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Loughborough University of Technology
Department of Chemistry.

Synthetic And Mechanistic Aspects Of Dioxirane Chemistry.

By

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A Doctoral Thesis.

Submitted In Partial Fulfilment Of The Requirements
For The Award Of Doctor Of Philosophy Of The

Loughborough University Of Technology.

Supervisor: Professor B.A. Marples.

This thesis is dedicated in loving memory to my mother Anne

died 7th October 1991.

and

To Denis, Georgina and Edward with love.

SYNOPSIS.

The range and understanding of oxidations by dioxiranes has been extended.

Epoxidation of cholesterol and 3β-acetoxycholest-5-ene with a range of dioxiranes generated *in situ,* affords the 5α,6α and 5β,6β-cholesteryl epoxides in the ratio 1:1. This result differs significantly from peroxyacid methods where α:β 4:1 is expected. 4,4-Dimethylcholest-5-enes were not epoxidised and instead a preferred allylic oxidation to give the 7-ketone was observed. The results have allowed mechanistic implications to be proposed in favour of a spiro transition state for the epoxidation of alkenes.

Oxidation of estradiol derivatives with dimethyldioxirane gave selective benzylic oxidation to form 9α-hydroxy compounds in good yield.

The conversion of alcohols to ketones has been investigated. Oxidation of ^{18}O cholestan-3β-ol by dimethyldioxirane has shown that there is a 40% loss in ^{18}O label from the alcohol. This result suggests that a mechanism involving oxygen atom insertion from the dioxirane into the C-H bond is occurring. Experiments have also shown that axial alcohols are oxidised faster than equatorial alcohols.

A series of benzyl ethers has been oxidised by dimethyldioxirane. Aromatic benzyl ethers afford the phenol whilst, 3-benzyloxycholestane yields cholestan-3-one via cholestan-3β-ol. Benzaldehyde dimethylacetal and phenylacetaldehyde dimethylacetal gave methyl benzoate and methyl phenylacetate respectively.

Epoxides derived from a series of chromenes have been obtained in excellent yields using dimethyldioxirane.

Approaches to a method for asymmetric epoxidation of alkenes using dioxiranes derived from chiral ketones have been investigated. However, only a low level of enantiomeric excess (ca 11%) has been achieved. Acetophenone and benzophenone derived fluoro-ketones have also been used and their potential as reactive dioxirane intermediates assessed.

Preliminary work on the application of dioxiranes to oxidation of β-lactams has been investigated.

CONTENTS.

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ABBREVIATIONS.

UV.	Ultraviolet.
IR.	Infrared.
NMR.	Nuclear Magnetic Resonance.
MS.	Mass Spectrometry.
ppm.	Parts Per Million.
TLC.	Thin Layer Chromatography.
GLC.	Gas Liquid Chromatography.
MeOH.	Methanol.
EtOH.	Ethanol.
t-Butanol.	Tertiary Butanol.
EtOAc.	Ethyl Acetate.
Ether.	Diethyl Ether.
Pet Ether.	Petroleum Ether 40/60.
DMF.	N,N-Dimethylformamide.
DMSO.	Dimethyl Sulphoxide.
DCM.	Dichloromethane.
HMPA.	Hexamethylphosphoramide. $(Me_2N)_3PO$
IPE.	Diisopropyl Ether.
Phosphate Buffer.	Phosphate buffer at pH7.5.
THF.	Tetrahydrofuran.
DMD.	Dimethyldioxirane.
HCl.	Hydrochloric acid.
TBAHS.	Tetrabutylammonium hydrogen sulphate.
p.TSA.	p-Toluenesulphonic acid.
mCPBA.	m-Chloroperoxybenzoic acid.
Caroate.	Monoperoxysulphate species (HSO_5^-).
Oxone®	Potassium monoperoxysulphate, Aldrich Chemical Company, ($2KHSO_5.KHSO_4.K_2SO_4$),in solution forms HSO_5^-.
NBS.	N-Bromosuccinimide.
MPCA.	Monoperoxycamphoric acid.
EDTA.	Ethylenediaminetetraacetic acid disodium salt.
AIBN.	Azo-bisisobutyronitrile.
Cholestanol.	Refers to cholestan-3β-ol unless stated.
t-BDMSCl.	Tertiary butyldimethylsilyl chloride.

LDA.	Lithium diisopropylamide.
PDC.	Pyridinium dichromate.
PCC.	Pyridinium chlorochromate.
Diazald®	N-Methyl-N-nitroso-p-toluenesulphonamide.
$Eu(hfc)_3$.	Europium D-3-heptafluorobutyrylcamphorate.
CAS.	Clavaminic Acid Synthase.
conv.	Conversion.
Equivs.	Equivalents.
Hr.	Hour.
Mins.	Minutes.
%wt.	Percentage weight.
Approx.	Approximately.
N.D.	Not Determined.
ee.	Enantiomeric Excess.
aq.	Aqueous.
Rf.	Retention factor.
mg.	Milligrams.
Lit.	Literature.
soln.	Solution.
Me.	Methyl.
Et.	Ethyl.
Bpt.	Boiling point.
Mpt.	Melting point.
V/V.	Volume/Volume.
EI.	Electron Impact.
CI.	Chemical Ionisation.
nm.	Nanometres.
ET.	Electron Transfer.
δ.	Chemical shift.
Hz.	Hertz.
J.	Coupling Constant reported in Hz.
FID.	Flame Ionisation Detection.
Ambient Temperature.	22°C.

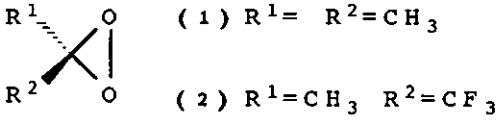
CHAPTER 1

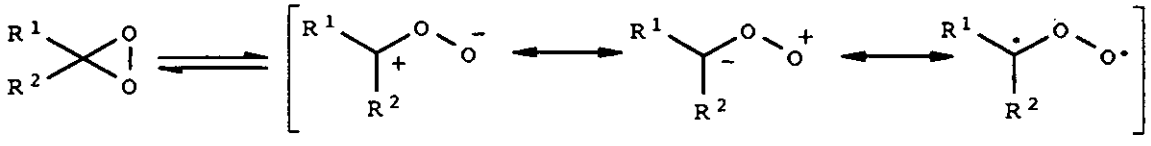
CHAPTER 1.

Review Of Dioxirane Chemistry.

1.1 Introduction.

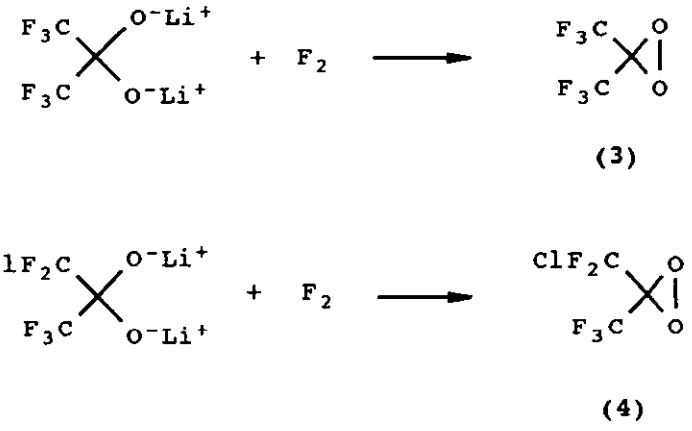
The last twenty years has seen the ever increasing interest in the chemistry of dioxiranes as illustrated by two recent reviews.[1,2] Until this time, these three membered cyclic peroxides were relatively unknown compounds. Perhaps the earliest report postulating the existence of dioxiranes was made by Baeyer and Villiger in 1899.[3] They suggested that for the conversion of the ketone menthone to its corresponding lactone by the reaction with monoperoxysulphuric acid, an intermediate bearing the structure of a dioxirane may be involved. It was work later by Doering and Dorfman[4] in an ^{18}O study which showed dioxiranes were not involved and that the now generally accepted alternative mechanism for lactone formation was favoured. Dioxiranes are recognised as being isomeric with carbonyl oxides which have a longer and well established history[5] (Scheme 1).





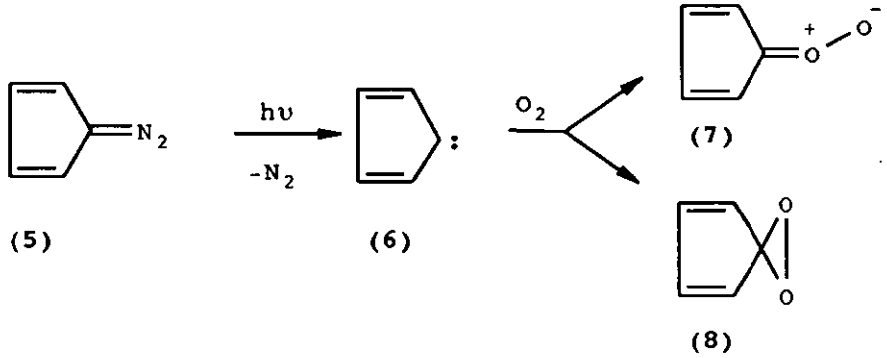
(Scheme 1)

The preparation of dioxiranes can be achieved either by the use of peroxyacids or by other non-peroxyacid methods. The first reported preparation of a dioxirane was in 1972 by Talbott and Thompson. This work involved the preparation of perfluoro-dimethyldioxirane (**3**) and chloro(difluoromethyl)(trifluoromethyl)dioxirane (**4**) by the fluorine oxidation of the corresponding dialkoxide precursor. These dioxiranes were seen to be pale yellow when isolated by low temperature gas chromatography, their structures being determined by ^{19}F NMR, infrared and mass spectral analysis[6] (Scheme 2).



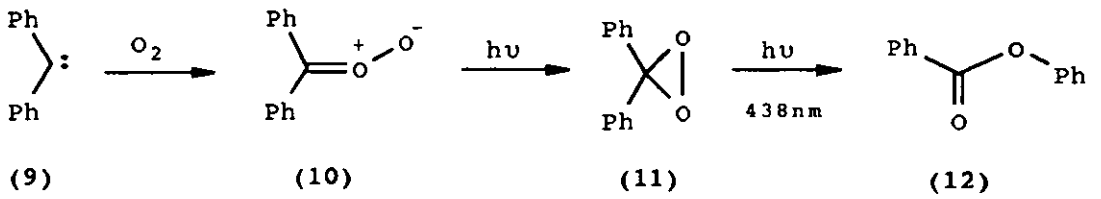
(Scheme 2)

As early as 1905 dioxiranes had been considered as possible intermediates in ozone chemistry.[7] However, good evidence for the Criegee mechanism involving carbonyl oxides as intermediates for solution ozonolysis tended to disfavour the dioxirane proposal. Evidence from microwave spectroscopy has shown that the parent dioxirane is a product of low temperature (-130 to -75°C) ozonolysis of ethylene. The microwave data showed that the dioxirane has a shorter C-O bond and a longer O-O bond than the ethylene ozonide.[8,9] The photooxidation of diazo compounds and diazirines could give a species which is either the carbonyl oxide (**7**) or the dioxirane (**8**) (Scheme 3).



(Scheme 3)

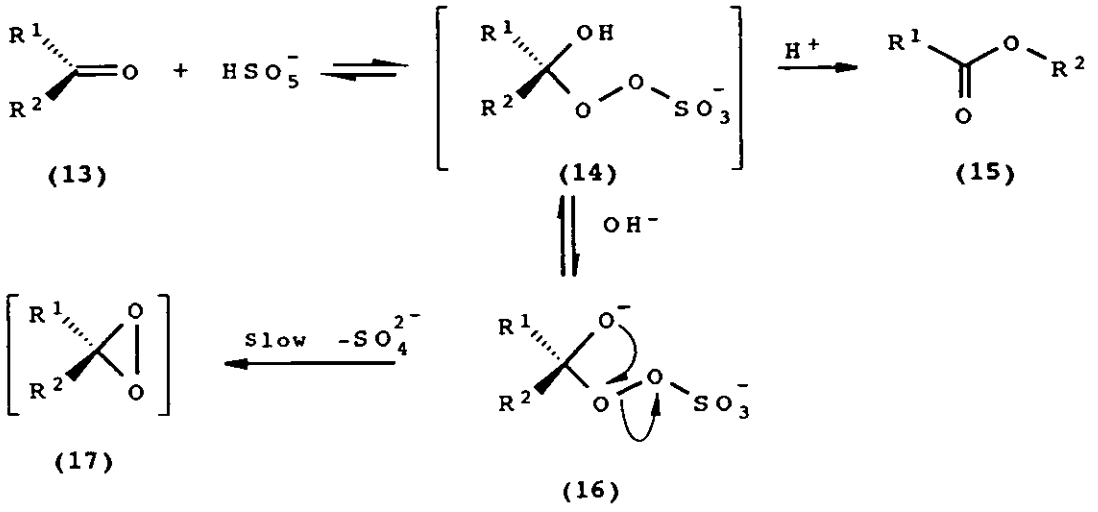
However, infrared spectra have shown that two non-equivalent oxygen atoms are present in the oxygen trapped species which suggests that the carbonyl oxide (**7**) is the preferred structure.[10,11,12] Later work by Dunkin and Shields[13] has shown that the carbonyl oxide (**7**) can be photoisomerised to the dioxirane (**8**). Similarly, quenching of diphenylcarbene (**9**) with molecular oxygen gives rise to the diphenyldioxirane (**11**).[14] The mechanism[15] of this is considered to proceed by photoisomerisation of the initially formed carbonyl oxide (**10**) (Scheme 4).



(9) (10) (11) (12)

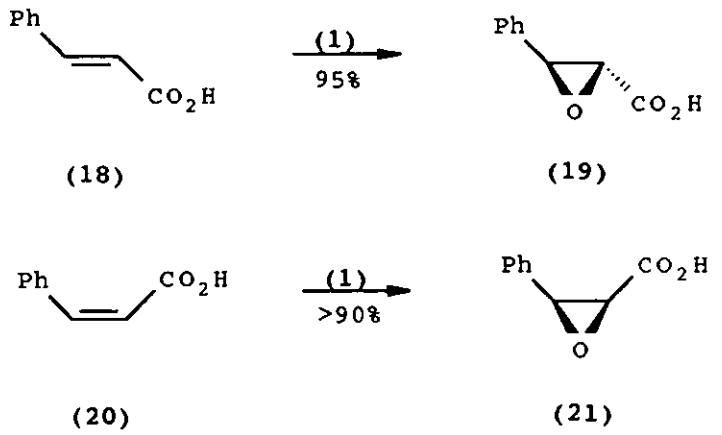
(Scheme 4)

A significant discovery, which allowed the development of a whole new area of dioxirane chemistry, was made by Montgomery in 1974.[16] He observed that certain ketones decompose potassium monoperoxysulphate (also referred to as caroate) with the evolution of oxygen gas in weakly alkaline solutions. The ketone action was found to be catalytic. However, with some of the ketones significant loss of ketone was observed. This was attributed to Baeyer-Villiger oxidation of the ketone yielding the corresponding ester or lactone with aliphatic and cyclic ketones respectively. The rate of caroate decomposition was proportional to the amount of ketone present which suggested the involvement of a highly reactive intermediate. Kinetic and ^{18}O labelling studies[17] have provided strong evidence for the dioxirane species and that they exhibit powerful oxidising properties. Now solution chemistry of dioxiranes had been established; Curci and Edwards[18,19] recognised the synthetic application of these species. Initially the epoxidation of alkenes was performed in an elegant experiment involving a biphasic, buffered water/dichloro-methane, system maintained strictly at pH7.5. The dioxirane was generated *in situ* from the ketone, when the caroate reagent was added, which in turn oxidised the alkene. The mechanism of the dioxirane formation is considered to proceed via the Criegee intermediate (**14**), which is formed by the attack of the monoperoxysulphate anion at the carbonyl carbon atom of the ketone (**13**). Below pH7.5 Baeyer-Villiger oxidation to give the product (**15**) becomes possible as deprotonation of the intermediate (**14**) is less probable. However, under weakly alkaline conditions generation of the anion (**16**) occurs allowing ring closure onto oxygen with elimination of sulphate ion to form the dioxirane (**17**) (Scheme 5).



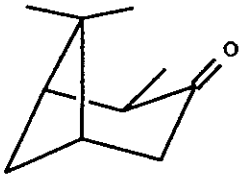
(Scheme 5)

An important feature of the epoxidations was the very high stereoselectivity which was obtained.[18] Trans-alkenes (**18**) have been shown to give trans-epoxides (**19**) while cis-alkenes (**20**) yield cis-epoxides (**21**) (Scheme 6).

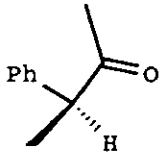


(Scheme 6)

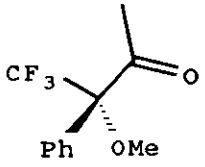
The excellent selective oxidation properties of dioxiranes led Curci and co-workers to determine whether enantioselective epoxidations were feasible using dioxiranes derived from chiral ketones.[20] Indeed, using (+)-isopinocamphone (**22**) and (S)-(+)-3-phenylbutan-2-one (**23**) as chiral ketones, prochiral alkenes such as 1-methylcyclohexene could be epoxidised in 92% yield with an enantiomeric excess of 12%. These reactions were very slow, the times for complete conversion of starting alkene being a matter of days rather than hours. However more recently higher enantioselectivities (20%) and faster reaction times using 4,4,4-trifluoro-3-phenyl-3-methoxy-2-butanone (**24**) have been reported.[21]



(22)



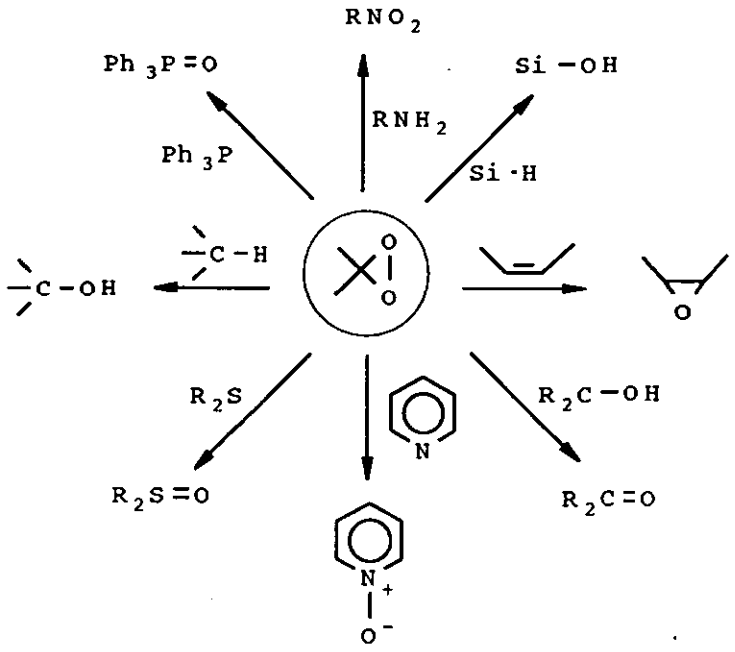
(23)



(24)

A major advance in dioxirane chemistry was made by Murray and Jeyaraman in 1985.[22] They developed a method by which low molecular weight dioxiranes could be isolated as a solution in their parent ketone. The dioxirane could be formed from the ketone/caroate system and collected by low temperature distillation as pale yellow solutions. The concentration of dioxirane in the solutions ranged from 0.04 to 0.18M. However, increasing the bulk of the alkyl substituents led to decreasing yields of dioxirane. The isolation of dimethyldioxirane (**1**) in acetone solution has allowed detailed spectral studies including ^{17}O and ^{13}C NMR which gave supporting evidence for the dioxirane structure. For dimethyldioxirane the data is as follows; ^{1}H NMR δ 1.65ppm (methyl), ^{13}C δ 22.73ppm (methyl), δ 102.3ppm (ring C) and ^{17}O δ 302ppm.[23] Physical properties such as thermodynamics and kinetic stability, have also been investigated.[24]

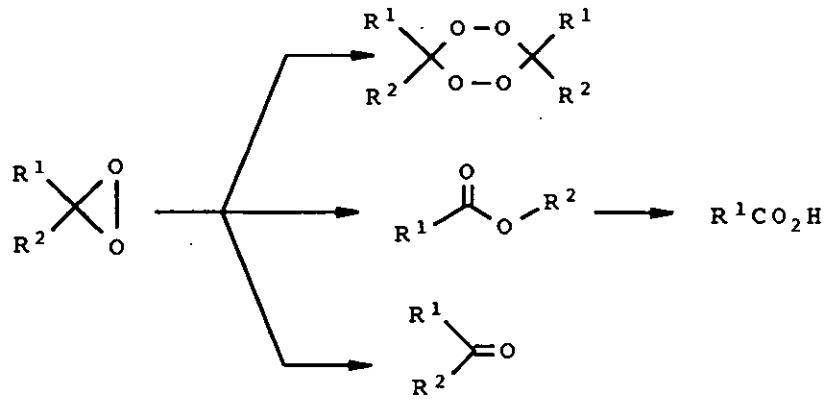
The type of chemical reactions which can be performed using the isolated dimethyldioxirane/acetone reagent are wide ranging. Clearly, unlike the *in situ* method of oxidation non-aqueous reactions can be performed, which may be important for certain substrates. The mild but powerful oxidising properties of dimethyldioxirane has been used with a variety of substrates. A few of the key oxidations which can be performed are: epoxidations, conversion of sulphides to sulphoxides and sulphones, phosphines to phosphine oxides and oxygen atom insertion into carbon-hydrogen bonds (Scheme 7).



(Scheme 7)

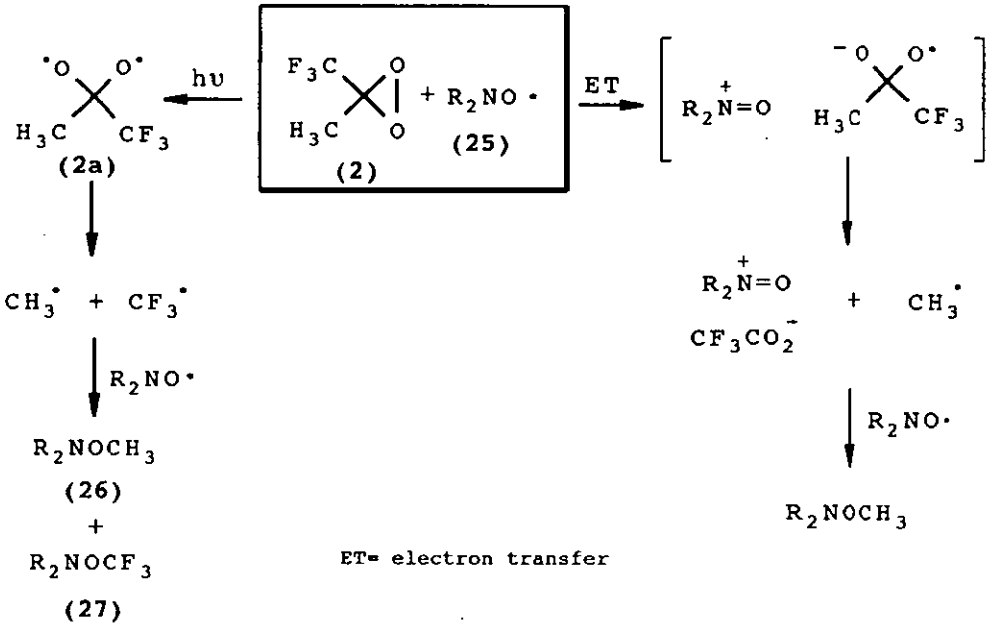
For synthetic purposes the ketone/caroate method of dioxirane generation is clearly the method of choice. A very wide range of ketones can be used for dioxirane generation if the *in situ* method is employed, one disadvantage being an autotitrator is required to control the pH efficiently. The isolation of dioxiranes allows them to be used more quantitatively as reagents. The more recent isolation of methyl(trifluoromethyl)dioxirane (**2**) by Curci and co-workers[25] has extended the usefulness of this methodology as this dioxirane is far more reactive than those previously prepared. For example, cyclohexane can be converted to cyclohexanol and cyclohexanone. The typical reaction time using dimethyldioxirane is about 20 hours, if two equivalents of methyl(trifluoro-methyl)dioxirane are used complete reaction to cyclohexanone can be achieved in just 30 minutes in >95% yield.

It is important that solutions of dioxiranes are kept well protected from light as exposure to ultraviolet or 586nm radiation causes exothermic decomposition of the dioxirane. For dimethyldioxirane, methyl acetate and the ketone diperoxide are the major products. However none of the diperoxide is formed in the decomposition of methyl-(trifluoromethyl)dioxirane. The formation of the acetates may involve radicals. Dioxiranes exhibit n-π^* absorptions in the UV region 300-350nm. However, the absorption extends into the visible region (ca.440nm) giving rise to the characteristic pale yellow colour[22,25,26] (Scheme 8).



(Scheme 8)

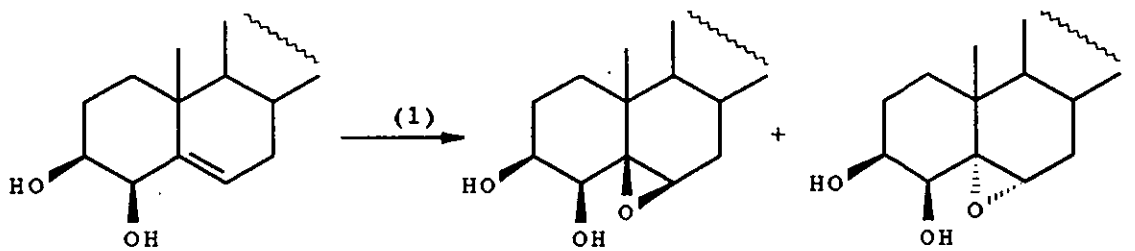
The photolysis of dioxiranes in the presence of a nitroxide radical scavenger **(25)** has been recently studied. Irradiation of methyl(trifluoromethyl)dioxirane **(2)** solution at λ >300nm has been shown to generate methyl and trifluoromethyl radicals,[27] which are trapped by a nitroxide radical to form the adducts **(26)** and **(27)**. The initial step for this pathway is considered to be the cleavage of the O-O bond to form the diradical **(2a)**. However, without the presence of light an electron transfer process with the dioxirane and nitroxide can occur leading to the formation of methyl radicals (Scheme 9).



(Scheme 9)

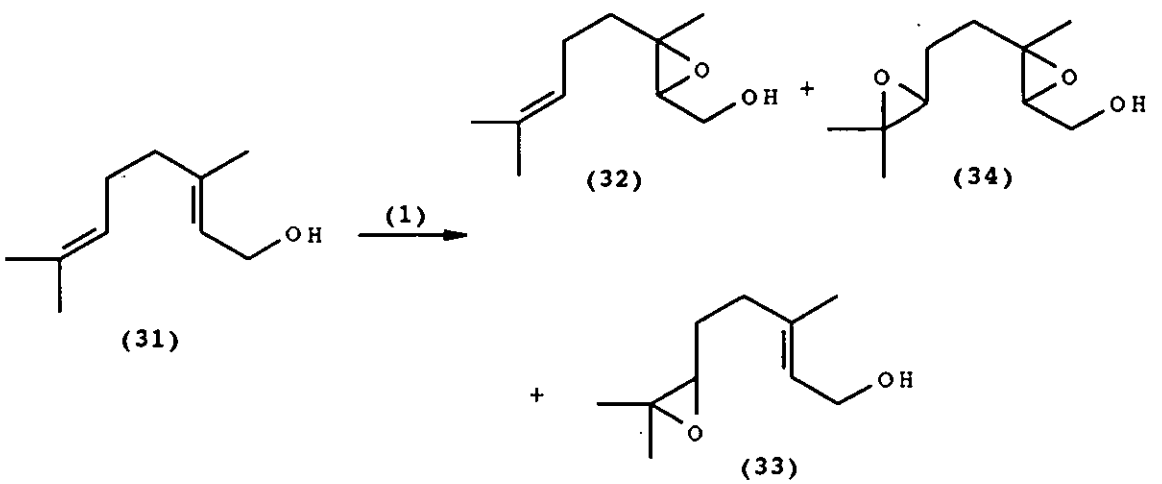
1.2 Epoxidations.

Without doubt the most widespread application of dioxiranes has been to the oxidation of alkenes where excellent yields and high stereo- and regioselectivity can be achieved. The oxidation of allylic alcohols which are of great importance in natural product chemistry has been demonstrated by the epoxidation of 4β-hydroxycholesterol (**28**). This gives a mixture of β (**29**) and α (**30**) epoxides in a ratio of 3:1, a peroxyacid generally gives a 2:1 mixture of the β:α oxide[28] (Scheme 10). Epoxidation of geraniol gives rise to three products: the 2,3 epoxide (**32**), 6,7 epoxide (**33**) and the diepoxide (**34**). At 40% conversion the 6,7 epoxide is found to be the major product whereas at higher conversions formation of the diepoxide occurs. Clearly the more nucleophilic 6,7 double bond is oxidised preferentially by dimethyldioxirane[28] (Scheme 11).



(28) (29) (30)

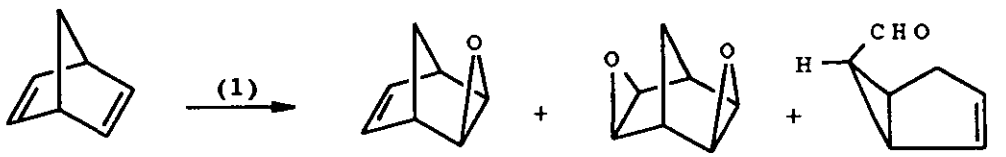
(Scheme 10)



(31) (32) (34) (33)

(Scheme 11)

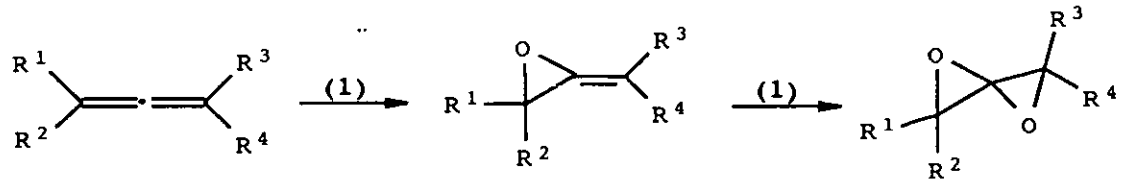
Similarly when norbornadiene (35) is reacted with dimethyldioxirane it gives rise to the monoepoxide (36) if a stoichiometric amount of dioxirane is added, or the diepoxide (37) if an excess of the dioxirane is used, with only a trace of the aldehyde (38)[29] (Scheme 12).



(35) (36) (37) (38)

(Scheme 12)

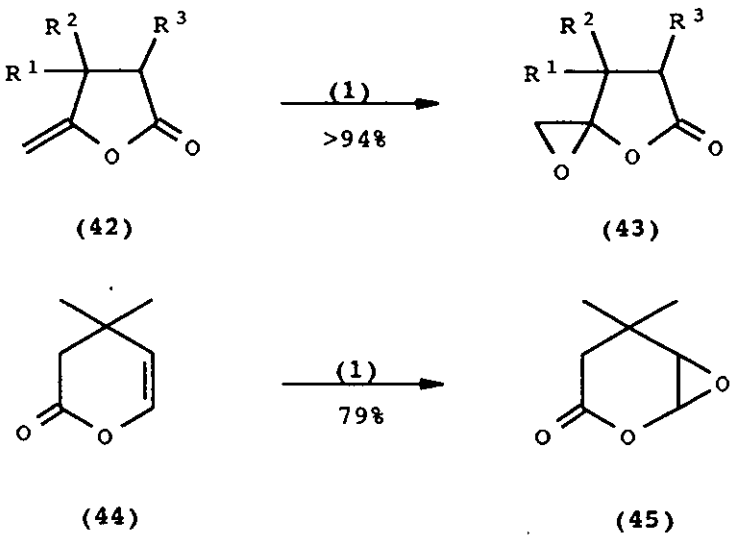
Oxidations using dimethyldioxirane are generally regarded as being efficient, even where highly labile groups are present or epoxides sensitive to acid hydrolysis are formed. This is highlighted by the epoxidation of enol lactones (42)[30] and conversion of allenes (39) to spirodioxides (41).[31] The major difficulty concerning the oxidation of allenes (39) using peroxyacids, is the mixture of products which is generally obtained. To successfully form the spirodioxide (41) as a sole product non-nucleophilic and mild oxidising conditions are required. Using dimethyldioxirane the more substituted double bond of the allene is oxidised initially which rapidly reacts on further oxidation to form the spirodioxide (41)[31] (Scheme 13).



(39) (40) (41)

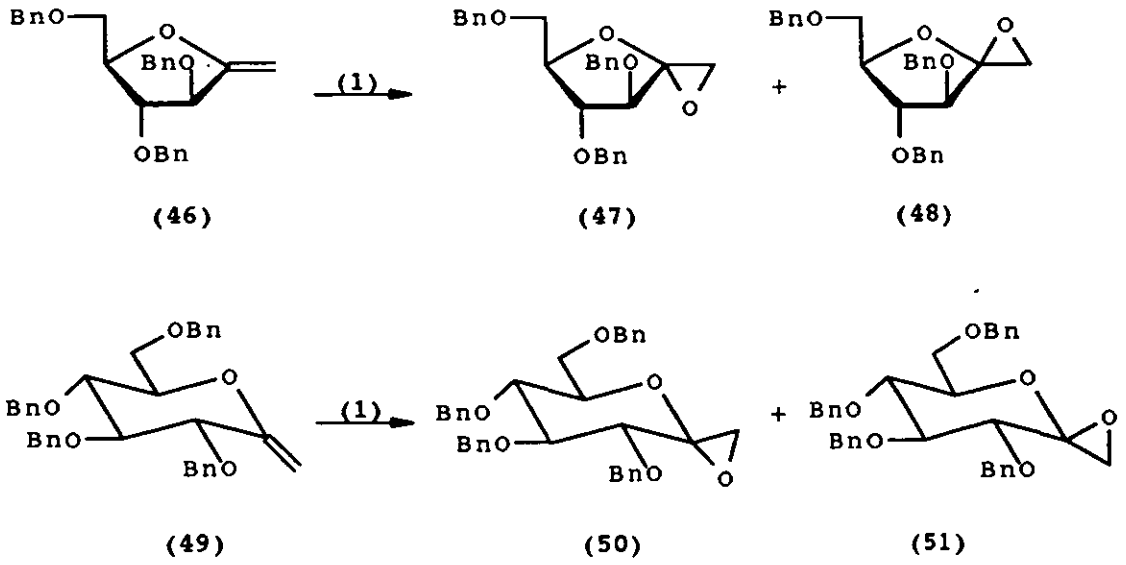
(Scheme 13)

The exocyclic double bond of an enol lactone **(42)** is quite unreactive such that epoxidation using mCPBA does not occur. This transformation has been shown to be possible using dimethyldioxirane as the neutral reaction conditions which can be achieved avoids acid-catalysed reactions of the epoxide **(43)**[30] (Scheme 14).



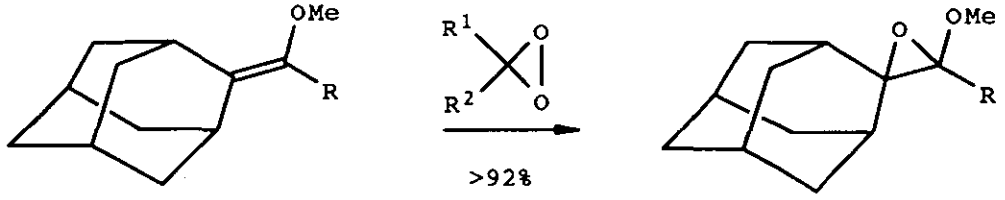
(Scheme 14)

The oxidation of exocyclic double bonds has also been demonstrated by the epoxidation of furanose **(46)** and pyranose **(49)** exocyclic glycals which would be important in the preparation of glycosides of ketosugars. A mixture of diastereomeric epoxides **(47)** and **(48)** is obtained.[32] However it is interesting to note oxidation does not occur at any other position in the molecule particularly at the methylene of the benzyl ether substituents (Scheme 15).



(Scheme 15)

These remarkable oxidations have been extended to the epoxidation of hindered enol ethers **(52)**, **(53)** and **(54)** employing the highly reactive methyl(trifluoromethyl)-dioxirane for the conversions. The epoxides were obtained in excellent yields with reaction times of less than six minutes.[33] Unlike peroxyacid oxidation of these compounds no rearrangement of the epoxide to α-alkoxy or α-hydroxy ketones was evident (Scheme 16).



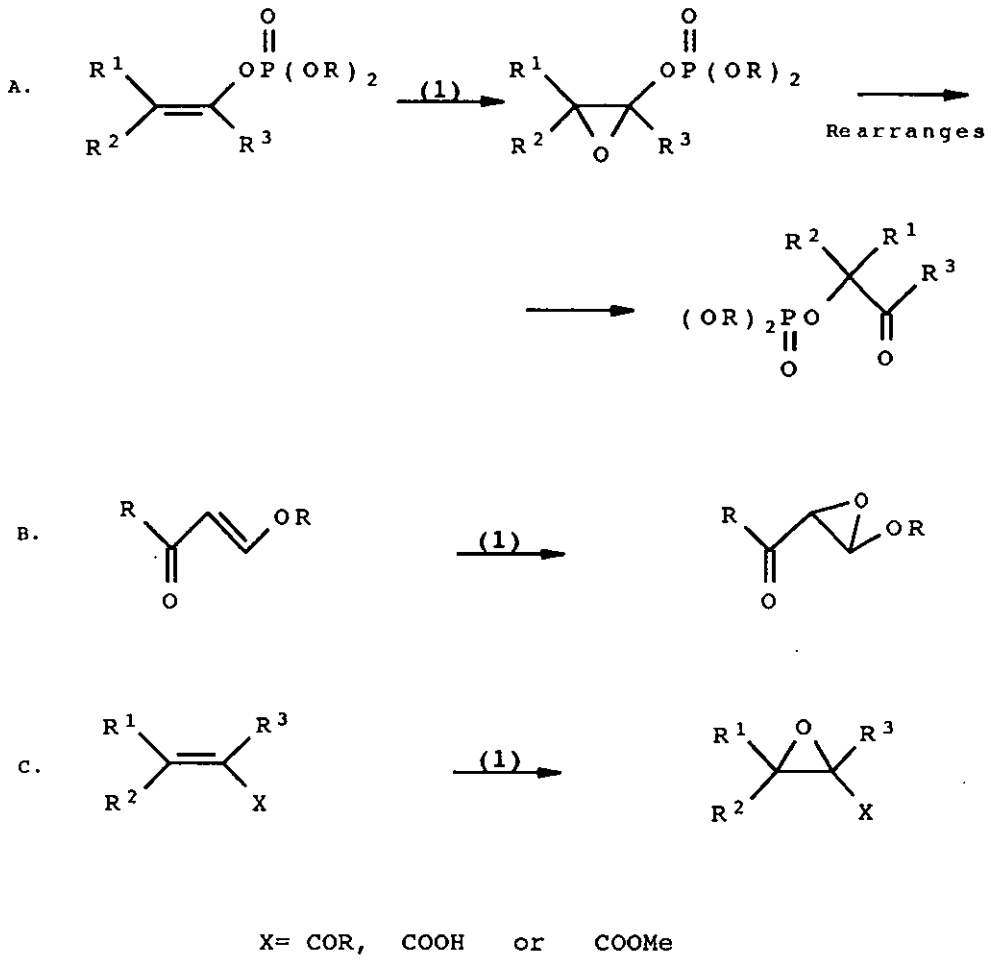
(52) R= Ph $R^1=CF_3$

(53) R= 1-Nap $R^2=CH_3$

(54) R= 2-Nap

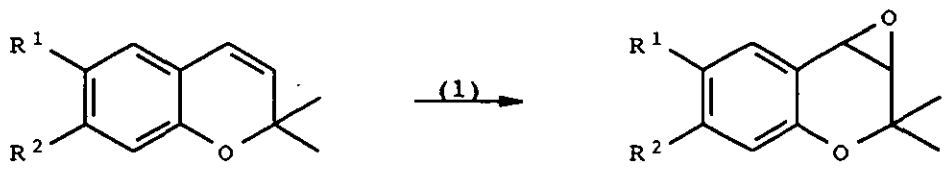
(Scheme 16)

The synthetic utility of dioxiranes for the preparation of sensitive epoxides has allowed access to an ever growing number of novel compounds. Other pertinent examples of this type are; the epoxidation of enol phosphates (**A**),[34] β-oxo enol ethers (**B**)[35] and α β-unsaturated ketones, acids and esters (**C**)[36] (Scheme 17).



(Scheme 17)

Many highly reactive and acid sensitive epoxides cannot be prepared by direct epoxidation methods using peroxyacids. As is often the case a synthetic procedure involving a bromohydrin and subsequent dehydrohalogenation to afford the epoxide is required. A direct route to convert an alkene to the epoxide would be highly desirable, especially in a synthesis involving a large number of steps. An example where dimethyldioxirane has been used to obtain reactive epoxides of this nature is for the direct epoxidation of precocenes (**55-58**). The 3,4-epoxy products were obtained in high yield and purity[37] (Scheme 18).



(55) $R^1=R^2=H$

(56) $R^1=H$; $R^2=Cl$

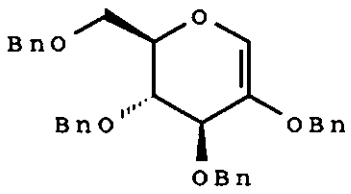
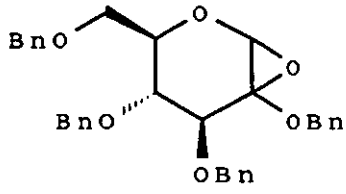
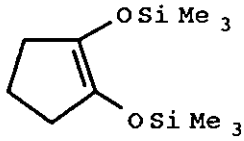
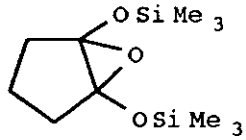
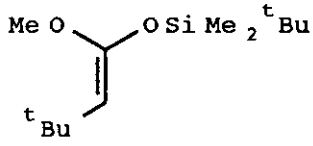
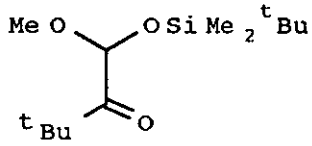
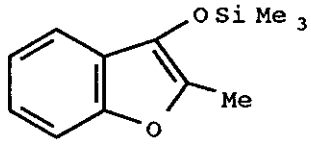
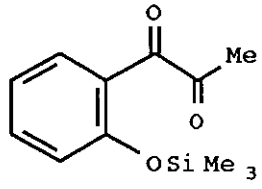
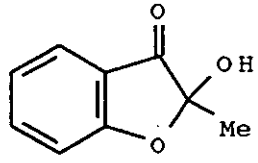
(57) $R^1=OCH_3$; $R^2=OCH_2CH_3$

(58) $R^1=OCH_3$; $R^2=OCH_2CF_3$

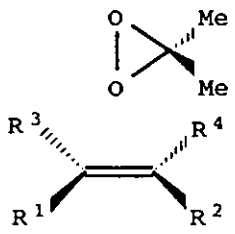
(Scheme 18)

Recent examples, of the ability of dimethyldioxirane to oxidise alkenes under extremely mild conditions, show how highly labile epoxides with two electron donating substituents can be isolated. O-Tetrabenzyl glycal (**59**) and 1,2-bis(trimethylsiloxy)alkenes (**61**) afford the epoxides (**60**) and (**62**) in high yields whilst the intermediacy of the epoxides of silyl ketene acetal (**63**) and 2-methyl-3-trimethyl-siloxybenzo[b]furan (**65**) are inferred by the rearrangement products isolated (**64**), (**66**) and (**67**) respectively, (Table 1).[38]

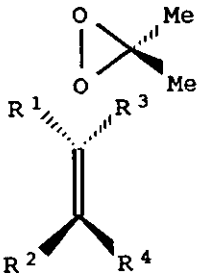
Table 1. *Oxidation of alkenes with two electron-donating substituents by* DMD/*acetone solution.*

Alkene	Product(s)	Yield %
 **(59)**	 **(60)**	100
 **(61)**	 **(62)**	97
 **(63)**	 **(64)**	100
 **(65)**	 **(66)**	72
	 **(67)**	28

The mechanism for the epoxidation process can be considered in terms of two types of transition state. For electrophilic oxygen atom transfer the possibilities are either a planar or a spiro transition state. Epoxidation by peroxyacids is generally viewed as being a cyclic planar concerted process ("butterfly" transition state),[39] where generally an increasing number of alkyl substituents in the alkene increases the reactivity.



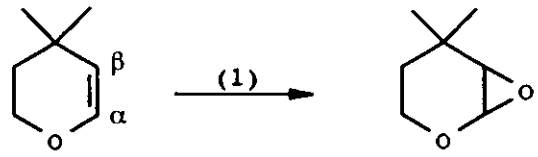
PLANAR



SPIRO

Epoxidations using dimethyldioxirane show many anomalies. Some trisubstituted alkenes have been found to be of greater reactivity than the tetrasubstituted derivatives whilst disubstituted trans-alkenes are eight times less reactive than their cis isomers. These observations would seem to favour the spiro transition state where steric interactions would become important. The cis/trans selectivity shown by dimethyldioxirane would also support the spiro arrangement as one side of cis-alkenes can be approached preferentially.[40]

Recent work by Murray and co-workers studying the oxidation of 4,4-dimethyldihydropyran **(68)** with dimethyldioxirane has shown that an unsymmetrical transition state may be involved for the epoxidation. Deuterium isotope effects were measured to determine whether the greater electron density at the β position (C-5) in the alkene has an influence on the manner in which the epoxidation proceeds. The results indicated that the reaction is a nonsynchronous concerted process and the mechanism did not involve a symmetrical transition state[41] (Scheme 19).

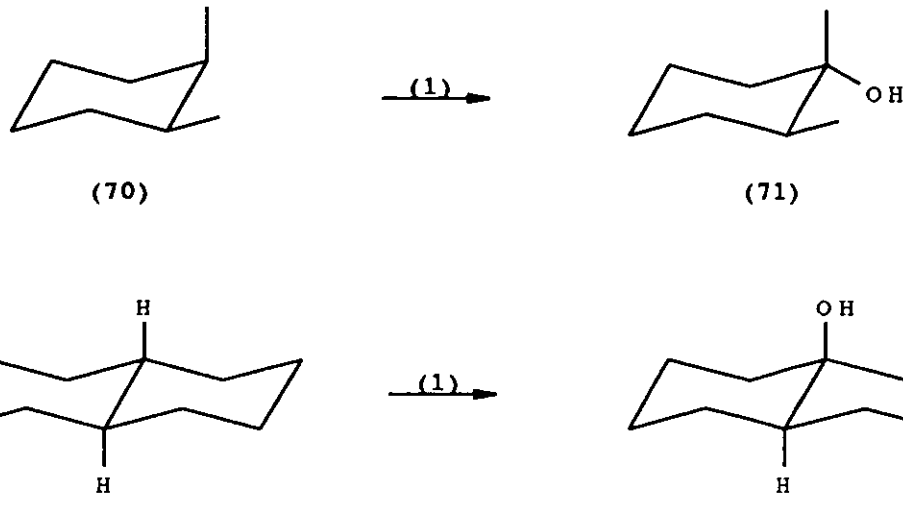


(68) (69)

(Scheme 19)

1.3 Oxidation of carbon-hydrogen bonds.

One of the most unusual oxidations which can be performed is the direct oxidation of carbon-hydrogen bonds. It was shown by Murray, soon after he had been able to isolate dimethyldioxirane as a solution in acetone, that oxygen atom insertion into carbon-hydrogen bonds of hydrocarbons was possible to give the corresponding alcohol or products arising from further oxidation. The oxidation of aldehydes to carboxylic acids and polycyclic aromatic hydrocarbons to arene oxides[42] had been noted previously but the interesting feature of the aliphatic hydrocarbon oxidation was that it occurred stereospecifically with retention. Using dimethyldioxirane in acetone solution it was possible to convert toluene to benzaldehyde,[43] aldehydes to carboxylic acids,[44] cyclohexane to cyclohexanol and cyclohexanone, 1,2-dimethylcyclohexane (**70**) to 1,2-dimethylcyclohexanol (**71**) and trans-decalin (**72**) gave trans-decanol (**73**) only[43] (Scheme 20).



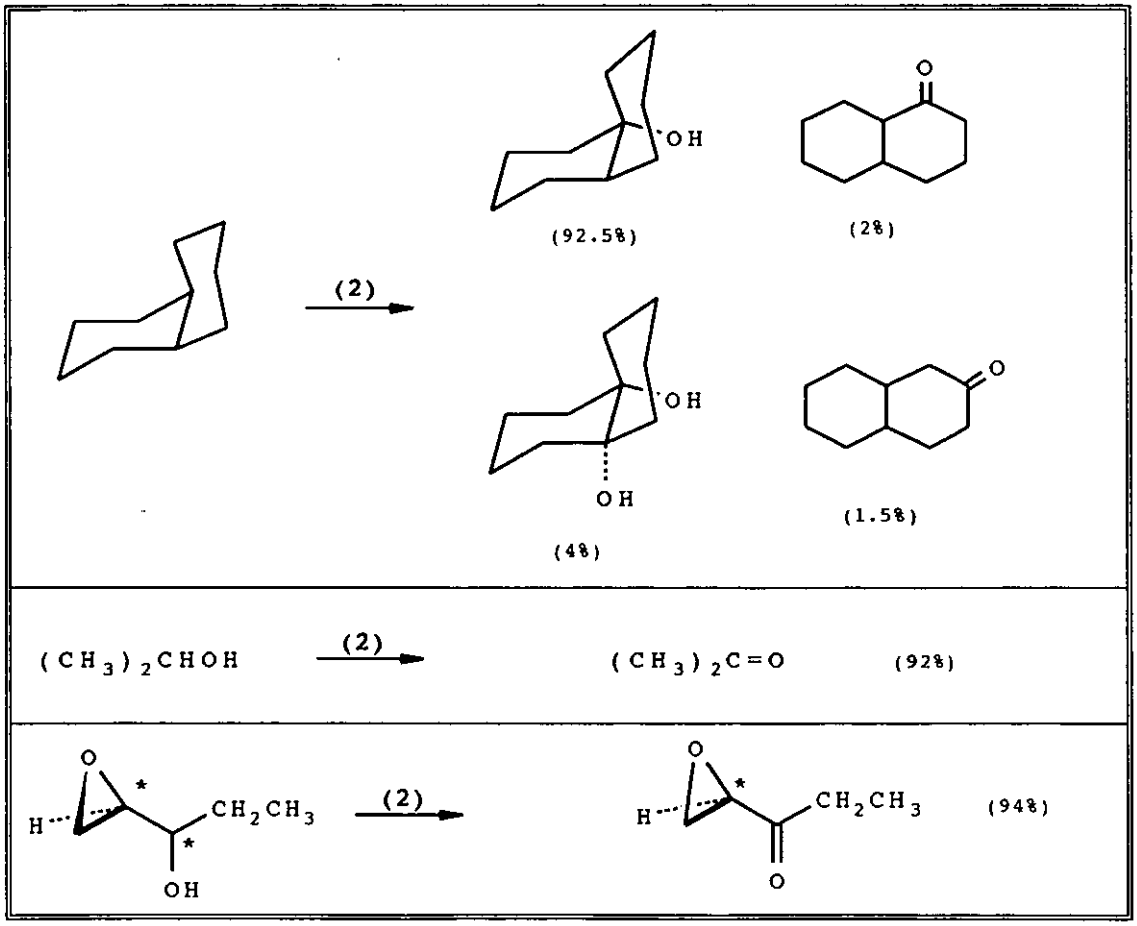
(70) (71)

(72) (73)

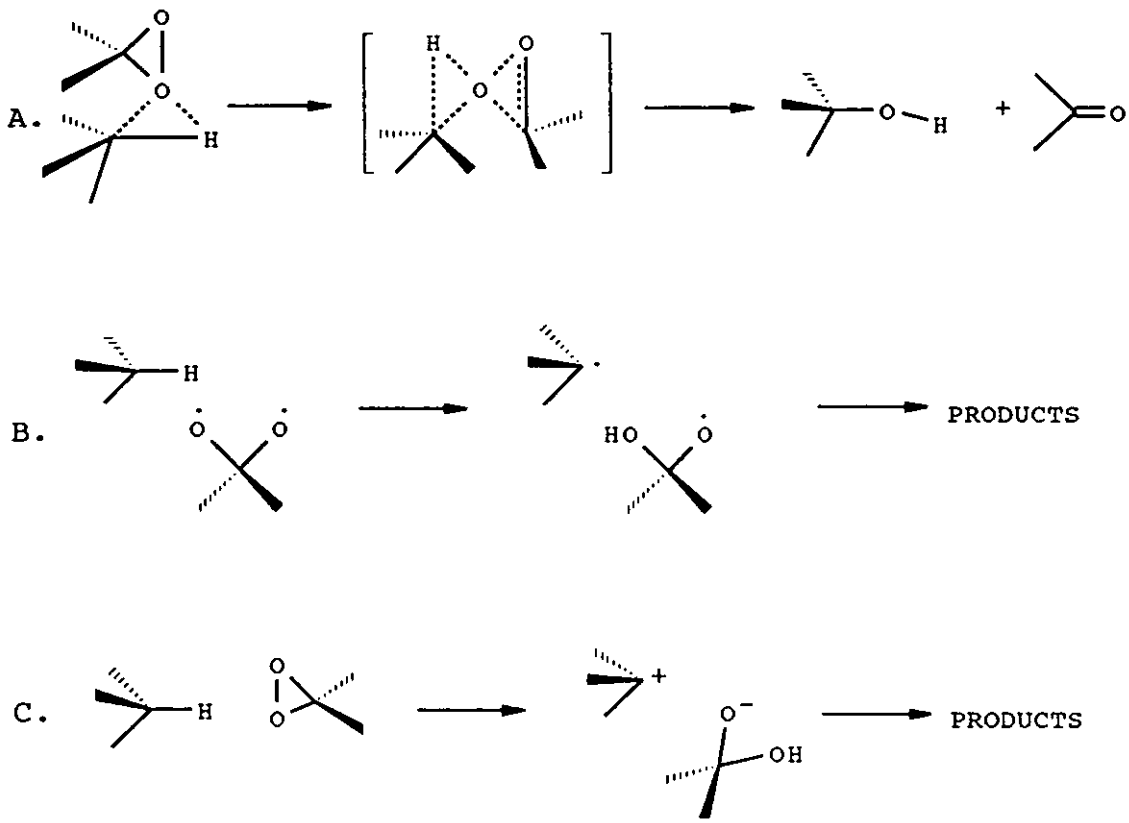
(Scheme 20)

The oxidation of alkanes is slower than epoxidations using dimethyldioxirane hence application of methyl(trifluoromethyl)dioxirane to these reactions was an important step forward. Curci and co-workers were able to oxidise a wide range of alkanes and alcohols using the more reactive dioxirane, where typical reaction times were less than 2 hours. A significant feature of the reaction is the high regioselectivity which is shown by the preferential oxidation of tertiary C-H bonds over secondary C-H bonds with few exceptions. High retention of configuration is observed whilst equatorial C-H bonds are oxidised in preference to axial C-H bonds.[26] The mild but extremely powerful oxidising ability of methyl(trifluoromethyl)dioxirane to convert alcohols into ketones has shown[45] that this reagent can be considered complementary if not an alternative to more traditional reagents. The neutral conditions under which substrates can be oxidised may be advantageous over transition metal and dimethyl sulphoxide based methods where acidic or alkaline conditions may be unavoidable, (Table 2).

Table 2. *Oxidations of alkanes and alcohols using methyl(trifluoromethyl)dioxirane* **(2)**.

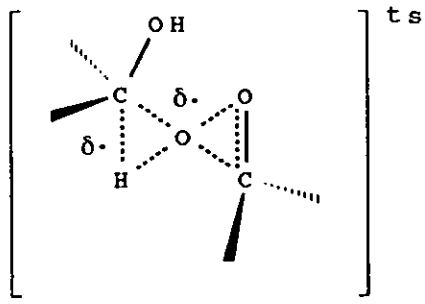


The mechanism for the oxygen atom insertion into carbon-hydrogen bonds is still very much speculative but enough understanding has been achieved to date, such that reasonable postulations can be made. A concerted "butterfly" type transition state **(A)** has been proposed for the oxygen insertion process into the C-H of alkanes. However other processes could occur, involving radicals **(B)** or ionic species **(C)**[26] (Scheme 21).



(Scheme 21)

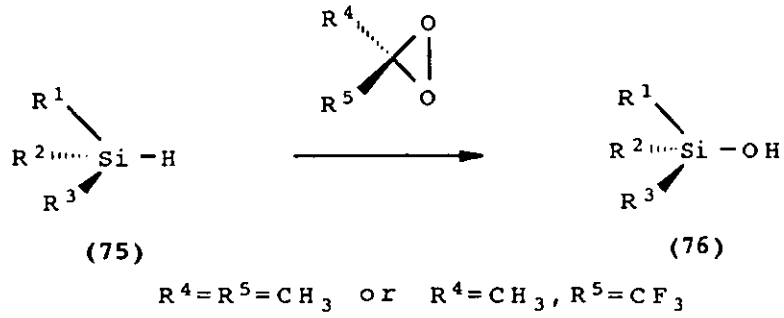
Kinetic experiments have shown that the oxidation is second-order, (first order with respect to the substrate and first order for the dioxirane). Deuterium isotope effect values indicate that the C-H bond which is α to the hydroxyl group is broken in the rate determining step. The most likely mechanism would involve O-atom insertion into the C-H bond where the possibility of partial radical formation may occur in the transition state **(74)**.[45]



(74)

1.4 Oxidation of silicon-hydrogen bonds.

Analogous to the oxidation of alkanes is the O-atom insertion into Si-H bonds. Recent work[46] has shown that silanes (**75**) can be converted directly and quantitatively in a highly stereoselective manner to silanols (**76**) using dioxiranes. Competition experiments have confirmed that Si-H is oxidised much more easily than C-H to the corresponding hydroxylation products. This could be primarily due to the fact that Si-H bonds are weaker than C-H bonds. The reaction may proceed by a mechanism similar to the "butterfly" transition state proposed for O-atom insertion into C-H bonds. It is considered unlikely, that silyl radicals are involved as complete retention of configuration is maintained in the oxidation (Scheme 22).



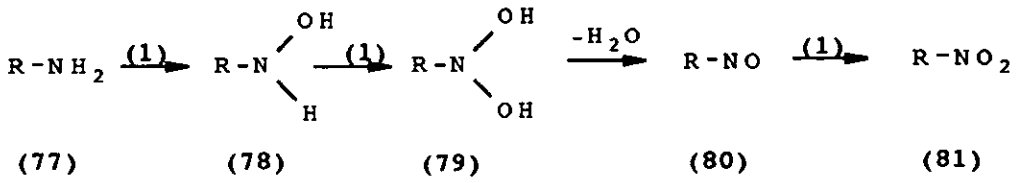
(75) (76)

$R^4=R^5=CH_3$ or $R^4=CH_3, R^5=CF_3$

(Scheme 22)

1.5 Oxidation of nitrogen-containing compounds.

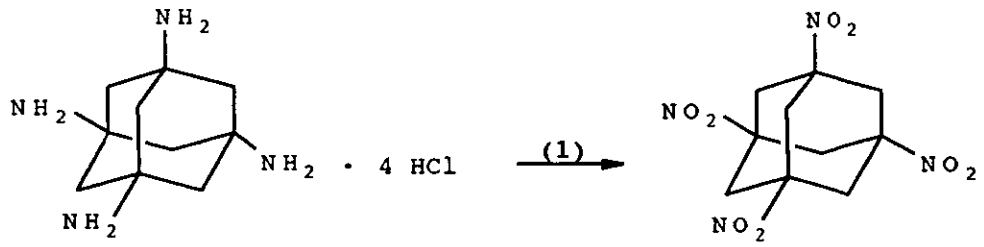
Primary amines (77) can be oxidised by dioxiranes to nitro compounds (**81**) in a stepwise manner via the hydroxylamine (**78**) and nitroso compounds (**80**)[47,48] (Scheme 23).



(77) (78) (79) (80) (81)

(Scheme 23)

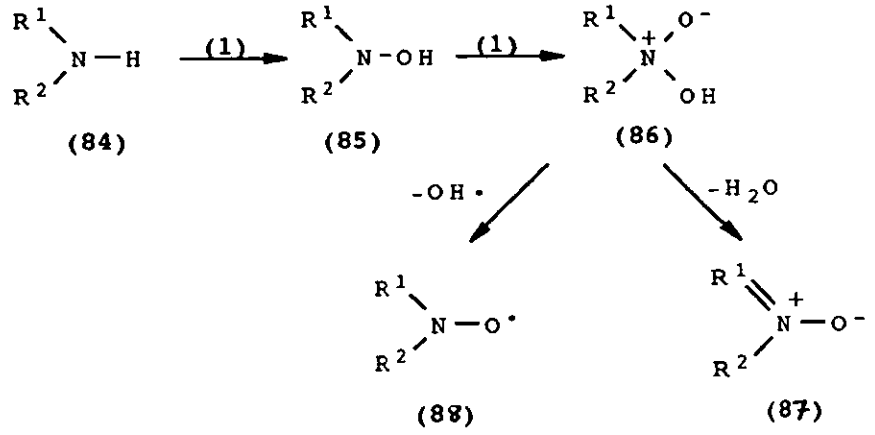
A useful variation has been described whereby amine hydrochlorides can be converted directly to nitro compounds. An interesting example is the oxidation of 1,3,5,7-tetraaminoadamantane tetrahydrochloride (**82**) to the corresponding tetra-nitro compound (**83**)[1] (Scheme 24).



(82) (83)

(Scheme 24)

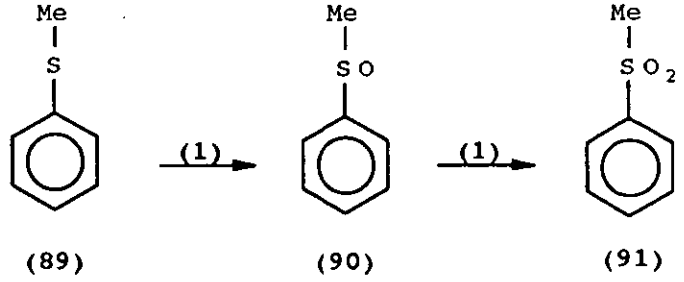
If equimolar quantities of dioxirane (**1**) and a secondary amine (**84**) are reacted the hydroxylamine (**85**) is formed. Addition of a second mole of dioxirane leads to the intermediate (**86**) which gives rise to the nitrone (**87**) if α-hydrogens are present, whereas the nitroxide (**88**) is formed if there are no α-hydrogens. Aromatic nitrogen containing compounds, such as pyridines lead to formation of the N-oxide whilst tertiary aliphatic amines are oxidised by dimethyldioxirane to amine oxides[49] (Scheme 25).



(Scheme 25)

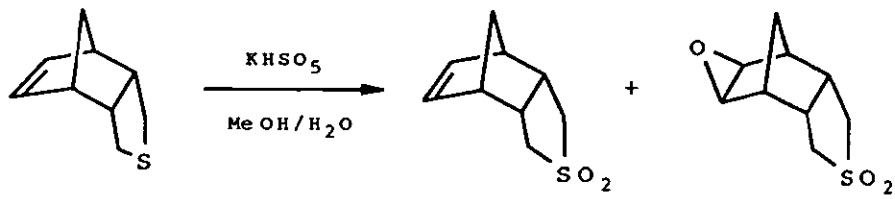
1.6 Oxidation of sulphur-containing compounds.

Sulphur nucleophiles such as sulphides, are oxidised by dioxiranes to sulphoxides and sulphones. The reaction is stepwise such that initially the sulphoxide is formed which on reaction with a further mole of dimethyldioxirane can be converted to the sulphone. A very interesting feature of dimethyldioxirane is the high degree of nucleophilic character which it exhibits. This is unusual as the majority of oxidations which it effects suggest the dioxirane is an electrophile. A simple example is the oxidation of phenyl methyl sulphide (**89**) which is converted to the sulphoxide (**90**) and sulphone (**91**) very rapidly[50] (Scheme 26).



(Scheme 26)

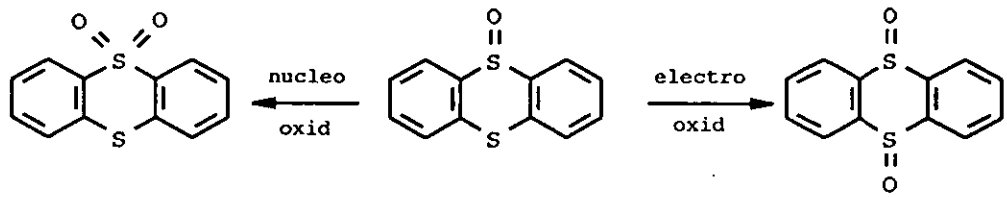
It is interesting to note that if a biphasic oxidation system is used where potassium monoperoxysulphate is present oxidation of the sulphide could occur without the presence of a ketone, hence with no involvement of a dioxirane. Bloch and co-workers[51] have reported the oxidation of 4-thiatricyclo[5.2.1.0]dec-8-ene (**92**) with Oxone at room temperature in methanol/water mixture at pH 6. The corresponding epoxy-sulphone (**94**) was formed (Scheme 27).



(92) (93) (94)

(Scheme 27)

The application of dioxiranes has proved to be more than merely another method for the oxidation of sulphur compounds. Adam and co-workers have designed a reaction system which allows the distinction between dioxiranes, carbonyl oxides and other oxidants to be made.[52,53] For this study thianthrene 5-oxide (SSO) (**95**) was used as a mechanistic probe. Intramolecular competition reactions were performed to assess the level of electrophilic character each oxidant possessed (Scheme 28).



(97) (95) (96)

(Scheme 28)

Oxidants which reacted at the sulphide centre to give the bis-(sulphoxide)(SOSO) (**96**), preferentially, are considered to be electrophilic. Nucleophilic character is evident for oxidants which primarily react at the sulphoxide site to give the sulphone (SSOO) (**97**) The electronic character for each oxidant was measured on a numerical scale (X_{so} scale; defined as the fraction of nucleophilic attack of (SSO), the values varied between 0 and 1, moving from electrophilic to nucleophilic character respectively. A general trend for the reactivity is as follows.

NUCLEOPHILIC ELECTROPHILIC

X_{so}= (1.0) (0.0)

Carbonyl oxides - Dioxiranes - Ozone - Peroxyacids - Free radicals

1.7 Concluding remarks.

The chemistry of dioxiranes has advanced considerably over the past 15 years. The work has developed from some early postulations, that dioxiranes could be intermediates in some oxidation processes to the development of methodology to isolate and characterise solutions of these unusual species. It is clear that this is perhaps only the beginning of a new and significant area of organic chemistry. Our aims are to address and investigate some of the mechanistic and synthetic aspects of dioxiranes. A thorough understanding of the way in which dioxiranes react, would be important for the development of some synthetic applications. We intend to look at the selectivity exhibited by a range of dioxiranes for the oxidation of a variety of substrates not previously investigated.

CHAPTER 2

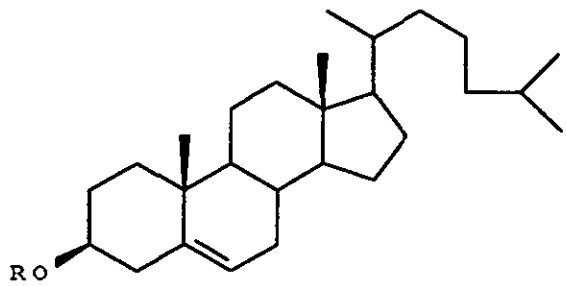
CHAPTER 2.

Dioxirane Mediated Oxidation Of Δ^5 Steroids.

The electrophilic nature of the epoxidation of relatively simple alkenes using dioxiranes has been established. Work by Baumstark[40] has suggested that a spiro transition state may be involved. However a change to a planar transition state has not been ruled out as the energy gap is thought to be small.

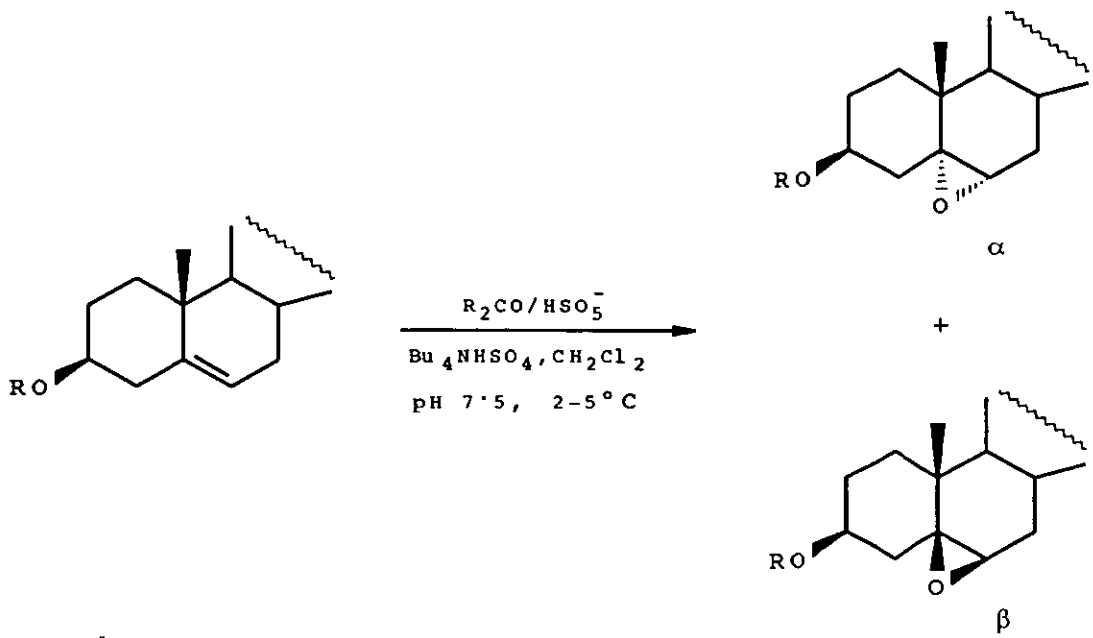
2.1 Oxidation of Δ^5 steroids using a range of dioxiranes.

Our aims were to epoxidise more complex steroidal alkenes (**98-100**) with a range of dioxiranes in an attempt to obtain more mechanistic information. The alkenes were oxidised using dioxiranes which were generated *in situ*[18] using a biphasic dichloromethane/buffered water system, containing the ketone, potassium mono-peroxysulphate and a catalytic amount of tetrabutylammonium hydrogen sulphate as phase transfer catalyst. The pH was maintained at 7.5 to allow efficient dioxirane formation.



(98) R=H
(99) R=OAc
(100) R=OBn

The biphasic oxidation of Δ^5-steroids gave a mixture of α- and β-epoxides in a ratio of about 1:1 (Scheme 29). This result is significantly different from that obtained by peroxyacids, where a ratio of about 4:1 is expected. The 5,6-epoxides were obtained in high yield and the α:β ratio was determined by integration of the C6-proton in the ^1H NMR spectra. The characteristic chemical shifts[54] are as follows; α-epoxide δ 2.9ppm and β-epoxide δ 3.1ppm. The results obtained are shown in table 1.



(Scheme 29)

Table 1. *Epoxidation of alkenes using a range of dioxiranes derived from the ketone/caroate system.*

Steroid	Ketone	α:β Epoxide ratio	Yield %
Cholesterol	Acetone	50:50[d]	90
Cholesterol	Cyclohexanone	55:45	59
Cholesterol	2-Methylcyclohexanone	35:65	70
Cholesterol	2-Hydroxy-2-methylcyclohexanone	40:60	37[a]
Cholesterol	Ethyl pyruvate	64:36	83
Cholesterol	α,α,α-Trifluoroacetophenone	48:52	crude[b]
Cholesterol	4'-Fluoroacetophenone	46:54	crude[b]
Cholesteryl acetate	Acetone	40:60	86
3-Benzyloxy-cholesterol	Isolated dimethyldioxirane/Acetone solution [c]	57:43	crude

a. Yield low due to cleavage of ketone.

b. α:β epoxide ratio determined by 250MHz ^{1}H NMR of crude product.

c. 1.0 Equivalent of DMD/acetone solution used.

d. Mean ratio of several experiments.

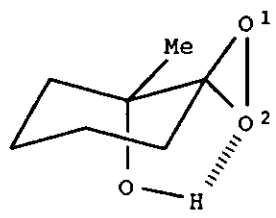
The acetone/caroate system was used initially to epoxidise cholesterol (**98**). Complete conversion to 3β-hydroxy-5,6-epoxycholestane in 90% yield with a mixture of α- and β-epoxides was achieved. From ^{1}H NMR integrations, the α:β ratio was determined, ensuring that the value obtained in the purified product compared satisfactorily with that in the crude. Several repetitions of this reaction have shown consistently the ratio of epoxides to be in the order of 50:50. This result suggested that dimethyldioxirane was able to approach the more sterically hindered β face as efficiently as the α face.

We thought that if the bulk of the dioxirane was increased steric factors may become important and oxidation on the more hindered β face may be less.

Oxidation with the *in situ* generated dioxirane of cyclohexanone (**101**) allowed 100% conversion of cholesterol in five hours to give 3β-hydroxy-5,6-epoxycholestane (59%; α:β 55:45). A large proportion of the cyclohexanone was converted to ε-caprolactone (**102**) highlighting the significance of Baeyer-Villiger oxidation as a competing process to dioxirane formation.

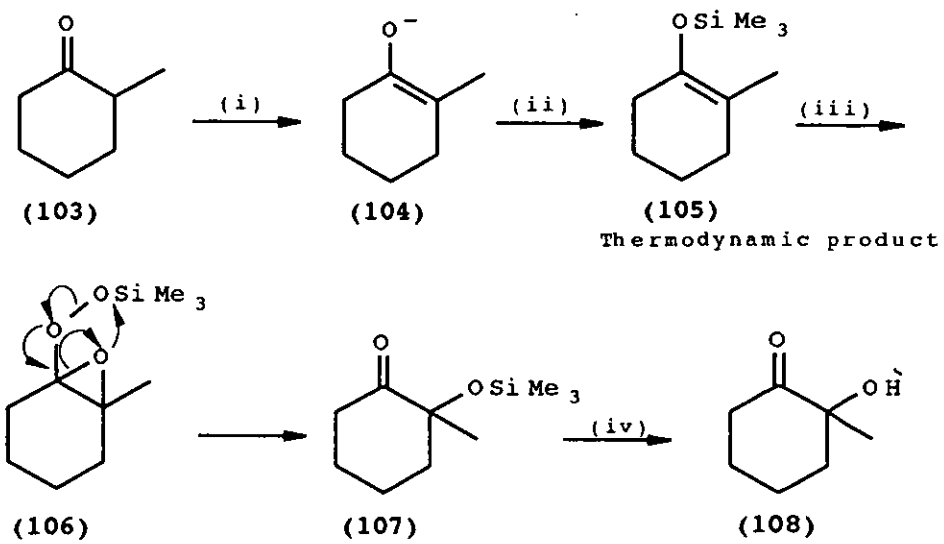
Similarly cholesterol was epoxidised with the 2-methylcyclohexanone (**103**)/caroate system. A 15:1 excess of the ketone was used and complete conversion of cholesterol was achieved in 26 hours. A mixture of α- and β-epoxides (α:β 35:65) was obtained in 70% yield.

It was evident that the rate of epoxidation becomes slower as the bulk of the substituent α to the carbonyl is increased. However it was interesting to observe that the α:β ratio is not changed significantly. A high proportion of β epoxide was evident in all cases. In an attempt to improve the rate of reaction, the introduction of a hydroxyl group at C-2 in 2-methylcyclohexanone was considered interesting. If there was an increase in the water solubility of this compound, then the efficiency of the caroate transfer to the ketone may be improved. Also it was considered interesting to determine whether the hydroxyl group could hydrogen bond to one of the dioxirane (**109**) ring oxygen atoms (O^2) This could allow the selective delivery of the non-hydrogen bonded oxygen atom (O^1) to the alkene.



(109)

2-Hydroxy-2-methylcyclohexanone (**108**) was synthesized from 2-methylcyclohexanone (**103**). The silyl enol ether (**105**) (88%) was prepared[55] by reaction of *in situ* generated iodotrimethylsilane with the enolate (**104**) of 2-methylcyclohexanone. Epoxidation of the silyl enol ether (**105**) using m-chloroperoxybenzoic acid in hexane followed by non-aqueous work-up gave the α-siloxy ketone (**107**) which was then hydrolysed using tetrabutylammonium fluoride to give 2-hydroxy-2-methylcyclohexanone (**108**)[56] (Scheme 30).

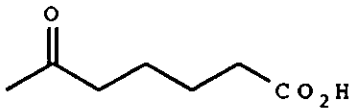


(i) $(C_2H_5)_3N$ (ii) $(CH_3)_3SiCl$, CH_3CN/NaI (iii)mCPBA/hexane (iv) Bu_4NF

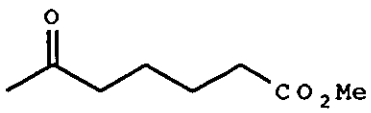
(Scheme 30)

2-Hydroxy-2-methylcyclohexanone (**108**)*/caroate system.*

Cholesterol(**98**) was reacted in this system. The reaction was monitored by TLC which showed formation of 3β-hydroxy-5,6-epoxycholestane. However, somewhat unexpectedly, it was evident that the α-hydroxy ketone (**108**) was decreasing in concentration. The reaction was stopped after 6 hours as there was no evidence of (**108**) in the organic phase. Work-up of the reaction gave a mixture of epoxides (37% yield; α:β 40:60) and unreacted cholesterol. Acidification and extraction (diethyl ether) of the aqueous phase gave rise to a compound containing a carboxylic acid functional group. The ^1H NMR spectrum indicated a deuterium oxide exchangeable proton at δ 11.2 ppm and a methyl ketone at δ 2.1 ppm. The structure (**110**) was preliminarily assigned.

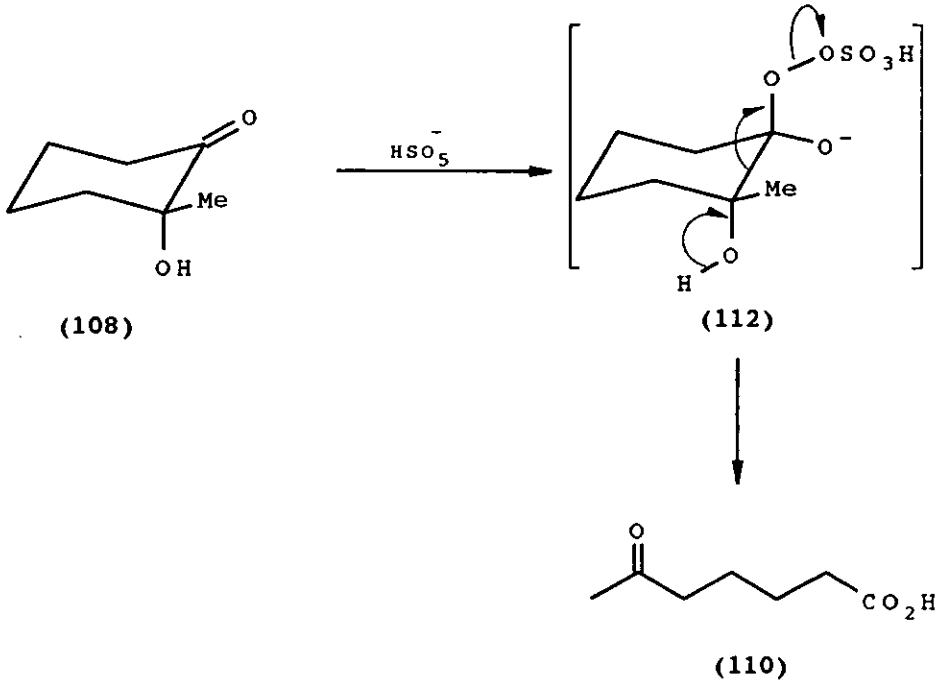


(110)



(111)

A reaction using the 2-hydroxy-2-methylcyclohexanone/caroate system without the presence of an alkene was performed. The pH was maintained at 7.5 and monitored by TLC. After 3 hours no compound corresponding to **(108)** was evident. Work-up gave the keto-acid **(110)**. This was allowed to react with diazomethane to form **(111)** which showed in the ^1H NMR spectrum a singlet (δ 3.7 ppm) indicative of a methyl ester. The IR and ^1H NMR spectra were identical to literature data[57] for methyl 6-oxo-heptanoate **(111)**. The carboxylic acid was thus identified as being 6-oxo-heptanoic acid **(110)**. Formation of **(110)** could be accounted for by a Grob type fragmentation[58] of the intermediate **(112)**. The Criegee intermediate **(112)** would be formed in the usual manner. However, it is presumed that the stereochemistry may be aligned for anti-elimination allowing ring opening to occur to give **(110)** (Scheme 31).



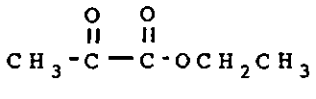
(108) (112) (110)

(Scheme 31)

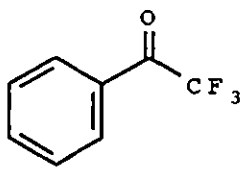
From work by Curci and co-workers,[25] it is known that the oxidising ability of the dioxirane is improved by the introduction of the powerful electron withdrawing trifluoromethyl group, α to the dioxirane ring. We have investigated the generation and reactions of further novel electron-deficient dioxiranes derived from ethylpyruvate **(113)**, α,α,α-trifluoroacetophenone **(114)** and 4'-fluoroacetophenone **(115)**.

Cholesterol was epoxidised with the ethyl pyruvate **(113)**/caroate system. A 6.5:1 excess of the ketone was used and complete conversion was achieved within 6 hours. This afforded a mixture of epoxides in 83% yield, their ratio being determined by ^{1}H NMR (α:β 64:36).

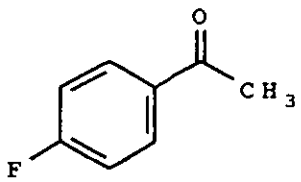
The α,α,α-trifluoroacetophenone **(114)**/caroate system was also used to oxidise cholesterol. 1.0 Equivalent of the ketone was used and a solution of Oxone (50 equivalents) was added over 6 hours. The reaction mixture was maintained at pH 7.5 for a further 18 hours. The ^{1}H NMR spectrum of the crude product revealed that 13% conversion to the epoxide had been achieved, (determined by comparison of the integrations of the C-6 proton of cholesterol and the C-6 oxirane protons). The ratio of α and β epoxides was found to be α:β 48:52. Similarly cholesterol was epoxidised using the 4'-fluoroacetophenone **(115)**/caroate system. 1.0 Equivalent of ketone and 173 equivalents of Oxone were used. The reaction was run for 21 hours and 42% conversion of cholesterol to the epoxide was achieved. The ratio of epoxides was found to be α:β 46:54.



(113)



(114)

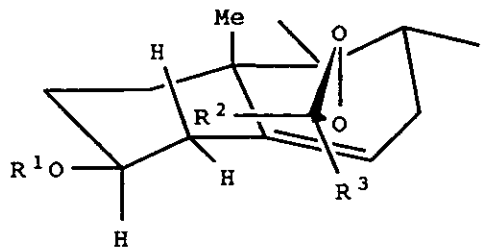


(115)

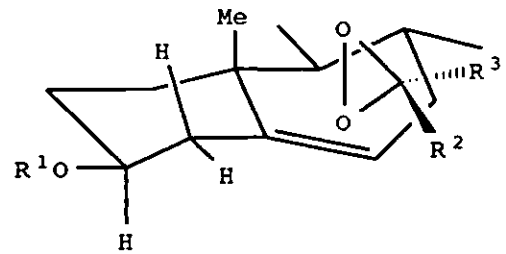
For all the ketone/caroate systems used a large amount of β-epoxide was formed. This prompted us to consider whether the 3β-hydroxyl of the steroid could perhaps, by hydrogen bonding, direct the approach of the dioxirane to the β-face. The 3β-acetoxy derivative **(99)** was allowed to react with the acetone/caroate system to give 3β-acetoxy-5,6-epoxycholestane **(99a)** (86% yield) with a α:β ratio of epoxides 40:60. Similarly 3-benzyloxycholesterol **(100)** was oxidised with a solution of dimethyldioxirane/acetone to give 3-benzyloxy-5,6-epoxycholestane **(100a)** α:β ratio of 57:43. No significant change in the amount of β-epoxide formed was observed.

2.2 Evidence for a spiro transition state for dioxirane epoxidations.

From models it can be shown that the dioxirane could approach the 5,6-double bond of the steroid in either a spiro or planar manner. The ratio of epoxides being close to 1 suggests that both faces of the steroid can be approached. The dioxirane could take up a spiro transition state without being too hindered. Conversely if the dioxirane approached in a planar manner (similar to peroxyacids) it too would suffer very little hindrance (Scheme 32).



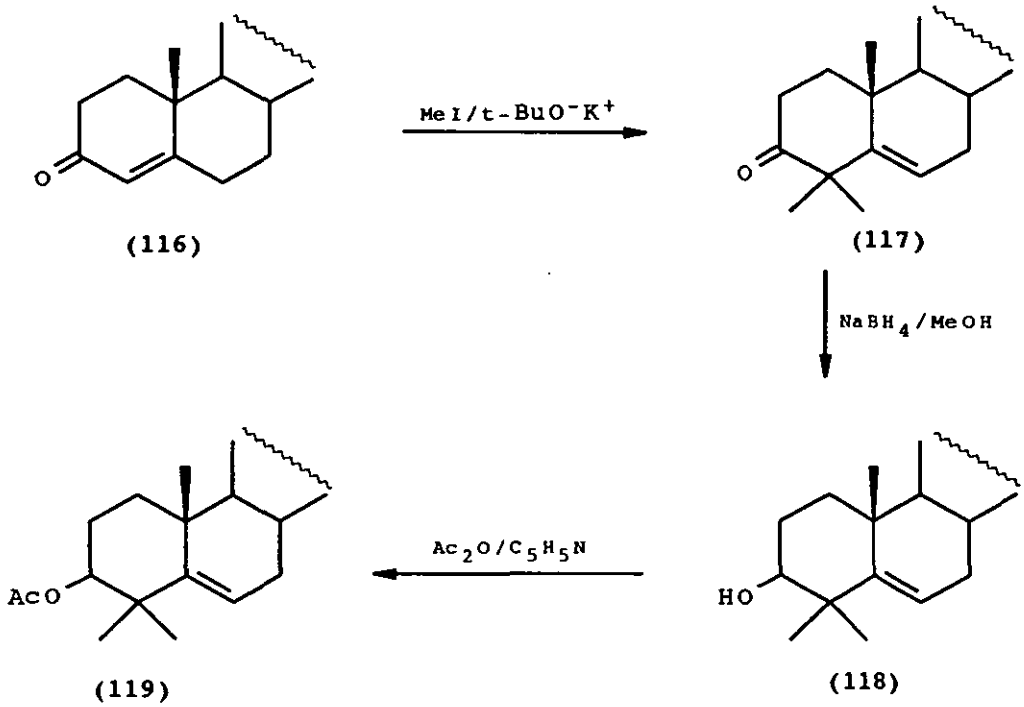
SPIRO



PLANAR

(Scheme 32)

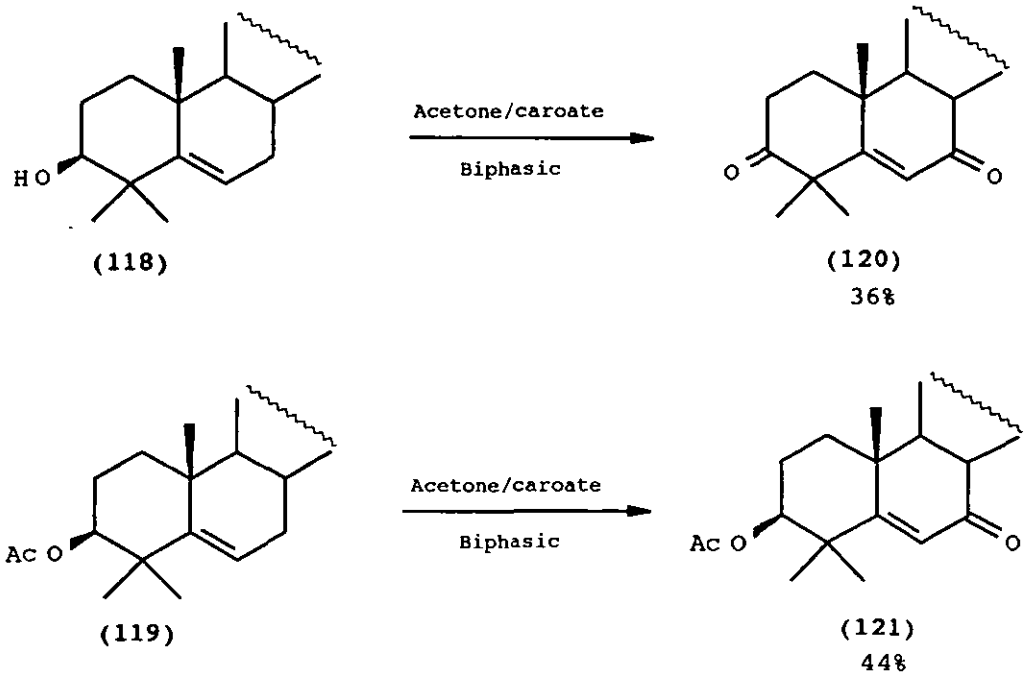
From the results thus far it was not possible to determine which transition state was involved. We decided a conclusive experiment would be to block the approach to the double bond for the spiro transition state by the introduction of geminal methyl groups at C-4. The likely distortion of the A-ring arising from steric interaction between the 10β-methyl and the 4β-methyl groups[59] would enhance the α-face hindrance to attack. This should still leave a planar approach unhindered. 4,4-Dimethylcholesterol **(118)** and 4,4-dimethylcholesteryl acetate **(119)** were prepared by the following procedure[60,61] (Scheme 33).



(116) (117) (118) (119)

(Scheme 33)

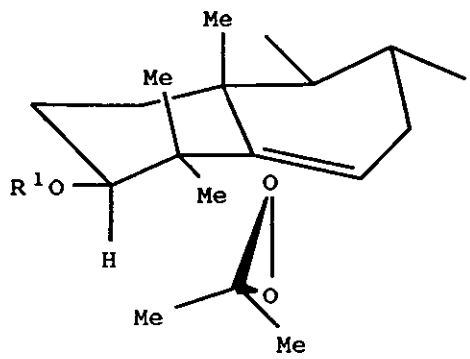
4,4-Dimethylcholesterol **(118)** and the acetate derivative **(119)** were allowed to react with dimethyldioxirane generated *in situ.* No epoxidation was evident in either case and instead allylic oxidation at C-7 occurred. This afforded 4,4-dimethyl-5-ene-3,7-dione **(120)**[62,63] in 36% yield and 4,4-dimethyl-7-oxocholest-5-en-3β-yl acetate **(121)**[62,63] in 44% yield respectively (Scheme 34).



(118) (120) 36% (119) (121) 44%

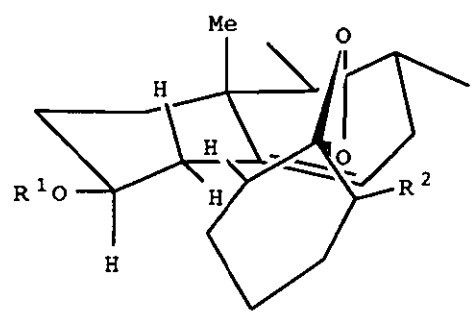
(Scheme 34)

Epoxidation of 4,4-dimethyl Δ^5-steroids is usually considered to be straightforward using peroxyacids,[64] where a planar transition state is involved for the oxidation. When the approach of dimethyldioxirane to the double bond is hindered, a change to a planar transition state is not favoured so oxygen atom delivery is not possible (Scheme 35).



(Scheme 35)

The results[65] are best explained by involvement of the spiro transition state for the epoxidation. In the absence of the geminal methyl groups at C-4, the steric interaction between the 4β-H or the 3α-H and the α-substituent of the dioxirane would seem to be more or less equivalent. The bulkier α-substituent of the dioxirane would be expected to take up the least congested position near C-6 of the steroid and hence the lack of sensitivity to the α:β ratio of epoxides obtained,with each dioxirane used (Scheme 36).



(Scheme 36)

CHAPTER 3

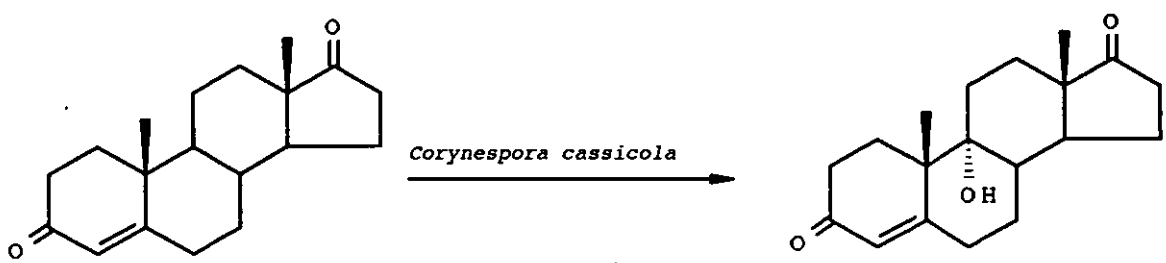
CHAPTER 3.

Oxidation Of Oestra-1,3,5(10)-trienes Using Dimethyldioxirane.

3.1 Introduction.

Our interesting observation that allylic C-H bonds can be oxidised in preference to a sterically hindered double bond, as described in the previous chapter,[65] prompted us to consider the oxidation of benzylic C-H bonds.[43,44]

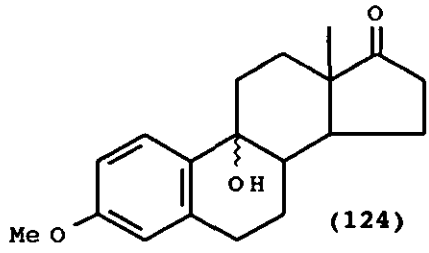
Steroids containing a non-aromatic A-ring can be hydroxylated at position 9 using microorganisms. 9α-Hydroxysteroids are used as key intermediates in the synthesis of 9α-halo-11β-hydroxysteroids. Selective 9α-hydroxylation methods are limited. An example is the conversion of androstenedione **(122)** into 9α-hydroxyandrostenedione **(123)** in >70% yield[66] (Scheme 37).



(122) **(123)**

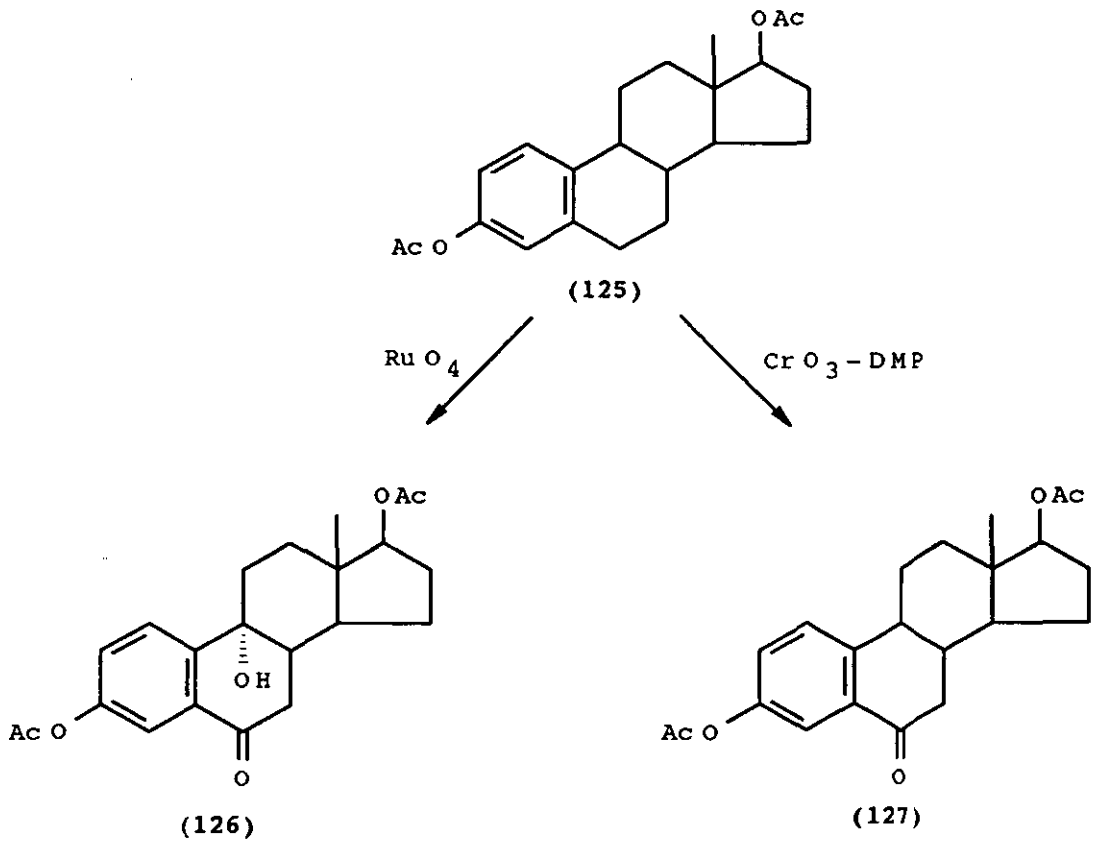
(Scheme 37)

Chemical methods are either low-yielding[67] or not very stereoselective.[68] The benzylic oxidation of 3-methoxy-oestra-1,3,5(10)-trienes has been achieved using a catalytic amount of tristriphenylphosphinerhodium chloride in the presence of oxygen gas. The 9α-hydroxy derivatives **(124)** were obtained in only 10-15% yield.[67] Similarly electrochemical oxidation in the presence of weakly nucleophilic solvents allowed the synthesis of 9-substituted compounds. The use of aqueous systems, eg; aqueous acetonitrile or N,N-dimethylformamide, as supporting electrolyte, gave 9-hydroxy derivatives but with poor stereoselectivity.[68]



(124)

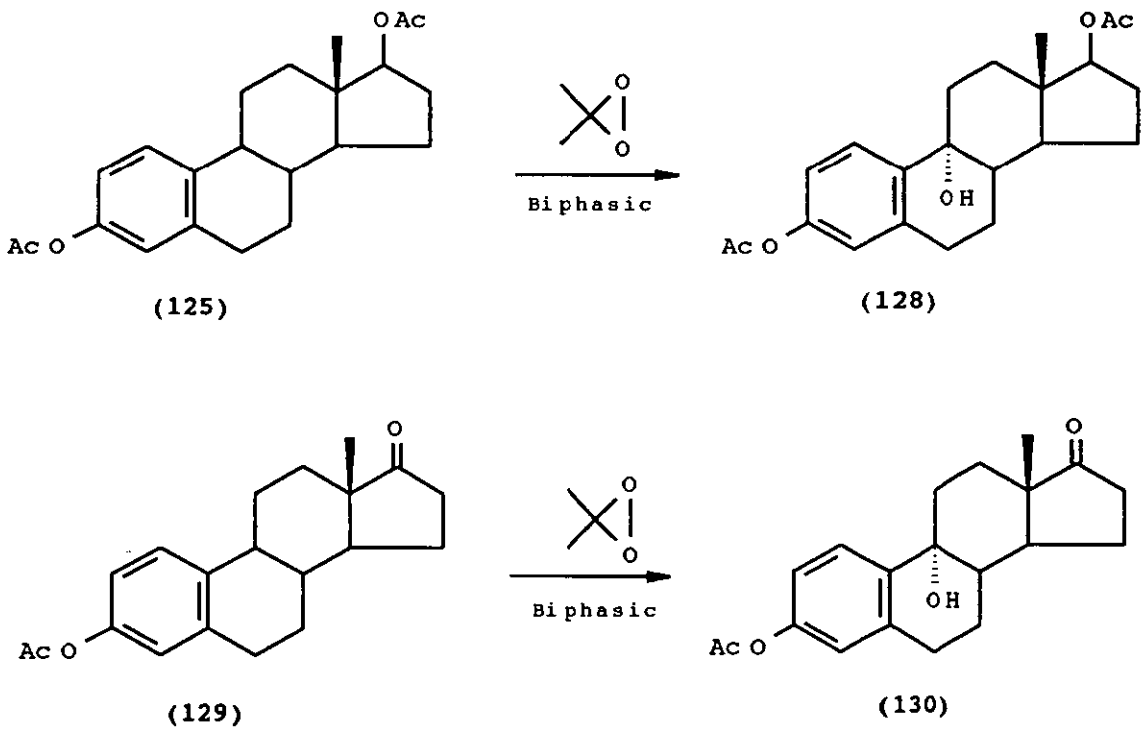
Oxidation of 3,17β-diacetoxy-oestra-1,3,5(10)-triene (**125**) by ruthenium tetroxide generated *in situ* from ruthenium dioxide and sodium periodate, gives 9α-hydroxy-6-ketotriene (**126**) as the major product.[69] However if chromium trioxide/3,5-dimethylpyrazole complex (CrO_3-DMP) is used, the 6-ketone (**127**) is obtained[70] (Scheme 38).



(Scheme 38)

3.2 Preparation of 9α-hydroxy-oestra-1,3,5(10)-trienes.

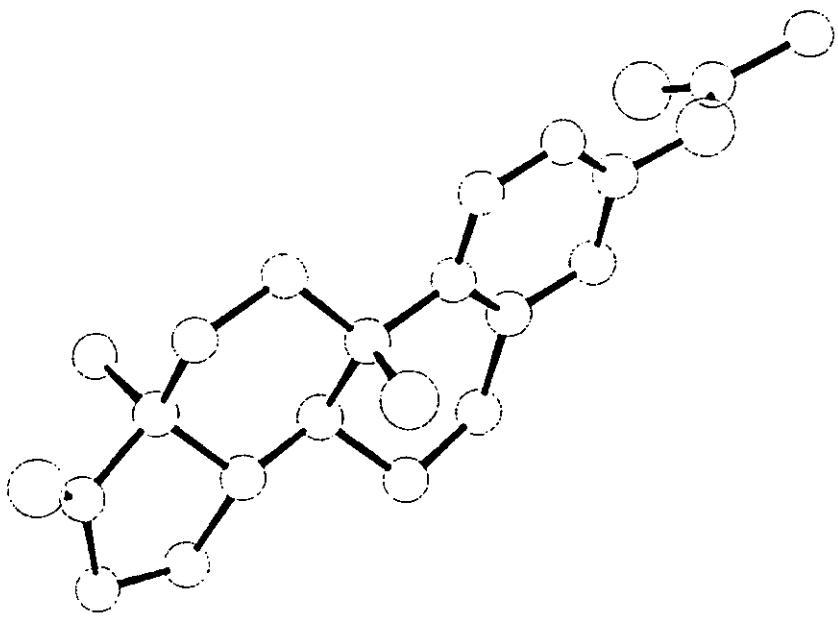
We now report the efficient hydroxylation of oestra-1,3,5,(10)-trienes at C-9 using dimethyldioxirane. 3,17β-Diacetoxy-oestra-1,3,5(10)-triene (**125**) and 3-acetoxy-oestra-1,3,5(10)-trien-17-one (**129**) were oxidised using *in situ* generated dimethyldioxirane.[71] The reactions were carried out in a biphasic dichloromethane/aqueous phosphate buffer system. The reaction conditions were maintained at pH7.5 and 0-5°C. The reactions were monitored by thin layer chromatography and in each case a compound more polar than the starting material was seen to form. The products were isolated by column chromatography. 3,17β-Diacetoxy-oestra-1,3,5(10)-triene (**125**) afforded 3,17β-diacetoxy-9α-hydroxy-oestra-1,3,5(10)-triene (**128**) in 75% yield and 3-acetoxy-oestra-1,3,5(10)-trien-17-one (**129**) gave 3-acetoxy-9α-hydroxyoestra-1,3,5(10)-trien-17-one (**130**) in 79% yield (Scheme 39).



(Scheme 39)

The products were fully characterised by standard methods. The infrared spectrum confirmed the presence of the hydroxyl group in (**128**) [3544cm^{-1}, nujol] and (**130**) [3672, 3592cm^{-1},dichloromethane]. Initially, the position of the hydroxyl group was determined by ^{13}C NMR. data. In both (**128**) [δ 69.87(C9), 42.62(C14), 41.24(C8)] and

(**130**) [δ 70.01(C9), 43.09(C14), 41.11(C8)] it seemed evident that the hydroxylation had occurred at position 9. The most important change[72] was the significant downfield shift (ca 25ppm) of the C9 signal, indicative of an oxygen atom bonded to a carbon atom. The downfield shift (ca 3ppm) of the C8 signal, and the upfield shift (ca 7ppm) of the C14 signal also suggested C9 hydroxylation. From ^{13}C NMR data alone it was not possible to determine the stereochemistry about C9. The assignment of the structure was finally confirmed by X-ray crystallographic analysis for compound (**130**)[73] and was indeed found to be the 9α-hydroxylated product.



X-ray structure for compound (**130**).

CHAPTER 4

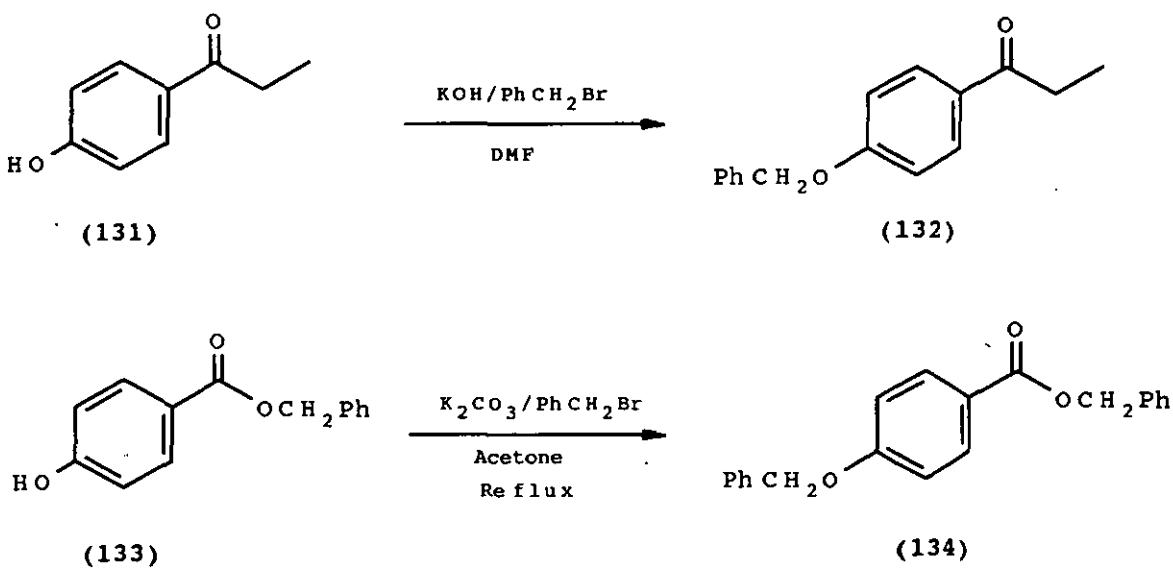
CHAPTER 4.

Benzylic Oxidations Using Dimethyldioxirane.

The selectivity shown by dimethyldioxirane towards the oxidation of benzylic hydrogens in oestra-1,3,5(10)-trienes **(125)** and **(129)**, as shown in chapter 3, prompted us to investigate other benzylic oxidations. We considered the oxidation of benzyl ethers to be of particular interest. If the benzylic methylene group could be oxidised to form the alcohol, then this would be expected to lead to cleavage of the benzyl group.

4.1 Oxidation of benzyl ethers.

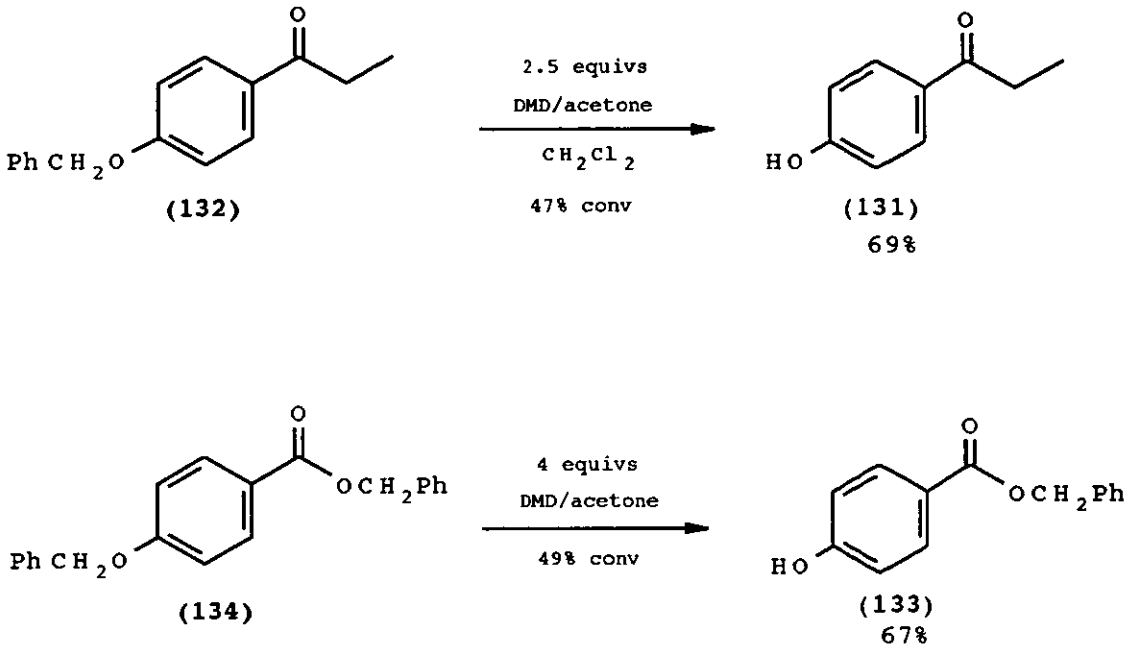
Initially two aromatic benzyl ethers were oxidised with dimethyldioxirane/acetone solution. 4-Benzyloxypropiophenone **(132)**[110] and benzyl 4-benzyloxybenzoate[120] **(134)** were prepared by reaction of the corresponding phenols **(131)** and **(133)** with benzyl bromide in the presence of a base (Scheme 40).



(Scheme 40)

4-Benzyloxypropiophenone **(132)** in dichloromethane was allowed to react with 2.5 equivalents of dimethyldioxirane/acetone solution. The mixture was allowed to stand at 20°C for 46 hours protected from light. TLC revealed the presence of two compounds. One corresponded to 4-benzyloxypropiophenone and the other, a more polar compound, to 4-hydroxypropiophenone **(131)**. Column chromatography afforded 4-hydroxy-propiophenone in 69% yield, based on 47% conversion of starting material **(132)**.

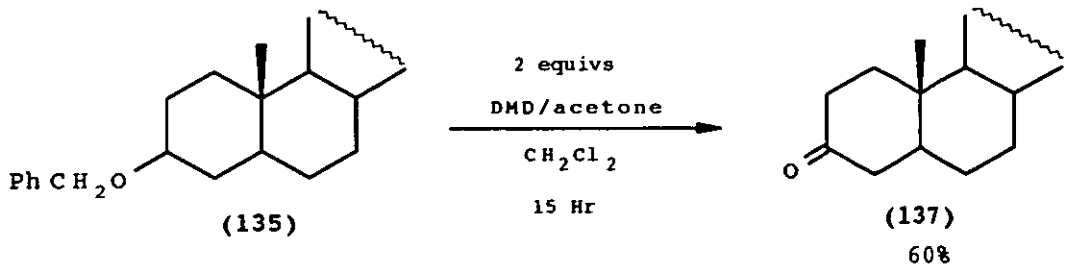
In a similar manner, benzyl 4-benzyloxybenzoate (**134**) in acetone solution was allowed to react with 4 equivalents of dimethyldioxirane. The mixture was allowed to react, protected from light, at 22°C for 48 hours. Chromatography afforded benzyl 4-hydroxybenzoate (**133**) in 67% yield, based on 49% conversion of starting material (**134**) (Scheme 41).



(Scheme 41)

It can be seen that benzyl ethers (**132**) and (**134**) are oxidised to their respective phenols quite cleanly. However, it is interesting to note that for the oxidation of benzyl 4-benzyloxybenzoate (**134**), the ester benzyl group is not oxidised.

We decided to extend this benzylic oxidation methodology to an aliphatic benzyl ether. 3-Benzyloxycholestane (**135**) was prepared,[74] by reaction of benzyl bromide with cholestanol (**136**) in the presence of sodium hydride. 3-Benzyloxycholestane in dichloromethane was then oxidised with 2 equivalents of dimethyldioxirane/acetone solution. The mixture was allowed to react at 22°C, protected from light, for 15 hours. TLC showed the presence of 3-benzyloxycholestane (**135**), cholestanol (**136**) and cholestan-3-one (**137**). From the crude ^{1}H NMR spectrum it was evident that cholestan-3-one was the main component of the mixture. Chromatography allowed the isolation of cholestan-3-one in 60% yield (Scheme 42).



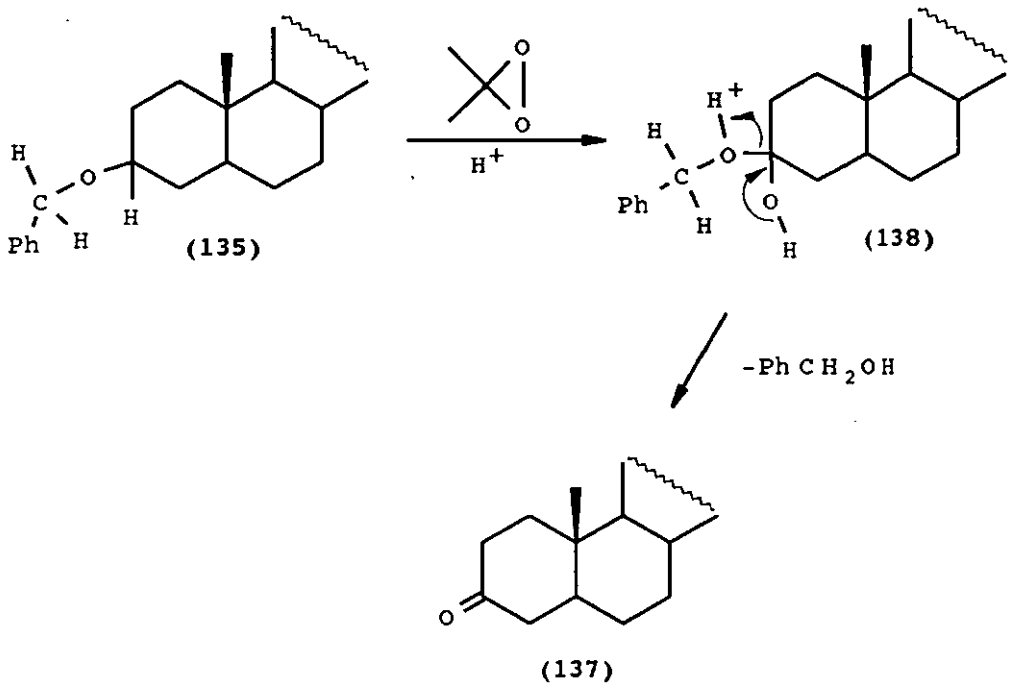
(Scheme 42)

To confirm the type of mechanism involved, the reaction was monitored by GLC. 3-Benzyloxycholestane **(135)** in dichloromethane was reacted with 1.0 equivalent of dimethyldioxirane. After 14 hours GLC showed the presence of 3-benzyloxycholestane **(135)**, cholestanol **(136)** and cholestan-3-one **(137)**. The relative percentage composition of the mixture for **(135)**, **(136)** and **(137)** was 38.3, 14.6 and 47.1%wt respectively. The formation of benzaldehyde was also confirmed by GLC.

It was interesting to observe that cholestan-3-one was the major product, and that cholestanol and benzaldehyde were also evident in small amounts. The presence of cholestanol and benzaldehyde, and the absence of any benzyl alcohol suggests that the mechanism involves insertion into the benzylic C-H bond (mechanism B). The alternative C-H insertion mechanism (Mechanism A) does not appear to operate not withstanding the observation that cholestanol may be oxidised to cholestan-3-one by a similar C-H insertion (see chapter 5). The low levels of cholestanol vs cholestan-3-one suggest that the oxidation of the alcohol is rapid relative to the benzylic C-H insertion. It is possible that hydrogen bonding facilitates the alcohol oxidation (see chapter 5).

Mechanism A.

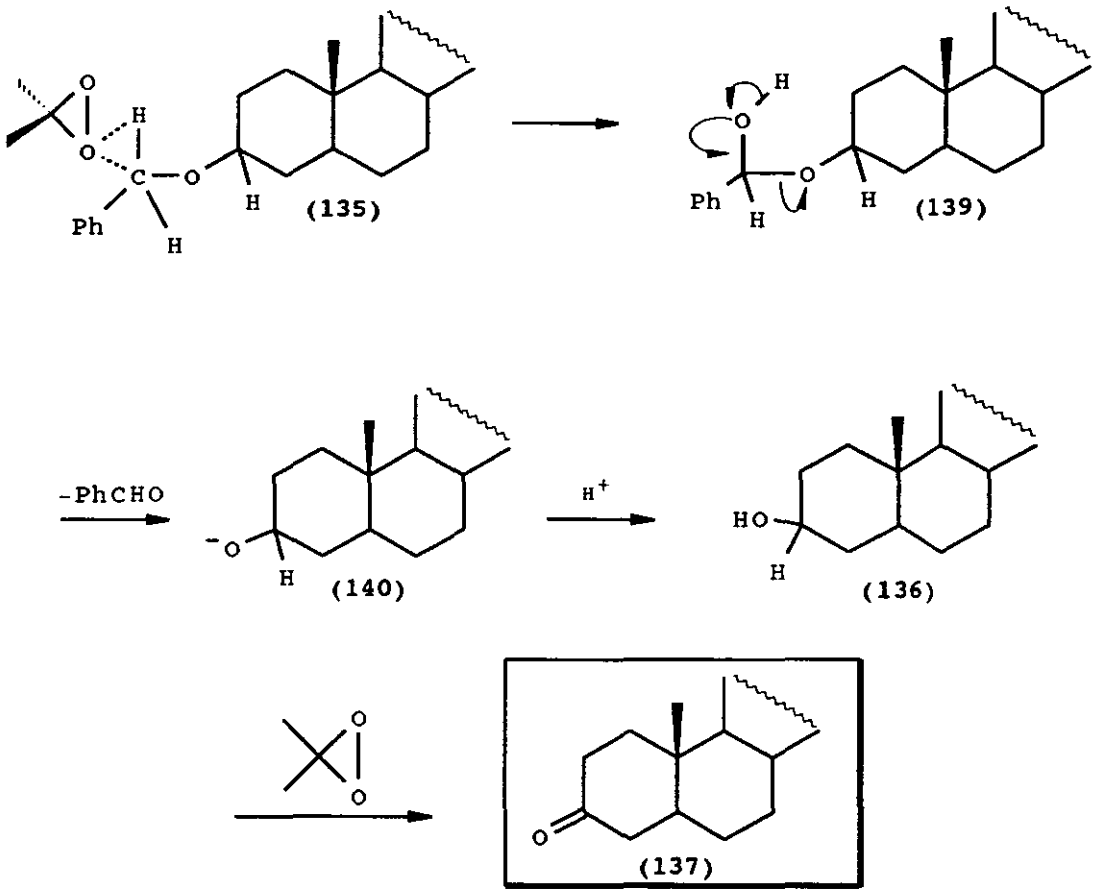
If the C-3 C-H bond of 3-benzyloxycholestane **(135)** were to be oxidised in preference to the benzylic position then only one molecule of dimethyldioxirane would be required. The intermediate **(138)** in protic conditions could eliminate a molecule of benzyl alcohol to give cholestan-3-one **(137)**.



(Mechanism A)

Mechanism B.

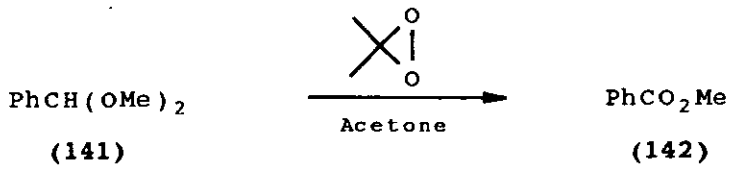
This would involve the oxidation of one of the methylene C-H bonds of the benzyl group of **(135)** by dimethyldioxirane. Formation of the alcohol **(139)** and elimination of benzaldehyde, with protonation of the resulting anion **(140)** would give cholestanol **(136)**. Oxidation of the C-3 C-H bond of cholestanol by a second molecule of dimethyldioxirane would afford cholestan-3-one **(137)**.



(Mechanism B)

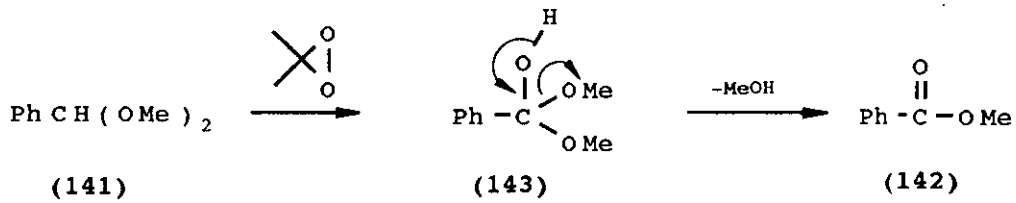
4.2 Oxidation of benzaldehyde dimethylacetal.

To investigate further the oxidation of benzylic hydrogens adjacent to an oxygen atom, we decided to consider the reaction of dimethyldioxirane with benzaldehyde dimethylacetal (**141**). Oxidation of the benzylic position would be expected to be preferred. Benzaldehyde dimethylacetal (**141**) was allowed to stand with 3.5 equivalents of dimethyldioxirane/acetone solution at 0-5°C for 24 hours protected from light. The reaction was monitored by GLC and the mixture was found to contain unreacted benzaldehyde dimethylacetal (**141**) (82%wt) and methyl benzoate (**142**) (18%wt). The mixture was allowed to stir for a further 24 hours at 22°C. After this time the mixture was found to contain benzaldehyde dimethylacetal (54%wt) and methyl benzoate (46%wt) (Scheme 43).



(Scheme 43)

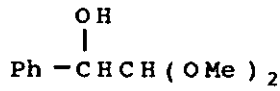
The formation of methyl benzoate was confirmed by GLC and by comparison of the ^1H NMR spectrum with that of an authentic sample of methyl benzoate. The reaction was clean but was seen to be rather slow at 0-5°C. The oxidation was repeated in the presence of dichloromethane as a co-solvent. 2.9 Equivalents of dimethyldioxirane/acetone solution was used and the reaction run for 24 hours at 0-5°C. The reaction was still found to be rather slow. The product mixture was found to contain benzaldehyde dimethylacetal (81%wt) and methyl benzoate (19%wt). The mechanism of the reaction would most likely involve an oxygen atom insertion into the benzylic C-H bond to form the alcohol **(143)** which could then eliminate a molecule of methanol to generate methyl benzoate (Scheme 44).



(Scheme 44)

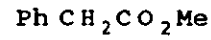
4.3 Oxidation of phenylacetaldehyde dimethylacetal.

A a further example of this type of reaction phenylacetaldehyde dimethylacetal **(144)** was oxidised. An interesting feature of this molecule is that it contains a benzylic methylene group in addition to the hydrogen atom on the carbon adjacent to the methoxy groups. Dimethyldioxirane is known to oxidise tertiary C-H bonds in preference to secondary C-H bonds. However, the fact that the methylene hydrogens are benzylic may alter the selectivity of the oxidation. Some of the possible products to consider are shown **(145)**, **(146)** and **(147)**.



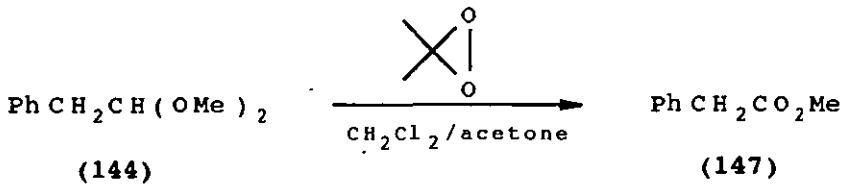
(145)

(146)



(147)

Phenylacetaldehyde dimethylacetal (**144**) in dichloromethane was allowed to react, protected from light for 43 hours, with 5.0 equivalents of dimethyldioxirane/acetone solution. ^1H NMR and IR spectrum and GLC showed the presence of methyl phenylacetate (**147**) and unreacted phenylacetaldehyde dimethylacetal. The composition of the mixture was 65%wt and 35%wt for phenylacetaldehyde dimethylacetal and methyl phenylacetate respectively by GLC (Scheme 45).



(144) (147)

(Scheme 45)

The mechanism of the reaction would involve the preferential oxygen atom insertion into the methine C-H bond to form the alcohol from which a molecule of methanol would be eliminated. It is interesting to observe that the benzylic methylene is not oxidised under these conditions. The mechanistic implications of these and other C-H insertion reactions are discussed in chapter 5.

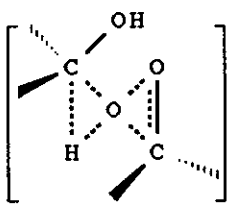
CHAPTER 5

CHAPTER 5.

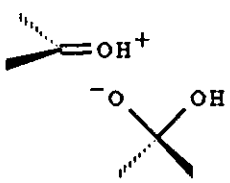
Oxygen Atom Insertions Into C-H Bonds Using Dimethyldioxirane.

5.1 Introduction.

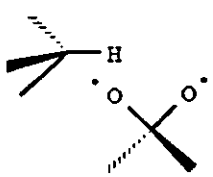
Perhaps one of the most interesting transformations which can be achieved using dioxiranes is the oxidation of alcohols to ketones. The oxidation of secondary alcohols is thought to proceed via an oxygen atom insertion into the C-H bond. The mechanism is still somewhat speculative but is thought to involve a "butterfly" transition state **(A)**. However, other mechanisms can be envisaged involving hydrogen atom abstraction where no transfer of oxygen from the dioxirane to the alcohol occurs **(B)**. Radicals could be implicated if the dioxirane were to exist as the oxygen diradical species **(C)**.[26,43,45]



(A)



(B)

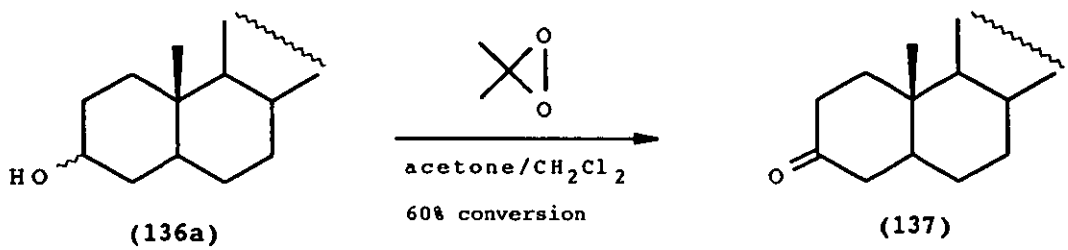


(C)

5.2 Oxidation of epimeric alcohols. *(Evidence for a difference in the rate of oxidation of equatorial and axial* C-H *bonds).*

It was considered of interest to investigate the oxidation of some steroidal alcohols and obtain further information about the mechanism. We decided to determine whether there was any selectivity in the oxidation of axial and equatorial alcohols using dioxiranes. Initially cholestan-3β-ol was oxidised using the biphasic system where dimethyl-dioxirane is generated *in situ.* A large molar excess of acetone over the alcohol was used (154:1). Ten equivalents of Oxone added over 7 hours was required to convert all the alcohol. Work-up and column chromatography afforded cholestan-3-one in 78% yield. The oxidation was then attempted using a solution of dimethyldioxirane in acetone. Cholestan-3β-ol in dichloromethane was allowed to react with dimethyldioxirane/acetone solution (0.03M) at 20°C for 20 hours. Removal of solvent *in vacuo* gave cholestan-3-one in 88% yield and high purity.

To determine any difference in the rate of oxidation of epimeric alcohols, an equimolar mixture **(136a)** of cholestan-3α-ol and cholestan-3β-ol was partially oxidised by dimethyldioxirane/acetone solution. The ratio of α:β cholestanol was determined before and after oxidation by gas liquid chromatography. The alcohols were analysed as the more volatile trimethylsilyl ethers. The mixture of alcohols was oxidised to about 60% conversion based on the amount of dimethyldioxirane used (Scheme 46).



(136a) (137)

(Scheme 46)

The reaction was repeated three times and a mean value obtained. The result is shown in table 1.

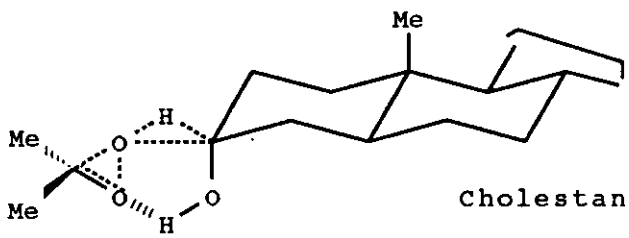
Table 1. *Oxidation of an equimolar mixture of cholestan-3α-ol and cholestan-3β-ol.*

Reaction time Hours	Conversion to ketone %	Before oxidation α:β	After oxidation α:β
15	58.8	1.06:1	0.54:1

Before the mixture of alcohols **(136a)** was oxidised the ratio of the epimers was 1:1 as expected. After stirring with dimethyldioxirane for 15 hours at room temperature and protected from light the ratio was found to change significantly, to 0.54:1. This result shows that the rate of oxidation of cholestan-3α-ol, where the hydroxyl is axial, is greater than 1.5 times that of the 3β-epimer, where the hydroxyl is equatorial.

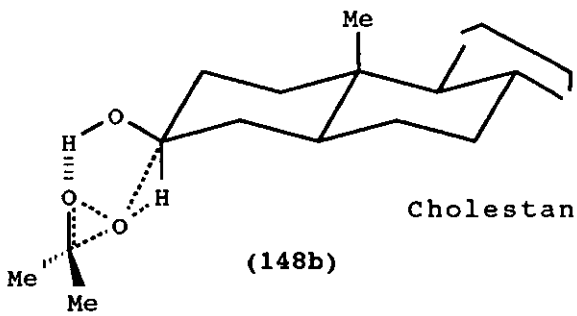
To rationalise the difference in rate observed, an oxygen atom insertion reaction proceeding via a butterfly transition state may be assumed. The higher reactivity of the axial alcohol, would suggest that the equatorial C-H bond is oxidised in preference to the axial C-H bond found in the 3β-epimer. The difference in rates of oxidation of the alcohols could be explained by the six-membered transition states **(148a)** and **(148b)**. It could be conceived, that the oxygen atom of the dioxirane which is not involved in oxygen atom transfer, could take part in hydrogen bonding with the hydroxyl group of the alcohol. This would give rise to a transition state which would be close to the required geminal diol **(149)** on the reaction coordinate. A higher ground state energy for the 3α-epimer may therefore be responsible for its enhanced reactivity.

Dimethyldioxirane/cholestanol six-membered transition states.



Cholestan-3α-ol

(148a)



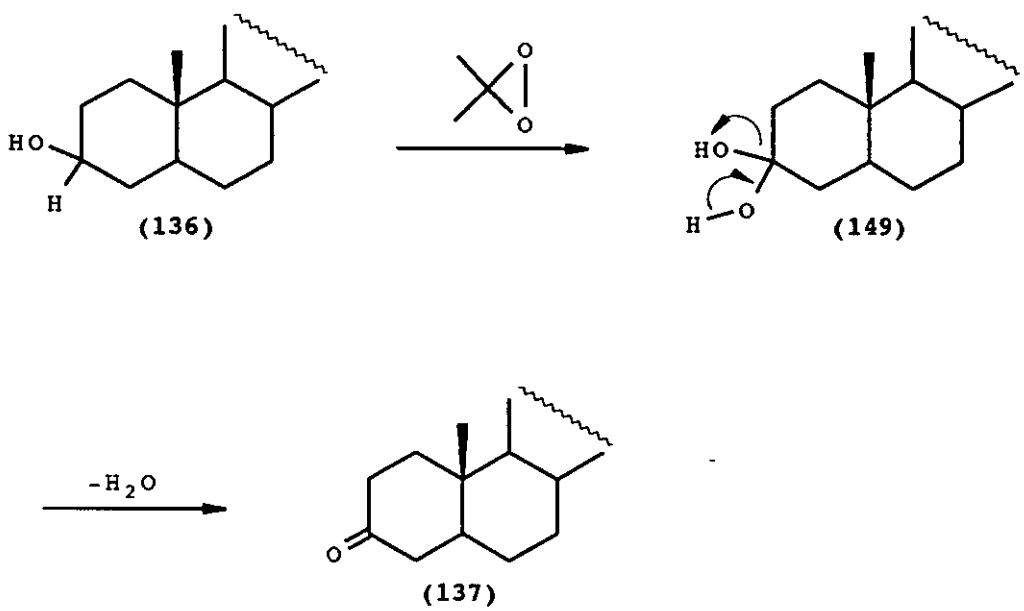
Cholestan-3β-ol

(148b)

The proposed six-membered transition states **(148a)** and **(148b)** would involve oxygen atom insertion into the C-H bond to give the geminal diol **(149)**. We decided that experimental evidence was necessary to determine whether the geminal diol was an intermediate. For this to occur, oxygen atom transfer from the dioxirane would be required but at least one alternative mechanism is possible.

(i) Oxygen atom insertion by the dioxirane and formation of the geminal diol (149).

As indicated above the intermediacy of the geminal diol (**149**) would result in theoretically, 50% of the oxygen atoms being derived from the dioxirane in (**137**) (Scheme 47).



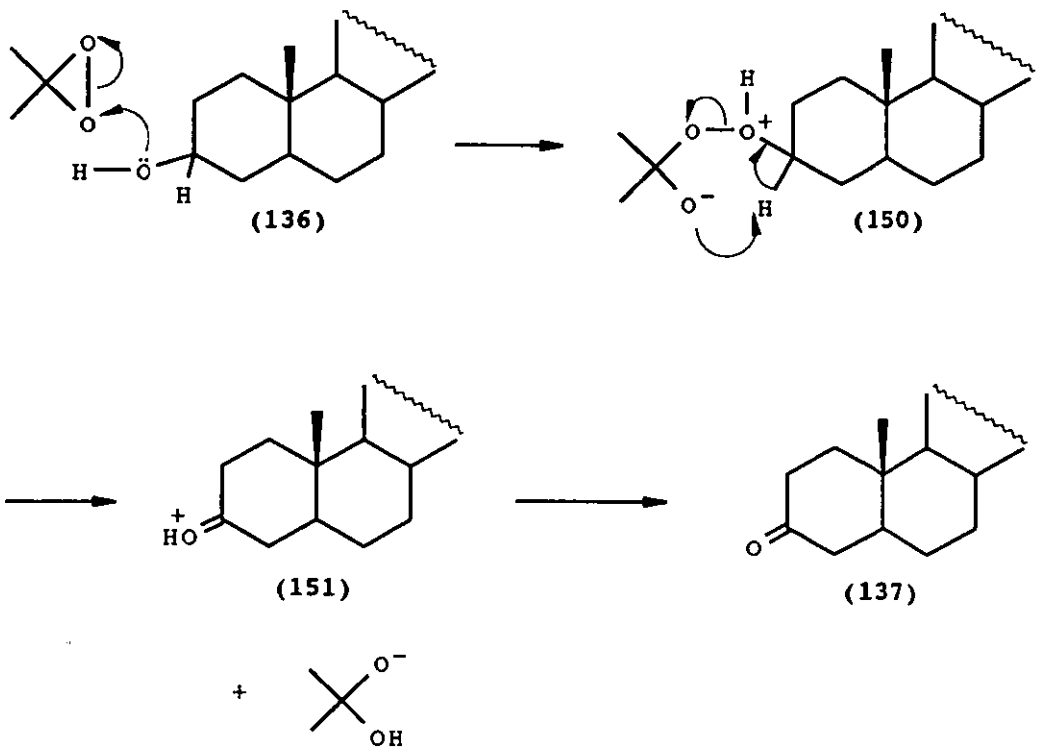
(136) (149) (137)

50% of the oxygen atoms in cholestanone derived from the dioxirane.

(Scheme 47)

(ii) Oxygen atom from the dioxirane not incorporated into the steroid.

If an oxygen atom from the dioxirane was not incorporated into the steroid, an alternative mechanism, involving hydrogen abstraction, could account for the product. The lone pair of electrons on the hydroxyl oxygen atom of **(136)**, could initiate the breaking of the O-O bond of the dioxirane. This would give rise to the oxygen anion **(150)** which in turn would abstract the hydrogen atom from the steroid. It is important to note, that the oxygen atom of the steroid is retained in the ketone and no transfer of oxygen from the dioxirane occurs (Scheme 48).[cf. chromium VI oxidations of alcohols to ketones].

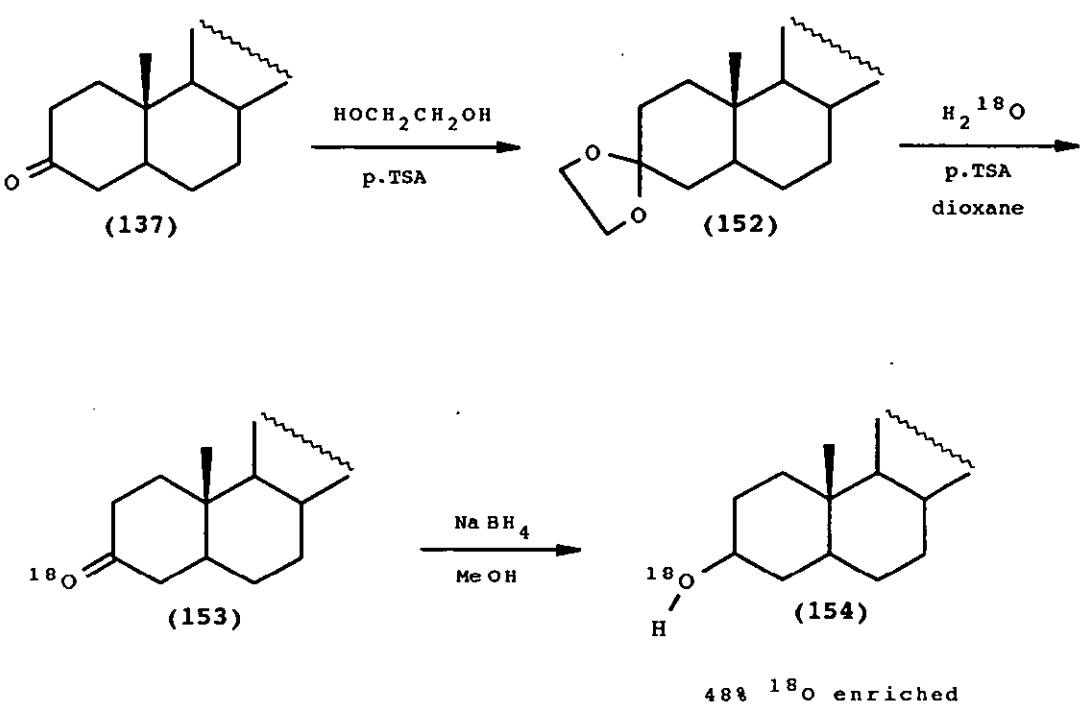


(Scheme 48)

5.3 ^{18}O Labelling study, supporting evidence for oxygen insertion mechanism.

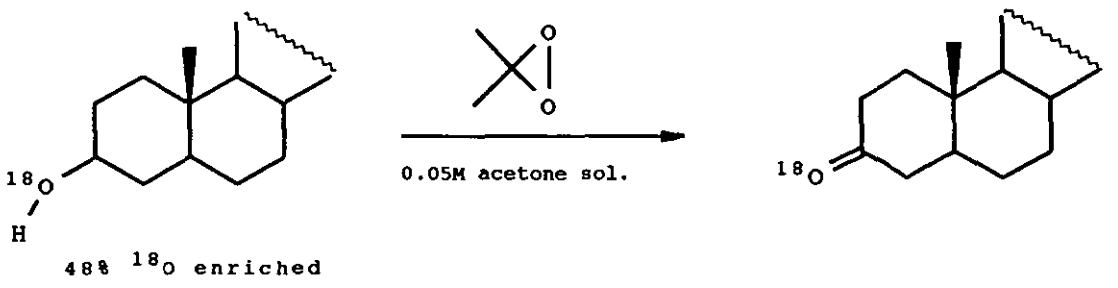
We decided a good way to determine whether the dioxirane transfers an oxygen atom to the steroid, would be to oxidise ^{18}O labelled cholestanol **(154)**. If there was no change in ^{18}O label in the cholestan-3-one formed, then the oxidation could not be an oxygen atom insertion process. However, if there was a reduction in ^{18}O label by about 50%, the mechanism of oxygen atom insertion would be occurring.

The preparation of ^{18}O labelled cholestan-3β-ol **(154)** was carried out by the following procedure. Cholestan-3-one **(137)** was allowed to react with ethane-1,2-diol in the presence of p-toluenesulphonic acid to form the ethylene ketal **(152)**. Acid hydrolysis of the ketal **(152)** using ^{18}O labelled water[75] afforded ^{18}O cholestan-3-one **(153)**. This was then reduced using sodium borohydride in methanol to give ^{18}O cholestanol **(154)**. Using electron impact mass spectrometry, the alcohol **(154)** was found to be 48% enriched with the ^{18}O label (Scheme 49).



(Scheme 49)

The ^{18}O cholestanol **(154)** was then oxidised with dimethyldioxirane. A 0.05M solution of dimethyldioxirane/acetone in dichloromethane was used and cholestan-3-one was obtained in 93% yield and high purity (Scheme 50).



(Scheme 50)

The cholestan-3-one obtained was analysed by mass spectrometry and the ^{18}O content was found to be 26.9%. The experiment was repeated and the ^{18}O content was found to be 34.0%, (Table 2).

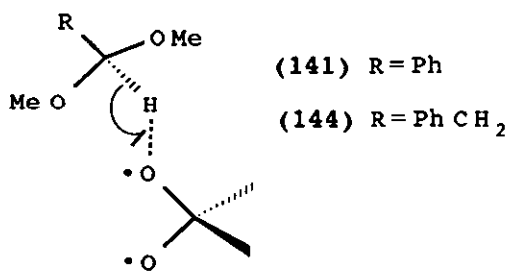
Table 2. *Oxidation of* ^{18}O *cholestan-*3β*-ol to cholestan-*3*-one using* DMD*/acetone solution.*

Run	^{18}O content in cholestan-3-one	% Reduction in ^{18}O content.
A	26.9	44.0
B	34.0	30.0

From these results it can be concluded that about 40% of the oxygen atoms are lost from the alcohol. This is consistent with the mechanism of oxygen atom insertion.

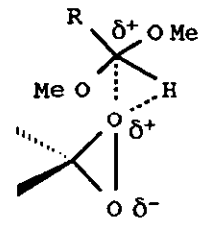
5.4 Concluding remarks for chapters 2-5.

For the oxidations of C-H bonds discussed in chapters 2-5 a high level of selectivity has been shown by DMD throughout. A series of reactivity trends shown by DMD towards C-H bonds has become evident. It is generally agreed that for unactivated C-H bonds the reactivity is $CH>CH_2>CH_3$ and our experiments along with others suggest that $ArCH>ArCH_2$. Our results also show that benzylic methylene groups of benzyl ethers are generally oxidised smoothly but benzyl esters appear to be unreactive. Interestingly, the C-H bond of the acetal **(144)** is preferentially oxidised rather than the benzylic methylene and at a rate comparable with that of the acetal **(141)**. The most likely alternative mechanisms for these C-H oxidations may involve either electrophilic radical attack **(D)** or a polar concerted insertion process **(E)**. It is difficult to distinguish these by consideration of benzyl esters/ethers and benzyl acetal **(144)**. However, a distinction between these may be made by comparison of the acetals **(141)** with **(144)**.



(141) R = Ph

(144) R = Ph C H_2



(D) **(E)**

The polar mechanism **(E)** would be expected to be more subject to steric constraints than **(D)** and would therefore explain the surprisingly low reactivity of the C-H of the acetal **(141)**, which on electronic grounds would be expected to be very reactive (tertiary benzylic group).

The fact that cholestanol **(136)** is oxidised faster than the benzyl ether **(135)** perhaps also supports a polar mechanism in which hydrogen bonding may be important,(cf. transition states **(148a)** and **(148b)**).

These conclusions agree broadly with those of Murray and Jeyaraman[43] who have made comparisons between DMD and t-butoxy radicals and shown that DMD has a much higher selectivity for oxidations. This is highlighted by oxygen insertion with toluene, ethylbenzene and isopropylbenzene. Increasing reactivity is exhibited by DMD towards the benzylic position in the order toluene<ethylbenzene<isopropylbenzene. In all cases the rate of oxygen insertion by DMD was considerably greater than hydrogen abstraction by t-butoxy radical. A kinetic isotope study for the oxidation of cyclododecane by DMD has shown that the C-H bond is being broken in the rate determining step. However, the observed value K_H/K_D=4.97 suggests that the C-H bond is probably not completely cleaved in the transition state. This work[43] and ours, including the ^{18}O experiments described earlier give good evidence for a concerted insertion process.

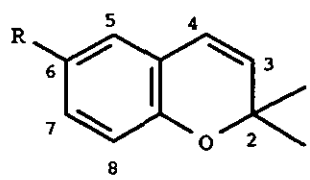
CHAPTER 6

CHAPTER 6.

Dioxirane Mediated Oxidations Of Chromenes.

6.1 Introduction.

The highly selective and mild oxidising nature of dioxiranes has been realised. Their potential as alternatives to more traditional oxidation methods, especially where highly labile compounds[30,31,33] are involved, is receiving increasing attention. Of interest to the industrial collaborators are a series of chromene compounds **(155-158)**.[76] Chromene **(155)** is of particular interest as the epoxide derivative **(160)** is a precursor to the antihypertensive agent, cromakalim **(161)**.[77,78]



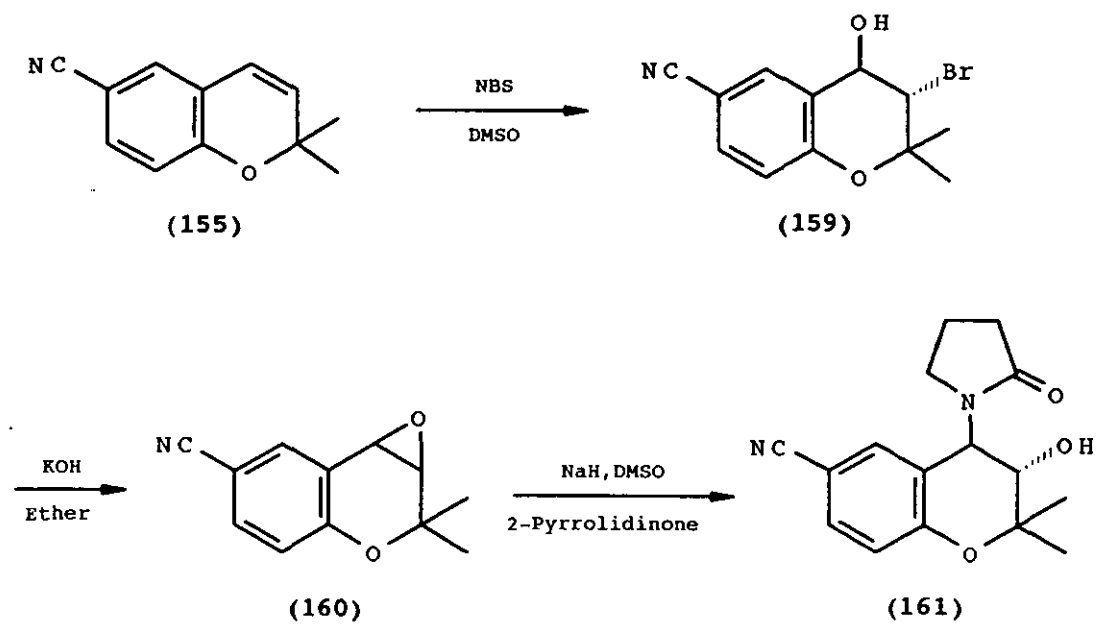
(155) R= CN

(156) R= $COCH_3$

(157) R= Cl

(158) R= CH_2CH_3

At present, cromakalim **(161)** is synthesized via the bromohydrin **(159)** which is required to obtain the epoxide **(160)**[78] (Scheme 51).



(155) **(159)**

(160) **(161)**

(Scheme 51)

Cromakalim is the first compound to allow the lowering of blood pressure by a novel mode of action, which involves activation of potassium channels in the membranes of smooth muscular tissue by the increase in outward movement of potassium ions which leads to muscle relaxation. The main interest in the development of this drug is concerned with the biologically active (-)-3S,4R enantiomer.[78]

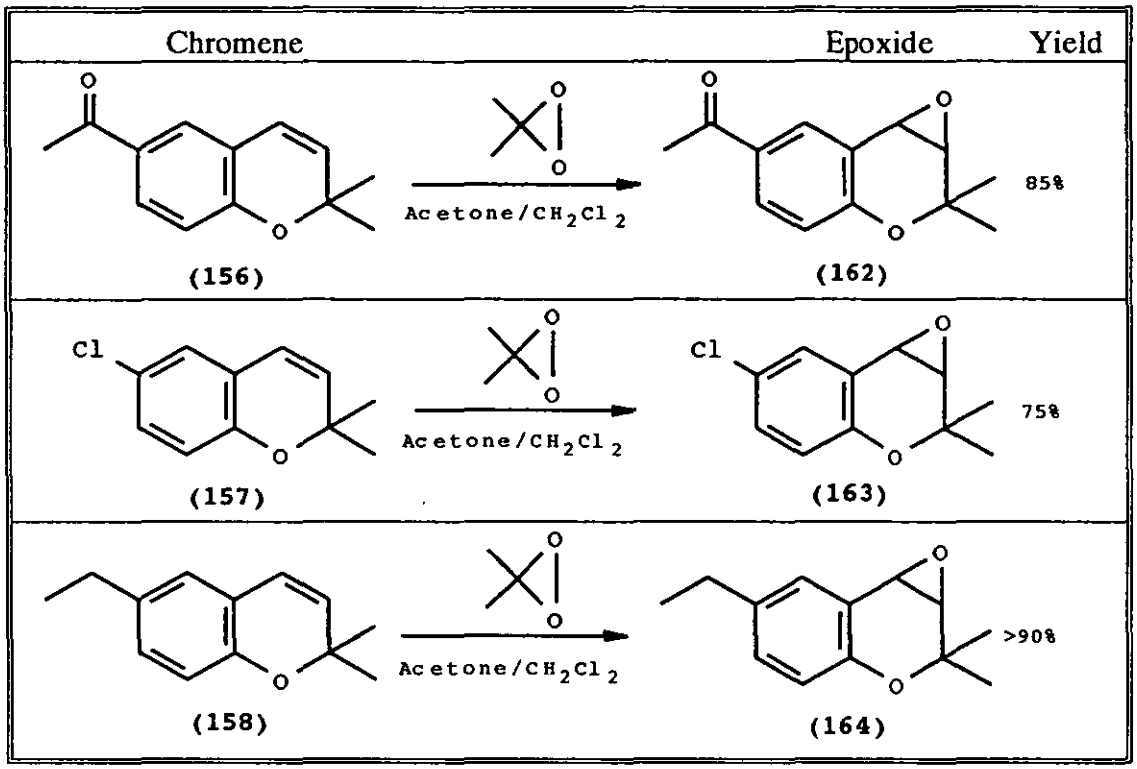
A major improvement in the synthesis of cromakalim would be to prepare the epoxide **(160)** directly from the chromene **(155)** as this epoxidation step using peroxyacids gives poor results. If the epoxidation were to be made highly enantioselective a significant step forward would be achieved by which one enantiomer of cromakalim could be obtained. Our aims were to attempt to use dioxiranes for the epoxidation of the chromene compounds with a view to developing enantioselective[20] methodology.

6.2 Oxidations using dimethyldioxirane/acetone solutions.

The chromenes **(156),(157)** and **(158)** were oxidised using isolated DMD/acetone solution and each product was characterised using IR, ^{1}H and ^{13}C NMR and mass spectrometry, selected data is included in the following discussion.

Reaction of 6-acetyl-2,2-dimethyl-2H-1-benzopyran **(156)** in dichloromethane with 0.05M DMD/acetone solution at 22°C for 11 hours allowed complete conversion to the epoxide **(162)**. The solvent was evaporated to afford the epoxide **(162)** in high purity and 85% yield. {IR υmax 1674cm^{-1}(C=O), ^{1}H NMR δ 3.9(d, J=4.4, 1H, H4 oxirane), 3.5(d, J=4.4, 1H, H3 oxirane), 2.5(s, 3H, acetyl Me), m/z 218}. Using the same procedure 6-chloro-2,2-dimethyl-2H-1-benzopyran **(157)** was converted to the epoxide **(163)** in 75% yield. {^{1}H NMR δ 3.8(d, J=4.4, 1H, H4 oxirane), 3.5(d, J=4.4, 1H, H3 oxirane), 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2 Me), m/z 210}. 6-Ethyl-2,2-dimethyl-2H-1-benzopyran **(158)** was oxidised with DMD/acetone solution. The reaction mixture was seen to change from colourless to a yellow solution. Evaporation of the solvent gave the epoxide **(164)** which was not further purified. {^{1}H NMR δ 3.9(d, J=4.3, 1H, H4 oxirane), 3.5(d, J=4.4, 1H, H3 oxirane), 2.5(q, 2H, CH_2CH_3), 1.6(s, 3H, C-2 Me), 1.3(s, 3H, C-2 Me and t, 3H, CH_2CH_3), m/z 204}. The results are summarised in Table 1.

Table 1. *Oxidation of a series of chromenes by* DMD/*acetone solution.*

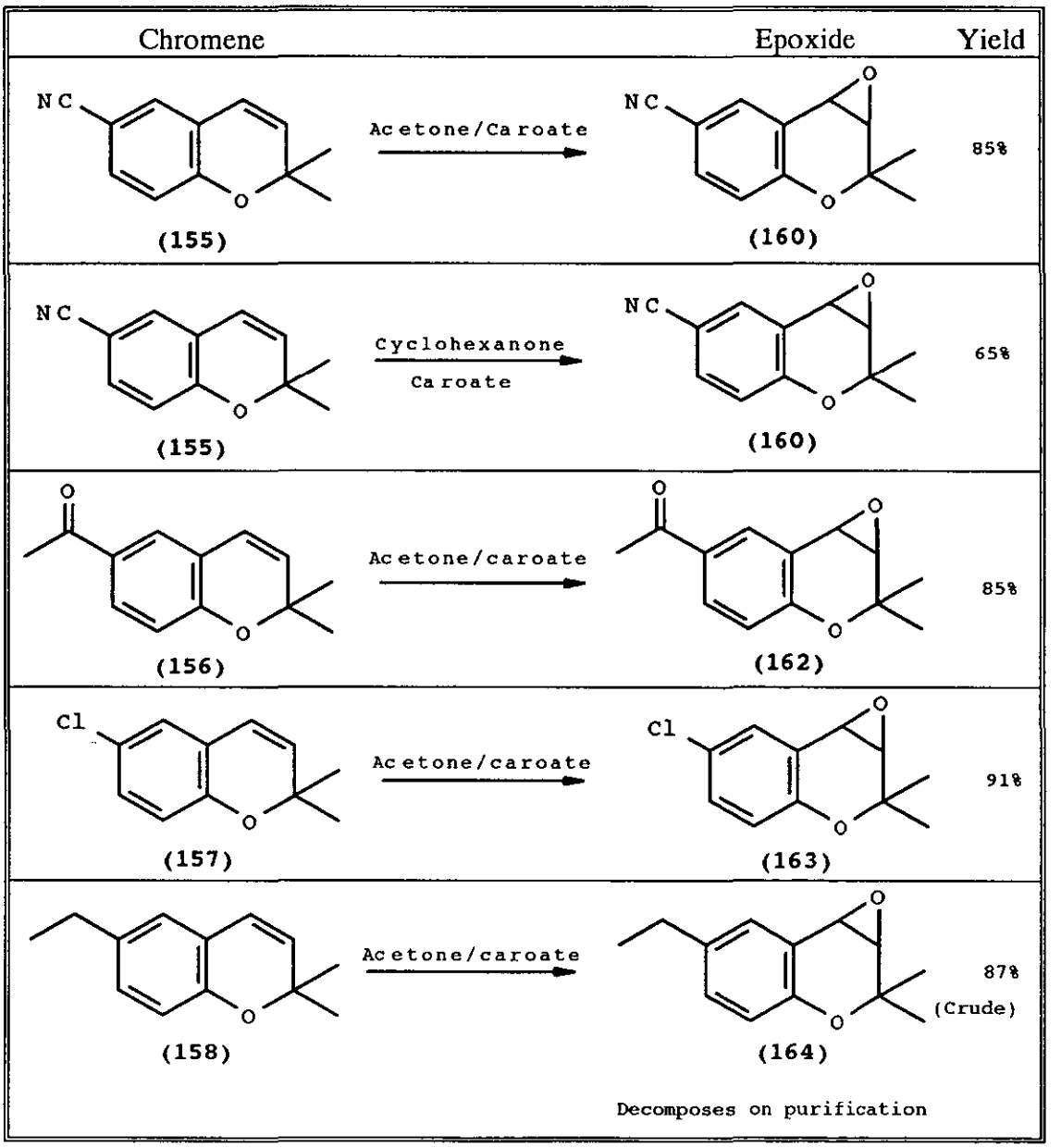


6.3 Oxidations using dioxiranes generated *in situ.*

The oxidations were also performed using the biphasic system where the dioxirane was generated *in situ.* Reaction of 6-cyano-2,2-dimethyl-2H-1-benzopyran **(155)** with the acetone/caroate system gave the corresponding epoxide **(160)**[77] in high purity and 85% yield. The reaction was notably clean and showed no formation of any other products. The acetone could be easily removed during evaporation. In a similar manner the cyclohexanone/caroate system was used with **(155)**. The epoxide **(160)** was obtained in 65% yield. The isolated yield was lowered in the purification step, as separation of cyclohexanone and some ε-caprolactone from the epoxide by column chromatography was quite difficult. The oxidation of 6-acetyl-2,2-dimethyl-2H-1-benzopyran **(156)** with the acetone/caroate system over 5 hours gave the epoxide **(162)** in 85% isolated yield. Similarly Reaction of 6-chloro-2,2-dimethyl-2H-1-benzopyran **(157)** in the acetone/caroate system allowed complete conversion to the epoxide **(163)** within 10 hours. Chromatography afforded the pure epoxide **(163)** in an excellent

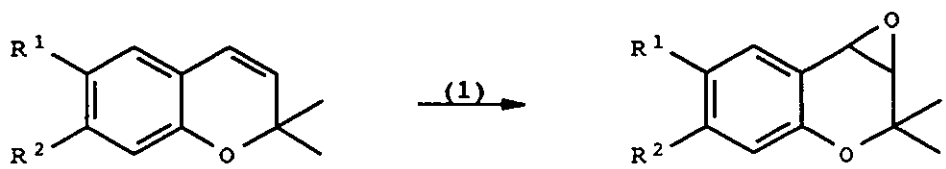
yield of 91%. 6-Ethyl-[illegible]-2,2-dimethyl-2H-1-benzopyran (**158**) was oxidised in the acetone/caroate system. As the reaction proceeded, the mixture was seen to change from colourless to yellow. After 4 hours, work-up gave the crude product, which was shown by ^{1}H NMR spectroscopy to be the epoxide (**164**). However, when the product was chromatographed using flash silica gel or neutral alumina (grade 3), decomposition of epoxide (**164**) was evident. The yield was estimated to be about 87%, based on the purity shown by the ^{1}H NMR spectrum and the weight of the crude product mixture. The results are summarised in Table 2.

Table 2. *Oxidation of a series of chromenes by in situ generated dioxiranes.*



6.4 Concluding remarks.

Since this work was carried out there has been a literature report[37] on the oxidation of precocenes **(55-58)** using dimethyldioxirane. The 3,4-epoxides were obtained in high purity and yield. The precocenes were substituted at C-6 and C-7 unlike the chromenes which had only C-6 substituents (Scheme 52).



(55) $R^1=R^2=H$

(56) $R^1=H$; $R^2=Cl$

(57) $R^1=OCH_3$; $R^2=OCH_2CH_3$

(58) $R^1=OCH_3$; $R^2=OCH_2CF_3$

(Scheme 52)

It is clear that dioxiranes provide an efficient means of epoxidising chromenes. The mild conditions under which the oxidations proceed is particularly important as the epoxides formed are often quite labile. Attempted asymmetric epoxidation of chromene **(155)** using chiral dioxiranes is discussed in chapter 7.

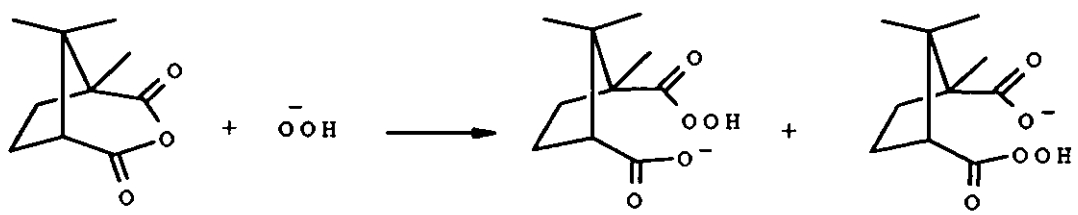
CHAPTER 7

CHAPTER 7.

Approaches To Asymmetric Epoxidations Using Chiral Dioxiranes.

7.1 Review of some current asymmetric epoxidation methods.

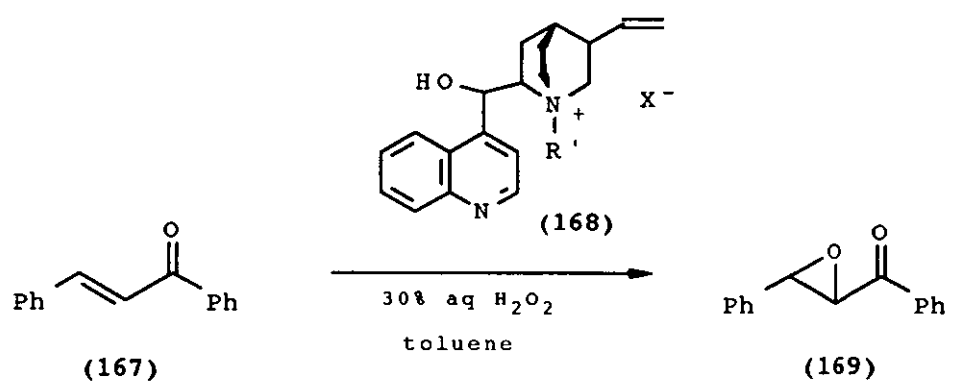
Optically active epoxides are important intermediates in organic synthesis.[79] However, there is still much scope for the development of asymmetric epoxidation reactions. The use of monoperoxycamphoric acid (MPCA) (**166**) has been reported for the epoxidation of alkenes. Styrene and β-methylstyrene were converted to the epoxides with an enantiomeric excess of 7.8% and 9.2% respectively. The MPCA reagent for asymmetric epoxidation was prepared by reaction of camphoric anhydride (**165**) with hydroperoxide ion, to give a mixture of the two isomers (**166a**) and (**166b**). By crystallisation it was possible to obtain pure (**166a**)[80] (Scheme 53) as the acid.



(165) (166a) (166b)

(Scheme 53)

The epoxidation of some α,β-unsaturated ketones (**167**) has allowed a 25% ee to be achieved using quaternary salts (**168**) derived from quinine with basic hydrogen peroxide[81] (Scheme 54).

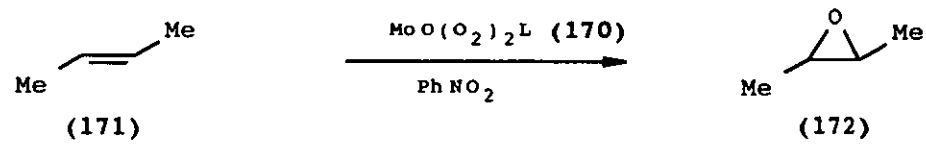


(168)

(167) (169)

(Scheme 54)

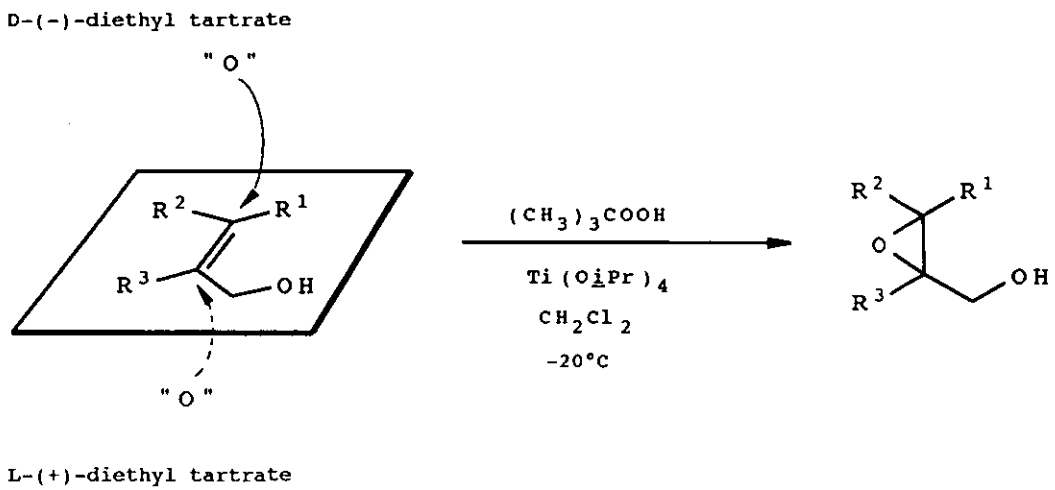
An interesting example of another approach to asymmetric epoxidation of unfunctionalised alkenes involves the use of an optically active molybdenum(VI) oxodiperoxo complex **(170)** (L=(*S*) - *N,N* - dimethyllactamide).
Simple prochiral alkenes such as propene or trans-2-butene **(171)** were epoxidised to optically active oxiranes by **(170)** in nitrobenzene at 20°C/1 bar in high yield (70%) and enantiomeric excess of about 30% [82] (Scheme 55).



(Scheme 55)

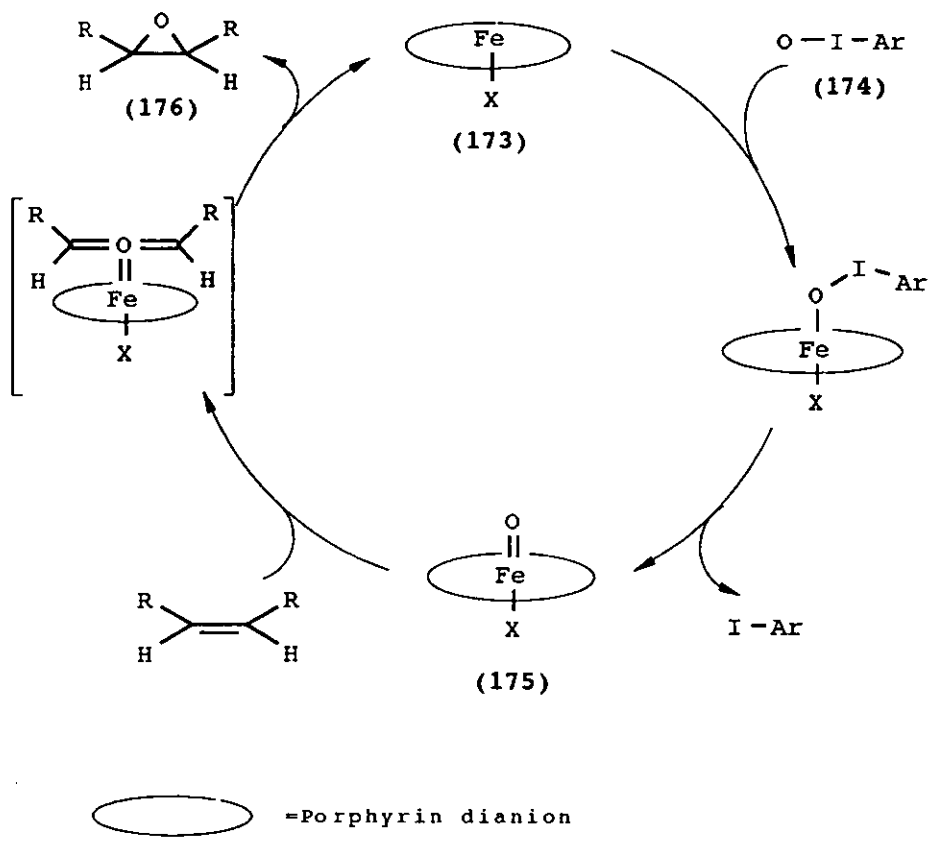
Similarly epoxidations have been performed by t-butyl hydroperoxide with Mo(VI) catalysts in the presence of an optically active diol. In general the highest asymmetric induction (10% ee) was achieved using 1,2-diols, which can coordinate to the molybdenum metal most effectively.[83]

The first chemical epoxidation method to give highly enantioselective oxidation(70-90% ee), was developed by Sharpless and Katsuki. The asymmetric epoxidation of allylic alcohols was possible using (+) or (-)-diethyl tartrate, titanium tetraisopropoxide and t-butyl hydroperoxide. It is interesting to note that for a given tartrate enantiomer the system delivers the epoxide oxygen atom to only one enantioface of the alkene[84] (Scheme 56).



(Scheme 56)

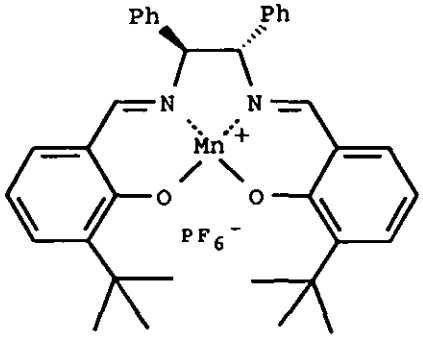
The success of the work by Sharpless encouraged the development of enantioselective catalysts for epoxidation. One of the major areas of interest has been involved with metalloporphyrins and related compounds, which catalyse the transfer of oxygen from oxidants such as iodosylmesitylene or sodium hypochlorite, to the prochiral substrate. Iron porphyrin catalysed epoxidation of styrene has allowed an induction of 31% ee to be achieved. The mechanism involves transfer of oxygen atom from the iodosylarene **(174)** to the porphyrin **(173)** giving the oxoiron species **(175)**. This in turn oxidises the alkene to form the epoxide **(176)**[85] (Scheme 57).



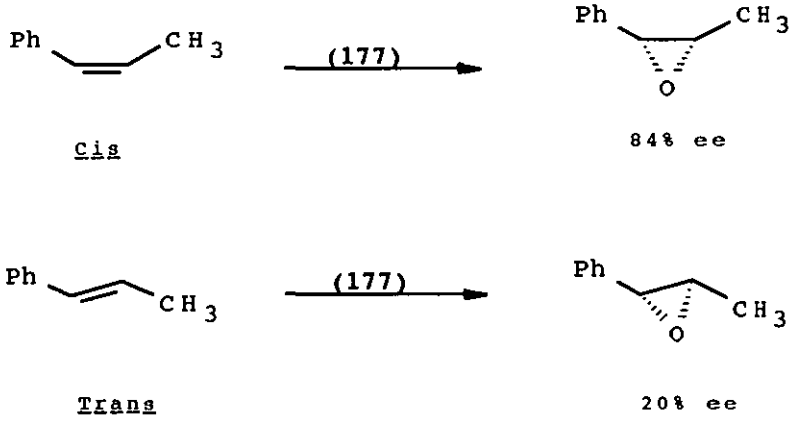
(Scheme 57)

More recent work[86] has involved the use of manganese(III) complexes. With the cationic (salen) manganese(III) complex (177) good asymmetric inductions of 20-93% ee can be achieved for the epoxidation of mono-, di- and trisubstituted alkenes. The transfer of oxygen from oxidants such as sodium hypochlorite is catalysed by the complex. The oxygen is transferred from the active oxomanganese(V) intermediate to the alkene by

enantiofacial approach of the substrate towards the manganese-oxygen bond. Interaction of the more hindered side of an unsymmetrical alkene with the complex, determines the orientation of the approach. Generally, cis-disubstituted alkenes are epoxidised with a higher asymmetric induction than the corresponding trans-alkenes[86] (Scheme 58).



(177)



(Scheme 58)

Similarly, other manganese(salen) complexes containing optically active substituents have been developed by other workers.[87] In the presence of 2-methylimidazole these catalysts have shown improved asymmetric induction for the epoxidation of some unfunctionalised alkenes.

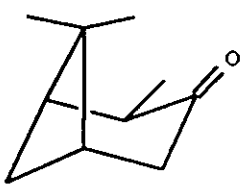
Asymmetric inductions of up to 65% ee have been obtained for the epoxidation of unfunctionalised alkenes using chiral, camphor derived, sulphonyloxaziridine **(178)**. Although not catalytic in their mode of action, they are capable of performing oxidations without the need for other oxidising agents, as required with the methods previously described. The configuration of the oxaziridine three-membered ring controls the stereochemistry, while steric factors are responsible for the chiral recognition[88] (Scheme 59).

R= H, Me, Ph

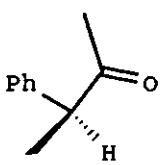
Z*=(-)3-bromocamphor, Ar=2-chloro-5-nitrophenyl

(Scheme 59)

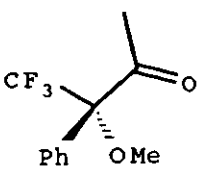
The application of dioxiranes to enantioselective epoxidations is rather limited. Chiral ketones have been used as precursors to dioxirane intermediates but only enantioselectivities of 5-20% ee have been achieved. Only three ketones **(22)**,**(23)**[20] and **(24)**[21] have been reported for these oxidations.



(22)



(23)

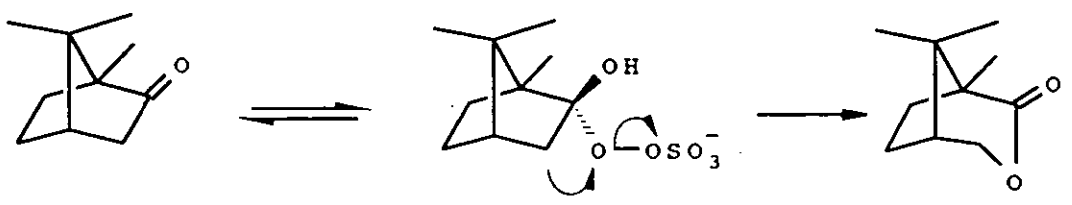


(24)

Our aims were to try and develop a catalytic method of asymmetric epoxidations based on dioxirane systems. The isopinocamphone (**22**) system has shown some asymmetric induction with simple alkenes (12%ee) but the reaction is rather slow.[20] To achieve enantiofacial approach of the dioxirane to the unfunctionalised alkene several constraints might be considered important; (i) A chiral centre close to the dioxirane ring, (ii) A sterically demanding environment near to the ring oxygens and (iii) Control over selective delivery of one dioxirane oxygen atom. Also, a compromise between selectivity and reactivity of the dioxirane would be important if these reagents are to be considered synthetically useful.

7.2 Epoxidations via novel *in situ* generated chiral dioxiranes.

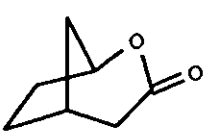
Our initial attempts at asymmetric epoxidations were based on the use of bicyclic ketones. Reactions were performed using the biphasic system to generate the dioxirane *in situ*. The use of the (+)-camphor (**179**)/caroate and (+)-isopinocamphone (**22**)/caroate systems to oxidise alkenes (**98**) and (**155**) showed no evidence of epoxidation after 24-48 hours. When the 2-methylcyclohexanone/caroate system was used, a high conversion of the alkene to the epoxide was evident after 24 hours (See Chapter 2). The carbonyl group of camphor (**179**) is quite sterically hindered by the C-1 and the C-7 methyl groups. This would suggest that if the dioxirane was formed oxidation of the alkene may be rather slow due to steric factors. The effect of steric factors is highlighted by the observed decrease in rate of oxidation moving from cyclohexanone to 2-methylcyclohexanone. Previous work[89] has shown that addition of Caro's acid to camphor does occur. Under acid conditions this leads to formation of the Baeyer-Villiger product, the lactone (**181**). The Caro's acid attacks the less sterically hindered *endo* face of the camphor (**179**) molecule to form the Criegee intermediate (**180**). Migration of the C-3 methylene group onto the oxygen atom gives the lactone (181) (Scheme 60).



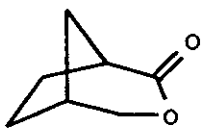
(179) (180) (181)

(Scheme 60)

Trans-stilbene **(204)** oxidation using the norcamphor **(182)**/caroate system was attempted. The pH was maintained at 7.5-8.0 and caroate was added over 1 hour. TLC analysis showed the disappearance of norcamphor and the appearance of a compound of smaller Rf value. Work-up gave a crude product which was found to contain trans-stilbene, the phase transfer catalyst and the unknown compound. Chromatography afforded unreacted trans-stilbene (91% recovery) and the unknown compound as a colourless liquid, which solidified on standing. The infrared spectrum of the unknown exhibited a carbonyl absorption at $1730cm^{-1}$, which would suggest formation of a lactone. Two possible lactones could form **(183)** or **(184)**. ^1H NMR spectroscopy data showed a broad signal downfield at δ 4.8ppm corresponding to a single methine proton (-CHOCOR-). This would suggest formation of the bridgehead lactone **(183)**. Indeed this assignment is identical to the literature data[90] for **(183)**.

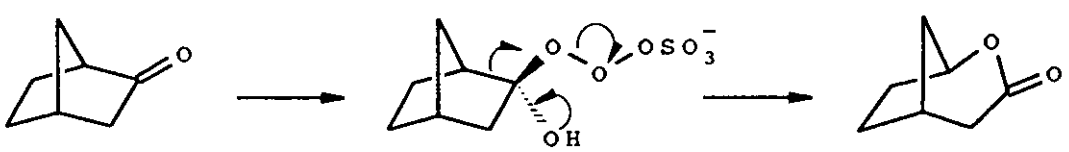


(183)



(184)

The product **(183)** would most likely have formed by Baeyer-Villiger oxidation of norcamphor. This could be explained by the addition of caroate to the *exo*-face of norcamphor to form the intermediate **(185)**. The stereochemistry may then be correct for anti-elimination and hence bridgehead migration (Scheme 61). Baeyer-Villiger oxidation would seem to occur very readily with norcamphor and formation of the dioxirane would appear not to be favoured. Hence, the observed depletion of norcamphor and little epoxidation of trans-stilbene.

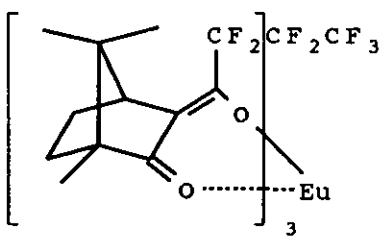


(182) **(185)** **(183)**

(Scheme 61)

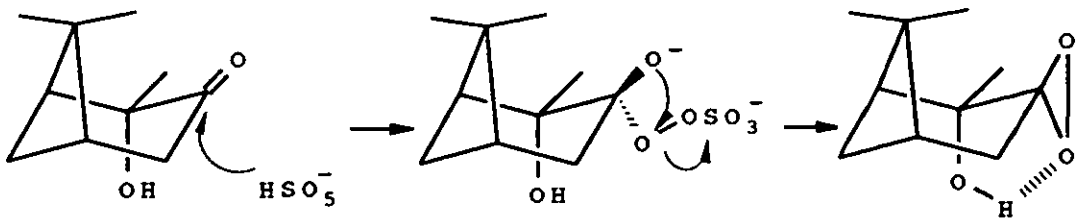
Oxidations using chiral ketones as dioxirane precursors were investigated where much longer reaction times and slow addition of larger quantities of caroate reagent were used than for the previous attempts with **(22)** and **(179)**. The results are summarised in table 1.

6-Cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (**155**) was allowed to react in the (+)-isopinocamphone/caroate system at pH7.5, (alkene:ketone molar ratio 1.0:5.9). Over a period of 11 days, 77 equivalents of Oxone was added. TLC analysis showed that conversion of the chromene (**155**) to the epoxide (**160**) had occurred cleanly. Purification by chromatography and recrystallisation afforded pure epoxide (**160**) in 31% yield. The isolated yield of pure epoxide (**160**) was rather low, as separation of the all the isopinocamphone from the epoxide was quite difficult, requiring preparative TLC in addition to column chromatography. The asymmetric induction was then determined by chiral shift NMR techniques. The chiral shift reagent Europium D-3-heptafluoro-butyrylcamphorate (**186**) was added to the epoxide (**160**) in 0.05 mole equivalents until resolution of the C-5 proton for the two enantiomers was observed. The enantiomeric excess was found to be 3.2%. (Table 1, entry 1).



(**186**)

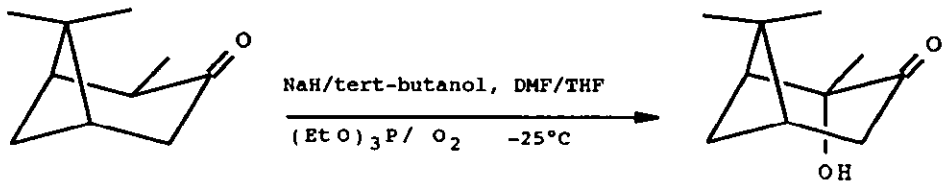
To determine whether a hydroxyl group α to the dioxirane ring could possibly allow preferential delivery of one oxygen atom and hence greater enantioselectivity and reactivity when a chiral dioxirane was used, we decided to investigate the 2-hydroxy-isopinocamphone (**187**)/caroate system. Unlike 2-hydroxy-2-methylcyclohexanone which has been shown to undergo ring cleavage (as described in chapter 2), the ketone (**187**) may allow dioxirane formation without the competing ring opening occurring. It can be seen that one face of the ketone is sterically hindered due to the bridgehead geminal methyl groups. Therefore, addition of the caroate may only occur from the other face, where the stereochemistry of the Criegee intermediate (**188**) would not be correct for a Grob fragmentation (Scheme 62).



(187) (188) (189)

(Scheme 62)

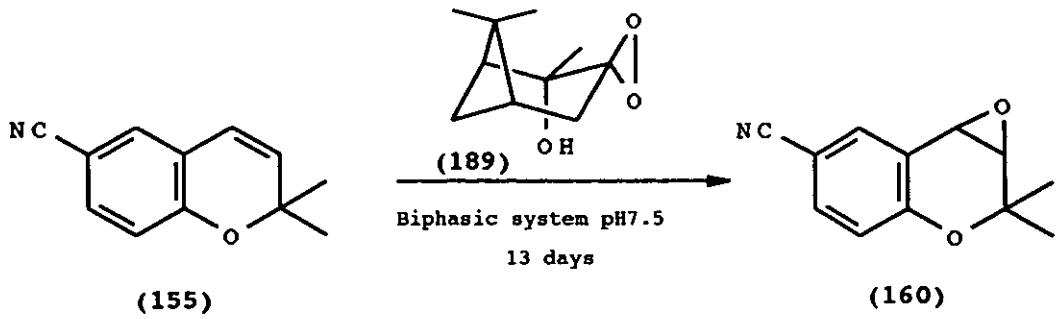
(-)-2-Hydroxyisopinocamphone **(187)** was prepared by the autooxidation[91] of the enolate of (-)-isopinocamphone **(22)** with molecular oxygen to form the hydroperoxide. This was then reduced *in situ* with triethyl phosphite to generate the α-hydroxy ketone **(187)**[92] (Scheme 63).



(22) (187)

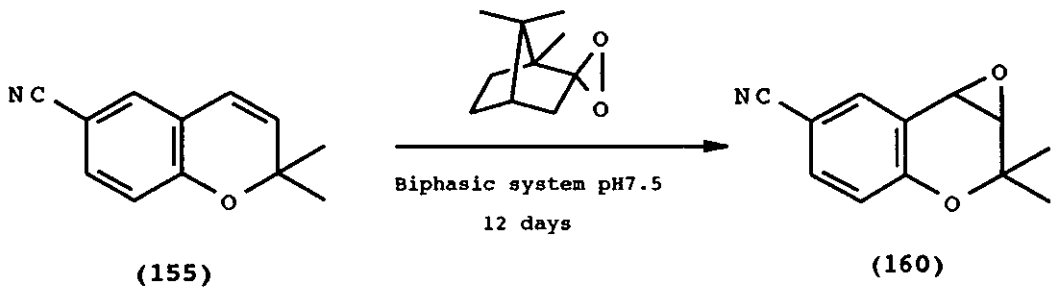
(Scheme 63)

The chromene **(155)** was oxidised with the (-)-2-hydroxyisopinocamphone/caroate system at pH7.5. The alkene:ketone molar ratio used was 1.0:1.0 and solutions of Oxone were added over 13 days to convert all the chromene **(155)** to the epoxide **(160)**. Purification by column and thin layer chromatography followed by recrystallisation afforded pure epoxide **(160)** in 17% yield. Separation of the ketone **(187)** from the epoxide **(160)** by chromatography was difficult as their Rf values were very similar, hence the low isolated yield. The asymmetric induction was then determined by high field ^{1}H NMR spectroscopy with the chiral shift reagent **(186)**. The epoxide **(160)** was found to have an enantiomeric excess of 2.4%. It was clear that there was no improvement in enantioselectivity with this ketone **(187)** and that the reaction time was still rather long. (Table 1, entry 2) (Scheme 64).



(Scheme 64)

In a similar manner chromene **(155)** was oxidised with the (+)-camphor/caroate biphasic system at pH7.5 (alkene:ketone molar ratio 1.0:1.3). Solutions of Oxone were added over 12 days to achieve complete conversion of the alkene to the epoxide **(160)**. Purification by chromatography afforded the epoxide **(160)** in 32% yield and by ^{1}H NMR, the epoxide **(160)** was found to have an enantiomeric excess of 3.0%. (Table 1, entry 3) (Scheme 65).

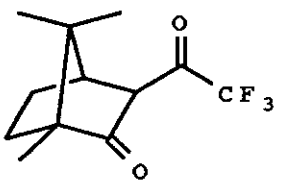


(Scheme 65)

From the oxidations using **(22)**, **(179)** and **(187)** as chiral ketones two main problems were evident; (i) the asymmetric inductions obtained were rather poor and (ii) the rate of epoxidation was extremely slow. Initially when the slow rate of epoxidation was observed it was thought that this may be a function of a high selectivity shown by the dioxirane. However, from the low enantiomeric excess obtained in each reaction this would seem not to be the case. It is perhaps worth considering the possibility that over the long reaction period, racemisation of the epoxide may occur.

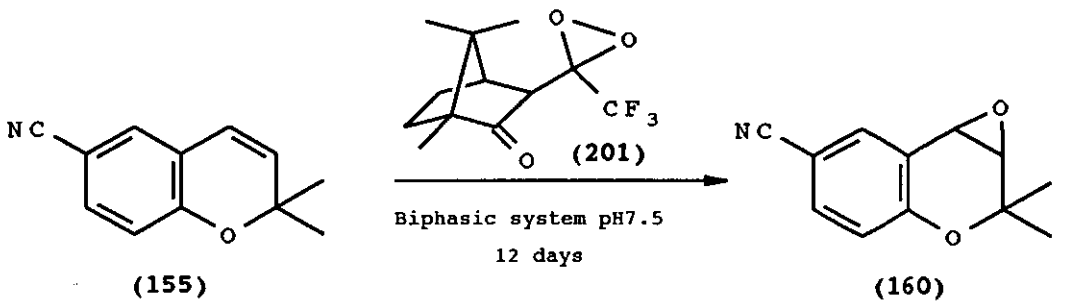
In addition to having a dioxirane which was enantioselective, one which exhibited enhanced reactivity and hence shorter reaction times was also important. From previous work it is known that a powerful electron withdrawing group α to the peroxide ring increases the reactivity of the dioxirane. In an attempt to improve the reactivity of the dioxiranes we decided to investigate the effect of trifluoromethyl and ester groups on the chiral ketones. An interesting and readily available[93] compound was (+)-3-

(trifluoroacetyl)camphor (**200**) which contains two carbonyl groups, one at the hindered C-2 position and the other at C-3 as the less hindered trifluoroacetyl group. It would be expected that a dioxirane (**201**) would be generated at the trifluoroacetyl carbon preferentially which should be highly reactive. However formation of a dioxirane at the C-2 carbonyl cannot be ruled out.



(200)

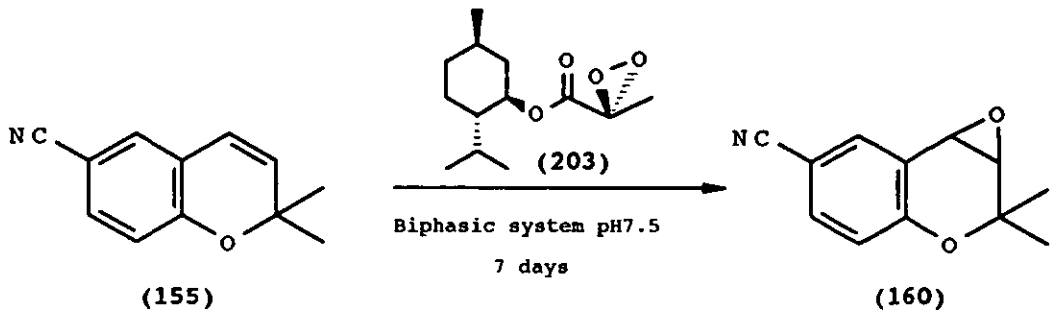
The chromene (**155**) was allowed to react in the (+)-(trifluoroacetyl)camphor (**200**)/caroate system at pH7.5. Solutions of Oxone were added over 12 days to allow complete conversion of the chromene (**155**) to the epoxide (**160**), (alkene:ketone molar ratio 1.0:0.8). Purification by preparative thin layer chromatography and recrystallisation afforded pure epoxide (**160**) in 27% yield. The asymmetric induction for the epoxide (**160**) was determined by ^{1}H NMR spectroscopy and found to be 11.2% ee. (Table 1, entry 4) (Scheme 66).



(Scheme 66)

We have shown that ethyl pyruvate can be used successfully as a dioxirane precursor, so it was considered of interest to develop a chiral pyruvate ester. The derivative of choice was (-)-menthyl pyruvate (**202**) which could be easily prepared by reacting (-)-menthol with pyruvic acid in the presence of p-toluenesulphonic acid in refluxing benzene under Dean and Stark conditions.[94] Reaction of chromene (**155**) with the (-)-menthyl pyruvate (**202**)/caroate system at pH 7.5, (alkene:ketone molar ratio 1.0:2.1) over 7 days allowed conversion of the chromene (**155**) to the epoxide (**160**). Column chromatography

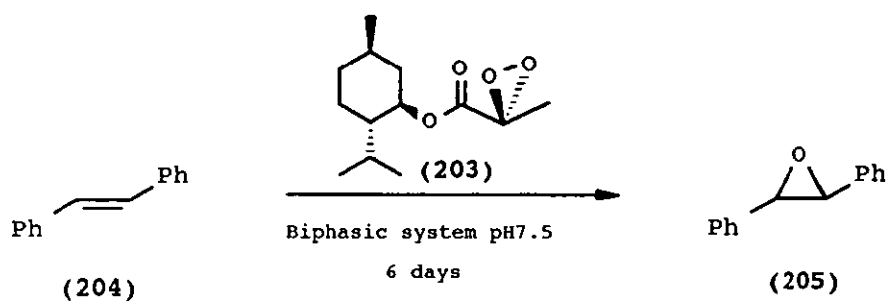
afforded the epoxide **(160)** with a trace of menthyl pyruvate present, (approximately 39% yield). Further purification was attempted using preparative TLC but the impurities were difficult to remove and the epoxide **(160)** was isolated as an oil which did not crystallise. The ^1H NMR spectrum of the epoxide **(160)** appeared quite clean and using chiral shift ^1H NMR spectroscopy an enantiomeric excess of 3.8% was determined. (Table 1, entry 5) (Scheme 67).



(Scheme 67)

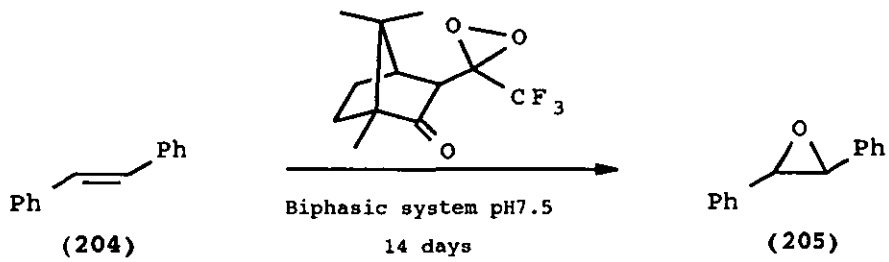
A factor which would effect the rate of epoxidation and also the asymmetric induction is the structure of the alkene used. Three of the chiral dioxiranes, **(187, 200** and **202)**, used for the oxidation of chromene **(155)** were used for the oxidation of trans-stilbene **(204)**.

Trans-stilbene was oxidised with the (-)-menthyl pyruvate/caroate biphasic system over 6 days, (alkene:ketone molar ratio 1.0:1.2). TLC revealed the formation of trans-stilbene oxide **(205)** however some trans-stilbene was still present. Trans-stilbene and the epoxide **(205)** were quite difficult to separate by chromatography however, a sample of pure trans-stilbene oxide[95] was obtained and using chiral shift ^1H NMR spectroscopic techniques the asymmetric induction was determined and was found to be negligible (0.2% ee). (Table 1 entry 6) (Scheme 68).



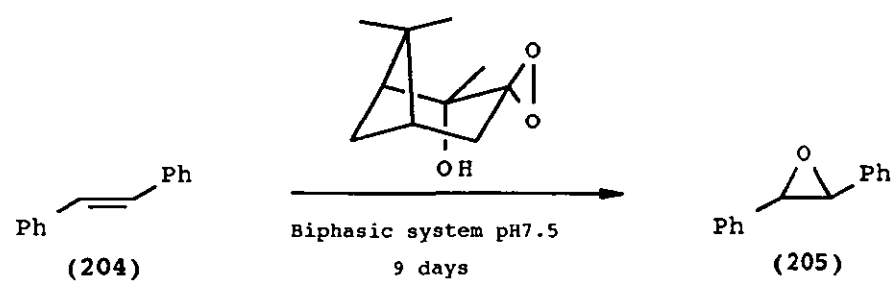
(Scheme 68)

Trans-stilbene was epoxidised in the (+)-(trifluoroacetyl)camphor/caroate biphasic system over 14 days at pH7.5 using an alkene:ketone molar ratio of 1.0:1.0. TLC revealed that a large amount of trans-stilbene oxide was present in the crude, although a trace of trans-stilbene was still evident. Purification of the epoxide (**205**) by chromatography afforded pure trans-stilbene oxide (**205**) in 18% yield. The enantiomeric excess of the epoxide (**205**) was determined by ^{1}H NMR spectroscopy and found to be 4.5%. (Table 1, entry 7) (Scheme 69).



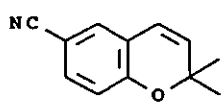
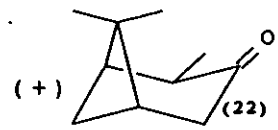
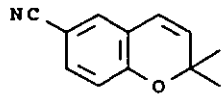
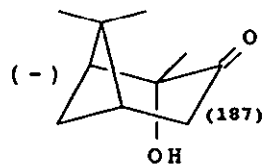
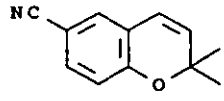
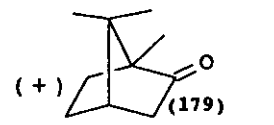
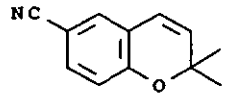
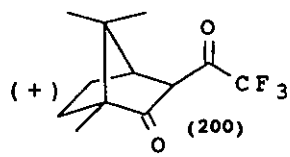
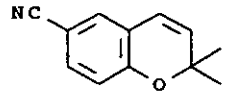
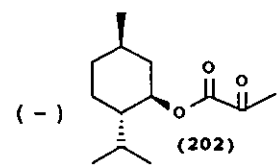
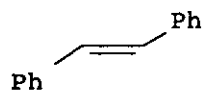
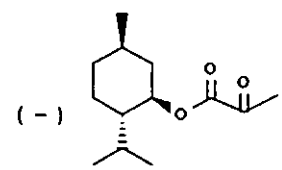
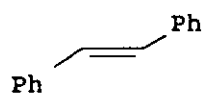
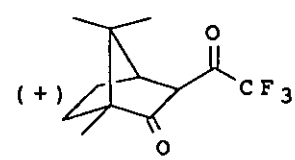
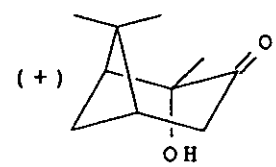
(Scheme 69)

Oxidation of trans-stilbene using the (-)-2-hydroxyisopinocamphone/caroate system over 9 days allowed complete conversion of the alkene (**204**) to trans-stilbene oxide, (alkene:ketone molar ratio 1.0:1.0). Purification by chromatography afforded the pure epoxide (**205**) in 43% yield and by ^{1}H NMR spectroscopy was found to have an enantiomeric excess of 3.9%. (Table 1, entry 8) (Scheme 70).



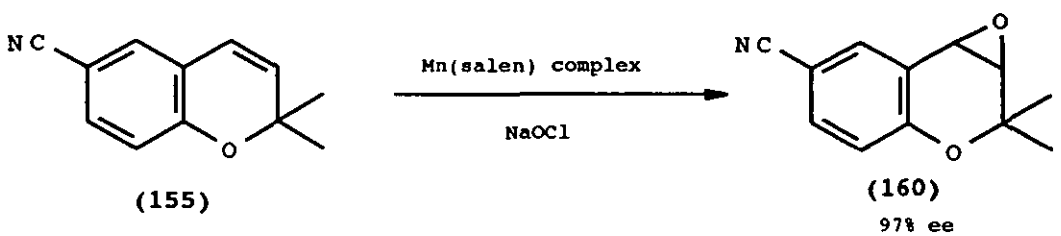
(Scheme 70)

Table 1. *Epoxidation of alkenes using dioxiranes derived from chiral ketones.*

Entry	Alkene	Chiral Ketone	Epoxide Yield % isolated	Epoxide ee %
1			31	3.2
2			17	2.4
3			32	3.0
4			27	11.2
5			N.D	3.8
6			N.D	0.2
7			18	4.5
8			43	3.9

7.3 Concluding remarks.

Since this work was carried out, a recent report by Jacobsen and co-workers[96] has described the asymmetric epoxidation of chromenes using a manganese (salen) complex in the presence of sodium hypochlorite. The epoxides were obtained in high yield and enantiomeric excesses of 97% achieved (Scheme 71).



(155) (160) 97% ee

(Scheme 71)

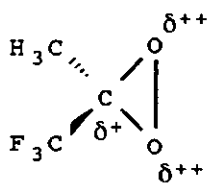
The approaches investigated to obtain enantioselective epoxidation using chiral dioxiranes do not show a significant improvement in enantiomeric excess over those previously reported.[20] It has become apparent that steric factors are an important consideration with respect to the rate of oxidation. However, to obtain good asymmetric oxygen atom transfer from the dioxirane to the substrate it is likely that a sterically demanding environment close to the dioxirane ring would be required. Some preliminary experiments to develop dioxiranes with improved reactivity are described in chapter 8.

CHAPTER 8

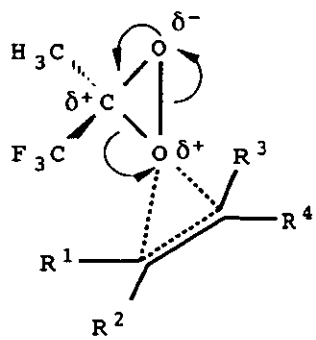
CHAPTER 8.

Investigation Of A Series Of Fluoro-ketone Derived *in situ* Generated Dioxiranes.

During this research a wide range of ketones have been used as dioxirane precursors (see chapters 2-7). One of the main problems which has become apparent is the decrease in reactivity associated with an increase in molecular weight and structural complexity of the ketone used. The introduction of a trifluoromethyl group α to the carbonyl in a ketone allows a more reactive electron-deficient dioxirane to be formed.[25] This effect on the reactivity may perhaps be explained by an increase in electrophilicity of the dioxirane (**A**). Also the electron deficiency at the carbonyl carbon atom may assist oxygen transfer of the dioxirane by moving the equilibrium towards ketone formation (**B**).



(A)

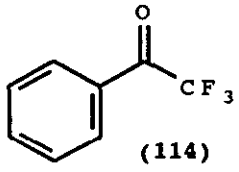
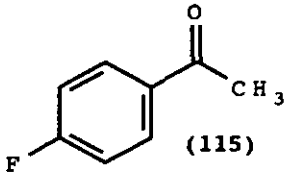
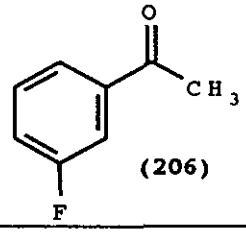
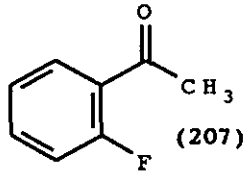
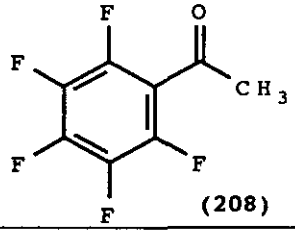
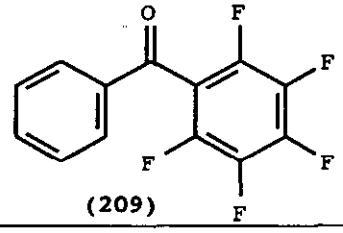


(B)

We decided that perhaps a fluorine substituted aromatic ring α to the carbonyl may also allow improved electrophilicity of the dioxirane. To test this theory a series of aromatic fluoro-ketones **(114)**, **(115)** and **(206-209)** were used in the biphasic ketone/caroate system as dioxirane precursors and their ability to oxidise cyclohexene to cyclohexene oxide assessed.

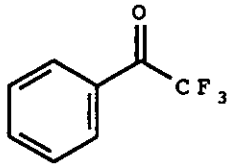
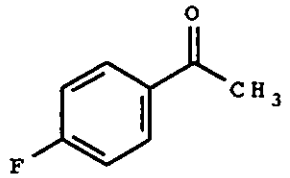
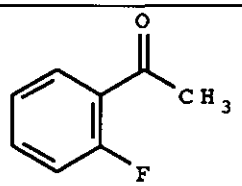
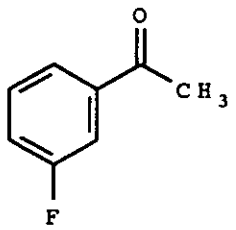
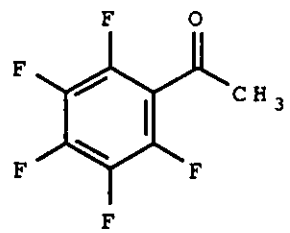
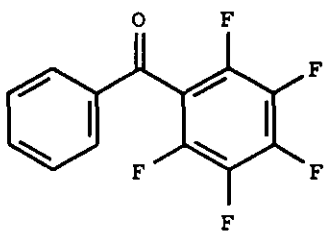
Each ketone was allowed to react under the same conditions (ie, same quantity and rate of addition of Oxone, dilution and reaction time). The experiment was run twice for each ketone using reaction times of 2¾ hours and 4 hours. The proportions of cyclohexene and cyclohexene oxide were determined by GLC after the reaction period, where the extent of oxidation observed was used to determine any differences in reactivity of the ketones. The results are shown in Table 1.

Table 1. *Oxidation of cyclohexene to cyclohexene oxide using fluoro-ketone derived dioxiranes.*

Ketone	%wt cyclohexene oxide 2¾ hours	%wt cyclohexene oxide 4 hours
 (114)	20.2	74.1
 (115)	20.9	56.9
 (206)	17.5	52.6
 (207)	18.0	55.8
 (208)	15.0	50.0
 (209)	20.8	45.3
ACETONE	----------	46.8

From these results an indication of the relative reactivity of each dioxirane can be obtained. The conclusions drawn from these results are summarised in Table 2

Table 2. *Relative reactivities of dioxiranes derived from fluoro-ketones.*

Entry. (decreasing reactivity)	Ketone	Reactivity of dioxirane
1.		MOST REACTIVE
2.		SIMILAR
3.		
4.		SIMILAR
5.		
6.		
7.	ACETONE	

From these results an indication of the relative reactivity of each dioxirane can be obtained (table 2). It is quite clear that α,α,α-trifluoroacetophenone **(114)** (entry 1) gives rise to the most reactive dioxirane species. The reactivity of the 2'- and 4'-fluoroacetophenones **(207)** and **(115)** respectively (entries 2 and 3) appears to be of a similar order but still more reactive than the remaining ketones (entries 4,5,6 and 7). From these results it can be concluded that a trifluoromethyl group α to the carbonyl group in acetophenones provides the best means of improving the reactivity of the dioxirane. It would appear also that some activation of the dioxirane ring is achieved for ortho and para fluorine substitution on the aromatic ring relative to meta substitution.

CHAPTER 9

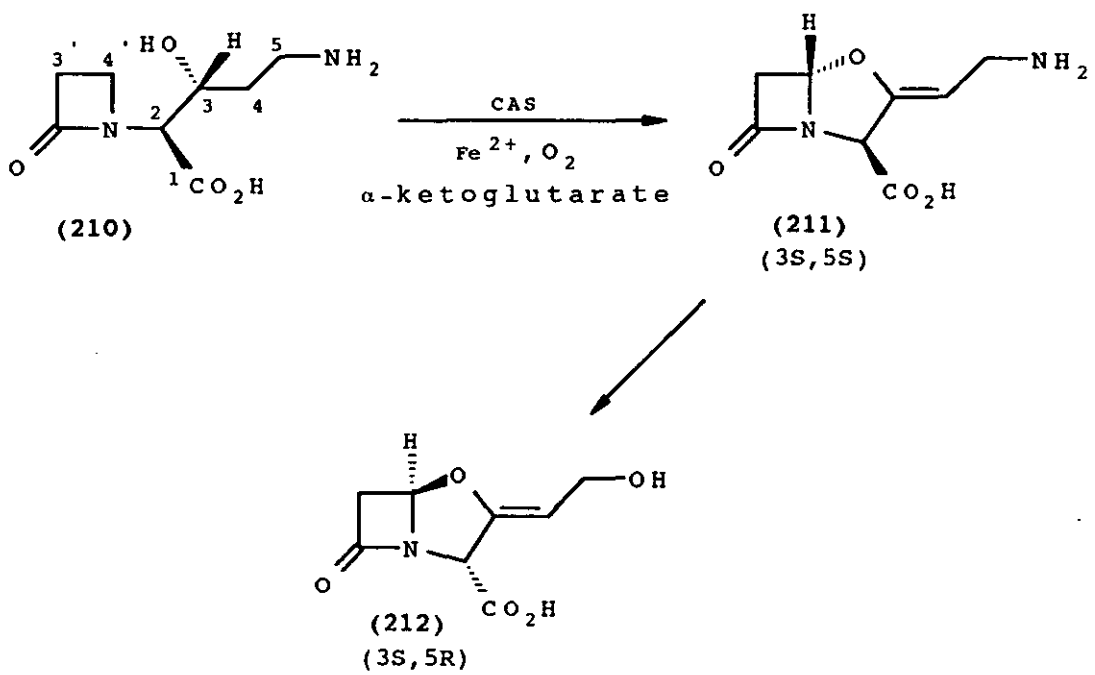
CHAPTER 9.

Approaches To The Application Of Dioxiranes As Possible Biomimetic Oxidants In β-Lactam Chemistry.

9.1 Introduction.

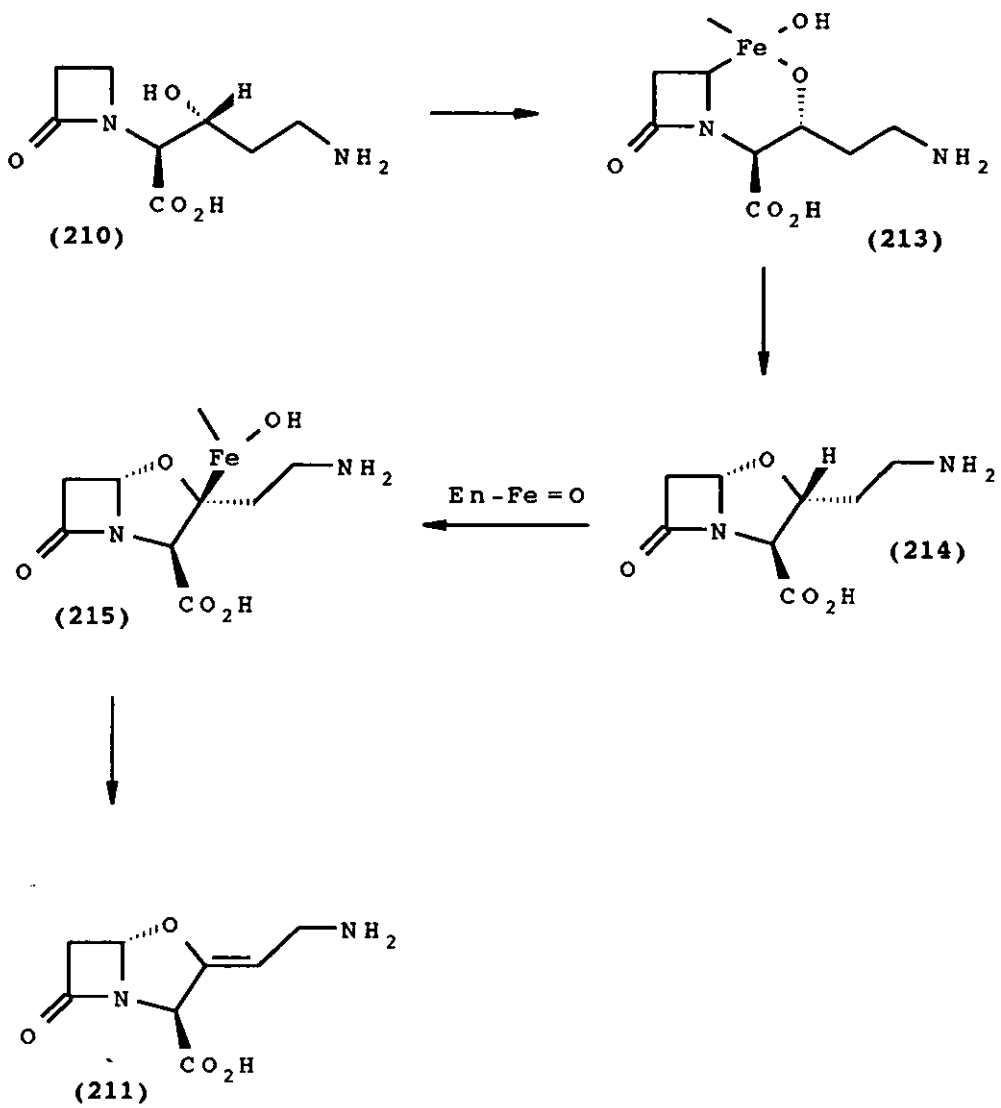
Many strains of bacteria are known to be resistant to penicillins which can be attributed to their production of β-lactamases. To improve the efficiency of penicillin and cephalosporin derivatives, inhibition of β-lactamases is necessary. A commercially important β-lactamase inhibitor which is of current interest to the industrial collaborators is clavulanic acid **(212)**.[97] This fused bicyclic β-lactam is produced by *Streptomyces clavuligerus* and is used in formulation with penicillins to treat β-lactamase producing bacteria.

It is known that biosynthetic precursors of clavulanic acid are clavaminic acid **(211)** and proclavaminic acid **(210)**[97] (Scheme 72).



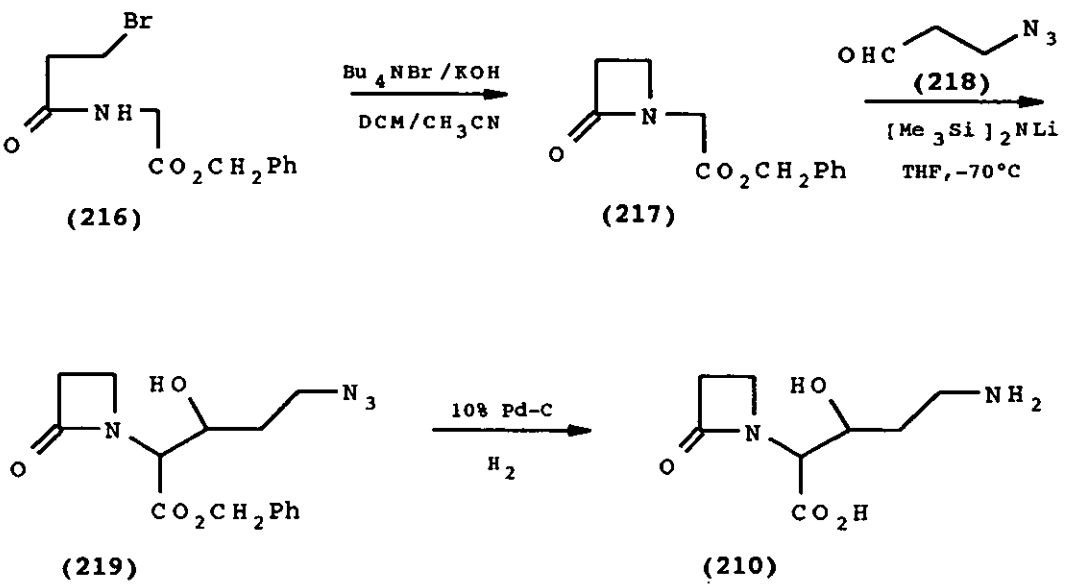
(Scheme 72)

The conversion of **(210)** to **(211)** has been shown to be carried out by an α-ketoglutarate and ferrous dependent oxygenase, clavaminic acid synthase (CAS). Recently this process has been shown to proceed via dihydroclavaminic acid[98] **(214)**. A mechanism for the oxidative cyclisation/desaturation process performed by CAS has been proposed (Scheme 73) and involves the ferryl (IV) species **(213)** similar to other oxygenases.[98,99,100]



(Scheme 73)

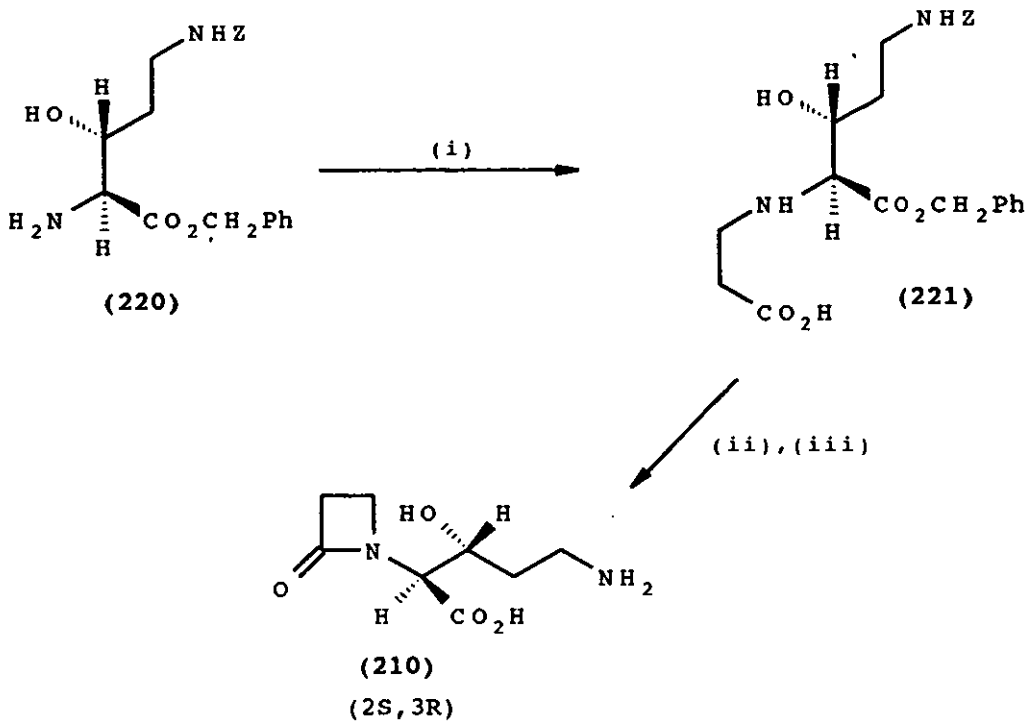
A useful synthetic route to **(210)** and its derivatives has been achieved by condensation of the azetidinone **(217)** with the aldehyde **(218)**. The aldol product **(219)** was formed as two diastereoisomers which after separation were each hydrogenated to form **(210)**[101] (Scheme 74.)



(Scheme 74)

It has been found that only one *threo* enantiomer of **(210)** is bioactive and separation of the enantiomers of threo **(219)** has been achieved by stereospecific enzymic hydrolysis using the protease substilisin Carlsberg [EC 3.4.21.14] to obtain bioactive (2S,3R) **(210)**.

A more recent method for the synthesis of **(210)** has been achieved via a route involving a resolved β-hydroxyornithine which has allowed the absolute stereochemistry of **(210)** to be deduced[102] (Scheme 75).



Z=Ph CH_2OCO-

Reagents.

(i) CH_2=$CHCO_2H/CH_3CN$

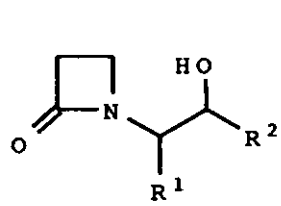
(ii) di-2-pyridyl disulphide, Ph_3P, CH_3CN

(iii) H_2, Pd-C(10%), EtOH

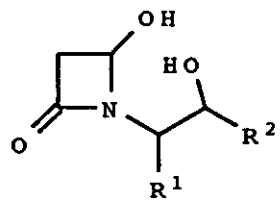
(Scheme 75)

9.2 Dioxiranes as potential oxygenase mimics.

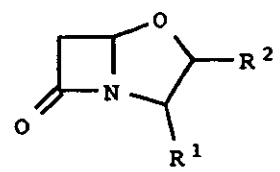
Oxidations of unactivated C-H bonds occur in many biosynthetic reactions, however these processes are less common in synthetic organic chemistry. Our aims were to use dioxiranes for the oxidation of β-lactams with a view to mimicking the cyclisation process of **(210)** to **(211)** carried out by CAS. The enzymic cyclisation involves oxidative cleavage of the C-H bond at C-4 on the β-lactam ring to form the ferryl (IV) intermediate **(213)** which consequently leads to the cyclised product **(214)**. The mechanism of this process using dioxiranes would be different but a possible cyclisation could be explained as follows: Dioxiranes are known to oxidise unactivated methylene C-H bonds to alcohols, e.g: cyclohexane to cyclohexanol[43] and it was therefore considered feasible for dioxiranes to be used to introduce a hydroxyl group at C-4 on the β-lactam ring in compounds such as **(222)**. This may then lead to compounds of the general type **(223)** which could perhaps undergo condensation to form bicyclic β-lactam **(224)** (Scheme 76).



(222)



(223)



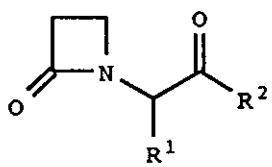
(224)

R^1=H, COOH or CO_2CH_2Ph.

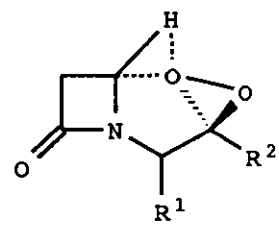
R^2=CH_3, CF_3 or CO_2R

(Scheme 76)

A particularly interesting investigation would be to determine whether oxidation of a monocyclic β-lactam would be possible by intramolecular oxidation. Oxygen atom insertion at C-4 on the β-lactam ring may be possible if dioxiranes of the type **(226)** are formed derived from the corresponding ketone **(225)**.



(225)

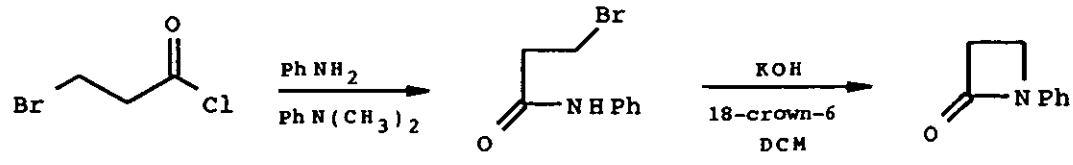


(226)

R^1 and R^2 as for Scheme 76.

9.3 Attempted oxidations of unsubstituted β-lactam rings using dimethyldioxirane.

Initially it was considered useful to prepare a simple β-lactam for model oxidation studies with dioxiranes. N-Phenylazetidin-2-one **(229)**[103a] was prepared in good yield by cyclisation of N-phenyl-3-bromopropanamide **(228)** using pulverised potassium hydroxide in the presence of a phase transfer catalyst (Scheme 77).



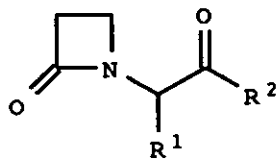
(227) (228) (229)

(Scheme 77)

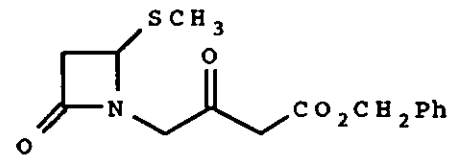
Oxidation of N-phenylazetidin-2-one (**229**) in dichloromethane was attempted using dimethyldioxirane/acetone solution. Four equivalents of dimethyldioxirane were added in three portions over 34 hours. Before each addition the reaction mixture was cooled to about -30°C then allowed to warm to ambient temperature. The mixture was allowed to stand for 53 hours before work-up. TLC revealed a large amount of N-phenylazetidin-2-one was still present and also some polar base-line material (**230**). The infrared spectrum of the crude product mixture (**230**) exhibited a broad absorption at υmax 3440cm^{-1} indicating the presence of a carboxylic acid. The polar material (**230**) which was not soluble in dichloromethane was separated from the N-phenylazetidin-2-one by trituration with deuterium oxide. The spectroscopic data obtained for the unknown mixture (**230**) was as follows; ^{1}H NMR δ 7.4-7.3 (multiplet), 3.6 (triplet), 2.6ppm (triplet), IR υmax 3416 (broad OH) and 1722cm^{-1} (C=O). To confirm the presence of a carboxylic acid and also to allow satisfactory chromatography of this material (**230**) the methyl ester was prepared using diazomethane. TLC showed that a mixture of compounds was present in the crude product (**231**) and in the ^{1}H NMR spectrum a singlet at δ 3.6ppm did indeed confirm formation of a methyl ester. Purification of the crude product (**231**) by preparative TLC afforded two main products (**232**) and (**233**). The minor component (**232**) was shown to be the methyl ester of the ring opened β-lactam (**229**), methyl β-anilinopropionate (**232**)[103b] the ^{1}H NMR spectrum of which was found to be identical to an authentic sample. The second compound (**233**) contained the methyl ester functional group and exhibited some rather unusual spectroscopic data. ^{1}H NMR δ 7.5(m, Ar-H), 4.3 (t), 3.6 (s, methyl ester), 2.6ppm (t) and the mass spectrum showed *m/z* 179. The ^{1}H NMR spectrum indicated the presence of two methylene groups each appearing as a triplet in the spectrum but one of which was at rather low field δ 4.3ppm and not consistent with a structure of the type (**232**). As yet this structure has not been elucidated and attempts to repeat this experiment have been unsuccessful. Oxidation of N-phenylazetidin-2-one is extremely slow with dimethyldioxirane and generally >90% recovery of starting material is obtained. A similar level of poor reactivity has also been found with benzyl (2-oxoazetidin-1-yl)acetate (**217**). It can therefore be concluded from these results that the β-lactam ring is not readily oxidised with dimethyldioxirane.

9.4 Approaches to β-lactams suitable for intramolecular dioxirane oxidations.

We turned our attention to the synthesis of β-lactams suitable for intramolecular oxidation. Compounds of the type **(234)** have been prepared[104] and we decided that a similar strategy could be employed to reach our desired target molecules **(225)**.

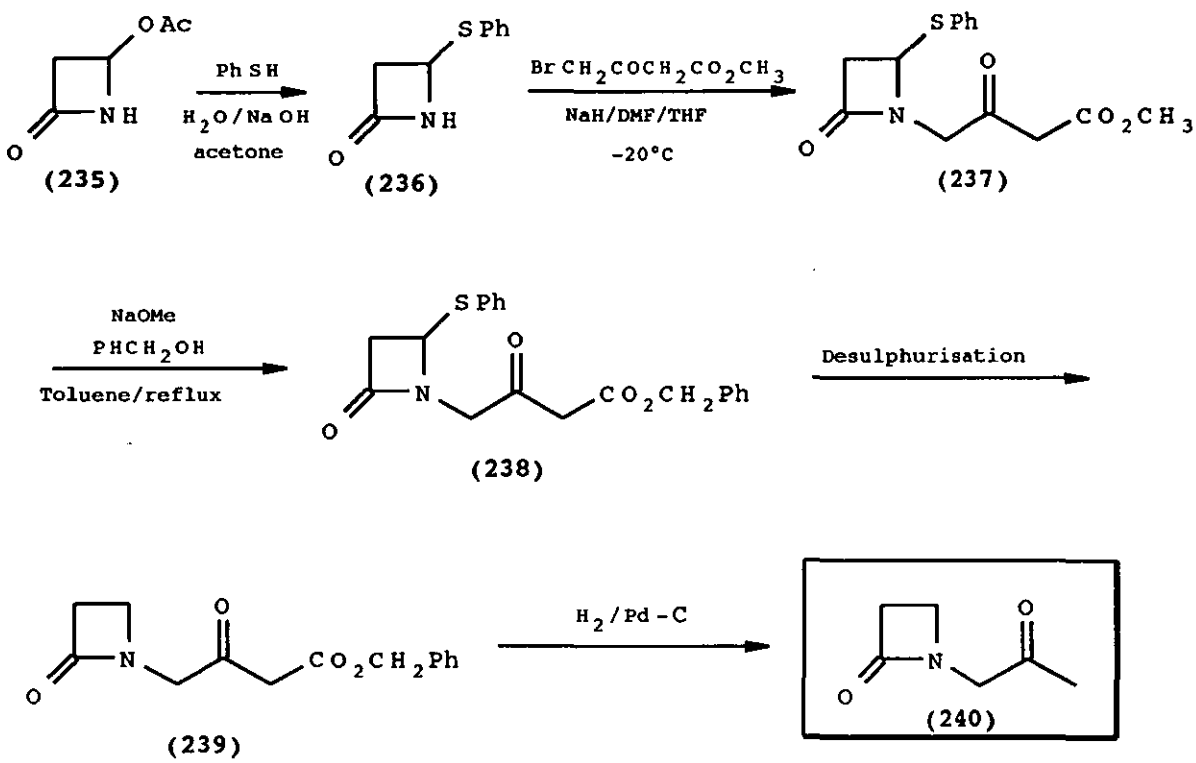


(225)



(234)

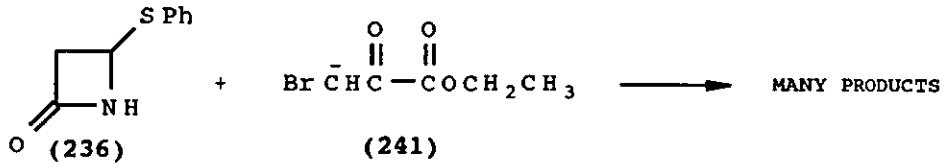
Our proposed synthesis was as follows, (Scheme 78).



(Scheme 78)

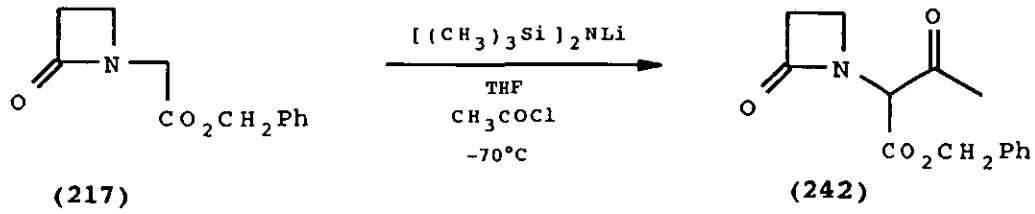
Reaction of 4-acetoxyazetidin-2-one (**235**) with thiophenol gave 4-phenyl thioazetidin-2-one (**236**) in 71% yield. N-alkylation of (**236**) with methyl 4-bromoacetoacetate afforded the keto-ester (**237**) in 16% yield which was trans-esterified to the benzyl ester (**238**) {IR υmax 1762(C=O), 1740cm^{-1}(C=O keto-ester), ^{1}H NMR δ 7.40-7.30(m, 10H, 2Ph), 5.20(s, 2H, OC$\underline{H}_2$Ph), 5.20-5.18(m, 1H, H4 β-lactam), 4.40(d, J=18.5, 1H, -NCH*H*CO-), 3.95(d,J=18.7, 1H, -NC*H*HCO-), 3.42(s, 2H, COC$\underline{H}_2$CO), 3.40(dd, J=15, J=5, 1H, H3 β-lactam), 2.85(dd, J=15, J=2, 1H, H3 β-lactam), Found: *m/z* 369(5), $C_{20}H_{19}NO_3S$ requires *m/z* 369}. Attempted desulphurisation of (**238**) using Raney nickel at neutral pH or AIBN/tributyl tin hydride[105] was unsuccessful and resulted in decomposition of the β-lactam (**238**).

It is interesting to note that bromopyruvate derivatives were found not to be suitable for N-alkylation of (**236**) as a mixture of products was obtained none of which were starting material nor required product. A possible explanation for this may be that the acidity of the methylene protons is such that deprotonation to form the anion (**241**) may occur which could then react with the β-lactam ring to give many possible products (Scheme 79).



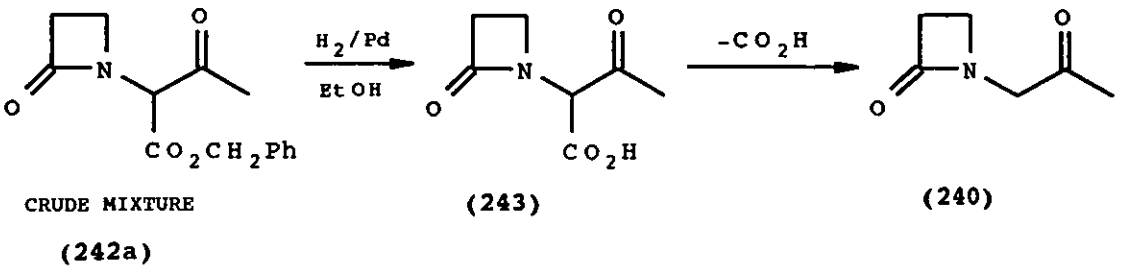
(Scheme 79)

As successful desulphurisation of (**238**) could not be achieved an alternative approach to these types of compounds was adopted. It is known[101] that aldol condensations can be performed with (**217**) (Scheme 74), so we attempted a similar reaction using an acid chloride instead of the aldehyde (Scheme 80).



(Scheme 80)

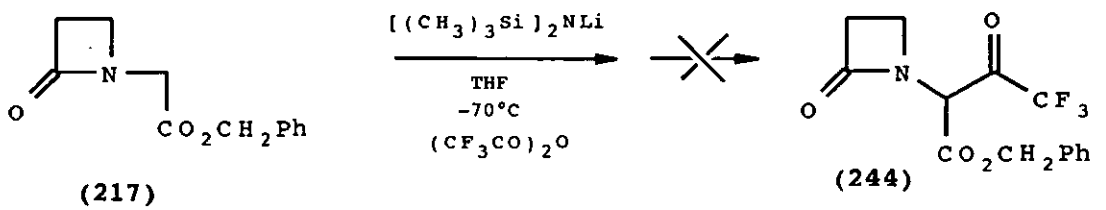
This reaction was rather poor however and only 30% conversion of (**217**) was possible (determined using ^1H NMR spectroscopy and by comparison of the integrations of the benzyl methylene groups of (**217**) and (**242**)). The product (**242**) was difficult to isolate by chromatography so the crude mixture (**242a**) was hydrogenated (Scheme 81).



(Scheme 81)

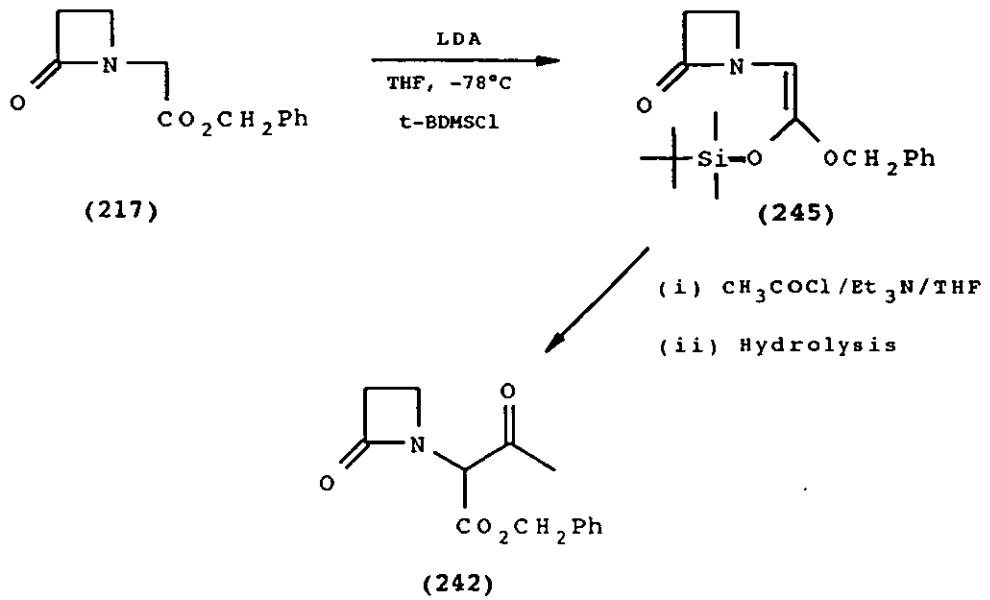
A small amount of the required product (**240**) was obtained (16% yield based on 30% conversion of starting material (**217**)). The inefficient step in this procedure was clearly the initial alkylation reaction (Scheme 80).

A similar reaction using trifluoroacetic anhydride was attempted to try and introduce a trifluoroacetyl group to form (**244**) but was unsuccessful and only unreacted (**217**) was recovered (Scheme 82).



(Scheme 82)

Silyl ketene acetals are known to condense with acid chlorides and anhydrides to form β-keto esters.[106] We therefore considered it reasonable to use this approach to obtain the required β-keto ester (**242**) (Scheme 83).

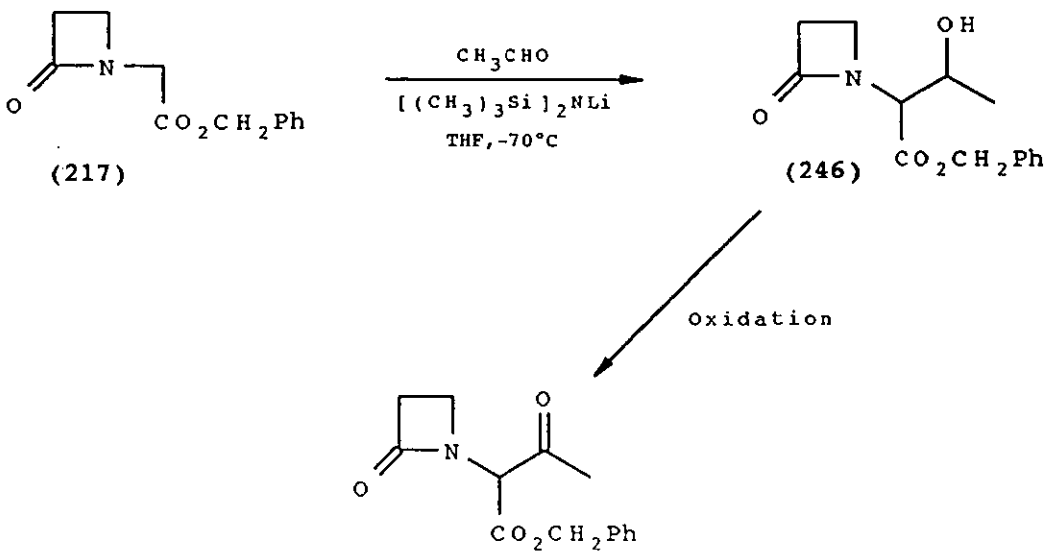


(217) (245) (242)

(Scheme 83)

Attempts to prepare the t-butyldimethylsilyl ketene acetal (245) of (217) using LDA as the base at -78°C in THF or using HMPA as a co-solvent were unsuccessful and only (217) was recovered.

As the aldol condensation of (217) with an aldehyde is known to proceed in good yields we decided an improved method would be to prepare the required aldol product and then oxidise the alcohol to the ketone (Scheme 84).



(217) (246) (242)

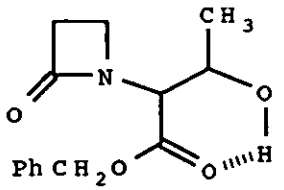
(Scheme 84)

Aldol condensation of (**217**) with acetaldehyde afforded the product (**246**) in moderate yield (48%), {IR υmax (film) 3400(s, OH), 1756cm^{-1}(br, C=O groups), ^{1}H NMR 250MHz δ 7.36(s, 5H, Ph), 5.23(s, 2H, $C\underline{H}_2$Ph), 4.3(m, 1H, H3), 4.08(d, J=3.8, 2H, H2 and OH), 3.38-3.29(m, 2H, H4 CH_2 β-lactam), 2.97(t, J=4.0, H3 CH_2 β-lactam), 1.3(d, J=7, 3H, CH_3) ratio of diastereomers 25:75}. The oxidation of (**246**) to (**242**) was attempted using several standard methods (Table 1), however this was found to be rather more difficult than expected. The use of PDC,[107a] PCC[107b] and also a Swern oxidation using oxalyl chloride/DMSO[107c] were found to give only starting material (**246**). Some oxidation of (**246**) in dichloromethane solution with two equivalents of DMD/acetone was achieved but the reaction was very slow and only 41% yield of (**242**) was obtained based on 58% conversion of (**246**).

Table 1. *Methods used for attempted oxidation of* (**246**) *to* (**242**).

Oxidation Method	Result
PDC/DCM	Recovery of (**246**)
PCC/DCM	Recovery of (**246**)
Swern oxidation	Recovery of (**246**)
DMD/acetone	Formation of (**242**) 41% yield based on 58% recovery of (**246**)

It is possible that the poor reactivity of the hydroxyl may be attributed to some intramolecular hydrogen bonding to the ester carbonyl (**247**). The industrial collaborators have found that a hydroxyl group at C-3 as for compound (**246**) is rather unreactive, highlighted by the difficulty in preparing silyl ether derivatives.[107d] As the dioxirane oxidation could proceed via an oxygen atom insertion mechanism into the C-H bond this could perhaps explain why some oxidation is observed. (cf. the mechanisms of the other oxidations proceed via attack of the oxidising agent on the hydroxyl group).



(247)

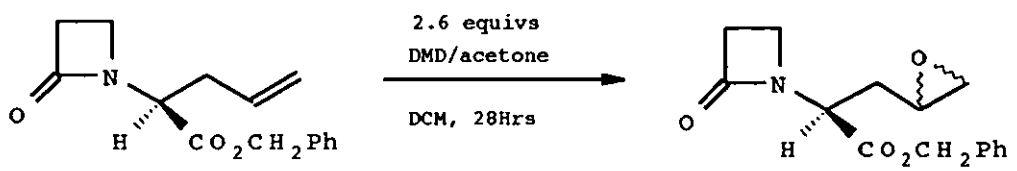
As satisfactory quantities of suitable β-lactams containing a carbonyl β to the ring nitrogen atom were not obtained no intramolecular oxidations were attempted during the course of this work.

9.5 Oxidation of Benzyl 2-(2-oxoazetidin-1-yl)-4-pentenoate.

The observation that dimethyldioxirane does not readily oxidise the β-lactam ring was found to be useful in that epoxidation of the β-lactam **(248)** could be achieved selectively. Oxidation using mCPBA has been found to be rather slow and poor yielding[108] and it was considered that dimethyldioxirane may allow the epoxidation to proceed more efficiently.(Note: dioxiranes are known to epoxidise terminal and exocyclic double bonds in good yields).[30,32]

The oxidation was performed in two ways, (i) using dimethyldioxirane/acetone solution and (ii) using the biphasic *in situ* generated dioxirane system.

(i).

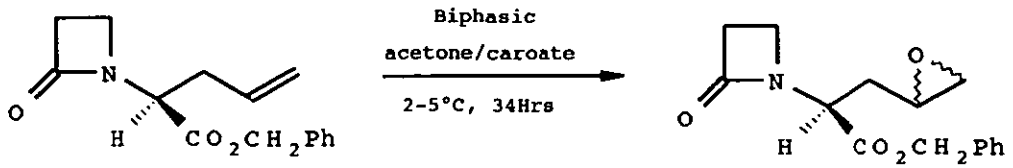


(248) (249)

(Scheme 85)

2.6 Equivalents of DMD/acetone solution were added to **(248)** in dichloromethane over 28 hours in three portions at 0-5°C. TLC of the crude product showed complete reaction of **(248)** and formation of the epoxide **(249)** and also some base-line material. Purification by preparative TLC afforded the epoxide **(249)** in 57% yield. Spectroscopic data for the product were identical to those of an authentic[108] sample of **(249)** (Scheme 85).

(ii).



(248) **(249)**

(Scheme 86)

Compound **(248)** was also oxidised using *in situ* generated dimethyldioxirane over 34 hours and afforded pure epoxide **(249)** in 36% yield (Scheme 86).

9.6 Concluding remarks.

As seen in Section **9.3**, an unsubstituted β-lactam ring is rather unreactive towards dimethyldioxirane. Also preparation of β-lactams of the general type **(225)** by several different methods has not been particularly successful. This was due either to poor yields in the alkylation step of the β-lactam as with compounds **(237)** and **(242)**, or the oxidation of a 3-hydroxyl group as for the aldol product **(246)**, has been rather difficult. The latter may be explained by involvement of intramolecular hydrogen bonding **(247)**. Dimethyldioxirane also provides quite an effective means of epoxidising the terminal double bond of the β-lactam **(248)**.

CONCLUSION

CONCLUSION.

During this research a variety of interesting results have been obtained. A range of ketones used to generate dioxiranes *in situ* not previously reported have been investigated throughout this work and their use as effective oxidants assessed. It has become clear that increasing the bulk of the dioxirane generally decreases the rate of oxidation.

Good evidence that dioxiranes epoxidise alkenes via a spiro transition state has been obtained. Where the double bond of an alkene is sterically hindered, oxidation at the allylic position may occur.

An efficient and selective oxidation of estradiol derivatives at the C-9 benzylic position to afford the corresponding 9α-hydroxy compounds has been established using dimethyldioxirane.

Dioxiranes provide an excellent means for oxidising C-H bonds and results supporting an oxygen atom insertion mechanism have been obtained. Equatorial C-H bonds are oxidised in preference to axial C-H bonds where a six-membered transition state involving hydrogen bonding has been proposed to explain the difference in rate for the oxidation of epimeric alcohols. Also oxidation of benzylic C-H bonds adjacent to an oxygen atom has been possible using dimethyldioxirane where benzyl ethers are oxidised to the corresponding hydroxy derivatives but benzyl esters appear unreactive. Furthermore this may provide a novel method for the oxidative cleavage of benzyl ethers.

Epoxides of chromenes which are often difficult to obtain using peroxyacid methods can be readily prepared using dimethyldioxirane in excellent yields.

Chiral dioxiranes generated *in situ* as potential asymmetric epoxidising agents have shown rather poor levels of asymmetric induction (ca 11%). Also slow rates of oxidation were observed which is attributed to steric hindrance about the dioxirane ring. Approaches to more reactive dioxiranes using fluorine substituted acetophenone derivatives as dioxirane precursors have been assessed. A trifluoromethyl group α to the dioxirane ring and ortho and para fluorine substitution increase the reactivity of the dioxirane compared with dimethyldioxirane.

Unsubstituted β-Lactam ring systems have been found not to be readily oxidised by dimethyldioxirane.

EXPERIMENTAL

EXPERIMENTAL.

GENERAL.

Preparative TLC. performed on either 0.2 metre or 1.0 metre glass backed plates coated with Merck Kieselgel $60PF_{254}$.

Column Chromatography. performed using Sorbsil C60 (40-60 μm).

IR. IR spectrum recorded using a Pye Unicam PU9516 spectrometer. The samples were recorded as a nujol mull unless stated otherwise.

^{1}H NMR. Spectra recorded using either a Varian EM360A (60MHz), Bruker AC 250 or a Bruker AM 250 (250MHz). Samples were recorded in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise stated. Chemical shifts (δ) are reported in ppm. Multiplicities are reported as follows: **br** (broad), **s** (singlet), **d** (doublet), **t** (triplet), **q** (quartet), **m** (multiplet). **J**-Values are given in Hz.

^{13}C NMR. Spectra recorded using a Bruker AC 250 (250MHz).

Mass Spectra. Recorded using either a Kratos M.S.80, VG70-250S or a VG 7070F.

Microanalysis. Performed at Medac Ltd. (Brunel University).

UV. Shimadzu UV160 ultraviolet spectrometer.

Melting points. Carried out using either a Kofler hot stage apparatus or a Electrothermal digital melting point apparatus and are uncorrected.

GLC. Performed on the following:

Pye Unicam Series 104. (25 metre BP1 capillary column).
Pye Unicam Series 104. (Carbowax 20M column).
Carlo Erba GC6000 Vega series 2. (12 metre BP1 capillary column).

Helium was used as the carrier gas in all cases.
Silyl ether derivatives of alcohols prepared using Tri-sil® obtained from Pierce Chemicals.

Optical Rotation. Recorded on a Optical Activity AA100 polarimeter. All samples run in chloroform solution at 25°C unless stated otherwise.

pH Stat. experiments controlled using a Radiometer autotitrator. Type ABU 11b.

Ketone/caroate reactions.

Notes:

(i) All glassware was washed thoroughly with a solution of EDTA, dried in an oven and rinsed with DCM (note: it is important that no residual acetone is present on the glass surfaces).

(ii) The symbol * at the top of an experimental procedure indicates that the pH of the reaction mixture was controlled using a pH Stat. by addition of 5M KOH solution. The reactions were also buffered using a pH7.5 phosphate buffer (prepared from potassium dihydrogen orthophosphate (1.179g) and disodium hydrogen phosphate (4.302g) diluted to 1L with distilled water).

(iii) Sodium sulphite was added to the reaction mixture before work-up to allow reduction of any residual peroxides.

Work-up. refers to the following general procedure:

The organic layer was separated from the aqueous layer and washed successively with sodium bicarbonate and saturated sodium chloride solutions. The organic layer was then separated and dried over anhydrous sodium sulphate. Filtration and evaporation of the solvent affords the product residue.

Evaporation of solvent- refers to removal of solvent *in vacuo* using a Büchi rotary evaporator.

SOLVENTS.

Solvents were dried and distilled using the following procedures.

Acetone.	Refluxed over potassium permanganate and distilled.
Methanol.	Magnesium/iodine added to form magnesium alkoxide, mixture refluxed and distilled.
Ethanol.	Method as for methanol.
t-Butanol.	Method as for methanol.
Ethyl Acetate.	Dried over calcium chloride and distilled.
Ether.	Distilled from calcium chloride and stored over sodium wire.
1,4-Dioxane.	Method as for ether.
Pet Ether 40/60.	Distilled from calcium chloride.
DMF.	Stirred over calcium hydride, filtered then distilled *in vacuo*.
DMSO.	Stirred over calcium hydride, filtered then distilled *in vacuo*.
THF.	Refluxed over potassium metal in the presence of benzophenone and distilled under nitrogen.
Triethylamine.	Refluxed over potassium hydroxide pellets and distilled.
Diisopropylamine.	Refluxed over calcium hydride and distilled.
Benzene.	Dried over sodium wire and distilled.
Dichloromethane.	Refluxed over phosphorous pentoxide and distilled.
Chloroform.	Refluxed over phosphorous pentoxide and distilled.
Acetonitrile.	Refluxed over phosphorous pentoxide and distilled.

Preparation of Dimethyldioxirane/acetone solutions (DMD/acetone).[115]

Safety note: *Reaction should be performed in the hood and behind a safety shield, dimethyldioxirane is a highly volatile peroxide of unknown toxicity therefore keep solutions below 30°C, avoid skin contact and do not inhale vapour.*

Method. Into a 500ml 3 neck round bottom flask was placed sodium bicarbonate (36g), distilled water (40ml), EDTA (0.2g), acetone (30ml) and a teflon magnetic stirrer bar. The flask was connected to the bottom of an air condenser (packed loosely with glass wool). The top of the condenser was connected to the top of a cooling condenser (-78°C, dry ice/acetone). The bottom of the cooling condenser was fitted with a 100ml collection flask and a trap connected to a water aspirator. The collection flask was cooled to -78°C. The mixture in the reaction flask was maintained below 10°C and stirred vigorously whilst solid Oxone (65g) was added in three portions over 15 minutes. The ice bath was then removed and a slight vacuum applied (ca. 100mmHg). The pale yellow *dimethyldioxirane/acetone* solution was seen to distil over (approx. 25ml). The distillation was complete after about 1 hour. DMD/acetone solution dried over sodium sulphate at -20°C for 1 hour then filtered and kept over 4Å molecular sieves.

Iodometric titration.

A sample of DMD/acetone solution (1.0ml) was pipetted into a 10ml volumetric flask (<0°C). To this was added a solution of 3:2(v/v) acetic acid/acetone (2ml) and saturated potassium iodide solution (2ml). The resultant mixture was stoppered and left to stand in the dark for 10 minutes at ambient temperature. The solution was made up to 10ml with water and 3 aliquots taken each of (1.0ml) titrated against sodium thiosulphate solution (ca. 0.8mM). Concentrations of DMD/acetone solutions are in the range 0.04M-0.10M.

Preparation of diazomethane solution in ether.[116]

Safety note: *Diazomethane is highly toxic and potentially explosive. Perform all operations in the hood and wear gloves.*

Method. Into the 1 litre reaction vessel of a 'diazomethane kit' was placed potassium hydroxide (1.0g) in water (1.6ml) and ethanol (5ml). The flask was fitted with a cooling condenser at -78°C. A dropping funnel was put onto the top of the flask and was charged with Diazald (0.2g,0.93mmol) in ether(10ml), (generally 1.1 mole equivalents of diazald used for each mole of diazomethane required). The reaction flask was warmed to 60°C using an oil bath and the diazald solution added dropwise such that the rate of addition was the same as that of the *diazomethane/ether* solution distilling into the cooled collection flask (in an ice bath) at the bottom of the cooling condenser.

CHAPTER 2.

Reaction of cholesterol (98) with the acetone/caroate system.*

To cholesterol (0.500g, 1.3mmol) in DCM (10ml) was added acetone (10ml), TBAHS (0.100g, 0.3mmol) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C. To this was added a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.008g, 0.2mmol) in water (20ml) dropwise over 7 hours. The mixture was then left stirring for a further 18 hours. Work-up gave the crude product (0.544g) containing 3β-hydroxy-5,6-epoxycholestane. The crude product mixture was passed through a short column (TLC silica gel, ether/MeOH 93:7) to remove the phase transfer catalyst to afford pure 3β-*hydroxy*-5,6-*epoxycholestane*[54] (0.471g, 90.4%). IR. υmax 3380 (OH), 1728, 1650cm^{-1}. ^{1}H NMR δ 3.5(br, 1H, H3), 3.1(d, 1H, β-H6), 2.9(d, 1H, α-H6), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19 Me), 0.8(s, 3H, C-18 Me).

Epoxide ratio: (α:β 65:35)

Reaction of cholesteryl acetate (99) with the acetone/caroate system.*

To cholesteryl acetate (2.0g, 4.6mmol) in DCM (45ml) was added acetone (20ml, 0.27mol), TBAHS (0.350g, 1.0mmol) and phosphate buffer (25ml). The mixture was maintained at pH7.5 and 2-5°C. A solution of Oxone (7.5g, 12.2mmol) in water (45ml) was added dropwise over 1½hours and the mixture left stirring for a further 16 hours. Work-up gave the crude product (2.210g) containing 3β-acetoxy-5,6-epoxy-cholestane.[54] Column chromatography (grade 3 alumina, ether) afforded pure 3β-*acetoxy*-5,6-*epoxycholestane* (**99a**) (1.779g, 85.7%). IR. υmax 1734(C=O), 1256, 1244cm^{-1}, ^{1}H NMR δ 5.2-4.8(br, 1H, H3), 3.1(d, 1H, β-H6), 2.9(d, 1H, α-H6), 2.1(s, 3H, CH_3CO), 1.9-0.6(complex, steroid ring system).

Epoxide ratio: (α:β 40:60)

Reaction of cholesterol with the cyclohexanone/caroate system.*

To cholesterol (0.500g, 1.3mmol) in dichloromethane (10ml) was added cyclohexanone (0.78g, 8.0mmol), TBAHS (0.15g, 0.44mmol) and phosphate buffer (20ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (4.0g, 6.5mmol) and EDTA (0.1g, 0.25mmol) in water (40ml) over 4 hours then left stirring for a further 1 hour. Work-up gave the crude product (0.740g) in which 3β-hydroxy-5,6-epoxycholestane, cyclohexanone and ε-caprolactone were present. Column chromatography (flash silica gel, Ether/Pet ether/DCM 80:19:1) afforded pure 3β-*hydroxy*-5,6-*epoxycholestane*[54] (0.308g, 59%). IR. υmax 3384(OH), 1728, 1650cm^{-1}, ^{1}H NMR δ 3.5(br, 1H, H3), 3.1(d, 1H, β-H6), 2.9(d, 1H, α-H6), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19Me), 0.8(s, 3H, C-18Me).

Epoxide ratio: (α:β 55:45)

Reaction of cholesterol with the 2-methylcyclohexanone (103)/caroate system.*

To cholesterol (0.507g, 1.3mmol) in dichloromethane (20ml) was added 2-methyl-cyclohexanone (2.158g, 19mmol), TBAHS (0.4g, 1.2mmol) and phosphate buffer (20ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (11.0g, 17.9mmol) and EDTA (0.2g, 5.4mmol) in water (40ml) over 12 hours then left stirring for a further 14 hours. Work-up gave the crude product (3.062g) containing 3β-hydroxy-5,6-epoxycholestane. Column chromatography (flash silica gel, Ether/DCM 80:20) afforded pure 3β-*hydroxy*-5,6-*epoxycholestane*[54] (0.372g, 70%). IR. υmax 3380cm^{-1}(OH), ^{1}H NMR δ 3.5(br, 1H, H3), 3.1(d, 1H, β-H6), 2.9(d, 1H, α-H6), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19Me), 0.8(s, 3H, C-18Me).

Epoxide ratio: (α:β 35:65)

SYNTHESIS OF 2-HYDROXY-2-METHYLCYCLOHEXANONE (108).

Conversion of 2-methylcyclohexanone to 2-methyl-1-trimethylsilyl-oxycyclohex-1-ene (105).[55]

To 2-methylcyclohexanone (11.20g, 0.1mmol) under an atmosphere of dry nitrogen was added triethylamine (14.00g, 0.14mmol). This was stirred well in an ice bath for 10 minutes then chlorotrimethylsilane (15.00g, 0.137mmol) was added dropwise over 10 minutes. The ice bath was then removed and replaced with a water bath at 40°C and the mixture left stirring for a further 15 minutes. The water bath was then removed and a solution of sodium iodide (dried in a vacuum oven 24 hours before use) (20.50g, 0.14mmol) in acetonitrile (130ml) was added dropwise at such a rate as to maintain a reaction temperature of 40-50°C. The mixture was left stirring for a further 3 hours then poured onto ice/water (500ml) and stirred. The mixture was then extracted with petroleum ether 40/60 (5x50ml). The organic layer was separated and distilled at atmospheric pressure through a 17cm vigreux column to remove the petroleum ether. The product residue was then distilled through a 5cm vigreux column and the silyl enol ether (**105**) was collected at 79°C @ 12mmHg (16.1g, 87%). ^{1}H NMR δ 2.0(m), 1.5(m), 0.17(s, 9H, $SiMe_3$).

Conversion of 2-methyl-1-trimethylsilyloxycyclohex-1-ene (105) to 2-trimethylsiloxy-2-methylcyclohexanone (107).[56]

To a well stirred suspension of mCPBA (9.00g, 52mmol) in dry hexane (450ml) at -19°C (cooled in an ice/MeOH bath) was added a solution of silyl enol ether (**105**) (7.00g, 38mmol) in hexane (20ml) dropwise over 15 minutes. The mixture was left stirring for a further 2 hours then filtered to remove the residual mCPBA. Evaporation of the hexane left *2-trimethylsiloxy-2-methylcyclohexanone* (**107**) as a clear oil (4.94g). ^{1}H NMR δ 1.8(m), 1.4(s, 3H, C-2Me group), 0.2(s, 9H, $SiMe_3$).

Hydrolysis of α-siloxy ketone (107) to 2-hydroxy-2-methylcyclohexanone.

To 2-trimethylsiloxy-2-methylcyclohexanone **(107)** (4.90g) in DCM (450ml) was added dropwise tetrabutylammonium fluoride (40ml, 1.1M solution in THF) over 5 minutes. The mixture was left stirring for a further 16 hours at ambient temperature. The DCM solution was then washed successively with aqueous sodium bicarbonate solution, 1.5M hydrochloric acid and aqueous sodium chloride. The DCM layer was dried (magnesium sulphate) then filtered and the solvent evaporated to give the crude product which was then distilled (75-78°C @ 12mmHg). TLC showed that two compounds were present, the major product being 2-hydroxy-2-methylcyclohexanone (confirmed by IR and NMR spectra). Further purification by column chromatography (silica gel, DCM/MeOH 50:1) and kugelrohr distillation gave pure *2-hydroxy-2-methylcyclohexanone* **(108)**[56] (1.71g, 35%). Bpt. 75-78°C @12mmHg, IR. υ_{max} (film) 3472(OH), 1712cm^{-1} (C=O), ^{1}H NMR δ 3.9(br, 1H, D_2O exchange O<u>H</u>), 2.4(m), 1.85(m), 1.33(s, 3H, Me).

Reaction of cholesterol with the 2-hydroxy-2-methylcyclohexanone/caroate system.*

To cholesterol (0.156g, 0.4mmol) in dichloromethane (10ml) was added 2-hydroxy-2-methylcyclohexanone (0.301g, 2.3mmol), TBAHS (0.10g, 0.3mmol) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (4.0g, 6.5mmol) and EDTA (0.1g, 0.25mmol) in water (20ml) over 6 hours then left stirring for a further 1 hour. TLC of DCM layer showed disappearance of 2-hydroxy-2-methylcyclohexanone but formation of 3β-hydroxy-5,6-epoxycholestane was evident. Work-up of the DCM layer gave the crude residue (0.274g). TLC showed that unreacted cholesterol, 3β-hydroxy-5,6-epoxycholestane, and TBAHS were present. Column chromatography (flash silica gel, Ether/Pet ether/DCM 80:19:1) gave unreacted cholesterol (0.100g) and 3β-*hydroxy*-5,6-*epoxycholestane* (0.060g, 37%). IR. υ_{max} 3384 (OH), 1728, 1650cm^{-1}, ^{1}H NMR δ 3.5(br, 1H, H3), 3.1(d, 1H, β-H6), 2.9(d, 1H, α-H6), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19 Me), 0.8(s, 3H, C-18 Me).

Epoxide ratio: (α:β 40:60)

The aqueous layer was then acidified (2M HCl) and extracted with ether (6x20ml). The ether layer was then dried (Magnesium sulphate). Filtration and evaporation of solvent gave a pale brown liquid (0.090g). IR υ_{max} (film) 3456-3000 (OH of -COOH), 1704cm^{-1} (C=O), ^{1}H NMR δ 10.3(s, 1H, D_2O exchanges COOH), 2.4(m), 2.1(s, CH_3CO), 1.87(m).

Fragmentation of 2-hydroxy-2-methylcyclohexanone with caroate.*

To 2-hydroxy-2-methylcyclohexanone (0.200g, 1.6mmol), in DCM (20ml) was added TBAHS (0.15g, 0.44mmol) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (4.0g, 6.5mmol) and EDTA (0.1g, 0.25mmol) in water (25ml) over 3 hours. TLC revealed the disappearance of the α-hydroxy ketone **(108)**. Work-up of the aqueous layer by acidification (2M HCl) and ether extraction afforded *6-oxo-heptanoic acid* **(110)** as a pale brown liquid (0.155g). IR υmax (film) 3500-3000(br, OH of COOH), 1706cm^{-1}(C=O), ^{1}H NMR δ 11.2(s, 1H, exchanges with D_2O, COOH), 2.4(m, 4H), 2.1(s, 3H, CH_3CO), 1.7(m, 4H). Total integration infers 12 protons are present in the compound.

Preparation of methyl 6-oxo-heptanoate (111).

To 6-oxo-heptanoic acid (0.125g, 0.87mmol) in ether (20ml) was added dropwise over 30 minutes a freshly prepared ether solution of diazomethane (0.9mmol). The mixture was cooled in ice and left stirring open to air for 2½ hours. The ether was then washed with sodium bicarbonate solution and water. The ether layer was dried, filtered and the solvent evaporated to give a pale yellow liquid **(111)**[57] (0.085g). IR υmax (film) 1735(C=O), 1716cm^{-1}, ^{1}H NMR δ 3.7(s, 3H), 2.3(m, 4H), 2.1(s, 3H), 1.7(m, 4H). Data identical to literature values.

Reaction of cholesterol with the ethyl pyruvate/caroate system.*

To cholesterol (0.507g, 1.3mmol) in dichloromethane (50ml) was added ethyl pyruvate (0.980g, 8.4mmol), TBAHS (0.17g, 0.5mmol) and phosphate buffer (50ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (10.0g, 16.0mmol) and EDTA (0.2g, 5.4mmol) in water (60ml) over 1½hours then left stirring for a further 4½hours. Work-up gave the crude product containing 3β-hydroxy-5,6-epoxy-cholestane and some ethyl pyruvate. The crude product was dissolved in methanol and stirred with potassium carbonate to convert ethyl pyruvate to the potassium salt. Water (500ml) was added to the mixture and extracted with ether. The ether layer was separated and dried, filtered and the solvent evaporated to afford 3β-*hydroxy*-5,6-*epoxycholestane* (0.440g, 83%). IR. υmax 3380 (s, OH), ^{1}H NMR δ 3.5(br, 1H, H3), 3.1(d, 1H, β-H6), 2.9(d, 1H, α-H6), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19 Me), 0.8(s, 3H, C-18 Me).

Epoxide ratio: (α:β 64:36)

Reaction of cholesterol with the α,α,α-trifluoroacetophenone/caroate system.*

To cholesterol (0.200g, 0.5mmol) in dichloromethane (15ml) was added α,α,α-trifluoroacetophenone (0.090g, 0.5mmol), TBAHS (0.2g, 0.6mmol) and phosphate buffer (20ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (16.0g, 26.0mmol) and EDTA (0.2g, 5.4mmol) in water (100ml) over 2 hours then left stirring for a further 18 hours. Work-up gave the crude product mixture containing 3β-*hydroxy*-5,6-*epoxycholestane.* ^{1}H NMR 250MHz δ (Crude product) 5.3(d, H6 from unreacted cholesterol), 3.5(br, 1H, H3), 3.1(d, 1H, β-H6 epoxide), 2.9(d, 1H, α-H6 epoxide), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19 Me), 0.8(s, 3H, C-18 Me).

Epoxide ratio: (α:β 48:52)

Reaction of cholesterol with the 4'-fluoroacetophenone/caroate system.*

To cholesterol (0.100g, 0.26mmol) in dichloromethane (20ml) was added 4'-fluoroacetophenone (0.035g, 0.26mmol), TBAHS (0.2g, 0.6mmol) and phosphate buffer (35ml). The mixture was maintained at pH7.5 and 2-5°C. To this was then added a solution of Oxone (28.0g, 46mmol) and EDTA (0.2g, 5.4mmol) in water (140ml) over 4 hours then left stirring for a further 18 hours. Work-up gave the crude product mixture containing 3β-*hydroxy*-5,6-*epoxycholestane.* ^{1}H NMR 250MHz δ (Crude product) 5.3(d, H6 from unreacted cholesterol), 3.1(d, 1H, β-H6 epoxide), 2.9(d, 1H, α-H6 epoxide), 2.0-0.5(complex, steroid ring system), 1.1(s, 3H, C-19 Me), 0.8(s, 3H, C-18 Me).

Epoxide ratio: (α:β 46:54)

Reaction of 3-benzyloxycholesterol (100) with DMD/acetone.

To 3-benzyloxycholesterol (0.150g, 0.3mmol) in DCM (5ml) was added 1.0 equivalent of DMD/acetone solution (5ml, 0.063M). Mixture protected from light and left stirring for 16 hours then solvent evaporated to give the crude residue containing the 3-*benzyloxy*-5,6-*epoxycholestane* (**100a**). ^{1}H NMR (crude) δ 7.3(s, 5H, CH_2**Ph**), 4.5(s, 2H, CH_2Ph), 3.5(br, 1H, H3), 3.1(d, β-oxirane proton), 2.9(d, α-oxirane proton), 2.0-0.7(complex, due to steroid ring system).

Epoxide ratio: (α:β 57:43)

Preparation of 4,4-dimethylcholest-5-en-3-one (117).[61]

To t-butanol (20ml) was added potassium metal (0.5g, 12.8mmol). When all the potassium had dissolved cholest-4-en-3-one **(116)**[60] (1.0g, 2.5mmol) in t-butanol (10ml) was added by syringe. The mixture was stirred well and methyl iodide (2ml, 32mmol) added. The mixture was left stirring for a further 18 hours then 2M hydrochloric acid (10ml) and ether (40ml) were added. The mixture was extracted by washing successively with water, aqueous sodium bicarbonate and sodium thiosulphate solution. The ether layer was separated and dried (sodium sulphate). Filtration and evaporation of solvent gave a white solid (0.653g). This was recrystallised (DCM/MeOH) to afford pure white crystals of 4,4-*dimethylcholest*-5-*en*-3-*one* (0.430g, 41%). Mpt. 172-173°C (lit. 176°C), IR. υ_{max} 1706, 1462cm^{-1}, ^{1}H NMR δ 5.5(m, 1H, H6), 1.2(s, 6H, 4α and 4β methyl groups), 0.9(s, 3H, C19Me), 0.7(s, 3H, C18Me).

Preparation of 4,4-dimethylcholest-5-en-3β-ol (118).[61]

To 4,4-dimethylcholest-5-en-3-one **(117)** (0.430g, 0.97mmol) in THF (40ml) was added methanol (130ml). Sodium borohydride (1.0g) was added in portions over 15 minutes. The mixture was left stirring for a further 4 hours. Water (380ml) and 2M hydrochloric acid were added (10ml) and the mixture extracted with ether (400ml). The ether layer was was separated and dried (magnesium sulphate). Filtration and evaporation of solvent gave the crude residue (0.395g). Column chromatography (silica gel, ether/pet ether/DCM 2:2:3) gave the required product (0.254g). Recrystallisation from ether/MeOH afforded pure 4,4-*dimethylcholest*-5-*en*-3β-*ol* (0.188g, 43%). Mpt. 144-146°C, $[\alpha]_D$ -63.5° (c. 1.0) (lit. -64.0° c. 1.16). ^{1}H NMR 250MHz δ 5.5(m, 1H, H5), 3.2(m, 1H, H3), 2.2-1.2(complex, due to steroid ring system), 1.14(s, 3H, 4α-Me), 1.07(s, 3H, C-19Me), 1.06(s, 3H, 4β-Me), 0.67(s, 3H, C-18Me).

Reaction of 4,4-dimethylcholest-5-en-3β-ol with the acetone/caroate. system.*

To 4,4-dimethylcholest-5-en-3β-ol (0.118g, 0.285mmol) in DCM (30ml) was added acetone (20ml), TBAHS (0.040g, 0.117mmol) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C. A solution of Oxone (4.0g, 6.5mmol) and EDTA (0.1g) in water (25ml) was added dropwise over 4 hours. TLC revealed the presence of 4 compounds. Work-up gave the crude residue (0.119g). Purification by preparative TLC (silica gel, ether/pet ether/DCM 10:10:15) afforded the major product as 4,4-*dimethylcholest-5-ene-3,7-dione* **(120)** (0.043g, 36%) this was then recrystallised from ethanol. Mpt 160-161°C (lit. 164°C). UV λmax 244.7nm ε=8764 (lit.[62,63] λmax 237nm ε=8500). IR υmax 1714(C=O), 1656(=CHC=O) 1616cm^{-1}(C=C). ^{1}H NMR δ 5.9(s, 1H, H6), 1.33(s, 6H, C-4Me groups), 1.1(s, 3H, C-19Me), 0.93(s, 3H, C-21Me), 0.84(s, 6H, C-26 and C-27Me groups), 0.7(s, 3H, C-18Me).

Preparation of 4,4-dimethylcholest-5-en-3β-acetate (119).[61]

To 4,4-dimethylcholest-5-en-3β-ol **(118)** (0.470g, 1.1mmol) in pyridine (5ml) was added acetic anhydride (2ml, 21mmol). The mixture was left stirring for 15 hours then poured onto ice/dilute HCl. The product appeared as a white solid. Filtration and washing of the residue with dilute HCl and water afforded the crude product (0.240g). Column chromatography (silica gel, pet ether/ether/EtOAc 25:4:2) and recrystallisation (Chloroform/ MeOH) of the crude product afforded pure 4,4-*dimethylcholest-5-en-3β-acetate* (0.155g, 31%). Mpt. 135-136°C (lit. 136-137°C), IR υmax 1736cm^{-1}(C=O), ^{1}H NMR δ 5.5(m, 1H, H6), 4.5(m, 1H, H3), 2.05(s, 3H, acetyl), 1.1(s, 1H, C-19Me), 0.9(s, 1H, C-21Me), 0.84(C-26 and C-27Me groups), 0.7(s, 1H, C-18Me).

Reaction of 4,4-dimethylcholest-5-en-3β-acetate with the acetone/caroate system.*

To 4,4-dimethylcholest-5-en-3β-acetate **(119)** (0.143g, 0.3mmol) in DCM (20ml) was added acetone (10ml), TBAHS (0.040g, 0.11mmol) and phosphate buffer (20ml). The mixture was maintained at pH7.5 and 2-5°C whilst a solution of Oxone (7.6g, 12.3mmol) and EDTA (0.1g) in water (20ml) was added dropwise over 4 hours. The mixture was then left to stir for a further 2 hours. Work-up gave the crude product (0.153g) which from the ^{1}H NMR spectrum was shown not to contain any 5,6-epoxide. The crude product was purified by preparative TLC (silica gel, pet ether/ether/EtOAc 25:4:4) to afford unreacted 4,4-dimethylcholest-5-en-3β-acetate (0.032g) and 4,4-*dimethyl-7-oxo-cholest-5-en-3β-yl acetate* **(121)** (0.050g, 44%) which was recrystallised from ethanol. Mpt. 152°C (lit.[62,63] 153-154°C), UV λmax 246.6nm (ε=11452) (lit. λmax 239nm, ε=12200), IR υmax 1738(C=O, acetyl), 1662(CH_2CHC=O), 1610(C=C), 1242cm^{-1}, ^{1}H NMR δ 5.9(s, 1H, H6), 4.5(m, 1H, H3), 2.08(s, 3H, Mc of acetyl), 2.0-0.8(complex, due to steroid ring system).

CHAPTER 3.

3,17β-diacetoxy-oestra-1,3,5(10)-triene (125) (Estradiol diacetate).

Prepared using standard procedure (as for preparation of estrone acetate) by stirring 3,17β-dihydroxy-oestra-1,3,5(10)-triene in dry pyridine with an excess of acetic anhydride for 24 hours to afford **(125)**. Mpt. 127-128°C, IR υ_{max} 1764, 1730, 1610, 1576cm^{-1}, ^{1}H NMR δ 7.26(m, 1H, ArH), 6.8(m, 2H, ArH), 4.7(br, 1H, C-17H), 2.6-3.0(m, 2H), 2.28(s, 3H, C-3 OAc), 2.06(s, 3H, C-17 OAc), 1.3-2.0(m), 0.85(s, 3H, C-13Me), ^{13}C δ 12.05(C-13 Me), 21.10 and 21.14(CH_3CO), 23.27(C-15), 26.06(C-11), 27.04(C-7), 27.58(C-16), 29.50(C-6), 36.90(C-12), 38.24(C-8), 42.90(C-13), 44.01(C-9), 49.88(C-14), 82.67(C-17), 118.52(C-2), 121.50(C-4), 126.39(C-1), 137.86(C-5), 138.16(C-10), 148.49(C-3), 169.00 and 170.00(COO of OAc groups).[72]

3,17β-Diacetoxy-9α-hydroxy-oestra-1,3,5(10)-triene (128).*

To a solution of estradiol diacetate **(125)** (0.30g, 0.84mmol) in DCM (20ml) was added TBAHS (0.1g), acetone (10ml) and phosphate buffer (25ml). The mixture was maintained at pH7.5 and 2-5°C. A solution of Oxone (9.00g, 14.6mmol) and EDTA (0.2g) in water (60ml) was added dropwise over 7 hours and the mixture stirred for a further 17 hours. Work-up gave the crude product (0.393g) which was purified by column chromatography (silica gel, ether/pet ether/EtOAc 15:10:1) to afford the 9α-*hydroxy compound* **(128)**. (0.240g, 75%). Mpt. 145-147.5°C (recrystallised from MeOH), $[\alpha]_D$ +56°(c 0.8, $CHCl_3$), υ_{max} 3544(OH), 1752, 1718cm^{-1}(C=O), ^{1}H NMR (250MHz) δ 7.55(d, J=8.56, 1H, H1), 6.80-6.90(m, 2H, H2 and H4), 4.70(m, 1H, H17), 2.80(m, 2H), 2.30(s, 3H, C-3 OAc), 2.05(s, 3H, C-17 OAc), 2.0-1.4(m), 0.82(s, 3H, C-13Me), ^{13}C δ 11.29(C-18), 20.58, 21.11 and 21.15(Me groups of OAc), 23.13(C-15), 27.70(C-16), 32.43, 32.80, 41.24(C-8), 42.63(C-14), 42.76(C-13), 69.87(C-9), 119.37(C-2), 122.18(C-4), 126.50(C-1), 138.51(C-5), 139.57(C-10), 149.87(C-3). Found: C, 71.10; H, 7.49% $C_{22}H_{28}O_5$ requires C, 70.95; H, 7.58%, found *m/z* 355 $C_{22}H_{28}O_5$ requires M-17 *m/z* 355.

3-Acetoxy-oestra-1,3,5(10)-trien-17-one (129).(Estrone acetate)

To estrone (0.230g, 0.85mmol) in pyridine (3ml) was added acetic anhydride (0.130g, 1.3mmol) and the mixture left stirring for 15 hours then poured onto ice/water and the white solid formed was filtered off and washed with dilute hydrochloric acid and water. Recrystallisation of the crude product from ethanol afforded pure *estrone acetate* as white crystals (0.20g, 75%). Mpt. 124-125.5°C, IR υmax 1762(C=O, OAc), 1730cm^{-1} (C=O, C-17), ^{1}H NMR 250MHz δ 7.31(m, 1H, ArH), 6.80-6.86(m, 2H, ArH), 2.88-2.93(m, 2H), 2.29(s, 3H, OAc), 2.00-1.47(complex, due to steroid ring system), 0.91(s, 3H, C-13Me), ^{13}C δ 220.76(C-17), 169.82, 148.48(C-3), 137.97(C-10), 137.36(C-5), 126.38(C-1), 121.55(C-4), 118.71(C-2), 50.36(C-14), 47.89, 44.09(C-9), 37.92(C-8), 35.81(C-12), 31.48(C-6), 29.34(C-16), 26.28(C-7), 25.68(C-11), 21.53(C-15), 21.09(CH_3CO), 13.77(C-18).[72]

3-Acetoxy-9α-hydroxy-oestra-1,3,5(10)-trien-17-one (130).*

To a solution of estrone acetate (**129**) (0.15g, 0.48mmol) in DCM (20ml) was added TBAHS (0.08g), acetone (10ml) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C. A solution of Oxone (26.0g, 42.3mmol) and EDTA (0.3g) in water (100ml) was added dropwise over 4 hours and the mixture stirred for a further 20 hours. Work-up gave the crude product (0.172g) which was purified by column chromatography (silica gel, ether/pet ether/DCM 50:48:2) to afford the 9α-*hydroxy compound* (**130**) which crystallised with a molecule of adventitious water (0.125g, 79%). Mpt. 165-166°C (recrystallised from EtOH), $[\alpha]_D$ +158°(c 0.3, $CHCl_3$),[109] υmax 3672, 3592(OH), 1752, 1734cm^{-1} (C=O), ^{1}H NMR (250MHz) δ 7.53(d, J=8.55, 1H, H1), 6.80-6.90(m, 2H, H2 and H4), 2.90(m, 2H), 2.29(s, 3H, C-3 OAc), 2.0-1.5(m), 0.90(s, 3H, C-13Me), ^{13}C δ 12.90(C-18), 19.95, 21.09(Me group of OAc), 21.41, 27.62, 29.36, 32.16, 35.89, 41.11(C-8), 43.09(C-14), 47.62(C-13), 70.01(C-9), 119.37(C-2), 122.28(C-4), 126.48(C-1), 138.40(C-5), 139.10(C-10), 149.97(C-3), 169.60(COO of OAc), 220.42(C-17). Found: *m/z* 310 $C_{20}H_{24}O_4$ requires M-18 *m/z* 310.

X-ray data: $C_{20}H_{24}O_4.H_2O$., Single crystal obtained from ethanol. Orthorhombic, a=8.008 (3), b=16.464 (5), c=13.69 (2), Space Group $P2_12_12_1$, Z=4, ρ_c=1.274gcm^{-3}. Stoe Stadi-2 two-circle diffractometer, 2091 unique refections measured of which 1721 'observed' (F>6σ(F)). Structure solved by direct methods and refined to a final R=0.05. Non-hydrogen atoms anisotropic, all hydrogen atoms except one methyl hydrogen on the acetyl group and the water hydrogen atoms located from a difference map and refined isotropically. The water molecule is involved in a network of hydrogen bonding with the 9-OH group and the oxygen of the acetyl group.

CHAPTER 4.

4-Benzyloxypropiophenone (132).[110]

To 4-hydroxypropiophenone **(131)**[110] (1.0g, 0.6mmol) in DMF (40ml) was added potassium hydroxide pellets (1.9g, 33mmol) and benzyl bromide (0.13g) the mixture was left stirring for 18 hours. Work-up and recrystallisation afforded pure 4-*benzyloxypropiophenone* **(132)**. Mpt. 99-99.5°C, ^{1}H NMR δ 8.0(d, J=9, 2H, ArH), 7.5(s, 5H, CH_2**Ph**), 7.0(d, J=9, 2H, ArH), 5.2(s, 2H, CH_2Ph), 2.9(q, J=7, 2H, CH_2), 1.2(t, J=7, 3H, CH_3).

Reaction of 4-benzyloxypropiophenone with DMD/acetone.

To 4-benzyloxypropiophenone (0.100g, 0.42mmol) in DCM (2ml) was added 0.055M DMD/acetone solution (7.6ml, 0.42mmol). The mixture was left stirring protected from light at 20°C for 21 hours. A further two aliquots of DMD/acetone solution (6ml, 0.34mmol, 0.055M) and 4 hours later (6ml, 0.34mmol, 0.057M) were added. The mixture was left standing for a total reaction time of 45¾ hours. Evaporation of the solvent gave the crude residue (0.102g). TLC showed the presence of only 4-benzyloxypropiophenone and 4-hydroxypropiophenone. Purification by column chromatography (silica gel, pet ether/EtOAc 20:5) afforded 4-*hydroxypropiophenone* **(131)** (0.020g, 69% based on recovery of 0.053g of unreacted **(132)**). Mpt. 146-146.5°C (authentic **(131)** 146-148°C), IR υmax 3172(OH), 1658cm^{-1}(C=O), ^{1}H NMR (d6 acetone/$CDCl_3$) δ 7.9(d, J=8, 2H, ArH), 6.9(d, J=8, 2H, ArH) 2.9(q, J=7, 2H, CH_2), 1.2(t, J=7, 3H, CH_3). Product data in accordance with that of the authentic sample.

Benzyl 4-benzyloxybenzoate (134).[120]

To benzyl 4-hydroxybenzoate **(133)**[110] (0.61g, 2.6mmol) under a nitrogen atmosphere was added acetone (40ml), potassium carbonate (6.0g) and benzyl bromide (4ml, 33mmol). This mixture was then refluxed gently for 18 hours. The reaction mixture was then diluted with DCM (50ml) and washed with saturated sodium chloride solution (4x20ml). The DCM layer was separated, dried, filtered and the solvent evaporated to give the crude product as a white solid (0.898g). Recrystallisation (EtOAc/pet ether) afforded pure *benzyl 4-benzyloxybenzoate* **(134)**[120] (0.558g, 67%). Mpt. 118-119°C, IR υmax 1694(C=O), 1602, 1505cm-1, ^{1}H NMR δ 8.0(d, J=8, 2H, ArH), 7.4(s, 10H, benzyl aromatic protons), 7.0(d, J=8, 2H, ArH), 5.4(s, 2H, -CO_2CH_2Ph), 5.1(s, 2H, -OCH_2Ph).

Reaction of benzyl 4-benzyloxybenzoate with DMD/acetone.

To benzyl 4-benzyloxybenzoate **(134)** (0.092g, 0.29mmol) was added DMD/acetone solution (23ml, 1.16mmol, 0.051M) and the mixture left stirring protected from light for 48 hours at 22°C. The solvent was evaporated to give the crude residue (0.100g). TLC showed a clean reaction where only benzyl 4-benzyloxybenzoate and benzyl 4-hydroxybenzoate were present. Purification by preparative TLC (silica gel, ether/pet ether/EtOAc 50:50:1) afforded unreacted benzyl benzyloxybenzoate and *benzyl 4-hydroxybenzoate* **(133)** (0.022g, 67% based on recovered **(134)**). Mpt. 110-111°C (recrystallised from EtOAc/pet ether) (authentic phenol 110-111°C), IR υmax (sol^{n}) 3356(OH), 1708(C=O), 1608cm^{-1}, ^{1}H NMR δ 7.9(d, J=8, 2H, ArH), 7.4(s, 5H, CH_2**Ph**), 6.9(d, J=8, 2H, ArH), 6.3(br, 1H, D_2O exchange OH), 5.3(s, 2H, CH_2Ph). Product data in accordance with that of the authentic sample.

3-benzyloxycholestane (135).[121]

To sodium hydride 80% (0.260g, 0.87mmol) (washed with pet ether prior to use to remove oil) was added DMF (5ml) and cholestan-3β-ol (0.400g, 1.0mmol) in THF. The mixture was stirred for 1 hour then benzyl bromide (0.211g, 0.146ml, 1.2mmol) in THF (2ml) was added. The mixture was then left to stir for 4 days. Work-up gave a residue which was redissolved in ether and washed with water (6x40ml) to remove any DMF. Ether layer separated, dried (sodium sulphate) and the solvent evaporated to give the crude product (0.311g). Recrystallisation from ethanol then further purification by column chromatography (silica gel, ether/pet ether/EtOAc 50:50:1) and recrystallisation gave pure *3-benzyloxycholestane* **(135)** (0.230g, 47%). Mpt. 104-105.2°C (Lit. 104-105°C)[121], ^{1}H NMR δ 7.4(s, 5H, Ph), 4.6(s, 2H, CH_2Ph), 2.0-0.5(complex, steroid ring system).

Oxidation of 3-benzyloxycholestane with DMD/acetone.

To 3-benzyloxycholestane (0.041g, 0.086mmol) in DCM (2ml) was added 2 equivalents of DMD/acetone (2.9ml, 0.18mmol, 0.063M). The mixture was protected from light and left stirring for 15 hours at 22°C. Evaporation of the solvent gave the crude residue (0.033g). TLC showed 3-benzyloxycholestane **(135)**, cholestan-3-one **(137)** and cholestan-3β-ol **(136)** to be present. ^{1}H NMR showed that cholestan-3-one was the predominant component of the mixture. Purification by preparative TLC (silica gel, ether/pet ether/EtOAc 50:50:1) and recrystallisation from ethanol afforded pure *cholestan-3-one* (0.020g, 60%). Mpt. 127-128°C (lit.[117] 129-130°C), IR υmax (sol^{n}) 1704cm^{-1}(C=O).

Oxidation of 3-benzyloxycholestane with DMD/acetone (GLC determination).

To 3-benzyloxycholestane (0.0030g, 6.3×10^{-6}mol) in DCM (0.5ml) was added 1.0 equivalent of DMD/acetone solution (0.18ml, 0.035M). The mixture was stirred protected from light for 14 hours at 22°C. The solvent was evaporated and 1.3mg of the residue taken for GLC analysis (derivatisation with Tri-sil to form the silyl ether of any alcohol present).

Capillary GLC showed the presence of 3-*benzyloxycholestane*, *cholestan*-3-*one* and *cholestan*-3β-*ol* where the relative quantities of each were 38.3, 47.1 and 14.6%wt. GLC conditions: 25 metre capillary column, temperature programmed 265°C (for 10mins) then at 3.5°C/min to 310°C. FID detection.

Qualitative GLC detection of benzaldehyde.

To 3-benzyloxycholestane (0.010g, 2.1×10^{-5}mol) in DCM (0.5ml) was added DMD/ acetone (0.5ml, 2.3×10^{-5}mol, 0.046M). The mixture was protected from light and left stirring at 22°C. GLC monitoring showed that *benzaldehyde* (Retention time 9.6 minutes) was formed (compared with an authentic sample of benzaldehyde). GLC conditions: Carbowax column 110°C. FID detection.

Oxidation of benzaldehyde dimethylacetal (141) with DMD/acetone.

To benzaldehyde dimethylacetal **(141)** (0.021g, 0.13mmol) was added 3.5 equivalents of DMD/acetone solution (0.46mmol, 7.5ml, 0.063M). The mixture was stirred protected from light at 0-5°C for 24 hours. GLC monitoring revealed a clean reaction had occurred and showed the presence of benzaldehyde dimethylacetal (82.4%wt) and methyl benzoate **(142)** (17.6%wt). The mixture was allowed to stir for a further 24 hours at 22°C after which time GLC showed *benzaldehyde dimethylacetal* (53.8%wt) and *methyl benzoate* (46.2%wt). Formation of methyl benzoate was confirmed by GLC and ^{1}H NMR by comparison of the data with an authentic sample.[110] IR υ_{max} (crude) 1720cm^{-1}(C=O), ^{1}H NMR (crude) δ 7.5(5H, ArH), 3.9(s, 3H, OMe of PhCOOMe). GLC conditions: Carbowax column 107°C, FID detection.

Oxidation of benzaldehyde dimethylacetal with DMD/acetone in the presence of DCM as a co-solvent.

To benzaldehyde dimethylacetal (**141**) (0.02g, 0.13mmol) in DCM (1.5ml) was added DMD/acetone solution (7.5ml, 0.05M, 2.9 equivalents). The mixture was protected from light and stirred for 24 hours at 0°C. GLC showed *benzaldehyde dimethylacetal* (81%wt) and *methyl benzoate* (19%wt).

GLC conditions: Carbowax column 107°C, FID detection.

Oxidation of phenylacetaldehyde dimethylacetal (144) with DMD/acetone.

To phenylacetaldehyde dimethylacetal (**144**) (0.055g, 0.33mmol) in DCM (1ml) was added 5 equivalents of DMD/acetone solution (32ml, 1.7mmol, 0.05M). The mixture was protected from light and left stirring for 43 hours at 0-5°C. GLC of the reaction mixture showed the presence of phenylacetaldehyde dimethylacetal (65%wt) and methyl phenylacetate (**147**) (35%wt). The solvent was then evaporated and the crude residue analysed. GLC revealed the presence of *phenylacetaldehyde dimethylacetal* (65%wt) and the ester *methyl phenylacetate* (35%wt). These compounds were confirmed by the IR and NMR spectra by comparison with authentic samples.[110] IR υ_{max} (sol^{n}) (crude) 1732(C=O), 1604cm^{-1}, ^{1}H NMR 250MHz δ 7.4-7.2(m, ArH), 4.55(t, J=5.6, 1H, C**H** of acetal), 3.69(s, 3H, Me of ester), 3.63(s, 2H, CH_2 of ester), 3.34(s, 6H, 2(OMe) of acetal), 2.90(d, J=5.6, 2H, CH_2 of acetal). GLC conditions: Carbowax column 140°C, FID detection.

CHAPTER 5.

Reaction of cholestan-3β-ol with the acetone/caroate system.*

To cholestan-3β-ol (0.505g, 1.3mmol) in DCM (40ml) was added acetone (15ml, 0.2mol), TBAHS (0.15g, 0.4mmol) and phosphate buffer (15ml). The mixture was maintained at pH7.5 and 2-5°C. A solution of Oxone (8.0g, 13mmol) and EDTA (0.1g) in water (50ml) was added dropwise over 7 hours and the mixture left stirring for a further 4 hours. Work-up gave the crude product (0.612g) which was purified by column chromatography (silica gel, DCM) to afford *cholestan-3-one* (0.392g, 78%). (TLC, mpt, IR and ^{1}H NMR of the product compared satisfactorily with an authentic sample of cholestan-3-one prepared by chromic acid oxidation of cholestan-3β-ol). Mpt. 127°C (authentic 129-130°C), IR υ_{max} 1710cm^{-1} (C=O). ^{1}H NMR δ 1.1(s, 3H, C-19Me), 0.95(s, 6H, C-26 and C-27Me's), 0.83(s, 3H, C-21Me), 0.7(s, 3H, C-18Me).

Oxidation of cholestan-3β-ol with DMD/acetone.

To cholestan-3β-ol (0.098g, 0.25mmol) in DCM (5ml) was added a solution of DMD/acetone (17ml, 0.56mmol). The mixture was stirred protected from light at 20°C for 20 hours. TLC confirmed complete conversion of cholestan-3β-ol to cholestan-3-one. The mixture was dried (magnesium sulphate), filtered and the solvent evaporated to give *cholestan-3-one* as a white solid (0.085g, 88%). Mpt. 126-127°C (lit.[117] 129-130°C), IR υ_{max} 1710cm^{-1}(C=O), ^{1}H NMR δ 1.1(s, 3H, C-19Me), 0.95(s, 6H, C-26 and C-27Me's), 0.83(s, 3H, C-21Me), 0.7(s, 3H, C-18Me).

Reaction of an equimolar mixture (136a) of cholestan-3α-ol and cholestan-3β-ol with DMD/acetone.

Into each of three 25ml round bottom flasks was accurately weighed about 0.021g of cholestan-3α-ol and 0.021g cholestan-3β-ol. The alcohols were dissolved in DCM (15ml) to allow good mixing then the solvent was evaporated. A sample of the mixed alcohols (0.0015g) was taken from each flask and derivatised to the silyl ethers using Tri-sil and analysed by GLC. The ratio of α:β cholestanol before the reaction was determined.

Reaction: To each of the flasks was added DMD/acetone solution (1ml) such that the molar ratio of total cholestanol:DMD was 1.3:1.0 (Table 1). (maximum theoretical conversion to cholestanone 76%). Each mixture was left stirring protected from light for 15 hours. The solvent was then evaporated and the product analysed by GLC, the results are shown in (Table 2).

Table 1.

Sample	Total cholestanol (α and β) for reaction	DMD/acetone
1	0.0399g, 0.1mmol	1.10ml, 7.7×10^{-5}mol
2	0.0402g, 0.1mmol	0.82ml, 7.9×10^{-5}mol
3	0.0394g, 0.1mmol	0.79ml, 7.8×10^{-5}mol

Table 2.

Sample	Time Hrs	Conversion to ketone %	Before α:β	After α:β
1	3	51.9	1.045	0.614
2	15	66.9	1.125	0.474
3	15	57.6	1.006	0.545
Mean result from 2 and 3	15	58.8	1.059	0.544

GLC conditions: 12 metre-BP1 capillary column (265°C), FID detection.

Oxidation of ^{18}O cholestan-3β-ol (154) to cholestan-3-one using DMD/acetone, evidence for O-atom insertion mechanism.

Ethylene ketal (152) of cholestan-3-one.

To cholestan-3-one (1.5g, 3.9mmol) in toluene (40ml) was added ethane 1,2-diol (0.26g, 4.1mmol) and pTSA (0.002g, 0.01mmol) in a flask fitted with a Dean and Stark separator. The mixture was refluxed vigorously for 5 hours until no more water collected in the separator. The mixture was allowed to cool then washed successively with 0.1M sodium hydroxide (3x20ml), water (2x20ml) and saturated sodium chloride solution (20ml). The toluene layer was separated and dried (potassium carbonate), filtered and the solvent evaporated to give the crude product (1.7g). Recrystallisation (Methanol/5% chloroform) afforded the pure *ketal* **(152)** (0.76g, 46%). Mpt. 112°C, (lit. 114°C[119] IR shows No C=O absorption at 1712cm^{-1} as expected with cholestanone, ^1H NMR δ 3.9(s, 4H, 2(CH_2) of ketal), 0.8(s, 3H, C-21Me), 0.6(s, 3H, C-18Me).

Hydrolysis[75] of ketal (152) using $H_2{}^{18}O$/pTSA to obtain ^{18}O enriched cholestan-3-one (153).

To ketal **(152)** (0.412g, 0.9mmol) in dry 1,4-dioxane (100ml) was added ^{18}O water (0.250g, 12.5mmol) and pTSA (0.005g, 0.03mmol). The mixture was left stirring with exclusion of moisture for 17 hours at ambient temperature. The mixture was then extracted with ether (100ml) and washed successively with 0.1M sodium hydroxide solution (20ml), sodium chloride solution and water. The ether layer was separated and dried, filtered and evaporated to give the crude residue (0.47g). TLC and IR υmax 3396(OH) and 1716cm^{-1}(C=O) revealed that the hydrolysis was not complete and that the ketal **(152)** and cholestan-3-one were difficult to separate by chromatography. The crude product was reduced with sodium borohydride. To crude product (0.36g) in DCM/MeOH (10ml/100ml) was added in portions sodium borohydride (0.351g, 9.3mmol), the mixture was left stirring for a further 15 hours. Ether (100ml), water (100ml) and 2M hydrochloric acid (10ml) was added and the mixture extracted with ether (2x200ml). The ether layer was separated, dried, filtered and the solvent evaporated to give the crude product (0.37g) which contained the ketal and cholestanol only. Purification by column chromatography (silica gel, ether/pet ether/EtOAc 20:20:1) afforded pure ^{18}O enriched *cholestan-3β-ol*. IR υmax 3052cm^{-1}(OH), Found *m/z* 388 (^{16}O, 52.01%) and *m/z* 390 (^{18}O, 47.99%), required *m/z* 388 and 390.

Oxidation of ^{18}O labelled cholestan-3β-ol (154) with DMD/acetone.

To ^{18}O labelled cholestan-3β-ol **(154)** (0.028g, 7.2×10^{-5}mol) in DCM (5ml) was added DMD/acetone solution (2ml, 0.1mmol, 0.05M). The mixture was left stirring protected from light at 0-5°C for 15 hours. TLC revealed the presence of cholestan-3-one only. The solvent was evaporated to give *cholestan-3-one* as a white solid (0.026g, 93%).Mpt. 128-129°C (lit.[117] 129-130°C).

The mass spectra of the crude cholestan-3-one and recrystallised (EtOH) cholestan-3-one were obtained and the level of ^{18}O cholestan-3-one determined. The experiment was repeated in an identical manner to the above, hence **Run A** and **Run B**.

RESULTS.

Run A.	^{18}O in cholestanol.....	47.99%
	^{18}O in cholestanone (product not recryst.).....	26.88%
	Therefore reduction in ^{18}O content is.....	21.11%
	% Reduction in ^{18}O label is.....	**44%**

Run B.	^{18}O in cholestanol.....	48.55%
	^{18}O in cholestanone (product not recryst.).....	34.01%
	Therefore reduction in ^{18}O content is.....	14.54%
	% Reduction in ^{18}O label is.....	**30%**

Conclusion: This experiment shows that approximately 40% of the ^{18}O label is lost in the oxidation which would be consistent with a mechanism of oxygen atom insertion for dimethyldioxirane.

CHAPTER 6.

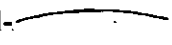
Note: Chromenes **(155-158)** were provided by Smithkline Beecham.

Oxidation of 6-acetyl-2,2-dimethyl-2H-1-benzopyran (156) with DMD/acetone.

To chromene **(156)** (0.074g, 0.37mmol) in DCM (2ml) was added DMD/acetone solution (7.0ml, 0.38mmol, 0.055M). The mixture was left stirring protected from light at 22°C for 11 hours. TLC showed complete conversion of **(156)** to the epoxide **(162)**. The solvent was evaporated to give the crude product (0.091g). Purification by preparative TLC (silica gel, ether/pet ether/EtOAc 10:10:1) afforded 6-*acetyl*-3,4-*epoxy*-2,2-*dimethyl*-2H-1-*benzopyran* **(162)** (0.068g, 85%) as an oil. IR υ_{max} 2980, 2924, 1674(C=O), 1576, 1360, 1272cm^{-1}, ^{1}H NMR 250MHz δ 8.0(d, J=2, 1H, H5), 7.8(q, J=8.4, 2.0, 1H, H7), 6.8(d, J=8.5, 1H, H8), 3.9(d, J=4.4, 1H ,H4 oxirane), 3.5(d, J=4.4, 1H, H3 oxirane), 2.5(s, 3H, acetyl Me), 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2Me), ^{13}C δ 196.4(C=O), 157.0, 131.2, 130.6, 130.4, 119.7, 117.9, 74.3(C-2), 62.3(CH, C-4), 50.6(CH, C-3), 26.3 (Me, acetyl), 25.6(Me), 23.0(Me). Found: *m/z* 218(100), 203(18), 189(9), 175(15), 162(26), 147(27), 84(22), 49(88), 43(59) $C_{13}H_{14}O_3$ requires *m/z* 218.

Oxidation of 6-chloro-2,2-dimethyl-2H-1-benzopyran (157) with DMD/acetone.

To chromene **(157)** (0.084g, 0.43mmol) in DCM (2ml) was added DMD/acetone solution (8.5ml, 0.47mmol, 0.055M). The mixture was left stirring protected from light at 22°C for 11 hours. TLC showed complete conversion of **(157)** to the epoxide **(163)**. The solvent was evaporated to give the crude product (0.097g). Purification by preparative TLC (silica gel, ether/pet ether/EtOAc 10:10:1) afforded 6-*chloro*-3,4-*epoxy*-2,2-*dimethyl*-2H-1-*benzopyran* **(163)** (0.068g, 75%) as an oil. IR υ_{max} 2976, 2932, 1268, 1204cm^{-1}, ^{1}H NMR 250MHz δ 7.3(d, J=2.5, 1H, H5), 7.1(q, J=8.6, 2.5, 1H, H7) 6.7(d, J=8.6, 1H, H8), 3.8(d, J=4.4, 1H, H4 oxirane), 3.5(d, J=4.4, 1H, H3 oxirane), 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2 Me), ^{13}C δ 151.0, 130.2, 129.2, 125.7, 121.6, 119.4, 73.4(C-2), 62.6(CH,C-4), 50.4(CH,C-3), 25.6(Me), 22.5(Me). Found: *m/z* 210(99), 195(12), 181(12), 167(10), 154(100), 141(16), 126(21), 89(31), 63(32), $C_{11}H_{11}ClO_2$ requires *m/z* 210.

Oxidation of 6-ethyl-  -2,2-dimethyl-2H-1-benzopyran (158) with DMD/acetone.

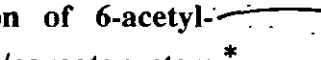
To chromene **(158)** (0.075g, 0.39mmol) in DCM (2ml) was added DMD/acetone solution (7.5ml, 0.41mmol, 0.055M). The mixture was left stirring protected from light at 22°C for 11 hours. Reaction solution was seen to change from colourless to yellow. The solvent was evaporated to give the crude product (0.089g) containing *6-ethyl*-3,4-*epoxy*-2,2-*dimethyl*-2H-1-*benzopyran* **(164)**. No further purification was performed as the epoxide **(164)** has been found to decompose when chromatographed. IR υmax 2964, 2928, 1492, 1258cm^{-1}, ^{1}H NMR 250MHz δ 7.1(d, J=2.1, 1H, H5), 7.0(q, J=10.4, 2.2, 1H, H7) 6.7(d, J=8.2, 1H, H8), 3.9(d, J=4.3, 1H, H4 oxirane), 3.5(d, J=4.4, 1H, H3 oxirane), 2.5(q, 2H, CH_2) 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2Me), 1.3(t, 3H, CH_2CH_3), ^{13}C δ 150.0, 136.7, 129.7, 128.9, 127.6, 72.8(C-2), 62.8(CH, C-4), 51.2(CH, C-3), 27.9(CH_2), 25.7(Me) 22.5(Me), 15.7(CH_2CH_3). Found: *m/z* 204(75), 189(9), 161(52), 148(100), 133(70), 119(18), 105(19), 91(48), 77(37), $C_{13}H_{16}ClO_2$ requires *m/z* 204

Reaction of 6-cyano-  -2,2-dimethyl-2H-1-benzopyran (155) with the acetone/caroate system.*

To chromene **(155)** (0.200g, 1.1mmol) in DCM (10ml) was added acetone (10ml, 0.14mmol), TBAHS (0.1g, 0.3mmol) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C whilst a solution of Oxone (2.5g, 4.0mmol) and EDTA (0.05g) in water (20ml) was added dropwise over 5 hours. The mixture was then left stirring for a further 19 hours. TLC showed complete conversion of **(155)**. Work-up gave the crude product as a white solid (0.263g). Purification by column chromatography (silica gel, ether/pet ether/EtOAc 50:48:2) afforded pure *6-cyano*-3,4-*epoxy*-2,2-*dimethyl*-2H-1-*benzopyran* **(160)**[77] (0.183g, 85%). Recrystallisation from EtOAc/pet ether gave the epoxide **(160)** as white crystals. Mpt. 110°C, mixed mpt. 110-111°C (authentic 110°C). IR υmax 2224cm^{-1}(CN), ^{1}H NMR δ 7.6-7.5(m, 2H, H5 and H7), 6.9(d, J=8, 1H, H8), 3.9(d, J=4, 1H, H4 oxirane), 3.5(d, J=4, 1H, H3 oxirane), 1.6(s ,3H, C-2Me), 1.3(s, 3H, C-2Me).

Reaction of 6-cyano-  -2,2-dimethyl-2H-1-benzopyran (155) with the cyclohexanone/caroate system.*

To chromene (**155**) (0.200g, 1.1mmol) in DCM (20ml) was added cyclohexanone (0.850g, 8.7mmol), TBAHS (0.1g, 0.3mmol) and phosphate buffer (40ml). The mixture was maintained at pH7.5 and 2-5°C whilst a solution of Oxone (4.0g, 6.5mmol) and EDTA (0.10g) in water (25ml) was added dropwise over 6 hours. The mixture was then left stirring for a further 15 hours. TLC showed complete conversion of (**155**). Work-up gave the crude product (1.14g) in which cyclohexanone and ε-caprolactone were present in addition to the epoxide (**160**). Purification by column chromatography (silica gel, ether/pet ether/DCM 82:11:7) afforded pure *6-cyano-3,4-epoxy-2,2-dimethyl-2H-1-benzopyran* (**160**)[77] (0.140g, 65%). Recrystallisation from EtOAc/pet ether gave the epoxide (**160**) as white crystals. Mpt. 109-110°C, (authentic 110°C), IR υ_{max} 2224cm^{-1} (CN), ^{1}H NMR δ 7.6-7.5(m, 2H, H5 and H7), 6.9(d, J=8, 1H, H8), 3.9(d, J=4, 1H, H4 oxirane), 3.5(d, J=4, 1H, H3 oxirane), 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2Me).

Reaction of 6-acetyl-  -2,2-dimethyl-2H-1-benzopyran (156) with the acetone/caroate system.*

To chromene (**156**) (0.164g, 0.8mmol) in DCM (8ml) was added acetone (10ml, 0.14mmol), TBAHS (0.1g, 0.3mmol) and phosphate buffer (20ml). The mixture was maintained at pH7.5 and 2-5°C whilst a solution of Oxone (2.5g, 4.0mmol) and EDTA (0.05g) in water (20ml) was added dropwise over 4 hours. The mixture was then left stirring for a further 1 hour. TLC showed complete conversion of (**156**). Work-up gave the crude product as a pale yellow oil (0.324g). Purification by column chromatography (silica gel, ether/pet ether/DCM 50:49:1) afforded pure *6-acetyl-3,4-epoxy-2,2-dimethyl-2H-1-benzopyran* (**162**) (0.148g, 85%) as a pale oil. IR υ_{max} 1678(C=O), 1608cm^{-1}, ^{1}H NMR δ 8.2-7.8(m, 2H, H5 and H7), 6.9(d, J=8, 1H, H8), 3.9(d, J=4, 1H, H4 oxirane), 3.5(d, J=4, 1H, H3 oxirane), 2.5(s, 3H, CH_3CO), 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2Me).

Reaction of 6-chloro-[illegible]-2,2-dimethyl-2H-1-benzopyran (157) with the acetone/caroate system.*

To chromene **(157)** (0.203g, 1.1mmol) in DCM (10ml) was added acetone (10ml, 0.14mmol), TBAHS (0.29g, 0.85mmol) and phosphate buffer (25ml). The mixture was maintained at pH7.5 and 2-5°C whilst a solution of Oxone (2.5g, 4.0mmol) and EDTA (0.10g) in water (20ml) was added dropwise over 3 hours. The mixture was then left stirring for a further 7 hours. TLC showed complete conversion of **(157)**. Work-up gave the crude product as a pale yellow oil (0.246g). Purification by column chromatography (silica gel, ether/pet ether/EtOAc 50:49:1) afforded pure *6-chloro*-3,4-*epoxy*-2,2-*dimethyl*-2H-1-*benzopyran* **(163)** (0.201g, 91%) as a pale oil. IR υ_{max} 3044, 2960, 1265, 1197cm^{-1}, ^{1}H NMR δ 7.3-7.1(m, 2H, H5 and H7), 6.9(d, J=8, 1H, H8), 3.9(d, J=4, 1H, H4 oxirane), 3.5(d, J=4, 1H, H3 oxirane), 1.6(s, 3H, C-2Me), 1.3(s, 3H, C-2Me).

Reaction of 6-ethyl-[illegible]-2,2-dimethyl-2H-1-benzopyran (158) with the acetone/caroate system.*

To chromene **(158)** (0.178g, 0.95mmol) in DCM (10ml) was added acetone (10ml, 0.14mmol), TBAHS (0.03g, 0.08mmol) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.10g) in water (20ml) was added dropwise over 4 hours. The mixture was then left stirring for a further 6 hours solution seen to change from colourless to yellow. TLC showed complete conversion of **(158)**. Work-up gave the crude product as a yellow oil (0.213g). The phase transfer catalyst was removed using column chromatography (silica gel, ether/pet ether 60:40) to afford *6-ethyl*-3,4-*epoxy*-2,2-*dimethyl*-2H-1-*benzopyran* **(164)** (0.169g, 87%) as an oil. However, the ^{1}H NMR spectrum showed some decomposition of the epoxide **(164)** and further chromatography using either silica gel or neutral grade 3 alumina led to complete degredation of the epoxide **(164)**.IR υ_{max} 3000, 1496, 1268cm^{-1}, ^{1}H NMR δ 7.1-6.9(m, 2H, H5 and H7), 6.7(d, J=8, 1H, H8), 3.9(d, J=4, 1H, H4 oxirane), 3.5(d, J=4, 1H, H3 oxirane), 2.5(q, 2H, CH_2CH_3), 1.6(s, 3H, C-2Me), 1.3-1.1(s, 3H, C-2Me; overlapping triplet, 3H, CH_2CH_3).

CHAPTER 7.

Oxidation of trans-stilbene (204) with the norcamphor (182)/caroate system.*

To trans-stilbene (0.200g, 1.1mmol) in DCM (10ml) was added norcamphor (0.122g, 1.1mmol), TBAHS (0.1g) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 2-5°C. A solution of Oxone (3.0g, 4.9mmol) and EDTA (0.1g) in water (20ml) was added over 2 hours (TLC revealed disappearance of norcamphor). Work-up gave the crude residue (0.367g). Column chromatography (silica gel, ether/pet ether/EtOAc 80:18:2) afforded trans-stilbene (0.181g, 91% recovery) and *lactone* **(183)** (0.080g) as a colourless liquid which formed a solid on standing. Lactone **(183)**: mpt. 53-55°C (lit. 56-58°C),[90] IR υ_{max} 1730cm^{-1}(C=O lactone), ^{1}H NMR δ 4.7(br, 1H, CHOCOR), 2.5-2.0(m, 9H, CH_2).

(+)-Isopinocamphone (22).[111]

To a well stirred solution of (-)-isopinocampheol (3.0g, 19.5mmol) in diethyl ether (50ml) was added a solution of sodium dichromate (5.9g, 19.5mmol) and 98% sulphuric acid (4.4ml) in water (35ml) dropwise over 20 minutes. The flask was warmed to 30°C (waterbath) and left stirring for a further 10 hours. The aqueous layer was separated and washed with ether (3x20ml) then the ether extracts washed successively with 2M hydrochloric acid (30ml), water (30ml) aqueous sodium bicarbonate solution (30ml) and sodium chloride solution (30ml). The ether layer was separated, dried, filtered and the solvent evaporated to give the crude product (2.83g). Purification by column chromatography (silica gel, pet ether/ether/DCM 200:200:2) and kugelrohr distillation afforded pure (+)-*isopinocamphone* (2.23g, 75%) as a colourless liquid. Bpt. 110°C @ 12mmHg, $[\alpha]_D$ +7.76°, c 1.2 (lit. +10.04°) IR υ_{max} (film) 1710cm^{-1}(C=O), ^{1}H NMR δ 2.6-2.0(m, 7H, ring CH and CH_2), 1.3(s, 3H, C-7 CH_3), 1.2(d, J=8, 3H, C-2 CH_3), 0.8(s, 3H, C-7, CH_3).

(-)-2-Hydroxyisopinocamphone (187).[92]

Sodium hydride 80% (0.451g, 15.1mmol) (washed with pet ether) under a nitrogen atmosphere was dissolved in t-butyl alcohol (10.4ml) and DMF (21ml). A further amount of DMF (24ml), triethyl phosphite (2.4ml), and (-)-isopinocamphone **(22)** (2.087g, 13.7mmol) in THF (42ml) was added. Oxygen gas was then bubbled through the reaction mixture for 20 hours at -25°C.[91] The mixture was then acidified with dilute acetic acid and the mixture extracted with ether (3x50ml). The ether layer was washed with water, aqueous sodium bicarbonate solution and sodium chloride solution. The ether layer was separated, dried, filtered and the solvent evaporated to give the crude residue. Purification by column chromatography (silica gel, ether/EtOAc 99:1) gave a liquid which was distilled at 60°C @ 12mmHg to remove trace amounts of triethyl phosphite. The remaining oil was then distilled at 60°C @ 0.2mmHg to give pure (-)-2-*hydroxyisopinocamphone* which sublimed and was collected as a white solid (1.097g, 48%). Bpt. 60°C @ 0.2mmHg, Mpt. 30-32°C, $[\alpha]_D$ -35.25°, c 1.2 {lit. mpt. 34-35°C,[92] $[\alpha]_D$ -27.50° (c 2.5 $CHCl_3$)}, IR υ_{max} (film) 3412(OH), 1712cm^{-1}(C=O), ^1H NMR δ 2.5(m, 3H, D_2O exchange shows 2H therefore OH present), 2.2-1.6(m, 4H, ring protons), 1.4(2 overlapping singlets, 6H, 2Me), 0.9(s, 3H, Me).

(-)-Menthyl pyruvate (202).[94]

To (-)-menthol (6.026g, 0.038mol) in benzene (25ml) was added pyruvic acid (3.278g, 0.036mol) and pTSA (0.161g, 0.86mmol). The mixture was refluxed for 3 hours (Dean and Stark apparatus). The benzene solution was then washed with aqueous sodium bicarbonate solution (2x50ml) and water (50ml). the benzene layer was dried, filtered and the solvent rotary evaporated to give the crude residue (7.89g). The residue was then kugelrohr distilled at 129°C @ 12mmHg to remove excess menthol. *Menthyl pyruvate* was collected as a colourless liquid(4.76g, 57%), Bpt. 140°C @ 12mmHg, $[\alpha]_D$ -85.20°, c 1.8 (lit. -84.1), IR υ_{max} (film) 1738(C=O of ester), 1722cm^{-1}(C=O), ^1H NMR δ 4.8(m, 1H, $(CH_3)_2CH$-), 2.4(s, 3H, $COCH_3$), 2.0-1.0(m, 9H), 1.0-0.7(9H, CH_3 groups).

Reaction of 6-cyano-4-phenyl-2,2-dimethyl-2H-1-benzopyran (155) with the (+)-isopinocamphone/caroate system.*

To chromene **(155)** (0.185g, 1.0mmol) in DCM (50ml) was added TBAHS (0.212g, 0.62mmol), phosphate buffer and (+)-isopinocamphone (0.900g, 5.9mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (10.2g,16.6mmol)/EDTA (0.4g) in water (55ml) was added dropwise over 4 hours. A further amount of Oxone (37.4g, 60.9mmol) was added in portions (approx. 4.0g of Oxone in water per day) over 8 days. The mixture was left stirring for a further 3 days. tlc revealed the presence of the required epoxide **(160)**. Work-up gave the crude residue (1.154g). TLC and ^{1}H NMR confirmed the presence of epoxide **(160)**. The crude was purified by column chromatography (silica gel, ether/pet ether/DCM 15:10:3) to give an oil containing predominantly epoxide **(160)** (0.080g) with a trace of impurity. Preparative TLC (silica gel, ether/pet ether/DCM) afforded pure epoxide **(160)** (0.062g,31%) which was recrystallised (EtOAc/pet ether) to give white crystals. Mpt.109-110°C, IR υ_{max} (sol^{n}) 2224(CN), 1612cm^{-1}, ^{1}H NMR 250MHz δ 7.65(d, J=2.0, 1H, H5), 7.51(q, J=8.5, 2.0, 1H, H7), 6.65 (d, J=8.5, 1H, H8), 3.90(d, J=4.4, 1H, H4), 3.55(d, J=4.4, 1H, H3), 1.60(s, 1H, C-2Me), 1.3(s, 1H, C-2Me). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$. The H5 proton signal is shifted downfield and resolved as 2 signals at 7.80 and 7.76ppm.

ee = 3.2%

Reaction of 6-cyano-2,2-dimethyl-2H-1-benzopyran (155) with the (-)-2-hydroxyisopinocamphone/caroate system.*

To chromene (**155**) (0.170g, 0.9mmol) in DCM (50ml) was added TBAHS (0.212g, 0.62mmol), phosphate buffer and (-)-2-hydroxyisopinocamphone (0.165g, 0.98mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (4.0g,6.5mmol)/EDTA (0.1g) in water (20ml) was added dropwise over 30 minutes and mixture left stirring for 24 hours. A further amount of Oxone (65.9g, 0.1mol) was added in portions (approx. 5.0g of Oxone in water per day) over 13 days. TLC revealed the presence of the required epoxide (**160**). Work-up gave the crude residue (0.813g). TLC and ^{1}H NMR confirmed the presence of (**160**). The epoxide (**160**) and 2-hydroxyisopinocamphone were found to have similar Rf values and were difficult to separate by column chromatography. Purification by preparative TLC (silica gel, ether/pet ether/DCM 5:11:1) gave the epoxide (**160**) as an oil (0.109g, 59%) containing a trace of impurity. Crystallisation (EtOAc/pet ether) afforded white crystals of the pure epoxide (**160**) (0.032g, 17%). Mpt.110-111°C, IR υ_{max} (sol^n) 2224(CN), 1612cm^{-1}, ^{1}H NMR 250MHz δ 7.65(d, J=2.0, 1H, H5), 7.51(q, J=8.5, 2.0, 1H, H7), 6.65(d, J=8.5, 1H, H8), 3.90(d, J=4.4, 1H, H4), 3.55(d, J=4.4, 1H, H3), 1.60(s, 1H, C-2Me), 1.3(s, 1H, C-2Me). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$. The H5 proton signal is shifted downfield and resolved as 2 signals at 7.80 and 7.76ppm.

ee = 2.4%

Reaction of 6-cyano-[illegible]-2,2-dimethyl-2H-1-benzopyran (155) with the (+)-camphor/caroate system.*

To chromene (**155**) (0.190g, 1.0mmol) in DCM (50ml) was added TBAHS (0.216g, 0.62mmol), phosphate buffer and (+)-camphor (0.200g, 1.3mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (5.0g, 8.1mmol)/EDTA (0.2g) in water (30ml) was added dropwise over 30 minutes and mixture left stirring for 24 hours. A further amount of Oxone (49.0g, 78mmol) was added in portions (approx. 4.0g of Oxone in water per day) over 12 days. TLC revealed the presence of the required epoxide (**160**). Work-up gave the crude residue (0.420g). Crude extracted with ether and washed with water to remove the phase transfer catalyst to give product residue 0.269g. TLC and ^{1}H NMR confirmed the presence of epoxide (**160**). Purification by preparative TLC (silica gel, ether/pet ether/DCM 9:10:1) gave the epoxide (**160**) as an oil (0.066g, 32%) containing a trace of impurity. Crystallisation (EtOAc/pet ether) was not possible and from the ^{1}H NMR spectrum the epoxide (**160**) was seen to be quite pure. IR υmax (sol^{n}) 2224(CN), 1612cm^{-1}, ^{1}H NMR 250MHz δ 7.65(d, J=2.0, 1H, H5), 7.51(q, J=8.5, 2.0, 1H, H7), 6.65(d, J=8.5, 1H, H8), 3.90(d, J=4.4, 1H, H4), 3.55(d, J=4.4, 1H, H3), 1.60(s, 1H, C-2Me), 1.3(s, 1H, C-2Me). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$. The H5 proton signal is shifted downfield and resolved as 2 signals at 7.80 and 7.76ppm.

ee = 3.0%

Reaction of 6-cyano-[benzene]-2,2-dimethyl-2H-1-benzopyran (155) with the (+)-3-(trifluoroacetyl)camphor (200)/caroate system.*

To chromene (**155**) (0.194g, 1.0mmol) in DCM (50ml) was added TBAHS (0.216g, 0.62mmol), phosphate buffer and (+)-3-(trifluoroacetyl)camphor[93] (0.196g, 0.79mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (7.9g, 11.7mmol)/EDTA (0.2g) in water (40ml) was added dropwise over 45 minutes and mixture left stirring for 18 hours. A further solution of Oxone (18.3, 29.8mmol) in water (100ml) added over 6 hours and TBAHS (0.45g). A further amount of Oxone (36.0g, 59mmol) was added in portions (approx. 4.0g of Oxone added as a solid per day) over 9 days and mixture left stirring for a further 3 days. TLC revealed the presence of the required epoxide (**160**). Work-up gave the crude residue which was extracted with ether and washed with water to remove the phase transfer catalyst to give product residue (0.200g). TLC and ^{1}H NMR confirmed the presence of (**160**). Purification by preparative TLC (silica gel, ether/pet ether/DCM 20:15:3) gave the epoxide (**160**) as an oil (0.115g) containing a trace of impurity. Preparative TLC rerun using alumina plates (ether/EtOAc 200:5) to afford pure epoxide (**160**) (0.056g, 27%). Recrystallised (EtOAc/pet ether) to give pure white crystals of epoxide (**160**). Mpt. 109-110°C, IR υ_{max} (sol^{n}) 2224(CN), 1612cm^{-1}, ^{1}H NMR 250MHz δ 7.65(d, J=2.0, 1H, H5), 7.51(q, J=8.5, 2.0, 1H, H7), 6.65(d, J=8.5, 1H, H8), 3.90(d, J=4.4, 1H, H4), 3.55(d, J=4.4, 1H, H3), 1.60(s, 1H, C-2Me), 1.3(s, 1H, C-2Me). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$. The H5 proton signal is shifted downfield and resolved as 2 signals at 7.80 and 7.76ppm.

ee = 11.2%

Reaction of 6-cyano-2,2-dimethyl-2H-1-benzopyran (155) with the (-)-menthyl pyruvate/caroate system.*

To chromene (**155**) (0.200g, 1.0mmol) in DCM (20ml) was added TBAHS (0.200g, 0.58mmol), phosphate buffer and (-)-menthyl pyruvate[94] (0.528g, 2.3mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (34.0g, 55.0mmol)/EDTA (0.6g) in water (140ml) was added in 2 portions dropwise over 6 hours and mixture left stirring for 17 hours. A further amount of Oxone (18.0g, 30mmol) was added in water over 1 hour. Then portions of Oxone as a solid were added over 6 days until a total of (80.0g, 0.13mol) had been added. TLC revealed the presence of the required epoxide (**160**). Work-up gave the crude residue which was extracted with ether to remove the phase transfer catalyst to give product residue 0.695g. TLC and ^{1}H NMR confirmed the presence of epoxide (**160**). Purification by column chromatography (silica gel,ether/pet ether/EtOAc 10:8:0.5 gave epoxide (**160**) (0.085g) which was further purified using preparative TLC (silica gel, ether/pet ether/EtOAc 10:8:0.5) gave the epoxide (**160**) as an oil (0.010g) containing a trace of impurity. However, the epoxide appeared quite clean from the NMR spectrum. IR υ_{max} (sol^n) 2224(CN), 1612cm^{-1}, ^{1}H NMR 250MHz δ 7.65(d, J=2.0, 1H, H5), 7.51(q, J=8.5, 2.0, 1H, H7), 6.65(d, J=8.5, 1H, H8), 3.90(d, J=4.4, 1H, H4), 3.55(d, J=4.4, 1H, H3), 1.60(s, 1H, C-2Me), 1.3(s, 1H, C-2Me). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$. The H5 proton signal is shifted downfield and resolved as 2 signals at 7.80 and 7.76ppm.

ee = 3.8%

Reaction of trans-stilbene (204) with the (-)-menthyl pyruvate/caroate system.*

To trans-stilbene (0.200g, 1.1mmol) in DCM (20ml) was added TBAHS (0.189g, 0.5mmol), phosphate buffer (30ml) and (-)-menthyl pyruvate (0.288g, 1.3mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (4.0g,6.5mmol)/EDTA (0.2g) in water (20ml) was added dropwise over 30 minutes and mixture left stirring for 21 hours. A further amount of Oxone (14.0g, 43mmol) was added in portions (approx. 4.0g of Oxone in water per day) over 3 days. Then Oxone (15.0g, 24mmol) added in portions as a solid over 2 days. Work-up gave the crude residue which was extracted with ether and washed with water to remove the phase transfer catalyst to give product residue 0.485g. ^{1}H NMR confirmed the presence of epoxide (**205**) δ 3.8ppm(s, 2H, oxirane protons). Separation of unreacted trans-stilbene and trans-stilbene oxide (**205**) by chromatography was quite difficult. Purification by column chromatography (silica gel, hexane/EtOAc 2.5%) and preparative TLC (silica gel, pet ether/EtOAc 2.5%) afforded *trans-stilbene oxide*[95] (0.008g). ^{1}H NMR 250MHz δ 7.34-7.38(m, 10H, ArH), 3.87(s, 2H, oxirane protons). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$ by resolution of the oxirane signal at δ 3.87ppm.

ee = 0.2%

Reaction of trans-stilbene with the (+)-3-(trifluoroacetyl)camphor/caroate system.*

To trans-stilbene (0.154g, 0.83mmol) in DCM (20ml) was added TBAHS (0.207g, 0.6mmol), phosphate buffer (30ml) and (+)-3-(trifluoroacetyl)camphor[93] (0.221g, 0.89mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (11.0g, 18mmol)/EDTA (0.2g) in water (50ml) was added dropwise over 6 hours and mixture left stirring for 17 hours. A further amount of Oxone (76.3g, 0.12mol) in solution was added in portions (approx. 6.0g of Oxone in water per day) over 13 days. Work-up gave the crude residue which was extracted with ether and washed with water to remove the phase transfer catalyst to give product residue 0.206g. ^{1}H NMR confirmed the presence of epoxide δ 3.8ppm(s, 2H, oxirane protons). Separation of unreacted trans-stilbene and trans-stilbene oxide (**205**) by chromatography was quite difficult. Purification by column chromatography (silica gel, pet ether/EtOAc 2.0%) gave trans-stilbene oxide (0.070g, 41%) containing a trace of trans-stilbene which was removed by preparative TLC (silica gel, pet ether/EtOAc 2.0%) to afford pure *trans-stilbene oxide*[95] (0.030g, 18%). ^{1}H NMR 250MHz δ 7.34-7.38(m, 10H, ArH), 3.87(s, 2H, oxirane protons). Determination of enantiomeric excess using chiral shift reagent $Eu(hfc)_3$ by resolution of the oxirane signal at δ 3.87ppm.

ee = 4.5%

Reaction of trans-stilbene with the (-)-2-hydroxyisopinocamphone/caroate system.*

To trans-stilbene (0.150g, 0.83mmol) in DCM (30ml) was added TBAHS (0.30g,), phosphate buffer (50ml) and (-)-2-hydroxyisopinocamphone (0.150g, 0.89mmol). The mixture was stirred well and maintained at 0-5°C and pH7.5 whilst a solution of Oxone (6.2g, 10mmol)/EDTA (0.2g) in water (30ml) was added dropwise over 3 hours and mixture left stirring for 20 hours. A further amount of Oxone (48.9g, 79mmol) in solution was added in portions (approx. 5.0g of Oxone in water per day) over 9 days. Work-up gave the crude residue which was extracted with ether and washed with water to remove the phase transfer catalyst to give product residue 0.211g. ^{1}H NMR confirmed the presence of epoxide **(205)** δ 3.8ppm (s, 2H, oxirane protons). Purification using preparative TLC (silica gel, pet ether/EtOAc 7.0%) to afford pure *trans-stilbene oxide* **(205)**[95] (0.071g, 43%). ^{1}H NMR 250MHz δ 7.34-7.38(m, 10H, ArH), 3.87(s, 2H, oxirane protons). Determination of enantiomeric excess using chiral shift reagent Eu(hfc)$_3$ by resolution of the oxirane signal at δ 3.87ppm.

ee = 3.9%

CHAPTER 8.

Epoxidations Of Cyclohexene Using The Ketone/caroate System.*

Note: The fluoro-ketones used in the following experiments were obtained from the Aldrich Chemical Company.

RUN 1. *Reaction time* **2¾ hours.**

α,α,α-Trifluoroacetophenone (114)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added α,α,α-trifluoroacetophenone (0.319g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 25 minutes. The mixture was then left stirring for 2 hours 20 minutes. (Total 2¾ hours).
The reaction mixture was then analysed by GLC (Carbowax column 69°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**79.8%wt**

Cyclohexene oxide.....**20.2%wt**

4'-Fluoroacetophenone (115)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added 4'-fluoroacetophenone (0.253g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 25 minutes. The mixture was then left stirring for 2 hours 20 minutes. (Total 2¾ hours).
The reaction mixture was then analysed by GLC (Carbowax column 60°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**79.1%wt**

Cyclohexene oxide.....**20.9%wt**

2'-Fluoroacetophenone (207)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added 2'-fluoroacetophenone (0.253g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 25 minutes. The mixture was then left stirring for 2 hours 20 minutes. (Total 2¾ hours).

The reaction mixture was then analysed by GLC (Carbowax column 69°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**82.0%wt**

Cyclohexene oxide.....**18.0%wt**

3'-Fluoroacetophenone (206)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added 3'-fluoroacetophenone (0.253g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 25 minutes. The mixture was then left stirring for 2 hours 20 minutes. (Total 2¾ hours).

The reaction mixture was then analysed by GLC (Carbowax column 60°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**82.5%wt**

Cyclohexene oxide.....**17.5%wt**

2',3',4',5',6'-Pentafluoroacetophenone (208)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added penta-fluoroacetophenone (0.384g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g,4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 25 minutes. The mixture was then left stirring for 2 hours 20 minutes. (Total 2¾ hours).
The reaction mixture was then analysed by GLC (Carbowax column 69°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**84.5%wt**

Cyclohexene oxide.....**15.5%wt**

2,3,4,5,6-Pentafluorobenzophenone (209)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added penta-fluorobenzophenone (0.498g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 25 minutes. The mixture was then left stirring for 2 hours 20 minutes. (Total 2¾ hours).
The reaction mixture was then analysed by GLC (Carbowax column 60°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**79.2%wt**

Cyclohexene oxide.....**20.8%wt**

RUN 2. *Reaction time* **4 hours.**

α,α,α-Trifluoroacetophenone (114)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added α,α,α-trifluoroacetophenone (0.319g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**25.9%wt**

Cyclohexene oxide.....**74.1%wt**

4'-Fluoroacetophenone (115)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added 4'-fluoroacetophenone (0.253g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**43.1%wt**

Cyclohexene oxide.....**56.9%wt**

2'-Fluoroacetophenone (207)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added 2'-fluoroacetophenone (0.253g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**44.2%wt**

Cyclohexene oxide.....**55.8%wt**

3'-Fluoroacetophenone (206)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added 3'-fluoroacetophenone (0.253g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**47.4%wt**

Cyclohexene oxide.....**52.6%wt**

2',3',4',5',6'-Pentafluoroacetophenone (208)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added pentafluoroacetophenone (0.384g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**50.0%wt**

Cyclohexene oxide.....**50.0%wt**

2,3,4,5,6-Pentafluorobenzophenone (209)/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added pentafluorobenzophenone (0.498g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**54.7%wt**

Cyclohexene oxide.....**45.3%wt**

Acetone/caroate system.

To cyclohexene (0.150g, 1.83mmol) in DCM (20ml) was added acetone (0.106g, 1.83mmol), TBAHS (0.200g, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH7.5 whilst a solution of Oxone (3.0g, 4.9mmol) and EDTA (0.2g) in water (50ml) was added dropwise over 5 minutes. The mixture was then left stirring for 35 minutes and a further amount of Oxone (3.0g) in water (50ml) added over 15 minutes. Stirred for 30 minutes then a solution of Oxone (3.0g) in water (50ml) added over 15 minutes. The reaction mixture was left for a further 2 hours 35 minutes. (Total 4 hours).

The reaction mixture was then analysed by GLC (Carbowax column 71°C/FID) and the relative proportions of *cyclohexene* and *cyclohexene oxide* determined.

Cyclohexene.....**53.2%wt**

Cyclohexene oxide.....**46.8%wt**

CHAPTER 9.

N-phenyl-3-bromopropanamide(228).[112]

To a well stirred solution of aniline (10.3ml, 0.113mol, 10.5g) and N,N-dimethylaniline (46.6ml, 0.37mol, 44.5g) in DCM (600ml) at -9°C (ice/MeOH) was added 3-bromopropionyl chloride **(227)** (23.5ml, 0.22mol) in DCM (100ml) dropwise over 20 minutes. The mixture was left stirring for 2½ hours then allowed to warm to ambient temperature and left standing overnight. The mixture was washed with 10% hydrochloric acid (4x200ml), water (200ml), aqueous sodium bicarbonate solution (200ml) and sodium chloride solution (200ml). DCM layer separated, dried (sodium sulphate), filtered and the solvent evaporated to give the crude solid product (26.7g). Crude recrystallised from ethanol (40ml) to give pure crystals of N-phenyl-3-bromopropanamide (16.6g, 65%). Mpt. 121-122°C (lit 118-119°C prepared by different method[113]), IR υ_{max} 3200(m, NH), 1658(C=O), 1552(NH bend), 1258(CN str), 1186cm^{-1}(CN str), ^{1}H NMR (d6 acetone) δ 9.3(br, 1H, NH), 7.6-7.0(m, 5H, Ph), 3.6(t, 2H, CH_2), 3.0(t, 2H, CH_2).

Cyclisation of N-phenyl-3-bromopropanamide to N-phenylazetidin-2-one (229).[103]

To a well stirred suspension of pulverised potassium hydroxide pellets (7.4g, 0.13mol) in DCM (750ml) was added 18-crown-6 (2.64g, 10mmol). A solution of N-phenyl-β-propionamide (11.3g, 50mmol) in DCM (750ml) was added dropwise over 8 hours at 25°C and the mixture left stirring for a further 13 hours. The solution was then filtered and the solvent evaporated to give the crude product which was purified by column chromatography (silica gel, DCM/EtOH 190:10) to afford N-phenylazetidin-2-one (8.0g). The product was further purified by recrystallisation from ethanol to give pure colourless crystals of *N-phenylazetidin-2-one* (5.1g, 69%). Mpt. 76-77°C (lit. 77-78°C)[113], IR υ_{max} (KBr) 1738cm^{-1}(C=O), ^{1}H NMR 250MHz δ 7.3(m, 4H, ArH), 7.1(m, 1H, ArH), 3.6(t, J=4.5, 2H, H4), 3.1(t, J=4.5, 2H, H3), ^{13}C δ 164.47(C=O), 138.58(-NCPh), 129.14, 123.81, 116.15 37.99(CH_2), 36.01(CH_2). Found: *m/z* 147(100), 119(16), 105(61), 104(48), 91(17), 77(20), C_9H_9NO, requires *m/z* 147.

4-Phenylthioazetidin-2-one (236).[118]

To thiophenol (3.8g, 3.5ml, 35mmol) in a mixture of water (25ml) and sodium hydroxide (1.4g, 35mmol) at 5°C was added a solution of 4-acetoxyazetidin-2-one **(235)** (5.0g, 3.9mmol) in acetone (25ml). The mixture was left standing at 0-5°C for 2½ hours then the acetone was removed under vacuum. The mixture was then extracted with ethyl acetate to give the crude product (6.5g) which was recrystallised from diisopropyl ether (IPE) to afford pure white crystals of *4-phenylthioazetidin-2-one*. The mother liquor was then passed through a silica gel column (eluent- EtOAc/hexane 2:3) to obtain a further amount of the product (4.9g, 71%). ^{1}H NMR δ 7.3(m, 5H, Ph), 4.9(m, 1H, H4 β-lactam), 3.1(dd, 1H, H3, 2.9(dd, 1H, H3).

Methyl 4-(4-phenylthio-2-oxoazetidinyl)-3-oxobutyrate (237).

To 4-phenylthioazetidin-2-one **(236)** (5.0g, 27.9mmol) in dry DMF (40ml) and dry THF (40ml) under an atmosphere of nitrogen at -20°C was added sodium hydride 50% dispersion in oil (63mmol, 3.0g) in one portion. The resultant yellow/orange mixture was stirred for 15 minutes until it became 'curdy' then methyl 4-bromoacetoacetate[114] (6.3g, 33mmol) in THF (50ml) was added dropwise over 5 minutes at -20°C. The mixture was stirred for 2 hours then poured onto ice/water (150ml) and the pH adjusted to 4.0 using cold 10% citric acid solution. The mixture was then stirred with ethyl acetate (400ml), filtered and the ethyl acetate/water mixture partitioned. The ethyl acetate layer was then separated, dried, filtered and the solvent evaporated to give the crude residue (9.0g). Purification by column chromatography (silica gel, ether/hexane/EtOAc 1:1:1) afforded methyl 4-(4-*phenylthio*-2-*oxoazetidinyl*)-3-*oxobutyrate.* as a yellow oil (1.3g, 16.3%), IR υ_{max} (KBr) 1767(C=O β-lactam), 1740cm^{-1}(C=O keto ester), ^{1}H NMR 250MHz δ 7.4(m, 5H, Ph), 5.2(m, J=2.3, 1H, ring H4), 4.5(d, J=18.7, 1H, -NCH*H*CO-), 4.0(d, J=18.7, 1H, NC*H*HCO-), 3.8(s, 3H, $COCH_3$), 3.5(dd, J=15, J=5, 1H, H3), 3.4(s, 2H, -$COCH_2CO$), 2.9(dd, J=15, J=2.1, 1H, H3).

Benzyl 4-(4-phenylthio-2-oxoazetidinyl)-3-oxobutyrate (238).

To methyl 4-(4-phenylthio-2-oxoazetidinyl)-3-oxobutyrate **(237)** (1.33g, 4.5mmol) in toluene (450ml) was added benzyl alcohol (1.98g, 18.4mmol) and sodium methoxide (0.090g, 1.7mmol). The mixture was refluxed under Dean and Stark conditions with azeotropic removal of methanol for 6 hours. The mixture was diluted with ethyl acetate and washed with water. The ethyl acetate layer was dried, filtered and the solvent evaporated to give the crude product (2.7g). Purification by column chromatography (silica gel, ether/hexane/EtOAc 2:1:2) and drying under vacuum (0.2mmHg,overnight) afforded pure *benzyl 4-(4-phenylthio-2-oxoazetidinyl)-3-oxobutyrate* **(238)** as a yellow oil (1.52g, 91%). IR υ_{max} (KBr) 1762(C=O β-lactam), 1740cm^{-1}(C=O keto ester), ^{1}H NMR 250MHz δ 7.40-7.30(m, 10H, 2Ph), 5.20(s, 2H, OCH_2Ph), 5.20-5.18(m, 1H, H4 β-lactam), 4.40(d, J =18.5, 1H, -NCH*H*CO-), 3.95(d, J=18.7, 1H, -NC*H*HCO-), 3.42(s, 2H, $COCH_2CO$), 3.40(dd, J=15, J=5, 1H, H3 β-lactam), 2.85(dd, J=15, J=2, 1H, H3 β-lactam), ^{13}C δ 196.42, 165.97, 165.52, 134.93, 134.00, 133.82, 130.20, 129.39, 128.78, 128.67, 128.51, 128.46, 127.58, 126.93, 67.49(CH_2), 59.58(CHSPh), 48.68(CH_2), 46.72(CH_2), 44.99(CH_2). Found: *m/z* 369(5), 260(72), 163(9), 135(8), 109(10), 91(100) $C_{20}H_{19}NO_3S$ requires *m/z* 369.

Methyl 4-bromoacetoacetate.[114]

To a stirred solution of methyl acetoacetate (10g, 86mmol) in DCM (100ml) at -10°C was added dropwise a solution of bromine (14.0g, 86mmol) in DCM (50ml) over 30 minutes. The mixture was stirred for a further 1 hour then allowed to warm to room temperature over 2 hours. Nitrogen gas was then passed through the reaction mixture to remove hydrogen bromide over 1½hours then the mixture was stirred open to air for 2 hours. Evaporation of the solvent gave the title compound as a pale orange liquid (28.2g). The product was used for subsequent reactions without further purification. ^{1}H NMR δ 4.00(s, 2H, $BrCH_2$), 3.70(s, 3H, CO_2CH_3), 3.69(s, 2H, CH_2CO_2).

Benzyl 3-oxo-2-(2-oxoazetidin-1-yl)butyrate (242).

To benzyl 2-(oxoazetidinyl) acetate **(217)**[98,101] (1.0g, 4.6mmol) in THF (150ml) at -70°C was added lithium bis(trimethylsilyl)amide (5ml, 5mmol, 1.0M soln in THF). This was stirred for 20 minutes then acetyl chloride (0.400g, 5mmol) in THF (50ml) was added and the mixture left stirring at -70°C for ¾ hours. Acetic acid (0.29ml, 5mmol) in water (25ml) and ethyl acetate (300ml) was added and the mixture allowed to warm to ambient temperature. The ethyl acetate layer was washed successively with sodium bicarbonate solution and saturated sodium chloride solution until the aqueous washings were neutral pH7.0. The ethyl acetate layer was separated, dried, filtered and the solvent evaporated to give the crude product (1.2g) as a yellow oil. TLC and the ^{1}H NMR spectrum showed that **(217)** and the required product **(242)** were present. By comparing the integrations of the benzyl methylene groups of **(217)** and **(242)** in the proton NMR spectrum it was evident that less than 30% conversion of the β-lactam **(217)** had occurred. The product **(242)** was found to be difficult to separate from (217) by chromatography so the crude mixture **(242a)** was used for the hydrogenation step. ^{1}H NMR 250MHz (crude) δ 7.40-7.30(m, Ph), 5.23(s, CH_2Ph, β-keto ester product **(242)**), 5.17(s, CH_2Ph, ester), 4.05(s, 2H, -NCH_2CO_2Ph ester).

Hydrogenation of (242a) to (240).

The crude product **(242a)** (0.946g) was hydrogenated using Pd/C catalyst (0.050g) in ethanol (20ml) at atmospheric pressure for 30 minutes. Pd/C catalyst filtered off and washed with ethanol and ethyl acetate. The solvent was evaporated to give crude mixture (0.500g). Purification by column chromatography (silica gel, EtOAc/MeOH 400:200) afforded the ketone **(240)** (0.028g, 16% yield based on 30% conversion of **(217)**). IR υ_{max} (KBr) 1748(C=O β-lactam), 1724cm^{-1}(C=O), ^{1}H NMR 250MHz δ 4.07(s, 2H, NCH_2CO-), 3.4(t, J=4.1, 2H, H4 β-lactam), 3.05(t, J=4.1, 2H, H3 β-lactam), 2.15(s, 3H, CH_3), Found *m/z* 127, $C_6H_9NO_2$, required *m/z* 127. CI(NH_3) Found *m/z* 145(100) MNH_4^+ requires *m/z* 145.

Benzyl 3-hydroxy-2-(2-oxoazetidin-1-yl)butyrate (246).

To benzyl 2-(oxoazetidinyl)acetate (**217**) (1.0g, 4.6mmol) in dry THF (120ml) under a nitrogen atmosphere at -70°C was added lithium bis(trimethylsilyl)amide (5ml, 5mmol, 1.0M sol^{n} in THF).[101] The mixture was stirred for 20 minutes to generate the anion (yellow colouration) then acetaldehyde (0.25g, 0.33ml, 5.8mmol) was added and the mixture left stirring for a further 2½ hours. To the mixture was added a solution of acetic acid (0.3ml) in water (30ml) and ethyl acetate (50ml) then the mixture was allowed to warm to room temperature. The ethyl acetate layer was washed successively with saturated sodium chloride solution and aqueous sodium bicarbonate. The ethyl acetate layer was separated, dried, filtered and the solvent evaporated to give the crude residue as a yellow oil (0.839g). Purification by column chromatography (silica gel, EtOAc/pet ether/EtOH 20:30:1) afforded the product (**246**) as a clear oil (0.575g, 48%) (mixture of diastereomers). IR υ_{max} (film) 3400(s, OH), 1756cm^{-1}(br, C=O groups), ^{1}H NMR 250MHz δ 7.36(s, 5H, Ph), 5.23(s, 2H, C**H**$_2$Ph), 4.3(m, 1H, H3), 4.08(d, J=3.8, 2H, H2 and OH), 3.38-3.29(m, 2H, H4 CH_2 β-lactam), 2.97(t, J=4.0, H3 CH_2 β-lactam), 1.3(d, J=7, 3H, CH_3) ratio of diastereomers 25:75. ^{13}C NMR δ 168.5, 135.0, 128.6, 128.5, 128.2, 67.4(C-OH), 67.2(C**H**$_2$Ph), 63.3(C-2), 39.7(C**H**$_2$ β-lactam), 36.1(C**H**$_2$ β-lactam), 19.8(C**H**$_3$). Found: 219(10), 174(7), 128(41), 91(100), 86(43), 77(5), $C_{14}H_{17}NO_4$, requires *m/z* 263. (Low resolution EI mass spectrum obtained, molecular ion not detected probably due to retro-aldol occurring under EI conditions to give *m/z* 219).

Methods for attempted oxidation of aldol product (246) to the β-keto ester (242).

PDC (pyridinium dichromate 1.5 equivs).[107a]

To β-lactam (**246**) (0.109g, 0.4mmol) in DCM (5ml) was added PDC (0.216g, 0.62mmol) as a suspension in DCM (15ml). The mixture was stirred for 5½ hours then ether (10ml) added and the mixture filtered through celite to remove the chromate residues. Solvent evaporated and the residue redissolved in ether (50ml) and washed with copper sulphate solution and water to remove any pyridine present. The ether layer was dried, filtered and the solvent evaporated to give the crude residue (0.090g) which was found to be unreacted β-lactam (**246**). (Confirmed using TLC, IR and ^{1}H NMR).

PCC (pyridinium chlorochromate 2.8 equivs).[107b]

To a suspension of PCC (0.140g, 0.65mmol) in DCM (20ml) under a nitrogen atmosphere was added β-lactam (**246**) (0.060g, 0.23mmol). The mixture was cooled to 2°C and stirred for 18 hours. Ether (50ml) was added and the mixture filtered through celite. Ether solution washed with copper sulphate solution, dried, filtered and the solvent evaporated to give the crude residue (0.055g) which was found to be unreacted β-lactam (**246**). (Confirmed using TLC, IR and ^{1}H NMR).

Swern oxidation (oxalyl chloride/DMSO).[107c]

To a solution of oxalyl chloride (0.027g, 0.22mmol) and DMSO (0.035g, 0.44mmol) in DCM (2.7ml) at -60°C was added β-lactam (**246**) (0.050g, 0.2mmol) in DCM (2ml) dropwise over 20 minutes. The mixture was left stirring for a further 15 minutes then triethylamine (0.5ml) was added. The mixture was left stirring for a further 15 minutes and then allowed to warm to ambient temperature. Water (1ml) was then added and the aqueous layer extracted with DCM (5ml). The DCM layer was then washed with 2M hydrochloric acid (10ml), sodium bicarbonate solution and sodium chloride solution. The DCM layer was dried, filtered and the solvent evaporated to give the crude residue (0.045g). Column chromatography (silica gel, EtOAc/pet ether/EtOH 20:30:1) afforded predominantly unreacted β-lactam (**246**) no evidence of required product (**242**).

DMD/acetone solution (2 equivs).

To β-lactam (**246**) (0.102g, 0.388mmol) in DCM (2ml) was added DMD/acetone solution (7.0ml, 0.39mmol, 0.56M). The mixture was protected from light and left stirring at 2-5°C. After 3 hours a further aliquot of DMD/acetone (7.0ml) was added and the mixture allowed to stir for a further 2 days at 20°C. Solvent evaporated to give the crude residue (0.109g). Purification by preparative TLC (silica gel, EtOAc/pet ether/EtOH 20:30:2) afforded starting material (**246**) (0.043g) and the required β-keto ester (**242**) (0.024g, 41%) containing some impurity and base-line material which was not purified further. IR υ_{max} (film) 1750cm^{-1}(br, C=O), ^{1}H NMR δ 7.3(s, 5H, Ph), 5.3(s, 2H, CH_2Ph), 3.6(t, 2H, H4 β-lactam), 3.1(t, 2H, H3 β-lactam), 2.2(s, 3H Me).

Reaction of benzyl 2-(oxoazetidinyl)acetate with trifluoroacetic anhydride.

To benzyl 2-(oxoazetidinyl)acetate **(217)**[98,101] (0.500g, 2.3mmol) in THF (100ml) under an atmosphere of nitrogen at -70°C was added 1.3 equivalents of lithium bis(trimethylsilyl)amide (2.4ml, 2.4mmol).[101] The mixture was left stirring for a further 3 hours. Ethyl acetate (50ml) and acetic acid (0.15ml) in water (20ml) was added and then the ethyl acetate layer separated and washed with sodium bicarbonate solution and sodium chloride solution. The ethyl acetate layer was separated, dried, filtered and the solvent evaporated to give the crude residue which was found to contain only unreacted β-lactam **(217)**.

Attempted preparation of the silyl ketene acetal (245) of benzyl 2-(oxoazetidinyl)acetate (217).

To LDA in THF solution (1ml, 0.5mmol) at -78°C under an atmosphere of nitrogen was added benzyl 2-(oxoazetidinyl)acetate in THF (4ml). This was left stirring for 1 hour at -78°C and then a solution of t-butyl dimethylsilyl chloride in THF (1ml) was added. The mixture was stirred for 1 hour then allowed to warm to room temperature. At this stage the silyl ketene acetal should form, however this product was not isolated and the yellow solution was used immediately for the condensation step.

The clear yellow solution was cooled to 0°C and acetyl chloride (0.040g,0.5mmol) in THF (1ml) added followed by triethylamine (0.050g, 0.5mmol) in THF (1ml). The mixture was then allowed to stir for 24 hours at room temperature. The solution was then extracted with ether and washed with water and sodium chloride solution.[106] The solvent layer was dried, filtered and the solvent evaporated to give the crude residue which contained only unreacted β-lactam **(217)** and acetyl chloride/acetic acid and TBDMS residues. (Confirmed by TLC and ^{1}H NMR).

Oxidation of benzyl 2-(2-oxoazetidin-1-yl)-4-pentenoate (248) with DMD/acetone (2.6 equivs).

To β-lactam (**248**)[108] (0.050g, 0.193mmol) in DCM (5ml) was added DMD/acetone solution (3ml, 0.19mmol, 0.061M). The mixture was protected from light and left stirring for 17½ hours then a further aliquot of DMD/acetone solution (2ml, 0.13mmol) was added and the mixture left stirring for 1 hour. A third portion of DMD/acetone (3ml) was added and the mixture left stirring for a further 10 hours at 0-5°C. The solvent was evaporated to give the crude residue (0.069g). TLC showed the presence of the epoxide (**249**) and some base-line material only. Purification by preparative TLC (silica gel, ether/pet ether/EtOAc 100:20:5) afforded pure epoxide (**249**) (0.030g, 57%). TLC, IR and ^{1}H NMR were data identical to an authentic sample[108] of the epoxide (**249**). IR υ_{max} (film) 1752-1734cm^{-1} (ester C=O and β-lactam C=O), ^{1}H NMR 250MHz 7.35-7.26(m, 5H, Ph), 5.18(s, 2H, CH_2Ph), 4.70-4.62 and 4.60-4.54(2 sets of multiplets, 1H, -NC**H**$COCH_2Ph$, ratio of diastereomers 45:55), 3.46-3.34(m, 2H, CH_2 H4 β-lactam), 3.00-2.95(m, 3H, CH_2 H3 β-lactam, overlapping oxirane proton 1H, -CH_2CHOCH_2), 2.82-2.71(t, 1H, -CH_2CHOCH***H*** ratio of diastereomers 45:55), 2.54-2.40(dd, 1H, -CH_2CHOC***H***H), 2.28-2.18(m, 1H, -NCHR CH***H***CHO-, R=CO_2CH_2Ph), 2.00-1.80(m, 1H, -NCHRC***H***HCHO-, R=CO_2CH_2Ph).

Oxidation of β-lactam (248) with the Acetone/caroate system.

To β-lactam (**248**)[108] (0.060g, 0.23mmol) in DCM (20ml) was added TBAHS (0.035g, 0.1mmol), acetone (10ml) and phosphate buffer (30ml). The mixture was maintained at pH7.5 and 1-4°C whilst a solution of Oxone (14.0g, 22.8mmol) and EDTA (0.3g) in water (75ml) was added in portions over 34 hours. TLC revealed complete conversion of (**248**). Work-up gave the crude residue (0.058g). Purification by preparative TLC (silica gel, ether/pet ether/EtOAc 10:5:1) afforded pure epoxide (**249**) (0.023g, 36%). TLC, IR and ^{1}H NMR were data identical to an authentic sample[108] of the epoxide (**249**).

Reaction of N-phenylazetidin-2-one (229) with DMD/acetone.

To N-phenylazetidin-2-one (**229**)[103] (0.053g, 0.36mmol) in DCM (5ml) at -13°C was added a solution of DMD/acetone (4ml, 0.067M). The mixture was stirred well and allowed to warm to ambient temperature over 18 hours. The mixture was then cooled to -44°C and a further aliquot of DMD/acetone solution (3ml, 0.04M) added and the mixture allowed to warm to ambient temperature. over 16 hours. TLC revealed that N-phenylazetidin-2-one was the major component of the reaction mixture. A further amount of DMD/acetone (17ml, 0.063M) was added at -28°C and the mixture allowed to warm to ambient temperature over 19 hours. Magnesium sulphate was added to the mixture then filtration and evaporation of solvent gave the crude residue (0.040g) as a brown oil which solidified on standing. Mixture of N-phenylazetidin-2-one and unknown base-line compound(s) (**230**) evident. IR υ_{max} (crude) 3440(br, OH, COOH), 1738cm^{-1} (C=O). Deuterium oxide added to dissolve the brown oil (**230**) (0.023g) and ^{1}H NMR spectrum obtained. ^{1}H NMR 250MHz (D_2O) δ 7.4-7.3(m, ArH), 3.6(t, -CH_2), 2.6(t, -CH_2). IR υ_{max} (film) 3416(br, OH, COOH), 1722cm^{-1}(C=O).

(Data indicates formation of a carboxylic acid)

The DCM soluble material recovered was found to be N-phenylazetidin-2-one (0.011g).

Reaction of unknown carboxylic acid mixture (230) with diazomethane.

To the unknown acid mixture (**230**) (0.015g) was added diazomethane (0.233mmol) in ether dropwise over 10 minutes and the mixture left stirring for a further 7 hours. Evaporation of the solvent gave the crude residue. ^{1}H NMR spectrum of the crude product (**231**) confirmed the formation of a methyl ester δ 3.6ppm (singlet, CO_2CH_3). TLC showed a mixture of compounds. Purification using preparative TLC (silica gel) afforded two compounds.

1. Compound (233). (0.008g). IR υ_{max} 1736cm^{-1}(C=O), ^{1}H NMR 250MHz δ 7.5(m, ArH), 4.3(t, -CH_2), 3.6(s, CH_3 of ester), 2.6(t, -CH_2). Found: *m/z* 179, 106(100).

Structure not elucidated.

2. Compound (232). (0.003g). ^{1}H NMR 250MHz δ 7.2(m, ArH), 6.6(m, ArH), 4.0(br, NH), 3.7(s, 3H, CH_3 ester), 3.4(t, 2H, CH_2), 2.6(t, 2H, CH_2).

^{1}H NMR spectrum identical to authentic sample of *methyl β-anilinopropionate* (**232**).

Attempts to repeat the above result and obtain compound (**233**) *have been unsuccessful.*

Methyl β-Anilinopropionate (232).[103b]

To a refluxing mixture of aniline (10g, 0.108mol) and acetic acid (2.8ml) was added methyl acrylate (9.3g, 0.108mol) over 1 hour. Stirring was continued for a further 8 hours then the mixture was allowed to cool. The red mixture was dissolved in ether (10ml) and washed successively with water (3x100ml) and 5% sodium bicarbonate solution (2x100ml). The ether layer was dried, filtered and the solvent evaporated to a red/brown residue. The mixture was distilled as a yellow liquid (118°C @ 0.8mmHg) which solidified on standing. Recrystallisation (MeOH/water) afforded colourless crystals of pure *methyl β-anilinopropionate* (2.95g, 15%). IR υmax (KBr) 3403(NH), 3025, 2946, 1720(C=O), 1608, 1321cm^{-1}, ^{1}H NMR 250MHz δ 7.2(t, J=7.4, 2H, ArH), 6.2(t, J=7.4, 1H, ArH), 6.1(d, J=7.8, 2H, ArH), 4.0(br, 1H, D_2O exchange NH), 3.7(s, 3H, CH_3 ester), 3.4(t,J=6.4, 2H, CH_2), 2.6(t,J=6.4, 2H, CH_2). ^{13}C NMR δ 172.82(CO), 147.59, 129.34, 117.79, 113.09, 51.73(CH_3), 39.47(CH_2), 33.77(CH_2). Found: *m/z* 179(53), 118(5), 106(100), 104(8), 91(4), 77(10), requires *m/z* 179.

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