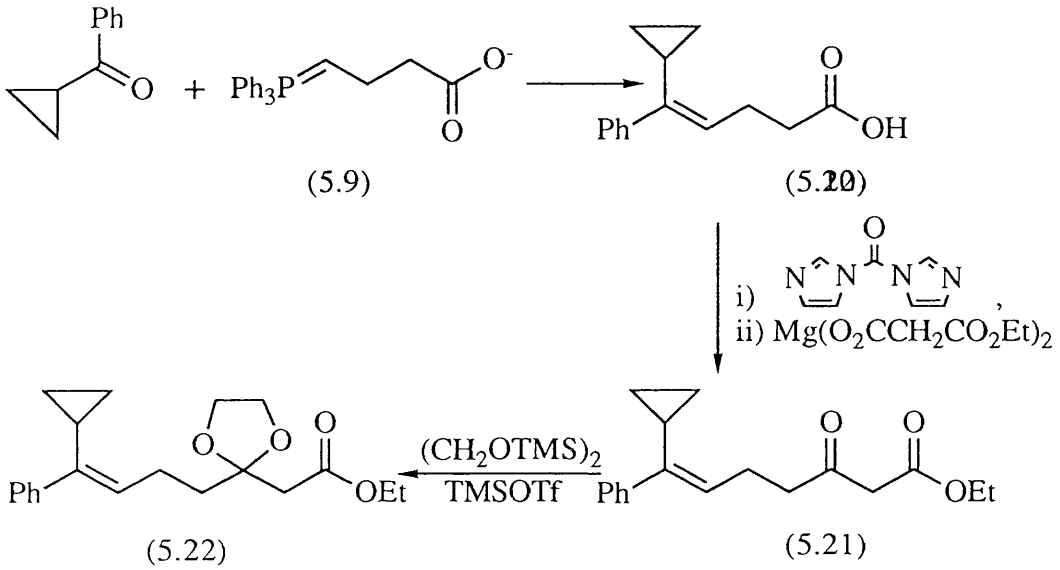


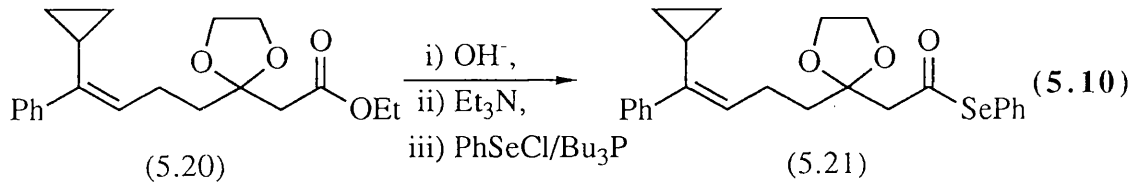
Figure 5.2 nOe Effect on Phenyl Substituted Cyclopropyl Acid

The trimethylsilyl triflate catalysed ketalisation of (5.19) gave the protected ester (5.20) in a 51 % yield, with 33 % recovered starting material (Scheme 5.5). For longer reaction times, there was no increase in yield and only decomposition of starting material (5.19) was observed.



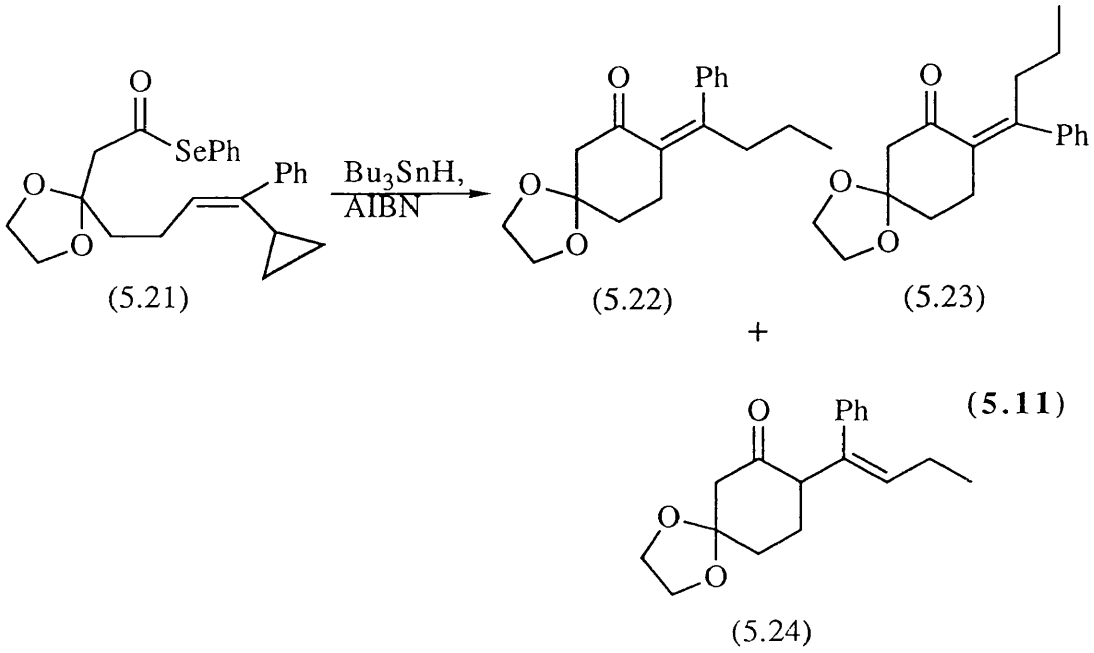
Scheme 5.5 Synthesis of the Phenylcyclopropyl Ester (5.20)

The standard saponification and selenoester preparation was then repeated on the protected ester (5.20) to give the required selenoester (5.21) in a 48 % yield (Equation 5.10).

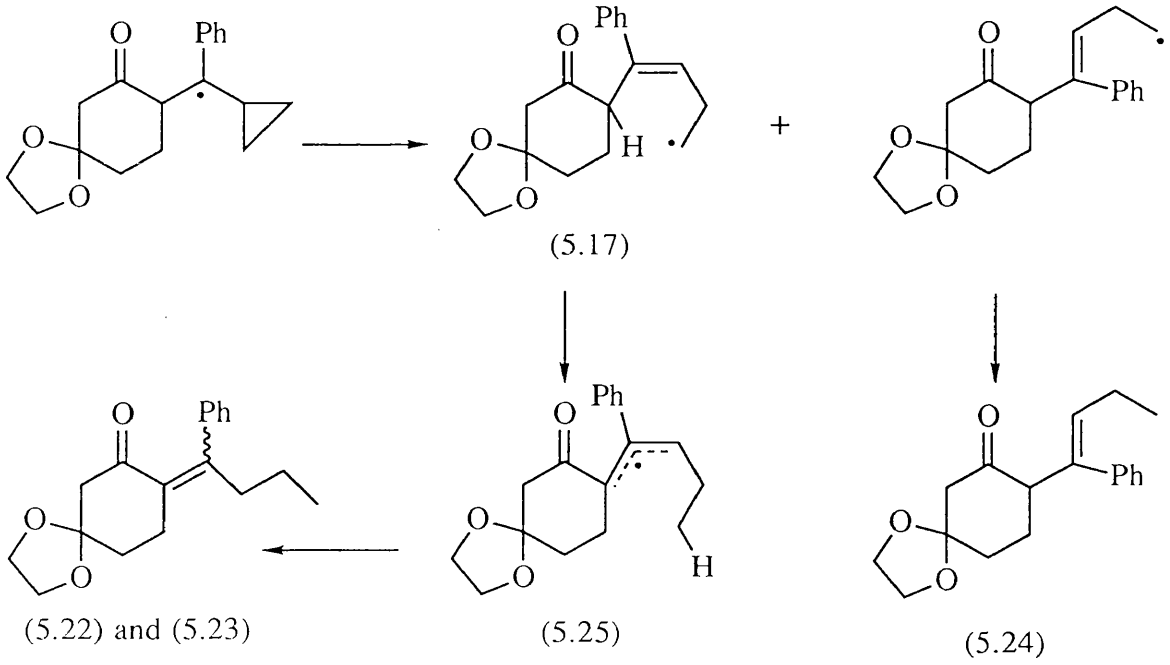


(5.10)

Radical cyclisation of selenoester (5.21), with the addition of the tin hydride solution over 30 min, gave the cyclohexanones (5.22) and (5.23) in 65 % yield, as a 1:6 mixture and the *Z*-butenyl cyclohexanone (5.24) in 30 % yield, but unfortunately none of the requisite cyclodecenone (Equation 5.11).



These observations may be rationalised by assuming that the ring opening of the cyclopropylmethyl radical took to give 2:1 *E*- to *Z*- ratio of the homoallyl radical , at least indicating that, as anticipated, the inclusion of the phenyl group had a beneficial effect on the direction of the ring opening (Scheme 5.6).

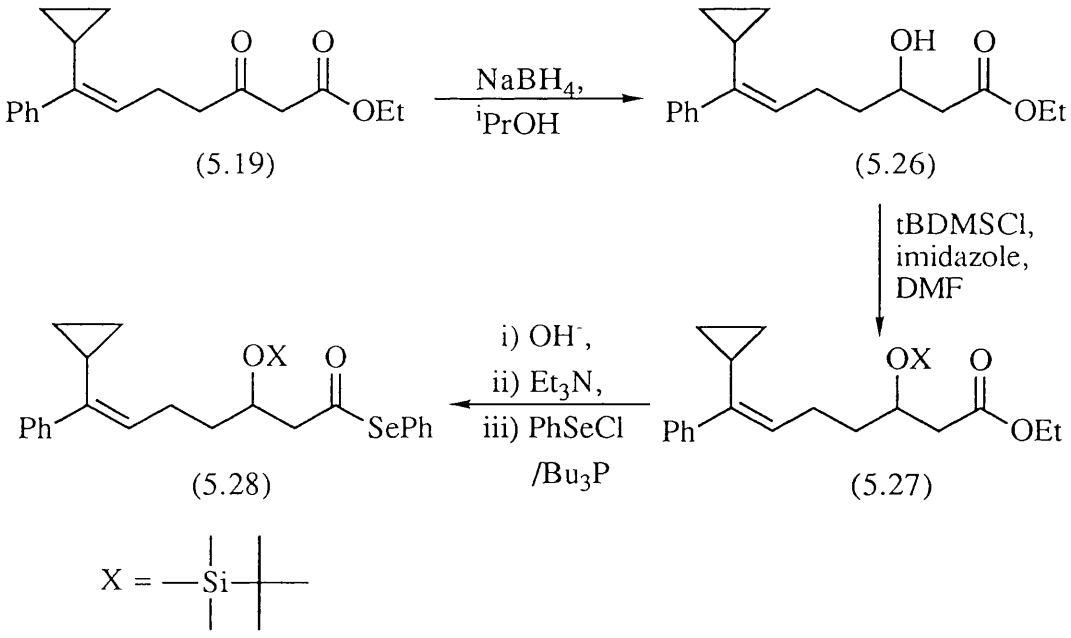


Scheme 5.6 δ-Hydrogen Abstraction Pathway

The *E*-isomer (5.17) undergoes δ- hydrogen abstraction from 2-C of the cyclohexanone moiety, rather than the expected cyclisation onto the ketone, to give the highly stabilised allylic radical (5.25). Quenching with tri-n-butyltin hydride then occurs from the least hindered end of the allyl system to give double bond migrated products. The major isomer from this process was assigned to be the *Z*-isomer (5.22) by consideration of the steric congestion at the enone centre, however, confirmatory nOe experiments were inconclusive.

To confirm that δ-hydrogen abstraction was indeed the major radical pathway, the cyclisation was repeated on a similarly substituted selenoester (5.28) with tri-n-butyltin deuteride in place of tri-n-butyltin hydride.

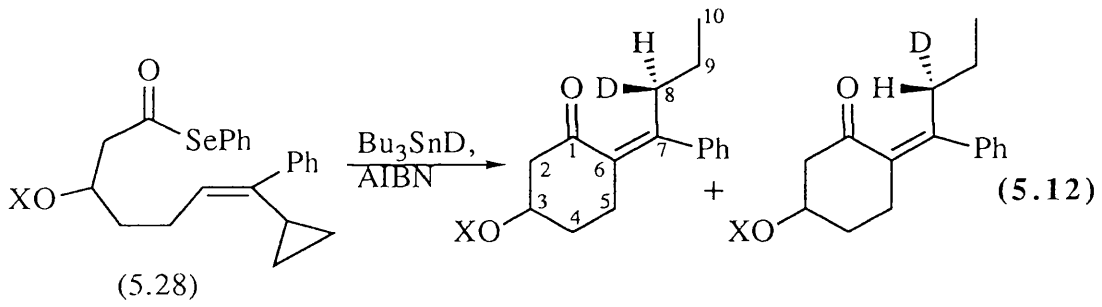
To this end, modification of the existing synthetic route by the reduction of the β-ketoester (5.19) with sodium borohydride and protection of the alcohol produced (5.26) as its t-butyldimethylsilyl ether (5.27) in a yield of 61 % over the two steps (Scheme 5.7).



Scheme 5.7 Preparation of (5.28)

This change in oxidation level and protecting group at the 3-position was introduced in order to avoid complications observed in the ketalisation of (5.19), whilst still maintaining a 3-alkoxy residue. Subsequent saponification and selenoester formation gave the selenoester (5.28) in a disappointing 24 % yield from the ester (Scheme 5.7). The low yield of the selenoester was attributed to its instability towards chromatography on silica gel.

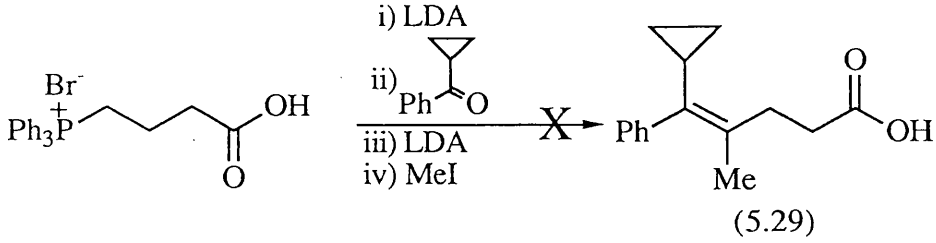
The cyclisation of selenoester (5.28), with the addition of the solution of tin deuteride over 30 min, gave a mixture of products. The intensity of the signals for the 8-H were reduced by 50 % over the tin hydride reaction and furthermore, the signals were resolved into two sets of double doublets, indicating a mixture of epimers with no geminal coupling (Equation 5.12) and hence, validating the proposed mechanism.



(5.28) **(5.12)**

To avoid this unwanted hydrogen abstraction, replacement of the δ-hydrogen atom with a methyl group was proposed entailing the preparation of the hindered tetrasubstituted olefinic acid (5.29).

In order to prepare the tetrasubstituted olefin (5.29) modification of the existing methodology for the preparation of the trisubstituted olefin (5.18) was first attempted. Therefore, the initial Wittig reaction on cyclopropyl phenyl ketone was repeated, with the addition of a second equivalent of base to the reaction at the betaine stage, in a Schlosser-Wittig fashion[11] followed by quenching with methyl iodide. However, none of the tetrasubstituted olefin (5.29) was detected (Equation 5.13).

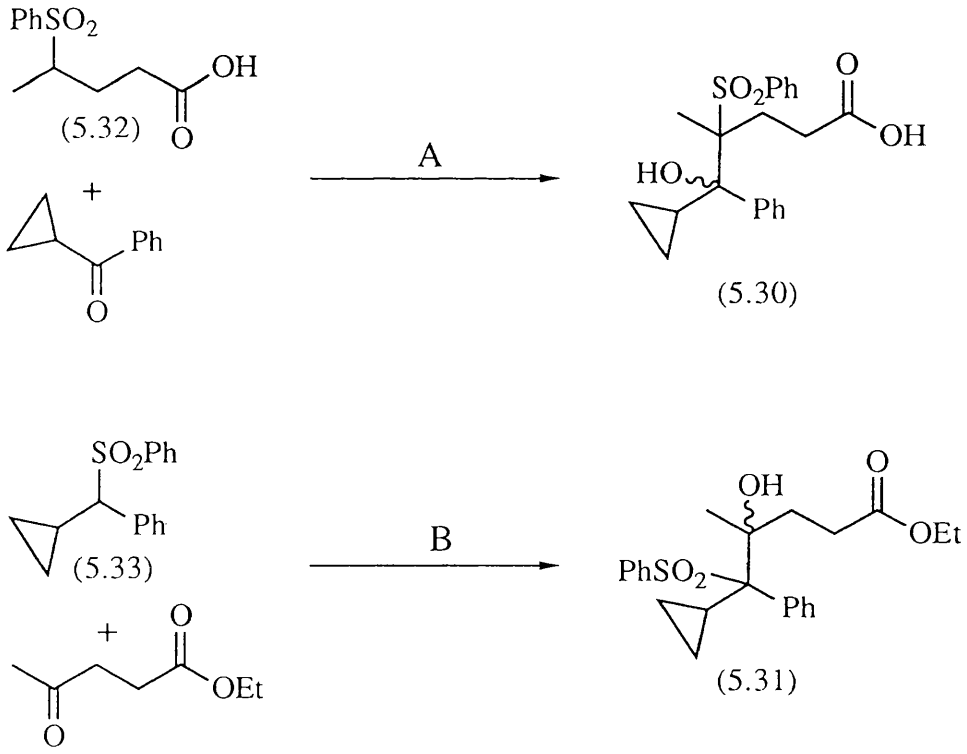


(5.13)

(5.29)

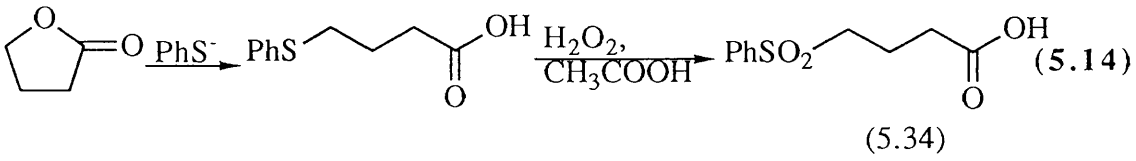
Consequently, it was decided to attempt preparation of the tetrasubstituted olefin by either a Julia olefin reaction[12] or a Barton-Kellogg 'double extrusion' process.[13]

For the preparation of the tetrasubstituted double bond via a Julia olefin synthesis, the required precursor was the β–hydroxysulphone (5.30), or its regioisomer (5.31), presumed to be prepared by coupling of either the phenylsulphone (5.32) and cyclopropyl phenyl ketone (Scheme 5.8, Path A),or coupling of the phenylsulphone (5.33) with ethyl levulinate respectively (Scheme 5.8, Path B).



Scheme 5.8 Proposed Route to Tetrasubstituted Double Bonds via Julia Olefin Synthesis

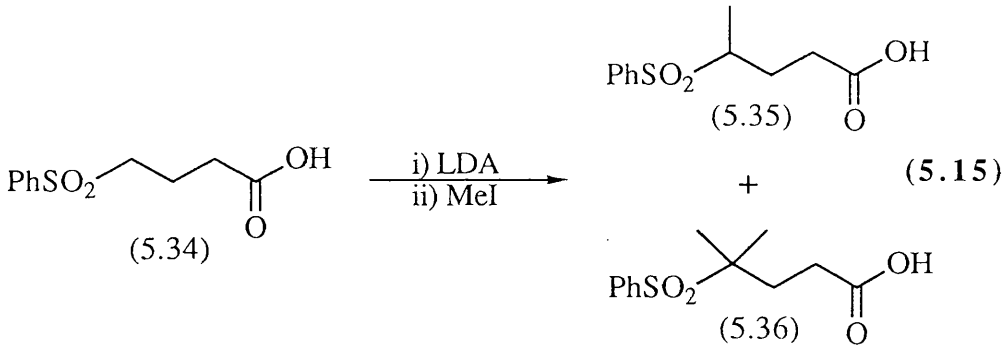
For the first synthetic route, path A, the phenylsulphone (5.34) was prepared in 56 % yield by the basic ring opening of γ-butyrolactone with thiophenate anion, as described by Treynelis and Love,[14] with subsequent oxidation with hydrogen peroxide/acetic acid, as described by Hammen (Equation 5.14).[15]



(5.14)

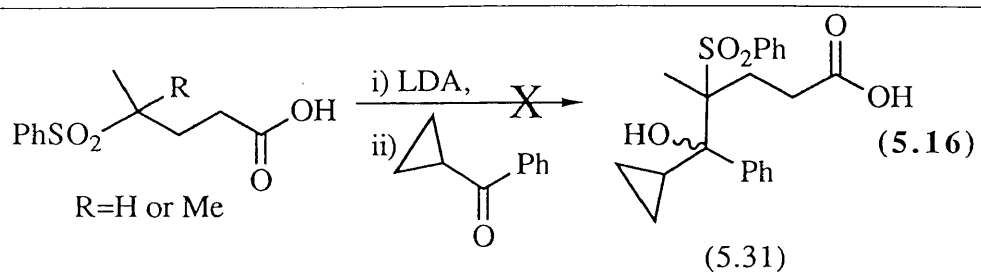
(5.34)

Alkylation of this phenylsulphone (5.34), with one equivalent of methyl iodide to give the monoalkylated product (5.35), proved to be difficult due to the low solubility of the di anion at low temperature. A significant quantity of the dialkylated product (5.36) was always detected, owing to the increased solubility of the monoalkylated product. At best, a 3:1 mixture of the mono- to dialkylated products was obtained (Equation 5.15).



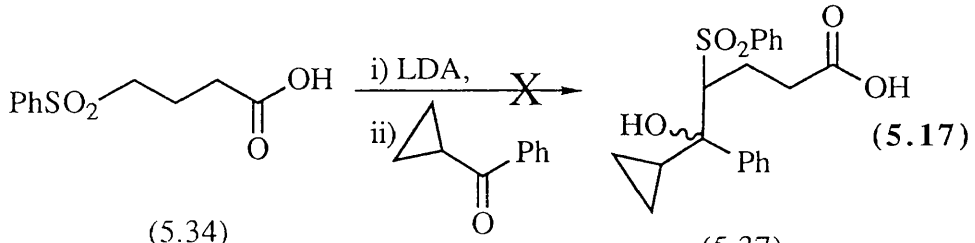
(5.15)

When this mixture of the mono- and dialkylated sulphones (5.35) and (5.36) was subjected to deprotonation and reaction with cyclopropyl phenyl ketone, none of the β-hydroxysulphone (5.31) was detected (Equation 5.16). Similarly, when the same reaction conditions were repeated for the non-alkylated sulphone (5.34), none of this less hindered β-hydroxysulphone (5.37)was detected either (Equation 5.17).



(5.16)

(5.31)

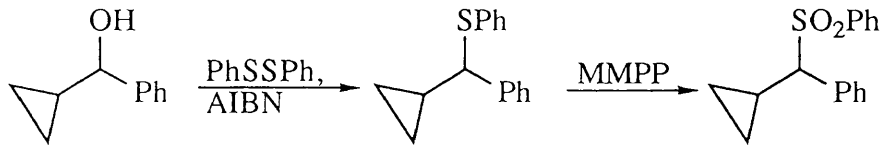


(5.17)

(5.34)

(5.37)

The failure of this coupling reaction was attributed to a combination of both the steric bulk of the sulphone and the steric conjestion of the ketone. In the alternative synthetic route, Path B (Scheme 5.8), the steric factors should be somewhat relieved. To this end, phenylcyclopropyl carbinol was allowed to react with a mixture of diphenyl disulphide and tributylphosphine, according to a procedure described by Nakagawa and Mata,[16] to give the phenylsulphide (5.38) in a 67 % yield. Subsequent oxidation of (5.38) with MMPP gave the sulphone (5.39) in 87 % yield (Equation 5.18).

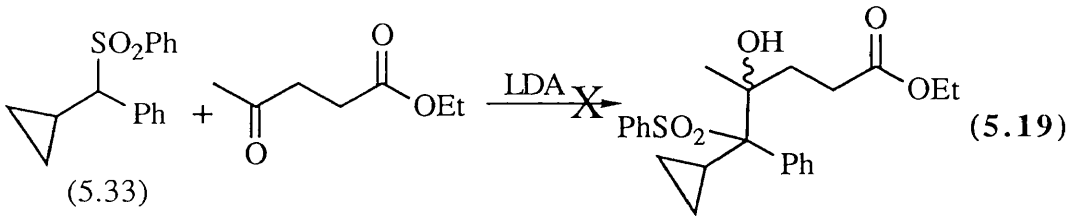


(5.18)

(5.38) (5.39)

Unfortunately, coupling of the phenylsulphone (5.39) with ethyl levulinate was also unsuccessful, with only the starting materials recovered (Equation 5.19). Once again, it was presumed that the steric constraints of the system prevented the coupling reaction. In this context it is interesting to note that although that the Julia synthesis is

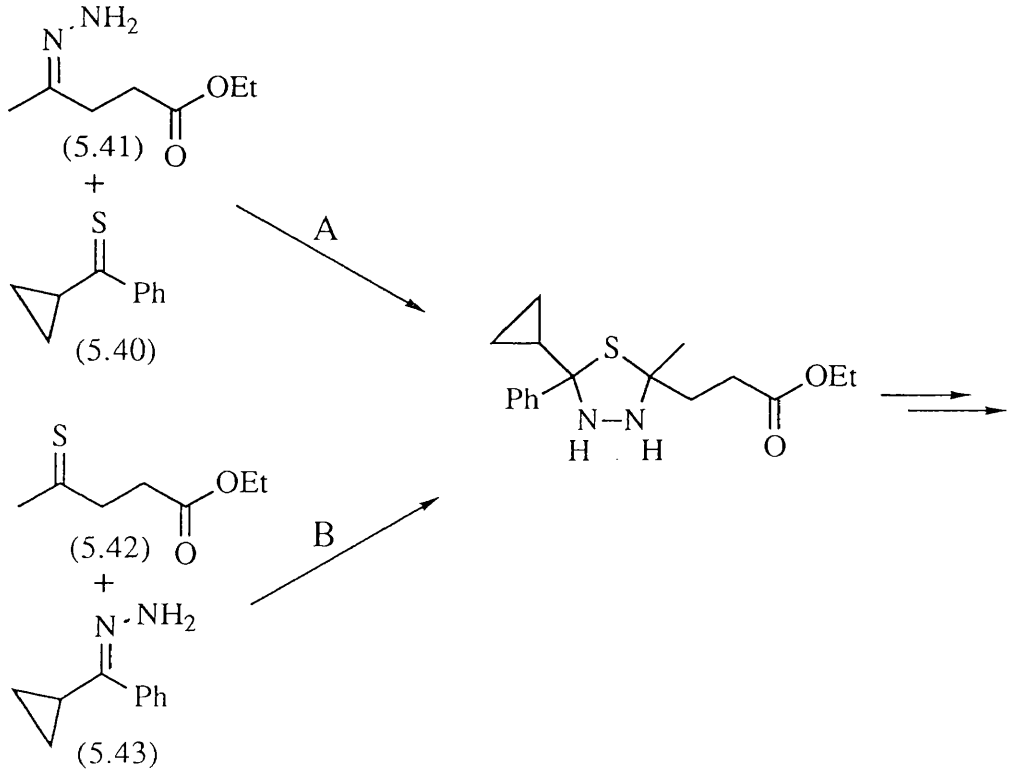
almost always applied to the preparation of 1,2-disubstituted alkenes, there is one example, in Julia's original paper, on the preparation of a tetrasubstituted alkene.



(5.19)

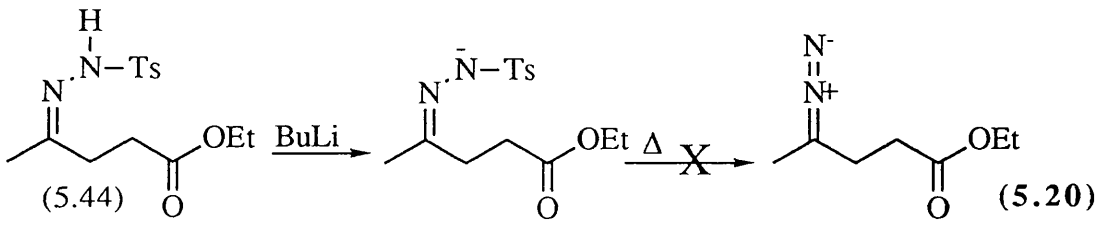
As the entry into the tetrasubstituted double bond via a Julia synthesis was unsuccessful, its preparation was now considered via a 'double extrusion' method.

For the double extrusion reaction proposed, coupling of either the phenylcyclopropyl thione (5.40) with the hydrazone of ethyl levulinate (5.41) (Scheme 5.9, Path A) or the coupling of the thione ester (5.42) with the cyclopropyl hydrazone (5.43) (Scheme 5.9, Path B), giving the thiadiazoline intermediate, was envisaged.



Scheme 5.9 Proposed Route via 'Double Extrusion' Method.

For the first route, Path A, the thione (5.40) was successfully prepared by reaction of phenyl cyclopropyl ketone with Lawessons reagent,[17] as alluded to by Adam and Heil.[18] However, attempts to prepare either the hydrazone of ethyl levulinate (5.41)[19] ,or the corresponding diazo compound from the tosyl hydrazone (5.44),[20] were unsuccessful (Equation 5.20).

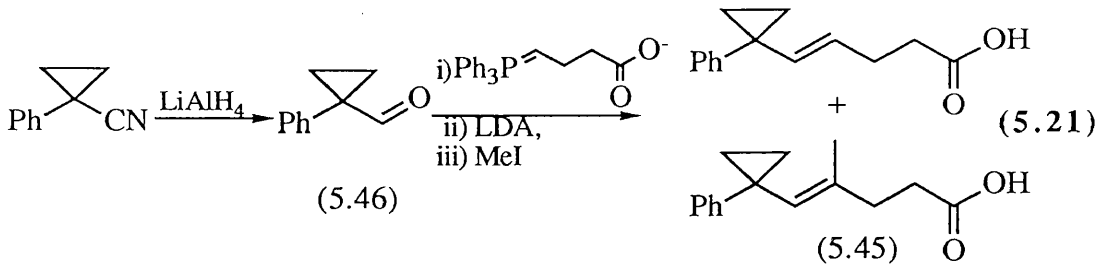


(5.20)

Turning to Path B (Scheme 5.10), reaction of ethyl levulinate with Lawessons reagent gave, not surprisingly, a complex mixture, possibly because of competition between thione and thioester formation.[21] In the light of these results, the Barton-Kellogg approach was abandoned.

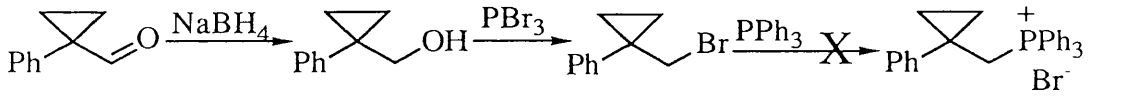
As all attempts to prepare the hindered tetrasubstituted double bond had failed, an alternative acid (5.45) was proposed, whereby the phenyl group required to direct ring opening of the cyclopropane ring was transposed onto the cyclopropane ring, thus giving a trisubstituted olefin.

Preparation of this trisubstituted alkene (5.45) was attempted by the modified Schlosser-Wittig conditions used in the unsuccessful attempt to prepare the tetrasubstituted alkene (5.29) from phenyl cyclopropyl ketone (Equation 5.12). Thus, 1-phenylcyclopropane carboxaldehyde (5.46), was prepared in 52 % yield by the lithium aluminium hydride reduction of phenylcyclopropane carbonitrile,[22] and subjected to the ylid (5.9) followed by *in situ* deprotonation of the betaine and quenching with methyl iodide.(Equation 5.21). This sequence was successful, in that the required trisubstituted alkene was formed, albeit in low yield and in admixture with the non-methylated product.



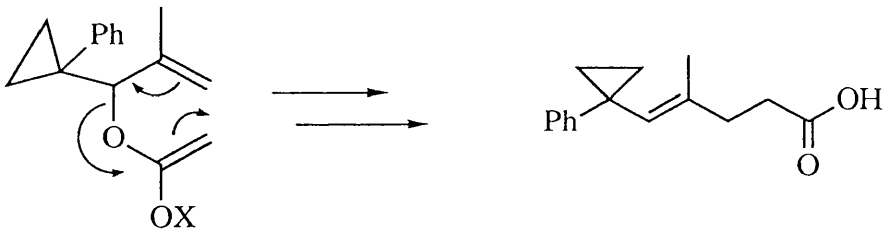
(5.21)

A more traditional Wittig reaction between the phosphonium salt derived from the aldehyde (5.46) and ethyl levulinate was envisaged. However, although reduction of the aldehyde (5.46) by ethanolic sodium borohydride gave the alcohol (5.47) in 92 % yield, and subsequent reaction with phosphorus tribromide gave the bromide (5.48) in 51 % yield, no reaction between triphenylphosphine and the bromide (5.48) was observed, even under prolonged forcing conditions (Equation 5.22).



(5.46) (5.47) (5.48) **(5.22)**

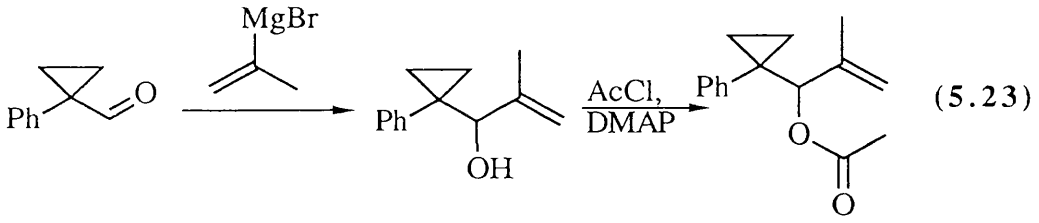
Once again, it was evident that the more conventional methods for olefin synthesis would be difficult to realise. Evidently, a completely different approach to the preparation of the olefin was called for. It was proposed that rather than trying to synthesis the double bond directly, it could be prepared from a rearrangement, which would circumvent the encountered steric problems. To this end, it was envisaged that a Claisen-Ireland[23,24] rearrangement of the vinyl acetate (5.49), via the t-butyldimethyl-silyl enol-ether (5.50), would give the trisubstituted olefinic acid (5.45) (Scheme 5.10), which could then be homologated.



(5.50) (5.45)

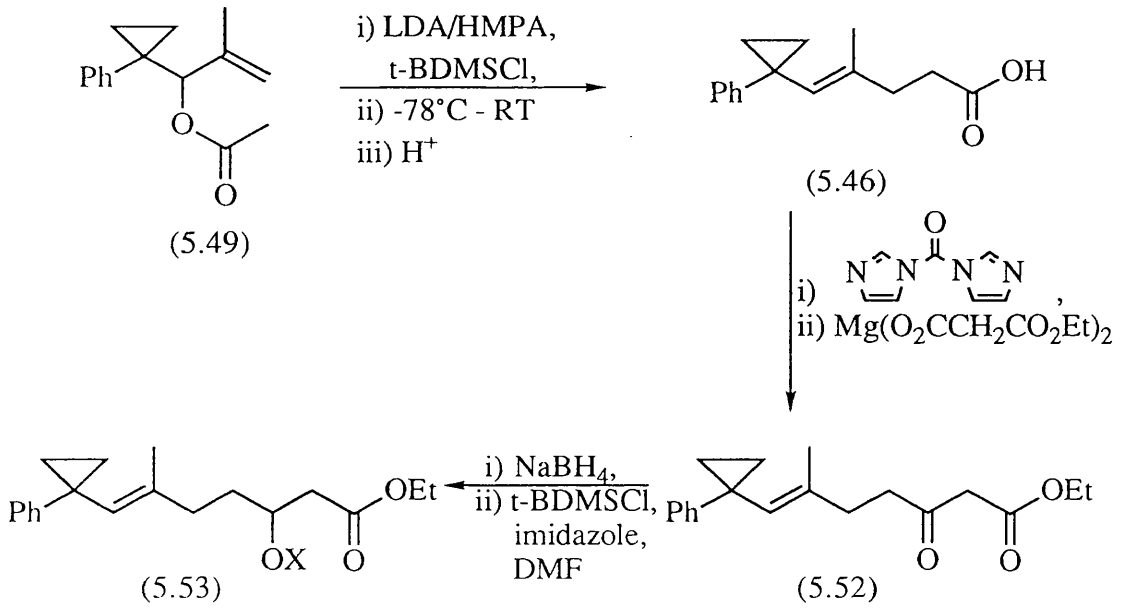
Scheme 5.10 Claisen-Ireland Rearrangement

To this end, the vinyl acetate (5.49) was prepared in two steps from the aldehyde (5.46), by Grignard reaction with 2-propenylmagnesium bromide,[23] to give the allylic alcohol (5.51), and subsequent acetylation in 66 % overall yield (Equation 5.23).



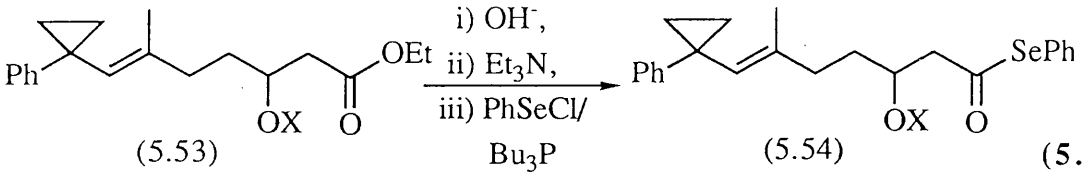
(5.46) (5.51) (5.49) **(5.23)**

The Claisen-Ireland rearrangement of the vinyl acetate (5.49) gave the expected trisubstituted olefinic acid (5.45) in 53 % yield, with 22 % of recovered starting material (Scheme 5.11). The homologation reaction conditions used on the cyclopropyl acid (5.10) (Scheme 5.2) and the phenylcyclopropyl acid (5.18) (Scheme 5.5) were repeated on this trisubstituted acid (5.45), to give the β-ketoester (5.52) in 73 % yield. Sodium borohydride reduction and silylation then gave the t-butyldimethylsilyloxy ester (5.53) in a yield of 64 % (Scheme 5.11).



Scheme 5.11 Homologation and Reductive Protection after Rearrangement

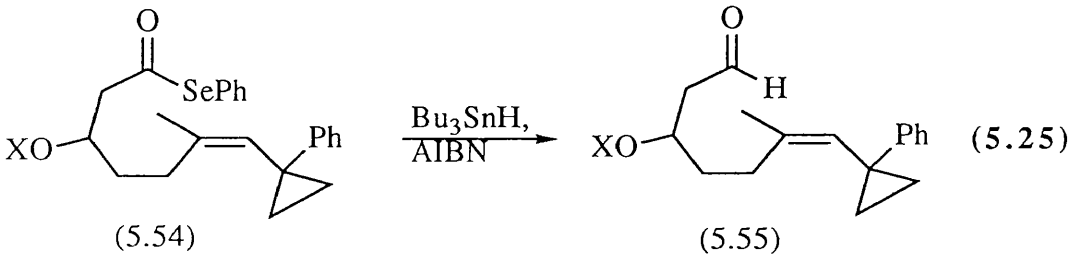
Once again, the standard saponification and selenoester formation were used on the protected ester (5.53) to give the required selenoester (5.54) in a disappointing 25 % yield (Equation 5.24). It is apparent that selenoesters with a silyloxy residue on the 3-position, (5.23) and (5.54), are unstable to silica gel chromatography. Moreover, when the silica gel was pretreated with a 1% solution of triethylamine, elimination of the silyloxy residue occurred, indicating that these compounds are unstable to mildly basic conditions as well.



(5.24)

Unfortunately, radical cyclisation of this selenoester (5.54) with the addition of the tin hydride solution over 10 h and with the further addition of a dilute solution of AIBN over 10 h, gave no cyclised products. The major product formed being the

aldehyde (5.55), which was isolated in 40 % yield (Equation 5.25), together with 17 % of recovered starting selenoester (5.54).



(5.54) (5.55) **(5.25)**

The inevitable conclusion from this latter reaction is that the rate of acyl radical cyclisation for the 6-methyl-6-heptenoyl system is, not unexpectedly, very slow and that even under the dilute reaction conditions employed, the rate of hydrogen abstraction from tin hydride was significantly higher.

5.3 PROPOSED ENTRY INTO CYCLONONENONES

The reduction in the rate of radical cyclisations when a substituent is incorporated into the olefin at the reaction site is well documented. For example, in the related 5-hexenyl system, Beckwith[25] has reported that the rate of cyclisation of the parent radical in the *exo*-mode is *ca.* 50 times faster than the rate of cyclisation for the 5-methyl substituted derivative in the *exo*-mode (Figure 5.3). However, it was also reported the rate of radical cyclisation of the 6-heptenyl radical system, in the *exo*-mode, was of the same order of magnitude as the rate of cyclisation of the 5-substituted 5-hexenyl radical (Figure 5.3).

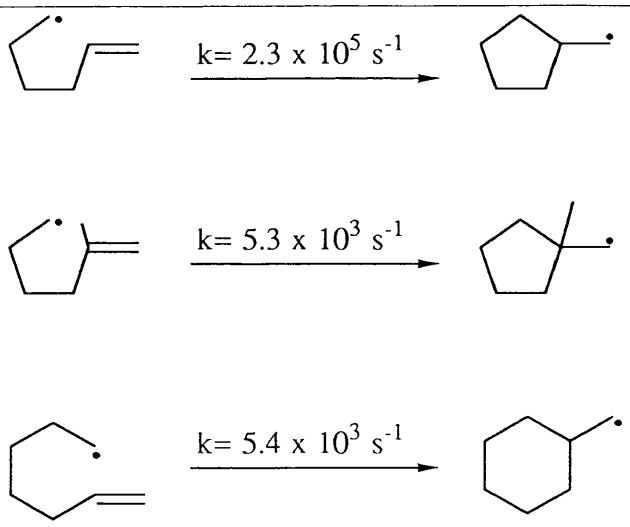
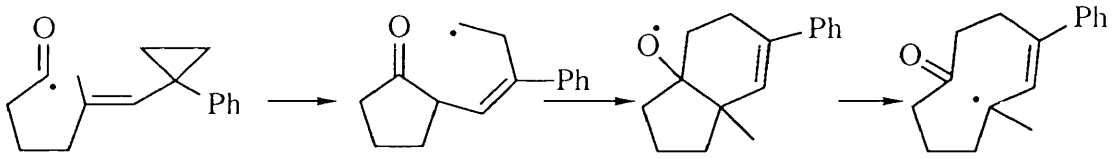


Figure 5.3 Rates of Cyclisation for some 5-Hexenyl and 6-Heptenyl Radicals

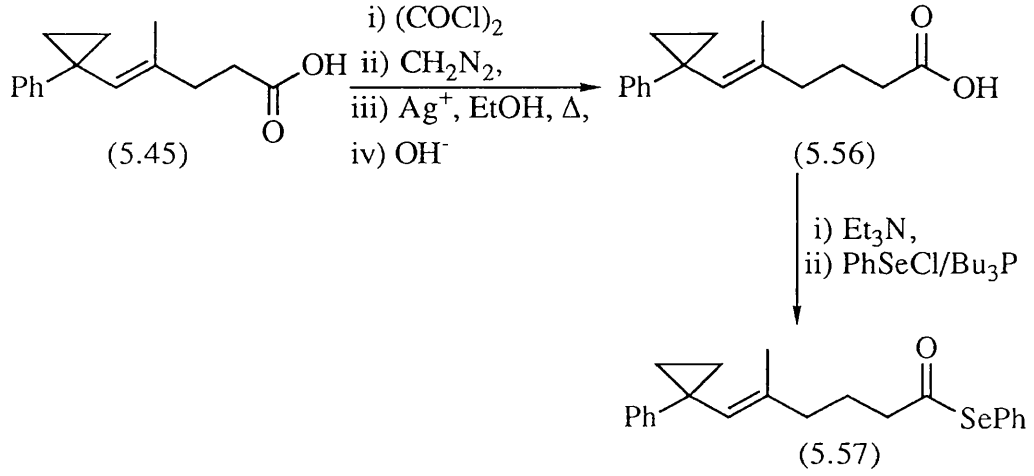
It was proposed therefore, that the rate of cyclisation of the 5-methyl-5-hexenoyl radical would be of the same order of magnitude as the rate of cyclisation for the 6-heptenoyl radical and moreover, as the 6-heptenoyl cyclisation in the original cyclisation/fragmentation sequence has been demonstated to be very efficient, the retardation in cyclisation rate introduced by the addition of the methyl group in (5.45) (Scheme 5.11), could be overcome by going to the lower homologue (Scheme 5.12).



Scheme 5.12 Proposed Radical Cyclisation/Fragmentation Sequences for Cyclononenones

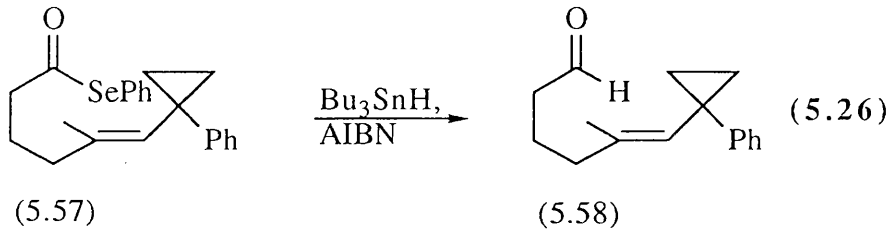
Therefore, one carbon homologation of the trisubstituted acid (5.45), was carried out by the Arndt-Eistert reaction[26] giving the phenylcyclopropyl 5-hexenoic acid (5.56) in 44 % yield as a 6:1 mixture with the starting acid (5.45).

Standard selenoester preparation on this mixture gave the selenoester (5.57) in 75 % yield, as a 6:1 mixture with the lower homologue (Scheme 5.13).



Scheme 5.13 Preparation of Selenoester (5.57)

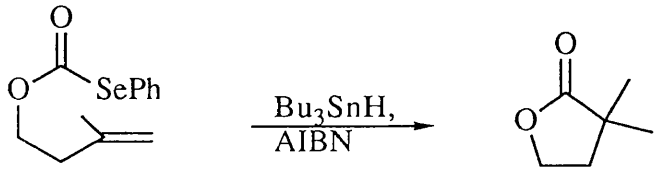
Attempted cyclisation of this selenoester (5.57), with addition of the tin hydride solution over 8 h, once again gave no cyclised products. The only isolated product was the reduced aldehyde (5.58) in a yield of 43 % (Equation 5.26), indicating that even the 5-methyl-5-hexenoyl cyclisation was too slow to compete with hydrogen abstraction from tin hydride.



(5.57) (5.58) **(5.26)**

Interestingly, in this context, Bachi reported[27] recently that under high dilution conditions the selenocarbonate (5.59) was cyclised in high yield to (5.60) with tri-n-butyltin hydride (Equation 5.27). At this stage it is only possible to speculate that the alkoxycarbonyl radical either cyclises more rapidly (is less susceptible to steric

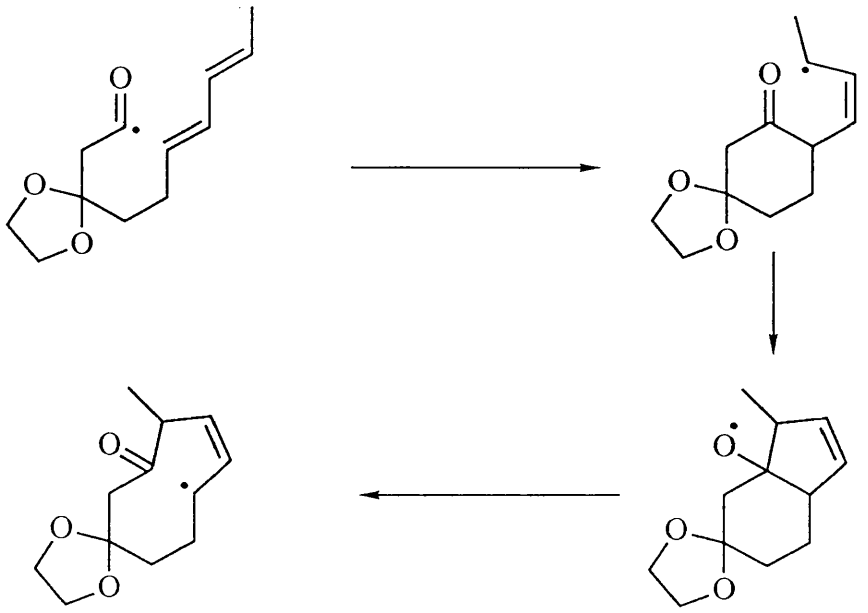
hindrance) than the corresponding acyl radical or abstracts hydrogen from the stannane less readily. This apparent difference in reactivity will be probed in this laboratory in the near future and if legitimate, exploited in the context of the current problem.



(5.59) (5.60) (5.27)

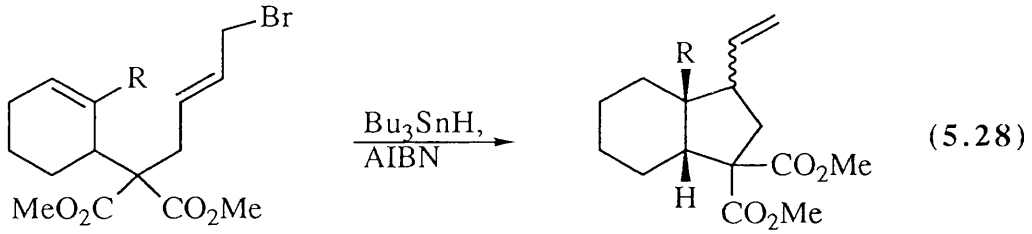
Finally, as the inclusion of a methyl substituent onto either the 5- or 6-position in the 5-hexenoyl or 6-heptenoyl radicals respectively, prevented the initial acyl radical cyclisation, the preparation of a system in which δ-hydrogen abstraction was less likely to occur and hence did not require a substituent, was investigated.

Intramolecular hydrogen atom abstraction usually occurs via a 6-membered transition state (*viz* the name δ-hydrogen abstraction). It can occur through larger transition states, but to our knowledge, is not known to do so via smaller ones.[28] Hence, the problem of δ-hydrogen abstraction could be overcome by shortening the chain by one methylene group. This concept can be reduced to the cyclisation of the acyl radical onto a conjugated diene rather than on a vinylcyclopropane (Scheme 5.14). The ultimate product from this sequence would be a cyclononenone.



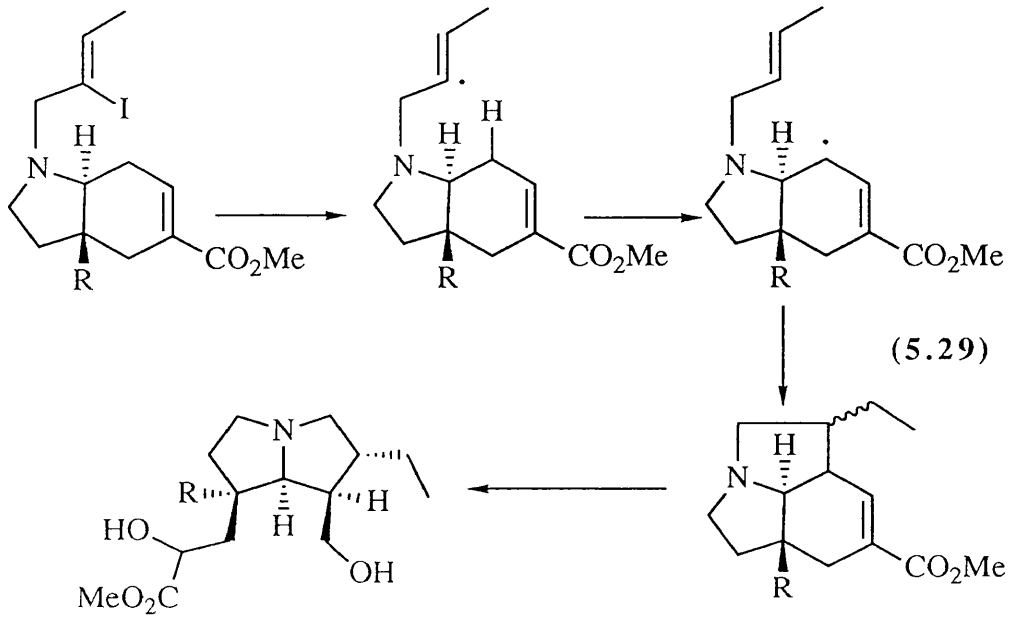
Scheme 5.14 Acyl Radical-Allyl Radical Cyclisation

The use of allyl radicals in cyclisation reactions has been described by Stork,[29] for the synthesis of bicyclo-[4,3,0]-nonanes (Equation 5.28). Parsons[30] has also reported a synthesis in which the cyclisation of an allylic radical onto a pendant double bond, via δ-hydrogen abstraction, is the key step towards a pyrrolizidine ring system (Equation 5.29).

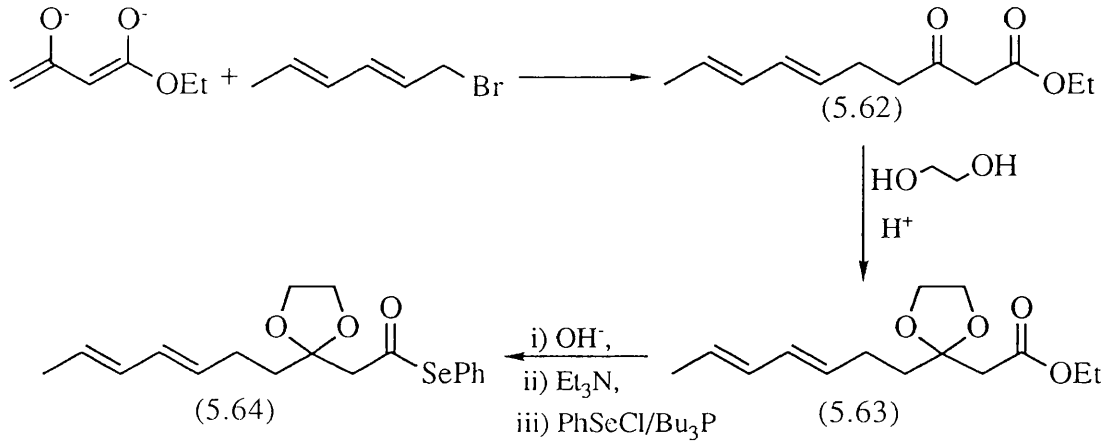


(5.28)

R=H	86 %
R=CH_3	92 %

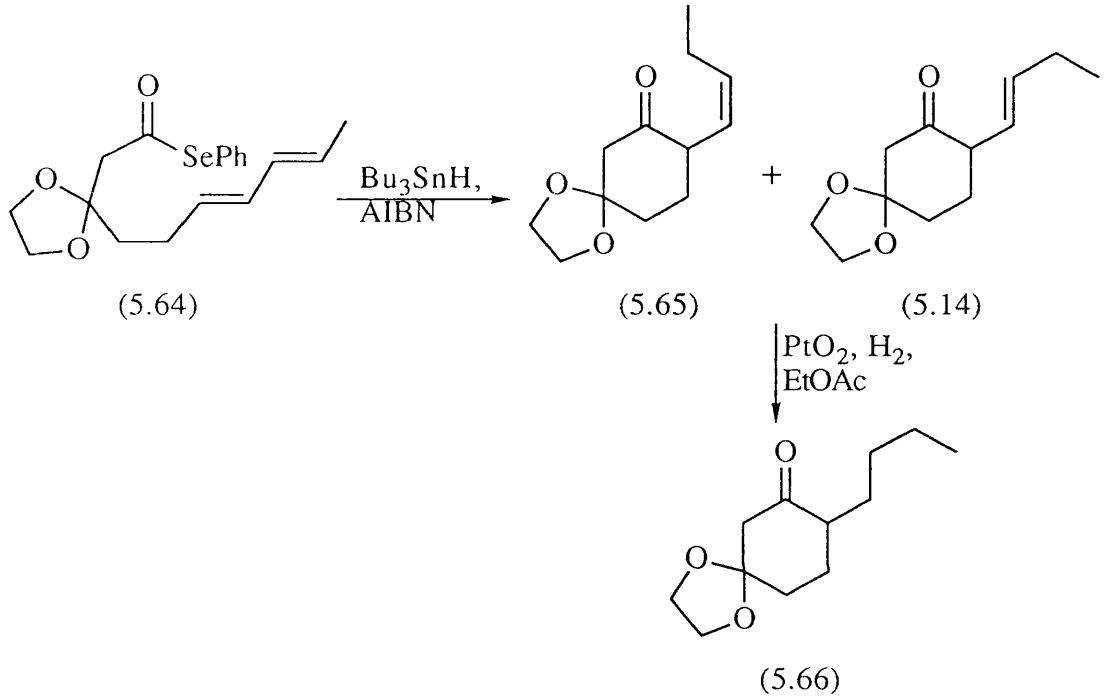


A direct entry into the carbon skeleton of the requisite decadiene system was accomplished by the alkylation of the dianion of ethyl acetoacetate with 1-bromo-hexa-4,6-diene,[31] giving the β-ketoester (5.62) in a 67 % yield (Scheme 5.15).[32] Simple acid catalysed reaction of the ketoester (5.62) with ethylene glycol, gave the ketal (5.63) in 88 % yield. Finally, standard saponification and selenoester preparation on the ketal (5.63) gave the radical precursor, selenoester (5.64), in a yield of 68 % from (5.63) (Scheme 5.15).



Scheme 5.15 Preparation of Selenoester (5.64)

The radical cyclisation of the selenoester (5.64), with the addition of the tin hydride solution over 8 h, gave a 1:1 mixture of the butenylcyclohexanones (5.65) and (5.14) (Scheme 5.16). Confirmation of the identities of (5.65) and (5.16) was accomplished by hydrogenation of the mixture, which gave only one product, the butylcyclohexanone (5.66) (Scheme 5.16).



(5.64) (5.65) (5.14) (5.66)

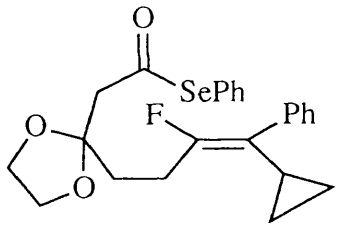
Scheme 5.16 Cyclisation and Subsequent Hydrogenation of (5.64)

In retrospect, the failure of this cyclisation is not surprising. Consideration of molecular models clearly indicates that the rigidity imposed on the side chain by the conjugated allylic nature of the radical prevents attainment of the transition state for cyclisation. Shortly after we made this observation Yadav and Fallis reported[33], without explanation, the failure of a related cyclisation. In the successful reactions of Stork and Parsons, the radical is conjugated to an alkene exocyclic to the ring to be formed, which does not constrain the chain in the same manner.

5.4 CONCLUSIONS

The high efficiency of 6-exo mode cyclisation for 6-heptenoyl radicals containing a 3-alkoxy substituent has once again been demonstrated. Furthermore, efficient ring opening of α-cyclopropylmethyl radicals after initial 6-heptenoyl radical cyclisation has been achieved. Selective ring opening of the α-cyclopropylmethyl radical was accomplished by the introduction of a phenyl substituent at the radical centre. However, the second cyclisation in this sequence failed owing to competing δ-hydrogen abstraction.

The problems encountered with the proposed multiple cyclisation/fragmentation sequence have, it is thought, all been identified so that with the correct choice of substituents as in (5.67), the sequence could be made to work, however, the usefulness of such a route as a general entry into medium sized rings would be questionable.



(5.67)

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EXPERIMENTAL SECTION

GENERAL EXPERIMENTAL

Elemental combustion microanalyses were carried out by either the microanalytical section of the Department of Chemistry at University College London or by Midwest Microanalytical Laboratories, Indianapolis. Melting points were determined on a Kofler hot-stage microscope and are reported uncorrected. The mass spectra were recorded on a VG 7070 H mass spectrometer with Finnigan INCOS II data system. For high resolution mass spectra of compounds containing selenium, the relative molecular mass for selenium is taken as that of the most abundant isotope. ^{1}H nmr spectra were recorded on either a Joel PMX-60, a Varian XL-200, Bruker WP-200, Bruker AC-300, Varian VXR-400, or Bruker AM-400 spectrometer, operating at 60, 200, 200, 300, 400 and 400 MHz respectively. ^{13}C nmr spectra were recorded on either a Bruker WP-200, Bruker AC-300, Varian VXR-400, or Bruker AM-400, operating at 50, 75, 100 and 100 MHz respectively. Unless otherwise stated, deuteriochloroform ($CDCl_3$) was used as solvent. Chemical shift values (δ) are reported in ppm downfield from tetramethylsilane, except where compounds contain a TBDMS or TMS protecting group, where δ-values were calculated from the proton or carbon-13 signal in deuteriochloroform. Infrared spectra were recorded on either a Perkin-Elmer 983 diffraction spectrometer or a Perkin-Elmer 1600 FTIR. Only significant bands are quoted. Optical rotations were measured at ambient temperature with an Optical Activity AA-10 polarimeter.

THF was used freshly distilled under nitrogen from sodium-benzophenone-ketyl. Petrol refers to the fraction boiling at 40-60 °C, and was re-distilled prior to use. Diethyl ether and benzene were dried by either distilling from sodium-benzophenone-ketyl or storing over sodium wire. All other solvents were purified and dried using standard methods.[1]

Analytical thin layer chromatography (tlc), was carried out using either plastic-backed plates supporting a 0.25 mm layer of silica gel 60 containing a fluorescent indicator, supplied by Aldrich (No. Z12, 278-5), or aluminium-backed plates supporting a 0.2 mm layer of silica gel 60 with a fluorescent indicator, supplied by Merck (No. 5554). Preparative tlc was carried out using 20 x 20 cm glass plates supporting a 1 mm layer of silica gel 60 containing a fluorescent indicator, supplied by Merck (No. 7739). Products were best visualised by uv light (254 nm) or by treatment of the plate with a solution of phosphomolybdic acid (ca. 5 % w/v). Column chromatography was carried out using 60-200 mesh silica gel, and products are described in the order of their elution. HPLC was performed with a 5 μm Spherisorb silica column coupled to a Spectra-Physics *isochrom* LC pump and a Spectra-Physics 100 UV detector, set at 254 nm.

Tri-n-butyltin hydride was prepared by the action of polymethylhydroxysilane on bis tri-n-butyltin oxide,[2] and was stored at -30 °C in the dark. The quality of the tin hydride was determined by ^{1}H nmr immediately before its use.

GENERAL PROCEDURE FOR PREPARATION OF SELENOESTERS FROM CARBOXYLIC ACIDS

Se-*PHENYL SELENOCINNAMATE*

To a stirred solution of cinnamic acid (2.9) (1.48 g, 10 mmol) in dry dichloromethane (20 ml), under nitrogen, was added a solution of triethylamine (1.01 g, 10 mmol) in dichloromethane (10 ml). The mixture was stirred for 10 min before evaporation of the solvent under reduced pressure gave the triethylammonium salt as a colourless oil.

Tributylphosphine (4.05 g, 20 mmol) was added slowly to a stirred solution of phenylselenenyl chloride (3.83 g, 20 mmol) in dry THF (30 ml), under nitrogen at room temperature. The yellow solution was stirred for 5 min before a solution of the triethylammonium salt in THF (25 ml) was slowly added. After consumption of the starting acid (tlc control, 2 h), the reaction mixture was poured into a 1:1 mixture of ether and water (500 ml). The aqueous phase was separated and extracted further with ether (3 x 100 ml). The combined ether layers were washed with water (100 ml) and saturated sodium chloride solution (100 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure, followed by silica gel column chromatogaphy (eluant : petrol-ether 8:1) afforded a yellow solid. Recrystallisation from petrol-ether mixture gave the title selenoester as yellow needles (2.10 g, 73 %).

^{1}H nmr (200 MHz) δ 6.76 (d, 1H, J=15.7 Hz) and 7.38-7.59 (m, 11H). **υ_{max}** ($CHCl_3$, cm^{-1}) 3058, 2939, 2885, 2851, 1721, 1608, 1581, 1471, 1451, 1437, 1361, 1254, 1084 and 1023. **mp.** 82°C. **ANALYSIS** Calcd. for $C_{15}H_{12}OSe$: C, 62.72 ; H, 4.22. Found: C, 62.44 ; H, 4.07 %.

Se-*PHENYL 3α-ACETOXY-5βH-SELENOLITHOCHOLANATE*

The standard procedure for the preparation of selenoesters was repeated on acetoxy lithocholic acid (2.5) (250 mg, 0.6 mmol) to give the selenoester as a white solid (0.28 g, 85 %).

^{1}H nmr (200 MHz) δ 0.84-1.96 (m, 34H), 2.03 (s, 3H), 2.68-2.76 (m, 2H), 4.62-4.78 (m, 2H) and 7.36-7.54 (m, 5H). **υmax** ($CHCl_3$, cm^{-1}) 3001, 2939, 2863, 1716, 1446, 1437, 1378, 1363 and 1204. **mp.**90-92°C **ANALYSIS** calcd. for $C_{32}H_{46}O_3Se$: C, 68.92 ; H, 8.31. Found: C, 68.92 ; H, 8.49 %.

HEDERAGENIN DIACETATE PHENYL SELENOESTER

The standard selenoester preparation was preformed on hederagenin diacetate (2.6) (250 mg, 0.45 mmol) to yield, after a reaction time of 48 h, the selenoester as a white solid (192 mg, 62 %).

^{1}H nmr (200 MHz) δ 0.82-1.98 (m, 41H), 2.03 (s, 3H), 2.07 (s, 3H), 3.72 (d, 1H, J=6 Hz), 3.81 (d, 1H, J=12 Hz), 4.72-4.86 (m, 1H), 5.28-5.38 (m, 1H) and 7.33-7.44 (m, 5H). **υmax** ($CHCl_3$, cm^{-1}) 2942, 1723, 1462, 1382, 1369, 1262, 1021 and 908. **mp.**165-167°C. **ANALYSIS** calcd. for $C_{40}H_{56}O_5Se$: C, 69.04 ; H, 8.11. Found: C, 69.14 ; H, 8.26 %.

Se-*PHENYL 2,3;5,6-DI-O-ISOPROPYLIDENE-2-KETO-L-SELENOGULONATE*

The selenoester of diacetone gulonic acid (2.7) (250 mg, 0.91 mmol) was prepared as a white crystalline solid (306 mg, 81 %).

^{1}H nmr (200 MHz) δ 1.45 (s, 3H), 1.46 (s, 3H), 1.54 (s, 6H) ,4.18 (d, 2H, J=2.3 Hz), 4.28 (d, 1H, J=1.6 Hz), 4.35 (d, 1H, J=2.2 Hz), 4.59 (s, 1H) and 7.37-7.57

(m, 5H). υ_{max} ($CHCl_3$, cm^{-1}) 2995, 2931, 1713, 1450, 1436, 1376, 1172, 1124, 1090, 1073, 1031, 977, 913, 866 and 838. **mp.** 144-145°C **ANALYSIS** calcd. for $C_{18}H_{22}O_6Se$: C, 52.30 ; H, 5.36. Found: C, 52.19 ; H, 5.38 %.

Se-*PHENYL* N-*PROP-2-ENYL-2-KETOPYRROLIDINE-5S-SELENO-CARBOXYLATE*

The cyclic amino acid (2.8) (250 mg, 1.5 mmol) was converted to the title selenoester by the standard method to give a colourless oil (300 mg, 65%).
^{1}H nmr (200 MHz) δ 2.12-2.78 (m, 4H),3.38-3.76 (m, 1H), 4.24-4.56 (m, 2H), 5.00-5.58 (m, 3H) and 7.35-7.44 (m, 5H). υ_{max} ($CHCl_3$, cm^{-1}) 3065, 2919, 1704, 1437, 1401, 1267, 1224, 1062, 983, 740 and 690. **ANALYSIS** Calcd. for $C_{14}H_{15}NO_2Se$: C, 54.55 ; H, 4.91 ; N, 4.54. Found: C, 54.31 ; H, 4.85 ; N, 4.65 %.

Se-*PHENYL SELENOBENZOATE*

The standard selenoester preparation was repeated on benzoic acid (500 mg, 4.1mmol) to afford the title selenoester as a white solid (884 mg, 83 %).
mp. 39-40°C [**Lit**[3]. 40 °C]

Se-*PHENYL SELENOACETATE*

Acetic acid (500 mg, 8.3 mmol) was converted to the title selenoester by the standard method, giving a colourless oil (1.23 g, 74 %).

^{1}H nmr (60 MHz) δ 2.40 (s, 3H), 7.23 (m, 5H). **υ_{max}** (film, cm^{-1}) 1722. **bp.** 135-140°C/20mmHg (Kugelrohr).

[**Lit.**[3] (CCl_4) 2.31 (s, 3H), 7.45 (m, 5H). **υ_{max}** (film, cm^{-1}) 1720 cm^{-1}. **bp.** 117-118°C/15mmHg].

3-(PHENYLTHIO)PROPANAL

To a stirred solution of thiophenol (10.0 ml, 98 mmol) in chloroform (75 ml) under nitrogen at 0 °C was added triethylamine (0.7 ml, 6.0 mmol) dropwise during 10 min, keeping the temperature below 5 °C. The mixture was allowed to stir for a further 10 min before acrolein (6.6 ml, 99 mmol) was added dropwise during 15 min. The solution was stirred for 60 min, allowing the mixture to warm up to room temperature. The reaction mixture was poured onto ether (250 ml) and washed with aqueous sodium hydroxide solution (2 M, 3 x 100 ml), water (2 x 100 ml), saturated sodium chloride solution (100 ml) and dried over magnesium sulphate. The solvents were evaporated under reduced pressure to yield 3-(phenylthio)propanal a pale green oil (13.31 g, 82 %) which was used without further purification.

^{1}H nmr (200 MHz) δ 2.75 (2H, t), 3.16 (2H, t), 7.18-7.37 (5H, m) and 9.74 (1H, br s).

(E)-*3-(PHENYLTHIO)PROP-2-ENAL* (3.24).

N-Chlorosuccinimide (15.67 g, 117.3 mmol) was stirred in ice-cooled dry benzene (100 ml) under an atmosphere of nitrogen. 3-(Phenylthio)propanal (13.00 g, 78.2 mmol) in benzene (75 ml) was added dropwise during 20 min, whilst the temperature was held below 5 °C. The reaction was complete after 2.5 h (t.l.c. control; eluant petrol-ether 3:1). The mixture was diluted with ether (500 ml) and washed with dilute hydrochloric acid (2 M; 3 x 150 ml), water (2 x 200 ml), saturated sodium chloride solution (100 ml).and dried over magnesium sulphate. Evaporation of the solvents under reduced pressure yielded a golden brown oil. Silica gel column chromatography (eluant : petrol-ether 3:1) afforded the title compound (3.24) as a pale yellow oil that solidified in the freezer (5.98 g, 47 %).

^{1}H nmr (200 MHz) δ : 5.96 (dd, 1H, J=18.0 Hz, 8.4 Hz), 7.53 (s, 5H), 7.63 (d, 1H, J=18.0 Hz) and 9.40 (d, 1H, J=8.4 Hz). [lit.[4]δ : 5.90 (dd, 1H, J=16.0.Hz, 7 Hz), 7.40 (s, 5H), 7.54 (d, 1H,.J=16.0 Hz), and 9.33 (1H,d, J=7.0 Hz)].

ETHYL (E)-5-HYDROXY-3-OXO-7-(PHENYLTHIO)HEPT-6-ENOATE (3.25).

Ethyl acetoacetate (1.57 g, 12 mmol) was added dropwise during 20 min to a stirred suspension of sodium hydride (80 %; 0.40 g, 13 mmol) in dry THF (25 ml) at 0 °C under nitrogen. The mixture was stirred for a further 10 min before a solution of n-butyllithium in hexanes (2.1 M; 6.3 ml, 13 mmol) was added during 20 min. Stirring was continued for 50 min before 3-(phenylthio)prop-2-enal (3.24) (1.80 g, 11.0 mmol), in THF (10 ml) was added during 30 min. The reaction was complete after 30 min (tlc. control). The mixture was diluted with cold ether (50 ml) and neutralised with dilute hydrochloric acid (2 M; 50 ml). After warming to room temperature, the aqueous phase was separated and extracted further with ether (2 x 25 ml). The combined ether layers were washed with dilute hydrochloric acid (2 M; 2 x 50 ml), water (2 x 50 ml), saturated sodium chloride solution (50 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure yielded the crude product as a red liquid. Purification by silica gel column chromatography (eluant : ether-petrol 3:2) yielded the title compound (3.25) as an orange oil (2.07 g, 70 %). **^{1}H nmr** (200 MHz) δ 1.24 (t, 3H, J=7.2 Hz), 2.75 (d, 2H, J=5.8 Hz), 3.07 (br s, 1H), 3.45 (s, 2H), 4.12 (q, 2H), 4.65 (m,1H), 5.76 (dd, 1H, J=15.0, 6.0 Hz), 6.48 (dd, 1H, J=15.2, 1.25 Hz) and 7.30 (m, 5H). υ_{max} ($CHCl_3$, cm^{-1}) 3472, 2978, 1738, 1708, 1581, 1317, 1024 and 943. **Mass Spec.** Calcd. for $C_{15}H_{18}O_4S$ 294.0926. Found: 294.0942. **m/z** 294, 276, 248, 230, 189, 167(100%), 139, 128, 121, 110, 109, 95, 94, 65 and 51.

(±)-ETHYL (E)*-7-(PHENYLTHIO)-(3RS, 5RS)-DIHYDROXYHEPT-6-ENOATE* (3.26) *AND (±)-ETHYL* (E)*-7-(PHENYLTHIO)-(3RS, 5SR)-DIHYDROXYHEPT-6-ENOATE* (3.27).

To a stirred solution of tetramethylammonium borohydride (1.48 g, 16.6 mmol) in dry acetonitrile (20 ml) at 10°C under nitrogen, was added glacial acetic acid (4.0 ml) during 20 min. When the effervescence had ceased, the reaction mixture was cooled to 0 °C and further glacial acetic acid (15.0 ml) was added. The temperature was lowered to -30 °C and a solution of the hydroxyketone (3.25), (0.77 g, 2.6 mmol) in acetonitrile (5.0 ml) was added during 15 min. The reaction was complete after 90 min (tlc control). The cold solution was poured onto a mixture of ether (250 ml) and an aqueous solution of sodium potassium tartrate (0.5 M; 100 ml). The mixture was allowed to warm up to room temperature and the aqueous phase was separated and extracted further with ether (2 x 50 ml). The combined ether layers were washed with sodium potassium tartrate solution (100 ml), water (2 x 100 ml), saturated sodium chloride solution (100 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure yielded the crude product as a yellow oil. Purification by silica gel column chromatography (eluant : petrol-ether 4:1), afforded the title dihydroxy compounds (3.26) and (3.27) in a 4.5:1 mixture, as a pale yellow oil that solidified on standing (0.65 g, 83%). A sample was recrystallised from petrol-ether to give the pure white crystalline solid (3.26) (needles).

^{1}H nmr (200 MHz) δ 1.27 (t, 3H, J=7.2Hz), 1.54-1.86 (m, 2H), 2.49 (d, 2H, J=4.9 Hz), 3.29 (br s, 2H), 4.18 (q, 2H), 4.27-4.43 (m, 1H), 4.44-4.59 (m, 1H), 5.77 (dd, 1H,J=16.8, 6.0 Hz), 6.51 (d, 1H, J=16.4 Hz) and 7.23-7.39 (m, 5H).
υ_{max} ($CHCl_3$, cm^{-1}) 3486, 2985, 1715, 1611, 1581, 1475, 1374, 1307, 1190, 1090, 1067, 1020 and 947. **mp.** 48-50°C. **ANALYSIS** Calcd. for $C_{15}H_{20}O_4S$: C, 60.79 ; H, 6.80. Found: C, 60.98 ; H, 6.76 %.

(±)-ETHYL (E)*-7-(PHENYLTHIO)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYL-SILYLOXY)HEPT-6-ENOATE* (3.28) *AND (±)-ETHYL* (E)*-7-(PHENYLTHIO)-(3RS,5SR)-BIS(t-BUTYLDIMETHYLSILYLOXY)HEPT-6-ENOATE* (3.29).

To a stirred solution of t-butyldimethylsilyl chloride (3.00 g, 20.0 mmol), and imidazole (3.00 g, 44.1 mmol) in dry DMF (15 ml) at room temperature under nitrogen was added a 4.5:1 mixture of the diols (3.26) and (3.27) (3.00 g, 10.1 mmol). The resulting solution was stirred at room temperature for 18 h, then poured into water (250 ml) and extracted with ether (3 x 100 ml). The combined extracts were washed successively with hydrochloric acid (2 M; 3 x 100 ml), water (3 x 100 ml), saturated sodium chloride solution (100 ml), and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure gave a golden oil. Purification by silica gel column chromatography (eluant : petrol-ether 20 : 1) afforded the *anti*-bissilyl ether (3.28) as a colourless oil (3.71 g, 70 %).

^{1}H nmr (400 MHz) δ -0.07 (s, 6H), -0.06 (s, 6H), 0.87 (s, 9H), 0.89 (s, 9H), 1.24 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.67-1.82 (m, 2H, 4-H_2), 2.49 (m, 2H, 2-H_2), 4.12 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.22-4.31 (m, 2H, 3- and 5-H), 5.78 (dd, 1H, J=15.2, 7.3 Hz, 6-H), 6.32 (d, 1H, J=15.2 Hz, 7-H) and 7.23-7.38 (m, 5H). **υmax** (film, cm^{-1}) 3058, 2945, 2885, 2851, 1735, 1608, 1581, 1471, 1254, 1160, 1307, 1084 and 940.

Further elution with the same solvent gave the *syn*-isomer (3.29), also as an oil (0.83 g, 16 %).

^{1}H nmr (400 MHz) δ -0.08 (s, 6H), 0.01 (s, 6H), 0.87 (s, 9H), 0.90 (s, 9H), 1.25 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.85 (m, 2H), 2.50 (m, 2H), 4.13 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.21-4.34 (m, 2H), 5.78 (dd, 1H, J=14.6, 6.7 Hz), 6.36 (d, 1H, J=14.6 Hz) and 7.20-7.40 (m, 5H). **υmax** (film, cm^{-1}) 1735.

GENERAL SAPONIFICATION PROCEDURE.

(±)-(E)-*7-(PHENYLTHIO)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)-HEPT-6-ENOIC ACID*(3.30).

To a solution of the *anti*-ester (3.28).(0.91 g, 1.7 mmol) stirring in a mixture of methanol (10 ml) and THF (10 ml) at room temperature, was added a solution of potassium hydroxide (0.55 g, 9.8 mmol) in water (3.5 ml), during 20 min. The reaction mixture was stirred overnight at room temperature before pouring into a mixture of ether (30 ml) and water (70 ml). After acidification to pH4-5 with hydrochloric acid (2 M; 10 ml) the aqueous phase was separated and extracted further with ether (2 x 30 ml). The combined organic phases were washed with water (30 ml), brine (30 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure and filtration on silica gel (eluant : petrol-ether 5 : 1) gave the title acid (3.30) as a colourless oil (0.75 g, 88 %).
^{1}H nmr (200 MHz) δ 0.06-0.09 (m, 12H), 0.88 (2s, 18H), 1.57-1.75 (m, 2H, 4-H_2), 2.36-2.58 (m, 2H, 2-H_2), 4.12-4.39 (m, 2H, 3- and 5-H), 5.63 (dd, 1H, J=15.7, 7.3 Hz, 6-H), 6.27 (d, 1H, J=15.7 Hz, 7-H), 7.17-7.34 (m, 5H), and 10.90 (br s, 1H). **υ_{max}** ($CHCl_3$, cm^{-1}) 3065, 2952, 2918, 2858, 1708, 1611, 1581, 1471, 1357, 1254, 1084 and 940.

(±)-(E)-*7-(PHENYLTHIO)-(3RS, 5SR)-BIS(t-BUTYLDIMETHYLSILYLOXY)-HEPT-6-ENOIC ACID* (3.32).

Saponification of the *syn*-ester (3.29) (1.47 g, 2.8 mmol), as described for the preparation of the *anti*-acid (3.30), gave the title acid (3.32) as an oil (1.03 g, 74 %).
^{1}H nmr (200 MHz) δ 0.06-0.09 (m, 12H), 0.86 (s, 9H), 0.88 (s,9H), 1.66-1.82 (m, 2H, 4-H_2), 2.38-2.65 (m, 2H, 2-H_2), 4.08-4.24 (m, 2H, 3- and 5-H), 5.68 (dd,

1H, J=16.2, 7.6 Hz, 6-H), 6.32 (d, 1H, J=16.2 Hz, 7-H), 7.15-7.34 (m, 5H) and 10.68 (br s, 1H).

(±)-Se-*PHENYL* (E)-*7-(PHENYLTHIO)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYL-SILYLOXY)SELENOHEPT-6-ENOATE* (3.23).

The standard procedure for preparation of selenoesters was repeated on the *anti*-acid (3.30) (2.50 g, 5.0 mmol), to give the title compound (3.23), as a colourless oil (2.32 g, 73 %)

^{1}H nmr (200 MHz) δ 0.06 (m, 6H), 0.09 (m, 6H), 0.88 (2s, 18H),1.62-1.88 (m, 2H, 4-H_2), 2.90 (d, 2H, J=5.7 Hz, 2-H_2), 4.28-4.36 (m, 2H, 3- and 5-H), 5.78 (dd, 1H, J=16.0, 7.5 Hz, 6-H), 6.32 (d, 1H, J=16.0 Hz, 7-H) and 7.25-7.40 (m, 10H). **υ_{max}** ($CHCl_3$, cm^{-1}) 3058, 2939, 2851, 2885, 1721, 1608, 1581, 1471, 1461, 1437, 1361, 1254, 1084 and 1023. **ANALYSIS** Calcd. for $C_{31}H_{48}O_3SSeSi_2$: C, 58.55 ; H, 7.61. Found: C, 58.4 ; H, 7.5 %.

(±)-Se-*PHENYL* (E)-*7-(PHENYLTHIO)-(3RS, 5SR)-BIS(t-BUTYLDIMETHYL-SILYLOXY)SELENOHEPT-6-ENOATE* (3.33).

Reaction of the *syn*-acid (3.32) (0.25 g, 0.5 mmol) with triethylamine and subsequently with phenylselenenyl chloride and tributylphosphine, as descibed in the general procedure for preparation of seleneoesters, gave the title selenoester (3.33) as a pale green oil (0.23 g, 72 %).

^{1}H nmr (200 MHz) δ 0.01-0.09 (m, 12H), 0.86 (s, 9H), 0.88 (s, 9H), 1.62-1.88 (m, 2H, 4-H_2), 2.90 (d, 2H, J=5.7 Hz, 2-H_2), 4.28-4.36 (m, 2H, 3- and 5-H), 5.78 (dd, 1H, J=16.3, 7.5 Hz, 6-H), 6.34 (d, 1H, J=16.3 Hz, 7-H) and 7.24-7.52 (m, 10H). **υ_{max}** ($CHCl_3$, cm^{-1}) 3053, 2942, 2929, 2922, 2908, 2852, 1709, 1606,

1580, 1462, 1436, 1405, 1375, 1361, 1190, 1107, 1057, 1040, 999, 951, 881, 845 and 826. **ANALYSIS** Calcd. for $C_{31}H_{48}O_3SSeSi_2$: C, 58.55 ; H, 7.61. Found: C, 58.43 ; H, 7.54 %.

(±)-2RS-(PHENYLTHIO)METHYL-(3RS,5RS)-BIS(t-BUTYLDIMETHYL-SILYLOXY)CYCLOHEXANONE (3.20) *AND (±)-2SR-(PHENYLTHIO)METHYL-(3RS,5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)CYCLOHEXANONE* (3.21)

To a stirred solution of selenoester (3.23) (2.30 g, 3.6 mmol), in dry benzene (30 ml) at reflux under nitrogen was added a solution of tributyltin hydride (1.21 g, 4.2 mmol) in benzene (8 ml), containing a trace of AIBN (*ca.* 10mg), duirng 5 min. After a further 60 min at reflux the reaction was complete (tlc. control) and, after cooling to room temperature, the solvent was evaporated under reduced pressure to give an oil. Chromatography of this oil on silica gel (eluant : petrol-ether 15 : 1) yielded the 2,3-cis-*cyclohexanone* (3.20), as a white crystalline solid (0.77 g, 45 %).
^{1}H nmr (400 MHz) δ 0.016 (s, 3H), 0.019 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.82 (s, 9H), 0.84 (s, 9H) ,1.73 (ddd, 1H, J=13.6, 10.8, 2 Hz,4-H_{ax}), 2.20 (m, 1H, $w_{1/2}$=26 Hz, 4-H_{eq}), 2.33 (ddd, 1H, J=13.2, 10.4, 0.8 Hz, 6-H_{ax}), 2.45 (m, 1H, $w_{1/2}$=18 Hz, 2-H_{ax}), 2.67 (ddd, 1H, J=13.2, 5.2, 2 Hz, 6-H_{eq}), 2.81 (dd, 1H, J=14, 4 Hz, C*H*HSPh), 3.41 (dd,1H, J=14, 4 Hz, CH*H*SPh), 4.26 (dddd, 1H, J=10.4, 10.4, 5.2, 4.8 Hz, 5-H_{ax}), 4.52 (dt, 1H, J=2, 2 Hz, 3-H_{eq}) and 7.13-7.29 (m, 5H);
^{13}C nmr (100 MHz) δ -5.06, -4.77, -4.72, -4.42, 17.90, 17.92, 25.64, 25.71, 28.91, 42.43, 51.50, 54.01, 67.21, 68.49, 126.08, 129.08, 135.78 and 206.88.
υmax ($CHCl_3$, cm^{-1}) 2952, 2925, 2885, 2851, 1712, 1601, 1465, 1357, 1104, 1057 and 993. **m.p.** (methanol) 51-52°C. **ANALYSIS** Calcd. for $C_{25}H_{44}O_3SSi_2$: C, 62.45 ; H, 9.22. Found: C, 62.43 ; H, 8.97 %.

Further elution with the same solvent gave the 2,3-*trans*-cyclohexanone (3.9) as an oil (0.93 g, 55 %).

^{1}H nmr (400 MHz) δ 0.023 (s, 6H), 0.034 (s, 3H), 0.067 (s, 3H), 0.84 (s, 9H), 0.89 (s, 9H), 1.84 (ddd, 1H, J=13.1, 9.6, 2.4 Hz, 4-H_{ax}), 2.12 (dddd, 1H, J=13.2, 4, 2, 2 Hz, 4-H_{eq}), 2.41 (ddd, 1H, J=14, 4, 2 Hz, 6-H_{eq}), 2.48 (dd, 1H, J=14, 3.2 Hz, 6-H_{ax}), 2.70 (ddd, 1H, J=8.8, 8.8, 4 Hz, 2-H_{ax}), 3.14 (dd, 1H, J=13.6,8.8 Hz, C*H*HSPh), 3.21 (dd,1H, J=13.6, 4 Hz, CH*H*SPh), 4.07 (ddd, 1H, J=9.6, 8.8, 4 Hz, 3-H_{ax}), 4.30 (m, 1H, $w_{1/2}$=10 Hz, 5-H_{eq}) and 7.07-7.32 (m, 5H). **^{13}C nmr** (100 MHz) δ –5.11, –4.96, –4.73, –4.48, 17.91, 19.92, 25.61, 25.76, 28.73, 41.95, 49.04, 59.85, 66.62, 70.59, 125.23, 127.74, 128.79, 137.53 and 206.27. **υmax** ($CHCl_3$, cm^{-1}) 2952, 2945, 2885, 2858, 1718, 1581, 1464, 1254, 1100, 1084, 1047 and 1007.

*REACTION OF (±)-*Se*-PHENYL* (E)*-7-(PHENYLTHIO)-(3RS, 5SR)-BIS(t-BUTYLDIMETHYLSILYLOXY)SELENOHEPT-6-ENOATE* (3.33) *WITH TRIBUTYLTIN HYDRIDE.*

The *syn*-selenoester (3.33) (0.58 g, 0.91 mmol) was treated in benzene at reflux with tributyltin hydride and AIBN as described in the preparation of cyclohexanones (3.20) and (3.21). After 1 h at reflux the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (eluant : petrol-ether 15 : 1) to give a mixture of the cyclohexanones (3.34) and (3.35) in the ratio 1.1:1 as a colourless oil (0.36g, 81 %).

Salient features for 2,3-*cis*-cyclohexanone (3.34).

^{1}H nmr (400 MHz) δ 3.18 (dd, 1H, J=12.8, 6.4 Hz, C*H*HSPh), 3.35 (dd, 1H, J=12.8, 7 Hz, CH*H*SPh), 4.00 (tt, 1H, J=9.6, 4.8 Hz, 5-H), and 4.21 (dt, 1H, J= 9.6,3.2 Hz, 3-H).

Salient features for 2,3-trans-*cyclohrxanone* (3.35).

^{1}H nmr (400 MHz) δ 3.10 (dd, 1H, J=12.8, 8.6 Hz, C*H*HSPh), 3.27 (dd, 1H, J=12.8, 2 Hz, CH*H*SPh), 3.55 (dt, 1H, J=11.2, 3.2 Hz, 3-H), and 3.76 (tt, 1H, J=10.2, 3.8 Hz, 5-H).

Common features to both isomers,

^{1}H nmr (400 MHz) δ 1.30 (m, 2H, 2 x 4-H_{ax}), 1.9 (m, 2H, 2 x 4-H_{eq}), and 2.2-2.8 (m, 6H, 2 x 2-H and 4 x 6-H).

ANALYSIS Calcd. for $C_{25}H_{44}O_3SSi_2$: C, 62.45 ; H, 9.22. Found: C, 62.17 ; H, 9.16 %.

(±)-anti-*(3RS, 5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)-2-METHYLENE-CYCLOHEXANONE* (3.22)

A solution of magnesium monoperoxyphthalate hexahydrate (MMPP) (115 mg, 0.23 mmol) in water (2 ml) was added to a stirred solution of the 2,3-cis-*cyclohexanone* (3.20) (200 mg, 0.42 mmol) in ethanol (3 ml) at room temperature under nitrogen. After completion of the reaction (t.l.c. control : 30 min), the solution was poured into a mixture of chloroform (25 ml) and water (2 ml). After filtration to remove solid residues, the aqueous phase was further extracted with chloroform (2 x 5 ml). The combined organic phases were washed with aqueous sodium hydrogen carbonate (5 %: 15 ml) and water (15 ml) and dried ($MgSO_4$). Filtration and evaporation of the volatiles under reduced pressure gave the crude sulphoxides as an oil (207 mg, 99%), that solidified on storage. The sulphoxides were taken up in a mixture of benzene (7.5 ml) and 2,3-dihydropyran (2.5 ml) and brought to reflux under nitrogen for 6 h. Removal of the volatiles under reduced pressure gave a green oil, which after chromatography on silica gel (eluant : petrol-ether 10 : 1) yielded the α-methylenecyclohexanone (3.22) as a white crystalline solid (92 mg, 62 %).

^{1}H nmr (400 MHz) δ 0.05-0.08 (m, 12H), 0.85 (s, 9H), 0.90 (s, 9H) ,1.80-1.96 (m, 1H, 4-H_{ax}), 2.02-2.16 (m, 1H, 4-H_{eq}), 2.50-2.66 (m, 2H, 6-H_2), 4.32-4.44 (m, 1H, 3-H), 4.66-4.74 (m, 1H, 5-H), 5.43 (br s, 1H, =C*H*H) and 5.84 (br s, 1H, =CH*H*). **^{13}C nmr** (100 MHz) δ -4.99, -4.91 ,-4.85, -4.81, 17.97, 18.15, 25.69, 25.78, 42.05, 49.07, 65.34, 68.93, 118.73, 149.77 and 200.48. **υ_{max}** ($CHCl_3$, cm^{-1}) 2930, 2884, 2852, 1691, 1622, 1461, 1107, 1092, 1066 and 839. **m.p.** (petrol-ether) 40-44°C. **ANALYSIS** Calcd. for $C_{19}H_{38}O_3Si_2$: C, 61.56 ; H, 10.33. Found: C, 61.28 ; H, 10.62 %.

The above procedure was repeated on the 2,3-trans-*cyclohexanone* (3.21) (200 mg, 0.42 mmol), to give the title product (3.22) (56 mg, 34 %).

(±)-1RS-(ETHOXYETHYNYL)-2RS-(PHENYLTHIOMETHYL)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)CYCLOHEXAN-1-OL (3.39).

To a stirred, freshly prepared solution of ethyl magnesium bromide (1.8 M, 0.58 ml, 1.0 mmol) in dry ether (5 ml) under nitrogen at room temperature,was added ethoxyacetylene (50 % solution in hexane; 0.22 g, 1.6 mmol), and the mixture was refluxed for 2.5 h. The reaction mixture was cooled to room temperature and a solution of the 2,3-trans-*cyclohexanone* (3.21) in dry ether (2 ml) was slowly added. The reaction was refluxed for a further 1 h before cooling to 10 °C and diluting with saturated ammonium chloride solution (4 ml). The aqueous layer was separated and extracted further with ether (2 x 10 ml). The combined organic phases were successively with water (2 x 5 ml) and saturated sodium chloride solution (5 ml), and dried over magnesium sulphate. Filtration and evaporation of solvents under reduced pressure yielded the title carbinol (3.39) as a brown oil (188 mg, 66 %). This was used without further purification.

υ_{max} ($CHCl_3$, cm^{-1}) 3431, 2944, 2930, 2889, 2851, 2264, 1582, 1463, 1256, 1128, 1091, 1004 and 903.

1RS-(ETHOXYETHYNYL)-2-METHYLENE-(3RS, 5RS)-BIS(t-BUTYL-DIMETHYLSILYLOXY)CYCLOHEXAN-1-OL (3.38).

The procedure for the preparation of carbinol (3.39) was repeated on the α-methylenecyclohexanone (3.22) (92mg, 0.2 mmol), to yield the crude hydroxy-acetylene (3.38) as a brown oil (100 mg, 50 %).

^{1}H nmr (60 MHz) δ 0.06 (s, 12 H), 0.88 (s, 18H), 1.23 (t, 3H), 1.59-1.88 (m, 2H), 2.05-2.44 (m, 2H), 3.18-3.30 (m, 1H), 3.80–4.32 (m, 4H) and 5.60-5.84 (m, 2H). υ_{max} ($CHCl_3$, cm^{-1}) 3446, 2980, 2929, 2877, 2852, 2261, 1641, 1581, 1462, 1387, 1288, 1045, 1001 and 828.

REACTION OF (±)-1RS-(ETHOXYETHYNYL)-2RS-(PHENYLTHIOMETHYL)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)CYCLOHEXAN-1-OL (3.39) *WITH AQUEOUS ACID*

Sulphuric acid (10 %; 5 ml) was added dropwise during 2 min to a stirred solution of hydroxy-alkyne (3.39) (260 mg, 0.47 mmol) in THF (20 ml) at room temperature. After consumption of all the starting material (t.l.c. control; 30 min) the mixture was poured into ether (10 ml) and the aqueous layer separated and extracted further with ether (2 x 5 ml). The combined ether extracts were washed with water (3 x 5 ml) and saturated sodium chloride solution (5 ml) before drying ($MgSO_4$). Filtration and evaporation of solvents under reduced pressure yielded a brown oil. Chromatography on silica gel (eluant : petrol-ether 5:1) gave a complex mixture of

compounds (36 mg) and followed by the saturated hydroxyester (3.40) (117mg, 44 %).

^{1}H nmr (200 MHz) δ 0.05 (s, 6H), 0.14 (s, 3H), 0.16 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.21 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.34-1.44 (m, 1H, 4-H_{ax}), 1.57-1.73 (m, 1H, 4-H_{eq}), 1.81 (d, 1H, J=10.9 Hz, 2-H_{ax}), 1.98-2.19 (m, 2H, 6-H_2), 2.54 (q, 2H, J=14.7 Hz, CH_2CO_2Et), 3.03 (dd, 1H, J=12.3, 11.0 Hz, CHHSPh), 3.33 (dd, 1H, J=13.0, 9.5 Hz, CHHSPh), 4.07 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.14-4.34 (m, 1H, 5-H_{ax}), 4.55 (s, 1H, -OH) and 4.63 (m, 1H, $w_{1/2}$=10 Hz, 3-H_{eq}). **υmax** ($CHCl_3$, cm^{-1}) 3442, 3059, 2945, 2929, 2881, 2852, 1724, 1581, 1468, 1370, 1257, 1108, 1025, 951 and 838.

Preparative HPLC on the mixture of compounds (5.0 mg) (eluant: petrol-ethyl acetate 200:1) gave the required α,β-unsaturated ester (3.41) (2.0 mg).

^{1}H nmr (400 MHz) δ 0.020 (s, 3H), 0.029 (s, 3H), 0.046 (s, 3H), 0.049 (s, 3H), 0.82 (s, 9H), 0.84 (s, 9H), 1.25 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.54-1.65 (m, 1H, 4-H_{ax}), 1.83-1.89 (m, 1H, 4-H_{eq}), 2.41 (m, 1H, 6-H_{ax}), 2.76-2.79 (m, 1H, 6-H_{eq}), 2.96 (dd, 1H, J=12.9, 7.7 Hz, CHHSPh), 3.05-3.08 (m, 1H, 2-H), 3.19 (dd, 1H, J=13.0, 6.3 Hz, CHHSPh), 4.04-4.10 (m, 1H, 5-H_{ax}), 4.12 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.34 (m, 1H, $w_{1/2}$=16 Hz, 3-H_{eq}), 5.64 (s, 1H, $CHCO_2Et$) and 7.17-7.32 (m, 5H).

3-(4-CHLOROPHENYLTHIO)PROPANAL

The procedure for the preparation of 3-(phenylthio)propanal was repeated, replacing thiophenol with 4-chlorothiophenol (15.00 g, 104 mmol) to yield 3-(4-chlorophenylthio)propanal as a colourless oil that solidified in the freezer (19.22g, 92 %).

^{1}H nmr (200 MHz) δ 2.70 (t, 2H, J=7.2 Hz), 3.13 (t, 2H, J=7.2 Hz), 7.25 (s,4H) and 9.73 (s, 1H). **υ_{max}** ($CHCl_3$, cm^{-1}) 2969, 2930, 2890, 2827, 2730, 1723, 1572, 1474, 1387, 1095 and 1010.

ANALYSIS Calcd. for C_9H_9ClOS: C, 53.86 ; H, 4.52 ; Cl, 17.67. Found: C, 53.84 ; H, 4.60 ; Cl 17.52 %.

(E)-*3-(4-CHLOROPHENYLTHIO)-2-PROPENAL* (3.47).

The procedure for preparation of 3-(phenylthio)prop-2-enal (3.24) was repeated on 3-(4-chlorophenylthio)propanal (2.00 g, 9.97 mmol), to yield the title compound (3.47) as a white cystalline solid (0.60g, 30 %).

^{1}H nmr (200 MHz) δ 5.93 (dd, 1H, J=15.1, 7.5 Hz, 2-H), 7.41 (s, 4H), 7.60 (d, 1H, J=15.1 Hz, 3-H) and 9.42 (d, 1H, J=7.6 Hz, C*H*O). **υ_{max}** ($CHCl_3$, cm^{-1}) 2970, 2815, 2726, 1670, 1561, 1474, 1387, 1126, 1094, 1013, 944 and 850 **mp.** (petrol-ether) 60-61 °C. **ANALYSIS** Calcd. for C_9H_7ClOS: C, 54.41 ; H, 3.55 . Found: C, 54.11 ; H, 3.23 %.

(±)-ETHYL (E)*-7-(4-CHLOROPHENYLTHIO)-5-HYDROXY-3-OXOHEPT-6-ENOATE* (3.48).

The procedure for the preparation of hydroxyketone (3.25), was repeated on 3-(4-chlorophenylthio)prop-2-enal (3.47) (6.12 g, 31 mmol), to give the title hydroxy-ester (3.48) as a red oil (6.26 g, 69 %).

^{1}H nmr (200 MHz) δ 1.23 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.74 (d, 2H, J=7.1 Hz, 4-H_2), 3.13 (br s, 1H, O*H*), 3.44 (s, 2H, 2-H_2), 4.14 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.56-4.70 (m, 1H, 5-H), 5.75 (dd, 1H, J=16.2, 7.0 Hz, 6-H), 6.42 (dd, 1H, J=16.2, 2.5 Hz, 7-H) and 7.24 (s, 4H). **υ_{max}** ($CHCl_3$, cm^{-1}) 3460, 2952, 1736, 1709, 1648, 1617, 1473, 1319, 1095, 1012 and 946. **Mass Spec.** Calcd. for

$C_{15}H_{17}ClO_4S$: 328.0536. Found: 328.0508 **m/z** 328, 311, 282, 239, 223, 199, 181, 167, 157, 144, 139, 135, 121, 115, 108, 95, 87, 75, 69, 63, 55, 51, 43 (100 %) and 39.

(±)-ETHYL (E)*-7-(4-CHLOROPHENYLTHIO)-(3RS, 5RS)-DIHYDROXYHEPT-6-ENOATE* (3.49).

To a stirred solution of tetramethylammonium triacetoxyborohydride (24.81 g, 94 mmol), in a mixture of dry acetonitrile and glacial acetic acid (1:1, 150 ml), at -30 °C under nitrogen, was slowly added a solution of the β-hydroxyketone (3.48) (6.20 g, 19 mmol) in acetonitrile (25 ml), and stirring was continued at -25 °C for 2 h. The reaction mixture was poured into an aqueous solution of sodium potassium tartrate (0.5 M; 150 ml) and after warming to room temperature, was extracted with dichloromethane (3 x 100 ml). The combined organic phases were washed successively with saturated sodium bicarbonate solution (2 x 100 ml), water (2 x 100 ml) and saturated sodium chloride solution (100 ml) before drying over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure yielded an orange oil that solidifed on standing. Purification by silica gel column chromatography (eluant : petrol-ether 4:1) yielded the title diol (3.49) as a white crystalline solid (4.87 g, 81 %).

^{1}H nmr (200 MHz) δ 1.26 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.64-1.86 (m, 2H, 4-H_2), 2.48 (m, 2H, 2-H_2), 3.06 (br s, 1H, O*H*), 3.53 (br s, 1H, O*H*), 4.16 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.24-4.41 (m, 1H, 3-H), 4.45-4.59 (m, 1H, 5-H), 5.89 (dd, 1H, J=15.0, 5.5 Hz, 6-H), 6.44 (dd, 1H, J=15.0, 1.4 Hz, 7-H) and 7.27 (s, 4H). **υmax** ($CHCl_3$, cm^{-1}) 3486, 2989, 2939, 2912, 1713, 1602, 1474, 1409, 1375, 1177, 1094, 1011 and 948. **mp.** (petrol-ether) 69°C. **ANALYSIS** Calcd. for $C_{15}H_{19}ClO_4S$: C,.54.46 ; H, 5.79.; Cl, 10.72 ; S, 9.69. Found: C, 54.42 ; H, 5.72 ; Cl, 10.93.; S, 9.42 %.

(±)-ETHYL (E)*-7-(4-CHLOROPHENYLTHIO)-(3RS, 5RS)-BIS(t-BUTYL-DIMETHYLSILYLOXY)HEPT-6-ENOATE* (3.50)

The protection of the diol (3.49) (3.50 g, 11 mmol), as its bis-TBDMS ether (3.37), was performed as descibed for the phenylthio-diol (3.36), to yield the disilylated product as a pale green oil (5.27 g, 89 %) with an *anti-* to *syn-* ratio of 8:1. **^{1}H nmr** (200 MHz) δ 0.03-0.06 (m, 12H), 0.85 (s, 9H), 0.87 (s, 9H), 1.24 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.60-1.84 (m, 2H, 4-H_2), 2.46 (d, 2H, J=6.9 Hz, 2-H_2), 4.10 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.16-4.23 (m, 2H, 3- and 5-H), 5.68 (dd, 1H, J=16.0, 8.0 Hz, 6-H), 6.16 (d, 1H, J=16.0 Hz, 7-H) and 7.27 (s, 4H). **υ_{max}** ($CHCl_3$, cm^{-1}) 2903, 2883, 2852, 1724, 1606, 1472, 1160, 1093, 1014, 938, 836 and 826. **ANALYSIS** Calcd. for $C_{27}H_{47}ClO_4SSi_2$: C, 57.98 ; H, 8.47.; Cl, 6.33 ; S, 5.73. Found: C, 58.14 ; H, 8.50 ; Cl, 6.54.; S, 5.43 %.

For the *syn*-isomer.

^{1}H nmr (400 MHz) δ -0.08 (s, 6H), 0.01 (s, 6H), 0.87 (s, 9H), 0.90 (s, 9H), 1.25 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.85 (m, 2H, 4-H_2), 2.50 (m, 2H, 2-H_2), 4.13 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.21-4.34 (m, 2H, 3- and 5-H), 5.78 (dd, 1H, J=14.6, 6.7 Hz, 6-H), 6.36 (d, 1H, J=14.6 Hz, 7-H) and 7.20-7.40 (m, 4H). **υ_{max}** (film, cm^{-1}) 2930, 2851, 2884, 1725, 1638, 1471, 1375, 1160, 1093, 1011, 978. 949 and 839.

(±)-(E)*-7-(4-CHLOROPHENYLTHIO)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYL-SILYLOXY)HEPT-6-ENOIC ACID* (3.51).

The disilylated ester (3.50) (2.00 g, 3.6 mmol) was saponified by the usual procedure to yield the title acid (3.51) as a pale green oil (1.77 g, 93 %).

^{1}H nmr (200 MHz) δ 0.02-0.05 (m, 12H), 0.84 (s, 9H), 0.86 (s, 9H), 1.58-1.86 (m, 2H, 4-H_2), 2.36-2.64 (m, 2H, 2-H_2), 4.12-4.35 (m, 2H, 3- and 5-H), 5.73 (dd, 1H, J=15.2, 7.4 Hz, 6-H), 6.13 (d, 1H, J=15.2 Hz, 7-H), 7.25 (s, 4H) and 9.20 (br s, 1H). **υ_{max}** ($CHCl_3$, cm^{-1}) 3508, 3066, 2929, 2892, 2852, 1709, 1606, 1472, 1388, 1361, 1254, 1093, 1011, 937 and 836.

(±)-ETHYL (E)*-9-(4-CHLOROPHENYLTHIO)-(5RS,7RS)-BIS(t-BUTYL-DIMETHYLSILYLOXY)NON-8-ENOATE* (3.52).

The magnesium salt of monoethylmalonate was prepared by stirring magnesium ethoxide (0.75 g, 6.6 mmol), with monoethyl malonate (1.74 g, 13.2 mmol), in dry THF (25 ml) under nitrogen for 1 hr. The solvent was evaporated under reduced pressure to yield the salt as an off-white foam. This product was used without any further purification.

To a stirred solution of the acid (3.51) (1.50 g, 2.8 mmol) in dry THF (20 ml), at room temperature under nitrogen, was added 1,1-carbonyl diimidazole (0.50 g, 3.1 mmol). The mixture was stirred for 6 h before freshly prepared magnesium monoethylmalonate (0.89 g, 3.1 mmol) was added. The reaction was stirred for a further 18 h before the solvent was evaporated under reduced pressure. The residue was dissolved in ether (60 ml) and acidified with dilute hydrochloric acid (0.5 M; 60 ml). The aqueous phase was separated and extracted further with ether (2 x 30 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution (60 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure and silica gel column chromatography (eluant : petrol-ether 10 : 1) yielded the β-ketoester(3.52) as a colourless oil (1.38g, 81 %).

^{1}H nmr (200 MHz) δ 0.03-0.06 (m, 12H), 0.85 (s, 9H), 0.87 (s, 9H), 1.25 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.59-1.82 (m, 2H, 6-H_2), 2.69 (d, 2H, J=5.4 Hz, 4-H_2), 3.44 (s,2H, 2-H_2), 4.05-4.33 (m, 4H, OCH_2CH_3, 5- and 7-H), 5.74 (dd, 1H,

J=16.4, 4.6, Hz, 8-H), 6.24 (d, 1H, J=16.4 Hz, 9-H) and 7.25 (s, 4H). υ_{max} ($CHCl_3$, cm^{-1}) 2940, 2889, 2851, 1740, 1711, 1647, 1627, 1469, 1387, 1367, 1319, 1289, 1096, 937, 839 and 827. **ANALYSIS** Calcd. for $C_{29}H_{49}ClO_5SSi_2$: C, 57.92 ; H, 8.21.; Cl, 5.90 ; S, 5.33 Found: C, 57.98 ; H, 8.08 ; Cl, 5.78.; S, 5.03 %.

ETHYL 3-(DIPHENYLPHOSPHOXY)BUT-2-ENE (3.59).

To a stirred solution of tetrabutylammonium hydrogen sulphate (0.52 g, 1.5 mmol) in aqueous sodium hydroxide (2 M; 7.7 ml, 15.4 mmol) at room temperature was added a solution of ethyl acetoacetate (1.00 g, 7.7 mmol) in dichloromethane during 5 min. Diphenyl chlorophosphate (2.06 g, 7.7 mmol) was slowly added and the mixture was stirred for a further 30 min before the aqueous phase was separated and extracted with dichloromethane (2 x 10 ml). The combined organic phases were washed with water and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure and silica gel column chromatography (eluant : petrol-ether 2:1) afforded the *E*-unsaturated phosphate (3.59E) as a colourless oil (1.66 g, 65 %).

^{1}H nmr (60 MHz) δ 1.13 (t, 3H), 2.27 (s, 3H), 4.07 (q, 2H), 5.85 (s, 1H) and 7.10 (s, 10 H).

Further elution with the same solvents afforded the *Z*-unsaturated phosphate (3.59Z) as a colourless oil (0.41 g, 16 %).

^{1}H nmr (60 MHz) δ 1.13 (t, 3H), 1.97 (s, 3H), 4.07 (q, 2H), 5.20 (s, 1H) and 7.10 (s, 10 H).

ETHYL 3-(DIPHENYLPHOSPHONOXY)BUT-2-ENE (3.60).

The phase transfer conditions for preparation of the unsaturated phosphate (3.59) were repeated, replacing diphenyl chlorophosphate with diphenyl chlorophosphinate (1.82 g, 7.7 mmol) to yield a 3:1 E/Z mixture of the title compound (3.60) (1.40 g, 60 %).

For E-isomer

^{1}H nmr (60 MHz) δ 1.20 (t, 3H), 2.38 (s, 3H), 4.08 (q, 2H), 5.81 (s, 1H), 7.34-7.92 (m, 10 H).

For Z-isomer

^{1}H nmr (60 MHz) δ 1.30 (t, 3H), 2.24 (s, 3H), 4.18 (q, 2H), 5.22 (s, 1H), 7.10-7.99 (m, 10 H).

(±)-ETHYL (2E,8E)*-3-(DIPHENYLPHOSPHOXY)-9-(4-CHLOROPHENYLTHIO)-(5RS,7RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)NONA-2,8-DIENOATE* (3.61).

To a stirred solution of tetrabutylammonium hydrogen sulphate (0.17 g, 0.5 mmol) in an aqueous solution of sodium hydroxide (0.5 M; 7.5 ml, 5.0 mmol) was added a solution of the β–ketoester (3.52) (1.50 g, 2.5 mmol) in dichloromethane (12 ml), dropwise during 5 min. Diphenyl chlorophosphate (0.67 g, 2.5 mmol) was added dropwise and the mixture was stirred until the reaction was complete (tlc control, 2 h). The aqueous layer was separated and extracted further with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (2 x 5 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent and silica gel column chromatography afforded the title phosphate (3.61) as a colourless oil (2.04 g, 98 %, E/Z 10:1).

For the E-isomer

^{1}H nmr (200 MHz) δ 0.01-0.05 (m, 12H), 0.85 (s, 9H), 0.86 (s, 9H), 1.25 (t, 3H), 1.57-1.82 (m, 2H, 6-H_2), 2.86-2.98 (m, 2H, 4-H), 3.08-3.22 (m,2H, 4-H), 4.07-4.33 (m, 4H, CH_2CH$_3$, 5- and 7-H), 5.78 (dd, 1H, J=22.2, 7.6, Hz, 8-H), 6.04, (s, 1H, 2-H), 6.28 (d, 1H, J=15.1 Hz, 9-H) and 7.15-7.38 (m, 14H).

υ_{max} ($CHCl_3$, cm^{-1}) 2951, 2927, 2888, 2853, 1716, 1647, 1590, 1488, 1473, 1312, 1301, 1254, 1187, 1122, 1095, 966, 946, 837 and 776.

ETHYL 3-(PHENYLSELENENYL)BUT-2-ENOATE (3.54).

A suspension of sodium phenylselenide in THF(2.0 ml) , generated by sonification of sodium dispersion (50 %; 221 mg, 4.6 mmol) with diphenyl diselenide (1.44 g, 4.6 mmol), was prepared as described by Ley.[5]

To a solution of the unsaturated phosphate (3.60) (250 mg, 0.75 mmol) in dry THF (5 ml) at room temperature under nitrogen, was added a suspension of sodium phenylselenide in THF (2.4 M; 0.35 ml, 0.83 mmol). After 20 min the reaction mixture was poured into a mixture of water (20 ml) and ether (20 ml). The aqueous layer was separated and extracted further with ether (2 x 10 ml). The combined ether fractions were washed with saturated sodium chloride solution (5 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvents under reduced pressure afforded the crude product as a yellow oil. Purification by silica gel column chromatography yielded the unsaturated phenylselenide (3.54) as a colourless oil (140 mg, 70 %).

The title unsaturated phenylselenide was also prepared as follows.

To a stirred solution of diphenyl diselenide (260 mg, 0.8 mmol) in ethanol (10 ml) under nitrogen at room temperature was added sodium borohydride (40 mg, 1.1 mmol). After effervescence had ceased a solution of a 5:1 mixture (E/Z) of the unsaturated phosphates (3.60) (500 mg, 1.5 mmol) in ethanol (5 ml) was slowly added.and the mixture was stirred for a further 16 h before it was poured into ether (20 ml). The etherial solution was washed with water (2 x 20 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure followed by silica gel column chromatography (eluant : petrol-ether 20 : 1) afforded the title unsaturated phenylselenide (3.54) as a colourless oil, in a 4:1 mixture of E/Z isomers (254 mg, 61 %).

For the *E*-isomer,

^{1}H nmr (200 MHz) δ 1.31 (t, 3H), 1.91 (d, 3H, J=1.2 Hz), 4.23 (q, 2H), 6.19 (d, 1H, J=1.2 Hz), 7.32-7.43 (m, 3H) and 7.64-7.71 (m, 2H). **υ_{max}** (film, cm^{-1}) 2923, 2849, 1684, 1588, 1433, 1367, 1321, 1174 and 829.

For the *Z*-isomer,

^{1}H nmr (200 MHz) δ 1.21 (t, 3H), 2.49 (d, 3H, 1.3 Hz), 4.09 (q, 2H), 5.76 (s, 1H), 7.25-7.43 (m, 3H) and 7.55-7.64 (m, 2H).

(±)-ETHYL (2E,8E)*-3-(PHENYLSELENYL)-9-(4-CHLOROPHENYLTHIO)-(5RS,7RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)NONA-2,8-DIENOATE* (3.63).

To a solution of the unsaturated phosphate (3.61) (200 mg, 0.24 mmol) stirring in THF (5 ml) was added a suspension of sodium phenylselenide (2.4 M; 0.13 ml, 0.30 mmol) during 5 min. The reaction was complete after 1.5 h (t.l.c. control). The reaction mixture was poured into a mixture of ether (10 ml) and water (10 ml), and the aqueous phase was separated and extracted further with ether (2 x 5 ml). The combined ether layers were washed with saturated sodium chloride solution (5 ml) and

dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure yielded a yellow oil. Purification by silica gel column chromatography (eluant : petrol-ether 25 : 1) afforded the*Z*-unsaturated phenylselenide (3.63Z) as a colourless oil (26 mg, 15 %).

^{1}H nmr (300 MHz) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H),.0.90 (s, 18H), 1.17 (t, 3H), 1.57-1.71 (m, 1H, 6-H), 1.61-1.70, (m, 1H, 6-H), 1.78-1.89 (m, 1H, 6-H), 3.11 (dd, 1H, J=13.5, 6.8 Hz, 4-H), 3.31 (dd, 1H, J=13.3, 7.4 Hz, 6-H), 4.00 (q, 2H, CH_2CH$_3$), 4.10 (tt, 1H, J=6.3, 6.3 Hz, 5-H), 4.32 (dt, 1H, J=6.5, 6.5 Hz, 7-H), 5.53, (s, 1H, 2-H), 5.85 (dd, 1H, J=15.0, 7.2, Hz, 8-H), 6.34 (d, 1H, J=15.0 Hz, 9-H), 7.27 (s, 4H), 7.36-7.43 (m, 3H) and 7.55-7.59 (m, 2H).

^{13}C nmr (75 MHz) δ -4.72, -4.51, -4.30, -3.95, 14.22, 18.05, 18.20, 25.97, 41.87, 46.41, 59.71, 69.32, 70.58, 116.92, 122.64, 127.11, 129.11, 129.18, 129.40, 129.88, 130.94, 132.74, 133.87, 136.62, 137.38, 159.86, and 164.52. **υmax** ($CHCl_3$, cm^{-1}) 2956, 2930, 2857, 1700, 1603, 1476, 1439, 1368, 1334, 1256, 1183, 1115, 1085, 1041, 1022, 1013, 939 and 838.

Further elution with the same solvents afforded the *E*-unsaturated phenylselenide (3.63E).(25 mg, 14 %) as a colourless oil.

^{1}H nmr (300 MHz) δ -0.15 (s, 3H), -0.09 (s, 3H), -0.01 (s, 3H), 0.00 (s, 3H),.0.79 (s, 9H), 0.87 (s, 9H), 1.30 (t, 3H), 1.35-1.39 (m, 1H, 6-H), 1.61-1.70, (m, 1H, 6-H), 2.40 (ddd, 2H, J=29.1, 15.7, 6.9 Hz, 4-H_2), 3.77 (tt, 1H, J=6.1, 6.1 Hz, 5-H), 3.93 (dt, 1H, J=6.3, 6.3 Hz, 7-H), 4.05-4.33 (m, 2H, CH_2CH$_3$), 5.63 (dd, 1H, J=15.0, 6.8, Hz, 8-H), 6.13 (dd, 1H, J=15.0, 0.9 Hz, 9-H), 6.22 (s, 1H, 2-H), 7.22-7.41 (m, 7H), and 7.58-7.63 (m, 2H). **^{13}C nmr** (75 MHz) δ -7.05, 14.37, 15.28, 17.93, 18.13, 25.81, 25.91, 45.45, 46.44, 60.19, 65.85, 67.99, 70.13, 102.66, 103.29, 116.79, 122.41, 128.09, 129.18, 129.26, 129.41, 131.01, 132.93, 133.67, 137.02, 137.28, 157.82 and 166.78. **υmax** ($CHCl_3$, cm^{-1}) 2929, 2852, 1684, 1585, 1472, 1174, 1110, 1095 and 837. **Mass Spec.** (F.A.B.) 763 (M+Na),

609, 439, 413, 387, 367, 339, 313, 275, 255, 235, 201, 176, 147, 105, 91, 73 (100 %) and 59.

Further elution (petrol-ether 4:1) afforded the β-ketoester (3.52) (284mg, 64 %).

REACTION OF (±)-ETHYL 3-(PHENYLSELENYL)-9-(4-CHLORO-PHENYLTHIO)-(5RS,7RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)NONA-2(E/Z),8(E)-DIENOATE (3.63) *WITH TRIBUTYLTIN HYDRIDE.*

A mixture of the *E*- and *Z*- unsaturated phenylselenides (3.63E) and (3.63Z) (150 mg, 0.20 mmol) was refluxed in benzene under nitrogen. A solution of tri-n-butyltin hydride (65 mg, 0.22 mmol) in benzene (1.0 ml) with a trace of AIBN was added dropwise during 20 min. The reaction was refluxed for a further 5 h before it was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluant : petrol-ether 30:1) to yield the *Z*-2,3-*cis*-cyclohexane (3.64), as a colourless oil (14 mg, 12 %).

^{1}H nmr (300 MHz) δ -0.07 (s, 3H), -0.02 (s, 3H), 0.05 (s, 6H), 0.79 (s, 9H), 0.88 (s, 9H), 1.24 (t, 3H), 1.67 (m, 1H, 4-H_{ax}), 1.87, (br d, 1H, J=13.6 HZ, 4-H_{eq}), 2.29-2.35 (m, 3H, 6-H_2, 2-H_{eq}), 2.94 (dd, 1H, J=12.9, 9.7 Hz, C*H*HSAr), 3.07 (dd, 1H, J=12.9, 6.5 Hz, CH*H*SAr), 4.10 (q, 2H, CH_2CH$_3$), 4.13 (m, 1H, 3-H_{ax}), 4.26 (m, 1H, $w_{1/2}$=11 Hz, 5-H_{eq}), 5.81 (s, 1H, C*H*CO$_2$Et) and 7.28 (m, 4H).

Further elution with the same solvents gave the *Z*-2,3-*trans* isomer (3.65), as a colourless oil (15mg, 13 %).

^{1}H nmr (300 MHz) δ 0.03 (s, 6H), 0.05 (s, 6H), 0.84 (s, 9H), 0.86 (s, 9H), 1.27 (t, 3H), 1.64 (ddd, 1H, J=16.9, 6.8, 3.6 Hz, 4-H_{ax}), 1.85, (ddd, 1H, J=16.6, 7.9,

3.3 Hz, 4-H_{eq}), 2.42 (m, 1H, 2-H_{eq}), 2.88-2.98 (m, 3H, 6-H_2 and C*H*HSAr), 3.21 (dd, 1H, J=13.0, 6.2 Hz, CH*H*SAr), 4.07-4.20 (m, 3H, CH_2CH$_3$ and 5-H_{ax}), 4.32 (m, 1H, $w_{1/2}$=16 Hz, 3-H_{eq}), 5.64 (s, 1H, C*H*CO_2Et) and 7.28 (s, 4H).

The *E*-2,3-*cis* isomer (3.66) was eluted next, as a colourless oil (27 mg, 23 %).
^{1}H nmr (300 MHz) δ -0.02 (s, 3H), 0.02 (s, 3H), 0.06 (s, 6H), 0.83 (s, 9H), 0.87 (s, 9H), 1.28 (t, 3H), 1.79 (m, 2H, $w_{1/2}$=15 Hz, 4-H_2), 2.32 (dt, 1H, J=7.8, 4.5 Hz, 2-H_{ax}), 2.44 (dd, 1H, J=13.0, 8.8 Hz, 6-H_{ax}), 2.98 (dd, 1H, J=13.3, 7.8 Hz, C*H*HSAr), 3.13 (dd, 1H, J=13.0, 6.8 Hz, CH*H*SAr), 3.46 (dd, 1H, J=13.5, 3.8 Hz, 6-H_{eq}), 4.08 (m, 2H, $w_{1/2}$=15 Hz, 3-H_{eq} and 5-H_{ax}), 4.15 (q, 2H, CH_2CH$_3$), 5.68 (s, 1H, C*H*CO_2Et), and 7.28 (s, 4H).

The *E*-2,3-*trans* isomer (3.67) was eluted finally, as a colourless oil (14 mg, 12 %).
^{1}H nmr (300 MHz) δ -0.01 (s, 3H), 0.05 (s, 3H), 0.06 (s, 6H), 0.84 (s, 9H), 0.89 (s, 9H), 1.21 (t, 3H), 1.68 (m, 1H, 4-H_{ax}), 1.81 (m, 1H, 4-H_{eq}), 2.38 (m, 1H, 2-H_{ax}), 2.81 (dd, 1H, J=12.9, 8.3 Hz, 6-H_{ax}), 3.02 (ABq, 2H, J=48.4, 15.2 Hz, CH_2SAr), 3.24 (dd, 1H, J=12.9, 3.2 Hz, 6-H_{eq}) 4.08 (q, 2H, CH_2CH$_3$), , 4.27 (m, 1H, $w_{1/2}$=15 Hz, 5-H_{ax}), 4.41 (m, 1H, $w_{1/2}$=15 Hz, 3-H_{eq}),5.65 (s, 1H, C*H*CO_2Et), and 7.25 (s, 4H).

A mixture of all 4 isomers was also recovered (9mg, 8 %) to give an overall cyclisation yield of 67 %.

For a mixture of all four isomers,
υ_{max} ($CHCl_3$, cm^{-1}) 2946, 2929, 2852, 1707, 1694, 1472, 1187, 1094 and 837.
Mass Spec. Calcd. for $C_{28}H_{46}ClO_4SSi_2$: 569.2332. Found 569.2344. **m/z** 569 $(M-CH_3)^+$, 527, 385, 257, 237, 225, 207, 197, 177, 165, 157, 147, 133, 105, 91, 73(100 %) and 59

(±)-ETHYL [(3RS, 5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)-2-METHYLENECYCLOHEXYLIDENE]ACETATE (3.68).

The *E*-2,3-*cis* cyclohexylidene derivative (3.66) (27mg, 0.05 mmol) was stirred in ethanol (2.0 ml) under nitrogen at room tmeperature. A solution of MMPP (80 %; 16 mg, 0.02 mmol) in water (0.5 ml) was slowly added and the mixture was stirred for 1 h. The mixture was poured into chloroform (10 ml) and washed with an aqueous solution of sodium bicarbonate (5 %; 2 x 5 ml) and dried over magnesium sulphate. Evaporation of the solvent under reduced pressure yielded the crude sulphoxides as a colourless oil. The sulphoxides were dissolved in toluene (0.2 ml) and added dropwise to refluxing toluene (5 ml) under nitrogen. The mixture was refluxed for a further 2.5 h before allowing to cool to room temperature and removal of the solvent under reduced pressure. Preparative tlc. (eluant : petrol-ether 20 : 1) afforded the known *E*-2-methylenecyclohexylidene derivative (3.68) as a colourless oil (13.3 mg, 67 %).
^{1}H nmr (300 MHz) δ 0.05 (s, 12H), 0.83 (s, 9H), 0.89 (s, 9H), 1.27 (t, 3H), 1.76 (ddd, 1H, J=12.7, 9.5, 3.3 Hz, 4-H_{ax}), 1.98 (ddd, 1H, J=12.7, 9,5, 5.2 Hz, 4-H_{eq}), 2.65 (d, 1H, J=14.9 Hz, 6-H_{ax}), 3.38 (dd, 1H, J=15.1, 6.5 Hz, 6-H_{eq}), 4.09 (q, 2H), 4.24 (m, 1H, $w_{1/2}$=15 Hz, 5-H_{ax}), 4.55 (dd, 1H, J=9.5, 4.3 Hz, 3-H_{eq}), 5.07 (dd, 2H, J=3.5, 1.8 Hz, C=CH_2), 5.90 (s, 1H, C*H*CO_2Et).

[Lit.[6] **^{1}H nmr** (300 MHz) δ 0.06 (s, 12H), 0.86 (s, 9H), 0.90 (s, 9H), 1.27 (t, 3H, J=7.2 Hz), 2.66 (br d, 1H, J=10.6 Hz), 3.36 (dr dd, 1H, J=10.6, 5.4 Hz), 4.16 (q, 2H, J=7.2 Hz), 4.25 (br m, 1H), 4.58 (br m, 1H), 5.07 (br s, 2H), 5.89 (br s, 1H)].

The above procedure was repeated on the *E*-2,3-*trans* isomer (3.67) (14 mg, 0.02 mmol), but refluxing was continued for 6 h to afford the same product (3.68) (1.4 mg, 13 %) and the *Z*-isomer (3.6) (4.5 mg, 43 %).
For the *Z*-isomer (3.6),

^{1}H nmr (100 MHz) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.08 (s, 6H), 0.88 (s, 9H), 0.89 (s, 9H), 1.23 (t, 3H), 1.66 (m, 1H, 4-H_{ax}), 1.87 (ddd, 1H, J=13.3, 8.7, 4.2 Hz, 4-H_{eq}), 2.01 (m, 1H, $w_{1/2}$=30 Hz, 6-H_{ax}), 2.31 (m, 1H, 6-H_{eq}), 4.12 (q, 2H), 4.38 (m, 1H, $w_{1/2}$=10 Hz, 5-H_{ax}), 4.46 (m, 1H, $w_{1/2}$=23 Hz, 3-H_{eq}), 5.07 (s, 1H, C=C*H*H), 5.22 (s, 1H, C=CH*H*), 5.70 (d, 1H, J=2.6 Hz, C*H*CO_2Et).

[Lit.[4] **^{1}H nmr** (100 MHz) δ 0.05 (s, 6H), 0.09 (s, 6H), 0.86 (s, 9H), 0.89 (s, 9H), 1.24 (t, 3H, J=7.6 Hz), 4.10 (q, 2H, J=7.6 Hz), 4.22 (br m, 1H), 4.51 (br m, 1H), 5.02 (br s, 1H), 5.18 (br s, 1H), 5.62 (br s, 1H)].

This procedure was also repeated on both the *Z*-cyclohexylidene derivatives (3.64) (14 mg) and (3.65) (15 mg) to give the *Z*-cyclohexylidene derivative (3.68) in 60 % and 79 % respectively.

(±)-Se-*PHENYL* (E)-*7-(4-CHLOROPHENYLTHIO)-(3RS, 5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)SELENOHEPT-6-ENOATE* (3.69).

The standard procedure was followed on acid (3.51) (1.12 g, 2.1 mmol) to yield the title selenoester (3.69) as a colourless oil (1.02 g, 72 %).

^{1}H nmr (300 MHz) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 6H), 0.88 (s, 18H), 1.68-1.88 (m, 2H, 4-H_2), 2.88 (dq, 2H, J=12.5, 9.8, 2-H_2), 4.25-4.33 (m, 2H, 3-H and 5-H), 5.74 (dd, 1H, J=15.9, 7.5 Hz, 6-H), 6.28 (d, 1H, J=15.8 Hz, 7-H), 7.28 (s, 4H), 7.35-7.42 (m, 3H) and 7.49-7.53 (m, 2H).

(±)-2RS-(4-CHLOROPHENYLTHIO)METHYL-(3RS,5RS)-BIS(t-BUTYL-DIMETHYLSILYLOXY)CYCLOHEXANONE (3.70) *AND (±)-2SR-(4-CHLORO-PHENYLTHIO)METHYL-(3RS,5RS)-BIS(t-BUTYLDIMETHYLSILYLOXY)-CYCLOHEXANONE* (3.71).

To a refluxing solution of selenoester (3.69).(575 mg, 0.86 mmol) in dry benzene (10 ml) under nitrogen was added a solution of tri-n-butyltin hydride (300 mg, 1.03 mmol) in benzene (2 ml) containing a trace of AIBN (ca. 5 mg) during 5 min. Reflux was continued for a further 1 h, before cooling to room temperature and evaporation of the solvents under reduced pressure. Silica gel column chromatography (eluant : petrol-ether 15 : 1) eluted the 2,3 -cis cyclohexanone (3.70) as a crystalline solid (184mg, 42 %).

^{1}H nmr (300 MHz) δ 0.04 (s, 6H), 0.06 (s, 3H), 0.10 (s, 3H), 0.84 (s, 9H), 0.86 (s, 9H) ,1.77 (ddd, 1H, J= 12.8, 10.6, 1.9 Hz,4-H_{ax}), 2.23 (m, 1H, 4-H_{eq}), 2.35 (dd, 1H, J=13.2, 10.9 Hz, 6-H_{ax}), 2.45 (dt, 1H, J=9.6, 4.1, 2-H_{ax}), 2.70 (ddd, 1H, J=13.4, 5.2, 2.0 Hz, 6-H_{eq}), 2.81 (dd, 1H, J=13.6, 9.6 Hz, C*H*HSAr), 3.39 (dd,1H, J=13.6, 4.1 Hz, CH*H*SAr), 4.28 (ddd, 1H, J=15.3, 10.2, 4.9 Hz, 5-H_{ax}), 4.51 (m, 1H, $w_{1/2}$=8.5 Hz, 3-H_{eq}) and 7.23 (s, 4H). **^{13}C nmr** (75 MHz) δ -5.24, -5.08, -4.77, -4.72, -4.71, 17.90, 25.64, 25.70, 29.31, 42.43, 51.42, 53.99, 67.14, 68.54, 129.13, 130.35, 132.09, 134.50 and 206.51. **υ_{max}** ($CHCl_3$, cm^{-1}) 2956, 2930, 2886, 2858, 1715, 1477, 1463, 1380, 1361, 1257, 1237, 1142, 1097, 1061, 1011, 966, 908, 965 and 837. **m.p.** (methanol) 70°C. **ANALYSIS** Calcd. for $C_{25}H_{43}ClO_3SSi_2$: C, 58.27 ; H, 8.41 ; Cl, 6.88 ; S, 6.22. Found: C, 58.32 ; H, 8.50 ; Cl, 6.75 ; S, 6.20 %.

Further elution with the same solvents afforded the 2,3-*trans* isomer (3.71) (237mg, 54 %), as a white crystalline solid.

^{1}H nmr (300 MHz) δ 0.04 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.85 (s, 9H), 0.90 (s,.9H) ,1.85 (ddd, 1H, J=13.2, 9.7, 2.1 Hz,4-H_{ax}), 2.15 (ddd, 1H, J=13.2, 6.9, 4.1 Hz, 4-H_{eq}), 2.39-2.52 (m, 2H, 2-H_{ax} and 6-H_{ax}), 2.67 (m, 1H, 6-H_{eq}), 3.17 (d, 1H,

J=12.3 Hz, C*H*HSAr), 3.19 (dd,1H, J=12;3, 4.9 Hz, CH*H*SAr), 4.08 (dt, 1H, J=9.7, 4.1 Hz, 3-H_{ax}), 4.32 (m, 1H, 5-H_{cq}), and 7.22 (m, 4H). **^{13}C nmr** (75 MHz) δ –5.18, –5.05, –4.77, –4.47, 17.82, 17.86, 25.54, 25.70, 28.96, 42.02, 48.93, 59.81, 66.55, 70.52, 128.80, 129.09, 131.10, 136.24 and 205.82. **υ_{max}** ($CHCl_3$, cm^{-1}) 2956, 2930, 2887, 2858, 1720, 1475, 1255, 1211, 1090, 1049, 1010, 954, 899 and 830. **m.p.** (methanol) 65°C. **ANALYSIS** Calcd. for $C_{25}H_{43}ClO_3SSi_2$: C, 58.27 ; H, 8.41 ; Cl, 6.88 ; S, 6.22. Found: C, 58.44 ; H, 8.28 ; Cl, 6.85 ; S, 6.47 %.

3,3-ETHYLENEDIOXY-2-METHYLENECYCLOHEXANONE (4.7).

To a stirred solution of the 2-phenylthiomethylcyclohexanone[7] (4.6) (115 mg, 0.41 mmol) in ethanol (5 ml) at room temperature under nitrogen, was added a solution of MMPP (80 %; 123 mg, 0.25 mmol) in water (1.5 ml), dropwise during 20 min. The reaction was stirred for a further 30 min before the mixture was poured into chloroform (25 ml). The mixture was washed with an aqueous solution of sodium bicarbonate (5 %; 2 x 15 ml) and saturated sodium chloride solution (15 ml) before drying over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure yielded the crude sulphoxides as a colourless oil (139 mg). This crude mixture of sulphoxides was dissolved in toluene (0.5ml) and slowly added to refluxing toluene (10 ml) under nitrogen. Refluxing was continued for 1 h before cooling to room temperature and evaporation of the toluene under reduced pressure. The residue was purified by silica column chromatography (eluant : petrol-ether 2:1) to afford the title α-methylene compound (4.7) as a colourless oil (56 mg, 81 %). **^{1}H nmr** (200 MHz) δ 1.92-2.03 (m, 4H), 2.46 (t, 2H, J=5.8 Hz), 3.88-4.04 (m, 4H), 5.56 (d, 1H, J=1.9 Hz), and 5.89 (d, 1H, J=1.9 Hz). **^{13}C nmr** (50 MHz) δ 18.20, 34.41, 34.69, 64.67, 108.09, 119.42, 147.37 and 200.56. **υ_{max}** ($CHCl_3$, cm^{-1}) 2982, 2950, 2875, 1692, 1627, 1460, 1439, 1386, 1352, 1323, 1295, 1250, 1174, 1111, 1078 and 938. **Mass Spec. m/z** 168, 131, 112, 99 (100 %), 86, 79, 55.

3,3-ETHYLENEDIOXY-2-(PHENYLSELENENYL)METHYLCYCLOHEXANONE (4.4)

To a stirred solution of diphenyl diselenide (100 mg, 0.32 mmol) in dry THF (3.0 ml) under nitrogen at room temperature was added sodium borohydride (24 mg, 0.64 mmol). Ethanol (0.15 ml) was added dropwise and the mixture was stirred for 5

min before a solution of the α-methylenecyclohexanone (4.7) (55 mg, 0.33 mmol) in THF (0.5 ml) was added. Stirring was continued for 18 h. The reaction mixture was poured into ether (50 ml) and washed with water (2 x 15 ml) and saturated sodium chloride solution (15 ml) before drying over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure and silica gel column chromatography (eluant : petrol-ether 3:2) afforded the crude product. Recrystallisation from petrol-ether afforded the title compound (4.4) as a white crystalline solid (26 mg, 25 %).

^{1}H nmr (200 MHz) δ 1.64-2.05 (m, 4H), 2.30 (dt, 1H, J=11.5, 6.4), 2.47 (dt, 1H, J=11.5, 3.3 Hz), 3.02 (dd, 1H, J=10.2, 7.9 Hz, C*H*HSePh), 3.14 (dd, 1H, J=10.2, 2.7 Hz, CH*H*SePh), 3.23 (dd, 1H, J=7.9, 2.7 Hz, 6-H), 3.88-4.12 (m, 4H) and 7.14-7.51 (m, 5H). **^{13}C nmr** (50 MHz) δ 19.99, 34.04, 40.19, 61.39, 65.16, 65.38, 112.14, 126.43, 128.96, 131.77 and 206.07 **υ_{max}** ($CHCl_3$, cm^{-1}) 3045, 2994, 2952, 2990, 1716, 1511, 1475, 1438, 1344, 1151, 1063, 1042, 1016 and 943. **mp.** 62 °C.

REACTION OF 3,3-ETHYLENEDIOXY-2-(PHENYLSELENENYL)METHYL-CYCLOHEXANONE WITH TRI- n-BUTYLTIN HYDRIDE

To a refluxing solution of alkyl selenide (4.4) (5.0 mg, 0.015 mmol.) in dry benzene (1.0 ml) under nitrogen was added a solution of tri-n-butyltin hydride (5.2 mg, 0.018 mmol.), in benzene (0.5 ml), containing a trace of AIBN, over 15 min. Refluxing was continued for a further 2h before cooling to room temperature and evaporating off the solvent under reduced pressure. The proton nmr spectrum (400 MHz) of the crude reaction mixture showed only the cyclohexanone derivative (4.8) as the reaction product. Neither the product from ring expansion, cycloheptanone (4.3) nor the product from ring opening, aldehyde (4.2) were detected.

The reaction was repeated with the addition of the stannane solution over 24h. Similarly, only the cyclohexanone (4.8) was detected in the crude reaction mixture.

Finally, a third reaction was performed. A solution of alkyl selenide (4.4) (5.0 mg, 0.015 mmol.) in dry benzene (1.0 ml) was added to a refluxing solution of tri-n-butyltin hydride (5.2 mg, 0.018 mmol.), in benzene (2.0 ml), containing a trace of AIBN, over 15 min. The crude reaction mixture from this inverse addition also indicated that cyclohexanone (4.8) was the only reaction product.

1,1;3,3-BIS(ETHYLENEDIOXY)-2-METHYLCYCLOHEXANE

2-Methyl-1,3-cyclohexanedione (500 mg, 4.0 mmol), ethylene glycol (984 mg, 16 mmol) and camphor-10-sulphonic acid (46 mg, 0.02 mmol) were refluxed in benzene under azeotropic conditions for 2.5 h. The mixture was cooled to room temperature and the solvent evaporated off under reduced pressure. The residue was dissolved in ether (100 ml) and washed with water (2 x 25 ml) and saturated sodium chloride solution (25 ml) before drying over magnesium sulphate. The solvent was evaporated under reduced pressure to yield the diketal as a colourless oil (542 mg, 64 %).

^{1}H nmr (200 MHz) δ 0.86 (d, 3H, J=6.7 Hz, C*H*$_3$), 1.20-1.38 (m, 2H), 1.40-1.58 (m, 2H), 1.62-1.75 (m, 2H), 2.00 (q, 1H, J=6.7 Hz, 2-H) and 3.74-3.99 (m, 8H). **^{13}C nmr** (50 MHz) δ 6.36, 19.32, 46.82, 64.39, 65.48 and 110.76. **υmax** (film, cm^{-1}) 2945, 2882, 1341, 1267, 1185, 1068, 1030, 949, 926, 903, 845 and 672.

3,3-ETHYLENEDIOXY-2-METHYLCYCLOHEXANONE

The diketal of 2-methyl-1,3-cyclohexanedione (400 mg, 1.9 mmol) was stirred in dichloromethane at room temperature. Silica gel (800 mg) and dilute sulphuric acid

(15 %; 0.1 ml) were added and the mixture was stirred for 2.5 h. The mixture was filtered and the resultant solution was washed with saturated sodium bicarbonate solution (20 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure and silica gel column chromatography (eluant : petrol-ether 1:1) yielded the title monoketal as a colourless liquid (228 mg, 72 %).
^{1}H nmr (400 MHz) δ 1.01 (d, 3H, J=6.7 Hz), 1.66-1.87 (m, 3H, 4-H_{ax} and 5-H_2), 1.95 (dt, 1H, J=11.7, 4.1 Hz, 4-H_{eq}), 2.24 (dt, 1H, J=11.0, 5.5 Hz, 6-H_{ax}), 2.39 (dt, 1H, J=11.0, 4.3 Hz, 6-H_{eq}), 2.70 (q, 1H, J=6.7 Hz, 2-H) and 3.87-3.97 (m, 4H). **^{13}C nmr** (100 MHz) δ 9.72, 20.03, 33.98, 39.83, 54.50, 65.27, 65.63, 112.01 and 209.00 **υ_{max}** (film, cm^{-1}) 2946, 2884, 1714, 1453, 1340, 1280, 1224, 1174, 1071, 1031, 1010, 950, 922 and 844.

3,3-DIMETHYL-1-(TRIMETHYLSILYLOXY)CYCLOHEX-1-ENE (4.11).

Copper (I) bromide-dimethyl sulphide complex (3.73 g, 18.2 mmol), was stirred in dry ether (50 ml) under nitrogen at 0°C. A solution of methyllithium in hexanes (1.4 M; 23.3 ml, 32.6 mmol) was slowly added and the resultant clear solution was stirred at 0 °C for 5 min before a solution of 3-methylcyclohex-2-enone (1.00 g, 9.1 mmol) and trimethylsilyl chloride (2.96 g, 27.2 mmol) in ether (10 ml) was added dropwise. The now yellow mixture was stirred for 15 min before triethylamine (3.8 ml) and HMPA (1.9 ml) were added sequentially. Stirring was continued at 0 °C for a further 1 h and then at at room temperature for 1 h. The mixture was poured into hexanes (100 ml) and quickly washed with dilute HCl (1 M; 2 x 25 ml) and saturated sodium bicarbonate (2 x 25 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure yielded the title silyl enol-ether (4.11) as a colourless oil (1.74 g, 99 %). This was used without any further purification.
^{1}H nmr (300 MHz) δ 0.20 (s, 9H), 1.00 (s, 6H, 2 x CH_3), 1.30-1.38 (m, 2H), 1.67 (m, 2H), 1.94 (t, 2H, J=4.4 Hz, 6-H_2) and 4.63 (s, 1H, 2-H). **υ_{max}** (film, cm^{-1})

3014, 2957, 2865, 1662, 1455, 1364, 1252, 1214, 1186, 1143, 1060, 1036, 992, 965, 884, 843 and 754.

[**Lit.**[8] (200 MHz) δ 0.16 (s, 9H), 0.96 (s, 6H), 1.32 (m, 2H), 1.66 (m, 2H), 1.92 (t, 2H, J=6.25 Hz) and 4.63 (s, 1H). υ_{max} (film, cm^{-1}) 3010, 2950, 2930, 2860, 1660, 1465, 1450, 1430, 1385, 1365, 1340, 1260, 1250, 1210, 1185, 1140, 1060, 990, 965, 890, 880, 840 and 750].

5,5-DIMETHYL-6-OXOHEXANOIC ACID (4.12)

A solution of the silyl enol-ether (4.11) (1.87 g, 9.7 mmol) at -78°C in a 1:1 mixture of dichloromethane and methanol (20 ml) was saturated with ozone. The reaction was then quenched with dimethyl sulphide (1 ml) and allowed to warm to room temperature and the solvents were evaporated under reduced pressure. The residue was dissolved in hexane (30 ml) and extracted with saturated sodium bicarbonate solution (4 x 10 ml). The combined bicarbonate extracts were carefully acidified with dilute HCl and extracted with ether (4 x 25 ml). The combined ether extracts were washed with saturated sodium chloride solution (25 ml) and dried over magnesium sulphate. Filtration and evaporation yielded the crude aldehydo-acid (4.12) as a colourless oil (627 mg, 44 %).

^{1}H nmr (300 MHz) δ 0.85 (s, 6H), 1.49-1.57 (m, 4H), 2.32 (t, 2H, J=6.9 Hz) and 9.42 (s, 1H). **^{13}C nmr** (75 MHz) δ 19.40, 21.12, 34.16, 36.18, 45.60, 179.09 and 206.01. υ_{max} (film, cm^{-1}) 3088, 2962, 2665, 1720, 1415, 1283, 1136, 1067, 1004 and 913.

5,5-DIMETHYLHEPT-6-ENOIC ACID (4.13)

Sodium hydride (80 %; 569 mg, 19 mmol) was heated in dry DMSO (40 ml) for 40 min at 70°C under nitrogen. The mixture was cooled to room temperature and methylenetriphenylphosphonium bromide (3.39 g, 9.5 mmol) was added. Stirring was continued for a further 30 min before a solution of the aldehydo-acid (4.12) (600 mg, 3.8 mmol) in DMSO (10 ml) was slowly added. After a further 2 h stirring, the red solution was poured into a 1:2 mixture of petrol and water (150 ml) and the aqueous layer was separated and acidified with dilute HCl. The acidic mixture was extracted with ether (4 x 25 ml) and the combined ether fractions were washed with brine (30 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure and silica gel column chromatography (eluant : petrol-ether 5:1) afforded the unsaturated acid (4.13) as a colourless oil (110 mg, 19 %).

^{1}H nmr (300 MHz) δ 0.98 (s, 6H), 1.25-1.32 (m,2H), 1.51-1.57 (m, 2H), 2.29 (t, 2H, J=7.5 Hz), 4.78-4.93 (m, 2H, CH=CH_2) and 5.73 (ddd, 1H, J=16.4, 10.0, 1.8 Hz, CH=CH_2). **^{13}C nmr** (75 MHz) δ 14.92, 26.52, 34.56, 36.37, 41.88, 58.12, 110.56, 147.87 and 179.43. **υ_{max}** (film, cm^{-1}) 3086, 2960, 2681, 1712, 1639, 1462, 1414, 1381, 1364, 1281, 1235, 1216, 1137, 1067, 1002 and 912. **Mass Spec. m/z** 156 (M^+), 110, 95, 83, 81, 69, 60, 55 (100 %).

Se-*PHENYL 5,5-DIMETHYLSELENOHEPT-6-ENOATE* (4.9)

The standard method for preparing selenoesters was repeated on the unsaturated acid (4.13) (80 mg, 0.51 mmol) to give the title selenoester (4.9) as a colourless oil (114 mg, 76 %).

^{1}H nmr (300 MHz) δ 1.00 (s, 6H), 1.30-1.36 (m, 2H), 1.58-1.66 (m, 2H), 2.68 (t, 2H, J=7.3 Hz), 4.84-4.95 (m, 2H, CH=CH_2), 5.75 (dd, 1H, J=17.2, 11.0 Hz, CH=CH_2) and 7.37-7.39 (m, 3H), 7.50-7.54 (m, 2H). **^{13}C nmr** (75 MHz) δ 20.68,

26.56, 36.45, 41.61, 110.76, 126.50, 128.72, 129.24, 135.72, 147.72 and 200.16. υ_{max} (film, cm^{-1}) 3079, 2959, 2882, 2868, 1726, 1640, 1580, 1478, 1439, 1413, 1381, 1364, 1147, 1067, 1000, 912, 738, 689 and 672. **Mass Spec.** Calcd for $C_{15}H_{20}OSe$ 296.0679 : Found: 296.0686. **m/z** 296 (M^+),157, 139 (100 %), 121, 95, 83, 69.

REACTION OF Se-*PHENYL 5,5-DIMETHYLSELENOHEPT-6-ENOATE* (4.9) *WITH TRI-n-BUTYLTIN HYDRIDE.*

To a refluxing solution of selenoester (4.10) (50 mg, 0.17 mmol), in dry benzene (5.0 ml) under nitrogen was added a solution of tri-n-butyltin hydride (59 mg, 0.20 mmol) in benzene (1.0 ml) containing a trace of AIBN (ca. 1 mg), during 15 min. After refluxing for a further 1 h, all the starting material had been consumed (tlc. control). The reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluant : petrol-ether 10:1) to yield 2,3,3-trimethylcyclohexanone (4.14) (5 mg, 20 %) as a colourless oil.
^{1}H nmr (300 MHz) δ 0.76 (s, 3H), 0.96 (d, 3H ,J=7.2 Hz). 1.04 (s, 3H), 1.57-1.69 (m, 3H), 1.76-1.97 (m, 2H) and 2.19-2.40 (m, 2H). **^{13}C nmr** (75 MHz) δ 9.57, 14.22, 20.84, 22.62, 29.56, 39.57, 40.83 and 54.56 υ_{max} ($CHCl_3$, cm^{-1}) 2968, 2874, 1701, 1457, 1082 and 938.

[Lit [9] **^{1}H nmr** (60 MHz, CCl_4) δ 0.73 (s, 3H), 0.87 (s, 3H), 0.87 (d, 3H, J=7 Hz), 1.03 (s, 3H) and 1.45-2.50 (m, 7H). υ_{max} (film, cm^{-1}) 1705, 1445, 1080 and 935]

Further elution with the same solvent system yielded 4,4-dimethylcycloheptanone (4.15) as a colourless oil (7 mg, 30 %).

^{1}H nmr (300 MHz) δ 0.95 (s, 6H), 1.24-1.71 (m, 6H) and 2.45 (dt, 4H, J=6.2, and 2.9 Hz). **^{13}C nmr** (75 MHz) δ 19.82, 28.68, 33.27, 36.21, 39.35, 43.19 and 43.73. υ_{max} ($CHCl_3$, cm^{-1}) 2967, 2929, 2855, 1709, 1602, 1462, 1161 and 962.

[Lit.[10] **^{1}H nmr** (60 MHz) δ 0.9 (s), 1.3-1.7 (m), 2.1-2.5 (m). **^{13}C nmr** δ 19.0 (C_6), 27.7 (2 x CH_3), 32.4 (C_4), 35.4 (C_3), 38.2 (C_2), 42.5 (C_5), 42.5 (C_7), and 210.9 (C_1). (Originally quoted for CS_2 as internal reference, converted to TMS using CS_2 as δ 192.3)]

ETHYL 6-OXOHEX-4-ENOATE (4.18)

Ethyl 4-oxobutyrate[11] (4.19) (15.10 g, 116 mmol) and (triphenylphosphoranylidene)acetaldehyde (40.00 g, 128 mmol) were refluxed in dry benzene (500 ml) under nitrogen for 18 h. The mixture was cooled and the solvent evaporated under reduced pressure. The product was extracted with ether (6 x 25 ml) and the combined ether fractions were evaporated under reduced pressure to yield a pale green oil that on distillation gave the unsaturated aldehyde (4.18) as a colourless liquid (11.14 g, 61 %). bp 120°C/20 mmHg

^{1}H nmr (200 MHz) δ 1.30 (t, 3H, J=7.2 Hz), 2.3-3.0 (m, 4H), 4.19 (q, 2H, J=7.2 Hz), 6.18 (dd, 1H, J=15.4, 7.1 Hz), 6.91 (dt, 1H, J=15.3, 7.8 Hz) and 9.56 (d, 1H, J=7.6 Hz)

[Lit.[12] **^{1}H nmr** (60 MHz) δ 1.30 (t, 3H, J=7 Hz), 2.3-3.0 (m, 4H), 4.20 (q, 2H, J=7 Hz), 6.18 (dd, 1H, J= 15, 7 Hz) and 6.93 (dt, 1H, J=15, 8 Hz)].

(+)-2,3-(DI-O-ISOPROPYLIDENE) -L-ERYTHROSE (4.25)

The erythrose derivative (4.25) was prepared by the method of Baxter[13] in 2 steps from L- rhamnose, with an overall yield of 71 %.

^{1}H nmr (200 MHz) δ 1.33 (s, 3H), 1.48 (s, 3H), 2.95 (br s, 1H), 3.87-4.15 (m, 2H), 4.58 (d, 1H, J=6.0 Hz), 4.80-4.89 (m, 1H) and 5.43 (s,1H). **υ_{max}** ($CHCl_3$ cm^{-1}) 3418, 2983, 2943, 1374, 1210, 1162, 1100, 1069, 986, 875 and 857.

(-)-2,3-(DI-O-ISOPROPYLIDENE)-1,2S,3R-TRIHYDROXYPENT-4-ENE (4.24)

To a slurry of methyl triphenylphosphonium bromide (3.21 g, 9.0 mmol) in dry THF (15 ml) at -20°C under nitrogen was added n-butyllithium (2.27 M; 3.86 ml, 8.8 mmol). The resulting yellow slurry was allowed to warm up to 0°C, until all the solid had dissolved. The solution was recooled to -20°C and a solution of L-erythrose (4.25) (0.72 g, 4.5 mmol) in THF (5 ml), was added dropwise. The reaction was stirred successively at -20°C for 30 min, room temperature for 60 min, and at reflux for 45 min. After cooling to room temperature, acetone (50 ml) was added and the mixture stirred for 5 min before being poured into ether (200 ml). The resulting mixture was filtered through celite and the clear solution was washed with saturated aqueous sodium bicarbonate solution (2 x 100 ml), water (2 x 100 ml), saturated sodium chloride solution (100 ml) and dried over magnesium sulphate. Filtration and evaporation of solvents under reduced pressure yielded a near colourless oil. Chromatography on silica gel (eluant : ether-petrol 3:1) gave the title compound (4.24) as a colourless liquid (0.35 g, 49 %).

^{1}H nmr (200 MHz) δ 1.34 (s, 3H), 1.46 (s, 3H), 2.41 (t, 1H, J=6.0 Hz, O*H*), 3.53 (t, 2H, J=6.0 Hz, 1-H_2), 4.24 (dt, 1H, J=7.1, 6.0 Hz, 2-H), 4.60 (dt, 1H, J=7.1, 0.9 Hz, 3-H), 5.22-5.44 (m, 2H, 5-H_2) and 5.81 (ddd, 1H, J=17.4, 10.1, 7.1 Hz, 4-H). **^{13}C nmr** (100 MHz) δ 25.19, 27.73, 61.97, 78.28, 78.42, 108.82,

118.44 and 133.23. υ_{max} (film, cm^{-1}) 3434, 2984, 2933, 2878, 1642, 1379, 1248, 1216, 1166, 1050, 926 and 878. **Mass Spec.** Calcd. for $C_7H_{11}O_2$: 127.0759. Found : 127.0757. **m/z** 143 (M^+), 127 $(M-CH_2OH)^+$, 113, 98, 83, 69, 59, 55, 43 (100%) and 31: $[\alpha]_D^{23}$ -36.5° [c=2, $CHCl_3$]

1-IODO-2,3-(DI-Q-ISOPROPYLIDENE)-2S,3S-DIHYDROXYPENT-4-ENE (4.26)

The hydroxyolefin (4.24) (0.23 g, 8.1 mmol) and triiodoimidazole (1.80 g, 4.0 mmol) were refluxed in toluene (20 ml) for 5 h under nitrogen. The cooled reaction was poured into a mixture of toluene (50 ml) and saturated aqueous sodium bicarbonate solution (200 ml) and shaken for 10 min before separating the aqueous phase. The aqueous phase was extracted further with toluene (2 x 25 ml). The combined toluene layers were washed with aqueous sodium thiosulphate solution (2 x 50 ml), saturated sodium bicarbonate solution (50 ml), saturated sodium chloride solution and dried over magnesium sulphate. Filtration and evaporation of solvents gave a yellow liquid which, on silica gel column chromatography (eluant : petrol-ether 10 :1), gave the title iodide (4.26) as a colourless liquid (0.21 g, 39 %).

^{1}H nmr (60 MHz) δ 1.40 (s, 3H), 1.52 (s, 3H), 3.09 (d, J=6 Hz), 4.24-4.73 (m, 2H), 5.16-5.94 (m, 3H).

1-IODO-2,3-(DI-Q-ISOPROPYLIDENE)-2,3-DIHYDROXYPROPANE (4.30)

A mixture of Solketal (3.00 g, 82.7 mmol), iodine (5.76 g, 45.4 mmol), imidazole (3.86 g, 56.7 mmol) and triphenylphosphine (14.88 g, 56.7 mmol) were refluxed in toluene (250 ml) for 2.5 h. The reaction mixture was cooled to room temperature and poured into a stirred, saturated solution of sodium hydrogen carbonate solution (250 ml). After stirring for a further 5 min, iodine was added portionwise until the toluene phase had a permanent colouration. A saturated solution of sodium

thiosulphate was added dropwise until the toluene phase was colourless. The mixture was diluted with toluene (250 ml) and the aqueous phase separated. The toluene layer was washed with water (2 x 100 ml) and dried over magnesium sulphate. Filtration and purification by silica gel column chromatography gave the title compound (4.30) as a colourless liquid (1.84 g, 34 %).

^{1}H nmr (60 MHz) δ 1.35 (s, 3H), 1.44 (s, 3H), 3.08-3.22 (m, 2H), 3.62-3.94 (m, 1H), 3.98-4.38 (m, 2H).

[**Lit** [14] **^{1}H nmr** (60 MHz) δ 1.38 (s, 3H), 1.48 (s, 3H), 3.1-3.4 (m, 2H), 3.7-4.7 (m, 3H).

This compound was also prepared following Jung's procedure[12], via the tosylate (4.31), to yield the title compound (4.30) in a 39 % overall yield.

1,2-(DI-Q-ISOPROPYLIDENE)-1,2R-DIHYDROXY-3-OXO-5-METHYLTHIO-PENTANE (4.40)

Dry dichloromethane (3 ml) and oxalyl chloride (221 mg, 1.74 mmol) were stirred under nitrogen at -78 °C. Dimethyl sulphoxide (309 mg, 3.95 mmol) in dichloromethane (1 ml) was added dropwise and the reaction stirred for 10 min before the hydroxyolefin (4.24) (250 mg, 1.58 mmol) in dichloromethane (1 ml) was slowly added. After 15 min triethylamine (800 mg, 7.90 mmol) was added and the mixture allowed to warm up to room temperature before pouring into water (20 ml). The aqueous layer was separated and extracted further with dichloromethane (2 x 10 ml). The combined organic layers were washed successively with dilute hydrochloric acid (2 M; 10 ml), water (10 ml), saturated sodium bicarbonate solution (10 ml), saturated sodium chloride solution (10 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent gave a brown liquid which on purification by silica gel

column chromatography (eluant : petrol-ether 2:1) gave the title compound (4.40) as a pale green liquid (108 mg, 33%).

^{1}H nmr (200 MHz) δ 1.40 (s, 3H), 1.50 (s, 3H), 2.12 (s, 3H, SCH_3), 2.72 (dd, 2H, J=13.0, 6.5, 4-H_2), 2.95 (dd, 2H, 13.4, 6.5, 5-H_2), 4.02 (dd, 1H, J=5.4, 3.2 Hz, 1-H), 4.21 (t, 1H, J=5.4 Hz, 2-H) and 4.46 (dd, 1H, J=5.4, 3.2 Hz, 1-H). **^{13}C nmr** (100 MHz) δ 15.75, 24.90, 26.05, 27.31, 38.49, 66.40, 80.21, 111.02 and 209.29. **υ_{max}** ($CHCl_3$, cm^{-1}) 2980, 2918, 1716, 1374, 1191, 1150, 1069 and 841. **Mass Spec.(F.A.B.)** 227 (M+Na), 204 (M^+), 149, 107, 101, 91, 86, 76, 69, 56, 52 and 44.

2,3-(DI-Q-ISOPROPYLIDENE)-2S,3S-PENT-4-ENAL (4.39)

To a stirred solution of the hydroxyolefin (4.24) (100 mg, 0.33 mmol) in benzene (10 ml), at room temperature under nitrogen, was sequentially added DMSO (10 ml), pyridine (50 mg, 0.63 mmol) , trifluoroacetic acid (36 mg, 0.32 mmol) and DCC (391 mg, 1.90 mmol). The mixture was stirred for 2 h before further benzene (10 ml) was added, and the precipitate filtered through celite. The resultant clear solution was washed with water (3 x 15 ml), saturated sodium chloride solution (15 ml) and dried over magnesium sulphate. Filtration and evaporation of solvents under reduced pressure gave an unstable off-white solid that was identified as the title compound (4.39) (60 mg, 62 %).

^{1}H nmr (60 MHz) δ 1.48 (s, 3H), 1.62 (s, 3H), 4.26-4.95 (m, 2H), 5.15-5.80 (m, 3H) and 9.44 (d, 1H, J=3.6 Hz).

ETHYL (3,4-[DI-Q-ISOPROPYLIDENE]-3S,4S-DIHYDROXYTETRAHYDRO-FURAN-2-YL)ACETATE (4.43)

Potassium hydride (35 wt%; 1.07 g, 9.4 mmol), after being stripped of oil, was stirred in dry THF (20 ml) at room temperature under nitrogen. Triethyl phosphonoacetate (2.30 g, 10.6 mmol) was added dropwise and stirred for 30 min before the L-erythrose derivative (4.25) (1.00 g, 6.2 mmol) in THF (10 ml) was added. The reaction mixture was refluxed for 1 h and allowed to cool before being poured into a mixture of water (50 ml) and ether (50 ml). The aqueous layer was separated and extracted further with ether (2 x 25 ml). The combined ether extracts were washed with water (20 ml), saturated sodium chloride solution (20 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure yielded a colourless oil. Chromatography on silica gel (eluant : ether-petrol 2:1) gave the title compound (4.43), a colourless liquid, as a mixture of anomers in a ratio of 1.4:1 (1.24 g, 86 %)

For the 2S isomer (4.45)

^{1}H nmr (200 MHz) δ 1.28 (t,3H, J=7.2 Hz, OCH_2CH_3), 1.33 (s, 3H), 1.48 (s, 3H), 2.79 (d, 2H, J=6.7 Hz, CH_2CO_2Et), 3.49 (dd, 1H, J=9.8, 6.3 Hz, 5-H), 3.78-3.89 (m, 1H, 2-H), 4.02 (d, 1H, J=9.8 Hz, 5-H), 4.18 (q, 2H, J=7.2 Hz, OCH_2CH_3) and 4.64-4.81 (m, 2H, 3-H and 4-H).

Salient features of the spectrum for 2R-isomer from a mixture with the 2S-isomer

^{1}H nmr (200 MHz) δ 1.45 (s, 3H), 1.51 (s, 3H), 2.48 (d, 2H, J=7.1 Hz), 4.18 (q, 2H, J=7.2 Hz), 4.46 (dd, J=3.8, 3.8 Hz, 4-H) and 4.58 (d, 1H, J=6.2 Hz, 3-H).

For the mixture (4.43)

υ_{max} (film, cm^{-1}) 2981, 2934, 2859, 1735, 1455, 1381, 1333, 1304, 1269, 1208, 1182, 1165, 1059, 1028 and 820. **Mass Spec.** Calcd. for $C_{10}H_{15}O_5$: 215.0937. Found: 215.0925. **m/z** 215 $(M-CH_3)^+$, 185, 155, 127, 85, 81, 71, 59, 55, 43(100%) and 30.

(+)-ETHYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S,6-TRIHYDROXYHEXANOATE (4.44)

To a stirred solution of the mixture of the isopropylidene tetrahydrofuran derivatives (4.43) (250 mg, 1.1 mmol) in ethanol (20 ml) was added an ethanolic solution of sodium ethoxide (1 M; 0.11 ml, 0.11 mmol). After 5 min, palladium on activated charcoal (5 wt%; 25 mg) was added and the reaction maintained under a positive pressure of hydrogen (balloon) for 7 days. The catalyst was removed through celite and the solvent was evaporated under reduced pressure to yield a pale green oil. Purification by silica gel column chromatography (eluant : ether-petrol 2:1) initially gave a less polar product , the 2S-anomer of the starting material (4.47) (32 mg, 15 %), and the required product (4.45) as a more polar , colourless liquid (94 mg, 36%), identical with the product prepared below.

(-)-ETHYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S,6-TRIHYDROXYHEX-2Z-ENOATE (4.46) *AND (-)-ETHYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S,6-TRIHYDROXYHEX-2E-ENOATE* (4.47)

L-Isopropylidene erythrose (4.25) (1.11 g, 6.9 mmol), carbethoxymethylene-triphenylphosphorane (2.90 g, 8.32 mmol) and benzoic acid (0.04 g, 0.4 mmol) were refluxed in dry benzene (80 ml) under nitrogen for 4 h. The mixture was allowed to

cool to room temperature before the solvent was evaporated under reduced pressure, to yield an off-white solid. The product was extracted by washing the solid with small aliquots of cold ether (5 x 10 ml.). The combined ether extracts were evaporated *in vacuo* to give the crude product as a green oil . Chromatography on silica gel (eluant : ether-petrol 2:1) gave the Z isomer (4.46) as a colourless oil (0.61 g, 38 %).

^{1}H nmr (200 MHz) δ 1.30 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.41 (s, 3H), 1.54 (s,3H), 2.26 (br t, 1H, J=5.6 Hz, O*H*), 3.38-3.66 (m, 2H, 6-H_2), 4.18 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.58 (q, 1H, J=2.3 Hz, 5-H), 5.60 (dd, 1H, J=6.2, 2.3 Hz, 4-H), 5.94 (dd, 1H, J=9.7, 1.8 Hz, 2-H) and 6.39 (dd, 1H, J=9.7, 6.2 Hz, 3-H). **^{13}C nmr** (100 MHz) δ 14.14, 24.76, 27.41, 60.53, 61.55, 74.81, 78.92, 108.88, 121.12, 147.00 and 165.91. **υ_{max}** (film, cm^{-1}) 3479, 2983, 2935, 2875, 1709, 1644, 1454, 1413, 1381, 857 and 825. **Mass Spec.** Calc. for $C_{10}H_{15}O_5$: 215.0920. Found: 215.0936.

m/z 215 $(M-CH_3)^+$, 169, 155, 141, 127, 112, 97, 84, 69, 59, 55, 43(100%) and 39. **Analysis** Calcd. for $C_{11}H_{18}O_5$: C, 57.38 ; H, 7.88 %. Found: C, 57.29 ; H, 7.73 %. $[\alpha]_D^{23}$ -111.3°[c=1.5, EtOH].

Further elution with the same solvents gave the E-isomer (4.47) as a colourless oil (0.82 g, 51 %).

^{1}H nmr (200 MHz) δ 1.30 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.40 (s, 3H), 1.53 (s, 3H), 2.56 (br s, 1H, O*H*), 3.57 (br d, 2H, J=5.(Hz, 6-H_2), 4.21 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.38 (q 1H, J=5.5 Hz, 5-H), 4.82 (t, J=5.5 Hz, 4-H), 6.14 (dd, 1H, J=15.6, 1.6 Hz, 2-H) and 6.91 (dd, 1H, J=15.6, 5.5 Hz, 3-H). **υ_{max}** (film, cm^{-1}) 3473, 2983, 2934, 1716, 1657, 1370, 1305, 1258, 1216, 1179, 1164, 1046, 985, 878 and 859 **Mass Spec.** Calcd. for $C_{10}H_{17}O_5$: 215.0920. Found: 215.0941.

m/z 215 $(M-CH_3)^+$, 127, 112, 99, 84, 69, 59, 55 and 43 (100 %). **Analysis** Calcd. for $C_{11}H_{18}O_5$ C, 57.38 ; H, 7.88. Found: C, 57.64 ; H, 8.10 %. $[\alpha]_D^{22}$ -6.6° [c=1.7, EtOH].

(+)-ETHYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S,6-TRIHYDROXY-HEXANOATE (4.44)

A mixture of the unsaturated hydroxyesters (4.46) and (4.47) (450 mg, 1.95 mmol) was stirred in ethanol (25 ml) with palladium on activated charcoal (5 wt%; 40 mg) under a positive atmosphere of hydrogen (balloon) for 2 h. The catalyst was removed by filtration through celite and the solvent evaporated under reduced pressure. Chromatography on silica gel (eluant : ether-petrol 4:1) gave the saturated hydroxy-ester (4.44) as a colourless liquid (410 mg, 91 %).
^{1}H nmr (200 MHz) δ 1.26 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.35 (s, 3H), 1.46 (s, 3H), 1.74-1.89 (m, 2H, 3-H_2), 2.30-2.65 (m,3H, 2-H_2 and O*H*), 3.66 (br d, 2H, J=4.8 Hz, 6-H_2) and 4.07-4.16 (m, 4H, OCH_2CH_3, 4-H and 5-H). **^{13}C nmr** (100 MHz) δ 13.88, 24.42, 25.17, 27.81, 30.79, 60.14, 60.96, 75.72, 77.59, 107.90 and 173.05. **υ_{max}** ($CHCl_3$, cm^{-1}) 3577, 2984, 2933, 2907, 1723, 1453, 1444, 1372, 1266, 1256, 1187, 1173, 1158, 1109, 1076, 1065, 1025 and 860. **Mass Spec.** Calcd. for $C_{10}H_{17}O_5$: 217.1076. Found: 217.1093. **m/z** 217 $(M-CH_3)^+$, 183, 143, 129, 123, 111, 101, 95, 85, 69, 59, 55 and 43 (100%). **Analysis** Calcd. for $C_{11}H_{20}O_5$: C, 56.88 : H, 8.68. Found: C, 56.90 ; H, 8.90. $[\alpha]_D^{22}$ +22.5° [c=2, EtOH].

ETHYL 5,6-(DI-O-ISOPROPYLIDENE)-5S,6-DIHYDROXY-4-OXOHEXANOATE (4.48)

To a stirred solution of the hydroxyester (4.44) (100 mg, 0.43 mmol) in benzene (10 ml), at room temperature under nitrogen, was sequentially added dimethyl sulphoxide (10 ml), pyridine (34 mg, 0.43 mmol), trifluoroacetic acid (25 mg, 0.22 mmol) and DCC (267 mg, 1.29 mmol). The mixture was stirred for 2 h before further benzene (10 ml) was added and the precipitate filtered through celite. The resultant

clear solution was washed with water (3 x 15 ml), saturated sodium chloride solution (15 ml) and dried over magnesium sulphate. Filtration and evaporation of solvents gave a colourless oil that on purification by silica gel column chromatography (eluant : ether-petrol 2:1) gave the title compound (4.48) as a colourless liquid (40 mg, 41 %). **^{1}H nmr** (200 MHz) δ 1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.41 (s, 3H), 1.51 (s, 3H), 2.54-2.65 (m, 2H), 2.87-2.97 (m, 2H), 4.02-4.26 (m, 4H, OCH_2CH_3 and 6-H_2) and 4.49 (dd, 1H, J=7.7, 5.7 Hz, 5-H). **υ_{max}** ($CHCl_3$, cm^{-1}) 1981, 1933,1721 , 1375, 1349, 1173, 1153, 1054 and 842. **Mass Spec.** Calcd. for $C_{10}H_{15}O_5$: 215.0937. Found: 215.0896. **m/z** 215 $(M-CH_3)^+$, 185, 129, 114, 101(100 %), 91, 85, 73, 61, 55 and 43

GENERAL METHOD FOR BUFFERED PCC OXIDATION.

ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-6-OXO-4R,5R-DIHYDROXY-HEXANOATE (4.42)

To a slurry of pyridinium chlorochromate (1.74 g, 8.1 mmol), sodium acetate (66 mg, 0.8 mmol) and powdered 4Å molecular sieves (ca. 0.75 g) stirred in dry dichloromethane (40 ml) under nitrogen at room temperature, was slowly added a solution of the hydroxyester (4.44) (750 mg, 3.23 mmol) in dichloromethane (8 ml). The mixture was stirred for 2.5 h before being filtered through silica gel, eluting with ether. Evaporation of the solvents under reduced pressure yielded the aldehyde (4.42) as a pale green oil (680 mg, 92 %). This was used for the next stage without further purification.

^{1}H nmr (200 MHz) δ 1.21 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.36 (s, 3H), 1.53 (s, 3H), 1.58-1.94 (m, 2H, 3-H_2), 2.33-2.46 (m, 2H, 2-H_2), 4.09 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.21-4.38 (m, 2H, 4-H and 5-H) and 9.63 (dd, 1H, J=2.2, 0.6 Hz,

C*H*O). υ_{max} (film, cm^{-1}) 2994, 2934, 2815, 1736, 1372, 1258, 1219, 1180, 1160, 1076 and 864.

(+)-ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-4R,5S-DIHYDROXYHEPT-6-ENOATE (4.41)

Methyl triphenylphosphonium bromide (0.84 g, 2.4 mmol) was slurried in dry THF (20 ml) at -20 °C under nitrogen. n-Butyllithium (2.33 M; 0.60 ml , 1.4 mmol) was slowly added and the yellow suspension was allowed to warm up to room temperature. After stirring at room temperature for 40 min the mixture was recooled to -20 °C and a solution of the aldehyde (4.42) (0.27 g, 1.2 mmol) in dry THF (3 ml) was slowly added. The reaction was maintained at -20 °C for 30 min before it was allowed to warm up to room temperature. The reaction was complete after 2 h (tlc control). The mixture was poured into ether (100 ml) and stirred for 5 min before filtering through celite and evaporating the solvents under reduced pressure. Purification by silica gel column chromatography (eluant : petrol-ether 2:1) gave the olefinic ester (4.41) as a colourless liquid (0.19 g, 71 %).

^{1}H nmr (200 MHz) δ 1.26 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.36 (s, 3H), 1.48 (s, 3H), 1.66-1.82 (m, 2H, 3-H_2), 2.17-2.58 (m, 2H, 2-H_2), 4.06-4.21 (m, 3H, OCH_2CH_3 and 4-H), 4.52 (t, 1H, J=6.3 Hz, 5-H), 5.11-5.42 (m, 2H, 7-H_2) and 5.72-5.94 (m, 1H, 6-H). υ_{max} (film, cm^{-1}) 2982, 2933, 2872, 1732, 1644, 1370, 1249, 1216, 1178, 1162, 1141, 1066, 1046, 1017, 930, 870 and 798. **Analysis** Calcd. for $C_{12}H_{20}O_4$: C, 63.14 ; H, 8.76. Found: C, 63.25 ; H, 8.86. $[\alpha]_D^{23}$ + 20.7° [c=1.5, EtOH]

(+)-Se-PHENYL 4,5-(DI-Q-ISOPROPYLIDENE)-4R,5S-DIHYDROXYSELENO-HEPT-6-ENOATE (4.49)

The olefinic ester (4.41) (200 mg, 0.88 mmol) was saponified under the standard conditions to yield the correponding acid as a colourless oil (151 mg, 86 %). **^{1}H nmr** (200 MHz) δ 1.34 (s, 3H), 1.45 (s, 3H), 1.66-1.78 (m, 2H, 3-H_2), 2.30-2.58 (m, 2H, 2-H_2), 4.15 (dt, 1H, J=7.8, 6.6 Hz, 4-H), 4.54 (t, 1H, J=7.8 Hz, 5-H), 5.22-5.37 (m, 2H, 7-H_2) and 5.71-5.95 (m, 1H, 6-H). **υ_{max}** (film, cm^{-1}) 3426, 2985, 2932, 2669, 1708, 1644, 1428, 1415, 1380, 1371, 1267, 1217, 1162, 1064, 933, 869 and 799. **Mass Spec.** Calcd. for $C_9H_{13}O_4$: 185.0814. Found: 185.0834. **m/z** 185 $(M-CH_3)^+$, 125, 98, 83, 69, 55 and 43 (100%). **$[\alpha]_D^{22}$** +14.2° [c=1.9, $CHCl_3$]

The standard procedure for the preparation of selenoesters was repeated on this unsaturated acid (150 mg, 0.75 mmol) to give the title selenoester (4.49) as a colourless liquid (183 mg, 72 %)

^{1}H nmr (200 MHz) δ 1.36 (s, 3H), 1.48 (s, 3H), 1.71-1.87 (m, 2H, 3-H_2), 2.69-2.99 (m, 2H, 2-H_2), 4.15 (q, 1H, J=6.3 Hz, 4-H), 4.52 (t, 1H, J=6.3 Hz, 5-H), 5.21-5.40 (m, 2H, 7-H_2), 5.71-5.82 (m, 1H, 6-H), 7.32-7.42 (m, 3H) and 7.43-7.54 (m, 2H). **υ_{max}** (film, cm^{-1}) 3072, 3056, 2982, 2930, 2872, 1722, 1644, 1475, 1436, 1379, 1369, 1246, 1216, 1164, 1112, 1051, 1020, 997, 930, 866, 740 and 690. **Mass Spec.** Calcd. for $C_{15}H_{17}O_3Se$: 325.0345. Found: 325.0312. **m/z** 325 $(M-CH_3)^+$, 283, 265, 223, 213, 195, 183, 157, 139, 125, ;107, 98, 91, 83, 79, 69, 59, 55, 51, 43 (100%) and 41. **Analysis** Calcd. for $C_{16}H_{20}O_3Se$: C, 56.64 ; H, 5.94. Found: C, 56.87 ; H, 6.15 %. **$[\alpha]_D^{24}$** +25.5° [c=2.0, $CHCl_3$]

REACTION OF (+)-Se-PHENYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S-DIHYDROXYSELENOHEPT-6-ENOATE (4.49) *WITH TRI-n-BUTYLTIN HYDRIDE*

The selenoester (4.49) (100 mg, 0.29 mmol) was refluxed in dry benzene (5 ml) under nitrogen. A solution of tri-n-butyltin hydride (94 mg, 0.32 mmol) in benzene (2 ml) with a catalytic amount of AIBN (ca. 5 mg) was added during 25 min. The mixture was refluxed for a further 1 h by when the reaction had gone to completion (tlc control). The reaction was cooled to room temperature and the solvent was evaporated under reduced pressure. Chromatography on silica gel (eluant : petrol-ether 5:1) eluted the aldehyde (4.50) as an unstable white solid (5 mg, 7 %).

^{1}H nmr (200 MHz) δ 1.53 (s, 3H), 1.71 (s, 3H), 1.71-1.81 (m, 2H, 3-H_2), 2.52-2.66 (m, 2H, 2-H_2), 4.13 (q, 1H, J=6.5 Hz, 4-H), 4.54 (t, 1H, J=6.5 Hz, 5-H), 5.21-5.40 (m, 2H, 7-H_2), 5.70-5.82 (m, 1H, 6-H) and 9.79 (s, 1H, C*H*O). **υmax** ($CHCl_3$, cm^{-1}) 2974, 2936, 2866, 1719, 1462, 1379, 1369, 1256, 1089, 1012, 927, 907 and 865.

Further elution with the same solvents afforded the 2R-methylcyclohexanone derivative (4.51) as a mixture with the 2S-methyl isomer (4.52) in a ratio of 2:1 (22 mg, 41 %). Further chromatography afforded a sample of the pure 2R-isomer (4.51).

For the 2R-methyl isomer (4.51).

^{1}H nmr (200 MHz) δ 1.15 (d, 3H, 7.1 Hz, C*H*$_3$), 1.35 (s, 3H), 1.48 (s, 3H), 2.01-2.23 (m, 3H), 2.39-2.71 (m, 2H), 4.05 (t, 1H, J=6.8 Hz, 3-H), 4.40 (q, 1H, J=6.7 Hz, 4-H). **^{13}C nmr** (100 MHz) δ 12.52, 24.46, 25.17, 27.05, 34.12, 46.79, 72.20, 78.85, 108.67 and 211.61. **υmax** ($CHCl_3$, cm^{-1}) 2976, 2967, 2933, 2922, 1710 (C=O), 1453, 1379, 1335, 1255, 1158, 1056, 973, 909 and 863. **Mass Spec.** Calcd. for $C_9H_{13}O_3$: 169.0865. Found: 169.0889. **m/z** 169 $(M-CH_3)^+$, 147, 127, 91 (100%), 57 and 48. $[\alpha]_D^{23}$ +24.4° [c= 0.9 , $CHCl_3$]

Salient features for the minor 2S-isomer (4.52) from a mixture with the 2R-isomer **^{1}H nmr** (200 MHz) δ 1.16 (d,3H, J=6.8 Hz), 1.32 (s, 3H), 1.37 (s, 3H), 4.40-4.60 (m, 2H).

Finally, the cycloheptanone derivative (4.53) was eluted as a colourless liquid (28 mg, 51%).

^{1}H nmr (400 MHz) δ 1.36 (s, 3H), 1.48 (s, 3H), 1.83 (ddt, 2H, J=15.1, 10.4, 2.4 Hz, 3-H_{ax} and 6-H_{ax}), 1.97-2.06 (m, 2H, 3-H_{eq} and 6-H_{eq}), 2.27 (ddd, 2H, J=14.6, 10.4, 2.4 Hz, 2-H_{ax} and 7-H_{ax}), 2.72 (ddd, 2H, J=14.6, 10.4, 2.5 Hz, 2-H_{eq} and 7-H_{eq}) and 4.37-4.40 (dt, 2H, J=6.6, 2.4 Hz, 4-H and 5-H). **^{13}C nmr** (100 MHz) δ 24.81, 24.85, 27.20, 37.69, 76.11, 107.41 and 211.53. **υmax** ($CHCl_3$, cm^{-1}) 2979, 2932, 1698, 1445, 1434, 1381, 1371, 1334, 1259, 1249, 1160, 1138, 1095, 1073, 1050, 1006, 941, 915, 891 and 848. **Mass Spec.** Calcd. for $C_9H_{13}O_3$: 169.0865. Found: 169.0874. **m/z** 169 $(M-CH_3)^+$, 127, 82, 69, 55 and 43 (100%)

2,3-(DI-Q-ISOPROPYLIDENE)-4-Q-BENZYL-1,2S,3S,4-TETRAHYDROXY-BUTANE (4.55)

Sodium hydride (60 %; 136 mg, 3.39 mmol) was stirred in dry DMSO (5 ml) under nitrogen at room temperature for 30 min. The L-isopropylidene threitol derivative[15] (4.54) (500 mg, 3.08 mmol) in DMSO (2 ml), was added dropwise and stirred for 30 min. before benzyl chloride (410 mg, 3.24 mmol) was added. The mixture was stirred for 1.5 h before pouring into iced water (25 ml) and extraction with ether (3 x 15 ml). The combined ether extracts were washed with water (5 ml), saturated sodium chloride solution (5 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure gave a pale green oil. Purification by silica gel column chromatography (eluant : petrol-ether 1:1) gave the mono-benzylated product (4.55) as a colourless oil (424 mg, 54 %).

^{1}H nmr (200 MHz) δ 1.40 (s, 6H), 2.42-2.53 (m, 1H, O*H*), 3.47-3.80 (m, 4H, 1-H_2 and 4-H_2), 3.86-4.09 (m, 2H, 2-H and 3-H), 4.57 (s, 2H, CH_2Ph) and 7.32 (s, 5H). **υ_{max}** (film, cm^{-1}) 3452, 2983, 2968, 1450, 1379, 1369, 1251, 1215, 1107, 1080, 1050, 1029, 846, 739 and 699. **Mass Spec.** Calcd. for $C_{14}H_{20}O_4$: 252.1362. Found: 252.1365. **m/z** 252 (M^+), 237, 221, 194, 176, 131, 91 (100 %), 65, 59 and 43. **ANALYSIS** Calcd. for $C_{14}H_{20}O_4$: C, 66.65 ; H, 7.99. Found: C, 66.54; H, 8.20 %. **$[\alpha]_D^{23}$** + 8.3° [c=2.9, $CHCl_3$]

However, when this experiment was repeated on a larger scale (17.00 g of the diol), it yielded the required product (4.55) (8.21 g,.31 %) and the migration product (4.56) (2.6 g, 11 %), which had

^{1}H nmr (200 MHz) δ 1.35 (s, 3H), 1.42 (s, 3H), 2.48 (br s, 1H, O*H*), 3.50 (d, 2H, J= 5.7 Hz, 1-H_2), 3.71-3.90 (m, 2H, 2-H and 3-H), 3.96-4.04 (m, 1H, 4-H), 4.09-4.22 (m, 1H, 4-H), 4.55 (s, 2H, CH_2Ph) and 7.33 (s, 5H). **υ_{max}** (film, cm^{-1}) 3455, 2982, 2923, 2864, 1450, 1379, 1369, 1255, 1213, 1099, 1067, 858, 738 and 698. **Mass Spec.** Calcd. for $C_{13}H_{17}O_4$: 237.1127. Found: 237.1097. **m/z** 237 $(M-CH_3)^+$, 194, 176, 149, 133, 107, 101, 91 (100%), 65, 59 and 43

2,3-(DI-Q-ISOPROPYLIDENE)-4-Q-BENZYL-2R,3S,4-TRIHYDROXYBUTANAL (4.57)

The standard pyridinium chlorochromate oxidation was repeated on the mono-benzylated alcohol (4.55) (400 mg, 1.59 mmol) to give the title aldehyde (4.57) as a colourless liquid (347 mg, 87 %).

^{1}H nmr (200 MHz) δ 1.41 (s, 3H), 1.49 (s, 3H), 3.67 (d, 2H, J=4.0 Hz, 4-H_2), 4.15-4.30 (m, 2H, 2-H and 3-H), 4.60 (s, 2H, CH_2Ph), 7.33 (s, 5H) and 9.75 (d, 1H, J=1.4 Hz). **υ_{max}** (film, cm^{-1}) 2985, 2926, 2863, 1731, 1451, 1380, 1371, 1254, 1165, 1090, 851, 738 and 699.

(-)-ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-6-Q-BENZYL-4S,5S,6-TRIHYDROXY-HEX-2Z-ENOATE (4.58Z) *AND ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-6-Q-BENZYL-4S,5S,6-TRIHYDROXYHEX-2E-ENOATE* (4.58E)

The benzylated aldehyde (4.57) (1.00 g, 4.0 mmol), carbethoxymethylene-triphenylphosphorane (2.09 g, 8.0 mmol) and benzoic acid (25 mg, 0.2 mmol) were refluxed in dry benzene (100 ml) under nitrogen for 4 h. The mixture was allowed to cool to room temperature before the solvent was evaporated under reduced pressure. The product was extracted by washing the residue with small aliquots of cold ether (5 x 10 ml.). The combined ether extracts were evaporated *in vacuo* to give the crude product as a pale green oil . Chromatography on silica gel (eluant : petrol-ether 5 :1) eluted the *Z*- α,β-unsaturated ester (4.58Z) as a colourless oil (0.43 g, 36 %) **^{1}H nmr** (200 MHz) δ 1.23 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.44 (s, 6H), 3.65-3.68 (m, 2H, 6-H_2), 3.91-4.03 (m, 1H, 5-H), 4.12 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.58 (q, 2H, J=12.0 Hz, CH_2Ph), 5.38 (t, 1H, J=8.3 Hz, 4-H), 5.92 (dd, 1H, J=11.7, 1.0 Hz, 2-H), 6.18 (dd, 1H, J=11.7, 8.4 Hz, 3-H) and 7.31 (s, 5H). **υmax** (film, cm^{-1}) 2982, 2932, 2900, 2963, 1716, 1652, 1450, 1415, 1379, 1370, 1194, 1165, 1079, 1033, 859, 738 and 698. **Analysis** Calcd. for $C_{11}H_{18}O_5$: C, 57.38 ; H, 7.88. Found: C, 57.29 ; H, 7.73 %. $[\alpha]_D$ -13.4° [c= 2.1, $CHCl_3$]

Further elution with the same solvents gave the *E*-α,β-unsaturated ester (4.58E)

^{1}H nmr (200 MHz) δ 1.27 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.42 (s, 3H), 1.44 (s, 3H), 3.62 (d, 2H, J=4.7 Hz, 6-H_2), 3.94 (dt, 1H, J=5.5, 4.6 Hz, 5-H), 4.18 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.41 (t, J=5.5 Hz, 4-H), 4.58 (s, 2H, $PhCH_2$), 6.08 (dd, 1H, J=15.8, 1.3 Hz, 2-H), 6.88 (dd, 1H, J=15.8, 5.5 Hz, 3-H) and 7.32 (s, 5H). **υmax** (film, cm^{-1}) 2983, 2931, 2899, 2899, 2865, 1718, 1661, 1451, 1379, 1369, 1301, 1261, 1236, 1216, 1165, 1096, 1034, 739 and 699. **Mass Spec.** Calcd. for

$C_{17}H_{21}O_5$: 305.1389. Found: 305.1425. **m/z** 305 $(M\text{-}CH_3)^+$, 199, 187, 170, 156, 141, 127, 112, 97, 91 (100 %), 84, 69, 59 and 43.

The unsaturated ester (4.58) was also prepared by a Wadsworth-Horner-Emmons reaction on the mono-benzylated aldehyde (4.57) (320 mg, 1.28 mmol.), in a repeat of the preparation for the tetrahydrofuranyl derivative (4.43) giving predominantly the trans isomer (4.58E) (204 mg, 50 %), identical to that prepared above.

(-)-ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S,6-TRIHYDROXYHEXANOATE (4.59)

The hydrogenation performed on the mixture (4.46) and (4.47) was repeated on a mixture of the E/Z isomers of the unsaturated hydroxyester (4.58) (0.76 g, 2.4 mmol) to give the title compound (4.59) as a colourless liquid (0.51 g, 91 %). **^{1}H nmr** (400 MHz) δ 1.20 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.34 (s, 3H), 1.35 (s, 3H), 1.72-1.83 (m, 1H, 3-H), 1.87-1.96 (m, 1H, 3-H), 2.33-2.52 (m, 3H, 2-H_2 and O*H*), 3.56 (dd, 1H, J=12.0, 5.6 Hz, 6-H), 3.69-3.77 (m, 2H, 4-H and 6-H), 3.86 (dt, 1H, J=12.0, 8.2 Hz, 5-H) and 4.09 (q, 2H, J=7.2 Hz, OCH_2CH_3). **^{13}C nmr** (100 MHz) δ 14.11, 26.94, 27.19, 27.88, 30.57, 60.45, 61.82, 76.09, 80.98, 108.82 and 173.22. **υ_{max}** (film, cm^{-1}) 3488, 2978, 2931, 2872, 1721, 1442, 1371, 1306, 1262, 1160, 1099, 1070, 1036, 1023, 989, 896 and 851. **Analysis** Calcd. for $C_{11}H_{20}O_5$: C, 56.88 ; H, 8.68. Found: C, 56.88 ; H, 8.90 %. **$[\alpha]_D^{24}$** -24.1° [c=2.6, $CHCl_3$]

ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S-DIHYDROXYHEPT-6-ENOATE (4.60)

Standard PCC oxidation of the *threo*-hydroxyester (4.59) (440 mg, 1.89 mmol) gave the *threo*-isopropylidene aldehyde as a colourless oil.(400 mg, 92 %).

^{1}H nmr (200 MHz) δ 1.20 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.34 (s, 3H), 1.36 (s, 3H), 1.64-1.96 (m, 2H, 3-H_2), 2.33-2.52 (m, 2H, 2-H_2), 3.69-3.93 (m, 2H, 4-H and 5-H), 4.09 (q, 2H, J=7.2 Hz, OCH_2CH_3), 9.63 (dd, 1H, J=2.2, 0.6 Hz). **υmax** (film, cm^{-1}) 2978, 2934, 2823, 1738, 1372, 1361, 1260, 1219, 1160, 1076, 1036, 989 and 864

Wittig reaction of this *trans*-isopropylidene aldehyde (330 mg, 1.95 mmol.) with methylenetriphenylphosphonium bromide, in a repeat of the preparation for the *cis*-isopropylidene unsaturated ester (4.41) gave the title compound (4.60) as a colourless liquid (172 mg, 52 %).

^{1}H nmr (200 MHz) δ 1.23 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.38 (s, 6H), 1.68-2.04 (m, 2H, 3-H_2), 2.28-2.62 (m, 2H, 2-H_2), 3.68 (dt, 1H, J=8.2, 3.8 Hz, 4-H), 3.99 (t, 1H, J=8.2 Hz, 5-H), 4.11 (q, 2H, J=7.2 Hz, OCH_2CH_3), 5.25 (d, 1H, J=10.1 Hz, CH=CHH), 5.38 (d, 1H, J=17.2 Hz, CH=CHH), and 5.79 (ddd, 1H, J=17.2, 10.1 and 8.2 Hz, 6-H). **^{13}C nmr** (100 MHz) δ 14.20, 26.79, 26.92, 27.18, 30.67, 60.43, 79.53, 82.41, 108.80, 119.20, 134.99, 173.12. **υmax** ($CHCl_3$, cm^{-1}) 2976, 2931, 2867, 1724, 1371, 1164, 1111, 1067, 989, 932, 908 and 871. **$[\alpha]_D$** 0° [c=0.9 , $CHCl_3$].

(-)-Se-PHENYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S-DIHYDROXYSELENO-HEPT-6-ENOATE (4.61)

Saponification of the olefinic ester (4.60) (150 mg, 0.66 mmol) under the standard conditions, gave the corresponding unsaturated acid as a colourless liquid

(107 mg, 82 %).

^{1}H nmr (200 MHz) δ 1.39 (s, 6H), 1.66-2.03 (m, 2H), 2.35-2.66 (m, 2H), 3.69 (dt, 1H, J=8.2, 3.9 Hz), 4.00 (t, 1H, J=8.2 Hz), 5.25 (d, 1H, J=10.1 Hz, CH=C*H*H), 5.38 (d, 1H, J=17.4 Hz, CH=CH*H*), and 5.79 (ddd, 1H, J=17.4, 10.1 and 8.2 Hz, 6-H). **υ_{max}** (film, cm^{-1}) 3146, 3079, 2980, 2930, 2868, 2652, 1709 , 1644, 1379, 1372, 1164, 1065, 988, 932 and 868. **Mass Spec.** Calcd. for $C_9H_{13}O_4$: 185.0814. Found: 185.0835. **m/z** 185 $(M-CH_3)^+$, 125, 98, 83, 69, 55, 43, 32 and 28 (100 %). **$[\alpha]_D^{24}$** +6.8° [c=0.59, $CHCl_3$]

The standard procedure for the preparation of selenoesters was repeated on this *threo*-isopropylidene acid (90 mg, 0.45 mmol.) to give the title selenoester (4.61) as a near colourless liquid (89 mg, 60 %).

^{1}H nmr (200 MHz) δ 1.40 (s, 6H), 1.68-2.07 (m, 2H, 3-H_2), 2.72-3.01 (m, 2H, 2-H_2), 3.69 (dt, 1H, J=8.2, 3.8 Hz, 4-H), 3.98 (t, J=8.2 Hz, 5-H), 5.25 (d, 1H, J=10.2 Hz, CH=C*H*H), 5.35 (d, 1H, J=17.4 Hz, CH=CH*H*), and 5.78 (ddd, 1H, J=17.4, 10.2 and 8.2 Hz, 6-H), 7.33-7.42 (m, 3H) and 7.44-7.53 (m, 2H). **υ_{max}** ($CHCl_3$, cm^{-1}) 2981, 2931, 2868, 1716, 1644, 1476, 1436, 1379, 1371, 1069, 988, 932 and 867. **Analysis** Calcd. for $C_{16}H_{20}O_3Se$: C, 56.64 ; H, 5.94. Found: C, 56.87 ; H, 6.25 %. **$[\alpha]_D^{24}$** -9.5° [c= 1.8, $CHCl_3$]

REACTION OF (-)-Se-PHENYL 4,5-(DI-O-ISOPROPYLIDENE)-4S,5S-DIHYDROXYSELENOHEPT-6-ENOATE (4.61) *WITH TRI-n-BUTYLTIN HYDRIDE*

To a stirred solution of the *threo*-isopropylidene selenoester (4.61) (58 mg, 0.17 mmol) in refluxing dry benzene (5 ml) under nitrogen, was added a solution of tri-n-butyltin hydride (61 mg, 0.21 mmol) in benzene (1.0 ml) containing a trace of AIBN (ca. 3 mg) during 30 min. The mixture was cooled to room temperature and the

solvents evaporated under reduced pressure. Silica gel column chromatography (eluant : petrol-ether 1 : 1) gave the aldehyde (4.62) as a colourless oil (14 mg, 44 %),

^{1}H nmr (200 MHz) δ 1.39 (s, 6H), 1.85-2.04 (m, 2H, 3-H_2), 2.52-2.67 (m, 2H, 2-H_2), 3.67 (dt, 1H, J=8.2, 3.8 Hz, 4-H), 3.99 (t, 1H, J=8.4 Hz, 5-H), , 5.25 (d, 1H, J=10.1 Hz, CH=C*H*H), 5.38 (d, 1H, J=17.2 Hz, CH=CH*H*), and 5.79 (ddd, 1H, J=17.2, 10.1 and 8.2 Hz, 6-H) and 9.79 (t, 1H, J=1.3 Hz). **υ_{max}** (film, cm^{-1}) 2984, 2932, 2872, 1711, 1644, 1426, 1379, 1370, 1239, 1168, 1067, 990, 934 and 873.

Further elution with the same solvents gave the cyclohexanone derivatives (4.63) as a 1:1 mixture (nmr) of isomers (6 mg, 19 %).

Salient features of the S-methyl cyclohexanone isomer from a mixture with the R-isomer .

^{1}H nmr (400 MHz) δ 1.17 (d, 3H, J=6.5 Hz, C*H*$_3$), 1.45 (s, 3H), 1.50 (s, 3H), 1.67-1.79 (m, 1H, 2-H), 2.22-2.62 (m, 4H, 5-H_2 and 6-H_2), 3.25 (dd, 1H, J=12.4, 8.8 Hz, 3-H) and 3.91 (ddd, 1H, J=11.7, 8.8, 4.1 Hz, 4-H).

Salient features for the R-isomer, from a mixture with the S-isomer.

^{1}H nmr (400 MHz) δ 1.19 (d, 3H, J=7.4 Hz, C*H*$_3$), 1.47 (s, 3H), 1.48 (s, 3H), 1.67-1.79 (m, 1H, 2-H), 2.22-2.62 (m, 4H, 5-H_2, and 6-H_2), 3.74 (dd, 1H, J=9.5, 6.0 Hz, 3-H) and 4.06 (ddd, 1H, J=11.7, 9.5, 4.3 Hz, 4-H).

From the mixture of isomers

Mass Spec. Calcd. for $C_9H_{13}O_3$: 169.0865. Found: 169.0879. **m/z** 169 (M-CH_3)$^+$, 127 (100 %), 109, 97, 85, 81, 69, 59, 56 and 43.

Finally, the cycloheptanone derivative (4.64) (3 mg, 10 %) was eluted as a colourless liquid.

^{1}H nmr (400 MHz) δ 1.40 (s, 6H), 1.68-1.80 (m, 2H), 2.18-2.25 (m, 2H), 2.43-2.57 (m, 4H, 2-H_2 and 6-H_2), 3.48-3.56 (m, 2H, 4-H and 5-H). **^{13}C nmr** (100 MHz) δ 25.36, 26.94, 39.27, 81.65, 108.38 and 212.13. **υ_{max}** ($CHCl_3$, cm^{-1}) 2978, 2933, 2867, 1698, 1452, 1379, 1370, 1327, 1148, 1126, 1077, 926, 865 and 840. **Mass Spec.** Calcd. for $C_9H_{13}O_3$: 169.0865. Found: 169.0856. **m/z** 169 $(M-CH_3)^+$, 127, 82, 69, 55 and 43 (100 %)

The reaction was repeated on (4.61) (75 mg, 0.22 mmol) with addition of tin hydride over 11 h (syringe pump), to give the aldehyde (4.62) (5.9 mg, 14 %), a 1:1 mixture (nmr) of the cyclohexanone derivatives (4.63) (11.8 mg, 29%), and the cycloheptanone derivative (4.64) (9.4 mg, 23 %).

ETHYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S-DIHYDROXYOCT-6Z-ENOATE (4.65)

Ethyl triphenylphosphonium iodide (2.70 g, 6.5 mmol) was slurried in dry THF at -50°C under nitrogen. A solution of n-butyllithium in hexanes (2.3 M; 1.54 ml, 3.55 mmol) was added dropwise and the resultant orange solution was stirred for 15 min before a solution of the aldehyde (4.42) (740 mg, 3.2 mmol) in THF (10 ml) was slowly added. The mixture was stirred at -50°C for a further 5 min before it was allowed to warm to 0 °C and poured into ether (200 ml). Filtration through celite and evaporation of solvents under reduced pressure afforded a greenish liquid that on silica gel column chromatography (eluant : petrol-ether 1 : 1) gave the title ester (4.65) as a colourless liquid (543 mg, 73 %).

^{1}H nmr (200 MHz) δ 1.26 (t, 3H, J=7.3 Hz, OCH_2CH_3), 1.36 (s, 3H), 1.46 (s, 3H), 1.70 (dd, 3H, J=6.7, 1.3 Hz, 8-H_3), 1.72-1.83 (m, 2H, 3-H_2), 2.26-2.58 (m, 2H, 2-H_2), 4.05-4.22 (m, 3H, OCH_2CH_3 and 4-H), 4.96 (dd, J=10.8, 6.3 Hz, 5-H), 5.47 (t, 1H, J=10.8 Hz, 6-H), 5.74 (m, 1H, 7-H). **^{13}C nmr** (100 MHz) δ 13.41,

14.24, 25.72, 25.98, 28.33, 30.83, 60.37, 73.61, 77.13, 108.06, 126.11, 128.98 and 173.39. υ_{max} (film, cm^{-1}) 2982, 2933, 1733, 1447, 1377, 1369, 1252, 1216, 1164, 1064 and 869. **Mass Spec.**Calcd. for $C_{12}H_{19}O_4$: 227.1283. Found: 227.1270. **m/z** 227 $(M-CH_3)^+$, 213, 185, 171, 139, 125, 112, 97, 83, 79, 69, 59, 55 and 43 (100%) **ANALYSIS** Calcd. for $C_{13}H_{22}O_4$: C, 64.44 ; H, 9.15. Found: C, 64.24 ; H, 9.02%.

(+)-Se-PHENYL 4,5-(DI-Q-ISOPROPYLIDENE)-4R,5S-DIHYDROXYSELENO-OCT-6Z-ENOATE (4.66)

Saponification of the octenyl ester (4.65) (450 mg, 1.86 mmol) by the standard procedure yielded the corresponding acid as a colourless liquid (330 mg, 83 %). **^{1}H nmr** (200 MHz) δ 1.38 (s, 3H), 1.48 (s, 3H), 1.70 (dd, 3H, J=7.0, 1.7 Hz, 8-H_3), 1.72-1.83 (m, 2H, 3-H_2), 2.32-2.63 (m, 2H, 2-H_2), 4.16 (dt, 1H, J=8.6, 4.7 Hz, 4-H), 4.97 (dd, 1H, J=8.6, 6.2 Hz, 5-H), 5.49 (dt, 1H, J=11.2, 6.2 Hz, 6-H), 5.77 (dq, 1H, J=11.2, 7.0 Hz, 7-H) and 10.20 (br s, 1H). υ_{max} (film, cm^{-1}) 3090, 3026, 2983, 2932, 2678, 1707, 1439, 1413, 1379, 1369, 1249, 1217, 1163, 1063, 937, 868, 801 and 700. **Mass Spec.** Calcd. for $C_{11}H_{18}O_4$: 214.1205. Found: 214.1232. **m/z** 213 (M^+), 199, 171, 139, 125, 112, 97, 83, 79, 69, 59, 55 and 43 (100%). $[\alpha]_D^{23}$ + 24.6° [c=2, $CHCl_3$]

The title selenoester (4.66) was prepared as a colourless liquid (392 mg, 80 %),by the standard method, from the corresponding octenoic acid (300 mg, 1.40 mmol).

^{1}H nmr (200 MHz) δ 1.37 (s, 3H), 1.47 (s, 3H), 1.68 (dd, 3H, J=7.0, 1.7 Hz, 8-H_3), 1.73-1.85 (m, 2H, 3-H_2), 2.71 (m, 2H, 2-H_2), 4.14 (t, 1H, J=7.1 Hz, 4-H), 4.92 (dd, 1H, J=11.2, 7.1 Hz, 5-H), 5.44 (t, 1H, J=11.2 Hz, 6-H), 5.75 (dq, 1H,

J=11.2, 7.0 Hz, 7-H), 7.32-7.41 (m, 3H) and 7.43-7.66 (m, 2H). **υ_{max}** (film, cm^{-1}) 2982, 2930, 1721, 1475, 1436, 1378, 1368, 1245, 1216, 1164, 1054, 1022, 940, 865, 739, 690 and 671. **Mass Spec.** Calcd. for $C_{16}H_{19}O_3Se$: 339.0499. Found: 339.0496. **m/z** 339 $(M-CH_3)^+$, 157, 139 (100 %), 121, 112, 97, 93, 83, 79, 69, 59, 55 and 43. $[\alpha]_D^{24}$ +50.4° [c=2.5, $CHCl_3$].

REACTION OF (+)-Se-PHENYL 4,5-(DI-O-ISOPROPYLIDENE)-4R,5S-DIHYDROXYSELENOOCT-6Z-ENOATE (4.66) *WITH TRI-n-BUTYLTIN HYDRIDE*

The octenyl selenoester (4.66) (300 mg, 0.85 mmol) was refluxed in dry benzene (18 ml) under nitrogen. A solution of tri-n-butyltin hydride (272 mg, 0.93 mmol) in benzene (5 ml) with a trace of AIBN (10 mg) was added dropwise during 30 min and refluxing was continued for a further 1 h. The mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (eluant : petrol-ether 5 : 1) to give a single isomer of the ethyl cyclohexanone derivative (4.68) (70 mg, 42 %),
^{1}H nmr (200 MHz) δ 0.94 (t, 3H, J=7.4 Hz, CH_2CH_3), 1.32 (s, 3H), 1.43 (s, 3H), 1.50-1.68 (m, 4H, CH_2CH_3 and 5-H_2), 2.00-2.17 (m, 3H, 2-H and 6-H_2), 4.24 (dd, 1H, J=6.9, 5.1 Hz, 3-H) and 4.37 (dt, 1H, J=6.9, 4.6 Hz, 4-H). **^{13}C nmr** (100 MHz) δ 12.22, 21.20, 24.38, 25.05, 26.85, 53.55, 71.85, 77.20, 108.24 and 211.34. **υ_{max}** ($CHCl_3$, cm^{-1}) 2981, 2934, 2875, 1707 (C=O), 1459, 1379, 1259, 1159, 1055, 979, 932, 890 and 863. **Mass Spec.** Calcd. for $C_{11}H_{18}O_3$: 198.1256. Found : 198.1286. **m/z** 198 (M^+), 183, 141, 123, 111, 95, 81, 55 and 43 (100 %). $[\alpha]_D^{24}$+12.7° [c= 1.6 , $CHCl_3$]

Further elution with the same solvents gave a 1:1 mixture of the cyclohexanone derivatives (4.68) and (4.69) as a colourless liquid (70 mg, 42 %)

Salient features of the minor ethyl cyclohexanone isomer (4.69) from a mixture with the methyl cycloheptanone derivative (4.71).

^{1}H nmr (200 MHz) δ 0.97 (t, 3H, J=7.5 Hz, CH_2CH_3), 1.34 (s, 3H), 1.47 (s, 3H), 1.47 (dt, 1H, J=14.3, 7.3 Hz, , $CHHCH_3$), 1.91-2.10 (m, 3H, CHHCH and 5-H_2), 2.19-2.28 (m, 2H, 6-H_2), 2.45 (ddd, 1H, J=12.5, 7.5, 4.3 Hz, 2-H), 4.55 (dt, 1H, J=7.6, 3.1 Hz, 4-H) and 4.62 (dd, 1H, J=7.5, 3.1 Hz, 3-H).

Finally, a 3:1 (nmr) mixture of the minor 6 membered ring isomer (4.69) and the 7 membered ring product (4.71) (12 mg, 7 %) was eluted.

Salient features for the methyl cycloheptanone derivative (4.71) from a mixture with the minor 6 membered product (4.69).

^{1}H nmr (200 MHz) δ 1.05 (d, 3H, J=6.9 Hz, CH_3), 1.38 (s, 3H), 1.53 (s, 3H), 1.60-1.74 (m, 2H), 2.28-2.34 (m, 2H), 2.66-2.74 (m, 2H), 2.95-3.02 (m, 1H), 4.34 (dt, 1H, J=7.0, 7.0, 2.8 Hz) and 4.42 (ddd, 1H, J=7.0, 5.4, 2.2 Hz).

The cyclisation reaction on this selenoester (4.66) (30 mg, 0.09 mmol.) was repeated, but with the addition of tri-n-butyltin hydride over 8 h (syringe pump), which gave a 2:1 (nmr) mixture of the 6S-*exo* product (4.68) and the 7S-*endo* product (4.70) (7.7 mg, 46 %) and a 2:1 (nmr) mixture of the 6R-*exo* product (4.69) and the 7R-*endo* product (4.71) (3.3 mg, 20 %).

Salient features for the 7S- product (4.70) from a mixture with the 6S-product (4.68).

^{1}H nmr (200 MHz) δ 1.32 (s, 3H), 1.37 (s, 3H), 4.60 (br s, 2H, 4-H and 5-H)

ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S-DIHYDROXY-6-OXOHEX-2Z-ENOATE (4.73)

The standard PCC oxidation was repeated on the unsaturated alcohol (4.46) (500 mg, 2.2 mmol) to yield the crude aldehyde as a colourless oil (459 mg, 93 %). **^{1}H nmr** (200 MHz) δ 1.24 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.37 (s, 3H), 1.54 (s, 3H), 4.12 (m, 3H, OCH_2CH_3 and 4-H), 4.73 (dd, 1H, J=6.8, 2.9 Hz, 5-H), 5.91 (dd, 1H, J=11.5, 1.7 Hz, 2-H), 6.17 (dd, 1H, J=11.5, 6.8 Hz, 3-H) and 9.41 (d, 1H, J=2.9 Hz, CHO). **υ_{max}** ($CHCl_3$, cm^{-1}) 2987, 2939, 2874, 2725, 1736, 1718, 1647, 1458, 1415, 1382, 1260, 1221, 1197, 1161, 1089, 1062, 1029, 979, 921, 861, 824 and 737.

REACTION OF ETHYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S-DIHYDROXY-6-OXOHEX-(2Z)-ENOATE (4.73) *WITH METHYLTRIPHENYLPHOSPHONIUM BROMIDE*

Methyltriphenylphosphonium bromide (1.55 g, 4.3 mmol) was slurried in dry THF (25 ml) at 0 °C, under nitrogen. A solution of n-butyllithium (2.5 M; 1.04 ml, 2.6 mmol) in hexanes was added slowly and the mixture was stirred for a further 40 min at 0°C , before cooling to -78 °C. A solution of the aldehyde (4.73) (496 mg, 2.2 mmol) in THF (5 ml) was added dropwise and stirring was continued at -78 °C for 30 min before the mixture was allowed to warm up to room temperature. The reaction mixture was stirred at room temperature for 2 h before pouring into ether (150 ml). Filtration through celite and evaporation of the solvents under reduced pressure afforded a red oil that on silica gel chromatography (eluant : petrol-ether 5 : 1) yielded the *E*-α,β-unsaturated ester (4.74) as a white solid (96 mg, 19 %).
^{1}H nmr (200 MHz) δ 1.28 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.39 (s, 3H), 1.52 (s, 3H), 4.18 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.71 (m, 2H, 4-H and 5-H), 5.28 (m, 2H,

7-H_2), 5.66 (ddd, 1H, J=15.7, 9.6, 6.7 Hz, 6-H), 6.04 (dd, 1H, J=16.0, 1.9 Hz, 2-H)and 6.76 (dd, 1H, J=16.0, 5.4 Hz, 3-H). **^{13}C nmr** (75 MHz) δ 14.13, 25.34, 27.74, 60.36, 77.60, 79.82, 109.58, 118.81, 122.87, 133.72, 143.41 and 166.12. **υmax** ($CHCl_3$, cm^{-1}) 2987, 2938, 2904, 1723, 1662, 1458, 1373, 1307, 1256, 1217, 1163, 1105, 1048, 985, 933, 886, 864, 800 and 734. **Mass Spec. m/z** 226(M^+), 195, 157 (100 %), 139, 126, 90, 83, 67 and 55. **mp.** 139-140°C.

ETHYL (4,5-DI-O-ISOPROPYLIDENE)HEPT-2,6-DIENOATE (4.38)

A mixture of the aldehyde (4.39) (99 mg, 0.63 mmol) and carbethoxymethyl-triphenylphosphorane (330 mg, 0.95 mmol) were stirred in benzene (10 ml) under nitrogen at room temperature for 2 h. The solvent was removed *in vacuo* and the solid residue was extracted with ether (3 x 5 ml). The combined ether extracts were concentrated *in vacuo* and the residue purified by silica gel column chromatography (eluant : petrol-ether 5:1) to firstly yield the *Z*-unsaturated ester (4.38) as a colourless oil (30 mg, 21 %)

^{1}H nmr (200 MHz) δ 1.32 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.41 (s, 3H), 1.54 (s, 3H), 4.07-4.30 (m, 4H, OCH_2CH_3, 4-H and 5-H), 5.12 (d, 1H, J=11.2 Hz, 7-H), 5.26 (d, 1H, J=16.8 Hz, 7-H), 5.55-5.73 (m, 1H, 6-H), 5.88 (d, 1H, J=11.2 Hz, 2-H) and 6.17 (dd, 1H, J=11.2, 7.3 Hz, 3-H). **υmax** (film, cm^{-1}) 2985, 2938, 2908, 2875, 1718, 1659, 1600, 1446, 1414, 1370, 1299, 1261, 1222, 1191, 1156, 1039, 981, 928, 874, 831, 776 and 705.

Further elution with the same solvents afforded the *E*-unsaturated ester (4.76) as a white solid (25 mg, 17 %), with the same spectral characteristics as its enantiomer (4.74).

(3,4-(DI-O-ISOPROPYLIDENE)-3S,4S-DIHYDROXYTETRAHYDROFURAN-2-YL)ACETIC ACID (4.75)

Saponification of the Z-α,β-unsaturated ester (4.46) (350 mg, 1.5 mmol) by the standard method afforded the cyclised acid (4.75) (259 mg, 84 %), as a white solid **^{1}H nmr** (200 MHz) δ 1.33 (s, 3H), 1.50 (s, 3H), 2.52 (d, 2H, J=7.0 Hz, CH_2CO_2H), 3.87 (dd, 1H, J=10.7, 4.2 Hz, 5-H_{ax}), 3.97 (dd, 1H, J=10.7, 1.6 Hz, 5-H_{eq}), 4.43 (dt, 1H, J=7.0, 1.4 Hz, 2-H), 4.56 (dd, 1H, J=6.2, 1.4 Hz, 3-H) and 4.82 (ddd, 1H, J=6.2, 4.2, 1.6 Hz, 4-H). **^{13}C nmr** (75 MHz) δ 25.10, 26.63, 36.10, 72.29, 80.90, 84.53, 113.28 and 174.88. **υ_{max}** ($CHCl_3$, cm^{-1}) 2986, 2942, 2878, 2660, 1726, 1383, 1275, 1233, 1210, 1162, 1086, 1053, 886 and 859. **Mass Spec. m/z** 187 ($M-CH_3^+$, 100 %), 143, 127, 113, 99, 85, 81, 71 and 59.

ETHYL 4,5-(DI-O-ISOPROPYLIDENE)-4S,5S-DIHYDROXYUNDEC-6Z-EN-10-YNOATE (4.77)

To a slurry of 4-pentynyltriphenylphosphonium iodide (1.88 g, 41 mmol) in dry THF (40 ml) at 0 °C under nitrogen was added a solution of n-butyllithium in hexanes (2.5 M; 1.65 ml, 4.1 mmol). The mixture was stirred for 20 min before a solution of the aldehyde (4.42) (900 mg, 3.9 mmol) in THF (10 ml) was added. Stirring was continued for further 2 h, with the temperature slowly rising to room temperature, before the reaction mixture was poured into ether (100 ml). Filtration through celite and concentration of the solvents under reduced pressure yielded a brown oil. Purification by silica gel column chromatography afforded the title ester (4.77) as a colourless oil (731 mg, 66 %).

^{1}H nmr (200 MHz) δ 1.15 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.24 (s, 3H), 1.35 (s, 3H), 1.66 (q, 2H, J=7.4 Hz, 3-H_2), 1.91 (s, 1H, 11-H), 2.10-2.46 (m, 6H, 2-H_2, 8-H_2 and 9-H_2), 3.92-4.02 (m, 3H, OCH_2CH_3, and 4-H), 4.81 (dd, 1H, J=8.7, 6.2

Hz, 5-H), 5.44 (dd, 1H, J=10.9, 8.7 Hz, 6-H) and 5.55-5.69 (m, 1H, 7-H). **^{13}C nmr** (50 MHz) δ 14.10, 18.55, 25.55, 26.09, 26.81, 28.17, 30.82, 60.06, 68.96, 73.89, 77.34, 83.23, 108.09, 127.10, 131.95 and 172.93. **υ_{max}** (film, cm^{-1}) 3292, 2985, 2937, 2118, 1734, 1446, 1375, 1247, 1217, 1167, 1106, 1061, 976, 941, 870 and 800. **ANALYSIS** Calcd. for $C_{16}H_{24}O_4$: C, 68.54 ; H, 8.63. Found: C, 68.21 ; H, 8.70 %.

Se-*PHENYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S-DIHYDROXYSELENO-UNDEC-6Z-EN-10-YNOATE* (4.78)

The standard saponification was performed on the alkynoic ester (4.77) (700 mg, 2.5 mmol) to give the corresponding acid as a colourless oil (628 mg, 99 %). **^{1}H nmr** (200 MHz) δ 1.37 (s, 3H), 1.48 (s, 3H), 1.78 (q, 2H, J=6.7 Hz, 3-H_2), 1.98 (s, 1H, 11-H), 2.18-2.60 (m, 6H, 2-H_2, 8-H_2 and 9-H_2), 4.15 (dt, 1H, J=6.7, 6.1 Hz, 4-H), 4.93 (dd, 1H, J=8.7, 6.1 Hz, 5-H), 5.56 (dd, 1H, J=10.9, 8.7 Hz, 6-H) and 5.61-5.78 (m, 1H, 7-H). **^{13}C nmr** (50 MHz) δ 18.65, 25.66, 25.99, 26.92, 28.34, 30.66, 60.08, 73.98, 77.33, 83.43, 108.45, 126.95, 132.37 and 178.55. **υ_{max}** (film, cm^{-1}) 3295, 2988, 2936, 2667, 2118, 1711, 1436, 1418, 1381, 1247, 1219, 1162, 1109, 1065, 975, 939, 869 and 802.

The standard preparation for selenoesters was repeated on this alkynoic acid (337 mg, 1.3 mmol) to afford the title selenoester (4.78) as a colourless oil (398 mg, 76 %).

^{1}H nmr (400 MHz) δ 1.38 (s, 3H), 1.48 (s, 3H), 1.74-1.84 (m, 2H, 3-H_2), 1.98 (t, 1H, J=1.1 Hz, 11-H), 2.21-2.37 (m, 4H, 8-H_2 and 9-H_2), 2.78 (ddd, 1H, J=8.0, 4.2, 3.6 Hz, 2-H), 2.88 (ddd, 1H, J=8.0, 4.2, 3.0 Hz, 2-H), 4.13 (ddd, 1H, J=4.8, 2.9, 2.2 Hz, 4-H), 4.89 (dd, 1H, J=4.7, 2.9 Hz, 5-H), 5.50 (dd, 1H, J=5.4, 4.6 Hz,

6-H), 5.64-5.78 (m, 1H, 7-H), 7.34-7.41 (m, 3H) and 7.48-7.52 (m, 2H). **^{13}C nmr** (100 MHz) δ 18.87, 25.93, 26.68, 27.08, 28.57, 44.39, 69.40, 74.05, 77.21, 83.62, 108.65, 126.67, 126.98, 129.14, 129.60, 132.70, 136.01 and 200.07. **υ_{max}** (film, cm^{-1}) 3294, 2985, 2934, 2118, 1723, 1580, 1478, 1440, 1380, 1245, 1217, 1163, 1056, 1022, 939, 867, 801, 740, 690 and 648. **ANALYSIS :** calcd. for $C_{20}H_{24}O_3Se$: C, 61.38 ; H, 6.18. Found: C, 60.96 ; H, 6.17 %.

REACTION OF Se-*PHENYL 4,5-(DI-Q-ISOPROPYLIDENE)-4S,5S-DIHYDROXY-SELENOUNDEC-6Z-EN-10-YNOATE* (4.78) *WITH TRI-n-BUTYLTIN HYDRIDE.*

To a refluxing solution of selenoester (4.78) (700mg, 1.8 mmol) in dry benzene (150 ml) under nitrogen, was added a solution of tri-n-butyltin hydride (625 mg, 2.2 mmol) in benzene (10 ml) containing a catalytic amount of AIBN, during 24 h. A further solution of AIBN (20 mg) in benzene (10 ml) was added during 24 h, until all the starting material had been comsumed (tlc. control). The mixture was cooled to room temperature before the solvent was evaporated under reduced pressure. Filtration through silica gel (Eluant : petrol-ether 5:1) gave a mixture of all the cyclised compounds (4.80), (4.81) and (4.82) (282 mg, 65 %) in an approximate ratio of 1:1:4 respectively, with a trace amount of aldehyde (4.79). Further purification by silica gel column chromatography (Eluant : petrol-ether 10 : 1), preparative tlc (Eluant : petrol-ether 10 : 1) and recrystallisation (petrol-ether) gave, in order of elution :
The aldehyde (4.79) as a mixture with the cyclohexanone (4.80). Salient features included,

^{1}H nmr (400 MHz) δ 1.32 (s, 3H), 1.48 (s, 3H), 1.97 (t, 1H, CC-H), 4.36-4.42 (m, 1H, 4-H), 4.87 (dd, 1H, J= 6.7, 2.2 Hz, 5-H), 5.48 (dd, 1H, J= 8.9, 2.2 Hz, 6-H), 5.61-5.76 (m, 1H, 7-H), 9.77 (t, 1H, J= 1.7 Hz, C*H*O).

The cyclohexanone (4.80) as a mixture with aldehyde (4.79). Salient features included,

^{1}H nmr (400 MHz) δ 1.36 (s, 3H), 1.49 (s, 3H), 1.95 (s, 1H, CC-*H*), 4.22 (dt, 1H, J=6.6, 5.6 Hz, 4-H), 4.41 (dd, 1H, J=11.6, 5.6 Hz, 5-H).

Cycloheptanone (4.81) as a colourless oil.

^{1}H nmr (300 MHz) δ 1.34 (s, 3H), 1.38 (s, 3H), 1.48-1.73 (m, 4H), 1.96 (t, 1H, J=2.8 Hz, CC-*H*), 1.98-2.13 (m, 3H), 2.22 (dd, 1H, J=7.0, 2.6 Hz), 2.27 (ddd, 1H, J=12.0, 5.0 and 2.0 Hz), 2.36 (t, 1H, J=6.7 Hz), 2.47 (dt, 1H, J=13.0 and 5.3 Hz), 4.58 (s, 2H, 4-H and 5-H). **^{13}C nmr** (75 MHz) δ 18.55, 24.64, 24.77, 25.77, 26.23, 33.37, 49.31, 68.41, 72.21, 76.05, 84.21, 93.16, 107.69, 111.08 and 210.12.

Tandem cyclisation product (4.85) as a mixture with (4.87). Salient features included,

^{1}H nmr (400 MHz) δ 4.24 (dd, 1H, J=9.6, 5.8 Hz, 5-H), 4.42 (ddd, 1H, J=8.8, 5.8 and 3.1 Hz, 6-H), 5.00 (s, 1H) and 5.23 (s, 1H).

Tandem cyclisation product (4.86) as a mixture with (4.85) and (4.87). Salient features included,

^{1}H nmr (400 MHz) δ 4.54 (ddd, 1H, J=7.9, 6.0 and 2.0 Hz, 6-H), 4.64 (dd, 1H, J=7.7, 2.0 Hz, 5-H), 4.96 (s, 1H) and 5.08 (s, 1H).

Tandem cyclisation product (4.87) as a mixture with (4.85). Salient features include,

^{1}H nmr (400 MHz) δ 4.54 (ddd, 1H, J=7.9, 6.0 and 2.0 Hz, 6-H), 4.64 (dd, 1H, J=7.7, 2.0 Hz, 5-H), 4.96 (s, 1H) and 5.08 (s, 1H).

Tandem product (4.88) was obtained pure as a cystalline solid (5 mg).

^{1}H nmr (400 MHz) δ 1.30 (s, 3H), 1.40 (s, 3H), 1.72-1.82 (m, 1H, 1-H), 1.96-2.03 (ddt, 1H, J=12.6, 8.6, 4.1 Hz, 7-H), 2.05 (dq, 1H, J=8.1, 4.1 Hz, 7-H), 2.14-2.19 (m, 1H, 4-H), 2.22-2.28 (m, 1H, 10-H), 2.36 (dt, 1H, J=17.9, 4.1 Hz, 8-H), 2.46 (dd, 1H, J=16.2, 8.5 Hz, 1-H), 2.78 (ddd, 1H, J=17.9, 12.6 and 4.1 Hz, 8-H), 3.05-3.18 (m, 2H, 2-H_2), 4.47 (t, 1H, J=4.1 Hz, 6-H), 4.60 (d, 1H, J=7.1 Hz, 5-H), 4.88 (s, 1H) and 5.06 (s, 1H). **^{13}C nmr** (75 MHz) δ 24.30, 25.41, 26.61, 32.75, 38.05, 42.16, 51.72, 74.85, 77.14, 105.50, 108.22, 153.64 and 204.92. **υ_{max}** ($CHCl_3$, cm^{-1}) 2932, 2855, 1701, 1601, 1456, 1383, 1371, 1160, 1086, 1053, 986, 900 and 866. **mp.** 124-126 °C.

5-(CYCLOPROPYL)PENT-4-ENOIC ACID (5.10)

Sodium hydride (80 %; 600 mg, 20 mmol) was stirred in DMSO (40 ml) for 30 min at 70°C under nitrogen. After cooling to room temperature, (4-carboxypropyl)-triphenylphosphonium bromide (4.29 g, 10 mmol)[16] was added portionwise and the mixture was stirred for 45 min at room temperature before a solution of cyclopropane carboxaldehyde (280 mg, 4 mmol) in DMSO (5 ml) was added. Stirring was continued for a further 2 h before the reaction mixture was poured into a 1:1 mixture of ether and water (400 ml) and carefully acidified with dilute hydrochloric acid. The aqueous phase was separated and extracted further with ether (2 x 50 ml). The combined ether layers were washed with water (50 ml) and saturated sodium chloride solution (50 ml) before drying over magnesium sulphate. Filtration and evaporation of solvents under reduced pressure yielded the crude acid. Purification by silica gel column chromatography (eluant: petrol-ether 1:1) gave the title acid (5.10) as a 3:1 mixture (nmr) of *Z*/*E* isomers (555 mg, 99 %), in the form of a colourless oil.
Salient features for the *Z*-isomer from a mixture with the *E*-isomer,
^{1}H nmr (200 MHz) δ 0.28-0.37 (m,2H), 0.62-0.80 (m, 2H), 1.46-1.65 (m, 1H), 2.24-2.65 (m, 4H), 4.81 (dd, 1H, J=13.2, 9.7 Hz, 5-H), 5.30 (dt, 1H, J=13.2, 8.2 Hz, 4-H) and 11.12 (br s, 1H).

Salient features for the *E*-isomer from a mixture with the *Z*-isomer,
^{1}H nmr (200 MHz) δ 5.05 (dd, 1H, J=15.2, 8.3 Hz, 5-H) and 5.49 (dt, 1H, J=15.2, 6.4 Hz, 4-H).

For the mixture of isomers,
^{13}C nmr (50 MHz) δ 6.37, 6.82, 9.48, 13.34, 22.97, 27.45, 34.22, 34.27, 125.43, 135.43, 135.68 and 179.53. **υ_{max}** (film, cm^{-1}) 3083, 3008, 2673, 1709, 1654, 1421,.1282, 1213, 1047, 1020, 886 and 811, 736. **ANALYSIS :** calcd. for

$C_{15}H_{20}O_4S$: C, 60.79 ; H, 6.80. Found: C, 60.98 ; H, 6.76 %. **Mass Spec.** (m/z) 140 (M^+), 122, 111, 95, 79 (100 %), 67, 55 and 53.

ETHYL 7-CYCLOPROPYL-3-OXOHEPT-6-ENOATE (5.11).

To a stirred solution of the acid (5.10) (500 mg, 3.6 mmol) in dry THF (40 ml) at room temperature under nitrogen, was added 1,1-carbonyl diimidazole (723 mg, 4.5 mmol). The mixture was stirred for 6 h before the magnesium salt of monoethyl malonate (1.29 g, 4.5 mmol) was added. The reaction was stirred for a further 18 h before the solvent was evaporated under reduced pressure. The residue was dissolved in ether (100 ml) and acidified with dilute hydrochloric acid (0.5 M; 50 ml). The aqueous phase was separated and extracted further with ether (2 x 50 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution (60 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure and purification by silica gel column chromatography (eluant: petrol-ether 5:1) yielded the β-ketoester (5.11) as a colourless oil, in a 3:1 mixture (nmr) of *Z/E* isomers (682 mg, 91 %).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.28-0.36 (m, 2H), 0.67-0.79 (m, 2H), 1.28 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.55-1.66 (m, 1H), 2.44 (dt, 2H, J=7.2, 6.7 Hz, 5-H_2), 2.64 (t, 2H, J=6.7 Hz, 4-H_2), 3.45, (s, 2H, 2-H_2), 4.19 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.77 (t, 1H, J=10.7 Hz, 7-H) and 5.24 (dt, 1H, J=10.7, 7.2 Hz, 6-H).

Salient features for the *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 3.42 (s, 2H, 2-H_2), 4.99 (dd, 1H, J=16.5, 7.3 Hz, 7-H) and 5.46 (dt, 1H, J=16.5, 6.7 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz) δ 6.32, 6.80, 9.45, 10.05, 21.88, 26.40, 42.96, 49.36, 61.23, 125.72, 135.39 and 167.06. **υ_{max}** (film, cm^{-1}) 3082, 3005, 2934, 1745, 1716, 1652, 1411, 1368, 1316, 1237, 1160, 1097, 1032, 941, 811 and 734.

ETHYL 7-CYCLOPROPYL-3,3-ETHYLENEDIOXYHEPT-6-ENOATE (5.12).

To a stirred solution of trimethylsilyl triflate (1 mg, 0.05 mmol) in dry dichloromethane (1 ml) at -78°C under nitrogen was added bis-trimethylsilyl ethylene glycol (196 mg, 0.95 mmol)[17]. After 2 min the β-ketoester (5.11) (100 mg, 0.48 mmol) was added and the mixture was stirred for 2.5 h before slowly warming up to room temperature. Stirring was continued at room temperature for 18 h. Pyridine (0.1 ml) was added and the mixture poured into saturated sodium bicarbonate solution (15 ml), and extracted with ether (3 x 20 ml). The ether extracts were dried over magnesium sulphate and after filtration and evaporation of the solvent under reduced pressure the residue was purified by silica gel column chromatography (eluant : petrol-ether 3 : 1) to yield the title ketal (5.12) as a colourless oil, in a 3:1 mixture (nmr) of Z/E isomers (95 mg, 79 %).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.25-0.34 (m,2H), 0.63-0.76 (m, 2H), 1.24 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.43-1.64 (m, 1H), 1.83-1.96 (m, 2H, 5-H_2), 2.18-2.35 (m, 2H, 4-H_2), 2.65 (s, 2H, 2-H_2), 3.99 (s, 4H), 4.14 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.72 (t, 1H, J=10.6 Hz, 7-H) and 5.28 (dt, 1H, J=10.6, 7.3 Hz, 6-H).

Salient features for the *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 2.62 (s, 2H, 2-H_2), 4.97 (dd, 1H, J=15.4, 8.4 Hz, 7-H) and 5.47 (dt, 1H, J=15.4, 6.7 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz) δ 6.26, 6.74, 9.45, 14.14, 21.89, 26.49, 37.74, 42.81, 60.38, 65.12, 109.18, 109.27, 127.32, 127.39, 133.80, 134.16 and 169.04. **υ_{max}** (film, cm^{-1}) 3082, 2983, 2890, 1738, 1653, 1447, 1430, 1369, 1318, 1218, 1098, 1048, 950, 885, 843, 810 and 734. **Mass Spec. m/z** 254 (M^+), 245, 209, 192, 187, 180, 175, 167 (100 %), 159, 146, 143, 136, 131, 127, 121, 117, 112, 105, 99, 94, 87, 80 and 73. **Analysis** calcd. for $C_{14}H_{22}O_4$, C 66.12; H, 8.72 ; Found C, 65.92 ; H, 8.69 %

Alternatively, the ketal (5.12) was also prepared as follows.

The β-ketoester (5.11) (100 mg, 0.48 mmol), ethylene glycol (59 mg, 0.95 mmol) and camphor 10-sulphonic acid (5 mg, 0.02 mmol) were refluxed in benzene under Dean-Stark conditions for 22 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was dissolved in ether (50 ml). The ether solution was washed with water (2 x 10 ml) and saturated sodium chloride solution (10 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure and purification by silica gel column chromatography (eluant : petrol-ether 5 : 1) gave the recovered starting β-ketoester (5.11) (34mg, 34 %) and the title ketal (5.12) (22mg, 18 %).

Se-*PHENYL 7-CYCLOPROPYL-3,3-ETHYLENEDIOXYSELENOHEPT-6-ENOATE* (5.13).

Saponification of the ketal (5.12) (280 mg, 1.1 mmol), by the standard method yielded the corresponding acid (159 mg, 65 %) as a 2 : 1 mixture (nmr) of Z/E isomers.

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.24-0.36 (m,2H), 0.68-0.75 (m, 2H), 1.16-1.38 (m, 1H), 1.80-1.95 (m, 2H, 4-H_2), 2.26 (dt, 2H, J=8.4, 7.1 Hz, 5-H_2), 2.72 (s, 2H, 2-H_2), 3.96-4.05 (m, 4H), 4.73 (t, 1H, J=10.1, Hz, 7-H) and 5.27 (dt, 1H, J=10.7, 7.1 Hz, 6-H).

Salient features for the *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 0.57-0.68 (m, 2H), 2.05 (dt, 2H,J=10.1, 3.9 Hz, 5-H_2), 2.67 (s, 2H, 2-H_2), 4.97 (dd, 1H, J=15.3, 8.5 Hz, 7-H) and 5.47 (dt, 1H, J=15.2, 8.9 Hz, 6-H).

For the mixture of isomers,

υmax (film, cm^{-1}) 3082, 3004, 2895, 2672, 1722, 1665, 1432, 1411, 1308, 1227, 1106, 1047, 951, 885, 854 and 810. **Mass Spec.** Calcd. for $C_{12}H_{18}O_4$ 226.1205. Found 226.1194

The standard procedure for preparation of selenoesters was repeated on this acid (150 mg, 0.66 mmol), to give the title compound (5.13) as a colourless oil in a 1.3:1 mixture (nmr) of the Z/E isomers (162 mg, 67 %).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.26-0.32 (m, 2H), 0.62-0.70 (m, 2H), 1.20-1.42 (m, 1H), 1.78-1.93 (m, 2H, 4-H_2), 2.07 (dt, 2H, J=7.4, 6.1 Hz, 5-H_2), 3.02 (s, 2H, 2-H_2), 3.94-4.08 (m, 4H), 4.74 (dd, 1H, J=10.8, 9.9 Hz, 7-H), 5.28 (dt, 1H, J=10.8, 7.4 Hz, 6-H), 7.33-7.43 (m, 3H) and 7.44-7.53 (m, 2H).

Salient features for *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 1.46-1.64, (m, 1H), 2.28, (dt, 2H, J=8.7, 6.9 Hz, 5-H_2), 3.06, (s, 2H, 2-H_2), 4.98 (dd, 1H, J=15.2, 8.4 Hz, 7-H) and 5.47 (dt, 1H, J=15.2, 8.7 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz) δ 6.26, 6.67, 9.45, 13.31, 21.86, 26.43, 38.04, 54.28, 64.24, 109.01, 127.06, 127.16, 128.76, 129.22, 134.12, 134.34 and 135.64. **υ_{max}** ($CHCl_3$, cm^{-1}) 3017, 2987, 2886, 1711, 1234 ,1216, 1140, 1089, 1047, 805. **Analysis** calcd. for $C_{18}H_{22}O_3Se$, C 59.18; H, 6.07 ; Found C, 59.60 ; H, 5.79 %

REACTION OF Se-*PHENYL 7-CYCLOPROPYL-3,3-ETHYLENEDIOXYSELENO-HEPT-6-ENOATE* (5.13) *WITH TRI-n-BUTYLTIN HYDRIDE.*

To a refluxing solution of selenoester (5.13) (75 mg, 0.21 mmol) in dry benzene (4.0 ml) was added a solution of tri-n-butyltin hydride (66 mg, 0.23 mmol) in benzene (1.0 ml), containing a trace of AIBN (ca. 3 mg), during 30 min. The mixture was refluxed for a further 90 min before allowing to cool to room temperature and evaporation of the solvent under reduced pressure. Silica gel column chromatography (eluant : petrol-ether 2 : 1) yielded the butenylcyclohexanone (5.14) (41 mg, 95 %) as a colourless liquid.

^{1}H nmr (400 MHz) δ 0.99 (t, 3H, J=7.4 Hz, 10-H_3), 1.68-1.77 (m, 1H, 5-H_{ax}), 1.92-2.10 (m, 5H, 4-H_2, 5-H_{eq} and 9-H_2), 2.64 (q, 2H, J=13.7 Hz, 2-H_2), 2.92-2.98 (m, 1H, 6-H), 3.93-3.99 (m, 4H), and 5.50-5.60 (m, 2H, H-7 and H-8). **^{13}C nmr** (100 MHz) δ 13.55, 25.69, 27.40, 33.53, 33.65, 50.92, 52.30, 64.64, 64.74, 110.19, 125.42, and 135.01 **υ_{max}** (film, cm^{-1}) 2961, 2876 ,1717, 1631, 1455, 1442, 1414, 1355, 1293, 1241, 1192, 1149, 1105, 1039, 969, 948, and 928. **Mass Spec.** Calcd. for $C_{12}H_{18}O_3$: 210.1256 : Found : 210.1269. **m/z** 210 (M^+), 184, 169, 156, 141, 127, 113, 99 (100%), 86, 69 and 55.

5-(CYCLOPROPYL)-5-PHENYLPENT-4Z-ENOIC ACID (5.18)

The procedure for the preparation of the cyclopropyl acid (5.10) from cyclopropane carboxaldehyde was repeated on cyclopropyl phenyl ketone (340 mg, 2.3 mmol), to give the *Z*-unsaturated acid (5.18) (489 mg, 97 %), as a white crystalline solid.

^{1}H nmr (200 MHz) δ 0.34–0.40 (m, 2H), 0.52-0.60 (m, 2H), 1.52-1.60 (m, 1H), 2.18 (q, 2H, J=7.5 Hz, 3-H_2), 2.31 (t, 2H, J=7.5 Hz, 2-H_2), 5.42 (t, 1H, J=7.4 Hz, 4-H) and 7.13-7.38 (m, 5H). **^{13}C nmr** (50 MHz) δ 5.16, 18.39, 24.14, 34.21, 122.78, 126.73, 127.99 and 128.67 **υ_{max}** ($CHCl_3$, cm^{-1}) 3081, 1710, 1410, 1279, 1135 and 915. **Analysis** Calcd. for $C_{14}H_{16}O_2$: C, 77.75 ; H, 7.46 ; Found C, 77.77 ; H, 7.47 %. **mp.** 54°C.

ETHYL 7-(CYCLOPROPYL)-3-OXO-7-PHENYLHEPT-6-ENOATE (5.19).

Homologation of the acid (5.18) (400 mg, 1.8 mmol) was achieved by repeating the process for preparation of β-ketoester (5.11), to give the title compound (5.19) as a colourless oil in a 20:1 mixture (nmr) of the *E*- and *Z*- isomers (412 mg, 78 %).

^{1}H nmr (200 MHz) δ 0.34–0.46 (m, 2H), 0.56-0.67 (m, 2H), 1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.50-1.64 (m, 1H), 2.16 (q, 2H, J=6.7 Hz, 5-H_2), 2.51 (t, 2H, J=6.7 Hz, 4-H_2), 3.33 (s, 2H, 2-H_2), 4.16 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.38 (t, 1H, J=6.7 Hz, 6-H) and 7.07-7.34 (m, 5H). **^{13}C nmr** (50 MHz) δ 5.19, 14.07, 18.43, 23.18, 41.72, 43.24, 49.25, 61.41, 123.06, 126.79, 128.06, 128.72, 143.79, 166.54 and 210.64. **υ_{max}** (film, cm^{-1}) 2984, 1745, 1722, 1668, 1599, 1443, 1410, 1368 ,1310, 1238, 1185, 1151, 1098, 1032, 763and 702.

ETHYL 7-(CYCLOPROPYL)-3,3-ETHYLENEDIOXY-7-PHENYLHEPT-6-ENOATE (5.20).

The procedure for ketalisation of the β-ketoester (5.11) with bistrimethylsilyl ethylene glycol was repeated on the phenylcyclopropyl β-ketoester (5.19) (100 mg, 0.35 mmol) to yield the corresponding ketal (5.20) as a colourless oil, in a 4:1 mixture (nmr) of *Z*- and *E*-isomers (58 mg, 51 %), with some recovered starting material (5.19) (33 mg, 33 %).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.40 (d, 2H, J=5.6 Hz), 0.60 (d, 2H, J=7.9 Hz), 1.24 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.47-1.65 (m, 1H), 1.82 (q, 2H, J=7.9 Hz, 5-H_2), 1.96 (t, 2H, J=7.9 Hz, 4-H_2), 2.52 (s, 2H, 2-H_2), 3.74-3.92 (m, 4H), 4.12, (q, 2H, J=7.2 Hz, OCH_2CH_3), 5.40 (t, 1H, J=7.9 Hz, 6-H) and 7.10-7.33 (m, 5H).

Salient features for *E*-isomer from a mixture with the Z-isomer,

^{1}H nmr (200 MHz) δ 0.30 (d, 2H, J=5.6 Hz), 0.79 (d, 2H, J=8.4 Hz), 2.69 (s, 2H, 2-H_2) and 5.66 (t, 1H, J=6.7 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz) δ 5.21, 6.34, 11.50, 14.13, 18.36, 22.76, 23.15, 37.45, 37.93, 42.64, 42.82, 60.28, 64.96, 65.13 ,109.14, 109.29, 124.76, 126.19, 126.50, 127.40, 127.63, 127.86, 128.70, 130.62, 140.44, 142.14 and 169.27. **υmax** (film, cm^{-1}) 3080, 2982, 2930, 1736, 1645, 1442, 1420, 1370, 1184, 1155, 1095, 1030, 763 and 702. **Analysis** Calcd. for $C_{20}H_{26}O_4$: C 72.70; H, 7.93 ; Found C, 72.73 ; H, 8.02 %.

Se-*PHENYL 7-(CYCLOPROPYL)-3,3-ETHYLENEDIOXY-7-PHENYLSELENO-HEPT-6-ENOATE* (5.21)

Saponification of ketal (5.20) (210 mg, 0.63 mmol) was carried out by the standard procedure, to give the corresponding acid as a colourless oil, in a 4:1 mixture of *Z* and *E*-isomers respectively (149 mg, 78 %).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.40 (d, 2H, J=5.6 Hz), 0.60 (d, 2H, J=7.3 Hz), 1.43-1.60 (m, 1H), 1.63-1.84 (m, 2H, 5-H_2), 1.84-2.02 (m, 2H, 4-H_2), 2.52 (s, 2H, 2-H_2), 3.58-3.98 (m, 4H), 5.34 (t, 1H, J=6.7 Hz, 6-H) and 7.08-7.33 (m, 5H).

Salient features for the *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 0.27 (d, 2H, J=5.6 Hz), 0.76 (d, 2H, J=7.9 Hz), 2.62 (s, 2H, 2-H_2) and 5.61 (t, 1H, J=7.9 Hz, 6-H).

υ_{max} ($CHCl_3$, cm^{-1}) 3081, 2896, 2690, 1711, 1435, 1233, 1115, 1072, 1046, 949, 872, 817 and 702.

The standard procedure for the preparation of selenoesters was carried out on this acid (85 mg, 0.28 mmol), to yield the title selenoester (5.21) as a colourless oil, in a 4:1 mixture (nmr) of the *Z*- and *E*-isomers respectively (76 mg, 61 %).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.39 (d, 2H, J=5.6 Hz), 0.59 (d, 2H, J=8.4 Hz), 1.43-1.60 (m, 1H), 1.67-1.84 (m, 2H, 5-H_2), 1.84-2.04 (m, 2H, 4-H_2), 2.90 (s, 2H, 2-H_2), 3.78-4.09 (m, 4H), 5.38 (t, 1H, J=6.7 Hz, 6-H) and 7.06-7.57 (m, 10H).

Salient features for *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 0.29 (d, 2H, J=5.0 Hz), 0.77 (d, 2H, J=7.3 Hz), 3.07 (s, 2H, 2-H_2) and 5.63 (t, 1H, J=6.7 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz), δ.5.98, 19.13 ,23.89, 38.97, 54.79, 65.89, 125.18, 127.33, 128.17, 128.42, 128.69, 129.47, 129.53, 129.99, 136.41 and 199.42 **υ_{max}** ($CHCl_3$, cm^{-1}) 3080, 3014, 2970, 2892, 1712, 1580, 1478, 1440, 1305, 1143, 1112, 1072, 1048, 1022, 999, 948 and 909.

REACTION OF Se-*PHENYL 7-(CYCLOPROPYL)-3,3-ETHYLENEDIOXY-7-PHENYLSELENOHEPT-6-ENOATE* (5.21) *WITH TRI-n-BUTYLTIN HYDRIDE.*

To a stirred solution of selenoester (5.21) (66 mg, 0.15 mmol) in dry benzene (2.9 ml) at reflux under nitrogen was added a solution of tri-n-butyltin hydride (66 mg, 0.23 mmol) in benzene (0.7 ml) with a trace of AIBN (ca. 2 mg). The mixture was refluxed for a further 2 h before cooling to room temperature and evaporation of the solvent under reduced pressure. Silica gel column chromatography (eluant : petrol-ether 2 : 1) yielded the migrated *E*-alkyidenecyclohexanone (5.23) as a colourless oil (4 mg, 9 %)

^{1}H nmr (200 MHz) 1.23 (t, 3H, J=7.6 Hz, 10-H_3), 1.47-1.86 (m, 2H, 9-H_2), 1.91 (t, 2H, J=6.3 Hz, 4-H_2), 2.56 (t, 2H, J=6.7 Hz, 5-H_2), 2.68 (t, 2H, J=6.7 Hz, 8-H_2), 2.90 (s, 2H, 2-H_2), 4.04 (s, 4H) and 7.23-7.42 (m, 5H). **υ_{max}** ($CHCl_3$, cm^{-1}) 2931, 2869, 1741, 1620, 1496, 1447, 1394, 1096, 1051, 947 and 916.

Further elution with the same solvents gave the migrated *Z*-alkylidenecyclohexanone (5.22) as a colourless oil (24 mg, 56 %).

^{1}H nmr (200 MHz) δ 0.85 (t, 3H, J=7.2 Hz, 10-H_3), 1.21-1.44 (m, 2H, 9-H_2), 1.82 (t, 2H, J=6.5 Hz, 4-H_2), 2.35 (t, 2H, J=6.5 Hz, 5-H_2), 2.52 (dd, 2H, J=7.9, 5.8 Hz, 8-H_2), 2.75 (s, 2H, 2-H_2), 3.90-4.01 (m, 4H) and 7.07-7.41 (m, 5H).

^{13}C nmr (50 MHz) δ 13.94, 21.76, 26.57, 34.81, 37.50, 53.13, 64.70, 127.24, 127.86 and 128.34. **υ_{max}** ($CHCl_3$, cm^{-1}) 2964, 2933, 2877, 1723, 1687, 1611,

1493, 1442, 1362, 1114, 1052 and 852. **Mass Spec.** Calcd for $C_{18}H_{22}O_3$: 286.1569. Found : 286.1573. **m/z** 286 (M^+, 100 %), 271, 259, 241, 227, 213, 199, 185, 171, 143, 129, 115, 99, 86, 77 and 55

Further elution with the same solvents gave the non-migrated phenyl butenyl-cyclohexanone (5.24) as a colourless oil (13 mg, 30 %).
^{1}H nmr (200 MHz) δ 0.92 (t, 3H, J=7.5 Hz, 10-H_2), 1.78-2.04 (m, 6H, 4-H_2, 5-H_2, and 9-H_2), 2.64 (d, 2H, J=2.9 Hz, 2-H_2), 3.25 (t, 1H, J=7.3 Hz, 6-H), 3.86-4.02 (m, 4H), 5.47 (t, 1H, J=6.2 Hz, 8-H) and 7.12-7.36 (m, 5H). **^{13}C nmr** (100 MHz) δ 14.35, 22.44, 25.90, 33.85, 51.45, 57.52, 64.63, 64.72, 110.14, 126.62, 127.98, 128.96, 132.80, 137.11, 140.33 and 206.55. **υ_{max}** ($CHCl_3$, cm^{-1}) 3009, 2963, 2933, 2875, 1714, 1640, 1609, 1493, 1455, 1360, 1307, 1106, 1040, 947, 920 and 861. **Mass Spec.** Calcd for $C_{18}H_{22}O_3$: 286.1569. Found : 286.1584. **m/z** 286 (M^+), 270, 257 (100 %), 241, 229, 213, 201, 184, 172, 157, 143, 129, 115, 99, 86, 77 and 55

ETHYL 7-(CYCLOPROPYL)-3-HYDROXY-7-PHENYLHEPT-6-ENOATE (5.26)

The β-ketoester (5.19) (300 mg, 1.1 mmol) was stirred in propan-2-ol (5 ml) at 0 °C and sodium borohydride (44 mg, 1.2 mmol) was added portionwise. The reaction was complete after 45 min (tlc. control). The resultant colourless solution was poured into a 2:1 mixture of ether and water (150 ml), and the aqueous layer was separated and extracted further with ether (3 x 25 ml). The combined ether extracts were washed with water (2 x 40 ml) and saturated sodium chloride solution (40 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure, followed by silica gel column chromatography (eluant : petrol-ether 3 : 1), yielded the title hydroxyester (5.26) as a colourless oil (233 mg, 77 %) in a 15:1 ratio of *Z*- to *E*-isomers (nmr).

^{1}H nmr (200 MHz) δ 0.40 (m, 2H), 0.61 (m, 2H), 1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.32-1.66 (m, 3H), 1.98 (dt, 2H, J=7.4, 6.7 Hz, 5-H_2), 2.33 (dd, 2H, J=4.0, 3.0 Hz, 2-H_2), 2.42-2.56 (m, 1H, -O*H*), 3.92 (tt, 1H, J=7.8, 4.2 Hz, 3-H), 4.14 (q, 2H, J=7.1 Hz, OCH_2CH_3) and 5.41 (t, 1H, J=6.7 Hz, 6-H). **^{13}C nmr** (50 MHz) δ 5.26, 14.23, 18.50, 24.99, 36.95, 41.40, 60.59, 67.72, 124.59, 126.71, 127.55, 127.78, 128.05 and 128.84. **υmax** ($CHCl_3$, cm^{-1}) 2964, 2933, 2877, 1723, 1687, 1611, 1493, 1442, 1362, 1114, 1052 and 852.

ETHYL 7-(CYCLOPROPYL)-3-(t-BUTYLDIMETHYLSILYLOXY)-7-PHENYLHEPT-6-ENOATE (5.27)

To a stirred solution of t-butyldimethylsilyl chloride (118 mg, 0.78 mmol) and imidazole (82 mg, 1.30 mmol) in dry DMF (3 ml) under nitrogen at room temperature was added a solution of the hydroxyester (5.26) (150 mg, 0.52 mmol) in DMF (1 ml). The reaction was stirred for 16 h before it was poured into water (50 ml) and extracted with ether (3 x 25 ml). The combined ether layers were washed successively with dilute hydrochloric acid (2 M; 2 x 20 ml), water (2 x 20 ml) and saturated sodium chloride solution (20 ml) before drying over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure, followed by silica gel column chromatography (Eluant : petrol-ether 15 : 1) yielded the title silyloxyether (5.27) as a colourless oil (165 mg, 79 %), in a 15:1 ratio of *Z*- to *E*-isomers (nmr).
^{1}H nmr (200 MHz) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.40 (m, 2H), 0.61 (m, 2H), 0.84 (s, 9H), 1.22 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.42-1.56 (m, 2H, 4-H_2), 1.60-1.71 (m, 1H), 1.81-1.97 (m, 2H, 5-H_2), 2.27 (dd, 2H, J=7.0, 3.6 Hz, 2-H_2), 4.05 (m, 3H, OCH_2CH_3,and 3-H), 5.39 (t, 1H, J=6.7 Hz, 6-H) and 7.05-7.34 (m, 5H). **^{13}C nmr** (50 MHz) δ −4.85, −4.62, 5.13, 14.13, 18.35, 24.68, 25.75, 37.96, 42.56, 60.08, 69.16, 124.78, 126.52, 127.38, 127.64, 127.89, 128.71, 142.44 and 171.57. **υmax** (film, cm^{-1}) 3081, 3057, 2856, 2930, 2857, 1738, 1600, 1472, 1443, 1375, 1304,

1255, 1186, 1155, 1094, 1032, 1006, 940, 837, 776 and 702. **Analysis** Calcd. for $C_{24}H_{38}O_3Si$: C 71.59 ; H, 9.51 ; Found C, 71.39 ; H, 9.62 %.

Se-*PHENYL 7-(CYCLOPROPYL)-3-(t-BUTYLDIMETHYLSILYLOXY)-7-PHENYLSELENOHEPT-6-ENOATE* (5.28)

Saponification of silyloxyester (5.27) (140 mg, 0.35 mmol) by the standard method yielded the corresponding acid as a colourless oil (118 mg, 91 %), in a 7:1 ratio of *Z*- to *E*-isomers (nmr).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.41 (dd, 2H, J=5, 2 Hz), 0.64 (dd, 2H, J=9, 2 Hz), 0.82 (s, 9H), 1.42-1.63 (m, 2H, 4-H_2), 1.63-1.78 (m, 1H), 1.81-1.96 (m, 2H, 5-H_2), 2.33 (d, 2H, J=5.7 Hz, 2-H_2), 3.99 (tt, 1H, J=5.7, 5.2 Hz, 3-H), 5.38 (t, 1H, J=6 Hz, 6-H) and 7.06-7.34 (m, 5H).

Salient features for *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 2.55 (d, 2H, J=5.8 Hz, 2-H_2), 4.19 (t, 1H, J=5.8 Hz, 3-H), 5.63 (t, 1H, J=6 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz) δ –4.91, –4.65, 5.14, 18.34, 24.76, 25.72, 37.65, 41.64, 69.09, 124.33, 126.62, 127.95 and 128.68. **υ_{max}** (film, cm^{-1}) 3081, 3008, 2955, 2929, 2857, 2665, 1712, 1493, 1442, 1410, 1306, 1256, 1098, 836, 776 and 701

The standard procedure for preparation selenoesters was performed on this silyloxy acid (110 mg, 0.29 mmol) to yield the title selenoester (5.28) as a colourless oil (39 mg, 26 %) in a 5:1 ratio of *Z*- and *E*- isomers (nmr).

Salient features for the *Z*-isomer from a mixture with the *E*-isomer,

^{1}H nmr (200 MHz) δ –0.03 (s, 3H), 0.01 (s,3H), 0.40 (dd, 2H, J=6, 2 Hz), 0.63 (dd, 2H, J=9, 2 Hz), 0.82 (s, 9H), 1.53 (t, 2H, J=6.7 Hz, 4-H_2), 1.60-1.76 (m, 1H), 1.81-1.97 (m, 2H, 5-H_2), 2.66 (dq, 2H, J=7.9, 6.7 Hz, 2-H_2), 4.07 (tt, 1H, J=7.8, 6.7 Hz, 3-H), 5.38 (t, 1H, J=6.2 Hz, 6-H) and 7.06-7.52 (m, 10H).

Salient features for *E*-isomer from a mixture with the *Z*-isomer,

^{1}H nmr (200 MHz) δ 2.90 (dd ,2H, J=9.0, 5.6 Hz, 2-H_2), 4.24 (tt, 1H, J=6.2, 5.6 Hz, 3-H) and 5.62 (t, 1H, J=6.7 Hz, 6-H).

For the mixture of isomers,

^{13}C nmr (50 MHz) δ -4.71, -4.61, 5.17, 6.40, 18.37, 24.60, 25.84, 54.72, 54.96, 68.99, 69.21, 124.50, 126.28, 126.61, 127.41, 127.69, 127.97, 128.73, 129.24, 130.45 and 135.62 **υ_{max}** (film, cm^{-1}) 3069, 3008, 2954, 2928, 2894, 2856, 1724, 1580, 1492, 1472, 1440, 1361, 1256, 1098, 993, 910, 836, 811, 776, 737 and 701

REACTION OF Se-*PHENYL 7-(CYCLOPROPYL)-3-(t-BUTYLDIMETHYL-SILYLOXY)-7-PHENYLSELENOHEPT-6-ENOATE* (5.28) *WITH TRI-n-BUTYLTIN DEUTERIDE.*

To a refluxing solution of the selenoester (5.28) (14 mg, 0.03 mmol) in dry benzene (1.0 ml) was added a solution of tri-n-butyltin deuteride (7 mg, 0.03 mmol) in benzene (0.2 ml), containing a catalytic amount of AIBN (*ca.* 1mg), during 30 min. The mixture was refluxed for a further 2 h before cooling to room temperature and evaporation of the solvents under reduced pressure.

For the major migrated product from the crude reaction mixture, some salient features were,

^{1}H nmr (400 MHz) δ 2.59 (dd, 1/2 H, J=14.8, 5.1 Hz, 8-H) and 2.75 (dd, 1/2 H, J=14.8, 7.4 Hz, 8-H), 4.04-4.08 (m, 1H, 3-H).

4-(PHENYLSULPHONYL)BUTANOIC ACID (5.34).

The ring opening of γ-butyrolactone with thiophenate anion, as described by Traynelis and Love[18], gave 4-(phenylthio)butanoic acid in a 72 % yield.

^{1}H nmr (200 MHz) δ 1.96, (quint, 2H, J=8.7 Hz, 3-H_2), 2.51 (t, 2H, J=8.7 Hz, 2-H_2), 2.96, (t, 2H, J=8.7 Hz,4-H_2), 7.11-7.35 (m, 5H) and 9.86, (br s, 1H). **^{13}C nmr** (50 MHz) δ 5.05, 6.37, 17.18, 58.98, 126.98, 127.07, 127.55, 127.89, 128.18, 128.48, 133.05 and 142.27. **υ_{max}** ($CHCl_3$, cm^{-1}) 3064, 2974, 2664, 1711, 1585, 1481, 1439, 1413, 1293, 1256, 1124, 1089, 1037, 937 and 914. **m.p.** 68°C [Lit.[16] 68-69°C].

The title acid (5.34) was prepared from 4-(phenylthio)butanoic acid in 78 % yield, as descibed by Hammam.[19]

^{1}H nmr (200 MHz) δ 2.05 (quint, 2H, J=7.1 Hz, 3-H_2), 2.53 (t, 2H, J=7.7 Hz, 2-H_2), 3.18 (t, 2H, J=7.1 Hz, 4-H_2), 7.48-7.70 (m, 3H), 7.90 (d, 2H, J=7.7 Hz) and 9.96 (br s, 1H). **^{13}C nmr** (50 MHz) δ 18.19, 32.01, 55.22, 128.17, 129.50, 133.90, 139.35 and 177.18. **υ_{max}** (mull, cm^{-1}) 2923, 2854, 2524, 1719, 1376, 1214, 1187, 1135, 1082, 1029, 993, 978, 843, 789, 748, 736 and 688. **m.p.**98°C [Lit.[17] 99°C].

α–CYCLOPROPYL-α–(PHENYLTHIO)TOLUENE (5.38)

Diphenyl disulphide (2.21 g, 10 mmol) was stirred in dry THF (10 ml) at room temperature under nitrogen. Tri-n-butylphosphine (2.05 g, 10 mmol) was added and the mixture stirred for 10 min before cyclopropyl-benzyl alcohol (500 mg, 3.4 mmol) was added. The mixture was stirred for 48 h before pouring into a mixture of ether (100 ml) and dilute sodium hydroxide solution (2 M; 100 ml). The aqueous layer was separated and extracted further with ether (2 x 50 ml). The combined ether layers were washed successively with sodium hydroxide solution (50 ml), water (2 x 50 ml) and saturated sodium chloride solution (50 ml) before drying over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure and silica gel column chromatography (eluant : petrol) afforded the title sulphide as a colourless oil (545 mg, 67 %).

^{1}H nmr (200 MHz) δ 0.19-0.41 (m, 2H), 0.41-0.60 (m ,1H), 0.60-0.75 (m, 1H), 1.24-1.40 (m, 1H), 3.50 (d, 1H, J=10.1 Hz) and 7.06-7.37 (m, 10H). **^{13}C nmr** (50 MHz) δ 5.05, 6.37, 17.18, 58.98, 126.98, 127.07, 127.55, 127.89, 128.18, 128.48, 133.05 and 142.27. **υ_{max}** (film, cm^{-1}) 3078, 3018, 1583, 1480, 1452, 1438, 1022, 953, 912, 841, 746 and 692.

α-CYCLOPROPYL-α-(PHENYLSULPHONYL)TOLUENE (5.39).

To a stirred solution of sulphide (5.38) (200 mg, 0.83 mmol), in ethanol (20 ml) at room temperature, was added a solution of MMPP (1.13 g, 1.8 mmol) in water (2 ml). After all the starting material had been consumed (t.l.c. control; 3 h), the reaction mixture was poured into chloroform (50 ml) and washed successively with saturated sodium bicarbonate solution (2 x 25 ml), water (25 ml), and saturated sodium chloride solution (25 ml) and dried over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure yielded a white solid.

Recrystallisation from ether/petrol yielded the title sulphone (5.39) as white needles (198 mg, 87 %).

^{1}H nmr (200 MHz) δ 0.05–016 (m, 1H), 0.32-0.48 (m, 1H), 0.48-0.67 (m, 1H), 0.67-0.83 (m, 1H), 1.47-1.67 (m, 1H), 3.30 (d, 1H, J=10.6 Hz) and 7.14-7.70 (m, 10 H). **^{13}C nmr** (50 MHz) δ 3.64, 7.39, 10.65, 76.40, 128.34, 128.62, 129.25, 129.89 and 133.34. **υ_{max}** ($CHCl_3$, cm^{-1}) 3034, 3024, 1448, 1307, 1144, 1082, 1025 and 860. **m.p.** 122-124°C. **Mass Spec.** 272 (M^+), 239, 211, 197, 161, 146, 135, 131 (100 %), 107, 91 and 77.

1-(1-PHENYLCYCLOPROPYL)-1-HYDROXY-2-METHYL-2-PROPENE (5.51)

To a stirred solution of the aldehyde (5.46) (250 mg, 1.7 mmol)[20] in dry THF (5 ml) in an ice bath, under nitrogen, was added a solution 2-propenylmagnesium bromide (2 M; 1.7 ml). The mixture was left in the ice bath for 5 min before it was alllowed to warm up to room temperature. After a further 1 h stirring, saturated ammonium chloride solution (3 ml) was added and the reaction mixture was poured into a 1:1 mixture of ether and water (100 ml). The aqueous layer was separated and extracted further with ether (2 x 20 ml). The combined ether layers were washed with saturated sodium chloride solution (25 ml), and dried over magnesium sulphate. Filtration and evaporation of solvents under reduced pressure, followed by silica gel column chromatography (eluant : petrol-ether 5:1) yielded the title alcohol (5.51) as a colourless liquid (352 mg, 82 %).

^{1}H nmr (200 MHz) δ 0.79–1.01 (m, 4H), 1.70 (s, 3H, CH=CHC*H*$_3$), 1.98 (s, 1H, C*H*OH), 3.76 (s, 1H, CHO*H*), 4.68 (d, 2H, J=6.9 Hz, CH=C*H*$_2$) and 7.15-7.34 (m, 5H). **^{13}C nmr** (50 MHz) δ 10.55, 10.67, 19.98,30.21, 80.84, 111.39, 126.62, 127.84, 130.49, 141.97 and 146.00. **υ_{max}** (film, cm^{-1}) 3450, 3081, 3016, 2869, 1652, 1602, 1498, 1445, 1374, 1290, 1215, 1052, 1026, 992, 975, 936, 899, 762, 736 and 700.

1-(1-PHENYLCYCLOPROPYL)-1-ACETOXY-2-METHYL-2-PROPENE (5.49)

Acetyl chloride (73 mg, 1.0 mmol) was added to a stirred solution of the alcohol (5.51) (100 mg, 0.5 mmol) and DMAP (113 mg, 0.6 mmol) in dry dichloromethane (5 ml) at 0 °C, under nitrogen. The mixture was stirred overnight, whilst the temperature was allowed to rise to room temperature. The reaction mixture was poured into a 2:1 mixture of ether and water (75 ml) and the aqueous phase was separated and extracted further with ether (2 x 15 ml). The combined ether fractions were washed successively with dilute hydrochloric acid (2 M; 15 ml), water (15 ml) and saturated sodium chloride solution (15 ml) before drying over magnesium sulphate. Filtration and evaporation of the solvents under reduced pressure, followed by silica gel column chromatography (eluant : petrol-ether 10:1) yielded the required acetate as a colourless oil (97 mg, 80 %) **^{1}H nmr** (200 MHz) δ 0.83 (br s, 1H), 0.96 (br s, 3H), 1.66 (s, 3H, H_2C=C-CH_3), 2.08 (s, 3H, CH_3CO_2), 4.68 (d, 2H, J=13.5 Hz, C=CH_2), 4.95 (s, 1H, CHO_2CCH_3) and 7.15-7.35 (m, 5H). **^{13}C nmr** (50 MHz) δ 11.17, 11.23, 20.21, 21.02, 28.49, 81.89, 112.37, 126.37, 126.71, 127.78, 130.52, 141.77, 142.36 and 169.92. **υmax** (film, cm^{-1}) 3084, 3026, 2922, 2855, 1740, 1654, 1559, 1492, 1452, 1374, 1239, 1027, 977, 901, 763, 738 and 700. **ANALYSIS :** calcd. for $C_{15}H_{18}O_2$: C, 78.23 ; H, 7.88. Found: C, 78.05 ; H, 7.92 %.

5-(1-PHENYLCYCLOPROPYL)-4-METHYL-5-PENTENOIC ACID (5.45).

To a stirred solution of LDA (1.0 M; 2.55 ml), in dry THF (15 ml) at -78 °C, under nitrogen, was added HMPA (1.5 ml), and a solution of the acetate (5.49) (490 mg, 2.1 mmol), in dry THF (1 ml). After 5 min a solution of t-butyldimethylsilyl chloride (385 mg, 2.6 mmol) in THF (1 ml) was added and the mixture was stirred at -78 °C for a further 1 h , before it was allowed to warm up to room temperature. After a further 2 h, the reaction mixture was poured into a 2:1 mixture of ether and water (75

ml) and acidified with dilute hydrochloric acid. The aqueous layer was separated and extracted further with ether (4 x 20 ml). The combined ether extracted were washed with water (20 ml) and saturated sodium chloride solution (20 ml) and dried over magnesium sulphate. Filtration and evaporation of solvents under reduced pressure yielded a green oil that was dissolved in THF (30 ml) and stirred with dilute hydrochloric acid (2 M; 10 ml), for 1 h. The reaction mixture was poured into dilute sodium hydroxide solution (2 M; 50 ml) and extracted with hexane (3 x 5 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether (4 x 25 ml). The combined ether layers were washed with water (25 ml) and saturated sodium chloride solution (25 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure yielded the crude acid as a colourless oil that solidified on standing. Recrystallisation from petrol gave the title acid (5.45) as prisms (260 mg, 53 %).

^{1}H nmr (400 MHz) δ 0.97 (br s, 2H), 1.11 (br s, 2H), 1.66 (s, 3H, CH_3-C=C), 2.37 (t, 2H, J=7.0 Hz, 3-H_2), 2.50 (t, 2H, J=7.0 Hz, 2-H_2), 5.60 (s, 1H, 5-H) and 7.09-7.26 (m, 5H). **^{13}C nmr** (100 MHz) δ 17.45, 18.41, 22.79, 32.90,33.96, 125.09, 125.81, 128.16, 128.82, 130.54, 138.66 145.54 and 179.52. **υ_{max}** ($CHCl_3$, cm^{-1}) 3083, 2916, 2857, 2657, 1710, 1602, 1496,1444, 1422, 1380, 1296, 1127, 1027 and 764. **ANALYSIS :** calcd. for $C_{15}H_{18}O_2$: C, 78.23 ; H, 7.88. Found: C, 78.32 ; H, 8.00 %. **mp.** 52°C.

The hexane fractions were combined and concentrated *in vacuo* to give recovered starting material (5.49) (107 mg, 22 %).

ETHYL 7-(1-PHENYLCYCLOPROPYL)-6-METHYL-3-OXO-6-HEPTENOATE (5.52)

Homologation of the acid (5.45) (400 mg, 1.7 mmol) was achieved by repeating the procedure for the preparation of β-ketoester (5.11), to yield the title compound (5.52) as a colourless oil (381 mg, 73 %).

^{1}H nmr (300 MHz) δ 0.98 (m, 2H), 1.12 (m, 2H), 1.29 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.66 (s, 3H, CH_3-C=C), 2.34 (t, 2H, J=7.2 Hz, 5-H_2), 2.69 (t, 2H, J=7.2 Hz, 4-H_2), 3.45 (s, 2H, 2-H_2), 4.12 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.58 (s, 1H, 7-H_2) and 7.10-7.28 (m, 5H). **υ_{max}** (film, cm^{-1}) 3081, 2988, 2920, 1747,1717,1650, 1600, 1495, 1446, 1411, 1368, 1316, 1236, 1186, 1152, 1099, 1030, 758 and 699.

ETHYL 3-(t-BUTYLDIMETHYLSILYLOXY)-7-(1-PHENYLCYCLOPROPYL)-6-METHYL--6-HEPTENOATE (5.53).

To a stirred solution of β-ketoester (5.52) (300 mg, 1.0 mmol) in propan-2-ol (25 ml), at room temperature was added sodium borohyride (42 mg, 1.1 mmol). Stirring was continued for 1 h before the mixture was poured into a 2:1 mixture of ether and water (75 ml). The aqueous phase was separated and extracted further with ether (3 x 15 ml). The combined ether layers were washed with water (20 ml) and saturated sodium chloride (20 ml) and dried ($MgSO_4$). Filtration and evaporation under reduced pressure, followed by silica gel column chromatography (eluant: petrol-ether 5:1) afforded the corresponding hydroxyester as a colourless oil (219 mg, 73 %).

^{1}H nmr (300 MHz) δ 0.94 (m, 2H), 1.10 (m, 2H), 1.24 (t, 3H, J=7.3 Hz, OCH_2CH_3), 1.50-1.72 (m, 2H, 4-H_2), 1.63 (s, 3H, CH_3-C=C), 2.03-2.25 (m, 2H, 5-H_2), 2.36-2.54 (m, 2H, 2-H_2), 3.08 (br s, 1H, O*H*), 3.99 (q, 1H, J=2 Hz, 3-H),

4.16 (q, 2H, J=7.3 Hz, OCH_2CH_3), 5.58 (s, 1H, 7-H) and 7.06-7.27 (m, 5H). **^{13}C nmr** (75 MHz) δ 14.21, 17.59, 18.43, 34.83, 35.14, 41.35, 60.70, 67.82, 125.03,125.84, 128.14, 140.18, 145.80 and 172.95. **υ_{max}** (film, cm^{-1}) 3437, 3081, 2982, 2935, 2864, 1734, 1600, 1495, 1456, 1446, 1374 ,1302, 1253, 1186, 1153, 1101, 1030, 757 and 698

t-Butyldimethylsilyl chloride (161 mg, 1.1 mmol) and imidazole (112 mg, 1.8 mmol), were stirred in dry DMF (4 ml) at room temperature, under nitrogen. A solution of the hydroxyester (215 mg, 0.71 mmol) in DMF (1 ml), was added and the mixture was stirred overnight. The resultant clear solution was poured into water (50 ml) and extracted with ether (4 x 25 ml). The combined organic extracts were washed successively with dilute hydrochloric acid (2 M; 25 ml), water (25 ml) and saturated sodium chloride solution (25 ml), and dried ($MgSO_4$). Filtration and evaporation of the solvents under reduced pressure, followed by silica gel column chromatography (eluant: petrol-ether 10:1), afforded the title silyloxyester (5.53) as a colourless liquid (262 mg, 89 %).

^{1}H nmr (300 MHz) δ (0.04 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.04 (br s, 2H), 1.09 (br s, 2H), 1.16 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.68-1.78 (m, 2H, 4-H_2), 1.72 (s, 3H, CH_3-C=C), 2.08-2.20 (m, 2H, 5-H_2), 2,52 (d, 2H, J=9.8 Hz, 2-H_2), 4.14-4.23 (m, 3H, OCH_2CH_3 and 3-H), 5.68 (s, 1H, 7-H) and 7.11-7.32 (m, 5H). **^{13}C nmr** (75 MHz) δ -4.69, -4.43, 14.29, 18.04, 22.88, 25.87, 34.69, 35.97, 42.62, 42.89, 60.27, 69.17, 125.04, 125.86, 127.99, 128.16, 140.33, 145.82 and 171.64. **υ_{max}** (film, cm^{-1}) 3081, 2955, 2857, 1736, 1601, 1495, 1462, 1375, 1305, 1255, 1189, 1151, 1090, 1030, 836, 812, 776, 756 and 698.

Se-PHENYL 3-(t-BUTYLDIMETHYLSILYLOXY)-7-(1-PHENYLCYCLO-PROPYL)-6-METHYL-6-SELENOHEPTENOATE (5.54)

Saponification of silyloxyester (5.54) (260 mg, 0.62 mmol) yielded the corresponding silyloxy acid as a colourless oil (205 mg, 85 %).

^{1}H nmr (300 MHz) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 0-94-1.02 (m, 2H), 1.11-1.16 (m, 2H), 1.66 (s, 3H, CH_3-C=C), 1.66-1.74 (m, 2H, 4-H_2), 2.05-2.13 (m, 2H, 5-H_2), 2.54 (dd, 2H, J=5.5, 1.2 Hz, 2-H_2), 4.16 (q, 1H, J=5.8 Hz, 3-H), 5.59 (s, 1H, 7-H) and 7.09-7.31 (m, 5H). **υ_{max}** (film, cm^{-1}) 3083, 2928, 2855, 2670, 1711, 1600, 1494, 1462, 1438, 1307, 1256, 1096, 1030, 939, 836, 811, 776, 756 and 698.

The standard preparation for selenoesters was repeated on the silyloxyacid (150 mg, 0.39 mmol), to afford the title selenoester (5.54) as a near colourless oil (59 mg, 29 %).

^{1}H nmr (300 MHz) δ 0.08 (s, 6H), 0.89 (s, 9H), 0.94-1.01 (m, 2H), 1.08-1.12 (m, 2H), 1.66 (s, 3H, CH_3-C=C), 1.66-1.74 (m, 2H, 4-H_2), 2.10-2.12 (m, 2H, 5-H_2), 2.84 (dq, 2H, J=14.8, 7.2 Hz, 2-H_2), 4.09 (quint, 1H, J=7 Hz, 3-H), 5.57 (s, 1H, 7-H) and 7.08-7.29 (m, 10H). **υ_{max}** ($CHCl_3$, cm^{-1}) 2955, 2930, 2857, 1718, 1600, 1579, 1494, 1472, 1440, 1362, 1095, 1022, 981 and 838. **Mass Spec.** Calcd. for $C_{29}H_{40}O_2SeSi$: 528.1963. Found : 528.1952. **m/z** 528 (M^+), 513, 471, 371, 331, 313, 284, 256, 239, 211, 197 (100 %), 171, 157 and 127.

REACTION OF Se-PHENYL 3-(t-BUTYLDIMETHYLSILYLOXY)-7-(1-PHENYL-CYCLOPROPYL)-6-METHYL-6-SELENOHEPTENOATE (5.54) *WITH TRI-n-BUTYLTIN HYDRIDE .*

The selenoester (5.54) (29 mg, 0.05 mmol) was refluxed in dry benzene (10 ml) under nitrogen. A solution of tri-n-butyltin hydride (18 mg) in benzene (5 ml) with a trace of AIBN (ca. 1mg) was added over 10 h (syringe pump). Refluxing was continued for a further 10 h, with slow addition of a solution of AIBN (ca.3 mg) in benzene (1 ml) throughout this period. The mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by preparative t.l.c. (eluant : petrol-ether 20:1), to afford the unstable aldehyde (5.55) (8 mg, 40 %) as a colourless oil.

^{1}H nmr (300 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H),0.97 (t, 2H, J=3.9 Hz), 1.11 (t, 2H, J=2.6 Hz), 1.64 (s, 3H, CH_3-C=C), 1.64-1.70 (m, 2H, 4-H_2), 2.02-2.08 (m, 2H, 5-H_2), 2.54 (dd, 2H, J=5.9, 2.5 Hz, 2-H_2), 4.18 (tt, 1H, J=5.9 Hz, 3-H), 5.56 (s, 1H, 7-H), 7.10-7.36 (m, 5H) and 9.81 (t, 1H, J=2.5 Hz). **^{13}C nmr** (75 MHz) δ -4.64, -4.40,22.88, 25.77, 34.78, 36.15, 50.74, 67.89, 102.64, 125.06, 125.88, 128.15, 132.43, 140.00 and 145.76. **υ_{max}** ($CHCl_3$, cm^{-1}) 3032, 2896, 1722, 1600, 1522, 1474, 1424, 1390, 1334, 1236, 1202, 1078,1045, 929, 877, 836 and 808.

A second fraction was recovered and was found to be starting selenoester (5.54) (4.9mg, 17 %).

6-(1-PHENYLCYCLOPROPYL)-5-METHYL-5E-HEXENOIC ACID (5.56)

The unsaturated acid (5.45) (250 mg, 1.1 mmol), was stirred in dry benzene (25 ml) with a drop of dry DMF at room temperature under nitrogen. Oxalyl choride

(344 mg, 2.7 mmol) was added dropwise and the mixture was stirred for 30 min before the solvents were removed *in vacuo*. The crude acid chloride was used without further purification.

A solution of the acid chloride (270 mg, 1.1 mmol), in ether (5 ml) was added dropwise to a freshly prepared solution of diazomethane (137 mg, 3.3 mmol)[21] in ether (30 ml) stirring at 0 °C under nitrogen. The mixture was stirred for 24 h before the solvents were evaporated under reduced pressure. The residue was dissolved in ethanol (30 ml) and silver acetate (20 mg) was added. The mixture was refluxed for 1 h before cooling to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in ether (25 ml) and the silver salts were removed by filtration. The ether solution was evaporated under reduced and silica gel column chromatography (eluant : petrol-ether 15:1) afforded a 6:1 mixture (nmr) of the ethyl ester of the title acid and the methyl ester of the starting acid (139 mg, 47 %). Salient features for the ethyl ester.

^{1}H nmr (200 MHz) δ 0.93–1.05 (m, 2H), 1.06–1.15 (m, 2H), 1.26 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.63 (s, 3H, CH_3-C=C), 1.77 (quint, 2H, J=7.2 Hz, 3-H_2), 2.06 (t, 2H, J=7.2 Hz, 2-H_2), 2.28 (t, 2H, J=7.2 Hz, 4-H_2), 4.14 (q, 2H, J=7.2 Hz, OCH_2CH_3), 5.57 (s, 1H, 6-H) and 7.07-7.28 (m, 5H). **^{13}C nmr** (50 MHz) δ 14.20, 17.32, 18.16, 23.31, 33.81, 38.58, 60.11, 125.04, 126.02, 128.11, 128.78, 139.62, 145.85 and 173.52. **υ_{max}** .(film, cm^{-1}) 3059, 2984, 2932, 2855, 1736, 1600, 1495, 1458, 1445, 1374, 1247, 1189, 1151, 1100, 1054, 1029, 910, 866, 756, 734 and 698. **Mass Spec.** 258 $(M-H)^+$, 244, 230, 215, 198, 184, 170, 155, 141, 129 (100 %), 115, 105, 91 and 77.

Saponification of the ethyl ester by the standard method gave the title acid (5.56) as a colourless oil in a 6:1 mixture (nmr) with the starting acid (5.45) (113 mg, 93 %).

For the Major product

^{1}H nmr (300 MHz) δ 0.96–1.06 (m, 2H), 1.10-1.15 (m, 2H), 1.66 (s, 3H, CH_3-C=C), 1.81 (quint, 2H, J=7.5 Hz, 3-H_2), 2.10 (t, 2H, J=7.5 Hz, 2-H_2), 2.36 (t, 2H, J=7.5 Hz, 4-H_2), 5.60 (s, 1H, 6-H) and 7.11-7.29 (m, 5H). **^{13}C nmr** (75 MHz) δ 17.28, 18.29, 22.79, 22.84, 33.42, 33.87, 38.34, 124.99, 125.82, 128.09, 128.68, 139.48, 145.69 and 180.05. **υ_{max}** (film, cm^{-1}) 3086, 3019, 2934, 2859, 2661, 1707, 1648, 1600, 1495, 1444, 1424, 1289, 1240, 1207, 1156, 1100, 1054, 1030, 936, 874, 838 and 756. **Mass Spec. m/z** 230 (M^+), 212, 195, 184, 170, 155, 141, 129, 115, 105, 91, 85, 83 (100 %) and 77.

Se-PHENYL 6-(1-PHENYLCYCLOPROPYL)-5-METHYL-5E-SELENO-HEXENOATE (5.57)

The standard method for preparation of selenoesters was repeated on the 6:1 mixture of cyclopropyl acids (5.56) and (5.45) (100 mg, 0.41 mmol) to give the title selenoester (5.57) as a 6:1 mixture (nmr) with the lower homologue (118 mg, 75 %). **^{1}H nmr** (300 MHz) δ 0.97–1.06 (m, 2H), 1.11-1.14 (m, 2H), 1.64 (s, 3H, CH_3-C=C), 1.84 (quint, 2H, J=7.4 Hz, 3-H_2), 2.10 (t, 2H, J=7.4 Hz, 2-H_2), 2.69 (t, 2H, J=7.4 Hz, 4-H_2), 5.59 (s, 1H, 6-H) and 7.14-7.54 (m, 10H). **υ_{max}** (film, cm^{-1}) 3058, 3012, 2933, 1726, 1599, 1494, 1439, 1066, 1022, 756, 738 and 697. **Mass Spec.** Calcd for $C_{22}H_{24}OSe$: 384.0992. Found : 384.0992. **m/z** 383 $(M-H)^+$, 355, 316, 293, 237, 225, 183, 169, 157, 141, 129 and 117.

REACTION OF Se-PHENYL 6-(1-PHENYLCYCLOPROPYL)-5-METHYL-5E-SELENO-HEXENOATE (5.57) *WITH TRI-n-BUTYLTIN HYDRIDE.*

The selenoester (5.57) (100 mg, 0.26 mmol), was refluxed in dry benzene (20 ml) under nitrogen. A solution of tri-n-butyltin hydride (114 mg, 0.39 mmol), in benzene (2 ml) containing a trace of AIBN (ca. 2 mg), was added dropwise during 8 h

(syringe pump). Refluxing was continued for a further 1 h before cooling to room temperature and removal of the solvent *in vacuo*. The residue was purified by silica gel column chromatography (eluant : petrol-ether 15:1) to yield the unsaturated aldehyde (5.58) (26mg, 43 %) as a colourless oil.

^{1}H nmr (300 MHz) δ 0.89–0.98 (m, 2H), 10.04-1.07 (m, 2H), 1.57 (s, 3H, C*H*$_3$-C=C), 1.73 (quint, 2H, J=7.4 Hz, 3-H$_2$), 2.00 (t, 2H, J=7.4 Hz, 2-H$_2$), 2.35 (dt, 2H, J=7.4, 1.5 Hz, 4-H$_2$), 5.51 (s, 1H, 6-H), 7.06-7.21 (m, 5H) and 9.71 (t, 1H, J=1.5 Hz). **^{13}C nmr** (75 MHz) δ 17.27, 18.21, 20.25, 22.86, 33.86, 38.36, 43.24, 125.02, 125.84, 128.08, 128.72, 139.51 and 145.65. **υmax** (film, cm^{-1}) 3082, 2935, 2852, 2720, 1726, 1600, 1495, 1458, 1409, 1384, 1101, 1077, 1031, 912, 872, 834, 757 and 699. **Mass Spec.** Calcd. for $C_{16}H_{20}O$: 228.1514. Found : 228.1510. **m/z** 228 (M^+), 213, 199, 185, 181, 171, 157 (100 %), 143, 129, 115, 105, 91 and 77.

ETHYL 3,3-ETHYLENEDIOXY-6(E),8(E),-DECADIENOATE (5.63).

Ethyl 3-oxo-6E,8E-decadienoate (5.62) (400 mg, 1.9 mmol),[22] ethylene glycol (590 mg, 9.5 mmol) and camphor 10-sulphonic acid (44 mg, 0.2 mmol) were refluxed in benzene under azeotropic conditions for 6 h. The reaction mixture was cooled to room temperature, poured into ether (50 ml) and washed with water (2 x 20 ml) and saturated sodium chloride solution (15 ml), before drying ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure and column chromatography on silica gel (eluant : petrol-ether 10:1), afforded the title compound (5.63) as a colourless oil (370 mg, 76 %).

^{1}H nmr (300 MHz) δ 1.23 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.68 (d, 3H, J=6.7 Hz, 10-H$_2$), 1.83-1.88 (m, 2H, 4-H$_2$),2.13 (dt, 2H, J=8.7, 6.9 Hz, 5-H$_2$), 2.61 (s, 2H, 2-H$_2$), 3.91-4.01 (m, 4H), 4.11 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.44-5.59 (m, 2H) and 5.92-6.03 (m, 2H). **^{13}C nmr** (75 MHz) δ 14.05, 17.85, 26.48, 37.18, 42.65,

60.38, 65.01, 108.94, 126.89, 130.38, 130.80, 131.44 and 169.30. υ_{max} (film, cm^{-1}) 2982, 2890, 1738, 1446,1370, 1303, 1274, 1221, 1102, 1047, 989,950, 928, 892, 842 and 773.

Se-PHENYL 3,3-ETHYLENEDIOXY-6(E),8(E),-SELENODECADIENOATE (5.64).

The standard procedure for saponification was repeated on the diene ester (5.63) (400 mg, 1.6 mmol) to yield the corresponding acid as a colourless oil (342 mg, 96 %). **^{1}H nmr** (300 MHz) δ 1.70 (d, 3H, J=6.2 Hz, 10-H_2), 1.84-1.95 (m, 2H, 4-H_2), 2.16 (dt, 2H, J=8.8, 6.8 Hz, 5-H_2), 2.68 (s, 2H, 2-H_2), 3.94-4.04 (m, 4H), 5.46-5.62 (m, 2H) and 5.91-6.05 (m, 2H). **^{13}C nmr** (75 MHz) δ 17.91, 26.45, 37.06, 42.47, 65.08, 102.57, 108.81, 127.12, 130.56, 131.40 and 174.90. υ_{max} (film, cm^{-1}) 3138, 3006, 2958, 2925, 2688, 1711, 1653, 1629, 1440, 1409, 1369, 1305, 1274, 1224, 1111, 1046, 989, 950, 880 and 734.

Standard selenoester formation on the diene acid (350 mg, 1.6mmol), yielded the title selenoester (5.64) as a colourless oil. (401 mg, 71 %).
^{1}H nmr (300 MHz) δ 1.70 (d, 3H, J=6.7 Hz, 10-Hz), 1.77-1.94 (m, 2H, 4-H_2), 2.08-2.30 (m, 2H, 5H_2), 3.02 (s, 2H, 2-H_2), 3.93-4.05 (m, 4H), 5.41-5.74 (m, 2H), 5.88-6.09 (m, 2H) and 7.06-7.26 (m, 5H). **^{13}C nmr** (75 MHz) δ 17.86, 26.55, 26.87,37.73, 54.26, 65.27, 108.93, 127.06, 128.82, 129.27, 130.63, 130.73, 131.60, 133.02, 135.67 and 195.90. υ_{max} (film, cm^{-1}) 3059, 3016, 2958, 2886, 1712, 1579.9, 1478, 1439, 1304, 1142, 1108, 1045, 989, 949, 926, 740 and 690.

REACTION OF Se-PHENYL 3,3-ETHYLENEDIOXY-6(E),8(E),-SELENO-DECADIENEOATE (5.64) *WITH TRI-n-BUTYLTIN HYDRIDE.*

To a stirring solution of selenoester (5.64) (150 mg, 0.41 mmol), in benzene (25 ml), at reflux under nitrogen, was added a solution of tri-n-butyltin hydride (143 mg, 0.49 mmol) in benzene (5 ml) with a catalytic amount of AIBN (ca. 5 mg), during 8 h (syringe pump). Refluxing was continued for a further 10 h, with slow addition of a solution of AIBN (ca. 5 mg) in benzene (2 ml) during the 10 h. The mixture was cooled to room temperature and the solvents removed *in vacuo*. Purification by silica gel column chromatography (eluant : petrol-ether 1:1) yielded a mixture of the cyclohexanones (5.14) and (5.65) as a colourless oil (76mg, 88 %).

Salient features for *Z*-isomer (5.65) from a mixture with the *E*-isomer (5.14)
^{1}H nmr (300 MHz) δ 0.88 (t, 3H, J=7.3 Hz, 10-H_2), 1.53-1.64 (m, 4H) and 2.37-2.49 (m, 1H, 6-H).

HYDROGENATION OF CYCLOHEXANONES (5.14) *AND* (5.65).

The mixture of cyclohexanones (5.14) and (5.65) (46 mg, 0.22 mmol), was stirred in ethyl acetate (10 ml) over a catalytic amount of platinum oxide monohydrate (2 mg), under 1 atm of hydrogen (manometer) for 14 h. The catalyst was filtered off through a pad of celite, and the solution was evaporated under reduced pressure to yield the saturated cyclohexanone (5.66), as a colourless oil (42 mg, 91 %).
^{1}H nmr (300 MHz) δ 0.88 (t, 3H, J=6.3 Hz, 10-H_3), 1.18-1.28 (m, 6H, 7-H_2, 8-H_2 and 9-H_2), 1.43-1.55 (m, 1H, 5-H_{ax}), 1.71-1.83 (m, 1H, 5-H_{eq}), 1.88-2.04 (m, 2H, 4-H_2), 2.19 (quint, 1H, J=3.8, 3.8 Hz, 6-H), 2.58 (s, 2H, 2-H_2) and 3.93 (s, 4H). **^{13}C nmr** (75 MHz) δ 13.89, 22.70, 26.62, 28.51, 29.26, 33.99, 49.20, 51.17, 64.54, 64.65, 110.35 and 208.26. **υ_{max}** (film, cm^{-1}) 2856, 2833, 2872, 1716,

1456, 1415, 1356, 1294, 1243, 1193, 1147, 1098, 1036, 948, 933 and 795. **Mass Spec.** Calcd. for $C_{12}H_{20}O_3$:212.1412. Found : 212.1469. **m/z** 212 (M^+), 169, 156, 141, 127, 113, 99 (100 %), 86, 69 and 55.

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APPENDIX

RESULTS OF FORCE FIELD CALCULATIONS

$$E_{TOT} = \Sigma E_{VDW} + \Sigma E_{coul} + \Sigma E_{angle} + \Sigma E_{H\text{-}bond} + \Sigma E_{torsion} + \Sigma E_{bond}$$

COMPOUND 1

```
-34.184384 kcal=total energy

  1.004344 kcal=bond energy
  6.136109 kcal=theta energy
  6.260539 kcal=phi energy
  0.012206 kcal=out of plane energy
  0.000000 kcal=hydrogen-bond energy
  5.142678 kcal=nonbond energy
 30.728403 kcal=non-bond repulsion energy
-25.585725 kcal=non-bond dispersion energy
-52.740260 kcal=coulomb energy
```

COMPOUND 2

```
-35.243941 kcal=total energy

  1.100439 kcal=bond energy
  7.809004 kcal=theta energy
  3.410547 kcal=phi energy
  0.001693 kcal=out of plane energy
  0.000000 kcal=hydrogen-bond energy
  5.938143 kcal=nonbond energy
 31.528714 kcal=non-bond repulsion energy
-25.590570 kcal=non-bond dispersion energy
-53.503766 kcal=coulomb energy
```

COMPOUND 3

```
-12.359849 kcal=total energy

  2.179538 kcal=bond energy
 15.406738 kcal=theta energy
 10.840119 kcal=phi energy
  0.040446 kcal=out of plane energy
  0.000000 kcal=hydrogen-bond energy
  7.260299 kcal=nonbond energy
 49.690057 kcal=non-bond repulsion energy
-42.429758 kcal=non-bond dispersion energy
-48.086989 kcal=coulomb energy
```

COMPOUND 4

-14.521626 kcal=total energy

2.139122 kcal=bond energy
14.624322 kcal=theta energy
10.526786 kcal=phi energy
0.005185 kcal=out of plane energy
0.000000 kcal=hydrogen-bond energy
7.406308 kcal=nonbond energy
48.375911 kcal=non-bond repulsion energy
-40.969603 kcal=non-bond dispersion energy
-49.223349 kcal=coulomb energy

COMPOUND 5

-15.473165 kcal=total energy

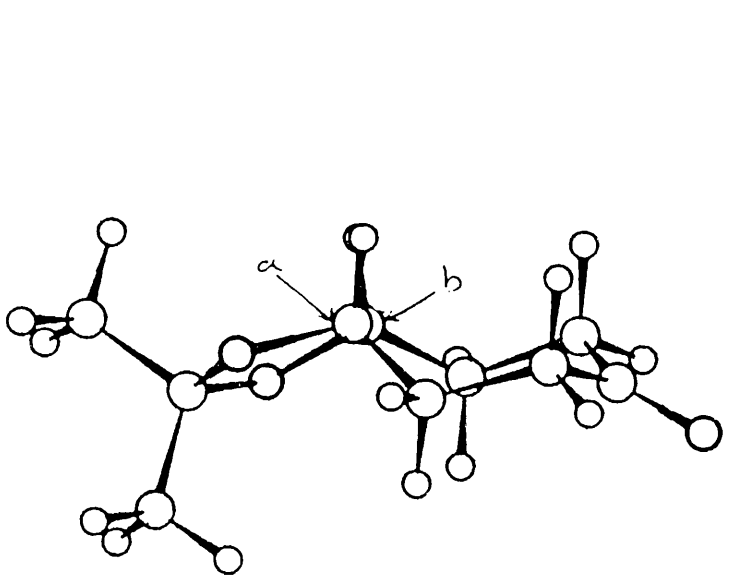
2.100069 kcal=bond energy
12.241523 kcal=theta energy
11.175456 kcal=phi energy
0.012813 kcal=out of plane energy
0.000000 kcal=hydrogen-bond energy
7.105308 kcal=nonbond energy
48.585056 kcal=non-bond repulsion energy
-41.479748 kcal=non-bond dispersion energy
-48.108336 kcal=coulomb energy

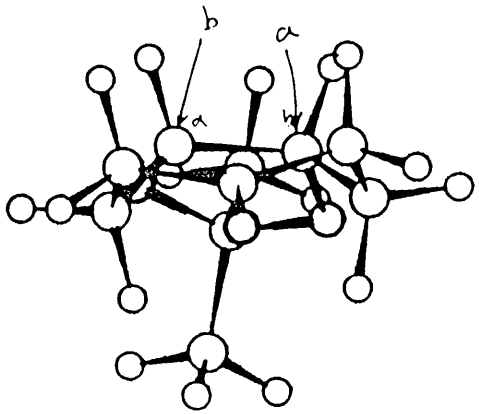
COMPOUND 6

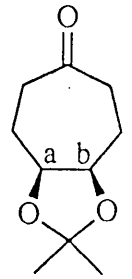
-16.872170 kcal=total energy

2.084807 kcal=bond energy
11.478548 kcal=theta energy
10.688146 kcal=phi energy
0.016033 kcal=out of plane energy
0.000000 kcal=hydrogen-bond energy
8.106164 kcal=nonbond energy
48.129568 kcal=non-bond repulsion energy
-40.023404 kcal=non-bond dispersion energy
-49.245868 kcal=coulomb energy

COMPOUND 1

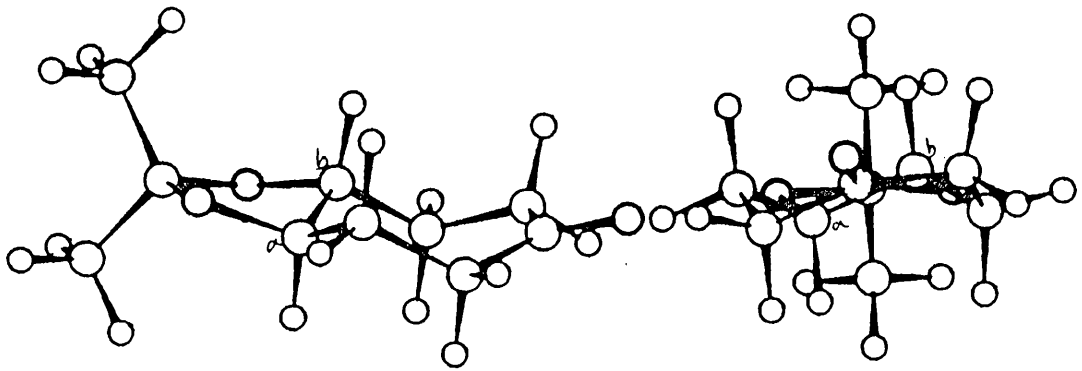


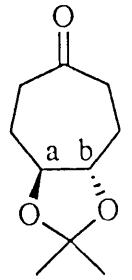




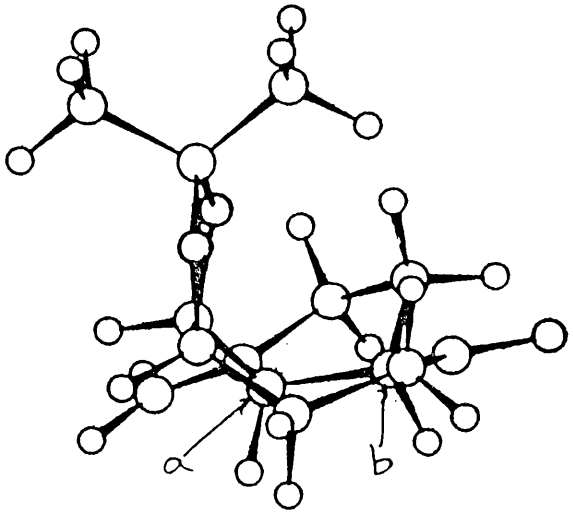
1. front/side

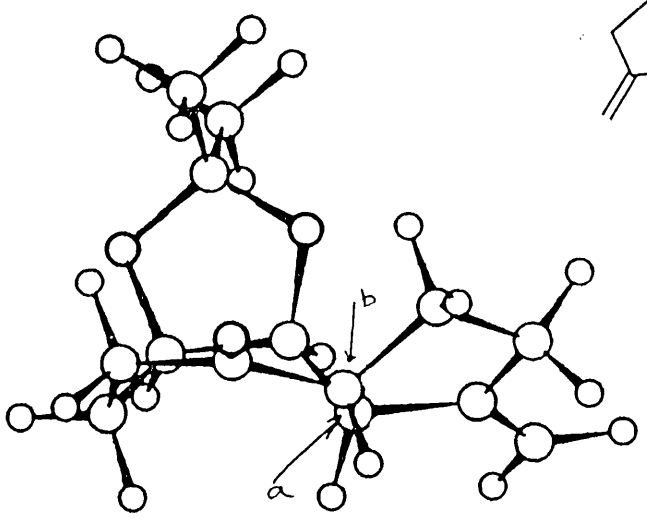
COMPOUND 2

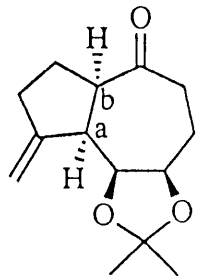


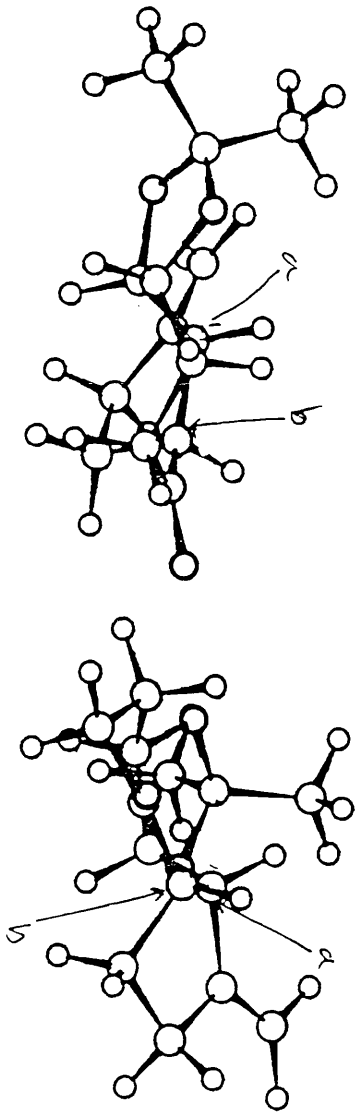


COMPOUND 3

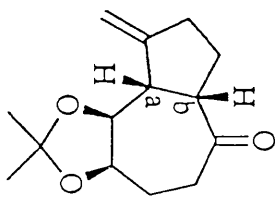








COMPOUND 4



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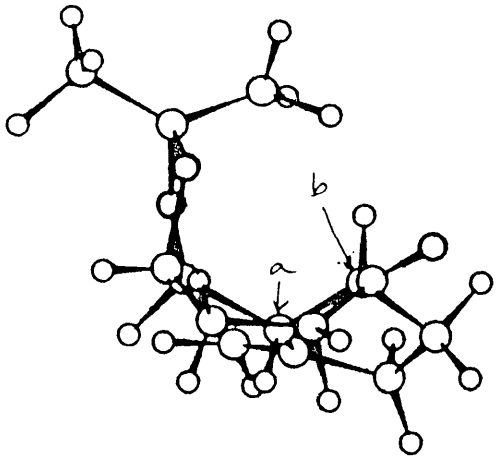

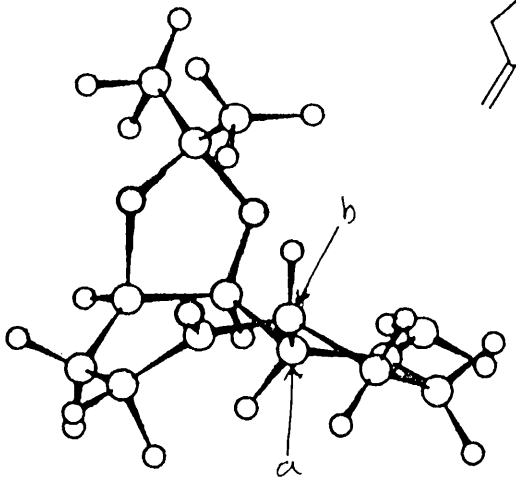

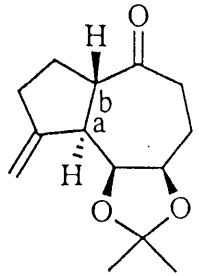

COMPOUND 6