Loughborough University of Technology
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Ring Opening/Cyclisation in Oxiranyl Carbinyl Free Radicals

by

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Supervisors:

Professor B.A. Marples
Doctor W.R. Bowman

STATEMENT

The experimental work in this thesis was carried out in the Department of Chemistry at Loughborough University of Technology by N.A. Zaidi between October 1987 and October 1990. This work has not previously been presented for any other degree.

N.A. Zaidi

October 1990

DEDICATION

To Ma, Dad and Family

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ABSTRACT

Ring Opening/Cyclisation in Oxiranyl Carbinyl Free Radicals

Author: Naveed Ahmed Zaidi.

A study aimed to examine the electronic and possible stereoelectronic factors controlling the opening of the epoxide C-O versus C-C bond in 4ξ,5-epoxy-5ξ-cholestan-3-yl-radicals, formed by photolysis of 3β-acetoxy-4ξ,5-epoxy-5ξ-cholestanes in HMPA/H_2O and by Bu_3SnH reduction of 4ξ,5-epoxy-3β-[imidazol-1-yl(thiocarbonyl)oxy]-5ξ-cholestanes. These derived radicals gave cholest-3-en-5β-ol via the cholest-3-en-5ξ-oxy-radicals and reversible cleavage of the C_5-C_{10} bond. The 4ξ,5-epoxy-5ξ-cholestan-6-yl-radicals, formed by photolysis of 6α-acetoxy-4ξ,5-epoxy-5ξ-cholestanes in HMPA/H_2O, and by Bu_3SnH reduction of 4ξ,5-epoxy-6α-[imidazol-1-yl(thiocarbonyl)oxyl-5ξ-cholestanes gave the cholest-5-en-4ξ-oxy-radicals, which were reduced to give the cholest-5-en-4ξ-ols.

In the study of bicyclo[2.2.1]heptane systems, the reduction with Bu_3SnH of *endo*-2-[imidazol-1-yl-(thiocarbonyl)oxyl-*anti*-3'-phenylbicyclo[2.2.1]heptan-3-spiro-2'-oxiranes and the *anti*-3'-*p*-chlorophenyl and 3'-methylene analogues failed to generate a radical at C-2 irrespective of the stereochemistry (*exo*- or *endo*-) of the epoxides. Unexpected products were derived from the reduction of the thioester group to methoxy and acetal groups; the epoxide groups remained unaltered. This novel reduction has not been observed before.

The photolysis in HMPA/H_2O of *endo*-2-acetoxy-*anti*-3'-phenylbicyclo[2.2.1]heptan-3-spiro-2'-oxiranes and the *anti*-3'-*p*-chlorophenyl and 3'-methylene analogues failed to generate a radical at C-2 irrespective of the stereochemistry (*exo*- or *endo*-) of the epoxides; but instead gave cleavage of the C-O bonds of the aryl epoxides which stereoselectively gave the *endo*-2-acetoxy-4ξ-phenylbicyclo-[3.2.1]octan-3-ones. The methylene epoxides were obtained unchanged after photolysis, in low yield.

The reaction between Bu_3SnH and the *exo*-2-bromo-*anti*-3'-phenylbicyclo[2.2.1]heptan-3-spiro-2'-oxiranes and the *anti*-3'-*p*-chlorophenyl analogue (*exo*- and *endo*-epoxides) generated a radical at C-2 and the products, norcamphor, benzyl alcohol and *p*-chlorobenzyl alcohol, were derived exclusively from C-C bond cleavage.

CONTENTS

CHAPTER 1

Introduction

Radical Chemistry dates back to 1900 when Gomberg[1] investigated the formation and reactions of the triphenylcarbinyl radicals. In the 1920's Paneth[2] showed that less stabilised alkyl radicals also exist, and measured the lifetime of these radicals in the gas phase. Organic synthesis with radicals began in 1937 when Hey and Waters[3] described the phenylation of aromatic compounds by benzoyl peroxide (as a radical reaction). The same year, Kharasch[4] recognised that the anti-Markovnikov addition of hydrogen bromide to alkenes proceeds *via* a radical chain process. The deeper insights into the formation, structure and reactions of radicals was gained in the 1950's and 60's. However, the 1970's witnessed the start of new synthetic methods involving radicals.

Organic radical reactions involve one or more of the following elementary mechanistic steps (**Equations 1A–E**).

Equation 1

A	X–Y	⟶	X$^{\bullet}$ + Y$^{\bullet}$	Homolysis
B	X$^{\bullet}$ + Y$^{\bullet}$	⟶	X–Y	Coupling
C	X$^{\bullet}$ + Y–Z	⟶	X–Y + Z$^{\bullet}$	Atom or group transfer (S_H2)
D	X$^{\bullet}$ + Y=Z	⟶	X–Y–Z$^{\bullet}$	Addition
E	X–Y–Z$^{\bullet}$	⟶	X$^{\bullet}$ + Y=Z	β–Fission

The direction of reaction of radical X˙ in the presence of an organic substrate may be controlled by regio– and/or stereo–selectivity in addition to unsaturated bonds (e.g. **Equation 1D**). The regioselectivity and stereoselectivity is of particular interest in unimolecular reactions.

Ring Closure of Hex–5–enyl and Related Radicals

The intramolecular addition of radicals onto unsaturated bonds has been a widely studied area, in particular because of the interesting regio– and stereo–selectivity effects. Central to this work is the ring closure of the hex–5–enyl radicals (**2**) which involves intramolecular addition. **Scheme 1** provides a nice example of a process which proceeds contrary to predictions based on thermochemical criteria. The stability of alkyl radicals (tertiary › secondary › primary) suggests that the cyclohexyl radical (**5**) would be more stable than the cyclopentylcarbinyl radical (**4**). The experimental observation in the gas phase at temperatures ›298°K showed the radical (**4**) rearranges to the secondary radical (**5**)[5,6].

Thus both theory and experimental observations unambiguously indicate that the cyclohexyl radical (**5**) is more stabilised than the cyclopentyl carbinyl radical (**4**). The behaviour predicted on thermochemical grounds for the radical (**2**) is therefore clear cut; indicating ring closure should proceed mainly by 1,6–bond formation to afford the cyclohexyl radical (**5**). The failure of the thermochemical approach to rationalise the outcome of intramolecular addition was not revealed until later, when careful analyses were carried out on the products formed from the hexenyl radical (**2**) from a variety of precursors[7,8]. **Table 1**, which shows the outcome of the ring closure of radical (**2**), is illustrative of the results obtained[9], indicating that intramolecular addition proceeds in a highly regioselective fashion to give mainly the exo radical product (**6**).

Scheme 1

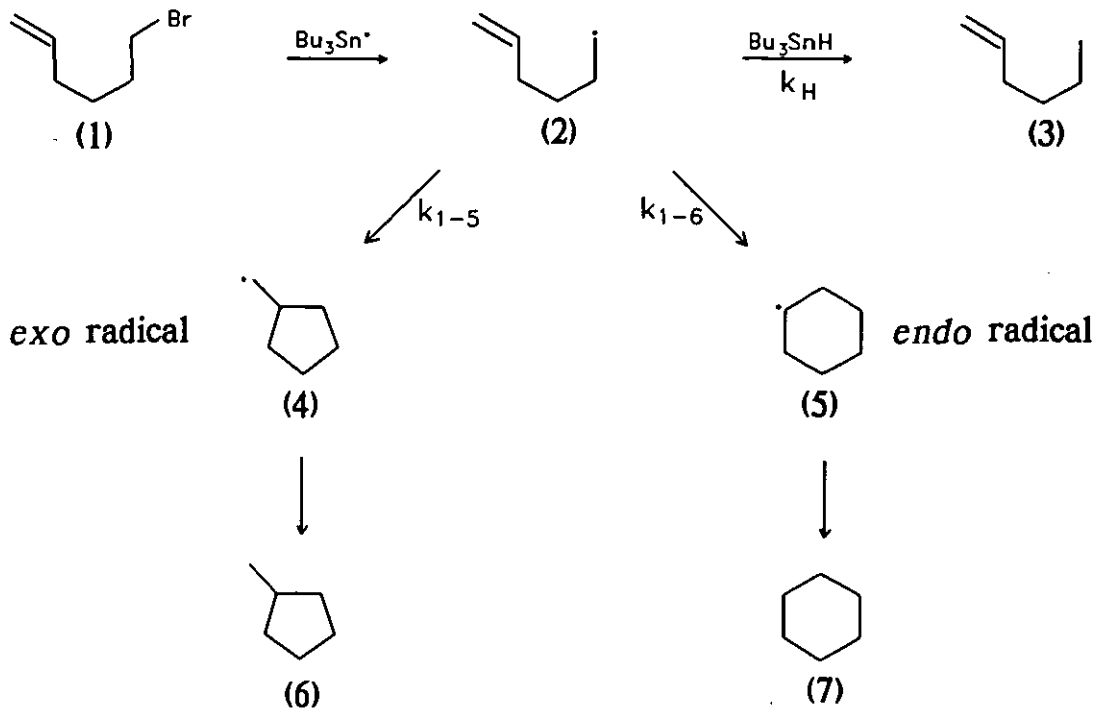
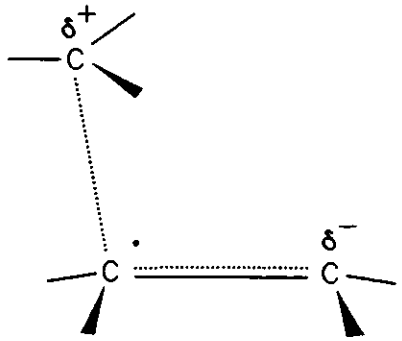


TABLE 1

T °C	[Bu_3SnH] (M)	3 (%)	6 (%)	7 (%)
25	0.093	29.9	69.1	0.9
25	0.195	45.0	54.1	0.8
40	0.077	22.1	76.7	1.3
40	0.260	44.9	54.4	0.9
60	0.078	17.3	81.1	1.6
60	0.347	45.0	53.9	1.1
80	0.260	33.0	65.4	1.6
80	0.454	45.1	53.5	1.4
100	0.162	21.3	76.1	2.7
100	0.582	45.0	53.3	1.7

The first explanation given to account for the regioselectivity was put forward by Capon and Rees[10] and then by Julia and LeBel[11,12]. The hypothesis[13,14], which is now generally considered to account for the behaviour of hex-5-enyl radical and a variety of related species, is that the ring closure depends on stereoelectronic factors. Essentially, this theory contends that the strain engendered in accommodating the mandatory disposition of reactive centres within the transition state (TS) complex for 1,6-ring closure outweighs those steric and thermochemical factors expected to favour the formation of the more thermodynamically stable possible products. When this hypothesis was first adumbrated[13] no direct evidence was available to show that structure of the TS for homolytic addition (8) incorporates the three participating atoms at the vertices of an obtuse triangle orthagonal to the nodal plane of the π-system. Indeed, this model of the TS complex was deduced from the outcome of hex-5-enyl radical (2) cyclisation reaction. However, a number of theoretical treatments[15] now support the structure (8) and indicate that the dominant interaction for attack of an alkyl radical on an olefinic bond involves overlap of the semi-occupied *p*-orbital of the radical atom with one lobe of the vacant π-orbital. Consequently, the TS complex is dipolar. Therefore the incoming radical behaves as a nucleophile and assumes a fractional positive charge whereas the olefinic moiety becomes fractionally negative. Inspection of models and statistical calculations reveals that the required disposition of centres in the TS (8) can be much more readily accommodated for 1,5-ring closure to give the exo radical (4) than for 1,6-ring closure to give endo radical (5). A similar conclusion has been reached by Baldwin on the basis of approach of vector analysis[16].

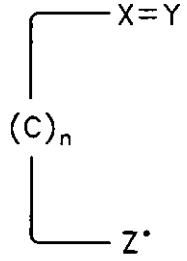
Because it has been established that the ring closure of hex-5-enyl radicals (2) is under stereoelectronic control, it is possible to make a more general statement about the outcome of intramolecular addition



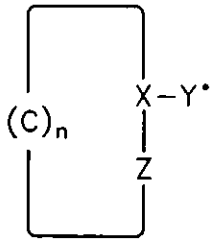
(8)

reactions of alkenyl radicals and similar species. The exo-ring closure (**Scheme 2**), (9) —>(10), will be kinetically favoured over the endo-process, (9) —>(11), which will be under thermodynamic control; where C is a chain of up to 5 atoms ($n \leq 5$), X=Y is a double bond, and Z represents a C, O or N radical centre.

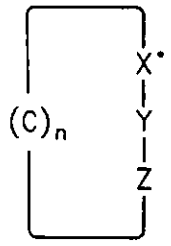
Scheme 2



(9)



(10)



(11)

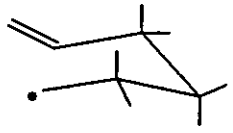
The generalised TS complex leading to radicals (10) and (11) indicates that the degree of preference for exo-ring closure will depend, on the length of the chain $(C)_n$. When the chain is short (n = 1 or 2) the TS complex for the endo-process is very highly strained, but when the chain is long and flexible the difference in strain energy between the TS complexes leading to radicals (10) and (11) will be small.

The two most useful guidelines governing the ring closure of substituted hexenyl radicals (12) were formulated by Beckwith[17]:

1. 1- or 3- substituted radicals preferentially give *cis*-disubstituted cyclopentyl products;

2. 2-or 4-substituted radicals give mainly *trans*-disubstituted cyclopentyl derivatives.

The rules can be explained by the TS structure (12), in which axial and equatorial positions are clearly distinguishable at C-2, C-3, and C-4. Thus, the more favourable conformer should contain the substituents in the equatorial position.



(12)

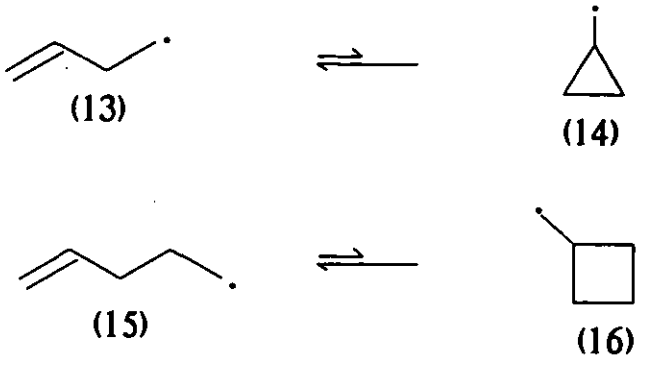
Ring Opening of Cyclopropyl and Cyclobutyl Carbinyl Radicals

Since both the reactivity and the selectivity requirements for chain reactions are fulfilled, radical cyclisation reactions are synthetically useful. But neither three nor four membered rings can be synthesized, because in the cyclopropylcarbinyl and cyclobutylcarbinyl radicals (14) and (16) (**Equation 2**) the rings cleave to form the more stable acyclic radicals (13) and (15), respectively[7,8].

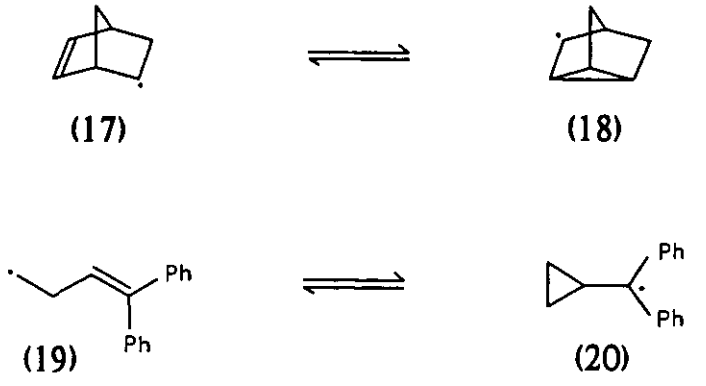
Cyclised products can be formed only in systems where a large proportion of the ring strain is already present in the non-cyclised radical, such as the norbornenyl radical (17)[18,19], or if the cyclic radicals

are stabilised by substituents, an example being the phenyl substituted radical (20)[20] (Equation 3).

Equation 2



Equation 3

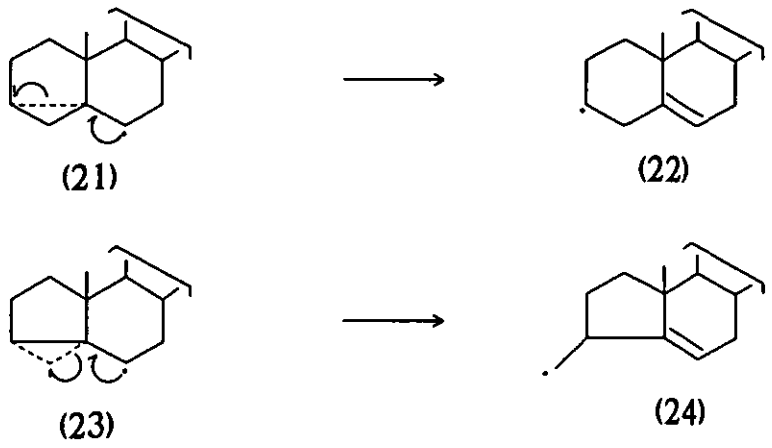


Stereoelectronic Control

The experimental evidence from both kinetic and product studies showed that the ring-opening of cyclopropylcarbinyl and cyclobutyl-carbinyl systems are under stereoelectronic control. A good example is provided by a comparison of the behaviour of the two isomeric steroidal

radicals (21) and (23), each of which undergoes regiospecific ring opening[21,22] (Scheme 3).

Scheme 3



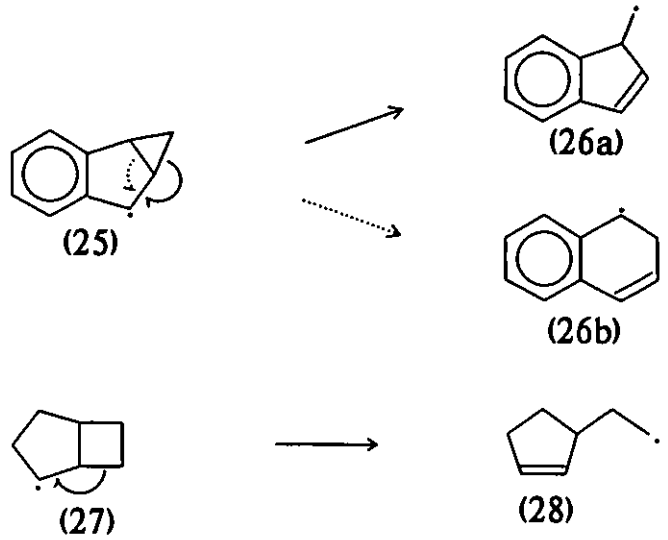
(21) (22)

(23) (24)

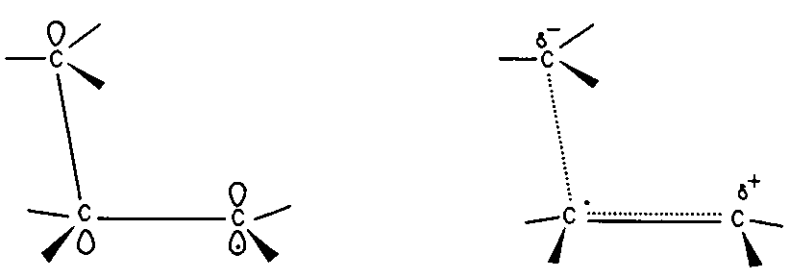
The formation of the more stabilised product (22) exclusively from radical (21), and the less stabilised product (24) from radical (23) clearly suggested that these reactions are relatively insensitive to thermodynamic factors. Inspection of models shows that the cleavage involves preferentially the bond which is most nearly in the eclipsed conformation with respect to the semi-occupied *p*-orbital radical centre. Several other examples[7,23] of these reactions are known. The opening of the cyclopropylcarbinyl radical (25) forming (26a)[24], and the cyclobutyl-carbinyl radical (27) which forms (28)[25], follow the less exothermic pathway possible, leading to the same observation (Scheme 4).

A possible explanation[14,25] for these observations is that the TS complex (30) for a β-fission process, like the TS complex (8) for the reverse reaction, involves a triangular disposition of reactive centres, which is generated by interaction in structure (29) of the semi-occupied *p*-orbital

Scheme 4

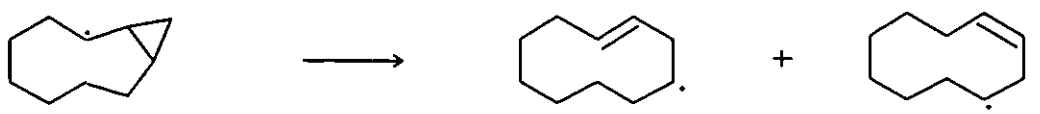


with the σ^* orbital of the bond undergoing cleavage. The orbital overlap would be readily attained in cycloalkylcarbinyl systems containing a freely rotating exocyclic radical centre, but would not be attained readily by the radical centre, situated within the ring. The experimental data agrees with this hypothesis; the conversion of a cyclopropylcarbinyl radical (**25**) into an alkyl radical (**26b**), although highly exothermic[26,27], has a large activation energy, and proceeds very much more slowly than does the mildly exothermic β-fission of the cyclopropylcarbinyl radical (**26a**) ($k \sim 1.3 \times 10^8\ s^{-1}$). Similarly, ring opening of the cyclobutylcarbinyl radical (**27**) is a very slow process[28].



The larger cycloalkyl radicals are sufficiently conformationally mobile and can therefore readily attain the stereoelectronic requirement for β-fission. The ring opening in such systems is endothermic and therefore not observed unless there is some additional factor such as in radical (**31**), which unlike the radical (**25**), undergoes ring expansion[29] (**Scheme 5**).

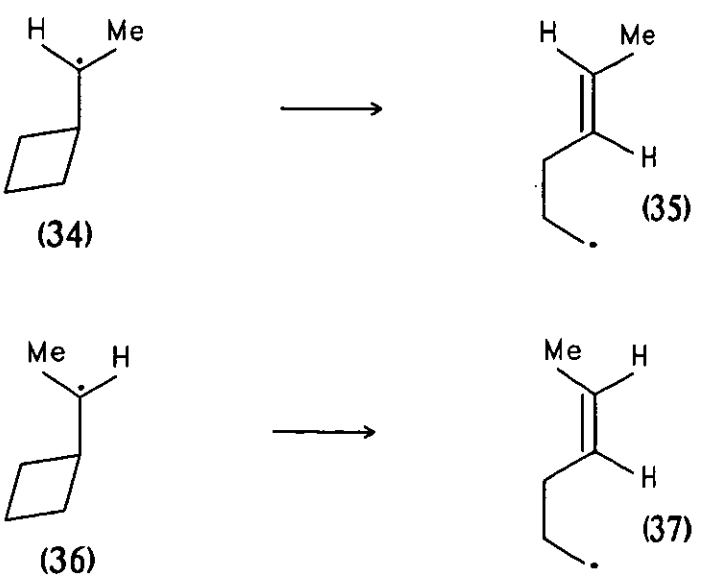
Scheme 5



(31) (32) (33)

Another example of stereoelectronic control is shown in the ring opening of the cyclobutylcarbinyl radicals (**34**) and (**36**)[25,30] (**Scheme 6**). The preferential formation of the *trans*-hex-2-enyl radical (**35**) from 1-cyclobutylcarbinyl radical reflects the greater stability of the transoid conformation (**34**), compared to the cisoid conformation (**36**). The latter has more severe non-bonded interaction.

Scheme 6



(34) (35)

(36) (37)

The curious behaviour of the cyclopropylcarbinyl radical (**38**)[30,31] also provides the basis for the explanation of the stereoelectronic effects. The radical (**38**) preferentially gave the less stabilised product (**39**), even though there are no obvious steric reasons why the less exothermic mode of fission should be favoured. However, if the dominant interaction leading to such processes are between the singly occupied *p*–orbital and an adjacent β, γ–σ * orbital, then this will generate a fractional positive charge at the original radical centre and the transition state complex (**8**) will be formed. The effects of an alkyl substituent at the γ–position will disfavour the formation of the TS through its polar effects (electron donating) on the developing fractional negative charge. The ring opening will therefore proceed in that direction which affords the less substituted product radical (**39**) (**Equation 4**).

Equation 4

(38) (39)

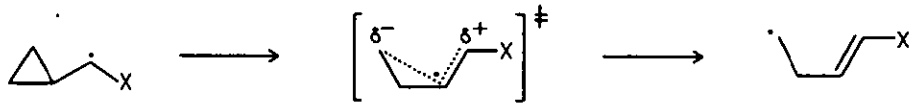
Ring Opening of Oxiranylcarbinyl Radicals

Polarised Transition State

In 1980 Beckwith and co-worker[32] demonstrated that the ring opening of cyclopropylcarbinyl radicals (**40**) most efficiently proceeds through the polarised TS (**41**) [In the case of oxiranylcarbinyl radicals this type of TS would be best achieved by the cleavage of C–O bond rather than C–C bond in the oxiran system (**Scheme 7**)]. Nonhebel *et al*[33] have also studied the influence of substituents (X = OR, COOR, C≡N,

C≡CH) at the radical centre on the rate of ring opening. The results indicated that the electron withdrawing groups substantially retard the rate of ring opening.

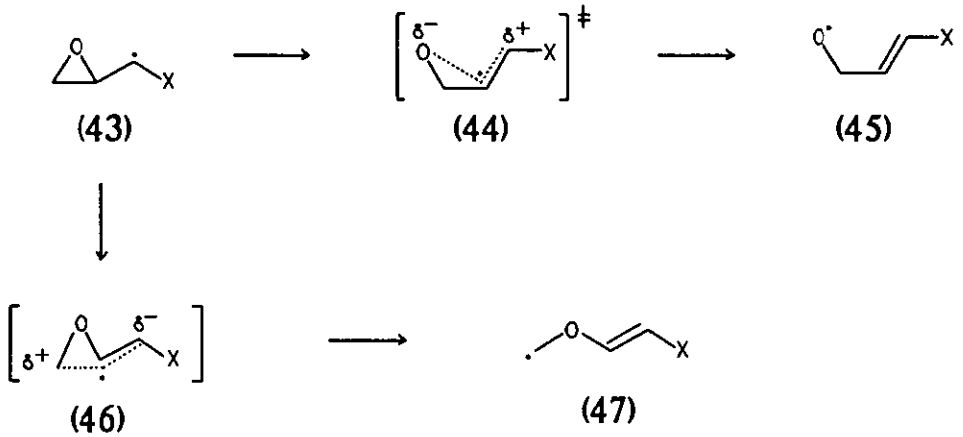
Scheme 7



(40) (41) (42)

If a polarised TS of the type described by Beckwith is also important in the cleavage of oxiranylcarbinyl radicals, it would be expected that C–O bond cleavage would generally be preferred to the alternative C–C bond cleavage (**Scheme 8**).

Scheme 8



(43) (44) (45)

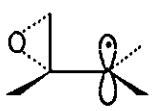
(46) (47)

The limited literature data on oxiranylcarbinyl free radicals support this view that the parent oxiranylcarbinyl radical (**43**) would rapidly open by C–O bond cleavage to give a TS complex (**44**), similar to TS

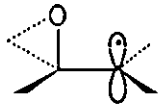
complex (41) proposed by Beckwith, as opposed to C–C bond cleavage leading to TS complex (46); but the effects of substituents on the oxiran ring are also observed to be quite important[42-45].

Electronic and Stereoelectronic Effects

If the singly occupied *p*–orbital next to an oxiran system is examined then it can be quite clearly seen that this can become co–planar with either the C–C bond (48) or the C–O bond (49), depending on the stereochemistry of the epoxide, and hence cleave either the C–C or the C–O bond.



(48)

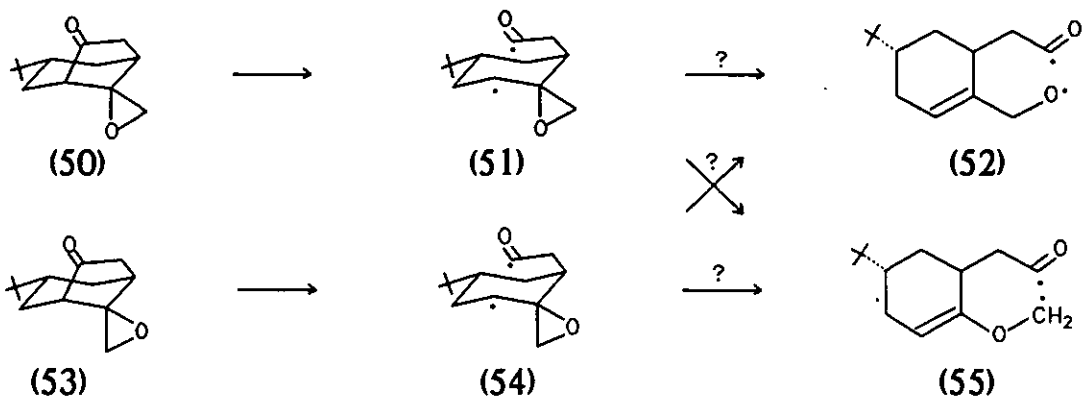


(49)

Agosta *et al*[34] in 1980 suggested that the photochemical ring opening of β,γ–cyclopropyl ketones[35] was under stereoelectronic control[22] and investigated whether such stereoelectronic effects also operated for β,γ–epoxyketones. They suggested that in a rigid system there is no free rotation about the C(α)– C(β) bond and that for oxirans this effect could manifest itself through an enhanced rate of C(β)–O cleavage or C(β)–C(γ) cleavage, depending which bond becomes co–planar with the singly occupied *p*–orbital on C(α). Thermochemical calculations gave an energy difference of approximately 3.2 K cal/mol for the homolysis of the carbon – oxygen bond over carbon – carbon bond for the simple oxiranylcarbinyl radicals[36]. The importance of stereoelectronic effects were assessed in the photochemistry of the two spiroepoxyketones (50) and (53). The α–cleavage should give the radicals (51) and (54), respectively, followed by the opening of the three membered ring to

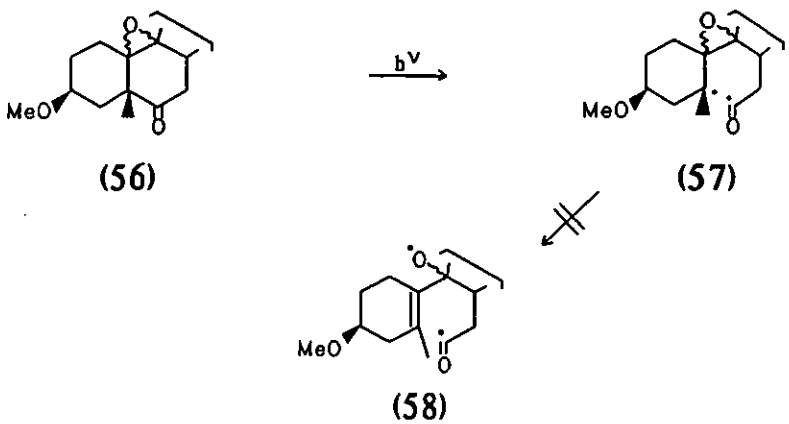
give (52). Simple spiroepoxyketones do follow this path[37]. Alternatively, C–C bond cleavage in the radicals (51) or (54) would give (55) (Scheme 9).

Scheme 9



The products isolated were those expected from the biradical (52) and not from the species (55). It was concluded that stereoelectronic effects appeared to be unimportant, notwithstanding the obvious importance in cyclopropylcarbinyl systems and the general observation that radical induced β–cleavage reactions are most efficient when the bond to be cleaved is co–planar with the *p*–orbital of the adjacent radical[38]. However, the observation by Marples *et al*[39,40] in the photochemistry of the β,γ–epoxyketone (56) suggested that stereoelectronic effects may be important. The failure of the intermediate radical (57)[38,41] to undergo cleavage at the C_{10}–O bond to produce the ring opened radical (58) can be explained by the inability of the radical produced to become planar and hence not achieve the required conformation for β–fission (Scheme 10).

Scheme 10

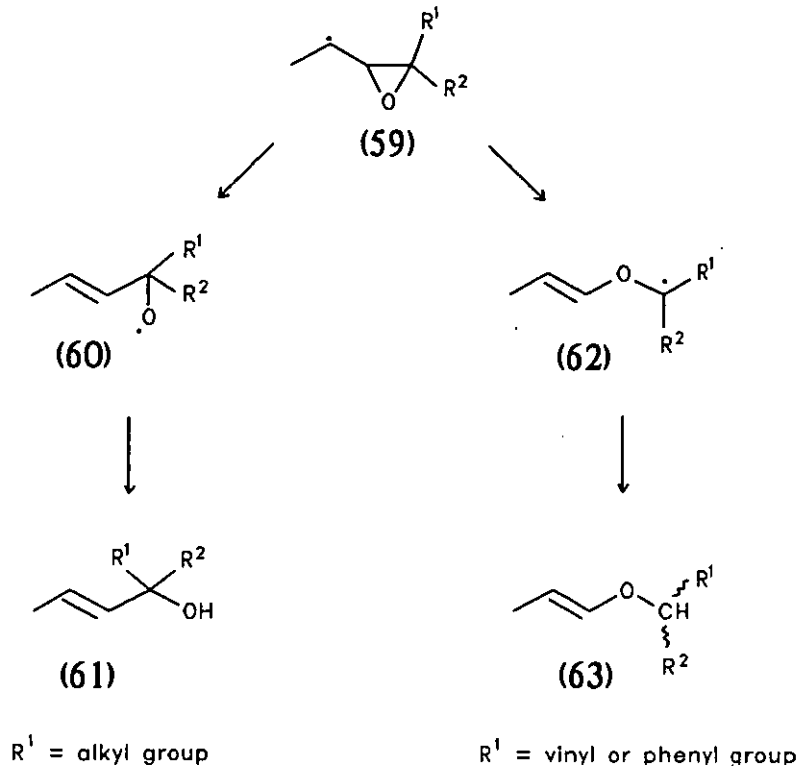


(56) (57) (58)

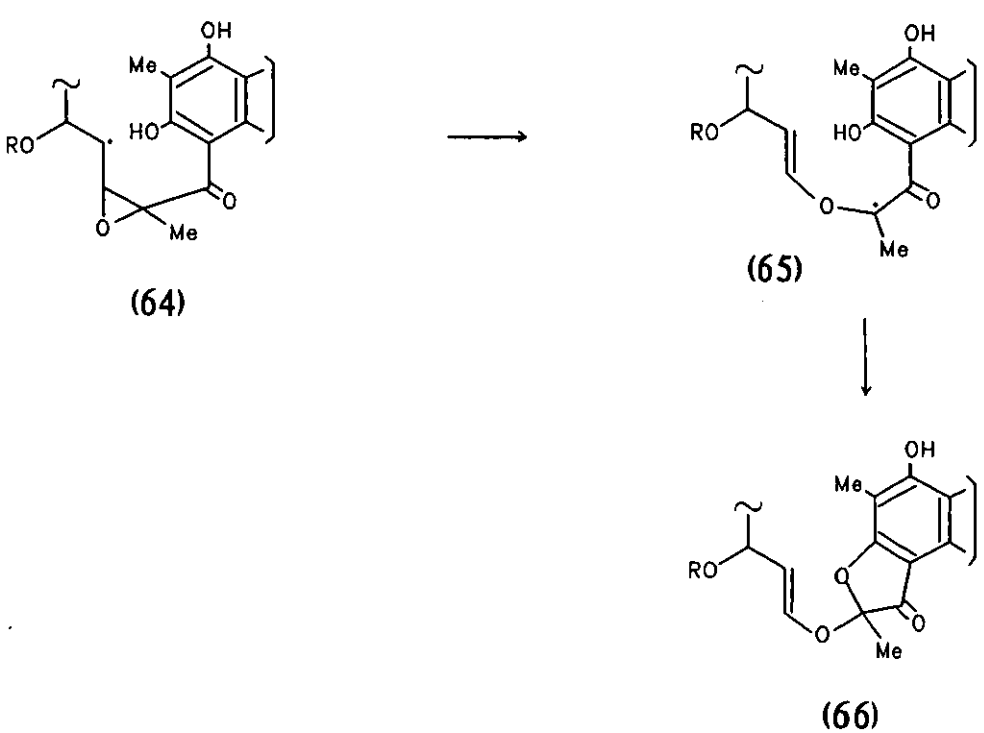
In 1970 Stogryn and Gianni[42] showed that the ring opening of oxirans is influenced by substituents present on the ring. The oxiranyl radical (**59**) rapidly opens up by the C–O bond cleavage, when the substituent R^1 is an alkyl group, to give a radical (**60**). The formation of the products obtained (**61**). However, when R^1 is a vinyl or a phenyl group then the C–C bond cleaves[43] to give radicals (**62**), and the products obtained (**63**) are a mixture of isomers (**Scheme 11**).

In 1987 Murphy *et al*[44,45] confirmed the observation made above, and demonstrated that the C–C bond cleavage can take place when the oxiranylcarbinyl radical (**64**) has an α–carbonyl[46,47]. The radical then cleaves the C–C bond to give a vinyl ether (**65**), which then gives the species (**66**) (**Scheme 12**).

Scheme 11

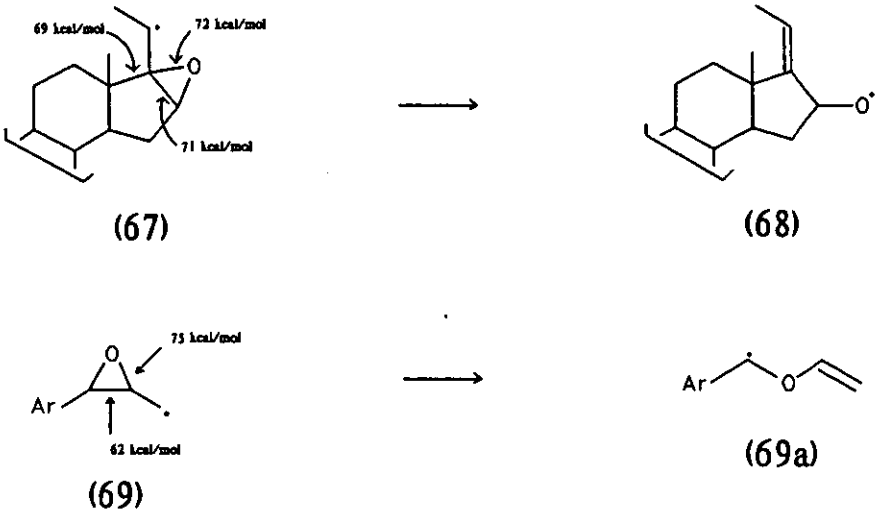


Scheme 12



Jorgensen *et al*[48] in 1990 calculated the bonds dissociation energy (BDE) for the cleavage of bonds β to the radical atom. Small ring cleavages, such as in the cyclopropyl radicals (**14**) which contain only one eligible β bond, yield homoallyl radical (**13**). If the radical atom is α to a three or four membered ring then the β bonds considered for fragmentation are limited to those within that ring, and the weakest of these is selected for cleavage. In oxirans (**67**) and (**69**) the radical is α to an epoxide ring, and the β C–O bond fragments unless the β C–C bond possesses a BDE of ≤ 65 kcal/mol (**Scheme 13**).

Scheme 13

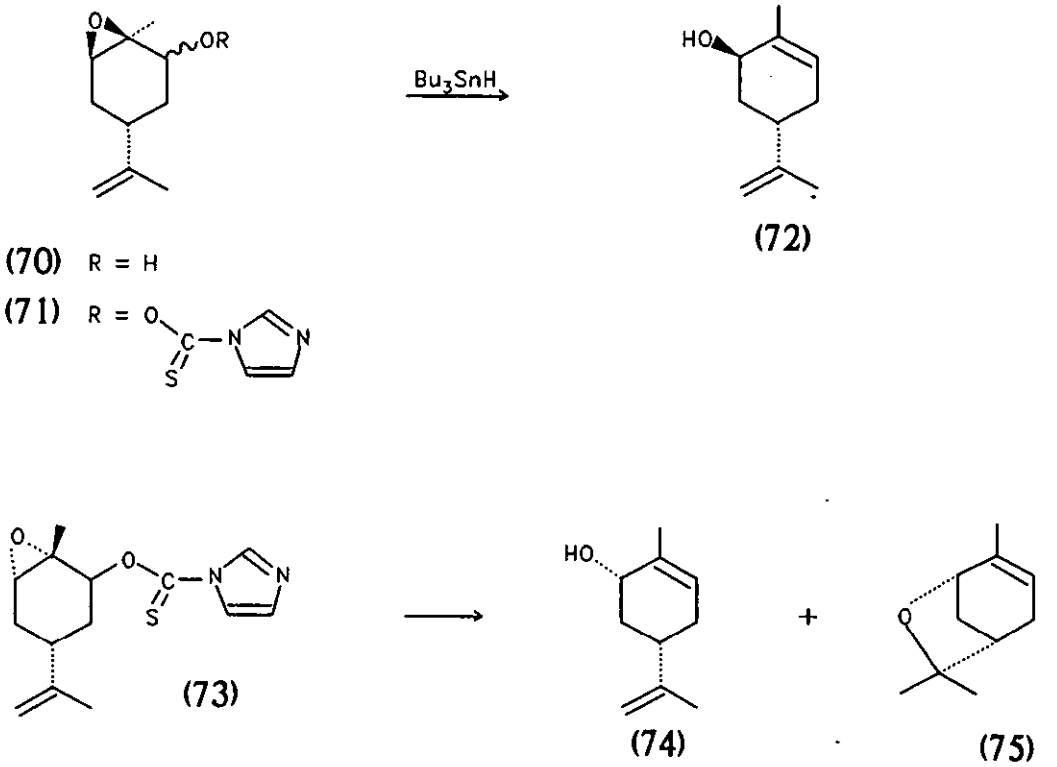


Examples of radical–induced ring opening of epoxides

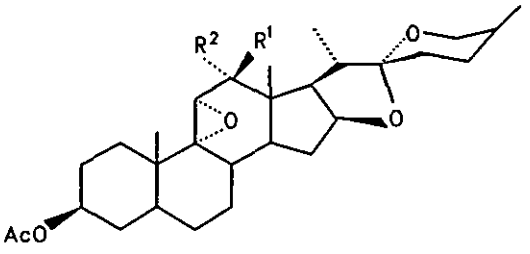
Barton *et al*[49] pioneered the deoxygenation of secondary alcohols with tri–*n*–butyltin hydride (Bu_3SnH)[50] *via* thioesters, dithiocarbonates, or thiocarbonylimidazolides. This work found wide application in natural product chemistry. The fate of the intermediate alkyl radical is influenced to some extent by the vicinal functional groups, and hence smooth fragmentation of 1,2–bis–dithiocarbonates and 1–isocyano–

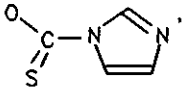
2-dithiocarbonates[51] gave olefins. The first preliminary study involving vicinal epoxides was carried out on the monoterpene alcohol, carveol (70). Barton and Motherwell[49] prepared the epoxy imidazolide derivative of carveol (71) and treatment with Bu_3SnH in refluxing benzene led smoothly to the formation of optically pure (+)-*trans*-carveol (72). However, the reaction of the optically pure isomer, (–)-*cis*-carveol (73), led to a different product, i.e. carveol (74), as well as a secondary cyclisation product pinol (75)[52] (Scheme 14). This secondary cyclisation can be minimised by adding the epoxy-imidazolides to a ten fold excess of Bu_3SnH (inverse addition).

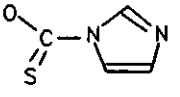
Scheme 14

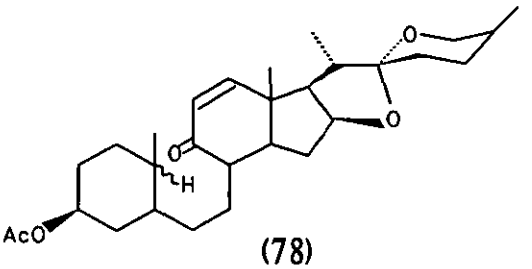


The deoxygenation of hecogenin derivatives (**76**) and (**77**) with Bu_3SnH gave the fragmentation product (unsaturated ketones, **78**) under normal conditions, whereas inverse addition gave the reduced enone (**79**). is known to occur with saturation of the C–C double bond[53].

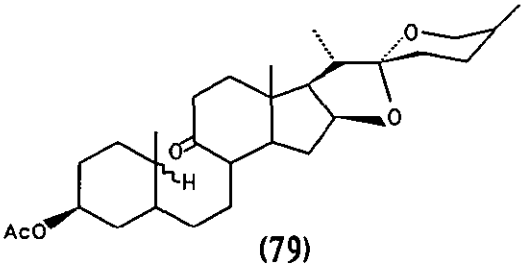


(**76**) R^1 =  , R^2=H

(**77**) R^1 =H, R^2= 



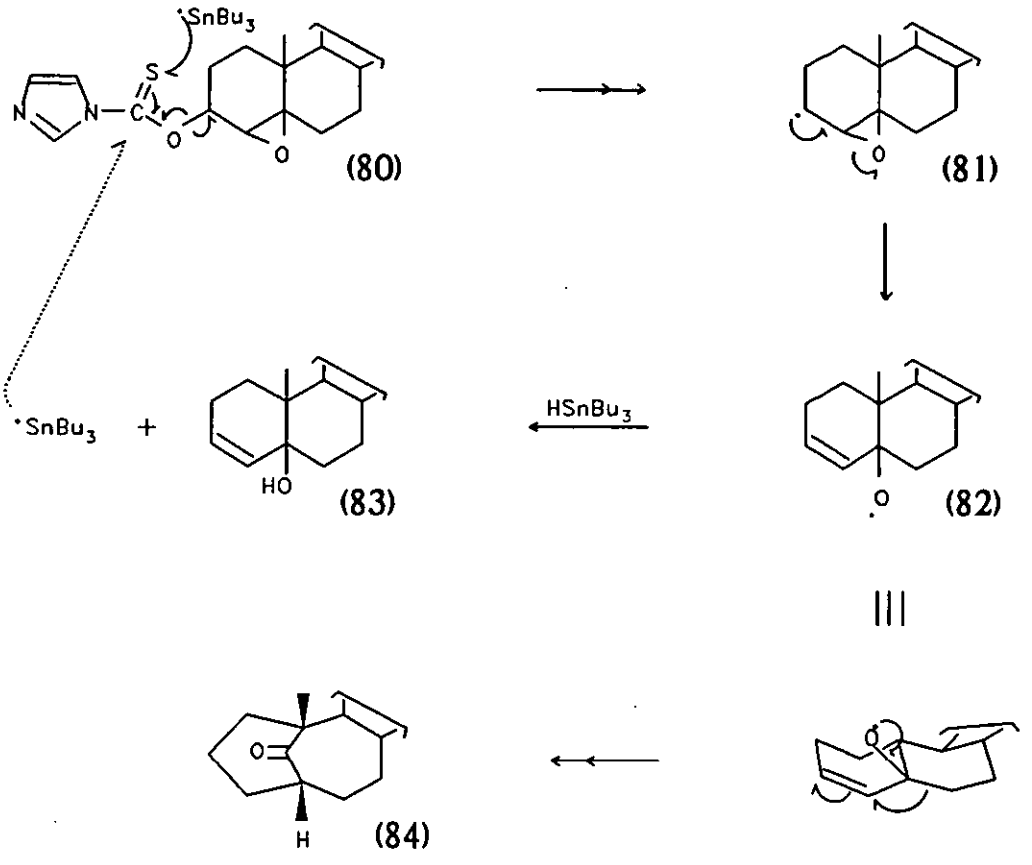
(**78**)



(**79**)

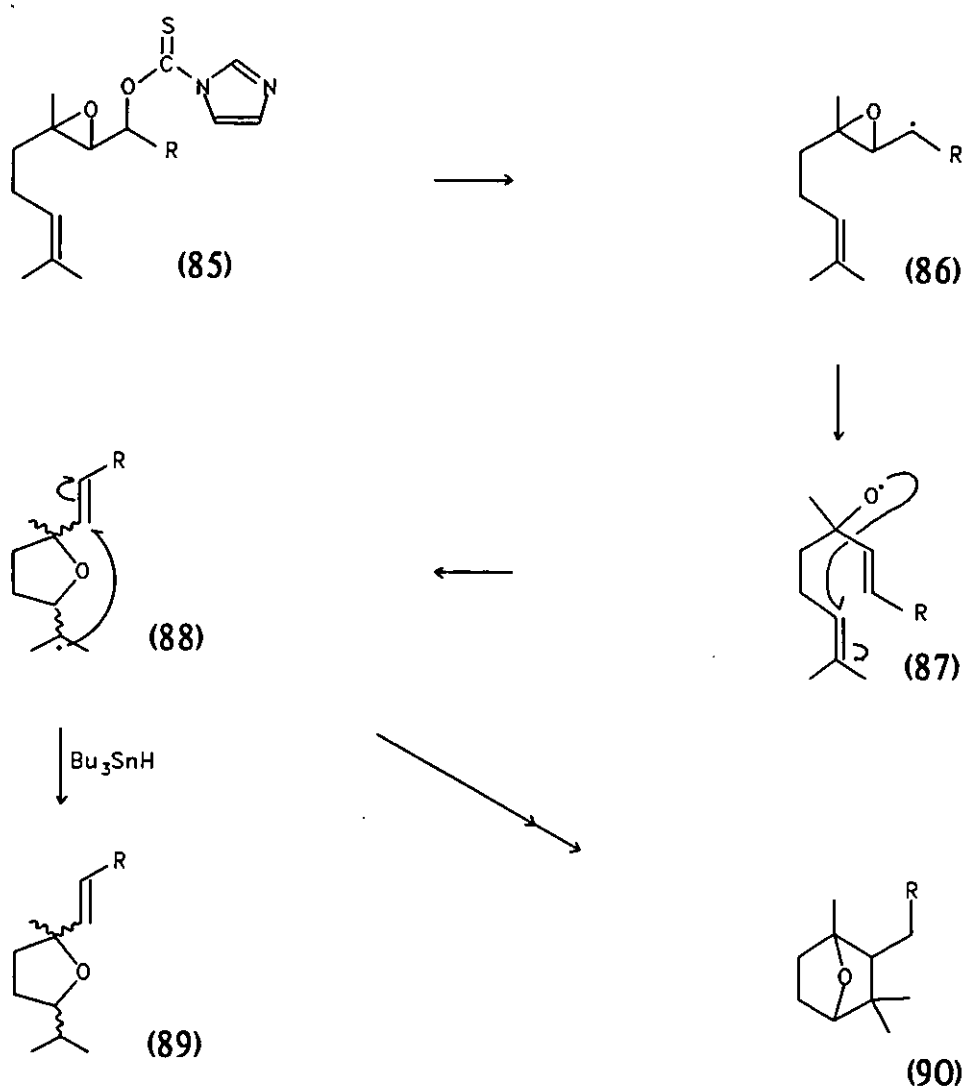
It was also shown that the treatment of the thiocarbonylimidazolide (**80**) derivative of 4β-epoxy-5β-cholestan-3ξ-ol with Bu_3SnH/azobisisobutyronitrile (AIBN) at 80°C, gave cholest-3-en-5β-ol (**83**). A minor product was the bridged bicyclic ketone (**84**). The proposed mechanisms for these transformations, which are outlined in **Scheme 15**, involve the formation of the alkoxy radical (**82**).

Scheme 15



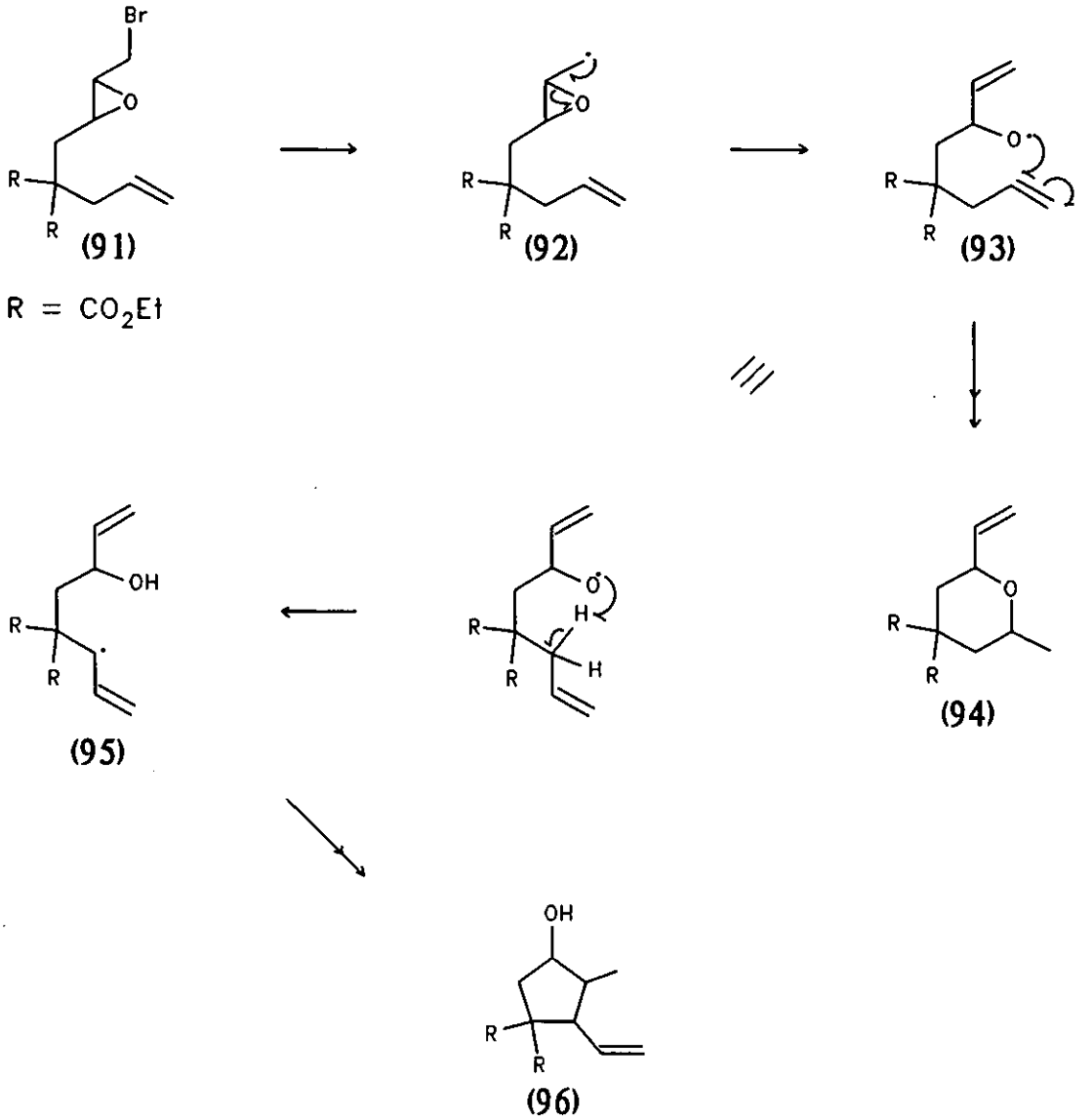
Murphy *et al*[54], using Barton's conditions, attracted by the formation of the cyclic ether (**75**), considered whether such cyclisations would provide stereoselective routes to tetrahydrofurans and tetrahydropyrans, and indeed when they reacted epoxide (**85**) (**Scheme 16**) they obtained the products (**89**) and (**90**). The latter presumably arises by further cyclisation of the *cis*-isomer as shown.

Scheme 16



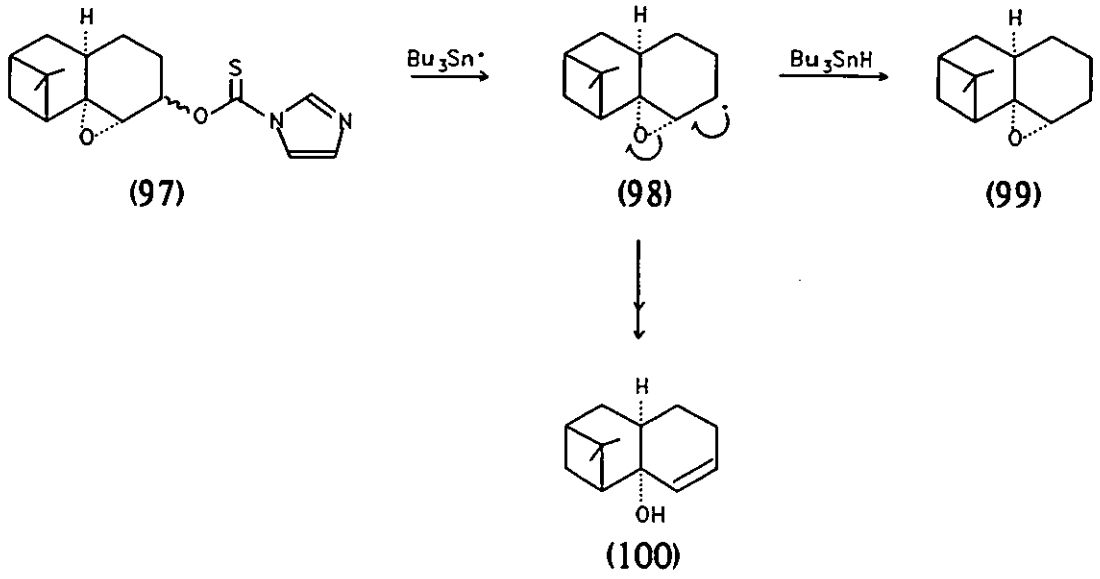
The tetrahydropyran (94) was obtained stereoselectively from the substrate (91) according to **Scheme 17**. A second product (96) which came from the abstraction of an hydrogen atom[55] by the alkoxy radical (93) was isolated.

Scheme 17



Interestingly, Thomas *et al*[56] using Barton's conditions, reacted the epoxy–imidazolide (**97**) to obtain a 4:1 ratio of the epoxide (**99**) and the desired 10,10–dimethyltricyclo[7.1.1.$0^{2,7}$]undec–3–en–2α–ol (**100**) (**Scheme 18**). In this sterically hindered system the radical formed at C–4 is under two competing reactions. It can either cleave the epoxide C–O bond to give the allylic alcohol (**100**), or reduce it to give the epoxide (**99**). The latter predominates, which suggests the radical cannot line up with the C–O bond fast enough (sterically not favourable) and therefore reduction with H$^{\cdot}$ predominates.

Scheme 18



(97) (98) (99)

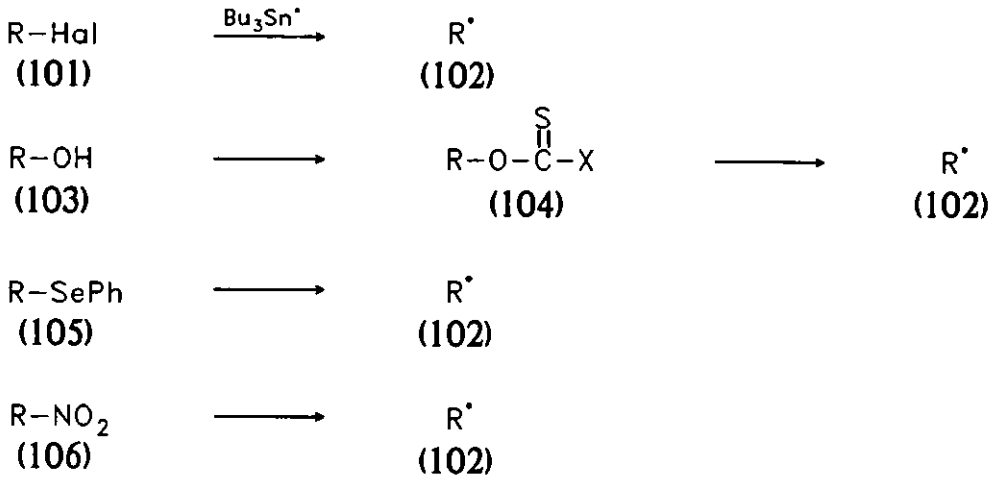
(100)

Methods of generating Carbon–Centred radicals

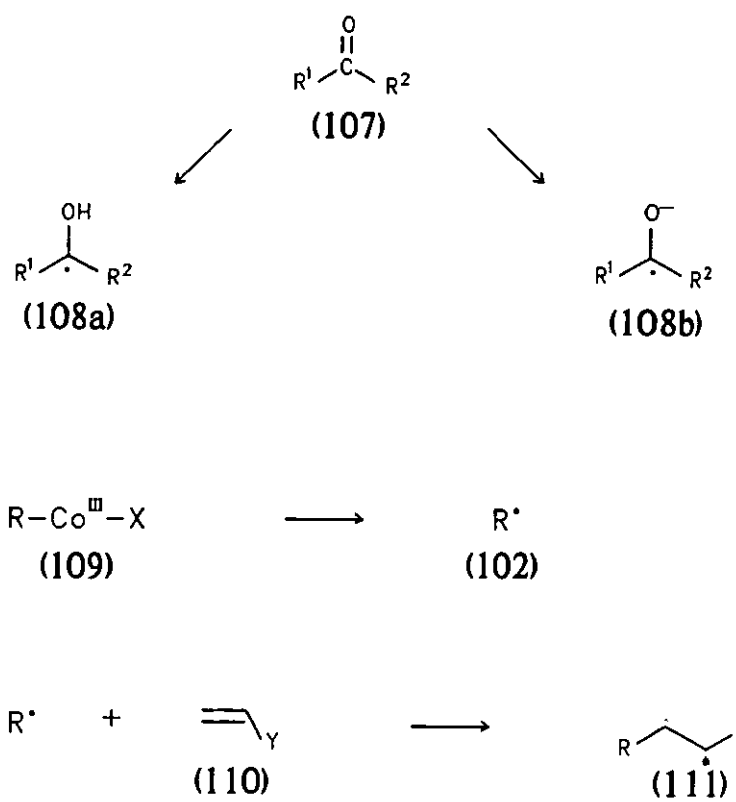
The early lack of attention given to the use of carbon–centred radicals in chemical reactions was due to the general belief that such reactions were not selective. A variety of methods of generating carbon–centred radicals (**102**) have been developed in recent years. **Equation 5** shows the reaction of Bu_3SnH with various substrates e.g. halides (**101**), alcohols (**103**) *via* thioesters (**104**), selenides (**105**), and nitro compounds (**106**), which can be used to generate radical precursors.

Carbon–centred radicals (**108**) can also be generated from ketones (**107**), either by cathodic reduction in an acidic solution or by magnesium / mercury (Mg/Hg) reduction[67]. Also, the cleavage of carbon–cobalt bonds of alkyl cobalamines (**109**) lead to radicals (**102**). The carbon–centred radicals can further be intermolecularly added to electron–deficient alkenes (**110**)[68] to generate a different carbon–centred radical (**111**) (**Equation 6**).

Equation 5



Equation 6

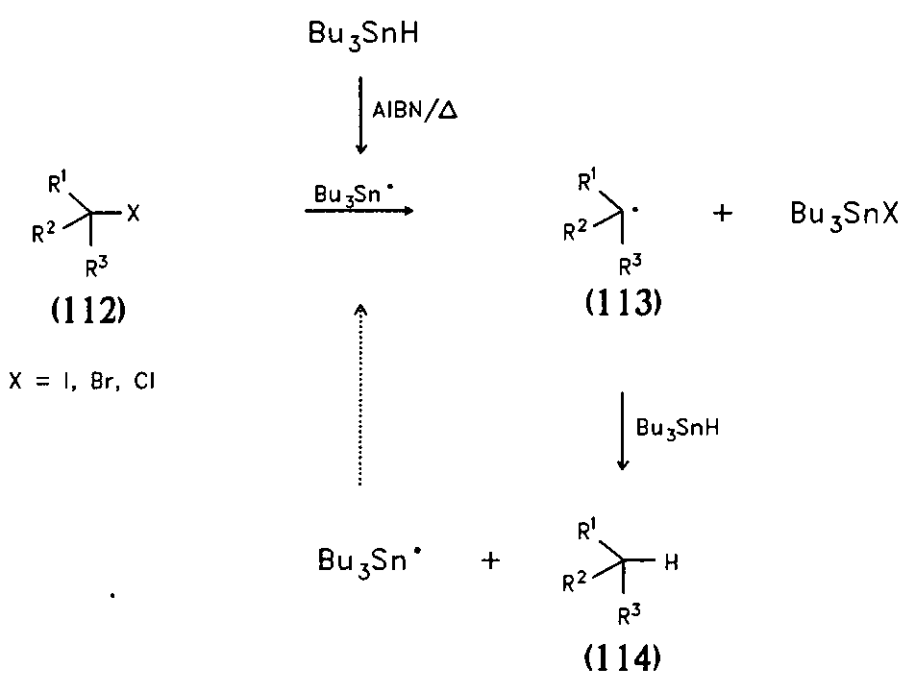


Some of the most important methods have been discussed briefly above and three of the most important modern methods are discussed in the rest of the section.

Use of tri-*n*-butyltin hydride (Bu_3SnH)

One selective radical reaction has been widely used. The reduction of halides with Bu_3SnH and other trialkyltin hydrides was discovered accidentally by Van der Kerk[69] in 1957. The Bu_3SnH reduction process of Van der Kerk works well due to the weakness of the tin–hydrogen bond. Many studies have been devoted to the mechanism and the reductions are generally considered as proceeding by a free radical chain mechanism (**Scheme 19**).

Scheme 19

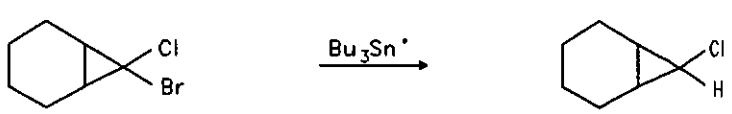


In some cases, the radical (**113**) can rearrange before abstracting hydrogen from the Bu_3SnH. Competition between rearrangement of the

intermediate radical and hydrogen abstraction from the Bu_3SnH will be abundantly exemplified later. It has been shown that polar contributions are important in the TS of dehalogenation by the nucleophilic stannyl radical[60]. As a consequence, the rate of halogen abstraction increases with stabilisation of the anionic character of the TS.

The reactivity of halides depends on the nature of the halogen according to the sequence RI › RBr › RCl » RF. Although iodides and bromides usually react spontaneously with trialkyl tin hydrides, radical initiators such as AIBN or irradiation with UV light are used as well as thermal initiation. Chlorides react with difficulty compared with bromides. Fluorides are practically unreactive but a few examples of fluorine abstraction are known[61]. The nature of the organic group strongly influences the development of the reaction. Therefore tertiary chlorides are expected to reduce faster than secondary chlorides, which in turn are reduced faster than primary chlorides. Taking advantage of the difference in reactivity between iodine, bromine, chlorine and fluorine, it is possible to reduce one halogen selectively in the presence of the others (**Equation 7**).

Equation 7

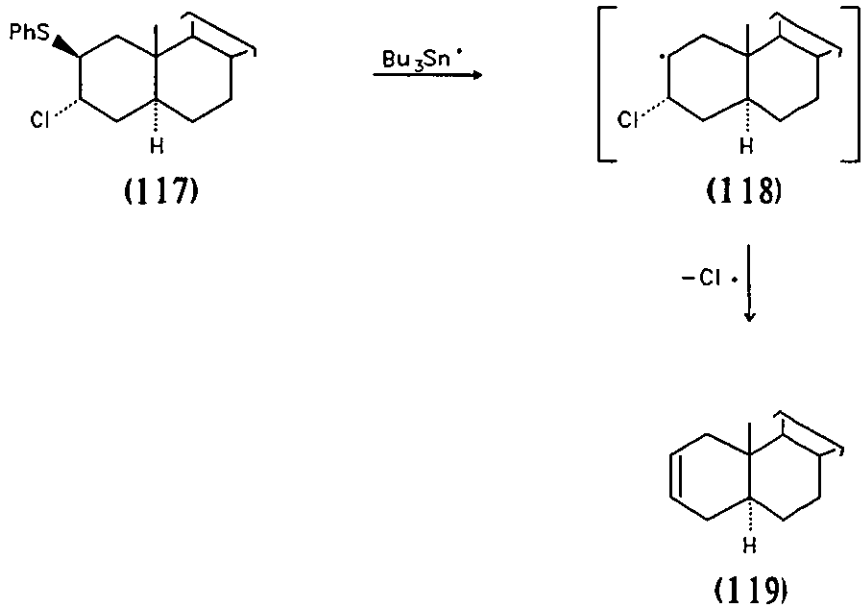


(115) (116)

This chemoselectivity can also be seen in the reduction of phenylselenides and phenylsulphides in the presence of halogen. Reactivity depends upon the sequence RI › RSePh › RBr › RSPh › RCl » RF. However, when halogen abstraction is as difficult as the reaction with another

functionality, a competitive reaction occurs; thus the C-SPh bond can be reduced before the carbon-chlorine bond (**Scheme 20**).

Scheme 20



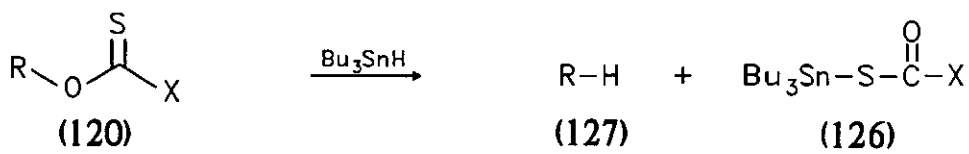
(117) (118) (119)

Barton - McCombie reaction

A carbon-iodine or -bromine bond is much weaker than the corresponding carbon-oxygen (C-O) bond. Therefore, to break a C-O bond to give a carbon radical, attention must be paid to thermodynamic considerations, i.e. there must be one or more driving forces to make the reaction thermodynamically possible. For a radical de-oxygenation process, it was clear that the high-energy of the hydroxyl group would be overcome. Therefore, the reaction shown in **Equation 8** was invented by Barton and McCombie[50], the driving forces being the affinity of the tin radical for sulphur, the overall conversion of the thiocarbonyl function to carbonyl, and the entropy increases associated with the dissociation of the intermediate radical into two particles. This

deoxygenation process of secondary alcohols is widely known as the Barton–McCombie reaction. The early development of this extremely useful reaction first described in 1975, has been discussed[62] in several reviews. Nevertheless this is a continually evolving area and as such we deal here first with mechanistic aspects of the reaction and go on to present an overview of its utility as a tool for the removal or manipulation of hydroxyl groups in organic synthesis.

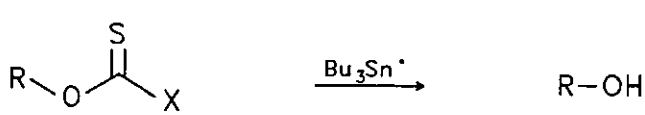
Equation 8



(120) (127) (126)

A variety of X groups have been studied in order to find a derivative that satisfies the ease of preparation, crystallinity, and most important of all, clean deoxygenation processes. It has been found that clean deoxygenation arises when R is a secondary alkyl group for X = SMe,[50,62] SPh[62,63] (dithiocarbonates or xanthates), Ph[50] (thiobenzoates), OMe[64], OPh[65] (thiocarbonates) and 1-imidazolyl[50]. Various X groups have also been found that do not give deoxygenation under radical conditions (e.g. X = H[50,66], Me[50]) which yield starting alcohols only (**Equation 9**).

Equation 9



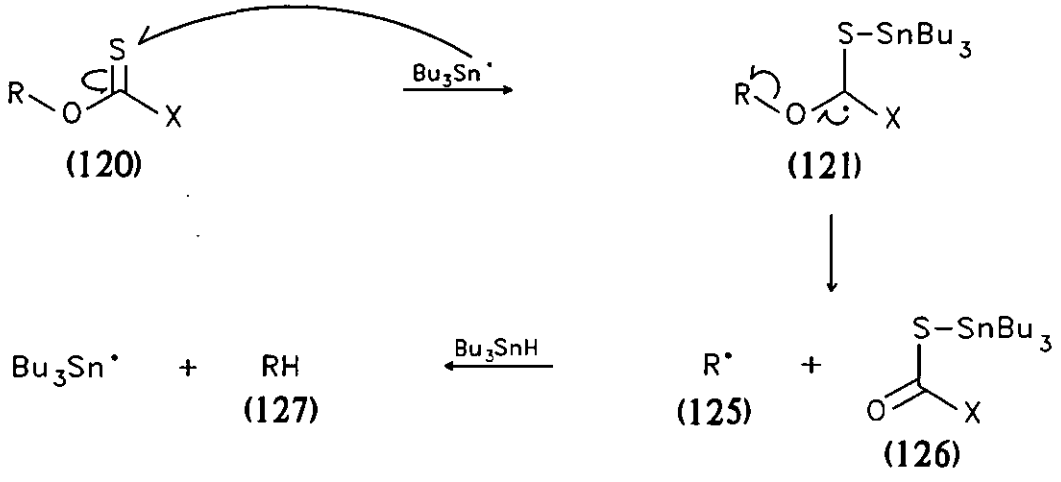
(120) (128)

(120a) X=H
(120b) X=Me

When X = NR_2, (aliphatic thiocarbonates[50]) unchanged starting material is recovered and a last category, the thiocinnamates (CH=CHPh)[50] are simply reduced and do not react further.

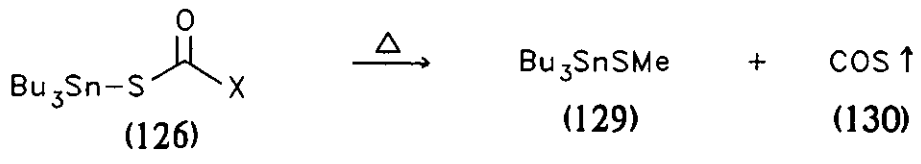
A radical chain mechanism was proposed by Barton and McCombie[50] to account for the successful deoxygenation reaction (**Scheme 21**).

Scheme 21



This mechanism allows for all variations of X. In the most common case (X = SMe), it is assumed that the initial product (**126a**) decomposes *in situ* to give the observed products, (methylthio)tributylstannane (**129**) and carbon oxysulphide (**130**) (**Equation 10**).

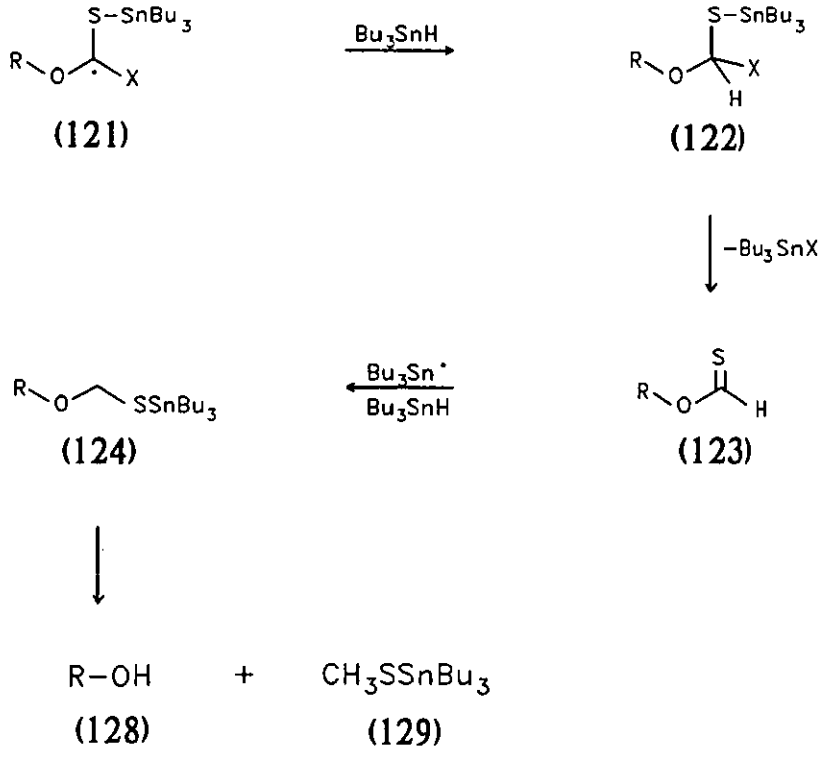
Equation 10



(**126a**) X=SMe

ESR spectroscopy[67] studies have provided support for the initial adduct radical (**121**) for X = H or Me, an example in which efficient fragmentation is not achieved, but has not been observed for the xanthates, thiocarbonates, or thiocarbonyl imidazolides. According to this chain mechanism, the formation of alcohols (**128**) (X = H, Me) is accounted for by inefficient fragmentation of radical (**121**), which is trapped by the stannane, giving an orthoester (**122**). The orthoester derivatives (**122**) are not observable[68] under typical radical conditions and if present must decay further to thioformates (**123**), which react to give hemithioacetals (**124**). The hemithioacetals give back the alcohol on work up (**Scheme 22**).

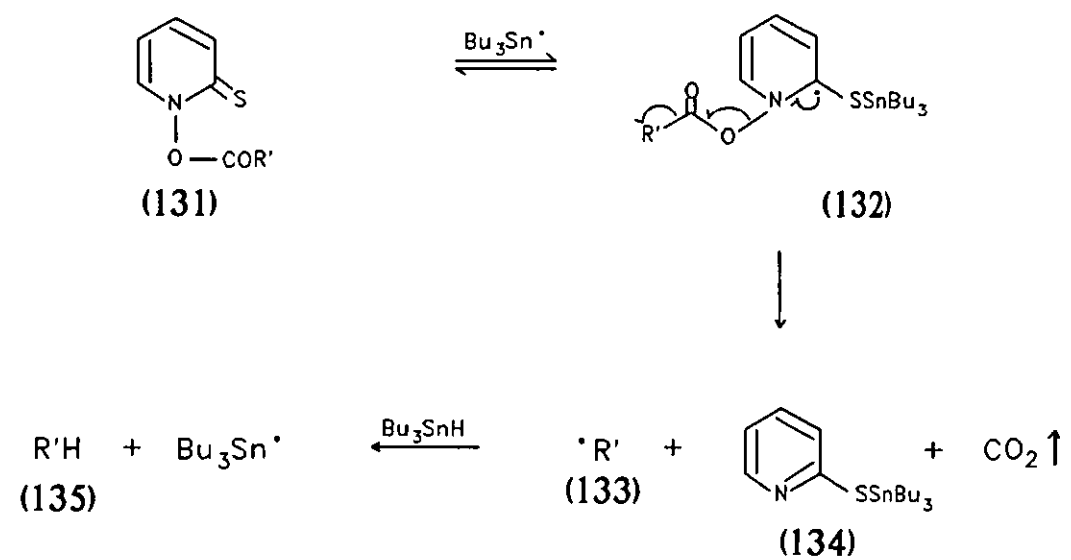
Scheme 22



Use of *N*-hydroxypyridine-2-thione esters in the generation of radicals

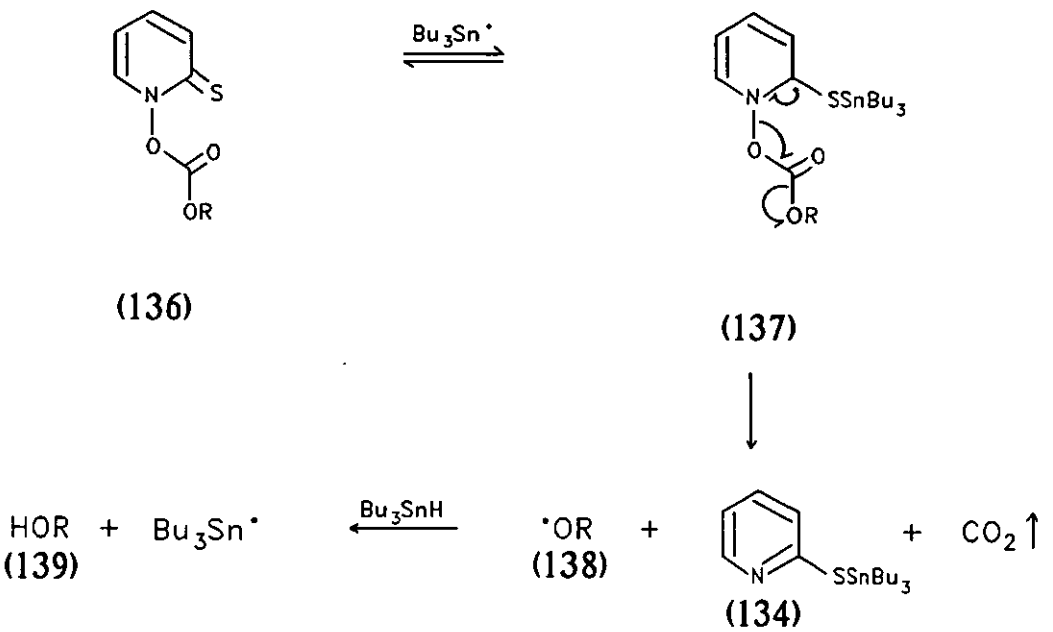
A more broadly based type of radical chemistry, derived from the O-acyl derivatives (**131**) of the thiohydroxamic acids, has also been reported recently[69-72]. These derivatives undergo facile reactions not only with stannyl radicals, but also with thiyl, alkyl, and many other thiophilic radicals, and bring a new dimension to preparative free-radical chemistry. In particular the acyl derivatives (**131**) lend themselves to the facile production of radicals, either on heating to 80°C, or better, by irradiating with a tungsten lamp. The important group in this system is the thiocarbonyl group (**Scheme 23**).

Scheme 23



If the Bu_3SnH is omitted, a smooth decarboxylative rearrangement is seen. It is characteristic of the acyl derivatives of *N*-hydroxy-pyridine-2-thione ester to give clean radical reactions with very high yields of single products[73]. Besides carbon centred radicals (**133**), modification of the system has given a convenient synthesis of alkoxy radicals (**138**)[74] (**Scheme 24**).

Scheme 24

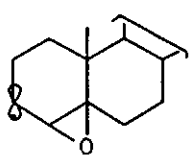

Bu3Sn•
SSnBu3
OR
(136)
(137)
HOR
(139)
Bu3Sn•
Bu3SnH
•OR
(138)
SSnBu3
(134)
CO2

CHAPTER 2

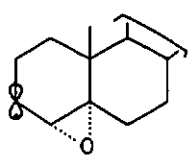
The work of Barton *et al*[49] (**Scheme 15**) prompted us to investigate;

(a) The effects of the stereochemistry of the 4,5-epoxide on the transformation, and
(b) the importance of temperature in the radical fragmentation.

To achieve this we prepared the 4α,5-epoxy-5α-cholestan-3β-ol (**145**) and compared the reaction of its thiocarbonyl imidazolide derivative with Bu_3SnH/AIBN at 80°C with that of its epimer. Further, we have examined the fragmentation of the radicals (**81**) and (**153**), generated photochemically at 35 °C from the acetates (**144**) and (**149**) in HMPA/H_2O using the procedure of Pete *et al*[81].



(81)



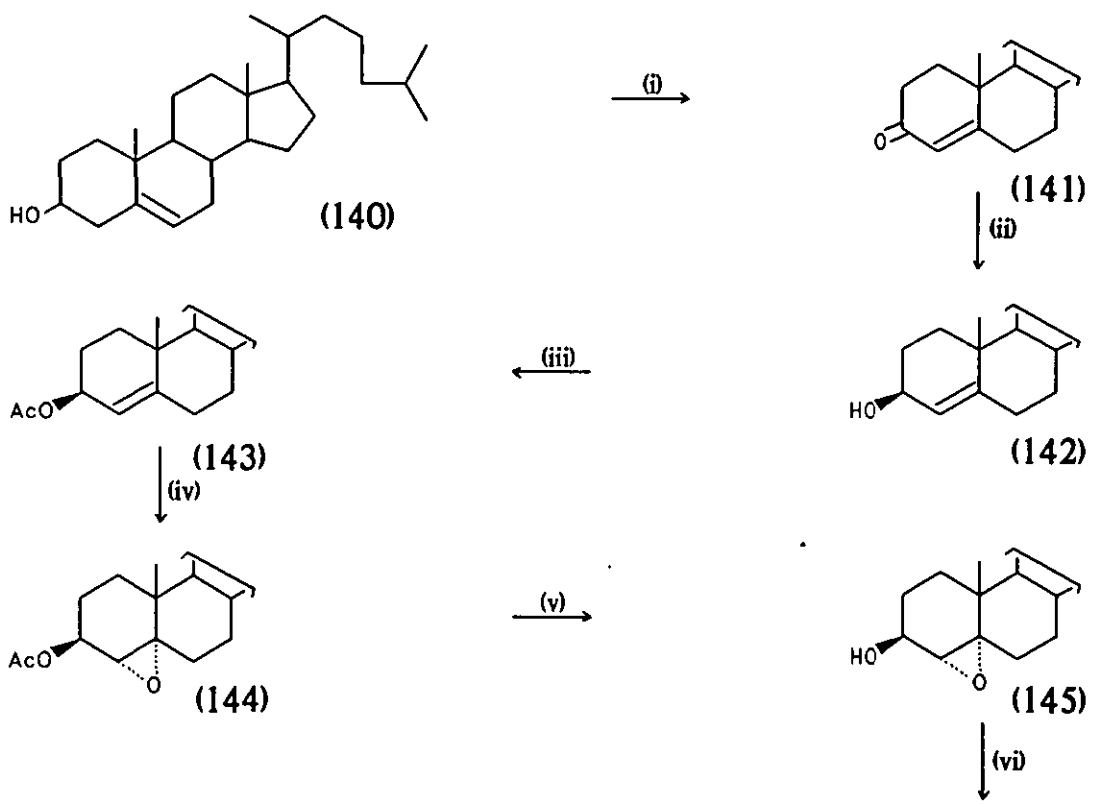
(153)

Synthesis of 4α,5-epoxy-3β-[imidazol-1-yl(thiocarbonyl)oxy]-5α-cholestane

The Oppenauer oxidation[76] of cholesterol (**140**) gave cholestenone (**141**). The reduction with cerous chloride[76] and sodium borohydride gave the thermodynamically more stable cholest-4-en-3β-ol (**142**), which was treated with acetic anhydride and pyridine to give the acetate (**143**)[77]. Epoxidation with *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane gave a mixture of epoxides[78]; the mixture was separated by preparative TLC to afford the major[79] pure α-epoxide (**144**). Base-catalysed

hydrolysis with methanolic potassium hydroxide gave the epoxy-alcohol (**145**)[80], which was treated under anhydrous conditions with *N*,*N*'-thiocarbonyldiimidazole in benzene to give the imidazolide (**146**) in satisfactory yield (**Scheme 25**). The ^{1}H NMR spectrum which had important signals at δ 8.35, 7.75 and 7.06 clearly indicated an imidazolide. Each peak integrated to one hydrogen. A 1H multiplet at about 5.65 corresponds to a methine at C-3, now shifted by 1.65 ppm due to the deshielding effect of the thiocarbonylimidazolide group. The epoxide 1H singlet is at 3.08 and the rest is same as epoxy-alcohol (**145**).

Scheme 25



Reagents i) $Al(iPrO)_3$/Cyclohexanone/Toluene/H^+

ii) $NaBH_4/CeCl_3$/MeOH

iii) Ac_2O/Py

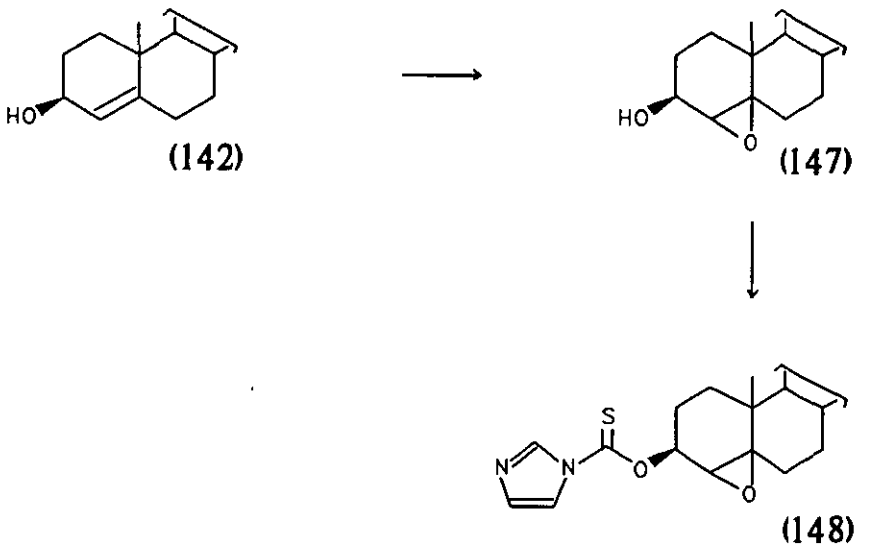
iv) *m*CPBA/CH_2Cl_2

v) KOH/MeOH

vi) *N*,*N*'-Thiocarbonyldiimidazole/Benzene

The other isomer was prepared by the Henbest[79] procedure, involving epoxidation of (**142**) with *m*CPBA in dichloromethane. The delivery of the oxygen is to the same face as the hydroxyl group and hence the β-epoxide (**147**)[80] is the major product. It was treated under Barton's conditions to give the imidazolide (**148**) in a good yield (**Scheme 26**). The ^{1}H NMR spectral data for (**148**) was in accordance with that obtained by Barton *et al*[49].

Scheme 26

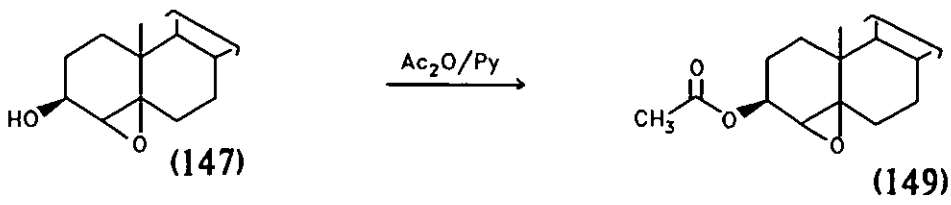


Reagents i) *m*CPBA/CH_2Cl_2
ii) *N*,*N*'-Thiocarbonyldiimidazole/Benzene

Synthesis of 3β-acetoxy-4β,5-epoxy-5β-cholestane

The epoxyalcohol (**147**) was treated with acetic anhydride and pyridine to give acetate (**149**)[79b] in good yield (**Equation 11**). The other isomer (**144**) was prepared according to **Scheme 25**.

Equation 11



(147) (149)

Reaction between 4α,5-Epoxy-3β-[imidazol-1-yl(thiocarbonyl)oxy]-5α-cholestane and Bu_3SnH

The dropwise addition of the imidazolide (**146**) and AIBN to a ten fold excess of Bu_3SnH (inverse addition) led to the formation of 5β-cholest-3-en-5-ol (**83**) in a good yield (71%). The expected product, the 5α-epimer (**150**), was not isolated. A minor unidentified product was also isolated (11%), which showed a carbonyl at ν_{max} 1696 cm^{-1}.

(83) (150)

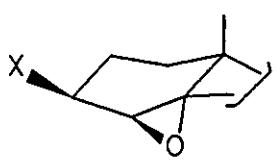
The reduction of imidazolide (**148**), under the same condition yielded the expected 5β-hydroxy-Δ^3-compound (**83**). A minor unidentified product (5%) showed a ν_{max} 1690 cm^{-1} (C=O). This carbonyl product is different from the product obtained from the α-epimer.

Photochemical fragmentation of 3β-acetoxy-4ξ,5-epoxy-5ξ-cholestanes in aqueous HMPA

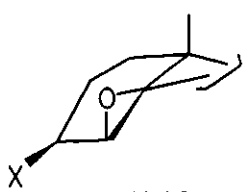
The photolysis[81] of epoxyacetate (**144**) under UV at 254nm for 6h gave again the unexpected product (**83**), in a good yield (74%), and not (**150**). No other product was isolated in any significant amount. The other isomer (**149**), under similar conditions, gave the expected 5β-hydroxy-Δ^3-compound (**83**).

Discussion of the results

The examination of conformationally constrained models of type (**151**) and (**152**) had suggested that the developing semi-occupied *p*-orbital would be approximately in plane with the C-O or C-C bond, depending on the stereochemistry of the epoxide.



(151)



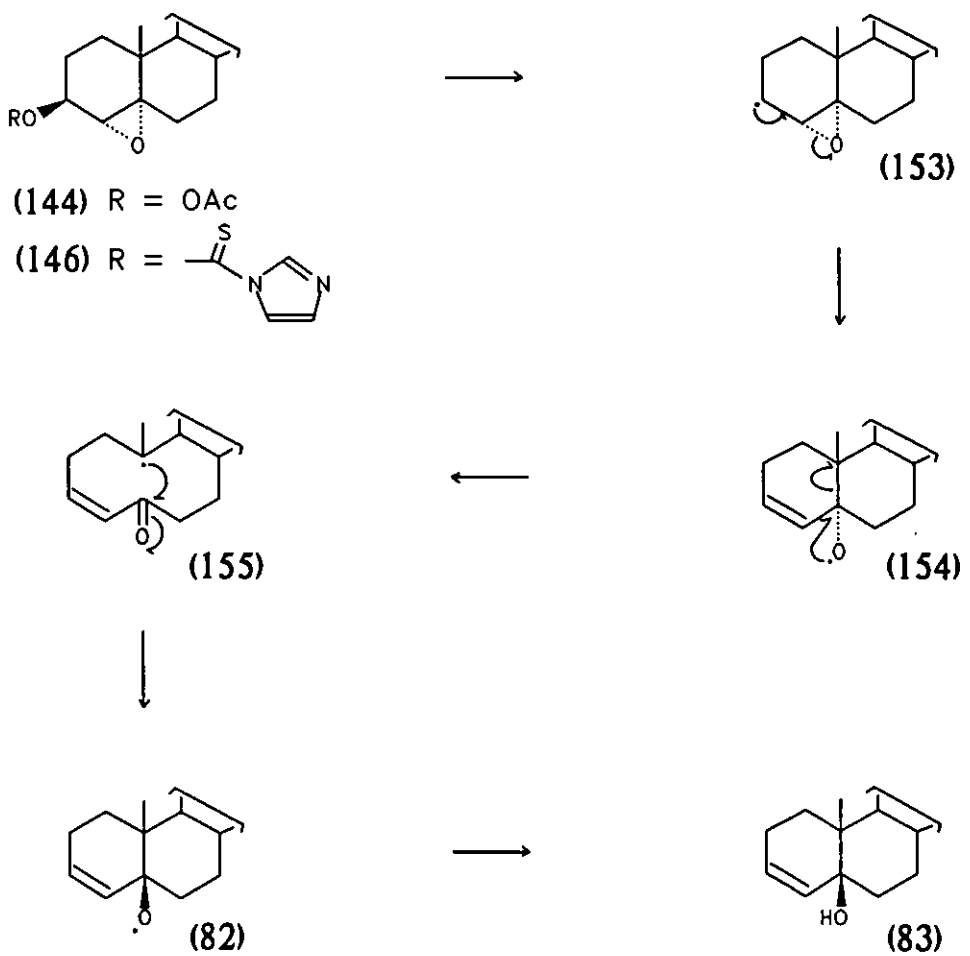
(152)

The absence of major difference both at 35°C and 110 °C in the observed reactions clearly suggests that the reactions are not concerted and that the radicals (**81**) and (**153**) are formed initially and have sufficient life time to conformationally adjust to allow the weaker C-O bond to achieve coplanarity with the semi-occupied *p*-orbital of the C_3 radical.

The conversion of α-epoxides (**146**) and (**144**), both under thermal and photochemical conditions respectively, to the product (**83**) was not

expected. The structure of the alcohol (**83**) was confirmed by comparison with an authentic sample derived by the Wharton rearrangement of 4β,5-epoxy- 5β-cholestan-3-one (**158b**)[82]. The formation of (**83**) is stereoselective and reproducible. The mechanism outlined in **Scheme 27** may explain the formation of a single major product from each of the compounds.

Scheme 27

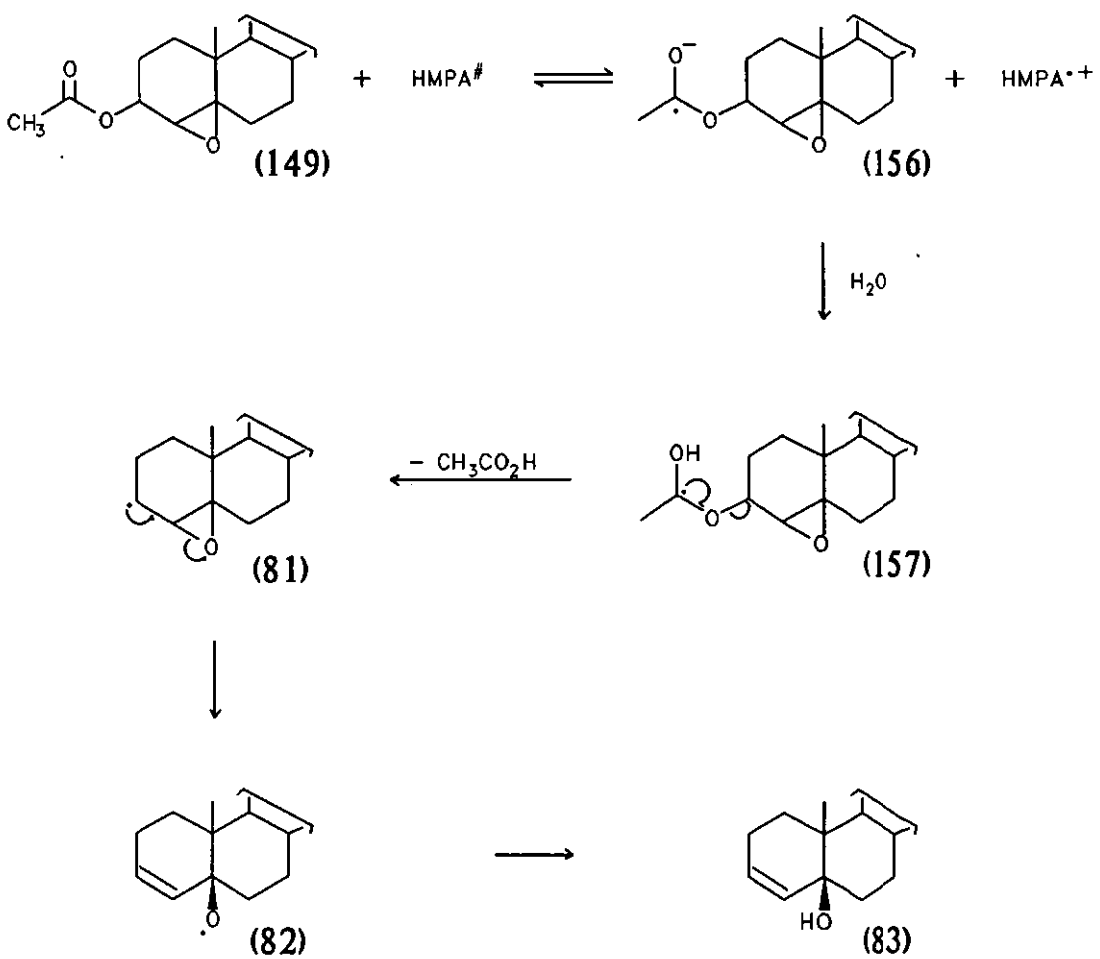


The formation of the discrete radical (**153**) is followed by cleavage of the oxiran C-O bond to form the 5α-alkoxy radical (**154**). The radical then cleaves open the C_5-C_{10} bond to give a ten membered ring species (**155**).

The tertiary alkyl radical may then add to the carbonyl group to give the 5β-alkoxy radical (**82**).

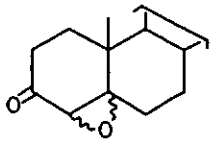
The formation of allylic alcohol (**83**) from the β-epoxyimidazolide (**148**) is readily explained by Barton's mechanism involving discrete radical formation (**Scheme 15**). Likewise the photolytic reaction of (**149**) may be explained by the formation of a discrete radical (**81**) (**Scheme 28**).

Scheme 28

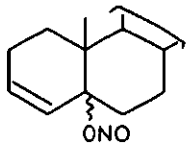


An attempt was made to generate the 5α-alkoxy-radical (**154**) by an alternative route. It was envisaged that the 5α-Δ^3-nitrite ester (**159a**) may

be a suitable precursor since on photolysis it would be expected to give (154). The alcohol (150) was prepared, but it proved impracticable to obtain the nitrite ester as it decomposed during purification.



(158a) = α
(158b) = β

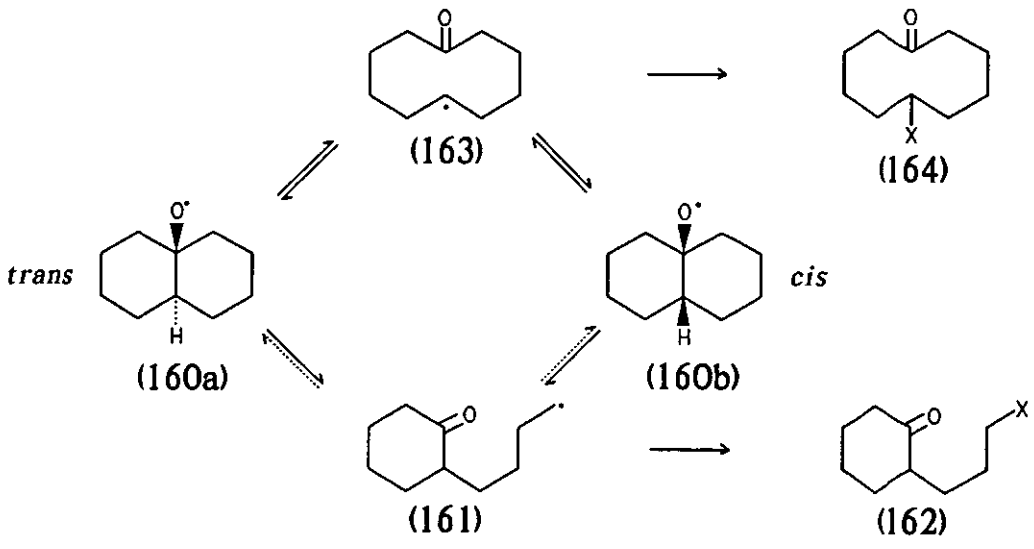


(159a) = α
(159b) = β

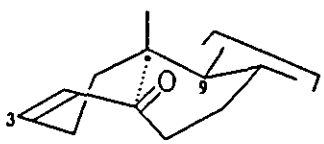
Conclusions

Although we were unable to confirm that (154) does become converted to (83), the mechanism proposed remains the best explanation. The highly selective cyclisation of the radical (155) to afford the 5β-alkoxy radical (82) contrasts with the observations made by Beckwith *et al*[83] on the cleavage of the 9-decalinoxyl radical (160) (**Scheme 29**), in which *cis*- and *trans*- fused rings were obtained. The *cis/trans* ratios were temperature dependent, at -60 °C the ratio is large but decreases with an increase in reaction temperature, at 60 °C the *cis/trans* ratio is 75/20.

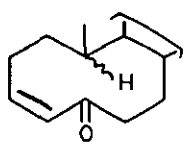
Scheme 29



Models suggest that for the radical (**155**) cyclisation to afford (**82**) is highly favoured if the energetically more acceptable approach[84], involving the O–C-----C˙ bond angle being close to 110°, is important in the transition state. However, closure to the radical (**154**) is highly unfavourable.



(155)



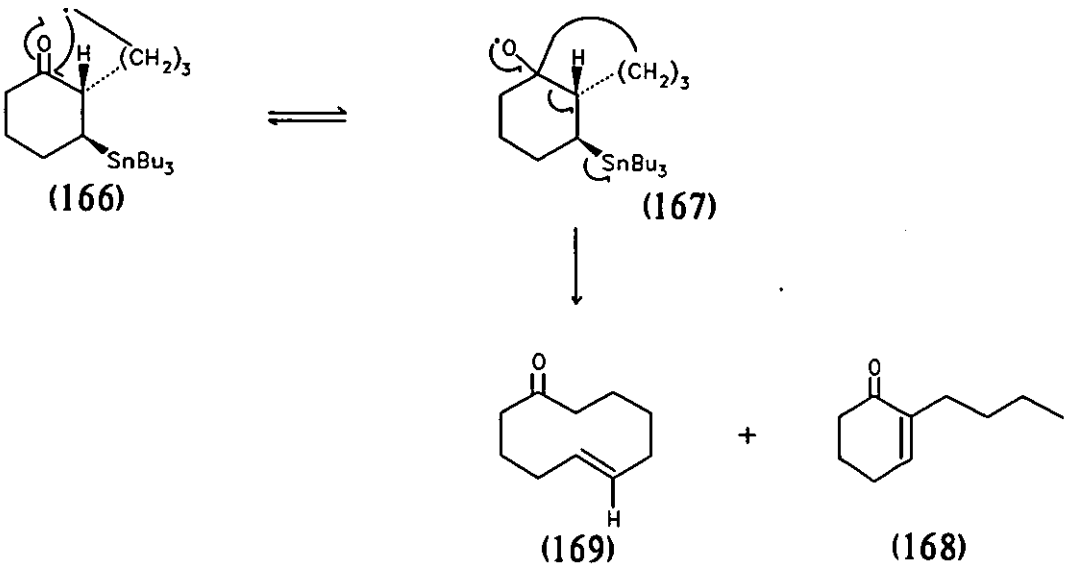
(165)

The absence of compound (**165**) may be due to the philicity of the reducing agent and the radical precursor (**155**). The Bu_3SnH is nucleophilic and the radical (**155**) is likewise nucleophilic, therefore hydrogen atom abstraction may be very slow relative to ring closure.

The observed cyclisation of the radical (**155**) provides further evidence of the addition of alkyl radicals to carbonyl groups[83, 85]. Baldwin *et al*[86] in the radical mediated ring expansion of *cis*– and *trans*–α–substituted–β–stannylcyclohexanones (**166**) provided efficient routes to *cis*– and *trans*– cyclononenones (**168**) and cyclodecenones (**169**) (**Scheme 30**).

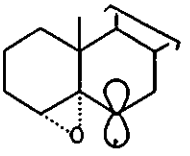
Dowd *et al*[87, 88] also observed competitive expansion followed by reduction, and direct reduction without expansion in related systems.

Scheme 30

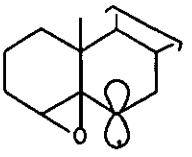


CHAPTER 3

The work of Beckwith *et al*[21] (**Scheme 3**) quite clearly suggests that the ring–opening of the cyclopropyl radicals (**21**) and (**23**) is under stereoelectronic control. The outcome of this study prompted us to investigate whether such stereoelectronic control would be operating in the cleavages of the radicals of the analogous (**170a**) and (**170b**) 4,5–epoxides. To achieve this we have prepared the epoxides and compared their reactions at both low and high temperature.



(170a)



(170b)

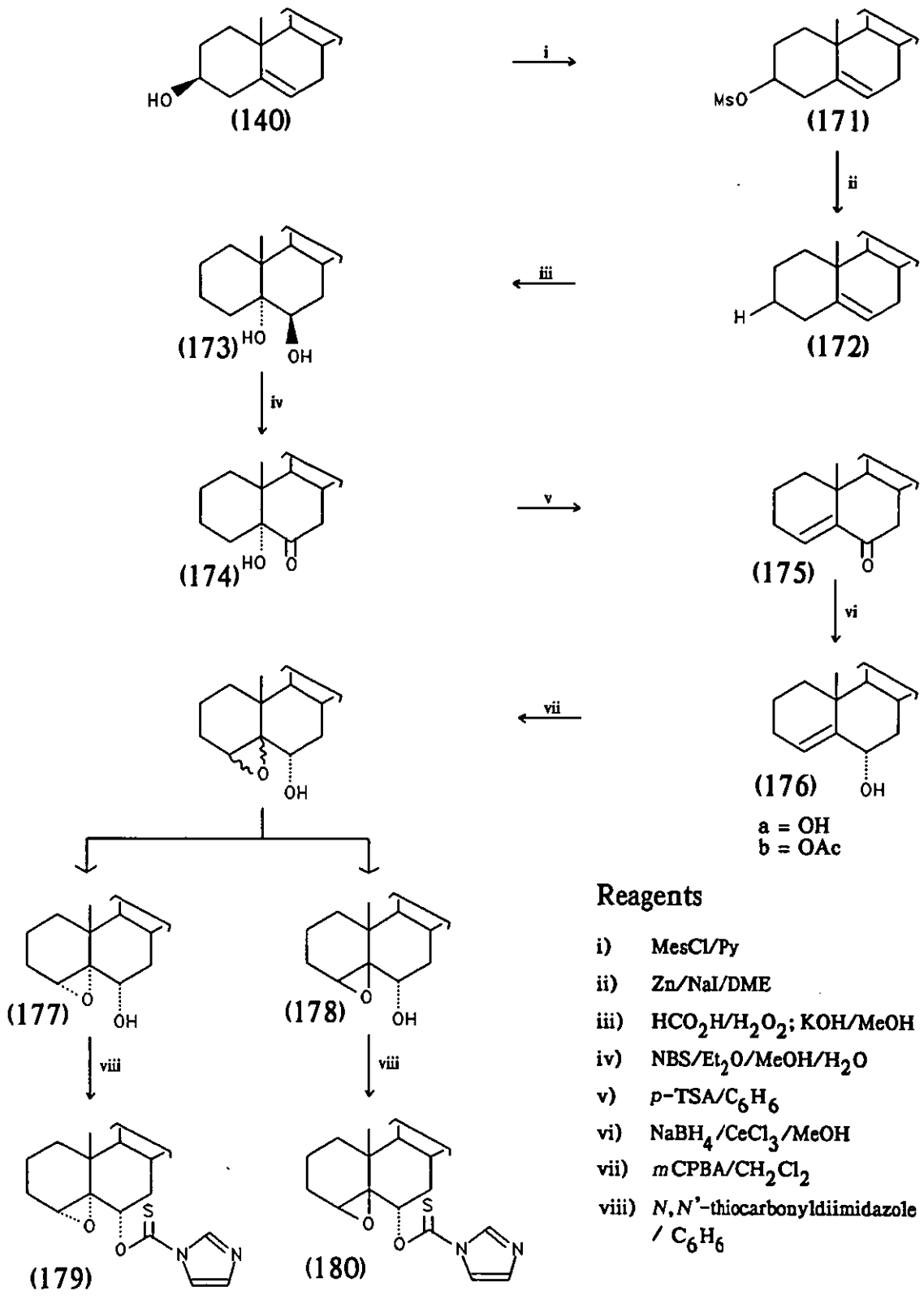
Synthesis of 4ξ,5–epoxy–6α–[imidazol–1–yl(thiocarbonyl)oxy]–5ξ–cholestanes

The Fujimoto and Tatsuno[89] procedure for mesylation of cholesterol (**140**)[90] with methanesulphonyl chloride and pyridine gave the mesylate ester (**171**) in quantitative yield. The mesylate was reduced without any purification with zinc powder and sodium iodide in dimethoxyethane to give cholest–5–ene (**172**). Treatment with performic acid and hydrogen peroxide, according to the Reich *et al*[91] procedure, followed by base hydrolysis, yielded the diol (**173**). Upon oxidation with *N*–bromosuccinimide the diol (**173**) afforded the hydroxyketone (**174**). Dehydration with thionyl chloride and pyridine was not very successful, giving only low yields of product and a lot of tar. Dehydration with a catalytic amount of *p*–toluenesulphonic acid[92] in refluxing benzene gave a good yield of α,β–unsaturated–ketone (**175**). The preparation of (**175**) described by

Ahmad *et al*[93], involving reaction of 3β-chloro-4α,5-epoxy-5α-cholestane with phenylisocyanate and a catalytic amount of lithium chloride in refluxing dimethylformamide, was found to be unsuccessful. Only the starting material was isolated in low yield and some aromatic solid. Reduction of (**175**) with sodium borohydride and cerous chloride[76] gave the 6α-allylic alcohol (**176**)[94,95]. Under the conditions used the thermodynamic equatorial product was obtained. The epoxidation of the 6α-allylic alcohol (**176a**) with *m*CPBA in dichloromethane yielded a mixture of epoxides[96]; the epoxides were separated by preparative TLC using alumina as adsorbent. The faster running product obtained was the α-epoxide (**177**). The 250 MHz ^{1}H NMR spectrum showed important signals at δ 0.67 (3H, s, C_{18}-Me), 1.05 (3H, s, C_{19}-Me), 3.44 (1H, d, J = 3.6 Hz, H-4), 3.83 (1H, td, J=4.9 and 11.6 Hz, H-6β), and 3.83 (1H, d, J=4.9 Hz, OH, D_2O exchange) ppm. This triple doublet at δ 3.83, upon D_2O exchange, changes to a double doublet with the same coupling constant. This suggests that the epoxide is involved in hydrogen bonding to the hydroxyl hydrogen. The methine at C-6 is now coupled to three hydrogens - two at the C-7 carbon and one at the bonded hydroxyl hydrogen and hence the triple doublet. This indicates that the epoxide is at the same side as the hydroxyl group and assigned the α-epoxide. It melted at 138-140°C and has a satisfactory elemental analysis.

The slower running product obtained was the β-epoxide (**178**). The 250 MHz ^{1}H NMR spectrum showed important signals at δ 0.68 (3H, s, C_{18}-Me), 0.99 (3H, s, C_{19}-Me), 3.41 (1H, d, J=4.3 Hz, H-4), and 4.00 (1H, dd, J=4.4 and 11.8 Hz, H-6) ppm. It melted at 86-88°C (lit.[96], m.p. 104-105°C). No such coupling as the α-isomer was observed and it was assigned the β-epoxide. The formation of both epoxides in 50:50 ratio was unexpected. It is generally accepted[97] that epoxidation takes place on the less hindered side of the molecule, and that the hydroxyl

Scheme 31



Reagents

i) MesCl/Py

ii) Zn/NaI/DME

iii) HCO_2H/H_2O_2; KOH/MeOH

iv) NBS/Et_2O/MeOH/H_2O

v) *p*-TSA/C_6H_6

vi) $NaBH_4/CeCl_3$/MeOH

vii) *m*CPBA/CH_2Cl_2

viii) *N,N'*-thiocarbonyldiimidazole / C_6H_6

group would deliver the oxygen on the same face of the molecule. Therefore one would expect to obtain predominantly the α-epoxide (**177**). The allylic acetate also gave the same ratio of α- and β-epoxides on treatment with *m*CPBA. The epoxides (**177**) and (**178**) were converted to the imidazolides (**179**) and (**180**) respectively (**Scheme 31**). Although the mass spectra of imidazolides did not show the molecular ions, satisfactory elemental analyses were obtained.

The 250 MHz ^{1}H NMR spectrum of the imidazolide (**179**) showed important signals at δ 0.71 (3H, s, C_{18}-Me), 1.17 (3H, s, C_{19}-Me), 3.12 (1H, d, J=3.4 Hz, H-4), 5.9 (1H, dd, J=4.5 and 11.5 Hz, H-6), 7.02 (1H, brs, H-31), 7.59 (1H, brs, H-30), and 8.31 (1H, brs, H-29) ppm. The imidazolide (**180**) showed important signals at 0.72 (3H, s, C_{18}-Me), 1.11 (3H, s, C_{19}-Me), 3.24 (1H, d, J=4.1 Hz, H-4), 5.96 (1H, dd, J=4.8 and 12.1 Hz, H-6), and the three imidazolide hydrogens at 7.00 (1H, brs, H-31), 7.55 (1H, brs, H-30), and 8.25 (1H, brs, H-29) ppm.

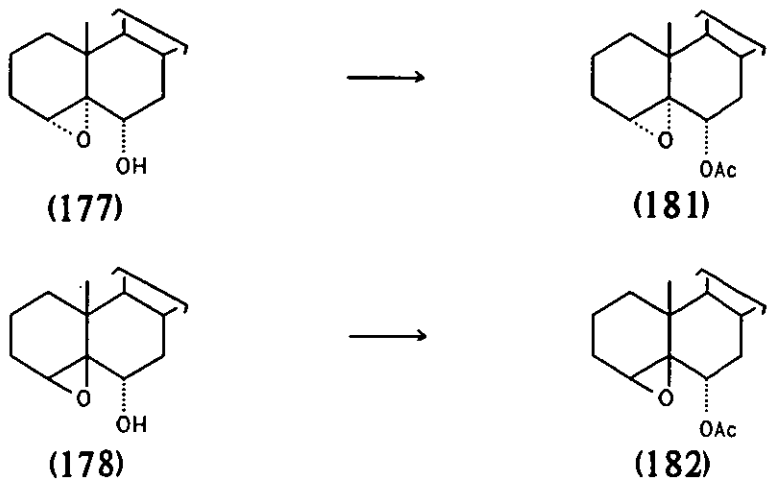
Synthesis of 6α-acetoxy-4ξ,5-epoxy-5ξ-cholestanes

The epoxyalcohols (**177**) and (**178**) were acetylated with acetic anhydride and pyridine and afforded the epoxy acetates, (**181**) and (**182**) respectively in good yield (**Scheme 32**).

Reaction between 4ξ,5-epoxy-6α-[imidazol-1-yl(thiocarbonyl)oxy]-5ξ-cholestanes and Bu_3SnH

The reduction of the 4α,5α-epoxy imidazolide (**179**) with Bu_3SnH (10 equiv., inverse addition) afforded three products. The expected product, choles-5-en-4α-ol (**183a**)[98] was isolated (30%) after

Scheme 32



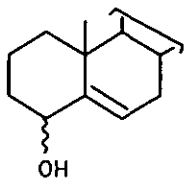
(177) (181)

(178) (182)

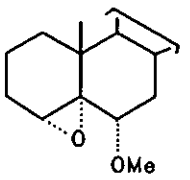
chromatography. The second product isolated was the methoxy epoxide (**184**), in similar yield. The methoxy epoxide displayed a molecular ion in the mass spectrum at m/z 416, and gave an accurate elemental analysis. The 250 MHz ^{1}H NMR spectrum showed important signals at δ 0.68 (3H, s, C_{18}–Me), 1.05 (3H, s, C_{19}–Me), 3.3 (3H, s, OMe), 3.4 (1H, d, J=3.4 Hz, H–4), and 3.50 (1H, dd, J= 4.5 and 11.8 Hz, H–6β) ppm.

The formation of this product is unusual and analogous products have not previously been reported. We have also observed this in the reductions of analogous bicycloheptane molecules and have discussed the mechanism and proved the origin of methoxy group (see Chapter 4).

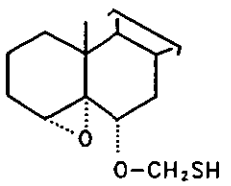
A third minor product isolated was the α–epoxy alcohol (**177**) in 7% yield. The formation of this type of product is also discussed later. It is likely to arise from the hydrolysis of acetal[99] (**185**) which was however not isolated in this case (see Chapter 4).



(183) a = α
b = β



(184)



(185)

When the reaction was performed with less Bu_3SnH (1.5 equivalents) only the rearranged product (**183a**) was isolated.

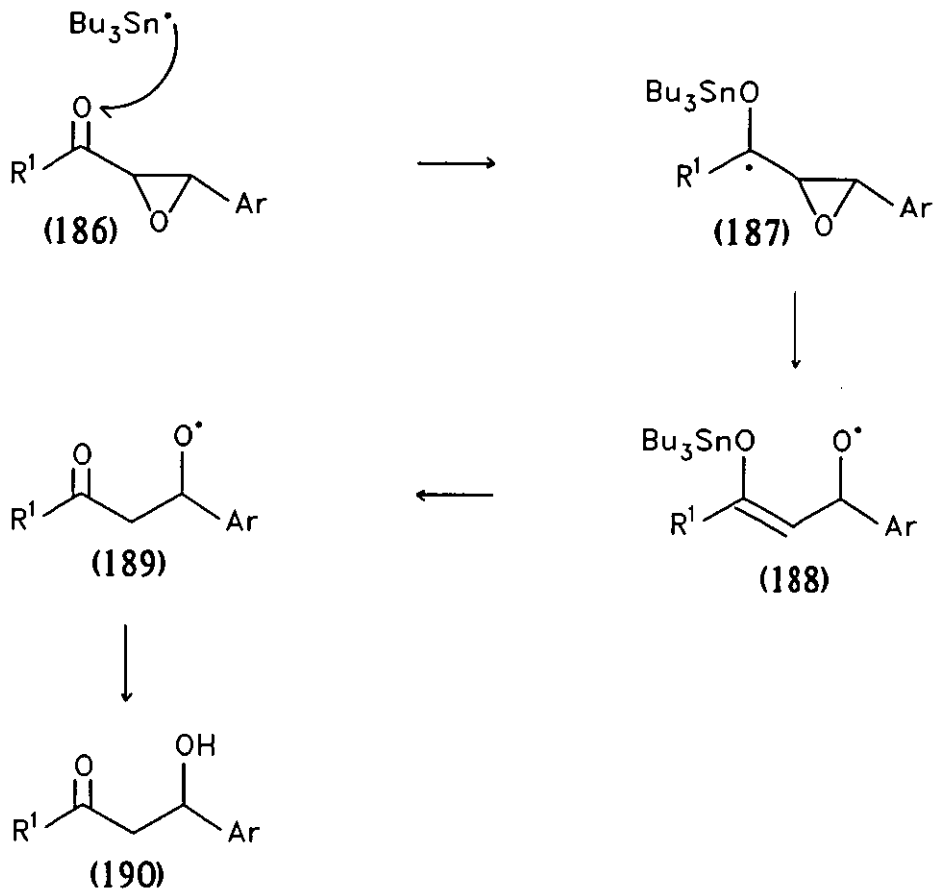
The other 4β,5β-epoxy imidazolide isomer (**180**)[98] was reacted under similar conditions to give the expected product, cholest-5-en-4β-ol (**183b**), isolated (46%) after chromatography.

Photochemical fragmentation of 6α-acetoxy-4ξ,5-epoxy-5ξ-cholestanes in HMPA/H_2O

The photolysis[81] of 4α,5α-epoxyacetate (**181**) in HMPA/H_2O under UV light at 254 nm for 6 hours gave the expected 4α-hydroxy-Δ^5-compound (**183a**) in 19% yield after chromatography. The other isomer, 4β,5β-epoxyacetate (**182**), was reacted under similar conditions to give 4β-hydroxy-Δ^5- compound (**183b**) in moderate yield (56%).

Recently the importance of stereoelectronic effects has been reported in oxiranylcarbinyl radicals (**187**) derived from epoxyketones (**186**) by addition of Bu_3SnH.[100] In particular, it was reported that selective C-O bond cleavage reactions induced by free-radical processes occurred, even when aryl groups were present, to give aldol products (**190**) (**Scheme 33**).

Scheme 33

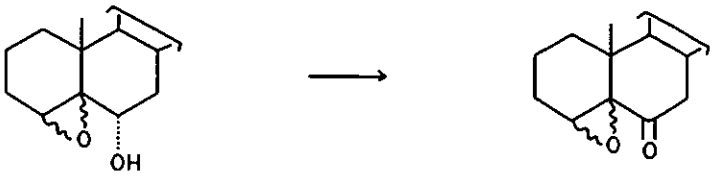


Preparation and reaction of 4ε,5-epoxy-5ε-cholestan-6-one with Bu_3SnH

To achieve this we prepared the epoxyketone (**192**) by oxidising a mixture of epoxyalcohols (**191**) with pyridinium dichromate in dichloromethane (**equation 12**). After chromatography a colourless oil was obtained as a 50:50 mixture of α- and β-epoxides, which was reacted without further purification.

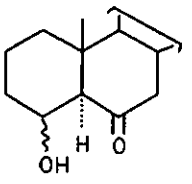
The reaction was carried out using the conditions reported by Hasegawa[100] and Pete *et al*[101], with Bu_3SnH and AIBN in refluxing toluene to give a mixture of aldol products (**196a**) and (**196b**). The crude ^1H NMR spectrum

Equation 12



(191) (192)

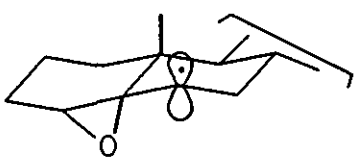
indicated traces of (**196a**) at δ 0.65 (C_{18}–Me) and δ 0.72 for the (C_{19}–Me) and also a 1H multiplet at δ 2.7 for the (C_4–OHα) group and a 1H multiplet at δ 3.8 for the methine at (C–4β). The same spectrum showed signals for (**196b**) [(C_{18}–Me), (C_{19}–Me), 1H multiplet for the β–hydroxyl group at δ 3.5, and the 1H multiplet at δ 4.28 which corresponds to a methine at (C–4α)]. These data are consistent with the reported literature values[101], which indicate perhaps C–O bond cleavage in both cases. A third product can also be seen in the crude spectra, which was later isolated and identified as the starting epoxyketone (**192**). But, after chromatography, only 5α–cholestan–4β–ol–6–one (**196b**) was isolated. The 250 MHz ^{1}H NMR spectrum showed important signals at δ 0.66 (3H, C_{18}–Me), 1.02 (3H, s, C_{19}–Me), 3.5 (1H, brs, OH, D_2O exchange), and 4.28 (1H, brm, H–4) with a coupling constant of W½=7 Hz as reported for the aldol product (**196b**)[101]. The stereochemistry at C–5 is α since the hydrogen comes from the least hindered α–face to give thermodynamically stable *trans* product. The IR spectrum showed a ν_{max} at 3536 cm^{-1} (free and bonded OH) and 1698 cm^{-1} (carbonyl). The mass spectrum showed a molecular ion at m/z 402.



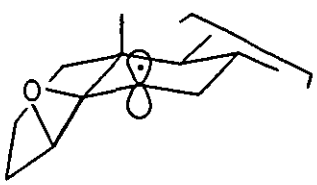
(196)
a = α
b = β

Discussion of the Results

The examination of the conformationally constrained models of the type **(197)** and **(198)** had suggested quite clearly that the semi-occupied *p*-orbital in the initially formed radical at C-6 would be coplanar with the C-O bond in the α-epoxide and the C-C bond in the case of the β-epoxide. It was thought therefore that this might be a better system than the 4,5-epoxycholestan-3-yl radicals for the detection of any stereoelectronic effects.

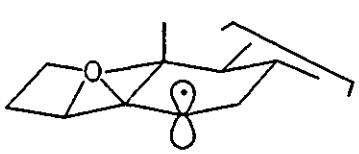


(197)



(198)

The formation of products under both thermal and photochemical conditions indicated that C-O bond cleavages had occurred selectively for both isomers. The explanation for the exclusive C-O bond cleavage arising from the discrete radicals can only be explained in terms of transition state energy. The TS energy for the C-C bond cleavage would be far too great as compared with the TS energy arising for the C-O bond cleavage, and hence to avoid this former energy barrier the radical resulting from the β- epoxide **(198)** adopts the less favourable twisted boat conformation **(199)** in ring B. The adopted conformation then allows the singly occupied *p*-orbital at C-6 to become co-planar with C-O bond and hence cleave the C-O bond selectively.



(199)

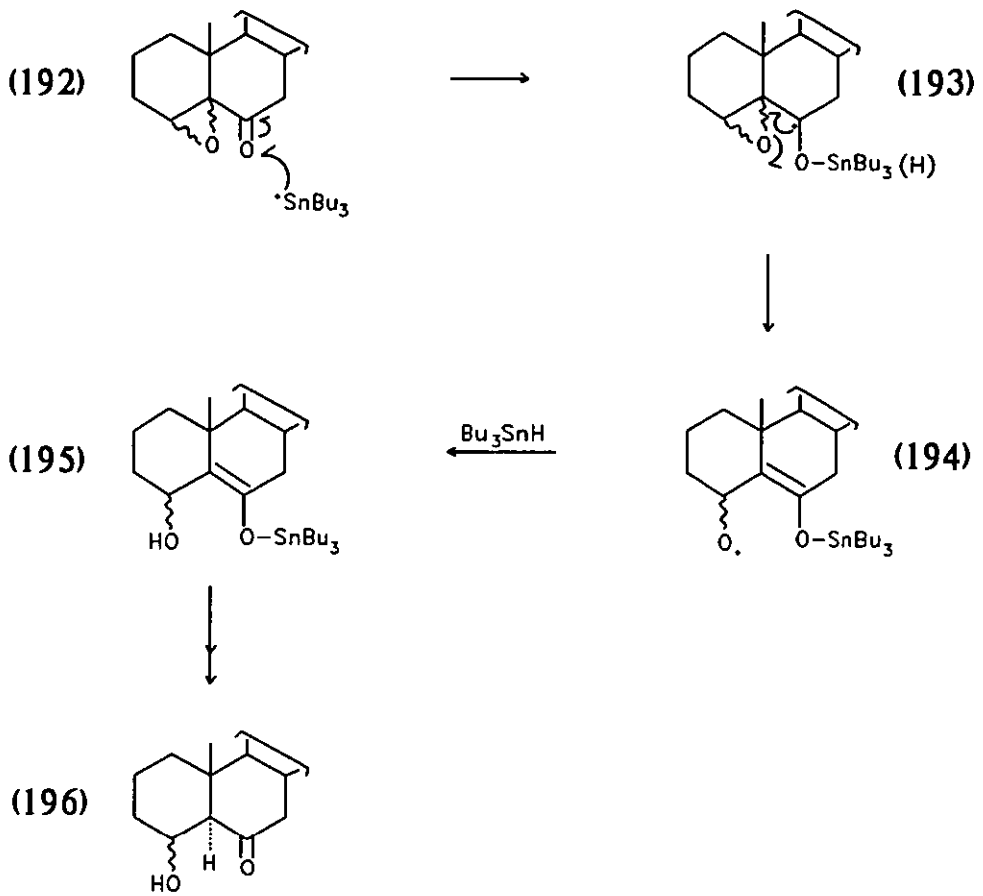
The mechanism for the formation of allylic alcohols (**183a**) and (**183b**) from both high and low temperature reactions can be explained by the mechanism of Barton[49], and the mechanism for the photolysis of acetate[81], proposed earlier. The formation of the methoxy epoxide (**184**) and the epoxy alcohol (**177**) is similar to that observed in the bicycloheptane system under high Bu_3SnH concentration and therefore a similar mechanism can be proposed (see Chapter 4).

The formation of hydroxyketone (**196**) under conditions reported by Pete *et al*[101] and Hasegawa[100] substantiated our results that the products arise from the selective C–O bond cleavage and that the radical generated had enough lifetime to conformationally adjust so that it can cleave the C–O bond. The mechanism involves the addition of $Bu_3Sn^{\cdot}$ to the carbonyl which generates a semi-occupied *p*–orbital at the C–6 Carbon (**193**). This *p*–orbital lines up with the epoxide C–O bond, with both α– and β–epoxide, and cleaves the C–O bond exclusively to give the alkoxy radical (**194**). The alkoxy radical (**194**) is subsequently reduced with Bu_3SnH to give compound (**195**) which then tautomerises to give the aldol product (**196**) (**Scheme 34**).

Conclusion

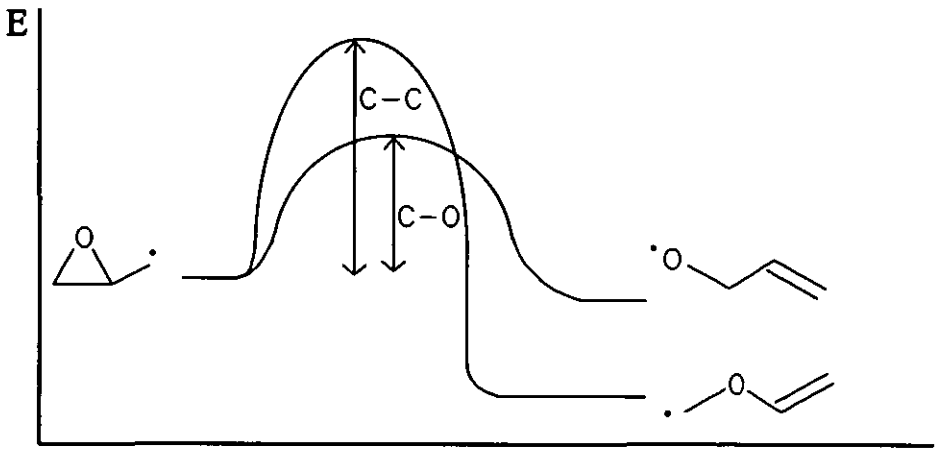
The formation of single major products from each of the compounds (**179, 180**) and (**181, 182**) presumably involves discrete radicals which selectively cleave the C–O bond to afford the allylic alcohol (**183**). This observation contrasts with the observation made by Beckwith *et al*[21] on the related cyclocholestanyl radicals (**21**) and (**23**) which indicated that the ring opening of these radicals was under stereoelectronic control.

Scheme 34



Although the C-6 radical precursors (**197**) and (**198**) is respectively co-planar with the C_4-O and the C_4-C_5 bonds, the absence of major differences in our experiments suggests that the discrete radicals are formed initially. The lack of C-C bond cleavage suggests that the TS energy (**Figure** 1) via C-O bond cleavage is lower and the molecules have sufficient lifetime to conformationally adjust and in doing so, override the favoured stereoelectronic effects for the C-C bond cleavages. The C-O bond cleavage is still faster, even when the radical has to adopt the less favoured conformation (**199**) and hence there is no obvious evidence of stereoelectronic effects.

Figure 1

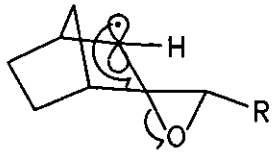


Reaction Co-ordinates

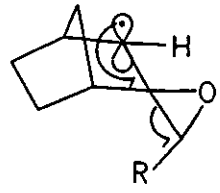
CHAPTER 4

The study of the ring opening of oxiranylcarbinyl radicals in the steroid examples discussed in **Chapters 2** and **3** suggested that no obvious stereoelectronic effects were operative. In the 4ξ,5-epoxy-5ξ-cholestan-3-yl radicals case it was the conformational mobility of ring A which allowed the semi-occupied *p*-orbital of discrete radicals of both isomers to become co-planar with the C-O bond and therefore only products arising from the C-O bond cleavages were observed. In the 4ξ,5-epoxy-5ξ-cholestan-6-yl radicals it was the conformational mobility of ring B which allowed C-O bond cleavage for both α- and β-epoxides. Therefore we decided to prepare conformationally rigid molecules in which such mobility was not possible and therefore some stereoelectronic effects might be observed.

One of the common rigid structures used in stereoselective synthesis and mechanistic studies is bicyclo[2.2.1]heptane. Therefore we set out to make precursors for ring opening reactions to generate the radicals shown below.



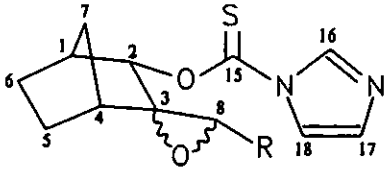
(200a)



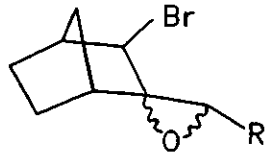
(200b)

The bond angles are not as clear cut as shown in the diagram but ring opening via C-O bond would be favoured in the *endo*-epoxide and C-C bond cleavage would be expected in the *exo*-isomer.

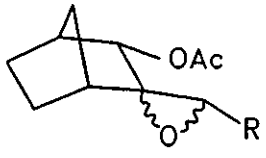
By changing the nature of the substituents on the oxirane, we envisaged that possibly changes in stereoselectivity would be obtained. For example, the effects of R=H versus R=Ph were considered. Similarly, the effect of different substituents on the phenyl ring was considered for study. These changes could influence electron availability and perhaps move the reaction between kinetic and thermodynamic control. The best precursors for generating these radical intermediates (**200**) using Bu_3SnH were considered to be the imidazolides (**206, 207, 212, 213, 227**) and the bromides (**265, 266, 268, 269**). The acetates (**252, 253, 254, 255, 262**) were required for the photolysis, and all these precursors were prepared from the corresponding alcohols.



(**206**), (**207**) R = Ph
(**212**), (**213**) R = p-ClC_6H_4
(**227**) R = H



(**265**), (**266**) R = Ph
(**268**), (**269**) R = p-ClC_6H_4



(**252**), (**253**) R = Ph
(**254**), (**255**) R = p-ClC_6H_4
(**262**) R = H

Section A describes the synthesis of the epoxy–imidazolide derivatives and their reactions with Bu_3SnH. **Section B** deals with the photolysis of the acetates and **Section C** with the Bu_3SnH reductions of the bromides.

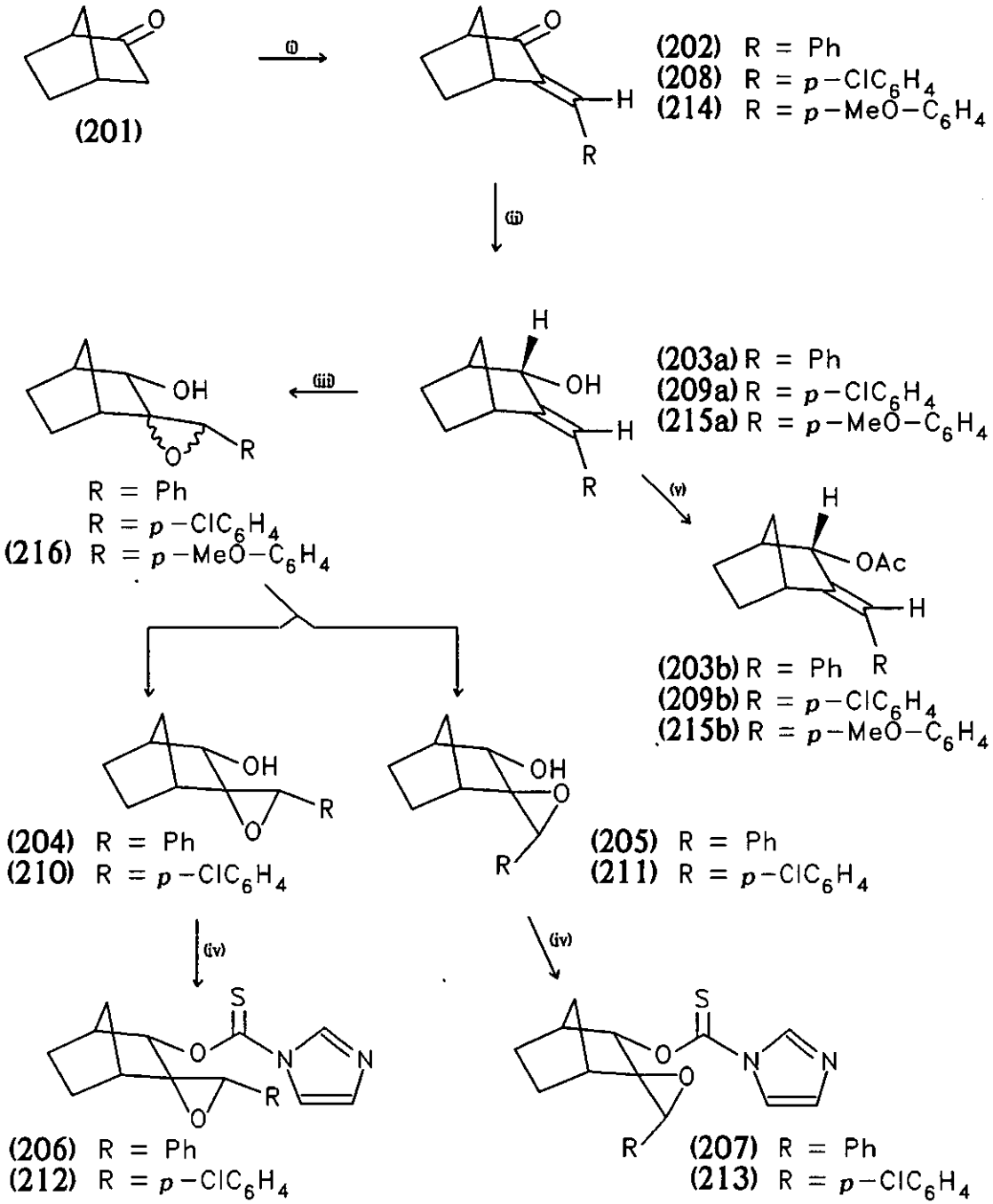
SECTION A

Synthesis and radical reactions of *endo*-2-[imidazol-1-yl(thiocarbonyl)oxy]-bicyclo-[2.2.1]heptan-3-spiro-2'-oxiranes.

Synthesis of the *anti*-3'-Phenyl derivative (206, 207).

The synthesis of (**206**, and **207**) was carried out as shown in **Scheme 35**. The enone (**202**)[102] was prepared by an aldol condensation between norcamphor (**201**) and benzaldehyde using KOH in refluxing ethanol by the procedure of Ross[103]. The mass spectrum of the enone (**202**) showed a strong molecular ion at m/z 198, and its IR spectrum showed characteristic bands for an α,β-unsaturated ketone at 1720 and 1640 (C=C-C=O) cm^{-1}. The reduction of the enone (**202**) with $NaBH_4$ and cerous chloride[76] gave the allylic alcohol (**203a**). The stereochemistry of the C-2 hydroxyl group was assigned *endo* because the hydride would be expected to be delivered from the least hindered *exo*-face. This was confirmed by X-ray crystal structure of the derived epoxide (**207**) (see **Appendix 1**). The cerous chloride was used to force the reduction at the carbonyl centre and not the double bond. The mass spectrum of the alcohol displayed a very strong molecular ion at m/z 200. An accurate elemental analysis was obtained. The IR spectrum showed bands at 3252 (OH group) and 1596 (C=C) cm^{-1} indicative of the allylic alcohol. The ^1H NMR spectrum had the following signals: the 5H broad singlet at δ 7.35 showed the presence of the phenyl group. The olefinic 1H multiplet is now at δ 6.4, shifted upfield by 0.8 ppm due to the absence of the carbonyl group at C-2. The 1H broad multiplet at δ 4.5 corresponds to an *exo*-hydrogen at C-2, coupled to the bridgehead hydrogen and allylically coupled to H-8 and some small W-coupling to

Scheme 35



Reagents

i) aldehyde/KOH/EtOH

ii) $CeCl_3/NaBH_4/MeOH$

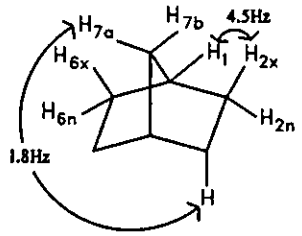
iii) *m*CBPA/CH_2Cl_2

iv) *N,N'*-thiocarbonyldiimidazole/C_6H_6

v) Acetic anhydride/pyridine

H_{6x} (J=2 and 4 Hz) (See diagram). Other peaks are at δ 3.25 (1H, brs, H–4), 2.4 (1H, brs, H–1), and 2.2 (1H, brs, OH, D_2O exchange).

In the bicycloheptanes in general the $^3J_{HH}$ coupling between H_1–H_{2x} is 4.5 Hz, whereas the $^3J_{HH}$ coupling between H_1–H_{2n} is 1.8 Hz. The $^3J_{HH}$ W coupling between H_{7a}–H_{2n} is 4.5 Hz and H_{6x}–H_{2n} is about 1.8 Hz. Therefore the stereochemistry at C–2 could not be predicted with certainty. However the X–ray structure of the derived epoxide confirmed that the hydrogen at C–2 was *exo*.



The allylic alcohol (**203a**) was epoxidised[79] with *m*CPBA and CH_2Cl_2 to give a 50:50 mixture of the *endo*– and *exo*–epoxides which were separated by preparative TLC to afford the pure *endo*– and *exo*–epoxides, (**204**) and (**205**). The allylic acetate (**203b**), was synthesised according to the **Scheme 35**. When this acetate (**203b**) was epoxidised using *m*CPBA it gave a 5:1 mixture of epoxides (**205**) and (**204**) compared with a 50:50 mixture when allylic alcohol was used. This is in accordance with the general belief that the hydroxyl group delivers the oxygen on the same face of the molecule. The *endo*–acetate therefore gives predominantly *exo*–epoxide. However, this phenomenon was not observed in our second steroidal example. The mass spectrum of *endo*–epoxide (**204**) displayed a molecular ion at m/z 216. A satisfactory elemental analysis was also obtained. The 250 MHz ^1H NMR spectrum showed important signals as follows: at δ 7.2–7.4 a 5H multiplet indicative of the phenyl group, and a 1H doublet (J = 2.7 Hz)

at δ 4.02 is the *exo*-hydrogen. Since there is no allylic coupling due to the disappearance of the olefin it appears as a doublet and not a multiplet. The presence of a new peak at δ 4.00 (1H, singlet) clearly suggests an epoxide hydrogen. The remainder of the spectrum appears at δ 2.51 (1H, brs, H-1), 2.41 (1H, brs, OH, D_2O exchange), and 1.90 (1H, brs, H-4) ppm. The mass spectrum of the *exo*-epoxide (**205**) displayed a molecular ion at m/z 216. A satisfactory elemental analysis was also obtained. The 250 MHz ^{1}H NMR spectrum showed important signals at δ 7.2-7.3 (5H, brs, Ph), 4.23 (1H, s, H-8), 4.08 (1H, d, J=3 Hz, H-2), 2.47 (1H, brs, H-1), and 1.99 (1H, brs, H-4) ppm.

These epoxides, (**204**) and (**205**), were treated under anhydrous conditions with *N*,*N*'-thiocarbonyldiimidazole[49] in refluxing benzene to give the imidazolides (**206**) and (**207**) (**Scheme 35**). The mass spectrum of the imidazolide (**206**) did not show a molecular ion at m/z 326, but instead showed a M^+ at m/z 327. This suggests that that the imidazolide is protonated before the molecule is broken down.

The elemental analysis of (**206**) was satisfactory and the ^{1}H NMR spectrum showed signals at δ 8.5 (1H, brs, H-16), 7.7 (1H, brs, H-17), and 7.5 (1H, brs, H-18) which clearly indicate three imidazolide hydrogens in the molecule. The 5H singlet at δ 7.4 confirmed a phenyl group and a 1H doublet (J=4 Hz) corresponds to an *exo*-methine at C-2 now shifted to 5.9 ppm. The epoxide hydrogen is now at δ 4.2 (1H, singlet) and the bridgehead hydrogens at δ 2.9 and 1.9 ppm. As previously described the structure of the imidazolide (**207**) was confirmed by an X-ray diffraction study on pure crystals (see **Appendix 1**). A satisfactory elemental analysis was obtained. The ^{1}H NMR spectrum showed important signals at δ 8.5 (1H, brs, H-16), 7.7 (1H, brs, H-17), 7.4 (5H, s, Ph) , 7.2 (1H, brs, H-18), 5.7 (1H, d, J = 4 Hz, H-2), 4.2 (1H, s, H-8), 3.1 (1H, brs, H-1) and 2.1 (1H, brs, H-4).

Synthesis of the *anti*-3'-*p*-Chlorophenyl Derivatives (212, 213)

We wanted to study the effects of substituents on the phenyl ring and therefore we first prepared the *p*-chlorophenyl derivative. A study of this compound would show whether a -I, +M group would have any effect. The synthesis was carried out as illustrated in **Scheme 35.** Norcamphor (**201**) was treated with *p*-chlorobenzaldehyde and KOH in refluxing ethanol to give the enone (**208**) in high yield by an aldol condensation[103]. The mass spectrum showed a strong molecular ion at m/z 234/232, and gave an appropriate elemental analysis. The IR spectrum showed characteristic bands at 1724 and 1638 cm^{-1} for C=C-C=O. The 90 MHz ^1H NMR spectrum displayed important signals at δ 7.22 (4H, brs, C_6H_4Cl) and 6.92 (1H, s, H-8). The enone (**208**) was reduced[76] as shown in **Scheme 35** to give *endo*-allylic alcohol (**209**). The IR spectrum showed a band at 3280 (hydroxy group), and the mass spectrum had molecular ions at m/z 236/234. The elemental analysis obtained was satisfactory and the 90 MHz ^1H NMR spectrum had signals at δ 7.1 (4H, s, C_6H_4Cl), 6.2 (1H, brs, H-8), 4.4 (1H, brm, J=2 and 4 Hz, H-2), 3.1 (1H, brs, H-1), 2.4 (1H, brs, H-4), and 1.9 (1H, s, OH, D_2O exchange).

The epoxidation[79] of the allylic alcohol (**209a**) with *m*CPBA gave a 50:50 mixture of epoxides which was separated by preparative TLC. The allylic acetate (**209b**), when epoxidised with *m*CPBA, gave a 5:1 mixture of epoxides. The mass spectrum of the pure *endo*-epoxide (**210**) showed a molecular ion at m/z 252/250, and gave an accurate elemental analysis. The IR spectrum showed a band at 3376 (hydroxy group) cm^{-1}, and the ^1H NMR spectrum had important signals at δ 7.1-7.4 (4H, ABq, J = 10 Hz, C_6H_4Cl), 4.1 (1H, d, J=4 Hz, H-2), 3.98 (1H, s, H-8), 2.5 (2H, m, H-1, 1H, D_2O exchange, OH), 1.9 (1H, brs,

H–4). The ^{1}H NMR spectrum of the pure *exo*–epoxide (**211**) had signals at δ 7.33 (4H, s, Ph), 4.23 (1H, s, H–8), 4.0 (1H, d, J = 4 Hz, H–2), 3.4 (1H, m, OH, D_2O exchange), 2.45 (1H, m, H–1), and 1.9 (1H, m, H–4) ppm. These are analogous to the phenyl epoxides prepared as above.

The epoxides (**210**) and (**211**) were converted into the imidazolides[49] (**212**) and (**213**) using *N,N'*–thiocarbonyldiimidazole. The *endo*–epoxy imidazolide (**212**) obtained as colourless oil, displayed a molecular ion in the mass spectrum at m/z 362/360. The ^{1}H NMR spectrum had important signals at δ 8.4 (1H, brs, H–16), 7.7 (1H, brs, H–17), 7.1–7.3 (4H, ABq, J = 10 Hz, C_6H_4Cl), 7.07 (1H, brs, H–18), 5.83 (1H, d, J = 4 Hz, H–2), 4.30 (1H, s, H–8), and 2.9 (1H, m, H–1), and 1.9 (1H, brs, H–4) ppm. The *exo*–epoxyimidazolide (**213**) displayed a molecular ion in the mass spectrum at m/z 362/360, and gave an accurate elemental analysis. The ^{1}H NMR spectrum showed signals at δ 8.4 (1H, brs, H–16), 7.7 (1H, brs, H–17), 7.3 (4H, s, C_6H_4Cl), 7.1 (1H, brs, H–18), 5.6 (1H, d, J = 4Hz, H–2), 4.1 (1H, s, H–8), 3.0 (1H, brs, H–1), and 2.0 (1H, brs, H–4) ppm.

Attempted synthesis of the *anti*–3'–*p*–methoxyphenyl derivative (216)

In order to further study the effects of phenyl substituents, we aimed to prepare the *p*–methoxy derivatives (–I, strongly +M) as shown in (**Scheme 35**).

Norcamphor (**201**) was treated under aldol reaction conditions[103] with *p*–methoxylbenzaldehyde and KOH gave the expected enone (**214**) as a brown coloured oil in good yield. The IR spectrum showed specific bands for enone at 1720 (C=O) and 1636 (C=C) cm^{-1}. The mass

spectrum of the enone displayed a strong molecular ion at m/z 228, and had important signals in its ^{1}H NMR spectrum at δ 6.9–7.5 (4H, ABq, J = 8 Hz, $MeOC_6H_4$) and 7.15 (1H, s, H–8), 3.74 (3H, s, OMe) ppm.

The reduction[76] of the enone (**214**) with $NaBH_4$ and cerous chloride gave the *endo*–allylic alcohol (**215**). The IR spectrum showed peaks at 3292 (hydroxyl) and 1608 (double bond) cm^{-1}. The mass spectrum had a strong molecular ion at m/z 230, and the compound gave a satisfactory elemental analysis. The ^{1}H NMR spectrum displayed important signals at δ 6.8–7.4 (4H, ABq, J = 10 Hz, $MeOC_6H_4$), an olefinic proton at 6.38 (1H, m, H– 8), 4.5 (1H, brm, J=2 and 4 Hz, H–2), 3.2 (1H, brs, H–1), 2.4 (1H, brs, H–4) and 1.8 (D_2O exchangeable, OH) ppm.

The epoxidation of the allylic alcohol (**215**) with *m*CPBA at 0°C afforded two products after chromatography, 3–(*p*–methoxyphenyl)–bicyclo[3.2.1]oct–3–en–2–one (**219**) and *exo*–2–[hydroxy(*p*–methoxy–benzyl)]bicyclo[2.2.1]heptan–2,3–diol (**221**) (**Scheme 36**) and not the expected epoxy–alcohols (**216a, 216b**). The mass spectrum of the enone (**219**) displayed a strong molecular ion at m/z 228. A satisfactory elemental analysis was obtained. The IR spectrum had characteristic bands at 1670 (C=O) and 1600 (C=C) cm^{-1} for an α,β–unsaturated ketone, and showed no hydroxyl stretching band. The ^{1}H NMR displayed important signals at δ 6.8–7.4 (4H, ABq, J = 8 Hz, $MeOC_6H_4$), 7.2–7.32 (1H, m, H–4), coupled to the bridgehead hydrogen at H– 5, 3.8 (3H, s, OMe), and 2.8–3.1 (2H, m, H–1, 5). Three days later the column was eluted further with methanol and the triol (**221**) was obtained. The IR spectrum displayed a strong hydroxyl stretching band at 3428 cm^{-1}. A satisfactory elemental analysis was obtained. The mass spectrum displayed a weak molecular ion at m/z 264 and the ^{1}H NMR spectrum

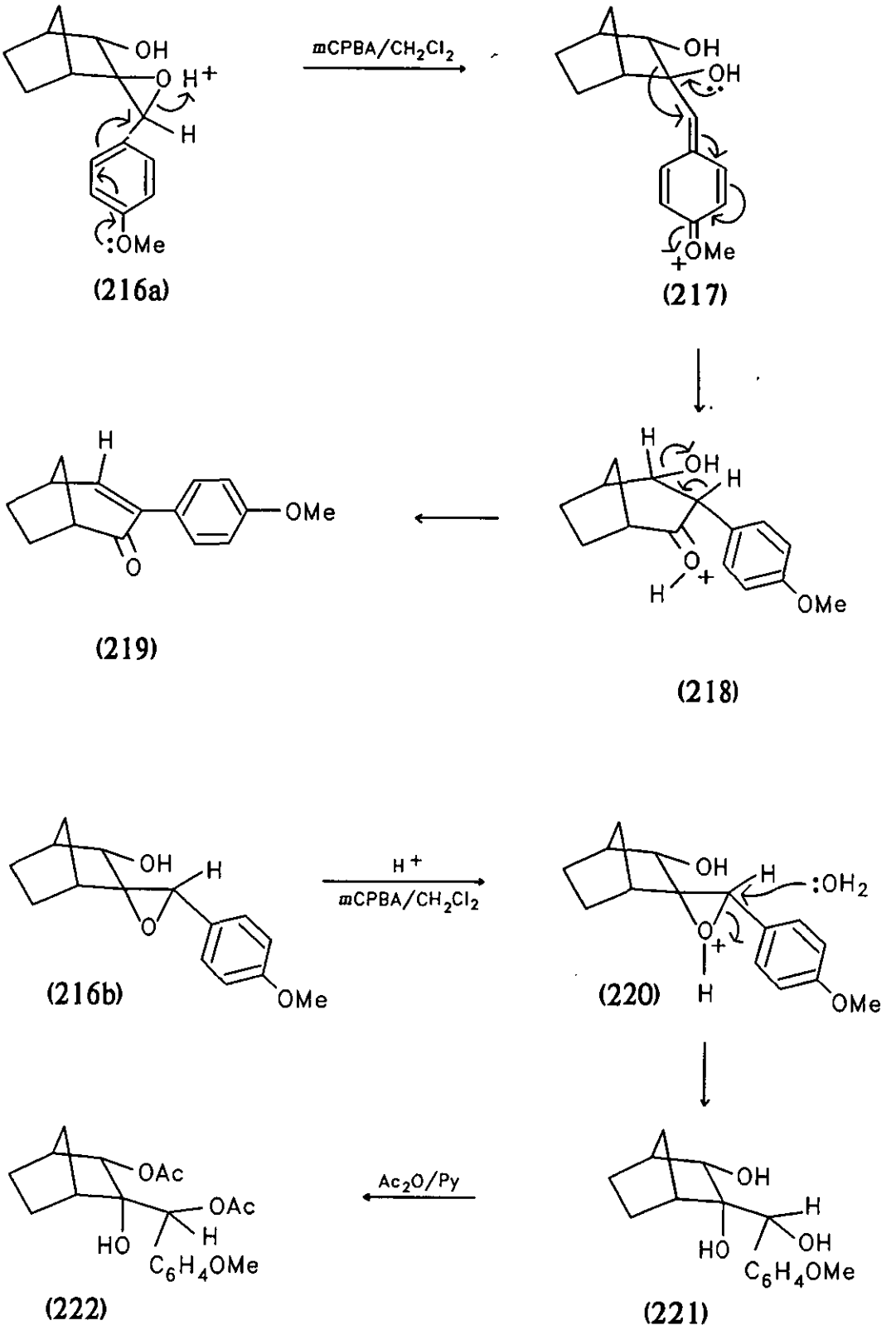
had signals at 6.8–7.5 (4H ABq, J = 8 Hz, $MeOC_6H_4$), 4.95 (1H, brs, H–8), 4.3 (1H, brs, OH, D_2O exchange), 3.92 (1H, d, J = 4 Hz, H–2), 3.8 (3H, s, OMe), 3.38 (1H, s, OH, D_2O exchange), 3.0 (1H, brs, OH, D_2O exchange), 2.4 (1H, brs, H–4), and 1.95 (1H, brs, H–1) ppm. In order to further support the structure the triol (**221**) was reacted with acetic anhydride and pyridine[77] to give diacetate (**222**). The IR spectrum showed bands at 3520 (hydroxyl group) 1740 and 1240 (acetate) cm^{-1}. A satisfactory elemental analysis was obtained. The mass spectrum had a molecular ion at m/z 348 and the ^1H NMR spectrum displayed important signals at δ 6.8–7.65 (4H, ABq, J = 9 Hz, $MeOC_6H_4$), 5.92 (1H, brs, H–8), 4.9 (1H, d, J = 4 Hz, H–2), 3.82 (3H, s, OMe), 2.8 (1H, brs, OH, D_2O exchange), 2.07 (3H, s, OAc), 2.0 (3H, s, OAc), 2.5 (1H, brs, H–1) and 1.9 (1H, brs, H–4) ppm. A possible mechanism for the formation of these products is outlined in the **Scheme 36**.

Synthesis of *endo*–2–[imidazol–1–yl(thiocarbonyl)oxy]–bicyclo–[2.2.1] –heptan–3–spiro–2'–oxirane (227)

We wished to study the radical ring opening of the simplest oxirane in the bicycloheptane series and therefore the synthesis of (**227**) was carried out as shown in (**Scheme 37**)

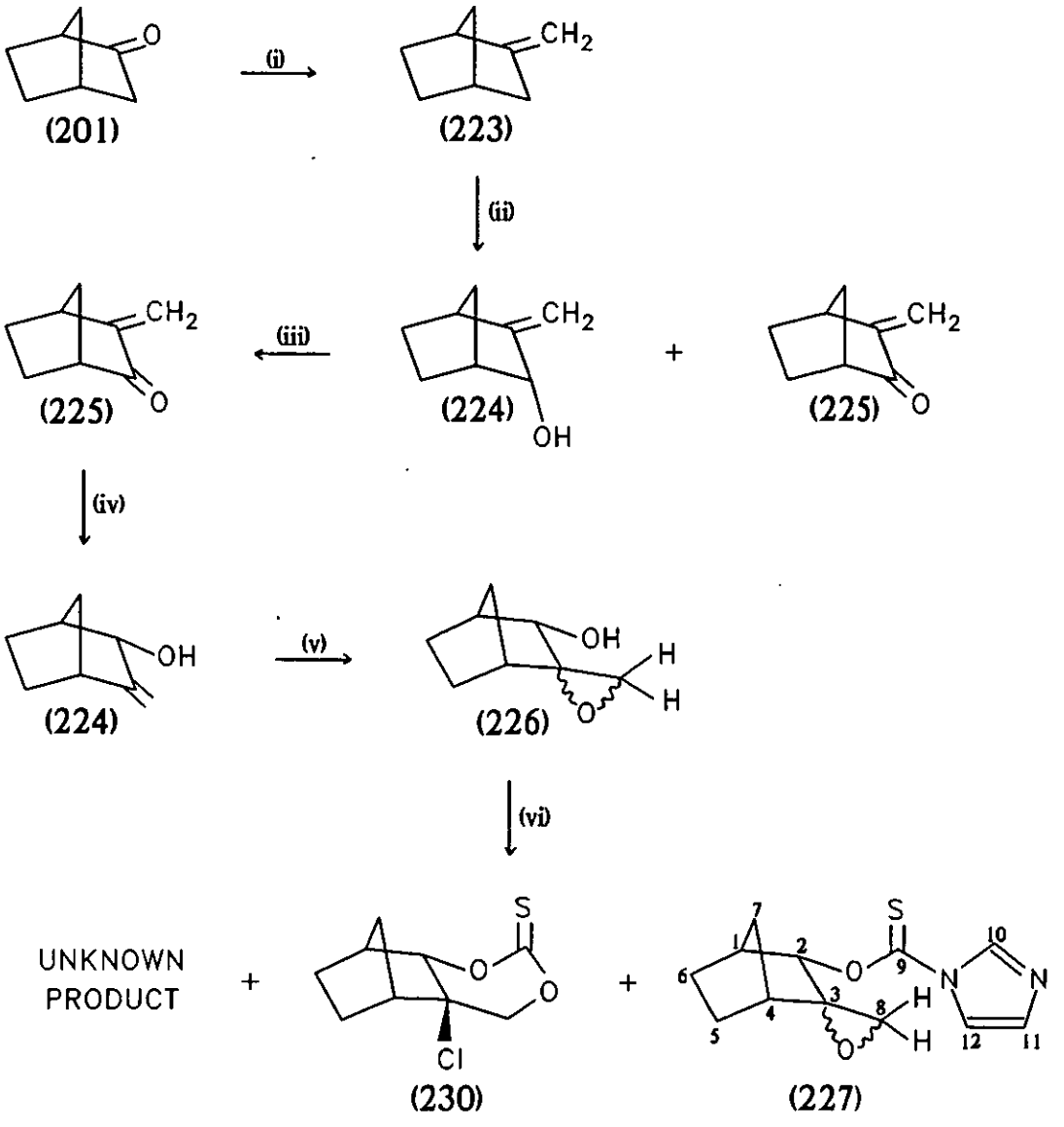
Norcamphor (**201**) was reacted using the Wittig reagent, prepared from methyltriphenyl phosphonium bromide and BuLi in Et_20, to give norcamphene (**223**)[104]. The norcamphene was treated under the conditions of Jefford *et al.*[105] for allylic hydroxylation with selenium dioxide and dioxan to give a mixture of the allylic alcohol (**224**) and the enone (**225**). The mixture was further oxidised with PDC to give the enone (**225**), and then reduced with $NaBH_4$ and cerous chloride to give the *endo*–allylic alcohol (**224**)[106]. Reduction with DIBAL gave the

Scheme 36



(216a) (217) (218) (219) (216b) (220) (221) (222)

Scheme 37



Reagents

i) $MePh_3P^+ Br^-/BuLi/Et_2O$

ii) SeO_2/dioxane/Δ

iii) PDC/CH_2Cl_2

iv) $NaBH_4/CeCl_3/MeOH$

v) *m*CPBA/CH_2Cl_2

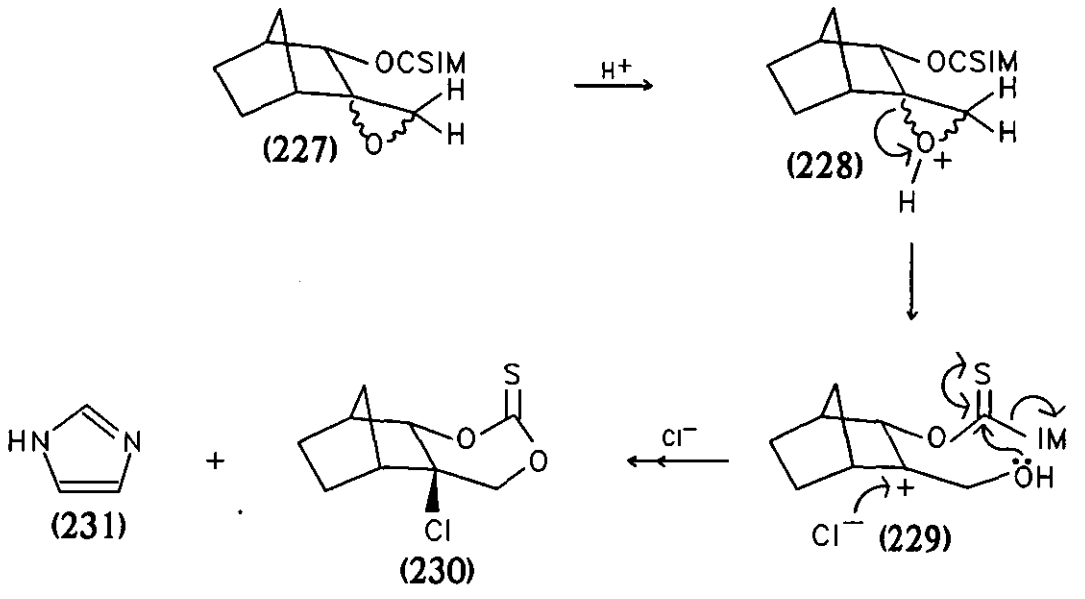
vi) *N,N'*–thiocarbonyldiimidazole/C_6H_6

same *endo*-alcohol[107]. The alcohol was epoxidised with *m*CPBA to give a 4:1 mixture of the *endo*- and *exo*-epoxy alcohols (**226**) as a colourless oil, which could not be separated by chromatography. The mass spectrum showed the molecular ion at m/z 140 and the IR spectrum had a hydroxyl band at 3436 cm^{-1}. The 90 MHz ^1H NMR displayed important signals at δ 3.9 (1H, d, J = 4 Hz, H-2) and 2.9-3.2 (3/2 H + 1/2 H, ABq, J = 4.5, H-8) assigned to the two diastereotopic epoxide methylene hydrogens.

The mixture of epoxyalcohols (**226**) was reacted with *N,N'*-thiocarbonyldiimidazole in refluxing benzene to give four products, the *exo*- and *endo*-epoxy imidazolides (**227**), an unexpected cyclic thiocarbonate (**230**), and an unidentified product which showed a carbonyl in its IR spectrum at 1736 cm^{-1}. The mass spectrum of the imidazolide (**227**) showed a molecular ion at m/z 250. A satisfactory elemental analysis was obtained. The ^1H NMR spectrum displayed important signals at δ 8.3 (1H, brs, H-10), 7.6 (1H, brs, H-11) and 7.1 (1H, brs, H-12) for the imidazolide protons. The methine proton at C-2 is downfield at δ 5.6 (1H, d, J = 4 Hz) and the epoxide protons at δ 2.9-3.25 (2H, ABq, J = 4.5 Hz). The unexpected *exo*-chlorothiocarbonate (**230**) was identified from the following data. The mass spectrum displayed a molecular ion at m/z 220/218. A satisfactory elemental analysis was obtained. The 250 MHz ^1H NMR spectrum showed important signals at δ 4.9 (1H, d, J = 4.8 Hz) assigned to the methine proton at C-2 and an ABq at 3.5-3.99 (2H, J = 12.6 Hz) assigned to two diastereotopic methylene protons (now shifted by 1 ppm, therefore next to an oxygen atom). The IR spectrum showed no evidence of hydroxyl or carbonyl groups. We propose that the formation of this product could occur as shown in **Scheme 38**. We have also discovered that the acidic workup increases the yield of chlorothiocarbonate (**230**), compared to the epoxy-imidazolide (**227**). We believe that the chloride

ion is present in the *N,N'*-thiocarbonyldiimidazole supplied by Aldrich (technical grade) since a typical synthesis would involve reaction of thiophosgene and imidazole to give *N,N'*-thiocarbonyldiimidazolide and HCl gas.

Scheme 38



Our intention was to generate radicals at C–2 (α to the oxiranes) as shown in **Scheme 40** by reacting the various epoxy–imidazolides with Bu_3SnH under the same conditions as reported by Barton and McCombie[50] and used for the previous steroid examples (**Chapters 2 and 3**). The reactions between the imidazolides and Bu_3SnH are as follows.

Reactions between the epoxyimidazolides and Bu_3SnH/AIBN

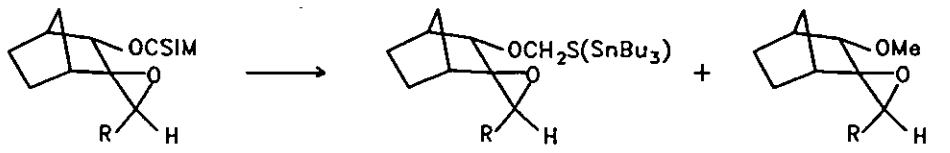
The *exo*-epoxyimidazolide (**207**) was reacted with Bu_3SnH (10 equiv.) in refluxing toluene to give three unexpected products. Chromatography afforded the methoxy epoxide (**233**), the acetal (**232**) and imidazole (**231**) (**Equation 13**). These products do not arise from the deoxygenation[49] of the imidazolide derivative but are due to the reduction of the thiocarbonyl group of the imidazolide derivative. This reduction of thiocarbonylimidazolide has not been reported in the literature as far as we know. Although the formation of acetals from thiocarbonylimidazolides has been reported in the literature[108, 109, 110], the full reduction is unknown.

Considerable difficulty was encountered initially in isolating and identifying the unusual and unexpected products.

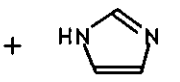
The methoxy epoxide (**233**) was obtained in good yield (50%). The mass spectrum displayed a strong molecular ion at m/z 230. A satisfactory elemental analysis was obtained. The 250 MHz ^1H NMR spectrum showed a singlet of 3H at δ 3.32, indicative of a methoxy group, and the 1H doublet (J = 2.8 Hz) at δ 3.58 suggested a hydrogen at C-2 as observed in all the present group of compounds. The 1H singlet at δ 4.22 remained unchanged, this suggested that the epoxide was intact and all other data were consistent with structure (**233**).

The acetal (**232**) was too unstable to purify completely to analytical purity. However, the high resolution ^1H NMR spectrum indicated the structure. The Bu_3Sn - moiety was confirmed by a multiplet at δ 0.8-0.93, and the ABq at δ 4.7-4.91 suggested a $-OCH_2S-$ functional group in a chiral environment. The rest of the hydrogen resonances were similar to those of the starting material.

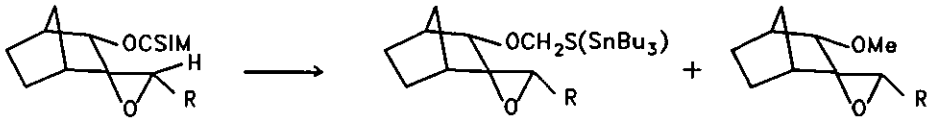
Equation 13



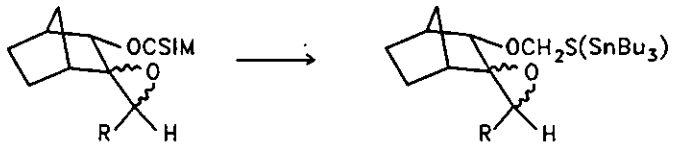
R = Ph (207) (232) (233)
R = *p*−ClC_6H_4 (213) (236) (237)



(231)



R = Ph (206) (234) (235)
R = *p*−ClC_6H_4 (212) (238) (239)



R = H (227) (240)

The third product isolated was imidazole (**231**) in moderate yield (40%). The IR and ^1H NMR spectra, the TLC, and melting points were identical to those of authentic imidazole.

The *endo*–epoxyimidazolide (**206**) gave the analogous *endo*–products. The acetal (**234**) was lost during purification. The mass spectrum of the methoxyepoxide (**235**) displayed a molecular ion at m/z 230. A satisfactory elemental analysis was also obtained. The 250 MHz ^1H NMR

spectrum showed important signals at δ 7.2–7.37 (5H, m, Ph), 3.96 (1H, s, H–8), 3.7 (1H, d, J = 2.8 Hz, H–2), 3.37 (3H, s, OMe), 2.59 (1H, brs, H–4), and 1.75 (1H, brs, H–1) ppm. The structure was further confirmed with a 2D ^{1}H NMR spectrum (see **Appendix 2**).

The *p*–chlorophenyl *endo*– and *exo*–epoxyimidazolides (**212**) and (**213**), also gave analogous *endo*– and *exo*–products (**238**), (**239**) and (**236**), (**237**). **Table 2** shows the ^{1}H NMR data for the products. An X–ray crystal structure was also obtained for (**237**) (See **Appendix 3**).

The methoxy epoxide (**237**) was synthesised by an independent route. The allylic alcohol (**209a**) was methylated with NaH/MeI in ether, and then epoxidised with *m*CPBA to give the methoxy epoxide. Chromat–ography gave pure (**237**).

Table 2

PRODUCTS	δ values						
	AROMATIC PROTONS	EPOXIDE H–8	EXO H–2	METHOXY C–2	$-OCH_2S-$ C–2	BRIDGE–HEAD H–4	BRIDGE–HEAD H–1
(236) (60 MHz)	δ(7.37) 4H, brs	δ(4.15) 1H, s	δ(4.23) 1H, d, J=3Hz	—	δ(4.7–4.91) 2H, ABq, J=10Hz	δ(2.59) 1H, brs	δ(1.97) 1H, brs
(237)	δ(7.2–7.30) 4H, m	δ(4.18) 1H, s	δ(3.5–3.57) 1H, d, J=2.8Hz	δ(3.31) 3H, s	—	δ(2.63) 1H, brs	δ(1.90) 1H, brs
(238)	δ(7.2–7.33) 4H, ABq, J=5.9Hz	δ(3.94) 1H, s	δ(4.1–4.18) 1H, d, J=2.8Hz	—	δ(4.7–5.01) 2H, ABq, J=9Hz	δ(2.54) 1H, brs	δ(1.7) 1H, brs
(239)	δ(7.1–7.33) 4H, ABq, J=5.8Hz	δ(3.92) 1H, s	δ(3.6–3.69) 1H, dd, J=2.8Hz	δ(3.36) 3H, s	—	δ(2.59) 1H, brs	δ(1.69) 1H, brs

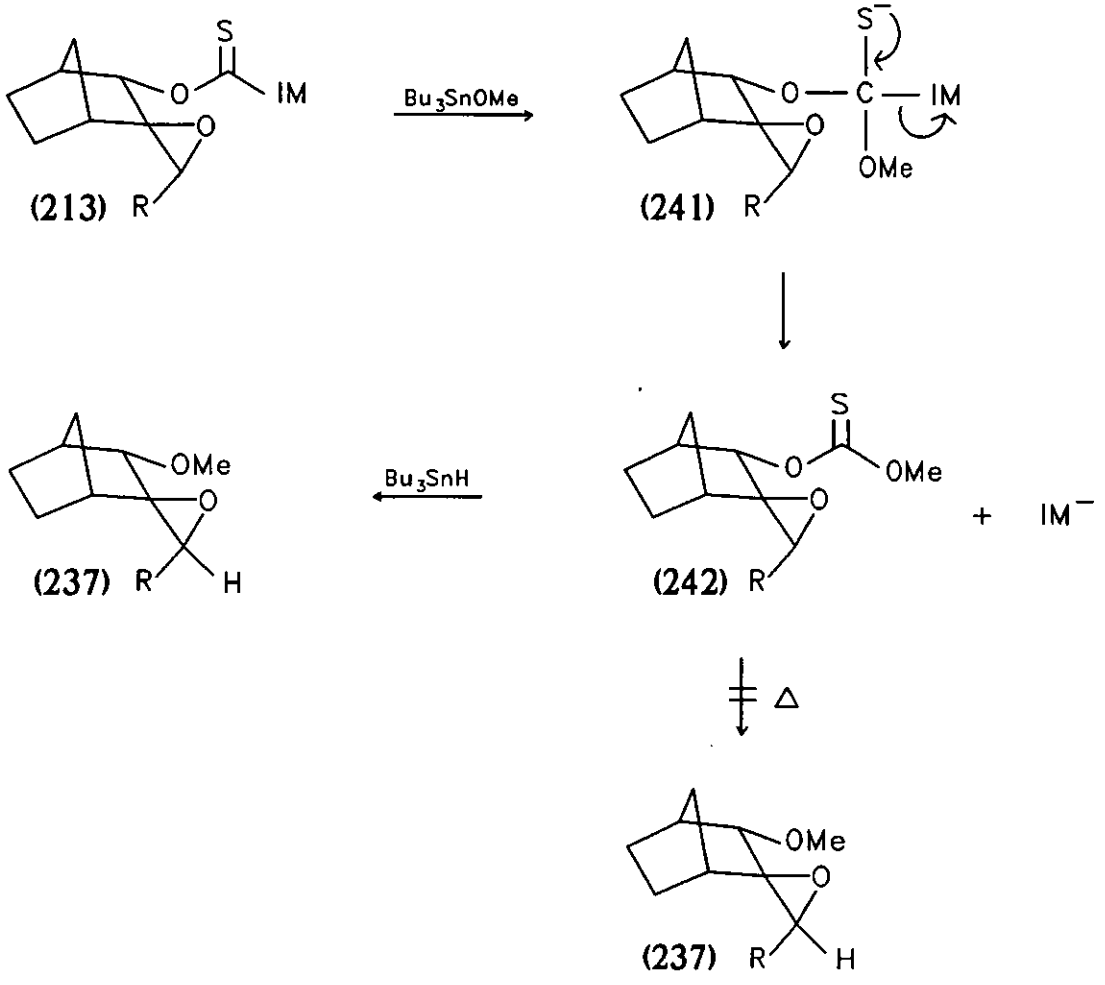
In addition to these products, the epoxyalcohol (**211**) was also isolated in low yield from the *exo*–epoxyimidazolide (**213**). This alcohol presumably arises from the acid catalysed hydrolysis of acetal (**236**) during chromatography on silica gel.

The mixture of methylene epoxyimidazolides (**227**) (**equation 13**) was reacted with Bu_3SnH. The crude product was partitioned between acetonitrile and light petroleum (b.p. 40–60°C) in order to separate out the tin residues. The CH_3CN layer was evaporated to dryness and yielded a mixture of acetal (**240**) as a colourless oil (25%). The high resolution ^1H NMR of acetals (**240**) indicated a butyl group (δ 0.8–0.93), and the 2H ABq (J=9.9 Hz) at δ 4.6–4.82 suggested a $-OCH_2S-$ functional group in a chiral environment. A doublet (J=2.7 Hz) at δ 4.15 confirmed the presence of the *exo*–hydrogen at C–2. The 2H ABq (J=5 Hz) at δ 2.6–2.91 (epoxide methylene hydrogens) and the remaining signals were analogous to the starting epoxide.

Initially the formation of these products puzzled us for a considerable period. We started to investigate by assuming that the methoxy products could arise from the traces of methanol either in the toluene or in the Bu_3SnH. GLC analysis revealed that the Bu_3SnH supplied by Aldrich contained MeOH as an impurity. However, we also observed that the methoxy products were dependent on the amount of Bu_3SnH used. If we used less Bu_3SnH then the yield of the methoxy product was reduced and that of the acetal increased. We also established in a separate experiment that the methoxy products do not arise from methanol, and that the imidazolides used, were stable under the usual reaction conditions employed. However, when the imidazolide (**213**) was treated with Bu_3SnOMe a new methoxy product, which was later identified as thiocarbonate (**242**), was isolated. The mass spectrum of thiocarbonate (**242**) displayed a molecular ion at m/z 326/324. A satisfactory elemental analysis was obtained. The ^1H NMR spectrum clearly showed the unaltered *endo*–epoxide hydrogen at δ 4.12, the C–2 hydrogen as a doublet (J=2.9 Hz) at δ 5.3 and a 3H singlet at δ 4.03 for the (OMe) group. When the thiocarbonate (**242**) was treated with Bu_3SnH a methoxy product (**237**) was obtained. This methoxy product had

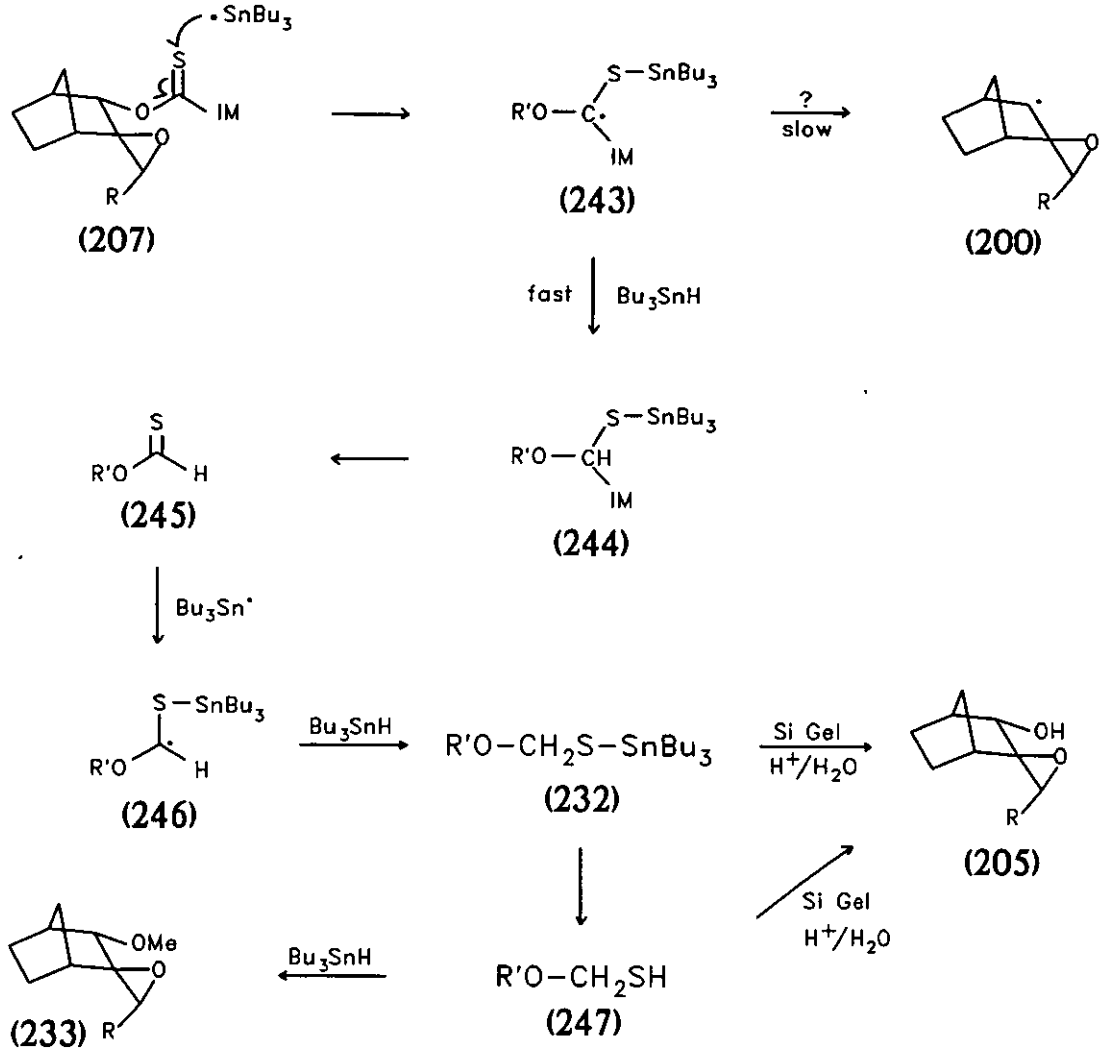
identical melting point and spectroscopic data with the product (**237**) obtained, when imidazolide (**213**) was reduced with Bu_3SnH. The thiocarbonate (**242**) remained unchanged when heated in toluene for 3 hours. **Scheme 39** shows a possible mechanism for the formation of this carbonate.

Scheme 39



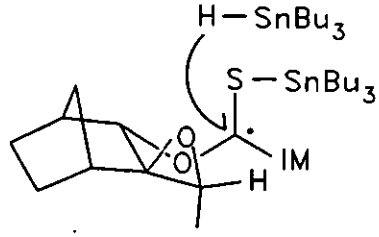
We propose **Scheme 40** to explain this unusual and previously unknown reduction of the epoxy imidazolides to methoxy compounds.

Scheme 40



The $Bu_3Sn^{\bullet}$ radical adds to the thiocarbonyl groups of the thiocarbonylimidazolides as expected and as normally observed. However, for some reason the intermediate radical does not break down rapidly and it is further reduced with Bu_3SnH. The alternative reaction is known in certain circumstances. We suggest that the reason for the slow breakdown with deoxygenation to give the C-2 radical is because of steric hindrance. Models of the intermediate suggest that the required

conformation to allow fragmentation is not possible, but that the approach by Bu_3SnH to carry out the reduction is sterically feasible. Trialkyltin cations are relatively stable and therefore the "ionic" breakdown to yield the thioformate (**245**) followed by further reduction to give the acetal (**232**) is feasible. The acetal under acidic conditions hydrolyses to epoxyalcohol (**205**) or further ionic breakdown to yield thiols (**247**). The methylene thiols have been reported to reduce to methyl with Bu_3SnH [112].



(243)

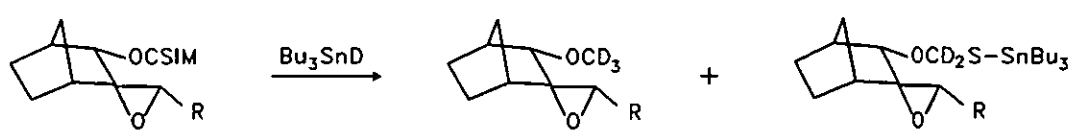
Table 3 shows that the methoxy product is favoured at high [Bu_3SnH]. At low [Bu_3SnH] mainly the acetal is formed. However, the addition of, or presence of methanol does not appear to significantly affect the course of the reaction. The results obtained above indicated that the thiocarbonyl carbon is reduced successively and that the reducing agent is the Bu_3SnH. If this assumption was correct then we could use Bu_3SnD to prove the origin of methoxy and thioacetal by deuterium labelling. To achieve this, the imidazolide (**212**) was treated with Bu_3SnD under the usual conditions and indeed the expected deuterium labelled methoxyepoxide (**251**) and acetal (**250**) were isolated (**Equation 14**). The high resolution ^1H NMR spectrum of the acetal (**250**) displayed important signals at δ 7.2–7.33 (4H, ABq, J = 5.8 Hz, *p*-ClC_6H_4), 4.31 (1H, d, J = 2.9 Hz, H–2), 3.92 (1H, s, H–8), 2.52 (1H, brs, H–4), the rest was identical to that of the undeuterated compound except that the 2H,

ABq at δ 4.6–4.8 for $-O-CH_2-S-$ was now deuteriated and therefore cannot be seen. The mass spectrum of the methoxyepoxide (**251**) showed a molecular ion at m/z 269/267 (i.e. an increase of 3 mass units for $-O-CD_3$) and the ^1H NMR spectrum was identical to the methoxyepoxide (**239**) except that the methoxy singlet at δ 3.36 was absent because of deuteriation. The outcome of these results provided strong evidence that our above mechanistic assumptions were broadly correct.

Table 3

Imidazolides	Methoxy Epoxide	Acetal	Thiocarbonate
Bu_3SnH (10eq)	50	50	—
Bu_3SnH (1eq)	traces	mainly	—
Bu_3SnH (10eq) + MeOH (1.5eq)	—	mainly	traces
Bu_3SnH (1eq) + Bu_3SnOMe (1eq)	traces	mainly	—
Bu_3SnH (0.1eq) + Bu_3SnOMe (1eq)	—	—	only
Bu_3SnH (10eq) + MeOH (10eq)	50	50	—

Equation 14



(212) (251) (250)

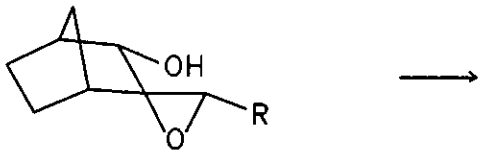
R = *p*–ClC_6H_4

SECTION B

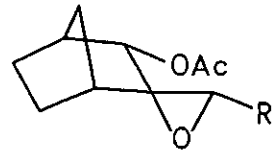
Synthesis and reactions of *endo*-2-acetoxy-*anti*-3'-phenylbicyclo-[2.2.1]heptan-3-spiro-2'-oxiranes (252, 253)

In **Chapters 2** and **3** the use of photolysis of acetates to generate oxiranylcarbinyl radicals was fully described. We hoped to generate radicals at the C-2 position of the epoxide derivatives (**252, 253**) and (**254, 255**) to study the ring opening of the epoxides. Therefore, the same range of bicycloheptane oxiranes were synthesised as shown in **Equation 15** and photolysed as shown in **Scheme 41** and **42.**

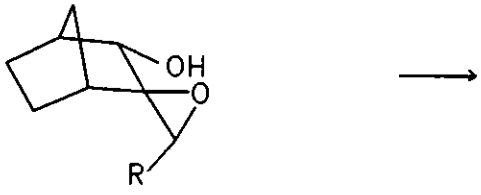
Equation 15



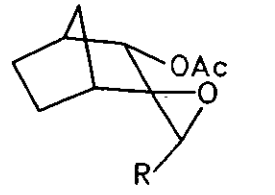
(204) R = Ph
(210) R = *p*-ClC_6H_4



(252) R = Ph
(254) R = *p*-ClC_6H_4



(205) R = Ph
(211) R = *p*-ClC_6H_4



(253) R = Ph
(255) R = *p*-ClC_6H_4

The *endo*- and *exo*-epoxyalcohols (**204**) and (**205**) were treated with acetic anhydride and pyridine to give the *endo*- and *exo*-epoxyacetates (**252**) and (**253**) (**Equation 15**). The mass spectrum of the

endo-epoxyacetate (**252**) showed a molecular ion at m/z 258. A satisfactory elemental analysis was obtained. The IR spectrum showed characteristic stretching bands for acetate at 1736 and 1258 cm^{-1} and the ^1H NMR spectrum clearly showed a three hydrogen singlet for an acetate at δ 2.4 and the doublet at δ 5.2 (J = 4 Hz) for the C-2 *exo*-hydrogen. The rest of the spectrum was similar to the *endo*-epoxide (**204**).

The mass spectrum of the *exo*-epoxyacetate (**253**) showed a molecular ion at m/z 258. A satisfactory elemental analysis was obtained. The IR spectrum clearly showed stretching bands specific for acetate group at 1738 and 1248 cm^{-1} and the ^1H NMR spectrum displayed a three hydrogen singlet at δ 2.35 (acetate) and a 1H doublet (J = 4 Hz) at δ 4.9 for C-2 hydrogen. The rest of the spectrum was similar to the *exo*-epoxide (**205**).

Synthesis and reactions of *endo*-2-acetoxy-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-3-spiro-2'-oxiranes (254, 255)

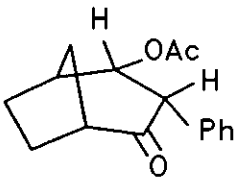
The epoxyalcohols (**210**) and (**211**) were converted into acetates (**254**) and (**255**) (**Equation 15**). The *endo*-epoxyacetate (**254**) gave a satisfactory elemental analysis. The mass spectrum showed a molecular ion at m/z 294/292. The IR spectrum displayed characteristic stretching bands for acetate at 1728 and 1248 cm^{-1}. The ^1H NMR spectrum had important signals at δ 7.1-7.41 (4H, ABq, J = 10 Hz, ClC_6H_4), 5.1 (1H, d, J = 4 Hz, H-2), 4.2 (1H, s, H-8), 2.5 (1H, brs, H-1), 2.1 (3H, s, OAc), and 1.8 (1H, brs, H-4) ppm.

The *exo*-epoxyacetate (**255**) gave a satisfactory elemental analysis. The mass spectrum showed a molecular ion at m/z 294/292. The IR spectrum had characteristic bands at 1728 and 1246 (acetate) cm^{-1}. The

^{1}H NMR spectrum displayed important signals at δ 7.3 (4H, s, ClC_6H_4), 4.9 (1H, d, J = 4Hz, H-2), 4.09 (1H, s, H-8), 2.8 (1H, brs, H-1), 2.2 (3H, s, OAc), and 1.9 (1H, brs, H-4) ppm.

Photochemical fragmentation of epoxyacetates (252), (253), (254), and (255) in HMPA/H_2O

The *endo*- and *exo*-epoxyacetates (**252**) and (**253**) were photolysed under UV light at 254 nm for 6 hours and gave the ketones (**257**) and (**260**) and unreacted starting epoxides, (**252**) and (**253**) respectively. The ketones do not arise from the fragmentation of acetates but from photolytic C-O bond cleavages of the aryl epoxides. The mass spectrum of the ketone (**257**) displayed a molecular ion at m/z 258. A satisfactory elemental analysis was obtained. The IR spectrum clearly showed an acetate 1744 and 1240 cm^{-1} and a carbonyl at 1724 cm^{-1}. The 250 MHz ^{1}H NMR spectrum had the following important signals at δ 7.2-7.37 (5H, m, Ar-H) and the *exo*-C-2 proton at δ 5.37 (1H, d, J = 2.6 Hz) slightly downfield compared to the starting material suggests a methine in the plane of the carbonyl. This rules out the structure (**258**). The 1H broad singlet at δ 3.82 corresponds to the *exo*-proton at C-4 with a very small coupling to the bridgehead hydrogen at C-5. Both bridgehead hydrogens, at C-1 and C-5, appeared at δ 2.6-2.74 as a broad doublet and acetate 3H singlet at δ 2.17. The apex (C-8) *syn*-proton at δ 2.2-2.3 is a doublet (J=3.6 Hz) because there is no coupling to the C-1 or C-5 protons (right angles, dihedral) in contrast to the double triplet (J=3.6 Hz) at δ 2.0-2.1 which corresponds to the (C-8) *anti*-proton, which arises because there is coupling to the protons at C-1 and C-5. This suggests a chair conformation of the six-membered ring system in structure (**257**) and not the boat conformation. The boat conformation would be too unstable, due to the severe interaction of aromatic hydrogen, and it can be ruled out (**Scheme 41**).

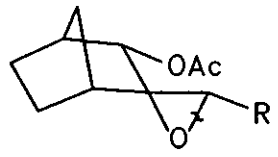


(258)

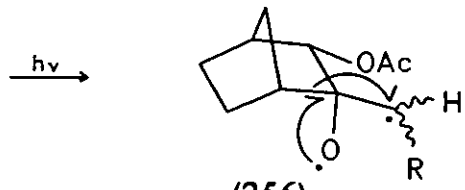
The mass spectrum of the ketone (**260**) also showed a molecular ion at m/z 258. A satisfactory elemental analysis was obtained. The IR spectrum displayed an acetate stretching frequency at 1744 and 1242 cm^{-1} and a carbonyl at 1722 cm^{-1}. The 250 MHz ^1H NMR spectrum had the following signals: a 5H multiplet at δ 7.2–7.3 showed a phenyl. A 1H doublet (J=2.6 Hz) belongs to the *endo*–methine at C–2, and the *endo*–methine at C–4 is at δ 3.77, which shows up as a singlet because it is not strongly coupled to C–5 (dihedral angle very close to 90°). The bridgehead at C–5, shifted downfield at δ 2.98 by 0.3 ppm, strongly suggests an *exo*–phenyl at C–4. The bridgehead hydrogen at C–1 is at δ 2.56, and the 3H singlet at δ 2.19 corresponds to the acetate at C–2. The apex (C–8) *syn*–proton at δ 2.0–2.12 is a doublet (J=3.6 Hz) shifted upfield by 0.2 ppm (shielding cone of C=O). The apex (C–8) *anti*–proton at δ 1.9–2.06 is a double triplet (J=3.6 Hz). This suggests strongly that the six–membered ring has a boat conformation and the structure (**260**).

Scheme 42 shows the mechanistic and stereochemical aspects of these interconversions. In the *endo*–epoxide (**252**) the C–O bond cleaves to give the *endo*–alkoxy radical (**256**). This radical (**256**) then rearranges to give the thermodynamically more stable ketone (**257**). Whereas, in the *exo*–epoxide (**253**) the C–O bond again cleaves open to give the *exo*–alkoxy radical (**259**). This radical (**259**) then rearranges to give the thermodynamically stable ketone (**260**). The *endo*– and *exo*–epoxides give different stereochemistry in the products formed in **Schemes 41, 42.**

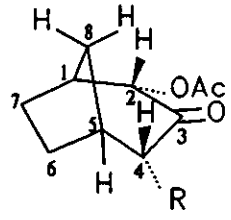
Scheme 41



(252) R = Ph
(254) R = p-ClC_6H_4

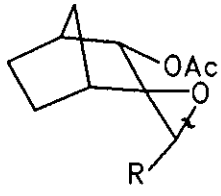


(256)

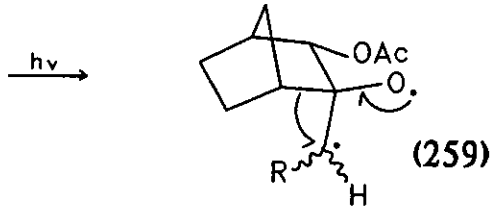


(257) R = Ph
(261) R = p-ClC_6H_4

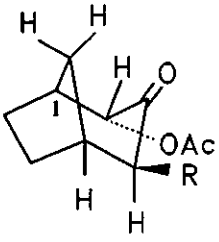
Scheme 42



(253) R = Ph
(255) R = p-ClC_6H_4



(259)



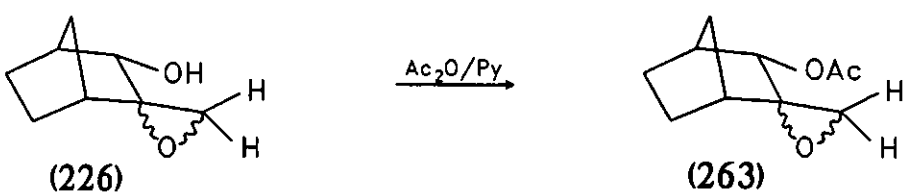
(260) R = Ph
(262) R = p-ClC_6H_4

The *anti*-3'-*p*-chlorophenyl derivatives (**254**) and (**255**) gave similar results as (**261**) and (**262**) (**Schemes 41, 42**), although the products were not fully characterised.

Synthesis and reaction of *endo*-2-acetoxybicyclo[2.2.1]heptan-3-spiro-2'-oxirane (263)

The epoxyalcohol (**226**) was treated with acetic anhydride and pyridine to give the epoxyacetate (**263**) (**Equation 16**). After chromatography a colourless oil was obtained, the mass spectrum showed a molecular ion at m/z 182. The IR spectrum displayed characteristic stretching bands for acetate at 1738 and 1240 cm^{-1} and the ^1H NMR spectrum showed a three hydrogen singlet at δ 2.0 (acetate) and a *exo*-hydrogen the usual doublet (J = 4 Hz) at δ 4.9. The rest of the spectrum was the same as (**226**).

Equation 16



(226) (263)

Attempted photolysis of epoxyacetates (263) in HMPA/H_2O

When a mixture of epoxyacetates (**263**) was photolysed only the starting material was isolated. Longer reaction times led to lower recovery of starting material. The reaction was abandoned and not further studied.

The photostability of these epoxyacetates shows that the acetate has not been able to fragment, as in the steroid cases, under these conditions. Photocleavage of the aryl epoxides follows the normal route for the photolysis of aryl oxiranes[110], and this reaction competes effectively against the photochemical acetoxy group reduction.

SECTION C

The failure of the Barton and McCombie deoxygenation of the conformationally rigid bicyclo[2.2.1]heptane thiocarbonylimidazolides, and the failure of the photolyses of the 2-acetoxy analogues, led us to prepare a range of analogous bromoepoxides. It was expected that these would allow generation of the radical at C-2.

Synthesis of the *exo*-2-bromo-*anti*-3'-phenylbicyclo[2.2.1]-heptan-3-spiro-2'-oxiranes (265, 266)

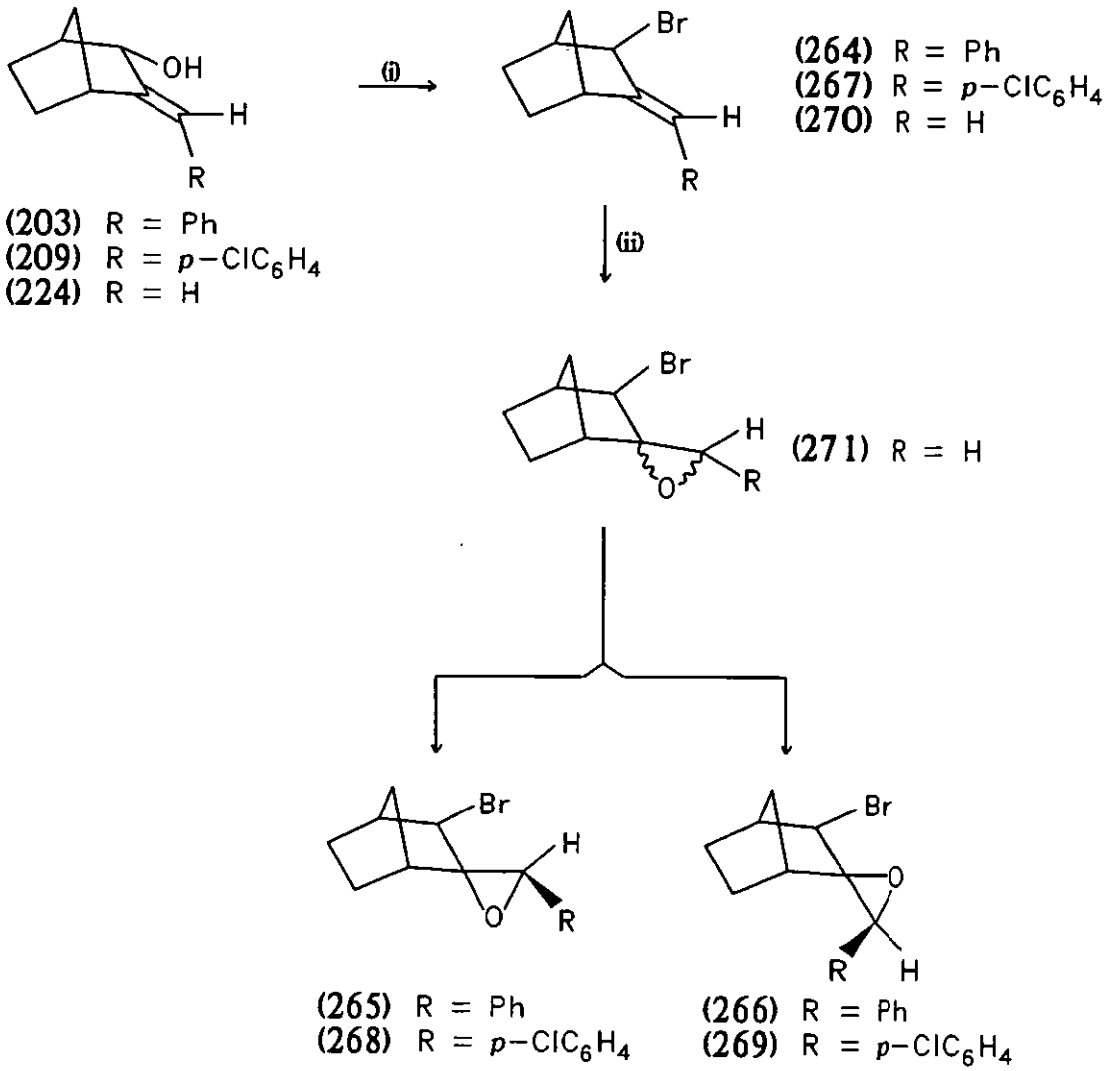
The allylic-alcohol (**203**) was treated with PBr_3[113] in diethylether overnight to give the allylic-bromide (**264**) (**Scheme 43**) which was obtained as an oil. It was expected that the bromide anion would attack from the *exo*-face by the S_N2 mechanism. The ^1H NMR spectrum displayed signals at δ 7.3 (5H, s, Ar-H), 6.6 (1H, s, H-8), and a 1H multiplet at δ 4.6 for the *endo*-proton at C-2, which is coupled with the C-1 proton and allylically couplied with the C-8 proton (J=1.8 and 3 Hz). The bridgehead hydrogens were at δ 3.3 (1H, brs, H-4), and 2.6 (1H, brs, H-1) ppm. The IR spectrum showed a stretching band at 1600 (C=C) cm^{-1}. The bromide (**264**) was further reacted without any purification. The *m*CPBA epoxidation gave a 50:50 mixture of epoxides (**265**) (**266**). These were separated by preparative TLC on silica gel. The mass spectrum of the pure *endo*-epoxybromide (**265**) displayed molecular ions at m/z 280/278. A satisfactory elemental analysis was obtained. The ^1H NMR spectrum showed a 5H singlet at δ 7.32 (Ar-H), and a 1H singlet at δ 4.4 for the epoxide proton. The signal for the *endo*-hydrogen at C-2 was at δ 3.9 (1H, d, J = 3 Hz), and the bridgehead protons gave peaks at δ 2.7 (1H, brs, H-4), and 2.0 (1H, brs, H-1) ppm.

The mass spectrum of the *exo*-epoxybromide (**266**) showed molecular ions at m/z 280/278. A satisfactory elemental analysis was obtained. The ^{1}H NMR spectrum displayed important signals at δ 7.4 (5H, s, C_6H_5-H), 4.4 (1H, s, epoxide-H), and 1H doublet (J = 3 Hz) at 4.3 ppm for the *endo*-C_2-H.

Synthesis of the exo-2-bromo-*anti*-3'-*p*-chlorophenyl-bicyclo-[2.2.1]heptan-3-spiro-2'-oxiranes (268) (269)

The allylic alcohol (**209**) was treated with PBr_3[113] to give the allylic bromide (**267**). The mass spectrum showed molecular ions at m/z 300/298/296. A satisfactory elemental analysis was obtained. The ^{1}H NMR spectrum displayed important signals at δ 7.4 (4H, s, *p*-ClC_6H_5-H), 6.7 (1H, brs, H-8) and 4.6 ppm for the *endo*-C-2 proton 1H multiplet (J=1.8 and 3 Hz). The allylic bromide (**267**) was reacted with *m*CPBA to give a 50:50 mixture of epoxides (**268**) and (**269**) (**Scheme 43**). These were separated by preparative TLC on silica gel. The mass spectrum of the pure *endo*-epoxide (**268**) showed a molecular ions at m/z 316/314/312. A satisfactory elemental analysis was obtained. The 250 MHz ^{1}H NMR spectrum displayed important signals at δ 7.2-7.4 (4H, ABq, J = 5.9 Hz, Cl-C_6H_4-H), 4.36 (1H, s, epoxide-H) and 1H doublet (J = 1.9 Hz) at δ 3.67 for the *endo*-C_2-H. The mass spectrum of the *exo*-epoxide (**269**) showed molecular ions at m/z 316/314/312. A satisfactory elemental analysis was obtained. The high resolution ^{1}H NMR spectrum had important signals at δ 7.2-7.34 (4H, m, Cl-C_6H_4-H), 4.3 (1H, s, epoxide-H), and 4.23 ppm 1H doublet (J=1.9 Hz) for the *endo*-C_2-H.

Scheme 43



Reagents i) Et_2O/PBr_3

ii) *m*CPBA/CH_2Cl_2

Attempted synthesis of *exo*-2-bromobicyclo[2.2.1]heptan-3-spiro-2'-oxiranes (271)

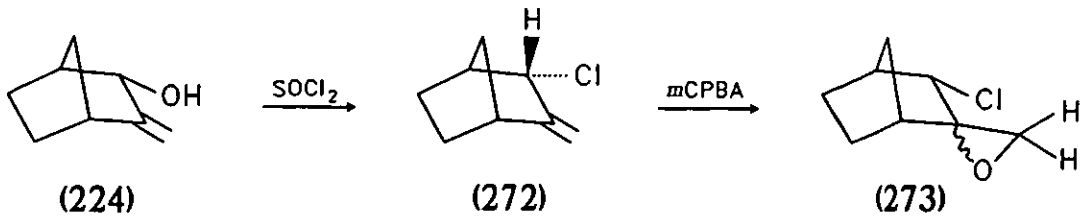
When the allylic alcohol (**224**) was treated with PBr_3, it gave intractable products. The ^1H NMR spectrum obtained almost certainly cannot be that of the allylic bromide (**270**) (**Scheme 43**). The TLC showed a

number of components. Several attempts at low temperature and shorter reaction times made no difference. This approach was abandoned. Allylic bromination of norcamphene (**223**) with NBS also gave a mixture. Jefford *et al.*[114,115] had reported the formation of six products including the allylic bromide (**270**). This approach was also abandoned. Having failed to prepare allylic-bromide (**270**), approaches to the allylic chloride (**272**) were investigated. (**Scheme 44**).

Synthesis of *endo*-2-chlorobicyclo[2.2.1]heptan-3-spiro-2'- oxiranes (273)

As a result of the problems encountered in the preparation of the bromo-oxirane, the more stable chloro analogue was prepared. The allylic alcohol (**224**) was reacted with $SOCl_2$ at -78°C in dry diethyl ether to give the allylic-chloride[21,22] (**272**) obtained after chromatography as a colourless oil in good yield. The mass spectrum of the allylic chloride (**272**) showed molecular ions at m/z 144/142. The IR spectrum showed a stretching band at 1668 (olefinic) cm^{-1}. The 250 MHz ^1H NMR spectrum displayed signals for 2H multiplet at δ 5.04-5.23 for the methylene protons. The 1H multiplet at δ 4.96 for the *exo*-proton at C-2 which is coupled to C-1 bridgehead proton and also allylic coupling to the methyl$_{exo}$protons (J=2 and 5 Hz). The other peaks for the bridgeheads were at δ 2.75 (1H, brs, H-4), and 2.57 (1H, brs, H-1) ppm. The allylic chloride (**272**) was treated with *m*CPBA to give a 50:50 mixture of *exo*- and *endo*-epoxides (**273a** and **273b**) (**Scheme 44**). These epoxides could not be separated by chromatography. The mass spectrum showed molecular ions at m/z 160/158, and the high resolution ^1H NMR spectrum displayed important signals at δ 4.6-4.69 (1H, 2 x d, J = 4.5 Hz, H-2), 2.7-2.96 (2H, 2 x ABq, J = 3 Hz, epoxide protons) and 2.59 (1H, brs, H-4), and 1.85 (1H, brs, H-1) ppm. These were used without any further purification.

Scheme 44



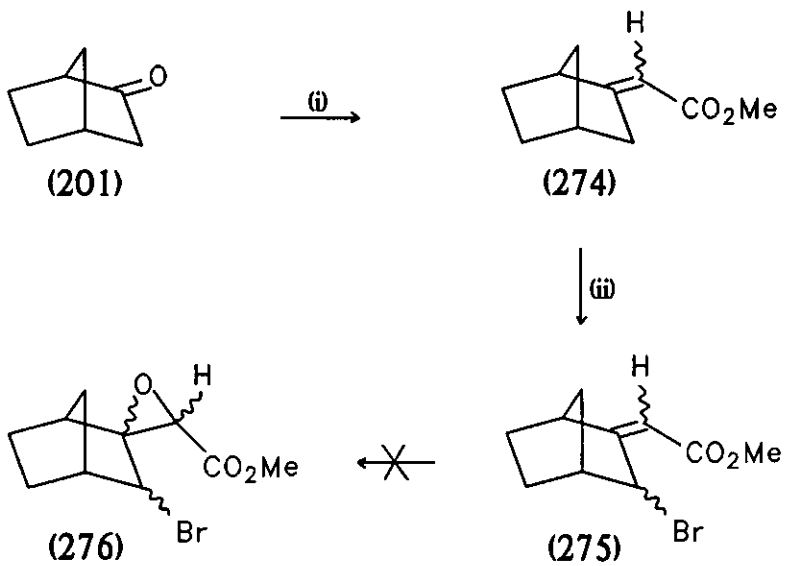
(224) (272) (273)

Attempted synthesis of *endo*-2-bromo-3'-carbomethoxy-bicyclo-[2.2.1]heptan-3-spiro-2'-oxiranes (276)

Norcamphor (**201**) was treated with trimethylphosphonoacetate and BuLi at -78°C in a Horner-Emmons reaction[115] to give a 2:1 mixture of the allylic esters (**274**). (**Scheme 45**). After chromatography a colourless oil was obtained, which showed a stretching band in the IR spectrum at 1725 (α,β-unsaturated ester carbonyl) and 1665 (double bond) cm^{-1}. The ^1H NMR spectrum displayed a 0.5H broad singlet proton at δ 5.75 for the olefinic hydrogen and a 0.5H broad singlet at δ 5.52 for the other stereoisomer, also a 3H singlet at δ 3.65 for the MeO groups. The allylic ester (**274**) was reacted with NBS[113, 114] to give the allylic bromide (**275**) as a colourless oil. The mass spectrum showed molecular ions at m/z 246/244. A satisfactory elemental analysis was obtained. The IR spectrum showed bands at 1725 (α,β-unsaturated ester carbonyl) and 1665 (double bond) cm^{-1}. The ^1H NMR spectrum displayed an unsaturated double bond 0.75H broad singlet at δ 6.0 and 0.25H broad-singlet at 5.85. A 1H multiplet at δ 4.5 was evident for the methine at C-2 which is coupled to C_1-H and allylically coupled with the olefinic methine (J=1.8 and 3 Hz). The stereochemistry is probably *endo*- for the C_2-hydrogen, being analogous to the aryl-bromide discussed earlier. The rest of the signals at δ3.95 (1H, brs, H-4), 3.75 (3H, s, OMe), and 2.6 (1H, brs, H-1) ppm.

Attempted epoxidation with *m*CPBA was unsuccessful and did not give the epoxide (**276**). Several other epoxidising reagents, including dimethyldioxirane[116], hydrogen peroxide and sodium hydroxide[117], trifluroacetic anhydride and urea-H_2O_2[118] were tried but only the starting material was obtained. The reaction was abandoned and not further studied. (**Scheme 45**).

Scheme 45



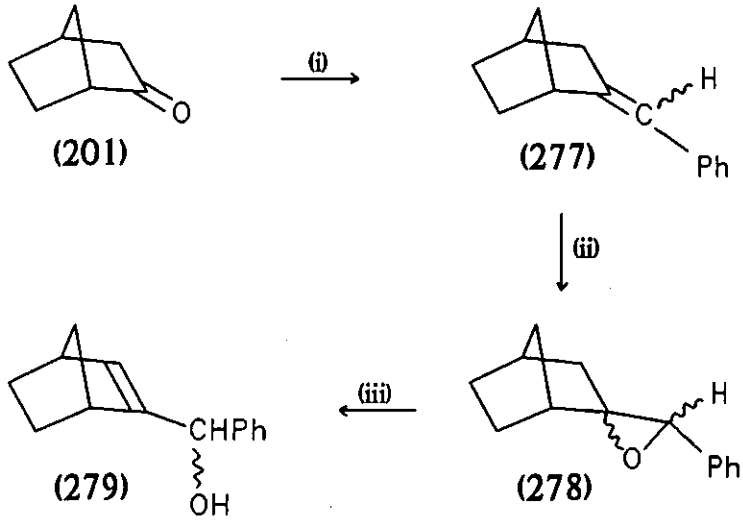
Reagents i) $(CH_3O)_2P(O)CH_2CO_2CH_3$ / THF / BuLi
ii) NBS / CCl_4

Synthesis of 2-hydroxybenzylbicyclo[2.2.1]hept-2-ene (279)

2-Hydroxybenzylbicyclo[2.2.1]hept-2-ene (**279**) was synthesised as a standard because it was one of the expected products of epoxide ring opening (via C-O bond cleavage) of the radical at C-2 of the bicyclo[2.2.1]heptane system. Norcamphor (**201**) was reacted with diethylbenzylphosphonate[115] and BuLi in THF to give benzylidenenorbornane (**277**) as a 3:1 mixture of stereoisomers. The IR

spectrum showed the disappearance of the carbonyl stretching band and the appearance of bands at 1655 and 1595 (C_6H_5–C=C–H) cm^{-1}. The ^1H NMR spectrum displayed signals at δ 7.3 (5H, s, C_6H_5–H), and a broad singlet at δ 6.3 for 0.75H, and also at δ 6.1 for 0.25 H for the benzylic proton at C–8 for the *Z* and *E* stereoisomers respectively. The oily mixture was epoxidised with *m*CPBA to give a 3:1 mixture of *endo*– and *exo*–epoxides (**278**) respectively, as a colourless oil. The ^1H NMR spectrum had signals at δ 7.3 (5H, brs, C_6H_5–H), and the singlet for the *exo*–epoxide 0.25H at δ 4.05 and *endo*–epoxide 0.75H at δ 3.95, similar to the values for the aryl–epoxides discussed earlier. The mixture was reacted with LDA[119] to give the allylic alcohols (**279**) (**Scheme 46**) which showed a molecular ion in the mass spectrum at m/z 200. A satisfactory elemental analysis was obtained. The IR spectrum showed bands at 3228 (hydroxyl) cm^{-1} and the ^1H NMR spectrum displayed important signals at δ 7.3 (5H, s, C_6H_5–H), 5.95 (1H, m, C=C–H), and 5.3 (1H, brs, H–8) ppm.

Scheme 46

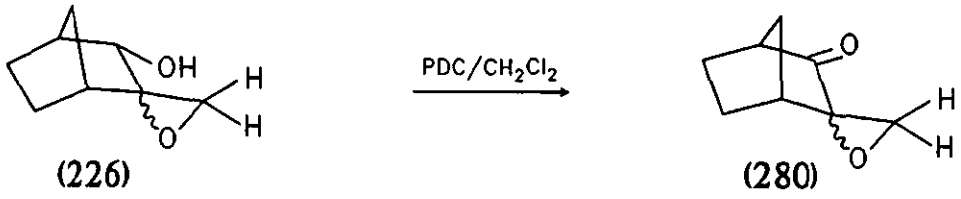


Reagents i) $C_6H_5CH_2P(O)(OC_2H_5)_2$ / BuLi / THF
ii) *m*CPBA / CH_2Cl_2
iii) LDA / THF

Synthesis of bicyclo[2.2.1]heptan-2-one-3-spiro-2'-oxiranes (280)

The oxirane (280) was prepared for studies of ring opening using the Bu_3SnH reduction[100, 101] of α-keto-oxiranes as a method of generating a radical at C-2 of the bicyclo[2.2.1]heptane model. The epoxyalcohol (226) was oxidised with PDC to give the epoxyketone (280) (Scheme 47) which was obtained as a colourless oil, the components of which could not be separated by chromatography. The mass spectrum showed a molecular ion at m/z 138. The IR spectrum displayed a strong carbonyl at 1754 cm^{-1} and the 250 MHz ^1H NMR spectrum had important signals at δ 2.8-3.26 (2H, 2 x ABq, J = 5.6 Hz epoxide-H), and the methine signal at δ 3.9 had disappeared. The epoxyketones were reacted without any further purification.

Scheme 47



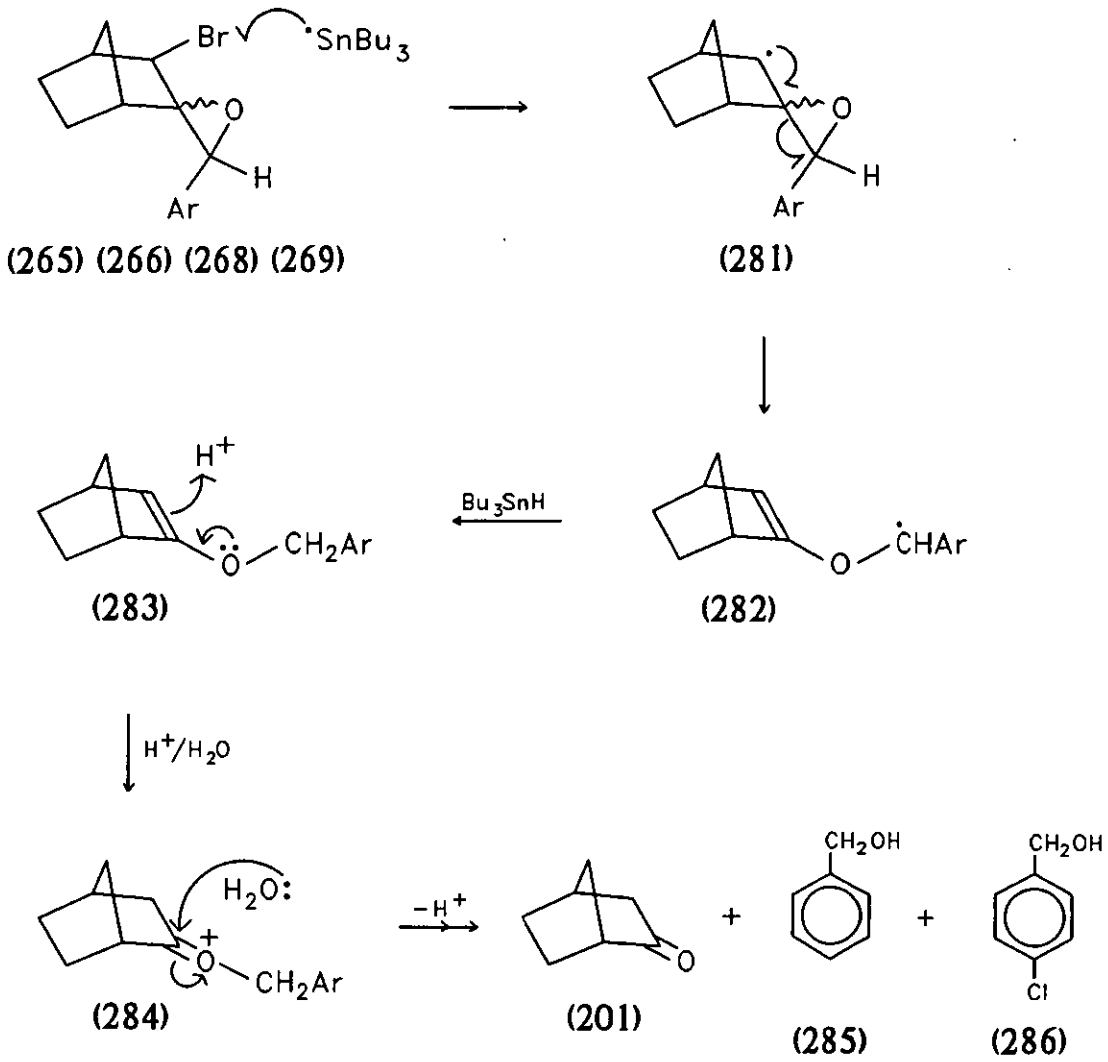
(226) (280)

Reactions between epoxybromides (265), (266), (268), (269) and Bu_3SnH/AIBN

The epoxybromides (265), (266), (268), and (269) were reacted with Bu_3SnH (2 equivalents) to give norcamphor (201) (33-54%) (Scheme 48), and benzyl alcohol (285), (34-60%) from (265) and (266) and *p*-chlorobenzylalcohol (286), (38-52%) from (268) and (269). The norcamphor was derivatised as its 2,4-dinitrophenylhydrazine m.p. 127-139°C. An authentic sample was made which melted at 131-133°C. Benzyl alcohol (285) was derived as its 3,5-dinitrobenzoate

m.p. 109–110°C (lit.[126] m.p. 109–110°C). *p*-Chlorobenzylalcohol (**286**) melted at 71–73°C (lit.[126] m.p. 71–73°C). All spectroscopic data were identical with those of authentic compounds.

Scheme 48

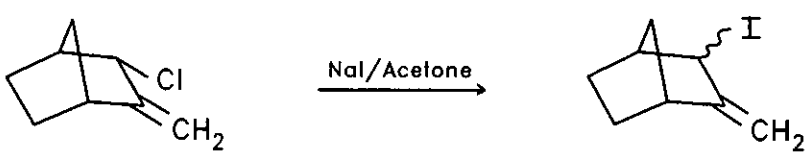


Attempted reaction between the epoxychloride (273) and Bu_3SnH/AIBN

The reduction of epoxychlorides (**273**) with Bu_3SnH afforded starting material only. After several unsuccessful attempts using longer reaction times and using Ph_3SnH, the reaction was abandoned.

We had also attempted to prepare the epoxy iodides (**287**), which may have been reduced with Bu_3SnH, but the Finkelstein reaction using the allylic chloride (**272**) and NaI (**Equation 17**) was unsuccessful, and therefore we were unable to proceed further and the reaction was abandoned.

Equation 17

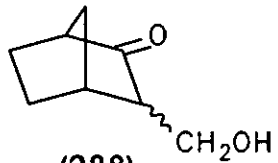


(272) (287)

Reaction between bicyclo[2.2.1]heptan-2-one-3-spiro-2'-oxiranes (280) and Bu_3SnH/AIBN

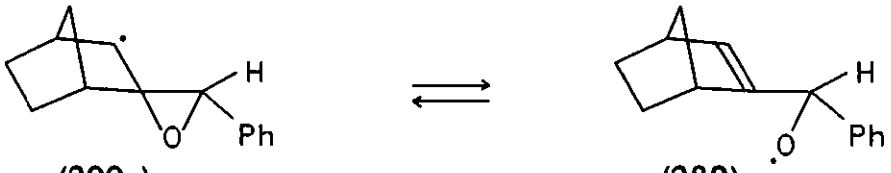
The epoxyketones (**280**) were reduced using the procedure of Hasegawa[100] and Pete *et al*[101] with Bu_3SnH, to give a mixture of the hydroxyketones (**288**) which arise from exclusive C–O bond cleavage. The mass spectrum of the hydroxyketones (**288**) showed a molecular ion at m/z 140. The IR spectrum displayed strong bands at 3428 (hydroxyl) and 1730 (carbonyl) cm^{-1}. The 250 MHz ^1H NMR spectrum showed important signals at δ 3.6–3.84 (2H, m, $-CH_2-OH$), and 3.6 (1H, brs, OH, D_2O exchange), 2.70 (1H, brs, H–1), 2.6 (1H, d, J=5 Hz,

H-4), and 2.36 (1H, m, H-3) ppm, which strongly suggests the expected structure (**288**).



(288)

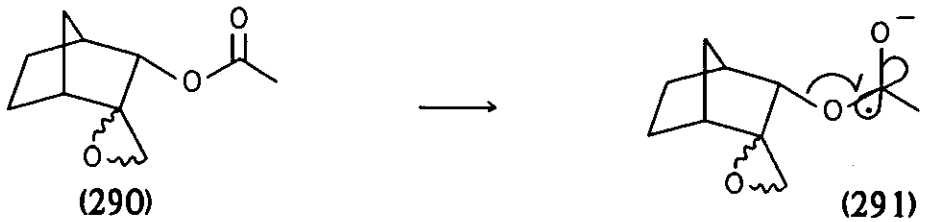
Equation 18



(200a) (289)

Discussion of the Results

In the Bu_3SnH reduction of epoxyimidazolides an alternative reduction reaction takes priority over the deoxygenation, i.e. reduction to a methoxy group. In the photolysis reactions the *p*-orbital contains the unpaired electron in the excited acetates possibly cannot line up with the σ^* molecular orbital as required for fragmentation (**290** and **291**) and probably revert to the acetates, and the alternative excitation of the aryl-epoxides takes priority. In the methylene epoxide this latter reaction is not an alternative and the acetate remains unreactive even after prolonged photolysis. The results of all these reactions indicate the importance of the *p*-orbital (radical) generated, which must be able to line up with the σ^*-orbital of the C-O bond in order to be cleaved to yield the C-2 radical. Therefore, neither of these series of reactions allowed study of the cleavage of oxiranylcarbinyl radicals as required.



(290) (291)

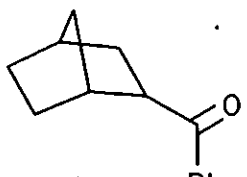
The examination of conformationally rigid models type (**292**) and (**293**) had suggested that the developing semi-occupied *p*-orbital would be in plane with either C-O or C-C epoxide bond depending on the stereochemistry of the epoxides.

(292) (293)

The absence of major differences in bond cleavage in the observed reactions of the epoxy bromides, (**265**), (**266**), (**268**), and (**269**) suggests that radicals are generated initially which then selectively cleave the weaker benzylic C-C bond instead of the C-O bond due to the aryl stabilisation effects. The mechanism for the formation of norcamphor and aryl alcohols are outlined in the **Scheme 48.**

We thought it may be possible that there was a reversible C-O bond cleavage in the epoxybromides (**Equation 18**). This could lead to the thermodynamically stable benzylic radical owing to the slow reduction of the intermediate alkoxy radical. Thus any selective C-O bond cleavage may not be detected. To test these assumptions we tried to generate an alkoxy radical by the photolysis of allylic alcohol (**279**)

with HgO/I_2, according to the Kraus[120] procedure, but to our disappointment only a reduced ketone (**294**), and no norcamphor (**201**) or benzyl alcohol (**285**), was detected.



(294)

The selective formation of hydroxyketones (**288**) in the Bu_3SnH reduction of the α-keto-oxiranes (**280**) indicated a selective C-O bond cleavage, and suggested no obvious stereoelectronic effects. The outcome of these results substantiates the work of Jorgensen[48], which suggested that the C-O bond cleaves unless the C-C bond energy ≤ 65 Kcal/mol.

Although the radicals at C-2 were not generated at either low or high temperature, we have discovered some unusual reduction reactions. The formation of the methoxy compound and acetal is proposed in the **Scheme 40.** However, the photolysis of acetates afforded products from C-O bond cleavages. The origin of these products could only be explained by the cleavage of aryl epoxides and not the radical at the C-2 carbon. We proposed the mechanism which may explain the formation of keto-products in **Schemes 41** and **42.**

Conclusion

In the steroidal examples, it was suggested that the conformational mobility of rings A and B overrides any obvious stereoelectronic effects. In the case of the rigid bicyclo[2.2.1]heptane molecules, aryl stabilisation effects override any stereoelectronic effects. The epoxyketones (**280**) selectively cleaved at the C–O bond and hence no obvious stereoelectronic effects were apparent. Although we have not achieved our aim conclusively, possibly because we may have not had the ideal system, we have discovered some unusual and useful reactions which have not been reported previously, some of which may have synthetic potential.

In conclusion, perhaps further studies should concentrate on the exploration of generating rigid oxiranylcarbinyl radicals in which it can be certain that the semi–occupied *p*–orbital aligns unambiguously with either the C–O or C–C bonds. The absence of complicating substituent effects (e.g. aryl groups) would also be desirable.

EXPERIMENTAL

GENERAL PROCEDURES

Solvents: All solvents were distilled before use. Dry solvents and reagents were obtained as follows:

$CHCl_3$, CH_2Cl_2 and CH_3CN: distilled over P_2O_5 then K_2CO_3 and stored over molecular sieves.

DMSO: Stirred with BaO under nitrogen for 18 hours, then distilled under reduced pressure and stored over molecular sieves.

DMF: Stirred with BaO under nitrogen for 18 hours, filtered, residual water evaporated as an azeotrope with benzene; the DMF was then distilled under reduced pressure and stored over molecular sieves under nitrogen.

EtOH: distilled over magnesium ethoxide

MeOH: distilled over magnesium methoxide.

Et_2O: distilled over $CaCl_2$, then $LiAlH_4$ and stored over molecular sieves under nitrogen.

THF: distilled over $LiAlH_4$/triphenylmethane and stored under nitrogen.

Hexane, pentane and light petroleum: distilled over $CaCl_2$ and stored under nitrogen.

Pyridine and triethylamine: distilled and stored over potassium hydroxide under nitrogen.

Thionyl chloride: distilled over quinoline and stored under nitrogen.

Ethyl acetate: shaken with concentrated H_2SO_4, water, dilute sodium hydroxide and water, dried and distilled over $CaCl_2$.

Toluene, benzene: eluted through a short TLC silica gel column, stirred with sodium hydride for 18 hours, distilled, and stored over molecular sieves under nitrogen.

Unless otherwise stated, all solutions of products in organic solvents were dried over anhydrous magnesium sulphate.

Chromatography: Flash chromatography was performed on silica gel (Merck Kieselgel 60 230–400 mesh). Dry flash chromatography was performed on silica gel (Merck Kieselgel 70–230 mesh, and Merck Kieselgel 7747). Preparative TLC was performed on one metre plates coated with either silica gel (Merck Kieselgel 7747) or alumina (Merck Alumina 1103) 0.75 mm thick. Products were detected by iodine vapour, ultra–violet or visible light.

Melting points: Melting points were determined with Kofler hot stage and digital melting point apparatus.

Analyses: Microanalysis were performed at Brunel University by W.P.E. Heamming.

Infra–red spectrum: IR spectra were recorded on a Perkin–Elmer 257 spectrophotometer; only selected absorbances are recorded. Spectra were recorded as thin films (neat), deuteriochloroform solution ($CDCl_3$), or as Nujol mulls (solids).

NMR spectrum: All NMR spectra were recorded in $CDCl_3$ using Varian EM360A (60 MHz) spectrophotometer unless otherwise stated and are referenced to TMS. The other spectra were recorded on a Perkin–Elmer R32 (90 MHz) and Brucker AC–250 (250 MHz). Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and double doublet (dd) and double triplet (dt) etc.

Mass spectrum: Mass spectra were recorded by electron impact on a Kratos M.S. 80 spectrometer.

Optical rotation: Rotations were measured at ambient temperature using an AA–10 polarimeter.

UV–visible spectrum: UV spectra were recorded on a Shimadzu UV–160 spectrophotometer; only selected absorbances are recorded. Spectra were recorded in ethanol or methanol solution.

General procedure for the reduction of enones

Cerous chloride (0.9 equiv.) was added to a solution of enone (ca. 6g) in methanol (150 ml). The mixture was stirred for 5 minutes while sodium borohydride ($NaBH_4$) (1 equiv.) was added slowly. The mixture was left to stir at room temperature for 30 minutes. The mixture was diluted with water and extracted with diethyl ether (3 x 100 ml). The combined ether extracts were washed with water (100 ml), dried and evaporated *in vacuo*.

General procedure for the *m*CPBA epoxidation of allylic alcohol

m-Chloroperbenzoic acid (*m*CPBA) (2 equiv.) was added to a solution of allylic alcohol (ca. 2g) in CH_2Cl_2 (50 ml). The mixture was stirred with solid sodium hydrogencarbonate, overnight, at room temperature. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous sodium sulphite solution (2 x 50 ml), 5% aqueous sodium hydrogencarbonate solution (100 ml), and finally with water (100 ml), then dried and the solvent removed *in vacuo*.

General procedure for acetylation

Acetic anhydride (25 ml) was added to a solution of alcohol (ca. 5g) in pyridine (50 ml), and the mixture was left to stir at room temperature overnight. The mixture was poured onto ice and left to stir for a further 1 hour. Solid products were filtered and washed with cold 2M aqueous hydrochloric acid (2 x 50 ml), 5% aqueous sodium hydrogen-carbonate solution (75 ml) and finally with water (100 ml). Oily products were dissolved in diethylether and the ether was washed sequentially as for a solid, dried and the solvent removed *in vacuo*.

General procedure for the oxidation of alcohols

Pyridinium dichromate (PDC) (2 equiv.) was added to a solution of the alcohol (ca. 1g) in CH_2Cl_2 (30ml). The mixture was left to stir at room temperature overnight. The crude product was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether as the eluant. The solvent was removed *in vacuo*.

General procedure for the photochemical reductive fragmentation of epoxyacetates

A solution of the epoxyacetate (0.1g) in HMPA and water (95:5) (20 ml) was O_2-degassed for 20 minutes by bubbling nitrogen through the solution. The nitrogen flow was maintained while the sample was irradiated in a quartz tube in a multi-lamp reactor fitted with low pressure Hg tubes (6 x 15 watts) emitting at 254 nm. The irradiation was continued until the reaction was completed, (TLC) 6 hours. The crude mixture was poured into water and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml), saturated brine (2 x 50 ml) and water again. The ether was dried and evaporated *in vacuo*.

General procedure for the reaction between epoxyimidazolides and tri-*n*-butyltin hydride (Bu_3SnH)

To a refluxing solution of Bu_3SnH (10 equiv.) in toluene (5-10 ml) under oxygen-free nitrogen was added the epoxyimidazolides (ca. 0.5g) and AIBN (1/10 equiv.) in toluene (2-6 ml) over 10-20 minutes. The reaction was completed after (TLC) 1 hour. After cooling the solvent was removed *in vacuo*. The crude residue was purified using short column chromatography on TLC silica gel (as adsorbent) and light petroleum (b.p. 40-60°C) as eluant to remove most of the Bu_3SnH. The column was then eluted with diethyl ether and the solvent was removed *in vacuo* from the collected fractions.

General procedure for the preparation of epoxyimidazolides

A solution of the epoxy alcohol (ca. 0.5g) and *N,N'*-thiocarbonyldi-imidazole (2.2 equiv.) in benzene (30 ml) was heated to reflux under oxygen-free nitrogen until the reaction was complete as indicated by TLC (usually 3 hours). The benzene was removed *in vacuo* and replaced by CH_2Cl_2.

The organic layer was washed with water (100 ml) and quickly with 1M aqueous hydrochloric acid (50 ml). Further washing with 5% aqueous sodium hydrogencarbonate solution (100 ml), water and finally brine was followed by drying and removal of the solvent *in vacuo*.

General procedure for aldol condensation

To a solution of norcamphor (ca. 5g) in ethanol (100 ml) was added aldehyde (1.5 equiv.) and potassium hydroxide (1.5 equiv.) at room temperature. The mixture was heated to reflux for 1 hour until TLC indicated consumption of starting material. The mixture was cooled and diluted with water and extracted into diethyl ether (3 x 75 ml). The combined ether extracts were washed with water (2 x 100 ml) and brine and dried and the solvent evaporated *in vacuo*.

General procedure for the bromination of allylic alcohols

To a solution of allylic alcohols (ca. 1g) in dry Et_2O (50 ml) was added PBr_3 (2 equiv.) at room temperature. The mixture was stirred overnight and then diluted with Et_2O and poured onto ice; two layers were separated. The organic layer was washed with water (2 x 50 ml), dried and the solvent evaporated *in vacuo*.

CHATER 2 EXPERIMENTAL

1. Synthesis of enone (141)

To a refluxing solution of cholesterol (**140**) (20g, 52 mmol) in toluene (200 ml) and cyclohexanone (100 ml) was added a solution of aluminium isopropoxide (6.9g, 34 mmol) in toluene (35 ml) over 30 minutes. During the addition toluene was distilled off via a Dean–Stark trap. The solution was cooled and saturated aqueous sodium potassium tartrate (80 ml) was added. The mixture was steam distilled until (600 ml) of distillate had been collected. The crude residue was cooled and extracted with chloroform (3 x 100 ml). The combined chloroform extracts were washed with water (100 ml), dried and solvent was evaporated *in vacuo*. Recrystallisation of the oily product from methanol gave colourless crystals of cholest–4–en–3–one (16g, 78%) m.p. 79–81°C (lit.[75] m.p. 79–81°C); ν_{max} (Nujol) 1672 and 1612 (C=C–C=O) cm^{-1}; δH 5.7 (1H, s, H–4), 1.17 (3H, s, C_{19}–Me), 0.7 (3H, s, C_{18}–Me).

2. Synthesis of allylic alcohol (142)

Cerous chloride (8g, 22 mmol) was added to a solution of cholestenone (**141**) (14g, 36 mmol) in methanol (200 ml). The mixture was stirred for 5 minutes and $NaBH_4$ (1.5g, 39 mmol) was added using the general procedure. Recrystallisation of the solid from light petroleum (b.p. 40–60°C) gave colourless crystals of cholestan–4–en–3β–ol (12g, 85%) m.p. 127.5–129.5°C (lit.[77] m.p. 132°C); ν_{max} (Nujol) 3356 (OH) and 1658 (C=C) cm^{-1}; δH 5.25 (1H, s, H–4), 4.0 (1H, m, H–3), 1.05 (3H, s, C_{19}–Me), 0.69 (3H, s, C_{18}–Me).

3. Synthesis of allylic acetate (143)

Acetic anhydride (25 ml) was added to a solution of cholestenol (**142**) (5.4g, 13 mmol) in pyridine (50 ml). The mixture was reacted using the general procedure for acetylation. Recrystallisation of the solid from methanol gave colourless crystals of 3β-acetoxycholestan-4-ene (4.8g, 80%) m.p. 83.5-85°C (lit.[77] m.p. 85°C); ν_{max} (Nujol) 1740, 1240 (OAc), and 1650 (C=C) cm^{-1}; δH 5.2 (2H, brs, H-3,4), 2.07 (3H, s, OAc), 1.07 (3H, s, C_{19}-Me), and 0.68 (3H, s, C_{18}-Me).

4. Synthesis of epoxyacetate (144)

m-Chloroperbenzoic acid (6g, 35 mmol) was added to a cool solution of acetoxycholestene (**143**) (8g, 18 mmol) in CH_2Cl_2 (70 ml). The mixture was reacted according to the general procedure for epoxidation. The crude mixture was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 3:17 as eluant. The solid obtained was recrystallised from methanol and gave colourless crystals of 3β-acetoxy-4α,5-epoxy-5α-cholestan (4g, 51%) m.p. 119.5-122°C (lit.[79] m.p. 117-119°C); ν_{max} (Nujol) 1736 and 1238 (OAc) cm^{-1}; δH 4.7 (1H, m, H-3), 2.9 (1H, s, H-4), 2.07 (3H, s, OAc), 1.10 (3H, s, C_{19}-Me), and 0.68 (3H, s, C_{18}-Me).

5. Synthesis of epoxyalcohol (145)

A solution of acetoxy-epoxycholestane (**144**) (1g, 2 mmol) in 5% methanolic potassium hydroxide (20 ml) was stirred for 30 minutes. The mixture was diluted with water and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (100 ml), dried and solvent was evaporated *in vacuo*. Recrystallisation of the solid from aqueous methanol gave colourless crystals of 4α,5-epoxy

-5α-cholestan-3β-ol (0.6g, 72%) m.p. 139-141°C (lit.[80] m.p. 136-137°C); ν_{max} (Nujol) 3540, 3364 and 3272 (OH, bonded) cm^{-1}; δH 3.8 (1H, m, H-3), 2.96 (1H, s, H-4), 1.15 (3H, s, C_{19}-Me), and 0.69 (3H, s, C_{18}-Me).

6. Synthesis of epoxy imidazolide (146)

A solution of epoxyalcohol (145) (0.4g, 0.9 mmol) and *N,N'*-thiocarbonyldiimidazole (0.3g, 1.8 mmol) in benzene (20 ml) was reacted using the general procedure. Recrystallisation of the oily product from light petroleum (b.p. 40-60°C) gave cream crystals of **4α,5-epoxy-3β-[imidazol-1-yl(thiocarbonyl)oxy]-5α-cholestane** (0.3g, 59%) m.p. 164-166°C; ν_{max} (Nujol) 3156 (›N-CS-), 1248 (epoxide), 1148 (-O-CS-N‹), 1040 (›C=S) cm^{-1}; δH 8.35 (1H, brs, H-29), 7.75 (1H, brs, H-30), 7.05 (1H, brs, H-31), 5.6 (1H, m, H-3), 3.05 (1H, s, H-4), 1.20 (3H, s, C_{19}-Me), and 0.68 (3H, s, C_{18}-Me); MS - M^+ not found.

7. Synthesis of β-epoxyalcohol (147)

m-Chloroperbenzoic acid (1.3g, 7.5 mmol) was added to a solution of cholestenol (142) (1.8g, 5mmol) in CH_2Cl_2 (20 ml). The mixture was reacted using the general procedure for epoxidation. Recrystallisation of the oily product from methanol gave colourless crystals of 4β,5-epoxy-5β-cholestan-3β-ol (1.3g, 67%) m.p. 81-85°C, an analytical sample was prepared using preparative TLC on silica gel (as absorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:2 as eluant; m.p. 96-97°C (lit.[79b, 80] m.p. 96-97°C); ν_{max} (Nujol) 3468 (OH) cm^{-1}; δH 4.0 (1H, m, H-3), 3.1 (1H, d, J = 4Hz, H-4), 1.03 (3H, s, C_{19}-Me), 0.67 (3H, s, C_{18}-Me).

8. Synthesis of epoxy imidazolide (148)

A solution of epoxyalcohol (**147**) (0.5g, 1.3 mmol) and *N,N'*-thiocarbonyldiimidazole (0.4g, 2.3 mmol) in benzene (30 ml) was reacted according to the general procedure for imidazolide synthesis. Recrystallisation of the oily product from aqueous methanol gave cream crystals of 4β,5-epoxy-3β-[imidazole-1-yl(thiocarbonyl)oxy]-5β-cholestane (0.5g, 73%) m.p. 89-92°C; ν_{max} (Nujol) 3176 (>N-CS-), 1242 (epoxide), 1148 (-O-CS-N<), 1042 (>C=S) cm^{-1}; δH 8.35 (1H, brs, H-29), 7.6 (1H, brs, H-30), 7.0 (1H, brs, H-31), 5.7 (1H, m, H-3), 3.28 (1H, d, J = 4Hz, H-4), 1.10 (3H, s, C_{19}-Me), and 0.68 (3H, s, C_{18}-Me); MS - M^+ not found.

9. Synthesis of epoxy acetate (149)

Acetic anhydride (5 ml) was added to a solution of epoxy alcohol (**147**) (1g, 3 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. Recrystallisation of the solid from aqueous acetone gave colourless crystals of 3β-acetoxy-4β,5-epoxy-5β-cholestane (**149**) (0.9g, 90%) m.p. 88-89°C (lit.[79b] 89-90°C); ν_{max} (Nujol) 1740 and 1230 (OAc) cm^{-1}; δH 5.1 (1H, brs, H-3), 3.2 (1H, d, J = 4Hz, H-4), 2.07 (3H, s, OAc), 1.05 (3H, s, C_{19}-Me), and 0.68 (3H, s, C_{18}-Me).

10. Reaction between 4α,5-epoxy-3β-[imidazol-1-yl(thiocarbonyl)-oxy]-5α-cholestane and Bu_3SnH

To a refluxing solution of Bu_3SnH (1.3g, 4.3 mmol) in toluene (5 ml) under oxygen-free nitrogen was added epoxy imidazolide (**146**) (0.3g, 0.6 mmol) and AIBN (0.01g, 0.01 mmol) in toluene (6 ml) over 10 minutes; and it was reacted according to the reduction of β-isomer.

The less polar product isolated was unidentified minor ketone (18%), ν_{max} (Neat) 1696 (C=O) cm^{-1}. The more polar product isolated was cholestan-3-en-5β-ol (**83**) (0.2g, 80%), recrystallisation from aqueous acetone gave colourless crystals, m.p. 88-92°C (lit.[82] 93.5-94.5); $[\alpha]_D$+95.4°C; ν_{max} (Nujol) 3596, 3444 (OH, bonded), and 1648 (C=C) cm^{-1}; δH 5.4 (2H, m, H-3,4), 0.97 (3H, s, C_{19}-Me), and 0.66 (3H, s, C_{18}-Me).

11. Reaction between 4β,5-epoxy-3β-[imidazol-1-yl(thiocarbonyl)-oxy]-5β-cholestane and Bu_3SnH

To a refluxing solution of Bu_3SnH (1g, 4 mmol) in toluene (5 ml) under oxygen-free nitrogen was added epoxy imidazolide (**148**) (0.4g, 0.8 mmol) and AIBN (0.02g, 0.1 mmol) in toluene (6 ml) over 10 minutes. The mixture was refluxed until the reaction was complete, 2 hours (TLC). The mixture was cooled and the solvent was removed *in vacuo*. The crude residue was purified using column chromatography with silica gel (as adsorbent) and 5% diethyl ether in light petroleum (b.p. 40-60°C) as eluant; slowly increasing ether from 5%-70%. The less polar product isolated was minor ketone (6%). The more polar product isolated was recrystallised from aqueous acetone to give colourless crystals of 5β-cholestan-3-en-5β-ol (**83**) (0.2g, 66%) m.p. 91-94°C (lit.[49, 82] 93.5-94.5°C); $[\alpha]_D$+96.5°; ν_{max} (Nujol) 3608, 3408 (OH, bonded), and 1648 (C=C) cm^{-1}; δH 5.4 (2H, m, H-3,4), 0.97 (3H, s, C_{19}-Me), and 0.66 (3H, s, C_{18}-Me).

12. Photochemical fragmentation of 3β-acetoxy-4α,5-epoxy-5α-cholestane

A solution of epoxy acetate (**144**) (0.2g, 0.5 mmol) was reacted using the general procedure. The crude product mixture was purified using

preparative TLC on silica gel (as adsorbent) and dichloromethane : diethyl ether (9:1) as eluant. The product isolated was recrystallised from aqueous acetone to give colourless crystals of cholestan-3-en-5β-ol (**83**) (0.1g, 58%) m.p. 92-94°C (lit.[49, 82] 93.5-94.5°C); ν_{max} (Nujol) 3604, 3436 (OH, bonded) and 1648 (C=C) cm^{-1}; δH 5.4 (2H, m, H-3,4), 0.97 (3H, s, C_{19}-Me), 0.66 (3H, s, C_{18}- Me).

13. Photochemical fragmentation of 3β-acetoxy-4β,5-epoxy-5β-cholestane (149)

Exactly as for α-isomer above, to give cholestan-3-en-5β-ol (**83**) (66%) m.p. 89-92°C.

14. Synthesis of epoxy ketone (158a)

Pyridinium dichromate (2g, 5 mmol) was added to a solution of epoxycholestanol (**145**) (1.0g, 2.4 mmol) in CH_2Cl_2 (25 ml). The mixture was reacted according to the general procedure for the oxidation. Recrystallisation from methanol gave colourless crystals of 4α,5-epoxy-5α-cholestan-3-one (**158a**) (1g, 90%) m.p. 124-125.5°C (lit.[80, 82] m.p. 124- 125°C); ν_{max} (Nujol) 1712 (C=O) cm^{-1}; δH 3.02 (1H, s, H-4), 1.09 (3H, s, C_{19}-Me), 0.74 (3H, s, C_{18}-Me).

15. Synthesis of epoxy ketone (158b)

To a cool solution of cholestenone (**141**) (4.7g, 12 mmol) in methanol (120 ml) was added 30% hydrogen peroxide (16 ml) slowly, followed by 4M aqueous sodium hydroxide solution (16 ml), keeping the temperature between 0-5°C. The mixture was stirred for 2 hours at 0°C and a further 18 hours at room temperature. The mixture was diluted with water and

extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (100 ml), dried and the solvent was evaporated *in vacuo*. Recrystallisation of the solid from methanol gave colourless crystals of 4β,5-epoxy-5β-cholestan-3-one (**158b**) (3g, 53%) m.p 121-122°C (lit.[79b] 116-117°C); ν_{max} (Nujol) 1715 (C=O) cm^{-1}; δH 2.95 (1H, s, H-4), 1.15 (3H, s, C_{19}-Me), 0.66 (3H, s, C_{18}-Me).

16. Synthesis of allylic alcohol (83)

Excess hydrazine hydrate (100 ml) was added to 4β,5-epoxy-5β-cholestan-3-one (**158b**) (0.6g, 1.4 mmol), and the suspension was heated for 10 minutes at 90°C. The suspension was further heated to reflux for 15 minutes at 120°C and the mixture was cooled and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml), dried and solvent was evaporated *in vacuo*. The crude product was purified using preparative TLC on silica gel (as adsorbent) and CH_2Cl_2 : diethyl ether (9:1) as eluant. Recrystallisation from aqueous acetone gave colourless crystals of cholestan-3-en-5β-ol (**83**) (0.3g, 54%) m.p. 89-91°C (lit.[49, 82] m.p. 89-91°C; analytical sample m.p. 93.5-94.5°C); ν_{max} (Nujol) 3604, 3468 (OH, bonded), and 1648 (C=C) cm^{-1}; δH 5.4 (2H, m, H-3,4), 0.98 (3H, s, C_{19}-Me), and 0.66 (3H, s, C_{18}-Me).

17. Synthesis of allylic alcohol (150)

Excess hydrazine hydrate (100 ml) was added to 4α,5-epoxy-5α-cholestan-3-one (**158a**) (0.5g, 1.2 mmol), and the suspension was heated for 10 minutes at 90°C. The suspension was further heated to reflux for 15 minutes at 120°C according to the β-isomer. The crude product was purified using column chromatography on neutral alumina

(as adsorbent) and CH_2Cl_2 ; light petroleum (b.p. 40–60°C) 3:17 as eluant. The solid obtained was 5α–cholestan–3–en–5α–ol (0.2g, 48%); ν_{max} (Nujol) 3600, 3432 (OH), and 1630 (C=C) cm^{-1}; δH 5.62 (2H, brs, H–3,4), 0.93 (3H, s, C_{19}–Me), 0.66 (3H, s, C_{18}–Me).

18. Synthesis of allylic nitrite ester (159a)

Exactly as with the β–isomer. The crude solid obtained was 5α–cholestan–3–en–5α–nitrite esters (0.2g); ν_{max} (Nujol) 1625 (ON=O) cm^{-1}; δH 5.37 (2H, m, H–3,4), 1.05 (3H, s, C_{19}–Me) and 0.67 (3H, s, C_{18}–Me). The sample was lost on recrystallisation.

19. Synthesis of allylic nitrite ester (159b)

Into a cool solution of cholestenol (**83**) (0.2g, 0.5 mmol) in pyridine (15 ml) at –30°C was bubbled nitrosyl chloride for 10 minutes. The mixture was poured onto ice and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml), dried and the solvent was removed *in vacuo*. The pyridine was removed azeotropically with benzene. The crude solid obtained was 5β–cholestan–3–en–5β–nitrite ester (0.2g); ν_{max} (Nujol) 1622 (–O–N=O) cm^{-1}; δH 5.2 (2H, m, H–3,4), 0.95 (3H, s, C_{19}–Me), and 0.65 (3H, s, C_{18}–Me). The product was lost during recrystallisation from aqueous acetone.

20. Synthesis of epoxy alcohol (158c)

To a solution of epoxyketone (**158b**) (3g, 7 mmol) in methanol (150 ml) was added $NaBH_4$ (0.6g, 1.5 mmol) using the general procedure for reduction. Recrystallisation of the crude product twice from aqueous acetone gave colourless crystals of 4β,5–epoxy–5β–cholestan–3–ol (1.2g,

43%) m.p. 158–159°C); ν_{max} (Nujol) 3448 (OH, Sharp) cm^{-1}; δH 3.8 (1H, m, H–3), 3.85 (1H, brs, H–4), 1.0 (3H, s, C_{19}–Me), and 0.68 (3H, s, C_{18}–Me).

CHAPTER 3 EXPERIMENTAL

21. Synthesis of the mesylate ester (171)

Methanesulphonyl chloride (2 ml) was added dropwise to a solution of cholesterol (140) (1 g, 2.6 m mol) in pyridine (20 ml) at 0°C. When the reaction was shown to be completed, 1.5 hour by TLC, the reaction mixture was poured onto ice and extracted into diethyl ether. The ether extract was washed with 2M hydrochloric acid (2 x 50 ml), 5% aqueous sodium hydrogencarbonate solution (2 x 50 ml), and water (2 x 50 ml). The organic layer was dried and the ether removed *in vacuo*. The crude colourless crystals obtained were 3β–methanesulphonyloxy–cholest–5–ene (0.9g, 81%); m.p. 118–120°C; ν_{max} (Nujol) 1172 (–SO_2–O–) cm^{-1}; δH (60 MHz) 0.68 (3H, s, C_{18}–Me), 1.02 (3H, s, C_{19}–Me), 3.00 (3H, s, $MeSO_2$), 4.32 (1H, brs, H–3α), and 5.35 (1H, m, H–6).

22. Synthesis of the cholestene (172)

The mesylate (171) (0.5g, 1.1 mmol) was dissolved in 1,2–dimethoxy–ethane (10 ml) and sodium iodide (0.5g, 3.3 mmol) was added, followed by zinc powder (0.5g, 7.7 mmol) and water (0.5 ml). The mixture was refluxed until the reaction was completed (by TLC), 6 hours. The reaction mixture was cooled, diluted with diethyl ether and filtered. The filtered solution was washed with water (50 ml), 5% 2M aqueous hydrochloric acid (50 ml), 5% aqueous sodium hydrogencarbonate solution (50 ml), 5% aqueous sodium thiosulphate solution (50 ml), and water (2 x 50 ml). The ether solution was dried and the solvent was

removed *in vacuo*. Recrystallisation of the solid from aqueous methanol/acetone mixture gave colourless crystals of cholest-5-ene (0.3g, 75%), m.p. 89-90.5°C (lit.[90,121,122] m.p. 91-93°C); δH (60 MHz) 0.68 (3H, s, C_{18}-Me), 0.97 (3H, s, C_{19}-Me), and 5.2 (1H, m, H-6).

23. Synthesis of the 5α-diol (173)

Hydrogen peroxide (30%, 0.5 ml) was added to a suspension of cholest-5-ene (**172**) (1.9g, 5 mmol) in formic acid (88%, 6 ml). The mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (200 ml) and extracted with diethyl ether (2 x 50 ml); the organic layer was washed with water (20 ml), 2M aqueous sodium hydroxide solution (20 ml), and water again. The organic layer was dried and evaporated *in vacuo*. The residue was heated under reflux with 3% methanolic potassium hydroxide solution (10 ml) for 1 hour. The mixture was cooled, diluted with water and extracted with diethyl ether. The ether layer was washed with water (4 x 20 ml), dried and the ether was removed *in vacuo*. The crude residue was purified using column chromatography with dry flash silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C), 1:2 as eluant. The less polar product obtained was 5α-cholest-5-ene (0.7g). The TLC, I.R. and ^{1}H NMR spectra were identical with that of the starting material. The more polar product was twice recrystallised with acetone to give 5α-cholestane-5,6β-diol (0.4g, 30%), m.p. 125-126°C (lit.[91,123] m.p. 125.5°C); $[\alpha]^{27}_D$ -10.99° ($CHCl_3$); ν_{max} (Nujol) 3412 (OH) cm^{-1}; δH (60 MHz) 0.68 (3H, s, C_{18}-Me), 1.18 (3H, s, C_{19}-me), and 3.5 (1H, t, H-6).

24. Synthesis of the 5α-hydroxy ketone (174)

A solution of the diol (173) (4g, 10 mmol) in diethyl ether (100 ml) was added to water (15 ml) and methanol (15 ml). The mixture was shaken with *N*-bromosuccinimide (3.3g, 19 mmol) in a separating funnel for 15 minutes and then water (80 ml) and ether (80 ml) were added to the orange-yellow coloured solution. The ether layer was washed with 5% sodium bisulphite solution (100 ml), 2M aqueous sodium hydroxide solution (100 ml), and water (2 x 100 ml), and dried. The solvent was removed *in vacuo*. The crude residue was purified using column chromatography with silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C), 1:2 as eluant. Recrystallisation from aqueous acetone gave colourless crystals of 5α-cholestan-5α-ol-6-one (2.3g, 59%), m.p. 150-152°C (lit.[91] 153-154°C); $[\alpha]^{27}_{D}$ -45.7° ($CHCl_3$); ν_{max} (Nujol) 3512 (OH, H bonded) and 1698 (C=O) cm^{-1}; δH (60 MHz) 0.68 (3H, s, C_{18}-Me), and 0.97 (3H, s, C_{19}- Me).

25. Synthesis of the enone (175)

A solution of the 5α-hydroxy ketone (174) (0.4g, 1 mmol) in benzene (40 ml) was heated to reflux with *p*-toluenesulphonic acid (0.1g, 0.5 mmol) using a reaction flask equipped with a conventional Dean and Stark trap. The reaction was completed in 40 minutes as shown by TLC. The mixture was cooled and purified by column chromatography using a short column with TLC silica gel (as adsorbent). The column was eluted with 5% diethyl ether in light petroleum (b.p. 40-60°C). The solvent was removed *in vacuo* to give a yellow solid of cholest-4-en-6-one (175) (0.34g). A small amount was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:3 as eluant. Recrystallisation from acetone

to give colourless crystals of enone m.p. 108–110°C (lit.[91] m.p. 108–109°C); $[\alpha]^{27}_{D}$ +32° ($CHCl_3$); ν_{max} (Nujol) 1678 and 1616 (C=C–C=O) cm^{-1}; δH (60 MHz) 0.7 (3H, s, C_{18}–Me), 0.99 (3H, s, C_{19}–Me), and 6.35 (1H, t, H–4).

26. Synthesis of the 6α-allylic alcohol (176a)

Cerous chloride (0.3g, 0.8 mmol) was added to a solution of the enone (**175**) (0.4g, 1 mmol) in methanol (20 ml) and allowed to react using the general procedure (as reported for the reduction of enone). The crude yellow solid obtained was cholest–4–en–6α–ol (0.32g, 80%). A small amount was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:2 as eluant. Recrystallisation from acetone gave colourless crystals of the cholest–4–en–6α–ol (**176a**); m.p. 135–137°C (lit.[95,96] m.p. 137–139°C); ν_{max} (Nujol) 3280 (OH) cm^{-1}; δH (250 MHz) 0.68 (3H, s, C_{18}–Me), 0.99 (3H, s, C_{19}–Me), 4.14 (1H, m, $W_{1/2}$ = 9.6 Hz, H–6), and 5.65 (1H, m, J = 2.6 and 4.9 Hz, H–4); δC (250 MHz) 69.13 (CH, C–6), 115.28 (CH, C–4), and 146.72 (q, C–5).

27. Synthesis of the 6α-allylic acetate (176b)

Acetic anhydride (15 ml) was added to a solution of 6α-allylic alcohol (**176a**) (2.5g, 6.5 mmol) in pyridine (20 ml) and reacted using the general procedure as reported for the acetylation. The crude oil obtained was 6α–acetoxycholest–4–ene (2.4g). A small amount was purified by preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:3 as eluant. Recrystallisation from methanol to give colourless crystals of 6α–acetoxycholest–4–ene (**176b**); m.p. 79–81°C (lit.[95] m.p. 95–98°C); ν_{max} (Nujol) 1744 and 1240 (OAc) cm^{-1};

δH (60 MHz) 0.68 (3H, s, C_{18}-Me), 1.05 (3H, s, C_{19}-Me), 2.1 (3H, s, OAc), 5.15 (1H, m, H-6), and 5.38 (1H, brs, H-4).

28. Synthesis of the epoxyalcohols (177, 178)

m-Chloroperbenzoic acid (2g, 12 mmol) was added to a solution of 6α-allylic alcohol (**176a**) (2.3g, 5 mmol) in dichloromethane (30 ml) and was allowed to react using the general procedure for the epoxidation of allylic alcohols. The mixture of the epoxyalcohol obtained was separated using preparative TLC on alumina (as adsorbent) and dichloromethane as eluant. The faster running product obtained was recrystallised from methanol to give colourless crystals of **4α,5-epoxy-5α-cholestan-6α-ol** (**177**) (0.2g, 31%), m.p. 138-140°C; $[\alpha]^{27}_{D}$ + 60.8° ($CHCl_3$); ν_{max} (Nujol) 3450 (OH, bonded) and 1080 (epoxide) cm^{-1}; δH (250 MHz) 0.67 (3H, s, C_{18}-Me), 1.05 (3H, s, C_{19}-Me), 3.44 (1H, d, J = 3.6 Hz, H-4) and 3.83 (1H, dt, J = 4.9 and 11.6 Hz, H-6β, [D_2O Exchange, 1H, dd, H-6β]); δC (250 MHz) 56.24 (CH, C-6), 65.16 (CH, C-4), and 67.54 (q, C-5); Elemental Analysis - Found: C, 80.34; H, 11.70. $C_{27}H_{46}O_2$ requires C, 80.54; H, 11.51%; MS - Found: M^+ 402.3497 (3.6%), $C_{27}H_{46}O_2$ requires 402.3494

The slower running product isolated was recrystallised from aqueous methanol to give colourless crystals of 4β,5-epoxy-5β-cholestan-6α-ol (**178**) (0.17g, 22%) m.p. 86-88°C (lit.[96] m.p. 104-105°C); $[\alpha]^{27}_{D}$ +4.84° ($CHCl_3$); ν_{max} (Nujol) 3444 (OH) and 1070 (epoxide) cm^{-1}; δH (250 MHz) 0.68 (3H, s, C_{18}-Me), 0.99 (3H, s, C_{19}-Me), 3.41 (1H, d, J = 4.3 Hz, H-4) and 4.00 (1H, dd, J = 4.4 and 11.8 Hz, H-6); δC (250 MHz) 56.27 (CH, C-6), 66.10 (CH, C-4), and 68.46 (q, C-5); MS - Found: M^+ 402.3497 (8.3%), $C_{27}H_{46}O_2$ requires 402.3481.

29. Synthesis of the α-epoxyimidazolide (179)

A solution of the α-epoxyalcohol (**177**) (0.35g, 0.9 mmol) and *N,N'*-thiocarbonyldiimidazole (0.34g, 1.9 mmol) in benzene (25 ml) was allowed to react using the same procedure as reported for the imidazolide. The crude product was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether as eluant. The colourless oil obtained was **4α,5-epoxy-6α-[imidazol-1-yl-(thiocarbonyl)oxy]-5α-cholestane (179)** (0.35g, 79%), which solidified on standing m.p. 58-60°C; ν_{max} (Nujol) 3030 (NH), 1530 (amide) and 1094 (epoxide) cm^{-1}; δH (250 MHz) 0.71 (3H, s, C_{18}-Me), 1.17 (3H, s, C_{19}-Me), 3.12 (1H, d, J = 3.4 Hz, H-4), 5.9 (1H, dd, J = 4.5 and 11.5 Hz, H-6), 7.02 (1H, brs, H-31), 7.59 (1H, brs, H-30), and 8.31 (1H, brs, H-29); δC (250 MHz) 56.40 (CH, C-6), 65.66 (q, C-5), 77.63 (CH, C-4), 117.81 (CH, C-31), 130.90 (CH, C-30), 137.07 (CH, C-29), and 183.80 ppm (q, C-28); Elemental Analysis - Found: C, 72.73; H, 9.37; N, 5.47. $C_{31}H_{48}N_2O_2S$ requires C, 72.61; H, 9.43; N, 5.46%; MS - M^+ not found.

30. Synthesis of the β-epoxyimidazolide (180)

A solution of the β-epoxyalcohol (**178**) (0.3g, 0.7 mmol) and *N,N'*-thiocarbonyldiimidazole (0.3g, 1.6 mmol) in benzene (20 ml) was reacted using the same procedure as reported for the imidazolide except that the mixture was refluxed for 14h instead of 3h. The crude product obtained was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 3:1 as eluant. The colourless oil obtained was **4β,5-epoxy-6α-[imidazol-1-yl-(thiocarbonyl)oxy]-5β-cholestane** (0.2g, 56%). ν_{max} (Neat) 3130 (NH), 1530 (amide) and 1045 (epoxide) cm^{-1}; δH (250 MHz) 0.72 (3H, s, C_{18}-Me), 1.11 (3H, s, C_{19}-Me), 3.24 (1H, d, J = 4.1 Hz, H-4), 5.96 (1H, dd, J = 4.8 and 12.1 Hz, H-6), 7.00 (1H, brs, H-31), 7.55 (1H, brs,

H-30) and 8.25 (1H, brs, H-29); δC (250 MHz) 56.22 (CH, C-6), 65.98 (q, C-5), 77.73 (CH, C-4), 117.92 (CH, C-31), 130.68 (CH, C-30), 136.66 (CH, C-29), and 183.50 (q, C-28); Elemental Analysis - Found: C, 72.20; H, 9.51; N, 5.27. $C_{31}H_{48}N_2O_2S$ requires C, 72.60; H, 9.43; N, 5.46%; MS - M^+ not found.

31. Synthesis of the α-epoxyacetate (181)

Acetic anhydride (5 ml) was added to a solution of α-epoxy alcohol (**177**) (0.4g, 0.9 mmol) in pyridine (10 ml) and was allowed to react using the general procedure as reported for the acetylation. Recrystallisation of the oily product with aqueous methanol gave colourless crystals of **6α-acetoxy-4α,5-epoxy-5α-cholestane (181)** (0.3g, 71%), m.p. 76.5-78.5°C; $[\alpha]^{27}_D$ + 74.3° ($CHCl_3$); ν_{max} (Nujol) 1738 and 1244 (OAc), and 1056 (epoxide) cm^{-1}; δH (250 MHz) 0.68 (3H, s, C_{18}-Me), 1.11 (3H, s, C_{19}-Me), 2.02 (3H, s, OAc), 3.14 (1H, d, J = 3.4Hz, H-4) and 5.19 (1H, dd, J = 4.7 and 11.9 Hz H-6); δC (250 MHz) 56.18 (CH, C-6), 65.98 (q, C-5), 67.79 (CH, C-4), and 170.06 (q, OAc); Elemental Analysis - Found: C, 78.21; H, 11.06. $C_{29}H_{48}O_3$ requires C, 78.33; H, 10.88%; MS - Found: M^+ 444.3603 (3.0%), $C_{29}H_{48}O_3$ requires 444.3610.

32. Synthesis of the β-epoxyacetate (182)

Acetic anhydride (5 ml) was added to a solution of β-epoxyalcohol (**178**) (0.3g, 0.8 mmol) in pyridine (10 ml) and reacted using the same procedure as reported for the acetylation. The crude oil obtained was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:3 as eluant. The colourless oil obtained was 6α-acetoxy-4β,5-epoxy-5β-cholestan (**182**) (0.2g, 60%),

which was difficult to crystallise (lit.[101] m.p. 42–44°C); ν_{max} (Neat) 1745 and 1239 (OAc), and 1078 (epoxide) cm^{-1}; δH (250 MHz) 0.68 (3H, s, C_{18}–Me), 1.04 (3H, s, C_{19}–Me), 1.99 (3H, s, OAc), 3.3 (1H, d, J = 3.9Hz, H–4), and 5.21 (1H, dd, J = 4.9 and 12.1 Hz, H–6); δC (250 MHz) 56.28 (CH, C–6), 65.69 (q, C–5), 67.99 (CH, C–4), and 170.57 (q, OAc); MS – Found: M^+ 444.3603 (1.5%), $C_{29}H_{44}O_2$ requires 444.3608.

33. Reaction between 4α,5–epoxy–6α–[imidazol–1–yl(thiocarbonyl)–oxy]–5α–cholestane (179) and tri–*n*–butyltin hydride (Bu_3SnH)

A solution of the α–epoxyimidazolide (179) (0.4g, 0.7 mmol) and AIBN (0.01g, 0.07 mmol) in toluene (15 ml) was added dropwise over 25 minutes to a refluxing solution of Bu_3SnH (1.8g, 10 equiv.) in toluene (6 ml) and was allowed to react using the general procedure as reported for the reduction of imidazolides. The mixture was separated using preparative TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:4 as eluant. Three products were isolated. The least polar product, obtained as a colourless oil was **6α–methoxy–4α,5–epoxy–5α–cholestane** (184) (0.1g, 31%). Crystallisation from methanol gave colourless crystals m.p. 70–72°C; δH (250 MHz) 0.68 (3H, s, C_{19}–Me), 1.05 (3H, s, C_{19}– Me), 3.3 (3H, s, H–28(OMe)), 3.4 (1H, d, J = 3.4 Hz, H–4) and 3.50 (1H, dd, J = 4.5 and 11.8 Hz, H–6); δC (250 MHz) 74.48 (CH, C–6), 66.64 (q, C–5), and 57.33 (CH, C–4). Elemental Analysis – Found: C, 80.71; H, 11.74; $C_{29}H_{48}O_2$ requires C, 80.71; H, 11.61%.

The intermediately polar product was obtained as colourless crystals, which were recrystallised from acetone – light petroleum (b.p. 40–60°C) to give cholest–5–en–4α–ol (183a) (0.1g, 33%), m.p. 140–142°C (lit.[95,124] m.p. 144–145°C); $[\alpha]^{27}_D$ –53°; ($CHCl_3$). ν_{max} (Nujol) 3292 (OH). cm^{-1};

δH (250 MHz) 0.68 (3H, s, C_{18}–Me), 0.99 (3H, s, C_{19}–Me), 4.21 (1H, brd, J = 9.8 Hz, H–4), and 5.65 (1H, dt, J = 2 and 4 Hz, H–6); δC (250 MHz) 69.6 (CH, C–4), 115.41 (CH, C–6), 145.9 (q, C–5).

The most polar product was obtained as colourless oil, which was crystallised from methanol to give colourless crystals of 4α,5–epoxy–5α–cholestan–6α–ol (**177**) (30 mg, 10%), m.p. 135–136.5°C; The IR and NMR spectra and TLC were identical to the epoxyalcohol (**177**) starting material.

When the epoxyimidazolide (**179**) (0.3g, 0.6 mmol) and AIBN (0.01g, 0.7 mmol) were reacted using the procedure reported above, with 1.5 equiv. of Bu_3SnH rather than 10 equiv., the only product isolated was cholestan–5–en–4α–ol (**183a**) (0.06g, 27%). The spectroscopic data obtained were identical to those reported above.

34. Reaction between 4β,5–epoxy–6α–[imidazol–1–yl(thiocarbonyl)–oxy]–5β–cholestane (180) and Bu_3SnH

A solution of the β–epoxy imidazolide (**180**) (0.1g, 0.2 mmol) and AIBN (4 mg, 0.02 mmol) in toluene (10 ml) was added dropwise over 25 minutes to a refluxing solution of Bu_3SnH (0.1g, 1.5 equiv.) and allowed to react using the general procedure. The product was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:3 as eluant. The colourless crystals obtained were cholest–5–en–4β–ol (**183b**) (0.04g, 56%), which was recrystallised with aqueous methanol m.p. 130–132°C (lit.[124] m.p. 128–130°C); ν_{max} (Nujol) 3353 (OH) cm^{-1}; δH (250 MHz) 0.68 (3H, s, C_{18}–Me), 1.20 (3H, s, C_{19}–Me), 4.22 (1H, d, J = 2.9 Hz, H–4) and 5.58 (1H, brdd, J = 2.2 and 5.1 Hz, H–6); δC (250 MHz) 74.94 (CH, C–4), 126.06 (CH, C–6), and 144.86 ppm (q, C–5).

35. Photochemical fragmentation of 6α-acetoxy-4α,5-epoxy-5α-cholestane (181) in HMPA/H_2O

A solution of the α-epoxyacetate (181) (0.2g, 0.5 mmol) was photolysed using the general procedure as reported for epoxy acetates. The crude product purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:3 as eluant. The colourless crystals obtained was cholest-5-en-4α-ol (**183a**) (0.04g, 23%). Recrystallisation from acetone - light petroleum (b.p. 40-60°C) to give colourless crystals m.p. 139-141°C (lit.[124] 140-142°C). ν_{max} (Nujol) 3520 and 3488 (OH, bonded) cm^{-1}; δH (250 MHz) 0.68 (3H, s, C_{18}-Me), 0.99 (3H, s, C_{19}-Me), 4.21 (1H, brd, J = 11 Hz, H-4) and 5.65 (1H, dt, J = 2 and 4.1 Hz, H-6).

36. Photochemical fragmentation of 6α-acetoxy-4β,5-epoxy-5β-cholestane (182) in HMPA/H_2O

A solution of the β-epoxyacetate (**182**) (0.1g, 0.3 mmol) was allowed to react using the general procedure as reported for epoxyacetates. The crude product was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:1 as eluant. The less polar material obtained was unchanged starting material (13%). The more polar product obtained was cholest-5-en-4β-ol (**183b**) (0.06g, 60%). Recrystallisation from aqueous methanol gave colourless crystals m.p. 133-135°C (lit.[124] m.p. 128-130°C); ν_{max} (Nujol) 3340 (OH) and 1640 (C=C-H) cm^{-1}; δH (60 MHz) 0.68 (3H, s, C_{18}-Me), 1.2 (3H, s, C_{19}-Me), 4.25 (1H, t, H-4), 5.6 (1H, m, H-6).

37. Synthesis of the epoxy ketone (192)

Pyridium dichromate (0.7g, 1.8 equiv.) was added to a solution of epoxyalcohol (**191**) (0.4g, 1 mmol) in dichloromethane (25 ml) and reacted using the general procedure for the oxidation of alcohols. The colourless oil obtained was 4ξ,5-epoxy-5ξ-cholestan-6-one (0.24g, 58.4%). ν_{max} ($CDCl_3$) 1718 (C=O) cm^{-1}; δH (60 MHz) 0.70 (3H, s, C_{19}-Me), 0.87 (3H, s, C_{19}-Me), and 3.05 (1H, t, H-4).

38. Reaction between 4ξ,5-epoxy-5ξ-cholestan-6-one and Bu_3SnH

A solution of the epoxyketone (**192**) (0.24g, 0.6 mmol) and AIBN (0.01g, 0.06 mmol) in toluene (10 ml) was added dropwise over 25 minutes to a refluxing solution of Bu_3SnH (0.3g, 1.5 equiv.) and allowed to react using the general procedure for the reduction of imidazolides. The crude residue was purified using preparative TLC on silica gel (as adsorbent) and 2.5% diethyl ether in light petroleum (b.p. 40-60°C) as eluant. The less polar product isolated was 5α-cholestan-4β-ol-6-one (**196b**) (0.06g, 27%) which was recrystallised with aqueous methanol to give colourless crystals, m.p. 122-124°C (lit.[101] 124-126°C); ν_{max} (Nujol) 3536 (OH free and OH bonded), and 1698 (C=O) cm^{-1}; δH (250 MHz) 0.66 (3H, s, C_{18}-Me), 1.02 (3H, s, C_{19}-Me), 3.5 (1H, brs, D_2O exchange, OH-4), and 4.28 (1H, brs, H-4); δC (250 MHz) 65.49 (CH, C-4) and 215.9 (q, C-6); UV spectrum λ_{max} (methanol) 280.5 nm.

The more polar material isolated was the starting epoxyketone (**192**) (0.1g, 41%). The spectroscopic data obtained were identical to the starting material.

39. Synthesis of the 5α,6-epoxyalcohol

A solution of the cholesterol (140) in CH_2Cl_2 was cooled and *m*CPBA (6g, 33 mmol) was reacted using the general procedure for epoxidation. Recrystallisation of the solid with aqueous acetone gave colourless crystals of 5α,6-epoxy-5α-cholestan-3β-ol (3.4g, 48%), m.p. 133-135°C (lit.[125] m.p. 142.5°C); ν_{max} (Nujol) 3396 (OH) and 1090 (epoxide) cm^{-1}; δH (60 MHz) 0.66 (3H, s, C_{18}-Me), 1.05 (3H, s, C_{19}-Me), 2.9 (1H, d, J = 4 Hz, H-6) and 3.65 (1H, m, H-3).

40. Synthesis of the α-epoxychloride

A solution of the cholesterylchloride (1.3g, 3.2 mmol) in CH_2Cl_2 was cooled and *m*CPBA (1g, 6 mmol) was reacted using the general procedure for epoxidation. The colourless crystals obtained were 3β-chloro-5α,6-epoxy-5α-cholestane (1.1g. 81.4%) m.p. 81-82.6 °C; ν_{max} (Nujol) 1104 (epoxide) cm^{-1}; δH (60 MHz) 0.63 (3H, s, C_{18}-Me), 1.08 (3H, s, C_{19}-Me), 2.9 (1H, d, J = 4 Hz, H-6), and 3.8 (1H, m, H-3).

41. Attempted synthesis of cholest-4-en-6-one (174)

A solution of 5α,6-epoxy-5α-cholestan-3β-ol (1g, 3 mmol) in DMF (100 ml) was added to phenylisothiocyanate (3 ml) and lithium chloride (0.1g) at room temperature. The mixture was refluxed under nitrogen for 4 hours. No colour change was observed as reported in the literature[93]. The mixture was cooled and diluted with diethyl ether (100 ml). The ether extracts were washed with water (2 x 100 ml), 5% aqueous sodium hydrogen carbonate solution (2 x 100 ml), water again, and finally brine. The ether layer was dried and the solvent removed

in vacuo. The crude residue was purified using column chromatography on TLC silica gel (as adsorbent) and diethyl ether as eluant. The yellow solid obtained was not the enone, instead ^{1}H NMR indicated that it contained aromatic protons only and no aliphatic protons. Several attempts using the 3β-chloro-5α,6-epoxy-5α-cholestane under the same conditions as above, yielded only starting material and some dimeric unidentified aromatic compound. This approach was therefore abandoned.

42. Attempted synthesis of 4β-phenyl-5α-cholestane-5α,6-diol

A solution of 4ξ,5-epoxy-5ξ-cholestan-6α-ol (1.6g, 4 mmol) in dry diethyl ether (50 ml) was added to phenyl magnesium bromide, made *in situ* from magnesium turnings (3g, 130 mmol) and bromobenzene (20g, 130 mmol) in dry ether (200 ml) under reflux in a nitrogen atmosphere for 1 hour. The whole mixture was refluxed for further 5 hours, cooled and poured into cold saturated aqueous ammonium chloride solution (50 ml). The organic phase was separated, washed with water (3 x 100 ml), dried and the ether removed *in vacuo* . The crude residue was purified using column chromatography with TLC silica gel (as adsorbent) and 5% diethyl ether in light petroleum (b.p. 40–60°C) as eluant. The yellow oil obtained (1.6g) was not the desired product. The ^{1}H NMR (250 MHz) indicated some of the starting β-epoxide and some unidentified aromatic was present. The reaction was abandoned and not further studied.

CHAPTER 4 EXPERIMENTAL

43. Synthesis of enone (202)

To a solution of bicyclo[2.2.1]heptan-2-one (**201**) (6g, 54 mmol) in ethanol (100 ml) was added benzaldehyde (8.5g, 80 mmol) and potassium hydroxide (4.5g, 80 mmol) at room temperature. The mixture was heated to reflux for 1 hour until the TLC indicated consumption of the starting material. The mixture was cooled and diluted with water and extracted into diethyl ether (3 x 75 ml). The combined ether extracts were washed with water (2 x 100 ml) and brine, dried and the solvent was evaporated *in vacuo* to give a dark coloured oil. The crude oil was purified using column chromatography on TLC silica gel (as adsorbent) and dichloromethane as eluant. The coloured oil obtained was 3-benzylidenebicyclo[2.2.1]heptan-2-one (8.8g, 83%). ν_{max} (Neat) 1724 (C=O) and 1640 (C=C, conjugated) cm^{-1}; δH (60 MHz) 7.5 (5H, brs, Ph), 7.2 (1H, s, H-8), 3.6 (1H, brs, H-1), 2.7 (1H, brs, H-4), and rest 1.5-2.2 (6H); MS - Found: M^+ 198.1045 (68.7%), $C_{14}H_{14}O$ requires 198.1043; UV spectrum λ_{max} (EtOH) 289.0 (24098) and 224.0 (11463) nm.

44. Synthesis of allylic alcohol (203a)

Cerous chloride (6.3g, 17 mmol) was added to a solution of 3-benzylidenebicyclo[2.2.1]heptan-2-one (**202**) (5.2g, 26 mmol) in methanol (150 ml). The mixture was stirred for 5 minutes and $NaBH_4$ (1g, 26 mmol) was added according to the general procedure for enone reduction. The crude product was recrystallised twice from light petroleum (b.p. 40-60°C) to give light yellow crystals of **3-benzylidenebicyclo-[2.2.1]-heptan-*endo*-2-ol** (3g, 58%) m.p. 78-81°C; ν_{max} (Nujol) 3252 (OH) and 1596 (C=C) cm^{-1}; δH (60 MHz) 7.35 (5H, brs, Ph), 6.40 (1H, m, H-8), 4.5 (1H, brm, J = 2 and 4 Hz, H-2), 3.25 (1H, brs, H-1), 2.4 (1H, brs, H-4),

and 2.2 (1H, brs, D_2O exchange, OH); Elemental Analysis - Found: C, 83.89 H, 8.11. $C_{14}H_{16}O$ requires C, 83.96, H, 8.05%; MS - Found: M^+ 200.1201 (100%), $C_{14}H_{16}O$ requires 200.1201.

45. Synthesis of allylic acetate (203b)

Acetic anhydride (5 ml) was added to a solution of 3-benzylidene-bicyclo[2.2.1]heptan-*endo*-2-ol (**203a**) (0.3g, 1.5 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. The solid was obtained, which was recrystallised from methanol to give colourless crystals of ***endo*-2-acetoxy-3-benzylidenebicyclo[2.2.1]-heptane** (0.2g, 60%), m.p. 39-40°C; ν_{max} (Nujol) 1738 and 1240 (OAc) cm^{-1}; δH (60 MHz) 7.35 (5H, brs, Ph), 6.35 (1H, brs, H-8), 5.6 (1H, brs, H-2), 3.3 (1H, brs, H-1), 2.6 (1H, brs, H-4) and 2.1 (3H, s, OAc); Elemental Analysis - Found: C, 79.28; H, 7.53. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49%); MS - Found: M^+ 242.1307 (33.6%), $C_{16}H_{18}O_2$ requires 242.1317.

When the allylic acetate made above was epoxidised with *m*CPBA, a mixture of epoxyacetates *exo*:*endo* (5:1) (calculated by ^1H NMR analysis) was obtained.

46. Synthesis of epoxyalcohols (204), (205)

m-Chloroperbenzoic acid (1.7g, 10 mmol) was added to a solution of 3-benzylidenebicyclo[2.2.1]heptan-*endo*-2-ol (**203a**) (1g, 5 mmol) in CH_2Cl_2 (40 ml) at room temperature. The mixture was reacted using the general procedure for epoxidation, except that the reaction was stirred for 4 hours instead of overnight. The crude residue was separated using preparative TLC on silica gel (as adsorbent) and diethyl ether : light

petroleum (b.p. 49–60°C) 1:1 as eluant. Two products were isolated in 50:50 mixture, the faster running product obtained was *anti*-**3'-phenylbicyclo[2.2.1]heptan-*endo*-2-ol-*endo*-3-spiro-2'-oxirane (204)** (0.34g, 32%). Recrystallisation from aqueous methanol gave colourless crystals, m.p. 89–91°C; ν_{max} (Nujol) 3240 (OH) and 1108 (epoxide) cm^{-1}; δH (250 MHz) 7.2–7.40 (5H, m, Ph), 4.02 (1H, d, J = 2.7 Hz, H–2), 4.00 (1H, s, H–8), 2.51 (1H, brs, H–1), 2.41 (1H, brs, D_2O exchange, OH), and 1.90 (1H, brs, H–4); δC (250 MHz) 135.62 (q, C–9), 128.24 (CH, C–11/13), 127.86 (CH, C–12), 126.04 (CH, C–10/14), 72.34 (q, C–3), 71.48 (CH, C–2), 65.01 (CH, C–8), 41.82 (CH, C–1), 35.94 (CH, C–4), 32.66 (CH_2, C–5), 24.41 (CH_2, C–7), 12.69 (CH_2, C–8); Elemental Analysis – Found: C, 77.89; H, 7.59. $C_{14}H_{16}O_2$ requires C, 77.75, H, 7.46%); MS – Found: M^+ 216.1150 (7.2%) $C_{14}H_{16}O_2$ requires 216.1153.

The slower running compound obtained was *anti*-**3'-phenylbicyclo-[2.2.1]heptan-*endo*-2-ol-*exo*-3-spiro-2'-oxirane (205)** (0.4g, 36%). Recrystallisation from aqueous methanol gave colourless crystals, m.p. 91.5–93°C; ν_{max} (Nujol) 3400 (OH) and 1094 (epoxide) cm^{-1}; δH (250 MHz) 7.2–7.3 (5H, m, Ph), 4.23 (1H, s, H–8), 4.08 (1H, d, J = 3 Hz, H–2), 2.47 (1H, brs, H–1) and 1.99 (1H, brs, H–4); δC (250 MHz) 136.51 (q, C–9), 128.08 (CH, C–11/13), 127.41 (CH, C–12), 125.96 (CH, C–10/14), 77.95 (CH, C–2), 76.36 (q, C–3), 58.89 (CH, C–8), 42.42 (CH, C–1), 39.04 (CH, C–4), 34.14 (CH_2, C–7), 24.15 (CH_2, C–5), and 19.05 (CH_2, C–6); Elemental Analysis – Found: C, 77.98; H, 7.60. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%; MS – Found: M^+ 216.1150 (9.6%), $C_{14}H_{16}O_2$ requires 216.1143.

47. Synthesis of *endo*-epoxyimidazolide (206)

A solution of *endo*-spiroepoxyalcohol (**204**) (0.4g, 1.8 mmol) and *N,N'*-thiocarbonyldiimidazole (0.7g, 4 mmol) in benzene (30 ml) was reacted according to the general procedure for imidazolide synthesis. The crude solid obtained was recrystallised with light petroleum (b.p.40–60°C) to give cream crystals of ***endo*-2-[imidazol-1-yl(thiocarbonyl)oxy]-*anti*-3'-phenylbicyclo[2.2.1]heptan-*endo*-3- spiro-2'-oxirane** (0.4g, 63%), m.p. 117.5–119°C; ν_{max} (Nujol) 3168 (–CS–N‹) (w), 1150 (–O–CS–N‹), 1040 (›C=S) and 1010 (epoxide) cm^{-1}; δH (60 MHz) 8.5 (1H, brs, H–16), 7.7 (1H, brs, H–17), 7.4 (5H, brs, Ph), 7.1 (1H, brs, H–18), 5.9 (1H, d, J = 4 Hz, H–2), 4.2 (1H, s, H–8), and 2.9 (1H, brs, H–1); Elemental Analysis - Found: C, 66.25; H, 5.61; N, 8.59. $C_{18}H_{18}N_2O_2S$ requires C, 66.03; H, 5.85; N, 8.56%; MS - Found: M^++1 327.1167 (17.9%) $C_{18}H_{18}N_2O_2S$ requires 327.1132.

48. Synthesis of *exo*-epoxyimidazolide (207)

A solution of *exo*-spiroepoxyalcohol (**205**) (0.5g, 2.3 mmol) and *N,N'*-thiocarbonyldiimidazole (1.1g, 6.2 mmol) in benzene (30 ml) was reacted using the general procedure for imidazolide synthesis. The crude oil was recrystallised from diethyl ether and light petroleum (b.p. 40–60°C) to give cream crystals of ***endo*-2-[imidazole-1-yl-(thiocarbonyl)oxy]-*anti*-3'-phenylbicyclo[2.2.1]heptan-*exo*-3-spiro-2'-oxirane** (0.6g, 7.8%), m.p. 150–152°C; ν_{max} (Nujol) 3168 (–CS–N‹) (w), 1150 (–O–CS–N‹), 1040 (›C=S) and 1012 (epoxide) cm^{-1}; δH (60 MHz) 8.5 (1H, brs, H–16), 7.7 (1H, brs, H–17), 7.4 (5H, s, Ph), 7.2 (1H, brs, H–18), 5.7 (1H, d, J = 4 Hz, H–2), 4.2 (1H, s, H–8), 3.1 (1H, brs, H–1), and 2.1 (1H, brs, H–4); Elemental Analysis - Found: C, 66.14; H, 5.67;

N, 8.54. $C_{18}H_{18}N_2O_2S$ requires C, 66.03; H, 5.85; N, 8.56%; MS – Found: M^++1 327 (30%) $C_{18}H_{18}N_2O_2S$ require 326.

49. Synthesis of enone (208)

To a solution of bicyclo[2.2.1]heptane-2-one (**201**) (4g, 34 mmol) in ethanol (100 ml) was added *p*-chlorobenzaldehyde (6g, 43 mmol) and potassium hydroxide (3g, 50 mmol) at room temperature, according to the general procedure for aldol condensation. The crude oil was purified using column chromatography with TLC silica gel (as adsorbent) and dichloromethane : ethyl acetate (13:1) as eluant. Recrystallisation from aqueous methanol to give yellow crystals of **3-*p*-chlorobenzylidene-bicyclo[2.2.1]-heptan-2-one** (6g, 71%), m.p. 88-90.5°C; ν_{max} (Nujol) 1724, 1638 (C=C-C=O) and 910, 734 (*p*-substituted aromatic) cm^{-1}; δH (90 MHz) 7.22 (4H, brs, ClC_6H_4), 6.92 (1H, s, H-8), 3.50 (1H, brs, H-1), and 2.72 (1H, brs, H-4); Elemental Analysis – Found: C, 72.22; H, 5.61; Cl, 15.26. $C_{14}H_{13}ClO$ requires C, 72.26; H, 5.63; Cl, 15.24%; MS – Found: M^+ 234:232 (33:100%).

50. Synthesis of allylic alcohol (209a)

Cerous chloride (8g, 22 mmol) was added to a solution of enone **(208)** (6g, 26 mmol) in methanol (150 ml). The mixture was stirred for 5 minutes and $NaBH_4$ (1g, 26 mmol) was added according to the general procedure for enone reduction. The crude solid was purified using column chromatography with TLC silica gel (as adsorbent) and dichloromethane : ethyl acetate (13:1) as eluant. Two recrystallisations from aqueous methanol to give colourless crystals of **3-*p*-chloro-benzylidenebicyclo[2.2.1]heptan-*endo*-2-ol** (3.2g, 53%), m.p. 103-106°C; ν_{max} (Nujol) 3280 (s) (OH) cm^{-1}. δH (90 MHz) 7.1 (4H, s, ClC_6H_4-H), 6.2

(1H, brs, H–8), 4.4 (1H, brm, J = 2 and 4 Hz, H–2), 3.1 (1H, brs, H–1), 2.4 (1H, brs, H–4) and 1.9 (1H, s, D_2O exchange, OH); Elemental Analysis – Found: C, 71.44; H, 6.38. $C_{14}H_{15}ClO$ requires C, 71.64; H, 6.44%; MS – Found: M^+ 236:234 (80:26%).

51. Synthesis of allylic acetate (209b)

Acetic anhydride (5 ml) was added to a solution of allylic alcohol (**209a**) (0.3g, 1.4 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. The crude oil was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) as eluant. Recrystallisation from aqueous methanol yielded colourless crystals of ***endo*–2–acetoxy–3–*p*–chlorobenzylidenebicyclo[2.2.1]heptane** (0.27g, 72%), m.p. 68–69°C ν_{max} (Nujol) 1734, 1234 (OAc) cm^{-1}; δH (60 MHz) 7.3 (4H, s, ClC_6H_4–H), 6.3 (1H, brs, H–8), 5.5 (1H, m, H–2), 3.3 (1H, brs, H–1), 2.6 (1H, brs, H–4) and 2.1 (3H, s, OAc); Elemental Analysis – Found: C, 69.19; H, 6.21. $C_{16}H_{17}ClO_2$ requires C, 69.44; H, 6.19%; MS – Found: M^+ 278:276 (6.7:20%).

When the allylic acetate made above was epoxidised with *m*CPBA according to the general procedure, a mixture of epoxyacetates *exo* : *endo* (5:1; calculated by ^1H NMR analysis) was obtained.

52. Synthesis of epoxyalcohols (210), (211)

m–Chloroperbenzoic acid (2.4g, 14 mmol) was added to a solution of allylic alcohol (**209a**) (2.2g, 9 mmol) in dichloromethane (50 ml) at room temperature. The mixture was reacted using the general procedure for epoxidation, except that the reaction was stirred for 2 hours instead of

overnight. The crude residue was separated using preparative TLC on silica gel (as adsorbent) and ethyl acetate : light petroleum (b.p. 40–60°C) (1:4) as eluant. The plate was eluted twice, and the fast running product isolated, and recrystallisation from aqueous methanol to give colourless crystals of ***anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-*endo*-2-ol-*endo*-3-spiro-2'-oxirane (210)** (0.53g, 23%), m.p. 85–88°C; ν_{max} (Nujol) 3376 (OH) cm^{-1}; δH (60 MHz) 7.1–7.4 (4H, ABq, J = 10 Hz, ClC_6H_4–H), 4.1 (1H, d, J = 4 Hz, H–2), 3.98 (1H, s, H–8), 2.5 (2H, brs, H–1, 1H D_2O exchange OH), 1.9 (1H, brs, H–4); Elemental Analysis – Found: C, 67.01; H, 6.09. $C_{14}H_{15}ClO_2$ requires C, 67.07; H, 6.03%; MS – Found: M^+ 252:250 (1:3%).

The slower running product was recrystallised from aqueous methanol affording colourless crystals of ***anti*-3'-*p*-chlorophenylbicyclo[2.2.1]-heptan-*endo*-2-ol-*exo*-3-spiro-2'-oxirane (211)** (0.7g, 30%),, m.p. 140–144°C; ν_{max} (Nujol) 3404 (OH) cm^{-1}; δH (60 MHz) 7.33 (4H, s, ClC_6H_4–H), 4.23 (1H, s, H–8), 4.0 (1H, d, J = 4Hz, H–2), 3.4 (1H, m, D_2O exchange, OH), 2.45 (1H, brs, H–1) and 1.9 (1H, brs, H–4); Elemental Analysis – Found: C, 66.93; H, 6.03. $C_{14}H_{15}ClO_2$ requires C, 67.07; H, 6.03%; MS – Found: M^+ 252:250 (1:3).

53. Synthesis of *endo*-epoxyimidazolide (212)

A solution of epoxyalcohol (210) (0.2g, 0.8 mmol) and *N*,*N*'-thiocarbonyl-diimidazole (0.3g, 1.6 mmol) in benzene (20 ml) was reacted using the general procedure for the synthesis of imidazolide. The crude oil was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) (1:4) as eluant. The colourless oil obtained, which was difficult to recrystallise from a variety of solvents, was ***endo*-2-[imidazol-1-yl(thiocarbonyl)oxy]-*anti*-3'-**

p-chlorophenylbicyclo[2.2.1]heptan-*endo*-3-spiro-2'- oxirane (0.2g, 69%). ν_{max} ($CDCl_3$) 3176 (-CS-N<), 1450, 1380, 1320, and 1280 cm^{-1}; δH (60 MHz) 8.5 (1H, brs, H-16), 7.7 (1H, brs, H-17), 7.2-7.5 (4H, ABq, J = 10Hz, ClC_6H_4-H), 7.32 (1H, brs, H-18), 5.9-6 (1H, d, J = 4.5 Hz, H-2) 4.35 (1H, s, H-8), and 2.9 (1H, brs, H-1), 1.9 (1H, brs, H-4); MS - Found: M^+ 362:360 (1:3).

54. Synthesis of *exo*-epoxyimidazolide (213)

A solution of epoxyalcohol (211) (0.4g, 1.6 mmol) and *N,N'*- thiocarbonyldiimidazole (0.6g, 3.4 mmol) in benzene (30 ml) was reacted according to the general procedure for imidazolide synthesis. The crude oil was recrystallised from light petroleum (b.p. 40-60°C) to give colourless crystals of *endo*-2-[imidazol-1-yl(thiocarbonyl)oxy]-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-*exo*-3-spiro-2'-oxirane (0.4g, 69%), m.p. 143-145°C; ν_{max} (Nujol) 3176 (-CS-N<) (w), 1148 (-O-CS-N<), 1045 (>C=S) cm^{-1}; δH (60 MHz) 8.4 (1H, brs, H-16), 7.7 (1H, brs, H-17), 7.3 (4H, s, ClC_6H_4-H), 7.1 (1H, brs, H-18), 5.6 (1H, d, J = 4 Hz, H-2), 4.1 (1H, s, H-8), 3.0 (1H, brs, H-1), and 2.0 (1H, brs, H-4); Elemental Analysis - Found: C, 59.64; H, 4.72; N, 7.68. $C_{18}H_{17}ClN_2O_2S$ requires C, 59.75; H, 4.73; N, 7.74%; MS - Found: M^+ 362:360 (1:3).

55. Synthesis of enone (214)

To a solution of norcamphor (8.5g, 77 mmol) in ethanol (150 ml) was added *p*-methoxylbenzaldehyde (13.7g, 102 mmol) and potassium hydroxide (5.7g, 102 mmol) at room temperature, using the general procedure for aldol condensation. The crude oil was separated from the starting material by distilling at 0.1 mm Hg/50°C. The remaining residue was purified using column chromatography with TLC silica gel (as adsorbent) and

diethyl ether : light petroleum (b.p. 40–60°C) 1:2 as eluant. The coloured oil obtained was **3–*p*–methoxybenzylidenebicyclo[2.2.1]heptan–2–one** (15.3g, 87%). ν_{max} (Neat) 1720, 1636 (C=C–C=O) and 1602 (Ar–H) cm^{-1}; δH (60 MHz) 6.9–7.5 (4H, ABq, J = 8 Hz, $MeOC_6H_4$–H), 7.15 (1H, s, H–8), 3.74 (3H, s, OMe), 3.6 (1H, brs, H–1) and 2.8 (1H, brs, H–4); MS – Found: M^+ 228.1150 (100%), $C_{15}H_{18}O_2$ requires 228.1154.

56a. Synthesis of allylc alcohol (215a)

Cerous chloride (1g, 2.7 mmol) was added to a solution of enone (**214**) (0.7g, 3 mmol) in methanol (30 ml). The mixture was stirred for 5 minutes and $NaBH_4$ (0.1g, 2.6 mmol) was added using the general procedure for enone reduction. The crude residue was recrystallised from light petroleum to yield cream crystals of **3–*p*– methoxybenzylidene–bicyclo[2.2.1]heptane–*endo*–2–ol** (0.3g, 43%), m.p. 85–87°C; ν_{max} (Nujol) 3292 (OH), 1608 (C=C–H) and 1572 ($MeOC_6H_4$–H) cm^{-1}; δH (60 MHz) 6.8–7.4 (4H, ABq, J = 10 Hz, $MeOC_6H_4$–H), 6.38 (1H, brs, H–8), 4.5 (1H, brm, J = 2 and 4 Hz, H–2), 3.8 (3H, s, OMe), 3.3 (1H, brs, H–1), 2.5 (1H, brs, H–4) and 1.8 (1H, s, D_2O exchange, OH); Elemental Analysis – Found: C, 77.7; H, 8.13. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.88%; MS – Found: M^+ 230.1307 (46%), $C_{15}H_{18}O_2$ requires 230.1303.

56b. Synthesis of allylic acetate (215b)

Acetic anhydride (10 ml) was added to a solution of allylic alcohol (**215a**) (0.6g, 2.6 mmol) in pyridine (15 ml). The mixture was reacted using the general procedure for acetylation. The crude oil was purified using column chromatography with TLC silica gel (as adsorbent) CH_2Cl_2 as eluant. Recrystallisation from aqueous methanol gave cream crystals of ***endo*–2–acetoxy–3–*p*–methoxybenzylidenebicyclo[2.2.1]heptane** (0.4g,

56%), m.p. 45–47°C; ν_{max} (Nujol) 1730 and 1238 (OAc) cm^{-1}; δH (90 MHz) 6.6–7.1 (4H, ABq, J = 9 Hz, $MeOC_6H_4$–H), 6.1 (1H, brs, H–8), 5.4 (1H, m, H–2), 3.7 (3H, s, OMe), 3.15 (1H, brs, H–1), 2.55 (1H, brs, H–4), and 2.05 (3H, s, OAc); Elemental Analysis – Found: C, 75.11; H, 7.48. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40%; MS – Found: M^+ 272.14123 (84.2%), $C_{17}H_{20}O_3$ requires 272.1410.

57. Attempted synthesis of epoxyalcohol (216)

m–Chloroperbenzoic acid (4g, 23 mmol) was added to a solution of allylic alcohol (**215a**) (3g, 13 mmol) in CH_2Cl_2 at 0°C and reacted using the general procedure for epoxidation, except that the reaction was stirred for 2 hours instead of overnight. ^{1}HNMR and TLC analysis of the crude mixture showed the presence of starting alcohol, as well as some other product, and some evidence of the desired epoxyalcohol (**216**) but not isolated. The crude product was separated using column chromatography with TLC alumina (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°) 1:1 as eluant. The less polar product obtained was recrystallised from aqueous methanol to give colourless crystals of **3–*p*–methoxyphenyl–bicyclo[3.2.1]oct–3–en–2–one** (**219**) (0.1g, 4%), m.p. 53–55°C; ν_{max} (Nujol) 1670, 1600 (C=C–C=O) and 1510 ($MeOC_6H_4$–H) cm^{-1}; δH (60 MHz) 6.8–7.4 (4H, ABq, J = 8 Hz, $MeOC_6H_4$–H), 7.3 (1H, m, H–4), 3.8 (3H, s, OMe) and 2.83–3.1 (2H, m, H–5,1); Elemental Analysis – Found: C, 78.76; H, 6.94. $C_{15}H_{16}O_2$ requires C, 78.91; H, 7.06%; MS – Found: M^+ 228.1150 (100%), $C_{15}H_{16}O_2$ requires 228.1153.

Three days later the column was eluted with methanol to obtained a solid which was recrystallised from diethyl ether to give colourless crystals of *exo*–**3–[hydroxy(*p*–methoxybenzyl)]bicyclo[2.2.1]heptan–*endo*–2,3–diol** (**221**) (0.2g, 6.4%), m.p. 149–151°C ν_{max} (Nujol) 3428

(OH) cm^{-1}; δH (60 MHz) 6.8–7.5 (4H, ABq, J = 8 Hz, $MeOC_6H_4$–H), 4.95 (1H, brs, H–8), 4.3 (1H, brs, D_2O exchange, OH), 3.92 (1H, d, J = 4.5 Hz, H–2), 3.8 (3H, s, OMe), 3.38 (1H, s, D_2O exchange, OH), 3.0 (1H, brs, D_2O exchange, OH), 2.4 (1H, brs, H–1) and 1.95 (1H, brs, H–4); Elemental Analysis – Found: C, 67.93; H, 7.28. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%; MS – Found: M^+ 264.1362 (0%), $C_{15}H_{20}O_4$ requires 264.1362.

58. Synthesis of diacetate (222)

Acetic anhydride (3 ml) was added to a solution of norbornanetriol (**221**) (0.1g, 0.4 mmol) in pyridine (5 ml). The mixture was reacted using the general procedure for acetylation. The crude product was purified using preparative TLC on silica gel (as adsorbent) and ethyl acetate : light petroleum (b.p. 40–60°C) 1:1 as eluant. Recrystallisation of the oily product from a mixture of diethyl ether and light petroleum (b.p. 40–60°C) to give colourless crystals of ***exo*-3-[acetoxy(*p*-methoxybenzyl)]-*endo*-2-acetoxybicyclo[2.2.1]heptan-*endo*-3-ol** (0.02g, 16%) m.p. 152–155°C; ν_{max} (Nujol) 3520 (OH), and 1740, 1240 (OAc) cm^{-1}; δH (60 MHz) 6.8–7.65 (4H, ABq, J = 9 Hz, $MeOC_6H_4$–H), 5.92 (1H, brs, H–8), 4.9 (1H, d, J = 4Hz, H–2), 3.82 (3H, s, OMe), 2.8 (1H, brs, D_2O exchange, OH), 2.07 (3H, s, OAc), 2.0 (3H, s, OAc) and 2.1–1.9 (2H, brs, H–1,4); Elemental Analysis – Found: C, 65.61; H, 6.97. $C_{19}H_{24}O_6$ requires C, 65.50; H, 6.94%; MS – Found: M^+ 348.1573 (1.6%), $C_{19}H_{24}O_6$ requires 348.1574.

59. Attempted synthesis of 3-*p*-nitrobenzylidenebicyclo[2.2.1]-heptan-2-one

To a solution of norcamphor (0.9g, 8 mmol) in ethanol (30 ml) was added *p*-nitrobenzaldehyde (1.5g, 10 mmol) and potassium hydroxide

(0.6g, 10 mmol) at room temperature. The resultant mixture was reacted according to general procedure for aldol condensation, except that CH_2Cl_2 was used for extraction instead of diethyl ether. The crude product obtained was purified using column chromatography with TLC silica gel (as adsorbent) and ethyl acetate : dichloromethane (1:13) as eluant. The brown solid obtained was recrystallised with methanol to give brown crystals (0.3g, 15%). ν_{max} (Nujol) 1724 and 1636 (C=C-C=O) cm^{-1}; δH (60 MHz) [8.2-8.4 (2H, q, ArH-11,13) 7.5-7.63 (2H, brd, ArH-10,14)], 7.2 (1H, brs, H-8), 3.7 (1H, brs, H-4), and 2.8 (1H, brs, H-1).

60. Synthesis of 2'-methylenebicyclo[2.2.1]heptane (223)

Methyltriphenylphosphonium bromide (40.4g, 113 mmol) was treated with butyllithium (7.2g, 113 mmol) in diethyl ether (500 ml) (dry) under nitrogen. It was left to stir at room temperature for 3 hours; a pale yellow mixture was formed. To this mixture was added a solution of norcamphor (8.3g, 75 mmol) in diethyl ether. The pale yellow colour was changed and the mixture was refluxed overnight. A blood red solution was obtained. In the morning the mixture was cooled and the ether was removed under distillation at atmospheric pressure. The remaining residue was distilled at water pump/40°C. The colourless oil obtained was norcamphene (5.8g, 72%). ν_{max} (Neat) 1664 (C=C-H) cm^{-1}; δH (60 MHz) 4.9 (bs, 1H), 4.6 (bs, 1H), 2.7 (bs, 1H), 2.3 (bs, 1H), rest 0.9-2.1.

61. Synthesis of 2'-methylenebicyclo[2.2.1]heptan]-3-ol (224)

To a hot solution of norcamphene (223) (3g, 28 mmol) in dioxan (20 ml) was added a hot solution of selenium dioxide (SeO_2) (1.6g, 14 mmol) in dioxan (50 ml) and water (3.3 ml). The mixture was heated at 60°C for

29 hours. It was diluted with water and extracted into ether (2 x 50 ml). The ether was washed with water (50 ml) and brine, dried and the solvent was removed *in vacuo*. The crude product obtained was allylic alcohol (2.2g, 65%). ν_{max} (Neat film) 3440 (OH), 1640 (C=C); δH (60 MHz) 5.1 (bs, 2H), 4.0 (m, 1H), 2.7 (bs, 1H), 2.3 (bs, 1H), rest 0.9–2; + minor oxidised ketone product (**225**). The crude was oxidised to a ketone.

62. Synthesis of 3'–methylenebicyclo[2.2.1]heptan–2–one (225)

Pyridinium dichromate (9.3g, 27 mmol) was added to a solution of alcohol (**224**) (2.2g, 18 mmol) in CH_2Cl_2 (100 ml). The mixture was reacted using the general procedure for oxidation. The crude product was purified using column chromatography with TLC silica gel (as adsorbent) and CH_2Cl_2 as eluant. The yellow coloured oil obtained was 3–ketonorcamphene (1g, 46%). ν_{max} (Neat) 1740 and 1640 (C=C–C=O) cm^{-1}; δH (60 MHz) 5.7 (1H, brs, H–8), 5.2 (1H, brs, H–8), 3.2 (1H, brs, H–1), and 2.7 (1H, brs, H–4).

63. Synthesis of 3'–methylenebicyclo[2.2.1]heptan–*endo*–2–ol (224)

Cerous chloride (3g, 8 mmol) was added to a solution of enone (**225**) (1.5g, 12.3 mmol) in methanol (70 ml). The mixture was stirred for 5 minutes and $NaBH_4$ (0.5g, 13 mmol) was added using the general procedure for enone reduction. The crude oil was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:4 as eluant. The colourless oil obtained was allylic alcohol (0.72g, 47%). ν_{max} (Neat) 3368 (OH) and 1664 (C=C–H) cm^{-1}; δH (60 MHz) 4.9 (2H, brs, H–8), 4.3 (1H, m, H–2), 2.7 (1H, brs, H–4) and 2.4 (1H, brs, H–1).

The same results were obtained when the enone (**225**) was reduced with DIBAL.

64. Synthesis of epoxyalcohol (226)

m-Chloroperbenzoic acid (2.6g, 15 mmol) was added to a solution of allylic alcohol (**224**) (1.6g, 13 mmol) in CH_2Cl_2 (50 ml) and the mixture was reacted using the general procedure for epoxidation, except that the reaction was stirred for 1 hour instead of overnight. The crude product was purified using column chromatography with TLC silica gel (as adsorbent) and dichloromethane as eluant. A colourless oil was obtained, which could not be separated by chromatography. ^{1}HNMR analysis showed a 4:1 mixture of *endo*-*exo*-epoxides (0.8g, 45%). ν_{max} (Neat) 3436 (OH) cm^{-1}; δH (90 MHz) 3.9 (1H, d, J = 4 Hz, H-2), 2.9-3.2 ($^3/_2$H + ½H = 2H, ABq, J = 4.5 Hz, H-8), 2.5 (1H, brs, H-1) and 2.05 (1H, brs, H-4); MS - Found: M^+ 140.0824 (2.7%), $C_8H_{12}O_2$ requires 140.082.

65. Synthesis of epoxyimidazolides (227)

A solution of epoxyalcohol (**226**) (0.6g, 4.3 mmol) and *N*,*N*'-thiocarbonyldiimidazole (1g, 5.6 mmol) in benzene (40 ml) was heated to reflux under oxygen-free nitrogen until the reaction was completed, (TLC) 2 hours. The mixture was cooled, and crude product was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether as eluant. Three products were isolated; the less polar product was recrystallised from diethyl ether to give colourless crystals of ***exo*-3-chlorobicyclo[2.2.1]heptan-; cyclic thiocarbonate ether** (**230**) (0.04g, 4.3%), m.p. 110-112.5°C; ν_{max}(CCl_4) 1540, 1462, 1380, and 1366 cm^{-1}; δH (250 MHz) 4.9 (1H, d, J = 4.8 Hz, H-2), 3.53-3.99 (2H, ABq, J = 12.6 Hz, H-8), 2.8 (1H, brs, H-4) and 2.52 (1H, brs, H-1); δC (250 MHz) 191.64 (q, C-9), 95.18 (q, C-3), 86.40 (CH, C-2), 44.03 (CH,

C-4), 40.63 (CH, C-1), 35.66 (CH_2, C-7), 22.56 (CH_2, C-5) and 20.02 (CH_2, C-6); Elemental Analysis - Found: C, 49.34; H, 5.01; S, 14.40. $C_9H_{12}ClO_2S$ requires C, 49.42; H, 5.08; S, 14.63%; MS - Found: M^+ 220.014:218.017 (16.9:48.8%), $C_9H_{12}ClO_2S$ requires 220.013:218.013.

The more polar product, which remained unidentified, was a minor product. ν_{max}(Neat) 1736 (C=O), 1450, 1380, 1360, 1280, and 1220 cm^{-1};

The most polar product isolated as colourless oil was *endo*-**2-[imidazol-1-yl(thiocarbonyl)oxy]-3'-methylenebicyclo[2.2.1]hept-an-3-spiro-2'-oxirane** (**227**) (0.1g, 10%). ν_{max}(Neat) 3176 (-CS-N<), 1450, 1380, 1320, 1280, and 970 (epoxide) cm^{-1}; δH (60 MHz) 8.3 (1H, brs, H-10), 7.6 (1H, brs, H-11), 7.1 (1H, brs, H-12), 5.6 (1H, d, J = 4 Hz, H-2), 3.1 (1H, brs, H-4) and 2.98 (2H, ABq, J = 4.5 Hz, H-8) 2.0 (1H, brs, H-1); Found: C, 57.86; H, 5.71; N, 10.93. $C_{12}H_{14}N_2O_2S$ requires C, 57.58; H, 5.60; N, 11.20%; MS - Found: M^+ 250.0776 (20%), $C_{12}H_{14}N_2O_2S$ requires 250.0773.

66. Reaction between *exo*-epoxy imidazolide (207) and tri-*n*-butyltin hydride (Bu_3SnH)

To a refluxing solution of Bu_3SnH (4.6g, 16 mmol) in toluene (10 ml) under oxygen-free nitrogen was added imidazolide (**207**) (0.5g, 1.5 mmol) and AIBN (50 mg, 0.3 mmol) in toluene (6 ml) over 10-20 minutes. The mixture was reacted according to the general procedure. Further purification using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:4 as eluant gave a less polar product which was further purified using preparative TLC on alumina (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:6 as

eluant; the colourless oil obtained was epoxy-acetal (**232**) (0.04g, 8%). δH (250 MHz) 7.26-7.34 (5H, m, Ar-H), 4.7-4.91 (2H, ABq, J = 6.9 Hz, H-15), 4.13 (1H, d, J = 3 Hz, H-2), 4.14 (1H, s, H-8), 2.62 (1H, brs, H-4) and 1.96 (1H, brs, H-1), rest 0.8-1.8.

The more polar product isolated was recrystallised from aqueous methanol gave colourless crystals of methoxy-epoxide (**233**) (0.2g, 57%) m.p. 47-48.5°C; ν_{max} (Nujol) 1106 (epoxide) cm^{-1}; δH (250 MHz) 7.2-7.36 (5H, m, Ar-H), 4.22 (1H, s, H-8), 3.58 (1H, d, J = 2.8 Hz, H-2), 3.32 (3H, s, OMe), 2.63 (1H, brs, H-4) and 1.94 (1H, brs, H-1); δC (250 MHz) 136.77 (q, C-9), 128.1 (CH, C-10,14), 127.4 (CH, C-12), 126.13 (CH, C-11,13). 86.4 (CH, C-2), 75.4 (q, C-3), 58.89 (CH, C-4), 57.28 (CH, C-1), 38.59 (CH_3, C-15), 33.92 (CH_2, C-7), 24.24 (CH_2, C-5) and 19.1 (CH_2, C-6); Elemental Analysis - Found: C, 73.45; H, 7.14. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37%; MS - Found: M^+ 230.1298 (55%), $C_{15}H_{18}O_2$ requires 230.1298.

The short column was eluted with methanol to yield a solid, which was recrystallised from diethyl ether to give colourless crystals of imidazole (**231**) (0.04g, 38%) m.p. 87-89°C (lit.[126] m.p. 90-91°C) TLC, IR and ^{1}HNMR were identical to the authentic sample.

67. Reaction between *endo*-epoxyimidazolide (206) and Bu_3SnH

To a refluxing solution of Bu_3SnH (2.3g, 8 mmol) in benzene (5 ml) under oxygen-free nitrogen was added imidazolide (**206**) (0.3g, 0.9 mmol) and AIBN (0.2g, 0.01 mmol) in benzene (6 ml) over 10-20 minutes. The mixture was reacted according to the general procedure. ^{1}HNMR analysis of the mixture showed the *endo*-methoxyepoxide (**235**) (50%) and acetal (**234**) (50%). The acetal (**234**) was lost during further purification. (δH [60 MHz) 5.3 [5H, s, Ar-H], 4.95 [2H, s, H-15], 4.35 [1H, d, J = 4 Hz],

4.0 [1H, s, H-8], 2.6 [1H, brs, H-4] and 1.95 [1H, brs, H-1]). The mixture was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°) 1:2 as eluant. The solid product obtained was recrystallised from aqueous methanol to give colourless crystals of *endo*-methoxyepoxide (**235**) (0.06g, 30%) m.p. 44-46.5°C; ν_{max} (Nujol) 1110 (epoxide) cm^{-1}; δH (250 MHz) 7.2-7.37 (5H, m, Ar-H), 3.96 (1H, s, H-8), 3.7 (1H, d, J = 2.8 Hz, H-2), 3.37 (3H, s, OMe) and 2.59 (1H, brs, H-4) 1.75 (1H, brs, H-1); δC (250 MHz) 136.47 (q, C-9), 128.1 (CH, C-11,13), 127.48 (CH, C-12), 126.1 (CH, C-10,14), 80.59 (CH, C-2), 71.1 (q, C-3), 64.47 (CH, C-8), 57.56 (CH_3, C-15), 39.34 (CH, C-4), 36.63 (CH, C-1), 32.72 (CH_2, C-7), 23.86 (CH_2, C-5) and 19.5 (CH_2, C-6); Elemental Analysis - Found: C, 78.04; H, 7.93. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%; MS - Found: M^+ 230.1307 (50%), $C_{15}H_{18}O_2$ requires 230.1310.

The short column was eluted with methanol to give colourless crystals, which were previously identified as imidazole (**231**) (60%).

68. Reaction between *exo*-epoxyimidazolide (213) and Bu_3SnH

To a refluxing solution of Bu_3SnH (2.6g, 9 mmol) in toluene (6 ml) under oxygen-free nitrogen was added imidazolide (**213**) (0.35g, 1 mmol) and AIBN (0.02g, 0.1 mmol) in toluene (6 ml) over 10-20 minutes. The mixture was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:4 as eluant. The faster running product, isolated as a colourless oil, was thioacetal (**236**) (0.1g, 33%). δH (60 MHz) 7.3 (4H, s, ClC_6H_4-H), 4.6-5 (2H, ABq, J = 10 Hz, H-15), 4.25 (1H, d, J = 4 Hz, H-2), 4.14 (1H, s, H- 8), 2.65 (1H, brs, H-4) and 1.97 (1H, brs, H-1).

The slower running product obtained was recrystallised from aqueous methanol to give colourless crystals of methoxyepoxide (**237**) (0.1g, 48%) m.p. 63–65°C; ν_{max} (Nujol) 1106 (epoxide) cm^{-1}; δH (250 MHz) 7.28 (4H, m, ClC_6H_4–H), 4.18 (1H, s, H–8), 3.56 (1H, d, J = 2.9 Hz, H–2), 3.31 (3H, s, OMe), 2.63 (1H, brs, H–4) and 1.90 (1H, brs, H–1); δC (250 MHz) 135.34 (q, C–12), 133.1 (q, C–9), 128.25 (CH, C–11,13), 127.43 (CH, C–10,14), 86.16 (CH, C–2), 75.49 (q, C–3), 58.24 (CH, C–8), 57.18 (CH_3, C–15), 38.61 (CH, C–4), 38.5 (CH, C–1), 33.83 (CH_2, C–7), 24.18 (CH_2, C–5) and 18.97 (CH_2, C–6); Elemental Analysis – Found: C, 67.99; H, 6.61. $C_{15}H_{17}ClO_2$ requires C, 68.05; H, 6.47%; MS – Found: M^+ 266/264.

The slowest running product obtained was recrystallised from aqueous methanol to give colourless crystals of *exo*–epoxyalcohol (**211**) (6%) m.p. 130–135°C; IR, TLC and ^1H NMR were identical to the *exo*–epoxyalcohol (**211**). This was previously not isolated. The short column was eluted with methanol and imidazole (**231**) was obtained.

69. Reaction between *endo*–epoxyimidazolide (212) and Bu_3SnH

Exactly as *exo*–isomer. The faster running product obtained was further purified using preparative TLC on alumina (as adsorbent) and diethyl ether : light petroleum (40–60°C) 1:4 as eluant to give a colourless oil which was previously identified as acetal (**238**) (20%). δH (250 MHz) 7.1–7.33 (4H, ABq, J = 5.9 Hz, ClC_6H_4–H), 4.8–5.0 (2H, ABq, J = 8 Hz, C–15), 4.17 (1H, d, J = 2.8 Hz, H–2), 3.99 (1H, s, H–8), 2.54 (1H, brs, H–4) and 1.7 (1H, brs, H–1).

The slower running product obtained was recrystallised from aqueous methanol gave colourless crystals of methoxy–epoxide (**239**) (0.1g, 35%) m.p. 47–50°C; δH (250 MHz) 7.2–7.33 (4H, ABq, J = 5.8 Hz, ClC_6H_4–H), 3.93 (1H, s, H–8), 3.68 (1H, d, J = 2.8 Hz, H–2), 3.36 (3H, s, OMe), 2.59

(1H, brs, H-4) and 1.69 (1H, brs, H-1); δC (250 MHz) 135.02 (q, C-12), 133.31 (q, C-9), 128.34 (CH, C-11,13), 127.42 (CH, C-10,14), 80.47 (CH, C-2), 71.25 (q, C-3), 63.86 (CH, C-8), 57.57 (CH_3, C-15), 39.30 (CH, C-4), 36.57 (CH, C-1), 32.67 (CH_2, C-7), 23.86 (CH_2, C-5) and 19.44 (CH_2, C-6); Elemental Analysis - Found: C, 68.10; H, 6.35. $C_{15}H_{17}ClO_2$ requires C, 68.05; H, 6.47%; MS - Found: M^+ 266/264.

70. Reaction between epoxyimidazolide (227) and Bu_3SnH

To a refluxing solution of Bu_3SnH (0.7g, 2.4 mmol) in toluene (6 ml) under oxygen-free nitrogen was added imidazolide (**227**) (0.24g, 1 mmol) and AIBN (0.02g, 0.1 mmol) in toluene for 2 hours, cooled and the solvent was removed *in vacuo*. The crude residue was partition between acetonitrile and light petroleum (b.p. 40-60°C). The acetonitrile layer was separated and evaporated *in vacuo* to give a colourless oil of hemithioacetal (**240**) (0.1g, 25%). δH (250 MHz) 4.6-4.82 (2H, ABq. J = 9.9 Hz, H- 9), 4.15 (1H, d, J = 2.8 Hz, H-2), 2.6-2.91 (2H, ABq, J = 5 Hz, H-8), 2.52 (1H, brs, H-4) and 1.79 (1H, brs, H-1).

71. Reaction between *exo*-epoxyimidazolide (213) and methoxide (Bu_3SnOMe)

To a refluxing solution of Bu_3SnOMe (0.3g, 0.9 mmol) and Bu_3SnH (0.03g, 0.1 mmol) in toluene (6 ml) under oxygen-free nitrogen was added imidazolide (**213**) (0.3g, 0.8 mmol) and AIBN (0.02g, 0.1 mmol) in toluene (6 ml) over 10-20 minutes. The mixture was refluxed for 1.5 hours, cooled and the solvent was evaporated *in vacuo*. The crude residue was purified using preparative TLC on alumina (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:10 as eluant. Recrystallisation of the oily product from aqueous methanol gave colourless crystals of *exo*-epoxythiocarbonate (**242**) (0.1g, 26%) m.p.

94–96°C; δH (60 MHz) 7.3 (4H, s, ClC_6H_4–H), 5.3 (1H, d, J = 4 Hz, H–2), 4.13 (1H, s, H–8), 4.08 (3H, s, OMe), 2.95 (1H, brs, H–4) and 1.97 (1H, brs, H–1); Elemental Analysis – Found: C, 59.44, H, 5.41. $C_{16}H_{17}ClO_3S$ requires C, 59.16; H, 5.28%; MS – Found: M^+ 326/324.

72. Reaction between *exo*–epoxythiocarbonate (242) and Bu_3SnH

To a refluxing solution of Bu_3SnH (0.5g, 1.7 mmol) in toluene (4 ml) under oxygen–free nitrogen was added thiocarbonate (**242**) (0.06g, 0.2 mmol) and AIBN (3 mg, 0.02 mmol) in toluene (4 ml) over 10–20 minutes. The mixture was refluxed for 1 hour, cooled and the solvent was removed *in vacuo*. The crude product was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petrol (40–60°C) 1:4 as eluant. Recrystallisation of the oily product from aqueous methanol gave colourless crystals of methoxy–epoxide (**237**) (6mg, 14%) m.p. 61–63°C). IR, TLC and ^1H NMR are identical to the authentic methoxy–epoxide (**237**).

73. Reaction between *endo*–epoxyimidazolide (212) and tri–*n*–butyltin deutrite (Bu_3SnD)

To a refluxing solution of Bu_3SnD (1.7g, 6 mmol) in toluene (6 ml) under oxygen–free nitrogen was added imidazolide (**212**) (0.2g, 0.6 mmol) and AIBN (0.01g, 0.06 mmol) in toluene (4 ml) over 10–20 minutes. The mixture was reacted according to the general procedure. The crude product mixture was separated using preparative TLC on alumina (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:4 as eluant. The faster running product obtained was deuterated hemithioacetal (**250**) (0.02g, 10%). δH (250 MHz) 7.2–7.33 (4H, ABq,

J = 5.8 Hz, ClC_6H_4-H), ABq for -O-CH_2-S- at 4.6-4.8 missing (deuterated), 4.31 (1H, d, J = 2.9 Hz, H-2), 3.92 (1H, s, H-8), 2.52 (1H, brs, H-4) and 1.69 (1H, brs, H-1).

The slower running product isolated was recrystallised from aqueous methanol gave colourless crystals of deuterated methoxyepoxide (**251**) (0.03g, 21%) m.p. 49.5-51.5°C; δH (60 MHz) 7.3 (4H, m, ClC_6H_4-H), 3.93 (1H, s, H-8), 3.66 (1H, d, J = 4 Hz, H-2), 3H singlet at 3.36 (OMe) missing (deuterated), and 2.6 (1H, brs, H-4) 1.7 (1H, brs, H-1); MS - Found: M^+ 269/267.

74. Synthesis of *endo*-epoxyacetate (252)

Acetic anhydride (5 ml) was added to a solution of *endo*-epoxyalcohol (**204**) (0.3g, 1.4 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. The colourless oil obtained was recrystallised from aqueous methanol to give colourless crystals of ***endo*-2-acetoxy-*anti*-3'-phenylbicyclo[2.2.1]heptan-*endo*-3-spiro-2'-oxirane** (0.2g, 56%), m.p. 48-49°C; ν_{max} (Nujol) 1736, 1258 (OAc) and 1066 (epoxide) cm^{-1}; δH (60 MHz) 7.3 (5H, s, Ph), 5.2 (1H, d, J = 4 Hz, H-2), 4.2 (1H, s, H-8), 2.6 (1H, brs, H-1), 2.4 (3H, s, OAc) and 1.9 (1H, brs, H-4); Elemental Analysis - Found: C, 74.43; H, 6.89. $C_{16}H_{18}O_3$ requires C, 74.40; H, 7.02%; MS - Found: M^+ 258.1256 (1.0%), $C_{16}H_{18}O_3$ requires 258.1246.

75. Synthesis of *exo*-epoxyacetate (253)

Acetic anhydride (5 ml) was added to a solution of epoxyalcohol (**205**) (0.32g, 1.5 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. The crude solid obtained was recrystallised from aqueous ethanol to give colourless crystals of

***endo*-2-acetoxy-*anti*-3'-phenylbicyclo[2.2.1]heptan-*exo*-3-spiro-2'-oxiran** (0.28g, 73%), m.p. 72-74°C; ν_{max} (Nujol) 1738, 1248 (OAc) and 1068 (epoxide) cm^{-1}; δH (60 MHz) 7.4 (5H, s, Ph), 4.9 (1H, d, J = 4 Hz, H-2), 4.1 (1H, s, H-8), 2.7 (1H, brs, H-1), 2.35 (3H, s, OAc) and 1.97 (1H, brs, H-4); Elemental Analysis - Found: C, 7404; H, 7.07. $C_{16}H_{18}O_3$ requires C, 74.40; H, 7.02%; MS - Found: M^+ 258.1256 (1.0%), $C_{16}H_{18}O_3$ requires 258.1256.

76. Synthesis of *endo*-epoxyacetate (254)

Acetic anhydride (8 ml) was added to a solution of epoxyalcohol (**210**) (0.5g, 1.9 mmol) in pyridine (15 ml). The mixture was reacted using the general procedure for acetylation. The crude oil was recrystallised from aqueous ethanol to give colourless crystals of ***endo*-2-acetoxy-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-*endo*-3-spiro-2'-oxirane** (0.3g, 55%), m.p. 69-72°C; ν_{max} (Nujol) 1728 and 1248 (OAc) cm^{-1}; δH (60 MHz) 7.1-7.4 (4H, ABq, J = 10 Hz, ClC_6H_4-H), 5.1 (1H, d, J = 4 Hz, H-2), 4.2 (1H, s, H-8), 2.5 (1H, brs, H-1) and 2.1 (3H, s, OAc) 1.75 (1H, brs, H-4); Elemental Analysis - Found: C, 65.52; H, 5.95. $C_{16}H_{17}ClO_3$ requires C, 65.64; H, 5.85%; MS - Found: M^+ 294:292 (8.3:25%).

77. Synthesis of *exo*-epoxyacetate (255)

Acetic anhydride (6 ml) was added to a solution of epoxyalcohol (**211**) (0.3g, 1.2 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. The crude oil was recrystallised from aqueous ethanol affording colourless crystals of ***endo*-2-acetoxy-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-*exo*-3-spiro-2'-oxirane** (0.23g, 63%), m.p. 90-94°C; ν_{max} (Nujol) 1728 and 1246 (OAc) cm^{-1}; δH (60 MHz) 7.3 (4H, s, ClC_6H_4-H), 4.9 (1H, d, J = 4 Hz, H-2), 4.09 (1H, s,

H–8), 2.8 (1H, brs, H–1), 2.2 (3H, s, OAc), and 1.9 (1H, brs, H–4); Elemental Analysis – Found: C, 65.62; H, 5.92. $C_{16}H_{17}ClO_3$ requires C, 65.64; H, 5.85%; MS – Found: M^+ 294:292 (8.3:25%).

78. Photochemical fragmentation of *endo*–2–acetoxy–*anti*–3'–phenylbicyclo[2.2.1]heptan–3–spiro–*endo*–2'–oxirane (252)

Endo–epoxyacetate (**252**) (0.2g, 0.8 mmol) was reacted using the general procedure. The crude residue was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:1 as eluant. The faster running product obtained was *endo*–epoxyacetate (**252**) (48%) TLC, IR and ^{1}HNMR were identical to the starting material. The slower running product, obtained as colourless crystals, was *endo*–2–acetoxy–*endo*–4–phenylbicyclo[3.2.1]octan–3–one (**257**) (0.04g, 20%) (recrystallisation from diethyl ether). m.p. 136.5–139°C; ν_{max} (Nujol) 1744 and 1244 (OAc), 1724 (C=O) cm^{-1}; δH (250 MHz) 7.2–7.37 (5H, m, Ar–H), 5.37 (1H, d, J = 2.6 Hz, H–2), 3.82 (1H, brs, H–4), 2.71 (2H, brs, H–1,5) and 2.17 (3H, s, OAc); δC (250 MHz) 202.37 (q, C–3), 170.42 (q, C–15, OAc), 136.54 (q, C–9), 129.5 (CH, C–10,14), 128.4 (CH, C–11,13), 127.2 (CH, C–12), 80.1 (CH, C–2), 60.79 (CH, C–4), 43.25 (CH, C–5), 42.1 (CH, C–1), 38.7 (CH_2, C–8), 25.6 (CH_2, C–6), 24.6 (CH_2, C–7), and 21.0 (CH_3, C–16); Elemental Analysis – Found: C, 73.33; H, 7.07. $C_{16}H_{18}O_3$ requires C, 73.15; H, 7.37%; MS – Found: M^+ 258.1256 (20%), $C_{16}H_{18}O_2$ requires 258.1257.

79. Photochemical fragmentation of *endo*–2–acetoxy–*anti*–3'–phenylbicyclo[2.2.1]heptane–3–spiro–*exo*–2'–oxirane (253)

Exo–epoxy acetate (**253**) (0.2g, 0.8 mmol) was reacted according to the general procedure. The crude residue was purified using preparative

TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:2 as eluant. The faster running product isolated was *exo*–epoxyacetate (**253**) (8%) TLC, IR and ^{1}HNMR were identical to the starting material. The slower running product, isolated as colourless crystals, was *endo*–2–acetoxy–*exo*–4–phenylbicyclo[3.2.1]octan–3–one (**260**) (0.03g, 15%) (recrystallisation from light petroleum [b.p. 40–60°C]). m.p. 95–97°C; ν_{max} (Nujol) 1744 and 1244 (OAc), 1722 (C=O) cm^{-1}; δH (250 MHz) 7.2–7.4 (5H, m, Ar–H), 5.31 (1H, d, J = 2.6 Hz, H–2), 3.77 (1H, brs, H–4), 2.99 (1H, brs, H–5), 2.57 (1H, brs, H–1) and 2.19 (3H, s, OAc); δC (250 MHz) 205.63 (q, C–3), 170.26 (q, C–15), 137.69 (q, C–9), 129.0 (CH, C–10,14), 127.0 (CH, C–11,13), 126.97 (CH, C–12), 79.87 (CH, C–2), 62.3 (CH, C–4), 41.93 (CH, C–5), 40.82 (CH, C–1), 33.24 (CH, C–8), 28.63 (CH_2, C–6), 23.99 (CH_2, C–7) and 20.9 (CH_3, C–16); Elemental Analysis – Found: C, 73.45; H, 7.14 $C_{16}H_{18}O_3$ requires C, 73.15; H, 7.37%; MS – Found: M^+ 258.1256 (18%), $C_{16}H_{18}O_3$ requires 258.1256.

80. Photochemical fragmentation of *endo*–2–acetoxy–*anti*–3'–*p*–chlorophenylbicyclo[2.2.1]heptan–3–spiro–*endo*–2'–oxirane (254)

Endo–epoxyacetate (**254**) (0.2g, 0.7 mmol) was reacted according to the general procedure. ^{1}HNMR analysis of the crude mixture showed *endo*–epoxyacetate (**254**) (40%) and *endo*–2–acetoxy–*endo*–4–*p*–chlorophenyl–bicyclo[3.2.1]octan–3–one (**261**) (20%). The crude product could not be isolated from starting material by chromatography. However, after several attempts using preparative TLC on silica gel (as adsorbent) and ethyl acetate : light petroleum (b.p. 40–60°C) 1:4 as eluant a small amount of slightly purer product was obtained. ν_{max} ($CDCl_3$) 1726 very broad (C=O) and 1246 (OAc) cm^{-1}; δH (60 MHz) 7.3 (4H, brs, ClC_6H_4–H). 5.35 (1H, m, H–2), 3.8 (1H, brs, H–4), 2.75 (2H, m, H–1,5) and 2.15 (3H, s, OAc).

81. Photochemical fragmentation of *endo*-2-acetoxy-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-3-spiro-*exo*-2'-oxirane (255)

Exo-epoxyacetate (**255**) (0.2g, 0.7 mmol) was reacted according to the general procedure. ^{1}HNMR analysis of the crude mixture showed *exo*-epoxyacetate (**255**) (40%) and *endo*-2-acetoxy-*exo*-4-*p*-chlorophenylbicyclo[3.2.1]octan-3-one (**262**) (15%). The crude product could not be separated from starting material by chromatography. ν_{max} ($CDCl_3$) 1730 very broad (C=O) and 1240 (OAc) cm^{-1}; δH (60 MHz) 7.4 (5H, br, ClC_6H_4-H), 5.3 and 4.95 (1H, m, H-2), 4.1 and 3.8 (1H), 2.8 (2H) and 2.15 and 2.23 (3H, 2-acetate).

82. Synthesis of epoxyacetate (263)

Acetic anhydride (5 ml) was added to a solution of epoxyalcohol (**226**) (0.3g, 2 mmol) in pyridine (10 ml). The mixture was reacted using the general procedure for acetylation. The crude product was purified using column chromatography with TLC alumina (as adsorbent) and dichloromethane as eluant. The colourless oil obtained was ***endo*-2-acetoxy-[3.3]spiroepoxybicyclo[2.2.1]heptane** (0.1g, 43%). ν_{max}(Neat) 1738 and 1240 (OAc) cm^{-1}; δH (60 MHz) 4.9 (1H, d, J = 4Hz, H-2), 2.8 (2H, m, H-8) and 2.0 (3H, s, OAc), rest 1.9-2 (8H); MS - Found: M^+ 182.094 (1%), $C_{10}H_{14}O_3$ requires 182.094.

83. Attempted photochemical fragmentation of *endo*-2-acetoxy-3'-methylenebicyclo[2.2.1]heptan-2'-oxirane (263)

Epoxyacetate (**263**) (0.1g, 0.6 mmol) was reacted using the general procedure. ^{1}HNMR analysis of the crude mixture showed the epoxyacetate (**263**) (50%). The TLC and IR spectrum were identical to thoses of the starting material and no other product was observed. Longer reaction

times only reduced the yield of starting material. The reaction was abandoned, and not studied further.

84. Synthesis of the *exo*-allylic bromide (264)

To a solution of allylic alcohol (**203**) (2g, 10 mmol) in dry ether (100 ml) was added phosphorous tribromide (PBr_3) (2.8g, 11 mmol) slowly. The mixture was reacted using the general procedure for bromination of allylic alcohol. The crude oil obtained was *exo*-2-bromo-3-benzylidenebicyclo[2.2.1]heptane (**264**) (2.0g, 76%) which was reacted without further purification. ν_{max} (Neat) 2940 (Ar-H) and 1600 (C=C) cm^{-1}; δH (60 MHz) 7.3 (5H, s, Ar-H), 6.6 (1H, s, H-8), 4.6 (1H, m, J = 1.8 and 3 Hz, H-2), 3.3 (1H, brs, H-4) and 2.6 (1H, brs, H-1).

85. Synthesis of the *exo*-bromoepoxide (265) (266)

m-Chloroperbenzoic acid (2.4g, 14 mmol) was added to a solution of allylic bromide (**264**) (1.8g, 7 mmol) in CH_2Cl_2 (50 ml). The mixture was reacted according to the general procedure for epoxidation, except that the mixture was stirred for 1 hour instead of overnight. The crude oil obtained was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:4 as eluant. The faster running product, isolated as a colourless oil, was ***exo*-2-bromo-*anti*-3'-phenylbicyclo[2.2.1]heptan-3-spiro-*endo*-2'-oxirane** (**265**) (0.6g, 31%). δH (60 MHz) 7.32 (5H, s, Ar-H), 4.4 (1H, s, H-8), 3.95 (1H, d, J = 4 Hz, H-2), 2.7 (1H, brs, H-4) and 2.0 (1H, brs, H-1); Elemental Analysis - Found: C, 60.18; H, 5.41. $C_{14}H_{15}BrO$ requires C, 60.23; H, 5.42%; MS - Found: M^+ 280/278.

The slower running product, isolated as a colourless oil, was ***exo*-2-bromo-*anti*-3'-phenylbicyclo[2.2.1]heptan-3-spiro-*exo*-2'-**

oxirane (266) (0.5g, 19%). δH (60 MHz) 7.4 (5H, s, Ar-H), 4.4 (1H, s, H-8), 4.3 (1H, d, J = 4 Hz, H-2), 2.6 (1H, brs, H-4), and 2.0 (1H, brs, H-1); Elemental Analysis - Found: C, 60.46; H, 5.53. $C_{14}H_{15}BrO$ requires C, 60.23; H, 5.42%; MS - Found: M^+ 280/278.

86. Synthesis of the *exo*-allylic bromide (267)

To a solution of allylic alcohol (**209**) (1g, 5 mmol) in dry diethyl ether (70 ml) was added PBr_3 (2g, 7 mmol). The reaction mixture was reacted using the general procedure for bromination of allylic alcohols. The crude product was recrystallised from a mixture of diethyl ether and ethanol to give colourless crystals of ***exo*-2-bromo-3-*p*-chlorobenzylidenebicyclo[2.2.1]heptane (267)** (0.5g, 40%), m.p. 85-88°C; δH (60 MHz) 7.4 (4H, s, ClC_6H_4-H), 6.7 (1H, brs, H-8), 4.6 (1H, m, J = 1.8 and 3 Hz, H-2), 3.3 (1H, brs, H-4) and 2.6 (1H, brs, H-1); Elemental Analysis - Found: C, 56.48; H, 4.72; Br, 26.62. $C_{14}H_{14}BrCl$ requires C, 56.60; H, 4.79; Br, 26.85%; MS - Found: M^+ 300/298/296 (1:4:3).

87. Independent synthesis of the methoxy epoxide (239)

a. To a solution of sodium hydride (1g, 41 mmol) in dry diethyl ether (10 ml) under oxygen-free nitrogen was added allylic alcohol (**209a**) (0.6g, 2.6 mmol). The mixture was refluxed for 15 minutes. To the resultant white precipitate was added methyl iodide (4g, 28 mmol) in dimethylsulphoxide (10 ml), over 15 minutes. The mixture was refluxed for 30 minutes, until the reaction was completed (TLC). The reaction mixture was cooled and diluted with water (15 ml), and hexane (10 ml) was added. The two layers were separated and the organic layer was washed with water (50 ml) and brine (50 ml), dried and the solvent was removed *in vacuo*. Recrystallisation of the oily product from aqueous methanol gave colourless crystals of ***endo*-2-methoxy-3-*p*-chloro-**

benzylidenebicyclo[2.2.1]heptane (0.4g, 63%) m.p. 80–82°C; δH (60 MHz) 7.3 (4H, s, ClC_6H_4–H), 6.3 (1H, brs, H–8), 4.1 (1H, m, H–2), 3.4 (3H, s, OMe), 3.2 (1H, brs, H–4) and 2.6 (1H, brs, H–1); MS – Found: M^+ 250/248.

b. *m*–Chloroperbenzoic acid (0.6g, 3.5 mmol) was added to a solution of allylic methoxide (0.5g, 2.4 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was reacted according to the general procedure for epoxidation, except that the reaction was completed in 1.5 hours instead of overnight. ^1H NMR analysis of the crude product showed a 2:1 mixture of *endo*– and *exo*–epoxides. The crude oil was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:2 as eluant. The major faster running product obtained was melted at 62–64°C; mix m.p. 62–64.5°C. ^1H NMR, IR, TLC were identical to the *endo*–methoxy epoxide (**239**).

88. Synthesis of 2–trimethylsiloxybicyclo[2.2.1]hept–2–ene

To lithium diisopropamide (LDA), made by reacting together *n*–butyllithium (1.7g, 26 mmol) and diisopropylamine (2.6g, 26 mmol) under oxygen–free nitrogen at –78°C, was added a solution of norcamphor (1.9g, 17 mmol) in THF (40 ml). The mixture was stirred for 1 hour at that temperature and overnight at room temperature. The mixture was diluted with saturated ammonium chloride solution (100 ml) and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water, dried and solvent was removed *in vacuo*. The crude residue was distilled using a Kugelröhr at 80°C/2 mm Hg. The colourless oil obtained was 2–trimethylsiloxybicyclo[2.2.1]hept–2–ene (2.6g, 79%). ν_{max} (Neat) 1610 (C=C–H), 1255 ($SiMe_3$), and 1005, 705

(Si–O) cm^{-1}; δH (60 MHz) 4.55 (1H, d, J = 4 Hz, H–3), 2.64 (1H, brs, H–4), 2.41 (1H, brs, H–1), 0.97–1.63 (6H) and rest 0.2 (9H).

89. Synthesis of *exo*–3–trimethylsiloxybicyclo[2.2.1]heptan–2–one

To a solution of 2–trimethylsiloxynorbornene (1.4g, 8 mmol) in CCl_4 (20 ml) containing *meso*–tetraphenylphorphrin (25 mg) was irradiated (2 x 160w) visible light bulb at 0°C. Dry oxygen was bubbled until the reaction was completed by IR; 7.5 hours. To the crude mixture was added triphenylphosphine (1 equiv.) at 0°C, and the mixture was stirred for 20 minutes at room temperature. The solvent was removed *in vacuo* and cold pentane was added. The mixture was filtered to remove triphenylphosphine oxide and the solvent was removed *in vacuo*. The crude residue was distilled using Kugelröhr at 50–57°C/0.5 mm Hg to give a colourless oil of *exo*–3–trimethylsiloxybicyclo[2.2.1]heptan–2–one (0.4g, 26%). ν_{max} (Neat) 1758 (C=O) cm^{-1}; δH (60 MHz, $CHCl_3$) 3.62 (1H, d, J = 3 Hz, H–3), 2.5 (1H, brs, H–4) and 2.15 (1H, brs, H–1).

90. Attempted synthesis of *exo*–3–hydroxybicyclo[2.2.1]heptan–2–one

A solution of trimethylsiloxynorbonanone (0.4g, 2 mmol) in 10% water–methanol was heated to reflux overnight. The solvent was removed *in vacuo* and diethyl ether was added, dried and filtered through a short florisil column. The solvent was evaporated in vacuo. ^1H NMR analysis of the crude showed a rearranged product. The reaction was abandoned. δH (60 MHz) 4.8 (1H, m, D_2O exchange), 3.43 (1H, m), and rest 0.8–2.2 (12H) and not further studied.

91. Synthesis of the *exo*-bromoepoxides (268) (269)

m-Chloroperbenzoic acid (0.8g, 4.6 mmol) was added to a solution of allylic bromide (**267**) (0.7g, 2.4 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was reacted using the general procedure for epoxidation, except that the mixture was stirred for 1 hour instead of overnight. The crude oil obtained was purified using preparative TLC on silica gel (as adsorbent) and dichloromethane : light petroleum (b.p. 40–60°C) 1:2 as eluant. The faster running product isolated was recrystallised from aqueous ethanol to give colourless crystals of ***exo*-2-bromo-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-3-spiro-*endo*-2'-oxirane (268)** (0.15g, 20%), m.p. 68–70°C; δH (250 MHz) 7.2–7.4 (4H, ABq, J = 5.9 Hz, ClC_6H_4-H), 4.36 (1H, s, H-8), 3.67 (1H, d, J = 1.9 Hz, H-2), 2.65 (1H, brs, H-4) and 2.1 (1H, brs, H-1); δC (250 MHz) 134.73 (q, C-12), 133.72 (q, C-9), 128.56 (CH, C-11,13), 127.40 (CH, C-10,14), 77.75 (q, C-3), 67.60 (CH, C-2), 58.47 (CH, C-8), 47.20 (CH, C-4), 37.81 (CH, C-1), 36.11 (CH_2, C-7), 27.43 (CH_2, C-5) and 23.54 (CH_2, C-6); Elemental Analysis – Found: C, 53.70; H, 4.48. $C_{14}H_{14}BrClO$ requires C, 53.62; H, 4.50%; MS – Found: M^+ 316/314/312.

The slower running product was isolated and recrystallised from aqueous ethanol to give colourless crystals of ***exo*-2-bromo-*anti*-3'-*p*-chlorophenylbicyclo[2.2.1]heptan-3-spiro-*exo*-2'-oxirane (269)** (0.08g, 11%), m.p. 86–90°C; δH (250 MHz) 7.2–7.34 (4H, m, ClC_6H_4-H), 4.3 (1H, s, H-8), 4.2 (1H, d, J = 2 Hz, H-2), 2.64 (1H, brs, H-4) and 1.97 (1H, brs, H-1); δC (250 MHz) 134.62 (q, C-12), 133.53 (q, C-9), 128.46 (CH, C-11,13), 127.25 (CH, C-10,14), 76.35 (q, C-3), 63.61 (CH, C-2), 58.6 (CH, C-8), 43.92 (CH, C-8), 38.73 (CH, C-1), 35.68 (CH_2, C-7), 23.5 (CH_2, C-5) and 23.68 (CH_2, C-6); Elemental Analysis – Found: C, 53.78; H, 4.51. $C_{14}H_{14}BrClO$ requires C, 53.62; H, 4.50%; MS – Found: M^+ 316/314/312.

92. Attempted synthesis of the allylic bromide (270)

To a solution of norcamphenol (**224**) (0.4g, 3 mmol) in dry diethyl ether (30 ml) was added PBr_3 (1.5g, 6 mmol). The mixture was reacted using the general procedure for bromination. The crude oil obtained was analysed using ^1H NMR, which showed a spectrum that could not be related to the *exo*-2-bromo-3-methylenebicyclo[2.2.1]heptane (**270**). The reaction was also tried at -78°C for 1 hour and the same results were obtained. The reaction was abandoned.

93. Synthesis of the allylic chloride (272)

To a solution of norcamphenol (**224**) (1g, 8 mmol) in dry diethyl ether (10 ml) at -78°C was added thionyl chloride (0.05 ml). The mixture was stirred for 20 minutes and ether was removed *in vacuo*. Light petroleum (b.p. 40-60°C) was added to the crude residue and eluted through a short column packed with calcium carbonate. The petroleum was removed *in vacuo* and the crude oil obtained was purified using column chromatography using TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:2 as eluant. The colourless oil obtained was a mixture of *endo*-2-chloro-3-methylenebicyclo[2.2.1]-heptane (**272**) (0.6g, 52%) which was reacted without further purification. ν_{max} (Neat) 1668 (C=C-H) cm^{-1}; δH (250 MHz) 5.0-5.3 (2H, m, H-8), 4.96 (1H, m, J = 2 and 5 Hz, H-2), 2.75 (1H, brs, H-4), and 2.57 (1H, brs, H-1);. δC (250 MHz) 157.57 (q, C-3), 106.96 (CH_2, C-8), 76.79 (CH, C-2), 44.64 (CH, C-4), 41.99 (CH, C-1), 35.94 (CH_2, C-7), 30.42 (CH_2, C-5) and 20.20 (CH_2, C-6); MS - Found: M^+ 144/142.

94. Synthesis of the chloroepoxide (273)

m-Chloroperbenzoic acid (2.4g, 14 mmol) was added to a solution of allylic chloride (**272**) (0.9g, 6.3 mmol) in CH_2Cl_2 (50 ml). The reaction mixture was reacted using the general procedure for epoxidation, except that the mixture was stirred for 1 hour instead of overnight. The crude oil was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:2 as eluant. The colourless oil obtained was a 50:50 mixture (*endo*:*exo* oxirane) of ***endo*-2-chlorobicyclo-[2.2.1]heptan-3-spiro-2'-oxirane (273)** (0.5g, 50%). δH (250 MHz) 4.64 (1H, d, J = 4.5 Hz, H-2), 2.7-2.92 (2H, ABq, J = 3 Hz, H-8), 2.59 (1H, brs, H-4) and 1.92 (1H, brs, H-1); δC (250 MHz) 78.6 (CH, C-2), 68.34 (q, C-3), 48.57 (CH_2, C-8), 42.36 (CH, C-4), 41.6 (CH, C-1), 34.99 (CH_2, C-7), 25.4 (CH_2, C-5) and 20.1 (CH_2, C-6); MS - Found: M^+ 160/158.

95. Synthesis of allylic esters (274)

To a solution of trimethylphosphoroacetate (3g, 17 mmol) in THF (30 ml) at -78°C under oxygen-free nitrogen was added *n*-butyllithium (0.9g, 14 mmol) and the mixture was brought to room temperature. The reaction mixture was then cooled to -78°C and a solution of norcamphor (1.1g, 10 mmol) in THF (15 ml) was added. The reaction mixture was stirred at that temperature for 1 hour and left overnight at room temperature. It was diluted with water and extracted with diethyl ether (2 x 50 ml), washed with water (2 x 50 ml) and brine, and dried. The solvent was removed *in vacuo*. The crude oil was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:6 as eluant. The colourless oil was obtained as a 2:1 (*cis*:*trans*) mixture of **bicyclo[2.2.1]heptan-2-methylethenoate**

(274) (0.5g, 30%). ν_{max} (Neat) 1725 and 1665 (C=C–C=O, esters) cm^{-1}; δH (60 MHz) 5.75 (1H, brs, H–8), 3.65 (3H, s, OMe) and 2.5 (2H, brs, H–1,4).

96. Synthesis of the allylic bromide (275)

To a solution of allylic ester **(274)** (0.3g, 2 mmol) in carbon tetrachloride (CCl_4) (20 ml) was added *N*–bromosuccinamide (0.4g, 2.2 mmol) and AIBN (0.04g, 0.2 mmol). The mixture was stirred for 2 hours under the visible light of (2 x 150w) tungston bulbs. The reaction mixture was diluted with water and extracted into diethyl ether (2 x 50 ml), washed with water, 5% aqueous sodium sulphite solution (50 ml), water and finally with brine. The organic layer was dried and solvent was removed *in vacuo*. The crude residue was purified using column chromatography with TLC silica gel (as adsorbent) and CH_2Cl_2 as eluant, to give a colourless oil of **bicyclo[2.2.1]heptan–2–bromo–3–methylethenoate (275)** (0.4g, 90%). ν_{max} (Neat) 1725 and 1665 (allylic ester) cm^{-1}; δH (60 MHz) 6.0 (1H, brs, H–8), 4.45 (1H, brm, J = 1.8 and 3 Hz, H–2), 3.95 (1H, brs, H–4), 3.75 (3H, s, OMe) and 2.6 (1H, brs, H–1); Elemental Analysis – Found: C, 49.17; H, 5.46. $C_{10}H_{13}BrO_2$ requires C, 49.00; H, 5.35%; MS – Found: M^+ 246/244.

97. Attempted synthesis of bicyclo[2.2.1]heptan–3–spiro–2'–oxiran–2–bromo–3'–methyl ester (276)

*m*CPBA

*m*CPBA (0.4g, 2.3 mmol) was added to a solution of allylic bromide **(275)** (0.3g, 1.1 mmol) in CH_2Cl_2 (20 ml) and the mixture was reacted according to the general procedure. The crude product obtained was analysed by ^1H NMR and IR spectrum, which indicated starting material only.

H_2O_2/OH^-

To a cool solution of allylic bromide (**275**) (0.7g, 3 mmol) was added 30% H_2O_2 (3 ml) and 4M aqueous NaOH respectively, keeping the temperature below 5°C. The mixture was stirred for 2 hours at 0°C and overnight at room temperature. After the usual workup starting material was isolated.

$(CF_3CO)_2O$/urea – H_2O_2

To a refluxing solution of allylic bromide (**275**) (1.6g, 6.5 mmol) in CH_2Cl_2 (40 ml), $NaHPO_4$ buffer (6g, 50 mmol) and urea-H_2O_2 (4g, 42 mmol) was added trifluoroacetic anhydride ($[CF_3CO]_2O$) (2 ml) slowly and the mixture was refluxed for 2 hours. It was cooled, diluted with CH_2Cl_2 washed with 10% aqueous sodium hydrogen carbonate solution (2 x 50 ml) and water, dried and the solvent was removed *in vacuo*. The crude product was analysed by ^1H NMR and IR spectrum, which indicated starting material.

Dimethyldioxiran

Dimethyldioxiran 0.05M in acetone (15 ml) was added to allylic bromide (**275**) (0.2g, 0.8 mmol) and the mixture was stirred overnight. The acetone was removed *in vacuo*, and the crude product obtained was analysed by ^1H NMR and IR spectrum, which indicated starting material. The reaction was abandoned, and not further studied.

98. Synthesis of 2-benzylidenebicyclo[2.2.1]heptane (277)

A solution of diethylbenzylphosphonate (16g, 68 mmol) in tetrahydrofuran (THF) (150 ml) was cooled to -78°C under oxygen-free nitrogen. To this cooled solution was added butyl lithium (4.4g, 69 mmol), and the mixture was stirred for 30 minutes and brought to room temperature. The mixture was left to stand at room temperature for 30 minutes, cooled to

-78°C, and a solution of norcamphor (**201**) (5.5g, 50 mmol) in THF was added. The mixture was left to stand for 1 hour at that temperature and stirred overnight at room temperature. The reaction mixture was diluted with water and extracted into diethyl ether (2 x 100 ml), washed with water (2 x 50 ml) and brine. The organic layer was dried and solvent was evaporated *in vacuo*. The crude product was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:3 as eluant. The colourless oil obtained was 2-benzylidenebicyclo[2.2.1]heptane (**277**) (8g, 80%). ^{1}HNMR analysis showed a 3:1 mixture of isomers. ν_{max} (Neat) 1655 (C=C-H) cm^{-1}; δH (60 MHz) 7.3 (5H, s, Ar-H), 6.3 (1H, brs, H-8), 2.87 (1H, brs, H-4) and 2.3 (1H, brs, H-1).

99. Synthesis of epoxide (278)

m-Chloroperbenzoic acid (9g, 52 mmol) was added to a solution of benzylidenenorbornane (**277**) (4.7g, 26 mmol) in CH_2Cl_2 (50 ml). The mixture was reacted according to the general procedure for epoxidation, except that the reaction was completed in 2 hours instead of overnight. The crude residue was purified using column chromatography with TLC silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:4 as eluant. The colourless oil obtained was 3'-phenylbicyclo[2.2.1]-heptan-3-spiro-2'-oxirane (**278**) (3g, 59%). δH (60 MHz) 7.2 (5H, s, Ar-H), 3.9 (1H, s, H-8), 2.34 (1H, brs, H-1) and 1.95 (1H, brs, H-4).

100. Synthesis of the allylic alcohol (279)

To a solution of lithium diisopropylamide (LDA), made *in situ* by reacting together diisopropylamine (0.6g, 6 mmol) and *n*-butyllithium (0.4g, 6 mmol) at -78°C under oxygen-free nitrogen, was added a solution

of epoxide **(278)** (0.6g, 3 mmol) in THF (20 ml). The mixture was brought to ambient temperature and refluxed for 2 days. The reaction mixture was cooled, poured into water and extracted with diethyl ether (2 x 100 ml). The ether was washed with 1M aqueous hydrochloric acid (100 ml), 5% aqueous sodium hydrogen carbonate (100 ml), water and finally brine, dried and the ether removed *in vacuo*. The crude residue was purified using column chromatography with TLC silica gel (as adsorbent) and dichloromethane : light petroleum (b.p. 40-60°C) 2:1 as eluant. The less polar product obtained was starting epoxide **(278)** (0.2g, 33%), IR, TLC, ^{1}HNMR identical to starting material. The more polar product isolated was recrystallised from aqueous ethanol to give **2-hydroxybenzyl-bicyclo[2.2.1]hept-2-ene (279)** (0.15g, 38%) m.p. 54-55.5°C; ν_{max} (Nujol) 3224 (OH) cm^{-1}; δH (60 MHz) 7.3 (5H, s, Ar-H), 5.9 (1H, m, H-3), 5.3 (1H, brs, H-8), 2.75 (2H, m, H-1,4), 2.0 (1H, s, D_2O exchange, OH); Elemental Analysis - Found: C, 83.50; H, 8.11. $C_{14}H_{16}O$ requires C, 83.90; H, 8.05%; MS - Found: M^+ 200.1201 (20%), $C_{14}H_{16}O$ requires 200.1189.

101. Synthesis of epoxyketone (280)

PDC (3g, 8 mmol) was added to a solution of epoxyalcohol **(226)** (0.6g, 4.3 mmol) in CH_2Cl_2 (50 ml). The mixture was reacted according to the general procedure. The colourless oil obtained was a 4:1 mixture of bicyclo[2.2.1]heptan-2-one-3-spiro-2'-oxirane **(280)** (0.24g, 41%). ν_{max} (Neat) 1754 (C=O) cm^{-1}; δH (250 MHz) 2.8-3.14 (2H, ABq, J = 5.6 Hz, H-8), 2.8 (1H, brs, H-1) and 2.41 (1H, brs, H-4); δC (250 MHz) 213.79 (q, C-2), 63.57 (q, C-3), 49.31 (CH_2, C-8), 48.97 (CH, H-1), 40.1 (CH, C-4), 35.97 (CH_2, C-7), 25.10 (CH_2, C-5) and 23.79 (CH_2, C-6); MS - Found: M^+ 138.0681 (4.4%), $C_8H_{10}O_2$ requires 138.0714.

102. Reaction between *endo*-epoxybromide (265) and Bu_3SnH

To a refluxing solution of Bu_3SnH (0.3g, 1.1 mmol) in toluene (6 ml) under oxygen-free nitrogen was added bromo-epoxide (**265**) (0.3g, 1.1 mmol) and AIBN (0.02g, 0.1 mmol) in toluene (4 ml) over 10 minutes, and the mixture was heated to reflux for 2 hours. The reaction was cooled and solvent was carefully removed *in vacuo*. The crude was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 1:1 as eluant. The less polar product isolated was bicyclo[2.2.1]heptan-2-one (**201**) (0.03g, 25%) IR ν_{max} ($CDCl_3$) 1745 (C=O) cm^{-1}. TLC, ^1H NMR identical to the authentic sample. Norcamphor was derivatised as 2,4-dinitrogenphenyl-hydrazone m.p. 127-129°C. An authentic derivative was prepared; m.p. 131-133°C.

The more polar product isolated was benzylalcohol (**285**) (0.07g, 61%). ν_{max} (Neat) 3500 (OH) cm^{-1}; δH (60 MHz, CCl_4) 7.3 (5H, s, Ar-H), 4.5 (2H, s, $-CH_2-OH$) and 3.3 (1H, D_2O exchange, OH). A 3,5-dinitrobenzoate derivative was prepared m.p. 109-110°C (lit.[126] 109-110°C).

103. Reaction between *exo*-epoxybromide (266) and Bu_3SnH

The same products as for the *endo*-isomer (**265**) were obtained.

104. Reaction between *endo*-epoxybromide (268) and Bu_3SnH

To a refluxing solution of Bu_3SnH (0.3g, 1.1 mmol) in toluene (6 ml) under oxygen-free nitrogen was added bromoepoxide (**268**) (0.2g, 0.6 mmol) and AIBN (0.01g, 0.06 mmol) in toluene (4 ml) over 10 minutes. The mixture was cooled and the solvent was carefully removed *in*

vacuo. The crude product was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°) 1:1 as eluant. The less polar product isolated was bicyclo[2.2.1]heptane (**201**) (0.03g, 45%). The TLC and IR spectrum were identical to those of norcamphor (**201**).

The more polar product isolated was recrystallised from the mixture of diethyl ether and light petroleum (b.p. 40–60°C) to give colourless crystals of *p*–chlorobenzylalcohol (**286**) (0.02g, 23%) m.p. 71–73°C (lit.[126] 70–72°C). ν_{max} (Nujol) 3250 (OH) cm^{-1}; δH (60 MHz) 7.3 (4H, s, ClC_6H_4–H), 4.6 (2H, s, $-CH_2$–OH), 2.25 (1H, D_2O exchange, OH).

105. Reaction between *exo*–epoxybromide (269) and Bu_3SnH

The results were the same as for the *endo*–isomer except that the bromoepoxide (**269**) used was (0.1g, 0.3 mmol) instead of (0.6 mmol). Analogous products were obtained.

106. Attempted reaction between epoxychloride (273) and Bu_3SnH

To a refluxing solution of Bu_3SnH (0.8g, 2.4 mmol) in benzene (6 ml) under oxygen–free nitrogen was added chloro–epoxide (**273**) (0.2g, 1.3 mmol) and AIBN (0.02g, 0.1 mmol) in benzene (6 ml) over 10 minutes and the mixture was heated to reflux 10 hours. The reaction mixture was cooled and the solvent was removed *in vacuo*. ^1H NMR analysis of the crude showed the starting chloro–epoxide was present. Longer reaction time using triphenyltin hydride and (2 x 150w) light bulbs only obtained starting epoxide (**273**). The reaction was abandoned and not stydied further.

107. Attempted synthesis of of 2-iodo-3-methylenebicyclo[2.2.1]-heptane (287)

Sodium iodide (0.1g, 0.8 mmol) in dry acetone (10 ml) was added to chloronorcamphene (272) (0.05g, 0.4 mmol) in acetone (2 ml). The reaction mixture was refluxed for 20 minutes, cooled and the acetone removed *in vacuo*. The crude residue was dissolved in diethyl ether and washed with water (2 x 20 ml), 5% aqueous sodium bisulphite solution (30 ml), and water again, dried and ether was evaporated *in vacuo*.

^{1}H NMR analysis of the crude mixture showed only the starting material to be present. Longer reaction time under reflux also afforded starting material. The reaction was abandoned, and not further studied.

108. Reaction between bicyclo[2.2.1]heptan-2-one-3-spiro-2'-oxirane (280) and Bu_3SnH

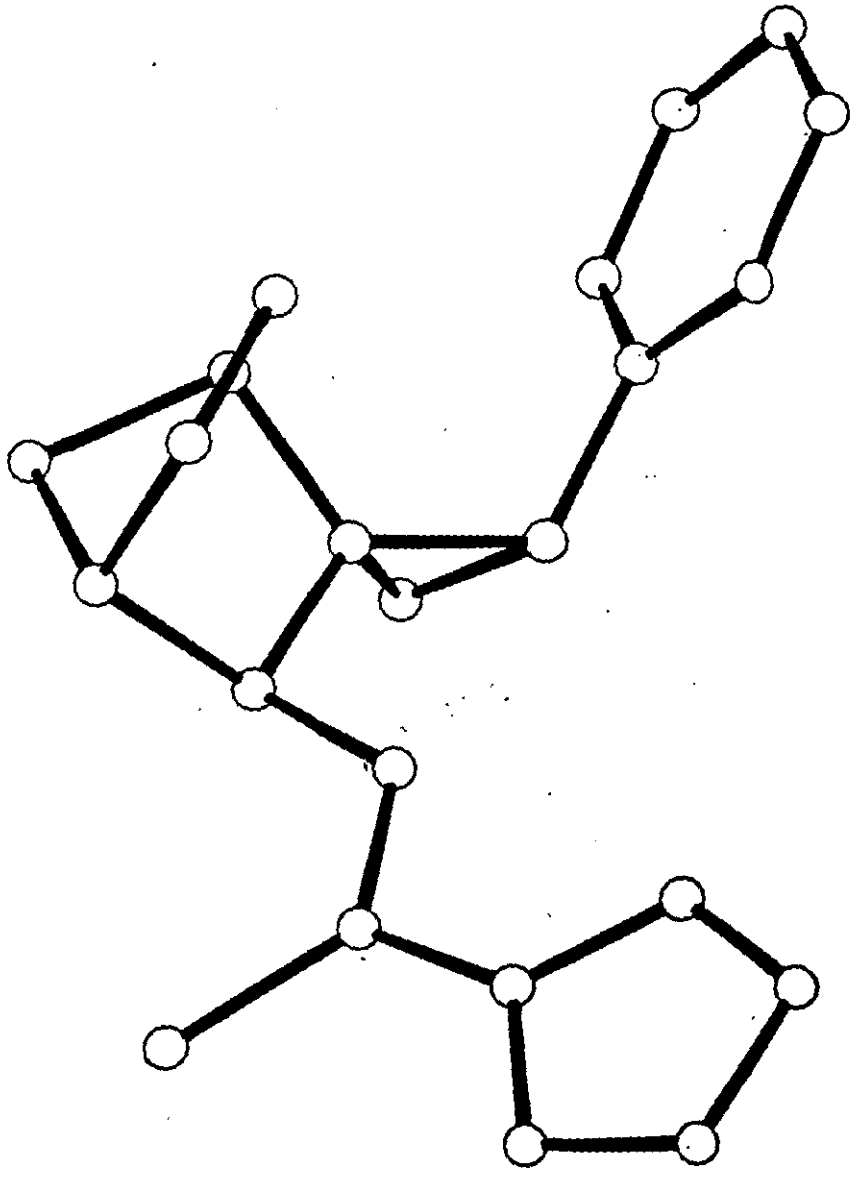
To a refluxing solution of Bu_3SnH (0.7g, 2.4 mmol) in benzene (6 ml) under oxygen-free nitrogen was added epoxyketone (280) (0.2g, 1.5 mmol) and AIBN (0.02g, 0.1 mmol) in benzene (6 ml) over 10 minutes and the mixture was refluxed for 6 hours. The reaction was cooled and the solvent was removed *in vacuo*. The crude product was partitioned between acetonitrile and light petroleum (b.p. 40-60°C). The acetonitrile layer was separated and evaporated *in vacuo*. ^{1}H NMR analysis of the product showed that the hydroxyketone (288) was present. The product was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40-60°C) 4:1 as eluant to give a colourless oil of 3-hydroxymethylbicyclo[2.2.1]heptan-2-one (288) (0.12g, 72%). ν_{max} (Neat) 3428 (OH) and 1730 (C=O) cm^{-1}; δH (250 MHz) 3.60-3.88 (2H, ABX, J = 7.4 Hz), 2.72 (1H, brs, H-1), 2.7 (1H, d, J = 5 Hz, H-4), 2.39 (2H, m, H-3, 1H D_2O exchange, OH),

and rest between 1.5–1.88 (6H); δC (250 MHz) 219.96 (q, C–2), 60.74 (CH_2, C–8), 55.32(CH, C–1), 50.45 (CH, C–3), 37.95 (CH, C–4), 37.95 (CH_2, C–7), 25.39 (CH_2, C–5), 21.80 (CH_2, C–7); MS – Found: M^+ 140.0837 (3.7%), $C_8H_{12}O_2$ requires 140.0846

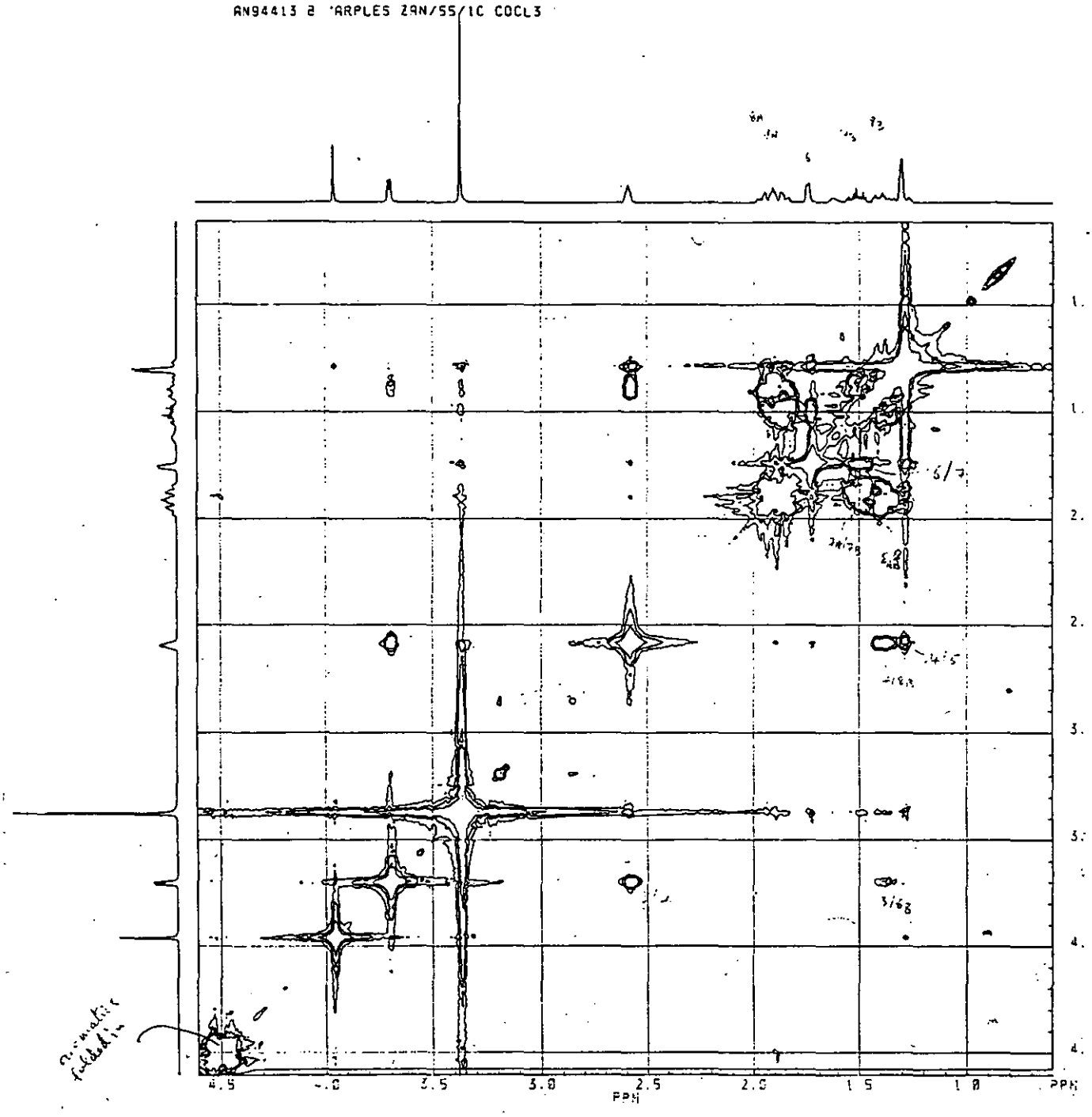
109. Photolysis of 2–hydroxybenzylbicyclo[2.2.1]heptan–2–ene (279) with mercuric II oxide (HgO) and iodine

To a solution of allylic alcohol (**279**) (0.4g, 2 mmol) in dry benzene (70 ml) was added iodine (0.9g, 7 mmol) and HgO (1.5g, 7 mmol) and the mixture was cooled at 0°C. The mixture was photolysed using a medium pressure Honovia lamp for 3 hours. The crude mixture was filtered and washed with 10% aqueous sodium bisulphite solution (2 x 50 ml), and the solvent was removed *in vacuo*. The crude residue was purified using preparative TLC on silica gel (as adsorbent) and diethyl ether : light petroleum (b.p. 40–60°C) 1:1 as eluant. The colourless oil obtained was *exo*–2–benzoyl–bicyclo[2.2.1]heptane (**294**) (0.14g, 35%). ν_{max} (Neat) 1718 and 1676 (aryl α,β–unsaturated C=O) cm^{-1}; δH (60 MHz) 8.0 (2H, m, Ar–H), 7.3–7.6 (3H, m, Ar–H), 2.4 (1H, brs, H–4) and 2.37 (1H, brs, H–1); MS – Found: M^+ 200 (20%).

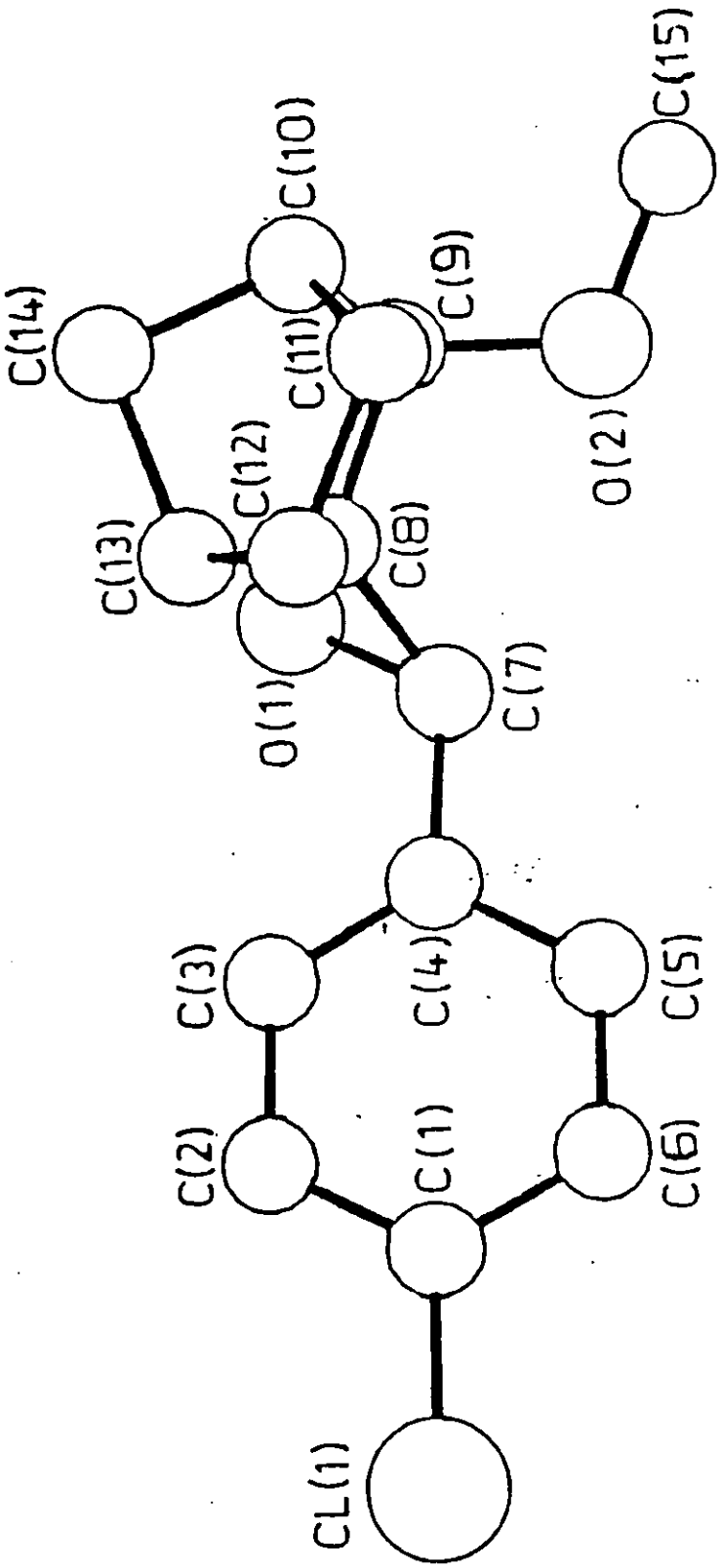
APPENDIX 1



APPENDIX 2



APPENDIX 3



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