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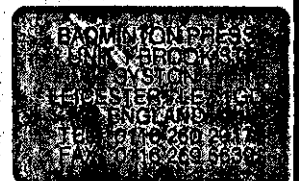
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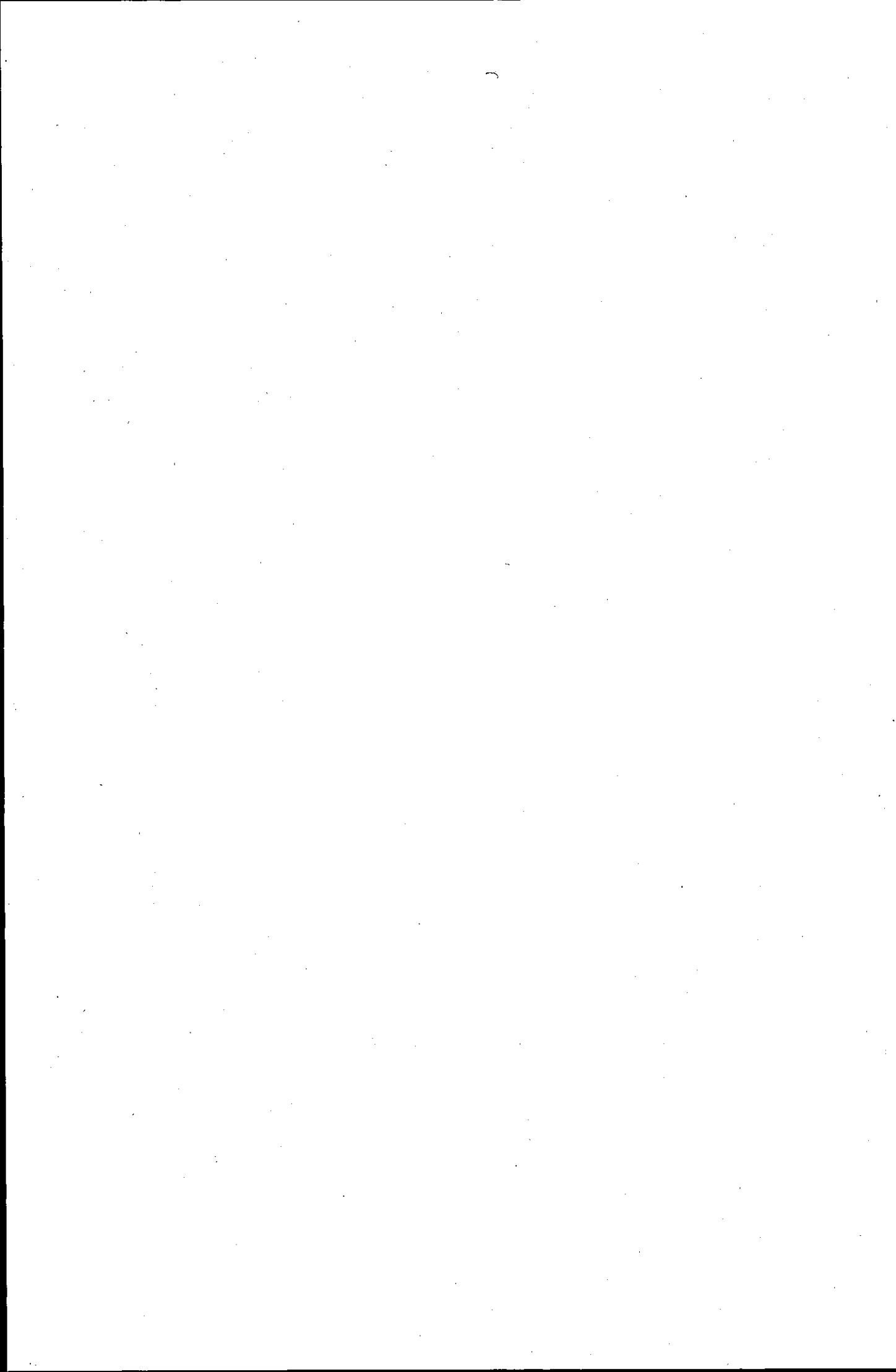
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Tandem Reactions of Oxiranylcarbinyloxy Radicals.

by

John Andrew Rudderham

A Doctoral Thesis

Submitted in partial fulfilment of the requirements

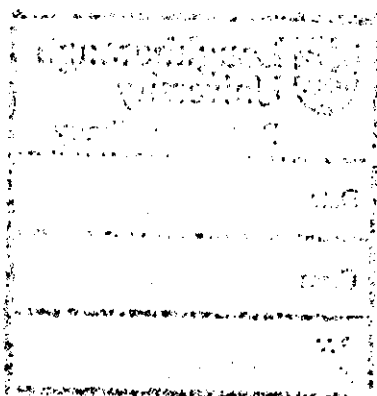
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For My Family

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Abstract

The work described in this thesis is an investigation into the reactivity and possible synthetic applications of oxiranylcabiny radicals. These radicals rapidly rearrange via β -cleavage, which can proceed by breakage of either the C-O or the C-C bond. Cleavage of the latter only occurs when the molecule has a vinyl or phenyl stabilising group attached to the epoxide ring.

Attempts to produce products derived from C-C bond cleavage and subsequent intermolecular tandem processes are described in chapter 2.

The results described in chapter 3 show that products of C-C cleavage are not obtained in aryl substituted systems when the alkoxy radical derived from C-O cleavage can undergo either a 5-exo cyclisation or a 1,5 hydrogen abstraction.

A study of stereochemical factors in the 1,5-hydrogen abstraction reactions has shown evidence of C-C cleavage prior to product formation. This shows that it is the relative reactivities of the alkoxy and carbon centred radicals that influence the product formation. Aryl-substituted oxiranylcabiny radicals are in dynamic equilibrium between the epoxide, C-O and C-C cleaved species.

The work in chapters 5 and 6 describes synthetic routes to precursors designed to test if oxiranylcabiny radicals can be used in the synthesis of medium ring lactones. An investigation into the use of these free radical reactions on a solid phase polymer support is also described.

Abbreviations

AIBN	Azoisobutyronitrile.
bp	Boiling Point.
DCM	Dichloromethane.
de	Diastereomeric Excess.
Diazald	N-methyl-N-nitroso- <i>p</i> -toluene sulfonamide.
DIBAL	Diisobutylaluminium Hydride.
DMAP	N,N-dimethyl-4-aminopyridine.
DMF	Dimethylformamide.
DMPU	1,3-Dimethyl-2-oxohexahydropyrimidine.
DMSO	Dimethylsulfoxide.
ESR	Electron Spin Resonance
GC-MS	Gas Chromatography Mass Spectrometry.
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital.
IR	Infra-red.
LDA	Lithium Diisopropylamide.
LUMO	Lowest Unoccupied Molecular Orbital.
MALDI-TOF MS	Matrix Assisted Laser Desorption Time of Flight Mass Spectrometry.
<i>m</i> CPBA	<i>meta</i> -Chloroperbenzoic acid.
mmol	Millimole(s).
mp	Melting Point.
nOe	Nuclear Overhauser Enhancement.
<i>p</i> TSA	<i>para</i> -Toluenesulfonic Acid.
NMR	Nuclear Magnetic Resonance.
psi	Pounds per Square Inch.
RT	Room Temperature.
SOMO	Singly Occupied Molecular Orbital.
TBAF	Tetrabutylammonium Fluoride.
THF	Tetrahydrofuran.
TMS	Trimethylsilyl.
TLC	Thin Layer Chromatography.

UV

Ultraviolet

Wang

para-Benzyloxybenzylalcohol Resin.

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1 A Review of the Chemistry of Oxiranylcarbonyl Radicals.

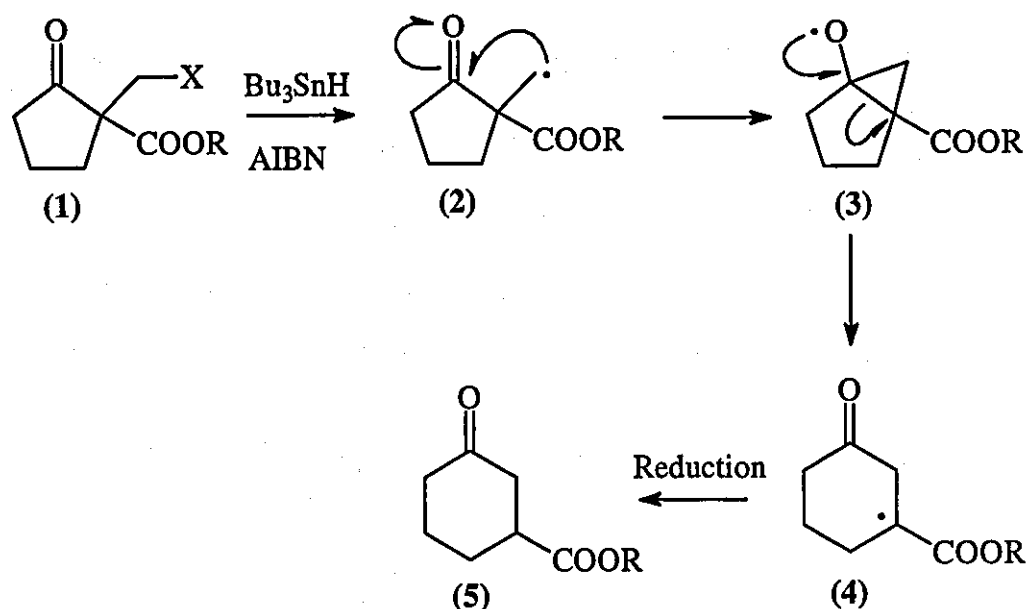
1.1 Introduction

Over the past twenty years the use of free radical chain reactions has become more widespread in organic chemistry and several review articles have been published in the area.¹⁻⁵ Such reactions are particularly useful in polar and hindered environments because free radicals are neutral and thus less prone to solvation or aggregation effects which can hinder reactions involving highly charged species. The main disadvantage with free radical reactions is that they often have several possible outcomes with the desired product being only one of several. However careful control of the reaction conditions can suppress formation of less desirable products. For example, in reactions where tributyltin hydride is used, very slow infusion of this reagent into the reaction mixture can minimise reduction of reaction intermediates before other steps in the propagation cycle, such as rearrangement or ring closure, are complete.

1.2 Ring Expansion Reactions.

Many compounds of synthetic interest contain 7 membered or larger carbocyclic or heterocyclic rings. These rings can be very difficult to prepare because methods used to synthesise five or six membered rings often fail when applied to larger systems.⁶ Ring closure reactions become less favourable as the ring size increases because of entropy loss and competition from intermolecular reactions. In some cases torsional strain in products and transition states also hinders these reactions.

An alternative approach to these systems is *via* ring expansion in which the bridging bond in a bicyclic system is broken to give a single larger ring. A variety of methods have been developed for this procedure using free radical reactions,⁷ an example of which is the ring expansion of β -ketoesters. The β -ketoesters are first alkylated with a halo-alkyl group. Tributyltin hydride reduction of (1) gives the ring-expanded β -ketoester (5) *via* cyclisation of the primary radical (2), β -cleavage to the stabilised radical (4) and reduction (see Scheme 1-1).



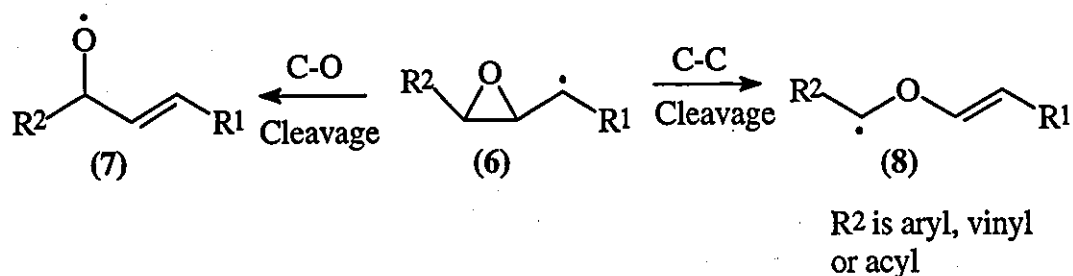
Scheme 1-1

A variety of radical generating groups have been used for the reaction ($X = \text{Br}, \text{I}, \text{SePh}$) and the reaction has also been used to expand rings ranging in size from five to fifteen atoms as well as acyclic systems. The incorporation of two, three or four carbon atoms into β -ketoesters *via* the use of bromo-ethyl, -propyl and -butyl sidechains respectively has also been demonstrated.

1.3 The Chemistry of Oxiranylcarbiny l Radicals.

1.3.1 Introduction.

The first example of an oxiranylcarbiny l radical was reported by Sabatino and Gritter in 1963.⁸ Oxiranylcarbiny l radicals (6) rapidly rearrange by β -cleavage in which either the C-O or C-C bond of the epoxide is broken (see Scheme 1-2). C-O bond cleavage gives rise to an allylic alkoxy radical (7) and occurs in all cases where there is no radical stabilising group at R^2 . C-C bond cleavage is less common and occurs when an aryl, vinyl or, in some cases, an acyl group is present at R^2 .

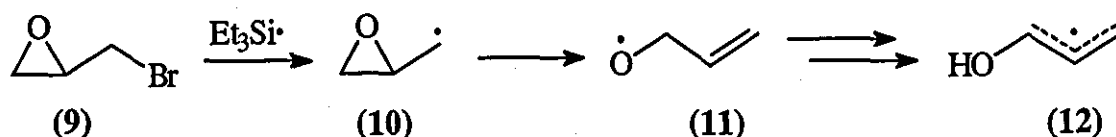


Scheme 1-2

Laird and Jorgensen have suggested from *ab initio* studies that C-C bond cleavage is the preferred route when the strength of the C-C bond is less than 273 kJmol^{-1} .⁹

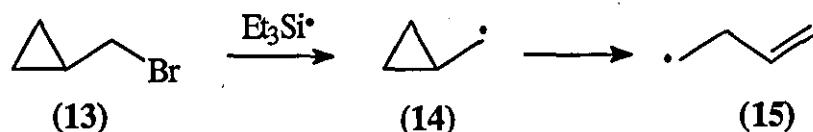
1.3.2 The Kinetics of Oxiranylcarbinyll Ring Opening Reactions.

Oxiranylcarbinyll radical rearrangement is an extremely fast process propelled by relief of ring strain (ca 115 kJmol^{-1}) in the epoxide. Kinetic ESR studies by Davies and Muggleton, and later by Walton *et al* have failed to detect oxiranylmethyl radicals (10) produced from bromomethyloxirane (9).¹⁰⁻¹² At 128 K, the only radical species seen was the 2-hydroxyallyl radical (12) (see Scheme 1-3).



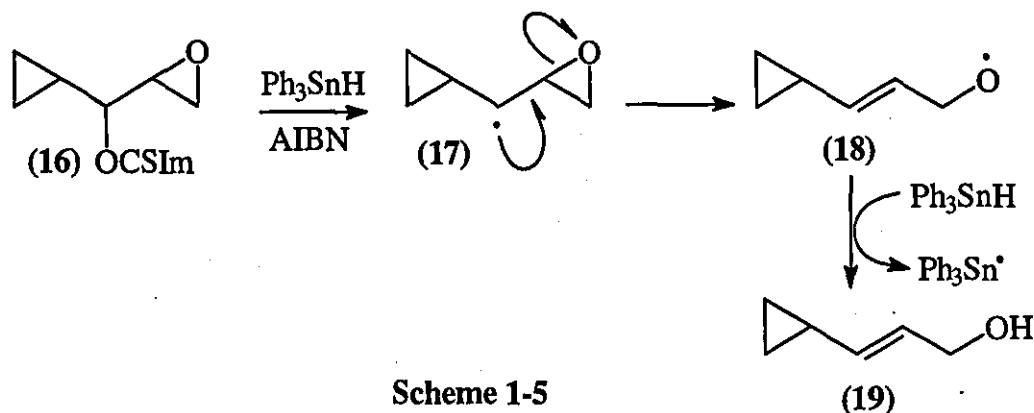
Scheme 1-3

This suggests an activation energy of $E_a < 25 \text{ kJmol}^{-1}$ and a rate constant $k > 4 \times 10^8 \text{ s}^{-1}$ for the rearrangement at 25°C . In the analogous reaction involving bromomethylcyclopropane (13), the cyclopropylmethyl radical (14) can be observed free of the but-3-enyl radical (15) at 133 K (see Scheme 1-4).¹³



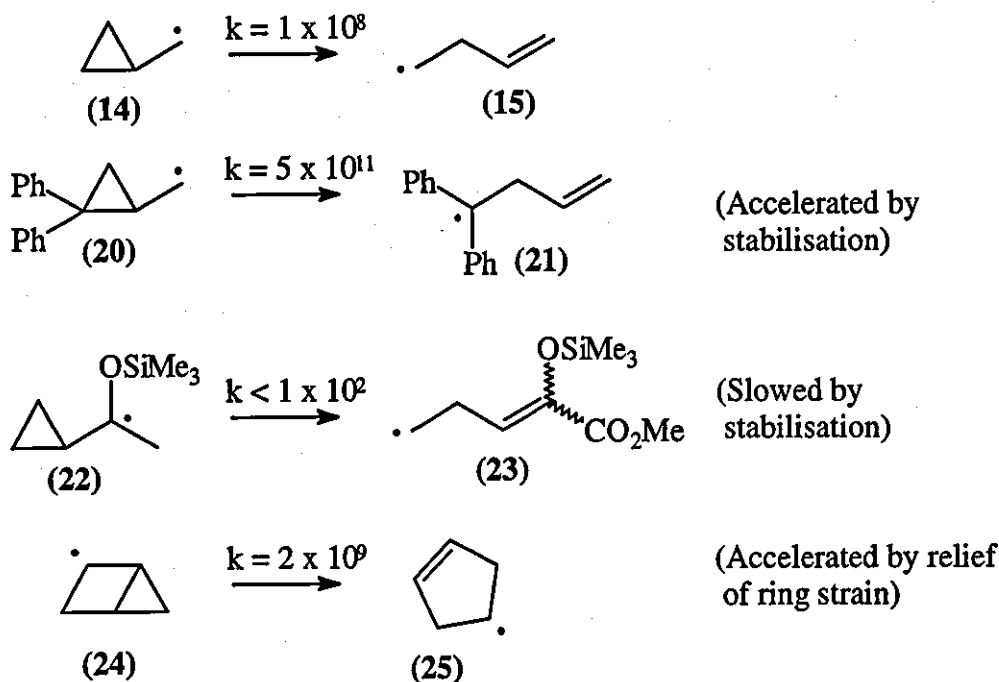
Scheme 1-4

A competitive fragmentation reaction against a cyclopropylcarbinyll radical has suggested that the rate of epoxide fragmentation is even higher. A lower limit of $k > 10^{10} \text{ s}^{-1}$ has been established based on the reaction of the thiocarbonylimidazolidone (16) which underwent exclusive epoxide cleavage to give (19) when treated with triphenyltin hydride and AIBN (see Scheme 1-5).¹⁴



Scheme 1-5

In more complex systems, radical stabilising groups may affect the rate of this rearrangement. The ring opening reactions of cyclopropylmethyl radicals are slowed by groups which stabilise the initially formed radical,¹⁵ but accelerated either by groups that stabilise the resulting ring opened radicals, or by the relief of ring strain (see Scheme 1-6).^{16,17}



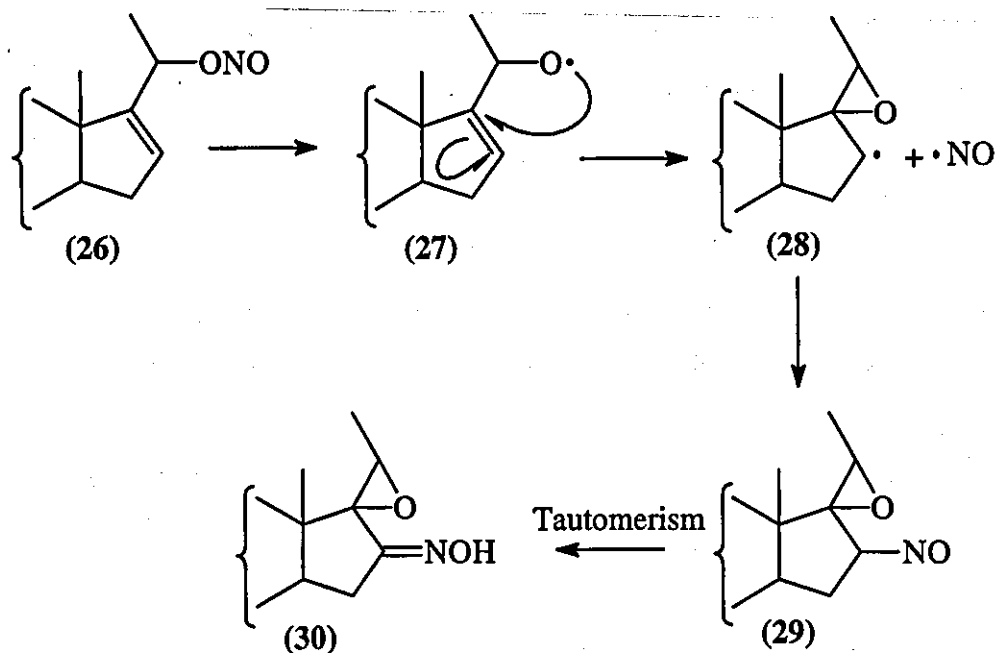
Scheme 1-6

1.3.3 Cyclisation of Allylic Alkoxy Radicals to Form Oxiranylcarbiny Radical.

There are several examples in the literature of the cyclisation of alkoxy radicals (7) to form oxiranylcarbiny radicals (6) (see Scheme 1-2).¹⁸⁻²³ In all cases the oxiranylcarbiny radical formed in this way is either trapped by radical recombination or rearranges by C-C cleavage to give an enol ether radical. Examples of the cyclisation of vinyl ether radicals (8) to give oxiranylcarbiny radicals (6) are given in Chapter 4 of this thesis.

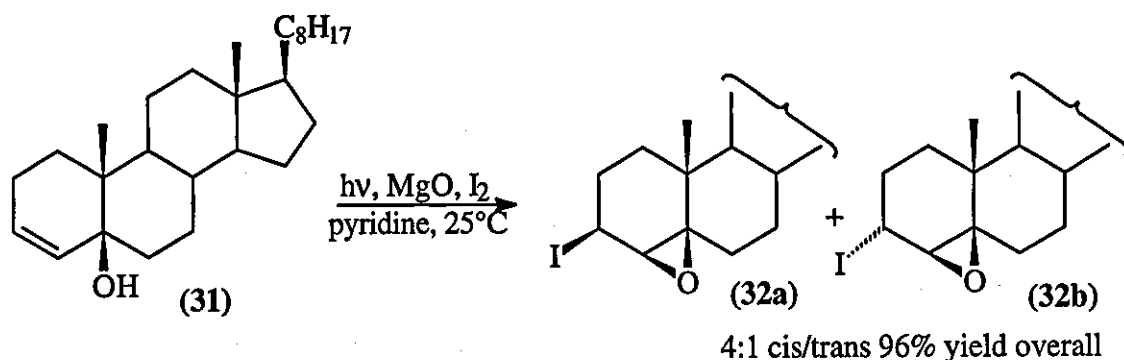
1.3.3.1 Cyclisations Followed by Trapping of the Resultant Radical.

The first example of cyclisation of an alkoxy radical to an oxiranylcarbiny radical was reported by Nussbaum *et al.*¹⁸ Photolysis of the nitrite (26) of 20 α -hydroxypregna-4,16-dien-3-one gave the allyloxy radical (27). This radical was found to cyclise to form the oxiranylcarbiny radical (28) which then recombined with nitric oxide to give the epoxyoxime (30) after tautomerism (see Scheme 1-7).



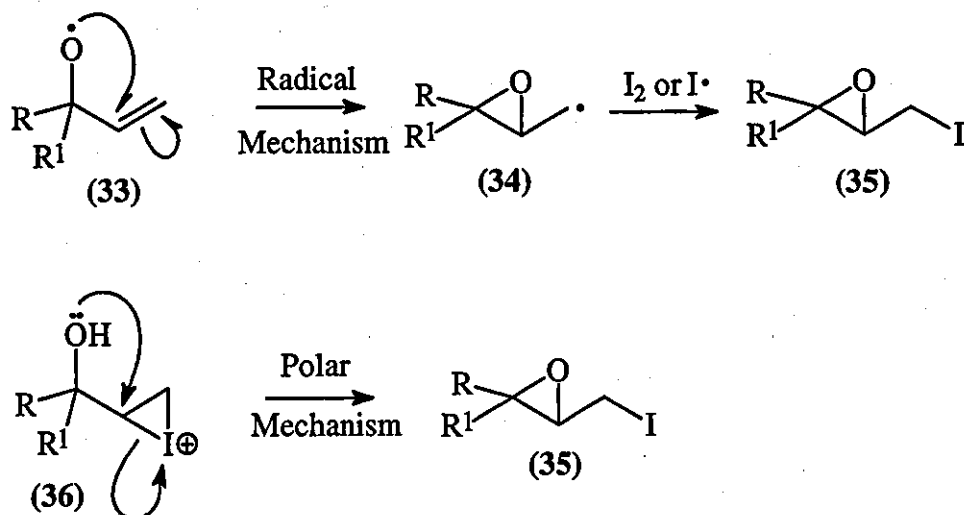
Scheme 1-7

Several examples of the cyclisation of tertiary allylic alcohols to give iodoepoxides have also been reported. Suginome and Wang obtained the isomeric iodoepoxides (32a) and (32b) in 96 % yield when a benzene solution of 5-hydroxy-5 β -cholest-3-ene (31) was irradiated with UV light in the presence of mercury (II) oxide, iodine and pyridine (see Scheme 1-8).¹⁹



Scheme 1-8

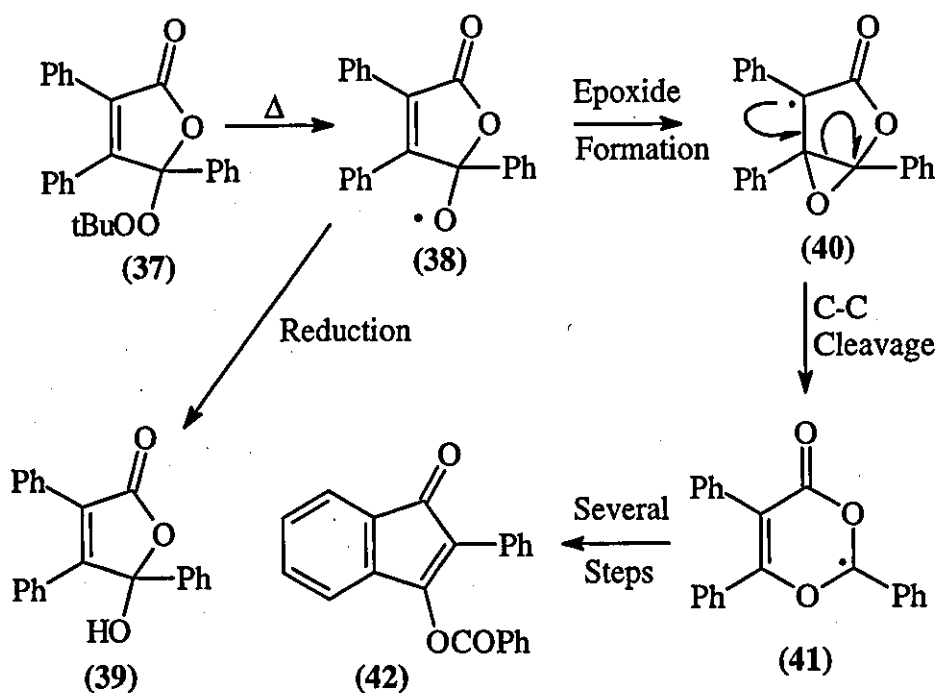
Galatsis and Millan,^{20,21} and later Rawal and Iwasa,²² also achieved similar results using ultraviolet irradiation of allylic alcohols in the presence of iodobenzene diacetate-iodine although it was noted that the reaction did not work for secondary or aryl substituted alcohols. The mechanism for this reaction is believed to involve attack of the alkene by the oxygen radical (see Scheme 1-9). An alternative polar mechanism suggested by Rawal, involving attack of an iodonium ion (36) by the hydroxy group is also shown.



Scheme 1-9

1.3.3.2 Cyclisation of Alkoxy Radicals Followed by C-C Bond Cleavage.

Weinberg and Miller have reported the rearrangement of the peroxy lactone (37) by cyclisation of the allyloxy radical (38) to form (40) and subsequent opening of this oxiranylcarbinyl radical *via* C-C bond cleavage.²³ The reaction was expected to proceed *via* decarboxylation but the only products observed were the 5-hydroxy-furanone (39) obtained by reduction of (38) and the rearranged, oxidised product (42), formed as shown in Scheme 1-10.

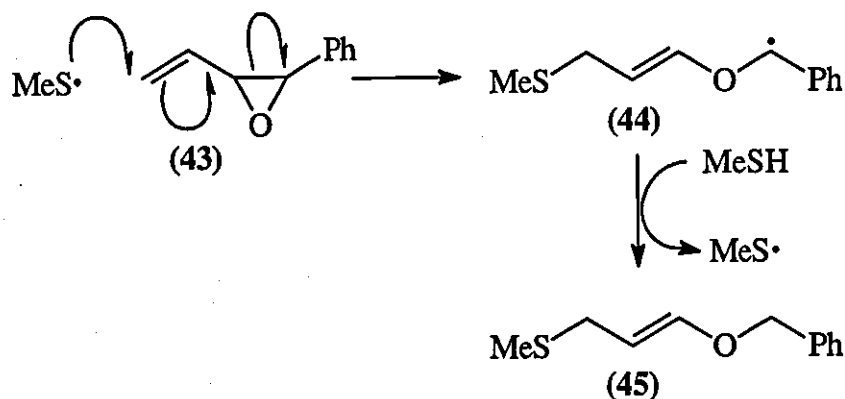


Scheme 1-10

1.3.4 Cleavage of the C-C Bond in Oxiranylcarbiny Radical.

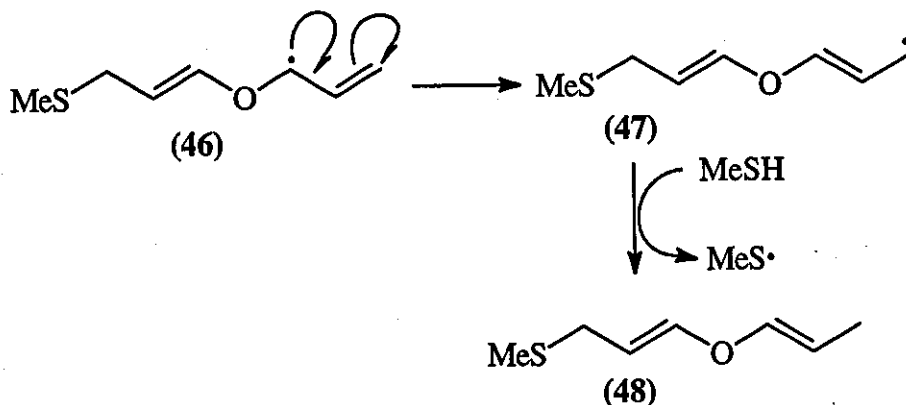
The C-C bond cleavage pathway of oxiranylcarbiny radicals has received relatively little attention and there are comparatively few reported examples of this process.²⁴⁻²⁹ This is presumably due to the relative difficulty encountered in promoting this type of cleavage. Aryl, vinyl or acyl π -system stabilisation is necessary (although not always sufficient) to ensure that products of C-C bond cleavage are obtained. There are no reported examples of C-C cleavage in systems without π -stabilisation, although there are examples of C-O cleavage in systems with π -stabilisation.^{33-35, 44, 45, 53}

The first examples of C-C bond cleavage in oxiranylcarbiny radicals were reported by Stogryn and Gianni in 1970.²⁴ The aryl substituted epoxide (43) was treated with thiomethyl radicals and was found to give the vinyl ether (45), derived exclusively from C-C bond cleavage (See Scheme 1-11).



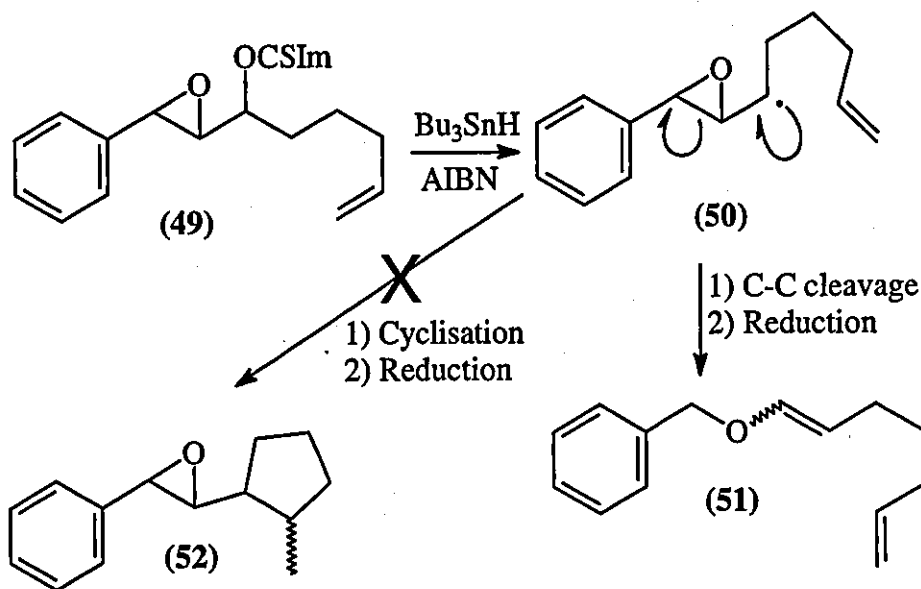
Scheme 1-11

A C-C bond cleavage product was observed when a vinyl group was used in place of the phenyl group, however in this case the double bond migrated after the epoxide cleavage such that a vinyl ether (48) was obtained instead of an allyl ether (see Scheme 1-12).



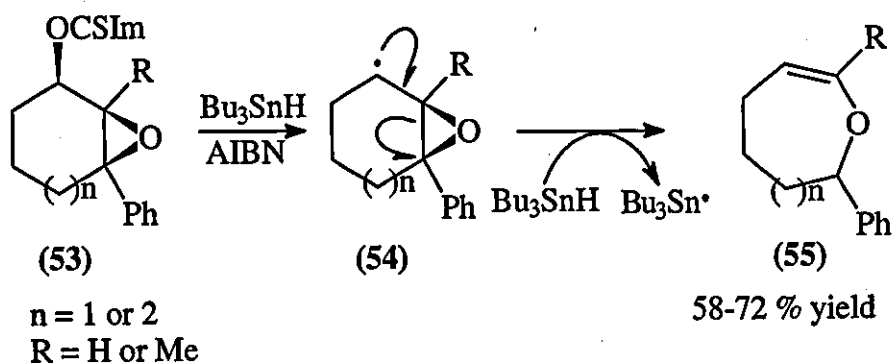
Scheme 1-12

Murphy *et al.* have demonstrated that C-C bond cleavage is a useful, discriminating probe for free radicals.²⁵ In a competition reaction, opening of an aryl substituted epoxide was shown to be faster than the 5-*exo* cyclisation of hexenyl radicals resulting in the exclusive formation of the epoxide fragmentation product (51) (see Scheme 1-13). Also cleavage of the C-C bond is not seen in polar ring opening reactions of epoxides whereas hex-5-enyl cyclisation has been reported under polar reaction conditions.³⁰



Scheme 1-13

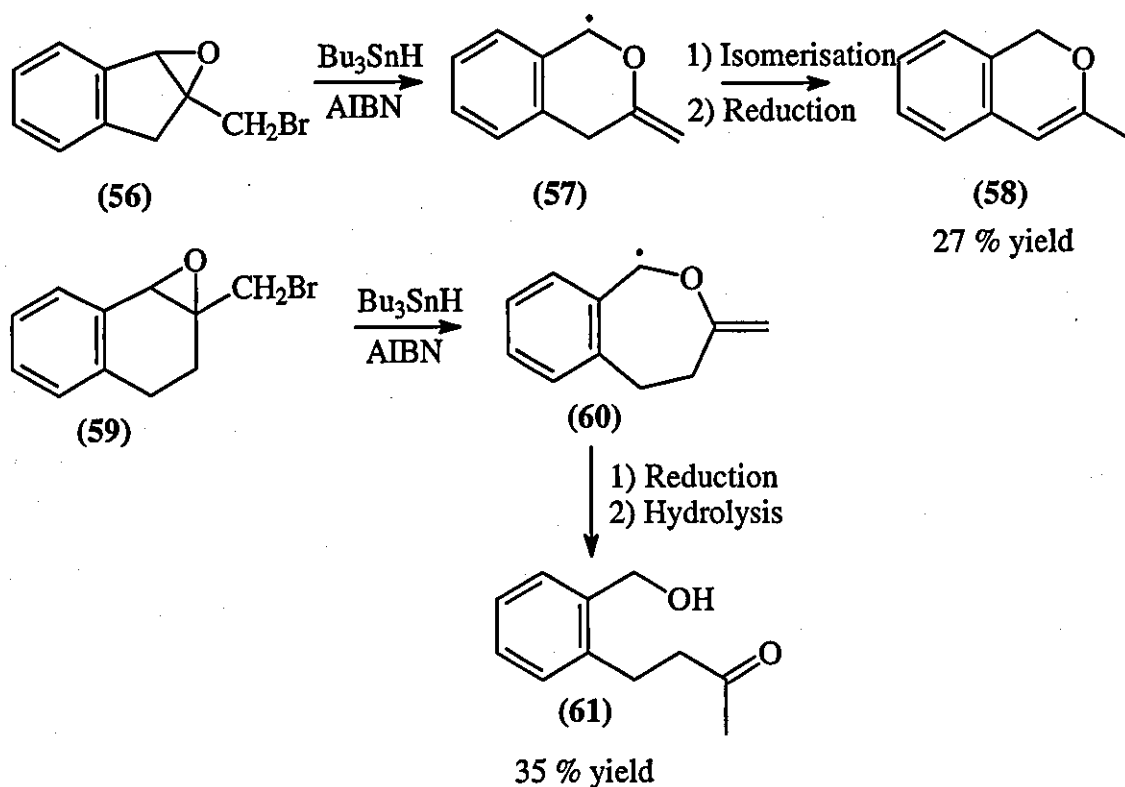
The fragmentation of the C-C bond in aryl substituted epoxides has been shown in these laboratories and others to be a useful method of ring expansion to form medium ring ethers.²⁶⁻²⁸ The epoxythio-carbonylimidazolides (53) were found to rearrange to the ring expanded enol ethers (55) when treated with tributyltin hydride and AIBN in refluxing benzene (see Scheme 1-14).²⁶



Scheme 1-14

Murphy *et al.* also obtained similar results with systems in which the cycloalkyl rings containing the epoxide function were fused to the phenyl ring (see Scheme 1-15)

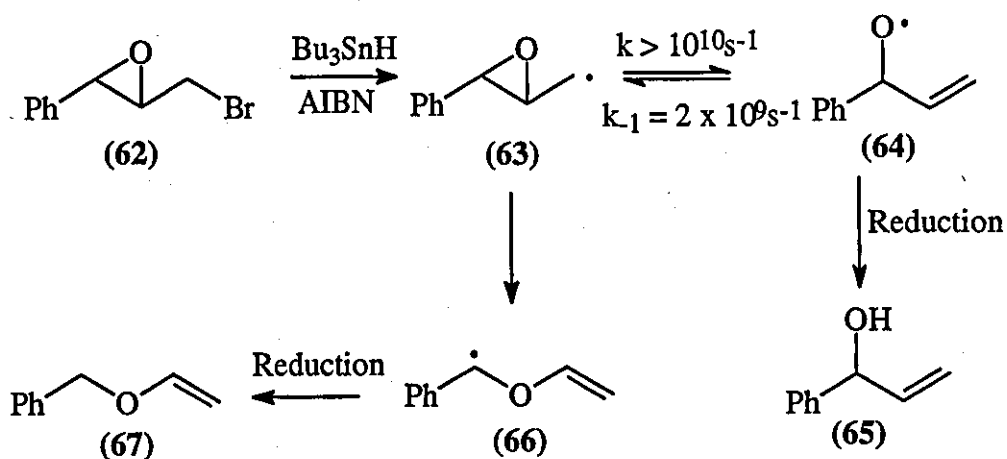
although it should be noted that in one particular case stereoelectronic effects were observed which directed the reaction towards C-O bond cleavage (see section 1.3.6).^{27,28}



Scheme 1-15

1.3.4.1 A Kinetic Study of C-O vs. C-C Cleavage Reactions.

In the reaction of the bromoepoxide (62) with tributyltin hydride and AIBN it was noted by Murphy *et al.* that products of both C-O (65) and C-C (67) cleavage pathways were obtained (see Scheme 1-16).²⁵



Scheme 1-16

A more detailed investigation by Ziegler and Peterson studied the effects of different hydride concentrations on this reaction.³¹ It was found that increasing the

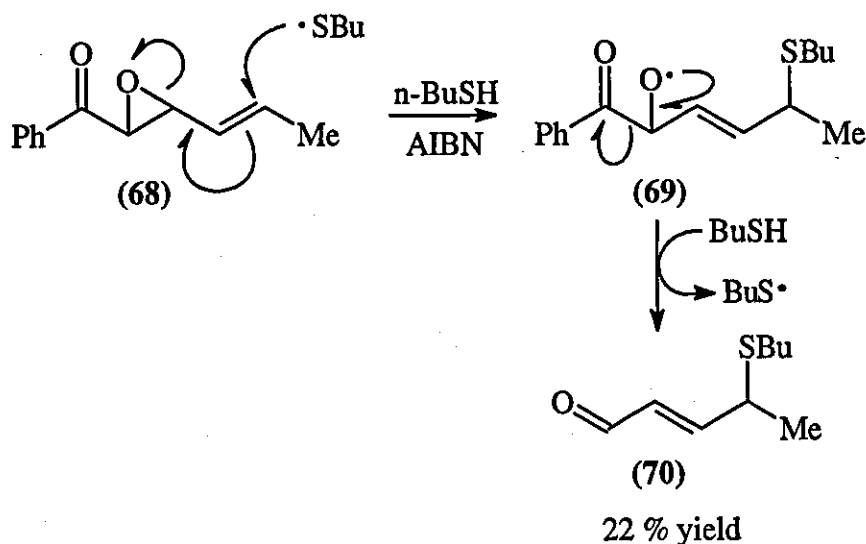
concentration of hydride favoured formation of the C-O cleavage derived product (65), implying that this product is kinetically favoured. It was also noted that the C-O cleavage reaction was approximately four times faster than C-C cleavage. The rate constant for ring closure of the alkoxy radical (64) was also estimated ($k = 2 \times 10^9 \text{ s}^{-1}$ at 70°C) from these results.

1.3.5 Fragmentation of Keto-epoxides.

The effect of a carbonyl group on the fragmentation of oxiranylcarbiny radicals has been investigated, both as a method of directing the cleavage (Section 1.3.5.1) and also as a method of generating the radical (Section 1.3.5.2).

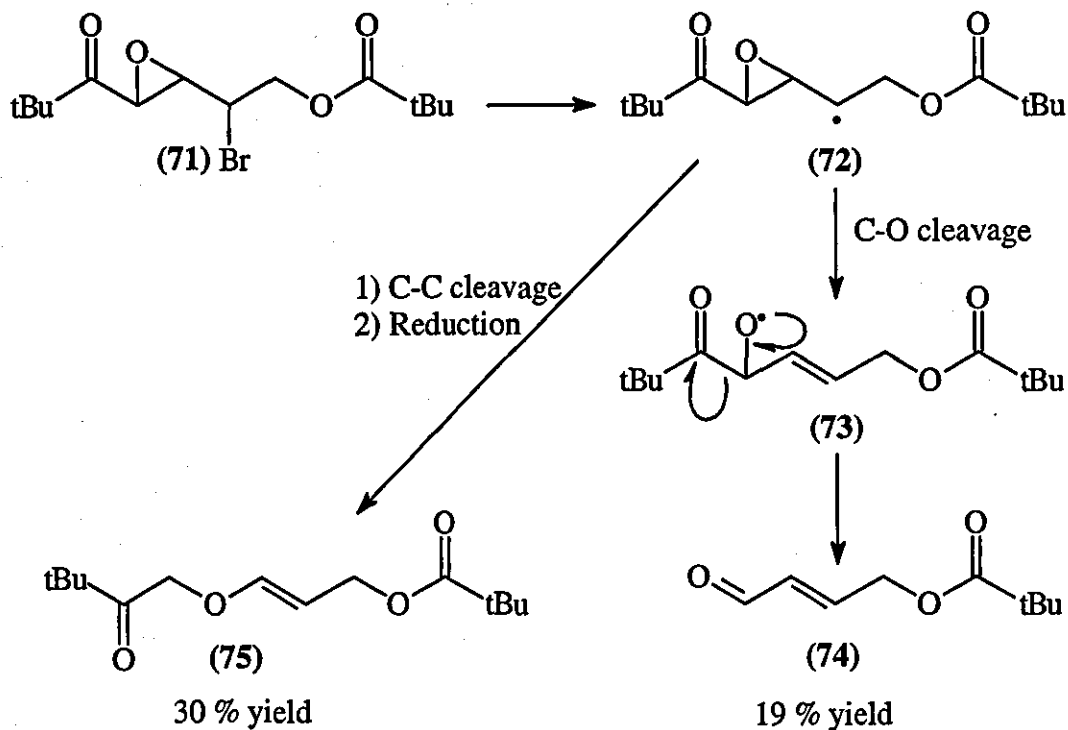
1.3.5.1 Ketone-stabilised Oxiranylcarbiny Radicals.

The carbonyl group, which is less able to stabilise radicals than the vinyl group, has a less pronounced effect on the fragmentation of an adjacent oxiranylcarbiny radical. Reaction of the ketoepoxide (68) with *n*-butanethiol and AIBN in benzene resulted in the formation of the α,β -unsaturated aldehyde (70) and no products from C-C bond cleavage were seen (see Scheme 1-17).³²



Scheme 1-17

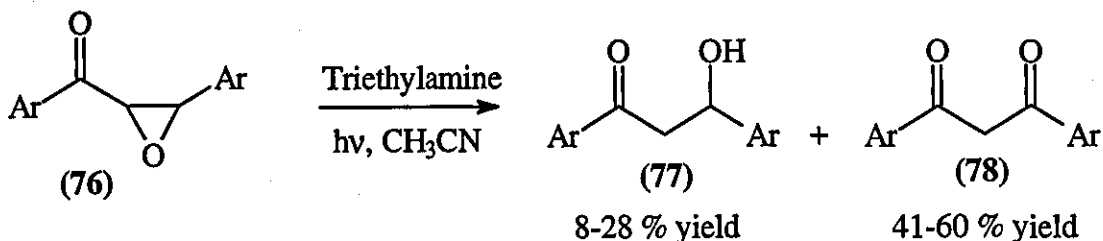
However, treatment of the bromopivalate (71) with tributyltin hydride and AIBN in benzene resulted in the formation of both the α,β -unsaturated aldehyde (74) from C-O bond cleavage and the vinyl ether (75) from C-C bond cleavage (see Scheme 1-18).



Scheme 1-18

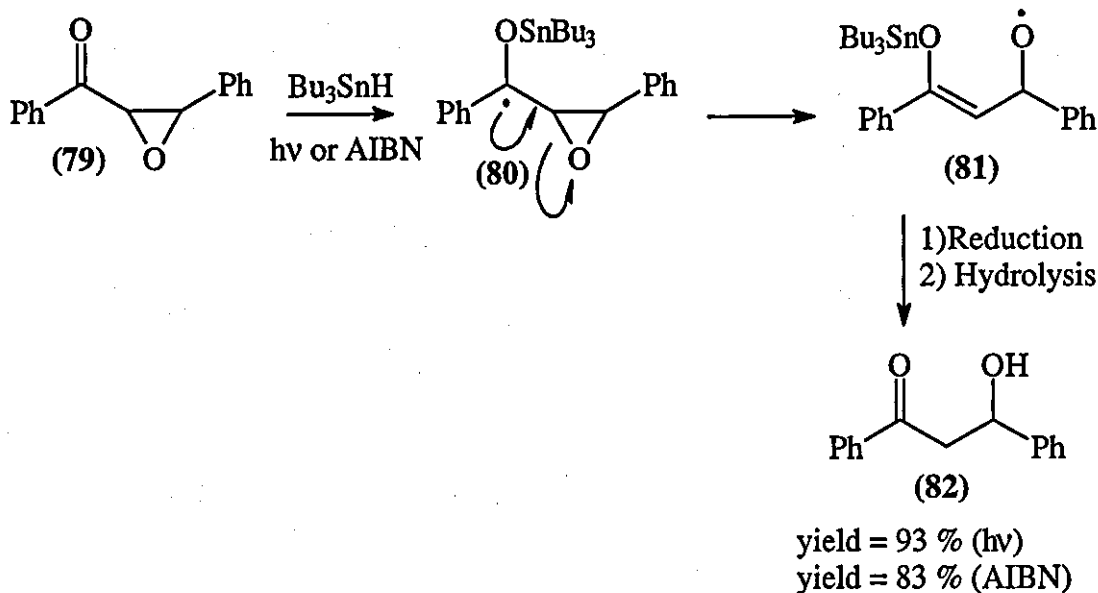
1.3.5.2 Single Electron Transfer and Tributyltin Radical Addition to Keto-epoxides.

Oxiranylcarbonyl radicals formed by photo-induced single electron transfer to a carbonyl group adjacent to an epoxide always rearrange *via* C-O bond cleavage irrespective of any aryl or vinyl stabilising groups present.^{33,34} A variety of aryl-substituted epoxyketones (76) were found to rearrange to give either the β -hydroxyketone (77) or the β -diketone (78) on irradiation with UV light in the presence of triethylamine (see Scheme 1-19). There was no evidence of C-C bond cleavage products in any of the examples reported by either Cossy or Hasegawa.



Scheme 1-19

The tributyltinoxymethyl radical (80) formed by addition of tributyltin radical to the carbonyl group of the phenyl-substituted epoxy ketone (79) also undergoes exclusive C-O bond cleavage, although the product obtained in this case is the β -hydroxyketone (82) (see Scheme 1-20).³⁵



Scheme 1-20

Hasegawa *et al* have proposed an explanation for the exclusive C-O bond cleavage in these systems by comparing the frontier molecular orbital energy values of the radicals (80) and (83) (see Figure 1-1).

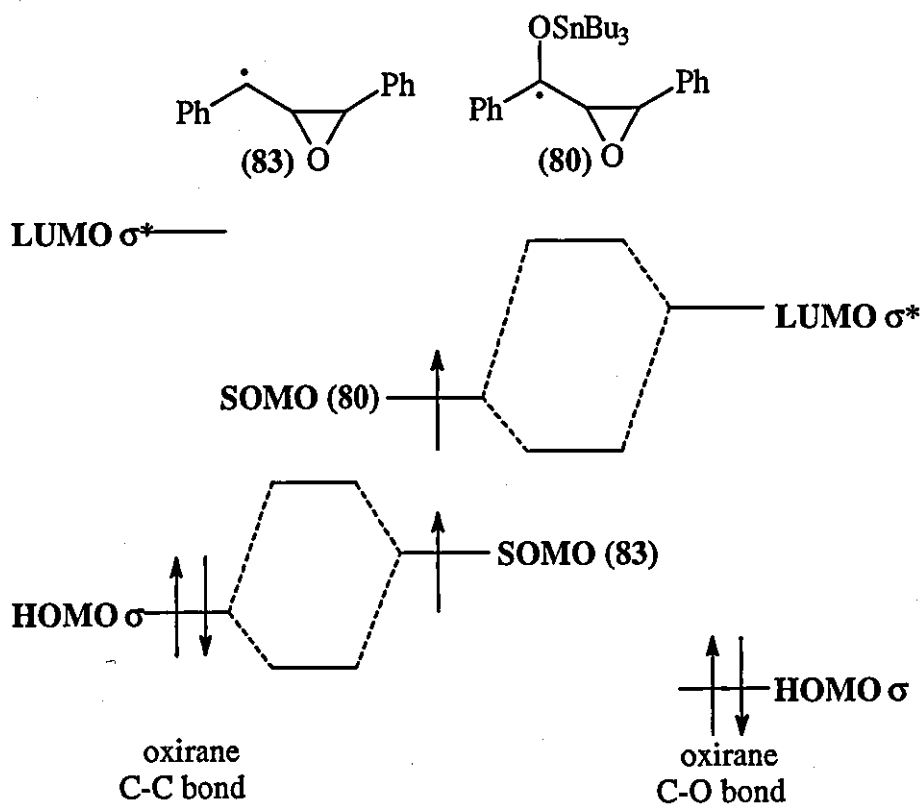
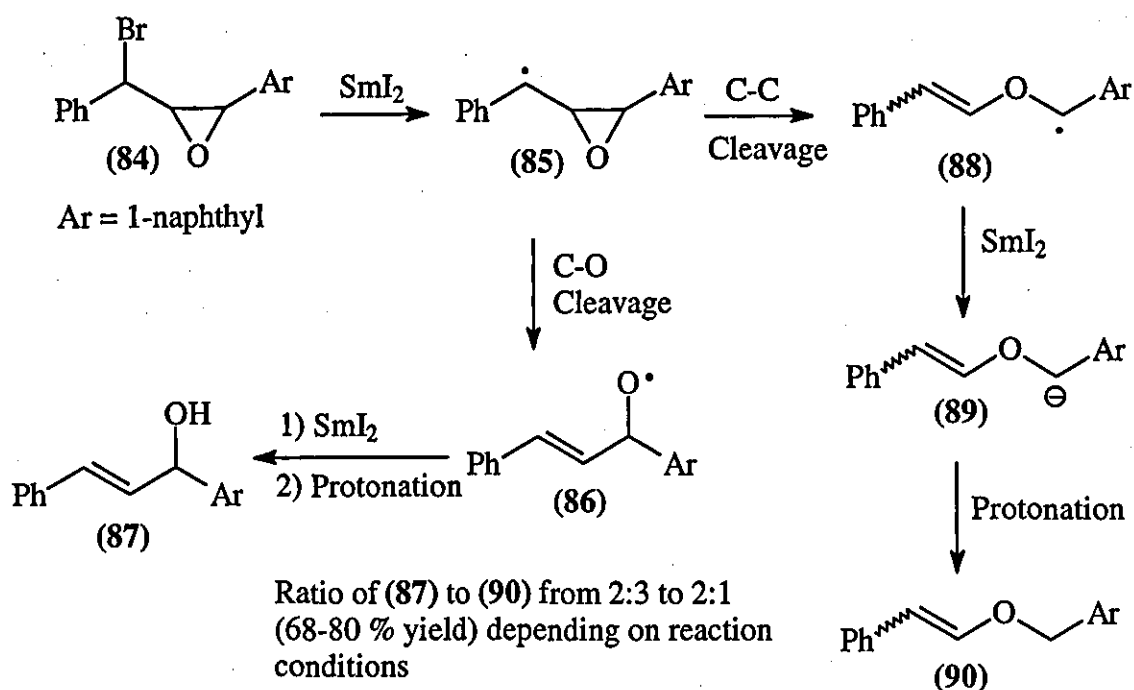


Figure 1-1. The Relative Energies of the Frontier Orbitals in the Radicals (80) and (83).

The singly occupied molecular orbital (SOMO) of the radical (80) is of a higher energy than that of (83) because of the electron donating OSnBu₃ group and its most favoured interaction (i.e. with the lowest energy difference) is with the lowest unoccupied molecular orbital of the oxirane C-O bond. The SOMO of (83) has a lower energy and the most favoured interaction in this case is with the highest occupied molecular orbital (HOMO) of the oxirane C-C bond.

Cleavage of the C-C bond has been demonstrated under single electron transfer conditions by Hasegawa *et al.* in later work on a similar system.²⁹ Treatment of the aryl-substituted bromoepoxide (84) with samarium diiodide was found to give a mixture of allylic alcohol (87) and vinyl ether (90) derived from the respective C-O and C-C cleavage pathways (see Scheme 1-21).



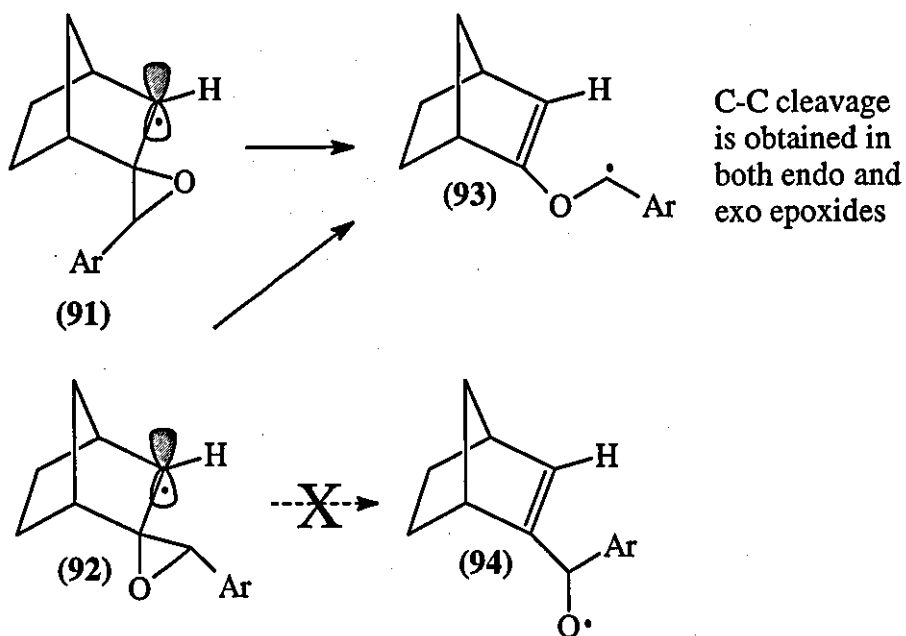
Scheme 1-21

1.3.6 Stereoelectronic Effects in Oxiranylcarbinyll Radical Ring Opening Reactions.

There is contrasting evidence in the literature concerning the role of stereoelectronic effects in the ring opening reactions of oxiranylcarbinyll radicals.

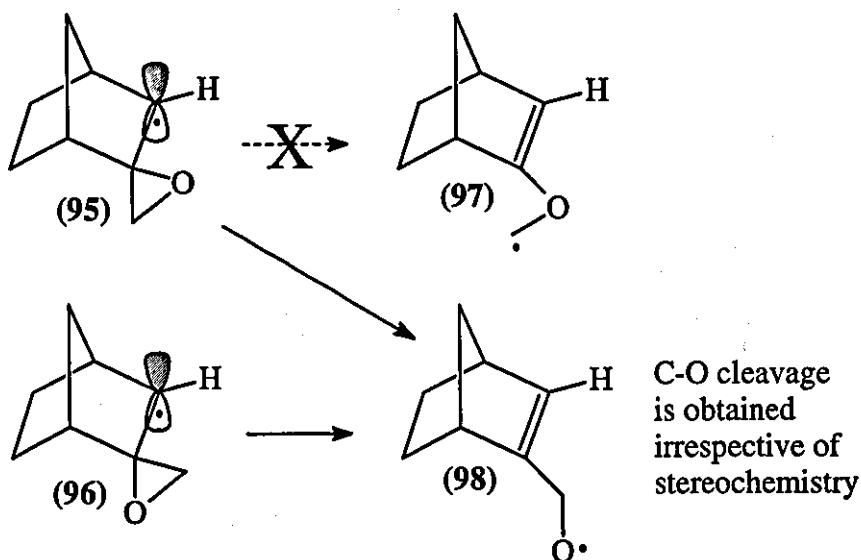
It has been shown in these laboratories that stereoelectronic effects appear to have little influence over the ring opening reactions of conformationally rigid oxiranylcarbinyll radicals. The aryl-substituted epoxides (91) and (92) were found to give products of C-C

cleavage even when stereochemical effects opposed this cleavage pathway (see Scheme 1-22).³⁶



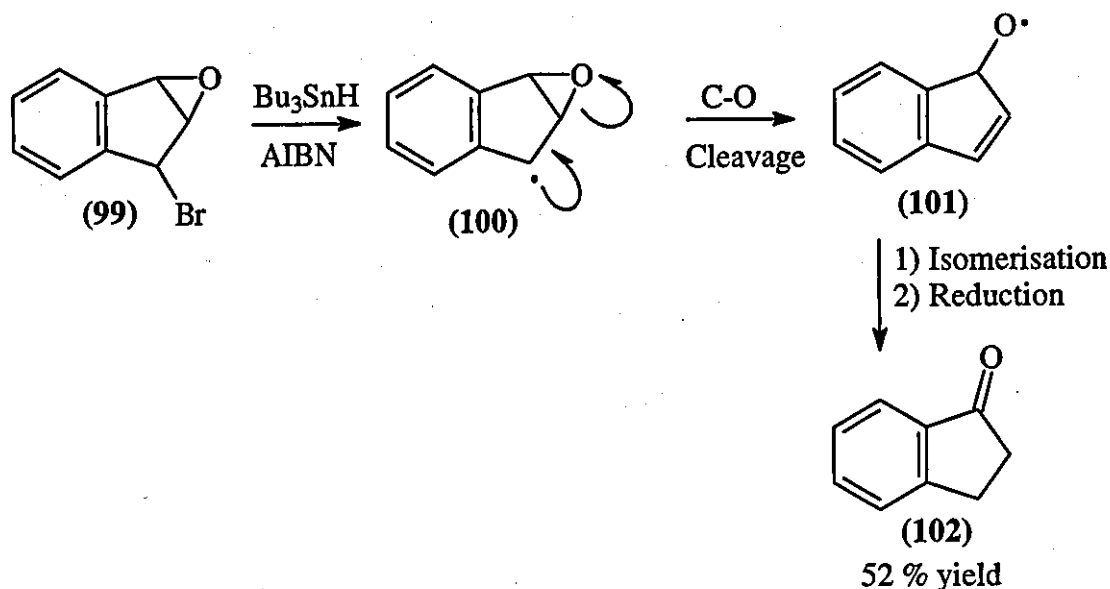
Scheme 1-22

The radical (92) would be expected to undergo C-O bond cleavage if stereoelectronic effects were predominant, because the C-O bond eclipses the singly-occupied molecular orbital containing the radical. The product of C-O cleavage (94) was not obtained, suggesting that stereoelectronic effects have little influence over these reactions. Similarly the analogous epoxides (95) and (96), which contained no aryl directing group, gave the C-O cleaved radical (98) exclusively (see Scheme 1-23). This is further evidence that stereoelectronic effects are unimportant in these systems.



Scheme 1-23

In contrast Murphy has suggested that stereoelectronic effects can be seen in epoxide fragmentations.²⁷ The ring fused epoxide radical (100) gives indanone (102) via exclusive C-O bond cleavage, despite aryl stabilisation and this has been attributed to stereoelectronic effects (see Scheme 1-24).

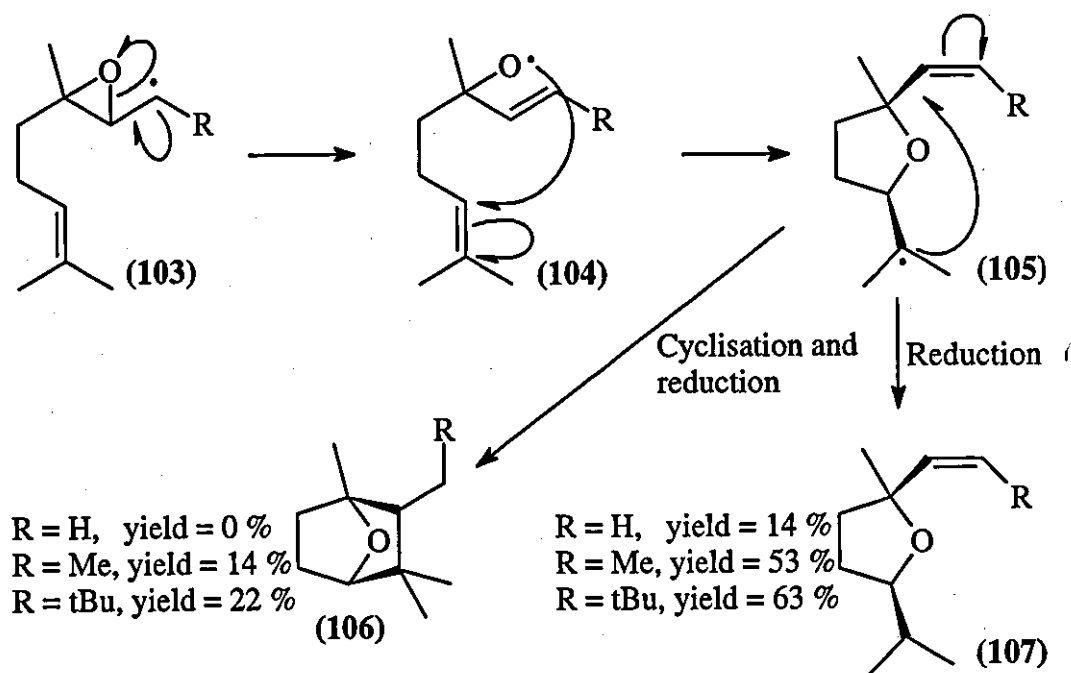


Scheme 1-24

1.3.7 Synthetic Applications of Oxiranylcabinyll Radicals.

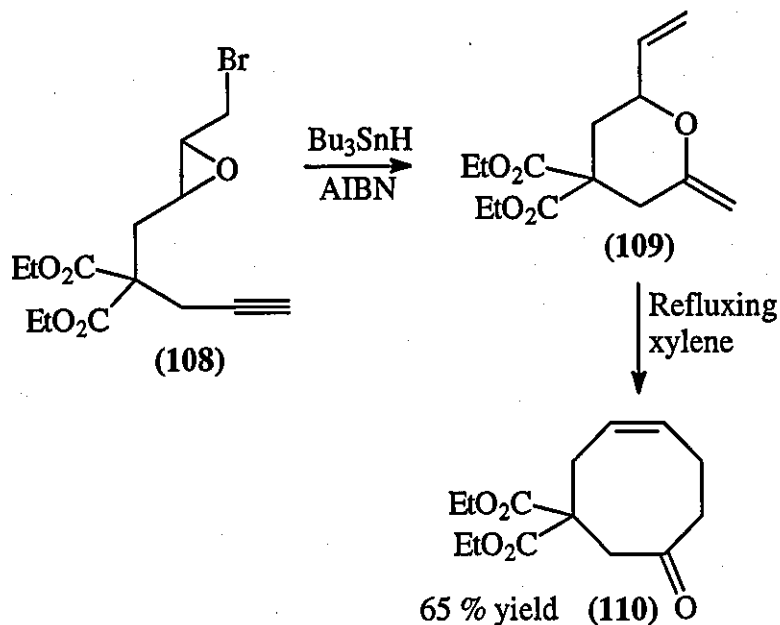
1.3.7.1 Ring Expansion Reactions Using Oxiranylcabinyll Radicals.

Johns and Murphy have used the rearrangement of oxiranylcabinyll radicals in tandem cyclisation sequences for the synthesis of tetrahydrofurans and tetrahydropyrans (see Scheme 1-25).³⁷



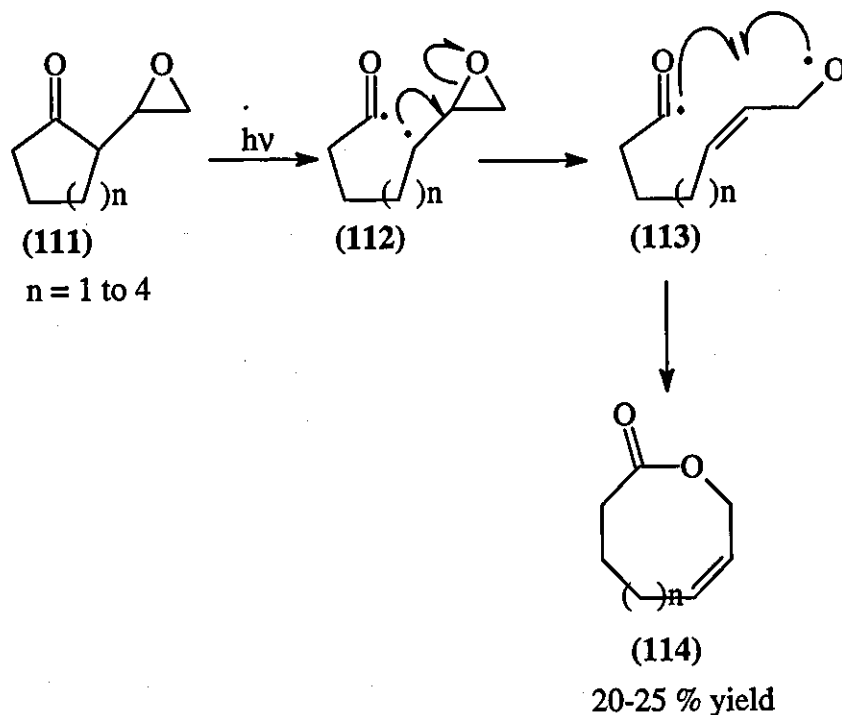
Scheme 1-25

The analogous cyclisation onto an alkyne leads to an exocyclic vinyl ether (109) which undergoes a Claisen rearrangement to give a medium ring ketone (110) (see Scheme 1-26).



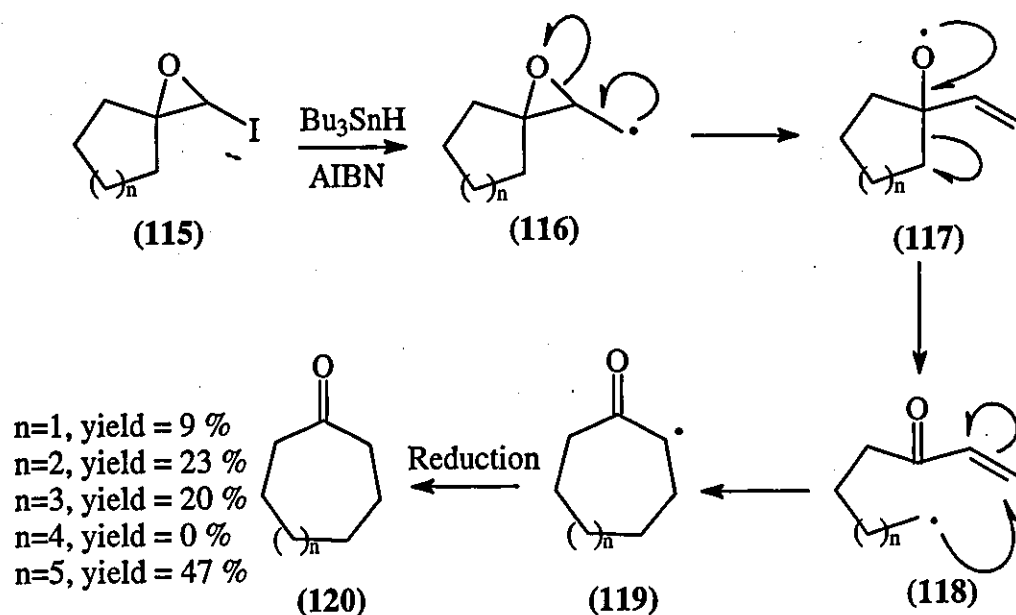
Scheme 1-26

Carlson *et al.* also employed oxiranylcarbinyl radicals in earlier work on photochemical ring expansions.³⁸ A variety of 2-(oxiranyl)cycloalkanones (111) were irradiated with ultraviolet light and were found to rearrange *via* a three atom ring expansion to give medium ring lactones (114), although yields were quite poor (see Scheme 1-27).



Scheme 1-27

Galatsis *et al.* have also used oxiranylcarbonyl radicals in a two carbon ring expansion reaction involving β -cleavage of both an oxiranylcarbonyl radical (116) and the resultant alkoxy radical (117), followed by cyclisation of the primary radical (118) (see Scheme 1-28).³⁹

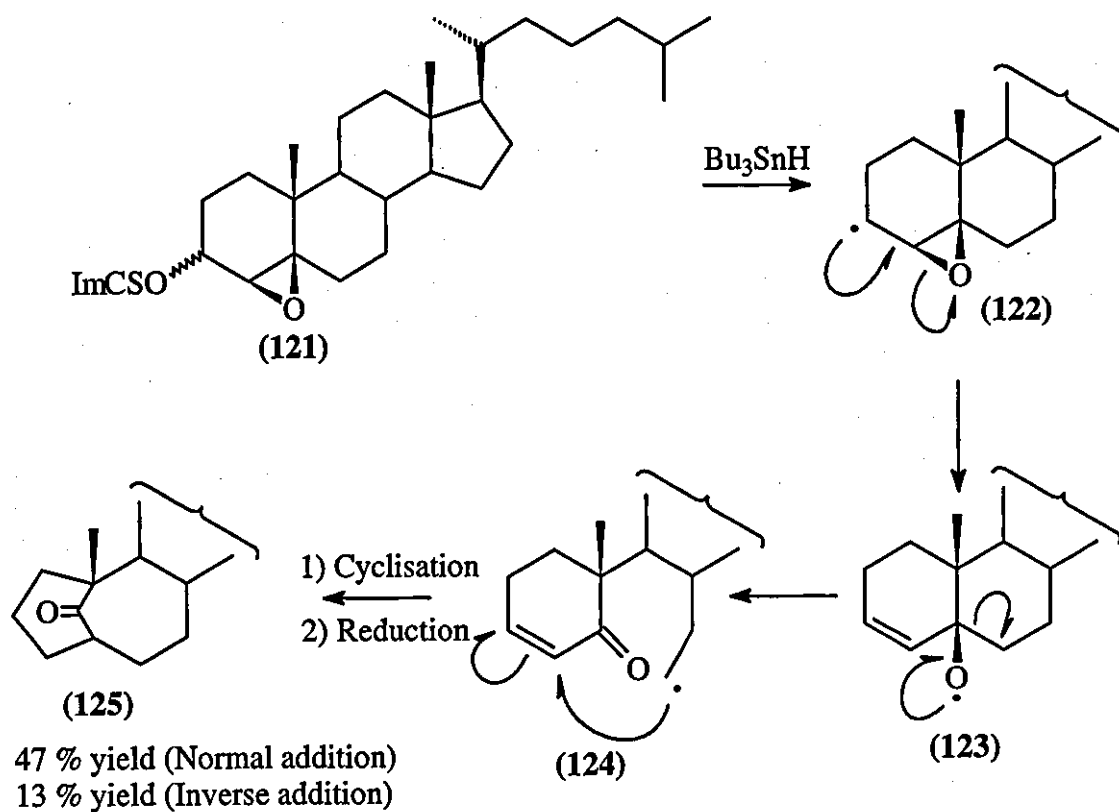


Scheme 1-28

As the size of the ring changed, different side reactions competed with this ring-expansion. For example when $n = 1$, 7-exo-cyclisation was observed and when $n = 4$, (117) underwent an intramolecular 1,5-hydrogen abstraction and none of the expected ketone (120) was obtained.

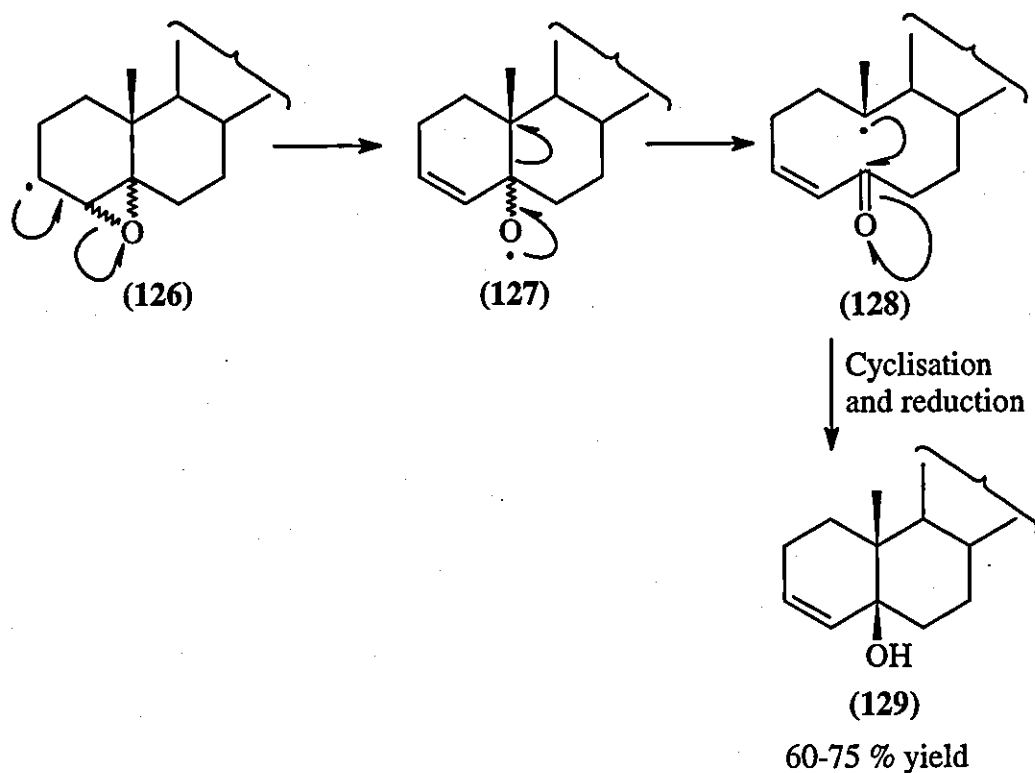
1.3.7.1.1 β -Cleavage Reactions of Alkoxy Radicals in Fused Cyclohexane Ring Systems.

In 1981 Barton *et al.* demonstrated that the ring opening reactions of epoxides were a viable alternative to the Wharton rearrangement.⁴⁰ In some cases however, under normal addition conditions it was found that the alkoxy radicals underwent further reaction e.g. the β -cleavage derived ring expansion shown in Scheme 1-29.



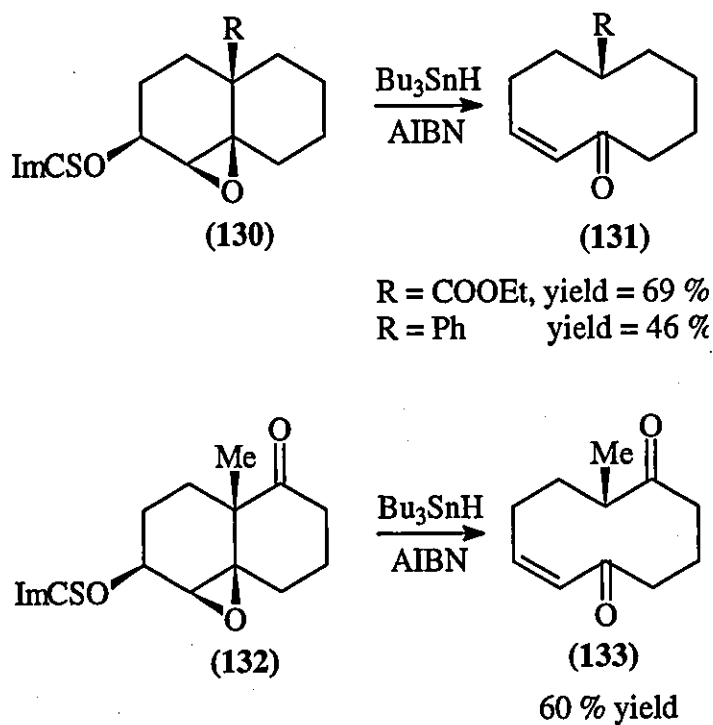
Scheme 1-29

Following on from this observation it has been demonstrated in these laboratories that the oxiranylcarbanyl radical (126) (formed either by tributyltin hydride reduction of the thiocarbonylimidazolide derivative or photoreduction of the acetate in HMPA/ H_2O) undergoes rearrangement to the alkoxy radical (127) which then undergoes a second reversible β -cleavage of the C_5 - C_{10} bond to give the radical (128).⁴¹ The product from the direct reduction of the radical (128) was not obtained however, the major product being 5-hydroxy-5 β -cholest-3-ene (60-75 % yield) (129) which was formed by stereoselective cyclisation of (128) and subsequent reduction (see Scheme 1-30).



Scheme 1-30

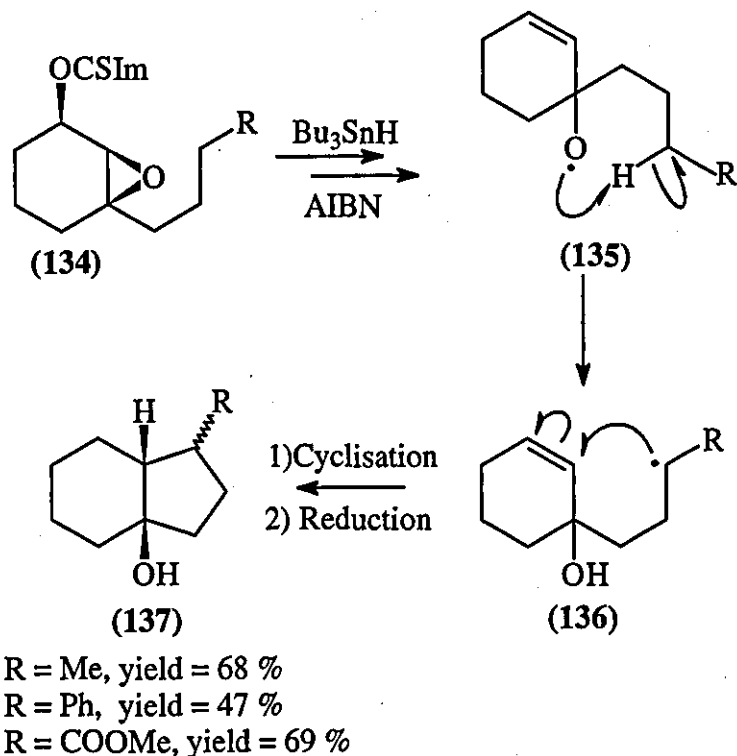
If a radical stabilising group is present in the ring opposite the alkoxy radical then it is possible to trap the ring expanded radical, thus providing a route to 10-membered enone systems e.g. (131) and (133) (see Scheme 1-31).^{26,42}



Scheme 1-31

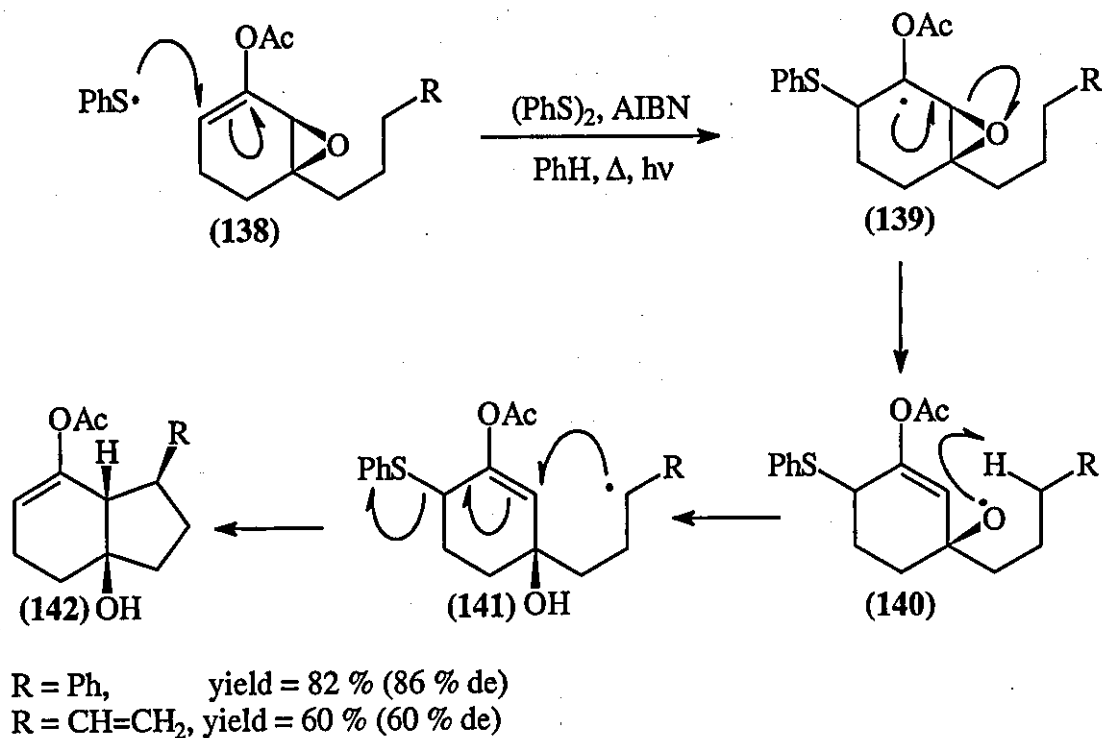
1.3.7.2 Preparation of Hydrindane Systems from Oxiranylcarbinyll Radicals.

Rawal *et al.* have also used oxiranylcarbinyll radicals in the synthesis of *cis*-fused bicyclic hydrindane systems.⁴³⁻⁴⁵ Treatment of thiocarbonylimidazolide (134) with tributyltin hydride and AIBN in refluxing benzene generated the alkoxy radical (135) via C-O bond cleavage. 1,5-Hydrogen abstraction and cyclisation gave the isomeric *cis*-fused bicyclic products (137) (see Scheme 1-25).⁴³



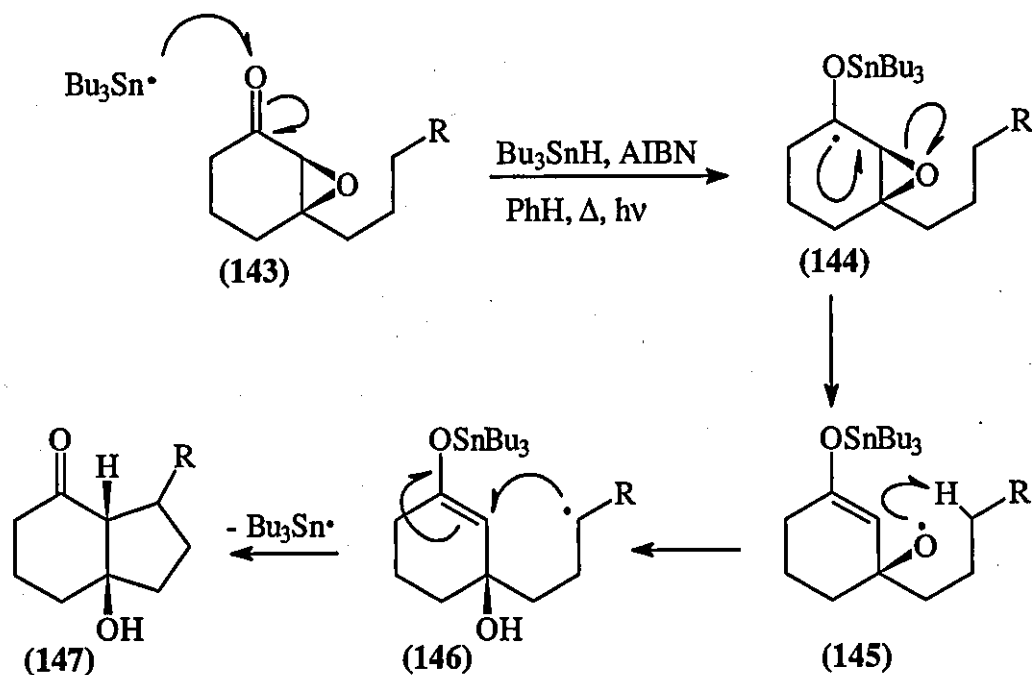
Scheme 1-32

Two catalytic processes were developed for this transformation in which oxygen functionality is retained in the initial carbocyclic ring. The first method involves the reversible addition of phenylthio radicals to an epoxy enolacetate (138) (see Scheme 1-33).⁴⁴ This method only requires a catalytic amount of diphenyldisulfide and has the advantage of not using tributyltin hydride which can be difficult to separate from reaction products.



Scheme 1-33

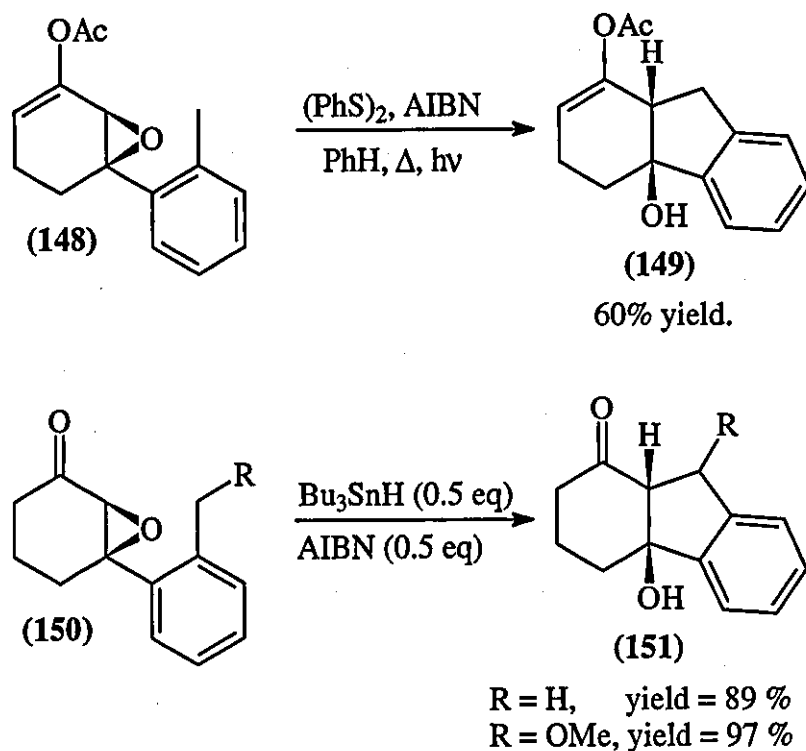
The second method involves reversible addition of tributyltin radical to a keto-epoxide (**143**) to form the oxiranylcarbiny radical (**144**) and the product (**147**) (see Scheme 1-34).⁴⁵



Scheme 1-34

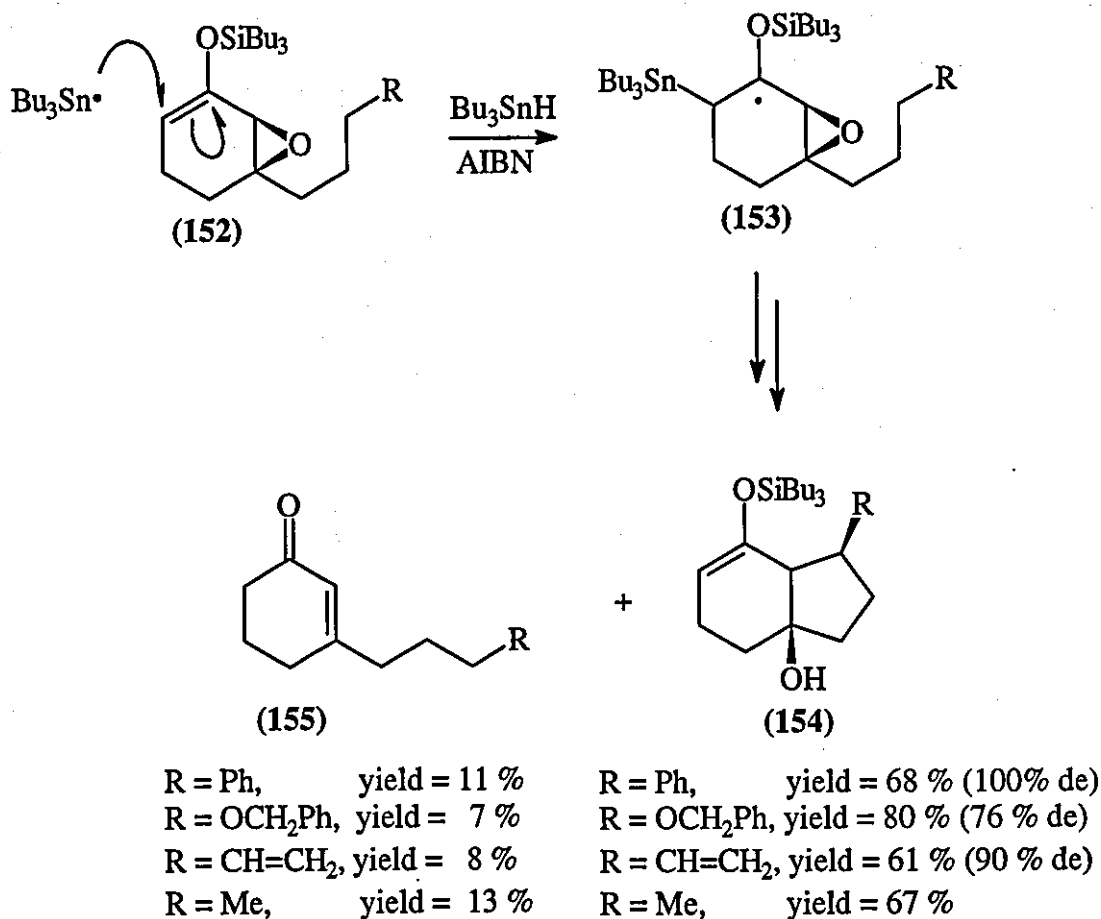
Interestingly, in the reactions of aryl-substituted epoxy-enolacetates (**148**) and epoxy ketones (**150**), the C-O cleavage products (**149**) and (**151**) were obtained exclusively

(see Scheme 1-35), presumably as a result of kinetic control (see Section 1.3.4.1) and/or frontier molecular orbital theory considerations (see Section 1.3.5.2).



Scheme 1-35

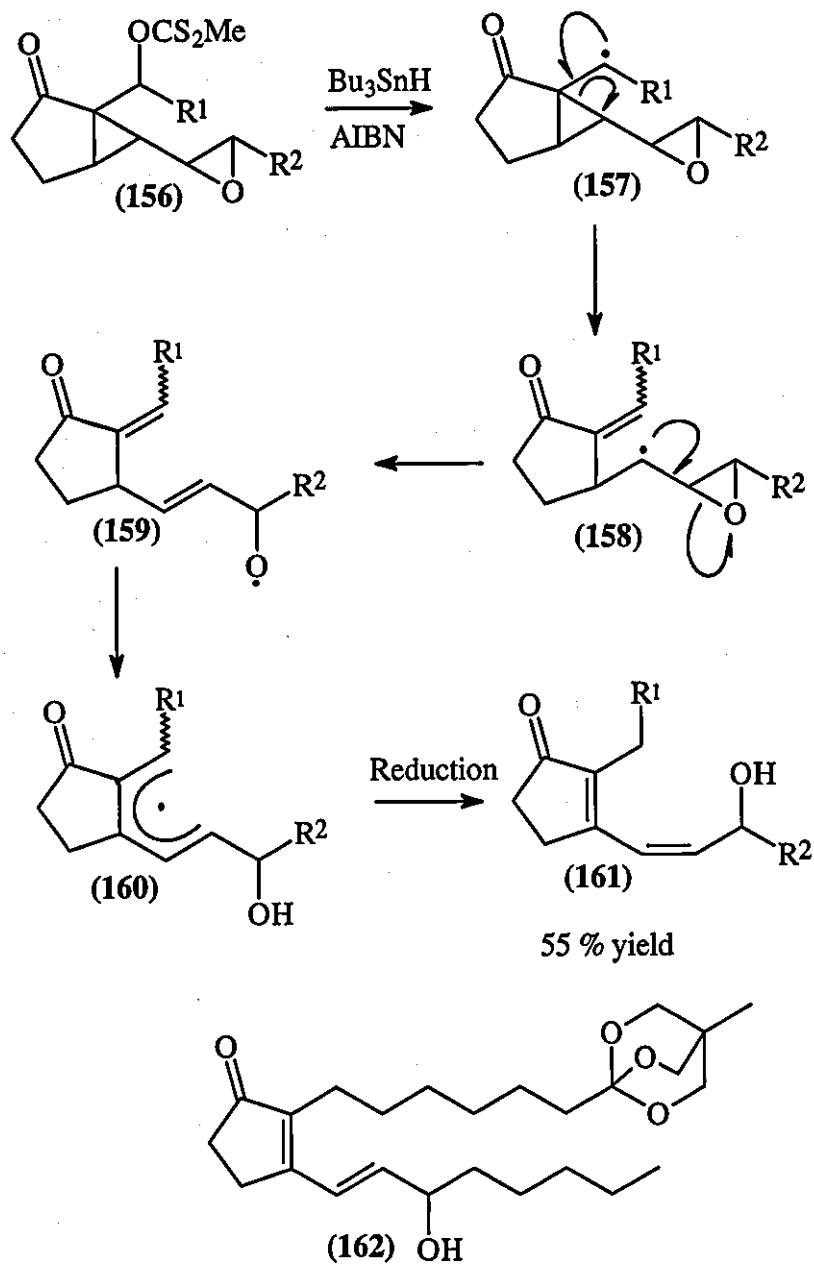
A variation of this type of transformation has also been reported.⁴⁶ Hydrindane systems were synthesised by a catalytic procedure involving reversible addition of tributyltin radical to a variety of tributylsilyl enol-ethers (152) (see Scheme 1-36). In this case however small amounts of the reduced cyclohexenone (155) were observed.



Scheme 1-36

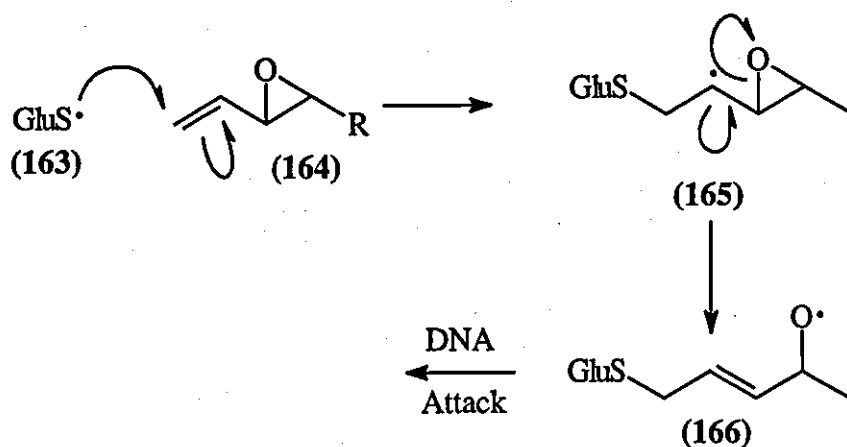
1.3.7.3 Other Applications of Oxiranylcarbinyl Radicals.

More recently a tandem cyclopropylcarbinyl/oxiranylcarbinyl fragmentation has been used in a synthetic route leading to the PGB₁ series of prostaglandins.⁴⁷ The key step of this synthesis is shown in Scheme 1-37 along with PGB₁ orthoester (162), the target molecule.



Scheme 1-37

The use of oxiranylcarbinyl radicals has also been considered as a method of increasing the reactivity of glutathione radicals, such that they may damage DNA.⁴⁸ Glutathione radicals (163) add to vinyl epoxides (164) which then rearrange to give alkoxy radicals (165), which have been shown to cleave DNA *in vitro* (see Scheme 1-38).



Scheme 1-38

1.3.8 Methods of Generation of Oxiranylcarbinyl Radicals.

Oxiranylcarbinyl radicals have been generated using numerous reagents and techniques, this section briefly summarises the methods which have been used to date for the formation of these radical species.

1.3.8.1 Abstraction Reactions.

Abstraction of halogens or thioesters to form oxiranylcarbinyl radicals is the most common method of generating these systems (See Table 1-1).

Substrate	Reagent(s)	Products	References
<p>X = Br, I</p>	Bu ₃ SnH, AIBN	<p>+ Bu₃SnX</p>	12, 21, 22, 25, 27, 28, 31, 36.
<p>X = OCSIm, OCS₂Me, or OCSOC₆F₅</p>	Bu ₃ SnH, AIBN	<p>+ Bu₃SnX</p>	26, 36, 37, 40, 41, 43, 47, 49
	SmI ₂	<p>+ SmI₂Br</p>	29
	^t BuO ₂	<p>+ ^tBuOH</p>	8

Table 1-1. Formation of Oxiranylcarbinyl Radicals *via* Abstraction Reactions.

1.3.8.2 Addition of Radicals to Double Bonds.

This method is often used where only a small amount of reagent is required to catalyse a rearrangement in the reaction substrate (see Table 1-2).

Substrate	Reagent(s)	Product	References
	Bu ₃ SnH AIBN		46, 50
	Bu ₃ SnH AIBN		35, 45, 52, 53
	RS• AIBN		24, 32, 44, 48

Table 1-2. Formation of OxiranylcarbinyI Radicals by Addition to Double Bonds.

1.3.8.3 Photolysis Techniques.

Substrate	Reagent	Products	References
	hν		38
	hν HMPA H ₂ O		41

Table 1-3. Formation of OxiranylcarbinyI Radicals by Photolysis.

1.3.8.4 Single Electron Transfer Reactions.

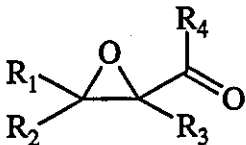
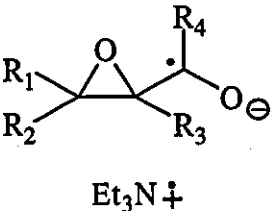
Substrate	Reagents	Products	References
	Triethylamine $h\nu$		33, 34

Table 1-4. Formation of Oxiranylcarbinyl Radicals by Single Electron Transfer.

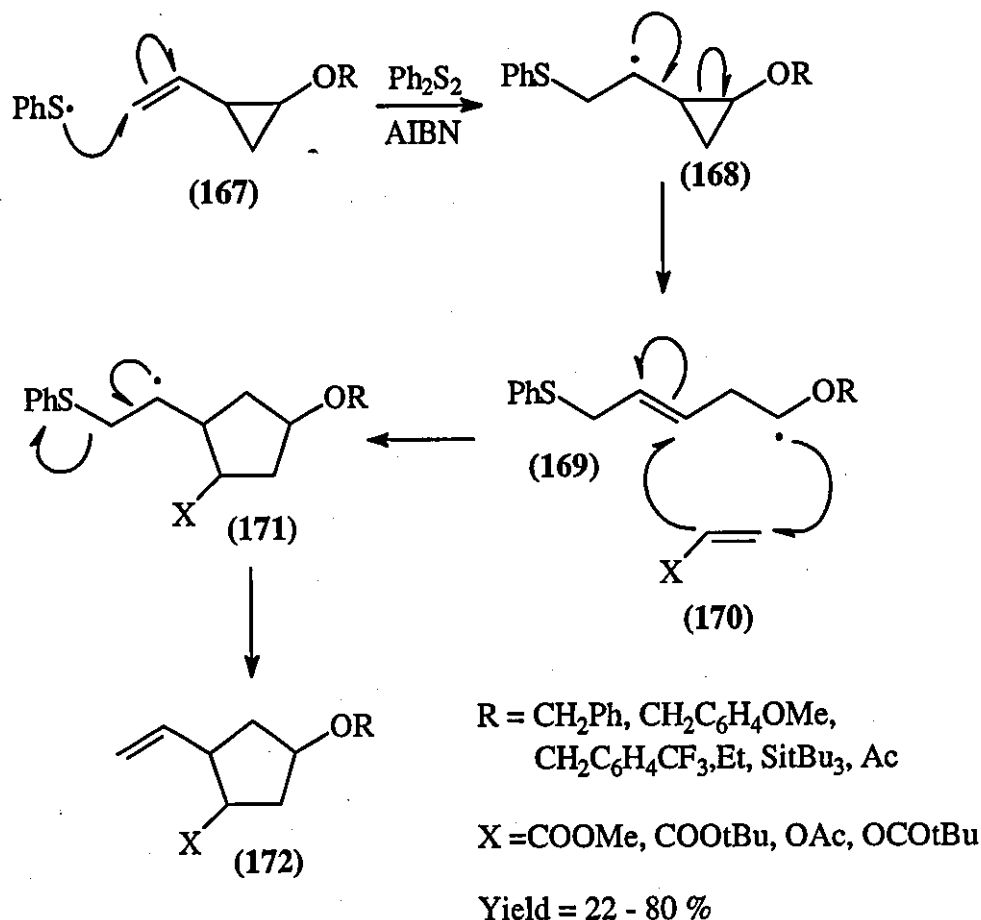
1.4 Aims.

The broad aims of this research were to explore the scope and mechanistic detail of the ring-expansion reactions that have been developed for medium ring ethers (section 1.3.4) and ketones (section 1.3.7.1.1) and to demonstrate the applications of this chemistry by applying it to the synthesis of natural products such as the medium ring ethers mentioned in Chapter 2 and the medium ring lactone didemnilactone mentioned in Chapter 5.

2 Intermolecular Addition Reactions of Oxiranylcarbinyl Radicals.

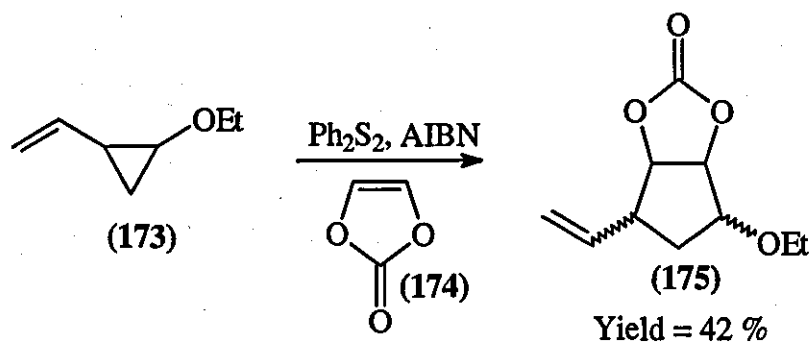
2.1 Introduction.

It has been shown that cyclopentane rings can be formed *via* trapping of alkenes by cyclopropylcarbinyl radicals.⁵⁴ Addition of phenylthio radicals to vinylcyclopropanes (167) gives rise to cyclopropylcarbinyl radicals (168) which undergo a ring opening β -cleavage and trap a molecule of alkene (170) \rightarrow (171) with concomitant expulsion of the phenylthio radical to give (172) (see Scheme 2-1).



Scheme 2-1

One alkene of particular interest which was used in this reaction was vinylene carbonate (174), which underwent cycloaddition onto the vinylcyclopropane (173) to give the *cis*-fused compound (175) in 42 % yield as a mixture of stereoisomers (see Scheme 2-2).

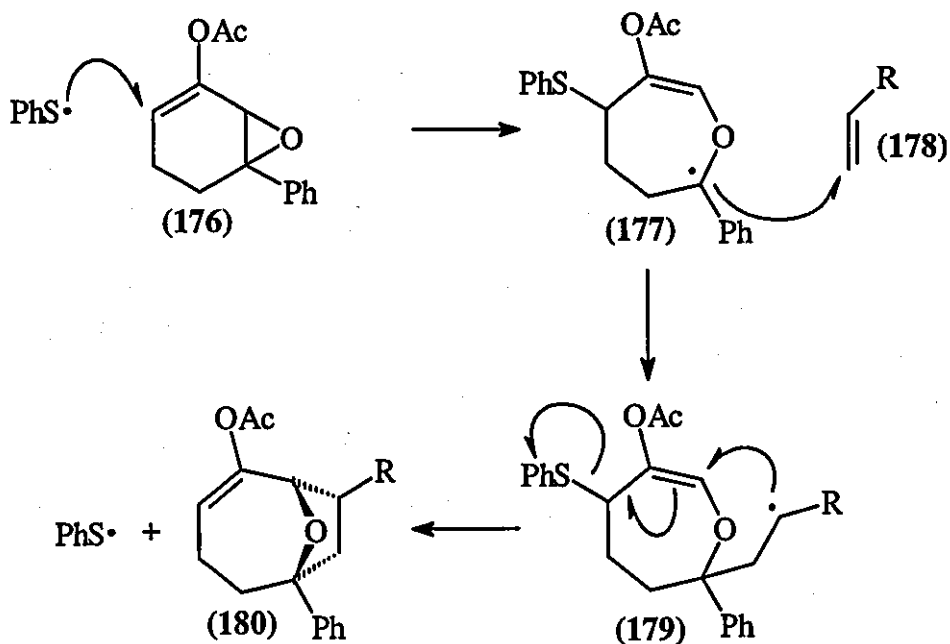


Scheme 2-2

As mentioned previously in section 1.3.7.2 the reversible addition of phenylthio radicals to enol-acetates has also been used to generate oxiranylcarbinyl radicals in a similar way.⁴⁴ There are several advantages in the use of phenylthio radicals over alternative reductive methods using tributyltin hydride. Only a catalytic amount of diphenyldisulfide is required and reduction of reaction intermediates prior to product formation is not possible. In addition the difficult chromatographic separations usually encountered with tributyltin hydride are avoided and the oxygen functionality on the ring, which is a useful handle for further synthetic transformations, is retained.

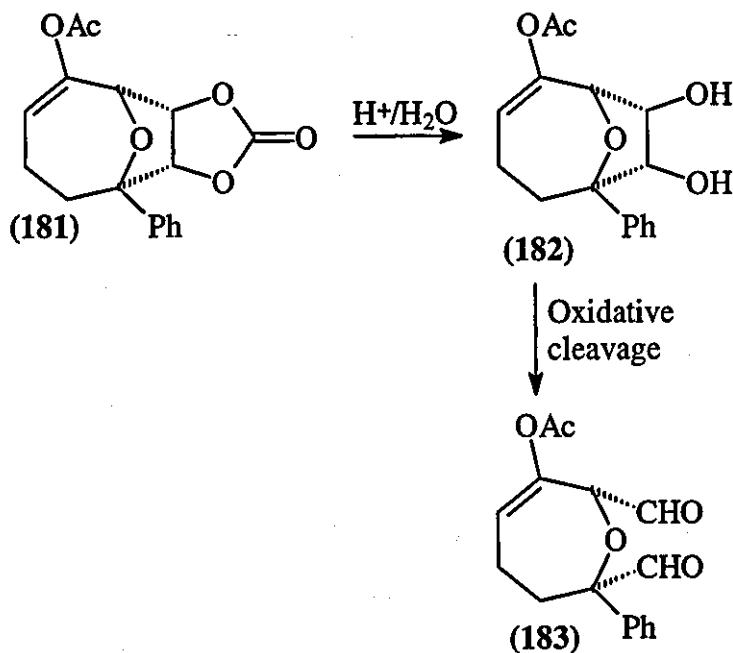
2.2 Aims

The intentions of this project were to combine the methodologies mentioned above and use epoxides instead of cyclopropyl rings in a tandem ring-expansion cyclisation reaction similar to that shown in Scheme 2-1. It was hoped that the phenyl substituted enol acetate (176) would open *via* C-C cleavage to give a benzylically stabilised radical (177). If this species were to trap an alkene (178), cyclisation and expulsion of the phenylthio radical would result in the formation of a ring expanded, bridged system (180) (see Scheme 2-3).



Scheme 2-3

The trapping of the alkene vinylene carbonate (174) would be of particular interest as this could be used as a route towards α,ω -*cis* disubstituted medium ring ethers such as (183) *via* hydrolysis and oxidation of the potential reaction product (181) (see Scheme 2-4).



Scheme 2-4

There are several natural products which contain this type of functionality, e.g. the biologically active diterpenoid zoapatanol (184),⁵⁵ and the *Laurencia* metabolites (+)laurencin (185),⁵⁶ and lauthisan (186),⁵⁷ and it was hoped that a general method for the synthesis of these types of compound could be developed.

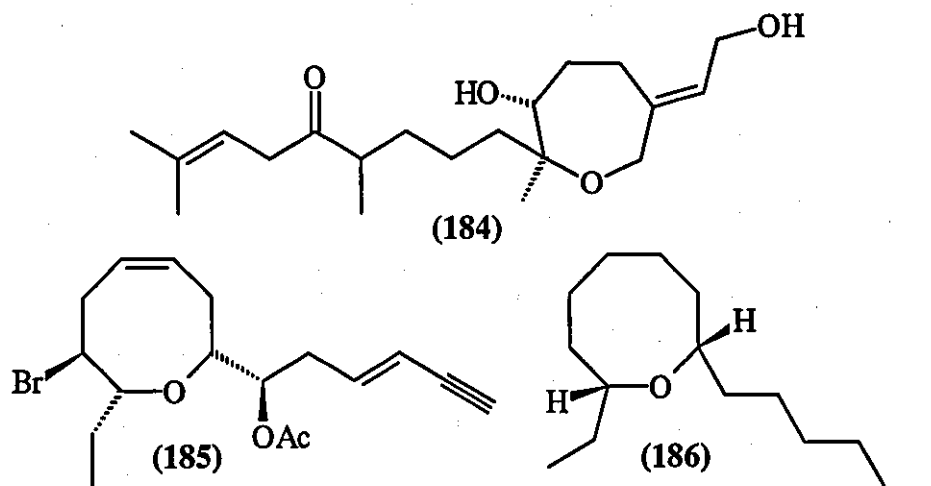
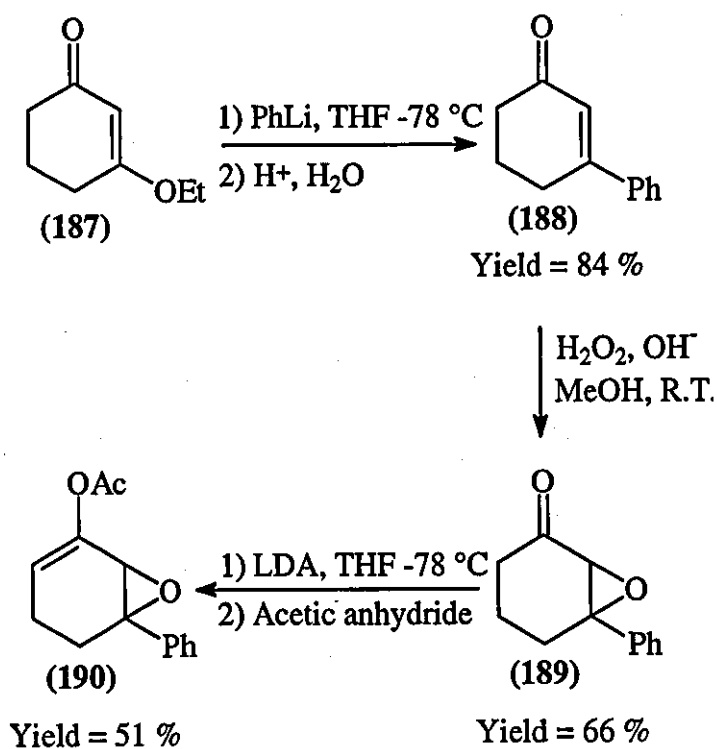


Fig 2-1

2.3 Results and Discussion.

The phenyl substituted vinyl-epoxide (190) was synthesised by the method shown in Scheme 2-5. It was intended to use this compound as a model system to study the reaction shown in Scheme 2-3.

2.3.1 Synthesis of the Reaction Substrate (190).



Scheme 2-5

Treatment of 3-ethoxy-2-cyclohexen-1-one (187) with phenyllithium followed by an aqueous acid work up gave 3-phenyl-2-cyclohexen-1-one (188),⁵⁸ and this was converted to the 2,3-epoxy-3-phenyl-2-cyclohexan-1-one (189) by treatment with alkaline hydrogen peroxide.⁵⁹ Kinetic deprotonation of (189) with lithium diisopropylamide followed by quenching of the enolate with acetic anhydride,⁴⁴ gave 2-acetoxy-3,4-epoxy-4-phenylcyclohex-1-ene (190).

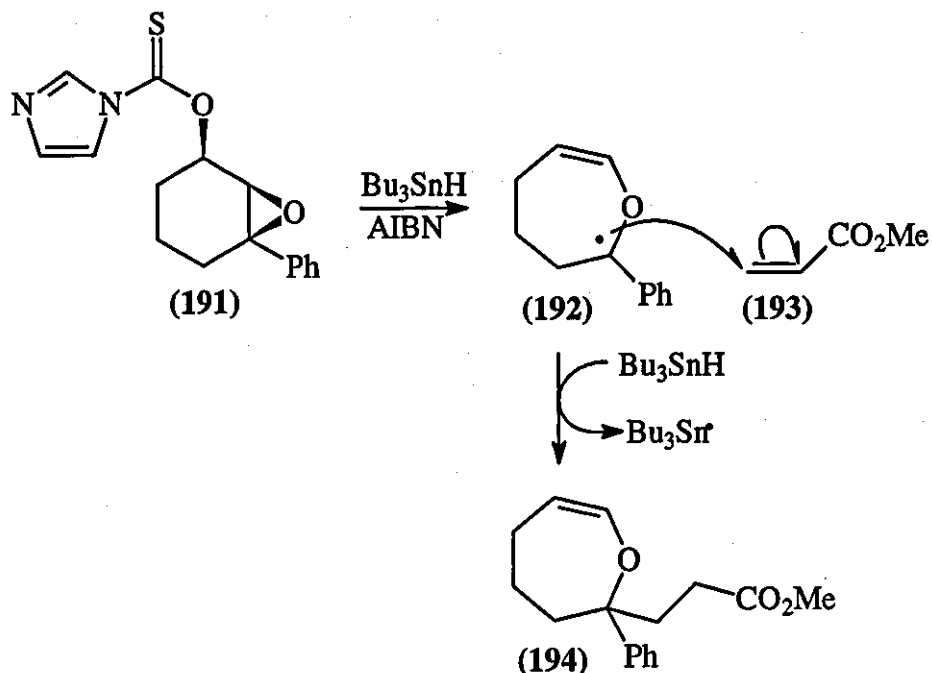
2.3.2 Attempted Radical Reactions of (190).

Initial attempts were made to couple (190) with a number of electronically different alkenes using the reaction conditions of Feldman in the above cyclopentane synthesis. These conditions involved slow addition of diphenyldisulfide (1 eq.) and AIBN (0.2 eq.) to a refluxing solution of the epoxy enolacetate (190) and the alkene with concomitant sunlamp irradiation.⁵⁴ Unfortunately attempts to couple both methyl acrylate and vinylene carbonate returned only starting materials.

Next the more forcing conditions used by Rawal for hydrindane syntheses (see Section 1.3.7.2) were investigated.⁴⁴ A solution of the epoxy enolacetate (190), the alkene, diphenyldisulfide (0.2 eq.) and AIBN (0.15 eq.) in benzene was refluxed in a Hanovia apparatus containing a 450 W medium pressure mercury lamp for 4 hours. Again the desired products were not obtained, use of the more powerful UV source resulted in the formation of complex mixtures when the reaction was attempted with the alkenes maleic anhydride and vinylene carbonate.

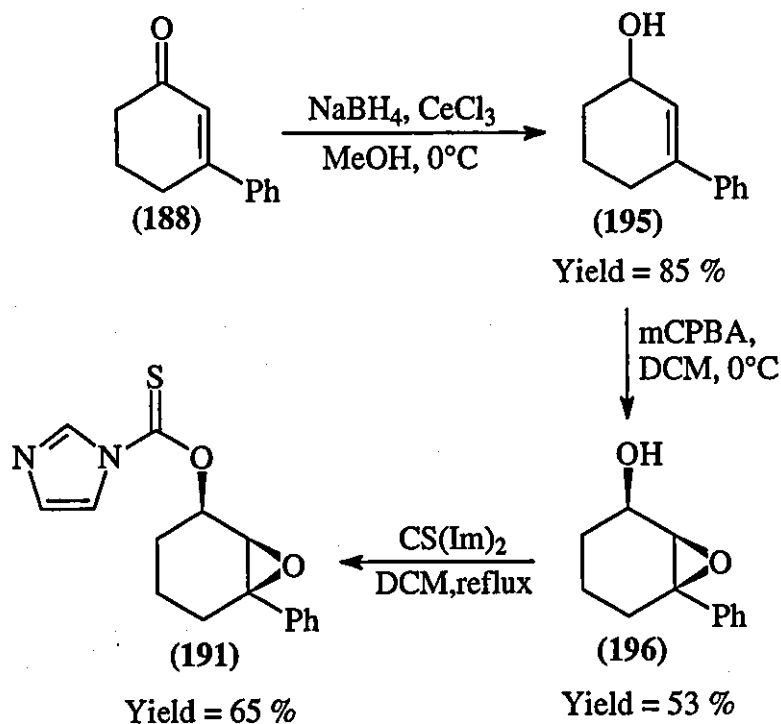
2.3.3 Attempted Tandem Reaction Using Tributyltin hydride.

A further attempt at the intermolecular addition of an alkene was made *via* a reductive process. It was hoped that the thiocarbonylimidazolide (191) would trap a molecule of methyl acrylate after the ring expansion (see Scheme 2-6).



Scheme 2-6

The thiocarbonylimidazolide (191) was synthesised from 3-phenyl-2-cyclohexen-1-one (188) by Luche reduction,⁶⁰ and subsequent *m*CPBA epoxidation,⁶¹ and treatment with 1,1'-thiocarbonyldiimidazole (see Scheme 2-7).⁴⁰ Both (191) and the epoxy alcohol (196) were obtained as single diastereomers which were assumed to be in the *cis* configuration, due to the directing effects of the hydroxy group in the epoxidation of allylic alcohols.⁶¹



Scheme 2-7

Although (191) is known to give the ring expanded enol-ether radical (192) on treatment with tributyltin hydride,²⁶ an identical reaction performed in the presence of methyl acrylate returned starting material and polymeric material, presumably derived from the methyl acrylate.

2.4 Concluding Remarks.

The failure of these systems to trap alkenes was disappointing and work on these intermolecular reactions was suspended in favour of investigating more favourable intramolecular trapping of alkenes (see chapter 3). Later results described in chapters 3 and 4, and also in the literature,³¹ have shown that when related systems have the opportunity to undergo a tandem reaction, it is usually the more reactive alkoxy radical derived from C-O cleavage that undergoes further transformations. It would therefore be very unlikely that any of the desired ring expanded compounds would have been obtained if this work had been pursued further.

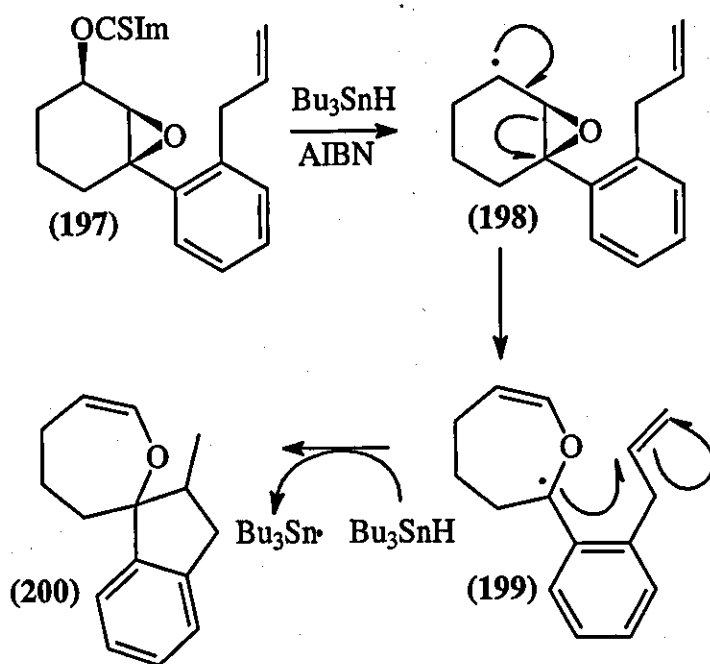
3. Intramolecular Reactions of Oxiranylcarbinyll Radicals.

3.1 Introduction

The results described in Chapter 2 showed that tandem reactions performed successfully with cyclopropylcarbinyll radicals could not simply be transferred to oxiranylcarbinyll radicals. It was thought that the heavily stabilised benzylic radical derived from C-C bond cleavage could be too unreactive to undergo the desired cyclisations and it was decided that tandem reactions of this radical could be best investigated intramolecularly. Intramolecular cyclisations are much more favourable because the double bond is always immediately available to the radical and entropy factors are more favourable.

3.2 Aims

The thiocarbonylimidazolide (197) containing an allyl group on the phenyl ring was synthesised. Directed C-C cleavage of the oxiranylcarbinyll radical (198) was expected to give rise to the benzylic radical (199) which could then undergo a 5-*exo* cyclisation onto the allylic double bond to give (200) (see Scheme 3-1).

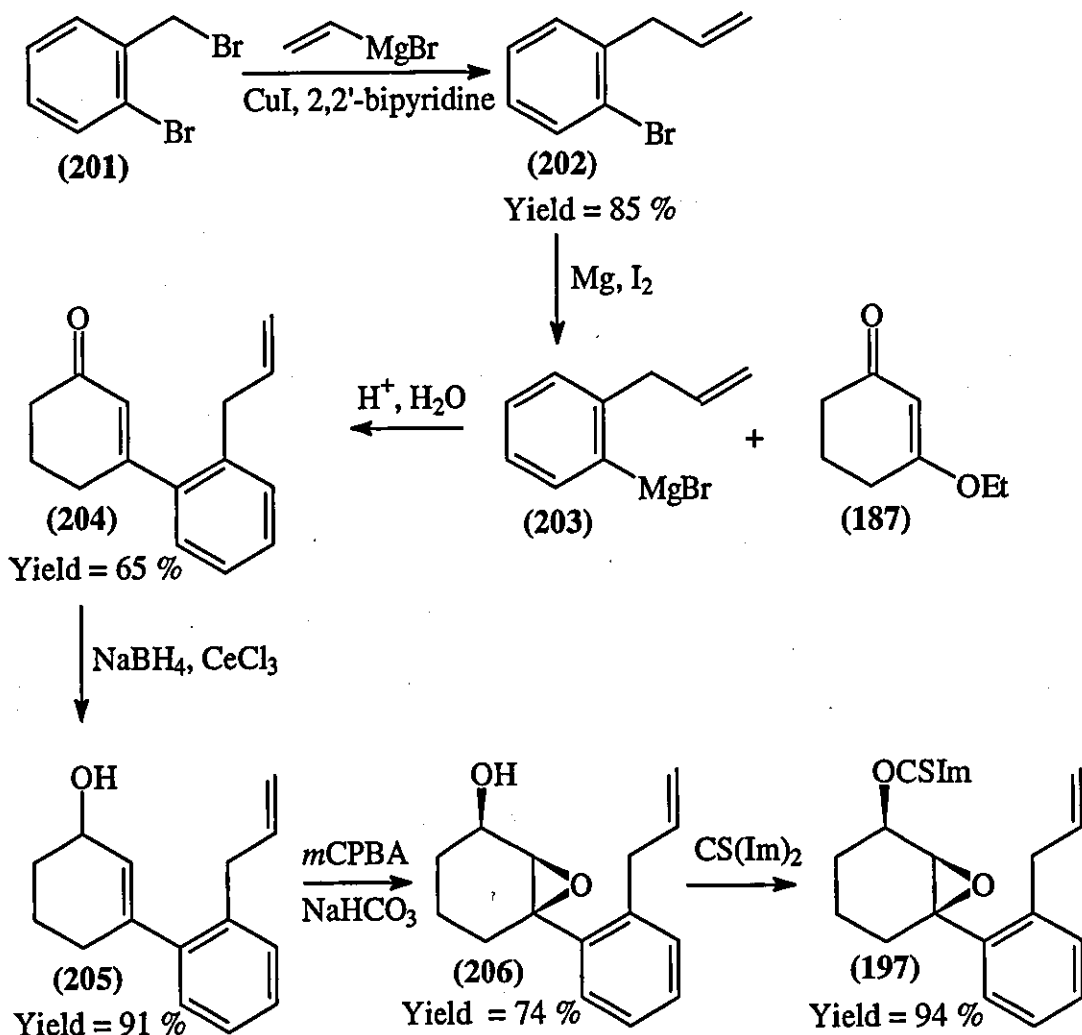


Scheme 3-1

3.3 Results and discussion

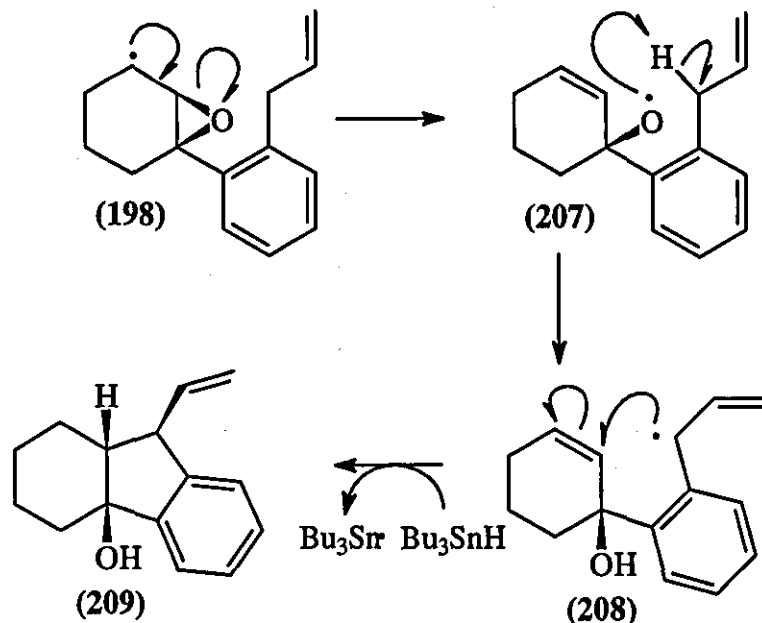
3.3.1 Synthesis and Tandem Reactions of (197).

3-(2-Allylphenyl)-2-cyclohexen-1-ol (**205**) was synthesised as recorded in the literature with comparable yields.⁶² A copper catalysed Grignard coupling of 2-bromobenzylbromide (**201**) and vinylmagnesiumbromide gave 2-allylbromobenzene (**202**) (85 % yield).⁶³ Formation of the Grignard reagent 2-allylphenylmagnesiumbromide (**203**) followed by addition to 3-ethoxy-2-cyclohexen-1-one (**187**) gave 3-(2-allylphenyl)-2-cyclohexen-1-one (**204**). Luche reduction,⁶⁰ and *m*CPBA epoxidation, gave the epoxy alcohol (**206**) as a single diastereomer with no noticeable epoxidation of the allyl group double bond. The stereochemistry has again been assumed to be *cis* based on the directing effects of the hydroxy group.⁶¹ Conversion to the thiocarbonylimidazolide (**197**) by treatment with 1,1'-thiocarbonyldiimidazole (94 %) also proceeded smoothly (see Scheme 3-2).⁴⁰



Scheme 3-2

Treatment of the thiocarbonylimidazolidone (197) with tributyltin hydride and AIBN in refluxing benzene was found to give no products derived from C-C bond cleavage. The hydrogenated (4a)-fluorenol (209) was the only product, formed presumably by C-O bond cleavage of the oxiranylcarbiny radical (198), followed by a 1, 5-hydrogen abstraction to give (208), 5-*exo* cyclisation and reduction (see Scheme 3-3).



Yield = 45 % Normal addition
32 % Inverse addition

Scheme 3-3

The tetrahydrofluorenol (209) was isolated as a single diastereomer and was the only isolable product using both normal (slow addition of tributyltin hydride to the substrate) and inverse addition (slow addition of the substrate to tributyltin hydride) conditions. NOe experiments (see Appendix A) have suggested that the isomer obtained is the *cis* isomer and this agrees with similar results reported by Rawal and Kim (see section 1.3.7.2). The ring junction is also assumed to be *cis* because of stereochemical and geometric factors,⁶⁴ as well as literature precedent.⁴³⁻⁴⁵ As mentioned previously, it has been suggested from frontier molecular orbital theory considerations that C-O bond cleavage predominates in some aryl substituted systems when there is oxygen functionality attached to the radical centre of the oxiranylcarbiny radical (see section 1.3.5.2). However the radical (198) does not have any oxygen functionality at the radical centre and the absence of C-C cleavage products is more likely to be a result of kinetic factors (see section 1.3.4.1). There is evidence to suggest that the C-O bond cleavage occurs kinetically,³¹ and it was thought that the reverse reaction to re-form the oxiranylcarbiny radical and

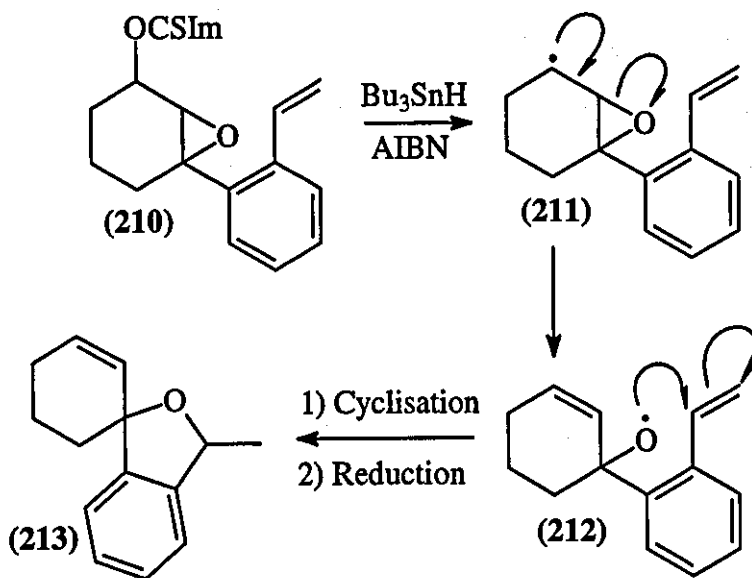
subsequent cleavage to the more thermodynamically stable carbon centred radical (199) (see Scheme 3-1) could be prevented by the 1, 5-hydrogen abstraction of the alkoxy radical (207) (see Scheme 3-3). The abstraction of hydrogen from the allyl group is both stereochemically (*via* a six membered transition state) and thermodynamically (giving rise to a highly stabilised radical) favoured and would be both rapid and irreversible.⁹

An alternative explanation is that C-C cleavage may occur to give the highly stabilised benzylic radical (199) which would be relatively inert towards reduction or cyclisation onto the allyl group. If the reverse reaction to reform the oxiranylcarbiny radical (198) were faster than 5-*exo* cyclisation onto the allyl group double bond or reduction by tributyltin hydride, this also could account for the observed product (209). No evidence for the reverse of C-C bond cleavage had been reported at this time.

It was decided to investigate the reactions of these radicals further by designing radical precursors to investigate both tandem cyclisation of the oxygen radical and also blocking of the hydrogen abstraction reaction in an attempt to promote the formation of products of C-C cleavage.

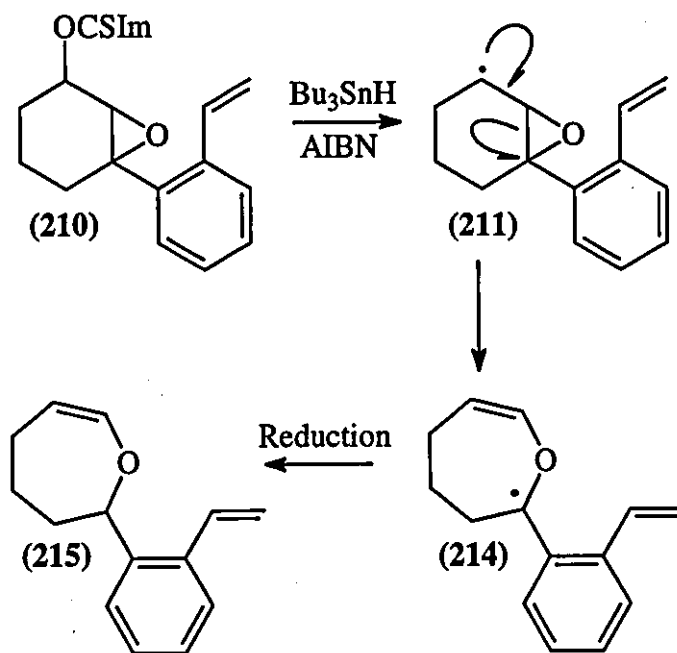
3.3.2 Tandem Cyclisation of Aryl-substituted Oxiranylcarbiny Radicals.

Alkoxy radicals formed from epoxide fragmentation have been shown to undergo tandem cyclisations in simple alkyl-substituted systems to form tetrahydrofurans (see section 1.3.7.1). The thiocarbonylimidazolide (210) was synthesised with a vinyl group in the *ortho* position on the phenyl ring. If this compound were to undergo C-O bond cleavage the resulting oxygen centred radical could then undergo a 5-*exo* cyclisation onto the vinyl group to form a benzo-fused tetrahydrofuran ring (213) (see Scheme 3-4).



Scheme 3-4

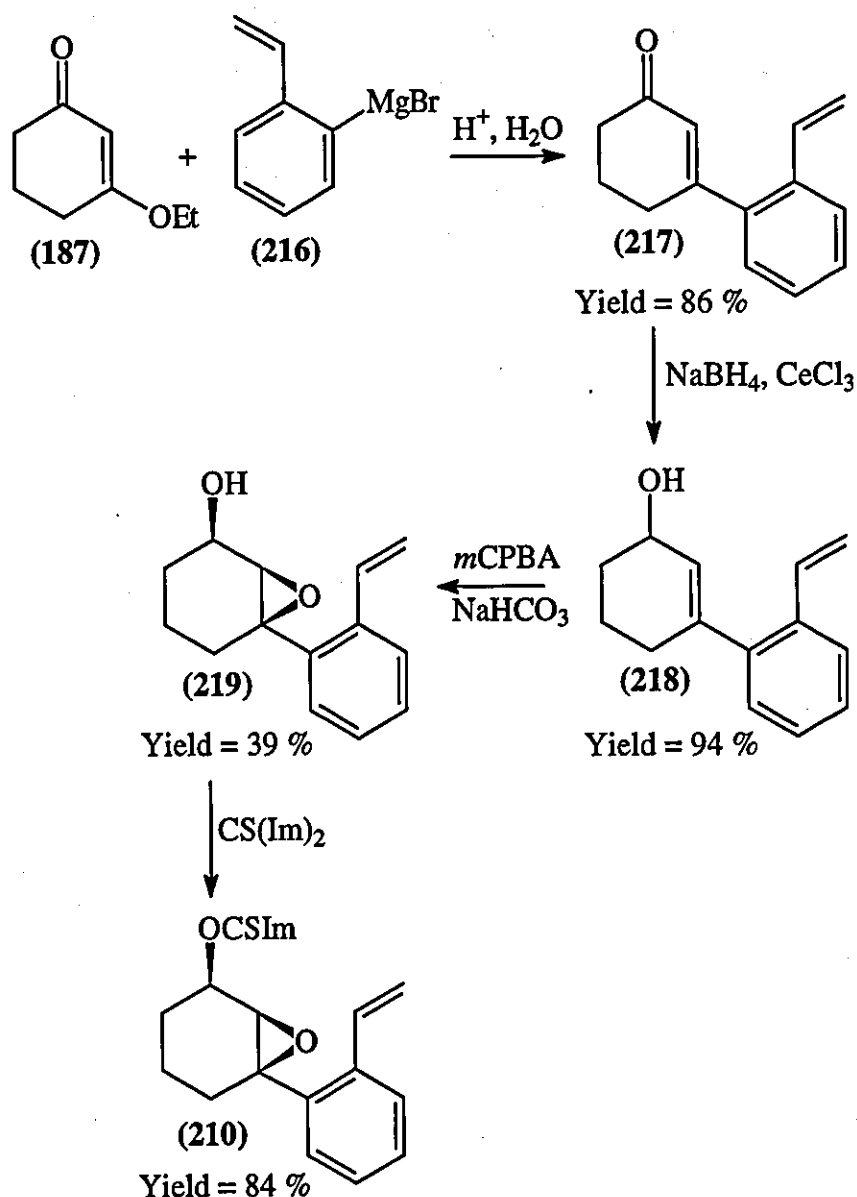
If however the rate of cyclisation was relatively slow, the product of C-C bond cleavage (215) might be obtained,²⁶ via a thermodynamically controlled route (see Scheme 3-5).



Scheme 3-5

Synthesis of the thiocarbonylimidazolide (210) proceeded smoothly using a similar route to that used in the synthesis of (197) (see Scheme 3-6). The Grignard reagent derived from 2-Bromostyrene (216) was added to 3-ethoxy-2-cyclohexen-1-one (187) to give (217). The remaining steps of the synthesis were identical to those in Scheme 3-2. The *m*CPBA epoxidation of (218) was less regioselective than in the previous synthesis and

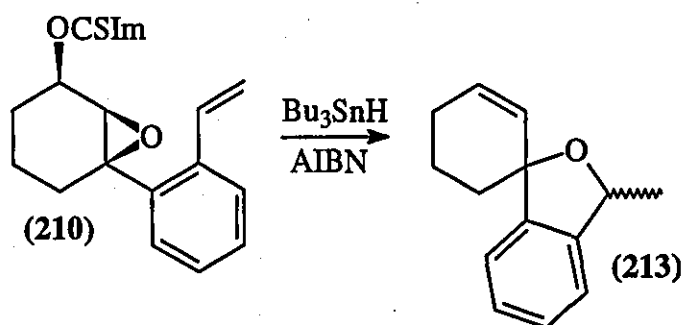
the reaction had to be monitored closely by T.L.C to ensure that epoxidation of the styrene double bond was minimised. The thiocarbonylimidazolid (210) was again isolated as a single diastereomer and was found to be highly crystalline. The X-ray analysis of the crystal structure confirms the *cis* relationship between the epoxide and the thiocarbonylimidazolid group which has been assumed throughout this work (see Appendix B).



Scheme 3-6

The tributyltin hydride reduction of (210) gave markedly different results under different addition conditions. Under inverse addition conditions the reaction gave the C-O bond cleavage derived *spiro* compound (213) in 33% isolated yield. Purification of the product was found to be exceptionally difficult. After initial flash chromatography on silica to remove the majority of the tributyltin residues, further chromatography on alumina and

distillation at reduced pressure was required. The product was obtained as an inseparable mixture (ratio 4:1) of diastereoisomers (see Scheme 3-7).



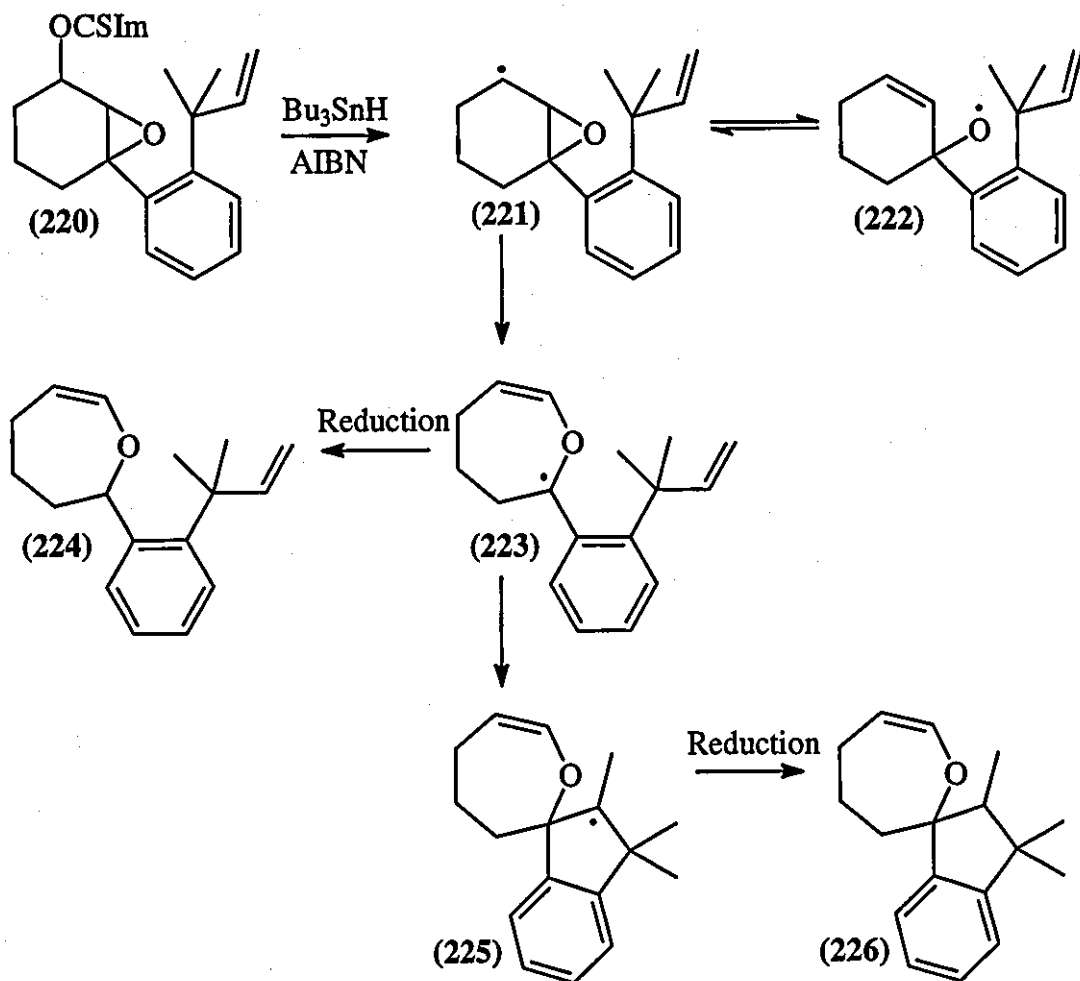
4:1 mixture of diastereomers
 0 % yield Normal addition
 33 % yield Inverse addition

Scheme 3-7

When (210) was treated with Bu_3SnH and AIBN under normal addition conditions an insoluble polymeric material was obtained. It appears that polymerisation of the styrene fragment of (210) may have occurred, favoured by the low concentration of reducing agent relative to the reaction substrate under these conditions. The result obtained under inverse addition conditions does however demonstrate that the oxygen radical will undergo ring closure onto the vinyl group in preference to the formation of products derived from C-C bond cleavage.

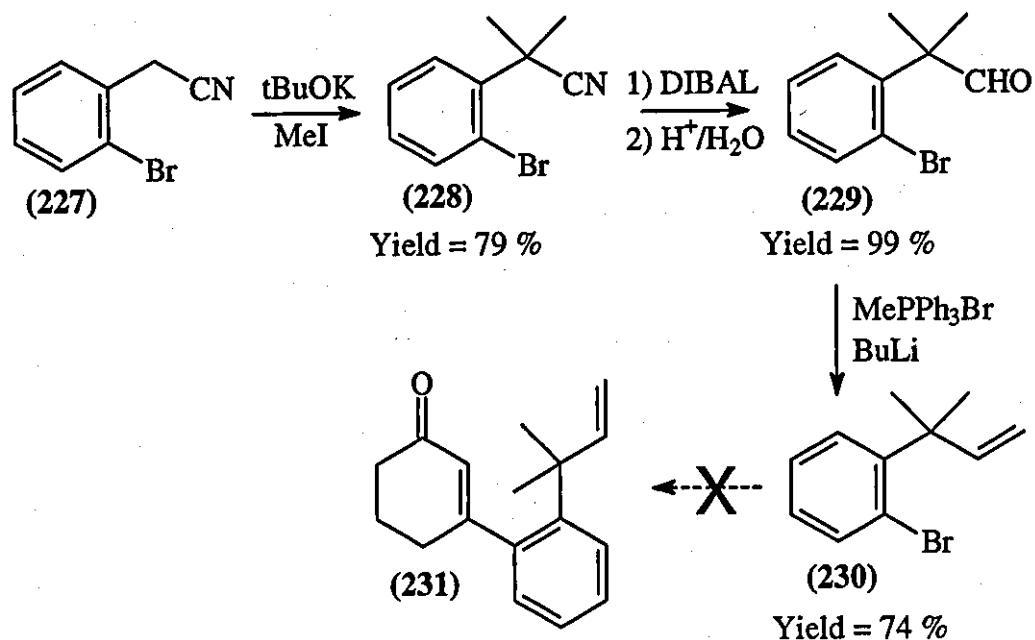
3.3.3 Attempted Synthesis of the Thiocarbonylimidazolid (220).

If the thiocarbonylimidazolid (220) was synthesised and treated with tributyltin hydride and AIBN it could be expected that the alkoxy radical (222) would not abstract a hydrogen atom from the dimethylated allyl group easily. A 1, 6-hydrogen abstraction would be required and although these reactions are known,⁹ they are much less favourable than 1, 5-abstractions. It was hoped that the radical (221) would undergo C-C bond cleavage in preference to abstraction by the oxygen centred radical (see Scheme 3-8).



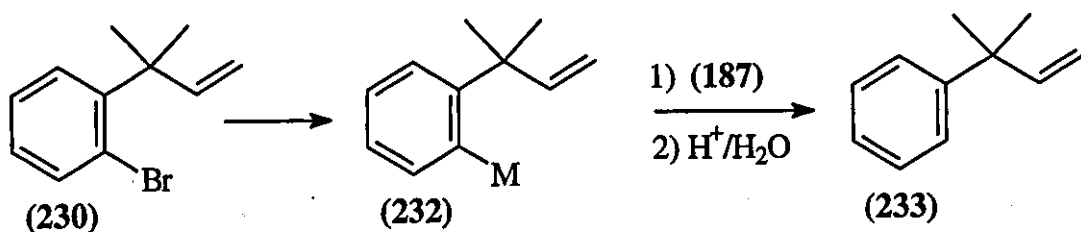
Scheme 3-8

If the benzylic radical **(223)** could be obtained, formation of either the product of direct reduction **(224)** or the cyclised system **(226)** would give an indication of the reactivity of **(222)** with respect to tandem reactions. Synthesis of **(220)** was attempted using a route similar to those previously employed in Schemes 3-2 and 3-6. The dimethylated 2-allylbromobenzene **(230)** was synthesised by a procedure similar to that reported for the isomeric 3-allylbromobenzene.⁶⁵ The bulky bromine atom adjacent to the acetonitrile group in **(227)** caused no steric problems and the dimethylation, reduction and Wittig reactions all proceeded smoothly (see Scheme 3-9).



Scheme 3-9

However all attempts at the conversion of (230) to the enone (231) using organometallic reagents failed. The Grignard reagent (232) ($M = \text{MgBr}$) yielded only the reduced compound (233) after addition of 3-ethoxy-2-cyclohexen-1-one (187) and acid workup (see Scheme 3-10).



Scheme 3-10

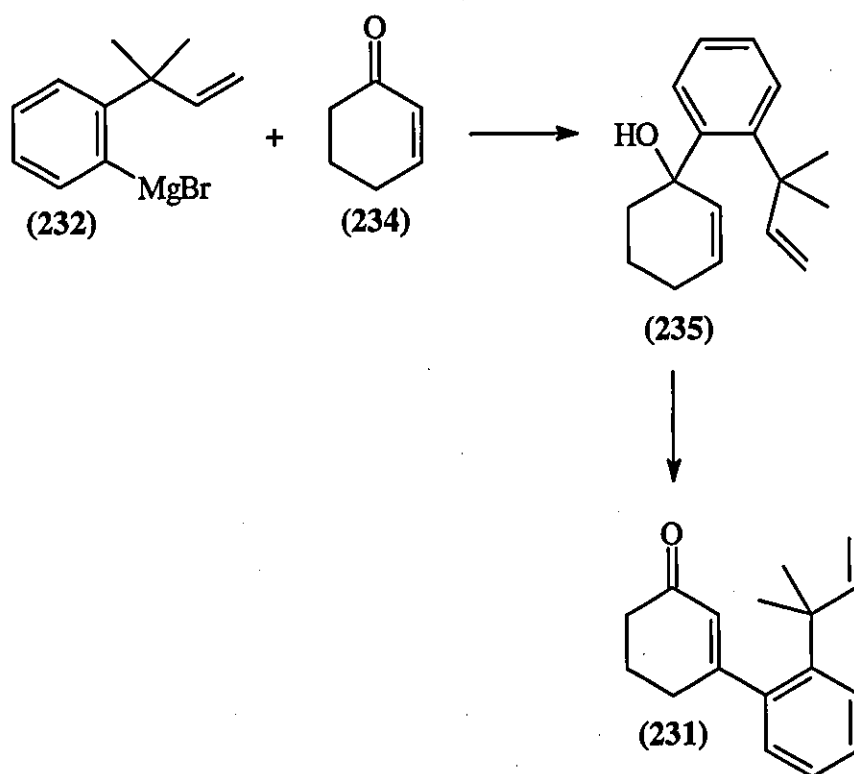
Further attempts were made using the analogous organolithium and organocerium reagents. Organocerium reagents have been reported to succeed where more conventional organometallic reagents have failed because of steric or acidity problems,^{66,67} but neither the organocerium reagent ((232), $M = \text{CeR}_2$) nor the organolithium reagent ((232) $M = \text{Li}$) resulted in any of the desired coupling.

3.4 Concluding Remarks.

The results described in this chapter have shown that when tandem reactions are available to alkoxy radicals derived from aryl-substituted oxiranylcarbinyl radicals, the C-O cleavage pathway predominates and no products of C-C cleavage are seen. It is interesting

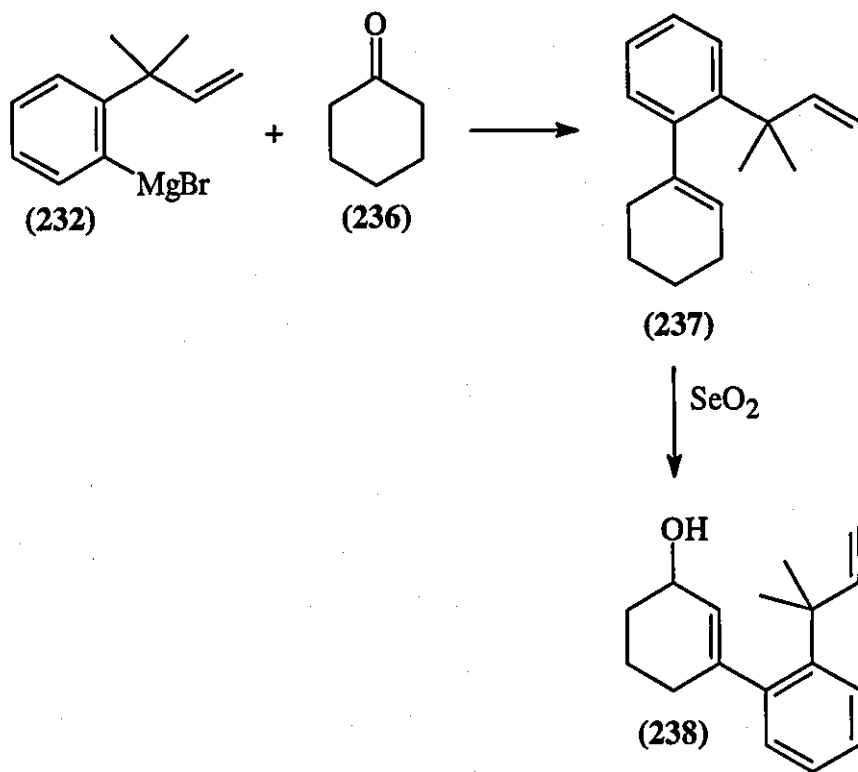
to note that cyclisation of the alkoxy radical can also prevent C-C cleavage in these systems.

The synthetic problems encountered with the synthesis of the thiocarbonylimidazolide (220) were disappointing, as the tributyltin hydride reduction of this compound could have given significant new insight into the reactions of these systems. Alternative synthetic routes to the enone (231) involving the use of 2-cyclohexen-1-one (234) or cyclohexanone in place of 3-ethoxy-2-cyclohexen-1-one (187) were considered but not attempted. 2-Cyclohexen-1-one (234) would be expected to be more reactive than (187) because the electron donating ethoxy group is not present. The proposed scheme for this route is shown in Scheme 3-11. After the Grignard reaction, oxidation of the tertiary alcohol (235) with pyridinium chlorochromate,⁶⁸ would be expected to give the desired enone (231).



Scheme 3-11

Alternatively the analogous reaction with cyclohexanone (236) would be expected to give the cyclohexene (237) after acid work-up (see Scheme 3-12). Allylic oxidation of (237) with selenium dioxide,⁶⁹ would then be expected to give the allylic alcohol (238) from which the thiocarbonylimidazolide (220) could be obtained.



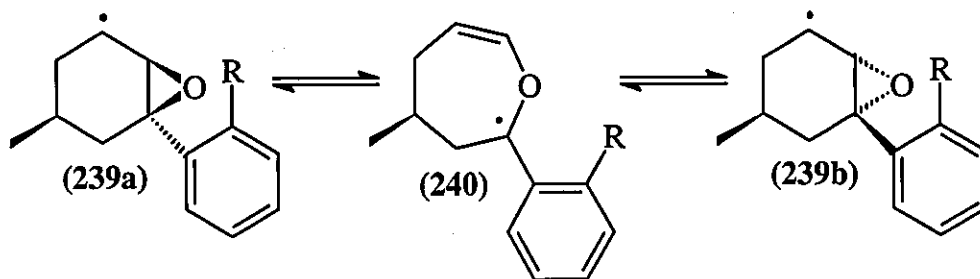
Scheme 3-12

It was decided however, that a different approach to the investigation of the C-C bond cleavage process would be used and the results of this work are discussed further in Chapter 4.

4. Demonstration of Reversible C-C Bond Cleavage in Oxiranylcarbinyll Radicals.

4.1 Introduction.

As mentioned in Section 1.3.3 the C-O bond cleavage of oxiranylcarbinyll radicals is known to be reversible and there is extensive kinetic and synthetic evidence for this process. Reactions involving C-C bond cleavage have received somewhat less attention however and although the reversibility of this cleavage has been suggested,²⁷ no direct evidence has been reported. It was considered that reversible C-C bond cleavage could result in the inversion of stereochemistry at the epoxide in systems such as the one shown in Scheme 4-1, because the conformational mobility of the C-C cleaved species (240) could allow the radical to attack both faces of the double bond.

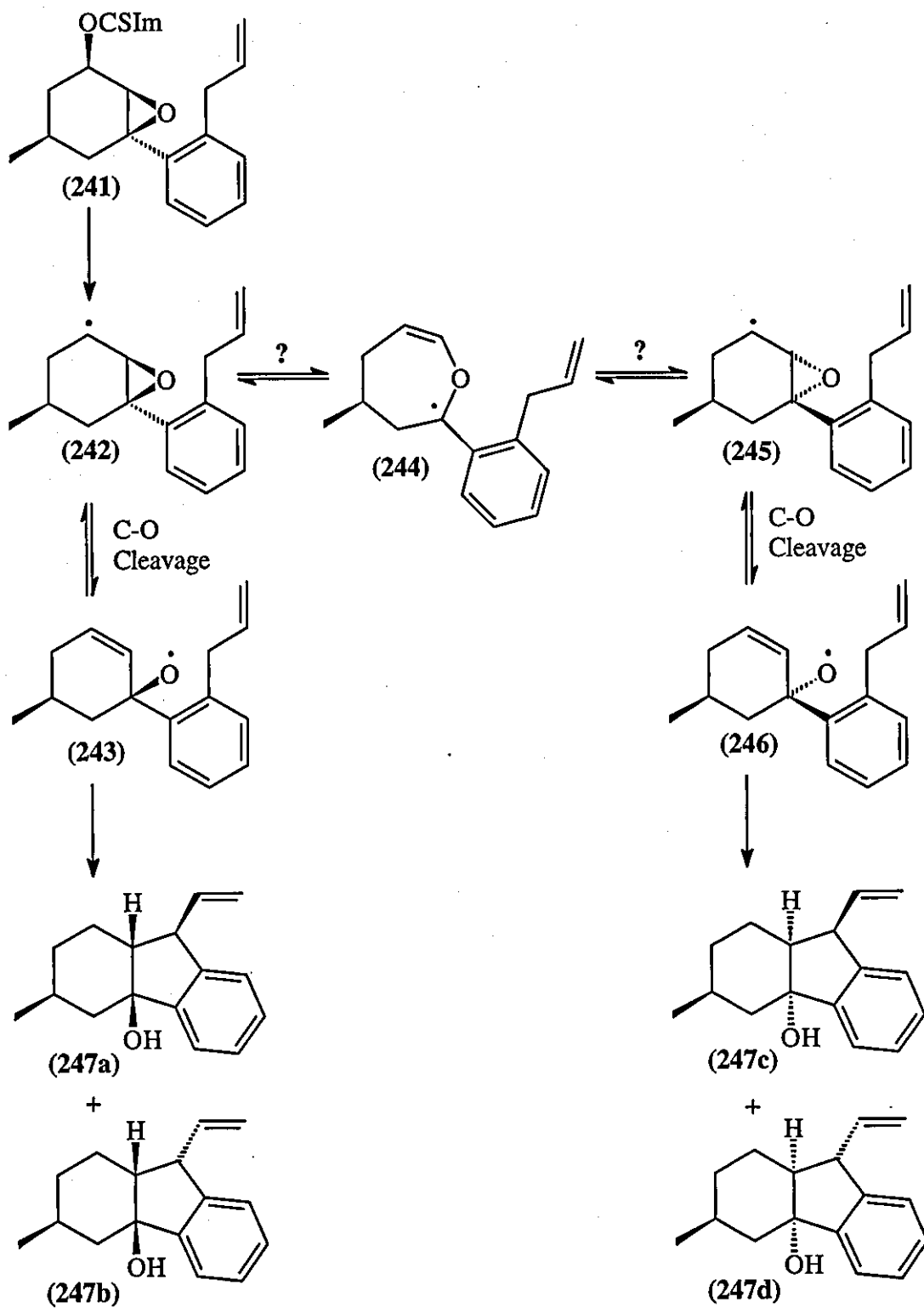


Scheme 4-1

4.2 Aims.

Treatment of the thiocarbonylimidazolide (241) with $\text{Bu}_3\text{SnH/AIBN}$ would be expected to give some or all of the diastereomeric fluorenols (247a) - (247d) (see Scheme 4-2). The number of diastereomers and the relative stereochemistry of the obtained products were of great importance to the mechanistic study, as the production of only (247a) and/or (247b), in which the relative chemistry of the oxygen and the methyl group was the same as in the reaction substrate would suggest that the C-C cleavage was not occurring prior to the formation of the products. The formation of three or four isomers however or the formation of isomers in which the relationship between the methyl and hydroxy groups was different to that in the reaction substrate ((247c) and (247d)) would suggest C-C cleavage is occurring reversibly in these systems. (see Scheme 4-2). As mentioned in Chapter 3 the formation of *trans* ring junctions in these systems is considered

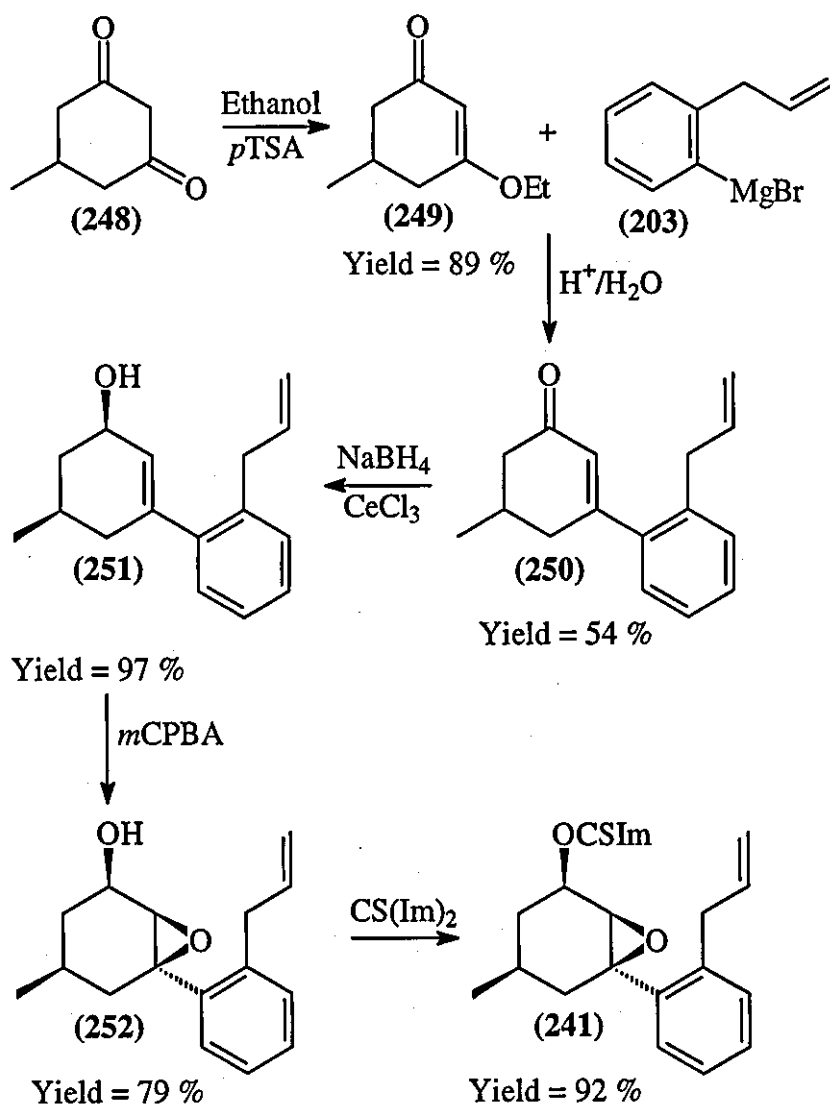
to be extremely unlikely and thus formation of more than four stereoisomers would not be expected.⁶⁴



Scheme 4-2

4.3 Results and Discussion.

The thiocarbonylimidazolide (**241**) was synthesised by the method shown in Scheme 4-3. 5-Methyl-1,3-cyclohexanedione (**248**) was treated with ethanol in refluxing toluene to give 3-ethoxy-5-methyl-2-cyclohexen-1-one (**249**) (89 % yield),⁷⁰⁻⁷² and this was converted to the 2-allylphenyl substituted enone (**250**) by treatment with 2-allylphenylmagnesium bromide (54 %).⁶³ Interestingly the Luche reduction,⁶⁰ of this compound gave a single diastereomer of the alcohol (**251**). *m*CPBA epoxidation (79 %),⁶¹ followed by treatment with 1,1'-thiocarbonyldiimidazole,⁴⁰ (92 %) gave the thiocarbonyl-imidazolide (**241**) as a single diastereomer. This was particularly fortuitous as for these studies it was intended that the tributyltin hydride reduction would be performed on a single diastereomer of (**241**). A potentially difficult chromatographic separation was therefore avoided.

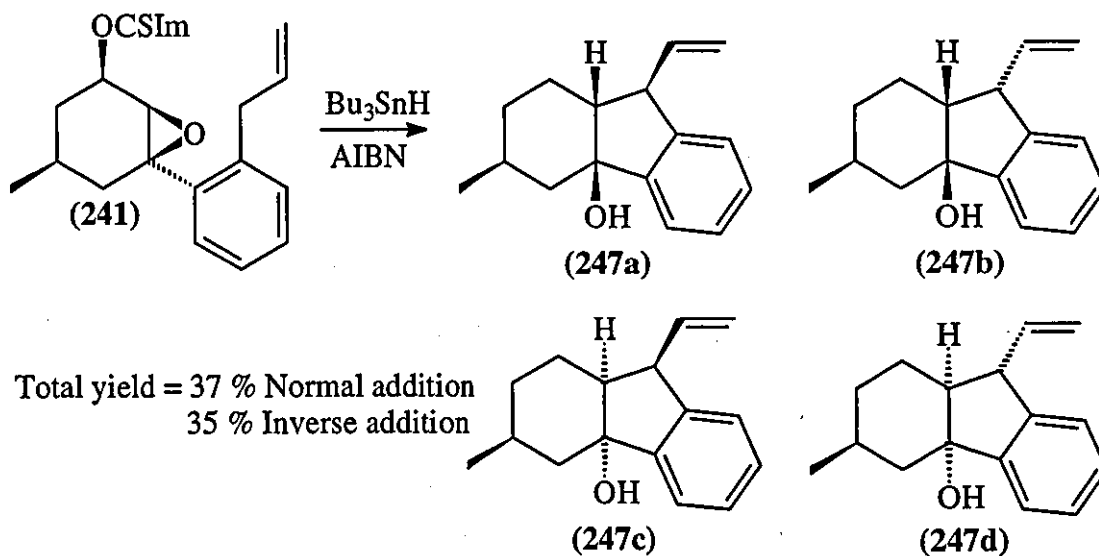


Scheme 4-3

The relationship between the methyl group and the thiocarbonylimidazolide group in (241) was apparent from spin-spin coupling constants. N.O.e. experiments have also supported this assignment which is discussed in greater detail in Appendix A. A reliable assignment of the epoxide stereochemistry is not possible from NMR experiments and the epoxide has again been assumed to be *cis* to the thiocarbonylimidazolide group because of the directing effect of the OH group in *m*CPBA epoxidations.⁶¹

Treatment of the thiocarbonylimidazolide (241) with tributyltin hydride and AIBN under both normal and inverse addition conditions gave isomeric mixtures of the hydrogenated fluorenol (247a-d) in yields of 37 % and 35 % respectively (see Scheme 4-4). In each case the product was obtained as a mixture of 4 diastereoisomers of which the major diastereomer was found to be appreciably less polar and was separable from the others by flash chromatography. GC-MS of the mixture showed that the four diastereoisomers were obtained in the ratio 10:48:22:4 (see Appendix C).

Although it was not possible to correlate these values to the actual diastereomers, the formation of four diastereomers of product is a good indication of reversible C-C bond cleavage in these systems. This suggests that both the *cis* ((247a) and (247b)) and *trans* ((247c) and (248d)) configurations between the methyl group and the hydroxy group are obtained, as well as two different configurations of the vinyl group (see Scheme 4-4).



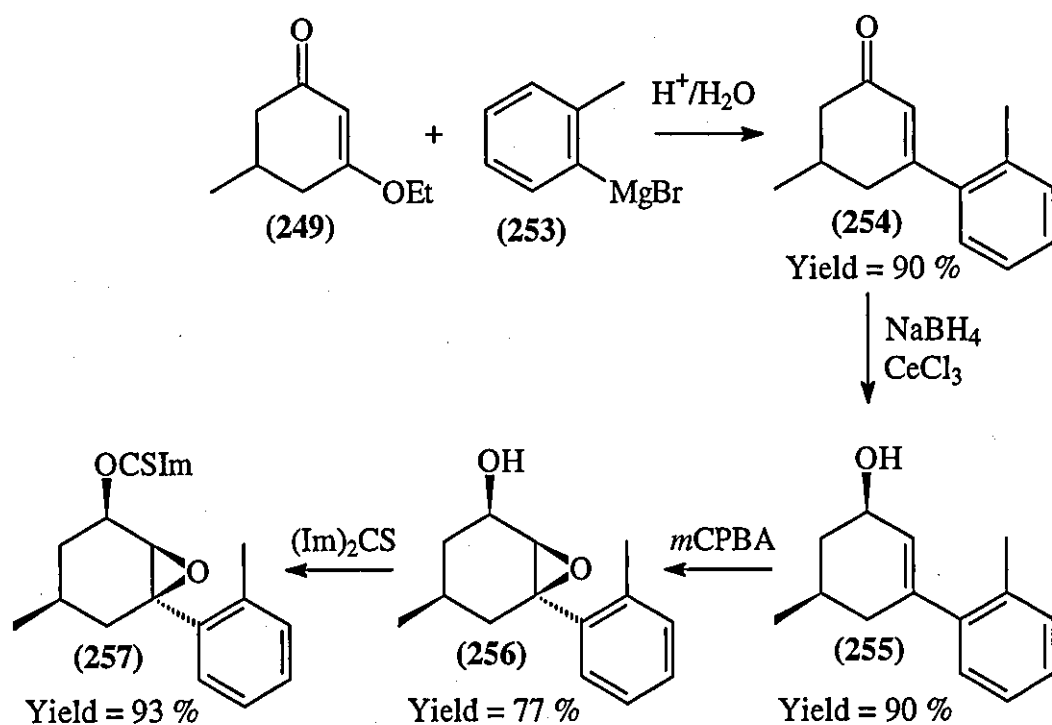
Scheme 4-4

This result is exactly as would be expected if epimerisation as a result of C-C cleavage is occurring. Unfortunately the isolable diastereomer was an oil so assignment of the stereochemistry by X-ray analysis was not possible. The NMR spectrum of the material

was also too complex to give definitive evidence as to the relative configuration of either the hydroxy or vinyl groups.

A similar stereochemical investigation was conducted with the thiocarbonylimidazolide (257) which has a 2-methylphenyl group in place of the 2-allylphenyl group. This experiment was intended to confirm the result described above and was expected to yield 2 diastereomers instead of four. It was hoped that the simplification of the system would allow isolation and characterisation of both of the expected diastereomers.

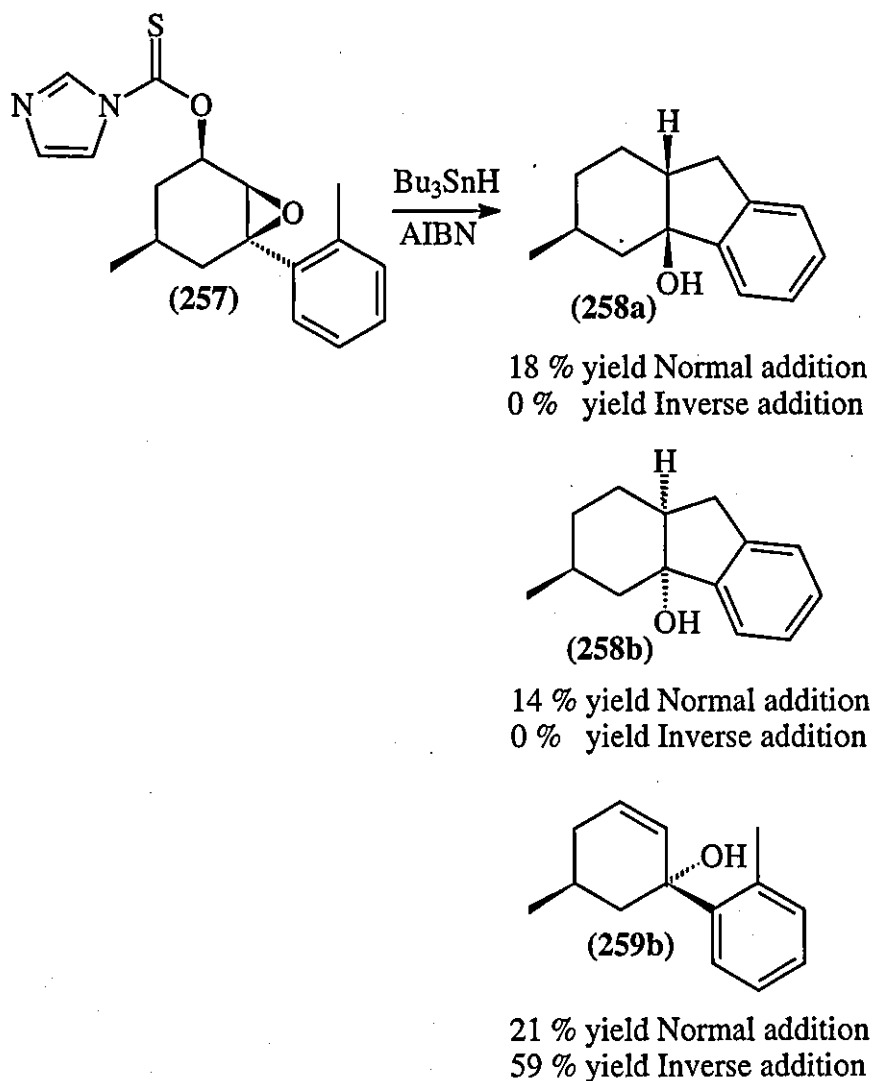
Synthesis of the thiocarbonylimidazolide (257) was performed exactly as for the synthesis of (241) except that the Grignard reagent used in the first reaction was 2-methylphenylmagnesiumbromide (253) derived from the commercially available 2-bromotoluene (see Scheme 4-5).



Scheme 4-5

Diastereoselectivity was again observed in the Luche reduction of the enone (254) and (257) was obtained as a single diastereomer with *cis* stereochemistry (see Appendix A). Although it was obtained as a solid, attempts to recrystallise this material yielded only crystallites which were not adequate for X-ray analysis. Also the thiocarbonylimidazolide group was found to be thermally labile and underwent gradual decomposition on prolonged heating.

Treatment of (257) with $\text{Bu}_3\text{SnH/AIBN}$ gave particularly interesting results which were also markedly different under normal and inverse addition conditions. The results of these two reactions are shown in Scheme 4-6.



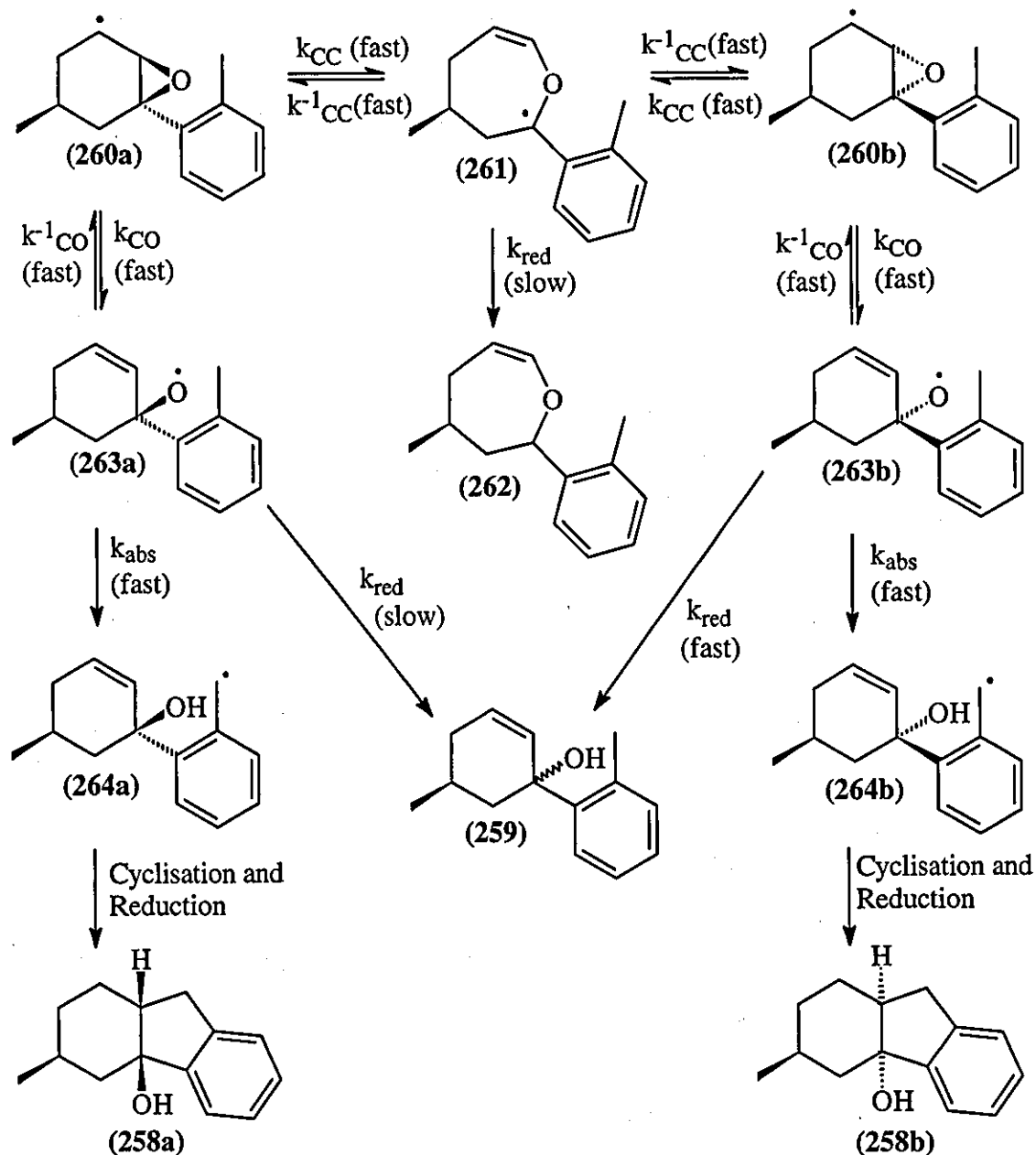
Scheme 4-6

As expected the reaction yielded two diastereomers of fluorenol, (258a) and (258b) under normal addition conditions. The cyclohexenol (259b) was also obtained by reduction of the alkoxy radical prior to abstraction and was the only product obtained under the inverse addition conditions. All three products were found to be solids; the stereochemistry of the tetrahydrofluorenol (258b) was assigned from the X-ray crystal structure (see Appendix B), the stereochemistry of (258a) is assumed by implication and the structure of (259b) has been deduced from spin-spin coupling constants (see Appendix A).

4.4 Concluding Remarks

The absence of a vinyl group on the sidechain appears to have strongly disfavoured the hydrogen abstraction such that direct reduction of the alkoxy radical could take place, resulting in the formation of the cyclohexenol (259b).

The X-ray crystal structure of (258b) is indisputable evidence that epimerisation is occurring prior to the product formation. It is also interesting to note that the structure of the directly reduced alcohol, (259b) also has a *trans* arrangement between the hydroxy group and the methyl group. The different product distributions obtained under normal and inverse addition conditions give significant insight into the relative rates of the various stages of these reactions. These rates are summarised in Scheme 4-7



Scheme 4-7

It is immediately apparent from the epimerisation that the values of k_{CO} , k^{-1}_{CO} , k_{CC} and k^{-1}_{CC} are all very high ($> k_{abs}$ and k_{red}) and the system reaches equilibrium before the abstraction and reduction reactions begin to give rise to the products. The product distribution is therefore dependent only on the relative rates of the abstraction and reduction reactions, which are irreversible. The isolation of approximately equal amounts of (258a) and (258b) suggests that $k_{abs}(263a) \approx k_{abs}(263b)$. It can also be seen that $k_{red}[H](263b) \approx k_{abs}(263a)$ and $k_{abs}(263b)$ under normal addition conditions and $k_{red}[H](263b) > k_{abs}(263a)$ and $k_{abs}(263b)$ under inverse addition conditions. The higher concentration of tributyltin hydride has no effect on the rate of the intramolecular abstraction reactions so reduction of (263b) is predominant when the concentration of hydride is high. It is also interesting to note that the reduction reactions of the radicals (261) and (263a) are too slow to give rise to the cyclohexen-1-ol (259a) or the ring expanded ether (262). The methyl group on the cyclohexyl ring appears to shield the alkoxy radical from reduction when it is in an axial position in (263a) (see Fig 4-1), resulting in the exclusive reduction of (263b) in which the methyl group is equatorial.

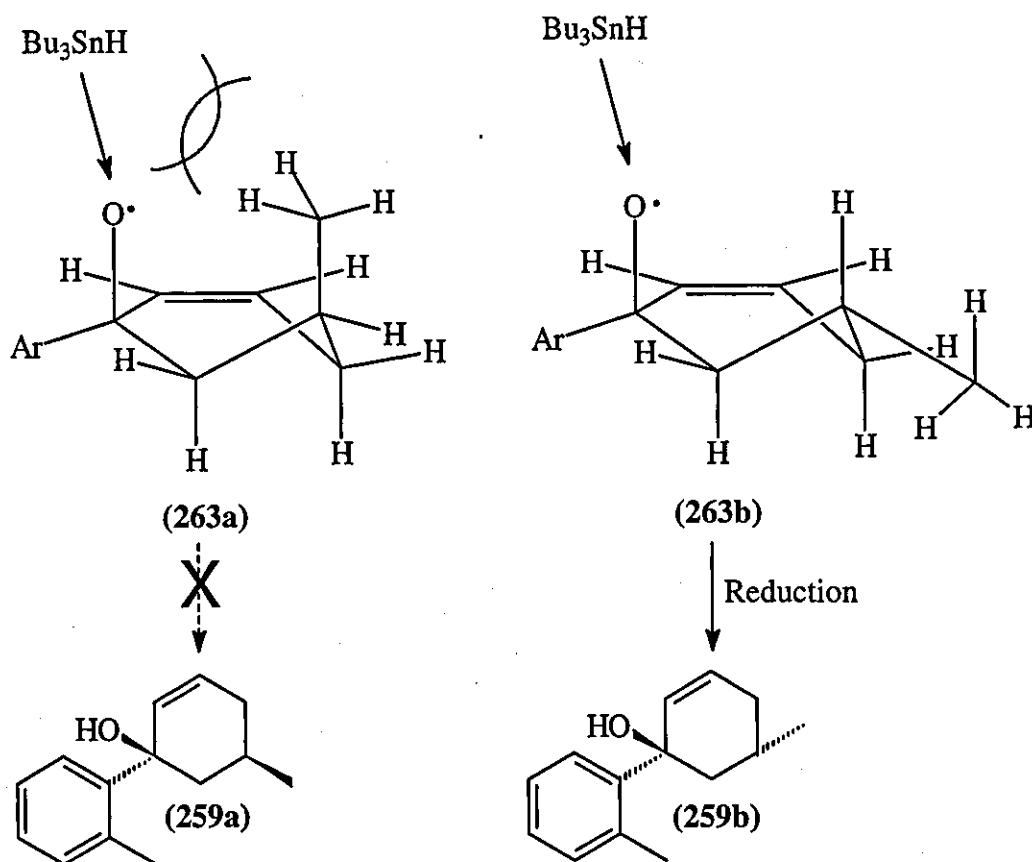
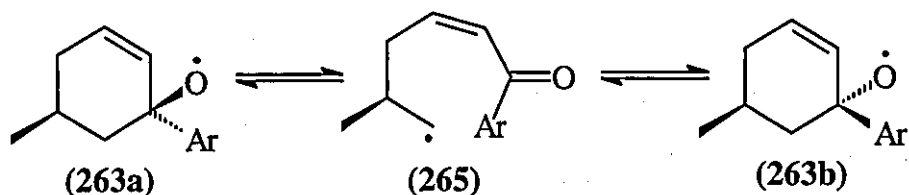


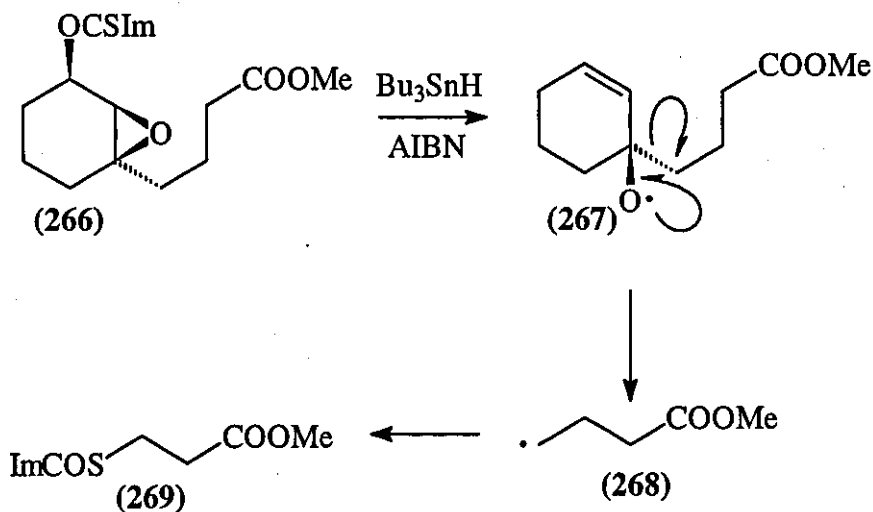
Fig 4-1

It could also be postulated that the epimerisation of the epoxides could occur via a mechanism involving a reversible β -cleavage reaction of the alkoxy radical. This would involve the reversible formation of a ring opened species (265) containing a carbonyl group and a primary alkyl radical (see Scheme 4-8).



Scheme 4-8

It has been noted that a similar β -cleavage of this type can occur to expel a side chain in a similar system (see Scheme 4-9), but it is a relatively minor side reaction (5-10 % yield).⁴³ This process is certainly unfavourable energetically,⁹ and would be expected to lead to the formation of other products.



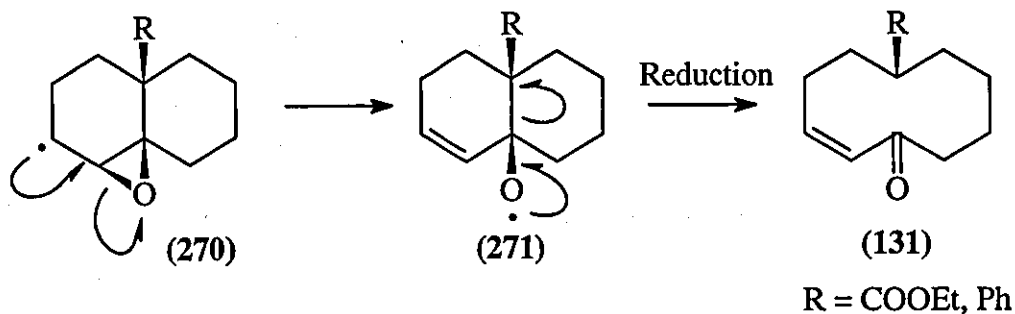
Scheme 4-9

The results in this chapter demonstrate some very interesting points in the chemistry of aryl substituted oxiranylcarbonyl radicals. It appears that subsequent reactions can influence the outcome of the direction of cleavage. Unfortunately from the point of view of this work the alkoxy radical derived from C-O cleavage appears to be much more reactive than the heavily stabilised benzylic radical derived from C-C cleavage. As a result a tandem reaction of the C-C cleaved radical would only be obtained if tandem reactions of the alkoxy radical were strongly disfavoured. The reactivity of the benzylic radical is also a relative unknown, it could be that tandem reactions of this radical could be difficult to obtain even if the competition from the C-O cleaved radical were removed.

5 The Preparation of Medium Ring Lactones.

5.1 Introduction

Section 1.3.7.1.1 described how the bridging bonds in decalin systems can be broken by the β -cleavage reactions of alkoxy radicals (271) formed from oxiranylcarbiny radicals (270) (see Scheme 5-1).

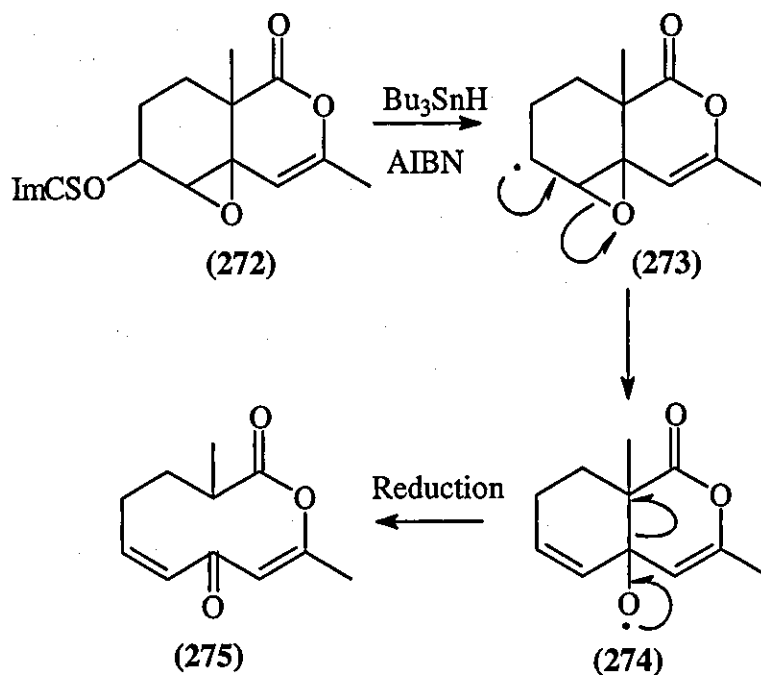


Scheme 5-1

It was considered that this type of reaction could be useful in the synthesis of medium ring lactones, which are difficult to make by standard methods because of the unfavourable loss of entropy involved in the cyclisation reaction and also because of competing intermolecular esterifications.

5.2 Aims

The intention of this work was to synthesise the thiocarbonylimidazolidone (272) and test if endocyclic ester groups could be used as radical stabilising groups in reactions such as that shown in Scheme 5-2. If successful the chemistry could be used for the preparation of medium ring lactones such as the natural product didemnilactone (276) (see fig 5-1).⁷³



Scheme 5-2

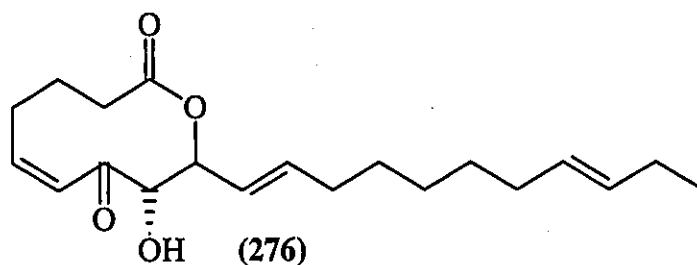
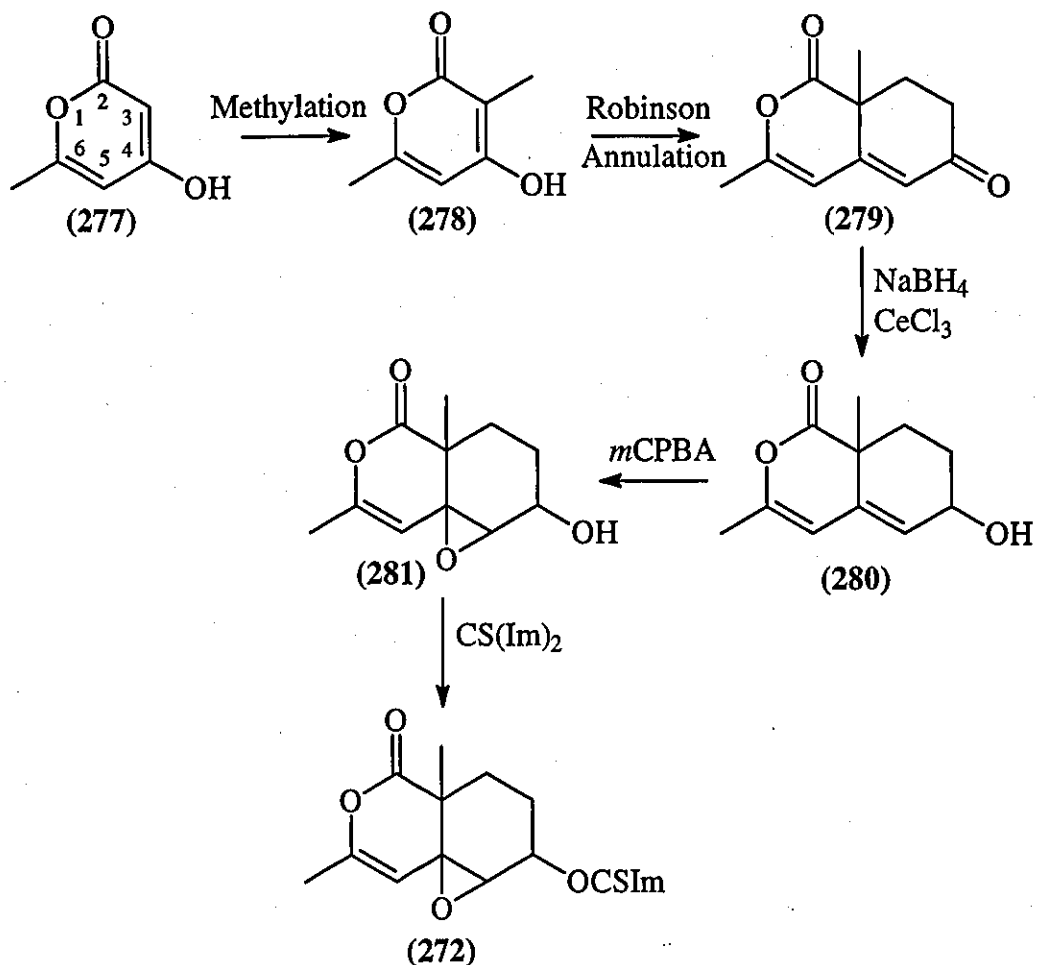


Fig 5-1

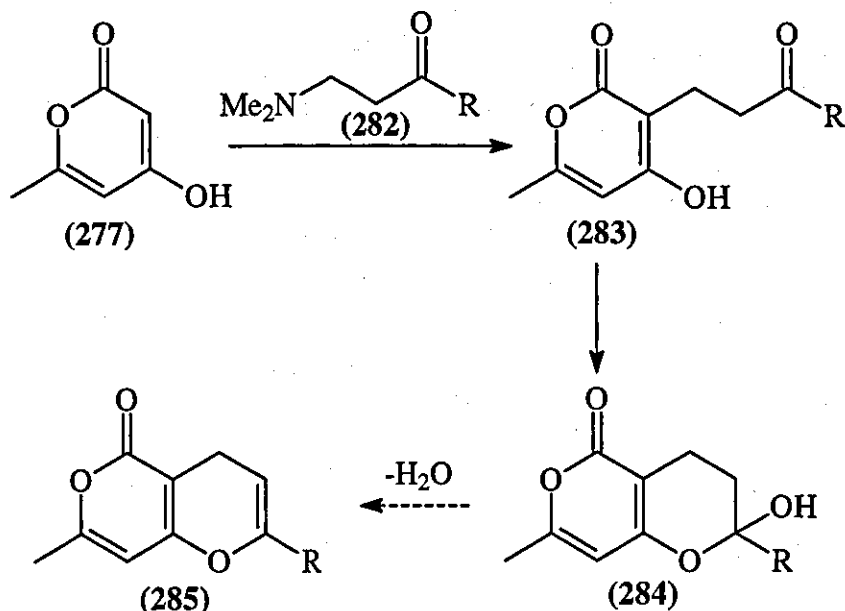
5.3 Results and Discussion

Synthesis of the epoxythiocarbonylimidazolidone (272) was attempted from the commercially available lactone 4-hydroxy-6-methyl-2-pyrone (277) by the route shown in Scheme 5-3.



Scheme 5-3

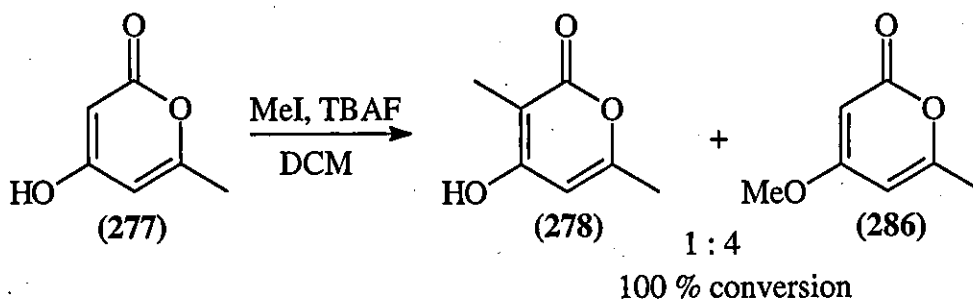
The chemistry of 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) (277) has been extensively studied and reviewed.^{74,75} It has been reported that Robinson annulation type reactions of (277) with mesityl oxide and methylvinylketone Mannich bases (282) give rise to hemi-acetal products (284) because of the strong enolisation in these systems (see Scheme 5-4).^{76,77}



Scheme 5-4

The enolisation and therefore the hemi-acetal formation should be prevented from occurring by methylation at C-3 prior to the Robinson alkylation. After formation of the bicyclic ring (279), Luche reduction followed by *m*CPBA epoxidation and thiocarbonylimidazolid formation was expected to yield the desired epoxy thiocarbonylimidazolid (272) (see Scheme 5-3).

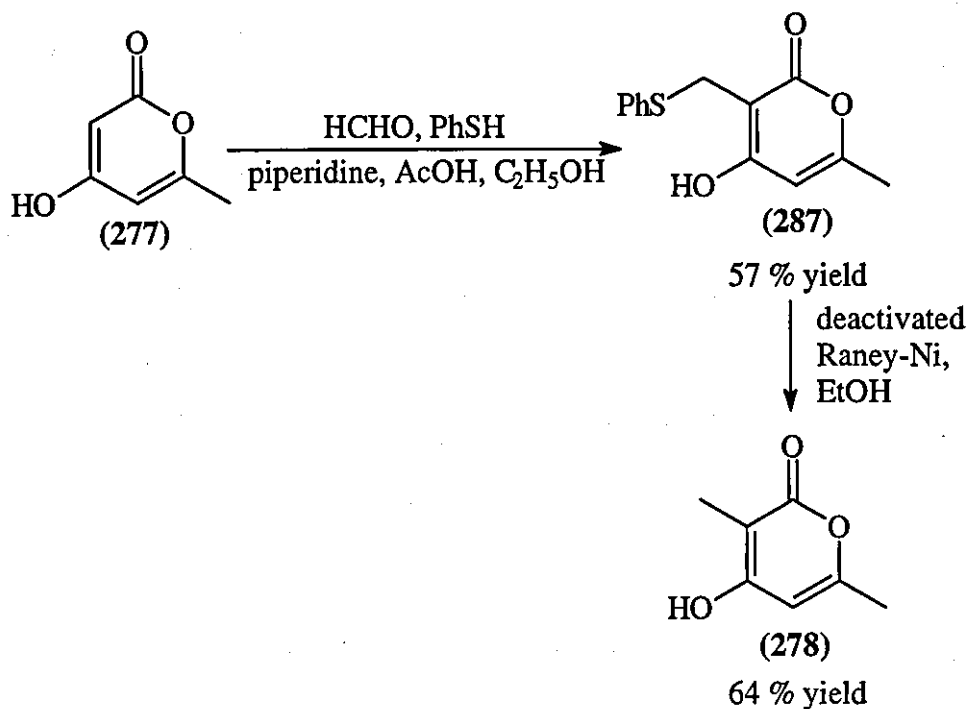
Standard methylation conditions generally favour methylation at oxygen rather than carbon when applied to (277) because of the strong enolisation (> 99 %).⁷⁴ Initial attempts at this reaction were made using tetrabutylammonium fluoride and methyl iodide, a method reported to give selective C-alkylation in a variety of β -dicarbonyl systems.⁷⁸ A trial experiment using tetrabutylammonium fluoride (1.5 eq.) and methyl iodide (4 eq.) in dichloromethane at room temperature yielded a 4:1 mixture of the O-methylated product (286) and the desired C-methylated product (278) (see scheme 5-5).



Scheme 5-5

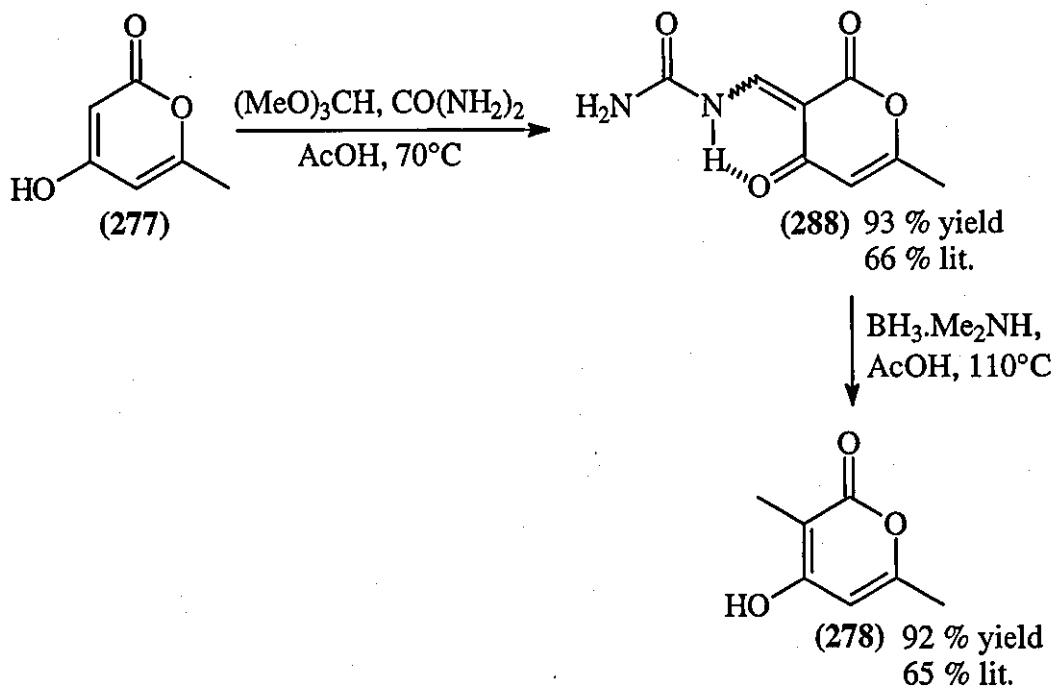
Two moderately low-yielding, two-step, regioselective methylations of 4-hydroxy-6-methyl-2-pyrone have been reported. Treatment of (277) with formaldehyde and

thiophenol followed by treatment with deactivated Raney nickel was reported to give (278) exclusively in 36 % overall yield (see scheme 5-6).⁷⁹



Scheme 5-6

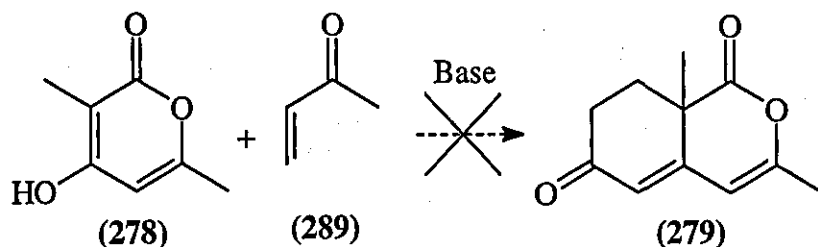
The second procedure involved the condensation of (277) with urea and methyl orthoformate in acetic acid at 70 °C, followed by reduction of (288) with borane-dimethylamine complex in refluxing acetic acid. This method appeared to be easier and was attempted in preference to the first method (see scheme 5-7).⁸⁰



Scheme 5-7

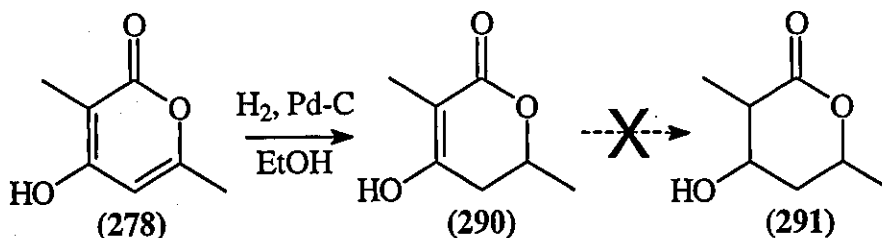
The yields for these two steps were reported as 66 % and 65 % respectively but in fact yields of 93 % and 92 % were obtained when these reactions were carried out.

Two attempts at a Robinson annulation of (278) were then made (see Scheme 5-8). Mesityl oxide has been reported to add to (277) in refluxing pyridine,⁷⁶ but the analogous reaction with (278) and methylvinylketone (289) yielded only (278) and polymeric impurities. Formation of the sodium enolate of (278) with sodium hydride in DMF followed by addition of (289) gave a complex inseparable mixture.



Scheme 5-8

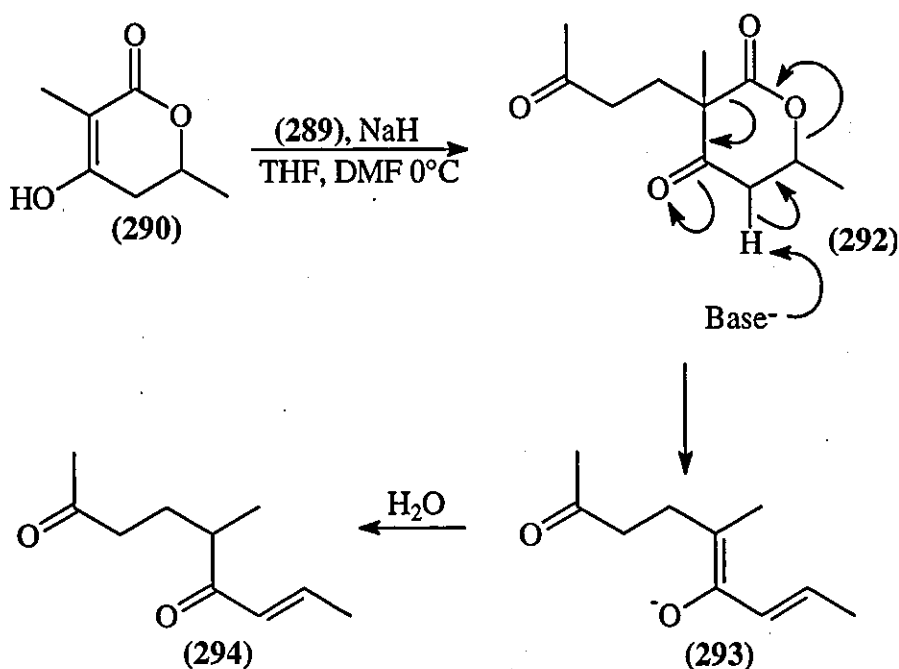
It was then decided to attempt the Robinson annulation after removal of the C5=C6 double bond in the ring. Removal of this double bond by hydrogenation is known,⁷⁴ and it is reported that quantitative hydrogenation of the pyrone (278) can be achieved by stirring in ethanol for 24 hours under hydrogen at room temperature and atmospheric pressure using 10 % palladium on carbon as a catalyst (see Scheme 5-9).⁸¹



Scheme 5-9

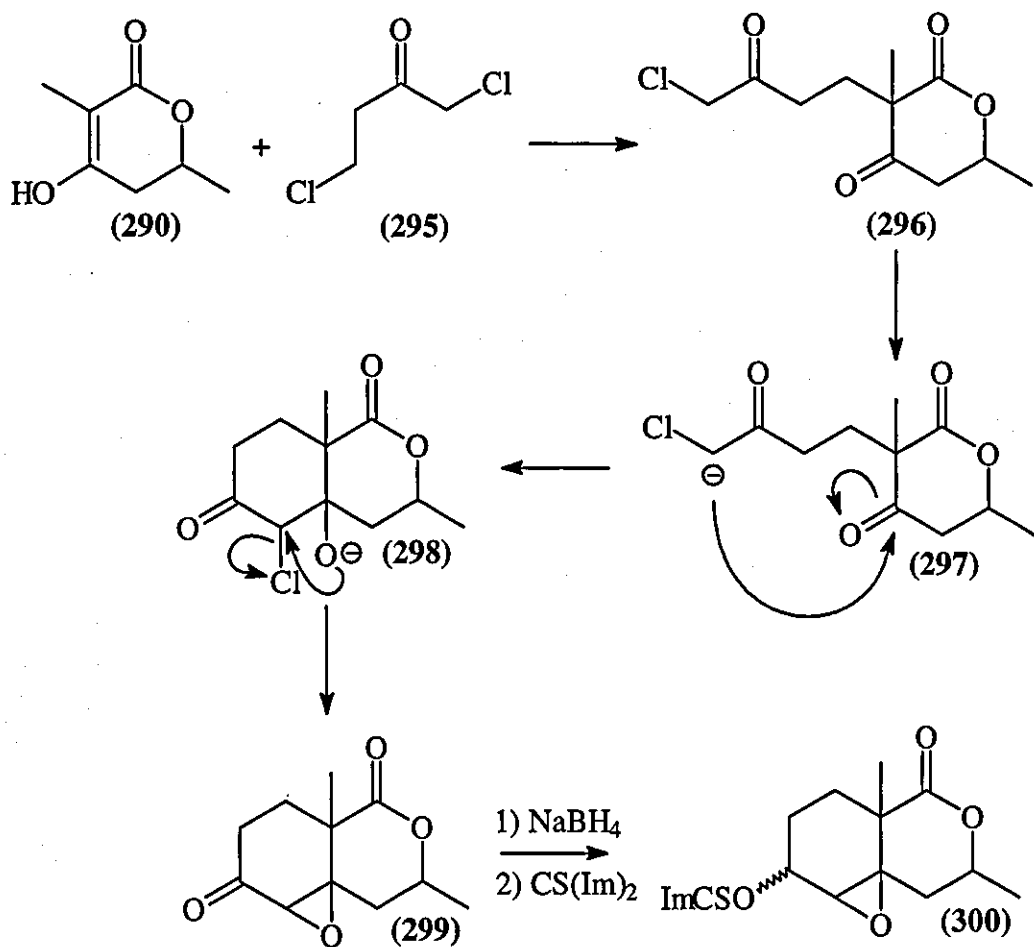
The reaction was attempted with 5% palladium on carbon and was found to be rather slow. No reaction occurred at all until the pressure was increased to 60 p.s.i. and at this pressure the reaction took three days to go to completion. Hydrogenations of (277) with either a palladium catalyst under pressure or with platinum and nickel catalysts at atmospheric pressure have been reported to result in reduction of the C3=C4 double bond,⁷⁴ but none of the analogous product (291) was seen in this system. The hydrogenation of the analogous 4-hydroxy-6-pentyl-2-pyrone at 60 p.s.i using 5 % palladium on carbon as a catalyst has also been reported with no hydrogenation to the fully saturated system being observed.⁸²

Attempts at a Robinson annulation reaction on the hydrogenated pyrone (290) failed because of a base catalysed decarboxylation. Treatment of (290) with sodium hydride and methylvinylketone (289) in a mixture of THF and DMF resulted in the formation of (294) as the major product. The methylvinylketone (289) added to the pyrone as desired, however the intermediate (292) underwent a base catalysed decarboxylation rather than the desired aldol condensation. A postulated mechanism for this reaction is given in Scheme 5-10.



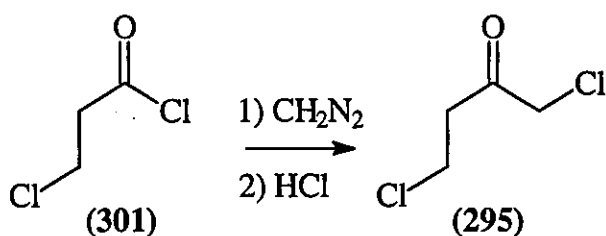
Scheme 5-10

An alternative approach to the target compounds was made using 1,4-dichlorobutan-2-one (295).⁸³ It was hoped that the chlorine atom in (296) would make the side-chain chloromethyl protons more acidic than the protons at the 5-position in the ring and this would favour the desired aldol reaction over the decarboxylation reaction (see Scheme 5-11). Instead of water loss, epoxidation by loss of chloride ion from (298) would also be expected. This would remove a step from the synthetic route but would probably result in the final product (300) being a mixture of diastereomers, as the stereocontrol given by the *m*CPBA epoxidation would be lost.



Scheme 5-11

1,4-Dichlorobutan-2-one (295) was synthesised by treatment of 3-chloropropionyl chloride (301) with diazomethane followed by addition of ethereal hydrochloric acid (see Scheme 5-12),⁸⁴ however addition of (295) to the sodium enolate of (290) gave a complex mixture of products.



Scheme 5-12

5.4 Concluding Remarks.

It was decided to abandon work on this synthetic route at this point because the apparent tendency of these systems to decarboxylate under basic conditions was believed to be too restrictive to circumvent easily. An alternative route for the synthesis of thiocarbonylimidazolides such as (272) and (301) was considered and this work is discussed in more detail in Chapter 6.

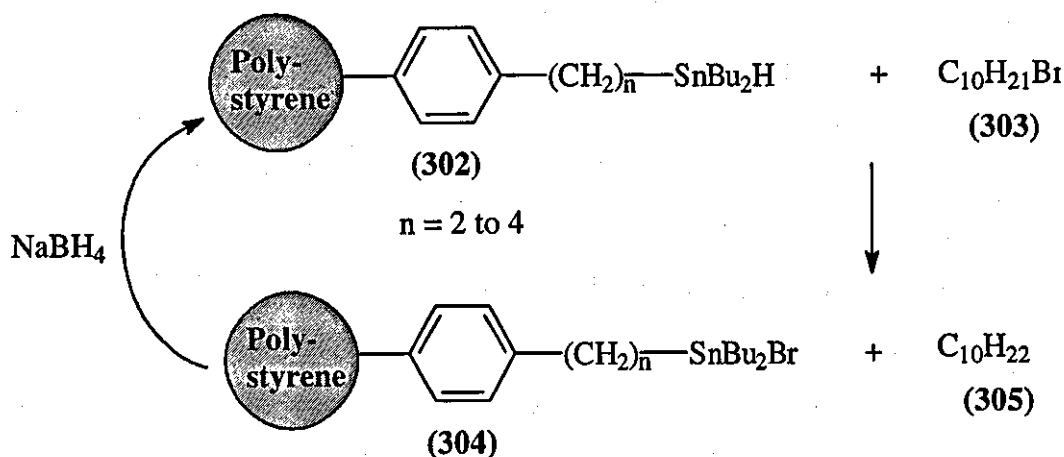
Chapter 6. Solid Phase Chemistry of Oxiranylcabinyl Radicals.

6.1 Introduction.

The first pioneering research in the area of solid phase synthesis was performed by Merrifield in 1963,⁸⁵ but for many years this area of synthetic chemistry received little attention, aside from synthesis of oligomers such as peptides, DNA and RNA. However the development of combinatorial chemistry and non-rational drug discovery techniques has generated considerable new interest in solid phase chemistry,⁸⁶⁻⁸⁹ particularly among major pharmaceutical companies, and in recent years much research has been carried out to develop organic chemistry on solid phase supports.⁹⁰⁻⁹²

Solid phase chemistry is particularly suited to automated synthesis and the generation of multi-component libraries because of the ease of work-up procedures.^{93,94} Washing with a suitable solvent to remove the excess reagents and by-products is all that is required for most reactions. Large excesses of reagents are routinely used to drive reactions to completion because of the ease with which they may be removed. However one limitation of solid phase synthesis is the relative difficulty encountered in the analysis of compounds whilst attached to the bead.⁹⁵ IR spectroscopy,⁹⁶ elemental analysis and the use of colorimetric reagents,^{97,98} are typical analytical methods used in solid phase synthesis, although none of these methods are universally applicable. Techniques such as Magic Angle Spinning NMR,^{99,100} and MALDI-TOF mass spectrometry,¹⁰¹ are more specialised but are extremely useful in the analysis of polymer-bound compounds.

The area of radical chemistry on solid supports has received little attention, however the difficulties often associated with the removal of tributyltin residues from reaction mixtures and the toxicity of these compounds, have led to the development of polymer supported organotin hydrides.¹⁰² These polymers ((302)) were found to contain up to 1.4 mmol/g of active hydride by reaction with bromodecane (303) and could be recycled by treatment of the tin halide polymer (304) with sodium borohydride (see Scheme 6-1).



Scheme 6-1

6.2 Aims.

There are several potential advantages in performing tributyltin hydride chemistry on a solid phase support. Firstly, isolation of the reaction products can be achieved without the need for extensive chromatography, providing that the resin is washed thoroughly with a suitable solvent prior to cleavage of the linker. Also, the use of solid phase supports might be expected to mimic the effect of high dilution, and thus favour intramolecular reactions over intermolecular ones. This feature would be most useful in the case of substrates such as (210) (see Chapter 3), which was found to polymerise rather than undergo an intramolecular cyclisation under normal addition conditions.

The intention of this project was to attempt a simple cleavage reaction of an oxiranylcarbiny radical on a polymer support. "Wang" (*p*-benzyloxybenzyl alcohol) resin (306) was selected to be used as the polymer support (see Fig 6-1) because it is polystyrene based and would therefore swell in non-polar solvents such as benzene, the intended solvent for use in the radical reaction. Also an additional advantage of this resin is that the reaction substrate is held at a distance from the polystyrene backbone by the *p*-benzyloxybenzyl spacer group. Because tributyltin hydride is such a bulky compound this could prevent steric problems during the radical reaction.

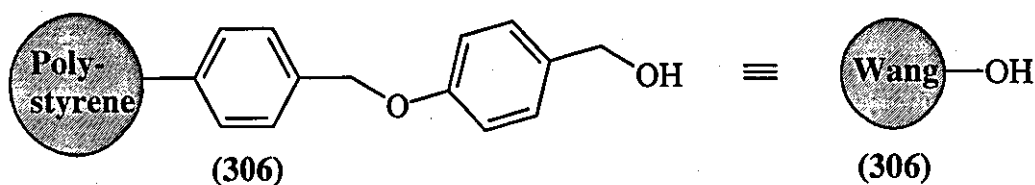
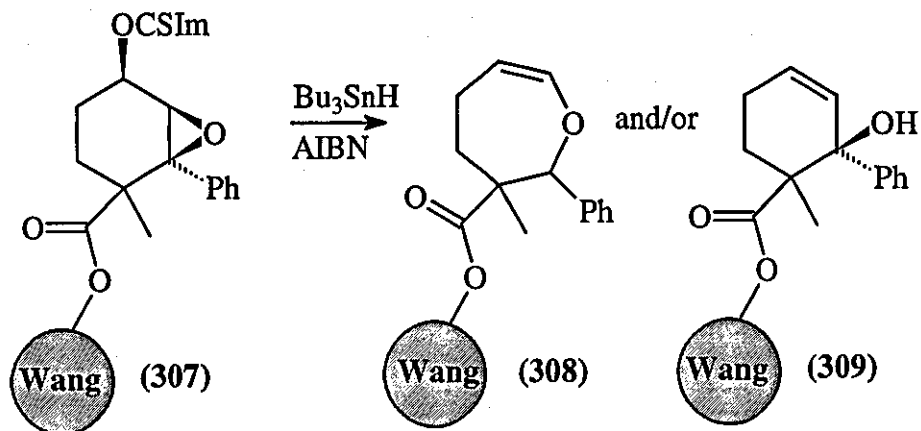


Fig 6-1

It was also decided that the reaction substrate would be attached to the resin *via* an ester linkage. This would be stable under the radical reaction conditions, but could easily be broken by treatment with trifluoroacetic acid to allow isolation and characterisation of the resin-cleaved reaction products.

The substrate chosen for this study was the simple phenyl-substituted epoxycyclohexane thiocarbonylimidazole (307). The intention was to repeat the ring expansion reactions of Marples *et al.* (See Scheme 1-14, section 1.3.4) on the solid phase support (see Scheme 6-2).



Scheme 6-2

The decision to attach the substrate to the resin at C-4 on the cyclohexane ring was made for two reasons. Although the synthesis would be complicated by the generation of an extra stereocentre at C-4, one advantage over a simpler attachment *via* the phenyl ring (310) (see Fig. 6-2) would be that the aromatic substituent could be changed relatively easily without affecting the overall synthetic route, to allow the study of tandem reactions such as those described in Chapter 3 without having to resort to an alternative synthetic route.

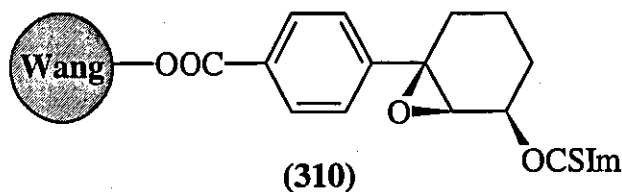


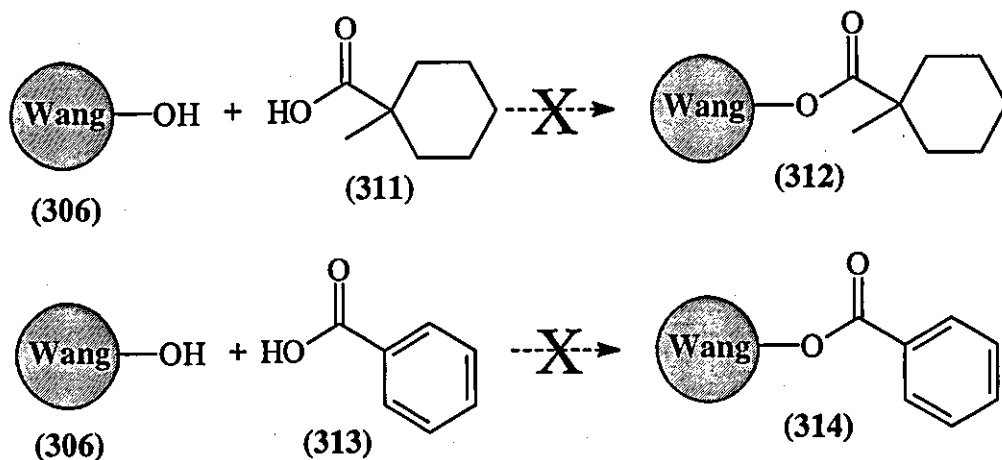
Fig. 6-2

The early stages of the synthetic route could also be used in an approach to the synthesis of medium ring lactones and this is discussed further in section 6.4. It was considered that the incorporation of the linker and the methyl group at C-4 in the ring could

result in the formation the alcohol (309) rather than the enol ether (308) if steric factors such as those seen in Chapter 4 were operating. In this particular investigation the actual product of the reaction was not critical, the intention of the project was to compare the results of the reaction in solution and on the solid phase.

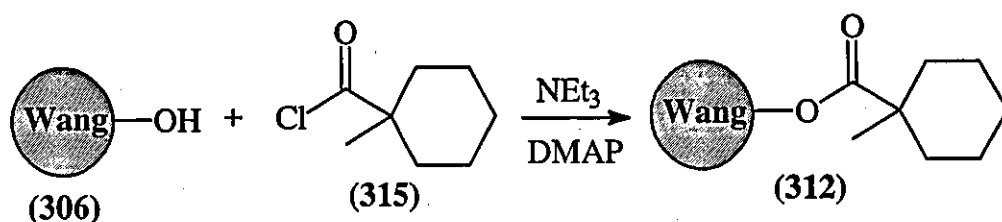
6.3 Results and Discussion.

Initial experiments were conducted on a model system, 1-methylcyclohexanecarboxylic acid (311) to ensure that attachment of the tertiary acid to the solid phase support was possible. An attempt to couple (311) (5 eq.) to the resin (306) using the coupling agent diisopropylcarbodiimide (10 eq.) failed, the IR spectrum before and after the attempted coupling was identical and no ester carbonyl band was evident. It was also found that benzoic acid (313) (10 eq.) did not couple using this coupling agent (see Scheme 6-3).



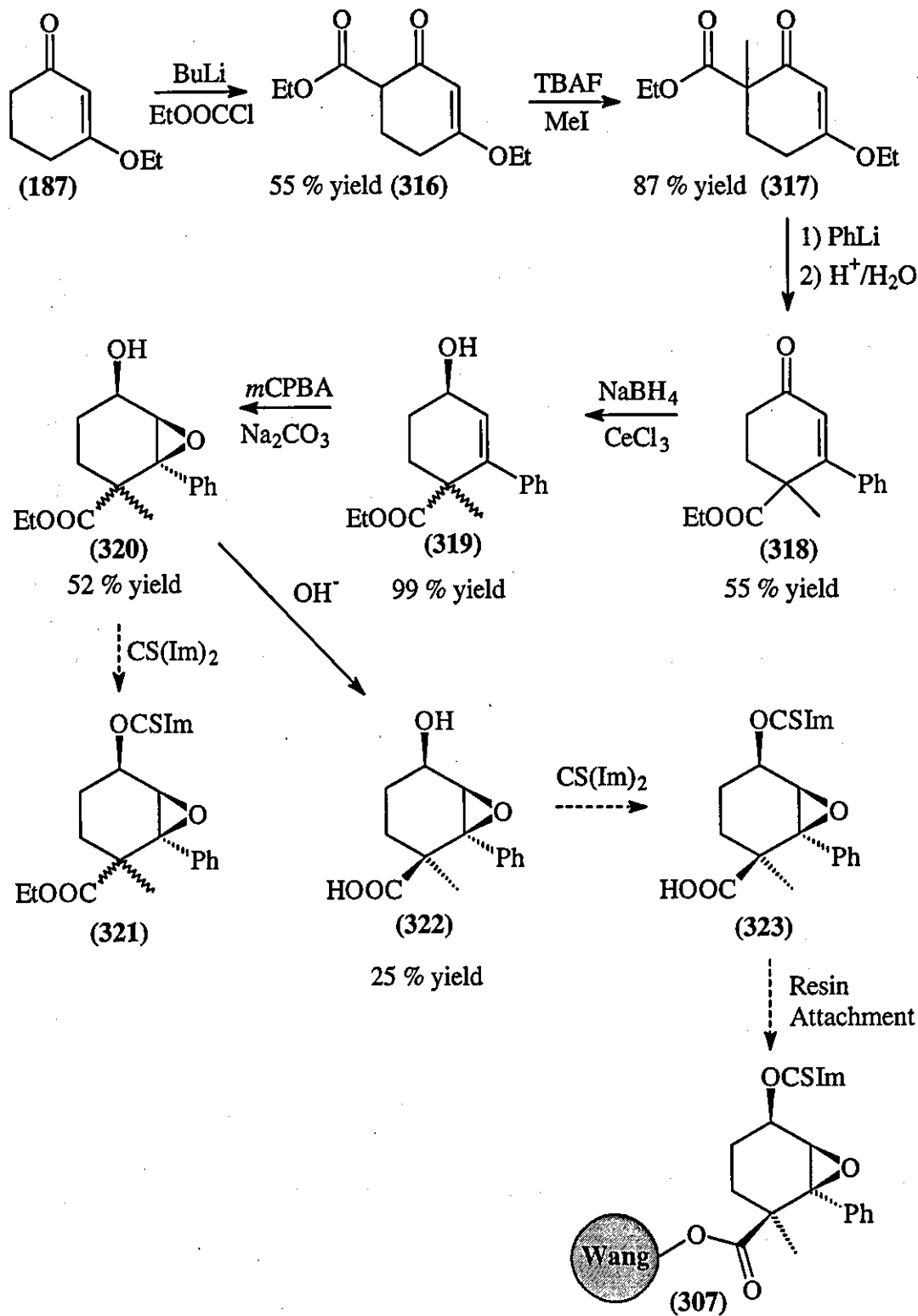
Scheme 6-3

Treatment of the Wang resin (306) with benzoyl chloride in the presence of triethylamine and DMAP was found to result in the formation of the Wang benzoate (314). It was also found that coupling of 1-methylcyclohexanecarboxylic acid could also be achieved by formation of the acid chloride (315) with oxalyl chloride and addition to the resin in the presence of triethylamine and DMAP (see Scheme 6-4).



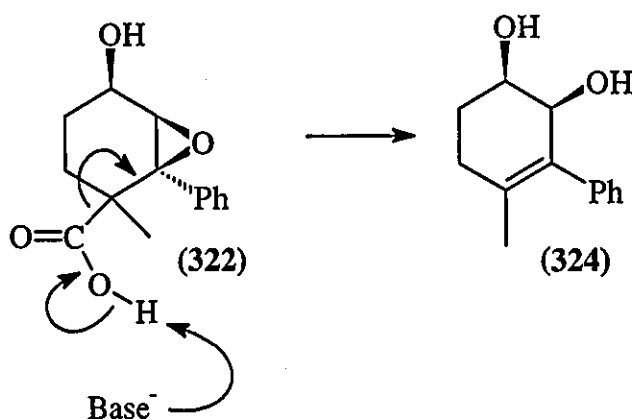
Scheme 6-4

After it had been established that a tertiary acid of this type could be coupled to Wang resin the synthesis of the radical reaction substrate was undertaken from 3-ethoxy-2-cyclohexen-1-one (187) (see Scheme 6-5).



Scheme 6-5

The ethyl ester (**316**) was prepared by deprotonation of the enone (**187**) with *n*-butyllithium followed by quenching of the enolate with ethyl chloroformate (55 %). Treatment of (**316**) with methyl iodide in the presence of tetrabutylammonium fluoride gave the methylated β -ketoester (**317**) (87 %), which was further transformed into the phenyl substituted enone (**318**) by treatment with phenyllithium and an acid work-up (55 %). Luche reduction of (**318**) was found to give (**319**) as a 2:1 mixture of diastereomers which were inseparable by flash chromatography (99 %). Treatment of (**319**) with *m*CPBA gave (**320**) as a 2:1 mixture of diastereomers (52 %) which were again inseparable by flash chromatography. Hydrolysis of the ester group in (**320**) proved difficult as a mild method was required to prevent the possible decarboxylation of the acid (**322**) to give (**324**) (see Scheme 6-6).



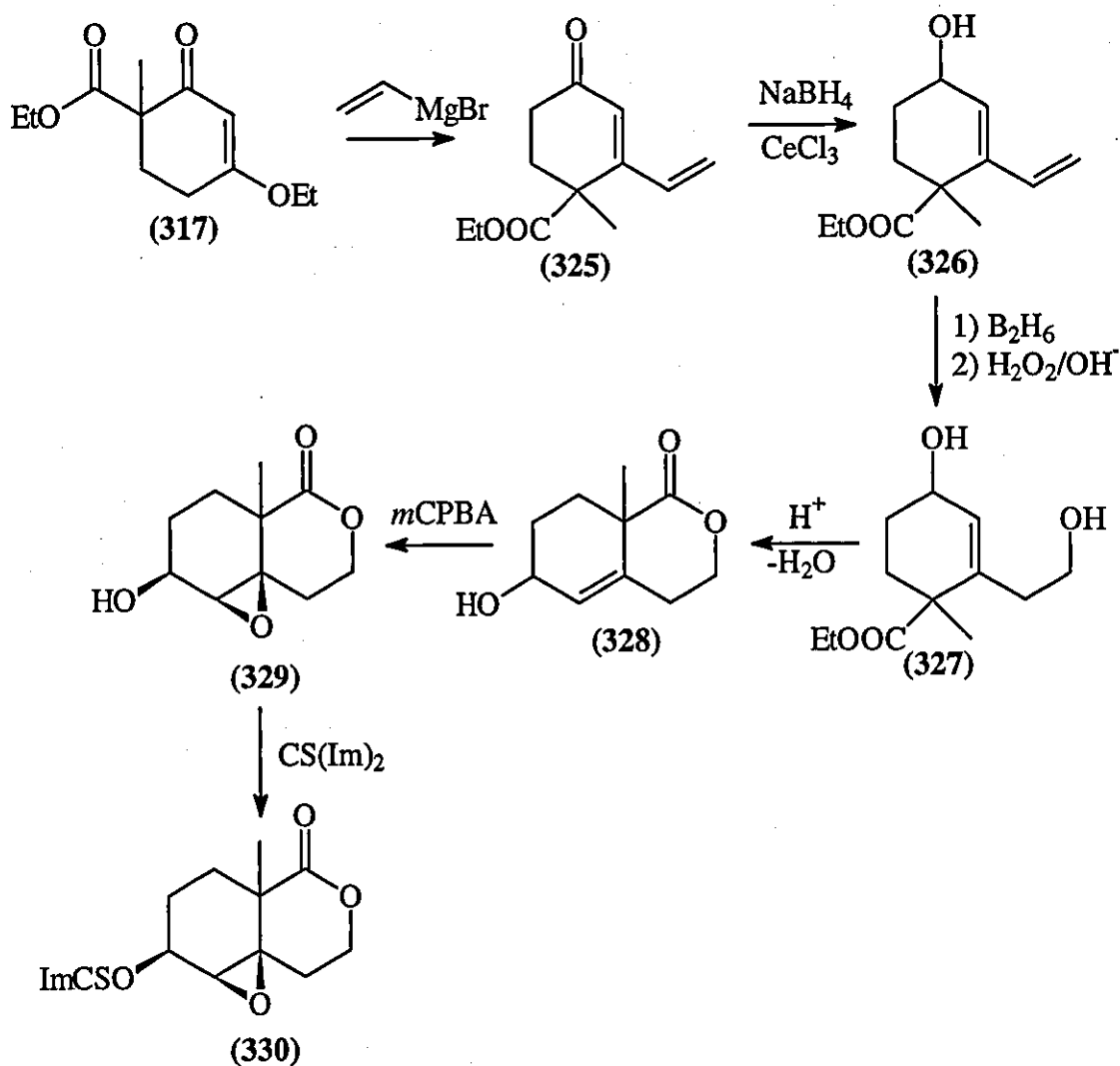
Scheme 6-6

Treatment with (a) lithium hydroxide in THF/water (10:1), (b) potassium hydroxide and 18-crown-6 in benzene and (c) pigs liver esterase returned only starting material and treatment with iodotrimethylsilane gave a complex mixture of products. The desired acid (**322**) was eventually obtained, albeit in poor yield by treatment with potassium hydroxide in methanol at 50 °C for 3 days. The acid (**322**) was isolated as a single diastereomer (25 %) and was found to be highly crystalline, the X-ray crystal structure is described in Appendix B.

6.4 The Preparation of Medium Ring Lactones.

It was hoped that the early stages of this synthetic route could also be used in the synthesis of the medium ring lactone precursor (**330**). Treatment of the ethoxycyclohexenone (**317**) with vinylmagnesium bromide would be expected to give the vinyl-substituted cyclohexenone (**325**), which could be converted into the thiocarbonylimidazolide (**330**) by the route shown in Scheme 6-7. Reaction of (**330**) with

tributyltin hydride and AIBN would be expected to give rise to a medium ring lactone by the postulated mechanism discussed in Chapter 5.



Scheme 6-7

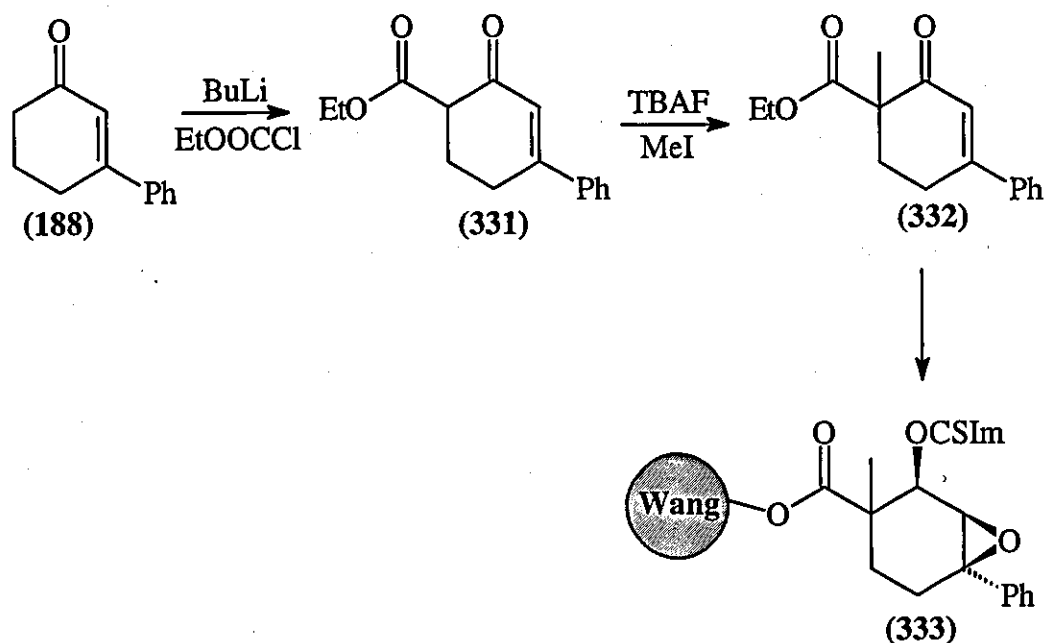
An initial attempt at the formation of (325) using commercially available vinylmagnesium bromide was disappointing and yielded only starting material.

6.5 Concluding Remarks.

Unfortunately due to time restraints the syntheses of the solid phase and medium ring lactone radical reaction substrates were not completed. The preparation of the vinyl substituted enone (325) might be achieved with the use of freshly prepared vinylmagnesium bromide which often gives better results than the commercially available material, or with the use of the more reactive reagent vinyl lithium. The reaction of (317) with phenyllithium (in Scheme 6-5) is encouraging evidence that formation of (325) should be possible when the correct reagents and reaction conditions are found. The poor yield of the acid from the

ester hydrolysis of (320) (see Scheme 6-5) may also be improved by careful control of the reaction conditions.

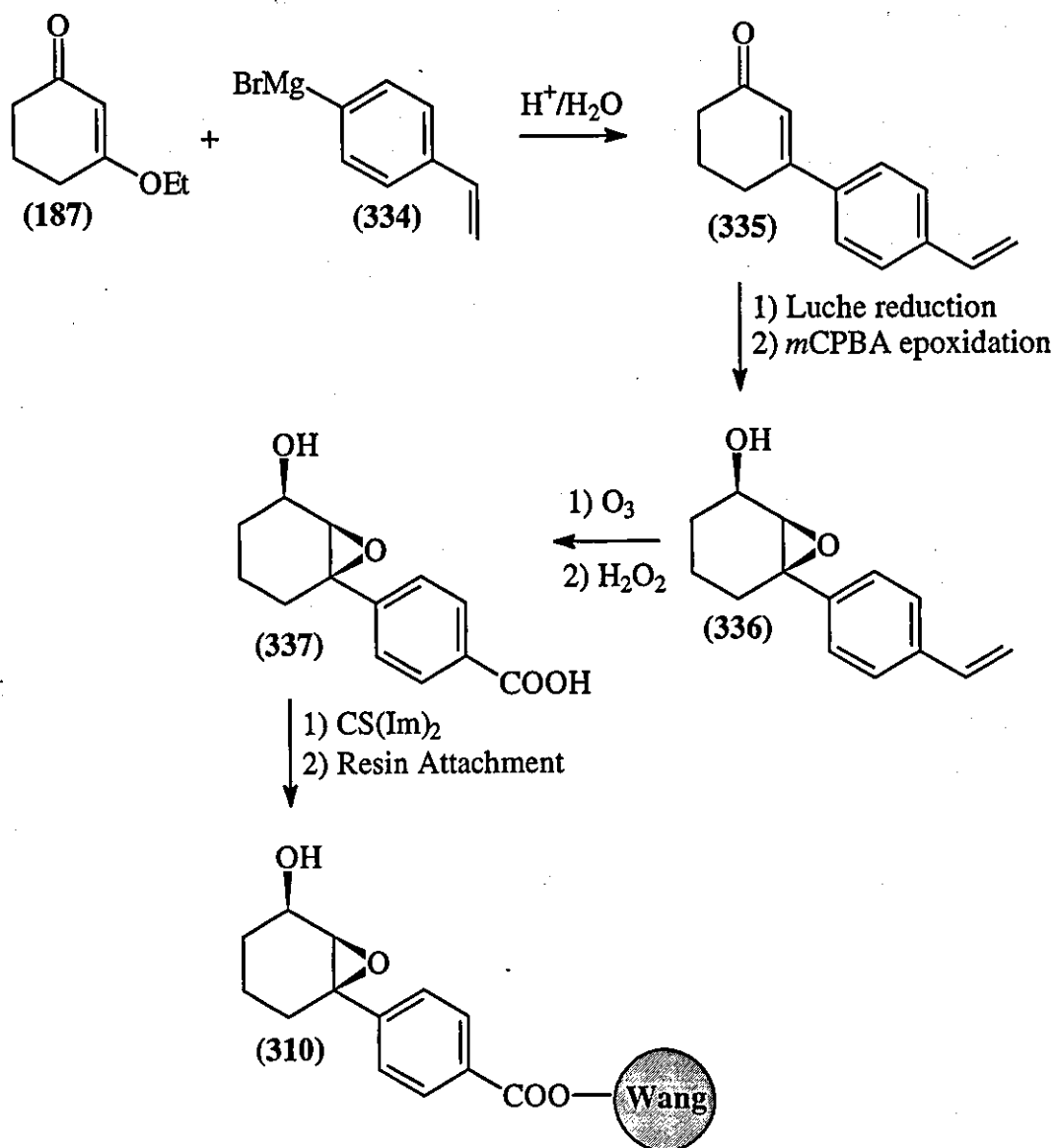
Two other methods for attachment of the reaction substrate to the polymer bead were considered and although they were not attempted, may still be of interest if the attachment at C-4 (see Scheme 6-2) causes difficulties in the radical reaction. The first method involved addition of the ester functionality to 3-phenyl-2-cyclohexen-1-one (188) rather than 3-ethoxy-2-cyclohexen-1-one (187) (see Scheme 6-8).



Scheme 6-8

This would result in the linker being attached to the resin at C-6 rather than C-4. At this position the linker would be further away from the epoxide functionality and would presumably have less influence on the radical reaction.

The second alternative would involve a simpler but less versatile route and would result in the substrate being attached by the aromatic ring (see Scheme 6-9).



Scheme 6-9

This would move the linker further still from the epoxide, but would have the disadvantage that the synthetic route would be much less versatile. For example addition of allyl or vinyl substituents onto the aromatic ring, such as those described in chapters 3 and 4 would probably require large changes to the synthetic route.

7. Experimental.

7.1 General Information.

7.1.1 Solvents and Reagents.

Light petroleum refers to the petroleum ether fractions boiling between 40 °C and 60 °C and ether refers to diethyl ether. Hexane and other solvents of analytical grade were used without purification, as were commercially available reagents. Technical grade solvents were purified prior to use as follows. Dichloromethane was distilled from phosphorus pentoxide. Ether, light petroleum and ethyl acetate were distilled from anhydrous calcium chloride. Benzene was distilled from calcium hydride and stored over molecular sieves under an atmosphere of nitrogen or argon. Tetrahydrofuran was distilled from the sodium benzophenone ketal or purchased from Aldrich in Sure-seal bottles.

7.1.2 Chromatographic Procedures.

Analytical thin layer chromatography was performed on aluminium backed plates coated with Merck Kieselgel 60 GF₂₅₄. Flash chromatography was carried out using Kieselgel 60 H silica.

7.1.3 Spectroscopic Techniques.

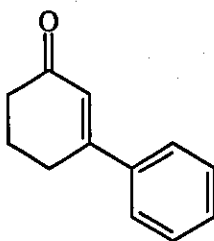
Fourier Transform infra red spectra were recorded in the range 4000-600 cm⁻¹ using either a Nicolet FT-205 or a Perkin Elmer Paragon 100 spectrometer, with internal calibration. ¹H and ¹³C NMR spectra were recorded on either a Bruker AC-250 or a DPX-400 spectrometer in deuteriochloroform or deuteriodimethylsulfoxide. Chemical shifts are quoted in ppm relative to tetramethylsilane as the internal standard and coupling constants are quoted in hertz (Hz). Spectroscopic data are annotated with the following abbreviations, s- singlet, d - doublet, t- triplet, q- quartet, m- multiplet or combinations thereof. Maj and min refer to the major or minor isomers in the case of inseparable mixtures of diastereomers. Mass spectra were recorded on a Kratos MS80 or a VG Analytical ZAB-E spectrometer.

7.1.4 Other Information.

Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Elemental analysis was performed on a Perkin Elmer 2400 Elemental Analyser.

7.2 Experimental For Chapter 2.

Preparation of 3-Phenyl-2-cyclohexen-1-one (188).



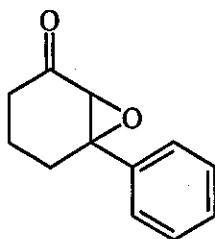
A solution of phenyllithium (1.8 M, 70 ml, 126 mmol) was added dropwise to a stirred solution of 3-ethoxy-2-cyclohexen-1-one (16.8 g, 120 mmol) in anhydrous THF (50 ml) at -78°C . The solution was then allowed to warm to room temperature and after stirring for 16 hours, hydrochloric acid (2 M, 50 ml) was added. This mixture was then extracted with diethyl ether (3 x 50 ml) and the combined extracts were washed with saturated brine (50 ml), dried over magnesium sulfate and evaporated *in vacuo*. Recrystallisation from light petroleum gave the title compound (17.5 g, 84 %) as colourless plates, m.p. $60-61^{\circ}\text{C}$; lit $63-66^{\circ}\text{C}$.⁵⁸

$\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 1661 (α,β -unsaturated C=O), 1604 (C=C), 1457, 770, 701.

δ_{H} (250 MHz; CDCl_3) 2.16 (2 H, tt, 5- CH_2), 2.46 (2 H, t, J 6.5, 4- CH_2), 2.75 (2 H, t, J 6, 6- CH_2), 6.41 (1 H, s, 2-CH), 7.35 (5 H, m, Ph).

δ_{C} (62.9 MHz; CDCl_3) 22.7 (5- CH_2), 28.0 (6- CH_2), 37.2 (4- CH_2), 125.3 (Ar-CH), 126.0 (Ar-CH), 128.7 (Ar-CH), 129.9 (2-CH), 138 (Ar-C), 160 (3-C), 200 (C=O).

Preparation of 2,3-Epoxy-3-phenylcyclohexan-1-one (189).



Sodium hydroxide solution (6M, 1.5 ml, 9 mmol) was added dropwise to a solution of 3-phenyl-2-cyclohexen-1-one (3.0 g, 17.4 mmol) and aqueous hydrogen peroxide (50 %, 3.6 ml, 54 mmol) in methanol (30 ml) at 0 °C. The solution was then allowed to warm up to room temperature and after stirring for two hours, ether (100 ml) and water were added. The aqueous fraction was extracted with ether (2 x 100 ml) and the combined organic fractions were washed with ferrous sulfate solution (5 %, 2 x 100 ml) and saturated brine (100 ml), dried over magnesium sulfate and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (3:1 light petroleum/ether) gave the *title compound* as colourless crystals (2.19 g, 66 %). A sample of this was recrystallised from light petroleum/ether to give colourless needles, m.p. 55.0-55.8 °C.

Found C, 76.40; H, 6.46. C₁₂H₁₂O₂ requires C, 76.58; H, 6.43 %.

Found M⁺, 188.0838. C₁₂H₁₂O₂ requires *m/z* 188.0837.

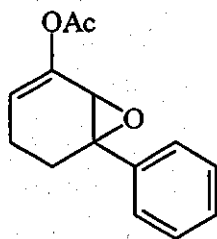
$\nu_{\max}/\text{cm}^{-1}$ (nujol) 1707 (C=O), 1452, 1386, 809, 792, 751, 657.

δ_{H} (250 MHz; CDCl₃) 1.81 (1 H, m, 5-CH), 2.15 (2 H, m, 4-CH, 5-CH), 2.43 (2 H, m, 6-CH₂), 2.60 (1 H, m, 4-CH), 3.26 (1 H, s, 2-CH), 7.36 (5 H, m, Ar-CH)

δ_{C} (62.9 MHz; CDCl₃) 16.7 (5-CH₂), 26.9 (6-CH₂), 35.8 (4-CH₂), 64.1 (2-CH and 3-C), 125.1 (Ar-CH), 128.2 (Ar-CH), 128.5 (Ar-CH), 138.7 (Ar-C), 205.1 (C=O)

m/z (E.I.) 188 (M⁺, 35 %), 160 (M-CO, 93), 159 (39), 143 (79), 117 (79), 115 (49), 105 (65), 104 (65), 103 (78), 91 (51), 77 (100), 39 (40), 32 (55), 27 (34).

Preparation of 2-Acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (190).



A solution of butyllithium (2.5 M, 5 ml, 12.5 mmol) was added dropwise to a stirred solution of diisopropylamine (1.8 ml, 13 mmol) in THF (10 ml) at 0 °C. After stirring for 15 minutes the solution was cooled to -78 °C and a solution of 2,3-epoxy-3-phenylcyclohexan-1-one (2.16 g, 11.4 mmol) in THF (15 ml) was added over 10 minutes. After a further 30 minutes at -78 °C, acetic anhydride (1.9 ml, 17.1 mmol) was added. The solution was allowed to warm to room temperature and ether (50 ml) and water (50 ml) were added. The aqueous fraction was extracted with ether (50 ml x 2) and the combined organic fractions were washed with water (100 ml) and brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant 3:1 light petroleum/ether) followed by crystallisation from ether (at -78 °C) gave the *title compound* as colourless crystals (1.34 g, 51 %); m.p. 48.7-49.7 °C.

Found M^+ , 230.0932. $C_{14}H_{14}O_3$ requires m/z 230.0943.

ν_{max}/cm^{-1} ($CHCl_3$ solution.) 2939, 1750, 1679, 1601, 1495, 1450, 1421, 1369, 1141, 1103, 1034, 1010, 938, 920, 895, 841, 698, 665, 654.

δ_H (250 MHz; $CDCl_3$) 2.18 (3 H, s, CH_3COO), 2.25 (2 H, m, 6- CH_2), 2.31 (2 H, s, 5- CH_2), 3.24 (1 H, d, J 2.5 Hz, 3-CH), 5.64 (1 H, m, 1-CH), 7.35 (5 H, m, Ar-CH).

δ_C (62.9 MHz; $CDCl_3$) 19.4 (6- CH_2), 25.0 (5- CH_2), 58.4 (3-CH), 64.70 (4-C), 115.4 (1-CH), 125.4 (Ar-CH), 127.7 (Ar-CH), 128.3 (Ar-CH), 139.5 (Ar-C), 144.9 (2-C), 169.6 (C=O)

m/z (E.I) 230 (M^+ , 21 %), 202 (42), 201 (20), 188 (32), 171 (24), 170 (54), 160 (100), 159 (51), 105 (44), 103 (57), 86 (24), 77 (26), 43 (85).

Attempted Phenylthio Radical Catalysed Coupling Between 2-Acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (190) and Methyl Acrylate Under Feldman Reaction Conditions.

A deoxygenated solution of diphenyldisulfide (130 mg, 0.6 mmol) and AIBN (50 mg, 0.3 mmol) in toluene (5 ml) was added over 4 hours to a deoxygenated solution of 2-acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (130 mg, 0.55 mmol) and methyl acrylate (500 mg, 6 mmol) under a nitrogen atmosphere in refluxing toluene (10 ml) with concomitant sunlamp irradiation. After a further hour of reflux the solution was allowed to cool and evaporated *in vacuo* to give a brown oil. N.M.R analysis of this oil showed it to be a mixture of diphenyldisulfide, 2-acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene and polymeric impurities.

Attempted Phenylthio Radical Catalysed Coupling Between 2-Acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (190) and Vinylene Carbonate Under Feldman Reaction Conditions.

A deoxygenated solution of diphenyldisulfide (240 mg, 1.1 mmol) and AIBN (50 mg, 0.3 mmol) in benzene (6 ml) was added over 6.5 hours to a deoxygenated solution of 2-acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (200 mg, 0.9 mmol) and vinylene carbonate (260 mg, 3 mmol) under a nitrogen atmosphere in refluxing toluene (10 ml) with concomitant sunlamp irradiation. After a further hour of reflux the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. N.M.R analysis of this oil showed it to contain only starting materials.

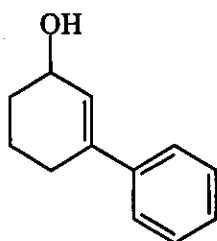
Attempted Phenylthio Radical Catalysed Coupling Between 2-Acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (190) and Maleic Anhydride Under Rawal Reaction Conditions.

A deoxygenated solution of diphenyldisulfide (60 mg, 0.28 mmol), AIBN (22 mg, 0.14 mmol), 2-acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (308 mg, 1.3 mmol) and maleic anhydride (1.3 g, 13 mmol) was irradiated in a hanovia apparatus (450 W medium pressure mercury lamp) under a nitrogen atmosphere in refluxing benzene (10 ml). After 4 hours of reflux the solution was allowed to cool and evaporated *in vacuo* to give a brown oil. N.M.R analysis of this oil showed it to be a complex mixture of products.

Attempted Phenylthio Radical Catalysed Coupling Between 2-Acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (190) and Vinylene Carbonate Under Rawal Reaction Conditions.

A deoxygenated solution of diphenyldisulfide (90 mg, 0.4 mmol), AIBN (33 mg, 0.2 mmol), 2-acetoxy-3,4-epoxy-4-phenyl-cyclohex-1-ene (310 mg, 0.9 mmol) and vinylene carbonate (260 mg, 3 mmol) was irradiated in a hanovia apparatus under a nitrogen atmosphere in refluxing benzene (10 ml). After 4 hours of reflux the solution was allowed to cool and evaporated *in vacuo* to give a brown oil. N.M.R analysis of this oil showed it to be a complex mixture of products.

Preparation of 3-Phenyl-2-cyclohexen-1-ol (195).



Sodium borohydride (790 mg, 21 mmol) was added portionwise to a solution of 3-phenyl-2-cyclohexen-1-one (3 g, 17.4 mmol) and cerium (III) chloride heptahydrate (6.5 g, 17.4 mmol) in dry methanol at 0°C. After stirring for 1 hour, water (200 ml) was added and the mixture was extracted with ether (3 x 100 ml). The combined extracts were washed with water (100 ml) and saturated brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the title compound as a pale yellow oil (2.57 g, 85 %).

Found M^+ , 174.1044. $C_{12}H_{14}O$ requires m/z 174.1045

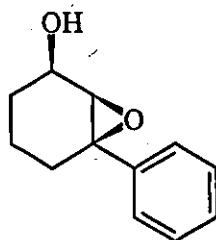
ν_{max}/cm^{-1} (neat) 3324, 2935, 2863, 1600, 1494, 1446, 1053, 974, 757, 695.

δ_H (400 MHz; $CDCl_3$) 1.55 (1 H, br s, OH), 1.70 (2 H, m, 5-CH, 6-CH), 1.93 (2 H, m, 5-CH, 6-CH), 2.39 (1 H, m, 4-CH), 2.44 (1 H, m, 4-CH), 4.39 (1 H, m, 1-CHOH), 6.12 (1 H, m, 2-CH), 7.33 (2 H, m, Ar-H), 7.41 (3 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 19.5 (5- CH_2), 27.4 (4- CH_2), 31.6 (6- CH_2), 66.2 (1-CHOH), 125.3 (Ar-CH), 126.7 (2-CH), 127.3 (Ar-CH), 128.3 (Ar-CH), 139.4 (Ar-C or 3-C), 141.3 (Ar-C or 3-C).

m/z (E.I.) 174 (M^+ , 100 %), 146 (89), 145 (85), 131 (55), 115 (43), 91 (46), 77 (27), 51 (23), 39 (27).

Preparation of 2,3-Epoxy-3-phenyl-2-cyclohexen-1-ol (196).



m-chloroperbenzoic acid (2.26 g, 50 %, 6.5 mmol) was added to a stirred solution of 3-phenyl-2-cyclohexen-1-ol (0.96 g, 5.5 mmol) and sodium bicarbonate (565 mg, 6.7 mmol) in DCM at 0 °C. After 50 minutes the solution was washed with saturated sodium bicarbonate (50 ml x 4) and saturated brine, dried over magnesium sulfate and evaporated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:2) gave the *title compound* as a colourless oil (559 mg, 53 %).

Found M^+ , 190.0994. $C_{12}H_{14}O_2$ requires m/z 190.0994.

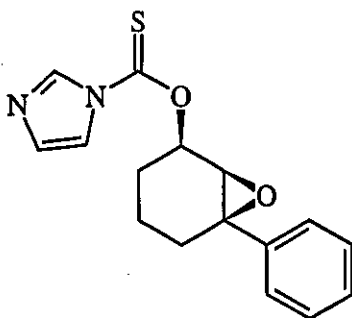
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3336, 2938, 2858, 1604, 1495, 1445, 1404, 1356, 1046, 955, 874, 758, 696, 661.

δ_{H} (400 MHz; CDCl_3) 1.48 (1 H, m, 5-CH), 1.68 (3 H, m, 5-CH, 6-CH, OH), 2.25 (2 H, m, 4-CH, 6-CH), 3.29 (1 H, d, J 3.5, 2-CH), 4.13 (1 H, m, 1-CH), 7.32 (5 H, m, Ph).

δ_{C} (100 MHz; CDCl_3) 18.2 (5- CH_2), 28.0 (4- CH_2), 29.0 (6- CH_2), 63.9 (3-C), 64.4 (2-CH), 66.3 (1-CH), 125.3 (2 x Ar-CH), 127.5 (Ar-CH), 128.4 (2 x Ar-CH), 141.2 (Ar-C).

m/z (E.I.) 190 (M^+ , 7 %), 173 (20), 133 (63), 121 (100), 105 (71), 91 (47), 77 (50).

Preparation of 2,3-Epoxy-1-(imidazol-1-yl-(thiocarbonyl)oxy)-3-phenylcyclohexane (191).



A solution of 2,3-epoxy-3-phenyl-2-cyclohexen-1-ol (800 mg, 4.2 mmol) and 1,1-thiocarbonyl diimidazole (1.2 g, 6.7 mmol) in DCM (30 ml) was stirred at gentle reflux for 24 hours. After cooling the solution was washed with water and saturated brine, dried over magnesium sulfate and evaporated *in vacuo* to give a colourless oil. Purification by flash

chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a colourless liquid (813 mg, 65 %).

Found M^+ , 300.0933. $C_{16}H_{16}O_2N_2S$ requires m/z 300.0932.

ν_{max}/cm^{-1} (neat) 2946, 1740, 1691, 1603, 1531, 1464.

δ_H (400 MHz; $CDCl_3$) 1.62 (1 H, m, 5-CH), 1.93 (3 H, m, 5-CH, 6- CH_2), 2.18 (1 H, m, 4-CH), 2.35 (1 H, m, 4-CH), 3.46 (1 H, d, J 2.5, 2-CH), 5.98 (1 H, m, 1-CH), 7.03 (1 H, d, J 1, Im-H), 7.35 (5 H, m, Ar-H), 7.68 (1 H, d, J 1.5, Im-H), 8.39 (1 H, d, J 1, Im-H).

δ_C (100 MHz; $CDCl_3$) 18.8 (5- CH_2), 24.8 (6- CH_2), 27.6 (4- CH_2), 60.3 (2-CH), 63.2 (3-C), 79.2 (1-CH), 118.0 (Im-CH), 125.3 (*m*-Ar-CH x 2), 127.9 (*p*-Ar-CH), 128.5 (*o*-Ar-CH x 2), 130.8 (Im-CH), 140.3 (Im-CH), 183.6 (C=S).

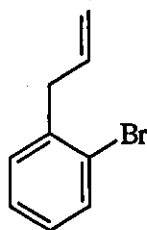
m/z (E.I.) 301 (MH^+ , 11 %), 300 (M^+ , 2), 241 (23), 173 (96), 144 (100), 105 (83), 91 (78), 77 (63), 68 (78).

Attempted Tributyltin Hydride Reduction of 2,3-Epoxy-1-(imidazol-1-yl-(thiocarbonyl)-oxy)-3-phenyl-cyclohexane (191) in the Presence of Methyl Acrylate.

A deoxygenated solution of tributyltin hydride (232 mg, 0.8 mmol) and AIBN (30 mg, 0.2 mmol) in benzene (5 ml) was added over 4 hours to a deoxygenated solution of 2,3-epoxy-1-(imidazol-1-yl-(thiocarbonyl)oxy)-3-phenyl-cyclohexane (200 mg, 0.66 mmol) and methyl acrylate (280 mg, 3.25 mmol) under nitrogen in refluxing benzene (5 ml). After a further hour of reflux the solution was allowed to cool to room temperature and the solvent was removed *in vacuo*. Flash chromatography (eluant light petroleum then ether) gave tributyltin hydride and the imidazolidine starting material (191) as the only identifiable products.

7.3 Experimental for Chapter 3

Preparation of 2-Allylbromobenzene (202).



Vinylbromide (2.82 ml, 40 mmol) in THF (10 ml) was added dropwise to a stirred mixture of magnesium (2.43 g, 100 mmol), iodine (1 crystal), and THF (40 ml) under nitrogen in a flask fitted with a dry ice condenser. The resulting solution of vinylmagnesiumbromide was allowed to cool, after which it was added via a syringe as rapidly as possible to a mixture of 2-bromobenzylbromide (5 g, 20 mmol), copper iodide (500 mg), and 2-2'-bipyridine (420 mg) in toluene (10 ml) at 0 °C. After stirring for 2 hours at room temperature, ammonium chloride (5 g) was added portionwise and after a further 10 minutes, ether (50 ml) and water (50 ml) were added. The organic fraction was separated and the aqueous fraction was further extracted with ether (3 x 50 ml). The combined organic fractions were washed with brine (150 ml) and evaporated *in vacuo* to give a brown oil. Purification by flash chromatography (eluant light petroleum) gave the title compound,⁶³ as a colourless oil (3.35 g, 85 %).

Found M^+ , 195.9888. C_9H_9Br requires m/z 195.9888.

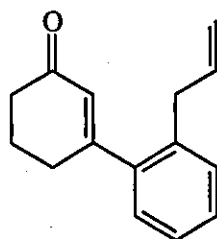
ν_{max}/cm^{-1} (neat) 3069, 3009, 2980, 2914, 1638, 1567, 1470, 1439, 1024, 994, 917, 745, 660, 640.

δ_H (250 MHz; $CDCl_3$) 3.50 (2 H, dt, J 6.5, 1.5, $ArCH_2R$), 5.06 (1 H, dt J 14, 1.5, $RCH=CH_2$ trans), 5.12 (1 H, dt, J 5.5, 1.5, $RCH=CH_2$ cis), 5.95 (1 H, dtt, J 5.5, 14, 6.5, $ArCH=CH_2$), 7.06 (1 H, m, $ArCH$), 7.23 (2 H, m, $Ar-CH$), 7.53 (1 H, d, J 8 Hz, $Ar-CH$).

δ_C (62.9 MHz; $CDCl_3$) 40.1 ($ArCH_2CH=CH_2$), 116.5 ($RCH=CH_2$), 124.5 ($Ar-C$), 127.3 ($Ar-CH$), 127.7 ($Ar-CH$), 130.3 ($Ar-CH$), 132.6 ($RCH=CH_2$), 135.4 ($Ar-CH$), 139.3 ($Ar-CBr$).

m/z (E.I.) 198 (52 %, M^+), 196 (55 %, M^+), 171 (15), 169 (13), 117 (97), 115 (100), 91 (54), 89 (46).

Preparation of 3-(2-Allylphenyl)-2-cyclohexen-1-one (204).



A solution of 2-allylbromobenzene (500 mg, 2.54 mmol) in dry THF (3 ml) was added dropwise to a stirred mixture of magnesium (122 mg, 5 mmol), iodine (1 crystal) and dry THF (5 ml) under nitrogen. After formation of the Grignard reagent the solution was stirred for 15 minutes and then 3-ethoxy-2-cyclohexen-1-one (355 mg, 2.54 mmol) was added. The solution was stirred for a further 2 hours at room temperature after which hydrochloric acid (2 M, 10 ml) was added and the mixture was extracted with ether (3 x 10 ml). The combined organic fractions were washed with saturated brine (50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 3:1) gave the title compound,⁶² as a colourless oil (352 mg, 65 %).

Found M^+ , 212.1204. $C_{15}H_{16}O$ requires m/z 212.1201.

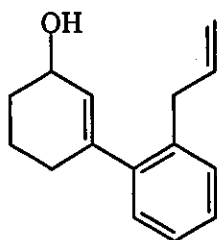
$\nu_{\max}/\text{cm}^{-1}$ (neat) 2933, 1670, 1618, 1597, 1346, 1326, 1246, 1188, 758.

δ_H (400 MHz; $CDCl_3$) 2.14 (2 H, quintet, J 6, 5- CH_2), 2.49 (2 H, t, J 6, 6- CH_2), 2.58 (2 H, dt, J 6, 1.5, 4- CH_2), 3.35 (2 H, dt, J 6, 1.5, $ArCH_2CH=CH_2$), 4.98 (1 H, dq, J 17, 1.5, $RCH=CH_2$), 5.07 (1 H, dq, J 10, 1.5, $RCH=CH_2$), 5.90 (1 H, ddt, J 17, 10, 6, $RCH=CH_2$), 6.00 (1 H, t, J 1.5, 2-CH), 7.11 (1 H, dt, J 6.5, 1.5, Ar-CH), 7.26 (3 H, m, Ar-CH).

δ_C (100 MHz; $CDCl_3$) 23.0 (5- CH_2), 31.7 (4- CH_2), 37.2 (6- CH_2), 37.4 ($ArCH_2CH=CH_2$), 116.2 (R- $CH=CH_2$), 126.3 (Ar-CH), 127.0 (Ar-CH), 128.4 (Ar-CH), 128.7 (2-CH), 130.1 (Ar-CH), 135.7 (Ar-C), 137.1 ($ArCH_2CH=CH_2$), 141.2 (Ar-C), 164.0 (3-C), 199.6 (1-C=O).

m/z (E.I.) 212 (M^+ , 13 %), 184 (67), 155 (43), 141 (100), 128 (60), 115 (50), 84 (58), 32 (63).

Preparation of 3-(2-Allylphenyl)-2-cyclohexen-1-ol (205).



Sodium borohydride (210 mg, 5.2 mmol) was added portionwise to a stirred solution of 3-(2-allylphenyl)-2-cyclohexen-1-one (1 g, 4.7 mmol) and cerium (III) chloride heptahydrate (1.86 g, 5 mmol) in methanol (20 ml) at 0 °C. After stirring at this temperature for 1 hour, water (30 ml) was added and the mixture was extracted with ether (3 x 30 ml). The combined organic fractions were washed with saturated brine, dried over magnesium sulfate and evaporated *in vacuo* to give the title compound,⁶² as a colourless oil (912 mg, 91 %).

Found M^+ , 214.1363. $C_{15}H_{18}O$ requires m/z 214.1358.

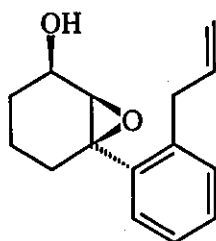
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3329 (OH), 2934 (CH), 2861, 1637, 1598, 1485, 1443, 1431, 1342, 1290, 1153, 1051, 972, 912, 756.

δ_H (400 MHz; $CDCl_3$) 1.74 (2 H, m, 5- CH_2), 1.93 (2 H, m, 6- CH_2), 2.22 (2 H, m, 4- CH_2), 3.38 (2 H, dt, J 6.5, 1.5, Ar- $CH_2CH=CH_2$), 5.02 (1 H, ddt, J 16.5, 2, 1.5, Ar $CH_2CH=CH_2$), 5.05 (1 H, ddt, J 10, 2, 1.5 Ar $CH_2CH=CH_2$), 5.64 (1 H, dt J 3.5, 2, 2-H), 5.92 (1 H, ddt, 16.5, 10, 6.5, Ar $CH_2CH=CH_2$), 7.07 (1 H, m, Ar-H), 7.19 (3 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 19.5 (5- CH_2), 30.9 (4- CH_2), 31.4 (6- CH_2), 37.3 (Ar $CH_2CH=CH_2$), 65.8 (1-COH), 115.7 (Ar $CH_2CH=CH_2$), 125.9 (Ar-CH), 127.0 (Ar-CH), 128.3 (Ar-CH), 128.4 (2-CH), 129.5 (Ar-CH), 136.6 (Ar-C), 138.0 (Ar $CH_2CH=CH_2$), 141.9 (Ar-C), 143.0 (3-C).

m/z (E.I) 214 (M^+ , 3.5 %), 196 (M^+-H_2O , 33), 181 (45), 167 (65), 155 (48), 141 (78), 129 (85), 115 (66), 91 (34), 77 (24), 51 (25), 39 (24), 28 (100).

Preparation of 3-(2-Allylphenyl)-2,3-epoxy-cyclohexan-1-ol (206).



m-Chloroperbenzoic acid (883 mg, 5.1 mmol) was added in one portion to a stirred solution of 3-(2-allylphenyl)-2-cyclohexen-1-ol (912 mg, 4.3 mmol) and sodium bicarbonate (429 mg, 5.1 mmol) in DCM (20 ml) at 0 °C. After 1 hour at this temperature the solution was washed with sodium sulfite solution (10 %, 20 ml), saturated sodium bicarbonate (4 x 20 ml) and saturated brine (20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a colourless oil (843 mg, 74 %).

Found M^+ , 230.1309. $C_{15}H_{18}O_2$ requires m/z 230.1308.

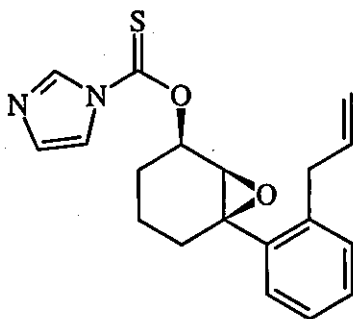
ν_{max}/cm^{-1} (neat) 3392, 2942, 1638, 1489, 1442, 1419, 1291, 1260, 1064, 996, 963, 912, 883, 847, 759, 733, 647.

δ_H (400 MHz; $CDCl_3$) 1.42 (1 H, m, 5-CH), 1.60 (1 H, m, 5-CH), 1.66 (2 H, m, 6- CH_2), 1.89 (1 H, m, 4-CH), 2.03 (1 H, m, 4-CH), 2.65 (1 H, br s, OH), 3.31 (1 H, d, J 2.6, 2-CH), 3.43 (2 H, dt, J 6.5, 1.5, $ArCH_2CH=CH_2$), 4.16 (1 H, m, 1-CH), 5.04 (1 H, dt, J 17, 1.5, $ArCH_2CH=CH_2$), 5.10 (1 H, dt, J 10, 1.5, $ArCH_2CH=CH_2$), 5.95 (1 H, ddt, J 6.5, 10, 17, $ArCH_2CH=CH_2$), 7.18 (3 H, m, Ar-H), 7.34 (1 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 18.9 (5- CH_2), 28.5 (6- CH_2), 29.8 (4- CH_2), 36.6 ($ArCH_2CH=CH_2$), 62.5 (2-CH), 65.0 (3-C), 67.1 (1-COH), 116.3 ($ArCH_2CH=CH_2$), 126.3 (Ar-CH), 126.7 (Ar-CH), 127.8 (Ar-CH), 129.4 (Ar-CH), 136.4 (Ar-C), 136.8 ($ArCH_2CH=CH_2$) 140.2 (Ar-C).

m/z (E.I.) 230 (M^+ , 5 %), 212 ($[M-H_2O]^+$, 11 %), 186 (25), 155 (26), 145 (44), 141 (49), 129 (100), 115 (64), 91 (40), 69 (50), 39 (28), 27 (22).

Preparation of 3-(2-allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxycyclohexane (197).



A solution of 3-(2-allylphenyl)-2,3-epoxy-cyclohexan-1-ol (840 mg, 3.13 mmol) and 1,1'-thiocarbonyldiimidazole (840 mg, 4.71 mmol) in DCM (20 ml) was stirred at gentle reflux for 16 hours. The solution was then allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a pale yellow oil (995 mg, 94 %).

Found MH^+ 341.1324. $C_{19}H_{21}N_2O_2S$ requires m/z 341.1324.

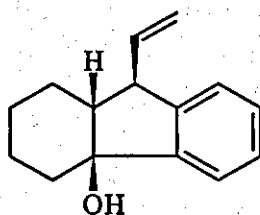
ν_{max}/cm^{-1} (neat) 2947, 1693, 1638, 1531, 1464, 1386, 1337, 1284, 1230, 1102, 995, 969, 898, 761, 656, 642.

δ_H (400 MHz; $CDCl_3$) 1.59 (1 H, m, 5-CH), 1.82 (1 H, m, 5-CH), 1.96 (3 H, m, 6- CH_2 , 4-CH), 2.10 (1 H, m, 4-CH), 3.47 (2 H, dd, J 6, 1.5, $ArCH_2CH=CH_2$), 3.52 (1 H, d, J 2, 2-CH), 5.09 (1 H, dq, J 17, 1.5, $ArCH_2CH=CH_2$), 5.16 (1 H, dq, J 8.5, 1.5, $ArCH_2CH=CH_2$), 6.03 (1 H, ddt, J 6, 8.5, 17, $ArCH_2CH=CH_2$), 6.05 (1 H, m, 1-CH), 7.04 (1 H, t, J 1, Im-CH), 7.24 (4 H, m, Ar-H), 7.67 (1 H, t, J 1.5, Im-CH), 8.39 (1 H, s, Im-CH).

δ_C (100 MHz; $CDCl_3$) 18.4 (5- CH_2), 22.8 (6- CH_2), 28.8 (4- CH_2), 35.7 ($ArCH_2CH=CH_2$), 57.7 (2-CH), 63.3 (3-C), 78.9 (1-CH), 115.6 ($ArCH_2CH=CH_2$), 116.9 (Im-CH), 125.4 (Ar-CH), 125.5 (Ar-CH), 127.1 (Ar-CH), 128.6 (Ar-CH), 129.8 (Im-CH), 135.3 (Ar-C), 135.5 ($ArCH_2CH=CH_2$), 136.1 (Im-CH), 138.3 (Ar-C), 182.6 (C=S).

m/z (C.I.) 341 (MH^+ , 6 %), 325 (6), 213 (14), 69 (100).

Tributyltin Hydride Reduction of 3-(2-allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (197) (Normal Addition).



A deoxygenated solution of tributyltin hydride (1.02 g, 3.5 mmol) and azobisisobutyronitrile (50 mg, 0.3 mmol) in benzene (20 ml) was added over 4 hours to a refluxing solution of 3-(2-allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (990 mg, 2.92 mmol) in benzene (20 ml). After a further 30 minutes at reflux the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *cis* diastereomer of 4a-hydroxy-1, 2, 3, 4-tetrahydro-9-vinylfluorene (209) as a colourless solid (282 mg, 45 %). m.p. 100.8 - 103.6 °C.

Found M^+ 214.1360. $C_{15}H_{18}O$ requires m/z 214.1358.

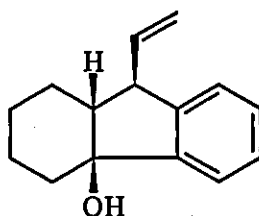
ν_{max}/cm^{-1} (KBr disc) 3350, 2926, 2856, 1641, 1460, 1449, 1154, 1021, 989, 918, 761, 744.

δ_H (400 MHz; $CDCl_3$) 1.42 (3 H, m, 2-H, 3-H, 4-H), 1.65 (3 H, m, 1-H, 2-H, 3-H), 1.78 (1 H, m, 1-H), 1.88 (1 H, br d, 4-H), 1.99 (1 H, m, 9(a)-H), 2.04 (1 H, br s, OH), 3.39 (1 H, t, J 9, 9-H), 5.19 (1 H, m, RCH=CH₂), 5.21 (1 H, s, RCH=CH₂), 5.76 (1 H, m, RCH=CH₂) 7.15 (1 H, m, Ar-H), 7.23 (2 H, m, Ar-H), 7.31 (1 H, m, Ar-H).

δ_c (100 MHz; $CDCl_3$) 21.3 (2 or 3-CH₂), 21.5 (2 or 3-CH₂), 22.7 (1-CH₂), 35.9 (4-CH₂), 49.8 (9-CH), 54.6 (9a-CH), 79.6 (4a-COH), 117.2 (RCH=CH₂), 121.5 (Ar-CH), 124.9 (Ar-CH), 127.3 (Ar-CH), 127.7 (Ar-CH), 139.7 (RCH=CH₂), 142.5 (Ar-C), 149.6 (Ar-C).

m/z (E.I.) 214 (M^+ , 33 %), 196 ($M^+ - H_2O$, 27), 171 (100), 170 (37), 167 (29), 158 (79), 157 (90), 153 (27), 141 (22), 129 (29), 128 (32), 115 (39).

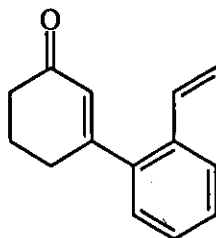
Tributyltin Hydride Reduction of 3-(2-Allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (197) (Inverse Addition).



A deoxygenated solution of 3-(2-allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (121 mg, 0.36 mmol) and azobisisobutyronitrile (12 mg, 0.07 mmol) in benzene (5 ml) was added over 4 hours to a refluxing solution of tributyltin hydride (114 mg, 0.4 mmol) in benzene (5 ml). After a further 30 minutes the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 3:1) gave 4a-hydroxy-1,2,3,4-tetrahydro-9-vinylfluorene (209) as a colourless solid (24 mg, 32 %).

The spectroscopic data for this compound were identical to the previously prepared material.

Preparation of 3-(2-Vinylphenyl)-2-cyclohexen-1-one (217).



A solution of 2-bromostyrene (2 g, 11 mmol) was added dropwise to a stirred mixture of magnesium (600 mg, 25 mmol), iodine (1 crystal) and dry THF (40 ml) under Argon. After formation of the Grignard reagent the solution was stirred for 15 minutes and then 3-ethoxy-2-cyclohexen-1-one (1.4 g, 10 mmol) was added. The solution was stirred for a further hour at room temperature after which hydrochloric acid (5 M, 40 ml) was added and the mixture was extracted with ether (3 x 40 ml). The combined organic fractions were washed with saturated brine, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 3:1) gave the *title compound* as a pale yellow oil (1.87 g, 86 %).

Found M^+ , 198.1045. $C_{14}H_{14}O$ requires m/z 198.1045.

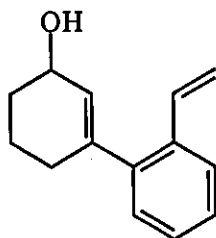
$\nu_{\max}/\text{cm}^{-1}$ (neat) 2949 (C-H) 1668 (C=O), 1613, 1346, 1326, 1245, 1189, 912, 770, 754, 733.

δ_{H} (400 MHz; CDCl_3) 2.14 (2 H, quintet, J 6, 5- CH_2), 2.47 (2 H, t, J 6, 6- CH_2), 2.59 (2 H, dt, J 6, 1.5, 4- CH_2), 5.28 (1 H, dd, J 11, 1, $\text{RCH}=\text{CH}_2$), 5.69 (1 H, dd, J 17.5, 1, $\text{RCH}=\text{CH}_2$), 6.03 (1 H, t, J 1.5, 2-CH), 6.74 (1 H, dd, J 11, 17.5, $\text{RCH}=\text{CH}_2$), 7.14 (1 H, dd, J 4, 1, Ar-H), 7.30 (2 H, m, Ar-H), 7.56 (1 H, dd, J 8, 2, Ar-H).

δ_{C} (100 MHz; CDCl_3) 23.1 (5- CH_2), 31.4 (4- CH_2), 37.2 (6- CH_2), 116.1 ($\text{RCH}=\text{CH}_2$), 126.2 (ArCH), 127.2 (ArCH), 127.7 (ArCH), 128.6 (ArCH), 129.4 (2-CH), 134.7 ($\text{RCH}=\text{CH}_2$), 139.5 (Ar-C), 162.7 (3-C) 199.3 (C=O).

m/z (E.I.) 198 (M^+ , 5 %), 180 (37), 170 (38), 155 (23), 142 (67), 141 (100), 128 (23), 115 (26).

Preparation of 3-(2-Vinylphenyl)-2-cyclohexen-1-ol (218).



Sodium borohydride (757 mg, 20 mmol) was added portionwise to a solution of 3-(2-vinylphenyl)-2-cyclohexen-1-one (3.37 g, 17 mmol) and cerium (III) chloride heptahydrate (7.45 g, 20 mmol) in methanol (50 ml) at 0 °C. After stirring at 0 °C for 1 hour, water (50 ml) was added and the mixture extracted with ether (3 x 50 ml). The combined organic fractions were washed with saturated brine (150 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the title compound as a clear and colourless oil (3.20 g, 94 %).

Found M^+ , 200.1197. $\text{C}_{14}\text{H}_{16}\text{O}$ requires m/z 200.1201.

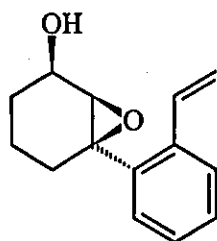
ν_{\max} (neat) 3357 (OH), 2934 (C-C), 2861, 1658, 1477, 1447, 1344, 1050, 972, 910, 774, 756.

δ_{H} (400 MHz; CDCl_3) 1.73 (2 H, m, 5- CH_2), 1.91 (2 H, m, 6- CH_2), 2.21 (2 H, m, 4- CH_2), 4.38 (1 H, m, 1-CH), 5.23 (1 H, dd, J 1, 11, ArCH= CH_2), 5.68 (1 H, dd, J 17.5, 1.5, ArCH= CH_2), 5.68 (1 H, quintet, J 1.5, 2-CH), 6.82 (1 H, dd, J 11, 17.5, ArCH= CH_2), 7.10 (1 H, m, Ar-H), 7.24 (2 H, m, Ar-H), 7.53 (1 H, m, Ar-H).

δ_c (100 MHz; CDCl_3) 19.5 (5- CH_2), 30.7 (4- CH_2), 31.6 (6- CH_2), 65.6 (1-COH), 114.5 (ArCH= CH_2), 125.4 (Ar-CH), 127.2 (Ar-CH), 127.6 (Ar-CH), 128.3 (Ar-CH), 129.5 (2-CH), 135.1 (3-C), 135.4 (ArCH= CH_2), 141.6 (Ar-C), 142.2 (Ar-C).

m/z (E.I.) 200 (M^+ , 26 %), 183 (100), 182 (78), 154 (19), 141 (30), 129 (22), 128 (21), 115 (14), 74 (73), 44 (25).

Preparation of 2, 3-Epoxy-3-(2-vinylphenyl)-2-cyclohexan-1-ol (219).



m-Chloroperbenzoic acid (6.21 g, 36 mmol) was added in one portion to a stirred solution of 3-(2-vinylphenyl)-2-cyclohexen-1-ol (6.96 g, 34.8 mmol) and sodium bicarbonate (3.36 g, 40 mmol) in DCM (140 ml) at 0 °C. After 1 hour at this temperature the solution was washed with sodium sulfite solution (10 %, 150 ml), saturated sodium bicarbonate (2 x 150 ml) and saturated brine (150 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a colourless oil (2.9 g, 39 %).

Found M^+ , 216.1152. $\text{C}_{14}\text{H}_{16}\text{O}$ requires m/z 216.1150.

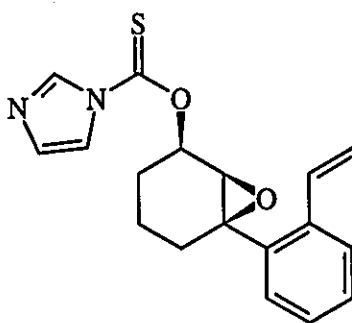
$\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3383 (OH), 2942 (C-H) 2861, 1482, 1442, 1417, 1066, 1050, 991, 961, 916, 883, 868, 848, 769, 756, 657, 627.

δ_{H} (400 MHz; CDCl_3) 1.44 (1 H, m, 5-CH), 1.64 (3 H, m, 6- CH_2 , 5-CH), 1.87 (1 H, m, 4-CH), 2.00 (2 H, m, 4-CH), 2.85 (1 H, br s, OH), 3.31 (1 H, d, J 2.5, 2-CH), 4.17 (1 H, m, 1-CHOH), 5.33 (1 H, d, J 11, ArCH= CH_2), 5.69 (1 H, d, J 17, ArCH= CH_2), 6.88 (1 H, dd, J 11, 17, ArCH= CH_2), 7.24 (2 H, m, Ar-H), 7.35 (1 H, m, Ar-H), 7.48 (1 H, m, Ar-H).

δ_c (100 MHz; CDCl_3) 19.0 (5- CH_2), 28.4 (6- CH_2), 29.7 (4- CH_2), 62.7 (3-C), 64.7 (2-CH), 67.2 (1-CHOH), 116.0 (ArCH= CH_2), 125.2 (Ar-CH), 126.4 (Ar-CH), 127.6 (2 x Ar-CH) 133.6 (ArCH= CH_2), 135.0 (Ar-C), 139.4 (Ar-C).

m/z (C.I.) 236 (15 %), 235 (31), 234 (100, $[\text{M}+\text{NH}_4]^+$), 216 (42, M^+), 199 (36), 181 (86), 91 (18).

Preparation of 2,3-epoxy-1-(imidazol-1-yl(thiocarbonyl)oxy)-3-(2-vinylphenyl)cyclohexane (210).



A solution of 3-(2-vinylphenyl)-2,3-epoxy-cyclohexan-1-ol (1.18 g, 5.53 mmol) and 1,1'-thiocarbonyldiimidazole (1.15 g, 6.45 mmol) in DCM (20 ml) was stirred at gentle reflux for 4 hours. The solution was then allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a pale yellow crystalline solid (1.50 g, 84 %). A sample of this was recrystallised from acetonitrile to give pale yellow crystals, m.p. 116-118 °C.

Found C, 65.98; H, 5.45; N 8.29. C₁₂H₁₂O₂ requires C, 66.23; H, 5.56; N 8.58 %.

$\nu_{\max}/\text{cm}^{-1}$ (KBr disc) 2949, 2924, 2854, 1474, 1463, 1385, 1335, 1319, 1275, 1230, 1100, 1089, 1064, 1032, 993, 970, 960, 951, 771, 651.

δ_{H} (400 MHz; CDCl₃) 1.59 (1 H, m, 5-CH), 1.82 (1 H, m, 5-CH), 1.96 (3 H, m, 4-CH, 6-CH₂), 2.12 (1 H, m, 4-CH), 3.52 (1 H, d, *J* 2, 2-CH), 5.40 (1 H, d, *J* 11, ArCH=CH₂), 5.73 (1 H, dd, *J* 17.5, 0.5, ArCH=CH₂), 7.02 (1 H, s, Im-H), 7.26 (2 H, d x quintet, *J* 7, 2, 2 x Ar-H), 7.35 (1 H, dd, *J* 7, 2, Ar-H), 7.50 (1 H, dd, *J* 8, 1.5), 7.66 (1 H, s, Im-H), 8.38 (1 H, s, Im-H).

δ_{C} (100 MHz; CDCl₃) 19.3 (5-CH₂), 23.9 (6-CH₂), 29.2 (4-CH₂), 58.7 (2-CH), 64.1 (3-C), 79.6 (1-CH), 116.6 (Ar-CH=CH₂), 117.9 (Im-CH), 125.4 (Ar-CH), 126.3 (Ar-CH), 127.7 (Ar-CH), 128.2 (Ar-CH), 130.7 (Im-CH), 133.6 (ArCH=CH₂), 135.1 (Ar-C), 137.1 (Im-CH), 138.5 (Ar-C), 183.6 (C=S).

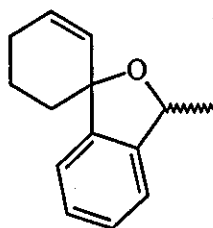
m/z (C.I.) 328 (24 %), 327 (MH⁺, 100 %), 199 (M⁺, 53), 69 (45).

(See Appendix B for X-ray crystallographic data)

Tributyltin Hydride Reduction of 3-(2-Vinylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (210) (Normal Addition).

A deoxygenated solution of tributyltin hydride (152 mg, 0.52 mmol) and azobisisobutyronitrile (7 mg, 0.04 mmol) in benzene (5 ml) was added over 4 hours to a refluxing solution of 3-(2-vinylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (118 mg, 0.36 mmol) in benzene (2 ml). After a further 30 minutes the solution was allowed to cool and evaporated *in vacuo* to give a mixture of tributyltin residues and an insoluble polymeric material for which no data was obtained.

Tri-n-butyltin Hydride Reduction of 2,3-epoxy-1-(imidazol-1-yl(thiocarbonyl)oxy)-3-(2-vinylphenyl)cyclohexane (210) (Inverse Addition).



A deoxygenated solution of 2,3-epoxy-1-(imidazol-1-yl(thiocarbonyl)oxy)-3-(2-vinylphenyl)cyclohexane (1.31 g, 4.0 mmol) and azobisisobutyronitrile (176 mg, 1.07 mmol) in benzene (25 ml) was added over 3.5 hours to a deoxygenated refluxing solution of tributyltin hydride (2.33 g, 8.0 mmol) in benzene under Argon. After a further 30 mins the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by column chromatography (basic alumina, eluant ether/hexane 1:20) followed by short path distillation gave *spiro*[2-cyclohexene-1, 1'-3'-methyl-(3H)-isobenzofuran] (213) as a 4:1 mixture of diastereoisomers (260 mg, 33 %, b.p. 75-100 °C, 1 mbar).

Found M^+ 200.1197. $C_{14}H_{16}O$ requires m/z 200.1201.

ν_{max} (neat) 3023, 2993, 1646, 1606, 1455, 1368, 1343, 1260, 1112, 1083, 1063, 1033, 1015, 936, 899, 752, 726, 689, 641.

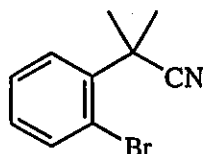
δ_H (400 MHz; $CDCl_3$) 1.54 (3 H, d, J 6, 3'- CH_3 maj), 1.57 (3 H, d, J ?, 3'- CH_3 min), 1.89 (1 H, m, 5-CH), 1.97 (2 H, m, 6-CH, 5-CH), 2.02 (1 H, m, 6-CH), 2.14 (2 H, m, 4- CH_2), 5.29 (1 H, q, J 6.5, 3'-CH min), 5.39 (1 H, q, J 6.5, 3'-CH maj), 5.65 (1 H, d, J 10, 2-CH maj), 5.71 (1 H, d, J 10, 2-CH min), 5.95 (1 H, ddd J 10, 4.5, 3, 3-CH maj), 6.03 (1 H, ddd, J 10, 4.5, 3, 3-CH min), 7.15 (2 H, m, Ar-H), 7.28 (2 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 18.6 (5- CH_2 , min), 19.5 (5- CH_2 , maj), 22.4 (3'- CH_3 , min), 23.6 (3'- CH_3 , maj), 24.7 (4- CH_2 , maj), 24.9 (4- CH_2 , min), 35.7 (6- CH_2 , min), 38.3 (6- CH_2 , maj),

77.0 (3'-CH, min), 78.1 (3'-CH, maj), 83.9 (1-C), 120.9 (Ar-CH min), 121.1 (Ar-CH, maj), 121.4 (Ar-CH, min), 121.7 (Ar-CH, maj), 127.5 (Ar-CH), 127.6 (Ar-CH), 130.1 (3-CH maj), 130.3 (2-CH maj), 131.0 (2-CH min), 131.3 (3-CH min), 143.7 (Ar-C), 145.7 (Ar-C).

m/z (C.I.) 418 ($[2M+NH_4]^+$, 4 %), 219 (19), 218 ($[M+NH_4]^+$, 201 ($[M+H]^+$, 12), 183 (30), 172 (19).

Preparation of 2-Methyl-2-(*o*-bromophenyl)propionitrile (228).



A solution of 2-bromophenylacetonitrile (5 g, 45 mmol) and iodomethane (7.6 ml, 117 mmol) in THF (50 ml) was added over 20 minutes to a stirred slurry of potassium *tert*-butoxide (13.1 g, 117 mmol) in THF (150 ml) at -78°C under nitrogen. After the addition was complete the solution was allowed to warm to room temperature and after stirring for a further hour, water (100 ml) was added. The mixture was then extracted with ether (3 x 100 ml) and the combined organic fractions were washed with saturated brine (200 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a dark yellow oil. Purification by flash chromatography (eluant light petroleum/ether 19:1) gave the *title compound* as a clear and colourless oil (8.017 g, 79 %).

Found M^+ , 222.9996. $C_{10}H_{10}BrN$ requires m/z , 222.9997.

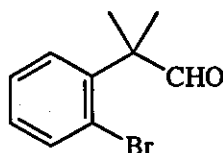
$\nu_{\max}/\text{cm}^{-1}$ (thin film) 2984, 2235, 1469, 1428, 1232, 1024, 758, 724, 648, 610.

δ_H (250 MHz; $CDCl_3$) 1.90 (6 H, s, 2 x CH_3), 7.19 (1 H, td, J 8, 1.5, Ar-H), 7.34 (1 H, td, J 7.5, 1.5, Ar-H), 7.48 (1 H, dd, J 8, 1.5, Ar-H), 7.66 (1 H, dd, J 8, 1.5, Ar-H).

δ_C (62.9 MHz; $CDCl_3$) 27.5 (2 x CH_3), 122.6 ($C\equiv N$), 123.4 (Ar-CBr), 127.3 (Ar-CH), 128.0 (Ar-CH), 129.7 (Ar-CH), 135.6 (Ar-CH), 138.0 (Ar-C).

m/z (E.I.) 225 (M^+ , 57 %), 223 (M^+ , 59), 210 (98), 208 (100), 183 (91), 102 (52), 51 (42).

Preparation of 3-Methyl-3-(2-bromophenyl)propanal (229).



A solution of diisobutylaluminium hydride (26.7 ml, 1.5 M in toluene, 40 mmol) was added dropwise to a stirred solution of 2-methyl-2-(2-bromophenyl)propionitrile (7.860 g, 35.1 mmol) in THF (140 ml) at 0° C under nitrogen. The solution was stirred at 0° C for 30 min and then for a further 2 hours at room temperature after which water was added *very* slowly until hydrogen evolution ceased. Concentrated sulfuric acid (5 ml) was added and the solution was stirred for an hour, after which it was diluted with water (100 ml) and extracted with ether (3 x 100 ml). The combined organic fractions were washed with saturated brine (150 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear and colourless oil (8.10 g, 99 %).

Found M^+ , 225.9997. $C_{10}H_{11}BrO$ require m/z 225.9993.

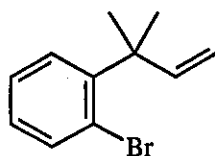
ν_{max}/cm^{-1} (neat) 2976, 2933, 1724, 1469, 1427, 1024, 757, 732, 723.

δ_H (250 MHz; $CDCl_3$) 1.51 (6 H, s, 2 x CH_3), 7.17 (1 H, m, Ar-H), 7.37 (2 H, m, Ar-H), 7.58 (1 H, dd, J 8, 1, Ar-H), 9.77 (1 H, s, RCHO).

δ_C (62.9 MHz; $CDCl_3$) 23.3 (2 x CH_3), 51.8 ($ArC(Me)_2CHO$), 123.4 (Ar-CBr), 127.9 (Ar-CH), 128.6 (Ar-CH), 129.2 (Ar-CH), 134.4 (Ar-CH), 142.3 (Ar-C), 203.1 (RCHO).

m/z (E.I.) 226 (M^+ , 3 %), 225 ($M-H^+$, 4), 224 (M^+ , 3), 223 ($M-H^+$, 4), 199 (63), 197 (64), 171 (97), 147 (M-Br, 100), 115 (43), 91 (42), 77 (29).

Preparation of 3-Methyl-3-(2-bromophenyl)-1-butene (230).



A solution of *n*-butyllithium (27 ml, 1.6 M in hexanes, 43 mmol) was added dropwise to a slurry of methyltriphenylphosphonium bromide (16 g, 45 mmol) in THF (200 ml) under nitrogen at room temperature. After stirring for 20 minutes 2-methyl-2-(2-bromophenyl)propanal (7.94 g, 35.1 mmol) was added. The solution was stirred for a further sixteen hours after which water (200 ml) was added and the mixture was extracted with ether (3 x 100 ml). The combined organic fractions were washed with saturated brine (200 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a brown oily

crystalline mixture. Purification by flash chromatography (eluant light petroleum) gave the *title compound* as a clear and colourless oil (5.855 g, 74 %).

Found M^+ 224.0201. $C_{11}H_{13}Br$ requires m/z 224.0201.

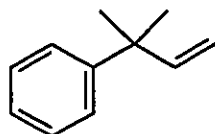
ν_{max}/cm^{-1} (neat) 2968, 2930, 1468, 1424, 1412, 1361, 1048, 1020, 909, 755, 728, 649.

δ_H (250 MHz; $CDCl_3$) 1.56 (6 H, s, 2 x CH_3), 4.94 (1 H, dd, J 17.5, 1, $RCH=CH_2$), 5.06 (1 H, dd J 10.5, 1, $RCH=CH_2$), 6.16 (1 H, dd, J 17.5, 10.5, $RCH=CH_2$), 7.05 (1 H, td, J 7.5, 1.5, Ar-H), 7.26 (1 H, td, J 8, 1.5, Ar-H), 7.45 (1 H, dd, J 8, 1.5, Ar-H), 7.57 (1 H, dd, J 8, 1.5, Ar-H).

δ_C (62.9 MHz; $CDCl_3$) 28.8 (2 x CH_3), 43.2 ($Ar-C(Me)_2CH=CH_2$), 112.6 ($RCH=CH_2$), 124.0 ($Ar-CBr$), 127.7 ($Ar-CH$), 128.3 ($Ar-CH$), 128.9 ($Ar-CH$), 136.0 ($Ar-CH$), 146.8 ($Ar-C$), 147.4 ($Ar-C(Me)_2CH=CH_2$).

m/z (E.I.) 226 (M^+ , 10 %), 224 (M^+ , 10 %), 211 (8), 209 (8), 171 (12), 169 (13), 145 (60), 130 (100), 115 (37).

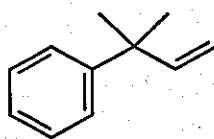
Attempted Coupling of 3-Methyl-3-(2-bromophenyl)-1-butene (230) with 3-Ethoxy-2-cyclohexen-1-one (187) via a Grignard Reagent.



A solution of 3-methyl-3-(2-bromophenyl)-1-butene (882 mg, 3.92 mmol) in dry THF (5 ml) was added dropwise to a stirred mixture of magnesium (146 mg, 6 mmol) and iodine (1 crystal) in dry THF (5 ml) under nitrogen. After formation of the Grignard reagent the solution was stirred for a further 15 minutes and then 3-ethoxy-2-cyclohexen-1-one (546 mg, 3.9 mmol) was added. The solution was stirred for a further 2 hours at room temperature after which hydrochloric acid (2 M, 10 ml) was added and the mixture was extracted with ether (3 x 10 ml). The combined organic fractions were washed with brine (50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. Purification of this oil by flash chromatography (eluant 3:1 light petroleum/ether) gave 3-methyl-3-phenylbut-1-ene,¹⁰³ (233) as a clear and colourless oil (481 mg, 84 %).

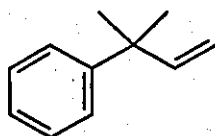
δ_H (250 MHz; $CDCl_3$) 1.40 (6 H, s, 3-C- CH_3 , 4- CH_3), 5.03 (1 H, d, J 10.5, 1-CH), 5.05 (1 H, d, J 17.5, 1-CH), 6.03 (1 H, dd, J 11, 17.5, 2-CH), 7.29 (5 H, m, Ar-H).

Attempted Coupling of 3-Methyl-3-(2-bromophenyl)-1-butene (230) with 3-ethoxy-2-cyclohexen-1-one (187) via an Organolithium Reagent.



n-Butyllithium (2.5 M, 0.52 ml, 1.3 mmol) was added dropwise to a solution of 3-methyl-3-(2-bromophenyl)-1-butene (882 mg, 3.92 mmol) in dry ether (2 ml) at 0 °C under nitrogen. After stirring for 30 minutes at this temperature, 3-ethoxy-2-cyclohexen-1-one (142 mg, 1 mmol) was added. The solution was then allowed to warm to room temperature and after a further 2 hours, hydrochloric acid (2 M, 5 ml) was added and the mixture was extracted with ether (3 x 5 ml). The combined organic fractions were washed with brine (20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. N.M.R analysis of this mixture showed that none of the desired coupling had taken place and the organolithium reagent had been converted to 3-methyl-3-phenylbut-1-ene (233).¹⁰³

Attempted Coupling of 3-Methyl-3-(2-bromophenyl)-1-butene with 3-Ethoxy-2-cyclohexen-1-one via an Organocerium Reagent.

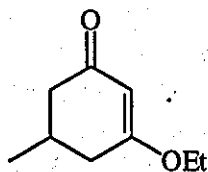


Cerium (III) chloride heptahydrate (3.73 g, 10 mmol) was heated to 120 °C under vacuum. After two hours at this temperature the flask was flushed with nitrogen and cooled to 0 °C. Dry THF (20 ml) was added and the suspension was sonicated for 1 hour. *n*-Butyllithium (1.6 M, 6.6 ml, 10.6 mmol) was added dropwise to a solution of 3-methyl-3-(2-bromophenyl)-1-butene (1 g, 4.44 mmol) in dry THF (10 ml) at 0 °C under nitrogen. After stirring for 30 minutes at this temperature, the organolithium reagent was transferred *via* a syringe to the flask containing the cerium (III) chloride at -78 °C. After 1 hour, 3-ethoxy-2-cyclohexen-1-one (700 mg, 5 mmol) was added and the solution was stirred at -78 °C for a further two hours, after which it was allowed to warm to room temperature. After a further 2 hours, hydrochloric acid (2 M, 20 ml) was added and the mixture was extracted with ether (3 x 20 ml). The combined organic fractions were washed with brine (50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil.

N.M.R analysis of this oil showed that none of the desired coupling had taken place and the organocerium reagent had been converted to 3-methyl-3-phenylbut-1-ene (233).¹⁰³

7.4 Experimental for Chapter 4

Preparation of 3-Ethoxy-5-methyl-2-cyclohexen-1-one (249).



A solution of 5-methylcyclohexane-1,3-dione (4.89 g, 38.76 mmol), *p*-toluenesulfonic acid (0.30 g, 1.57 mmol) and ethanol (30 ml) in toluene (80 ml) was heated on a Dean-Stark apparatus for 6 hours. After cooling the solution was washed with 5 % potassium hydroxide solution saturated with sodium chloride (100 ml) and saturated sodium chloride solution (100 ml). Evaporation of the solvent *in vacuo* gave the title compound as a clear and colourless liquid (5.32 g, 89 %).⁷⁰⁻⁷²

Found M^+ , 154.0994. $C_9H_{14}O_2$ requires 154.0994.

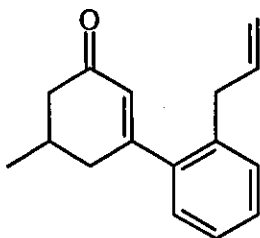
$\nu_{\max}/\text{cm}^{-1}$ (neat) 2957, 1656, 1605, 1379, 1339, 1214, 1158, 1139, 1031.

δ_{H} (400 MHz; CDCl_3) 0.92 (3 H, d, J 5.5, 5- CH_3), 1.21 (3 H, t, J 7, OCH_2CH_3), 1.87 (1 H, dd, J 11.5, 17, 4-CH or 6-CH), 1.99 (1 H, dd, J 10, 16, 4-CH or 6-CH), 2.06 (1 H, m, 5-CH), 2.25 (2 H, 2 x dd, J 17, 4, 4-CH and 6-CH), 3.75 (2 H, m, OCH_2CH_3), 5.17 (1 H, s, 2-CH).

δ_{C} (100 MHz; CDCl_3) 14.0 (OCH_2CH_3), 20.7 (5- CH_3), 28.7 (5-CH), 37.1 (4- or 6- CH_2), 45.0 (4- or 6- CH_2), 64.1 (OCH_2CH_3) 102.1 (2-CH), 177.1 (3-C), 199.4 (1-C=O).

m/z (E.I.) 155 (MH^+ , 44 %), 154 (M^+ , 67), 126 (27), 112 (100), 98 (39), 84 (100), 69 (95), 68 (90), 56 (47), 55 (26), 43 (39), 42 (46), 41 (44).

Preparation of 3-(2-Allylphenyl)-5-methyl-2-cyclohexen-1-one (250).



A solution of 2-allylbromobenzene (2.21 g, 11.2 mmol) in dry THF (20 ml) was added dropwise to a stirred mixture of magnesium (408 mg, 17 mmol), iodine (1 crystal) and dry THF (20 ml) under argon. After formation of the Grignard reagent the solution was stirred for 30 minutes and then 3-ethoxy-5-methyl-2-cyclohexen-1-one (1.54 g, 10 mmol) was added. The solution was stirred for a further 2 hours at room temperature after which hydrochloric acid (5 M, 40 ml) was added and the mixture was extracted with ether (3 x 50 ml). The combined organic fractions were washed with saturated brine (100 ml) dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant hexane/ether 3:1) gave the *title compound* as a clear, pale yellow oil (1.215 g, 54 %).

Found M^+ , 226.1355. $C_{16}H_{18}O$ requires m/z 226.1358.

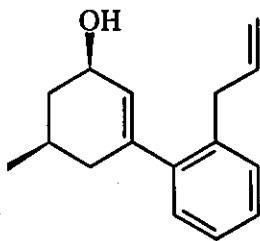
$\nu_{\max}/\text{cm}^{-1}$ (neat) 2956, 1667, 1619, 1456, 1365, 1295, 1274, 1243, 913, 757.

δ_{H} (400 MHz; CDCl_3) 1.12 (3 H, d, J 6, 5- CH_3), 2.17 (1 H, dd, J 12.5, 16, 4-CH), 2.34 (2 H, m, 6-CH, 5-CH), 2.56 (2 H, m, 4-CH, 6-CH), 3.36 (2 H, d, J 6, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 4.98 (1 H, dd, J 17, 1.5, $\text{RCH}_2\text{CH}=\text{CH}_2$), 5.06 (1 H, dd, J 10, 1.5, $\text{RCH}_2\text{CH}=\text{CH}_2$), 5.90 (1 H, ddt, J 17, 10, 6, $\text{RCH}_2\text{CH}=\text{CH}_2$), 5.99 (1 H, s, 2-CH), 7.10 (1 H, d, J 7.5 Ar-H), 7.25 (3 H, m, Ar-H).

δ_{C} (100 MHz; CDCl_3) 21.1 (5- CH_3), 30.6 (5-CH), 37.4 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 40.1 (6- CH_2), 45.5 (4- CH_2), 116.3 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 126.4 (Ar-CH), 127.0 (Ar-CH), 128.4 (Ar-CH), 128.4 (2-CH), 130.1 (Ar-CH), 135.8 (Ar-C), 136.6 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 140.7 (Ar-C), 162.3 (3-C), 199.6 (1-C=O).

m/z (E.I.) 226 (M^+ , 11 %), 184 (84), 156 (43), 155 (38), 153 (20), 142 (30), 141 (100), 128 (72), 115 (59), 91 (67), 77 (19), 69 (21), 51 (18), 39 (43), 27 (20).

Preparation of 3-(2-Allylphenyl)-5-methyl-2-cyclohexen-1-ol (251).



Sodium borohydride (204 mg, 5.4 mmol) was added portionwise to a stirred solution of 3-(2-allylphenyl)-5-methyl-2-cyclohexen-1-one (938 mg, 4.14 mmol) and cerium (III) chloride heptahydrate (2.01 g, 5.4 mmol) in methanol (20 ml) at 0 °C. After stirring at this temperature for 20 minutes, water (30 ml) was added and the mixture was extracted with ether (3 x 20 ml). The combined organic fractions were washed with saturated brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear, pale yellow oil (914 mg, 97 %).

Found M^+ , 228.1516. $C_{16}H_{20}O$ requires m/z , 228.1514.

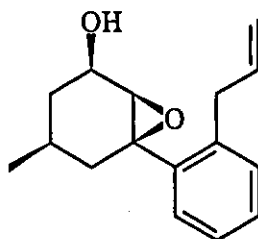
ν_{max}/cm^{-1} (neat) 3320, 2951, 2926, 2873, 1456, 1020, 913, 756.

δ_H (400 MHz; $CDCl_3$) 1.01 (3 H, d, J 6, 5- CH_3), 1.22 (1 H, q, J 11, 6-CH), 1.88 (2 H, m, 4-CH, 5-CH), 2.10 (2 H, m, 4-CH, 6-CH), 3.36 (2 H, d, J 6.5, $ArCH_2CH=CH_2$), 4.42 (1 H, m, 1-CHOH), 5.00 (1 H, dq, J 17.5, 1.5, $ArCH_2CH=CH_2$), 5.03 (1 H, dd, J 10, 1.5, $ArCH_2CH=CH_2$), 5.54 (1 H, s, 2-CH), 5.91 (1 H, ddt, J 17.5, 10, 6.5, $ArCH_2CH=CH_2$), 7.06 (1 H, d, J 7, Ar-H), 7.18 (3 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 22.5 (5- CH_3), 29.3 (5-CH), 38.0 ($ArCH_2CH=CH_2$), 40.3 (6- CH_2), 41.6 (4- CH_2), 69.0 (1-CHOH), 116.4 ($ArCH_2CH=CH_2$), 126.7 (Ar-CH), 127.7 (Ar-CH), 128.9 (Ar-CH), 130.2 (Ar-CH), 130.4 (2-CH), 137.3 (Ar-C), 138.7 ($ArCH_2CH=CH_2$), 140.9 (Ar-C), 143.4 (3-C).

m/z (E.I.) 228 (M^+ , 5 %), 197 (48), 195 (52), 167 (74), 141 (100), 129 (87), 115 (81), 91 (43), 77 (30), 51 (62), 41 (44).

Preparation of 3-(2-Allylphenyl)-2,3-epoxy-5-methylcyclohexan-1-ol (252).



m-chloroperbenzoic acid (1.21 g, 4.9 mmol) was added in one portion to a stirred solution of 3-(2-allylphenyl)-5-methyl-2-cyclohexen-1-ol (796 mg, 3.26 mmol) and sodium bicarbonate (420 mg, 5.0 mmol) in DCM (20 ml) at 0 °C. After 1 hour at this temperature the solution was washed with saturated sodium sulfite (20 ml), saturated sodium bicarbonate (3 x 30 ml) and saturated brine (30 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a colourless oil (630 mg, 79 %).

Found M^+ , 244.1471. $C_{16}H_{20}O_2$ requires m/z 244.1463.

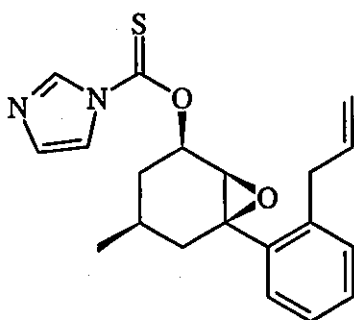
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3408, 2952, 2928, 2872, 1638, 1489, 1456, 1419, 1369, 1306, 1253, 1083, 1032, 997, 910, 870, 851, 828, 806, 760, 733, 648.

δ_{H} (400 MHz; CDCl_3) 0.91 (3 H, d, J 6, 5- CH_3), 1.28 (1 H, q, J 12, 6-CH), 1.64 (2 H, m, 5-CH, 4-CH), 1.72 (1 H, m, 6-CH), 1.95 (1 H, m, 4-CH), 2.55 (1 H, br s, OH), 3.27 (1 H, s, 2-CH), 3.40 (2 H, dd, J 1, 6, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 4.16 (1 H, m, 1-CHOH), 5.04 (1 H, dd, J 17, 1.5, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 5.10 (1 H, dd, J 10, 1, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 5.96 (1 H, ddt, J 17, 10, 6, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 7.22 (3 H, m, Ar-H), 7.34 (1 H, d, J 7.5, Ar-H).

δ_{C} (100 MHz; CDCl_3) 21.4 (5- CH_3), 28.5 (5-CH), 35.7 (6- CH_2), 36.6 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 38.2 (4- CH_2), 63.3 (2-CH), 64.6 (3-C), 69.0 (1-CHOH), 116.3 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 126.3 (Ar-CH), 126.4 (Ar-CH), 127.7 (Ar-CH), 129.5 (Ar-CH), 136.2 (Ar-C), 136.6 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 140.7 (Ar-C).

m/z (C.I.) 506 ($[\text{2M} + \text{NH}_4]^+$, 11 %), 326 (27), 263 (43), 262 ($[\text{MNH}_4]^+$, 100), 245 (30), 244 (40), 228 (30), 227 ($[\text{MH}-\text{H}_2\text{O}]^+$, 96), 209 (40), 147 (19), 91 (67), 85 (32).

Preparation of 3-(2-Allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-5-methyl-cyclohexane (241).



A solution of 3-(2-allylphenyl)-2,3-epoxy-5-methyl-cyclohexan-1-ol (512 mg, 2.1 mmol) and 1,1'-thiocarbonyldiimidazole (534 mg, 3.0 mmol) in DCM (20 ml) was stirred at gentle reflux for 1 hour. The solution was then allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a pale yellow oil (683 mg, 92 %).

$\nu_{\max}/\text{cm}^{-1}$ (neat) 3128, 3075, 2955, 2930, 2871, 1636, 1531, 1464, 1392, 1345, 1324, 1284, 1223, 1184, 1158, 1100, 1042, 884, 918, 872, 829, 762, 697, 656, 640.

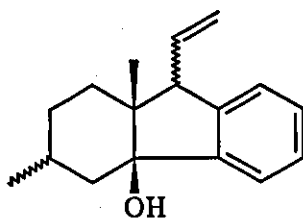
δ_{H} (400 MHz; CDCl_3) 1.00 (3 H, m, 5- CH_3), 1.67 (1 H, q, J 11.5, 6-CH), 1.77 (1 H, dd, J 11.5, 14, 4-CH), 1.88 (1 H, m, 5-CH), 1.96 (1 H, br dd, J 12, 5.5, 6-CH), 2.09 (1 H, ddd, J 15, 5.5, 1, 4-CH), 3.46 (2 H, dd, J 6, 1, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 3.48 (1 H, s, 2-CH), 5.08 (1 H, dd, J 17, 1.5, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 5.15 (1 H, dd, J 10, 1.5, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 5.99 (1 H, ddt, J 17, 10, 6, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 6.10 (1 H, ddd, J 11, 5.5, 1.5, 1-CH), 7.03 (1 H, s, Im-H), 7.22 (3 H, m, Ar-H), 7.36 (1 H, d, J 7.5, Ar-H), 7.66 (1 H, s, Im-H), 8.38 (1 H, s, Im-H).

δ_{C} (100 MHz; CDCl_3) 21.3 (5- CH_3), 28.2 (5-CH), 30.8 (6- CH_2), 36.8 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 37.9 (4- CH_2), 59.2 (2-CH), 64.2 (3-C), 80.9 (1-CH), 116.6 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 117.9 (Im-CH), 126.3 (Ar-CH), 126.5 (Ar-CH), 128.1 (Ar-CH), 129.6 (Ar-CH), 130.9 (Im-CH), 136.3 (Ar-C), 136.4 ($\text{ArCH}_2\text{CH}=\text{CH}_2$), 137.1 (Im-CH), 139.5 (Ar-C), 183.7 (C=S).

m/z (C.I.) (MH^+ , 59 %), 291 (9), 227 (31), 69 (100).

See Appendix A for stereochemical assignment.

Tributyltin Hydride Reduction of 3-(2-Allylphenyl)-2,3-epoxy-5-methyl-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (241) (Normal Addition).



A deoxygenated solution of tributyltin hydride (1.02 g, 3.5 mmol) and azobisisobutyronitrile (50 mg, 0.3 mmol) in benzene (20 ml) was added over 4 hours to a refluxing solution of 3-(2-allylphenyl)-2,3-epoxy-5-methyl-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (700 mg, 1.97 mmol) in benzene (20ml). After a further 30 minutes the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum then ether) gave 4a-hydroxy-3-methyl-1, 2, 3, 4-tetrahydro-9-vinylfluorene (247a-d) as a mixture (ratio 10:48:22:4 by GCMS) of 4 diastereomers, (167 mg, 37 %). Further chromatography (eluant hexane/ether 6:1) gave the major diastereomer as a colourless oil (100 mg, 22 %).

Found M^+ 228.1512. $C_{16}H_{20}O$ requires m/z 228.1514.

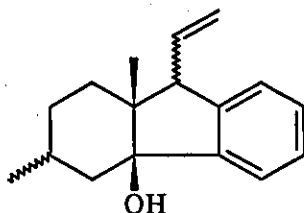
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3553, 3410, 3070, 3022, 2922, 1634, 1457, 1374, 1274, 1104, 1007, 910, 855, 749, 733, 672.

δ_{H} (400 MHz; CDCl_3) 0.96 (1 H, m, 1-CH), 1.00 (3 H, d, J 6, 3- CH_3), 1.03 (1 H, m, 2-H), 1.23 (1 H, m, 3-CH), 1.50 (1 H, m, 2-CH), 1.51 (1 H, dd, J 13.5, 11.5, 4-CH), 1.96 (1 H, m, 1-CH), 2.15 (1 H, ddd, J 10.5, 6.5, 1.5, 9(a)-CH), 2.32 (1 H, dq, J 13.5, 1.5, 4-CH), 3.30 (1 H, d, J 6, 9-CH), 4.96 (1 H, dt, J 17, 1.5, $\text{RCH}=\text{CH}_2$), 5.01 (1 H, dt, J 10, 1.5, $\text{RCH}=\text{CH}_2$), 6.24 (1 H, ddd, J 17, 10, 6, $\text{RCH}=\text{CH}_2$), 7.30 (4 H, m, Ar-H).

δ_{C} (100 MHz; CDCl_3) 21.9 (3- CH_3), 28.9 (3-CH), 29.7 (1- CH_2), 32.5 (2- CH_2), 42.1 (4- CH_2), 53.4 (9(a)-CH), 54.4 (9-CH), 82.6 (4(a)-COH), 114.2 ($\text{RCH}=\text{CH}_2$), 122.5 (Ar-CH), 126.9 (Ar-CH), 127.5 (Ar-CH), 128.5 (Ar-CH), 143.2 ($\text{RCH}=\text{CH}_2$), 144.5 (Ar-C), 146.3 (Ar-C).

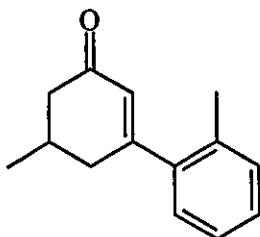
m/z (E.I.) 228 (M^+ , 5 %), 179 (30), 178 (100), 41 (84), 40 (43).

Tributyltin Hydride Reduction of 3-(2-Allylphenyl)-2,3-epoxy-5-methyl-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (241) (Inverse Addition).



A deoxygenated solution of 3-(2-allylphenyl)-2,3-epoxy-5-methyl-1-imidazol-1-yl-thio-carbonyloxy-cyclohexane (609 mg, 1.72 mmol) and azobisisobutyronitrile (71 mg, 0.43 mmol) in benzene (20 ml) was added over 4 hours to a refluxing solution of tributyltin hydride (900 mg, 3.1 mmol) in benzene (20 ml). After a further 30 minutes the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum then ether) gave 4a-hydroxy-3-methyl-1, 2, 3, 4-tetrahydro-9-vinylfluorene (**247a-d**) as a mixture of 4 diastereomers (140 mg, 36 %). Further chromatography gave the major diastereomer as a colourless oil (98 mg, 25 %). The spectroscopic data for this compound were identical to the previously prepared material.

Preparation of 3-(2-Methylphenyl)-5-methyl-2-cyclohexen-1-one (254).



2-Bromotoluene (7.72 g, 45.15 mmol) was added dropwise to a stirred mixture of magnesium (1.44 g, 60 mmol), iodine (1 crystal) and dry THF (100 ml) under nitrogen. After formation of the Grignard reagent the solution was stirred for 30 minutes and then 3-ethoxy-5-methyl-2-cyclohexen-1-one (5.355 g, 34.73 mmol) was added. The solution was stirred for a further 2 hours at room temperature after which hydrochloric acid (5 M, 50 ml) was added and the mixture was extracted with ether (3 x 50 ml). The combined organic fractions were washed with saturated brine (200 ml) dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear, pale yellow oil (6.250 g, 90 %).

Found M^+ , 200.1202. $C_{14}H_{16}O$ requires m/z 200.1201.

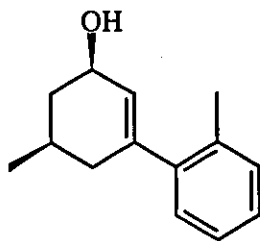
$\nu_{\max}/\text{cm}^{-1}$ (neat) 2956, 1667, 1619, 1456, 1365, 1295, 1274, 1243, 913, 757.

δ_{H} (400 MHz; CDCl_3) 1.14 (3 H, d J 6.5, 5- CH_3), 2.19 (1 H, dd, J 13, 16, 4-CH), 2.30 (3 H, s, Ar- CH_3), 2.38 (2 H, m, 5-CH, 6-CH), 2.58 (2 H, m, 4-CH, 6-CH), 5.98 (1 H, s, 2-CH), 7.13 (1 H, m, Ar-H), 7.26 (3 H, m, Ar-H).

δ_{C} (100 MHz; CDCl_3) 19.8 (Ar- CH_3), 20.9 (5- CH_3), 30.4 (5-CH), 39.3 (4- CH_2 or 6- CH_2), 45.3 (4- CH_2 or 6- CH_2), 125.8 (Ar-CH), 126.7 (Ar-CH), 128.0 (2-CH), 128.1 (Ar-CH), 130.5 (Ar-CH), 133.6 (Ar-C), 140.5 (Ar-C), 162.4 (3-C), 199.0 (1-C=O).

m/z (E.I.) 200 (M^+ , 73 %), 185 (18), 158 (29), 143 (11), 130 (100), 115 (45), 91 (7), 77 (7), 69 (9), 51 (8), 39 (13).

Preparation of 3-(2-Methylphenyl)-5-methyl-2-cyclohexen-1-ol (255).



Sodium borohydride (1.32 g, 35 mmol) was added portionwise to a stirred solution of 3-(2-methylphenyl)-5-methyl-2-cyclohexen-1-one (6.15 g, 30.75 mmol) and cerium (III) chloride heptahydrate (13.04 g, 35 mmol) in methanol (100 ml) at 0 °C. After stirring at this temperature for 60 minutes, water (100 ml) was added and the mixture was extracted with ether (3 x 100 ml). The combined organic fractions were washed with saturated brine (200 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear, pale yellow oil (5.612 g, 90 %).

Found M^+ 202.1360. $C_{14}H_{18}O$ requires m/z 202.1358.

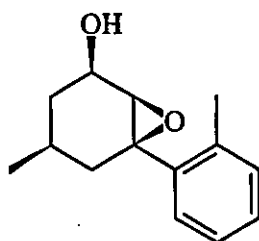
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3330 (br, OH), 3059, 3021, 2950, 2924, 2871, 1603, 1487, 1449, 1086, 1023, 964, 912, 755, 725.

δ_H (400 MHz; $CDCl_3$) 1.04 (3 H, d, J 6.5, 5- CH_3), 1.23 (1 H, m, 6-CH), 1.58 (1 H, br s, OH), 1.91 (2 H, m, 4-CH, 5-CH), 2.12 (2 H, m, 4-CH, 6-CH), 2.27 (3 H, m, Ar- CH_3), 4.45 (1 H, m, 1-CH), 5.54 (1 H, d, J 2, 2-CH), 7.05 (1 H, m, Ar-H), 7.15 (3 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 19.0 (Ar- CH_3), 21.1 (5- CH_3), 27.9 (5-CH), 38.2 (4- CH_2), 40.3 (6- CH_2), 67.6 (1-CHOH), 124.8 (Ar-CH), 126.1 (Ar-CH), 127.3 (Ar-CH), 128.7 (2-CH), 129.4 (Ar-CH), 133.9 (Ar-C), 140.0 (Ar-C), 142.0 (3-C).

m/z (E.I.) 202 (M^+ , 24 %), 187 (11), 169 (11), 160 (18), 145 (100), 128 (14), 115 (23), 105 (16), 91 (21), 77 (11), 39 (17).

Preparation of 3-(2-Methylphenyl)-2,3-epoxy-5-methylcyclohexan-1-ol (256).



m-chloroperbenzoic acid (12.08 g, 50 %, 35 mmol) was added in one portion to a stirred solution of 3-(2-methylphenyl)-5-methyl-2-cyclohexen-1-ol (6.014 g, 29.8 mmol) and sodium carbonate (4.24 g, 40 mmol) in DCM (150 ml) at 0°C. After stirring for 90 minutes at this temperature the solution was washed with sodium sulfite solution (2 x 100 ml), saturated sodium bicarbonate (100 ml) and saturated brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a colourless oil (5.01 g, 77 %).

Found M^+ , 218.1306. $C_{14}H_{18}O_2$ requires m/z 218.1307.

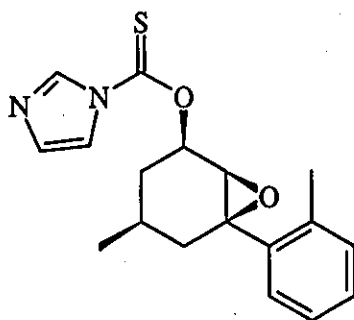
$\nu_{\max}/\text{cm}^{-1}$ (neat) 3383, 2958, 2936, 2870, 1727, 1602, 1490, 1452, 1418, 1260, 1086, 1033, 759, 727, 649.

δ_H (400 MHz; $CDCl_3$) 0.93 (3 H, d, J 6, 5- CH_3), 1.26 (1 H, q, J 11.5, 6-CH), 1.67 (1 H, m, 4-CH), 1.75 (3 H, m, 5-CH, 6-CH, 1-OH), 1.93 (1 H, m, 6-CH), 2.32 (3 H, s, Ar- CH_3), 3.24 (1 H, s, 2-CH), 4.16 (1 H, m, 1-CH), 7.15 (3 H, m, Ar-H), 7.31 (1 H, m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 19.3 (Ar- CH_3), 21.4 (5- CH_3), 28.5 (5-CH), 35.7 (6- CH_2), 37.7 (4- CH_2), 63.2 (2-CH), 64.8 (3-C), 69.2 (1-CHOH), 125.8 (Ar-CH), 125.9 (Ar-CH), 127.5 (Ar-CH), 129.9 (Ar-CH), 134.4 (Ar-C), 140.7 (Ar-C).

m/z (E.I.) 218 (M^+ , 9 %), 203 (23), 200 (13), 161 (49), 145 (29), 135 (61), 119 (100), 105 (31), 91 (55), 84 (97).

Preparation of 3-(2-Methylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-5-methyl-cyclohexane (257).



A solution of 3-(2-methylphenyl)-2,3-epoxy-5-methyl-cyclohexan-1-ol (3.05 g, 14.0 mmol) and 1,1'-thiocarbonyldiimidazole (3.56 g, 20 mmol) in DCM (60 ml) was stirred at gentle reflux for 2 hours. The solution was then allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave the *title compound* as a colourless amorphous solid (4.25 g, 93 %). A sample of this was recrystallised from ether to give colourless crystallites (m.p. 88.6 - 90.4 °C).

Found C, 65.8; H, 5.7; N, 8.4. $C_{18}H_{20}O_2N_2S$ requires C, 65.8; H, 6.1; N, 8.5 %.

Found M^+ 328.1245. $C_{18}H_{20}O_2N_2S$ requires m/z , 328.1245.

ν_{max}/cm^{-1} (KBr disk) 3141, 2959, 2871, 1471, 1393, 1320, 1287, 1107, 983, 875, 762, 725, 654.

δ_H (400 MHz; $CDCl_3$) 1.00 (3 H, d, J 6.5, 5- CH_3), 1.67 (1 H, q, J 11.5, 6-CH), 1.78 (1 H, dd, J 11.5, 14.5, 4-CH), 1.89 (1 H, m, 5-CH), 1.95 (1 H, m, 6-CH), 2.08 (1 H, ddd, J 5.5, 1.5, 14.5, 4-CH), 2.38 (3 H, s, Ar- CH_3), 3.47 (1 H, s, 2-CH), 6.10 (1 H, ddd, J 1.5, 5.5, 11, 1-CH), 7.02 (1 H, s, Im-CH), 7.16 (3 H, m, Ar-CH), 7.32 (1 H, m, Ar-CH), 7.66 (1 H, s, Im-CH), 8.39 (1 H, s, Im-CH).

δ_C (100 MHz; $CDCl_3$) 19.3 (Ar- CH_3), 21.3 (5- CH_3), 28.3 (5-CH), 30.8 (6- CH_2), 37.4 (4- CH_2), 59.0 (2-CH), 64.4 (3-C), 81.1 (1-CH), 117.9 (Im-CH), 125.9 (Ar-CH), 126.0 (Ar-CH), 127.9 (Ar-CH), 130.1 (Ar-CH), 130.9 (Im-CH), 134.4 (Ar-C), 137.1 (Im-CH), 139.7 (Ar-C), 183.7 (C=S).

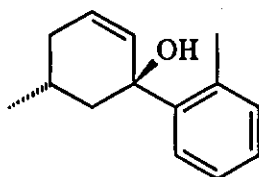
m/z (E.I.) 329 (MH^+ , 4 %), 328 (M^+ , 3 %), 201 (100), 128 (40), 119 (85), 105 (72), 91 (74), 68 (81), 50 (72), 39 (52).

See Appendix A for stereochemical assignment

Tributyltin Hydride Reduction of 3-(2-Methylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (257) (Normal Addition).

A deoxygenated solution of tributyltin hydride (2.62 g, 9 mmol) and azobisisobutyronitrile (80 mg, 0.5 mmol) in benzene (25 ml) was added over 4 hours to a refluxing solution of 3-(2-methylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (2.0 g, 6.1 mmol) in benzene (25 ml). After a further 30 minutes the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ethyl acetate 9:1) gave (least to most polar) *trans*-3-hydroxy-5-methyl-3(2-methylphenyl)cyclohex-1-ene (259b) as colourless crystals (260 mg, 21 %), *trans*-4a-hydroxy-3-methyl-1, 2, 3, 4-tetrahydrofluorene (258b) as colourless crystals (168 mg, 14 %) and *cis*-4a-hydroxy-3-methyl-1, 2, 3, 4-tetrahydrofluorene (258a) as a colourless amorphous solid (225 mg, 14 %). Samples of the first two products were recrystallised from hexane for characterisation.

***trans*-3-Hydroxy-5-methyl-3(2-methylphenyl)cyclohex-1-ene (259b).**



m.p. 119.2 - 119.8 °C (from hexane).

Found C, 83.3; H, 9.0. C₁₄H₁₈O requires C, 83.1; H, 9.0 %.

Found M⁺ 202.1360. C₁₄H₁₈O requires *m/z* 202.1358.

$\nu_{\max}/\text{cm}^{-1}$ (KBr disc) 3299, 3016, 2961, 2911, 1484, 1452, 1380, 1207, 1097, 1020, 969, 924, 856, 775, 756, 730, 712, 675.

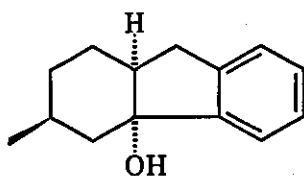
δ_{H} (400 MHz; CDCl₃) 0.88 (3 H, d, *J* 6.5, 5-CH₃), 1.50 (1 H, m, 5-CH), 1.57 (1 H, t, *J* 12.5, 6-CH), 1.73 (1 H, ddt, *J* 18, 10, 2.5, 4-CH), 2.13 (1 H, dtt, *J* 18, 5, 1.5, 4-CH), 2.36 (1 H, dq, *J* 11.5, 1.5, 6-CH), 2.64 (3 H, s, Ar-CH₃), 5.71 (1 H, ddt, *J* 10, 2.5, 1.5, 2-CH), 5.99 (1 H, ddd, *J* 2.5, 5, 10, 3-CH), 7.09 (1 H, m, Ar-H), 7.18 (2 H, m, Ar-H), 7.34 (1 H, dd, *J* 7.5, 1.5, Ar-H).

δ_{C} (100 MHz; CDCl₃) 21.79 (Ar-CH₃), 21.84 (4-CH₃), 26.4 (4-CH), 33.9 (5-CH₂), 45.2 (3-CH₂), 76.4 (2-C), 124.6 (Ar-CH), 127.2 (Ar-CH), 128.3 (6-CH), 128.6 (Ar-CH), 132.8 (Ar-CH), 133.5 (7-CH), 136.8 (Ar-C), 143.0 (Ar-C).

m/z (E.I.) 202 (M^+ , 62 %), 185 (24), 160 (36), 145 (100), 119 (27), 111 (32), 100 (32), 92 (42), 91 (44), 39 (24).

See Appendix A for stereochemical assignment.

trans-4a-Hydroxy-3-methyl-1, 2, 3, 4-tetrahydrofluorene (258b).



m.p. 88.0 - 88.6 °C (from hexane).

Found C, 83.1; H, 9.1. $C_{14}H_{18}O$ requires C, 83.1; H, 9.0 %.

Found M^+ 202.1362. $C_{14}H_{18}O$ requires m/z 202.1358.

ν_{max}/cm^{-1} (KBr disc) 3363, 3033, 2919, 2848, 1458, 1065, 1019, 969, 954, 758, 744, 666.

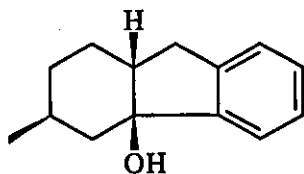
δ_H (400 MHz; $CDCl_3$) 0.87 (3 H, d, J 6.5, 3- CH_3), 1.00 (1 H, m, 4-CH), 1.07 (1 H, m, 2-CH), 1.61 (1 H, m, 2-CH), 1.75 (2 H, m, 1-CH), 3-CH), 1.83 (1 H, m, 4-CH), 1.92 (1 H, m, 1-CH), 2.28 (1 H, m, 9a-CH), 2.74 (2 H, m, 9- CH_2), 7.20 (3 H, m, Ar-H), 7.31 (1 H, m, Ar-H).

δ_c (100 MHz; $CDCl_3$) 22.3 (3- CH_3), 24.0 (1- CH_2), 27.2 (3-CH), 29.8 (2- CH_2), 33.9 (9- CH_2), 44.4 (4- CH_2), 48.3 (9a-CH), 81.1 (4a-COH), 121.4 (Ar-CH), 125.0 (Ar-CH), 126.6 (Ar-CH), 127.4 (Ar-CH), 140.2 (Ar-C), 150.8 (Ar-C).

m/z (E.I.) 202 (M^+ , 32 %), 145 (100), 132 (34).

See Appendix B for X-ray crystallographic data.

cis-4a-Hydroxy-3-methyl-1, 2, 3, 4-tetrahydrofluorene (258a).



Found M^+ 202.1362. $C_{14}H_{18}O$ requires m/z 202.1358.

ν_{max}/cm^{-1} (KBr disc) 3337, 2928, 2850, 1461, 1324, 1003, 930, 760, 728.

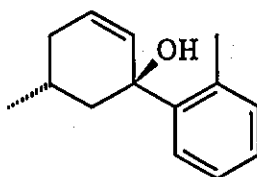
δ_H (400 MHz; $CDCl_3$) 0.82 (1 H, m, 1-CH), 0.94 (3 H, d, J 6.5, 3- CH_3), 0.95 (1 H, m, 2-CH), 1.19 (1 H, m, 3-CH), 1.47 (2 H, m, 2-CH, 4-CH), 1.82 (1 H, ddt, J 13.5, 6, 3, 1-CH),

2.21 (1 H, dt, J 12, 6, 9a-CH), 2.34 (1 H, d, J 15.5, 9-CH), 2.43 (1 H, dt, J 13.5, 2.5, 4-CH), 3.31 (1 H, dd, J 7, 14, 9-CH), 7.25 (4 H, m, Ar-H).

δ_c (100 MHz; CDCl_3) 22.3 (3- CH_3), 29.7 (3-CH), 30.9 (1- CH_2), 33.4 (2- CH_2), 36.7 (9- CH_2), 42.2. (4- CH_2), 47.2 (9a-CH), 82.6 (4a-COH), 122.0 (Ar-CH), 126.3 (Ar-CH), 126.5 (Ar-CH), 128.5 (Ar-CH), 144.5 (Ar-C), 145.3 (Ar-C).

m/z (E.I.) 202 (M^+ , 28 %), 145 (100), 132 (23).

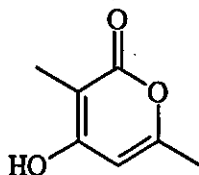
Tributyltin Hydride Reduction of 3-(2-Methylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (257) (Inverse Addition).



A deoxygenated solution of 3-(2-methylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-cyclohexane (825 mg, 2.5 mmol) in benzene (15 ml) was added over 4 hours to a refluxing, deoxygenated solution of tributyltin hydride (1.16 g, 4 mmol) and azobisisobutyronitrile (33 mg, 0.2 mmol) in benzene (15 ml). After a further 30 minutes the solution was allowed to cool and evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ether 9:1) gave *trans*-3-hydroxy-5-methyl-3(2-methylphenyl)cyclohex-1-ene as colourless crystals (300 mg, 59 %). The spectroscopic data were as for the previously prepared material.

7.5 Experimental for Chapter 5.

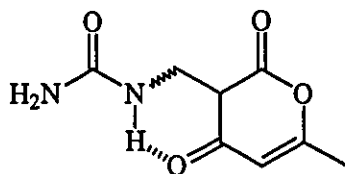
Attempted Preparation of 3,6-Dimethyl-4-hydroxy-2-pyrone (278).



A solution of tetra-*n*-butylammonium fluoride (1 M in THF, 3 ml, 3 mmol) was evaporated *in vacuo* and the resulting solid was dried under vacuum (1 mm Hg) at 80 °C for 1 hour. After cooling to room temperature under nitrogen, molecular sieves were added, followed by a solution of 4-hydroxy-6-methyl-2-pyrone (250 mg, 2 mmol) in DCM (10 ml). The resulting solution was stirred for 20 minutes after which methyl iodide was added (1.1 g, 8 mmol). After a further 24 hours the solution was filtered, washed with water (3 x 10 ml) and brine (10 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a brown solid.

¹H NMR analysis of the crude reaction mixture showed it to be a 4:1 mixture of 4-methoxy-6-methyl-2-pyrone (286) (δ 5.40, d, *J* 2, 5-CH) and 3,6-dimethyl-4-hydroxy-2-pyrone (278) (δ 6.04, s, 5-CH).^{74,75}

Preparation of (6-Methyl-2,4-dioxo-pyran-3(4H)-ylidene)methylurea (288).



Methyl orthoformate (3.65 g, 34 mmol) was added to a solution of 4-hydroxy-6-methyl-2-pyrone (3 g, 24 mmol) and urea (1.7 g, 28 mmol) in glacial acetic acid at 70 °C. After stirring for one hour at this temperature, suction filtration gave the title compound as a mixture of *cis* and *trans* isomers (pale pink crystals, 4.35 g, 93 %).⁸⁰

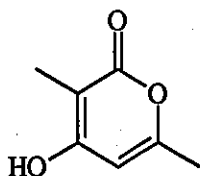
$\nu_{\max}/\text{cm}^{-1}$ (nujol) 3382, 3320, 3219, 3090, 1751, 1719, 1702, 1676, 1623, 1547, 1285, 1166, 989, 926, 918, 877, 800, 760, 660, 615.

δ_{H} (250 MHz; D₆-DMSO) 2.14 (6 H, s x 2, 6-CH₃), 5.83 (1 H, s, 5-CH), 5.85 (1 H, s, 5-CH), 6.44 (1 H, br d, *J* 13, R=CHNH), 7.48 (1 H, br d, *J* 13.5, =CHNH), 7.63 (2 H, br s x 2, exchanged with D₂O, NH), 7.91 (1 H, br s, exchanged with D₂O, NH), 8.02 (1 H, br s,

exchanged with D₂O, NH), 8.63 (1 H, d, *J* 13, s after D₂O exchange, =CHNH), 8.76 (1 H, d, *J* 13.5, s after D₂O exchange, =CHNH).

δ_C (62.9 MHz, D₆-DMSO) 24.7(6-CH₃), 24.9 (6-CH₃), 104.6 (6-C), 112.2 (5-CH), 112.6 (5-CH), 157.0 (=CHNH), 157.9(=CHNH), 158.7 (C=O), 168.5 (C=O), 170.5 (C=O), 171.2 (C=O), 185.3 (4-C=O), 188.2 (4-C=O).

Preparation of 3,6-dimethyl-4-hydroxy-2-pyrone (278).



A solution of borane methylamine complex (1.15 g, 19.5 mmol) in glacial acetic acid (35 ml) was added dropwise to a suspension of (6-methyl-2,4-dioxo-pyran-3-(4H)-ylidene)methylurea in glacial acetic acid (40 ml). The resulting solution was heated to reflux for 1 hour after which the solvent was evaporated *in vacuo*. After the addition of water (50 ml) the title compound was collected by suction filtration as colourless crystals (1.97 g, 92 %).m.p. 207-209°C; lit. 209-213°C.^{79,80}

δ_H (250 MHz; D₆-DMSO) 1.72 (3 H, s, 3-CH₃), 2.12 (3 H, s, 6-CH₃), 5.97 (1 H, s, 5-CH).

δ_C (62.9 MHz; D₆-DMSO) 13.4 (3-CH₃), 24.3 (6-CH₃), 101.4 (3-C), 104.9 (5-CH), 164.4 (4 =COH), 170.3 (2-C=O).

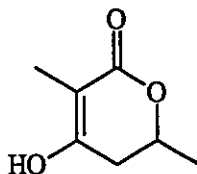
Attempted Robinson Annulation of 3,6-Dimethyl-4-hydroxy-2-pyrone (278) Using Pyridine as a Base.

A solution of methylvinylketone (200 mg, 2.8 mmol) in pyridine (5 ml) was added over 2 hours *via* a syringe pump to a refluxing solution of 3,6-dimethyl-4-hydroxy-2-pyrone (200 mg, 1.4 mmol) in dry pyridine (10 ml) under nitrogen. After stirring for 24 hours at this temperature the solvent was evaporated *in vacuo* to give a brown solid. ¹H NMR analysis of this material showed it to be a mixture of the title compound and polymeric material.

Attempted Robinson Annulation of 3,6-Dimethyl-4-hydroxy-2-pyrone (278) Using Sodium Hydride as a Base.

A solution of 3,6-dimethyl-4-hydroxy-2-pyrone (200 mg, 1.4 mmol) in dry DMF (5 ml) was added dropwise to a suspension of sodium hydride (80 mg, 2 mmol) in DMF (5 ml) under nitrogen at 0 °C. After 10 mins methylvinylketone (200 mg, 2.8 mmol) in DMF (5 ml) was added over 2 hours *via* a syringe pump. The solution was allowed to warm to room temperature and stirred for a further 24 hours after which, water (20 ml) was added. The mixture was then extracted with ethyl acetate (4 x 20 ml) and the combined organic fractions were washed with water (3 x 80 ml) and brine (80 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a brown oil. ¹H NMR analysis of this brown oil showed it to be a complex polymeric mixture.

Preparation of 5,6-Dihydro-3,6-dimethyl-4-hydroxy-2-pyrone (290).

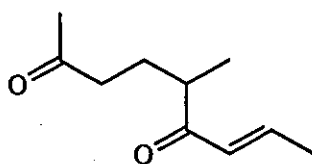


A solution of 3,6-dimethyl-4-hydroxy-2-pyrone (1.02g, 7.3 mmol) in methanol was stirred under an atmosphere of hydrogen at 60 p.s.i. for 3 days. After filtration through celite the solvent was removed *in vacuo* to give the title compound as a colourless amorphous solid (930 mg, 90 %).^{74,81}

δ_{H} (250 MHz; D₆-DMSO) 1.31 (3 H, d, 6-CH₃), 1.61 (3 H, d, 3-CH₃), 2.51 (2 H, d, 5-CH₂), 4.38 (1 H, q, 6-CH).

δ_{C} (62.9 MHz; D₆-DMSO) 8.6 (6-CH₃), 20.3 (3-CH₃), 34.4 (5-CH₂), 70.4 (6-CH), 96.9 (3-C), 165.4 (4=C-OH), 168.3 (2-C=O).

Attempted Robinson Annulation of 5,6-Dihydro-3,6-dimethyl-4-hydroxy-2-pyrone (290).



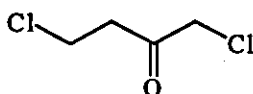
A solution of 5,6-dihydro-3,6-dimethyl-4-hydroxy-2-pyrone (0.95 g, 6.7 mmol) in THF (40 ml) and dimethylformamide (10ml) was added dropwise to a suspension of sodium hydride (0.27 g, 6.7 mmol) in THF under nitrogen at room temperature. The resulting solution was cooled to 0°C and methylvinylketone (0.71 g, 10 mmol) was added over two hours via a syringe pump. After stirring for a further 3 hours the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate(20 ml). This solution was washed with water (2 x 20 ml) and saturated brine (20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a brown oil. Purification by flash chromatography (eluant light petroleum/ether 1:1) gave 5-methyl-non-2-ene-4,8-dione as a clear and colourless oil (360 mg, 32 %).

$\nu_{\max}/\text{cm}^{-1}$ (neat) 3498, 2968, 2935, 2876, 1716, 1693, 1666, 1628, 1458, 1376, 1287, 1167, 1058, 972, 946.

δ_{H} (250 MHz; CDCl_3) 1.11 (3 H, d, J 6, 5-Me), 1.65 (1 H, m, 6-CH), 1.90 (3 H, dd, 1- CH_3), 1.95 (1 H, m, 6-CH), 2.12 (3 H, s, 9- CH_3), 2.41 (2 H, m, 7- CH_2), 2.79 (1 H, m, 5-CH), 6.19 (1 H, dq, J 15.5, 1.5, 3-CH), 6.92 (1 H, dq, J 15.5, 7, 2-CH).

δ_{C} (250 MHz; CDCl_3) 16.6 (5- CH_3), 18.2 (1- CH_3), 26.5 (8- CH_2), 29.8 (9- CH_3), 40.8 (7- CH_2), 42.5 (5-CH), 130.3 (3-CH), 142.9 (2-CH), 203.0 (4-C=O), 208.3 (8-C=O).

Preparation of 1,4-Dichlorobutan-2-one (295).



A solution of diazald (9.3 g, 43 mmol) in ether (100 ml) was added dropwise *via* an addition funnel to a solution of potassium hydroxide (2.6 g, 46 mmol) in 2-(2-ethoxyethoxy)-ethanol (12 ml) and water (12 ml) at 50 °C. The ethereal diazomethane evolved in this reaction was condensed with a dry ice trap into a solution of 3-chloropropionyl chloride (2 g, 15.7 mmol) in ether (40 ml) at -78 °C. After the addition of diazomethane was complete the solution was allowed to warm to room temperature over

two hours, after which it was cooled to $-20\text{ }^{\circ}\text{C}$ and a solution of ethereal hydrogen chloride (4 M, 20 ml) was added. After again allowing the solution to warm to room temperature, acetic acid (5 ml) was added and the solution was washed with water (40 ml), saturated sodium bicarbonate solution (40 ml) and brine (40 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the title compound as a pale yellow oil. (1.51 g, 68 %).⁸⁴
 δ_{H} (250 MHz; CDCl_3) 3.11 (2 H, t, J 7, 3- CH_2), 3.76 (2 H, t, J 7, 4- CH_2), 4.12 (2 H, s, 1- CH_2Cl).

Attempted Robinson Annulation of 3,6-Dimethyl-4-hydroxy-2-pyrone (290) using 1, 4-dichlorobutan-2-one (295).

A solution of 3,6-dimethyl-4-hydroxy-2-pyrone (100 mg, 0.7 mmol) in dry DMF (3 ml) was added dropwise to a suspension of sodium hydride (56 mg, 1.4 mmol) in DMF (3 ml) under nitrogen at $0\text{ }^{\circ}\text{C}$. After 20 mins 1,4-dichlorobutan-2-one (100 mg, 0.7 mmol) in DMF (4 ml) was added over 2 hours *via* a syringe pump. The solution was allowed to warm to room temperature and stirred for a further 24 hours after which, water (10 ml) was added. The mixture was extracted with ethyl acetate (3 x 10 ml) and the combined organic fractions were washed with water (2 x 20 ml) and brine (50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a brown oil. ^1H NMR analysis of this oil showed it to be a complex mixture of products.

7.6 Experimental for Chapter 6.

Attempted Coupling of 1-Methylcyclohexanecarboxylic Acid (311) and Wang Resin (306).

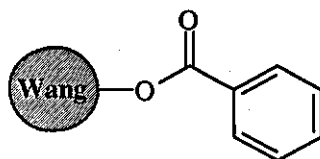
Diisopropylcarbodiimide (169 mg, 1.32 mmol) was added to a stirred suspension of Wang resin (200 mg, 0.132 mmol) and 1-methylcyclohexanecarboxylic acid (94 mg, 0.66 mmol) in DCM (5 ml) under nitrogen. After stirring at room temperature for 2 hours the resin was collected by suction filtration, washed with DMF (3 x 10 ml), DMF/H₂O (1:1, 3 x 10 ml), THF (3 x 10 ml) and DCM (3 x 10 ml). The resin was then redissolved in DCM (5 ml) and 1-methylcyclohexanecarboxylic acid (94 mg, 0.66 mmol) and diisopropylcarbodiimide (169 mg, 1.32 mmol) were again added. After stirring overnight at room temperature under nitrogen, the resin was again filtered off and washed as above. IR analysis of the resin was identical to that of the starting resin and no carbonyl band was seen.

$\nu_{\max}/\text{cm}^{-1}$ 3448 (m), 3024 (s), 2918 (s), 1944 (w), 1870 (w), 1802 (w), 1601 (s), 1583 (m), 1510 (s), 1492 (s), 1451 (s), 1374 (w), 1302 (w, broad), 1220 (m), 1170 (m), 1120 (m), 1027 (m), 906 (w), 873 (m), 821 (m), 755 (s), 694 (s).

Attempted Coupling of Benzoic Acid (313) and Wang Resin (306).

Diisopropylcarbodiimide (169 mg, 1.32 mmol) was added to a stirred suspension of Wang resin (200 mg, 0.132 mmol) and benzoic acid (161 mg, 1.32 mmol) in DCM (5 ml) under nitrogen. After stirring at room temperature overnight, the resin was collected by suction filtration and washed with DMF (3 x 10 ml), DMF/H₂O (1:1, 3 x 10 ml), THF (3 x 10 ml) and DCM (3 x 10 ml). IR analysis of the resin was identical to that of the starting resin and no carbonyl band was seen.

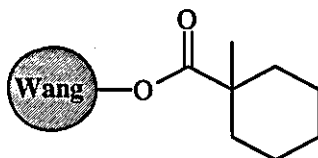
Preparation of Wang Bezoate (314).



Benzoyl chloride (153 μl , 1.32 mmol) was added dropwise to a stirred suspension of Wang resin (200 mg, 0.132 mmol), DMAP (161 mg, 1.32 mmol) and triethylamine (181 μL , 2.5 mmol) in DCM (5 ml) under nitrogen. After stirring at room temperature overnight, the resin was collected by suction filtration and washed with DMF (3 x 10 ml), DMF-H₂O (1:1, 3 x 10 ml), THF (3 x 10 ml) and DCM (3 x 10 ml). IR analysis of the resin confirmed that the desired esterification had taken place.

$\nu_{\text{max}}/\text{cm}^{-1}$ 3422 (w, broad), 3025 (s), 2920 (s), 2848 (s), 1944 (w), 1871 (w), 1803 (w), 1718 (s), 1679 (s), 1601 (m), 1512 (m), 1490 (s), 1451 (s), 1376 (m, broad), 1313 (w), 1268 (s, broad), 1173 (m), 1095 (m), 1068 (m), 1026 (m), 906 (w), 824 (w), 757 (s, broad), 696 (s, broad).

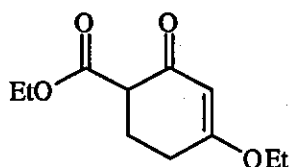
Coupling Reaction of 1-Methylcyclohexanecarbonyl Chloride (315) and Wang Resin (306).



Oxalyl chloride (0.6 ml, 1.32 mmol) was added dropwise to a stirred solution of 1-methylcyclohexane carboxylic acid in DCM at 0 °C under nitrogen. DMF (1 drop) was then added and the solution was stirred at 0 °C for 1 hour. This solution was then transferred *via* a syringe to a flask containing Wang resin (200 mg, 0.132 mmol), DMAP (161 mg, 1.32 mmol) and triethylamine (181 μL , 2.5 mmol) in DCM (5 ml) under nitrogen. After stirring at room temperature overnight, the resin was collected by suction filtration and washed with DMF (3 x 10 ml), DMF-H₂O (1:1, 3 x 10 ml), THF (3 x 10 ml) and DCM (3 x 10 ml). IR analysis of the resin confirmed that the desired esterification had taken place.

$\nu_{\text{max}}/\text{cm}^{-1}$ 3432 (w, broad), 3024 (s), 2920 (s), 2848 (s), 1943 (w), 1871 (w), 1802 (w), 1724 (m), 1648 (w), 1601 (m), 1511 (m), 1492 (s), 1451 (s), 1373 (m, broad), 1307 (w), 1203 (m, broad), 1155 (m), 1130 (m), 1027 (m, broad), 906 (w), 823 (w), 757 (s, broad), 696 (s, broad).

Preparation of ethyl-6-carboxylate-3-ethoxy-2-cyclohexen-1-one (316).



n-Butyllithium (19 ml, 30 mmol, 1.6 M soln. in hexanes) was added dropwise to a stirred solution of diisopropylamine (4.21 ml, 30 mmol) in dry THF (50 ml) at 0°C under nitrogen. After stirring for 20 minutes the solution was cooled to -78 °C and 3-ethoxy-2-cyclohexen-1-one (3.5 g, 25 mmol) was added. After 10 minutes at this temperature DMPU (3.6 ml, 30 mmol) was added followed, after a further ten minutes by ethyl chloroformate (2.87 g, 30 mmol). The solution was then allowed to warm to room temperature and after stirring for 2 hours, water (50 ml) and ether (50 ml) were added. The aqueous fraction was extracted with ether (2 x 50 ml) and the combined organic fractions were washed with brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a dark orange oil. After standing at 0 °C overnight the *title compound* crystallised and was separated from the supernatant oil. Recrystallisation from ether gave colourless crystals (2.94 g, 55 %); m.p. 97.7 - 98.6 °C.

Found C, 62.6; H, 7.5. C₁₁H₁₆O₄ requires C, 62.3; H, 7.6.

Found M⁺, 212.1051. C₁₁H₁₆O₄ requires *m/z* 212.1049.

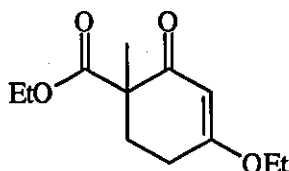
$\nu_{\max}/\text{cm}^{-1}$ (KBr disk) 3065, 2984, 1730, 1650, 1605, 1458, 1373, 1310, 1253, 1203, 1027, 918, 875, 815, 628.

δ_{H} (400 MHz; CDCl₃) 1.28 (3 H, t, *J* 7, CO₂CH₂CH₃), 1.37 (3 H, t, *J* 7, ROCH₂CH₃), 2.08 (1 H, m, 5-CH), 2.26 (1 H, m, 5-CH), 2.37 (1 H, m, 4-CH), 2.49 (1 H, m, 4-CH), 3.24 (1 H, dd, *J* 5, 9, 6-CH), 3.93 (2 H, dq, *J* 2, 7, OCH₂CH₃), 4.21 (2 H, q, *J* 7, CO₂CH₂CH₃), 5.38 (1 H, s, 2-CH).

δ_{C} (100 MHz; CDCl₃) 14.5 (ROCH₂CH₃), 14.6 (CO₂CH₂CH₃), 24.6 (5-CH₂), 27.8 (4-CH₂), 52.7 (6-CH), 61.6 (RCO₂CH₂CH₃), 64.9 (ROCH₂CH₃), 102.5 (2-CH), 170.8 (RCO₂Et), 178.0 (3-C), 194.2 (1-C=O).

m/z (E.I.) 213 (MH⁺, 100 %), 212 (M⁺, 43), 167 (26), 134 (39), 112 (57), 84 (66), 69 (61), 67 (59), 55 (34), 43 (30), 29 (47).

Preparation of ethyl-6-carboxylate-3-ethoxy-6-methyl-2-cyclohexen-1-one (317).



A solution of tetrabutylammonium fluoride in THF (1 M, 29 ml, 29 mmol) was evaporated *in vacuo*, and then dried thoroughly at 80 °C under vacuum. After cooling to room temperature under nitrogen a solution of ethyl-6-carboxylate-3-ethoxy-2-cyclohexen-1-one (5 g, 23.6 mmol) in THF (100 ml) was added. After dissolution of the fluoride in an ultrasonic bath the solution was stirred for 20 minutes and methyl iodide (4.25 g, 30 mmol) was added. After a further 4 hours water (100 ml) and ether (100 ml) were added. The aqueous fraction was extracted with ether (2 x 50 ml) and the combined organic fractions were washed with water (2 x 100 ml) and brine, dried over magnesium sulfate, and evaporated *in vacuo* to give an orange oil. Flash chromatography (eluant light petroleum/ethyl acetate 4:1) gave the *title compound* as a pale yellow oil (4.63 g, 87 %).

Found M^+ , 226.1206. $C_{12}H_{18}O_4$ requires m/z 226.1205.

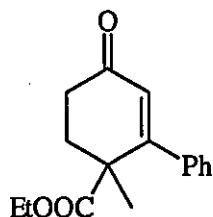
ν_{max}/cm^{-1} (neat) 2983, 2939, 1730, 1660, 1609, 1449, 1380, 1256, 1195, 1108, 1024, 902, 862, 819.

δ_H (400 MHz; $CDCl_3$) 1.26 (3 H, t, J 7, $CO_2CH_2CH_3$), 1.36 (3 H, t, J 7, $ROCH_2CH_3$), 1.39 (3 H, s, 6- CH_3), 1.86 (1 H, m, 5-CH), 2.37 (1 H, dt, J 17, 5, 4-CH), 2.47 (1 H, dt, J 13.5, 5, 5-CH), 2.56 (1 H, m, 4-CH), 3.91 (2 H, dq, J 2, 7, $ROCH_2CH_3$), 4.16 (2 H, q, J 7, $CO_2CH_2CH_3$), 5.36 (1 H, s, 2-CH).

δ_C (100 MHz; $CDCl_3$) 14.1 ($ROCH_2CH_3$, $CO_2CH_2CH_3$), 20.5 (6- CH_3), 26.5 (4- CH_2), 31.7 (5- CH_2), 52.3 (6-C), 61.2 ($RCO_2CH_2CH_3$), 64.6 ($ROCH_2CH_3$), 101.5 (2-CH), 172.8 (RCO_2Et), 177.0 (3-C), 197.3 (1-C=O).

m/z (E.I.) 213 (MH^+ , 100 %), 212 (M^+ , 43), 167 (26), 134 (39), 112 (57), 84 (66), 69 (61), 67 (59), 55 (34), 43 (30), 29 (47).

Preparation of ethyl-4-carboxylate-4-methyl-3-phenyl-2-cyclohexen-1-one (318).



A solution of phenyllithium (8 ml, 1.8 M, 14.4 mmol) was added dropwise to a stirred solution of ethyl-6-carboxylate-3-ethoxy-6-methyl-2-cyclohexen-1-one (2 g, 8.9 mmol) in THF (40 ml) at -78°C . The solution was then allowed to warm to room temperature and after stirring for a further 2 hours the reaction was quenched with water (10 ml) and hydrochloric acid (2 M, 10 ml) was added. The solution was extracted with ether (3 x 30 ml) and the combined organic fractions were washed with water (100 ml) and brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a brown oil. Flash chromatography (eluant ethyl acetate, light petroleum 15:85) gave the title compound as a yellow oil (1.26 g, 55 %).

Found M^+ , 258.1257. $\text{C}_{16}\text{H}_{18}\text{O}_3$ requires m/z 258.1256.

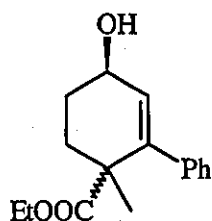
$\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2981, 2938, 1727, 1676, 1254, 1183, 1105, 1021, 765, 700.

δ_{H} (400 MHz; CDCl_3) 1.14 (3 H, t, J 7, $\text{RCO}_2\text{CH}_2\text{CH}_3$), 2.02 (3 H, s, 4- CH_3), 2.12 (1 H, m, 5-CH), 2.55 (3 H, m, 6- CH_2 , 5-CH), 4.16 (2 H, q, J 7, $\text{RCO}_2\text{CH}_2\text{CH}_3$), 6.20 (1 H, s, 2-CH), 7.28 (2 H, m, Ar-H), 7.35 (3 H, m, Ar-H).

δ_{C} (100 MHz; CDCl_3) 13.7 ($\text{RCO}_2\text{CH}_2\text{CH}_3$), 23.7 (4- CH_3), 33.8 (6- CH_2), 36.2 (5- CH_2), 46.7 (4-C), 61.2 ($\text{RCO}_2\text{CH}_2\text{CH}_3$), 126.7 (*m*-Ph-CH x 2), 128.2 (*o*-Ph-CH x 2), 128.5 (*p*-Ph-CH), 138.4 (Ar-C), 162.2 (3-C), 174.1 ($\text{RCO}_2\text{CH}_2\text{CH}_3$), 197.9 (1-C=O).

m/z (E.I.) 258 (M^+ , 20 %), 230 (27), 185 (31), 157 (41), 129 (33), 115 (27), 91 (25), 55 (33), 29 (100).

Preparation of *ethyl-4-carboxylate-4-methyl--3-phenyl-2-cyclohexen-1-ol* (319).



Sodium borohydride (265 mg, 7 mmol) was added portionwise to a stirred solution of ethyl-4-carboxylate-3-phenyl-4-methyl-2-cyclohexen-1-one (1.47 g, 5.7 mmol) and cerium (III) chloride heptahydrate (2.61 g, 7 mmol) in methanol (20 ml) at 0 °C. After 1 hour at this temperature water (50 ml) was added and the solution was extracted with ether (3 x 30 ml). The combined organic fractions were washed with water (100 ml) and brine (100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a 2:1 mixture of diastereomers (1.47 g, 99 %).

Found M^+ , 260.1413. $C_{16}H_{20}O_3$ requires m/z 260.1412.

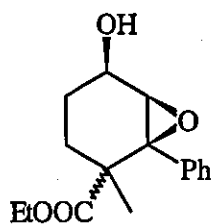
ν_{max}/cm^{-1} (neat) 3429, 2979, 2937, 2870, 1724, 1453, 1263, 1190, 764, 701.

δ_H (400 MHz; $CDCl_3$) 1.23 (m, 4- CH_3 (maj)), OCH_2CH_3 , (min + maj)), 1.29 (s, 4- CH_3 (min)), 1.67 (m, 5-CH (maj)), 1.82 (m, 6-CH (maj), 5-CH (min), 6-CH (min)), 2.05 (m, 6-CH (maj), 5-CH (min), 6-CH (min)), 2.15 (m, 5-CH (maj)), 4.17 (m, OCH_2CH_3 , (min + maj)), 4.34 (m, 1-CH (maj)), 4.40 (m, 1-CH (min)), 5.92 (m, 2-CH (min + maj)), 7.17 (m, Ar-H), 7.26 (m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 16.8 (OCH_2CH_3 (min + maj)), 26.7 (4- CH_3 (min)), 27.0 (4- CH_3 (maj)), 30.8 (6- CH_2 (min)), 31.4 (6- CH_2 (maj)), 35.7 (5- CH_2 (min)), 37.5 (5- CH_2 (maj)), 48.9 (4-C (maj)), 49.2 (4-C (min)), 63.7 (OCH_2CH_3 (min)), 63.9 (OCH_2CH_3 (maj)), 67.7 (1-CH (min)), 69.3 (1-CH (maj)), 129.9 (Ar-CH), 130.7 (Ar-CH), 133.3 (2-CH (min)), 134.8 (2-CH (maj)), 143.6 (3-C or Ar-C (min + maj)), 145.5 (3-C or Ar-C (maj)), 146.4 (3-C or Ar-C (min)), 179.0 ($RCO_2CH_2CH_3$ (min)), 179.4 ($RCO_2CH_2CH_3$ (maj)).

m/z (E.I.) 260 (M^+ , 5 %), 186 (20), 146 (100).

Preparation of ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (320).



m-chloroperbenzoic acid (3.45 g, 10 mmol) was added in one portion to a stirred solution of ethyl-4-carboxylate-4-methyl-3-phenyl-2-cyclohexen-1-ol (2.19 g, 7.92 mmol) and sodium bicarbonate (840 mg, 10 mmol) in DCM (40 ml) at 0 °C. After 1 hour at this temperature the solution was washed with saturated sodium sulfite (40 ml), saturated sodium bicarbonate (3x 40 ml) and saturated brine (40 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (eluant light petroleum/ethyl acetate 4:1) gave the *title compound* as a pale yellow oil (1.14 g, 52 %).

Found M^+ , 276.1363. $C_{16}H_{20}O_4$ requires m/z 276.1359.

$\nu_{\max}/\text{cm}^{-1}$ (neat) 3432, 2980, 1730, 1448, 1262, 1194, 1078, 960, 762, 703.

δ_H (400 MHz; $CDCl_3$) 1.09 (s, 4- CH_3 (maj)), 1.12 (t, J 7, OCH_2CH_3 (min)), 1.25 (m, 5-CH (maj)), 1.30 (t, J 7, OCH_2CH_3 (maj)), 1.32 (s, 4- CH_3 (min)), 1.58 (m, 6-CH, (min)), 1.72 (m, 5- CH_2 (min), 6-CH (maj)), 1.80 (m, 6-CH (maj)), 1.92 (m, 6-CH (min)), 2.26 (ddd, J 14, 7.5, 3, 5-CH (maj)), 3.29 (d, J 2.5, 2-CH (maj)), 3.51 (d, J 3.5, 2-CH (min)), 4.01 (dq, J 2.5, 7, OCH_2CH_3 , (min)), 4.19 (m, OCH_2CH_3 (maj), 1-CH (min + maj)), 7.29 (m, Ar-H), 7.39 (m, Ar-H).

δ_C (100 MHz; $CDCl_3$) 14.3 (OCH_2CH_3 , (min)), 14.6 (OCH_2CH_3 (maj)), 20.6 (4- CH_3 (min)), 24.8 (4- CH_3 (maj)), 26.6 (6- CH_2 (maj)), 27.0 (6- CH_2 (min)), 30.8 (5- CH_2 (min)), 32.1 (5- CH_2 (maj)), 45.8 (4-C (maj)), 46.8 (4-C (min)), 61.2 (OCH_2CH_3 (min)), 61.3 (OCH_2CH_3 (maj)), 63.1 (2-CH (maj)), 64.5 (2-CH (min)), 65.3 (1-CH (min)), 67.3 (1-CH (maj)), 68.4 (3-C (min)), 68.8 (3-C (maj)), 127.9 (Ar-CH x 2 (maj)), 128.1 (Ar-CH (maj) or Ar-CH x 2 (min)), 128.2 (Ar-CH (maj) or Ar-CH x 2 (min)), 128.3 (Ar-CH (min)), 128.6 (Ar-CH (maj) or Ar-CH x 2 (min)), 128.8 (Ar-CH x 2 (maj)), 138.6 (Ar-C (min)), 139.1 (Ar-C (maj)), 174.9 (RCOOEt (maj + min)).

m/z (E.I.) 277 (MH^+ , 5 %), 276 (M^+ , 3), 207 (73), 206 (45), 105 (100).

Attempted Ester Hydrolysis of Ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (320) Using LiOH/THF.

A solution of ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (109 mg, 0.4 mmol) and lithium hydroxide (33 mg, 0.8 mmol) in THF/water (10:1, 3 ml) was stirred at room temperature for 3 days. Ether (10 ml) and hydrochloric acid (2 M, 10 ml) were then added. The organic layer was separated, washed with brine (10 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. N.M.R analysis of this oil showed it to be starting material.

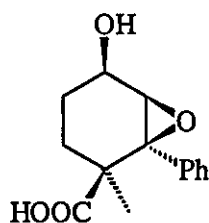
Attempted Ester Hydrolysis of Ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (320) Using Trimethylsilyl iodide.

Trimethylsilyl iodide (172 mg, 0.86 mmol) was added to a solution of ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (100 mg, 0.36 mmol) in DCM at 0 °C. After 1 hour at this temperature the solution was evaporated *in vacuo* to give a brown/purple oil. N.M.R. analysis of this oil showed it to be a complex mixture containing no epoxide protons (δ 3.0 - 3.5 ppm).

Attempted Ester Hydrolysis of Ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (320) Using Pigs Liver Esterase.

A solution of ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (100 mg, 0.4 mmol) and pigs liver esterase (12 mg, 228 units) in phosphate buffer (10 ml) and acetone (3 ml) was stirred at room temperature for 24 hours. Ethyl acetate (10 ml) and hydrochloric acid (2 M, 10 ml) were then added and the aqueous fraction was further extracted with ethyl acetate (2 x 10 ml). The combined organic fractions were washed with brine (30 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil. N.M.R analysis of this oil showed it to be starting material.

Preparation of 2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol-4-carboxylic Acid (322)
Using Potassium Hydroxide in Warm Methanol.



A solution of ethyl-4-carboxylate-2,3-epoxy-4-methyl-3-phenyl-cyclohexan-1-ol (309 mg, 1.12 mmol) and potassium hydroxide (94 mg, 1.68 mmol) in methanol (3 ml) was stirred at 50 °C for 3 days. Ethyl acetate (10 ml) and hydrochloric acid (2 M, 10 ml) were then added and the aqueous fraction was further extracted with ethyl acetate (2 x 10 ml). The combined organic fractions were washed with water (30 ml) and brine (30 ml) dried over magnesium sulfate and evaporated in vacuo to give a yellow oil. Purification by flash chromatography (eluant light petroleum/ethyl acetate 1:1) followed by crystallisation (from CDCl_3), gave the *title compound* as colourless crystals (60 mg, 25 %).

$\nu_{\text{max}}/\text{cm}^{-1}$ (KBr Disk) 3341, 2960, 1694, 1462, 1384, 1284, 1205, 1078, 1047, 1031, 1025, 960, 865, 777, 714.

Found M^+ , 248.10485. $\text{C}_{14}\text{H}_{16}\text{O}_4$ requires m/z 248.10486.

δ_{H} (400 MHz; CDCl_3) 1.06 (3 H, s, 4- CH_3), 1.32 (1 H, m, 5-CH), 1.70 (2 H, m, 6- CH_2), 2.22 (1 H, dt, J 13.5, 4.5, 5-CH), 3.16 (1 H, d, J 2, 2-CH), 4.18 (1 H, broad t, J 7.5, 1-CH), 7.28 (3 H, m, Ar-H), 7.54 (2 H, m, Ar-H).

δ_{C} (100 MHz; CDCl_3) 25.2 (4- CH_3), 26.3 (6- CH_2), 33.0 (5- CH_2), 45.2 (4-C), 63.9 (2-CH), 67.6 (1-CH), 127.5 (Ar-CH x 2), 127.7 (Ar-CH), 129.1 (Ar-CH x 2), 140.3 (Ar-C), 175.4 (COOH)

m/z (E.I.) 249 (MH^+ , 5 %), 248 (M^+ , 7 %), 230 ($M-\text{H}_2\text{O}$, 65), 174 (47), 160 (51), 129 (79), 115 (100), 91 (95), 77 (56).

Appendix A. Stereochemical Assignments from NMR experiments.

A.1. Assignment of the Structure of 3-(2-Allylphenyl)-2,3-epoxy-1-imidazol-1-yl-thiocarbonyloxy-5-methyl- cyclohexane (241).

The imidazolidine and methyl groups have been shown to be in a *cis* arrangement as shown in the diagram below:

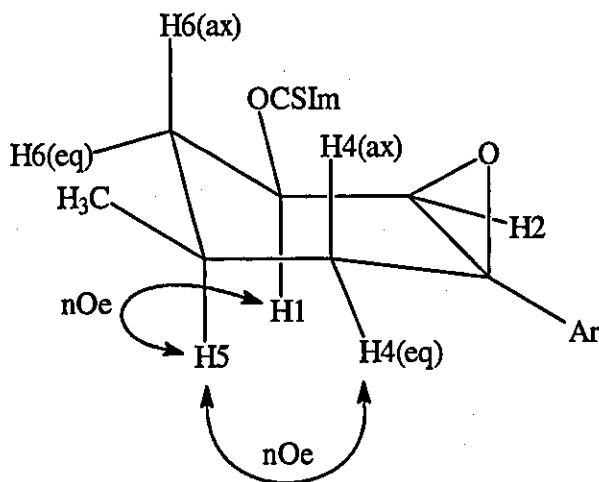


Fig A-1. Structure and Observed *nOe*'s in Thiocarbonylimidazolidine (241).

The ^1H proton resonances of this compound were assigned by analysis of the ^1H , ^{13}C , hetcor (^1H - ^{13}C) and cosy (^1H - ^1H) spectra. The high resolution of the 400 MHz ^1H spectrum and the lack of signal overlapping has allowed the determination of the J values for most of the spin couplings in the molecule and these values are reported below in table A-1. From this table it can be seen that the axial proton H6(ax) shows large couplings (J 11.5 Hz) to the protons H1 and H5 in addition to a large geminal coupling (J 11.5 Hz) to H6(eq). This is consistent with the J values that would be expected for two vicinal antiperiplanar couplings. The axial proton H4(ax) also shows a large coupling with H5 (J 11.5 Hz), again consistent with antiperiplanar coupling.

Table A-1. Coupling Constant Values for (241).

δ (ppm)	6.10 H1	3.48 H2	2.09 H4(eq)	1.96 H6(eq)	1.88 H5	1.77 H4(ax)	1.67 H6(ax)	1.00 5-CH ₃
6.10 H1	X	1.5		5.5			11.5	
3.48 H2	1.5	X						
2.09 H4(eq)			X	1 ????	5.5	14-15		
1.96 H6(eq)	5.5		1 ????	X			11.5-12	
1.88 H5			5.5		X	11.5	11.5	6.5
1.77 H4(ax)			14-15		11.5	X		
1.67 H6(ax)	11.5			11.5-12	11.5		X	
1.00 5-CH ₃					6.5			X

These values provide very strong evidence that H1 and H5 are both axial and are therefore *cis*. One other coupling of interest can be seen in H4(eq) (1 Hz). This has been tentatively assigned as a W coupling to H6(eq). The evidence for this is not clear at H6(eq) but the signal appears to be broadened slightly and it may be that this coupling has not resolved well.

Additional evidence for this stereochemical assignment is provided by the NOESY spectrum. Several key nOes can be observed:

H1-H2, H1-H5, H1-H6(eq) (no H1-H6(ax))

5-CH₃-H6(ax), 5-CH₃-H6(eq), 5-CH₃-H4(eq),

H5-H4(eq), H5-H6(eq), H5-H1 (no H5-H4(ax) or H5-H6(ax))

The nOe between H1 and H5 is further evidence that these protons are in a 1, 3-diaxial arrangement. Furthermore both of these protons show nOe's to the equatorial proton H6(eq) but not to the axial proton H6(ax).

A.2. Assignment of the Structure of 2,3-Epoxy-1-(imidazol-1-yl-thiocarbonyl-oxy)-5-methyl-3-(2-methylphenyl)-cyclohexane (257).

The imidazolidine and methyl groups appear to be arranged exactly as for the allyl substituted compound (241). The chemical shift and coupling constant data for the cyclohexyl ring protons are shown in Table A-2. These values are almost identical to those observed for (241) and the antiperiplanar couplings H6(ax)-H5 and H4(ax)-H5 (both J 11.5 Hz) are again apparent.

Table A-2. Coupling Constant Values for (257).

δ (ppm)	6.10 H1	3.47 H2	2.08 H4(eq)	1.95 H6(eq)	1.89 H5	1.78 H4(ax)	1.67 H6(ax)	1.00 5-CH ₃
6.10 H1	X	1.5		5.5			11.5	
3.47 H2	1.5	X						
2.08 H4(eq)			X	1.5	5.5	14.5		
1.95 H6(eq)	5.5		1.5	X			11.5	
1.89 H5			5.5		X	11.5	11.5	6.5
1.78 H4(ax)			14.5		11.5	X		
1.67 H6(ax)	11.5			11.5	11.5		X	
1.00 5-CH ₃					6.5			X

A.3. Assignment of the Structure of 5-Methyl-1-(2-methylphenyl)-2-cyclohexen-1-ol. (259b)

The methyl and phenyl groups have been confirmed to be in a *cis* diequatorial arrangement as shown in the diagram below:

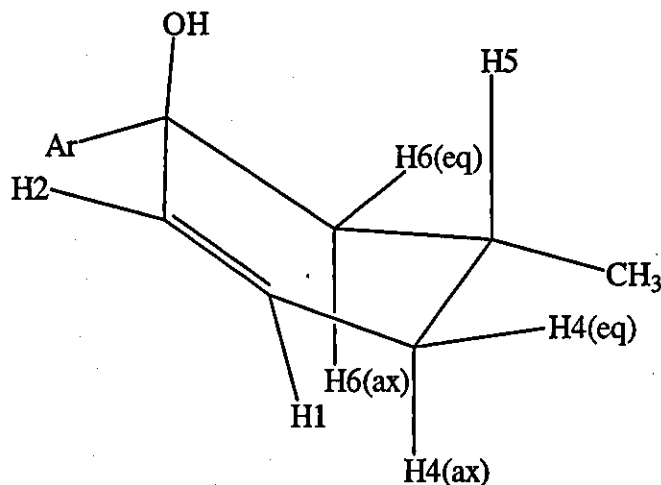


Fig A-2. Structure of the Cyclohexenol (259b).

The ^1H proton resonances of this compound were assigned by analysis of the ^1H , ^{13}C , hetero (^1H - ^{13}C) and cosy (^1H - ^1H) spectra. There was no overlapping of signals in the aliphatic region of the ^1H N.M.R. spectrum and homonuclear decoupling experiments have allowed the determination of the J values for almost all of the spin couplings in the cyclohexyl ring, the values are reported below in table A-3. It is apparent from a model of this compound that the ring can flip in such a way that the aromatic ring can assume either a pseudo-axial or pseudo-equatorial position on the cyclohexenyl ring. The pseudo-axial conformation would be expected to be strongly disfavoured for steric reasons and it has been assumed that the aromatic ring is pseudoequatorial.

Table A-3. Coupling Constant Values for (259b).

δ (ppm)	5.99 H3	5.71 H2	2.36 H6(eq)	2.13 H4(eq)	1.73 H4(ax)	1.57 H6(ax)	1.50 H5	0.88 5-CH ₃
5.99 H3	X	10		5	2.5			
5.71 H2	10	X	1.5	1.5				
2.36 H6(eq)		1.5	X	1.5		12	1.5	
2.13 H4(eq)	5	1.5	1.5	X	18		5	
1.73 H4(ax)	2.5	2.5		18	X		10	
1.57 H6(ax)			12			X	12	
1.50 H5(ax)			1.5	5	10	12	X	6.5
0.88 5-CH ₃							6.5	X

These values provide very strong evidence that the 5-CH₃ group is in an equatorial position. Both of the axial protons H4(ax) and H6(ax) show large splittings (J 10, J 12 Hz respectively) to the proton H5 and these values are consistent with antiperiplanar coupling. Interestingly the W-coupling (1.5 Hz) between H4(eq) and H6(eq) can also be seen in the spectrum.

The 5-CH₃ group shows a strong nOe to H6(ax), weaker nOe's are also observed to H4(ax), H6(eq) and H4(eq). If the methyl group was in an axial position, nOe's would not be expected to be seen in the axial protons H4(ax) and H6(ax).

A.4. Assignment of the relative stereochemistry of 4(a)-hydroxy-1, 2, 3, 4-tetrahydro-9-vinylfluorene (209).

The stereochemistry of this compound has been assigned by nOe experiments used in conjunction with an X-ray structure of the analogous compound (258b). The structure is assumed to have a *cis* ring junction because of the 5-exo cyclisation by which it was made. The 9-vinyl group is believed to be in an equatorial position *cis* to the hydroxy group.

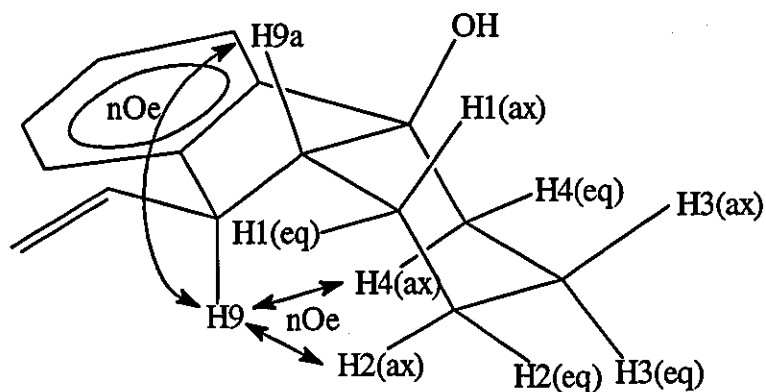


Fig A-3. Structure and Observed nOe's in (209).

There was a substantial degree of signal overlap in the aliphatic region of the ^1H NMR spectrum but an nOe difference experiment showed a large nOe (5 %) to a group containing the most upfield protons of the 2, 3 and 4 methylene groups (presumably the axial protons H2(ax) and H4(ax)) and weaker nOes (1 %) to the 9(a) proton and a group containing one of the H1 protons, H2(eq) and H3(eq).

In the crystal structure of (258b) the axial proton at C9 is 2.78 Å and 2.46 Å from H4(ax) and H2(ax) respectively, the distance to H1(eq) is 2.72 Å (see Fig A-4).

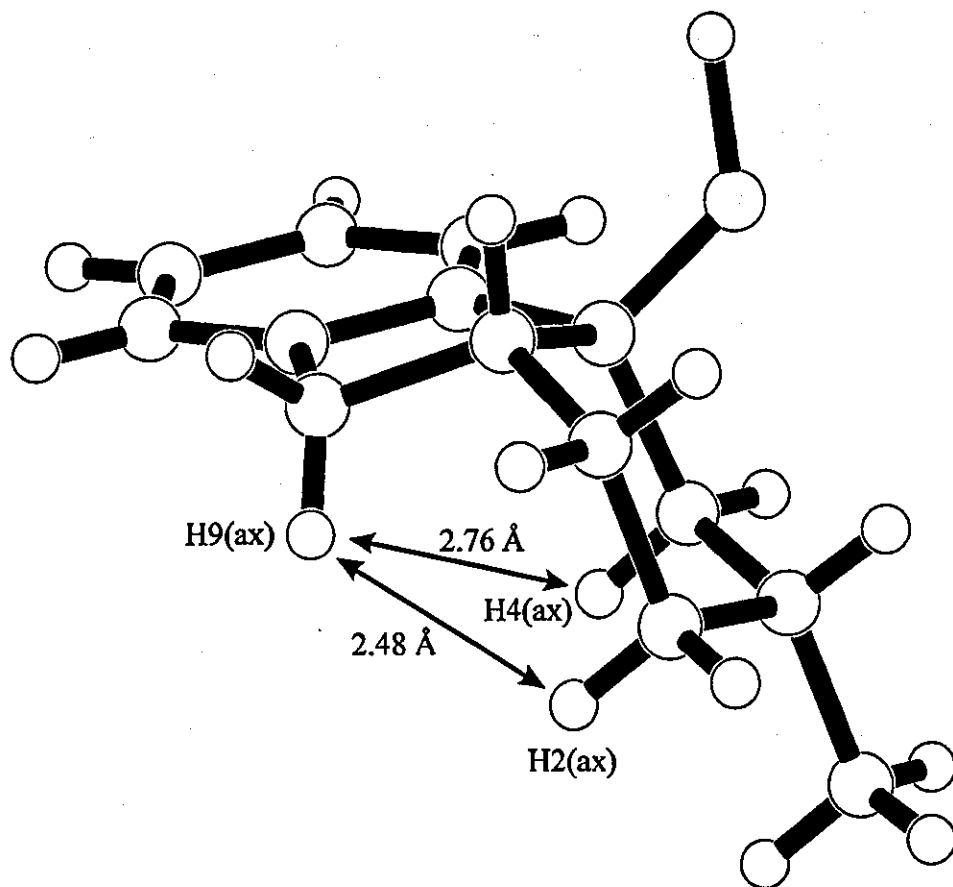


Fig A-4. X-ray Crystal Structure of (258b).

Assuming that the structures of (209) and (258b) are similar it is difficult to see how the H9 proton in (209) could show an nOe to H4 and/or H2 if it was in an equatorial position.

Appendix B. X-ray Structure Reports.

B.1. X-ray Structure Report for 2,3-epoxy-1-(imidazol-1-yl(thiocarbonyl)oxy)-3-(2-vinylphenyl)cyclohexane (210).

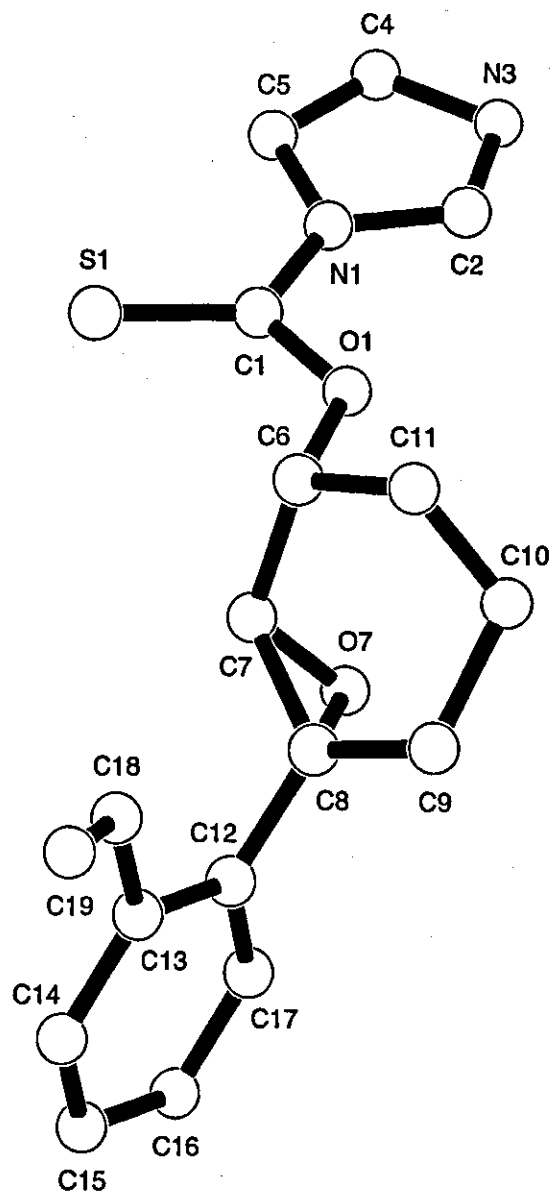


Fig B-1. X-ray Structure of (210).

B.1.1. Experimental

B.1.1.1. Data Collection

A clear block crystal of $C_{18}H_{18}N_2O_2S$ having approximate dimensions of 0.30 x 0.40 x 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-K α radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 14 carefully centered reflections in the range $39.30 < 2\theta < 42.37^\circ$ corresponded to a primitive monoclinic cell with dimensions:

$$a = 14.904(2) \text{ \AA}$$

$$b = 6.995(2) \text{ \AA} \quad \beta = 103.89(1)^\circ$$

$$c = 16.174(3) \text{ \AA}$$

$$V = 1636.8(6) \text{ \AA}^3$$

For $Z = 4$ and F.W. = 326.41, the calculated density is 1.33 g/cm³. The systematic absences of:

$$h0l: \neq 2n$$

$$0k0: \neq 2n$$

uniquely determine the space group to be:

$$P2_1/c(\#14)$$

The data were collected at a temperature of 20° C using the ω scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.34° with a take-off angle of 6.0°. Scans of $(1.00 + 0.35 \tan \theta)^\circ$ were made at a speed of 16.0° min (in omega). The weak reflections ($I < 15.0 \sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the

crystal to detector distance was 400 mm, the computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

B.1.1.2 Data Reduction.

Of the 2781 reflections which were collected, 2667 were unique ($R_{int} = 0.142$). The intensities of three representative reflections were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.2 %. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ , for Cu-K α radiation is 18.5 cm^{-1} . An empirical absorption correction using the program DIFABS¹⁰⁴ was applied which resulted in transmission factors ranging from 0.52 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = $1.66451\text{e-}06$).

B.1.1.3 Structure Solution and Refinement.

The structure was solved by heavy-atom Patterson methods¹⁰⁵ and expanded using Fourier techniques.¹⁰⁶ The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement¹⁰⁷ was based on 1725 observed reflections ($I > 4.00\sigma(I)$) and 209 variable parameters and converged (largest parameter shift was 0.09 times its esd) with unweighted and weighted agreement factors of:

$$R = \sum |F_o| - |F_c| / \sum |F_o| = 0.069$$

$$R_w = \sqrt{(\sum w(|F_o| - |F_c|)^2) / \sum w F_o^2} = 0.055$$

The standard deviation of an observation of unit weight¹⁰⁸ was 4.14. The weighting scheme was based on counting statistics and included a factor ($p = 0.002$) to downweight the intense reflections. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin^2 \theta / \lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.67 and $-0.69 \text{ e}^- / \text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.¹⁰⁹ Anomalous dispersion effects were included in F_{calc} ¹¹⁰; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.¹¹¹ The values for the mass attenuation coefficients are those of Creagh and Hubbel.¹¹² All calculations were performed using the teXsan¹¹³ crystallographic software package of Molecular Structure Corporation.

B.1.2. Crystallographic Data

Table B-1. Atomic coordinates and $B_{\text{iso}}/B_{\text{eq}}$

Atom	x	y	z	B_{eq}
S(1)	0.0386(1)	0.2691(2)	0.47984(9)	5.91(4)
O(1)	0.1719(2)	0.0202(6)	0.5406(2)	4.97(9)
O(7)	0.3335(3)	0.1769(6)	0.4944(2)	5.9(1)
N(1)	0.0952(3)	0.1159(6)	0.6333(3)	4.5(1)
N(3)	0.1183(4)	0.0187(8)	0.7672(3)	6.6(2)
C(1)	0.1041(4)	0.1318(8)	0.5501(3)	4.6(1)
C(2)	0.1437(4)	-0.0017(9)	0.6962(3)	5.4(2)
C(4)	0.0494(5)	0.156(1)	0.7490(4)	6.5(2)
C(5)	0.0345(4)	0.2176(9)	0.6688(4)	5.4(2)
C(6)	0.1868(4)	-0.0092(9)	0.4542(3)	5.0(1)
C(7)	0.2474(4)	0.1443(8)	0.4340(3)	4.8(1)
C(8)	0.3359(4)	0.0964(8)	0.4121(3)	4.2(1)
C(9)	0.3676(4)	-0.1061(9)	0.4159(4)	6.1(2)
C(10)	0.3197(6)	-0.227(1)	0.4722(6)	10.1(3)
C(11)	0.2226(5)	-0.2085(10)	0.4517(4)	6.8(2)
C(12)	0.3722(4)	0.2292(8)	0.3560(3)	4.2(1)
C(13)	0.3393(4)	0.2226(8)	0.2677(3)	4.4(1)
C(14)	0.3759(4)	0.3501(9)	0.2180(3)	5.1(2)
C(15)	0.4443(4)	0.4776(9)	0.2549(4)	6.0(2)
C(16)	0.4776(4)	0.4810(9)	0.3420(4)	5.8(2)
C(17)	0.4416(4)	0.3584(8)	0.3923(3)	5.0(1)

C(18)	0.2666(4)	0.0869(9)	0.2278(3)	5.2(2)
C(19)	0.2500(5)	0.0183(9)	0.1503(4)	6.7(2)
H(1)	0.1937	-0.0908	0.6885	6.5320
H(2)	0.0166	0.2035	0.7911	7.6122
H(3)	-0.0113	0.3144	0.6401	6.5999
H(4)	0.1268	-0.0035	0.4134	5.8843
H(5)	0.3522	-0.1657	0.3597	7.0715
H(6)	0.4340	-0.1157	0.4359	7.0715
H(7)	0.3391	-0.3592	0.4758	9.9847
H(8)	0.3421	-0.1796	0.5327	9.9847
H(9)	0.1965	-0.2913	0.4870	7.7140
H(10)	0.2027	-0.2609	0.3936	7.7140
H(11)	0.3517	0.3513	0.1555	6.0713
H(12)	0.4702	0.5653	0.2188	7.1113
H(13)	0.5286	0.5692	0.3687	7.1110
H(14)	0.4657	0.3599	0.4552	5.9940
H(15)	0.2249	0.0404	0.2621	6.0190
H(16)	0.2287	-0.1083	0.1351	7.6043
H(17)	0.2626	0.0983	0.1045	7.6043
H(18)	0.2149	0.2582	0.4033	3.0000

$$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Bond Lengths (Å).

Atom	Atom	Distance	Atom	Atom	Distance
S(1)	C(1)	1.623(5)	O(1)	C(1)	1.315(6)
O(1)	C(6)	1.480(6)	O(7)	C(7)	1.432(6)
O(7)	C(8)	1.453(6)	N(1)	C(1)	1.388(6)
N(1)	C(2)	1.371(7)	N(1)	C(5)	1.380(7)
N(3)	C(2)	1.301(7)	N(3)	C(4)	1.387(8)
C(2)	H(1)	1.00	C(4)	C(5)	1.333(8)
C(4)	H(2)	0.99	C(5)	H(3)	0.99
C(6)	C(7)	1.490(8)	C(6)	C(11)	1.497(8)
C(6)	H(4)	0.98	C(7)	C(8)	1.483(7)
C(7)	H(18)	1.00	C(8)	C(9)	1.490(7)
C(8)	C(12)	1.489(7)	C(9)	C(10)	1.537(9)
C(9)	H(5)	0.98	C(9)	H(6)	0.97
C(10)	C(11)	1.410(9)	C(10)	H(7)	0.97
C(10)	H(8)	1.01	C(11)	H(9)	0.96
C(11)	H(10)	0.99	C(12)	C(13)	1.395(6)
C(12)	C(17)	1.393(7)	C(13)	C(14)	1.395(7)
C(13)	C(18)	1.468(7)	C(14)	C(15)	1.378(8)
C(14)	H(11)	0.99	C(15)	C(16)	1.377(8)
C(15)	H(12)	0.99	C(16)	C(17)	1.376(8)
C(16)	H(13)	0.99	C(17)	H(14)	0.99
C(18)	C(19)	1.309(7)	C(18)	H(15)	0.98
C(19)	H(16)	0.95	C(19)	H(17)	0.98

Table B-3. Bond Angles(°).

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(1)	O(1)	C(6)	119.1(4)	C(7)	O(7)	C(8)	61.9(3)
C(1)	N(1)	C(2)	127.7(5)	C(1)	N(1)	C(5)	126.0(5)
C(2)	N(1)	C(5)	106.4(5)	C(2)	N(3)	C(4)	104.2(5)
S(1)	C(1)	O(1)	128.3(4)	S(1)	C(1)	N(1)	123.0(4)
O(1)	C(1)	N(1)	108.7(5)	N(1)	C(2)	N(3)	112.1(6)
N(1)	C(2)	H(1)	123.8	N(3)	C(2)	H(1)	124.1
N(3)	C(4)	C(5)	111.8(6)	N(3)	C(4)	H(2)	123.5
C(5)	C(4)	H(2)	124.7	N(1)	C(5)	C(4)	105.4(6)
N(1)	C(5)	H(3)	127.0	C(4)	C(5)	H(3)	127.6
O(1)	C(6)	C(7)	110.1(5)	O(1)	C(6)	C(11)	106.9(5)
O(1)	C(6)	H(4)	108.2	C(7)	C(6)	C(11)	115.3(5)
C(7)	C(6)	H(4)	109.1	C(11)	C(6)	H(4)	107.1
O(7)	C(7)	C(6)	117.2(5)	O(7)	C(7)	C(8)	59.8(3)
O(7)	C(7)	H(18)	117.4	C(6)	C(7)	C(8)	120.7(5)
C(6)	C(7)	H(18)	115.9	C(8)	C(7)	H(18)	114.4
O(7)	C(8)	C(7)	58.3(3)	O(7)	C(8)	C(9)	114.1(5)
O(7)	C(8)	C(12)	114.2(4)	C(7)	C(8)	C(9)	119.8(5)
C(7)	C(8)	C(12)	118.6(5)	C(9)	C(8)	C(12)	117.4(5)
C(8)	C(9)	C(10)	110.9(5)	C(8)	C(9)	H(5)	111.5
C(8)	C(9)	H(6)	111.6	C(10)	C(9)	H(5)	106.2
C(10)	C(9)	H(6)	110.3	H(5)	C(9)	H(6)	106.0
C(9)	C(10)	C(11)	114.1(7)	C(9)	C(10)	H(7)	112.7
C(9)	C(10)	H(8)	107.7	C(11)	C(10)	H(7)	111.9
C(11)	C(10)	H(8)	106.3	H(7)	C(10)	H(8)	103.2
C(6)	C(11)	C(10)	115.4(6)	C(6)	C(11)	H(9)	110.4
C(6)	C(11)	H(10)	110.1	C(10)	C(11)	H(9)	110.2
C(10)	C(11)	H(10)	104.3	H(9)	C(11)	H(10)	105.8
C(8)	C(12)	C(13)	120.9(5)	C(8)	C(12)	C(17)	119.3(5)
C(13)	C(12)	C(17)	119.8(5)	C(12)	C(13)	C(14)	118.5(5)

C(12)	C(13)	C(18)	120.8(5)	C(14)	C(13)	C(18)	120.7(5)
C(13)	C(14)	C(15)	121.1(5)	C(13)	C(14)	H(11)	119.8
C(15)	C(14)	H(11)	119.1	C(14)	C(15)	C(16)	120.0(6)
C(14)	C(15)	H(12)	120.0	C(16)	C(15)	H(12)	119.9
C(15)	C(16)	C(17)	119.9(6)	C(15)	C(16)	H(13)	120.3
C(17)	C(16)	H(13)	119.8	C(12)	C(17)	C(16)	120.7(5)
C(12)	C(17)	H(14)	119.2	C(16)	C(17)	H(14)	120.1
C(13)	C(18)	C(19)	127.4(6)	C(13)	C(18)	H(15)	117.7
C(19)	C(18)	H(15)	114.8	C(18)	C(19)	H(16)	124.3
C(18)	C(19)	H(17)	119.1	H(16)	C(19)	H(17)	116.5

Table B-4. Torsion Angles(°).

Atom	Atom	Atom	Atom	Angle	Atom	Atom	Atom	Atom	Angle
S(1)	C(1)	O(1)	C(6)	-8.5(8)	S(1)	C(1)	N(1)	C(2)	176.7(5)
S(1)	C(1)	N(1)	C(5)	-3.2(8)	O(1)	C(1)	N(1)	C(2)	-3.3(8)
O(1)	C(1)	N(1)	C(5)	176.8(5)	O(1)	C(6)	C(7)	O(7)	52.4(7)
O(1)	C(6)	C(7)	C(8)	121.7(5)	O(1)	C(6)	C(11)	C(10)	-92.9(8)
O(7)	C(7)	C(6)	C(11)	-68.5(7)	O(7)	C(7)	C(8)	C(9)	101.5(6)
O(7)	C(7)	C(8)	C(12)	-102.2(5)	O(7)	C(8)	C(7)	C(6)	-105.6(5)
O(7)	C(8)	C(9)	C(10)	45.9(7)	O(7)	C(8)	C(12)	C(13)	-147.5(5)
O(7)	C(8)	C(12)	C(17)	34.1(7)	N(1)	C(1)	O(1)	C(6)	171.5(4)
N(1)	C(2)	N(3)	C(4)	0.3(8)	N(1)	C(5)	C(4)	N(3)	0.4(8)
N(3)	C(2)	N(1)	C(1)	-180.0(5)	N(3)	C(2)	N(1)	C(5)	-0.1(7)
C(1)	O(1)	C(6)	C(7)	86.8(6)	C(1)	O(1)	C(6)	C(11)	-147.3(5)
C(1)	N(1)	C(5)	C(4)	179.7(6)	C(2)	N(1)	C(5)	C(4)	-0.2(7)
C(2)	N(3)	C(4)	C(5)	-0.5(8)	C(6)	C(7)	O(7)	C(8)	111.4(6)
C(6)	C(7)	C(8)	C(9)	-4.1(8)	C(6)	C(7)	C(8)	C(12)	152.2(5)
C(6)	C(11)	C(10)	C(9)	-56.9(10)	C(7)	O(7)	C(8)	C(9)	-111.3(6)
C(7)	O(7)	C(8)	C(12)	109.9(5)	C(7)	C(6)	C(11)	C(10)	29.7(9)
C(7)	C(8)	C(9)	C(10)	-20.1(8)	C(7)	C(8)	C(12)	C(13)	-81.7(7)
C(7)	C(8)	C(12)	C(17)	99.8(6)	C(8)	C(7)	C(6)	C(11)	0.8(8)

C(8)	C(9)	C(10)	C(11)	50.9(9)	C(8)	C(12)	C(13)	C(14)	-179.8(5)
C(8)	C(12)	C(13)	C(18)	1.1(8)	C(8)	C(12)	C(17)	C(16)	179.1(5)
C(9)	C(8)	C(12)	C(13)	75.1(7)	C(9)	C(8)	C(12)	C(17)	-103.3(6)
C(10)	C(9)	C(8)	C(12)	-176.7(5)	C(12)	C(13)	C(14)	C(15)	1.2(9)
C(12)	C(13)	C(18)	C(19)	-155.4(6)	C(12)	C(17)	C(16)	C(15)	0.5(10)
C(13)	C(12)	C(17)	C(16)	0.6(9)	C(13)	C(14)	C(15)	C(16)	-0.1(10)
C(14)	C(13)	C(12)	C(17)	-1.4(8)	C(14)	C(13)	C(18)	C(19)	25.6(10)
C(14)	C(15)	C(16)	C(17)	0(1)	C(15)	C(14)	C(13)	C(18)	-179.8(6)
C(17)	C(12)	C(13)	C(18)	179.6(5)					

B.2 X-ray Structure Report for *trans*-4a-hydroxy-3-methyl-1, 2, 3, 4-tetrahydrofluorene (258b)

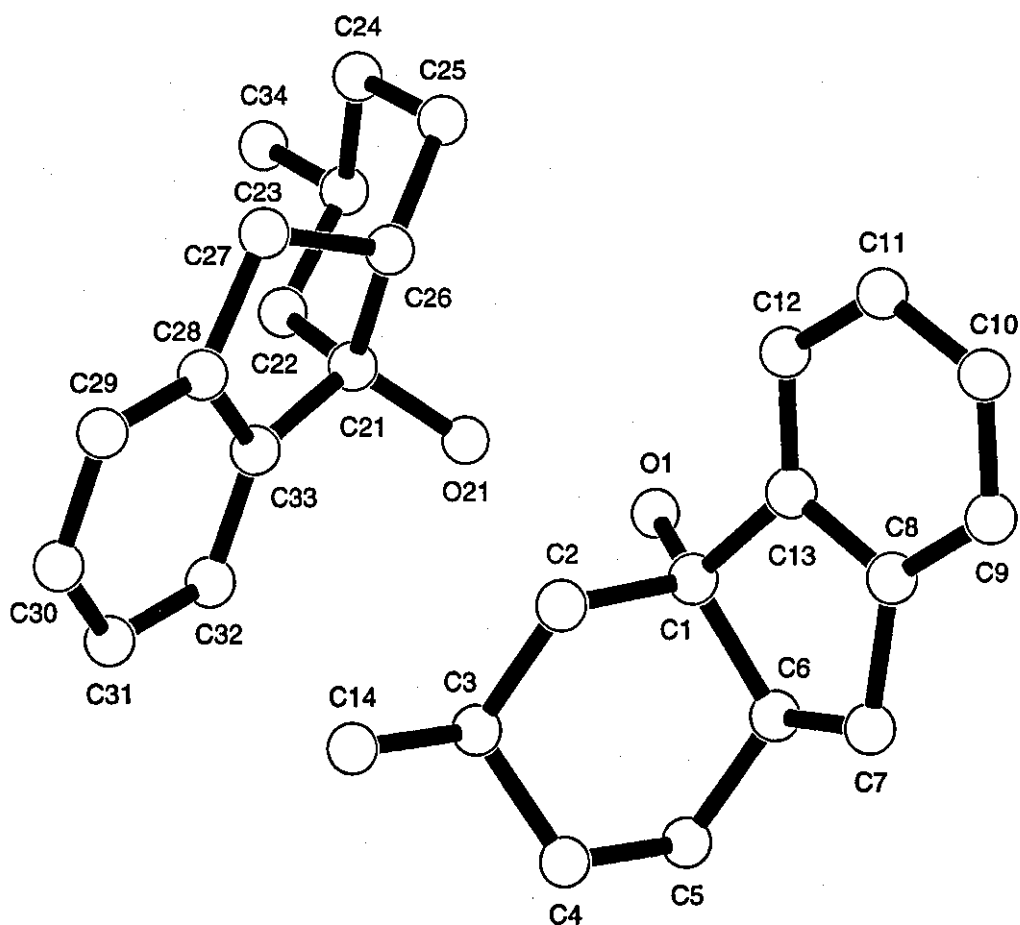


Fig B-2. X-ray Structure of (258b).

B.2.1. Experimental

B.2.1.1. Data Collection

A clear block crystal of $C_{14}H_{18}O$ having approximate dimensions of 0.12 x 0.21 x 0.36 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated $Cu-K\alpha$ radiation.

Cell constants and an orientation matrix for data collection, obtained from a least squares refinement using the setting angles of 25 carefully centered reflections in the range $50.97 < 2\theta < 63.04^\circ$ corresponded to a C-centered orthorhombic cell with dimensions:

$$a = 23.578(4) \text{ \AA}$$

$$b = 23.579(6) \text{ \AA}$$

$$c = 8.557(4) \text{ \AA}$$

$$V = 4757(2) \text{ \AA}^3$$

For $Z = 16$ and F.W. = 202.30, the calculated density is 1.13 g/cm^3 . Based on the systematic absences of:

$$hkl: h+k \neq 2n$$

$$0kl: l \neq 2n$$

$$h0l: l \neq 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$Ccc2$ (#37)

The data were collected at a temperature of $20 \pm 1 \text{ }^\circ\text{C}$ using the ω scan technique to a maximum 2θ value of 120.1° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29° with a take-off angle of 6.0° . Scans of $(0.94 + 0.35 \tan \theta)^\circ$ were made at a speed of $16.0^\circ/\text{min}$ (in omega). The weak reflections ($I < 15.0 \sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, the computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

B.2.1.2. Data Reduction

A total of 2014 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 2.9 %. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ , for Cu-K α radiation is 5.0 cm⁻¹. An empirical absorption correction using the program DIFABS¹⁰⁴ was applied which resulted in transmission factors ranging from 0.83 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 4.63415e-07).

B.2.1.3. Structure Solution and Refinement.

The structure was solved by direct methods¹⁰⁵ and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically.¹⁰⁶ Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement¹⁰⁷ was based on 1146 observed reflections ($I > 2.00 \sigma(I)$) and 272 variable parameters and converged (largest parameter shift was 0.13 times its esd) with unweighted and weighted agreement factors of:

$$R = \sum |F_o| - |F_c| / \sum |F_o| = 0.034$$

$$R_w = \sqrt{[\sum w(|F_o| - |F_c|)^2] / \sum w F_o^2} = 0.022$$

The standard deviation of an observation of unit weight¹⁰⁸ was 1.89. The weighting scheme was based on counting statistics. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.07 and -0.09 e⁻/Å³, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.¹⁰⁹ Anomalous dispersion effects were included in F_{calc} ¹¹⁰; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.¹¹¹ The values for the mass attenuation coefficients are those of Creagh and Hubbel.¹¹² All calculations were performed using the teXsan¹¹³ crystallographic software package of Molecular Structure Corporation.

B.2.2. X-ray Crystallographic Data.**Table B-5. Atomic coordinates and B_{iso}/B_{eq} .**

Atom	x	y	z	B_{eq}
O(1)	0.27291(7)	0.32937(9)	-0.0029(9)	5.80(6)
O(21)	0.17057(8)	0.27267(9)	-0.0530(10)	5.92(6)
C(1)	0.3051(1)	0.3741(1)	0.063(1)	5.16(8)
C(2)	0.2637(1)	0.4214(1)	0.112(1)	5.61(9)
C(3)	0.2323(1)	0.4110(2)	0.263(1)	6.55(10)
C(4)	0.2745(1)	0.3993(2)	0.394(1)	7.6(1)
C(5)	0.3115(2)	0.3484(2)	0.355(1)	7.7(1)
C(6)	0.3432(1)	0.3541(2)	0.200(1)	6.00(9)
C(7)	0.3941(1)	0.3943(2)	0.196(1)	6.8(1)
C(8)	0.3986(1)	0.4110(2)	0.028(1)	6.12(10)
C(9)	0.4423(1)	0.4368(2)	-0.054(1)	7.8(1)
C(10)	0.4344(2)	0.4504(2)	-0.210(1)	8.5(1)
C(11)	0.3844(2)	0.4388(2)	-0.2834(10)	8.0(1)
C(12)	0.3408(2)	0.4128(2)	-0.203(1)	6.6(1)
C(13)	0.3481(1)	0.3987(1)	-0.0490(10)	5.25
C(14)	0.1944(1)	0.4613(2)	0.302(1)	8.8(1)
C(21)	0.1257(1)	0.3053(1)	-0.118(1)	4.99(8)
C(22)	0.0794(1)	0.2636(1)	-0.168(1)	5.10(8)
C(23)	0.0894(1)	0.2314(2)	-0.318(1)	6.20(9)
C(24)	0.1008(2)	0.2743(2)	-0.448(1)	7.4(1)
C(25)	0.1513(2)	0.3110(2)	-0.411(1)	7.5(1)
C(26)	0.1456(1)	0.3432(1)	-0.255(1)	5.86(9)
C(27)	0.1051(1)	0.3941(2)	-0.252(1)	6.6(1)
C(28)	0.0888(1)	0.3990(2)	-0.084(1)	5.94(9)
C(29)	0.0632(2)	0.4427(2)	-0.004(1)	7.7(1)
C(30)	0.0503(2)	0.4352(2)	0.151(1)	8.3(1)
C(31)	0.0613(2)	0.3854(2)	0.2278(10)	7.7(1)
C(32)	0.0874(1)	0.3412(2)	0.148(1)	6.6(1)

C(33)	0.1010(1)	0.3487(1)	-0.0068(10)	5.10(8)
C(34)	0.0392(1)	0.1939(2)	-0.357(1)	8.8(1)
H(1)	0.2924	0.2863	-0.0685	10.9926
H(2b)	0.2364	0.4257	0.0322	6.7214
H(2a)	0.2847	0.4556	0.1238	6.7214
H(3)	0.2091	0.3785	0.2512	7.8822
H(4b)	0.2542	0.3920	0.4888	9.1236
H(4a)	0.2979	0.4317	0.4090	9.1236
H(5b)	0.2880	0.3158	0.3520	9.1616
H(5a)	0.3385	0.3441	0.4381	9.1616
H(6)	0.3568	0.3174	0.1751	7.1766
H(7a)	0.3875	0.4265	0.2617	8.1394
H(7b)	0.4276	0.3755	0.2313	8.1394
H(9)	0.4773	0.4450	-0.0016	9.3469
H(10)	0.4642	0.4681	-0.2645	10.2314
H(11)	0.3798	0.4485	-0.3889	9.6210
H(12)	0.3060	0.4048	-0.2530	7.9244
H(14c)	0.1732	0.4533	0.3948	10.5974
H(14a)	0.2172	0.4941	0.3200	10.5974
H(14b)	0.1692	0.4682	0.2186	10.5974
H(21)	0.1969	0.2967	-0.0038	10.9926
H(22a)	0.0750	0.2366	-0.0847	6.1280
H(22b)	0.0451	0.2844	-0.1780	6.1280
H(23)	0.1220	0.2081	-0.3037	7.4671
H(24a)	0.1079	0.2545	-0.5413	8.8403
H(24b)	0.0684	0.2978	-0.4591	8.8403
H(25a)	0.1840	0.2874	-0.4033	9.0232
H(25b)	0.1561	0.3378	-0.4907	9.0232
H(26)	0.1822	0.3571	-0.2272	7.0481
H(27a)	0.1236	0.4276	-0.2856	7.8688
H(27b)	0.0727	0.3873	-0.3139	7.8688
H(29)	0.0544	0.4775	-0.0530	9.1886

H(30)	0.0333	0.4655	0.2091	9.8944
H(31)	0.0510	0.3812	0.3361	9.2867
H(32)	0.0957	0.3065	0.2016	7.8994
H(34b)	0.0464	0.1741	-0.4505	10.5564
H(34c)	0.0333	0.1672	-0.2739	10.5564
H(34a)	0.0061	0.2166	-0.3675	10.5564

$$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + U_{23}bb^*cc^*\cos)$$

Table B-6. Bond Lengths (Å)

Atom	Atom	Distance	Atom	Atom	Distance
O(1)	C(1)	1.417(5)	O(21)	C(21)	1.421(5)
C(1)	C(2)	1.540(6)	C(1)	C(6)	1.551(6)
C(1)	C(13)	1.508(6)	C(2)	C(3)	1.508(6)
C(3)	C(4)	1.523(7)	C(3)	C(14)	1.522(6)
C(4)	C(5)	1.519(7)	C(5)	C(6)	1.531(7)
C(6)	C(7)	1.529(6)	C(7)	C(8)	1.498(8)
C(8)	C(9)	1.386(7)	C(8)	C(13)	1.388(6)
C(9)	C(10)	1.385(8)	C(10)	C(11)	1.363(7)
C(11)	C(12)	1.378(6)	C(12)	C(13)	1.374(7)
C(21)	C(22)	1.532(6)	C(21)	C(26)	1.548(7)
C(21)	C(33)	1.513(6)	C(22)	C(23)	1.510(6)
C(23)	C(24)	1.533(7)	C(23)	C(34)	1.513(6)
C(24)	C(25)	1.506(7)	C(25)	C(26)	1.539(8)
C(26)	C(27)	1.535(6)	C(27)	C(28)	1.498(8)
C(28)	C(29)	1.378(7)	C(28)	C(33)	1.386(6)
C(29)	C(30)	1.371(8)	C(30)	C(31)	1.367(8)
C(31)	C(32)	1.390(7)	C(32)	C(33)	1.377(7)
O(1)	H(1)	1.25	O(21)	H(21)	0.94
C(2)	H(2b)	0.94	C(2)	H(2a)	0.95

C(3)	H(3)	0.95	C(4)	H(4b)	0.96
C(4)	H(4a)	0.95	C(5)	H(5b)	0.95
C(5)	H(5a)	0.96	C(6)	H(6)	0.95
C(7)	H(7a)	0.96	C(7)	H(7b)	0.95
C(9)	H(9)	0.96	C(10)	H(10)	0.94
C(11)	H(11)	0.94	C(12)	H(12)	0.94
C(14)	H(14c)	0.96	C(14)	H(14a)	0.95
C(14)	H(14b)	0.94	C(22)	H(22a)	0.96
C(22)	H(22b)	0.95	C(23)	H(23)	0.95
C(24)	H(24a)	0.94	C(24)	H(24b)	0.95
C(25)	H(25a)	0.95	C(25)	H(25b)	0.94
C(26)	H(26)	0.95	C(27)	H(27a)	0.95
C(27)	H(27b)	0.94	C(29)	H(29)	0.94
C(30)	H(30)	0.96	C(31)	H(31)	0.96
C(32)	H(32)	0.96	C(34)	H(34b)	0.94
C(34)	H(34c)	0.96	C(34)	H(34a)	0.95

Table B-7. Bond Angles (°).

Atom	Atom	Atom	Home	Atom	Atom	Atom	Angle
O(1)	C(1)	C(2)	107.8 (3)	O(1)	C(1)	C(6)	112.5(4)
O(1)	C(1)	C(13)	113.3(4)	C(2)	C(1)	C(6)	112.5 (4)
C(2)	C(1)	C(13)	108.7(4)	C(6)	C(1)	C(13)	102.0(4)
C(1)	C(2)	C(3)	115.2(4)	C(2)	C(3)	C(4)	109.9(3)
C(2)	C(3)	C(14)	110.5(5)	C(4)	C(3)	C(14)	111.3(5)
C(3)	C(4)	C(5)	111.1(5)	C(4)	C(5)	C(6)	113.5(5)
C(1)	C(6)	C(5)	113.6(4)	C(1)	C(6)	C(7)	104.4(4)
C(5)	C(6)	C(7)	117.1(5)	C(6)	C(7)	C(8)	103.8(5)
C(7)	C(8)	C(9)	130.6(5)	C(7)	C(8)	C(13)	109.8(5)
C(9)	C(8)	C(13)	119.6(6)	C(8)	C(9)	C(10)	118.9(6)
C(9)	C(10)	C(11)	121.1(6)	C(10)	C(11)	C(12)	120.2(6)
C(11)	C(12)	C(13)	119.5(5)	C(1)	C(13)	C(8)	110.9(5)

C(1)	C(13)	C(12)	128.2(5)	C(8)	C(13)	C(12)	120.7(5)
O(21)	C(21)	C(22)	106.9(3)	O(21)	C(21)	C(26)	112.5(4)
O(21)	C(21)	C(33)	114.1(4)	C(22)	C(21)	C(26)	112.1(4)
C(22)	C(21)	C(33)	109.6(3)	C(26)	C(21)	C(33)	101.7(4)
C(21)	C(22)	C(23)	116.6(4)	C(22)	C(23)	C(24)	108.4(4)
C(22)	C(23)	C(34)	111.2(4)	C(24)	C(23)	C(34)	111.1(5)
C(23)	C(24)	C(25)	111.2(5)	C(24)	C(25)	C(26)	113.6(5)
C(21)	C(26)	C(25)	113.4(4)	C(21)	C(26)	C(27)	104.5(4)
C(25)	C(26)	C(27)	117.0(5)	C(26)	C(27)	C(28)	103.5(5)
C(27)	C(28)	C(29)	130.5(6)	C(27)	C(28)	C(33)	109.8(5)
C(29)	C(28)	C(33)	119.7(6)	C(28)	C(29)	C(30)	118.7(6)
C(29)	C(30)	C(31)	112.2(6)	C(30)	C(31)	C(32)	119.5(6)
C(31)	C(32)	C(33)	118.6(6)	C(21)	C(33)	C(28)	111.2(5)
C(21)	C(33)	C(32)	127.4(5)	C(28)	C(33)	C(32)	121.3(5)
C(1)	O(1)	H(1)	126.0	C(21)	O(21)	H(21)	109.8
C(1)	C(2)	H(2b)	108.4	C(1)	C(2)	H(2a)	108.2
C(3)	C(2)	H(2b)	107.5	C(3)	C(2)	H(2a)	107.3
H(2b)	C(2)	H(2a)	110.2	C(2)	C(3)	H(3)	109.1
C(4)	C(3)	H(3)	107.8	C(14)	C(3)	H(3)	108.2
C(3)	C(4)	H(4b)	109.4	C(3)	C(4)	H(4a)	109.6
C(5)	C(4)	H(4b)	109.1	C(5)	C(4)	H(4a)	109.3
H(4b)	C(4)	H(4a)	108.3	C(4)	C(5)	H(5b)	108.1
C(4)	C(5)	H(5a)	107.8	C(6)	C(5)	H(5b)	109.4
C(6)	C(5)	H(5a)	109.1	H(5b)	C(5)	H(5a)	108.8
C(1)	C(6)	H(6)	107.8	C(5)	C(6)	H(6)	106.2
C(7)	C(6)	H(6)	107.2	C(6)	C(7)	H(7a)	110.6
C(6)	C(7)	H(7b)	110.8	C(8)	C(7)	H(7a)	111.5
C(8)	C(7)	H(7b)	111.7	H(7a)	C(7)	H(7b)	108.5
C(8)	C(9)	H(9)	119.7	C(10)	C(9)	H(9)	121.4
C(9)	C(10)	H(10)	118.7	C(11)	C(10)	H(10)	120.2
C(10)	C(11)	H(11)	119.8	C(12)	C(11)	H(11)	120.0
C(11)	C(12)	H(12)	121.0	C(13)	C(12)	H(12)	119.5

C(3)	C(14)	H(14c)	109.6	C(3)	C(14)	H(14a)	109.6
C(3)	C(14)	H(14b)	109.9	H(14c)	C(14)	H(14a)	108.4
H(14c)	C(14)	H(14b)	109.4	H(14a)	C(14)	H(14b)	109.9
C(21)	C(22)	H(22a)	107.3	C(21)	C(22)	H(22b)	107.5
C(23)	C(22)	H(22a)	108.2	C(23)	C(22)	H(22b)	108.3
H(22a)	C(22)	H(22b)	108.7	C(22)	C(23)	H(23)	108.0
C(24)	C(23)	H(23)	109.2	C(34)	C(23)	H(23)	108.9
C(23)	C(24)	H(24a)	108.7	C(23)	C(24)	H(24b)	108.3
C(25)	C(24)	H(24a)	109.2	C(25)	C(24)	H(24b)	108.8
H(24a)	C(24)	H(24b)	110.6	C(24)	C(25)	H(25a)	108.6
C(24)	C(25)	H(25b)	108.9	C(26)	C(25)	H(25a)	107.6
C(26)	C(25)	H(25b)	107.9	H(25a)	C(25)	H(25b)	110.2
C(21)	C(26)	H(26)	106.4	C(25)	C(26)	H(26)	107.9
C(27)	C(26)	H(26)	107.0	C(26)	C(27)	H(27a)	111.1
C(26)	C(27)	H(27b)	111.2	C(28)	C(27)	H(27a)	110.2
C(28)	C(27)	H(27b)	110.2	H(27a)	C(27)	H(27b)	110.5
C(28)	C(29)	H(29)	121.4	C(30)	C(29)	H(29)	119.9
C(29)	C(30)	H(30)	119.6	C(31)	C(30)	H(30)	118.2
C(30)	C(31)	H(31)	120.2	C(32)	C(31)	H(31)	120.2
C(31)	C(32)	H(32)	120.0	C(33)	C(32)	H(32)	121.5
C(23)	C(34)	H(34b)	109.9	C(23)	C(34)	H(34c)	109.3
C(23)	C(34)	H(34a)	109.5	H(34b)	C(34)	H(34c)	109.3
H(34b)	C(34)	H(34a)	110.4	H(34c)	C(34)	H(34a)	108.4

B.3 X-ray Structure Report for 2,3-Epoxy-4-methyl-3-phenyl-cyclohexan-1-ol-4-carboxylic Acid (322).

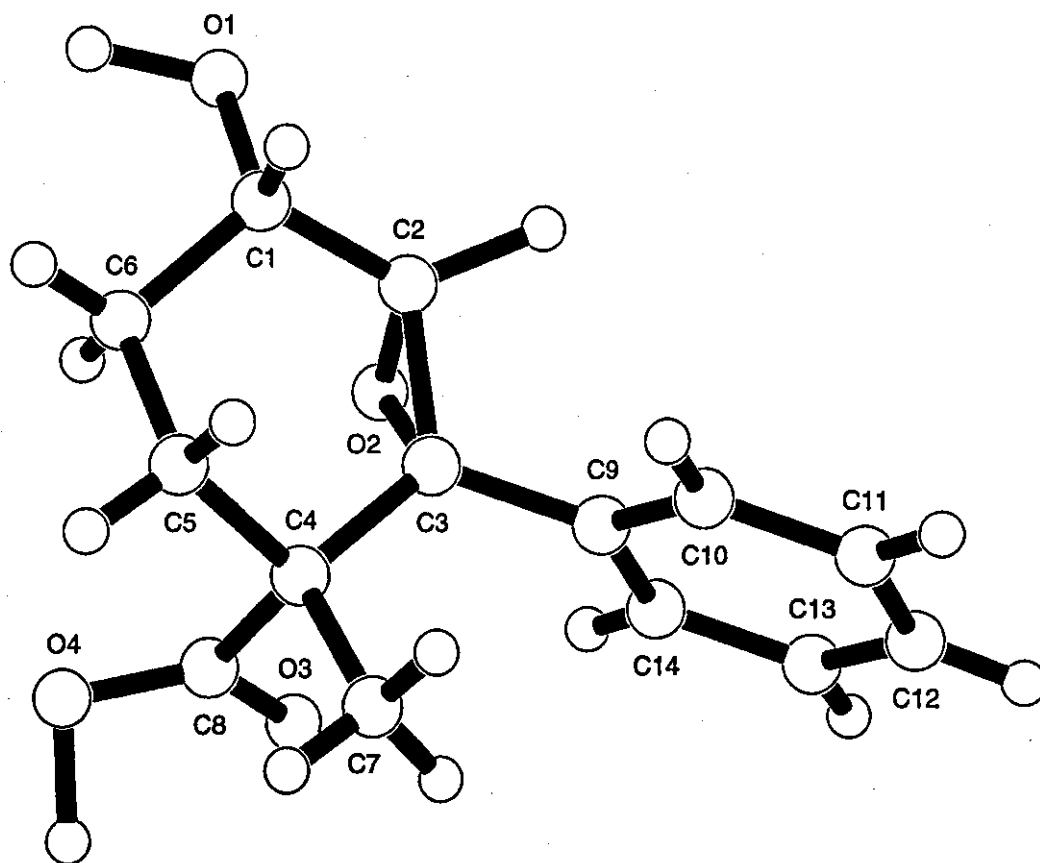


Fig B-3. Xray Structure of (322).

B.3.1 Experimental.

B.3.1.1 Data Collection.

A clear needle crystal of $C_{14}H_{16}O_4$ having approximate dimensions of 0.03 x 0.03 x 0.15 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated $Cu-K\alpha$ radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 19 carefully centered reflections in the range $21.02 < 2\theta < 34.07^\circ$ corresponded to a primitive orthorhombic cell with dimensions:

$$a = 14.073(2) \text{ \AA}$$

$$b = 10.186(2) \text{ \AA}$$

$$c = 8.973(2) \text{ \AA}$$

$$V = 1286.2(3) \text{ \AA}^3$$

For $Z = 4$ and $F.W. = 248.28$, the calculated density is 1.28 g/cm^3 .

Based on the systematic absences of:

$$0kl: l \neq 2n$$

$$h0l: h \neq 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$Pca2_1$ (#29)

The data were collected at a temperature of $20 \pm 0 \text{ } ^\circ\text{C}$ using the ω scan technique to a maximum 2θ value of 120.1° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.30° with a take-off angle of 6.0° . Scans of $(0.89 + 0.35 \tan \theta)^\circ$ were made at a speed of $16.0^\circ/\text{min}$ (in omega). The weak reflections ($I < 15.0 \sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, the computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

B.3.1.2 Data Reduction.

A total of 1144 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.4 %. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ , for Cu-K α radiation is 7.7 cm^{-1} . An empirical absorption correction using the program DIFABS¹⁰⁴ was applied which resulted in transmission factors ranging from 0.75 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = $7.11409\text{e-}06$).

B.3.1.3. Structure Solution and Refinement.

The structure was solved by direct methods¹⁰⁵ and expanded using Fourier techniques¹⁰⁶. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement,¹⁰⁷ was based on 657 observed reflections ($I > 1.50 \sigma(I)$) and 164 variable parameters and converged (largest parameter shift was 0.05 times its esd) with unweighted and weighted agreement factors of:

$$R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.061$$

$$R_w = \sqrt{[\sum w(|F_o| - |F_c|)^2] / \sum w F_o^2} = 0.041$$

The standard deviation of an observation of unit weight¹⁰⁸ was 1.77. The weighting scheme was based on counting statistics and included a factor ($p = 0.002$) to downweight the intense reflections. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.26 and $-0.27e^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber¹⁰⁹. Anomalous dispersion effects were included in F_{calc} ¹¹⁰, the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.¹¹¹ The values for the mass attenuation coefficients are those of Creagh and Hubbel.¹¹² All calculations were performed using the teXsan¹¹³ crystallographic software package of Molecular Structure Corporation.

B.3.2 X-ray Crystallographic Data.

Table B-8. Atomic coordinates and $B_{\text{iso}}/B_{\text{eq}}$.

Atom	x	y	z	B_{eq}
O(1)	0.8013(3)	0.0966(5)	0.651(3)	3.4(2)
O(2)	1.0015(4)	0.1915(5)	0.621(3)	2.9(1)
O(3)	1.1826(4)	0.1059(5)	0.715(3)	4.2(2)
O(4)	1.1289(4)	-0.0423(6)	0.875(3)	3.7(2)
C(1)	0.8573(6)	0.1504(7)	0.769(3)	3.0(2)
C(2)	0.9230(6)	0.2476(8)	0.704(3)	2.9(2)

C(3)	1.0233(6)	0.2622(7)	0.756(3)	2.2(2)
C(4)	1.0610(6)	0.1741(8)	0.884(3)	2.8(2)
C(5)	0.9766(6)	0.1074(8)	0.965(3)	3.3(3)
C(6)	0.9079(6)	0.0447(8)	0.857(3)	3.6(2)
C(7)	1.1188(6)	0.2508(9)	0.997(3)	4.0(3)
C(8)	1.1256(6)	0.0698(9)	0.822(3)	3.1(2)
C(9)	1.0688(6)	0.3926(7)	0.730(3)	2.8(2)
C(10)	1.0409(6)	0.5008(9)	0.814(3)	4.2(3)
C(11)	1.0846(9)	0.6211(10)	0.789(3)	5.9(4)
C(12)	1.1555(8)	0.633(1)	0.690(4)	6.8(5)
C(13)	1.1838(7)	0.527(1)	0.604(3)	6.1(4)
C(14)	1.1411(6)	0.4060(8)	0.628(3)	4.7(3)
H(1)	0.8158	0.1955	0.8329	3.5575
H(1o)	0.7750	-0.0042	0.6719	6.1588
H(2)	0.9052	0.3515	0.6396	6.1588
H(5b)	0.9436	0.1718	1.0196	3.9992
H(5a)	1.0006	0.0417	1.0279	3.9992
H(6b)	0.9417	-0.0112	0.7895	4.2709
H(6a)	0.8626	-0.0054	0.9097	4.2709
H(7a)	1.1386	0.1938	1.0735	4.8414
H(7b)	1.1731	0.2872	0.9481	4.8414
H(7c)	1.0810	0.3195	1.0359	4.8414
H(8o)	1.2111	-0.0472	0.8957	6.1588
H(10)	0.9927	0.4925	0.8861	5.0768
H(11)	1.0638	0.6963	0.8406	7.0571
H(12)	1.1867	0.7152	0.6769	8.1707
H(13)	1.2317	0.5364	0.5286	7.3262
H(14)	1.1620	0.3315	0.5719	5.6839

$$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + U_{23}bb^*cc^*\cos\alpha)$$

Table B-9. Bond Lengths(Å).

Atom	Atom	Distance	Atom	Atom	Distance
O(1)	C(1)	1.43(1)	O(2)	C(2)	1.450(10)
O(2)	C(3)	1.445(10)	O(3)	C(8)	1.30(1)
O(4)	C(8)	1.236(9)	C(1)	C(2)	1.47(1)
C(1)	C(6)	1.52(1)	C(2)	C(3)	1.49(1)
C(3)	C(4)	1.55(1)	C(3)	C(9)	1.493(10)
C(4)	C(5)	1.55(1)	C(4)	C(7)	1.52(1)
C(4)	C(8)	1.51(1)	C(5)	C(6)	1.51(1)
C(9)	C(10)	1.39(1)	C(9)	C(14)	1.37(1)
C(10)	C(11)	1.39(1)	C(11)	C(12)	1.34(2)
C(12)	C(13)	1.39(2)	C(13)	C(14)	1.39(1)

Table B-10. Bond Lengths(Å).

Atom	Atom	Distance	Atom	Atom	Distance
O(1)	H(1o)	1.11	O(4)	H(8o)	1.17
C(1)	H(1)	0.94	C(2)	H(2)	1.23
C(5)	H(5b)	0.94	C(5)	H(5a)	0.94
C(6)	H(6b)	0.96	C(6)	H(6a)	0.94
C(7)	H(7a)	0.94	C(7)	H(7b)	0.96
C(7)	H(7c)	0.94	C(10)	H(10)	0.94
C(11)	H(11)	0.94	C(12)	H(12)	0.95
C(13)	H(13)	0.96	C(14)	H(14)	0.96

Table B-11. Bond Angles(°).

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(2)	O(2)	C(3)	62.2(5)	O(1)	C(1)	C(2)	108.1(8)
O(1)	C(1)	C(6)	112.0(7)	C(2)	C(1)	C(6)	112.9(7)
O(2)	C(2)	C(1)	114.5(7)	O(2)	C(2)	C(3)	58.8(5)
C(1)	C(2)	C(3)	122.4(8)	O(2)	C(3)	C(2)	59.1(5)
O(2)	C(3)	C(4)	114.0(6)	O(2)	C(3)	C(9)	113.8(8)
C(2)	C(3)	C(4)	119.8(7)	C(2)	C(3)	C(9)	116.4(7)
C(4)	C(3)	C(9)	118.9(8)	C(3)	C(4)	C(5)	109.6(7)
C(3)	C(4)	C(7)	112.4(7)	C(3)	C(4)	C(8)	109.8(8)
C(5)	C(4)	C(7)	109.2(8)	C(5)	C(4)	C(8)	109.1(7)
C(7)	C(4)	C(8)	106.7(7)	C(4)	C(5)	C(6)	112.5(8)
C(1)	C(6)	C(5)	109.6(7)	O(3)	C(8)	O(4)	121.2(8)
O(3)	C(8)	C(4)	116.5(8)	O(4)	C(8)	C(4)	122.2(9)
C(3)	C(9)	C(10)	119.9(8)	C(3)	C(9)	C(14)	120.7(8)
C(10)	C(9)	C(14)	119.4(8)	C(9)	C(10)	C(11)	118.9(10)
C(10)	C(11)	C(12)	121(1)	C(11)	C(12)	C(13)	120(1)
C(12)	C(13)	C(14)	118(1)	C(9)	C(14)	C(13)	120.9(10)

Table B-12. Bond Angles(°).

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(1)	O(1)	H(1o)	114.3	C(8)	O(4)	H(8)	97.9
O(1)	C(1)	H(1)	107.4	C(2)	C(1)	H(1)	107.7
C(6)	C(1)	H(1)	108.5	O(2)	C(2)	H(2)	104.7
C(1)	C(2)	H(2)	129.3	C(3)	C(2)	H(2)	104.7
C(4)	C(5)	H(5b)	108.4	C(4)	C(5)	H(5a)	108.5
C(6)	C(5)	H(5b)	108.3	C(6)	C(5)	H(5a)	108.3
H(5b)	C(5)	H(5a)	110.8	C(1)	C(6)	H(6b)	108.8
C(1)	C(6)	H(6a)	109.1	C(5)	C(6)	H(6b)	109.8
C(5)	C(6)	H(6a)	110.2	H(6b)	C(6)	H(6a)	109.3
C(4)	C(7)	H(7a)	109.1	C(4)	C(7)	H(7b)	108.7
C(4)	C(7)	H(7c)	109.0	H(7a)	C(7)	H(7b)	109.8

H(7a)	C(7)	H(7c)	110.8	H(7b)	C(7)	H(7c)	109.4
C(9)	C(10)	H(10)	120.3	C(11)	C(10)	H(10)	120.7
C(10)	C(11)	H(11)	119.8	C(12)	C(11)	H(11)	119.0
C(11)	C(12)	H(12)	120.3	C(13)	C(12)	H(12)	119.1
C(12)	C(13)	H(13)	120.8	C(14)	C(13)	H(13)	120.4
C(9)	C(14)	H(14)	120.0	C(13)	C(14)	H(14)	119.1

Table B-13. Torsion Angles(°).

Atom	Atom	Atom	Atom	Angle	Atom	Atom	Atom	Atom	Angle
O(1)	C(1)	C(2)	O(2)	-73.8(9)	O(1)	C(1)	C(2)	C(3)	-141.1(8)
O(1)	C(1)	C(2)	H(2)	63.6	O(1)	C(1)	C(6)	C(5)	171.7(7)
O(1)	C(1)	C(6)	H(6b)	51.6	O(1)	C(1)	C(6)	H(6a)	-67.6
O(2)	C(2)	C(1)	C(6)	50(1)	O(2)	C(2)	C(1)	H(1)	170.5
O(2)	C(2)	C(3)	C(4)	-101.7(8)	O(2)	C(2)	C(3)	C(9)	103.1(9)
O(2)	C(3)	C(2)	C(1)	101.0(9)	O(2)	C(3)	C(2)	H(2)	-98.5
O(2)	C(3)	C(4)	C(5)	-81.4(9)	O(2)	C(3)	C(4)	C(7)	157.0(7)
O(2)	C(3)	C(4)	C(8)	38.4(10)	O(2)	C(3)	C(9)	C(10)	137.9(8)
O(2)	C(3)	C(9)	C(14)	-44(1)	O(3)	C(8)	O(4)	H(8o)	49.8
O(3)	C(8)	C(4)	C(3)	39(1)	O(3)	C(8)	C(4)	C(5)	159.6(8)
O(3)	C(8)	C(4)	C(7)	-82(1)	O(4)	C(8)	C(4)	C(3)	-144.6(9)
O(4)	C(8)	C(4)	C(5)	-24(1)	O(4)	C(8)	C(4)	C(7)	93(1)
C(1)	C(2)	O(2)	C(3)	-114.3(9)	C(1)	C(2)	C(3)	C(4)	0(1)
C(1)	C(2)	C(3)	C(9)	-155.9(9)	C(1)	C(6)	C(5)	C(4)	-68.2(10)
C(1)	C(6)	C(5)	H(5b)	51.6	C(1)	C(6)	C(5)	H(5a)	171.9
C(2)	O(2)	C(3)	C(4)	111.6(8)	C(2)	O(2)	C(3)	C(9)	-107.6(8)
C(2)	C(1)	O(1)	H(1o)	153.0	C(2)	C(1)	C(6)	C(5)	49(1)
C(2)	C(1)	C(6)	H(6b)	-70.7	C(2)	C(1)	C(6)	H(6a)	170.0
C(2)	C(3)	C(4)	C(5)	-14(1)	C(2)	C(3)	C(4)	C(7)	-136.2(8)
C(2)	C(3)	C(4)	C(8)	105.2(9)	C(2)	C(3)	C(9)	C(10)	72(1)
C(2)	C(3)	C(9)	C(14)	-110(1)	C(3)	O(2)	C(2)	H(2)	98.5
C(3)	C(2)	C(1)	C(6)	-16(1)	C(3)	C(2)	C(1)	H(1)	103.2
C(3)	C(4)	C(5)	C(6)	48.6(10)	C(3)	C(4)	C(5)	H(5b)	-71.2

C(3)	C(4)	C(5)	H(5a)	168.4	C(3)	C(4)	C(7)	H(7a)	178.5
C(3)	C(4)	C(7)	H(7b)	-61.8	C(3)	C(4)	C(7)	H(7c)	57.4
C(3)	C(9)	C(10)	C(11)	179.6(10)	C(3)	C(9)	C(10)	H(10)	-1.0
C(3)	C(9)	C(14)	C(13)	-179(1)	C(3)	C(9)	C(14)	H(14)	1.0
C(4)	C(3)	C(2)	H(2)	159.8	C(4)	C(3)	C(9)	C(10)	-83.3(10)
C(4)	C(3)	C(9)	C(14)	93(1)	C(4)	C(5)	C(6)	H(6b)	51.2
C(4)	C(5)	C(6)	H(6a)	171.7	C(4)	C(8)	O(4)	H(8o)	-125.9
C(5)	C(4)	C(3)	C(9)	139.9(8)	C(5)	C(4)	C(7)	H(7a)	56.7
C(5)	C(4)	C(7)	H(7b)	176.4	C(5)	C(4)	C(7)	H(7c)	-64.5
C(5)	C(6)	C(1)	H(1)	-69.9	C(6)	C(1)	O(1)	H(1o)	28.0
C(6)	C(1)	C(2)	H(2)	-171.9	C(6)	C(5)	C(4)	C(7)	172.1(7)
C(6)	C(5)	C(4)	C(8)	-71.7(9)	C(7)	C(4)	C(3)	C(9)	18(1)
C(7)	C(4)	C(5)	H(5b)	52.3	C(7)	C(4)	C(5)	H(5a)	-68.1
C(8)	C(4)	C(3)	C(9)	-100.2(9)	C(8)	C(4)	C(5)	H(5b)	168.6
C(8)	C(4)	C(5)	H(5a)	48.1	C(8)	C(4)	C(7)	H(7a)	-61.1
C(8)	C(4)	C(7)	H(7b)	58.6	C(8)	C(4)	C(7)	H(7c)	177.8
C(9)	C(3)	C(2)	H(2)	4.6	C(9)	C(10)	C(11)	C(12)	-2(1)
C(9)	C(10)	C(11)	H(11)	176.4	C(9)	C(14)	C(13)	C(12)	3(1)
C(9)	C(14)	C(13)	H(13)	-176.3	C(10)	C(9)	C(14)	C(13)	-2(1)
C(10)	C(9)	C(14)	H(14)	178.2	C(10)	C(11)	C(12)	C(13)	3(1)
C(10)	C(11)	C(12)	H(12)	-177.1	C(11)	C(10)	C(9)	C(14)	2(1)
C(11)	C(12)	C(13)	C(14)	-3(1)	C(11)	C(12)	C(13)	H(13)	175.8
C(12)	C(11)	C(10)	H(10)	177.7	C(12)	C(13)	C(14)	H(14)	-177.6
C(13)	C(12)	C(11)	H(11)	-175.7	C(14)	C(9)	C(10)	H(10)	-178.3
C(14)	C(13)	C(12)	H(12)	177.1	H(1)	C(1)	O(1)	H(1o)	-91.0
H(1)	C(1)	C(2)	H(2)	-52.1	H(1)	C(1)	C(6)	H(6b)	170.0
H(1)	C(1)	C(6)	H(6a)	50.8	H(5b)	C(5)	C(6)	H(6b)	171.1
H(5b)	C(5)	C(6)	H(6a)	-68.5	H(5a)	C(5)	C(6)	H(6b)	-68.7
H(5a)	C(5)	C(6)	H(6a)	51.8	H(10)	C(10)	C(11)	H(11)	-3.0
H(11)	C(11)	C(12)	H(12)	3.5	H(12)	C(12)	C(13)	H(13)	-3.5
H(13)	C(13)	C(14)	H(14)	3.0					

Appendix C. GCMS Data.

C.1 General Experimental Conditions.

All GCMS was performed on a Fisons GC8000 instrument fitted with a Fisons MD800 Mass Spectrometer. The GC column used was a 15 m, non polar capillary column with a 0.25 mm bore (J & W column 1225512, phase DB515). The solid phase consisted of 5 % (phenyl)methyl-polysiloxane (minimum 3700 plates/m).

The injector port was maintained at a temperature of 250 °C. The temperature cycle used was 50 °C for 5 mins then a ramp of 10 °C/min up to 250 °C. The temperature was then maintained at 250 °C for 10 minutes prior to cool down.

C.2 Chromatogram of the Diastereomeric Fluorenols (247a-d).

From this chromatogram it is apparent that the peaks at 17.003, 17.153, 17.378 and 17.653 correspond to the 4 diastereomers of the fluorenol. The peak at 18.928 mins appears to be isomeric, with M^+ 228, although there is no peak at 210 ($M^+ - H_2O$). The peaks at 22.953 and 23.328 correspond to compounds which appear to be structurally different to the fluorenols (M^+ 274?).

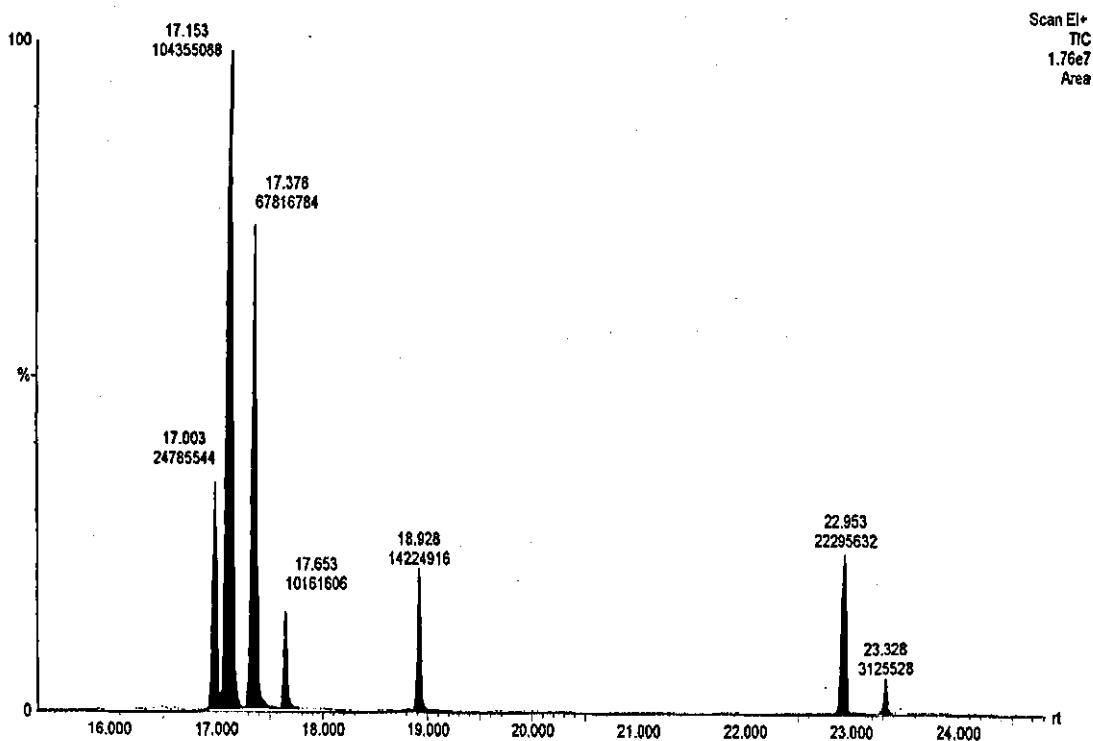


Fig C-1. GCMS Chromatogram of the Diastereomeric Fluorenols (247a-d).

Table C-1. Mass spectrometry data for the diastereomeric fluorenols (247a-d).

Retention Time (mins)	Integration (%)	<i>m/z</i>
17.003	24785544 (10 %)	211 (13 %), 210 (77), 195 (78), 167 (100), 165 (58), 153 (50), 141 (36), 115 (35), 67 (40).
17.153	104355088 (42 %)	211 (17 %), 210 (100), 195 (50), 167 (91), 153 (98), 141 (30), 115 (29).
17.378	67816784 (28 %)	228 (6 %), 211 (16), 210 (100), 195 (61), 167 (97), 153 (91), 141 (44), 128 (38), 115 (51).
17.653	10161606 (4 %)	228 (26 %), 211 (14), 210 (91), 195 (57), 167 (100), 153 (94), 141 (43), 128 (52), 115 (69).
18.928	14224916 (6 %)	228 (39 %), 172 (20), 132 (100), 115 (24).
22.953	22295632 (9 %)	274 (28 %), 183 (50), 141 (100), 115 (20), 91 (25).
23.328	3125528 (1 %)	274 (20 %), 183 (100), 141 (49), 115 (20), 91 (28).

C.3 Chromatogram of the Major Diastereomer of (247).

This chromatogram is of the major diastereomer which was found to be appreciably less polar than the other three and was separable by flash chromatography.

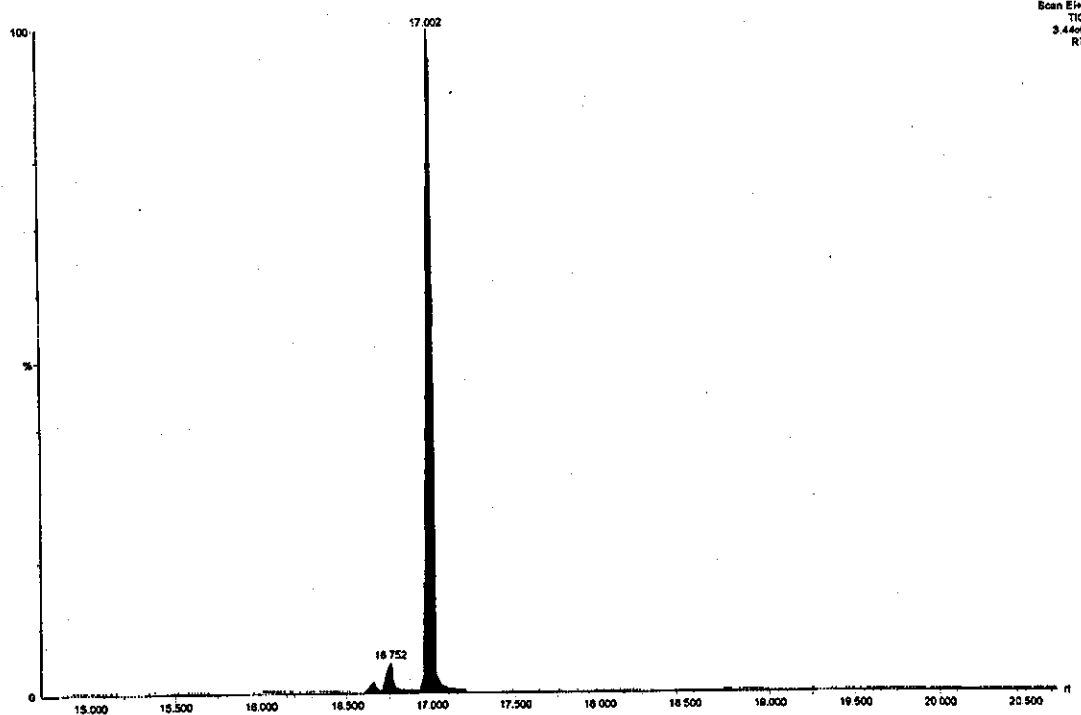


Fig C-2. GCMS Chromatogram of the Major Diastereomer of Fluorenol (247)

Table C-2. Mass spectrometry Data for the Major Diastereomer of the Fluorenol (247).

Retention Time (mins)	Integration	<i>m/z</i>
17.002	99 %	228 (10 %), 211 (14), 210 (87), 195 (59), 171 (94), 167 (100), 153 (99), 141 (59), 128 (67), 115 (85).

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$$\sigma^2(F_o^2) = \frac{S^2(C + R^2B) + (pF_o^2)^2}{Lp^2}$$

 S = Scan rate
 C = Total integrated peak count
 R = Ratio of scan time to background counting time
 B = Total background count
 Lp = Lorentz-polarization factor
 p = p-factor
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 $\sqrt{\sum w(|F_o| - |F_c|)^2 / (N_o - N_v)}$
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 N_v = number of variables
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